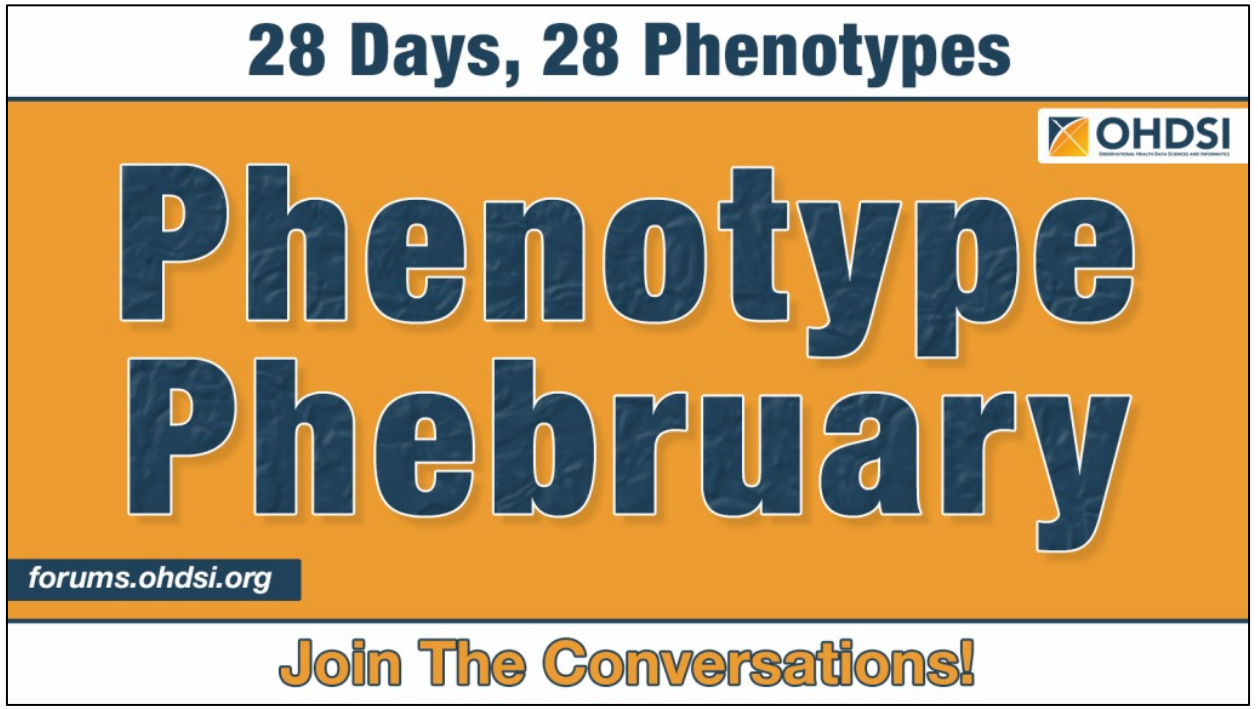
2024 Edition!



Azza Shoaibi, Anna Ostropolets, James Weaver, Gowtham Rao, Asieh Golozar

30 January 2024

Why do we still care about phenotyping? A recent example…

Research

24Jan2024

JAMA Psychiatry | Original Investigation

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

Supplemental content

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.

Research

24Jan2024

JAMA Psychiatry | Original Investigation

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

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 va[illegible] were used to define each outcome (eTable 1 in Supplement 1).[23] This composite outcome was considered given the frequent co-occurrence of NDDs and the potential for shared mechanisms across NDDs.[24] 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,[25] and ADHD, the most common NDD, as individual outcomes.[24]

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eTable 1. Outcome definitions for neurodevelopmental disorders

Outcome	Algorithm[1,2]
Autism Spectrum Disorder/Pervasive Developmental Disorder	At ≥ 1 year of age: ≥ 2 dates with ICD-9 Dx 299.xx (except 299.1x) *Sensitivity analyses starting follow-up at age 2:* *At ≥ 2 year of age:* *≥ 2 dates with ICD-9 Dx 299.xx (except 299.1x)*
Attention Deficit Hyperactivity Disorder/ Hyperkinetic Syndrome of Childhood	At ≥ 2 years of age, any of the following: ≥ 2 dates with ICD-9 Dx 314.xx ≥ 2 dispensings of atomoxetine, clonidine, guanfacine, (dextro/lisdex)amphetamine, (dex)methylphenidate ≥ 1 Dx 314.xx & ≥ 1 dispensing

PDS Pharmacoepidemiology & Drug Safety

ispe Official Journal of the International Society for Pharmacoepidemiology

Received: 27 April 2021 | Revised: 13 July 2021 | Accepted: 17 September 2021

DOI: 10.1002/pds.5369

ORIGINAL ARTICLE

WILEY

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

Loreen Straub[1] | Brian T. Bateman[1,2] | Sonia Hernandez-Diaz[3] | Cassandra York[1] | Yanmin Zhu[1] | Elizabeth A. Suarez[1] | Barry Lester[4] | Lyndon Gonzalez[2,5] | Ryan Hanson[2,6] | Clara Hildebrandt[7] | Joseph Homsi[2] | Daniel Kang[2] | Ken W. K. Lee[2] | Zachary Lee[2] | Linda Li[2,8] | Mckenna Longacre[2] | Nidhi Shah[7] | Natalie Tukan[2] | Frances Wallace[2] | Christina Williams[2,9,10] | Salim Zerriny[2] | Helen Mogun[1] | Krista F. Huybrechts[1]

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ORIGINAL ARTICLE

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

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.

TABLE 1 Claims-based algorithms of neurodevelopmental disorders

Outcome	ICD-9 Dx	Description	Algorithm[a]
Autism spectrum disorder/pervasive developmental disorder (ASD)	299.xx except 299.1x	Pervasive developmental disorders Childhood disintegrative disorder	At ≥1 year of age: ≥ 2 dates with ICD-9 Dx
Attention deficit disorder/hyperkinetic syndrome of childhood (ADHD)	314.xx	Hyperkinetic syndrome of childhood	At ≥2 years of age, any of the following: • ≥ 2 dates with ICD-9 Dx • ≥ 2 dispensings of atomoxetine, clonidine, guanfacine, (dextro/lisdex) amphetamine, (dex)methylphenidate • ≥ 1 ICD-9 Dx & ≥ 1 dispensing

values of neurodevelopmental disorders

	N cases identified	*N* records reviewed	*N* true positives	*N* false positives	PPV (95% CI)	evaluation of false positives
	4093	50	47	3	0.94 (0.83–0.99)	All diagnosed with ADHD
Attention deficit disorder/ hyperkinetic syndrome of childhood (ADHD)	9709	50	44	6	0.88 (0.76–0.95)	• 3 identified based on prescriptions only • 1 did not meet all criteria of ADHD • 1 diagnosed with high-functioning autism

How have others defined the same outcome in other recent high-impact journals?

Research

10Oct2021

JAMA Internal Medicine | Original Investigation

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

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.

Outcomes

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

Invited Commentary
page 1341

Multimedia

Supplemental content

CME Quiz at

How does this align with what we've done in the community?

OHDSI

Phenotype Phebruary Day 13 - Attention Deficit Hyperactivity Disorder

General

P **Patrick_Ryan** Feb '22

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 @jweave17 @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,

Feb 2022

1 / 1
Feb 2022

Feb 2022

[P] First event of Attention-deficit hyperactivity (ADHD) disorder or procedure

Definition | Concept Sets | Generation | Samples | Reporting | Export | Versions | Messages 4

cohortNameLong : First event of Attention-deficit hyperactivity (ADHD) disorder or procedure;
librarian : rao@ohdsi.org;
status : Pending;
addedVersion : ;
logicDescription : First occurrence of Attention-deficit hyperactivity disorder (ADHD) condition or related procedures, indexed on the earliest occurrence of ADHD condition, procedure or treatment (limited to drug exposure followed by a related condition or procedure), with 365d prior observation, exit at end of observation;
hashTag : #InL #Indication;

Cohort Entry Events

Events having any of the following criteria:

+ Add Initial Event...

a condition occurrence of ADHD condition or procedure — + Add attribute... — Delete Criteria

a procedure occurrence of ADHD condition or procedure — + Add attribute... — Delete Criteria

a drug exposure of ADHD medications — + Add attribute... — Delete Criteria

having any of the following criteria: + Add criteria to group...

with at least 1 using all occurrences of: — Delete Criteria
a condition occurrence of ADHD condition or procedure — + Add attribute...
where event starts between
0 days Before and 365 days After index start date *add additional constraint*
The index date refers to the drug exposure of ADHD medications.
☐ restrict to the same visit occurrence
☐ allow events from outside observation period

Does phenotyping matter?

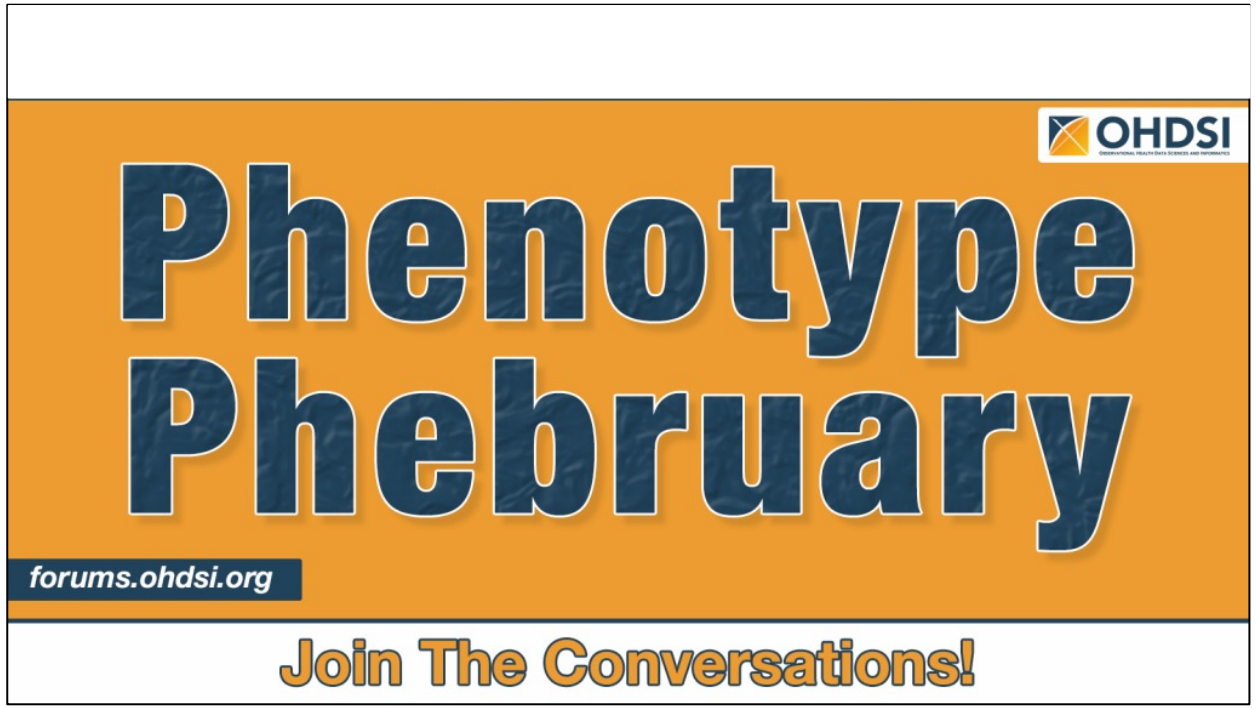
	CCAE	MDCD	Pharmetrics	JMDC	Optum SES	Iqvia Germany	Iqvia France
Suarez et al. JAMA Psych 2024: >=2 Dx OR >=2 Rx Or (1 Dx AND 1 Rx)	6953079	2623436	6989350	129504	3903191	103596	2208
Wang et al., JAMA Internal Medicine, 2021: >=1 Dx OR >=1 Rx	6209993	2514310	6628578	138303	3277264	185709	3598
OHDSI Phenotype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

Up to 230% variation in cases identified

2024 Edition!

"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

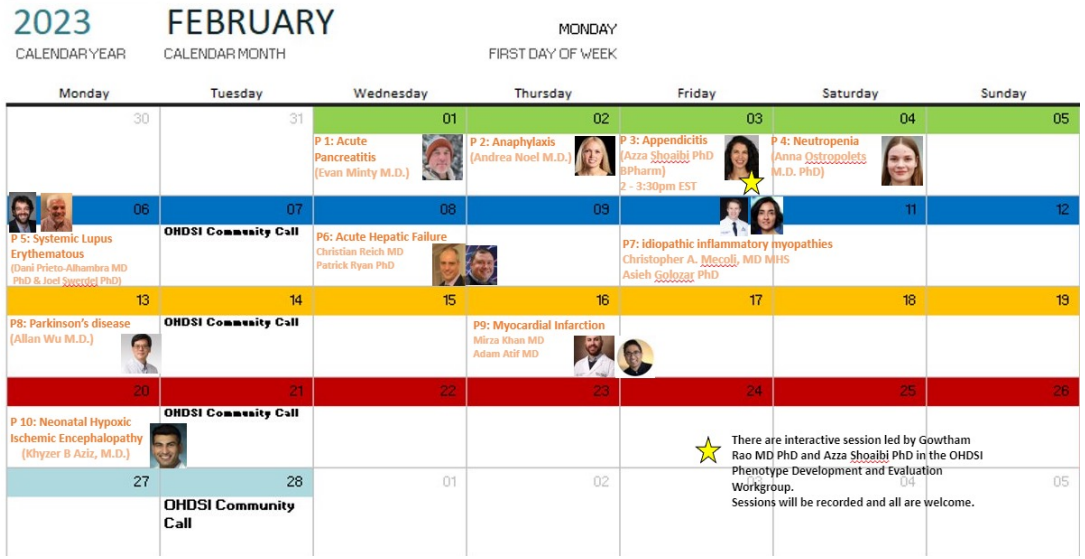
Phenotype Phebruary 22,23: 2 years of phun!

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

Phenotype Phebruary 2024, more phun!

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

GUIDANCE DOCUMENT

Real-World Data: Assessing Electronic Health Records and Medical Claims Data To Support Regulatory Decision-Making for Drug and Biological Products

Draft Guidance for Industry

SEPTEMBER 2021

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 defi

Conceptual definitions should be able to be operationalized in RWD sources

https://www.fda.gov/media/152503/download

Phenotype algorithm

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

https://www.ncbi.nlm.nih.gov/books/NBK482468/

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

Strengtheners:

Common causes of AP are gallstones and alcohol use. Drugs associated with AP are azathioprine, 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.

Principles of phenotyping

PHARMACOEPIDEMIOLOGY AND DRUG SAFETY 2015; **24**: 1009–1016
Published online 18 August 2015 in Wiley Online Library (wileyonlinelibrary.com) **DOI**: 10.1002/pds.3856

REVIEW

Identifying health outcomes in healthcare databases†

Stephan Lanes[1]*, Jeffrey S. Brown[2], Kevin Haynes[1], Michael F. Pollack[1] and Alexander M. Walker[3]

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

Principles of phenotyping

Journal of the American Medical Informatics Association, 25(3), 2018, 289–294
doi: 10.1093/jamia/ocx110
Advance Access Publication Date: 12 October 2017
Perspective

Perspective

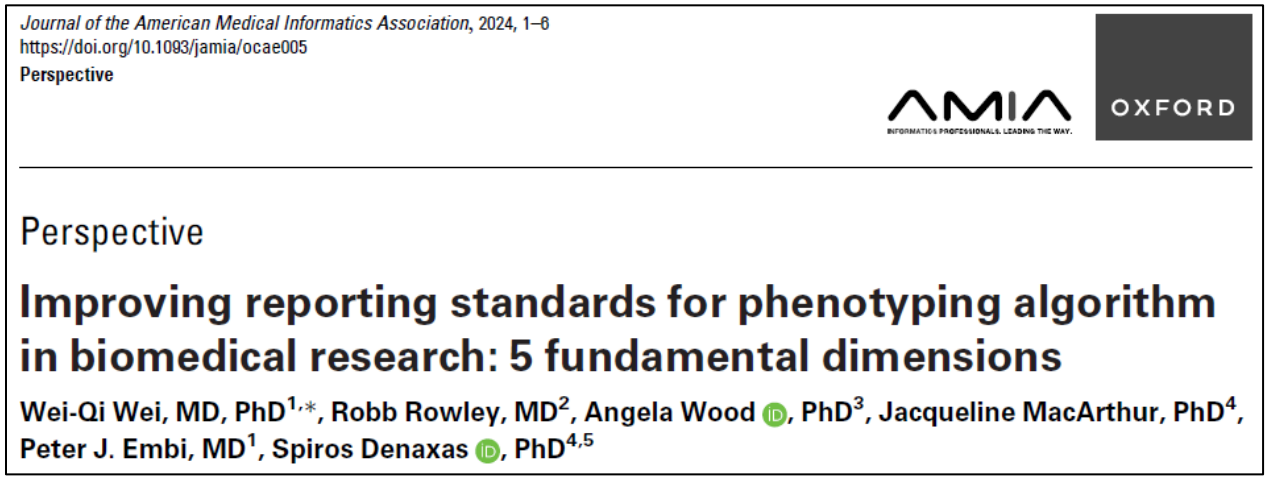
High-fidelity phenotyping: richness and freedom from bias

George Hripcsak[1] and David J Albers[1]

- 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



Journal of the American Medical Informatics Association, 2024, 1–6
https://doi.org/10.1093/jamia/ocae005
Perspective

AMIA INFORMATICS PROFESSIONALS. LEADING THE WAY.

OXFORD

Perspective

Improving reporting standards for phenotyping algorithm in biomedical research: 5 fundamental dimensions

Wei-Qi Wei, MD, PhD[1,*], Robb Rowley, MD[2], Angela Wood, PhD[3], Jacqueline MacArthur, PhD[4], Peter J. Embi, MD[1], Spiros Denaxas, PhD[4,5]

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

Initial cohort

Qualifying cohort

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

Study tasks (cont.)

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!