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Original Article

Opioid receptor mu 1 (OPRM1) A118G polymorphism (rs1799971) and postoperative nausea and vomiting

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Abstract: Background: OPRM1-A118G polymorphism (A > G, rs1799971) is associated with interindividual variability in both response to postoperative pain and opioid treatment. The aim of this meta-analysis is to identify the predictive strength in the current literature of OPRM1-A118G polymorphism to postoperative anesthetic reactions, including nausea, vomiting, pruritus and dizziness. Methods: PubMed, EMBASE, Cochrane Library, Web of Knowledge, Google Scholar and CNKI database were searched to find gene-association researches exploring the impacts of OPRM1-A118G polymorphism on postoperative side effects (time: up to July 2016). Odd ratios (ORs) with 95% confidence intervals (95% CIs) were estimated in allele model, homozygote model, heterozygote model, dominant model and recessive model. Sensitivity analysis and potential bias were also assessed. Results: 137 articles were retrieved from databases. 17 eligible studies, including 4690 patients were considered in the meta-analysis. The ORs with 95% CIs of postoperative nausea, vomiting, nausea and vomiting (PONV), pruritus and dizziness in the five genetic models mentioned above were determined. Postoperative vomiting was significantly associated with OPRM1-A118G polymorphism in homozygote (OR: 0.422; 95% CI: 0.254, 0.701; P = 0.001), dominant (OR: 0.765; 95% CI: 0.592, 0.987; P = 0.040) and recessive (OR: 0.439; 95% CI: 0.268, 0.717; P = 0.001) models. The 118G allele was associated with a reduced risk of vomiting. No other associations were detected. There was no evidence of publication bias. Conclusions: OPRM1-A118G polymorphism (A > G) is associated with a reduced risk of postoperative vomiting, but not nausea, pruritus and dizziness. The results should be interpreted with caution due to limited sample and possible heterogeneity between the included studies. Well-designed and large-scale studies are necessary to confirm our results.

Keywords: Opioid receptor mu 1, A118G, postoperative, nausea and vomiting, rs1799971

Introduction

Despite identifying risk factors and improving treatments for prevention, postoperative nausea and vomiting (PONV) remains a common occurrence after general anesthesia with estimated rates of PONV as high as 80% in certain high-risk settings [1, 2]. Aside from the distress associated with nausea and vomiting, occurrence of PONV can lend significant morbidity [3, 4]. Although PONV is often regarded as a necessary circumstance of surgery, efforts have been forged to eliminate its occurrence especially in the highest-risk populations [5, 6]. Multimodal approaches to the prevention of PONV have been borne of this collective enterprise, but a great deal of work remains.

The μ-opioid receptor (OPRM1) A118G single nucleotide polymorphism has been a major focus of research for the pharmacogenetics of opioid response [7]. Emerging knowledge regarding the molecular mechanisms regulating pain in animal models has increased the hopes

Table 1. Inclusion criteria for study selection in this meta-analysis

Number	Inclusion criteria
1	Original observational studies published in full text and those for which we had full access to all original data and protocols
2	The studies evaluated the associations between OPRM1 A118G polymorphism and postoperative side effects.
3	The studies included detailed genotyping data (total number of cases and controls, number of cases and controls with A/A, A/G, and G/G genotypes).
4	Studies focusing on human being.
5	predefined outcomes: incidence of postoperative nausea, vomiting, nausea and vomiting (PONV), pruritus, dizziness, et al.
6	No minimal sample size or dosing regimen was required for inclusion.
Number	Exclusion criteria
1	The report focused exclusively on other topics, such as addiction or sensitivity.
2	No human data were included.
3	The human 118A > G variant was not included, or no data were reported for this variant.
4	The genotype distribution of the control population was not in accordance with the Hardy-Weinberg equilibrium (HWE).
5	Reviews and duplicated publications.

of identifying personalized pain therapies [8]. Many studies also investigated the association between OPRM1-A118G polymorphism and the risks of postoperative reactions to anesthesia, including nausea, vomiting, pruritus and dizziness, but no consensus has been achieved. For example, Tan et al. found that 118G allele was associated with a reduced risk of nausea in spite of higher morphine usage [9]. The AA group had the highest nausea score of 0.033 (SD = 0.006) while the GG group had the lowest at 0.009 (SD = 0.004) [9]. In Sia et al.'s study, however, there was no statistically significant association of OPRM1 118A > G with time-averaged nausea scores or the incidence of vomiting [10]. To further elucidate this relationship, we accumulated data from different case control studies to perform this meta-analysis

Methods

We conducted this meta-analysis of observational prospective studies in accordance to the recommendations of the Meta-analysis of Observational Studies in Epidemiology (MOOSE) group and the reporting guideline of the PRISMA statement.

Publication search and selection criteria

Two authors independently searched the database of Embase, PubMed, Cochrane Library, Chinese National Knowledge Infrastructure (CNKI), and Web of Knowledge (time: ~ March 1st, 2017) to enroll case control studies studying the correlation between the polymorphism of OPRM1-A118G (rs1799971) and postoperative adverse reactions to anesthesia. Search terms include "postoperative" and "rs1799971 or A118G or OPRM1". We also reviewed related references to find other potentially eligible studies. The inclusion and exclusion criteria are listed in **Table 1**. Detailed searching strategies were in **Table 2**. Reference lists attached in retrieved articles were also collected. Related meeting abstracts were also searched to overcome publication bias. No language restrictions were imposed.

Data extraction

According to the inclusion criteria set in **Table 1**, two independent authors reviewed and extracted the needed data and information from the included articles. We gathered the following data: author name, publication year, country, ethnicity (Asian, Caucasian or others), language, surgery name, genotyping methods, sample size with three or two genotype groups, total number of cases with and without adverse reactions in A/A, A/G and G/G genotype groups, and *P* value for Hardy-Weinberg equilibrium (HWE). Disagreements between evaluators were resolved by consensus or consultation with a third investigator.

Methodological quality assessment

According to the methodological quality assessment scale (see **Table 3**), which was adjusted from a previous publication [11], two authors independently estimated the qualities of the included studies. Disagreement would be solved by discussion. In this methodological quality assessment scale, five items, including quality control of genotyping methods, source

Table 2. Searching strategies and results for different databases

Database	Database URL	Search strategy	Results
Pubmed	https://www.ncbi.nlm.nih.gov/pubmed/	Postoperative [Title/Abstract] AND ((rs1799971 [Title] OR A118G [Title]) OR OPRM1 [Title])	30
Embase	https://www.embase.com/	rs1799971:ti OR A118G:ti OR OPRM1:ti AND postoperative:ab,ti	38
Cochrane Library	http://www.cochranelibrary.com/	A118G and postoperative:ti,ab,kw (Word variations have been searched)	4
Web of Science	http://apps.webofknowledge.com/	TOPIC: (A118G AND postoperative) Timespan: All years. Indexes: SCI-EXPANDED, SSCI, A&HCI, ESCI.	59
CNKI	http://www.cnki.net/	Search criteria: ((topic = A118G or topic = OPRM1) and (title = postoperative or title = anesthesia)) (exact match), album navigation: all; Database: literature cross-library retrieval method: cross-library retrieval database: literature	6

Searching results and information of relevant academic meeting abstracts

Year	City	Meeting name	Article title	Whether included
2014	Chengdu, Sichuan Province, P.R. China	The 14th Academic Annual Conference of Chinese Medical Association Clinical Pharmacy Branch	Genetic-opioid association of the OPRM1 A118G Polymorphism in postoperative pain: systemic review and meta-analysis	No

Table 4. The statistical methods used in this meta-analysis and there explanation

Statistic means	Goals and Usages	Explanation
Labbe plot	To evaluate heterogeneity between the included studies	In Labbe figure, if the points basically present as a linear distribution, it can be taken as an evidence of homogeneity.
Cochran's Q test	To evaluate heterogeneity between the included studies	Cochran's Q test is an extension to the McNemar test for related samples that provides a method for testing for differences between three or more matched sets of frequencies or proportions. Heterogeneity was also considered significant if $P < 0.05$ using the Cochran's Q test.
I^2 index test	To evaluate heterogeneity between the included studies	The I^2 index measures the extent of true heterogeneity dividing the difference between the result of the Q test and its degrees of freedom (k-1) by the Q value itself, and multiplied by 100. I^2 values of 25%, 50% and 75% were used as evidence of low, moderate and high heterogeneity, respectively.
Sensitivity analysis	To examine the stability of the pooled results	A sensitivity analysis was performed using the one-at-a-time method, which involved omitting one study at a time and repeating the meta-analysis. If the omission of one study significantly changed the result, it implied that the result was sensitive to the studies included.
Contour-enhanced funnel plot	Publication bias test	Visual inspection of the Contour-enhanced funnel plots was used to assess potential publication bias. Asymmetry in the plots, which may be due to studies missing on the left-hand side of the plot that represents low statistical significance, suggested publication bias. If studies were missing in the high statistical significance areas (on the right-hand side of the plot), the funnel asymmetry was not considered to be due to publication bias

Table 3. Scale for methodological quality assessment

Criteria	Score
Representativeness of cases	
RA diagnosed according to acknowledged criteria	2
Mentioned the diagnosed criteria but not specifically described	1
Not Mentioned	0
Source of controls	
Population or community based	3
Hospital-based RA-free controls	2
Healthy volunteers without total description	1
RA-free controls with related diseases	0.5
Not described	0
Sample size	
> 300	2
200-300	1
< 200	0
Quality control of genotyping methods	
Repetition of partial/total tested samples with a different method	2
Repetition of partial/total tested samples with the same method	1
Not described	0
Hardy-Weinberg equilibrium (HWE)	
Hardy-Weinberg equilibrium in control subjects	1
Hardy-Weinberg disequilibrium in control subjects	0

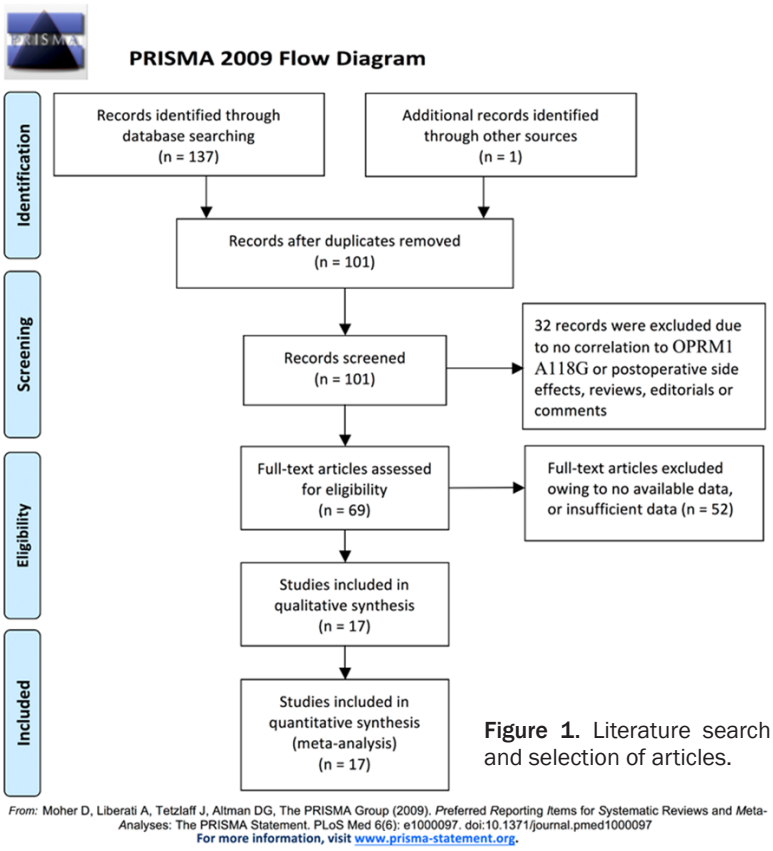


Figure 1. Literature search and selection of articles.

of controls, sample size, cases representativeness and HWE were carefully checked. The quality scores range between 0~10 with best quality of 10 and worst quality of 0.

Statistical analysis

This meta-analysis was in accordance with the PRISMA checklists and guidelines [12]. HWE in each study was first assessed, followed by the calculation of ORs with 95% CIs reflecting the correlation strength between OPRM1-A118G polymorphism and the incidence of adverse reactions to anesthesia. The pooled ORs were estimated and used for comparisons respectively in allele model (G vs. A), homozygote model (GG vs. AA), heterozygote model (AG vs. AA), dominant model (AG + GG vs. AA), and recessive model (GG vs. AA + AG). As Caucasian-population-based studies were not sufficient, ethnicity-specific subgroup (Caucasian and Asian) meta-analysis was not performed at this time. The Labbe plot, I^2 test and Cochran's Q-test (**Table 4**) were all conducted to estimate the heterogeneity among the studies [13]. If no evidence of statistical heterogeneity was detected, we chose to use a fixed-effects model [14]. Otherwise, Laird's and DerSimonian's random-effects model would be adopted [14]. To access the stability of the pooled values, we also performed sensitivity analyses (explanation in **Table 4**) [11]. Using contour-enhanced funnel plots (**Table 4**), potential publication biases were estimated.

Table 5. Characteristics of studies included in the meta-analysis

Author	Year	Country	Ethnicity	Language	Surgery	Side effects	AA			AG			GG			P for HWE	Quality
							Total	Event	Normal	Total	Event	Normal	Total	Event	Normal		
Chou et al.	2006a	China Taiwan	Asian	English	Total knee arthroplasty	Nausea	74	6	68	33	0	33	13	1	12	0.0164	7
						Vomiting	74	17	57	33	4	29	13	1	12	0.0133	
						Pruritus	74	3	71	33	0	33	13	0	13	0.0064	
Chou et al.	2006b	China Taiwan	Asian	English	Hysterectomy	Vomiting	43	7	36	19	4	15	18	1	17	0.0000	6
Coulbault et al.	2006	France	Caucasian	English	Colorectal surgery	PONV	57	17	40	15	6	9	2	0	2	0.1402	8
Sia et al.	2008	Singapore	Asian	English	Cesarean section	Nausea	272	6	266	234	3	231	82	1	81	0.0085	7
						Pruritus	272	115	157	234	3	231	82	1	81	0.801	
Chen et al.	2008	China	Asian	Chinese	Myomectomy or hysterectomy	Nausea	82	19	63	38	6	32	4	1	3	0.6586	8
						Vomiting	82	2	80	38	4	34	4	0	4	0.8687	
Tan et al.	2009	Singapore	Asian	English	Cesarean section	Vomiting	389	54	335	435	51	384	170	7	389	0.0049	7
Zhang et al.	2009	China	Asian	Chinese	Myomectomy or hysterectomy	PONV	94	31	63	76	23	53	24	3	21	0.0874	8
						Pruritus	94	1	93	76	0	76	24	0	24	0.1777	
Zhang et al.	2010	China	Asian	English	Gynecologic surgery	PONV	86	28	58	67	17	50	21	3	18	0.1876	8
						Pruritus	86	1	85	67	0	67	21	0	21	0.1771	
Zhang et al.	2011	China	Asian	English	Gynecologic surgery	Nausea	80	28	52	63	16	47	22	3	19	0.1402	7
						Vomiting	80	17	63	63	8	55	22	2	20	0.1686	
Zwisler et al.	2012	Denmark	Caucasian	English	Primarily thyroidectomy	PONV	219	44	175	Total: 47		Event: 10		Normal: 37		NA	8
						Pruritus	219	22	197	Total: 47		Event: 5		Normal: 42		NA	
						Dizziness	219	153	66	Total: 47		Event: 38		Normal: 9		NA	
Zhang et al.	2013	China	Asian	Chinese	Radical gastrectomy	Nausea	54	16	38	53	22	31	21	9	12	0.1869	6
						Vomiting	54	8	46	53	13	40	21	6	15	0.2071	
						Dizziness	54	14	40	53	22	31	21	7	14	0.0718	
Sia et al.	2013	Singapore	Asian	English	Hysterectomy	Nausea	354	26	328	474	41	433	145	13	132	0.5733	9
						Pruritus	354	8	346	474	14	460	145	4	141	0.5536	
Liu et al.	2014	China	Asian	English	Gynecologic surgery	Nausea	78	41	37	Total: 100		Event: 36		Normal: 64		NA	6
						Vomiting	78	17	61	Total: 100		Event: 17		Normal: 83		NA	
						Pruritus	78	5	73	Total: 100		Event: 3		Normal: 97		NA	
Zhu et al.	2014	China	Asian	Chinese	Gynecologic surgery	PONV	127	4	123	62	2	60	11	3	8	0.8417	7
Chen et al.	2015	China	Asian	Chinese	Hysterectomy	Nausea	112	16	96	136	17	119	24	1	23	0.1091	7
						Vomiting	112	14	98	136	16	120	24	0	24	0.1435	
Zhang et al.	2015	China	Asian	Chinese	-	Nausea	57	5	52	51	7	44	15	1	14	0.3367	8
						Vomiting	57	3	54	51	4	47	15	1	14	0.8504	
						Dizziness	57	4	53	51	2	49	15	0	15	0.4914	
Sugino	2016	Japan	Asian	English	Abdominal or orthopedic surgery	PONV	20	7	13	20	10	10	19	6	13	0.0077	8

Table 6. The results of meta-analysis for different postoperative side effects in various genotype models

Genetic model		Heterogeneity test						Test of Association					Publication bias
Name	Side effects	Q value	d.f.	I-squared	Tau-squared	*P* Value	Heterogeneity	Effect model	Pooled OR	95% CI	Z value	*P* value	Statistical significance	
Allele model (G vs. A)	Nausea	9.96	7	29.7%	NA	0.191	No	Fixed	0.922	[0.753, 1.130]	0.78	0.436	No	No
	Vomiting	14.59	7	52.0%	0.1248	0.042	Yes	Random	0.787	[0.549, 1.128]	1.30	0.192	No	
	PONV	10.18	4	60.7%	0.1903	0.038	Yes	Random	0.929	[0.562, 1.536]	0.29	0.774	No	
	Pruritus	58.66	4	93.2%	6.1569	0.000	Yes	Random	0.258	[0.024, 2.830]	1.11	0.268	No	
	Dizziness	2.24	1	55.3%	NA	0.135	No	Fixed	1.145	[0.700, 1.871]	0.54	0.589	No	
Homozygote model (GG vs. AA)	Nausea	7.07	7	1.0%	NA	0.422	No	Fixed	0.865	[0.553, 1.353]	0.64	0.524	No	No
	Vomiting	12.26	7	42.9%	NA	0.092	No	Fixed	0.422	[0.254, 0.701]	3.33	0.001	Yes	
	PONV	14.36	4	72.1%	1.5879	0.006	Yes	Random	0.854	[0.225, 3.244]	0.23	0.817	No	
	Pruritus	20.79	4	80.8%	5.5890	0.000	Yes	Random	0.445	[0.042, 4.749]	0.67	0.502	No	
	Dizziness	0.67	1	0.0%	NA	0.412	No	Fixed	1.152	[0.426, 3.112]	0.28	0.781	No	
Heterozygote model (AG vs. AA)	Nausea	7.44	7	5.9%	NA	0.384	No	Fixed	0.956	[0.715, 1.276]	0.31	0.758	No	No
	Vomiting	9.03	7	22.5%	NA	0.251	No	Fixed	0.912	[0.686, 1.213]	0.63	0.528	No	
	PONV	2.50	4	0.0%	NA	0.644	No	Fixed	0.954	[0.636, 1.431]	0.23	0.819	No	
	Pruritus	39.27	4	89.8%	6.6836	0.000	Yes	Random	0.248	[0.020, 3.040]	1.09	0.276	No	
	Dizziness	1.82	1	44.9%	NA	0.178	No	Fixed	1.568	[0.762, 3.226]	1.22	0.222	No	
Dominant model (AG + GG vs. AA)	Nausea	12.63	8	36.6%	NA	0.125	No	Fixed	0.833	[0.650, 1.067]	1.45	0.148	No	No
	Vomiting	11.53	8	30.6%	NA	0.173	No	Fixed	0.765	[0.592, 0.987]	2.06	0.040	Yes	
	PONV	4.59	5	0.0%	NA	0.468	No	Fixed	0.888	[0.632, 1.248]	0.68	0.494	No	
	Pruritus	55.12	6	89.1%	4.1175	0.000	Yes	Random	0.308	[0.057, 1.662]	1.37	0.171	No	
		2.61	2	23.3%	NA	0.271	No	Fixed	1.609	[0.966, 2.681]	1.83	0.068	No	
Recessive model (GG vs. AA + AG)	Nausea	5.09	7	0.0%	NA	0.648	No	Fixed	0.857	[0.562, 1.306]	0.72	0.473	No	No
	Vomiting	9.31	7	24.8%	NA	0.231	No	Fixed	0.439	[0.268, 0.717]	3.29	0.001	Yes	
	PONV	15.37	4	74.0%	1.5419	0.004	Yes	Random	0.832	[0.226, 3.062]	0.28	0.782	No	
	Pruritus	14.09	4	71.6%	3.1823	0.007	Yes	Random	0.653	[0.096, 4.446]	0.44	0.663	No	
	Dizziness	0.18	1	0.0%	NA	0.673	No	Fixed	0.905	[0.357, 2.293]	0.21	0.833	No	

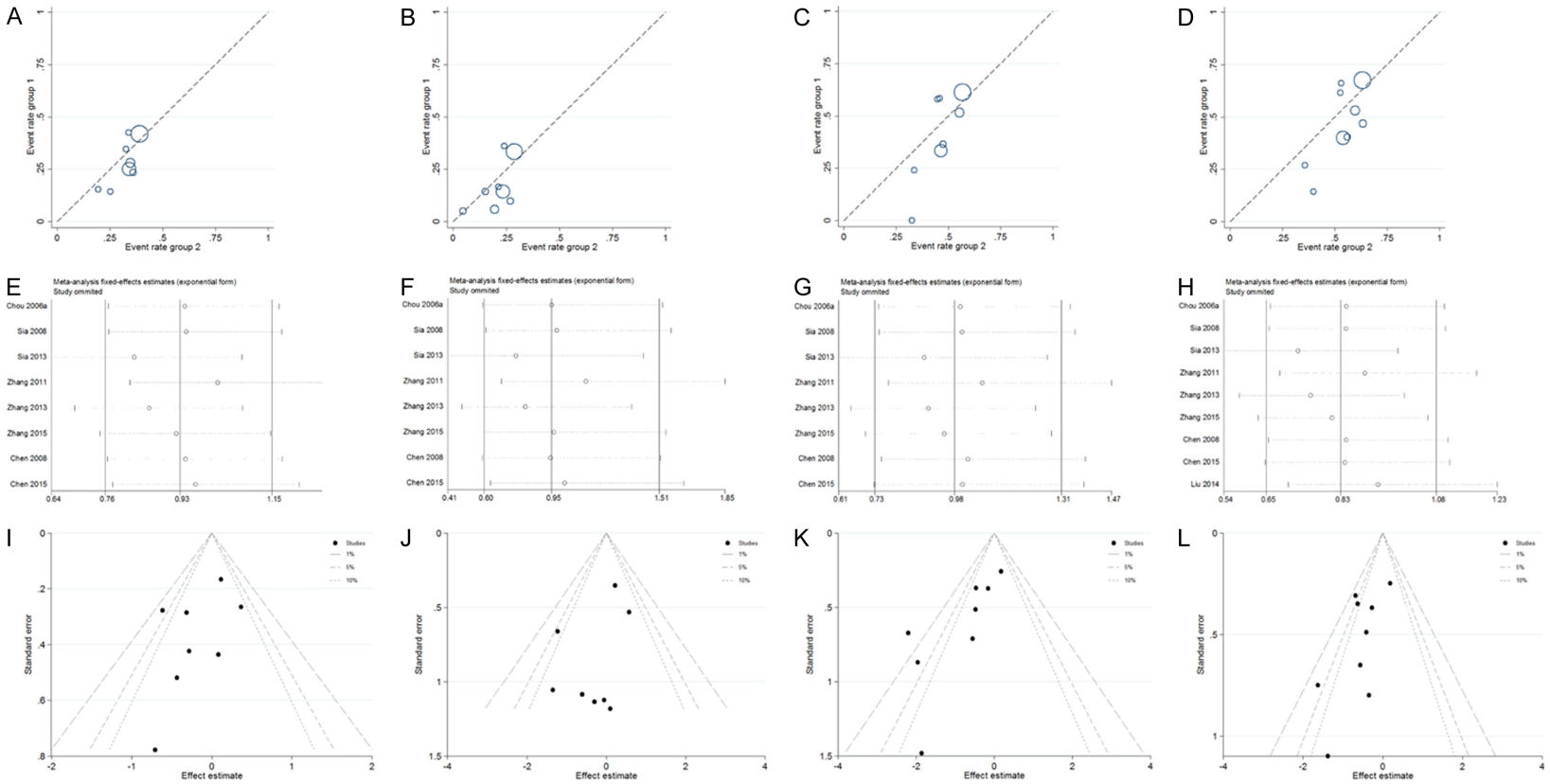
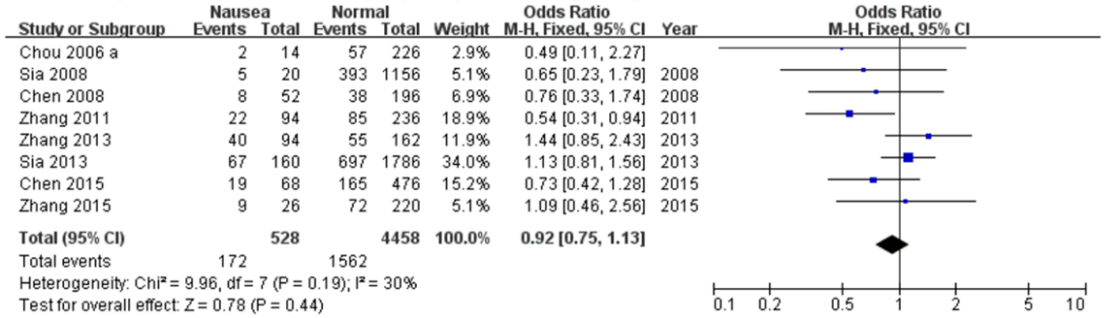


Figure 2. Labbe plots, sensitivity analysis plots and contour-enhanced funnel plots of the included studies focusing on the association between OPRM1-A118G Polymorphism and postoperative nausea risks. Labbe plots in allele model (A), homozygote model (B), heterozygote model (C) and dominant model (D). Sensitivity analysis for nausea in allele model (E), homozygote model (F), heterozygote model (G), and dominant model (H). Contour-enhanced funnel plots for nausea in allele model (I), homozygote model (J), heterozygote model (K), and dominant model (L).

A **Forest plot for OPRM1 A118G polymorphism and postoperative nausea risk in allele model**

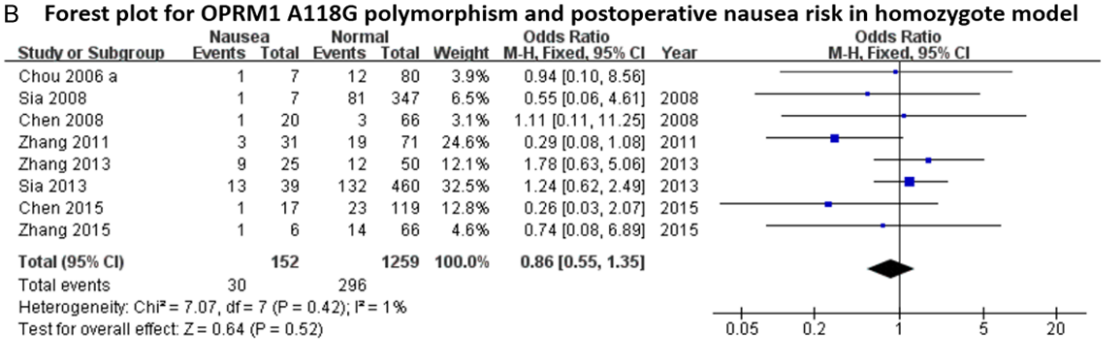


Study or Subgroup	Nausea Events	Nausea Total	Normal Events	Normal Total	Weight	Odds Ratio M-H, Fixed, 95% CI	Year
Chou 2006 a	2	14	57	226	2.9%	0.49 [0.11, 2.27]	
Sia 2008	5	20	393	1156	5.1%	0.65 [0.23, 1.79]	2008
Chen 2008	8	52	38	196	6.9%	0.76 [0.33, 1.74]	2008
Zhang 2011	22	94	85	236	18.9%	0.54 [0.31, 0.94]	2011
Zhang 2013	40	94	55	162	11.9%	1.44 [0.85, 2.43]	2013
Sia 2013	67	160	697	1786	34.0%	1.13 [0.81, 1.56]	2013
Chen 2015	19	68	165	476	15.2%	0.73 [0.42, 1.28]	2015
Zhang 2015	9	26	72	220	5.1%	1.09 [0.46, 2.56]	2015
Total (95% CI)		**528**		**4458**	**100.0%**	**0.92 [0.75, 1.13]**	
Total events	172		1562				

Heterogeneity: Chi² = 9.96, df = 7 (P = 0.19); I² = 30%
Test for overall effect: Z = 0.78 (P = 0.44)

Odds Ratio M-H, Fixed, 95% CI
0.1 0.2 0.5 1 2 5 10

B **Forest plot for OPRM1 A118G polymorphism and postoperative nausea risk in homozygote model**

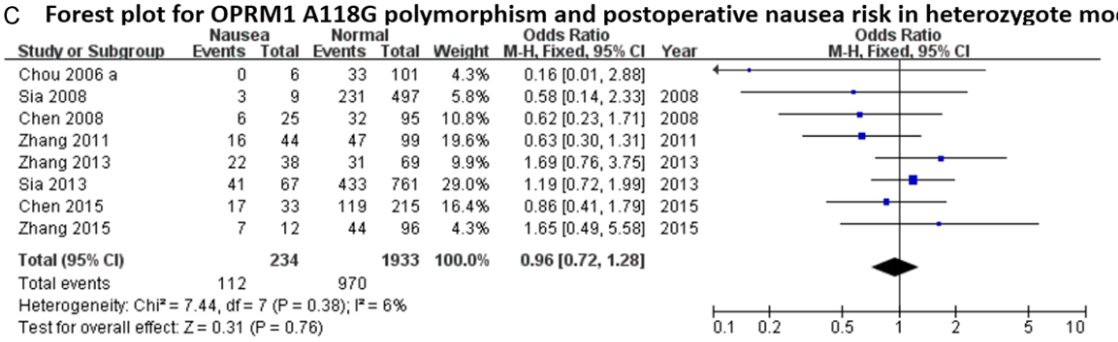


Study or Subgroup	Nausea Events	Nausea Total	Normal Events	Normal Total	Weight	Odds Ratio M-H, Fixed, 95% CI	Year
Chou 2006 a	1	7	12	80	3.9%	0.94 [0.10, 8.56]	
Sia 2008	1	7	81	347	6.5%	0.55 [0.06, 4.61]	2008
Chen 2008	1	20	3	66	3.1%	1.11 [0.11, 11.25]	2008
Zhang 2011	3	31	19	71	24.6%	0.29 [0.08, 1.08]	2011
Zhang 2013	9	25	12	50	12.1%	1.78 [0.63, 5.06]	2013
Sia 2013	13	39	132	460	32.5%	1.24 [0.62, 2.49]	2013
Chen 2015	1	17	23	119	12.8%	0.26 [0.03, 2.07]	2015
Zhang 2015	1	6	14	66	4.6%	0.74 [0.08, 6.89]	2015
Total (95% CI)		**152**		**1259**	**100.0%**	**0.86 [0.55, 1.35]**	
Total events	30		296				

Heterogeneity: Chi² = 7.07, df = 7 (P = 0.42); I² = 1%
Test for overall effect: Z = 0.64 (P = 0.52)

Odds Ratio M-H, Fixed, 95% CI
0.05 0.2 1 5 20

C **Forest plot for OPRM1 A118G polymorphism and postoperative nausea risk in heterozygote model**

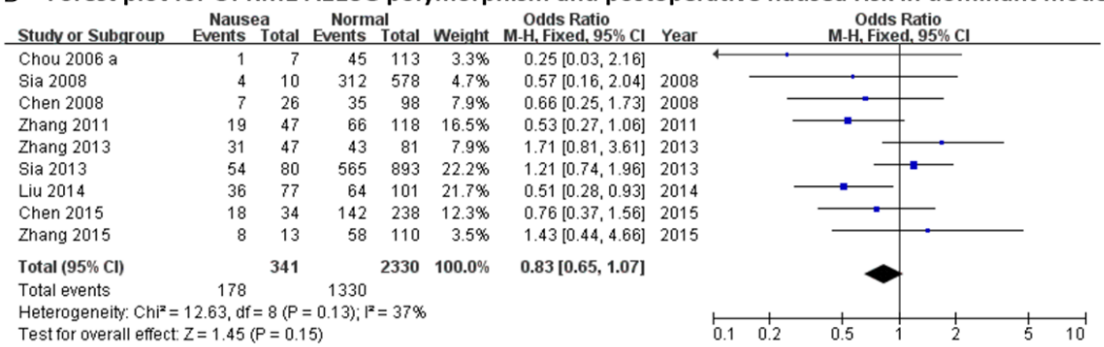


Study or Subgroup	Nausea Events	Nausea Total	Normal Events	Normal Total	Weight	Odds Ratio M-H, Fixed, 95% CI	Year
Chou 2006 a	0	6	33	101	4.3%	0.16 [0.01, 2.88]	
Sia 2008	3	9	231	497	5.8%	0.58 [0.14, 2.33]	2008
Chen 2008	6	25	32	95	10.8%	0.62 [0.23, 1.71]	2008
Zhang 2011	16	44	47	99	19.6%	0.63 [0.30, 1.31]	2011
Zhang 2013	22	38	31	69	9.9%	1.69 [0.76, 3.75]	2013
Sia 2013	41	67	433	761	29.0%	1.19 [0.72, 1.99]	2013
Chen 2015	17	33	119	215	16.4%	0.86 [0.41, 1.79]	2015
Zhang 2015	7	12	44	96	4.3%	1.65 [0.49, 5.58]	2015
Total (95% CI)		**234**		**1933**	**100.0%**	**0.96 [0.72, 1.28]**	
Total events	112		970				

Heterogeneity: Chi² = 7.44, df = 7 (P = 0.38); I² = 6%
Test for overall effect: Z = 0.31 (P = 0.76)

Odds Ratio M-H, Fixed, 95% CI
0.1 0.2 0.5 1 2 5 10

D **Forest plot for OPRM1 A118G polymorphism and postoperative nausea risk in dominant model**

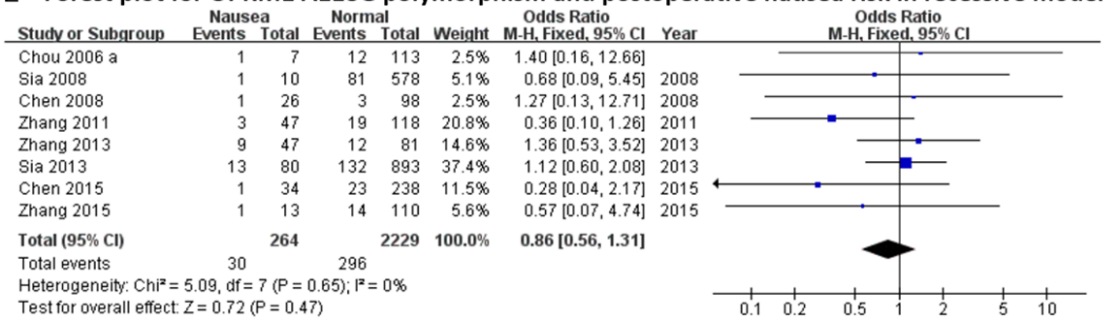


Study or Subgroup	Nausea Events	Nausea Total	Normal Events	Normal Total	Weight	Odds Ratio M-H, Fixed, 95% CI	Year
Chou 2006 a	1	7	45	113	3.3%	0.25 [0.03, 2.16]	
Sia 2008	4	10	312	578	4.7%	0.57 [0.16, 2.04]	2008
Chen 2008	7	26	35	98	7.9%	0.66 [0.25, 1.73]	2008
Zhang 2011	19	47	66	118	16.5%	0.53 [0.27, 1.06]	2011
Zhang 2013	31	47	43	81	7.9%	1.71 [0.81, 3.61]	2013
Sia 2013	54	80	565	893	22.2%	1.21 [0.74, 1.96]	2013
Liu 2014	36	77	64	101	21.7%	0.51 [0.28, 0.93]	2014
Chen 2015	18	34	142	238	12.3%	0.76 [0.37, 1.56]	2015
Zhang 2015	8	13	58	110	3.5%	1.43 [0.44, 4.66]	2015
Total (95% CI)		**341**		**2330**	**100.0%**	**0.83 [0.65, 1.07]**	
Total events	178		1330				

Heterogeneity: Chi² = 12.63, df = 8 (P = 0.13); I² = 37%
Test for overall effect: Z = 1.45 (P = 0.15)

Odds Ratio M-H, Fixed, 95% CI
0.1 0.2 0.5 1 2 5 10

E **Forest plot for OPRM1 A118G polymorphism and postoperative nausea risk in recessive model**



Study or Subgroup	Nausea Events	Nausea Total	Normal Events	Normal Total	Weight	Odds Ratio M-H, Fixed, 95% CI	Year
Chou 2006 a	1	7	12	113	2.5%	1.40 [0.16, 12.66]	
Sia 2008	1	10	81	578	5.1%	0.68 [0.09, 5.45]	2008
Chen 2008	1	26	3	98	2.5%	1.27 [0.13, 12.71]	2008
Zhang 2011	3	47	19	118	20.8%	0.36 [0.10, 1.26]	2011
Zhang 2013	9	47	12	81	14.6%	1.36 [0.53, 3.52]	2013
Sia 2013	13	80	132	893	37.4%	1.12 [0.60, 2.08]	2013
Chen 2015	1	34	23	238	11.5%	0.28 [0.04, 2.17]	2015
Zhang 2015	1	13	14	110	5.6%	0.57 [0.07, 4.74]	2015
Total (95% CI)		**264**		**2229**	**100.0%**	**0.86 [0.56, 1.31]**	
Total events	30		296				

Heterogeneity: Chi² = 5.09, df = 7 (P = 0.65); I² = 0%
Test for overall effect: Z = 0.72 (P = 0.47)

Odds Ratio M-H, Fixed, 95% CI
0.1 0.2 0.5 1 2 5 10

Figure 3. Forest plots (individual and pooled effects with 95% CI) regarding the association between OPRM1-A118G polymorphism and postoperative nausea in allele model (A), homozygote model (B), heterozygote model (C), dominant model (D) and recessive model (E).

$P < 0.05$ was deemed as statistical significance. The statistical analysis was done through Review Manager 5.3 (The Cochrane Collaboration, Oxford, UK) and STATA 12.0 (StataCorp LP, College Station, TX, USA) software.

Results

Search results and characteristics of the studies

A total of 138 studies were identified in search: 30 in Pubmed, 38 in Embase, 4 in Cochrane Library, 59 in Web of Science, 6 in CNKI, and 1 academic meeting reports (**Table 2**).

Figure 1 showed the literature search process. A total of 17 articles [9, 10, 15-29] involving 4690 patients were included in the final analysis, 2 studies were performed in on patients of Caucasian backgrounds in France and Denmark (340 cases in total), and 15 were performed on patients of Asian backgroundsin China, Singapore, and Japan (4350 cases in total). The surgeries include orthopedic, gynecologic, abdominal, and thyroid surgeries. In all of the included studies, genotype distributions of OPRM1-A118G polymorphism (A > G) in the controls were consistent with HWE. A variety of genotyping methods were applied including direct sequencing, PCR-RFLP, SNPstream, etc Genomic miRNA was isolated from blood samples in all included studies. Postoperative nausea and postoperative vomiting results were both reported in 9 studies. Six studies reported PONV as a whole. Seven reported postoperative pruritus and 3 reported dizziness. The characteristics and methodological quality assessment of the studies included in this meta-analysis are shown in **Table 5**.

Meta-analysis results

The main results regarding heterogeneity tests, effect models adopted accordingly, and the pooled OR with 95% CI and *P* value of this meta-analysis were shown in **Table 6**. The Labbe plots for nausea in allele model, homozygote model, heterozygote model and dominant model were shown in **Figure 2A-D**. Postoperative vomiting was significantly associated with OPRM1-A118G polymorphism in homozygote (OR: 0.422; 95% CI: 0.254, 0.701; P = 0.001; **Figure 4B**), dominant (OR: 0.765; 95% CI: 0.592, 0.987; P = 0.040; **Figure 4D**) and recessive (OR: 0.439; 95% CI: 0.268, 0.717; P = 0.001; **Figure 4E**) models, but not in the allele model (OR: 0.787; 95% CI: 0.549, 1.128; P = 0.192; **Figure 4A**) and the heterozygote model (OR: 0.912; 95% CI: 0.686, 1.213; P = 0.528; **Figure 4C**). The 118G allele was associated with a reduced risk of vomiting. For postoperative nausea, pruritus, dizziness and PONV as a whole based on the available data, the associations were not statistically significant in any of the five genetic models (see **Figures 3** and **5-7**; **Table 6**). Although ethnicity may have an effect on this association, since there were only two Caucasian-population-based studies, ethnicity-specific subgroup analysis was not performed.

Sensitivity analysis and publication bias

To assess if a single study could affect the final ORs, each individual study was removed one time and the data re-pooled. The analysis results demonstrated that the pooled ORs were not affected by deleting every single study. **Figure 2E-H** showed Sensitivity analysis results for postoperative nausea in the allele model, homozygote model, heterozygote model and dominant model. The contour-enhanced funnel plots were adopted to estimate potential publication biases, showing that the studies had missing areas for high statistical significance (the right-hand side of the plot), indicating no publication bias in this study (**Figure 2I-L** for nausea in the first four models).

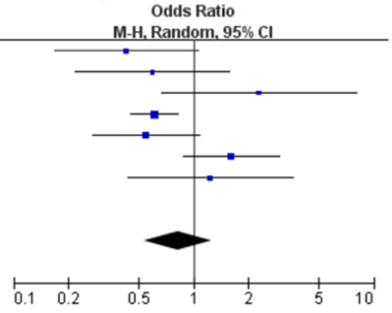
Discussion

The exon 1 A118G (rs1799971) is located at the coding region of OPRM1, causing an Asn40Asp amino acid substitution. OPRM1-A118G has attracted much attention recently because it is associated with many pathophysiologic process, including opioid response [30], tumorigeness, tumor progression [31-33] and evenauto-immune diseases [34]. The number of studies related to OPRM1-related polymor-

A **Forest plot for OPRM1 A118G polymorphism and postoperative vomiting risk in allele model**

Study or Subgroup	Vomiting Events	Vomiting Total	Normal Events	Normal Total	Weight	Odds Ratio M-H, Random, 95% CI	Year
Chou 2006a	6	44	53	196	12.2%	0.43 [0.17, 1.07]	
Chou 2006b	6	24	49	136	11.2%	0.59 [0.22, 1.59]	
Chen 2008	4	12	42	236	8.3%	2.31 [0.66, 8.03]	2008
Tan 2009	65	224	710	1764	24.0%	0.61 [0.45, 0.82]	2009
Zhang 2011	12	54	95	276	16.1%	0.54 [0.27, 1.08]	2011
Zhang 2013	25	54	70	202	17.7%	1.63 [0.88, 2.99]	2013
Zhang 2015	6	16	75	230	10.4%	1.24 [0.43, 3.54]	2015
Chen 2015	0	0	0	0		Not estimable	2015
Total (95% CI)		**428**		**3040**	**100.0%**	**0.82 [0.53, 1.26]**	
Total events	124		1094				

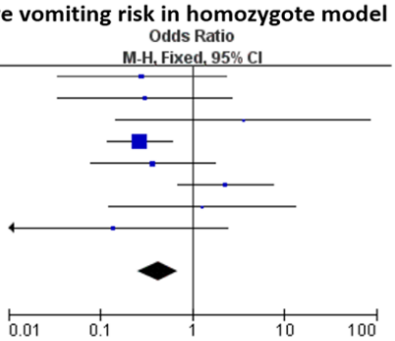
Heterogeneity: Tau² = 0.18; Chi² = 14.57, df = 6 (P = 0.02); I² = 59%
Test for overall effect: Z = 0.92 (P = 0.36)



B **Forest plot for OPRM1 A118G polymorphism and postoperative vomiting risk in homozygote model**

Study or Subgroup	Vomiting Events	Vomiting Total	Normal Events	Normal Total	Weight	Odds Ratio M-H, Fixed, 95% CI	Year
Chou 2006a	1	18	12	69	8.3%	0.28 [0.03, 2.31]	
Chou 2006b	1	8	17	53	6.9%	0.30 [0.03, 2.66]	
Chen 2008	0	2	4	84	0.5%	3.58 [0.15, 86.15]	2008
Tan 2009	7	61	163	498	55.7%	0.27 [0.12, 0.60]	2009
Zhang 2011	2	19	20	83	11.8%	0.37 [0.08, 1.74]	2011
Zhang 2013	6	14	15	61	5.7%	2.30 [0.69, 7.70]	2013
Zhang 2015	1	4	14	68	2.1%	1.29 [0.12, 13.32]	2015
Chen 2015	0	14	24	122	9.1%	0.14 [0.01, 2.41]	2015
Total (95% CI)		**140**		**1038**	**100.0%**	**0.42 [0.25, 0.70]**	
Total events	18		269				

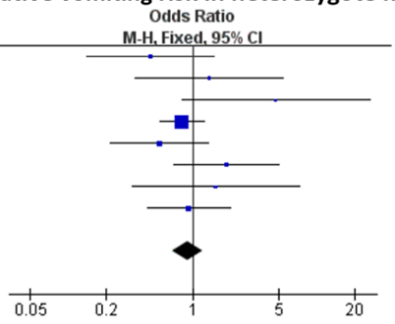
Heterogeneity: Chi² = 12.26, df = 7 (P = 0.09); I² = 43%
Test for overall effect: Z = 3.33 (P = 0.0009)



C **Forest plot for OPRM1 A118G polymorphism and postoperative vomiting risk in heterozygote model**

Study or Subgroup	Vomiting Events	Vomiting Total	Normal Events	Normal Total	Weight	Odds Ratio M-H, Fixed, 95% CI	Year
Chou 2006a	4	21	29	86	9.3%	0.46 [0.14, 1.50]	
Chou 2006b	4	11	15	51	3.4%	1.37 [0.35, 5.39]	
Chen 2008	4	6	34	114	1.1%	4.71 [0.82, 26.92]	2008
Tan 2009	51	105	384	719	50.7%	0.82 [0.55, 1.24]	2009
Zhang 2011	8	25	55	118	13.2%	0.54 [0.22, 1.35]	2011
Zhang 2013	13	21	40	86	6.0%	1.87 [0.70, 4.97]	2013
Zhang 2015	4	7	47	101	2.6%	1.53 [0.33, 7.20]	2015
Chen 2015	16	30	120	218	13.6%	0.93 [0.43, 2.01]	2015
Total (95% CI)		**226**		**1493**	**100.0%**	**0.91 [0.69, 1.21]**	
Total events	104		724				

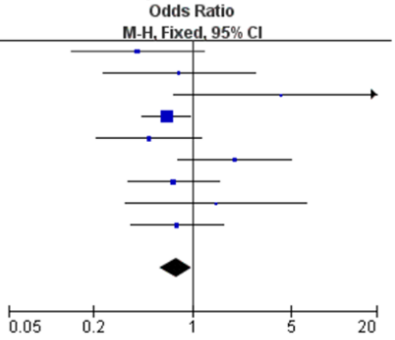
Heterogeneity: Chi² = 9.03, df = 7 (P = 0.25); I² = 22%
Test for overall effect: Z = 0.63 (P = 0.53)



D **Forest plot for OPRM1 A118G polymorphism and postoperative vomiting risk in dominant model**

Study or Subgroup	Vomiting Events	Vomiting Total	Normal Events	Normal Total	Weight	Odds Ratio M-H, Fixed, 95% CI	Year
Chou 2006a	5	22	41	98	8.7%	0.41 [0.14, 1.20]	
Chou 2006b	5	12	32	68	4.2%	0.80 [0.23, 2.78]	
Chen 2008	4	6	38	118	0.9%	4.21 [0.74, 24.01]	2008
Tan 2009	58	112	547	882	44.4%	0.66 [0.44, 0.98]	2009
Zhang 2011	10	27	75	138	11.5%	0.49 [0.21, 1.16]	2011
Zhang 2013	19	27	55	101	5.1%	1.99 [0.80, 4.96]	2013
Liu 2014	17	34	83	144	11.8%	0.73 [0.35, 1.55]	2014
Zhang 2015	5	8	61	115	2.2%	1.48 [0.34, 6.46]	2015
Chen 2015	16	30	144	242	11.1%	0.78 [0.36, 1.67]	2015
Total (95% CI)		**278**		**1906**	**100.0%**	**0.76 [0.59, 0.99]**	
Total events	139		1076				

Heterogeneity: Chi² = 11.53, df = 8 (P = 0.17); I² = 31%
Test for overall effect: Z = 2.06 (P = 0.04)



E **Forest plot for OPRM1 A118G polymorphism and postoperative vomiting risk in recessive model**

Study or Subgroup	Vomiting Events	Vomiting Total	Normal Events	Normal Total	Weight	Odds Ratio M-H, Fixed, 95% CI	Year
Chou 2006a	1	22	12	98	6.8%	0.34 [0.04, 2.77]	
Chou 2006b	1	12	17	68	7.6%	0.27 [0.03, 2.27]	
Chen 2008	0	6	4	118	0.8%	1.96 [0.09, 40.38]	2008
Tan 2009	7	112	163	882	55.7%	0.29 [0.13, 0.64]	2009
Zhang 2011	2	27	20	138	9.8%	0.47 [0.10, 2.15]	2011
Zhang 2013	6	27	15	101	8.0%	1.64 [0.57, 4.73]	2013
Zhang 2015	1	8	14	115	2.6%	1.03 [0.12, 9.01]	2015
Chen 2015	0	30	24	242	8.8%	0.15 [0.01, 2.47]	2015
Total (95% CI)		**244**		**1762**	**100.0%**	**0.44 [0.27, 0.72]**	
Total events	18		269				

Heterogeneity: Chi² = 9.31, df = 7 (P = 0.23); I² = 25%
Test for overall effect: Z = 3.29 (P = 0.001)

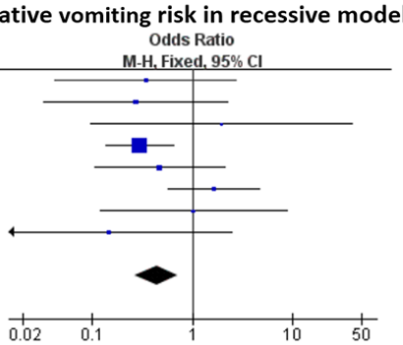


Figure 4. Forest plots (individual and pooled effects with 95% CI) regarding the association between OPRM1-A118G polymorphism and postoperative vomiting in allele model (A), homozygote model (B), heterozygote model (C), dominant model (D) and recessive model (E).

phisms show a general tendency to increase yearly. A timeline of the literatures is shown as **Figure 8**.

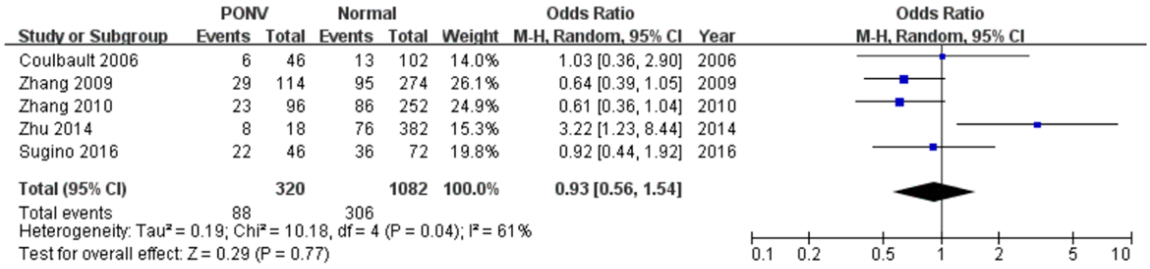
Walter et al.'s review, investigating the influence of OPRM1-A118G polymorphism on pain response suggested that it was premature to integrate pharmacogenetics into the clinic with respect to pain control [35]. Hwang et al. recently in a meta-analysis suggested that The OPRM1-A118G polymorphism was associated with inter-individual variability in postoperative response to opioids [7]. In a subpopulation, identifying OPRM1-A118G polymorphism may provide valuable information regarding the individual analgesic doses that are required to achieve satisfactory pain control [7]. In the studies they reviewed plus subsequent newer studies, some authors did investigate the effects of OPRM1-A118G polymorphism on postoperative adverse reactions to anesthesia as secondary outcomes, mainly PONV. Although there were reports indicating the association between A118G and postoperative side effects, the results among different studies varied widely. Zhang et al. found that the incidence of nausea in the AA, AG and GG groups were 35.0%, 25.4% and 13.6%, respectively. The incidence of vomiting in the AA, AG and GG groups were 21.3%, 12.7% and 9.1%, respectively. There were no statistically significant differences among the genotype groups with respect to nausea or vomiting (P = 0.114 and P = 0.239, respectively) [22]. Liu in 2014 also examined the relationship between OPRM1-A118G polymorphism and incidence of postoperative nausea, vomiting, and pruritus. After Bonferroni correction, there were no significant differences in the postoperative side effects between the A/A genotype group and A/G + G/G genotype group [18].

Some possible reasons for the inconsistent results include ethnic background differences and small sample sizes. After all, a single study cannot confirm the correlation between OPRM1-A118G polymorphism and alcohol dependence risks convincingly. Meta-analysis is a statistical procedure that can create more strengthful assessments of the true effects by combining data from multiple literatures. In light of this, we combined PubMed, EMBASE, Cochrane Library, Web of Knowledge, Google Scholar and CNKI databases to analyze the associations between the risks of postoperative side effects and the OPRM1-A118G polymorphism. In our study, the statistical correlation between OPRM1-A118G polymorphism and reduced postoperative vomiting risks was detected in homozygote (OR: 0.422; 95% CI: 0.254, 0.701; P = 0.001), dominant (OR: 0.765; 95% CI: 0.592, 0.987; P = 0.040) and recessive (OR: 0.439; 95% CI: 0.268, 0.717; P = 0.001) models, but not in the allele model and heterozygote model. For other postoperative side effects, no associations were detected in our meta-analysis. Due to a limited sample and possible heterogeneity, the results should be interpreted with caution. To the best of our knowledge, this analysis is the first evaluation of the correlations between OPRM1-A118G polymorphism and postoperative adverse reactions to anesthesia including nausea, vomiting, pruritus and dizziness.

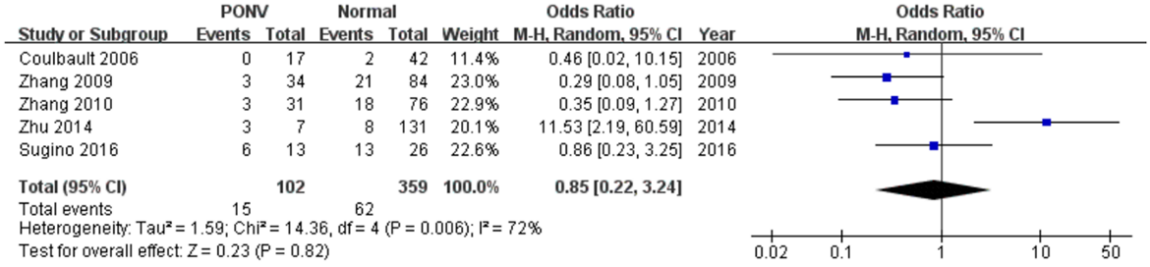
In contour-enhanced funnel plots, every single circle represents a study. Generally speaking, if studies appear to be missing in areas of low statistical significance (the left part of the plot), then it is very possible that the asymmetry is due to publication bias. Conversely, if the area where studies are perceived to be missing are areas of high statistical significance (the right part of the plot), then publication bias isn't the cause of funnel asymmetry [36]. In the current meta-analysis, the funnel plot indicated no publication bias.

There may be limitations in our meta-analysis. Firstly, the number of literatures and the sample size for each ethnicity were somewhat small. Thus, type-II error should not be dismissed [37]. Secondly, the effects of gene-environment interactions and gene-gene interactions were not emphasized because not all studies provided this information, or even if they provided, adjusted factors were reported differently among different literatures. Thirdly, more accurate ORs should be adjusted by patient factors such as gender, age, living

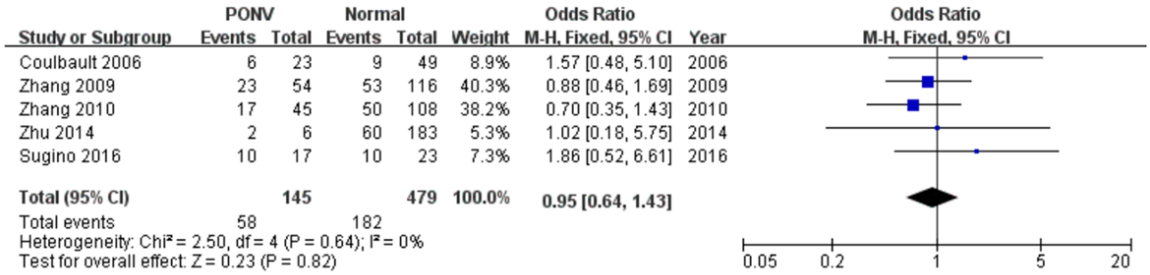
A **Forest plot for OPRM1 A118G polymorphism and PONV risk in allele model**



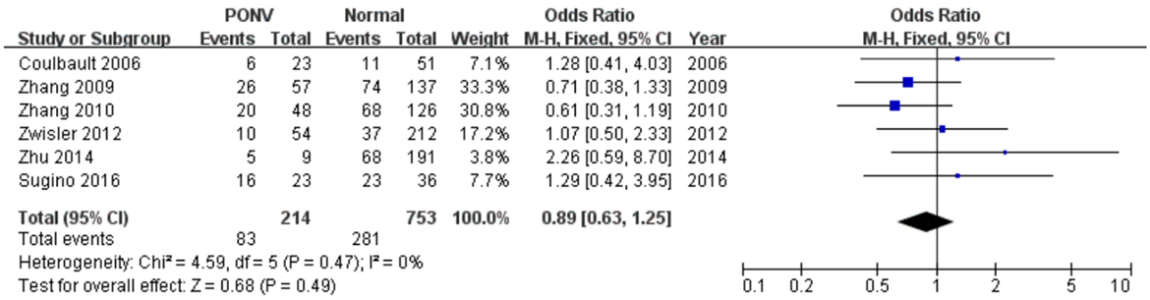
B **Forest plot for OPRM1 A118G polymorphism and PONV risk in homozygote model**



C **Forest plot for OPRM1 A118G polymorphism and PONV risk in heterozygote model**



D **Forest plot for OPRM1 A118G polymorphism and PONV risk in dominant model**



E **Forest plot for OPRM1 A118G polymorphism and PONV risk in recessive model**

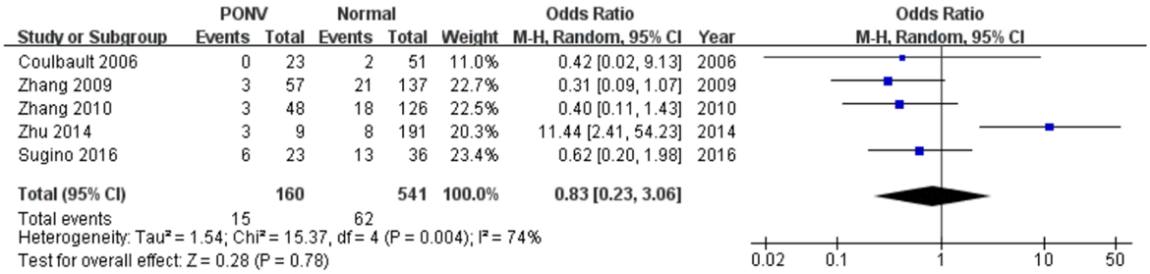


Figure 5. Forest plots (individual and pooled effects with 95% CI) regarding the association between OPRM1-A118G polymorphism and postoperative nausea plus vomiting (PONV) in allele model (A), homozygote model (B), heterozygote model (C), dominant model (D) and recessive model (E).

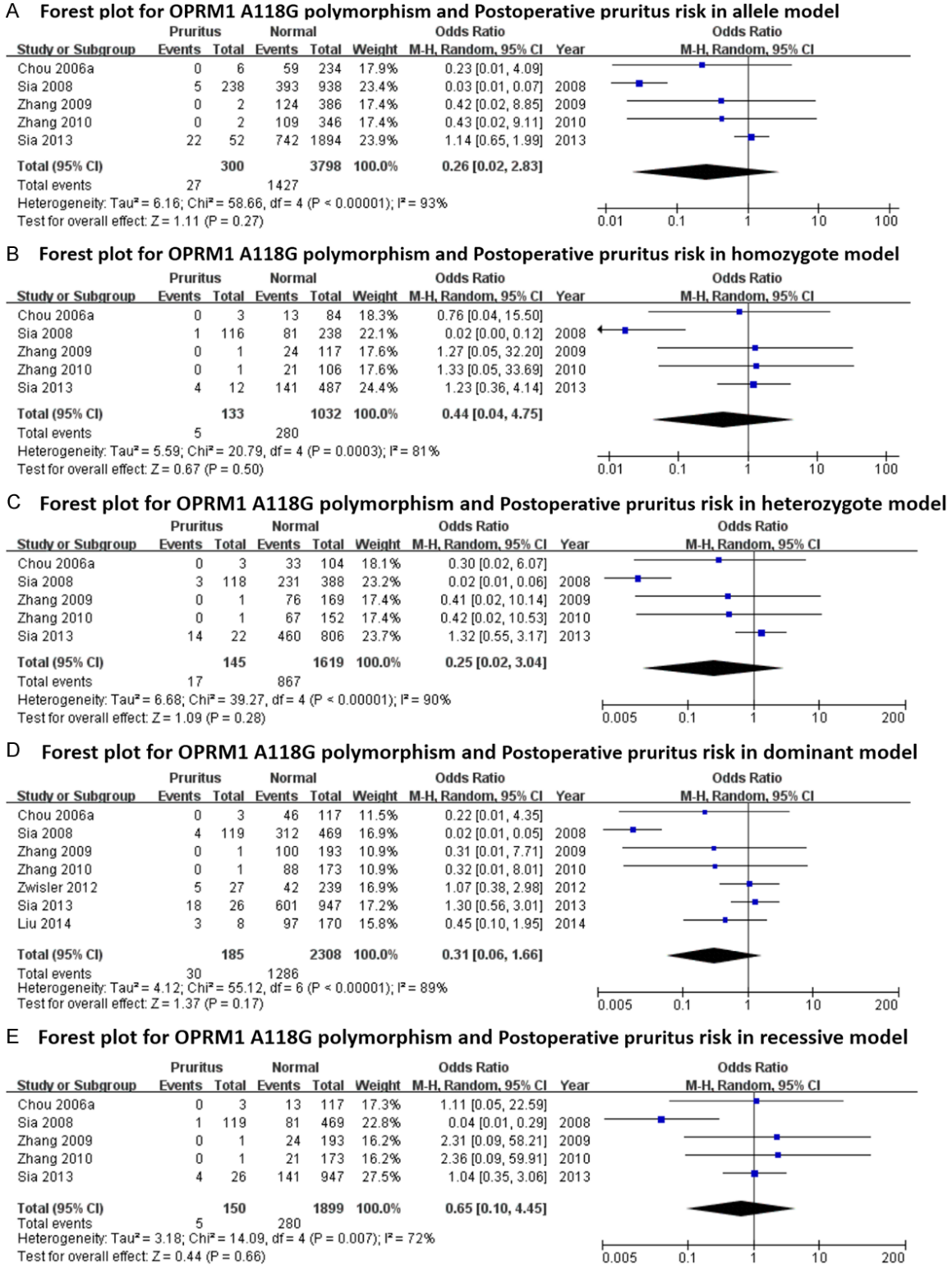


Figure 6. Forest plots (individual and pooled effects with 95% CI) regarding the association between OPRM1-A118G polymorphism and postoperative pruritus in allele model (A), homozygote model (B), heterozygote model (C), dominant model (D) and recessive model (E).

styles, race, medication consumption and other exposure factors. Fourth, only published articles were included, the unpublished and ongoing studies could convert our result.

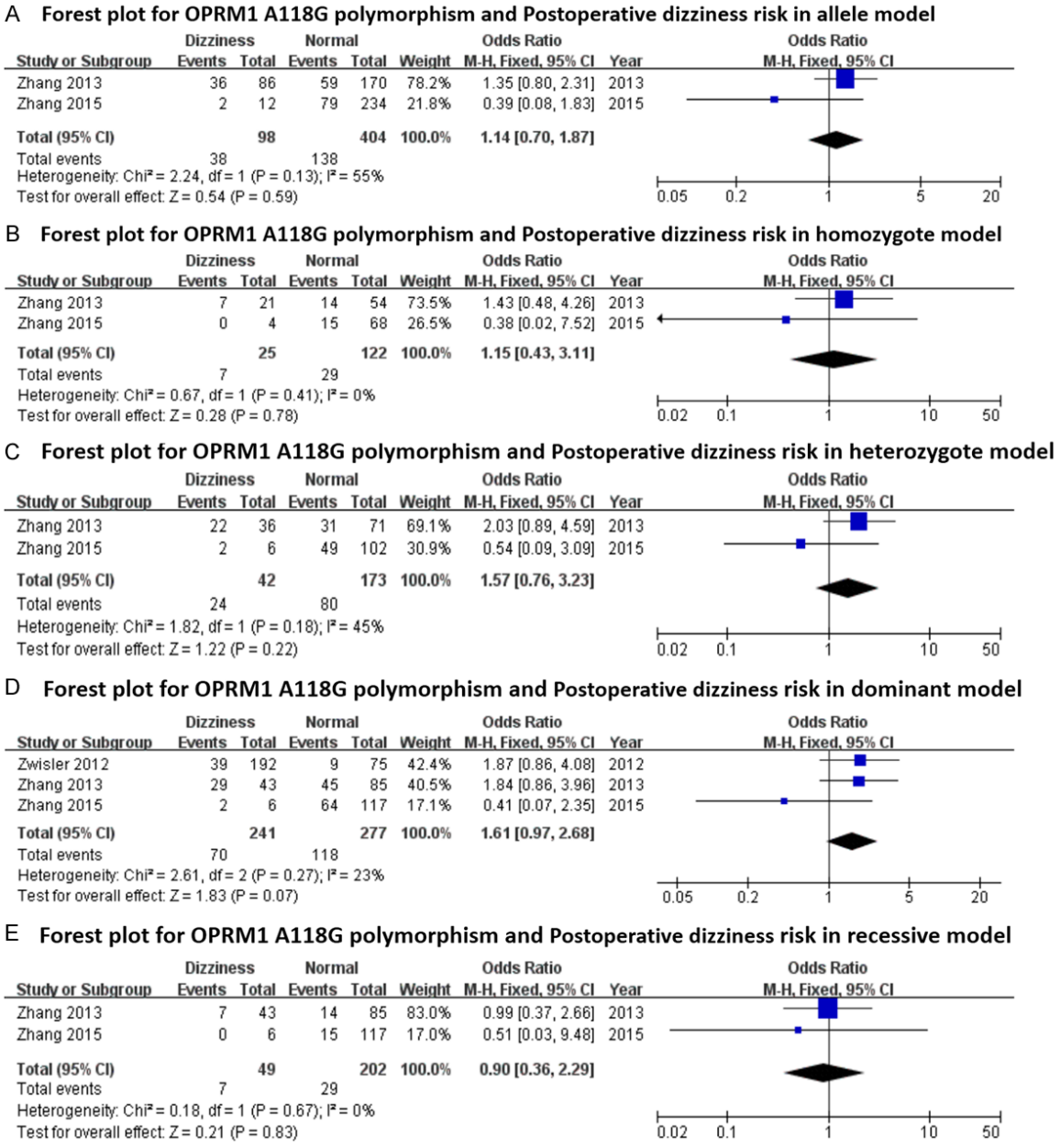


Figure 7. Forest plots (individual and pooled effects with 95% CI) regarding the association between OPRM1-A118G polymorphism and postoperative dizziness in allele model (A), homozygote model (B), heterozygote model (C), dominant model (D) and recessive model (E).

Conclusions

In conclusion, our results suggest that Opioid Receptor mu 1 (OPRM1) A118G Polymorphism (rs1799971) may be associated with postoperative vomiting, but not with nausea, pruritus or dizziness. Well-designed studies with large-size sample and more ethnic groups are necessary in the future to validate the risks demonstrated in this present meta-analysis.

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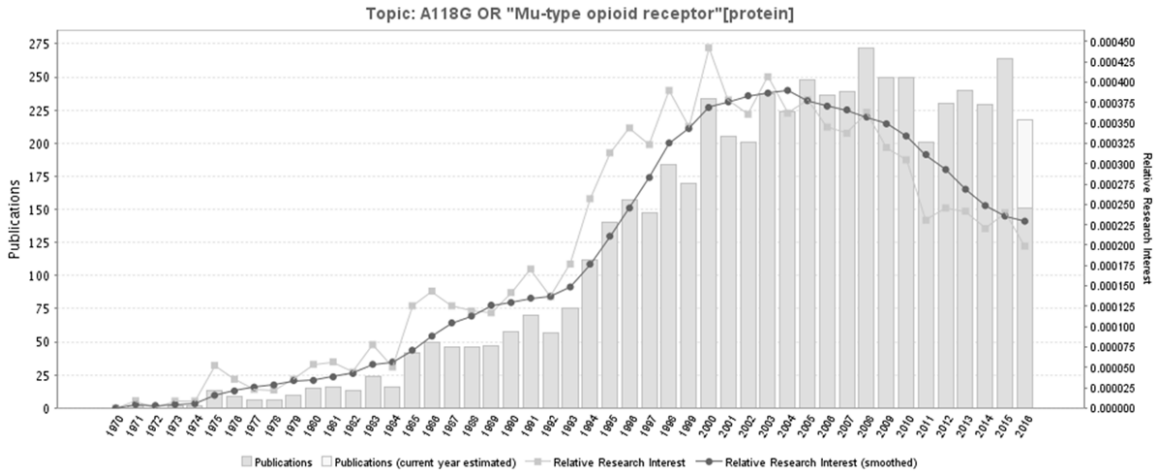

Figure 8. A timeline of the publications related to OPRM1-related polymorphisms. **Figure 4** was generated through GoPubMed (website: http://www.gopubmed.com). GoPubMed is a knowledge-based search engine for biomedical texts. The technologies used in GoPubMed are generic and can in general be applied to any kind of texts and any kind of knowledge bases. The system was developed at the Technische Universität Dresden by Michael Schroeder and his team at Transinsight. Creation steps for this timeline: import search items to the Search Box at the home page, then click "Statistics" and download related statistical charts including the timeline and map.

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Disclosure of conflict of interest

None.

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