Original Article

Xiaoke Decoction in treatment of type II diabetes: A Meta-analysis

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ARTICLE INFO

ABSTRACT

Objective: To systematically evaluate the clinical effect of Xiaoke Decoction in the treatment of type 2 diabetes.
Methods: Chinese databases such as CNKI, Wanfang, Weipu Chinese Biomedical Journal Database, and Chinese Medical Biological Literature Database, PubMed, Cochrane Library, Embase, and Web of Science were searched for English language literature from their inception until November 2019. A Meta-analysis was performed using RevMan 5.3 and Stata 12.0.
Results: Thirty-eight studies were included in this study, with a total of 3757 patients. It was found that adding Xiaoke Decoction could improve total efficiency. The Xiaoke Decoction groups surpassed the western medicine groups regarding improvement in total efficiency (OR = 3.49; 95% CI: 2.78–4.39, $P < 0.00001$). Adding Xiaoke Decoction could lower the fasting plasma glucose (FPG) level. The Xiaoke Decoction groups surpassed the western medicine groups regarding reduction in FPG levels (MD = −1.14; 95% CI: −1.36 to 0.92, $P < 0.00001$). Adding Xiaoke Decoction could lower the 2 h postprandial blood glucose (2hPG) level. The Xiaoke Decoction groups surpassed the western medicine groups regarding reduction in 2hPG (MD = −1.40; 95% CI: −1.61 to 1.19, $P < 0.00001$). Adding Xiaoke Decoction could lower glycated hemoglobin (HbA1c). The Xiaoke Decoction groups surpassed the western medicine groups regarding reduction in HbA1c (MD = −0.77; 95% CI: −0.95 to 0.58, $P < 0.00001$). It was found that adding Xiaoke Decoction could lower the traditional Chinese medicine (TCM) syndrome score. The TCM syndrome scores among patients in the Xiaoke Decoction group were lower than those among patients in the control group after treatment (MD = −4.90; 95% CI: −7.22 to 2.57, $P < 0.0001$). At the same time, we conducted a subgroup and sensitivity analysis of age and intervention duration on the heterogeneity of total efficiency, FPG, 2hPG, HbA1c, and TCM syndrome score outcome indicators. For detecting publication bias, an egger test was conducted.
Conclusion: Compared with western medicine alone, Xiaoke Decoction has more advantages for the treatment of type 2 diabetes with respect to total efficiency, FPG, 2hPG, HbA1c, and TCM syndrome score.

1. Introduction

Diabetes is a metabolic endocrine disease characterized by high blood glucose concentration. Type 2 diabetes accounts for more than 90% of all diabetes patients and has a very high incidence worldwide. It is characterized by either absolute or relative insufficient insulin secretion (impaired insulin secretion) or decreased sensitivity of the target organs or tissues to insulin (insulin resistance) (Chinese Medical Association Diabetes Branch, 2017). It is often accompanied by a variety of chronic complications, thereby causing severe damage to multiple organ systems in the body (Zhang & Jiang, 2012). In 2017, the World Diabetes Federation reported that there were approximately 451 million diabetes patients worldwide and is expected to soar to 693 million in 2045. In recent years, the number of diabetes patients in China has increased dramatically, and diabetes has become the third most common disease after cardiovascular diseases and tumors. At present, type 2 diabetes is mostly managed using western

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medicine. Treatment methods are mostly oral hypoglycemic drugs or insulin injections. Western medicine alone has obvious hypoglycemic effects. However, long-term use is likely to cause liver and kidney damage, and the effect of improving certain complications is not obvious. Traditional Chinese medicine (TCM) has been used for thousands of years in China and plays an important role in medical care. Since ancient times, several Chinese herbs and herbal formulas have been widely used to treat diabetes (Gong, Ji, & Xu, 2019). TCM has its unique advantages in the treatment process. It is characterized by wide sources, convenient material collection, simple production, easy storage, low price, and small side effects. Thus, it has become widely used in the treatment of diabetes.

In TCM, diabetes belongs to the category of "Xiaoke" and has the appellation, eliminate sensation of spleen, eliminate medium, and so on. The treatment principle is to clear heat, moisten dryness, nourish *yin*, and produce fluid. The Xiaoke Decoction comes from the "*Danxi's Experimental Therapy*" (Danxi Xinfa in Chinese) of Dan-xi Zhu, which was composed of *Coptidis Rhizoma*, *Trichosanthis Radix*, *Lotus Rhizoma*, *Rehmanniae Radix*, *Zingiberis Recens Rhizoma*, Mel, human milk (or cow's milk) among others. Moreover, Xiaoke Decoction and its derivative prescriptions showed their beneficial efficacy in treating type 2 diabetes. Only by eliminating thirst can effectively reduce oxidative stress response, improve islet function, and enhance insulin sensitivity in patients. The efficacy of the prescription has been widely recognized (Jin & Jin, 2019). We comprehensively searched domestic and foreign literatures for randomized clinical control trials on the treatment of type 2 diabetes using Xiaoke Decoction, and assessed the treatment of type 2 diabetes by means of Meta-analysis. This study aims to comprehensively evaluate the effectiveness and safety of Xiaoke Decoction for the treatment of type 2 diabetes.

2. Materials and methods

2.1. Inclusion and exclusion criteria

The included literatures met the following criteria: (1) Type of study: Randomized control trial of Xiaoke Decoction for the treatment of type 2 diabetes, regardless of the method of allocation and concealment used; (2) No limit on the sample size: All the selected candidates met the diagnostic criteria listed in the Guidelines for the Prevention and Treatment of Type 2 Diabetes in China (2017 Edition), (Chinese Diabetes Society, 2018); (3) Interventions: patients in the experimental group were given Xiaoke Decoction plus or minus, or combined with hypoglycemic drugs or insulin. Patients in the control group were treated with hypoglycemic drugs or insulin; and (4) Outcome indicators: At least one or more times of the total effective rate (Ministry of Health, 2002), fasting plasma glucose (FPG), 2h postprandial blood glucose level (2h-PBG), glycated hemoglobin (HbA1c), and TCM syndrome score (Diabetes Branch of Chinese Medical Association, 2017).

Documents with the following characteristics were excluded: (1) Non-compliance with the diagnostic criteria; (2) The use of other efficacy evaluation indicators; (3) The original data were unpublished literature or conference articles, animal experiments, reviews, and so on; (4) Original literature was a non-clinical randomized control experiment; And (5) the original literature trial design was not rigorous with no control group.

2.2. Literature search

We searched academic Chinese databases such as CNKI, Wanfang, Chinese Biomedical Journal Database (CMJD), Chinese Medical and Biological Literature Database (CBM), and those in foreign languages such as PubMed, Cochrane Library, Embase, and Web of Science. The retrieval time for each database was set from the time of inception to November 2019. The Chinese search terms used were "Xiaoke Decoction", "type 2 diabetes", "clinical observation", "random", and so on. The English search terms used were "Xiaoke Decoction", "type 2 diabetes mellitus", "clinical observation", and "random". We searched for relevant literature that may have met the criteria.

2.3. Literature screening and quality evaluation

The downloaded documents were screened and evaluated by the two researchers in accordance to the established inclusion and exclusion criteria. The titles and abstracts of all documents were further read to eliminate duplicates and to exclude those that clearly did not meet the inclusion criteria. When the preliminary
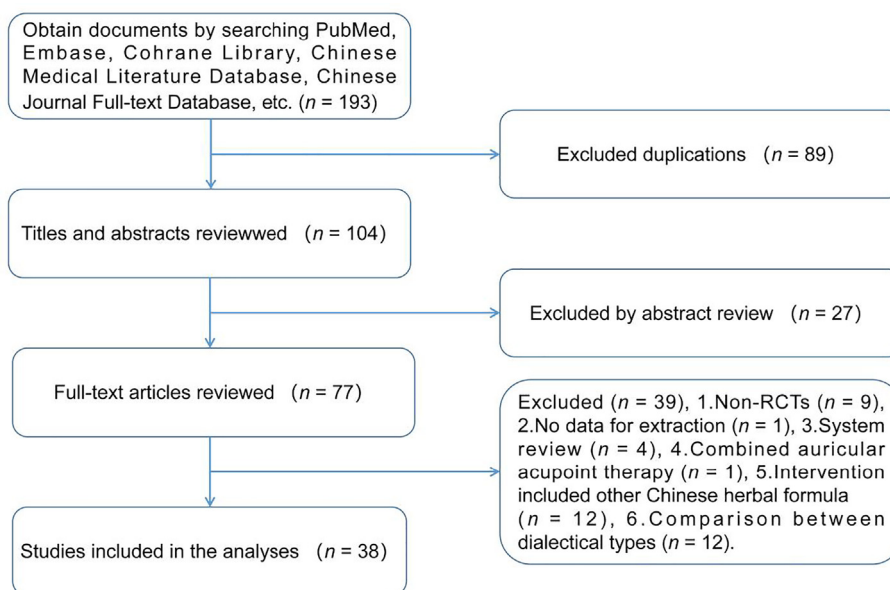

Fig. 1. Flow chart of selection process.

determination that the text may meet the inclusion criteria was made, we read the full text of the literature and selected articles that met the inclusion criteria. When the opinions of the two researchers were not unified, discussions and consultations were conducted or a third researcher could have been invited to jointly resolve the problem.

2.4. Statistical methods

Count data are presented as odds ratios (ORs), and measurement data as the weighted average value (MD) or standardized mean difference (SMD) and its 95% confidence interval (CI). Heterogeneity among the included studies was analyzed using the χ^2 test. In the test of heterogeneity, $P > 0.10$ and $I^2 < 50\%$ indicated that there was no statistical heterogeneity among the studies and that a fixed-effects model was used for analysis. Otherwise, a random-effects model was used. An inverted funnel plot was used to assess publication bias based on the main blood glucose indicators and TCM syndrome scores. Meta-analysis was performed using RevMan 5.3 and Stata 12.0. Items with $P < 0.05$ were considered statistically significant.

Table 1
Basic information included in literatures.

Author/Publishing Year	Test group (n)	Control group (n)	Test group treatment	Control group treatment	Course/week	Average age mean (SD)	Outcome indicator
Wang Ping (2016)	50	50	Xiaoke Decoction + Metformin Tablets	Metformin Tablets	12	48(7.29)	abcd
Dai Yuancheng (2013)	60	60	Xiaoke Decoction + Regraine	Regraine	8	55(1.2)	abc
Xie Junyan (2018)	30	30	Self-made Wuwei Xiaoke Decoction + Metformin Tablets	Metformin Tablets	4	54(1.79)	abc
Wen Wu (2018)	20	20	Xiaoke Decoction + Metformin Tablets	Metformin Tablets	8	46.2(1.52)	abcd
Yang Ling (2014)	44	44	Xiaoke Decoction + Metformin Tablets	Metformin Tablets	–	48(12.58)	abc
Zhou Lai le (2014)	40	40	Xiaoke Decoction + Metformin Tablets	Metformin Tablets	–	45.5(6.3)	bce
Zhang Guoping (2015)	30	30	Xiaoke Decoction + Metformin Tablets	Metformin Tablets	12	49.6(7.07)	abcd
Shi Ying (2000)	20	20	Xiaoke Decoction + Glibenclamide + Metformin Tablets	Glibenclamide + Metformin Tablets	–	53.5(1.52)	abc
Zhang Guige (2006)	20	20	Xiaoke Decoction + Glibenclamide + Metformin Tablets	Glibenclamide + Metformin Tablets	–	53.5(1.52)	abc
Duan Yutong (2012)	36	36	Xiaoke decoction + Xiaoke Pills + Metformin Tablets	Xiaokepills + Metformin Tablets	–	55.5(0.5)	abc
Li Yu (2014)	39	39	Xiaoke decoction + Metformin Tablets	Metformin Tablets	–	42.26(3.84)	bcd
Feng Yulian (2016)	40	40	Xiaoke Decoction + Metformin Tablets	Metformin Tablets	8	65.8(1.55)	abcd
(Eri et al., 2018)	60	60	Xiaoke Decoction + Metformin Tablets	Metformin Tablets	12	56.6(8.26)	abc
Du Xueyuan (2018)	50	50	Xiaoke Decoction + Gliclazide Tablets	Gliclazide Tablets	4	50.7(10.93)	abc
Zhu Xiaohong (2014)	39	39	Xiaoke Decoction + Metformin Tablets	Metformin Tablets	12	48.3(7.03)	a
Xie Shujun (2016)	48	48	Xiaoke Decoction + Metformin Tablets	Metformin Tablets	8	50.2(7.35)	abcd
Wang Haixia (2018)	45	45	Xiaoke Decoction + Metformin Tablets	Metformin Tablets	8	45.2(2.24)	abc
Zhang Haitao (2017)	40	40	Xiaoke Decoction + Metformin Tablets	Metformin Tablets	8	55(9.01)	abcd
Li Xiuxia (2010)	82	82	Xiaoke Decoction + Metformin Tablets	Metformin Tablets	8	58.76(10.37)	abcd
Chen Qi (2013)	43	43	Self made Xiaoke Decoction + Sitagliptin	Sitagliptin	12	49.2(2.22)	bcd
Shan Liangliang (2017)	62	63	Wuwei Xiaoke Decoction	1/20 Original medicine + Rice	4	54.1(11.33)	abcd
Sun & Chen, 2019	42	41	Wuwei Xiaoke decoction + Metformin Tablets	Metformin Tablets	12	46.8(5.22)	abcde
Han Junling (2019)	45	45	Wuwei Xiaoke decoction + Metformin Tablets	Metformin Tablets	4	55.8(8.6)	abcd
Zheng Zhenxiong (2014)	98	98	Matsuba Xiaoke decoction + Damicon + Gehuazhi	Damicon + Gehuazhi	12	56.5(1.5)	abcd
Zhang Tao (2017)	82	82	Huangqi Xiaoke Decoction + Metformin Tablets	Metformin Tablets	12	57.2(8.87)	abcd
Lai Changqin (2013)	60	60	Qijing Xiaoke Decoction + Metformin Tablets	Metformin Tablets	8	50.9(6)	abce
Cheng Hongwei (2017)	40	40	Qidi Xiaoke decoction + Eugenol 25	Eugenol 25	12	60.5(6.78)	abcd
Xu Yinglie (2015)	72	72	Jiangtang Xiaoke Decoction + Metformin Tablets	Metformin Tablets	4	53.5(15.4)	abcde
Xia Zhengqin (2017)	146	146	Modified Xiaoke Decoction + Intensive insulin treatment	Intensive insulin treatment	2	53.3(13.15)	bce
Liu Yaning (2016)	50	50	Xiaoke Decoction + Metformin Tablets	Metformin Tablets	4	52.3(3.4)	bcde
Zhu Tingting (2019)	50	50	Huangqi Xiaoke Decoction + Insulin	Insulin	8	53.5(4.28)	bcd
Feng Xiaonan (2017)	60	60	Huangqi Xiaoke Decoction + Insulin	Insulin	12	48.7(10.1)	bcd
Cui Can (2017)	40	40	Huangqi Xiaoke Decoction + Insulin	Insulin	8	54.4(4.66)	bcd
Ge Zhihua (2019)	44	44	Huangqi Xiaoke Decoction + Insulin	Insulin	8	–	abcd
Zeng Jibin (2014)	30	30	Huangqi Xiaoke Decoction + Metformin Tablets	Metformin Tablets	12	54.7(9.63)	abcd
Liu Shanghua (2019)	32	32	Huangqi Xiaoke Decoction + Metformin Tablets	Metformin Tablets	12	62.4(5.2)	a
Yan Fengzuo (2015)	50	50	Tongluo Xiaoke decoctiong + Insulin	Insulin	–	–	abcd
Zhang Zhaoxia (2015) (Zhang & Gong, 2015)	36	36	Xiaoke Decoction + Metformin Tablets	Metformin Tablets	8	64.8(5.5)	abcd

Note: a: total efficiency; b: FPG; c: 2 h-PBG; d: HbA1c; e: TCM syndrome point.

3. Results

3.1. Literature search results and basic information of included studies

A total of 193 articles were retrieved in the preliminary search. Duplicate articles that did not meet the inclusion criteria were excluded. Finally, 38 articles were included. A total of 3750 patients, including 1875 patients in the experimental group and 1875 patients in the control group, were identified. The literature screening process was shown in Fig. 1. The basic information of the included studies was shown in Table 1.

3.2. Results of evaluation of literature quality

Of the 38 selected papers, 33 mentioned random methods. The remaining five were grouped according to treatment plan, and 38 did not mention allocation and blinding. One mentioned double-blinding, whereas the remaining 37 did not mention double-blinding. The 38 articles were complete with outcome data and selection reports. The bias risk assessments included in the study were shown in Figs. 2 and 3.

3.3. Results of evaluation of included studies

3.3.1. Comparison of total efficiency
The 30 tentative (including 2810 patients) results were compared regarding the total therapeutic efficiency of Xiaoke Decoction combined with western medicine and western medicine only. The number of participants among the trials ranged between 20 and 98. It was found that adding Xiaoke Decoction could improve total efficiency (Fig. 4). The Xiaoke Decoction groups surpassed the western medicine groups in terms of improvement in total efficiency. The OR of the comparison between the Xiaoke Decoction groups and the control groups was 3.49 (95% CI: 2.78–4.39, $P < 0.00001$).

3.3.2. Comparison of FPG
The 36 tentative (including 3688 patients) results compared the therapeutic FPG of Xiaoke Decoction combined with western medicine to that of western medicine only. The number of participants among the trials ranged between 20 and 146. It was found that adding Xiaoke Decoction could lower the FPG (Fig. 5). There was statistical heterogeneity among the studies. The Xiaoke Decoction groups surpassed the western medicine groups in terms of reduction in FPG. The MD between the Xiaoke Decoction groups and control groups was −1.14 (95% CI: −1.36 to −0.92, $P < 0.00001$).

3.3.3. Comparison of 2hPG
The 36 tentative (including 3688 patients) results compared the therapeutic 2hPG of Xiaoke Decoction combined with western medicine to that of western medicine only. The number of participants in the trials ranged between 20 and 146. We found that adding Xiaoke Decoction could lower the 2hPG (Fig. 6). The Xiaoke Decoction groups surpassed the western medicine groups in terms of reduction in 2hPG. The MD between the Xiaoke Decoction groups and control groups was −1.40 (95% CI: −1.61 to −1.19, $P < 0.00001$).

3.3.4. Comparison of HbA1c
The 24 tentative (including 2466 patients) results compared the therapeutic HbA1c of Xiaoke Decoction combined with western medicine to that of western medicine only. The number of participants in the trials ranged between 20 and 98. We found that adding Xiaoke Decoction could lower the HbA1c (Fig. 7). The Xiaoke Decoction groups surpassed the western medicine groups in terms of reduction in HbA1c. The MD between the Xiaoke Decoction groups and control groups was −0.77 (95% CI: −0.95 to −0.58, $P < 0.00001$).

3.3.5. Comparison of TCM syndrome score
The six tentative (including 819 patients) results compared the therapeutic TCM syndrome score of Xiaoke Decoction combined with western medicine to that of western medicine only. The number of participants in the trials ranged between 40 and 146. We found that adding Xiaoke Decoction could lower the TCM syndrome score (Fig. 8). The TCM syndrome score of patients in the Xiaoke Decoction group was obviously lower than that of the control group after treatment. The MD between the Xiaoke Decoction groups and control groups was −4.90 (95% CI: −7.22 to −2.57, $P < 0.0001$).

3.4. Analysis of combination of Xiaoke Decoction with metformin and insulin

As Xiaoke Decoction was used in combination with a variety of western medicines, it was necessary to examine the effect of Xiaoke Decoction according to the categories of western medicine. Primarily, 10 western drugs or combinations were included: insulin, metformin tablets, Eugenol 25, Damicon + Gehuazhi, 1/20 original medicine + rice, sitagliptin, gliclazide tablets, Xiaoke Pills + metformin tablets, glibenclamide + metformin tablets, and regraine. Among them, metformin and insulin were the most commonly used. Therefore, the former two medicines were investigated separately in the present study.
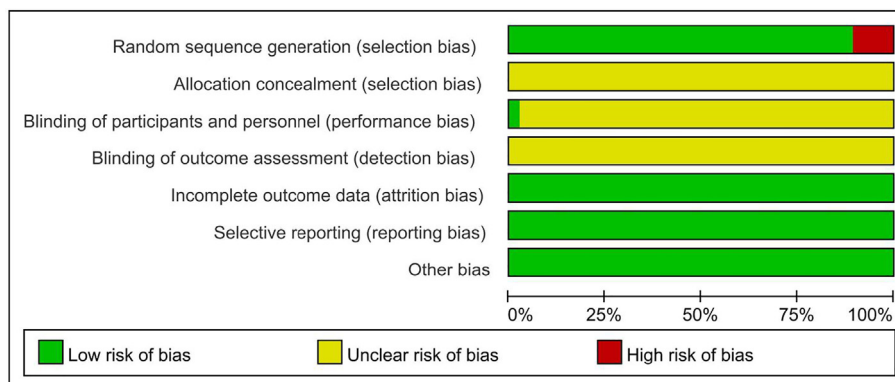

Fig. 2. Overall evaluation results of biased risk assessment included in literature.

Fig. 3. Biased risk assessment results for each included literature.

Twenty-three studies based on metformin showed that the combined use of Xiaoke Decoction could significantly improve the treatment of diabetes. Twenty of these studies showed that Xiaoke Decoqion was effective in improving total efficiency (OR = 3.20, 95% CI: 2.42–4.24, P < 0.00001).

Twenty-one of these studies showed that Xiaoke Decoction was effective in lowering FPG and 2hPG levels (FPG: MD = −1.08, 95% CI: −1.31 to −0.86, P < 0.00001; 2hPG: MD = −1.57, 95% CI: −1.93 to −1.21, P < 0.00001). Fifteen of these studies showed that Xiaoke Decoction was effective in lowering HbA1c levels (MD = −0.68, 95% CI: −1.00 to −0.36, P < 0.0001). Five studies reported that Xiaoke Decoction was effective in reducing the TCM syndrome score (MD = −4.30, 95% CI: −6.67 to −1.94, P = 0.0004). Six studies that assessed the combined use of insulin and Xiaoke Decoction consistently showed that Xiaoke Decoction could effectively reduce FPG levels (MD = −1.26, 95% CI: −2.07 to −0.46, P = 0.002) and 2hPG (MD = −1.55, 95% CI: −2.29 to −0.81, P < 0.00001). Two studies showed that Xiaoke Decoction was effective in improving total efficiency (OR = 4.90, 95% CI: 2.21–10.91, P < 0.0001). Finally, five studies showed that Xiaoke Decoction was effective in lowering HbA1c levels (MD = −0.70, 95% CI: −0.82 to −0.58, P < 0.00001).

3.5. Subgroup analysis

Subgroup analysis according to intervention duration found that in terms of total efficiency, the total efficiency (OR: 4.069) of intervention duration in 9–12 weeks was higher than that in 4–8 weeks. The intervention duration lasted 4–8 weeks; 2hPG (SMD: −1.597; 95% CI: −2.087 to −1.107) and HbA1c (SMD: −0.775; 95% CI: −1.017 to −0.532). The effect was better than 9–12 weeks. Moreover, the effect of FPG was relatively stable after taking Xiaoke Decoction. Subgroup analysis of the <50 age group and ≥50 age group showed that, within age <50, total efficiency (OR: 5.412), FPG (SMD: −1.328; 95% CI: −1.851 to −0.804) and 2hPG (SMD: −0.927; 95% CI: −1.076 to −0.779) had better therapeutic effects than age ≥50. In terms of HbA1c (SMD: −0.693; 95% CI: −0.797 to −0.589), age ≥50 was more effective than age <50 (Table 2).

3.6. Source analysis of heterogeneity

The Meta-analysis results of FPG, 2hPG, HbA1c, and TCM syndrome score showed heterogeneity among studies included in the indicators. By eliminating the studies one by one and analyzing the remaining studies, the heterogeneity was still large and showed that the results before and after treatment have not changed significantly. According to the subgroup analysis based on the treatment time, the heterogeneity was still large and showed that the results before and after treatment have not changed, thereby suggesting low sensitivity and high stability. The sensitivity analysis results were shown in Fig. 9.

3.7. Publication bias

The results of the Meta-analysis including more than 10 articles were evaluated for the risk of publication bias, total efficiency, FPG, 2hPG. The funnel chart showed that the left and right sides were not completely symmetrical with a skewed distribution. At the same time, the egger's test was performed. Results showed that the total efficiency (t = 7.20, p = 0.00), FPG (t = −3.78, p = 0.001), 2hPG (t = −4.49, p = 0.00) further proves the existence of publication bias, which may be related to the quality of the included literature, the small sample size, or the unpublished negative results. Observe the HbA1c funnel chart and perform egger's test at the same time. HbA1c (t = −0.36, p = 0.725) dots were concentrated on both sides, showing a roughly symmetrical distribution and suggesting that the publication bias of the included literature may be small (Fig. 10).
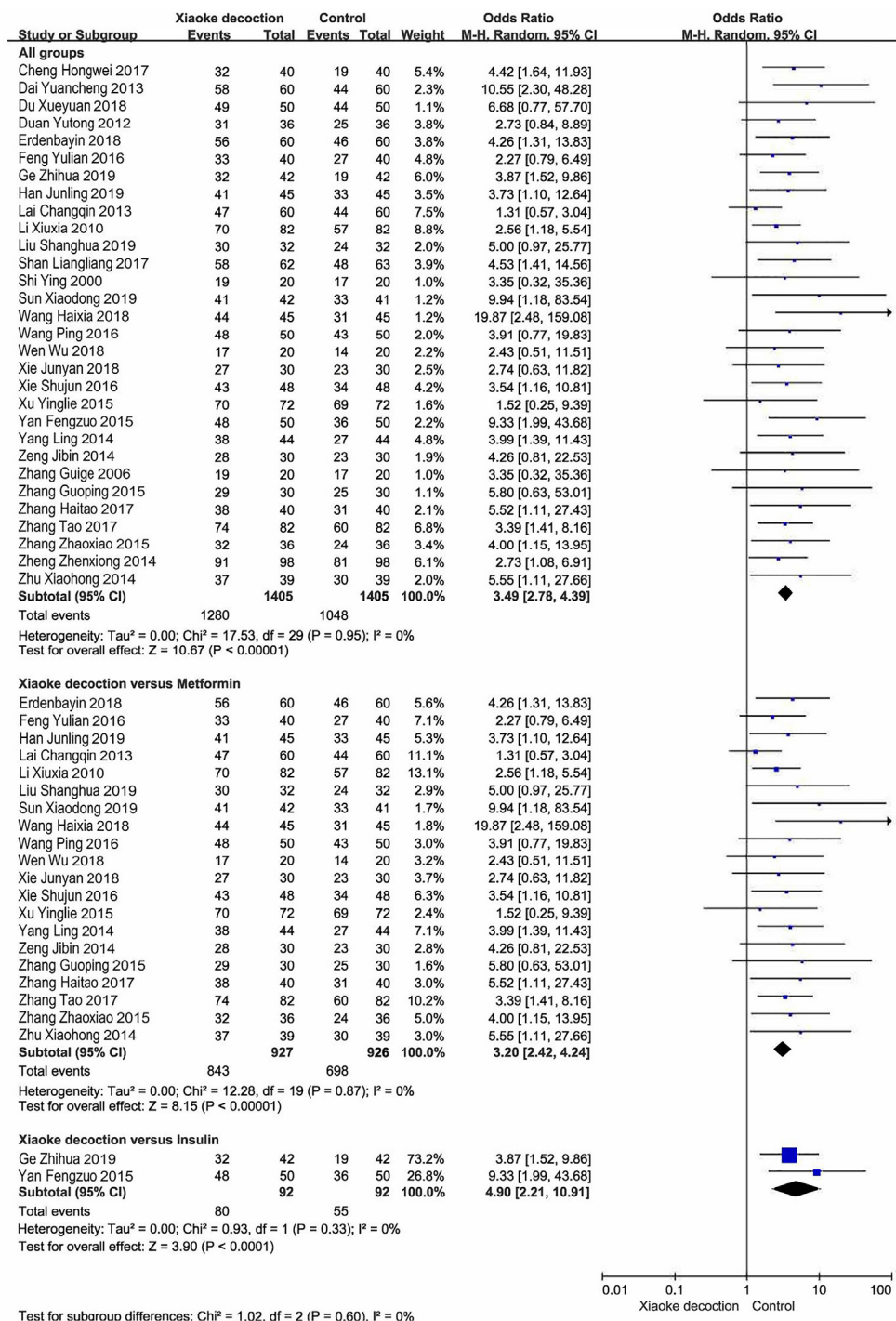
Study or Subgroup	Xiaoke decoction Events	Total	Control Events	Total	Weight	Odds Ratio M-H, Random, 95% CI
All groups						
Cheng Hongwei 2017	32	40	19	40	5.4%	4.42 [1.64, 11.93]
Dai Yuancheng 2013	58	60	44	60	2.3%	10.55 [2.30, 48.28]
Du Xueyuan 2018	49	50	44	50	1.1%	6.68 [0.77, 57.70]
Duan Yutong 2012	31	36	25	36	3.8%	2.73 [0.84, 8.89]
Erdenbayin 2018	56	60	46	60	3.8%	4.26 [1.31, 13.83]
Feng Yulian 2016	33	40	27	40	4.8%	2.27 [0.79, 6.49]
Ge Zhihua 2019	32	42	19	42	6.0%	3.87 [1.52, 9.86]
Han Junling 2019	41	45	33	45	3.5%	3.73 [1.10, 12.64]
Lai Changqin 2013	47	60	44	60	7.5%	1.31 [0.57, 3.04]
Li Xiuxia 2010	70	82	57	82	8.8%	2.56 [1.18, 5.54]
Liu Shanghua 2019	30	32	24	32	2.0%	5.00 [0.97, 25.77]
Shan Liangliang 2017	58	62	48	63	3.9%	4.53 [1.41, 14.56]
Shi Ying 2000	19	20	17	20	1.0%	3.35 [0.32, 35.36]
Sun Xiaodong 2019	41	42	33	41	1.2%	9.94 [1.18, 83.54]
Wang Haixia 2018	44	45	31	45	1.2%	19.87 [2.48, 159.08]
Wang Ping 2016	48	50	43	50	2.0%	3.91 [0.77, 19.83]
Wen Wu 2018	17	20	14	20	2.2%	2.43 [0.51, 11.51]
Xie Junyan 2018	27	30	23	30	2.5%	2.74 [0.63, 11.82]
Xie Shujun 2016	43	48	34	48	4.2%	3.54 [1.16, 10.81]
Xu Yinglie 2015	70	72	69	72	1.6%	1.52 [0.25, 9.39]
Yan Fengzuo 2015	48	50	36	50	2.2%	9.33 [1.99, 43.68]
Yang Ling 2014	38	44	27	44	4.8%	3.99 [1.39, 11.43]
Zeng Jibin 2014	28	30	23	30	1.9%	4.26 [0.81, 22.53]
Zhang Guige 2006	19	20	17	20	1.0%	3.35 [0.32, 35.36]
Zhang Guoping 2015	29	30	25	30	1.1%	5.80 [0.63, 53.01]
Zhang Haitao 2017	38	40	31	40	2.1%	5.52 [1.11, 27.43]
Zhang Tao 2017	74	82	60	82	6.8%	3.39 [1.41, 8.16]
Zhang Zhaoxiao 2015	32	36	24	36	3.4%	4.00 [1.15, 13.95]
Zheng Zhenxiong 2014	91	98	81	98	6.1%	2.73 [1.08, 6.91]
Zhu Xiaohong 2014	37	39	30	39	2.0%	5.55 [1.11, 27.66]
Subtotal (95% CI)		1405		1405	100.0%	3.49 [2.78, 4.39]
Total events	1280		1048			

Heterogeneity: Tau² = 0.00; Chi² = 17.53, df = 29 (P = 0.95); I² = 0%
Test for overall effect: Z = 10.67 (P < 0.00001)

Study or Subgroup	Xiaoke decoction Events	Total	Control Events	Total	Weight	Odds Ratio M-H, Random, 95% CI
Xiaoke decoction versus Metformin						
Erdenbayin 2018	56	60	46	60	5.6%	4.26 [1.31, 13.83]
Feng Yulian 2016	33	40	27	40	7.1%	2.27 [0.79, 6.49]
Han Junling 2019	41	45	33	45	5.3%	3.73 [1.10, 12.64]
Lai Changqin 2013	47	60	44	60	11.1%	1.31 [0.57, 3.04]
Li Xiuxia 2010	70	82	57	82	13.1%	2.56 [1.18, 5.54]
Liu Shanghua 2019	30	32	24	32	2.9%	5.00 [0.97, 25.77]
Sun Xiaodong 2019	41	42	33	41	1.7%	9.94 [1.18, 83.54]
Wang Haixia 2018	44	45	31	45	1.8%	19.87 [2.48, 159.08]
Wang Ping 2016	48	50	43	50	3.0%	3.91 [0.77, 19.83]
Wen Wu 2018	17	20	14	20	3.2%	2.43 [0.51, 11.51]
Xie Junyan 2018	27	30	23	30	3.7%	2.74 [0.63, 11.82]
Xie Shujun 2016	43	48	34	48	6.3%	3.54 [1.16, 10.81]
Xu Yinglie 2015	70	72	69	72	2.4%	1.52 [0.25, 9.39]
Yang Ling 2014	38	44	27	44	7.1%	3.99 [1.39, 11.43]
Zeng Jibin 2014	28	30	23	30	2.8%	4.26 [0.81, 22.53]
Zhang Guoping 2015	29	30	25	30	1.6%	5.80 [0.63, 53.01]
Zhang Haitao 2017	38	40	31	40	3.0%	5.52 [1.11, 27.43]
Zhang Tao 2017	74	82	60	82	10.2%	3.39 [1.41, 8.16]
Zhang Zhaoxiao 2015	32	36	24	36	5.0%	4.00 [1.15, 13.95]
Zhu Xiaohong 2014	37	39	30	39	3.0%	5.55 [1.11, 27.66]
Subtotal (95% CI)		927		926	100.0%	3.20 [2.42, 4.24]
Total events	843		698			

Heterogeneity: Tau² = 0.00; Chi² = 12.28, df = 19 (P = 0.87); I² = 0%
Test for overall effect: Z = 8.15 (P < 0.00001)

Study or Subgroup	Xiaoke decoction Events	Total	Control Events	Total	Weight	Odds Ratio M-H, Random, 95% CI
Xiaoke decoction versus Insulin						
Ge Zhihua 2019	32	42	19	42	73.2%	3.87 [1.52, 9.86]
Yan Fengzuo 2015	48	50	36	50	26.8%	9.33 [1.99, 43.68]
Subtotal (95% CI)		92		92	100.0%	4.90 [2.21, 10.91]
Total events	80		55			

Heterogeneity: Tau² = 0.00; Chi² = 0.93, df = 1 (P = 0.33); I² = 0%
Test for overall effect: Z = 3.90 (P < 0.0001)

Test for subgroup differences: Chi² = 1.02, df = 2 (P = 0.60), I² = 0%

Fig. 4. Meta-analysis forest map of efficacy on total efficiency between Xiaoke Decoction groups and control groups.

4. Discussion

The results of 38 articles included in this study show that, based on conventional western medicine treatment, the clinical efficacy of including Xiaoke Decoction in the treatment of type 2 diabetes yielded results which were significantly better than that of the conventional western medicine group. Compared with the conventional western medicine group, we found that there were significant differences in total efficiency, FPG, 2hPG, HbA1c, and TCM syndrome score. Particularly, when we studied metformin or insulin combined with Xiaoke Decoction, the declines in FPG, 2hPG,

HbA1c were more obvious. Because of the high heterogeneity among the studies, a subgroup analysis was performed. The results showed that the Xiaoke Decoction group can effectively reduce FPG, 2hPG, and HbA1c in different intervention times, but the treatment effect was obvious during the intervention time (4–8 weeks). The effect stabilized at 9–12 weeks. The results of age showed that: Age <50 has a significant effect, possibly due to the increasing age of patients, the reduction in basic functions and overall level of the body to a certain extent, especially the sensitivity of the patients to drugs had decreased. The prevalence of type 2 diabetes has been high in China. In the past 30 years, the
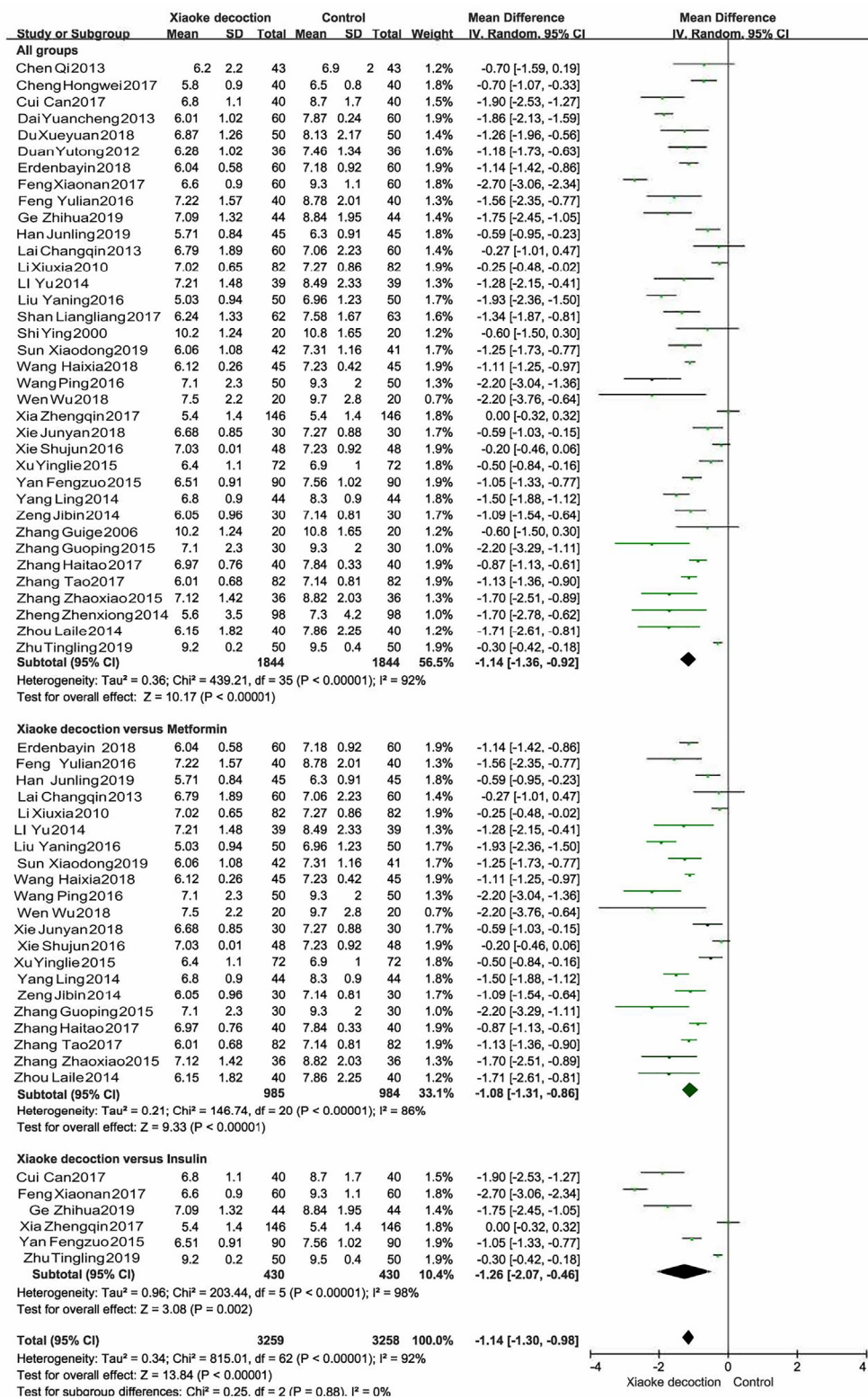
Fig. 5. Meta-analysis forest map of FPG in Xiaoke Decoction groups and control groups of patients.

prevalence of adult diabetes in China has seen a significant increase. Studies showed that the prevalence of adult diabetes in China in 2013 was 10.4% (Chinese Diabetes Society, 2018).

Diabetes belongs to the category of "Xiaoke" in TCM and has a history of thousands of years. TCM believes that the loss of *yin*, body fluids, and internal heat is the main pathogenesis. Among

the 38 documents included in this study, 19 had a clear TCM syndrome type. All of which were *qi* and *yin* deficiency, and *yin* deficiency and internal heat syndrome. Therefore, doctors of the past dynasties believed that the treatment of diabetes should be based on clearing the lungs and moisturizing dryness, nourishing *yin* and promoting fluid, and nourishing the liver and kidneys. Xiaoke
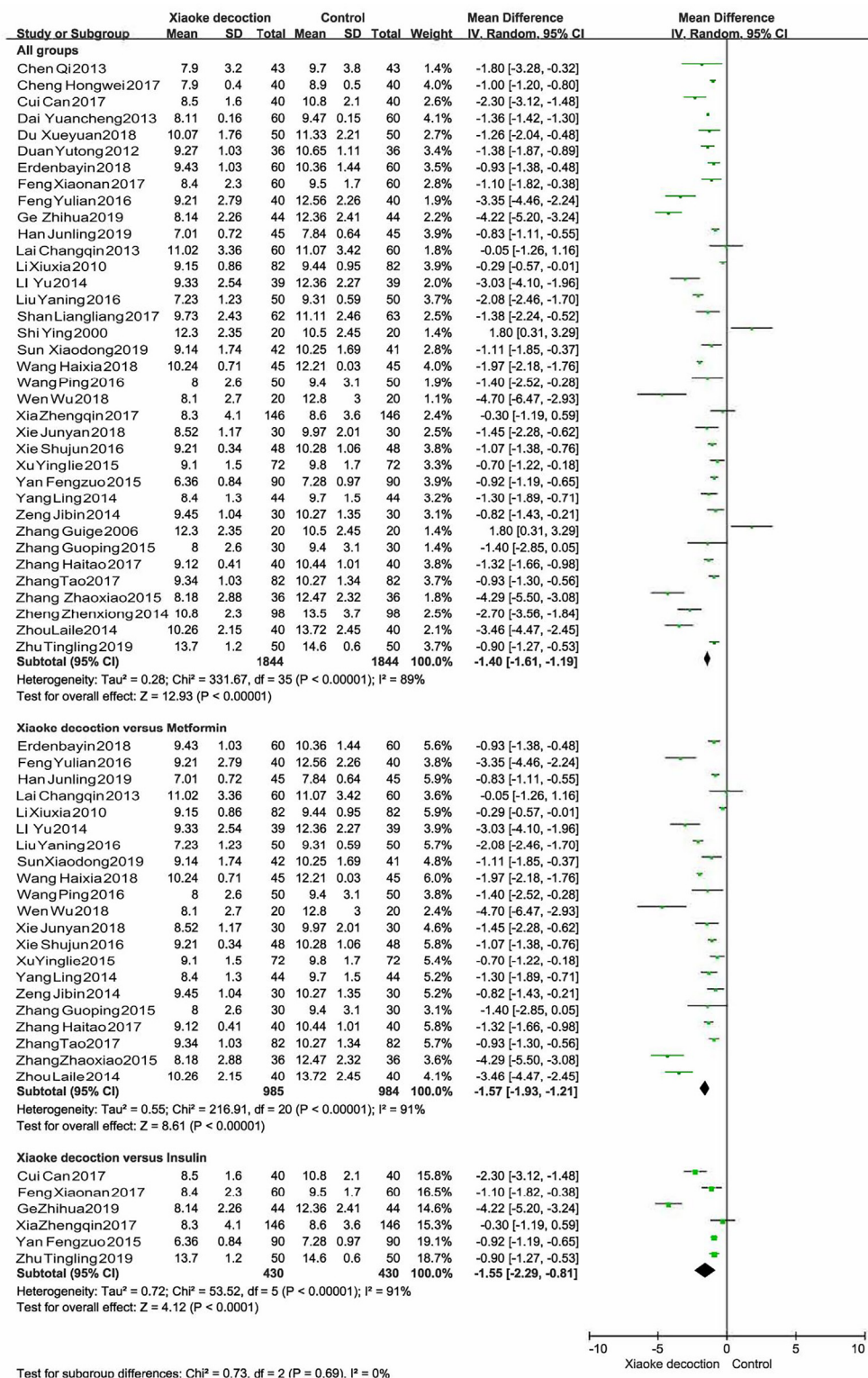
Fig. 6. Meta-analysis forest map of 2hPG in Xiaoke Decoction groups and control groups of patients.

Decoction was first seen in Dan xi Zhu's "Dan Xi Xin Fa" in the Yuan Dynasty. The main medicines were *Coptidis Rhizoma*, *Trichosanthis Radix*, *Lotus Rhizoma*, *Rehmanniae Radix*, *Zingiberis Recens Rhizoma*, Mel among others. *Trichosanthis Radix* can promote body fluid production to quench thirst, clear away heat, and moisturize dryness. It also acts as the main medicine. The bitter cold of *Coptidis Rhizoma* can relieve heart fire. *Lotus Rhizome* and *Rehmanniae Radix* can nourish *yin* and moisturize dryness. All medicines were compatible and used together to nourish *yin*, moisturize dryness, clear heat, and promote fluid. The purpose is to treat diabetes with the basic functions of nourishing yin and clearing heat. Sun Fenghui et al. (Sun, Wang, & Qiu, 2018) believed that both TCM, TCM prescriptions, and proprietary Chinese medicines were effective in treating type 2 diabetes, and that TCM treatment can also be
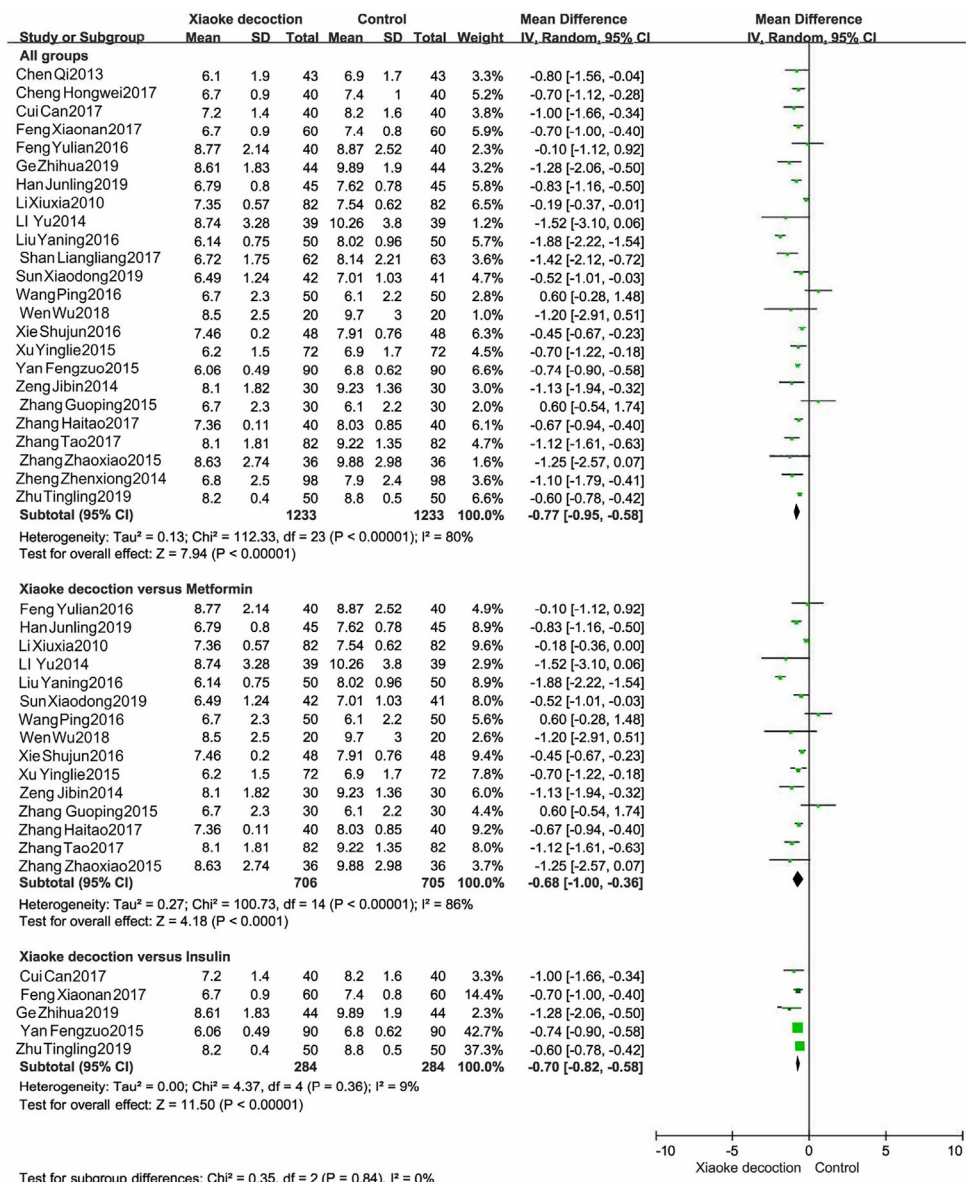
Fig. 7. Meta-analysis forest map of HbAlc in Xiaoke Decoction groups and control groups of patients.
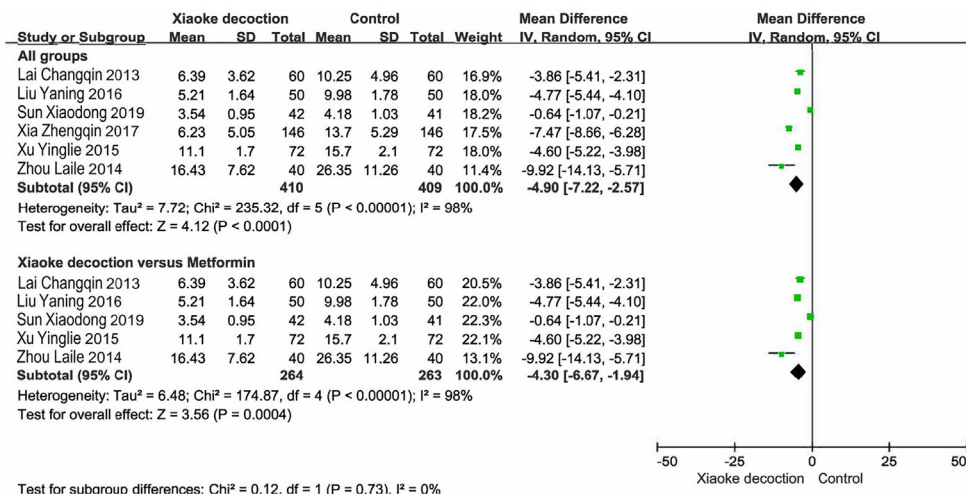
Fig. 8. Meta-analysis forest map of TCM syndrome points in Xiaoke Decoction groups and control groups of patients.

Table 2

Relationship between Xiaoke Decoction and western medicine based on subgroup analysis.

Variables	Xiaoke decoction group (n)/Control group (n)	Pooled SMD	OR	95% CI	Z-value	P- value	I-squared/%
Intervention duration (weeks)							
4–8	732/733	–	3.346	2.478–4.518	7.88	0.000	0.0
9–12	503/502	–	4.069	2.722–6.083	6.84	0.000	0.0
FPG							
4–8	874/875	−1.048	–	−1.366 to 0.729	6.44	0.000	89.7
9–12	535/534	−1.158	–	−1.563 to 0.753	5.60	0.000	89.2
2hPG							
4–8	874/875	−1.597	–	−2.087 to 1.107	6.39	0.000	95.2
9–12	535/534	−0.775	–	−1.017 to 0.532	6.26	0.000	72.1
HbA1c							
4–8	609/608	−0.758	–	−1.041 to 0.475	5.25	0.000	82.3
9–12	475/474	−0.428	–	−0.682 to 0.175	3.31	0.001	72.5
Age							
<50	270/269	–	5.412	3.004–9.749	5.62	0.000	0.0
≥50	1003/1004	–	3.185	2.441–4.155	8.54	0.000	0.0
FPG							
<50	413/412	−1.328	–	−1.851 to 0.804	4.97	0.000	91.2
≥50	1257/1258	−0.884	–	−1.135 to 0.634	6.92	0.000	88.7
2hPG							
<50	413/412	−0.927	–	−1.076 to 0.779	12.26	0.000	90.6
≥50	1257/1258	−0.736	–	−0.820 to 0.652	17.17	0.000	94.0
HbA1c							
<50	284/283	−0.314	–	−0.481–0.146	3.68	0.000	72.3
≥50	775/776	−0.693	–	−0.797 to 0.589	13.10	0.000	81.1
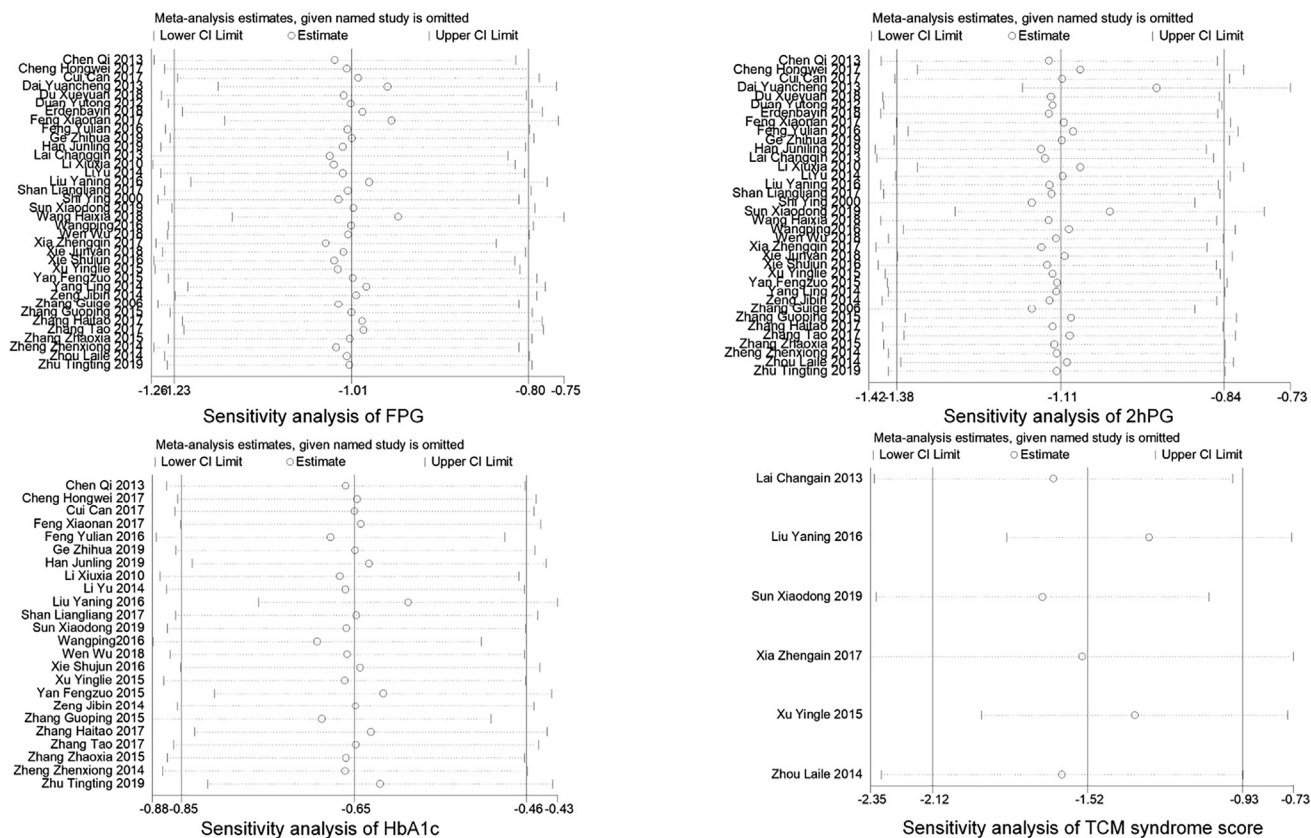
Fig. 9. Sensitivity analysis.

advantageous in treating the complications of diabetes (Qu, Yang, & Ning, 2018). Therefore, there is a need to develop a combination of TCM and western medicine treatment. Combined Chinese and western medical treatment aim to improve patients quality of life, reduce clinical symptoms of patients, and delay the development of type 2 diabetes.

In summary, compared with western medicine alone, Xiaoke Decoction has more advantages for the treatment of type 2
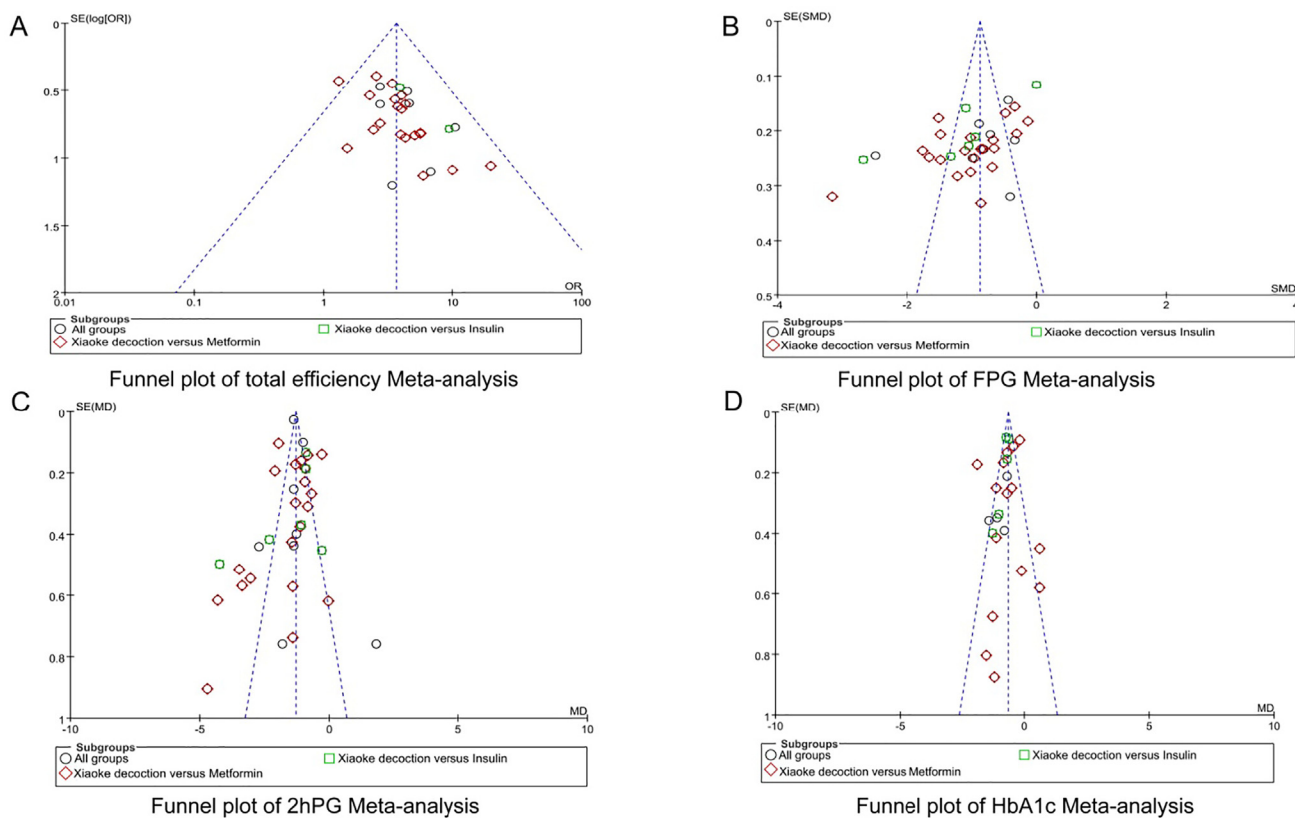
Fig. 10. Funnel plot of Meta-analysis.

diabetes with respect to total efficiency, FPG, 2hPG, HbAlc, and TCM syndrome score. However there are still some gaps in knowledge that need to be clarified. Future potential clinical studies should address the following issues: (a) Inconsistencies or lack of standards regarding patients' oral dose and TCM Xiaoke Decoction active ingredient. The dosage of TCM is very important to achieve the ideal therapeutic effect. Changes often affect the curative effect, pharmacological action, and side effects of TCM. Therefore, standardizing dosage and active ingredient content is the basis to ensure clinical efficacy; (b) In recent years, more studies have shown that type 2 diabetes and obesity were interrelated and influenced each other pathologically (Saadeldeen, Niu, & Wang, 2020). In future studies, the influence of diabetes and obesity should be included in the diagnostic indicators; (c) All the included trials were conducted in China, which means that there was a high risk of bias. The sample size of the included literature was small and the quality of the literature was generally low. Therefore, it is necessary to carry out more high-quality and high-level clinical research; (d) At present, there is a lack of clinical trials on the treatment of type 2 diabetes with Xiaoke Decoction alone as compared with western medicine, thereby making it impossible to reveal whether its curative effect was therapeutic or beneficial. Therefore, clinical trials of Xiaoke Decoction alone should be urgently conducted. If there are studies that can make such comparisons, then people can expect Xiaoke Decoction as an independent treatment.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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