Supplementary Material

Supplementary Table 1: Inclusion and exclusion criteria for primary studies

Inclusion Criteria	Randomised controlled trials, non-randomised trials, observational studies Samples genotypes for CYP2D6 functional polymorphisms Blood/plasma prolactin levels measured and reported Patients treated with antipsychotics or healthy volunteers given a single oral dose of antipsychotic
Exclusion Criteria	Single case report, narrative reviews, systematic reviews, opinions, editorials, conference abstracts, in vitro studies Participants not genotyped for CYP2D6 gene Prolactin levels not measured/reported Studies in which Aripiprazole was used, since despite being metabolised by CYP2D6, it tends to decrease prolactin levels

Supplementary Table 2: CYP2D6 phenotypes

Phenotype	Genotype
Poor Metaboliser (PM)	mt/mt
Intermediate Metaboliser (IM)	mt/red
Extensive/Normal Metaboliser (EM)	wt/wt, wt/DUPred, red/DUPred, red/red, mt/wt, mut/DUPred
Ultra-rapid Metaboliser (UM)	wt/wtDUP, red/wtDUP

wt = normal function allele (*1 and *2), mt = non-functional allele (*3, *4, *5,*6, *7, *8, *11 and *15), red = reduced function allele (*9, *10, *17, *29 and *41) , DUPwt = duplication of normal function allele, DUPred = duplication of reduced function allele
(Bertilsson *et al.* 2002; Stingl & Viviani 2015; Hicks *et al.* 2015).

Overview of the sixteen informative studies

The number of subjects genotyped in each study ranged from 22 to 150. Five of the 16 studies were conducted in children (dos Santos Júnior et al., 2015; Roke et al., 2013; Sukasem et al., 2016; Troost et al., 2007; Youngster et al., 2014). In five of the 11 studies conducted in adults the participants were healthy volunteers receiving a single dose of antipsychotic medication (Cabaleiro et al., 2013, 2015, 2014; Novalbos et al., 2010; Ozdemir et al., 2007). In the other five studies, the sample consisted of subjects with a psychotic disorder treated with antipsychotic medication for several weeks (Yasui-Furukori *et al.* 2001; Wang *et al.* 2007; Choong *et al.* 2013; Vandenberghe *et al.* 2015; Ivanova et al., 2016; Schoretsanitis, de Leon, & Diaz, 2018). Two of these studies used data from the same set of healthy volunteers (Cabaleiro et al., 2014; Novalbos et al., 2010). Only one of these studies was included in the meta-analysis for this reason (Cabaleiro et al., 2014).

Risperidone was the most commonly prescribed antipsychotic in the selected studies (12 out of 16 studies) (Troost *et al.* 2007; Wang *et al.* 2007; Novalbos *et al.* 2010; Roke *et al.* 2013; Choong *et al.* 2013; Cabaleiro *et al.* 2014; Youngster *et al.* 2014; dos Santos Júnior *et al.* 2015; Vandenberghe *et al.* 2015; Ivanova *et al.* 2016; Sukasem *et al.* 2016; Schoretsanitis et al., 2018)). Regarding CYP2D6 alleles, the most commonly genotyped loss of function alleles were: *3 (11 studies) and *4 (12 studies). Followed by *5 (ninestudies) and *6 (eight studies). The most commonly decreased function allele genotyped was *10 (eight studies).

In regard to sex distribution, eight studies included 60% or more men (Troost *et al.*, 2007; Ozdemir *et al.*, 2007; Choong *et al.*, 2013; Roke *et al.*, 2013; Youngster *et al.*, 2014; Cabaleiro *et al.*, 2014, 2015; dos Santos Júnior *et al.*, 2015; Sukasem *et al.*, 2016) and two studies included 60% or more female participants (Yasui-Furukori *et al.*, 2001; Wang *et al.*, 2007).

Supplementary table 3: Key characteristics of the sixteen primary studies included in this review

Study	Total n	Sex (% male)	PMs n	Adults	Diagnosis	Antipsychotic	CYP2D6 Alleles Genotyped
Cabaleiro et al. 2013	61	52.4	2	Y	Healthy	Olanzapine (single dose)	Done but not stated
Cabaleiro et al. 2014	36	50	5	Y	Healthy	Risperidone (single dose)	*1, *2, *3, *4, *5, *6, *7, *8, *9, *10, *11, *14A, *14B, *15, *17, *19, *20, *25, *26, *29, *30, *31, *35, *40, *41, *1xN, *2xN, *4xN, *10xN, *17xN, *35xN, and *41xN
Cabaleiro et al. 2015	26	38.5	5	Y	Healthy	Quetiapine (single dose)	Done but not stated
Choong et al. 2013	42	71.4	1	Y	Psychotic disorder	Risperidone long-acting injection	*3, *4, *5, *6
dos Santos Junior et al. 2015	120		$	N	Psychiatric Outpatients	Risperidone	*10
Ivanova et al. 2016	122	46.7	$	Y	Schizophrenia	Long-term neuroleptic therapy	*3, *4
Novalbos et al. 2010	36	50	6	Y	Healthy	Risperidone (single dose)	*3, *4, *5, *6, *7, *9
Ozdemir et al. 2007	22	100	0	Y	Healthy	Perphenazine (single dose)	*5, *10

Roke et al. 2012	46	100	2	N	Autism spectrum disorders and disruptive behavioural disorders	Risperidone	*3, *4, *5, *6
Schoretsanitis et al. 2018	110	55.5	3	Y	Schizophrenia, schizoaffective disorder, bipolar disorder, major depressive disorder	Risperidone	*2, *3, *4, *5, *6, *8, *9, *10, *11, *15, *17, *19, *20, *29, *35, *36, *40, *41, and a number of duplicated alleles
Sukasem et al. 2016	147	86.4	$	N	Autism spectrum disorders	Risperidone	*4, *10, *41 , *5
Troost et al. 2007	23	100	4	N	Pervasive Developmental Disorders	Risperidone	*3, *4, *5, *6, *7, gene duplication
Vandenberghe et al. 2015	150	54.7	10	Y	Psychiatric Cohort	Risperidone	*3, *4, *6
Wang et al. 2007	118	33.9		Y	Schizophrenia	Risperidone	*3, *4, *5, *10
Yasui-Furukori et al. 2001	76	36.8		Y	Schizophrenia	Haloperidol	*1, *3, *4, *5, *10
Youngster et al. 2014	35	82.8	2	N	Autism spectrum disorders	Risperidone	*2, *3, *4, *5, *6, *8, *9, *10, *11, *14, *15, *17, *18, *19, *20, *25, *26, *29, *30, *31, *35, *36, *37, *40, *41, *43, *52, and a number of duplicated alleles.

n= number, M= males, PMs = Poor Metabolisers, Y = adults, N = children and adolescents

Supplementary table 4: Summary of outcomes as reported in each primary study

Study	Outcome measures for prolactin	Prolactin Unit	Males outcome as reported	Female outcome as reported
Cabaleiro et al. 2013*	Mean ± SD	ng/ml	PM (n = 1): 9.03 IM (n = 11): 7.98 ± 4.52 EM (n = 17): 11.22 ± 5.29 UM (n = 3): 14.36 ± 9.02	PM (n = 1): 25.75 IM (n = 11): 15.19 ± 6.62 EM (n = 16): 14.58 ± 6.2 UM (n = 1): 15.87
Cabaleiro et al. 2014*	Mean ± SD	ng/ml	PM (n = 2): 35.75 ± 10.05 IM (n = 5): 30.68 ± 4.57 EM (n = 7): 22.85 ± 8.53 UM (n = 4): 24.52 ± 3.2	PM (n= 2): 55.53 ± 6.97 IM (n = 8): 77.57 ± 33.93 EM (n = 7): 62.38 ± 15.48 UM (n = 1): 42.21
Cabaleiro et al. 2015*	Mean ± SD	ng/ml	PM (n = 1): 7.98 IM (n = 2): 6.14 ± 0.88 EM (n = 7): 7.5 ± 2.83	IM (n = 6): 8.07 ± 1.79 EM (n = 10): 11.19 ± 4.02
Choong et al. 2013	Median ± IQR	ng/mL	$	$
dos Santos Junior et al. 2015	Hyperprolactinemia		$	$
Ivanova et al. 2016	Hyperprolactinemia		$	$
Novalbos et al. 2010	C_{max}	ng/ml	$	$
Ozdemir et al. 2007	Net change from baseline over 6 hours	ng/ml	$	$
Roke et al. 2012	Mean ± SD	ng/ml	PM (n=2): 49 ± 0 IM (n=17): 18.4 ± 17 EM (n=25): 19.8 ± 17 UM (n=2): 6.8 ± 6	
Schoretsanitis et al. 2018	Mean ± SD	ng/ml	n=61: 31.9 ± 13.1	n=49: 63.6 ± 32.6

Sukasem et al. 2016	Hyperprolactinemia		$	$
Troost et al. 2007	Mean ± SD	ng/ml	wt/wt (n=9): 31.7 ± 12 wt/DUPwt (n=2): 58.5 ± 27.6 m/wt (n=8): 32.4 ± 6.4 m/m (n=4): 23.7 ± 5.6	EM (n=2): 36.5 ± 3.5
Vandenberghe et al. 2015	Median ± IQR	µg/L	$	$
Wang et al. 2007	Mean ± SD	MIU/L	$	$
Yasui-Furukori et al. 2001	Mean ± SD	ng/ml	wt/wt (n=11): 20.5 ± 7.8 m/wt and m/m (n=17): 32.4 ± 16.4	wt/wt (n=20): 71.2 ± 46.5 m/wt and m/m (n=28): 32.4 ± 50.8
Youngster et al. 2014	Mean ± SD	mcg/L	EM (n=21): 27 ± 17.6 UM(n=2): 18.3 ± 1.5 IM (n=4): 21.7 ± 19.1 PM(n=2): 50.3 ± 2.7	EM (n=4): 21.3 ± 7.9 IM (n=2): 17 ± 0

* Unpublished data provided by authors $ Outcomes not reported

All authors contacted for further information.

Supplementary table 5: Overview of data included in meta-analysis

Study	Sex	Poor			Intermediate			Extensive/Normal			Ultra-rapid		
		Total n	Mean PRL (ng/ml)	SD	Total n	Mean PRL (ng/ml)	SD	Total n	Mean PRL (ng/ml)	SD	Total n	Mean PRL (ng/ml)	SD
Cabaliro et al. 2013	M	1	9.03	NA	11	7.98	4.52	17	11.22	5.29	3	14.36	9.02
Cabaliro et al. 2013	F	1	25.75	NA	11	15.19	6.62	16	14.58	6.2	1	15.87	NA
Cabaliro et al. 2014	M	2	35.72	10.05	5	30.68	4.57	7	22.85	8.53	4	24.52	3.2
Cabaliro et al. 2014	F	2	55.53	6.97	8	77.57	33.93	7	62.38	15.48	1	42.21	NA
Cabaliro et al. 2015	M	1	7.98	NA	2	6.14	0.88	7	7.5	2.83			
Cabaliro et al. 2015	F				6	8.07	1.79	10	11.19	4.02			
Roke et al. 2012	M	2	49	0.01	17	18.4	17	25	19.8	17	2	6.8	6
Troost et al. 2007	M	5	25	5.57	6	34.67	7.47	10	31.9	11.3	2	58.5	27.58
Youngster et al. 2014	M	2	50.3	2.69	4	21.68	19.14	21	26.98	17.63	2	18.31	1.54
Youngster et al. 2014	F				2	17.01	0.01	4	21.27	7.94			
Yasui-Furukori et al. 2001	M	11	20.5	7.8				17	32.4	16.4			
Yasui-Furukori et al. 2001	F	20	71.2	46.5				28	72.1	50.8			
Total		**47**			**72**			**169**			**15**		

Figure 1: Forest plot comparing prolactin levels between 22 poor (PMs) and 80 extensive metabolisers (EMs) in male subjects only.

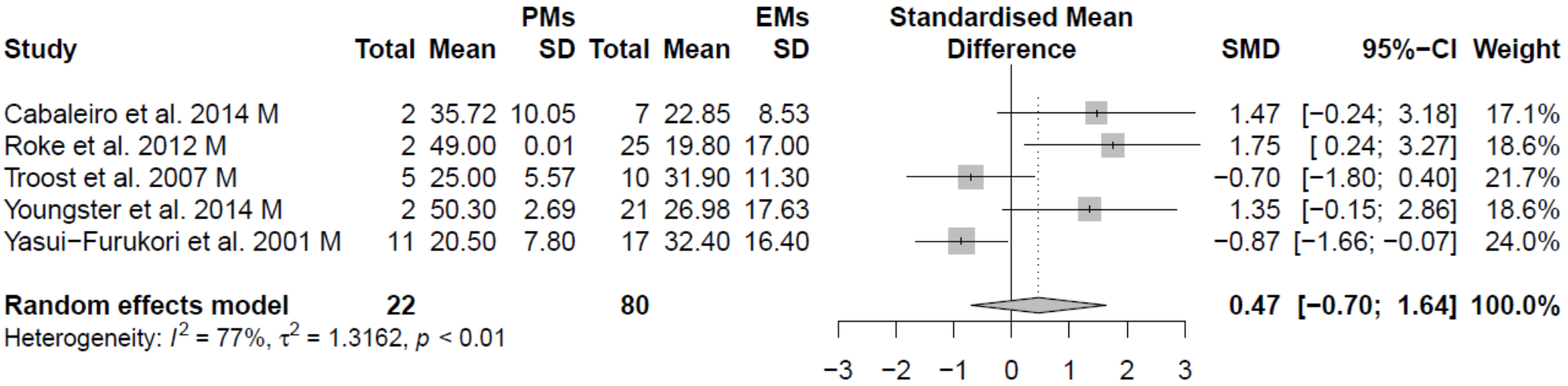

Figure 2: Forest plot comparing prolactin levels between 45 intermediate (IMs) and 87 extensive metabolisers (EMs) in male subjects only.

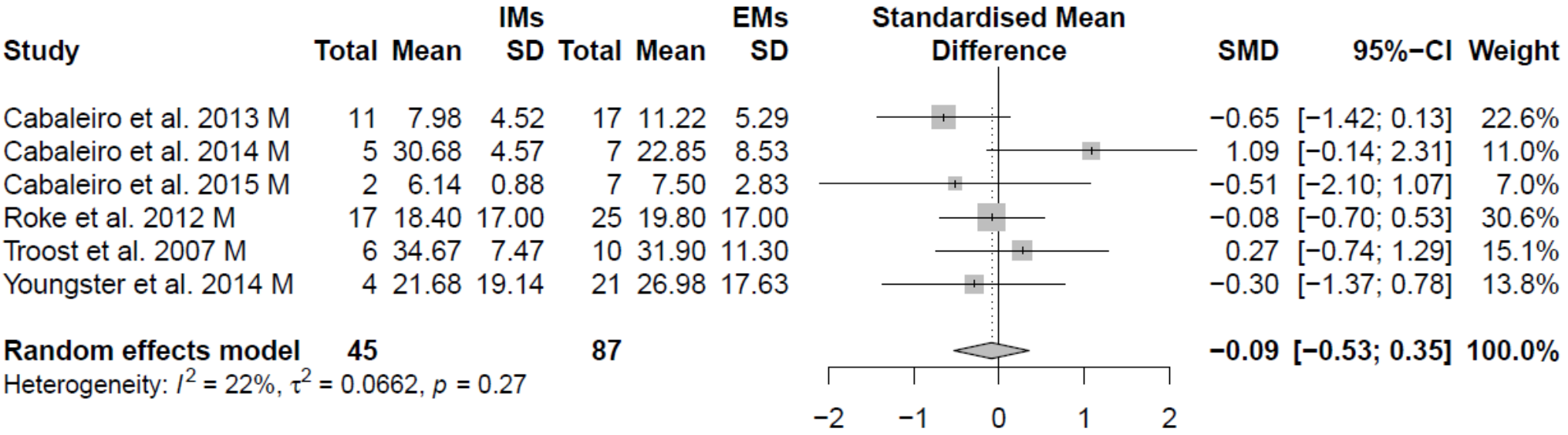

Figure 3: Forest plot comparing prolactin levels between 75 poor and intermediate metabolisers combined (PMs + IMs) versus 111 extensive and ultra-rapid metabolisers combined (EMs + UMs) in male subjects only.

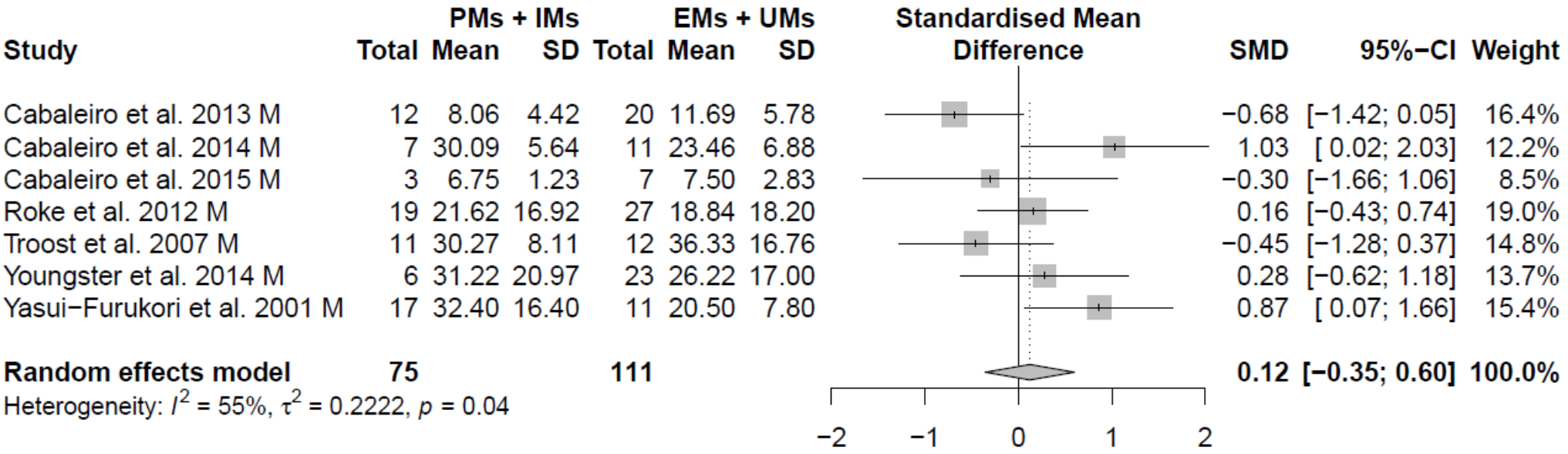

Figure 4: Forest plot comparing prolactin levels between 35 poor (PMs) and 59 extensive metabolisers (EMs) in adult subjects only.

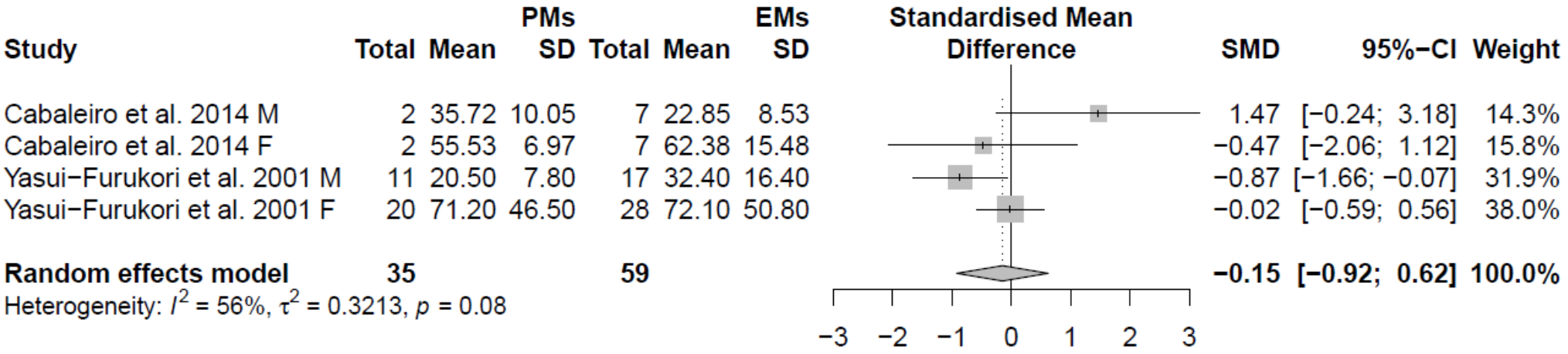

Figure 5: Forest plot comparing prolactin levels between 43 poor (PMs) and 64 extensive metabolisers (EMs) in adult subjects only.

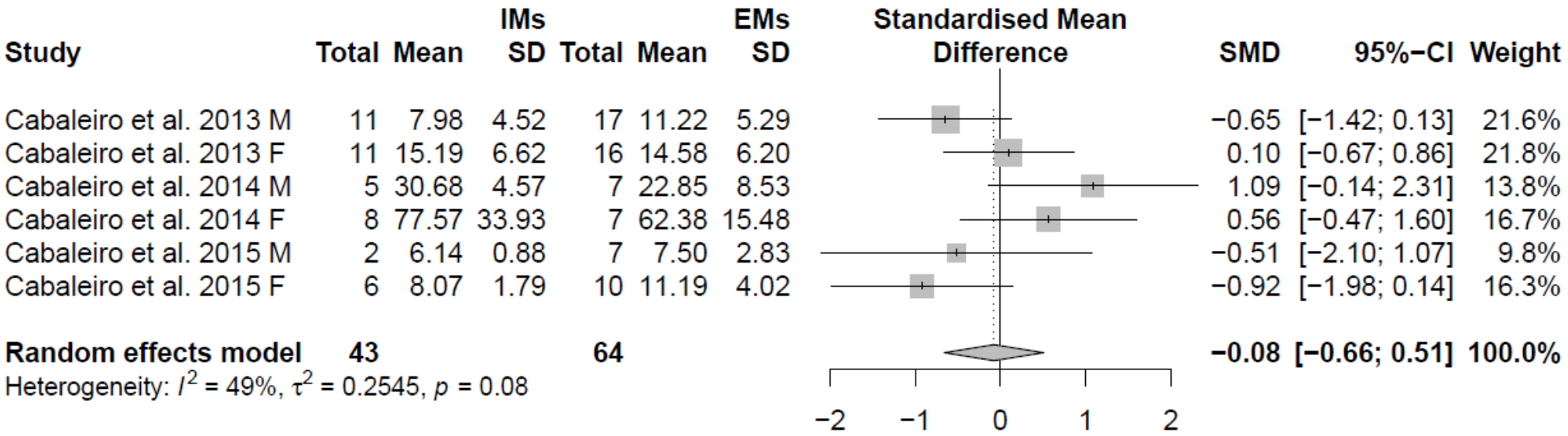

Figure 6: Forest plot comparing prolactin levels between 95 poor and intermediate metabolisers combined (PMs + IMs) versus 104 extensive and ultra-rapid metabolisers combined (EMs + UMs) in adult subjects only.