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META-ANALYSIS

Meta-analysis of association studies between five candidate genes and type 2 diabetes in Chinese Han population

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Abstract The multiple small-scale association studies of candidate genes for type 2 diabetes mellitus in the Chinese Han population have shown inconsistent results. Here, we performed a meta-analysis to evaluate the contribution of five candidate genes to the pathogenesis of type 2 diabetes in the Chinese Han population. We searched for relevant published papers and used STATA v.11.0 to perform a meta-analysis on six single-nucleotide polymorphisms in five genes—*ADIPOQ*-rs2241766 (SNP45) and -rs1501299 (SNP276), *ADRB3*-rs4994 (Trp64Arg), *CAPN10*-rs379 2267 (SNP43), *ENPP1*-rs1044498 (K121Q), and *PPARGC 1A*-rs8192678 (Gly482Ser)—in the Chinese Han population under an additive genetic model. The pooled odds ratios (95% confidence intervals and *P*-values) were 0.71 (0.60–0.83; $P < 0.001$) for *ADIPOQ*-rs2241766, 0.79 (0.64–0.97; $P = 0.027$) for *ADIPOQ*-rs1501299, 1.27 (1.07–1.51; $P = 0.006$) for *ADRB3*-rs4994, 0.79 (0.57–1.10; $P = 0.163$) for *CAPN10*-rs3792267, 1.41 (1.13–1.76; $P = 0.003$) for *ENPP1*-rs1044498, and 1.54 (1.34–1.81; $P < 0.001$) for *PPARGC1A*-rs8192678. There was high heterogeneity for *ADIPOQ*-rs2241766, *ADIPOQ*-rs1501299, and *CAPN10*-rs3792267 ($I^2 = 74.9$, 69.4, and 75.8%, respectively), but not for *ADRB3*-rs4994, *ENPP1*-rs1044498, and *PPARGC1A*-rs8192678 ($I^2 = 0.0$, 43.4, and 23.3%, respectively). Under an additive genetic model, the C allele of *ADRB3*-rs4994, the C allele of *ENPP1*-rs1044498, and the A allele of *PPARGC1A*-rs8192678 increase the risk of type 2 diabetes in the Chinese Han population.

Keywords Meta-analysis · Candidate genes · Type 2 diabetes · Chinese · Han

Abbreviations

T2DM	Type 2 diabetic mellitus
NGT	Normal glucose tolerance
GWAS	Genome wide association study
SNP	Single-nucleotide polymorphism
ADIPOQ	Adiponectin C1Q and collagen domain containing
ADRB3	Adrenergic-beta-3-receptor
ENPP1	Ectoenzyme nucleotide pyrophosphate phosphodiesterase 1
PPARGC1A	Peroxisome proliferator-activated receptor gamma, coactivator 1 alpha
CAPN10	Calpain 10
FTO	Fat mass and obesity
OR	Odds ratios
CNKI	China National Knowledge infrastructure
HWE	Hardy–Weinberg equilibrium
ADA	American Diabetes Association
WHO	World Health organization

Introduction

Type 2 diabetes mellitus (T2DM) is a multifactorial disease, influenced by both genetic and environmental factors. Approximately 40 genetic loci for T2DM have been identified by genome-wide association studies in several different populations since 2007 [1]. However, candidate

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gene studies are still a valid approach, because the known loci account for only approximately 10% of the susceptibility to T2DM. Recently, several T2DM susceptibility genes identified by genome-wide association studies in other ethnic populations have been replicated in large studies of the Chinese population but not those candidate genes investigated by candidate gene approach before 2007. There were many case–control studies of T2DM conducted in mainland China before 2007, but it is difficult to draw conclusions from them because of their low-sample sizes and inconsistent results. It is now important to re-evaluate the genes implicated in these studies in a large sample from the Chinese population.

In this study, we performed a meta-analysis on single nucleotide polymorphisms (SNPs) in adiponectin C1Q and collagen domain containing (*ADIPOQ*), adrenergic beta-3-receptor (*ADRB3*), calpain 10 (*CAPN10*), ectonucleotide pyrophosphate phosphodiesterase 1 (*ENPP1*), and peroxisome proliferator-activated receptor gamma, coactivator 1 alpha (*PPARGC1A*) to evaluate the relationships between these genetic loci and T2DM in the Chinese Han population.

Methods

Figure 1 summarizes the workflow for our meta-analysis of *ADIPOQ*-rs2241766, *ADIPOQ*-rs1501299, *ADRB3*-rs49

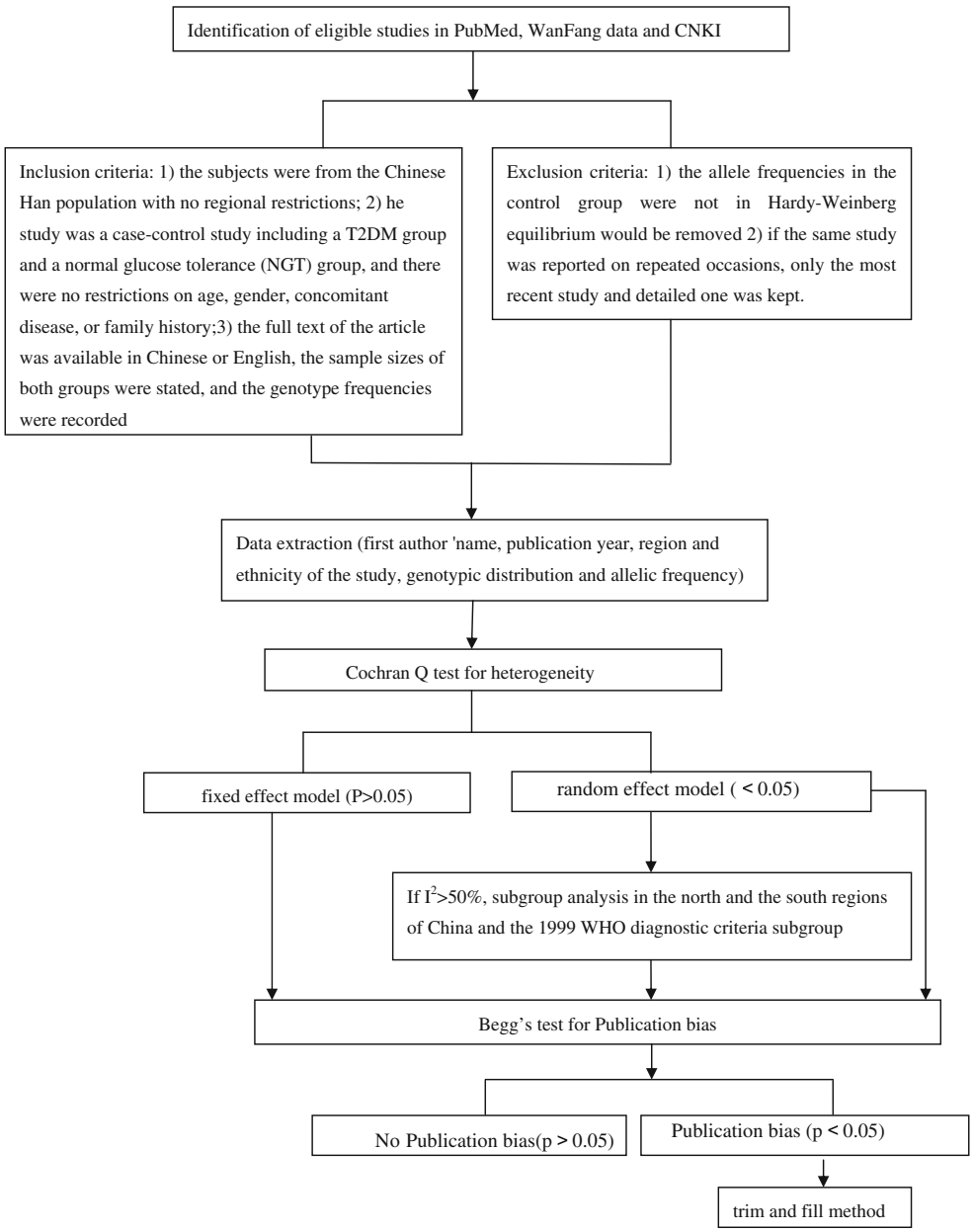


Fig. 1 The flowchart of the meta-analysis

94, *CAPN10*-rs3792267, *ENPP1*-rs1044498, and *PPARGC 1A*-rs8192678.

Identification of eligible studies

We searched three databases—PubMed (http://www.ncbi.nlm.nih.gov/pubmed/), WanFang data (http://www.wanfangdata.com.cn/), and China National Knowledge infrastructure (CNKI) database (http://dlib.edu.cnki.net/kns50/)—for case–control studies in the Chinese Han population on ADIPOQ, ADRB3, CAPN10, ENPP1, or PPARGC1A that were published in Chinese or English up to November 2010. The search terms were [(ADIPOQ OR ADRB3 or CAPN10 or CANP10 or NIDDM1or ENPP1 or PPARGC 1A) AND Chinese AND type 2 diabetes] in PubMed, or [ADIPOQ OR ADRB3 or CAPN10 or CANP10 or NIDDM1or ENPP1 or PPARGC1A] in the WanFang data and CNKI. From the results, we selected papers describing studies of the following SNPs: ADIPOQ-rs2241766 (SNP 45), ADIPOQ-rs1501299 (SNP267), ADRB3-rs4994 (Trp 64Arg), CAPN10-rs3792267 (SNP43), ENPP1-rs1044 498 (K121Q), and PPARGC1A-rs8192678 (Gly482Ser) (Table 1).

Criteria for article inclusion or exclusion

The articles included in the study had to meet the following criteria: (1) the subjects were from the Chinese Han population with no regional restrictions; (2) the study was a case–control study including a T2DM group and a normal glucose tolerance (NGT) group, and there were no restrictions on age, gender, concomitant disease, or family history; and (3) the full text of the article was available in Chinese or English, the sample sizes of both groups were stated, and the genotype frequencies were recorded. Studies were excluded if the allele frequencies in the control group were not in Hardy–Weinberg equilibrium (HWE), and if the same study was reported on repeated occasions, only the most recent and detailed study was kept.

Data extraction and statistical analysis

From each publication, we extracted the first author's name, the publication year, the region and ethnicity of the study, and the genotypic distributions. We performed a meta-analysis using STATA version 11.0 under an additive genetic model. Heterogeneity was assessed by the Cochran Q test ($P < 0.05$ was considered statistically significant). The degree of heterogeneity was assessed by the I^2 statistical test ($I^2 < 25\%$: low heterogeneity; $I^2 = 25$–50%: moderate heterogeneity; $I^2 = 50$–75%: high heterogeneity; $I^2 > 75\%$: extreme heterogeneity) [2]. The pooled odds ratios (ORs) and 95% confidence intervals (CIs) were calculated under a fixed- or random-effect model. If P was greater than 0.05 by the Cochran Q test, the pooled ORs and 95% CIs were calculated under a fixed-effect model; otherwise, they were calculated under a random-effect model. If there was high heterogeneity ($I^2 > 50\%$), we performed a subgroup analysis for North and South China, and for those meeting the 1999 World Health Organization (WHO) diagnostic criteria [3]. Publication bias was evaluated by Begg's test ($P < 0.05$ was considered significant); if there was publication bias, the "trim and fill" method was used to evaluate the missing papers [4].

Results

We searched the PubMed, CNKI, and WanFang data for papers relating to *ADIPOQ*-rs2241766, *ADIPOQ*-rs1501299, *ADRB3*-rs4994, *CAPN10*-rs3792267, *ENPP1*-rs1044498, or *PPARGC1A*-rs8192678 that were published up to November 2010. We identified 19, 8, 9, 11, 13, and 6 articles that met our inclusion criteria, respectively (Tables 1, 2). The results are summarized in Table 3.

*ADIPO*Q-rs2241766

The pooled sample comprised of 3737 T2DM- and 3247 NGT-subjects from 19 case–control studies in the Chinese Han population. There was high heterogeneity among

Table 1 Results of study selection of rs2241766 and rs1501299 of ADPOQ, rs4994 of ADRB3, rs3792267 of CAPN10, rs1044498 of ENPP1, rs8192673 of PPARGC1a

SNPs	Gene	Papers included	Total number of DM group	Total number of NDM group	References
rs2241766	ADIPOQ	19	3737	3247	[26–44]
rs1501299	ADIPOQ	8	2108	1894	[27, 31, 37, 42, 44–47]
rs4994	ADRB3	9	1087	979	[48–56]
rs3792267	CAPN10	11	1677	1386	[57–67]
rs1044498	ENPP1	13	2509	2135	[68–80]
rs8192673	PPARGC1a	6	757	748	[81–86]

NS not stated, *WHO* World Health organization, *ADA* American Diabetes Association, *M/F* male/female

Table 2 Characteristics of the papers included in the meta-analysis of rs2241766 and rs1501299 of ADPOQ, rs4994 of ADRB3, rs3792267 of CAPN10, rs1044498 of ENPP1, rs8192673 of PPARGC1a

SNPs	Study and year	Region	Diagnostic criteria	Control source	Case		Control	
					No (M/F)	Age (years)	No (M/F)	Age (years)
rs2241766	Wang et al. [26]	Guangdong	1999 WHO criteria	Healthy checkup attenders	200 (110/90)	NS	200 (108/92)	54 ± 14
	Hao et al. [27]	Hainan	1999 WHO criteria	Healthy checkup attenders and blood donors	106 (62/44)	NS	58 (30/28)	NS
	Wang et al. [28]	Hubei	1997 ADA criteria	NS	84	57.21 ± 15.38	84	57.74 ± 18.26
	Shi et al. [29]	Heilongjiang	1999 WHO criteria	NS	180 (70/110)	56.9 ± 11.6	286 (162/124)	45.2 ± 5.8
	Ye et al. [30]	Fujian	1997 ADA criteria	NS	131 (78/53)	48.6 ± 8.9	105 (62/43)	47.1 ± 9.7
	Dong et al. [31]	Shanghai	1985 WHO criteria	NS	195 (85/110)	59.7 ± 11.6	184 (74/113)	59.5 ± 11.4
	Li et al. [32]	Yunnan	1999 WHO criteria	Healthy checkup attenders	113 (88/45)	49.0 ± 12.6	57 (26/31)	33.3 ± 13.3
	Zhai et al. [33]	Beijing	1999 WHO criteria	NS	195 (106/89)	64.95 ± 11.8	139 (80/59)	67.64 ± 6.48
	Su et al. [34]	Guangxi	1999 WHO criteria	NS	95	48.93 ± 7.75	115	47.65 ± 11.02
	Wei et al. [35]	Zhejiang	1999 WHO criteria	Healthy checkup attenders	100	56.19 ± 11.18	101	52.19 ± 10.18
	Wang et al. [36]	Hebei	1999 WHO criteria	Healthy checkup attenders	104	52.34 ± 11.05	90	51.23 ± 8.86
	Xia et al. [37]	Jiangsu	1999 WHO criteria	Healthy checkup attenders	78 (43/35)	NS	85 (45/40)	NS
	Cheng et al. [38]	Henan	1999 WHO criteria	NS	168	NS	150	NS
	Gu et al. [39]	Jiangsu	1999 WHO criteria	Healthy checkup attenders	180 (111/69)	NS	144 (90/54)	NS
	Kang et al. [40]	Yunnan	1999 WHO criteria	NS	86 (40/46)	58.0 ± 12	65 (34/31)	53.0 ± 12
	Wang et al. [41]	Shandong	1999 WHO criteria	NS	138 (70/68)	57.2 ± 10.5	132 (76/56)	35.2 ± 12.0
	Wang et al. [42]	Shandong	1999 WHO criteria	Healthy checkup attenders	100 (58/42)	NS	100	NS
	Sun et al. [43]	Fujian	WHO criteria	NS	225 (138/117)	48.6 ± 10.7	120 (53/67)	47.1 ± 11.0
	Wang et al. [44]	Shanghai	WHO criteria	NS	1832 (1322/510)	64.9 ± 10.6	1940 (1355/585)	58.7 ± 9.6
rs1501299	Hao et al. [27]	Hainan	1999 WHO criteria	Healthy checkup attenders and blood donors	106 (62/44)	NS	58 (30/28)	NS
	Sun et al. [45]	Shanxi	1999 WHO criteria	Healthy checkup attenders	134 (59/75)	53 ± 7	76 (33/43)	55 ± 7
	Ru et al. [46]	Anhui	1999 WHO criteria	Healthy checkup attenders	276 (131/145)	52.09 ± 7.86	141 (67/74)	52.37 ± 7.95
	Dong et al. [31]	Shanghai	1985 WHO criteria	NS	195 (85/110)	59.7 ± 11.6	184 (74/113)	59.5 ± 11.4
	Wang et al. [47]	Tianjin	1999 WHO criteria	Healthy checkup attenders	196 (92/104)	59.0 ± 12.0	165 (80/85)	53.0 ± 9.0
	Xia et al. [37]	Jiangsu	1999 WHO criteria	Healthy checkup attenders	78 (43/35)	NS	85 (45/40)	NS
	Wang et al. [42]	Shandong	1999 WHO criteria	Healthy checkup attenders	100 (58/42)	NS	100	NS
	Wang et al. [44]	Shanghai	WHO criteria	NS	1832 (1322/510)	64.9 ± 10.6	1940 (1355/585)	58.7 ± 9.6

Table 2 continued

SNPs	Study and year	Region	Diagnostic criteria	Control source	Case		Control	
					No (M/F)	Age (years)	No (M/F)	Age (years)
rs4994	Bao et al. [48]	Anhui	1985 WHO criteria	Healthy checkup attenders	124 (67/57)	NS	138 (91/47)	NS
	Chen et al. [49]	Nanjing	WHO criteria	Epidemiological Investigation	130 (51/79)	56 ± 1.72	130 (53/77)	52 ± 1.46
	He et al. [50]	Shandong	1999 WHO criteria	Healthy checkup attenders	151 (62/89)	61.1 ± 11.02	80 (30/50)	62.2 ± 8.55
	Hui et al. [51]	Shandong	1999 WHO criteria	Healthy checkup attenders	52 (28/24)	58.96 ± 6.61	40 (22/18)	60.23 ± 4.8
	Li et al. [52]	Shandong	WHO criteria	NS	132 (75/57)	55.4 ± 12.3	80 (46/34)	54.1 ± 13.6
	Li et al. [53]	Guangdong	1997 ADA criteria	NS	52	NS	123	NS
	Sun et al. [54]	Beijing	WHO criteria	NS	126 (77/46)	59.0 ± 12.0	137 (70/67)	65 ± 6
	Xiu et al. [55]	Guangdong	WHO criteria	Healthy checkup attenders	173 (76/97)	57.0 ± 12.0	177 (68/109)	56.0 ± 8.0
	Zhang et al. [56]	Shandong	1999 WHO criteria	Healthy checkup attenders	151 (62/89)	NS	80 (30/50)	NS
rs3792267	Dong et al. [57]	Southwest China	WHO criteria	NS	144 (79/65)	NS	98 (52/47)	NS
	Sun et al. [58]	North China	1985 WHO criteria	Clinic patients	192	NS	165	NS
	Zhang et al. [59]	Yunnan	1999 WHO criteria	Community attenders	131 (37/94	59.37 ± 0.8	131	NS
	Wang et al. [60]	Jiangsu	1999 WHO criteria	NS	123 (64/59)	54.37 ± 10.28	109	NS
	Li et al. [61]	Tianjin	1999 WHO criteria	Healthy checkup attenders	255 (128/127)	58.77 ± 8.89	125 (68/57)	58.49 ± 8.84
	Zhou et al. [62]	Anhui	1999 WHO criteria	NS	100	NS	100	NS
	Ji et al. [63]	Beijing	1997 ADA	Healthy checkup attenders	211 (125/86)	60.7 ± 10.9	127 (52/75)	50.0 ± 9.4
	Wang et al. [64]	Liaoning	WHO criteria	Hospital patients	119 (76/43)	57.0 ± 12.0	121 (724/9)	NS
	Li et al. [65]	Ningxia	1999 WHO criteria	Healthy checkup attenders	120	57.0 ± 11.0	132	59.0 ± 8.0
	Xiang et al. [66]	Shanghai	1999 WHO criteria	Healthy checkup attenders	148 (66/82)	55.8 ± 10.1	128 (57/71)	53.6 ± 11.5
	Gong et al. [67]	Yunnan	1999 WHO criteria	NS	126	NS	126	NS
rs1044498	Cai et al. [68]	Shandong	WHO criteria	Healthy checkup attenders	92	56.4 ± 11.9	47	50.3 ± 10.94
	Gao et al. [69]	Guangdong	WHO criteria	Healthy checkup attenders	295 (160/135)	NS	214 (128/86)	55.92 ± 11.01
	Lan et al. [70]	Shandong	1999 WHO criteria	Healthy checkup attenders	50 (22/28)	NS	48 (23/25)	NS
	Li et al. [71]	Yunnan	1999 WHO criteria	Healthy checkup attenders	127 (68/59)	61.43 ± 10.89	67 (38/29)	44.15 ± 9.17
	Liu et al. [72]	Guangdong	1999 WHO criteria	Healthy checkup attenders	133 (75/58)	62.62 ± 12.68	110 (66/44)	53.23 ± 12.28
	Peng et al. [73]	Hubei	1997 ADA criteria	Healthy checkup attenders	322 (172/150)	NS	188 (101/87)	NS
	Ren et al. [74]	Sichuan	1997 ADA criteria	Healthy checkup attenders	206 (104/112)	52 ± 12	106 (46/60)	45 ± 13
	Shi et al. [75]	Beijing	1999 WHO criteria	NS	228 (84/144)	69.2 + 6.3	308 (136/172)	67.85 ± 5.69
	Wang et al. [76]	Hubei	1997 ADA criteria	NS	539 (273/266)	55.46 ± 12.79	404 (207/197)	61.10 ± 12.67
	Xu et al. [77]	Shandong	WHO criteria	NS	107 (52/55)	56.4 ± 11. 9	92 (45/47)	50.3 ± 10.4
	Yu et al. [78]	Shanghai	1997 ADA criteria	NS	165 (96/69)	55.56 ± 10. 65	98 (63/35)	53.81 ± 15.17
	Zhang et al. [79]	Shandong	1997 ADA criteria	NS	100 (52/48)	56.4 ± 12. 1	150 (78/72)	55.2 ± 15.1
	Zhong et al. [80]	Shandong	1999 WHO criteria	Healthy checkup attenders	50	58.74 ± 14.06	50	58.73 ± 8.05

Table 2 continued

SNPs	Study and year	Region	Diagnostic criteria	Control source	Case		Control	
					No (M/F)	Age (years)	No (M/F)	Age (years)
rs8192673	Hui et al. [81]	Liaoning	1999 WHO criteria	Healthy checkup attenders	140 (69/71)	61. 4 ± 9. 2	88 (58/30)	62. 6 ± 11. 2
	Lu et al. [82]	Guangdong	1999 WHO criteria	Healthy Volunteers	120 (58/62)	62 ± 7	106 (50/56)	65 ± 5
	Shan et al. [83]	Beijing	WHO criteria	NS	266	NS	297	NS
	Wang et al. [84]	Jilin	1997 ADA criteria	NS	20	NS	39	NS
	Wang et al. [85]	Shanghai	1997 ADA criteria	Healthy checkup attenders	164	NS	111	NS
	Zhang et al. [86]	Guangdong	1999WHO criteria	NS	263 (156/107)	63.64 ± 5.53	282 (165/117)	61.25 ± 4.96

studies by the Cochran Q test ($P < 0.05$; $I^2 = 74.9\%$) and an additive, random-effect model was used. The pooled OR of the G risk allele was 0.71 (95% CI, 0.6–0.83; $P < 0.001$) (Fig. 2a). No publication bias was found (corrected $z = 0.42$; corrected $P = 0.673$) (Fig. 3a). Because of the high heterogeneity, we performed a subgroup analysis on the North and South of China, but the high heterogeneity remained ($I^2 = 79.2\%$ and 75.5%, respectively) (Table 4). Using a subgroup of cases who met the 1999 WHO diagnostic criteria, the heterogeneity was reduced ($I^2 = 42\%$), the pooled OR was 1.46 (95% CI, 1.26–1.69; $P = 0.004$ (Table 5; Fig. 4a). No publication bias was found in the subgroup analysis of cases who met the 1999 WHO diagnostic criteria (corrected $z = 0.48$; corrected $P = 0.63$) (Fig. 4b).

ADIPOQ-rs1501299

The pooled sample comprised of 2108 T2DM- and 1894 NGT-subjects from eight case–control studies in the Chinese Han population. There was high heterogeneity by the Cochran Q test ($P < 0.05$; $I^2 = 69.4\%$) and an additive, random-effect model was used. The pooled OR for the minor T allele was 0.79 (95% CI, 0.64–0.97; $P = 0.027$) (Fig. 2b). No publication bias was found (corrected $z = 0.62$; corrected $P = 0.536$) (Fig. 3b). The high heterogeneity remained after separating the populations into those from North and South China ($I^2 = 50.1\%$ and 57.4%, respectively) (Table 4). The heterogeneity was reduced by using only subjects who met the 1999 WHO diagnostic criteria ($I^2 = 38\%$); the pooled OR was 0.70 (95% CI, 0.57–0.86; $P = 0.001$) (Table 5; Fig. 4c). No publication bias was found in the subgroup analysis of cases who met the 1999 WHO diagnostic criteria (corrected $z = 0.38$; corrected $P = 0.71$) (Fig. 4d).

ADRB3-rs4994

The pooled sample comprised of 1087 T2DM- and 979 NGT-subjects from nine case–control studies in the Chinese Han population. There was no heterogeneity among the studies by the Cochran Q test ($P > 0.05$, $I^2 = 0.0$) and an additive, fixed-effect model was used. The pooled OR of the C risk allele was 1.2 (95% CI, 1.07–1.51; $P = 0.006$) (Fig. 2c). No publication bias was found (corrected $z = 0.94$; corrected $P = 0.348$) (Fig. 3c).

CAPN10-rs3792267

The pooled sample comprised of 1682 T2DM- and 1393 NGT-subjects from 11 case–control studies in the Chinese Han population. There was high heterogeneity among the studies by the Cochran Q test ($I^2 = 75.8\%$; $P < 0.05$) and an additive, random-effect model was used. The pooled OR of

Table 3 Meta-analysis results of the relationship between rs2241766 and rs1501299 of ADPOQ, rs4994 of ADRB3, rs3792267 of CAPN10, rs1044498 of ENPP1, rs8192673 of PPARGC1a and T2DM

SNPs	Gene	Meta-analysis model	Pooled OR (95%CI)	*P* for overall effect	Heterogeneity		Publication bias	
					I^2 (%)	*P*	*z*	*P*
rs2241766	ADPOQ	Random	0.71 (0.60–0.83)	<0.0001	74.9	<0.001	0.28	0.78
rs1501299	ADIPOQ	Random	0.79 (0.64–0.97)	0.027	69.4	0.002	0.62	0.536
rs4994	ADRB3	Fixed	1.27 (1.07–1.51)	0.006	0.0	0.809	0.94	0.348
rs3792267	CAPN10	Random	0.79 (0.57–1.10)	0.163	75.8	<0.001	0.23	0.815
rs1044498	ENPP1	Fixed	1.41 (1.13–1.76)	0.003	43.4	0.054	0.79	0.428
rs8192673	PPARGC1a	Fixed	1.54 (1.34–1.81)	0.000	23.3	0.259	0.75	0.452

the A risk allele was 0.79 (95% CI, 0.57–1.10; $P = 0.163$) (Fig. 2d). No publication bias was found (corrected $z = 0.23$; corrected $P = 0.815$) (Fig. 3d). The high heterogeneity remained after separating the populations into those from the North and South of China ($I^2 = 59.9\%$ and 83.4%, respectively) (Table 4). The heterogeneity also remained when using only subjects who met the 1999 WHO diagnostic criteria ($I^2 = 80.9\%$); the pooled OR was 0.83 (95% CI, 0.53–1.31; $P = 0.43$) (Tables 5; Fig. 4c). No publication bias was found in the subgroup analysis of cases who met the 1999 WHO diagnostic criteria (corrected $z = 1.2$; corrected $P = 0.23$) (Fig. 4d).

ENPP1-rs1044498

The pooled sample comprised of 2509 T2DM- and 2135 NGT-subjects from 13 case–control studies in the Chinese Han population. There was no heterogeneity among the studies by the Cochran Q test ($P > 0.05$, $I^2 = 43.4\%$) and an additive, fixed-effect model was used. The pooled OR of the risk allele C was 1.41 (95% CI, 1.13–1.76; $P = 0.003$) (Fig. 2e). No publication bias was found (corrected $z = 0.79$; corrected $P = 0.428$) (Fig. 4e).

PPARGC1A-rs8192678

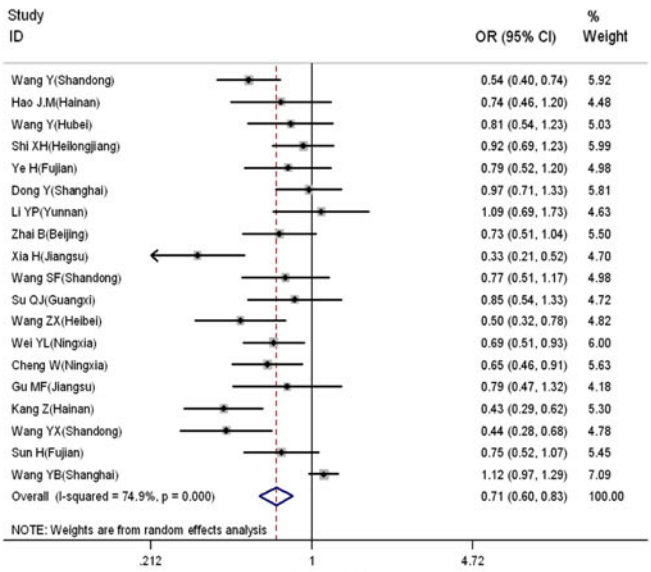
The pooled sample comprised of 757 T2DM- and 748 NGT-subjects from six case–control studies in the Chinese Han population. There was no heterogeneity among the studies by the Cochran Q test ($P > 0.05$, $I^2 = 23.3\%$) and an additive, fixed-effect model was used. The pooled OR of the A risk allele was 1.54 (95% CI, 1.34–1.81; $P < 0.001$) (Fig. 4f). No publication bias was found (corrected $z = 0.75$; corrected $P = 0.452$) (Fig. 4f).

Discussion

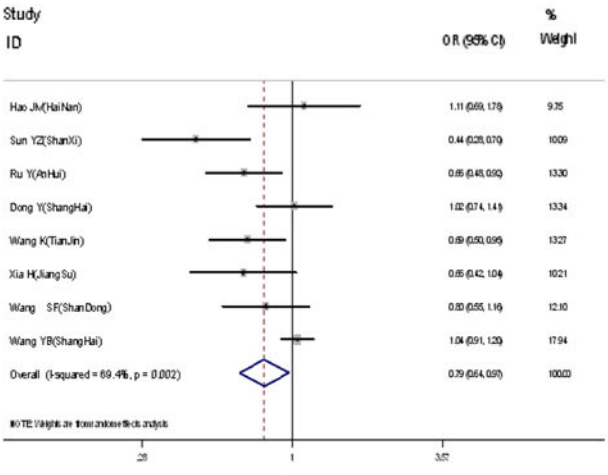
We found that the C allele of *ADRB3*-rs4994, the C allele of *ENPP1*-rs1044498, and the A allele of *PPARGC1A*-rs8192678 increase the risk of T2DM in the Chinese Han population under an additive genetic model. The pooled ORs (95% CIs) were 1.27 (1.07–1.51), 1.41 (1.13–1.76), and 1.54 (1.34–1.81), respectively.

ADRB3 is located on chromosome 8p12. ADBR3 plays an important role in energy metabolism, and is associated with weight gain, insulin resistance and the early onset of T2DM [5]. Ethnic differences in the Trp64Arg distribution have been reported; the Arg allele is found more frequently in Pima Indians and Asians, the incidence of the Arg was 0.31 in Pima Indians, 0.12 in blacks, 0.08 in United States Caucasians, 0.21 in Japanese, and 0.18 in Chinese in the data of our meta-analysis [5, 6]. The Trp64Arg (rs4994) SNP may accelerate the onset of T2DM by changing the balance of energy metabolism in the visceral adipose tissue [5]. Among the 1685 subjects in the Funagata Diabetes Study, the Arg/Arg genotype was associated with type 2 diabetes [7]. However, in a large population-based study of 1259 Caucasians in Germany, there was no association of this SNP with T2DM [8]. In our meta-analysis in the Chinese Han population, we found that this SNP increases the risk of T2DM by 27% per risk allele under an additive genetic model, with a sample of 1087 T2DM- and 979 NGT-subjects (OR = 1.27; $P = 0.008$). This discrepancy might be caused by differences in the Trp64Arg genotype distribution in different ethnic backgrounds.

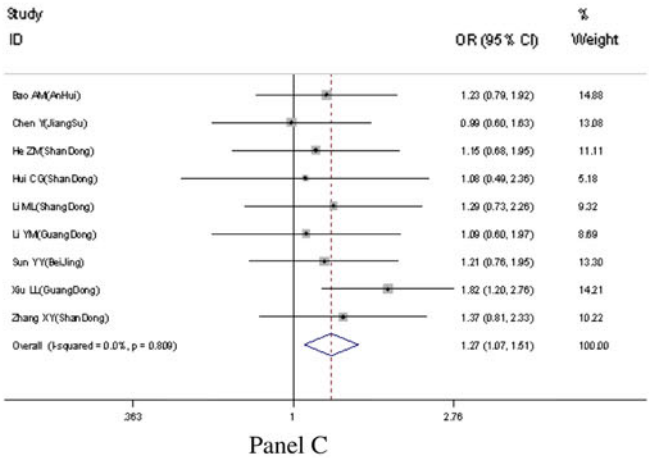
In addition to T2DM, Trp64Arg also plays a role in obesity. A meta-analysis of the relationship between *ADRB3* and body mass index (BMI) suggested that the Trp64Arg SNP was associated with BMI in East Asians, but not Europeans [9]. Another obesity-related gene, 'fat mass and obesity associated' (*FTO*), was identified through a genome-wide association scan for obesity-related quantitative traits and the strongest association was observed for rs9930506 in *FTO* ($P = 8.6 \times 10^{-7}$) [10]. In a study of 2351 individuals in Chinese Han population, FTO rs9939 609 per-A allele can increase the risk of obesity (OR = 1.42, 95% CI 1.39–3.74) [11]. In a genome-wide scan for T2DM susceptibility genes in 1924 British T2DM and 2938 British controls, the diabetes-risk alleles in *FTO* were



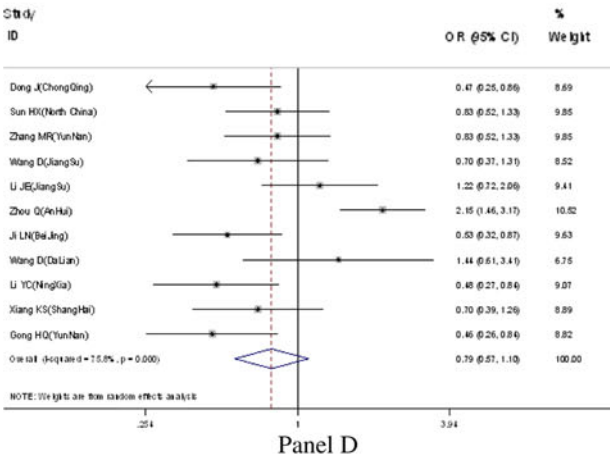
Panel A



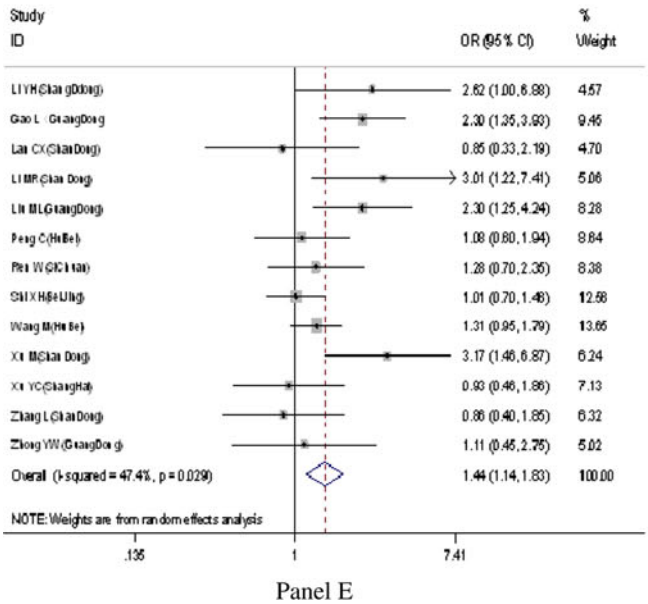
PanelB



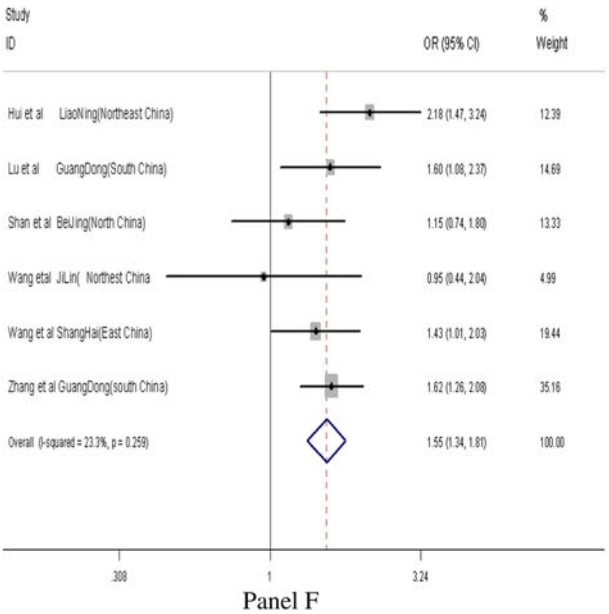
Panel C



Panel D



Panel E



Panel F

◀ **Fig. 2** **a** Meta-analysis results for relationship between T2DM and Adiponectin rs2241766 (SNP45). **b** Meta-analysis results for relationship between T2DM and Adiponectinrs1501299 (SNP276) G/T. **c** Meta-analysis results for relationship between T2DM and at risk T allele of ADRB3-rs4994 (Trp64Arg). **d** Meta-analysis results for relationship between T2DM and at risk A allele of CAPN 10-rs3792267 (SNP43). **e** Meta-analysis results for relationship between T2DM and at risk G allele of PPARGC1a-rs8192678 (Gly482Ser). **f** Meta-analysis results for relationship between T2DM and at risk PPARGC1a-rs8192678 (Gly482Ser)

associated with increased BMI [9]. However, in a meta-analysis of 96,551 East and South Asians, *FTO* was associated with T2DM independently of BMI; this discrepancy may be because of the different adiposity phenotypes between Asians and Europeans, and the smaller effect of *FTO* in Asians than in Europeans [12]. Similarly, the different adiposity phenotype and ethnic difference Trp64Arg

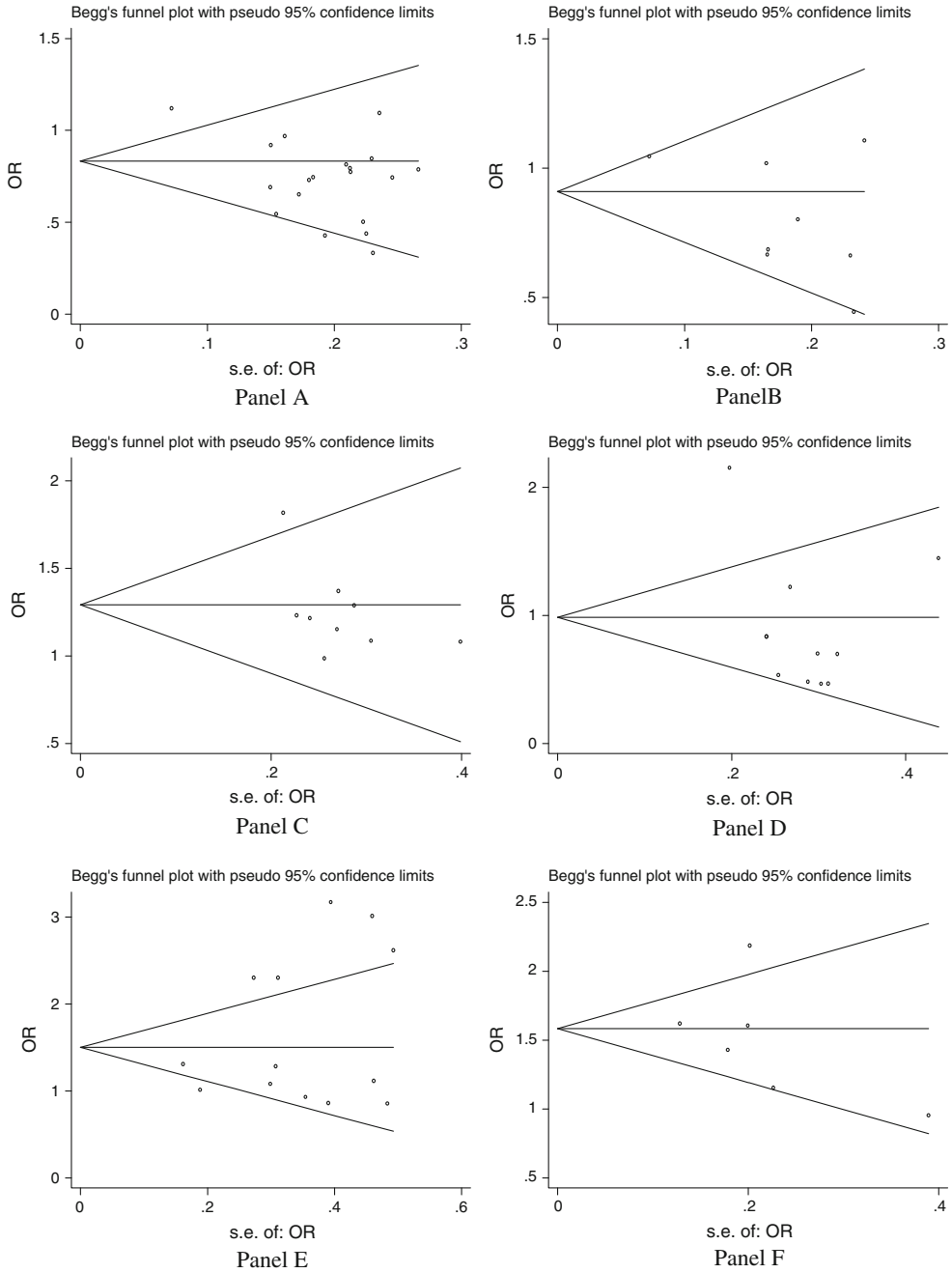


Fig. 3 **a** Begg's funnel plot of the publication bias of Adiponectin rs2241766 (SNP45) (corrected $z = 0.28$ and corrected $P = 0.78$). **b** Begg's funnel plot of publication bias of Adiponectinrs rs1501299 (SNP276) (corrected $z = 0.62$ and corrected $P = 0.536$). **c** Begg's funnel plot of the publication bias of ADRB3-rs4994 (Trp64Arg) (corrected $z = 0.94$ and corrected $P = 0.348$). **d** Begg's funnel plot of publication bias of CAPN 10-rs3792267 (SNP43) (corrected $z = 0.23$ and corrected $P = 0.815$). **e** Begg's funnel plot of the publication bias of ENPP1-rs1044498 (K121Q) (corrected $z = 0.79$ and corrected $P = 0.428$). **f** Begg's funnel plot of the publication bias of PPARGC1a-rs8192678 (Gly482Ser) (corrected $z = 0.75$ and corrected $P = 0.452$)

genotype distribution may play a role in the discrepancy between East Asians and Europeans inTrp64Arg. However, the data on BMI were not available in these included papers in our meta-analysis, so the association between BMI, Trp64Arg, and T2DM were not sufficiently studied. It needs further investigation in the following research.

The *ENPP1* gene is located at chromosome 6q22–q23 and is associated with insulin resistance by inhibiting the insulin receptor signaling pathway [13]. Studies in transfected cells have shown that the C allele is a stronger inhibitor of insulin-stimulated autophosphorylation than is the more common T allele [14]. In a case–control study of 1040 subjects, early phase insulin secretion was reduced in subjects with the rs1044498 C allele compared with that in subjects without the C allele [15]. In a meta-analysis of a European population, the rs1044498 C allele increased the risk of T2DM under a recessive model; the risk was further increased for CC homozygotes (OR = 1.38; 95% CI, 1.10–1.74; $P = 0.005$) [16]. In a study of South Asians and Caucasians, this SNP was shown to confer genetic susceptibility to T2DM in both populations [17]. Consistently, in our meta-analysis the C allele of *ENPP1*-rs1044498 increased the risk of T2DM (OR = 1.41; $P = 0.003$).

PPARGC1A is located at chromosome 4p15.1 and interacts with PPAR gamma in insulin signaling, mitochondrial regulation, and adaptive thermogenesis [18]. *PPARGC1A* mRNA expression was reduced by 90% in human T2DM islets, accompanied by a 41% reduction in insulin secretion ($P \leq 0.01$) [19]. In a meta-analysis of Gly482Ser (rs8192678) in *PPARGC1A* of T2DM in European populations, the pooled OR was 1.11 (95% CI, 1.04–1.20, $P = 0.004$) [20]. Similarly, in a North Indian population, the rs8192673 GA and AA genotypes were associated with a higher risk of T2DM [21]. Consistently, in our study, the pooled OR was 1.54 (95% CI, 1.34–1.81; $P < 0.001$), suggesting that the A allele increases the risk of T2DM.

Adiponectin is secreted from adipose tissue and plays an insulin-sensitizing and anti-atherogenic role. It is involved in the pathogenesis of diabetes [22]. In the Japanese population, *ADIPOQ*-rs2241766 and -rs1501299 have been associated with T2DM ($P = 0.003$ and $P = 0.002$, respectively) [23]. In a case–control study of 1105 T2DM patients and 1107 normal control subjects in Chinese Han population, the variant genotypes rs7649121 AT and rs7649121AT/TT, compared with the AA genotype, can significantly reduce the risk of T2DM [Adjusted OR (95%

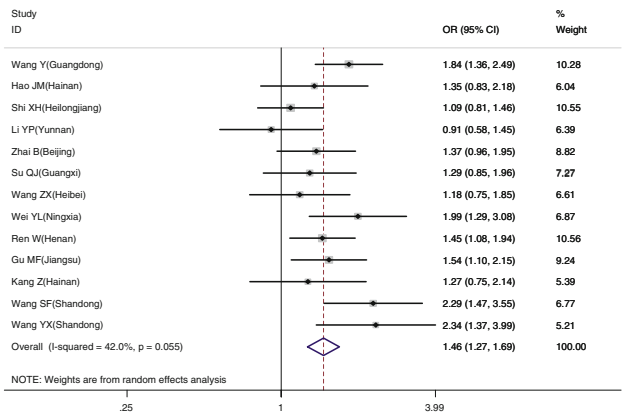
Fig. 4 **a** Meta-analysis of the 1999 WHO diagnostic criteria subgroup results for relationship between T2DM and at risk G allele of Adiponectinrs 2241766 (SNP45). **b** Begg's funnel plot of the publication bias of Adiponectin rs2241766 (SNP45) in the 1999 WHO diagnostic criteria subgroup analysis (corrected $z = 0.48$ and corrected $P = 0.63$). **c** Meta-analysis of the 1999 WHO diagnostic criteria subgroup results for relationship between T2DM and at risk G allele of Adiponectinrs rs1501299 (SNP276). **d** Begg's funnel plot of the publication bias of Adiponectinrs rs1501299 (SNP276) (corrected $z = 0.38$ and corrected $P = 0.71$). **e** Meta-analysis of the 1999 WHO diagnostic criteria subgroup results for relationship between T2DM and CAPN 10-rs3792267 (SNP43). **f** Begg's funnel plot of the publication bias of CAPN 10-rs3792267 (SNP43) (corrected $z = 0.12$ and corrected $P = 0.23$)

Table 4 Meta-analysis results of the subgroup analysis in the north and south regions of China of t between rs2241766, rs1501299 of ADPOQ, rs3792267 of CAPN10 and T2DM

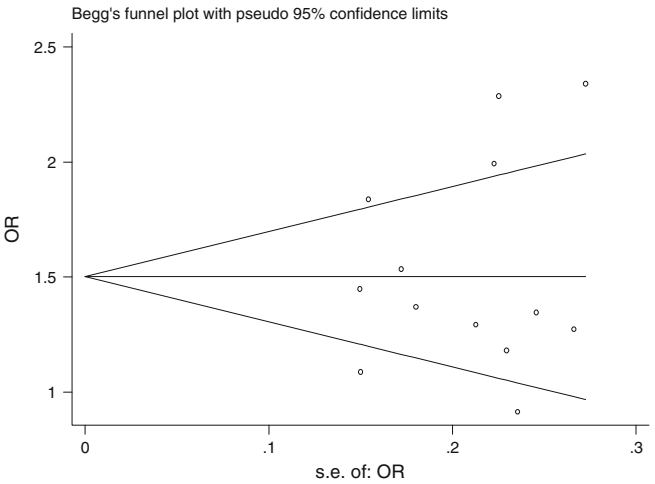
SNPs	Gene	Region	Meta-analysis model	Pooled OR (95%CI)	*P* for overall effect	Heterogeneity		Publication bias	
						I^2 (%)	*P*	*z*	*P*
rs2241766	ADIPOQ	North regions of China	Random	1.28 (0.93–1.76)	0	79.2	0	0.3	0.76
		South regions of China	Random	0.76 (0.62–0.93)	0.007	75.5	0	0.07	0.95
rs1501299	ADIPOQ	North regions of China	Fixed	0.66 (0.53–0.82)	0	50.1	0.135	0	1
		South regions of China	Fixed	0.96 (0.86–1.08)	0.496	57.4	0.052	0.24	0.806
rs3792267	CAPN10	North regions of China	Random	0.79 (0.53–1.17)	0.235	59.9	0.041	0.94	0.348
		South regions of China	Random	0.78 (0.46–1.32)	0.351	83.4	0	1.5	0.133

Table 5 Meta-analysis results of the 1999 WHO diagnostic criteria subgroup of the relationship between rs2241766, rs1501299 of ADPOQ, rs3792267 of CAPN10and T2DM

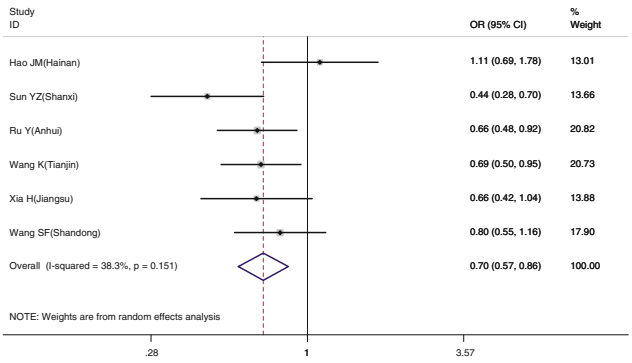
SNPs	Gene	Meta-analysis model	Pooled OR (95%CI)	*P* for overall effect	Heterogeneity		Publication bias	
					I^2 (%)	*P*	*z*	*P*
rs2241766	ADPOQ	Random	1.46 (1.26–1.69)	0.004	42	0.09	0.48	0.63
rs1501299	ADIPOQ	Random	0.70 (0.57–0.86)	0.027	38.3	0.15	0.38	0.71
rs3792267	CAPN10	Random	0.83 (0.53–1.31)	0.43	80.9	0.000	1.2	0.23



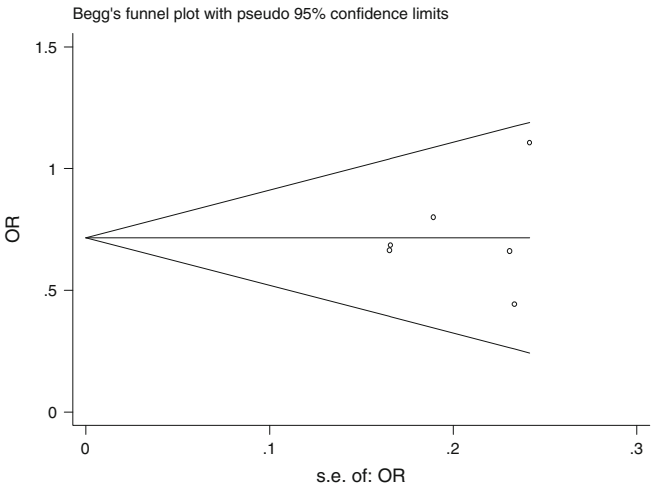
Panel A



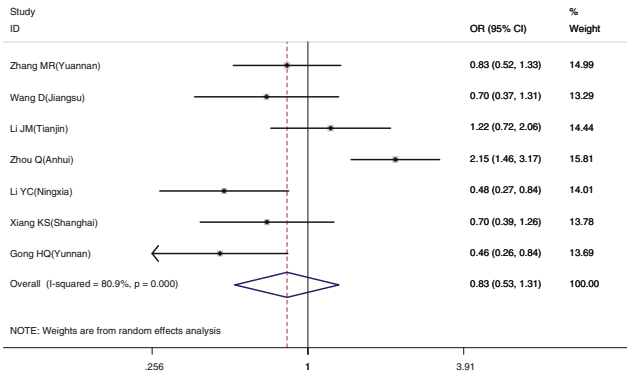
Panel B



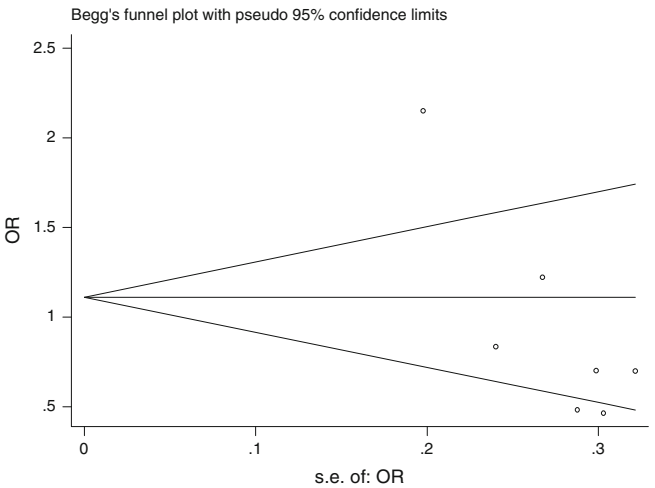
Panel C



Panel D



Panel E



Panel F

CI) = 0.79 (0.66–0.95), 0.80 (0.67–0.96)]. rs2241767 AG genotype increased the risk of T2DM in obesity group [Adjusted OR (95% CI) = 1.32 (1.03–1.69)] in stratified analysis [24]. In the Finnish Diabetes Prevention Study, the T allele of rs2241766 was associated with an increased adjusted hazard ratio of developing T2DM, and rs1501299

was significantly associated with body weight ($P < 0.05$) [22]. Our meta-analysis of both *ADIPOQ*-rs2241766 and -rs1501299 was hampered by high heterogeneity. This may have been caused by regional variations and different diagnostic criteria [1997 American Diabetes Association (ADA), 1985 WHO, or 1999 WHO]. For both SNPs, geographic subgrouping into those from North and South China had little or no effect, but we were able to reduce the heterogeneity by restricting the analysis to those diagnosed using the 1999 WHO criteria only. Some T2DM subjects based on the 1999 WHO criteria would have been classified as NGT according to the 1985 WHO criteria. For the 1999 WHO diagnostic subgroup, the pooled ORs were 1.46 (95% CI, 1.26–1.69, $P = 0.004$) and 0.70 (95% CI, 0.57–0.86, $P = 0.001$) for *ADIPOQ*-rs2241766 and -rs1501299, respectively, which suggests that the G allele of rs2241766 increases the risk of T2DM by 46% per allele and that the T allele of rs1501299 also increases the risk of T2DM in the Chinese population.

CAPN10 is located on chromosome 2q37 and is associated with impaired insulin secretion. *CAPN10* was the first gene to be identified by positioning cloning to influence the risk of T2DM [25]. In our study, there was extreme heterogeneity ($I^2 > 75\%$), which unfortunately was not reduced by either geographic or diagnostic criteria subgrouping. We cannot estimate the effect of this gene on T2DM in the Chinese Han population.

In conclusion, we have identified one SNP in each of three genes (*ADRB3*, *ENPP1*, and *PPARGC1A*) that increases the risk of T2DM in the Chinese Han population. A further two SNPs in *ADIPOQ* increased T2DM susceptibility but only under stringent diagnostic conditions. The role of *CAPN10* could not be determined because of high heterogeneity. The role of all of these genes in T2DM is worthy of further study.

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Conflict of interest The authors declare that they have no conflict of interests.

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