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FULL RESEARCH PAPER
Nutrition/obesity (diet, alcohol)

Association between tomato consumption and blood pressure in an older population at high cardiovascular risk: observational analysis of PREDIMED trial

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Aims

Clinical studies have produced conflicting evidence on the effects of the consumption of tomatoes on blood pressure, and there are limited data from epidemiologic studies. This study assesses whether tomato consumption (*Solanum lycopersicum* L.) is associated with systolic and diastolic blood pressure, and the risk of hypertension in a prospective 3-year longitudinal study in older adults at high cardiovascular risk.

Methods and results

The present study was carried out within the PREDIMED (Prevención con Dieta Mediterránea) trial involving 7056 (82.5% hypertensive) participants. The consumption of tomato (g/day) was measured using a validated Food Frequency Questionnaire and categorized into four groups: lowest (<44 g), intermediate (44–82 g), upper-intermediate (82–110 g), and highest (>110 g). Multilevel linear mixed models examined blood pressure and tomato consumption association. Cox proportional-hazards models analysed hypertension risk in 1097 non-hypertensive participants, studying risk reductions vs. the lowest tomato consumers. An inverse association between tomato consumption and diastolic blood pressure was observed between the intermediate group β = −0.65 mmHg [95% confidence interval (CI): −1.20, −0.10] and the lowest consumption group. A significant inverse association was observed for blood pressure in grade 1 hypertension

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Conclusion

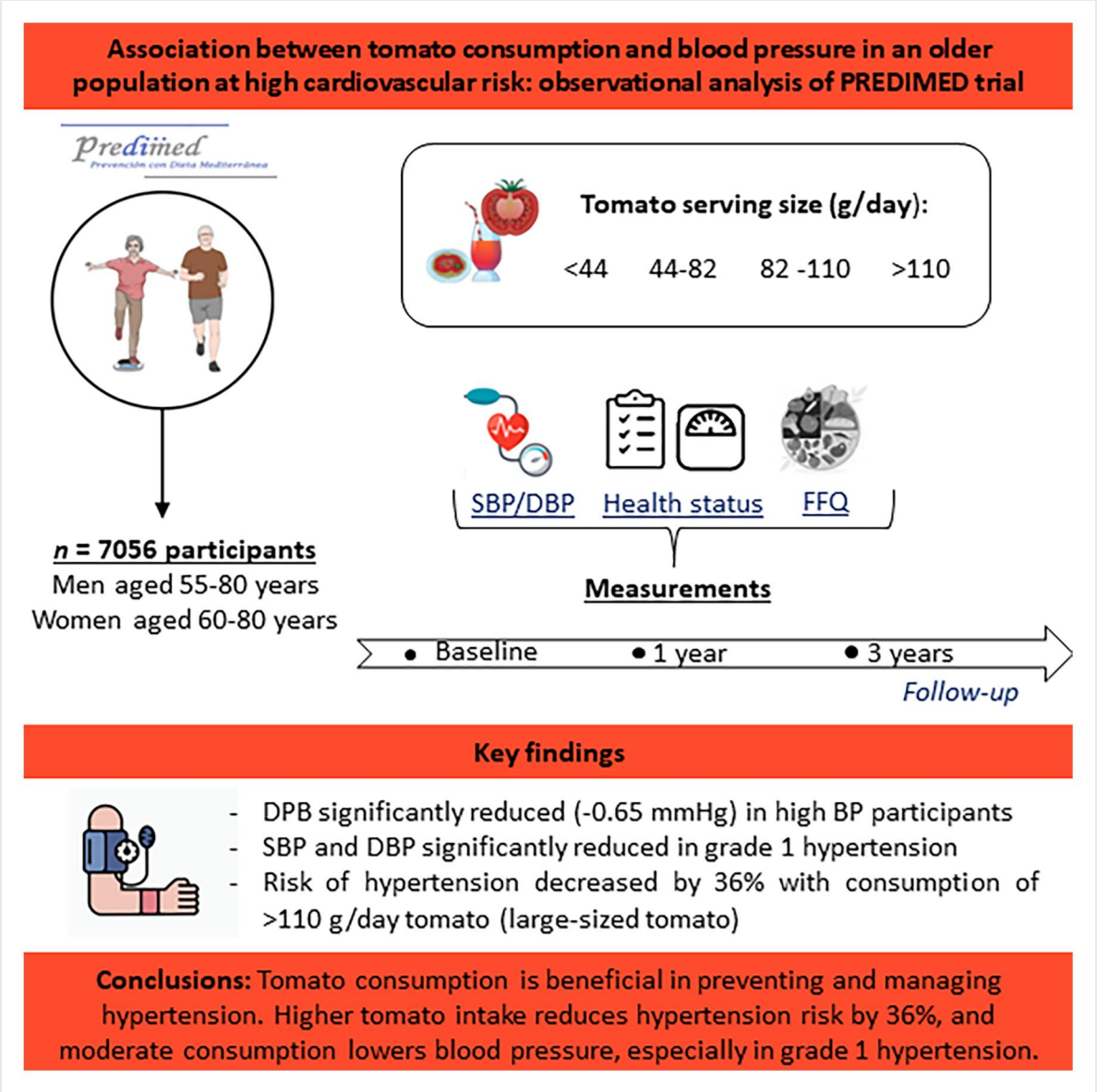
participants in the intermediate tomato consumption group. The risk of hypertension decreased with consumption of >110 g/day tomato (highest vs. lowest consumption; hazard ratio, 0.64 [95% CI, 0.51–0.89]).

Tomato consumption, including tomato-based products, is beneficial in preventing and managing hypertension. Higher tomato intake reduces hypertension risk by 36%, and moderate consumption lowers blood pressure, especially in grade 1 hypertension.

Lay summary

- Tomato consumption may play a favourable clinical role in the prevention and management of elevated blood pressure.
- Tomato consumption was associated with both blood pressure measurements in mildly elevated blood pressure participants.
- A higher consumption of tomato was associated with a reduction in the risk of high blood pressure, equivalent to a large-sized tomato.

Graphical Abstract



Keywords Lycopene • Hypertension • Cardiovascular disease • Observational study • Mediterranean diet • PREDIMED

Introduction

Arterial hypertension is a public health problem worldwide, with prevalence increasing yearly.[1] Approximately 1.16 million [95% uncertainty range (UI): 0.86 to 1.28 million] deaths and 21.5 million (95% UI: 16.4 to 23.9 million) disability-adjusted life years annually are caused by heart disease due to high blood pressure (BP), which affects 18.6 million people globally (95% UI: 13.5 to 24.9 million).[2] The American College of Cardiology/American Heart Association recommends reducing cardiovascular risk factors by the promotion of a healthy lifestyle, including a diet rich in fruits and vegetables.[3]

Tomato is one of the most consumed, widely available, and affordable vegetables worldwide,[4] and it is an important component of the best diets, such as the Mediterranean diet (MedDiet). In 2009, tomato consumption in Spain was 53.3 g/day, tomato puree 0.51 g/day, and preserved tomato 0.46 g/day (mean) in adults according to the Spanish Agency for Food Safety (AESAN).[5] Tomato composition includes water (95%), carbohydrates (3%), protein (1.2%), and lipids (1%), and it also contains non-sodium minerals (calcium, magnesium, phosphorus, potassium, zinc, manganese), vitamins (A, C, thiamine, riboflavin, niacin, pantothenic acid, and pyridoxine), carotenoids, and phenolic compounds.[6] Among the carotenoids, the most abundant is lycopene,[7,8] which is a potent singlet oxygen quencher with antioxidant activity 10-fold higher than vitamin E.[6] Tomato polyphenols include naringenin, caffeic, coumaric, ferulic, and protocatechuic acids.[9] The majority of our lycopene intake in our diet, specifically ~85%, comes from tomatoes and tomato-derived products,[10] and lycopene half-life in plasma ranges from 12 to 33 days.[11] Evidence from experimental and clinical studies supports the beneficial health effects of tomato,[11–13] tomato-based products (e.g. sauce, juice, paste, puree, ketchup, and soup), and even lycopene taken as a supplement.[12–15]

Clinical research has generated mixed results regarding the impact of tomato consumption on BP, and there is a scarcity of information from epidemiological studies. Concerning BP, there is conflicting evidence from clinical trials that tomato consumption may reduce systolic blood pressure (SBP),[11] while lycopene supplementation has been reported to both reduce SBP and diastolic BP (DBP),[14] but there is no general consensus on the effects of tomato intake on BP.[14] Therefore, we assessed whether tomato consumption was associated with SBP and DBP and the risk of hypertension in a prospective 3-year longitudinal study.

Methods

Study population

The PREDIMED study is a large, parallel-group, multicentre, randomized, controlled trial that included 7447 high-risk participants, men (age: 55–80 years) and women (age: 60–80 years), recruited in 11 Spanish primary healthcare centres designed to evaluate the effects of a dietary intervention consuming the MedDiet (supplemented with extra-virgin olive oil (EVOO)/MedDiet supplemented with mixed nuts/Control diet—advice to reduce dietary fat) on cardiovascular events (www.predimed.es). Participant selection considered volunteers who had either type 2 diabetes mellitus or a combination of three or more of the following risk factors: smoking, high BP, high levels of low-density lipoprotein cholesterol, low levels of high-density lipoprotein cholesterol, being overweight or obese, or a family history of early-onset coronary heart disease. The study design and methodology are described in detail elsewhere.[16] The PREDIMED study was registered at http://www.controlled-trials.com/ (ISRCTN35739639) and the study protocol and procedures were approved by the Institutional Review Boards at all study sites (including: Hospital Clínic of Barcelona, the University of Barcelona, Valencia, Rovira-Virgili, Málaga, and Las Palmas, the Municipal Institute for Medical Research, the Primary Care Division of Barcelona and Sevilla, the Institute of Research in Health Sciences at Palma de Mallorca, Hospital Txangorritxu of Vitoria, and the University Hospital of Bellvitge) in accordance with the Declaration of Helsinki. Written informed consent was obtained from the participants. In the present analyses, conducted as an observational prospective study, we included data at baseline, first and third year of follow-up, considering tomato consumption as the exposure.

Dietary and covariate assessment

At baseline and annually thereafter, participants completed questionnaires about sociodemographic and lifestyle factors, health status, medication use (including anti-hypertensive agents, insulin treatment, and cholesterol-lowering drugs), and dietary habits assessed using a validated Food Frequency Questionnaire (FFQ).[17] Physical activity was measured through the validated Spanish version of the Minnesota Leisure Time Questionnaire,[18] and adherence to the MedDiet was evaluated using a 14-item questionnaire (minimum adherence = 0 points, maximum adherence = 14 points).[17] All questionnaires were administered by trained dietitians. Participants were asked to indicate how often they had consumed a certain food item over the previous year through nine response categories ranging from never/almost never to >6 times per day. Energy and nutrient intake were calculated from Spanish food tables.[19,20] Daily tomato consumption was determined from items in the FFQ (raw tomato, tomato sauce, and *gazpacho*—a cold Spanish tomato soup blended with EVOO, garlic, and other vegetables). Daily lycopene intake (mg per grams of consumed food) was calculated from the same items plus watermelon using the FoodData Central database.[21] To facilitate comparisons with the literature, daily tomato consumption was categorized into four groups, based on the average daily intake of lycopene from foods (0.5–5.0 mg/day, intakes up to 8 mg/day) observed in dietary surveys.[22] Hence, the serving sizes were classified as: lowest (<44 g), intermediate (44–82 g), upper-intermediate (82–110 g), and highest (>110 g). Food and nutrient covariates were adjusted for total energy intake using the residual method.[23]

Outcome ascertainment

The primary outcomes of this study were SBP and DBP measurements, in mmHg, obtained in 7056 participants (82.5% with hypertension at baseline). The secondary outcome was new medical diagnoses of arterial hypertension or anti-hypertensive medication initiation (diuretics, angiotensin-converting enzyme inhibitors, beta blockers, and calcium channel blockers) as a sensitivity analysis. Trained personnel measured BP in both arms, with the subject in a seated position, using a semi-automatic oscillometer (Omron HEM—705 CP, Hoofddorp, The Netherlands). At each visit, three measurements were obtained, separated by 2 min, and the average of the second and third measurements was recorded in the data collection form. BP was measured at baseline, one and three years of follow-up. Definitions of hypertension grades in this study are classified as follows: grade 1 hypertension (SBP, 140–159 mmHg and/or DBP, 90–99 mmHg), grade 2 hypertension (SBP, 160–179 mmHg and/or DBP, 100–109 mmHg), and grade 3 hypertension (SBP, ≥ 180 mmHg and/or DBP, ≥ 110 mmHg).[24]

Statistical analyses

Participants with energy intake outside predefined limits (<500 or >3500 kcal/day for women and <800 or >4000 kcal/day for men) were excluded.[25] SPB and DBP were truncated at the 1st and 99th percentiles at baseline to minimize outliers. After exclusions, 7056 participants (82.5% hypertensive) were included in the study (*Figure 1*). Covariates were continuously assessed through repeated measurements at the baseline, after one year, and after three years as a longitudinal dataset. Missing covariates were observed in <13.6% of participants for SBP and DBP, during the follow-up. Missing values were imputed with an expectation-maximization algorithm.[26]

Analyses were performed using Stata (Stata-Corp LP, TX, USA) version 16.1. Normality was verified by the Kolmogorov–Smirnov test. One-factor ANOVA and Pearson χ^2 tests were used to compare the quantitative and categorical variables, respectively. *P*-values of <0.05 were considered significant. The linear trend was tested using orthogonal polynomial contrasts.

Multilevel linear mixed models were generated to assess the association between SBP and DBP and tomato consumption with baseline, first year, and third year measurements included as covariates considering the total sample and a subgroup analysis of hypertension grades. Data were clustered

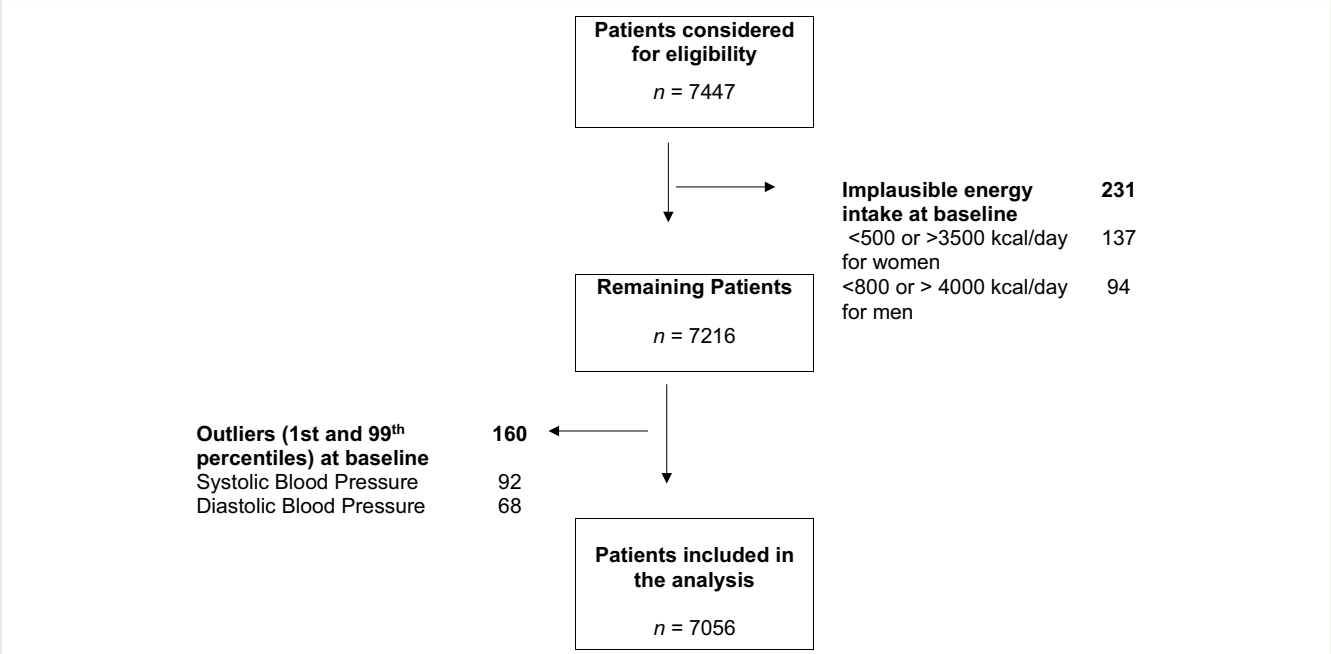


Figure 1 Flow chart of participants throughout the study.

at the recruitment centre level, considering a random intercept for each participant and individual visit. Outcomes were adjusted using three different multivariable models of increasing complexity. Model A included the following covariates: sex (men/women), age (<60/60–70/>70 years), education (primary/secondary/academic-graduate), and intervention group: MedDiet supplemented with EVOO/MedDiet supplemented with mixed nuts/control diet (advice to reduce dietary fat). Model B included the variables of model A plus smoking (never/former/current), body mass index (BMI, kg/m^2), physical activity [<500 metabolic equivalents (METs)-min-week/500–1000 METs-min-week/>1000 METs-min-week], diabetes status (yes/no), hypercholesterolaemia (yes/no), and anti-hypertensive medication (yes/no). Model C further included the variables of model B plus cumulative variables for adherence to the MedDiet (modified 13-point score, excluding tomato-based *sofrito*), energy intake (continuous, kcal/day), alcohol (continuous, g/day), fibre (continuous, g/day), coffee (continuous, g/day), saturated fat (continuous, g/day), fruits (continuous, g/day), and vegetables (continuous, g/day), as well as dietary sodium and potassium ratio (continuous). The intraclass correlation coefficient assessed the reliability agreement in each prediction model.

Additionally, Cox regression models were used to assess the association (hazard ratios—HRs) of the time-to-first event method and compared between groups of tomato consumption (g/day) and hypertension risk in 1097 non-hypertensive participants who were not taking any anti-hypertensive medication at baseline. Data were adjusted in three multivariable models using the baseline covariates described in each previously detailed mixed model. The *E*-value was utilized to evaluate the residual confounding considering unmeasured covariates as a sensitivity analysis.[27] We stratified and did interaction tests for sex. Furthermore, we also investigated dose-response associations using restricted cubic spline (RCS) Cox regression with four knots, using RStudio (version 2023.09.0+463 'Desert Sunflower'), to assess the relationship between tomato consumption (g/day, continuous) and the development of hypertension, using the baseline covariates described in the Cox regression model.

Results

Figure 1 details the flow of participants throughout the study. The participants were elderly men and women (55 to 80 years of age, 57% women) at high cardiovascular risk but no overt cardiovascular disease at enrolment. Participant's baseline characteristics are summarized in *Table 1*. In the highest tomato consumption group, the participants were significantly younger, adherence to the MedDiet was higher, and type 2 diabetes was more prevalent compared to the lowest consumption group. No statistical differences were found in baseline levels of SBP. A total of 73.3% of the participants used anti-hypertensive drugs. Baseline dietary intakes of nutrients and key foods are described in *Table 2*. The participants with highest tomato consumption had a significantly lower intake of total energy, carbohydrates, proteins, fat, sodium, coffee, and alcohol compared to those with lowest tomato consumption, whereas fruit and vegetables consumption, including tomato-based products such as *gazpacho*, was significantly higher. The mean lycopene intake in lowest, intermediate, upper-intermediate, and highest tomato consumption groups was 0.98, 2.1, 3.5, and 5.4 mg/day, respectively. Non-hypertensive participant's baseline characteristics are summarised in *Table 3*.

Linear trends for decreasing SBP and DBP with increasing tomato consumption during the 3-year study period were significant (*Table 4*), except in model C for SBP. A significant inverse association with tomato consumption was observed for SBP and DBP in the crude mixed models (*Figure 2*). In this model, SBP was significantly reduced in the highest vs. lowest tomato consumption group while for DBP a significant reduction was observed in the intermediate vs. lowest tomato consumption group, and in the highest vs. lowest consumption group. The significant inverse associations of tomato consumption with both SBP and DBP remained after adjustment for medication and lifestyle factors. Associations with SBP were no longer significant after adjustment for dietary factors but remained for DBP (*Table 4*).

In the subgroup analysis of hypertension grades (*Table 5*), a significant inverse association was observed for SBP and DBP in grade 1 hypertension for intermediate tomato consumption. No associations were found between tomato consumption and BP in grades 2 and 3 hypertension. In a sensitivity analysis, we excluded anti-hypertensive drug use in grade 1 hypertension participants (see Supplementary material online, *Table S1*).

Table 1 Baseline characteristics of the participants according to groups of energy-adjusted tomato consumption, *n* = 7056

Characteristics	Lowest (<44 g/day) *n* = 1943	Intermediate (44–82 g/day) *n* = 1956	Upper-intermediate (82–110 g/day) *n* = 2019	Highest (>110 g/day) *n* = 1138	*P*-value*
Demographics					
Age, (years) mean (SD)	67.3 (6.3)	67.3 (6.2)	66.7 (6.2)	66.7 (6.1)	**<0.001**
Sex, female	1050 (54.0)	1170 (59.8)	1114 (55.2)	725 (63.7)	**<0.001**
Education (%)					
Academic/graduate	165 (8.5)	124 (6.3)	141 (7.0)	79 (6.9)	**0.06**
Secondary	313 (16.1)	299 (15.3)	295 (14.6)	155 (13.6)	
Primary	1465 (75.4)	1533 (78.3)	1583 (78.4)	904 (79.4)	
Lifestyle and risk factors					
Smoking status (%)					
Never	1148 (59.1)	1245 (63.7)	1209 (59.9)	737 (64.8)	**<0.001**
Former	395 (20.3)	291 (14.9)	326 (16.1)	166 (14.6)	
Current	400 (20.6)	420 (21.5)	484 (24.0)	235 (20.7)	
BMI (kg/m^2)	29.9 (3.7)	30.1 (3.7)	29.8 (4.0)	30.1 (4.0)	**0.012**
Waist circumference (cm)	99.8 (10.4)	100.7 (10.2)	100.6 (10.4)	100.8 (10.3)	**0.017**
BMI status (%)					
Overweight	906 (46.6)	854 (43.7)	946 (46.9)	512 (45.0)	**0.021**
Obese	892 (45.9)	972 (49.7)	898 (44.5)	544 (47.8)	
Abdominal obesity (%)	1267 (66.4)	1357 (71.7)	1346 (68.2)	803 (73.7)	**<0.001**
Low Adh. MedDiet (0–8 score), *n* (%)	1470 (75.7)	1270 (64.9)	1187 (58.8)	583 (51.2)	**<0.001**
Physical activity (METs/min-day)	232.0 (226.0)	233.9 (256.4)	237.6 (245.1)	217.5 (220.0)	0.14
Moderate intensity PA (500–1000 METs-min-week), *n* (%)	1672 (86.1)	1645 (84.1)	1706 (84.5)	939 (82.5)	0.17
Hypertension (%)	1612 (83.0)	1637 (83.7)	1660 (82.2)	915 (80.4)	0.12
Hypercholesterolaemia (%)	1396 (71.8)	1434 (73.3)	1450 (71.8)	815 (71.6)	0.64
Type 2 diabetes (%)	897 (46.2)	952 (48.7)	1002 (49.6)	602 (52.9)	**0.004**
SBP (mmHg)	148.2 (17.9)	148.1 (18.5)	147.6 (17.9)	146.7 (18.2)	0.11
DBP (mmHg)	83.1 (9.7)	82.0 (9.6)	82.0 (9.7)	82.1 (9.6)	**<0.001**
Drug use (*n*, %)					
Anti-hypertensive agents	1442 (74.2)	1467 (75.0)	1446 (71.6)	817 (71.8)	**0.047**
Hypolipidaemic agents	819 (42.2)	905 (46.3)	905 (44.8)	499 (43.9)	0.07
Insulin	106 (5.5)	151 (7.7)	140 (7.0)	90 (7.9)	**0.017**
Aspirin	458 (23.6)	466 (23.9)	418 (20.8)	229 (20.2)	**0.015**
Vitamins supplements	209 (11.0)	247 (12.9)	200 (10.2)	116 (10.5)	**0.041**

Data are given as means (SDs) or *n* (%). *P*-value for comparisons across categories of tomato consumption. $P < 0.05$ considered significant, values shown in bold are statistically significant. BMI, body mass index; Adh. MedDiet, adherence to Mediterranean diet (14-point score); PA, physical activity; SBP, systolic blood pressure; DBP, diastolic blood pressure; cLDL, low-density lipoprotein cholesterol; cHDL, high-density lipoprotein cholesterol; SD, standard deviation.
*Data normality was verified by Kolmogorov–Smirnov test. *P*-value based on one-way ANOVA, or Kruskal–Wallis test was used when assumption of normality was not met, and χ^2 test was used for categorical variables.

Data on hypertension risk in non-hypertensive participants (*Table 6*) showed a 36% (HR, 0.64 [95% confidence interval (CI), 0.51–0.89]) reduced risk with highest tomato consumption in the fully adjusted model, even when the control diet—advice to reduce dietary fat—was followed (44% (HR, 0.56 [95% CI, 0.39–0.81]); Supplementary material online, *Table S2*). Mean follow-up period was ∼1.4 years. The *E*-value in the highest dietary tomato consumers was 2.07 (CI: 1.51). Sex stratified analyses of Cox regression model for tomato consumption and hypertension yielded significance, except in the upper-intermediate tomato consumers in both sexes (see Supplementary material online, *Table S3*).

We found no interaction between tomato consumption and obesity, diabetes mellitus, hypertension or treatment with anti-hypertensive agents (data not shown).

The results of the RCS Cox regression model showed a non-significant J-shaped association between tomato consumption and incidence of hypertension ($P = 0.15$ for curvature).

Discussion

This is the first large longitudinal study to explore the association of the consumption of tomato and tomato-based products with BP and incident hypertension in an elderly population at high risk to develop cardiovascular disease. Results showed that long-term consumption of tomato was associated with a BP-lowering effect, both for SBP and DBP, in grade 1 hypertension. An inverse association between highest tomato consumption (>110 g/day) and incident hypertension was also

Table 2 Baseline dietary pattern of the participants according to groups of energy-adjusted tomato consumption, *n* = 7056

	Lowest (<44 g/day) *n* = 1943	Intermediate (44–82 g/day) *n* = 1956	Upper-intermediate (82–110 g/day) *n* = 2019	Highest (>110 g/day) *n* = 1138	*P*-value*
Nutritional intake					
Total energy intake (kcal/day)	2320.9 (579.2)	2154.3 (505.5)	2342.2 (519.1)	2029.6 (501.0)	**<0.001**
Carbohydrates (g/day)	247.0 (81.3)	224.0 (64.3)	245.5 (71.6)	209.7 (66.9)	**<0.001**
Proteins (g/day)	91.2 (21.9)	88.2 (19.9)	96.5 (21.6)	87.5 (20.4)	**<0.001**
Fat (g/day)	99.6 (28.1)	94.9 (28.5)	101.3 (27.6)	89.1 (26.9)	**<0.001**
Sodium intake (mg/day)	2386.1 (885.2)	2237.4 (774.2)	2527.3 (844.9)	2193.6 (819.4)	**<0.001**
Potassium intake (mg/day)	4075.1 (1032.5)	4110.6 (964.8)	4591.6 (1056.2)	4462.6 (1144.8)	**<0.001**
Dietary sodium:potassium ratio	0.59 (0.20)	0.55 (0.17)	0.55 (0.16)	0.49 (0.16)	**<0.001**
Dietary lycopene (mg/day)	0.97 (1.7)	2.1 (2.1)	3.5 (1.9)	5.4 (3.4)	**<0.001**
Food intake (g/day)					
Dairy	397.7 (235.0)	377.5 (218.8)	379.0 (212.6)	354.1 (209.1)	**<0.001**
Cheese	13.2 (15.7)	13.7 (15.1)	15.9 (17.6)	12.3 (14.7)	**<0.001**
Meat	133.4 (59.6)	126.6 (53.8)	138.5 (58.4)	120.1 (49.0)	0.054
Fish	92.4 (50.2)	96.9 (45.8)	105.2 (53.6)	104.6 (51.3)	**<0.001**
Legumes	20.0 (14.6)	20.5 (13.2)	21.2 (13.7)	20.6 (12.1)	**0.015**
Nuts	9.9 (13.8)	9.4 (12.6)	11.8 (14.9)	8.9 (12.8)	**<0.001**
Vegetables	234.1 (96.8)	293.5 (98.3)	391.8 (113.6)	474.0 (184.4)	**<0.001**
Raw tomato	18.7 (16.9)	50.5 (14.7)	95.1 (12.8)	121.5 (52.3)	**<0.001**
Gazpacho	5.1 (13.8)	11.7 (21.7)	8.1 (17.4)	28.2 (37.2)	**<0.001**
Tomato sauce	1.2 (1.8)	0.9 (1.6)	0.6 (1.4)	0.6 (1.3)	**<0.001**
Fruits	361.3 (210.3)	356.7 (186.5)	376.3 (202.4)	383.6 (204.9)	**<0.001**
Watermelon	23.3 (33.6)	27.5 (43.4)	28.0 (39.4)	38.0 (55.0)	**<0.001**
Cereals	156.8 (94.5)	132.4 (74.7)	151.4 (85.4)	121.32 (73.4)	**<0.001**
Sugar	6.5 (11.3)	5.2 (10.1)	4.7 (9.2)	3.2 (7.6)	**<0.001**
Sweetened beverages	19.4 (65.5)	16.3 (57.1)	18.0 (56.7)	15.0 (55.0)	**0.002**
Total olive oil	39.6 (17.5)	38.7 (18.3)	39.5 (17.4)	37.7 (18.0)	**0.019**
Common olive oil	18.2 (20.6)	17.4 (20.0)	17.6 (19.8)	16.0 (19.1)	**0.03**
Extra-virgin olive oil	20.8 (23.1)	20.8 (23.0)	21.5 (23.2)	21.5 (23.3)	0.64
Butter	0.6 (2.4)	0.4 (1.9)	0.4 (2.0)	0.5 (2.0)	0.40
Margarine	0.9 (2.9)	1.0 (3.0)	1.1 (3.8)	0.9 (2.6)	0.34
Alcohol	10.2 (17.3)	7.4 (12.3)	8.9 (13.9)	5.6 (9.8)	**<0.001**
Coffee	33.9 (51.4)	29.7 (47.0)	30.4 (47.4)	25.7 (45.9)	**<0.001**

Data are given as means (SDs) or *n* (%). *P*-value for comparisons across categories of tomato consumption. $P < 0.05$ considered significant, values shown in bold are statistically significant. SD, standard deviation.

*Data normality was verified by Kolmogorov–Smirnov test. *P*-value based on one-way ANOVA, Kruskal–Wallis test was used when assumption of normality was not met, and χ^2 test was used for categorical variables.

observed. The analyses were robust, as most outcomes retained significance after adjustments for an array of confounders.

In line with these results, recent meta-analyses of the effects of tomato, raw or processed,[11,13,28] found that both SBP and DBP were significantly reduced in hypertensive patients who consumed tomato products from 70 to 400 g/day, standardized tomato extract containing 10–15 mg of lycopene/day, or lycopene at doses ranging from 4 to 30 mg/day. In addition, a prospective cohort study, in a non-Western country, has observed the reduction for new-onset hypertension incidence by 56% when tomato was consumed even in low amounts (10 to 13 g/day) in a population with baseline SBP of 114.1 mmHg and DBP 74.2 mmHg.[29] In uncomplicated grade 1 hypertension, diet modification is key in the initial management before medication prescription,[30] hence tomato consumption may be a vital component in healthy eating plans.

In our study, the absence of an inverse association between tomato consumption and BP in grades 2 and 3 hypertension could be attributed to the elderly nature of the study population, most of whom had long-standing hypertension at baseline, as well as high cardiovascular risk factors (obesity, blood cholesterol, and co-existing diabetes), that difficult to reach significant changes.[31] In fact, ageing brings physiological changes that may affect BP control and individual response to medication for hypertension, including arterial stiffness, changes in renin and aldosterone levels, decreased renal function, and changes in autonomic nervous system sensitivity and endothelial function.[32] Moreover, lycopene bioavailability and the carotenoid level are also influenced by body composition, hormone changes, and genetic variations affecting absorption and metabolism during ageing.[33,34]

Interestingly, health benefits in reducing elevated BP, even low changes, on the circulatory system and cardiovascular risk well

Table 3 Baseline characteristics of non-hypertensive participants at baseline according to groups of energy-adjusted tomato consumption, *n* = 1097

Characteristics	Lowest (<44 g/day) *n* = 296	Intermediate (44–82 g/day) *n* = 284	Upper-intermediate (82–110 g/day) *n* = 318	Highest (>110 g/day) *n* = 199	*P*-value*
Demographics					
Age, (years) mean (SD)	65.6 (6.2)	65.9 (6.7)	65.7 (6.1)	65.4 (6.0)	**<0.001**
Sex, female	124 (25.2)	124 (25.2)	140 (28.3)	105 (21.2)	0.097
Education (%)					
Academic/graduate	27 (9.1)	17 (6.0)	19 (6.0)	26 (13.1)	**<0.001**
Secondary	67 (22.6)	45 (15.8)	40 (12.6)	23 (11.6)	
Primary	202 (68.2)	222 (78.2)	259 (81.4)	150 (75.4)	
Lifestyle and risk factors					
Smoking status (%)					
Never	133 (44.9)	139 (48.9)	150 (47.1)	116 (58.3)	0.074
Former	71 (23.9)	73 (25.7)	83 (26.1)	43 (21.6)	
Current	92 (31.1)	72 (25.4)	85 (26.7)	40 (20.1)	
BMI (kg/m^2)	29.0 (3.6)	29.3 (3.8)	28.1 (3.6)	28.9 (3.7)	**<0.001**
Waist circumference (cm)	99.2 (9.5)	99.4 (10.8)	97.7 (10.2)	99.0 (10.5)	**<0.001**
BMI status (%)					
Overweight	163 (55.1)	141 (49.7)	170 (53.5)	107 (53.8)	**0.007**
Obese	104 (35.1)	114 (40.1)	91 (28.6)	71 (35.6)	
Abdominal obesity (%)	168 (57.9)	158 (57.0)	171 (54.8)	117 (62.5)	0.402
MedDiet (0–8 score), *n* (%)	219 (73.9)	185 (65.1)	198 (62.2)	109 (54.7)	**<0.001**
Physical activity (METs/min-day)	254.6 (247.6)	291.7 (351.8)	264.7 (265.5)	224.7 (233.3)	**<0.001**
Moderate intensity PA (500–1000 METs-min-week), *n* (%)	254 (85.8)	261 (91.9)	283 (88.9)	168 (84.4)	**0.042**
Hypercholesterolaemia (%)	181 (61.2)	192 (67.6)	177 (55.7)	131 (65.8)	**0.014**
Type 2 diabetes (%)	216 (73.0)	209 (73.6)	250 (78.6)	142 (71.4)	0.226
SBP (mmHg)	138.1 (16.5)	139.0 (16.2)	140.9 (18.1)	138.0 (16.8)	**<0.001**
DBP (mmHg)	78.9 (9.3)	78.5 (8.6)	78.9 (9.4)	78.5 (8.2)	**<0.001**
Nutritional intake					
Total energy intake (kcal/day)	2387.1 (582.0)	2237.1 (523.1)	2406.8 (532.6)	2091.2 (565.7)	**<0.001**
Carbohydrates (g/day)	244.3 (78.3)	225.6 (63.6)	246.7 (72.0)	213.4 (76.1)	**<0.001**
Proteins (g/day)	94.4 (22.9)	92.4 (20.8)	101.1 (23.7)	89.1 (22.0)	**<0.001**
Fat (g/day)	104.5 (28.5)	100.2 (30.8)	104.7 (28.2)	92.0 (30.3)	**<0.001**
Sodium intake (mg/day)	2553.8 (931.2)	2427.6 (862.7)	2653.5 (865.5)	2314.5 (939.2)	**<0.001**
Potassium intake (mg/day)	4128.2 (1110.1)	4208.1 (971.2)	4705.2 (982.6)	4547.8 (1235.6)	**<0.001**
Dietary lycopene (mg/day)	1.1 (1.8)	2.2 (1.9)	3.8 (2.4)	5.5 (3.7)	**<0.001**
Raw tomato (g/day)	18.9 (17.2)	52.4 (15.6)	96.5 (12.2)	121.0 (51.9)	**<0.001**
Gazpacho (g/day)	6.7 (23.8)	12.7 (20.7)	7.7 (15.2)	30.8 (41.0)	**<0.001**
Tomato sauce (g/day)	1.1 (1.8)	0.9 (1.7)	0.7 (1.5)	0.6 (1.4)	**<0.001**

Data are given as means (SDs) or *n* (%). *P*-value for comparisons across categories of tomato consumption. $P < 0.05$ considered significant, values shown in bold are statistically significant. BMI, body mass index; Adh. MedDiet, adherence to Mediterranean diet (14-point score); PA, physical activity; SBP, systolic blood pressure; DBP, diastolic blood pressure; SD, standard deviation.

*Data normality was verified by Kolmogorov–Smirnov test. *P*-value based on one-way ANOVA, or Kruskal–Wallis test was used when assumption of normality was not met, and χ^2 test was used for categorical variables.

established.[30] According to a comprehensive meta-analysis, a 10 mmHg reduction in SBP could reduce cardiovascular disease risk by 20%, coronary heart disease by 17%, stroke by 27%, heart failure by 28%, and all-cause mortality by 13%.[35] At the population-level, decreasing 2–5 mmHg (mean) BP could also reduce fatal cardiovascular disease risk by 9%, stroke by 14%, and all-cause mortality by 7%.[30,36] An interesting result from the subgroup hypertension grades in our study, suggest that even a consumption of tomato (44–82 g/day), equivalent to one-half or one medium portion, respectively, lowers BP in grade 1 hypertension patients.

The cardioprotective mechanisms involved in the reduction of BP could be attributed to the presence of lycopene, particular flavonoid compounds, and ascorbic acid in tomatoes by their antioxidant, anticancer, and anti-inflammatory effects.[37] Tomatoes contain a significant amount of lycopene, and it is the most studied tomato component.[6] Lycopene not only inhibits the angiotensin-converting enzyme and its gene expression, thus blocking the production of angiotensin II, a vasoconstrictor that increases BP,[38] but can also indirectly increase nitric oxide generation in the endothelium.[11] Lower levels of nitric oxide, through reactive oxygen species, induce oxidative stress causing

Table 4 Mixed-effect linear regression model for the association between total tomato consumption (g/day), and systolic and diastolic blood pressure as outcomes

Tomato consumption	Lowest (<44 g/day) n = 4125	Intermediate (44–82 g/day) n = 4911				Upper-intermediate (82–110 g/day) n = 5481				Highest (>110 g/day) n = 3763				*P*-trend	ICC
		β	CI (95%)		*P*-value	β	CI (95%)		*P*-value	β	CI (95%)		*P*-value		
SBP															
Model A	Ref.	−0.43	−1.39	0.54	0.39	−0.74	−2.25	0.77	0.34	−2.80	−4.69	−0.90	**0.004**	**0.025**	0.51
Model B	Ref.	−0.52	−1.49	0.45	0.29	−0.76	−2.26	0.74	0.32	−2.91	−4.84	−0.98	**0.003**	**0.018**	0.49
Model C	Ref.	−0.05	−0.93	0.84	0.92	−0.10	−2.06	1.85	0.92	−0.08	−2.38	2.23	0.95	1.00	0.51
DBP															
Model A	Ref.	−0.97	−1.60	−0.33	**0.003**	−1.08	−2.31	0.14	0.08	−1.96	−3.30	−0.63	**0.004**	**0.001**	0.53
Model B	Ref.	−0.99	−1.58	−0.41	**0.001**	−1.08	−2.26	0.10	0.07	−1.93	−3.22	−0.65	**0.003**	**0.000**	0.51
Model C	Ref.	−0.65	−1.20	−0.10	**0.021**	−0.67	−1.97	0.64	0.32	−0.46	−1.97	1.05	0.55	**0.010**	0.53

Multilevel linear mixed models (with independent structure correlation matrix, with maximum likelihood, standard errors and variance of the estimates by clustering at recruitment centres level) with a random intercept for each participant and individual visit (baseline, first year, and third year) to conduct this analysis. Multivariable model A: sex (male/female), age (<60/60–70/>70), education (primary/secondary/higher), intervention group (MedDiet supplemented with EVOO/MedDiet supplemented with mixed nuts/control diet (advice to reduce dietary fat). Model B: those variables given in model A plus BMI (continuous), smoking (never/former/current), physical activity (<500 METs-min-week/500–1000 METs-min-week/>1000 METs-min-week), diabetes status (yes/no), hypercholesterolaemia status (yes/no), anti-hypertensive medications (yes/no). Model C: those variables given for the model B plus cumulative variables for adherence to MedDiet (modified 13-point score), energy intake (continuous), alcohol (continuous), fibre (continuous), dietary sodium and potassium ratio (continuous), coffee (continuous), saturated fat (continuous), fruits (continuous), and vegetables (continuous). Nutritional covariates were adjusted for total energy. $P < 0.05$ considered significant, values shown in bold are statistically significant.

SBP, systolic blood pressure; DBP, diastolic blood pressure; BMI, body mass index; MedDiet, Mediterranean diet; β, beta regression coefficient; CI, confidence interval; ICC, intraclass correlation.

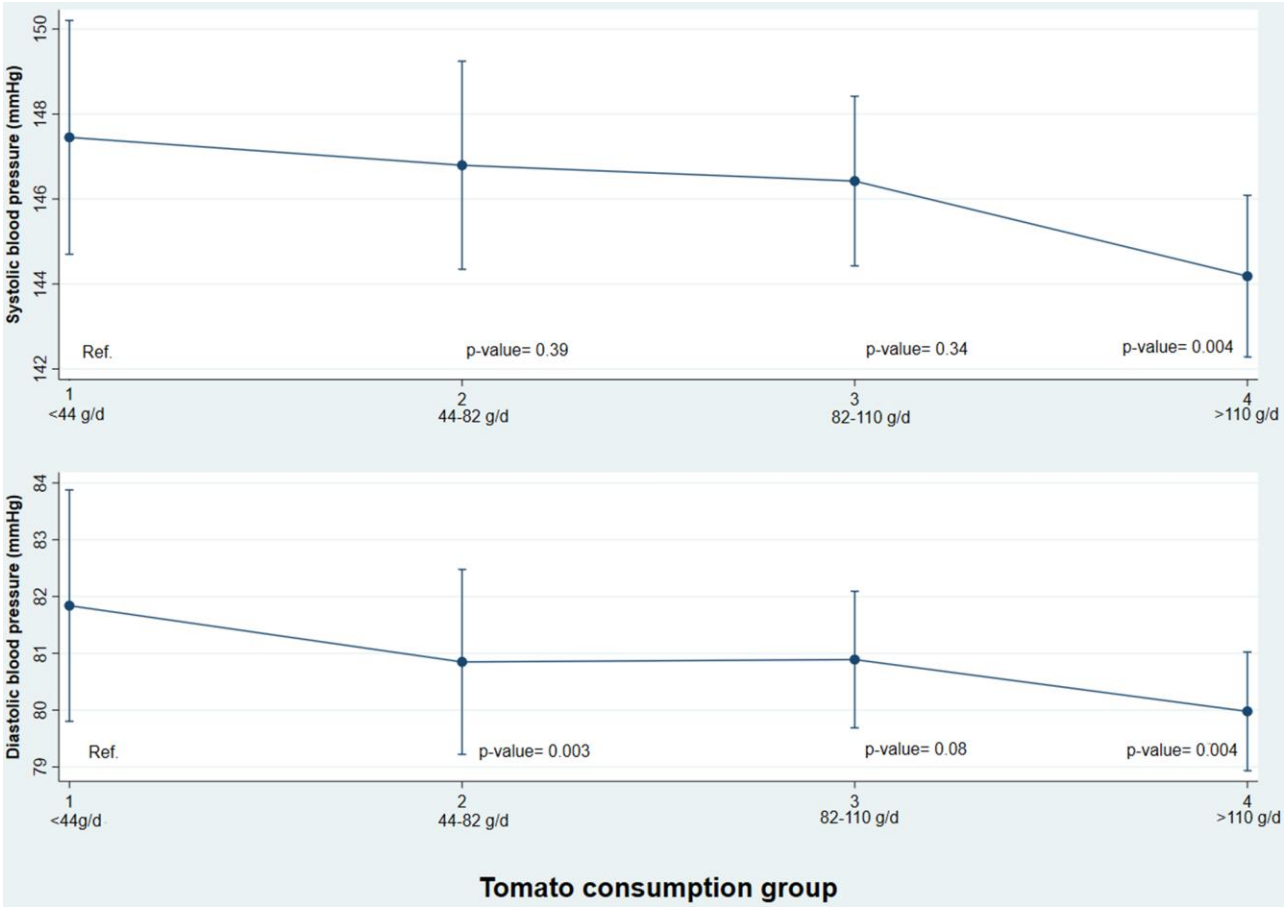


Figure 2 Adjusted mean systolic and diastolic blood pressure for each tomato consumption group with 95% CIs. Values are adjusted for sex, age group, education, and intervention group. (i) Lowest (<44 g/day), (ii) intermediate (44–82 g/day), (iii) upper-intermediate (82–110 g/day), and (iv) highest (>110 g/day) tomato consumption.

changes in the structure of blood vessels,[38] increasing vascular growth, migration,[38] and leading to endothelial dysfunction and thrombotic activity by inhibiting platelet adhesion and aggregation.[11] Bioactive tomato compounds have also demonstrated protective action against inflammation caused by certain chemical mutagens (lipopolysaccharide, hydrogen peroxide, and methyl methanesulphonate), suppressing proinflammatory molecules such as interleukins, TNF-a, cyclooxygenase, and NF-κB.[39,40] Lycopene also triggers the activation of the antioxidant response element, leading to the synthesis of cellular enzymes such as glutathione S-transferase, superoxide dismutase, and quinone reductase.[11]

In line with our results, the effects of tomato and lycopene intake on BP and hypertension have been evaluated by recent clinical studies and systematic reviews, highlighting their beneficial effects.[41–45] Intake of lycopene and tomato consumption reduced the risk of stroke (26%), mortality (37%), and cardiovascular diseases (14%) in epidemiological studies,[41] and 26% risk reduction of CVD (HR = 0.74, 95% CI: 0.58–0.94).[42] Consistent with our results in new-onset hypertension, a high intake of lycopene improves cardiovascular health in elderly and overweight participants by lowering the risk of stroke.[42] A significant 6% reduction (average) in BP, consuming a tomato extract drink (equivalent to six tomatoes) was observed in pre-hypertensive participants.[43] A 15 mg lycopene/day dose significantly reduced SBP (from 144 to 134 mmHg, $P < 0.001$) and DBP (87.4 to 83.4 mmHg, $P < 0.05$) in grade 1 hypertension volunteers.[44] In addition, a 15 mg lycopene/day dose lowered significantly the SBP after 6 weeks of supplementation from 145.8 to 132.2 mmHg ($P < 0.001$), and the DBP from 82.1 to 77.9 mmHg ($P = 0.001$) in hypertensive participants with uncontrolled BP, being treated with anti-hypertensive medication.[45] A consumption of 1–19 g/day of *gazpacho* (a Spanish cold tomato soup) and >20 g/day was also inversely associated with SBP (−1.9 mmHg) and DBP (−1.5 mmHg) in high-risk cardiovascular participants.[37]

The strengths of the present study are its large sample size, multicentre design, long duration, and complete dietary and medical data during follow-up. A limitation is that changes in BP were secondary outcomes in the PREDIMED trial, although they were evaluated from the beginning of the study. The self-reported information on drug use, dietary intake, physical activity, and some other covariates may imply some residual confounding in the analyses. Despite the reduction in errors and controlled confounding were achieved through the use of repeated diet measurements and time-varying covariates, updating changes in dietary habits among participants in the analysis,[46] and by the use of validated FFQ in in the present study population showing good reproducibility and validity administered by trained dietitians.[17] A high *E*-value in our results demonstrated more robust findings to mitigate concerns about unmeasured confounding. An advantage of this study design is that it reduces measurement error due to intraindividual variation over time

Table 5 Subgroup analysis according to hypertension grades of the European Society of Cardiology and the European Society of Hypertension for the association between total tomato consumption (g/day), and systolic and diastolic blood pressure as outcomes during follow-up

Tomato consumption	Lowest (<44 g/day) n = 4151	Intermediate (44–82 g/day) n = 4937				Upper-intermediate (82–110 g/day) n = 5525				Highest (>110 g/day) n = 6555				*P*-trend	ICC
		β	CI (95%)		*P*-value	β	CI (95%)		*P*-value	β	CI (95%)		*P*-value		
Grade 1 hypertension															
SBP	Ref.	−0.83	−1.56	−0.10	**0.025**	−1.26	−2.64	0.11	0.07	−1.13	−2.96	0.71	0.23	0.11	0.23
DBP	Ref.	−1.00	−1.55	−0.46	**0.000**	−1.14	−2.56	0.28	0.12	−0.90	−2.88	1.08	0.37	**0.000**	0.48
Grade 2 hypertension															
SBP	Ref.	0.24	−1.08	1.56	0.73	0.07	−2.44	2.58	0.96	0.59	−2.32	3.50	0.69	0.70	0.16
DBP	Ref.	−0.62	−1.64	0.40	0.23	−0.59	−2.45	1.26	0.40	−0.03	−1.79	1.74	0.98	0.56	0.50
Grade 3 hypertension															
SBP	Ref.	−0.48	−2.11	1.15	0.56	−1.58	−4.58	1.42	0.30	0.54	−4.46	5.53	0.83	0.43	0.10
DBP	Ref.	−1.52	−3.33	0.28	0.10	−1.53	−3.86	0.79	0.20	0.38	−3.00	3.75	0.83	0.08	0.30

Multilevel linear mixed models (with independent structure correlation matrix, with maximum likelihood, standard errors and variance of the estimates by clustering at recruitment centres level) with a random intercept for each participant and individual visit (baseline, first year, and third year) to conduct this analysis. Multivariable model: sex (male/female), age (<60/60–70/>70), education (primary/secondary/higher), intervention group (MedDiet supplemented with EVOO/MedDiet supplemented with mixed nuts/control diet (advice to reduce dietary fat), baseline BMI (continuous), smoking (never/former/current), baseline physical activity (<500 METs-min-week/500–1000 METs-min-week/>1000 METs-min-week), diabetes status (yes/no), hypercholesterolaemia status (yes/no), and cumulative variables at first and third year for anti-hypertensive medications (yes/no), adherence to the MedDiet (13-point score), energy intake (continuous), alcohol (continuous), fibre (continuous), dietary sodium and potassium ratio (continuous), coffee (continuous), saturated fat (continuous), fruits (continuous), and vegetables (continuous). Nutritional covariates were adjusted for total energy. $P < 0.05$ considered significant, values shown in bold are statistically significant.

SBP, systolic blood pressure; DBP, diastolic blood pressure; BMI, body mass index; MedDiet, Mediterranean diet; β, beta regression coefficient; CI, confidence interval; ICC, intraclass correlation.

Table 6 Estimated Cox regression model to assess tomato consumption (g/day) and subsequent risk of hypertension during follow-up in 1097 non-hypertensive participants

Tomato consumption	Lowest (<44 g/day)				Intermediate (44–82 g/day)				Upper-intermediate (82–110 g/day)				Highest (>110 g/day)				
Cases/person-years (957/1521)	176/221				219/285				326/383				236/632				
Rate	0.80				0.77				0.85				0.37				
Cases per 100 person-years	80				77				85				37				
Hazard ratio (HR)		**HR**	**CI (95%)**		***P*-value**	**HR**	**CI (95%)**		***P*-value**	**HR**	**CI (95%)**		***P*-value**	***P*-trend**			
Model A	1.00	0.97	0.91	1.04	0.42	1.05	0.98	1.12	0.13	0.67	0.51	0.88	**0.004**	**0.022**			
Model B	1.00	0.97	0.89	1.05	0.46	1.02	0.97	1.08	0.41	0.67	0.51	0.89	**0.005**	**0.022**			
Model C	1.00	0.93	0.84	1.03	0.18	0.99	0.92	1.06	0.74	0.64	0.50	0.89	**0.005**	**0.009**			

Cox regression (Breslow method, standard errors and variance of the estimates by clustering at recruitment centres level) to conduct this analysis. Multivariable model A: sex (male/female), age (<60/60–70/>70 years), education (primary/secondary/academic-graduate), intervention group (MedDiet supplemented with EVOO/MedDiet supplemented with mixed nuts/control diet (advice to reduce dietary fat). Model B: variables of model A plus BMI (continuous), smoking (never/former/current), physical activity (<500 METs-min-week/500–1000 METs-min-week/>1000 METs-min-week), diabetes status (yes/no), hypercholesterolaemia status (yes/no), anti-hypertensive medications (yes/no) Model C: variables of model B plus adherence to MedDiet (modified 13-point score), energy intake (continuous), alcohol (continuous), fibre (continuous), dietary sodium and potassium ratio (continuous), coffee (continuous), saturated fat (continuous), fruits (continuous), and vegetables (continuous). Nutritional covariates were adjusted for total energy. *P*-values of <0.05 are considered significant. Values in bold are statistically significant.

EVOO, extra-virgin olive oil; BMI, body mass index; HR, hazard ratio; MedDiet, Mediterranean diet; CI, confidence interval.

compared to designs that only use baseline or most recent dietary information. Findings may not be applicable to other populations because most participants were living in a Mediterranean country, were older, had high cardiovascular risk and high BP. Additionally, this study design only allows for the observation of the association of tomato consumption on outcomes and does not establish causality. More rigorous evaluation of tomato consumption could have been attained considering plasma levels of lycopene allowing for personalized nutritional responses. While raw tomato is extensively consumed in the sample compared to others tomato products, tomato processing should be considered in future studies. Seasonal BP variation could have been confirmed by repeated ambulatory BP monitoring.

Conclusions

Tomato and tomato-based products are important components of the MedDiet and may play a favourable role in the prevention and management of hypertension, mainly reducing DBP in participants with elevated BP, and SBP and DBP in grade 1 hypertension participants. Daily consumption > 110 g/day (roughly equivalent to a large-sized tomato) is also associated with a 36% reduction in the risk of hypertension.

Authors' contributions

D.M.-L. contributed to the design, acquisition, analysis, and interpretation of data for the work; and drafted the manuscript. R.M.L.-R., E.P.L.-S., I.D.-L., A.T.-R., and S.C.-B. critically revised the manuscript. R.E. designed conceived and initiated the PREDIMED study, supervised its conduct and data analysis, and provided critical comments on all drafts of the manuscript. All other authors co-ordinated the study and collected data for the PREDIMED study in their respective medical centre and provided comments on drafts of the manuscript. All gave final approval and agree to be accountable for all aspects of work ensuring integrity and accuracy.

Supplementary material

Supplementary material is available at *European Journal of Preventive Cardiology*.

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Data availability

The data underlying this article will be shared on reasonable request with the corresponding author.

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