PIZZA CONSUMPTION AND DISEASE ACTIVITY IN RHEUMATOID ARTHRITIS

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Introduction

Rheumatoid arthritis (RA) is a chronic inflammatory disease involving multiple joints, with a multifactorial and autoimmune pathogenesis [1] and a prevalence below 1% in Italy [2, 3].

While composite measures of activity (such as Simplified Disease Activity Index (SDAI) and Disease Activity Score based on 28 joints with C-reactive protein (DAS28-CRP)) have been increasingly suggested [4, 5], sustained remission or low disease activity are difficult to achieve in a non-negligible proportion of patients. Due to its impact on systemic inflammation [6, 7], diet is a suitable candidate to integrate pharmacological therapy [8]. While most observational studies about RA and diet focused on disease onset [9], studies investigating on disease activity are mostly interventions and showed well-known flaws [10-18]. However, even a minor but persistent real-life dietary effect is likely to exert great impact on long-term health outcomes in chronic patients [12].

DAS28-CRP and SDAI usually lead to different classifications of patients in remission/RA activity level; their joint use has been recently suggested to improve patient's assessment. In addition, their scale is different (DAS28-CRP: 0-10; SDAI: 0-100), although they both show highly skewed frequency distributions. DAS28-CRP is the most used in the clinical practice and therefore thresholds of minimal clinically important improvements have been defined in clinical trials; as it allows for comparisons of effect sizes across papers, DAS28-CRP is preferred by clinicians and usually treated as a continuous variable, thus requiring robust regression model for the analysis. However, in recent years, patients in remission might reach 60% and a logistic regression model might be more appropriate in some populations.

Pizza is a relevant component of the Italian diet, with a yearly consumption of 7.8 kg per capita (Coldiretti 2023), second to United States only (13 kg/capita). Studies on the role of pizza on health are, however, scanty, with a few Italian studies observing a protective effect on cardiovascular disease and some cancers [19-22]. Differently from Italy [23], pizza is considered alongside with most junk-foods [24-28], within a Western-like dietary pattern, in the US and outside Italy in general. In addition, pizza's composition might be different from that of other countries, with 44% of Italians making it at home (Coldiretti 2023).

Aims

The present work aims to assess the effect on RA activity, as defined by either DAS28-CRP and SDAI, of: (1) (Italian) pizza consumption; (2) pizza's main ingredients, as available from the FFQ (mozzarella cheese, olive oil, and refined grains); (3) overall and in strata of RA severity or duration.

Methods

This observational, cross-sectional, single-center study was performed from January 2018 to December 2019, at Gaetano Pini Hospital, Milan Italy. Participants had to be 18-65 years old, with a disease duration of at least 3 months, and conformed to well defined clinical criteria [13, 30-33]. Information on sociodemographics, anthropometric factors, lifestyle habits, and a medical history was collected at baseline,

together with RA disease activity (DAS28-CRP and SDAI) and current RA treatment. Diet in the previous 6 months was assessed through a reproducible and valid [34] 110-item food frequency questionnaire.

Robust linear (with the MM estimator [35]) and logistic regression models were fitted with tertile-based consumption categories of each food item/group (i.e., pizza, refined grains, mozzarella cheese, and olive oil) and selected confounders as independent variables and each of two measures of RA disease activity (i.e., DAS28-CRP and SDAI) as the dependent variable. Stratified analyses by disease duration and severity were performed; heterogeneity across strata was assessed with the likelihood ratio test.

Results

Participants eating half a pizza more than once a week (3rd tertile), as compared to those eating it up to 2 times a month included (1st tertile), were less likely to have an active disease according to SDAI both overall (OR: 0.274, 95% CI: 0.079-0.952) and when restricting to the more severe variant (OR: 0.161, 95% CI: 0.032-0.825). These results were confirmed via robust linear regression models on the overall sample (beta: -3.587, p=0.02) and in the more severe disease stratum (beta: -5.279, p=0.012). Results on DAS28-CRP revealed a reduced mean disease activity for the 3rd tertile of pizza consumption on the overall sample (beta:-0.730, p=0.044) and when restricting to long-standing RA (beta:-1.120, p=0.018). Odds of an active disease, as computed by DAS28-CRP, were also reduced for the 3rd tertile of pizza consumption, when analyses were restricted to the more severe RA (OR: 0.195, 95% CI: 0.039-0.969).

Concerning pizza ingredients, mozzarella cheese was likely the stronger driver of the protective effect identified for pizza, with a significant risk reduction ranging between 60 and 80% and a lower mean DAS28-CRP in the 3rd tertile when restricting to more severe (beta: -0.573, p=0.013) or long-standing RA (beta: -0.651, p=0.023). In addition, using more than a tablespoon a day of olive oil (compared to up to a tablespoon a day included) resulted in a lower mean DAS28-CRP (beta: -0.371, p=0.023), when restricting to more severe RA; finally, the refined grains food group was not significantly related to RA disease activity.

Conclusions

When looking for easily accessible, unexpensive foods, RA patients might consider increasing consumption of pizza and mozzarella, especially when RA is severe. These results need confirmation based on well-designed cohort studies referring to validated dietary assessment tools and objective measures of activity, to find the expected small dietary effects and to adjust for the large set of confounders typical of RA.

Table: Odds ratios (OR) of rheumatoid arthritis (RA) disease activity and corresponding 95% confidence intervals (CI) (upper panel) and increase/decrease in mean Disease Activity Score based on 28 joints with C-reactive protein (DAS28-CRP) and Simplified Disease Activity Index (SDAI) (lower panel) in 365 patients and restricting analyses to rheumatoid factor (RF) and/or anti-citrullinated protein antibodies (ACPA) positive patients (more severe RA) and to patients with disease duration >15 years (long-standing RA), according to the highest tertile categories of consumption of the four investigated food items/group (pizza, refined grain (without pizza), mozzarella cheese, and olive oil)[1]. Italy 2018–2019.

Logistic regression		Overall Analysis			More severe RA			Long-standing RA		
Food items/group	Tertile categories	OR	95% CI		OR	95% CI		OR	95% CI	
DAS28-CRP										
Pizza	II (0.065; 0.142]	0.821	0.484	1.391	0.435	0.211	0.897	0.55	0.236	1.28
	III (0.142; 1]	0.252	0.062	1.028	0.195	0.039	0.969	NE	NE	NE
Refined grains (without pizza)	II (0.142; 2.357]	1.900	1.002	3.602	1.741	0.757	4.006	0.880	0.337	2.294
	III (2.357; 9.675]	1.135	0.550	2.344	1.115	0.437	2.846	0.791	0.271	2.308

Food items/group	Tertile categories									
Mozzarella cheese	II (0.065; 0.142]	0.852	0.496	1.465	0.682	0.328	1.420	0.310	0.124	0.779
	III (0.142; 1]	0.490	0.236	1.018	0.369	0.141	0.968	0.178	0.049	0.650
Olive oil[2]	II (1; 3]	0.729	0.443	1.201	0.537	0.269	1.071	0.481	0.210	1.104
SDAI										
Pizza	II (0.065; 0.142]	0.484	0.269	0.870	0.204	0.087	0.478	0.389	0.138	1.092
	III (0.142; 1]	0.274	0.079	0.952	0.161	0.032	0.825	0.190	0.020	1.830
Refined Grains (without pizza)	II (0.142; 2.357]	0.641	0.313	1.315	0.814	0.326	2.033	0.308	0.091	1.036
	III (2.357; 9.675]	0.489	0.224	1.068	0.546	0.200	1.492	0.591	0.151	2.320
Mozzarella cheese	II (0.065; 0.142]	0.788	0.423	1.466	0.576	0.242	1.370	0.513	0.169	1.563
	III (0.142; 1]	0.321	0.151	0.683	0.200	0.068	0.586	0.299	0.074	1.207
Olive oil[2]	II (1; 3]	0.993	0.575	1.715	0.567	0.267	1.202	0.615	0.231	1.634

Robust linear regression

Food items/group	Tertile categories	Beta	SE	p-value	Beta	SE	p-value	Beta	SE	p-value
DAS28-CRP										
Pizza	II (0.065; 0.142]	-0.356	0.157	0.024	-0.584	0.163	0.000	-0.517	0.209	0.015
	III (0.142; 1]	-0.730	0.350	0.044	-0.675	0.341	0.052	-1.120	0.479	0.018
Refined Grains (without pizza)	II (0.142; 2.357]	0.168	0.145	0.251	0.349	0.200	0.086	0.179	0.247	0.474
	III (2.357; 9.675]	-0.051	0.162	0.754	0.017	0.223	0.941	-0.041	0.278	0.884
Mozzarella cheese	II (0.065; 0.142]	-0.045	0.159	0.782	-0.261	0.181	0.154	-0.402	0.218	0.074
	III (0.142; 1]	-0.362	0.213	0.087	-0.573	0.230	0.013	-0.651	0.285	0.023
Olive oil[2]	II (1; 3]	-0.201	0.146	0.171	-0.371	0.161	0.023	-0.384	0.201	0.059
SDAI										
Pizza	II (0.065; 0.142]	-1.302	0.683	0.056	-3.232	0.980	0.001	-2.760	1.291	0.035
	III (0.142; 1]	-3.587	1.537	0.021	-5.279	2.053	0.012	-5.174	2.963	0.073
Refined Grains (without pizza)	II (0.142; 2.357]	0.541	0.838	0.525	1.342	1.118	0.240	-0.251	1.434	0.864
	III (2.357; 9.675]	-0.469	0.935	0.617	0.184	1.246	0.883	-0.575	1.614	0.723
Mozzarella cheese	II (0.065; 0.142]	0.294	0.723	0.688	-0.475	1.041	0.657	-1.611	1.296	0.226
	III (0.142; 1]	-1.372	0.919	0.135	-2.439	1.320	0.063	-2.699	1.695	0.110
Olive oil[2]	II (1; 3]	-0.865	0.654	0.190	-2.094	0.962	0.034	-2.193	1.202	0.073

[1] Estimated from multiple logistic regression models or robust linear regression models adjusted for age (≤55, >55 years old), sex, education (maximum level attained: primary school, middle school, high school, university), total energy intake, body mass index (BMI, <18.5, 18.5–24, 25–29, ≥30 kg/m2), alcohol drinking intensity (never drinker, <1, 1–<2, ≥2 drinks/day), cigarette smoking status (never, former, current), presence of any therapy (yes, no), conventional synthetic (cs)DMARDs (Disease Modifying Anti-Rheumatic Drugs, no, yes), biologic (b)DMARDs (no, yes), targeted synthetic (ts)DMARDs (no, yes), steroids (no, yes), disease duration (≤5, 5–≤10, 10–≤15, 15–≤25, >25 years), RF

(negative, positive), and ACPA (negative, positive). The reference category included the lowest consumers of each food item/group, i.e., participants consuming up to the first tertile value included.

[2] For the olive oil food item, the third tertile category (III) was not available because the second tertile value was equal to 3, which was also the maximum consumption attainable for olive oil.

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