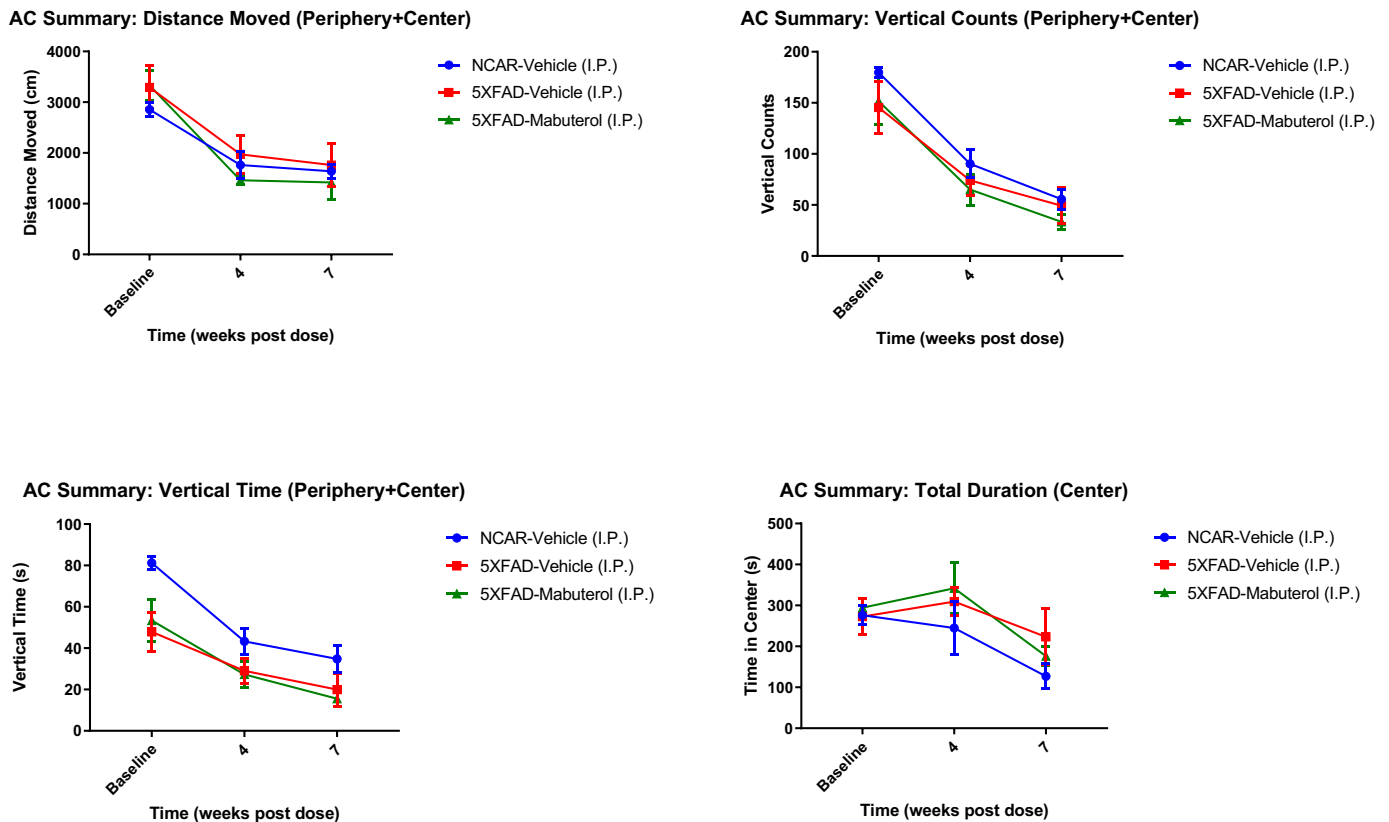
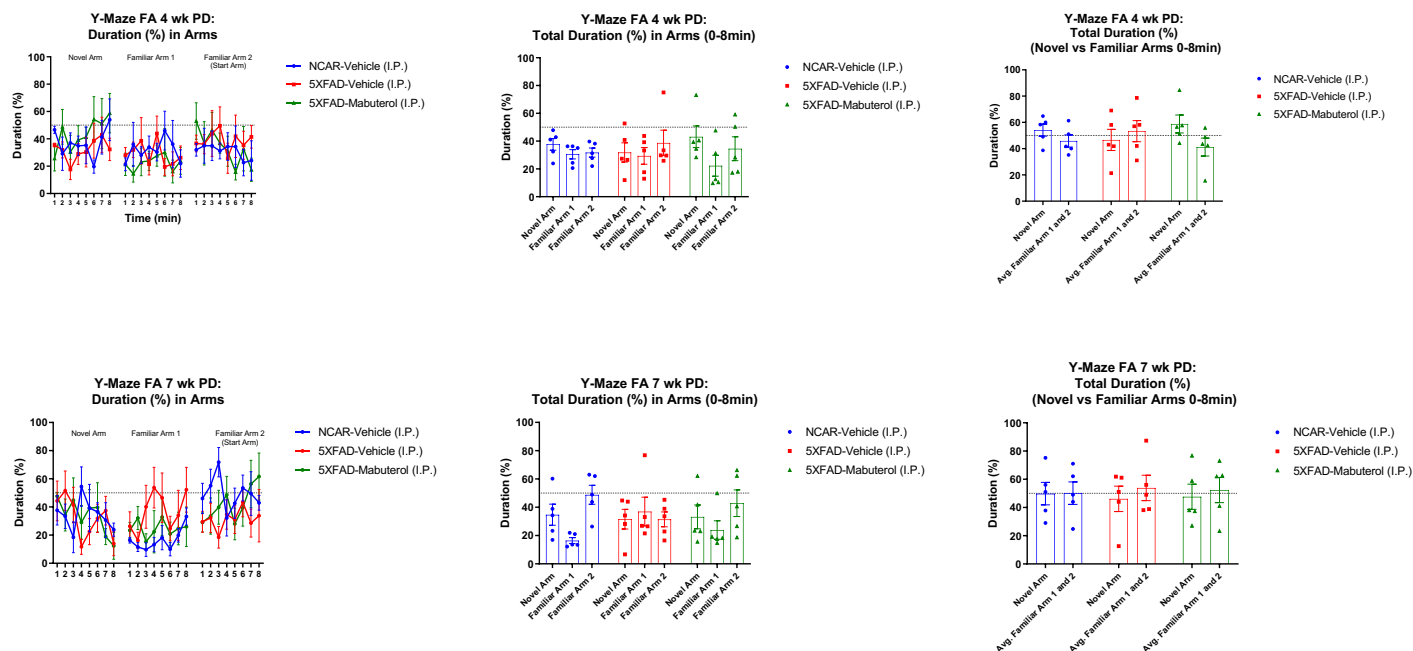


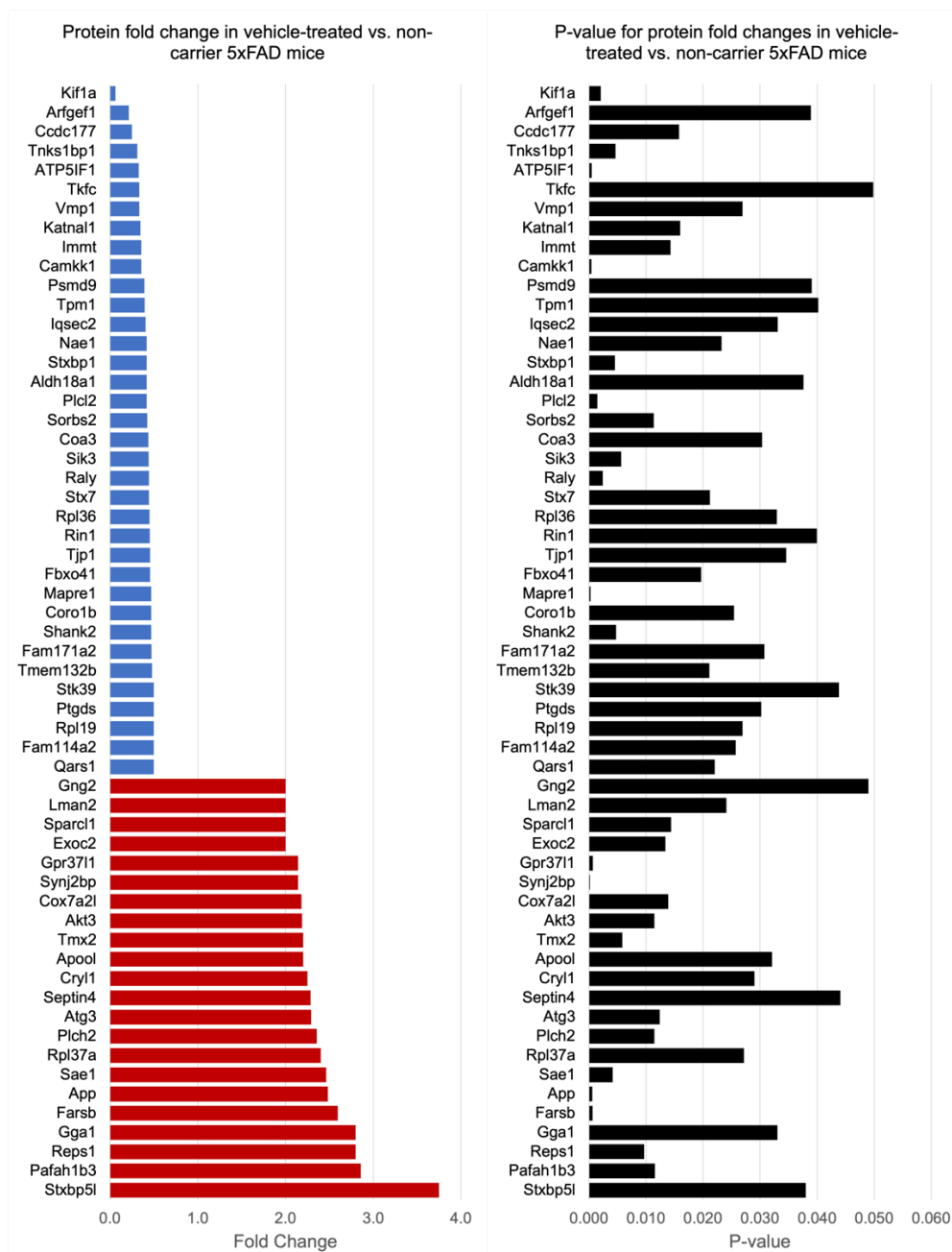
Supplementary Figure 1. Mouse body weight and survival during *in vivo* study. Mice maintained body weight, and all mice survived through the study. Vehicle-treated non-carriers (NCAR-Veh), vehicle-treated 5XFAD (Hemi-Veh), and mabuterol-treated 5XFAD (Hemi-Mabuterol) are represented by blue, red, and green data curves.



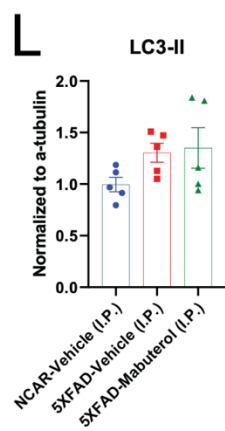
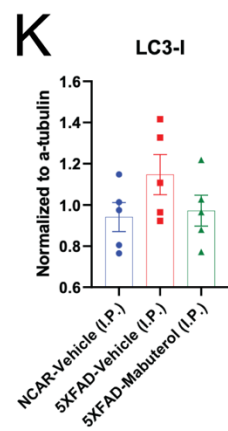
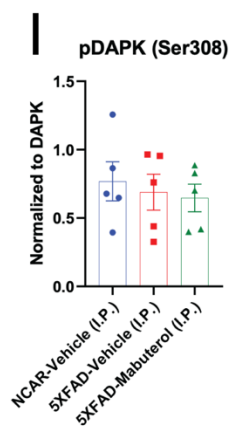
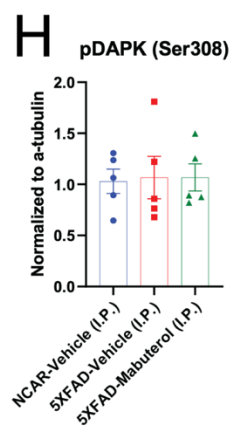
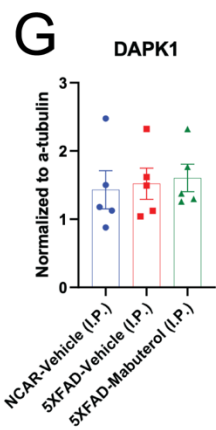
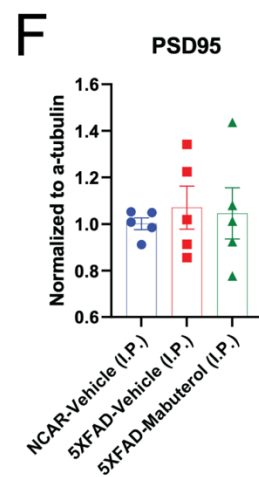
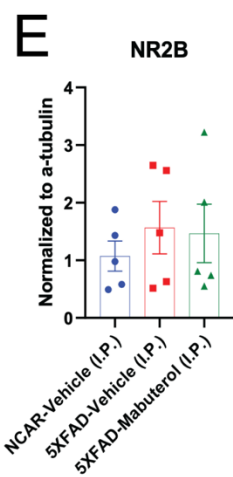
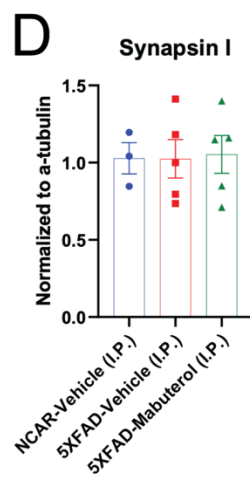
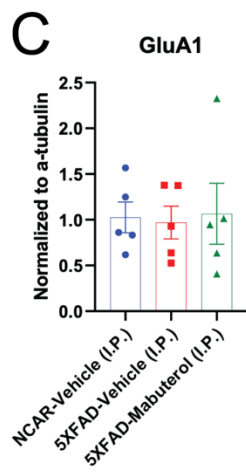
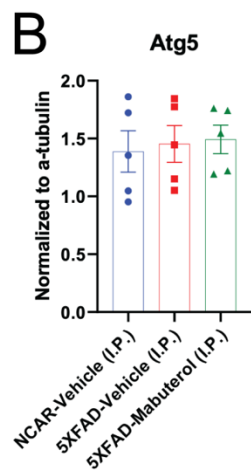
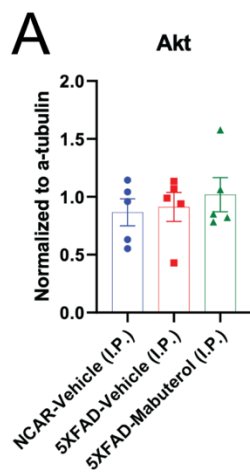
Supplementary Figure 2. Activity Chamber showed no significant changes in spontaneous activity over the course of the study. We measured the distance moved (upper left), vertical counts (upper right), vertical time (lower left), and total duration spent in the center of the arena (lower right) over the course of the study and observed no statistically significant differences. Vehicle-treated non-carriers (NCAR-Veh), vehicle-treated 5XFAD (Hemi-Veh), and mabuterol-treated 5XFAD (Hemi-Mabuterol) are represented by blue, red, and green data curves.



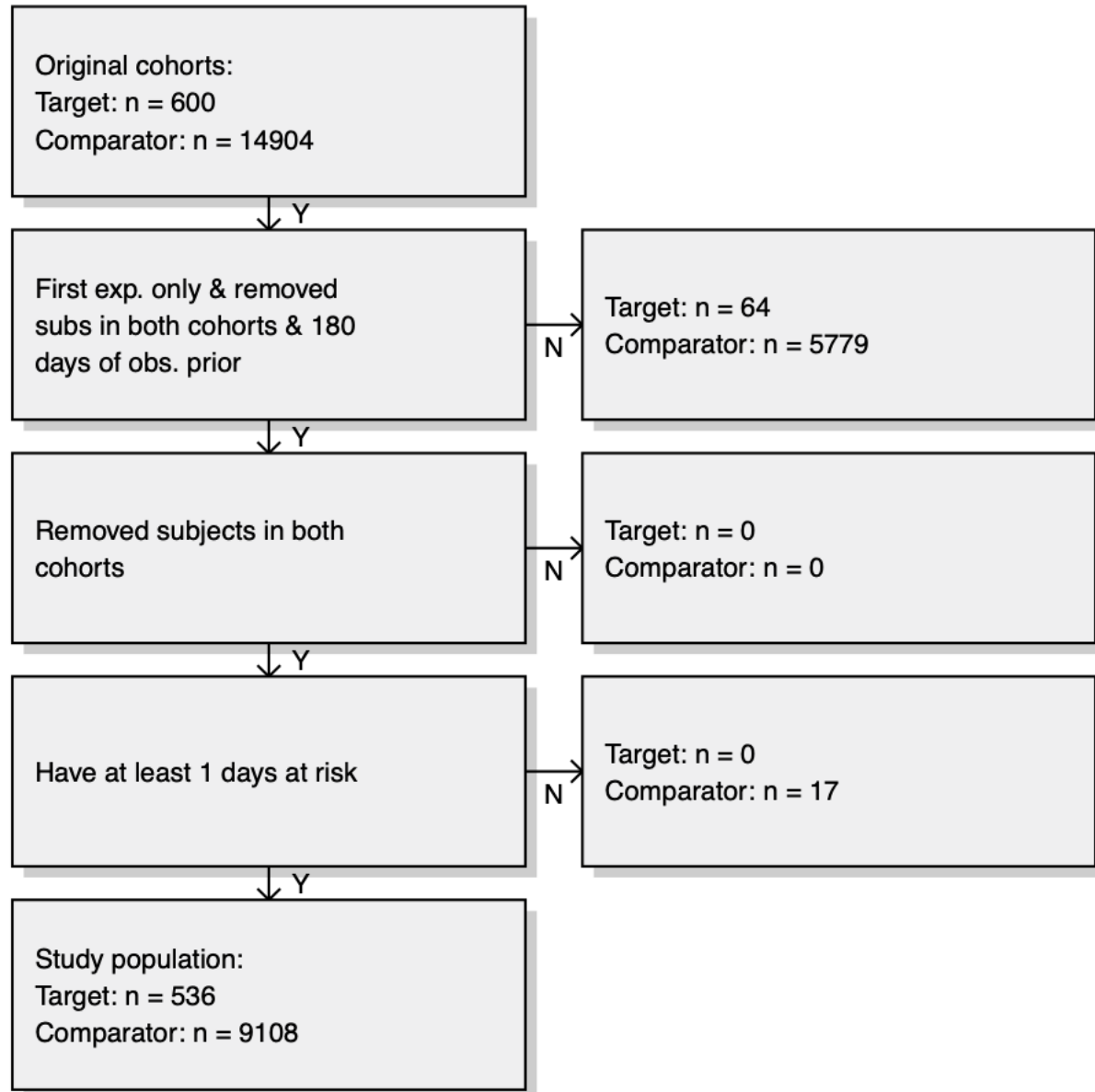
Supplementary Figure 3. Y-maze: Forced Alternation showed no changes in spatial reference memory across treatment groups. We examined the total duration spent in the novel and familiar arms at 4 weeks (top) and 7 weeks (bottom) post-dosing. We analyzed this information based on the duration in each arm (left) and based on the duration in the novel arm compared to the average of the duration in the familiar arms (right). Vehicle-treated non-carriers (NCAR-Veh), vehicle-treated 5XFAD (Hemi-Veh), and mabuterol-treated 5XFAD (Hemi-Mabuterol) are represented by blue, red, and green data curves.



Supplementary Figure 4. Protein expression level changes detected by proteomics in 5XFAD mice compared to controls. Protein expression changes and their significance were assessed for vehicle-treated 5XFAD (Hemi-Veh) compared to vehicle-treated non-carriers (NCAR-Veh) (A,B). Blue and red bars indicate down- and up-regulated proteins respectively.



Supplementary Figure 6. Targeted Western blot analysis did not uncover any protein level changes in a handful of selected proteins. We analyzed protein level changes for Akt (**A**), Atg5 (**B**), GluA1 (**C**), synapsin I (**D**), NR2B (**E**), PSD95 (combined bands: **F**), DAPK1 (**G**), phospho-DAPK Ser308 (“pDAPK”) (normalized to alpha-tubulin: **H**, normalized to DAPK1: **I**), LC3-I (**K**), and LC3-II (**L**). Vehicle-treated non-carriers (NCAR-Veh), vehicle-treated 5XFAD (Hemi-Veh), and mabuterol-treated 5XFAD (Hemi-Mabuterol) are shown in blue, red, and green respectively.



Supplementary Figure 7. Observational study attrition diagram.

| | | Effect | Phagocytosis of synaptosomes (% of control) | | | | |
|---------------------------------|--------------------------------------|---------------|--|-----------------------------------|-----------------------------------|------------------------------------|------------------------------------|
| Adrenoceptor Agonists | | | 1.39 μM | 2.78 μM | 5.56 μM | 11.11 μM | 22.22 μM |
| <i>Moxonidine hydrochloride</i> | <i>Alpha 2a Adrenoceptor Agonist</i> | ↑ | 118 | 127.8 | 128.5 | 130.6 | 167.2 |
| <i>Salmeterol xinafoate</i> | <i>Beta2 Adrenoceptor Agonist</i> | ↓ | 92 | 82.7 | 61.5 | 72.5 | 43.1 |

| Sulfonylureas | | | | | | | |
|----------------------|--|---|------|-------|-------|-------|-------|
| <i>Tolazamide</i> | | ↑ | 93.7 | 111.1 | 104.8 | 136.3 | 158.8 |
| <i>Glibenclamide</i> | | ↑ | 92.6 | 134.1 | 120.2 | 104 | 138.7 |

| Androgen/Estrogen | | | | | | | |
|---------------------------|----------------------|---|------|------|------|------|------|
| <i>Triptophenolide</i> | <i>Anti Androgen</i> | ↓ | 69.8 | 54.5 | 57.1 | 32.1 | 21.9 |
| <i>Estradiol benzoate</i> | | ↓ | 4.2 | 4.2 | 33.6 | 5.5 | 69.9 |

| Inflammatory | | | | | | | |
|--------------------------------------|--|---|------|------|------|------|------|
| <i>Prednisolone sodium phosphate</i> | | ↓ | 76.3 | 59.1 | 36.5 | 14.9 | 8.5 |
| <i>Gitoxigenin diacetate</i> | | ↓ | 71.9 | 52.7 | 18.2 | 12.2 | 47.2 |

| Glutamate receptor agonists | | | | | | | |
|--|--|---|-------|-------|-------|-------|-------|
| <i>Kynurenic acid</i> | | ↓ | 107.2 | 90.3 | 67.5 | 76 | 54.6 |
| <i>(±)-2-Amino-4-phosphonobutyric acid</i> | | ↑ | 98.6 | 101.3 | 120.2 | 132.4 | 131.5 |
| <i>Acamprosate calcium</i> | | ↓ | 86.5 | 35.5 | 28 | 6.6 | 5.9 |

| Other | | | | | | | |
|-------------------------------------|--|---|-------|------|------|------|------|
| <i>Fluphenazine dihydrochloride</i> | | ↓ | 103.6 | 93.6 | 84.5 | 49 | 47.3 |
| <i>Montelukast Sodium</i> | | ↓ | 46.4 | 2.7 | 24.9 | 28.5 | 0 |

Supplementary Table 1. Selected hit compounds and percent phagocytosis of synaptosomes by human astrocytes relative to control.

| Molecule Name | Activity | Toxicity | Molecule Mechanism |
|---------------------------------|-----------------------|-----------|--|
| LOPAC Results | | | |
| Terbutaline hemisulfate | inactive | non-toxic | beta-Adrenoceptor agonist; bronchodilator |
| Tulobuterol hydrochloride | inactive | non-toxic | beta-Adrenoceptor agonist related to structurally to terbutaline; bronchodilator |
| Isotharine mesylate | inactive | non-toxic | beta-Adrenoceptor agonist; bronchodilator |
| (-)-Isoproterenol hydrochloride | inactive | non-toxic | beta-Adrenoceptor agonist; increases cytosolic cAMP |
| Salmeterol xinafoate | Decrease phagocytosis | non-toxic | Beta-2 adrenoceptor agonist |
| MS Results | | | |
| Tulobuterol hydrochloride | inactive | non-toxic | beta-Adrenoceptor agonist related to structurally to terbutaline; bronchodilator |
| Isotharine mesylate | decrease phagocytosis | non-toxic | beta-Adrenoceptor agonist; bronchodilator |
| Nylidrin hydrochloride | inactive | non-toxic | beta Adrenoceptor agonist; peripheral vasodilator |
| Salbutamol | inactive | non-toxic | beta2-Adrenoceptor agonist |
| Amiodarone hydrochloride | decrease phagocytosis | toxic | alpha and beta adrenoceptor agonist; inhibits binding of 1,4-dihydropyridine to L-type Ca ²⁺ channels; coronary vasodilator |
| Fenoterol hydrobromide | inactive | non-toxic | Beta2-adrenoceptor agonist; bronchodilator |

Supplementary Table 2. Selected adrenoceptor agonist compounds and their effects. These data are also included in **Supplementary File 1**.

| | | | | | |
|---------------------------|---------|---------|---------|----------|----------|
| <i>Dose</i> | 1.39 uM | 2.78 uM | 5.56 uM | 11.11 uM | 22.22 uM |
| <i>Percent inhibition</i> | 92 | 82.7 | 61.5 | 72.5 | 43.1 |

Supplementary Table 3. Salmeterol had a dose-dependent decrease in phagocytosis. These data are also included in **Supplementary File 1**.

| | <i>Before matching</i> | | | <i>After matching</i> | | |
|---|------------------------|------------|-----------|-----------------------|------------|-----------|
| | Target | Comparator | | Target | Comparator | |
| Characteristic | % | % | Std. diff | % | % | Std. diff |
| Age group | | | | | | |
| 15 - 19 | 35.6 | 12.9 | 0.55 | 34.1 | 31.5 | 0.06 |
| 20 - 24 | 58.8 | 48.3 | 0.21 | 59.9 | 63.1 | -0.07 |
| 25 - 29 | 5.6 | 32.3 | -0.72 | 6 | 4.6 | 0.06 |
| 30 - 34 | | 6.5 | | | 0.8 | |
| Gender: female | 29.9 | 34.3 | -0.09 | 30.5 | 27.7 | 0.06 |
| Medical history: General | | | | | | |
| Acute respiratory disease | 39 | 23.6 | 0.34 | 36.9 | 38.7 | -0.04 |
| Attention deficit hyperactivity disorder | 24.8 | 12.8 | 0.31 | 22.6 | 22.6 | 0 |
| Chronic obstructive lung disease | 0.7 | 0.9 | -0.01 | 0.8 | 1.6 | -0.07 |
| Depressive disorder | 54.3 | 45.9 | 0.17 | 53.5 | 48.9 | 0.09 |
| Gastroesophageal reflux disease | 9.9 | 6.7 | 0.12 | 10 | 10 | 0 |
| Hyperlipidemia | 4.9 | 7.5 | -0.11 | 5 | 4.2 | 0.04 |
| Hypertensive disorder | 10.1 | 9.8 | 0.01 | 9.8 | 7.4 | 0.09 |
| Obesity | 8.4 | 7.6 | 0.03 | 8.6 | 7.4 | 0.04 |
| Urinary tract infectious disease | 8.8 | 8.9 | 0 | 8.4 | 6.8 | 0.06 |
| Visual system disorder | 14.9 | 12.3 | 0.08 | 15.4 | 15.2 | 0.01 |
| Medical history: Cardiovascular disease | | | | | | |
| Heart disease | 12.3 | 8.6 | 0.12 | 12.2 | 11.6 | 0.02 |
| Medication use | | | | | | |
| Agents acting on the renin-angiotensin system | 1.9 | 2.1 | -0.02 | 1.6 | 0.8 | 0.07 |
| Antibacterials for systemic use | 54.5 | 39.1 | 0.31 | 54.1 | 49.7 | 0.09 |
| Antidepressants | 53.2 | 42.3 | 0.22 | 51.7 | 49.5 | 0.04 |
| Antiepileptics | 38.4 | 30.2 | 0.17 | 37.1 | 33.9 | 0.07 |
| Antiinflammatory and antirheumatic products | 18.5 | 14.9 | 0.09 | 18.4 | 15.4 | 0.08 |
| Beta blocking agents | 7.6 | 5.2 | 0.1 | 7.6 | 7.4 | 0.01 |
| Calcium channel blockers | 0.9 | 1 | -0.01 | 1 | 0.6 | 0.04 |
| Drugs for acid related disorders | 10.3 | 7.3 | 0.1 | 10.2 | 8.2 | 0.07 |
| Drugs for obstructive airway diseases | 19.2 | 7.7 | 0.34 | 17.4 | 14.8 | 0.07 |
| Opioids | 13.6 | 10.3 | 0.1 | 13.2 | 13 | 0.01 |
| Psycholeptics | 70 | 62.1 | 0.17 | 68.5 | 66.3 | 0.05 |
| Psychostimulants, agents used for adhd and nootropics | 22.2 | 11.5 | 0.29 | 21.2 | 20.4 | 0.02 |

Supplementary Table 4. Abbreviated covariate balance between treatment and comparator groups after matching containing features with > 5% representation and a few selected cardiovascular features. Full covariate table provided in Supplementary File 9.

| Cohort Descriptor | Cohort Count |
|---|--------------|
| beta2 agonist exposure while age <=18 and age > 6 | 1,295,938 |
| schizophrenia young adult (SYA) diagnosis while age >= 18 | 15,504 |
| patients with pediatric exposure and SYA diagnosis | 600 |
| SYA diagnosis minus those with pediatric exposure | 14,904 |
| In patient visits associated with a schizophrenia diagnosis (SZD) | 31,292 |
| SYA patients with pediatric exposure and subsequent SZD inpatient visits | 15 |
| SYA patients without pediatric exposure and subsequent SZD inpatient visits | 1,075 |

Supplementary Table 5. Patient counts for analysis of effect of exposure to beta-2 agonists on schizophrenia-associated (SZD) in-patient visits in young adult patients.