Big Data in OB and OB Anesthesia Research

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Disclosures

- Research funding:
  - National Institutes of Health
  - Icelandic Centre for Research
  - Pfizer
  - Lilly
  - Baxalta
  - GSK
  - Pacira

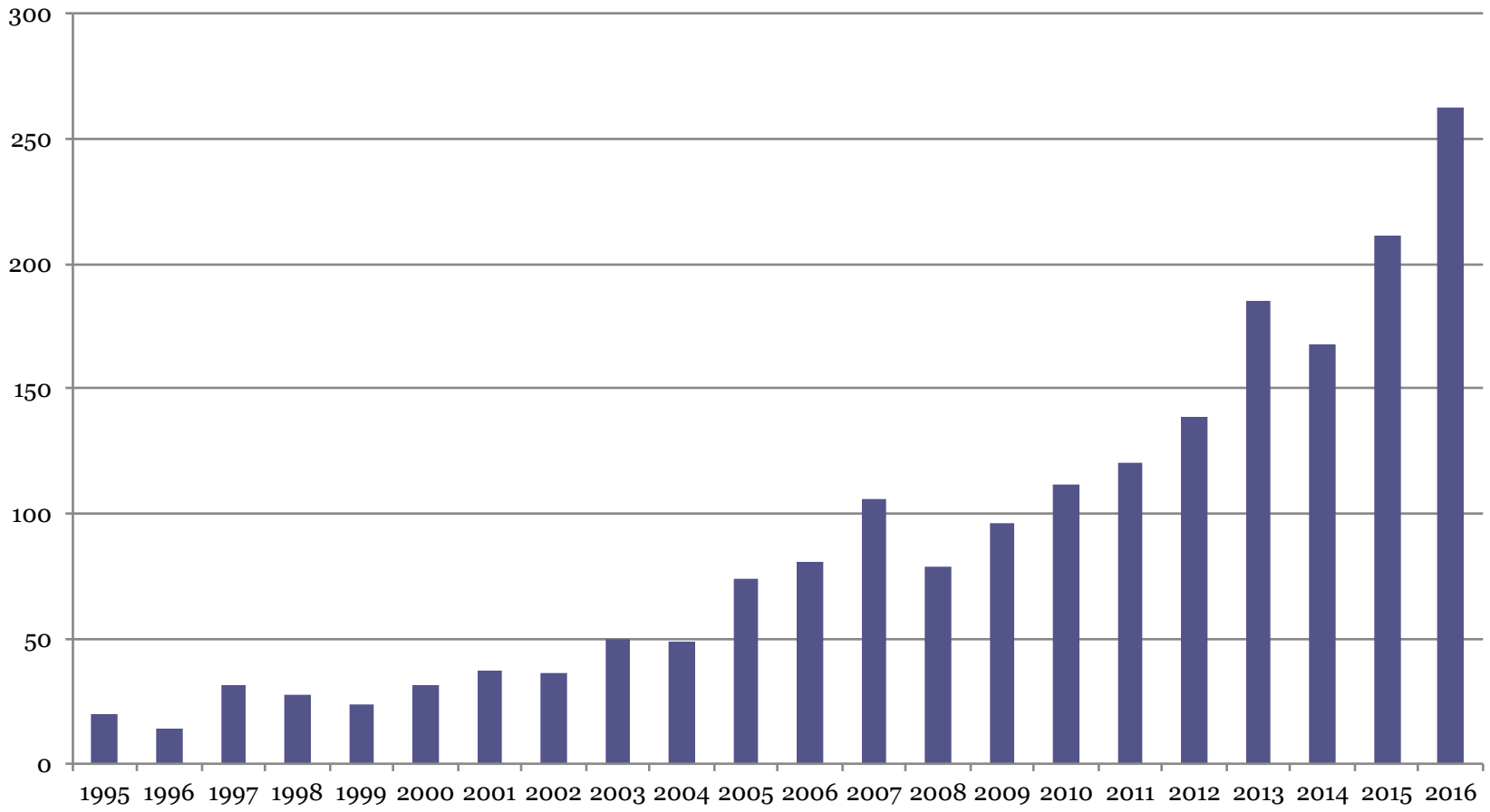
Outline

- Overview of research based on healthcare utilization data
  - Types of data sources
  - Types of research
- Methodological considerations in comparative effectiveness/ safety research
  - Example of statins and congenital malformations
- Novel methods to control for unmeasured confounders
  - Example of induction and the risk of autism

Healthcare utilization data

- Routinely collected for the payment and administration of health services
  - Claims for services/procedures/medications
  - Diagnoses used to justify services
- **Not collected primarily for research purposes**

Publications in obstetrics based on healthcare utilization data



Source: Pubmed

Advantages of healthcare utilization data

- **Large**
  - Rare events
  - Power to analyze subgroups
- **Representative**
  - Real-world effectiveness and utilization patterns
- **Informative regarding health systems**
  - Information on volume, hospital/physician characteristics, costs
- **Accessible**
  - Data are available at low cost
  - Near real-time

Available data sources

- Types: Longitudinal and episodic
- Longitudinal databases
  - Claims for outpatient, inpatient, laboratory, imaging services, medication dispensing
- Examples:
  - Medicaid Analytic eXtract (MAX)
  - United Healthcare database
  - Kaiser Permanente

Available data sources

- Episodic databases
- Information derived from single, inpatient encounter
- Examples:
  - Nationwide Inpatient Sample
    - 20% stratified-sample of all US hospitalizations
  - State Inpatient Databases
    - Complete claims for admissions from selected states
  - Premier Perspective Database
    - ~1/6 of all US hospitalizations; granular data on hospital charges

Healthcare utilization data

- Types of studies:
  - Descriptive studies
    - Disease/complication epidemiology
    - Healthcare utilization
  - Disease/complication risk prediction
  - Comparative effectiveness/safety research

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PERIOPERATIVE MEDICINE

Cardiac Arrest during Hospitalization for Delivery in the United States, 1998–2011

Jill M. Mhyre, M.D., Lawrence C. Tsen, M.D., Sharon Einav, M.D., Elena V. Kuklina, M.D., Ph.D., Lisa R. Leffert, M.D., Brian T. Bateman, M.D., M.Sc.

Anesthesiology. 2014 Apr;120(4):810-8.

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- Nationwide Inpatient Sample
- 56 million deliveries
- Frequency: 1 in 12,000
- Leading etiology: Hemorrhage (40%)
- Post-arrest survival: 58.9%

Anesthesiology. 2014 Apr;120(4):810-8.

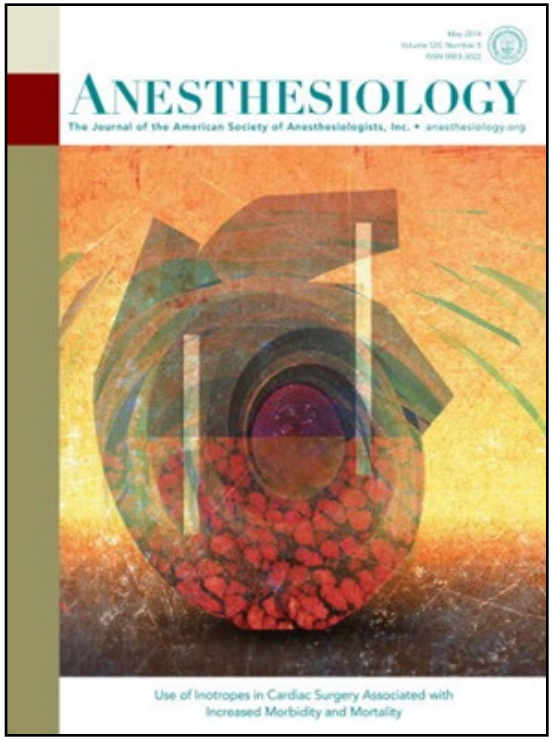
Healthcare utilization data

- Types of studies:
  - Descriptive studies
    - Disease/complication epidemiology
    - Healthcare utilization
  - Disease/complication risk prediction
  - Comparative effectiveness/safety research

PAIN MEDICINE

Patterns of Opioid Utilization in Pregnancy in a Large Cohort of Commercial Insurance Beneficiaries in the United States

Brian T. Bateman, M.D., M.Sc., Sonia Hernandez-Diaz, M.D., Dr.P.H., James P. Rathmell, M.D., John D. Seeger, Pharm.D., Dr.P.H., Michael Doherty, M.S., Michael A. Fischer, M.D., M.S., Krista F. Huybrechts, M.S., Ph.D.



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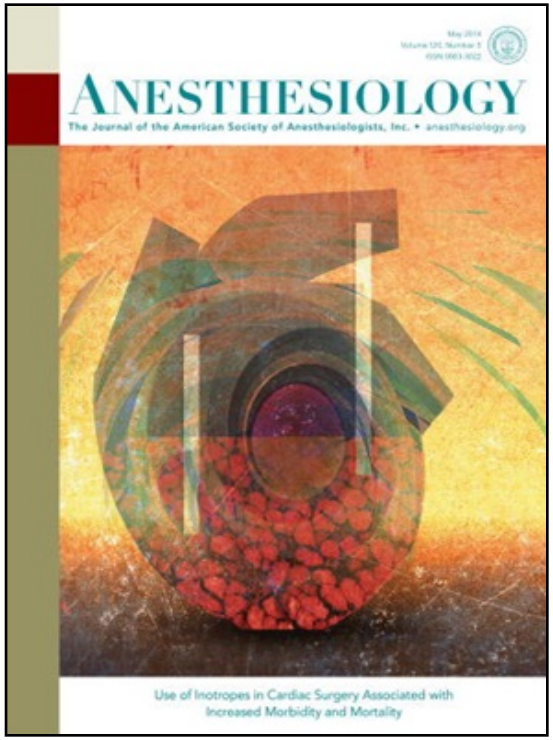

- United Healthcare
- 534,500 pregnancies from 2005 to 2011
- 14.4% opioid exposed during pregnancy
- Significant regional variation

Anesthesiology. 2014 May;120(5):1216-24.

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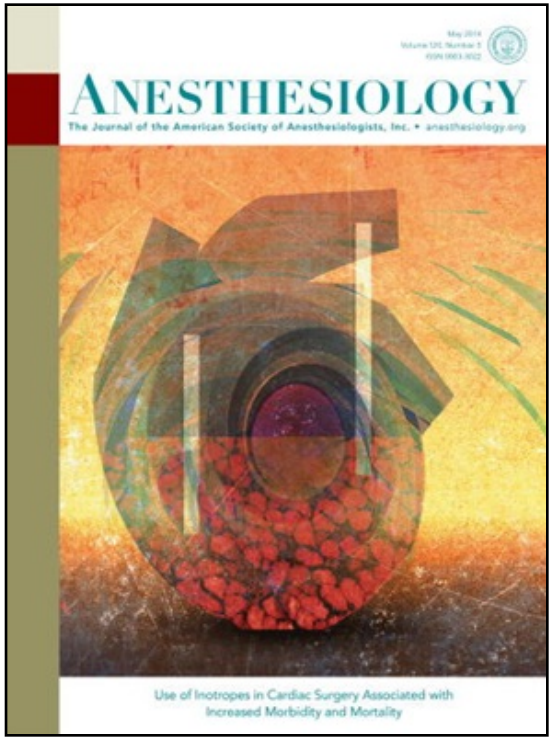

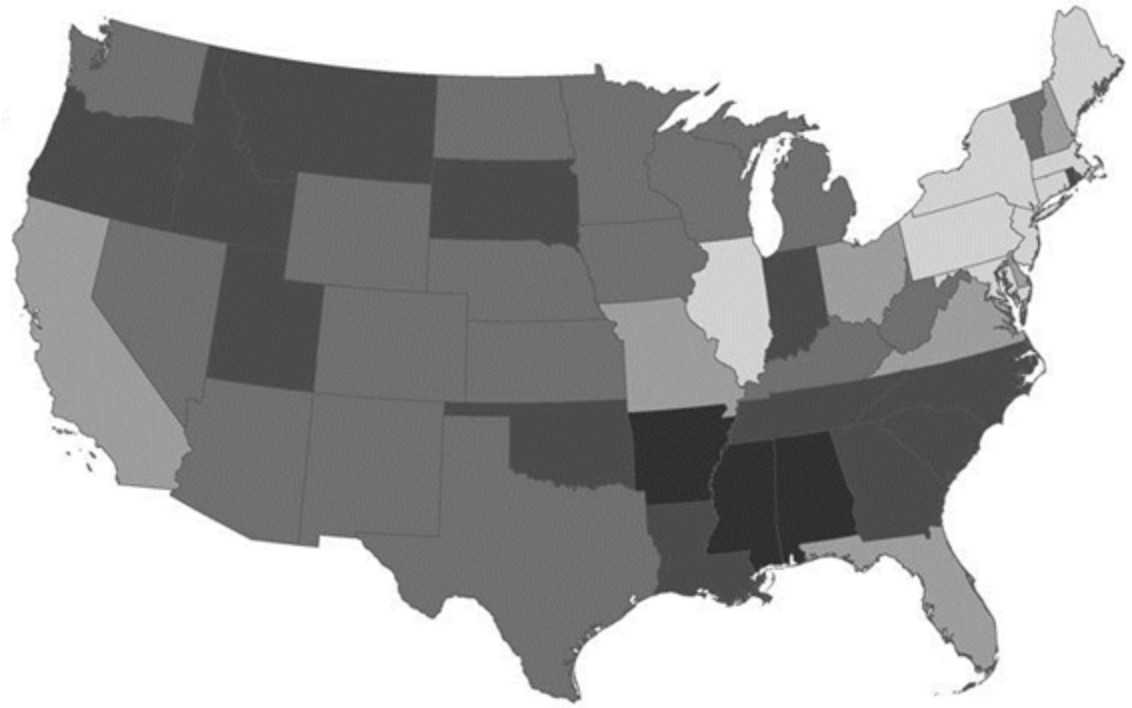

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Healthcare utilization data

- Types of studies:
  - Descriptive studies
    - Disease/complication epidemiology
    - Healthcare utilization
  - Disease/complication risk prediction
  - Comparative effectiveness/safety research

Original Research

Development of a Comorbidity Index for Use in Obstetric Patients

Brian T. Bateman, MD, MSc, Jill M. Mhyre, MD, Sonia Hernandez-Diaz, MD, DrPH, Krista F. Huybrechts, MS, PhD, Michael A. Fischer, MD, MS, Andreea A. Creanga, MD, PhD, William M. Callaghan, MD, MPH, and Joshua J. Gagne, PharmD, ScD

Obstet Gynecol. 2013 Nov;122(5):957-65..

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- Medicaid Analytic eXtract
- 854,823; 1.2% severe morbidity
- Includes 20 maternal conditions
- Risk=0.68% for score 0; 10.9% if >10

Obstet Gynecol. 2013 Nov;122(5):957-65..

Healthcare utilization data

- Types of studies:
  - Descriptive studies
    - Disease/complication epidemiology
    - Healthcare utilization
  - Disease/complication risk prediction
  - Comparative effectiveness/safety research

Comparative effectiveness and safety research

- Gold standard → Randomized controlled clinical trials
  - Lack problem of confounding
  - May lack generalizability
  - Less useful in establishing safety
  - Limited follow-up time
  - Not all relevant questions will be answered with RCTs

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Healthcare utilization data

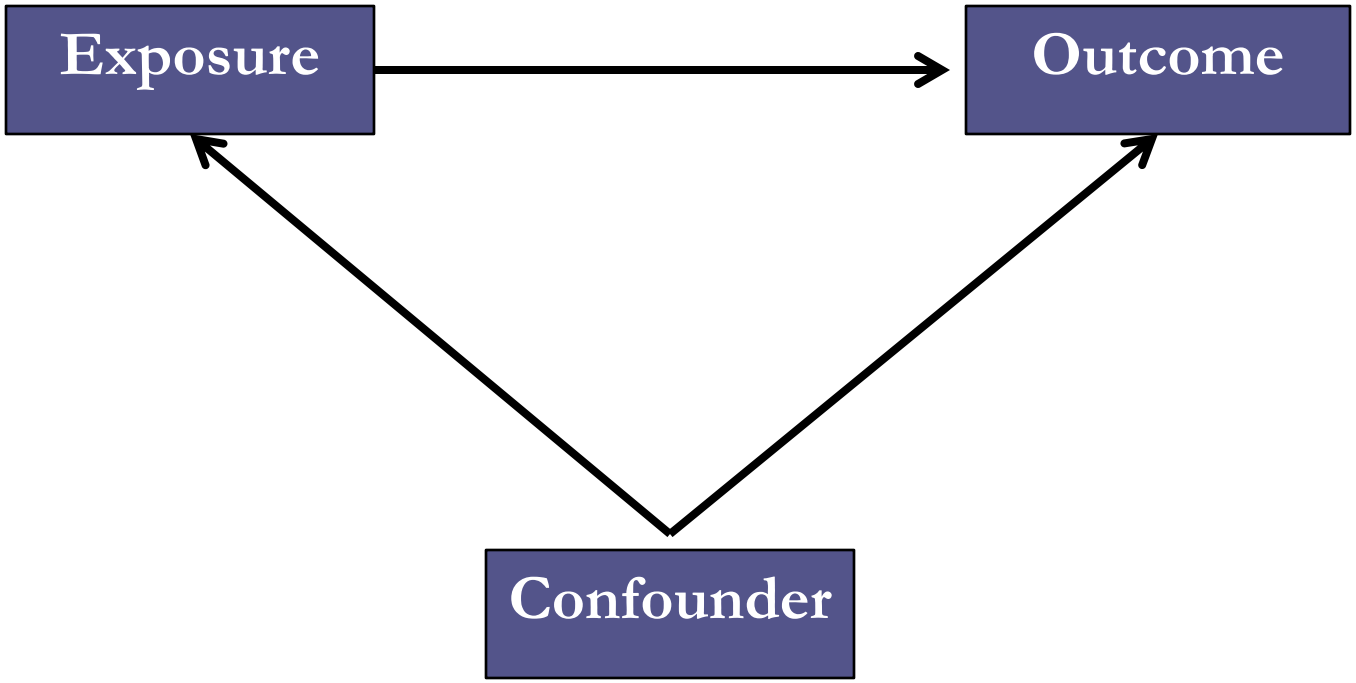
- **Challenges**

- Those inherent to all observational research
  - Selection bias
  - Information bias
  - Confounding bias

- Those particular to healthcare utilization data
  - Strong potential for misclassification/underascertainment of outcomes, exposures, and confounders

Study question

Study question



Challenges: Outcome misclassification

- Not as problematic as one might think…
- Important to define the outcome with specificity
  - If the outcome is defined with 100% specificity, then relative risk estimates will be unbiased assuming that misclassification is non-differential

Kelsey et al, Methods in observational epidemiology (2nd edition). Oxford University Press, 1996

The truth

	Outcome	Total
Exposed	20	100
Unexposed	10	100

The truth

	Outcome	Total
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The truth

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Outcome measured with 50% sensitivity

The truth

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RR = 2

Outcome measured with 50% sensitivity

	Outcome	Total
Exposed	10	100
Unexposed	5	100

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The truth

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Outcome measured with 50% sensitivity

	Outcome	Total
Exposed	10	100
Unexposed	5	100

RR = 2

	Sensitivity (%)	Specificity (%)
Obstetric hemorrhage	75	99.8
Episiotomy	70	99.9
Obstetric wound infection	68	98
Venous thromboembolism	87	98
Renal failure	88	99.4
Endometritis	46	98
Venous thromboembolism	87	98

- *Aronsky et al, Am J Med Qual, 2005;20:319-28*
- *Romano and Mark, Med Care, 1994; 32: 81-90*
- *Kiyota et al, Am Heart J, 2004; 148: 99-104*
- *Shaklee et al, Infect Dis J 2011;30:e38-40*
- *Li et al, Pharmacoepidemiol Drug Saf. 2011 Jul;20(7):700-8.*
- *Henderson et al, Jt Comm J Qual Patient Saf. 2009 Jul;35(7):370-6.*
- *Goff et al, Paediatr Perinat Epidemiol. 2012 Sep;26(5):421-9*
- *Romano et al, Obstet Gynecol. 2005;106(4):717-25.*

Challenges: Outcome misclassification

- Specificity further improved with treatment codes or LOS
  - Infection: Appropriate antibiotics
  - PPH: Transfusion
  - Severe preeclampsia: Magnesium
  - MI: LOS >3 days

- Kiyota et al, Am Heart J, 2004; 148: 99-104
- Shaklee et al, Infect Dis J 2011;30:e38-40

Challenges: Exposure misclassification

- Can often be measured with sensitivity and specificity
  - Charges for drugs, procedures
- When the exposure is a diagnosis, misclassification may create bias of effect estimates

Challenges: Exposure misclassification

- Particularly problematic in episodic databases
  - **Overcoding**: Patient with peridelivery MI may have more codes for known risk factors than comparable patient without the complication
  - **Undercoding**: Patients that have a long and complicated hospital course may have fewer codes for chronic conditions
    - DM paradoxically appears to decrease the risk peridelivery sepsis in administrative datasets

Challenges: Confounder underascertainment/misclassification

- Misclassification of or inability to measure confounders is the greatest threat to validity of studies using administrative data

Challenges: Confounder underascertainment/ misclassification

- Minimize the degree of confounding at the design phase
  - Use of active comparators
- Use proxies to identify relevant comorbidities
  - Insulin → DM
  - Labetalol→HTN
  - Number of outpatient medications as a marker for general health status

High-dimensional Propensity Score Adjustment in Studies of Treatment Effects Using Health Care Claims Data

Sebastian Schneeweiss, Jeremy A. Rassen, Robert J. Glynn, Jerry Avorn, Helen Mogun, and M. Alan Brookhart

- Draws on range of data dimension including diagnoses, procedures, laboratory tests, and medications
- Empirically identifies candidate covariates from thousands of codes
- Prioritizes covariates, and integrates them into a propensity-score
- Improves confounding control in some circumstances

(*Epidemiology* 2009;20: 512–522)

Statins and congenital malformations

Statins and congenital malformations

- Food and Drug Administration Category X
  - Animal data showing the potential for toxicity
  - Role of cholesterol biosynthesis for prenatal development
- Few human data
  - Mixed results
  - Registries, small cohort studies, and spontaneous reports
- Important:
  - Use in women of reproductive age
  - Potential use in preventing preeclampsia

OPEN ACCESS

Statins and congenital malformations: cohort study

Brian T Bateman,[1, 2] Sonia Hernandez-Diaz,[3] Michael A Fischer,[1] Ellen W Seely,[4] Jeffrey L Ecker,[5] Jessica M Franklin,[1] Rishi J Desai,[1] Cora Allen-Coleman,[1] Helen Mogun,[1] Jerry Avorn,[1] Krista F Huybrechts[1]

- Medicaid Analytic eXtract 2000-2007
  - N = 886,996
  - 1,152 (0.13%) statin exposed in 1st trimester
- Outcome → Congenital malformations
  - Defined by codes of 2 separate dates
  - One code + corrective surgery (high specificity)
- 50 covariates drawn from claims
  - Demographics, diagnoses, medications, healthcare utilization (robust confounder control incld many proxies)

BMJ. 2015 Mar 17;350:h1035.

Statins and congenital malformations

	Risk	Unadjusted
Unexposed	3.55%	Referent
Exposed	6.34%	1.79 (1.43 to 2.23)

Statins and congenital malformations

	Risk	Unadjusted	Stratified on diabetes
Unexposed	3.55%	Referent	Referent
Exposed	6.34%	1.79 (1.43 to 2.23)	1.34(1.07 to 1.68)

Statins and congenital malformations

	Risk	Unadjusted	Stratified on diabetes	Propensity-score matched (1:3)*
Unexposed	3.55%	Referent	Referent	Referent
Exposed	6.34%	1.79 (1.43 to 2.23)	1.34(1.07 to 1.68)	1.04 (0.79 to 1.37)

Novel design approaches to overcome residual confounding

- Circumstances where traditional designs are likely to result in residual confounding
- In this circumstance novel epidemiological designs are needed
- Example: Induction of labor and autism

Background

Autism Spectrum Disorders (ASD):

- Permanent developmental disabilities
  - Impairment in social interaction
  - Language development
  - Stereotyped or repetitive behaviors
  - Incidence: 1 in 90

- Genetics and early environmental exposures implicated in pathophysiology
  - Investigation of association with perinatal exposures

Gardener et al. Pediatrics 2011;128:344-55
CDC. Morbidity and Mortality Weekly Report 2012;61:1-19

Background

Oxytocin:

- Key role in social function and cognition
- Used to induce/augment labor

Hypothesis:

- *In-utero* exposure causes down-regulation of oxytocin receptors predisposing to ASD

Glasson et al. Arch Gen Psychiatry 2004;61:618-27
Wahl. Medical hypotheses 2004;63:456-60

Research

Original Investigation

Association of Autism With Induced or Augmented Childbirth in North Carolina Birth Record (1990-1998) and Education Research (1997-2007) Databases

Simon G. Gregory, PhD; Rebecca Anthopolos, MA; Claire E. Osgood, BS; Chad A. Grotegut, MD; Marie Lynn Miranda, PhD

JAMA Pediatr. 2013;167(10):959-966. doi:10.1001/jamapediatrics.2013.2904
Published online August 12, 2013.

- Linked information on 625,042 births to educational records
  - Exposure: Induction
  - Outcome: Autism exceptionality designation
  - After adjustment for confounders:
    - Relative risk: 1.27 (95% CI 1.05-1.52)

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Autism Might Be Linked With Inducing And Speeding Up Labor (STUDY)

AP | By LINDSEY TANNER

Posted: 08/12/2013 5:06 pm EDT | Updated: 08/12/2013 5:06 pm EDT

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Induced Labor Linked to Raised Risk of Autism, Study Suggests

Male children seem to be most vulnerable, researchers report

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AUTISM

Induced Labor Linked to Higher Autism Risk

By Alexandra Sifferlin @acsifferlin | Aug. 13, 2013 | 0

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Brain changes of autism may begin in the womb

Liz Szabo, USA TODAY 6:54 p.m. EDT August 13, 2013

CBSNEWS Video | US | World | Politics | Entertainment | Health | MoneyWatch

By MICHELLE CASTILLO / CBS NEWS / August 12, 2013, 6:03 PM

Induced labor may increase risk of autism in offspring

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Induced labour 'linked to autism'

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DR MANNY'S NOTES

Can inducing labor make your child autistic?

Study Links Inducing/Augmenting Labor with Modestly Higher Autism Risk

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HEALTH & WELLNESS

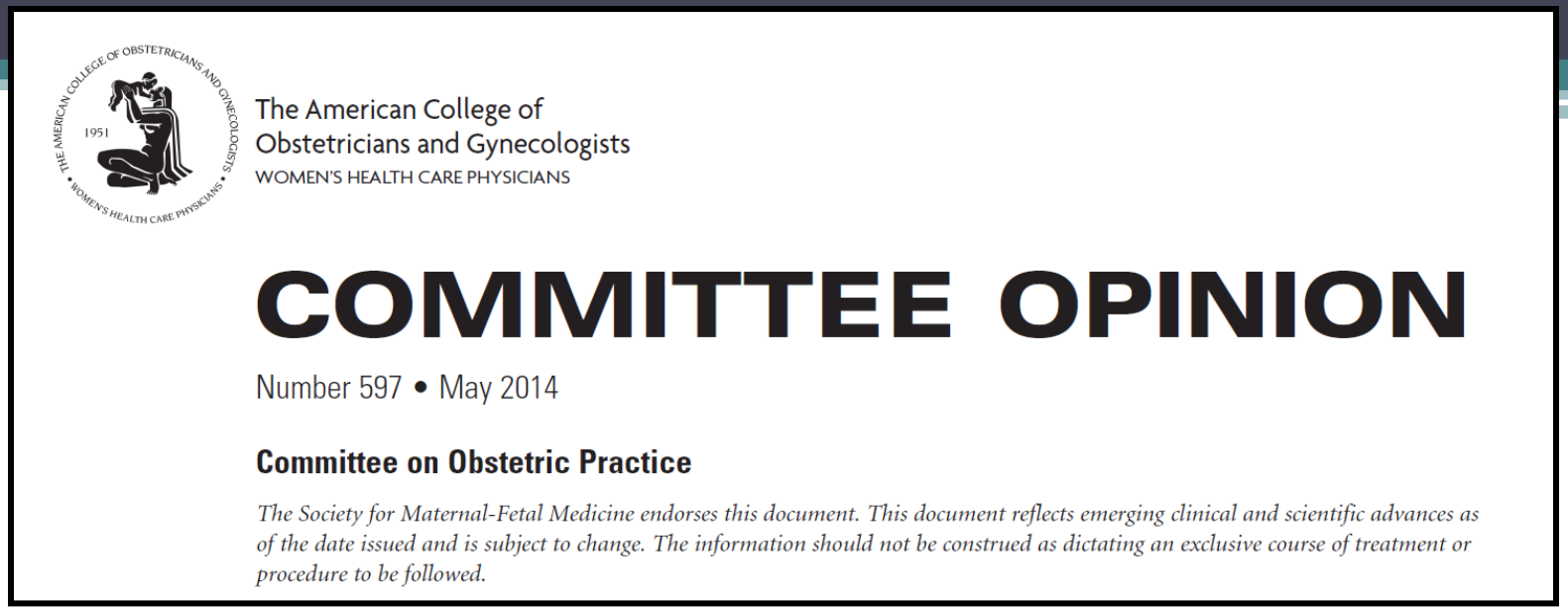
Study Finds Link Between Induced Labor and Autism Diagnoses

Researchers Don't Suggest Any Change in Current Medical Practices

496

PHARMA & HEALTHCARE 8/14/2013 @ 3:43PM | 45,810 views

Autism Risk And Labor Induction: Is There A Link?



The American College of Obstetricians and Gynecologists
WOMEN'S HEALTH CARE PHYSICIANS

COMMITTEE OPINION

Number 597 • May 2014

Committee on Obstetric Practice

The Society for Maternal-Fetal Medicine endorses this document. This document reflects emerging clinical and scientific advances as of the date issued and is subject to change. The information should not be construed as dictating an exclusive course of treatment or procedure to be followed.

- ACOG issued a Committee Opinion:
  - *"against a change in current guidance regarding counseling and indications for and methods of labor induction…"*
- Avoiding induction may lead to more stillbirth, cesareans, and adverse effects on maternal health

JAMA Pediatrics | Original Investigation

Association of Labor Induction With Offspring Risk of Autism Spectrum Disorders

Anna Sara Oberg, PhD; Brian M. D'Onofrio, PhD; Martin E. Rickert, PhD; Sonia Hernandez-Diaz, DrPH; Jeffrey L. Ecker, MD; Catarina Almqvist, PhD; Henrik Larsson, PhD; Paul Lichtenstein, PhD; Brian T. Bateman, MD

- A significant concern regarding prior study is potential for residual confounding
- Use Swedish nationwide population register data to identify differentially exposed siblings

JAMA Pediatr. 2016 Sep 6;170(9):e160965

Methods

Study Population:

- Births in Sweden 1992 to 2001
- N=978,98

Exposure:

- Induction indicator on standardized delivery chart

Outcome:

- Diagnoses of Autism Spectrum Disorder
- 1.1%

Methods

Analysis:

- Association between induction and ASD modelled using Cox proportional hazard regression

- **Models:**
  - Model 1: Baseline
  - Model 2: Stable maternal characteristics: Demographics
  - Model 3: Model 2+ individual birth characteristics: Risk factors for induction like postdates, preeclampsia, etc

Methods

Model 4:

- Fixed effects model in which the underlying hazard is allowed to vary between mothers (=fixed for all births to same woman)
  - Contrast is made within siblings
    - Only siblings discordant with respect to induction status contribute to the estimation of effect
  - Maintain adjustment for factors unique to each birth
- Controls for all factors shared by siblings

Results

	Baseline
	HR (95% CI)
Autism spectrum disorders	1.27 (1.19 - 1.37)

Results

	Baseline	Stable maternal
	HR (95% CI)	HR (95% CI)
Autism spectrum disorders	1.27 (1.19 - 1.37)	1.27 (1.18 - 1.36)

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Results

	Baseline	Stable maternal	Individual birth
	HR (95% CI)	HR (95% CI)	HR (95% CI)
Autism spectrum disorders	1.27 (1.19 - 1.37)	1.27 (1.18 - 1.36)	1.18 (1.09 - 1.27)

Results

	Baseline	Stable maternal	Individual birth	Within siblings
	HR (95% CI)	HR (95% CI)	HR (95% CI)	HR (95% CI)
Autism spectrum disorders	1.27 (1.19 - 1.37)	1.27 (1.18 - 1.36)	1.18 (1.09 - 1.27)	1.05 (0.87 - 1.27)

Conclusions

- Big data are a powerful tool for research in OB and OB anesthesia
- Attention to study design and limitations of data needed
- Novel approaches can help minimize the risk for residual confounding and yield valid estimates