Postnatal growth deficiency and neurodevelopmental delay phenotypes to study drug safety during pregnancy

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Background

Post-marketing studies using real-world data (RWD) to assess drug safety during pregnancy are necessary because clinical trials rarely include this patient population. These studies consider a suite of health outcomes for the pregnant person and the newborn, two of which are postnatal growth deficiency and neurodevelopmental delay in infants. Growth deficit usually refers to failure to gain weight or gain at a suboptimal rate; however, it may impact height and head circumference in severe cases. Developmental delay is when children do not achieve the expected developmental milestones in social-emotional, language-communication, cognitive, or motor function domains according to the predicted timeline. Such delay may be early signs of autism spectrum disorder, attention deficit hyperactivity disorder, cerebral palsy, or vision/hearing impairments. No validated approach to measuring these two phenotypes in RWD exists. This study aimed to develop RWD phenotypes for postnatal growth deficiency and neurodevelopmental delay in infants.

Methods

Based on medical literature and outcome definitions in post-marketing studies, we conducted a comprehensive literature review to define the clinical concept. We also searched for previously published code algorithms in PubMed, which had limited yield. Thus, we used the clinical concept description to construct an initial concept set and refined it through review by epidemiology experts and clinical consultation. Phenotype cohorts were defined in two nationwide US health insurance claims databases (Optum's de-identified Clinformatics® Data Mart Database and Merative MarketScan Commercial Claims and Encounters Database (CCAE)), both transformed to the Observational Medical Outcomes Partnership (OMOP) Common Data Model (version 5.4). Our primary cohort logic required at least one code for the condition of interest among infants aged ≤1. We also created a secondary definition for developmental delay by requiring a second code 31-365 days after cohort entry to improve performance metrics. Several OHDSI software tools, i.e., PHOEBE, ATLAS, Cohort Diagnostics, and PheValuator, facilitated this phenotype development project.

Results

The ATLAS concept set expression had 29 standard concepts for growth deficiency (20 exclusions) and 23 standard concepts for developmental delay (14 exclusions) from observation and condition domains, resulting in a total of 306 and 2236 included codes in the concept sets, respectively. We identified approximately 186,000 cases in Clinformatics® and 294,000 in CCAE with growth deficiency and 167,000 and 267,000 cases with developmental delay, respectively. In the growth deficiency cohort, about 70% of subjects had "*failure to thrive"* (standard concept code: 437986), and 25% had "*failure to thrive in neonate"* (36717004) as the index event in both databases. In the developmental delay phenotype, about 16-18% of subjects had "*delayed milestone"* (436233), and 13-15% had "*disorder of speech and language development"* (435232) at index. The annual incidence rate estimates in Cohort Diagnostics did not show abrupt changes over time for both phenotypes across the databases (Figure 1). The PheValuator tool

estimated the sensitivity of the growth deficiency phenotype at 73% and 71%, with positive predictive values of 89% and 91% in Clinformatics® and CCAE databases. The estimated sensitivity for the developmental delay was 71% and 74%, with positive predictive values of 47 % and 51% in the databases, respectively. The secondary definition for this phenotype (2 codes) improved the positive predictive value to 64% and 68% in Clinformatics® and CCAE via improved specificity but at the cost of diminished sensitivity (46% and 47%). Characterizations of the primary and secondary definitions showed minimal differences, though the incidence rate estimates were about 50% lower. The PheValuator model for this phenotype included several therapeutic procedure concepts related to developmental delay with large coefficients, implying that post-index treatment is predictive of a true case. One potential reason for poor positive predictive value compared to the growth deficiency phenotype could be that the clinical concept of developmental delay relies on subjective assessments or questionnaire-based tools. However, growth deficiency is assessed by objective and easy-to-measure metrics (infant weight and length). We should note that the exact date of birth was not available in our data sources, and the age criterion included infants two days old up to 1 year, 11 months, and 29 days.

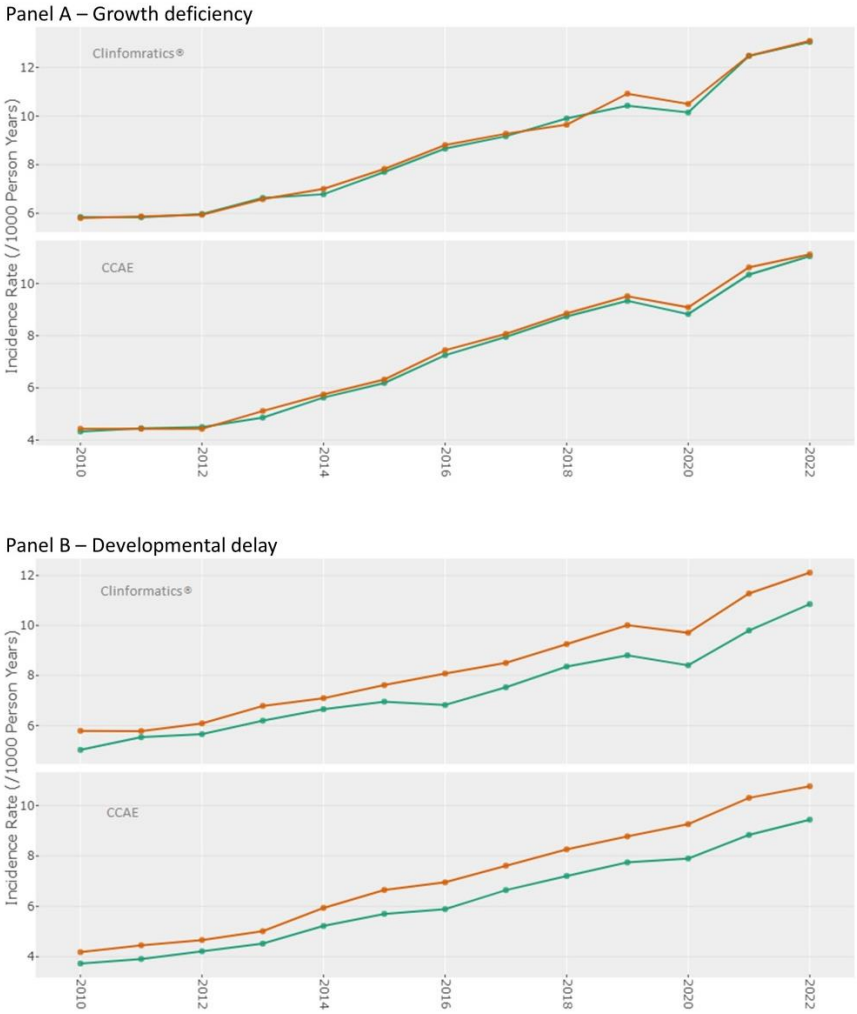

Figure 1. Incidence rate pattern over time generated by Cohort Diagnostics (Panel A: Growth deficiency, Panel B: Developmental delay; Optum's de-identified Clinformatics® Data Mart Database (Clinformatics®) and Merative MarketScan

Commercial Claims and Encounters Database (CCAE))

Table 1- Summary of phenotype performance metrics estimated via PheValuator tool

Phenotype Name	Database Name	PheValuator sensitivity	PheValuator PPV	PheValuator specificity	PheValuator NPV
Growth deficiency – 1 code	CCAE	0.708 (0.697 – 0.719)	0.911 (0.903 – 0.919)	0.997 (0.997 – 0.998)	0.989 (0.988 – 0.989)
Growth deficiency – 1 code	Clinformatics®	0.728 (0.715 – 0.740)	0.894 (0.883 – 0.903)	0.996 (0.996 – 0.997)	0.989 (0.988 – 0.989)
Developmental delay – 1 code	CCAE	0.744 (0.733 – 0.754)	0.512 (0.503 – 0.522)	0.971 (0.970 – 0.972)	0.989 (0.989 – 0.990)
Developmental delay – 1 code	Clinformatics®	0.712 (0.699 – 0.724)	0.472 (0.461 – 0.483)	0.964 (0.963 – 0.966)	0.987 (0.986 – 0.987)
Developmental delay – 2 codes	CCAE	0.469 (0.457 – 0.481)	0.680 (0.667 – 0.694)	0.991 (0.991 – 0.991)	0.978 (0.978 – 0.979)
Developmental delay – 2 codes	Clinformatics®	0.461 (0.447 – 0.475)	0.640 (0.624 – 0.655)	0.988 (0.988 – 0.989)	0.976 (0.975 – 0.977)

Conclusion

We developed two computable phenotypes to measure postnatal growth deficiency and neuro-developmental delay. While the growth deficiency phenotype appears to have acceptable performance metrics, the developmental delay phenotype has modest performance. Future studies can explore probabilistic algorithms rather than rule-based approaches to improve the performance metrics for this phenotype.

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