Supplementary Online Content

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Egger's plot of 14 estimates included in the meta-analysis of the effect of metformin on long-term, all-cause mortality of breast cancer ($P < 0.001$).

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Begg's funnel plot of 14 estimates included in the meta-analysis of the effect of metformin on long-term, all-cause mortality of breast cancer (continuity corrected, $P = 0.827$).

eFigure 3.

Funnel plot after trim and fill method. Abbreviation: s.e., standard error. Each hollow circle represents an individual study for the indicated association in original observation studies.

eFigure 4.

Meta-analysis and pooled hazard ratio of breast cancer specific mortality in three studies comparing breast cancer patients with and without metformin. Abbreviations: CI, confidence interval; HR, hazard ratio. Weights are from random-effects analysis. Data markers are proportional to study sample sizes. Squares indicate relative risk in each study. The square size is proportional to the weight of the corresponding study in the meta-analysis; the length of the horizontal lines represents the 95% CI. The unshaded diamond indicates the pooled relative risk and 95% CI.

eFigure 5.

Meta-analysis and pooled hazard ratio of long-term, all-cause mortality in three studies (six estimates) comparing diabetic breast cancer patients with metformin and non-diabetic counterparts. Abbreviations: CI, confidence interval; HR, hazard ratio. Xiao (1)-(3) indicate Luminal A, Luminal B (high Ki-67), and Luminal B (her-2/neu+) subgroups, respectively. Xu (1)-(2) indicate Vanderbilt and Mayo Clinic subgroups, respectively. Weights are from random-effects analysis. Data markers are proportional to study sample sizes. Squares indicate relative risk in each study. The square size is proportional to the weight of the corresponding study in the meta-analysis; the length of the horizontal lines represents the 95% CI. The unshaded diamond indicates the pooled relative risk and 95% CI.

eTable 1. Literature search strategy (PubMed)

Database	Year included	Search terms
PubMed	Inception to January 10, 2015	breast AND cancer [sb] AND (metformin) AND (incidence[MeSH:noexp] OR mortality[MeSH Terms] OR follow up studies[MeSH:noexp] OR survival OR prognos*[Text Word] OR predict*[Text Word] OR course*[Text Word])

eTable 2. Characteristics of the 11 studies included in the meta-analysis of the effect of metformin on breast cancer mortality (supplementary)

Study, year, country	Date of recruitment (range)	Study source	Exclusion criteria	Patients with DM No./Total no. (%)	Dose of metformin	Adjustments
Bayraktar, 2012, USA[21]	1995-2007	MD Anderson	Metastatic or bilateral disease, a prior history of cancer, resolved gestational diabetes, or diabetes diagnosed after the period of adjuvant chemotherapy	130/1448(9.0%)	NA	Age, body weight, tumor size, lymph node status, nuclear grade, LVI, and type of adjuvant chemotherapy received
He, 2012, USA[22]	1998.1.1-2010.9.30	MD Anderson	Ductal carcinoma in situ or stage 1 disease, male, unknown ER or PR status, resolved gestational diabetes, type 1 diabetes, diabetic patients on dietary management only and not on any form of anti-diabetic pharmacotherapy before and after diagnosis of breast cancer, incomplete records (including medication records)	154/1983 (7.8%)	NA	Age, BMI, stage, ER/PR, insulin, insulin secretagogues, thiazolidinedione
Zhao, 2012, China[26]	2000.1-2005.12	The Second Affiliated Hospital Zhejiang University School of Medicine			NA	Age, menopausal status, cancer stages
Cleveland, 2012, USA[27]	1996.8.1-1997.7.31	Long Island Breast Cancer Study Project (LIBCSP)			NA	Menopausal status, obesity (BMI <30, BMI ≥30), race (white, other), and history of BMI
Lega, 2013, Canada[23]	1997.4.1-2008.3.31	Ontario health care databases			NA	Sulfonylurea, insulin, TZD use, age at breast cancer diagnosis, duration of diabetes (years) before breast cancer, comorbidity score based on adjusted ACG score at time of cohort entry, breast cancer treatments received within l year of diagnosis (surgery, radiotherapy, chemotherapy, aromatase inhibitor, tamoxifen), and exposure to glucose-lowering drugs before breast cancer diagnosis (yes/no).
Xiao, 2013, China[31]	2002.1-2006.12	Tianjin Medical University Cancer Institute and Hospital	Incomplete medical records; multiple primary cancer; male; not receive surgery, chemotherapy, or endocrine therapy; not take hypoglycemic drugs	680/5785 (11.8%)	NA	Age, BMI, cardiovascular and cerebrovascular complications, amenorrhea, pathologic stage, lymph node, vessel carcinoma embolus, chemotherapy and endocrine regimen
Peeters, 2013, Denmark[24]	1996-2008	National registers in Denmark	Receiving biguanide agents other than metformin (i.e. phenformin, buformin)		NA	Age, Charlson Comorbidity Index, number of years between Jan1, 1997 and the date of breast cancer diagnosis, use of concomitant medication during follow-up: metformin, sulfonylureas,

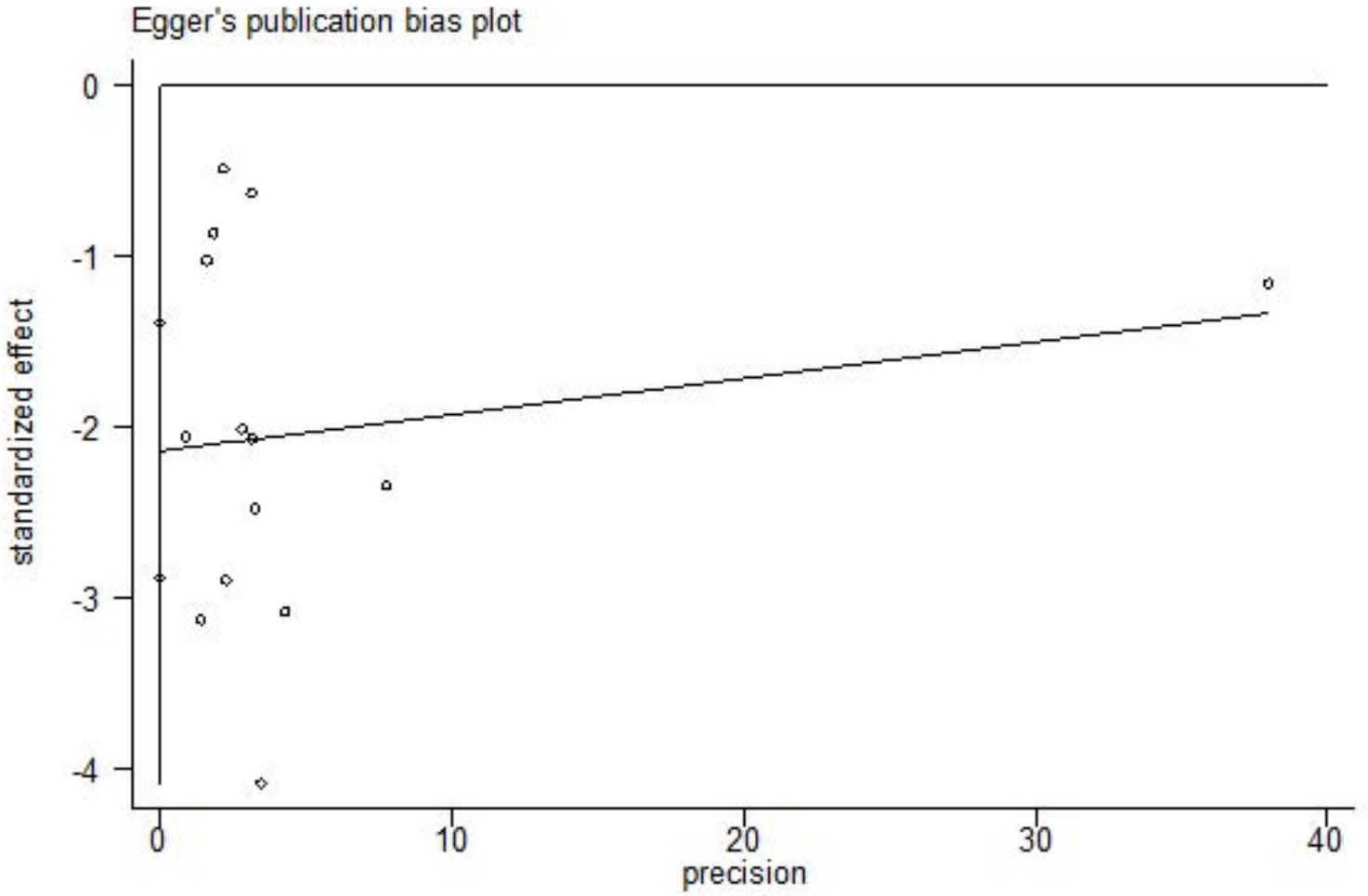
						thiazolinediones, other anti-diabetic drugs, hormone replacement therapy, and statins in the past 6 months
Zhu, 2013, China[25]	2006.1-2011.12	Qilu Hospital of Shandong University	Male, bilateral breast cancer, DCIS, stage IV, failure to follow cancer practice guidelines, type 1 diabetes, secondary diabetes, impaired fasting glucose, but not constituting diagnosed with diabetes.		NA	Age, menopausal status, histological grade, lymph node metastasis status, ER, PR, HER2, TNM stage, chemotherapy, diabetes
El-Benhawy, 2014, Egypt[28]	2008.01.01-2008.12.31	Medical Research Institute, University of Alexandria	Diagnosis of diabetes after starting of anticancer treatment, resolved gestational diabetes, second concurrent primary cancer, and administration of other anti-diabetic therapy for the metformin group	39/439 (8.9%)	Ranged from 500 to 2000 mg orally once a day with the evening meal (extended release tablets) or 500 mg twice daily. Maximum daily dose was 2500 mg	Age (<50 vs ≥50), ER and PR, lymph node metastasis status, tumor grade (III vs. II and I), clinical stage (III vs. II and I)
Xu, 2014, USA[29]	1995.01.01-2010.12.31	Vanderbilt University Medical Center and Mayo Clinic	Congestive heart failure or chronic kidney disease prior to tumor diagnosis	Vanderbilt:9% of 32415 Mayo: 11% of 79258	NA	Age, race, BMI, tobacco use, insulin, cancer type, and non-cancer Charlson index
Oppong, 2014, USA[30]	2000.01.01-2005.12.31	Memorial Sloan Kettering	Male, type I DM, gestational or steroid-induced diabetes, diagnosed with DM >6 months after breast cancer diagnosis	-	NA	Age, stage, hormone receptor

Abbreviations: BMI, body mass index; DM, diabetes mellitus; ICD-9, International Classification of Diseases, 9th revision; ICD-O, International Classification of Diseases for Oncology; LVI, lymphovascular invasion; NA, not available.

eTable 3. Study quality assessment

Reference	Population source		Diabetes ascertainment		Metformin ascertainment			Outcome ascertainment				Metformin evaluated as		Statistical analysis adjusted model
	Population-based cohort	Clinic-based cohort	Medical record or medication use	Laboratory results	Medical record	Questionnaire	Not reported	Registry	Medical record	Telephone/mail follow-up	Not reported	Primary exposure	One of multiple exposures	
Bayraktar, 2012, USA[21]		■	■		■						■	■		■
He, 2012, USA[22]		■	■		■			■	■	■		■		■
Zhao, 2012, China[26]		■	■		■				■	■		■		■
Cleveland, 2012, USA[27]		■	■			■		■					■	■
Lega, 2013, Canada[23]	■		■		■			■				■		■
Xiao, 2013, China[31]		■	■	■			■	■	■	■		■		■
Peeters, 2013, Denmark[24]	■		■		■			■				■		■
Zhu, 2013, China[25]		■	■		■				■	■		■		■
El-Benhawy, 2014, Egypt[28]		■	■		■						■	■		■
Xu, 2014, USA[29]		■	■	■	■			■				■		■
Oppong, 2014, USA[30]		■	■		■						■	■		■

■ Present in study.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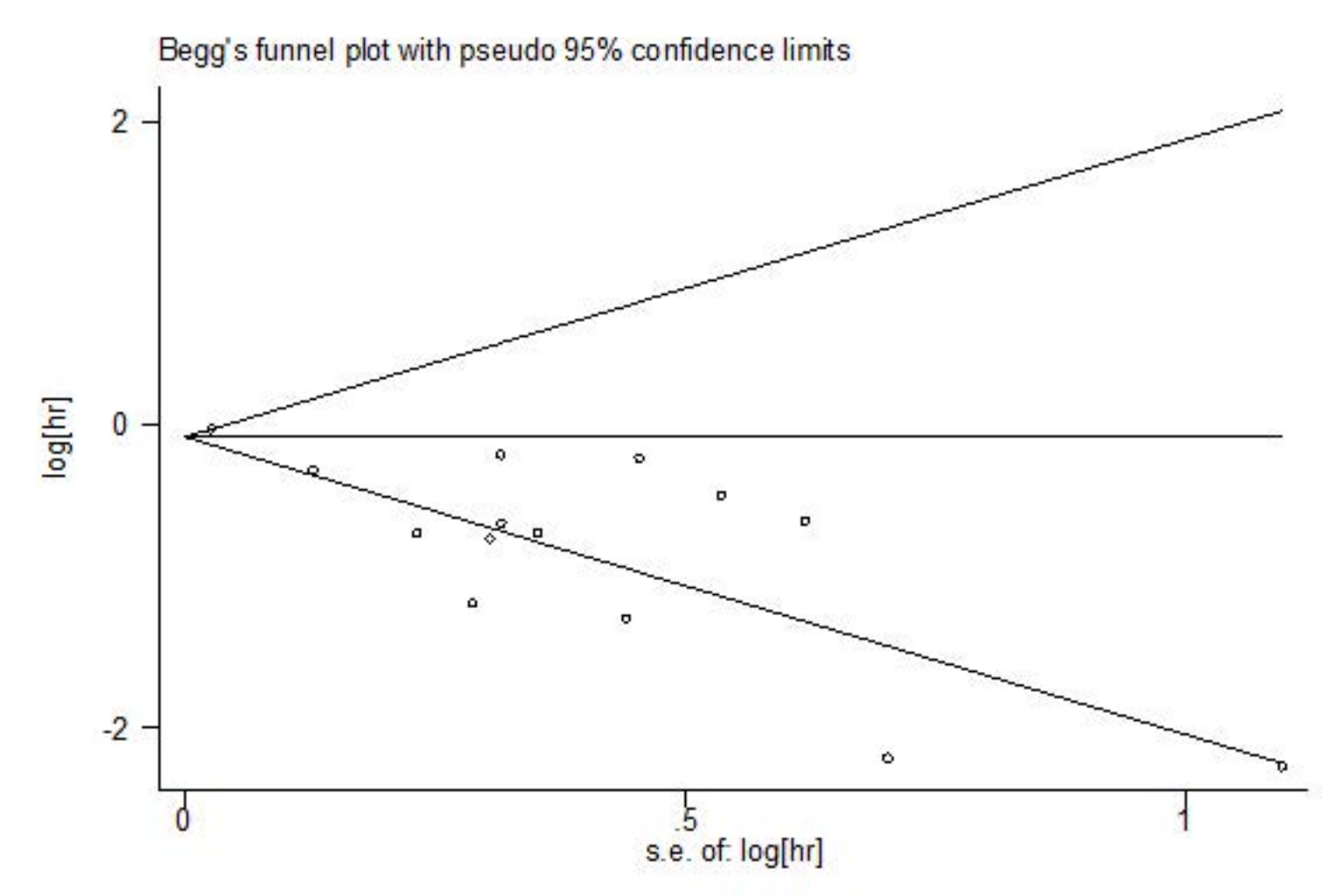
Begg's funnel plot with pseudo 95% confidence limits
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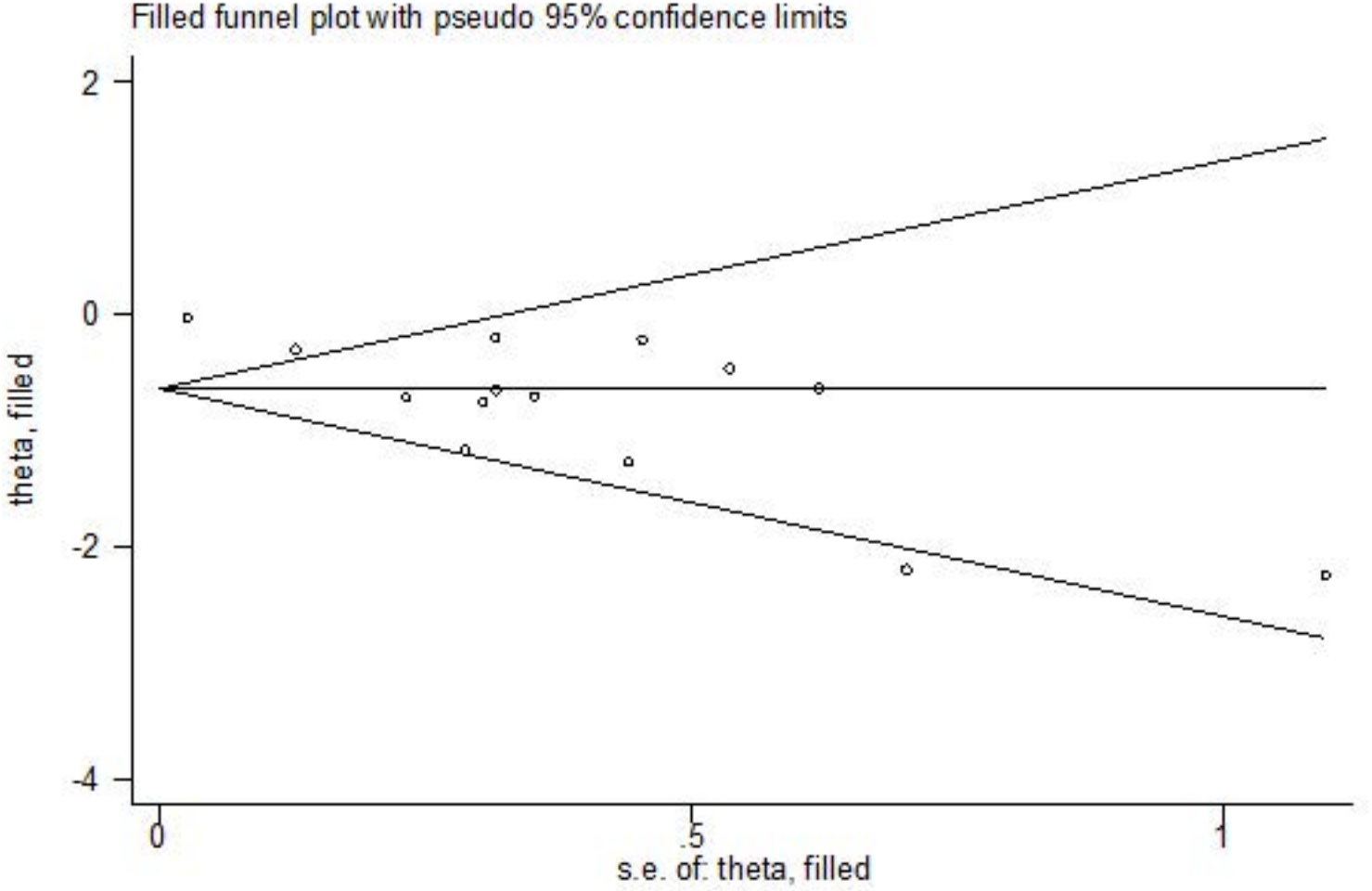
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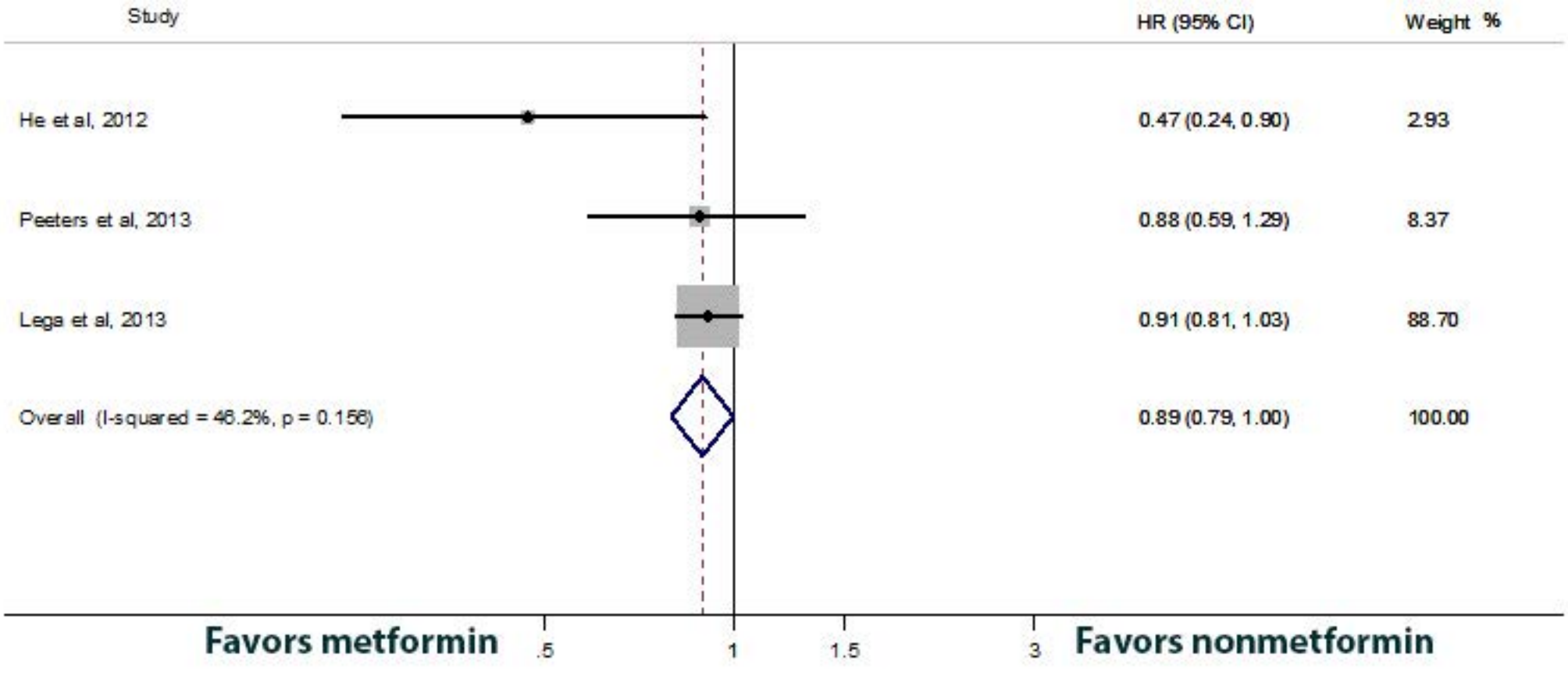
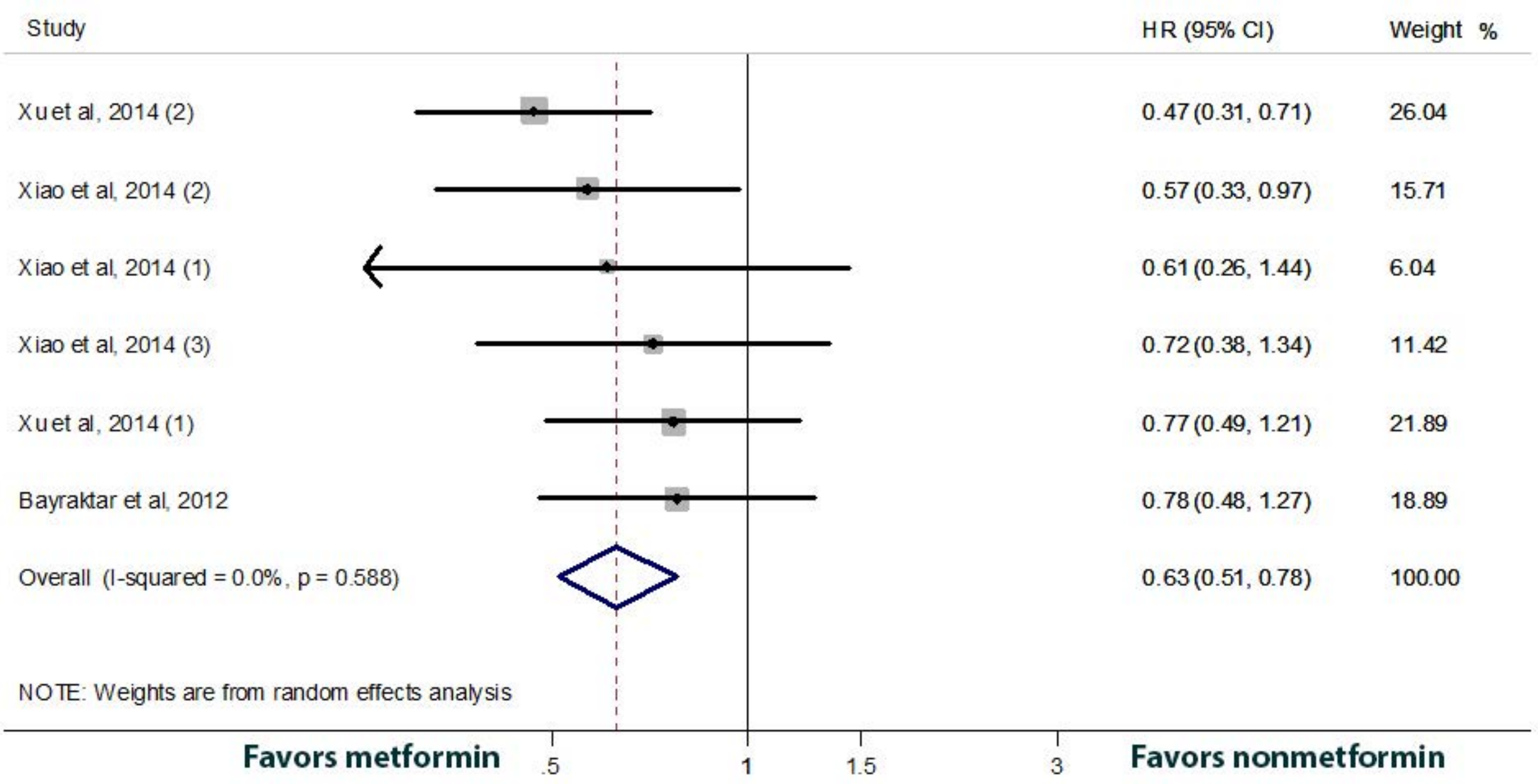

Study
HR (95% CI)
Weight %
He et al, 2012
0.47 (0.24, 0.90)
2.93
Peeters et al, 2013
0.88 (0.59, 1.29)
8.37
Lega et al, 2013
0.91 (0.81, 1.03)
88.70
Overall (I-squared = 46.2%, p = 0.156)
0.89 (0.79, 1.00)
100.00
Favors metformin
.5
1
1.5
3
Favors nonmetformin


Study
HR (95% CI)
Weight %
Xu et al, 2014 (2)
0.47 (0.31, 0.71)
26.04
Xiao et al, 2014 (2)
0.57 (0.33, 0.97)
15.71
Xiao et al, 2014 (1)
0.61 (0.26, 1.44)
6.04
Xiao et al, 2014 (3)
0.72 (0.38, 1.34)
11.42
Xu et al, 2014 (1)
0.77 (0.49, 1.21)
21.89
Bayraktar et al, 2012
0.78 (0.48, 1.27)
18.89
Overall (I-squared = 0.0%, p = 0.588)
0.63 (0.51, 0.78)
100.00
NOTE: Weights are from random effects analysis
Favors metformin
.5
1
1.5
3
Favors nonmetformin