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Article

Are dietary indices associated with polycystic ovary syndrome and its phenotypes? A case-control study

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Abstract:

Polycystic ovary syndrome (PCOS) is a complex hormonal disorder which impair ovarian function. The adherence to healthy dietary patterns and physical exercise are the first line of recommended treatment for PCOS patients, but it is no clear what type of diet is more adequate. In this case-control study, we explore the association between the adherence to five dietary quality indices widely used and PCOS. We enrolled 126 cases of PCOS and 159 controls (Murcia, Spain). Diagnostic of PCOS and its phenotypes were established following the Rotterdam criteria [hyperandrogenism (H), oligoanovulation (O), polycystic ovaries morphology (POM)]. We used a validated food frequency questionnaires to calculate the scores for five dietary indices: alternate Healthy Eating index (AHEI), AHEI-2010, relative Mediterranean Dietary Score (rMED), alternate Mediterranean Dietary Score (aMED) and Dietary Approaches to Stop Hypertension (DASH). We used multivariable logistic regression to estimate adjusted odds ratios and confidence intervals. In the multivariable analysis, AHEI-2010 index was inversely associated with "H+O" PCOS' phenotype ($OR_{Q3 \text{ vs } Q1}$= 0.1; 95% CI :(0.0; 0.9); $P_{\text{for trend}}$= 0.02). In conclusion, we did not find any statistical significative association between dietary indices and total, anovulatory and ovulatory PCOS, but it seems interesting explore these association among the diverse phenotypes of PCOS in studies with higher sample size.

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Keywords: Polycystic Ovary Syndrome (PCOS); PCOS phenotypes; Rotterdam Criteria; hyperandrogenism; Mediterranean Diet Score (MDS); Alternate Healthy Index (AHEI); Alternate Healthy Index 2010 (AHEI-2010) and DASH index

Abbreviations:
PCOS Polycystic Ovarian Syndrome
NIH National Institute of Health
ESHRE European Society of Human Reproduction and Embryology ASRM American
BMI Body Mass Index
aMED Alternate Mediterranean Diet Score
rMED Relative Mediterranean Diet Score
AHEI, Alternate Healthy Index
AHEI-2010 Alternate Healthy Index 2010
DASH Dietary Approaches to Stop Hypertension
H Hyperandrogenism
O Oligo/amenorrhea
POM Polycystic ovaries morphology
H+O "Hyperandorgenism + Oligo/amenorrhea" phenotype
H+O+POM "Hyperandorgenism + Oligo/amenorrhea + Polycystic ovaries morphology" phenotype
H+O "Hyperandorgenism + Oligo/amenorrhea" phenotype
O+POM "Oligo/amenorrhea + Polycystic ovaries morphology" phenotype

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1. Introduction

Polycystic ovary syndrome (PCOS) is a complex hormonal disorder which impair ovarian function (1). It could be considered a polygenic, polyfactorial, systemic, inflammatory, autoimmune disease [2]. Its reported overall prevalence according to diagnostic criteria of Rotterdam is about 10% (95% CI: 8-13%) (Skiba et al., 2018). The impact of PCOS is considerable because it is linked to higher risk of obesity [3–6], insulin resistance and diabetes [7–9], higher cardiovascular risk profile [10–12], poorly thyroid function [13,14], infertility [15,16] , gestational diabetes [17–20], sleep disturbances [21] and, even, mental health problems [22]

Lifestyle modifications for PCOS, especially, physical activity and diet are of major importance in the clinical management of these women to improve most of the adverse outcomes related to this condition. Diet is focused on weight loss in overweight PCOS women, the subgroup with higher risk of metabolic deregulation and type 2 diabetes. However, it is unclear what type of diet is better for this: hypocaloric or low in carbohydrates.

On the one hand, some case-control studies have shown that PCOS women consumed higher quantity of monounsaturated fatty acids, and ω-3 polyunsaturated fatty acid and simple carbohydrate (Barrea et al., 2019). Moreover, they presented higher fibre intake, high glycemic index and glycemic load than controls [23,24]. All these key aspects are considered in different dietary indices such as aMED, AHEI and DASH.

On the other hand, most of the interventional studies have employed low carbohydrates and high protein diets for improving different PCOS' manifestations [25–30]. A recent meta-analysis of eight randomized controlled trials, concluded that low carbohydrate diet had a stronger effect on increasing FSH level, rising SHBG levels and decreasing testosterone levels comparing with higher carbohydrates diet (diet composition carbohydrates: 40% vs 50%) [25]. However long-term adherence may be difficult. Moreover, unanswered question is to what extent improvements will be maintained in association with a transition to a less carbohydrate-restricted diet. Indeed, low carbohydrates diet

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interventions do not often compare with other frequent healthy dietary patterns such as Mediterranean diet (MD) as the control group. In this way, Dietary Approaches to Stop Hypertension (DASH) interventions for PCOS women have had beneficial effects on Body Mass Index (BMI), androstenedione, Sex Hormone-Binding Globulin (SHBG), insulin metabolism, cardiovascular risk factors and oxidative stress [31–34].

To our knowledge, this is the first study assessing the association between Mediterranean Diet indices [Alternate Mediterranean Diet Score (aMED) and Relative Mediterranean Diet Score (rMED)] and different phenotypes of PCOS. Additionally, Alternate Healthy Index (AHEI), Alternate Healthy Index 2010 (AHEI-2010) and DASH were also assessed. Because of that, our aim was to evaluate if there are differences in dietary indices in women diagnosed with PCOS and its phenotypes compared to controls. This scope would allow us to know if diet is related to PCOS, and not only specific macro or micronutrients. Besides, we would be able to report more easily nutritional recommendations potentially adapted to PCOS women.

2. Materials and Methods

This was a case-control study taken place in Southeast of Spain (Murcia Region) from September 2014 to May 2016. All participants were between 18 and 40 years old (n=300). Exclusion criteria were: pregnancy or lactating, oncological treatment, hormonal medication during the 3 months prior to the study, genitourinary prolapse or endocrine disorders (n=5). Methods have been explained in previous works [35]. Concisely, we finally enrolled, voluntarily, 126 cases of PCOS and 159 women from the Department of Obstetrics and Gynecology, outpatient clinics at the Virgen de la Arrixaca University Clinical Hospital. Diagnostic of PCOS was established following the Rotterdam criteria resulting from the consensus of European Society for Human Reproduction and Embryology and the American Society for Reproductive Medicine [36]. Thus, PCOS was diagnosed with 2 or more of the following criteria:

1. Oligovulation/ amenorrhea or anovulation (menstrual cycles > 35 days or amenorrhea > 3 months).
2. Biochemical hyperandrogenism (total testosterone level ≥ 2.6nmol or clinical (Ferriman-Galwey score ≥ 12) [37] .
3. Polycystic ovaries morphology (POM) using transvaginal ultrasound (TVUS) (≥12 follicles measuring 2–9 mm in diameter, mean of both ovaries) [38].

Moreover, the following phenotypes of PCOS were also assessed [39]:

- Hyperandrogenism + oligo/amenorrhea + POM (H+O+POM) (n=52).
- Hyperandrogenism + oligo/amenorrhea (H+O) (n= 18).
- Hyperandrogenism + POM (H+POM) (n=33).
- Oligo/amenorrhea + POM (O+POM) (n=18).

Also, H+O+POM, H+O and O+POM phenotypes were reclassified, as “anovulatory phenotype” (n=88) and H+POM type as “ovulatory phenotype” (n=33), and evaluated separately in the current study.

Controls were women without PCOS (or other major gynecological conditions) attending the gynecological outpatient clinic for routine gynecological examinations. The same methods were performed in both, cases and controls: anamnesis and questionnaires, physical examination, transvaginal ultrasound and blood draw, between days 2–5 of the menstrual cycle. Written informed consent was obtained from all women. This study was approved by the Ethics Research Committee of the University of Murcia and the Clinical University Hospital (no. 770/2013, approved 3 October 2013).

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Dietary assessment and dietary indices

We used a validated 117-food item semi-quantitative food frequency questionnaire (FFQ) to assess the normal food intake (available at: http://epinut.edu.umh.es/cfa-117-ddm/) which has been previously validated for Spanish population [40,41]. This questionnaire is based on a FFQ used by Willett in the Nurse Health Study Cohort [42]. Subjects had to choose one of the nine options about how often, on average, they had consumed each never or less than once a month to six or more times a day. Nutrient values for each food were obtained from the US Department of Agriculture and supplemented with Spanish sources [43,44].

The FFQ dietary information was used to calculate the following five a priori-defined dietary indices: AHEI, AHEI-2010, relative MDS (rMED), alternate MDS (aMED) and Dietary Approaches to Stop Hypertension (DASH). All represents healthy dietary pattern but use different range of score, variations in food components and calculation. They have been described in detail in a previous publication [45]. AHEI, AHEI-2010 and DASH were created in United States for defining a Prudent dietary pattern high in vegetables, fruit, whole grains, legumes and lower in saturated fats and alcohol[46–48]. AHEI-2010 is the AHEI's version for evaluate chronic diseases. Both establish a specific reference values of servings per day or grams per day for each food component and sum 10 if the subject reaches this amount. The overall scoring range is 0 to 80 for AHEI and 0 to 110 for AHEI-2010. However, DASH, RMED and aMED establish the scoring criteria using quintiles, terciles and the median intake of the study sample, respectively. DASH was developed for controlling blood pressure [49] but, nowadays, is useful for obesity, diabetes, metabolic syndrome and cardiovascular disease. Unlike the previous ones, RMED and AMED define Mediterranean Diet and they are version of the original MDS [50,51]. AMED considers red and processed meat and establishes ratio of mono/polyunsaturated fats [46], while RMED evaluates dairy products, only uses olive oil as the primary fat source, evaluates in one item all types of meat and is more specific for Spanish population [52]. The total score is 9 and 18, respectively.

Energy-adjusted intakes were computed using the residual method [53]. Five subjects did not complete the FFQ and four did not have a plausible energy intake (≤ 500 or ≥ 4500 kcal). Finally, the study sample for the final analyses was 276 women, being 121 cases and 155 controls.

Statistical analyses

Data were checked for normal distributions using Kolmogorov-Smirnov test. Continuous data with skewed distribution was described with median and interquartile range (IQR: 25^{th}–75^{th}) and comparisons were performed by Kruskal –Wallis tests. We used Chi-squared test for categorical variables and they were represented by frequency and percentage. The five dietary indices were recategorized in quartiles, being the lowest quartile the reference group.

We considered several variables as potential confounders and covariates (e.g. energy intake, nutrients intakes, physical activity, anthropometrics variables, age, gynaecological history, etc.). When inclusion of a potential covariate resulted in a change of the p-value corresponding to the dietary index variable less than 0.10, this covariate was kept in the final models. Hence, the covariates contained in the final models were: total energy intake (kcal/day), BMI (Kg/m^2), moderate-vigorous exercise (hours/week), adjusted caffeine intake (mg/day) and adjusted carbohydrates intake (g/day). We used logistic regression to analyse the association between dietary indices (quartiles) and presence of PCOS, as well as PCOS' phenotypes

P-values ≤ 0.05 were considered statistically significant. All statistical analyses were performed in IBM SPSS 25.0 (IBM Corporation, Armonk, New York, USA).

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3. Results

The average age was 29.1 (SD: 5.7) years. Table 1 shows demographic characteristics and nutrient intake across quartiles of adherence to healthful dietary scores for the study sample. AHEI, AHEI-2010, AMED indices presented a similar "pattern": women with higher adherence to any of these dietary scores had a higher age, physical activity and caffeine, carbohydrates and ω-3 fatty acids intake, but lower BMI. There was an increase of total energy intake across quartiles for AHEI, AMED and DASH scores, a decrease for rMED and no differences for AHEI-2010. In addition, greater adherence to any of these scores was associated with less intake of saturated fatty acids, except DASH score. Differences between median values scores across quartiles of rMED index score were different compared to the other dietary indices. Lastly, women with greatest adherences to rMED presented lower total energy and ω-3 fatty acids intake and were less physically active (Table 1).

In the multivariable analysis, we did not find any associations between the diet scores and total PCOS, neither ovulatory nor anovulatory PCOS (Table 2). In the analyses by PCOS phenotypes, women with higher adherences to the AHEI-2010 pattern were less likely to present PCOS, specifically "H+O" phenotype (P for trend= 0.02) (Table 3). This association was only significantly conducted by vegetables food item of AHEI-2010 index (P for trend= 0.081). In contrast, we observed an inverse lineal trend between DASH index and "O+POM" phenotype (P for trend =0.05).

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Table 1. Demographic characteristics and nutrient intake according to quintiles of adherence to dietary quality indices (n = 275)

Median value	AHEI			AHEI -2010			aMED			rMED			DASH		
	Q1 (13-32) n=70	Q4 (48-78) n= 68	P[1]	Q1 (27-56) n=69	Q4 (72-97) n= 68	P	Q1 (0-3) n=69	Q4 (7-10) n= 55	P	Q1 (2-9) n=165	Q4 (13-15) n= 27	P	Q1 (11-19) n=74	Q4 (28-35) n= 61	P[1]
Age (years)	27.5 (23.0; 32.0)	31.0 (26.0; 34.8)	0.07	28.0 (23.5; 32.0)	33.0 (29.0; 35.0)	0.00	27.0 (23.0; 32.0)	30.0 (26.0; 34.0)	0.01	29.0 (24.0;33.0)	31.0 (26.0;34.0)	0.43	31.0 (23.8; 35.0)	28.0 (24.0; 33.0)	0.25
BMI (kg/m^2)	25.2 (21.4; 32.3)	21.6 (20.1; 23.9)	0.00	25.9 (20.5; 30.9)	21.7 (20.1; 23.7)	0.01	24.2 (20.9; 30.9)	21.9 (20.6; 24.6)	0.00	22.7 (20.1;27.5)	22.0 (19.7;24.3)	0.14	23.2 (20.8; 28.1)	21.9 (20.4; 26.6)	0.91
Calories intake (Kcal)	1537.5 (1230.6; 1972.7)	2188.3 (1723.1; 2847.6)	0.00	1908.1 (1448.5; 2310.5)	1737.8 (1420.7; 2358.6)	0.67	1456.9 (1178.5; 1937.7)	2131.7 (1672.4; 2928.4)	0.00	1945.3 (1605.1;2384.6)	1466.2 (1288.2;1832.3)	0.00	1338.0 (1086.8; 1570.6)	2775.2 (2211.5; 3307.3)	0.00
Physical activity (h/wk)	3.6 (0.5; 11.9)	8.4 (5.5; 14.0)	0.00	5.0 (2.0; 14.0)	8.0 (5.3; 14.3)	0.00	4.7 (0.6; 10.8)	8.0 (5.5; 13.8)	0.00	6.0 (2.3;13.7)	4.3 (0.0; 8.5)	0.01	5.0 (0.8; 10.3)	8.0 (3.1; 15.9)	0.17
Alcohol (g/day)	0.4 (0.0; 1.4)	3.6 (1.9; 6.3)	0.00	0.5 (0.0; 1.7)	3.6 (1.3; 6.6)	0.00	0.9 (0.0; 2.4)	5.8 (2.9; 8.1)	0.00	1.3 (0.0;3.5)	7.0 (3.8; 10.0)	0.00	1.3 (0.5; 5.9)	2.9 (0.6; 5.4)	0.64
Caffeine (mg/day)	31.2 (8.3; 49.4)	48.3 (18.5; 77.1)	0.02	33.4 (13.5; 55.2)	51.7 (22.4; 81.3)	0.04	35.4 (13.2; 56.2)	56.6 (22.0; 94.8)	0.05	37.0 (14.7;68.4)	46.3 (20.4; 99.0)	0.21	37.3 (12.5; 67.3)	47.3 (18.0; 79.9)	0.46
Carbohydrate (g/day)	158.5 (131.4; 181.5)	192.4 (170.9; 207.2)	0.00	170.5 (137.3; 196.1)	190.5 (167.8; 207.0)	0.00	165.0 (132.8; 193.6)	186.8 (164.5; 198.2)	0.01	175.0 (149.7;200.4)	167.2 (155.4; 193.5)	0.83	163.4 (139.3; 189.1)	185.3 (166.7; 204.0)	0.00
Saturated fats (g/day)	22.1 (19.7; 25.3)	17.9	0.00	22.5	16.6	0.00	21.3	18.8	0.00	21.2 (18.5;24.4)	17.9 (15.6; 21.4)	0.00	19.7	21.6	0.02

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Median value	AHEI			AHEI -2010			aMED			rMED			DASH		
	Q1 (13-32) n=70	**Q4 (48-78) n= 68**	**P[1]**	**Q1 (27-56) n=69**	**Q4 (72-97) n= 68**	**P**	**Q1 (0-3) n=69**	**Q4 (7-10) n= 55**	**P**	**Q1 (2-9) n=165**	**Q4 (13-15) n= 27**	**P**	**Q1 (11-19) n=74**	**Q4 (28-35) n= 61**	**P[1]**
Omega-3 (mg/day)	1.3 (1.2; 1.4)	(14.2; 21.4) 1.7 (1.5; 2.2)	0.00	(19.9; 26.0) 1.3 (1.1; 1.5)	(13.8; 19.7) 1.6 (1.4; 2.0)	0.00	(19.2; 24.9) 1.2 (1.0; 1.4)	(16.3; 22.1) 1.7 (1.5; 2.2)	0.00	1.5 (1.3;2.0)	1.4 (1.1; 1.5)	0.00	(16.2; 22.5) 1.3 (1.1; 1.5)	(19.3; 25.4) 1.8 (1.5; 2.2)	0.00

. [1]Kruskal-Wallis tests were used to test for associations between the level of diet indeces

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Table 2. Multivariate adjusted[1] ORs between dietary indices[2] and total, anovulatory and ovulatory PCOS (total *n* = 276; cases = 121, controls n = 155).

Range for each quartile of index[2]		Total PCOS Cases= 121			Anovulatory Cases= 88			Ovulatory Cases= 33		
		OR[1]	95%CI	P	OR	95%CI	P	OR	95%CI	P
AHEI2010										
Q1 (27-56)		Ref.			Ref.			Ref.		
Q2 (57-63)		1.0	(0.5; 2.0)	0.93	1.1	(0.5; 2.3)	0.81	0.8	(0.3; 2.3)	0.69
Q3 (64-71)		0.6	(0.3; 1.2)	0.14	0.5	(0.2; 1.1)	0.09	1.1	(0.4; 2.9)	0.89
Q4 (72-97)		0.7	(0.3; 1.6)	0.44	0.9	(0.4; 2.0)	0.79	0.7	(0.2; 2.1)	0.50
	P trend		0.41			0.24			0.84	
AHEI										
Q1 (13-32)		Ref.			Ref.			Ref.		
Q2 (33-40)		1.6	(0.8; 3.5)	0.22	1.8	(0.8; 3.9)	0.17	1.0	(0.4; 2.8)	1.00
Q3 (41-47)		1.0	(0.5; 2.3)	0.94	1.2	(0.5; 2.8)	0.66	0.8	(0.2; 2.4)	0.65
Q4 (48-78)		0.8	(0.3; 2.0)	0.65	1.0	(0.4; 2.6)	0.97	0.7	(0.2; 2.2)	0.50
	P trend		0.31			0.41			0.86	
aMED										
Q1 (0-3)		Ref.			Ref.			Ref.		
Q2(4)		0.6	(0.3; 1.2)	0.16	0.8	(0.4; 1.7)	0.58	0.5	(0.2; 1.5)	0.23
Q3 (5-6)		0.9	(0.4; 2.0)	0.86	1.2	(0.5; 2.6)	0.70	0.7	(0.2; 2.0)	0.50
Q4 (7-10)		0.8	(0.4; 2.0)	0.68	0.8	(0.3; 2.1)	0.71	1.0	(0.3; 3.3)	0.97
	P trend		0.48			0.75			0.55	
rMED										
Q1 (2-9)		Ref.			Ref.			Ref.		
Q2 (10)		0.9	(0.4; 2.0)	0.82	1.1	(0.5; 2.5)	0.82	0.7	(0.2; 2.3)	0.59
Q3 (11-12)		0.6	(0.3; 1.3)	0.19	0.9	(0.4; 2.0)	0.74	0.3	(0.1; 1.5)	0.15
Q4 (13-15)		1.6	(0.7; 3.9)	0.31	1.6	(0.6; 4.1)	0.33	1.1	(0.3; 3.8)	0.85
	P trend		0.33			0.73			0.48	
DASH										
Q1 (11-19)		Ref.			Ref.			Ref.		
Q2 (20-23)		0.8	(0.4; 1.7)	0.58	1.0	(0.5; 2.3)	0.98	0.6	(0.2; 1.9)	0.44
Q3 (24-27)		1.1	(0.5; 2.5)	0.84	0.9	(0.4; 2.3)	0.90	1.3	(0.4; 3.9)	0.66
Q4 (28-35)		1.6	(0.5; 4.7)	0.39	2.9	(0.9; 9.3)	0.07	0.4	(0.1; 2.0)	0.26
	P trend		0.51			0.09			0.26	

[1]Adjusted for calories intake (kcal/day), BMI, moderate-vigorous physical activity (h/week), caffeine intake (mg/day) and carbohydrates intake (g/day)

[2]AHEI-2010, Alternate Healthy Index 2010; AHEI, Alternate Healthy Index; aMED, Alternate Mediterranean Diet Score; rMED, Relative Mediterranean Diet Score; DASH, Dietary Approaches to Stop Hypertension

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Table 3. Multivariate adjusted[1] ORs between dietary indices[2] and phenotypes[3-6] of PCOS (*n* = 276).

Index[2]	H + O+POM[3] Cases= 52			H+ O[4] Cases= 18			H+ POM[5] Cases= 33			O+POM[6] Cases= 18		
	OR	**95%CI**	**P**	**OR**	**95%CI**	**P**	**OR**	**95%CI**	**P**	**OR**	**95%CI**	**P**
AHEI-2010												
Q1 (27-56)	Ref.			Ref.			Ref.			Ref.		
Q2 (57-63)	1.5	(0.7; 3.5)	0.34	**0.2**	**(0.0; 0.7)**	**0.01**	0.8	(0.3; 2.3)	0.69	4.9	(0.9; 25.6)	0.06
Q3 (64-71)	0.7	(0.3; 1.8)	0.43	**0.1**	**(0.0; 0.9)**	**0.04**	1.1	(0.4; 2.9)	0.89	2.5	(0.4; 16.7)	0.35
Q4 (72-97)	1.1	(0.4; 2.9)	0.85	0.2	(0.0; 1.2)	0.08	0.7	(0.2; 2.1)	0.50	4.9	(0.8; 30.4)	0.09
P trend		0.42			**0.02**			0.84			0.24	
AHEI												
Q1 (13-32)	Ref.			Ref.			Ref.			Ref.		
Q2 (33-40)	2.3	(0.9; 6.3)	0.09	0.4	(0.1; 1.5)	0.17	1.0	(0.4; 2.8)	1.00	2.9	(0.7; 12.9)	0.15
Q3 (41-47)	2.7	(1.0; 7.3)	0.06	0.0	(0.0; −)	1.00	0.8	(0.2; 2.4)	0.65	1.8	(0.4; 8.8)	0.48
Q4 (48-78)	1.7	(0.5; 5.5)	0.38	0.3	(0.0; 1.6)	0.15	0.7	(0.2; 2.2)	0.50	1.5	(0.2; 9.5)	0.69
P trend		0.21			0.41			0.86			0.48	
aMED												
Q1 (0-3)	Ref.			Ref.			Ref.			Ref.		
Q2(4)	1.5	(0.6; 3.7)	0.38	**0.2**	**(0.0; 0.9)**	**0.04**	0.5	(0.2; 1.5)	0.23	1.1	(0.2; 5.8)	0.90
Q3 (5-6)	1.4	(0.6; 3.7)	0.46	0.3	(0.1; 1.4)	0.13	0.7	(0.2; 2.0)	0.50	3.6	(0.8; 16.8)	0.11
Q4 (7-10)	1.1	(0.4; 3.5)	0.86	0.2	(0.0; 1.8)	0.15	1.0	(0.3; 3.3)	0.97	3.2	(0.5; 18.7)	0.20
P trend		0.78			0.12			0.55			0.28	
rMED												
Q1 (2-9)	Ref.			Ref.			Ref.			Ref.		
Q2 (10)	1.1	(0.4; 2.9)	0.86	0.7	(0.1; 6.3)	0.77	0.7	(0.2;2.3)	0.59	1.4	(0.4; 5.6)	0.63
Q3 (11-12)	0.8	(0.3; 2.1)	0.60	1.5	(0.4; 5.6)	0.57	0.3	(0.1; 1.5)	0.15	0.5	(0.1; 2.4)	0.35
Q4 (13-15)	1.9	(0.6; 5.4)	0.25	1.6	(0.3; 9.1)	0.61	1.1	(0.3; 3.8)	0.85	0.6	(0.1; 4.9)	0.60
P trend		0.60			0.88			0.48			0.68	

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Index	H + O+POM Cases= 52			H+ O Cases= 18			H+ POM Cases= 33			O+POM Cases= 18		
	OR	**95%CI**	**P**	**OR**	**95%CI**	**P**	**OR**	**95%CI**	**P**	**OR**	**95%CI**	**P**
DASH												
Q1 (11-19)	Ref.			Ref.			Ref.			Ref.		
Q2 (20-23)	1.0	(0.4; 2.6)	0.96	1.1	(0.3; 4.3)	0.84	0.6	(0.2; 1.9)	0.44	0.8	(0.1; 5.1)	0.79
Q3 (24-27)	0.8	(0.2; 2.4)	0.64	0.3	(0.1; 2.3)	0.27	1.3	(0.4; 3.9)	0.66	4.6	(0.9; 24.4)	0.08
Q4 (28-35)	3.2	(0.9; 11.9)	0.08	0.0	(0.0; −)	1.00	0.4	(0.1; 2.0)	0.26	**9.2**	**(1.1; 74.7)**	**0.04**
P $_{trend}$		0.07			0.84			0.26			**0.05**	

[1]Adjusted for calories intake (kcal/day), BMI, moderate-vigorous physical activity (h/week), caffeine intake (mg/day) and carbohydrates intake (g/day)

[2]AHEI-2010, Alternate Healthy Index 2010; AHEI, Alternate Healthy Index; aMED, Alternate Mediterranean Diet Score; rMED, Relative Mediterranean Diet Score; DASH, Dietary Approaches to Stop Hypertension

[3]H+O+POM "Hyperandorgenism + Oligo/amenorrhea + Polycystic ovaries morphology" phenotype

[4]H+O "Hyperandorgenism + Oligo/amenorrhea" phenotype

[5]H+POM "Hyperandorgenism + Polycystic Ovary Morphology" phenotype

[6]O+POM "Oligo/amenorrhea + Polycystic Ovary Morphology" phenotype

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4. Discussion

We found an association between the prior dietary indices AHEI-2010 and PCOS, specifically "H+O" phenotype. Besides, there was a borderline inverse relation between DASH score and "O+POM" PCOS' phenotype.

In detail, women with higher adherences to the AHEI-2010 score were less likely to present "H+O" PCOS' phenotype. At this point in time, there are two studies evaluating the association between AHEI and PCOS. No differences were detected in diet quality (using Alternate Healthy Index-2015) and dietary intake, between PCOS cases and controls in a sample of women from New York [54]. However, a comparable study found that Brazilian Healthy Eating Index was negatively correlated with BMI and waist circumference [55].

In contrast, we have not found an explanation for the inverse relationship between DASH index and "O+POM" phenotype. Another question is, our study subjects were incident and prevalent PCOS cases, so women could have recently changed their dietary patterns due to their symptoms. In fact, healthy dietary pattern adherence and physical exercise are the first line of treatment recommended for PCOS patients [56–60]. However, the monitoring of these changes in diet and physical activity is not integrated in the usual clinical practice [56,61]. So, it is difficult to evaluate the diet effect on quality of life of PCOS patients. Moreover, there are few studies that have explored diet changes after PCOS diagnostic, and their results are diverse [62–66] . We may also note that "H+O" phenotype had a smaller sample size (n=18), therefore we cannot rule out it may be a chance finding.

Lastly, we have not found similar studies that explore the association of diet among PCOS phenotypes. In fact, clinical manifestations of PCOS are notably different among PCOS phenotypes, such as presenting androgenism or not, although all of them join together the same syndrome [67].

So, we found Mediterranean diet was a protective factor only for "H+O" phenotype. It may be due to diet may be more beneficial in these women than other phenotypes or controls. One reason which could possibly explain this association is "H+O" phenotype women presented higher prevalence of overweight and obesity (52.9%) than controls (33.1%) and other PCOS phenotypes (33.9%). Indeed, nutritional randomized controlled trials in PCOS patients have shown more effective reducing symptoms in women with overweight or obesity. Other reason could be that these randomized controlled trials, through diet, have accomplished the reduction in hyperinsulinemia and, as a consequence, to diminish hyperandrogenism. In previous studies, PCOS with hyperandrogenism increased around two fold (OR= 2.2; 95% CI: 1.9-2.6) the incidence of metabolic syndrome and three times (OR = 3.1; 95%CI : 2.3–4.2) the incidence of insulin resistance compared to PCOS women without hyperandrogenism [68].

To our knowledge, our study is the first one analysing dietary indices among different PCOS phenotypes according to the Rotterdam criteria, instead other classification such as "anovulatory" and "ovulatory" PCOS. Our modest findings may reveal that it would be necessary a dietary recommendations based on PCOS phenotypes, according to their physiological differences. Likewise, it has been reported that a phenotypic approach would be highly convenient for clinical practice and epidemiologic research (Lizneva et al. 2016).

Another question is we found significatively differences between AHEI-2010 index and no the other indices. AHEI-2010 is the only one of the five indices, which stablishes the maximum score for whole grains is 75g/day. This quantity reduces more the glycemic load than the other indices. The other different item is that if the subjects do not drink any sugar-sweetened beverages and fruit juice they get a maximum score, but are given 0 points if they drink one or more servings per day compared to the other four? 5 indices. DASH score has an item for sweetened beverages; however, it is based on quintiles intake. If subject drinks sweetened beverages would be more penalized in AHEI-2010 than in DASH index. We explored if a higher consumption of any single food group of AHEI-2010 index could explain the inverse association. Only vegetables intake was close to statistical significance (Thus, the effect of AHEI-2010 dietary pattern in PCOS phenotype with hyperandrogenism and oligovulation may a synergic effect of food group and not an isolate action. Moreover, compared to

individual food items, dietary patterns measured a priori via dietary indices can incorporate complex interactions among foods/nutrients and can better the risk for some diseases [70]
Unexpectedly, the highest quartile of DASH index was positively associated with the "O+POM" phenotype, increasing the risk of PCOS with a high DASH adherence. Contrarily, DASH diet may improve BMI and other metabolic parameters which could reduce PCOS symptomatology. Three studies have observed that adherence to the DASH diet between 8 and 12 weeks among PCOS women could have beneficial effects on BMI, androstenedione, AMH, insulin and lipid metabolism [71] [72]. An interventional study with DASH diet for 8 weeks led to a significant reduction in serum insulin, triglycerides and very-low-density lipoprotein cholesterol, and a significant increase in total antioxidant capacity, glutathione levels [73] and c-reactive protein [33]. DASH diet is one kind of the healthy dietary patterns favoring seafood, poultry, whole grains, fruits, and vegetables consumption which have been related to better fertility in women and better semen quality in men [74]. The small sample size for the "O+POM" (n= 18) phenotype in the present study, the missing values in some items of the FFQ and the high rage of confidence interval may explain it as a potential chance finding. Furthermore, the relation between diet and fertility in women has been studied along the last decades [75]. Based on Nurse Health Study cohort, it was defined the Fertility Diet with an attributable risk of ovulatory disorder infertility of 66% (95% CI: 29-86%) [76]. Although some studies have evaluated PCOS related to dietary patterns like AHEI and DASH, most of the literature on this topic have evaluated low carbohydrate high proteins diets [77,78]. In women with PCOS, it would be worthwhile to carry out interventional studies with a mix approximation: firstly, to follow a high protein low carbohydrate diet and, secondly, a Mediterranean Diet. High protein low carbohydrate diet may allow reducing body weight, hyperinsulinemia and inflammation rapidly. Mediterranean Diet may be the second step for maintenance the previous results with less secondary effects, and increment adherence to healthy diet to long term.
The current study has some limitations. First, we used a FFQ as dietary assessment method that has limitations, but comparable to other tools for assessment of food intake in nutritional epidemiology studies. In addition, all self-reported dietary intakes are subject to misreporting, with different types of foods likely to be either over or under-reported [79]. However, we used a validated FFQ with a mean correlation coefficient for nutrient intakes equal to 0.40 for reproducibility and 0.47 for validity. Second, case-control studies present higher risk of selection and information bias than other study designs. Nevertheless, we selected both cases and controls from the same population of women who visited the same medical services in the same time period: a public hospital and outpatient clinics. Concerning information bias, if misclassification of PCOS status may have occurred, it would have contributed to underestimating the true magnitude of the relationship. Finally, we employed the Rotterdam criteria, which are widely used in gynecological studies and clinical practice.

In conclusion, we did not find any association between dietary indices (AHEI, AHEI 2010, AMED, RMED and DASH) and PCOS and its phenotypes. We only observed an inverse association between AHEI -2010 score and less probabilities of H+O phenotype. To our knowledge, our study is the first one evaluating the association between dietary indices and four different phenotypes of PCOS, according to the Rotterdam criteria and using Mediterranean Diet indices (aMED and rMED) to assess dietary patterns in women with PCOS. Further adequately powered studies are required to clarify if there are an association between dietary indices and PCOS' phenotypes. In addition, it is necessary prospective studies to monitor and evaluate the effect of diet in PCOS women during regular clinical practice, which is one of the first treatment options for many women with PCOS according the international guidelines.

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