Title: Genetics-Based Population Pharmacokinetics and Pharmacodynamics of Risperidone in a Psychiatric Cohort.

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eTable 1: Numbers and frequencies of side effects by using the Udvalg for Kliniske Undersøgelser (UKU) Side Effect Rating Scale.

UKU side effects rating scale	n obs.	Absent		Light		Medium		Severe	
		n (%)	CI_{95} (%)	n (%)	CI_{95} (%)	n (%)	CI_{95} (%)	n (%)	CI_{95} (%)
Neurologic[a]	**47**	**27 (57)**	**42-71**	**7 (15)**	**7-29**	**13 (28)**	**16-43**	**0 (0)**	**0-9**
Akathisia	47	35 (74)	59-86	6 (13)	5-26	6 (13)	5-26	0 (0)	0-9
Rigidity	46	37 (80)	66-90	6 (13)	5-27	3 (7)	2-19	0 (0)	0-10
Tremor	47	34 (72)	57-84	6 (13)	5-26	7 (15)	7-29	0 (0)	0-9
Co-medications of interest[b]									
Anticholinergic drugs		biperiden = 6		biperiden = 2		biperiden = 3			
Antipsychotics		halo.= 3		lev. = 1 / halo.=1		halo.= 1 / pip. = 1			
n patients excluded from analysis		4		2		3			
Autonomic[a]	**43**	**26 (60)**	**44-75**	**11 (26)**	**14-41**	**6 (14)**	**6-29**	**0 (0)**	**0-10**
Constipation	42	34 (80)	65-91	4 (10)	3-24	4 (10)	3-24	0 (0)	0-10
Increased salivation	41	37 (91)	76-97	3 (7)	3-21	1 (2)	0-14	0 (0)	0-11
Nausea	42	40 (95)	83-99	2 (5)	1-17	0 (0)	0-10	0 (0)	0-10
Reduced salivation	43	36 (84)	69-93	6 (14)	6-29	1 (2)	0-14	0 (0)	0-10
Cardiovascular[a]	**40**	**37 (93)**	**79-98**	**2 (5)**	**1-18**	**0 (0)**	**0-11**	**1 (3)**	**0-15**
Hypertension	40	40 (100)	89-100	0 (0)	0-11	0 (0)	0-11	0 (0)	0-11
Hypotension	40	39 (98)	85-100	1 (3)	0-15	0 (0)	0-11	0 (0)	0-11
Lower-extremity edema	40	38 (96)	82-99	1 (2)	0-14	0 (0)	0-11	1 (2)	0-14
Psychic[a]	**42**	**23 (55)**	**39-70**	**10 (24)**	**13-40**	**8 (19)**	**9-35**	**1 (2)**	**0-14**
Asthenia	40	27 (68)	51-81	8 (20)	10-36	5 (13)	5-28	0 (0)	0-11
Sleepiness	42	31 (74)	58-86	7 (17)	8-32	3 (7)	2-21	1 (2)	0-14
Sexual dysfunction[a,c]	**23**	**16 (70)**	**47-86**	**4 (17)**	**6-40**	**2 (9)**	**2-20**	**1 (4)**	**0-23**
Diminished sexual desire	23	18 (78)	56-92	3 (13)	4-29	2 (8)	4-29	0 (0)	0-13
Ejaculatory dysfunction	22	20 (91)	69-98	1 (5)	0-19	0 (0)	0-14	1 (5)	0-19
Erectile dysfunction	22	20 (91)	69-98	1 (5)	0-19	1 (5)	0-19	0 (0)	0-14
Orgasmic dysfunction	19	18 (95)	72-99	1 (5)	0-20	0 (0)	0-15	0 (0)	0-20

[a] Total number for each group was calculated based on the highest side effect for each patient. Due to the fact that patients can have several sides effects, total number of each side effect group does not correspond to the total number of the corresponding side effects.
[b] Only co-medication used to treat and those known to possibly induce neurologic symptoms are reported. Abreviations: halo.= haloperidol, lev. = levomepromazine, pip. = pipamperone.
[c] Reported only for male patients.

eTable 2: Genotype frequency.

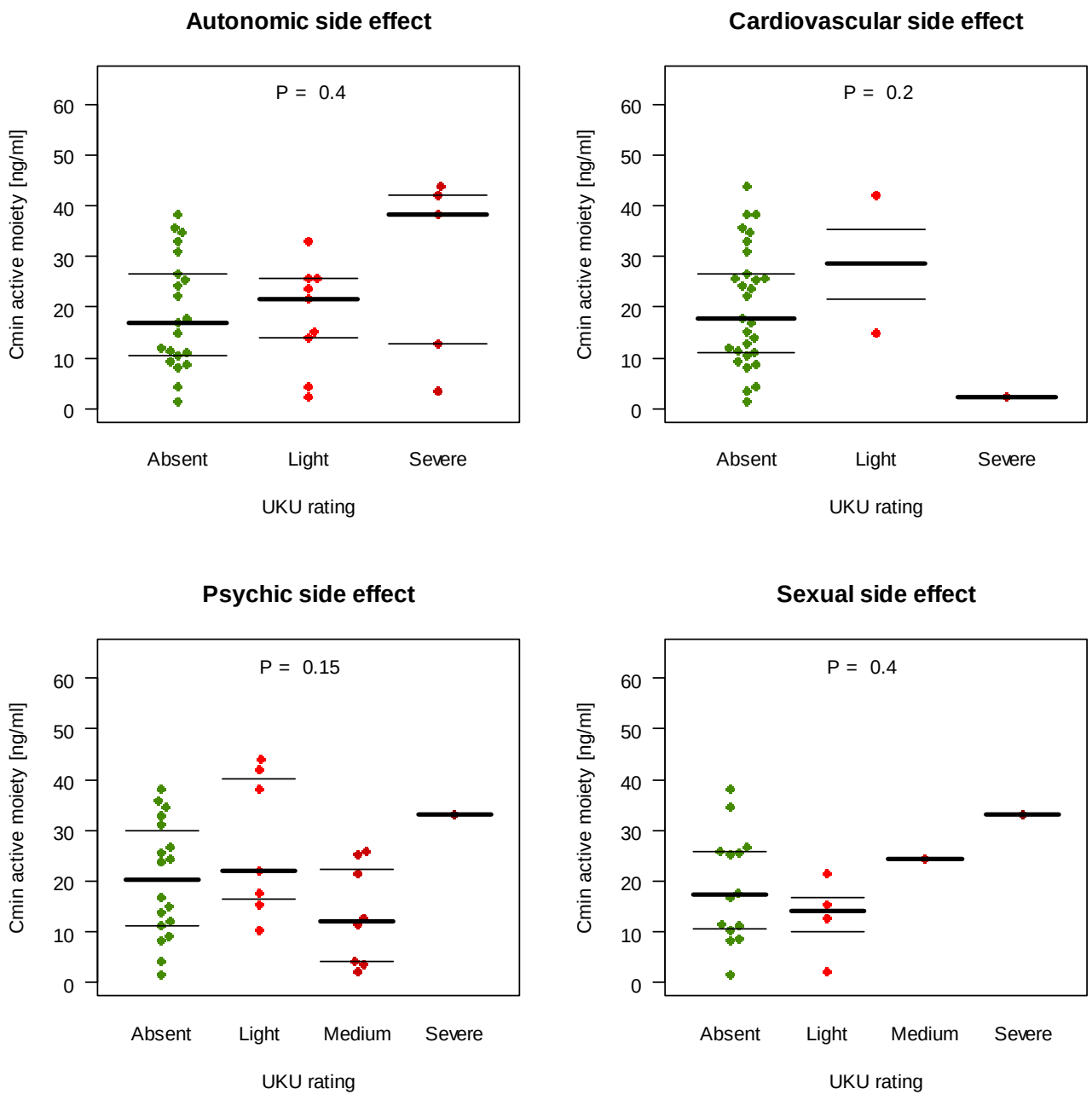
	n (%)	$CI_{95\%}$	HW p-value [a]		n (%)	$CI_{95\%}$	HW p-value [a]		n (%)	$CI_{95\%}$	HW p-value [a]
ABCB1 rs9282564			0.5	***CYP3A4 rs2740574***			0.7	***NR1I2 rs1523130***			0.8
AA	134 (89)	83-94		*1/*1	132 (88)	81-93		CC	50 (33)	26-42	
AG	15 (10)	6-16		*1/*1B	16 (11)	6-17		CT	71 (47)	39-56	
GG	1 (1)	0-4		*1B/*1B	2 (1)	0-5		TT	29 (19)	14-27	
ABCB1 rs1045642			0.9	***CYP3A5 rs776746***			0.3	***NR1I2 rs2276707***			0.5
CC	45 (30)	23-38		*1/*1	4 (3)	1-7		CC	92 (61)	53-69	
CT	71 (47)	39-56		*1/*3	30 (20)	14-27		CT	50 (33)	26-42	
TT	34 (23)	16-30		*3/*3	116 (77)	70-84		TT	8 (5)	3-11	
ABCB1 rs1128503			0.3	***CYP3A7 2262T>A***			0.5	***NR1I2 rs2472677***			0.9
CC	49 (33)	25-41		*1/*1	135 (90)	84-94		CC	20 (13)	9-20	
CT	76 (51)	42-59		*1/*1C	15 (10)	6-16		CT	71 (47)	39-56	
TT	25 (17)	11-24		*1C/*1C	0 (0)	0-3		TT	59 (39)	32-48	
ABCB1 rs2229109			0.7	***CYP3A4 rs35599367***			0.7	***NR1I2 rs7643645***			0.3
AA	0 (0)	0-3		GG	140 (93)	88-97		AA	79 (53)	44-61	
GA	9 (6)	3-11		GA	10 (7)	3-12		AG	52 (35)	27-43	
GG	141 (94)	89-97		AA	0 (0)	0-3		GG	19 (13)	8-19	
ABCB1 rs2032582			0.2	***CYP3A4 rs4646437***			0.1	***POR rs1057868***			0.6
AA	1 (1)	0-4		CC	106 (71)	63-78		CC	80 (53)	45-61	
AG	4 (3)	1-7		CT	40 (27)	20-35		CT	57 (38)	30-46	
GG	50 (33)	26-42		TT	4 (3)	1-7		TT	13 (9)	5-15	
GT	70 (47)	39-55		***PPARA rs4253728***			0.5	**CYP2D6 phenotype [b]**			
TT	21 (14)	9-21		AA	10 (7)	3-12		UM	6 (4)	2-9	
TA	4 (3)	1-7		AG	51 (34)	27-42		EM	93 (62)	54-70	
				GG	89 (59)	51-67		IM	41 (27)	21-35	
								PM	10 (7)	3-12	

[a] Hardy-Weinberg equilibrium was calculated in the Caucasian sub-sample.

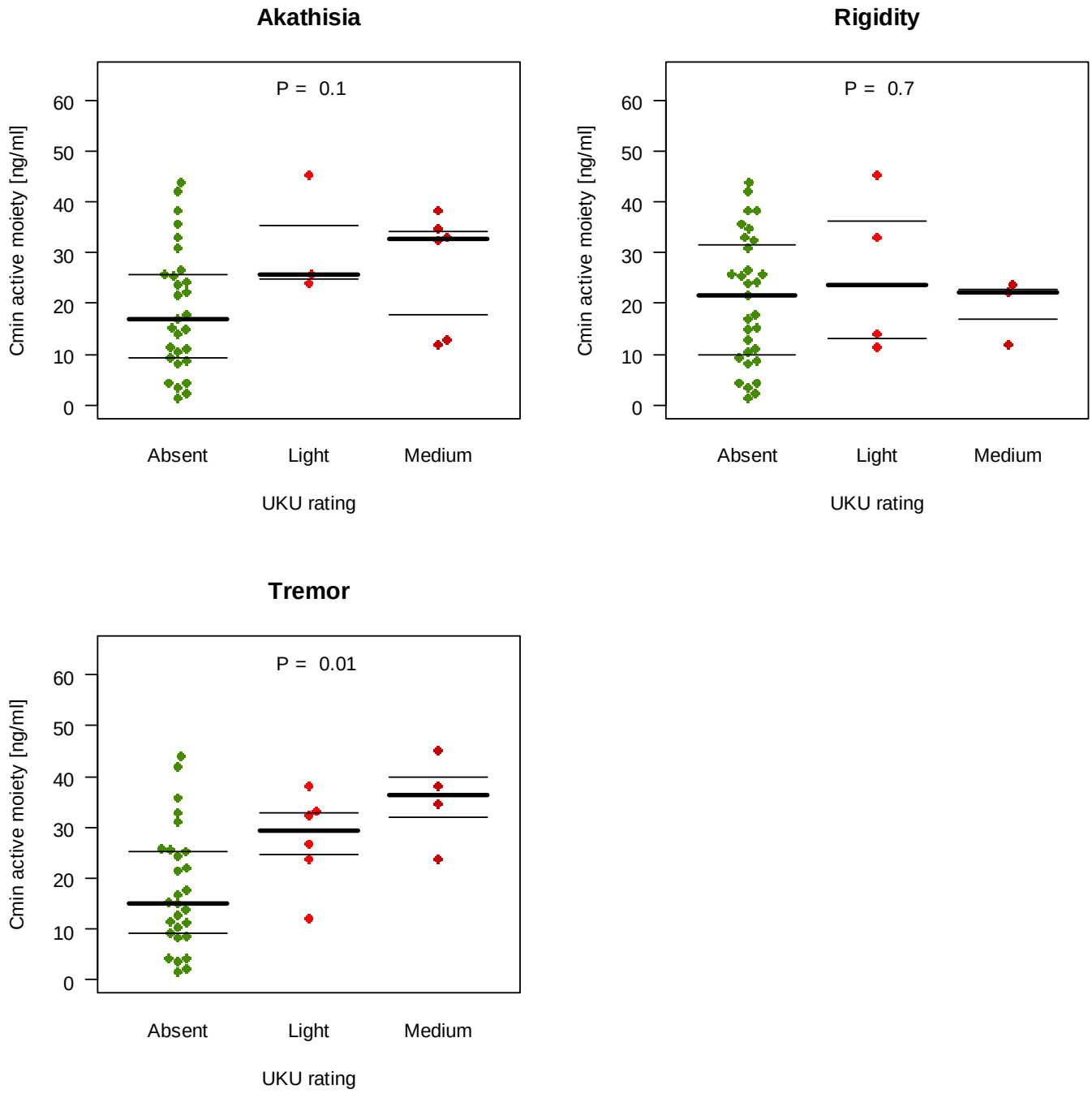
[b] CYP2D6: PM: *4/*4 n = 6, *4/*5 n = 3, *5/*5 n = 1; IM: *1/*3 n = 3, *1/*4 n = 32, *1/*5 n = 4, *1/*6 n = 2; EM: *1/*1 n = 92; UM: *XN/*XN or *1/*XN n = 6.

eTable 3: Model based simulations comparing AUC_{RISP}, AUC_{9OHR} and $AUC_{active\ moiety}$ for different CYP2D6 phenotypes.

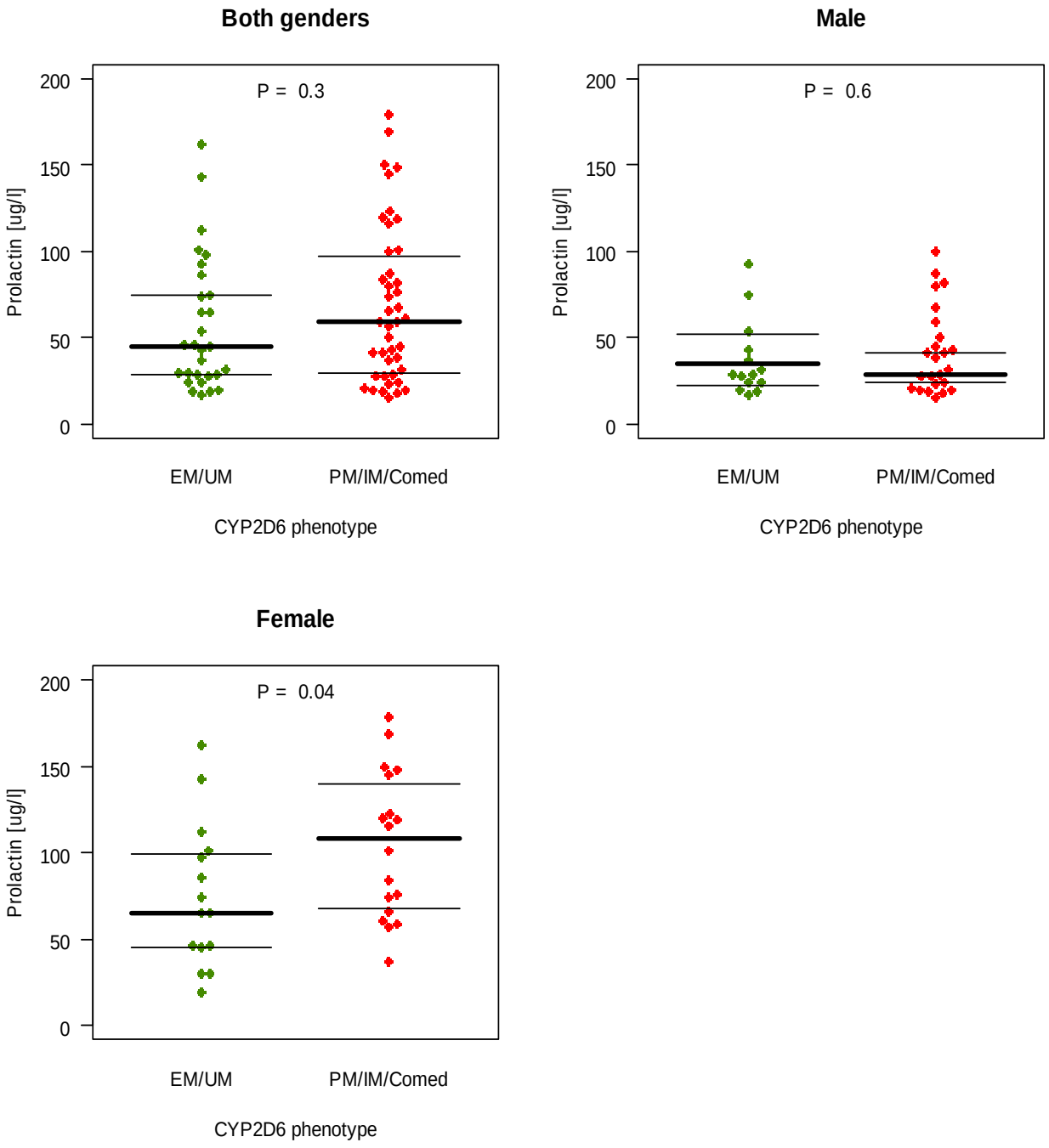
CYP 2D6 Phenotype	AUC_{RISP} ($CI_{95\%}$) [ng/ml·h]	AUC_{9OHR} ($CI_{95\%}$) [ng/ml·h]	$AUC_{Active\ moiety}$ ($CI_{95\%}$) [ng/ml·h]
EM/UM	94 (86-98)	643 (634-656)	737 (720-754)
IM	168 (159-176)	579 (575-592)	747 (734-768)
PM	754 (733-774)	259 (251-264)	1013 (984-1038)



eFigure 1: C_{min} of active moiety in relation to the severity of each group of reported side effect. The severity of each group is considered by the highest reported side effect of the corresponding group. The bold horizontal line shows the median value and the two other lines represent the upper and lower quartile.



eFigure 2: C_{min} of active moiety in relation to the severity of each side effect present in the neurologic side effect group. Bold horizontal line shows the median value and the two other lines represent the upper and lower quartile.



eFigure 3: Last observed prolactin concentration in relation to CYP2D6 phenotype. Poor metabolizer, intermediate metabolizer and presence of weak or strong CYP2D6 inhibitor were pooled together. Bold horizontal line shows the median value and the two other lines represent the upper and lower quartile.