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# Chili Pepper Consumption and Mortality in Italian Adults

Marialaura Bonaccio, PhD,[a] Augusto Di Castelnuovo, PhD,[b] Simona Costanzo, PhD,[a] Emilia Ruggiero, MSc,[a] Amalia De Curtis, BSc,[a] Mariarosaria Persichillo, MSc,[a] Claudio Tabolacci, PhD,[c] Francesco Facchiano, MD, PhD,[c] Chiara Cerletti, PhD,[a] Maria Benedetta Donati, MD, PhD,[a] Giovanni de Gaetano, MD, PhD,[a] Licia Iacoviello, MD, PhD,[a,d] on behalf of the Moli-sani Study Investigators

## ABSTRACT

**BACKGROUND** Chili pepper is a usual part of a traditional Mediterranean diet. Yet epidemiological data on the association between chili pepper intake and mortality risk are scarce, with a lack of studies from Mediterranean populations.

**OBJECTIVES** This study sought to examine the association between chili pepper consumption and risk of death in a large sample of the adult Italian general population, and to account for biological mediators of the association.

**METHODS** Longitudinal analysis was performed on 22,811 men and women enrolled in the Moli-sani Study cohort (2005 to 2010). Chili pepper intake was estimated by the EPIC (European Prospective Investigation Into Cancer) Food Frequency Questionnaire and categorized as none/rare consumption, up to 2 times/week, >2 to ≤4 times/week, and >4 times/week.

**RESULTS** Over a median follow-up of 8.2 years, a total of 1,236 deaths were ascertained. Multivariable hazard ratios (HRs) for all-cause and cardiovascular disease (CVD) mortality among participants in the regular (>4 times/week) relative to none/rare intake were 0.77 (95% confidence interval [CI]: 0.66 to 0.90) and 0.66 (95% CI: 0.50 to 0.86), respectively. Regular intake was also inversely associated with ischemic heart disease (HR: 0.56; 95% CI: 0.35 to 0.87) and cerebrovascular (HR: 0.39; 95% CI: 0.20 to 0.75) death risks. The association of chili pepper consumption with total mortality appeared to be stronger in hypertension-free individuals (p for interaction = 0.021). Among known biomarkers of CVD, only serum vitamin D marginally accounted for such associations.

**CONCLUSIONS** In a large adult Mediterranean population, regular consumption of chili pepper is associated with a lower risk of total and CVD death independent of CVD risk factors or adherence to a Mediterranean diet. Known biomarkers of CVD risk only marginally mediate the association of chili pepper intake with mortality.
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From the [a]Department of Epidemiology and Prevention, IRCCS Neuromed, Via dell'Elettronica, Pozzilli, Italy; [b]Mediterranea Cardiocentro, Napoli, Italy; [c]Department of Oncology and Molecular Medicine, Istituto Superiore di Sanità, Roma, Italy; and the [d]Department of Medicine and Surgery, Research Center in Epidemiology and Preventive Medicine (EPIMED), University of Insubria, Varese, Italy. The enrollment phase of the Moli-sani Study was supported by research grants from Pfizer Foundation (Rome, Italy), the Italian Ministry of University and Research (MIUR, Rome, Italy)-Programma Triennale di Ricerca, Decreto no. 1588, and Instrumentation Laboratory, Milan, Italy. Drs. Bonaccio and Tabolacci were supported by a Fondazione Umberto Veronesi Fellowship. Dr. Costanzo was the recipient of a Fondazione Umberto Veronesi travel grant. The present analyses were partially supported by a grant to Dr. Bonaccio from the Italian Ministry of Health 2013 grant number GR-2013-02356060, a grant to Dr. Iacoviello from the Italian Association for Cancer Research (AIRC) (AIRC "5xMILLE" n. 12237), and a grant to Dr. Iacoviello as a partner of BiomarCaRE (Biomarkers for Cardiovascular Risk Assessment in Europe) by the European Commission Seventh Framework Programme FP7/2007-2013 (HEALTH-F2-2011-278913). The funders had no role in study design; collection, analysis, and interpretation of data; writing of the manuscript; or the decision to submit the article for publication. The authors have reported that they have no relationships relevant to the contents of this paper to disclose.

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**ABBREVIATIONS AND ACRONYMS**

**BMI** = body mass index

**CI** = confidence interval

**CRP** = C-reactive protein

**CV** = coefficient of variability

**CVD** = cardiovascular disease

**HDL** = high-density lipoprotein

**HR** = hazard ratio

**ICD-9** = International Classification of Diseases-9th Revision

**IHD** = ischemic heart disease

**MD** = Mediterranean diet

**MDS** = Mediterranean Diet Score

**NRI** = Net Reclassification Index

**NT-proBNP** = N-terminal pro-B-type natriuretic peptide

**PA** = physical activity

Spices have long been an essential part of the traditional Mediterranean diet (MD), and are placed, along with herbs, at the base of the MD pyramid both for their nutritional properties and as a valuable substitute for salt (1–3). Chili peppers, belonging to the genus *Capsicum*, are native to Central and Southern America, but are largely present in different cultures' diets worldwide (4), and are used to flavor traditional dishes from the southern Italian regions.

SEE PAGE 3150

Health benefits of chili peppers have been ascribed to capsaicin, its major pungent compound, which has been observed to favorably improve cardiovascular function and metabolic regulation in experimental and population studies (5). In addition to its anti-inflammatory and analgesic properties and atheroprotective effects (4), capsaicin reportedly induces apoptosis of the tumor cells (6); high concentrations, however, likely evoke deleterious effects (7).

Studies in humans concluded that chili pepper intake facilitates weight loss through activation of different receptors and improved control of insulin (8). Evidence from a large epidemiological study appears to corroborate the weight-loss properties of chili peppers by showing inverse associations with incidence of overweight/obesity (9).

More recently, animal studies uncovered an interaction between dietary capsaicin and gut microbiota as a novel mechanism for the antiobesity effect of capsaicin acting through prevention of microbial dysbiosis, gut barrier dysfunction, and chronic low-grade inflammation (10). To date, epidemiological evidence longitudinally addressing the association of chili pepper intake on disease/mortality risk is scarce.

With the exception of 2 population studies from China (11) and the United States (12), both showing lower mortality risk associated with regular chili pepper intake, no epidemiological investigation on the potential health benefits associated with consumption of chili pepper is currently available from European cohorts or from Mediterranean areas. In addition, none of the aforementioned studies has addressed possible biological mechanisms through which regular chili pepper intake may provide the observed health advantages.

The primary aim of this study was to prospectively estimate the association of chili pepper consumption with total and cause-specific mortality in a large Mediterranean population of adult men and women; as a secondary purpose, we examined some biological mechanisms that could be on the pathway between chili pepper intake and mortality by analyzing the possible contribution of established biomarkers of cardiovascular risk. Finally, we assessed whether inclusion of chili pepper was able to improve risk prediction associated with a traditional Mediterranean Diet Score (MDS).

## METHODS

**STUDY POPULATION.** We used data from the Moli-sani Study, a prospective cohort study established in 2005 to 2010 with an enrollment of 24,325 men and women (≥35 years of age) randomly recruited from the general population of Molise, a southern Mediterranean region in Italy, with the main purpose of investigating genetic and environmental risk factors of cardiovascular, cerebrovascular, and tumor diseases. Details of the Moli-sani Study have been previously described (13).

Participants reporting implausible energy intakes (<800 kcal/day in men and <500 kcal/day in women or >4,000 kcal/day in men and >3,500 kcal/day in women; 3.2%) were excluded, as well as individuals with unreliable medical/dietary questionnaires (1% and 3.9%, respectively), individuals with missing information on main covariates (0.3%), exposure (0.4%), and cause-specific mortality (0.2%), and 23 participants (0.1%) lost to follow-up. The final sample consisted of 22,811 subjects.

The cohort was followed up for mortality until December 31, 2015. Overall and cause-specific mortality was assessed by the Italian mortality registry (ReNCaM registry), validated by Italian death certificates (ISTAT form) and coded according to the International Classification of Diseases-9th Revision (ICD-9).

Cardiovascular disease (CVD) mortality included deaths from diseases of the circulatory system, when the underlying cause of death included ICD-9 codes 390 to 459. ICD-9 codes 430 to 438 were used to define specific cause of death for cerebrovascular disease, and ICD-9 codes 410 to 414 and 429 for ischemic heart disease (IHD). Cancer death was considered when the underlying cause of death included ICD-9 codes 140 to 208.

Noncardiovascular/noncancer causes of death were included in the "other-cause mortality" group. The Moli-sani Study complies with the Declaration of Helsinki and was approved by the ethical committee of the Catholic University Medical School in Rome, Italy. All participants provided written informed consent.

**COVARIATE ASSESSMENT.** History of cardiovascular disease (angina, myocardial infarction, revascularization procedures, peripheral artery diseases, and cerebrovascular events) was self-reported and confirmed by medical records and therapy. History of cancer was self-reported and confirmed by medical records. Hypertension, hyperlipidemia, and diabetes were defined by use of pharmacological treatment.

Leisure-time physical activity (PA) was expressed as daily energy expenditure in metabolic equivalent task-hours/day for sport, walking, and gardening. Height and weight were measured, and body mass index (BMI) was calculated as $kg/m^2$ and then grouped into 3 categories as normal (≤25), overweight (>25 to <30), or obese (≥30).

Subjects were classified as never-smokers, current smokers, or ex-smokers (quit at least 1 year ago). Education was based on the highest qualification attained and was categorized as up to lower secondary (approximately ≤8 years of study), upper secondary school (>8 to ≤13 years), and postsecondary education (>13 years).

Occupational social class was based on the Registrar General's occupation-based classification scheme and ranked as previously described within the Molisani population (14), and categorized as professional/managerial, skilled nonmanual occupations, skilled manual occupations, partly skilled occupations, and unskilled, retired/housewife, unemployed/unclassified subjects.

**DIETARY ASSESSMENT.** Food intake during the year before enrollment was assessed by the EPIC (European Prospective Investigation Into Cancer) Food Frequency Questionnaire validated and adapted to the Italian population (15). Frequency of chili pepper intake was estimated through the question: "How often do you consume foods containing chili pepper," with possible answers being "never or almost never," "occasionally," "often," and "very often."

Chili pepper was then categorized as consumption on a weekly basis that is never/rare intake, up to 2 times/week, >2 to ≤4 times/week, and >4 times/week. Other herbs and spices including garlic, parsley, and black pepper were categorized as yes/no.

Adherence to the traditional MD was assessed through the MDS developed by Trichopoulou et al. (16), and was obtained by assigning 1 point to healthy foods (fruits and nuts, vegetables, legumes, fish, cereals, monounsaturated-to-saturated fats ratio) whose consumption was above the sex-specific medians of intake of the Moli-sani Study population, free from CVD, cancer, and diabetes; foods presumed to be detrimental (meat and dairy products) were scored positively if their consumption was below the median. All other intakes received 0 points. For ethanol, men who consumed 10 to 50 g/day and women who consumed 5 to 25 g/day received 1 point; otherwise, the score was 0. The MDS ranged from 0 to 9 (the latter reflecting maximal adherence). The vegetable food group included in the MDS did not include sweet peppers; the latter were used as a covariate in survival analysis and also independently tested as predictors of mortality.

Food antioxidant content was appraised by a score determining the content in antioxidant vitamins and phytochemicals of each food group, and ranged from −99 to 99, with higher values indicating increased consumption of foods rich in antioxidants (17). The polyphenol content of diet was measured by a polyphenol antioxidant content score calculated as in Pounis et al. (18).

Variety of fruit and/or vegetable intake was assessed by 4 different (fruit, vegetables, vegetable subgroups, and fruit/vegetables combined) Diet Diversity Scores, following similar approaches tested within EPIC cohorts (19). Diversity was intended as the total number of individual vegetable/fruit products eaten at least once in 2 weeks.

**BIOMARKERS OF CVD RISK.** Antecubital venous blood samples were obtained from participants who had fasted overnight and had refrained from smoking for at least 6 h. Serum lipids (total cholesterol, high-density lipoprotein [HDL]-cholesterol, triglycerides) and blood glucose were assayed by enzymatic reaction methods using an automatic analyzer (ILab 350; Instrumentation Laboratory, Milan, Italy).

Quality control for lipids and glucose was obtained by a commercial standard (Ser 1 and Ser 2) provided by Instrumentation Laboratory and an in-house serum standard pool. The coefficients of variability (CVs) were respectively 4.9%, 5.2%, and 4% for blood cholesterol; 3.2%, 3%, and 4.5% for HDL-cholesterol; 5.2%, 5.3%, and 5% for triglycerides; and 4.7%, 4.1%, and 3.9 for blood glucose.

High-sensitivity C-reactive protein (CRP) was measured in fresh serum samples by a particle-enhanced immunoturbidimetric assay (ILab 350). Quality control for CRP was maintained using an in-house serum pool and internal laboratory standard at 1.5 mg/l; interday CVs for CRP were 5.5% and 4.2%, respectively. Hemochromocytometric analysis was performed by cell count (Coulter HMX; Beckman Coulter, Milan, Italy) within 3 h from blood collection.

Quality control was performed by using 3 different levels of standards Abn (abnormal) I, Abn II, and Normal (Coulter HMX). The CV for white blood

**TABLE 1 Baseline Characteristics of the Study Population by Intake of Chili Pepper in the Moli-sani Study Cohort (N = 22,811)**

| | Chili Pepper Intake (Times/Week) | | | | |
|---|---|---|---|---|---|
| | None/Rare (n = 7,689, 33.7%) | Up to 2 (n = 4,360, 19.1%) | >2 to ≤4 (n = 5,216, 22.9%) | >4 (n = 5,546, 24.3%) | p Value |
| Times/week | 0.0 | 0.8 ± 0.4 | 2.8 ± 0.6 | 7.0 ± 3.8 | – |
| Age, yrs | 55 ± 13 | 54 ± 11 | 55 ± 11 | 56 ± 11 | <0.0001 |
| Male | 34.6 | 50.7 | 52.5 | 58.8 | <0.0001 |
| Post-secondary education | 11.5 | 14.1 | 13.4 | 13.5 | <0.0001 |
| Professional/managerial workers | 18.7 | 21.3 | 21.8 | 21.6 | <0.0001 |
| Smokers | 18.6 | 22.0 | 24.8 | 28.1 | 0.0022 |
| Leisure-time PA, MET-h/day | 3.4 ± 3.8 | 3.3 ± 3.7 | 3.7 ± 4.0 | 3.7 ± 4.4 | <0.0001 |
| Drugs for diabetes | 4.3 | 4.6 | 4.9 | 5.5 | 0.015 |
| Drugs for hypertension | 27.3 | 25.8 | 27.0 | 28.8 | 0.016 |
| Lipid-lowering drugs | 7.4 | 7.0 | 7.7 | 8.5 | 0.0011 |
| Cardiovascular disease | 4.8 | 5.2 | 4.8 | 6.0 | 0.010 |
| Cancer | 3.9 | 3.0 | 3.1 | 2.6 | 0.0090 |
| Mediterranean Diet Score* | 4.2 ± 1.6 | 4.3 ± 1.6 | 4.4 ± 1.6 | 4.8 ± 1.6 | <0.0001 |
| Sweet pepper intake, g/day | 2.7 ± 3.2 | 2.8 ± 2.9 | 3.2 ± 3.3 | 3.7 ± 3.9 | <0.0001 |
| Black pepper† | 11.0 | 19.3 | 25.0 | 26.0 | <0.0001 |
| Garlic† | 82.6 | 85.0 | 89.3 | 92.4 | <0.0001 |
| Parsley† | 91.7 | 95.1 | 95.6 | 96.7 | <0.0001 |

Values are mean ± SD or %, unless otherwise indicated. Means and p values are adjusted for age, sex, and energy intake (Kcal/day). *Not including sweet pepper intake. †Black pepper, garlic, and parsley consumption was reported as prevalence of consumers.

MET = metabolic equivalent of task; PA = physical activity.

cells was 6.2%, 3.3%, and 3.0% for Abn I, Abn II, and Normal, respectively. N-terminal pro-B-type natriuretic peptide (NT-proBNP), high-sensitivity troponin I (hsTnI), apolipoprotein A1 (ApoA), apolipoprotein B100 (ApoB100), lipoprotein a [Lp(a)], markers of renal function (cystatin C, creatinine), insulin, C-peptide, and serum vitamin D were measured in the framework of the collaborative BiomarCaRE (Biomarker for Cardiovascular Risk Assessment across Europe) project (20).

**STATISTICAL ANALYSIS.** Baseline characteristics of the participants by categories of chili pepper intake were summarized and compared by using analysis of variance adjusted for age, sex, and energy intake (GENMOD procedure for categorical variables and GLM procedure for continuous variables in SAS software, version 9.4 [SAS Institute, Cary, North Carolina]) (Table 1).

Risk estimates for mortality were expressed as hazard ratios (HRs) with 95% confidence interval (CI) and calculated by using Cox regression models with time-on-study on the time scale and competing risk of dying for other causes. Multivariable-adjusted HRs were calculated across 4 categories of intake (none/rare consumption—referent category, up to 2 times/week, >2 to ≤4 times/week, and >4 times/week) as well as considering consumers as opposed to nonconsumers.

Based on previous published reports and biological plausibility, 2 multivariable models were fitted: the first (model 1) was adjusted for age (continuous), sex, and energy intake (kcal/day; continuous); the second (model 2) as in model 1 and further controlled for educational level, occupational social class, smoking, leisure-time PA, treatment for diabetes, medication for hypertension, lipid-lowering drugs, history of CVD or cancer at baseline, MDS (continuous), and sweet pepper intake (g/day, ordered quartiles), garlic, parsley, and black pepper (yes/no).

Several panels of biomarkers were tested as possibly mediating the association of chili pepper intake with mortality risk. In addition to cardiac troponin (hsTnI) and NT-proBNP, we tested biomarkers of renal function (cystatin C, creatinine), glucose metabolism (blood glucose, insulin, C-peptide), lipid metabolism (total blood cholesterol, HDL-cholesterol, triglycerides, Lp(a), apoA1, and apoB100), serum vitamin D, inflammatory markers (CRP and white blood cells), and a panel including systolic and diastolic blood pressure and BMI.

The multivariable model 2 served as the reference for the mediation analysis used to quantify the contribution of each set of potential mediators, which were alternately included into model 2. For the mediation analysis, the %MEDIATE macro in SAS (21) was used, which calculates the point and interval

estimates of the percent of exposure effect explained by 1 or more intermediate variables, with 95% CI and p values. Biomarkers were entered into the mediation analysis as ordered quintiles.

Subgroup analyses were performed within a healthy sample (individuals without CVD or cancer and who were not using drugs for diabetes at baseline) and excluding early deaths (follow-up >2 years). We tested the interaction between chili pepper and a large panel of potential effect modifiers by introducing in a Cox analysis a product term of chili pepper intake (yes vs. no) × a given effect modifier (2 categories, with the exception of adherence to MD, 3 categories).

Consumption of chili pepper (none/rare intake = 0 points; regular intake = 1 point) was included as an additional component into the original MDS, thus originating an MDS "supplemented" with chilies, ranging from 0 to 10; to allow comparison among scores, they were entered into risk analyses scaled by their standard deviation.

The area under the receiver-operating curve statistic, the categorical net reclassification index (NRI) and the integrated discrimination improvement (22) were used to quantify the predictive value of the MDS "supplemented" with chilies over the traditional MDS. To estimate these metrics, the follow-up time was censored at 10 years. The risk categories chosen for NRI calculation were <5% and ≥5%. Observed mortality rates over time were showed as curves obtained by using the LIFETEST procedure in SAS. Dummy variables for missing values were created. Positively skewed variables were log transformed before analysis. Subgroup and interaction analyses were run by excluding missing categories. The data analysis was generated using SAS/STAT software, Version 9.4 of the SAS System for Windows 2009.

## RESULTS

Regular consumption (>4 times/week) of chili pepper was reported by 24.3% of the study participants, whereas 33.7% declared none/rare intake (**Table 1**). Regular consumers were more likely to be men, slightly older, to report higher educational level and occupation, and showed higher prevalence of risk factors (diabetes, hypertension, hyperlipidemia, and history of CVD), but greater leisure-time PA (**Table 1**). Higher consumption of chili pepper was also associated with closer adherence to MD, higher intake of other spices (**Table 1**), and a global higher diet quality as measured by dietary polyphenol and antioxidant content (Online Table 1). Regular consumers also tended to have higher levels of blood lipids and blood glucose, and higher BMI, and slightly higher blood leukocyte counts, whereas no substantial differences were observed for CRP (Online Table 2). NT-proBNP levels were lower in regular consumers, whereas troponin I and serum vitamin D were more likely associated with higher chili intake.

Over a median follow-up of 8.2 years (interquartile range: 7.3 to 9.3 years; 187,584 person years), a total of 1,236 deaths were ascertained (CVD = 444, IHD/cerebrovascular = 258, cancer = 482, and 310 from other causes). In a model adjusted only for age, sex, and energy intake, regular consumption (>4 times/week) of chili pepper was associated with 23% (95% CI: 10% to 34%) lower risk of all-cause mortality, as opposed to none/rare intake, and results remained substantially unchanged in the fully adjusted model (**Table 2**).

In comparison with individuals reporting none/rare intake, regular consumers experienced 34% (14% to 50%) lower risk of CVD mortality, whereas multivariable HRs for IHD and cerebrovascular death were 0.56 (95% CI: 0.35 to 0.87) and 0.39 (95% CI: 0.20 to 0.75), respectively (**Table 2**).

For all mortality outcomes under study, we failed to find a clear stepwise dose-response relation with chili pepper, indicating that the actual advantage in terms of survival improvement is likely attributable to the fact of consuming chilies rather than not consuming them (**Table 2**). Observed mortality rates and multivariable Kaplan-Meier estimates for consumers versus none/rare consumers are well-separated (**Central Illustration**).

Cancer mortality risk was slightly, though not significantly, affected by chili pepper consumption, although a downward trend was observed (**Table 2**). Finally, consumption of chili pepper was inversely associated with mortality for other causes (**Table 2**). Sweet pepper intake was associated with lower total and IHD mortality risk, whereas no association was found with cerebrovascular mortality (Online Table 3), after adjustment for potential confounders.

Established biomarkers of CVD did not substantially modify the relation between chili pepper and mortality, although a marginal role was played by serum vitamin D levels and biomarkers of lipid metabolism, explaining 6.1% and 5.3% of the association with all-cause mortality, respectively (**Table 3**). Subgroup analyses showed no difference of effect across levels of main covariates, with the exception of hypertension, which was likely to modify the magnitude of the association between chili pepper intake and total mortality risk. Specifically, the positive effect of chilies was stronger in hypertension-free individuals (p for interaction = 0.021) (**Table 4**). Overall diet quality, measured by MDS, was not an

**TABLE 2 Chili Pepper Intake and Risk of Death in the Moli-sani Study Cohort (N = 22,811)**

| | Weekly Consumption of Chili Pepper | | | | Consumers vs. None/Rare Consumers |
|---|---|---|---|---|---|
| | None/Rare | Up to 2 Times/Week | >2 to ≤4 Times/Week | >4 Times/Week | |
| All-cause mortality | 500/7,689 | 212/4,360 | 244/5,216 | 280/5,546 | – |
| Crude model | ref | 0.74 (0.63-0.87) | 0.73 (0.63-0.85) | 0.75 (0.65-0.87) | 0.74 (0.66-0.83) |
| Model 1 | ref | 0.85 (0.73-1.00) | 0.80 (0.69-0.94) | 0.77 (0.66-0.89) | 0.80 (0.72-0.90) |
| Model 2 | ref | 0.86 (0.73-1.01) | 0.82 (0.70-0.96) | 0.77 (0.66-0.90) | 0.81 (0.72-0.92) |
| Cardiovascular mortality | 193/7,689 | 73/4,360 | 91/5,216 | 87/5,546 | – |
| Crude model | ref | 0.66 (0.50-0.86) | 0.71 (0.55-0.91) | 0.60 (0.47-0.77) | 0.65 (0.54-0.79) |
| Model 1 | ref | 0.84 (0.64-1.10) | 0.86 (0.67-1.11) | 0.69 (0.54-0.90) | 0.79 (0.65-0.96) |
| Model 2 | ref | 0.81 (0.61-1.06) | 0.85 (0.66-1.10) | 0.66 (0.50-0.86) | 0.77 (0.63-0.94) |
| Ischemic heart disease mortality | 74/7,689 | 22/4,360 | 37/5,216 | 29/5,546 | – |
| Crude model | ref | 0.52 (0.32-0.83) | 0.75 (0.50-1.11) | 0.52 (0.34-0.80) | 0.60 (0.44-0.81) |
| Model 1 | ref | 0.62 (0.38-1.00) | 0.87 (0.58-1.29) | 0.58 (0.37-0.89) | 0.69 (0.50-0.94) |
| Model 2 | ref | 0.60 (0.37-0.97) | 0.86 (0.57-1.30) | 0.56 (0.35-0.87) | 0.67 (0.48-0.94) |
| Cerebrovascular mortality | 48/7,689 | 15/4,360 | 21/5,216 | 12/5,546 | – |
| Crude model | ref | 0.54 (0.30-0.97) | 0.65 (0.39-1.09) | 0.33 (0.18-0.63) | 0.50 (0.34-0.75) |
| Model 1 | ref | 0.72 (0.40-1.29) | 0.84 (0.50-1.42) | 0.41 (0.21-0.78) | 0.64 (0.43-0.97) |
| Model 2 | ref | 0.67 (0.37-1.21) | 0.82 (0.48-1.39) | 0.39 (0.20-0.75) | 0.62 (0.40-0.96) |
| Cancer mortality | 173/7,689 | 88/4,360 | 98/5,216 | 123/5,546 | – |
| Crude model | ref | 0.89 (0.69-1.15) | 0.85 (0.66-1.09) | 0.95 (0.76-1.20) | 0.90 (0.75-1.08) |
| Model 1 | ref | 0.95 (0.73-1.23) | 0.86 (0.67-1.10) | 0.89 (0.70-1.13) | 0.89 (0.74-1.08) |
| Model 2 | ref | 0.97 (0.74-1.26) | 0.86 (0.67-1.11) | 0.89 (0.70-1.14) | 0.90 (0.74-1.10) |
| Other cause mortality | 134/7,689 | 51/4,360 | 55/5,216 | 70/5,546 | – |
| Crude model | ref | 0.66 (0.48-0.92) | 0.61 (0.45-0.84) | 0.70 (0.52-0.94) | 0.66 (0.53-0.83) |
| Model 1 | ref | 0.77 (0.56-1.07) | 0.68 (0.50-0.94) | 0.74 (0.55-0.99) | 0.73 (0.58-0.92) |
| Model 2 | ref | 0.80 (0.57-1.10) | 0.72 (0.52-1.00)* | 0.78 (0.58-1.06) | 0.77 (0.61-0.96) |

Values are events/n subjects or hazard ratio (95% confidence interval). Model 1 = hazard ratios with 95% confidence interval obtained from the multivariable model adjusted for age, sex, and energy intake. Model 2 = as in model 1 and further adjusted for educational level, occupational class, smoking, leisure-time physical activity, cardiovascular disease, cancer, drugs for diabetes, lipid-lowering drugs, medication for hypertension, Mediterranean Diet Score (not including sweet pepper intake), sweet pepper intake (g/day, ordered quartiles), garlic, parsley, black pepper (consumption yes/no). *$p < 0.05$.

ref = reference.

effect modifier of the relation between chili pepper and mortality risk.

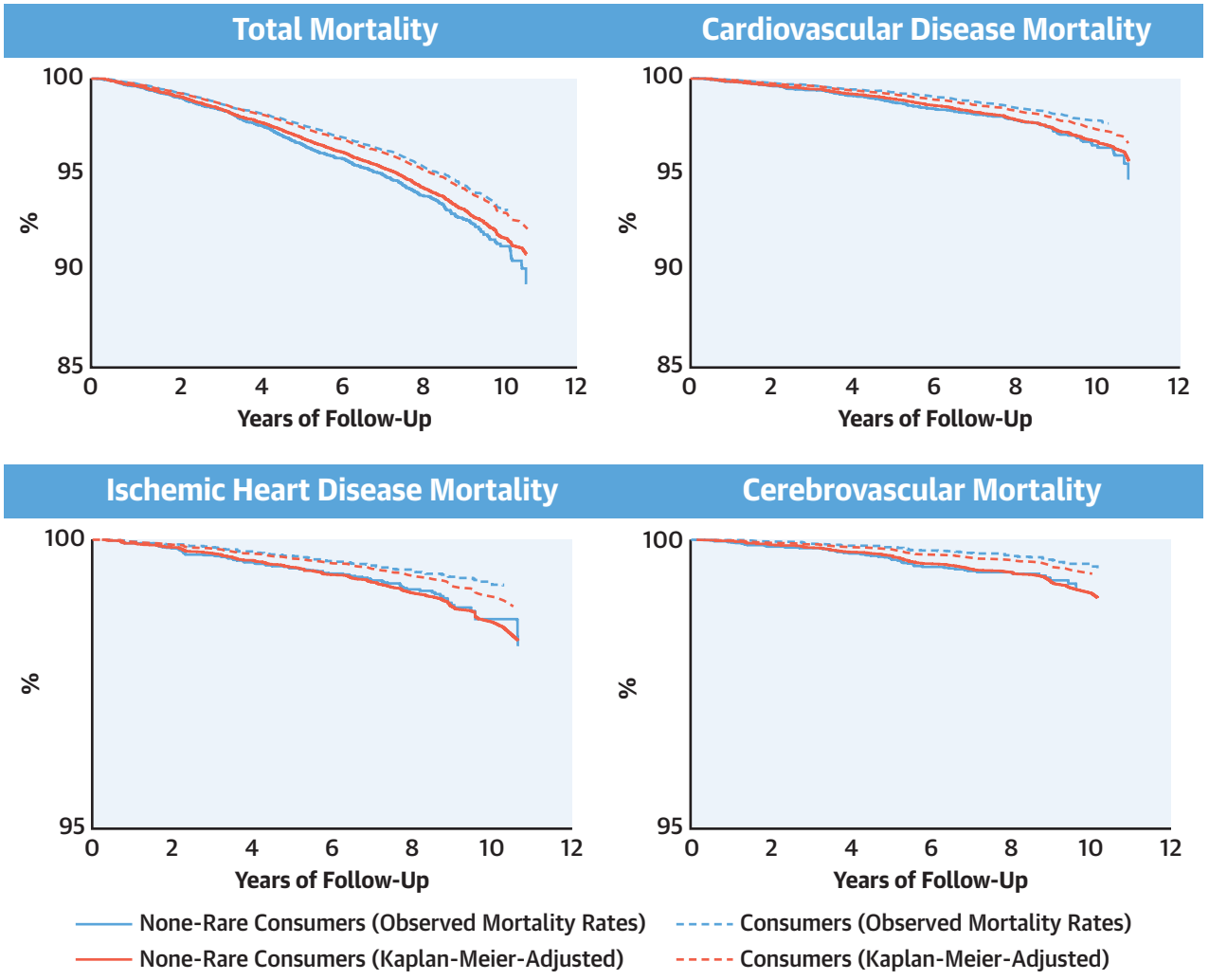
Risk of CVD mortality associated with a 1 SD increment in the MDS was 0.92 (95% CI: 0.83 to 1.02) and became 0.89 (95% CI: 0.80 to 0.98) in association with 1 SD increment in the MDS "supplemented" with chili pepper. Similarly, risk reduction of IHD/cerebrovascular death went from 14% to 19%, whereas no substantial modifications were observed for cancer and other causes of mortality (data not shown). The inclusion of chili pepper consumption as an additional component of the traditional MDS did not improve discrimination ability of the model, with the exception of cerebrovascular mortality. However, the improved prediction associated with the MDS supplemented with chilies was slightly over the model including the traditional MDS (integrated discrimination improvement = 0.005; p = 0.026; NRI = 0.010; p = 0.66; p value for difference in area under the curve = 0.31) (Online Table 4).

## DISCUSSION

Findings from this large Mediterranean population-based cohort show that regular consumption of chili pepper is associated with lower risk of total and CVD mortality, with larger magnitude observed for IHD and cerebrovascular-related deaths. On the contrary, no cancer death risk reduction was found, whereas regular intakes were associated with lower risk of other causes of mortality.

Our findings are in agreement and corroborate the main results of 2 earlier studies from non-Mediterranean cohorts. Evidence from the China Kadoorie Biobank on about 500,000 men and women (11) showed that regular consumption of spicy food (almost every day) lowered the risk of total mortality by 14% and of IHD death by 22%; reductions were also observed for deaths due to cancer (−8%), or respiratory diseases (−29%). More recently, in the large NHANES (National Health and Nutrition Examination

**CENTRAL ILLUSTRATION** **Chili Pepper and Mortality**




**Bonaccio, M. et al. J Am Coll Cardiol. 2019;74(25):3139–49.**

Observed rates and Kaplan-Meier estimates for all-cause, cardiovascular disease, ischemic heart disease, and cerebrovascular mortality for consumers and none/rare-consumers of chili pepper in the Moli-sani Study cohort. Kaplan-Meier estimates were obtained from the multivariable model adjusted for age, sex, educational level, occupational class, smoking, leisure-time physical activity, cardiovascular disease, cancer, drugs for diabetes, lipid-lowering drugs, medication for hypertension, Mediterranean diet score (not including sweet pepper intake), sweet pepper intake (g/day, ordered quartiles), garlic, parsley, black pepper (consumption yes/no), and energy intake (kcal/day).

Survey) cohort, the consumption of hot red chili peppers appeared to be associated with a 13% reduction in total mortality risk (12).

Our study reveals that the health benefits associated with chili pepper intake are independent of the overall quality of the diet, as measured by a traditional Mediterranean diet, thus suggesting an independent effect of chili pepper toward mortality risk. Moreover, risk estimates for total and cause-specific mortality in the minimally adjusted and fully adjusted multivariable models were very similar, suggesting that, although chili pepper consumption was associated with several risk factors for CVD, its relationship with total or cause-specific mortality was independent from such factors.

Furthermore, sensitivity analysis showed that the association between chili consumption and mortality was similar across risk factor categories, with the exception of hypertension, where the association was significantly stronger in normotensive subjects,

**TABLE 3 Mediation Analysis for the Association of Chili Pepper Intake With Total and Cause-Specific Mortality Risk**

| | Chili Pepper Consumption | | | |
|---|---|---|---|---|
| | None/Rare Consumers (n = 7,689) | Consumers (n = 15,122) | PTE (%) | PTE p Value |
| All-cause mortality, deaths | 500 (6.5) | 736 (4.9) | – | |
| Model 2 | ref | 0.81 (0.72-0.92) | – | |
| Model 2 + cardiac troponin | ref | 0.81 (0.72-0.91) | Null | |
| Model 2 + natriuretic peptide | ref | 0.82 (0.72-0.92) | Null | |
| Model 2 + biomarkers of renal function | ref | 0.82 (0.72-0.92) | Null | |
| Model 2 + biomarkers of glucose metabolism | ref | 0.81 (0.72-0.91) | Null | |
| Model 2 + biomarkers of lipid metabolism | ref | 0.82 (0.73-0.93) | 5.3 [1.6-16.5] | 0.033 |
| Model 2 + serum vitamin D (ng/ml) | ref | 0.83 (0.73-0.93) | 6.1 [2.0-16.6] | 0.014 |
| Model 2 + inflammatory biomarkers | ref | 0.81 (0.72-0.91) | Null | |
| Model 2 + BP + BMI | ref | 0.82 (0.73-0.92) | 2.4 [0.4-13.1] | 0.12 |
| Cardiovascular mortality, deaths | 193 (2.5) | 251 (1.7) | – | |
| Model 2 | ref | 0.77 (0.63-0.94) | – | |
| Model 2 + cardiac troponin | ref | 0.75 (0.62-0.93) | Null | |
| Model 2 + natriuretic peptide | ref | 0.76 (0.62-0.93) | Null | |
| Model 2 + biomarkers of renal function | ref | 0.77 (0.63-0.95) | 1.7 [0.0-38.2] | 0.28 |
| Model 2 + biomarkers of glucose metabolism | ref | 0.76 (0.62-0.94) | Null | |
| Model 2 + biomarkers of lipid metabolism | ref | 0.77 (0.63-0.95) | 3.1 [0.2-31.0] | 0.21 |
| Model 2 + serum vitamin D (ng/ml) | ref | 0.78 (0.64-0.96) | 5.9 [1.4-21.9] | 0.048 |
| Model 2 + inflammatory biomarkers | ref | 0.76 (0.62-0.93) | Null | |
| Model 2 + BP + BMI | ref | 0.77 (0.63-0.94) | Null | |
| Ischemic heart disease mortality, deaths | 74 (1.0) | 88 (0.6) | – | |
| Model 2 | ref | 0.67 (0.48-0.94) | – | |
| Model 2 + cardiac troponin | ref | 0.67 (0.48-0.93) | Null | |
| Model 2 + natriuretic peptide | ref | 0.67 (0.48-0.93) | Null | |
| Model 2 + biomarkers of renal function | ref | 0.67 (0.48-0.93) | Null | |
| Model 2 + biomarkers of glucose metabolism | ref | 0.66 (0.47-0.92) | Null | |
| Model 2 + biomarkers of lipid metabolism | ref | 0.66 (0.48-0.92) | Null | |
| Model 2 + serum vitamin D (ng/ml) | ref | 0.68 (0.48-0.95) | 2.7 [0.2-29.2] | 0.20 |
| Model 2 + inflammatory biomarkers | ref | 0.67 (0.48-0.93) | Null | |
| Model 2 + BP + BMI | ref | 0.67 (0.48-0.93) | Null | |
| Cerebrovascular mortality, deaths | 48 (0.6) | 48 (0.3) | – | |
| Model 2 | ref | 0.62 (0.40-0.96) | – | |
| Model 2 + cardiac troponin | ref | 0.61 (0.39-0.95) | Null | |
| Model 2 + natriuretic peptide | ref | 0.62 (0.40-0.96) | 1.2 [0.0-91.3] | 0.38 |
| Model 2 + biomarkers of renal function | ref | 0.62 (0.40-0.96) | Null | |
| Model 2 + biomarkers of glucose metabolism | ref | 0.62 (0.40-0.96) | 1.0 [0.0-49.8] | 0.33 |
| Model 2 + biomarkers of lipid metabolism | ref | 0.61 (0.39-0.95) | Null | |
| Model 2 + serum vitamin D (ng/ml) | ref | 0.62 (0.40-0.96) | Null | |
| Model 2 + inflammatory biomarkers | ref | 0.61 (0.39-0.94) | Null | |
| Model 2 + BP + BMI | ref | 0.62 (0.40-0.96) | Null | |

*Continued on the next page*

suggesting that the high prevalence of hypertension in chili pepper consumers could partially mask its protective effect on total mortality.

With respect to a potential improvement of risk prediction deriving from the inclusion of chilies into the traditional MDS, we found no significant changes in the discrimination ability of the modified score. The fact that an explanatory variable significantly correlated with the outcome does not lead to improvements in prediction is a well-known and widespread occurrence, and does not entirely devaluate the association between the variable and the outcome (23). More importantly, the association of chili pepper with mortality risk was independent of the adherence to the MD, supporting the notion that minor dietary changes, such as adding chilies to usual diet, could be valuable measures for improving health, especially cardiovascular health, independent of overall diet quality.

We also aimed to examine whether some biological mechanisms could be on the pathway between chili pepper and mortality. Our results showed that the majority of established biomarkers of CVD risk poorly accounted for the observed lower risk of death; only serum vitamin D was likely to explain a modest

**TABLE 3 Continued**

| | Chili Pepper Consumption | | | |
|---|---|---|---|---|
| | None/Rare Consumers (n = 7,689) | Consumers (n = 15,122) | PTE (%) | PTE p Value |
| Cancer mortality, deaths | 173 (2.2) | 309 (2.0) | – | |
| Model 2 | ref | 0.90 (0.74–1.10) | – | |
| Model 2 + cardiac troponin | ref | 0.90 (0.74–1.10) | Null | |
| Model 2 + natriuretic peptide | ref | 0.91 (0.74–1.10) | 1.2 [0.0–71.4] | 0.35 |
| Model 2 + biomarkers of renal function | ref | 0.90 (0.74–1.10) | Null | |
| Model 2 + biomarkers of glucose metabolism | ref | 0.90 (0.74–1.10) | Null | |
| Model 2 + biomarkers of lipid metabolism | ref | 0.91 (0.75–1.11) | 5.8 [0.2–61.9] | 0.21 |
| Model 2 + serum vitamin D (ng/ml) | ref | 0.91 (0.75–1.11) | 8.9 [0.7–57.5] | 0.064 |
| Model 2 + inflammatory biomarkers | ref | 0.90 (0.73–1.09) | Null | |
| Model 2 + BP + BMI | ref | 0.91 (0.74–1.11) | 4.2 [0.1–61.6] | 0.24 |
| Other cause mortality, deaths | 173 (2.2) | 309 (2.0) | – | |
| Model 2 | ref | 0.77 (0.61–0.96) | – | |
| Model 2 + cardiac troponin | ref | 0.75 (0.60–0.95) | Null | |
| Model 2 + natriuretic peptide | ref | 0.77 (0.61–0.97) | Null | |
| Model 2 + biomarkers of renal function | ref | 0.77 (0.61–0.97) | Null | |
| Model 2 + biomarkers of glucose metabolism | ref | 0.77 (0.61–0.96) | Null | |
| Model 2 + biomarkers of lipid metabolism | ref | 0.78 (0.62–0.99) | 7.7 [1.2–35.6] | 0.10 |
| Model 2 + serum vitamin D (ng/ml) | ref | 0.77 (0.61–0.98) | 3.9 [0.8–16.5] | 0.059 |
| Model 2 + inflammatory biomarkers | ref | 0.77 (0.61–0.97) | Null | |
| Model 2 + BP + BMI | ref | 0.77 (0.61–0.98) | 4.0 [0.6–23.9] | 0.13 |

Values are n (%), hazard ratio (95% confidence interval), or PTE [95% confidence interval]. Hazard ratios were obtained from the multivariable model adjusted for age, sex, educational level, occupational class, smoking, leisure-time physical activity, cardiovascular disease, cancer, drugs for diabetes, lipid-lowering drugs, medication for hypertension, Mediterranean Diet Score (not including sweet pepper intake), sweet pepper intake (g/day, ordered quartiles), garlic, parsley, black pepper (consumption yes/no), and energy intake (Kcal/day). Cardiac troponin = high-sensitivity troponin I (pg/ml; logarithm). Natriuretic peptide = N-terminal pro-B-type natriuretic peptide (pg/ml; logarithm). Biomarkers of renal function include cystatin C and creatinine (mg/l; logarithm). Biomarkers of glucose metabolism include blood glucose (mg/dl; logarithm), insulin (pmol/l; logarithm), C-peptide (ng/ml; logarithm). Biomarkers of lipid metabolism = blood cholesterol (mg/dl), high-density lipoprotein cholesterol (mg/dl), triglycerides (mg/dl; logarithm), apolipoprotein A1 (g/l), apolipoprotein B100 (g/l), lipoprotein a (mg/dl). Inflammatory biomarkers include C-reactive protein (mg/l; logarithm), white blood cell count ($\times 10^9$/l; logarithm). BMI was categorized as normal weight, overweight, obese.

BP = blood pressure; BMI = body mass index; Null = not mediating the effect; PTE = percent of exposure effect; ref = reference.

proportion of the relation of chili pepper with total, CVD, and other-cause mortality death risk, while biomarkers of lipid metabolism appeared to slightly mediate the association of chilies with all-cause mortality.

In our population sample, regular chili pepper intake was associated with increased levels of lipids, a finding in agreement with previous epidemiological observations on serum triglycerides from a cohort of Chinese adults, but in apparent contrast with their reported inverse association of spicy food consumption with serum cholesterol (24). By contrast, a human intervention on 27 participants reported that regular consumption of freshly chopped chilies for 4 weeks had no effect on serum lipids and lipoproteins (25).

Other biological mechanisms potentially linking chili peppers to lower mortality risk, especially CVD-related, could be ascribed to the weight loss–promoting properties of chilies (8,9,12): protection against obesity leads indeed to decreased risk of cardiovascular and metabolic diseases; yet, in our population, regular chili pepper consumers were more likely to be obese than nonconsumers, and the inclusion of BMI in the mediating pathways did not substantially affect mortality risk.

Finally, in light of the well-known anti-inflammatory properties of chili peppers (26), we tested the role of inflammatory processes, by 2 widely used biomarkers but failed to detect any attenuation of risk; however, the use of only 2 markers could lead to an underestimation of the role of inflammation as a likely mediating mechanism linking chili pepper consumption to death risk.

None of the biological mechanisms tested were able to explain the health benefits associated with chilies; however, we could not explore other pathways that could link chili pepper intake to improved health outcomes, such as reduced oxidation or antiatherogenic potential (4).

Of note, an inverse association with total and IHD mortality was also observed for sweet peppers, which contain capsaicin in smaller, yet possibly beneficial, amounts, although no effect was observed toward CVD and cerebrovascular mortality risk; these findings suggest that the health advantages associated with chili peppers are likely to be ascribed to the high

**TABLE 4 Subgroup Analysis for the Association of Chili Pepper Intake (Consumers vs. None/Rare-Consumers) With Total and CVD Mortality Risk**

| | Total Mortality | | | CVD Mortality | | |
|---|---|---|---|---|---|---|
| | Deaths/Subjects | HR (95% CI) | p Value for Interaction | Deaths | HR (95% CI) | p Value for Interaction |
| Age <65 yrs | 337/17,613 | 0.74 (0.58–0.94) | 0.51 | 79 | 0.79 (0.47–1.31) | 0.53 |
| Age ≥65 yrs | 899/5,198 | 0.85 (0.74–0.97) | | 365 | 0.78 (0.63–0.97) | |
| Women | 429/11,938 | 0.84 (0.69–1.02) | 0.79 | 162 | 0.93 (0.67–1.28) | 0.29 |
| Men | 807/10,873 | 0.78 (0.67–0.91) | | 282 | 0.66 (0.51–0.84) | |
| Up to lower secondary education | 896/11,918 | 0.85 (0.74–0.98) | 0.22 | 337 | 0.80 (0.64–0.996) | 0.84 |
| Upper secondary/post-secondary | 340/10,893 | 0.73 (0.57–0.92) | | 107 | 0.67 (0.44–1.03) | |
| Nonsmokers | 989/17,568 | 0.84 (0.74–0.96) | 0.71 | 367 | 0.85 (0.69–1.06) | 0.20 |
| Smokers | 247/5,243 | 0.76 (0.58–1.01) | | 77 | 0.53 (0.33–0.85) | |
| Low physical activity | 678/11,545 | 0.82 (0.70–0.96) | 0.79 | 256 | 0.85 (0.66–1.11) | 0.25 |
| High physical activity | 558/11,266 | 0.79 (0.66–0.95) | | 188 | 0.63 (0.46–0.85) | |
| Free from CVD | 956/21,274 | 0.80 (0.70–0.92) | 0.93 | 289 | 0.78 (0.61–0.998) | 0.46 |
| CVD subjects | 235/1,177 | 0.82 (0.62–1.08) | | 131 | 0.64 (0.45–0.93) | |
| Free from cancer | 1,105/21,985 | 0.81 (0.71–0.92) | 0.36 | 415 | 0.72 (0.59–0.88) | 0.069 |
| Cancer subjects | 116/736 | 0.79 (0.53–1.18) | | 25 | 1.72 (0.61–4.85) | |
| Free from diabetes | 1,016/21,442 | 0.82 (0.72–0.94) | 0.75 | 1,016 | 0.74 (0.59–0.92) | 0.70 |
| Subjects with diabetes | 188/1,088 | 0.70 (0.51–0.96) | | 80 | 0.80 (0.48–1.31) | |
| Free from hyperlipidemia | 1,045/20,849 | 0.82 (0.72–0.94) | 0.88 | 359 | 0.79 (0.63–0.98) | 0.86 |
| Subjects with hyperlipidemia | 169/1,756 | 0.83 (0.59–1.16) | | 76 | 0.77 (0.46–1.29) | |
| Free from hypertension | 563/16,203 | 0.68 (0.57–0.81) | 0.021 | 141 | 0.67 (0.47–0.94) | 0.54 |
| Subjects with hypertension | 637/6,231 | 0.94 (0.80–1.12) | | 287 | 0.82 (0.64–1.05) | |
| Low MD (MDS 0–3) | 384/6,898 | 0.91 (0.73–1.12) | 0.32 | 142 | 0.85 (0.60–1.20) | 0.62 |
| Average MD (MDS 4–5) | 545/10,053 | 0.73 (0.61–0.88) | | 196 | 0.77 (0.57–1.04) | |
| High MD (MDS 6–9) | 307/5,860 | 0.85 (0.66–1.10) | | 106 | 0.64 (0.42–0.97) | |
| Healthy subjects* | 710/19,479 | 0.84 (0.71–0.98) | – | 224 | 0.74 (0.56–0.97) | – |
| Excluding early deaths (follow-up >2 yrs) | 1,067/22,642 | 0.81 (0.71–0.92) | – | 373 | 0.78 (0.63–0.96) | – |

Values are n/N or n, unless otherwise indicated. Hazard ratios are obtained from the multivariable model adjusted for age, sex, educational level, occupational class, smoking, leisure-time physical activity, cardiovascular disease, cancer, drugs for diabetes, lipid-lowering drugs, medication for hypertension, MDS (not including sweet pepper intake), sweet pepper intake (g/day, ordered quartiles), garlic, parsley, black pepper (consumption yes/no), energy intake (Kcal/day). Low physical activity = leisure-time physical activity ≤2.27 metabolic equivalent task-hours/day (population median). *Subjects without history of CVD or cancer, nor reporting drugs for diabetes.

CVD = cardiovascular disease; MD = Mediterranean diet; MDS = Mediterranean Diet Score.

content of capsaicin, which is far more abundant in chili than in sweet nonspicy peppers. Similar conclusions were reached by a study revealing a positive correlation between frequency of chili consumption, but not sweet peppers, and muscle strength in adult males (27). However, *Capsicum* species contain a large variety of phytochemicals with well-known antioxidant properties, such as carotenoids (β-carotene), capsaicinoids (capsaicin), and flavonoids (quercetin and luteolin) (28,29). Therefore, a possible synergistic activity of these bioactive compounds cannot be ruled out.

**STUDY STRENGTHS AND LIMITATIONS.** Major strengths of this study include a large sample size, a prospective cohort design, and careful ascertainment of established and potential risk factors for death; moreover, analyses were controlled for several dietary covariates that may be correlated with intake of chili peppers. Finally, it is the first investigation addressing the association of chili pepper intake and mortality risk in a large Mediterranean population.

The present study has, however, several limitations. First, given the observational nature of our investigation, causality can only be suggested, and residual confounding or confounding by unmeasured factors cannot be fully ruled out.

Second, cause-specific mortality analysis in this dataset are limited by the relatively small number of deaths. Lastly, subjects' information was collected at baseline only, thus changes that may have occurred during the follow-up could not be considered.

## CONCLUSIONS

Regular consumption of chili peppers is associated with lower risk of total and CVD mortality in a large Mediterranean cohort of adults. The mechanisms through which chili peppers could lower mortality risk are still unclear, although a modest role was found for traditional CVD risk factors. The inclusion of chili pepper intake into a traditional MDS offered no or small added value in the discrimination ability of the modified score. To the best of our knowledge, this study is the first to report a negative association between chili pepper intake and (all-cause and specific) mortality risk in a Mediterranean prospective

cohort, and to assess possible biological mechanisms underlying such association.

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**ADDRESS FOR CORRESPONDENCE:** Dr. Marialaura Bonaccio, Department of Epidemiology and Prevention, IRCCS Neuromed, Via dell'Elettronica, 86077 Pozzilli (IS), Italy. E-mail: marialaura.bonaccio@neuromed.it. Twitter: @Mbonaccio.

## PERSPECTIVES

**COMPETENCY IN MEDICAL KNOWLEDGE:** In an Italian population, regular consumption of chili peppers is associated with a lower long-term risk of mortality from cardiovascular causes.

**TRANSLATIONAL OUTLOOK:** Further studies are needed to understand the biological mechanisms responsible for apparent beneficial effect of chili peppers on cardiovascular risk.

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**KEY WORDS** cardiovascular mortality, cerebrovascular mortality, chili pepper, inflammation, Mediterranean diet, risk factors, total mortality

**APPENDIX** For supplemental tables and a list of the Moli-sani Study Investigators, please see the online version of this paper.