2024 Edition!

28 Days, 28 Phenotypes

Phenotype Phebruary

Join The Conversations!

Azza Shoaibi, Anna Ostropolets, James Weaver, Gowtham Rao, Asieh Golozar
30 January 2024
Why do we still care about phenotyping? A recent example...

Prescription Stimulant Use During Pregnancy and Risk of Neurodevelopmental Disorders in Children

Elizabeth A. Suarez, MPH, PhD; Brian T. Bateman, MD, MS; Sonia Hernandez-Diaz, MD, DrPH; Loreen Straub, MD, MS; Christopher J. McDougle, MD; Katherine L. Wisner, MD, MS; Kathryn J. Gray, MD, PhD; Page B. Pennell, MD; Barry Lester, PhD; Yanmin Zhu, MS, PhD; Helen Mogun, MS; Krista F. Huybrechts, MS, PhD

**IMPORTANCE** Use of medications for attention-deficit/hyperactivity disorder (ADHD) during pregnancy is increasing in the US. Whether exposure to these medications in utero impacts the risk of neurodevelopmental disorders in children is uncertain.

**OBJECTIVE** To evaluate the association of childhood neurodevelopmental disorders with in utero exposure to stimulant medications for ADHD.
Neurodevelopmental Outcomes

Any NDD was defined as a composite of ASD, ADHD, specific learning disorders, developmental speech or language disorder, developmental coordination disorder, intellectual disability, and behavioral disorder. Validated claims-based algorithms with high positive predictive values were used to define each outcome (eTable 1 in Supplement). This composite outcome was considered given the frequent co-occurrence of NDDs and the potential for shared mechanisms across NDDs. In addition to this composite outcome, we considered ASD, one of the more severe NDDs for which there has been a steady increase in diagnoses over the study period, and ADHD, the most common NDD, as individual outcomes.
ORIGINAL ARTICLE

Validity of claims-based algorithms to identify neurodevelopmental disorders in children

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TABLE 1  Claims-based algorithms of neurodevelopmental disorders

<table>
<thead>
<tr>
<th>Outcome</th>
<th>ICD-9 Dx</th>
<th>Description</th>
<th>Algorithma</th>
</tr>
</thead>
<tbody>
<tr>
<td>Autism spectrum disorder/pervasive developmental disorder (ASD)</td>
<td>299.xx</td>
<td>Pervasive developmental disorders</td>
<td>At ≥1 year of age; ≥ 2 dates with ICD-9 Dx</td>
</tr>
<tr>
<td>exception 299.1x</td>
<td></td>
<td>Childhood disintegrative disorder</td>
<td></td>
</tr>
<tr>
<td>Attention deficit disorder/hyperkinetic syndrome of childhood (ADHD)</td>
<td>314.xx</td>
<td>Hyperkinetic syndrome of childhood</td>
<td>At ≥2 years of age, any of the following:</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• ≥ 2 dates with ICD-9 Dx</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• ≥ 2 dispensings of atomoxetine,</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>clonidine, guanfacine, (dextro/lisdex)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>amphetamine, (dextro/methyl)phenidate</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• ≥ 1 ICD-9 Dx &amp; ≥ 1 dispensing</td>
</tr>
</tbody>
</table>

Finally, we did not validate ICD-10 codes to define NDDs. However, when converting our codes, we found good correspondence between ICD-9 and -10 codes of NDDs; for instance, ICD-9 code category 299—pervasive developmental disorders—corresponds directly to ICD-10 code category F84—pervasive developmental disorders. We therefore expect a very similar performance of NDD algorithms using the ICD-10 codes that we have identified. Nevertheless, in future studies it will be important to directly validate these ICD-10 based definitions using a similar approach.
How have others defined the same outcome in other recent high-impact journals?

Association Between Prenatal Exposure to Antipsychotics and Attention-Deficit/Hyperactivity Disorder, Autism Spectrum Disorder, Preterm Birth, and Small for Gestational Age

Zixuan Wang, MSc; Adrienne Y. L. Chan, MPH; David Coghill, MD; Patrick Ip, MPH; Wallis C. Y. Lau, PhD; Emily Simonoff, MD; Ruth Brauer, PhD; Li Wei, PhD; Ian C. K. Wong, PhD; Kenneth K. C. Man, PhD

Study outcomes were ADHD (ICD-9-CM code 314 or prescription for ADHD medication, namely methylphenidate or atomoxetine [British National Formulary chapter 4.4], which

**Outcomes**

**IMPORTANCE** The risk of birth and neurodevelopmental complications with prenatal exposure to antipsychotics is unclear.

**OBJECTIVE** To evaluate the association between prenatal antipsychotics exposure and the risk of birth and neurodevelopmental problems.
How does this align with what we’ve done in the community?

Phenotype Phebruary Day 13 - Attention Deficit Hyperactivity Disorder

Team:

Today, while many in the US are preparing for their Super Bowl football/commercial viewing parties, I'd like to discuss phenotyping Attention Deficit Hyperactivity Disorder (ADHD). This is work that several colleagues (@ericaVoss @weave17 @Jill_Hardin @conovermitch) and I conducted over the past couple years that yielded a bunch of lessons learned the hard way. But the experience gave us insights to some complementary recommended practices that I’ve carried forward in my own research, so I thought I’d walk through the development process to show the pitfalls and ways to overcome them.

Clinical description:

Attention deficit hyperactivity disorder (ADHD) is a neurodevelopmental disorder characterized by patterns of inattention or impulsive behaviors that interferes with functions. ADHD can be classified by the most common symptoms, be it ‘predominantly inattentive’ presentation - where patients may struggle to organize or complete tasks, follow directions, or remember details of daily activities-or ‘predominantly hyperactive-impulsive’ presentation - where patients are constantly moving around or talking or interrupting when not appropriate. ADHD is most commonly diagnosed in childhood (though can occur with onset in adults), through physician examination and evaluation of ADHD symptoms over time and its impact in social settings (and ruling out alternative diagnosis from other mental health disorders or environmental factors). Management of ADHD may involve behavioral therapy or pharmacologic treatment (including stimulants such as methylphenidate, amphetamine,
First event of Attention-deficit hyperactivity (ADHD) disorder or procedure.

Cohort Entry Events:

- A condition occurrence of ADHD condition or procedure
- A procedure occurrence of ADHD condition or procedure
- A drug exposure of ADHD medications

Criteria:

- Having any of the following criteria:
  - With at least 1 occurrence of ADHD condition or procedure
  - Where event starts between 0 days Before and 365 days After index start date

Additional Constraint:

- Add additional constraint

Restrictions:

- Restrict to the same visit occurrence
- Allow events from outside observation period
## Does phenotyping matter?

<table>
<thead>
<tr>
<th>Study Description</th>
<th>CCAE</th>
<th>MDCD</th>
<th>Pharmetrics</th>
<th>JMDC</th>
<th>Optum SES</th>
<th>Iqvia Germany</th>
<th>Iqvia France</th>
</tr>
</thead>
<tbody>
<tr>
<td>Suarez et al. JAMA Psych 2024: &gt;=2 Dx OR &gt;=2 Rx OR (1 Dx AND 1 Rx)</td>
<td>6953079</td>
<td>2623436</td>
<td>6989350</td>
<td>129504</td>
<td>3903191</td>
<td>103596</td>
<td>2208</td>
</tr>
<tr>
<td>Wang et al., JAMA Internal Medicine, 2021: &gt;=1 Dx OR &gt;=1 Rx</td>
<td>6209993</td>
<td>2514310</td>
<td>6628578</td>
<td>138303</td>
<td>3277264</td>
<td>185709</td>
<td>3598</td>
</tr>
<tr>
<td>OHDSI Phenotype Library: Entry event: &gt;=1 Dx OR &gt;=1 Proc OR &gt;=1 Rx with Dx in next 365d</td>
<td>5553126</td>
<td>2395571</td>
<td>6208364</td>
<td>136503</td>
<td>2971635</td>
<td>176639</td>
<td>1081</td>
</tr>
</tbody>
</table>

Up to 230% variation in cases identified
"Team:
It's finally arrived. That wonderful month when you can put all your troubles aside, cast off those New Year’s resolutions you’ve already failed at, enjoy the freezing cold Northeastern US weather or the Australian heat, and JUST FOCUS ON PHENOTYPING!"
PR FEB.1st 2022

https://forums.ohdsi.org/t/ohdsi-phenotype-phebruary-2024/20940
Phenotype Phebruary 22,23: 2 years of phun!

Phenotype Phebruary 2022
- We collectively started a discussion of 28 phenotypes for 28 days
- 15 phenotypes were developed, evaluated and discussed and we learned few things

Phenotype Phebruary 2023
- 11 phenotypes discussed in the forums
- 4 debates/discussions addressed
- 32 collaborators interacted in the forums or attended calls
Phenotype Phebruary 2024
A collaborative study

Goal: A goal to understand what is the current practices in the field and how much researchers introduce variability in the process of phenotype development and evaluation.

Month-long collaborative study focused on assessing consistency in:

- Phenotype definition Components
- Phenotype representation structure
- Phenotype validation methods

https://forums.ohdsi.org/t/ohdsi-phenotype-phebruary-2024/20940
Objective: Assess heterogeneity in phenotype definitions, representations, and evaluation methods across published observational studies for four clinical conditions.

Approach and Timeline:
- Weekly Focus: Study 1 clinical condition per week.
- Vote on the 4 phenotypes today.
- Task Division: Break down the study into specific, manageable tasks.
- Progress Tracking: Weekly summaries of our progress.

Communication and Collaboration:
- Platforms: Utilize the forum and Teams for ongoing communication and updates.

Final Deliverables
- Research Manuscript: Summarize our findings in a comprehensive manuscript.
- Standardized Template: Develop and recommend a template for representing phenotype definitions in OHDSI studies.
Principles of phenotyping

Clinical description

(diagnosis and classification criteria, coding the same event in different ways), FDA recommends defining an outcome of interest based on the clinical, biological, psychological, and functional concepts of the condition, as appropriate. The conceptual definition for the outcome of interest (also referred to as the case definition) should reflect the medical and scientific understanding of the condition and might vary by study. For example, for anaphylaxis, the conceptual definition

Conceptual definitions should be able to be operationalized in RWD sources.

https://www.fda.gov/media/152503/download
Principles of phenotyping

Clinical description elements:

1) Overview
2) Presentation
3) Assessment
4) Plan
5) Prognosis
6) Disqualifiers/strengtheners

Elements are the guide to phenotype development
Principles of phenotyping

Acute pancreatitis example

Overview:
Acute pancreatitis (AP) is an acute inflammatory process of the pancreas, suspected in patients with severe acute upper abdominal pain but requires biochemical or radiologic evidence to establish the diagnosis. AP is categorized as mild (no organ failure or complications), moderately severe (transient organ failure/complication that resolves within 48 hours), or severe (persistent organ failure of ≥1 organ).

AP pathophysiology is tissue destruction through pancreatic duct and acinar injury mechanisms, whereby premature activation of digestive enzymes leads to auto-digestion of the pancreas which can initiate inflammatory cascade.

Chronic pancreatitis (CP) results from recurrent AP events but is otherwise unlike AP. CP patients may be asymptomatic for long periods, interspersed with abdominal pain that may require hospitalization. Magnetic resonance cholangiopancreatography is used for CP diagnosis and the treatment goal is pain control and malabsorption management from pancreatic insufficiency. There are no diagnostic criteria for CP and diagnosis is challenging. Drug-induced AP is rare. Several drugs can cause AP with latency weeks to months.

AP annual incidence proportion is 600-700 cases per 100,000 people in the US.

Presentation:
AP diagnosis requires two of the following three criteria: 1) acute onset of severe epigastric pain, 2) serum lipase or amylase elevation ≥3x the upper limit of normal, and 3) AP characteristic findings from diagnostic imaging.

Assessment:
AP is assessed by serum lipase and/or amylase measurement and/or abdominal diagnostic imaging (endoscopic ultrasonography, computed tomography, or magnetic resonance imaging). CP patients may have a normal lipase and amylase measurements. Pancreatic calcifications are suggestive of CP diagnosis. Carrier testing for cystic fibrosis is undertaken in children.

Plan:
AP therapy includes fluid replacement, pain control, nutrition management, and intravenous hydration. For AP patients with acute cholangitis, gastroenterology consultation and endoscopic retrograde cholangiopancreatography (ERCP) is recommended. Cholecystectomy may be performed for AP patients with gallstones. In AP caused by hypertriglyceridemia, standard therapy is to initiate an insulin drip which activates lipoprotein lipase.

Prognosis:
AP patients can fully recover. AP minimum median duration is 1-7 days, and the maximum median duration is 30 days. A new AP episode can independently reoccur in the same patient after recovery from a prior episode.

Disqualifiers:
CP: pancreatitis is a broad clinical idea that includes CP and AP. CP onset cannot be accurately identified, rendering this phenotype infeasible for drug safety surveillance where accurate onset dates are required. Discriminating CP patients from AP patients presents difficulty because CP patients may have exacerbating “flares”, which present similarly to AP events.
Hereditary/congenital pancreatitis: these conditions are considered distinct clinical entities.
Differential diagnoses: acute mesenteric ischemia, perforated viscus, intestinal obstruction, peptic ulcer disease, hepatitis

Strengthens:
Common causes of AP are gallstones and alcohol use. Drugs associated with AP are azathiprine, 6-mercaptopurine, didanosine, valproic acid, angiotensin-converting–enzyme inhibitors, and mesalamine. Complications resulting from AP include acute peripancreatic fluid collection, acute necrotic collections within 4-weeks of AP onset, portosplenomesenteric venous thrombosis, and systemic inflammatory response syndrome.
Accurate case ascertainment requires knowledge of:

- Clinical Dx/Tx patterns relevant to phenotype
- Care-seeking behavioral characteristics of phenotype
- Database intent, construction, completeness/reliability of content
• Phenotype: observable, potentially changing state of organism – health isn’t static
• Goal: draw conclusions about target clinical concept from clinically relevant data
• Phenotype algorithms: identify phenotypes, generated by domain experts, knowledge engineers
• Maximize fidelity of phenotype algorithms to clinical description via richness and acknowledging bias from health care processes
Principles of phenotyping

- Phenotypes crucial to biomedical research BUT...
  - ↓ standardization, ↓ transparency inhibits evidence validity/promise of RWD/RWE
- Recommendations: Fundamental dimensions of phenotype algorithms
  1. Complexity
  2. Performance
  3. Efficiency
  4. Implementability
  5. Maintenance

1) Does this recommended state sound like what we just heard about current ADHD phenotypes?
2) Does this recommended state sound like something achievable by OHDSI?
Cohort definitions

• Cohort definition = phenotype algorithm = specification for how to identify a cohort
• Applying a phenotype algorithm to data returns a cohort
• Cohort: “≥0 persons who satisfy ≥1 inclusion criteria for a duration of time
  • Several objective consequences to OHDSI definition “cohort”
Cohort definition components

• Entry events (index)
  • Time-stamped observations for the persons, such as drug exposures, conditions, procedures, measurements, and visits
  • events have a start date and end date, though some events may have a start date and end date

• Entry event inclusion criteria

• Additional qualifying inclusion criteria
  • qualifying cohort: all persons with entry event, satisfy initial event inclusion criteria, and fulfill all additional qualifying inclusion criteria

• Exit criteria
  • End of observation, fixed duration, cohort era end, censoring
Cohort definition components

- **Domain**: defines allowable concepts for fields in CDM tables
  - Condition, Drug, Procedure, etc.

- **Concept set**: expression defining ≥1 concepts for clinical entity of interest
  - E.g., SNOMED clinical concept + descendants for T2DM

- **Domain specific attribute**
  - E.g., days supply for drug exposure records

- **Temporal logic**: interval during which relationship to inclusion criterion and entry event is evaluated
LET'S VOTE

What phenotypes should we review and evaluate together during 2024 Phenotype Phebruary?

https://pollev.com/patrickryan800
Study tasks

For each condition, we will together:

1. Do literature search to find already published phenotypes

2. Summarize papers:
   2.1 What phenotypes were used
   2.2 How phenotypes are similar and different
   2.3 How they are validated
   2.4 How they are reported
3. Replicate cohort definitions in ATLAS
4. Run Cohort Diagnostics for replicated cohorts
5. Examine Cohort Diagnostics output:
   5.1 Look at population characteristics
   5.2 Look at incidence rates
6. Write everything up!
What we will get at the end

• Replication of published phenotypes for 4 conditions

• Orientations and practical sessions on how to use OHDSI tools (Atlas, CD, Phevaluator)

• Summary of current practices for phenotype development, reporting and validation

• A template we can all use when describing the phenotype definitions used in a study

• A paper!
Please sign up

Google form with 3 questions:
- Your name and email
- Conditions you are interested in (as many or as few)
- Tasks you want to do (as many or as few)

Once you sign up, we will get the information together and will set up the Week 1 orientation in Teams. Watch out for an email!