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Appendix References

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Appendix Table 1: Abstracted data for each manuscript.

Study Characteristics	Patient Characteristics	Clinical Outcomes
Multicentre trial (y/n)	Mean age (years)	Baseline A1C by placebo and treatment group(s)
Sample size (total and each study arm)	% Male	End of study A1C by placebo and treatment group(s)
Duration (weeks)	Ethnicity (as listed by authors)	Absolute change in A1C by placebo and treatment group(s)
Run in period (using a placebo – in weeks)	Duration of Diabetes (years)	
Follow up % ($\geq$ 70%)	Weight (kg)	
Drug	BMI	
Dose (fixed or titrated)	Baseline A1C (%)	
Background OAD use		
Type of analysis (all patients treated, efficacy/per protocol or intention to treat analysis)		
Funding source (Government, private non-profit, private for profit, not funded or not reported)		

Appendix Table 2: Study characteristics

Study/Year	Duration (weeks)	Intervention N	Intervention Follow up %	Drug and Dose	Control N	Control Follow up %	Background Drug
Ahren, 2004 ‡ [10]	12	56	89	Vildagliptin 50 mg OD	51	92	Metformin
Aschner, 2006 * [40]	24	238	87.8	Sitagliptin 100 mg OD	253	85.3	OAD Discontinued
		250	85.6	Sitagliptin 200 mg OD			
Barnett, 2003 * [11]	26	84	94	Rosiglitazone 8 mg OD	87	79	Sulphonylurea
Berhanu, 2007 * [41]	20	110	87.3	Pioglitazone 45 mg OD	112	87.3	Insulin +/- OAD
Bosi, 2007 * [12]	24	177	86.4	Vildagliptin 50 mg OD	182	83.5	Metformin
		185	84.9	Vildagliptin 50 mg BID			
Charbonnel, 2006 * [42]	24	464	89.7	Sitagliptin 100 mg OD	237	81	Metformin
Chiasson, 2001 * [61]	36	82	86.6	Miglitol 100 mg TID	83	97.6	OAD Discontinued
		83	94	Metformin 500 mg TID			
Chan, 1998 * [62]	24	63	82.5	Acarbose 100 mg TID	63	90.5	Drug Naïve
Coniff, 1994 * [43]	24	105	86.7	Acarbose 300 mg TID	107	91.6	OAD Discontinued
Coniff, 1995 * [44]	24	76	96	Acarbose 200 mg TID	72	83	OAD Discontinued
Coniff, 1995 § [13]	16	73	79.5	Acarbose 100 mg TID	73	87.7	Drug Naïve
		72	75	Acarbose 200 mg TID			
		72	73.6	Acarbose 300 mg TID			
Dargie, 2007 § [45]	52	110	72.7	Rosiglitazone 8 mg OD	114	71.9	Any OAD
Davidson, 2007 § [46]	24	121	77.7	Rosiglitazone 8 mg OD	124	75.8	Glyburide
De Jager, 2005 * [14]	16	196	87.2	Metformin 2550 mg/day	194	93.8	Insulin, Metformin
Del Prato, 2003 ‡ [15]	29	144	84	Metformin 2550 mg/day	284	75	Any OAD
Dormandy, 2005 * [63]	138	2633	93.2	Pioglitazone 45 mg OD	2605	92.9	Any OAD
Einhorn, 2000 § [47]	16	168	83	Pioglitazone 30 mg OD	160	70	Metformin
Feinglos, 2005 * [64]	16	61	91.8	Glipizide 2.5 mg OD	61	91.8	Metformin
Fischer, 1998 § [16]	24	102	84.3	Acarbose 25 mg TID	97	83.5	Drug Naïve
		99	88.9	Acarbose 50 mg TID			
		99	78.8	Acarbose 100 mg TID			
		98	88.8	Acarbose 200 mg TID			
Fonseca, 2000 * [48]	26	119	84.9	Rosiglitazone 4 mg OD	116	81.03	Metformin
		113	84.01	Rosiglitazone 8 mg OD			
Fonseca, 2003 *‡ [17]	24	200	85	Nateglinide 120 mg TID	202	80	Rosiglitazone
Fujioka, 2005 § [18]	16	128	78.9	Metformin XR 500 mg OD	117	76.1	Drug Naïve
		120	88.3	Metformin XR 1000 mg OD			
		120	81.7	Metformin XR 1500 mg OD			
		134	88.8	Metformin XR 2000 mg OD			
		123	89.4	Metformin XR 1000 mg BID			
Garber, 2006 * [19]	24	147	84.4	Vildagliptin 50 mg OD	158	81	TZD
		158	78.5	Vildagliptin 50 mg BID			
Goldstein, 2007 * [49]	24	179	97.8	Sitagliptin 100 mg OD	176	93.8	OAD Discontinued
		182	97.8	Metformin 500 mg BID			
		182	97.3	Metformin 1000 mg BID			
Gonzalez-Clemente, 2008 * [50]	12	55	96.4	Nateglinide 120 mg TID	54	94.4	Drug Naïve
Halimi, 2000 § [20]	24	78	89.7	Acarbose 100 mg TID	74	79.7	Metformin
Hanefeld, 2000 * [21]	12	51	86.3	Nateglinide 30 mg TID	60	90	OAD Discontinued
		58	93.1	Nateglinide 60 mg TID			
		63	95.2	Nateglinide 120 mg TID			
		57	93	Nateglinide 180 mg TID			

Table 2 cont'd

Study/Year	Duration (weeks)	Intervention N	Intervention Follow up %	Drug and Dose	Control N	Control Follow up %	Background Drug
Hanefeld, 2007 * [51]	12	111	96.4	Sitagliptin 25 mg OD	111	96.4	OAD Discontinued
		112	95.5	Sitagliptin 50 mg OD			
		110	96.4	Sitagliptin 100 mg OD			
		111	97.3	Sitagliptin 50 mg BID			
Hedblad, 2007 * [22]	52	99	78.8	Rosiglitazone 4 mg BID	101	82.2	Any OAD Except TZD
Hermansen, 2007 * [52]	24	222	83.3	Sitagliptin 100 mg OD	219	82.1	Glimepiride +/- Metformin
Herz, 2003 * [23]	16	99	92.9	Pioglitazone 30 mg OD	99	88.9	Drug Naïve
		99	92.9	Pioglitazone 45 mg OD			
Hollander, 2007 [a] [53]	24	209	75.6	Rosiglitazone 2 mg OD	212	70.2	Insulin
		209	70.3	Rosiglitazone 4 mg OD			
Holman, 1999 * [65]	156	973	83.3	Acarbose 100 mg TID	973	83.7	OAD +/- Insulin
Horton, 2004 * [45]	24	104	97.1	Nateglinide 120 mg TID	104	94.2	Drug Naïve
		104	97.1	Metformin 500 mg TID			
Hwu, 2003 * [25]	18	56	96.4	Acarbose 100 mg TID	56	94.6	Insulin
Johnston, 1994 * [26]	14	61	93.4	Miglitol 50 mg TID	63	88.9	Sulphonylurea
		68	85.3	Miglitol 100 mg TID			
Johnston, 1998 § [27]	56	104	91	Miglitol 25 mg TID	101	91.1	Drug Naïve
		102	83	Miglitol 50 mg TID			
		104	88.4	Glyburide 20 mg/day			
Kelley, 1998 * [28]	24	98	73.5	Acarbose 100 mg TID	97	75.3	Insulin
Kipnes, 2001 § [66]	16	184	95.7	Pioglitazone 15 mg OD	187	96.8	Sulphonylurea
		189	96.3	Pioglitazone 30 mg OD			
Manzella, 2004 ‡ [29]	16	60	100	Metformin 850 mg BID	60	100	Drug Naïve
Marre, 2002 * [30]	24	155	88.4	Nateglinide 60 mg TID	152	89.5	Metformin
		160	90.1	Nateglinide 120 mg TID			
Mattoo, 2005 * [67]	24	142	90.1	Pioglitazone 30 mg OD	147	91.8	Any OAD +/- Insulin
Mitrakou, 1998 † [54]	24	60	96.7	Miglitol 100 mg TID	60	98.3	Insulin
Moses, 2001 * [31]	16	138	81.1	Repaglinide 1 mg TID	270	70.3	Drug Naïve
Nonaka, 2008 * [55]	12	76	98.7	Sitagliptin 100 mg OD	76	98.7	OAD Discontinued
Patel, 1999 § [56]	12	74	78	Rosiglitazone 0.05 mg BID	75	85	Drug Naïve
		72	76	Rosiglitazone 0.25 mg BID			
		79	82	Rosiglitazone 1 mg BID			
		80	86	Rosiglitazone 2 mg BID			
Raskin, 2001 § [68]	26	106	81	Rosiglitazone 2 mg BID	104	79	Insulin
		103	77	Rosliglitazone 4 mg BID			
Raz, 2006 * [69]	18	205	91.2	Sitagliptin 100 mg OD	110	82.7	OAD Discontinued
		206	89.3	Sitagliptin 200 mg OD			
Raz, 2008 * [57]	30	96	82.3	Sitagliptin 100 mg OD	94	85.1	Metformin
Riddle, 1998 * [70]	24	72	97.2	Glimepiride 8 mg BID	73	84.9	Insulin
Roberts, 2005 * [58]	26	85	83.3	Glimepiride 8 mg OD	85	72.6	Metformin, TZD
Rosenstock, 2006 * [59]	24	175	85.1	Sitagliptin 100 mg OD	178	88.8	Pioglitazone
Rosenstock, 2008 * [32]	26	56	96.4	Rosiglitazone 4 mg OD	57	91.2	Glimepiride
		59	96.6	Rosiglitazone 8 mg OD			
Scherbaum, 2002 * [33]	26	83	73.5	Pioglitazone 15 mg OD	78	75.6	Drug Naïve
		72	88.9	Pioglitazone 30 mg OD			
Scherbaum, 2008 * [34]	108	68	76.1	Vildagliptin 50 mg OD	63	74.6	Drug Naïve
Scherbaum, 2008 * [35]	52	156	88.5	Vildagliptin 50 mg OD	150	87.3	Drug Naïve

Table 2 cont'd

Study/Year	Duration (weeks)	Intervention N	Intervention Follow up %	Drug and Dose	Control N	Control Follow up %	Background Drug
Scott, 1999 § [36]	16	53	77.4	Acarbose 100 mg TID	52	80.8	Drug Naïve
Scott, 2007 * [37]	12	123	81.3	Glipizide 20 mg/day	125	86.4	OAD Discontinued
		125	85.6	Sitagliptin 5mg BID			
		123	94.3	Sitagliptin 12.5 mg BID			
		123	87.8	Sitagliptin 25 mg BID			
		124	90.3	Sitagliptin 50 mg BID			
Scott, 2008 * [38]	18	94	90	Sitagliptin 100 mg OD	92	91	Metformin
		87	98	Rosiglitazone 8 mg OD			
Testa, 1998 *†‡ [60]	12	377	90.2	Glipizide 20 mg/day	192	84.4	Drug Naïve
Van Gaal, 2001 * [39]	32	77	72.7	Miglitol 100 mg TID	75	84	Metformin

Study funding is indicated as the following: * - private for profit; † - private non-profit; ‡ - governmental; and § - not reported.

Appendix Table 3: Patient characteristics

Study	Intervention						Control					
	Age (y)	% Male	% White	Duration of DM (y)	BMI	Initial A1C (%)	Age (y)	% Male	% White	Duration of DM (y)	BMI	Initial A1C (%)
Ahren, 2004 [10]	57.9	69.6	N/R	5.6	29.4	7.2	55.7	66.7	N/R	5.5	30.2	7.8
Aschner, 2006 [40]	53.4	57.1	51.3	4.3	30.3	8	54.3	51.4	50.2	4.6	30.8	8
	54.9	46.8	52.8	4.3	30.3	8.1						
Barnett, 2003 [11]	54.3	80	N/R	6.5	26.8	9.2	54.1	75	N/R	6.5	26.4	9.1
Berhanu, 2007 [41]	52.9	43.6	34.9	7.7	30.7	8.4	52.5	41.1	25.9	8.5	31.8	8.6
Bosi, 2007 [12]	54.3	57.3	74.1	6.8	32.1	8.4	54.5	53.1	73.1	6.2	33.2	8.3
	53.9	61.5	74.1	5.8	32.9	8.4						
Charbonnel, 2006 [42]	54.4	55.8	63.1	6	30.9	8.0	54.7	59.5	67.1	6.6	31.5	8.0
Chiasson, 2001 [61]	57.3	78.1	89	5.2	31.1	8.2	57.7	67.5	91.6	5.1	31.1	8.1
	57.9	73.5	88	7.5	30.7	8.2						
Chan, 1998 [62]	52.8	50.8	N/R	2.7	25.4	8.2	54	50.8	N/R	2.1	25.6	8.6
Coniff, 1994 [43]	56	45	59	N/R	N/R	6.8	55.6	54	60	N/R	N/R	6.7
Coniff, 1995 [44]	56.2	39	51	5.1	29.7	6.9	56.3	52	45	5.5	29.9	7.1
Coniff, 1995 [13]	55	52	74	6	31	8.7	54	58	81	5	32	8.7
	56	59	74	5	31	9.0						
	54	58	75	5	30	9.5						
Dargie, 2007 [45]	64.3	84.3	99.1	4.5	28.8	7.8	63.9	79.1	99.1	4	28.6	7.8
Davidson, 2007 [46]	52	45.3	0	6	31.3	9.2	53	48.3	0	6.2	31.9	9.4
De Jager, 2005 [14]	63	44	N/R	14	29.9	7.8	59	51.5	N/R	12	29.5	7.8
Del Prato, 2003 [15]	56	59	N/R	N/R	29.7	7.8	56	63	N/R	N/R	29.9	7.4
Dormandy, 2005 [63]	61.9	67	98	8*	30.7	7.8*	61.6	66	99	8*	31	7.9*
Einhorn, 2000 [47]	55.5	54.8	81	N/R	32.1	9.9	55.7	60	86.9	N/R	32.1	9.8
Feinglos, 2005 [64]	57.7	45.9	78.7	6.5	31.7	7.5	58.8	41.0	68.9	4.6	32.1	7.6
Fischer, 1998 [16]	58.5	53	N/R	2.2	27.3	7.4	52.7	53	N/R	2	26.9	7.3
	55.5	49	N/R	1.7	27.6	7.5						
	56.8	59	N/R	1.4	27.6	7.4						
	59.4	51	N/R	1.8	27.2	7.5						
Fonseca, 2000 [48]	57.5	62.1	80.2	7.5	30.2	8.9	58.8	74.3	81.4	7.3	30.3	8.6
	58.3	68.2	77.3	8.3	29.8	8.9						
Fonseca, 2003 [17]	56.5	N/R	N/R	5.9	31.6	8.3	56.8	N/R	N/R	5.8	30.5	8.4
Fujioka, 2005 [18]	55	44	N/R	3.3	30.1	8.2	54	49	N/R	2.7	30.7	8.3
	56	58	N/R	3	30.6	8.4						
	56	48	N/R	2.9	29.7	8.4						
	55	41	N/R	2.7	30.9	8.4						
	57	47	N/R	3.1	30.6	8.4						
Garber, 2006 [19]	54	54.8	83.9	4.7	32.6	8.6	54.8	50.7	78.3	4.8	32.3	8.7
	54	44.9	79.4	4.6	32.2	8.7						

Table 3 cont'd:

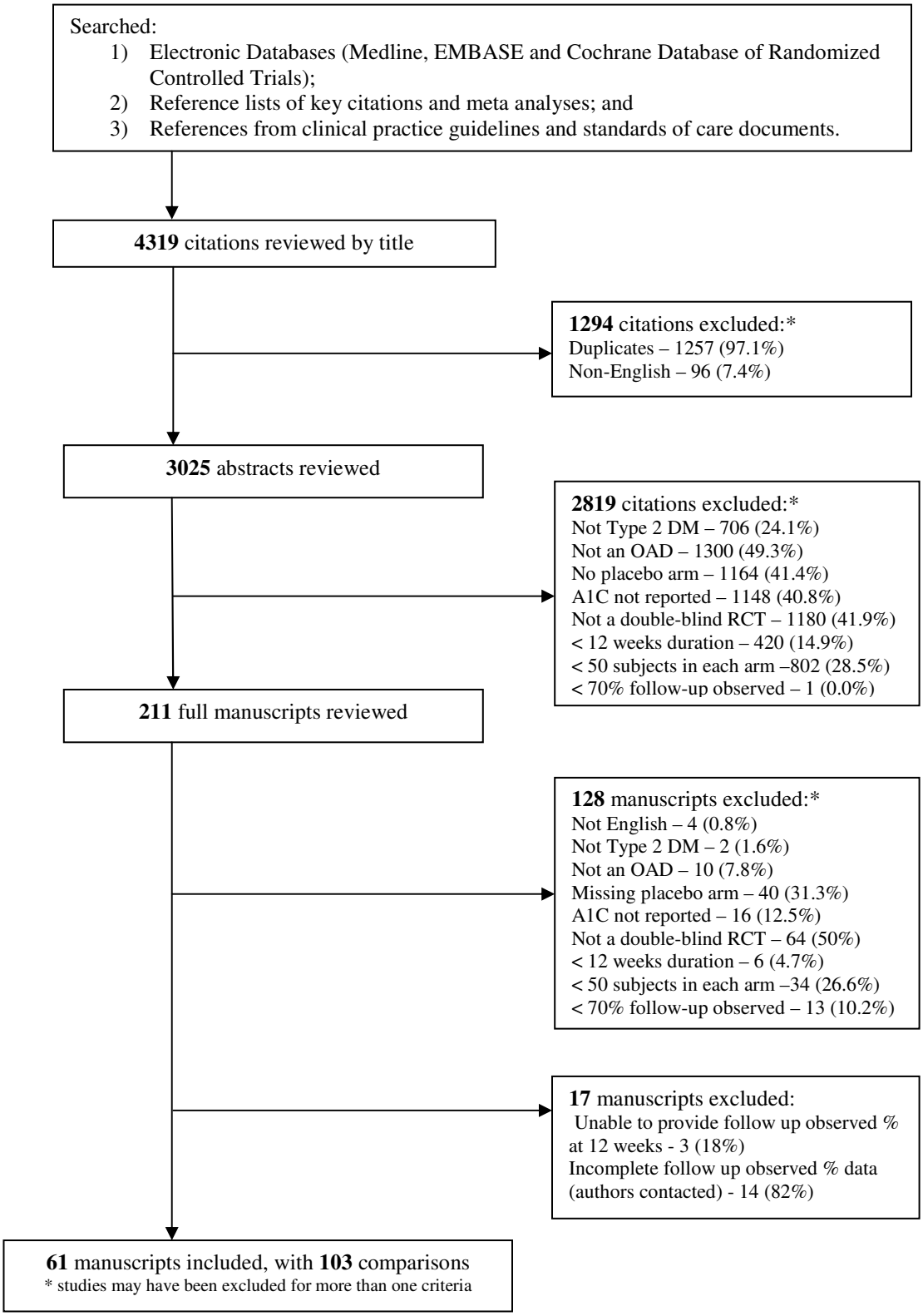
Study	Intervention						Control					
	Age (y)	% Male	% White	Duration of DM (y)	BMI	Initial A1C (%)	Age (y)	% Male	% White	Duration of DM (y)	BMI	Initial A1C (%)
Goldstein, 2007 [49]	53.3	52	52	4.4	31.2	8.9	53.6	52.8	46	4.6	32.5	8.7
	53.4	48.9	47.8	4.5	32.1	8.9						
	53.2	45.1	58.2	4.4	32.2	8.7						
Gonzalez-Clemente, 2008 [50]	59.9	56.4			28.9	7.2	57.2	63			28.7	7.1
Halimi, 2000 [20]	56	47.5	N/R	9.5	30.1	8.6	55	62.9	N/R	9	29.7	8.5
Hanefeld, 2000 [21]	58	70.6	N/R	4.5	29	8.4	57.4	60	N/R	5.4	28.3	8.5
	56.1	70.7	N/R	6.2	28.1	8.3						
	54.4	69.8	N/R	4.4	28.6	8.3						
	56.5	63.2	N/R	3.7	28.8	8.5						
Hanefeld, 2007 [51]	55	51.4	88.3	3.6	31.9	7.7	55.9	63.1	78.4	3.3	31.4	7.6
	55.3	45.5	85.7	3.3	31.6	7.6						
	56	55.5	88.2	3.6	31.3	7.8						
	55.2	44.1	81.1	4.5	32.7	7.8						
Hedblad, 2007 [22]	67	51	N/R	3.7	30	6.9	66	59	N/R	4.5	29	6.9
Hermansen, 2007 [52]	55.6	52.7	61.3	8.3	31.2	8.3	56.5	53.4	63.9	9.3	30.7	8.3
Herz, 2003 [23]	59	59.6	98	1.9	31.7	7.5	58	49.5	97	1.5	31.7	7.5
	58.1	52.5	94	1.8	30.8	7.6						
Hollander, 2007 [53]	52.7	57	57	12.5	32.8	8.9	53.8	46.2	56.5	12.6	33	9.1
	52.6	57.1	57.1	13	33.7	9						
Holman, 1999 [65]	60	N/R	N/R	7.9	29.8	8.7 *	60			8	29.6	8.7 *
Horton, 2004 [24]	57.9	56.7	N/R	4.7	29.9	8.1	59	64.4	N/R	4.2	29.5	8.2
	55.4	67.3	N/R	3.7	29.9	8.3						
Hwu, 2003 [25]	58.1	50	N/R	13.4	24.1	9.1	54.7	49.1	N/R	10.2	23.9	9.5
Johnston, 1994 [26]	58	67	63	10	31	8.8	59	48	66	8	30	8.9
	58	55	60	8	30	8.9						
Johnston, 1998 [27]	67.2	60	86	7.5	29.7	8.3	68.5	66	89	7	30.4	8.4
	67.8	61	78	6.8	29.4	8.4						
	67.7	59	90	7.2	29.3	8.4						
Kelley, 1998 [28]	61.5	59	88	12.4	31.5	8.8	61.2	49	86	12.5	31.1	8.7
Kipnes, 2001 [66]	56.5	59	79	N/R	31.4	10	56.9	58	75	N/R	32	9.9
	56.6	60	83	N/R	32.4	9.9						
Manzella, 2004 [29]	N/R	51.7	N/R	N/R	29.5	8	N/R	55	N/R	N/R	29.2	8.1
Marre, 2002 [30]	57.9	61.3	90.3	6.5	29.6	8.3	56.4	55.3	90.8	6.5	29.6	8.3
	57.3	61.3	91.3	6.8	29.3	8.2						

Table 3 cont'd:

Study	Intervention						Control					
	Age (y)	% Male	% White	Duration of DM (y)	BMI	Initial A1C (%)	Age (y)	% Male	% White	Duration of DM (y)	BMI	Initial A1C (%)
Mattoo, 2005 [67]	58.8	43.7	96.5	13.6	32.5	8.9	58.9	42.9	96.6	13.4	31.8	8.8
Mitrakou, 1998 [54]	57.4	48.3	N/R	8.5	24.4	9.9	57.4	61	N/R	7.9	24.5	9.9
Moses, 2001 [31]	57.5	53.5	98.8	3.0	30	7.8	57.4	57.5	98.5	3.07	30.9	7.6
Nonaka, 2008 [55]	55.6	60		4	25.2	7.5	55	66		4.1	25.1	7.7
Patel, 1999 [56]	56.7	66.2	74.3	4.9	29.4	9.1	56.8	69.3	73.3	4.2	28.9	9.1
	55.8	70.8	73.6	6.7	28.6	8.9						
	59.8	64.6	79.7	4.4	29.5	9						
	59.7	68.8	72.5	5.8	28.4	9						
Raskin, 2001 [68]	57.1	56.6	66.0	12.7	32.1	9.1	55.6	55.8	68.3	11.7	32.7	8.9
	57.7	54.4	70.9	12.5	32.3	9						
Raz, 2006 [69]	54.5	53.7	69.3	4.5	31.8	8	55.5	62.7	61.8	4.7	32.5	8
	55.4	50.5	70.9	4.5	32	8.1						
Raz, 2008 [57]	53.6	51	42	8.4	30.1	9.3	56.1	41.5	47	7.3	30.4	9.1
Riddle, 1998 [70]	58	62.5	79.2	7	32.2	9.7	58	54.8	79.5	7	33.7	9.9
Roberts, 2005 [58]	56.5	61	67.1	7.9	34.0	8.2	56.4	62.3	72.7	8.7	32.8	8.2
Rosenstock, 2006 [59]	55.6	53.1	72.6	6.1	32	8.1	56.9	57.9	72.5	6.1	31	8
Rosenstock, 2008 [32]	61	57	100	7.1	28.8	8.2	65	60	100	6.6	29.1	7.9
	63	44	100	6.4	29.9	8.1						
Scherbaum, 2002 [33]	58	62.9	N/R	5.4	29.9	9.3	59.1	56	N/R	5.6	29.2	8.8
	59.6	41	N/R	4.6	29.3	9.1						
Scherbaum, 2008 [34]	63.1	60.3	100	2.1	30.4	6.6	63.2	58.7	100	2.5	30.1	6.7
Scherbaum, 2008 [35]	63.3	59.6	99.4	2.5	30.4	6.7	62.8	59.3	99.3	2.7	30	6.8
Scott, 1999 [36]	56	62	N/R	1.8	31	7	57	65	N/R	2.2	29	6.9
Scott, 2007 [37]	54.7	56.9	61	4.7	30.6	7.8	55.3	62.4	66.4	4.8	31.6	7.9
	55.1	49.6	68.8	4.3	30.8	7.9						
	56.2	48	63.4	4.9	30.5	7.9						
	55.6	57.7	61	5	31.4	7.9						
	55.1	52.4	69.4	4.2	30.4	7.8						
Scott, 2008 [38]	55.2	55	61	4.9	30.3	7.8	55.3	59	61	5.4	30	7.7
	54.8	63	59	4.6	30.4	7.7						
Testa, 1998 [60]	58.7	54.9	71.9	5.6	30.1	8.5	58.4	58.9	72.9	4.7	30	8.7
Van Gaal, 2001 [39]	57.9	41.6	N/R	6 *	30	8.5	57.9	49.3	N/R	6 *	29.7	8.4

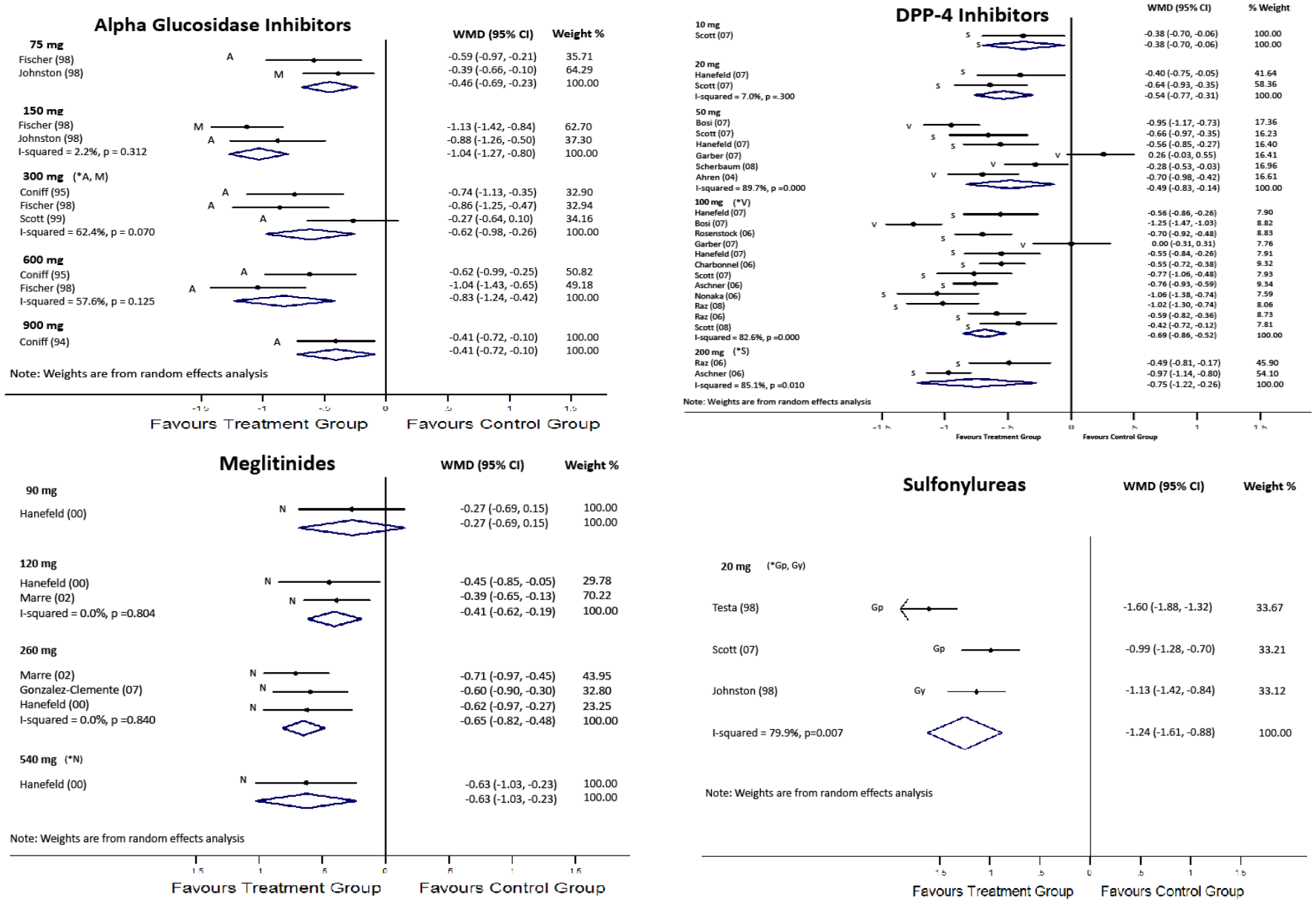
Mean values presented. *Median values.

Appendix Figure 1: Study flow diagram. Studies may have been excluded base on more than one criterion (*). DM-diabetes mellitus; OAD-oral antidiabetic agent; RCT-randomized controlled trial.

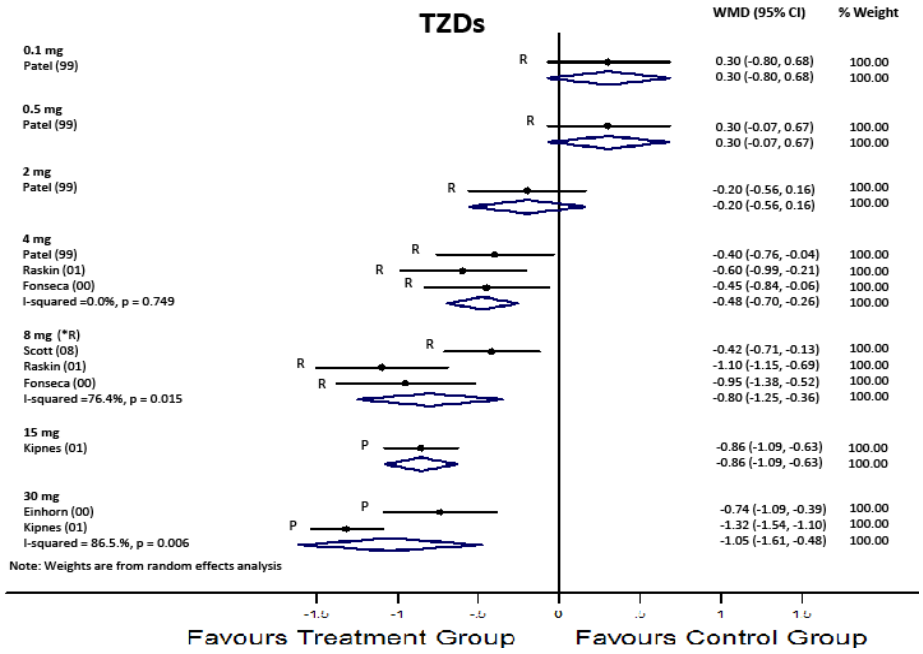


Appendix Figures 2-7: Treatment effect by OAD class at 12 (Figure 2), 19-24 (Figure 3), 25-39 (Figure 4), 40-47 (Figure 5), 48-55 (Figure 6) and 56-104 weeks (Figure 7). Each line represents a treatment effect (circle) and 95% confidence intervals (ends of the line). The diamond shape represents a meta-analyzed mean difference for a particular OAD class and dose. * illustrates the generally accepted maximum daily dose. Abbreviations include: A-Acarbose; DPP-4-Dipeptidyl Peptidase-4; Gm-Glimepiride; Gp-Glipizide; Gy-Glyburide; M-Miglitol; Me-Metformin; Ml-Metformin (long-acting); N-Nateglinide; P-Pioglitazone; R-Rosiglitazone; Re-Repaglinide; S-Sitagliptin; TZDs-Thiazolidinediones; and V-Vildagliptin

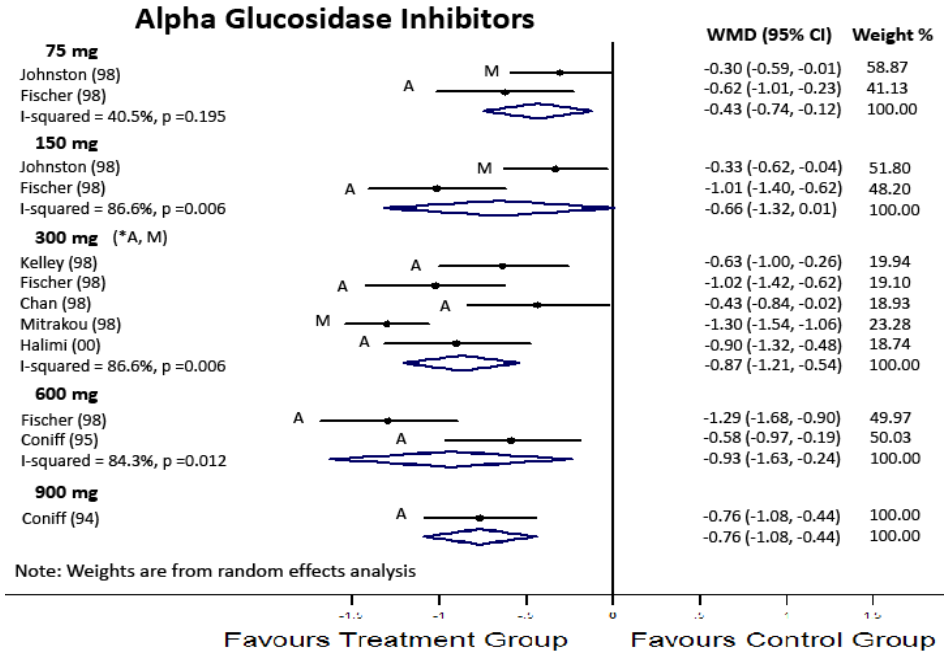
Appendix Figure 2

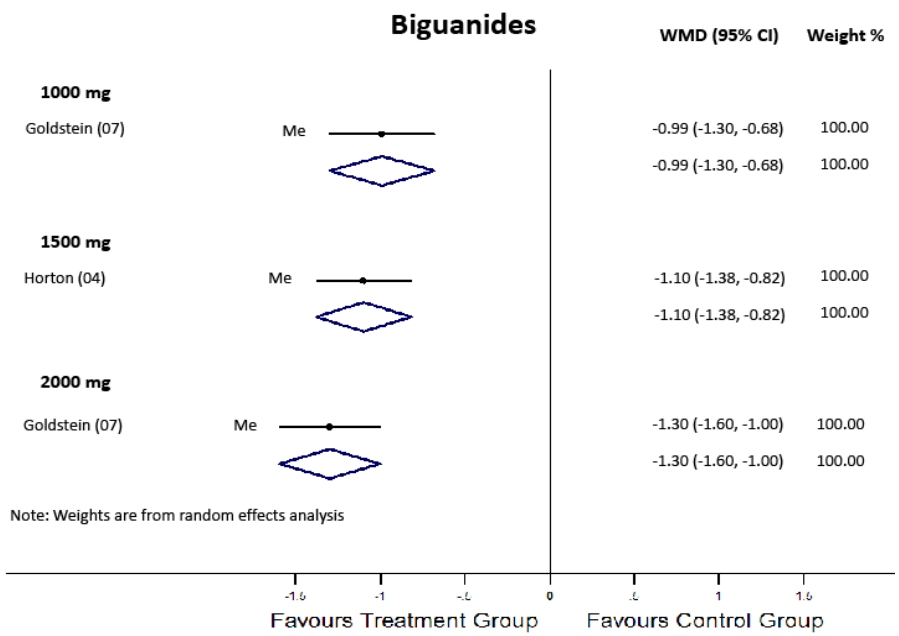


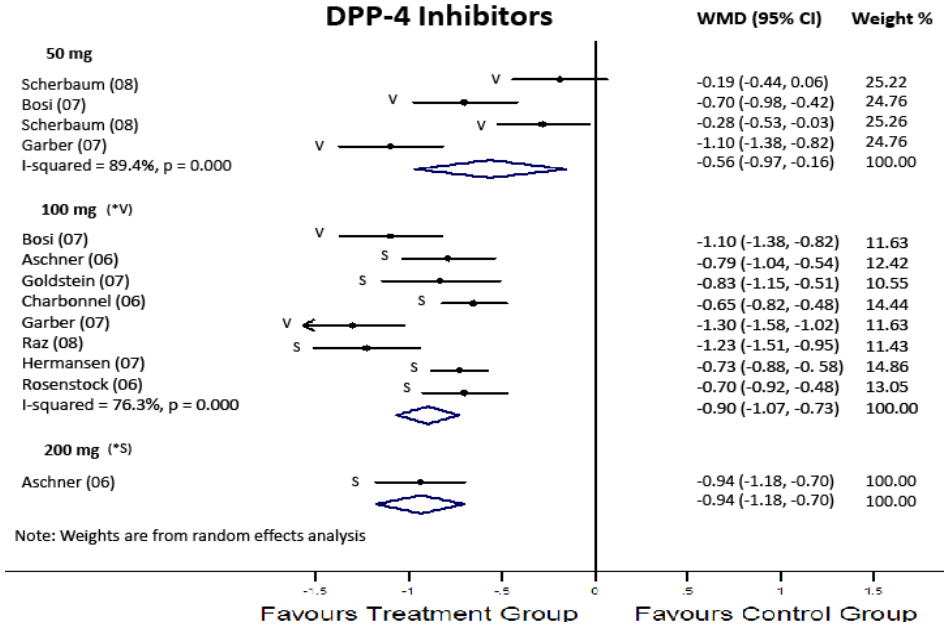
Appendix Figure 2, cont'd.

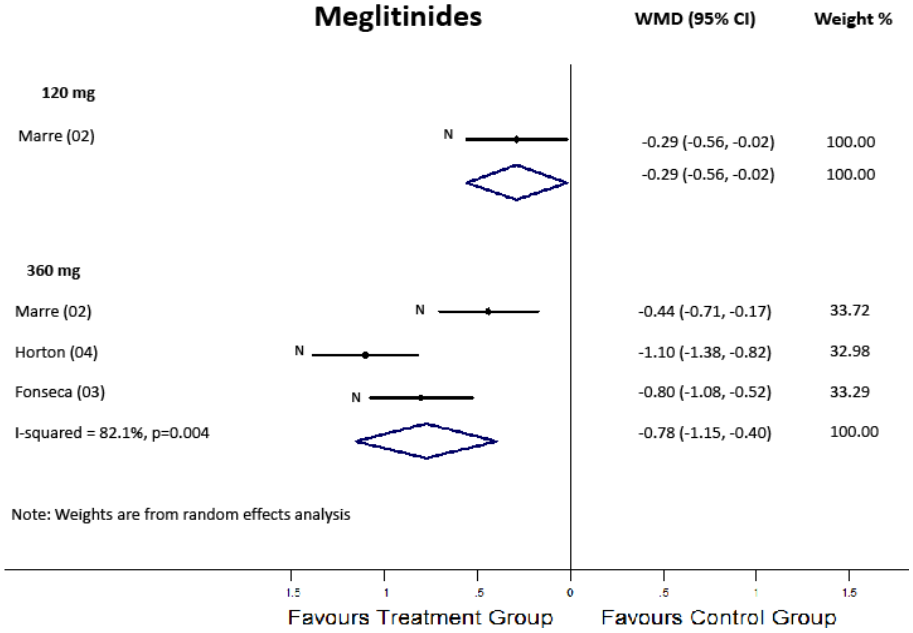


Appendix Figure 3.

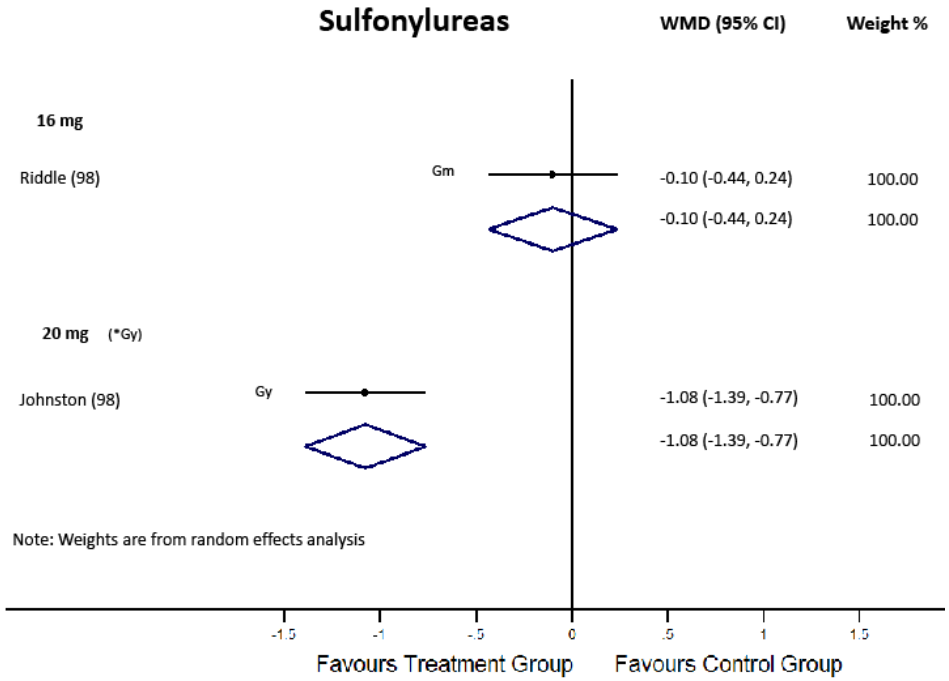


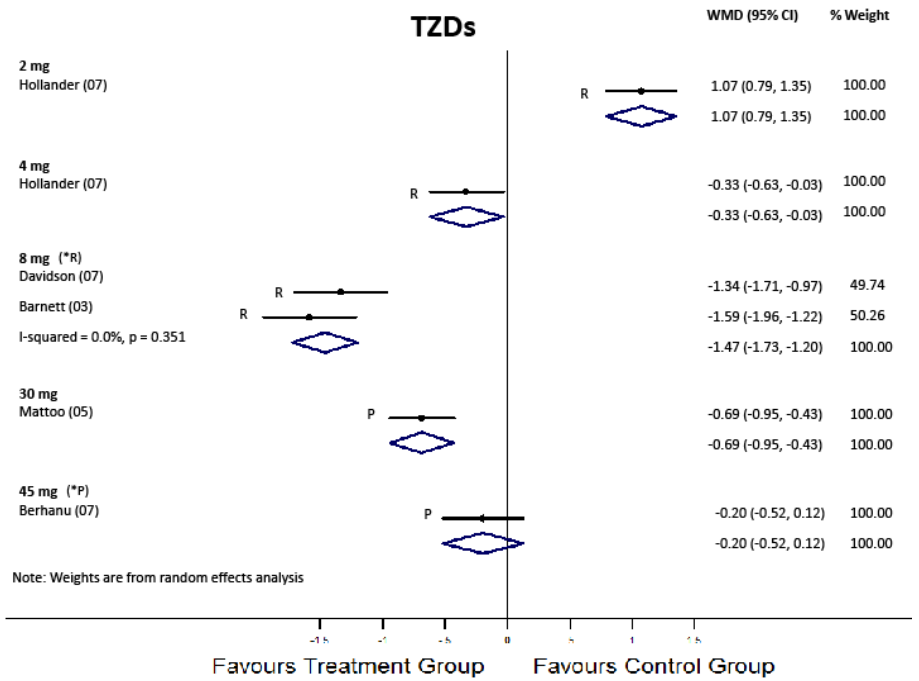




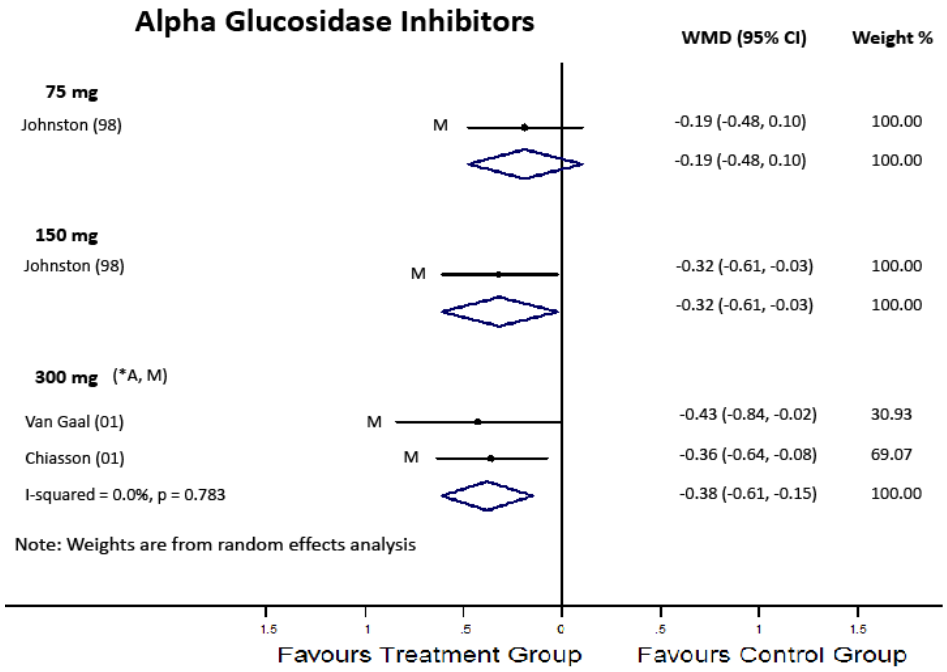


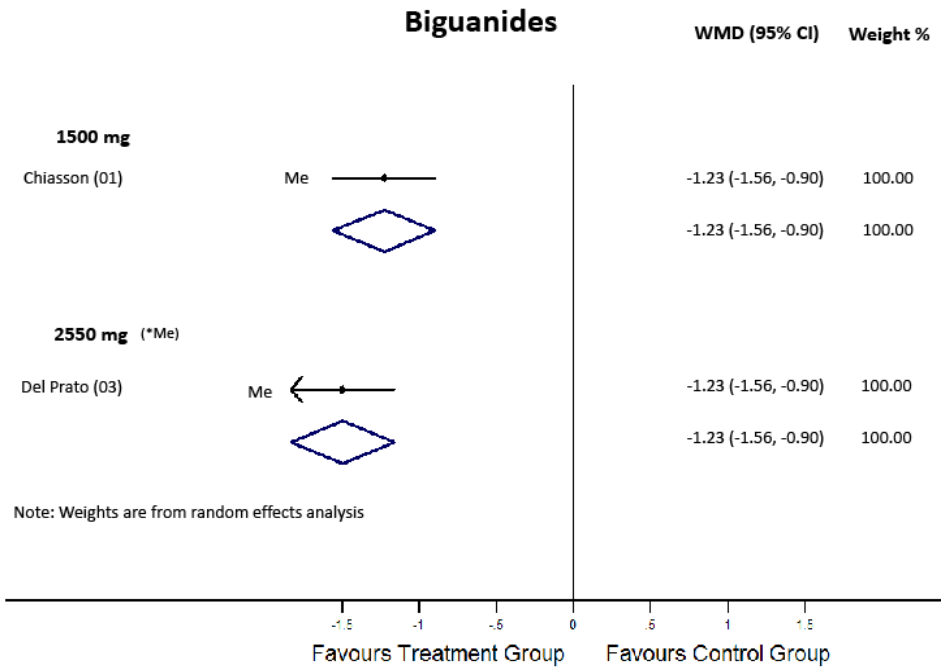
Appendix Figure 3, cont'd.

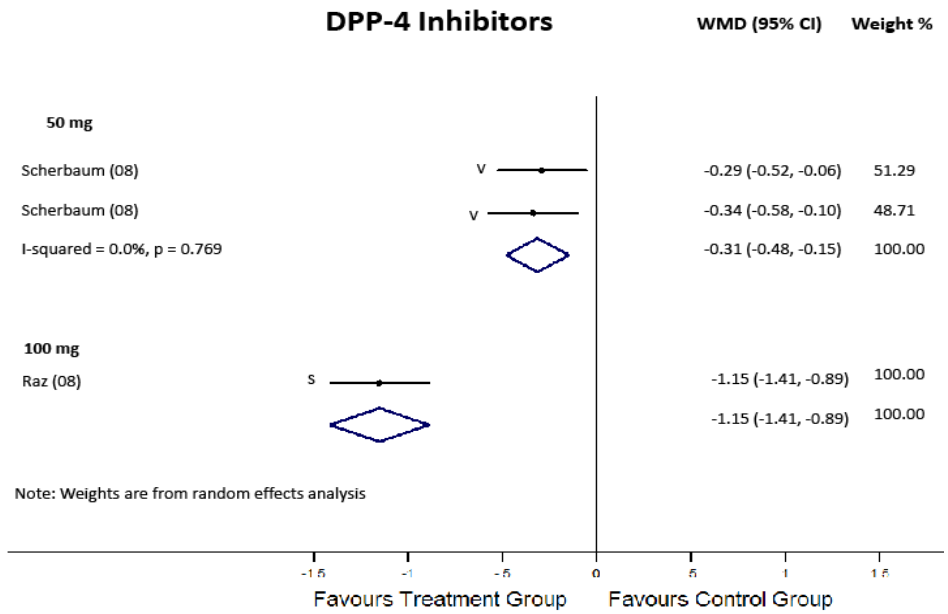


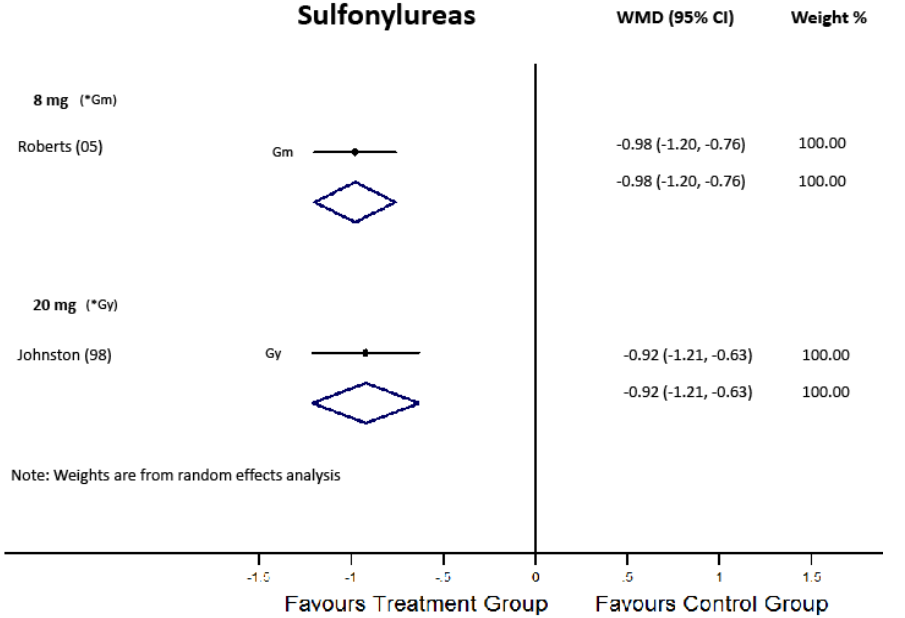


Appendix Figure 4.

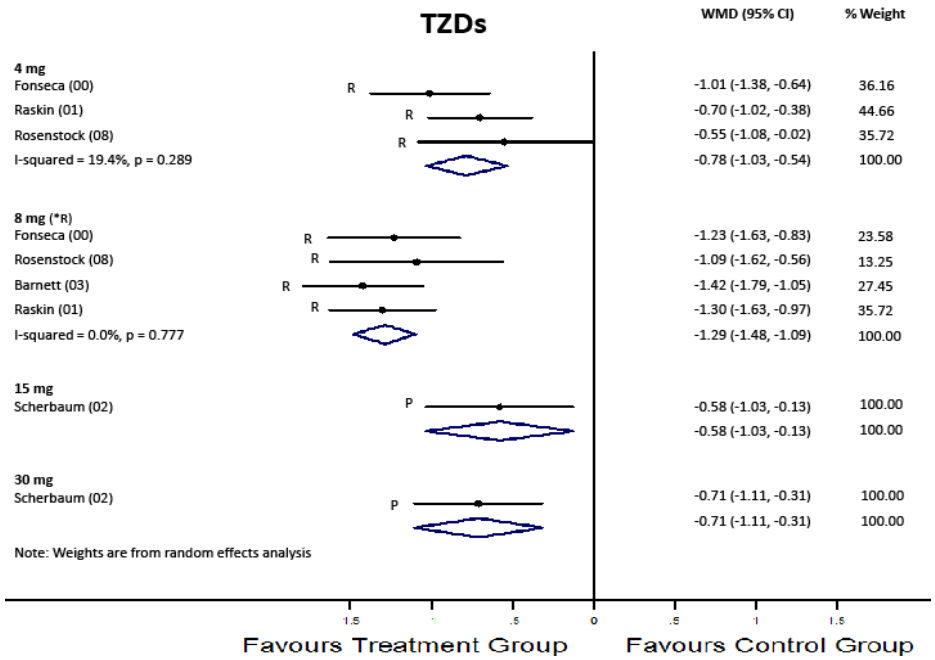




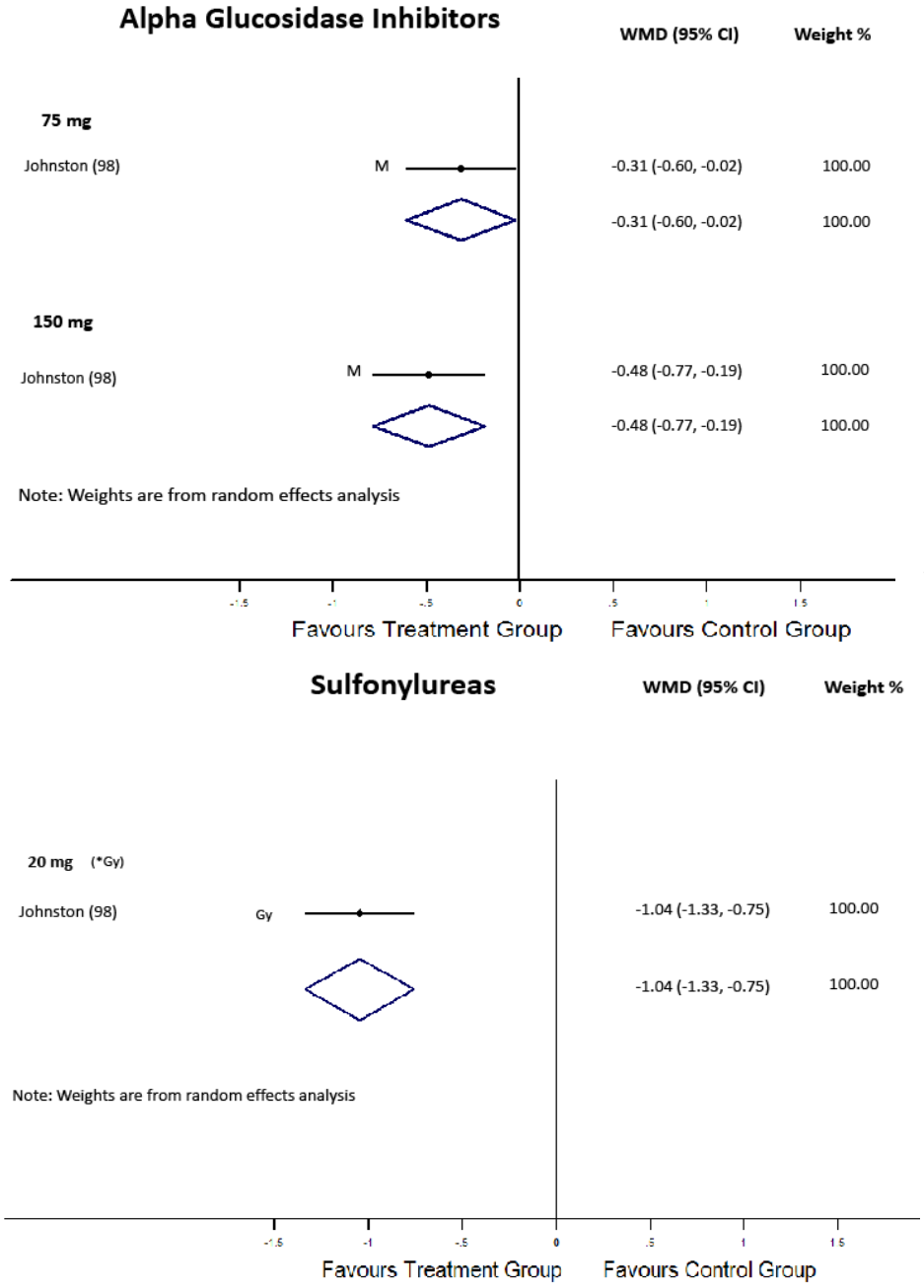


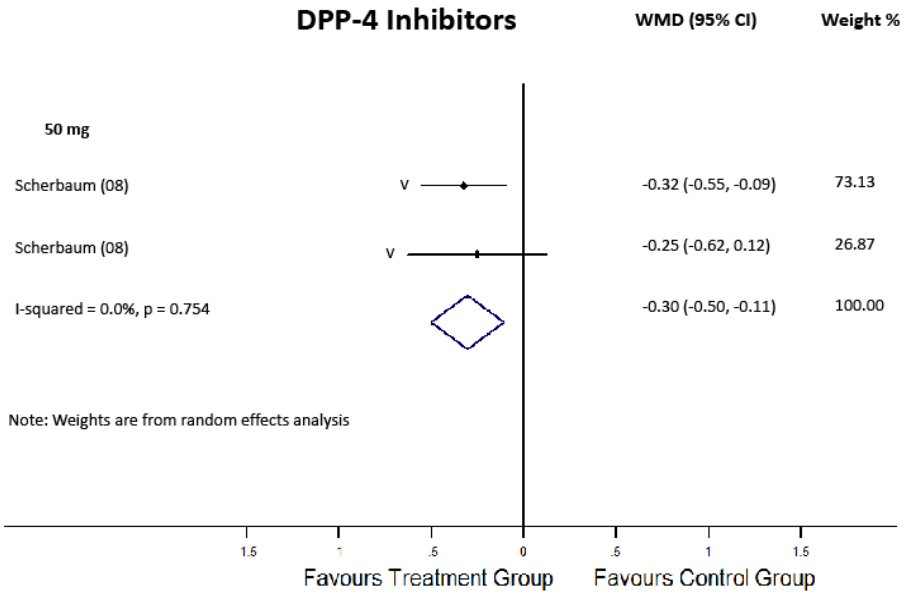


Appendix Figure 4, cont'd.

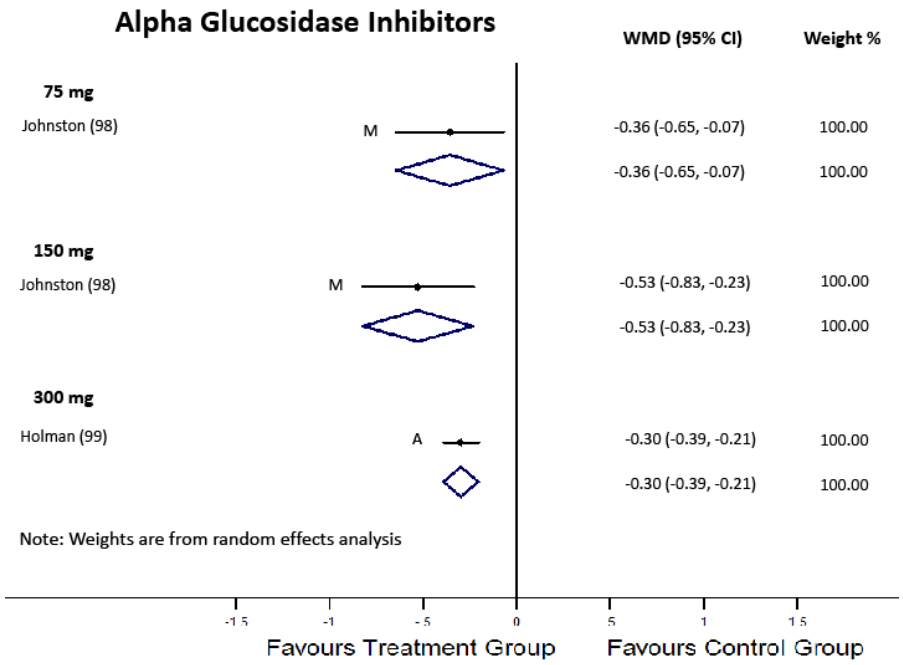


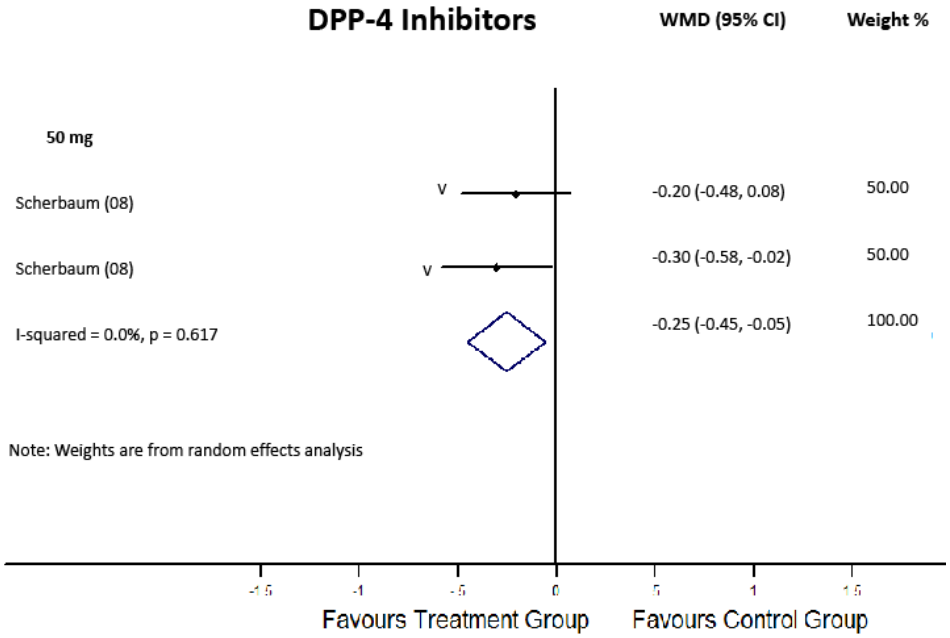
Appendix Figure 5.

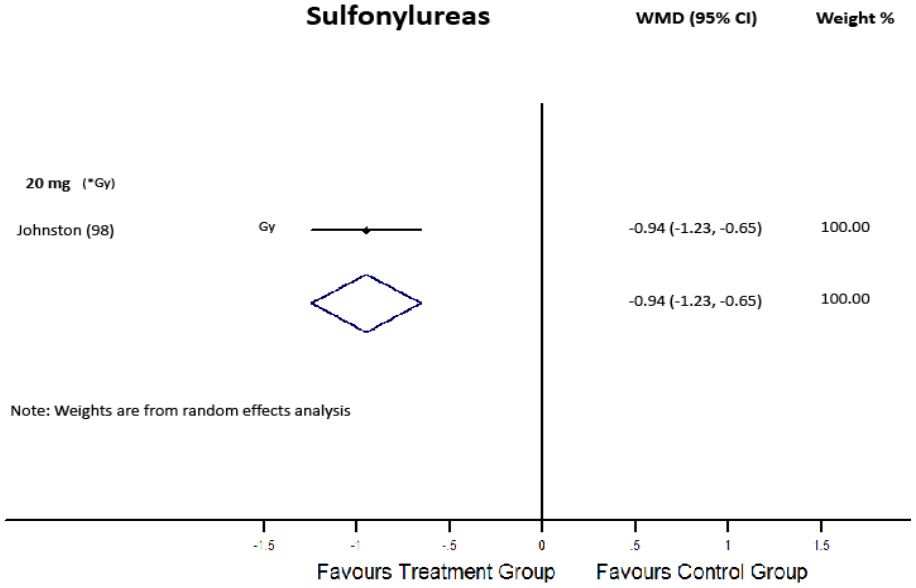


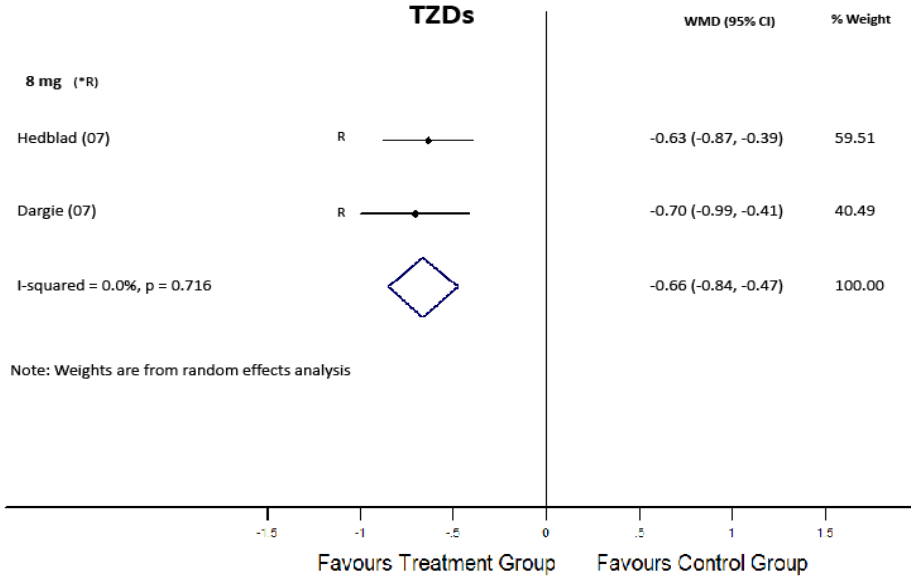


Appendix Figure 6.









Appendix Figure 7.