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Nut consumption is inversely associated with both cancer and total mortality in a Mediterranean population: prospective results from the Moli-sani study

Marialaura Bonaccio[1,2]*, Augusto Di Castelnuovo[1], Amalia De Curtis[1], Simona Costanzo[1], Francesca Bracone†, Mariarosaria Persichillo[1], Maria Benedetta Donati[1], Giovanni de Gaetano[1], and Licia Iacoviello[1] on behalf of the Moli-sani Project investigators‡

[1]*Department of Epidemiology and Prevention, IRCCS Istituto Neurologico Mediterraneo, Neuromed, 86077 Pozzilli, Isernia, Italy*
[2]*Fellow of the Fondazione Umberto Veronesi, Milan, Italy*

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Abstract

Nut intake has been associated with reduced inflammatory status and lower risk of CVD and mortality. The aim of this study was to examine the relationship between nut consumption and mortality and the role of inflammation. We conducted a population-based prospective investigation on 19 386 subjects enrolled in the Moli-sani study. Food intake was recorded by the Italian version of the European Project Investigation into Cancer and Nutrition FFQ. C-reactive protein, leucocyte and platelet counts and the neutrophil to lymphocyte ratio were used as biomarkers of low-grade inflammation. Hazard ratios (HR) were calculated using multivariable Cox proportional hazard models. During a median follow-up of 4·3 years, 334 all-cause deaths occurred. As compared with subjects who never ate nuts, rare intake (≤2 times/month) was inversely associated with mortality (multivariable HR = 0·68; 0·54, 0·87). At intake ≥8 times/month, a greater protection was observed (HR = 0·53; 0·32, 0·90). Nut intake (*v.* no intake) conveyed a higher protection to individuals poorly adhering to the Mediterranean diet (MD). A significant reduction in cancer deaths (HR = 0·64; 0·44, 0·94) was also observed, whereas the impact on CVD deaths was limited to an inverse, but not significant, trend. Biomarkers of low-grade inflammation were reduced in nut consumers but did not account for the association with mortality. In conclusion, nut intake was associated with reduced cancer and total mortality. The protection was stronger in individuals with lower adherence to MD, whereas it was similar in high-risk groups (diabetics, obese, smokers or those with metabolic syndrome), as compared with low-risk subjects. Inflammation did not explain the observed relationship.

Key words: **Nuts: Mortality: Inflammation: Cancer: CVD: Stroke**

A Mediterranean diet (MD) has been associated with reduced risk for major chronic diseases[1,2] such as CVD, cancer, diabetes and neurodegenerative diseases; its beneficial effects have been partially ascribed to its high content of PUFA, antioxidants and fibres that exhibit an anti-inflammatory action[3]. Nuts represent an important component of the MD pattern and are rich in unsaturated fatty acids, minerals (magnesium, potassium and calcium) and other bioactive compounds[4]. Epidemiological evidence has linked nut intake to reduced inflammatory status[5] or lower risk of CVD[6–8]. Limited evidence also suggests an inverse association with cancer risk attributable to the presence of anti-carcinogenic compounds[9]. Benefits of nut intake on cardiovascular health have been ascribed to the direct effect of nuts on oxidation, inflammation and vascular reactivity[10]. In addition, possible mechanisms that are able to explain the CVD advantages of nuts may be found in the documented positive effects on blood pressure[11,12], blood lipids[13,14], diabetes[15,16] and metabolic syndrome[17]. Yet the possible role of inflammation as a mediator of the association between nut consumption and total mortality has been poorly explored so far[18–21].

The purpose of this study was to address the relationship between nut intake and total and cause-specific mortality in a large Mediterranean cohort. Furthermore, our study investigated a possible role of inflammation[22] in explaining the association and likely advantages of nut intake in population groups sharing common risk factors for both CVD and cancer, with particular focus on subjects with obesity, diabetes, metabolic syndrome, smokers or those with poor adherence to an MD.

† Epicomed Research Srl, Campobasso, Italy

‡ Moli-sani study investigators are listed in the Appendix.

Abbreviations: CRP, C-reactive protein; MD, Mediterranean diet; NLR, neutrophil to lymphocyte ratio.

* **Corresponding author:** M. Bonaccio, fax +39 0865927575, email marialaura.bonaccio@neuromed.it

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Methods

Study population

Data presented here are from the Moli-sani study, which is a large population-based cohort study that recruited 24 325 subjects from the general population of the Molise region, a central-southern area of Italy[23]. Individuals were enrolled from March 2005 to April 2010 and were followed up for mortality for a median of 4·3 years (interquartile range: 3·5–5·3 years, 84 302 person/years).

After excluding individuals with prevalent CVD (*n* 1320), cancer (*n* 781) or missing data for both diseases (*n* 543), unreliable medical (*n* 235) or dietary questionnaires (*n* 955), subjects lost to follow-up (*n* 44) or with incomplete personal data (*n* 408), those reporting extremely low or high values for total energy intake (<3347·2 kJ/d (<800 kcal/d) in men and 2092 kJ/d (500 kcal/d) in women or >16 736 kJ/d (>4000 kcal/d) in men and 14 644 kJ/d (3500 kcal/d) in women) and individuals with missing information on blood pressure (*n* 186), lipid profile (*n* 373) or diabetes (*n* 229), a total of 19 386 subjects were included in the analysis. Mortality was recorded until December 2011. Overall mortality and cause-specific mortality were assessed by the Italian mortality registry (ReNCaM registry), validated by Italian death certificates (ISTAT form) and coded according to the International Classification of Diseases (ICD-9). Cardiovascular deaths were defined when the underlying cause of death had an ICD-9 code of 390-459 or 745-747, and for cancer deaths an ICD-9 code of 140-208. A critical evaluation of the diagnosis was performed, by analysing hospital medical records for hospital deaths and for other deceased patients if previously hospitalised during the follow-up. The process of ascertainment of death causes was conducted by qualified personnel blinded to the present analyses.

The Moli-sani study was approved by the Ethics Committee of the Catholic University of Rome, Italy. All participants signed an informed consent.

Dietary information

Food intake during the year before enrolment was ascertained by the validated Italian version of the 'European Project Investigation into Cancer and Nutrition' (EPIC) FFQ[24,25], which includes 188 food items, classified into forty-five predefined food groups on the basis of similar nutrient characteristics or culinary usage.

The EPIC questionnaire has a specific question about nut intake, including the frequency of consumption of walnuts, hazelnuts, almonds and peanuts. Frequency was categorised as never, rare (≤2 times/month), 3–7 or ≥8 times/month.

Adherence to the MD was evaluated by the Mediterranean diet score (MDS) developed by Trichopoulou *et al.*[26]. The scoring was based on the intake of the following nine items: vegetables, legumes, fruit and nuts, dairy products, cereals, meat and meat products, fish, alcohol and monounsaturated/saturated fats. For most items, consumption above the study population median received 1 point; all other intakes received 0 points. Consumption below the median of dairy products, meat and meat products received 1 point. Medians were sex-specific. For ethanol, men who consumed 10–50 g/d and women who consumed 5–25 g/d received 1 point; otherwise, the score was 0. The possible scores thus ranged between 0 and 9, the latter reflecting the maximal adherence to MD. In the present study, nut intake was not included in the MDS in order to control for dietary habits. Adherence to the MD was also categorised as poor (0–3), average (4–5) and good (>5). Daily energy intake (kcal/d) was divided into quintiles.

Laboratory analyses

All blood samples were obtained from participants who had fasted overnight and had refrained from smoking for at least 6 h. Serum lipids and blood glucose were assayed by enzymatic reaction methods using an automatic analyser (ILab 350; Instrumentation Laboratory). LDL-cholesterol was calculated according to Friedewald[27].

High-sensitivity (hs) C-reactive protein (CRP) was measured in fresh serum samples within 3 h of collection by a particle-enhanced immunoturbidimetric assay (IL-Coagulation-Systems ACL9000; Instrumentation Laboratory). Quality control for hs-CRP was maintained using in-house serum pool and internal laboratory standard at 1·5 mg/l; inter-day CV of hs-CRP were 5·5 and 4·2 %, respectively.

Hemocromocytometric analysis was performed by cell count (Coulter HMX, Beckman Coulter; Instrumentation Laboratory). Neutrophil (granulocyte) to lymphocyte ratio (NLR) was calculated as a marker of low-grade inflammation[22,28].

Assessment of risk factors

BMI was calculated as kg/m^2 and then categorised into three levels as normal (≤25), overweight (>25 and <30) or obese (≥30). Hypertension was defined as systolic blood pressure ≥ 140 mm Hg or diastolic blood pressure ≥ 90 mm Hg or treatment for hypertension. Hypercholesterolaemia was defined as total cholesterol ≥240 mg/dl (6.2 mmol/l) or the use of specific medication. Diabetes was defined as blood glucose ≥ 126 mg/dl or the use of specific pharmacological treatment. Metabolic syndrome was defined according to Adult Treatment Panel III criteria[29], based on at least three of these criteria: elevated waist circumference (>102 cm in men, >88 cm in women); elevated TAG (triglycerides) (>150 mg/dl) or drug treatment for elevated TAG; reduced HDL-cholesterol < 40 mg/dl (1·03 mmol/l) in men and <50 mg/dl (1·3 mmol/l) in women or drug treatment for reduced HDL-cholesterol, elevated blood pressure (>130 mm Hg systolic blood pressure or >85 mm Hg diastolic blood pressure) or anti-hypertensive drug treatment in a patient with a history of hypertension; and elevated fasting glucose (>100 mg/dl) or drug treatment for elevated glucose. Subjects were classified as never-smokers, current smokers or ex-smokers (quitting from at least 1 year).

Leisure-time physical activity was assessed by a structured questionnaire (questions on walking, gardening and sport participation)[30], and expressed as daily energy expenditure in metabolic equivalent task-hours (MET/d) and then categorised as below (≤2·27) or above the median (>2·27).

Educational level as an indicator of socio-economic status was considered as secondary school or lower and high school or higher.

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Statistical analysis

ANOVA for continuous or categorical variables was used to identify variables associated with the frequency of nut consumption and included socio-demographic variables (age, sex, smoking habit, educational level and leisure-time physical activity), BMI, hypertension, systolic and diastolic blood pressure, hypercholesterolaemia, diabetes, blood glucose, adherence to the MD and total energy intake. In addition, associations with biomarkers of low-grade inflammation (CRP, platelet and leucocyte counts or NLR) and lipid profile (HDL-cholesterol, LDL-cholesterol, total cholesterol and TAG) were tested. Associations with P value $< 0{\cdot}10$ were used in the multivariable model. However, hypercholesterolaemia and diabetes were not included in the multivariable model, as these factors are likely to be in the causal pathway of mortality protection by nuts.

Crude, age/sex-adjusted or multivariable hazard ratios (HR) with corresponding 95 % confidence intervals were calculated using the Cox proportional hazard model considering subjects in the lowest category of nut consumption as the reference group. The multivariable model was controlled for energy intake, leisure-time physical activity, smoking, educational level, BMI and the MDS not including nut consumption. An additional multivariable model was further controlled for inflammatory biomarkers to test their role as possible mediators of the effect. Sensitivity analyses were undertaken to estimate the impact of nut intake within subgroups at different CVD risk. Appropriate interaction terms were added to the models to test for differences of the effect. In cause-specific and sensitivity analyses, nut intake was compared with the no-intake group.

The data analysis was generated using the SAS/STAT software, version 9.1.3 of the SAS System for Windows©2009. SAS Institute Inc. and SAS are registered trademarks of SAS Institute Inc.

Results

Baseline characteristics of the population according to the frequency of nut intake are reported in Table 1. Compared with subjects with no nut consumption, those with the highest nut consumption had lower prevalence of diabetes and lower blood glucose levels, higher total cholesterol, LDL-cholesterol and HDL-cholesterol levels and higher energy intake.

During a median follow-up of 4·3 years, 334 overall deaths occurred, among which 104 CVD and 124 cancer deaths could be identified. Compared with those reporting no nut intake, a reduction in mortality was observed at increased consumption of nuts (P for trend = 0·0010), with a protection of 47 % (10–68 %) at highest intake (Table 2, model 1); these values likely reflect a plateau-like effect.

Cause-specific risks of death are reported in Table 3. As compared with those who never ate nuts, subjects consuming nuts showed a lower risk of overall mortality of 34 % (17, 47 %) and reduced cancer death of 36% (6, 56 %); CVD mortality exhibited a similar, but not significant, inverse trend (HR = 0·87; 0·57, 1·32). When CVD deaths were limited to CHD, a non-significant trend of protection of 26 % was found (Table 3). Stroke deaths were not associated with any nut intake (Table 3).

Subgroup analyses are reported in Table 4. The protection against mortality of nut intake was more evident in subjects with poor adherence to MD (HR = 0·47; 0·31, 0·71) as compared with those with greater adherence (P for interaction = 0·022; Table 4). Among all other subgroups, the effects of nuts on mortality were similar across different categories of consumption (Table 4).

The relationship between nut intake and biomarkers of low-grade inflammation is reported in Table 1. More frequent nut consumption was associated with lower levels of CRP, platelet count and the NLR. No association was found with leucocyte count.

The association between mortality and nut intake was not modified by the inclusion of CRP, platelet count and NLR (Table 2, model 2; Table 3, model 2), or by the inclusion of lipid profile (HDL- and LDL-cholesterol; data not shown).

Discussion

Results from this large prospective study show that nut intake is associated with a reduced risk of all-cause death in a general Italian population that is apparently free, at enrolment, from CVD and cancer.

As compared with subjects who did not eat nuts, participants consuming nuts ≥8 times/month showed a reduced risk (47 %) of dying from any cause after controlling for potential confounders, including other dietary components of the MD. In addition, those eating nuts more rarely (≤2 times/month) exhibited a lower risk of mortality of 32 %. When analyses were restricted to the two main groups – that is, nut consumers *v.* no consumers – we found a protection of 34 % for those consuming nuts.

Cause-specific risks of death

An effort was made to address the association of nut intake with specific causes of death. Our results show that nut intake was inversely and significantly associated with reduced risk of cancer death, in agreement with a recent investigation suggesting a beneficial effect of nuts, even at modest intakes, in lowering cancer deaths in two large, independent cohorts of nurses and other male health care professionals, from the USA[18]. Further studies will be needed to identify possible biological mechanisms explaining the observed inverse relationship; so far, limited evidence supports benefits of nut consumption on some types of cancer, such as colorectal cancer[31] or endometrial cancer in women[32], but the consumption of nuts has often been reported in association with seeds and legumes[33]. In addition, in previous studies, the anti-carcinogenic advantages of nuts appeared only in women, whereas poor effects have been documented in men[31,33]. Unfortunately, we were not able to address cancer or sex-specific analyses because of lack of a sufficient number of cases. It is noteworthy that our findings are also in agreement with results of an analysis conducted within the framework of the PREDIMED study, the very first large intervention trial on MD[8,19]: that analysis[19] revealed that increased frequency of nut consumption was associated with a 40 % reduced risk of

Table 1. Main characteristics of the study population according to the frequency of nut intake
Mean values and standard deviation (SD) for continuous variables (age, biochemical parameters, biomarkers of inflammation, systolic/diastolic BP and energy intake); number and percentages for categorical variables

	Frequency of nut intake (times/month)								
	Never		≤2		3–7		≥8		*P*
Number of subjects (n, %)	4271	22·0	12 341	63·7	1292	6·7	1482	7·6	–
Age (years, mean and SD)	55·6	12·4	54·1	11·1	53·7	10·5	55·5	10·9	<0·0001
Sex (n, %)									<0·0001
Women	2570	60·2	6569	53·2	623	48·2	747	50·4	
Men	1701	39·8	5772	46·8	669	51·8	735	49·6	
Education (n, %)*									<0·0001
Secondary school or lower	2411	56·5	6109	49·5	618	47·8	706	47·6	
High school or higher	1856	43·5	6225	50·4	674	52·2	775	52·3	
BMI (n, %)									<0·0001
Normal (≤25)	1216	28·5	3472	28·1	399	30·9	459	31·0	
Overweight (>25 and <30)	1722	40·3	5363	43·5	547	42·3	690	46·6	
Obese (≥30)	1333	31·2	3506	28·4	346	26·8	333	22·4	
Smokers (n, %)	1073	25·1	2889	23·4	308	23·8	324	21·9	0·0004
Leisure-time PA (n, %)									<0·0001
≤2·27 (below median)	2291	53·6	6359	51·5	574	44·4	576	38·9	
>2·27 (above median)	1980	46·4	5982	48·5	718	55·6	906	61·1	
Hypertension (n, %)	2380	55·7	6624	53·7	679	52·6	828	55·9	0·62
Systolic BP (mean and SD)	140·0	21·6	140·1	20·0	139·5	19·6	140·3	21·0	0·58
Diastolic BP (mean and SD)	82·4	9·7	82·6	9·5	82·7	9·8	82·6	9·8	0·58
Hypercholesterolaemia (n, %)	1235	28·9	3709	30·1	332	25·7	498	33·6	<0·0001
Total cholesterol (mg/dl; mean and SD)	210·8	42·0	215·2	41·3	210·1	41·5	217·1	39·9	<0·0001
HDL-cholesterol (mg/dl; mean and SD)	56·4	15·0	57·6	14·8	56·6	14·6	58·5	15·0	<0·0001
LDL-cholesterol (mg/dl; mean and SD)	128·6	34·9	132·1	34·7	128·6	34·7	133·7	33·7	<0·0001
TAG (mg/dl; mean and SD)	131·4	84·4	129·6	85·2	127·1	84·8	128·1	87·2	0·30
Diabetes (n, %)	467	10·9	942	7·6	92	7·1	128	8·6	<0·0001
Blood glucose (mg/dl; mean and SD)	101·6	27·2	100·4	22·8	99·2	22·9	100·8	22·7	0·0020
Energy intake (kJ/d; mean and SD)	7932·8	2301·2	8748·7	2192·4	9250·8	2192·4	9539·5	2217·5	<0·0001
Energy intake (kcal/d; mean and SD)	1896	550	2091	524	2211	524	2280	530	
Mediterranean diet score (n, %)									<0·0001
0–3	1446	33·9	3871	31·4	321	24·9	330	22·3	
4–5	1849	43·3	5433	44·0	560	43·3	643	43·4	
>5	976	22·9	3037	24·6	411	31·8	509	34·4	
Biomarkers of inflammation									
CRP (mg/l)†	1·54	1·49, 1·58	1·48	1·46, 1·51	1·36	1·29, 1·44	1·31	1·24, 1·37	0·0048
Leucocyte count (10^9/l means and SD)†	6·28	1·67	6·22	1·72	6·14	1·52	6·16	1·57	0·77
Platelet count (10^9/l means and SD)†	248·1	64·1	250·6	64·4	249·4	59·1	246·5	59·7	0·044
Neutrophil/lymphocyte†	2·01	0·79	1·99	0·82	1·95	0·78	1·92	0·70	0·0053

PA, physical activity; BP, blood pressure; CRP, C-reactive protein.
Means for biomarkers of inflammation, biochemical parameters and systolic or diastolic BP are adjusted for age and sex. All *P* values are adjusted for age and sex. Values for CRP are reported as geometric means with corresponding 95 % confidence intervals.
* Numbers do not add up to 100 % because of missing values.
† *P* values obtained from the model adjusted for age, sex, educational level (low/high), smoking (never, smoker, former), leisure-time PA (continuous), BMI (continuous), energy intake (continuous), Mediterranean diet score without nuts (continuous).

Table 2. Risk of death associated with the frequency of nut intake
(Hazard ratios and 95 % confidence intervals)

	Frequency of nut intake								
	Never		≤2 times/month		3–7 times/month		≥8 times/month		
	Hazard ratio	95 % CI	Hazard ratio	95 % CI	Hazard ratio	95 % CI	Hazard ratio	95 % CI	*P* trend
Number of deaths/number of subjects	122/4271		182/12 341		13/1292		17/1482		–
Crude	-reference-		0·50	0·40, 0·63	0·37	0·21, 0·65	0·40	0·24, 0·66	<0·0001
Age/sex adjusted	-reference-		0·63	0·50, 0·80	0·49	0·27, 0·86	0·44	0·26, 0·73	<0·0001
Model 1	-reference-		0·68	0·54, 0·87	0·56	0·31, 1·00	0·53	0·32, 0·90	0·0010
Model 2	-reference-		0·68	0·54, 0·87	0·57	0·32, 1·02	0·55	0·33, 0·92	0·0015

Model 1: multivariable hazard ratios with corresponding 95 % confidence intervals obtained from the model adjusted for age, sex, educational level (low/high), smoking (never, smoker, former), leisure-time physical activity (continuous), BMI (continuous), energy intake (continuous), Mediterranean diet score without nuts (continuous). Model 2: same as model 1, but further controlled for biomarkers of inflammation (C-reactive protein, platelet count and the neutrophil to lymphocyte ratio).

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Table 3. Cause-specific risks of death by nut intake *v.* no intake (Hazard ratios and 95 % confidence intervals)

		Nut intake							
		Age/sex adjusted		Model 1		Model 2			
	Number of deaths/number of subjects	Hazard ratio	95% CI	Hazard ratio	95% CI	Hazard ratio	95% CI	*P* (1)	*P* (2)
All-cause mortality	334/19 386	0·60	0·48, 0·75	0·66	0·53, 0·83	0·66	0·53, 0·84	0·0004	0·0005
CVD mortality	104/19 386	0·73	0·49, 1·11	0·87	0·57, 1·32	0·87	0·57, 1·32	0·50	0·50
CHD mortality	39/19 386	0·56	0·29, 1·08	0·74	0·38, 1·45	0·76	0·39, 1·49	0·39	0·43
Stroke mortality	19/19 386	0·93	0·35, 2·47	0·98	0·36, 2·66	1·01	0·37, 2·76	0·97	0·98
Cancer mortality	124/19 386	0·58	0·40, 0·85	0·64	0·44, 0·94	0·64	0·44, 0·94	0·022	0·023

Model 1 and *P* (1): hazard ratios with 95% confidence intervals and *P* values obtained from the model adjusted for age, sex, educational level (low/high), smoking (never, smoker, former), leisure-time physical activity (continuous), BMI (continuous), energy intake (continuous) and Mediterranean diet score without nuts (continuous). Model 2 and *P* (2): same as in model 1, but further controlled for C-reactive protein platelet count and the neutrophil to lymphocyte ratio.

Table 4. Subgroup analyses by nut intake *v.* no intake for total mortality (Hazard ratios and 95 % confidence intervals)

		Nut intake			
		Multivariable HR			
	Number of deaths/number of subjects	HR	95% CI	*P* value	*P* for interaction
All	334/19 386	0·68	0·54, 0·85	0·0009	–
Sex					
Women	106/10 509	0·88	0·59, 1·33	0·54	0·23
Men	228/8877	0·59	0·44, 0·77	0·0002	
Age					
≤65	109/15 587	0·83	0·53, 1·30	0·40	0·32
>65	225/3799	0·62	0·47, 0·81	0·0006	
Smoking habit					
No	135/9821	0·76	0·53, 1·10	0·15	0·35
Yes	85/4595	0·82	0·51, 1·32	0·41	
Former	114/4970	0·50	0·34, 0·74	0·0005	
BMI					
<30	221/13 868	0·68	0·51, 0·91	0·0083	0·92
≥30	113/5518	0·63	0·42, 0·93	0·021	
Diabetes					
No	258/17 757	0·64	0·49, 0·83	0·0009	0·36
Yes	76/1629	0·80	0·50, 1·30	0·37	
Mediterranean diet score (without nuts)					
0–3	98/5968	0·47	0·31, 0·71	0·0003	0·022
4–5	150/8485	0·73	0·52, 1·04	0·085	
>5	86/4933	0·91	0·56, 1·47	0·69	
Metabolic syndrome*					
No	199/14 485	0·68	0·51, 0·92	0·013	0·86
Yes	135/4896	0·66	0·46, 0·94	0·021	

Hazard ratios (HR) with 95 % confidence intervals and *P* values obtained from the model adjusted for age, sex, educational level (low/high), smoking (never, smoker, former), leisure-time physical activity (continuous), BMI (continuous), energy intake (continuous), Mediterranean diet score without nuts (continuous).
* Numbers do not add up to 100 % because of missing values.

cancer death, comparable with a 36 % reduction in cancer mortality observed in our study. As the PREDIMED study was conducted within high CVD risk subjects older than 55 years, our study somehow extends the positive results documented in the PREDIMED trial to a more general, younger population. The actual role of nut intake in relation to cancer risk surely deserves further investigation[9].

When specific CVD mortality was considered, a non-statistically significant trend for protection was found. However, when only CHD death was considered, the reduction in death risk was similar to that observed for cancer mortality, but, most probably, the small number of CHD cases did not allow to reach any statistical significance. Yet, a recent meta-analysis found that cardiovascular advantages from nut consumption were primarily driven by decreased coronary artery disease deaths[34].

It is noteworthy that the association of nut consumption with stroke deaths was weaker than that observed for other causes, and no statistical significance was reached. Our overall results on CVD events also appear in agreement with data from

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a meta-analysis that suggested similar protection for CVD, ischaemic heart disease and total mortality, but no protection for type 2 diabetes or stroke[7].

However, benefits from nut intake against diabetes were observed in the PREDIMED-Reus trial[35].

Subgroup analyses

Our study has also examined the effects of nut intake within subgroups at different risk for both CVD or cancer. The protection against mortality offered by nut intake was more evident in subjects with poor adherence to the MD as compared with those showing greater adherence. Nut intake appeared to add no additional protection against mortality within individuals who already followed an MD, probably because they already benefit from other fundamental components of this healthy dietary pattern, such as olive oil, moderate alcohol intake or antioxidant-rich foods. Conversely, nut intake alone seems to convey some health advantage to those who stick less to this dietary pattern. These data are in agreement with those observed in non-Mediterranean population settings, such as in the USA, in which health advantages from nut consumption have been reported[36].

Role of inflammation

Finally, we addressed the possible role of low-grade inflammation on the causal pathway between nuts and the risk of death. Results showed that subjects consuming higher amounts of nuts had lower values of biomarkers of inflammation (CRP, platelet count or NLR), probably indicating a reduced subclinical inflammatory status in nut consumers, in agreement with previous studies[5]. However, we observed that inflammation did not account for the inverse associations between nut intake and overall or cancer deaths. Similarly, adjustment for lipid status did not modify the association.

Strengths and limitations of this study

The strengths of this large epidemiological study in a Mediterranean population are represented by its prospective nature. In addition, further control of all analyses by a wide panel of possible confounding factors and diet-related behaviours should assure consistency to the observed association.

A major limitation of the present study in an apparently healthy population is the relatively small number of deaths, but this did not prevent statistically significant differences to be consistently observed, at least for both total and cancer mortality. The relatively low number of CVD, CHD or stroke events did not allow to provide conclusive and consistent results or to explore more deeply the plateau effect, which may be linked to specific death causes (i.e. stroke, for which a J-shape was already observed[37]) rather than others. As far as total and cancer deaths are concerned, our study did reach the same major conclusions of a much larger population study[18].

Conclusions

The present results obtained in people living in a Mediterranean country provide evidence of an inverse association between nut consumption and risk of death in a general population that is apparently free from CVD and cancer at enrolment. To our knowledge, this study is one of the first observational investigations to address the health advantages of nut intake for subjects at risk for CVD or cancer, such as subjects who are obese, affected by diabetes, metabolic syndrome or are less adherent to the MD. In addition, this study adds knowledge on the relationship between nut consumption and cancer, an issue on which evidence is still scarce and controversial.

Finally, our findings suggest the opportunity to consider nuts as an important part of a healthy dietary pattern for the prevention of chronic diseases, as already suggested by the PREDIMED study[8,19,38,39]. Possibly, nut consumption should be mainly encouraged in countries in which nut intake is not regular and MD is not followed as a regular eating pattern.

The health advantages of nuts observed at low to moderate doses are in agreement with the beneficial effects of specific foods such as salt[40], dark chocolate[41] or alcohol[42], whose protective role has only been detected at low to moderate intakes.

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M. B., L. I. and A. Di. C. designed the present research; A. De. C., S. C., M. P. and F. B. managed data collection; M. B. and A. Di. C. analysed the data; M. B. wrote the paper; and M. B. D., G. d. G. and L. I. originally inspired the research and critically reviewed the manuscript.

There are no conflicts of interest.

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Appendix: Moli-sani study investigators

Steering committee

Licia Iacoviello (Neuromed, Pozzilli, Italy), Chairperson, Maria Benedetta Donati and Giovanni de Gaetano (Neuromed, Pozzilli, Italy) and Simona Giampaoli (Istituto Superiore di Sanità, Roma, Italy).

Safety and data monitoring committee

Jos Vermylen (Catholic Univesity, Leuven, Belgio), Chairman, Ignacio De Paula Carrasco (Accademia Pontificia Pro Vita, Roma, Italy), Fabrizio Oleari (Istituto Superiore di Sanità, Roma, Italy) and Antonio Spagnolo (Catholic University, Roma, Italy).

Event adjudicating committee

Deodato Assanelli (Brescia, Italy), Vincenzo Centritto (Campobasso, Italy), Paola Muti (Hamilton, Ontario, Canada), Holger Schünemann (Hamilton, Ontario, Canada), Pasquale Spagnuolo and Dante Staniscia (Termoli, Italy).

Scientific and organizing secretariat

Francesco Zito (Coordinator), Americo Bonanni, Chiara Cerletti, Amalia De Curtis, Augusto Di Castelnuovo, Licia Iacoviello, Roberto Lorenzet, Antonio Mascioli, Marco Olivieri and Domenico Rotilio.

Data management and analysis

Augusto Di Castelnuovo (Coordinator), Marialaura Bonaccio, Simona Costanzo and Francesco Gianfagna.

Informatics

Marco Olivieri (Coordinator), Maurizio Giacci, Antonella Padulo and Dario Petraroia.

Biobank and biochemical analyses

Amalia De Curtis (Coordinator), Federico Marracino, Maria Spinelli and Christian Silvestri.

Communication and press office

Americo Bonanni (Coordinator), Marialaura Bonaccio and Francesca De Lucia.

Moli-family project

Francesco Gianfagna and Branislav Vohnout.

Recruitment staff

Franco Zito (General Coordinator); Secretariat: Mariarosaria Persichillo (Coordinator), Angelita Verna, Maura Di Lillo, Irene Di Stefano; Blood sample: Agostino Pannichella, Antonio Rinaldo Vizzarri, Branislav Vohnout, Agnieszka Pampuch; Spirometry: Antonella Arcari (Coordinator), Daniela Barbato, Francesca Bracone, Simona Costanzo, Carmine Di Giorgio, Sara Magnacca, Simona Panebianco, Antonello Chiovitti, Federico Marracino, Sergio Caccamo, Vanesa Caruso; Electrocardiograms: Livia Rago (Coordinator), Daniela Cugino, Francesco Zito, Francesco Gianfagna, Alessandra Ferri, Concetta Castaldi, Marcella Mignogna; Tomasz Guszcz; Questionnaires: Romina di Giuseppe (Coordinator), Paola Barisciano, Lorena Buonaccorsi, Floriana Centritto, Antonella Cutrone, Francesca De Lucia, Francesca Fanelli, Iolanda Santimone, Anna Sciarretta, Maura Di Lillo, Isabella Sorella, Irene Di Stefano, Emanuela Plescia, Alessandra Molinaro and Christiana Cavone.

Call center

Giovanna Galuppo, Maura Di Lillo, Concetta Castaldi, Dolores D'Angelo and Rosanna Ramacciato.

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