Consideration of Factors Occurring between Pediatric Exposures and Outcomes that Could Confound Signals Derived from "Big Data"

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Disclosures

- I serve on a Biogen Pregnancy Registry Advisory Committee for the multiple sclerosis drug tecfidera.

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Let’s begin by describing what is meant by “confounding”:

- A confounding factor is one that is associated with both the exposure and outcome and which itself may account, at least in part, for the observed outcome.

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In pharmacoepidemiology, a critical concern is “confounding by indication”

- Such confounding occurs when the indication for the treatment under study itself may account, at least in part, for the observed outcome.

- Indication *severity* is an important variant of confounding by indication.

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Consider the following hypothetical signal identified in big data*:

- Hospital admission for dehydration is strongly associated with short-term ibuprofen use for fever in young children
- A similar increased risk is not observed for short-term acetaminophen use for fever in young children.

*When ibuprofen was restricted to Rx use in children

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- Confounding by indication?
  - Unlikely--Both exposure groups had fever.

*When ibuprofen was restricted to Rx use in children

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Consider the following hypothetical signal identified in big data*:

- Hospital admission for dehydration is strongly associated with short-term ibuprofen use for fever in young children
- A similar increased risk is not observed for short-term acetaminophen use for fever in young children.

- But what about confounding by indication severity?

*When ibuprofen was restricted to Rx use in children

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Risk differences likely explained by confounding by indication severity

- Because ibuprofen was available only by prescription, and acetaminophen was available OTC, ibuprofen users had illnesses severe enough to prompt physician contact/visit, whereas acetaminophen would likely be used for less severe illness.

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Risk differences likely explained by confounding by indication severity

- Because ibuprofen was available only by prescription, and acetaminophen was available OTC, ibuprofen users had illnesses severe enough to prompt physician contact/visit, whereas acetaminophen would likely be used for less severe illness.

- Dehydration is more likely to occur among children with more severe febrile illnesses.

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Risk differences likely explained by confounding by indication severity

- Because ibuprofen was available only by prescription, and acetaminophen was available OTC, ibuprofen users had illnesses severe enough to prompt physician contact/visit, whereas acetaminophen would likely be used for less severe illness.
- Dehydration is more likely to occur among children with more severe febrile illnesses.
- Therefore, there is a strong possibility that the ibuprofen/dehydration signal is confounded by illness severity.

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With that background, let's turn to an overview of pediatric exposures and outcomes

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Stages of Pediatric Development

Preconception	Conception	Pregnancy	Newborn	Infancy	Childhood	Adolescence	Adulthood
6 mos.	1 wk.	9 mos.	3 mos.	3 mos. – 2 yrs.	3 – 11 yrs.	12 – 18 yrs.	19+ yrs.

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Stages of Pediatric Development

- Exposures and outcomes of interest can occur at any of these developmental stages, but it is critical to understand the specific stages in relation to the time intervals of the exposures and outcomes.

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Stages of Pediatric Development

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A few examples of intervals between exposures (E) and outcomes (O)

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Consider some extreme examples:

Preconception	Conception	Pregnancy	Newborn	Infancy	Childhood	Adolescence	Adulthood
6 mos.	1 wk.	9 mos.	3 mos.	3 mos. – 2 yrs.	3 – 11 yrs.	12 – 18 yrs.	19+ yrs.

E→O

Exposure/stage	Outcome/stage	Interval
Penicillin/infancy	anaphylaxis/infancy	20 minutes

Consider some extremes:

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Exposure/stage	Outcome/stage	Interval
SSRIs/pregnancy	bipolar disorder/adulthood	20 years

Exposure/stage	Outcome/stage	Interval
Penicillin/infancy	anaphylaxis/infancy	20 ***minutes***
SSRIs/pregnancy	bipolar disorder/adulthood	20 ***years***

Concerns about confounding?

Penicillin/anaphylaxis: Interval is too short to be affected by most factors other than exposure

SSRIs/bipolar disorder: Across 20 years and many stages of pediatric development, the number of potential confounders is daunting.

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In General,

-The longer the intervals between exposures and outcomes,

and

-The more stages they cross,

the greater the concern that signals might be explained by confounding

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Now consider just a few of many other outcomes:

Birth Defects

Neurobehavioral/developmental conditions

Childhood cognition

Growth

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SSRIs in pregnancy represent an example of the potential for false signals due to confounding and other forms of bias

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Hypothetical Finding from Big Data:

Antenatal SSRIs/Birth Defects

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Hypothetical Finding from Big Data:

Antenatal SSRIs/Birth Defects

Consider a finding of increased risk of ventricular septal defects (VSDs)

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Antenatal SSRIs and VSDs

Since SSRI users tend to be from higher SES categories, are they more likely to receive care at hospitals that conduct more intensive newborn diagnostic studies (and therefore have higher rates of VSD)?

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Antenatal SSRIs and VSDs

Since SSRI users tend to be from higher SES categories, are they more likely to receive care at hospitals that conduct more intensive newborn diagnostic studies (and therefore have higher rates of VSD)?

Could knowledge of prenatal SSRI exposure prompt physicians to screen more aggressively for cardiac defects, or to more likely read an imaging study as positive?

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Antenatal SSRIs in relation to:

Neurobehavioral/developmental Conditions
Childhood Cognition
Growth

1) Might the indication for SSRIs in the mother itself be a risk factor for these outcomes in the offspring?

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Antenatal SSRIs in relation to:

Neurobehavioral/developmental Conditions
Childhood Cognition
Growth

1) Might the indication for SSRIs in the mother itself be a risk factor for these outcomes in the offspring?
2) Are factors associated with the indication captured in big data?

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Potential confounders: Antenatal SSRIs in relation to:

Neurobehavioral/developmental conditions

- shared genetic predispositions
  (e.g., is depression/anxiety genetically linked to autism and/or ADHD?)
- altered nurturing, maternal-child interactions

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Potential confounders: Antenatal SSRIs in relation to:

Childhood cognition

- altered nurturing, maternal-child interactions
- diminished intellectual stimulation

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Potential confounders: Antenatal SSRIs in relation to:

Growth

- diminished attention to diet

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Conclusions

It is possible to identify signals related to pediatric exposures that might not be subject to confounding; however, “due diligence” requires rigorous attention to the potential role of confounding, whether or not the relevant factors are identifiable in big data.

As reflected in presentations over the past two days, development and interpretation of signals from big data require multidisciplinary expertise, including that provided by pharmacoepidemiology.

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Thank you

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