

## **Supplemental Online Content**

**eFigure 1.** Cohort Assembly of Mother-Child Dyads Born at Kaiser Permanente Northern California (KPNC) from 2011-2017.

**eAppendix 1:** Ascertainment of Prenatal Substance Use

**eAppendix 2:** Ascertainment of Maternal Medical and Mental Health Comorbidities

**eAppendix 3:** Child Utilization Censoring Criteria

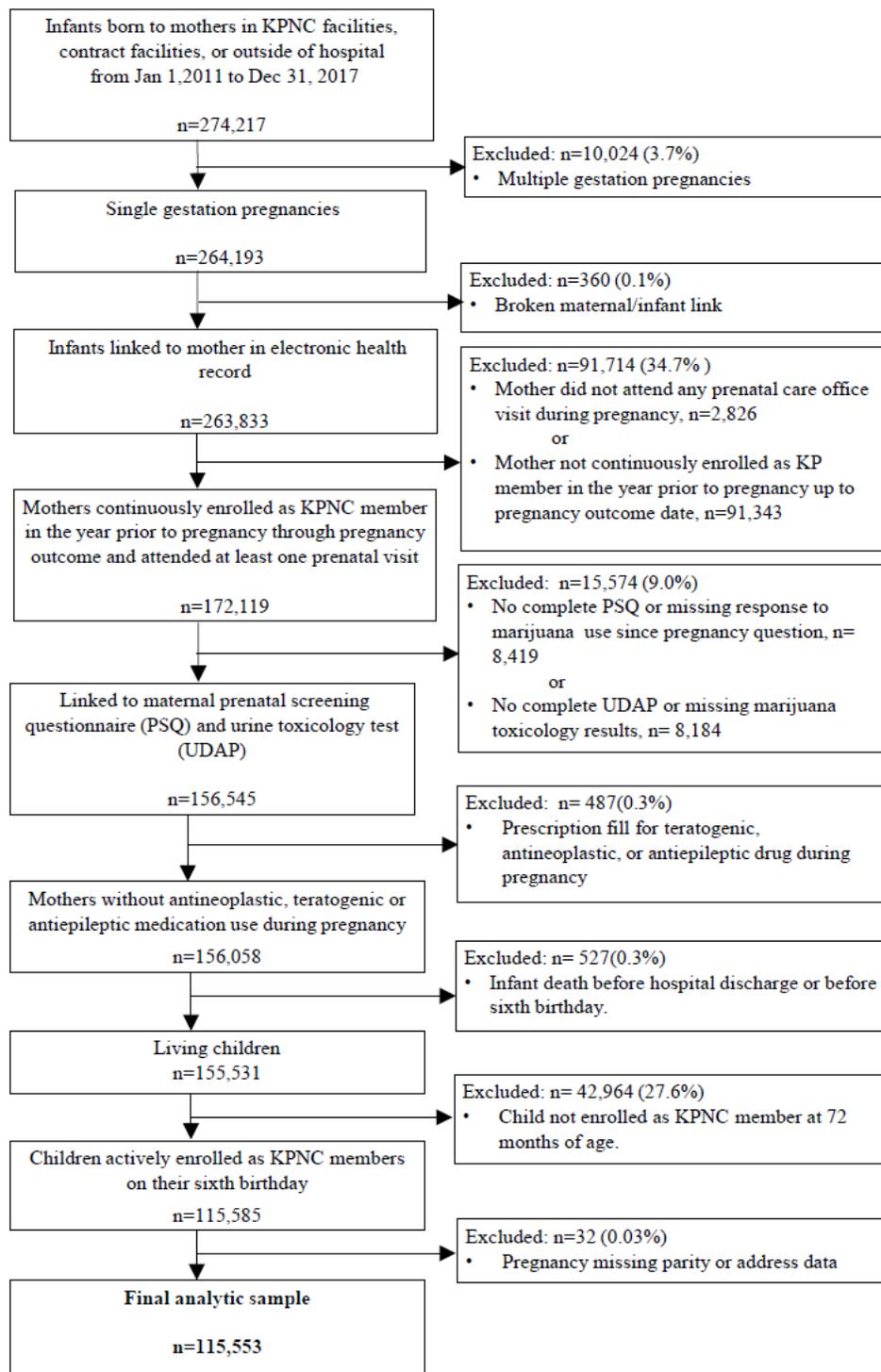
**eAppendix 4:** Child Anxiety and Depression Outcome Definitions

**eTable 1:** Adjusted Hazard Ratios for Associations Between Maternal Prenatal Cannabis Use and Offspring Anxiety and Depressive Disorders, Excluding Maternal-Child Dyads with Any Non-Cannabis Prenatal Substance Use

**eTable 2:** Adjusted Hazard Ratios for Associations Between Any Prenatal Cannabis Use and Offspring Anxiety and Depressive Disorders, Stratified by Maternal Anxiety and Depressive Disorders

**eTable 3.** Characteristics of 263,833 Mother-Child Dyads born 2011-2017, by Study Exclusion Criteria

**eFigure 1. Cohort Assembly of Mother-Child Dyads Born at Kaiser Permanente Northern California (KPNC) from 2011-2017.**



## eAppendix1: Ascertainment of Prenatal Substance Use

As part of standard prenatal care at KPNC, patients are universally screened for prenatal substance use by both self-report (via a self-administered questionnaire) and urine toxicology tests to which they provide consent at entrance into care. Of those individuals with continuous health plan membership in the year prior to pregnancy through delivery and attendance at a minimum of one prenatal care visit, 90.9% were screened by self-report and urine test for prenatal cannabis use (See eFigure 1).

*Prenatal cannabis use* was defined as self-reported cannabis use since becoming pregnant and/or a positive urine toxicology test at entrance to prenatal care. Results obtained from the first urine test during pregnancy ordered by OB/GYN department were used. If no urine test was ordered by OB/GYN department, results from the test closest to 8 weeks gestation were used. Cannabis toxicology screening tests were performed on a Beckman Coulter AU680 chemistry analyzer using the Emit II Plus Cannabinoid Assay from Siemens with a cutoff of 45ng/mL. Confirmatory testing for the presence of the cannabis metabolite, 11-nor-9-carboxy-delta 9- THC, was performed by liquid chromatography-tandem mass spectrometry for all positive immunoassay results. The confirmation test methodology was LC-MS/MS on a triple quadrupole system with a cutoff for positivity of 15ng/mL.

Prenatal substance use was defined as the following:

Variable	Definition
Prenatal alcohol use	<ul style="list-style-type: none"> <li>• Self-report for prenatal alcohol use at entrance to prenatal care</li> <li>• Toxicology for ethanol at entrance to prenatal care<sup>1</sup></li> </ul>
Prenatal opioid use	<ul style="list-style-type: none"> <li>• Self-report for prenatal heroin, methadone, or buprenorphine use at entrance to prenatal care</li> <li>• Toxicology for 6-monoacetylmorphine (6-MAM, heroin), morphine, codeine, hydrocodone, norhydrocodone, hydromorphone, oxycodone, nor oxycodone, or oxymorphone at entrance to prenatal care<sup>1</sup></li> <li>• Opioid prescription filled during pregnancy before first prenatal visit date or before pregnancy with supply lasting past pregnancy start date</li> </ul>
Prenatal stimulant use	<ul style="list-style-type: none"> <li>• Self-report for prenatal cocaine, crack, or methamphetamine use at entrance to prenatal care</li> <li>• Toxicology for benzoylecgonine, amphetamine, methamphetamine, MDMA (3,4-methylenedioxymethamphetamine) or MDA (3,4-methylenedioxyamphetamine) at entrance to prenatal care<sup>1</sup></li> <li>• Amphetamine prescription filled during pregnancy before first prenatal visit date or before pregnancy with supply lasting past pregnancy start date</li> </ul>
Prenatal nicotine use	<ul style="list-style-type: none"> <li>• Self-report for prenatal nicotine use at entrance to prenatal care</li> <li>• Self-report for tobacco smoking during pregnancy before first prenatal visit date</li> <li>• Nicotine replacement therapy prescription filled during pregnancy before first prenatal visit date or before pregnancy with supply lasting past pregnancy start date</li> </ul>

Prenatal anxiolytic/sedative medication use	<ul style="list-style-type: none"> <li>• Self-report for anxiety medication use at entrance to prenatal care</li> <li>• Self-report for sleep medication use at entrance to prenatal care</li> <li>• Toxicology for barbiturates at entrance to prenatal care<sup>1</sup></li> <li>• Toxicology for benzodiazepines at entrance to prenatal care<sup>1</sup></li> <li>• Anxiolytic or sedative prescription filled during pregnancy before first prenatal visit date or before pregnancy with supply lasting past pregnancy start date</li> </ul>
Prenatal SSRI use	<ul style="list-style-type: none"> <li>• SSRI prescription filled during pregnancy before first prenatal visit date or before pregnancy with supply lasting past pregnancy start date</li> </ul>
Prenatal non-SSRI antidepressant use	<ul style="list-style-type: none"> <li>• Non-SSRI antidepressant prescription filled during pregnancy before first prenatal visit date or before pregnancy with supply lasting past pregnancy start date</li> </ul>

<sup>1</sup>Results from the first test urine test during pregnancy ordered by OB/GYN department. If no urine test was ordered by OB/GYN department, results from the test closest to 8 weeks gestation were used.

### Self-reported prenatal substance use

Items from KPNC Early Start Prenatal Screening Questionnaire (revised 2014) used in this analysis:

In general, how often have you used the following **since pregnancy**:

1. Alcohol (wine, beer, liquor, etc.)
2. Nicotine (cigarettes, Nicorette gum, chewing tobacco, nicotine replacement therapy [NRT])
3. Sleep medication (Trazodone, Ambien, Restoril, etc.)
4. Pain medication (Vicodin, Norco, Oxycontin, Percocet, Codeine, etc.)
5. Anxiety medication (Valium, Xanax, Ativan, etc.)
6. Marijuana
7. Cocaine or Crack
8. Methamphetamine (Speed, Crank, Ecstasy, Ice, etc.)
9. Heroin
10. Other street drugs, please specify:
11. Methadone or Buprenorphine (Suboxone or Subutex)

Response options: Never, Monthly or Less, Weekly, Daily

Self-reported nicotine use was also assessed from EHR data on current tobacco use; patients are routinely asked about current tobacco use by medical assistants taking vital signs at the start of primary care visits.

### Prenatal urine toxicology testing

**Alcohol:** Alcohol screening tests were performed on a Beckman Coulter AU680 chemistry analyzer using the Emit II Plus Ethyl Alcohol Assay from Siemens with a cutoff of 10 mg/dL. Confirmatory testing for the presence of ethanol was performed by gas chromatography-mass spectrometry for all positive immunoassay results, also with a positive cutoff of 10 mg/dL.

**Opioids:** Opiate screening tests were performed on a Beckman Coulter AU680 chemistry analyzer using the Emit II Plus Opiate 300 Assay from Siemens with a cutoff of 300 ng/mL. Confirmatory

testing for the presence of opiate species was performed by liquid chromatography- tandem mass spectrometry for all positive immunoassay results. Opiate species detected by the confirmation assay include morphine, 6-monoacetylmorphine (6-MAM), codeine, hydrocodone, norhydrocodone, hydromorphone, oxycodone, noroxycodone, and oxymorphone. All species have a positive cutoff of 50 ng/mL except for 6-MAM which has a positive cutoff of 10 ng/mL.

Amphetamine/Methamphetamine: Amphetamine screening tests were performed on a Beckman Coulter AU680 chemistry analyzer using the DRI Amphetamines Assay with a cutoff of 500 ng/mL. Confirmatory testing for the presence of amphetamine species was performed by liquid chromatography- tandem mass spectrometry for all positive immunoassay results. Amphetamine species detected by the confirmation assay include amphetamine, methamphetamine, MDMA, and MDA. All species have a positive cutoff of 250 ng/mL.

Cocaine: Cocaine screening tests were performed on a Beckman Coulter AU680 chemistry analyzer using the Emit II Plus Cocaine Metabolite Assay which detects the cocaine metabolite benzoylecgonine with a positive cutoff of 150 ng/mL. Confirmatory testing for the presence of benzoylecgonine was performed by liquid chromatography- tandem mass spectrometry for all positive immunoassay results. The positive cutoff for the confirmation assay was 100 ng/mL.

Barbiturates: Barbiturate screening tests were performed on a Beckman Coulter AU680 chemistry analyzer using the Emit II Plus Barbiturate Assay from Siemens with a cutoff of 180 ng/mL. Confirmatory testing for the presence of barbiturate species was performed by liquid chromatography-tandem mass spectrometry for all positive immunoassay results. Barbiturate species detected by the confirmation assay include butalbital and phenobarbital. All species have a positive cutoff of 100 ng/mL.

Benzodiazepines: Benzodiazepine screening tests were performed on a Beckman Coulter AU680 chemistry analyzer using the CEDIA Benzodiazepine Assay from Thermo Fisher Scientific with a cutoff of 200 ng/mL. This assay incorporates beta-glucuronidase treatment to detect total benzodiazepine species for those that have glucuronidated metabolites. Confirmatory testing for the presence of benzodiazepine species was performed by liquid chromatography-tandem mass spectrometry for all positive immunoassay results. Benzodiazepine species detected by the confirmation assay include alprazolam/alpha-hydroxyalprazolam, clonazepam/7-aminoclonazepam, flunitrazepam/7-aminoflunitrazepam, lorazepam, nordiazepam, oxazepam, temazepam, alpha-hydroxytriazolam, and zolpidem. All species have a positive cutoff of 25 ng/mL except for zolpidem which has a positive cutoff of 2.5 ng/mL.

Prescriptions filled during pregnancy

<b>Class</b>	<b>Active Ingredient</b>
Amphetamines	DEXMETHYLPHENIDATE, DEXTROAMPHETAMINE, DEXTROAMPHETAMINE/AMPHETAMINE, LISDEXAMFETAMINE, METHAMPHETAMINE, METHYLPHENIDATE, SERDEXMETHYLPHENIDATE/DEXMETHYLPHENIDATE
Antiepileptics	METHYLPHENOBARBITAL, PHENOBARBITAL, PRIMIDONE, BARBEXACLONE, METHARBITA, ETHOTOIN, PHENYTOIN, AMINO(DIPHENYLHYDANTOIN) VALERIC ACID, MEPHENYTOIN, FOSPHENYTOIN, PHENYTOIN COMBINATIONS, MEPHENYTOIN COMBINATIONS,

	<p>PARAMETHADIONE, TRIMETHADIONE, ETHADIONE, ETHOSUXIMIDE, PHENSUXIMIDE, MESUXIMIDE, ETHOSUXIMIDE COMBINATIONS, CLONAZEPAM, CARBAMAZEPINE, OXCARBAZEPINE, RUFINAMIDE, ESLICARBAZEPINE, VALPROIC ACID, VALPROMIDE, AMINOBUTYRIC ACID VIGABATRIN, PROGABIDE, TIAGABINE SULTIAME, PHENACEMIDE, LAMOTRIGINE, FELBAMATE, TOPIRAMATE, GABAPENTIN, PHENETURIDE, LEVETIRACETAM, ZONISAMIDE, PREGABALIN, STIRIPENTOL, LACOSAMIDE, CARISBAMATE, RETIGABINE, PERAMPANEL, BRIVARACETAM, CANNABIDIOL, BECLAMIDE</p>
Antineoplastics	<p>CYCLOPHOSPHAMIDE, CHLORAMBUCIL, MELPHALAN, CHLORMETHINE, IFOSFAMIDE, TROFOSFAMIDE, PREDNIMUSTINE, BENDAMUSTINE, BUSULFAN, TREOSULFAN, MANNOSULFAN, THIOTEPA, TRIAZIQUONE, CARBOQUONE, CARMUSTINE, LOMUSTINE, SEMUSTINE, STREPTOZOCIN, FOTEMUSTINE, NIMUSTINE, RANIMUSTINE, URAMUSTINE, ETOGLUCID, MITOBRONITOL, PIPOBROMAN, TEMOZOLOMIDE, DACARBAZINE, METHOTREXATE , RALTITREXED, PEMETREXED, PRALATREXATE, MERCAPTOPURINE, TIOGUANINE, CLADRIBINE, FLUDARABINE, CLOFARABINE, NELARABINE, CYTARABINE, FLUOROURACIL, TEGAFUR, CARMOFUR, GEMCITABINE, CAPECITABINE, AZACITIDINE, DECITABINE, FLOXURIDINE, FLUOROURACIL, COMBINATIONS, TEGAFUR, COMBINATIONS, TRIFLURIDINE, COMBINATIONS, VINBLASTINE, VINCRISTINE, VINDESINE, VINOELBINE, VINFLUNINE, VINTAFOLIDE, ETOPOSIDE, TENIPOSIDE , DEMECOLCINE, PACLITAXEL, DOCETAXEL, PACLITAXEL POLI GLUMEX , CABAZITAXEL, TRABECTEDIN, DACTINOMYCIN, DOXORUBICIN, DAUNORUBICIN, EPIRUBICIN, ACLARUBICIN, ZORUBICIN, IDARUBICIN, MITOXANTRONE, PIRARUBICIN, VALRUBICIN, AMRUBICIN, PIXANTRONE, BLEOMYCIN, PLICAMYCIN, MITOMYCIN, IXABEPILONE, CISPLATIN, CARBOPLATIN, OXALIPLATIN, SATRAPLATIN, POLYPLATILLEN, PROCARBAZINE, EDRECOLOMAB, RITUXIMAB, TRASTUZUMAB, GEMTUZUMAB OZOGAMICIN, CETUXIMAB, BEVACIZUMAB, PANITUMUMAB, CATUMAXOMAB, OFATUMUMAB, IPILIMUMAB, BRENTUXIMAB VEDOTIN, PERTUZUMAB, TRASTUZUMAB EMTANSINE, OBINUTUZUMAB, DINUTUXIMAB BETA, NIVOLUMAB, PEMBROLIZUMAB, BLINATUMOMAB, RAMUCIRUMAB, NECITUMUMAB, ELOTUZUMAB, DARATUMUMAB, MOGAMULIZUMAB, INOTUZUMAB OZOGAMICIN, OLARATUMAB, DURVALUMAB, BERMEKIMAB, AVELUMAB, ATEZOLIZUMAB, CEMIPILIMAB, PORFIMER SODIUM, METHYL AMINOLEVULINATE, AMINOLEVULINIC ACID,</p>

	<p>TEMOPORFIN, EFAPROXIRAL, PADELIPORFIN, IMATINIB, GEFITINIB, ERLOTINIB, SUNITINIB, SORAFENIB, DASATINIB, LAPATINIB, NILOTINIB, TEMSIROLIMUS, EVEROLIMUS, PAZOPANIB, VANDETANIB, AFATINIB, BOSUTINIB, VEMURAFENIB, CRIZOTINIB, AXITINIB, RUXOLITINIB, RIDAFOROLIMUS, REGORAFENIB, MASITINIB, DABRAFENIB, PONATINIB, TRAMETINIB, CABOZANTINIB, IBRUTINIB, CERITINIB, LENVATINIB, NINTEDANIB, CEDIRANIB, PALBOCICLIB, TIVOZANIB, OSIMERTINIB, ALECTINIB, ROCILETINIB, COBIMETINIB, MIDOSTAURIN, OLMUTINIB, BINIMETINIB, RIBOCICLIB, BRIGATINIB, LORLATINIB, NERATINIB, ENCORAFENIB, DACOMITINIB, ICOTINIB, ABEMACICLIB, ACALABRUTINIB, QUIZARTINIB, LAROTRECTINIB, GILTERITINIB, ENTRECTINIB, FEDRATINIB, AMSACRINE, ASPARAGINASE, ALTRETAMINE, HYDROXYCARBAMIDE, LONIDAMINE, PENTOSTATIN, MASOPROCOL, ESTRAMUSTINE, TRETINOIN, MITOGUAZONE, TOPOTECAN, TIAZOFURINE, IRINOTECAN, ALITRETINOIN, MITOTANE, PEGASPARGASE, BEXAROTENE, ARSENIC TRIOXIDE, DENILEUKIN DIFTITOX, BORTEZOMIB, CELECOXIB, ANAGRELIDE, OBLIMERSEN, SITIMAGENE CERADENOVEC, VORINOSTAT, ROMIDEPSIN, OMACETAXINE MEPESUCCINATE, ERIBULIN, PANOBINOSTAT, VISMODEGIB, AFLIBERCEPT, CARFILZOMIB, OLAPARIB, IDELALISIB, SONIDEGIB, BELINOSTAT, IXAZOMIB, TALIMOGENE LAHERPAREPVEC, VENETOCLAX, VOSAROXIN, NIRAPARIB, RUCAPARIB, ETIRINOTECAN PEGOL, PLITIDEPSIN, EPACADOSTAT, ENASIDENIB, TALAZOPARIB, COPANLISIB, IVOSIDENIB, GLASDEGIB, ENTINOSTAT, ALPELISIB, SELINEXOR, TAGRAXOFUSP, BELOTECAN, CYTARABINE, DAUNORUBICIN</p>
Anxiolytics	<p>ALPRAZOLAM, ATENOLOL, BUSPIRONE, CHLORIAZEPOXIDE, CHLORMEZANONE, CLONAZEPAM, CLORAZEPATE, CHLORDIAZEPOXIDE, CLOBAZAM, DIAZEPAM, ESTAZOLAM, FLURAZEPAM, HYDROXYZINE, MIDAZOLAM, OXAZEPAM, PREGABALIN, PROPRANOLOL, QUAZEPAM, TEMAZEPAM, TIAGABINE, TRIAZOLAM, TIAGABINE, MEPROBAMATE</p>
Nicotine Replacement	<p>NICOTINE</p>
Non-SSRI Antidepressants	<p>DESVENLAFAXINE, DULOXETINE, MILNACIPRAN, VENLAFAXINE, AMITRIPTYLINE, AMOXAPINE, CLOMIPRAMINE, DESIPRAMINE, DOXEPIN, IMIPRAMINE, NORTRIPTYLINE, PROTRIPTYLINE, TRIMIPRAMINE, ATOMOXETINE, BUPROPION, MIRTAZAPINE, NEFAZODONE, PHENELZINE, TRANLYCYPROMINE, SELEGILINE, TRAZODONE, VILAZODONE</p>
Opioids	<p>BUPRENORPHINE, BUTALBITAL, BUTORPHANOL TARTRATE, CODEINE, DIHYDROCODEINE, FENTANYL, HYDROCODONE, HYDROMORPHONE, LEVORPHANOL</p>

	TARTRATE, MEPERIDINE, METHADONE, MORPHINE SULFATE, MORPHINE SULFATE/NALTREXONE, OPIUM/BELLADONNA ALKALOIDS, OXYCODONE, OXYMORPHONE, PENTAZOCINE/ACETAMINOPHEN, PENTAZOCINE/ASPIRIN, PROPOXYPHENE, TAPENTADOL, TRAMADOL
Sedatives	AMOBARBITAL, DEXMEDETOMIDINE, ESTAZOLAM, ESZOPICLONE, FLURAZEPAM, METHOHEXITAL, MIDAZOLAM, PENTOBARBITAL, QUAZEPAM, RAMELTEON, SCOPOLAMINE, SECOBARBITAL, SUVOREXANT, TASIMELTEON, TEMAZEPAM, TRIAZOLAM, ZALEPLON, ZOLPIDEM
Selective Serotonin Reuptake Inhibitors (SSRIs)	CITALOPRAM, ESCITALOPRAM, FLUOXETINE, FLUVOXAMINE, PAROXETINE, SERTRALINE, VORTIOXETINE
Teratogenics	ISOTRETINOIN, ACITRETIN, METHOTREXATE, MYCHOPHENOLATE, MISOPROSTOL, CARBIMAZOLE

Comorbidity	ICD-9 and ICD-10 Diagnosis Codes
<b>Medical</b>	
Asthma	ICD-9: 493.*, 495.8, 518.3, 518.81-518.84, 519.11, 786.07 ICD-10: J45.*, J82.83, J82.89, J96.*, J98.01, R06.2
Diabetes mellitus	a) Patient is included in the KPNC Diabetes Registry* within 2 years prior to pregnancy onset date OR b) A recorded A1C $\geq$ 6.5 in the first trimester (onset date+84 days)  *The KPNC Diabetes Registry which is updated annually using a validated algorithm to identify KPNC members with diabetes. See: Weiner JZ, Gopalan A, Mishra P, et al. Use and Discontinuation of Insulin Treatment Among Adults Aged 75 to 79 Years with Type 2 Diabetes. JAMA Intern Med. 2019;179(12):1633–1641. doi:10.1001/jamainternmed.2019.3759.
Nausea and vomiting in pregnancy	ICD-9: 536.2, 643.*, 787.01 - 787.04, ICD-10: G43.A0, G43.A1, O21.*, R11.*
Chronic pain	ICD-9: 307.8*, 307.2, 338.* ICD-10: G89.*, F45.4*
Hypertensive disorders	ICD-9: 404.0*, 404.1*, 404.9*, 405.0*, 405.1*, 405.9*, 642.0*, 642.1*, 642.2*, 642.7* ICD-10: I10, I11, I11.0, I11.9, I12, I12.0, I12.9, I13, I13.0, I13.1*, I13.2, I15.*, O10.0*, O10.1*, O10.2*, O10.3*, O10.4*, O10.9*, O11.*
Thyroid disorders	ICD-9: 240.*, 241.*, 242.*, 243, 244.*, 245.*, 246.* ICD-10: E00.*, E01.*, E02, E03.*, E04.*, E05.*, E06.*, E07.*
<b>Mental Health</b>	
Anxiety disorders	ICD-9: 293.84, 300.02, 300.09, 309.24, 648.4 ICD-10: F06.4, F41.1, F41.3, F41.8, F41.9, F43.22
Depression	ICD-9: 296.2X (except 296.26), 296.3* (except 296.36), 296.82, 300.4, 309.0, 309.1, 311, 648.4* ICD-10: F06.31, F06.32, F32.0, F32.1, F32.2, F32.3, F32.4, F32.8, F32.81, F32.89, F32.9, F33.0, F33.1, F33.2, F33.3, F33.41, F33.8, F33.9, F34.1, F43.21, F43.23, F53.0, O90.6, O99.34*
Other psychiatric disorders	<b>ADHD</b> ICD-9: 314.* ICD-10: F90.* <b>Adjustment disorder</b> ICD-9: 309.22, 309.23, 309.29, 309.3, 309.4, 309.8X, 309.9, 313.* ICD-10: F43.2* (except F43.23) <b>Bipolar disorder</b> ICD-9: 296.0* (except 296.06) 296.1* (except 296.16), 296.4* (except 296.46), 296.5* (except 296.56), 296.6* (except 296.66), 301.13, 309.28 ICD-10: F06.33, F30.* (except F30.4), F31.* (except F31.70, F31.72, F31.74, F31.76, F31.78), F34.0 <b>Alcohol-induced disorders</b> ICD-9: 291.* ICD-10: F10.121, F10.131, F10.14, F10.15*, F10.18* (except F10.181), F10.19, F10.221, F10.231, F10.232, F10.24, F10.25*, F10.26, F10.27, F10.28* (except F10.281), F10.29, F10.98* (except F10.981), F10.99 <b>Conduct disorder</b> ICD-9: 312.*, 313.81 ICD-10: F91.* <b>Dementia</b>

	<p>ICD-9: 290.*, 294.1*, 294.2*, 310.8*, 331.*, 780.93, 780.97  ICD-10: F01.5*, F02.8*, F03.*, F48.8, G30.*, G31.84, R41.82</p> <p><i>Drug-induced disorders</i>  ICD-9: 292.*  ICD-10: F11.121, F11.122, F11.14, F11.15*, F11.18* (except F11.181), F11.19, F11.221, F11.222, F11.24, F11.25*, F11.28* (except F11.281), F11.29, F11.921, F11.922, F11.94, F11.95*, F11.98* (except F11.981); F12.121, F12.122, F12.15*, F12.18*, F12.19, F12.221, F12.222, F12.25*, F12.28* F12.29, F12.921, F12.922, F12.95*, F12.98*, F12.99; F13.132, F13.15*, F13.232, F13.25*, F13.932, F13.95*; F14.121, F14.122, F14.14, F14.15*, F14.18* (except F14.181), F14.19, F14.221, F14.222, F14.24, F14.25*, F14.28* (except F14.281), F14.29, F14.921, F14.922, F14.94, F14.95*, F14.98* (except F14.981); F15.121, F15.122, F15.14, F15.15*, F15.18* (except F15.181), F15.19, F15.221, F15.222, F15.24, F15.25*, F15.28* (except F15.281), F15.29, F15.921, F15.922, F15.94, F15.95*, F15.98* (except F15.981); F16.121, F16.122, F16.14, F16.15*, F16.18*, F16.19, F16.221, F16.24, F16.25*, F16.28*, F16.29, F16.921, F16.94, F16.95*, F16.98*, F16.99; F17.208, F17.209, F17.218, F17.219, F17.228, F17.229, F17.298, F17.299; F18.121, F18.14, F18.15*, F18.17, F18.18*, F18.19, F18.221, F18.24, F18.25*, F18.27, F18.28*, F18.29, F18.921, F18.94, F18.95*, F18.97, F18. F18.98*, F18.99; F19.121, F19.122, F19.131, F19.132, F19.14, F19.15*, F19.16, F19.17, F19.18*, F19.19, F19.221, F19.222, F19.231, F19.232, F19.24, F19.25*, F19.26, F19.27, F19.28*, F19.29, F19.921, F19.922, F19.931, F19.932, F19.94, F19.95*, F19.96, F19.97, F19.98*, F19.99;</p> <p><i>Eating disorders</i>  ICD-9: 307.1, 307.5*  ICD-10: F50.*, R63.0</p> <p><i>Other psychological disorders</i>  ICD-9: 297.*, 298.* 300.5, 300.6, 300.7, 300.8*, 307.3, 307.5, 316  ICD-10: F21, F22, F23, F24, F28, F29, F53.1</p> <p><i>Personality disorders</i>  ICD-9: 301.* (except 301.13)  ICD-10: F60.*</p> <p><i>Schizophrenia</i>  ICD-9: 295.*  ICD-10: F20.*</p> <p><i>Suicide and self-inflicted injury</i>  ICD-9: E950.*-E958.*, E980.*-E988.*  ICD-10: T14.91*, T36.* – T65.*, T71.*, X71.*-X83.*, Y21.*-Y33.*</p> <p><i>Tic disorders</i>  ICD-9: 307.2*  ICD-10: F95.*</p>
<p>Substance use disorders (except cannabis use disorders)</p>	<p>ICD-9: 303.* (except 303.03, 303.93), 304.* (except 304.03, 304.13, 304.23, 304.3*, 304.43, 304.53, 304.63,304.73, 304.83, 304.93), 305.* (except 305.03, 305.13, 305.2*, 305.33, 305.43, 305.53, 305.63, 305.73, 305.83, 305.93)  ICD-10: F10.1, F10.10, F10.12* (except F10.121) F10.13* (except F10.131, F10.132), F10.181, F10.2, F10.20, F10.22* (except F10.221) F10.23* (except F10.231, F10.232), F10.281, F10.929, F10.93*(except F10.931, F10.932) F10.981;</p>

F11.1, F11.10, F11.12\* (except F11.121, F11.122) F11.13, F11.181, F11.2, F11.20, F11.22\* (except F11.221, F11.222), F11.23, F11.281, F11.9, F11.90, F11.92\* (except F11.921, F11.922), F11.93, F11.981; F13.1, F13.10, F13.12\*, F13.13\* (except F13.132), F13.20, F13.22\*, F13.23\*, F13.9, F13.90, F13.92\*, F13.930;

F14.1, F14.10, F14.12\* (except F14.121, F14.122) F14.13, F14.181, F14.2, F14.20, F14.22\* (except F14.221, F14.222), F14.23, F14.281, F14.9, F14.90, F14.92\* (except F14.921, F14.922), F14.93, F14.981;

F15.1, F15.10, F15.12\* (except F15.121, F15.122) F15.13, F15.181, F15.2, F15.20, F15.22\* (except F15.221, F15.222), F15.23, F15.281, F15.9, F15.90, F15.92\* (except F15.921, F15.922), F15.93, F15.981;

F16.1, F16.10, F16.12\* (except F16.121, F16.122) F16.2, F16.20, F16.22\* (except F16.221), F16.9, F16.90, F16.92\* (except F16.921); F17.2, F17.20\* (except F17.208, F17.209), F17.21\* (except F17.218, F17.219) F17.22\* (except F17.228, F17.229), F17.29\* (except F17.298, F17.299);

F18.1, F18.10, F18.12\* (except F18.121) F18.2, F18.20, F18.22\* (except F18.221), F18.9, F18.90, F18.92\* (except F18.921);

F19.1, F19.10, F19.12\* (except F19.121, F19.122) F19.13\* (except F19.131, F19.132), F19.181, F19.2, F19.20, F19.22\* (except F19.221, F19.222), F19.23\* (Except F19.231, F19.232), F19.281, F19.9, F19.90, F19.92\* (except F19.921, F19.922), F19.93\*(except F19.931, F19.932), F19.981;

Z71.6

### eAppendix 3. Child Utilization Censoring Criteria

*Mental Health visits* were defined as encounters at a Psychiatry, Pediatric Psychiatry, Behavioral Health, or Pediatric Learning and Development specialty office.

*Non-Mental Health Pediatric visits* were defined as encounters at a Pediatric, Pediatric Neurology, or Pediatric Physical Medicine and Rehab specialty office.

Visits were categorized by calculating the child's age on the encounter date based on the number of months from their birth date as follows: 6-9 year visit:  $\geq 72$  to  $< 108$  months old, 9-12 year visit:  $\geq 108$  to  $< 144$  months old, 12-13 year visit:  $\geq 144$  to 156 months.

Age Interval		Censoring Criteria
Years	Months	
6-9 years	$\geq 72$ months to $< 108$ months	At least 1 mental health/non mental health pediatric visit required. If none, censor at 108 months.
9-12 years	$\geq 108$ months to $< 144$ months	At least 1 mental health/non mental health pediatric visit required. If none, censor at 144 months.
12-13 years	$\geq 144$ months to $< 156$ months	n/a

#### eAppendix 4. Child Anxiety and Depression Outcome Definitions

The following International Classification of Disease (ICD) Version 10 codes were used to ascertain the first diagnosis for child anxiety and child depression during follow-up:

<b>International Classification of Diseases, Tenth Revision Diagnosis Codes</b>	
<b>Anxiety</b>	F40.00, F40.10, F40.210, F40.218, F40.230, F40.231, F40.232, F40.240, F40.241, F40.248, F40.298, F40.8, F40.9, F41.0, F41.1, F41.8, F41.9, F43.0, F43.10, F43.11, F43.12, F43.20, F43.21, F43.22, F43.23, F43.24, F43.25, F43.29, F43.8, F43.9, F94.0, F94.1, F94.2, F94.9
<b>Depression</b>	F32.0, F32.1, F32.2, F32.3, F32.81, F32.89, F32.9, F32.A, F33.0, F33.1, F33.2, F33.3, F33.8, F33.9, F34.1

**eTable 1.** Hazard Ratios for Associations of Prenatal Cannabis Use and Child Anxiety and Depression Among Pregnancies with no Other Prenatal Substance Use, n=93,477

		HR <sup>a</sup> (95% CI)
<b>Child Anxiety, n (%)</b>		
Prenatal Cannabis Use		
No	6,612 (7.3)	1.00 (Ref)
Yes	155 (6.1)	0.82 (0.68-0.98)
Frequency of Cannabis Use		
None	6,612 (7.3)	1.00 (Ref)
Monthly	19 (5.2)	0.67 (0.41-1.10)
Weekly	12 (8.0)	1.12 (0.61-2.05)
Daily	4 (3.6)	0.61 (0.22-1.70)
Unknown <sup>b</sup>	120 (6.3)	0.84 (0.68-1.03)
<b>Child Depression, n (%)</b>		
Prenatal Cannabis Use		
No	825 (0.9)	1.00 (Ref)
Yes	23 (0.9)	1.00 (0.62-1.60)
Frequency of Cannabis Use		
None	825 (0.9)	1.00 (Ref)
Monthly	3 (0.8)	0.85 (0.24-3.01)
Weekly	1 (0.7)	0.85 (0.12-6.05)
Daily	0 (0.0)	
Unknown <sup>b</sup>	19 (1.0)	1.09 (0.65-1.83)

<sup>a</sup>Adjusted for maternal sociodemographic characteristics, time of prenatal care initiation, and medical and mental health comorbidities.

<sup>b</sup>Unknown frequency includes pregnancies that self-reported no cannabis use but tested positive for THC on urine toxicology.

**eTable 2.** Hazard Ratios for Associations of Prenatal Cannabis Use with Child Anxiety Stratified by Maternal Anxiety, and Child Depression Stratified by Maternal Depression

	No Maternal Anxiety n=111,759		Maternal Anxiety n=3,774	
	Child Anxiety, n (%)	HR <sup>a</sup> (95% CI)	Child Anxiety, n (%)	HR <sup>a</sup> (95% CI)
Prenatal Cannabis Use				
No	8,468 (7.9)	1.00 (Ref)	265 (10.0)	1.00 (Ref)
Yes	380 (7.9)	0.87 (0.77-0.98)	17 (5.9)	0.42 (0.22-0.80)

	No Maternal Depression n=106,590		Maternal Depression n=8,943	
	Child Depression, n (%)	HR <sup>b</sup> (95% CI)	Child Depression, n (%)	HR <sup>b</sup> (95% CI)
Prenatal Cannabis Use				
No	978 (1.0)	1.00 (Ref)	175 (2.1)	1.00 (Ref)
Yes	57 (1.3)	1.16 (0.84-1.61)	14 (1.8)	1.05 (0.51-2.13)

<sup>a</sup>Adjusted for maternal sociodemographic characteristics, time of prenatal care initiation, prenatal substance use, and medical and mental health comorbidities (excluding maternal anxiety).

<sup>b</sup>Adjusted for maternal sociodemographic characteristics, time of prenatal care initiation, prenatal substance use, and medical and mental health comorbidities (excluding maternal depression).

**eTable 3.** Characteristics of 263,833 Mother-Child Dyads born 2011-2017, by Study Exclusion Criteria

	<b>Included n (%)</b>	<b>Excluded n (%)</b>	<b>Standardized Difference<sup>a</sup> (95% CI)</b>
<b>Total</b>	115,533 (43.8)	148,300 (56.2)	
<b>Characteristic</b>			
<b>Age at Pregnancy Onset, Median (IQR)</b>	31.0 (28.0-34.0)	29.0 (25.0-33.0)	1.8 (1.8, 1.9)
Unknown	0	25	
<b>Any Prenatal Cannabis Use</b>	5,082 (4.4)	9,334 (7.8)	-3.4% (-3.6%, -3.3%)
Unknown	0	29,336	
<b>Frequency of Prenatal Cannabis Use</b>			0.12 (0.11, 0.13)
None	110,451 (95.6)	109,630 (92.9)	
Monthly or less	1,160 (1.0)	2,069 (1.8)	
Weekly	561 (0.5)	1,019 (0.9)	
Daily	422 (0.4)	778 (0.7)	
Positive UDAP, Frequency			
Unknown	2,939 (2.5)	4,516 (3.8)	
Unknown	0	30,288	
<b>Race/Ethnicity</b>			0.10 (0.09, 0.11)
Asian/Pacific Islander	31,929 (27.6)	36,231 (24.4)	
Non-Hispanic Black	6,959 (6.0)	11,331 (7.6)	
Hispanic	28,780 (24.9)	40,473 (27.3)	
Non-Hispanic White	45,146 (39.1)	56,717 (38.2)	
Other/Unknown	2,719 (2.4)	3,543 (2.4)	
Unknown	0	5	
<b>Parity</b>			0.16 (0.16, 0.17)
0	46,687 (40.4)	71,546 (48.4)	
1	43,475 (37.6)	46,721 (31.6)	
2+	25,371 (22.0)	29,443 (19.9)	
Unknown	0	590	
<b>Medicaid Insurance</b>	4,934 (4.3)	16,395 (11.1)	-6.8% (-7.0%, -6.6%)
<b>Prenatal Alcohol Use</b>	10,645 (9.2)	11,700 (9.0)	0.2%, (0.0%, 0.5%)
Unknown	0	18,040	
<b>Prenatal Nicotine Use</b>	4,849 (4.2)	8,335 (6.6)	-2.4% (-2.6%, -2.2%)
Unknown	0	21,686	
<b>Prenatal Opioid Use</b>	3,459 (3.0)	948 (1.4)	1.6% (1.5%, 1.7%)
Unknown	0	81,011	
<b>Prenatal Sleep/Anxiety Medication Use</b>	3,286 (2.8)	3,762 (3.2)	-0.4% (-0.5%, -0.2%)
Unknown	0	30,642	
<b>Prenatal Stimulant Use</b>	641 (0.6)	814 (0.7)	-0.1% (-0.2%, -0.1%)
Unknown	0	29,979	
<b>Month of Prenatal Care Initiation</b>			0.49 (0.49, 0.50)
Adequate Plus (Month 1-2)	76,616 (66.3)	75,836 (52.1)	
Adequate (Month 3-4)	37,111 (32.1)	49,798 (34.2)	
Intermediate (Month 5-6)	1,345 (1.2)	10,198 (7.0)	
Inadequate (Month 7+)	461 (0.4)	9,639 (6.6)	
Unknown	0	2,829	

<sup>a</sup>Welch Two Sample t-test (Continuous Variables); Two sample test for equality of proportions (Multilevel Categorical Variables); Standardized Mean Difference (Binary Variables)