Review Article

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The CCR5-Delta32 genetic polymorphism and HIV-1 infection susceptibility: a meta-analysis

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Abstract: The CC chemokine receptor 5 (CCR5) is a chemokine receptor which is widely expressed in several immune cells involved in the inflammatory responses. Previous published studies revealed the relation of the CCR5 gene (CCR5-delta32) with the risk of HIV-1 infection, but the results are debatable and inconclusive. Here by meta-analysis, we have systematically evaluated the relation between the CCR5-delta32 polymorphism and the risk of HIV-1 infection. A comprehensive search in PubMed, EMBASE, CNKI, Cochrane Library, and WanFang database was performed up to April 15, 2018. The pooled odds ratio (ORs) along with its 95% credible interval (95%CI) was used to evaluate the relation between the CCR5-delta32 polymorphism and HIV-1 infection risk. The study included 24 case-control studies involving 4,786 HIV-1 infection patients and 6,283 controls. Compared with the wild-type homozygous genotypes, the results showed that the CCR5-delta32 heterozygotes (OR=1.16, 95%CI=1.02-1.32) had an increased susceptibility to HIV-1 and the delta32 homozygous (OR=0.25, 95%CI=0.09-0.68) had significantly reduced the susceptibility to HIV-1 for healthy controls. Moreover, we have found the delta32 allele carriers (OR=0.71, 95%CI=0.54-0.94) had significantly cut down the HIV-1 infection susceptibility when using exposed uninfected (EU) as controls. We also conducted the stratified analysis by ethnicity, and there significant association was detected in Caucasian in delta32 allele carrier genotype. To summarize, our meta-analysis suggests that the CCR5-delta32 homozygous genotype (delta32/delta32) confer possible protection against HIV-1, especially the exposed uninfected groups.

Keywords: CCR5-Delta32; Polymorphism; HIV-1; Susceptibility; Meta-analysis

1 Introduction

Human Immunodeficiency Virus-1 (HIV-1)/Acquired Immunodeficiency Syndrome (AIDS), the world major infectious killer remains one of the most important public health challenges in the world. It was estimated that about 36.7 (34.0-39.8) million people were living with HIV in 2016, and 1.8 million people have died from HIV/AIDS every year. Therefore, HIV prevalence can be considered as the greatest issue in contemporary society, including economic and health crisis [1]. However, many basic questions about the HIV-1 infection pathogenesis have not been answered. Several studies demonstrated that they have a significant difference in susceptibility and progression of HIV-1 infection [2-4]. Host genetic diversity has an important role in either disease susceptibility or resistance [4, 5]. However, the positive role of different genes in HIV/AIDS progression has still remained controversial [6, 7].

Its chemokines and their natural receptors act a key part in HIV-1 binding and entry [8]. Chemokine receptors act on CD4 as a relevant receptor for HIV-1 to regulate the first step in the entry of HIV-1 virus. CCR5, a chemokine receptor of gene product, is expressed on macrophages, monocytes, T and dendritic cells. This is a specific receptor for the CC ligand 3 (CCL3), CCL4, and CCL5 chemokine and a key part in the transferring of immune cells to inflammatory sites [9]. The CCR5Δ32 variant is characterized by a 32 base-pair (bp) deletion of the CCR5's gene coding region; the deletion of CCR5-delta32 was initially discovered and gained the greatest interest in the relation to infection with the HIV-1. This lack of homozygosity is associated with preventing the risk of HIV-1 infection [10]. Liu et al performed a meta-analysis and demonstrated that there

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was no statistical correlation between the CCR5-delta32 polymorphism and the risk of HIV-1 infection. For adults, the CCR5-delta32 polymorphism was investigated for their association with the risk of HIV-1 infection, but the results from the previous published researches remains conflicting and inconclusive [11-34]. Thus, we conducted the present meta-analysis by pooling all available publications to evaluate the possible role of CCR5-delta32 polymorphism and HIV-1 infection susceptibility.

2 Methods

2.1 Literature search

From inception to April 2018, we conducted electronic searches using the terms "CCR5-delta32", "polymorphism*" or "variant*" or "mutation", "HIV" through PubMed, EMBASE, China National Knowledge Internet (CNKI), WanFang, and the Cochrane Library for relevant studies. No language restriction was applied.

2.2 Selection criteria

Articles must satisfy the following criteria: (a) evaluated the relation between CCR5-delta32 and the risk of HIV-1 infection; (b) case-control studies on human beings, no language restriction was applied; (c) sufficient data to evaluate the odds ratios (ORs) and 95% credible interval (CI), and *P* values; and (e) genotype distribution in controls must be in Hardy-Weinberg equilibrium (HWE) ($P < 0.001$). Review articles, conference abstracts, case reports and insufficient data to evaluate ORs and 95%CI were excluded.

2.3 Data extraction

Data extraction was done by two authors through a standardized form independently, such as first author, year of publication, country, ethnicity, source of the controls, genotype distribution of cases and controls, and *P* values for HWE in controls. Discrepancies were settled by discussion, with disagreements resolved by consensus.

2.4 Statistical analyses

The pooled odds ratio (ORs) along with 95% credible interval (95%CI) was utilized to access the strength of relation between the CCR5-delta32 and HIV-1 infection risk. We also conducted stratified analyses by ethnicity and sources of controls. The I^2 and Cochran's *Q*-test statistics were used to quantify the statistical heterogeneity, and the random-effect model was conducted if heterogeneity was significant ($P < 0.05$) [35]; otherwise, the fixed-effect model was conducted[36]; $P < 0.05$ was considered as a significant difference in the value between the two groups. Sensitivity analysis was performed by sequentially excluding studies to assess the stability of the pooled results. Begg's funnel plot and the Egger's tests was performed to evaluate the potential publication bias of the researches ($P < 0.05$ was considered significant) [37,38]. The present meta-analysis was carried out by STATA 12.0 (Stata Corp LP, College Station, TX, USA).

3 Results

3.1 Characteristics of included studies

In this meta-analysis, the selection of eligible researches included is shown in Figure 1, 517 potentially relevant researches were initially obtained from the PubMed, EMBASE, China National Knowledge Internet (CNKI), WanFang, and the Cochrane Library. After the exclusion of irrelevant studies, a total of 24 published researches were identified to be eligible for the current study. The flow diagram describing selected studies inclusion or exclusion is in Figure 1. The baseline features of the selected researches are recorded in Table 1.

3.2 Meta-analysis results

A total of 24 case-control studies were included in the present work to estimate the relation between the CCR5-delta32 polymorphism and the HIV-1 infection risk. To sum up, pooled risk evaluations shows a statistically significant relation between the CCR5-delta32 polymorphism and increased HIV-1 infection risk in the CCR5-delta32 heterozygotes genotype (OR=1.16, 95%CI=1.02-1.32, P=0.024) for healthy controls (Figure 2 and Table 3). Meanwhile, we found the risk of HIV-1 infection was significantly reduced in the delta32 homozygous genotype (OR=0.25, 95%CI=0.09-0.68, P=0.006) for healthy

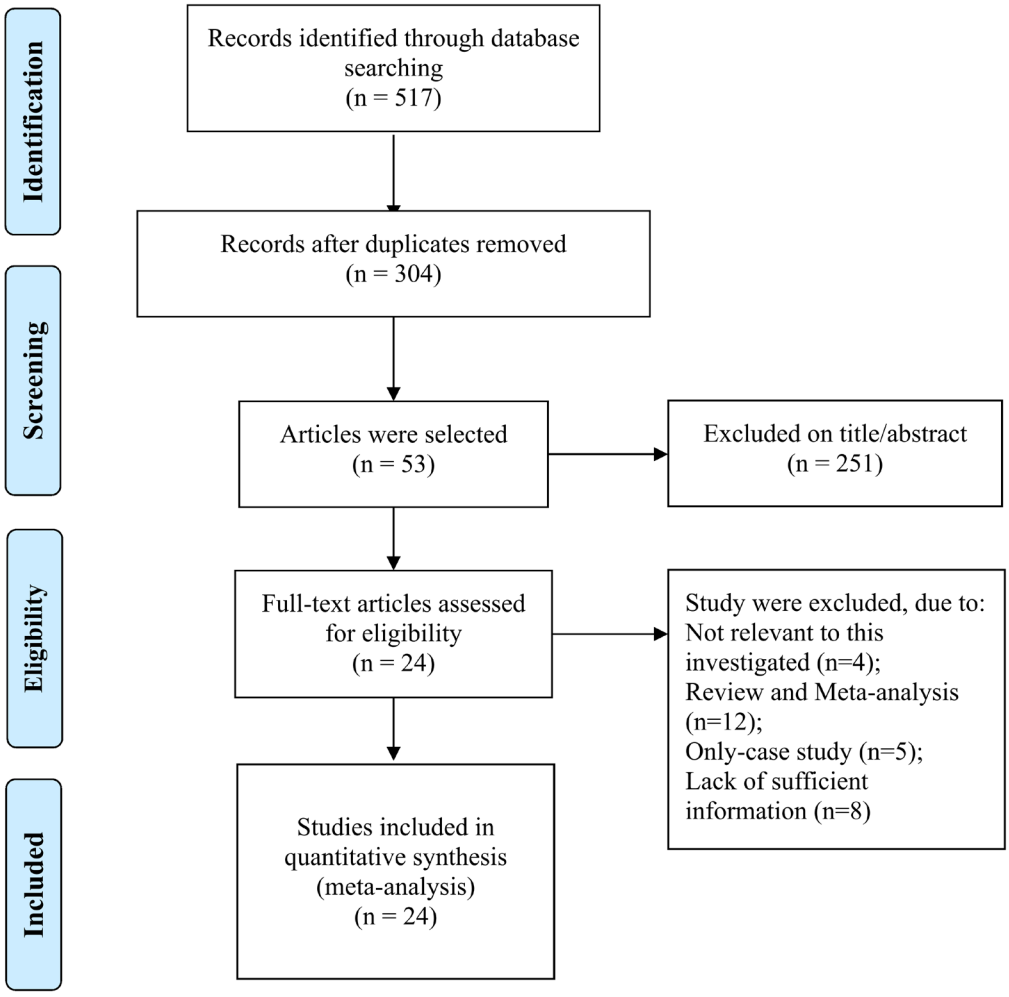

Figure 1: Flow diagram of the publication selection process.

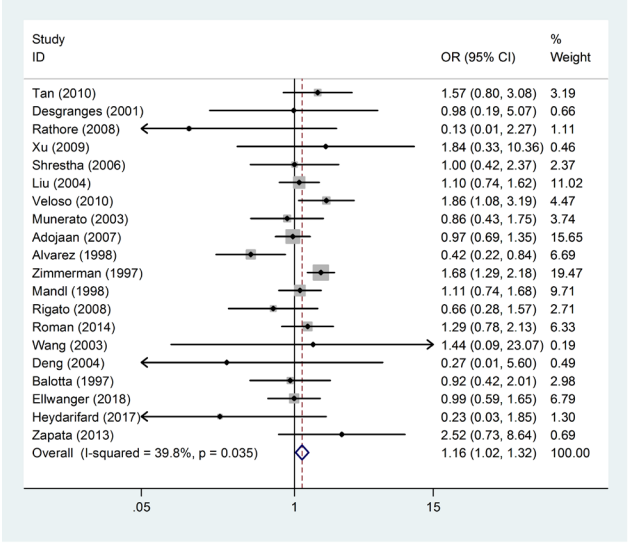

Figure 2: Forest plots demonstrating the association between CCR5-delta32 polymorphism and HIV-1 infection susceptibility in the CCR5-delta32 heterozygote model.

controls (Table 3). When we conducted stratified analysis by sources of control, we also detected a significantly risk decline of HIV-1 infection in the delta32 allele carriers (OR=0.71, 95%CI=0.54-0.94, P=0.015) among exposed uninfected populations (Figure 3 and Table 3). We also performed the stratified analysis by ethnicity, there was significant association in Caucasian with delta32 allele carrier genotype.

3.3 Sensitivity analysis and publication bias

Sensitivity analysis was conducted by sequentially excluding individual studies to assess the impact of each study on the summarized findings. This revealed that the findings were statistically robust and credible (data not shown) (Figure 4). Begg's and Egger's test (Table 3) was utilized to examine the potential bias of the publication [37,38]. The shape of the funnel plot was symmetrical as

Table 1: Main characteristics of studies included in the meta-analysis

Author	Year	Country	Ethnicity	Genotyping methods	Sample size		HWE
					Case	Control	
Tan	2010	China	Asians	PCR	251	238	0.1899
Desgranges	2001	Santiago	Mixed	PCR	63	62	0.8452
Rathore	2008	India	Asians	PCR	190	370	0.8656
Xu	2009	China	Asians	PCR-RFLP	78	70	0.9035
Shrestha	2006	American	Caucasian	PCR	266	532	0.7247
Liu	2004	American	Caucasian	PCR	316	519	0.8926
Veloso	2010	Spanish	Caucasian	PCR-RFLP	184	236	0.3255
Munerato	2003	Brazilian	Caucasian	PCR	183	115	0.4544
Adojaan	2007	Estonia	Caucasian	PCR	3000	488	0.0026
Alvarez	1998	Spanish	Caucasian	PCR	150	250	0.6120
Zimmerman	1997	American	Caucasian	PCR	745	1096	0.8830
Mandl	1998	Austria	Caucasian	PCR	225	451	0.4286
Wang	2008	China	Asians	PCR-RFLP	104	155	0.9863
Tiensiwakul	2004	Thailand	Asians	PCR-RFLP	116	622	0.9610
Rigato	2008	Brazil	Caucasian	PCR-RFLP	200	82	0.5990
Roman	2014	Luxembourg	Mixed	PCR-RFLP	288	155	0.7356
Wang	2003	China	Asians	PCR-RFLP	330	474	0.9817
Deng	2004	China	Asians	PCR	88	119	0.9263
Balotta	1997	Italy	Caucasian	PCR	152	122	0.3977
Ellwanger	2018	Brazil	Caucasian	PCR	300	274	0.4210
Heydarifard	2017	Iran	Asians	PCR	140	300	0.7920
Zapata	2013	Colombia	Mixed	PCR	57	112	0.8091
Li	2003	China	Asian	PCR-RFLP	24	46	0.9406
Rugeles	2002	Colombia	Mixed	PCR	36	50	0.0381

HWE, Hardy-Weinberg equilibrium; AA, CCR5 homozygotes; AB, CCR5-delta32 heterozygotes; BB, delta32 homozygotes.

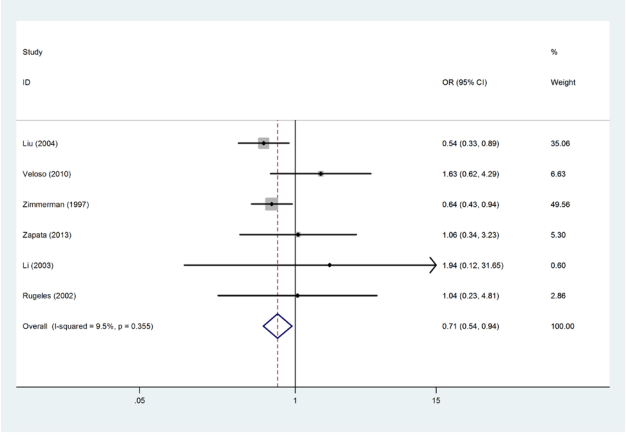

Figure 3: Forest plots demonstrating the association between CCR5-delta32 polymorphism and HIV-1 infection susceptibility in the delta32 homozygote model.

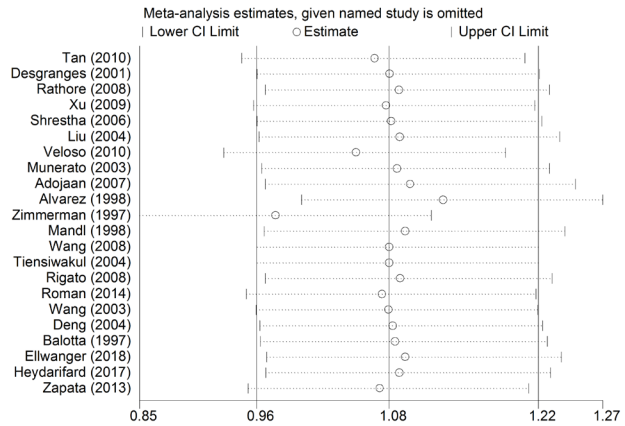

Figure 4: Sensitivity analysis for the influences of CCR5-delta32 polymorphism and HIV-1 infection susceptibility under the allele model.

shown in Figure 5 suggesting there was no obvious publication bias.

4 Discussion

AIDS remains one of the biggest public health challenges of the world, as we all know, it is a complex infectious

Table 2: The distribution of CCR5-delta32 genotype of included studies.

Author	Ethnicity	HIV-1 infected			Healthy Controls			Exposed uninfected		
		AA	AB	BB	AA	AB	BB	AA	AB	BB
Tan	Asians	226	24	1	222	15	1			
Desgranges	Mixed	60	3	0	59	3	0			
Rathore	Asians	190	0	0	314	6	0	50	0	0
Xu	Asians	74	4	0	68	2	0			
Shrestha	Caucasian	258	8	0	516	16	0			
Liu	Caucasian	261	55	0	354	68	3	69	22	3
Veloso	Caucasian	144	40	0	174	26	0	31	5	0
Munerato	Caucasian	162	21	0	100	15	0			
Adojaan	Caucasian	230	70	0	371	117	0			
Alvarez	Caucasian	138	12	0	205	42	3			
Zimmerman	Caucasian	601	144	0	846	121	4	94	26	5
Mandl	Caucasian	182	43	0	367	78	6			
Wang	Asians	104	0	0	104	0	0	51	0	0
Tiensiwakul	Asians	116	0	0	432	0	0	190	0	0
Rigato	Caucasian	185	15	0	73	9	0			
Roman	Mixed	226	62	0	127	27	1			
Wang	Asians	329	1	0	473	1	0			
Deng	Asians	88	0	0	117	2	0			
Balotta	Caucasian	136	15	1	108	13	1			
Ellwanger	Caucasian	265	35	0	240	32	2			
Heydarifard	Asians	139	1	0	291	9	0			
Zapata	Mixed	51	6	0	107	5	0	63	7	0
Li	Asian	23	1	0				45	1	0
Rugeles	Mixed	33	3	0				47	2	1

AA, CCR5 homozygotes; AB, CCR5-delta32 heterozygotes; BB, delta32 homozygotes.

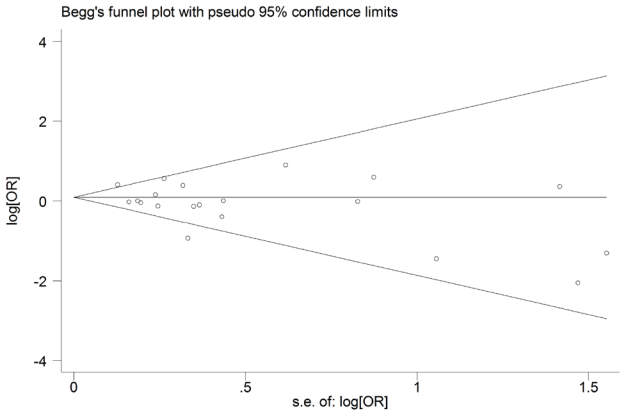

Figure 5: Funnel plot of publication biases on the association between CCR5-delta32 polymorphism and HIV-1 infection susceptibility.

disease, including HIV-1 infection, host immune response, and gene-environment interactions. Several studies have already found that both viral genetics and host genetic factors are important determinants of HIV-1 infection [4,5,10]. Chemokines and chemokine receptors are critical for immune response in HIV-1 infection. Although many researches demonstrated the association between chemokine and chemokine receptor gene polymorphisms, and host's susceptibility to HIV-1 infection, the conclusions are still controversial [11-33].

Meta-analysis, a useful statistical tool through integrating and comparing the results of many related researches and taking into consideration of variations in characteristics that can affect overall estimate of the outcome of interest, which is used to evaluate the literature in both quantitative and qualitative ways. So it is especially worthy when previous researches could not provide significant differences among treatments because of sample sizes limitations, or when there is no consensus [39]. Despina et al. performed a meta-analysis and demonstrated that perinatal infection is not determined by heterozygosity for CCR5-delta32 in the children [40]. In addition, Liu et al. performed a meta-analysis suggested that no statistical relation was detected between the CCR5-delta32 polymorphism and HIV-1 infection risk in any genetic model [41].

Table 3: Meta-analysis of the association between CCR5-delta32 polymorphism and HIV-1 infection susceptibility

Comparison	Subgroup	Studies	Heterogeneity test		Association test		Model	Publication bias
			P Value	I^2(%)	OR(95%CI)	P Value		Egger
B vs. A	Overall	24	0.037	39.4	1.08(0.96-1.22)	0.222	F	0.125
	Mixed	3	0.000	0	1.26(0.83-1.92)	0.277	R	
	Caucasian	11	0.070	56.8	0.99(0.79-1.23)	0.918	R	
	Asian	6	0.267	24.2	0.90(0.39-2.06)	0.803	R	
	EUs	6	0.355	9.5	0.71(0.54-0.94)	0.015	F	
AB vs. AA	Overall	20	0.035	39.8	1.16(1.02-1.32)	0.024	F	0.078
	Mixed	3	0.564	0	1.38(0.88-2.16)	0.157	R	
	Caucasian	11	0.010	57.0	1.05(0.83-1.33)	0.665	R	
	Asian	6	0.228	27.5	0.89(0.37-2.13)	0.791	R	
	EUs	6	0.549	0	0.91(0.66-1.25)	0.568	F	
BB vs. AA	Overall	8	0.965	0	0.25(0.09-0.68)	0.006	F	0.058
	Caucasian	6	0.966	0	0.22(0.07-0.69)	0.009	F	
	EUs	3	0.274	22.8	0.06(0.01-0.32)	0.001	F	
AB+BB vs. AA	Overall	20	0.028	41.3	1.12(0.99-1.28)	0.071	F	0.096
	Mixed	3	0.541	0	1.34(0.86-2.09)	0.196	R	
	Caucasian	11	0.007	58.5	1.02(0.81-1.29)	0.871	R	
	Asian	6	0.235	26.6	0.89(0.38-2.10)	0.791	R	
	EUs Overall	6	0.441	0	0.80(0.59-1.08)	0.141	F	
BB vs. AA+AB	Caucasian	8	0.963	0	0.25(0.09-0.67)	0.006	F	0.058
	EUs	6	0.962	0	0.21(0.07-0.68)	0.009	F	
		3	0.292	18.8	0.06(0.01-0.32)	0.001	F	

OR, odds ratio; CI, confidence interval; F, fixed-effects model; R, random-effects model; EUs, exposed uninfected.

Considering that many researches have produced conflicting results, we conducted the present meta-analysis involving 24 eligible researches with 4,786 cases and 6,283 controls. The present researches showed there is a significant relation between CCR5-delta32 polymorphism and the risk of HIV-1 infection in the total population. In CCR5-delta32 heterozygotes genetic model, we have detected a statistically significant increased susceptibility to HIV-1 infection (OR=1.16, 95%CI=1.02-1.32, P=0.024) for healthy control. Meanwhile, we have found significantly reduced the risk of HIV-1 infection in the delta32 homozygous genetic model (OR=0.25, 95%CI=0.09-0.68, P=0.006). In healthy subjects, CCR5-delta polymorphism may be protective effects against HIV-1 infection only in the delta32 homozygous individuals (OR=0.25, 95%CI=0.09-0.68, P=0.006). Stratified analysis by EU population, the results demonstrated that CCR5-delta32 polymorphism may be protect effects against HIV-1 infection susceptibility in the delta32 allele carriers (OR=0.71, 95%CI=0.54-0.94, P=0.015), which was in accordance with that in the healthy subjects. Meanwhile, we also conducted the stratified analyses by ethnicity, we have detected significant relation between the CCR5-delta32 polymorphism and HIV-1 infection susceptibility in Caucasian subjects.

There are several limitations in the current study. Firstly, suitable English or Chinese-language studies were only enrolled in current meta-analysis, which means related researches published in other languages may have been overlooked, which may also lead to selection bias. Secondly, the number as well as the sample size of some included studies was limited and the results should be interpreted with caution. Finally, the influences of other relevant components such as age, gender, life style as well as their interactions with CCR5-delta32 polymorphism on HIV-1 infection susceptibility were not analyzed due to the lack of original data.

5 Conclusion

In conclusion, our findings indicated that the CCR5-delta32 homozygous genotype (delta32/delta32) confer possible protection against HIV-1 infection, especially in exposed uninfected population. However, this conclusion should be confirmed by multi-center and large-scale studies based on multiple ethnic groups.

Interest conflict: The authors claim no conflict of interest.

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