Systematic Review

The Relevance of the OPRM1 118A>G Genetic Variant for Opioid Requirement in Pain Treatment: A Meta-Analysis

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Background: There is obvious difference in individual response to opioids. Many studies have examined the correlation between the μ-opioid receptor 1 (OPRM1) 118A>G genetic variation and opioid requirement in pain treatment, but the conclusion remains elusive.

Objectives: To investigate whether the OPRM1 118A>G genetic variation is associated with the opioid requirement.

Study Design: Systematic review and meta-analysis.

Methods: PubMed, Cochrane library, and EMBASE databases were systematically searched up to May 5, 2018, using the keywords "OPRM1," "genetic variant," "opioid," and "pain" to identify reviews or meta-analyses on this topic. Two independent reviewers performed the data extraction and assessed study quality. The authors investigated the standardized mean difference (SMD) of opioid requirement between AA homozygotes and G allele carriers. The authors also examined the association between the OPRM1 118A>G genetic variation and adverse effects such as nausea and vomiting. Potential bias was assessed using the Egger's test and the Begg's test.

Results: A total of 530 articles were retrieved from the databases searched, and 36 studies involving 8,609 patients were included in the final analysis. G allele carriers required a higher mean opioid dose (SMD: 0.17; 95% confidence interval [CI]: [0.12, 0.22]; $P < 0.001$) and displayed less nausea risk difference (RD): –0.04; 95% CI: [–0.06, –0.01]), but the incident rate of vomiting has no relationship with the genetic variant than AA homozygotes in a random-effects meta-analysis. Although there was no evidence of publication bias (Begg's test: $P = 0.333$; Egger's: $P = 0.561$), heterogeneity was present among studies ($I^2 = 54.3\%$). In the subgroup meta-analyses, there was also significance observed in the postoperative pain setting.

Limitations: In all of the articles reviewed, postoperative pain and cancer pain were mostly discussed except for one in other pain setting.

Conclusions: In this meta-analysis, the results indicate the OPRM1 A118G polymorphism was associated with the opioid requirement and the adverse effects in pain treatment especially in postoperative pain. This may provide valuable information for clinicians to adopt personalized pain management by properly using the opioids in individual patients.

Key words: OPRM1, genetic variation, opioid, pain, side effect, review, meta-analysis

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Pain management is mainly relying on drug treatment. Opioids are currently the most effective analgesics used for moderate to severe pain. Morphine, fentanyl, sufentanil, and oxycodone are commonly used opioids in the clinic. However, individual differences in pain sensitivity and response make it difficult for clinicians to use opioids properly. Inappropriate use of opioids may be one

of the main causes of side effects such as nausea, vomiting, respiratory depression, constipation, and others. Therefore, patients are either suffering from inadequate pain relief or suffering from side effects caused by drugs when the opioids are not properly used (1). Genetic factors may be an important cause of these individual differences (2-4). The μ-opioid receptor 1 (OPRM1), a primary binding site for morphine, is an important target for treating pain (5,6). The OPRM1 A118G genetic variation has been a major area of focus for research in the pharmacogenetics study of opioid response (7-9). Some animal or human studies show G carriers had reduced analgesic response to morphine compared with the AA homozygotes (10,11). However, the same correlation was not observed in other studies (12). A large number of research has been conducted to study the correlation between OPRM1 A118G genetic variation and opioid needs and the corresponding adverse effects. Therefore, it is very important to provide accurate evidence to prove the association between OPRM1 A118G genetic variation and opioid requirements in different pain settings that remains elusive. Therefore, a systematic review and meta-analysis was performed to evaluate this association.

Methods

This meta-analysis was performed according to the Cochrane Handbook for Systematic Reviews of Interventions 6 and presented based on Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines.

Search Trials

We searched the PubMed, Cochrane library, and EMBASE databases from the inception dates to May 5, 2018, using the keywords "OPRM1," "genetic variation," "opioid," and "pain" to identify published systematic reviews or meta-analyses evaluating the association between OPRM1 A118G genetic variation and opioid requirements in different pain settings. The references of the identified original articles or review articles were also retrieved and reviewed to provide a complete and precise literature search.

Study Selection and Inclusion Criteria

Two researchers (X.Y.Z. and Y.Y.) independently assessed the articles for their eligibility for inclusion. The following criteria was used to determine the articles eligibility for inclusion, articles must be: 1) randomized or cohort studies; 2) in clinical pain settings including postoperative pain, cancer pain, or other pain; 3) containing opioid dosage requirements; and 4) containing side effects such as nausea, vomiting, and respiration depression.

Data Extraction

Two researchers (X.Y.Z. and Y.Y.) independently extracted the following information from each study: first author, year of publication, race, numbers of patients, genetic variants, whether genotype frequencies agreed with the Hardy–Weinberg equilibrium (HWE), amounts of opioids (mean ± standard deviation [SD]), pain setting, and clinical outcome. Disagreements between the 2 researchers were resolved by consensus or consultation with a third author (F.X.H.). We determined whether the genotype frequencies agreed with HWE by calculating the $\chi 2$ goodness-of-fit. The endpoints of our meta-analysis included opioid consumption and side effects during the pain treatment. When the data format in the articles were not suitable for the analyses, we contacted the article corresponding author to get the data set. If the data included in the article were not complete and the authors could not be contacted for more information, the article was excluded for analysis. The details for identifying qualified studies and the exclusion of the studies are shown in Fig. 1. The main information extracted from the included studies are shown in Table 1.

Statistical Analysis

Data extracted from each article were processed and analyzed using RevMan 5.2 (The Nordic Cochrane Centre for The Cochrane Collaboration, Copenhagen, Denmark) and Stata SE Version 12.0 (StataCorp LP, College Station, TX) software packages. We calculated the standardized mean difference (SMD) to standardize the data of opioid consumption because this was represented in different units. We used odds ratio as the parameters of drug side effects. A random-effects model was used to pool the data, and statistical heterogeneity between summary data were evaluated using the I^2 statistic. I^2 ranged from 0 to 100% (I^2 > 50% shows significant heterogeneity) (13). The results are illustrated as point estimates and 95% confidence intervals (CIs). We used the Egger's test and the Begg's test to construct plots illustrating the standardized effect and the corresponding standard errors to evaluate potential bias.

Review: the Role of OPRM1 A118G in Pain

The μ-opioid receptor gene OPRM1, a member of the G-protein-coupled receptor superfamily, is one of the genes with a high probability of relevance for pain and pain treatment. It encodes the predominant receptor of opioids, which are still the major analgesics used in pain therapy, and it was among the first pain-related genes screened for functional variants. Genetic variants of OPRM1 were found to be associated with opioid individual responses in different pain conditions including acute postoperative pain (8,14-16), chronic pain (17,18), and cancer-related pain (19,20).

The OPRM1 118 A>G (rs1799971) genetic variation emerged as one of the most promising candidates for a genetic modulation of analgesia. The variant G allele carriers of cancer patients and postoperative patients requires an increase in the doses of morphine to achieve pain control (7,21). Although a meta-analysis showed G allele carriers indeed need an increase in mean opioid dose than in AA homozygotes carriers, the evaluation is only performed in the postoperative pain setting (22). For the side effects of opioids and OPRM1 A118G, the correlation remains unclear. A study genotyped 165 Chinese women undergoing gynecologic surgery and showed no correlation between OPRM1 A118G with individual variation of postoperative nausea and vomiting, which are common side effects of fentanyl (23). However, some studies showed opposite results that the severity of postoperative nausea and vomiting in carriers of the variant haplotype was significantly lower than in the carriers of the other haplotypes (24).

Results

Study Selection and Characteristics

The details of identifying qualified studies and the exclusion criteria are shown in Fig. 1. A total of 530 articles were retrieved from PubMed, Cochrane library, and EMBASE databases, and 36 studies involving 8,609 patients were included in the final analyses. From the 530 articles, 188 articles were removed owing to duplication, with the remainder independently reviewed by 2 researchers. A total of 91 reviews were excluded. The full texts of the remaining 251 articles were reviewed and among them 215 articles were excluded for the following reasons: 154 articles were not consistent with our research topics; 34 articles were nonhuman experiments; and 27 articles did not have effective data that we needed. In the final analysis, 36 articles were included, of these, 28 articles were regarding the relationship between OPRM1 and opioid demand, and 15 articles and 12 articles included were regarding the study on nausea and vomiting, respectively.

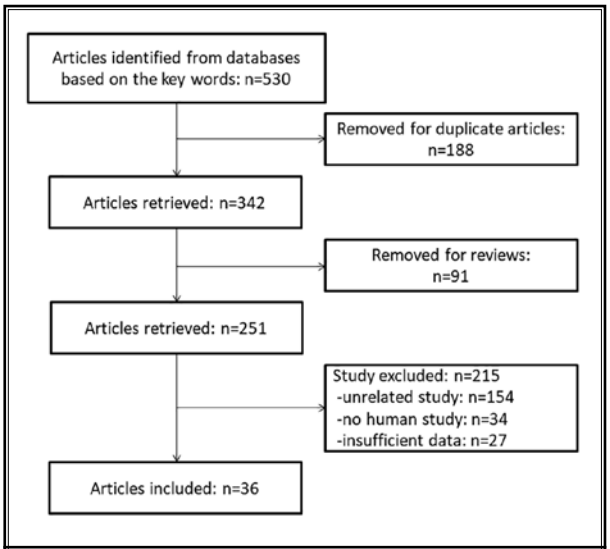

Fig. 1. *The details for identifying qualified studies and the exclusion criteria of the studies.*

Table 1 shows the general characteristics of the 36 studies included in the final analysis. There were 8,609 patients represented in these studies, and the sample size of each study ranged from 38 to 994. There were 4,586 AA homozygous genotypes and 4,023 G carriers including GG homozygote and AG heterozygote. Sixteen studies chose Caucasians as research subjects, 18 selected Asians, and 2 additional studies included mixed races. The countries in these studies include China (12), United States (5), Japan (3), Singapore (3), France (2), Korea (2), Germany (1), Sweden (1), Finland (1), Norway (1), Lebanon (1), Estonia (1), Czech (1), Denmark (1), and Australia (1). Thirty-one studies were in the postoperative pain setting, 4 studies were in the cancer pain setting, and one study was in another pain setting.

Meta-Analysis of A118G and Opioid Intake Requirement

Opioid consumption data including the numbers, mean dose, and SD of opioid consumption in each group, were available from 28 studies (7,9,11,14,15,19,23,25-46). These studies included 3,782 homozygous 118AA patients and 3,245 118G allele carriers. The relative SMD of the pain treatment requirement for opioids in each study is presented in a forest plot, along with the

Table 1. *The general characteristics of the 36 studies included in the final analysis.*

NO.	Study	Country	Population	N	AA	G carriers	HWE	Setting	Opioid	Adverse events
1.	Bartosova et al (2015) (25)	Czech	Caucasian	51	38	13	Yes	Postoperative pain	PIR	
2.	Bastami et al (2014) (26)	Sweden	Caucasian	38	29	9	Yes	Postoperative pain	MOR	
3.	Boswell et al (2013) (47)	USA	Caucasian	158	131	27	Yes	Postoperative pain	MIX	Nausea, vomiting
4.	Cajanus et al (2014) (27)	Finland	Caucasian	993	631	362	Yes	Postoperative pain	OXC	
5.	Chen et al (2013) (48)	China	Asian	129	56	73	Yes	Postoperative pain	MOR	Nausea, vomiting
6.	Chou et al (2006a) (28)	China	Asian	80	43	37	No	Postoperative pain	MOR	Vomiting
7.	Chou et al (2006b) (29)	China	Asian	120	74	46	No	Postoperative pain	MOR	Nausea, vomiting
8.	Coulbault et al (2006) (29)	France	Caucasian	74	57	17	Yes	Postoperative pain	MOR	Nausea, vomiting
9.	Fukuda et al (2010) (8)	Japan	Asian	108	31	77	Yes	Postoperative pain	FEN	
10.	Gong et al (2013) (19)	China	Asian	112	44	68	Yes	cancer pain	MIX	
11.	Hajj et al (2017) (9)	Lebanon	Mixed	89	69	20	Yes	cancer pain	MOR	
12.	Hayashida et al (2008) (32)	Japan	Asian	138	41	97	Yes	Postoperative pain	MIX	
13.	Janicki et al (2006) (33)	USA	Caucasian	101	70	31	Yes	Postoperative pain	MOR	
14.	Kim et al (2013) (34)	Korea	Caucasian	196	72	124	Yes	Postoperative pain	FEN	
15.	Klepstad et al (2004) (12)	Norway	Caucasian	99	78	21	Yes	cancer pain	MOR	
16.	Kolesnikov et al (2011) (35)	Estonia	Caucasian	102	82	20	Yes	Postoperative pain	MOR	
17.	Lee et al (2016) (49)	Korea	Asian	88	36	52	Yes	Postoperative pain	MOR	Nausea
18.	Liao et al (2013) (50)	China	Asian	97	42	55	Yes	Postoperative pain	FEN	Nausea, vomiting
19.	Liu et al (2014) (51)	China	Asian	178	78	100	Yes	Postoperative pain	RFEN	Nausea, vomiting
20.	Lotsch et al (2009) (36)	Germany	Caucasian	503	406	97	Yes	outpatient pain	MIX	
21.	Mamie et al (2013) (37)	USA	Caucasian	168	130	38	Yes	Postoperative pain	MOR	
22.	Pettini et al (2018) (52)	USA	Caucasian	63	45	18	Yes	Postoperative pain	MOR	Nausea
23.	Reyes-Gibby et al (2007) (11)	USA	Caucasian	207	166	41	Yes	cancer pain	MOR	
24.	Sia et al (2008a) (38)	Singapore	Asian	585	271	314	Yes	Postoperative pain	MOR	Nausea, vomiting
25.	Sia et al (2013b) (15)	Singapore	Asian	973	354	619	Yes	Postoperative pain	MOR	
26.	Somogyi et al (2016) (39)	Australia	Mixed	960	375	585	Yes	Postoperative pain	MOR	Nausea
27.	Sugino et al (2014) (24)	Japan	Caucasian	82	27	55	Yes	Postoperative pain	FEN	Nausea
28.	Tan et al (2009) (54)	Singapore	Asian	994	389	605	Yes	Postoperative pain	MOR	Vomiting
29.	Thomazeau et al (2016) (40)	France	Caucasian	108	90	18	Yes	Postoperative pain	MOR	
30.	Wang et al (2016) (41)	China	Asian	120	46	74	Yes	Postoperative pain	SFEN	
31.	Xu et al (2015) (42)	China	Asian	161	63	98	Yes	Postoperative pain	SFEN	Nausea, vomiting
32.	Zhang et al (2010a) (14)	China	Asian	174	86	88	Yes	Postoperative pain	FEN	Nausea, vomiting
33.	Zhang et al (2011b) (23)	China	Asian	165	80	85	No	Postoperative pain	FEN	Nausea, vomiting
34.	Zhang et al (2018) (45)	China	Asian	240	102	138	Yes	Postoperative pain	FEN	
35.	Zhang et al (2013) (44)	China	Asian	96	35	61	Yes	Postoperative pain	FEN	Nausea, vomiting
36.	Zwisler et al (2012) (46)	Denmark	Caucasian	266	219	47	Yes	Postoperative pain	OXC	

Abbreviations: PIR, Piritramide; MOR, Morphine; OXC, Oxycodone; FEN, Fentanyl; RFEN, remifentanil; SFEN, sufentanil

overall results of the meta-analysis (Fig. 2). The results showed G allele carriers required a higher dose of opioids when compared with the wild-type AA homozygotes (SMD: 0.17; 95% CI: [0.12, 0.22]; $P < 0.001$). The heterogeneity was significant (I2 = 54.3%; $P < 0.001$).

We performed analysis in the subgroups based on the type of pain setting such as postoperative pain, cancer pain, and other pain. The results are shown in

a forest plot, along with the overall results of the meta-analysis (Fig. 3). In the postoperative pain group, the results showed that G allele carriers required a higher dose of opioids when compared with the requirement for the wild-type AA homozygotes (SMD: 0.18; 95% CI: [0.13, 0.23]; $P < 0.001$). The heterogeneity was not significant ($I^2 = 48.7\%$). In the cancer pain group, similar results were shown. The heterogeneity was also not significant ($I^2 = 44.7\%$).

We used the Egger's test and the Begg's test to plot the standardized effect and the corresponding standard errors to evaluate potential bias. The results showed no publication bias in these studies (Fig. 4. Begg's test: $P = 0.333$; Egger's: $P = 0.561$). We also conducted the influence analysis, and the results showed that the impacts of these articles on the results were relatively stable, and the quality of the literature was relatively high (Fig. 5).

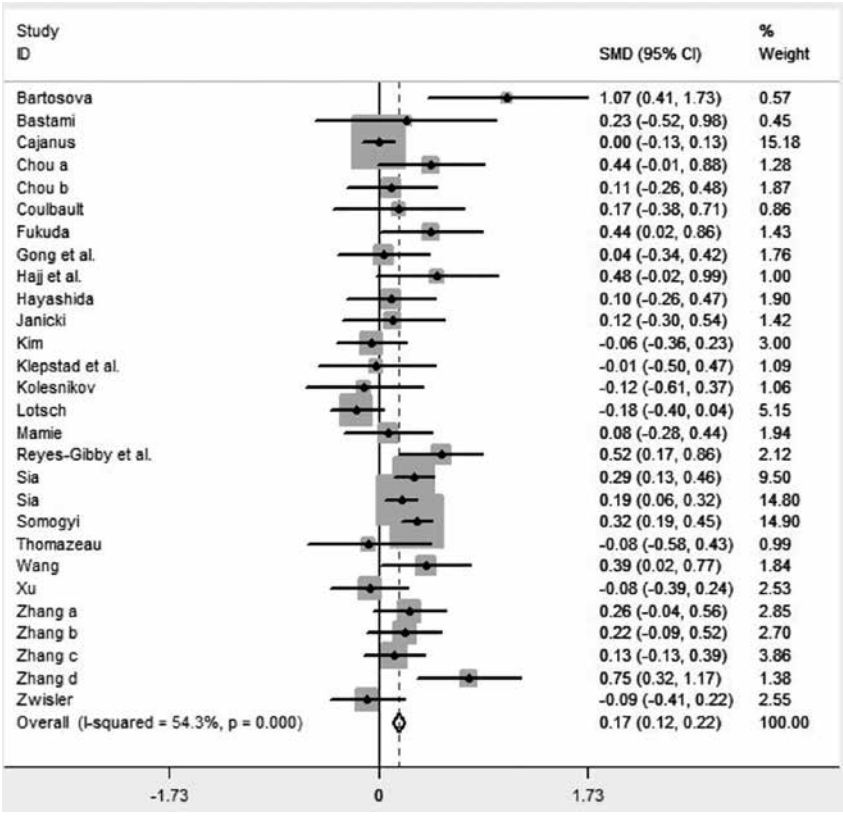

Fig. 2. *Opioid requirement in OPRM1 118G allele carriers versus 118AA carriers. G allele carriers required a higher dose of opioid (SMD: 0.17; 95% CI: [0.12, 0.22]; P < 0.001).*

Meta-Analysis of A118G and Drug Side Effects

Data for side effects, including nausea and vomiting, were available from 16 studies (14,23,24,29,30,38,39,42,47-54). They were divided into 2 groups: nausea and vomiting. The nausea group included 1,475 118AA homozygotes and 1,687 118G carriers, whereas the vomiting group included 1,361 118AA homozygotes and 1,521 118G carriers. We performed the analysis in these 2 groups separately (Figs. 6 and 7). For the nausea group, the results showed less nausea events in G carriers than in the AA homozygotes (RD: –0.04; 95% CI: [–0.06, –0.01]), but in the vomiting group, there was no significant correlation found between the A118G and vomiting (RD: 1.29; 95% CI: [0.99, 1.69]).

Discussion

OPRM1, ending gene for the predominant receptor of opioids, is one of the genes with a high probability of relevance for pain and pain treatment. Although there has been a meta-analysis about this scheme in 2009 (55), the meta-analysis only included 9 articles. Moreover, their results showed only weak evidence of increased opioid dosage requirements in homozygous carriers of the G allele. The authors did not perform a meta-analysis on the available evidence of the clinical relevance of the OPRM1 118A>G polymorphism. Our meta-analysis and review included 36 articles of OPRM1 A118G and opioid requirement and side effects in pain management. The main findings of our meta-analysis showed that the OPRM1 G allele carriers required a higher mean opioid dose, but the events of nausea were reduced than in AA homozygotes in a random-effects meta-analysis. In another meta-analysis of genetic variation on sensitivity to opioid analgesics in

patients with postoperative pain, the results show that the G carrier is not only related to reduced nausea events but also is related to vomiting (56). This may account for the increased number of studies from our research in recent years (51), which weights 9.8% in the results from 12 articles (Fig. 7), and its results showed there was no significant association between OPRM1 A118G and nausea or vomiting.

Our meta-analysis showed that the sensitivity to opioids of 118G allele carriers had reduced, reflected by increased opioid consumption and reduced nausea events. This can be partially explained by related basic research studies, but for the main findings of the opioid requirement, the heterogeneity of these 28 articles remained high. To investigate the source of this heterogeneity, we carried out the subgroup analysis based on the different pain settings including postoperative pain, cancer pain, and other pain. The results show that this heterogeneity is mainly derived from the different pain settings (Fig. 3).

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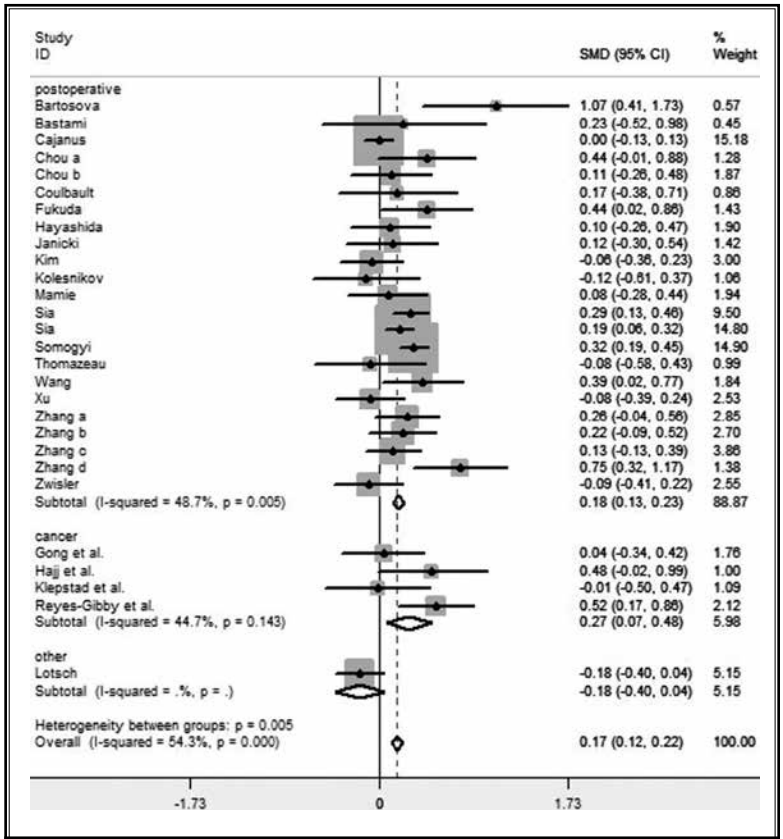

Fig. 3. *Opioid requirement in OPRM1 118G allele carriers versus 118AA carriers based on the type of pain setting. In neither the postoperative pain nor cancer pain subgroup, heterogeneity was significant (I2 = 48.7%; I2 = 44.7%).*

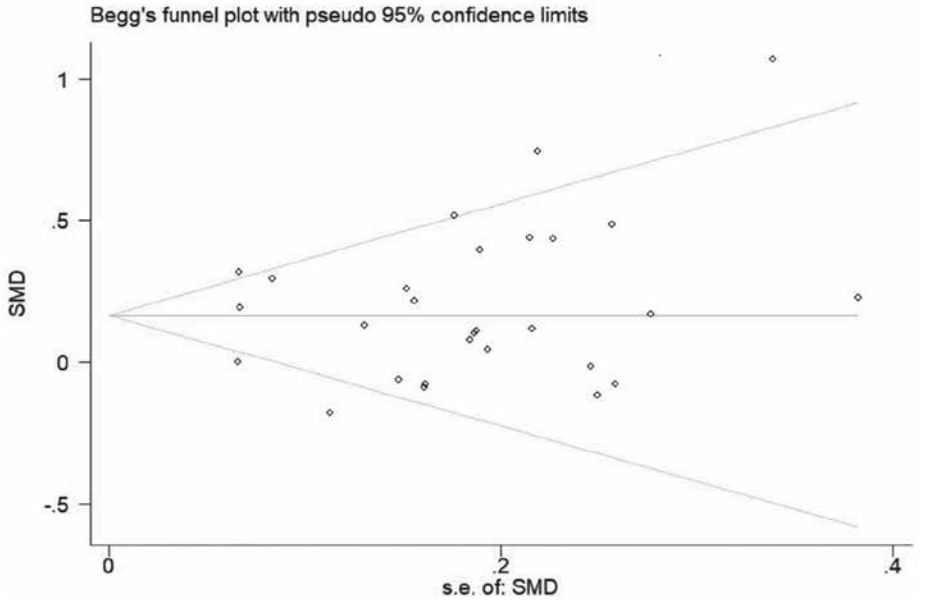

Fig. 4. *The results showed no publication bias in these studies.*

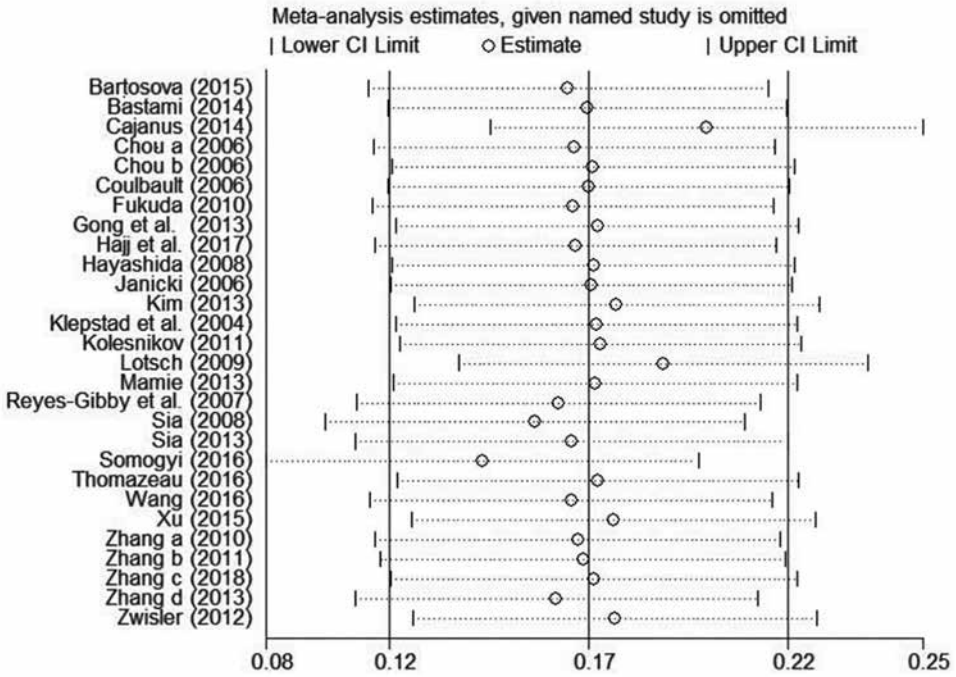

Fig. 5. *The influence analysis, with the results showing that the impacts of these articles on the results were relatively stable, and the quality of the literature was relatively high.*

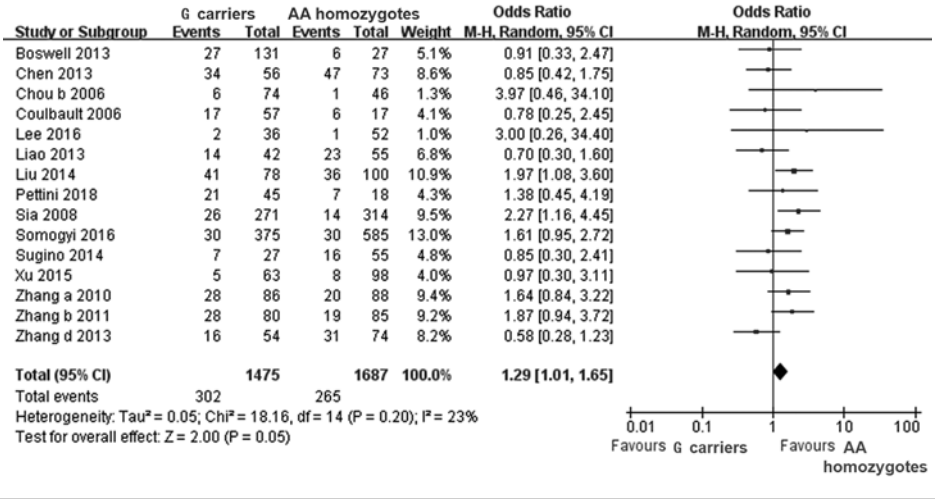

Fig. 6. *The results showed less nausea events in G carriers than in the AA homozygotes (RD: –0.04; 95% CI: [–0.06, –0.01]).*

sequencing and bioengineering, it has been possible to prevent and treat diseases through genetic testing. Individual differences make pain treatment very difficult to manage. The research progress on pain-related genes has led to new directions in pain management. Supported by a large amount of literature, and based on our results of meta-analysis, OPRM1 A118G genetic variation has a great influence on the sensitivity of individuals to pain. Based on the type of gene mutation, clinicians may be able to individualize pain treatment to achieve better effects.

Conclusions

Our meta-analysis also had some limitations. Some other factors including nongenetic ones such as ages, gender, race, and genetic factors like gene-to-gene interaction may also influence the requirement of opioids. Also, only one of the articles included in our

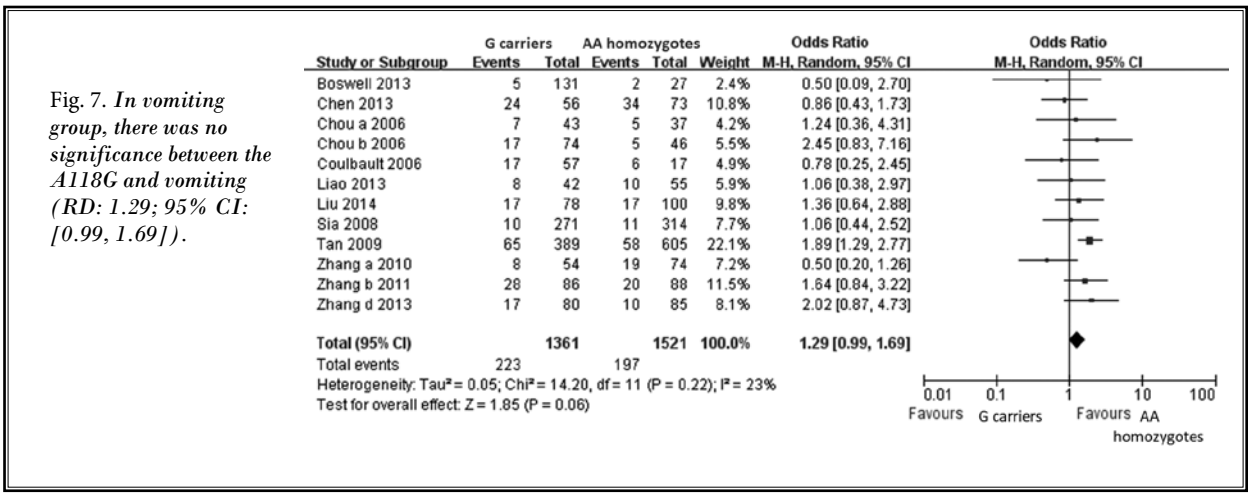

Fig. 7. *In vomiting group, there was no significance between the A118G and vomiting (RD: 1.29; 95% CI: [0.99, 1.69]).*

analysis had pain settings other than postoperative pain and cancer pain.

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