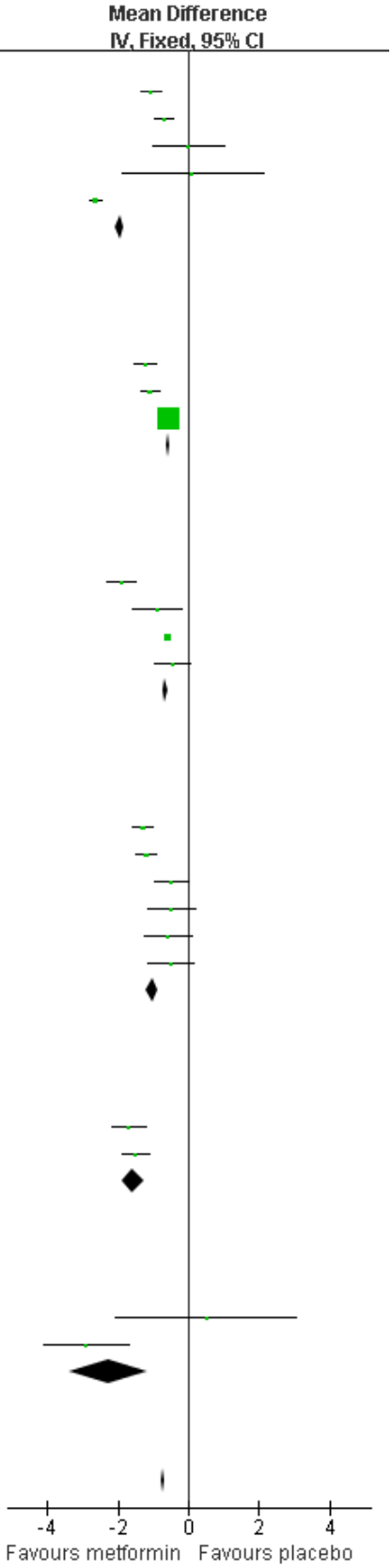
Study or Subgroup	metformin Mean	metformin SD	metformin Total	placebo Mean	placebo SD	placebo Total	Weight	Mean Difference IV, Fixed, 95% CI
1.1.1 Metformin 1000 mg/d								
Goldstein 2007	-0.86	1.33	178	0.2	1.41	165	1.3%	-1.06 [-1.35, -0.77]
Haak 2012	-0.6	1.19	141	0.1	0.81	65	1.4%	-0.70 [-0.98, -0.42]
Mather 2001	-0.3	1.16	28	-0.3	1.82	15	0.1%	0.00 [-1.02, 1.02]
Uehara 2001	-0.7	1.41	11	-0.8	3.09	11	0.0%	0.10 [-1.91, 2.11]
Wu 2001	-2.19	0.34	60	0.46	0.52	60	4.5%	-2.65 [-2.81, -2.49]
Subtotal (95% CI)			**418**			**316**	**7.4%**	**-1.94 [-2.06, -1.82]**
Heterogeneity: Chi² = 207.90, df = 4 (P < 0.00001); I² = 98%								
Test for overall effect: Z = 30.97 (P < 0.00001)								
1.1.2 Metformin 1500 mg/d								
Chiasson 2001	-0.85	1.08	81	0.38	1.09	82	1.0%	-1.23 [-1.56, -0.90]
Horton 2004	-0.8	0.99	98	0.3	0.99	98	1.4%	-1.10 [-1.38, -0.82]
List 2009	-0.73	0.1	51	-0.18	0.1	44	68.5%	-0.55 [-0.59, -0.51]
Subtotal (95% CI)			**230**			**224**	**70.9%**	**-0.57 [-0.61, -0.53]**
Heterogeneity: Chi² = 30.06, df = 2 (P < 0.00001); I² = 93%								
Test for overall effect: Z = 28.24 (P < 0.00001)								
1.1.3 Metformin 1700mg/d								
Chakraborty 2011	-1.8	1.3	110	0.1	1.64	98	0.7%	-1.90 [-2.31, -1.49]
Lee 1998	-1	1.4	24	-0.1	1.07	24	0.2%	-0.90 [-1.60, -0.20]
Manzella 2004	-0.8	0.18	60	-0.2	0.29	60	14.9%	-0.60 [-0.69, -0.51]
Pirags 2012	-0.15	0.88	33	0.31	1.25	33	0.4%	-0.46 [-0.98, 0.06]
Subtotal (95% CI)			**227**			**215**	**16.2%**	**-0.65 [-0.74, -0.57]**
Heterogeneity: Chi² = 38.77, df = 3 (P < 0.00001); I² = 92%								
Test for overall effect: Z = 15.50 (P < 0.00001)								
1.1.4 Metformin 2000mg/d								
Goldstein 2007	-1.1	1.23	177	0.2	1.41	165	1.4%	-1.30 [-1.58, -1.02]
Haak 2012	-1.1	1.17	138	0.1	0.81	65	1.4%	-1.20 [-1.48, -0.92]
Hällsten 2002	-0.7	0.79	13	-0.2	0.41	14	0.5%	-0.50 [-0.98, -0.02]
Hällsten 2004	-0.6	0.99	9	-0.1	0.36	11	0.2%	-0.50 [-1.18, 0.18]
Karlsson 2005	-0.7	0.99	9	-0.1	0.36	11	0.2%	-0.60 [-1.28, 0.08]
Viljanen 2005	-0.6	0.89	12	-0.1	0.72	11	0.3%	-0.50 [-1.16, 0.16]
Subtotal (95% CI)			**358**			**277**	**4.1%**	**-1.03 [-1.20, -0.87]**
Heterogeneity: Chi² = 16.01, df = 5 (P = 0.007); I² = 69%								
Test for overall effect: Z = 12.22 (P < 0.00001)								
1.1.5 Metformin 2550mg/d								
DeFronzo 1995	-1.3	1.31	143	0.4	2.65	146	0.5%	-1.70 [-2.18, -1.22]
Del Prato 2003	-1.02	1.63	250	0.48	1.86	127	0.8%	-1.50 [-1.88, -1.12]
Subtotal (95% CI)			**393**			**273**	**1.2%**	**-1.58 [-1.88, -1.28]**
Heterogeneity: Chi² = 0.41, df = 1 (P = 0.52); I² = 0%								
Test for overall effect: Z = 10.35 (P < 0.00001)								
1.1.6 Metformin 3000mg/d								
Damsbo 1998	-2.8	1.66	9	-3.3	3.57	9	0.0%	0.50 [-2.07, 3.07]
Dornan 1991	-1.4	2.4	30	1.5	2.4	30	0.1%	-2.90 [-4.11, -1.69]
Subtotal (95% CI)			**39**			**39**	**0.1%**	**-2.28 [-3.38, -1.18]**
Heterogeneity: Chi² = 5.49, df = 1 (P = 0.02); I² = 82%								
Test for overall effect: Z = 4.07 (P < 0.0001)								
Total (95% CI)			**1665**			**1344**	**100.0%**	**-0.72 [-0.75, -0.69]**
Heterogeneity: Chi² = 787.36, df = 21 (P < 0.00001); I² = 97%								
Test for overall effect: Z = 42.20 (P < 0.00001)								
Test for subgroup differences: Chi² = 488.73, df = 5 (P < 0.00001), I² = 99.0%								



S3 Fig. Sensitivity analysis: Glucose lowering effect (reduction of HbA_{1c}) of metformin versus placebo (use a fixed-effect model instead)