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Dietary fats, olive oil and respiratory diseases in Italian adults: A population-based study

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Summary

Background: Fat intake has been associated with respiratory diseases, with conflicting results.

Objective: We studied the association between asthma and rhinitis with dietary fats, and their food sources in an Italian population.

Methods: Clinical and nutritional information was collected for 871 subjects (aged 20-84) from the population-based multi-case-control study Genes Environment Interaction in Respiratory Diseases (GEIRD): 145 with current asthma (CA), 77 with past asthma (PA), 305 with rhinitis and 344 controls. Food intake was collected using the EPIC (European Investigation into Cancer and Nutrition) Food Frequency Questionnaire. The associations between fats and respiratory diseases were estimated by multinomial models. Fats and their dietary sources were analysed both as continuous variables and as quartiles.

Results: Monounsaturated fatty acids and oleic acid were associated with a reduced risk of CA in both continuous (RRR = 0.68, 95%CI: 0.48; 0.96; RRR = 0.69; 95%CI: 0.49; 0.97, per 10 g, respectively) and per-quartile analyses (p for trend = 0.028 and 0.024, respectively). Olive oil was associated with a decreased risk of CA (RRR = 0.80; 95%CI: 0.65; 0.98 per 10 g). An increased risk of rhinitis was associated with moderate total fat and SFA intake.

Conclusions: High dietary intakes of oleic acid and of olive oil are associated with a lower risk of asthma but not of rhinitis.

1 | INTRODUCTION

Asthma is one of the most common airway diseases and is associated with bronchial hyperresponsiveness (BHR), inflammation and recurrent airway obstruction.[1] Asthma and other allergic diseases such as rhinitis have a high prevalence in developed countries, affecting between 5% and 40% of the European adult population.[2] The high prevalence in asthma and allergy has been suggested to be related to environment and lifestyle habits, being diet an important factor.[3] Recent studies focused on the components of the Western diet (rich in processed food and with fewer sources of high quality fatty acids such as olive oil) which may contribute to allergic sensitization. A particular consideration was put on dietary fat intake, with overall conflicting results.[3] Notably, former studies were mainly conducted among populations following a typical Western diet.[4] On the other side, few data are available for Mediterranean countries where an high intake of olive oil is traditionally observed.[3]

Olive oil, the principal source of fat in Mediterranean diet,[5] is a rich source of monounsaturated fatty acids (MUFA) and of several bio-compounds including polyphenols. Different studies highlight the protective role of oleic acid (the primary component of olive oil) in cardiovascular diseases and cancers[6,7] while information on the respiratory system is scarce. In animals, some studies have shown that olive oil supplementation reduces airway inflammation and bronchial hyperresponsiveness in experimental models of induced asthma[8] and allergic airways disease.[9] Moreover, a reduced risk of wheeze was seen in offspring of mothers assuming a regular intake of olive oil during pregnancy[10] and epidemiological evidence has shown that in children, regular consumption of olive oil is associated with lower prevalence of doctor-diagnosed asthma.[11] Several studies have concluded that a Mediterranean diet might contribute to reduce the prevalence and severity of asthma, in children[12,13] and in adults,[14] but the specific effect of olive oil on respiratory illness in adults has been seldom investigated in population-based studies. Data regarding rhinitis are even less abundant, in particular when addressing adult populations.[15]

In a population-based multi-case-control study of Italian adults, we investigated the association of dietary fatty acids and of olive oil with asthma and rhinitis, using the data collected in the Gene—Environment Interactions in Respiratory Disease (GEIRD) study.

2 | METHODS

2.1 | Study design

The GEIRD project is a population-based multi-case-control study involving seven Italian centres (Ancona, Palermo, Pavia, Sassari, Terni, Torino and Verona as the co-ordinating centre).[16] In the first stage of the study, new random samples or pre-existing randomly sampled cohorts[17,18] from the general population (20-84 years of age, male/female = 1/1) were mailed a questionnaire on respiratory symptoms. In the second stage, all the subjects reporting symptoms suggestive of chronic bronchitis (CB), chronic obstructive pulmonary disease (COPD) or asthma, and random samples of subjects reporting symptoms of rhinitis and without symptoms were invited to clinics.

All measurement protocols were in agreement with international guidelines (www.geird.org).[16] Ethical approval was obtained in each centre from the appropriate ethics committee. The ethical committee of the co-ordinating centre is the Comitato Etico per la Sperimentazione - Azienda Ospedaliera di Verona. Written informed consent was obtained from each participant.

For this analysis, only the subjects recruited in the centres of Pavia, Sassari, Torino and Verona were considered. The other centres were excluded because of the lack of complete information on dietary and/or spirometric data.

The number of subjects eligible for the screening phase in these centres was 18 543, out of them 10 873 (58.6%) filled in the postal questionnaire. Overall, out of 6011 subjects invited to clinics, 2189 (36.4%) attended the clinical stage (Figure S1 in the Online Repository). Out of the 2189 subjects participating in the clinical stage, 994 (45%) filled in the FFQ.

2.2 | Clinical visit

Each subject underwent a detailed interview. During this interview, the information on gender, birth date and age at completing full-time education was collected, as well as the information on self-reported smoking habits and physical activity (estimated by asking participants how often—frequency—and for how many hours—duration—a week they usually exercised so much that they got out of breath or sweaty).

The subjects were weighed to the nearest 0.1 kg with light clothing and no shoes, and height was measured to the nearest 0.5 cm while they stood barefoot.

2.3 | Lung function and skin prick test (SPT) measurements

During the clinical visit, lung function tests and SPT were performed in order to define the case-control status of the subjects. Participants underwent forced spirometry according to the ATS reproducibility criteria.[19] FEV_1% predicted (Forced Expiratory Volume in the 1st second) and the lower limit of normal (LLN) for the FEV_1/FVC (Forced Vital Capacity) were calculated on the basis of Quanjer et al equation.[20] Subjects with a $FEV_1/FVC \geq 70\%$ and $\geq$LLN underwent methacholine challenge test, which followed a protocol described elsewhere.[21] Subjects with a $FEV_1/FVC < 70\%$ or <LLN underwent the bronchodilator challenge test and were invited (if eligible) to undergo the methacholine challenge test. Skin prick tests to 14 common allergens were carried out as described elsewhere[22] and atopy was defined as having a >3 mm reaction.

2.4 | Food frequency questionnaire (FFQ)

The subjects also answered a FFQ. The FFQ used is the Italian version of the validated European Investigation into Cancer and

Nutrition (EPIC) questionnaire.[23] The NAF software (Nutritional Analysis of Food Frequency Questionnaires, National Cancer Institute, Milan, Italy)[24] was used to derive daily food intake (grams) and to estimate macro- and micro-nutrient composition. Nutrient data for specific foods consumed in Italy were obtained from the food composition database for epidemiological studies in Italy.[25] Some implausibly high and low intakes of nutrients resulted from the questionnaire, so cut-points were set to exclude outliers. Seventeen subjects with less than 70% of the total number of questions were excluded from the analyses. Then, the ratio of energy intake (EI) to basal metabolic rate (BMR; EI:BMR) was calculated, where BMR was estimated using sex-specific equations for adults (≤60 year old)[26] and for elderly subjects (>60 year old).[27] Cut-points based on the top and bottom 0.5% of the distribution of EI:BMR were introduced, and eight more subjects were excluded. Moreover, we excluded seven subjects with extremely low levels (<600 kcal for women and <800 kcal for men) of EI.[28]

The final number of subjects with clinical and nutritional information was 962.

2.5 | Identification of cases and controls in clinics

The 962 subjects were hierarchically classified as follows:

- 145 cases of current asthma, CA:
  - a reported history of asthma *and* asthma-like symptoms/medicines in the last 12 months;
  - a reported history of asthma *or* asthma-like symptoms/medicines in the last 12 months *plus* one of the following conditions: (a) a positive methacholine challenge test with a provocative dose of methacholine causing a 20% drop in FEV_1 (PD20) <1 mg; (b) pre-bronchodilator FEV_1/FVC <70% or <LLN[19] with a positive reversibility test (i.e. FEV_1 >12% and >200 mL after the administration of 400 μg of salbutamol); and (c) pre-bronchodilator FEV_1/FVC <70% or <LLN with a post-bronchodilator FEV_1/FVC >LLN and >70% and a post-bronchodilator FEV_1 >80% predicted[19];
- 77 cases of past asthma, PA: a history of asthma that did not fulfil the criteria for CA;
- six cases of COPD: post-bronchodilator FEV_1/FVC <70% or <LLN without asthma;
- 305 cases of rhinitis: reported nasal allergies or nasal symptoms;
- 344 controls: no nasal/respiratory symptoms/conditions reported *plus* both (a) pre-bronchodilator FEV_1/FVC > LLN and >70% and (b) FEV_1 >70% predicted;
- 85 subjects could not be classified.

The controls were not paired to the cases.

The six subjects with COPD and the 85 unclassified were excluded from the analyses.

2.6 | Dietary exposures

The following dietary sources of fats were included as dietary exposures of interest:

1. Macro-nutrients: total fatty acid intake, fractional fatty acid groups namely MUFA, saturated fats (SFA), polyunsaturated fatty acids (PUFA), oleic acid, animal fats and vegetable fats.
2. Olive oil and butter.

The following covariates were considered as potential confounders: study sample/cohort, centre, gender, age, body mass index (BMI, computed dividing weight by height squared), education (low = completed before the age of 16) as a proxy of socio-economic status, smoking habit (never smoker, past smoker i.e. not smoking in the last month, current smoker), self-reported physical activity (heavy, moderate and light), alcohol intake, total protein intake and total EI.

Alcohol intake, total protein intake and total EI were determined based on the information provided in the FFQ.

2.7 | Statistical analyses

Our primary exposures of interest (different types of fats, oleic acid, butter and olive oil) were energy-adjusted according to the residual method.[29] According to the residual method, the exposure residuals obtained by regressing the exposure intake on total EI are included as independent variables. Total EI is also included as a covariate. We used log transformation of the dietary intake variables to create residuals with a more constant variance across the levels of total EI.[29] To express nutrients and foods in a more acquainted scale, a back-transformation was then made by adding a constant (the predicted value for the logarithm of the mean total EI) and then taking the antilogarithm.[30]

The main exposures of interest were considered as continuous variables, and they were also categorized into quartiles based on the distribution of the exposure in controls.

To investigate the associations of dietary exposures of interest and case-control status, several multinomial regression models were fitted to the data, using a 4-level dependent variable (CA, PA, rhinitis, and control). Since different types of fats are inter-correlated due to the same food sources, we followed the suggestion by Hu et al,[30] who recommend to adjust fats simultaneously for each other in the analyses. The multinomial regression models were built to include: (a) animal and vegetable fat; (b) SFA, MUFA and PUFA; and (c) oleic acid, SFA and PUFA, in the same model. In addition, we considered two types of food containing fat: olive oil and butter. We assessed the associations between olive oil and case-control status and between butter and case-control status in separate models.

Multivariable associations of exposures with case-control status were expressed by relative risk ratios (RRRs; using control as the reference category) and their 95% CIs. These associations were determined for dietary exposures either as continuous variables or in

quartiles. To test for linear trend across intake quartile categories, we assigned the median intake of each quartile category to everyone with intakes in the category and then we included this quartile median variable as a continuous factor in the statistical models. The *P*-value for trend was the resulting *P*-value for the associated model coefficient.

The statistical analysis was performed using STATA software, release 15.0 (Stata Corp, College Station, TX, USA).

3 | RESULTS

3.1 | Participation in the nutritional protocol

The distribution of socio-demographic and lifestyle factors was compared among the participants, as opposed to the non-participants in the nutritional protocol, separately in cases and in controls. In each group of cases and in the controls, the subjects who participated in the nutritional protocol were similar to the subjects who did not with regard to the distribution of gender, smoking habits, drinking habits, BMI and education level. Age was significantly associated to participation in the nutritional protocol, in particular in subjects with CA (mean age: 45.6 and 49.5 years, in non-participants and participants, respectively, $P = 0.001$) and with rhinitis (mean age: 47.7 and 50.4 years, in non-participants and participants, respectively, $P = 0.02$), but not in PA, and in controls. Subjects with rhinitis participating in the clinical protocol were significantly more physically active than subjects not participating ($P = 0.02$). (Table S1 in the Online Repository)

3.2 | Main characteristics of cases and controls

The distribution of gender, smoking and drinking habits, total daily alcohol intake, BMI and self-reported physical activity was not significantly different between cases and controls (Table 1). Age was significantly different across groups: mean age was comprised between 44.9 years in subjects with PA and 51.5 years in controls.

3.3 | Association between fats and respiratory diseases

Table 2 shows the median, 1st and 3rd quartiles of fats and selected food intakes for subjects with and without respiratory diseases.

Intakes of MUFA and oleic acid were associated with a reduced risk of CA. When considering fat intake as a continuous variable, the risk to be a case of CA rather than a control decreased by about 30% for an increase of 10 g/d in the MUFA intake (RRR = 0.68; 95% CI: 0.48; 0.96). A similar decrease was found for oleic acid (RRR =

TABLE 1 Main characteristics of the subjects participating in the nutritional protocol by case-control status in the GEIRD study

	Controls (n = 344)	CA (n = 145)	PA (n = 77)	Rhinitis (n = 305)	*P*
Age at the clinical visit, years (mean, SD)	51.5 (11.5)	49.5 (11.7)	44.9 (11.4)	50.4 (12.6)	**<0.001**
Gender (%)					
Male	48.0	47.6	44.2	48.9	0.91
Smoking habits (%)					
Non-smoker	52.2	49.0	56.6	50.8	0.24
Ex-smoker	32.9	27.6	26.3	28.2	
Current smoker	14.9	23.4	17.1	21.0	
Drinking habits (%)					
Current drinker	35.3	46.9	36.4	41.8	0.08
Total alcohol (g/d)					
Abstainers	64.0	52.4	63.6	56.6	0.09
Ex-drinkers	1.5	0.7	0.0	2.0	
<5	7.1	15.9	10.4	9.9	
5-15	17.1	17.2	18.2	14.2	
15-30	6.2	8.3	5.2	11.6	
30-120	4.1	5.5	2.6	5.6	
BMI, kg/m^2 (mean, SD)	25.4 (4.7)	25.2 (4.2)	24.8 (4.4)	25.3 (4.1)	0.68
BMI, kg/m^2 (median, 1st quartile, 3rd quartile)	25.0 (22.3;27.8)	24.7 (21.8;27.5)	24.0 (21.7;26.9)	24.4 (22.5;27.4)	0.62
Physical activity (%)					
Heavy	4.9	4.8	6.5	8.5	0.24
Moderate	37.8	35.9	31.2	40.7	
Light	57.3	59.3	62.3	50.8	
Education level (%)					
High	74.1	76.6	85.7	73.9	0.16

Statistically significant *P*-values are shown in bold.

TABLE 2 Median, first (p25) and third (p75) quartile of fat intake and of selected foods (g/die) in subjects without respiratory diseases (controls), and in subjects with CA, PA and rhinitis in the GEIRD study

	Controls (n = 344)		CA (n = 145)		PA (n = 77)		Rhinitis (n = 305)		
	Median	p25;p75	Median	p25;p75	Median	p25;p75	Median	p25;p75	*P*
Total fat	72.4	56.5;94.1	71.9	57.4;89.7	80.4	59.1;107.5	77.0	60.5;96.1	0.07
Animal fat	39.9	26.9;53.5	38.4	29.4;51.7	42.5	29.8;58.8	42.5	30.3;54.7	0.41
Vegetable fat	33.4	22.5;42.3	32.8	21.0;39.0	35.3	26.2;47.0	32.6	25.0;42.6	0.12
Saturated fat	24.9	18.6;32.7	24.0	19.0;32.2	24.8	20.6;37.3	26.9	19.4;33.2	0.20
Monounsaturated fat	35.4	27.1;44.7	35.2	25.9;41.7	37.0	29.4;49.8	36.6	28.7;46.0	0.07
Polyunsaturated fat	8.2	6.5;10.7	8.0	6.2;10.3	9.2	6.9;11.5	8.5	6.8;10.7	0.07
Oleic acid	33.5	25.4;42.1	32.9	24.1;38.9	35.3	27.7;48.0	34.1	26.8;43.2	0.08
Olive oil	21.2	14.1;29.4	19.8	12.9;27.2	22.2	18.1;33.9	21.1	15.0;30.1	0.06
Butter	0.3	0.1;0.9	0.4	0.1;1.1	0.3	0.1;0.4	0.4	0.1;1.0	0.38

0.69; 95%CI: 0.49; 0.97) (Table 3). A reduced risk of CA was detectable even when MUFA and oleic acid were categorized in quartiles. For both kinds of fat, the risk of having CA decreased as fat intake increased with a significant *P*-value for trend (*P* = 0.03 and 0.02, for MUFA and oleic acid, respectively), and the subjects in the highest quartile of MUFA and oleic acid intake had less than half the risk of having CA with respect to the subjects in the lowest quartile (RRR = 0.44; 95%CI: 0.21; 0.95 and RRR = 0.42; 95%CI: 0.20; 0.88, for MUFA and oleic acid, respectively; Table 4).

The risk to be a subject with CA, rather than a control, decreased when the intake of vegetable fat increased, though not significantly (*P*-value for trend = 0.06). The RRR for the highest vs lowest quartile was 0.49 (95%CI: 0.26; 0.93; Table 4).

An increase in the risk of rhinitis occurred only for a modest increase in the SFA intake and in the total fat intake (i.e. in the 2nd quartile of intake vs 1st; Table 4). However, there was no increase in trend of rhinitis by fat intake (Table 4).

3.4 | Association between selected foods and respiratory diseases

Olive oil was associated with a reduced risk of CA; in particular, when considering olive oil intake as a continuous variable, the risk to be a case of CA, rather than a control, decreased by 20% for an increase of 10 g/d in olive oil intake (RRR = 0.80; 95%CI: 0.65; 0.98) (Table 5). A consistent trend was evident when observing the RRRs of CA for quartiles of olive oil intake, which decreased from 0.88 for the 2nd quartile to 0.58 for the 4th quartile; however, this trend was only borderline significant (*P* for trend = 0.06) (Table 6). An increased risk of PA was associated with a high intake of olive oil (4th quartile vs

TABLE 3 Adjusted RRR (and 95%CI) to be a case of CA, PA and rhinitis, rather than a control (n = 344), according to the intake of fats in the GEIRD study

	CA (n = 145)	PA (n = 77)	Rhinitis (n = 305)
Animal fat (10 g)	0.90 (0.72;1.13)	1.01 (0.74;1.37)	1.10 (0.92;1.32)
Vegetable fat (10 g)	0.81 (0.66;1.01)	1.24 (0.96;1.62)	1.07 (0.91;1.26)
Total Energy (100 kcal)	0.98 (0.95;1.01)	1.03 (0.99;1.07)	1.00 (0.98;1.03)
Saturated fat (10 g)[a]	1.02 (0.68;1.55)	0.91 (0.53;1.57)	1.13 (0.82;1.57)
Monounsaturated fat (10 g)	0.68 (0.48;0.96)*	1.26 (0.82;1.93)	1.05 (0.80;1.37)
Polyunsaturated fat (1 g)[a]	1.04 (0.93;1.17)	1.04 (0.89;1.23)	1.01 (0.91;1.11)
Total Energy (100 kcal)	0.98 (0.95;1.01)	1.03 (0.99;1.07)	1.00 (0.98;1.03)
Saturated fat[a]	0.99 (0.66;1.49)	0.93 (0.54;1.58)	1.14 (0.82;1.57)
Oleic acid (10 g)	0.69 (0.49;0.97)*	1.26 (0.82;1.91)	1.04 (0.80;1.36)
Polyunsaturated fat (1 g)[a]	1.04 (0.93;1.16)	1.05 (0.89;1.23)	1.01 (0.92;1.11)
Total Energy (100 kcal)	0.98 (0.95;1.01)	1.03 (0.99;1.07)	1.00 (0.98;1.03)
Total fat (10 g)	0.85 (0.71;1.02)	1.15 (0.91;1.45)	1.08 (0.93;1.24)
Total Energy (100 kcal)	0.98 (0.95;1.02)	1.03 (0.99;1.07)	1.00 (0.98;1.03)

The estimates were adjusted for age, gender, centre, study cohort, BMI, smoking habits, alcohol intake, physical activity, educational level, total protein intake and total energy intake. The marked areas in grey/white separate the variables comprised in different models.

[a]Two different, but generally similar, RRRs are proposed for the association of SFA with each considered disease, due to the fact that SFA was included in two different models: one model with MUFA as a covariate and the other one with oleic acid as a covariate. The same applies for PUFA.

*$P < 0.05$.

TABLE 4 Adjusted RRR (and 95%CI) to be a case of CA, PA and rhinitis, rather than a control (n = 344), according to quartiles of fat intake (based on the distribution of controls) in the GEIRD study

	Quartile of intake				
	1	2	3	4	*P* (Trend)
CA (n = 145)					
Animal fat	1.00	1.30 (0.72;2.35)	0.88 (0.46;1.69)	1.09 (0.55;2.14)	0.90
Vegetable fat	1.00	0.77 (0.44;1.54)	0.87 (0.49;1.54)	0.49 (0.26;0.93)*	0.06
Saturated fat[a]	1.00	1.43 (0.79;2.61)	1.05 (0.55;2.00)	1.40 (0.71;2.76)	0.57
Monounsaturated fat	1.00	0.80 (0.44;1.44)	0.58 (0.30;1.11)	0.44 (0.21;0.95)*	**0.03**
Polyunsaturated fat[a]	1.00	0.91 (0.50;1.65)	1.03 (0.64;1.97)	1.09 (0.53;2.21)	0.78
Saturated fat[a]	1.00	1.45 (0.79;2.64)	1.05 (0.55;1.99)	1.37 (0.70;2.69)	0.61
Oleic acid	1.00	0.67 (0.37;1.22)	0.59 (0.31;1.12)	0.42 (0.20;0.88)*	**0.02**
Polyunsaturated fat[a]	1.00	0.94 (0.52;1.70)	1.04 (0.54;1.97)	1.09 (0.54;2.21)	0.78
Total fat	1.00	0.98 (0.56;1.69)	0.58 (0.31;1.08)	0.62 (0.33;1.16)	0.06
PA (n = 77)					
Animal fat	1.00	2.02 (0.94;4.37)	0.91 (0.37;2.20)	1.24 (0.49;3.14)	0.80
Vegetable fat	1.00	1.04 (0.49;2.61)	1.13 (0.49;2.61)	1.78 (0.79;4.00)	0.14
Saturated fat[a]	1.00	1.12 (0.52;2.41)	0.59 (0.25;1.37)	0.74 (0.31;1.81)	0.28
Monounsaturated fat	1.00	1.30 (0.57;2.96)	0.87 (0.35;2.19)	1.60 (0.57;2.96)	0.49
Polyunsaturated fat[a]	1.00	1.50 (0.63;3.58)	1.87 (0.77;4.57)	1.39 (0.52;3.58)	0.53
Saturated fat[a]	1.00	1.15 (0.53;2.47)	0.61 (0.26;1.43)	0.78 (0.32;1.87)	0.31
Oleic Acid	1.00	1.25 (0.56;2.78)	0.66 (0.26;1.67)	1.50 (0.61;3.71)	0.59
Polyunsaturated fat[a]	1.00	1.51 (0.63;3.58)	1.97 (0.82;4.76)	1.46 (0.57;3.85)	0.44
Total fat	1.00	2.18 (1.01;4.71)*	1.01 (0.42;2.43)	1.48 (0.63;3.49)	0.86
Rhinitis (n = 305)					
Animal fat	1.00	1.61 (1.01;2.58)	1.06 (0.63;1.78)	1.46 (0.85;2.52)	0.43
Vegetable fat	1.00	0.71 (0.44;1.15)	1.06 (0.66;1.69)	0.96 (0.59;1.57)	0.72
Saturated fat[a]	1.00	1.85 (1.13;3.03)*	1.38 (0.82;2.32)	1.72 (0.99;2.99)	0.21
Monounsaturated fat	1.00	0.99 (0.60;1.62)	0.74 (0.43;1.27)	0.90 (0.50;1.63)	0.54
Polyunsaturated fat[a]	1.00	0.78 (0.48;1.28)	1.13 (0.67;1.89)	0.89 (0.50;1.57)	0.99
Saturated fat[a]	1.00	1.82 (1.11;2.97)*	1.35 (0.81;2.27)	1.66 (0.96;2.87)	0.25
Oleic Acid	1.00	1.01 (0.62;1.64)	0.82 (0.49;1.40)	0.95 (0.54;1.70)	0.72
Polyunsaturated fat[a]	1.00	0.76 (0.47;1.25)	1.09 (0.65;1.81)	0.87 (0.49;1.52)	0.91
Total fat	1.00	1.60 (1.00;2.56)*	1.28 (0.78;2.11)	1.38 (0.83;2.32)	0.43

Statistically significant *P*-values for trend are shown in bold.
The estimates were adjusted for age, gender, centre, study cohort, BMI, smoking habits, alcohol intake, physical activity, educational level, total protein intake and total energy intake. The marked areas in grey/white separate the variables comprised in different models.
[a]Two different, but generally similar, RRRs are proposed for the association of SFA with each considered disease, due to the fact that SFA was included in two different models: one model with MUFA as a covariate and the other one with oleic acid as a covariate. The same applies for PUFA.
*$P < 0.05$.

1st: RRR = 2.07; 95%CI: 1.01; 4.26; Table 6). There was no evidence of an association between butter and the considered diseases.

4 | DISCUSSION

We investigated the relationship between dietary intake of fatty acids, including their dietary food sources, and the risk of respiratory diseases, within the frame of the GEIRD project.

For the first time, we found a significant inverse association between the dietary intake of MUFA and oleic acid with the risk of CA in a sample of adults from the general population. Of interest, a similar association was found between the consumption of olive oil and CA, whereas the opposite association was identified with PA. The reduced risk of CA with the intake of oleic acid is in contrast with the data reported by Nagel et al who found a significant positive association between dietary oleic acid (lipid numbers C18:1) and margarine with the risk of asthma in adulthood. The authors hypothesize that this association may be explained by an increased intake of *trans*-C18:1, which is high in margarine.[31] In our study, the fact that the main source of oleic acid is olive oil, rich of the *cis* isomer, may justify the apparently opposite findings. In other words, we speculate

TABLE 5 Adjusted RRR (and 95%CI) to be a case of CA, PA and rhinitis, rather than a control (n = 344), according to the intake of selected foods (olive oil and butter, considered in two separate models) in the GEIRD study

	CA (n = 145)	PA (n = 77)	Rhinitis (n = 305)
Olive oil[a] (10 g)	0.80 (0.65;0.98)*	1.23 (0.97;1.56)	1.02 (0.87;1.18)
Total Energy[a] (100 kcal)	0.98 (0.95;1.01)	1.03 (0.99;1.07)	1.00 (0.98;1.03)
Butter (1 g)[b]	0.99 (0.92;1.06)	0.95 (0.83;1.08)	0.98 (0.92;1.04)
Total Energy[b] (100 kcal)	0.99 (0.96;1.03)	1.04 (1.00;1.09)	1.00 (0.98;1.03)

The estimates were adjusted for age, gender, centre, study cohort, BMI, smoking habits, alcohol intake, physical activity, educational level, total protein intake and total energy intake.

[a]The estimates were also adjusted for saturated fat.

[b]The estimates were also adjusted for total fat.

*$P < 0.05$.

that the different isoforms of oleic acid contained in olive oil and margarine may influence the occurrence of respiratory diseases in different ways. Our data indirectly contrast with the findings by Heinrich et al who reported that the energy-adjusted dietary intake of MUFA was positively related to the prevalence of atopy.[32] The different designs and outcomes of the studies (allergic sensitization vs a clinical condition like rhinitis in the present study), the different populations (mainly from Central-Northern Europe in Heinrich's study) and the probable different dietary sources of MUFA (animal derived products in the study by Heinrich) can explain the discordant results.

Consistent with our study are the data reported in the Nurses' Health Study, which found that energy-adjusted intake of MUFA was inversely associated with asthma[33]; the same inverse association between MUFA intake and asthma was shown by Huang et al,[34] although in a cohort of teenagers from Taiwan. The mechanisms at the base of the decreased risk of CA associated with MUFA intake are not clear. MUFA may have an anti-inflammatory effect, as demonstrated in a controlled trial[35] where subjects consuming olive oil (containing a high percentage of MUFA) for 2 months showed a decreased expression of adhesion molecules in peripheral blood mononuclear cells.

To the best of our knowledge, this is the first study showing a reduced risk of CA associated with the intake of olive oil in adults. This indirectly supports a Spanish study where olive oil consumption during pregnancy was found to prevent wheezing in the first year of life of offspring,[10] while a Swedish study found a negative association between olive oil and doctor-diagnosed asthma in children. Of interest, no association between olive oil and CA was found in the latter study.[11]

There is epidemiological evidence that Mediterranean diet is associated with lower asthma prevalence.[12] However, previous investigations did not take olive oil as a specific component into account,[12,36] so that the relationship between this nutrient and asthma has not been studied in detail.

The main active components of olive oil are oleic acid, phenolic derivatives and squalene, which have been found to have antioxidant and anti-inflammatory activity.[37] Since inflammation and oxidative stress are key components in asthma pathogenesis,[38] we have good reason to believe that the properties of olive oil may positively influence the disease development.

Two studies carried out in Denmark[39,40] investigated the effect of fish oil supplementation during pregnancy on the occurrence of asthma in offspring using olive oil as placebo, assuming that the intake of olive oil in the doses provided was inert.[39] Our results are in contrast with the assumption that olive oil is inert in relation to asthma, even if the considered quantities in our study were 5-10 times higher.

The influence of fatty acid consumption on the prevalence of rhinitis and atopic diseases has been object of interest in recent

TABLE 6 Adjusted RRR (and 95%CI) to be a case of CA, PA and rhinitis, rather than a control (n = 344), according to quartile intake of selected foods (olive oil, butter) (based on the distribution of controls) in the GEIRD study

	Quartile of intake				
	1	2	3	4	*P* (Trend)
CA (n = 145)					
Olive oil[a]	1.00	0.88 (0.51;1.54)	0.73 (0.42;1.29)	0.58 (0.32;1.04)	0.06
Butter[b]	1.00	1.21 (0.64;2.29)	1.00 (0.52;1.92)	1.32 (0.70;2.49)	0.53
PA (n = 77)					
Olive oil[a]	1.00	1.17 (0.54;2.53)	0.84 (0.37;1.93)	2.07 (1.01;4.26)*	0.07
Butter[b]	1.00	1.04 (0.48;2.26)	0.63 (0.27;1.48)	0.60 (0.26;1.41)	0.15
Rhinitis (n = 305)					
Olive oil[a]	1.00	1.03 (0.65;1.62)	0.71 (0.44;1.14)	0.91 (0.58;1.45)	0.40
Butter[b]	1.00	0.87 (0.52;1.44)	0.93 (0.56;1.54)	1.00 (0.61;1.64)	0.94

The estimates were adjusted for age, gender, centre, study cohort, BMI, smoking habits, alcohol intake, physical activity, educational level, total protein intake and total energy intake.

[a]The estimates were also adjusted for saturated fat.

[b]The estimates were also adjusted for total fat.

*$P < 0.05$.

years. Some epidemiological studies support the hypothesis that dietary fat intake might play a role in atopy and related diseases.[41,42]

Our study adds a further piece of evidence on the possible role that animal and SFA intake could have in rhinitis.[43] However, our results have to be interpreted with great caution owing to the fact that the increase in the risk of rhinitis occurred only for moderate but not high consumption of animal fat and SFA.

The study strengths are (a) the accurate identification of cases and controls, based either on an extensive clinical interview or on objective clinical tests, (b) the simultaneous comparison of cases of several diseases to controls, (c) the selection of subjects from the general population and (d) the careful dietary assessment using validated food frequency questionnaires.[23,24]

Some caveats should also be taken into account. The rate of participation in the clinical stage was 36%. This could have led to a selection bias; that is, cases and controls consuming a high quantity of lipids were less (or more) prone to participate, even though the scenario seems to be unlikely. Also the participation rate to the FFQ was fairly low (45%), but there were only minor differences between the two groups (participants vs non-participants in the nutritional protocol) related to age, with a very limited, if any, clinical relevance.

There is potential measurement error in the ascertainment of diet.[44] As this is a case-control study, recall bias might have affected the results. No dietary recall was administered to participants; however, the EPIC questionnaire was previously validated in an Italian population sample.[23] Moreover, subjects with a low-quality questionnaire were excluded (see Section 2) and the FFQ provided visual aids for the assessment of portion sizes, likely improving the accuracy of the reported information.

The GEIRD study is a case-control study, and we acknowledge that the relatively short distance between the reporting of dietary habits and case-control definition could constitute a limit for the assessment of a causal association. However, it is of importance to remark that there is evidence that adults maintain relatively stable long-term dietary habits.[45]

5 | CONCLUSIONS

The results of this population-based study provide evidence that dietary fats affect the risk of asthma in adults. A high dietary intake of oleic acid and a high consumption level of olive oil were found to decrease the risk of asthma. These results suggest that a diet rich in olive oil, which plays a central role in the Mediterranean diet, besides having beneficial effects against cardiovascular diseases, may also be useful for the respiratory system.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

AUTHOR CONTRIBUTION

LCazzoletti and MF conceived and designed the study; LCazzoletti, MEZ, RB, IC, AG, PP and MF contributed to the data collection; LCazzoletti performed the statistical analysis; LCazzoletti, MF, MEZ and FS drafted the manuscript; and LCazzoletti, MEZ, FS, RB, LChamitava, IC, VGL, AG, VM, PP and MF contributed to the interpretation of data, revised the paper critically for important intellectual content and approved the version to be published.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

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