Global and Regional Effects of Bladder Cancer Risk Associated with Pioglitazone Therapy in Patients with Diabetes

A Systematic Review and Meta-Analysis

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Supplementary Online Content

eAppendix 1. Literature Search Strategy

eFigure 1. Initial analysis of Other Cancer Risks in Patients with DM Receiving Pioglitazone Versus Control from OB Studies

eFigure 2. Bladder Cancer Risks Related to Pioglitazone Use Versus Control for Patients with DM in Global from OB Studies plus RCTs

eFigure 3. Subgroup Analyses of Bladder Cancer Risk Related to Pioglitazone Use Versus Control for Patients with DM in Global from OB Studies plus RCTs

eFigure 4. Subgroup Analyses of Bladder Cancer Risk Related to Pioglitazone Use Versus Control for Patients with DM in America plus Asia and Europe Separately, from OB Studies plus RCTs

eFigure 5. Other Cancer Risks in Patients with DM Receiving Pioglitazone Versus Control from OB Studies plus RCTs

eFigure 6. Egger's Test for Publication Bias Analysis Regarding Bladder Cancer Risk and Pioglitazone Use

eFigure 7. Begg's Test for Publication Bias Analysis Regarding Bladder Cancer Risk and Pioglitazone Use

eFigure 8. HbA1c-Adjustment Subgroup Analyses of Bladder Cancer Risk Related to Pioglitazone Use Versus Control for Patients with DM in Global from OB Studies

eFigure 9. HbA1c-Adjustment Subgroup Analyses of Bladder Cancer Risk Related to Pioglitazone Use Versus Control for Patients with DM in America plus Asia and Europe Separately, from OB Studies

eTable 1. Characteristics of Studies Regarding Bladder Cancer Risk and Pioglitazone Use

eTable 2. Quality Assessment of Studies Regarding Bladder Cancer Risk and Pioglitazone Use

eReferences. For eFigure 1, 2, 5, 8 and 9, eTable 1 and 2

MOOSE Checklist

Supplement Figure Legends

eFigure 1. Initial Analysis of Other Cancer Risks in Patients with DM Receiving Pioglitazone Versus Control from OB Studies[a]

Abbreviations: DM, diabetes mellitus; OB, observational studies.

[a] With Vallarino et al, 2013 included.

eFigure 2. Bladder Cancer Risks Related to Pioglitazone Use Versus Control for Patients with DM in Global from OB Studies plus RCTs

Abbreviations: RCTs, randomized controlled trials.

[a] Given that both the exposed and control groups did not report bladder cancer incidence, the OR was not estimable.

eFigure 3. Subgroup Analyses of Bladder Cancer Risk Related to Pioglitazone Use Versus Control for Patients with DM in Global from OB Studies plus RCTs

Abbreviations: T2DM, type 2 diabetes mellitus; T1DM, type 1 diabetes mellitus.

[a] With T1DM excluded.

[b] With T1DM included.

eFigure 4. Subgroup Analyses of Bladder Cancer Risk Related to Pioglitazone Use Versus Control for Patients with DM in Europe, and America plus Asia, Separately, from OB Studies plus RCTs

[a] With T1DM excluded.

[b] With T1DM included.

eFigure 5. Other Cancer Risks in Patients with DM Receiving Pioglitazone Versus Control from OB Studies plus RCTs[a]

[a] With Vallarino et al, 2013 excluded.

eFigure 6. Egger's Test for Publication Bias Analysis Regarding Bladder Cancer Risk and Pioglitazone Use

eFigure 7. Begg's Test for Publication Bias Analysis Regarding Bladder Cancer Risk and Pioglitazone Use

eFigure 8. HbA1c-Adjustment Subgroup Analyses of Bladder Cancer Risk Related to Pioglitazone Use Versus Control for Patients with DM in Global from OB Studies

Abbreviations: HbA1c, hemoglobin A1c concentration.

[a] Given that both the exposed and control groups did not report bladder cancer case, the OR was not estimable.

eFigure 9. HbA1c-Adjustment Subgroup Analyses of Bladder Cancer Risk Related to Pioglitazone Use Versus Control

for Patients with DM in America plus Asia and Europe Separately, from OB Studies

[a] Given that both the exposed and control groups did not report bladder cancer case, the OR was not estimable.

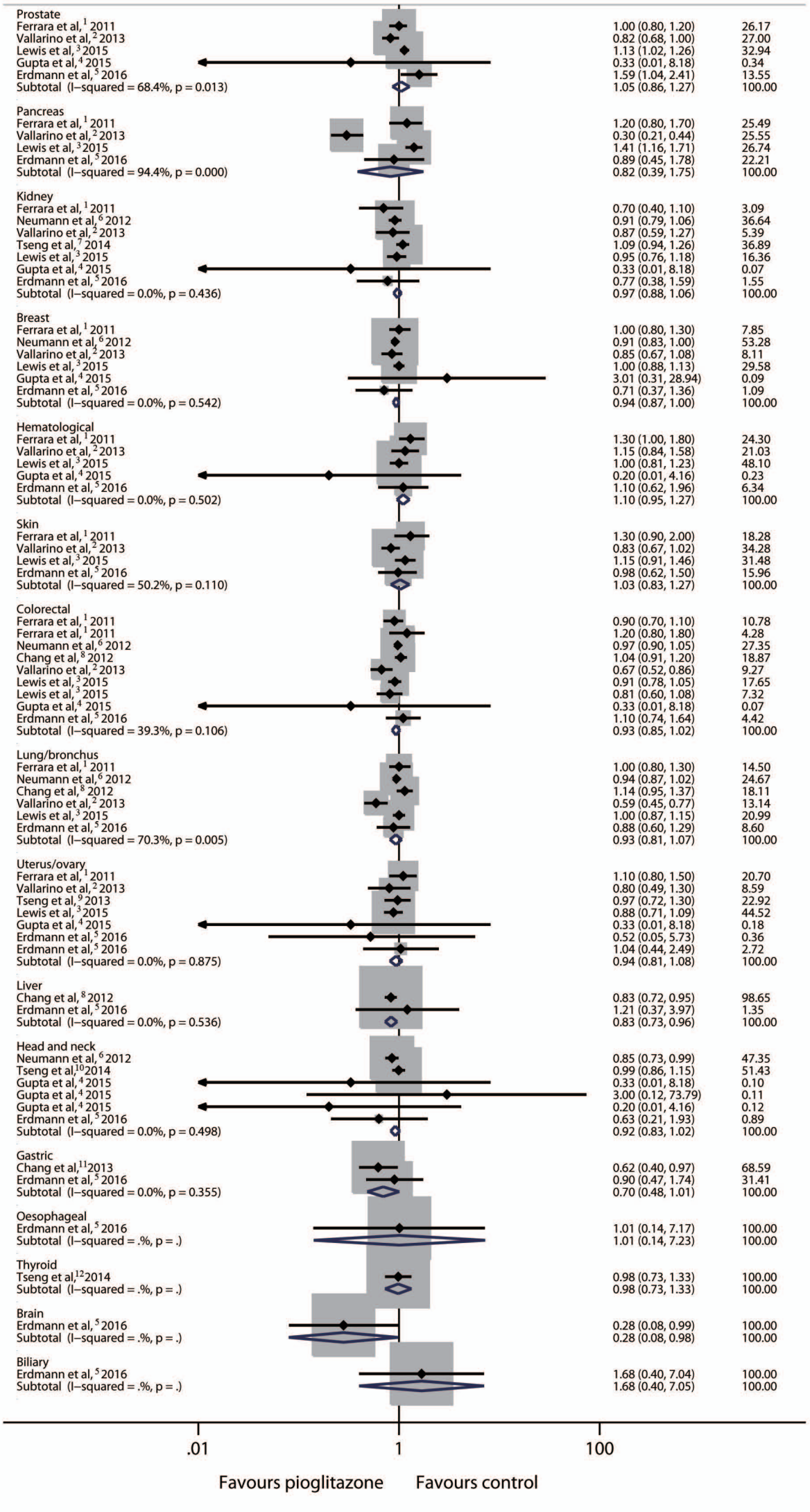
eAppendix 1. Literature Search Strategy

1) Following search strategy was used: PPAR or peroxisome proliferator activated receptor agonist* or peroxisome proliferator-activated receptor agonist* OR peroxisome proliferator activated receptor activator* OR peroxisome proliferator-activated receptor activator* OR thiazolidinedione*/exp OR thiazolidinedione* OR TZD OR TZDs OR pioglitazone/exp OR pioglitazone OR actos/exp OR actos) AND (cancer/exp OR cancer OR tumor/exp OR tumor OR carcinoma/exp OR carcinoma OR neoplasm/exp OR neoplasm OR malignancy)))) NOT ((((((PPAR or peroxisome proliferator activated receptor agonist* or peroxisome proliferator-activated receptor agonist* OR peroxisome proliferator activated receptor activator* OR peroxisome proliferator-activated receptor activator* OR thiazolidinedione*/exp OR thiazolidinedione* OR TZD OR TZDs OR pioglitazone/exp OR pioglitazone OR actos/exp OR actos) AND (cancer/exp OR cancer OR tumor/exp OR tumor OR carcinoma/exp OR carcinoma OR neoplasm/exp OR neoplasm OR malignancy))) AND Animals [Mesh:noexp])) NOT ((((PPAR or peroxisome proliferator activated receptor agonist* or peroxisome proliferator-activated receptor agonist* OR peroxisome proliferator activated receptor activator* OR peroxisome proliferator-activated receptor activator* OR thiazolidinedione*/exp OR thiazolidinedione* OR TZD OR TZDs OR pioglitazone/exp OR pioglitazone OR actos/exp OR actos) AND (cancer/exp OR cancer OR tumor/exp OR tumor OR carcinoma/exp OR carcinoma OR neoplasm/exp OR neoplasm OR malignancy))) AND Humans[Mesh]))

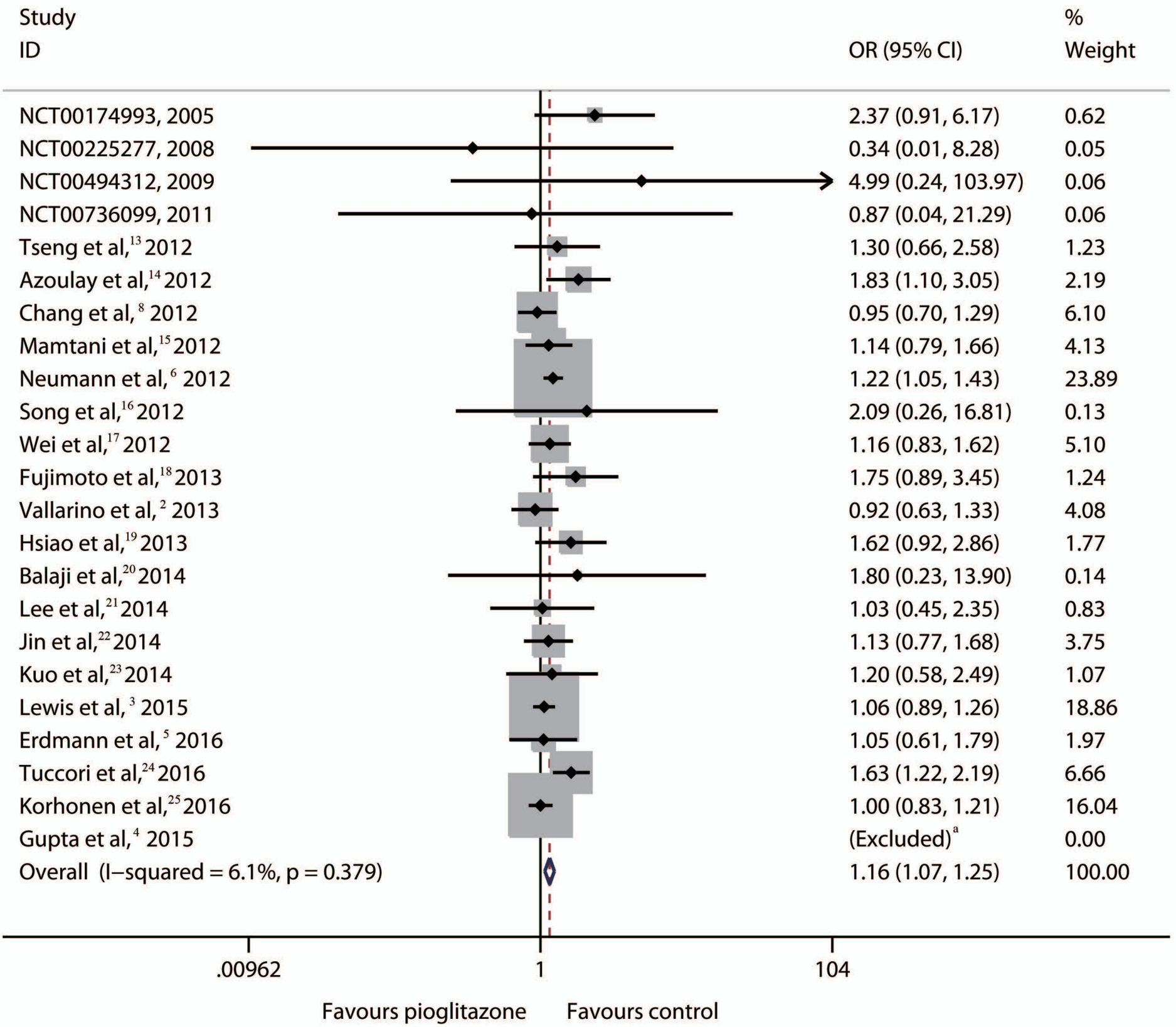
2) For **Cochrane Central Register of Controlled Trials (CENTRAL)** following search strategy was used: (PPAR or peroxisome proliferator activated receptor agonist* or peroxisome proliferator-activated receptor agonist* or peroxisome proliferator activated receptor activator* or peroxisome proliferator-activated receptor activator* or thiazolidinedione* or TZD* or pioglitazone or Actos) AND (cancer* or tumor* or carcinoma* or neoplasm* or malignancy*)

3) For **ClinicalTrials.gov** following search strategy was used: "thiazolidinediones" OR "TZDs" OR "pioglitazone" OR "Actos" | Studies With Results (We did not use the general terms to search the ClinicalTrails.gov, such as “PPAR” and “peroxisome proliferator activated receptor agonist”, as this registry is designed so that one can capture relevant trials using generic drug names directly.)

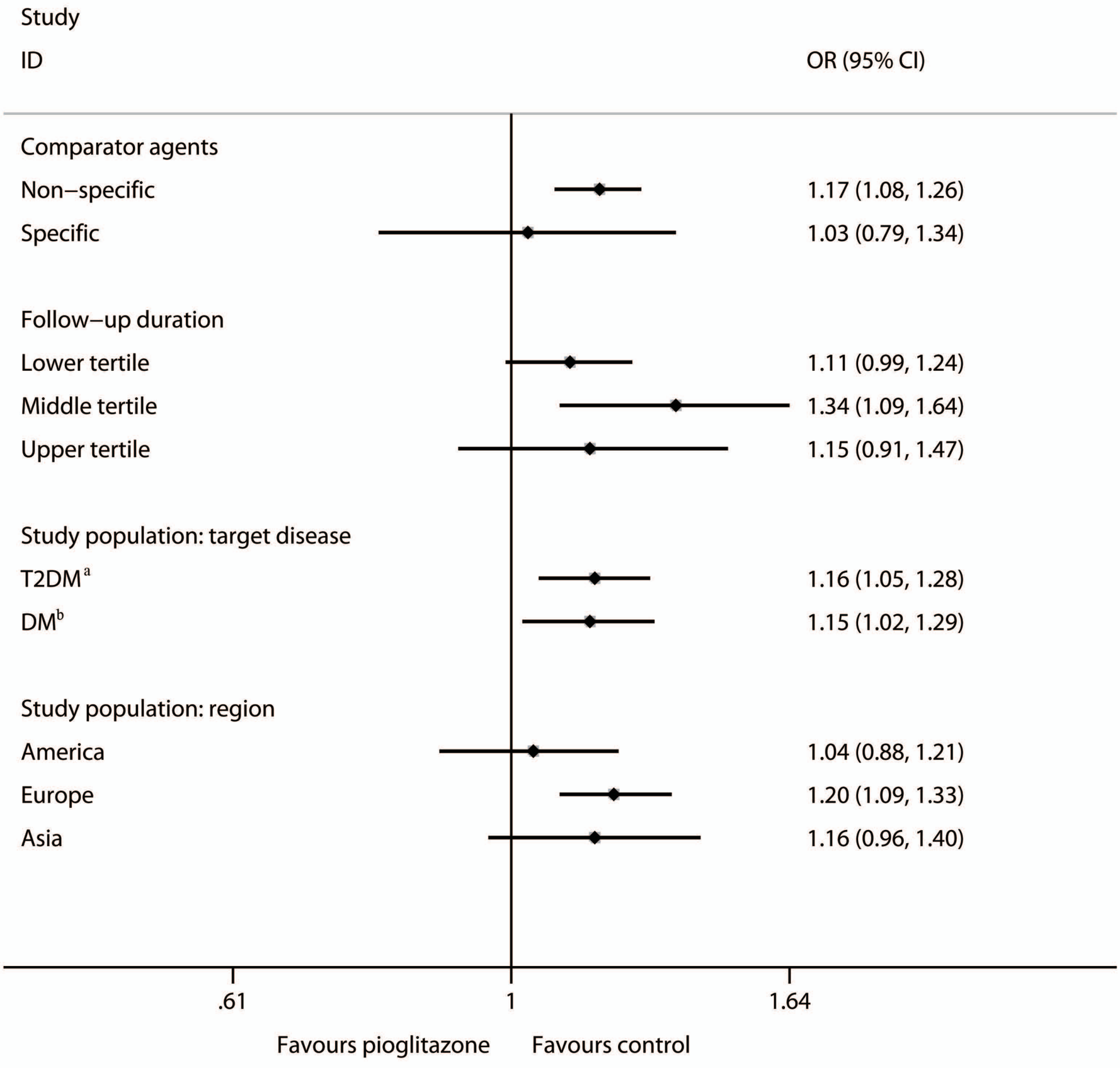
eFigure 1


Study ID
OR (95% CI)
% Weight
Prostate
Ferrara et al,[1] 2011 1.00 (0.80, 1.20) 26.17
Vallarino et al,[2] 2013 0.82 (0.68, 1.00) 27.00
Lewis et al,[3] 2015 1.13 (1.02, 1.26) 32.94
Gupta et al,[4] 2015 0.33 (0.01, 8.18) 0.34
Erdmann et al,[5] 2016 1.59 (1.04, 2.41) 13.55
Subtotal (I–squared = 68.4%, p = 0.013) 1.05 (0.86, 1.27) 100.00
Pancreas
Ferrara et al,[1] 2011 1.20 (0.80, 1.70) 25.49
Vallarino et al,[2] 2013 0.30 (0.21, 0.44) 25.55
Lewis et al,[3] 2015 1.41 (1.16, 1.71) 26.74
Erdmann et al,[5] 2016 0.89 (0.45, 1.78) 22.21
Subtotal (I–squared = 94.4%, p = 0.000) 0.82 (0.39, 1.75) 100.00
Kidney
Ferrara et al,[1] 2011 0.70 (0.40, 1.10) 3.09
Neumann et al,[6] 2012 0.91 (0.79, 1.06) 36.64
Vallarino et al,[2] 2013 0.87 (0.59, 1.27) 5.39
Tseng et al,[7] 2014 1.09 (0.94, 1.26) 36.89
Lewis et al,[3] 2015 0.95 (0.76, 1.18) 16.36
Gupta et al,[4] 2015 0.33 (0.01, 8.18) 0.07
Erdmann et al,[5] 2016 0.77 (0.38, 1.59) 1.55
Subtotal (I–squared = 0.0%, p = 0.436) 0.97 (0.88, 1.06) 100.00
Breast
Ferrara et al,[1] 2011 1.00 (0.80, 1.30) 7.85
Neumann et al,[6] 2012 0.91 (0.83, 1.00) 53.28
Vallarino et al,[2] 2013 0.85 (0.67, 1.08) 8.11
Lewis et al,[3] 2015 1.00 (0.88, 1.13) 29.58
Gupta et al,[4] 2015 3.01 (0.31, 28.94) 0.09
Erdmann et al,[5] 2016 0.71 (0.37, 1.36) 1.09
Subtotal (I–squared = 0.0%, p = 0.542) 0.94 (0.87, 1.00) 100.00
Hematological
Ferrara et al,[1] 2011 1.30 (1.00, 1.80) 24.30
Vallarino et al,[2] 2013 1.15 (0.84, 1.58) 21.03
Lewis et al,[3] 2015 1.00 (0.81, 1.23) 48.10
Gupta et al,[4] 2015 0.20 (0.01, 4.16) 0.23
Erdmann et al,[5] 2016 1.10 (0.62, 1.96) 6.34
Subtotal (I–squared = 0.0%, p = 0.502) 1.10 (0.95, 1.27) 100.00
Skin
Ferrara et al,[1] 2011 1.30 (0.90, 2.00) 18.28
Vallarino et al,[2] 2013 0.83 (0.67, 1.02) 34.28
Lewis et al,[3] 2015 1.15 (0.91, 1.46) 31.48
Erdmann et al,[5] 2016 0.98 (0.62, 1.50) 15.96
Subtotal (I–squared = 50.2%, p = 0.110) 1.03 (0.83, 1.27) 100.00
Colorectal
Ferrara et al,[1] 2011 0.90 (0.70, 1.10) 10.78
Ferrara et al,[1] 2011 1.20 (0.80, 1.80) 4.28
Neumann et al,[6] 2012 0.97 (0.90, 1.05) 27.35
Chang et al,[8] 2012 1.04 (0.91, 1.20) 18.87
Vallarino et al,[2] 2013 0.67 (0.52, 0.86) 9.27
Lewis et al,[3] 2015 0.91 (0.78, 1.05) 17.65
Lewis et al,[3] 2015 0.81 (0.60, 1.08) 7.32
Gupta et al,[4] 2015 0.33 (0.01, 8.18) 0.07
Erdmann et al,[5] 2016 1.10 (0.74, 1.64) 4.42
Subtotal (I–squared = 39.3%, p = 0.106) 0.93 (0.85, 1.02) 100.00
Lung/bronchus
Ferrara et al,[1] 2011 1.00 (0.80, 1.30) 14.50
Neumann et al,[6] 2012 0.94 (0.87, 1.02) 24.67
Chang et al,[8] 2012 1.14 (0.95, 1.37) 18.11
Vallarino et al,[2] 2013 0.59 (0.45, 0.77) 13.14
Lewis et al,[3] 2015 1.00 (0.87, 1.15) 20.99
Erdmann et al,[5] 2016 0.88 (0.60, 1.29) 8.60
Subtotal (I–squared = 70.3%, p = 0.005) 0.93 (0.81, 1.07) 100.00
Uterus/ovary
Ferrara et al,[1] 2011 1.10 (0.80, 1.50) 20.70
Vallarino et al,[2] 2013 0.80 (0.49, 1.30) 8.59
Tseng et al,[9] 2013 0.97 (0.72, 1.30) 22.92
Lewis et al,[3] 2015 0.88 (0.71, 1.09) 44.52
Gupta et al,[4] 2015 0.33 (0.01, 8.18) 0.18
Erdmann et al,[5] 2016 0.52 (0.05, 5.73) 0.36
Erdmann et al,[5] 2016 1.04 (0.44, 2.49) 2.72
Subtotal (I–squared = 0.0%, p = 0.875) 0.94 (0.81, 1.08) 100.00
Liver
Chang et al,[8] 2012 0.83 (0.72, 0.95) 98.65
Erdmann et al,[5] 2016 1.21 (0.37, 3.97) 1.35
Subtotal (I–squared = 0.0%, p = 0.536) 0.83 (0.73, 0.96) 100.00
Head and neck
Neumann et al,[6] 2012 0.85 (0.73, 0.99) 47.35
Tseng et al,[10] 2014 0.99 (0.86, 1.15) 51.43
Gupta et al,[4] 2015 0.33 (0.01, 8.18) 0.10
Gupta et al,[4] 2015 3.00 (0.12, 73.79) 0.11
Gupta et al,[4] 2015 0.20 (0.01, 4.16) 0.12
Erdmann et al,[5] 2016 0.63 (0.21, 1.93) 0.89
Subtotal (I–squared = 0.0%, p = 0.498) 0.92 (0.83, 1.02) 100.00
Gastric
Chang et al,[11] 2013 0.62 (0.40, 0.97) 68.59
Erdmann et al,[5] 2016 0.90 (0.47, 1.74) 31.41
Subtotal (I–squared = 0.0%, p = 0.355) 0.70 (0.48, 1.01) 100.00
Oesophageal
Erdmann et al,[5] 2016 1.01 (0.14, 7.17) 100.00
Subtotal (I–squared = .%, p = .) 1.01 (0.14, 7.23) 100.00
Thyroid
Tseng et al,[12] 2014 0.98 (0.73, 1.33) 100.00
Subtotal (I–squared = .%, p = .) 0.98 (0.73, 1.33) 100.00
Brain
Erdmann et al,[5] 2016 0.28 (0.08, 0.99) 100.00
Subtotal (I–squared = .%, p = .) 0.28 (0.08, 0.98) 100.00
Biliary
Erdmann et al,[5] 2016 1.68 (0.40, 7.04) 100.00
Subtotal (I–squared = .%, p = .) 1.68 (0.40, 7.05) 100.00
.01
1
100
Favours pioglitazone
Favours control

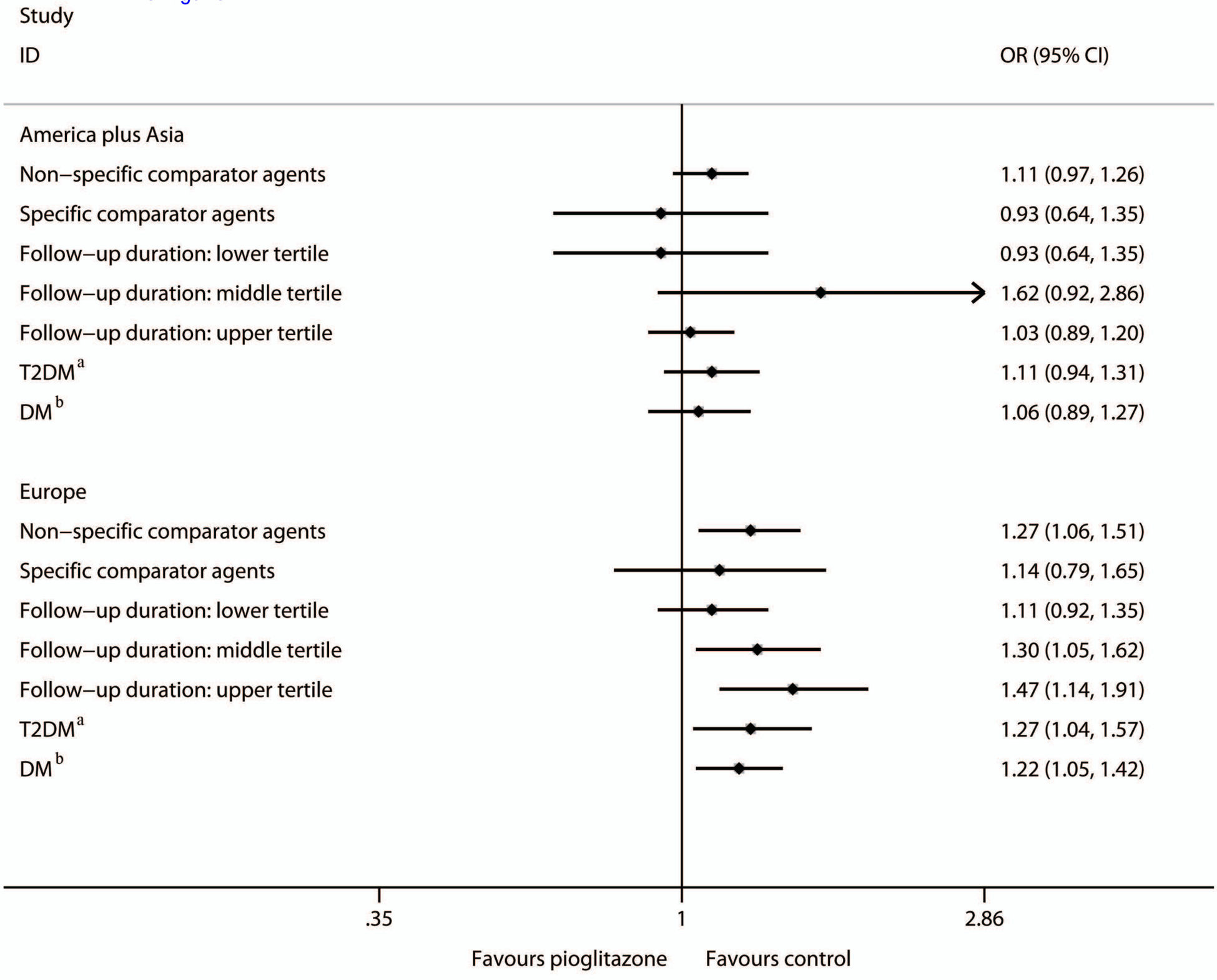
eFigure 2


Study ID
OR (95% CI)
% Weight
NCT00174993, 2005
2.37 (0.91, 6.17)
0.62
NCT00225277, 2008
0.34 (0.01, 8.28)
0.05
NCT00494312, 2009
4.99 (0.24, 103.97)
0.06
NCT00736099, 2011
0.87 (0.04, 21.29)
0.06
Tseng et al,[13] 2012
1.30 (0.66, 2.58)
1.23
Azoulay et al,[14] 2012
1.83 (1.10, 3.05)
2.19
Chang et al,[8] 2012
0.95 (0.70, 1.29)
6.10
Mamtani et al,[15] 2012
1.14 (0.79, 1.66)
4.13
Neumann et al,[6] 2012
1.22 (1.05, 1.43)
23.89
Song et al,[16] 2012
2.09 (0.26, 16.81)
0.13
Wei et al,[17] 2012
1.16 (0.83, 1.62)
5.10
Fujimoto et al,[18] 2013
1.75 (0.89, 3.45)
1.24
Vallarino et al,[2] 2013
0.92 (0.63, 1.33)
4.08
Hsiao et al,[19] 2013
1.62 (0.92, 2.86)
1.77
Balaji et al,[20] 2014
1.80 (0.23, 13.90)
0.14
Lee et al,[21] 2014
1.03 (0.45, 2.35)
0.83
Jin et al,[22] 2014
1.13 (0.77, 1.68)
3.75
Kuo et al,[23] 2014
1.20 (0.58, 2.49)
1.07
Lewis et al,[3] 2015
1.06 (0.89, 1.26)
18.86
Erdmann et al,[5] 2016
1.05 (0.61, 1.79)
1.97
Tuccori et al,[24] 2016
1.63 (1.22, 2.19)
6.66
Korhonen et al,[25] 2016
1.00 (0.83, 1.21)
16.04
Gupta et al,[4] 2015
(Excluded)[a]
0.00
Overall (I–squared = 6.1%, p = 0.379)
1.16 (1.07, 1.25)
100.00
.00962
1
104
Favours pioglitazone
Favours control

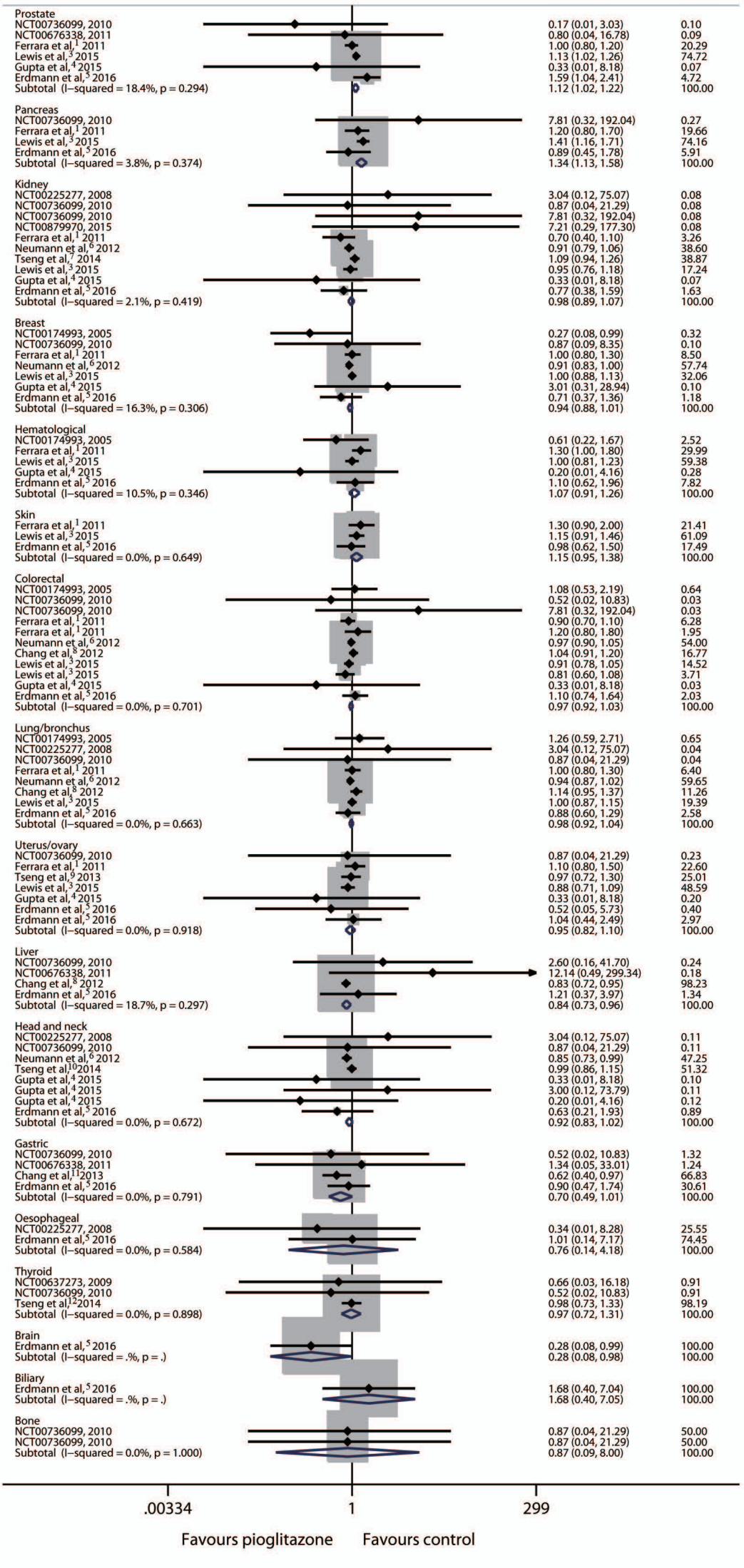
eFigure 3


Study
ID
OR (95% CI)
Comparator agents
Non−specific
1.17 (1.08, 1.26)
Specific
1.03 (0.79, 1.34)
Follow−up duration
Lower tertile
1.11 (0.99, 1.24)
Middle tertile
1.34 (1.09, 1.64)
Upper tertile
1.15 (0.91, 1.47)
Study population: target disease
T2DM[a]
1.16 (1.05, 1.28)
DM[b]
1.15 (1.02, 1.29)
Study population: region
America
1.04 (0.88, 1.21)
Europe
1.20 (1.09, 1.33)
Asia
1.16 (0.96, 1.40)
.61
1
1.64
Favours pioglitazone
Favours control

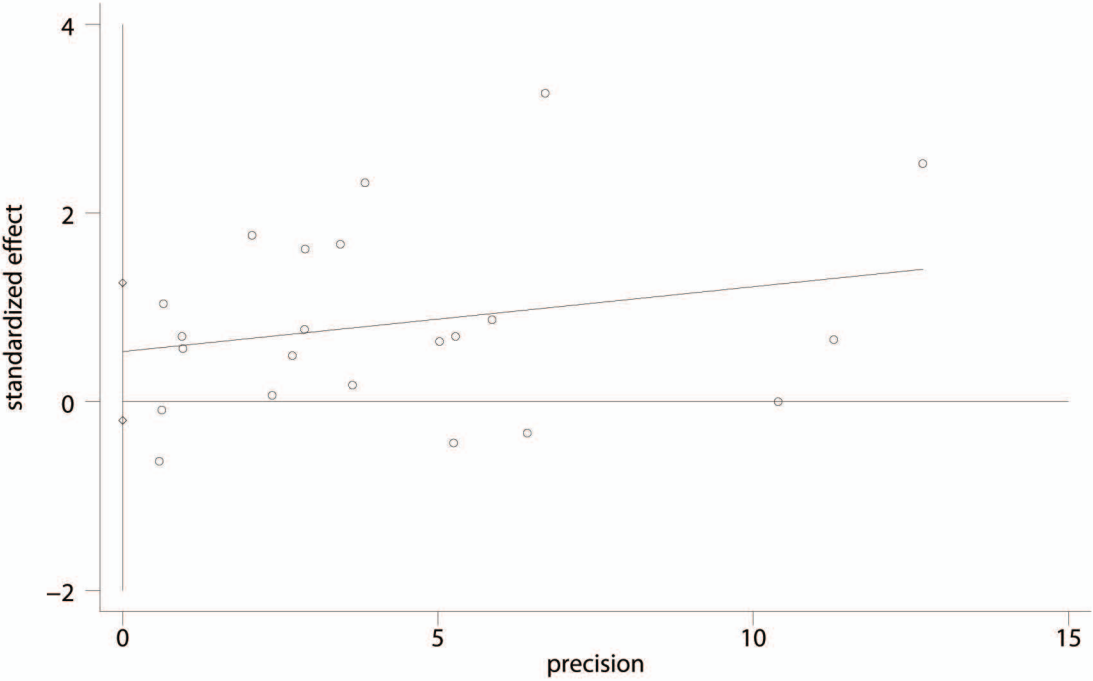
eFigure 4


Study
ID
OR (95% CI)
America plus Asia
Non−specific comparator agents
1.11 (0.97, 1.26)
Specific comparator agents
0.93 (0.64, 1.35)
Follow−up duration: lower tertile
0.93 (0.64, 1.35)
Follow−up duration: middle tertile
1.62 (0.92, 2.86)
Follow−up duration: upper tertile
1.03 (0.89, 1.20)
T2DM[a]
1.11 (0.94, 1.31)
DM[b]
1.06 (0.89, 1.27)
Europe
Non−specific comparator agents
1.27 (1.06, 1.51)
Specific comparator agents
1.14 (0.79, 1.65)
Follow−up duration: lower tertile
1.11 (0.92, 1.35)
Follow−up duration: middle tertile
1.30 (1.05, 1.62)
Follow−up duration: upper tertile
1.47 (1.14, 1.91)
T2DM[a]
1.27 (1.04, 1.57)
DM[b]
1.22 (1.05, 1.42)
.35
1
2.86
Favours pioglitazone
Favours control

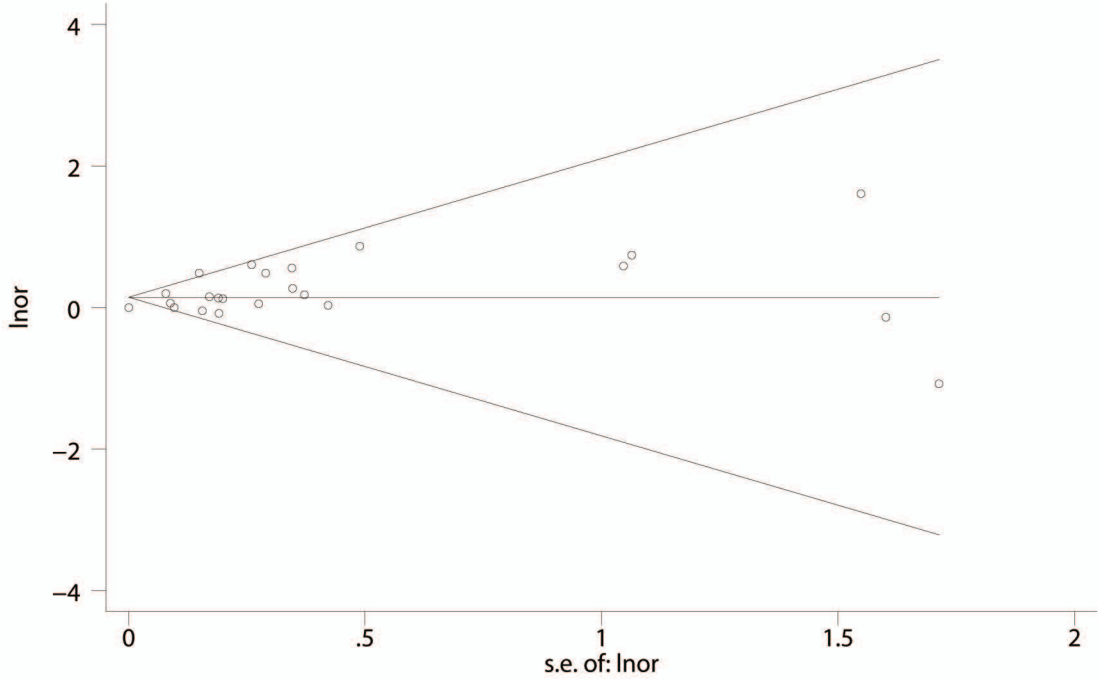
eFigure 5


Study ID
OR (95% CI)
% Weight
Prostate
NCT00736099, 2010 0.17 (0.01, 3.03) 0.10
NCT00676338, 2011 0.80 (0.04, 16.78) 0.09
Ferrara et al,[1] 2011 1.00 (0.80, 1.20) 20.29
Lewis et al,[3] 2015 1.13 (1.02, 1.26) 74.72
Gupta et al,[4] 2015 0.33 (0.01, 8.18) 0.07
Erdmann et al,[5] 2016 1.59 (1.04, 2.41) 4.72
Subtotal (I–squared = 18.4%, p = 0.294) 1.12 (1.02, 1.22) 100.00
Pancreas
NCT00736099, 2010 7.81 (0.32, 192.04) 0.27
Ferrara et al,[1] 2011 1.20 (0.80, 1.70) 19.66
Lewis et al,[3] 2015 1.41 (1.16, 1.71) 74.16
Erdmann et al,[5] 2016 0.89 (0.45, 1.78) 5.91
Subtotal (I–squared = 3.8%, p = 0.374) 1.34 (1.13, 1.58) 100.00
Kidney
NCT00225277, 2008 3.04 (0.12, 75.07) 0.08
NCT00736099, 2010 0.87 (0.04, 21.29) 0.08
NCT00736099, 2010 7.81 (0.32, 192.04) 0.08
NCT00879970, 2015 7.21 (0.29, 177.30) 0.08
Ferrara et al,[1] 2011 0.70 (0.40, 1.10) 3.26
Neumann et al,[6] 2012 0.91 (0.79, 1.06) 38.60
Tseng et al,[7] 2014 1.09 (0.94, 1.26) 38.87
Lewis et al,[3] 2015 0.95 (0.76, 1.18) 17.24
Gupta et al,[4] 2015 0.33 (0.01, 8.18) 0.07
Erdmann et al,[5] 2016 0.77 (0.38, 1.59) 1.63
Subtotal (I–squared = 2.1%, p = 0.419) 0.98 (0.89, 1.07) 100.00
Breast
NCT00174993, 2005 0.27 (0.08, 0.99) 0.32
NCT00736099, 2010 0.87 (0.09, 8.35) 0.10
Ferrara et al,[1] 2011 1.00 (0.80, 1.30) 8.50
Neumann et al,[6] 2012 0.91 (0.83, 1.00) 57.74
Lewis et al,[3] 2015 1.00 (0.88, 1.13) 32.06
Gupta et al,[4] 2015 3.01 (0.31, 28.94) 0.10
Erdmann et al,[5] 2016 0.71 (0.37, 1.36) 1.18
Subtotal (I–squared = 16.3%, p = 0.306) 0.94 (0.88, 1.01) 100.00
Hematological
NCT00174993, 2005 0.61 (0.22, 1.67) 2.52
Ferrara et al,[1] 2011 1.30 (1.00, 1.80) 29.99
Lewis et al,[3] 2015 1.00 (0.81, 1.23) 59.38
Gupta et al,[4] 2015 0.20 (0.01, 4.16) 0.28
Erdmann et al,[5] 2016 1.10 (0.62, 1.96) 7.82
Subtotal (I–squared = 10.5%, p = 0.346) 1.07 (0.91, 1.26) 100.00
Skin
Ferrara et al,[1] 2011 1.30 (0.90, 2.00) 21.41
Lewis et al,[3] 2015 1.15 (0.91, 1.46) 61.09
Erdmann et al,[5] 2016 0.98 (0.62, 1.50) 17.49
Subtotal (I–squared = 0.0%, p = 0.649) 1.15 (0.95, 1.38) 100.00
Colorectal
NCT00174993, 2005 1.08 (0.53, 2.19) 0.64
NCT00736099, 2010 0.52 (0.02, 10.83) 0.03
NCT00736099, 2010 7.81 (0.32, 192.04) 0.03
Ferrara et al,[1] 2011 0.90 (0.70, 1.10) 6.28
Ferrara et al,[1] 2011 1.20 (0.80, 1.80) 1.95
Neumann et al,[6] 2012 0.97 (0.90, 1.05) 54.00
Chang et al,[8] 2012 1.04 (0.91, 1.20) 16.77
Lewis et al,[3] 2015 0.91 (0.78, 1.05) 14.52
Lewis et al,[3] 2015 0.81 (0.60, 1.08) 3.71
Gupta et al,[4] 2015 0.33 (0.01, 8.18) 0.03
Erdmann et al,[5] 2016 1.10 (0.74, 1.64) 2.03
Subtotal (I–squared = 0.0%, p = 0.701) 0.97 (0.92, 1.03) 100.00
Lung/bronchus
NCT00174993, 2005 1.26 (0.59, 2.71) 0.65
NCT00225277, 2008 3.04 (0.12, 75.07) 0.04
NCT00736099, 2010 0.87 (0.04, 21.29) 0.04
Ferrara et al,[1] 2011 1.00 (0.80, 1.30) 6.40
Neumann et al,[6] 2012 0.94 (0.87, 1.02) 59.65
Chang et al,[8] 2012 1.14 (0.95, 1.37) 11.26
Lewis et al,[3] 2015 1.00 (0.87, 1.15) 19.39
Erdmann et al,[5] 2016 0.88 (0.60, 1.29) 2.58
Subtotal (I–squared = 0.0%, p = 0.663) 0.98 (0.92, 1.04) 100.00
Uterus/ovary
NCT00736099, 2010 0.87 (0.04, 21.29) 0.23
Ferrara et al,[1] 2011 1.10 (0.80, 1.50) 22.60
Tseng et al,[9] 2013 0.97 (0.72, 1.30) 25.01
Lewis et al,[3] 2015 0.88 (0.71, 1.09) 48.59
Gupta et al,[4] 2015 0.33 (0.01, 8.18) 0.20
Erdmann et al,[5] 2016 0.52 (0.05, 5.73) 0.40
Erdmann et al,[5] 2016 1.04 (0.44, 2.49) 2.97
Subtotal (I–squared = 0.0%, p = 0.918) 0.95 (0.82, 1.10) 100.00
Liver
NCT00736099, 2010 2.60 (0.16, 41.70) 0.24
NCT00676338, 2011 12.14 (0.49, 299.34) 0.18
Chang et al,[8] 2012 0.83 (0.72, 0.95) 98.23
Erdmann et al,[5] 2016 1.21 (0.37, 3.97) 1.34
Subtotal (I–squared = 18.7%, p = 0.297) 0.84 (0.73, 0.96) 100.00
Head and neck
NCT00225277, 2008 3.04 (0.12, 75.07) 0.11
NCT00736099, 2010 0.87 (0.04, 21.29) 0.11
Neumann et al,[6] 2012 0.85 (0.73, 0.99) 47.25
Tseng et al,[10] 2014 0.99 (0.86, 1.15) 51.32
Gupta et al,[4] 2015 0.33 (0.01, 8.18) 0.10
Gupta et al,[4] 2015 3.00 (0.12, 73.79) 0.11
Gupta et al,[4] 2015 0.20 (0.01, 4.16) 0.12
Erdmann et al,[5] 2016 0.63 (0.21, 1.93) 0.89
Subtotal (I–squared = 0.0%, p = 0.672) 0.92 (0.83, 1.02) 100.00
Gastric
NCT00736099, 2010 0.52 (0.02, 10.83) 1.32
NCT00676338, 2011 1.34 (0.05, 33.01) 1.24
Chang et al,[11] 2013 0.62 (0.40, 0.97) 66.83
Erdmann et al,[5] 2016 0.90 (0.47, 1.74) 30.61
Subtotal (I–squared = 0.0%, p = 0.791) 0.70 (0.49, 1.01) 100.00
Oesophageal
NCT00225277, 2008 0.34 (0.01, 8.28) 25.55
Erdmann et al,[5] 2016 1.01 (0.14, 7.17) 74.45
Subtotal (I–squared = 0.0%, p = 0.584) 0.76 (0.14, 4.18) 100.00
Thyroid
NCT00637273, 2009 0.66 (0.03, 16.18) 0.91
NCT00736099, 2010 0.52 (0.02, 10.83) 0.91
Tseng et al,[12] 2014 0.98 (0.73, 1.33) 98.19
Subtotal (I–squared = 0.0%, p = 0.898) 0.97 (0.72, 1.31) 100.00
Brain
Erdmann et al,[5] 2016 0.28 (0.08, 0.99) 100.00
Subtotal (I–squared = .%, p = .) 0.28 (0.08, 0.98) 100.00
Biliary
Erdmann et al,[5] 2016 1.68 (0.40, 7.04) 100.00
Subtotal (I–squared = .%, p = .) 1.68 (0.40, 7.05) 100.00
Bone
NCT00736099, 2010 0.87 (0.04, 21.29) 50.00
NCT00736099, 2010 0.87 (0.04, 21.29) 50.00
Subtotal (I–squared = 0.0%, p = 1.000) 0.87 (0.09, 8.00) 100.00
.00334
1
299
Favours pioglitazone
Favours control

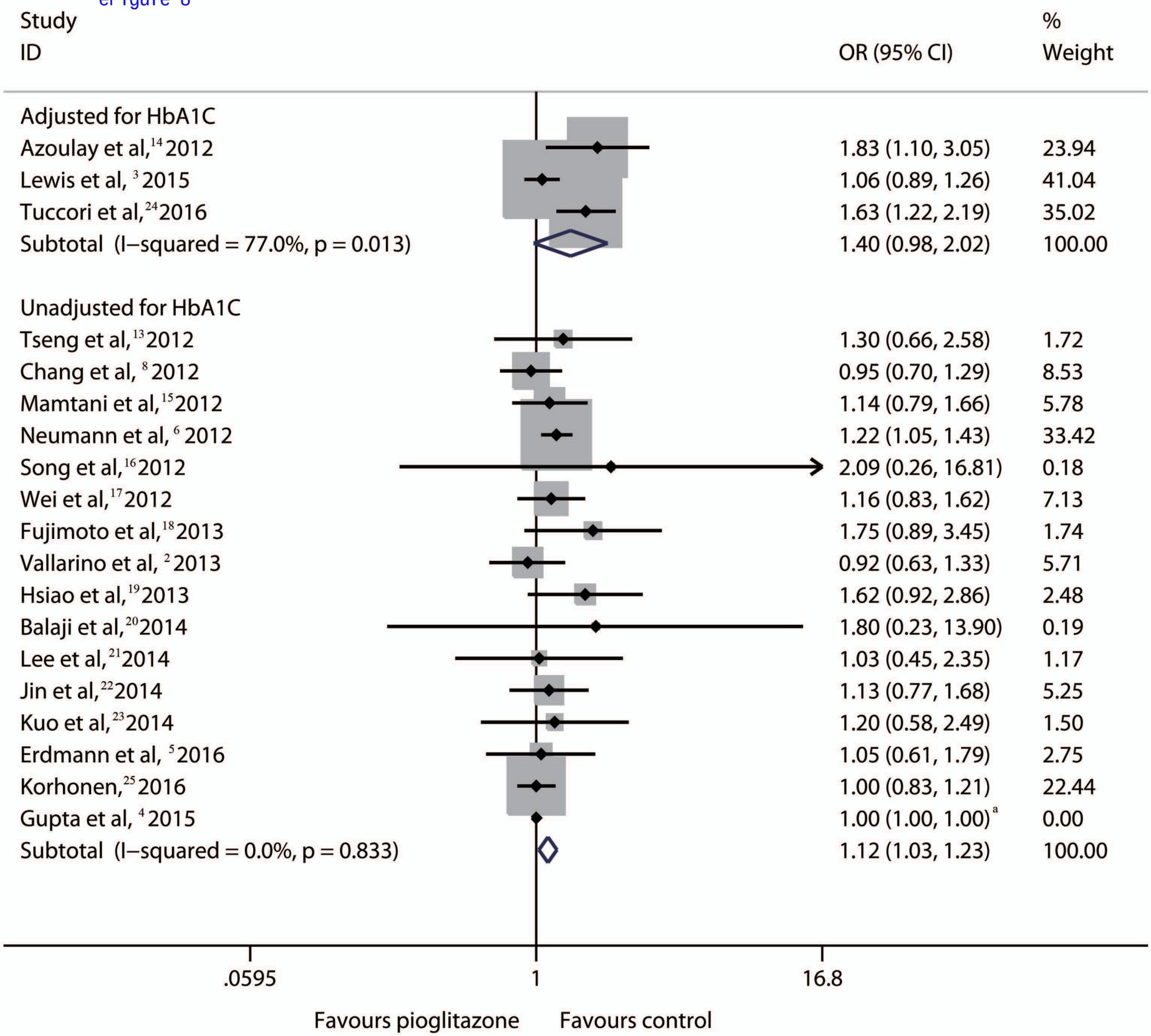
eFigure 6 Egger's publication bias plot



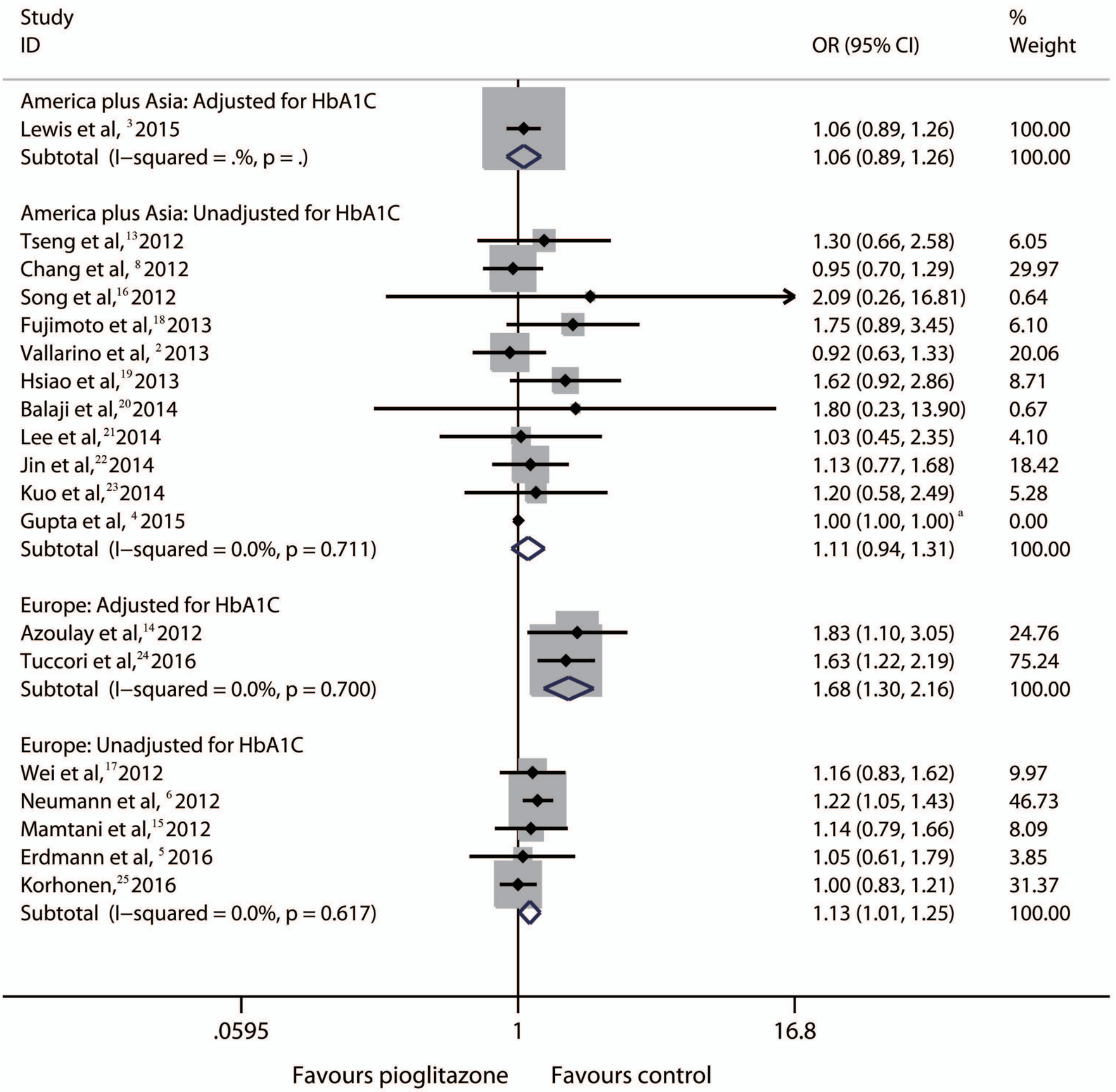
eFigure 7 Begg's funnel plot with pseudo 95% confidence limits



eFigure 8


Study ID
OR (95% CI)
% Weight
Adjusted for HbA1C
Azoulay et al,[14] 2012
1.83 (1.10, 3.05)
23.94
Lewis et al, [3] 2015
1.06 (0.89, 1.26)
41.04
Tuccori et al,[24] 2016
1.63 (1.22, 2.19)
35.02
Subtotal (I–squared = 77.0%, p = 0.013)
1.40 (0.98, 2.02)
100.00
Unadjusted for HbA1C
Tseng et al,[13] 2012
1.30 (0.66, 2.58)
1.72
Chang et al, [8] 2012
0.95 (0.70, 1.29)
8.53
Mamtani et al,[15] 2012
1.14 (0.79, 1.66)
5.78
Neumann et al, [6] 2012
1.22 (1.05, 1.43)
33.42
Song et al,[16] 2012
2.09 (0.26, 16.81)
0.18
Wei et al,[17] 2012
1.16 (0.83, 1.62)
7.13
Fujimoto et al,[18] 2013
1.75 (0.89, 3.45)
1.74
Vallarino et al, [2] 2013
0.92 (0.63, 1.33)
5.71
Hsiao et al,[19] 2013
1.62 (0.92, 2.86)
2.48
Balaji et al,[20] 2014
1.80 (0.23, 13.90)
0.19
Lee et al,[21] 2014
1.03 (0.45, 2.35)
1.17
Jin et al,[22] 2014
1.13 (0.77, 1.68)
5.25
Kuo et al,[23] 2014
1.20 (0.58, 2.49)
1.50
Erdmann et al, [5] 2016
1.05 (0.61, 1.79)
2.75
Korhonen,[25] 2016
1.00 (0.83, 1.21)
22.44
Gupta et al, [4] 2015
1.00 (1.00, 1.00)[a]
0.00
Subtotal (I–squared = 0.0%, p = 0.833)
1.12 (1.03, 1.23)
100.00
.0595
1
16.8
Favours pioglitazone
Favours control

eFigure 9


Study ID
OR (95% CI)
% Weight
America plus Asia: Adjusted for HbA1C
Lewis et al, [3] 2015 1.06 (0.89, 1.26) 100.00
Subtotal (I–squared = .%, p = .) 1.06 (0.89, 1.26) 100.00
America plus Asia: Unadjusted for HbA1C
Tseng et al, [13] 2012 1.30 (0.66, 2.58) 6.05
Chang et al, [8] 2012 0.95 (0.70, 1.29) 29.97
Song et al, [16] 2012 2.09 (0.26, 16.81) 0.64
Fujimoto et al, [18] 2013 1.75 (0.89, 3.45) 6.10
Vallarino et al, [2] 2013 0.92 (0.63, 1.33) 20.06
Hsiao et al, [19] 2013 1.62 (0.92, 2.86) 8.71
Balaji et al, [20] 2014 1.80 (0.23, 13.90) 0.67
Lee et al, [21] 2014 1.03 (0.45, 2.35) 4.10
Jin et al, [22] 2014 1.13 (0.77, 1.68) 18.42
Kuo et al, [23] 2014 1.20 (0.58, 2.49) 5.28
Gupta et al, [4] 2015 1.00 (1.00, 1.00) [a] 0.00
Subtotal (I–squared = 0.0%, p = 0.711) 1.11 (0.94, 1.31) 100.00
Europe: Adjusted for HbA1C
Azoulay et al, [14] 2012 1.83 (1.10, 3.05) 24.76
Tuccori et al, [24] 2016 1.63 (1.22, 2.19) 75.24
Subtotal (I–squared = 0.0%, p = 0.700) 1.68 (1.30, 2.16) 100.00
Europe: Unadjusted for HbA1C
Wei et al, [17] 2012 1.16 (0.83, 1.62) 9.97
Neumann et al, [6] 2012 1.22 (1.05, 1.43) 46.73
Mamtani et al, [15] 2012 1.14 (0.79, 1.66) 8.09
Erdmann et al, [5] 2016 1.05 (0.61, 1.79) 3.85
Korhonen, [25] 2016 1.00 (0.83, 1.21) 31.37
Subtotal (I–squared = 0.0%, p = 0.617) 1.13 (1.01, 1.25) 100.00
.0595
1
16.8
Favours pioglitazone
Favours control

eTable 1. Characteristics of Studies Regarding Bladder Cancer Risk and Pioglitazone Use

Author (year)	Study Type	Region	Target disease	Mean period of follow-up (years)	Dose-response gradient (Y/N)	Duration-response gradient (Y/N)	Mean age (years)	Male patient No. (%)	Exposure group	Control group	No. of pioglitazone (events/ total)	No. of control (events/ total)	Adjusted estimates (95% CI)	Adjusted covariate
Tseng et al,[13] (2012)	Cohort	Taiwan	T2DM	NR	Y[a]	Y[a]	NR	NR	Pioglitazone	No use	10 /2545	155 /52383	HR 1.30 (0.66, 2.58)	Age, sex, diabetes duration, nephropathy, urinary tract disease, hypertension, COPD, cerebrovascular disease, ischemic heart disease, peripheral arterial disease, eye disease, dyslipidemia, heart failure, rosiglitazone, sulfonylurea, meglitinide, metformin, acarbose, insulin, statin, fibrate, ACE inhibitor/angiotensin receptor blocker, calcium channel blocker, region of residence, occupation, and other cancer before baseline.
Azoulay et al,[14] (2012)	Nested case/control	UK	T2DM	4.6 (mean)	Y[a]	Y[a]	68.9	81.4	Pioglitazone	No use of TZDs	19 /210	357 /6865	Rate ratio 1.83 (1.10, 3.05)	Excessive alcohol use, obesity, smoking status, HbA1c, previous bladder conditions, previous cancer (other than non-melanoma skin cancer), Charlson comorbidity score, and ever use of other antidiabetic agents. Matched on year of birth, year of cohort entry, sex, and duration of follow-up
Chang et al,[8] (2012)	Nested case/control	Taiwan	T2DM	7.9 (median)	Y[a]	N	70.9	66.8	Pioglitazone	No use	84 /401	1499 /7490	OR 0.95 (0.70, 1.29)	Pioglitazone, rosiglitazone, short-acting human insulin, metformin (mean daily dosage in quartiles), sulfonylurea (mean daily dosage in quartiles), number of oral anti-diabetic agents, nephropathy, glinides, ACE inhibitors, chronic kidney disease, calcium channel blockers,

													neuropathy. Matched on age and sex
Mamtani et al,[15] (2012)	Cohort	Europe	T2DM	3.6 (median)	Y[a]	N	62.6[d]	57.2	Pioglitazone	Rosiglitazone	41 /10900	86 /17614	HR 1.14 (0.79, 1.66)	Age (<60, 60–69, ≥70 years), sex, smoking (ever vs. never), history of myocardial infarction, and past sulfonylurea use
Neumann et al,[6] (2012)	Cohort	France	DM	3.125 (mean)	Y[a]	Y[a]	63.2	53.4	Pioglitazone	No use	175 /155535	1841 /1335525	HR 1.22 (1.05, 1.43)	Age, sex (when applicable) and exposure to glucose-lowering drugs
Song et al,[16] (2012)	Case–control	Korea	T2DM	NR	N	N	69.4	84.2	Pioglitazone	No use	21 /120	308 /867	OR 2.09 (0.26,16.81)	Smoking Matched on sex and age.
Wei et al,[17] (2012)	Cohort	UK	T2DM	4.4 (mean)	N	N	64.6	54.4	Pioglitazone	No use	66 /23548	803 /184166	HR 1.16 (0.83,1.62)	Age, gender, smoking status, BMI and duration of diabetes
Fujimoto et al,[18] (2013)	Cohort	Japan	T2DM	NR	Y[a]	N	NR	NR	Pioglitazone	No use	9 /663	673 /20672	Unadjusted HR 1.75 (0.89,3.45)	NR
Vallarino et al,[2] (2013)	Cohort	US	T2DM	2.1 (mean)	N	N	58.6	57.5	Pioglitazone	Insulin	84 /38588	44 /17948	HR 0.92 (0.63,1.33)	Demographics (age, sex, tobacco use), use of medications (defined as any prescription claim within 180 days prior to the index date) and medical history (defined as any diagnosis claim prior to the index date)
Hsiao et al,[19] (2013)	Nested case/control	Taiwan	T2DM	3.68 (mean)	Y[a]	N	66.3	68.5	Pioglitazone	No use	153 /676	3259 /19796	OR 1.62 (0.92,2.86)	Duration of diabetes, chronic renal failure, bladder conditions (calculus of kidney, ureter, lower urinary tract, cystitis and urinary tract infection) and COPD, other hypoglycemic agents, including sulfonylureas, biguanides, a-glucosidase

														inhibitors and insulin. Matched on sex and age.
Balaji et al,[20] (2014)	Cohort	India	DM	NR	N	N	NR	NR	Pioglitazone	No use	1 /31	19 /1046	NR	NR
Lee et al,[21] (2014)	Cohort	Taiwan	T2DM	NR	Y[b]	Y[b]	NR	47.5	Pioglitazone	No use	12 /3497	72 /31473	HR 1.03 (0.45,2.35)	Sex, age, duration of diabetes, other diabetes medications, income (monthly income, NT$20,000; monthly income, NT$20,000), residential area, nephritis, chronic kidney disease, kidney infections, hydronephrosis, calculus of the lower urinary tract, cystitis, other disorders of the urethra and urinary tract, hypertension and hyperlipidemia.
Jin et al,[22] (2014)	Cohort +Nested case/control	Korea	T2DM	NR	Y[c]	N	63.4	53.3	Pioglitazone	No use	30 /11240	237 /101953	HR 1.13 (0.77, 1.68)	Age and sex
Kuo et al,[23] (2014)	Nested case/control	Taiwan	DM	NR	N	Y[c]	69.6	61.8	Pioglitazone	No use	15 /67	244 /1228	OR 1.20 (0.58, 2.49)	Nephropathy, urinary tract diseases, urinary tract infection, urinary tract stone, hypertension, chronic obstructive pulmonary disease, stroke, ischemic heart disease, peripheral arterial diseases, eye disease, and dyslipidemia. Matched on sex, age, and time from entry into cohort to the index date.
Lewis et al,[3] (2015)	Cohort +Nested case/control	US	DM	7.2 (median)	Y[a]	Y[a]	Reported by segment	53.5	Pioglitazone	No use	186 /34181	1075 /158918	HR 1.06 (0.89, 1.26)	Age, sex, and year of cohort entry, use of other diabetes medication, smoking, race/ethnicity, other diabetes medications, other bladder conditions, median household income, congestive heart

													failure, cancer other than bladder cancer, renal insufficiency, HbA1c and the interaction with new diagnosis of diabetes, and duration of diabetes, the 3-level time-updated proteinuria testing variable (no testing, negative and positive testing result for proteinuria)
Erdmann et al,[5] (2016)	Cohort	Europe	T2DM	7.8 (mean)	N	N	NR	NR	Pioglitazone	Placebo	27 /2605	26 /2633	Unadjusted relative risk 1.05 (0.61, 1.79)	NR
Tuccori et al,[24] (2016)	Cohort	UK	T2DM	4.8 (mean)	Y[a]	Y[a]	63.7	56.8	Pioglitazone	No use of TZDs	54 /921	479 /142758	HR 1.63 (1.22, 2.19)	Age, year of cohort entry, sex, alcohol related disorders, smoking status, obesity, HbA1c, previous cancer, bladder conditions, Charlson comorbidity score, duration of treated diabetes, and urine protein testing.
Korhonen et al,[25] (2016)	Cohort	Europe	T2DM	2.9 (mean)	Y[c]	Y[c]	63.2	56.3	Pioglitazone	No use	130 /56337	970 /317109	HR 1.00 (0.83, 1.21)	age, sex, metformin use, sulfonylurea use, insulin use, use of other diabetes drugs, history of relevant comorbidities, history of other relevant medications, history of bladder comorbidities.
Gupta et al,[4] (2015)	Cohort	India	T2DM	NR	N	N	52.0	63.5	Pioglitazone	No use	0 /1111	0 /1111	NR	NR

Author (year)	**Region**	**No. of study sites**	**Study phase**	**Target disease**	**Drug treatments used across groups**	**Intervention group**		**Control group**		**Duration of treatment (weeks)**
						Type	**Events/analyzed patients (No.)**	**Type**	**Events/analyzed patients (No.)**	
NCT00174993 (2005)	Europe	321	III	T2DM	None	Pioglitazone	14/2605	Placebo	6/2633	48 months

NCT00225277 (2008)	America	97	III	T2DM	None	Pioglitazone	0/270	Glimepiride	1/273	72 weeks
NCT00494312 (2009)	US	171	IV	T2DM	Glyburide placebo-matching capsules or Pioglitazone placebo-matching tablets	Pioglitazone	2/1051	Glyburide	0/1046	156 weeks
NCT00736099 (2011)	Multi-regions	232	III	T2DM	Linagliptine	Pioglitazone	0/589	None	1/1532	78 weeks

Abbreviations: DM, diabetes mellitus; T2DM, type 2 diabetes mellitus; TZDs, thiazolidinediones; 95% CI, 95% confidence interval; HR, hazard ratio; OR, odds ratio; NR, not reported; COPD, chronic obstructive pulmonary disease; HbA1c, hemoglobin A1c concentration; ACE, angiotensin-converting enzyme; BMI, body mass index.

[a]Trials used the same categories that were used in the interim analysis of the Kaiser Permanente Northern California (KPNC) study.

[b]Trials used categories which were partly consistent with the one in the interim analysis of the KPNC study.

[c]Trials used categories which were inconsistent with the one in the interim analysis of the KPNC study.

[d]Median age (years).

eTable 2. Quality Assessment of Studies Regarding Bladder Cancer Risk and Pioglitazone Use

Author (year)	Ascertainment of diabetes	Representativeness of the exposed cohort	Selection of the non-exposed cohort	Ascertainment of exposure to pioglitazone	Demonstration that outcome of interest was not present at start of study	Comparability of study controls for important factors	Assessment of outcome	Completeness of outcome	Score
Tseng et al,[13] (2012)	T2DM were identified based on ICD-9 codes 250.1–250.9	Generally representative of the population in corresponding region	Drawn from the same population as the exposed cohort	Statement not explicit; likely from the drug prescription in the electronic medical records	Yes, patients who had bladder cancer before entry were excluded	Cox regression was used to estimate confounders, including age, sex, diabetes duration, nephropathy, urinary tract disease, hypertension, other combined disease, other diabetes medications, statin, fibrate, ACE inhibitor/angiotensin receptor blocker, calcium channel blocker, region of residence, occupation, and other cancer before baseline, extracted by ICD-9 codes	Bladder cancer was identified based on ICD-9 codes 188.xx	Authors did not mention the completeness of outcome	8
Mamtani et al,[15] (2012)	Statement not explicit; T2DM likely identified from database	Generally representative of the population in corresponding region	Drawn from the same population as the exposed cohort	Drug prescription in the electronic medical records	Yes, patients who had bladder cancer before entry were excluded	Cox proportional hazards regression models were used to estimate potential confounders, including other diabetes medications and variables believed to affect either the risk of bladder cancer or the probability of receiving a TZD	Bladder cancer was identified by The Read Codes (Version 2)	Authors did not mention the completeness of outcome	8

Neumann et al,[6] (2012)	Statement not explicit; DM likely from identifying ICD-9 code in the database	Generally representative of the population in corresponding region	Drawn from the same population as the exposed cohort	Drug prescription in the electronic medical records	Yes, patients had bladder cancer diagnosed before study entry or within the first 6 months after study entry were excluded	Cox proportional hazard models were used to estimate covariates, including age, sex and use of other glucose-lowering drugs	Bladder cancer was identified by ICD-10 code C67 and specific surgical procedure and/or intravesical instillation of pharmacological product by urethral catheter and/or chemotherapy and/or radiation therapy performed during the same hospital stay	Authors did not mention the completeness of outcome	8
Wei et al,[17] (2012)	T2DM was defined based on the record of General Practice Research Database (GPRD) during the study period	Generally representative of the population in corresponding region	Drawn from the same population as the exposed cohort	Drug prescription in the electronic medical records	Yes, the study outcome was incident bladder cancer during the follow-up period	Cox proportional hazard model was used to adjust for age, gender, smoking status, BMI and duration of diabetes	Data collected during the follow up	There were 45 and 3683 subjects with missing data about smoking history, and 499 and 11948 subjects with missing data about BMI in pioglitazone treatment group and other oral hypoglycaemic drugs treatment group, respectively	9

Fujimoto et al,[18] (2013)	Statement not explicit; T2DM identified likely from database	NR	Selection of the non-exposed cohort	Statement not explicit; likely from the drug prescription in the database	Yes, patients who had bladder cancer before entry were excluded.	No adjusted analysis was conducted	Statement not explicit; likely identified from the database	Authors did not mention the completeness of outcome	5
Vallarino et al,[2] (2013)	T2DM identified by ICD-9 codes 250.x0 or 250.x2	Generally representative of the population in corresponding region	Drawn from the same population as the exposed cohort	Statement not explicit; likely from the drug prescription in the database	Yes, patients who had bladder cancer before entry were excluded	Cox regression models were used to estimate covariates, including demographics, use of medications and medical history	Bladder cancer was identified based on ICD-9 codes 188.xx, 233.7	Authors did not mention the completeness of outcome	8
Balaji et al,[20] (2014)	DM was identified by medical records screening from the hospital	NR	Drawn from the same population as the exposed cohort	Statement not explicit; likely identified by medical records screening from the hospital	NR	NR	Bladder cancer cases were identified by medical records screening from the hospital	Authors did not mention the completeness of outcome	4
Lee et al,[21] (2014)	T2DM identified by ICD-9-CM code 250.1–250.9	Generally representative of the population in corresponding region	Drawn from the same population as the exposed cohort	From the drug prescription in the database	Yes, patients who had bladder cancer before entry were excluded.	Cox regression analysis was used to estimate confounders, including sex, age, duration of diabetes, other diabetes medications, income, residential area, nephritis, chronic kidney disease, kidney infections, hydronephrosis, calculus of the lower urinary tract, cystitis, other disorders of the urethra and urinary tract, hypertension and hyperlipidemia	Bladder cancer cases were identified according to ICD-9-CM code 188 and were confirmed by the issuance of catastrophic illness cards	Authors did not mention the completeness of outcome	8

Jin et al,[22] (2014)	Statement not explicit; T2DM likely identified from database	NR	Drawn from the same population as the exposed cohort	From the drug prescription in the database	Yes, patients who had bladder cancer before entry were excluded	Cox regression model was used to control for age at baseline and sex	Bladder cancer cases were identified according to ICD-10 code C67	Authors did not mention the completeness of outcome	6
Lewis et al,[3] (2015)	DM identified basis of hospital and physician diagnoses, prescription medications, and laboratory tests.	Generally representative of the population in corresponding region	Drawn from the same population as the exposed cohort	From the drug prescription in the database	Yes, patients with a diagnosis of bladder cancer before entry or within 6 months of entry were excluded	Cox regression analysis was used to estimate confounders, including age, sex, and year of cohort entry, use of other diabetes medication, smoking, race/ethnicity, other diabetes medications, other bladder conditions, median household income, congestive heart failure, cancer other than bladder cancer, renal insufficiency, HbA1c and the interaction with new diagnosis of diabetes, and duration of diabetes, the 3-level time-updated proteinuria testing variable	Bladder cancer cases were identified from the KPNC cancer registry, which reports to the California Cancer Registry and the National Cancer Institute's Surveillance, Epidemiology and End Results program of registries	There were missing data regarding race/ethnicity, renal function at baseline, income, baseline HbA1c, and diabetes duration at baseline, in the pioglitazone group and never use group, respectively	9
Erdmann et al,[5] (2016)	T2DM patients identified by physicians	NR	Drawn from the same population as the exposed cohort	Drug prescription in the routine clinical practice	Statement not explicit; 11 patients were diagnosed bladder cancer within 1 years	There were no adjustments have been done.	Statement not explicit; likely from the data collected during the follow up	A similar percentage of patients on pioglitazone or placebo groups withdrew consent to follow-up (<1%), were confirmed lost to follow-up	6

								(~9%), and had an unconfirmed status [i.e. last contact ≥9 years (<5%)].	
Tuccori et al,[24] (2016)	T2DM was identified by Read code from the database	Generally representative of the population in corresponding region	Drawn from the same population as the exposed cohort	A coded drug dictionary based on the UK Prescription Pricing Authority Dictionary is used to record prescriptions	Yes, patients who had bladder cancer before entry were excluded	Time dependent Cox proportional hazards models were used to estimate covariates, including age, sex, year of cohort entry, body mass index, smoking status, alcohol related disorders, HbA1cace, duration of treated diabetes, previous bladder conditions, history of cancer, presence of at least one urine protein test in the year before cohort entry, and Charlson comorbidity score 26	Bladder cancer was identified by Read code from the database	There were 9 and 1530 patients with unknown data about BMI, 14 and 3434 patients with unknown data about smoking, 236 and 49,480 patients with unknown data about HbA1c, in pioglitazone group and no pioglitazone group, respectively	9
Korhonen et al,[25] (2016)	T2DM was identified from database	Generally representative of the population in corresponding region	Drawn from the same population as the exposed cohort	Drug use data were based on outpatient prescription data and outpatient dispensing data	Yes, patients with histories of malignant or benign bladder neoplasms were excluded	Age, sex, metformin use, sulfonylurea use, insulin use, use of other diabetes drugs, all exact matching variables, propensity scores, and all propensity score variables evaluated at cohort entry date	Bladder cancer cases were identified from cancer registries and hospital records	Authors did not mention the completeness of outcome	8

Gupta et al,[4] (2015)	Statement not explicit; T2DM likely identified from database	NR	Drawn from the same population as the exposed cohort	Statement not explicit; likely from the drug prescription in the database	NR	NR		Bladder cancer was assessed by taking history and detailed urinary analysis including urine routine, microscopy, hematuria, and cytology examination	Authors did not mention the completeness of outcome	4

Author (year)	**Is case definition adequate**	**Ascertainment of diabetes**	**Representativeness of the cases**	**Selection of controls**	**Definition of controls**	**Comparability of study controls for important factors**	**Ascertainment of exposure to pioglitazone**	**Same method of ascertainment for exposure to pioglitazone in both arms**	**Completeness of data within database**	**Score**

Azoulay et al,[14] (2012)	Statement not explicit; likely from identifying the clinical diagnoses according to the ICD codes	Statement not explicit; T2DM likely from identifying patients newly treated with noninsulin antidiabetic drugs	Representative of the population in corresponding region	Up to 20 controls were randomly selected from the case's risk set, after matching on year of birth, year of cohort entry, sex, and duration of follow-up. And all controls were alive, had no previous diagnosis of bladder cancer	Patients had no previous diagnosis of bladder cancer	Conditional logistic models were used to control for year of birth, year of cohort entry, sex, and duration of follow-up,HbA1c, excessive alcohol use, obesity, smoking, previous cancer, previous bladder conditions, and Charlson comorbidity score	Statement not explicit; likely from the drug prescription in the electronic medical records	Yes, both cases and controls who had been prescribed TZDs identified with claims database	Authors did not mention the completeness of data in the database, however, HbA1c information was reported as missing for 19% of the cases and controls	9
Chang et al,[8] (2012)	All potential cases were validated by a linkage through National Cancer Registry	T2DM patients were identified by diagnostic codes (ICD-9-CM)	Obviously representative series of cases in corresponding region	A risk-set sampling matched by age, sex, and the number of days of follow-up was used to find controls for the cohort	Patients had no previous diagnosis of bladder cancer	Conditional logistic regression was used to test potential covariates, including socioeconomic status, diabetes complications and comorbidities at cancer diagnosis, other antidiabetic agents, antihypertensive medications, statin, and aspirin	From the outpatient pharmacy prescription database	Statement not explicit; likely from the outpatient pharmacy prescription database	Authors did not mention the completeness of data in the database	9

Song et al,[16] (2012)	Bladder cancer diagnosis confirmed by cytology	Statement not explicit; T2DM patients likely identified from electronic medical records	Obviously representative series of cases in corresponding region	Age- and sex-matched diabetics without bladder cancer were enrolled as the control group	Patients had no previous diagnosis of bladder cancer	Multivariate conditional logistic regression model was used to determine the factors, such as, age, sex, duration of diabetes, obesity, alcohol, smoking, and anti-diabetic agents, and potential underlining medical conditions	Statement not explicit; likely from the drug prescription in the electronic medical records	Statement not explicit; likely from the drug prescription in the electronic medical records	Authors did not mention the completeness of data in the database, but to avoid incomplete or missing data on potential confounders, authors were selected from the Severance diabetes registry	9
Hsiao et al,[19] (2013)	Diagnosis of bladder cancer was identified by ICD-9-CM codes: 188.xx	Diagnosis of T2DM identified by ICD-9-CM code 250.xx	Obviously representative series of cases in corresponding region	For each case, five matched controls were randomly selected from the same diabetic cohort using the incidence density sampling approach, and were matched to the cases for age, sex and entry date	Statement not explicit; likely patients without bladder cancer	Multivariable conditional logistic regressions were used to estimate the associated factors, including duration of diabetes, co-morbid conditions and concomitant medications. Co-morbid conditions included chronic renal failure, bladder conditions and chronic obstructive pulmonary disease (COPD)	The exposure to pioglitazone was based on identified prescriptions	Yes, both cases and controls who had been prescribed pioglitazone identified from claims database	Authors did not mention the completeness of data in the database	9

Kuo et al,[23] (2014)	Diagnoses of bladder cancer was identified by ICD-9 188.** codes	T2DM patients were identified by diagnostic codes for diabetes ICD-9-CM	Obviously representative series of cases in corresponding region	For each case, four control individuals were randomly selected from the set of all eligible controls, and matched to the cases by sex, age, and time from entry into cohort to the index date	Patients had no previous diagnosis of bladder cancer	Conditional logistic regression model was used to estimate relative factors, including documented risk factors for bladder cancer and comorbidities, were retrieved by ICD-9 codes	Information on pioglitazone exposure was extracted from the prescription database	Statement not explicit, likely extracted from the prescription database	Authors did not mention the completeness of data in the databaseBMIH	9

Author (year)	Randomization sequence generation	Allocation concealment	Blinding of participants and personnel	Blinded assessment bladder cancer events	Incomplete outcome data	Selective reporting
NCT00174993 (2005)	Low	Low	Low	Low	Low[a]	Low
NCT00225277 (2008)	Low	Low	Low	Low	Low[a]	Low
NCT00494312 (2009)	Low	Low	Low	Low	Low[a]	Low
NCT00736099 (2011)	Unclear	Unclear	Unclear	Unclear	NR[a]	Unclear

Abbreviations: DM, diabetes mellitus; T2DM, type 2 diabetes mellitus; ICD, international Classification of diseases; ACE, angiotensin-converting enzyme; TZDs, thiazolidinediones; NR, not reported; HbA1c, hemoglobin A1c concentration; BMI, body mass index

[a] Data extracted from serious adverse events.

eReferences. For eFigure 1, 2, 5, 8 and 9, eTable 1 and 2

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eAppendix 2. MOOSE Guidelines Checklist

Criteria		Brief description of how the criteria were handled in the meta-analysis
Reporting of background should include		
√	Problem definition	The association between pioglitazone use and bladder cancer risk was announced and debated for many years.
√	Hypothesis statement	Pioglitazone use may be associated with increased bladder cancer risk.
√	Description of study outcome(s)	Bladder and other cancer risks.
√	Type of exposure or intervention used	Pioglitazone use.
√	Type of study designs used	We included observational studies and randomized controlled trials.
√	Study population	Patients with diabetes.
Reporting of search strategy should include		
√	Qualifications of searchers	The credentials of all investigators are indicated in the author list.
√	Search strategy, including time period included in the synthesis and keywords	Three authors performed the literature search from the inception through Jan, 5 2017 without language restriction.
√	Databases and registries searched	Embase, PubMed, Web of Science, Cochrane Library, and ClinicalTrials.gov.
√	Search software used, name and version, including special features used	No specific search software was employed. Endnote was used to eliminate duplications.
√	Use of hand searching	We hand-searched bibliographies of retrieved manuscripts for additional references.
√	List of citations located and those excluded, including justification	Details of the literature search process are presented in the Figure 1.
√	Method of addressing articles published in languages other than English	We placed no restrictions on language. If necessary, we resorted to our colleagues who fluent in the corresponding language for translation.
√	Method of handling abstracts and unpublished studies	We contacted a few authors to make clarifications regarding their unpublished studies, but none of these studies were included in our analyses.
√	Description of any contact with authors	Not available.
Reporting of methods should include		
√	Description of relevance or appropriateness of studies assembled for assessing the hypothesis to be tested	The inclusion and exclusion criteria were described in the methods section.
√	Rationale for the selection and coding of data	Data extracted from each study were relevant to the study design, population characteristics, exposure and control conditions, outcome, etc.
√	Assessment of confounding	Subgroup and sensitivity analyses were performed to address potential confounders.

√	Assessment of study quality, including blinding of quality assessors; stratification or regression on possible predictors of study results	The Newcastle-Ottawa quality assessment scale and the Cochrane Collaboration's tool were used to assess the study quality.
√	Assessment of heterogeneity	The heterogeneity was evaluated by the use of I-squared for all analyses.
√	Description of statistical methods in sufficient detail to be replicated	Description of methods, subgroup analyses, sensitivity analyses, and assessment of publication bias are all detailed in the methods section.
√	Provision of appropriate tables and graphics	Five figures, one table, one eAppendixes, nine efigures and two etables were provided.
Reporting of results should include		
√	Graphic summarizing individual study estimates and overall estimate	Figure 2
√	Table giving descriptive information for each study included	eTable 1
√	Results of sensitivity testing	Results section.
√	Indication of statistical uncertainty of findings	95% confidence intervals were presented with all summary estimates.
Reporting of discussion should include		
√	Quantitative assessment of bias	No significant publication bias presented in our study, and sensitivity analyses were performed to quantify potential biases.
√	Justification for exclusion	We excluded studies that didn't relevant to pioglitazone and cancer incidence.
√	Assessment of quality of included studies	The study quality was reported both in the eTable 2 and sensitivity analysis section.
Reporting of conclusions should include		
√	Consideration of alternative explanations for observed results	Alternative explanations were provided in the discussion section.
√	Generalization of the conclusions	Our results are generalizable as we included studies from different population regions.
√	Guidelines for future research	We make recommendations in the discussion section.
√	Disclosure of funding source	This study was supported by grants from National Key R&D Program of China (No. 2016YFC1101100), National Natural Science Foundation of China (No. 81471039, No. 81270893, No. 81228023 and No. 81401601, and No.81402202) and the Natural Science Foundation Project of Chongqing (CSTC2014jcyjjq10006, CSTC2012jjB10023, and CSTC2016jcyjA0518).