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Association between HLA-Cw*0602 polymorphism and psoriasis risk: a meta-analysis

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ABSTRACT. Numerous studies have evaluated the association between human leukocyte antigen (HLA) Cw*0602 polymorphism and psoriasis risk. However, the results have been inconsistent. We made a meta-analysis of the association between HLA-Cw*0602 polymorphism and psoriasis risk. Eighteen studies were retrieved, reporting a total of 3419 psoriasis patients and 3297 healthy controls. The associations between HLA-Cw*0602 polymorphism and psoriasis risk were estimated by pooled odds ratio (OR) and 95% confidence interval (95%CI). We found significant associations between HLA-Cw*0602 polymorphism and psoriasis risk in the comparisons of positive versus negative alleles (OR = 4.55, 95%CI = 3.65-5.67, P < 0.00001); positive homozygote versus negative homozygote combined with heterozygote (OR = 14.00, 95%CI = 8.47-23.15, P < 0.00001); positive homozygote combined with heterozygote versus negative homozygote (OR = 5.11, 95%CI = 3.86-6.76, P < 0.00001); positive homozygote versus negative homozygote (OR = 23.03, 95%CI = 13.95-38.00, P < 0.00001), and

positive homozygote versus heterozygote (OR = 4.21, 95%CI = 2.35-7.00, P < 0.00001). In conclusion, the positive allele of HLA-Cw*0602 polymorphism appears to be a risk factor for psoriasis.

Key words: Human leukocyte antigen; Polymorphism; Psoriasis; Risk; Meta-analysis

INTRODUCTION

Psoriasis is a chronic life-long inflammatory disease that primarily affects the skin (Raychaudhuri and Gross, 2000a). Patients with psoriasis usually have sharply demarcated chronic erythematous plaques covered by silvery white scales, which most commonly appear on the elbows, knees, scalp, umbilicus, and lumbar area (Luft, 2005; Schon and Boehncke, 2005). The pathologic characteristics of psoriasis are marked hyperplasia and altered differentiation of the epidermis, accelerated blood flow, leukocytic infiltration of the skin, and a poorly understood relationship with nervous-system function (Schon and Boehncke, 2005). Although only rarely life-threatening, psoriasis has a high degree of morbidity and causes poor quality of life, and also impacts health care systems and society in general (Nestle et al., 2009). The prevalence and incidence estimates of psoriasis show ethnic and geographic variations, being generally more common in the colder north than in the tropics. The population prevalence of psoriasis has been reported to range from 0 to 11.8% (Chandran and Raychaudhuri, 2010). Psoriasis is less prevalent in China and Japan than in Europe, and is entirely absent in natives of the Andean region of South America (Chandran and Raychaudhuri, 2010; Naldi and Mercuri, 2010).

Genetic epidemiologic studies have shown that genetic and environmental factors both contribute to the pathophysiology of psoriasis (Lowes et al., 2007; Griffiths and Barker, 2007). Environmental risk factors including streptococcal pharyngitis, stressful life events, low humidity, drugs, HIV infection, trauma, smoking, and obesity have been associated with psoriasis (Raychaudhuri and Gross, 2000b; Raychaudhuri and Farber, 2001; Reveille and Williams, 2006; Chandran and Raychaudhuri, 2010). Numerous family and twin studies have clearly demonstrated that psoriasis has a strong genetic basis. The illness develops in as many as half of the siblings of persons with psoriasis when both parents are affected, but prevalence falls to 16% when only one parent has psoriasis and to 8% when neither parent is affected (Watson et al., 1972). The concordance rate for monozygotic twins is around 70%, as compared with some 20% for dizygotic twins, which further supports the concept of genetic predisposition (Farber et al., 1974; Brandrup et al., 1982). Within the past decade, a number of psoriasis susceptibility loci have been mapped using linkage methods. These include psoriasis susceptibility locus PSORS1~PSORS9 within the major histocompatibility complex (MHC) (Duffin et al., 2008). However, the identities of the candidate genes involved remain unclear. By far, the strongest association is with a locus on chromosome 6p21 (PSORS1), which appears to be associated with up to 50% of cases of psoriasis. The common gene candidates in PSORS1 locus include human leukocyte antigen (HLA) Cw6, CDSN, HCR, HERV-K, POU5F1, and PSORS1C3 (Duffin et al., 2008). Since the PSORS1 locus provides the strongest linkage with psoriasis in genome-wide linkage scans, candidate genes in this region have been investigated in different populations. Psoriasis was found to be associated with HLA-C and confirmed by molecular methods. Recent data strongly indicate that HLA-Cw*0602 is the susceptibil-

ity allele of psoriasis in the PSORS1 locus (Nair et al., 2006; Fan et al., 2007; Liu et al., 2008; Mallbris et al., 2009). This is consistent with the idea that the pathogenesis of psoriasis involves autoantigen recognition by epidermal $CD8^+$ T lymphocytes (Valdimarsson, 2007).

Meta-analysis can be a useful tool in detecting an association that could otherwise remain masked in the sample size studies, especially in those evaluating rare allele frequency polymorphisms (Attia et al., 2003). The aim of this study was to investigate the association between HLA-Cw*0602 polymorphism and psoriasis risk by conducting a meta-analysis from all eligible case-control studies published to date.

MATERIAL AND METHODS

Literature search strategy

We searched Pubmed and Embase databases by two reviewers (D. Wu and Y. Wu) to retrieve papers linking HLA-Cw*0602 polymorphism and psoriasis risk available by October 2010 without language restrictions, using the following key words: "HLA-CW*0602 antigen", "HLA-CW*0602", "HLA-Cw6", "HLA-C Antigens", "HLA-C", "polymorphism", "single nucleotide polymorphism", "genetic polymorphism", "psoriasis", and "psoriasis vulgaris". The reference lists of major textbooks, reviews, and included articles were identified through manual searches to find other potentially eligible studies.

Inclusion and exclusion criteria

Studies were included in this meta-analysis if they met the following criteria: i) case-control studies that addressed psoriasis cases and healthy controls; ii) studies that evaluated the association between HLA-Cw*0602 polymorphism and psoriasis risk; iii) studies that included sufficient genotype data for extraction, and iv) healthy controls were in Hardy-Weinberg equilibrium (HWE). Studies were excluded when: i) not case-control studies that evaluated the association between HLA-Cw*0602 polymorphism and psoriasis risk; ii) case reports, letters, reviews, meta-analysis, and editorial articles; iii) studies that were based on incomplete raw data and those with no usable data reported; iv) duplicate data were contained in the studies; v) family-based design was used, and vi) healthy controls were not in HWE.

Data extraction

Using a standardized form, data from published studies were extracted independently by two reviewers (J.L. Liu and B. Wang) to populate the necessary information. From each of the included articles the following information was extracted: first author, year of publication, country, ethnicity, study design, source of cases and controls, number of cases and controls, detection methods, and evidence of HWE in controls. For conflicting evaluations, an agreement was reached following a discussion.

Quality assessment of included studies

The quality of papers was also independently assessed by two reviewers (D. Wu and

Y. Wu) based on the STROBE quality score systems (Vandenbroucke et al., 2007). Thirty items relevant to the quality appraisal were used for assessment in this meta-analysis. Quality scores ranged from 0 to 30. We defined 10, 20 and 30 scores as low, moderate and high grade, respectively. Any discrepancies between the two reviewers were resolved by discussion and consultation with a third reviewer (X.D. Zhang).

Statistical analysis

Meta-analysis was performed using the Review Manager version 5.0.25 (provided by The Cochrane Collaboration) and STATA package version 9.2 (Stata Corporation, College Station, TX, USA). The following contrasts for HLA-Cw*0602 polymorphism were evaluated: the comparison of positive allele versus negative allele; the comparison of positive homozygote versus negative homozygote combined with heterozygote; the comparison of positive homozygote combined with heterozygote versus negative homozygote; the comparison of positive homozygote versus negative homozygote, and the comparison of positive homozygote versus heterozygote. The strength of the associations between HLA-Cw*0602 polymorphism and psoriasis risk was estimated by odds ratio (OR) and 95% confidence interval (95%CI). Between-study heterogeneities were estimated using the Cochran *Q*-test (Higgins and Thompson, 2002; Zintzaras and Ioannidis, 2005). We also quantified the effect of heterogeneity by the I^2 test. I^2 ranges between 0 and 100% and represents the proportion of inter-study variability that can be attributed to heterogeneity rather than chance. I^2 values of 25, 50 and 75% were defined as low, moderate and high estimates, respectively. When a significant *Q*-test ($P < 0.10$) or $I^2 > 50\%$ indicated heterogeneity across studies, the random effects model was used for meta-analysis, or else the fixed effects model was used. We tested whether genotype frequencies of controls were in HWE using the χ^2 test. Subgroup analysis based on ethnicity was used to explore and to explain the diversity among the results of different studies. Sensitivity analysis was mainly performed by sequential omission of individual studies. Publication bias was investigated by Begg's funnel plot, and funnel plot asymmetry was assessed by the Egger linear regression test (Peters et al., 2006), statistical significance was considered when the P value of the Egger test was <0.05. All P values were two-sided. To ensure the reliability and the accuracy of the results, two reviewers (J.L. Liu and B. Wang) populated the data in the statistic software programs independently and got the same results.

RESULTS

Studies included in the meta-analysis

The search strategy retrieved 145 potentially relevant studies. According to the inclusion criteria, 18 studies with full-text were included in this meta-analysis (Rani et al., 1998; Gonzalez et al., 1999; Asumalahti et al., 2000; Brazzelli et al., 2000; Gudjonsson et al., 2003; Luszczek et al., 2003; Zhang et al., 2003; Sánchez et al., 2004; Martínez-Borra et al., 2003, 2005; Holm et al., 2005a,b; Chang et al., 2004, 2005, 2006; Płoski et al., 2006; Jobim et al., 2008; Fojtíková et al., 2009) and 127 studies were excluded. The flow chart for the study selection is summarized in Figure 1. These 18 case-control studies selected included a total of 3419 psoriasis cases and 3297 healthy controls. All studies were case-control studies,

which evaluated the association between HLA-Cw*0602 polymorphism and psoriasis risk. The publishing year of the included studies ranged from 1998 to 2009. All the articles were written in English. The source of controls was mainly based on healthy populations. The HWE test was performed on genotype distribution of the controls, all of them were in HWE ($P > 0.05$). The baseline characteristics and methodological quality of all studies included are summarized in Table 1. The genotype distribution and risk allele frequency are summarized in Table 2.

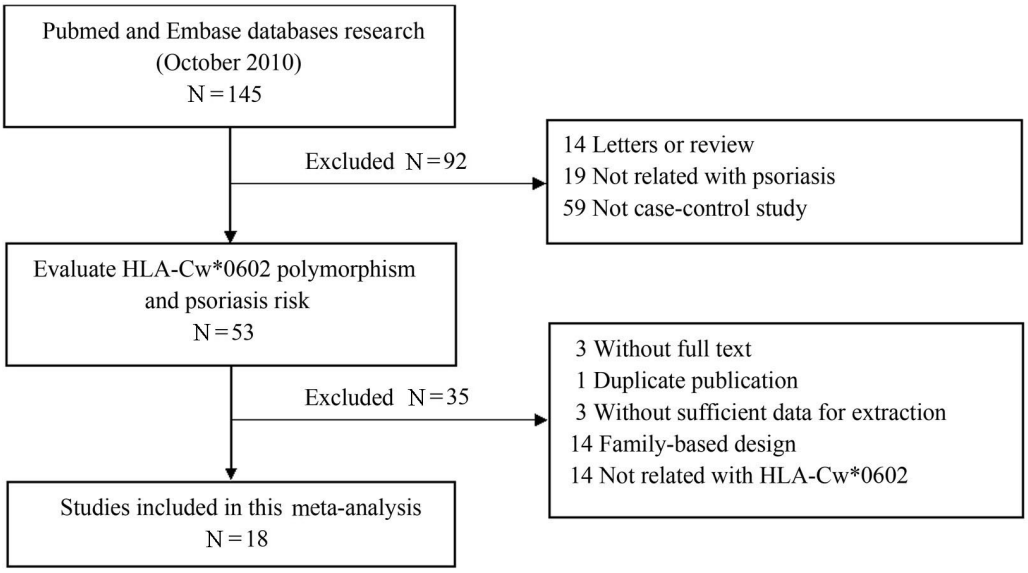

Figure 1. Flow chart showing study selection procedure.

Main results, subgroup and sensitivity analysis

A summary of the meta-analysis findings of the association between HLA-Cw*0602 polymorphism and psoriasis risk is shown in Table 3. Meta-analysis results showed significant associations between HLA-Cw*0602 polymorphism and psoriasis risk in all comparisons of positive allele versus negative allele (OR = 4.55, 95%CI = 3.65-5.67, $P < 0.00001$); positive homozygote versus negative homozygote combined with heterozygote (OR = 14.00, 95%CI = 8.47-23.15, $P < 0.00001$); positive homozygote combined with heterozygote versus negative homozygote (OR = 5.11, 95%CI = 3.86-6.76, $P < 0.00001$); positive homozygote versus negative homozygote (OR = 23.03, 95%CI = 13.95-38.00, $P < 0.00001$), and positive homozygote versus heterozygote (OR = 4.21, 95%CI = 2.35-7.00, $P < 0.00001$).

In the subgroup analysis based on ethnicity, subjects of all studies included were divided into Caucasian and Asian populations. Results of subgroup analysis confirmed that there were significant associations between HLA-Cw*0602 polymorphism and psoriasis risk in both Caucasian and Asian populations (Table 4).

Table 1. Baseline characteristics of studies included in the meta-analysis.

First author (year)	Country	Ethnicity	Source of cases	Source of controls	Detection method	Number of subjects		Quality score
						Case	Control	
Rani, 1998	India	Asian	Hospital-based	Population-based	PCR-SSOP	38	84	21
Gonzalez, 1999	Spain	Caucasian	Hospital-based	Population-based	PCR-SSP	45	177	19
Asumalahti, 2000	Finland	Caucasian	Hospital-based	Population-based	PCR-SSP	100	93	22
Brazzelli, 2000	Italy	Caucasian	Hospital-based	Population-based	PCR-SSP	40	122	23
Gudjonsson, 2003	Iceland	Caucasian	Hospital-based	-	-	1006	512	17
Łuszczek, 2003	Poland	Caucasian	Hospital-based	Population-based	PCR-SSP	102	123	24
Martínez-Borra, 2003	Spain	Caucasian	Hospital-based	Population-based	PCR-SSP	95	104	21
Zhang, 2003	China	Asian	Hospital-based	Population-based	PCR-SSP	166	204	23
Chang, 2004	Taiwan	Asian	Hospital-based	Population-based	PCR	115	103	22
Sánchez, 2004	Sweden	Caucasian	Hospital-based	Population-based	PCR	98	120	24
Chang, 2005	Taiwan	Asian	Hospital-based	Population-based	PCR-RFLP	143	188	22
Holm, 2005a	Sweden	Caucasian	Hospital-based	Population-based	PCR	239	371	25
Holm, 2005b	Sweden	Caucasian	Hospital-based	Population-based	PCR	218	127	26
Martínez-Borra, 2005	Spain	Caucasian	Hospital-based	Population-based	PCR-SSP	59	79	21
Chang, 2006	Taiwan	Asian	Hospital-based	Population-based	PCR	178	203	22
Płoski, 2006	Poland	Caucasian	Hospital-based	Population-based	PCR-SSP	116	123	24
Jobim, 2008	Brazil	Caucasian	Hospital-based	Population-based	PCR-SSP	79	110	26
Mallbris, 2009	Sweden	Caucasian	Hospital-based	Population-based	PCR	582	454	24

PCR = polymerase chain reaction; SSOP = sequence-specific oligonucleotide probes; SSP = sequence-specific primer; RFLP = restriction fragment length polymorphism.

Table 2. The genotype distribution and risk allele frequency of all studies included.

First author (year)	Cases					Controls					HWE test in controls	
	Total	+/+	+/−	−/−	Frequency	Total	+/+	+/−	−/−	Frequency	χ^2	P value
Rani, 1998	38	5	17	16	0.355	84	1	16	67	0.107	0.002	0.968
Gonzalez, 1999	45	6	20	19	0.356	177	1	31	145	0.093	0.229	0.632
Asumalahti, 2000	100	4	33	63	0.205	93	0	8	85	0.043	0.188	0.665
Brazzelli, 2000	40	3	14	23	0.250	122	1	19	102	0.086	0.012	0.912
Gudjonsson, 2003	1006	68	578	360	0.355	512	4	77	431	0.083	0.075	0.784
Łuszczek, 2003	102	31	50	21	0.549	123	1	20	102	0.089	0.000	0.986
Martínez-Borra, 2003	95	8	39	48	0.289	104	1	15	88	0.082	0.159	0.690
Zhang, 2003	166	5	49	112	0.178	204	1	20	183	0.054	0.312	0.577
Chang, 2004	115	4	34	77	0.183	103	0	13	90	0.063	0.467	0.494
Sánchez, 2004	98	15	46	37	0.388	120	0	13	107	0.054	0.394	0.530
Chang, 2005	143	3	38	102	0.154	188	0	18	170	0.048	0.475	0.491
Holm, 2005a	239	7	66	166	0.167	371	1	38	332	0.054	0.006	0.937
Holm, 2005b	218	28	100	90	0.358	127	0	15	112	0.059	0.500	0.479
Martínez-Borra, 2005	59	4	15	36	0.195	79	0	19	60	0.120	1.476	0.224
Chang, 2006	178	5	50	123	0.169	203	1	23	179	0.062	0.078	0.780
Płoski, 2006	116	1	14	101	0.069	123	0	8	115	0.033	0.139	0.709
Jobim, 2008	79	3	26	50	0.203	110	1	18	91	0.091	0.011	0.916
Mallbris, 2009	582	32	208	342	0.234	454	1	48	405	0.055	0.115	0.734

+ = positive allele; - = negative allele; HWE = Hardy-Weinberg equilibrium.

Table 3. Meta-analysis of associations between HLA-Cw*0602 polymorphism and psoriasis risk.

Comparison	Cases (n/N)	Controls (n/N)	OR	95%CI	P value	Heterogeneity		Effects model
						I^2	P value	
+ versus -	1861/6838	447/6594	4.55	3.65-5.67	<0.00001	69%	<0.00001	Random
Caucasian	1576/5686	351/5192	4.51	3.53-5.76	<0.00001	67%	0.0003	Random
Asian	285/1151	96/1402	4.66	2.69-8.06	<0.00001	78%	0.001	Random
+/+ versus -/- and +/-	232/3419	14/3297	14.00	8.47-23.15	<0.00001	0%	0.97	Fixed
Caucasian	210/2779	11/2515	15.61	8.83-27.60	<0.00001	0%	0.88	Fixed
Asian	22/640	3/782	7.94	2.70-23.32	0.0002	0%	0.99	Fixed
+/+ and +/- versus -/-	1629/3419	433/3297	5.11	3.86-6.79	<0.00001	76%	<0.00001	Random
Caucasian	1392/2843	340/2596	5.05	3.67-6.97	<0.00001	76%	<0.00001	Random
Asian	237/576	93/701	5.30	2.79-10.07	<0.00001	79%	0.0008	Random
+/+ versus -/-	232/2018	14/2878	23.03	13.95-38.00	<0.00001	0%	0.82	Fixed
Caucasian	184/1631	11/2267	21.81	12.28-38.73	<0.00001	0%	0.89	Fixed
Asian	48/387	3/611	28.10	10.17-77.63	<0.00001	19%	0.29	Fixed
+/+ versus +/-	232/1629	14/433	4.21	2.35-7.00	<0.00001	0%	0.99	Fixed
Caucasian	184/1392	11/340	3.91	2.19-6.98	<0.00001	0%	0.98	Fixed
Asian	48/237	3/93	5.36	1.86-15.44	0.002	0%	0.85	Fixed

+ = positive allele; - = negative allele; OR = odds ratio; 95%CI = 95% confidence interval. n = the number of participants with susceptibility alleles; N = the number of all participants in this group.

Table 4. Evaluation of publication bias by the Egger linear regression test.

Comparison	Coefficient	Standard error	*t*	P > |t|	95%CI
+ versus -	-1.55	1.19	-1.30	0.21	[-4.07-0.97]
+/+ versus -/- and +/-	0.20	0.52	0.38	0.71	[-0.90-1.29]
+/+ and +/- versus -/-	-2.15	1.30	-1.66	0.23	[-4.90-0.60]
+/+ versus -/-	-2.15	1.30	-1.66	0.23	[-4.07-0.97]
+/+ versus +/-	-0.31	0.63	-0.49	0.63	[-1.66-1.03]

+ = positive allele; - = negative allele; 95%CI = 95% confidence interval.

Significant heterogeneity ($P < 0.05$ or $I^2 > 50\%$) between studies was observed in the comparisons of positive allele versus negative allele and positive homozygote combined with heterozygote versus negative homozygote. Therefore, the random effects model was used to pool the result. Sensitivity analysis was performed by sequential omission of individual studies. The significance of pooled OR in all individual analyses and subgroup analyses was not influenced excessively by omitting any single study.

Publication bias of the literature was accessed by Begg's funnel plot and the Egger linear regression test. The Egger linear regression test was used to measure the asymmetry of the funnel plot. The results of the Egger linear regression test are shown in Table 4. Results showed that there was no publication bias (all $P > 0.05$).

DISCUSSION

Psoriasis is a multifactoral and heterogenetic inherited disease that has a major impact on health. Genetic factors have long been recognized to play an important role in psoriasis (Duffin et al., 2008). Despite numerous genetic linkage studies yielding at least 19 candidate loci, the identities of the genes involved remain unclear. Nevertheless, there is general agreement that a major genetic determinant of psoriasis, designated "psoriasis susceptibility 1" (PSORS1), resides in the MHC I region on chromosome 6p21.3 (Nair et al., 2006). Interestingly, psoriasis is the only chronic inflammatory disease that has a strong association with the HLA-C allele in the PSORS1 locus, and about two-thirds of the patients carry the HLA-Cw*0602 allele compared to 10~15% in the population at large (Gudjonsson et al., 2004). This specific allele of the HLA-C region, HLA-Cw*0602, is also the only genetic variant repeatedly observed to associate with phenotypic features of psoriasis. HLA-Cw*0602 has been repeatedly indicated to be the most significant marker for the risk prediction of psoriasis (Szczerkowska-Dobosz, 2005). Homozygosity for HLA-Cw*0602 predisposes to the likelihood of development of psoriasis and to earlier onset, but it otherwise does not impact clinical course (Gudjonsson et al., 2003). Furthermore, individuals who are homozygous for the HLA-Cw*0602 allele have about 2.5 times higher disease risk than heterozygote (Gudjonsson et al., 2003).

Although many research studies have evaluated the association of HLA-Cw*0602 polymorphism with psoriasis risk, the specific association is still controversial. Our meta-analysis quantitatively assessed the association between HLA-Cw*0602 polymorphism and psoriasis risk. Finally, 18 case-control studies were included and assessed, encompassing a total of 3419 psoriasis patients and 3297 healthy controls. The main meta-analysis results showed that there were significant associations between HLA-Cw*0602 polymorphism and psoriasis risk in the comparisons of positive allele versus negative allele, positive homozygote versus nega-

tive homozygote combined with heterozygote, positive homozygote combined with heterozygote versus negative homozygote, positive homozygote versus negative homozygote, and positive homozygote versus heterozygote. Therefore, the positive allele of HLA-Cw*0602 polymorphism might be a potential risk factor for psoriasis. Similarly, in the subgroup analysis by ethnicity, significant associations were also found between HLA-Cw*0602 polymorphism and psoriasis risk in all comparisons in both Caucasian and Asian populations, which indicated that the positive allele of HLA-Cw*0602 polymorphism might also be a potential risk factor for psoriasis in both Caucasian and Asian populations. Results showed obvious heterogeneity between studies in the comparisons of positive allele versus negative allele and positive homozygote combined with heterozygote versus negative homozygote, suggesting a possible role of ethnic differences in genetic backgrounds and the environment they lived in. No evidence showed publication bias in this meta-analysis.

There were still some limitations in our meta-analysis. First, some relevant studies could not be included in our analysis due to incomplete raw data. Secondly, we were not able to address the sources of heterogeneity that existed among all studies. Thirdly, although all cases and controls of each study were well defined with similar inclusion criteria, there may be potential factors that were not taken into account that may have influenced our results. Finally, the genotype information stratified for the main confounding variables was not available in the original papers and the confounding factors addressed across the different studies were variable.

In conclusion, our meta-analysis of 18 case-control studies demonstrated that the HLA-Cw*0602-positive allele might be a potential risk factor for psoriasis in both Caucasian and Asian populations, although few studies are available in this field and current evidence remains limited. Therefore, large studies with an adequate methodological quality, properly controlling for possible confounds in order to obtain valid results, are greatly needed.

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