Data supplement to Pillinger et al. Cholesterol and triglyceride levels in first-episode psychosis: systematic review and meta-analysis**.** Br J Psychiatry doi: 10.1192/bjp.bp.117.200907

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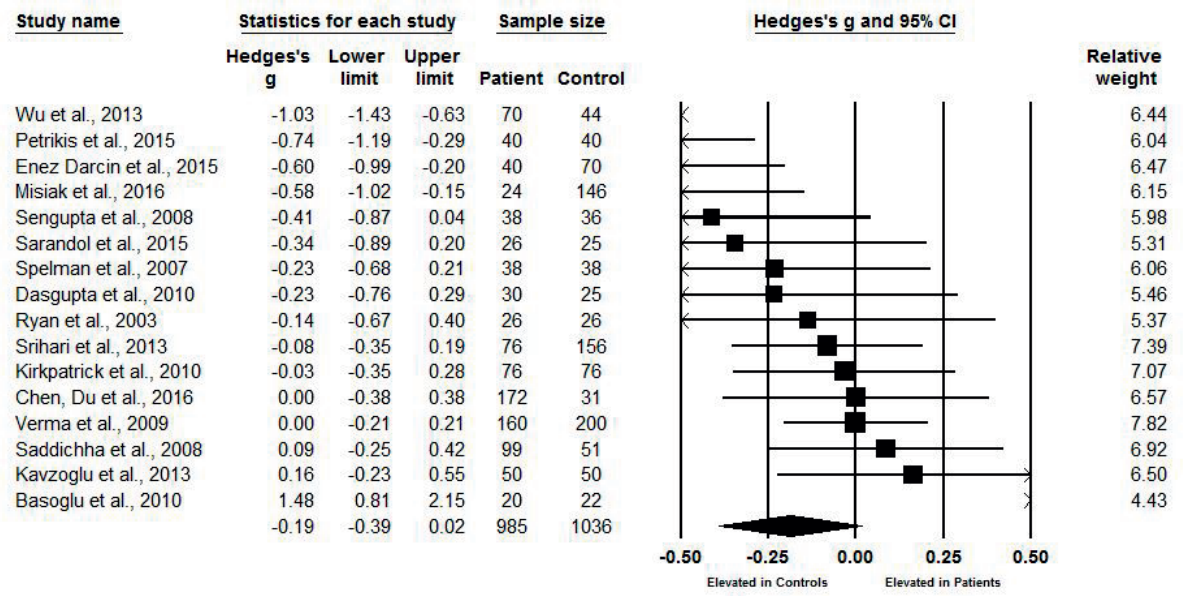
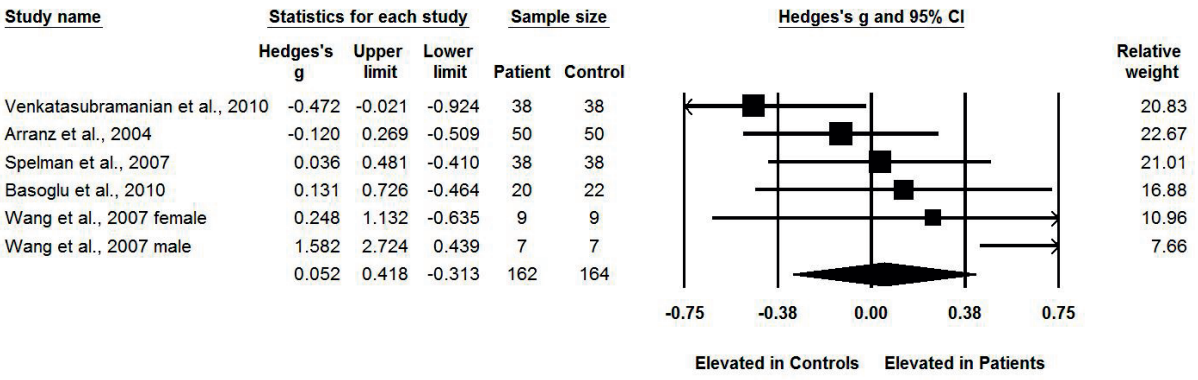
Fig. DS1 Forest plot showing HDL cholesterol concentration in patients with first episode schizophrenia and controls. HDL cholesterol concentration was not altered in patients compared with controls (Hedges g = -0.19; 95% CI -0.39 – 0.02; P = 0.072). Each square shows the effect size for a single study, with the horizontal line running through each square illustrating the width of the 95% CI. The size of the square reflects the weight attributed to each study. The diamond represents the summary effect size. The middle of the diamond represents the summary effect size, and the width of the diamond depicts the width of the overall 95% CI.



Study name	Hedges's g	Lower limit	Upper limit	Patient	Control	Relative weight
Wu et al., 2013	-1.03	-1.43	-0.63	70	44	6.44
Petrikis et al., 2015	-0.74	-1.19	-0.29	40	40	6.04
Enez Darcin et al., 2015	-0.60	-0.99	-0.20	40	70	6.47
Misiak et al., 2016	-0.58	-1.02	-0.15	24	146	6.15
Sengupta et al., 2008	-0.41	-0.87	0.04	38	36	5.98
Sarandol et al., 2015	-0.34	-0.89	0.20	26	25	5.31
Spelman et al., 2007	-0.23	-0.68	0.21	38	38	6.06
Dasgupta et al., 2010	-0.23	-0.76	0.29	30	25	5.46
Ryan et al., 2003	-0.14	-0.67	0.40	26	26	5.37
Srihari et al., 2013	-0.08	-0.35	0.19	76	156	7.39
Kirkpatrick et al., 2010	-0.03	-0.35	0.28	76	76	7.07
Chen, Du et al., 2016	0.00	-0.38	0.38	172	31	6.57
Verma et al., 2009	0.00	-0.21	0.21	160	200	7.82
Saddichha et al., 2008	0.09	-0.25	0.42	99	51	6.92
Kavzoglu et al., 2013	0.16	-0.23	0.55	50	50	6.50
Basoglu et al., 2010	1.48	0.81	2.15	20	22	4.43
	-0.19	-0.39	0.02	985	1036	

Fig. DS2 Forest plot showing leptin concentration in patients with first episode schizophrenia and controls. Leptin concentration was not altered in patients compared with controls (Hedges g = 0.05; 95% CI -0.31 – 0.42; p = 0.779). Each square shows the effect size for a single study, with the horizontal line running through each square illustrating the width of the 95% CI. The size of the square reflects the weight attributed to each study. The diamond represents the summary effect size. The middle of the diamond represents the summary effect size, and the width of the diamond depicts the width of the overall 95% CI.



Study name	Hedges's g	Upper limit	Lower limit	Patient	Control	Relative weight
Venkatasubramanian et al., 2010	-0.472	-0.021	-0.924	38	38	20.83
Arranz et al., 2004	-0.120	0.269	-0.509	50	50	22.67
Spelman et al., 2007	0.036	0.481	-0.410	38	38	21.01
Basoglu et al., 2010	0.131	0.726	-0.464	20	22	16.88
Wang et al., 2007 female	0.248	1.132	-0.635	9	9	10.96
Wang et al., 2007 male	1.582	2.724	0.439	7	7	7.66
	0.052	0.418	-0.313	162	164	

Table DS1 Raw data used in total cholesterol analysis

Study Name	Patient Mean	Patient SD	Patient Sample Size	Control Mean	Control SD	Control Sample size
Ryan et al., 2003(1)	4.02	0.78	26	4.57	0.81	26
Chen, Du et al., 2016(2)	4.4	0.9	172	4.2	1	31
Chen, Broqueres-You et al., 2016(3)	4.69	0.98	60	4.31	0.82	28
Petrikis et al., 2015(4)	188.21	46.92	40	196.96	43.57	40
Dasgupta et al., 2010(5)	157.6	42.88	30	169.2	17.08	25
Spelman et al., 2007(6)	4.3	0.9	38	4.4	0.6	38
Sengupta et al., 2008(7)	4.04	0.77	38	4.17	0.9	36
Verma et al., 2009(8)	4.7	1	160	5.1	0.9	200
Kirkpatrick et al., 2010(9)	168.1	34.8	76	175.4	32.2	76
Wu et al., 2013(10)	4.16	0.77	70	4.54	0.76	44
Srihari et al., 2013(11)	169.8	25.4	76	171.7	32	156
Venkatasubramanian et al., 2010(12)	170.7	32.5	38	172.2	34.1	38
Misiak et al., 2016(13)	4.22	0.85	24	4.49	0.89	146
Sarandol et al., 2015(14)	155	29	29	167	25	25
Kavzoglu et al., 2013(15)	171.92	31.17	50	174.92	35.33	50

Table DS2 Raw data used in LDL Cholesterol analysis

Study Name	Patient Mean	Patient SD	Patient Sample Size	Control Mean	Control SD	Control Sample size
Ryan et al., 2003(1)	2.39	0.84	26	2.91	0.69	26
Chen, Du et al., 2016(2)	2.6	0.7	172	2.7	0.8	31
Dasgupta et al., 2010(5)	89.14	37.01	30	101.55	18.43	25
Spelman et al., 2007(6)	2.9	0.9	38	2.8	0.6	38
Sengupta et al., 2008(7)	2.48	0.63	38	2.52	0.72	36
Verma et al., 2009(8)	2.7	0.9	160	3.1	0.8	200
Kirkpatrick et al., 2010(9)	99.6	31.4	76	105.8	28.8	76
Wu et al., 2013(10)	2.5	0.67	70	2.62	0.63	44
Basoglu et al., 2010(16)	96.9	34.2	20	90.1	18.3	22
Misiak et al., 2016(13)	2.17	0.60	24	2.34	0.76	146
Srihari et al., 2013(11)	91.8	10.2	76	96.2	16.3	156
Sarandol et al., 2015(14)	92	26	26	102	25	25
Kavzoglu et al., 2013(15)	109.85	29.27	50	107.08	30.05	50

Table DS3 Raw data used in HDL Cholesterol analysis

Study Name	Patient Mean	Patient SD	Patient Sample Size	Control Mean	Control SD	Control Sample size
Ryan et al., 2003(1)	1.2	0.44	26	1.25	0.25	26
Chen, Du et al., 2016(2)	1.4	0.3	172	1.4	0.2	31
Petrikis et al., 2015(4)	51.3	10.75	40	61.68	16.53	40
Enez Darcin 2015(17)	36	12.5	40	45	16.25	70
Dasgupta et al., 2010(5)	39.26	7.51	30	40.72	4.1	25
Spelman et al., 2007(6)	1.15	0.3	38	1.21	0.2	38
Sengupta et al., 2008(7)	1.06	0.26	38	1.19	0.36	36
Verma et al., 2009(8)	1.5	0.4	160	1.5	0.3	200
Saddichha et al., 2008(18)	36.4	8.9	99	35.6	10	51
Kirkpatrick et al., 2010(9)	51.5	17.3	76	52	12.6	76
Wu et al., 2013(10)	1.29	0.26	70	1.58	0.31	44
Basoglu et al., 2010(16)	43.3	9.1	20	31.9	5.8	22
Misiak et al., 2016(13)	1.41	0.41	24	1.69	0.49	146
Srihari et al., 2013(11)	50.9	10.7	76	51.9	13.2	156
Sarandol et al., 2015(14)	45	7	26	48	10	25
Kavzoglu et al., 2013(15)	46.69	13.14	50	44.58	12.39	50

eTable 4: Raw data used in triglyceride analysis

Study Name	Patient Mean	Patient SD	Patient Sample Size	Control Mean	Control SD	Control Sample size
Ryan et al., 2003(1)	0.99	0.43	26	0.92	0.3	26
Chen, Du et al., 2016(2)	1.2	0.7	172	1.1	0.7	31
Chen, Broqueres-You et al., 2016(3)	1.32	1.03	60	0.7	0.34	28
Petrikis et al., 2015(4)	93.29	51.87	40	85.54	40.88	40
Enez Darcin 2015	101	55	40	101	57	70
Dasgupta et al., 2010(5)	145.96	71.83	30	138.64	20.99	25
Spelman et al., 2007(6)	1.3	0.7	38	1.1	0.45	38
Sengupta et al., 2008(7)	1.1	0.65	38	1	0.72	36
Saddichha et al., 2008(18)	116.3	16.9	99	101.3	46.4	51
Kirkpatrick et al., 2010(9)	84.9	38.6	76	87.5	52.2	76
Wu et al., 2013(10)	1.12	0.75	70	0.99	0.41	44
Basoglu et al., 2010(16)	89.5	46.9	20	97.1	48.7	22
Venkatasubramanian et al., 2010(12)	119.2	58.7	38	105.3	59.2	38
Misiak et al., 2016(13)	1.44	0.95	24	1.09	0.55	146
Srihari et al., 2013(11)	89.5	16.7	76	92.9	20.2	156
Sarandol et al., 2015(14)	83	40	26	82	44	25
Kavzoglu et al., 2013(15)	93.62	44.04	50	118.44	70.04	50

Table DS5 Raw data used in leptin analysis

Study Name	Patient Mean	Patient SD	Patient Sample Size	Control Mean	Control SD	Control Sample size
Arranz et al., 2004(19)	1.13	6.43	50	1.8	4.46	50
Spelman et al., 2007(6)	3.7	2.3	38	3.6	3.2	38
Basoglu et al., 2010(16)	3.1	2.3	20	2.8	2.2	22
Venkatasubramanian et al., 2010(12)	7.6	10.7	38	12.9	11.5	38
Wang et al., 2007 male(20)	28.37	16.25	7	8.01	5.13	7
Wang et al., 2007 female(20)	19.26	22.38	9	14.56	12.19	9

Fig. DS3 Funnel Plot for total cholesterol analysis. The horizontal line indicates the average effect size, the diagonal lines represent the 95% confidence interval around the overall effect estimate.

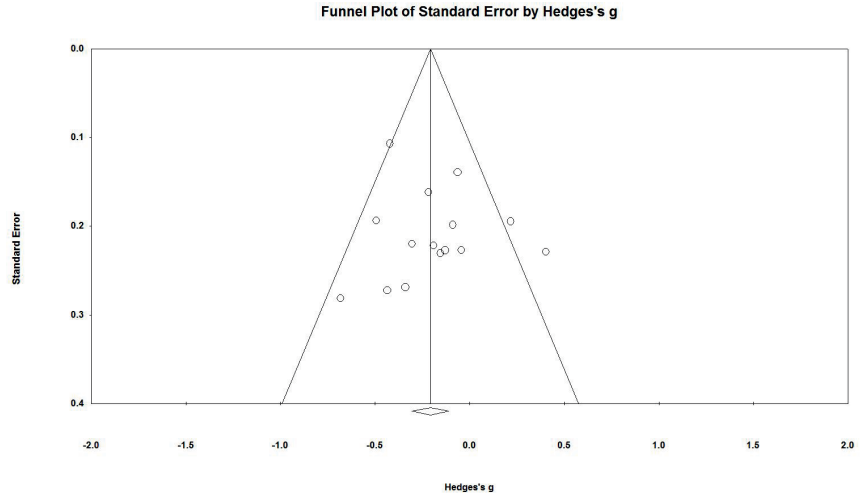


Fig. DS4 Funnel Plot for LDL cholesterol analysis. The horizontal line indicates the average effect size, the diagonal lines represent the 95% confidence interval around the overall effect estimate.

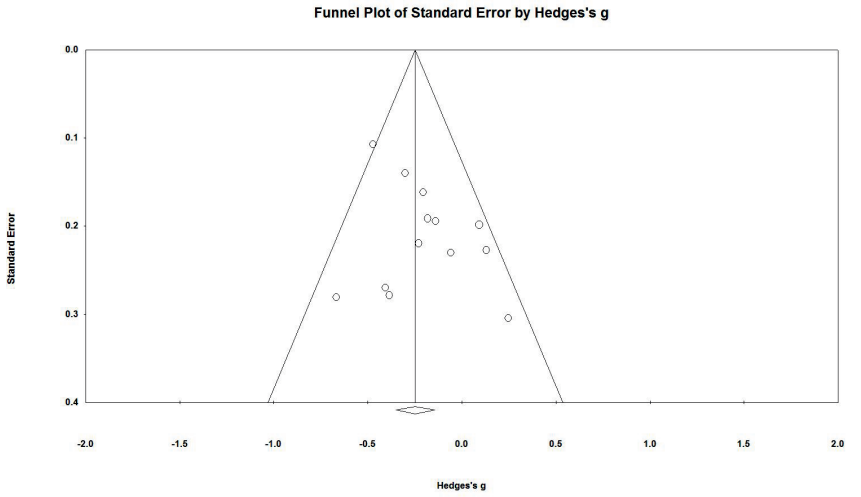


Fig. DS5 Funnel Plot for triglyceride analysis. The horizontal line indicates the average effect size, the diagonal lines represent the 95% confidence interval around the overall effect estimate.

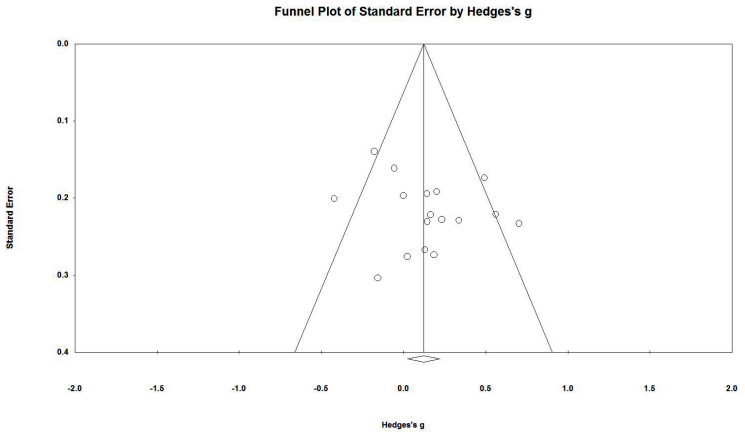


Fig. DS6 Funnel Plot for HDL cholesterol analysis. The horizontal line indicates the average effect size, the diagonal lines represent the 95% confidence interval around the overall effect estimate.

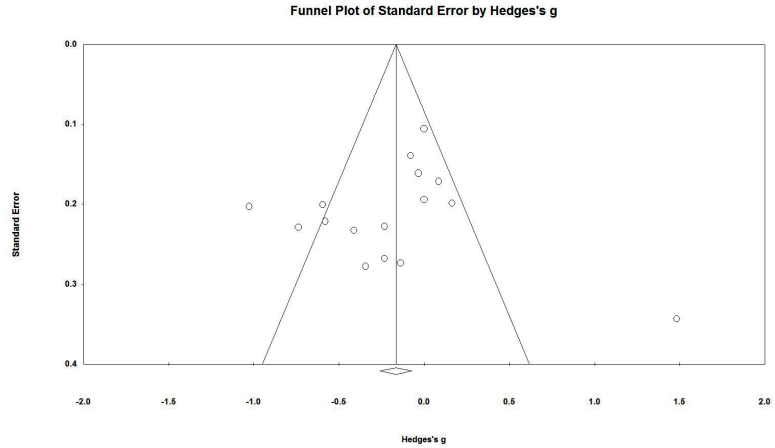


Fig. DS7 Funnel Plot for leptin analysis. The horizontal line indicates the average effect size, the diagonal lines represent the 95% confidence interval around the overall effect estimate.

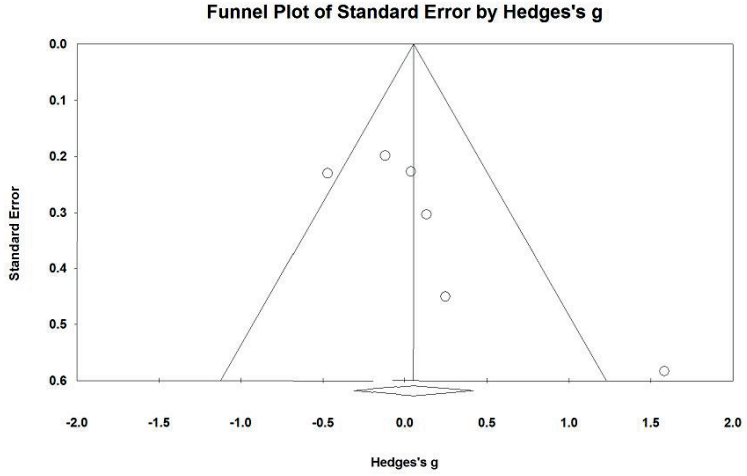


Fig. DS8 Scatterplot for regression of ES for total cholesterol on absolute difference in BMI between patient and control groups. BMI difference between the two cohorts was not a significant moderator of the total cholesterol effect size (β = 0.05; 95% CI = -0.30 – 0.40; P = 0.764). Each circle represents a study, its size corresponding to the study weight. Single straight line represents the regression coefficient, the curved lines the 95% confidence interval.

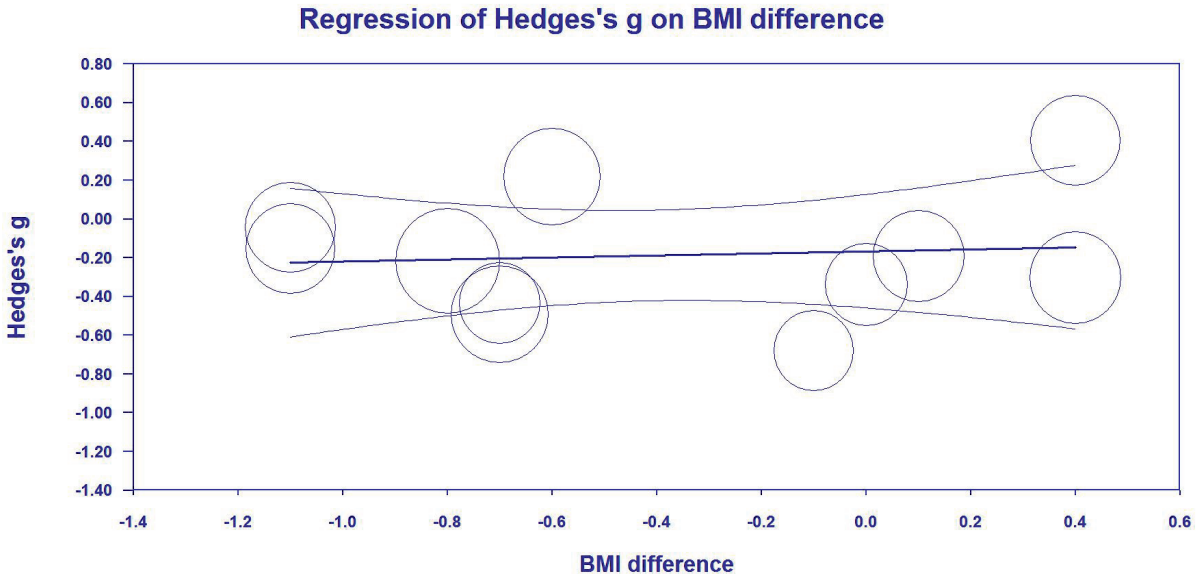


Fig. DS9 Scatterplot for regression of ES for LDL cholesterol on absolute difference in BMI between patient and control groups. BMI difference between the two cohorts was not a significant moderator of the LDL cholesterol effect size (β = -0.15; 95% CI -0.49 – 0.18; P = 0.377). Each circle represents a study, its size corresponding to the study weight. Single straight line represents the regression coefficient, the curved lines the 95% confidence interval.

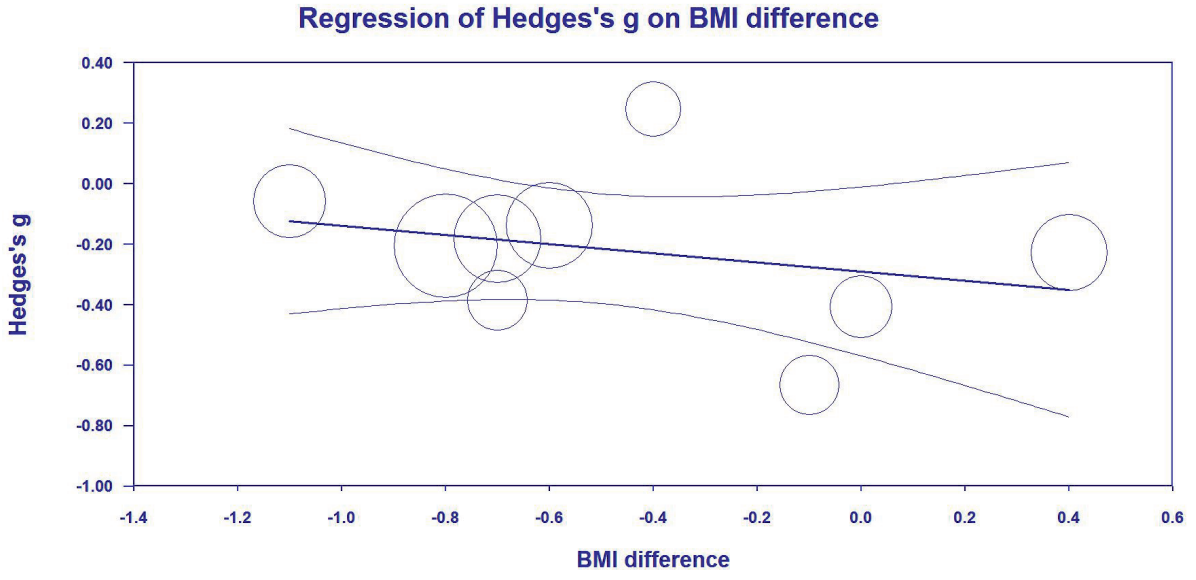


Fig. DS10 Scatterplot for regression of ES for triglycerides on absolute difference in BMI between patient and control groups. BMI difference between the two cohorts was a significant moderator of the triglyceride effect size (β = 0.29; 95% CI = 0.04 – 0.53; P = 0.024). Each circle represents a study, its size corresponding to the study weight. Single straight line represents the regression coefficient, the curved lines the 95% confidence interval.

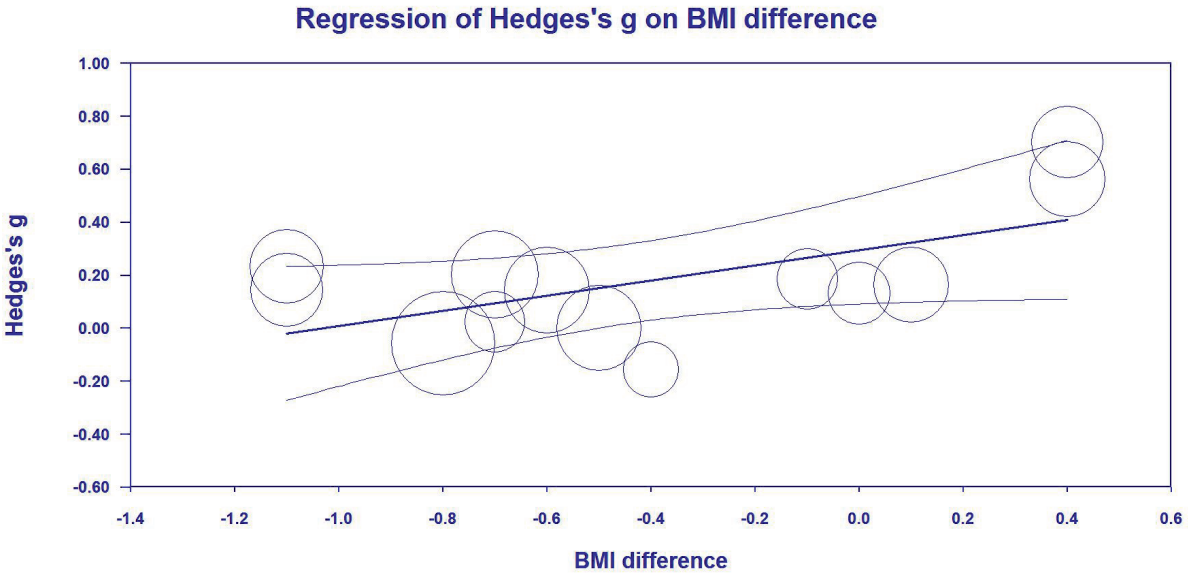


Fig. DS11 Scatterplot for regression of ES for HDL cholesterol on absolute difference in BMI between patient and control groups. BMI difference between the two cohorts was not a significant moderator of the HDL cholesterol effect size (β = -0.10; 95% CI -0.85 – 0.65; P = 0.790). Each circle represents a study, its size corresponding to the study weight. Single straight line represents the regression coefficient, the curved lines the 95% confidence interval.

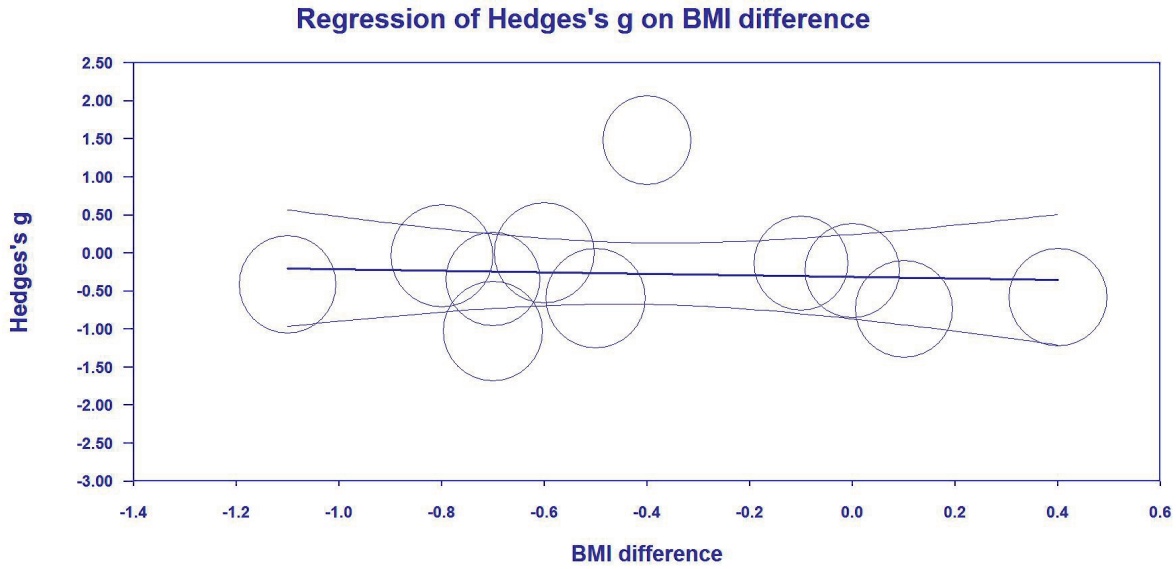


Table DS6 Raw data in SI units (mmol/L) for total cholesterol analysis (to allow for calculation of absolute differences in mean total cholesterol)

Study Name	Patient Mean	Patient SD	Patient Sample Size	Control Mean	Control SD	Control Sample size
Ryan et al., 2003(1)	4.02	0.78	26	4.57	0.81	26
Chen, Du et al., 2016(2)	4.4	0.9	172	4.2	1	31
Chen, Broqueres-You et al., 2016(3)	4.69	0.98	60	4.31	0.82	28
Petrikis et al., 2015(4)	3.06	1.22	40	5.10	1.13	40
Dasgupta et al., 2010(5)	4.08	1.11	30	4.38	0.44	25
Spelman et al., 2007(6)	4.3	0.9	38	4.4	0.6	38
Sengupta et al., 2008(7)	4.04	0.77	38	4.17	0.9	36
Verma et al., 2009(8)	4.7	1	160	5.1	0.9	200
Kirkpatrick et al., 2010(9)	4.4	0.9	76	4.5	0.8	76
Wu et al., 2013(10)	4.16	0.77	70	4.54	0.76	44
Srihari et al., 2013(11)	4.39	0.66	76	4.44	0.83	156
Venkatasubramanian et al., 2010(12)	4.4	0.8	38	4.5	0.9	38
Misiak et al., 2016(13)	4.22	0.85	24	4.49	0.89	146
Sarandol et al., 2015(14)	4.01	0.75	26	4.32	0.65	25
Kavzoglu et al., 2013(15)	4.45	0.81	50	4.52	0.91	50

Table DS7 Raw data in SI units (mmol/L) for LDL cholesterol analysis (to allow for calculation of absolute differences in mean LDL cholesterol)

Study Name	Patient Mean	Patient SD	Patient Sample Size	Control Mean	Control SD	Control Sample size
Ryan et al., 2003(1)	2.39	0.84	26	2.91	0.69	26
Chen, Du et al., 2016(2)	2.6	0.7	172	2.7	0.8	31
Dasgupta et al., 2010(5)	2.31	0.96	30	2.63	0.48	25
Spelman et al., 2007(6)	2.9	0.9	38	2.8	0.6	38
Sengupta et al., 2008(7)	2.48	0.63	38	2.52	0.72	36
Verma et al., 2009(8)	2.7	0.9	160	3.1	0.8	200
Kirkpatrick et al., 2010(9)	2.58	0.81	76	2.74	0.75	76
Wu et al., 2013(10)	2.5	0.67	70	2.62	0.63	44
Basoglu et al., 2010(16)	2.51	0.89	20	2.33	0.47	22
Misiak et al., 2016(13)	2.17	0.60	24	2.34	0.76	146
Srihari et al., 2013(11)	2.37	0.26	76	2.49	0.42	156
Sarandol et al., 2015(14)	2.38	0.67	26	2.64	0.65	25
Kavzoglu et al., 2013(15)	2.84	0.76	50	2.77	0.78	50

Table DS8 Raw data in SI units (mmol/L) for triglyceride analysis (to allow for calculation of absolute differences in mean triglyceride)

Study Name	Patient Mean	Patient SD	Patient Sample Size	Control Mean	Control SD	Control Sample size
Ryan et al., 2003(1)	0.99	0.43	26	0.92	0.3	26
Chen, Du et al., 2016(2)	1.2	0.7	172	1.1	0.7	31
Chen, Broqueres-You et al., 2016(3)	1.32	1.03	60	0.7	0.34	28
Petrikis et al., 2015(4)	1.05	0.59	40	0.97	0.46	40
Enez Darcin 2015	1.14	0.62	40	1.14	0.64	70
Dasgupta et al., 2010(5)	1.65	0.81	30	1.57	0.24	25
Spelman et al., 2007(6)	1.3	0.7	38	1.1	0.45	38
Sengupta et al., 2008(7)	1.1	0.65	38	1	0.72	36
Saddichha et al., 2008(18)	1.3	0.2	99	1.1	0.5	51
Kirkpatrick et al., 2010(9)	1.0	0.4	76	1.0	0.6	76
Wu et al., 2013(10)	1.12	0.75	70	0.99	0.41	44
Basoglu et al., 2010(16)	1.0	0.5	20	1.1	0.6	22
Venkatasubramanian et al., 2010(12)	1.4	0.7	38	1.2	0.7	38
Misiak et al., 2016(13)	1.44	0.95	24	1.09	0.55	146
Srihari et al., 2013	1.01	0.19	76	1.05	0.23	156
Sarandol et al., 2015(14)	0.94	0.45	26	0.93	0.50	25
Kavzoglu et al., 2013(15)	1.06	0.50	50	1.34	0.79	50

Table DS9 Summary of study characteristics with regards study definitions of first episode schizophrenia, anti-psychotic status, other neuroleptic drug status, physical health medication status, physical health status, lifestyle status, ethnicity, and other matching criteria. DUP: Duration of Untreated Psychosis; BMI: Body Mass Index.

	Setting	Definition of First Episode Schizophrenia	Anti-psychotic Status	Other neuroleptic use	Physical health medication	Physical health diagnoses	Documentation of Lifestyle	Matching for ethnicity	Other Matching Criteria	Plasma/serum	Fasting/non-fasting
Chen et al., 2016(2)	China	<60 months' duration of symptoms Mean (SD) DUP: 23.4 (19.1) months	Naïve	Not specified	Not specified but participants 'in good physical health'	Participants 'in good physical health…any subjects with medical illnesses were excluded'	Matched for education	Yes, all Han Chinese	BMI, age, ethnicity, sex, smoking	Plasma	Fasting
Petrikis et al., 2015(4)	Greece	Mean (SD) DUP: 10.72 (8.24) weeks	Naïve	Not specified	Not specified, but any disorder associated with insulin resistance an exclusion criterion	Participants with diabetes or any disorder associated with insulin resistance excluded	Not documented	Not specified	BMI, age, sex, smoking	Both Plasma and serum referred to in paper.	Fasting
Enez Darcin et al., 2015(17)	Turkey	Mean (SD) DUP: 1.7 (1.2) years Mean (SD) DUP: 1.7(1.2) years	Naïve	Not specified	Prescriptions for medical illnesses an exclusion criterion	Participants with severe medical illnesses excluded (defined as medical illness longer than 3-month duration)	Exercise status quantified in both groups	Not specified	BMI, age, smoking	Not specified for lipids	Fasting
Dasgupta et al., 2010(5)	India	First outpatient contact DUP not specified	Naïve	No mood stabilisers or antidepressants	Use of any medicine associated with insulin resistance an exclusion criterion	Participants with any somatic illness excluded	Groups of similar socio-economic status and dietary habits	'approximately similar ethnicity', but not quantified	BMI, age, sex	Serum	Fasting
Arranz et al., 2004(19)	Spain	First inpatient admission DUP not specified	Naive	No mood stabilisers or antidepressants	Any active treatment that could influence glucose	Participants with any physical illness excluded	Not documented	Not specified	BMI, sex	Plasma	Fasting

					homeostasis an exclusion criterion						
Ryan et al., 2003(1)	UK	First inpatient admission DUP not specified	Naïve	Not specified	Use of over-the- counter or prescribed medications an exclusion criterion	All participants documented as 'physically healthy'	Diet and exercise status quantified in both groups	Yes, all Caucasian	BMI, age, sex, smoking	Plasma	Fasting
Basoglu et al., 2010(16)	Turkey	<6 months' duration of symptoms DUP not specified	Naïve	Use of antiepileptic drugs	See next column	'having an important medical problem such as Wilson's disease, Down's syndrome, malnutrition, diabetes mellitus, chronic renal failure, cancer, liver cirrhosis and thyroid diseases, known endocrine illnesses, BMI greater than 30, severe neurological disorders such as epilepsy	Not documented	Not documented	Age, sex, smoking, BMI	Plasma	Fasting
Spelman et al., 2007(6)	Ireland	First inpatient admission. DUP not specified	Naïve	Not specified, but participants specified as receiving 'no form of prescribed or over the counter medication'	Use of over-the- counter or prescribed medications an exclusion criterion	All participants 'screened to exclude comorbid physical illness'	Diet and exercise status quantified	Yes, all Caucasian	Age, sex, smoking,	Not specified but leptin is plasma	Fasting
Kirkpatrick et al., 2010(9)	Spain	<12 months following first clinical contact DUP not specified	<7 days' total antipsychotic use	'not taking phenytoin'	'not taking medication associated with glucose intolerance or insulin resistance including hydrochlorthalidone, beta blockers, glucocorticoids, phenytoin, nicotinic acid,	No history of diabetes or any other serious medical condition associated with insulin resistance or/and glucose intolerance	Socioeconomic status	Not specified	Age, Sex, smoking, BMI	Not specified	Fasting

					cyclosporine, pentamidine, and narcotics'.						
Wang et al., 2007(20)	Taiwan	Mean (SD) DUP 2.0 (2.3) years	Naïve	Not documented	Not documented	Patients with any major physical illness or a history of alcohol or substance dependence were excluded	Not documented	Not documented	Age, sex, BMI	Plasma	Fasting
Venkatasubramanian et al., 2010(12)	India	Mean (SD) DUP 37.1(38.6) mo	Naïve	No psychotropic meds	Not documented	Physically healthy	Not documented	Not documented	BMI, age, sex, socio-economic status	Plasma	Fasting
Sengupta et al., 2008(7)	Canada	Median DUP: 25 weeks	<10 days of total antipsychotic use	Not documented	Not documented, but major physical illness an exclusion criterion	Participants with major physical illness excluded	Not documented	Yes, Caucasian	BMI, age, sex	Plasma	Fasting
Chen et al., 2016(3)	China	Duration of symptoms <3 years DUP not specified	<14 days' total antipsychotic use	No history of previous treatment with psychotropic drugs or, if previously treated, a total life time usage of less than 14 days	Not documented, but 'physically healthy with no other metabolic disorders'.	physically healthy and no other metabolic disorders	Not documented	Not documented	BMI, age, sex, smoking	Serum	Fasting
Wu et al., 2013(10)	China	Mean (SD) DUP 0.50 (0.02) years	Naïve	Not documented	Not documented although 'All patients received a thorough medical check-up to be physically healthy'	'All patients received a thorough medical check-up to be physically healthy'	Not specified	Not documented	BMI, age, gender, ethnicity	Plasma	Fasting
Verma et al., 2009(8)	Singapore	Mean (SD) DUP 18.3 (36.7) months	<3 days' total antipsychotic use	Not documented	Not documented	Not documented	Not documented	Yes	Age, gender, ethnicity	Plasma	Fasting

Misiak et al., 2016(13)	Poland	Mean (SD) DUP 60.2 (104.7) weeks	Naive	Not documented	Not documented	severe somatic health impairment an exclusion criterion	Not documented	Not documented	Age gender BMI	Serum	Fasting
Saddichha et al., 2008(18)	India	Mean (SD) DUP 20.5 ± 18.5 months	Naïve	Not documented	Not documented	History of severe physical illness an exclusion criterion	Diet and exercise	Not documented	Age, gender	Not documented	Fasting
Srihari et al., 2013(11)	USA	<5 years following onset of psychosis DUP not specified	Naïve	Not specified	Not specified	Not specified	Not specified	Yes	BMI, age, ethnicity, sex, smoking	Not specified	Fasting
Sarandol et al., 2015(14)	Turkey	First presentation with positive symptoms of hallucinations or delusions, DUP not specified	Naïve	Not specified	'taking anti-inflammatory medication' an exclusion criterion	'other concomitant illnesses (including active inflammatory illness)' an exclusion criterion.	Not specified	Not documented	Age, sex, smoking status,	Serum and Plasma	Fasting
Kavzoglu et al., 2013(15)	Turkey	First hospital admission, DUP not specified	Up to 72 hours' total antipsychotic use	Not specified	Not specified	Stipulation of study: Participants only included if 'no significant disease was detected in the general internal medicine examination and who did not report any former diagnosis or treatment for a chronic cardiovascular, endocrinologic, hematologic, neurological or renal condition,'	Not specified	Not specified	Age, sex, BMI, smoking	Serum	Fasting

Data was not forthcoming from any of the studies that included individuals with minimal antipsychotic exposure regarding which antipsychotics had been prescribed, and therefore an association between our lipid findings with use of specific antipsychotics was not possible.

Table DS10 Quality assessment of studies included in meta-analysis. Newcastle Ottowa Quality Assessment scale, and assessments of study rigour with regards confirmation of patient participant status, biochemical analysis validity, quality of healthy control selection, and confirmation regarding duration of fasting pre-venepuncture, and in what environment this fast was performed (inpatient or outpatient).

Author/Year	Study Type	Selection				Comparability	Exposure			Score/9	Confirmation of Psychosis?	Lab quality?	Quality of healthy control	Fasting status? In or outpatient?
		1	2	3	4	(max 2)	1	2	3					
Chen et al., 2016(2)	Case Control	1	1	1	1	2	1	1	1	9	Yes – 2 independent psychiatrists followed up to 3 months using DSM-IV criteria for SCZ	Automatic Biochemical Analyzer (Beckman Coulter AU5811; Beckman Coulter, Inc., USA).	Advert – people from local area. Matched gender age and education	Inpatient: 12h fast
Petrikis et al., 2015(4)	Case Control	1	1	1	1	2	1	1	1	9	Psychiatric diagnosis was established independently by two experienced psychiatrists using the Structured Clinical Interview for DSM-IV (SCID).	Olympus AU5400 analyzer (Beckman-Brea-California-USA) and reagents supplied by Beckman	Advert - advertising amongst Ioannina University students and employees as well as from local enterprise employees	Outpatient 10h fast
Srihari et al., 2013(11)	Case Control	1	1	1	0	2	1	0	1	7	SCID at baseline and follow-up 1 year	Not documented	NHANES – physical comorbidity not documented	Outpatient 8h fast
Enez Darcin et al., 2015(17)	Case Control	1	1	1	1	2	0	0	0	6	DSM-IV Criteria for schizophrenia	Not documented	relatives of the clinical staff	Outpatient 12h fast
Dasgupta et al., 2010(5)	Case Control	1	1	1	1	2	0	1	1	8	DSM-IV diagnosis	autoanalyser ERBA XL 600 Bio-Rad lab USA	persons accompanying the patients in OPD who were free from any metabolic or	Outpatient 12h fast

													psychiatric disorders. Relatives of the patients were excluded during this selection	
Arranz et al., 2004(19)	Case Control	1	1	0	1	1	0	0	1	5	DSM IV diagnosis after 6 months	Plasma leptin: Linco research Inc	Hospital staff	Inpatient, fasting
Ryan et al., 2003(1)	Case Control	1	1	1	1	2	1	1	1	9	DSM IV diagnosis	Roche Diagnostics GmbH, Mannheim, Germany	Hospital and university staff, and local community	Inpatient 12h fast
Basoglu et al., 2010(16)	Case Control	1	1	0	1	2	0	1	1	7	DSM-IV criteria of Schizophrenia	Beckman-Coulter Synchron LX-20 Automated Analyser (Beckman Coulter Inc., Palo Alto, California, USA)	Army recruits	Inpatient 12h fast
Kirkpatrick et al., 2010(9)	Case Control	1	0	1	1	2	0	0	1	6	DSM-IV criteria	Not specified	Advertisements (unclear if community or hospital)	Overnight fast
Spelman et al., 2007(6)	Case Control	1	0	1	1	2	0	1	1	7	DSM-IV criteria	Measured according to accurate SOP	Community	12h overnight fast
Wang et al., 2007(20)	Case Control	1	0	1	1	2	0	0	1	6	DSM-IV criteria	direct sandwich ELISA (Linco Research, St. Charles, Mo., USA).	Community	Outpatient 9am ?fasting One patient - afternoon
Saddichha et al., 2008(18)	Case Control	1	1	1	1	1	0	1	1	7	DSM-IV criteria	Not specified	Community attenders of patients attending our OPD consecutively, who were not related to the subject under investigation	Inpatient Overnight fast

Sengupta et al., 2008(7)	Case Control	1	0	0	1	1	0	1	1	5	DSMI IV diagnosis	EDTA tubes	Local universities, hospital employees, and general population	12h fast
Venkatasubramanian et al., 2010(12)	Case Control	1	0	0	1	2	0	1	1	6	DSMI IV diagnosis	Olympus AU400 analyzer, Enzyme-linked immunosorbent assay was used to quantify leptin level (Biosource Europe S.A., Nivelles, Belgium)	'word of mouth'	12h fast
Chen et al., 2016(3)	Case Control	1	0	0	0	1	0	1	1	4	DSMI IV diagnosis	Olympus AU2700 automatic biochemical analyser (Beckman Coulter Inc., USA).	Not specified	Inpatient 'overnight fast'
Wu et al., 2013(10)	Case Control	1	1	0	1	2	0	1	1	7	DSMI IV diagnosis	Sichuan Maker Biotechnology Co., Ltd. Chengdu, China	University students, hospital employees, local enterprise employees	Inpatient 12h overnight fast
Verma et al., 2009(8)	Case Control	1	0	0	0	1	0	1	1	4	DSM IV diagnosis	SYNCHRON LX System(s), UniCel DxC 600/800 System(s), and SYNCHRON Systems Lipid Calibrator	Hospital workers	12h overnight fast
Misiak et al., 2016(13)	Case Control	1	1	0	0	1	0	1	1	5	DSM IV diagnosis	Cobas 6000 analyzer (Roche, Switzerland).	Not specified	10h overnight fast
Sarandol et al., 2015(14)	Case Control	1	0	0	1	2	1	1	0	6	DSM IV diagnosis	Architect c 16 000 and Architect	University Staff	Overnight fast

												i2000 (Abbott Lab., Dallas, TX, USA).		
Kavzoglu et al., 2013(15)	Case Control	1	0	0	1	2	0	1	1	5	DSM IV diagnosis	ERTHN biochemistry laboratory with standard enzymatic procedures,	Not specified	Inpatient 8h fast

Newcastle Ottawa Scale: A study can be awarded a maximum of four stars for selection (four questions relate to whether the case definition is adequate, the representativeness of the cases, the selection of controls and definition of controls), a maximum of two stars for comparability (cases and controls must be matched in the design and/or confounders must be adjusted for in the analysis) and a maximum of three stars for exposure (ascertainment of exposure, same method of ascertainment for cases and controls, non-response rate).

DATA SUPPLEMENT DS1

Protocol (a priori)

Working title:

Lipid status in first episode psychosis: a systematic review and meta-analysis

Type of review:

Systematic review and meta-analysis

Language:

English

Key words:

Schizophrenia, psychosis, metabolic, lipid, cholesterol, triglycerides

Details of any existing review of the same topic by the same authors:

None

Start date:

1st November 2016

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Funding Sources:

MRC-UK, Maudsley Charity, Brain&Behavior Research Foundation, Wellcome Trust.

Conflicts of Interest:

Dr Howes has received investigator-initiated research funding from and/or participated in advisory/ speaker meetings organised by Astra-Zeneca, Autifony, BMS, Eli Lilly, Heptares, Janssen, Lundbeck, Lyden-Delta, Otsuka, Servier, Sunovion, Rand and Roche. Neither Professor Howes nor his family have been employed by or have holdings/a financial stake in any biomedical company. Drs Pillinger, Beck and Stubbs report no financial relationships with commercial interests.

Review Question:

The extent of metabolic and lipid changes in first episode psychosis (FEP) is unclear. We plan to **c**onduct a meta-analysis examining if individuals with FEP and no or minimal antipsychotic exposure show lipid and adipocytokine abnormalities compared with healthy controls.

Searches:

MEDLINE, EMBASE and PsycINFO will be searched using the following keywords: ('schizophrenia' OR 'schizoaffective' OR 'psychosis') AND ('early' OR 'first episode' OR 'risk' OR 'prodrome') AND ('metabolic' OR 'lipid' OR 'cholesterol' OR 'HDL' OR 'LDL' OR 'lipoprotein' OR 'triglyceride' OR 'adiponectin' OR 'ghrelin' OR 'leptin' OR 'resistin' OR 'chemerin' OR 'omentin' OR 'apelin' or 'adipocytokine' OR 'adipokine')

Searches will be complemented by hand-searching of meta-analyses and review articles published in the field of cardiometabolic risk in psychotic illness and agreed by the authors. These papers are:

1. Mitchell AJ, Vancampfort D, De Herdt A, Yu W, De Hert M. Is the prevalence of metabolic syndrome and metabolic abnormalities increased in early schizophrenia? A comparative meta-analysis of first episode, untreated and treated patients. *Schizophr Bull* 2013; **39**(2): 295-305.
2. Mitchell AJ, Vancampfort D, Sweers K, van Winkel R, Yu W, De Hert M. Prevalence of metabolic syndrome and metabolic abnormalities in schizophrenia and related disorders--a systematic review and meta-analysis. *Schizophr Bull* 2013; **39**(2): 306-18.
3. Vancampfort D, Correll CU, Galling B, et al. Diabetes mellitus in people with schizophrenia, bipolar disorder and major depressive disorder: a systematic review and large scale meta-analysis. *World Psychiatry* 2016; **15**(2): 166-74.
4. Stubbs B, Vancampfort D, De Hert M, Mitchell AJ. The prevalence and predictors of type two diabetes mellitus in people with schizophrenia: a systematic review and comparative meta-analysis. *Acta Psychiatr Scand* 2015; **132**(2): 144-57.
5. Vancampfort D, Stubbs B, Mitchell AJ, et al. Risk of metabolic syndrome and its components in people with schizophrenia and related psychotic disorders, bipolar disorder and major depressive disorder: a systematic review and meta-analysis. *World Psychiatry* 2015; **14**(3): 339-47.

6. Pillinger T, Beck K, Gobjila C, Donocik JG, Jauhar S, Howes OD. Impaired Glucose Homeostasis in First-Episode Schizophrenia: A Systematic Review and Meta-analysis. *In submission.*
7. De Hert M, Schreurs V, Vancampfort D, R VANW. Metabolic syndrome in people with schizophrenia: a review. *World Psychiatry* 2009; **8**(1): 15-22.

Condition being studied:

Lipid parameters in First Episode Psychosis (FEP) and individuals at-risk mental state for psychosis (ARMS) compared with healthy controls will be examined. We plan to study the following lipid parameters: concentration of total cholesterol, high-density lipoprotein (HDL) cholesterol, low-density lipoprotein (LDL) cholesterol, triglycerides, adiponectin, ghrelin, leptin, resistin, chemerin, omentin, or apelin. Both fasting and non-fasting values will be accepted.

Participants/Population, and Comparator/Control:

Inclusion criteria for patients with FEP/ARMS will be defined as follows:

1) a Diagnostic and Statistical Manual of Mental Disorders (DSM) or International Statistical Classification of Diseases and Related Health Problems (ICD) diagnosis of schizophrenia, schizoaffective disorder schizophreniform disorder, schizophrenia spectrum or psychotic disorder not otherwise specified OR an at-risk mental state for psychosis
2) first episode of illness (defined either as first treatment contact (inpatient or outpatient) or duration of illness up to 5 years following illness onset)
3) antipsychotic naïve or minimal exposure (≤2 weeks total antipsychotic treatment)

Exclusion criteria for patients with FEP/ARMS will be defined as follows:

1) patients with multiple episodes of schizophrenia
2) chronic antipsychotic treatment (>2-weeks lifetime exposure)
3) substance or medication induced psychotic disorder
4) physical co-morbidity that may impact on lipid homeostasis (e.g. familial hypercholesterolemia, thyroid dysfunction, nephrotic syndrome)

Healthy controls must also satisfy criteria of having no physical co-morbidity that may impact on lipid homeostasis.

Primary Outcomes:

The following lipid parameters will be examined: concentration of total cholesterol, high-density lipoprotein (HDL) cholesterol, low-density lipoprotein (LDL) cholesterol, triglycerides, adiponectin, ghrelin, leptin, resistin, chemerin, omentin, or apelin. Both fasting and non-fasting values will be accepted. Studies not reporting absolute values (i.e. studies that only provided data regarding the dichotomous presence/absence of raised lipid parameters as defined by diagnostic criteria) will be excluded.

Data Extraction:

Screening based on title and abstract will be performed independently by two authors (T.P. and K.B.). Where full texts, abstracts or group estimate data are not available, authors will be contacted and articles/data requested. We will allow 4 weeks for authors to respond, with repeat contact attempts made after 2 weeks.

Data extraction will be performed independently (by T.P. and K.B.), and any disagreements will be resolved by rechecking original articles. For every study, data will be extracted according to the following model: author,

year of publication, country, type of publication (i.e. prospective, cross-sectional, case-control, retrospective), matching criteria for patients and controls (confirmed by review of study methodology, or by confirmation of non-significance between mean parameter levels of patient and control groups (a two tailed P value ≤0·05 was deemed significant)), whether or not patient groups are totally antipsychotic naïve (and if not, duration of treatment), and mean (with standard deviation) measure of lipid/adipocytokine parameter in patient and control groups. Where there are multiple publications for the same data set, data will be extracted from the study with the largest data set.

Risk of Bias Assessment:

Publication bias and selective reporting will be assessed using Egger's test of the intercept (although this will not be calculated when fewer than 10 studies are analysed as recommended by the Cochrane Collaboration), and represented diagrammatically with funnel plots.

Strategy for Data Synthesis:

Comprehensive Meta-Analysis Software version 3.0 (CMA, Bornstein, USA) will be employed in all analyses. A two-tailed p value less than 0.05 ill be deemed significant. A random-effects model will be used in all analyses owing to an expectation of heterogeneity of data across studies. Standardised mean differences in lipid parameters and adipocytokine levels between patient and control cohorts ill be used as the effect size (ES), using Hedges' adjusted g and 95% confidence interval (95% CI).

Analysis of subgroups of subsets:

To address whether or not differences in body mass index (BMI) or dietary intake between patient and control groups influence results, separate sensitivity analyses examining groups matched for BMI and dietary intake will be performed. Matching will either be confirmed by review of study methodology, or by confirmation of no significant difference between mean parameters in patient and control groups (a two tailed p value less than 0.05 deemed significant). To further investigate the influence of difference in BMI between patient and control groups on lipid parameter effect size, random effects meta-regression analyses will be performed, regressing lipid parameter effect size on difference in BMI between patient and control groups. Meta-regression will not be performed when fewer than 10 studies are analysed as recommended by the Cochrane Collaboration.

Studies and data not included in meta-analysis

Two studies that met inclusion criteria were identified as using data already included in the meta-analysis and were therefore excluded.(21, 22)

One study that examined glucose homeostasis in first episode psychosis was excluded as the definition of psychosis did not use ICD/DSM criteria.(23)

Six studies were unable to provide data/did not respond to request for data by time of submission.(15, 24-28)

One study, although had data included in the meta-analysis for total cholesterol and triglyceride levels, were unable to provide data for HDL and LDL cholesterol levels after approach.(3)

Sensitivity Analyses

Sensitivity analyses with removal of 4 studies where recruitment strategy for controls not specified (3, 12, 13, 15)

Reduced total cholesterol in patients compared with controls (g = -0.25; 95% CI -0.39 - -0.11; P = 0.001)

Reduced LDL cholesterol in patients compared with controls (g = -0.25; 95% CI -0.39 - -0.12; P < 0.001)

No difference in HDL cholesterol between patients and controls (g = -0.19; 95% CI -0.41 - -0.04; P = 0.101)

Increased triglycerides in patients compared with controls (g = 0.14; 95% CI 0.01 - 0.28; P = 0.036)

Sensitivity analyses with removal of 6 studies where fasting duration was not specified (3, 9, 14, 18-20)

Reduced cholesterol in patients compared with controls (g = -0.22; 95% CI -0.36 - -0.08; P = 0.002)

Reduced LDL cholesterol in patients compared with controls (g = -0.26; 95% CI -0.40 - -0.12; P < 0.001)

No difference in HDL cholesterol between patients and controls (g = -0.21; 95% CI -0.46 - -0.04; P = 0.096)

No difference in triglycerides in patients compared with controls (g = 0.09; 95% CI -0.06 - 0.23; P = 0.227)

No difference in leptin levels in patients compared with controls (g = -0.13; 95% CI -0.50 – 0.25; P = 0.512).

Further information regarding inclusion/exclusion criteria rationale

Our inclusion of participants with up to 5 years' duration of illness, is in keeping with first episode services in the UK and the expert review of the operational definition of First Episode Psychosis by Breitborde and colleagues(29), who state: *'…the term is typically used to refer to individuals who have experienced a short duration of illness (e.g. 2–5 years)'*.

Our inclusion of patients who had received minimal antipsychotic medication (up to 2 weeks' total antipsychotic use) was a pragmatic decision based on a real-world expectation that a proportion of individuals included within analyses would have received some treatment by time of lipid assay. Longitudinal studies examining previously antipsychotic naïve FEP report evidence of lipid dysregulation 8-12 weeks after initiation of treatment(30-32), although pre-clinical studies have reported weight gain and increase in triglyceride levels in rats 2 weeks after introduction of olanzapine or aripiprazole(33, 34).'

MOOSE CHECKLIST

Criteria	Brief description of how the criteria were handled in the meta-analysis
Reporting of background should include	
Problem definition	The presence and extent of metabolic and lipid changes in first episode antipsychotic naïve schizophrenia is unclear. We set out to **c**onduct a meta-analysis to determine if individuals with first episode schizophrenia with no or minimal antipsychotic exposure show lipid abnormalities and derangements in adipocytokine activity compared with healthy controls.
Hypothesis statement	Abnormalities in lipid and adipocytokine parameters may occur in the absence of the effects of chronic illness and long-term treatment.
Description of study outcomes	Standardised mean differences in total cholesterol, LDL cholesterol, HDL cholesterol, triglycerides and leptin levels in individuals with first episode schizophrenia (with no or minimal antipsychotic exposure) vs healthy controls were calculated.
Type of exposure or intervention used	N/A
Type of study designs used	All study designs were included, but only case-control studies were identified.
Study Population	Drug naïve (up to 2 weeks' total antipsychotic lifetime exposure) first episode schizophrenia, and healthy controls.
Reporting of search strategy should include	
Qualifications of searchers	Indicated in the authors list.
Search strategy, including time period included in the synthesis and key words	Major electronic databases were searched from inception to December 2016 for case control studies examining lipid and adipocytokine parameters in individuals with first episode schizophrenia versus healthy controls. Key words and inclusion/exclusion criteria are described in methods section.
Databases and registries searched	MEDLINE, EMBASE and PsycINFO were searched.
Search Software used, name and version	https://ovidsp.uk.ovid.com/
Use of hand searching	The search was complemented by hand-searching of meta-analyses and review articles
List of citations located and those excluded, including justifications	Detailed in flow chart (figure 1), with further supplemental information provided in Supplementary Information (eAppendix).
Method of addressing articles published in languages other than English	No language restrictions were in place, although all the included papers were in English
Methods of handling abstracts and unpublished studies	We contacted a number of authors for full report of relevant unpublished studies.
Reporting of methods should include	
Description of relevance or appropriateness of studies assembled for assessing the hypothesis to be tested	Detailed inclusion and exclusion criteria are described in the methods section.
Rationale for the selection and coding of data	A data extraction sheet was developed (available on request). Data on study characteristics, methodological quality and results were independently extracted from each selected article.
Assessment of confounding	We conducted sub-group analyses examining studies where participants were BMI matched, as

	well as meta-regression analyses examining the role of difference in BMI between patients and controls in moderating changes in lipid parameters.
Assessment of study quality	Bias was assessed using Egger's test of the intercept and represented diagrammatically with Funnel Plots.
Assessment of heterogeneity	The I^2 value was used to assess heterogeneity.
Description of statistical methods in sufficient detail to be replicated	We mentioned the type of analysis we used, and the type of software utilised. Raw data is presented in the appendix.
Provision of appropriate tables and graphics	Figures 2, 3, and 4 in the manuscript describe the main outcomes of the study (total cholesterol, LDL and TG). Table 1 describes the demographics of the studies used in the meta-analysis. eFigures 1 and 2 (supplementary information) provide additional meta-analyses (HDL and leptin). eFigures 3-7 (supplementary information) show funnel plots for each meta-analysis. eFigures 8-11 (supplementary information) show scatter plots for each meta-regression analysis.
Reporting of results should include	
Graph summarising individual study estimates and overall estimate	Figures 2, 3 and 4 of the main manuscript and eFigures 1 and 2 of Supplementary Information.
Table giving descriptive information for each study included	Table 1
Results of sensitivity testing	Described in results (sensitivity analyses for BMI matched studies).
Indication of statistical uncertainty of findings	95% confidence intervals were presented for all analyses with P values together with I^2 values for the meta-analyses.
Reporting of discussion should include	
Quantitative assessment of bias	Risk of publication bias was assessed using Egger's test of the intercept and represented diagrammatically with Funnel Plots (eFigures 3-7 of Supplementary Information).
Justification for Exclusion	Reasons for exclusion were reported in Figure 1, and in Supplementary Information (eAppendix).
Assessment of quality of included studies	In addition to assessment of bias, discussed in context of limitations in discussion section.
Reporting of conclusions should involve	
Considerations of alternative explanations for observed results	In depth discussion of the potential pathoaetiological mechanisms driving the observations provided.
Generalisation of the conclusions	Provided in discussion.
Guidelines for future research	Provided in discussion.
Disclosure of funding source	Funding statement was provided.

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