

Efficacy and safety of combination therapy with vildagliptin and metformin vs. metformin monotherapy for Type 2 Diabetes Mellitus therapy: a meta-analysis

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Abstract. – **OBJECTIVE:** The aim is to assess the comparative efficacy and safety of combination therapy with vildagliptin and metformin vs. metformin monotherapy in the treatment of type 2 diabetes mellitus (T2DM).

MATERIALS AND METHODS: We searched on PubMed, Cochrane Library, Web of Science, and Embase databases for randomized controlled trials (RCTs) of combination therapy with vildagliptin and metformin vs. metformin monotherapy in patients with T2DM published up to 30 February 2021. The Cochrane tool and Revman 5.3 software was used to assess the risk of bias and conducted the meta-analysis in the included RCTs. Evidence level was assessed by the Grades of Recommendation, Assessment, Development and Evaluation (GRADE) approach.

RESULTS: A total of 11 RCTs and 8533 patients were included. For the efficacy, we found that combination therapy with vildagliptin and metformin (dose of metformin ≥ 1500 mg/d) had a significantly higher reduction in hemoglobin A1c (HbA1c) [mean differences (MD)= -0.59, 95% CI (-0.28, -0.16), $p < 0.00001$] and fasting plasma glucose (FPG) level [MD= -0.82, 95% CI (-1.09, -0.56), $p < 0.00001$] than combination therapy with vildagliptin and metformin (dose of metformin < 1500 mg/d). Vildagliptin plus metformin as combination therapy reduced body weight loss ratio [MD=0.22, 95% CI (0.17, 0.27), $p < 0.00001$] when compared with metformin monotherapy. In terms of safety, the vildagliptin plus metformin as combination therapy did not increase risk of total adverse events (AEs) [RR=0.98, 95% CI (0.94, 1.02), $p = 0.29$], however there were significant statistical difference and did not increase the risk of diarrhea [RR=0.55, 95% CI (0.40, 0.76), $p = 0.0003$] and Gastrointestinal (GI) disorders [RR=0.72, 95% CI (0.58, 0.91), $p = 0.006$], but significantly increased risk of dizziness [RR=1.41, 95% CI (1.06, 1.88), $p = 0.02$] when compared with metformin monotherapy.

CONCLUSIONS: Compared with metformin, vildagliptin combined with metformin could significantly reduce FPG, HbA1c and body weight. When the dose of metformin in the combination group of vildagliptin and metformin is ≥ 1500 mg/d, the results showed significant reduction in HbA1c and FPG. In addition, it had no risk of increase in total AEs, diarrhea, and GI disorders, but had significant risk of increase in dizziness. GRADE showed that the quality of evidence had high certainty in FPG and moderate certainty in HbA1c, body weight and all AEs.

Key Words:

Vildagliptin, Meta-analysis, Metformin, Type 2 diabetes mellitus.

Introduction

T2DM is a chronic and progressive disease, increasing rapidly in its incidence and prevalence, presenting a major challenge to health care worldwide. It was estimated by the International Diabetes Federation (IDF) that there were 366 million people with diabetes in 2011. By 2030 the number will rise to 552 million all over the world¹, among which 90% of these patients may have type 2 diabetes.

Current guidelines recommend a stepwise treatment approach, including initial lifestyle modification followed by monotherapy such as standard first-line metformin, and when that fails, combination therapy follows²⁻⁵. Metformin reduces hepatic glucose production, improves metabolic variables, and thereby, reduces macrovascular complications^{6,7}. It is also safe and well tolerated. Although dose escalation of monotherapy could improve glycemic control,

dose-dependent adverse events (AEs), such as GI disorders often lead to poor patient compliance and possibly treatment termination⁸. Such limitations have led to the use of early combination therapy to achieve better glycemic control by acting on different pathological T2DM-related pathways, to lower the required dose of monotherapy, and to reduce AEs and improve tolerability^{4,8}.

Vildagliptin is a highly selective, reversible, and competitive dipeptidyl peptidase-4 (DPP-4) inhibitor. Since 2009, the American Society for Clinical Endocrinology released the diabetes control guidelines^{9,10} which indicate DPP-4 inhibitors as first-line drugs for type 2 diabetes. DPP-4 inhibitors increase circulating levels of the biological active, intact glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP) by inhibiting GLP-1/GIP degrading DPP-4, and thereby, improve pancreatic α - and β -cell sensitivity to glucose and also suppress glucagon release¹¹⁻¹⁴. DPP-4 inhibitors thus complement the action of metformin that decreases hepatic glucose production without improving insulin secretion^{12,13}. Vildagliptin (LAF237) is a member of the DPP-4 inhibitor family. The choice of exploring the combination of a dipeptidyl peptidase-4 inhibitor with metformin is supported by glucose-dependent β -cell stimulation by vildagliptin¹⁵ and concomitant insulin sensitization by metformin¹⁶, as well as the established favorable safety profile of both drugs^{15,17}.

In addition, according to the guidelines, if the clinical effect of applying metformin or thiazolidinediones is not favorable, DPP-4 inhibitors may be used in combination to support the therapy. According to the 2020 ADA guidelines, although there are numerous trials comparing dual therapy with metformin alone, there is little evidence to support one combination over another. Through clinical research, it has been shown that the combination of vildagliptin and metformin has a synergistic effect, enhances the efficacy and also has very low adverse reactions. But there is still a lack of evidence support in evidence-based medicine. Although there had been some RCT trials, there was a lack of higher-level evidence. Therefore, we conducted a meta-analysis which aims to provide an up-to-date and systematic assessment, as well as a comprehensive picture of the clinical efficacy and safety of combination therapy with vildagliptin and metformin vs. metformin monotherapy in the treatment of type 2 diabetes mellitus (T2DM).

Materials and Methods

Search Strategy

Search databases, such as PubMed, Web of Science, Embase and Cochrane Library were comprehensively searched for RCTs based on the following search terms: 'vildagliptin', 'metformin' and 'type 2 diabetes mellitus'. References of the included studies were searched to find additional papers. The last search was conducted on 30 February 2021 and there were no language restrictions. Detailed information on the search strategy was reported in (Supplementary Table I and Table II).

Two investigators (Y.D. and F.D.) independently searched for papers, reviewed abstracts of cited studies to determine the relevance. Articles were further considered and judged the relevance by one reviewer or two reviewers. Differences were identified and resolved to reach consistency, if needed, with a third reviewer. If there were many reports from the same trial, the most complete and recent data were chosen. This study is registered on PROSPERO (CRD42021244438) and conducted according to the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines.

Selection Criteria

The inclusion criteria were as follows: (1) the RCTs research on combination therapy with vildagliptin and metformin vs. metformin monotherapy for T2DM; (2) the trial enrolled individuals aged 18-78 years with T2DM; (3) body-mass index (BMI) of 22-40; (4) combination therapy with vildagliptin and metformin vs. metformin monotherapy in the experiment and control group as intervening methods.

The exclusion criteria were as follows: (1) patients enrolled by a clinical diagnosis of type 1 diabetes; ongoing congestive heart failure (New York Heart Association Functional Classification III-IV); any type of malignancy; liver and kidney damage; pregnant women and nursing; (2) studies not comparing combination therapy with vildagliptin and metformin vs. metformin monotherapy in T2DM; (3) incomplete or repeatedly reported data.

To evaluate the risk of bias of the included trials, the Cochrane risk of bias tool was used to assess the methodological quality of the qualified trials¹⁸. If randomization, allocation concealment, blinding of participants, personnel and outcome assessors were judged to be adequate, trials were

decided to be low risk of bias, otherwise, moderate or high risk of bias.

Data Extraction

Potentially qualified articles were extracted by two independently reviewed investigators (Y.D. and F.D.), resolving differences by consensus with the corresponding authors. The data of each study was extracted and counted in the main outcome indicators (reduction of HbA1c, FPG and body weight), and the related adverse events were collected. The main studies and **Supplementary Materials** were examined and cross-checked, and any discrepancy was discussed. We gathered all the data agreement analysis to reach consistency and summarized the clinical characteristics of each study.

Study Quality Assessment

According to the assessment criteria of Cochrane Risk of Bias tool for RCTs. We conducted an assessment by Begg's funnel plot for publication bias. The level of evidence by using the Grades of Recommendation, Assessment, Development and Evaluation (GRADE) approach was evaluated¹⁹. The GRADE profiler version 3.6 software was used to create the evidence profile, including high, moderate, low and very low qualities.

Statistical Analysis

For efficacy indicators, the mean changes of continuous variables were evaluated in HbA1c, FPG and body weight as well as weighted mean differences (MD) and 95% confidence interval (CI) were calculated for changes from baseline in these continuous variables. For safety indicators, the dichotomous variables (AEs) were evaluated by risk ratio (RR) with 95% CI.

Statistical heterogeneity was evaluated by the Q statistic and I^2 tests in the trial. The significance of the Q statistical test ($p < 0.05$) indicates that there is a considerable level of heterogeneity²⁰. The I^2 statistics show that the percentage of the estimated influence of variation is a heterogeneous result, not a sampling error. $I^2 > 50\%$ and Chi-squared test $p < 0.1$ reveal significant heterogeneity. Due to statistical heterogeneity in some analysis, random effects models were used. Subgroup analysis was performed to assess the potential confounding effect of heterogeneity, and stratified for drug dose, tests characteristics, data from a particular population²¹.

All the above specified analysis was conducted by RevMan 5.3; Copenhagen: The Nordic

Cochrane Centre, The Cochrane Collaboration, 2014.

Results

Study Characteristics

A total of 840 articles were searched. Then, 27 articles were included by screening. 16 articles were excluded based on reading the full text. Finally, 11 RCTs²²⁻³² were included for meta-analysis (Figure 1). The pooled analysis included 8533 patients. It was satisfactory in the overall quality of trials for all items of the Cochrane tool. Detailed graph and summary of risk of bias was reported in Figure 1A. Details of the included studies, basic characteristics of the enrolled patients, and drug treatment were provided in Table I.

Efficacy

Compared with the metformin monotherapy, the results of meta-analysis showed that the vildagliptin plus metformin as combination therapy was associated with higher reduction in HbA1c level [MD=-0.68, 95% CI (-1.05, -0.31), $p=0.0003$, but with a substantial amount of heterogeneity ($I^2=97\%$); Figure 2]. Therefore, a subgroup analysis was further performed based on dose of (experiment group) metformin. As shown in Figure 3, we found that combination therapy with vildagliptin and metformin (dose of metformin ≥ 1500 mg/d) had a significantly higher reduction in HbA1c level [MD= -0.59, 95% CI (-0.28-0.16), $p < 0.00001$]. In contrast, combination therapy with vildagliptin and metformin (dose of metformin < 1500 mg/d) had a lower reduction in HbA1c level [MD= -0.12, 95% CI (-0.19, -0.05), $p=0.0005$].

Besides, we found that the combination of vildagliptin and metformin had significant higher reduction in FPG level [MD= -0.84, 95% CI (-1.08-0.59), $p < 0.00001$; Figure 4], but lowered body weight loss [MD=0.22, 95% CI (0.17, 0.27), $p < 0.00001$; Figure 5] when compared with the metformin monotherapy. To explore the effect of dosage of metformin on FPG, we performed a subgroup analysis based on dose of (experiment group) metformin. As shown in Figure 6, we found that combination therapy with vildagliptin and metformin (dose of metformin ≥ 1500 mg/d) significantly reduced in FPG level [MD= -0.82, 95% CI (-1.09-0.56), $p < 0.00001$]. However, combination therapy with vildagliptin and metformin (dose of metformin < 1500 mg/d) had no signif-

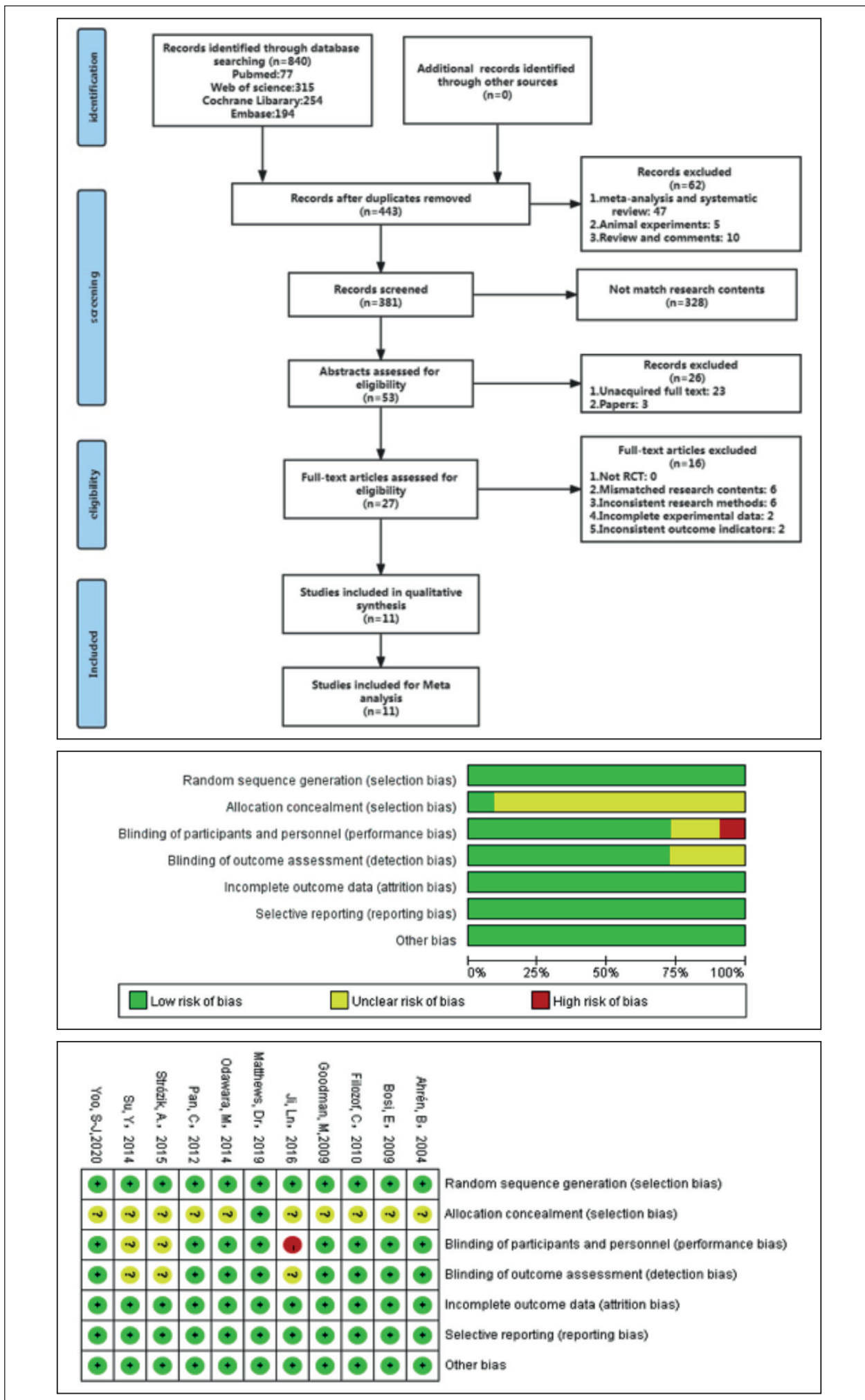


Figure 1. A, Flow diagram of the study selection process. **B**, Risk of bias graph and summary: review authors' judgements about each risk of bias item presented as percentages across all included studies.

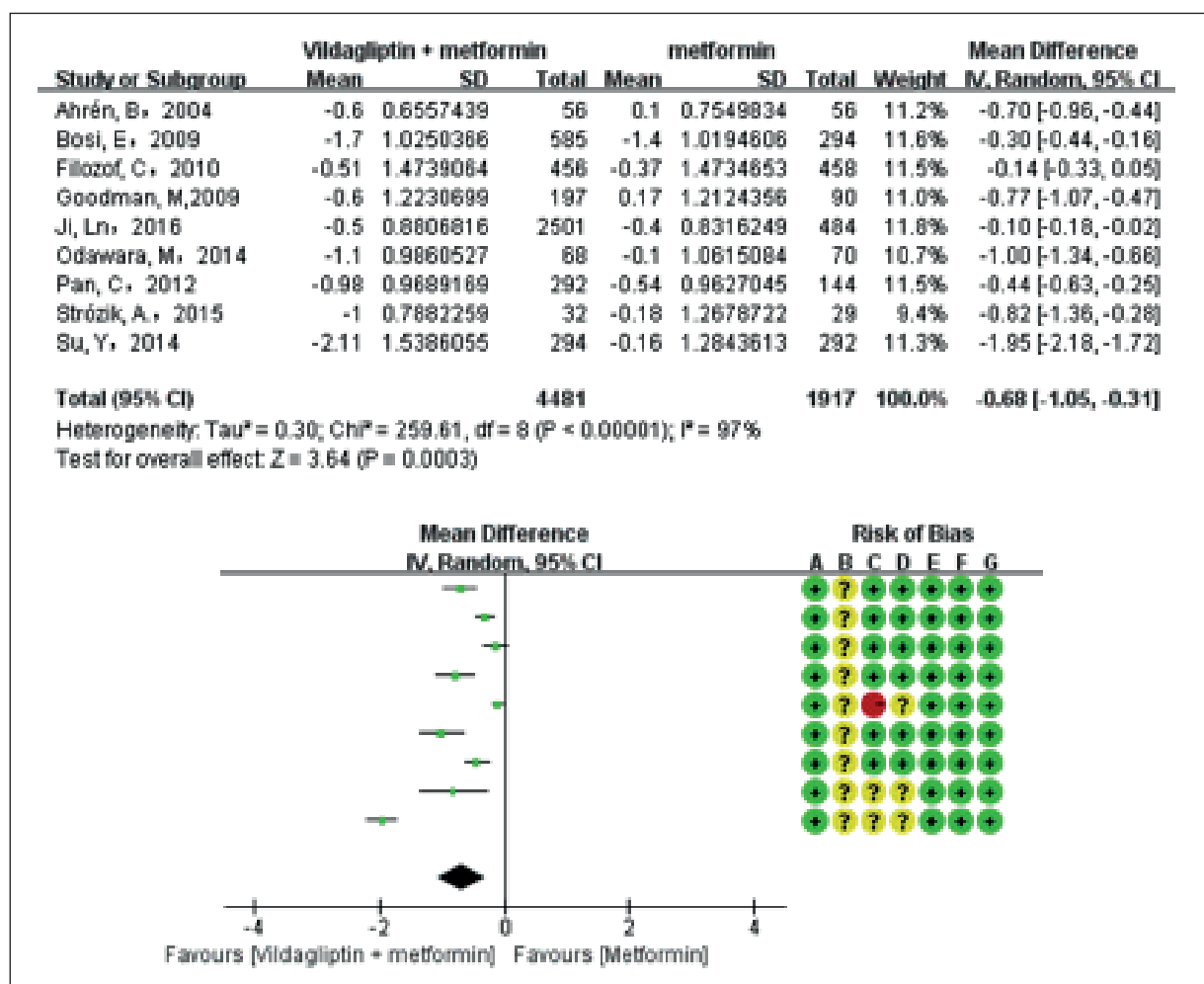


Figure 2. Forest plot of the efficacy of vildagliptin combined with metformin vs. metformin monotherapy on the level of HbA1c in T2DM patients (difference from baseline mean). 95% CI: 95% confidence interval. Weight%: weight coefficient.

icant difference in lower reduction in FPG level [MD=-0.21, 95%CI (-0.55,0.12), *p*=0.22] when compared with the metformin monotherapy. No publication bias was detected at visual analysis of the Funnel plot (Supplementary Figure 1A-C).

Safety

The meta-analysis for AEs showed that the vildagliptin plus metformin as combination therapy had no significant difference for increasing the incidence of AEs [RR=0.98, 95% CI (0.94,1.02), *p*=0.29], the vildagliptin plus metformin as combination therapy did not increase risk of total adverse events (AEs) [RR=0.98, 95% CI (0.94,1.02), *p*=0.29], however, there were significant statistical difference and did not increased the risk of diarrhea [RR=0.55, 95% CI (0.40, 0.76), *p*=0.0003] and Gastrointestinal (GI) disorders [RR=0.72, 95% CI (0.58, 0.91),

p=0.006], but significantly increased risk of dizziness [RR=1.41, 95% CI (1.06, 1.88), *p*=0.02] when compared with metformin monotherapy. The details were shown in Figure 7.

As presented in Figure 7, we found that the combination of vildagliptin and metformin had no significant statistical difference in the risk of the following events compared with metformin monotherapy. The vildagliptin plus metformin as combination therapy had no increased risk of Back pain [RR=0.68, 95% CI (0.41, 1.13), *p*=0.14], fatigue [RR=0.69, 95% CI (0.38, 1.26), *p*=0.23], metabolism and nutrition disorders [RR=0.73, 95% CI (0.50, 1.04), *p*=0.08], pain in extremity [RR=0.77, 95% CI (0.42, 1.41), *p*=0.40], hypertension [RR=0.80, 95% CI (0.64, 1.00), *p*=0.05], upper respiratory tract infection [RR=0.81, 95% CI (0.49, 1.36), *p*=0.42], and renal and urinary disorders [RR=0.84, 95% CI (0.36, 1.98),

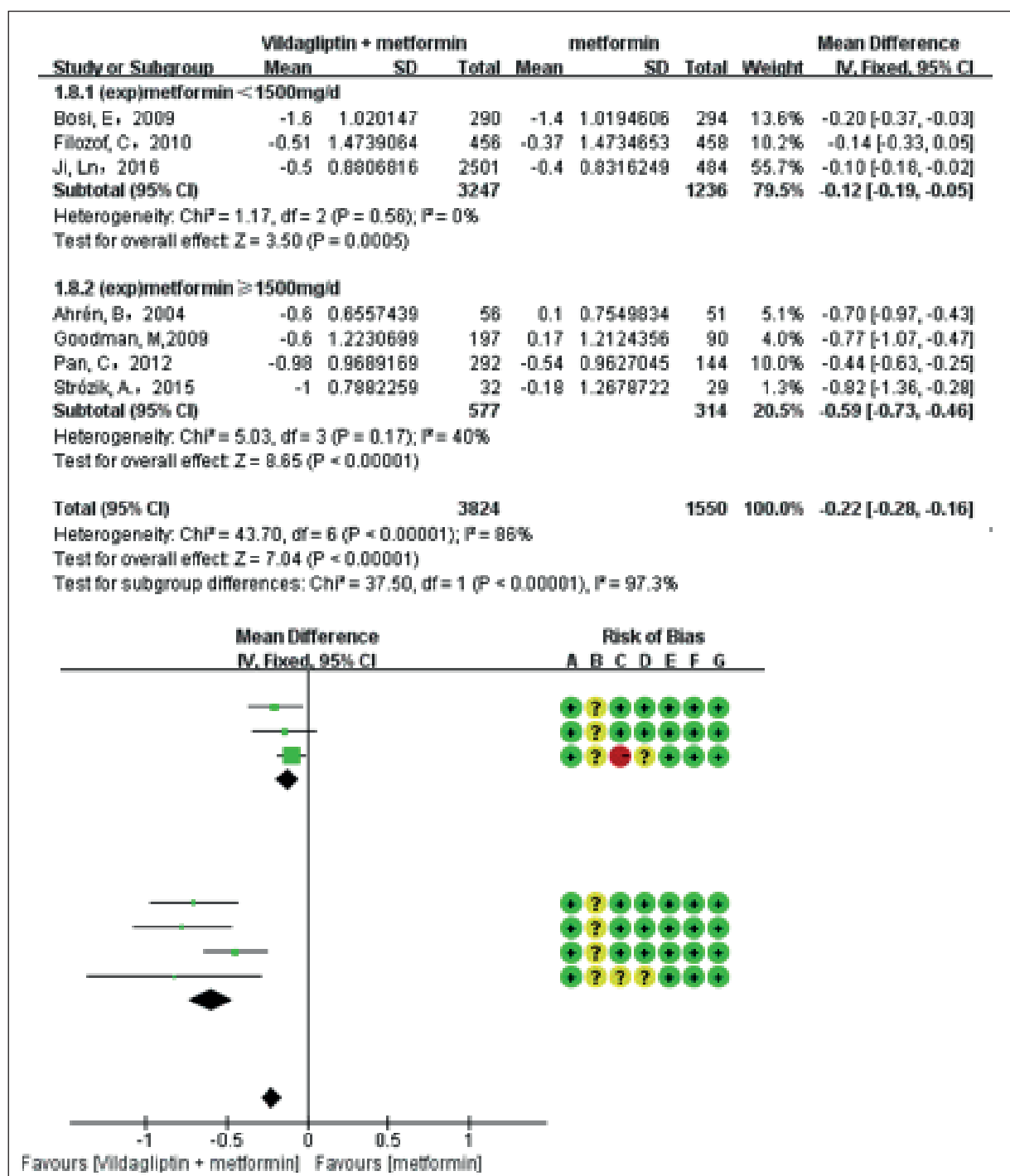


Figure 3. Forest plot of the efficacy of vildagliptin combined with metformin (dose of metformin <1500 mg/d and ≥1500 mg/d) vs. metformin monotherapy on the level of HbA1c in T2DM patients (difference from baseline mean). 95% CI: 95% confidence interval. Weight%: weight coefficient.

$p=0.69$], serious adverse event (SAEs) [RR=0.91, 95% CI (0.76, 1.10), $p=0.34$], hypoglycemia events [RR=0.96, 95% CI (0.55, 1.69), $p=0.89$] and cough [RR=0.98, 95% CI (0.65, 1.46), $p=0.91$] when compared with metformin mono-

therapy. However, the combination of vildagliptin and metformin was not associated with the risk of headache [RR=1.00, 95% CI (0.79, 1.27), $p=1.00$] compared with metformin monotherapy. Besides, we also concluded that combination ther-

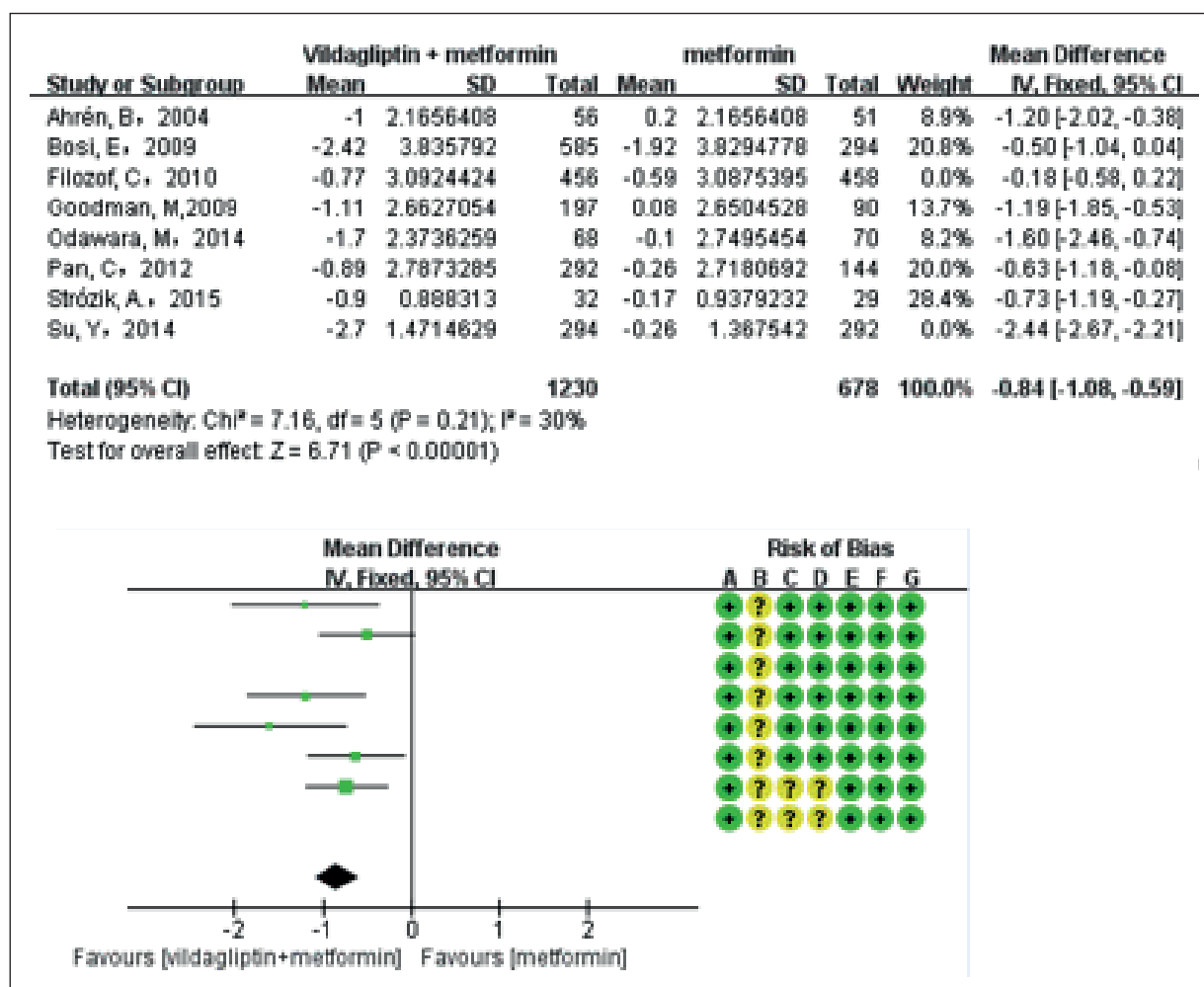


Figure 4. Forest plot of the efficacy of vildagliptin combined with metformin vs. metformin monotherapy on the level of FPG in T2DM patients (difference from baseline mean). 95% CI: 95% confidence interval. Weight%: weight coefficient.

apy with vildagliptin and metformin had slightly higher risk of nasopharyngitis [RR=1.01, 95% CI (0.82, 1.24), *p*=0.95], infections and infestations [RR=1.03, 95% CI (0.72, 1.47), *p*=0.89], Nausea [RR=1.07, 95% CI (0.77, 1.49), *p*=0.69], arthralgia [RR=1.10, 95% CI (0.85, 1.42), *p*=0.48], benign, malignant, and unspecified neoplasms (including cysts and polyps) [RR=1.12, 95% CI (0.79, 1.59), *p*=0.52] and hepatobiliary disorders [RR=1.27, 95% CI (0.55, 2.91), *p*=0.57], but significant higher risk of vomiting [RR=1.60, 95% CI (0.59, 4.33), *p*=0.36] when compared with metformin monotherapy. No publication bias was detected at visual analysis of the Funnel plot (**Supplementary Figure 1D**).

Quality of Evidence

The results of GRADE for HbA1c, FPG, body weight and AEs showed that FPG was supported

by high certainty of evidence and there was moderate certainty of evidence in HbA1c, body weight and AEs (all related adverse events). Table II also showed the GRADE summary of findings to illustrate absolute effects based on the risk of HbA1c, FPG, body weight and AEs between vildagliptin plus metformin as combination therapy and metformin monotherapy.

Vildagliptin plus metformin as combination therapy lowered the risk of AEs to a certain extent in anticipated absolute effects compared with metformin monotherapy; 11, 38 and 36 fewer per 1000 for Total AEs, diarrhea and GI disorders respectively; 1 and 15 more for nasopharyngitis and dizziness respectively; 0, 0 and 16 fewer per 1000 for very hypoglycemia events, headache and hypertension respectively; 2 and 7 more for Nausea and vomiting respectively; 1, 10, 12, 5 and 2 fewer per 1000 for Cough, fa-

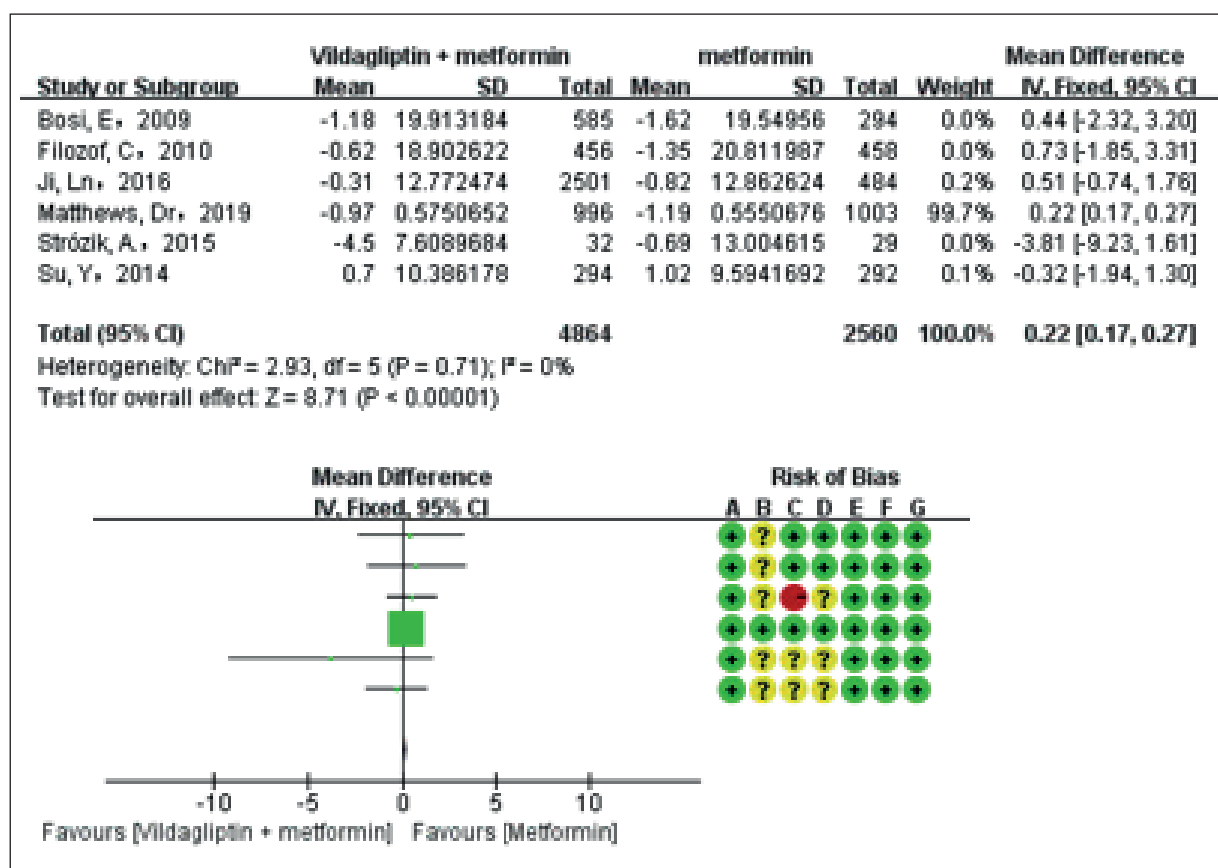


Figure 5. Forest plot of the efficacy of vildagliptin combined with metformin vs. metformin monotherapy on the level of Body weight in T2DM patients (difference from baseline mean). 95% CI: 95% confidence interval. Weight%: weight coefficient.

tigue, Back pain, Pain in extremity and Renal and urinary disorders respectively; 7 and 4 more for arthralgia and hepatobiliary disorders respectively; 10, 19 and 5 fewer per 1000 for SAEs, metabolism and nutrition disorders and upper respiratory tract infection respectively; 2 more for Infections and infestations (moderate certainty; Table II).

Discussion

This meta-analysis compared the combination of vildagliptin and metformin with metformin monotherapy in T2DM. When the dose of metformin in the combination group of vildagliptin and metformin is ≥ 1500 mg/d, the results showed significantly greater reduction in HbA1c and FPG, but lower reduction in the combination group (the dose of metformin < 1500 mg/d) than metformin monotherapy. This showed that the dose of metformin will

affect the reduction of HbA1c and FPG. The combination of vildagliptin and metformin had lower reduction in body weight than metformin monotherapy. In summary, the vildagliptin plus metformin as combination therapy had more significant reduction in FPG than metformin monotherapy. Therefore, applying vildagliptin was an effective treatment for T2DM when added to the treatment with metformin for patients not sufficiently controlled under metformin monotherapy.

Regarding safety, compared with metformin monotherapy, vildagliptin combined with metformin did not affect the incidence of total AEs and any hypoglycemic events. The main side effect of metformin was gastrointestinal reaction, including nausea, vomiting and diarrhea. Our analysis showed that the combination of vildagliptin and metformin did not increase the risk of gastrointestinal-related AEs, such as nausea and vomiting, and did not significantly affect the risk of diarrhea and GI disorders, but signifi-

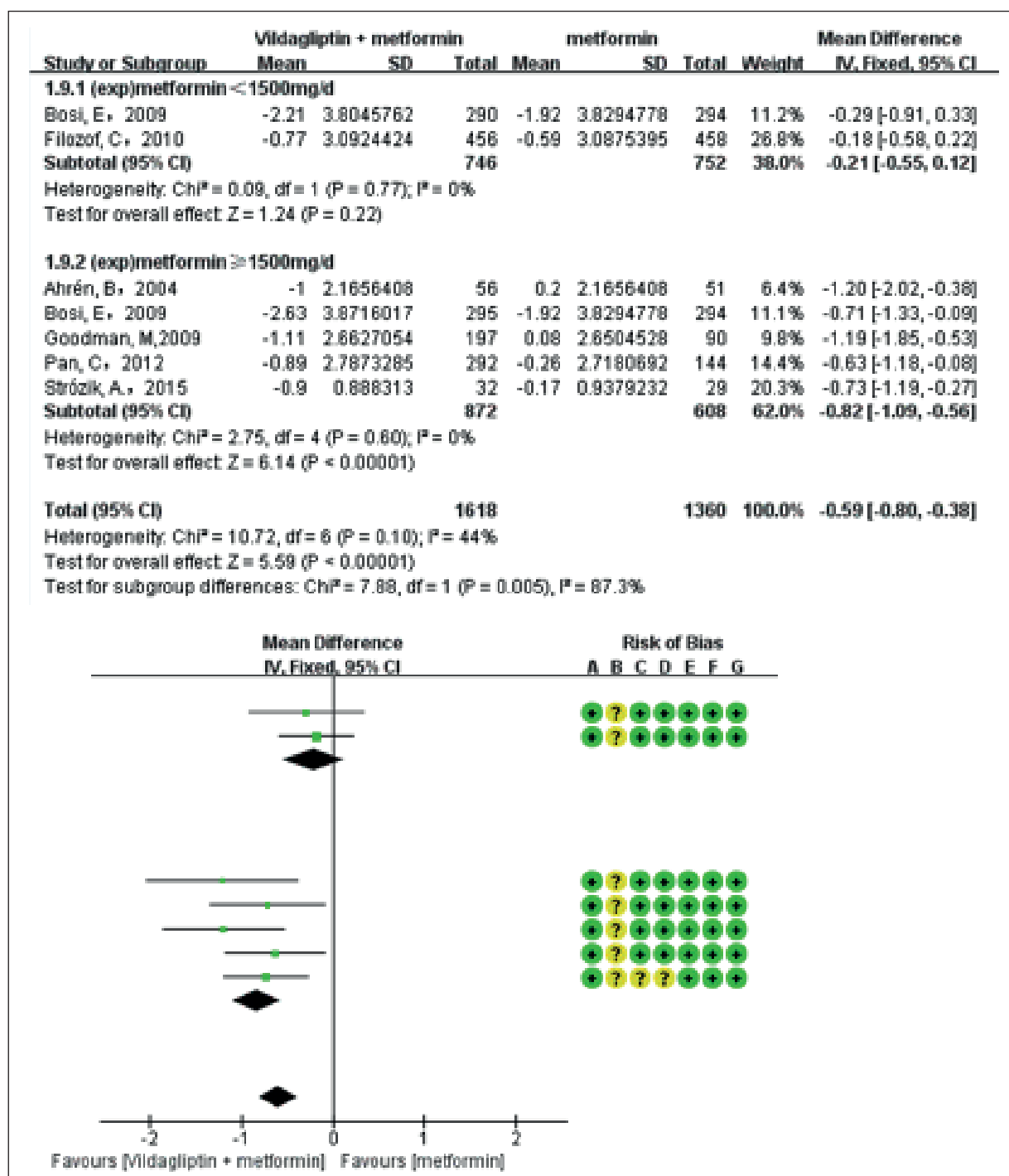


Figure 6. Forest plot of the efficacy of vildagliptin combined with metformin(dose of metformin<1500 mg/d and ≥1500 mg/d) vs. metformin monotherapy on the level of FPG in T2DM patients (difference from baseline mean). 95% CI: 95% confidence interval. Weight%: weight coefficient.

cantly increased the risk of dizziness. The most common adverse reactions of vildagliptin were headache, nasopharyngitis and cough³³, however our results showed that vildagliptin combined with metformin had no increase in the incidence

of headache, nasopharyngitis and cough. Moreover, compared with metformin monotherapy, vildagliptin combined with metformin neither increased the incidence of back pain, pain in extremity, hypertension, renal and urinary dis-

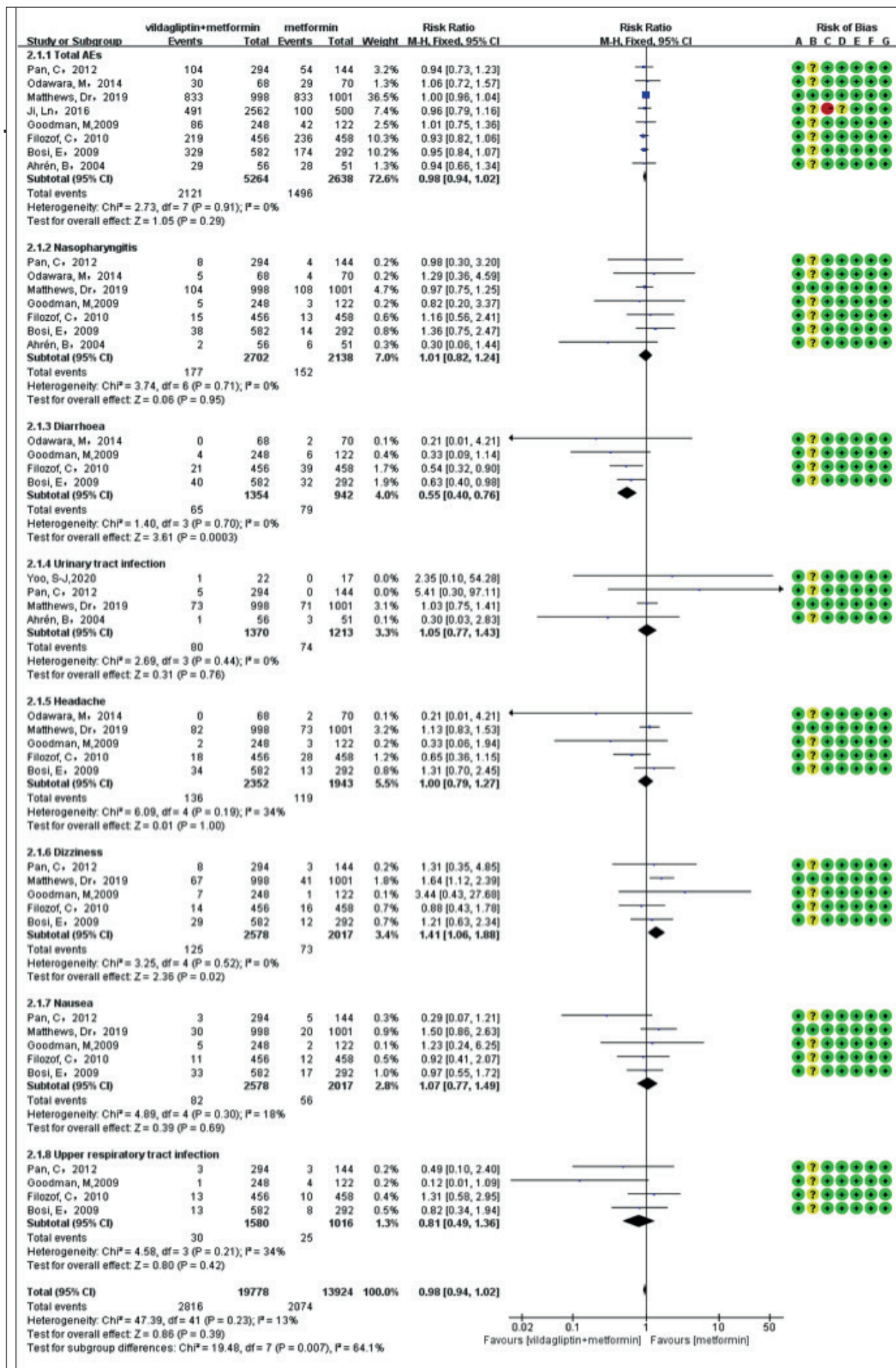


Figure 7. Meta-analysis of safety between vildagliptin plus metformin as combination therapy and metformin monotherapy. 95% CI: 95% confidence interval. Weight%: weight coefficient.

Figure continued

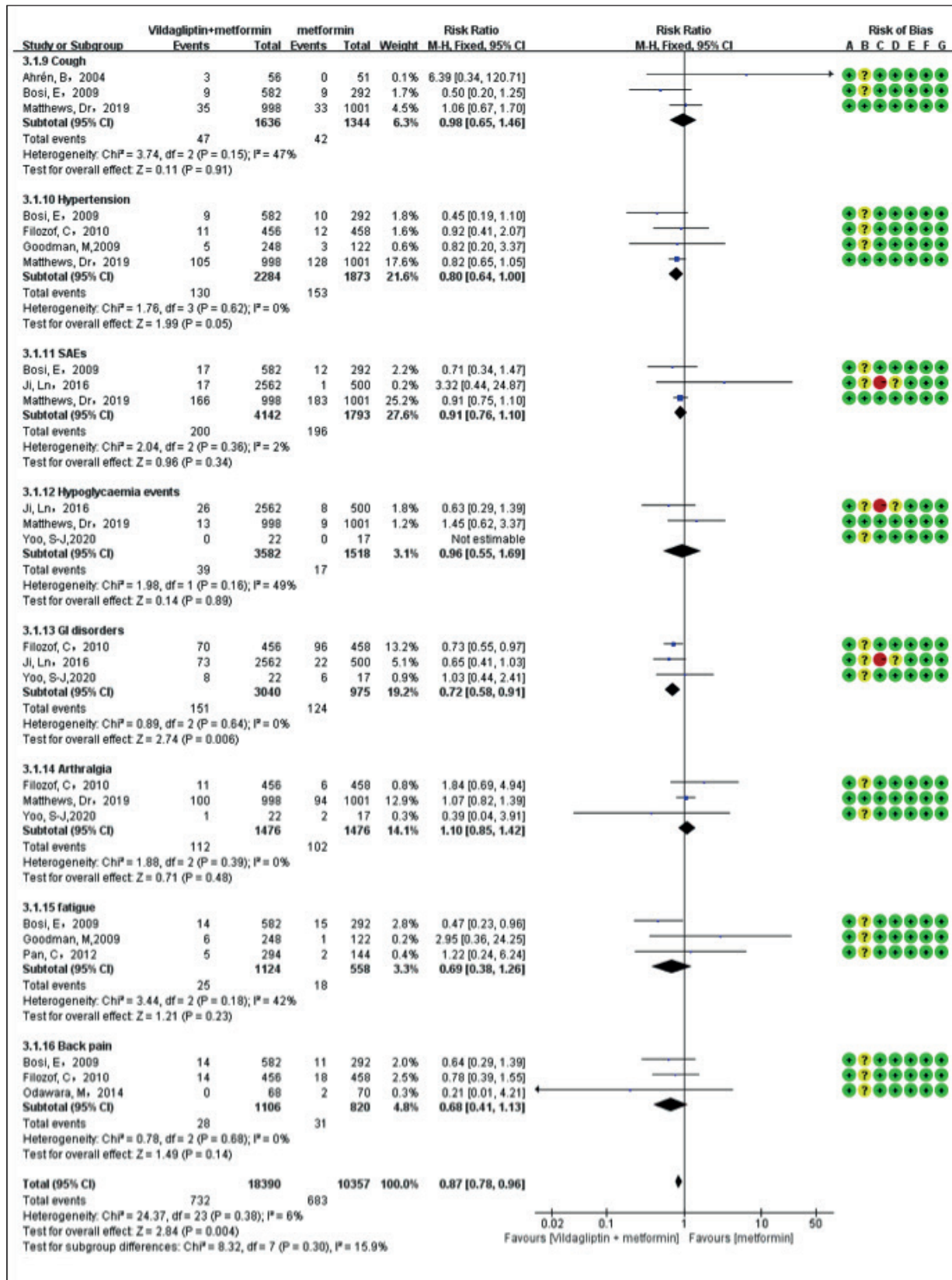


Figure 7. Meta-analysis of safety between vildagliptin plus metformin as combination therapy and metformin monotherapy. 95% CI: 95% confidence interval. Weight%: weight coefficient.

Figure continued

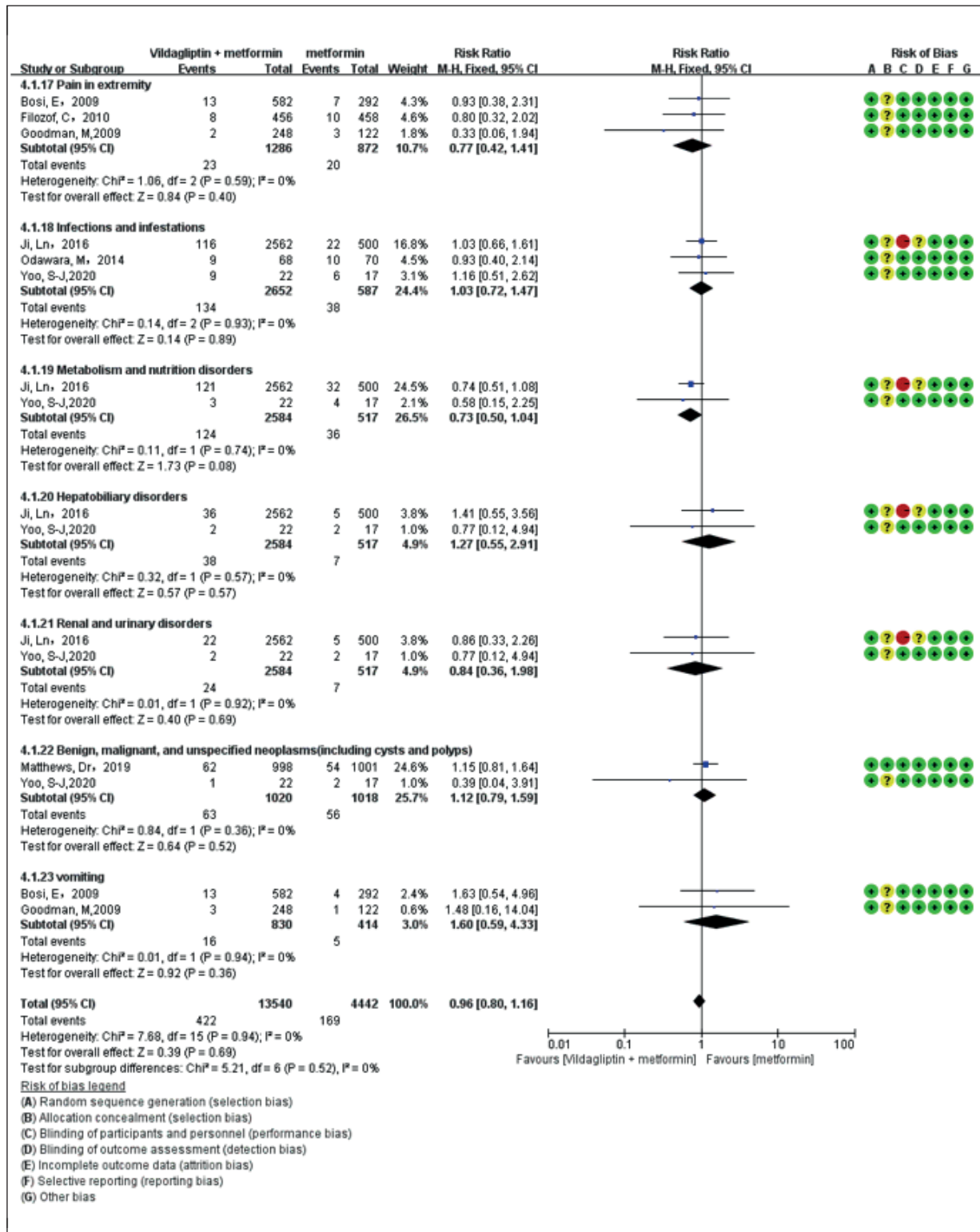


Figure 7. Meta-analysis of safety between vildagliptin plus metformin as combination therapy and metformin monotherapy. 95% CI: 95% confidence interval. Weight%: weight coefficient.

Table I. Basic characteristics of included studies.

Study	Mean age (years)	Male	Mean BMI	Duration of T2DM mean (Y/M)	VILD plus MET combination therapy daily dose and frequency	MET monotherapy daily dose and frequency	Study Duration (weeks)	Study size
Matthews et al ²² 2019	54	47%	31	3.3M	VILD 50 mg bid + MET 1000/1500/2000 mg/d	MET 1000/1500/2000 mg/d	240	2001
Ahrén et al ²³ 2004	56	68%	29	5.3Y	VILD 50 mg qd + MET 1500-3000 mg/d	MET 1500-3000 mg/d	48	107
Yoo et al ²⁴ 2020	53	51%	26	3.5M	VILD 50 mg bid + MET 1000/1500/2000 mg/d	MET 1000/1500/2000 mg/d	240	39
Ji et al ²⁵ 2016	56	52%	25	4.2Y	VILD 50 mg bid + MET 500 mg bid	MET 1000 mg bid	24	2985
Su et al ²⁶ 2014	48	54%	—	—	—	—	24	600
Bosi et al ²⁷ 2009	52	58%	31	24.3M	VILD 50 mg bid + MET 500 mg bid/1000 mg bid	MET 1000 mg bid	24	879
Pan et al ²⁸ 2012	53	52%	25	4.9Y	VILD 50 mg qd/50 mg bid + MET \geq 1500 mg/d	MET \geq 1500 mg/d	24	438
Strózik et al ²⁹ 2015	51	62%	30	—	VILD 100 mg/d + MET 1500/3000 mg/d	MET 1500/3000 mg/d	12	61
Odawara et al ³⁰ 2014	58	66%	25	7.1Y	VILD 50 mg bid + MET 250 mg bid/500 mg bid	MET 250 mg bid/500 mg bid	12	139
Goodman et al ³¹ 2009	54	56%	31	—	VILD 100 mg am/100 mg pm + MET \geq 1500 mg/d	MET \geq 1500 mg/d	24	370
Filozof et al ³² 2010	56	47%	31	4.6Y	VILD 100 mg qd + MET 500 mg bid	MET 1000 mg bid	24	914

orders, urinary tract infection and hepatobiliary disorders and arthralgia, nor increased the risk of fatigue, upper respiratory tract infection, metabolism and nutrition disorders, infections and infestations, SAEs as well as benign, malignant, and unspecified neoplasms (including cysts and polyps).

Thus, our study suggested that vildagliptin can collaborate metformin to perform better regulation of blood glucose and seem to be with good tolerance. When the dose of metformin in the combination group of vildagliptin and metformin is \geq 1500 mg/d, the results showed significantly greater reduction in HbA1c and FPG than combination therapy with vildagliptin and metformin (dose of metformin <1500 mg/d). Compared with the metformin, vildagliptin combined with metformin could reduce gastrointestinal reactions, but significantly increase the risk of Dizziness.

The results of our study should be interpreted carefully because it had some limitations. Firstly, a limited number of studies, evaluating patients from a limited number of countries, was found. Secondly, although we tried to decrease

some heterogeneity by using subgroup analyses, high statistical heterogeneity existed in some effect sizes, which might be due to the diversity in the baseline characteristics of included subjects or in methods for the assessment of eligibility and study populations. Thirdly, some studies had considerable bias by not including a sufficient number of samples or a broad enough geographical, economic, and age diversity. Lastly, the results of the studies may differ from the real world. It is necessary to consider more population factors, including adding subjects with special conditions such as an individual with ethnic and geographical diversity. We, thus, should be careful to generalize these results to clinical practice.

Through the above analysis, it has shown that the combination of vildagliptin and metformin has synergistic effect and enhancement of efficacy, and very low adverse reactions. The present study evaluated the safety and efficacy of vildagliptin in patients with T2DM. More high-quality, large-sample, further long-term follow-up clinical trials are needed to confirm the long-term safety and efficacy of vildagliptin.

Table II. Quality of evidence.

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with [Metformin]	Risk difference with [Vildagliptin+Metformin]
HbA1c	6398 (9 studies)	MODERATE	—	The mean HbA1c was 0 SD	MD 0.68 SD lower (0 higher to 0.31 lower)
FPG	1908 (6 studies)	⊕⊕⊕ HIGH	—	The mean FPG was 0 SD	MD 0.84 SD lower (1.08 to 0.59 lower)
Total AEs	7902 (8 studies)	⊕⊕⊕ MODERATE	RR 0.98 (0.94 to 1.02)	567 per 1,000	11 fewer per 1,000 (34 fewer to 11 more)
Nasopharyngitis	4840 (7 studies)	⊕⊕⊕ MODERATE	RR 1.01 (0.82 to 1.24)	71 per 1,000	1 more per 1,000 (13 fewer to 17 more)
Diarrhoea	2296 (4 studies)	⊕⊕⊕ MODERATE	RR 0.55 (0.40 to 0.76)	84 per 1,000	38 fewer per 1,000 (20 fewer to 50 fewer)
Dizziness	4595 (5 studies)	⊕⊕⊕ MODERATE	RR 1.41 (1.06 to 1.88)	36 per 1,000	15 more per 1,000 (2 more to 32 more)
GI disorders	4015 (3 studies)	⊕⊕⊕ MODERATE	RR 0.72 (0.58 to 0.91)	127 per 1,000	36 fewer per 1,000 (11 fewer to 53 fewer)
SAEs	5935 (3 studies)	⊕⊕⊕ MODERATE	RR 0.91 (0.76 to 1.1)	109 per 1,000	10 fewer per 1,000 (26 fewer to 11 more)
Infections and infestations	3239 (3 studies)	⊕⊕⊕ MODERATE	RR 1.03 (0.72 to 1.47)	65 per 1,000	2 more per 1,000 (18 fewer to 30 more)
Metabolism and Nutrition disorders	3101 (2 studies)	⊕⊕⊕ MODERATE	RR 0.73 (0.50 to 1.04)	70 per 1,000	19 fewer per 1,000 (35 fewer to 3 more)
Upper respiratory tract infection	2596 (4 studies)	⊕⊕⊕ MODERATE	RR 0.81 (0.49 to 1.36)	25 per 1,000	5 fewer per 1,000 (13 fewer to 9 more)
Body weight	7424 (6 studies)	⊕⊕⊕ MODERATE	—	The mean body weight was 0 SD	MD 0.22 SD higher (0.17 to 0.27 higher)
Urinary tract infection	2583 (4 studies)	⊕⊕⊕ MODERATE	RR 1.05 (0.77 to 1.43)	61 per 1,000	3 more per 1,000 (14 fewer to 26 more)
Hypoglycaemia events	5100 (3 studies)	⊕⊕⊕ MODERATE	RR 0.96 (0.55 to 1.69)	11 per 1,000	0 fewer per 1,000 (5 fewer to 8 more)
Headache	4295 (5 studies)	⊕⊕⊕ MODERATE	RR 1.00 (0.79 to 1.27)	61 per 1,000	0 fewer per 1,000 (13 fewer to 17 more)
Nausea	4595 (5 studies)	⊕⊕⊕ MODERATE	RR 1.07 (0.77 to 1.49)	28 per 1,000	2 more per 1,000 (6 fewer to 14 more)
Hypertension	4157 (4 studies)	⊕⊕⊕ MODERATE	RR 0.80 (0.64 to 1.00)	82 per 1,000	16 fewer per 1,000 (29 fewer to 0 more)
Vomiting	1244 (2 studies)	⊕⊕⊕ MODERATE	RR 1.60 (0.59 to 4.33)	12 per 1,000	7 more per 1,000 (5 fewer to 40 more)
Cough	2980 (3 studies)	⊕⊕⊕ MODERATE	RR 0.98 (0.65 to 1.46)	31 per 1,000	1 fewer per 1,000 (11 fewer to 14 more)
Arthralgia	2952 (3 studies)	⊕⊕⊕ MODERATE	RR 1.10 (0.85 to 1.42)	69 per 1,000	7 more per 1,000 (10 fewer to 29 more)
Fatigue	1682 (3 studies)	⊕⊕⊕ MODERATE	RR 0.69 (0.38 to 1.26)	32 per 1,000	10 fewer per 1,000 (20 fewer to 8 more)
Back pain	1926 (3 studies)	⊕⊕⊕ MODERATE	RR 0.68 (0.41 to 1.13)	38 per 1,000	12 fewer per 1,000 (22 fewer to 5 more)
Pain in extremity	2158 (3 studies)	⊕⊕⊕ MODERATE	RR 0.77 (0.42 to 1.41)	23 per 1,000	5 fewer per 1,000 (13 fewer to 9 more)
Hepatobiliary disorders	3101 (2 studies)	⊕⊕⊕ MODERATE	RR 1.27 (0.55 to 2.91)	14 per 1,000	4 more per 1,000 (6 fewer to 26 more)
Renal and urinary disorders	3101 (2 studies)	⊕⊕⊕ MODERATE	RR 0.84 (0.36 to 1.98)	14 per 1,000	2 fewer per 1,000 (9 fewer to 13 more)

*The risk in the intervention group (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).

CI: Confidence interval; MD: Mean difference; RR: Risk ratio

GRADE Working Group grades of evidence

High certainty: Further research is very unlikely to change our confidence in the estimate of the effect.

Moderate certainty: Further research is very likely to have an important impact on our confidence in the estimate of effect and may change the estimate.

Low certainty: Further research is very likely to have an important on our confidence in the estimate of effect and is likely to change the estimate.

Very low certainty: We are very uncertain about the estimate.

Conclusions

The results indicated that compared with the metformin, vildagliptin combined with metformin could significantly reduce FPG, HbA1c and body weight. When the dose of metformin in the combination group of vildagliptin and metformin is ≥ 1500 mg/d, the results showed significant reduction in HbA1c and FPG. In addition, it had no risk of increase in total AEs, diarrhea and GI disorders, but had significant risk of increasing dizziness. GRADE showed that the quality of evidence had high certainty in FPG and moderate certainty in HbA1c, body weight and all AEs. Further clinical studies are required to explore long-term efficacy and safety of vildagliptin. This study is expected to provide relevant strategies and guiding significance for treatment of T2DM.

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Conflict of Interest

The Authors declare that they have no conflict of interests.

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