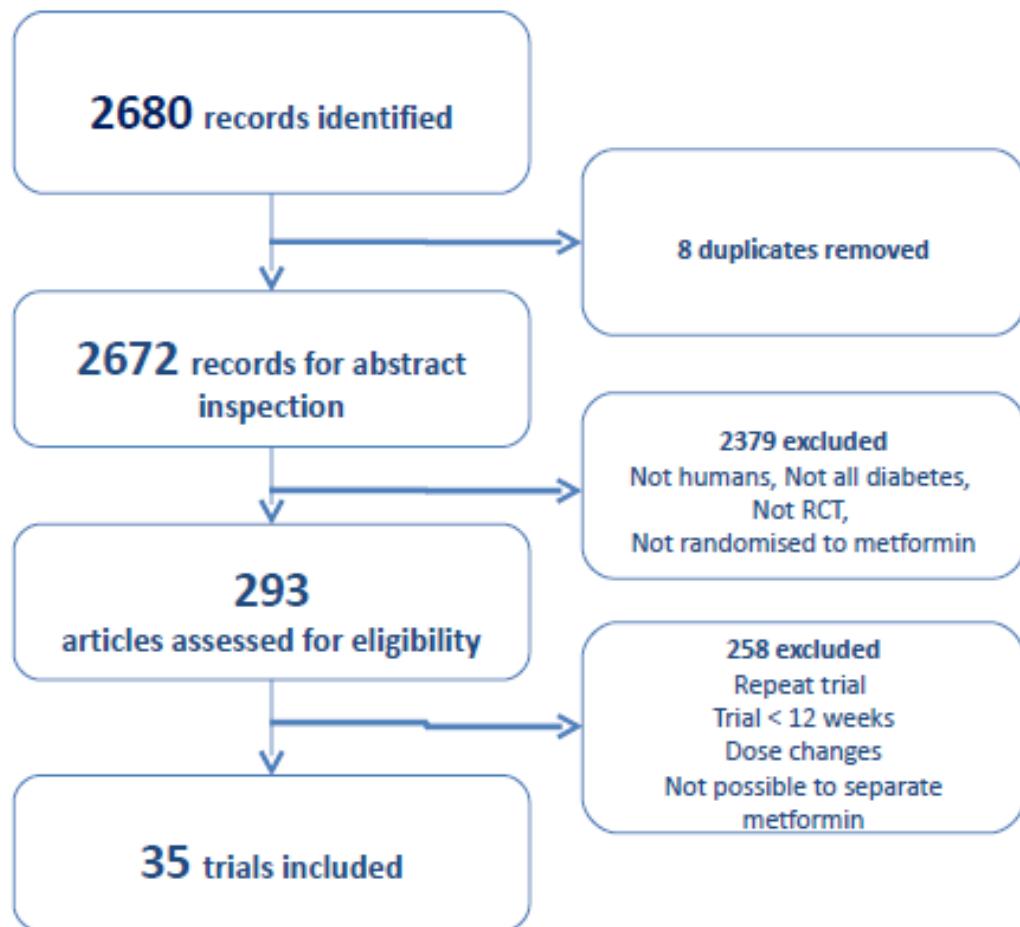


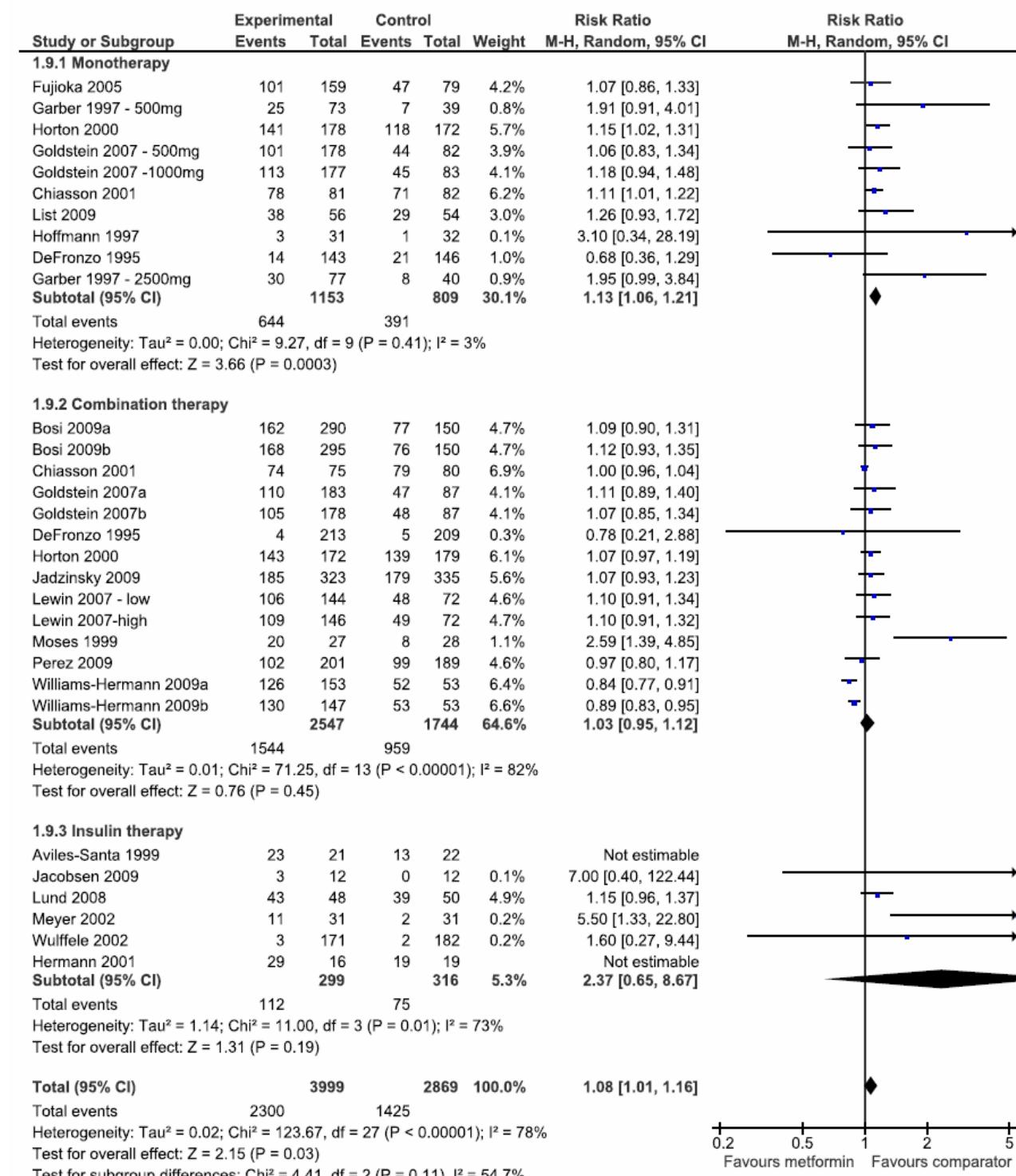
SUPPLEMENTARY DATA

Supplementary Figure 1. Flow chart showing number of citations retrieved in searches and number of trials included in the review



SUPPLEMENTARY DATA

Supplementary Figure 2. Relative risk of adverse events during trials of metformin treatment versus comparator (boxes) and pooled estimates across trials (diamonds) calculated by the Mantel-Haenszel method using a random effects model in trials of metformin monotherapy, metformin as add-on therapy to oral medication and metformin as add-on therapy to insulin. Horizontal bars and diamond widths denote 95% confidence intervals and box sizes indicate relative weight in the analysis.



SUPPLEMENTARY DATA

References

- Avilés-Santa L, Sinding J, Raskin P. *Effects of metformin in patients with poorly controlled, insulin-treated type 2 diabetes mellitus. A randomized, double-blind, placebo-controlled trial.* Ann Intern Med. 1999 Aug 3;131(3):182-8.
- Bosi E, Dotta F, Jia Y, Goodman M. *Vildagliptin plus metformin combination therapy provides superior glycaemic control to individual monotherapy in treatment-naïve patients with type 2 diabetes mellitus.* Diabetes Obes Metab. 2009 May;11(5):506-15.
- Chiasson JL, Naditch L; Miglitol Canadian University Investigator Group. *The synergistic effect of miglitol plus metformin combination therapy in the treatment of type 2 diabetes.* Diabetes Care. 2001 Jun;24(6):989-94.
- Damsbo P, Hermann LS, Vaag A, Hother-Nielsen O, Beck-Nielsen H. *Irreversibility of the defect in glycogen synthase activity in skeletal muscle from obese patients with NIDDM treated with diet and metformin.* Diabetes Care. 1998 Sep;21(9):1489-94.
- DeFronzo RA, Goodman AM. *Efficacy of metformin in patients with non-insulin-dependent diabetes mellitus. The Multicenter Metformin Study Group.* N Engl J Med. 1995 Aug 31;333(9):541-9.
- Derosa G, Maffioli P, Salvadeo SA, Ferrari I, Gravina A, Mereu R, Palumbo I, D'Angelo A, Cicero AF. *Direct comparison among oral hypoglycemic agents and their association with insulin resistance evaluated by euglycemic hyperinsulinemic clamp: the 60's study.* Metabolism. 2009 Aug;58(8):1059-66.
- Douek IF, Allen SE, Ewings P, Gale EA, Bingley PJ; Metformin Trial Group. *Continuing metformin when starting insulin in patients with Type 2 diabetes: a double-blind randomized placebo-controlled trial.* Diabet Med. 2005 May;22(5):634-40.
- Fujioka K, Brazg RL, Raz I, Bruce S, Joyal S, Swanink R, Pans M. *Efficacy, dose-response relationship and safety of once-daily extended-release metformin (Glucophage XR) in type 2 diabetic patients with inadequate glycaemic control despite prior treatment with diet and exercise: results from two double-blind, placebo-controlled studies.* Diabetes Obes Metab. 2005 Jan;7(1):28-39.
- Garber AJ, Duncan TG, Goodman AM, Mills DJ, Rohlf JL. *Efficacy of metformin in type II diabetes: results of a double-blind, placebo-controlled, dose-response trial.* Am J Med. 1997 Dec;103(6):491-7.
- Giugliano D, Quatraro A, Consoli G, Minei A, Ceriello A, De Rosa N, D'Onofrio F. *Metformin for obese, insulin-treated diabetic patients: improvement in glycaemic control and reduction of metabolic risk factors.* Eur J Clin Pharmacol. 1993;44(2):107-12.
- Goldstein BJ, Feinglos MN, Lunceford JK, Johnson J, Williams-Herman DE; Sitagliptin 036 Study Group. *Effect of initial combination therapy with sitagliptin, a dipeptidyl peptidase-4 inhibitor, and metformin on glycemic control in patients with type 2 diabetes.* Diabetes Care. 2007 Aug;30(8):1979-87.

SUPPLEMENTARY DATA

Grant PJ. *The effects of high- and medium-dose metformin therapy on cardiovascular risk factors in patients with type II diabetes*. Diabetes Care. 1996 Jan;19(1):64-6.

Hällsten K, Virtanen KA, Lönnqvist F, Sipilä H, Oksanen A, Viljanen T, Rönnemaa T, Viikari J, Knuuti J, Nuutila P. *Rosiglitazone but Not Metformin Enhances Insulin- and Exercise-Stimulated Skeletal Muscle Glucose Uptake in Patients With Newly Diagnosed Type 2 Diabetes*. Diabetes. 2002 Dec;51(12):3479-85.

Hermann LS, Kalén J, Katzman P, Lager I, Nilsson A, Norrhamn O, Sartor G, Ugander L. *Long-term glycaemic improvement after addition of metformin to insulin in insulin-treated obese type 2 diabetes patients*. Diabetes Obes Metab. 2001 Dec;3(6):428-34.

Hoffmann J, Spengler M. *Efficacy of 24-week monotherapy with acarbose, metformin, or placebo in dietary-treated NIDDM patients: the Essen-II Study*. Am J Med. 1997 Dec;103(6):483-90.

Horton ES, Clinkingbeard C, Gatlin M, Foley J, Mallows S, Shen S. *Nateglinide alone and in combination with metformin improves glycemic control by reducing mealtime glucose levels in type 2 diabetes*. Diabetes Care. 2000 Nov;23(11):1660-5.

Iozzo P, Hallsten K, Oikonen V, Virtanen KA, Parkkola R, Kemppainen J, Solin O, Lonnqvist F, Ferrannini E, Knuuti J, Nuutila P. *Effects of metformin and rosiglitazone monotherapy on insulin-mediated hepatic glucose uptake and their relation to visceral fat in type 2 diabetes*. Diabetes Care. 2003 Jul;26(7):2069-74.

Jacobsen IB, Henriksen JE, Beck-Nielsen H. *The effect of metformin in overweight patients with type 1 diabetes and poor metabolic control*. Basic Clin Pharmacol Toxicol. 2009 Sep;105(3):145-9.

Jadzinsky M, Pfützner A, Paz-Pacheco E, Xu Z, Allen E, Chen R; CV181-039 Investigators. *Saxagliptin given in combination with metformin as initial therapy improves glycaemic control in patients with type 2 diabetes compared with either monotherapy: a randomized controlled trial*. Diabetes Obes Metab. 2009 Jun;11(6):611-22.

Khan AS, McLoughney CR, Ahmed AB. *The effect of metformin on blood glucose control in overweight patients with Type 1 diabetes*. Diabet Med. 2006 Oct;23(10):1079-84.

Lewin A, Lipetz R, Wu J, Schwartz S. *Comparison of extended-release metformin in combination with a sulfonylurea (glyburide) to sulfonylurea monotherapy in adult patients with type 2 diabetes: a multicenter, double-blind, randomized, controlled, phase III study*. Clin Ther. 2007 May;29(5):844-55.

List JF, Woo V, Morales E, Tang W, Fiedorek FT. *Sodium-glucose cotransport inhibition with dapagliflozin in type 2 diabetes*. Diabetes Care. 2009 Apr;32(4):650-7.

Lund SS, Tarnow L, Astrup AS, Hovind P, Jacobsen PK, Alibegovic AC, Parving I, Pietraszek L, Frandsen M, Rossing P, Parving HH, Vaag AA. *Effect of adjunct metformin treatment in patients with type-1 diabetes and persistent inadequate glycaemic control. A randomized study*. PLoS One. 2008;3(10):e3363.

SUPPLEMENTARY DATA

Meyer L, Bohme P, Delbachian I, Lehert P, Cugnarney N, Drouin P, Guerci B. *The benefits of metformin therapy during continuous subcutaneous insulin infusion treatment of type 1 diabetic patients.* Diabetes Care. 2002 Dec;25(12):2153-8.

Moses R, Slobodniuk R, Boyages S, Colagiuri S, Kidson W, Carter J, Donnelly T, Moffitt P, Hopkins H. *Effect of repaglinide addition to metformin monotherapy on glycemic control in patients with type 2 diabetes.* Diabetes Care. 1999 Jan;22(1):119-24.

Natali A, Baldeweg S, Toschi E, Capaldo B, Barbaro D, Gastaldelli A, Yudkin JS, Ferrannini E. *Vascular effects of improving metabolic control with metformin or rosiglitazone in type 2 diabetes.* Diabetes Care. 2004 Jun;27(6):1349-57.

Perez A, Zhao Z, Jacks R, Spanheimer R. *Efficacy and safety of pioglitazone/metformin fixed-dose combination therapy compared with pioglitazone and metformin monotherapy in treating patients with T2DM.* Curr Med Res Opin. 2009 Dec;25(12):2915-23.

Ponssen HH, Elte JW, Lehert P, Schouten JP, Bets D. *Combined metformin and insulin therapy for patients with type 2 diabetes mellitus.* Clin Ther. 2000 Jun;22(6):709-18.

Robinson AC, Burke J, Robinson S, Johnston DG, Elkeles RS. *The effects of metformin on glycemic control and serum lipids in insulin-treated NIDDM patients with suboptimal metabolic control.* Diabetes Care. 1998 May;21(5):701-5.

Ryysy L, Yki-Järvinen H. *Improvement of glycemic control by 1 year of insulin therapy leads to a sustained decrease in sE-selectin concentrations in type 2 diabetes.* Diabetes Care. 2001 Mar;24(3):549-54.

Viljanen AP, Virtanen KA, Järvisalo MJ, Hällsten K, Parkkola R, Rönnemaa T, Lönnqvist F, Iozzo P, Ferrannini E, Nuutila P. *Rosiglitazone treatment increases subcutaneous adipose tissue glucose uptake in parallel with perfusion in patients with type 2 diabetes: a double-blind, randomized study with metformin.* J Clin Endocrinol Metab. 2005 Dec;90(12):6523-8.

Williams-Herman D, Johnson J, Teng R, Luo E, Davies MJ, Kaufman KD, Goldstein BJ, Amatruda JM. *Efficacy and safety of initial combination therapy with sitagliptin and metformin in patients with type 2 diabetes: a 54-week study.* Curr Med Res Opin. 2009 Mar;25(3):569-83.

Wolever TMS, Assiff L, Basu T. et al. *Miglitol, an (alpha)-glucosidase inhibitor, prevents the metformin-induced fall in serum folate and vitamin B12 in subjects with type 2 diabetes.* Nutr Res. 2000;20(10):1447-56

Wulffelé MG, Kooy A, Lehert P, Bets D, Ogterop JC, Borger van der Burg B, Donker AJ, Stehouwer CD. *Combination of insulin and metformin in the treatment of type 2 diabetes.* Diabetes Care. 2002 Dec;25(12):2133-40.

SUPPLEMENTARY DATA

Yki-Järvinen H, Ryysy L, Nikkilä K, Tulokas T, Vanamo R, Heikkilä M. *Comparison of bedtime insulin regimens in patients with type 2 diabetes mellitus. A randomized, controlled trial.* Ann Intern Med. 1999 Mar 2;130(5):389-96.