Riboflavin intake and 5-year blood pressure change in Chinese adults: Interaction with hypertensive medication

Zumin Shi, Baojun Yuan, Anne W. Taylor, Shiqi Zhen, Hui Zuo, Yue Dai, and Gary A. Wittert

Abstract

Background. *One previous large cross-sectional study across four countries suggests that riboflavin intake may be inversely associated with blood pressure.*

Objective. *The aim of this analysis was to investigate a possible association between riboflavin intake and change in blood pressure over 5 years.*

Methods. *The study population comprised Chinese men and women who participated in the Jiangsu Nutrition Study. Quantitative data relating to riboflavin intake at baseline in 2002 and measurements of blood pressure at baseline and follow-up in 2007 were available for 1,227 individuals.*

Results. *Overall, 97.2% of the participants had inadequate riboflavin intake (below the Estimated Average Requirement). In multivariable analysis adjusted for sociodemographic and lifestyle factors and dietary patterns, a higher riboflavin intake was inversely associated with change in systolic blood pressure (*$p = .036$*). In participants taking antihypertensive medication at baseline, the relationship between riboflavin intake and systolic blood pressure persisted; whereas, in those not taking antihypertensive medication, the diastolic blood pressure was less likely to increase with the increasing intake of riboflavin (*$p = .031$*). There was a three-way interaction between antihypertensive medications, body mass index, and riboflavin intake. Among those who were obese and taking antihypertensive medication, a higher riboflavin intake was associated with a smaller increment in systolic blood pressure and pulse pressure.*

Conclusions. *There are complex interactions between riboflavin intake and blood pressure change that depend on prior antihypertensive use and the presence or absence of obesity.*

Key words: Blood pressure change, epidemiology, longitudinal study, nutrition, riboflavin intake

Introduction

In 2002, one in six adults in China had hypertension [1], and at the same time both awareness (24%) and adequate control (19%) of blood pressure were poor [1]. The prevalence of hypertension reached 33.5% in 2010, and was comparable in urban and rural areas (34.7% and 32.9%, respectively) [2]. However, the proportion of the hypertensive population with adequate control of blood pressure (defined as the pharmacological treatment of hypertension associated with an average systolic blood pressure less than 140 mm Hg and an average diastolic blood pressure less than 90 mm Hg) was low overall and was as little as 3.7% in some regions [3]. In accordance with the burden of hypertension, the incidence of stroke is high [4]. Increasing overweight and obesity, insufficient physical activity, and high salt intake have been implicated as the primary contributors to the burden of hypertension in China [3, 5].

Riboflavin is a water-soluble vitamin present in a variety of foods, especially milk and meat. It is the central component of two cofactors, flavin adenine dinucleotide (FAD) and flavin mononucleotide (FMN). Adequate intake of riboflavin is essential to human health [6]; it plays an important role in energy metabolism, hematologic status, and regulation of homocysteine levels [6]. According to Chinese nutrition recommendations, the Estimated Average Requirement (EAR) for riboflavin intake is above 1.2 mg/day for

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adults, depending on age and sex (1.4 mg/day for men aged 18 years or above, 1.2 mg/day for women aged 18 to 49 years, and 1.4 mg/day for women aged 50 years or above) [7]. In places where rice is the staple food and meat and milk intake is low, riboflavin deficiency is common [6]. The mean riboflavin intake in the Chinese population is around 0.8 mg/day, which is well below the Chinese EAR [8].

Currently, there is only one cross-sectional population study assessing the association between riboflavin intake and blood pressure. Based on data from the International Study of Macro/Micro-nutrients and Blood Pressure (INTERMAP), including China, Japan, the United States, and the United Kingdom, Tzoulaki et al. found that riboflavin intake was inversely related to both systolic and diastolic blood pressure [9]. In an intervention trial, it has been shown that riboflavin supplements significantly lower blood pressure, specifically among patients with the methylenetetrahydrofolate reductase (MTHFR) 677TT genotype [10, 11]. Cumulative evidence suggests there is a causal relationship between suboptimal vitamin B status and cardiovascular disease [12].

Since there are no prospective cohort studies that examine the relationship between riboflavin intake and blood pressure, the objective of this study was to assess the association between riboflavin intake and blood pressure change and the interaction between antihypertensive medication and riboflavin intake in relation to blood pressure change over 5 years in a Chinese cohort.

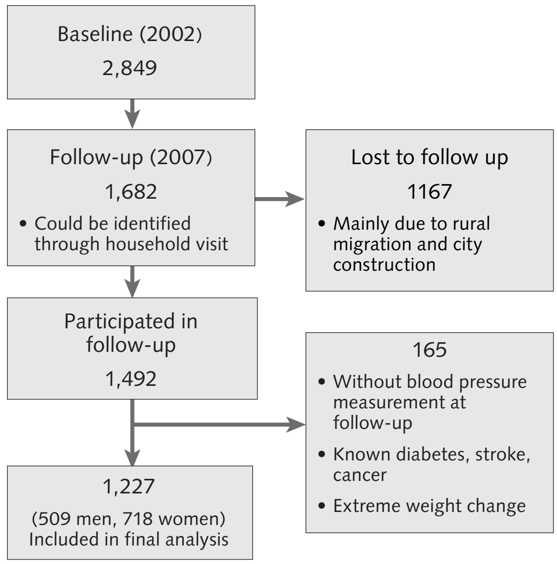

FIG. 1. Description of Jiangsu Nutrition Study sample

Subjects and methods

Sample

The Jiangsu Nutrition Study cohort study of persons aged 20 years or older and the methods of sampling have been described previously [13–15]. In 2002, 2,849 adults aged 20 years or above living in two cities and six rural areas had their blood pressure measured. In 2007, only 1,682 participants could be identified through household visits, and 1,492 of them participated in the follow-up interview. One hundred ninety-two of these declined to participate further. Height and weight measurements were obtained from 1,282 participants (76.2%), and 210 participants completed the interview at home but missed the measurement in the clinic. For the current analyses, we excluded those participants who had extreme values of weight change (> 20 kg, n = 11) and those who had known diabetes, stroke, or cancer at baseline (n = 40). The final sample examined consisted of 509 men and 718 women (total n = 1,227) with detailed dietary intake information and blood pressure measurements (**fig. 1**). The study was conducted according to the guidelines laid down in the Declaration of Helsinki, and all procedures involving human subjects or patients were approved by the Jiangsu Provincial Centre for Disease Control and Prevention. Written consent to participate was obtained from all subjects.

Data collection and measurements

The participants were interviewed in their homes by health workers with the use of a standard questionnaire [15]. The health workers were intensively trained in all aspects of data collection.

Outcome variables

At baseline and follow-up, blood pressure was measured twice by mercury sphygmomanometer on the right upper arm of the subject, who was seated for 5 minutes before the measurement. The mean of these two measurements was used in the analyses. The appropriate cuff size was selected on the basis of upper arm circumference [1]. Hypertension was defined as systolic blood pressure above 140 mm Hg and/or diastolic blood pressure above 90 mm Hg, or use of antihypertensive drugs. Pulse pressure was defined as the difference between systolic and diastolic blood pressure. The change in pulse pressure between baseline and follow-up was calculated.

Dietary intake

In 2002, dietary intake patterns during the previous year were investigated by a series of detailed questions about the usual frequency and quantity of intake of 33 food groups and beverages. The food frequency questionnaire has been validated and compared with weighed food records [16–18] and reported to be a useful method for the collection of individual food consumption information in face-to-face interviews, but not in self-administered surveys due to the current educational level of the majority of the Chinese population.

Baseline intakes of riboflavin (the exposure variable), other nutrients (e.g., vitamin C, protein), alcohol, and vegetable oil were assessed with the use of a three-day weighed food diary that recorded all foods consumed by each individual on three consecutive days. We did not consider under- and overreporting of energy intake to be an issue, because upon reviewing the food diaries with the subjects, the health workers would clarify any intake value for a particular food that fell below or above the usual value reportedly consumed by the population within the region. Food consumption data were analyzed with the use of the Chinese Food Composition Table [19]. Inadequate riboflavin intake was defined as usual riboflavin intake below the Chinese EAR (1.4 mg/day for men aged 18 years or above, 1.2 mg/day for women aged 18 to 49 years, and 1.4 mg/day for women aged 50 years or above) [7]. To estimate the prevalence of inadequate riboflavin intake, we used the EAR cutpoint method [20]. We used the National Cancer Institute method to estimate the distribution of usual riboflavin intake [21].

Dietary patterns

Dietary patterns were identified by factor analysis based on food intake measured by the food frequency questionnaire, with the use of standard principal component analysis as described elsewhere [22]. Four food patterns were obtained. Factor 1 ("macho") was characterized by various kinds of animal foods and alcohol. Factor 2 (the "traditional" pattern) loaded heavily on rice and fresh vegetables and inversely on wheat flour. Factor 3 ("sweet tooth") included cake, milk, yogurt, and drinks. Factor 4 ("vegetable-rich") included whole grains, fruits, root vegetables, fresh and pickled vegetables, milk, eggs, and fish. These four factors explained 28.5% of the variance in intake.

Other lifestyle factors

Participants were classified as smokers if they reported that they smoked cigarettes daily. Cigarette smoking was assessed by asking the frequency of daily cigarette smoking. Eating out was assessed by asking whether individuals ate out on a frequent basis and was coded as yes or no. Alcohol consumption was assessed by asking the frequency and amount of alcohol consumed. Information on passive smoking was obtained. Data on daily commuting were grouped into three categories: using motorized transportation or not working (0 minutes of walking or cycling), walking or bicycling for 1 to 29 minutes, and walking or bicycling for 30 minutes or more. Data on daily leisure-time physical activity were grouped into three categories: 0, 1 to 29, and 30 or more minutes. Time spent on sedentary activities each day (watching television, using the computer, playing video games, and reading during leisure time) was classified into four categories: less than 1, 1 to 1.9, 2 to 2.9, and 3 or more hours. Educational level was recoded as low (illiterate or attended only primary school), medium (junior middle school), or high (high middle school or higher), based on six categories of educational levels in the questionnaire. Occupation was recoded as manual or nonmanual based on a question with 12 occupational categories. Antihypertensive medication use (yes/no) was asked at baseline and follow-up.

Anthropometric measurements

In both 2002 and 2007, anthropometric measurements were obtained with the use of standard protocols and techniques [1, 18]. Body weight was measured to the nearest 100 g with the subject wearing light indoor clothing without shoes. Height was measured to the nearest millimeter with a stadiometer with the subject not wearing shoes. Waist circumference was measured to the nearest millimeter midway between the inferior margin of the last rib and the crest of the ilium, in the midaxillary line in a horizontal plane. Family history of hypertension was defined as the presence of known family members with hypertension in any of three generations (siblings, parents, or grandparents).

Statistical analysis

Riboflavin intake was recoded into quartiles. The chi-square test was used to compare categorical variables, and analysis of variance (ANOVA) was used to compare continuous variables between groups. Mixed-effects linear regression was used to determine the association between riboflavin intake (quartiles) and changes in systolic and diastolic blood pressure with adjustment for age, education, occupation, active commuting, leisure-time physical activity, smoking, passive smoking, alcohol consumption, overweight (yes/no) at baseline, change in body mass index (BMI), eating out, family history of hypertension, and intakes of energy, sodium, fiber, and potassium. These multivariate models were adjusted for household cluster using the xtmixed command. Food patterns were also put into the multivariate models to control for residual confounding, as suggested by Imamura et al. [23]. Interactions between riboflavin intake and covariates (e.g., sex, antihypertensive medication use, BMI) were examined by putting the product term of the interacting variables in the model. There was no significant interaction between sex and riboflavin intake, and therefore we presented data from both sexes combined. When assessing the nonlinear association between riboflavin intake and blood pressure change, a quadratic term was added in the regression model. Marginal means were calculated and used to visually examine (using the marginsplot command) the relationship between riboflavin intake (continuous, in milligrams per day) and blood pressure change. In the provinces, it is difficult to define the difference between urban and rural locations because of ongoing economic development. Since we have adjusted for education and job status as well as dietary patterns, the decision was made not to adjust for urban or rural dwelling. All the analyses were performed with STATA 12. Results were considered statistically significant when $p < .05$ (two sided).

Results

The mean ± SD intake of riboflavin was 0.80 ± 0.33 mg/day. The median riboflavin intake among those in quartiles 1 and 4 of riboflavin intake was 0.50 and 1.20 mg/day, respectively.

Overall, 97.2% of the sample (98.0% of the women and 96.2% of the men) had a usual riboflavin intake below the Chinese EAR. **Supplement table 1** shows the proportions of the sample below different cutoff values of usual riboflavin intake according to the National Cancer Institute method. Riboflavin intake was positively associated with intakes of energy, fat, protein, and potassium at baseline (**table 1**). There were no significant differences in sodium intake across the quartiles of riboflavin intake. There were no significant differences in systolic or diastolic blood pressure associated with baseline level of riboflavin intake.

There was an overall inverse U-shaped association between riboflavin intake and change in systolic, but not diastolic, blood pressure (**table 2**). Systolic blood pressure was 3.78 mm Hg lower among those in the fourth quartile of riboflavin intake than among those in the second quartile of riboflavin intake, (95% CI, −7.30 to −0.25, $p = .036$). A significant interaction between riboflavin intake and use of antihypertensive medications was found. There was an inverse U-shaped association between riboflavin intake and systolic blood pressure change among those taking antihypertensive medications at baseline (**fig. 2**). Exclusion of the results from subjects who reported a change in diet ($n = 46$) in order to control weight or chronic diseases did not

TABLE 1. Baseline characteristics of sample of Chinese adults according to quartile of riboflavin intake[a]

Characteristic	Q1 (low) 0.5 mg/day (median) ($n = 307$)	Q2 0.7 mg/day ($n = 307$)	Q3 0.8 mg/day ($n = 307$)	Q4 1.2 mg/day ($n = 306$)	p
Energy intake (kJ/day)[b]	1,900 (31)	2,228 (30)	2,499 (30)	2,705 (31)	< .001
Fat intake (g/day)[c]	78.6 (1.6)	79.0 (1.4)	83.4 (1.4)	85.3 (1.5)	.008
Protein intake (g/day)[c]	62.4 (0.8)	68.7 (0.7)	74.7 (0.7)	83.5 (0.8)	< .001
Fiber intake (g/day)[c]	13.1 (0.5)	11.1 (0.5)	10.2 (0.5)	11.8 (0.5)	< .001
Total iron intake (mg/day)[c]	23.1 (0.4)	22.8 (0.4)	24.5 (0.4)	29.1 (0.4)	< .001
Sodium intake (g/day)[c]	7.1 (0.2)	6.5 (0.2)	6.9 (0.2)	6.4 (0.2)	.189
Potassium intake (g/day)[c]	1.4 (0.2)	1.6 (0.2)	1.7 (0.2)	2.0 (0.2)	< .001
Salt intake (g/day)[b]	11.3 (0.6)	10.7 (0.6)	12.3 (0.6)	12.4 (0.6)	.105
Male sex (%)	21.2	35.8	51.1	57.8	< .001
Age (yr)	50.9 (0.8)	49.5 (0.7)	48.4 (0.7)	47.2 (0.7)	.004
Obesity (BMI ≥ 28 kg/m^2) (%)	10.1	10.1	9.1	6.5	.547
BMI (kg/m^2)[b]	23.2 (0.2)	23.3 (0.2)	23.5 (0.2)	23.4 (0.2)	.770
Central obesity (%)[d]	34.2	29.3	30.0	25.0	.101
Hypertension (%)	30.6	28.0	32.6	29.7	.666
Systolic blood pressure (mm Hg)[b]	126.2 (1.1)	125.3 (1.1)	127.6 (1.1)	126.4 (1.1)	.497
Diastolic blood pressure (mm Hg)[b]	79.9 (0.7)	78.3 (0.6)	80.2 (0.6)	79.9 (0.6)	.137
Pulse pressure (mm Hg)[b]	46.4 (0.8)	47.0 (0.8)	47.4 (0.8)	46.5 (0.8)	.779
Antihypertensive medication use (%)	9.5	7.2	10.1	6.5	.308
Low education (%)	63.5	56.7	53.1	39.2	< .001
Manual job (%)	52.1	48.5	55.4	51.6	.409
No active commuting (%)	40.7	44.6	38.4	38.2	.368
No leisure-time physical activity (%)	92.8	92.8	92.5	88.6	.308
Smoker (%)	16.6	21.2	31.6	39.5	< .001
Drinks alcohol (%)	12.1	18.2	29.6	39.2	< .001

a. Numbers other than percentages are means (SE). Energy and nutrient intakes were calculated from weighed food records.
b. Adjusted for age and sex.
c. Adjusted for age, sex, and energy intake.
d. Based on the International Diabetes Federation definition for Chinese population.

affect the association.

Figure 3 shows diastolic blood pressure change over 5 years according to antihypertensive medication use and riboflavin intake. No significant interaction was found between antihypertensive medication use and riboflavin intake. Because the graph suggested a possible association between riboflavin intake and diastolic blood pressure among those not taking antihypertensive medications, we undertook a sensitivity analysis. In the fully adjusted model, among those not taking antihypertensive medications at baseline, there was an inverse association between riboflavin intake and diastolic blood pressure: β −2.84 (95% CI, −5.42 to −0.26) (p = .031). No such association was found for systolic blood pressure among those not taking antihypertensive medications at baseline (data not shown).

In the fully adjusted model, there was an inverse nonlinear association between riboflavin intake (continuous) and pulse pressure change among those taking antihypertensive medications. No such association was found among those not taking antihypertensive medications (**fig. 4**).

There was a three-way interaction between use of antihypertensive medications, BMI, and riboflavin intake. Among those taking antihypertensive medications at baseline, high riboflavin intake was associated with a favorable change in systolic blood pressure and pulse pressure change among obese participants (**figs. 5–7**).

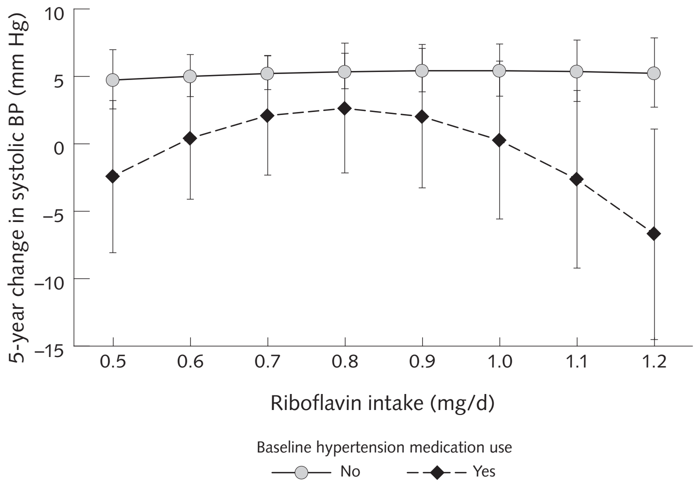

FIG. 2. Marginal mean change in systolic blood pressure over 5 years according to riboflavin intake and antihypertensive medication use at baseline. *P* for medication × riboflavin × riboflavin interaction = .002. *P* for medication × riboflavin interaction = .006. Model adjusted for age, sex, smoking, active commuting, leisure-time physical activity, sedentary activity, education, occupation, overweight (BMI ≥ 24 kg/m^2, yes/no), BMI change (continuous), central obesity (waist circumference ≥ 90 cm for men, ≥ 80 cm for women), eating out, passive smoking, family history of hypertension, energy intake, sodium intake, fiber intake, potassium intake, dietary pattern

Discussion

In this cohort study, inadequate intake of riboflavin was common among Chinese adults. We observed an inverse association between riboflavin intake and 5-year blood pressure change, with an inverse U-shaped association between riboflavin intake and systolic blood pressure change in those taking antihypertensive

TABLE 2. Linear regression β coefficients (95% CI) for quartiles (Q1–Q4) of riboflavin intake predicting 5-year change in blood pressure in 1,227 adults participating in the Jiangsu Nutrition Study[a]

Model[b]	Q1 (low) 0.5 mg/day (median) (n = 307)	Q2 0.7 mg/day (n = 307)	Q3 0.8 mg/day (n = 307)	Q4 1.2 mg/day (n = 306)	p for quadratic term
Systolic blood pressure					
Model 1	−3.19 (−6.33, −0.05)	0	−2.53 (−5.63, 0.58)	−2.33 (−5.62, 0.96)	.752
Model 2	−2.25 (−5.42, 0.92)	0	−2.62 (−5.73, 0.48)	−3.70 (−7.19, 0.21)	.115
Model 3	−2.25 (−5.42, 0.93)	0	−2.34 (−5.45, 0.76)	−3.78 (−7.30, −0.25)	.149
Diastolic blood pressure					
Model 1	−1.69 (−3.50, 0.13)	0	−1.70 (−3.49, 0.10)	−1.55 (−3.44, 0.34)	.516
Model 2	−1.46 (−3.29, 0.38)	0	−1.72 (−3.52, 0.08)	−1.90 (−3.91, 0.12)	.260
Model 3	−1.44 (−3.29, 0.40)	0	−1.55 (−3.35, 0.25)	−1.96 (−4.00, 0.08)	.241

a. Values are β (95% CI) from multilevel mixed-effects linear regression model adjusted for household clusters.
b. Model 1: adjusted for age and sex. Model 2: model 1 + smoking (0, 1–19, ≥ 20 cigarettes/day), alcohol drinking (g/day), active commuting (none, 1–29 min/day, ≥ 30 min/day), leisure-time physical activity (none, 1–29 min/day, ≥ 30 min/day), sedentary activity (< 1, 1–1.9, 2–2.9, ≥ 3 h/day), educational level (low, medium, high), occupation (manual, nonmanual), overweight (BMI ≥ 24 kg/m^2, yes/no), BMI change (continuous), central obesity (waist circumference ≥ 90 cm for men, ≥ 80 cm for women), eating out, passive smoking, family history of hypertension. Model 3: model 2 + energy intake, sodium intake, fiber intake, potassium intake, dietary pattern, hypertension medication use (baseline, follow-up).

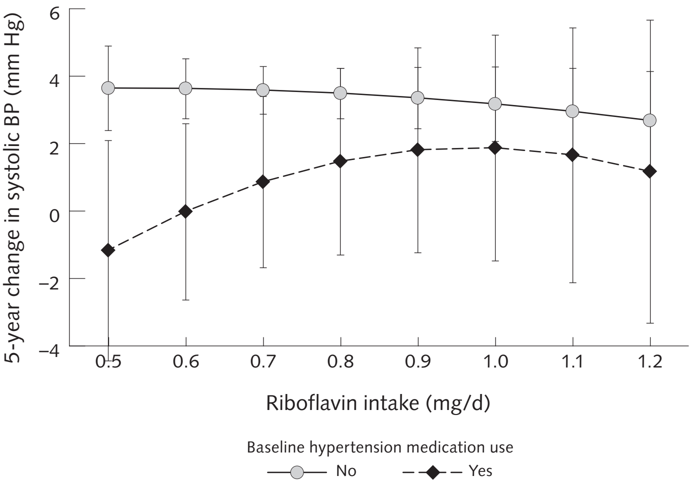

FIG. 3. Marginal mean change in diastolic blood pressure over 5 years according to riboflavin intake and antihypertensive medication use at baseline. *P* for medication × riboflavin × riboflavin interaction = .254. *P* for medication × riboflavin interaction = .175. Model adjusted for age, sex, smoking, active commuting, leisure-time physical activity, sedentary activity, education, occupation, overweight (BMI ≥ 24 kg/m^2, yes/no), BMI change (continuous), central obesity (waist circumference ≥ 90 cm for men, ≥ 80 cm for women), eating out, passive smoking, family history of hypertension, energy intake, sodium intake, fiber intake, potassium intake, dietary pattern

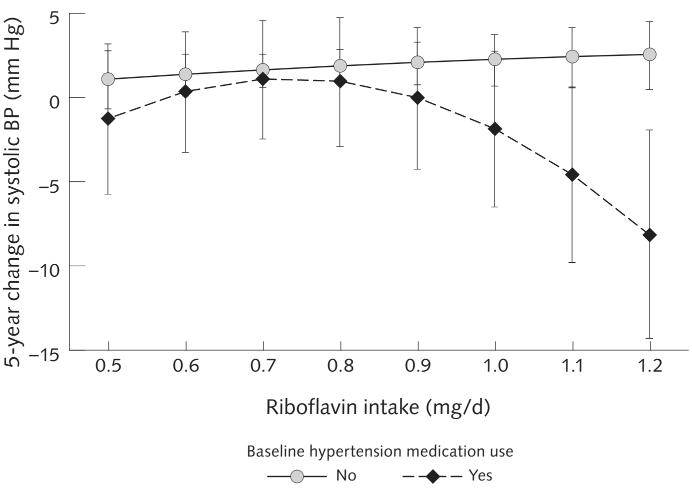

FIG. 4. Marginal mean change in pulse pressure over 5 years according to riboflavin intake and antihypertensive medication use at baseline. *P* for medication × riboflavin × riboflavin interaction = .003. *P* for medication × riboflavin interaction = .017. Model adjusted for age, sex, smoking, active commuting, leisure-time physical activity, sedentary activity, education, occupation, overweight (BMI ≥ 24 kg/m^2, yes/no), BMI change (continuous), central obesity (waist circumference ≥ 90 cm for men, ≥ 80 cm for women), eating out, passive smoking, family history of hypertension, energy intake, sodium intake, fiber intake, potassium intake, dietary pattern

medications at baseline. Among the participants not taking antihypertensive medications, there was an inverse linear association between riboflavin intake and diastolic blood pressure change. Pulse pressure and riboflavin intake were inversely associated in those taking antihypertensive medications only.

The low intake of riboflavin observed is consistent with findings from the China Nutrition and Health Survey, where the mean intake was persistently around 0.7 to 0.9 mg/day among adults aged 18 to 45 years over six surveys between 1989 and 2004 [8]. Findings from another large study in China suggest that more than 90% of Chinese adults are riboflavin deficient [24]. However, the authors argued that the riboflavin allowances are set too high both in China and in Western countries [24].

To the best of our knowledge, this is the first prospective population study assessing riboflavin intake and blood pressure change. Our findings are consistent with those of the cross-sectional INTERMAP study [9] and riboflavin supplement trials [10, 11] and are also in accordance with the inverse association between consumption of dairy products, which are rich in riboflavin, and blood pressure [25].

Riboflavin is a cofactor for MTHFR. The MTHFR 677TT genotype produces an MTHFR enzyme with decreased activity and leads to high elevated plasma homocysteine levels [26]. A raised homocysteine level is a risk factor for cardiovascular disease [12]. Hyperhomocysteinemia is common (> 50%) among Chinese adults with hypertension [27]. The MTHFR TT genotype is a risk factor for hypertension [28, 29]. Riboflavin status is a determinant of blood pressure in hypertensive patients with the TT genotype of MTHFR. Improving riboflavin status can correct genotype-related elevations in blood pressure [10, 11]. Among the Chinese Han ethnic group, the prevalence of the MTHFR TT genotype is 19.8% in the north and 8.1% in the south [30]. Consistently with this regional difference in the MTHFR TT genotype, the north has a higher prevalence of hypertension than the south [1]. It could be hypothesized that the interaction between the MTHFR TT genotype and the overall low riboflavin intake in the population contributes to the disparity between south and north in the prevalence of hypertension in China.

There is a plausible biological basis for a mechanistic effect of riboflavin on the regulation of blood pressure and in particular the interaction with antihypertensive use. Riboflavin has been shown to inhibit calcium

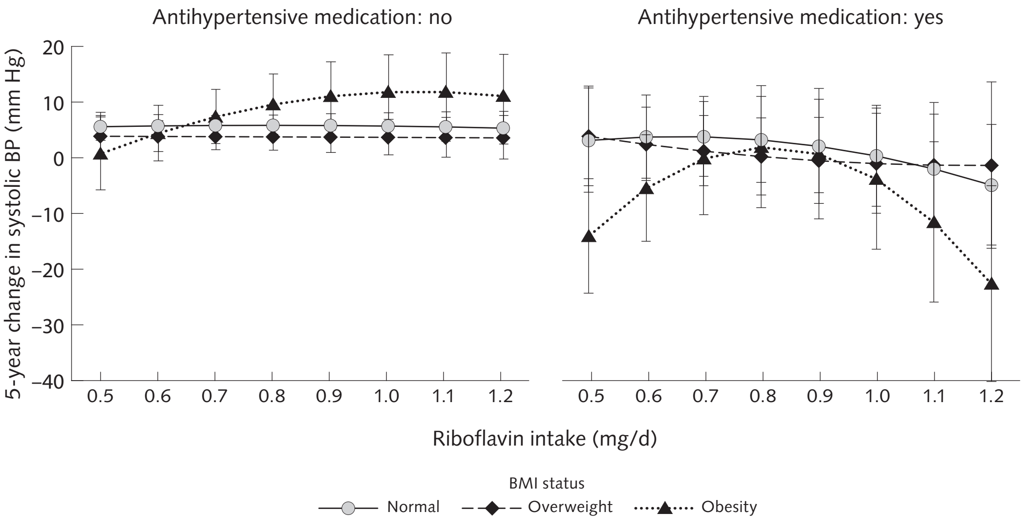

FIG. 5. Three-way interaction between BMI status, riboflavin intake, and antihypertensive medication use in relation to systolic blood pressure change. *P* for medication, BMI status, and riboflavin intake (square term) interaction = .03. Model adjusted for age, sex, smoking, active commuting, leisure-time physical activity, sedentary activity, education, occupation, central obesity (waist circumference ≥ 90 cm for men, ≥ 80 cm for women), eating out, passive smoking, family history of hypertension, energy intake, sodium intake, fiber intake, potassium intake, dietary pattern. Overweight and obesity were defined as BMI ≥ 24 and ≥ 28 kg/m^2, respectively

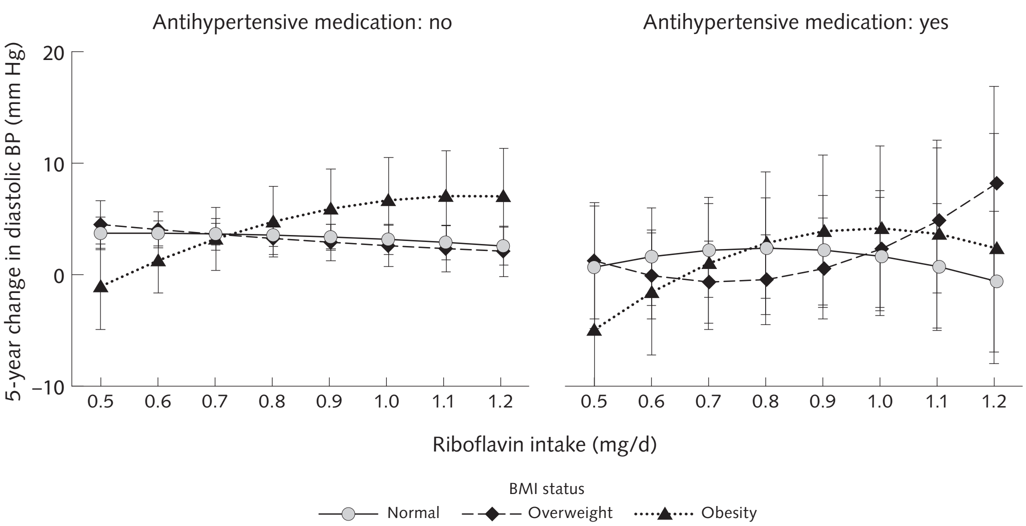

FIG. 6. Three-way interaction between BMI status, riboflavin intake, and antihypertensive medication use in relation to diastolic blood pressure change. *P* for medication, BMI status, and riboflavin intake (square term) interaction = .09. Model adjusted for age, sex, smoking, active commuting, leisure-time physical activity, sedentary activity, education, occupation, central obesity (waist circumference ≥ 90 cm for men, ≥ 80 cm for women), eating out, passive smoking, family history of hypertension, energy intake, sodium intake, fiber intake, potassium intake, dietary pattern. Overweight and obesity were defined as BMI ≥ 24 and ≥ 28 kg/m^2, respectively

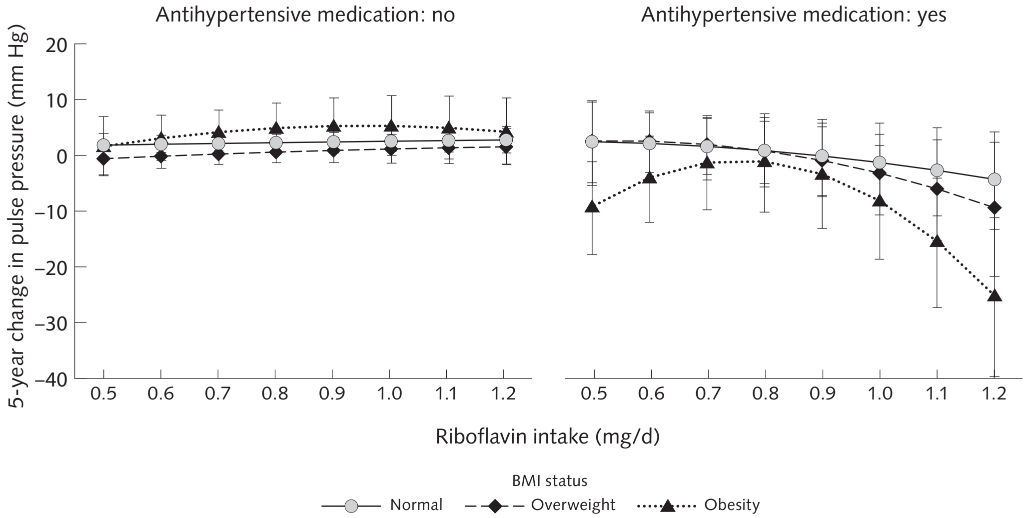

FIG. 7. Three-way interaction between BMI status, riboflavin intake, and antihypertensive medication use in relation to pulse pressure change. *P* for medication, BMI status, and riboflavin intake (square term) interaction = .04. Model adjusted for age, sex, smoking, active commuting, leisure-time physical activity, sedentary activity, education, occupation, central obesity (waist circumference ≥ 90 cm for men, ≥ 80 cm for women), eating out, passive smoking, family history of hypertension, energy intake, sodium intake, fiber intake, potassium intake, dietary pattern. Overweight and obesity were defined as BMI ≥ 24 and ≥ 28 kg/m^2, respectively

channels and block the release of glutamate [31]. Calcium channel blockers are the most commonly used medications to treat hypertension in China. The mechanism for some of the relationships is not entirely clear, but based on previous observations we raise some testable hypotheses. Monosodium glutamate (MSG) is positively associated with blood pressure increase among those taking antihypertensive medications [15]. MSG has been reported to open calcium channels [32], and we hypothesized that this may be a mechanism linking MSG and blood pressure. The effect of riboflavin seems opposite to that of MSG. In a sensitivity analysis, we assessed the interaction among riboflavin intake, MSG intake, and antihypertensive medication use in relation to blood pressure change and observed a borderline significant interaction with systolic blood pressure change ($p = .056$) (data not shown). Among those with high riboflavin intake who are taking antihypertensive medication, the inverse association between riboflavin intake and systolic blood pressure change was attenuated by MSG intake. Because there are at least some data to suggest an effect of riboflavin on calcium channels in the opposite direction to that of MSG [31], there may well be a common mechanism, but acting in opposite directions, by which riboflavin and MSG affect blood pressure. It is known that calcium channel blockers reduce systolic blood pressure more than diastolic blood pressure [33]. If riboflavin interacts with calcium channel blockers, it will have different effects on systolic and diastolic blood pressure. This may explain the different effects of riboflavin intake on systolic and diastolic blood pressure in our study.

At the lower end of riboflavin intake, there was a smaller increase in blood pressure among those taking antihypertensive medications. Although a very low intake of riboflavin could suggest the participant is a vegetarian or has changed diet to control blood pressure, no significant difference in vegetable intake across quartiles of riboflavin intake was observed among those taking antihypertensive medications (data not shown). In addition, more people with high riboflavin intake than those with low riboflavin intake reported having changed their diet. A significantly lower total iron intake was observed among those in the first quartile of riboflavin intake than among those in the fourth quartile (age-, sex-, and energy-adjusted intake: 18 vs. 28 mg/day). In the sample, iron intake was positively associated with blood pressure change among those with high BMI (data not shown). Further research is needed to explore why this group has a smaller increase in systolic blood pressure. An inverse association between riboflavin intake and pulse pressure change among those taking antihypertensive medications is important. It is known that high pulse pressure is a risk factor for cardiovascular disease [34]. The three-way interaction among riboflavin intake, use of antihypertensive medication, and obesity is interesting, because recent findings from clinical trials suggest an interaction between the type of hypertension treatment and BMI on cardiovascular outcomes. Hypertension is clearly a heterogeneous condition, with mechanisms occurring in the obese that may be quite different from those in people of normal body weight [35].

One of the limitations of this study is the high attrition rate due to rural migration and city construction. Another limitation is that we do not have detailed information on the types of medication used. Further research is needed on the interactions between riboflavin intake and different types of medication, and the MTHFR genotype. The strength of the study is the use of three-day weighed food records. Blood pressure was measured at both time points by health workers.

Conclusions

Riboflavin intake is associated with blood pressure change among adults in China, with different associations with systolic and diastolic blood pressure and complex interactions with use of antihypertensive medications and obesity. On the whole, however, an adequate intake of riboflavin favors blood pressure control, and intervention trials using riboflavin supplement to prevent hypertension in the Chinese population are warranted.

Authors' contributions

The study was conceived and the statistical analysis carried out by Zumin Shi. Zumin Shi had full access to the data and drafted the manuscript. Baojun Yuan, Hui Zuo, and Yue Dai collected the data. Baojun Yuan, Shiqi Zhen, Yue Dai, Hui Zuo, Anne W. Taylor, and Gary A. Wittert critically reviewed the manuscript for intellectual content.

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Supplement TABLE 1. Proportion (%) of men and women whose usual riboflavin intake was below the Estimated Average Requirement (EAR) cutoffs[a]

	Riboflavin cutoff (mg/day)			
Sex and age group	0.8	1.0	1.2	1.4
Men (n = 509)				
Total	42.6	72.2	89.0	96.2
20–39 yr	31.9	62.2	83.1	93.5
40–49 yr	40.9	71.9	88.8	96.1
≥ 50 yr	47.7	76.7	91.6	97.2
Women (n = 718)				
Total	70.0	90.1	97.3	99.3
20–39 yr	66.9	88.4	96.6	99.1
40–49 yr	68.2	89.0	96.8	99.2
≥ 50 yr	73.7	92.0	97.9	99.6

a. Usual riboflavin intake adjusted for intraindividual variability was calculated by the National Cancer Institute method.