

The Efficacy and Tolerability of Exenatide in Comparison to Placebo; A Systematic Review and Meta-Analysis of Randomized Clinical Trials

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ABSTRACT - Recent investigations in finding new drugs in the treatment of diabetes have led to the discovery of several pathological pathways involved in diabetes. Exenatide a drug with incretin mimetic activity was studied in several in vivo and in vitro as well as human studies. It has shown promising results in controlling metabolic indices in type-2 diabetes and was approved by FDA but still there is an active safety alert on it. In this study we aimed to meta-analyze all placebo-controlled clinical trials on the efficacy or tolerability of exenatide in type 2 diabetes.

The literature search provided 1016 articles while only 14 articles were eligible to be included in the meta-analysis with a total of 2583 patients enrolled in the study. According to the wide variation in design of various studies, the study duration of 16 weeks and less or more and dose (5 µg bid versus 10 µg bid) were considered and analyzed.

The results of this meta-analysis show that exenatide decreases fasting plasma glucose and HbA1C significantly regardless of dose and study duration. The effect of exenatide on weight reduction was more prominent at the dose of 10 µg bid regardless of the study duration, however at the dose of 5 µg bid, significant results were observed after drug administration for more than 16 weeks. Exenatide usage decreased serum triglycerides indifferent to dose and study duration while its effect on cholesterol was not prominent. Along with these impacts, exenatide changed LDL and HDL cholesterol at the lower dose. The hemodynamic effect of exenatide was observed as significant decrements in systolic and diastolic blood pressure at the higher dose. The risk of nausea, vomiting and hypoglycemia was significant and indifferent to dose while headache and nasopharyngitis were seen more at lower dose.

It is concluded that exenatide can be considered as a good hypoglycemic agent in type-2 diabetic patients with benefits on lipid profile and blood pressure with partially questionable tolerability.

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INTRODUCTION

Uncontrolled diabetes results in complications with a burden of costs to patients and governments. Optimal glycemic control slows the disease progression but reaching glycemic control, which is targeted at glycated hemoglobin (HbA1c) level equal to or less than 7%, is not easily possible [1]. Not only optimal glycemic control is important, control of the other associated metabolic abnormalities, such as hyperlipidemia, are also of paramount importance.

Although many medications with different mechanism of action are used in the management of

type 2 diabetes, failure in achieving glycemic control in some patients [2] and launching side effects such as weight gain [3] are forcing scientists to investigate for new medications.. Overweight is considered a risk factor for hyperglycemia, hyperinsulinemia, insulin resistance, dyslipidemia, nonalcoholic fatty liver disease (NAFLD), hypertension and cardiovascular disease [4,5] and also the risk of diabetes is proportionate to body mass index (BMI) [6].

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Furthermore in type 2 diabetes, weight loss ameliorates glycemic control and is considered as one of the key steps in treatment [7]. Currently the older hypoglycemic agents such as sulfonylurea, metformin, and thiazolidinediones are used for glycemic control. Recently, some new medications including analogues of hormone glucagon-like peptide-1 (GLP-1) and incretin mimetic agents (for example, exenatide) are under post marketing investigations. The mechanism of action of exenatide is similar to incretin that enhances glucose dependent insulin secretion, inhibits glucose dependent glucagon secretion, slows gastric emptying, and reduces food intake [8]. In vivo and in vitro models of diabetes show that exenatide improves first and second phase of insulin secretion in type 2 diabetic patients [9] and enhances β cell proliferation and pancreatic islet cells regeneration [10,11]. Because of the importance of lipid and hemodynamic control most diabetic patients need different classes of drugs. For instance, the oxidative stress in diabetes can be reduced by phosphodiesterase inhibitors [12], carvedilol [13], herbal medicines [14-16], and pentoxifylline [17]. Therefore it seems logical to look for new medications which may affect different pathological pathways. Although exenatide has been recently approved as an adjunct to diet and exercise to improve glycemic control in type 2 diabetes, exenatide still has an active FDA safety alert which shows the substantial need for monitoring, reporting and tracking drug investigations. The aim of this meta-analysis is to assess the cumulative data of clinical trials and providing qualified results.

METHODS

PubMed, Web of Sciences (ISI), Scopus, and Cochrane databases were searched by keywords type 2 diabetes, exenatide, and incretin. We limited our search to the randomized clinical trials written in English. The studies were included in the meta-analysis if they met the inclusion criteria including trials enrolling patients with type 2 diabetes and trials comparing exenatide with placebo. More than one reviewer evaluated each article independently to lessen the probability of duplication, analyzing reviews, case studies and uncontrolled trials. Studies were excluded if they did not have control group or their results did not consider our

outcomes. According to the wide variation in the design of various studies in the term of study duration (4-30 weeks) and the dose of exenatide (5 μg bid versus 10 μg bid), the study duration of 16 weeks and less or more and dose (5 μg bid versus 10 μg bid) were considered and analyzed.

Assessment of trial quality

The Jadad score, which indicates the quality of the studies based on their description of randomization, blinding, and dropouts (withdrawals) was used to assess the methodological quality of trials [18]. The quality scale ranges from 0 to 5 points with a low quality report of score 2 or less and a high quality report of score at least 3.

STATISTICAL ANALYSIS

Data from selected studies were extracted in the form of 2x2 tables by study characteristics. Included studies were weighted by effect size and pooled. Data were analyzed using Statsdirect software version 2.7.8. Weighted mean difference and 95% confidence intervals (95% CI) were calculated using Mulrow-Oxman (for fixed effects) or Der Simonian-Laird (for random effects) methods. Relative risk (RR) and 95% confidence intervals (CI) were calculated using Mantel-Haenszel or Der Simonian-Laird methods. The Cochran Q test was used to test heterogeneity and $p < 0.05$ considered significant. In case of heterogeneity or few included studies in meta-analysis, the random effects model was used. The event rate in the experimental (intervention) group against the event rate in the control group was calculated using L'Abbe plot as an aid to explore the heterogeneity of effect estimates. Funnel plot was used as publication bias indicator.

RESULTS

The electronic search provided 1016 articles; 80 from PubMed, 323 from Web of Science, 544 from Scopus, and 69 from Cochrane library. Of those, 25 studies were evaluated in full text, of which, 11 trials didn't fulfill inclusion criteria while 14 trials were analyzed (Figure 1). Totally 2583 patients enrolled in the study. Summary of each trial is shown in Table 1.

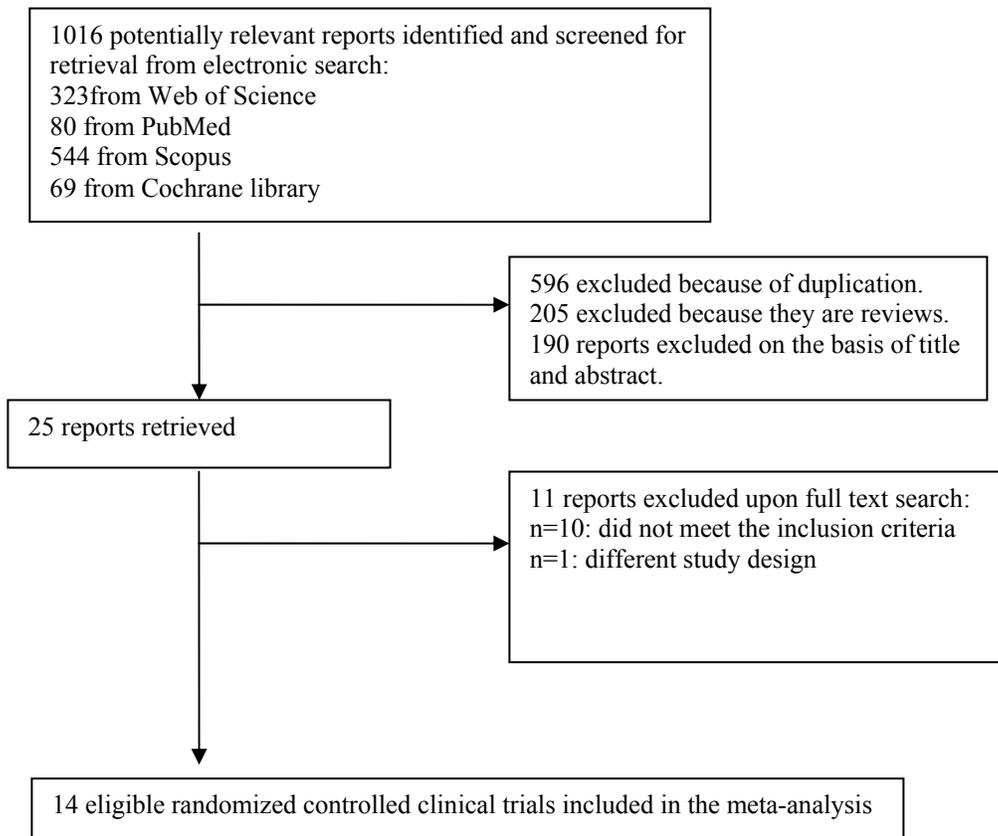


Figure 1. Flow diagram for study selection

Table 1. Summary of trials

Author	Duration	Intervention	SS	Indices	Jadad Score
Apovian et al., (26)	24w	exenatide/Placebo	142	FPG, HbA1c, BW, TG, SEs	5
Gill et al., (29)	12w	exenatide/Placebo	45	HbA1c, BW, SEs	2
Arnolds et al., (31)	4 w	exenatide/Placebo	31	BW, Chole, LDL, HDL, SEs	2
Gao et al., (30)	16w	exenatide/Placebo	401	FPG, HbA1c, BW, SEs	4
Kadowaki et al., (19)	12w	exenatide/Placebo	137	FPG, HbA1c, BW, Chole, LDL, HDL, TG, SEs	3
Iwamoto et al., (20)	10w	exenatide/Placebo	28	FPG, HbA1c, BW, SEs	3
Moretto et al., (21)	24w	exenatide/Placebo	232	FPG, HbA1c, BW, Chole, LDL, HDL, SEs	4
Kim et al., (22)	15w	exenatide/Placebo	43	FPG, HbA1c, BW, SEs	2
Zinman et al., (27)	16w	exenatide/Placebo	182	FPG, HbA1c, BW, SEs	5
Defronzo et al., (23)	30w	exenatide/Placebo	270	FPG, HbA1c, BW, SEs	4
Kendall et al., (24)	30w	exenatide/Placebo	593	FPG, HbA1c, BW, SEs	4
Poon et al., (28)	4w	exenatide/Placebo	141	HbA1c, BW, SEs	4
Buse et al., (25)	30w	exenatide/Placebo	255	FPG, HbA1c, BW, SEs	4
Fineman et al., (32)	4w	exenatide/Placebo	83	HbA1c	4

yr= year; W= week, SS= sample size; FPG= fasting plasma glucose; HbA1c= hemoglobin A1c; BW= body weight; Chole= cholesterol; LDL= low density lipoprotein; HDL= high density lipoprotein; TG= triglyceride; CRP= c-reactive protein; SEs= side effects.

Efficacy***Fasting plasma glucose***

The summary effect size for weighted mean difference of mean variation of fasting plasma glucose (Δ FPG) for all included data for exenatide 5 μ g twice daily or its equivalent long acting dosage form in different duration of times for treatment in seven trials [19-25] was -1.05 mmol/L with 95% CI of -1.48 to -0.62 ($P < 0.0001$) and for exenatide 10 μ g twice daily or its equivalent long acting dosage form in different duration of time for treatment in nine trials [19-27] was -1.34 mmol/L with 95% CI of -1.63 to -1.05 ($P < 0.0001$). The Cochrane Q test for heterogeneity indicated that the studies are heterogeneous for both doses ($P = 0.04$ and $P = 0.01$, respectively) and could not be combined using fixed effects model, thus the random effects for individual and summary of effect size for weighted mean difference was applied.

Summary effect size for weighted mean difference of mean variation of FPG (Δ FPG) for all included data for exenatide 5 μ g twice daily or its equivalent long acting dosage form in less than 16 weeks duration of time for treatment in three trials [19,20,22] was -1.5 mmol/L (95% CI= -3 to -0.06, $P = 0.04$). The Cochrane Q test for heterogeneity indicated that the studies are heterogeneous ($P = 0.01$) and could not be combined using fixed effects model; thus the random effects for individual and summary of effect size for weighted mean difference was applied.

Summary effect size for weighted mean difference of mean variation of FPG (Δ FPG) for all included data for exenatide 10 μ g twice daily or its equivalent long acting dosage form in less than 16 weeks duration of time for treatment in four trials [19,20,22,27] was -1.86 mmol/L (95% CI= -2.29 to -1.43; $P < 0.0001$). The Cochrane Q test for heterogeneity indicated that the studies are not heterogeneous ($P = 0.42$) and could be combined; thus the fixed effects for individual and summary of effect size for weighted mean difference was applied.

Summary effect size for weighted mean difference of mean variation of FPG (Δ FPG) for all included data for exenatide 5 μ g twice daily or its equivalent long-acting dosage form in more than 16 weeks duration of time for treatment in four trials [21, 23-25] was -0.97 mmol/L (95% CI= -1.28 to -0.67, $P < 0.0001$). The Cochrane Q test for heterogeneity indicated that the studies are not heterogeneous for ($P = 0.34$) and could be combined, thus the fixed effects for individual and

summary of effect size for weighted mean difference was applied.

Summary effect size for weighted mean difference of mean variation of FPG (Δ FPG) for all included data for exenatide 10 μ g twice daily or its equivalent long acting dosage form in more than 16 weeks duration of time for treatment in five trials [21,23-26] was -1.08 mmol/L (95% CI= -1.17 to -0.99, $P < 0.0001$). The Cochrane Q test for heterogeneity indicated that the studies are not heterogeneous ($P = 0.39$) and could be combined; thus the fixed effects for individual and summary of effect size for weighted mean difference was applied.

The summary effect size for weighted mean difference of mean variation of FPG (Δ FPG) for all included data for exenatide 5 μ g twice daily vs. exenatide 10 μ g twice daily in seven trials [19-25] was -0.24 mmol/L with 95% CI of -0.50-0.03 (fixed effects, $P = 0.09$, heterogeneity P value= 0.48), a non significant result.

Body weight

The summary effect size for weighted mean difference of mean variation of BW (Δ BW) for all included data for exenatide 5 μ g twice daily or its equivalent long acting dosage form in different duration of time for treatment in eight trials [19-25,28] was -0.56 kg with 95% CI of -1.07 to -0.06 ($P = 0.0002$) and for exenatide 10 μ g twice daily or its equivalent long-acting dosage form in different duration of times for treatment in twelve trials [19-25,27-31] was -1.24 kg with 95% CI= -1.69 to -0.78 ($P < 0.0001$). The Cochrane Q test for heterogeneity indicated that the studies are heterogeneous for both doses ($P = 0.02$ and $P = 0.0002$, respectively) and could not be combined using fixed effects model; thus the random effects for individual and summary of effect size for weighted mean difference was applied.

Summary effect size for weighted mean difference of mean variation of body weight (Δ BW) for all included data for exenatide 5 μ g twice daily or its equivalent long acting dosage form in less than 16 weeks duration of time for treatment in four trials [19,20,22,28] was -0.08 kg (95% CI= -0.56 to 0.41, $P = 0.76$). The Cochrane Q test for heterogeneity indicated that the studies are not heterogeneous for ($P = 0.11$) and could be combined; thus the fixed effects for individual and summary of effect size for weighted mean difference was applied.

Summary effect size for weighted mean difference of mean variation of BW (Δ BW) for all included data for exenatide 10 μ g twice daily or its equivalent long-acting dosage form in less than 16 weeks duration of time for treatment in eight trials [19,20,22,27-31] was -1.15 kg (95% CI= -1.88 to -0.42, P= 0.0004). The Cochrane Q test for heterogeneity indicated that the studies are heterogeneous (P= 0.0006) and could not be combined using fixed effects model; thus the random effects for individual and summary of effect size for weighted mean difference was applied.

Summary effect size for weighted mean difference of mean variation of BW (Δ BW) for all included data for exenatide 5 μ g twice daily or its equivalent long acting dosage form in more than 16 weeks duration of time for treatment in four trials [21,23-25] was -0.85 kg (95% CI= -1.22 to -0.47, P< 0.0001). The Cochrane Q test for heterogeneity indicated that the studies are not heterogeneous (P= 0.22) and could be combined; thus the fixed effects for individual and summary of effect size for weighted mean difference was applied.

Summary effect size for weighted mean difference of mean variation of BW (Δ BW) for all included data for exenatide 10 μ g twice daily or its equivalent long acting dosage form in more than 16 weeks duration of time for treatment in four trials [21,23-25] was -1.37 kg (95% CI= -2.10 to -0.65, P= 0.0002). The Cochrane Q test for heterogeneity indicated that the studies are heterogeneous for (P= 0.02) and could not be combined using fixed effects model; thus the random effects for individual and summary of effect size for weighted mean difference was applied.

The summary effect size for weighted mean difference of mean variation of BW (Δ BW) for all included data for exenatide 5 μ g twice daily vs. exenatide 10 μ g twice daily in eight trials [19-25,28] was -0.48 kg with 95% CI of -0.79 to -0.17 (fixed effects, P= 0.0024, heterogeneity P value= 0.08).

Hemoglobin A1c (HbA1c)

The summary effect size for weighted mean difference of mean variation of hemoglobin A1c (Δ HbA1c) for all included data for exenatide 5 μ g twice daily or its equivalent long acting dosage form in different duration of time for treatment in nine trials [19-25, 28, 32] was -0.68% with 95% CI of -0.89 to -0.48 (P< 0.0001) and for exenatide 10 μ g twice daily or its equivalent long-acting dosage

form in different duration of time for treatment in nine trials [19-25,27,28] was -0.99% with 95% CI= -1.18 to -0.8 (P< 0.0001). The Cochrane Q test for heterogeneity indicated that the studies are heterogeneous for both doses (P= 0.0002 and P= 0.0004, respectively) and could not be combined using fixed effects model; thus the random effects for individual and summary of effect size for weighted mean difference was applied.

Summary effect size for weighted mean difference of mean variation of HbA1c (Δ HbA1c) for all included data for exenatide 5 μ g twice daily or its equivalent long acting dosage form in less than 16 weeks duration of time for treatment in five trials [19,20,22,28,32] was -0.83% (95% CI= -1.25 to -0.41, P= 0.0001). The Cochrane Q test for heterogeneity indicated that the studies are heterogeneous (P< 0.0001) and could not be combined using fixed effects model; thus the random effects for individual and summary of effect size for weighted mean difference were applied.

Summary effect size for weighted mean difference of mean variation of HbA1c (Δ HbA1c) for all included data for exenatide 10 μ g twice daily or its equivalent long acting dosage form in less than 16 weeks duration of time for treatment in five trials [19,20,22,27,28] was -1.15% (95% CI= -1.54 to -0.76, P< 0.0001). The Cochrane Q test for heterogeneity indicated that the studies are heterogeneous (P< 0.0001) and could not be combined; thus the random effects for individual and summary of effect size for weighted mean difference were applied.

Summary effect size for weighted mean difference of mean variation of HbA1c (Δ HbA1c) for all included data for exenatide 5 μ g twice daily or its equivalent long-acting dosage form in more than 16 weeks duration of time for treatment in four trials [21,23-25] was -0.61% (95% CI= -0.73 to -0.49, P< 0.0001). The Cochrane Q test for heterogeneity indicated that the studies are not heterogeneous for (P= 0.44) and could be combined; thus the fixed effects for individual and summary of effect size for weighted mean difference was applied.

Summary effect size for weighted mean difference of mean variation of HbA1c (Δ HbA1c) for all included data for exenatide 10 μ g twice daily or its equivalent long-acting dosage form in more than 16 weeks duration of time for treatment in four trials [21,23-25] was -0.89% (95% CI= -1.01 to -0.76, P< 0.0001). The Cochrane Q test for

heterogeneity indicated that the studies are not heterogeneous ($P= 0.5$) and could be combined; thus the fixed effects for individual and summary of effect size for weighted mean difference was applied.

The summary effect size for weighted mean difference of mean variation of HbA1c (Δ HbA1c) for all included data for exenatide 5 μ g twice daily vs. exenatide 10 μ g twice daily in eight trials [19-25,28] was -0.25% with 95% CI of -0.35 to -0.14 (fixed effects, $P< 0.0001$, heterogeneity P value= 0.76).

Triglyceride

The summary effect size for weighted mean difference of mean variation of triglyceride (Δ TG) for all included data for exenatide 10 μ g twice daily in two trials [19,26] was 0.17 mmol/L (95% CI= 0.14 to 0.2) ($P< 0.0001$, Figure 2). The Cochrane Q test for heterogeneity indicated that the studies are not heterogeneous ($P= 0.55$) and could be combined but because of too few include studies, the random effects for individual and summary of effect size for weighted mean difference was applied.

Cholesterol

The summary effect size for weighted mean difference of mean variation of cholesterol (Δ cholesterol) for all included data for exenatide 5 μ g twice daily treatment in two trials [19,21] was -0.14 mmol/L (95% CI= -0.32 to 0.03, $P= 0.11$) and for exenatide 10 μ g twice daily treatment in three trials [19,21,31] was -0.33 mmol/L (95% CI= -0.63 to -0.02, $P= 0.03$). The Cochrane Q test for heterogeneity indicated that the studies are homogenous and heterogeneous ($P= 0.16$ and $P= 0.01$, respectively) and because of too few included studies, the random effects for individual and summary of effect size for weighted mean difference was applied.

The summary effect size for weighted mean difference of mean variation of cholesterol (Δ cholesterol) for all included data for exenatide 5 μ g twice daily vs. exenatide 10 μ g twice daily in two trials [19,21] was -0.04 mmol/L with 95% CI of -0.14 to 0.07 (random effects, $P= 0.5$, heterogeneity P value= 0.38).

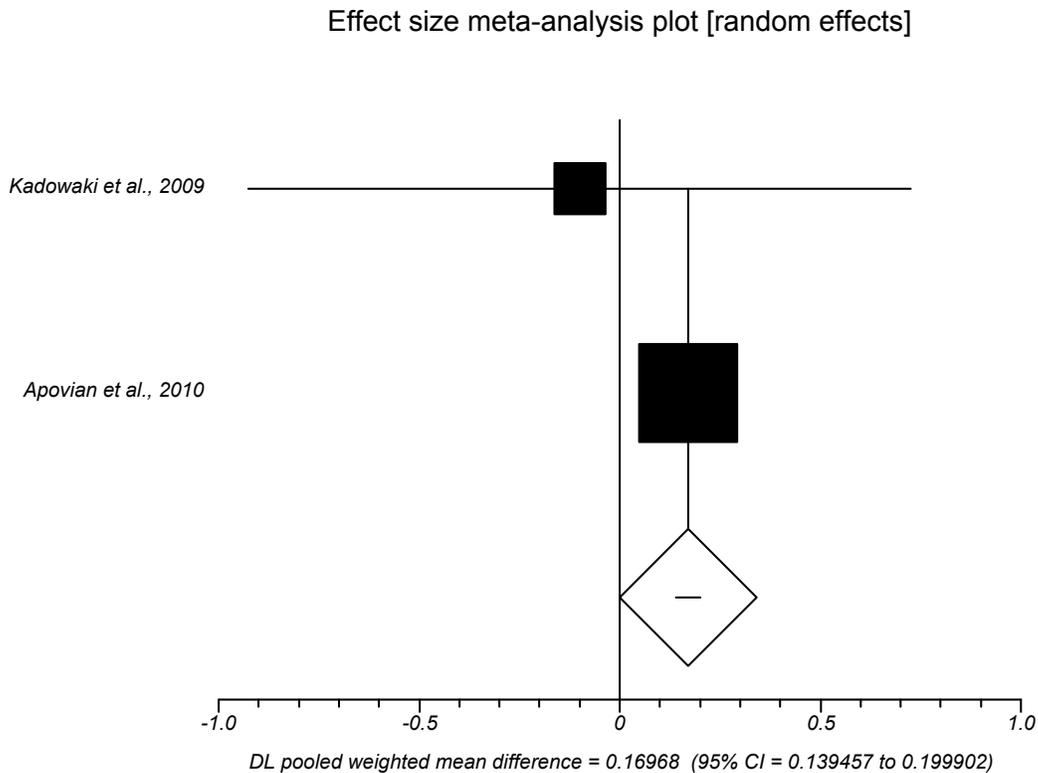


Figure 2. Individual and pooled effect size for weighted mean difference for the outcome of “ Δ TG” in the studies considering exenatide 10 μ g comparing to placebo therapy.

Low density lipoprotein

The summary effect size for weighted mean difference of mean variation of low density lipoprotein (Δ LDL) for all included data for exenatide 5 μ g twice daily treatment in two trials [19,21] was -0.09 mmol/L (95% CI= -0.16 to -0.01, P= 0.03) and for exenatide 10 μ g twice daily treatment in three trials [19,21,31] was -0.13 mmol/L (95% CI= -0.3 to 0.04, P= 0.14). The Cochrane Q test for heterogeneity indicated that studies are not heterogeneous (P= 0.66 and P= 0.1) and could be combined but because of too few included studies, the random effects for individual and summary of effect size for weighted mean difference was applied.

The summary effect size for weighted mean difference of mean variation of LDL (Δ LDL) for all included data for exenatide 5 μ g twice daily vs. exenatide 10 μ g twice daily in two trials [19,21] was 0.03 mmol/L with 95% CI of -0.05 to 0.1 (random effects, P= 0.50, heterogeneity P value= 0.64).

High density lipoprotein

The summary effect size for weighted mean difference of mean variation of high density lipoprotein (Δ HDL) for all included data for exenatide 5 μ g bid treatment in two trials [19,21] was -0.04 mmol/L (95% CI= -0.17 to 0.086138, P=

0.53) and for exenatide 10 μ g twice daily treatment in three trials [19,21,31] was -0.09 mmol/L (95% CI= -0.21 to 0.03, P= 0.14). The Cochrane Q test for heterogeneity indicated that the studies are heterogeneous (P= 0.0007 and P< 0.0001, respectively) thus, the random effects for individual and summary of effect size for weighted mean difference was applied.

The summary effect size for weighted mean difference of mean variation of HDL (Δ HDL) for all included data for exenatide 5 μ g twice daily vs. exenatide 10 μ g twice daily in two trials [19,21] was -0.02 mmol/L with 95% CI of -0.05 to 0.003 (random effects, P= 0.09, heterogeneity P value= 0.50).

Systolic blood pressure

The summary effect size for weighted mean difference of mean variation of systolic blood pressure (Δ Systolic BP) for all included data for exenatide 10 μ g twice daily in two trials [21,26] was -5.78 mmHg (95% CI= -9.71 to -1.9) (P=0.004, Figure 3). The Cochrane Q test for heterogeneity indicated that the studies are heterogeneous (P= 0.02) and could not be combined using fixed effects model, thus the random effects for individual and summary of effect size for weighted mean difference was applied.

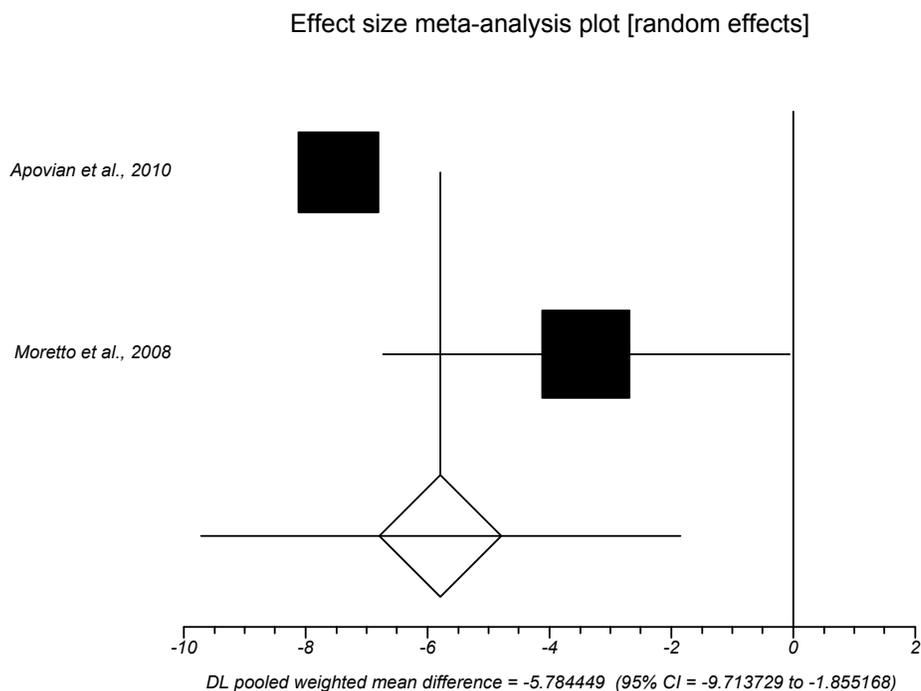


Figure 3. Individual and pooled effect size for weighted mean difference for the outcome of “ Δ Systolic BP” in the studies considering exenatide 10 μ g comparing to placebo therapy.

Diastolic blood pressure

The summary effect size for weighted mean difference of mean variation of diastolic blood pressure (Δ Diastolic BP) for all included data for exenatide 10 μ g twice daily in two trials [21,26] was -2.67 mmHg (95% CI= -2.99 to -2.35) ($P < 0.0001$, Figure 4). The Cochrane Q test for heterogeneity indicated that the studies are not heterogeneous ($P = 0.49$) and could be combined but because of too few included studies, the random effects for individual and summary of effect size for weighted mean difference was applied.

Tolerability

Nasopharyngitis

The summary RR for the number of patients who reported nasopharyngitis by exenatide 10 μ g twice daily in three trials [19,27,30] was 1.02 with a 95% CI of 0.64 to 1.62 and an insignificant RR ($P = 0.93$, Figure 5-a). The Cochrane Q test for heterogeneity indicated that the studies are not heterogeneous ($P = 0.43$, Figure 5-b) and could be combined but because of too few included studies the random

effects for individual and summary of RR was applied. Regression of normalized effect versus precision for all included studies for the number of patients who reported nasopharyngitis by exenatide vs. placebo therapy could not be calculated because of too few strata.

Headache

The summary RR for the number of patients who reported headache by exenatide 5 μ g twice daily in four trials [21,22,24,25] was 2.40 with a 95% CI of 1.41 to 4.09 and a significant RR ($P = 0.0012$, Figure 6-a). The Cochrane Q test for heterogeneity indicated that the studies are not heterogeneous ($P = 0.22$, Figure 6-b) and could be combined, thus the fixed effects for individual and summary of RR was applied. Regression of normalized effect versus precision for all included studies for the number of patients who reported headache by exenatide 5 μ g vs. placebo therapy was 1.11 (95% CI= -5.8 to 8.03, $P = 0.56$), and Kendall's test on standardized effect vs. variance indicated $\tau = 0.33$, $P = 0.75$ (Figure 6-c).

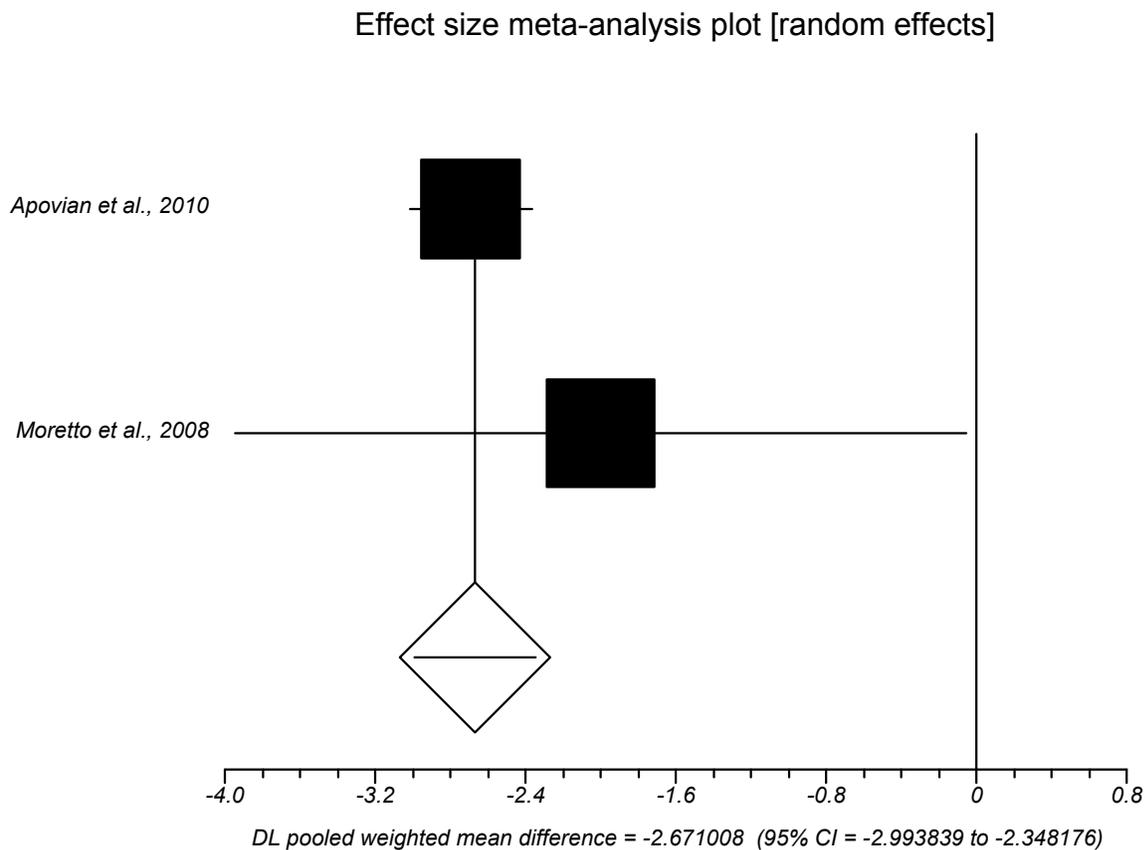


Figure 4. Individual and pooled effect size for weighted mean difference for the outcome of “ Δ Diastolic BP” in the studies considering exenatide 10 μ g comparing to placebo therapy.

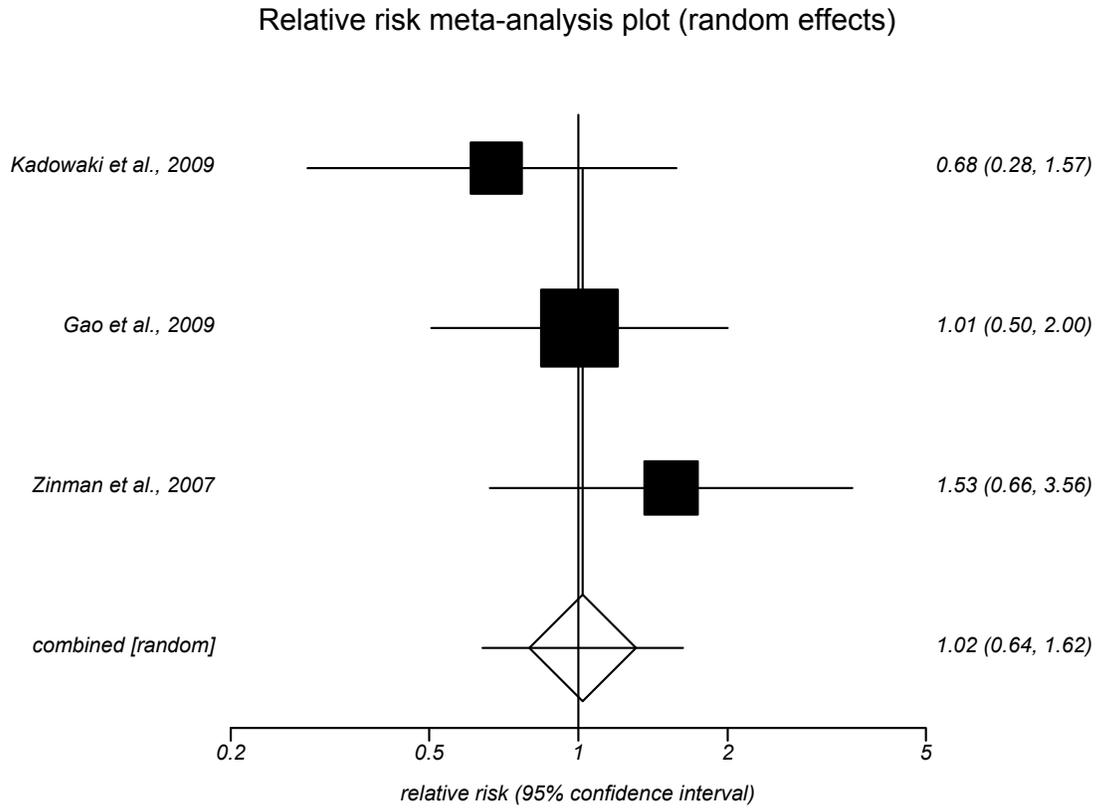


Figure 5-a. Individual and pooled effect size for weighted mean difference for the outcome of “Nasopharyngitis” in the studies considering exenatide 10 µg comparing to placebo therapy.

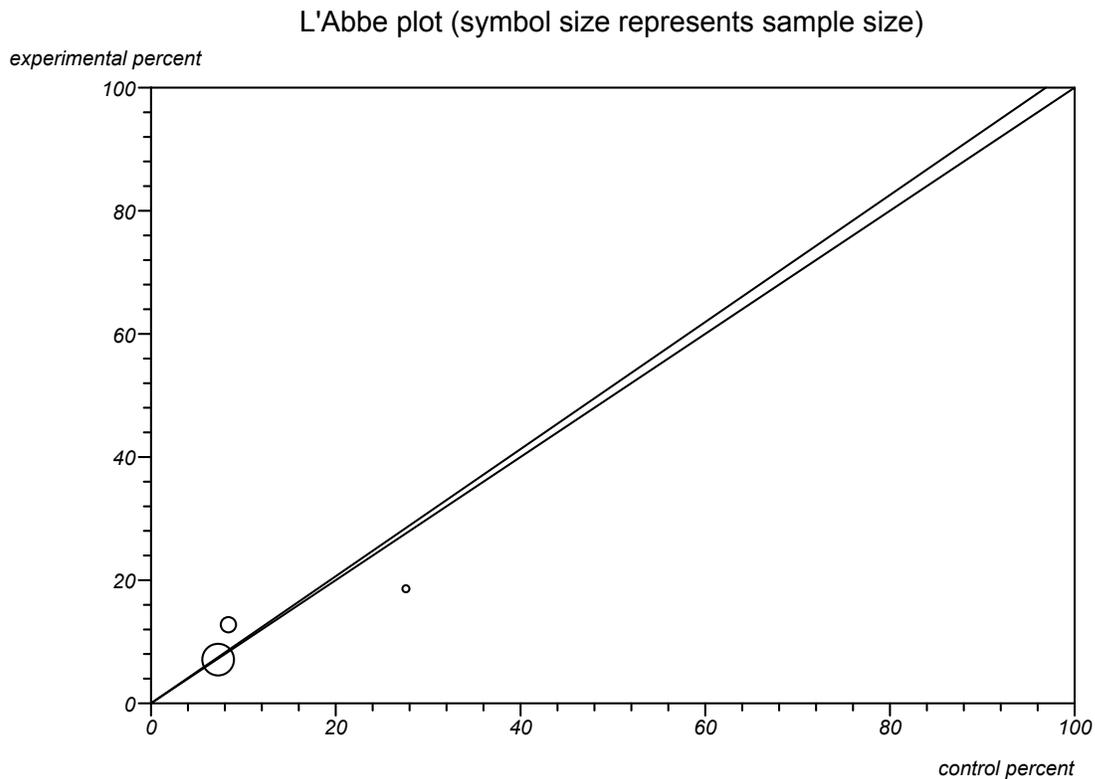


Figure 5-b. Heterogeneity indicators for the outcome of “Nasopharyngitis” in the studies considering exenatide 10 µg comparing to placebo therapy.

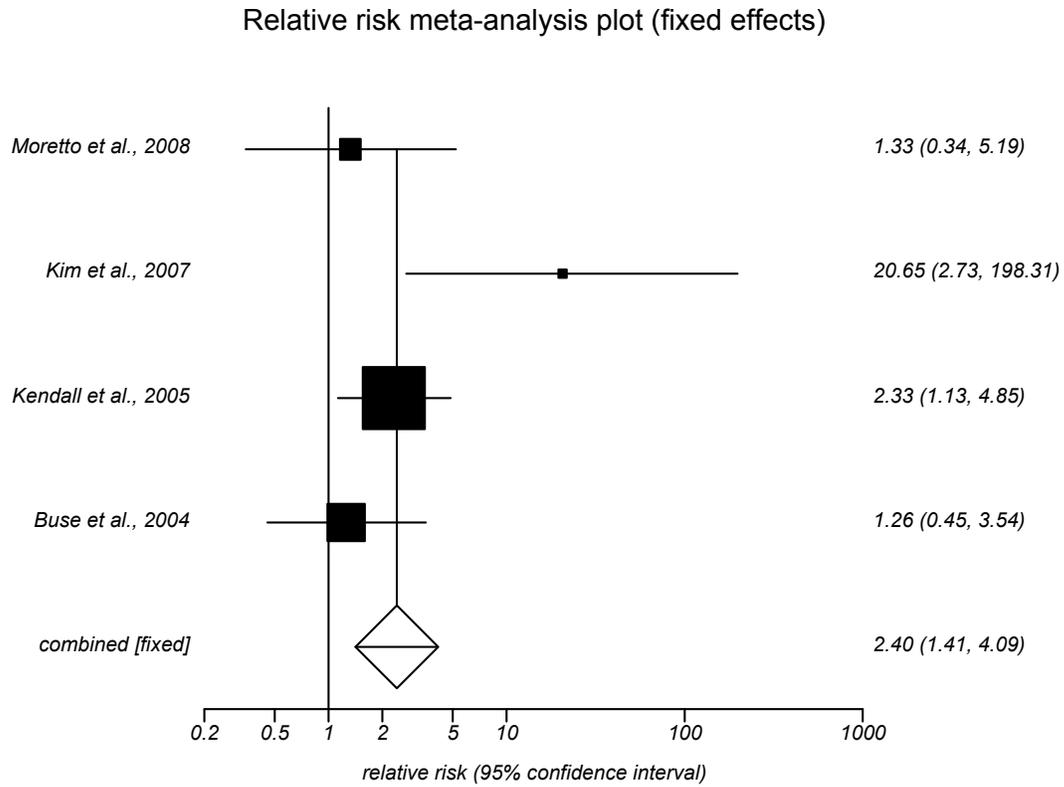


Figure 6-a. Individual and pooled effect size for weighted mean difference for the outcome of “Headache” in the studies considering exenatide 5 µg comparing to placebo therapy.

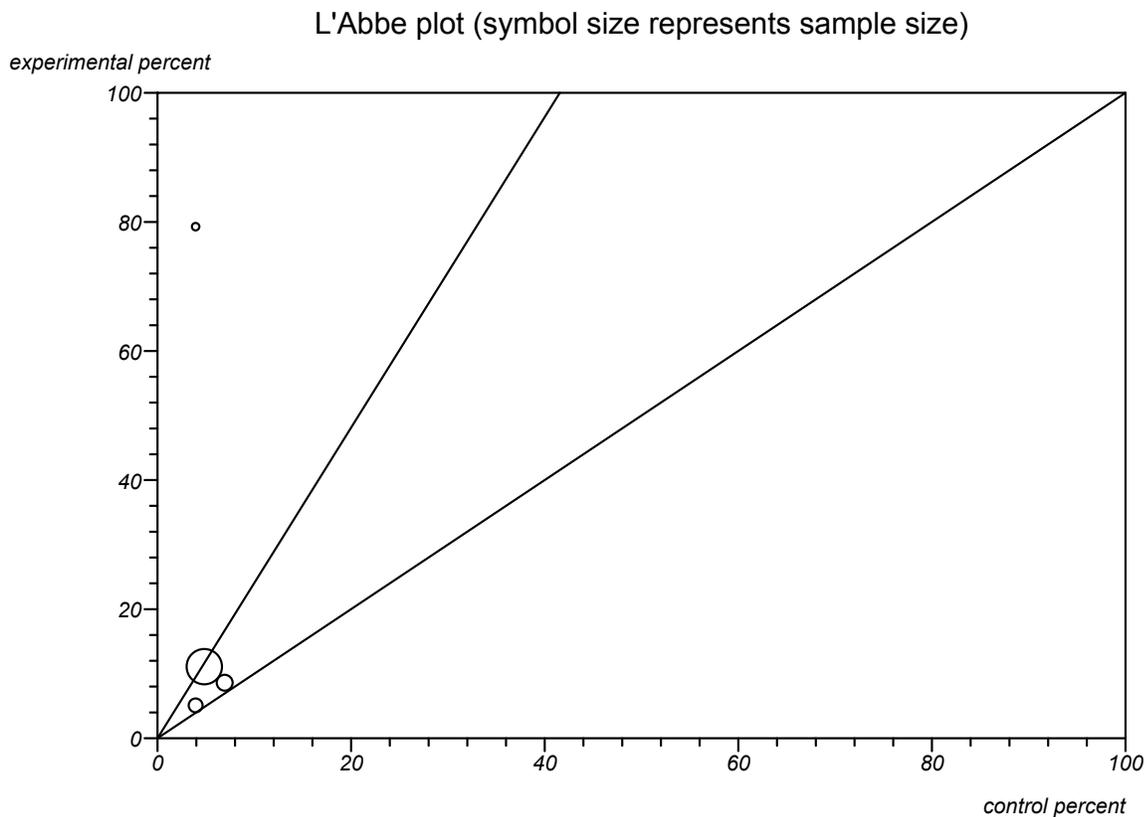


Figure 6-b. Heterogeneity indicators for the outcome of “Headache” in the studies considering exenatide 5 µg comparing to placebo therapy.

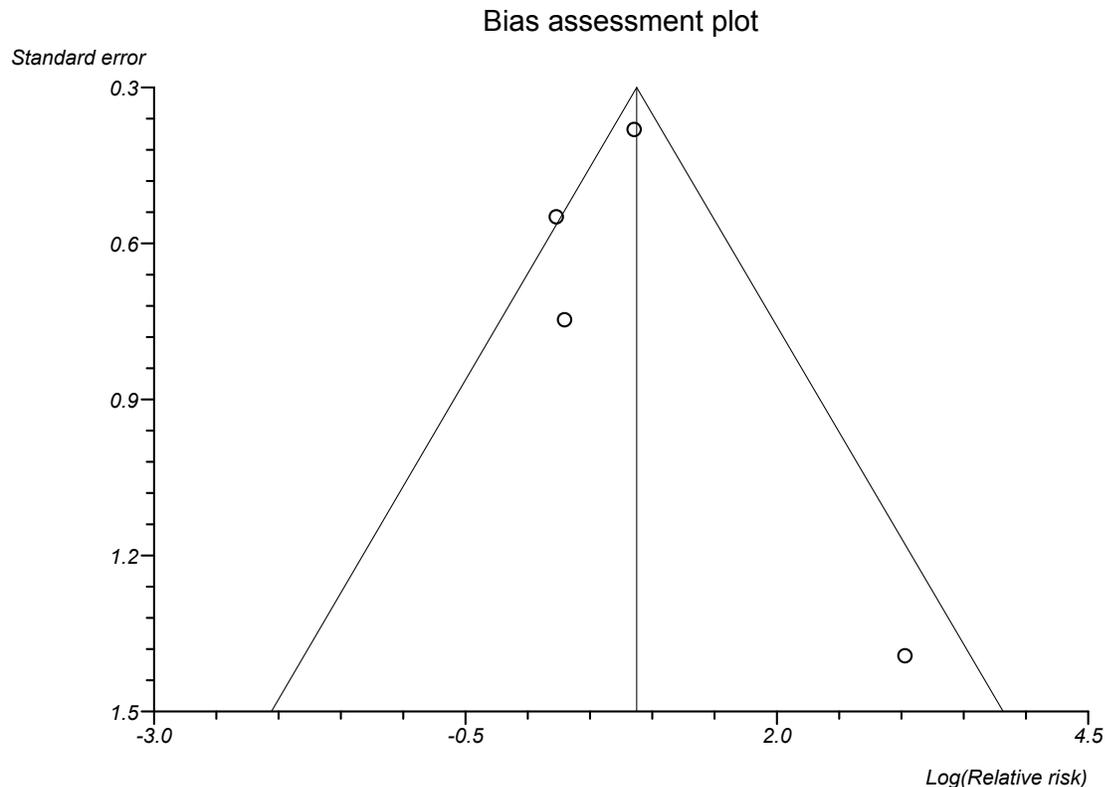


Figure 6-c. Publication bias indicators for the outcome of “Headache” in the studies considering exenatide 5 μ g comparing to placebo therapy.

The summary RR for the number of patients who reported headache by exenatide 10 μ g twice daily in six trials [21,22,24,25,27,30] was 1.17 with a 95% CI of 0.71 to 1.92 and a non significant RR ($P= 0.53$, Figure 6-d). The Cochrane Q test for heterogeneity indicated that the studies are not heterogeneous ($P= 0.78$, Figure 6-e) and could be combined, thus the fixed effects for individual and summary of RR was applied. Regression of normalized effect versus precision for all included studies for the number of patients who reported headache by exenatide 10 μ g vs. placebo therapy was -0.53 (95% CI= -2.94 to 1.87, $P= 0.57$), and Kendall’s test on standardized effect vs. variance indicated tau= -0.2, $P= 0.47$ (Figure 6-f).

Nausea

The summary RR for the number of patients who reported nausea by exenatide 5 μ g twice daily in six trials [19, 22-25, 28] was 2.13 with a 95% CI of 1.66 to 2.72 and a significant RR ($P< 0.0001$, Figure 7-a). The Cochrane Q test for heterogeneity indicated that the studies are not heterogeneous ($P= 0.15$, Figure 7-b) and could be combined; thus the

fixed effects for individual and summary of RR was applied. Regression of normalized effect versus precision for all included studies for the number of patients who reported nausea by exenatide 5 μ g vs. placebo therapy was 0.82 (95% CI= -1.71 to 3.35, $P= 0.42$), and Kendall’s test on standardized effect vs. variance indicated tau= 0.2, $P= 0.72$ (Figure 7-c).

The summary RR for the number of patients who reported nausea by exenatide 10 μ g twice daily in ten trials [19,22-30] was 3.16 with a 95% CI of 2.13 to 4.68 and a significant RR ($P< 0.0001$, Figure 7-d). The Cochrane Q test for heterogeneity indicated that the studies are heterogeneous ($P= 0.0023$, Figure 7-e) and could not be combined using fixed effects model; thus the random effects for individual and summary of RR was applied. Regression of normalized effect versus precision for all included studies for the number of patients who reported nausea by exenatide 10 μ g vs. placebo therapy was 1.8 (95% CI= -0.07 to 3.68, $P= 0.06$), and Kendall’s test on standardized effect vs. variance indicated tau= 0.33, $P= 0.22$ (Figure 7-f).

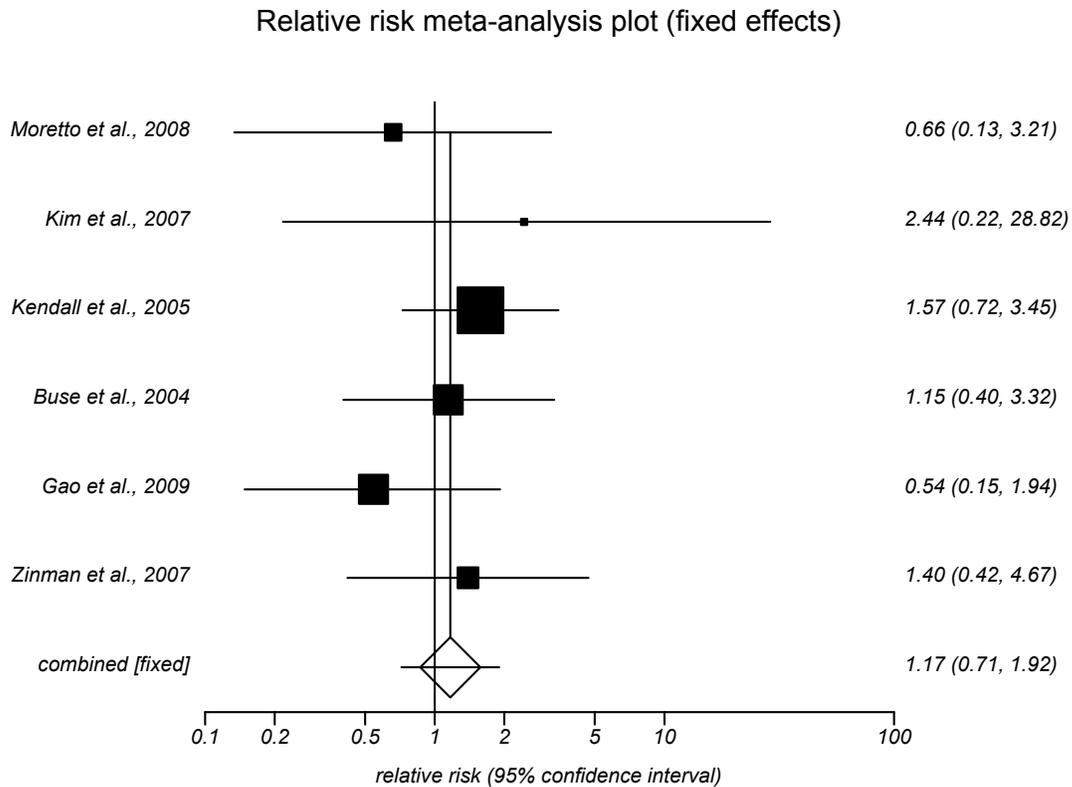


Figure 6-d. Individual and pooled effect size for weighted mean difference for the outcome of “Headache” in the studies considering exenatide 10 µg comparing to placebo therapy.

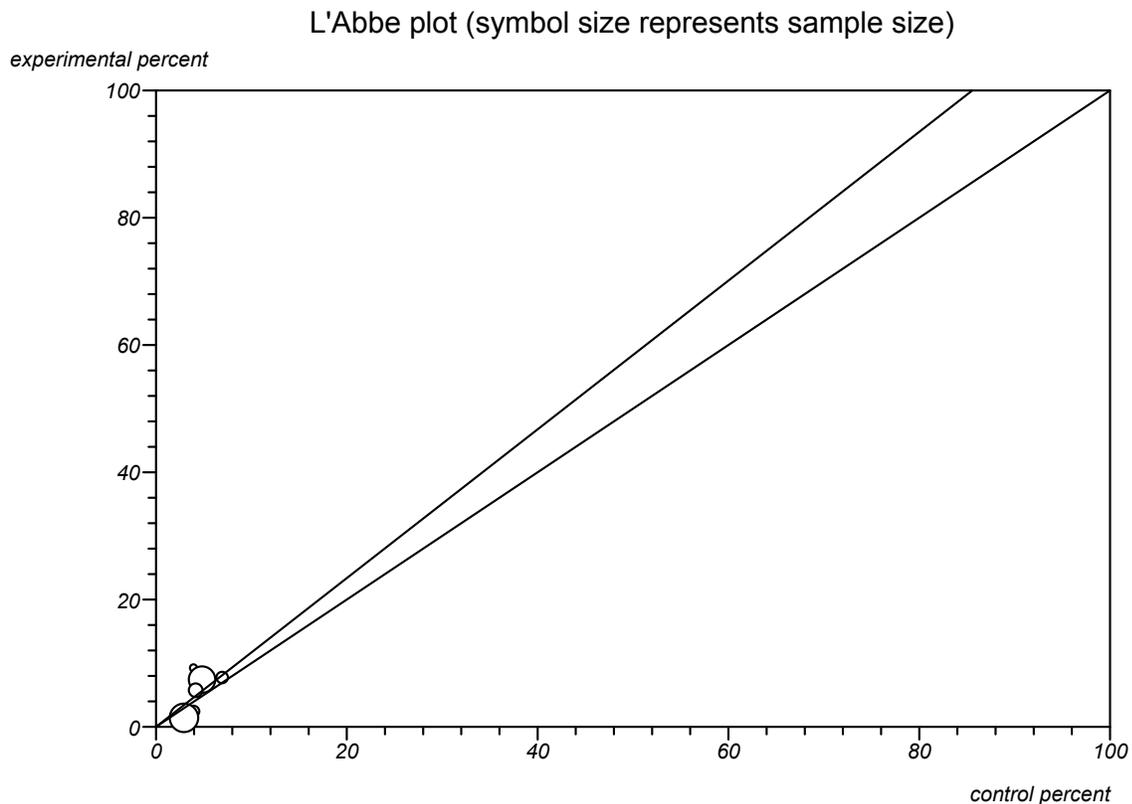


Figure 6-e. Heterogeneity indicators for the outcome of “Headache” in the studies considering exenatide 10 µg comparing to placebo therapy.

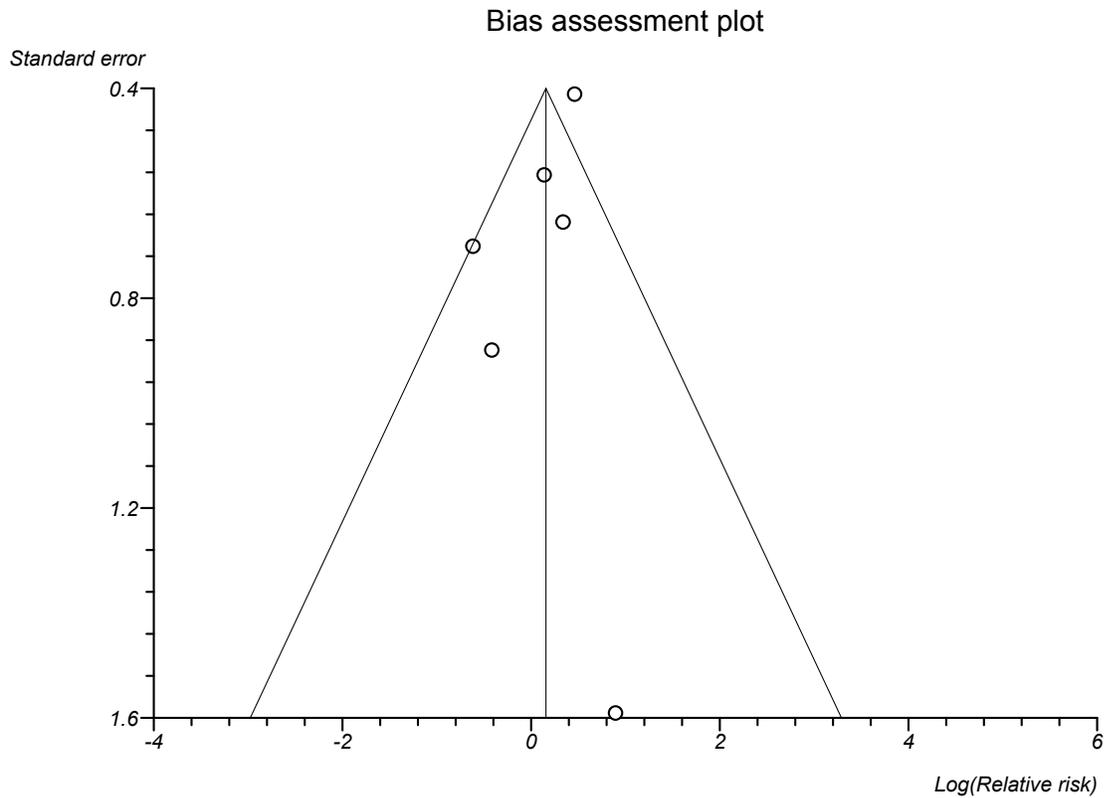


Figure 6-f. Publication bias indicators for the outcome of “Headache” in the studies considering exenatide 10 µg comparing to placebo therapy.

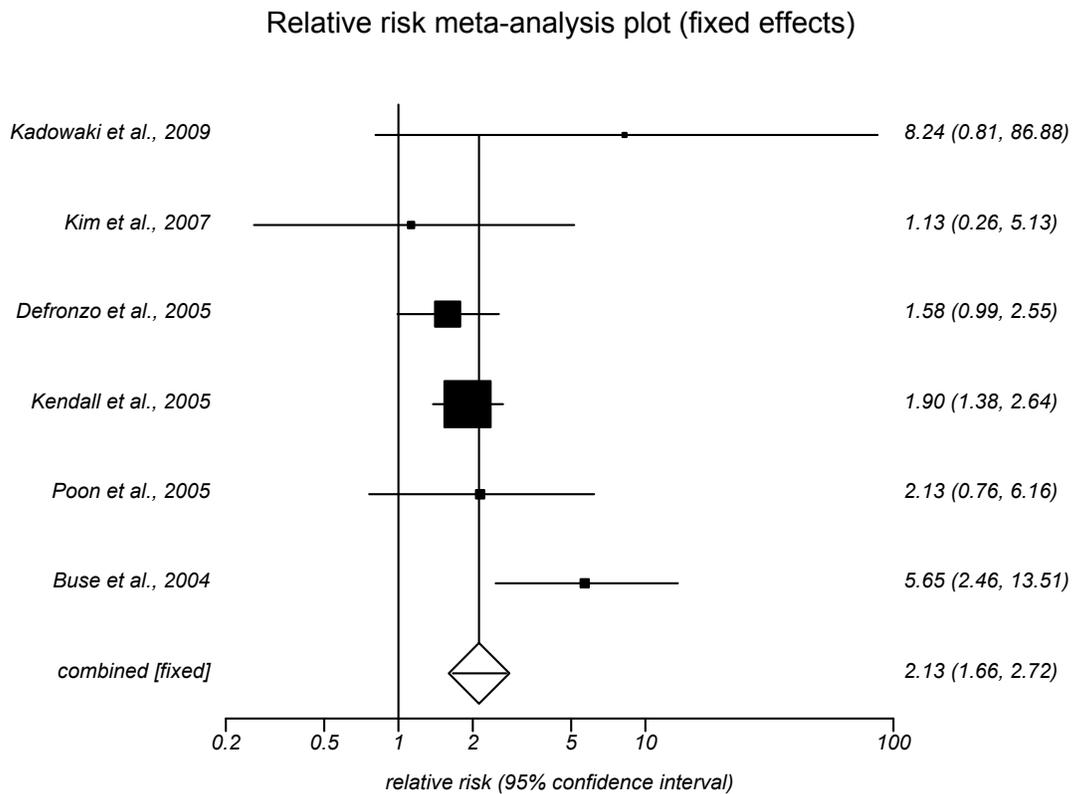


Figure 7-a. Individual and pooled effect size for weighted mean difference for the outcome of “Nausea” in the studies considering exenatide 5 µg comparing to placebo therapy.

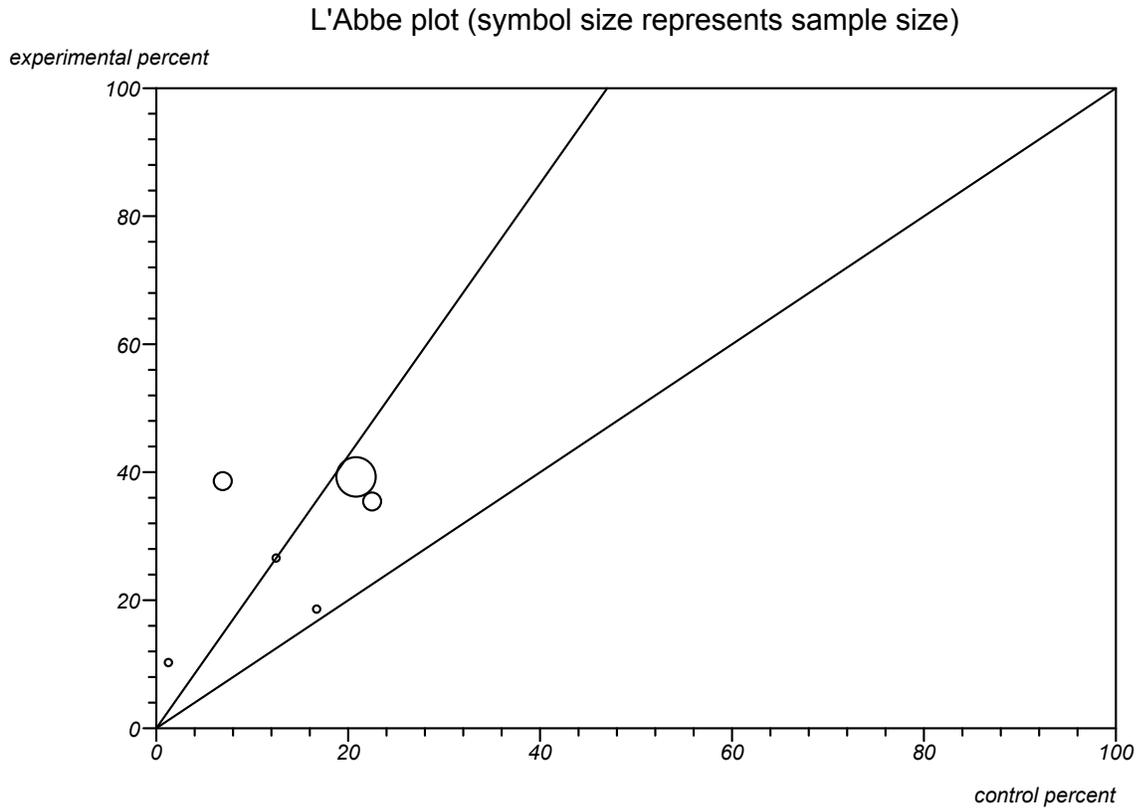


Figure 7-b. Heterogeneity indicators for the outcome of “Nausea” in the studies considering exenatide 5 μ g comparing to placebo therapy.

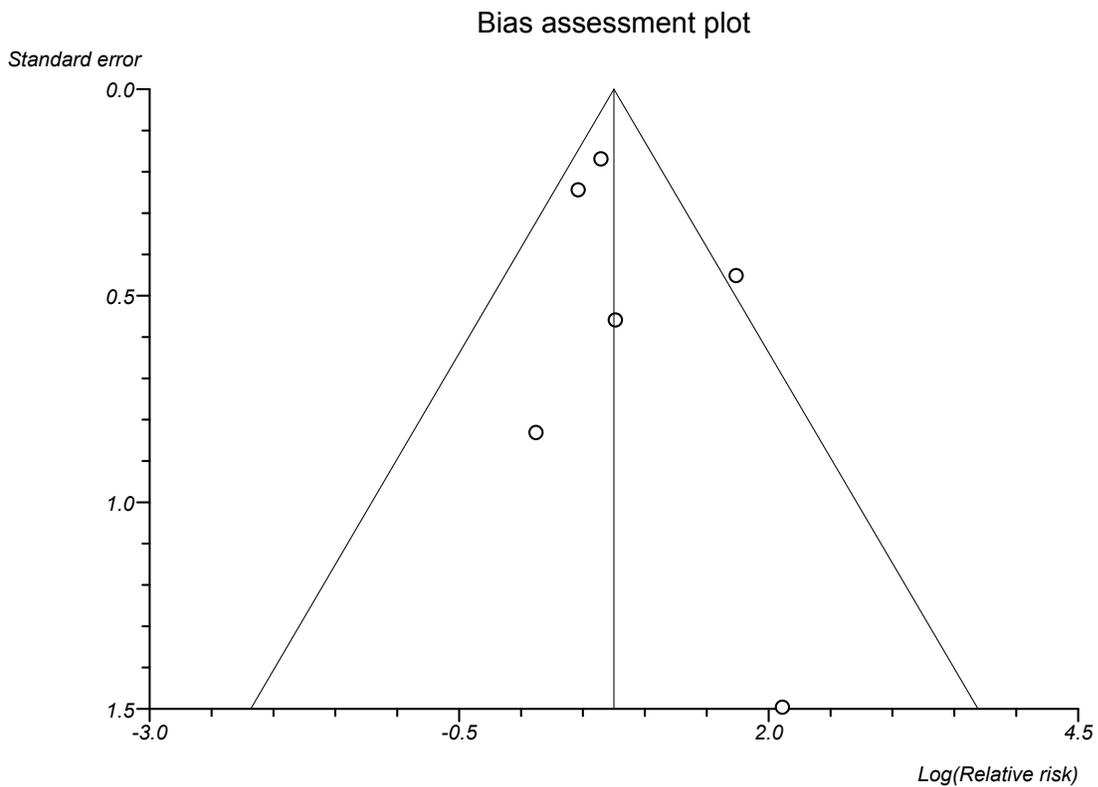


Figure 7-c. Publication bias indicators for the outcome of “Nausea” in the studies considering exenatide 5 μ g comparing to placebo therapy.

Relative risk meta-analysis plot (random effects)

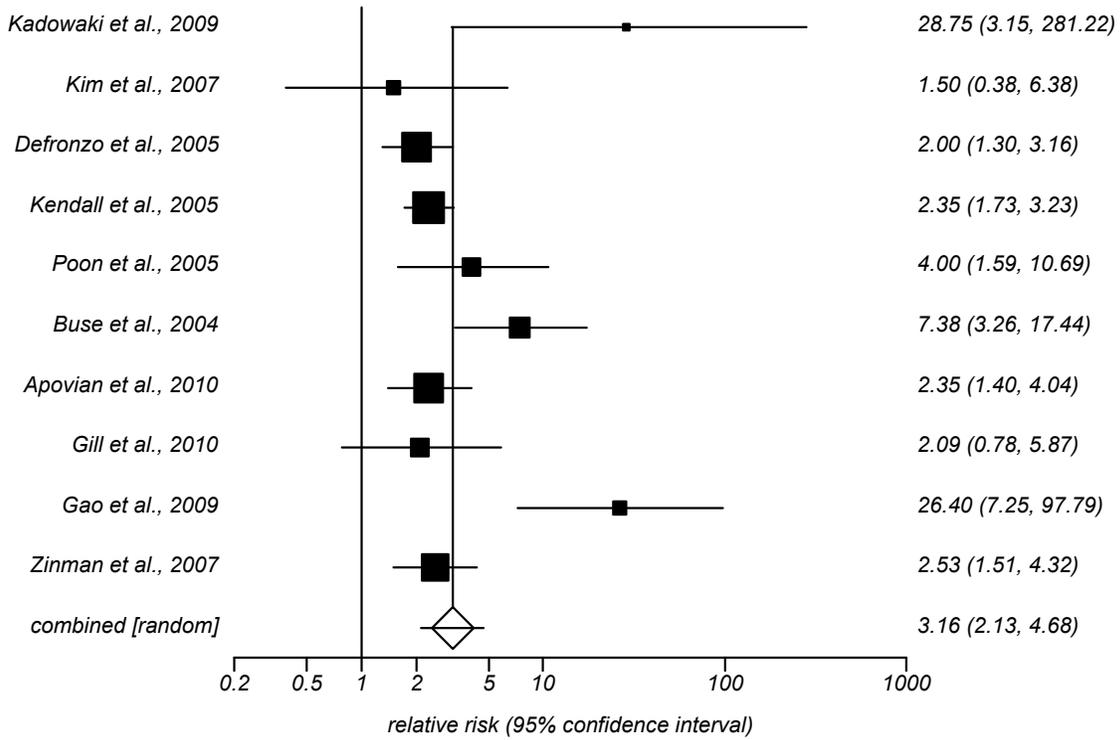


Figure 7-d. Individual and pooled effect size for weighted mean difference for the outcome of “Nausea” in the studies considering exenatide 10 µg comparing to placebo therapy.

L'Abbe plot (symbol size represents sample size)

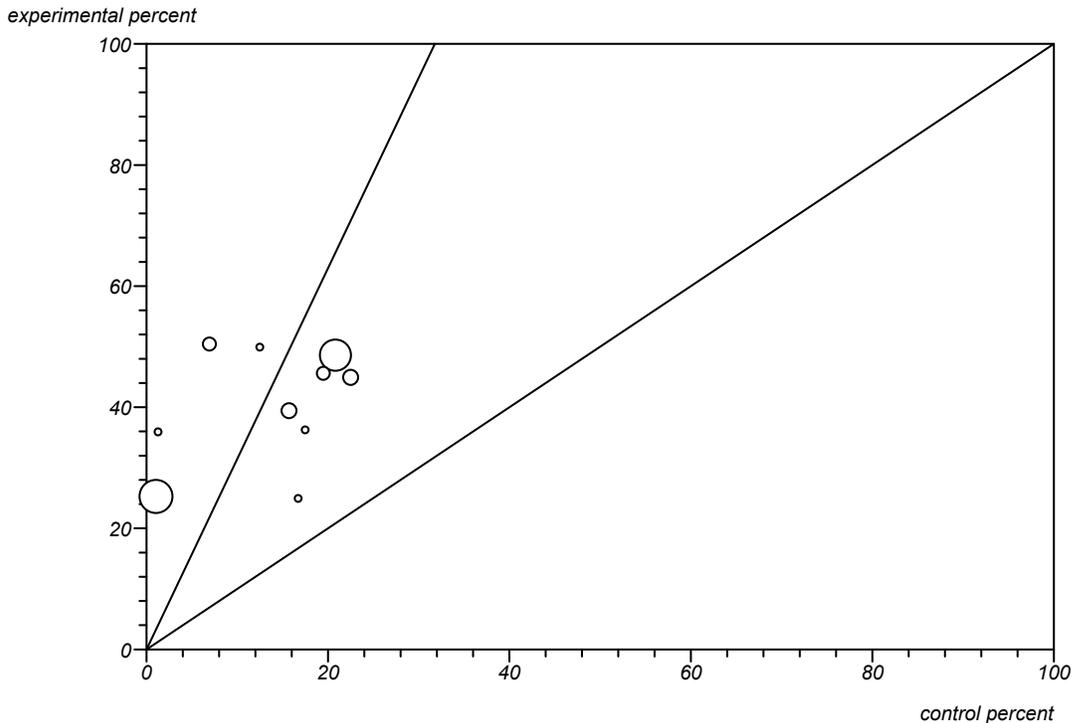


Figure 7-e. Heterogeneity indicators for the outcome of “Nausea” in the studies considering exenatide 10 µg comparing to placebo therapy.

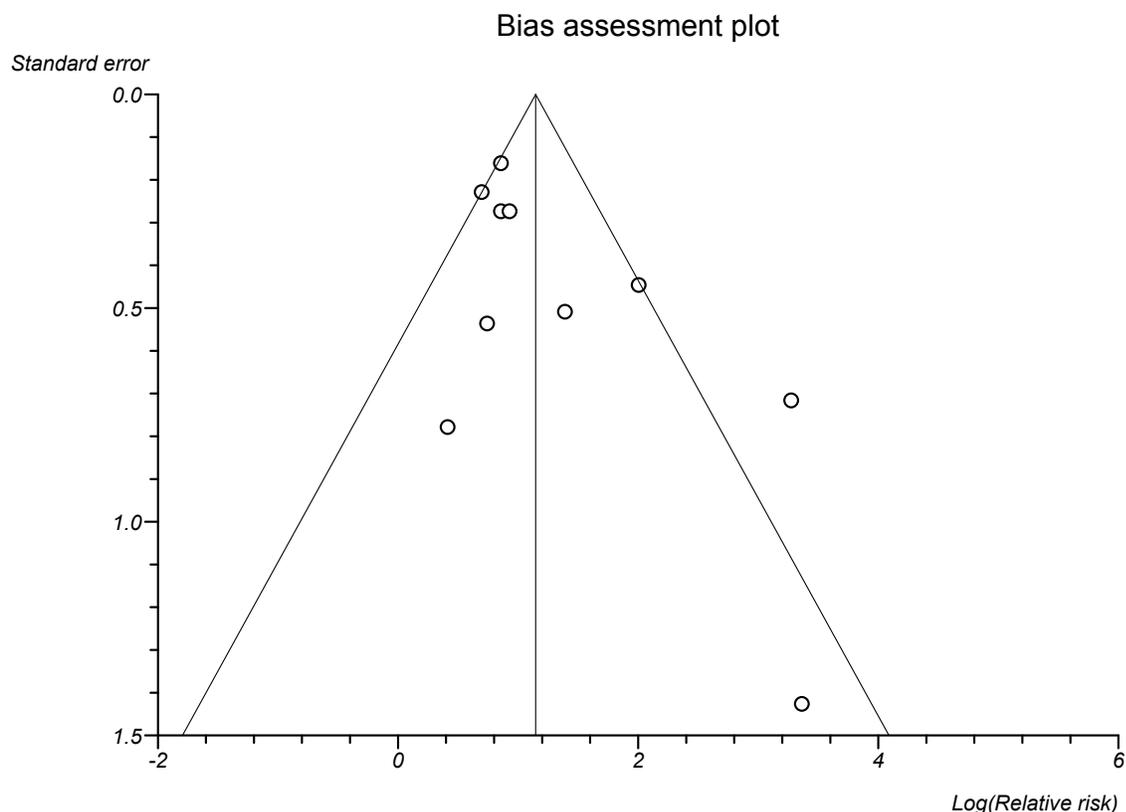


Figure 7-f. Publication bias indicators for the outcome of “Nausea” in the studies considering exenatide 10 µg comparing to placebo therapy.

Diarrhea

The summary RR for the number of patients who reported diarrhea by exenatide 5 µg twice daily in four trials [19,23-25] was 1.43 with a 95% CI of 0.92 to 2.21 and a non significant RR ($P= 0.11$, Figure 8-a). The Cochrane Q test for heterogeneity indicated that the studies are not heterogeneous ($P= 0.32$, Figure 8-b) and could be combined; thus the fixed effects for individual and summary of RR was applied. Regression of normalized effect versus precision for all included studies for the number of patients who reported diarrhea by exenatide 5 µg vs. placebo therapy was 1.66 (95% CI= -3.81 to 7.14, $P= 0.32$), and Kendall’s test on standardized effect vs. variance indicated $\tau= 0.33$, $P= 0.75$ (Figure 8-c).

The summary RR for the number of patients who reported diarrhea by exenatide 10 µg twice daily in six trials [19,23-25,27,30] was 1.87 with a 95% CI of 1.28 to 2.74 and a significant RR ($P= 0.0011$, Figure 8-d). The Cochrane Q test for heterogeneity indicated that the studies are not heterogeneous ($P= 0.16$, Figure 8-e) and could be combined, thus the fixed effects for individual and summary of RR was applied. Regression of

normalized effect versus precision for all included studies for the number of patients who reported diarrhea by exenatide 10 µg vs. placebo therapy was 0.22 (95% CI= -3.84 to 4.28, $P= 0.89$), and Kendall’s test on standardized effect vs. variance indicated $\tau= 0.07$, $P > 1$ (Figure 8-f).

Vomiting

The summary RR for the number of patients who reported vomiting by exenatide 5 µg twice daily in five trials [19,21,23-25] was 4.31 with a 95% CI of 2.46 to 7.55 and a significant RR ($P < 0.0001$, Figure 9-a). The Cochrane Q test for heterogeneity indicated that the studies are not heterogeneous ($P= 0.91$, Figure 9-b) and could be combined; thus the fixed effects for individual and summary of RR was applied.

Regression of normalized effect versus precision for all included studies for the number of patients who reported vomiting by exenatide 5 µg vs. placebo therapy was 0.69 (95% CI= -0.21 to 1.59, $P= 0.09$), and Kendall’s test on standardized effect vs. variance indicated $\tau= 0.4$, $P= 0.48$ (Figure 9-c).

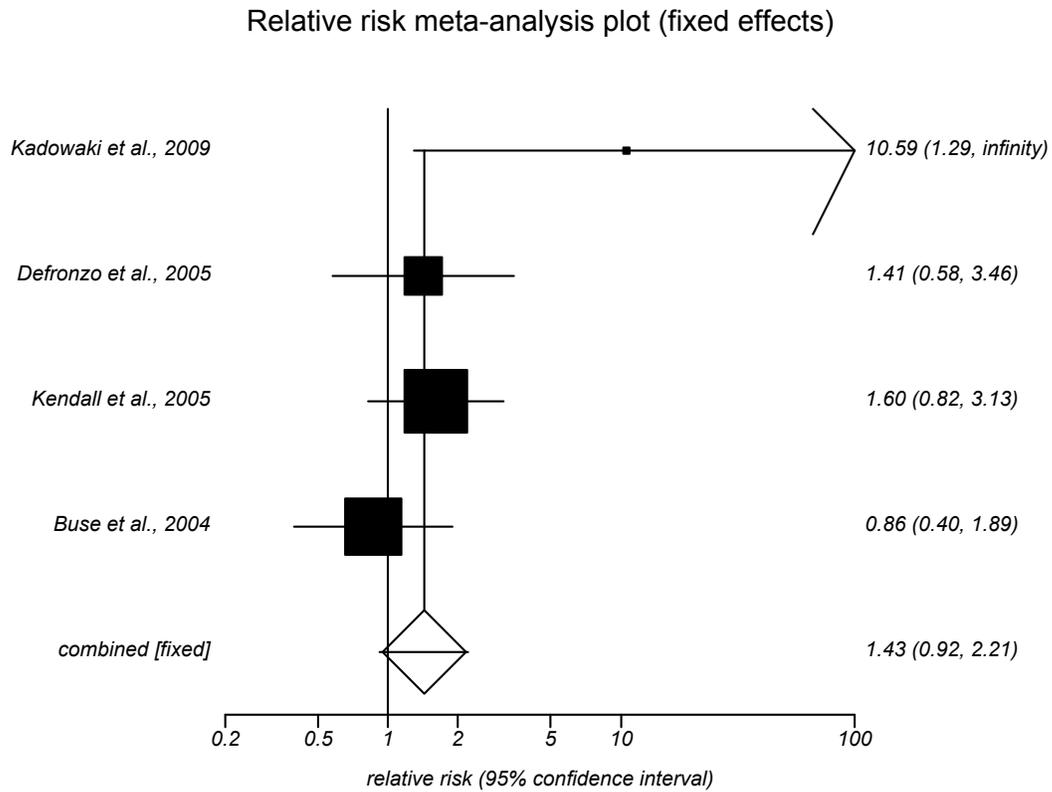


Figure 8-a. Individual and pooled effect size for weighted mean difference for the outcome of “Diarrhea” in the studies considering exenatide 5 µg comparing to placebo therapy.

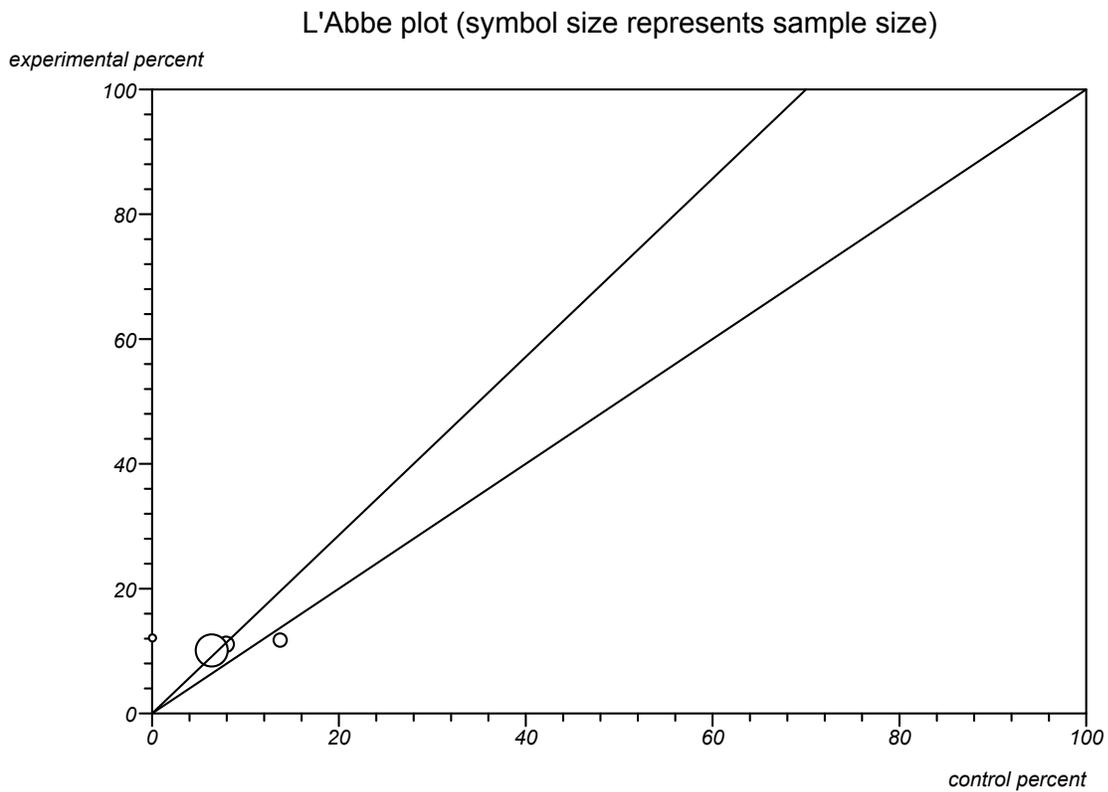


Figure 8-b. Heterogeneity indicators for the outcome of “Diarrhea” in the studies considering exenatide 5 µg comparing to placebo therapy.

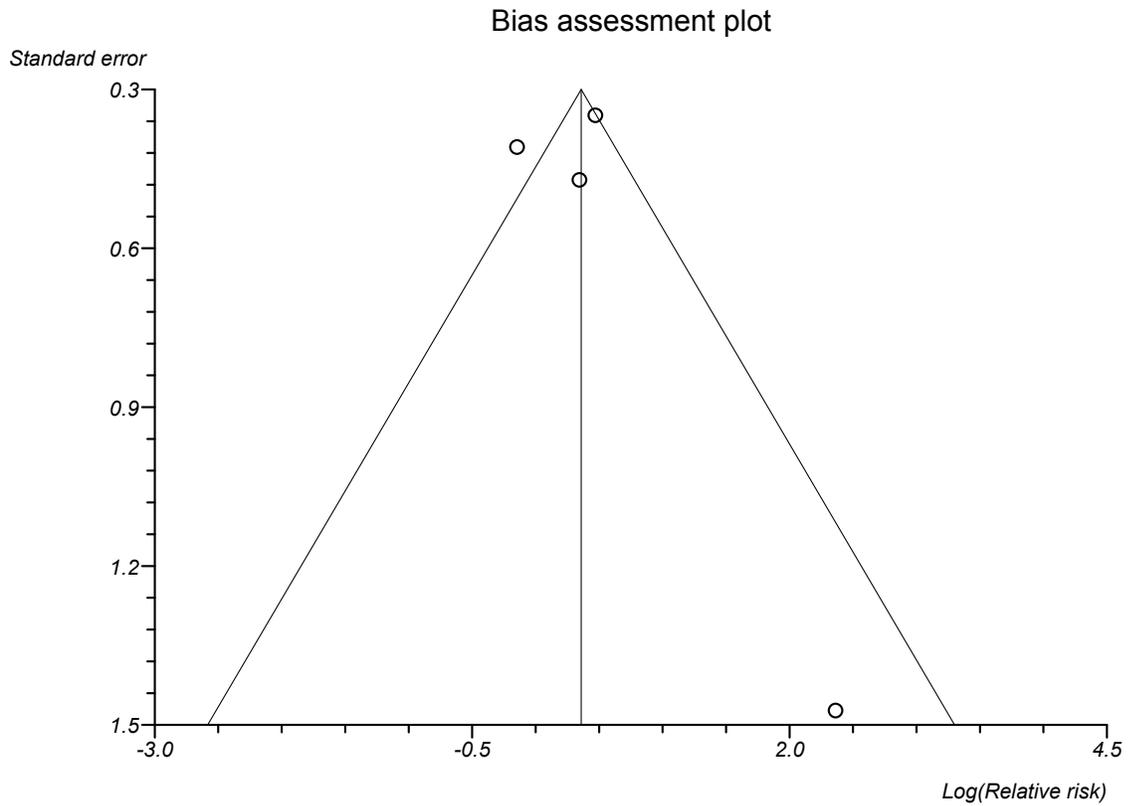


Figure 8-c. Publication bias indicators for the outcome of “Diarrhea” in the studies considering exenatide 5 µg comparing to placebo therapy.

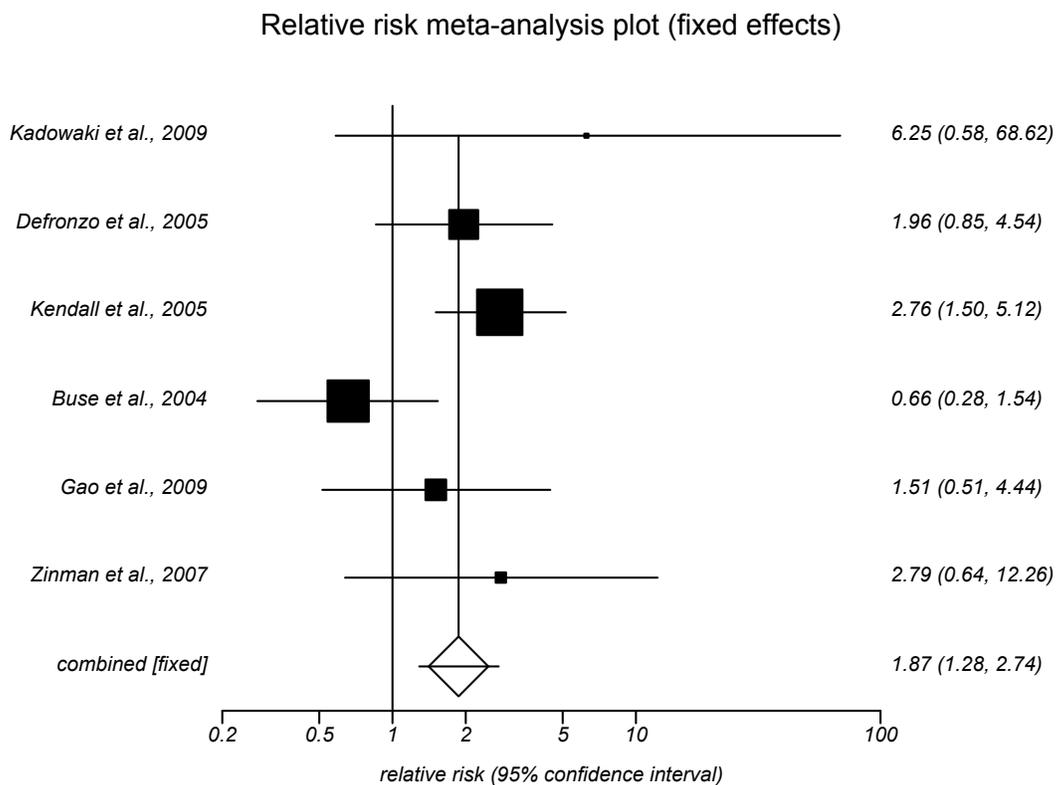


Figure 8-d. Individual and pooled effect size for weighted mean difference for the outcome of “Diarrhea” in the studies considering exenatide 10 µg comparing to placebo therapy.

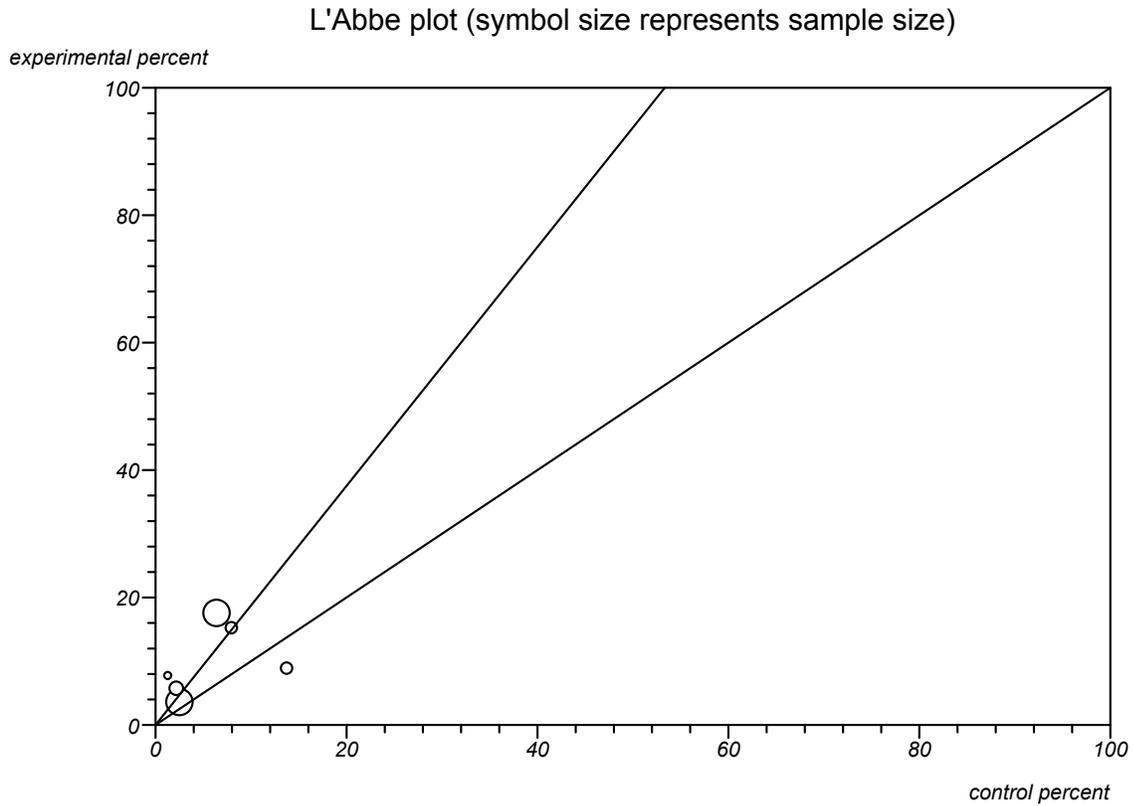


Figure 8-e. Heterogeneity indicators for the outcome of “Diarrhea” in the studies considering exenatide 10 µg comparing to placebo therapy.

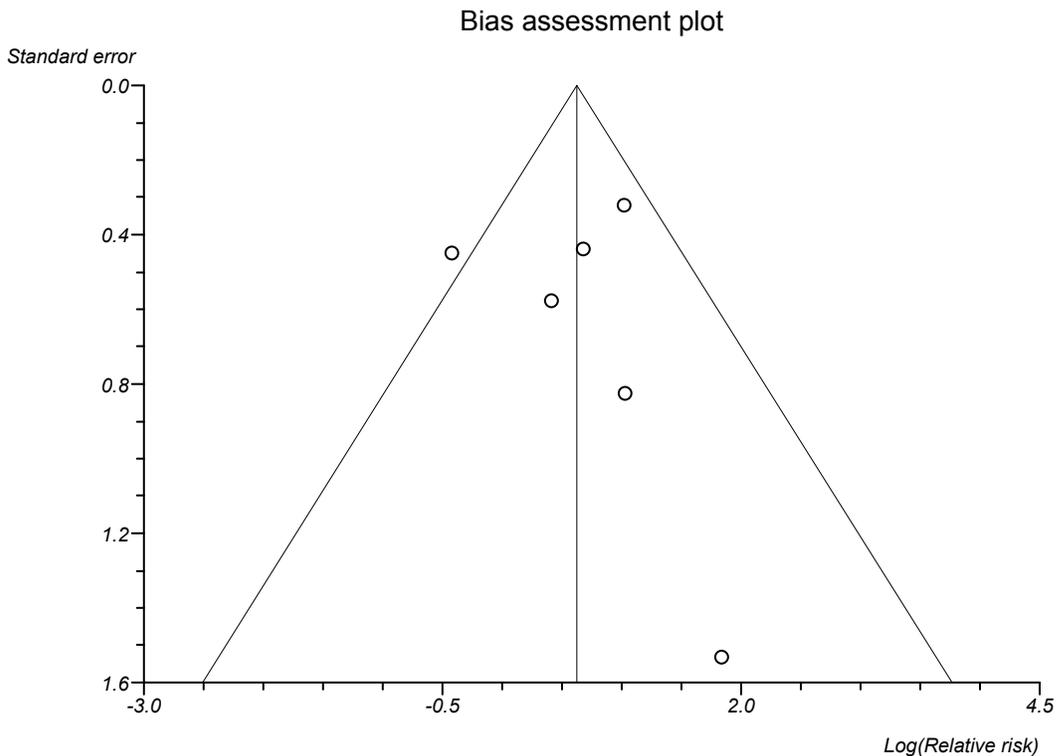


Figure 8-f. Publication bias indicators for the outcome of “Diarrhea” in the studies considering exenatide 10 µg comparing to placebo therapy.

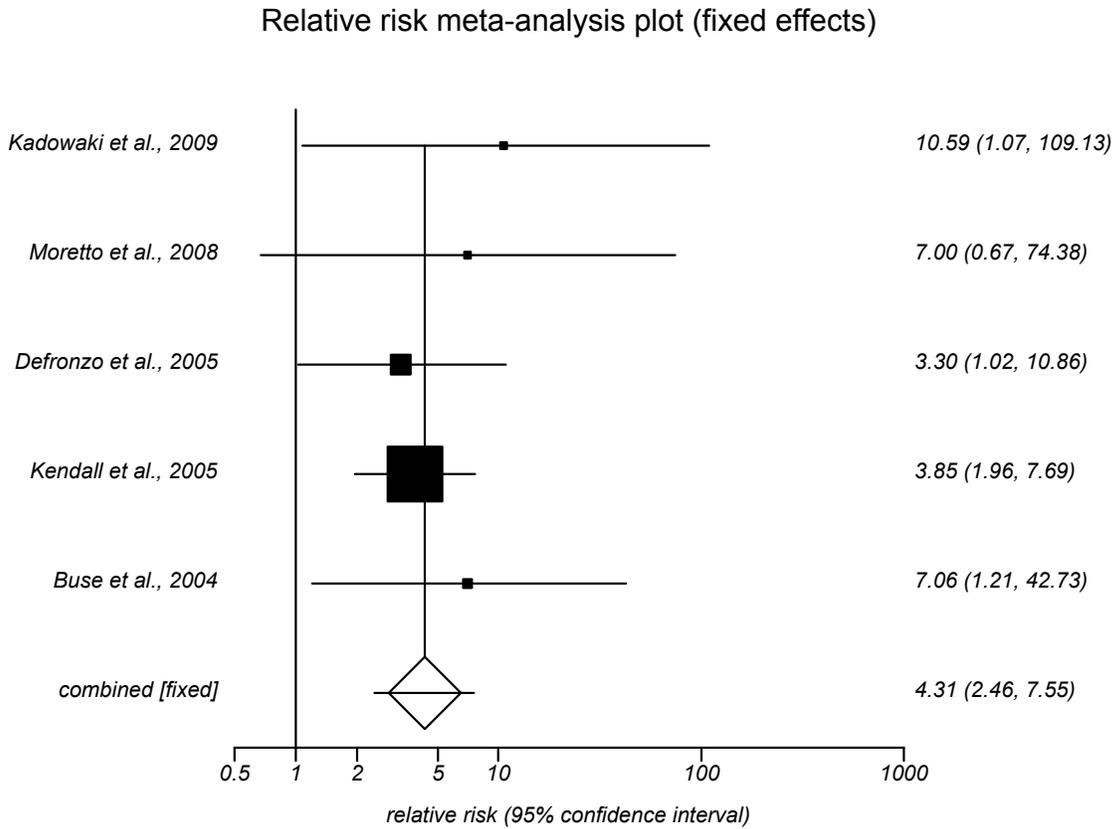


Figure 9-a. Individual and pooled effect size for weighted mean difference for the outcome of “Vomiting” in the studies considering exenatide 5 µg comparing to placebo therapy.

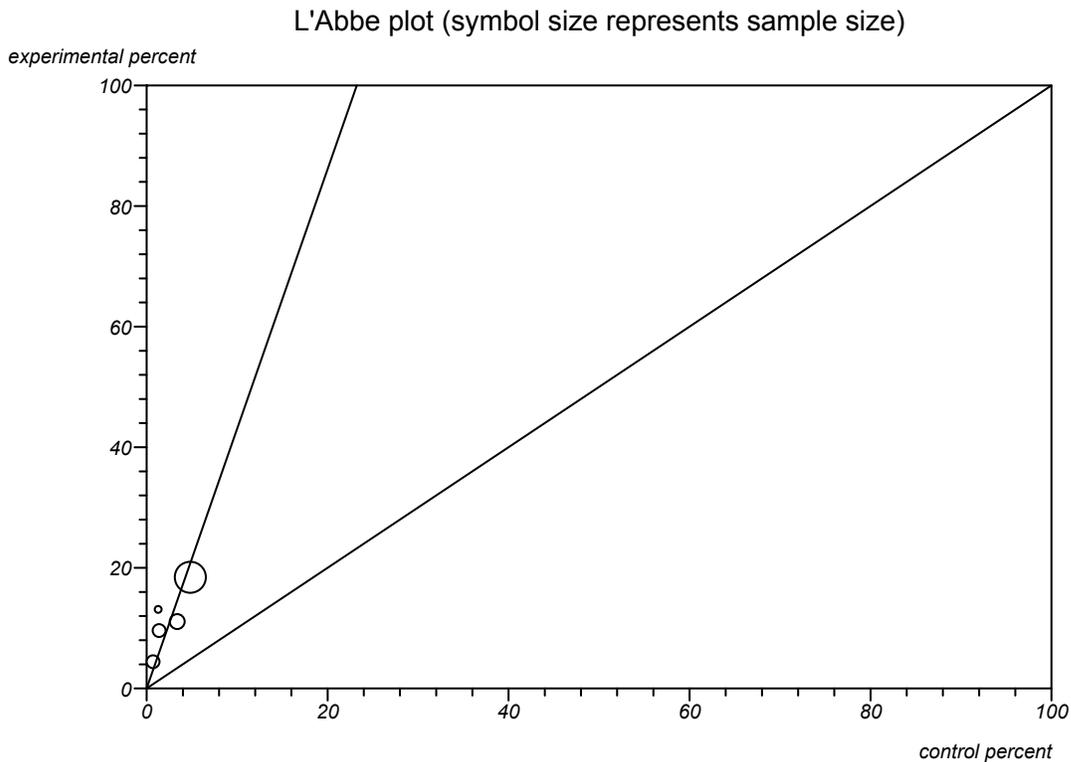


Figure 9-b. Heterogeneity indicators for the outcome of “Vomiting” in the studies considering exenatide 5 µg comparing to placebo therapy.

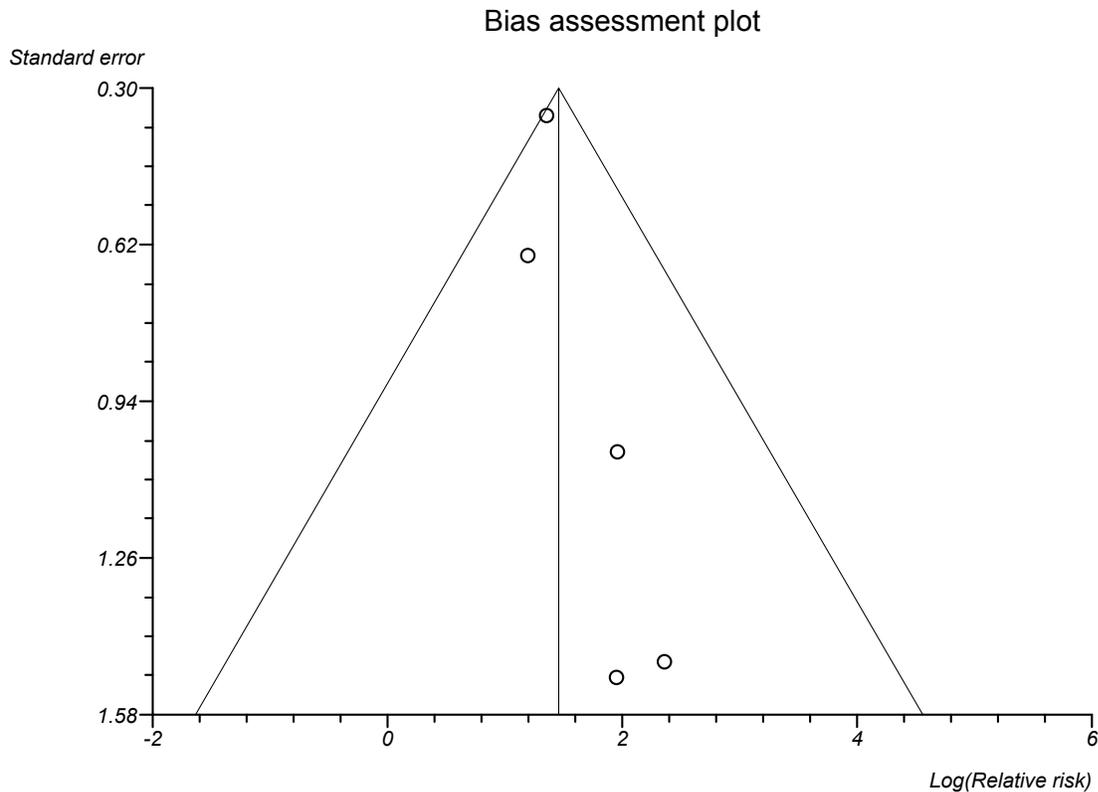


Figure 9-c. Publication bias indicators for the outcome of “Vomiting” in the studies considering exenatide 5 μg comparing to placebo therapy.

The summary RR for the number of patients who reported vomiting by exenatide 10 μg twice daily in nine trials [19-21,23-27,30] was 4.87 with a 95% CI of 3.17 to 7.48 and a significant RR ($P < 0.0001$, Figure 9-d). The Cochrane Q test for heterogeneity indicated that the studies are not heterogeneous ($P = 0.20$, Figure 9-e) and could be combined, thus the fixed effects for individual and summary of RR was applied. Regression of normalized effect versus precision for all included studies for the number of patients who reported vomiting by exenatide 10 μg vs. placebo therapy was 1.47 (95% CI= 0.26 to 2.67, $P = 0.02$), and Kendall’s test on standardized effect vs. variance indicated tau= 0.39, $P = 0.18$ (Figure 9-f).

Hypoglycemia

The summary RR for the number of patients who reported hypoglycemia by exenatide 5 μg twice daily in six trials [19,21-25] was 2.19 with a 95% CI of 1.49 to 3.2 and a significant RR ($P < 0.0001$, Figure 10-a). The Cochrane Q test for heterogeneity indicated that the studies are not heterogeneous ($P = 0.15$, Figure 10-b) and could be combined, thus the

fixed effects for individual and summary of RR was applied. Regression of normalized effect versus precision for all included studies for the number of patients who reported hypoglycemia by exenatide 5 μg vs. placebo therapy was 1.31 (95% CI= -0.9 to 3.52, $P = 0.18$), and Kendall’s test on standardized effect vs. variance indicated tau= 0.2, $P = 0.72$ (Figure 10-c).

The summary RR for the number of patients who reported hypoglycemia by exenatide 10 μg twice daily in ten trials [19,21-25,27,29-31] was 3.18 with a 95% CI of 2.42 to 4.16 and a significant RR ($P < 0.0001$, Figure 10-d). The Cochrane Q test for heterogeneity indicated that the studies are not heterogeneous ($P = 0.09$, Figure 10-e) and could be combined, thus the fixed effects for individual and summary of RR was applied. Regression of normalized effect versus precision for all included studies for the number of patients who reported hypoglycemia by exenatide 10 μg vs. placebo therapy was -0.3 (95% CI= -1.93 to 1.3, $P = 0.68$), and Kendall’s test on standardized effect vs. variance indicated tau= 0.02, $P > 1$ (Figure 10-f).

Relative risk meta-analysis plot (fixed effects)

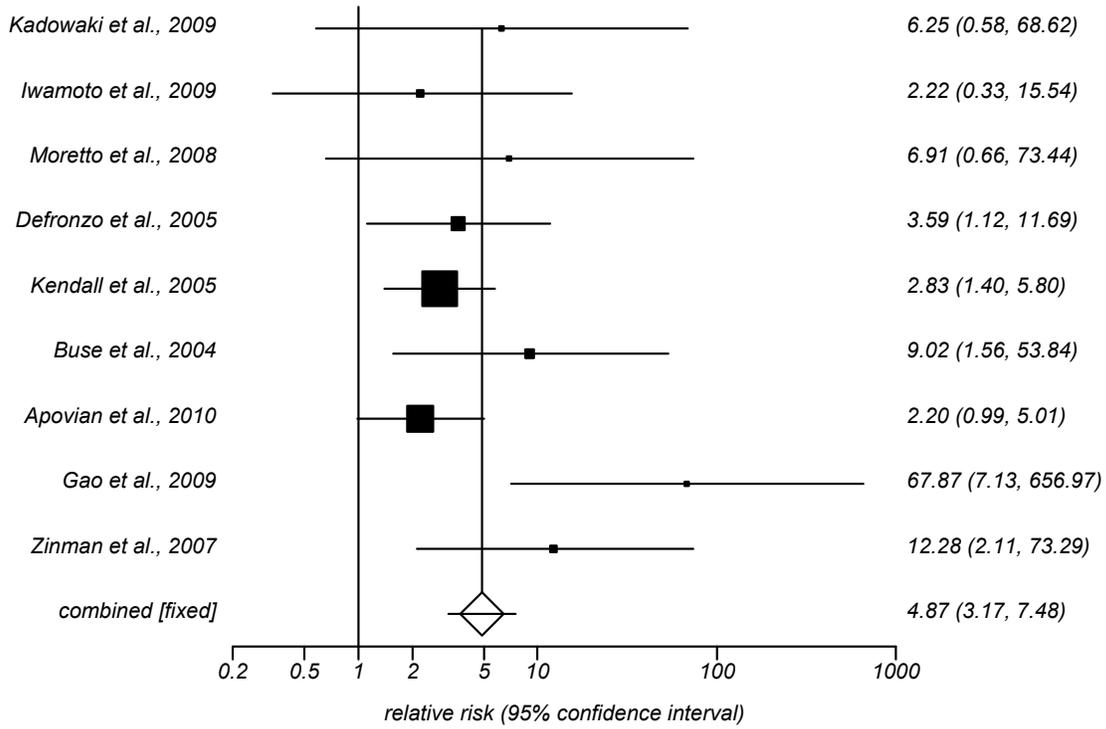


Figure 9-d. Individual and pooled effect size for weighted mean difference for the outcome of “Vomiting” in the studies considering exenatide 10 µg comparing to placebo therapy.

L'Abbe plot (symbol size represents sample size)

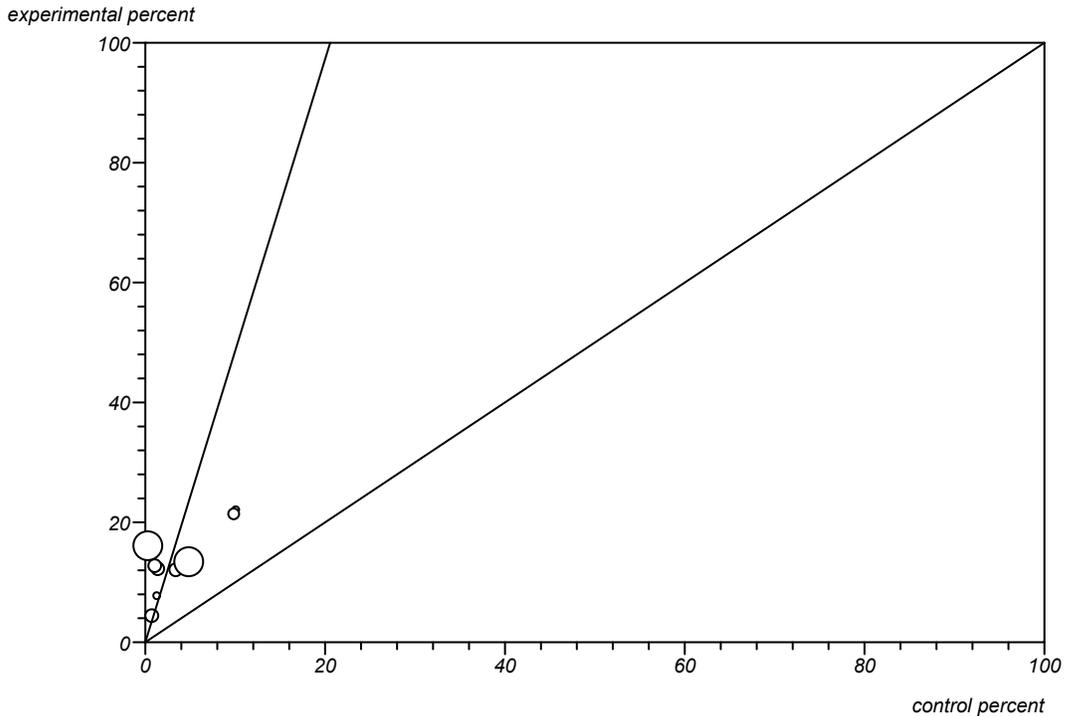


Figure 9-e. Heterogeneity indicators for the outcome of “Vomiting” in the studies considering exenatide 10 µg comparing to placebo therapy.

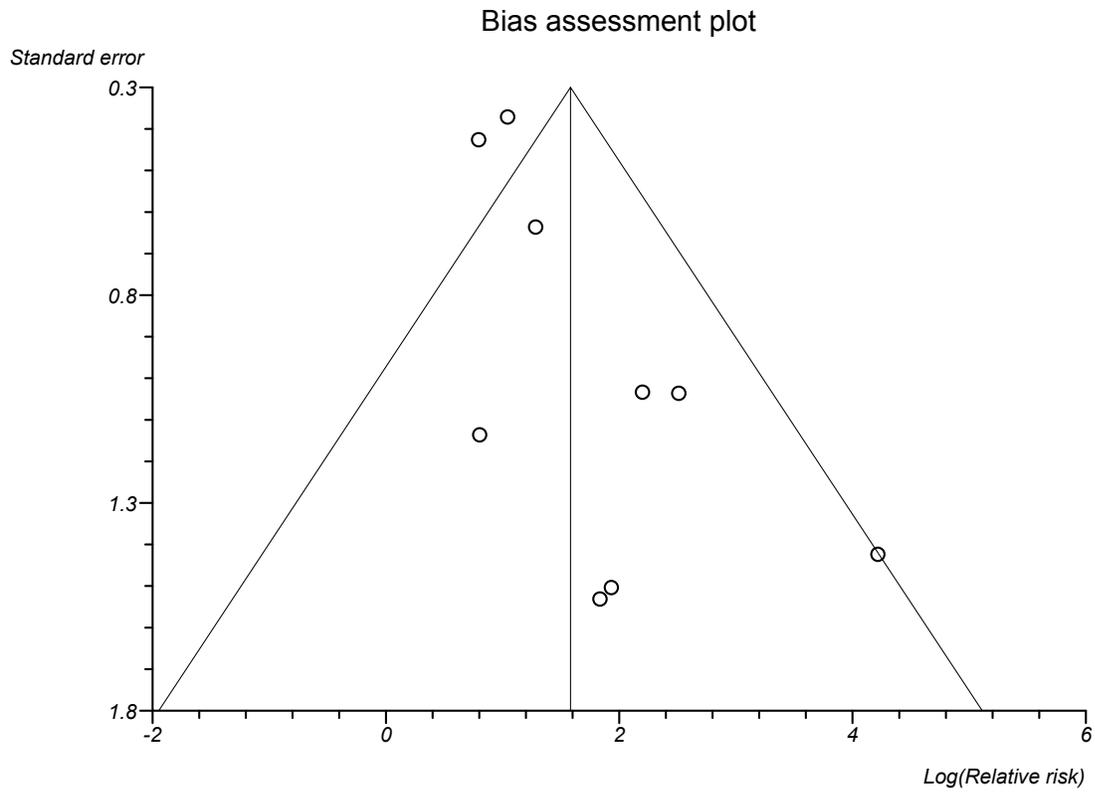


Figure 9-f. Publication bias indicators for the outcome of “Vomiting” in the studies considering exenatide 10 µg comparing to placebo therapy.

Relative risk meta-analysis plot (fixed effects)

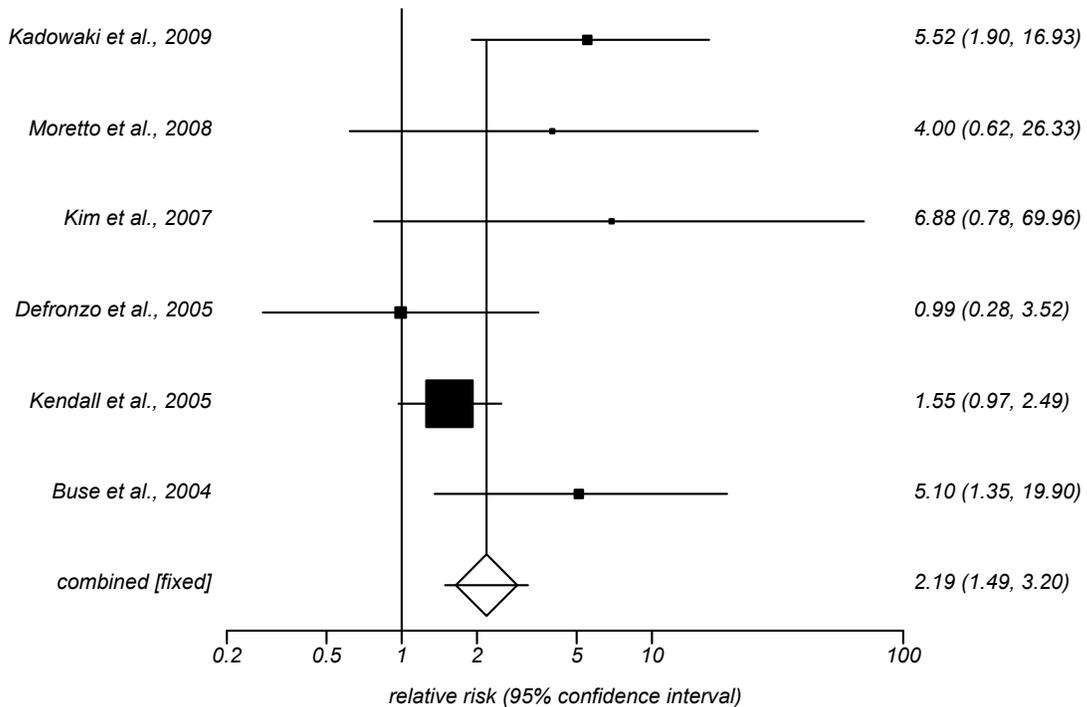


Figure 10-a. Individual and pooled effect size for weighted mean difference for the outcome of “Hypoglycemia” in the studies considering exenatide 5 µg comparing to placebo therapy.

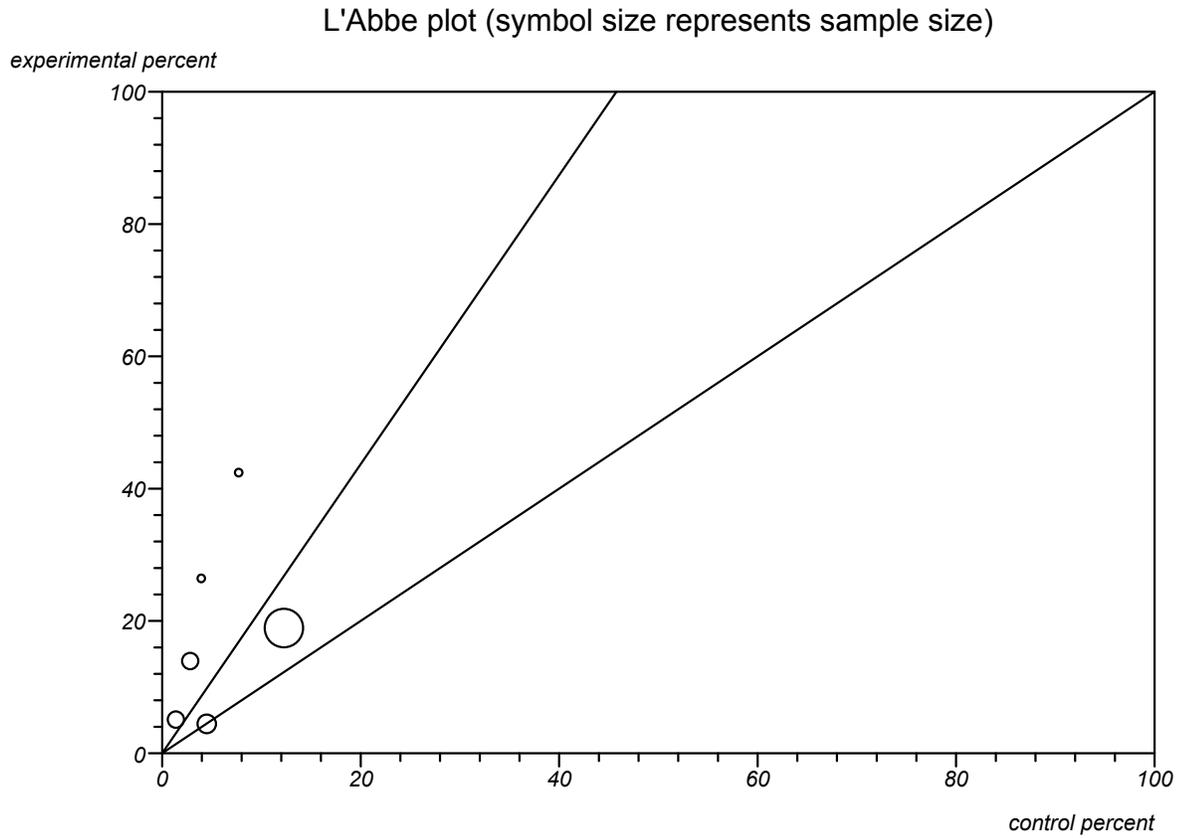


Figure 10-b. Heterogeneity indicators for the outcome of “Hypoglycemia” in the studies considering exenatide 5 μg comparing to placebo therapy.

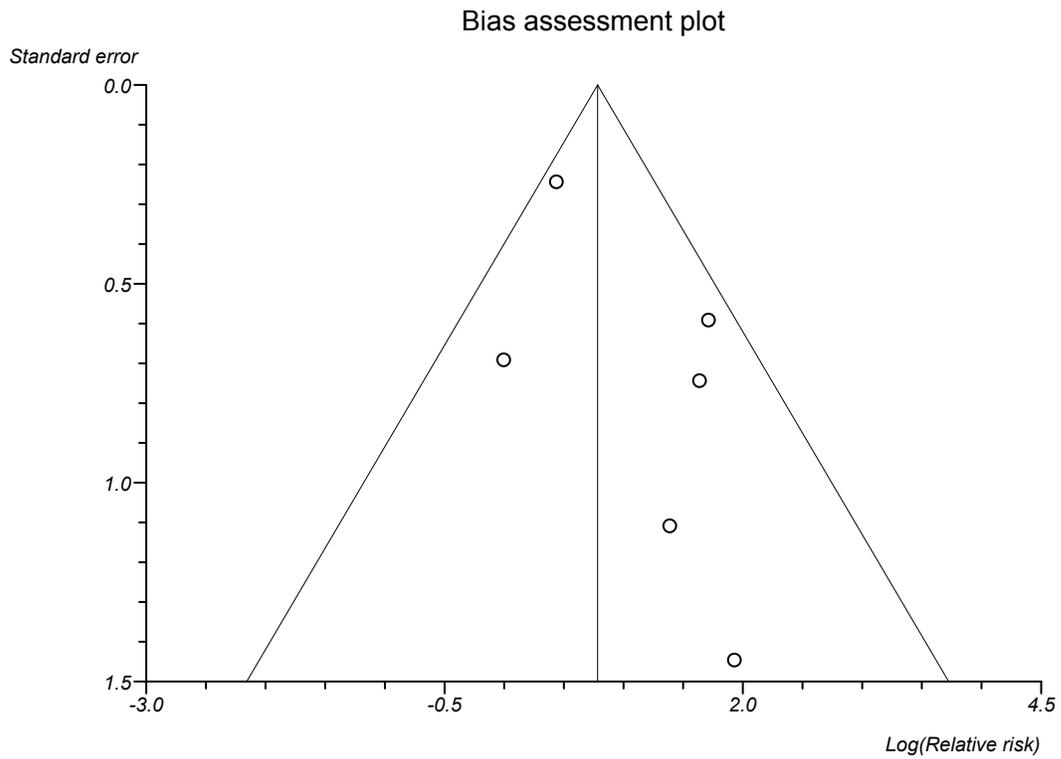


Figure 10-c. Publication bias indicators for the outcome of “Hypoglycemia” in the studies considering exenatide 5 μg comparing to placebo therapy.

Relative risk meta-analysis plot (fixed effects)

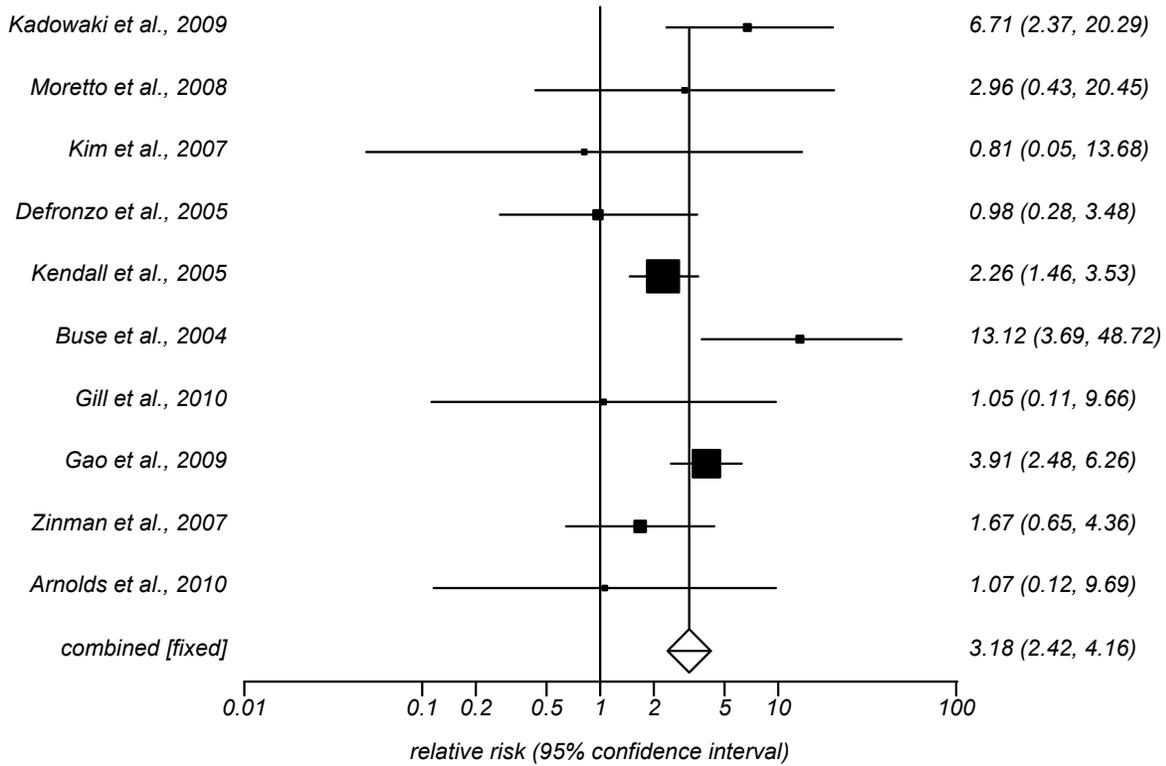


Figure 10-d. Individual and pooled effect size for weighted mean difference for the outcome of “Hypoglycemia” in the studies considering exenatide 10 µg comparing to placebo therapy.

L'Abbe plot (symbol size represents sample size)

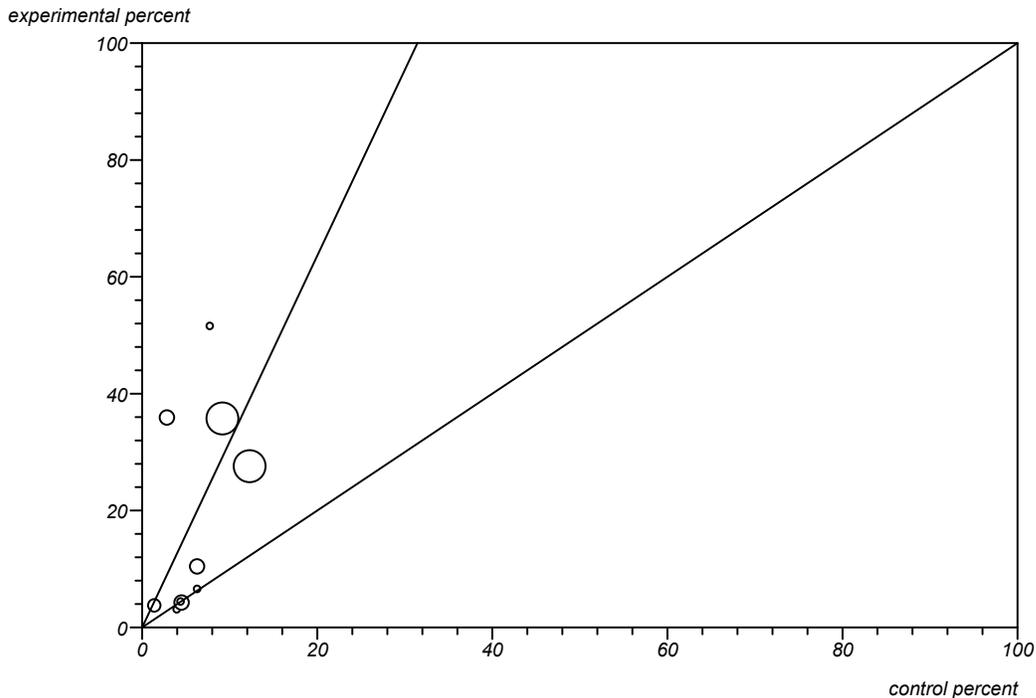


Figure 10-e. Heterogeneity indicators for the outcome of “Hypoglycemia” in the studies considering exenatide 10 µg comparing to placebo therapy.

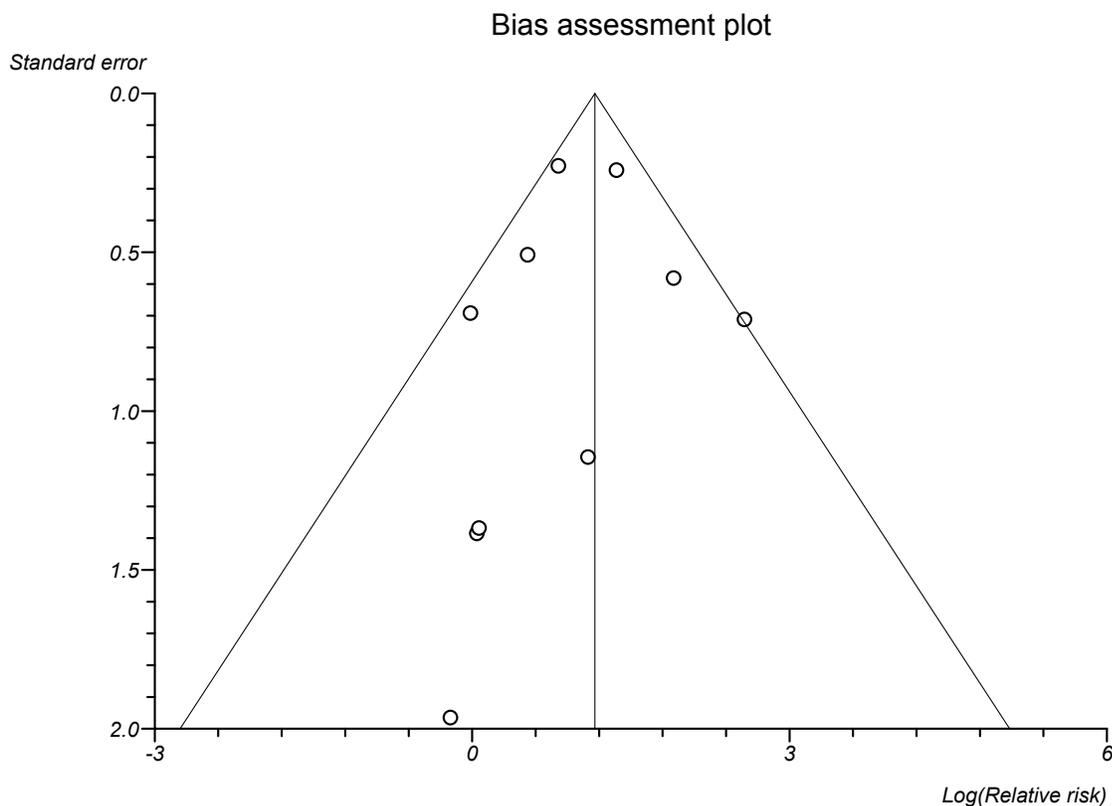


Figure 10-f. Publication bias indicators for the outcome of “Hypoglycemia” in the studies considering exenatide 10 μg comparing to placebo therapy.

DISCUSSION

Several clinical trials have examined efficacy of exenatide in controlling blood sugar as well as its safety profile. Although most of the studies showed similarities in its effectiveness on decreasing FPG and HbA1c, the results of the trials on body weight and also the prevalence of its adverse effects are not conclusive. An important notification is the study design in different trials which was different according to their duration and dosage of treatment. Therefore, we analyzed data only provided by placebo-controlled trials considering study periods of 16 weeks and less or more as well as the dosage of exenatide (5 or 10 μg /twice daily). Considering the crucial role of glycemic control in decreasing the complications of the disease, several protocols are available; some of them propose adding a hypoglycemic agent to the insulin which showed favorable effects [33, 34]. So in this study we decided to analyze the placebo-controlled clinical trials. To prevent bias, in cases which studies showed heterogeneity, the random effects method for individual and summary of RR was applied. The

present results show that exenatide fundamentally decreases FPG regardless of its dosage or duration of administration. Pinelli et al. observed similar results in their meta-analysis but they included all exenatide clinical trials (placebo and non-placebo trials) and excluded the studies with less than 24 weeks duration [35]. In a meta-analysis performed by Amori et al in spite of considering all exenatide trials (placebo and non-placebo trials) and excluding studies shorter than 12 weeks, a modest decrease in FPG was observed [36]. Although Fakhoury et al. conducted a meta-analysis which excluded samples size less than 100 patients, their results in FPG was the same as our results [37].

In accordance with controlling FPG, the analysis of the results demonstrated significant decrement in HbA1C regardless of the dose and study period. Although Fakhoury et al. did not measure the effect of exenatide or other incretin mimetics on FPG, their results showed similar decrements in HbA1C (37). The study design of Fakhoury et al was similar to our study. Monami et al. designed their study similar to the study of Amori et al. while their results on HbA1c support

our findings [38]. In accordance with these findings, two other meta-analysis with different designs confirmed the efficacy of exenatide on HbA1c [35,36], however Pinelli et al. insisted on the superiority of thiazolidindiones on reducing HbA1c [35].

According to the strict association between body weight and diabetes, body weight reduction seems highly favorable and in this direction many drugs and herbal medicines were examined [39]. Our results showed that exenatide administration at 5 µg twice daily in less than 16 weeks does not change weight significantly while exenatide administration more than 16 weeks decreases weight significantly regardless of dosage. In addition using exenatide at the dose of 10 µg twice daily for less than 16 weeks can change patients' weight significantly. Although our results are in agreement with previous reports [37, 38], Pinelli et al suggested weight reduction only in obese patients [35], and Amori et al. stated progressive reduction in weight even after 30 weeks [36].

In addition to the other favorable metabolic effects of exenatide, it showed satisfactory effect on lipid profile. Lipid profile has crucial importance in the incidence of diabetes complications especially vascular events. The influence of tight lipid control on the reduction of incidence of vascular events in Japanese population has been reported [40]. Statins as the most effective lipid lowering agents are used for a long time in diabetes but their efficacy and tolerability are different [41]. Some short-term studies reported the impartial effect of exenatide on serum lipid concentration [23,25,27], however other clinical trials observed promising as well as variable results depending on the type of lipid [19,21,26]. Regardless of dosage and duration, our analysis represents significant reduction in TG with no effect on total cholesterol. Consistent with these results, we analyzed the results of two clinical trials and found significant reduction in LDL and significant increase in HDL concentration at the dose of 5 µg twice daily. In an interim analysis, significant changes in HDL and TG levels with neutral effect of exenatide on total cholesterol and LDL were reported [42].

Cardiovascular events are considered as one of the leading causes of death in diabetic patients. Obviously blood pressure control reduces the risk of cardiovascular events. Exenatide has agonistic effect on glucagon-like peptide-1 (GLP-1) receptors. Although GLP-1 affects heart rate and blood pressure by activating its receptors [43, 44] or

acting peripherally [45, 46] in rodents, little is known about its hemodynamic effects in human. In long term clinical trials it was reported that exenatide improves systolic blood pressure [21, 26].

Although the changes in BP were evaluated in a limited number of clinical trials, to date no convincing data are available. Our meta-analysis indicates that exenatide at the dose of 10 µg twice daily decreases both systolic and diastolic BP significantly but the effect is not seen at lower doses. In agreement with our results, a previous interim analysis reported significant decrease in diastolic BP with a non-significant decrease in systolic BP [42].

One of the most important issues in introduction of new drugs is their safety profile which has been evaluated for exenatide in many clinical trials; however there is no common evaluation system to make comparison easy.

The most common reported adverse effect of exenatide was nausea and vomiting which are not related to the dose or duration of treatment. In our meta-analysis, the relative risk of nausea and vomiting was significant at both doses. The RR of hypoglycemic events was significant at both doses which is in accordance with other meta-analyses [36-38], however some other studies could not achieve similar results [35,42]. Although, the nonlinear relationship between hypoglycemic episodes and study duration has been suggested [37] but no correlation was found in our study. The other side effect, diarrhea showed significant RR at the dose of 10 µg twice daily. Thus, this side effect seems to be dose-related. Other studies did not analyze data about diarrhea and headache. Although, the RR of headache was not significant at the dose of 10 µg twice daily, the significant effect was found at the dose of 5 µg twice daily. The risk of nasogastritis was not significant at both doses. Recently, in a meta-analysis, the efficacy and tolerability of exenatide to insulin was studied. The results showed that there is no superiority for exenatide over insulin even in its weight reduction advantage. However, the high risk of gastrointestinal side effects including nausea and vomiting is of major concern. Authors concluded that current evidence does not support the advantage of exenatide over insulin but more clinical trials are needed to reach a convincing conclusion [47]. In addition to this Pinelli et al compared the efficacy and safety of maximum dose of liraglutide, and exenatide once weekly with exenatide twice daily and sitagliptin in patients with

type 2 diabetes in a meta-analysis. Their results showed better efficacy of liraglutide, and exenatide once weekly in reducing HbA1C and fasting plasma glucose however exenatide twice daily provided greater reduction in postprandial glucose. The weight reduction was similar in both groups. Vomiting was reduced significantly in exenatide once weekly regimen [48].

One of the advantages of the present meta-analysis is considering some points which helped achieving more accurate results. The first point is categorizing the studies based on dose and duration of treatment; because there was much variability in different studies. Trials were lasted among 4-30 weeks; thus to manage this we adjusted duration to 16 weeks and less or more, while some other meta-analysis had limited their study to a definite study duration. Taken together, we assume that the major metabolic effect of exenatide on FPG and HbA1C does not relate to study duration.

ACKNOWLEDGMENT

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