Addressing Inadequate Information on Important Health Factors in Pharmacoepidemiology Studies relying on Healthcare Databases

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Outline

- Background – Drug safety and pharmacoepidemiology studies
- Background – Confounding concepts
- Select Examples
- Workshop goals and agenda

Background: Evaluation of Drug Safety

- Knowledge about the safety of a new product is incomplete at approval
  - Evidence drawn from non-clinical data and clinical trials
  - Safety signals before approval may lead to requirement of post-approval studies
    - Pharmacosurveillance, pharmacoepidemiology, clinical trials

- New safety signals may arise after approval
  - Increased use by a broader and more diverse population
  - May be evaluated from drug utilization studies, spontaneous case reports, case series or post approval clinical trials and observational studies

Background: Pharmacoepidemiology in Drug Safety

- Population-based approach
- Reflects drug use patterns in the general population
- Ability to capture the clinical experience of large number of people over time
  - Suitable source for studying safety of medications
- Prospective or retrospective data collection
  - Existing healthcare data sources are increasingly being utilized
  - FDA issued guidance on conducting and reporting pharmaceopidemiologic safety studies[1]

[1] http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM243537.pdf

Background: Retrospective data analysis

Advantages

- Timely evaluation of safety signals
- Large number of persons followed over time
- Broad diverse populations e.g. children, pregnant women, patients with multiple health conditions
- Absence of invasive recruitment and follow-up procedures

Limitations

- Repurposing of claims data for research
- Inadequate / unavailable information on key covariates

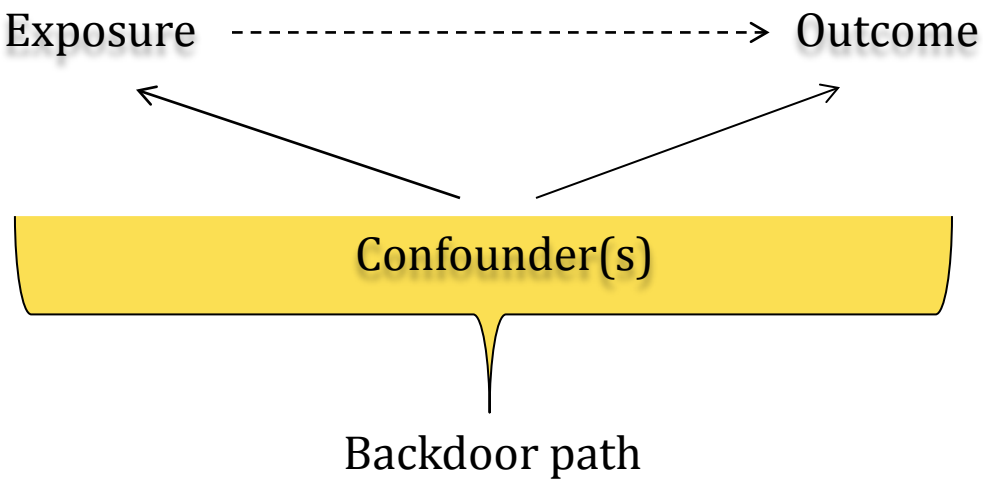
Confounding in Observational Post-Approval Studies

- Causality requires
  - Exposure status
  - Outcome status
  - Each individual's "counterfactual outcome" (unobserved outcome state based on unobserved exposure status)

- Counterfactual outcomes
  - Not observed, missing
  - (Ideal) Randomized: missing is random; comparability
  - Non randomized: absence of comparability (no exchangeability) since exposure is related to other factors

Confounding in Observational Post-Approval Studies

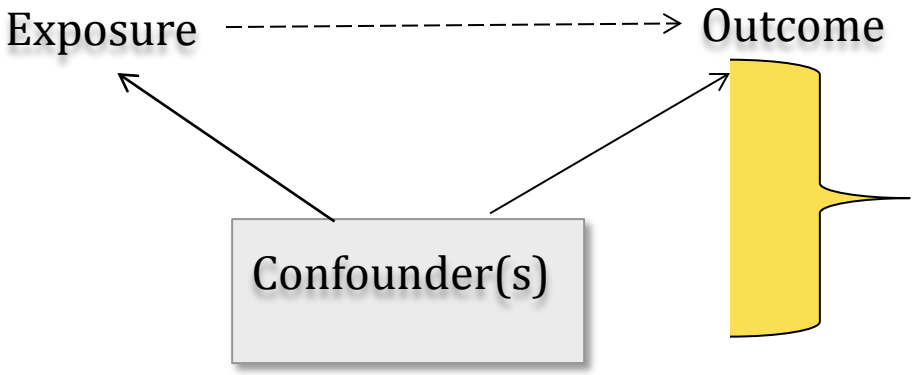
- Effects of the exposure on outcome become mixed, or *confounded* due to a third factor



- Confounding arises when treatment (exposure) and outcome share a common cause

Confounding in Observational Post-Approval Studies

- The *Backdoor path* can be blocked by conditioning on measured covariates that are not a consequence of treatment



Universe of several backdoor path:

- Measurable
- Measurable but poorly captured
- Known but unmeasurable
- Unknown

- The strength of evidence of studies is directly related to ability to eliminate known, measureable *backdoor paths*

Select Examples

- Illustrate challenges in using existing (claims) databases in the evaluation of drug safety
  - Particularly as related to absence/inadequate information on confounding factors

- Example 1: Medication exposure in pregnancy and birth defects
- Example 2: Drospirenone-containing contraceptives and VTE

Example 1: Medication exposure in pregnancy and birth defects

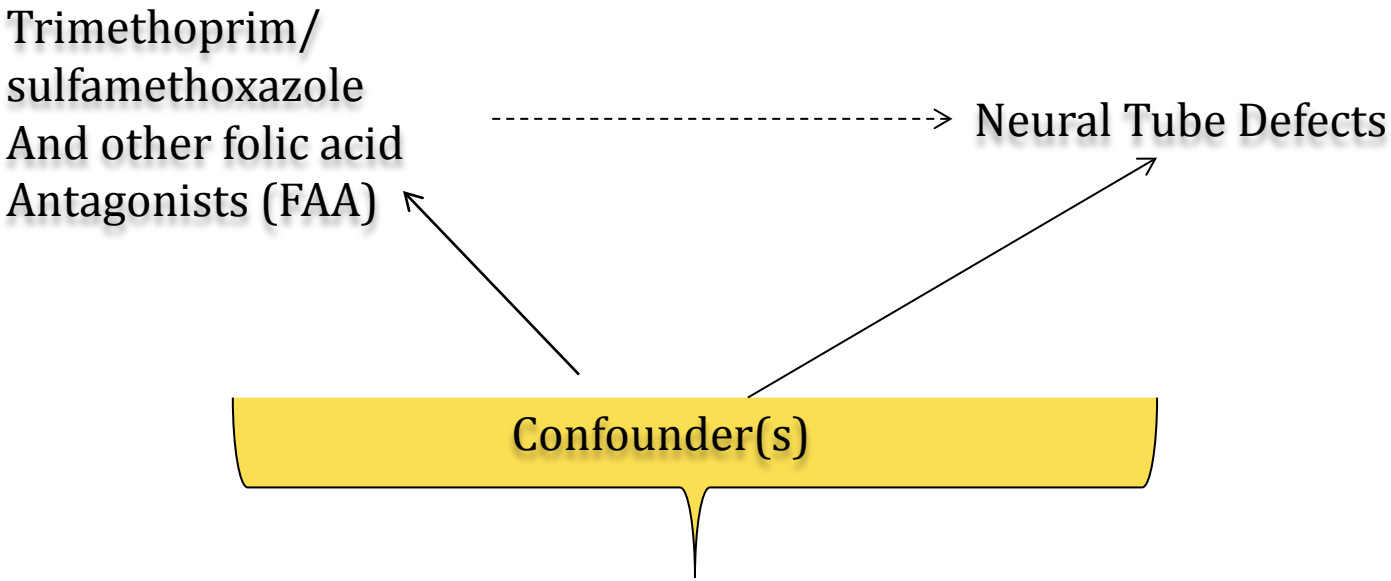
- Neural tube defects (NTDs): group of anomalies of CNS from failure of neural tube to close
  - Most severe forms: anencephaly and spina bifida
  - Four to six per 10,000 live births (likely under-estimated)
  - Genetic and environmental risk factors
    - Folate deficiency has been identified a major preventable risk factor linked to an increased risk of NTDs.
    - Prenatal folate supplementation and fortification of foods as public health measures to reduce NTDs

Example 1: Medication exposure in pregnancy and birth defects

- Medications that can affect availability of folic acid may increase risk of NTDs
  - E.g. trimethoprim-sulfamethoxazole during pregnancy

- Published literature is conflicting
  - Most studies obtained information on maternal exposure and confounding factors through interview
    - Recall bias is a concern in many studies
  - Studies in large existing claims databases may circumvent this issue, but information on folic acid intake and other factors is not adequate

Example 1: Medication exposure in pregnancy and birth defects



Possible backdoor paths:

1. Alcohol and smoking information (measurable but poorly captured)
2. Folic acid supplementation (known but not captured)

Example 2: Drospirenone-containing contraceptives and VTE

- Drospirenone (DRSP) containing contraceptives are derivatives of the endogenous hormones, estrogen and progestin
- Act as extensions of the physiological effects of these hormones
- Risk of Venous Thromboembolic events (VTE) increased by hormonal contraceptives
- To improve cardiovascular risk profile:
  - Reduction in the delivered estrogen dose (50µg to 20-35µg)
  - Newer progestins molecules
  - DRSP: lack of weight gain, antimineralocorticoid activity

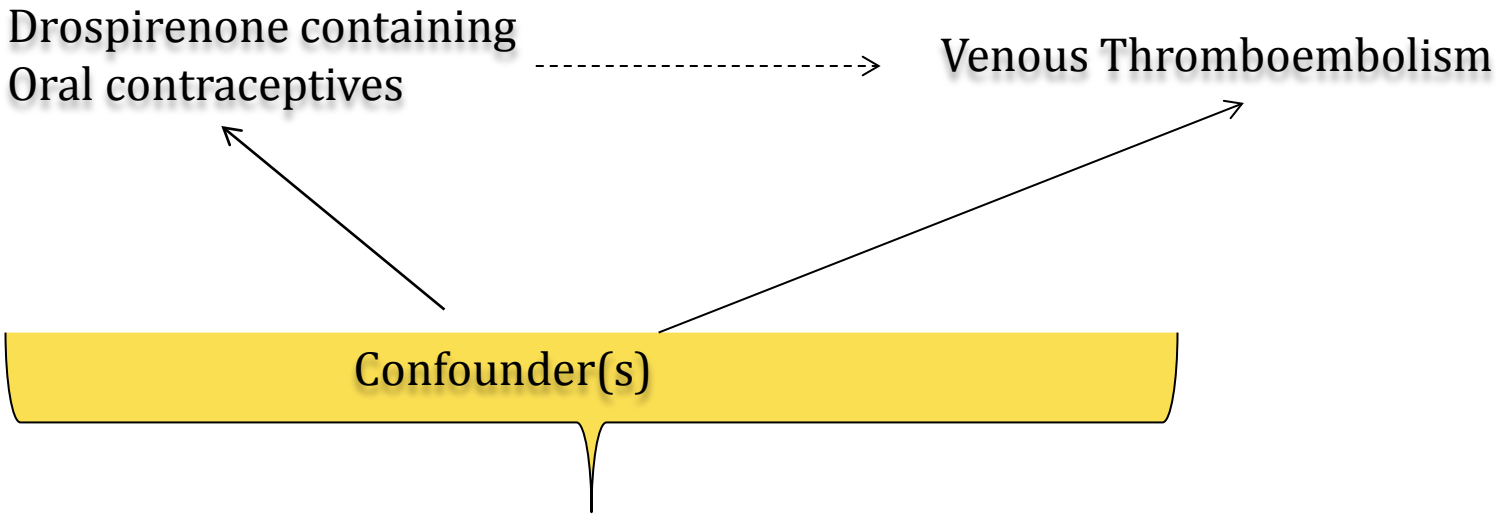
Example 2: Drospirenone-containing contraceptives and VTE

- Conflicting evidence for DRSP-VTE association
- Studies based on personal interviews show no increased risk of VTE when DRSP is compared to other frequently prescribed oral contraceptives

- Vast majority of studies based on electronic or claims-based data show increased risk

- It remains unknown whether the increased risk observed is due to inadequate adjustment of confounders such as family history, BMI, smoking that are poorly captured

Example 2: Drospirenone-containing contraceptives and VTE



Possible backdoor paths:

1. Smoking, BMI (measurable but poorly captured)
2. Family history of VTE (known but not captured)

The bottom line

- Design and analytical tools can be used to account for confounding
- Modest drug-associated increased in risk, it is often difficult to rule out role of (residual, unmeasured) confounding
- Understanding the impact of poorly measured confounding variables on observed risk estimates will help make these data more useful for regulatory decision making

Goals of the workshop

- Initiate discussions on creative strategies to improve the capture of potential confounders in studies using electronic health care data

- Facilitate constructive dialogue on potential strategies for making inferences using information from other sources for poorly captured confounders

- Discuss methodological considerations to minimize the influence of residual/unmeasured confounding

Workshop Agenda

- **[9:00] Session 1: Introduction**
  - Background Presentations by the FDA and UMD

- **[10:15] Session 2: Creative Methods to improve confounding information**
  - *Theme 1: Supplementing data with surveys and linkages*
  - *Theme 2: Making greater use of the data at hand*

- **[15:30-14:45] Session 3, Panel Discussions**

Thank you!