

# Meta-analyses of the association between the *PPARGC1A* Gly482Ser polymorphism and athletic performance

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**ABSTRACT:** Peroxisome proliferator-activated receptor  $\gamma$  coactivator 1 $\alpha$  (PGC1 $\alpha$ ) encoded by the *PPARGC1A* gene is a vital regulator of glucose and fatty acid oxidation, mitochondrial biogenesis, and skeletal muscle fibre conversion. Several studies have investigated the association between *PPARGC1A* Gly482Ser polymorphism and athletic performance in humans. However, the results were contradictory. In the present study, two meta-analyses were performed to assess the association between the Gly482Ser polymorphism and endurance or power athletic performance to resolve this inconsistency. Ten articles were identified, including a total of 3,708 athletes and 6,228 controls. Higher frequencies of the Gly/Gly genotype (OR, 1.26; 95% CI, 1.11–1.42) and the Gly allele (OR, 1.29; 95% CI, 1.09–1.52) were observed in Caucasian endurance athletes. Furthermore, higher incidences of the Gly/Gly genotype (OR, 1.30; 95% CI, 1.16–1.46) and the Gly allele (OR, 1.22; 95% CI, 1.12–1.33) were observed in power athletes compared to controls. This finding demonstrates that the Gly/Gly genotype and the Gly allele of the *PPARGC1A* Gly482Ser polymorphism may facilitate athletic performance regardless of the type of sport, as well as providing solid evidence to support the possible influence of genetic factors on human athletic performance.

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## INTRODUCTION

Human athletic performance is a multifactorial trait determined by the interaction of genetic and environmental factors. It is estimated that around 66% of the variance in athletic status could be explained by genetic factors [1]. The remaining variance is dependent on environmental factors, such as physical training, nutrition, and technological support. With the development of molecular research in sport, at least 155 genetic variants have been found to be associated with athletic performance, with the angiotensin converting enzyme (*ACE*) gene I/D and the alpha actinin-3 (*ACTN3*) gene R577X polymorphisms having been the most extensively studied [2–4]. However, partly owing to the small sample size of studies, a considerable number of these proposed associations have not been consistently replicated in independent investigations by different teams of researchers [5].

*PPARGC1A* has been suggested to be associated with athletic performance because of its role in a wide variety of biological responses [6, 7]. It encodes peroxisome proliferator-activated receptor  $\gamma$  coactivator 1 $\alpha$  (PGC1 $\alpha$ ), a transcriptional coactivator of the peroxisome proliferator-activated receptor (PPAR) family. PGC1 $\alpha$  regulates the expression of several key genes involved in glucose and fatty acid oxidation [8, 9]. It is also a key stimulator of mitochondrial biogen-

esis by activating transcription of the nuclear respiratory factors NRF1 and NRF2, inducing expression of mitochondrial transcription factor A (TFAM) [10]. PGC1 $\alpha$  is also important for skeletal muscle fibre conversion. Over-expression of *PPARGC1A* leads to the conversion of fast-twitch type IIb muscle fibres to type IIa and slow-twitch type I fibres by 20% and 10%, respectively [11]. Furthermore, *PPARGC1A* expression correlates with both short-term exercise and endurance training in rodents and humans [12–14].

The *PPARGC1A* gene is located on chromosome 4 (4p15.2). The Gly482Ser (rs8192678) polymorphism is the most frequently analyzed of all the gene variations that have been discovered. The polymorphism has been reported to be associated with type 2 diabetes, obesity and elevated blood pressure [15–17]. In three case-control studies, a significantly lower frequency of the Ser allele has been reported in elite endurance athletes compared with sedentary controls [18–20]. However, several other studies have failed to replicate the same association [21–26]. Furthermore, two studies observed a higher frequency of the Gly/Gly genotype in power athletes [20, 24]. Therefore, no definitive conclusions have been drawn about the relationship between the *PPARGC1A* Gly482Ser polymorphism and athletic performance. Tharabenjasin et al. recently reported the results

of a meta-analysis about the association of the *PPARGC1A* Gly428Ser polymorphism with athletic ability and sports performance [27].

The aim of this study is to summarize the association between the *PPARGC1A* Gly482Ser polymorphism and athletic performance by conducting meta-analyses, which might provide a more definitive answer compared with individual research reports.

## MATERIALS AND METHODS

### Literature identification

All procedures involved in the meta-analyses were carried out in accordance with the PRISMA guidelines [28]. A comprehensive literature search was performed using the PubMed and Web of Science databases, from inception to September 2018. The combination of the following keywords was used: “*PPARGC1A* or PGC1 $\alpha$ ”, “polymorphisms”, “rs8192678” and “sports”. No language limitations or publication restrictions were applied to the search strategy.

### Inclusion and exclusion criteria

Studies that reported the distribution of *PPARGC1A* polymorphism among both athletes and sedentary controls were considered. If the same data were presented in multiple studies, the highest quality

study was included. Exclusion criteria were: (i) review articles or conference literatures; (ii) studies involving animal experiments, or the target population was not athletes; (iii) articles did not provide sufficient original data; (iv) genotype distribution deviated from Hardy–Weinberg equilibrium (HWE) in the control group; (v) studies only concerning mixed endurance-power type of sports, such as football.

### Quality assessment

The Newcastle-Ottawa Scale (NOS) was used to evaluate the methodological quality of the included studies by two reviewers independently [29]. Each study was assessed and scored based on three aspects: case and control selection, comparability, and exposure. NOS score ranges from 0 to 9 stars. Studies that scored seven or more stars were considered to be of high quality.

### Statistical analysis

Hardy–Weinberg equilibrium was examined in controls for each study by Pearson’s chi-squared test. Heterogeneity across the studies was assessed by the *I* square statistic ( $I^2$ ), with  $I^2 < 50\%$  indicating reduced statistical difference [30]. A fixed-effects model was used in cases of low statistical heterogeneity, otherwise a random-effects

**TABLE 1.** Summary of primary data for association between *PPARGC1A* Gly482Ser polymorphism and endurance performance.

Authors	Year	Country	Ethnicity	Group	Number (N)	Genotype (N)			MAF	$P_{\text{HWE}}$	NOS Score
						Gly/Gly	Gly/Ser	Ser/Ser			
Lucia et al.	2005	Spain	Caucasian	Case	104	52	43	9	0.293	1.0000	7
				Control	100	36	48	16	0.400		
Eynon et al.	2010	Israeli	Caucasian	Case	74	37	37	0	0.250	0.9529	7
				Control	240	79	117	44	0.427		
Muniesa et al.	2010	Spanish	Caucasian	Case	141	65	52	24	0.355	0.2261	7
				Control	123	47	63	13	0.362		
Ginevičienė et al.	2011	Lithuanian	Caucasian	Case	77	40	33	4	0.266	0.5177	9
				Control	250	129	104	17	0.276		
Maciejewska et al.	2012	Polish	Caucasian	Case	84	46	34	4	0.250	0.8938	8
				Control	684	280	314	90	0.361		
		Russian	Caucasian	Case	548	273	239	36	0.284		
				Control	1132	489	505	138	0.345		
He et al.	2015	Chinese	Asian	Case	235	73	115	47	0.445	0.6321	7
				Control	504	156	244	104	0.448		
Yvert et al.	2016	Japanese	Asian	Case	175	45	87	43	0.494	0.8741	8
				Control	649	191	324	134	0.456		
Peplonska et al.	2017	Polish	Caucasian	Case	225	102	105	18	0.313	0.0871	6
				Control	451	199	213	39	0.323		
Guilherme et al.	2018	Brazilian	Caucasian	Case	316	153	140	23	0.294	0.6187	7
				Control	893	428	385	80	0.305		

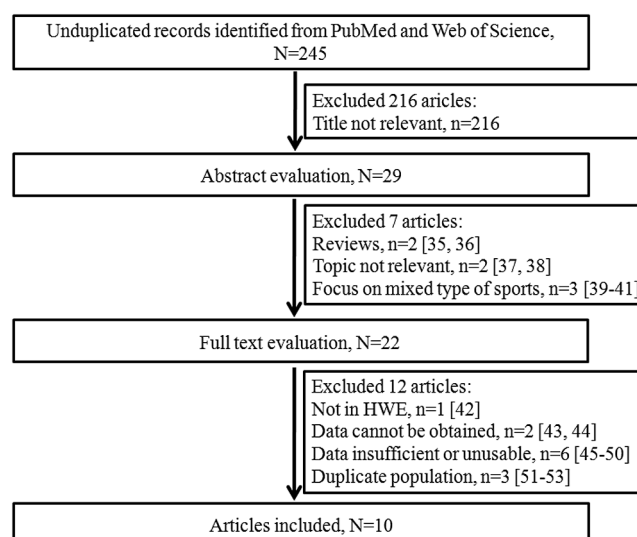
MAF = minor allele frequency,  $P_{\text{HWE}}$  = *P* value for Hardy–Weinberg equilibrium of controls, NOS = Newcastle-Ottawa Scale.

model was applied [31, 32]. The association between polymorphism and athletic performance was estimated by calculating the odds ratio (OR) with corresponding 95% confidence interval (95% CI), comparing athletes and controls. Potential publication bias was examined by Begg's and Egger's tests and funnel plots [33, 34]. Sensitivity analysis was also conducted to examine the stability of the overall results by sequential exclusion of one study at a time. All statistical analyses were conducted with STATA software (version 15, StataCorp, College Station, Texas).

**RESULTS**

The initial search of electronic databases identified 245 unduplicated articles. As shown in Figure 1, after excluding articles whose titles were not relevant, 29 abstracts were retrieved for the next step. After abstract evaluation, 22 articles were included in a more detailed full text evaluation [35–41]. Then 12 articles were excluded [42–53]. Ultimately 10 articles were included in this study (Fig. 1).

The 10 studies involved a total of 3,708 athletes and 6,228 controls. The athletes were divided into endurance-type and power-type groups in accordance with their sporting discipline [4]. The endurance group included athletes who participated in marathon, biathlon, long-distance swimming, pentathlon, rowing, long-distance running, road cycling, cross-country skiing, long-distance track and field athletics, triathlon, race walking and mountain biking. The power group included athletes involved in sprinting, weightlifting, short-distance



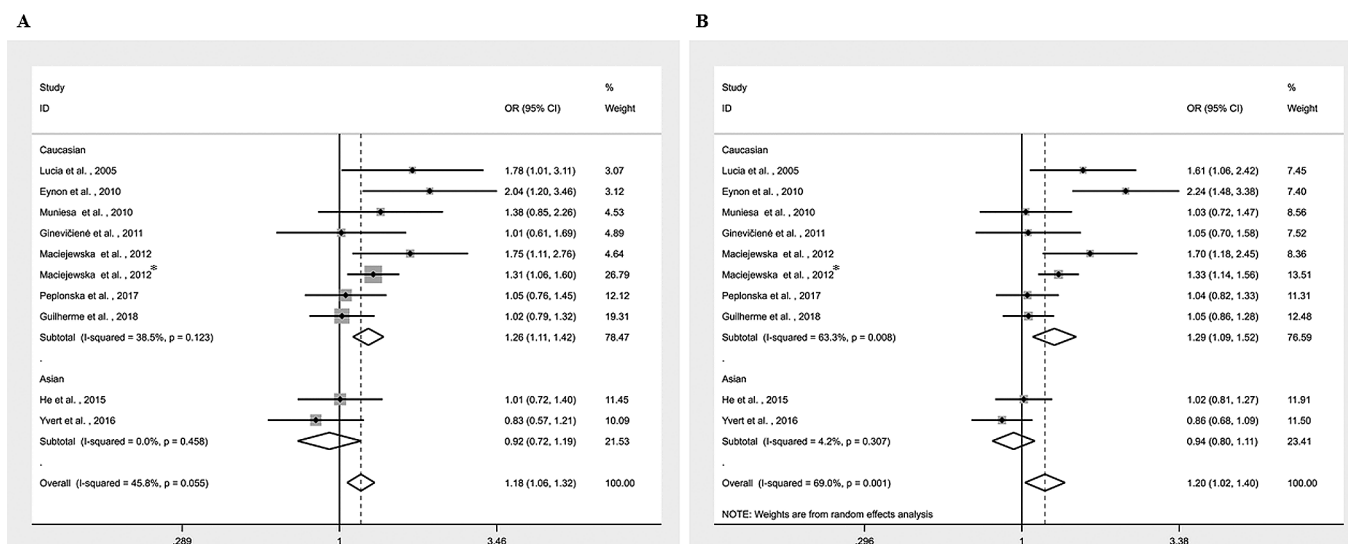
**FIG. 1.** Flow diagram of literature search and screen.

track and field athletics, powerlifting, kayaking, judo, wrestling, boxing, fencing, short-distance swimming, alpine skiing, artistic gymnastics, and throwing and jumping events. It should be pointed out that no clear-cut distinction can be drawn between endurance and

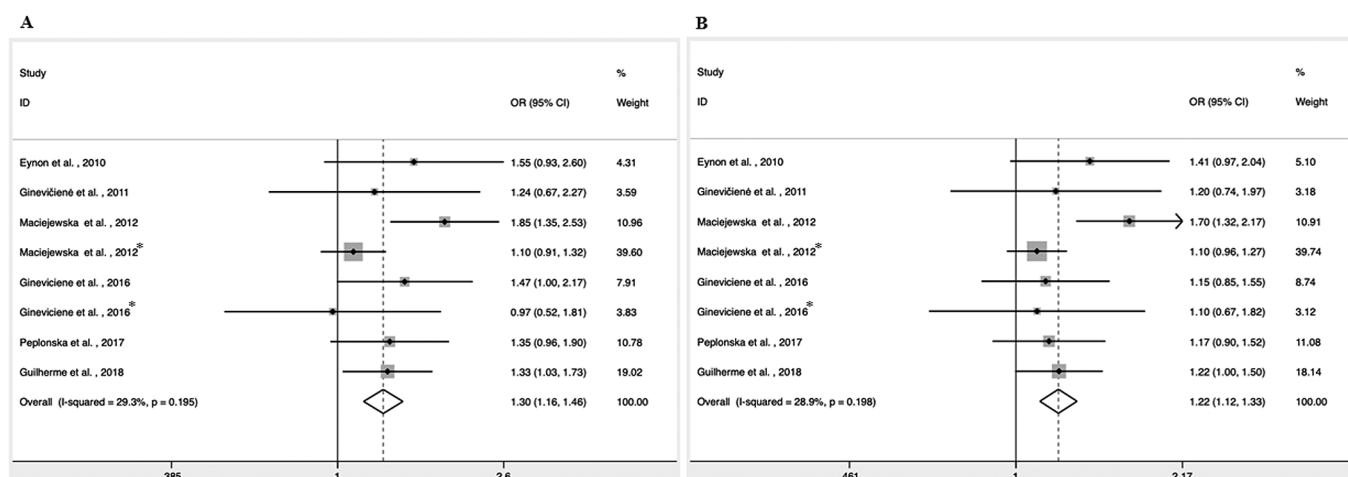
**TABLE 2.** Summary of primary data for association between *PPARGC1A* Gly482Ser polymorphism and power performance.

Authors	Year	Country	Ethnicity	Group	Number (N)	Genotype (N)			MAF	$P_{HWE}$	NOS Score
						Gly/Gly	Gly/Ser	Ser/Ser			
Eynon et al.	2010	Israeli	Caucasian	Case	81	35	36	10	0.346	0.9529	7
				Control	240	79	117	44	0.427		
Ginevičienė et al.	2011	Lithuanian	Caucasian	Case	51	29	21	1	0.225	0.5177	9
				Control	250	129	104	17	0.276		
Maciejewska et al.	2012	Polish	Caucasian	Case	210	118	79	13	0.25	0.8938	8
				Control	684	280	314	90	0.361		
		Russian	Caucasian	Case	724	329	322	73	0.323		
				Control	1132	489	505	138	0.345		
Gineviciene et al.	2016	Russian	Caucasian	Case	114	62	35	17	0.303	0.7450	8
				Control	947	424	416	107	0.333		
		Lithuanian	Caucasian	Case	47	24	22	1	0.255		
				Control	255	132	106	17	0.275		
Peplonska et al.	2017	Polish	Caucasian	Case	188	97	73	18	0.290	0.0871	6
				Control	451	199	213	39	0.323		
Guilherme et al.	2018	Brazilian	Caucasian	Case	314	173	116	25	0.264	0.6187	7
				Control	893	428	385	80	0.305		

MAF = minor allele frequency,  $P_{HWE}$  =  $P$  value for Hardy–Weinberg equilibrium of controls, NOS = Newcastle-Ottawa Scale.



**FIG. 2.** Meta-analysis of the association between endurance performance and PPARGC1A Gly482Ser polymorphism. (A) Gly/Gly vs. Gly/Ser+Ser/Ser; (B) Allele Gly vs. Ser. CI= confidence interval; OR= odds ratio. \*Different study population from the same article.



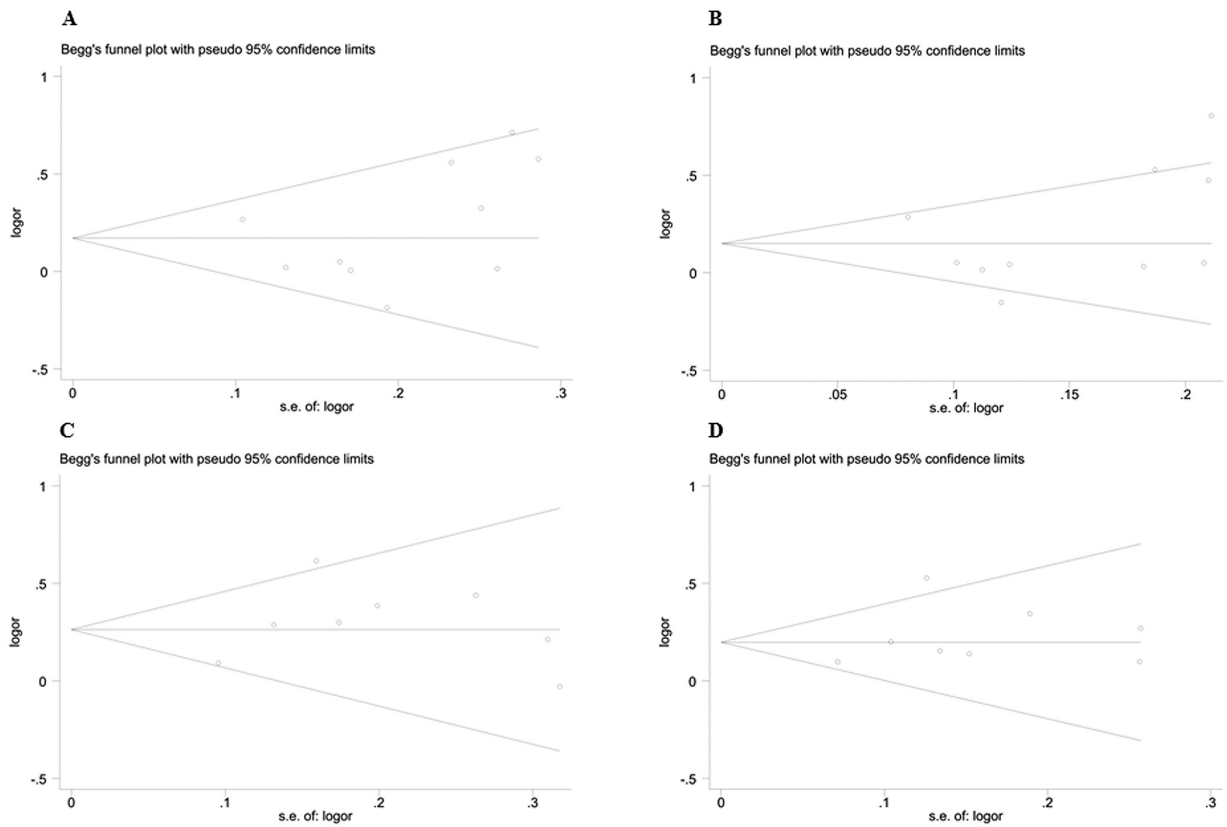
**FIG. 3.** Meta-analysis of the association between power performance and PPARGC1A Gly482Ser polymorphism. (A) Gly/Gly vs. Gly/Ser+Ser/Ser; (B) Allele Gly vs. Ser. CI= confidence interval; OR= odds ratio. \*Different study population from the same article.

power sports. There are elements of power in the endurance sports mentioned, as there are endurance elements in power sports. All the power athletes were from Caucasian populations. The data for athletes who participated in mixed-type sports were not extracted from the studies included.

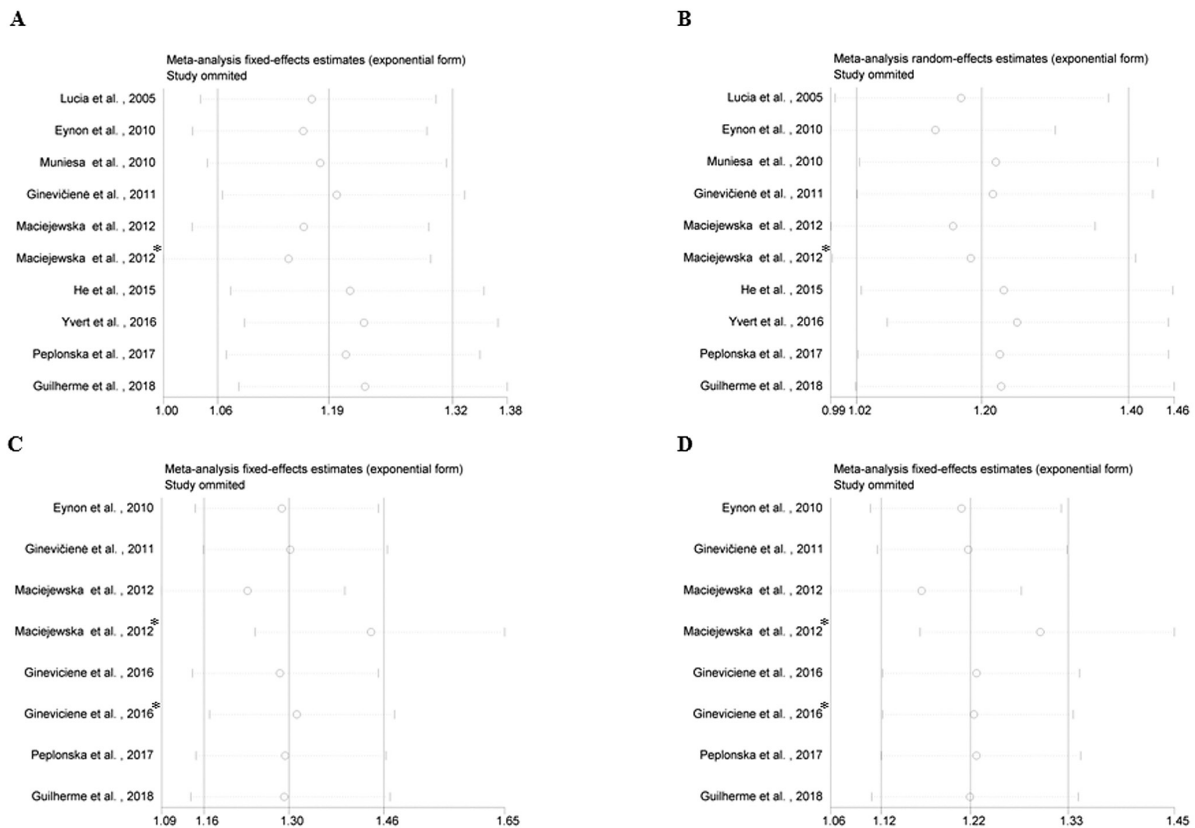
For all articles, the following data were extracted from original publications: first author and year of publication, country of the study, total number of athletes and controls, type of athletes and controls, race of participants, and genotype and allele frequencies among athletes and controls and for each of the subgroups (Table 1 and Table 2). The results of HWE tests demonstrated that the genotype distributions in controls were all in HWE (all  $P > 0.05$ ). And according to the quality criteria, the NOS score for all articles is greater than or equal to 7, except for one article [23]. Two meta-analyses were carried out with the endurance group and power group.

As shown in Fig. 2A, a higher frequency of the Gly/Gly genotype was observed in endurance athletes compared to controls in Caucasian populations. The combined OR for the Gly/Gly genotype compared to the Gly/Ser + Ser/Ser genotype was 1.26 (95% CI, 1.11–1.42). The degree of heterogeneity across the studies was moderate ( $I^2 = 38.5\%$ ). There was no significance observed in Asian endurance athletes (OR, 0.92; 95% CI, 0.72–1.19). A higher frequency of the Gly allele (OR, 1.29; 95% CI, 1.09–1.52) was also observed in Caucasian endurance athletes, but not in Asian counterparts (OR, 0.94; 95% CI, 0.80–1.11; Fig. 2B).

Fig. 3 shows the results of the overall associations between the PPARGC1A Gly482Ser polymorphism and power performance. A significant correlation was found for the Gly/Gly genotype in athletes compared to controls (OR, 1.30; 95% CI, 1.16–1.46; Fig. 3A). The degree of heterogeneity across studies was low ( $I^2 = 29.3\%$ ). A higher



**FIG. 4.** Begg's funnel plot for eligible studies of association between PPARGC1A Gly482Ser polymorphism and athletic performance. (A) Homozygotes Gly/Gly vs. Gly/Ser+Ser/Ser for endurance performance; (B) Allele Gly vs. Ser for endurance performance; (C) Homozygotes Gly/Gly vs. Gly/Ser+Ser/Ser for power performance; (D) Allele Gly vs. Ser for power performance. OR= odds ratio.



**FIG. 5.** Sensitivity analysis of the association PPARGC1A Gly482Ser polymorphism and athletic performance. (A) Homozygotes Gly/Gly vs. Gly/Ser+Ser/Ser for endurance performance; (B) Allele Gly vs. Ser for endurance performance; (C) Homozygotes Gly/Gly vs. Gly/Ser+Ser/Ser for power performance; (D) Allele Gly vs. Ser for power performance. \*Different study population from the same article.



frequency of the Gly allele was also observed in power athletes (OR, 1.22; 95% CI, 1.12–1.33; Fig. 3B). Here, the degree of heterogeneity across studies was also low ( $I^2 = 28.9\%$ ).

Publication bias was assessed by Begg's and Egger's tests and funnel plots. There was no obvious asymmetry in the Begg's funnel plot (Figure 4). The results of Begg's test (Gly/Gly vs. Gly/Ser+Ser/Ser for endurance performance:  $P = 0.269$ ; allele Gly vs. Ser for endurance performance:  $P = 0.066$ ; Gly/Gly vs. Gly/Ser+Ser/Ser for power performance:  $P = 1.0$ ; allele Gly vs. Ser for power performance:  $P = 1.0$ ) and Egger's test (Gly/Gly vs. Gly/Ser+Ser/Ser for endurance performance:  $P = 0.093$ ; allele Gly vs. Ser for endurance performance:  $P = 0.200$ ; Gly/Gly vs. Gly/Ser+Ser/Ser for power performance:  $P = 0.481$ ; allele Gly vs. Ser for power performance:  $P = 0.525$ ) also suggested no statistically significant publication bias.

Sensitivity analysis was performed to evaluate the effect of each included study on the overall results. One study was excluded each time. Then pooled ORs were recomputed and compared with the overall OR. Significant associations between the *PPARGC1A* Gly allele and endurance performance were not observed after excluding the Maciejewska *et al.* article [20] (Fig. 5A; Fig. 5B). It indicated that the results were unstable. Moreover, the overall results of the associations between *PPARGC1A* Gly482Ser polymorphism and power performance were rather stable (Fig. 5C; Fig. 5D).

## DISCUSSION

*PPARGC1A* encodes a key regulator of cellular energy metabolism. This study estimated the association of human athletic performance with *PPARGC1A* Gly482Ser polymorphism by means of meta-analysis. The main finding of the current study is that higher frequencies of the Gly/Gly genotype 1.26 (95% CI, 1.11–1.42) and the Gly allele (OR, 1.29; 95% CI, 1.09–1.52) were observed in Caucasian endurance athletes, but not in Asian counterparts. Furthermore, higher incidences of the Gly/Gly genotype (OR, 1.30; 95% CI, 1.16–1.46) and the Gly allele (OR, 1.22; 95% CI, 1.12–1.33) were observed in power athletes compared to controls.

To date, the results of individual studies on the associations between the *PPARGC1A* Gly482Ser polymorphism and athletic performance have been discrepant. Lucia *et al.* first detected a significantly lower frequency of the Ser allele in Spanish endurance athletes [18]. A later study supported this association [19, 20], although there were also some exceptions [21–26]. One of the greatest limitations of these case–control association studies is their small sample size, which often leads to statistical insignificance and results in controversial conclusions. The current meta-analyses overcame this limitation by combining the findings from 10 studies. The analyses involved 3,708 athletes and 6,228 controls. The results revealed that higher frequencies of the Gly/Gly genotype and the Gly allele were observed in Caucasian endurance and power athletes. Thus, the study provides solid evidence for an association between *PPARGC1A* polymorphism and athletic performance.

It is interesting to note that higher frequencies of the Gly/Gly genotype and the Gly allele of the *PPARGC1A* Gly482Ser polymorphism were found in both endurance athletes and power athletes from Caucasian populations. Endurance sports are generally considered to mainly use the aerobic energy system to produce energy, while power sports rely mostly on anaerobic metabolism as the energy source [54]. However, they are not totally distinct entities. Modern endurance sports also require very powerful muscle contractions at competitively critical stages [55], while the contribution of the aerobic energy system to some kinds of speed/power sports is considerable [56]. A previous study demonstrated that the Ser allele is associated with lower expression of *PPARGC1A* [57]. Several studies have shown the effect of Gly482Ser polymorphism on the functional activity of PGC1 $\alpha$ , but the results are controversial. Choi *et al.* firstly suggested that the PGC1 $\alpha$  482Gly variant had impaired co-activator activity on the *TFAM* promoter [58]. In contrast, Okauchi *et al.* reported no difference in activity between the variants when activating the adiponectin promoter [59]. A study performed by Michael *et al.* demonstrated that PGC1 $\alpha$  could bind to and co-activate the muscle-selective transcription factor (MEF) 2C, then increased the expression of glucose transporter 4 (*GLUT4*) [60]. Also, the change from Gly to Ser at position 482 in PGC1 $\alpha$  decreased its binding interaction with MEF2C [61]. Thus, the decreased interaction might impair the GLUT4 insulin-stimulated glucose uptake, which would then affect glycogen synthesis and the subsequent synthesis of fatty acids. Finally, the PGC1 $\alpha$  482Ser variant might weaken the efficiency of aerobic metabolism. Moreover, the Pgc1 $\alpha$ /Mef2c complex could bind to the *Ppargc1a* promoter and activate it [62]. So the decreased interaction between PGC1 $\alpha$ /MEF2C might decrease the expression of *PPARGC1A* itself. Therefore, the Gly allele of the Gly482Ser polymorphism may facilitate athletic performance through increasing the expression of *PPARGC1A* and enhancing the efficiency of aerobic metabolism.

Although the current study was about a similar topic as a recently published meta-analysis [27], this study contributes to the *PPARGC1A* research in athletic performance. First, the present study corrects the mistakes that appeared in the Tharabenjasin *et al.* study. This study excluded articles that there were duplicate genotype data of athletes or controls. For example, genotype data of 1132 Russian controls and partial Russian athletes were duplicated between the Ahmetov *et al.* article and Maciejewska *et al.* article [20, 52]. Duplicate data may affect overall results, especially when it comes to large samples. Thus only the Maciejewska *et al.* article was included in this study. By contrast, both articles were included in the Tharabenjasin *et al.* study. Second, the results of this study indicated that endurance-type and power-type sports might have more in common than was generally believed regarding the genetic background, especially when a specific gene polymorphism was taken into account.

Several limitations should be considered in interpreting the results of this study. First, owing to the inconsistent definition of endurance

events among some studies, phenotypic heterogeneity cannot be completely avoided. Second, owing to the different standards of elite, sub-elite and non-elite athletes, the present study did not consider the potential confounding effects of performance levels. In addition, Begg's and Egger's tests as well as funnel plots were used to assess publication bias in this study, whereas such tests have low power when applied to studies whose number is < 10 [63]. Finally, because not all the relevant data could be obtained from the included studies, further detailed sub-analysis was limited. For example, if the athletes could have been subdivided into male and female groups, more comprehensive results could be presented.

## CONCLUSIONS

In conclusion, the current meta-analyses based on 10 studies revealed that higher frequencies of the Gly/Gly genotype and the Gly allele of

the *PPARGC1A* Gly482Ser polymorphism were observed in Caucasian endurance athletes, and the Gly/Gly genotype and the Gly allele were significantly associated with power athletes compared to controls. The results demonstrate that the Gly/Gly genotype and the Gly allele of the *PPARGC1A* Gly482Ser polymorphism may facilitate athletic performance regardless of the type of sport. This finding also provides solid evidence to support the possible influence of genetic factors on human athletic performance.

## Conflict of interest declaration

The authors have no conflict of interests.

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