Supplementary Material: Metabolic activity of CYP2C19 and CYP2D6 on antidepressant response from 13 clinical studies using genotype imputation: a meta-analysis

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Supplementary Materials

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234, China Kadoorie Biobank Collaborative Group
235, Genes & Health Research Team
236, HUNT All-In Psychiatry
237, The BioBank Japan Project
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259, Pathophysiology of Psychiatric Diseases, INSERM, Univ Paris Cité, GHU Paris, Paris, FR
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290, Psychiatry, Veterans Affairs San Diego Healthcare System, San Diego, CA, US
291, Psychiatry, UCSD School of Medicine, La Jolla, CA, US
292, Public Health, UCSD School of Public Health, La Jolla, CA, US
293, Department of Mental Health and Suicide, Norwegian Institute of Public Health, Oslo, NO
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295, Social and Behavioral Science, Harvard T.H. Chan School of Public Health, Boston, MA, US
296, Population Health Sciences, Bristol Medical School, University of Bristol, Bristol, UK
297, Psychiatry, Dalhousie University, Halifax, NS, CA
298, Psychiatry, Amsterdam UMC, location University of Amsterdam, Amsterdam, NL
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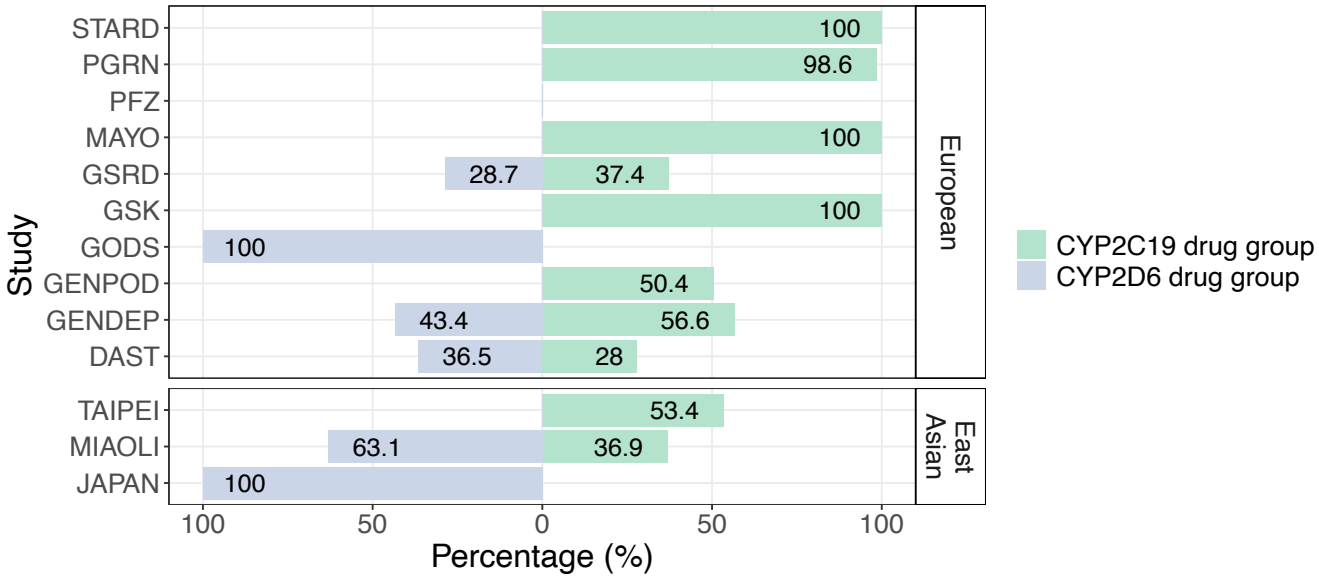
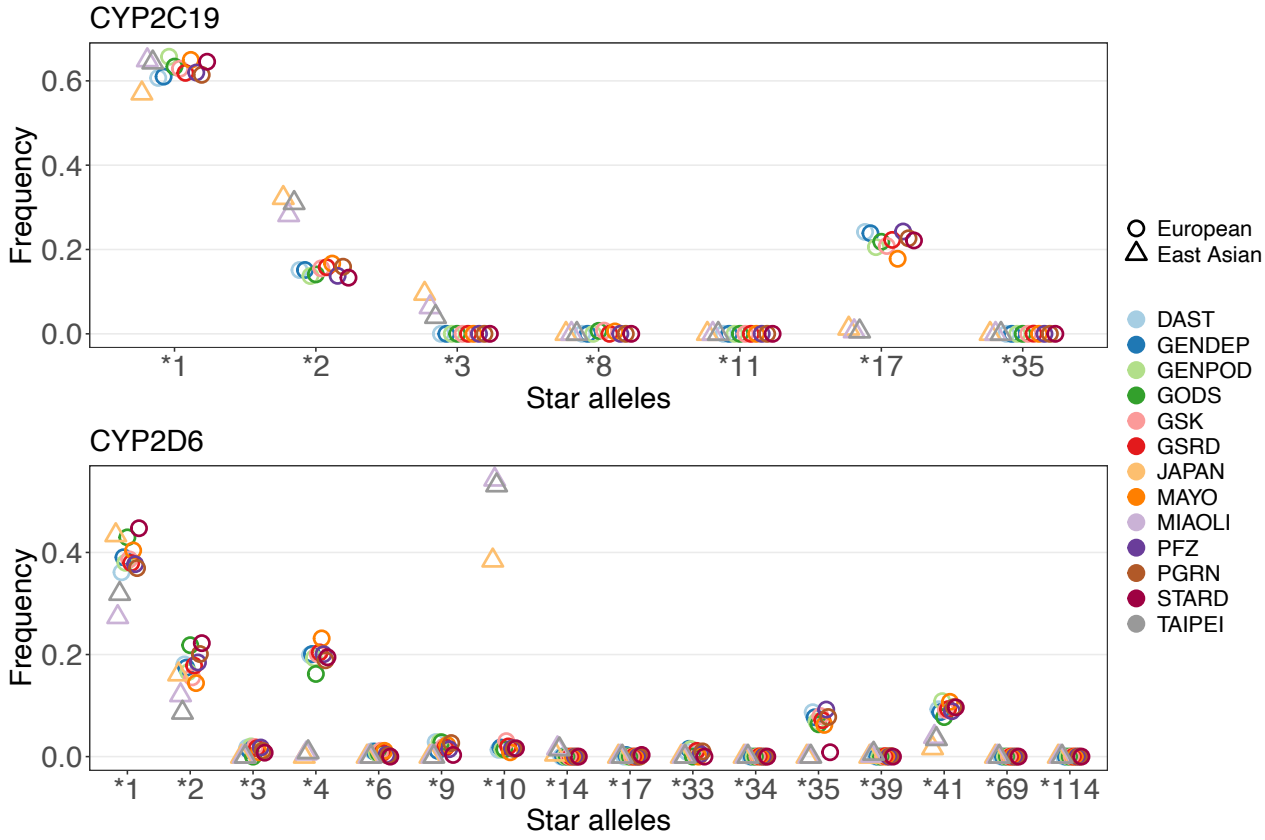
303, Department of Medical & Molecular Genetics, King's College London, London, UK
304, Institute for Genomics and Cancer, University of Edinburgh, Edinburgh, UK

Supplementary Figures

Supplementary Figure 1. Distribution of CYP2C19 and CYP2D6 antidepressants in each cohort

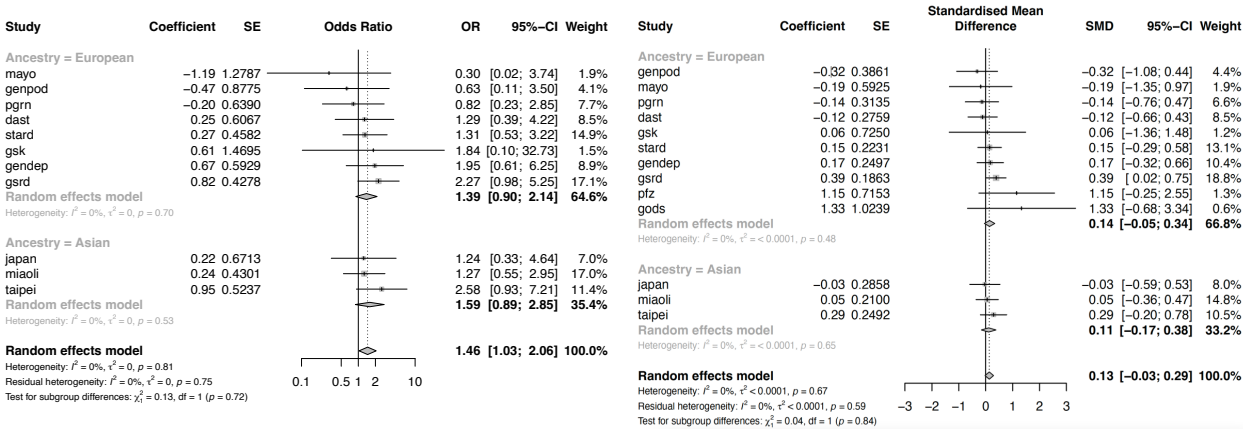


Supplementary Figure 2. Frequency of CYP2C19 and CYP2D6 star alleles

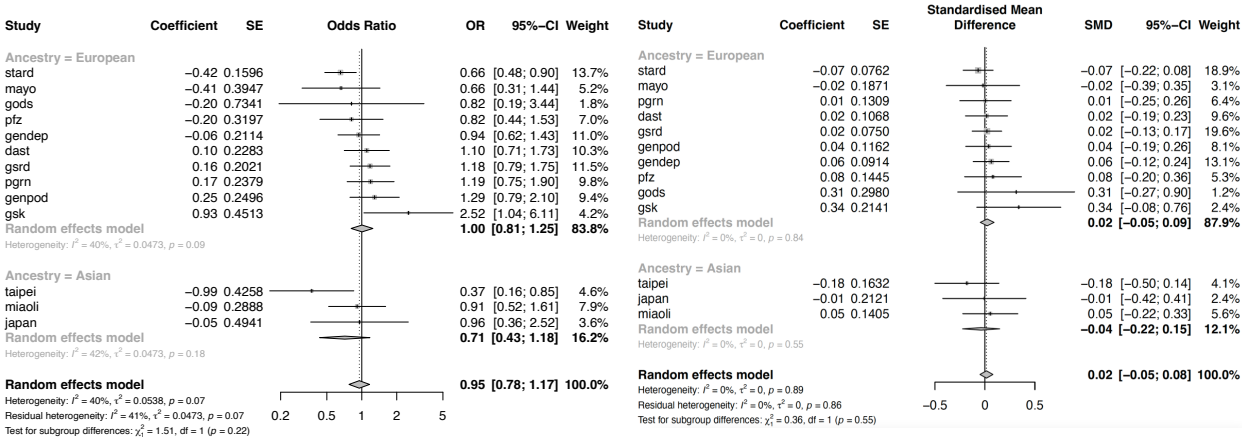


Supplementary Figure 3. Meta-analyses of CYP2C19 poor, intermediate, and ultrarapid metabolizers in all samples

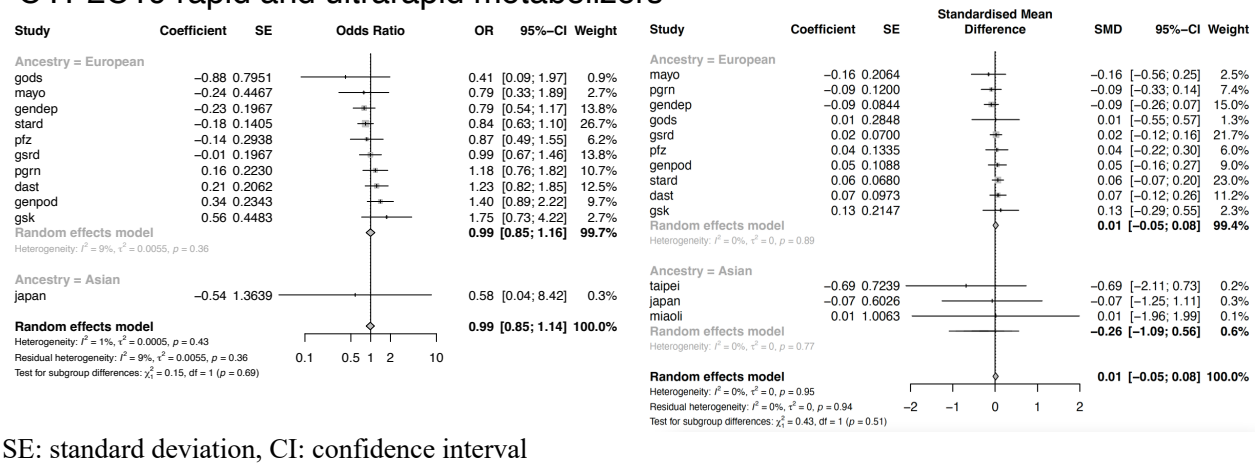
CYP2C19 poor metabolizers



CYP2C19 intermediate metabolizers



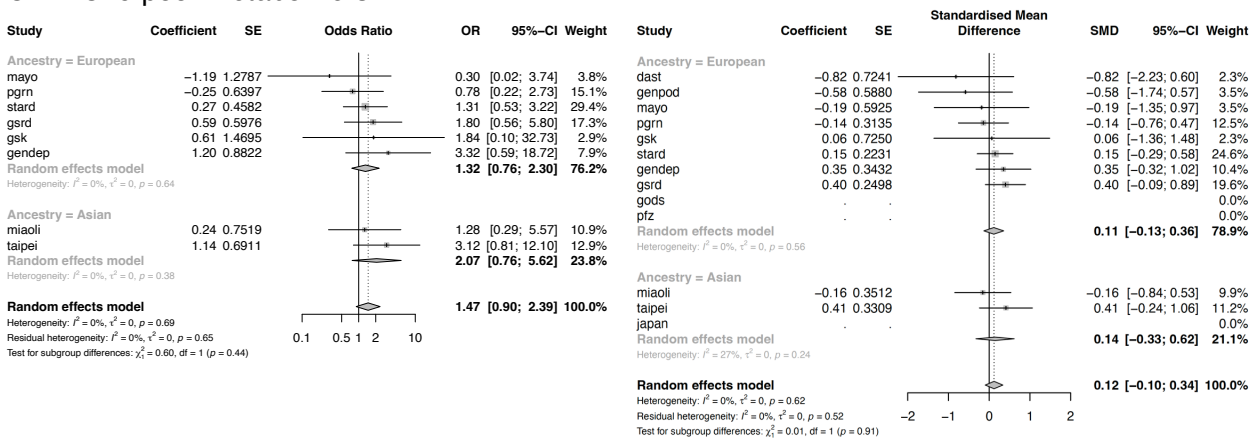
CYP2C19 rapid and ultrarapid metabolizers



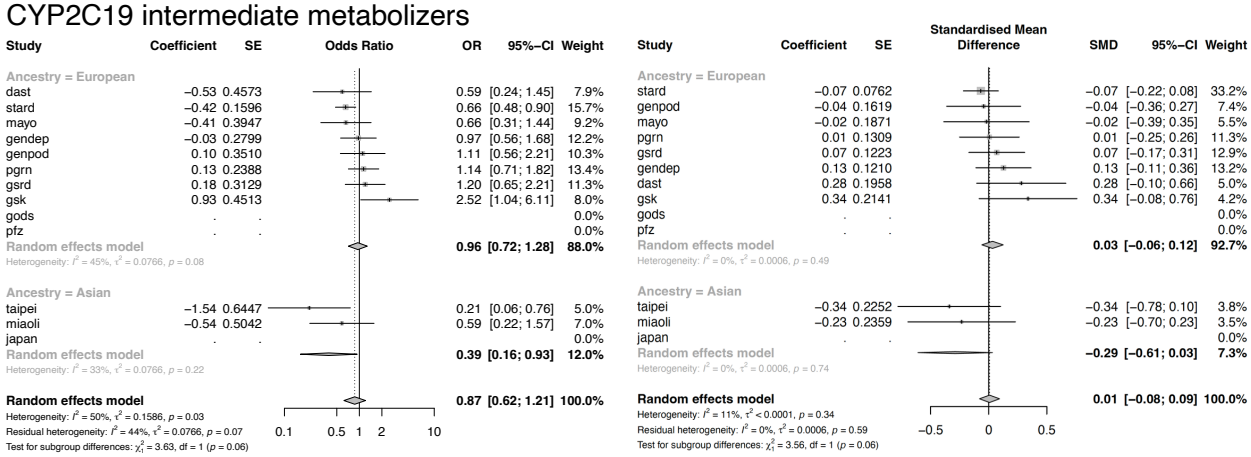
SE: standard deviation, CI: confidence interval
GODS and PFZ were removed in the meta-analysis of poor metabolizer for remission outcome and MIAOLI and TAIPEI were not reported in the meta-analysis of ultrarapid metabolizer for remission outcome due to insufficient sample size.

Supplementary Figure 4. Meta-analyses of CYP2C19 poor, intermediate, and ultrarapid metabolizers in CYP2C19 antidepressant group

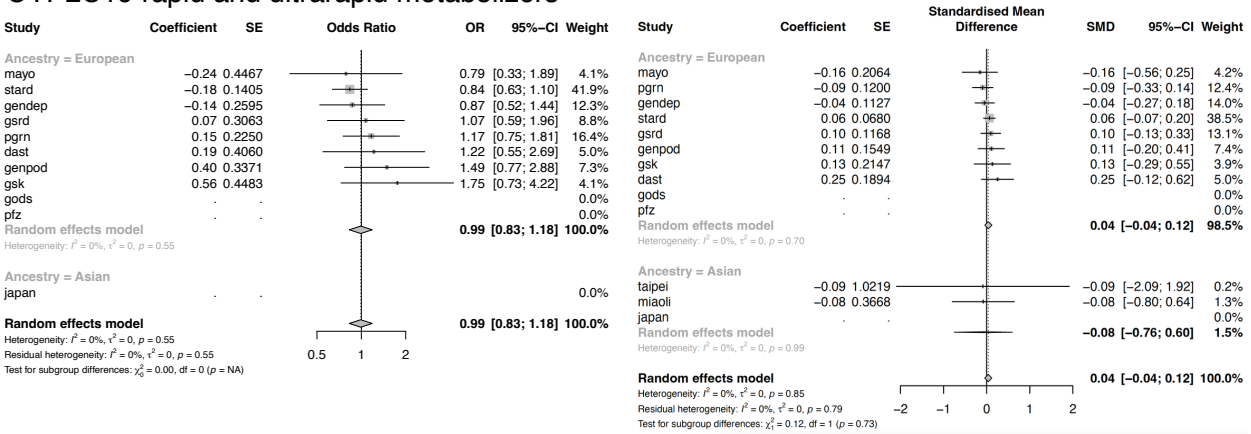
CYP2C19 poor metabolizers



CYP2C19 intermediate metabolizers

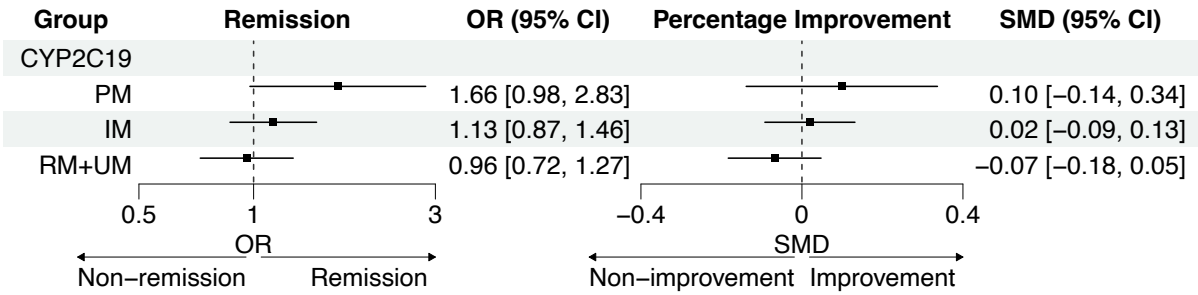


CYP2C19 rapid and ultrarapid metabolizers

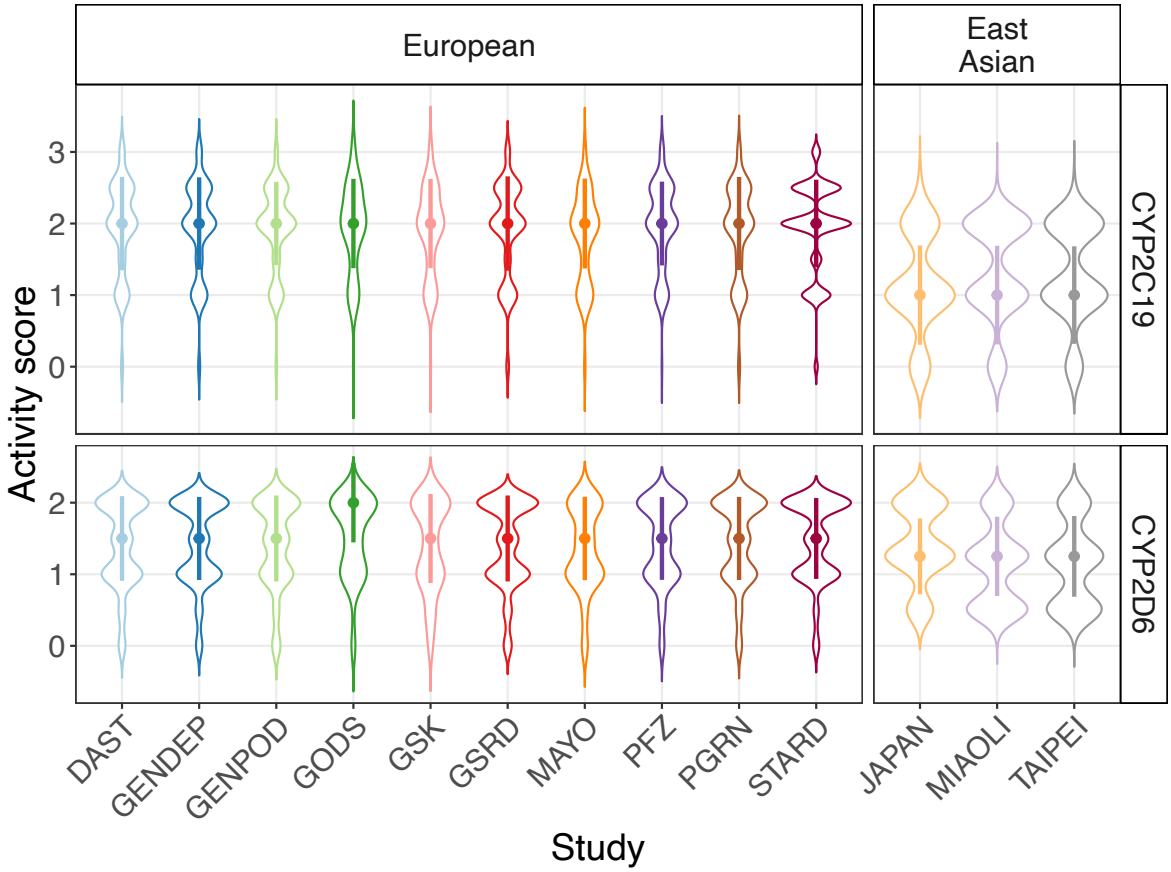


For the remission outcome, DAST, GENPOD, and JAPAN were removed in the meta-analysis of poor metabolizer and MIAOLI and TAIPEI were not reported in the meta-analysis of rapid+ultrarapid metabolizer due to insufficient sample size.

Supplementary Figure 5. Association of metabolizer status with antidepressant outcomes in drugs not primarily metabolized by CYP2C19



Supplementary Figure 6. Distribution of activity score in each cohort



Supplementary Tables

Supplementary Table 1. Characteristics of 13 clinical studies

Studies	Sample size (N = 5843)	Study design	Study weeks	Measures	Antidepressants	Age	Sex (Female)	Remission rate
European								
STARD	1163	Open label	12	QIDSC	Citalopram	43.33 (13.49)	675 (58.0%)	43.5%
GSRD	1152	Naturalistic	≥4	MADRS	Various	52.23 (14.02)	758 (65.8%)	16.4%
GENDEP	783	Partially randomized open label	12	MADRS	Escitalopram, nortriptyline	42.28 (11.59)	490 (62.6%)	37.2%
DAST	586	Naturalistic inpatient	6	HAMD-21	Various	49.47 (15.48)	335 (57.2%)	41.8%
PGRN	490	Open label	8	QIDSC	Citalopram, escitalopram	39.86 (13.64)	307 (62.7%)	40.8%
GENPOD	474	Open label	12	BDI	Citalopram, reboxetine	39.39 (12.50)	327 (69.0%)	35.7%
PFZ	309	RCT	6-8	HAMD-17	Sertraline, fluoxetine, paroxetine	43.17 (13.06)	208 (67.3%)	32.0%
MAYO	156	Open label	8	HAMD-17	Citalopram, escitalopram	40.03 (13.88)	96 (61.5%)	51.3%
GSK	132	RCT	8	HAMD-17	Escitalopram	36.36 (11.90)	72 (54.5%)	42.4%
GODS	71	Open label	8	MADRS	Paroxetine	37.32 (10.34)	37 (52.1%)	23.9%
East Asian								
MIAOLI	233	Open label	8	HAMD-17	Escitalopram, paroxetine	41.36 (13.60)	192 (82.4%)	44.2%
TAIPEI	174	Open label	8	HAMD-17	Fluoxetine, citalopram	47.01 (15.13)	96 (55.2%)	25.9%
JAPAN	120	RCT	6	HAMD-17	Fluvoxamine, paroxetine	45.99 (15.25)	56 (46.7%)	65.0%

Mean with standard deviation for age and frequency with proportion for sex were displayed.

BDI, Beck Depression Inventory; HAMD-17, 17-item Hamilton Depression Rating Scale; HAMD-21, 21-item Hamilton Depression Rating Scale; MADRS, Montgomery Åsberg Depression Rating Scale; QIDSC, Quick Inventory of Depressive Symptomatology; RCT: randomized controlled trial.

Supplementary Table 2. Star alleles in CYP2C19 and CYP2D6

Star alleles	Defining variants	Function	Activity value
CYP2C19			
*1	Reference allele	Normal	1
*2	rs4244285	No	0
*3	rs4986893	No	0
*8	rs41291556	No	0
*11	rs58973490	Normal	1
*17	rs12248560	Increased	1.5
*35	rs12769205	No	0
CYP2D6			
*1	Reference allele	Normal	1
*2	rs16947, rs1135840	Normal	1
*3	rs35742686	No	0
*4	rs3892097	No	0
*6	rs5030655	No	0
*9	rs5030656	Decreased	0.5
*10	rs1135840, rs1065852	Decreased	0.25
*14	rs5030865, rs16947, rs1135840	Decreased	0.5
*17	rs28371706, rs16947, rs1135840	Decreased	0.5
*33	rs28371717	Normal	1
*34	rs16947	Normal	1
*35	rs769258	Normal	1
*39	rs1135840	Normal	1
*41	rs28371725, rs16947, rs1135840	Decreased	0.5
*69	rs28371725 rs1065852	No	0
*114	rs5030865, rs1065852	No	0

Defining variants were based on the Clinical Pharmacogenetics Implementation Consortium (CPIC) allele definition table.

Supplementary Table 3. Concordance rate and misclassification of CYP2C19 and CYP2D6 metabolic phenotypes between imputed genotype and Roche AmpliChip CYP450 microarray/TaqMan SNP genotyping in GENDEP

	Roche AmpliChip CYP450 microarray/TaqMan SNP genotyping CYP2C19/CYP2D6			
Imputed genotype	Poor	Intermediate	Normal	Rapid+Ultrarapid
CYP2C19				
Poor	88.2%	5.9%	5.9%	0
Intermediate	0	96.1%	3.4%	0.5%
Normal	0	1.4%	96.6%	0.7%
Rapid+Ultrarapid	0	2.6%	0	97.0%
CYP2D6				
Poor	88.2%	5.9%	2.9%	0
Intermediate	6.9%	83.8%	6.2%	0
Normal	1.5%	13.7%	76.7%	5.2%

Supplementary Table 4. CYP2C19 and CYP2D6 antidepressants

Gene	Antidepressants
CYP2C19	citalopram, escitalopram, sertraline, amitriptyline, clomipramine, doxepin, trimipramine
CYP2D6	paroxetine, nortriptyline, venlafaxine, fluvoxamine, amitriptyline, clomipramine, trimipramine, desipramine, doxepin

Supplementary Table 5. Remission and percentage improvement in CYP2C19 and CYP2D6 antidepressant groups

Metabolizers	N	Remission	Percentage Improvement
CYP2C19 antidepressant group (N = 3390)			
Poor	92	42 (45.7%)	0.190 (1.040)
Intermediate	907	353 (38.9%)	0.018 (0.975)
Normal	1343	571 (42.5%)	0.007 (1.037)
Rapid+Ultrarapid	1048	438 (41.8%)	0.039 (1.016)
CYP2D6 antidepressant group (N = 1223) (incomplete assessment*)			
Poor	43	16 (37.2%)	-0.084 (0.892)
Intermediate	433	153 (35.3%)	-0.118 (0.973)
Normal	747	295 (39.5%)	-0.032 (0.991)

Frequency with proportion for remission and mean with standard deviation for percentage improvement were displayed

* Due to undetected variants in genotype, imputation of CYP2D6 metabolic phenotypes was less accurate

Supplementary Table 6. Meta-analyses of activity score with antidepressant outcomes

Outcomes	OR/COR	95% CI	P
CYP2C19 activity score			
Remission	0.94	0.86, 1.03	0.197
Percentage Improvement	-0.02	-0.05, 0.01	0.170

COR: correlation

Supplementary Table 7. Meta-analyses of metabolic phenotypes for percentage improvement adjusting for baseline severity of depression

Metabolizers	SMD	95% CI	P
CYP2C19			
Poor	0.13	-0.03, 0.29	0.103
Intermediate	0.01	-0.05, 0.08	0.683
Rapid+Ultrarapid	0.01	-0.05, 0.07	0.777

Supplementary Table 8. Meta-analyses of CYP2C19 metabolic effect in citalopram and escitalopram

	OR/SMD	95% CI	P
Remission			
Poor	1.41	0.84, 2.34	0.192
Intermediate	0.89	0.65, 1.21	0.455
Rapid+Ultrarapid	0.99	0.83, 1.18	0.876
Percentage Improvement			
Poor	0.069	-0.16, 0.30	0.559
Intermediate	-0.004	-0.09, 0.09	0.929
Rapid+Ultrarapid	0.015	-0.07, 0.10	0.732