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*CYP17 Msp*A1 polymorphism and age at menarche: A meta-analysis

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Abstract. *Objective:* Literature data on the effects of *CYP17 Msp*A1 polymorphism on age at menarche (AAM) are inconsistent. To reexamine this controversy, we performed a meta-analysis.
Study design: In total 16 studies containing more than 11000 individuals of various ethnicities were selected for the analyses. For 11 case-control studies, odds ratio (OR) was employed to evaluate the risk of late AAM for each study, using homozygote at the wild-type allele as a control group. For the 5 studies with continuous outcomes, the effect size was estimated using the Hedges' adjusted g, which is calculated based on the standardized mean difference between groups of subjects with early and late AAM.
Results: We did not find evidence for association of the *Msp*A1 polymorphism with AAM in the combined case-control sample with mixed ethnic background (OR $= 1.03$, 95% CI: 0.90–1.18, $P = 0.66$), in the monoethnic case-control sample of Caucasian females (OR $= 1.09$, 95% CI: 0.99–1.20, $P = 0.08$) and in the combined sample with continuous traits (Hedges' $g = 0.33$ and -0.041, 95% CI: -0.14–0.80 and -0.18–0.10, P values 0.17 and 0.56 for the pooled population sample and monoethnic sample of Caucasian females, respectively).
Conclusion: Our study showed that *CYP17 Msp*A1 polymorphism was not a significant independent risk factor of AAM. Further studies are needed to clarify the effects of the interaction between this gene and other genetic and/or environment factors on AAM.

Keywords: Age at menarche, *CYP17*, meta-analysis, publication bias

1. Introduction

Age at menarche (AAM) is an important trait related to women's health. An early onset of menarche is associated with elevated risks of breast cancer [1] and endometrial cancer [2]. On the other hand, late menarche increases the risk of Alzheimer's disease [3] and osteoporosis [4], but decreases the incidence of coronary heart disease [3]. Therefore, from a clinical point of view, understanding the potential factors responsible for AAM may shed light on the pathophysiology of these diseases. Height, weight, body mass index (BMI), increased fat uptake, and maternal early menarche were reported as positive predictive factors of early menarche [5,6], while sports activity seems to delay menarche [6]. Twin and family studies have suggested that about 53–74% variation of AAM can be attributed to genetic factors [7–9]. Several genes have been reported to be associated with AAM, such as estrogen receptor α (*ER-*α) [10, 11], sex hormone-binding globulin (*SHBG*) [12], androgen receptor (*AR*) [13], *CYP19* [14], *CYP3A4* and cytochrome P450c17α (*CYP17*) [15,16].

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AAM depends on the maturation of the female reproductive system and other endocrine organs. Estrogen plays an important role in the maturation and function of the reproductive system [17]. Menarche is initiated by the increased amplitude of estrogen exposure during puberty [18].

The human *CYP17* gene, located on chromosome 10 (10q24.3) [19], is a key gene controlling biosynthesis of estrogen in the lipid precursor cells. A product of the gene, a steroidogenic enzyme P450c17α, displays both steroid 17α-hydroxylase and 17, 20-lyase activities in the estrogen biosynthesis pathway [20]. Supposedly, altering activity of the enzyme cytochrome P450c17α may influence estrogen biosynthesis. Hence, there is a possibility that the effect of different hormonal risk factors depends on different *CYP17* genotypes. Some studies have suggested that the *CYP17* gene is associated with hormonal risk factors, and thus the association between these factors (e.g., AAM, age at menopause and hormonal replacement therapy, etc.) and breast cancer depends on *CYP17* genotypes [16,21–23].

Three polymorphisms in the human *CYP17* gene have been commonly used for association studies. One of these polymorphisms, *Msp*A1 (a T→C nucleotide substitution 34 base pairs upstream of the translation initiation site in the 5' promoter region), has been of particular interest as a candidate gene for the breast cancer risk [15,21,24–31]. A subset of the literature refers to the wild-type T allele as $A1$, and the variant C allele as $A2$ [7,24]. In studies of association between the *Msp*A1 polymorphism and breast or ovarian cancer risks this polymorphism was also analyzed for its effect on AAM. However, the results were contradictory and reported either the significant association [15,16] or no association [21,24–36].

The aim of this study is to investigate putative association between the *CYP17 Msp*A1 polymorphism and AAM using a meta-analysis [37]. This method examines whether the aggregate data across several studies provides evidence of statistical significance. A meta-analysis has been commonly used to resolve ambiguities about association/non-association between various polymorphisms and complex traits [38–40]. The present study utilizes this approach to investigate putative association between the *CYP17 Msp*A1 polymorphism and AAM using the data from the available association studies published during 1997–2007.

2. Materials and methods

2.1. Identification and eligibility of relevant studies

The sample data were obtained by conducting a search of literatures using PubMed and MEDLINE over the period from 1997 to 2007 to identify studies with information on the *CYP17 Msp*A1 polymorphism and AAM. The search strategy was based on the various combinations of terms "breast cancer", "ovarian cancer", "menarche" and "*CYP17*". In addition, the citations in the identified articles were screened to find additional publications on the topic. Any human population-based association study, regardless of sample size, was included.

As the $A2$ allele was initially suggested to increase expression of the gene [25], most studies divided the total sample into subsets of wild homozygous ($A1A1$) and combined variants ($A1A2 + A2A2$). So, in this study we did alike. A total of 16 studies were identified to have the data on AAM and the *CYP17 Msp*A1 polymorphism [15,16,21,24–36]. Five of them reported mean AAM according to the genotype of *CYP17* [16, 33–36] and the other 11 divided the subjects into groups of early or late AAM [15,21,24–32]. Among these 11 articles, 10 partitioned the data with the threshold of 13 years [15,21,24–28,30–32] and the other one partitioned with threshold of 14 [29]. Women with breast cancer or ovarian cancer were not excluded from the analysis because menarche affects disease states, but not vise versa.

Each study with binary outcomes provided a two-by-two table classifying subjects by AAM (early or late) and *CYP17 Msp*A1 $A2$ allele (present or not). Each study with continuous outcomes provided sample sizes of the subgroups (*CYP17 Msp*A1 $A2$ allele presents or not) and mean, standard deviation (sd) of AAM in each subgroup.

2.2. Data extraction

Following the Meta-analysis Of Observational Studies in Epidemiology (MOOSE) statement for reporting meta-analysis of observational studies [41], we used a standardized reporting form to independently abstract data from each included study. The following information was sought from each report: authors, year of publication, country of origin, mean age of the sample, selection and ethnic background of the study population (Caucasian, Asian, African or Mixed), number of eligible and genotyped cases and controls. Relevant information is shown in details in Tables 1 and 2.

Table 1
A summary of eligible case-control studies used for the meta-analysis of association between the *CYP17 Msp*A1 polymorphism and AAM

Author	Place of study	Ethnicity	Mean age	threshold	Number of samples		Power[1]
					$A1A1$	$A1A2 + A2A2$	(%)
Feigelson et al. (1997)	USA	Mixed	62	13	145	314	52.62
Helzlsouer et al. (1998)	USA	Caucasian	60.3	13	68	123	26.96
Haiman et al. (1999)	USA	Caucasian	58.3	13	394	678	89.09
Mitrunen et al. (2000)	Finland	Caucasian	56.2	13	391	549	73.54
Goodman et al. (2001)	USA	Mixed	–	13	96	173	35.39
Ambrosone et al. (2003)	USA	Caucasian	55.6	13	205	189	51.56
Wu et al. (2003)	Singapore	Asian	>45	13	146	713	48.63
Shin et al. (2005)	Korea	Asian	–	14	70	264	24.33
Verla-Tebit et al. (2005)	Germany	Caucasian	41.7	13	502	925	94.91
Chang et al. (2005)	Australia	Caucasian	41.1	13	776	1181	99.19
Einarsdottir et al. (2005)	Sweden	Caucasian	63.2	13	933	1652	99.05
Pooled					3726	6761	100
Caucasian sample					3269	5297	100

[1]The power was calculated based on the assumption that the true odds ratio was 1.5 at the significance level 0.05.

Table 2
A summary of eligible studies with continuous outcomes used for the meta-analysis of association between the *CYP17 Msp*A1 polymorphism and AAM

Author	Place of study	Ethnicity	Mean age	Number of samples	
				$A1A1$	$A1A2 + A2A2$
McCann et al. (2002)	USA	Caucasian	55.64	205	190
Gorai et al. (2003)	Japan	Asian	59.9	101	149
Onland-Moret et al. (2005)	Holland	Caucasian	57.55	166	207
Small et al. (2005)	USA	Mixed	32.08	61	103
Jasienska et al. (2006)	Poland	Caucasian	29.52	21	37
Pooled				554	686
Caucasian sample				392	434

2.3. Statistical analysis

The effect sizes and pooled estimates of the effects across the studies were calculated with the Comprehensive Meta-Analysis software package [42]. For the studies with binary outcomes, odds ratio (OR) was used to evaluate the risk of late AAM for each study using homozygotes of the wild-type allele as a control group. The power of the study was estimated as the probability of finding a significant association between *CYP17 Msp*A1 and AAM at the 0.05 significance level, assuming that the OR was 1.5. For the studies with continuous outcomes, the measure of the effect size was Hedges' adjusted g [43]. This is a commonly used estimator of the effect size that is calculated based on the standardized mean difference between two groups being studied. Heterogeneity across the studies was examined using the Q statistics and was considered significant at $P < 0.10$ [44]. Depending on whether heterogeneity was present or not, the meta-analysis was conducted using random effects or fixed effects model, respectively.

Finally, for the primary outcomes, we performed a cumulative meta-analysis and a recursive cumulative meta-analysis to evaluate whether the summary effects changed as more data are accumulated. The cumulative meta-analysis was conducted stepwise after adding a single new study at a time. The recursive cumulative analysis estimates the relative change in each step and provides a measure of how much the effect size changes as evidence accumulates. For the case-control studies, the relative change was defined as the pooled OR at the next step divided by the pooled OR at the current step. For the studies with continuous outcomes, the relative change was defined as the pooled Hedges' g at the next step minus the g at the current step [45–47]. We also estimated publication bias by using both funnel plot and the method proposed by Egger et al. [48]. Funnel plot is a scatterplot of studies' effect sizes against standard errors. In the absence of bias the plot will resemble a symmetrical inverted funnel. Conversely, if there is bias, funnel plots will often be skewed and asymmetrical. The Egger's method is based on the funnel plot, where the standardized effect estimate is regressed on a measure the precision (1/Standard Error). The result-

ing publication bias statistics is an intercept of the regression, which will be significantly greater than zero in the presence of publication bias.

3. Results

3.1. Meta-analysis database

The eligible studies with binary outcomes included 10487 subjects in total (Table 1); all of them had genotype data. The sample size varied substantially (ranging from 83 to 2585 individuals), and so did the statistical power (24.33–99.19%). The power of the pooled sample was 100%. Among these 11 case-control studies, seven studies employed subjects of Caucasian descent; two studies used Asians and the other two used subjects of mixed ethnicities. After excluding the latter four, the total number of the subjects in the pooled sample became 8566 and the statistical power still reached 100% (Table 1).

The studies with continuous outcomes totaled 1240 subjects with a sample size varying from 58 to 395 (Table 2). Three studies employed subjects of Caucasian descent and the other two employed subjects of Asians and mixed ethnical background, respectively. After excluding the latter two, the total number of the subjects in the pooled sample became 826.

3.2. Meta-analysis

The tests for heterogeneity across the studies were performed before the studies were pooled for the meta-analysis. The statistically significant heterogeneity among the individual studies was observed for both studies with binary outcomes and continuous outcomes ($Q = 19.48$, $P = 0.04$ and $Q = 63.33$, $P < 0.01$, respectively). Therefore we used the random effects model in the subsequent analyses. There was no statistically significant association in overall groups ($P = 0.66$ for the studies with binary outcomes and $P = 0.17$ for the studies with continuous outcomes).

The results of the pooled analysis and the individual studies for association of the *CYP17 Msp*A1 polymorphism and AAM are presented in Tables 3 and 4. The ORs of association between *CYP17 Msp*A1 and AAM varied slightly (between 0.66 and 1.52) for the data from the studies with binary outcomes. One study showed a significant association ($P < 0.01$) between *CYP17* and AAM and an increased risk of later AAM in women carrying the $A2$ allele ([15] Table 3). For the studies with continuous outcomes, the standard difference of means ranged from -0.15 to 1.44. Two studies [16,36] showed significant difference between the genotypes ($P < 0.01$, Table 4).

The above results are based on the pooled data from different ethnic groups and may thus carry a bias due to the ethnic heterogeneity. For example, the frequency of the $A1A1$ homozygote in Asians was significantly different from that in Caucasians (Tables 1 and 2). Therefore, we also performed the meta-analyses for the pooled samples composed only of Caucasians.

The pooled Caucasian samples showed no heterogeneity for the studies with both types of outcomes ($Q = 10.50$, $P = 0.11$, Table 3 and $Q = 2.10$, $P = 0.35$, Table 4, respectively). The analysis under the fixed effects model showed no association between the *CYP17 Msp*A1 polymorphism and AAM in both cases ($P = 0.08$ and $P = 0.56$, respectively).

3.3. Bias diagnostics

The results of the cumulative and recursive cumulative meta-analysis for case-control studies are shown in Fig. 1. As more data were accumulated, the 95% CI became narrower, but there was no evidence that the magnitude of the cumulative effect estimates changed in the same direction.

Figure 2 shows the result of the cumulative and recursive cumulative meta-analysis for the studies with continuous outcomes. While no change in the magnitude of the cumulative effect estimates was determined for the pooled sample of mixed ethnicity, the Hedges' g decreased from 0.06 to -0.41 in the aggregated Caucasian sample.

Figure 3 demonstrates the funnel plots for both case-control studies and studies with continuous outcomes. The plots are roughly symmetric, thus suggesting no publication bias. The publication bias statistics [49] were not significant for the studies with binary outcomes (intercept of the regression $a = -0.98$, $t = 0.95$, $P = 0.36$ for the total sample; intercept of the regression $a = -0.52$, $t = 0.31$, $P = 0.77$ for Caucasians), and so were for the studies with continuous outcomes (intercept $a = 5.26$, $t = 0.90$, $P = 0.43$ for the total sample; intercept $a = -0.15$, $t = 0.06$, $P = 0.96$ for Caucasians).

4. Comments

The presented meta-analysis summarizes the data of 16 observational studies (11 with binary outcomes and

Table 3
The summary of ORs for the *CYP17 Msp*A1 polymorphism and AAM of studies with binary outcomes

Study	AAM				Weight	OR (95% CI)	P^1
	$A1A1$		$A1A2 + A2A2$			*A1A2+A2A2 vs A1A1*	
	Early AAM	Late AAM	Early AAM	Late AAM			
Feigelson et al. (1997)	63	82	161	153	24.50	0.73 (0.49–1.08)	0.12
Helzlsouer et al. (1998)	36	32	57	66	10.90	1.30 (0.72–2.36)	0.38
Haiman et al. (1999)	203	191	348	330	62.24	1.01 (0.79–1.29)	0.95
Mitrunen et al. (2000)	88	303	111	438	38.53	1.15 (0.87–1.57)	0.40
Goodman et al. (2001)	56	40	83	90	15.15	1.52 (0.92–2.51)	0.10
Ambrosone et al. (2003)	88	117	91	98	24.33	0.81 (0.54–1.20)	0.30
Wu et al. (2003)	17	129	118	595	13.03	0.66 (0.39–1.14)	0.14
Shin et al. (2005)	8	62	37	227	5.80	0.79 (0.35–1.78)	0.57
Verla-Tebit et al. (2005)	191	311	318	607	75.51	1.17 (0.94–1.47)	0.17
Chang et al. (2005)	350	426	456	725	113.94	1.31 (1.09–1.57)	0.00
Einarsdottir et al. (2005)	198	735	378	1274	101.61	0.91 (0.75–1.10)	0.33
Pooled (heterogeneity test: $Q = 19.48$, $P = 0.04$)							
Random effect model	1298	2428	2158	4603	485.54	1.03 (0.90–1.18)	0.66
Pooled after excluding Asians and mixed populations: (heterogeneity test: $Q = 10.50$, $P = 0.11$)							
Fixed effect model	1154	2115	1759	3538	427.06	1.09 (0.99–1.20)	0.08

[1] All P values are two-sided.

Table 4
Summary of studies with continuous outcomes

Study	AAM								P^1
	$A1A1$			$A1A2 + A2A2$					
	Mean	Std	N	Mean	Std	N	Weight	Hedges' g (95% CI)	
McCann et al. (2002)	12.82	1.52	205	12.72	1.76	190	98.56	0.06 (−0.14−0.26)	0.54
Gorai et al. (2003)	14.10	1.30	101	13.66	1.22	249	70.94	0.35 (0.12−0.59)	0.00
Onland-Miret et al. (2005)	13.40	1.50	166	13.63	1.58	207	91.87	−0.15 (−0.35−0.05)	0.15
Small et al. (2005)	12.46	0.22	61	12.16	0.20	103	30.80	1.44 (1.09−1.80)	0.00
Jasienska et al. (2006)	13.10	3.15	21	13.2	1.03	37	13.39	−0.05 (−0.58−0.49)	0.86
Pooled (heterogeneity test: $Q = 63.33$, $P < 0.01$)									
Random effect model			554			786	305.57	0.33 (−0.14−0.80)	0.17
Pooled after excluding Asians and mixed populations: (heterogeneity test: $Q = 2.10$, $P = 0.35$)									
Fixed effects model			392			434	203.83	−0.041 (−0.18−0.10)	0.56

[1] All P values are two-sided.

the others with continuous outcomes) about the effect of the *CYP17 Msp*A1 polymorphism on AAM. Overall, the obtained results suggest no association between this polymorphism and AAM in both the pooled multiethnic samples and monoethnic Caucasian samples. However, the low P value (0.08) for the pooled Caucasian sample from studies with binary outcomes reserves some probability that the *CYP17 Msp*A1 polymorphism may be a modifier, but likely is not a significant independent risk factor of AAM on a wide population basis.

The *CYP17 Msp*A1 polymorphism has three genotypes: a homozygous wild type ($A1A1$), a heterozygous variant ($A1A2$), and the homozygous variant ($A2A2$). The T($A1$) →C($A2$) substitution was initially hypothesized to create an Sp-1 promoter site, which could lead to up-regulation of transcriptional activation of the variant allele and which in turn might affect the synthesis of estrogen [49]. Some studies reported higher estrogen levels in women carrying the $A2$ allele [22,26]. Generally, there is limited evidence for the effect of the *CYP17* genotype on estrogen mediated factors such as AAM. While some data suggested weak though not statistically significant association between the $A2A2$ genotype and earlier menarche [50], the majority of the studies, including those used in our meta-analysis, reported no such association [27,29,31, 51].

Indeed, among the 11 case-control studies included in the present analysis, only one [15] reported the positive result, namely, suggesting an increased risk for later AAM among women with the C ($A2$) allele (Table 3). There is a potential factor, which might produce this discrepancy. The subjects recruited in this study were on average younger than those in the other studies (Table 1). This might yield more accurate recall of AAM. As was recently showed, after 30 years, about

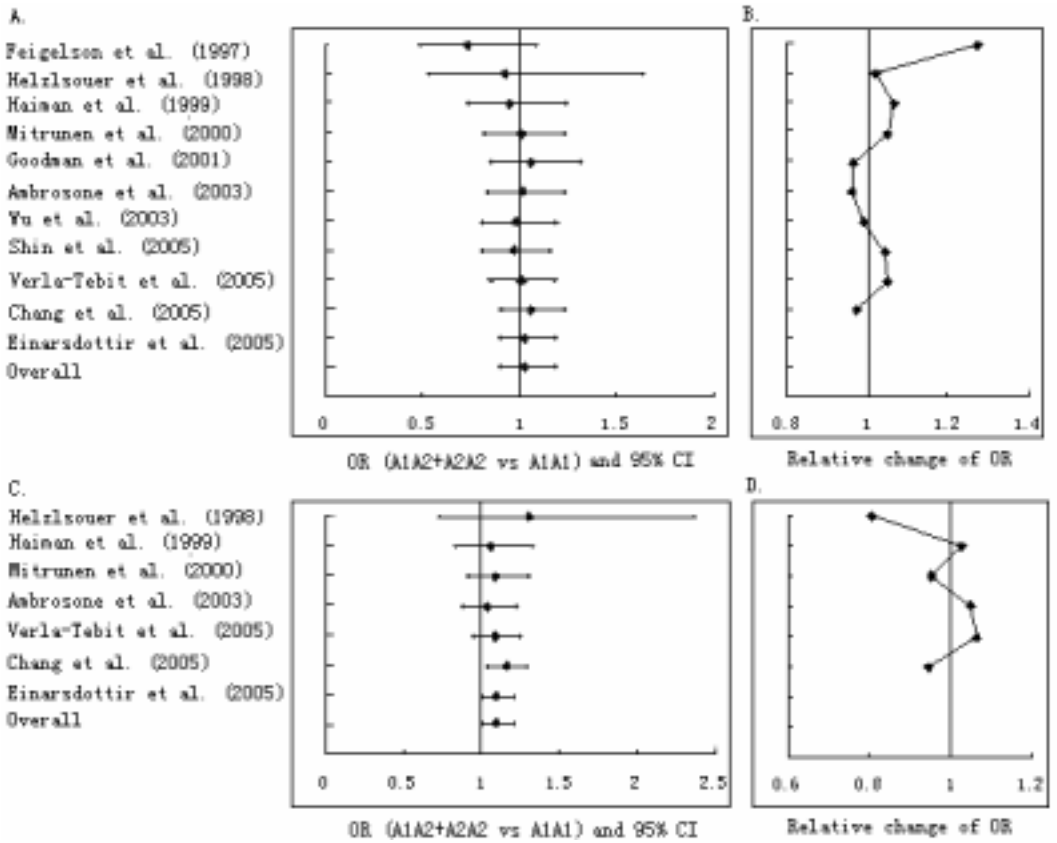

Fig. 1. Cumulative meta-analysis (A and C) and recursive cumulative meta-analysis (B and D) of association between the *CYP17 Msp*A1 polymorphism and AAM based on the studies with binary outcomes. Each line represents the OR and 95% CI of that study combined with all previous studies. A and B: all ethnicities; C and D: Caucasians only.

79 percent of women may recall their AAM with accuracy of within one year of original menarche [52]. The recall bias, albeit small, still exists [53]. In a case of the bias, it would most likely have been biased toward the null, leading to an underestimation of the true effect of the tested polymorphism.

Ideally, to avoid a bias in the results, the estimates of ORs should be adjusted for the factors known to contribute to AAM, such as age and ethnicity [51,54]. However, since some of the studies used in the current meta-analysis did not contain respective data, the crude ORs were calculated using only tabular data from the published reports. This might affect the overall accuracy of the meta-analysis in either way.

Among the 5 studies with continuous outcomes, the two, which used non-Caucasian subjects [16,36], suggested a decreased risk for later AAM among women with the C ($A2$) allele (Table 4). AAM has well-known ethnic background: e.g., African-American girls have earlier menarche than Asians and Caucasians [51,54]. Homozygotes for the $A2$ variant of the *CYP*17 gene appear to be more common in Japanese (22%) and other East Asian (32%) populations than in Caucasians (14%) and African-Americans (13%) [51,54]. The significant difference in the *CYP17* allele frequencies between Caucasians and Asians (Table 2) suggests that ethnicity may indeed be a potential factor contributing to AAM and other traits associated with this gene. Similar differences in allele frequencies were reported for candidate genes of other complex traits with ethnic background, e.g., osteoporosis [55], cardiovascular disease [56], renal disease [57], and others.

There was some heterogeneity between the results of various studies. The heterogeneity may be caused by ethnic differences between study samples. Among the 11 case-control studies used in the present analysis, two employed samples of mixed ethnicities; two employed samples of Asians while the other seven used Caucasians (Table 1). Among the 5 studies with continuous outcomes, one employed a sample of mixed ethnicities; one used Asians and the other three used Caucasians (Table 2). After excluding the data of non-

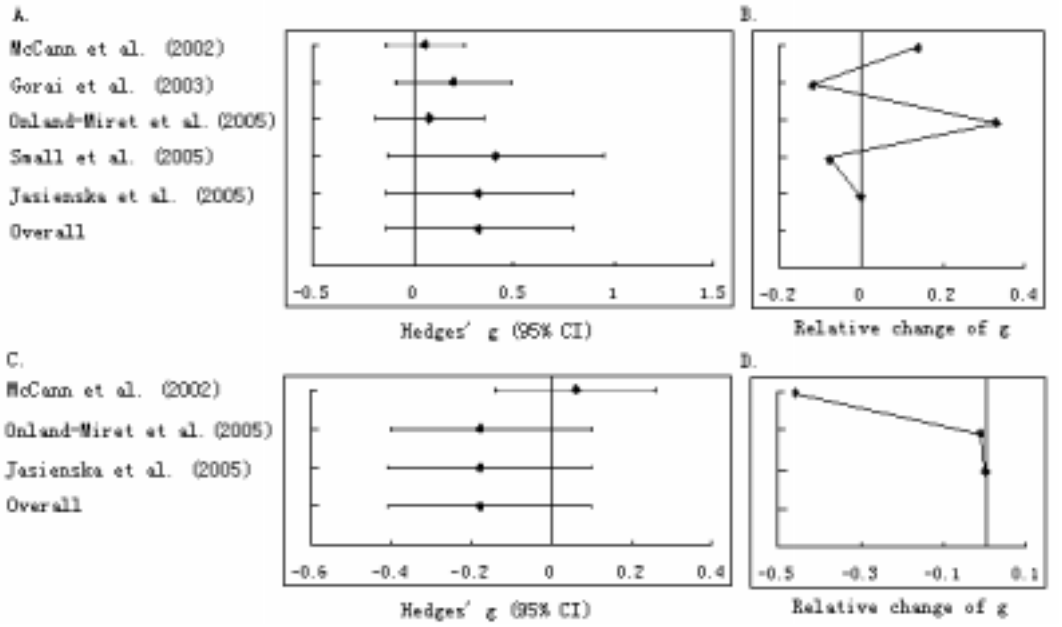

Fig. 2. Cumulative meta-analysis (A and C) and recursive cumulative meta-analysis (B and D) of association between the *CYP17 Msp*A1 polymorphism and AAM based on the studies with continuous outcomes. Each line represents Hedges' g and 95% CI of that study combined with all previous studies. A and B: all ethnicities; C and D: Caucasians only.

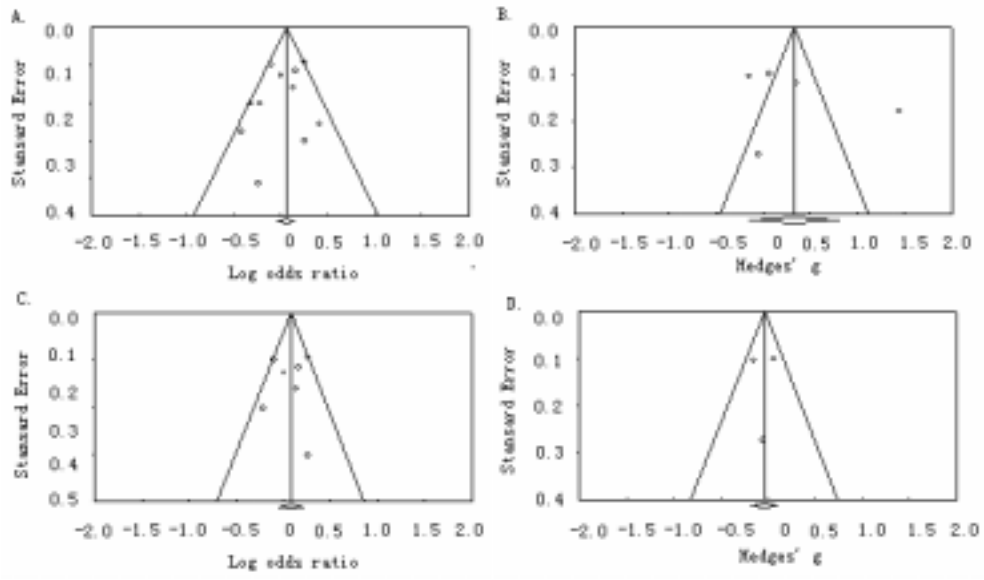

Fig. 3. Funnel plots of the publication bias. A and B: all ethnicities; C and D: Caucasians only.

Caucasian subjects, no heterogeneity was determined among the remaining studies.

Several studies demonstrated that AAM shares substantial proportion of genetic variation with obesity and osteoporosis [7,58,59]. Along with the other results [14,60–62], those are in support that AAM is a complex trait, and, therefore, potential contribution of many genes to it may be modest. From this point of view, the nearly significant association of the *CYP17 Msp*A1 polymorphism does not completely rejects a probability that it may be a weak modifier of AAM in Caucasian females, especially when interacting with

other genetic or environmental factors. For example, an interaction between the *ER-*α gene and the *VDR* gene had a significant effect on AAM, but neither is a significant independent risk factor [63]. Likewise, interaction between *5-HTTLPR* and stressful life-style factors significantly influences depression symptoms, but the *5-HTTLPR* is not a significant independent risk factor of depression [64]. Further studies of *CYP17* are needed to determine whether there are the effects of the interaction between this gene and other genetic or environment factors on AAM.

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