

Clinical Drug Investigation

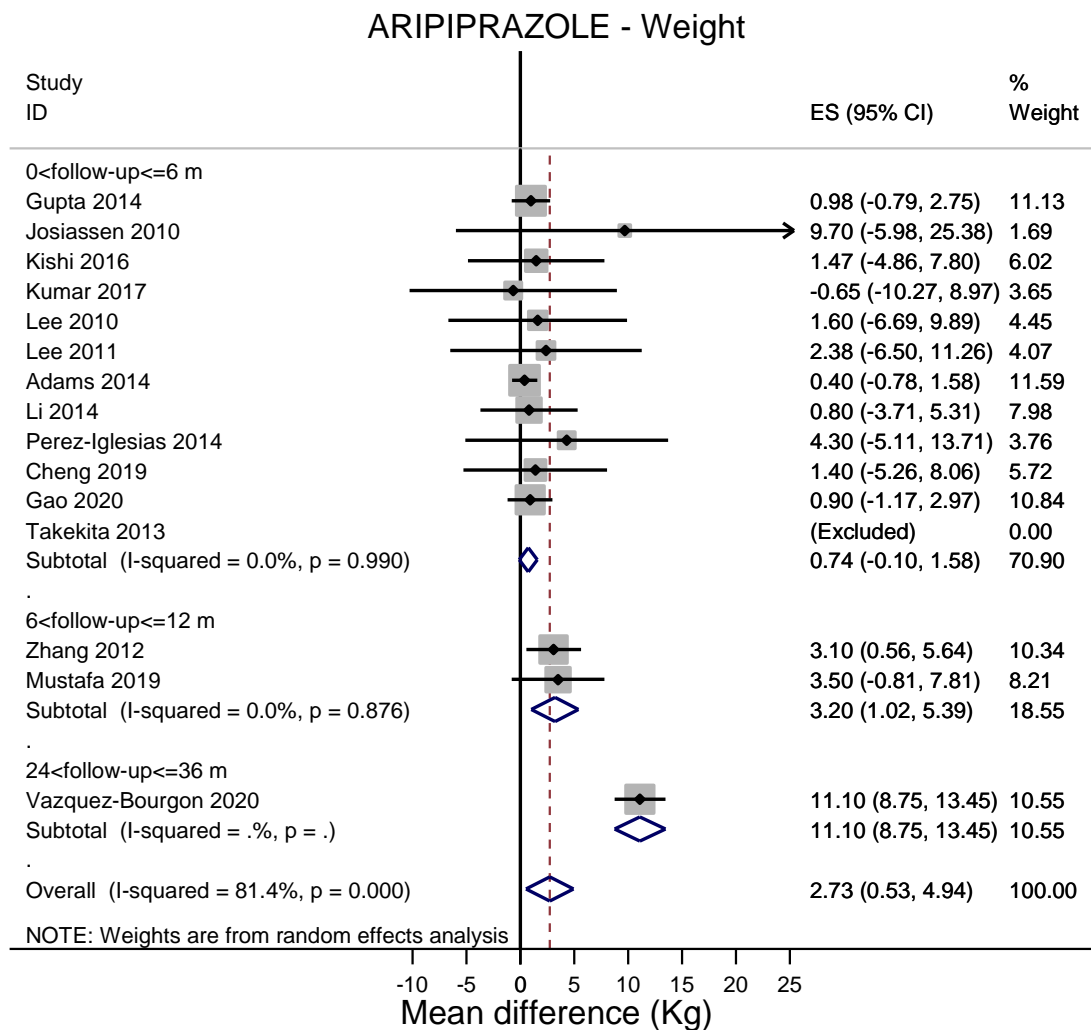
**SECOND-GENERATION ANTIPSYCHOTIC DRUGS FOR PATIENTS WITH SCHIZOPHRENIA:
SYSTEMATIC LITERATURE REVIEW AND META-ANALYSIS OF METABOLIC AND
CARDIOVASCULAR SIDE EFFECTS**

Carla Rognoni¹, Arianna Bertolani¹, Claudio Jommi¹

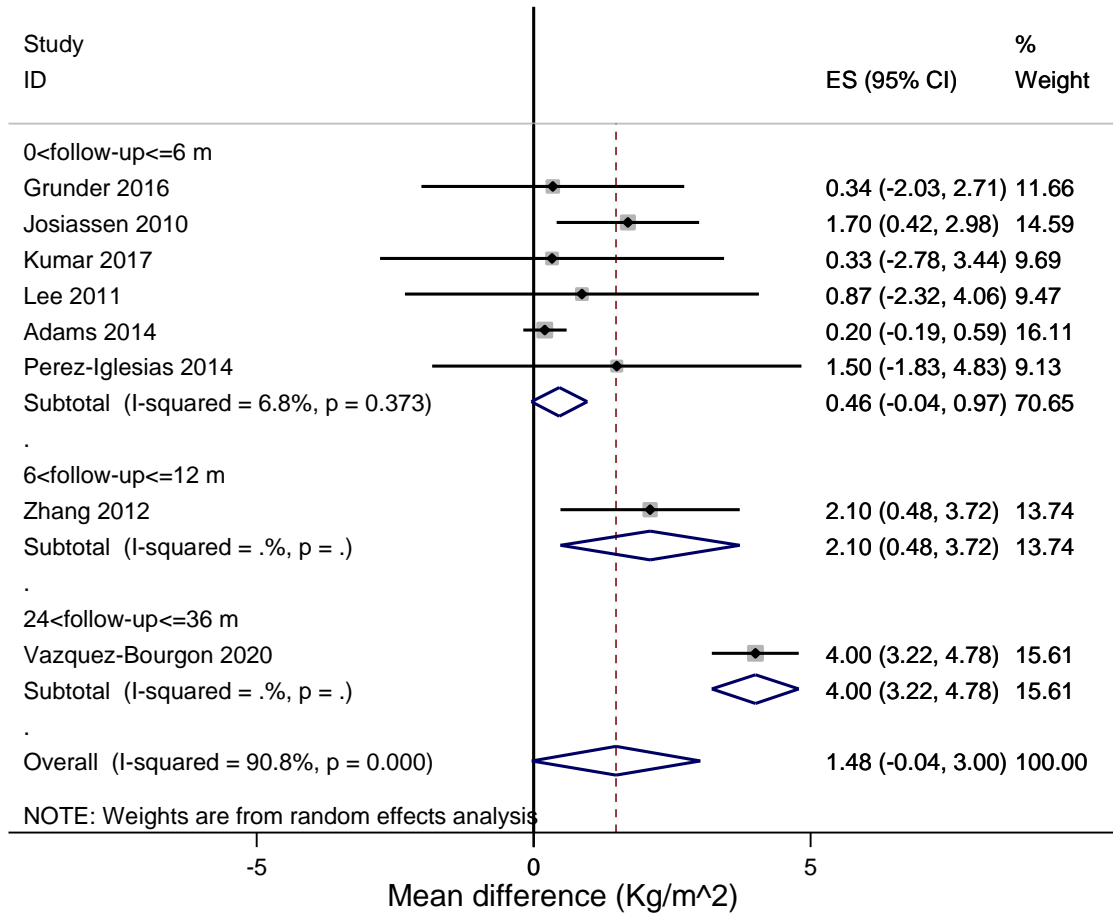
¹ Centre for Research on Health and Social Care Management (CERGAS), SDA Bocconi School of Management, Bocconi University, Milan, Italy

Supplementary material

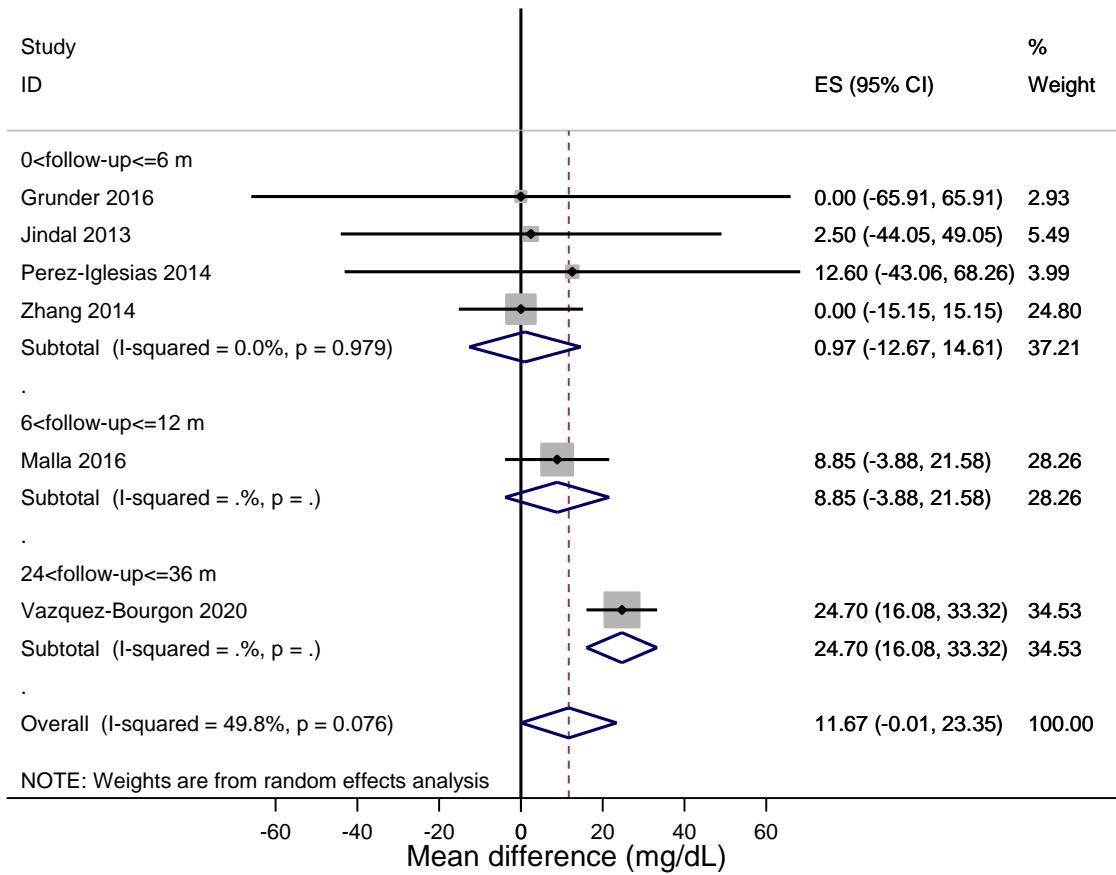
Results of the meta-analyses for different follow-up durations (m=months)



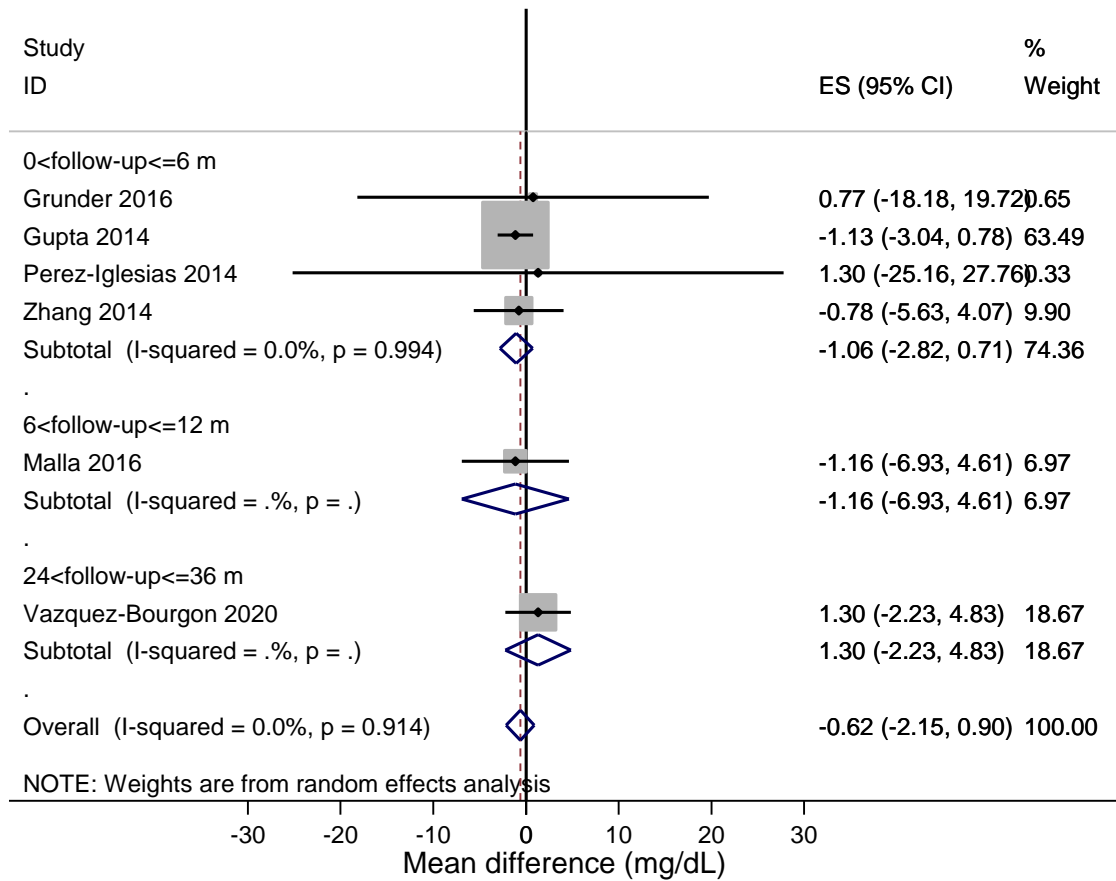
ARIPIPIRAZOLE - BMI



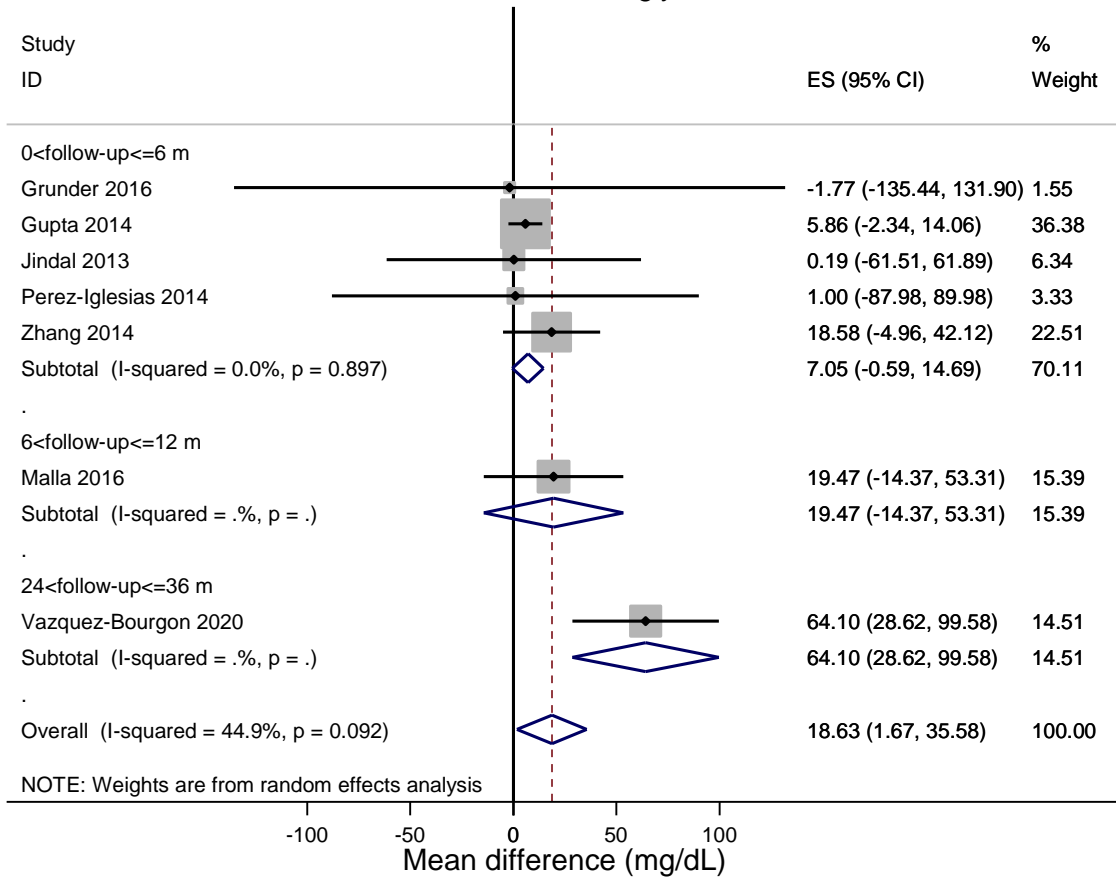
ARIPIPRAZOLE - Total cholesterol



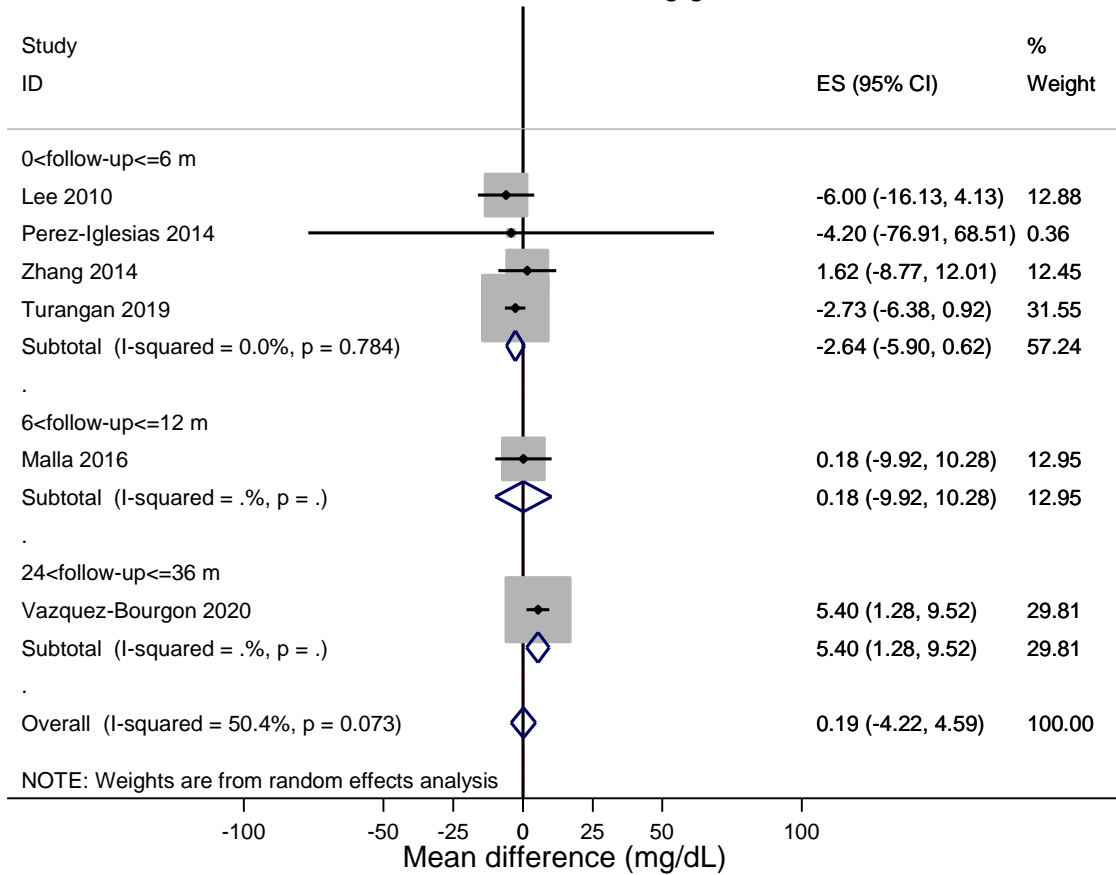
ARIPIPRAZOLE - Cholesterol HDL



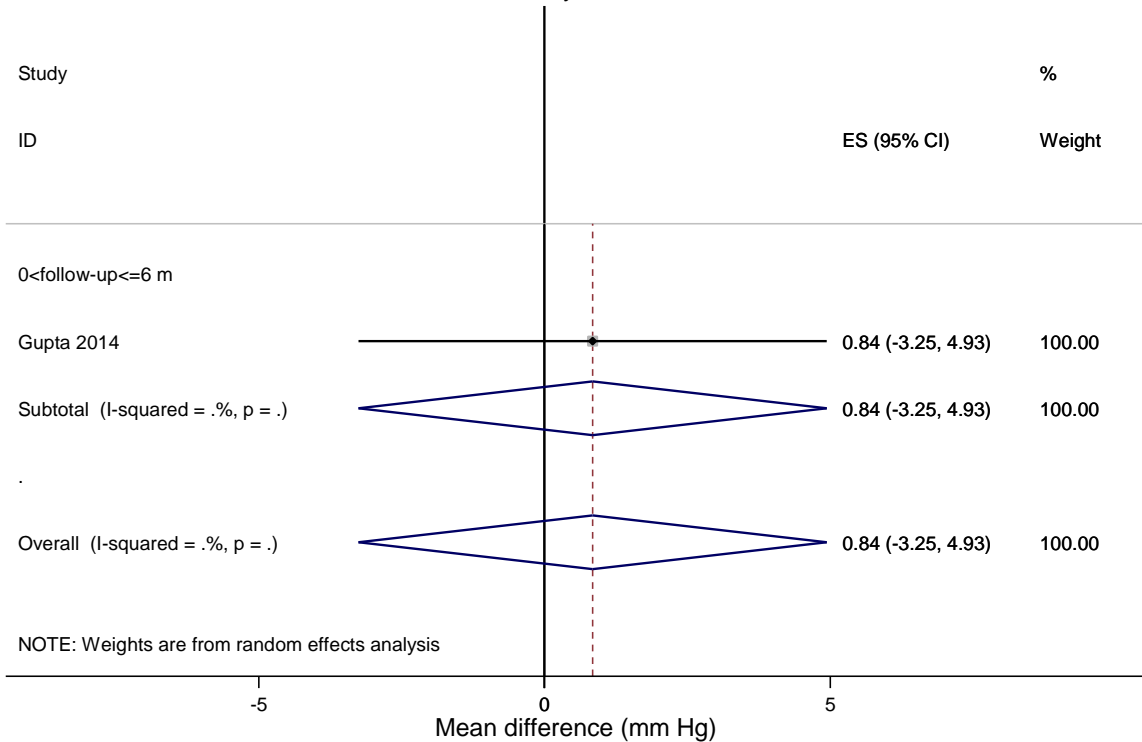
ARIPRAZOLE - Triglycerides



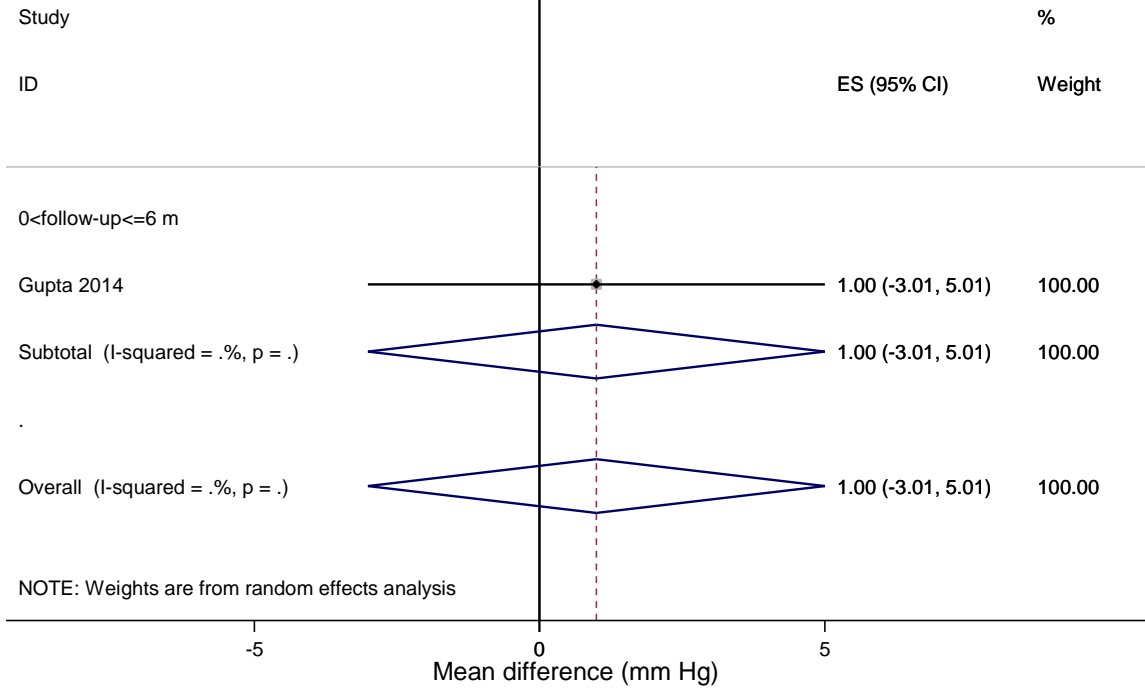
ARIPIPRAZOLE - Fasting glucose



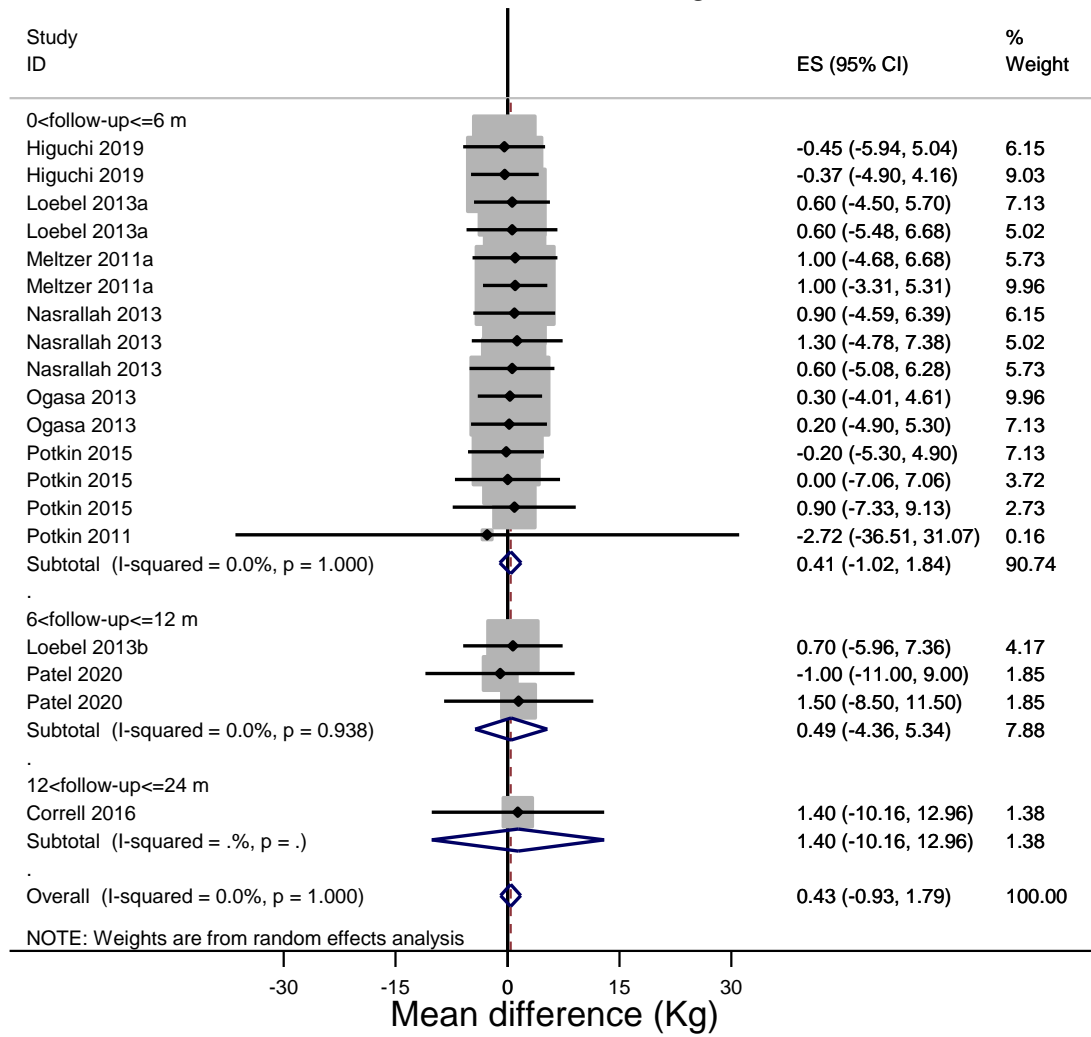
ARIPIPRAZOLE - Systolic Blood Pressure



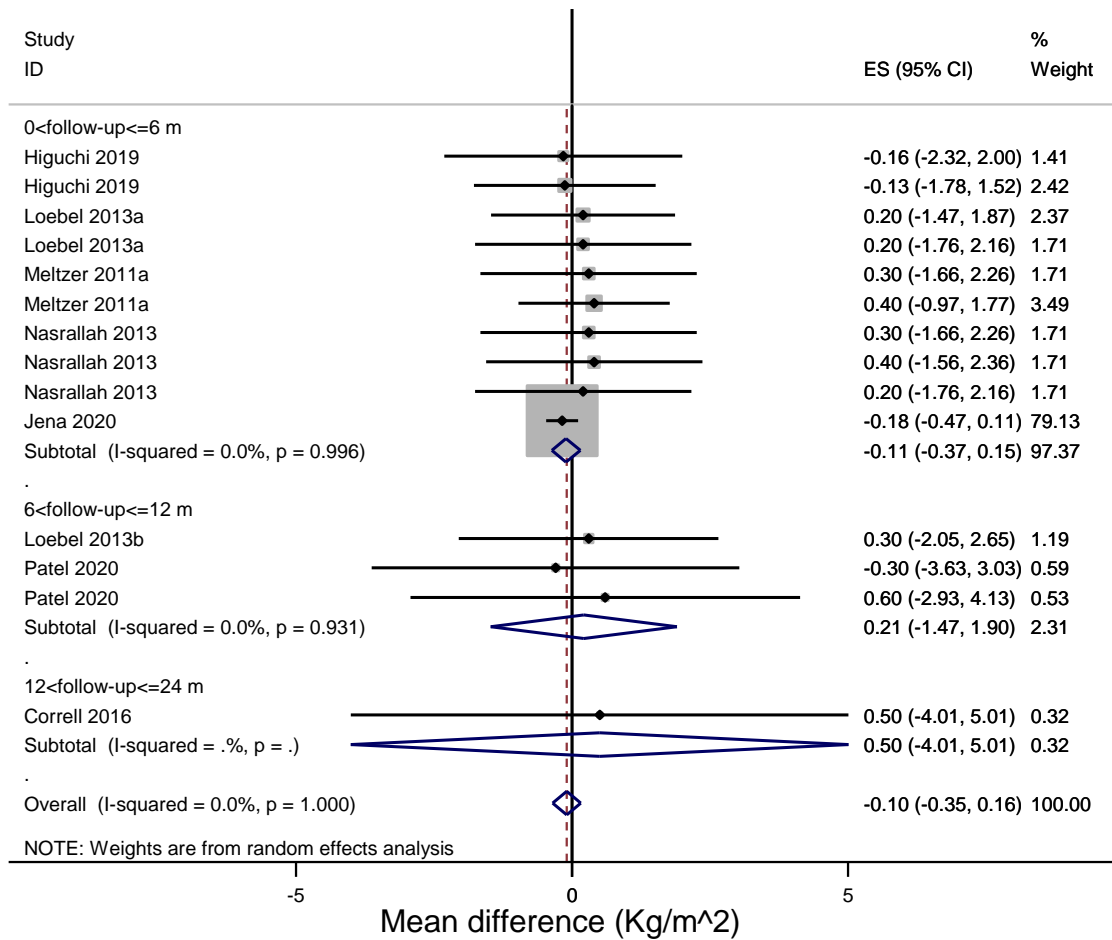
ARIPRAZOLE - Diastolic Blood Pressure



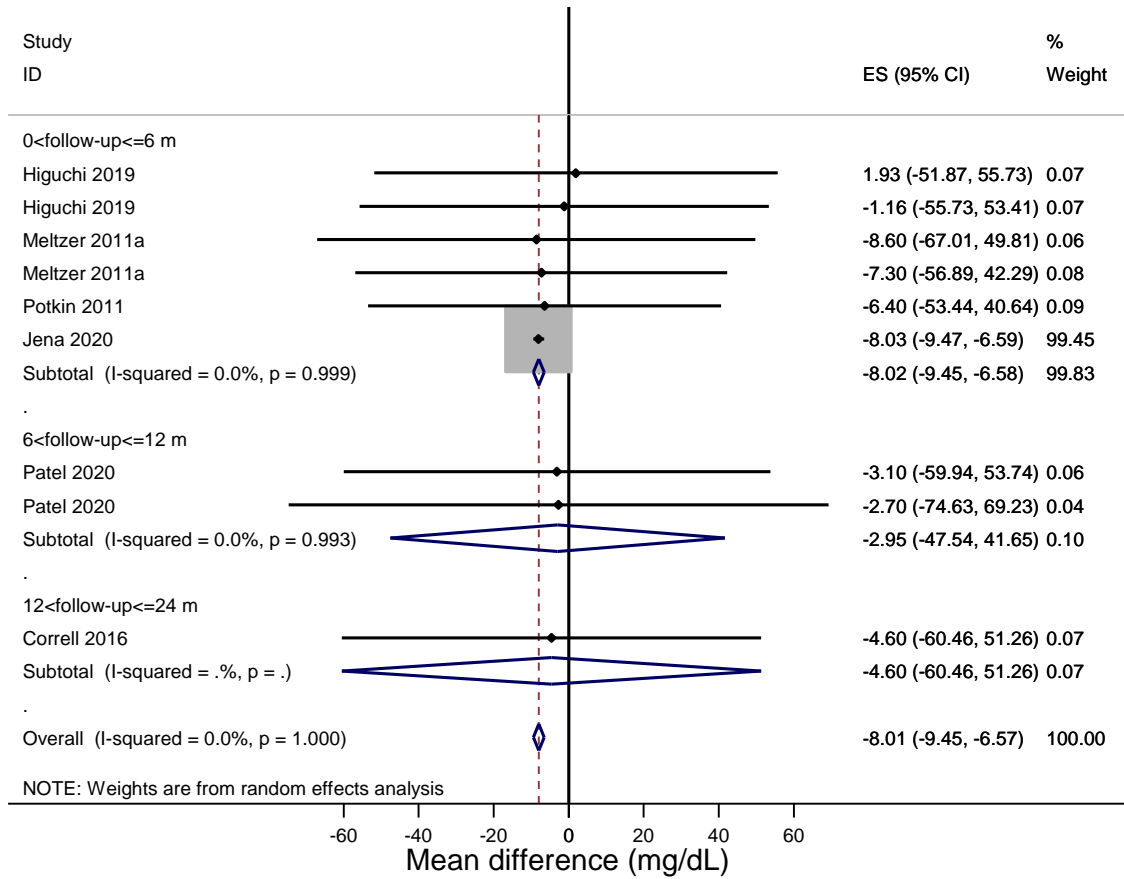
LURASIDONE - Weight



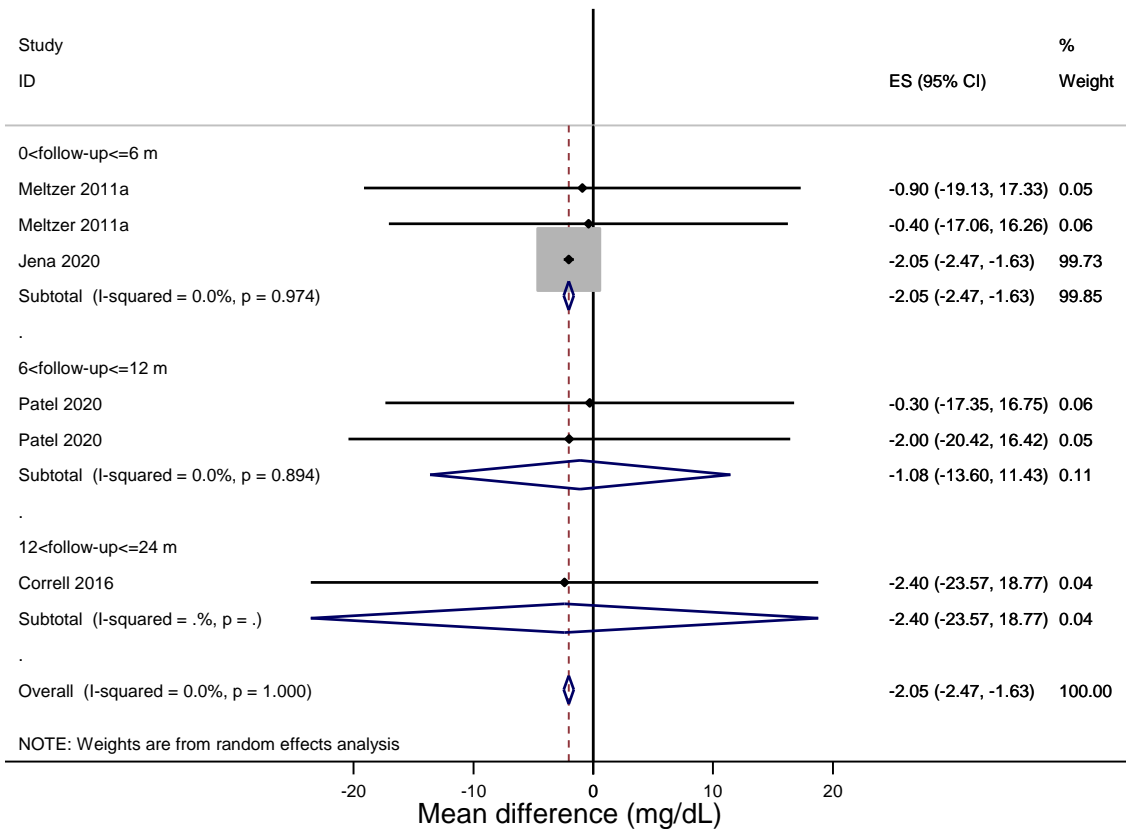
LURASIDONE - BMI



LURASIDONE - Total cholesterol

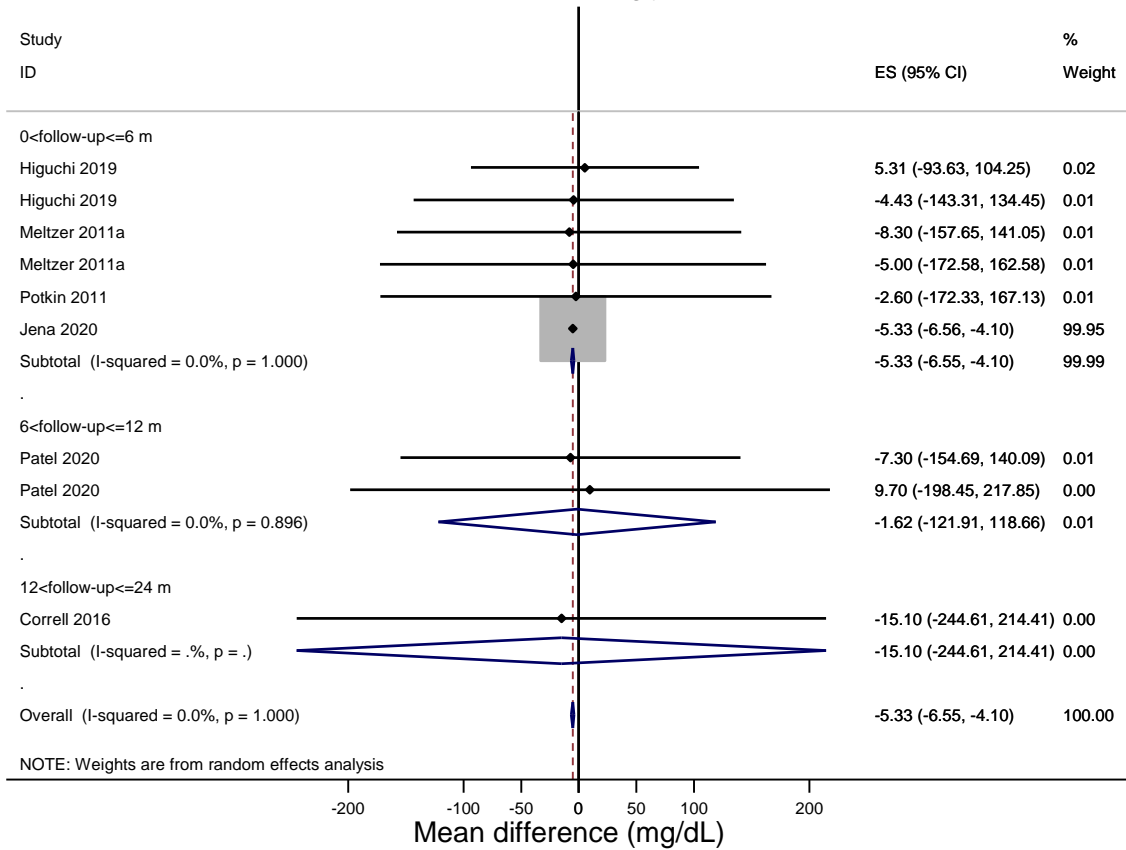


LURASIDONE - Cholesterol HDL

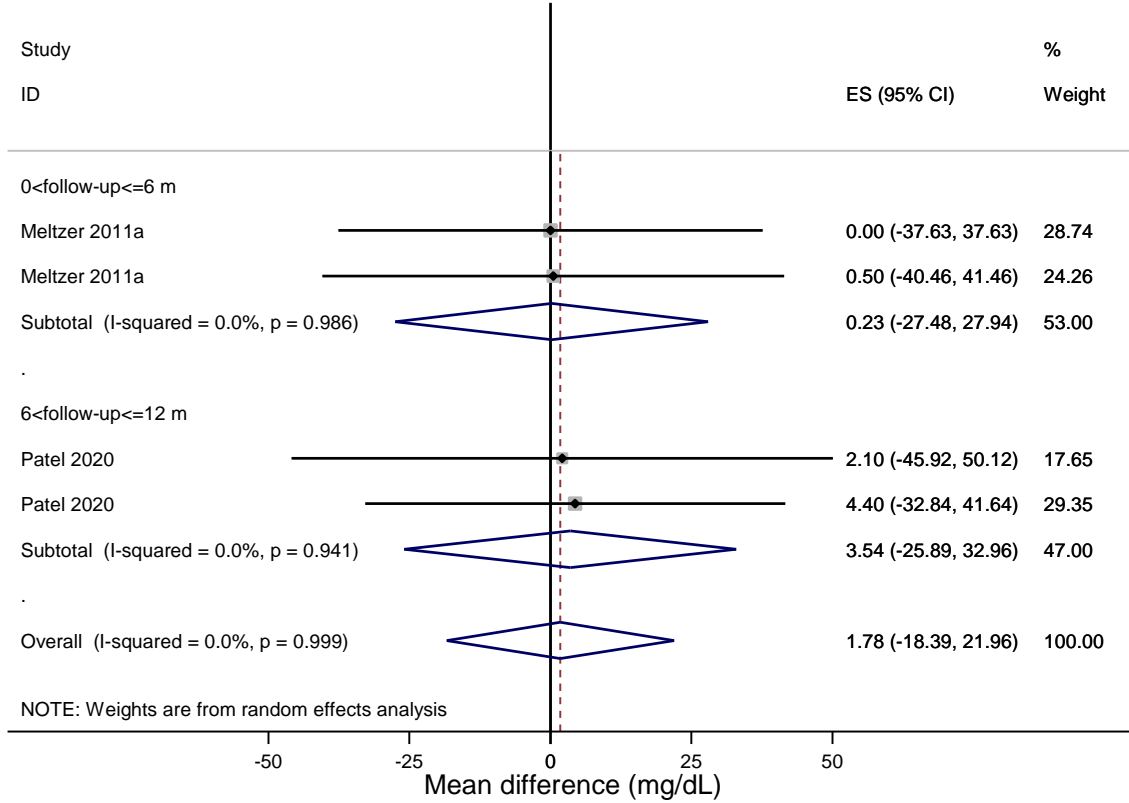


NOTE: Weights are from random effects analysis

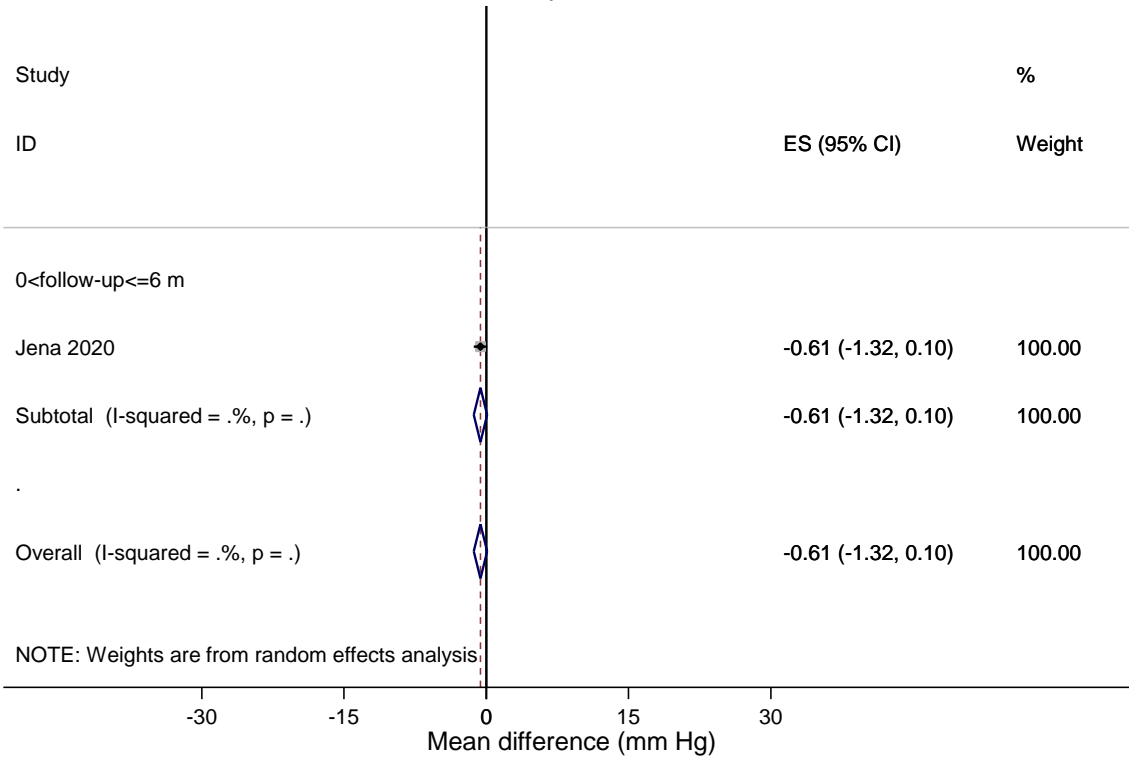
LURASIDONE - Triglycerides



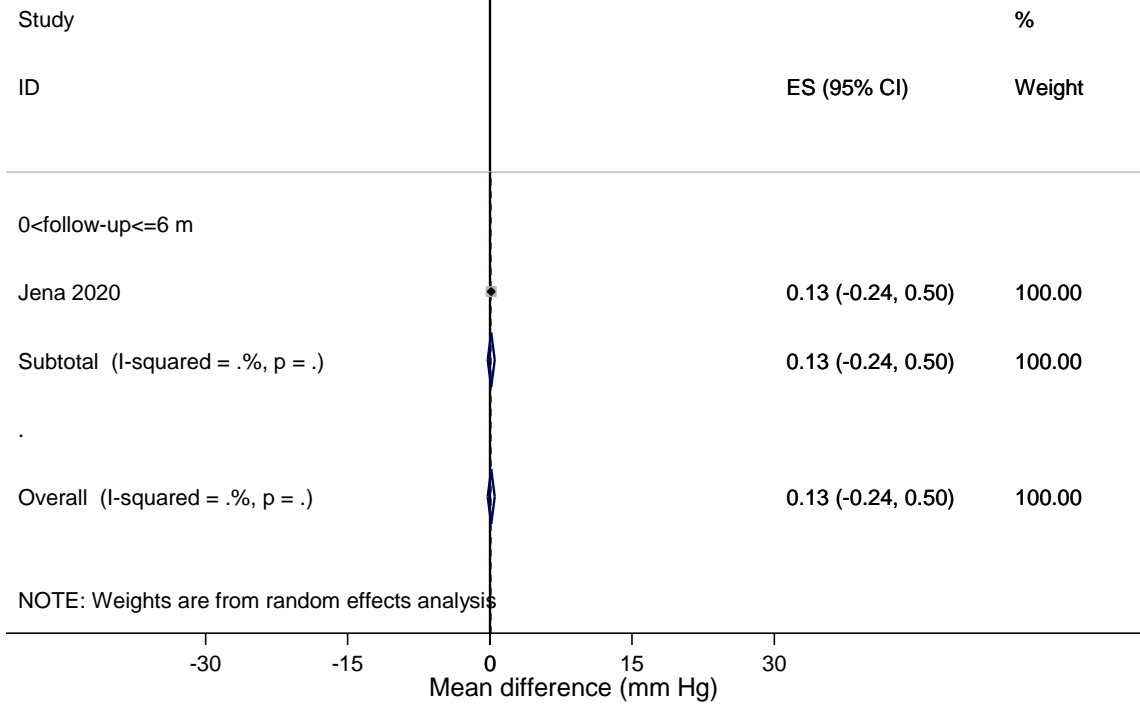
LURASIDONE - Fasting glucose



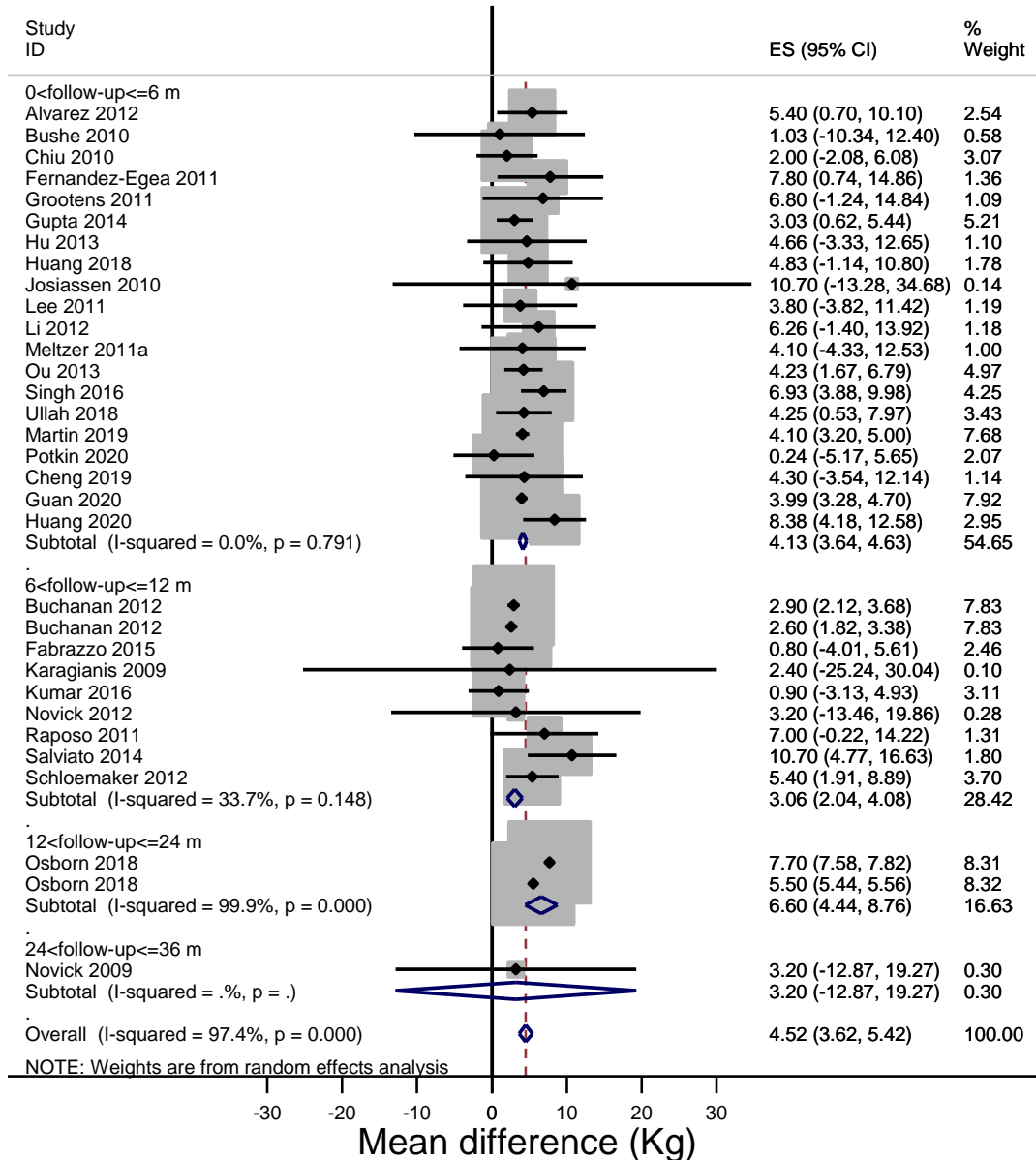
LURASIDONE - Systolic Blood Pressure



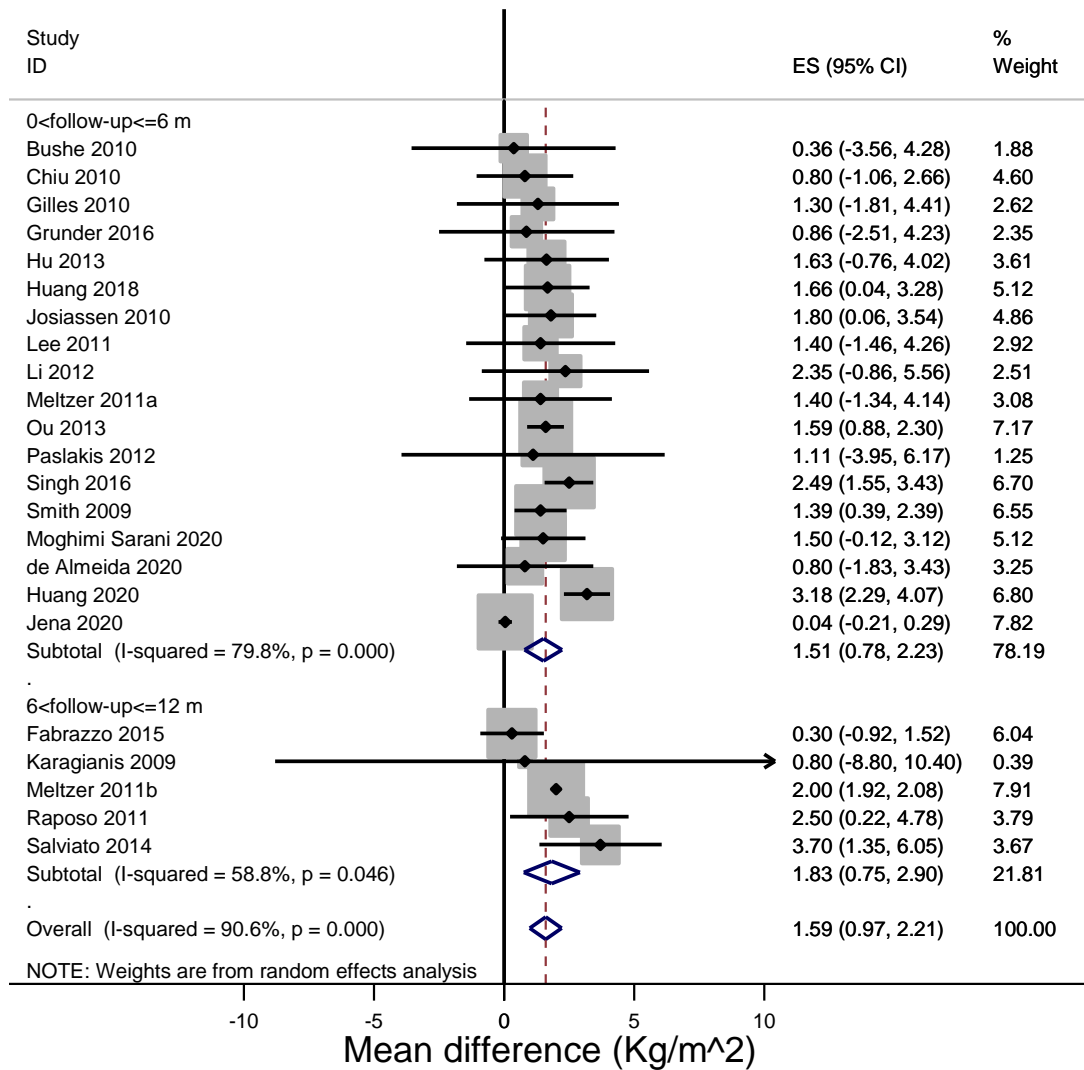
LURASIDONE - Diastolic Blood Pressure



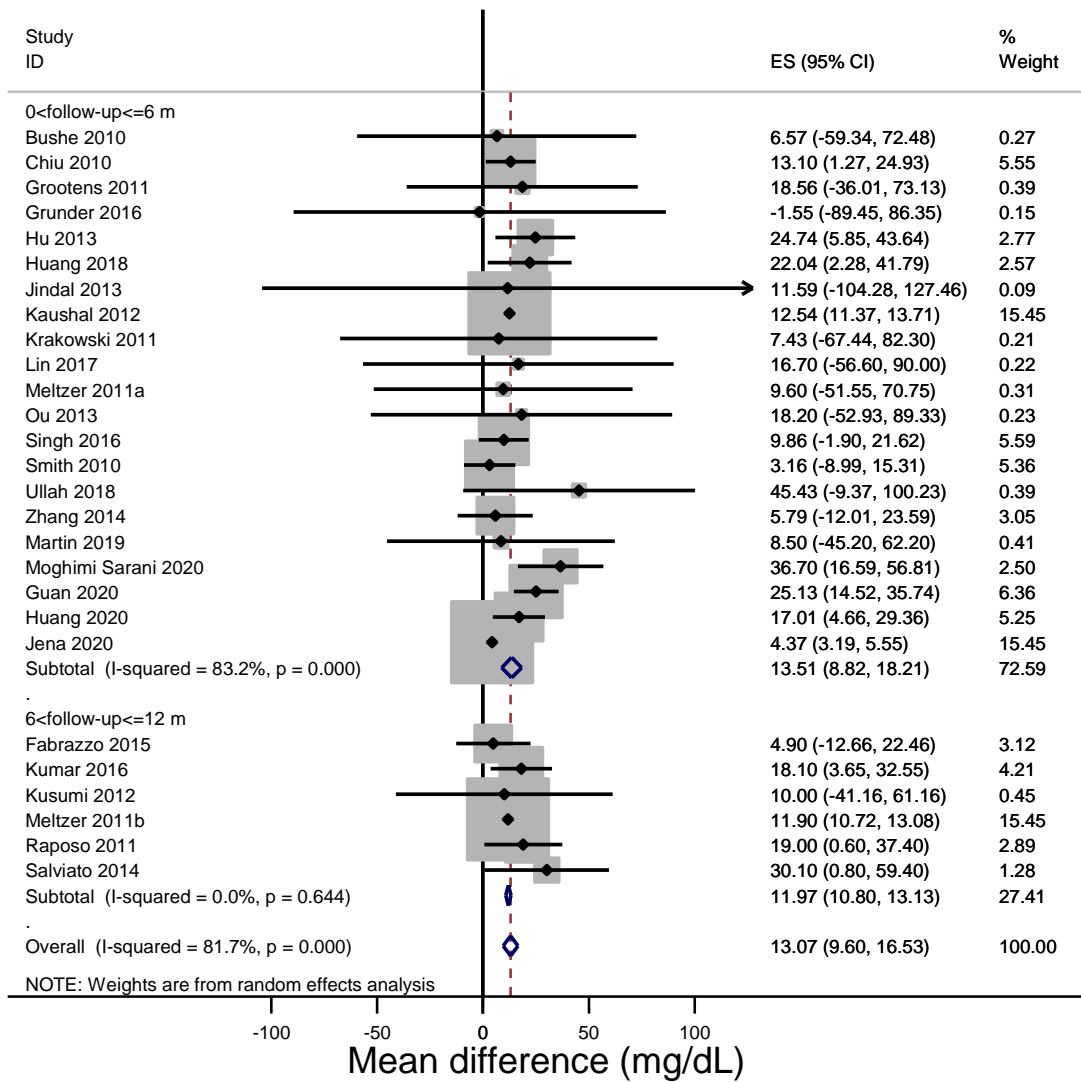
OLANZAPINE - Weight



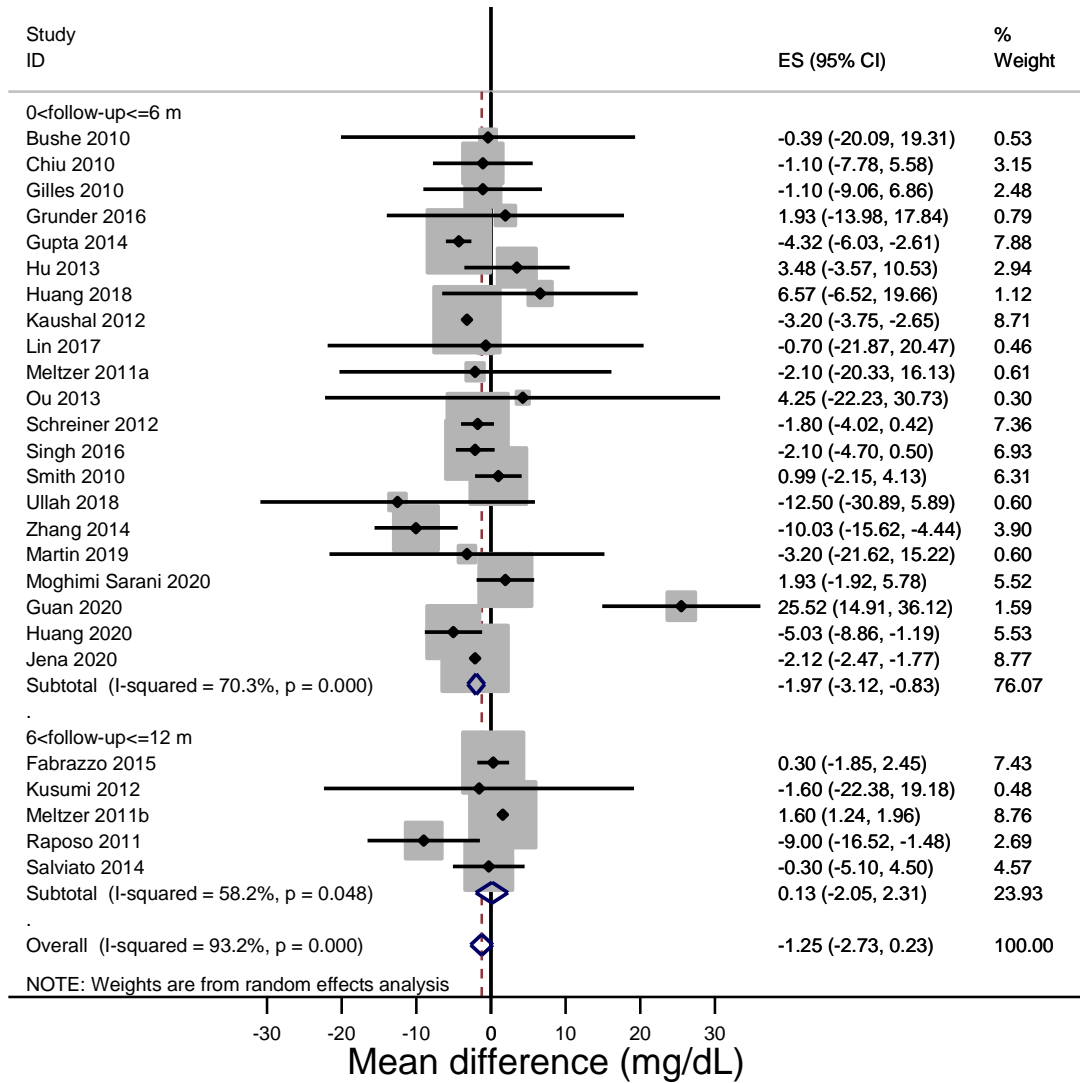
OLANZAPINE - BMI



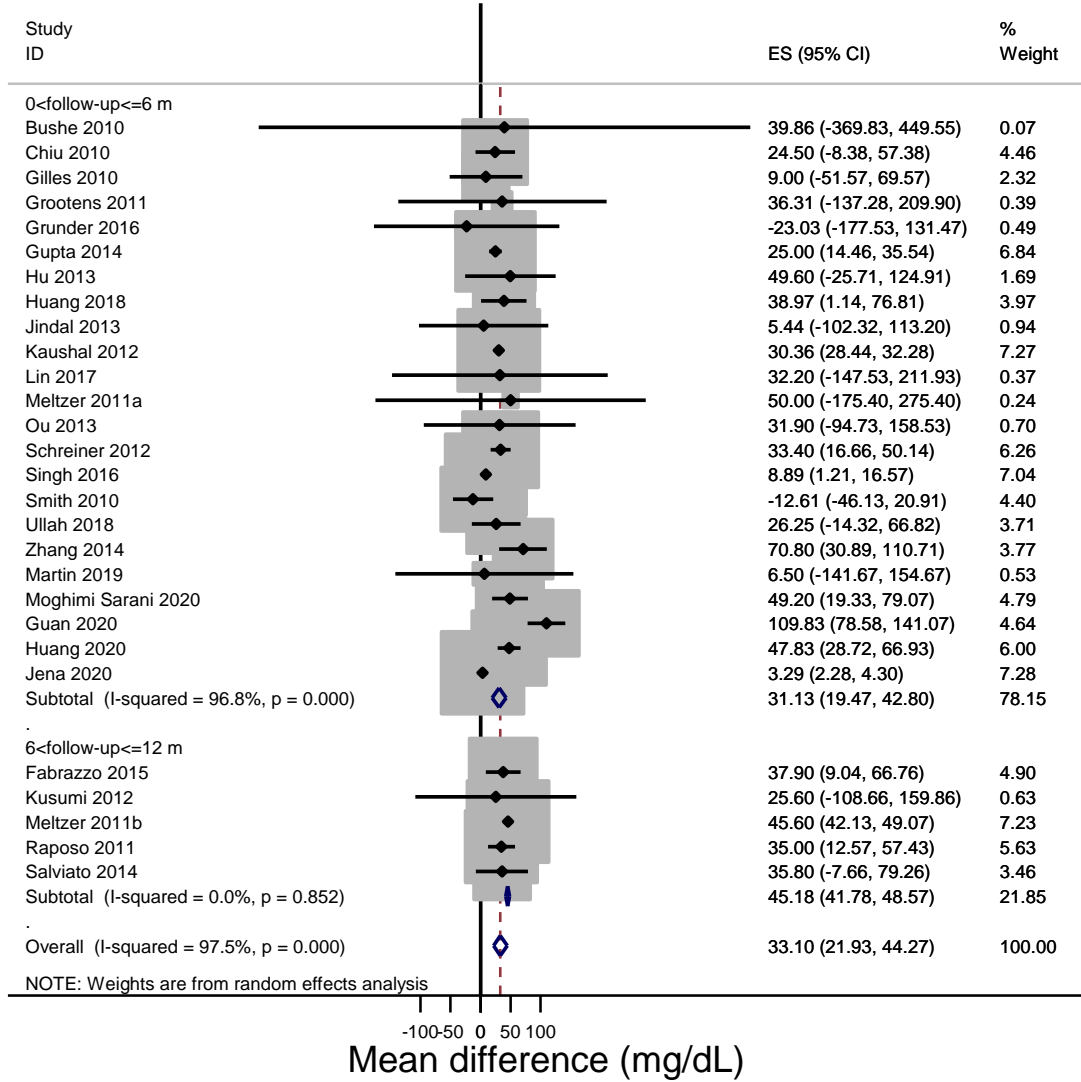
OLANZAPINE - Total cholesterol



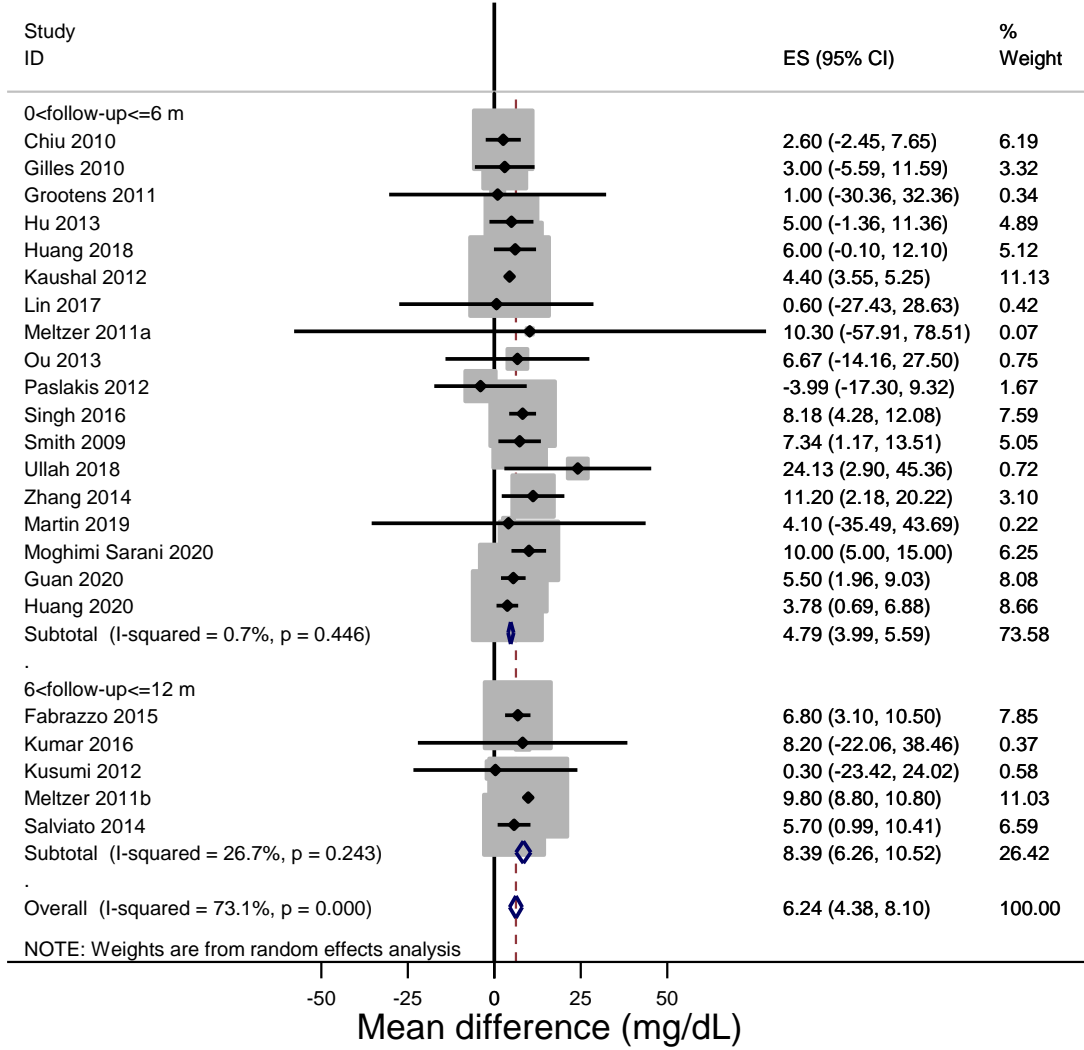
OLANZAPINE - Cholesterol HDL



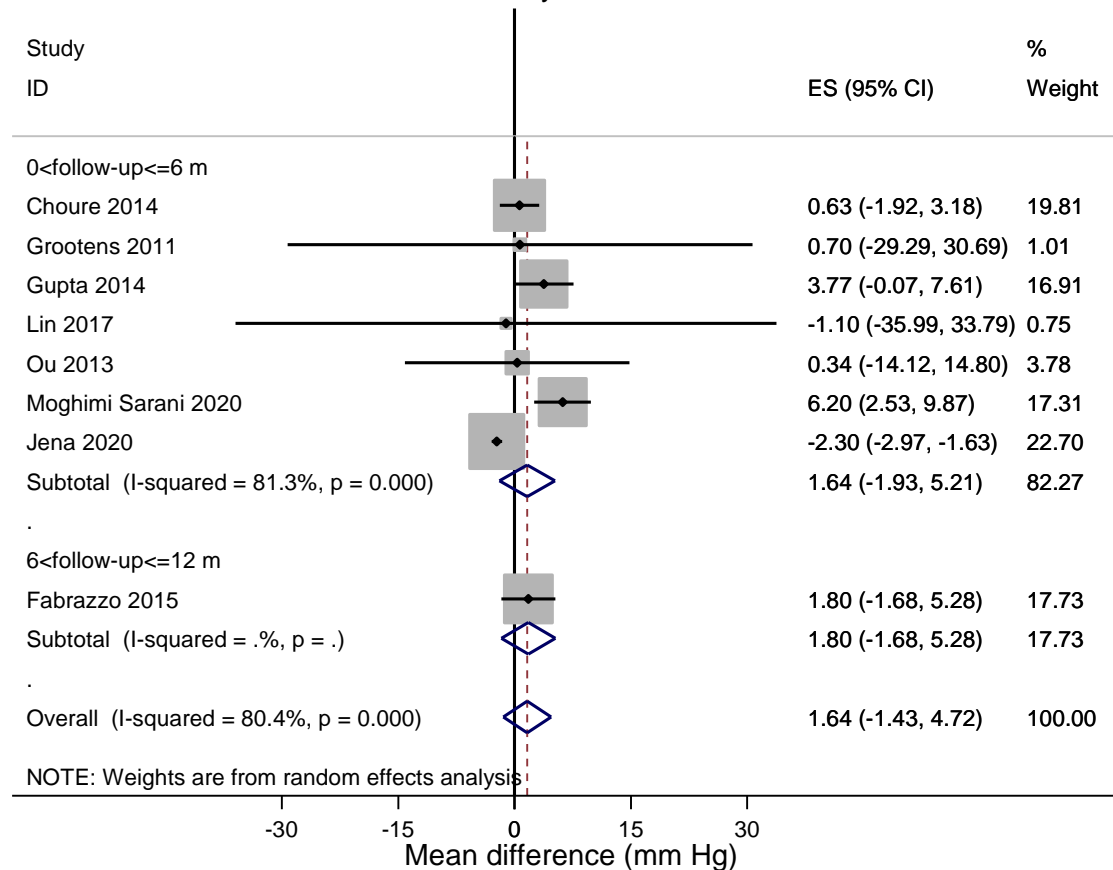
OLANZAPINE - Triglycerides



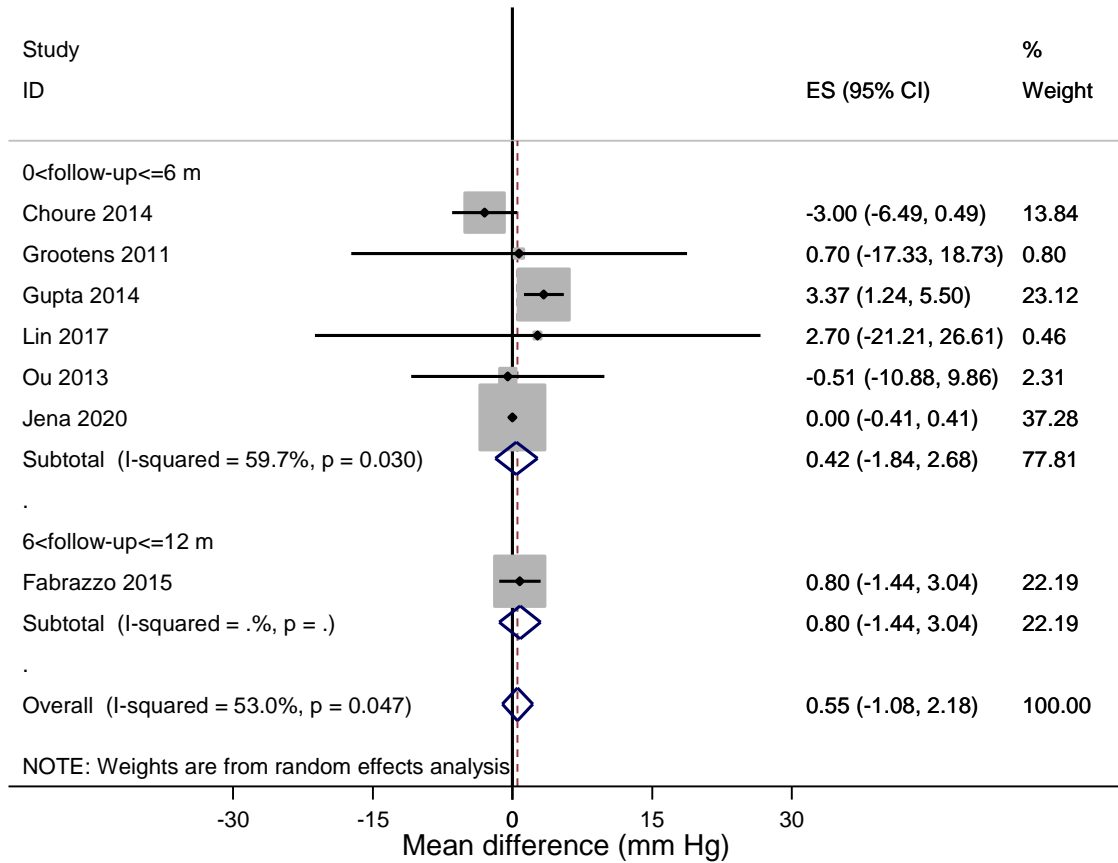
OLANZAPINE - Fasting glucose



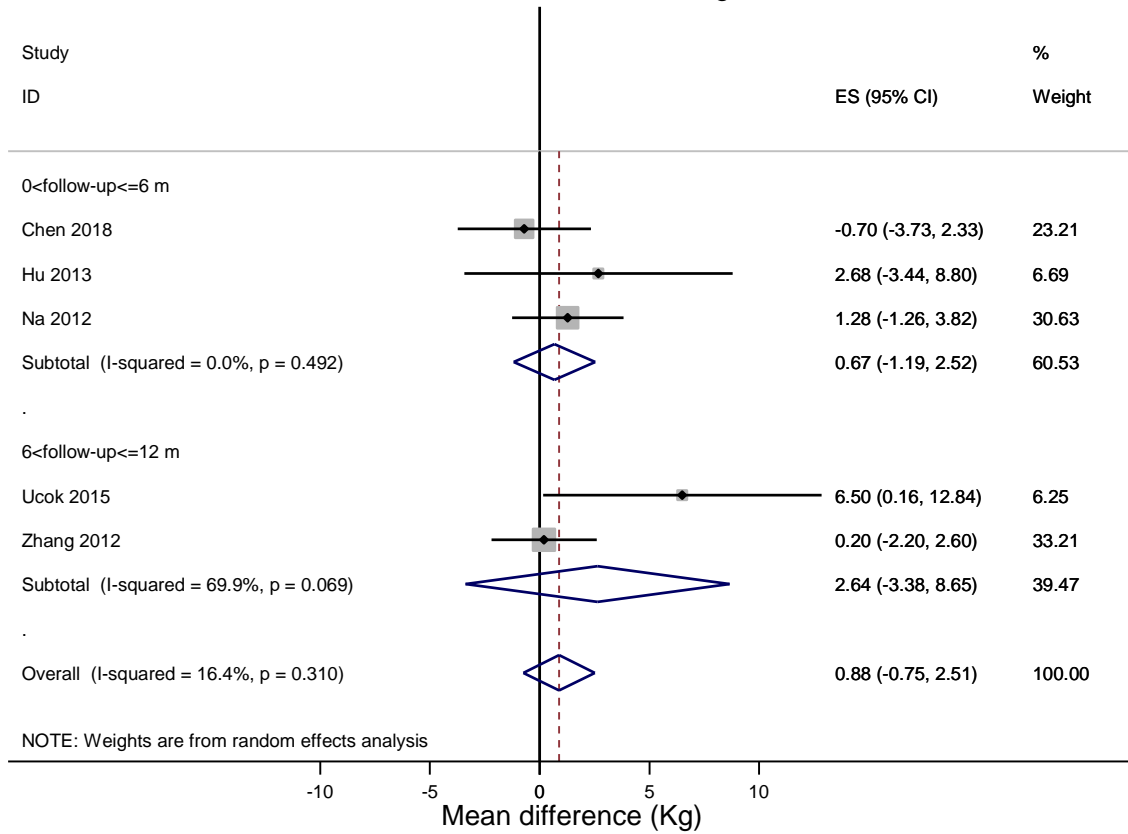
OLANZAPINE - Systolic Blood Pressure



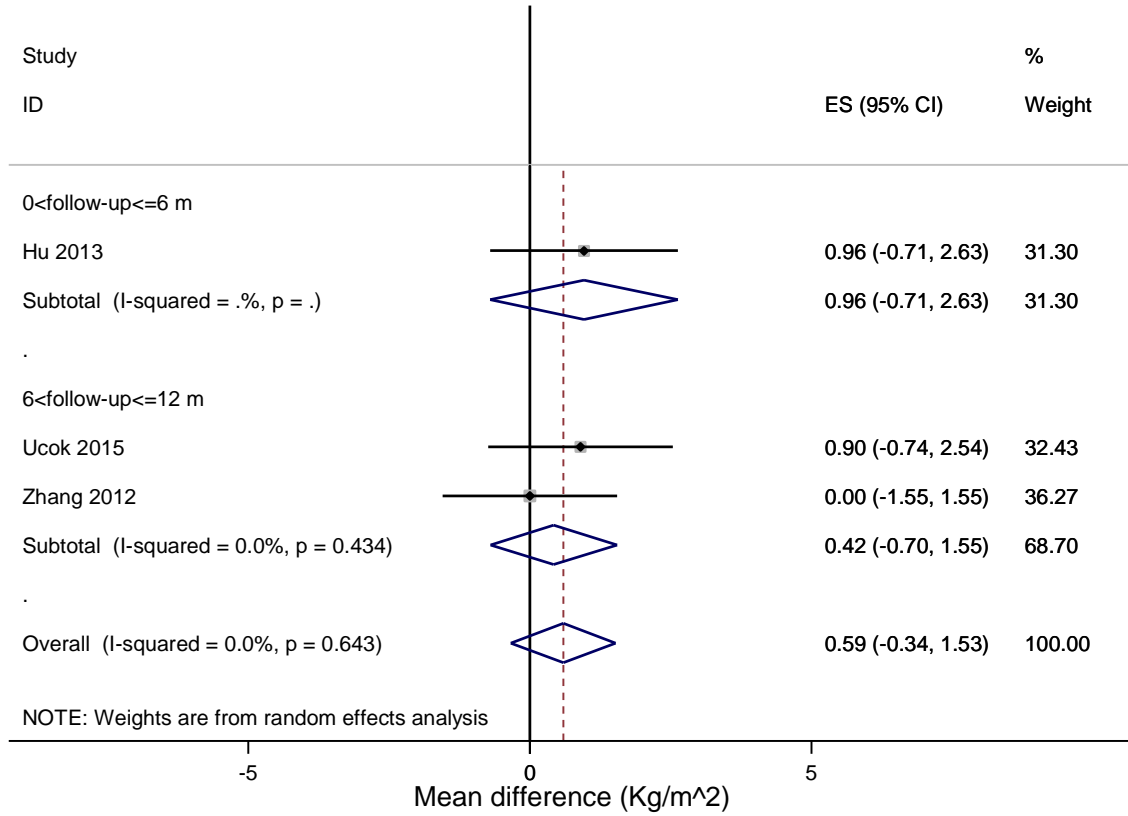
OLANZAPINE - Diastolic Blood Pressure



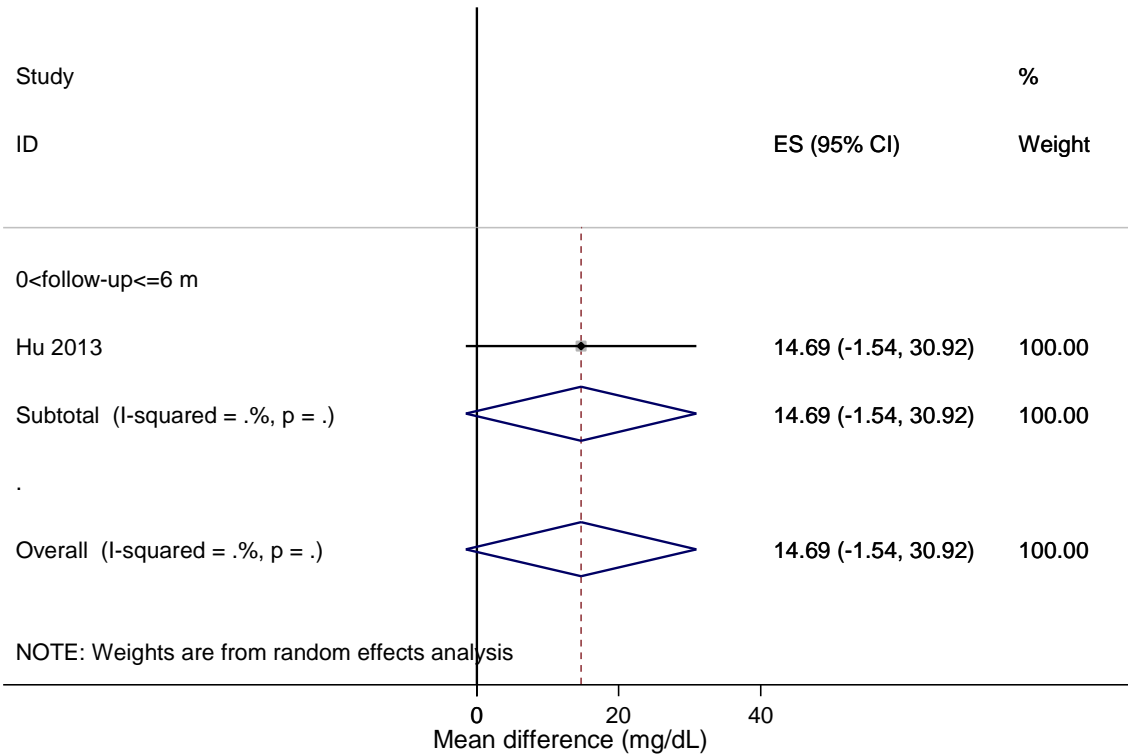
PALIPERIDONE XR - Weight



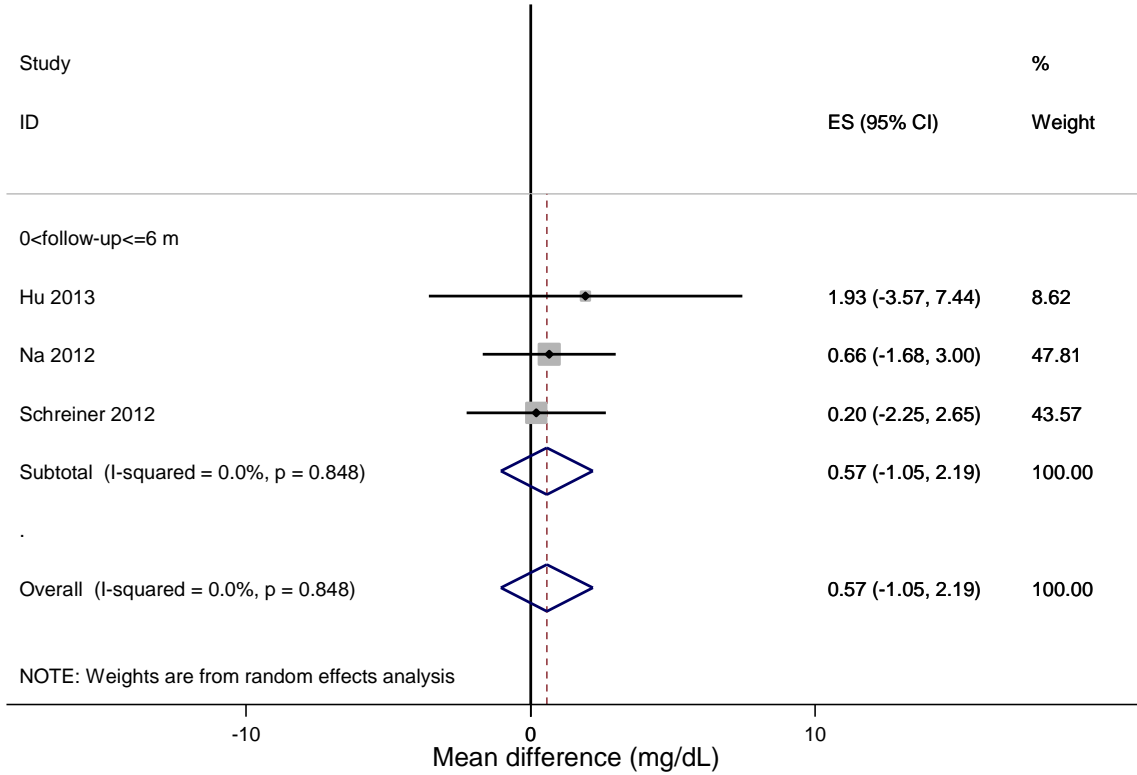
PALIPERIDONE XR - BMI



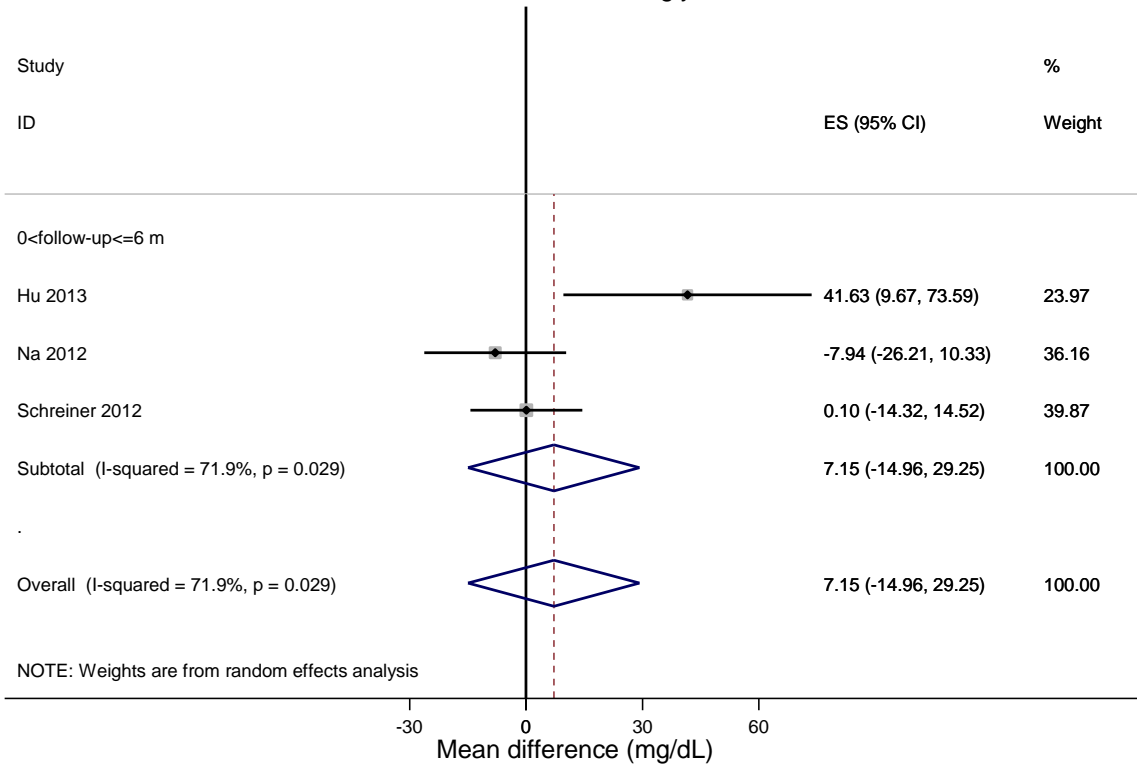
PALIPERIDONE XR - Total cholesterol



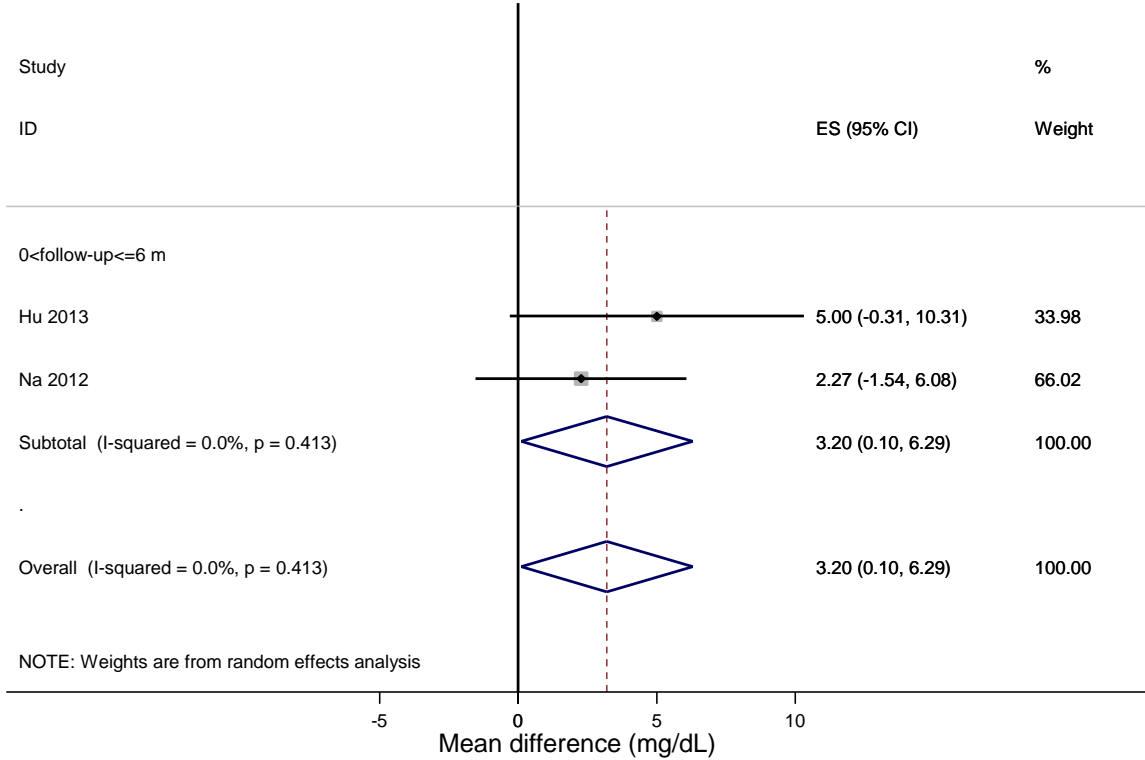
PALIPERIDONE XR - Cholesterol HDL



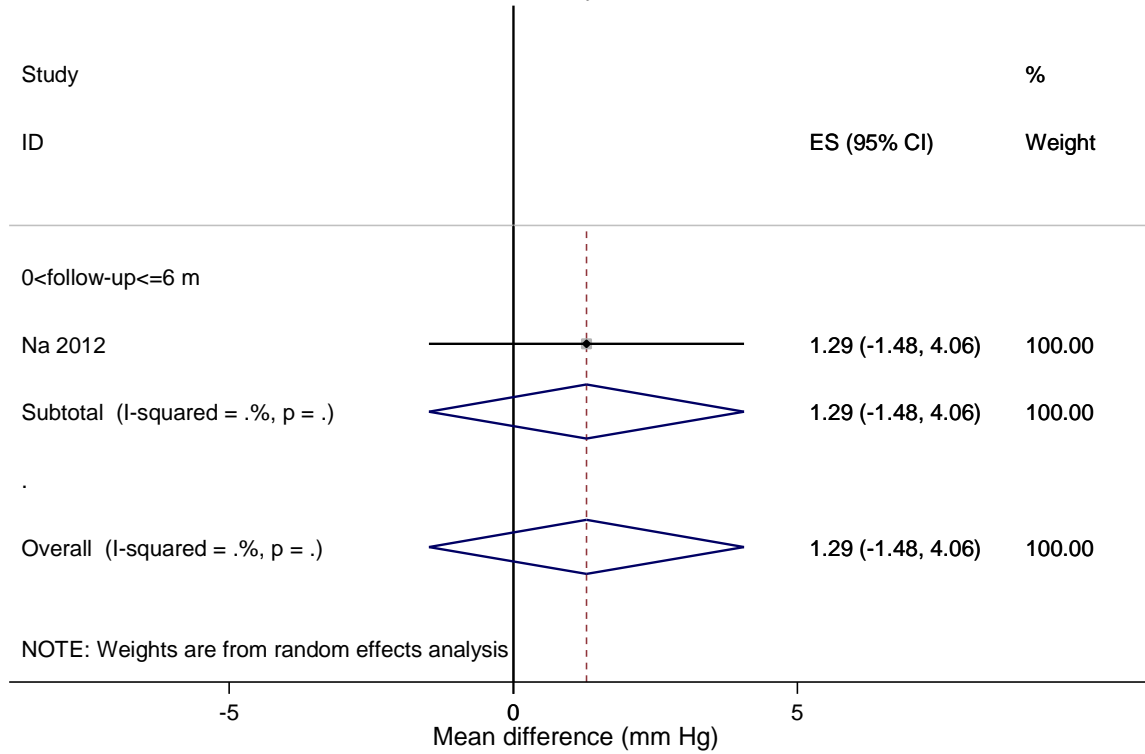
PALIPERIDONE XR - Triglycerides



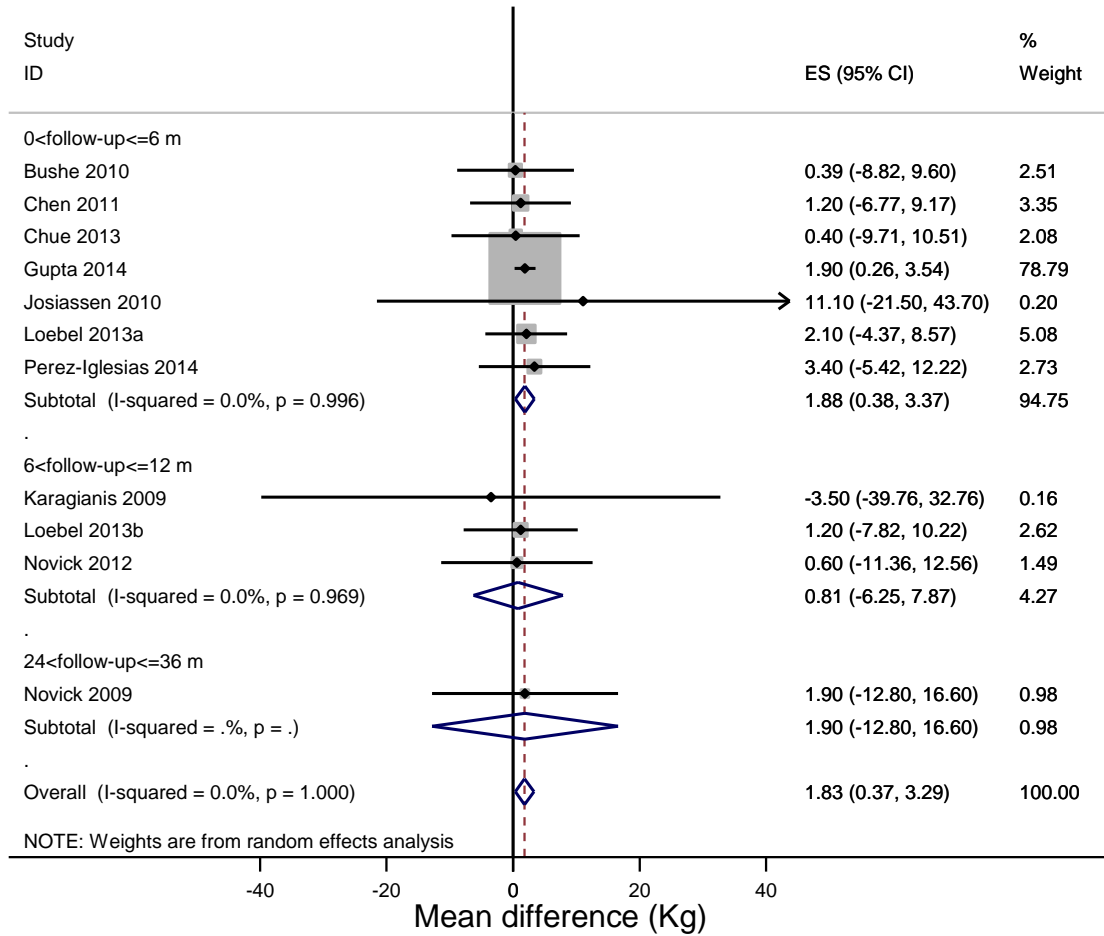
PALIPERIDONE XR - Fasting glucose



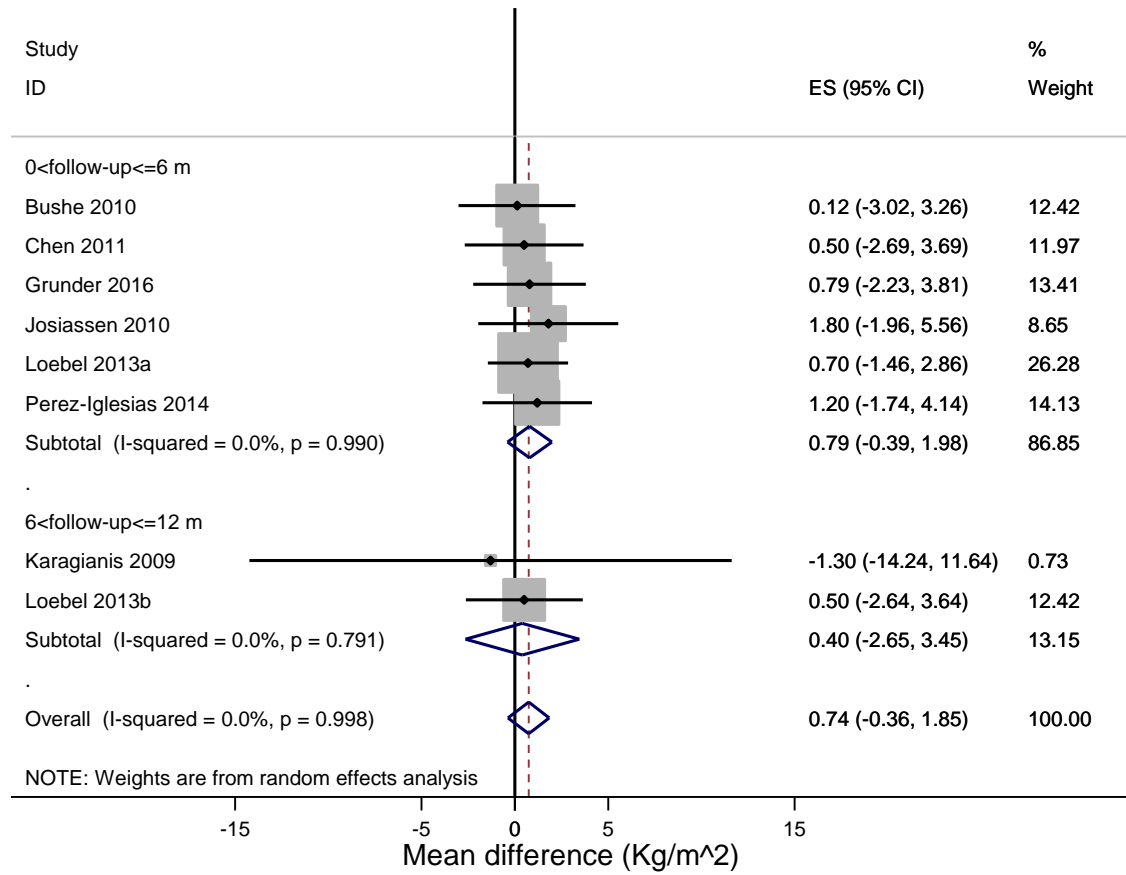
PALIPERIDONE XR - Systolic Blood Pressure



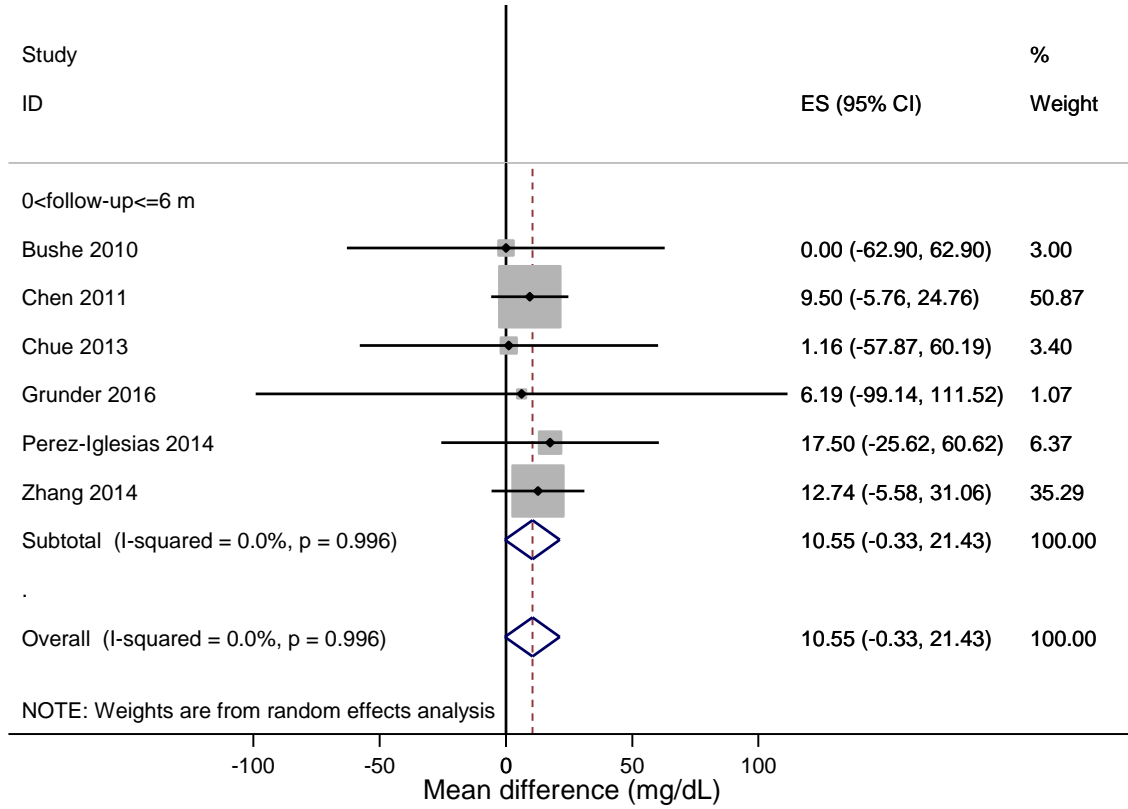
QUETIAPINE XR - Weight



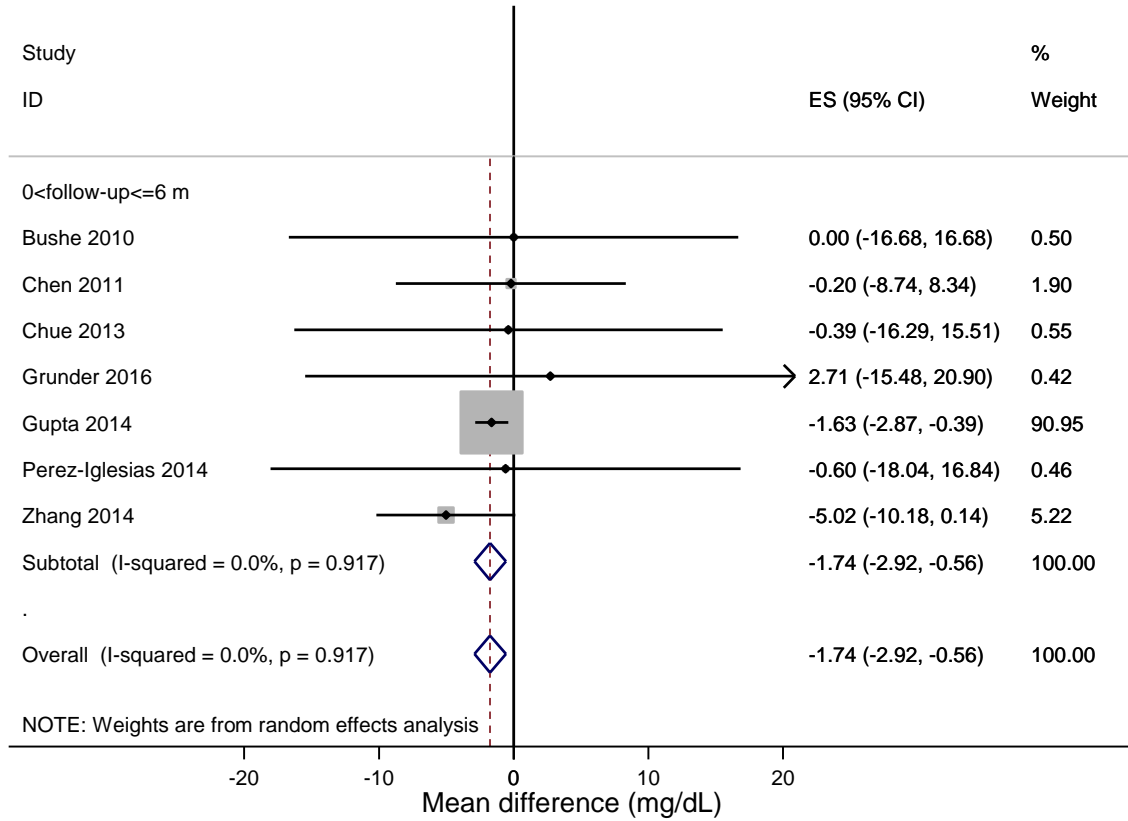
QUETIAPINE XR - BMI



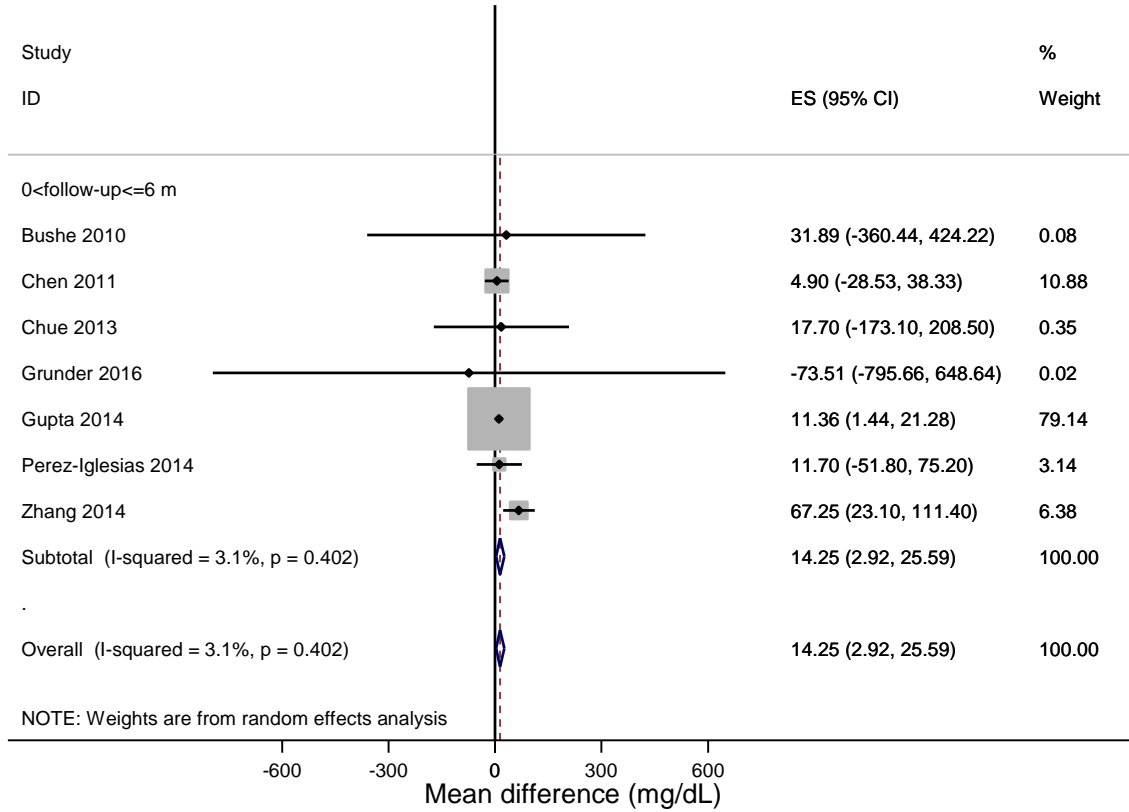
QUETIAPINE XR - Total cholesterol



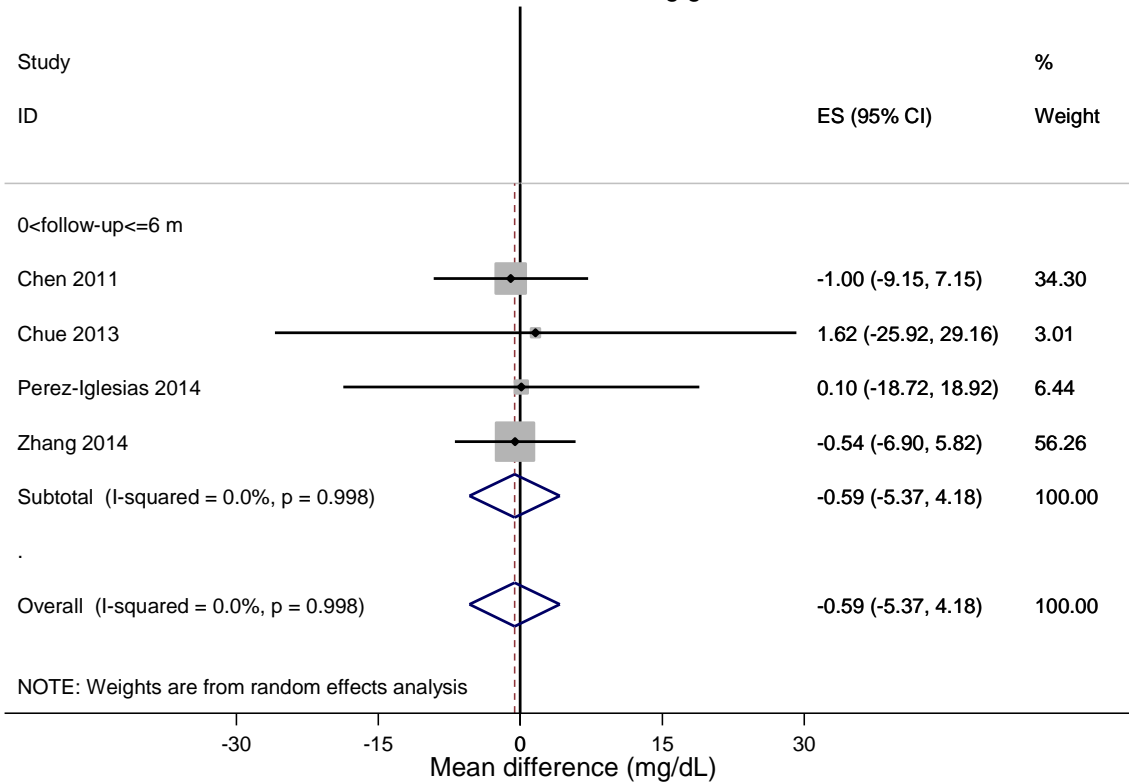
QUETIAPINE XR - Cholesterol HDL



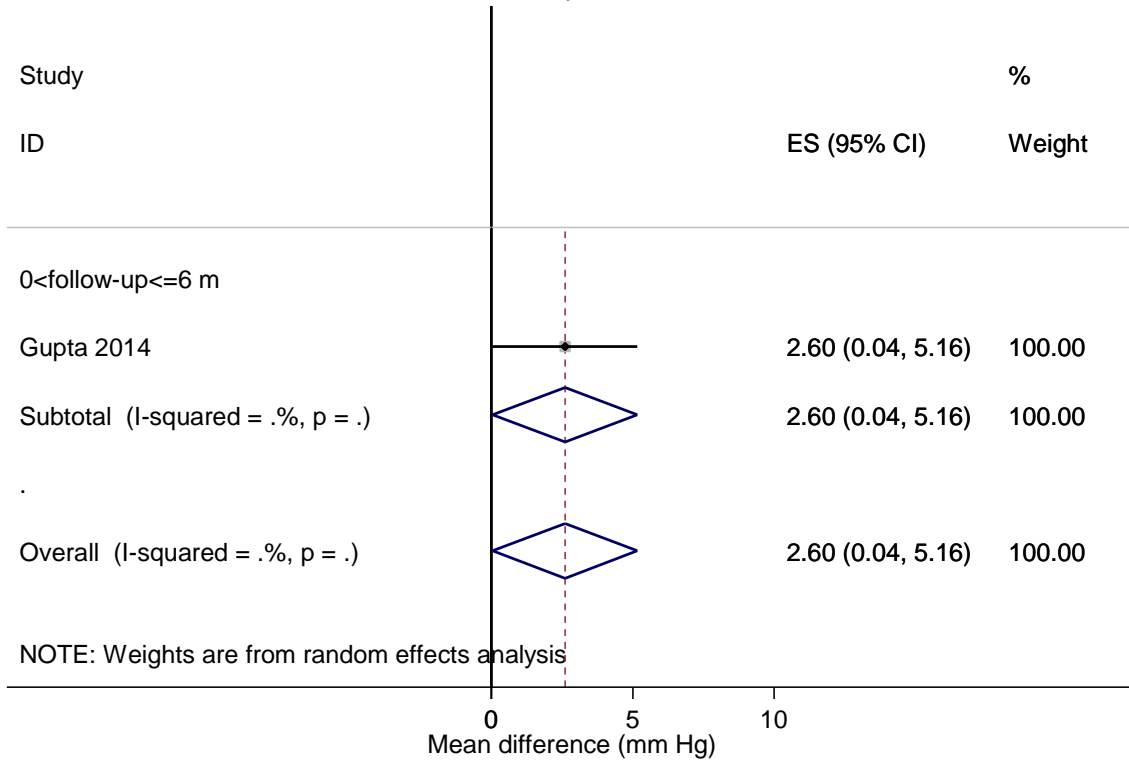
QUETIAPINE XR - Triglycerides



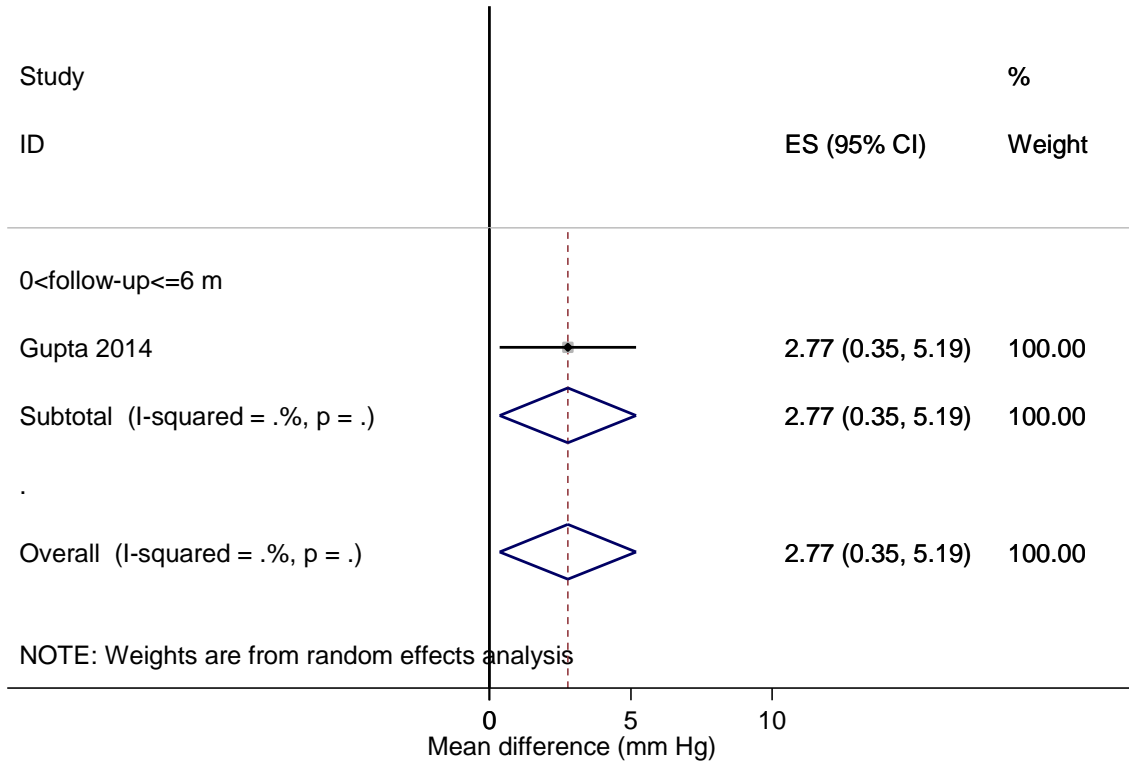
QUETIAPINE XR - Fasting glucose



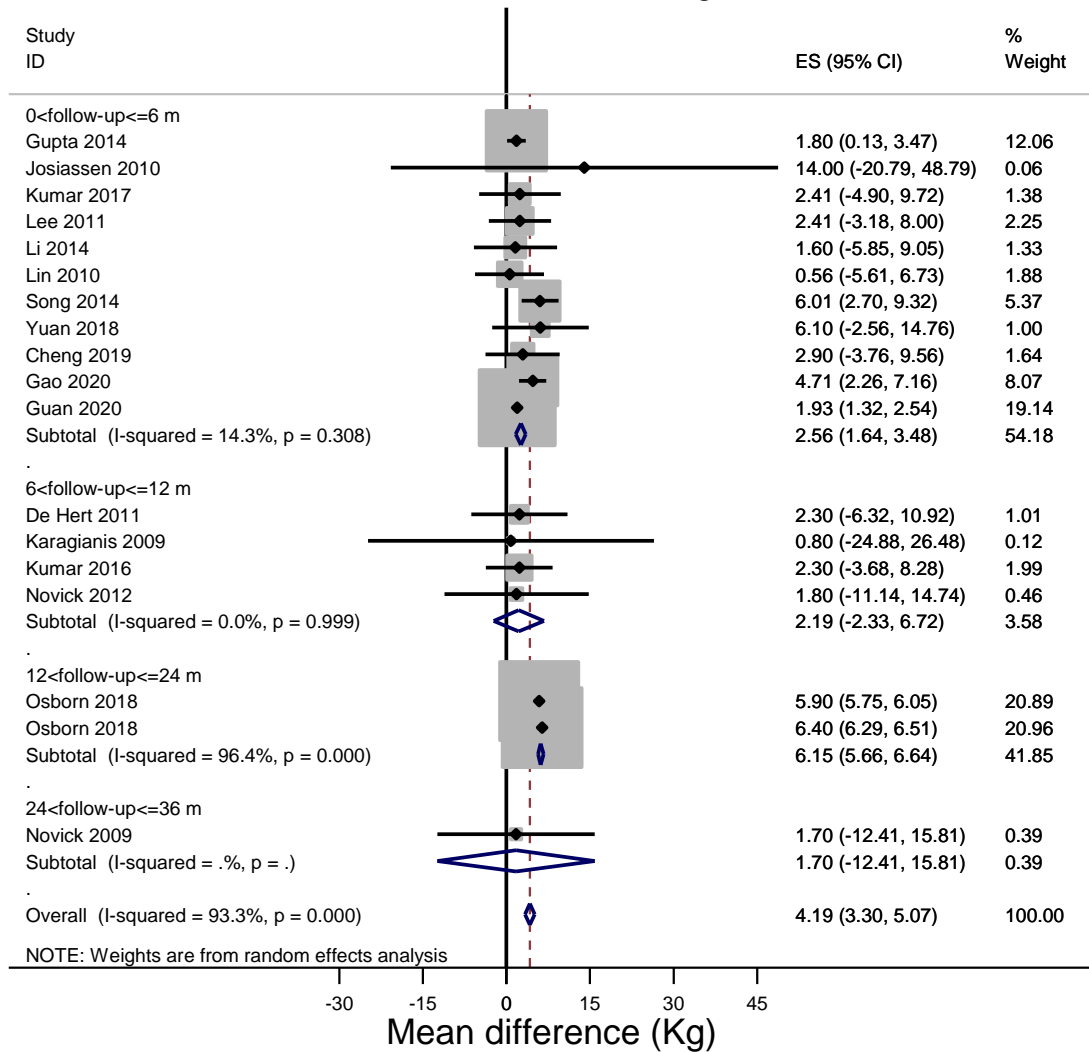
QUETIAPINE XR - Systolic Blood Pressure



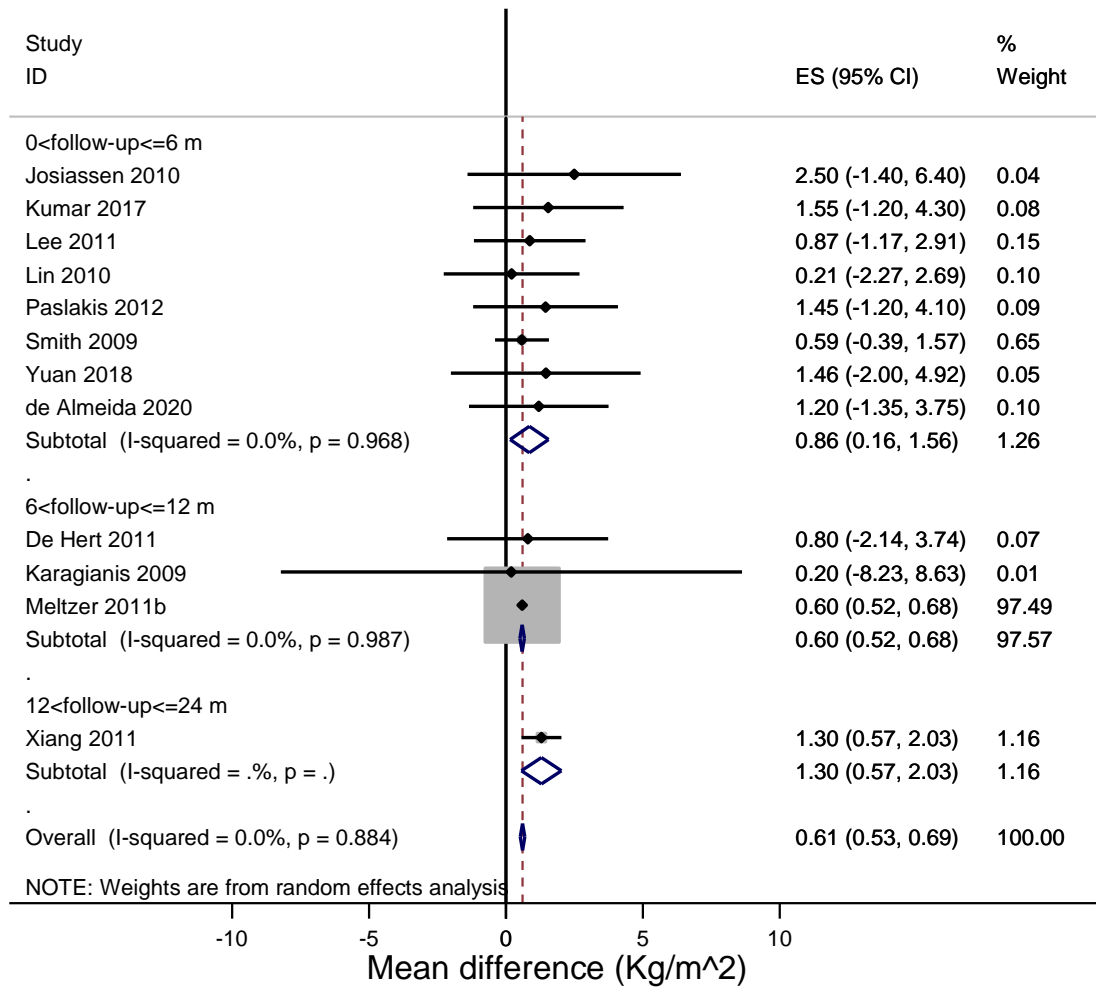
QUETIAPINE XR - Diastolic Blood Pressure



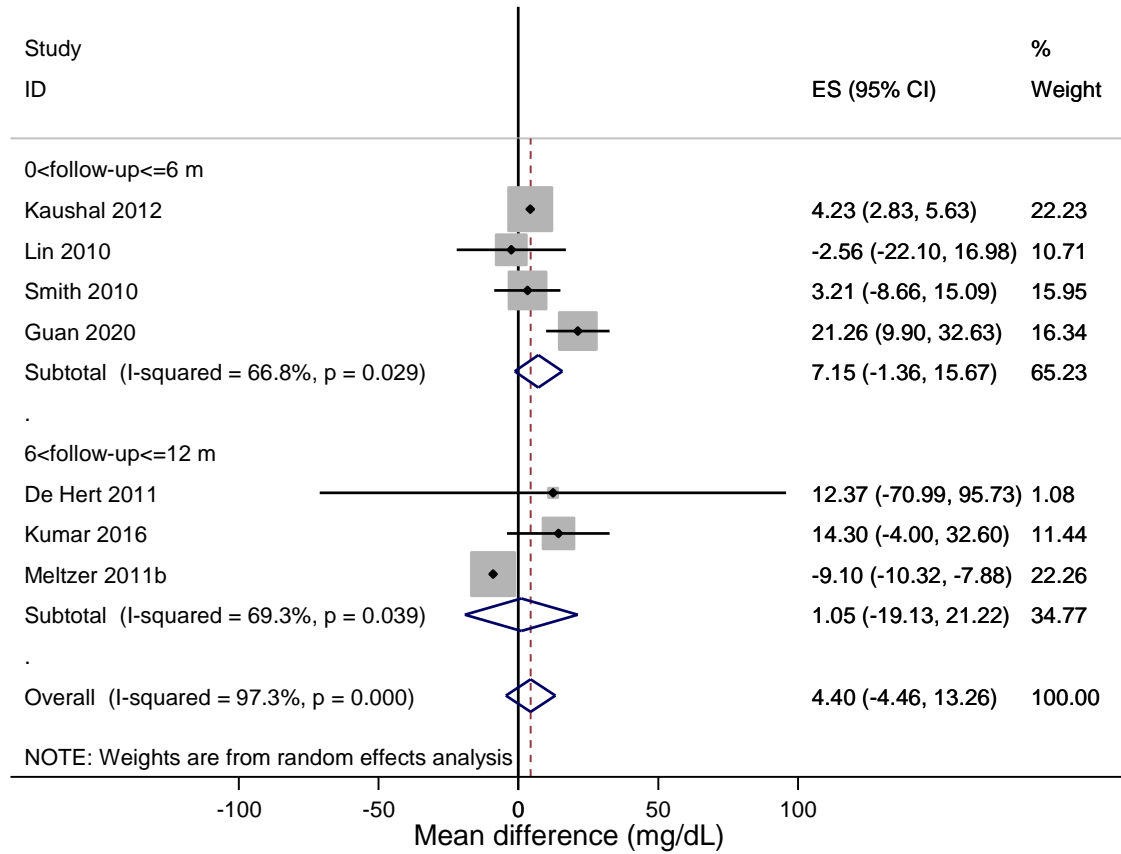
RISPERIDONE - Weight



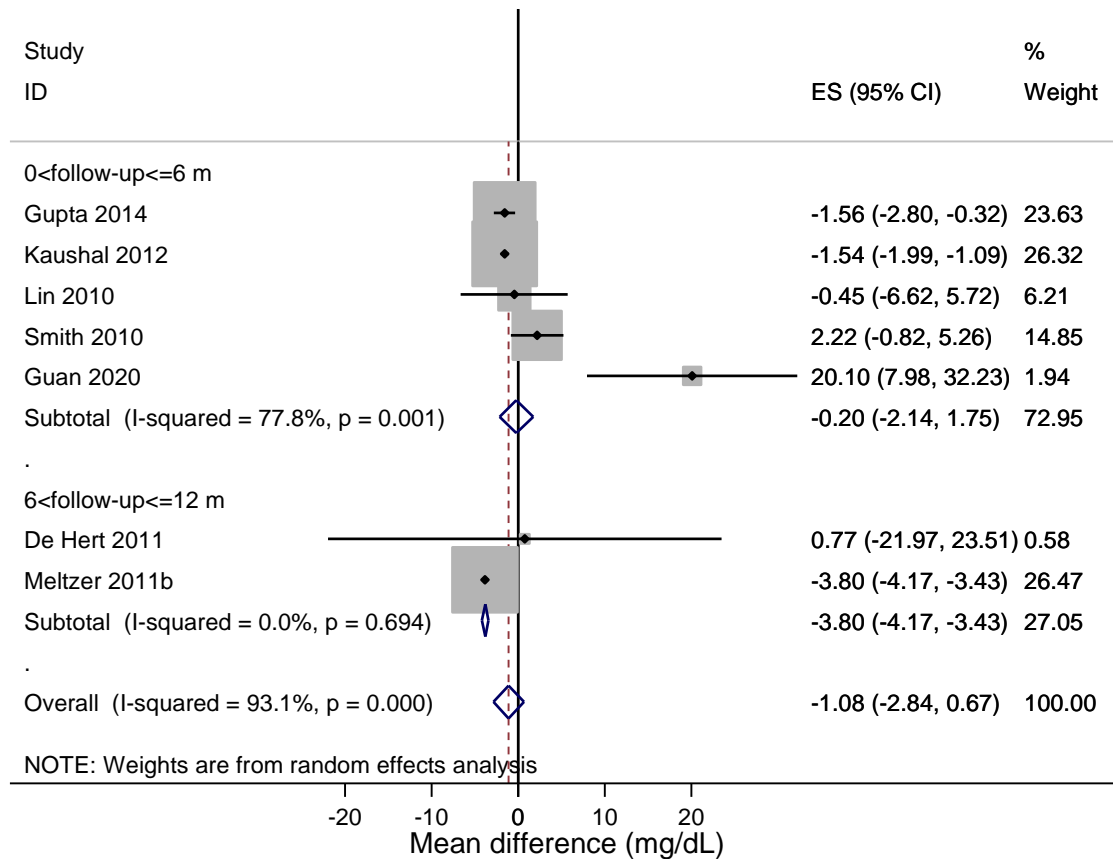
RISPERIDONE - BMI



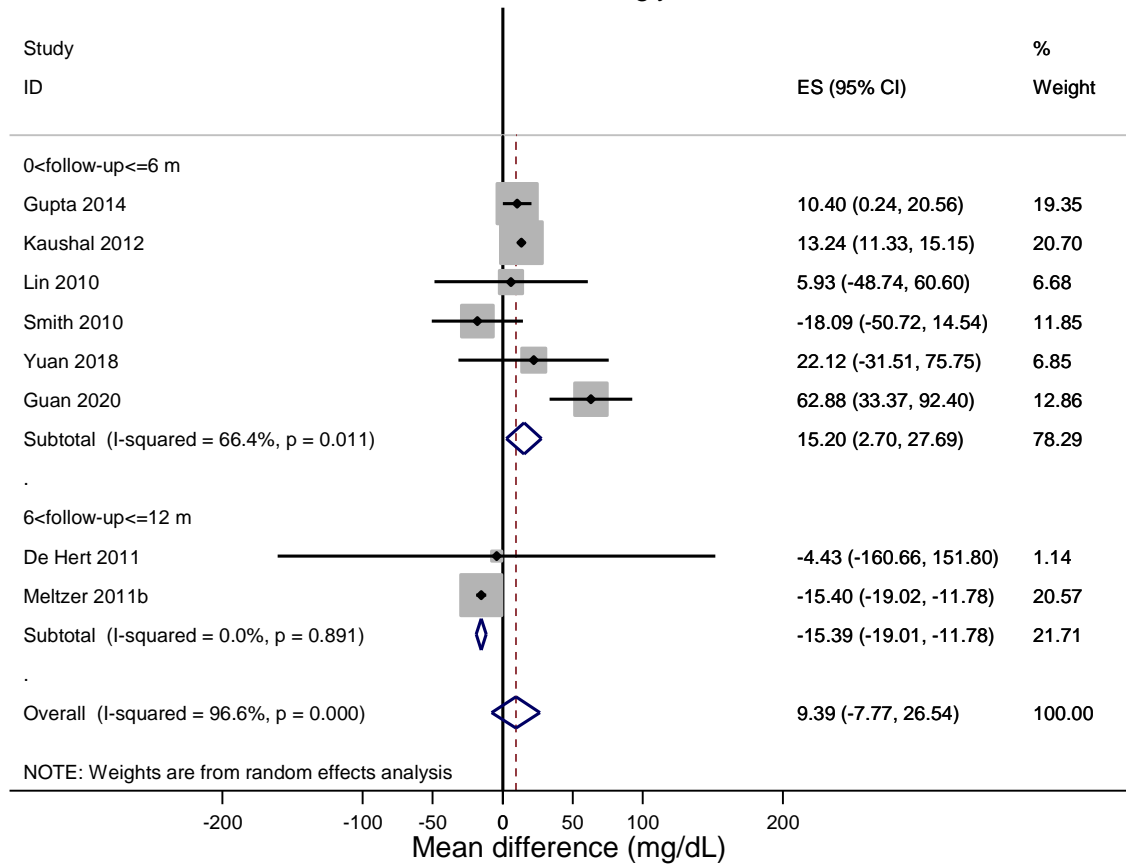
RISPERIDONE - Total cholesterol



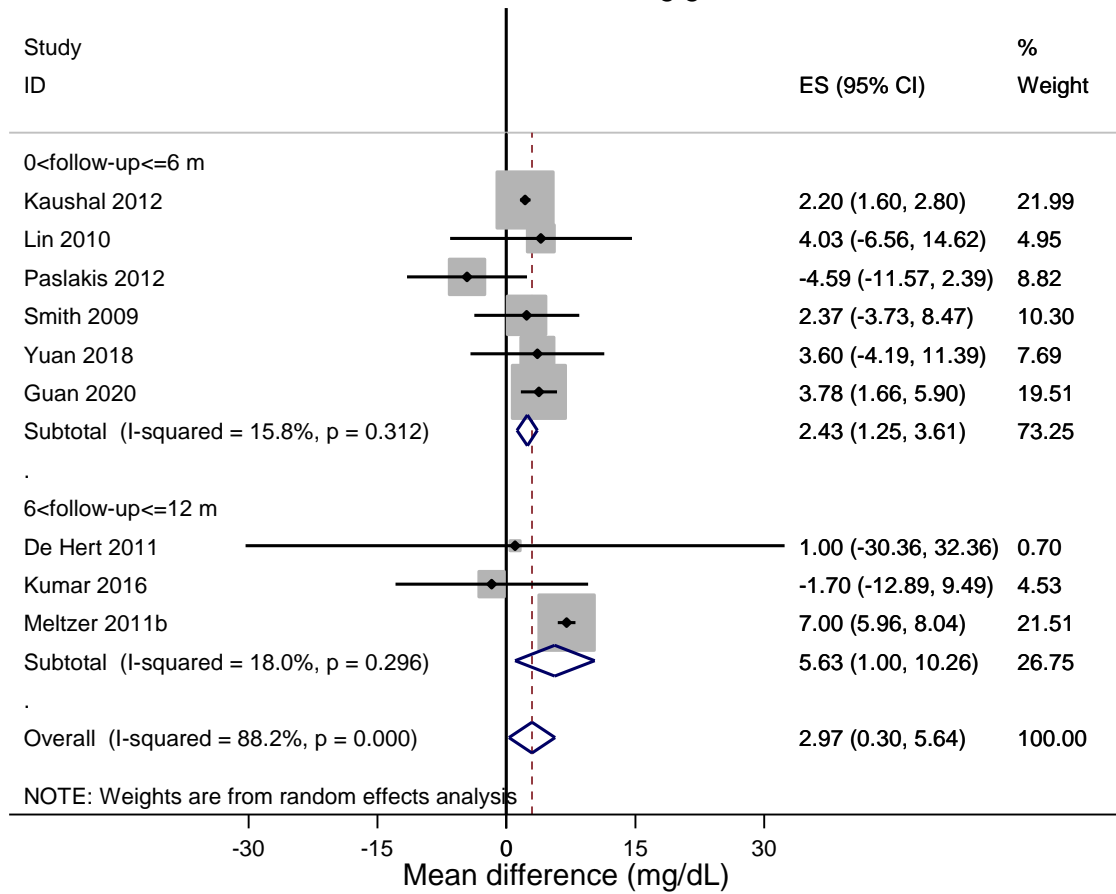
RISPERIDONE - Cholesterol HDL



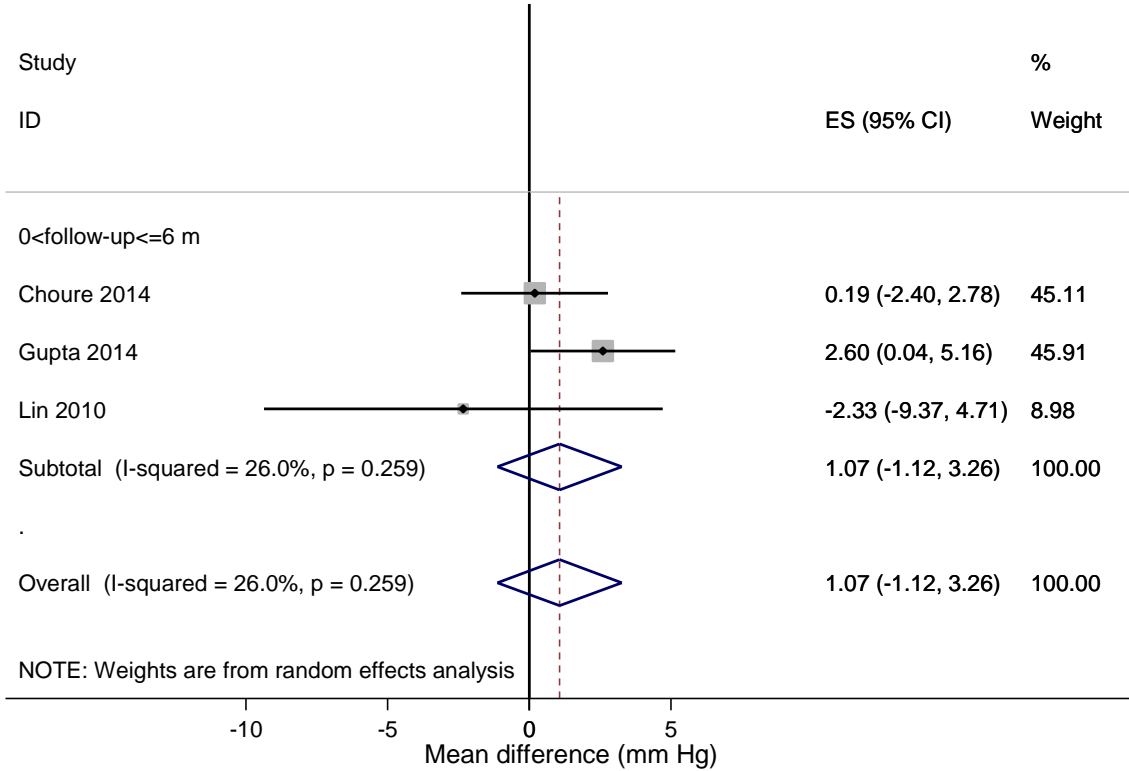
RISPERIDONE - Triglycerides



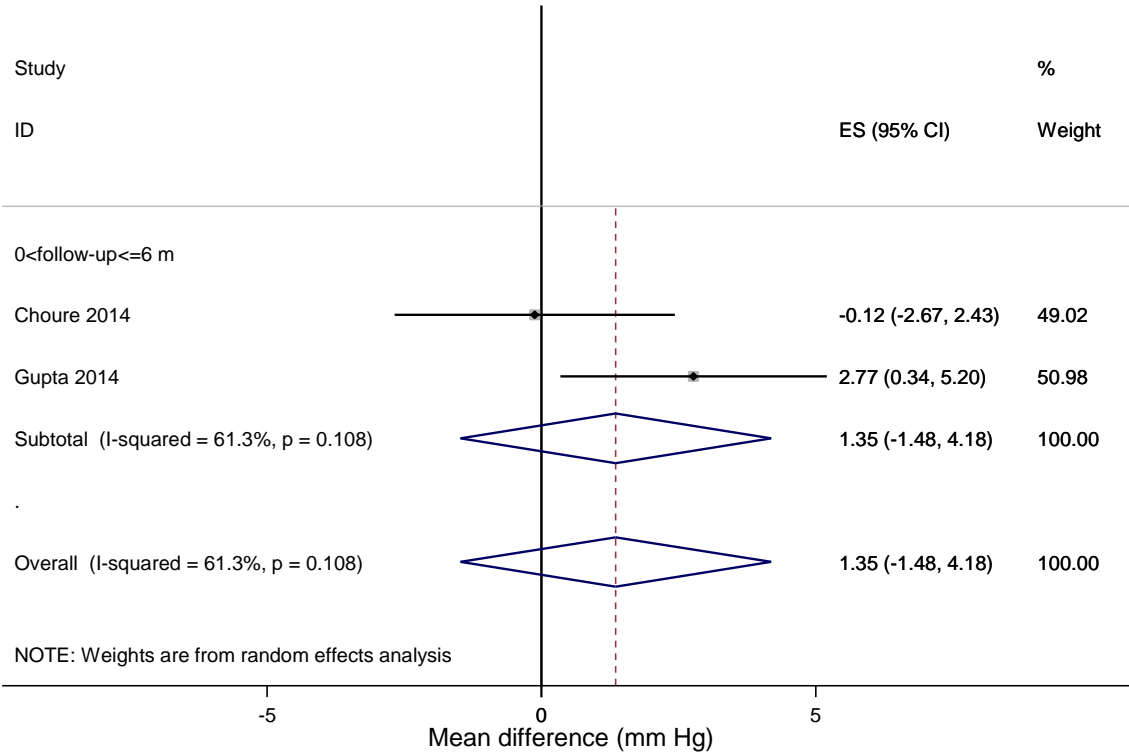
RISPERIDONE - Fasting glucose



RISPERIDONE - Systolic Blood Pressure



RISPERIDONE - Diastolic Blood Pressure



Clinical Drug Investigation

SECOND-GENERATION ANTIPSYCHOTIC DRUGS FOR PATIENTS WITH SCHIZOPHRENIA: SYSTEMATIC LITERATURE REVIEW AND META-ANALYSIS OF METABOLIC AND CARDIOVASCULAR SIDE EFFECTS

Carla Rognoni¹, Arianna Bertolani¹, Claudio Jommi¹

¹ Centre for Research on Health and Social Care Management (CERGAS), SDA Bocconi School of Management, Bocconi University, Milan, Italy

Supplementary Table 1 - Metabolic parameters derived by the considered studies

Study	Drug	Weight (kg)		BMI (kg/m ²)		Total cholesterol (mg/dL)		HDL cholesterol (mg/dL)		Triglycerides (mg/dL)		Fasting Glucose (mg/dL)		Systolic blood pressure (mm Hg)		Diastolic blood pressure (mm Hg)	
		Δ	SE	Δ	SE	Δ	SE	Δ	SE	Δ	SE	Δ	SE	Δ	SE	Δ	SE
Josiassen 2010[28]	aripiprazole	9.70	8.00	1.70	0.66												
Lee 2010[29]	aripiprazole	1.60	4.23									-6.00	5.17				
Lee 2011[30]	aripiprazole	2.38	4.53	0.87	1.63												
Zhang 2012[31]	aripiprazole	3.10	1.30	2.10	0.83	1.93		1.16		-15.04		10.81					
Jindal 2013[33]	aripiprazole					2.50	23.75			0.19	31.48						
Takekita 2013[32]	aripiprazole	0.00	0.00														
Gupta 2014[36]	aripiprazole	0.98	0.90					-1.13	0.98	5.86	4.18			0.84	2.09	1.00	2.04
Adams 2014[35]	aripiprazole	0.40	0.60	0.20	0.20												
Li 2014[34]	aripiprazole	0.80	2.30														
Perez-Iglesias 2014[38]	aripiprazole	4.30	4.80	1.50	1.70	12.60	28.40	1.30	13.50	1.00	45.40	-4.20	37.10				
Zhang 2014[37]	aripiprazole					0.00	7.73	-0.78	2.47	18.58	12.01	1.62	5.30				
Gründer 2016[39]	aripiprazole			0.34	1.21	0.00	33.63	0.77	9.67	-1.77	68.20						
Kishi 2016[41]	aripiprazole	1.47	3.23														
Malla 2016[40]	aripiprazole					8.85	6.49	-1.16	2.95	19.47	17.26	0.18	5.15				
Kumar 2017[42]	aripiprazole	-0.65	4.91	0.33	1.58												
Mustafa 2019[45]	aripiprazole	3.50	2.20														
Turangan 2019[43]	aripiprazole											-2.73	1.86				

Study	Drug	Weight (kg)		BMI (kg/m ²)		Total cholesterol (mg/dL)		HDL cholesterol (mg/dL)		Triglycerides (mg/dL)		Fasting Glucose (mg/dL)		Systolic blood pressure (mm Hg)		Diastolic blood pressure (mm Hg)	
Smith 2009[61]	olanzapine			1.39	0.51							7.34	3.15				
Bushe 2010[64]	olanzapine	1.03	5.80	0.36	2.00	6.57	33.63	-0.39	10.05	39.86	209.03						
Chiu 2010[63]	olanzapine	2.00	2.08	0.80	0.95	13.10	6.04	-1.10	3.41	24.50	16.78	2.60	2.58				
Gilles 2010[62]	olanzapine			1.30	1.59			-1.10	4.06	9.00	30.90	3.00	4.38				
Josiassen 2010[28]	olanzapine	10.70	12.23	1.80	0.89												
Smith 2010[65]	olanzapine					3.16	6.20	0.99	1.60	-12.61	17.10						
Fernandez-Egea 2011[69]	olanzapine	7.80	3.60														
Grootens 2011[67]	olanzapine	6.80	4.10			18.56	27.84			36.31	88.57	1.00	16.00	0.70	15.30	0.70	9.20
Krakowski 2011[66]	olanzapine					7.43	38.20										
Lee 2011[30]	olanzapine	3.80	3.89	1.40	1.46												
Meltzer 2011b[68]	olanzapine			2.00	0.04	11.90	0.60	1.60	0.18	45.60	1.77	9.80	0.51				
Meltzer 2011a[48]	olanzapine	4.10	4.30	1.40	1.40	9.60	31.20	-2.10	9.30	50.00	115.00	10.30	34.80				
Raposo 2011[70]	olanzapine	7.00	3.68	2.50	1.16	19.00	9.39	-9.00	3.84	35.00	11.44						
Alvarez 2012[78]	olanzapine	5.40	2.40	1.80													
Buchanan 2012[76]	olanzapine	2.90	0.40														
Buchanan 2012[76]	olanzapine	2.60	0.40														
Kaushal 2012[74]	olanzapine					12.54	0.60	-3.20	0.28	30.36	0.98	4.40	0.43				
Kusumi 2012[72]	olanzapine					10.00	26.10	-1.60	10.60	25.60	68.50	0.30	12.10				
Li 2012[34]	olanzapine	6.26	3.91	2.35	1.64												
Novick 2012[73]	olanzapine	3.20	8.50														
Paslakis 2012[71]	olanzapine			1.11	2.58							-3.99	6.79				
Schloemaker 2012[77]	olanzapine	5.40	1.78														
Schreiner 2012[75]	olanzapine	4.60		1.40				-1.80	1.13	33.40	8.54						
Hu 2013[80]	olanzapine	4.66	4.08	1.63	1.22	24.74	9.64	3.48	3.60	49.60	38.43	5.00	3.24				
Jindal 2013[33]	olanzapine					11.59	59.12			5.44	54.98						
Ou 2013[79]	olanzapine	4.23	1.31	1.59	0.36	18.20	36.29	4.25	13.51	31.90	64.61	6.67	10.63	0.34	7.38	-0.51	5.29
Choure 2014[82]	olanzapine													0.63	1.30	-3.00	1.78

Study	Drug	Weight (kg)		BMI (kg/m ²)		Total cholesterol (mg/dL)		HDL cholesterol (mg/dL)		Triglycerides (mg/dL)		Fasting Glucose (mg/dL)		Systolic blood pressure (mm Hg)		Diastolic blood pressure (mm Hg)	
Song 2014[104]	risperidone	6.01	1.69														
Kumar 2016[85]	risperidone	2.30	3.05			14.30	9.34					-1.70	5.71				
Kumar 2017[42]	risperidone	2.41	3.73	1.55	1.40												
Osborn 2018[89]	risperidone	5.90	0.08														
Osborn 2018[89]	risperidone	6.40	0.05														
Yuan 2018[105]	risperidone	6.10	4.42	1.46	1.77					22.12	27.36	3.60	3.98				
Cheng 2019[44]	risperidone	2.90	3.40														
de Almeida 2020[93]	risperidone			1.20	1.30												
Gao 2020[47]	risperidone	4.71	1.25														
Guan 2020[95]	risperidone	1.93	0.31			21.26	5.80	20.10	6.19	62.88	15.06	3.78	1.08				
Patel 2020[58]	risperidone flexibly dosed, 2–6 mg/day	1.50	5.10	0.60	1.80	-2.70	36.70	-2.00	9.40	9.70	106.20	4.40	19.00				

Δ: difference, SE: standard error, BMI: body mass index

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Supplementary Table 2 – Appraisal of risk of bias and level of evidence of the considered studies

Randomized Controlled Trials:

1. Was true randomization used for assignment of participants to treatment groups?
2. Was allocation to treatment groups concealed?
3. Were treatment groups similar at the baseline?
4. Were participants blind to treatment assignment?
5. Were those delivering treatment blind to treatment assignment?
6. Were outcomes assessors blind to treatment assignment?
7. Were treatment groups treated identically other than the intervention of interest?
8. Was follow up complete and if not, were differences between groups in terms of their follow up adequately described and analyzed?
9. Were participants analyzed in the groups to which they were randomized (Intention to treat analysis)?
10. Were outcomes measured in the same way for treatment groups?
11. Were outcomes measured in a reliable way?
12. Was appropriate statistical analysis used?

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Supplementary Table 3 – Scenario analysis performed considering only data from RCTs

Parameter	Drug					
	Aripiprazole	Lurasidone	Olanzapine	Paliperidone XR	Quetiapine XR	Risperidone
Δ Weight (Kg)	3.34 (-0.65, 7.34)	0.42 (-0.95, 1.79)	3.53* (2.89, 4.18)	0.53 (-1.70, 2.76)	1.86 (-2.19, 5.92)	1.89 (-1.15, 4.93)
Δ BMI (Kg/m ²)	1.68 (-0.45, 3.81)	-0.10 (-0.36, 0.16)	1.54* (0.74, 2.34)	0.44 (-0.69, 1.58)	0.68 (-0.56, 1.93)	0.61* (0.53, 0.69)
Δ Total cholesterol (mg/dL)	11.78 (-4.58, 28.14)	-8.01 (-9.45, -6.57)	11.83* (7.96, 15.69)	14.69 (-1.54, 30.92)	12.42 (-3.68, 28.51)	1.05 (-8.40, 10.50)
Δ Cholesterol HDL (mg/dL)	0.59 (-2.21, 3.40)	-2.05* (-2.47, -1.63)	-1.45 (-3.23, 0.32)	0.49 (-1.75, 2.72)	-3.84 (-8.43, 0.74)	-1.51 (-3.49, 0.46)
Δ Triglycerides	27.55* (0.77, 54.33)	-5.33* (-6.55, -4.10)	28.23* (14.69, 41.76)	18.31 (-22.07, 58.70)	48.70* (12.65, 84.75)	-3.69 (-26.38, 19.00)

(mg/dL)						
Δ Fasting glucose (mg/dL)	4.86* (1.04, 8.68)	1.78 (-18.39, 21.96)	7.59* (4.93, 10.25)	5.00 (-0.31, 10.31)	-0.47 (-6.50, 5.55)	3.61* (0.00, 7.22)
Δ Systolic blood pressure (mm Hg)	-	-0.61 (-1.32, 0.10)	1.38 (-5.18, 7.93)	-	-	-2.33 (-9.37, 4.71)
Δ Diastolic blood pressure (mm Hg)	-	0.13 (-0.24, 0.50)	0 (-0.41, 0.41)	-	-	-

BMI: body mass index, * statistical significance

Clinical Drug Investigation

SECOND-GENERATION ANTIPSYCHOTIC DRUGS FOR PATIENTS WITH SCHIZOPHRENIA: SYSTEMATIC LITERATURE REVIEW AND META-ANALYSIS OF METABOLIC AND CARDIOVASCULAR SIDE EFFECTS

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Supplementary Table 4 – Scenario analysis conducted excluding low-quality studies

Parameter	Drug					
	Aripiprazole	Lurasidone	Olanzapine	Paliperidone XR	Quetiapine XR	Risperidone
Δ Weight (Kg)	2.97* (0.38, 5.56)	0.43 (-0.93, 1.79)	3.81* (3.20, 4.42)	0.88 (-0.75, 2.51)	1.83* (0.37, 3.29)	2.05* (1.50, 2.60)
Δ BMI (Kg/m ²)	1.55 (-0.08, 3.17)	-0.10 (-0.35, 0.16)	1.69* (1.03, 2.35)	0.59 (-0.34, 1.53)	0.74 (-0.36, 1.85)	0.61* (0.53, 0.69)
Δ Total cholesterol (mg/dL)	11.67 (-0.01, 23.35)	-8.01* (-9.45, -6.57)	13.24* (9.81, 16.87)	14.69 (-1.54, 30.92)	10.55 (-0.33, 21.43)	4.40 (-4.46, 13.26)
Δ Cholesterol HDL (mg/dL)	-0.62 (-2.15, 0.90)	-2.05* (-2.47, -1.63)	-1.38 (-2.95, 0.20)	0.57 (-1.05, 2.19)	-1.74* (-2.92, -0.56)	-1.08 (-2.84, 0.67)
Δ Triglycerides	18.63* (1.67, 35.58)	-5.33* (-6.55, -4.10)	33.45* (21.84, 45.05)	7.15 (-14.96, 29.25)	14.25* (2.92, 25.59)	9.39 (-7.77, 26.54)

(mg/dL)						
Δ Fasting glucose (mg/dL)	0.19 (-4.22, 4.59)	1.78 (-18.39, 21.96)	6.31* (4.28, 8.34)	3.20* (0.10, 6.29)	-0.59 (-5.37, 4.18)	2.97* (0.30, 5.64)
Δ Systolic blood pressure (mm Hg)	0.84 (-3.25, 4.93)	-0.61 (-1.32, 0.10)	1.64 (-1.93, 5.21)	1.29 (-1.48, 4.06)	2.60* (0.04, 5.16)	1.07 (-1.12, 3.26)
Δ Diastolic blood pressure (mm Hg)	1.00 (-3.01, 5.01)	0.13 (-0.24, 0.50)	0.42 (-1.84, 2.68)	-	2.77* (0.35, 5.19)	1.35 (-1.48, 4.18)

BMI: body mass index, * statistical significance