The Association of Hot Red Chili Pepper Consumption and Mortality: A Large Population-Based Cohort Study

Mustafa Chopan*, Benjamin Littenberg

University of Vermont College of Medicine, Burlington, Vermont, United States of America

* mustafa.chopan@med.uvm.edu

Abstract

The evidence base for the health effects of spice consumption is insufficient, with only one large population-based study and no reports from Europe or North America. Our objective was to analyze the association between consumption of hot red chili peppers and mortality, using a population-based prospective cohort from the National Health and Nutritional Examination Survey (NHANES) III, a representative sample of US noninstitutionalized adults, in which participants were surveyed from 1988 to 1994. The frequency of hot red chili pepper consumption was measured in 16,179 participants at least 18 years of age. Total and cause-specific mortality were the main outcome measures. During 273,877 person-years of follow-up (median 18.9 years), a total of 4,946 deaths were observed. Total mortality for participants who consumed hot red chili peppers was 21.6% compared to 33.6% for those who did not (absolute risk reduction of 12%; relative risk of 0.64). Adjusted for demographic, lifestyle, and clinical characteristics, the hazard ratio was 0.87 ($P = 0.01$; 95% Confidence Interval 0.77, 0.97). Consumption of hot red chili peppers was associated with a 13% reduction in the instantaneous hazard of death. Similar, but statistically nonsignificant trends were seen for deaths from vascular disease, but not from other causes. In this large population-based prospective study, the consumption of hot red chili pepper was associated with reduced mortality. Hot red chili peppers may be a beneficial component of the diet.

Introduction

The role of diet in health has become increasingly relevant and investigated. In the past 40 years, the number of PubMed articles indexing diet has increased by at least 700% [1]. While much of the focus has been on macro- and micronutrients, gastronomical aspects have also been investigated.

Peppers and other spices have long been used to color, flavor and preserve foods, as well as for medicinal purposes. Based on the theories of Hippocrates and Galen, spices were thought to help restore the humoral imbalances responsible for disease and illness in medieval times [2]. The benefits of spices and their bioactive compounds have since been suggested by various *in vitro*, *in vivo* and experimental models. Pungent spices, for example chili peppers, increase

lipid catabolism in different organs and tissues [3–5], which could protect against hypercholes-terolemia and obesity, reducing the risks of hypertension, type 2 diabetes, and atherosclerotic cardiovascular disease. The anti-microbial activity of spices, as highlighted by inhibitory effects against *H. pylori* and other bacteria and fungi [6–8], may alter the gut microbiota and influence various metabolic diseases [9–11]. Many spices possess antioxidant [12] and anti-inflamma-tory effects [13–15], and could serve to prevent and mitigate various chronic diseases.

The potential anti-tumorigenic properties [16] of some spices have been supported by an ecological study of the U.S. and India, which revealed an inverse relationship between spice production (and, presumably, consumption) and cancer incidence [17]. A prospective cohort analysis in China provided the most convincing evidence to date of the clinical benefits of spices, particularly peppers [18]. It showed an inverse relationship between chili pepper con-sumption and mortality from all-causes, cancer, respiratory and cardiovascular disease.

Although data on the consumption patterns in various populations are not available, other groups may differ significantly in the amount and type of peppers used compared to the Chi-nese. The association between peppers and health has not been studied on a large scale in the west. We sought to measure the association between hot red chili pepper consumption and mortality in a large and representative population of US adults.

Materials and Methods

We studied the National Health and Nutritional Examination Survey (NHANES), a represen-tative sample of the US noninstitutionalized population. Data were analyzed from a subsample of participants in the NHANES III survey conducted from 1988 to 1994. We included all sub-jects at least 18 years old with complete data for the outcome and the predictors. NHANES participants undergo extensive interviews and laboratory assessments including blood and urine tests and measures of socioeconomic factors, clinical characteristics and personal habits [19]. Usual consumption of foods and drinks during the past month was assessed with an 81-item food frequency questionnaire administered at baseline; however, portion size was not assessed. Vital status provided by the National Death Index was linked with the dataset through December 31, 2011. NHANES was originally a cross-sectional survey; however, the inclusion of follow-up vital status enables a prospective cohort analysis.

The primary predictor was hot red chili pepper consumption per month, derived from sub-jects' responses to "How often did you have hot red chili peppers? Do not count ground red chili peppers." The primary outcome was long-term mortality. Chili pepper consumers were classified as subjects who reported any value greater than zero when asked about the frequency of hot red chili pepper intake per month.

Deaths were ascertained by a probabilistic matching algorithm with the National Death Index, based on various identifying information (social security number, first and last name, date of birth, *etc.*), or death certificate when possible [20]. Causes of death were classified as Heart Disease (ICD-10 codes I00-I09, I11, I13, I20-I51), Cancer (C00-C97), Chronic Pulmo-nary Diseases (J40-J47), Accidents (V01-X59, Y85-Y86), Stroke (I60-I69), Dementia (G30), Diabetes (E10-E14), Pneumonia including influenza (J09-J18), Kidney Disease (N00-N07, N17-N19, N25-N27) and all other causes. We also created a combined category of all Vascular Disease including deaths from either Heart Disease or Stroke.

The personal and laboratory characteristics considered as covariates were chosen to mini-mize the possibility of confounding by social characteristics and personal habits that were plausibly associated with either hot red chili pepper consumption or mortality. Age, gender, education, race, ethnicity, marital status, employment, annual income, physical activity, and consumption of meats, vegetables and fruits were reported by the participants. Educational

attainment was divided into four categories: none, grade school, middle school, or high school graduate or beyond. Race was categorized as White, Black, or Other. Ethnicity was categorized as Mexican-American, other Hispanic, or non-Hispanic. Low income was defined as annual income less than $20,000 at the time of the interview in 1984–1994. Marital status was defined as married, divorced or separated, widowed, or never married. Frequency of fruit intake per month included a summative value of numerical responses for orange juice, other fruit juices, citrus fruits, melons, peaches, nectarines, and any other fruits. Similarly, vegetable intake per month included carrots, broccoli, Brussel sprouts/cauliflower, spinach, greens, tossed salad, cabbage, coleslaw, sauerkraut, and any other vegetables. Meat intake per month included bacon, sausage, processed meats, liver and other organ meats, beef, pork and ham. Current use of cigarettes was defined as a confirmatory response to "Do you now smoke cigarettes?" Current use of alcohol was defined as reporting using alcohol in the last 12 months. Because the duration of various exercises were not solicited at the time of survey, physical activity level was indirectly measured, as outlined in a prior study [21], and subjects were classified into three categories: no regular exercise, regular low-to-moderate exercise, or regular vigorous exercise.

Additional characteristics of the subjects representing the possible intermediate effects of hot red chili pepper consumption were also collected. Body measurements were taken by trained NHANES staff using standard protocols [22]. Body Mass Index (BMI) was calculated by dividing weight in kilograms by height in meters squared. Obesity was specified as BMI $\geq$ 30 kg/m^2. Cholesterol measurements were standardized according to criteria from the CDC and Prevention Lipid Standardization Program [23, 24]. HDL and total cholesterol values are based on serum samples taken regardless of fasting state. The presence of diabetes was determined by a glycated hemoglobin A1C level $\geq$6.5% or fasting serum glucose $>$ 125 mg/dl or positive response to "Have you ever been told by a doctor that you have diabetes or sugar diabetes?" The presence of hypertension was determined by a systolic blood pressure $\geq$ 140 mmHg or diastolic blood pressure $\geq$ 90 mm Hg or a positive response to both "Because of your (high blood pressure/hypertension), have you ever been told by a doctor or other health professional to take prescribed medicine?" and "Are you now taking prescribed medicine?"

Analysis

Data were retrieved from the NHANES website [19] and statistical analyses were conducted with Stata 14.1 (StataCorp, College Station, Texas). Wilcoxon-rank sum and chi-squared tests were used to compare cohort characteristics for continuous and categorical variables, respectively. Association between the predictor and outcome was assessed by multivariate Cox proportional hazards regressions.

Three models were devised. Model 1 consisted of the predictor (hot red chili pepper consumption) and the outcome (mortality). Model 2 added demographic and socioeconomic information to the prior model. Personal habits were added for Model 3. Because markers of obesity, hypertension, diabetes or inflammation might be intermediate factors in the potential causal pathway between hot red chili pepper consumption and mortality, we did not include them in the multivariate models. We calculated hazard ratios and their 95% confidence intervals (CI). A two-tailed P <0.05 was required for statistical significance. We also calculated the unadjusted absolute risk reduction associated with hot red chili pepper consumption and it's inverse, the number of subjects who would need to consume hot red chili peppers to prevent one death (analogous to the number-needed-to-treat [25]). All analyses were adjusted for the stratified sampling scheme used in NHANES to represent the non-institutionalized US adult population [26].

We performed secondary analyses of the relationship of hot pepper consumption and cause-specific mortality using Cox proportional hazards models adjusted for the same variables retained in Model 3 above.

Results

The NHANES III survey for 1988 to 1994 included 33,199 records. After excluding children and adults missing either the outcome, the main predictor, or any of the covariates, 16,179 eligible participants were analyzed (Fig 1).

Table 1 presents the baseline characteristics of the participants according to hot red chili pepper consumption. Compared with participants who did not consume hot red chili peppers, those who did consume them were more likely to be younger, male, white, Mexican-American, married, and to smoke cigarettes, drink alcohol, and consume more vegetables and meats. They had lower HDL-cholesterol, lower income, and less education.
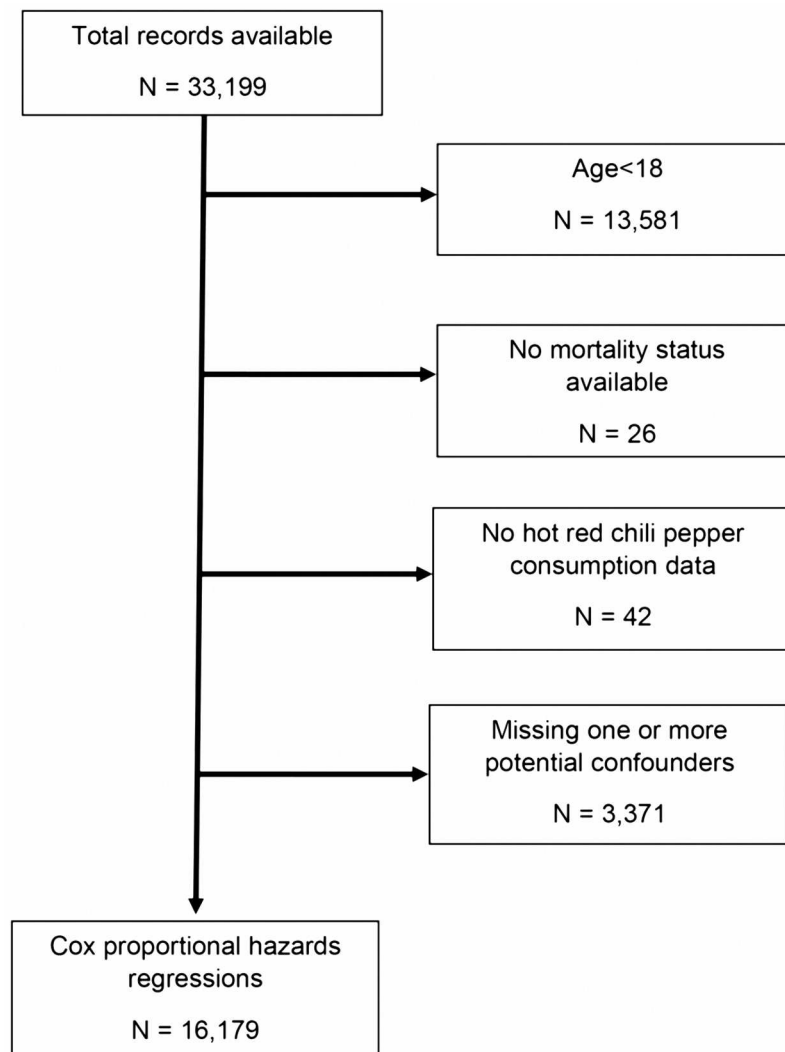

Fig 1. Subject Inclusion.

doi:10.1371/journal.pone.0169876.g001

Table 1. Characteristics of the study population.

Characteristic	Does not consume chili peppers N = 12,071			Consumes chili peppers N = 4,107			P*
	Mean or percent	Median	Range	Mean or percent	Median	Range	
Age (years)	48.2	45	18–90	41.9	38	18–90	<0.001
Male sex	43.0%			58.1%			<0.001
Race							<0.001
White	65.4%			76.0%			
Black	32.2%			18.9%			
Other	2.5%			5.2%			
Ethnicity							<0.001
Mexican-American	16.6%			58.3%			
Other Hispanic	2.8%			1.6%			
Non-Hispanic	80.6%			40.1%			
Marital status							<0.001
Married	58.0%			64.8%			
Divorced or separated	11.2%			10.2%			
Never married	19.2%			19.6%			
Widowed	11.6%			5.4%			
Education							<0.001
None	7.4%			17.4%			
Grade School	12.4%			16.0%			
Middle School	50.6%			42.6%			
High School graduate	29.6%			24.0%			
Annual income < $20,000	47.0%			54.0%			<0.001
Current smoker	24.9%			28.0%			0.001
Current drinker	42.2%			54.7%			<0.001
Physical activity							<0.001
No regular activity	26.8%			30.2%			
Regular low-to-moderate	64.7%			60.6%			
Regular vigorous	8.5%			9.2%			
Diet (portions per month)							
Fruits	49	42	0–619	50	41	0–622	0.19
Vegetables	51	44	0–374	55	49	0–309	<0.001
Meats	23	19	0–624	25	21	0–156	<0.001
Obesity	25.4%			23.9%			0.02
Diabetes	12.1%			10.4%			0.011
Hypertension	27.1%			19.9%			<0.001
Total cholesterol (mg/dl)	205	201	59–702	202	199	81–491	0.003
HDL cholesterol (mg/dl)	51	49	12–196	50	48	8–158	<0.001
Years of observation	17	19	0–23	18	19	0–23	<0.001

Continuous variables were compared using Wilcoxon's rank-sum test. Categorical variables were compared with the chi-square test.

doi:10.1371/journal.pone.0169876.t001

During a median follow-up of 18.9 years (range 1 day-23 years) including 273,877 person-years of observation), we observed 4,946 deaths. Unadjusted mortality for participants who consumed hot red chili peppers was 21.6% (887/4,107) compared to 33.6% (4.059/12,071) for those who did not, resulting in an absolute risk reduction of 12% (P<0.001; 95% CI -13.5, -10.5) and a relative risk of 0.64. The number-needed-to-prevent one death was 8.3.

Table 2. Cox proportional hazards models of the effect of eating hot peppers on total mortality among 16,179 adults in NHANES III.

Variable	Model 1			Model 2			Model 3		
	HR	CI	P	HR	CI	P	HR	CI	P
Eats hot peppers	**0.59**	**0.52, 0.68**	**<0.001**	**0.87**	**0.77, 0.98**	**0.020**	**0.87**	**0.77, 0.97**	**0.014**
Age at Interview				1.09	1.09, 1.10	<0.001	1.10	1.09, 1.10	<0.001
Sex				1.62	1.50, 1.75	<0.001	1.65	1.50, 1.80	<0.001
Race = White				1.00	-	-	1.00	-	-
Black				1.17	1.04, 1.31	0.01	1.09	0.98, 1.21	0.11
Other				0.72	0.49, 1.06	0.09	0.66	0.44, 0.97	0.034
Ethnicity = Mexican-American				1.00	-	-	1.00	-	-
Other Hispanic				0.68	0.56, 0.84	<0.001	0.64	0.51, 0.81	<0.001
Non-Hispanic				1.14	0.998, 1.30	0.053	1.12	0.99, 1.28	0.08
Education = None				1.00	-	-	1.00	-	-
Grade School				0.93	0.78, 1.12	0.47	0.97	0.80, 1.18	0.75
Middle School				0.97	0.82, 1.15	0.73	1.02	0.85, 1.22	0.85
High School Grad				0.71	0.59, 0.86	0.001	0.83	0.68, 1.01	0.064
Marital Status = Married				1.00	-	-	1.00	-	-
Divorced/Separated				1.25	1.06, 1.48	0.01	1.21	1.02, 1.44	0.031
Never married				1.24	1.003, 1.53	0.047	1.29	1.05, 1.59	0.017
Widowed				1.03	0.93, 1.15	0.53	1.006	0.90, 1.12	0.90
Income < $20K				1.57	1.43, 1.72	<0.001	1.48	1.35, 1.62	<0.001
Current Smoker							1.87	1.66, 2.11	<0.001
Current Drinker							0.89	0.80, 0.98	0.26
Fruits per month							0.999	0.999, 1.0001	0.98
Vegetables per month							1.0006	0.999, 1.002	0.31
Meat portions per month							1.001	0.9997, 1.003	0.13
Activity Level = No Regular Exercise							1.00	-	-
Regular Low-to-moderate							0.73	0.65, 0.81	<0.001
Regular Vigorous							0.72	0.57, 0.89	0.004

4,946 deaths over 23 years of observation; HR = hazard ratio; CI = 95% confidence interval

doi:10.1371/journal.pone.0169876.t002

In model 1, the unadjusted Cox-proportional hazard ratio was 0.59 (P<0.001; CI 0.52, 0.68). See Table 2. With the addition of socioeconomic and demographic variables (model 2), the hazard ratio became 0.87 (P = 0.02, CI 0.78, 0.98). The inclusion of a diet and lifestyle habits (model 3) had little impact with a hazard ratio of 0.87 (P = 0.01; CI 0.77, 0.97).

Analyses of specific causes of death (Table 3), adjusted for all the variables in Model 3 above, showed similar (but statistically nonsignificant) magnitudes of reduction in the hazard of death from heart disease and stroke, but not from other causes.

Discussion

In this large prospective study, we observed an inverse relationship between hot red chili pepper consumption and all-cause mortality, after adjusting for potential confounders. Adults who consumed hot red chili peppers had a 13% lower hazard of death, compared to those who did not. These results add to the literature by corroborating the main results of an earlier study [18]. They are distinct in that they are drawn from a different population and thus support the generalizability of the protective effects of hot red chili peppers.

Table 3. Cox proportional hazards models of the effect of eating hot peppers on cause specific mortality among 16,179 adults in NHANES III.

Cause of Death	Number of deaths	HR	95% CI	P
Total	**4,946**	**0.87**	**0.77, 0.97**	**0.01**
Heart Disease	1,211	0.81	0.61, 1.07	0.14
Cancer	1,069	0.89	0.70, 1.13	0.33
Chronic Pulmonary Disease	216	1.03	0.64, 1.67	0.89
Accidents	141	1.14	0.55, 2.36	0.73
Stroke	352	0.64	0.35, 1.16	0.14
Dementia	103	0.88	0.30, 2.54	0.80
Diabetes	178	0.76	0.37, 1.55	0.45
Pneumonia or Influenza	147	0.81	0.35, 1.92	0.63
Kidney Disease	74	1.30	0.36, 4.68	0.68
Other	1,401	0.87	0.67, 1.15	0.32
Vascular disease (Heart disease or Stroke)	1,563	0.86	0.74, 1.001	0.052

All models are adjusted for age, sex, race, ethnicity, education, marital status, income, consumption of alcohol, fruits, vegetables and meats, and physical activity at baseline. HR = hazard ratio; CI = 95% confidence interval.

doi:10.1371/journal.pone.0169876.t003

Although the mechanism by which peppers could delay mortality is far from certain, Transient Receptor Potential (TRP) channels, which are primary receptors for pungent agents such as capsaicin (the principal component in chili peppers), may in part be responsible for the observed relationship. Activation of TRP vanilloid type 1 (TRPV1) appears to stimulate cellular mechanisms against obesity, by altering mediators of lipid catabolism and thermogenesis [27]. Protection against obesity leads to decreased risk of cardiovascular, metabolic and lung diseases. Capsaicin may also defend against heart disease via a TRP-mediated modulation of coronary blood flow [28]. Capsaicin's antimicrobial properties [29] may indirectly affect the host by altering the gut microbiota. For instance, changes in bacterial composition, production of metabolites, and number of colonies have been linked to obesity [30], diabetes [9], cardiovascular disease [10] and liver cirrhosis [11], although the mechanisms for these associations are unknown. Nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB), an important regulator of cellular growth, is inactivated by various spices, including capsaicin, and could mediate anti-tumor effects [31]. Finally, hot red chili peppers also contain other nutrients, including B-vitamins, vitamin C and pro-A vitamin, which may partly account for its protective effect.

This analysis has several important limitations. Although the narrow confidence intervals and small *P*-values argue against random error, the apparent association between hot red chili pepper consumption and mortality could be due to confounding by some factor not controlled in the analysis. For example, differences in other foods often consumed with hot red chili peppers, such as other spices, could serve as potential confounders. In fact, one or more of the social or demographic variables included in Model 2 appear to partially confound the unadjusted association between red hot chili pepper consumption and mortality, as demonstrated by the change in Hazard Ratio between Model 1 and Model 2. Nonetheless, the association remains statistically and epidemiologically significant, with no evidence of further confounding by the additional lifestyle characteristics included in Model 3.

Dietary information was gathered in a cross-sectional manner, and may not represent long-term consumption of hot red chili peppers. "Hot red chili peppers" could include a variety of different types, and may represent a narrower selection than seen in the Chinese study (perhaps because of the qualifier "red"). With the exception of ground peppers, the data do not

allow for delineation between fresh or dried peppers. The limitations of dietary recall are well recognized [32]. Nonetheless, dietary intake data in the NHANES survey are collected using standardized, validated protocols [33, 34].

The sample cohort is representative of a U.S. non-institutionalized population, but not necessarily generalizable to other groups. The NHANES III survey was conducted during the years 1988 to 1994, and recent patterns of chili pepper consumption may differ.

Cause-specific mortality analysis in this data set are limited by the relatively small numbers of deaths. Nonetheless, the trends towards protection from deaths due to vascular disease stands in contrast to the lack of any apparent protection from death due to accidents, chronic pulmonary disease and kidney disease, and may provide a clue to hot red chili pepper's mechanism of action.

Our analyses showed a significant decrease in mortality associated with hot red chili pepper consumption. The results support the findings of Lv, *et al.* [18]. which revealed an inverse relationship between spicy food consumption and mortality, and strengthen its generalizability. Given the observational nature of both investigations, causality can only be suggested, not confirmed. Further studies should aim to investigate the benefits of other spices and differential effects of certain chili pepper subtypes. Such evidence may lead to new insights into the relationships between diet and health, updated dietary recommendations, and the development of new therapies.

Author Contributions

Conceptualization: MC BL.

Data curation: BL.

Formal analysis: MC BL.

Investigation: MC BL.

Methodology: MC BL.

Software: BL.

Supervision: BL.

Validation: MC BL.

Visualization: BL.

Writing – original draft: MC.

Writing – review & editing: MC BL.

References

1. PubMed. Results by Year 2016 [updated 1/25/2016]. http://www.ncbi.nlm.nih.gov/pubmed/?term=diet.

2. Nam JK. Medieval European medicine and Asian spices. Ui sahak. 2014; 23(2):319–42. Epub 2014/09/17. doi: 10.13081/kjmh.2014.23.319 PMID: 25223223

3. Lee MS, Kim CT, Kim IH, Kim Y. Effects of capsaicin on lipid catabolism in 3T3-L1 adipocytes. Phytotherapy research: PTR. 2011; 25(6):935–9. Epub 2011/06/01. doi: 10.1002/ptr.3339 PMID: 21626599

4. Zhu Z, Luo Z, Ma S, Liu D. TRP channels and their implications in metabolic diseases. Pflugers Archiv: European journal of physiology. 2011; 461(2):211–23. Epub 2010/11/27. doi: 10.1007/s00424-010-0902-5 PMID: 21110037

5. Li L, Chen J, Ni Y, Feng X, Zhao Z, Wang P, et al. TRPV1 activation prevents nonalcoholic fatty liver through UCP2 upregulation in mice. Pflugers Archiv: European journal of physiology. 2012; 463 (5):727–32. Epub 2012/03/08. doi: 10.1007/s00424-012-1078-y PMID: 22395410

6. Bergonzelli GE, Donnicola D, Porta N, Corthesy-Theulaz IE. Essential oils as components of a diet-based approach to management of Helicobacter infection. Antimicrobial agents and chemotherapy. 2003; 47(10):3240–6. Epub 2003/09/25. doi: 10.1128/AAC.47.10.3240-3246.2003 PMID: 14506036

7. Lai PK, Roy J. Antimicrobial and chemopreventive properties of herbs and spices. Current medicinal chemistry. 2004; 11(11):1451–60. Epub 2004/06/08. PMID: 15180577

8. Liu ZH N H. Antibacterial activity of spice extracts against food-related bacteria. J Fac Appl Biol Sci. 1996; 35:181–90.

9. Qin J, Li Y, Cai Z, Li S, Zhu J, Zhang F, et al. A metagenome-wide association study of gut microbiota in type 2 diabetes. Nature. 2012; 490(7418):55–60. Epub 2012/10/02. doi: 10.1038/nature11450 PMID: 23023125

10. Tang WH, Wang Z, Levison BS, Koeth RA, Britt EB, Fu X, et al. Intestinal microbial metabolism of phosphatidylcholine and cardiovascular risk. The New England journal of medicine. 2013; 368(17):1575–84. Epub 2013/04/26. doi: 10.1056/NEJMoa1109400 PMID: 23614584

11. Qin N, Yang F, Li A, Prifti E, Chen Y, Shao L, et al. Alterations of the human gut microbiome in liver cirrhosis. Nature. 2014; 513(7516):59–64. Epub 2014/08/01. doi: 10.1038/nature13568 PMID: 25079328

12. Halvorsen BL, Carlsen MH, Phillips KM, Bohn SK, Holte K, Jacobs DR Jr., et al. Content of redox-active compounds (ie, antioxidants) in foods consumed in the United States. The American journal of clinical nutrition. 2006; 84(1):95–135. Epub 2006/07/11. PMID: 16825686

13. Chen YC, Shen SC, Lee WR, Hou WC, Yang LL, Lee TJ. Inhibition of nitric oxide synthase inhibitors and lipopolysaccharide induced inducible NOS and cyclooxygenase-2 gene expressions by rutin, quercetin, and quercetin pentaacetate in RAW 264.7 macrophages. Journal of cellular biochemistry. 2001; 82(4):537–48. Epub 2001/08/14. PMID: 11500931

14. Hong J, Bose M, Ju J, Ryu JH, Chen X, Sang S, et al. Modulation of arachidonic acid metabolism by curcumin and related beta-diketone derivatives: effects on cytosolic phospholipase A(2), cyclooxygenases and 5-lipoxygenase. Carcinogenesis. 2004; 25(9):1671–9. Epub 2004/04/10. doi: 10.1093/carcin/bgh165 PMID: 15073046

15. Comalada M, Camuesco D, Sierra S, Ballester I, Xaus J, Galvez J, et al. In vivo quercitrin anti-inflammatory effect involves release of quercetin, which inhibits inflammation through down-regulation of the NF-kappaB pathway. European journal of immunology. 2005; 35(2):584–92. Epub 2005/01/26. doi: 10.1002/eji.200425778 PMID: 15668926

16. Aggarwal BB, Shishodia S. Molecular targets of dietary agents for prevention and therapy of cancer. Biochemical pharmacology. 2006; 71(10):1397–421. Epub 2006/03/28. doi: 10.1016/j.bcp.2006.02.009 PMID: 16563357

17. Aggarwal BB, Van Kuiken ME, Iyer LH, Harikumar KB, Sung B. Molecular targets of nutraceuticals derived from dietary spices: potential role in suppression of inflammation and tumorigenesis. Experimental biology and medicine (Maywood, NJ). 2009; 234(8):825–49. Epub 2009/06/06.

18. Lv J, Qi L, Yu C, Yang L, Guo Y, Chen Y, et al. Consumption of spicy foods and total and cause specific mortality: population based cohort study. BMJ (Clinical research ed). 2015; 351:h3942. Epub 2015/08/06.

19. Centers for Disease Control and Prevention. Questionaires, Datasets, and Related Documentation, Prior NHANES, NHANES III Hyattsville, MarylandNovember 10, 2015. http://www.cdc.gov/nchs/nhanes/nh3data.htm.

20. National Center for Health Statistics. Office of Analysis and Epidemiology. NCHS 2011 Linked Mortality Files Matching Methodology Hyattsville, Maryland. September, 2013. http://www.cdc.gov/nchs/data_access/data_linkage/mortality/linkage_methods_analytical_support/2011_linked_mortality_file_matching_methodology.pdf.

21. Parekh N, Lin Y, Craft LL, Vadiveloo M, Lu-Yao GL. Longitudinal associations of leisure-time physical activity and cancer mortality in the Third National Health and Nutrition Examination Survey (1986–2006). J Obes. 2012; 2012:518358. Epub 2012/06/08. doi: 10.1155/2012/518358 PMID: 22675612

22. Centers for Disease Control and Prevention. Plan and Operation of the Third National Health and Nutrition Examination Survey, 1988–94 Hyattsville, MarylandJuly, 1997. http://www.cdc.gov/nchs/data/series/sr_01/sr01_032.pdf.

23. Carroll MD, Lacher DA, Sorlie PD, Cleeman JI, Gordon DJ, Wolz M, et al. Trends in serum lipids and lipoproteins of adults, 1960–2002. JAMA: the journal of the American Medical Association. 2005; 294 (14):1773–81. Epub 2005/10/13. doi: 10.1001/jama.294.14.1773 PMID: 16219880

24. Myers GL, Cooper GR, Winn CL, Smith SJ. The Centers for Disease Control-National Heart, Lung and Blood Institute Lipid Standardization Program. An approach to accurate and precise lipid measurements. Clin Lab Med. 1989; 9(1):105–35. Epub 1989/03/01. PMID: 2538292

25. Laupacis A, Sackett DL, Roberts RS. An Assessment of Clinically Useful Measures of the Conse-
     quences of Treatment. New England Journal of Medicine. 1988; 318(26):1728–33. doi: 10.1056/
     NEJM198806303182605 PMID: 3374545

26. Centers for Disease Control and Prevention. Analytic and Reporting Guidelines: The Third National
     Health and Nutrition Examination Survey, NHANES III (1988–94) Hyattsville, MarylandAugust 1996.
     http://www.cdc.gov/nchs/data/nhanes/nhanes3/nh3gui.pdf.

27. Zsombok A. Vanilloid receptors—do they have a role in whole body metabolism? Evidence from
     TRPV1. Journal of diabetes and its complications. 2013; 27(3):287–92. Epub 2013/01/22. doi: 10.1016/
     j.jdiacomp.2012.11.006 PMID: 23332888

28. Guarini G, Ohanyan VA, Kmetz JG, DelloStritto DJ, Thoppil RJ, Thodeti CK, et al. Disruption of TRPV1-
     mediated coupling of coronary blood flow to cardiac metabolism in diabetic mice: role of nitric oxide and
     BK channels. American journal of physiology Heart and circulatory physiology. 2012; 303(2):H216–23.
     Epub 2012/05/23. doi: 10.1152/ajpheart.00011.2012 PMID: 22610171

29. Sherman PW, Billing J. Darwinian Gastronomy: Why We Use Spices: Spices taste good because they
     are good for us. BioScience. 1999; 49(6):453–63.

30. Turnbaugh PJ, Ley RE, Mahowald MA, Magrini V, Mardis ER, Gordon JI. An obesity-associated gut
     microbiome with increased capacity for energy harvest. Nature. 2006; 444(7122):1027–31. Epub 2006/
     12/22. doi: 10.1038/nature05414 PMID: 17183312

31. Nilius B, Appendino G. Spices: the savory and beneficial science of pungency. Reviews of physiology,
     biochemistry and pharmacology. 2013; 164:1–76. Epub 2013/04/23. doi: 10.1007/112_2013_11 PMID:
     23605179

32. Drenowatz C, Jakicic JM, Blair SN, Hand GA. Differences in correlates of energy balance in normal
     weight, overweight and obese adults. Obesity research & clinical practice. 2015; 9(6):592–602. Epub
     2015/04/13.

33. Moshfegh AJ, Rhodes DG, Baer DJ, Murayi T, Clemens JC, Rumpler WV, et al. The US Department of
     Agriculture Automated Multiple-Pass Method reduces bias in the collection of energy intakes. The
     American journal of clinical nutrition. 2008; 88(2):324–32. Epub 2008/08/12. PMID: 18689367

34. Rhodes DG, Murayi T, Clemens JC, Baer DJ, Sebastian RS, Moshfegh AJ. The USDA Automated Mul-
     tiple-Pass Method accurately assesses population sodium intakes. The American journal of clinical
     nutrition. 2013; 97(5):958–64. Epub 2013/04/05. doi: 10.3945/ajcn.112.044982 PMID: 23553153