American Heart Association®

Turmeric, Pepper, Cinnamon, and Saffron Consumption and Mortality

Maryam Hashemian, MD, PhD; Hossein Poustchi, MD, PhD; Gwen Murphy, PhD, MPH; Arash Etemadi, MD, PhD; Farin Kamangar, MD, PhD; Akram Pourshams, MD; Masoud Khoshnia, MD; Abdolsamad Gharavi, MD; Paul J. Brennan, PhD; Paolo Boffetta, MD, PhD; Sanford M. Dawsey, MD; Christian C. Abnet, PhD, MPH; Reza Malekzadeh, MD

Background—Previous studies have reported the beneficial effects of spice consumption on lipid profiles, fasting glucose, and blood pressure, which suggests that spice consumption could affect the risk of cardiovascular disease, diabetes mellitus, and consequently mortality. The objective of this study was to evaluate the relationship between consumption of turmeric, black or chili pepper, cinnamon, and saffron with overall and cause-specific mortality in an adult population in Iran.

Methods and Results—We used data from the Golestan Cohort Study, which has followed 50 045 participants aged 40 to 75 years from baseline (2004–2008). After establishing the exclusion criteria, 44 398 participants were included in the analyses. Spice consumption data were extracted from the baseline Food Frequency Questionnaire. Cox models were used to estimate hazard ratios (HR) and 95% CI for overall and cause-specific mortality, comparing the ever consumers to the never consumers as a reference group for each type of spice (adjusted for known and suspected confounders). During 11 years of follow-up, 5121 people died. Turmeric consumption was associated with significantly reduced risk of overall mortality (HR=0.90, 95% CI=0.85–0.96) and cardiovascular mortality (HR=0.91, 95% CI=0.82–0.99). Black or chili pepper consumption was associated with significantly reduced risk of overall mortality (HR=0.91, 95% CI=0.86–0.98). Saffron consumption was associated with significantly reduced risk of overall (HR=0.85, 95% CI=0.77–0.94) and cardiovascular mortality (HR=0.79, 95% CI=0.68–0.92). We found no associations with cinnamon consumption or between any of these spices and cancer mortality.

Conclusions—Consuming turmeric or saffron was associated with decreased risk of overall and cardiovascular mortality. The hypothesis of a protective effect of spice consumption on mortality should be tested in other prospective studies. (*J Am Heart Assoc*. 2019;8:e012240. DOI: 10.1161/JAHA.119.012240.)

Key Words: cardiovascular disease • chili • curcumin • mortality • pepper • saffron • tumeric

Dietary guidelines suggest limiting the consumption of sugar, saturated fats, and sodium. Instead, dietitians advise adding spices and herbs to keep flavor in food.[1] However, the long-term effects of spice consumption on health are not clear. There is evidence of an adverse association between daily consumption of chili (and its component, capsaicin) and gastric cancer in previous case–control studies.[2,3] On the other hand, there are previous in vitro and animal studies that suggested potential benefits from consuming several types of spices.[4] Red and black pepper, and their bioactive components (capsaicin and piperine, respectively) have antioxidative properties, and have been shown to offer protection against oxidation of human low-density lipoprotein.[4] Turmeric and its component, curcumin, have antiatherogenic, anti-inflammatory, and antioxidant activities.[4] The antioxidant activity of turmeric is time- and dose-dependent, and is even

Clinical Perspective

What Is New?

- Consumption of turmeric, pepper, or saffron is associated with decreased overall mortality.
- Consuming turmeric and saffron is associated with decreased risk of cardiovascular mortality.

What Are the Clinical Implications?

- Turmeric and saffron consumption for culinary purposes has positive public health implications, especially for cardiovascular disease, and adding spice may be recommended to keep flavor while limiting the consumption of sugar, saturated fats, and sodium.
- Spices consumed for culinary purposes are not associated with risk of cancer mortality.

higher than α-tocopherol and β-carotene.[4] Both in vivo and in vitro studies have shown that cinnamon decreases insulin resistance and has antitumor effects.[5] These findings suggest that spices may affect the risk of cardiovascular diseases, diabetes mellitus, cancer, and consequently mortality, in humans through multiple biological processes. However, alternative explanations are plausible, in particular confounding by other dietary factors (ie, spice consumption being a marker of healthy diet).

Clinical trials have evaluated the effects of turmeric, chili pepper, and cinnamon consumption on lipid profiles or plasma glucose with promising results.[5–8] However, these studies serve a specific purpose and may not be generalizable to a free-living population. First, participants in clinical trials receive high doses of spice or its bioactive component that is provided via capsule (up to 4 g/d curcumin and up to 30 g/d chopped chili).[6,7,9,10] The observed health effects of spice consumption in a clinical study may not be achievable with doses used for domestic/culinary purposes. Even in Indian diets, in which spicy foods are common, the curcumin intake is 0.004 to 0.1 g/d and red pepper is 2.4 to 4.1 g/d for adults.[4] Second, most of these clinical trials included subjects with specific conditions such as metabolic syndrome, fatty liver disease, or hyperlipidemia[11–13]; thus, the effects of spice consumption in healthy populations has not been established. Third, these trials administered the spices for short periods, typically only several weeks. Fourth, these studies have mainly focused on intermediate outcomes. For example, many trials have assessed hypertension and dyslipidemia as end points, and while these are important risk factors for cardiovascular disease, the effects of spice consumption on chronic disease outcomes such as cardiovascular disease, or cancer, remain unclear. Therefore, data from large, long-term observational studies may be the best way to understand the association between typical spice consumption and mortality.

Two previous prospective studies explored the association between daily consumption of chili and mortality.[1,14] However, data are lacking to clarify the long-term effects of other types of spice consumption on mortality. Since spice consumption is relatively common in Iran, we used dietary intake data from the Golestan Cohort Study to evaluate the association of spice consumption with overall- and cause-specific mortality. This study provided us with the opportunity to investigate consumption of different types of spices including turmeric, black or chili pepper, cinnamon, and saffron and the quantity of each spice consumed in relation to overall- and cause-specific mortality.

Materials and Methods

The data that support the findings of this study are available from the corresponding author upon reasonable request, and with approval by the study steering committee.

Study Design and Participants

The Golestan Cohort Study was established in 2004 to 2008 with the enrollment of 50 045 participants aged 40 to 75 years from Golestan Province, Iran. Participants were followed for major causes of death, incident cancer, and cardiovascular disease, with a follow-up success rate of >99%. At baseline, trained interviewers administered the Food Frequency Questionnaire (FFQ) and a demographic questionnaire to participants. Before baseline enrollment, participants provided written informed consent. The study protocol was approved by the Institutional Review Boards of the US National Cancer Institute, the International Agency for Research on Cancer, and the Digestive Disease Research Institute of the Tehran University of Medical Sciences.

Participants were excluded from the final analysis if they (1) had an incomplete FFQ (n=872); (2) had energy intake that was more than twice the interquartile range above the 75th percentile (3690 kcal/d for women and 4145 kcal/d for men) or less than twice the interquartile range below the 25th percentile of calorie intake (300 kcal/d for women and 525 kcal/d for men) (n=599); and (3) self-reported history of heart disease, stroke, or cancer at baseline (n=3454). To address the proportional hazard assumption violation, we also excluded the first 2 years of follow-up (n=722). In total, 44 398 subjects were included in the analyses.

Exposure Assessment

The 116-item FFQ administered at baseline assessed the frequency of consumption and typical portion sizes of several

food items based on daily, weekly, monthly, or yearly intake. The reproducibility and validity of the questionnaire was assessed using 4 repeated administrations of the FFQ and twelve 24-hour dietary recalls for 1 year.[15] The correlation coefficients were 0.75 for total energy, 0.75 for carbohydrates, 0.76 for proteins, and 0.65 for fat, and ranged from 0.66 to 0.89 for the reproducibility of the FFQ.[15] To calculate energy and nutrient intake, we multiplied the daily intake (g/d) by the energy or nutrient content of each food item according to the Iranian food composition tables[16] or the US Department of Agriculture reports (release 23), if the food items were not available in the Iranian tables.[17] Spice consumption was assessed using 4 separate questions for turmeric, black or chili pepper, cinnamon, and saffron.

The demographic questionnaire captured data on smoking status, lifestyle, and past medical history. Participants who reported using opium or tobacco at least once a week for >6 months were defined as ever users of opium or tobacco.[18] Pack-years and nokhod-year were calculated using the durations and amount of smoking or opium. Nokhod is a local unit for opium consumption, equal to 200 mg. Wealth score was calculated using a composite score based on ownership of vehicles, furniture, and other factors associated with wealth.[19] The quintiles of this composite score were used to create 5 levels of wealth status. Physical activity at work was categorized into 3 groups: irregular nonintense, regular nonintense, and irregular or regular intense. Physical activity at leisure time was not included in the models because it is uncommon in this population.[20] Only 149 participants reported moderate or vigorous leisure time physical activities.[20] Weight (in kg) and height (in cm) were measured by trained staff at baseline and used to calculate body mass index (BMI) in kg/m^2.

Outcome Ascertainment

The Golestan Cohort Study team followed the participants by phone, and a review questionnaire was completed annually to ask about the participants' health status, any admission to a hospital, and any outpatient procedures. If a participant was not accessible by phone, after 7 failed calls in 2 weeks, family members, friends, or local health workers were contacted. Using these methods, the follow-up success rate was >99% in this cohort. When a death was reported through phone calls, local health workers, friends, or monthly provincial reports of death registration, a team including a general practitioner visited the home of the deceased person and obtained the death certificate and all medical documents, when available, or completed a verbal autopsy by interviewing the closest relative of the deceased person. The validity of verbal autopsy in this population has been evaluated previously.[21] About 65% of the deceased participants had extensive medical documents.[22] Two internists ascertained the cause of death independently using medical documents or verbal autopsy according to the *International Classification of Diseases, Tenth Revision* (*ICD-10*). If there were any discrepancies in coding decisions, a third internist decided on the final code.[18] If the cause of death could not be diagnosed, it was coded as "unknown." For cause-specific mortality, we included the most common causes of mortality in this population: death from cardiovascular disease, including ischemic heart disease (*ICD-10* codes I20–I25), stroke (*ICD-10* codes I60–I69), and other disease of circulatory system; and death from cancer (*ICD-10* codes C00–C97). Details of the study have been reported before.[18]

Statistical Analysis

To investigate whether spice consumption is associated with food groups in this population, the correlations between each spice and other food groups/items consumed were examined using the Spearman test (Table S1). Multivariate Cox proportional hazards regression models were applied to calculate the hazard ratios (HR) and 95% CI for mortality associated with turmeric, black or chili pepper, cinnamon, or saffron consumption separately. Age at baseline was used as the underlying time metric (using person-years as the time metric showed similar results). Follow-up time was estimated from the date of the completion of the FFQ until death, loss to follow-up, or July 30, 2018, whichever came first. We tested the proportional hazard assumption and it was violated: the curves crossed in the first 2 years of follow-up. To account for this deviation from the proportional hazards assumption, we excluded the first 2 years of follow-up, we retested the assumption, and observed no significant deviation. We used multivariable models and adjusted for the risk factors of mortality in this population[23] including age (years), sex (male, female), place of residence (rural, urban), ethnicity (Turkmen, non-Turkmen), formal education (yes, no), marital status (married, other), physical activity (irregular nonintense, regular nonintense, irregular or regular intense), wealth score (quintiles) (a derived variable combining many assessments of personal and household wealth[20]), history of hypertension (yes, no), history of diabetes mellitus (yes, no), BMI (<18.5, 18.5 to <25, 25 to <30, ≥30 kg/m^2), smoking (pack-years), opium user (nokhod-years), energy intake (kcal/d), and Dietary Approach to Stop Hypertension index (because spice consumption may reflect an overall healthy diet). A previous analysis showed that Dietary Approach to Stop Hypertension is associated with lower overall- and cause-specific mortality in this population.[24] Since just 30% of participants consumed cinnamon and 22% consumed saffron, we used ever consumers *versus* never consumers in the models for each of the 4 spices. For turmeric and pepper, we also categorized the

consumers into tertiles and used nonconsumers as a reference in an additional analysis, because consumption of these 2 spices was more common. The *P* for trend was determined using a variable where each person's consumption level was set to the median value of their category.

Potential interactions with each spice were assessed using the likelihood ratio test for sex, age, wealth score, education, place of residence, BMI, ethnicity, smoking status, opium use, energy intake, and Dietary Approach to Stop Hypertension score separately, by multiplying each type of spice by each potential effect modifier. In a series of stratified analyses, we stratified the continuous variables according to median to report the HRs in each category. In an additional analysis, instead of using the Dietary Approach to Stop Hypertension index, we included the food groups/items correlated with turmeric, pepper, cinnamon, and saffron consumption. In a sensitivity analysis, we excluded participants who reported a history of hypertension or diabetes mellitus at baseline.

All *P* values were 2-sided. We used STATA software for statistical analyses (version 14, STATA Corp, College Station, TX).

Results

During a median follow-up (interquartile range) of 11.1 (10.1–12.1) years, 5121 people died: 1851 because of cardiovascular diseases, 1061 deaths because of cancer, and 2209 deaths because of other causes. Turmeric, pepper, cinnamon, and saffron ever consumers composed about 65%, 70%, 30%, and 22% of the population (Table 1). The mean ($\pm$SD) intake of turmeric was 100 ± 13 mg/d; pepper was 56 ± 76 mg/d; cinnamon was 71 ± 196 mg/d; and saffron was 3 ± 22 mg/d.

Spice consumers were more likely to be women, live in urban areas, to be non-Turkmen, educated, married, intensely physically active during work, to have higher wealth score, to be younger, have a higher BMI, and to have a healthier dietary score. The spice consumers were less likely to report a history of hypertension, to smoke cigarettes, or use opium. Spice consumers were more likely to report a history of diabetes mellitus (Table 1).

In multivariable models, turmeric consumption was associated with significantly decreased risk of overall mortality (HR=0.90, 95% CI=0.85–0.96), and cardiovascular mortality (HR=0.91, 95% CI=0.82–0.99) (Table 2). Pepper consumption was associated with significantly decreased risk of overall mortality (HR=0.91, 95% CI=0.86–0.98), and saffron consumption was associated with significantly decreased risk of overall mortality (HR=0.85, 95% CI=0.77–0.94) and cardiovascular mortality (HR=0.79, 95% CI=0.68–0.92).

The results of HRs for mortality by tertiles of turmeric and pepper consumption are shown in Table 3. We observed dose–response relationships between turmeric consumption

and both overall (P_{trend}=0.02) and cardiovascular mortality (P_{trend}=0.02), and between pepper consumption and overall mortality (P_{trend}=0.02), but not for the other exposures we tested (Table 3).

A significant positive correlation was found among different types of spice (Table S1). The highest correlation was between turmeric and pepper (r=0.48), and the lowest correlation was between cinnamon and saffron (r=0.26). Mutual adjustment for pepper and turmeric consumption slightly attenuated the overall mortality results for these 2 spices (for turmeric: HR=0.92, 95% CI=0.85–0.99, and for pepper: HR=0.94, 95% CI=0.87–1.00). In multivariable models, in participants who reported both turmeric and pepper consumption, turmeric and pepper consumers had significantly decreased risk of overall mortality (HR=0.88, 95% CI=0.82–0.94) and cardiovascular mortality (HR=0.87, 95% CI=0.79–0.96), but not cancer mortality (HR=0.91, 95% CI=0.80–1.05) (data not shown in the tables). We observed significant weak correlations between spice consumption and legume, fish, or vegetable consumption, and saffron was positively correlated with nut, fruit, or rice consumption (Table S1). Adjustment for food groups/items correlated (r>0.2) with turmeric (legume and vegetable), pepper (legume, fish, and vegetable), and saffron consumption (legume, fish, vegetable, nut, fruit, and rice) did not materially alter results (Table S2). We reported the results for overall mortality stratified by subgroups of potential effect modifiers in Table S3, and inverse associations persisted across subgroups for turmeric, pepper, and saffron.

When excluding the participants with a history of hypertension (n=7737) or diabetes mellitus (n=2662) at baseline, the results remained unaltered (data not shown).

Discussion

This study demonstrated that consumption of turmeric, pepper, or saffron was associated with decreased mortality. We also observed inverse associations between turmeric or saffron consumption and risk of cardiovascular mortality. No significant moderating effects were found, and inverse associations persisted among subgroups of potential effect modifiers, such as different strata of wealth score. Our study is the first prospective study that evaluated the association of consuming different types of spices with mortality.

Previous studies have described biological mechanisms that support the inverse association between turmeric and its components and mortality. A previous study showed that curcumin ingestion increased blood flow–mediated vascular dilation, indicating that curcumin may improve the decline in endothelial function because of age.[25] Curcumin also increases serum zinc levels,[26] and zinc deficiency is potentially associated with increased risk of cardiovascular

Table 1. Baseline Characteristics of Participants by Spice Consumption in the Golestan Cohort Study

	Nonconsumers	Spice Consumers			
	N=7312	Turmeric (N=28 741)	Pepper (N=31 071)	Cinnamon (N=13 427)	Saffron (N=9936)
Ever consumers (%)		28 741 (64.7)	31 071 (70.0)	13 427 (30.3)	9936 (22.4)
Age, y, mean±SD	52.5±9.0	51.3±8.6	51.3±8.6	51.5±8.6	50.9±8.4
Sex, female (%)	4076 (55.7)	16 923 (58.9)	18 122 (58.3)	7984 (59.5)	5823 (58.6)
Place of residence, rural (%)	6906 (94.5)	21 304 (74.1)	23 649 (76.1)	9652 (71.9)	4725 (47.6)
Ethnicity, Turkmen (%)	6961 (95.2)	18 400 (64.0)	22 116 (71.2)	8057 (60.0)	4229 (42.6)
Education, no formal (%)	6001 (82.1)	18 728 (65.2)	20 607 (66.3)	8589 (64.0)	4747 (47.8)
Marital status, married (%)	6325 (86.7)	25 504 (88.9)	27 731 (89.4)	11 911 (88.9)	8895 (89.7)
Physical activity at work, intense (%)	768 (10.5)	3738 (13.1)	3843 (12.4)	1708 (12.8)	1137 (11.5)
Wealth score, the highest quintile (%)	564 (7.7)	1843 (11.8)	1541 (11.6)	5174 (16.7)	4380 (12.7)
History of hypertension (%)	1409 (19.3)	4879 (17.0)	5194 (16.7)	2368 (17.6)	1637 (16.5)
History of diabetes mellitus (%)	390 (5.3)	1834 (6.4)	1864 (6.0)	930 (6.9)	756 (7.6)
Body mass index, kg/m^2, mean±SD	25.8±5.3	26.8±5.4	26.9±5.4	26.9±5.4	27.8±5.3
Smoking, pack-y, mean±SD	2.9±9.7	2.7±9.3	2.7±9.3	2.5±8.8	2.6±8.8
Opium use, nokhod-year*, mean±SD	12.1±58.6	8.1±45.6	8.6±47.8	6.9±33.9	5.0±32.3
Energy, kcal, mean±SD	2051±577	2173.9±556.4	2149.1±554.1	2202.8±555.0	2223.8±546.7
DASH score, mean±SD	20.9±3.2	22.4±3.5	22.2±3.5	22.6±3.5	23.7±3.5

DASH indicates Dietary Approach to Stop Hypertension.
*A local unit for opium consumption that weighs about 200 mg.

disease[27] and risk of esophageal cancer,[28–30] which is one of the most common cancers in this population.[31,32] In addition to curcumin, turmeric has several components including desmethoxycurcumin, bisdemethoxycurcumin, alpha-turmerone, beta-turmerone, and Ar-turmerone, which have several biological activities and may have synergistic effects.[33] Curcuminoids significantly improve oxidative status and lipid profiles in metabolic syndrome.[6,34]

Our findings on black or chili pepper are consistent with previous studies on chili pepper and overall mortality.[1,14] Lv et al assessed consuming spicy foods and chili pepper in a Chinese population, and showed that the risks of overall and cause-specific mortalities (ischemic heart diseases, cancer, and respiratory diseases) were lower in those who often ate spicy food than in those who ate spicy food less than once a week.[1] Chopan et al demonstrated that the risk of overall, but not cause-specific, mortality was lower in participants who ate hot red chili pepper versus nonconsumers in the US National Health and Nutritional Examination Survey III (NHANES III).[14] Our results support the inverse association of black or chili pepper intake with overall mortality. Capsaicin (a biologically active red pepper component) has been reported to inhibit platelet aggregation.[35] Regular consumption of chili also prevents the oxidation of serum lipoproteins in humans.[36] There are inconsistent reports regarding the rate of carcinogenesis with use of capsaicin.[35] Also, piperine (a biologically active black pepper

component) increases the bioavailability of curcumin.[37] This effect of piperine is greater in human than in rats.[38] Our results showed that in the participants who reported both turmeric and pepper consumption, HRs were lower than in those participants who reported either turmeric or black pepper consumption alone, both for overall and cardiovascular mortality.

We found no association between cinnamon consumption and overall or cause-specific mortality. Although this is the first study to evaluate the association between cinnamon and mortality, previous studies have shown beneficial effects of cinnamon on fasting glucose and blood pressure in humans.[39,40] The current result could be because of the relatively modest consumption of cinnamon in this population, with 30% of the cohort consuming cinnamon. It may also be because of the small amount of cinnamon consumed. A review article has concluded that cinnamon consumption may need to exceed 3 g/d to improve insulin resistance.[5]

Saffron, at pharmaceutical doses, may affect cardiovascular disease through several mechanisms.[41] Saffron extract (10, 20, 40 mg/kg per day for 5 weeks) decreases systolic blood pressure in rats.[42] Heat shock proteins are expressed in atherosclerotic plaques, and antibody titers to some heat shock proteins indicate the severity of cardiovascular disease.[43] Saffron decreases anti–heat shock protein-27 and anti–heat shock protein-70 levels significantly in patients with metabolic syndrome.[43]

Table 2. HRs and 95% CI for Overall- and Cause-Specific Mortality by Ever Versus Never Spice Consumption

	Total Mortality (n=5121)	Cardiovascular Mortality (n=1851)	Cancer Mortality (n=1061)
Turmeric			
Death, n	2982	1086	613
Crude HR (95% CI)	0.76 (0.71–0.80)	0.77 (0.70–0.84)	0.74 (0.66–0.84)
Fully adjusted HR* (95% CI)	0.90 (0.85–0.96)	0.91 (0.82–0.99)	0.90 (0.79–1.04)
Pepper			
Death, n	3257	1201	672
Crude HR (95% CI)	0.74 (0.70–0.78)	0.78 (0.71–0.86)	0.73 (0.65–0.83)
Fully adjusted HR* (95% CI)	0.91 (0.86–0.98)	0.95 (0.86–1.05)	0.89 (0.78–1.02)
Cinnamon			
Death, n	1434	525	300
Crude HR (95% CI)	0.90 (0.84–0.95)	0.91 (0.82–1.01)	0.91 (0.79–1.04)
Fully adjusted HR* (95% CI)	0.97 (0.91–1.05)	0.98 (0.88–1.09)	1.05 (0.90–1.21)
Saffron			
Death, n	833	312	182
Crude HR (95% CI)	0.64 (0.60–0.69)	0.69 (0.61–0.77)	0.70 (0.60–0.82)
Fully adjusted HR* (95% CI)	0.85 (0.77–0.94)	0.79 (0.68–0.92)	0.99 (0.81–1.22)

HR indicates hazard ratio.

*Adjusted for age (years), sex (M, F), place of residence (rural, urban), ethnicity (Turkmen, non-Turkmen), formal education (yes, no), marital status (married, other), physical activity (irregular nonintense, regular nonintense, irregular, or regular intense), wealth score (quintiles), history of hypertension (yes, no), history of diabetes mellitus (yes, no), body mass index (<18.5, 18.5 to <25, 25 to <30, ≥30 kg/m^2), smoking (pack-years), opium use (nokhod-years), energy intake (kcal/d), and Dietary Approach to Stop Hypertension (DASH) index.

We found nonsignificant inverse associations between turmeric, pepper, and saffron and cancer mortality in this study. These nonsignificant associations could be because of lack of efficacy, low numbers of cancer deaths in this study period, or the low doses of these spices consumed for culinary purposes. The antioxidant property of turmeric is because of curcumin.[4] The doses of curcumin in the clinical trials evaluating different cancers were 100 to 15 000 mg curcumin per day.[44] Pure turmeric powder has about 3.14% curcumin concentration,[45] so the mean intake of curcumin in the Golestan population was equal to 3.14 mg/d, which is much less than the minimum dose that showed beneficial effects in the clinical trials.[44] The anticancer effect of saffron has also been achieved only with high doses of saffron.[46] The administration of 100 mg per body weight (kg) of saffron extracts decreased tumor incidence of induced sarcomas in mice.[46]

The inverse associations observed in our study between spice consumption and mortality may reflect a true beneficial effect of the spices, but several things suggest that our results should be interpreted cautiously until they are confirmed by other studies. We observed that spice consumption was highly confounded by behaviors and conditions related to mortality, and as in all observational studies, although we adjusted for many potential confounders, we cannot rule out the possibility of residual confounding. We note with interest, however, that our analyses stratified by smoking, BMI, education, etc showed comparable point estimates across strata. The observed associations could also reflect the protective effect of other dietary components usually consumed with spice, such as fish. In a previous study exploring the confounding effect of tea, it was suggested that chili consumers may consume greater amounts of tea.[47] In the current study there was no correlation between drinking tea and any types of spice. However, there were significant correlations between spice consumption and legume, nut, fish, fruit, and vegetable consumption. All of these food groups/items have previously been reported to be inversely associated with mortality or cancer in this population.[48–52] Additional adjustment for these food groups did not alter our results significantly, but such a possibility should still be kept in mind. Altering (decreasing) spice consumption during early stages of disease is another potential explanation for the observed associations, although we excluded participants who reported a history of chronic disease and the first 2 years of follow-up.

We observed that inverse associations persisted across most subgroups for turmeric, pepper, and saffron. However, the associations of pepper consumption and mortality were stronger in women. Women know more about their intake because they cook, and accurate reporting may move the HRs farther away from 1. The stronger association for women may be because of less misclassification of spice use compared with men.

Table 3. HRs and 95% CI for Overall- and Cause-Specific Mortality by Tertiles of Turmeric and Pepper Consumption

	Nonconsumer	Tertile 1	Tertile 2	Tertile 3	P_{trend}
Turmeric					
Total mortality					
Death, n	2139	1089	899	994	
Fully adjusted HR* (95% CI)	1	0.90 (0.83–0.98)	0.91 (0.83–0.99)	0.88 (0.80–0.96)	0.02
Cardiovascular					
Death, n	765	411	316	359	
Fully adjusted HR* (95% CI)	1	0.98 (0.87–1.11)	0.85 (0.73–0.99)	0.83 (0.71–0.97)	0.02
Cancer					
Death, n	448	210	207	196	
Fully adjusted HR* (95% CI)	1	0.83 (0.71–0.98)	0.97 (0.81–1.17)	0.95 (0.78–1.16)	0.9
Pepper					
Total mortality					
Death, n	1864	1142	1050	1065	
Fully adjusted HR* (95% CI)	1	0.93 (0.87–1.01)	0.91 (0.83–0.98)	0.90 (0.82–0.99)	0.02
Cardiovascular					
Death, n	650	426	365	410	
Fully adjusted HR* (95% CI)	1	1.03 (0.91–1.16)	0.87 (0.76–0.99)	0.94 (0.81–1.08)	0.3
Cancer					
Death, n	389	227	235	210	
Fully adjusted HR* (95% CI)	1	0.84 (0.71–1.00)	0.96 (0.81–1.14)	0.88 (0.73–1.06)	0.4

HR indicates hazard ratio.

*Adjusted for age (years), sex (M, F), place of residence (rural, urban), ethnicity (Turkmen, non-Turkmen), formal education (yes, no), marital status (married, other), physical activity (irregular nonintense, regular nonintense, irregular, or regular intense), wealth score (quintiles), history of hypertension (yes, no), history of diabetes mellitus (yes, no), body mass index (<18.5, 18.5 to <25, 25 to <30, ≥ 30 kg/m^2), smoking (pack-years), opium use (nokhod-years), energy intake (kcal/d), and Dietary Approach to Stop Hypertension (DASH) index.

One limitation of this study was the use of a self-report questionnaire to estimate spice consumption, which may result in misclassification. In addition, participants may have changed their spice consumption over the course of follow-up and we could only use data collected at baseline. We also did not have information about consumption of foods not prepared at home. However, the study population is mainly rural, and eating outside the home is uncommon. The participants who do not prepare food may not be as reliable as food preparers in estimating the amount of spice consumed. We excluded the participants with a self-reported history of chronic disease at baseline, which limits the generalizability of the results. We did not have a National Death Index to link the data. However, in addition to the provincial registration of death, a Golestan Cohort Study team visited the home of a deceased person to collect the medical documents for verifying the cause of death.

Our study also had several strengths: the large size of the cohort, its prospective design and long follow-up, low ($<1\%$) loss to follow-up rate, the administration of several questions on spice consumption, and the quantity of each spice consumed. We also had extensive data on possible confounders, which we incorporated into our analysis.

In conclusion, consuming turmeric and saffron was associated with decreased risk of overall- and cardiovascular-mortality in this population. However, spices consumed for culinary purposes were not associated with risk of cancer mortality. Further research is needed to evaluate the association between spice consumption and mortality in other populations, to replicate our findings.

Research Program of the US National Cancer Institute at the National Institutes of Health; and the International Agency for Research on Cancer.

Disclosures

None.

References

1. Lv J, Qi L, Yu C, Yang L, Guo Y, Chen Y, Bian Z, Sun D, Du J, Ge P, Tang Z, Hou W, Li Y, Chen J, Chen Z, Li L; China Kadoorie Biobank Collaborative Group. Consumption of spicy foods and total and cause specific mortality: population based cohort study. *BMJ*. 2015;351:h3942.

2. Mathew A, Gangadharan P, Varghese C, Nair MK. Diet and stomach cancer: a case-control study in South India. *Eur J Cancer Prev*. 2000;9:89–97.

3. Lopez-Carrillo L, Lopez-Cervantes M, Robles-Diaz G, Ramirez-Espitia A, Mohar-Betancourt A, Meneses-Garcia A, Lopez-Vidal Y, Blair A. Capsaicin consumption, *Helicobacter pylori* positivity and gastric cancer in Mexico. *Int J Cancer*. 2003;106:277–282.

4. Srinivasan K. Antioxidant potential of spices and their active constituents. *Crit Rev Food Sci Nutr*. 2014;54:352–372.

5. Gruenwald J, Freder J, Armbruester N. Cinnamon and health. *Crit Rev Food Sci Nutr*. 2010;50:822–834.

6. Panahi Y, Khalili N, Hosseini MS, Abbasinazari M, Sahebkar A. Lipid-modifying effects of adjunctive therapy with curcuminoids-piperine combination in patients with metabolic syndrome: results of a randomized controlled trial. *Complement Ther Med*. 2014;22:851–857.

7. Panahi Y, Kianpour P, Mohtashami R, Jafari R, Simental-Mendia LE, Sahebkar A. Curcumin lowers serum lipids and uric acid in subjects with nonalcoholic fatty liver disease: a randomized controlled trial. *J Cardiovasc Pharmacol*. 2016;68:223–229.

8. Mang B, Wolters M, Schmitt B, Kelb K, Lichtinghagen R, Stichtenoth DO, Hahn A. Effects of a cinnamon extract on plasma glucose, HbA, and serum lipids in diabetes mellitus type 2. *Eur J Clin Invest*. 2006;36:340–344.

9. Zhao Y, Chen ZY. Roles of spicy foods and their bioactive compounds in management of hypercholesterolemia. *J Agric Food Chem*. 2018;66:8662–8671.

10. Yang YS, Su YF, Yang HW, Lee YH, Chou JI, Ueng KC. Lipid-lowering effects of curcumin in patients with metabolic syndrome: a randomized, double-blind, placebo-controlled trial. *Phytother Res*. 2014;28:1770–1777.

11. Ziegenfuss TN, Hofheins JE, Mendel RW, Landis J, Anderson RA. Effects of a water-soluble cinnamon extract on body composition and features of the metabolic syndrome in pre-diabetic men and women. *J Int Soc Sports Nutr*. 2006;3:45–53.

12. Askari F, Rashidkhani B, Hekmatdoost A. Cinnamon may have therapeutic benefits on lipid profile, liver enzymes, insulin resistance, and high-sensitivity C-reactive protein in nonalcoholic fatty liver disease patients. *Nutr Res*. 2014;34:143–148.

13. Amiot MJ, Riva C, Vinet A. Effects of dietary polyphenols on metabolic syndrome features in humans: a systematic review. *Obes Rev*. 2016;17:573–586.

14. Chopan M, Littenberg B. The association of hot red chili pepper consumption and mortality: a large population-based cohort study. *PLoS One*. 2017;12:e0169876.

15. Malekshah AF, Kimiagar M, Saadatian-Elahi M, Pourshams A, Nouraie M, Goglani G, Hoshiarrad A, Sadatsafavi M, Golestan B, Yoonesi A, Rakhshani N, Fahimi S, Nasrollahzadeh D, Salahi R, Ghafarpour A, Semnani S, Steghens JP, Abnet CC, Kamangar F, Dawsey SM, Brennan P, Boffetta P, Malekzadeh R. Validity and reliability of a new food frequency questionnaire compared to 24 h recalls and biochemical measurements: pilot phase of Golestan Cohort Study of esophageal cancer. *Eur J Clin Nutr*. 2006;60:971–977.

16. Azar M, Sarkisian E. *Food Composition Table of Iran*. Iran: National Nutrition and Food Technology Research Institute of Iran; 1981.

17. U.S. Department of Agriculture, A.R.S. *USDA National Nutrient Database for Standard Reference. Release 23, Nutrient Data Laboratory*. 2010. Available at: http://www.ars.usda.gov/ba/bhnrc/ndl. Accessed August 12, 2019.

18. Pourshams A, Khademi H, Malekshah AF, Islami F, Nouraei M, Sadjadi AR, Jafari E, Rakhshani N, Salahi R, Semnani S, Kamangar F, Abnet CC, Ponder B, Day N, Dawsey SM, Boffetta P, Malekzadeh R. Cohort profile: the Golestan Cohort Study—a prospective study of oesophageal cancer in northern Iran. *Int J Epidemiol*. 2010;39:52–59.

19. Islami F, Kamangar F, Nasrollahzadeh D, Aghcheli K, Sotoudeh M, Abedi-Ardekani B, Merat S, Nasseri-Moghaddam S, Semnani S, Sepehr A, Wakefield J, Moller H, Abnet CC, Dawsey SM, Boffetta P, Malekzadeh R. Socio-economic status and oesophageal cancer: results from a population-based case-control study in a high-risk area. *Int J Epidemiol*. 2009;38:978–988.

20. Etemadi A, Abnet CC, Kamangar F, Islami F, Khademi H, Pourshams A, Poustchi H, Bagheri M, Sohrabpour AA, Aliasgar A, Khoshnia M, Wacholder S, Matthews CC, Pharoah PD, Brennan P, Boffetta P, Malekzadeh R, Dawsey SM. Impact of body size and physical activity during adolescence and adult life on overall and cause-specific mortality in a large cohort study from Iran. *Eur J Epidemiol*. 2014;29:95–109.

21. Khademi H, Etemadi A, Kamangar F, Nouraie M, Shakeri R, Abaie B, Pourshams A, Bagheri M, Hooshyar A, Islami F, Abnet CC, Pharoah P, Brennan P, Boffetta P, Dawsey SM, Malekzadeh R. Verbal autopsy: reliability and validity estimates for causes of death in the Golestan Cohort Study in Iran. *PLoS One*. 2010;5:e11183.

22. Khademi H, Malekzadeh R, Pourshams A, Jafari E, Salahi R, Semnani S, Abaie B, Islami F, Nasseri-Moghaddam S, Etemadi A, Byrnes G, Abnet CC, Dawsey SM, Day NE, Pharoah PD, Boffetta P, Brennan P, Kamangar F. Opium use and mortality in Golestan Cohort Study: prospective cohort study of 50,000 adults in Iran. *BMJ*. 2012;344:e2502.

23. Nalini M, Oranuba E, Poustchi H, Sepanlou SG, Pourshams A, Khoshnia M, Gharavi A, Dawsey SM, Abnet CC, Boffetta P, Brennan P, Sotoudeh M, Nikmanesh A, Merat S, Etemadi A, Shakeri R, Sohrabpour AA, Nasseri-Moghaddam S, Kamangar F, Malekzadeh R. Causes of premature death and their associated risk factors in the Golestan Cohort Study, Iran. *BMJ Open*. 2018;8:e021479.

24. Hashemian M, Farvid MS, Poustchi H, Murphy G, Etemadi A, Hekmatdoost A, Kamangar F, Sheikh M, Pourshams A, Sepanlou SG, Fazeltabar Malekshah A, Khoshnia M, Gharavi A, Brennan PJ, Boffetta P, Dawsey SM, Reedy J, Subar AF, Abnet CC, Malekzadeh R. The application of six dietary scores to a Middle Eastern population: a comparative analysis of mortality in a prospective study. *Eur J Epidemiol*. 2019;34:371–382.

25. Akazawa N, Choi Y, Miyaki A, Tanabe Y, Sugawara J, Ajisaka R, Maeda S. Curcumin ingestion and exercise training improve vascular endothelial function in postmenopausal women. *Nutr Res*. 2012;32:795–799.

26. Safarian H, Parizadeh SMR, Saberi-Karimain M, Darroudi S, Javandoost A, Mohammadi F, Moammeri M, Ferns GA, Ghayour-Mobarhan M, Mohebati M. The effect of curcumin on serum copper and zinc and Zn/Cu ratio in individuals with metabolic syndrome: a double-blind clinical trial. *J Diet Suppl*. 2018. Available at: https://www.tandfonline.com/doi/abs/10.1080/19390211.2018.1472711?journalCode=ijds20. Accessed August 28, 2019.

27. Hashemian M, Poustchi H, Mohammadi-Nasrabadi F, Hekmatdoost A. Systematic review of zinc biochemical indicators and risk of coronary heart disease. *ARYA Atheroscler*. 2015;11:357–365.

28. Hashemian M, Poustchi H, Abnet CC, Boffetta P, Dawsey SM, Brennan PJ, Pharoah P, Etemadi A, Kamangar F, Sharafkhah M, Hekmatdoost A, Malekzadeh R. Dietary intake of minerals and risk of esophageal squamous cell carcinoma: results from the Golestan Cohort Study. *Am J Clin Nutr*. 2015;102:102–108.

29. Hashemian M, Murphy G, Etemadi A, Poustchi H, Brockman JD, Kamangar F, Pourshams A, Khoshnia M, Gharavi A, Dawsey SM, Brennan PJ, Boffetta P, Hekmatdoost A, Malekzadeh R, Abnet CC. Toenail mineral concentration and risk of esophageal squamous cell carcinoma, results from the Golestan Cohort Study. *Cancer Med*. 2017;6:3052–3059.

30. Hashemian M, Hekmatdoost A, Poustchi H, Mohammadi Nasrabadi F, Abnet CC, Malekzadeh R. Systematic review of zinc biomarkers and esophageal cancer risk. *Middle East J Dig Dis*. 2014;6:177–185.

31. Roshandel G, Sadjadi A, Aarabi M, Keshtkar A, Sedaghat SM, Nouraie SM, Semnani S, Malekzadeh R. Cancer incidence in Golestan Province: report of an ongoing population-based cancer registry in Iran between 2004 and 2008. *Arch Iran Med*. 2012;15:196–200.

32. Murphy G, McCormack V, Abedi-Ardekani B, Arnold M, Camargo MC, Dar NA, Dawsey SM, Etemadi A, Fitzgerald RC, Fleischer DE, Freedman ND, Goldstein AM, Gopal S, Hashemian M, Hu N, Hyland PL, Kaimila B, Kamangar F, Malekzadeh R, Mathew CG, Menya D, Mulima G, Mwachiro MM, Mwasamwaja A, Pritchett N, Qiao YL, Ribeiro-Pinto LF, Ricciardone M, Schuz J, Sitas F, Taylor PR, Van Loon K, Wang SM, Wei WQ, Wild CP, Wu C, Abnet CC, Chanock SJ, Brennan P. International cancer seminars: a focus on esophageal squamous cell carcinoma. *Ann Oncol*. 2017;28:2086–2093.

33. Amalraj A, Pius A, Gopi S, Gopi S. Biological activities of curcuminoids, other biomolecules from turmeric and their derivatives—a review. *J Tradit Complement Med*. 2017;7:205–233.

34. Panahi Y, Hosseini MS, Khalili N, Naimi E, Majeed M, Sahebkar A. Antioxidant and anti-inflammatory effects of curcuminoid-piperine combination in subjects with metabolic syndrome: a randomized controlled trial and an updated meta-analysis. *Clin Nutr*. 2015;34:1101–1108.

35. Sharma SK, Vij AS, Sharma M. Mechanisms and clinical uses of capsaicin. *Eur J Pharmacol*. 2013;720:55–62.

36. Luo XJ, Peng J, Li YJ. Recent advances in the study on capsaicinoids and capsinoids. *Eur J Pharmacol*. 2011;650:1–7.

37. Prasad S, Tyagi AK, Aggarwal BB. Recent developments in delivery, bioavailability, absorption and metabolism of curcumin: the golden pigment from golden spice. *Cancer Res Treat*. 2014;46:2–18.

38. Shoba G, Joy D, Joseph T, Majeed M, Rajendran R, Srinivas PS. Influence of piperine on the pharmacokinetics of curcumin in animals and human volunteers. *Planta Med*. 1998;64:353–356.

39. Akilen R, Pimlott Z, Tsiami A, Robinson N. Effect of short-term administration of cinnamon on blood pressure in patients with prediabetes and type 2 diabetes. *Nutrition*. 2013;29:1192–1196.

40. Magistrelli A, Chezem JC. Effect of ground cinnamon on postprandial blood glucose concentration in normal-weight and obese adults. *J Acad Nutr Diet*. 2012;112:1806–1809.

41. Rameshrad M, Razavi BM, Hosseinzadeh H. Saffron and its derivatives, crocin, crocetin and safranal: a patent review. *Expert Opin Ther Pat*. 2018;28:147–165.

42. Imenshahidi M, Razavi BM, Faal A, Gholampoor A, Mousavi SM, Hosseinzadeh H. The effect of chronic administration of saffron (*Crocus sativus*) stigma aqueous extract on systolic blood pressure in rats. *Jundishapur J Nat Pharm Prod*. 2013;8:175–179.

43. Shemshian M, Mousavi SH, Norouzy A, Kermani T, Moghiman T, Sadeghi A, Ghayour-Mobarhan M, Ferns GA. Saffron in metabolic syndrome: its effects on antibody titers to heat-shock proteins 27, 60, 65 and 70. *J Complement Integr Med*. 2014;11:43–49.

44. Kunnumakkara AB, Bordoloi D, Harsha C, Banik K, Gupta SC, Aggarwal BB. Curcumin mediates anticancer effects by modulating multiple cell signaling pathways. *Clin Sci (Lond)*. 2017;131:1781–1799.

45. Tayyem RF, Heath DD, Al-Delaimy WK, Rock CL. Curcumin content of turmeric and curry powders. *Nutr Cancer*. 2006;55:126–131.

46. Salomi MJ, Nair SC, Panikkar KR. Inhibitory effects of *Nigella sativa* and saffron (*Crocus sativus*) on chemical carcinogenesis in mice. *Nutr Cancer*. 1991;16:67–72.

47. Forouhi NG. Consumption of hot spicy foods and mortality—is chilli good for your health? *BMJ*. 2015;351:h4141.

48. Farvid MS, Malekshah AF, Pourshams A, Poustchi H, Sepanlou SG, Sharafkhah M, Khoshnia M, Farvid M, Abnet CC, Kamangar F, Dawsey SM, Brennan P, Pharoah PD, Boffetta P, Willett WC, Malekzadeh R. Dietary protein sources and all-cause and cause-specific mortality: the Golestan Cohort Study in Iran. *Am J Prev Med*. 2017;52:237–248.

49. Farvid MS, Malekshah AF, Pourshams A, Poustchi H, Sepanlou SG, Sharafkhah M, Khoshnia M, Farvid M, Abnet CC, Kamangar F, Dawsey SM, Brennan P, Pharoah PD, Boffetta P, Willett WC, Malekzadeh R. Dairy food intake and all-cause, cardiovascular disease, and cancer mortality: the Golestan Cohort Study. *Am J Epidemiol*. 2017;185:697–711.

50. Hashemian M, Murphy G, Etemadi A, Poustchi H, Sharafkhah M, Kamangar F, Pourshams A, Malekshah AF, Khoshnia M, Gharavi A, Hekmatdoost A, Brennan PJ, Boffetta P, Dawsey SM, Abnet CC, Malekzadeh R. Nut consumption and the risk of oesophageal squamous cell carcinoma in the Golestan Cohort Study. *Br J Cancer*. 2018;119:176–181.

51. Eslamparast T, Sharafkhah M, Poustchi H, Hashemian M, Dawsey SM, Freedman ND, Boffetta P, Abnet CC, Etemadi A, Pourshams A, Malekshah AF, Islami F, Kamangar F, Merat S, Brennan P, Hekmatdoost A, Malekzadeh R. Nut consumption and total and cause-specific mortality: results from the Golestan Cohort Study. *Int J Epidemiol*. 2017;46:75–85.

52. Sheikh M, Poustchi H, Pourshams A, Etemadi A, Islami F, Khoshnia M, Gharavi A, Hashemian M, Roshandel G, Khademi H, Zahedi M, Abedi-Ardekani B, Boffetta P, Kamangar F, Dawsey SM, Pharaoh PD, Abnet CC, Day NE, Brennan P, Malekzadeh R. Individual and combined effects of environmental risk factors for esophageal cancer based on results from the Golestan Cohort Study. *Gastroenterology*. 2019;156:1416–1427.

SUPPLEMENTAL MATERIAL

Table S1. Spearman's correlation coefficients for spice consumption*.

	Turmeric	Pepper	Cinnamon	Saffron
Turmeric	1			
Pepper	0.48	1		
Cinnamon	0.26	0.27	1	
Saffron	0.27	0.37	0.26	1
Tea	0.01	0.04	0.02	-0.03
Egg	0.09	0.11	0.08	0.13
Legumes	0.33	0.23	0.14	0.24
Nuts	0.07	0.13	0.11	0.21
Poultry	0.15	0.09	0.05	0.09
Fish	0.18	0.22	0.17	0.21
Red meat	-0.03	0.04	0.05	0.09
Dairy	0.04	0.11	0.10	0.16
Vegetables	0.27	0.26	0.16	0.33
Fruits	0.05	0.11	0.10	0.22
Grains	-0.01	0.01	-0.001	-0.01
Rice	-0.07	0.03	0.004	0.22

*Correlation coefficients between different types of spice were significant, with $p < 0.001$.

Table S2. Hazard ratios and confidence intervals [HR (95% CI)]* for overall and cause-specific mortality by ever vs. never spice consumption adjusted for food items that are correlated with spice consumption.

	Total mortality (n=5,121)	Cardiovascular mortality (n=1,851)	Cancer mortality (n=1,061)
Turmeric			
Adjusted HR † (95% CI)	**0.90 (0.85-0.96)**	0.91 (0.82-1.00)	0.93 (0.81-1.06)
Pepper			
Adjusted HR‡ (95% CI)	**0.92 (0.87-0.98)**	0.96 (0.87-1.06)	0.91 (0.80-1.04)
Saffron			
Adjusted HR¶ (95% CI)	**0.83 (0.76-0.91)**	**0.80 (0.69-0.93)**	1.07 (0.88-1.30)

* Adjusted for age (years), sex (M, F), place of residence (rural, urban), ethnicity (Turkmen, non-Turkmen), formal education (yes, no), marital status (married, other), physical activity (irregular non-intense, regular non-intense, irregular or regular intense), wealth score (quintiles), history of hypertension (yes, no), history of diabetes (yes, no), body mass index (<18.5, 18.5 to <25, 25 to <30, ≥30 kg/m^2), smoking (pack-years), opium use (nokhod-years), and energy intake (kcal/d)

† Additionally, adjusted for legume and vegetable consumption

‡ Additionally, adjusted for legume, fish, and vegetable consumption

¶ Additionally, adjusted for legume, fish, and vegetable, nuts, fruits, and rice consumption

Note: Cinnamon consumption was not correlated with consumption of any food groups

Table S3. Adjusted hazard ratios* (confidence intervals) for overall mortality stratified by sub-groups of potential risk factors.

	Turmeric	P interaction	Pepper	P interaction	Cinnamon	P interaction	Saffron	P interaction
Age		0.97		0.77		0.89		0.76
<50 years	0.83 (0.71-0.97)		0.88 (0.75-1.02)		1.00 (0.85-1.18)		0.79 (0.64-0.99)	
≥50 years	0.92 (0.85-0.99)		0.92 (0.86-0.99)		0.96 (0.89-1.04)		0.86 (0.77-0.96)	
Sex		0.98		0.02		0.85		0.97
Female	0.88 (0.79-0.98)		0.84 (0.76-0.93)		0.95 (0.86-1.06)		0.85 (0.73-0.98)	
Male	0.92 (0.84-1.01)		0.99 (0.90-1.08)		1.00 0.91-1.11)		0.86 (0.75-0.98)	
Place of residence		0.69		0.05		0.11		0.97
Rural	0.90 (0.83-0.97)		0.94 (0.87-1.01)		0.92 (0.85-1.00)		0.84 (0.74-0.96)	
Urban	0.88 (0.74-1.05)		0.77 (0.65-0.91)		1.17 (1.00-1.35)		0.86 (0.73-1.01)	
Ethnicity		0.08		0.99		1		0.51
Turkmen	0.92 (0.86-0.99)		0.91 (0.84-0.98)		0.97 (0.89-1.06)		0.89 (0.78-1.02)	
Non- Turkmen	0.74 (0.61-0.89)		0.91 (0.79-1.06)		0.97 (0.85-1.11)		0.80 (0.68-0.93)	
Education		0.99		0.94		0.06		0.19
No formal	0.88 (0.82-0.95)		0.89 (0.83-0.96)		0.91 (0.84-0.99)		0.87 (0.77-0.98)	
Formal	0.96 (0.82-1.14)		0.98 (0.83-1.16)		1.24 (1.06-1.44)		0.80 (0.66-0.97)	
Wealth score		0.09		0.24		0.52		0.81
Below median	0.94 (0.86-1.03)		0.94 (0.86-1.02)		0.95 (0.87-1.05)		0.78 (0.67-0.92)	
Above median	0.84 (0.75-0.94)		0.87 (0.78-0.98)		1.02 (0.91-1.14)		0.96 (0.84-1.10)	
Body Mass Index		0.47		0.29		0.38		0.08
<26	0.87 (0.80-0.96)		0.92 (0.85-1.01)		0.99 (0.90-1.09)		0.83 (0.72-0.95)	
≥26	0.93 (0.83-1.03)		0.89 (0.80-0.99)		0.95 (0.85-1.06)		0.87 (0.75-1.01)	
Smoking		0.98		0.76		0.31		0.60
Never	0.88 (0.81-0.95)		0.90 (0.83-0.97)		0.93 (0.86-1.02)		0.79 (0.70-0.89)	
Ever	0.93 (0.81-1.06)		0.97 (0.85-1.11)		1.10 (0.95-1.27)		0.99 (0.82-1.19)	
Opium		0.86		0.07		0.58		0.93
Never	0.89 (0.82-0.97)		0.87 (0.80-0.94)		0.95 (0.88-1.04)		0.84 (0.75-0.94)	

Ever	0.91 (0.81-1.04)		1.03 (0.91-1.16)		1.03 (0.90-1.17)		0.87 (0.72-1.06)	
Energy intake (kcal)		0.98		0.63		0.81		0.03
<2031	0.90 (0.82-0.99)		0.96 (0.88-1.06)		0.97 (0.87-1.07)		0.73 (0.63-0.85)	
≥2031	0.90 (0.82-0.99)		0.87 (079-0.96)		0.99 (0.90-1.10)		0.97 (0.85-1.12)	
DASH score		0.26		0.45		0.06		0.91
Below median	0.92 (0.84-1.01)		0.94 (0.86-1.02)		0.90 (0.81-0.99)		0.82 (0.71-0.95)	
Above median	0.86 (0.77-0.96)		0.87 (079-0.97)		1.08 (0.97-1.20)		0.87 (0.76-1.00)	

* Adjusted for age (years), sex (M, F), place of residence (rural, urban), ethnicity (Turkmen, non-Turkmen), formal education (yes, no), marital status (married, other), physical activity (irregular non-intense, regular non-intense, irregular or regular intense), wealth score (quintiles), history of hypertension (yes, no), history of diabetes (yes, no), body mass index (<18.5, 18.5 to <25, 25 to <30, ≥30 kg/m^2), smoking (pack-years), opium use (nokhod-years), energy intake (kcal/d), and Dietary Approach to Stop Hypertension (DASH) index.