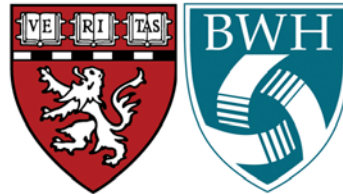


# Cardiac Safety Assessment

## Measurement: Prospective Cohort studies

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Division of Pharmacoepidemiology and Pharmacoeconomics,  
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# Assessing the CV harm of medications in observational research

## ❖ **Accurate assessment of Exposure:**

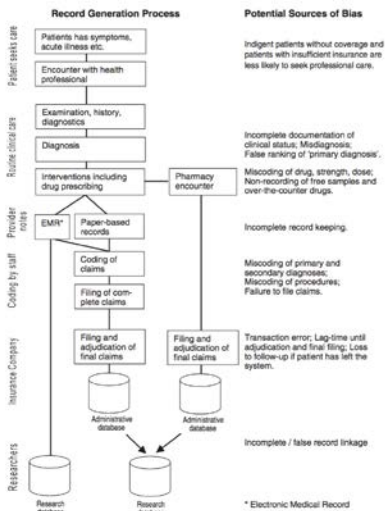
- Completeness of repeated uses
- Prescribing vs. dispensing vs. use of drugs

## ❖ **Accurate assessment of Outcome:**

- High specificity of outcome assessment when estimating relative effect measures: risk ratio, rate ratio, hazard ratio
- Reasonable sensitivity to preserve event counts

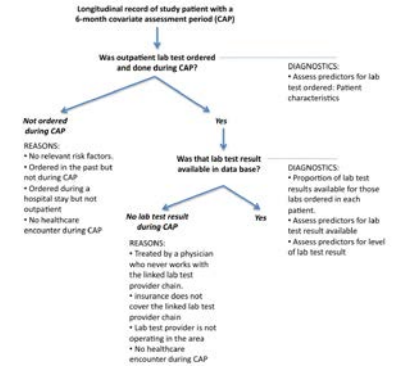
## ❖ **Complete assessment of confounders:**

- Unobserved confounding
- Pre-exposure measurement to avoid adjustment for intermediates



Schneeweiss, JClinEpi 2005

# How were data generated?



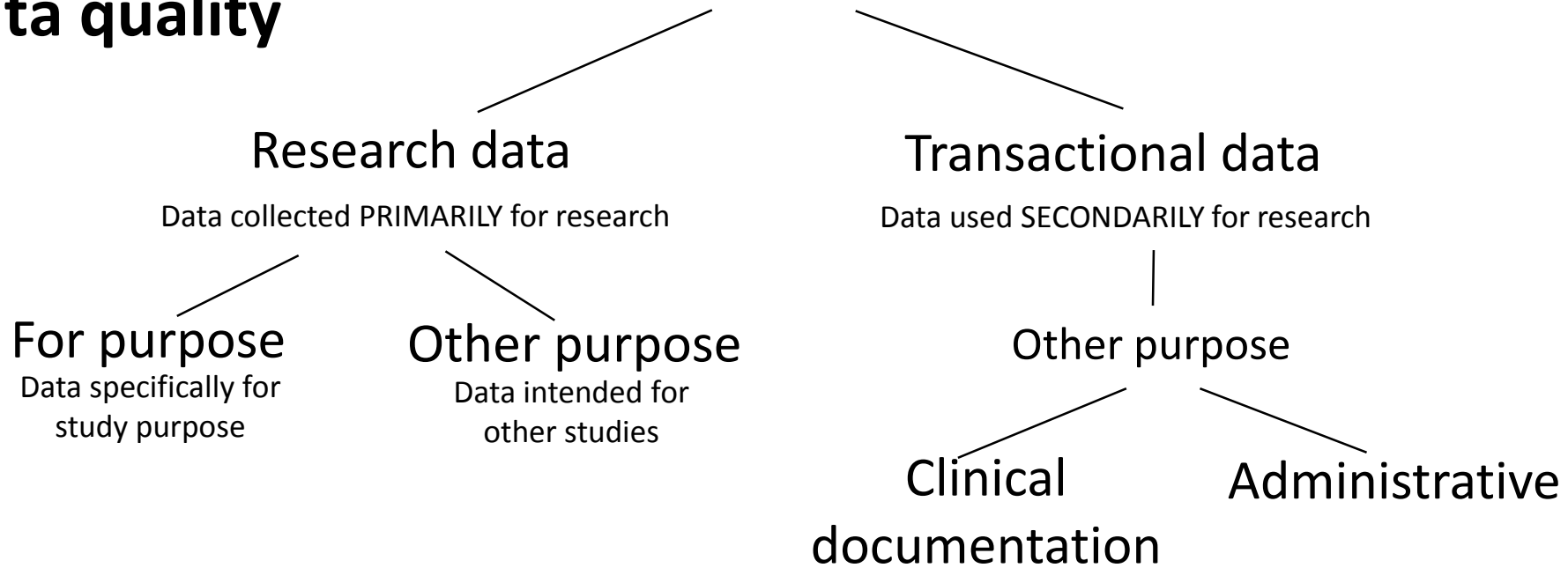
Schneeweiss, BMC 2012

# What does that tell us about the quality of data?

# For our study? (Fit-for-Purpose)

# Clarity in approach to data quality

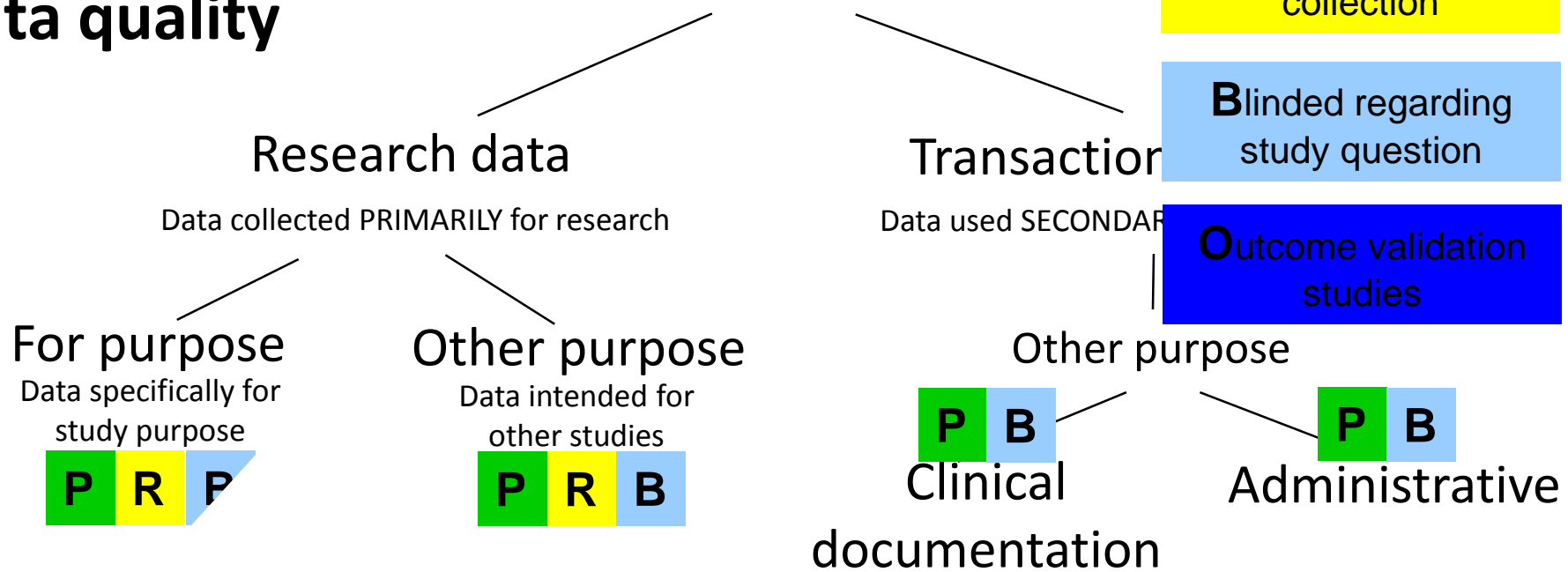
Observational data to study cv safety of drugs



Example	<ul style="list-style-type: none"> <li>▪ Framingham Study</li> <li>▪ Cardiovas Health Study</li> <li>▪ Slone Birth Defects Study</li> <li>▪ <i>Some registries</i></li> </ul>	<ul style="list-style-type: none"> <li>▪ Nurses' Health Study 1</li> <li>▪ <i>Some registries</i></li> </ul>	<ul style="list-style-type: none"> <li>▪ EHR-based studies</li> <li>▪ NDI linkage</li> <li>▪ Lab test databases</li> <li>▪ <i>Some registries</i></li> </ul>	<ul style="list-style-type: none"> <li>▪ Claims data studies</li> <li>▪ Geocoding/census</li> </ul>
E				
O				
C				

# Clarity in approach to data quality

Observational data to study cv safety of drugs



Example	<ul style="list-style-type: none"> <li>Framingham Study</li> <li>Cardiovas Health Study</li> <li>Slone Birth Defects Study</li> <li>Some registries</li> </ul>	<ul style="list-style-type: none"> <li>Nurses' Health Study 1</li> <li>Some registries</li> </ul>	<ul style="list-style-type: none"> <li>EHR-based studies</li> <li>NDI linkage</li> <li>Lab test databases</li> <li>Some registries</li> </ul>	<ul style="list-style-type: none"> <li>Claims data studies</li> <li>Geocoding/census</li> </ul>
O	O	O	O	O
C				

# Framingham Study (cohort)

Major: **Biennial examination** procedures with extensive examination + interview

Additional: NDI linkage

Drug exposure assessment	Current or past use of estrogen @ biennial exam; <b>No start date, no stop date</b>
Outcome assessment	Physician review of <b>clinical notes, hospital and physician records and death certificates.</b> New Q waves in ECG since last visit. Stroke confirmed by review panel w/ neurologists
Confounder assessment	Very detailed, pre-exposure
Population size	5k – 20k

# Nurses' Health Study (cohort)

Major: **Biennial self-administered questionnaires**

Additional: Endpoint validation with medical records; NDI linkage

Drug exposure assessment	"Are you currently taking any of the following medications at least once a week" <b>No start date, no stop date</b> (Consequences: Hernan et al)
Outcome assessment	Non-fatal events: permission for <b>medical records review</b> (exposure blinded) Fatal events: Family + Med Records + NDI linkage
Confounder assessment	Very detailed, pre-exposure
Population size	100k

Michels KB, Rosner BA, Manson JE, et al. Prospective study of calcium channel blocker use, cardiovascular disease, and total mortality among hypertensive women: the Nurses' Health Study. *Circulation*. Apr 28 1998;97(16):1540-1548.

Stampfer MJ, Colditz GA, Willett WC, et al. Postmenopausal estrogen therapy and cardiovascular disease. Ten-year follow-up from the nurses' health study. *N Engl J Med*. Sep 12 1991;325(11):756-762.

Hernan MA, Alonso A, Logan R, et al. Observational studies analyzed like randomized experiments: an application to postmenopausal hormone therapy and coronary heart disease. *Epidemiology*. Nov 2008;19(6):766-779

# Cardiovascular Health Study (cohort)

Major: **Annual surveillance visits** with examination and interview

Additional: NDI linkage

Drug exposure assessment	Current or past use; transcribed from medication containers @ annual visit <b>No start date, no stop date</b>
Outcome assessment	Patient interviews and <b>medical records review</b> Carotid ultrasound
Confounder assessment	Very detailed, pre-exposure
Population size	5k

Psaty BM, Savage PJ, Tell GS, et al. Temporal patterns of antihypertensive medication use among elderly patients. The Cardiovascular Health Study. *JAMA*. Oct 20 1993;270(15):1837-1841

Jonas HA, Kronmal RA, Psaty BM, et al. Current estrogen-progestin and estrogen replacement therapy in elderly women: association with carotid atherosclerosis. CHS Collaborative Research Group. Cardiovascular Health Study. *Ann Epidemiol*. Jul 1996;6(4):314-323.

Rea TD, Psaty BM, Heckbert SR, et al. Hormone replacement therapy and the risk of incident congestive heart failure: the Cardiovascular Health Study. *Journal of women's health*. May 2003;12(4):341-350



# Slone Epidemiology Center Birth Defects Study (case-control)

Major: Case control study using **maternal interviews**

Additional:

Drug exposure assessment	Past maternal medication use before and during pregnancy; Including start date and stop date
Outcome assessment	CV birth defects identified through a surveillance system Control babies from same hospitals
Confounder assessment	Very detailed, pre-exposure
Population size	5k

Yau WP, Lin KJ, Werler MM, Louik C, Mitchell AA, Hernandez-Diaz S. Drug certainty-response in interview-based studies.

*Pharmacoepidemiol Drug Saf.* Nov 2011;20(11):1210-1216.

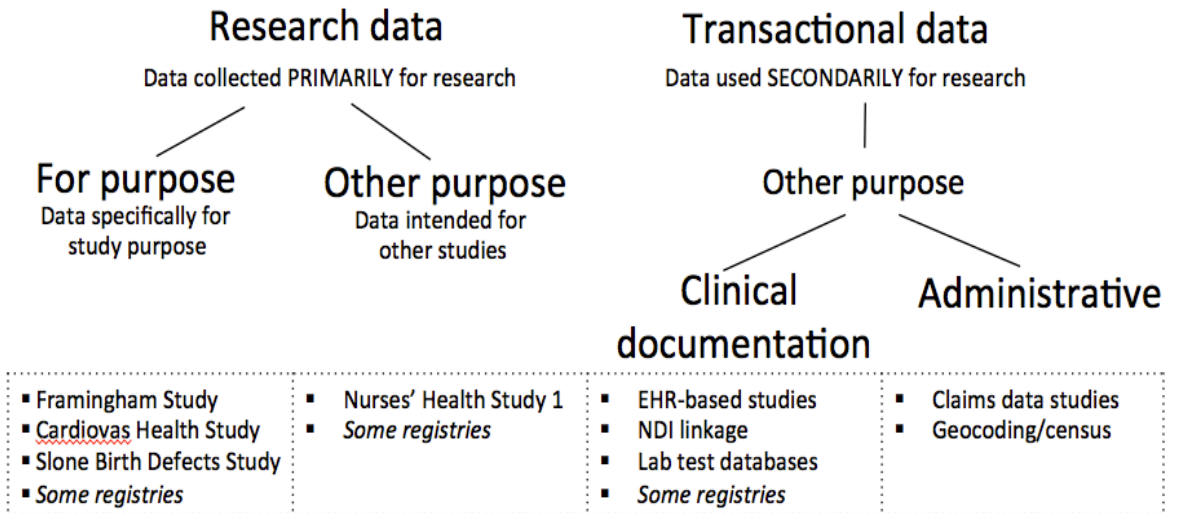
Margulis AV, Mitchell AA, Gilboa SM, et al. Use of topiramate in pregnancy and risk of oral clefts. *American journal of obstetrics and gynecology.* Nov 2012;207(5):405 e401-407.

Louik C, Lin AE, Werler MM, Hernandez-Diaz S, Mitchell AA. First-trimester use of selective serotonin-reuptake inhibitors and the risk of birth defects. *N Engl J Med.* Jun 28 2007;356(26):2675-2683.

# Fundamental difference between primary vs. secondary data (generalization)

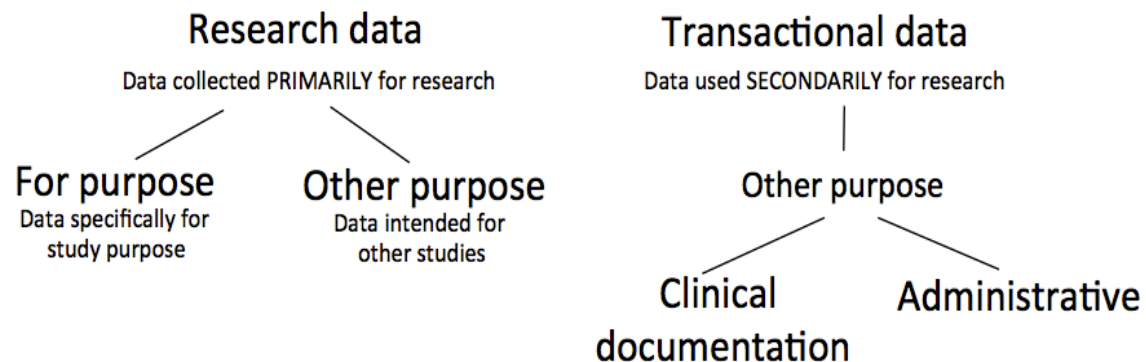
	Primary (research) data: <b>Investigator defines measurements</b>	Secondary (transactional): <b>Business purpose defines measurement</b>
What will be measured	Targeted measurements for research study	Information necessary to get the business done
How will it be measured	Measurement methods designed by investigator -> sufficient accuracy	Measurement good enough for business purpose
Surveillance	Measurements actively scheduled -> high completeness	Measurements tied to healthcare encounters -> informative missingness (sicker patients have more opportunity to get recorded)

# Examples: Exposure assessment



Start of drug				
D/c of drug				
Quantity				
Strength				

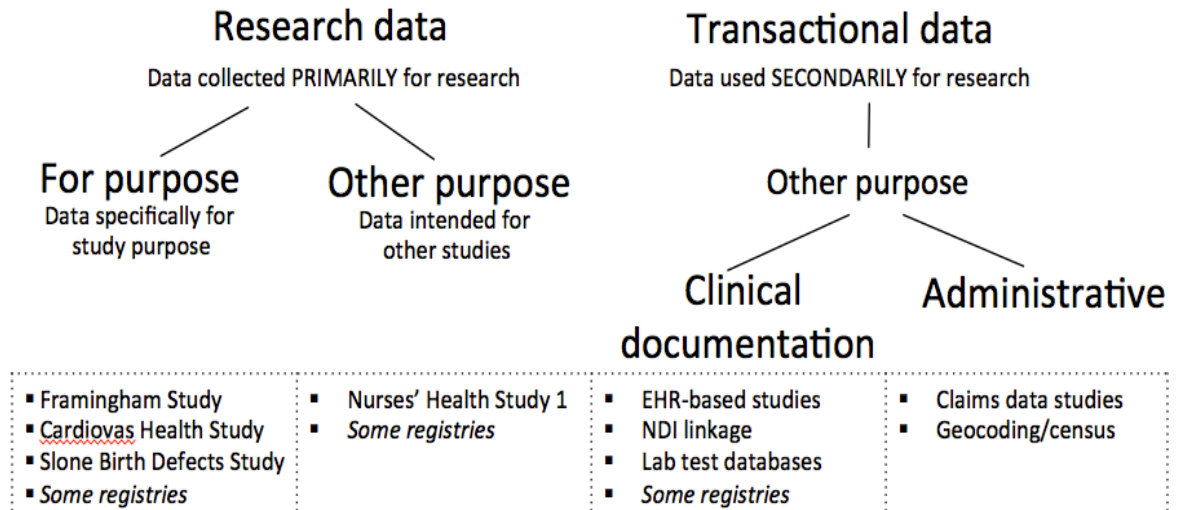
# Examples: Outcome assessment



- |   |  |  |   |
|---|--|--|---|
| <ul style="list-style-type: none"> <li>▪ Framingham Study</li> <li>▪ Cardiovas Health Study</li> <li>▪ Slone Birth Defects Study</li> <li>▪ <i>Some registries</i></li> </ul> | <ul style="list-style-type: none"> <li>▪ Nurses' Health Study 1</li> <li>▪ <i>Some registries</i></li> </ul> | <ul style="list-style-type: none"> <li>▪ EHR-based studies</li> <li>▪ NDI linkage</li> <li>▪ Lab test databases</li> <li>▪ <i>Some registries</i></li> </ul> | <ul style="list-style-type: none"> <li>▪ Claims data studies</li> <li>▪ Geocoding/census</li> </ul> |
|---|--|--|---|

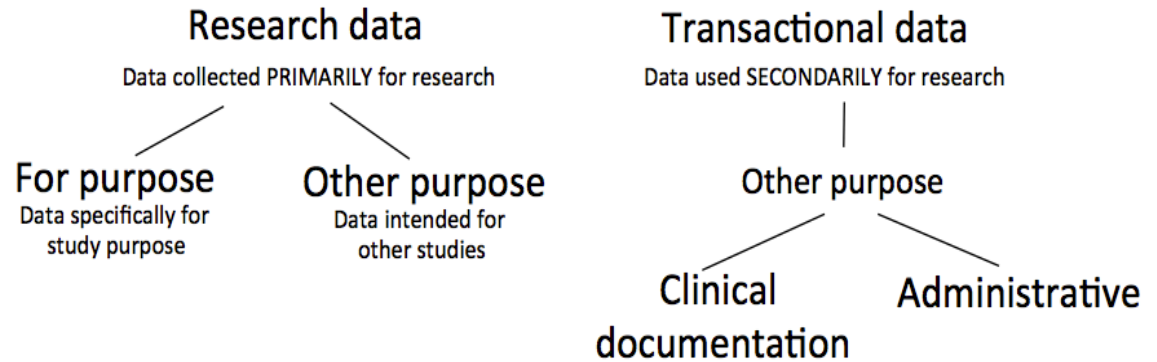
Event surveillance				
Medial records review				
Death certificate				
Ultrasound				

# Examples: Confounder assessment



Pre-existing conditions				
Severity assessment				
Family Hx				
Lab test results				
Life style; smoke, BMI etc.				
Imaging results				

# Summary



- |   |  |  |   |
|---|--|--|---|
| <ul style="list-style-type: none"> <li>▪ Framingham Study</li> <li>▪ Cardiovas Health Study</li> <li>▪ Slone Birth Defects Study</li> <li>▪ <i>Some registries</i></li> </ul> | <ul style="list-style-type: none"> <li>▪ Nurses' Health Study 1</li> <li>▪ <i>Some registries</i></li> </ul> | <ul style="list-style-type: none"> <li>▪ EHR-based studies</li> <li>▪ NDI linkage</li> <li>▪ Lab test databases</li> <li>▪ <i>Some registries</i></li> </ul> | <ul style="list-style-type: none"> <li>▪ Claims data studies</li> <li>▪ Geocoding/census</li> </ul> |
|---|--|--|---|

Drug exposure assessment	C (A-)	C-	C-	A-
Confounder assessment	A	B+	A	B
Outcome assessment	A	A	A	B
Population size	5k – 20k	100k	10m	100m
1% exposed	50-200	1k	100k	1m
10% exposed	500-2k	10k	1m	10m <sub>14</sub>

# Conclusion

- ❖ There is no single perfect data source or study character
- ❖ Fit-for-purpose considerations
  - Drug exposure assessment: Type, strength, start, discontinuation
  - CV endpoint assessment
  - CV risk factors assessment before drug exposure
- ❖ Clinical data do well
  - In detailed risk factor assessment
  - Outcome assessment
- ❖ Clinical data struggle:
  - Prescription drug assessment

# References

1. Yau WP, Lin KJ, Werler MM, Louik C, Mitchell AA, Hernandez-Diaz S. Drug certainty-response in interview-based studies. *Pharmacoepidemiol Drug Saf.* Nov 2011;20(11):1210-1216.
2. Lin KJ, Mitchell AA, Yau WP, Louik C, Hernandez-Diaz S. Maternal exposure to amoxicillin and the risk of oral clefts. *Epidemiology.* Sep 2012;23(5):699-705.
3. Margulis AV, Mitchell AA, Gilboa SM, et al. Use of topiramate in pregnancy and risk of oral clefts. *American journal of obstetrics and gynecology.* Nov 2012;207(5):405 e401-407.
4. Louik C, Lin AE, Werler MM, Hernandez-Diaz S, Mitchell AA. First-trimester use of selective serotonin-reuptake inhibitors and the risk of birth defects. *N Engl J Med.* Jun 28 2007;356(26):2675-2683.
5. Michels KB, Rosner BA, Manson JE, et al. Prospective study of calcium channel blocker use, cardiovascular disease, and total mortality among hypertensive women: the Nurses' Health Study. *Circulation.* Apr 28 1998;97(16):1540-1548.
6. Stampfer MJ, Willett WC, Colditz GA, Rosner B, Speizer FE, Hennekens CH. A prospective study of postmenopausal estrogen therapy and coronary heart disease. *N Engl J Med.* Oct 24 1985;313(17):1044-1049.
7. Hernan MA, Alonso A, Logan R, et al. Observational studies analyzed like randomized experiments: an application to postmenopausal hormone therapy and coronary heart disease. *Epidemiology.* Nov 2008;19(6):766-779.
8. Psaty BM, Savage PJ, Tell GS, et al. Temporal patterns of antihypertensive medication use among elderly patients. The Cardiovascular Health Study. *JAMA.* Oct 20 1993;270(15):1837-1841.
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11. Wilson PW, Garrison RJ, Castelli WP. Postmenopausal estrogen use, cigarette smoking, and cardiovascular morbidity in women over 50. The Framingham Study. *N Engl J Med.* Oct 24 1985;313(17):1038-1043.