# Supplementary Online Content

Janecka M, Kodesh A, Levine SZ, et al. Association of autism spectrum disorder with prenatal exposure to medication affecting neurotransmitter systems. *JAMA Psychiatry.* Published online October 31, 2018. doi:10.1001/jamapsychiatry.2018.2728

This supplementary material has been provided by the authors to give readers additional information about their work.

eFigure 1. Classification of Exposure and Inferences Drawn From Our Design vs Standard Design
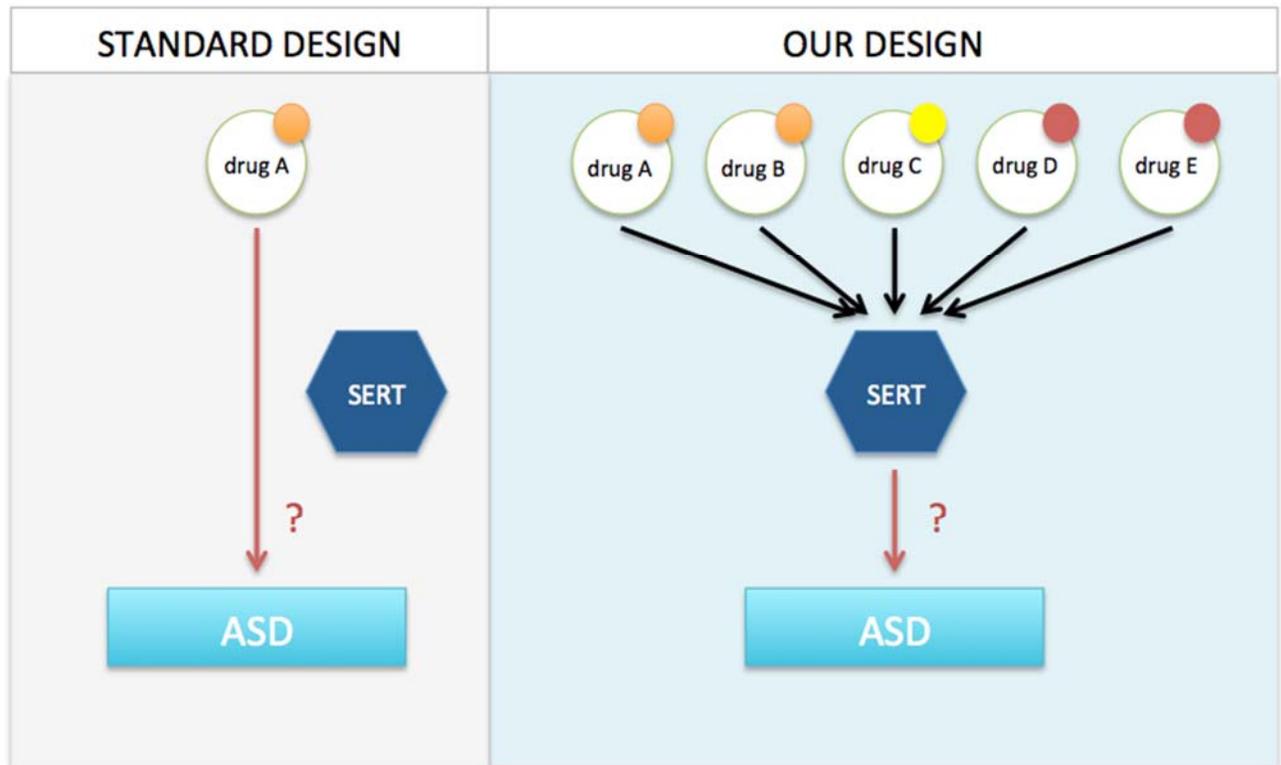
Traditionally, exposure to single (drug A) / narrow group of medications was tested for an association with ASD, and presence of significant effects was interpreted as suggestive of involvement of the drug's target in the disease etiology (left box). Under this scenario, there exists a strong association between the exposure, and other factors that are associated with the medication use (e.g. physiological effects of the underlying indication, familial effects – here represented by an orange dot). Instead, our approach first creates the "target signal", by grouping together several drugs (drugs A-E) that all act on certain target (e.g. serotonin transporter (SERT)), but are associated with different potentially confounding factors (yellow, orange and red dots), and only then tests the association of this signal with ASD (right box). The red arrow indicates the step at which the association with ASD is tested.

ASD rates
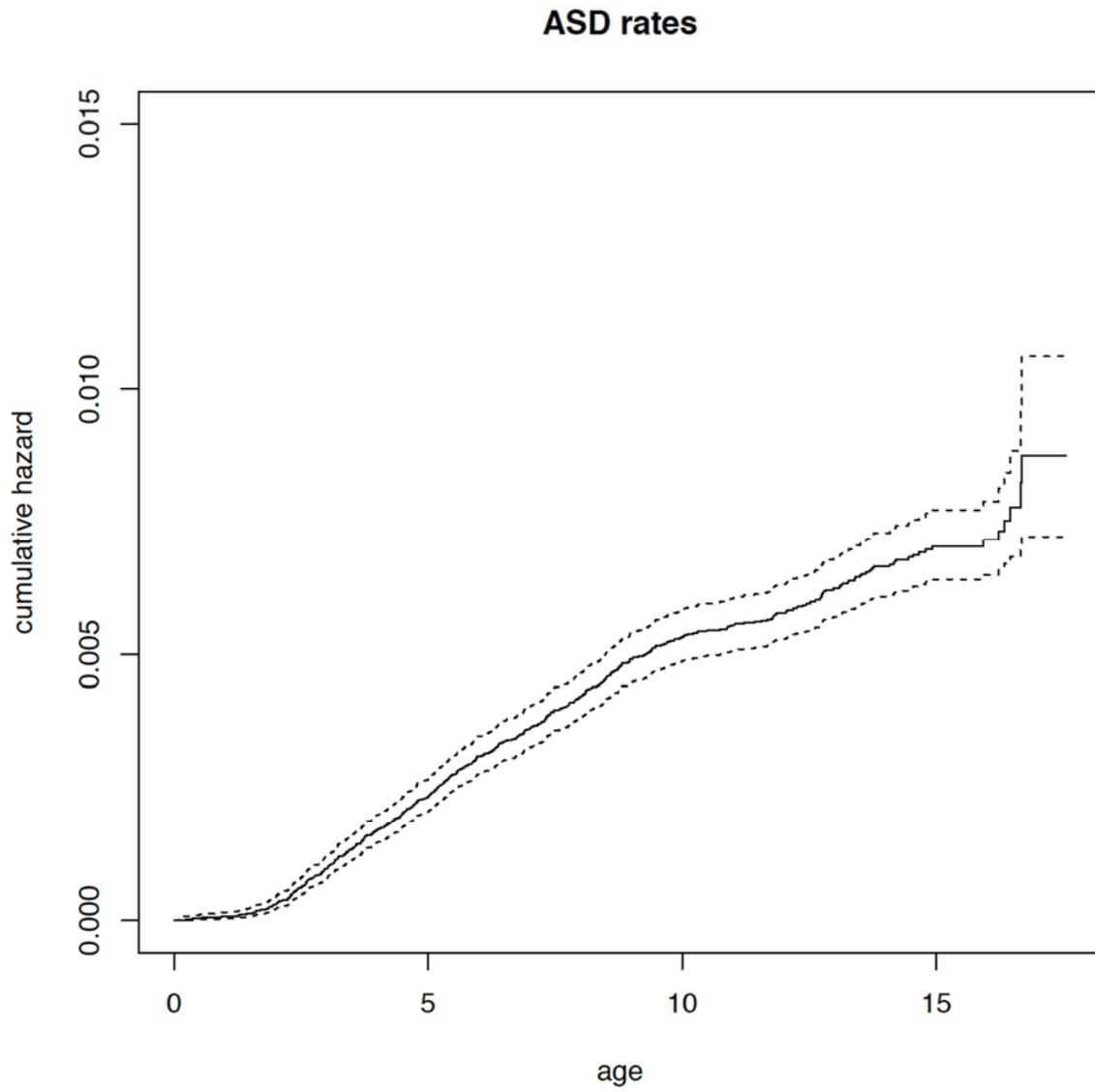
eFigure 3. Study Cohort
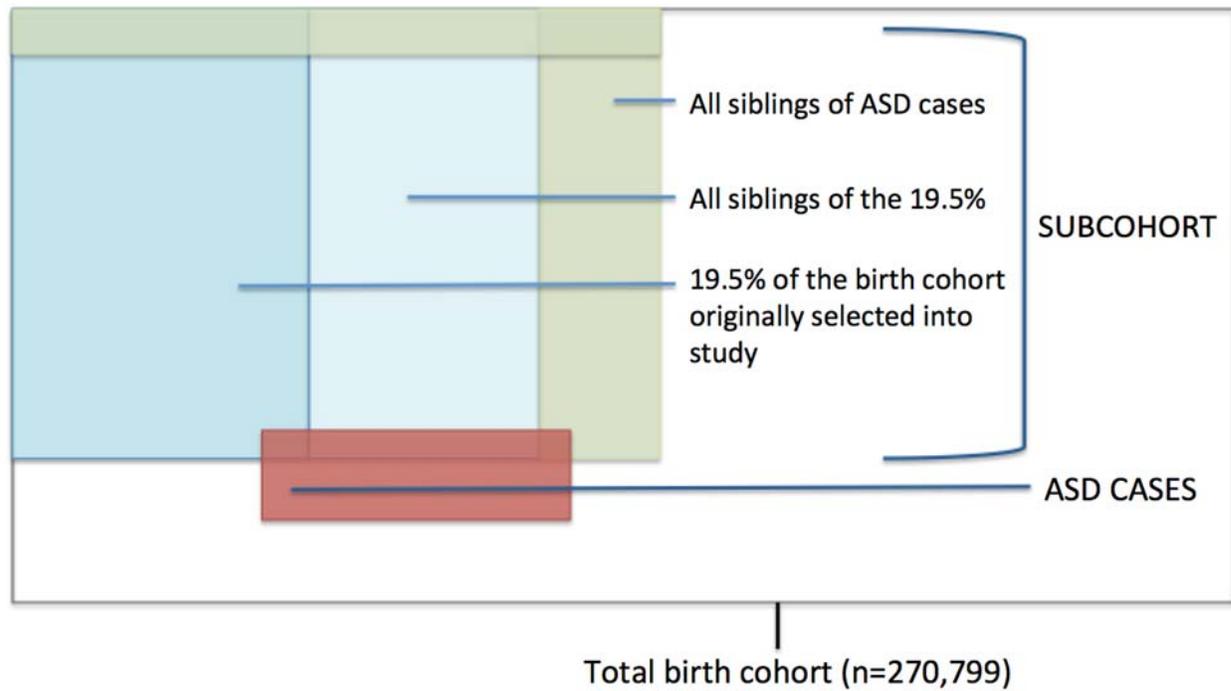
The total birth cohort comprised of 270,799 individuals, born between 1997 and 2007, and registered in the Meuhedet Health Maintenance Organization. For the study cohort, we selected random 19.5% of those individuals and all their siblings who were also born in the cohort years. Additionally, we selected all individuals diagnosed with ASD before end of follow-up period (26th January, 2015), as well as their siblings. The subgroups of (i) initial 19.5%, (ii) their siblings, and (iii) siblings of cases, were part of the final subcohort (35.6% of the total birth cohort). Due to random sampling strategies, there was a partial overlap between the groups i-iii in the subcohort (e.g. a child could be selected as a part of the random 19.5%, and as a sibling of a child with ASD), and those duplicates were removed from the sample prior to the analyses. For the same reason, the subcohort included some children with ASD diagnosis.

eFigure 4. Models Tested in the Main Analyses
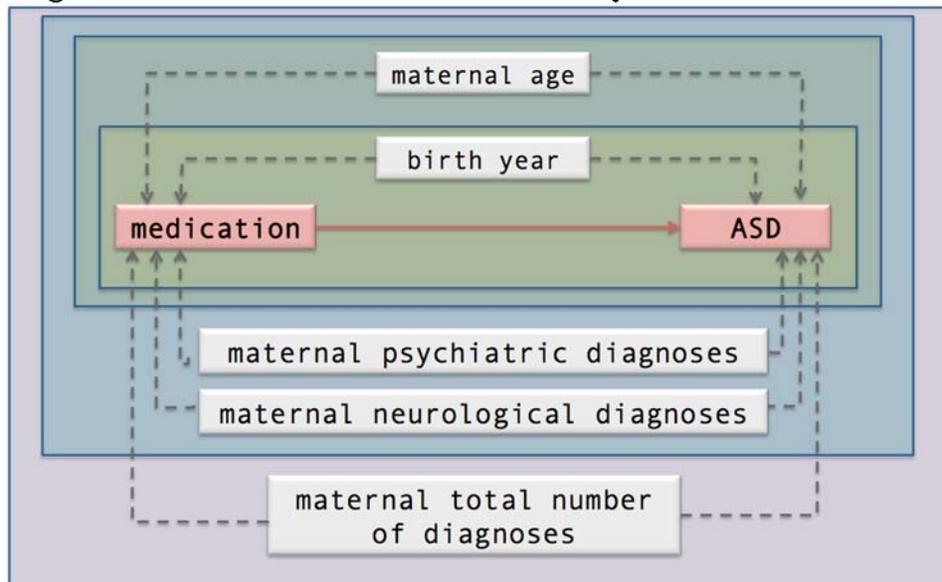
Model 1: exposure + year of birth. Model 2: Model 1 + maternal age at birth. Model 3: Model 2 + maternal history of affective disorders + maternal history of anxiety disorders + maternal history of psychotic disorders + maternal history of neurological disorders. Model 4: Model 3 + maternal number of diagnoses / health issues.

eFigure 5. Calculation of the Family-Based Sampling Probabilities and Weights Used in the Regression
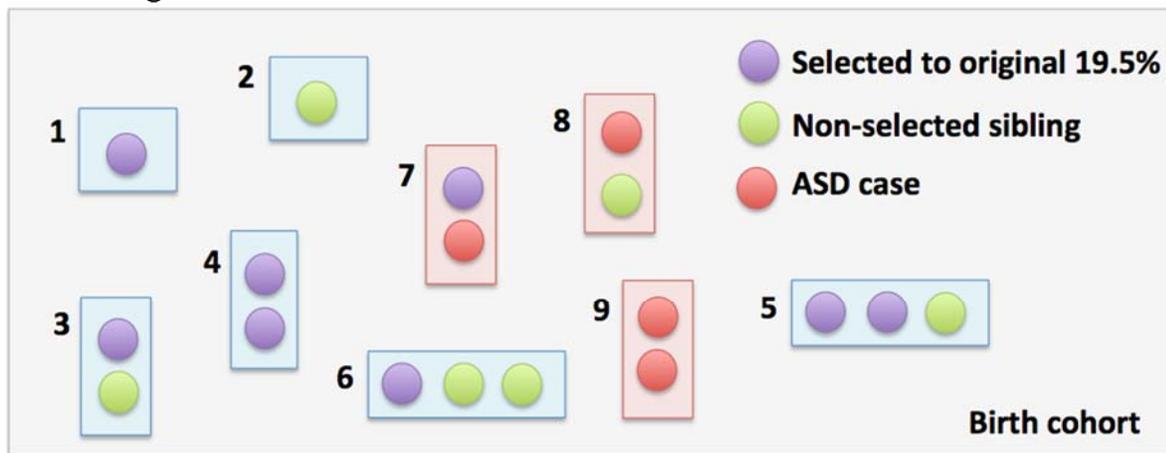
Family	N children in family	N children in the original 19.5%	Siblings of the original 19.5%	ASD cases in family	Siblings of ASD cases	Not in the study cohort	(P) Selection for each child in family	Weights (inverse (P)) for each child in family
1	1	1	0	0	0	0	0.195	5.128
2	1	0	0	0	0	1	0.195	5.128
3	2	1	1	0	0	0	0.352	2.841
4	2	2	0	0	0	0	0.352	2.841
5	3	3	0	0	0	0	0.540	1.853
6	3	1	2	0	0	0	0.540	1.853
7	2	1	0	1	0	0	1	1
8	2	0	0	1	1	0	1	1
9	2	0	0	2	0	0	1	1

All ASD cases and their siblings were included with a probability of 1 (families 7, 8, 9). For the rest of the cohort, the baseline probability of being selected is 0.195 (19.5% sample selected at random), increasing for children from larger families due to sibling sampling approach. E.g. in families 3-6, each child is selected if either him or his sibling is selected, thus the family probability for being in the study (A u B) was 0.352, reflecting joint probability of two non-mutually exclusive events, each happening with a probability of 0.195. To obtain weights used in the regression, the probability of being selected was inversed, and was thus 1 for all cases (1/1), 5.128 for children from single-child families (1/0.195), etc.
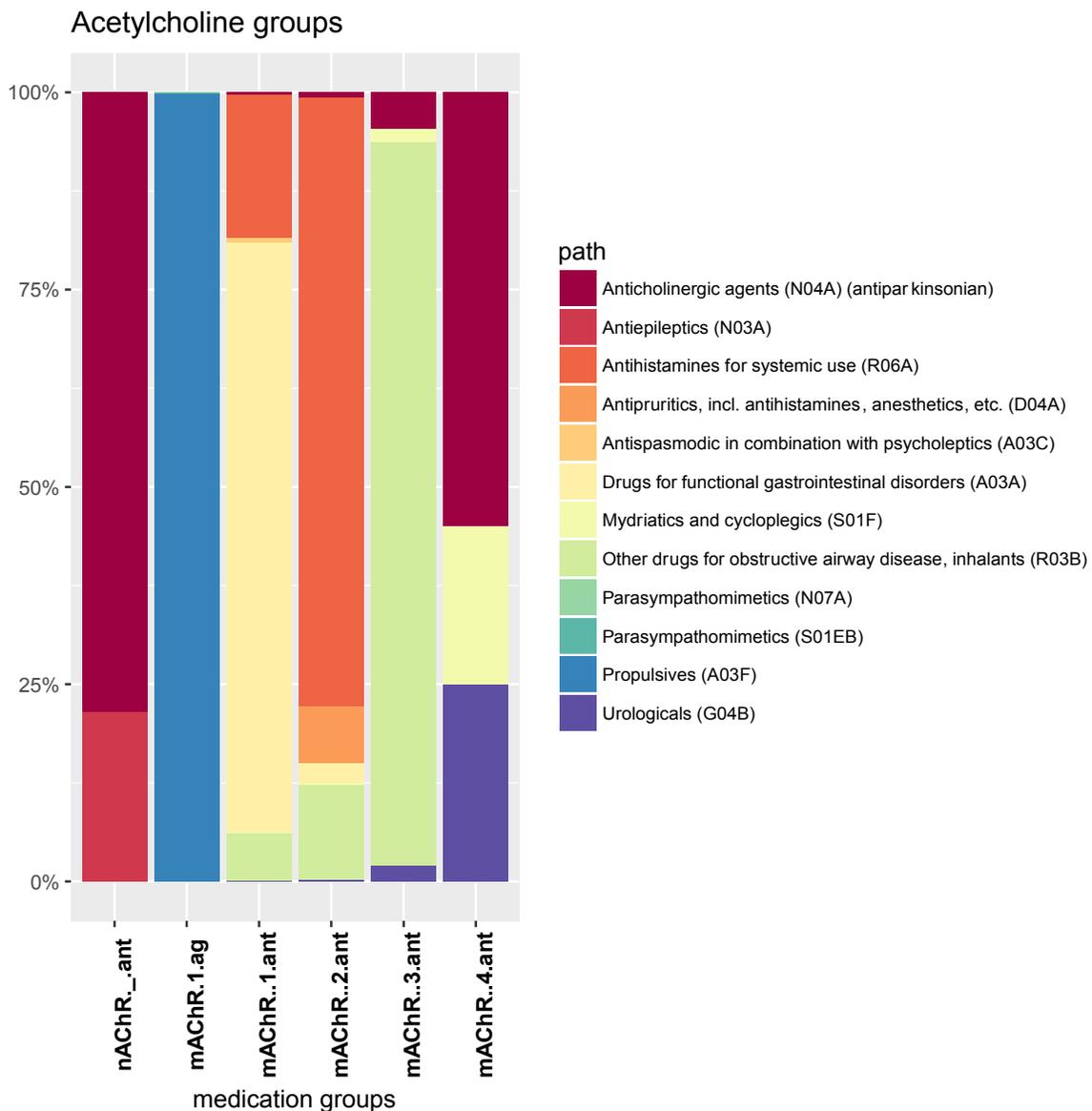
nAchR_ant = neuronal acetylcholine receptor α antagonists; mAChR.1.ag = muscarinic receptor 1 agonist; mAChR.1.ant = muscarinic receptor 1 antagonist; mAChR.2.ant = muscarinic receptor 2 antagonists; mAChR.3.ant = muscarinic receptor 3 antagonists; mAChR.4.ant = muscarinic receptor 4 antagonists.

eFigure 7. Proportion of Individuals Exposed to Drugs With Different ATC Codes, Within Each (Nor)adrenaline Medication Group
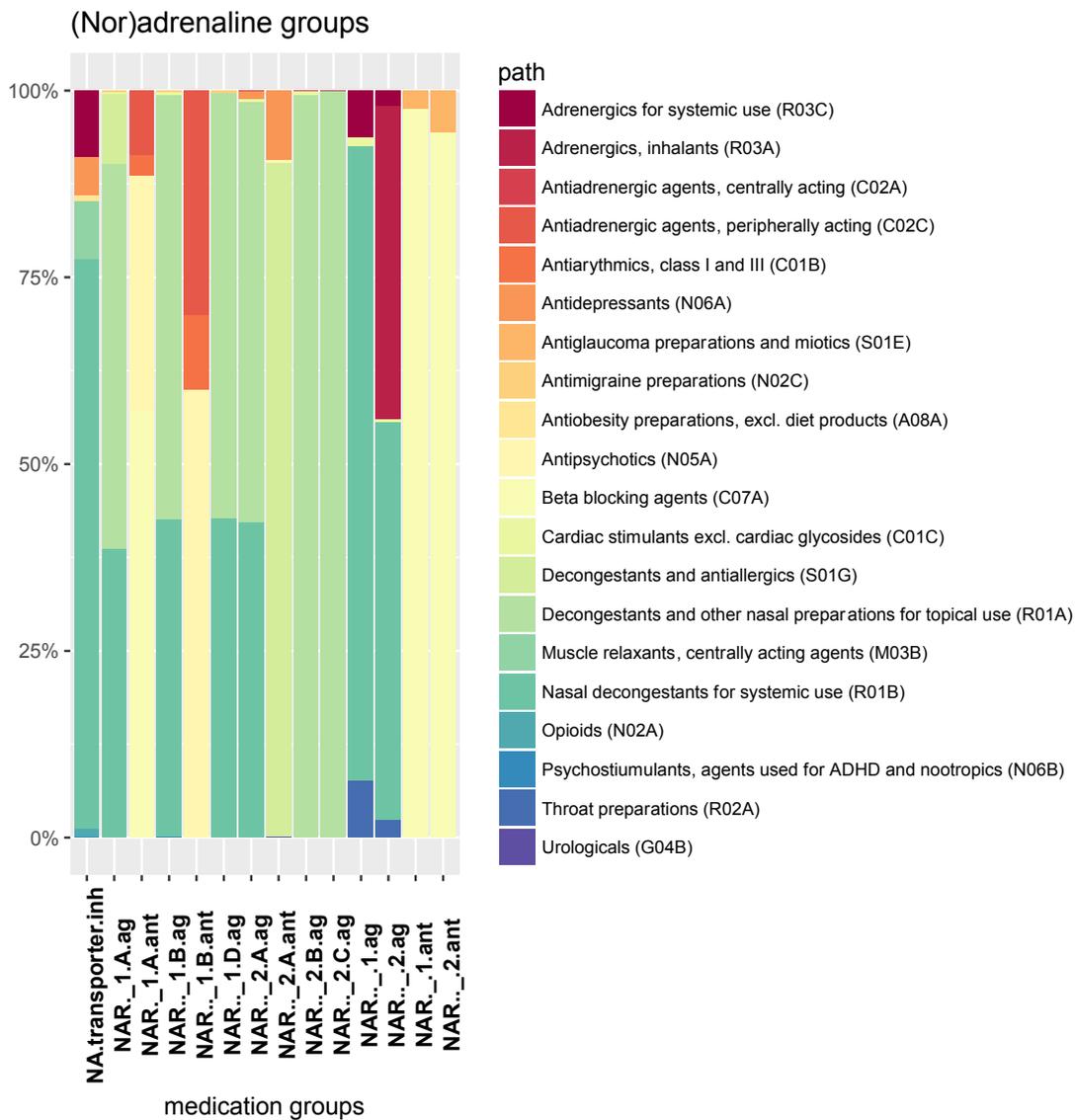
NA.transporter.inh = noradrenaline transporter inhibitors; NAR_1.A.ag = adrenergic receptor α 1A agonists; NAR_1.A.ant = adrenergic receptor α 1A antagonists; NAR_1.B.ag = adrenergic receptor α 1B agonists; NAR_1.B.ant = adrenergic receptor α 1B antagonists; NAR_1.D.ag = adrenergic receptor α 1D agonists; NAR_2.A.ag = adrenergic receptor α 2A agonists; NAR_2.A.ant = adrenergic receptor α 2A antagonist; NAR_2.B.ag = adrenergic receptor α 2B agonists; NAR_2.C.ag = adrenergic receptor α 2C agonists; NAR_1.ag = adrenergic receptor β1 agonists; NAR_1.ant = adrenergic receptor β1 antagonists; NAR_2.ag = adrenergic receptor β2 agonists; NAR_2.ant = adrenergic receptor β2 antagonists.

eFigure 8. Proportion of Individuals Exposed to Drugs With Different ATC Codes, Within Each Dopamine Medication Group
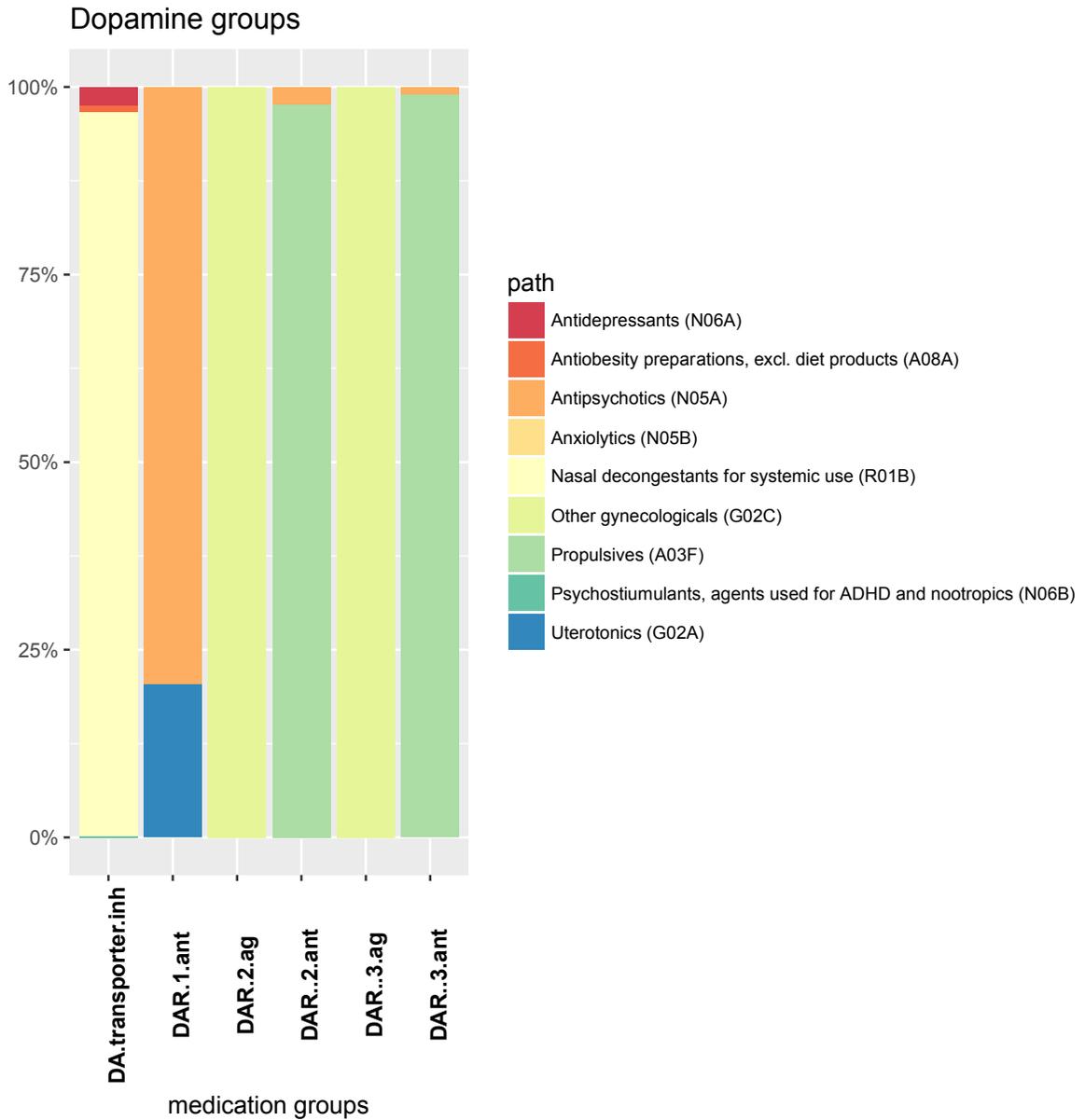
DA.transporter.inh = Dopamine transporter inhibitors; DAR.1.ant = dopamine receptor 1 antagonists; DAR.2.ag = dopamine receptor 2 agonist; DAR.2.ant = dopamine receptor 2 antagonists; DAR.3.ag = dopamine receptor 3 agonists; DAR.3.ant = dopamine receptor 3 antagonists.

eFigure 9. Proportion of Individuals Exposed to Drugs With Different ATC Codes, Within Each GABA/Glutamate Medication Group

GABA/Glutamate groups
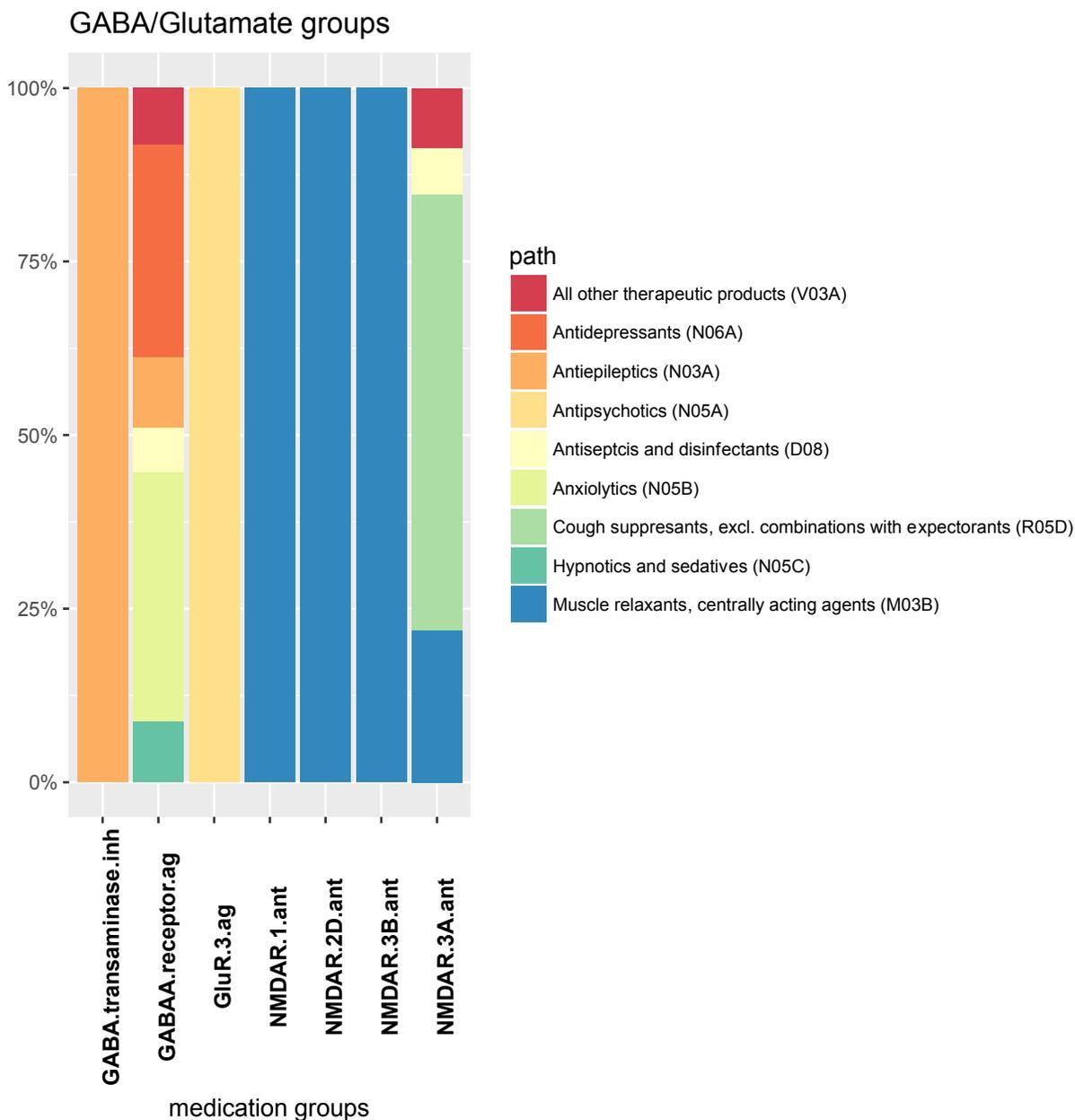
GABA.transaminase.inh = GABA transaminase inhibitors; GABAA.receptor.ag = GABAA receptor agonists; GluR.ag = glutamate receptor 3 agonists; NMDAR.1.ant = NMDA receptor 1 antagonists; NMDAR.2D.ant = NMDA receptor 2D antagonists; NMDAR.3B.ant = NMDA receptor 3B antagonists; NMDAR.3A.ant = NMDA receptor 3A antagonists.

eFigure 10. Proportion of Individuals Exposed to Drugs With Different ATC Codes, Within Each GABA/Glutamate Medication Group
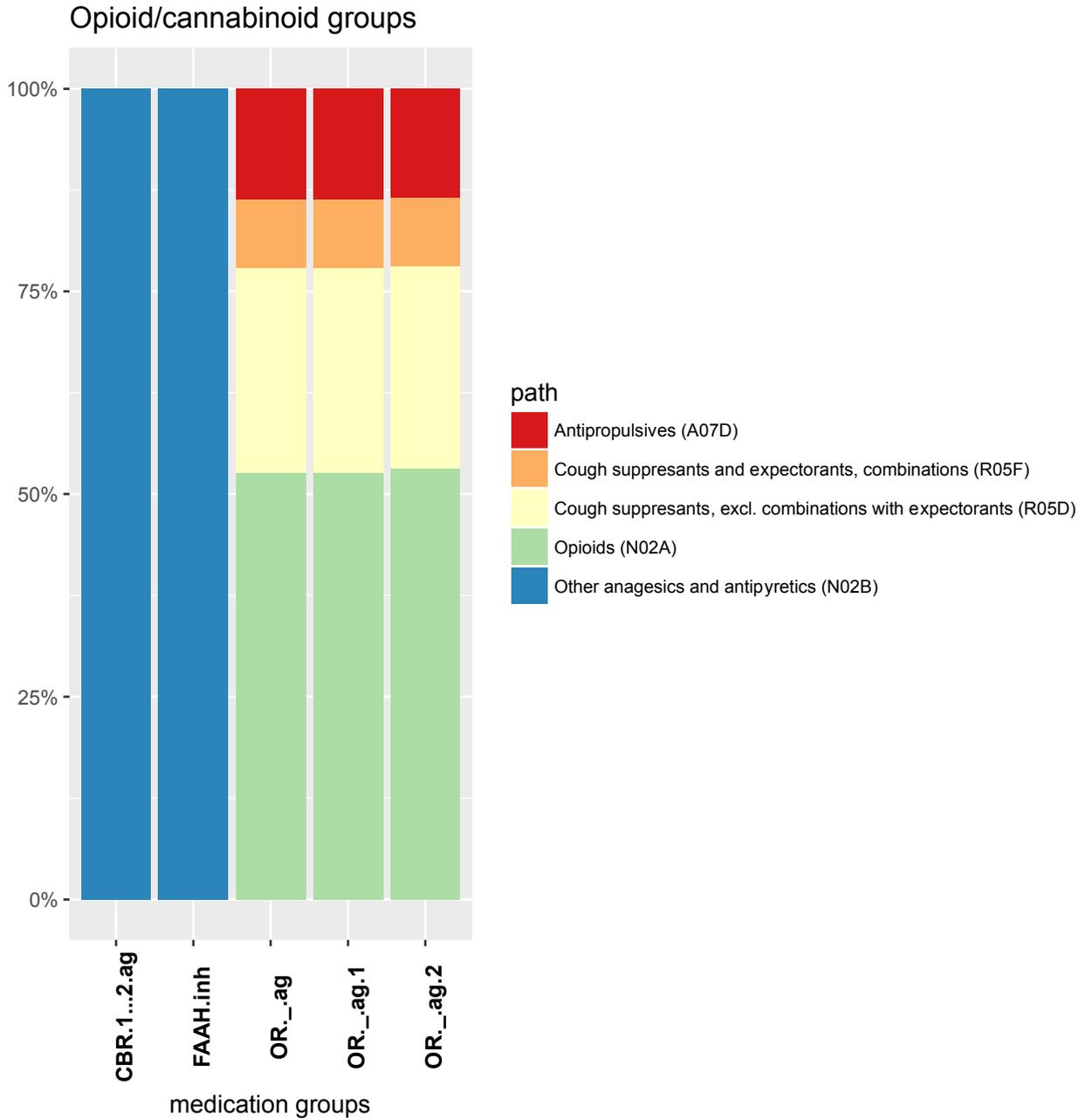
CBR.1.2.ag = cannabinoid receptor 1/2 agonists; FAAH.inh = fatty acid amide hydrolase inhibitors; OR_ag = Opioid κ receptor agonists; OR_ag.1 = opioid ε receptor agonists; OR_ag.2 = opioid μ receptor agonists.

eFigure 11. Proportion of Individuals Exposed to Drugs With Different ATC Codes, Within Each Serotonin (5HT) Medication Group
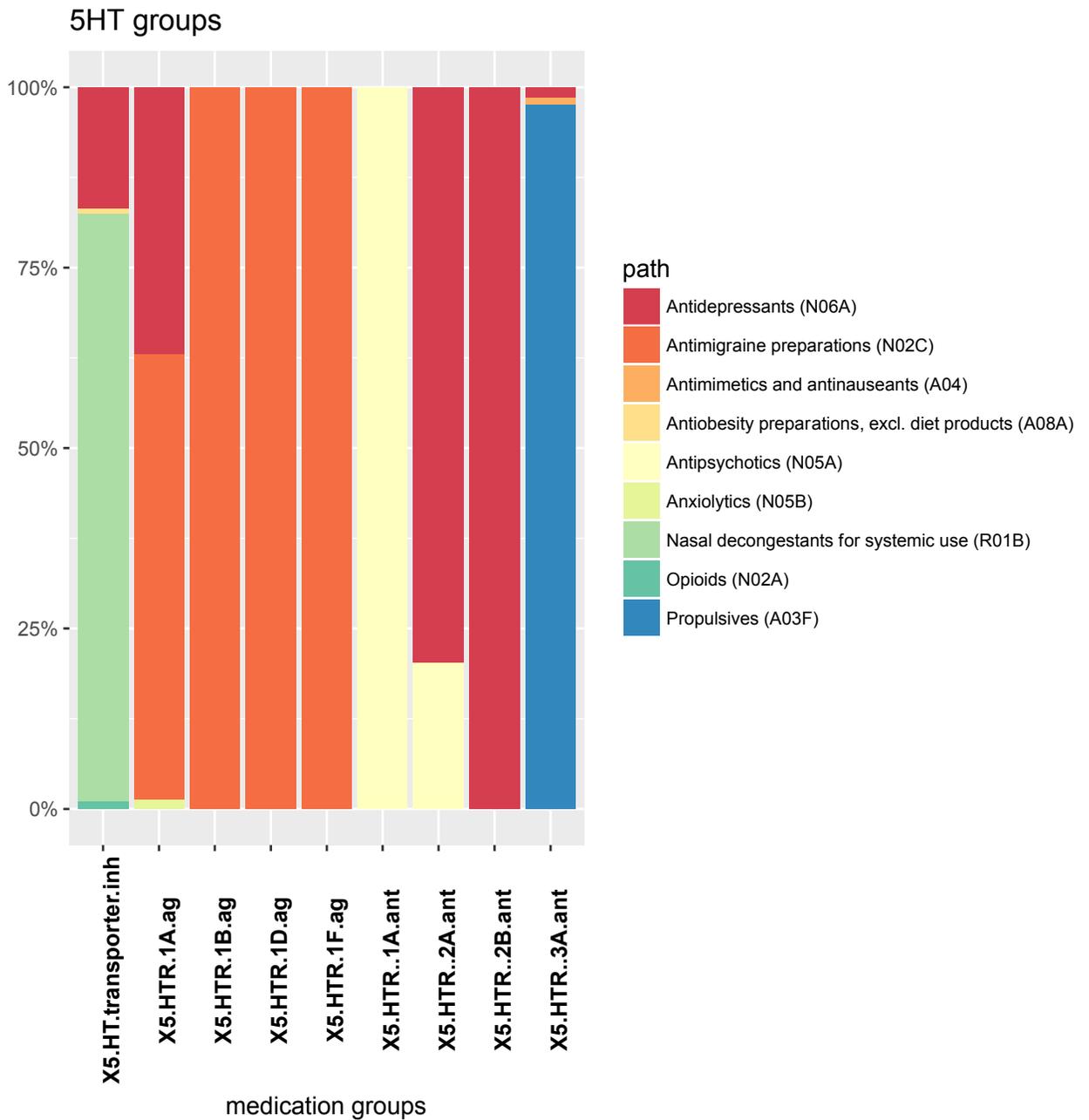
X5.HT.transporter.inh = serotonin re-uptake inhibitors; X5.HTR.1A.ag = serotonin receptor 1A agonists; X5.HTR.1B.ag = serotonin receptor 1B agonists; X5.HTR.1D.ag = serotonin receptor 1D agonists; X5.HTR.1F.ag = serotonin receptor 1F agonists; X5.HTR.1A.ant = serotonin receptor 1A antagonists; X5.HTR.2A.ant = serotonin receptor 2A antagonists; X5.HTR.2B.ant =serotonin receptor 2B antagonists; X5.HTR.3A.ant = serotonin receptor 3A antagonists.

eFigure 12. Proportion of Individuals Exposed to Drugs With Different ATC Codes, Within Each Adenosine, Histamine, and Vesicular Amine Transporter Medication Group

Misc groups
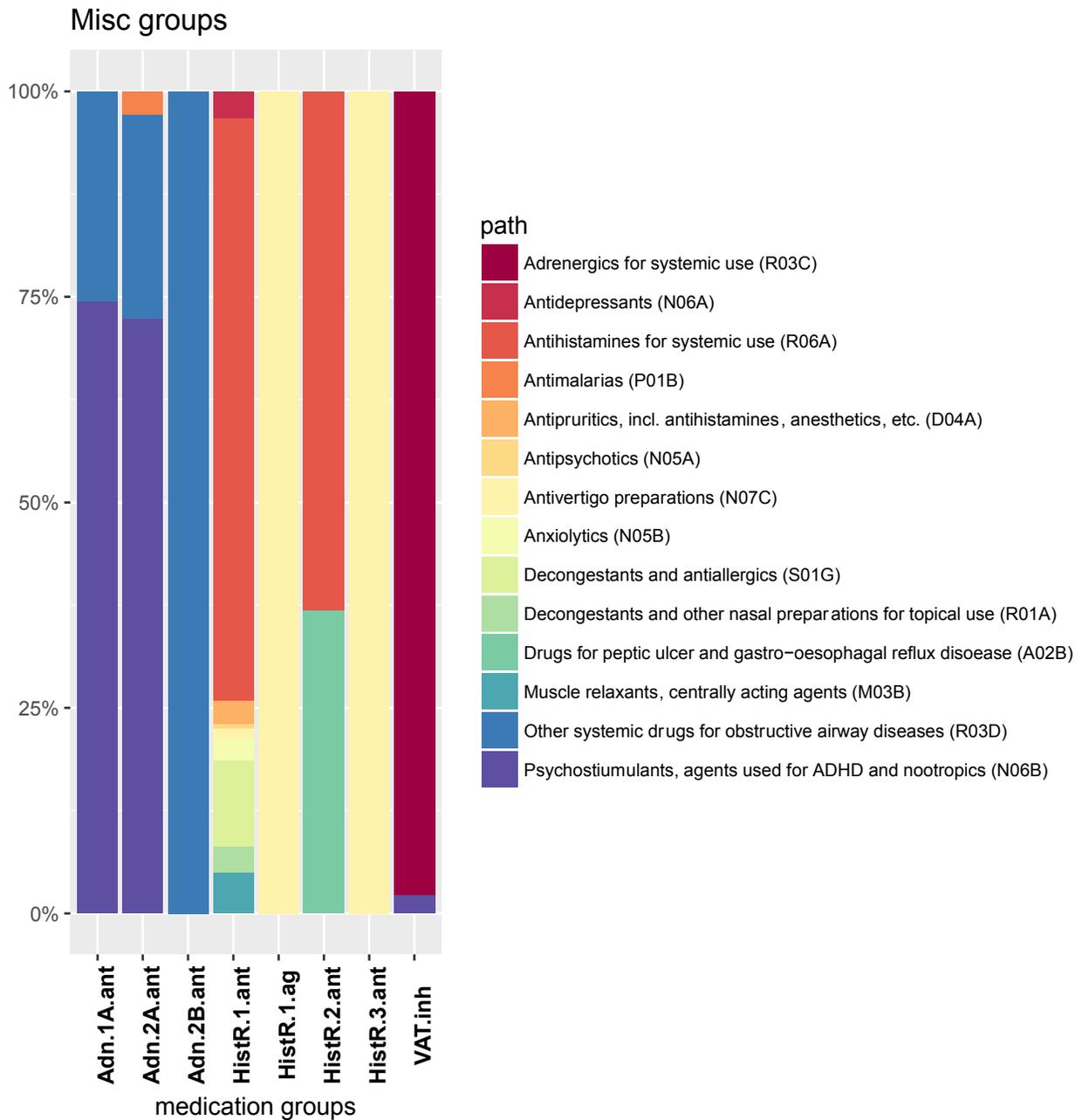
Adn.1A.ant = adenosine receptor A1 antagonists; Adn.2A.ant = adenosine receptor A 2A antagonists; Adn.2B.ant = adenosine receptor A 2B antagonist; HistR.1.ant = histamine receptor 1 antagonists; HistR.1.ag = histamine receptor 1 agonists; HistR.2.ant = histamine receptor 2 antagonists; HistR.3.ant = histamine receptor 3 antagonists; VAT.inh = vesicular amine transporter inhibitors.

eFigure 13. Kaplan-Meier Plots Showing Risk in Different Exposure and Covariate Groups
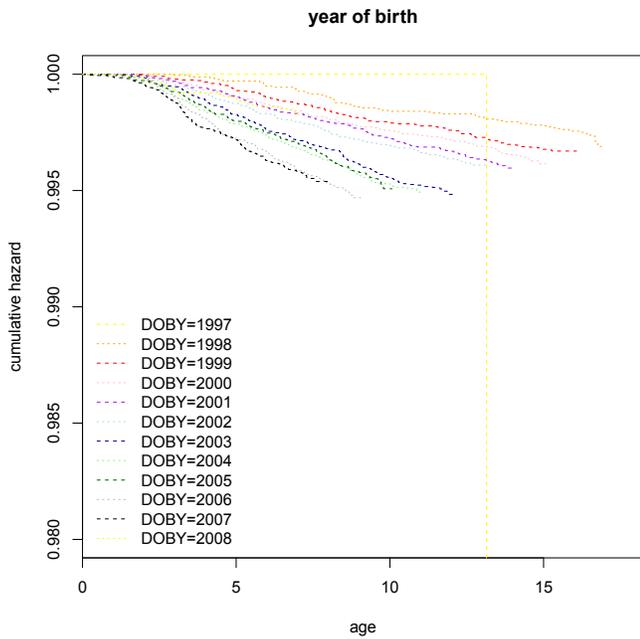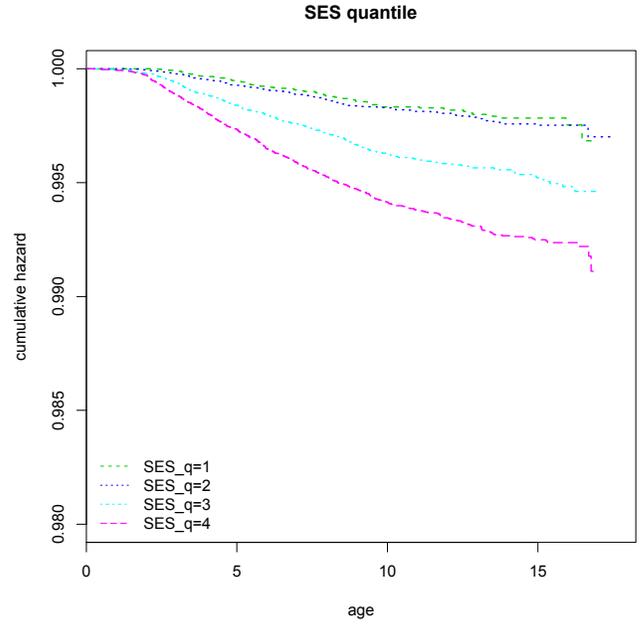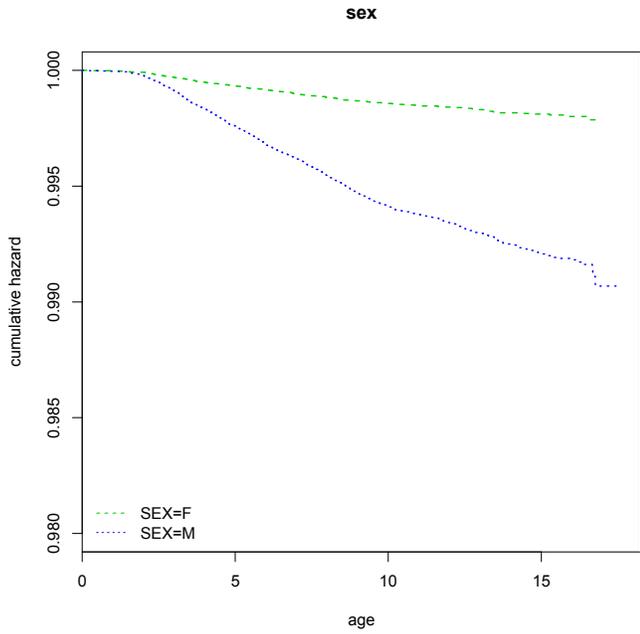
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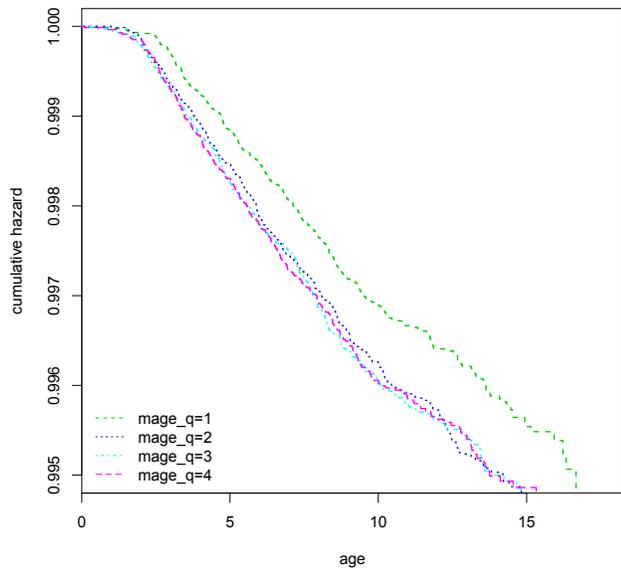
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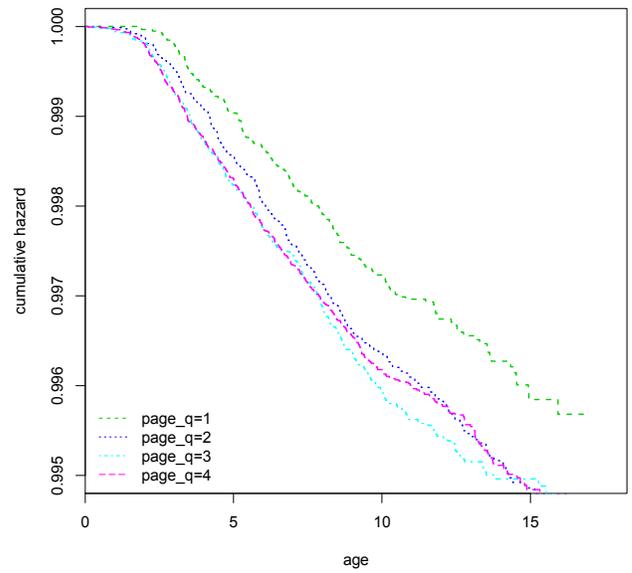
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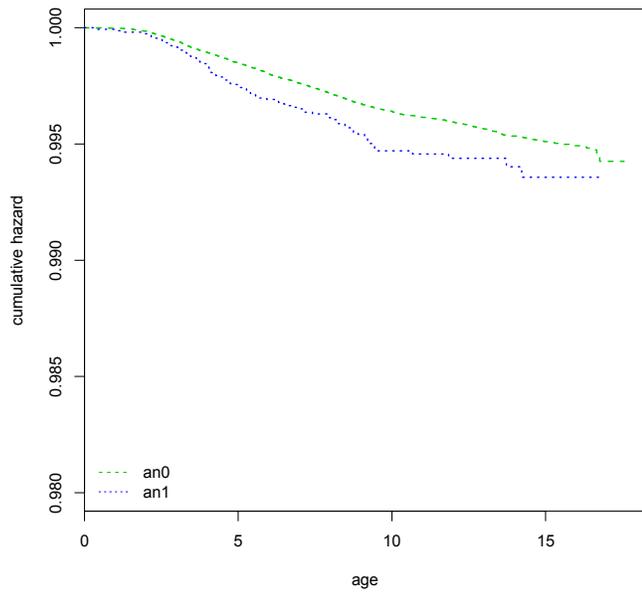
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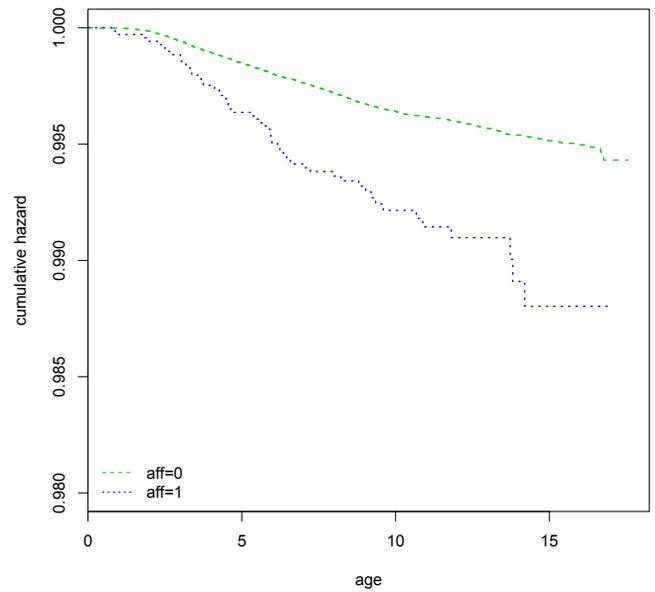
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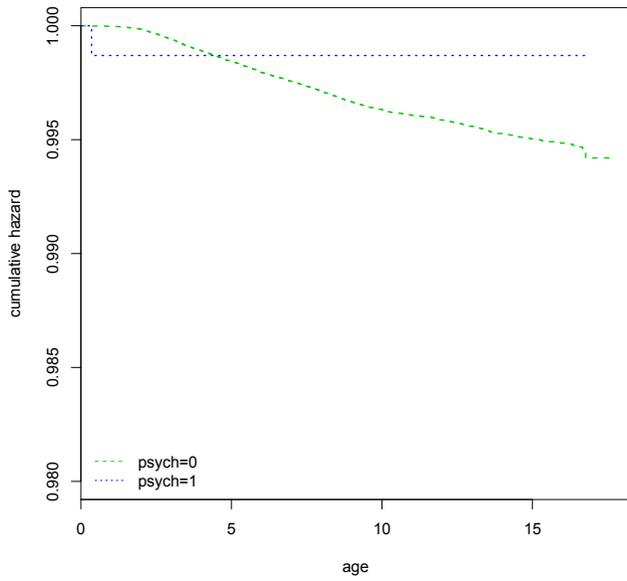
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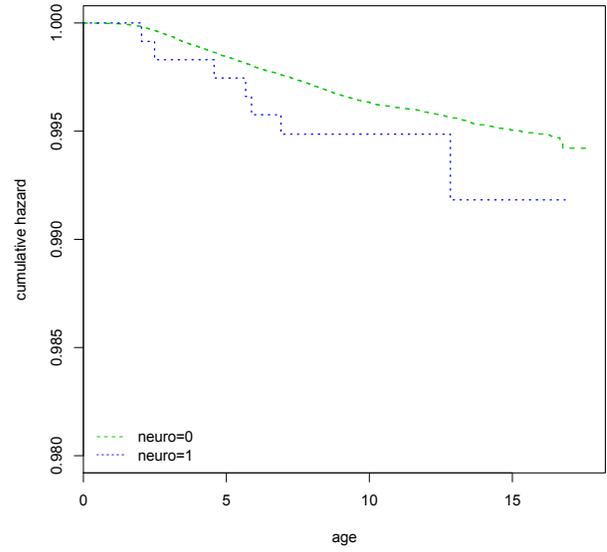
Adrenergic receptor alpha 1A agonist
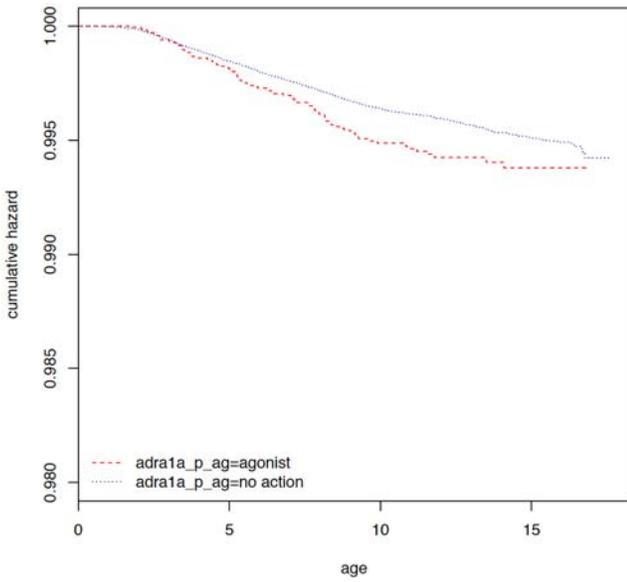
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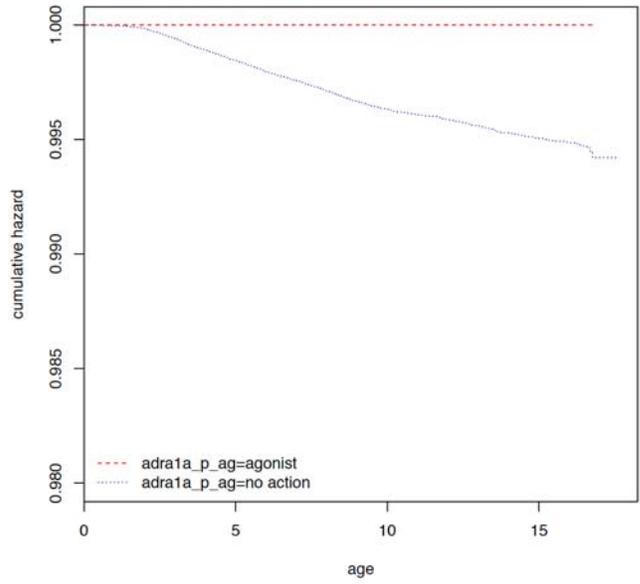
Adrenergic receptor alpha 1B agonist
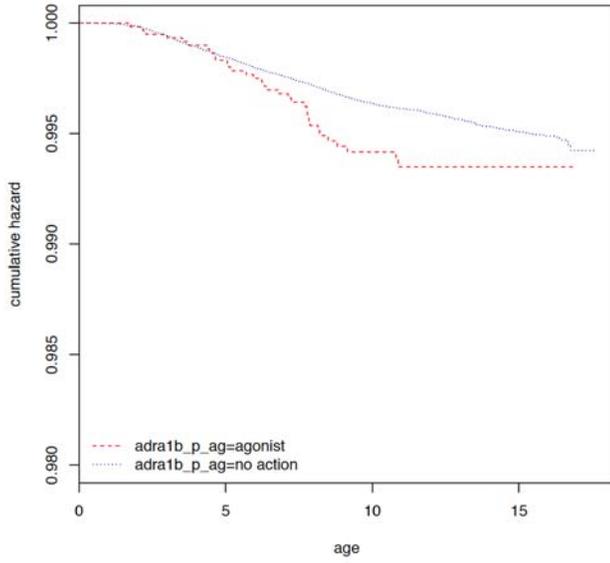
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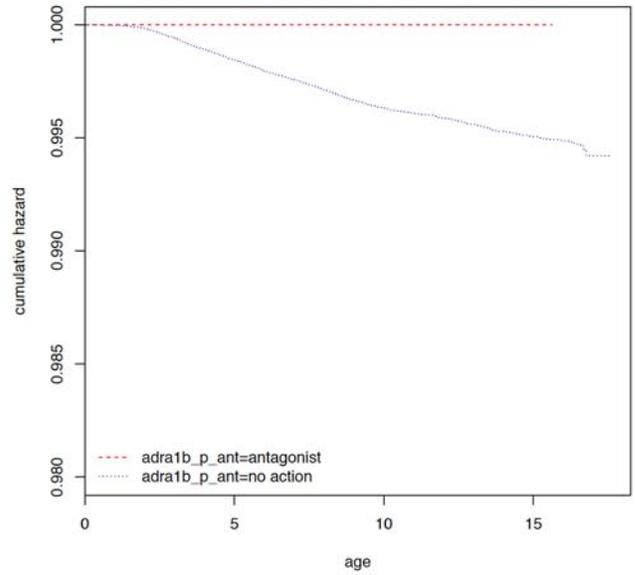
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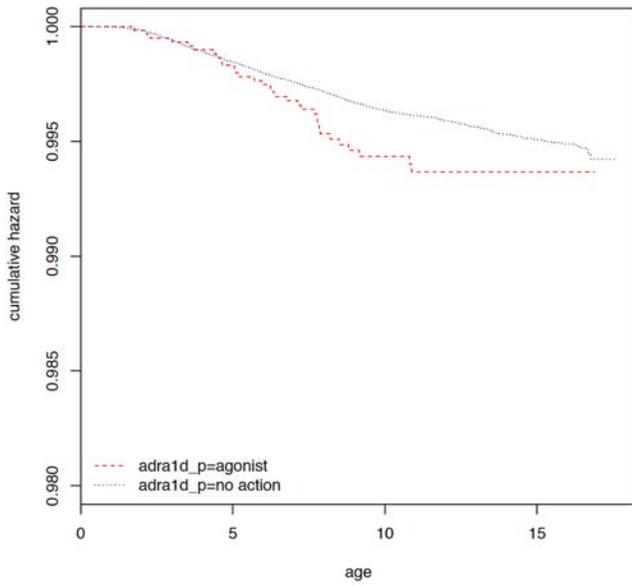
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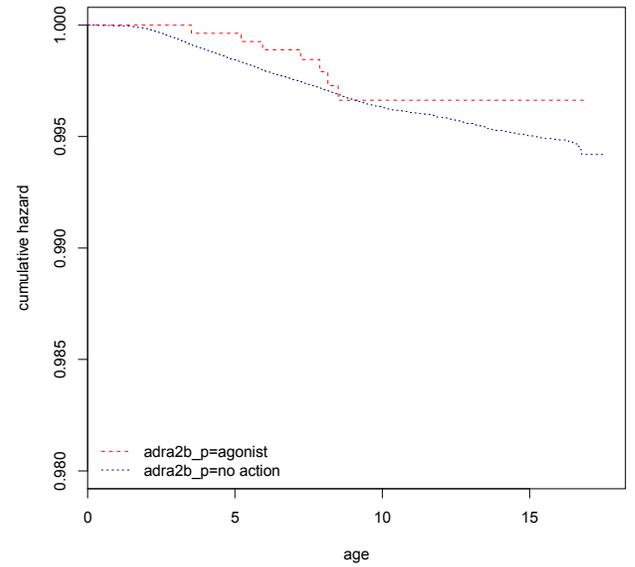
Adrenergic receptor alpha 2A agonist exposure

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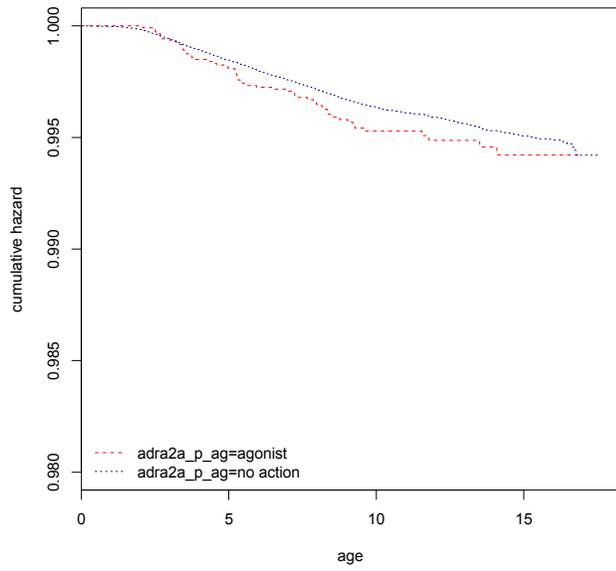
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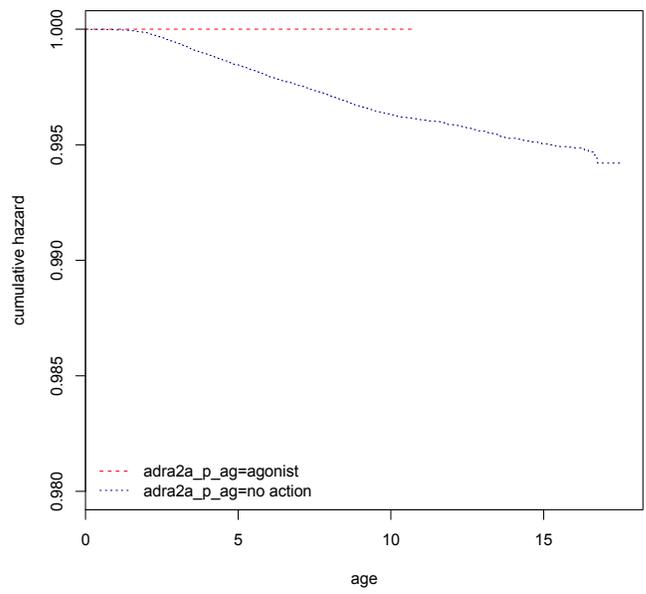
Adrenergic receptor beta 1 agonist exposure

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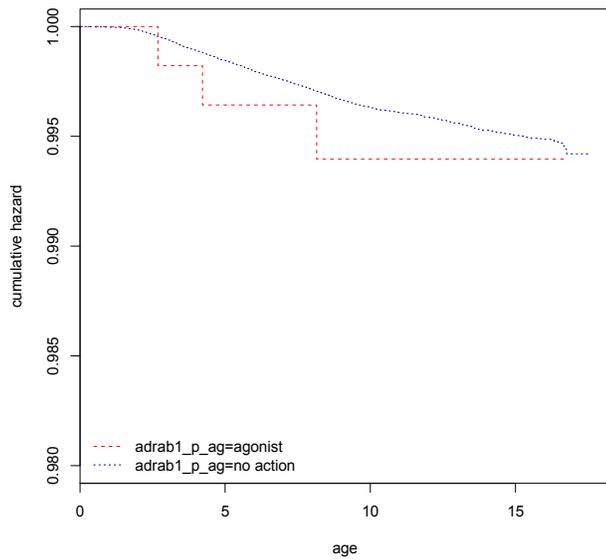
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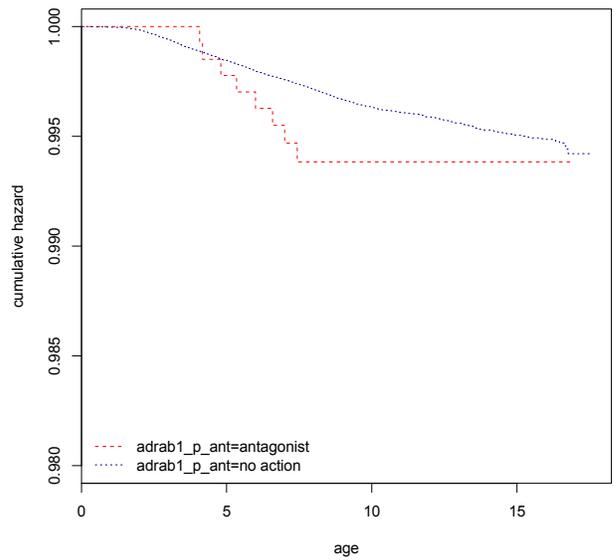
Adrenergic receptor beta 2 agonist exposure

cumulative hazard vs age

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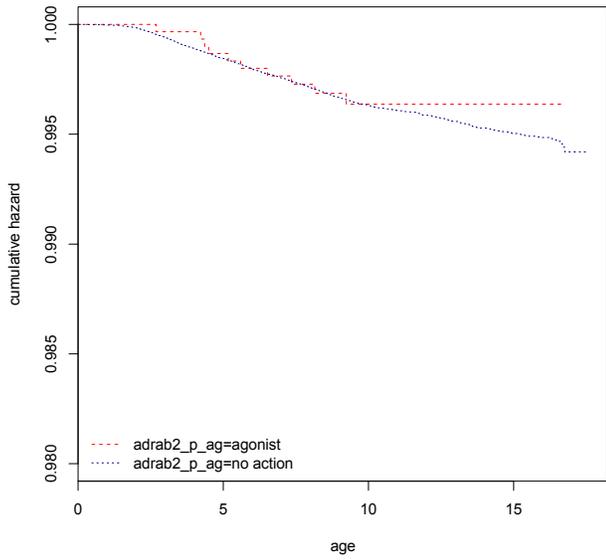
Adrenergic receptor beta 2 antagonist exposure

cumulative hazard vs age

- adrab2_p_ant=antagonist
- adrab2_p_ant=no action

adenosine receptor 1 antagonist exposure

cumulative hazard vs age

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- adna1_p=no action
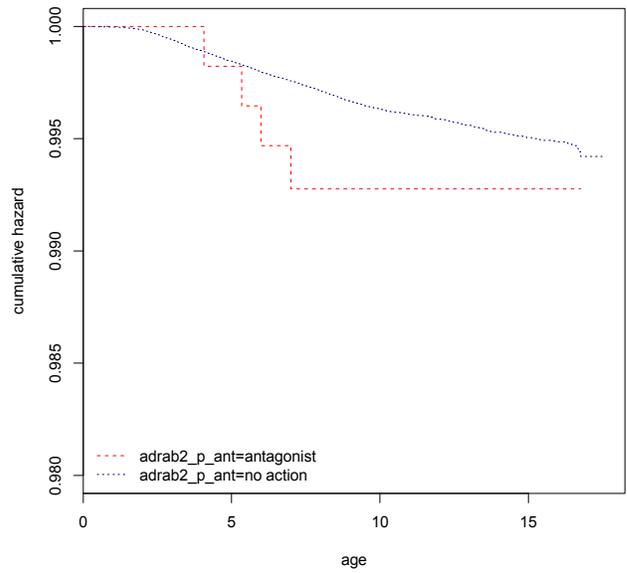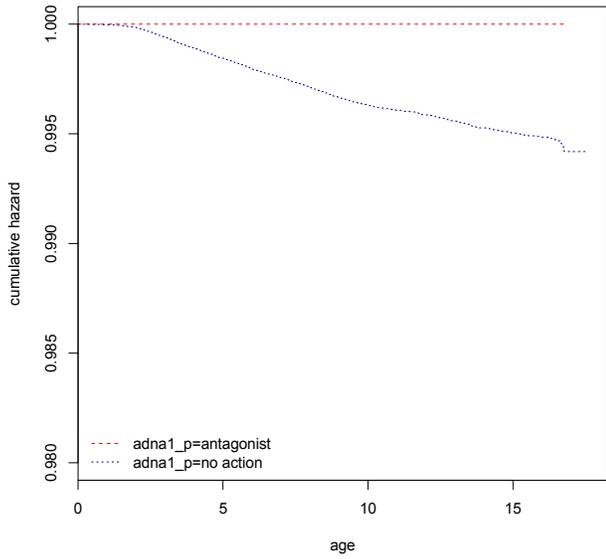
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cumulative hazard vs age

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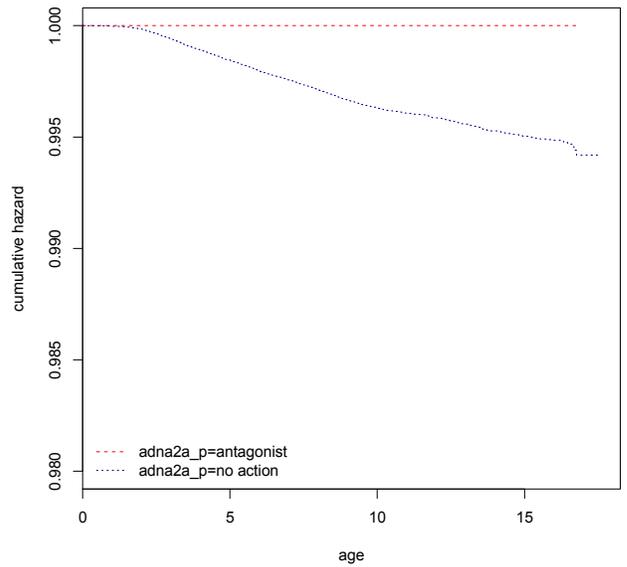
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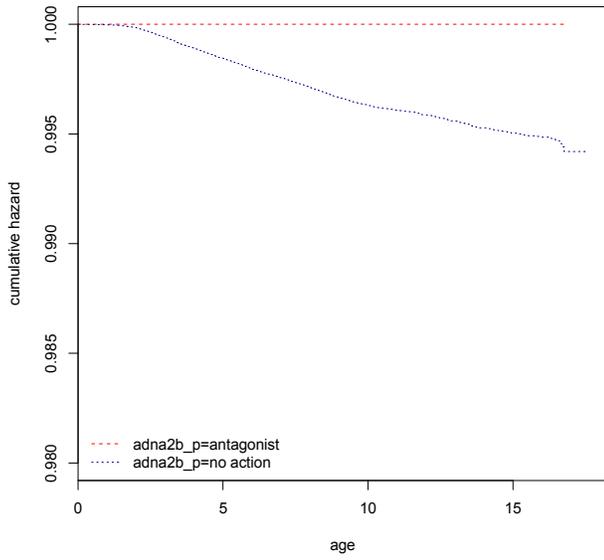
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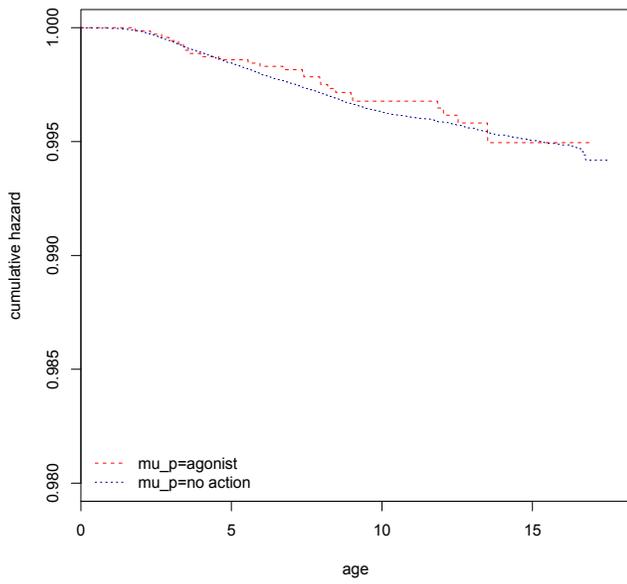
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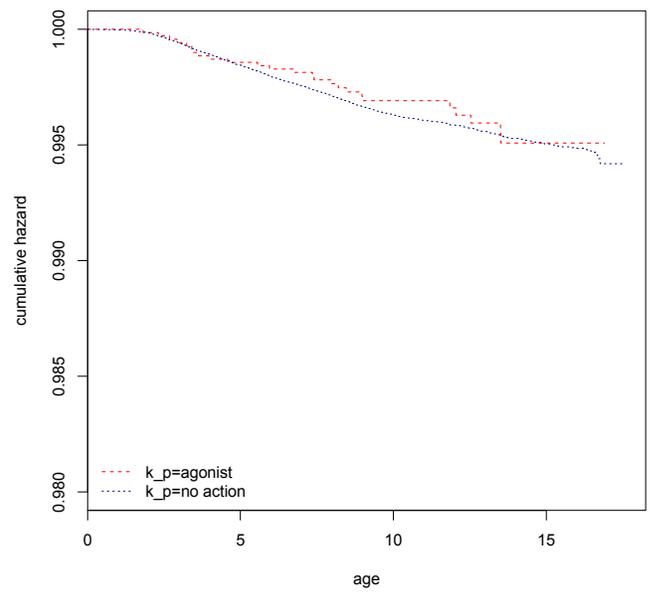
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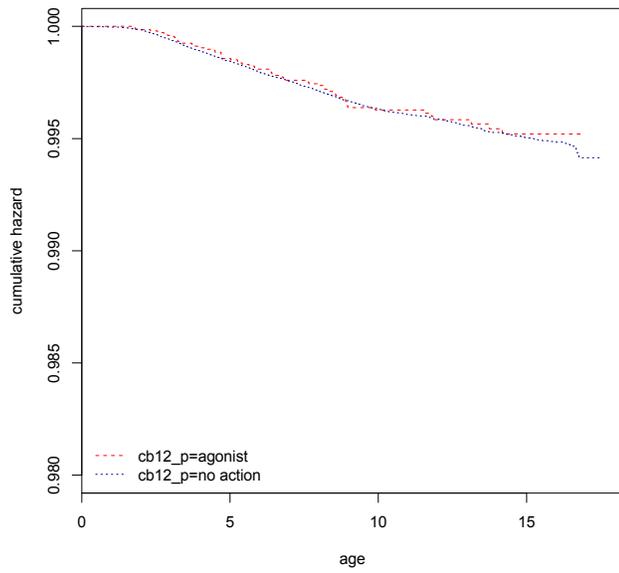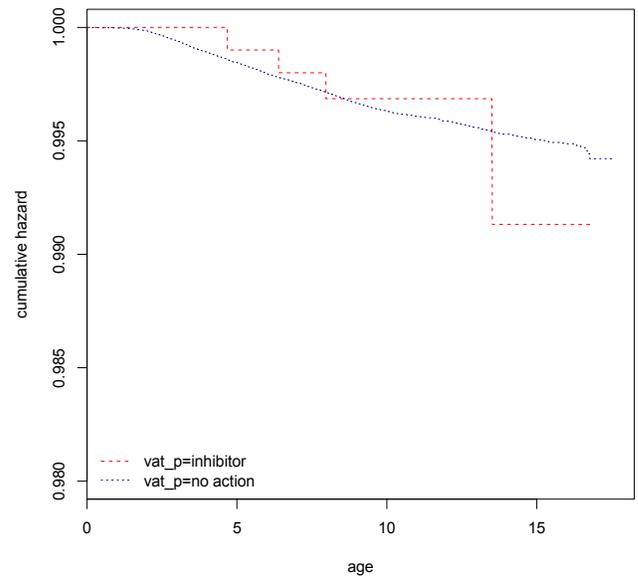
cb12_p=agonist
cb12_p=no action

VAT inhibitor exposure

vat_p=inhibitor
vat_p=no action

DA re-uptake inhibitor exposure

dare_p=inhibitor
dare_p=no action

NA re-uptake inhibitor exposure

norre_p=inhibitor
norre_p=no action

5−HT re−uptake inhibitor exposure

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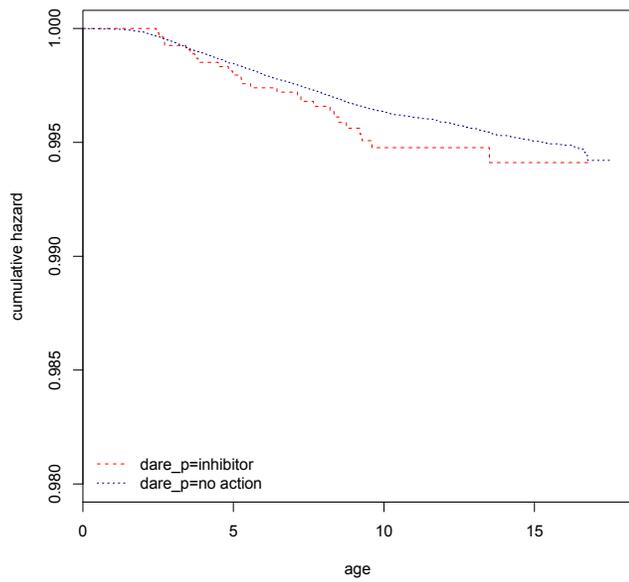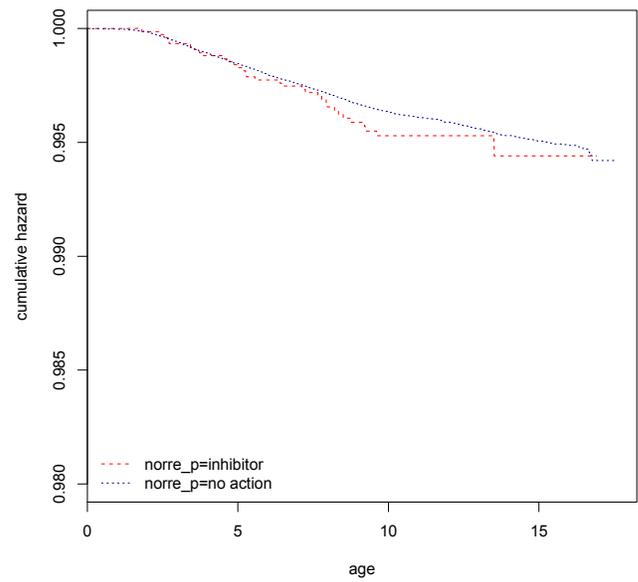
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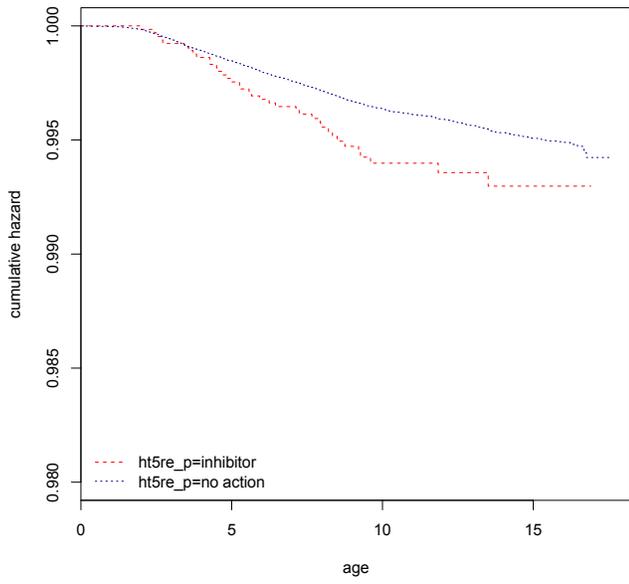
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gabare_p=no action
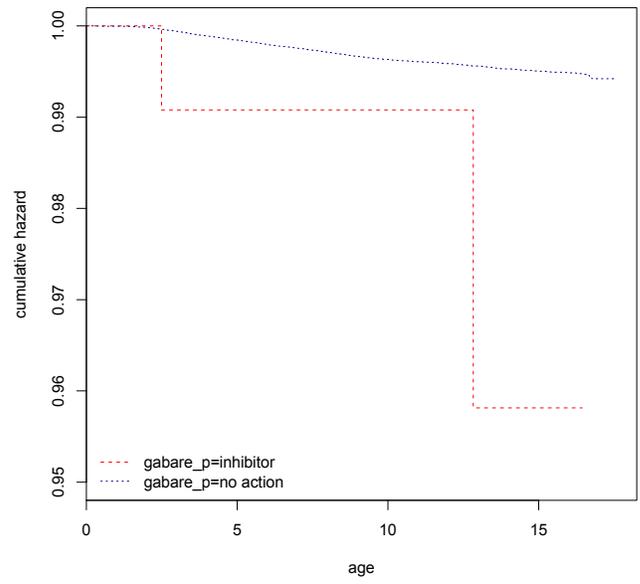
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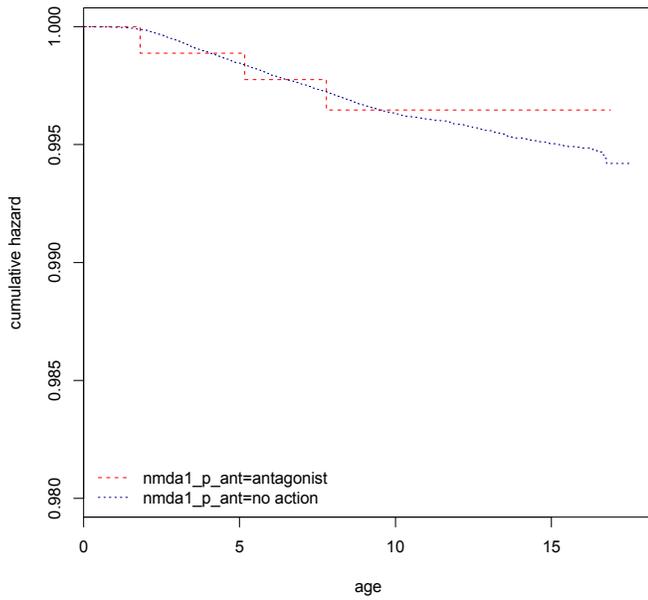
NMDA 3A receptor antagonist exposure

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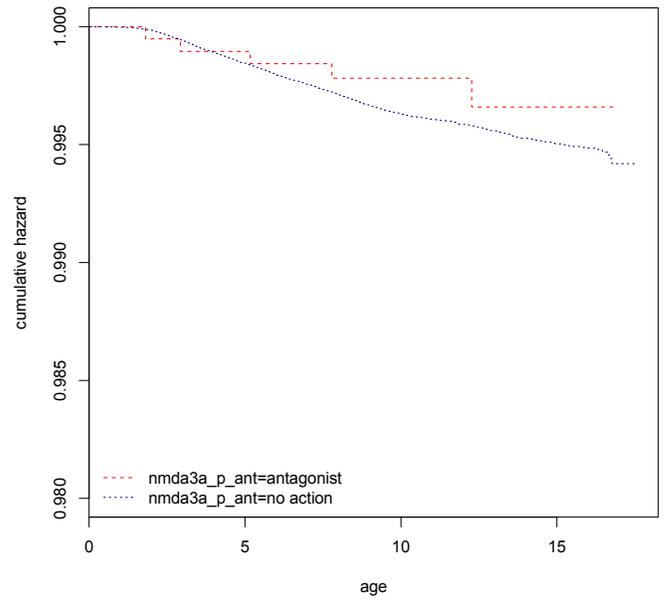
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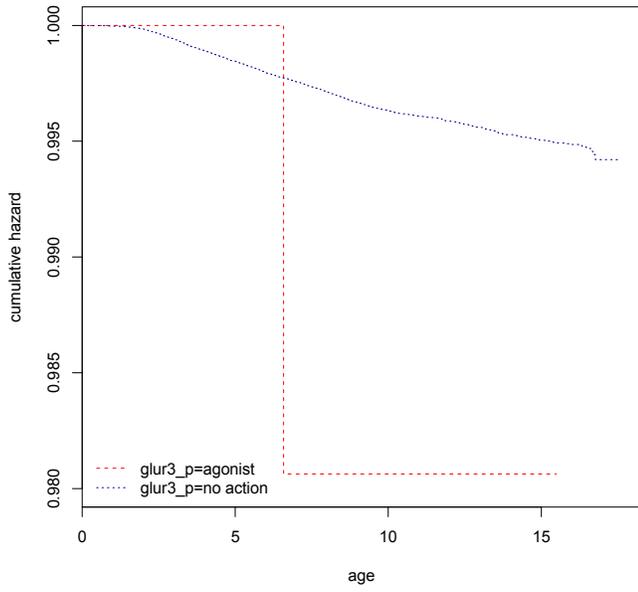
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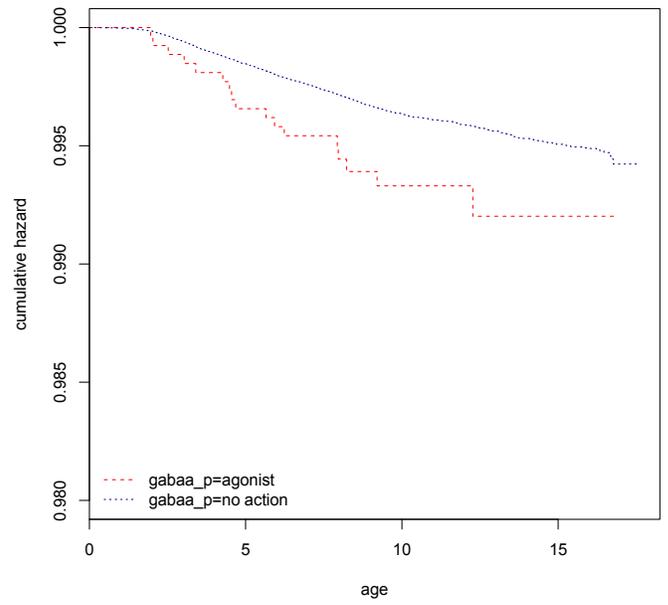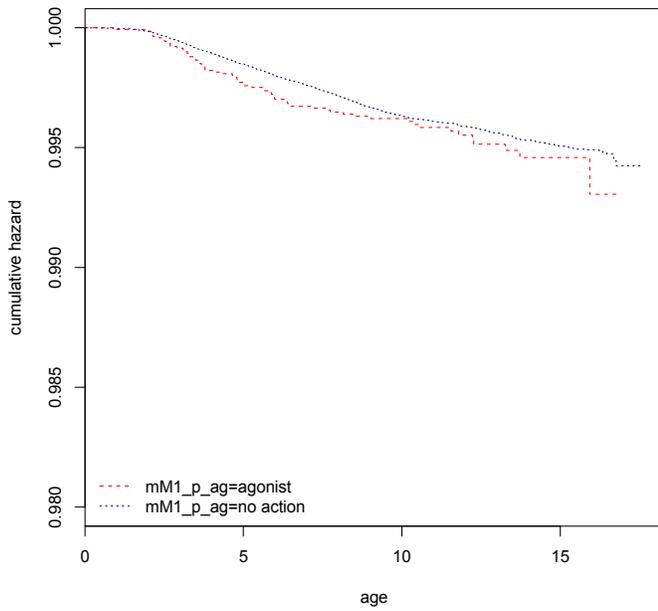
muscarinic receptor 1 agonist exposure

muscarinic receptor 1 antagonist exposure

muscarinic receptor 2 antagonist exposure

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..... mM2_p_ant=no action

muscarinic receptor 3 antagonist exposure

- - - mM3_p_ant=antagonist
..... mM3_p_ant=no action

muscarinic receptor 4 antagonist exposure

- - - mM4_p_ant=antagonist
..... mM4_p_ant=no action
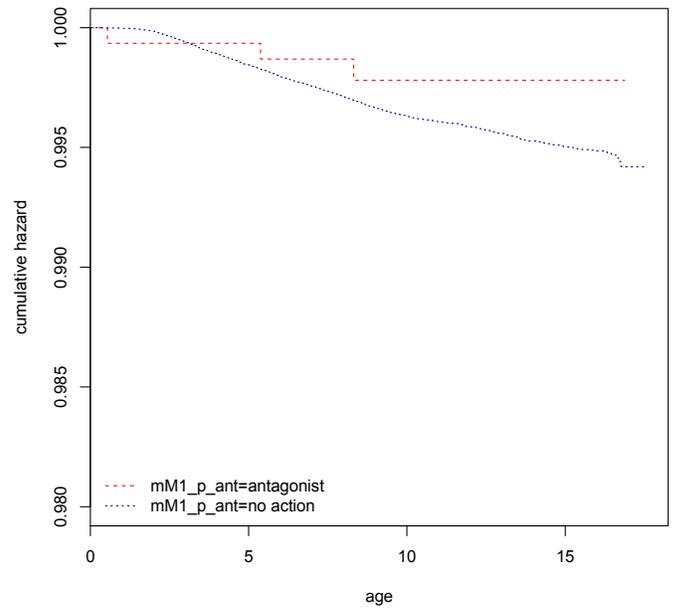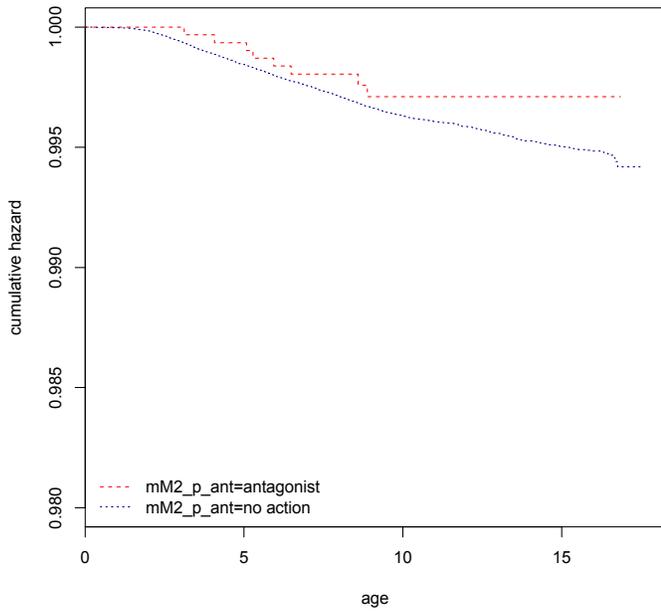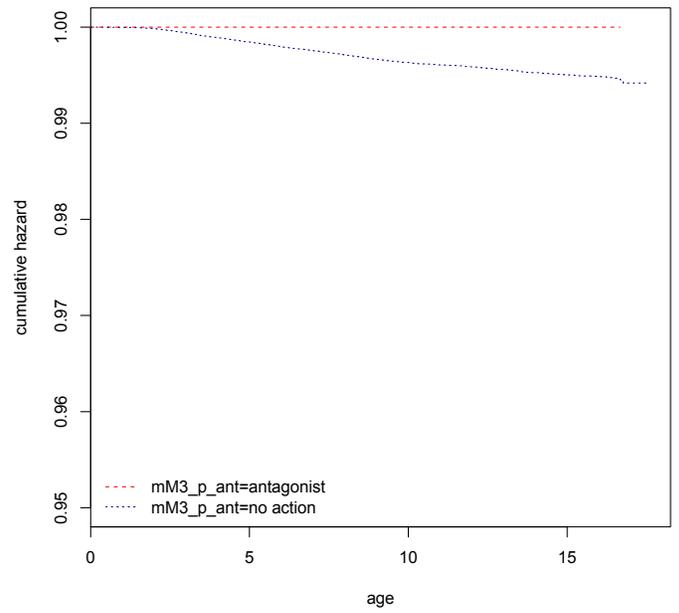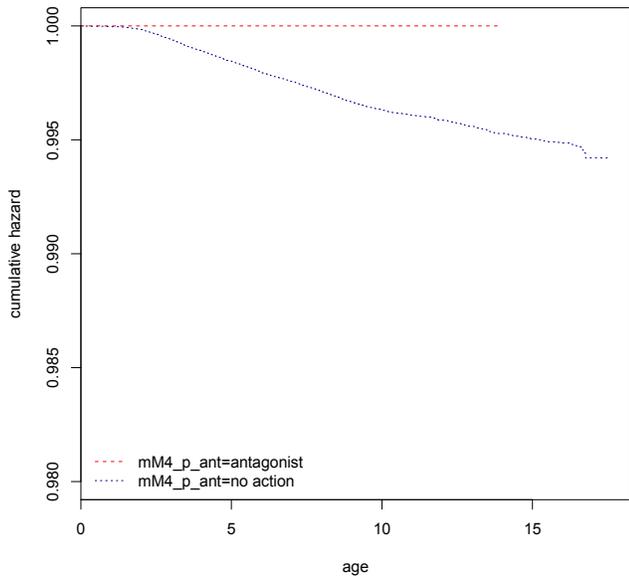
acetylcholine nicotinic receptor antagonist
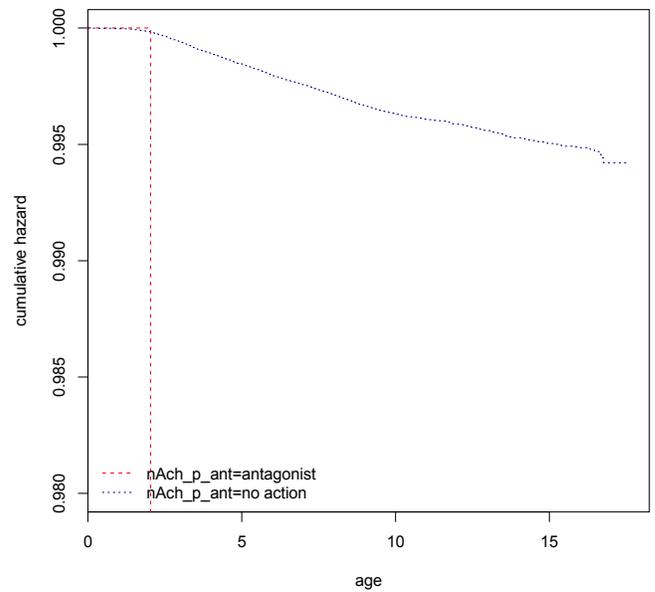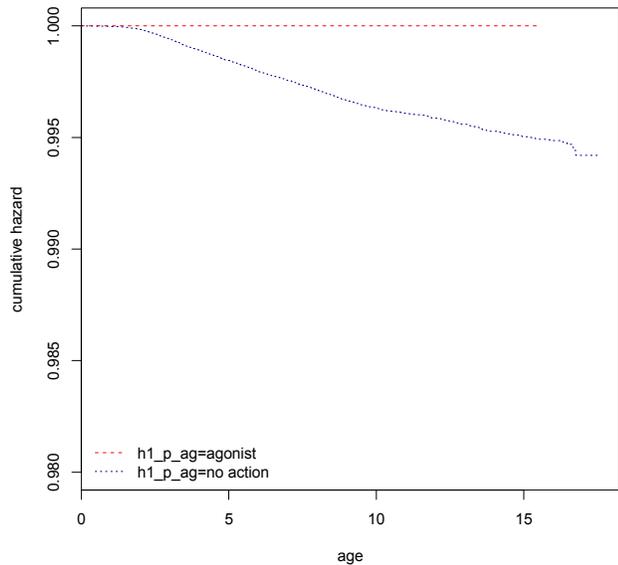
- - - nAch_p_ant=antagonist
..... nAch_p_ant=no action

histamine receptor 1 agonist exposure

histamine receptor 1 antagonist exposure
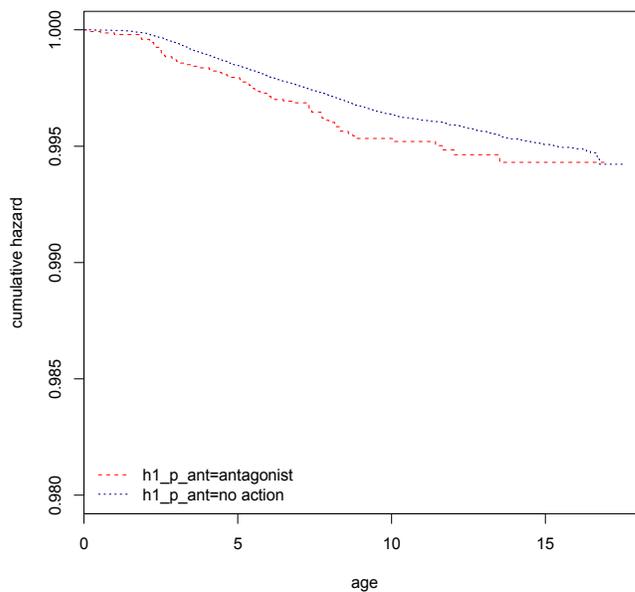
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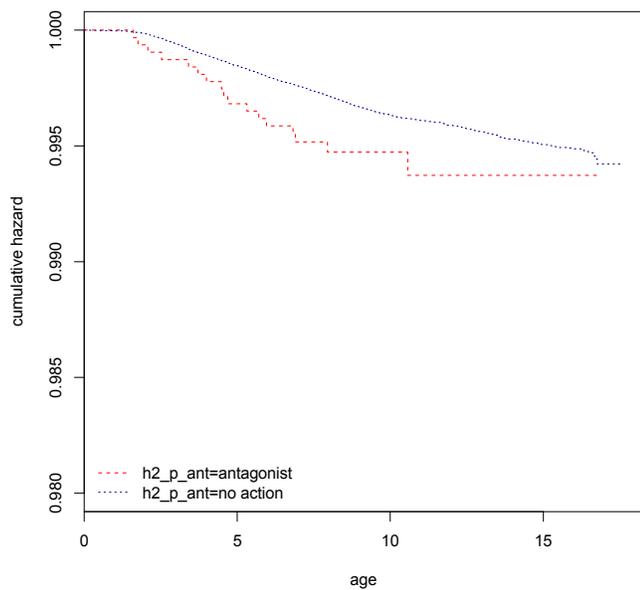
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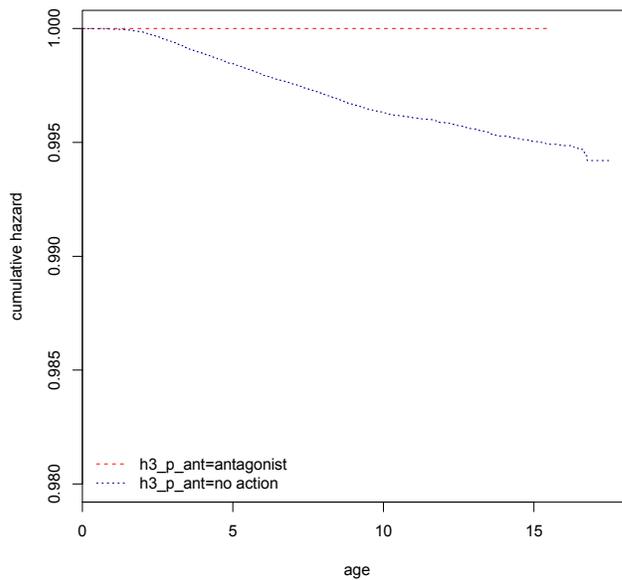
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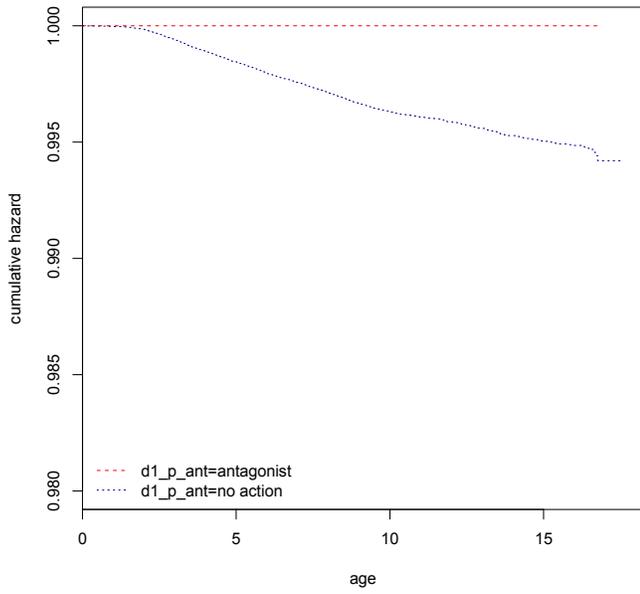
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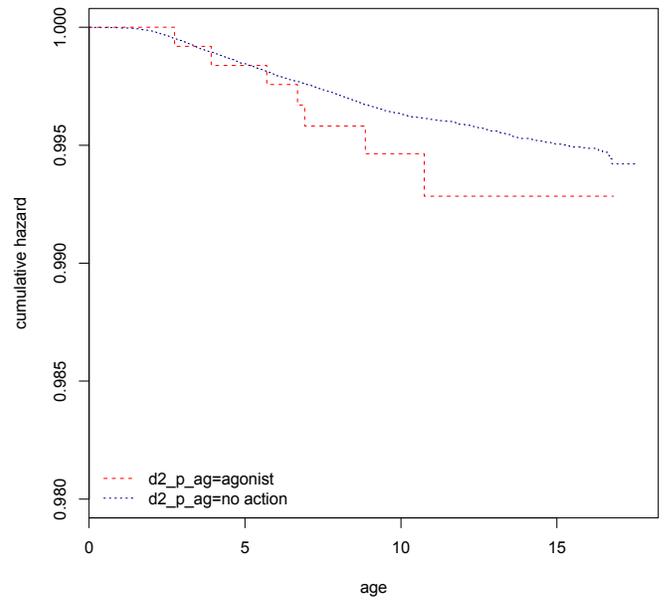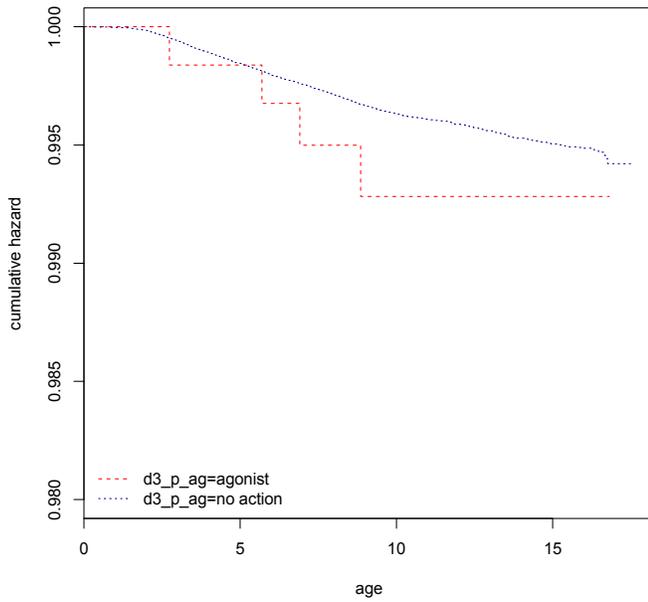
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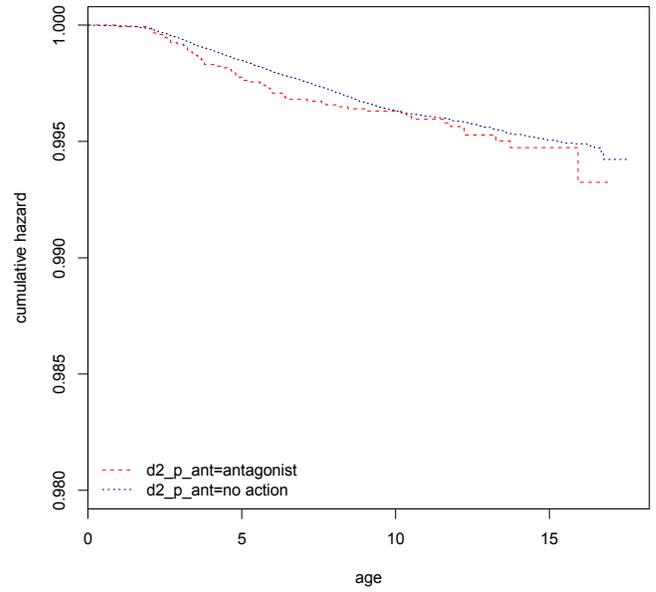
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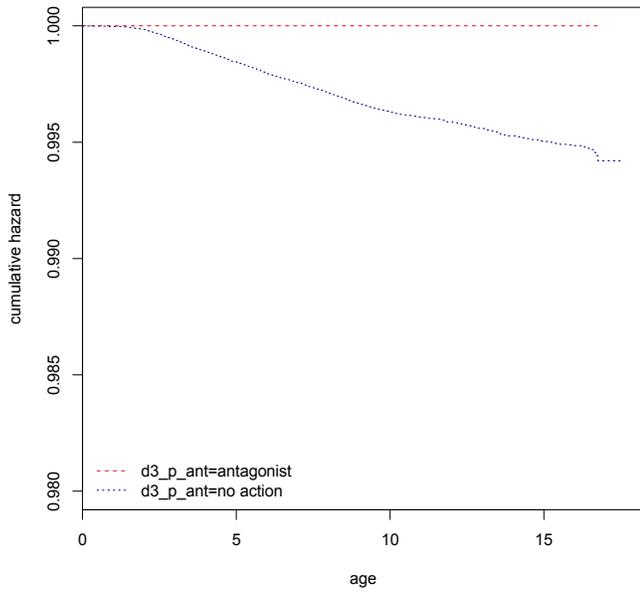
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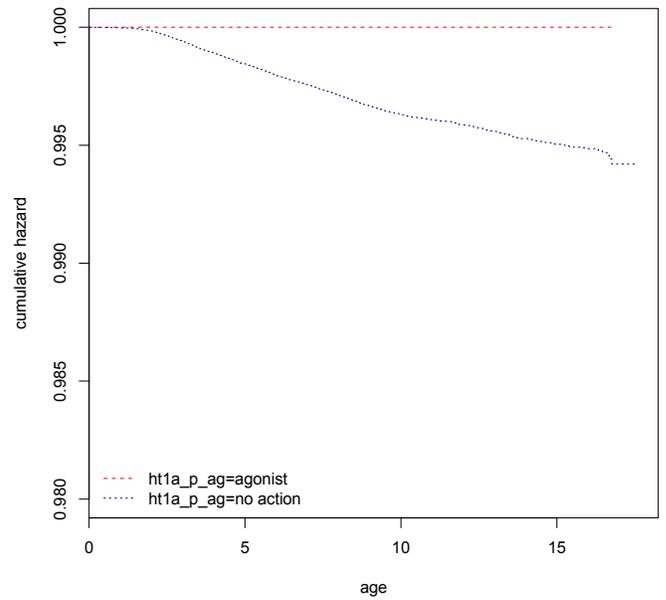
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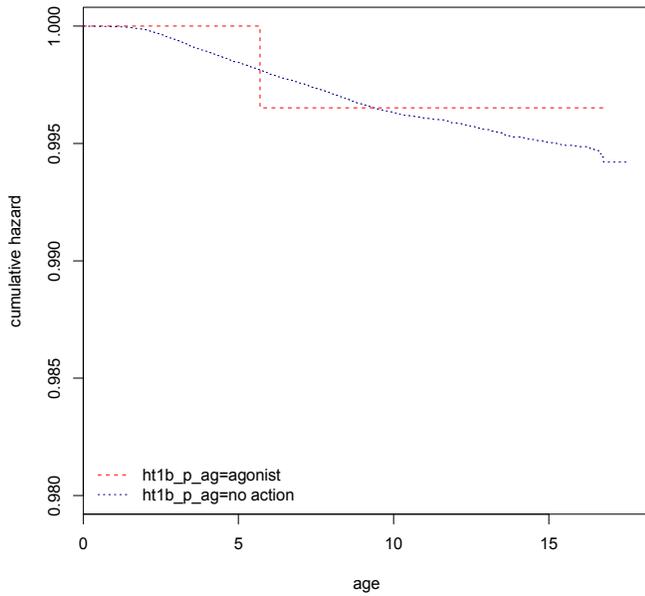
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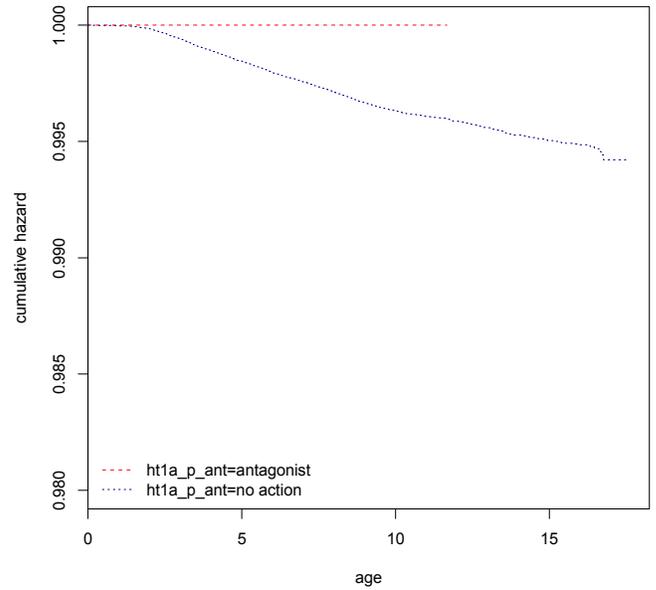
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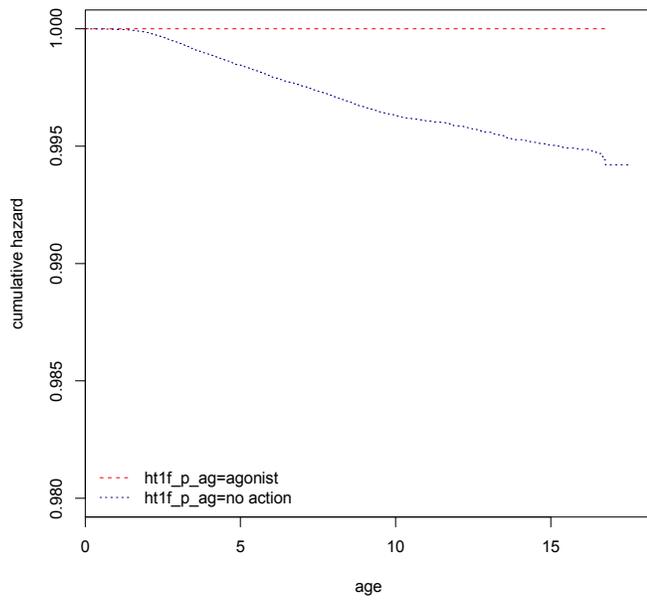
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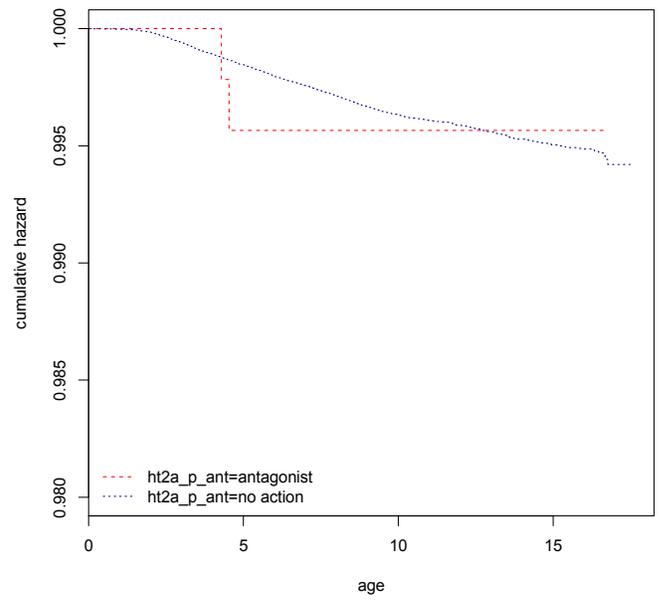
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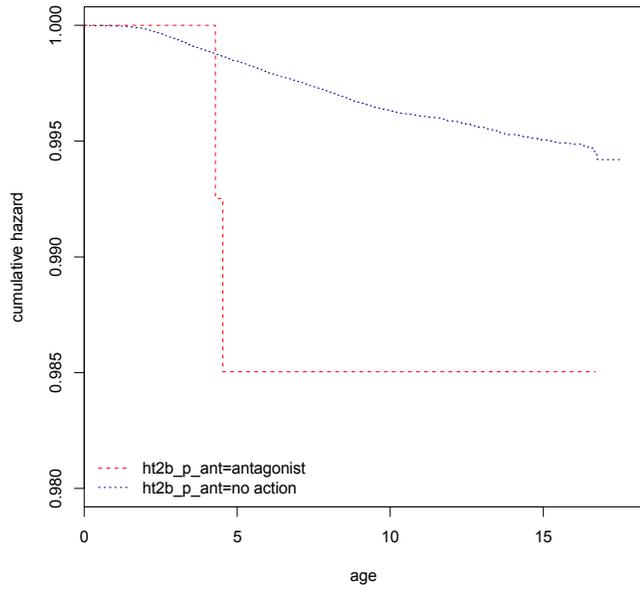
5−HT receptor 3A antagonist exposure
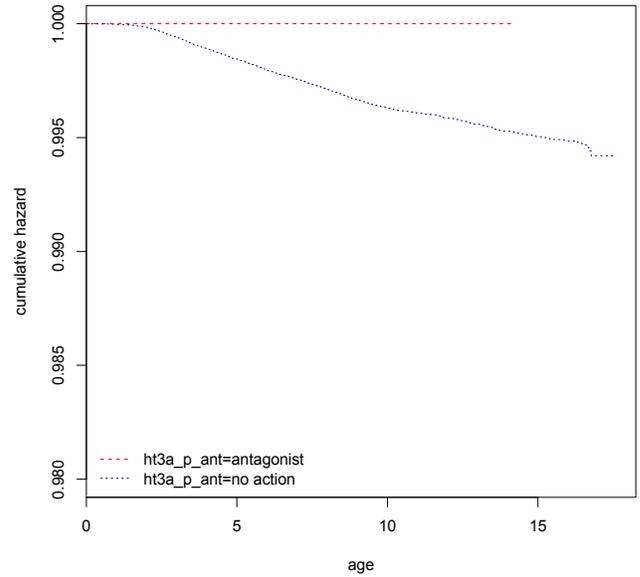
eFigure 14. ASD Rates in the Subcohort in Relation to the Number of Maternal Diagnoses Between Year Before Pregnancy Start and Child's Date of Birth

ASD rates and maternal number of diagnoses
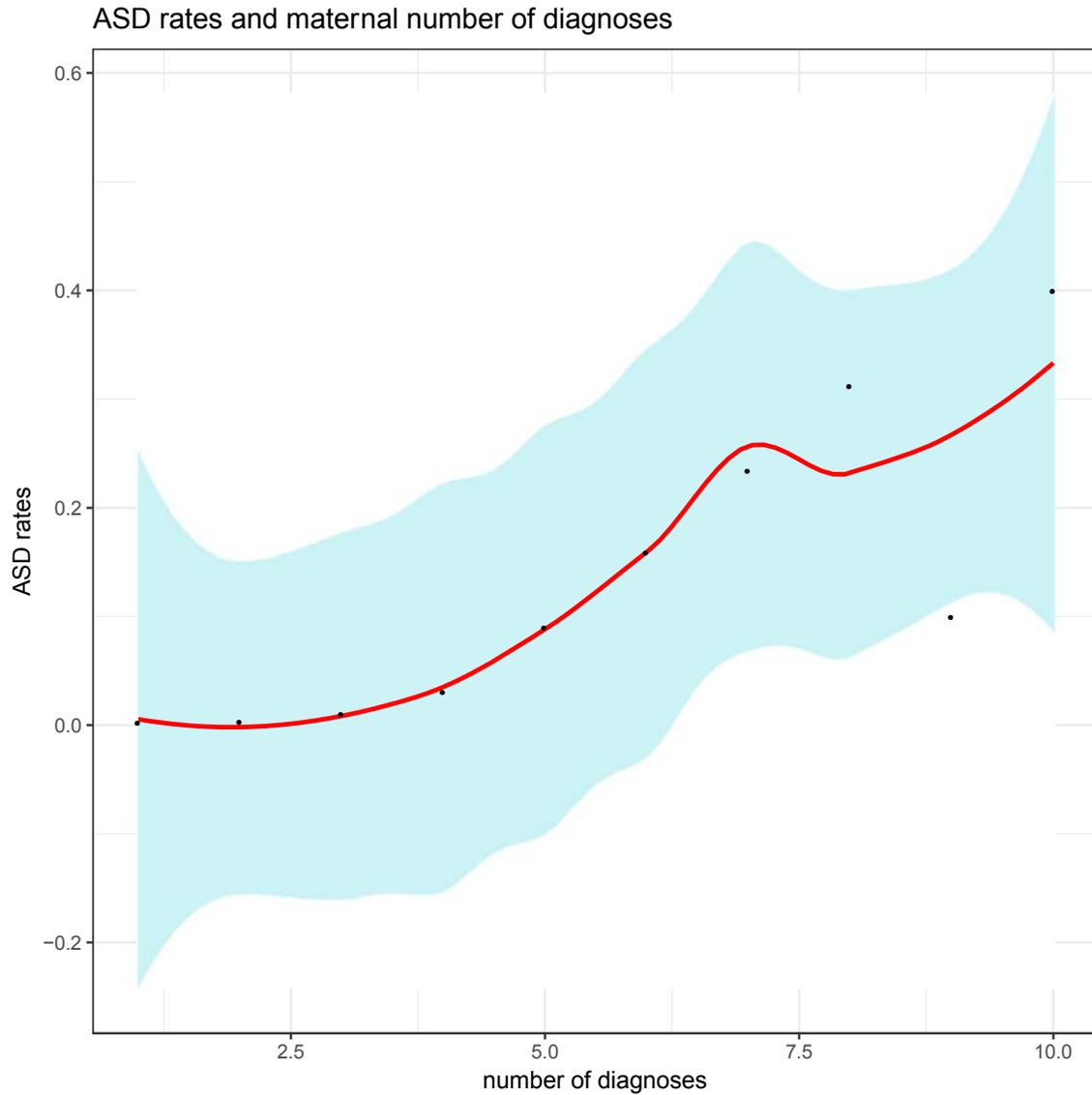
The y-axis represents the number of ASD cases per 100 individuals. The x-axis represents the number of diagnoses mother received before and during the pregnancy, divided by 10 and rounded up to the nearest 10 (e.g. point at 2 on the x axis indicated the mean ASD rates in women who received between 11 and 20 diagnoses).

eTable 1. Comparison of Prescription Rates in Israeli Meuhedet Data and Swedish National Register

DIABETES					
		Sweden		**Israel**	
		frequency	**percent**	**frequency**	**percent**
pre-pregnancy	**non-exposed**	100645	99.17	10856	99.26
	exposed	839	0.83	81	0.74
pregnancy	**non-exposed**	100405	98.94	12992	99.08
	exposed	1079	1.06	120	0.92

HYPERTENSION					
		Sweden		**Israel**	
		frequency	**percent**	**frequency**	**percent**
pre-pregnancy	**non-exposed**	101466	99.98	10927	99.91
	exposed	18	0.02	10	0.09
pregnancy	**non-exposed**	101432	99.95	13076	99.73
	exposed	52	0.05	36	0.27

ORAL CONTRACEPTIVES					
		Sweden		**Israel**	
		frequency	**percent**	**frequency**	**percent**
pre-pregnancy	**non-exposed**	80430	79.25	9655	88.28
	exposed	21054	20.75	1282	11.72
pregnancy	**non-exposed**	100604	99.13	13005	99.18
	exposed	880	0.87	107	0.82

ANY ANTIDEPRESSANT					
		Sweden		**Israel**	
		frequency	**percent**	**frequency**	**percent**
pre-pregnancy	**non-exposed**	96407	95	10771	98.48
	exposed	5077	5	166	1.52
pregnancy	**non-exposed**	98867	97.42	12990	99.07
	exposed	2617	2.58	122	0.93

SSRI					
		Sweden		**Israel**	
		frequency	**percent**	**frequency**	**percent**
pre-pregnancy	**non-exposed**	97406	95.98	10825	98.98
	exposed	4078	4.02	112	1.02
pregnancy	**non-exposed**	99298	97.85	13015	99.26
	exposed	2186	2.15	97	0.74

The exposure windows were standardized to only include individuals for whom the pregnancy period started after July 1 2005, and the date of child's birth was on or before December 31, 2007 in both countries, ensuring comparability of the data. The restrictions were due to availability of Swedish data. Pregnancy period was defined as 280 days prior to the child's date of birth.

eTable 2. Drug Categories: ATC Codes and Names of the Medications

	Drug categories - ATC codes
Serotonin re-uptake inhibitors	A08AA10 (sibutramine), N02AX02 (tramadol), N02AX52 (tramadol, combinations), N06AA01 (desipramine), N06AA02 (imipramine), N06AA04 (clomipramine), N06AA06 (trimipramine), N06AA09 (amitriptyline), N06AA10 (nortriptyline), N06AB03 (fluoxetine), N06AB05 (paroxetine), N06AB06 (sertraline), N06AB08 (fluvoxamine), N06AB10 (escitalopram), N06AX05 (trazodone), N06AX17 (milnacipran), N06AX21 (duloxetine), R01BA02 (pseudoephedrine), R01BA52 (pseudoephedrine, combinations)
Serotonin receptor 1A agonists	N02CC01 (sumatriptan), N02CC02 (naratriptan), N02CC03 (zolmitriptan), N05BE01 (buspirone), N06AX05 (trazodone), N02CC06 (eletriptan; migraine), N06AX05 (trazodone)
Serotonin receptor 1B agonists	N02CC01 (sumatriptan), N02CC02 (naratriptan), N02CC03 (zolmitriptan), N02CC06 (eletriptan), N02CA72 (ergotamine)
Serotonin receptor 1D agonists	N02CC01 (sumatriptan), N02CC02 (naratriptan), N02CC03 (zolmitriptan), N02CC06 (eletriptan), N02CA72 (ergotamine)
Serotonin receptor 1F agonists	N02CC01 (sumatriptan; migraine), N02CC02 (naratriptan; migraine), N02CC03 (zolmitriptan; migraine), N02CC06 (eletriptan; migraine)
Serotonin receptor 1A antagonists	N05AA01 (chlorpromazine)
Serotonin receptor 2A antagonists	N05AA01 (chlorpromazine), N05AE03 (sertindole), N05AE04 (ziprasidone), N05AF01 (flupentixol), N05AH02 (clozapine), N05AH06 (clotiapine), N05AX08 (risperidone), N05AX12 (aripiprazole), N05AX13 (paliperidone), N06AA01 (desipramine), N06AA04 (clomipramine), N06AA09 (amitriptyline), N06AA10 (nortriptyline), N06AX05 (trazodone), N06AX11 (mirtazapine)
Serotonin receptor 2B antagonists	N06AA04 (clomipramine)
Serotonin receptor 3A antagonists	A03FA02 (cisapride), A04AA01 (ondansetron), A04AA02 (granisetron), A04AA05 (palonosetron), N06AX11 (mirtazapine), N06DX01 (memantine), N07BC02 (methadone)
GABA transaminase inhibitors	N03AG01 (valproic acid)
GABA$_A$ receptor agonists	D08AX08 (ethanol), N03AA02 (phenobarbital), N03AA03 (primidone), N03AE01 (clonazepam), N05BA01 (diazepam), N05BA04 (oxazepam), N05BA05 (potassium clorazepate), N05BA06 (lorazepam), N05BA08 (bromazepam), N05BA09 (clobazam), N05BA12 (alprazolam), N05BC01 (meprobamate), N05CD02 (nitrazepam), N05CD03 (flunitrazepam), N05CD09 (brotizolam), N05CF01 (zopiclone), N05CF02 (zolpidem), N05CM09 (Valerianae radix), N06AB03 (fluoxetine), V03AB16 (ethanol)
Glutamate receptor 3 agonists	N05AN01 (lithium)
NMDA receptor 1 antagonists	M03BC01 (orphenadrine), M03BC51 (orphenadrine, combinations), N06DX01 (memantine)
NMDA receptor 2D antagonists	M03BC01 (orphenadrine), M03BC51 (orphenadrine, combinations), N06DX01 (memantine)
NMDA receptor 3B antagonists	M03BC01 (orphenadrine), M03BC51 (orphenadrine, combinations), N06DX01 (memantine)
NMDA receptor 3A antagonists	D08AX08 (ethanol), M03BC01 (orphenadrine), M03BC51 (orphenadrine, combinations), N04BB01 (amantadine), N06DX01 (memantine), N07BC02 (methadone), V03AB16 (ethanol), R05DA09 (dextromethorphan)
Neuronal acetylcholine receptor α antagonists	N03AA03 (primidone), N04AA02 (biperiden), N07BC02 (methadone), N03AA02 (phenobarbital)
Muscarinic receptor 1 agonist	A03FA01 (metoclopramide), N07AX01 (pilocarpine), S01EB01 (pilocarpine)
Muscarinic receptor 1 antagonist	A03CA02 (clidinium and psycholeptics), A03DA06 (trospium and analgesics), A04AD01 (scopolamine), G04BD04 (oxybutynin), G04BD07 (tolterodine), G04BD09 (trospium), N04AA01 (trihexyphenidyl), N04AA02 (biperiden), N04AA04 (procyclidine), R03BB01 (ipratropium bromide), R03BB04 (tiotropium bromide), R06AE51 (buclizine, combinations), S01FA01 (atropine), S01FA04 (cyclopentolate), A03AA07 (dicycloverine; IBS), R06AA09 (doxylamine), R06AD08 (oxomemazine), G04BD11 (fesoterodine)
Muscarinic receptor 2 antagonists	A03AA07 (dicycloverine), D04AA13 (dimetindene), G04BD04 (oxybutynin), G04BD07 (tolterodine), N04AA04 (procyclidine), R03BB01 (ipratropium bromide), R06AA52 (diphenhydramine, combinations), R06AB03 (dimetindene), S01FA01 (atropine), A04AD01 (scopolamine), R03BB04 (tiotropium bromide), G04BD11 (fesoterodine)
Muscarinic receptor 3	G04BD04 (oxybutynin), G04BD07 (tolterodine), G04BD08 (oxybutynin), G04BD11 (fesoterodine),

antagonists	N04AA04 (procyclidine), R03BB01 (ipratropium bromide), R03BB04 (tiotropium bromide), S01FA01 (atropine), A04AD01 (scopolamine)
Muscarinic receptor 4 antagonists	G04BD07 (tolterodine), N04AA04 (procyclidine), S01FA01 (atropine), S01FA06 (tropicamide), G04BD11 (fesoterodine); A04AD01 (scopolamine)
Cannabinoid receptor 1/2 agonists	N02BE01 (paracetamol), N02BE51 (paracetamol, combinations), N02BE71 (paracetamol, combinations)
Fatty acid amide hydrolase inhibitors	N02BE01 (paracetamol), N02BE51 (paracetamol, combinations), N02BE71 (paracetamol, combinations)
Opioid κ receptor agonists	A07DA03 (loperamide), A07DA53 (loperamide,, combinations), N02AA01 (morphine), N02AA05 (oxycodone), N02AA55 (oxycodone and naloxone), N02AA59 (codeine comb), N02AA79 (codeine, combinations), N02AB03 (fentanyl), N02AC54 (dextropropoxyphene, combinations), N02AC74 (dextropropoxyphene, combinations), R05DA20 (opium alkaloids,, combinations), R05FA02 (opium derivatives), N02AE01 (buprenorphine)
Opioid ε receptor agonists	A07DA03 (loperamide), A07DA53 (loperamide,, combinations), N02AA01 (morphine), N02AA05 (oxycodone), N02AA55 (oxycodone and naloxone), N02AA59 (codeine comb), N02AA79 (codeine, combinations), N02AB03 (fentanyl), N02AC54 (dextropropoxyphene, combinations), N02AC74 (dextropropoxyphene, combinations), R05DA20 (opium alkaloids,, combinations), R05FA02 (opium derivatives), N02AE01 (buprenorphine)
Opioid μ receptor agonists	A07DA03 (loperamide), A07DA53 (loperamide,, combinations), N02AA01 (morphine), N02AA05 (oxycodone), N02AA55 (oxycodone and naloxone), N02AA59 (codeine, combinations), N02AA79 (codeine, combinations), N02AB03 (fentanyl), N02AC54 (dextropropoxyphene, combinations), N02AC74 (dextropropoxyphene, combinations), N02AE01 (buprenorphine), N02AX02 (tramadol), N02AX52 (tramadol, combinations), N07BC02 (methadone), R05DA20 (opium alkaloids,, combinations), R05FA02 (opium derivatives)
Dopamine transporter inhibitors	A08AA10 (sibutramine), N06AX12 (bupropion), N06BA01 (amfetamine), N06BA02 (dexamfetamine), N06BA04 (methylphenidate), N06BA07 (modafinil), R01BA02 (pseudoephedrine), R01BA52 (pseudoephedrine, combinations)
Dopamine receptor 1 antagonists	G02AB01 (methylergometrine), N05AA01 (chlorpromazine), N05AA02 (levomepromazine), N05AB02 (fluphenazine), N05AB03 (perphenazine), N05AC01 (periciazine), N05AF01 (flupentixol), N05AF05 (zuclopenthixol)
Dopamine receptor 2 agonists	G02CB01 (bromocriptine), G02CB03 (cabergoline), G02CB04 (quinagolide), N04BA02 (levodopa and decarboxylase inhibitor), N04BA03 (levodopa and decarboxylase inhibitor), N04BB01 (amantadine), N04BC02 (pergolide), N04BC04 (ropinirole), N04BC05 (pramipexole), N04BC06 (cabergoline), N04BC09 (rotigotine), N06DX01 (memantine)
Dopamine receptor 2 antagonists	A03FA01), A03FA03 (domperidone), N05AA01 (chlorpromazine), N05AA02 (levomepromazine), N05AB02 (fluphenazine), N05AB03 (perphenazine), N05AD01 (haloperidol), N05AE03 (sertindole), N05AE04 (ziprasidone), N05AF01 (flupentixol), N05AF05 (zuclopenthixol), N05AG02 (pimozide), N05AG03 (penfluridol), N05AH02 (clozapine), N05AH06 (clotiapine), N05AL01 (sulpiride), N05AL05 (amisulpride), N05AX08 (risperidone), N05AX12 (aripiprazole), N05AX13 (paliperidone), N05BE01 (buspirone)
Dopamine receptor 3 agonists	G02CB01 (bromocriptine), N04BA02 (levodopa and decarboxylase inhibitor), N04BA03 (levodopa and decarboxylase inhibitor), N04BC02 (pergolide), N04BC04 (ropinirole), N04BC05 (pramipexole), N04BC09 (rotigotine)
Dopamine receptor 3 antagonists	A03FA03 (domperidone), N05AG02 (pimozide), N05AG03 (penfluridol), N05AL01 (sulpiride), N05AL05 (amisulpride), N05AX13 (paliperidone)
Noradrenaline transporter inhibitors	A08AA10 (sibutramine), M03BC01 (orphenadrine (citrate)), M03BC51 (orphenadrine (citrate)), N02AX02 (tramadol), N02AX52 (tramadol, combinations), N06AA01 (desipramine), N06AA02 (imipramine), N06AA06 (trimipramine), N06AA08 (dibenzepin), N06AA09 (amitriptyline), N06AA10 (nortriptyline), N06AA21 (maprotiline), N06AX03 (mianserin), N06AX12 (bupropion), N06AX17 (milnacipran), N06AX18 (reboxetine), N06AX21 (duloxetine), N06BA02 (dexamfetamine), N06BA09 (atomoxetine), R01BA02 (pseudoephedrine), R01BA52 (pseudoephedrine, combinations), R03CA02 (ephedrine)
Adrenergic receptor α 1A agonists	C01CA24 (epinephrine), G04CA01 (alfuzosin), N02CA72 (ergotamine), R01AA05 (oxymetazoline), R01AA06 (tetryzoline), R01AA07 (xylometazoline), R01AB02 (naphazoline), R01AB06 (xylometazoline), R01AB07 (oxymetazoline), R01BA02 (pseudoephedrine), R01BA52 (pseudoephedrine, combinations), R01BA53 (phenylephrine), S01GA01 (naphazoline), S01GA02 (tetryzoline), S01GA05 (phenylephrine), S01GA52 (tetryzoline, combinations)
Adrenergic receptor α 1A antagonists	C01BD07 (dronedarone), C02CA04 (doxazosin), C04AE54 (dihydroergocristine), C04AX02 (phenoxybenzamine), C07AG01 (labetalol), C07AG02 (carvedilol), G04CA02 (tamsulosin), N05AA01 (chlorpromazine), N05AF01 (flupentixol)
Adrenergic receptor α 1B agonists	C01CA24 (epinephrine), G04CA01 (alfuzosin), N06BA07 (modafinil), R01AA07 (xylometazoline), R01AB06 (xylometazoline), R01BA53 (phenylephrine), N02CA72 (ergotamine)

Adrenergic receptor α 1B antagonists	C01BD07 (dronedarone), C02CA04 (doxazosin), C04AX02 (phenoxybenzamine), G04CA02 (tamsulosin), N05AA01 (chlorpromazine)
Adrenergic receptor α 1D agonists	G04CA01 (alfuzosin), R01AA07 (xylometazoline), R01AB06 (xylometazoline), R01BA53 (phenylephrine), N02CA72 (ergotamine)
Adrenergic receptor α 2A agonists	C01CA24 (epinephrine), C02AC01 (clonidine), N02BG07 (flupirtine), R01AA05 (oxymetazoline), R01AA07 (xylometazoline), R01AB02 (naphazoline), R01AB06 (xylometazoline), R01AB07 (oxymetazoline), R01BA02 (pseudoephedrine), R01BA52 (pseudoephedrine, combinations), S01EA05 (brimonidine), S01GA01 (naphazoline), N05AC01 (periciazine), N06AX03 (mianserin)
Adrenergic receptor α 2A antagonists	C04AE54 (dihydroergocristine), C04AX02 (phenoxybenzamine), G04BE04 (yohimbine), N05AC01 (periciazine), N06AX11 (mirtazapine)
Adrenergic receptor α 2B agonists	C01CA24 (epinephrine), C02AC01 (clonidine), R01AA07 (xylometazoline), R01AB06 (xylometazoline), S01EA05 (brimonidine)
Adrenergic receptor α 2C agonists	C02AC01 (clonidine), R01AA07 (xylometazoline), R01AB06 (xylometazoline), S01EA05 (brimonidine)
Adrenergic receptor β1 agonists	C01CA24 (epinephrine), R01BA51 (phenylpropanolamine), R02AA03 (dichlorobenzyl alcohol), R03CC02 (salbutamol)
Adrenergic receptor β1 antagonists	C07AA05 (propranolol), C07AA07 (sotalol), C07AB02 (metoprolol), C07AB03 (atenolol), C07AB04 (acebutolol), C07AB07 (bisoprolol), C07AG01 (labetalol), C07AG02 (carvedilol), S01ED01 (timolol), S01ED02 (betaxolol), S01ED51 (timolol, combinations)
Adrenergic receptor β2 agonists	C01CA24 (epinephrine), R01BA51 (phenylpropanolamine), R02AA03 (dichlorobenzyl alcohol), R03AC03 (terbutaline), R03AC12 (salmeterol), R03AC13 (formoterol), R03AK06 (salmaterol with fluticasone), R03AK07 (formoterol and budesonide), R03AK10 (vilanterol and fluticasone fluorate), R03CC02 (salbutamol)
Adrenergic receptor β2 antagonists	C07AA05 (propranolol), C07AA07 (sotalol), C07AG01 (labetalol), C07AG02 (carvedilol), S01ED01 (timolol), S01ED51 (timolol, combinations)
Adenosine receptor A1 antagonists	N06BC01 (caffeine), R03DA04 (theophylline)
Adenosine receptor A 2A antagonists	N06BC01 (caffeine), P01BC02 (mefloquine), R03DA04 (theophylline)
Adenosine receptor A 2B antagonist	R03DA04 (theophylline)
Histamine receptor 1 antagonists	D04AA13 (dimetindene), D04AA22 (isothipendyl), M03BC01 (orphenadrine), M03BC51 (orphenadrine, combinations), N05AA01 (chlorpromazine), N05AH06 (clotiapine), N05BB01 (hydroxyzine), N06AA08 (dibenzepin), N06AA21 (maprotiline), N06AX03 (mianserin), N07CA02 (cinnarizine), R01AC02 (levocabastine), R01AC03 (azelastine), R06AA09 (doxylamine), R06AA52 (diphenhydramine, combinations), R06AB03 (dimetindene), R06AB04 (chlorphenamine), R06AB05 (pheniramine), R06AB54 (chlorphenamine, combinations), R06AD02 (promethazine), R06AD08 (oxomemazine), R06AD52 (promethazine, combinations), R06AE07 (cetirizine), R06AE51 (buclizine, combinations), R06AX13 (loratadine), R06AX17 (ketotifen), R06AX24 (epinastine), R06AX25 (mizolastine), R06AX26 (fexofenadine), R06AX27 (desloratadine), S01GX02 (levocabastine), S01GX06 (emedastine), S01GX07 (azelastine), S01GX08 (ketotifen)
Histamine receptor 1 agonists	N07CA01 (betahistine)
Histamine receptor 2 antagonists	A02BA01 (cimetidine), A02BA02 (ranitidine), A02BA03 (famotidine), R06AX24 (epinastine)
Histamine receptor 3 antagonists	N07CA01 (betahistine)
Vesicular amine transporter inhibitors	N06BA01 (amfetamine), N06BA02 (dexamfetamine), N07XX06 (tetrabenazine), R03CA02 (ephedrine)

eTable 3. Drug Categories: Common Indications

	Drug categories - predominant indications
Serotonin transporter inhibitors	Obesity, analgesic, depression, psychosis, anxiety, nasal congestion, stimulant
Serotonin receptor 1A agonists	Migraine
Serotonin receptor 1B agonists	Migraine
Serotonin receptor 1D agonists	Migraine
Serotonin receptor 1F agonists	Migraine
Serotonin receptor 1A antagonists	Psychosis
Serotonin receptor 2A antagonists	Psychosis, depression
Serotonin receptor 2B antagonists	Depression
Serotonin receptor 3A antagonists	Reflux disease, nausea, depression, dementia, opioid dependency
GABA transaminase inhibitors	epilepsy, bipolar disorder
GABA$_A$ receptor agonists	Seizures, anxiety, alcohol withdrawal, insomnia
Glutamate receptor 3 agonists	Bipolar disorder, mania
NMDA receptor 1 antagonists	Parkinson's disease, dementia
NMDA receptor 2D antagonists	Parkinson's disease, dementia
NMDA receptor 3B antagonists	Parkinson's disease, dementia
NMDA receptor 3A antagonists	Parkinson's disease, parkinsonism, dementia, opioid dependence, analgesic, cough
Neuronal acetylcholine receptor α antagonists	Seizures, parkinsonism, extrapyramidal symptoms, opioid dependence
Muscarinic receptor 1 agonists	Reflux disease, glaucoma
Muscarinic receptor 1 antagonists	Irritable Bowel Syndrome, ulcer disease, urinary incontinence and discomfort, nausea, extrapyramidal symptoms, parkinsonism, obstructive pulmonary disease, nerve agent poisoning, anterior uveitis, rhinitis, cough, overactive bladder
Muscarinic receptor 2 antagonists	Irritable Bowel Syndrome , allergic reactions, urinary incontinence, parkinsonism, extrapyramidal symptoms, obstructive pulmonary disease, nerve agent poisoning, nausea, overactive bladder
Muscarinic receptor 3 antagonists	Urinary incontinence, overactive bladder, parkinsonism, extrapyramidal symptoms, obstructive pulmonary disease, nerve agent poisoning, nausea
Muscarinic receptor 4 antagonists	Urinary incontinence, parkinsonism, extrapyramidal symptoms, ulcers, nerve agent poisoning, mydriasis, overactive bladder, motion sickness
Cannabinoid receptor 1/2 agonists	Analgesic
Fatty acid amide hydrolase inhibitors	Analgesic
Opioid μ receptor agonists	Analgesic, diarrhea, opioid dependence
Opioid κ receptor agonists	Analgesic, diarrhea, opioid dependence
Opioid ε receptor agonists	Analgesic, diarrhea, opioid dependence
Dopamine transporter inhibitors	obesity, depression, narcolepsy, ADHD, nasal congestion, stimulant
Dopamine receptor 1 antagonists	Psychosis, excessive bleeding after childbirth
Dopamine receptor 2 agonists	Parkinson's disease, hyperprolactemic disorder, parkinsonism, dementia
Dopamine receptor 2 antagonists	Reflux disease, gastroinestinal symptoms, psychosis, anxiety
Dopamine receptor 3 agonists	Parkinson's disease, parkinsonism
Dopamine receptor 3 antagonists	Gastroinestinal symptoms, tics, psychosis
Noradrenaline transporter inhibitors	muscle relaxant, analgesic, obesity, depression, anxiety, ADHD, narcolepsy, nasal congestion, stimulant
Adrenergic receptor α 1A agonists	respiratory problems, hypertension, headache, nasal congestion, occular problems, stimulant, hypotension
Adrenergic receptor α 1A antagonists	atrial fibrillation, hypertension, dementia, angina, bladder obstruction, psychosis
Adrenergic receptor α 1B agonists	respiratory problems, hypertension, ADHD, narcolepsy, nasal congestion, hypotension, headache
Adrenergic receptor α 1B antagonists	atrial fibrillation, hypertension, bladder obstruction, psychosis
Adrenergic receptor α 1D agonists	Hypertension, nasal congestion, hypotension, headache
Adrenergic receptor α 2A agonists	respiratory problems, tics, Tourette's syndrome, ADHD, analgesic, nasal congestion, stimulant, rosacea, psychosis, depression
Adrenergic receptor α 2A antagonists	Dementia, hypertension, mydriasis, psychosis, depression
Adrenergic receptor α 2B agonists	respiratory problems, tics, Tourette's syndrome, ADHD, nasal congestion, rosacea
Adrenergic receptor α 2C agonists	Tics, Tourette's syndrome, ADHD, nasal stuffness, rosacea
Adrenergic receptor β 1 agonist	respiratory problems, nasal congestion
Adrenergic receptor β 1 antagonist	Migraine, atrial fibrillation, angina, anginal pain, hypertension
Adrenergic receptor β 2 agonists	respiratory problems, nasal congestion
Adrenergic receptor β 2 antagonist	Migraine, atrial fibrillation, angina, anginal pain, hypertension
Adenosine receptor A 1 antagonists	Stimulant, respiratory problems
Adenosine receptor A 2A antagonist	Stimulant, respiratory problems, malaria
Adenosine receptor A 2B antagonist	Respiratory problems

Histamine receptor 1 antagonists	Allergic reactions, Parkinson's disease, psychosis, nausea, anxiety, depression, vertigo, conjunctivitis, rhinitis, cough
Histamine receptor 1 agonists	Vertigo
Histamine receptor 2 antagonists	Reflux disease, ulcer disease, conjuctivitis
Histamine receptor 3 antagonists	Vertigo
Vesicular amine transporter inhibitors	ADHD, narcolepsy, tics, Tourette's syndrome, Huntington's disease, nasal congestion, stimulant

eTable 4. Drug Categories: Exposure Numbers by ASD Diagnosis

	Drug categories - exposures and ASD						
	Total children exposed (n)	ASD children exposed (n)	ASD in exposed children (%)	Total children non-exposed (n)	ASD children non-exposed (n)	ASD in non-exposed children (%)	Exposed (%)
Serotonin transporter inhibitors	1749	37	2.12	94486	1369	1.45	1.817
Serotonin receptor 1A agonists	66	0	0.00	96169	1406	1.46	0.069
Serotonin receptor 1A antagonists	4	0	0.00	96231	1406	1.46	0.004
Serotonin receptor 1B agonists	73	1	1.37	96162	1405	1.46	0.076
Serotonin receptor 1D agonists	73	1	1.37	96162	1405	1.46	0.076
Serotonin receptor 1F agonists	59	0	0.00	96176	1406	1.46	0.061
Serotonin receptor 2A antagonists	119	2	1.68	96116	1404	1.46	0.124
Serotonin receptor 2B antagonists	33	2	6.06	96202	1404	1.46	0.034
Serotonin receptor 3A antagonists	47	0	0.00	96188	1406	1.46	0.049
GABA transaminase inhibitors	29	2	6.90	96206	1404	1.46	0.030
GABA$_A$ receptor agonists	732	17	2.32	95503	1389	1.45	0.761
Glutamate receptor 3 agonists	21	1	4.76	96214	1405	1.46	0.022
NMDA receptor 1 antagonists	227	3	1.32	96008	1403	1.46	0.236
NMDA receptor 2D antagonists	227	3	1.32	96008	1403	1.46	0.236
NMDA receptor 3B antagonists	227	3	1.32	96008	1403	1.46	0.236
NMDA receptor 3A antagonists	518	5	0.97	95717	1401	1.46	0.538
Neuronal acetylcholine receptor α antagonists	12	1	8.33	96223	1405	1.46	0.012
Muscarinic receptor 1 agonists	3613	62	1.72	92622	1344	1.45	3.754
Muscarinic receptor 1 antagonists	403	3	0.74	95832	1403	1.46	0.419
Muscarinic receptor 2 antagonists	821	8	0.97	95414	1398	1.47	0.853
Muscarinic receptor 3 antagonists	224	0	0.00	96011	1406	1.46	0.233
Muscarinic receptor 4 antagonists	4	0	0.00	96231	1406	1.46	96235
Cannabinoid receptor 1/2 agonists	3871	56	1.45	92364	1350	1.46	4.022
Fatty acid amide hydrolase inhibitors	3871	56	1.45	92364	1350	1.46	4.022
Opioid μ receptor agonists	1867	26	1.39	94368	1380	1.46	1.940
Opioid κ receptor agonists	1840	25	1.36	94395	1381	1.46	1.912
Opioid ε receptor agonists	1840	25	1.36	94395	1381	1.46	1.912
Dopamine transporter inhibitors	1422	26	1.83	94813	1380	1.46	1.478
Dopamine receptor 1 antagonists	43	0	0.00	96192	1406	1.46	0.045
Dopamine receptor 2 agonists	307	7	2.28	95928	1399	1.46	0.319
Dopamine receptor 2 antagonists	3790	63	1.66	92445	1343	1.45	3.938
Dopamine receptor 3 agonists	152	4	2.63	96083	1402	1.46	0.158
Dopamine receptor 3 antagonists	149	0	0.00	96086	1406	1.46	0.155
Noradrenaline transporter inhibitors	1980	34	1.72	94255	1372	1.46	2.057
Adrenergic receptor α 1A agonists	4409	84	1.91	91826	1322	1.44	4.581
Adrenergic receptor α 1A antagonists	26	0	0.00	96209	1406	1.46	0.027
Adrenergic receptor α 1B agonists	1579	33	2.09	94656	1373	1.45	1.641
Adrenergic receptor α 1B antagonists	9	0	0.00	96226	1406	1.46	0.009
Adrenergic receptor α 1D agonists	1565	32	2.04	94670	1374	1.45	1.626
Adrenergic receptor α 2A agonists	3177	55	1.73	93058	1351	1.45	3.301
Adrenergic receptor α 2A antagonists	9	0	0.00	96226	1406	1.46	0.009
Adrenergic receptor α 2B agonists	726	7	0.96	95509	1399	1.46	0.754
Adrenergic receptor α 2C agonists	712	6	0.84	95523	1400	1.47	0.740
Adrenergic receptor β1 agonists	148	3	2.03	96087	1403	1.46	0.154
Adrenergic receptor β1 antagonists	337	8	2.37	95898	1398	1.46	0.350
Adrenergic receptor β2 agonists	800	10	1.25	95435	1396	1.46	0.831
Adrenergic receptor β2 antagonists	144	4	2.78	96091	1402	1.46	0.150
Adenosine receptor A1 antagonists	140	0	0.00	96095	1406	1.46	0.145
Adenosine receptor A 2A antagonists	144	0	0.00	96091	1406	1.46	0.150
Adenosine receptor A 2B antagonists	36	0	0.00	96199	1406	1.46	0.037
Histamine receptor 1 antagonists	3947	68	1.72	92288	1338	1.45	4.101
Histamine receptor 1 agonists	14	0	0.00	96221	1406	1.46	0.015

Histamine receptor 2 antagonists	806	17	2.11	95429	1389	1.46	0.838
Histamine receptor 3 antagonists	14	0	0.00	96221	1406	1.46	0.015
Vesicular amine transporter inhibitors	259	5	1.93	95976	1401	1.46	0.269

. **eTable 5. ICD Codes Used to Identify Cases of ASD**

ICD-9	ICD-10
299.0: Infantile Autism 299.1: Childhood disintegrative Disorder 299.8: Other Pervasive Developmental Disorders 299.9: Other Pervasive Developmental Disorders NOS	F84.0: Autistic disorder F84.1: Atypical Autism F84.2: Rett Syndrome F84.5: Asperger Syndrome F84.8: Other Pervasive Developmental Disorders F84.9 Other Pervasive Developmental Disorders NOS

eTable 6. *ICD* Codes Used to Identify Mothers With a History of Psychiatric and Neurological Disorders

ICD-9	ICD-10
Affective disorders: 296- : Episodic mood disorders 298.0: Depressive type psychosis 300.4: Dysthymic disorder 311: Depressive disorder, not elsewhere classified **Anxiety disorders:** 300.0-: Anxiety states 300.2-: Phobic disorders 300.3: Obsessive-compulsive disorder **Non-affective psychosis:** 295-: Schizophrenic disorders 297-: Delusional disorders 298-: Other nonorganic psychoses **Neurological:** 345-: Epilepsy	**Affective disorders:** F30-: Manic episode F31-: Bipolar disorder F32-: Major depressive disorder, single episode F33-: Major depressive disorder, recurrent F34-: Persistent mood [affective] disorders F39: Unspecified mood [affective] disorders **Anxiety disorders:** F40-: Phobic anxiety disorders F41-: Other anxiety disorders F42-: OCD **Non-affective psychosis:** F20-: Schizophrenia F21-: Schizotypal disorder F22-: Delusional disorders F23-: Brief psychotic disorder F24-: Shared psychotic disorder F25-: Schizoaffective disorders F28-: Other psychotic disorder not due to a substance or known physiological condition F29-: Unspecified psychosis not due to a substance or known physiological condition **Neurological:** G40-: Epilepsy and recurrent seizures

eTable 7. Demographic Characteristics of the Full Sample

	cases	controls	p
% females	19.1	49.3	<2e-16
mean SES (SD)	10.3 (4.2)	7.6 (4.3)	<2e-16
mean maternal age (SD)	29.9 (5.4)	29.7 (5.4)	0.225
mean paternal age (SD)	32.8 (6.2)	32.4 (6.1)	0.032
% maternal anxiety disorders	5.5	4.2	0.015
% maternal mood disorders	3.9	1.9	7.26e-08
% maternal non-affective psychotic disorders	<0.1	0.2	0.247
% mothers neurological disorders	0.5	0.3	0.275
Mean maternal diagnoses /healthcare contacts year before pregnancy (SD)	16.2 (15.2)	12.3 (8.7)	<2e-16
sample size	**1407**	**94863**	

Controls' descriptives were calculated based on the individuals in the subcohort, excluding the ASD cases. Sample means are presented with their standard deviations. Significance of the group differences was computed using t-test for continuous data and Pearson's Chi2 for count data.

eTable 8. Schoenefeld Residuals for All Tested Medication Groups

	rho	p
5-HTR transporter inh	0.002	0.936
5-HTR 1B & 1D ag	-0.002	0.933
5-HTR 2A ant	-0.018	0.335
5-HTR 2B ant	-0.023	0.209
GABA transaminase inh	0.009	0.747
GABA$_A$R ag	-0.017	0.519
GluR 3 ag	0.002	0.933
NMDAR 1 & 2D & 3B ant	-0.022	0.407
NMDAR receptor 3A ant	-0.010	0.714
nAchR α ant	-0.037	0.151
mAChR 1 ag	-0.041	0.126
mAChR 1 ant	-0.013	0.637
mAChR 2 ant	-0.002	0.940
CBR 1 & 2 ag	0.005	0.858
OR μ ag	0.016	0.542
OR κ & ε ag	0.013	0.626
DA transporter inh	-0.002	0.946
DAR 2 ag	**0.016**	**0.542**
DAR 2 ant	**-0.041**	**0.126**
DAR 3 ag	**0.003**	**0.914**
NA transporter inh	**0.003**	**0.918**
NAR α 1A ag	**-0.003**	**0.902**
NAR α 1B ag	0.010	0.716
NAR α 1D ag	0.006	0.811
NAR α 2A ag	-0.010	0.700
NAR α 2B ag	0.027	0.319
NAR α 2C ag	0.019	0.473
NAR β 1 ag	-0.015	0.575
NAR β 1 ant	-0.006	0.829
NAR β 2 ant	0.008	0.751
NAR β 2 ag	-0.010	0.671
Histamine receptor 1 ant	-0.040	0.125
Histamine receptor 2 ant	-0.026	0.323
VAT inh	0.044	0.097

eTable 9. Associations Between Prenatal Exposure to Medications and Subsequent Diagnosis of ASD in the Subsample With SES Data

	ANALYSES WITH SES							
	Model 1		Model 2		Model 3		Model 4	
	HR (95% CI)	p	HR (95% CI)	p	HR (95% CI)	p	HR (95% CI)	p
5-HTR transporter inh	1.57 (1.11-2.22)	0.01	1.54 (1.09-2.19)	0.02	1.40 (0.99-1.98)	0.06	1.15 (0.81-1.62)	0.44
5-HTR 1B & 1D ag	1.04 (0.14-7.48)	0.97	0.87 (0.12-6.32)	0.89	0.83 (0.11-6.00)	0.85	0.66 (0.09-4.83)	0.69
5-HTR 2A ant	1.16 (0.16-8.33)	0.89	1.23 (0.17-8.93)	0.84	0.90 (0.12-6.60)	0.91	0.83 (0.11-6.12)	0.86
5-HTR 2B ant	4.06 (0.54-30.5)	0.17	3.45 (0.44-27.10)	0.24	2.18 (0.27-17.34)	0.46	2.40 (0.31-18.63)	0.40
GABA transaminase inh	6.08 (1.47-25.1)	0.01	5.07 (1.17-22.07)	0.03	3.43 (0.81-14.63)	0.10	3.39 (0.81-14.29)	0.10
GABA$_A$R ag	1.73(1.05-2.85)	0.03	1.96 (1.19-3.23)	0.01	1.61 (0.98-2.62)	0.06	1.35 (0.83-2.22)	0.22
GluR 3 ag	4.83 (0.67-34.8)	0.12	6.83 (1.02-45.9)	0.05	4.05 (0.58-28.3)	0.16	4.23 (0.58-30.9)	0.16
NMDAR 1 & 2D & 3B ant	1.02 (0.32-3.19)	0.98	1.01 (0.32-3.16)	0.99	1.00 (0.32-3.16)	1.00	0.68 (0.21-2.14)	0.51
NMDAR receptor 3A ant	0.75 (0.31-1.82)	0.53	0.82 (0.34-1.99)	0.66	0.80 (0.33-1.95)	0.63	0.59 (0.25-1.43)	0.24
nAchR α ant	9.78 (1.22-78.4)	0.03	17.5 (2.19-140.4)	0.01	40.68 (2.82-587.8)	0.01	54.3 (3.45-856.6)	0.01
mAChR 1 ag	1.12 (0.86-1.48)	0.40	1.05 (0.80-1.38)	0.74	1.03 (0.78-1.36)	0.83	0.80 (0.61-1.06)	0.12
mAChR 1 ant	0.18 (0.03-1.30)	0.09	0.16 (0.02-1.15)	0.07	0.16 (0.02-1.13)	0.07	0.12 (0.02-0.87)	0.04
mAChR 2 ant	0.74 (0.37-1.49)	0.40	0.70 (0.35-1.41)	0.32	0.70 (0.35-1.41)	0.32	0.53 (0.27-1.07)	0.08
CBR 1 & 2 ag	1.03 (0.78-1.36)	0.86	1.08 (0.81-1.42)	0.61	1.07 (0.81-1.42)	0.64	0.83(0.62-1.10)	0.18
OR μ ag	0.95 (0.63-1.44)	0.81	0.95 (0.62-1.44)	0.79	0.94 (0.62-1.43)	0.77	0.70 (0.46-1.07)	0.10
OR κ & ε ag	0.92 (0.60-1.41)	0.70	0.92 (0.60-1.40)	0.69	0.91 (0.59-1.39)	0.67	0.68 (0.44-1.04)	0.07
DA transporter inh	1.36 (0.92-2.03)	0.13	1.32 (0.88-1.97)	0.18	1.30 (0.87-1.94)	0.20	1.02 (0.68-1.52)	0.93
DAR 2 ag	1.35 (0.60-3.04)	0.46	1.10 (0.49-2.46)	0.83	1.06 (0.47-2.38)	0.90	0.95 (0.42-2.13)	0.90
DAR 2 ant	1.08 (0.83-1.42)	0.54	1.02 (0.78-1.34)	0.89	1.00 (0.76-1.31)	1.00	0.78 (0.59-1.03)	0.08
DAR 3 ag	1.38 (0.44-4.36)	0.58	1.24 (0.39-3.93)	0.72	1.18 (0.37-3.76)	0.78	0.99 (0.31-3.16)	0.99
NA transporter inh	1.29 (0.91-1.82)	0.16	1.25 (0.88-1.78)	0.21	1.23 (0.87-1.75)	0.24	0.95 (0.67-1.35)	0.78
NAR α 1A ag	1.41 (1.12-1.78)	<0.01	1.34 (1.07-1.69)	0.01	1.33 (1.06-1.67)	0.02	1.05 (0.83-1.32)	0.70
NAR α 1B ag	1.58 (1.11-2.26)	0.01	1.44 (1.01-2.05)	0.05	1.42 (0.99-2.03)	0.05	1.14 (0.80-1.63)	0.47
NAR α 1D ag	1.54 (1.07-2.21)	0.02	1.40 (0.97-2.01)	0.07	1.38 (0.96-1.99)	0.08	1.11 (0.77-1.60)	0.57
NAR α 2A ag	1.24 (0.94-1.65)	0.13	1.17 (0.88-1.55)	0.29	1.15 (0.87-1.53)	0.33	0.91 (0.69-1.21)	0.51
NAR α 2B ag	0.74 (0.35-1.56)	0.43	0.68 (0.32-1.44)	0.31	0.67 (0.32-1.42)	0.30	0.55 (0.26-1.16)	0.12
NAR α 2C ag	0.64 (0.28-1.43)	0.28	0.59 (0.26-1.32)	0.20	0.58 (0.26-1.31)	0.19	0.48(0.21-1.07)	0.07
NAR β 1 ag	0.962 (0.24-3.9)	0.96	1.02 (0.25-4.12)	0.98	0.99 (0.24-4.02)	0.99	0.74 (0.18-3.00)	0.67
NAR β 1 ant	1.50 (0.71-3.17)	0.29	1.63 (0.77-3.47)	0.20	1.57 (0.74-3.34)	0.24	1.06 (0.50-2.27)	0.88
NAR β 2 ant	2.01 (0.74-5.46)	0.17	2.08 (0.76-5.67)	0.15	1.95 (0.71-5.34)	0.20	1.27 (0.46-3.49)	0.65
NAR β 2 ag	0.78 (0.36-1.69)	0.52	0.77 (0.35-1.68)	0.51	0.76 (0.35-1.65)	0.48	0.57 (0.26-1.25)	0.16
Histamine receptor 1 ant	1.20 (0.92-1.57)	0.17	1.16 (0.88-1.51)	0.29	1.14 (0.87-1.49)	0.34	0.90 (0.69-1.18)	0.44
Histamine receptor 2 ant	1.40 (0.85-2.31)	0.19	1.44 (0.87-2.38)	0.16	1.39 (0.84-2.30)	0.20	0.95 (0.57-1.58)	0.85
VAT inh	1.46 (0.60-3.54)	0.41	1.35 (0.56-3.27)	0.51	1.36 (0.56-3.29)	0.50	1.10 (0.46-2.66)	0.83

Hazard ratios (HR) are presented with their 95% confidence intervals, and accompanying p-values. Model 1: exposure + year of birth. Model 2: Model 1 + maternal age at birth + SES. Model 3: Model 2 + maternal affective disorders + maternal anxiety disorders + maternal psychotic disorders + maternal neurological disorders. Model 4: Model 3 + maternal general health. All nominally significant results are presented in bold. Ag = agonist; ant = antagonist; inh=inhibitor; 5HTR = serotonin receptor; GABAAR = gamma-Aminobutyric acid A receptor; GluR = glutamate receptor; NMDAR = N-methyl-D-aspartate receptor; nAchR = neuronal acetylcholine receptor; mAChR = muscarinic acetylcholine receptor; CBR = cannabinoid receptor; OR = opioid receptor; DAR = dopamine receptor; NAR = adrenergic receptor; HistR = histamine receptor; VAT = vesicular amine transporter;

eTable 10. Associations Between Prenatal Exposure to Medications and Subsequent Diagnosis of ASD, Adjusting for Paternal Age

	ANALYSES WITH PATERNAL AGE							
	Model 1		Model 2		Model 3		Model 4	
	HR (95% CI)	p	HR (95% CI)	p	HR (95% CI)	p	HR (95% CI)	p
5-HT transporter inh	1.51 (1.02-2.23)	0.04	1.49 (1.01-2.21)	0.05	1.40 (0.94-2.07)	0.09	1.08 (0.73-1.60)	0.70
5-HT receptor 1B & 1D ag	-		-		-		-	
5-HT receptor 2A ant	1.48 (0.21-10.7)	0.70	1.47 (0.21-10.59)	0.70	1.21 (0.17-8.74)	0.85	0.96 (0.13-7.08)	0.97
5-HT receptor 2B ant	5.18 (0.69-38.8)	0.11	5.04 (0.67-37.64)	0.12	3.80 (0.50-28.65)	0.20	3.85 (0.50-29.57)	0.20
GABA transaminase inh	1.58 (0.89-2.80)	0.12	1.57 (0.82-2.78)	0.13	1.39 (0.79-2.45)	0.26	1.12 (0.64-1.97)	0.68
GABA$_A$ receptor ag	1.58 (0.89-2.80)	0.12	1.57 (0.88-2.78)	0.13	1.39 (0.79-2.45)	0.26	1.12 (0.64-1.97)	0.68
Glu receptor 3 ag	6.29 (0.87-45.4)	0.07	6.06 (0.84-43.9)	0.07	4.38 (0.58-33.2)	0.15	5.03 (0.62-40.6)	0.13
NMDAR 1 & 2D & 3B ant	1.16 (0.37-3.66)	0.79	1.15 (0.37-3.60)	0.81	1.14 (0.36-3.56)	0.83	0.70 (0.22-2.20)	0.54
NMDAR 3A ant	0.90 (0.37-2.17)	0.81	0.89 (0.37-2.16)	0.80	0.88 (0.36-2.12)	0.77	0.59 (0.25-1.42)	0.24
nAChR α ant	10.4 (1.33-82.0)	0.03	10.61 (1.34-83.9)	0.03	17.52 (1.58-194.3)	0.02	26.69 (2.26-315.3)	0.01
mAChR 1 ag	1.27 (0.96-1.68)	0.10	1.26 (0.95-1.67)	0.11	1.25 (0.94-1.67)	0.12	0.86 (0.64-1.16)	0.32
mAChR 1 ant	0.67 (0.22-2.09)	0.49	0.66 (0.21-2.07)	0.48	0.66 (0.21-2.08)	0.48	0.45 (0.14-1.41)	0.17
mAChR 2 ant	0.67 (0.30-1.50)	0.33	0.67 (0.30-1.49)	0.33	0.67 (0.30-1.49)	0.33	0.46 (0.21-1.04)	0.06
CBR 1 & 2 ag	1.02 (0.75-1.39)	0.90	1.01 (0.74-1.37)	0.96	1.01 (0.74-1.37)	0.95	0.72 (0.53-0.98)	0.04
OR μ ag	1.25 (0.83-1.86)	0.28	1.24 (0.83-1.85)	0.30	1.23 (0.83-1.84)	0.31	0.86 (0.57-1.29)	0.46
OR κ & ε ag	1.21 (0.80-1.82)	0.37	1.20 (0.80-1.81)	0.38	1.20 (0.79-1.80)	0.39	0.83 (0.55-1.26)	0.38
DA transporter inh	1.49 (0.99-2.26)	0.06	1.48 (0.97-2.24)	0.07	1.46 (0.96-2.21)	0.08	1.09 (0.72-1.65)	0.69
DAR 2 ag	1.95 (0.92-4.12)	0.08	1.94 (0.92-4.12)	0.08	1.91 (0.90-4.05)	0.09	1.65 (0.78-3.49)	0.19
DAR 2 ant	1.21 (0.91-1.60)	0.20	1.20 (0.90-1.59)	0.21	1.19 (0.90-1.58)	0.23	0.82 (0.61-1.11)	0.20
DAR 3 ag	2.25 (0.83-6.10)	0.11	2.26 (0.83-6.15)	0.11	2.19 (0.80-5.96)	0.13	1.76 (0.65-4.79)	0.27
NA transporter inh	1.35 (0.93-1.95)	0.12	1.33 (0.92-1.94)	0.13	1.32 (0.91-1.91)	0.15	0.95 (0.65-1.38)	0.78
NAR α 1Aag	1.50 (1.17-1.91)	<0.01	1.49 (1.16-1.90)	<0.01	1.48 (1.16-1.89)	<0.01	1.08 (0.85-1.38)	0.54
NAR α 1B ag	1.41 (0.94-2.12)	0.10	1.40 (0.93-2.11)	0.11	1.40 (0.93-2.11)	0.11	1.04 (0.69-1.55)	0.87
NAR α 1D ag	1.36 (0.89-2.06)	0.15	1.35 (0.89-2.05)	0.16	1.35 (0.89-2.05)	0.16	1.00 (0.66-1.51)	0.99
NAR α 2A ag	1.46 (1.10-1.95)	0.01	1.46 (1.09-1.94)	0.01	1.45 (1.09-1.93)	0.01	1.06 (0.80-1.41)	0.69
NAR α 2B ag	0.75 (0.34-1.68)	0.48	0.75 (0.34-1.68)	0.49	0.75 (0.34-1.69)	0.49	0.57 (0.26-1.28)	0.18
NAR α 2C ag	0.63 (0.26-1.52)	0.31	0.63 (0.26-1.53)	0.31	0.64 (0.26-1.54)	0.31	0.49 (0.20-1.17)	0.11
NAR β 1 ag	1.82 (0.58-5.72)	0.31	1.81 (0.57-5.69)	0.31	1.80 (0.57-5.67)	0.32	1.29 (0.41-4.073)	0.67
NAR β 1 ant	1.04 (0.39-2.79)	0.94	1.02 (0.38-2.75)	0.96	1.00 (0.37-2.67)	0.99	0.62 (0.23-1.67)	0.35
NAR β 2 ag	1.02 (0.49-2.12)	0.95	1.02 (0.49-2.10)	0.97	1.01 (0.49-2.08)	0.98	0.68 (0.33-1.41)	0.30
NAR β 2 ant	1.22 (0.30-4.93)	0.78	1.20 (0.30-4.87)	0.80	1.15 (0.28-4.69)	0.84	0.69 (0.17-2.78)	0.60
HistR 1 ant	1.24 (0.93-1.65)	0.15	1.23 (0.92-1.64)	0.16	1.22 (0.92-1.63)	0.18	0.89 (0.67-1.20)	0.43
HistR 2 ant	1.31 (0.73-2.32)	0.36	1.29 (0.73-2.29)	0.39	1.27 (0.72-2.26)	0.41	0.81 (0.46-1.44)	0.48
VAT inh	1.05 (0.34-3.27)	0.94	1.05 (0.34-3.28)	0.93	1.05 (0.34-3.28)	0.93	0.81 (0.26-2.50)	0.72

Hazard ratios (HR) are presented with their 95% confidence intervals, and accompanying p-values. Model 1: exposure + year of birth. Model 2: Model 1 + maternal age at birth + paternal age at birth. Model 3: Model 2 + maternal affective disorders + maternal anxiety disorders + maternal psychotic disorders + maternal neurological disorders. Model 4: Model 3 + maternal general health. All nominally significant results are presented in bold. None of the children with paternal age data and serotonin receptor 1B/1D agonist exposure developed ASD. Ag = agonist; ant = antagonist; inh=inhibitor; 5HTR = serotonin receptor; GABAAR = gamma-Aminobutyric acid A receptor; GluR = glutamate receptor; NMDAR = N-methyl-D-aspartate receptor; nAChR = neuronal acetylcholine receptor; mAChR = muscarinic acetylcholine receptor; CBR = cannabinoid receptor; OR = opioid receptor; DAR = dopamine receptor; NAR = adrenergic receptor; HistR = histamine receptor; VAT = vesicular amine transporter;

eTable 11. Associations Between Prenatal Exposure to Medications and Subsequent Diagnosis of ASD, Full Set of Results, Considering Indications 5 and 1 Year Before the Start of Pregnancy

| | ANALYSES WITH DIFFERENT WINDOWS FOR MATERNAL DIAGNOSES | | | | | | | |
| | Model 3 (5yrs) | | Model 4 (5yrs) | | Model 3 (1yr) | | Model 4 (1yr) | |
	HR (95% CI)	p	HR (95% CI)	p	HR (95% CI)	p	HR (95% CI)	p
5-HT transporter inh	1.28 (0.91-1.79)	0.15	1.10 (0.79-1.54)	0.58	1.29 (0.92-1.80)	0.14	1.06 (0.76-1.48)	0.74
5-HTR 1B & 1D ag	0.79 (0.11-5.71)	0.82	0.64 (0.09-4.66)	0.66	0.80 (0.11-5.77)	0.82	0.61 (0.85-4.44)	0.63
5-HTR 2A ant	0.79 (0.11-5.73)	0.82	0.71 (0.10-5.15)	0.73	0.83 (0.12-5.87)	0.85	0.69 (0.10-4.98)	0.72
5-HTR 2B ant	2.49 (0.33-18.87)	0.38	2.69 (0.36-20.42)	0.34	2.74 (0.37-20.51)	0.33	2.59 (0.34-1.97)	0.36
GABA transaminase inh	3.61 (0.90-14.49)	0.07	3.52 (0.90-13.72)	0.07	3.37 (0.85-1.34)	0.09	2.87 (0.74-11.12)	0.13
GABA$_A$R ag	1.30 (0.81-2.09)	0.28	1.18 (0.74-1.90)	0.49	1.33 (0.82-2.14)	0.25	1.14 (0.71-1.83)	0.58
GluR 3 ag	3.08 (0.42-22.65)	0.27	2.74 (0.35-21.58)	0.34	3.16 (0.42-2.36)	0.26	3.17 (0.42-2.40)	0.26
NMDAR 1 & 2D & 3B ant	0.82 (0.26-2.58)	0.74	0.64 (0.20-2.00)	0.44	0.83 (0.26-2.59)	0.75	0.57 (0.18-1.80)	0.34
NMDAR 3A ant	0.63 (0.26-1.53)	0.31	0.51 (0.21-1.24)	0.14	0.64 (0.27-1.55)	0.32	0.47 (0.20-1.14)	0.09
nAChR α antagonist	**13.1 (1.34-127.7)**	**0.03**	**15.8 (1.42-175.8)**	**0.03**	**13.6 (1.68-109.4)**	**0.01**	**15.5 (1.97-122.0)**	**0.01**
mAChR 1 ag	1.08 (0.83-1.39)	0.57	0.90 (0.69-1.17)	0.42	1.08 (0.84-1.40)	0.55	0.83 (0.64-1.08)	0.17
mAChR 1 ant	0.47 (0.15-1.48)	0.20	0.37 (0.12-1.15)	0.09	0.49 (0.16-1.52)	0.22	0.36 (0.11-1.12)	0.08
mAChR 2 ant	0.64 (0.32-1.28)	0.21	0.51 (0.25-1.02)	0.06	0.64 (0.32-1.29)	0.21	**0.49 (0.24-0.97)**	**0.05**
CBR 1 & 2 ag	0.95 (0.73-1.24)	0.71	0.80 (0.61-1.05)	0.10	0.95 (0.73-1.25)	0.73	**0.74 (0.57-0.97)**	**0.03**
OR μ ag	0.91 (0.61-1.34)	0.62	0.73 (0.49-1.09)	0.12	0.91 (0.62-1.35)	0.63	0.69 (0.46-1.02)	0.06
OR κ & ε ag	0.88 (0.59-1.32)	0.54	0.71 (0.48-1.07)	0.10	0.89 (0.59-1.32)	0.55	**0.67 (0.45-1.00)**	**0.05**
DA transporter inh	1.18 (0.80-1.75)	0.40	0.98 (0.66-1.45)	0.93	1.19 (0.81-1.76)	0.38	0.95 (0.64-1.40)	0.79
DAR 2 ag	1.33 (0.63-2.83)	0.46	1.19 (0.56-2.52)	0.65	1.34 (0.63-2.84)	0.44	1.18 (0.56-2.49)	0.67
DAR 2 ant	1.04 (0.81-1.34)	0.77	0.87 (0.67-1.13)	0.29	1.05 (0.81-1.35)	0.73	0.81 (0.63-1.05)	0.11
DAR 3 ag	1.54 (0.56-4.19)	0.40	1.36 (0.50-3.71)	0.54	1.56 (0.57-4.24)	0.39	1.30 (0.48-3.52)	0.61
NA transporter inh	1.10 (0.78-1.55)	0.59	0.91 (0.64-1.28)	0.58	1.11 (0.79-1.56)	0.56	8.65 (0.61-1.22)	0.41
NAR α1 A ag	**1.27 (1.01-1.58)**	**0.04**	1.05 (0.84-1.31)	0.65	**1.27 (1.02-1.58)**	**0.04**	1.00 (0.80-1.25)	1.00
NAR α 1B ag	1.37 (0.97-1.95)	0.08	1.15 (0.81-1.64)	0.42	1.38 (0.97-1.95)	0.07	1.10 (0.77-1.56)	0.60
NAR α 1D ag	1.34 (0.94-1.91)	0.11	1.13 (0.79-1.61)	0.51	1.34 (0.94-1.91)	0.11	1.07 (0.75-1.53)	0.71
NAR α 2A ag	1.13 (0.86-1.48)	0.37	0.94 (0.72-1.23)	0.66	1.13 (0.87-1.49)	0.36	0.90 (0.68-1.18)	0.43
NAR α 2B ag	0.62 (0.30-1.31)	0.21	0.53 (0.25-1.12)	0.10	0.62 (0.30-1.31)	0.21	0.51 (0.24-1.07)	0.07
NAR α2 C ag	0.54 (0.24-1.21)	0.13	0.46 (0.21-1.03)	0.06	0.54 (0.24-1.21)	0.13	**0.44 (0.20-0.99)**	**0.05**
NAR β 1 ag	1.30 (0.41-4.10)	0.65	1.08 (0.35-3.37)	0.89	1.33 (0.42-4.18)	0.63	1.04 (0.33-3.25)	0.95
NAR β 1 ant	1.22 (0.58-2.60)	0.60	0.97 (0.45-2.06)	0.93	1.22 (0.58-2.60)	0.60	0.86 (0.40-1.83)	0.70
NAR β 2 ag	0.80 (0.41-1.59)	0.53	0.62 (0.31-1.23)	0.17	0.82 (0.41-1.62)	0.56	0.61 (0.31-1.21)	0.15
NAR β 2 ant	1.62 (0.59-4.41)	0.35	1.26 (0.46-3.45)	0.65	1.63 (0.60-4.42)	0.34	1.11 (0.40-3.02)	0.85
HistR 1 ant	1.13 (0.88-1.46)	0.34	0.94 (0.73-1.21)	0.64	1.14 (0.89-1.47)	0.31	0.90 (0.70-1.16)	0.41
HistR 2 ant	1.26 (0.78-2.05)	0.35	0.94 (0.58-1.53)	0.80	1.27 (0.78-2.05)	0.34	0.89 (0.55-1.45)	0.65
VAT inh	1.25 (0.52-3.03)	0.62	1.10 (0.46-2.67)	0.83	1.25 (0.52-3.03)	0.62	1.03 (0.43-2.49)	0.95

Hazard ratios (HR) are presented with their 95% confidence intervals, and accompanying p-values. Model 1: exposure + year of birth. Model 2: Model 1 + maternal age at birth. Model 3: Model 2 + maternal affective disorders + maternal anxiety disorders + maternal psychotic disorders + maternal neurological disorders. Model 4: Model 3 stratified by maternal general health. Models 1 and 2 unchanged compared to those in the main analyses and thus not shown. All nominally significant results are presented in bold. Ag = agonist; ant = antagonist; inh=inhibitor; 5HTR = serotonin receptor; GABAAR = gamma-Aminobutyric acid A receptor; GluR = glutamate receptor; NMDAR = N-methyl-D-aspartate receptor; nAChR = neuronal acetylcholine receptor; mAChR = muscarinic acetylcholine receptor; CBR = cannabinoid receptor; OR = opioid receptor; DAR = dopamine receptor; NAR = adrenergic receptor; HistR = histamine receptor; VAT = vesicular amine transporter;

eTable 12. Associations Between Prenatal Exposure to Medications and Subsequent Diagnosis of ASD, Full Set of Results, in a Sample Without Sibling Matches

	ANALYSES WITHOUT SIBLING MATCHES							
	Model 1		Model 2		Model 3		Model 4	
	HR (95% CI)	p	HR (95% CI)	p	HR (95% CI)	p	HR (95% CI)	p
5-HTR transporter inh	1.196 (0.834-1.715)	0.33	1.214 (0.847- 1.740)	0.292	1.123 (0.787-1.603)	0.522	0.975 (0.683-1.391)	0.888
5-HTR 1B & 1D ag	0.701 (0.097-5.064)	0.725	0.744 (0.103-5.373)	0.769	0.692 (0.953-5.020)	0.716	0.580 (0.080-4.2220)	0.591
5-HTR 2A ant	1.012 (0.140-7.301)	0.991	1.042 (0.144-7.515)	0.968	0.881 (0.123-0.633)	0.899	0.851 (0.118-6.127)	0.873
5-HTR 2B ant	3.221 (0.433-23.990)	0.253	3.373 (0.452-25.145)	0.236	2.404 (0.319-18.120)	0.395	2.224 (0.292-1.692)	0.44
GABA transaminase inh	4.146 (0.963-17.852)	0.056	4.025 (0.935-17.322)	0.062	3.783 (0.896-15.970)	0.07	3.881 (0.916-16.440)	0.066
GABA$_A$R ag	1.369 (0.830-2.256)	0.219	1.441 (0.874-2.378)	0.152	1.265 (0.774-2.067)	0.348	1.149 (0.707-1.867)	0.576
GluR 3 ag	3.695 (0.479-28.529)	0.21	3.626 (0.464-28.357)	0.22	3.177 (0.378-26.730)	0.288	3.086 (0.352-2.705)	0.309
NMDAR 1 & 2D & 3B ant	0.804 (0.256-2.526)	0.709	0.808 (0.257-2.540)	0.716	0.800 (0.254-2.519)	0.703	0.629 (0.199-1.985)	0.429
NMDAR receptor 3A ant	0.618 (0.256-1.495)	0.286	0.621 (0.257-1.502)	0.291	0.614 (0.254-1.488)	0.28	0.499 (0.208-1.199)	0.12
nAChR α ant	5.753 (0.676-48.984)	0.109	6.366 (0.748-54.195)	0.09	0.146 (0.138-155.1)	0.026	1.938 (1.819-206.40)	0.014
mAChR 1 ag	0.907 (0.692-1.189)	0.481	0.893 (0.681-1.170)	0.411	0.888 (0.677-1.164)	0.39	0.748 (0.569-0.983)	0.038
mAChR 1 ant	0.142 (0.020-1.011)	0.051	0.146 (0.020-1.039)	0.055	0.145 (0.020-1.037)	0.054	0.118 (0.016-0.842)	0.033
mAChR 2 ant	0.567 (0.269-1.199)	0.138	0.576 (0.272-1.216)	0.148	0.578 (0.274-1.221)	0.151	0.476 (0.226-1.005)	0.052
CBR 1 & 2 ag	0.812 (0.613-1.074)	0.144	0.806 (0.609-1.066)	0.131	0.805 (0.608-1.065)	0.129	0.691 (0.523-0.913)	0.009
OR μ ag	0.800 (0.536-1.193)	0.274	0.806 (0.540-1.203)	0.292	0.803 (0.5381-1.198)	0.282	0.678 (0.456-1.010)	0.056
OR κ & ε ag	0.777 (0.517-1.169)	0.226	0.783 (0.521-1.178)	0.24	0.780 (0.5.18-1.172)	0.232	0.659 (0.439-0.9.891)	0.044
DA transporter inh	1.006 (0.663-1.525)	0.979	1.016 (0.670-1.541)	0.942	1.006 (0.663-1.525)	0.979	0.844 (0.557-1.281)	0.427
DAR 2 ag	1.284 (0.605-2.725)	0.515	1.309 (0.616-2.779)	0.484	1.276 (0.599-2.717)	0.527	1.173 (0.552-2.496)	0.678
DAR 2 ant	0.877 (0.671-1.148)	0.34	0.865 (0.661-1.131)	0.29	0.862 (0.659-1.127)	0.278	0.729 (0.556-0.956)	0.022
DAR 3 ag	1.529 (0.562-4.163)	0.406	1.499 (0.551-4.083)	0.428	1.434 (0.524-3.924)	0.483	1.295 (0.474-3.541)	0.614
NA transporter inh	0.965 (0.673-1.383)	0.845	0.973 (0.679-1.395)	0.883	0.959 (0.670-1.374)	0.82	0.803 (0.560-1.151)	0.232
NAR α 1A ag	1.092 (0.867-1.376)	0.454	1.093 (0.867-1.377)	0.452	1.085 (0.862-1.367)	0.487	0.924 (0.735-1.162)	0.501
NAR α 1B ag	1.277 (0.895-1.824)	0.178	1.269 (0.889-1.811)	0.19	1.258 (0.881-1.797)	0.207	1.092 (0.766-1.558)	0.625
NAR α 1D ag	1.241 (0.864-1.781)	0.243	1.233 (0.859-1.770)	0.257	1.222 (0.851-1.755)	0.277	1.063 (0.7.408-1.525)	0.741
NAR α 2A ag	0.961 (0.723-1.278)	0.786	0.967 (0.727-1.286)	0.817	0.962 (0.724-1.279)	0.791	0.816 (0.614-1.083)	0.159
NAR α 2B ag	0.533 (0.238-1.195)	0.127	0.529 (0.236-1.185)	0.122	0.529 (0.236-1.186)	0.122	0.464 (0.207-1.038)	0.061
NAR α 2C ag	0.447 (0.185-1.082)	0.074	0.444 (0.184-1.074)	0.071	0.444 (0.184-1.074)	0.072	0.391 (0.162-0.944)	0.037
NAR β 1 ag	0.952 (0.234-3.875)	0.946	0.971 (0.239-3.952)	0.967	0.993 (0.244-4.045)	0.992	0.817 (0.202-3.311)	0.777
NAR β 1 ant	1.339 (0.661-2.715)	0.418	1.486 (0.734-3.010)	0.271	1.464 (0.722-2.968)	0.291	1.115 (0.548-2.269)	0.765
NAR β 2 ant	1.606 (0.589-4.376)	0.354	1.707 (0.626-4.653)	0.296	1.641 (0.599-4.493)	0.335	1.226 (0.447-3.364)	0.692
NAR β 2 ag	0.555 (0.263-1.170)	0.122	0.573 (0.272-1.207)	0.143	0.572 (0.271-1.205)	0.142	0.473 (0.224-0.997)	0.049
Histamine receptor 1 ant	1.024 (0.786-1.335)	0.86	1.032 (0.792-1.345)	0.816	1.026 (0.787-1.338)	0.85	0.866 (0.665-1.128)	0.287
Histamine receptor 2 ant	1.253 (0.770-2.040)	0.364	1.278 (0.785-2.081)	0.324	1.267 (0.778-2.062)	0.342	0.989 (0.607-1.612)	0.966
VAT inh	1.102 (0.453-2.680)	0.831	1.111 (0.457-2.704)	0.816	1.116 (0.459-2.713)	0.809	0.969 (0.400-2.346)	0.944

Hazard ratios (HR) are presented with their 95% confidence intervals, and accompanying p-values. Model 1: exposure + year of birth. Model 2: Model 1 + maternal age at birth. Model 3: Model 2 + maternal affective disorders + maternal anxiety disorders + maternal psychotic disorders + maternal neurological disorders. Model 4: Model 3 stratified by maternal general health. Models 1 and 2 unchanged compared to those in the main analyses and thus not shown. All nominally significant results are presented in bold. Ag = agonist; ant = antagonist; inh=inhibitor; 5HTR = serotonin receptor; GABAAR = gamma-Aminobutyric acid A receptor; GluR = glutamate receptor; NMDAR = N-methyl-D-aspartate receptor; nAChR = neuronal acetylcholine receptor; mAChR = muscarinic acetylcholine receptor; CBR = cannabinoid receptor; OR = opioid receptor; DAR = dopamine receptor; NAR = adrenergic receptor; HistR = histamine receptor; VAT = vesicular amine transporter;

eTable 13. Associations Between Prenatal Exposure to Medications and Subsequent Diagnosis of ASD, in a Permuted Sample With Random Assignment of ASD Diagnosis to the Cohort Members

		ANALYSES AFTER RANDOM ASSIGNMENT OF ASD DIAGNOSIS					
		Run 1		*Run 2*		*Run3*	
		HR (95% CI)	*p*	*HR (95% CI)*	*p*	*HR (95% CI)*	*p*
5-HTR transporter inh	C	1.310 (0.903-1.899)	0.155	1.098 (0.728-1.656)	0.655	0.897 (0.573-1.403)	0.633
	A	1.305 (0.897-1.899)	0.165	1.075 (0.715-1.617)	0.727	0.893 (0.568-1.404)	0.625
5-HTR 1B & 1D ag	C	0.706 (0.155-3.202)	0.651	1.184 (0.266-5.277)	0.824	0.306 (0.0441-2.122)	0.231
	A	0.684 (0.150-3.125)	0.624	1.135 (0.257-5.008)	0.867	0.302 (0.043-2.124)	0.229
5-HTR 2A ant	C	1.862 (0.551-6.294)	0.317	0.772 (0.111-5.373)	0.794	0.796 (0.118-5.388)	0.815
	A	1.823 (0.534-6.224)	0.338	0.788 (0.116-5.355)	0.807	0.756 (0.114-5.002)	0.771
5-HTR 2B ant	C	2.735 (0.360-20.780)	0.331	-	-	-	-
	A	2.718 (0.363-20.355)	0.330		-	-	-
GABA transaminase inh	C	-	-	-	-	3.567 (0.502-25.33)	0.204
	A	-	-	-	-	6.096 (0.642-57.856)	0.115
GABA$_A$R ag	C	1.301 (0.726-2.333)	0.377	1.271 (0.706-2.287)	0.423	0.936 (0.471-1.858)	0.849
	A	1.248 (0.679-2.295)	0.476	1.298 (0.710-2.373)	0.398	0.895 (0.446-1.795)	0.755
GluR 3 ag	C	-	-	-	-	-	-
	A	-	-	-	-	-	-
NMDAR 1 & 2D & 3B ant	C	0.804 (0.259-2.496)	0.706	0.804 (0.259-2.496)	0.706	0.804 (0.259-2.496)	0.706
	A	1.469 (0.604-3.569)	0.396	0.843 (0.212-3.355)	0.809	0.433 (0.0619-3.033)	0.4
NMDAR receptor 3A ant	C	1.423 (0.766-2.641)	0.264	0.914 (0.401-2.083)	0.830	0.606 (0.234-1.567)	0.302
	A	1.418 (0.763-2.638)	0.270	0.881 (0.387-2.006)	0.763	0.606 (0.234-1.566)	0.301
nAchR α ant	C		-	-	-	-	-
	A	-	-	-	-	-	-
mAChR 1 ag	C	0.875 (0.648-1.182)	0.384	0.971 (0.728-1.297)	0.844	0.960 (0.714-1.290)	0.786
	A	0.874 (0.647-1.180)	0.378	0.950 (0.710-1.272)	0.731	0.956 (0.709-1.288)	0.767
mAChR 1 ant	C	0.812 (0.334-1.972)	0.645	0.643 (0.223-1.851)	0.413	0.518 (0.157-1.707)	0.28
	A	0.801 (0.328-1.952)	0.625	0.613 (0.212-1.775)	0.367	0.514 (0.155-1.705)	0.276
mAChR 2 ant	C	0.713 (0.353-1.441)	0.346	0.863 (0.451-1.653)	0.657	0.602 (0.268-1.352)	0.219
	A	0.710 (0.351-1.436)	0.340	0.826 (0.431-1.584)	0.565	0.604 (0.269-1.359)	0.223
CBR 1 & 2 ag	C	1.096 (0.839-1.431)	0.503	1.015 (0.768-1.342)	0.917	0.938 (0.701-1.254)	0.664
	A	1.096 (0.839-1.433)	0.501	0.988 (0.747-1.308)	0.935	0.934 (0.696-1.253)	0.648
OR μ ag	C	0.938 (0.624-1.409)	0.756	0.892 (0.585-1.359)	0.594	0.828 (0.538-1.276)	0.393
	A	0.934 (0.621-1.405)	0.744	0.859 (0.562-1.311)	0.480	0.834 (0.541-1.287)	0.412
OR κ & ε ag	C	0.949 (0.632-1.426)	0.801	0.902 (0.592-1.375)	0.632	0.839 (0.545-1.292)	0.426
	A	0.946 (0.629-1.422)	0.789	0.869 (0.569-1.327)	0.516	0.845 (0.548-1.304)	0.447
DA transporter inh	C	1.242 (0.817-1.888)	0.311	0.905 (0.551-1.488)	0.695	0.944 (0.590-1.511)	0.811
	A	1.240 (0.815- 1.886)	0.316	0.873 (0.530-1.439)	0.595	0.951 (0.592-1.526)	0.834
DAR 2 ag	C	0.727 (0.225-2.350)	0.594	1.916 (0.993-3.698)	0.053	1.682 (0.795-3.563)	0.174
	A	0.720 (0.223-2.326)	0.582	1.882 (0.976-3.628)	0.059	1.682 (0.791-3.574)	0.177
DAR 2 ant	C	0.911 (0.682-1.218)	0.53	0.965 (0.728-1.281)	0.807	0.948 (0.710-1.267)	0.720
	A	0.911 (0.680-1.219)	0.529	0.946 (0.711-1.259)	0.702	0.944 (0.703-1.266)	0.698
DAR 3 ag	C	1.261 (0.309-5.140)	0.747	1.645 (0.612-4.421)	0.324	1.581 (0.492-5.074)	0.442
	A	1.271 (0.312-5.183)	0.739	1.611 (0.599-4.331)	0.345	1.582 (0.492-5.082)	0.442
NA transporter inh	C	1.350 (0.960-1.899)	0.084	1.011 (0.673-1.520)	0.957	0.950 (0.634-1.424)	0.805
	A	1.349 (0.957-1.900)	0.087	0.977 (0.649-1.471)	0.91	0.954 (0.635-1.434)	0.821
NAR α 1A ag	C	1.117 (0.873-1.429)	0.381	0.858 (0.642-1.147)	0.301	0.889 (0.670-1.181)	0.418
	A	1.114 (0.868-1.429)	0.397	0.831 (0.621-1.113)	0.215	0.889 (0.667-1.184)	0.421
NAR α 1B ag	C	0.936 (0.606-1.443)	0.763	0.773 (0.473-1.264)	0.305	0.755 (0.448-1.275)	0.294
	A	0.933 (0.603-1.443)	0.754	0.756 (0.461-1.238)	0.266	0.755 (0.448-1.272)	0.291
NAR α 1D ag	C	0.938 (0.608-1.447)	0.771	0.754 (0.456-1.246)	0.27	0.757 (0.449-1.278)	0.298
	A	0.935 (0.604-1.446)	0.762	0.736 (0.445-1.220)	0.235	0.757 (0.449-1.275)	0.295
NAR α 2A ag	C	1.058 (0.787-1.424)	0.708	0.856 (0.611-1.199)	0.365	1.098 (0.813- 1.483)	0.544
	A	1.052 (0.780-1.417)	0.742	0.827 (0.589-1.161)	0.272	1.102 (0.813-1.494)	0.532
NAR α 2B ag	C	0.697 (0.325-1.494)	0.353	0.639 (0.295-1.384)	0.256	1.026 (0.527-1.996)	0.941
	A	0.692 (0.323-1.486)	0.346	0.627 (0.289-1.360)	0.237	1.027 (0.529-1.996)	0.937
NAR α 2C ag	C	0.700 (0.327-1.501)	0.36	0.597 (0.264-1.351)	0.215	1.031 (0.530-2.006)	0.929
	A	0.696 (0.324-1.493)	0.352	0.585 (0.258-1.327)	0.200	1.033 (0.531-2.006)	0.925
NAR β 1 ag	C	1.023 (0.239-4.385)	0.976	0.231 (0.033-1.633)	0.142	0.348 (0.048-2.543)	0.298
	A	1.019 (0.236-4.389)	0.980	0.229 (0.033-1.582)	0.153	0.350 (0.049-2.514)	0.301
NAR β 1 ant	C	1.443 (0.676-3.082)	0.343	0.839 (0.313-2.246)	0.726	0.339 (0.073-1.582)	0.169

	A	1.396 (0.649-3.002)	0.393	0.764 (0.284-2.057)	0.595	0.341 (0.073-1.602)	0.173
NAR β 2 ant	C	1.342 (0.452-3.980)	0.596	1.026 (0.273-3.854)	0.970	0.198 (0.027-1.440)	0.110
	A	1.305 (0.439-3.879)	0.632	0.965 (0.257-3.621)	0.958	0.197 (0.027-1.437)	0.109
NAR β 2 ag	C	0.840 (0.446-1.586)	0.591	0.847 (0.437-1.641)	0.622	0.699 (0.340-1.439)	0.331
	A	0.827 (0.437-1.565)	0.56	0.812 (0.419-1.573)	0.537	0.705 (0.341-1.454)	0.343
Histamine receptor 1 ant	C	1.005 (0.753-1.340)	0.975	1.128 (0.853-1.491)	0.397	0.959 (0.696-1.320)	0.795
	A	1.003 (0.750-1.340)	0.986	1.091 (0.822-1.449)	0.546	0.969 (0.702-1.337)	0.848
Histamine receptor 2 ant	C	1.542 (0.944-2.519)	0.084	0.728 (0.363-1.459)	0.371	1.334 (0.775-2.298)	0.298
	A	1.534 (0.932-2.524)	0.092	0.680 (0.338-1.367)	0.279	1.344 (0.778-2.321)	0.289
VAT inh	C	2.094 (0.973-4.507)	0.059	1.503 (0.617-3.664)	0.37	1.250 (0.484-3.228)	0.645
	A	2.086 (0.968-4.496)	0.061	1.442 (0.591-3.524)	0.422	1.265 (0.489-3.270)	0.628

Runs 1-3 represent independent sets of analyses with different (random) assignment of ASD diagnosis. Rows marked with C show results from the crude (exposure + year of birth), and those marked with A from fully adjusted models (exposure + year of birth maternal affective disorders + maternal anxiety disorders + maternal psychotic disorders + maternal neurological disorders + maternal number of diagnoses). All nominally significant results are presented in bold. Due to low frequenciues of certain exposures, after random assignment of ASD diagnoses there were no exposed "cases" for certain groups of drugs in certain runs – in those instances, we entered (-) into appropriate cell. Ag = agonist; ant = antagonist; inh=inhibitor; 5HTR = serotonin receptor; GABAAR = gamma-Aminobutyric acid A receptor; GluR = glutamate receptor; NMDAR = N-methyl-D-aspartate receptor; nAChR = neuronal acetylcholine receptor; mAChR = muscarinic acetylcholine receptor; CBR = cannabinoid receptor; OR = opioid receptor; DAR = dopamine receptor; NAR = adrenergic receptor; HistR = histamine receptor; VAT = vesicular amine transporter;

eTable 14. Calculations of Necessary Increases in the Standard Errors to Render the Observed Associations Nonsignificant

	Model 1					Model 4				
	B	SE	RSE	hypSE	% change tolerable	B	SE	RSE	hypSE	% change tolerable
GABA transamin inh	**1.408**	0.708	0.715	**0.718**	0.471*	1.147	0.741	0.685	**0.585**	-14.569
nAchR α ant	1.763	1.000	1.034	0.900	-13.009	**2.560**	1.074	1.154	**1.306**	13.182*
mAChR 2 ant	-0.493	0.355	0.356	0.251	-29.345	**-0.723**	0.355	0.356	**0.369**	3.617*
CBR 1 & 2 ag	-0.115	0.136	0.137	0.059	-56.857	**-0.323**	0.137	0.137	**0.164**	20.289*
OR κ & ε ag	-0.173	0.202	0.203	0.088	-143.480	**-0.407**	0.202	0.204	**0.207**	2.292*
NAR α 2C ag	-0.668	0.409	0.410	**0.341**	-16.874	**-0.843**	0.410	0.410	**0.430**	4.903*

B represents effect sizes calculated in the regression (Model 1 – crude, and Model 4 – fully adjusted), SE their standard errors, RSE robust standard errors, hypSE hypothetical standard errors necessary to make the observed associations non-significant (so that hypSE * 1.96 ±B = 0). % change tolerable column indicates how much the recorded robust standard error could increase (expressed as their own %) before the associations become non-significant. Negative values in that column indicate by how much the standard errors would need to decrease for the effect to be significant. Text highlighted in red indicates the associations that were significant in the main analysis. nAchR = neuronal acetylcholine receptor; mAChR = muscarinic acetylcholine receptor; CBR = cannabinoid receptor; OR = opioid receptor; NAR – adrenergic receptor; inh – inhibitor; ant – antagonist; ag – agonist;