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Tomato and lycopene consumption is inversely associated with total and cause-specific mortality: a population-based cohort study, on behalf of the International Lipid Expert Panel (ILEP)

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Abstract

No data exist on the associations of dietary tomato and lycopene consumption with total and cause-specific mortality. Using the National Health and Nutrition Examination Surveys 1999–2010, we evaluted the long-term impact of tomato and lycopene intake on total and cause-specific (CHD and cerebrovascular disease) mortality. We also assessed the changes in cardio-metabolic risk factors according to tomato and lycopene intake. Vital status to 31 December 2011 was ascertained. Cox proportional hazard regression models (followed by propensity score matching) were used to investigate the link between tomato and lycopene consumption total, CHD and cerebrovascular mortality. Among the 23 935 participants included (mean age = 47·6 years, 48·8 % men), 3403 deaths occurred during 76·4 months of follow-up. Tomato intake was inversely associated with total (risk ratio (RR) 0·86, 95 % CI 0·81, 0·92), CHD (RR 0·76, 95 % CI 0·70, 0·85) and cerebrovascular (RR 0·70, 95 % CI 0·62, 0·81) mortality. Similar inverse associations were found between lycopene consumption, total (RR 0·76, 95 % CI 0·72, 0·81), CHD (RR 0·73, 95 % CI 0·65, 0·83) and cerebrovascular (RR 0·71, 95 % CI 0·65, 0·78) mortality; these associations were independent of anthropometric, clinical and nutritional parameters. Age and obesity did not affect the association of tomato and lycopene consumption with total, CHD and cerebrovascular mortality. C-reactive protein significantly moderated the link between lycopene and tomato intake with total, CHD and cerebrovascular mortality. ANCOVA showed that participants with a higher tomato and lycopene consumption had a more cardio-protective profile compared with those with a lower intake. Our results highlighted the favourable effect of tomato and lycopene intake on total and cause-specific mortality as well as on cardio-metabolic risk factors. These findings should be taken into consideration for public health strategies.

Key words: **Mortality: Tomatoes: Lycopene: CHD: Cardio-metabolic risk factors: Cerebrovascular disease**

Globally, behavioural parameters including a range of dietary risk factors, for example, low intake of fruit and vegetables, can impair human health and promote disease such as CVD and stroke[1]. A variety of epidemiological evidence indicates that, particularly, cardiovascular health is strongly affected by a healthy diet; fruit and vegetables are considered an important element of a cardio-protective diet[2–4]. Fruit and vegetable consumption in the commonly recommended range (e.g. >5 servings) is associated with 21–26 % reductions in the risk of stroke[5], and with 17–25 % reductions in the risk of CHD[6].

Tomatoes represent one of the most frequently consumed vegetables, just below the consumption of potatoes, lettuce and vegetable salads and onions[7]. Tomatoes are fruits that are rich in lycopene, an antioxidant with immunostimulatory properties, and contain moderate amounts of α- and β-carotene and vitamin C[7,8]. A systematic review reported that tomato or

Abbreviations: AMPM, automated multiple-pass method; apVAT, anthropometrically predicted visceral adipose tissue; CRP, C-reactive protein; DBP, diastolic blood pressure; DM, diabetes mellitus; FBG, fasting blood glucose; FMD, flow-mediated dilation; HR, hazard ratio; HTN, hypertension; NHANES, US National Health and Nutrition Examination Survey; PSM, propensity score matching; RR, risk ratio; SBP, systolic blood pressure; USDA, US Department of Agriculture; WC, waist circumference.

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lycopene supplementation significantly improved CVD risk factors including LDL-cholesterol, IL-6, flow-mediated dilation (FMD) and systolic blood pressure (SBP)[7]. A previous study (*n* 5135) reported that a higher intake of tomato products was significantly associated with a reduced incidence of CVD[9]. No significant link was observed between the risk of stroke and tomato consumption (hazard ratio (HR) 0·99, 95 % CI 0·90, 1·10)[9]. In contrast, another study including 38 445 participants found that tomato product consumption was not significantly related to the risk of CVD and myocardial infarction[10]; however, tomato intake decreased the risk of stroke[10]. A meta-analysis by Song *et al.* showed that dietary lycopene intake was significantly linked to CHD risk (risk ratio (RR) 0·87; 95 % CI 0·76, 0·98) and stroke (RR 0·83; 95 % CI 0·69, 0·96)[11]. The authors concluded that further research is needed to evaluate potential pathways between lycopene/tomato consumption and CVD outcomes, focusing on whether lycopene has independent effects on the risk of CVD[11]. The above-mentioned findings triggered an interest on the effects of lycopene and tomato intake on health outcomes.

To the best of our knowledge, there is currently no study evaluating the association between tomato consumption and mortality (total or cause specific). In this context, we prospectively examined the relationship of tomato and lycopene intake with total and cause-specific (CHD and stroke) mortality. As a secondary objective, we evaluated the changes in cardio-metabolic risk factors according to the tomato and lycopene consumption levels; we implemented these by applying on a nationally representative sample of USA adults. We hypothesised that a higher consumption of tomato and lycopene is associated with a lower risk of total and cause-specific mortality; furthermore, those individuals would have a more favourable cardio-metabolic profile.

Methods

Population

This was a prospective cohort study using data from the US National Health and Nutrition Examination Survey (NHANES). The National Center for Health Statistics Research Ethics Review Board approved the underlying protocol, and written informed consent was obtained from all participants. The present study is based on the analysis of data from 2-year NHANES survey cycles (between 1999 and 2010) restricted to participants aged ≥20 years. Details on the NHANES Laboratory/Medical Technologists Procedures and Anthropometry Procedures are described elsewhere[12,13].

Dietary intake was assessed via 24-h recalls obtained by a trained interviewer, using a computer-assisted dietary interview system with standardised probes, that is, the US Department of Agriculture (USDA) Automated Multiple-Pass Method (AMPM)[14,15]. Briefly, the type and quantity of all beverages and foods consumed in a 24-h period before the interview (from midnight to midnight) were collected by performing AMPM. The AMPM can enhance accurate and complete data collection while reducing respondent burden[15,16]. The USDA food and nutrient database for dietary studies were used to determine the nutrient content of foods.

Cardio-metabolic risk factors

A blood specimen was drawn from an antecubital vein. Fasting blood glucose (FBG) was measured by a hexokinase method using a Roche/Hitachi 911 Analyzer and Roche Modular P Chemistry Analyzer. Levels of TAG were measured enzymatically. Insulin was measured using ELISA (Mercodia)[17]. Serum C-reactive protein (CRP) concentrations were measured by latex-enhanced nephelometry (Seattle, USA)[18,19]. Other laboratory test details are available in the NHANES Laboratory/Medical Technologists Procedures Manual[20]. The anthropometrically predicted visceral adipose tissue (apVAT) was predicted with sex-specific validated equations that included age, BMI, waist circumference (WC) and thigh circumference[21]. The equation for men was 6 × WC – 4·41 × proximal thigh circumference + 1·19 × age – 213·65, and the equation for women was 2·15 × WC – 3·63 × proximal thigh + 1·46 × age + 6·22 × BMI – 92·713[21]. Diabetes mellitus (DM) was diagnosed as a self-reported history of diabetes or fasting plasma glucose ≥126 mg/dl. Hypertension (HTN) was diagnosed in individuals with SBP ≥140 mmHg and/or diastolic blood pressure (DBP) ≥90 mmHg as well as in those taking antihypertensive drugs[22].

A digital scale was used to measure weight to the nearest 100 g and a fixed stadiometer to measure height to the nearest millimetre. BMI was calculated as weight in kg divided by the square of height in metres. WC was measured at the iliac crest to the nearest millimetre, using a steel tape[18].

Mortality

The de-identified and anonymised data of the NHANES 1999–2010 participants were linked to longitudinal Medicare and mortality data using the NHANES assigned sequence number. Mortality follow-up data are available from the date of survey participation until 31 December 2011. We examined all-cause mortality as well as mortality due to CHD (I00–I09, I11, I13, I20–I51) and cerebrovascular disease (I60–I69). Cause of death was determined using the *Tenth Revision* of the *International Classification of Diseases*.

Statistical analysis

Since the present study is of an observational design, it is vulnerable to selection bias[23] to identify a more robust measure of the association between tomato consumption and mortality. Therefore, propensity score matching (PSM) was applied. Analyses were conducted according to the guidelines set by the Centers for Disease Control and Prevention for analysis of the NHANES data set, accounting for the masked variance and using their suggested weighting methodology[24,25]. Continuous and categorical demographic variables were compared across tertiles of tomato and lycopene consumption using ANOVA and χ^2 tests, respectively. Adjusted (for age, sex, race, education, marital status, poverty: income ratio, total energy intake, physical activity, smoking, alcohol consumption and intake of fibre, fat and meat) means of cardio-

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metabolic factors across tomato and lycopene consumption tertiles were calculated using ANCOVA.

Multivariable Cox proportional hazards were performed to determine the HR and 95 % CI of mortality for each quartile of tomato and lycopene intake, with the lowest quartile (Q1) always used as reference. To derive the HR and 95 % CI, we used two different models: model 1: adjusted for age, sex, race, education, marital status, poverty:income ratio, total energy intake, physical activity, smoking and alcohol consumption; and model 2: adjusted for age, sex, race, education, marital status, poverty: income ratio, total energy intake, physical activity, smoking, alcohol consumption, dietary intake of fat, fibre, meat and carbohydrates, BMI, CRP, HTN and DM. A two-sided $P < 0{\cdot}05$ was used to characterise significant results. Data were analysed using the SPSS® complex sample module version 22.0.

Furthermore, we performed sensitivity analyses to evaluate the HR of all-cause mortality in participants in the first quartile (Q1) of tomato intake compared with those in the fourth quartile (Q4) using PSM Cox proportional analyses. PSM was applied to control for confounding factors. PSM was first proposed by Rosenbaum & Rubin in 1983[26]. This statistical method is based on a counterfactual concept and can help reinforce causal arguments in observational studies by reducing selection bias[26]. First, tomato intake (Q1: 0; Q4: 1) was the dependent variable, whereas the confounding factors (age, sex, race, education, marital status, poverty:income ratio, total energy intake, physical activity, smoking, alcohol consumption, BMI, dietary intake of fat, fibre, meat and carbohydrates, CRP, BMI, HTN and DM) were used as covariates. This model yielded a C-index of 0·593 (95 % CI 0·528, 0·611; $P < 0{\cdot}001$), indicating an appropriate ability to differentiate between subjects with lowest and highest tomato intake. For the prediction model, calibration was assessed using the Hosmer–Lemeshow goodness-of-fit test, which showed good calibration ($P = 0{\cdot}312$). Second, treatment case (Q1 of tomato intake) was matched with control case (Q4 of tomato intake) using 1:1 nearest neighbourhood matching.

We also quantified the impact of CRP on the link between lycopene consumption, total, CHD and stroke mortality by applying the moderation model using the SPSS Macro developed by Preacher & Hayes[27]. By applying this Macro, we could simultaneously test the moderator impact of the variable of interest, CRP, adjusting for the confounding factors. Furthermore, this approach permitted the visualisation of the impact of each standard deviation change in the potential moderators on the relationship between independent and dependent variables. We tested for the presence of CRP effect in the adjusted (for age, sex, race, education, marital status, poverty:income ratio, total energy intake, physical activity, smoking, alcohol consumption, dietary intake of fat, fibre, meat and carbohydrates, BMI, HTN and DM) model.

Results

General information

Overall 23 935 participants were included, with a mean age of 47·6 years, comprising 48·8 % men. The demographic characteristics of the participants according to tomato and lycopene consumption are shown in Table 1. Individuals with a higher tomato intake (1·8 cups/d) were significantly younger compared with those with the lowest tomato consumption (0·02 cups/d) (43·3 *v.* 49·2 years, respectively, $P < 0{\cdot}001$; Table 1). Men consisted the majority in the highest compared with the lowest tomato consumption group (53·0 *v.* 47·0 %, respectively, $P < 0{\cdot}001$), whereas women had the highest percentage in the lowest category (53·6 *v.* 46·4 %, respectively, $P < 0{\cdot}001$; Table 1). With regard to race/ethnicity, in the highest tomato intake group, the distribution was as follows: non-Hispanic White (52·4 %), non-Hispanic Black (23·3 %) and Mexican-American (12·2 %) ($P < 0{\cdot}001$; Table 1). The majority of individuals with 'more than high school' education (49·3 %) was in the higher tomato consumption group, while most of those with 'less than high school' education (30·1 %) were in the lowest category (Table 1). Similar results were obtained for the lycopene intake groups (Table 1).

Associations of cardiovascular risk factors with tomato and lycopene intake

The adjusted means of cardiovascular risk factors across the tertiles of tomato and lycopene consumption are presented in Table 2. With increasing tomato intake, participants had more favourable levels of SBP, HDL-cholesterol, FBG, insulin and CRP ($P < 0{\cdot}001$ for all comparisons; Table 2). For example, HDL-cholesterol and SBP were 51·6 mg/dl and 124·1 mmHg for subjects in the lowest tomato consumption group, increasing to 53·6 mg/dl and 120·6 mmHg, respectively, for those in the highest tomato intake group. In contrast, no significant changes were found for BMI, WC, apVAT, DBP and TAG across tomato consumption groups (Table 2).

Furthermore, as the consumption of lycopene increased, subjects also had a more protective profile of cardio-metabolic factors, including SBP, DBP, TAG, HDL-cholesterol, FBG and CRP ($P < 0{\cdot}001$ for all comparisons; Table 2). For example, both SBP and DBP decreased from 125·1 and 125·1 mmHg in the lowest lycopene intake group, to 121·2 and 68·1 mmHg, respectively, in the highest lycopene consumption group (both $P < 0{\cdot}001$; Table 2). No significant modifications were observed for the anthropometrical parameters (i.e. BMI, WC and apVAT) and insulin levels in relation to lycopene intake (Table 2).

Associations of total, CHD and stroke mortality with tomato and lycopene consumption

A negative link between tomato consumption and total mortality was found both in model 1 (HR 0·79, 95 % CI 0·74, 0·82) and in model 2 (RR 0·86, 95 % CI 0·81, 0·92; Table 3). Similarly, a reverse association was observed between tomato intake, CHD and stroke mortality in both model 1 and model 2 (Table 3). Interestingly, after adjustments for more confounders (in model 2), this link became greater for stroke mortality (model 1: 0·76, 95 % CI 0·69, 0·82, model 2: 0·70, 95 % CI 0·62, 0·81); whereas for CHD death, it remained significant but to a lesser extent (model 1: 0·53, 95 % CI 0·37, 0·73; model 2: 0·76, 95 % CI 0·70, 0·85) (Table 3).

Lycopene intake was also negatively associated with total, CHD and cerebrovascular mortality in both models (Table 3).

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Table 1. Characteristics of the study participants according to tomato and lycopene consumption*
(Mean values with their standard errors; percentages; numbers of participants)

		Tomato consumption (cups consumed/d)				Lycopene consumption (μg) 50th (25th–75th)			
		0·02 (cups consumed/d) (*n* 7869)	0·3 (cups consumed/d) (*n* 7991)	1·8 (cups consumed/d) (*n* 8075)	*P*	485 (265–796) (*n* 8025)	1605 (1029–2685) (*n* 7962)	9365 (5934–12 463) (*n* 7948)	*P*
Age (years)	Mean	49·2	46·1	43·3	<0·001	50	47	44	<0·001
	SE	0·2	0·1	0·2		0·1	0·2	0·1	
Sex	Men (%)	46·4	45·9	53·0	<0·001	46·4	45·1	53·9	<0·001
Race/ethnicity	Mexican-American (%)	19·3	17·4	12·2	<0·001	21·1	19·6	14·1	<0·001
	Non-Hispanic White (%)	46·2	48·1	52·4		47·1	49·6	54·2	
	Non-Hispanic Black (%)	19·6	22·4	23·3		20·4	21·4	22·0	
Marital status	Married (%)	51·3	53·3	52·1	<0·001	52·3	53·1	52·4	<0·001
	Divorced (%)	10·8	10·1	11·2		11·1	10·1	11·4	
	Never married (%)	17·5	9·2	20·1		19·8	17·5	18·6	
Education status	Less than high school (%)	30·1	28·2	27·6	<0·001	28·5	24·3	26·8	<0·001
	Completed high school (%)	24·2	23·9	24·2		25·8	23·2	26·2	
	More than high school (%)	46·3	47·1	49·3		47·6	45·2	48·3	
Mortality status	Total mortality (*n*)	1095	1082	1226	<0·001	1234	1096	1273	<0·001
	CHD mortality (*n*)	268	209	235	<0·001	301	209	202	<0·001
	Cerebrovascular disease mortality (*n*)	73	69	89	<0·001	80	76	57	<0·001

* Groups were compared by either χ^2 or ANOVA.

All associations, however, were slightly weakened after adjusting for more confounders in model 2, as shown in Table 3).

Sensitivity analysis

After matching, no significant difference was observed between subjects at the lowest (Q1) and the highest quartile (Q4) of tomato intake in relation to our confounders. After performing PSM Cox regression, we found that subjects in the highest quartile (Q4) of tomato consumption had a 17 % increased risk of total mortality (RR 0·83, 95 % CI 0·79, 0·91).

In the adjusted model, no difference was found between non-obese and obese (BMI > 30 kg/m^2) subjects, with regard to the link between both tomato and lycopene consumption with total, CHD and stroke mortality (data not shown). Furthermore, the reverse association between lycopene intake, total, CHD and stroke mortality was more pronounced in non-smokers compared with smokers ($P < 0·001$ for all comparisons) (data not shown). This was not observed for tomato intake, thus implying a detrimental role of smoking in the link between lycopene and mortality. No difference was found between older (age > 50 years) and younger adults in relation to the association of both tomato and lycopene consumption with total, CHD and stroke mortality (data not shown).

CRP significantly moderated the relationship between total, CHD and stroke mortality with lycopene intake ($P < 0·001$ for all comparisons). For example, for the same level of lycopene consumption, subjects with higher CRP levels had a greater risk of mortality. In this context, in the adjusted model for CHD mortality, when lycopene intake increased from low (154 μg, mean − SD) to high (224 μg, mean + SD), the risk of CHD mortality among subjects with low CRP levels (0·37 mg/dl, mean − SD) changed from 0·96 to 0·72 (a decrease of 0·24). However, among those at high CRP concentrations (0·47 mg/dl, mean + SD), CHD mortality risk was reduced from 0·97 to 0·92 (a decrease of 0·5). These findings suggest that CRP may strongly modulate the impact of lycopene consumption on CHD mortality, since subjects at higher CRP levels seem to benefit less from lycopene intake compared with those having lower CRP concentrations.

Discussion

By applying on a nationally representative sample of USA adults, we evaluated the impact of tomato and lycopene consumption on total and cause-specific mortality. Furthermore, we investigated the changes in cardio-metabolic risk factors across the tomato and lycopene intake groups. We found that there was the association between total, CHD and stroke mortality with tomato and lycopene intake (i.e. a higher intake of tomato and lycopene consumption was linked to a lower risk of all-cause and cause-specific mortality). These associations were robust even after further adjustments for clinical, dietary and anthropometrical confounders. Furthermore, individuals with a higher tomato and lycopene intake had a more favourable profile of cardio-metabolic risk factors; these relationships were independent of demographic, lifestyle and dietary factors. The beneficial impact of lycopene consumption on total, CHD and

Table 2. Clinical characteristics of the study participants by tomato and lycopene consumption adjusted for age, sex, race, education, marital status, poverty:income ratio, total energy intake, physical activity, smoking, alcohol consumption and intake of fibre, carbohydrate, fat and meat*
(Mean values and standard deviations)

	Tomato consumption							Lycopene consumption						
	Tertile 1		Tertile 2		Tertile 3			Tertile 1		Tertile 2		Tertile 3		
	Mean	SD	Mean	SD	Mean	SD	*P*	Mean	SD	Mean	SD	Mean	SD	*P*
BMI (kg/m^2)	27·9	0·1	28·4	0·1	28·3	0·1	0·283	28·1	0·2	27·9	0·1	28·2	0·2	0·134
Waist circumference (cm)	96·9	0·3	97·5	0·2	97·4	0·3	0·276	97·1	0·2	96·3	0·2	97·1	0·2	0·345
apVAT	180·1	2·9	181·7	2·7	179·3	2·2	0·144	181·6	2·3	181·3	2·4	178·7	2·3	0·483
Systolic blood pressure (mmHg)	124·1	0·2	122·9	0·2	120·6	0·2	<0·001	125·1	0·1	123·9	0·3	121·2	0·2	<0·001
Diastolic blood pressure (mmHg)	69·2	0·3	68·2	0·7	68·4	0·2	0·142	70·1	0·2	69·4	0·4	68·1	0·1	<0·001
TAG (mg/dl)	157·3	2·6	154·6	3·1	155·0	2·9	0·235	158·1	2·2	153·6	3·3	155·3	2·1	<0·001
HDL-cholesterol (mg/dl)	51·6	0·2	52·1	0·3	53·6	0·2	<0·001	51·1	0·1	52·3	0·2	54·1	0·1	<0·001
FBG (mg/dl)	100·2	0·4	99·8	0·3	98·3	0·7	<0·001	100·6	0·2	99·4	0·1	98·7	0·4	<0·001
Insulin (mU/ml)	14·4	0·2	13·8	0·2	13·2	0·3	<0·001	14·1	0·1	13·1	0·2	13·8	0·2	0·246
CRP (mg/dl)	0·41	0·01	0·38	0·01	0·36	0·01	<0·001	0·39	0·02	0·36	0·01	0·34	0·01	<0·001

apVAT, anthropometrically predicted visceral adipose tissue; FBG, fasting blood glucose; CRP, C-reactive protein.
* Adjusted means were compared by ANCOVA.

Table 3. Multivariable-adjusted risk for mortality according to tomato and lycopene consumption*†
(Hazard ratios (HR) and 95 % confidence intervals)

		Tomato consumption						Lycopene consumption					
			Tertile 2		Tertile 3				Tertile 2		Tertile 3		
		Tertile 1: HR	HR	95 % CI	HR	95 % CI	*P*	Tertile 1: HR	HR	95 % CI	HR	95 % CI	*P*
Total mortality	Model 1	1 Reference	0·86	0·81, 0·92	0·79	0·74, 0·82	<0·001	1 Reference	0·73	0·64, 0·84	0·68	0·60, 0·79	<0·001
	Model 2	1 Reference	0·89	0·83, 0·94	0·86	0·81, 0·92	<0·001	1 Reference	0·82	0·78, 0·86	0·76	0·72, 0·81	<0·001
CHD mortality	Model 1	1 Reference	0·60	0·40, 0·81	0·53	0·37, 0·73	<0·001	1 Reference	0·76	0·69, 0·83	0·66	0·48, 0·92	<0·001
	Model 2	1 Reference	0·78	0·70, 0·86	0·76	0·70, 0·85	<0·001	1 Reference	0·81	0·78, 0·86	0·73	0·65, 0·83	<0·001
Cerebrovascular disease mortality	Model 1	1 Reference	0·79	0·68, 0·88	0·76	0·69, 0·82	<0·001	1 Reference	0·75	0·66, 0·88	0·67	0·48, 0·93	<0·001
	Model 2	1 Reference	0·85	0·61, 1·17	0·70	0·62, 0·81	<0·001	1 Reference	0·76	0·55, 1·09	0·71	0·65, 0·78	<0·001

* Model 1: adjusted for age, sex, race, education, marital status, poverty:income ratio, total energy intake, dietary intake of fat, fibre and meat, physical activity, smoking and alcohol consumption
† Model 2: adjusted for age, sex, race, education, marital status, poverty:income ratio, total energy intake, dietary intake of fat, fibre, meat and carbohydrates, physical activity, smoking, alcohol consumption, BMI, C-reactive protein, hypertension and diabetes.

stroke mortality was more pronounced in non-smokers; this was not observed for tomato intake. Finally, CRP was found to significantly mediate the link between lycopene consumption, total, CHD and stroke mortality (i.e. subjects with similar levels of lycopene intake had a greater risk of mortality when they also had higher compared with lower CRP levels).

Lycopene is one of the most potent antioxidants and a predominant carotenoid in human plasma[28]. It is also assumed to be one of the active compounds responsible for the health benefits of tomato[29]. Our results highlight the beneficial impact of both lycopene and tomato consumption on total and cause-specific mortality. A recent meta-analysis of prospective studies was in agreement with the findings from the present study, indicating that dietary intake and/or blood carotenoids which included lycopene were inversely associated with CHD, stroke, CVD, cancer and/or all-cause mortality[30]. Epidemiological evidence indicates an inconsistent association between tomato products and/or lycopene and lower CVD incidence[9,10]. However, to the best of our knowledge, no study has examined the link between tomato or lycopene consumption and death. Furthermore, the majority of the previous original studies has important limitations, including a small sample size and short follow-up[31]. Participant selection, lycopene metabolism, characteristics of lycopene consumption (time, type, quantity, etc.), interaction with other antioxidants and conventional CVD risk factors should be taken into account when conducting and interpreting such studies[31]. In this context, a previous meta-analysis demonstrated that dietary lycopene intake was related to a significant reduction in the risk of both CHD and stroke[11]. The pooled RR was similar for circulating lycopene levels but the only significant association was for stroke[11]. No significance was found in relation to the link between circulating lycopene concentrations and CHD incidence, with a high heterogeneity ($I^2 = 61{\cdot}5$ %), which may be partly due to the small sample size in the CHD subgroup[11]. A previous systematic review, including human intervention trials in relation to the cardio-protective effects of lycopene, demonstrated mixed results[28]. Our findings on the association of lycopene and tomato intake with cardio-metabolic factors are in agreement with earlier reports such as a meta-analysis of 21 studies, showing that lycopene supplementation from different sources significantly reduced the lipid profile[7]. Other meta-analyses also found that lycopene supplementation

significantly improved lipids[31] and BP[31,32]. The BP-lowering properties of lycopene and tomato have been attributed to the stimulation of nitric oxide production in the endothelium[33]. In this context, several studies demonstrated that at least 4 weeks of daily oral supplementation with tomato extract or tomato juice significantly decreased BP[32–37], while others showed no association[38,39]. In contrast, Paterson *et al.* found that lycopene intake (4·5 mg/d, for 4 weeks) could elevate BP[40].

In the present study, subjects with a higher tomato and lycopene intake had lower CRP levels. Similarly, three randomised controlled trials reported beneficial effects of tomato supplementation on CRP concentrations[41–43]; whereas only in one study, tomato intake increased CRP levels[44]. However, in a meta-analysis of twenty-one studies by Chen *et al.*[7], tomato and lycopene supplementation did not affect CRP concentrations. In relation to lycopene supplementation, results are also controversial; only one study reported improvements in CRP levels after lycopene supplementation[35], whereas two studies found increases in CRP concentrations following lycopene consumption[35,43]. No significant changes in CRP levels were reported in another two studies subsequent to lycopene supplementation[42,45]. Furthermore, evidence for the effects of lycopene supplementation on oxidative stress is scarce[44].

A number of potential mechanisms are responsible for our findings. Tomatoes are the primary source of lycopene, the most powerful antioxidant, and are therefore likely to lower oxidative stress (induced by reactive oxygen species, inflammation and platelet aggregation), decrease lipid peroxidation and reduce LDL-cholesterol[46]. Lycopene, the major carotenoid in tomatoes, might be more important than other carotenoids in preventing atherosclerosis and CVD[28]. However, tomatoes contain also other compounds (e.g. antioxidants, such as vitamin C) possessing lipid-lowering properties[47,48]. Potential biological mechanisms by which lycopene could protect against CVD have been suggested, including cholesterol reduction, modulation of inflammatory markers, inhibition of oxidation processes, enhanced intercellular communication, induction of apoptosis and anti-angiogenic effects[31,49]. In this context, it has been widely accepted that lycopene played an important role in the reduction of intracellular cholesterol levels through inhibition of cholesterol synthesis, modulation of LDL receptor and acyl-CoA:cholesterol acyltransferase activity[50].

Implications for health and future research

Our results showed a significant improvement in cardio-metabolic risk factors as well as total and cause-specific mortality across tomato and lycopene intake groups in a nationally representative USA population. These findings may have important implications in the primary and secondary prevention of atherosclerosis, CVD morbidity and mortality. In this context, the seventh report of the Joint National Committee on BP estimated that an SBP reduction of at least 5 mmHg (similar to the observed decline in SBP after lycopene supplementation) could decrease the risk of stroke death by 13–14 %[51] and CVD mortality by 9 %[51]. Results from the Global Burden of Disease Collaboration[52] indicate that cardio-metabolic risk factors, such as HTN (first) and hypercholesterolemia (seventh) as well as behavioural risk factors including low fruit (thirteenth) and vegetable (twentieth) consumption, are among the top thirty leading causes of death and disability.

Strengths and limitations

The misclassification of exposure to tomato and lycopene is unavoidable in dietary assessments. Although we included major possible confounders of lifestyle and dietary factors in the present multivariable analysis, residual or unmeasured confounding might still exist. Furthermore, since this is an observational study, we cannot establish causality between tomato/lycopene consumption and the outcomes. In clinical trials, maintaining high adherence to a dietary intervention for a long time is typically difficult, in part because of dietary changes contradicting participants' long-term dietary references. Hence, poor adherence may dilute the true effect of an intervention. Lycopene content and bioavailability can be influenced by climate, soil, tomato varieties, geography and processing[53]. Furthermore, the preparation method including cooking, which is known to enhance lycopene bioavailability, is also relevant for the association between tomato consumption and risk of mortality. Roasted and fried tomatoes are carriers of salt and fats; acrylamide formation may be an additional problem in tomatoes cooked at temperatures above 120°C[54]. However, information on the way of preparation was not available in the present analysis, thus representing a limitation; prospective studies focusing on this issue are needed. Since data collection in the NHANES was performed on all weekdays, throughout the year, the potential for day-specific information bias is very low[55,56]. It would be nice for the future studies to perform the analysis based on the source of the tomato. Finally, total carotenoid intake was not available in the data set used and thus could not be adjusted for in the analysis.

To the best of our knowledge, this is the first cohort study evaluating the long-term impact of tomato and lycopene consumption on total and cause-specific mortality. The strengths of the present study include the consistency of findings across the cross-sectional data and prospective findings, which reflect the validity of our findings. Furthermore, the validity of the results is strengthened by the evaluation of both tomato and lycopene intake. Circulating levels of tomato and lycopene were not measured in the NHANES, which could provide more valid results. However, it has been reported that lycopene consumption has been associated with higher plasma lycopene concentrations, thus dietary intake could represent a marker of circulating lycopene levels[57].

Conclusions

In a large, nationally representative sample of USA adult population, lycopene and tomato intake were associated with lower risks of total, CHD and stroke mortality as well as with a more favourable cardio-metabolic profile. Smoking could moderate the beneficial impact of lycopene consumption on mortalities. Furthermore, CRP was shown to strongly modulate the link between lycopene intake, total, CHD and cerebrovascular mortality. The present findings provide reasonable and consistent

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evidence supporting the important role of tomato products and lycopene as a part of a healthy cardio-protective diet. These results are useful for policy makers, contributing to increased public awareness about the role of the diet on health and the controversy regarding lycopene and tomato consumption.

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