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Er det galt å justere for gestasjonsalder i epidemiologisk årsaksforskning?

Seminar

21 August 2018
Stian Lydersen

http://folk.ntnu.no/slyderse/Pres_Ananth_21aug2018.pdf

Manuscript:

Prolonged rupture of membranes and the association with cerebral palsy in term born children: A national registry-based cohort study.

Maren Mynarek[1], Solveig Bjellmo[1,2], Kristin Melheim Strand[3], Guro L. Andersen[1,4], Stian Lydersen[5], Torstein Vik[1].

AJOG Editor's comment:
"…
A straight adjustment for gestational age as a confounder is grossly inappropriate! GA is an intermediate variable on the causal pathway (between ROM and … CP), and an adjustment will induce a strong collider stratification bias. I've written about this very issue:
Ananth & Schisterman (2017).
The reviewers' suggestion of additional adjustment for birthweight may be inappropriate too. Please ignore this suggestion since any adjustment for birthweight will induce a strong collider bias. "

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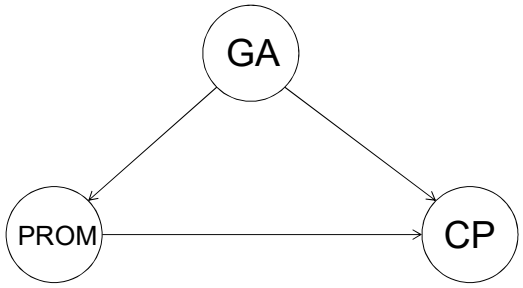

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Confounding, causality, and confusion: the role of intermediate variables in interpreting observational studies in obstetrics

Cande V. Ananth, PhD, MPH; Enrique F. Schisterman, PhD

Am.J.Obstet.Gynecol., 217, (2) 167-175

Randomized controlled trials (RCT), by design, are the least affected by biases that otherwise remain entrenched in observational studies. Despite biases, prospective and retrospective cohort and case-control studies are one of the most important study designs in epidemiology because, under certain assumptions, they can mimic a randomized trial. These assumptions include properly accounting for the numerous possible sources of biases (see recent text books[1,2] for a comprehensive review of biases), notably confounding and selection biases. Failure to address these biases can render the findings from an otherwise persuasive observational study from difficult to interpret at best, to downright meaningless at worst.

Inferring causal associations was once thought feasible only in randomized controlled trial designs. However, with

Prospective and retrospective cohorts and case-control studies are some of the most important study designs in epidemiology because, under certain assumptions, they can mimic a randomized trial when done well. These assumptions include, but are not limited to, properly accounting for 2 important sources of bias: confounding and selection bias. While not adjusting the causal association for an intermediate variable will yield an unbiased estimate of the exposure-outcome's total causal effect, it is often that obstetricians will want to adjust for an intermediate variable to assess if the intermediate is the underlying driver of the association. Such a practice must be weighed in light of the underlying research question and whether such an adjustment is necessary should be carefully considered. Gestational age is, by far, the most commonly encountered variable in obstetrics that is often mislabeled as a confounder when, in fact, it may be an intermediate. If, indeed, gestational age is an intermediate but if mistakenly labeled as a confounding variable and consequently adjusted in an analysis, the conclusions can be unexpected. The implications of this overadjustment of an intermediate as though it were a confounder can render an otherwise persuasive study downright meaningless. This commentary provides an exposition of confounding bias, collider stratification, and selection biases, with applications in obstetrics and perinatal epidemiology.

Key words: causal pathway, collider stratification bias, confounder, descending proxy, inappropriate adjustment, intermediate variable, overadjustment, perinatal paradox, selection bias, unmeasured confounding

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Background:

What are confounders, colliders, and mediators?

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Definition of a confounder

(Rothman: ”Epidemiology: An Introduction”. 2nd ed. Oxford University Press, 2012, page 108.)

Confounding can be thought of as a mixing of effects. A confounding factor, therefore, must have an effect and must be imbalanced between the exposure groups to be compared.

- A confounder must be associated with the disease (either as a cause or a proxy for a cause but not as an effect of the disease).
- A confounder must be associated with the exposure.
- A confounder must not be an effect of the exposure.

Comment: Data can only show us an association. The plausible direction of a causual effect must stem from other substantive knowledge about the phenomenon.

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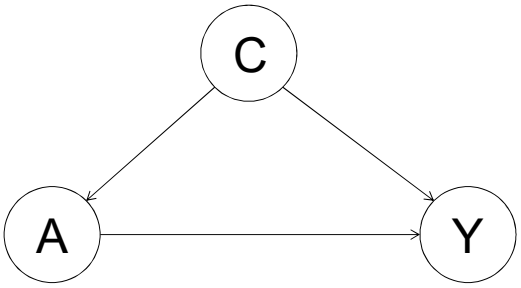
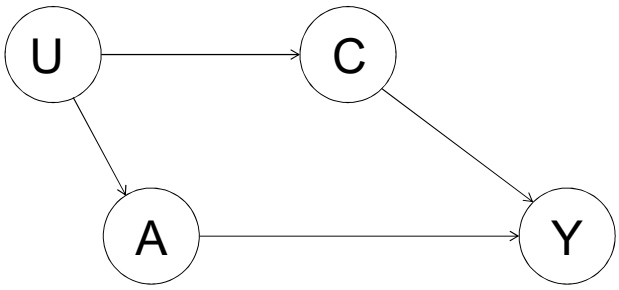
C is a confounder:
Adjust for C in the analysis. Else it would introduce bias.



Directed Acyclic Graph (DAG):
Arrows show the direction of (assumed) cause-effect

8

U is an umeasured confounder.
Adjusting for C removes the bias caused by U.



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How to adjust (control) for a variable (potential confounder)

- The variable as covariate in regression analysis
- Stratified analysis
- Separate analyses
- Restriction (to one value of the variable)

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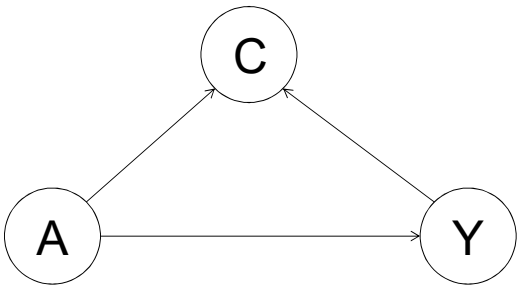
C is a collider:
Do not adjust for C in the analysis
– that would introduce bias.



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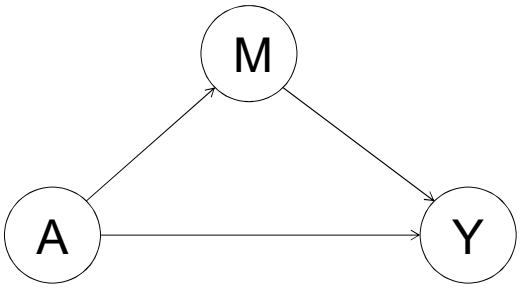
M is a mediator:
Adjust for M? Depends on the research question.
If you adjust for M, the estimated effect of A on Y would be only the direct effect not mediated through M.



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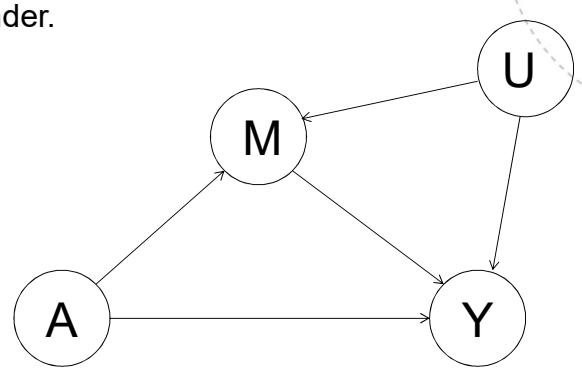
M is a mediator:
Adjusting for M may introduce bias due to an unmeasured confounder.



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Comprehensive geriatric care for patients with hip fractures: a prospective, randomised, controlled trial

Anders Prestmo, Gunhild Hagen*, Olav Sletvold, Jorunn L Helbostad, Pernille Thingstad, Kristin Taraldsen, Stian Lydersen, Vidar Halsteinli, Turi Saltnes, Sarah E Lamb, Lars G Johnsen, Ingvild Saltvedt*

Summary

Background Most patients with hip fractures are characterised by older age (>70 years), frailty, and functional deterioration, and their long-term outcomes are poor with increased costs. We compared the effectiveness and cost-effectiveness of giving these patients comprehensive geriatric care in a dedicated geriatric ward versus the usual orthopaedic care.

Methods We did a prospective, single-centre, randomised, parallel-group, controlled trial. Between April 18, 2008, and Dec 30, 2010, we randomly assigned home-dwelling patients with hip-fractures aged 70 years or older who were able to walk 10 m before their fracture, to either comprehensive geriatric care or orthopaedic care in the emergency department, to achieve the required sample of 400 patients. Randomisation was achieved via a web-based, computer-generated, block method with unknown block sizes. The primary outcome, analysed by intention to treat, was mobility measured with the Short Physical Performance Battery (SPPB) 4 months after surgery for the fracture. The type of treatment was not concealed from the patients or staff delivering the care, and assessors were only partly masked to the treatment during follow-up. This trial is registered with ClinicalTrials.gov, number NCT00667914.

Findings We assessed 1077 patients for eligibility, and excluded 680, mainly for not meeting the inclusion criteria such as living in a nursing home or being aged less than 70 years. Of the remaining patients, we randomly assigned 198 to comprehensive geriatric care and 199 to orthopaedic care. At 4 months, 174 patients remained in the comprehensive geriatric care group and 170 in the orthopaedic care group; the main reason for dropout was death. Mean SPPB scores at 4 months were 5·12 (SE 0·20) for comprehensive geriatric care and 4·38 (SE 0·20) for orthopaedic care (between-group difference 0·74, 95% CI 0·18–1·30, p=0·010).

Interpretation Immediate admission of patients aged 70 years or more with a hip fracture to comprehensive geriatric care in a dedicated ward improved mobility at 4 months, compared with the usual orthopaedic care. The results suggest that the treatment of older patients with hip fractures should be organised as orthogeriatric care.

Funding Norwegian Research Council, Central Norway Regional Health Authority, St Olav Hospital Trust and Fund for Research and Innovation, Liaison Committee between Central Norway Regional Health Authority and the Norwegian University of Science and Technology, the Department of Neuroscience at the Norwegian University of Science and Technology, Foundation for Scientific and Industrial Research at the Norwegian Institute of Technology (SINTEF), and the Municipality of Trondheim.

Lancet 2015; 385: 1623–33

Published Online February 5, 2015 http://dx.doi.org/10.1016/S0140-6736(14)62409-0

See **Comment** page 1594

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Eur J Clin Pharmacol (2017) 73:937–947
DOI 10.1007/s00228-017-2263-x

CLINICAL TRIAL

Patterns of drug prescriptions in an orthogeriatric ward as compared to orthopaedic ward: results from the Trondheim Hip Fracture Trial—a randomised clinical trial

Marianne Heltne[1,2] · Ingvild Saltvedt[2,3] · Stian Lydersen[4] · Anders Prestmo[2,3] · Olav Sletvold[2,3] · Olav Spigset[5,6]

Received: 13 January 2017 / Accepted: 3 May 2017 / Published online: 26 May 2017

Abstract

Purpose In the Trondheim Hip Fracture Trial, 397 home-dwelling patients with hip fractures were randomised to comprehensive geriatric care (CGC) in a geriatric ward or traditional orthopaedic care (OC). Patients in the CGC group had significantly better mobility and function 4 months after discharge. This study explores group differences in drug prescribing and possible associations with the outcomes in the main study.

Methods Drugs prescribed at admission and discharge were registered from hospital records. Mobility, function, fear of falling and quality of life were assessed using specific rating scales. Linear regression was used to analyse association between drug changes and outcomes at 4 months.

Results The mean age was 83 years, and 74% were females. The mean number (± SD) of drugs in the CGC and OC groups was 3.8 (2.8) and 3.9 (2.8) at inclusion and 7.1 (2.8) and 6.2 (3.0) at discharge, respectively ($p = 0.003$). The total number of withdrawals was 209 and 82 in the CGC and OC groups, respectively ($p < 0.0001$), and the number of starts was 844 and 526, respectively ($p < 0.0001$). A significant negative association was found between the number of drug changes during the hospital stay and mobility and function 4 months later in both groups. However, this association disappeared when adjusting for baseline function and comorbidities.

Conclusion These secondary analyses suggest that there are significant differences in the pharmacological treatment between geriatric and orthopaedic wards, but these differences could not explain the beneficial effect of CGC in the Trondheim Hip Fracture Trial.

Marianne Heltne and Ingvild Saltvedt are joint first authors.

Electronic supplementary material The online version of this article (doi:10.1007/s00228-017-2263-x) contains supplementary material, which is available to authorized users.

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thebmj

BMJ 2013;347:f4089 doi: 10.1136/bmj.f4089 (Published 9 July 2013) Page 1 of 10

RESEARCH

Mediators of the association between pre-eclampsia and cerebral palsy: population based cohort study

OPEN ACCESS

Kristin Melheim Strand *medical student*[1], Runa Heimstad *senior consultant in obstetrics and gynaecology*[2], Ann-Charlotte Iversen *senior researcher*[1], Rigmor Austgulen *professor of paediatrics*[1], Stian Lydersen *professor of medical statistics*[3], Guro L Andersen *senior consultant in paediatrics*[4], Lorentz M Irgens *professor of preventive medicine*[5], Torstein Vik *professor of paediatrics*[6]

[1]Department of Cancer Research and Molecular Medicine, Norwegian University of Science and Technology (NTNU), PO Box 8905, MTFS, N-7491 Trondheim, Norway; [2]Department of Obstetrics and Gynecology, St Olav's University Hospital, Trondheim, Norway; [3]The Regional Centre for Child and Adolescent Mental Health, NTNU, Trondheim, Norway; [4]Norwegian Cerebral Palsy Registry, Habilitation Center, Vestfold Hospital, Tønsberg, Norway; [5]Medical Birth Registry of Norway, Locus of Registry Based Epidemiology, Department of Public Health and Primary Health Care, University of Bergen and the Norwegian Institute of Public Health, Norway; [6]Department of Laboratory Medicine, Children's and Women's Health, NTNU, Trondheim, Norway

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Data:
Singleton births from Medical Birth Registry of Norway and the Cerebral Palsy Registry of Norway 1996 to 2006.

Preeklampsi * Cerebral parese Crosstabulation

			Cerebral parese		
			nei	ja	Total
Preeklampsi	nei	Count	593777	774	594551
		% within Preeklampsi	99,9%	,13	100,0%
	ja	Count	22881	75	22956
		% within Preeklampsi	99,7%	,33	100,0%
Total		Count	616658	849	617507
		% within Preeklampsi	99,9%	,14	100,0%

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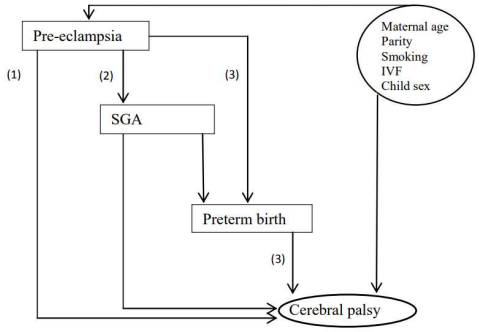
Supplementary figure 2. Proposed conseptual hierarchical framework for the relationship between pre-eclampsia and cerebral palsy (CP). Hypothesized causal pathways added in models 1-3, as well as potential confounders, are shown in the figure. Covariates in the models were:

Model 1: Pre-eclampsia
Model 2: Pre-eclampsia + small for gestational age (SGA)
Model 3: Pre-eclampsia + SGA + gestational age (GA)
Model 4: Pre-eclampsia + SGA + GA + Pre-eclampsia*GA



Adapted from Victora et al (1997)

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Table 2| **Unadjusted (model 1) and adjusted odds ratios for cerebral palsy after exposure to pre-eclampsia**

Potential mediators	Odds ratios (95% CI)		
	Model 1*	Model 2†	Model 3‡
Pre-eclampsia	2.52 (1.98 to 3.19)	2.14 (1.67 to 2.74)	0.73 (0.56 to 0.96)
Small for gestational age	—	2.30 (1.91 to 2.76)	1.90 (1.58 to 2.30)
Duration of pregnancy:			
37-40 weeks	—	—	1.00 (reference)
32-36 weeks	—	—	5.10 (4.18 to 6.20)
<32 weeks	—	—	40.71 (33.70 to 49.17)

← Direct effect

*Unadjusted odds ratio for association between pre-eclampsia and cerebral palsy.
†Adjusted for small for gestational age.
‡Adjusted for small for gestational age and duration of pregnancy.

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Table 3| **Prevalence and odds of cerebral palsy according to exposure to pre-eclampsia and small for gestational age, stratified by duration of pregnancy**

Duration of pregnancy and exposure	Total No at risk	Cerebral palsy	No cerebral palsy	No of cases of cerebral palsy/1000	Odds ratio (95% CI)
≥37 weeks					
Non-small for gestational age:					
No pre-eclampsia	508 228	418	507 810	0.8	1.0 (reference)
Pre-eclampsia	14 323	14	14309	1.0	1.19 (0.70 to 2.03)
Small for gestational age:					
No pre-eclampsia	40 930	76	40 854	1.9	2.26 (1.77 to 2.89)
Pre-eclampsia	2683	7	2676	2.6	3.18 (1.50 to 6.71)
32-36 weeks					
Non-small for gestational age:					
No pre-eclampsia	21 027	87	20 940	4.1	1.0 (reference)
Pre-eclampsia	2736	12	2724	4.4	1.06 (0.58 to 1.94)
Small for gestational age:					
No pre-eclampsia	2225	19	2206	8.5	2.07 (1.26 to 3.41)
Pre-eclampsia	1372	9	1363	6.6	1.59 (0.80 to 3.16)
<32 weeks					
Non-small for gestational age:					
No pre-eclampsia	2964	119	2845	40.1	1.0 (reference)
Pre-eclampsia	705	13	692	18.4	0.45 (0.25 to 0.80)
Small for gestational age:					
No pre-eclampsia	355	16	339	45.1	1.13 (0.66 to 1.93)
Pre-eclampsia	499	15	484	30.1	0.74 (0.43 to 1.28)
Missing data on gestational age:					
No pre-eclampsia	18 231	27	18 204	1.5	1.0 (reference)
Pre-eclampsia	610	3	607	4.9	3.33 (1.01 to 11.01)

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Table 4| **Odds for cerebral palsy according to exposure to pre-eclampsia and duration of pregnancy, compared with reference group of children unexposed to pre-eclampsia and born at term (model 4, adjusted for small for gestational age)**

Pre-eclampsia	Duration of pregnancy	Adjusted odds ratio (95% CI)
Absent	Term	1.00 (reference)
Present	Term	1.28 (0.83 to 1.98)
Absent	Moderately preterm	4.99 (4.05 to 6.16)
Present	Moderately preterm	4.64 (2.98 to 7.23)
Absent	Very preterm	45.90 (37.81 to 55.72)
Present	Very preterm	20.37 (13.74 to 30.22)
Small for gestational age	—	1.95 (1.61 to 2.36)

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Conclusions:
"Exposure to pre-eclampsia was associated with an increased risk of cerebral palsy, and this association was mediated through the children being born preterm or small for gestational age, or both. Among children born at term, pre-eclampsia was a risk factor for cerebral palsy only when the children were small for gestational age."

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BMJ article published 9 July 2013

Chiolero, A. and Kaufman, J.: "Adjustment for a mediator can induce bias." Rapid response, BMJ, 25 July 2013.

"Indeed, if there was an unmeasured common cause of both the mediator gestational age and the outcome cerebral palsy (i.e., a confounder of the association between gestational age and cerebral palsy), adjustment for gestational age could create a spurious association between preeclampsia and cerebral palsy. Intrauterine infection could be such a common cause [3]."

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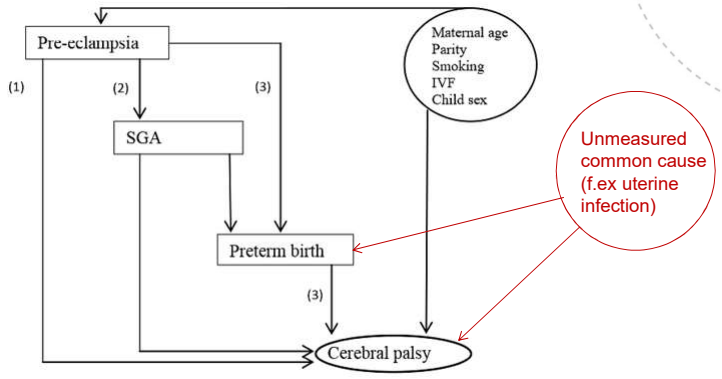

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Article published 9 July 2013
Rapid response, BMJ, 25 July 2013.

Vik, T., and Strand, K.: "Does preeclampsia protect preterm babies from cerebral palsy? " Rapid response, BMJ, 7 August 2013.

" … the lower odds for cerebral palsy probably means that very preterm births "caused by" preeclampsia (mainly iatrogenic, through caesarean section) may have less detrimental effects on the foetal brain than the causes of spontaneous preterm birth. We underscore this interpretation by stating that "In our study, among children with cerebral palsy born very preterm and unexposed to preeclampsia, 65.9% of mothers went into labour spontaneously. The corresponding proportion in children with cerebral palsy exposed to preeclampsia was 13.3%."
We appreciate this opportunity to re-emphasize that our study should not be interpreted as evidence that preeclampsia protects against cerebral palsy. "

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Prospective and retrospective cohorts and case-control studies are some of the most important study designs in epidemiology because, under certain assumptions, they can mimic a randomized trial when done well. These assumptions include, but are not limited to, properly accounting for 2 important sources of bias: confounding and selection bias. While not adjusting the causal association for an intermediate variable will yield an unbiased estimate of the exposure-outcome's total causal effect, it is often that obstetricians will want to adjust for an intermediate variable to assess if the intermediate is the underlying driver of the association. Such a practice must be weighed in light of the underlying research question and whether such an adjustment is necessary should be carefully considered. Gestational age is, by far, the most commonly encountered variable in obstetrics that is often mislabeled as a confounder when, in fact, it may be an intermediate. If, indeed, gestational age is an intermediate but if mistakenly labeled as a confounding variable and consequently adjusted in an analysis, the conclusions can be unexpected. The implications of this overadjustment of an intermediate as though it were a confounder can render an otherwise persuasive study downright meaningless. This commentary provides an exposition of confounding bias, collider stratification, and selection biases, with applications in obstetrics and perinatal epidemiology.

Key words: causal pathway, collider stratification bias, confounder, descending proxy, inappropriate adjustment, intermediate variable, overadjustment, perinatal paradox, selection bias, unmeasured confounding

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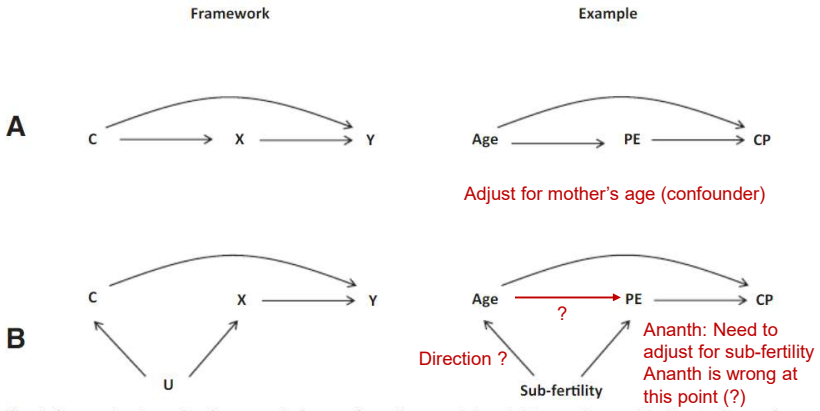
FIGURE 1
DAGs representing two scenarios for confounding



The left panels show the framework for confounding, and the right panels provide illustrations of confounding of the PE and CP association with maternal age (Age) as a potential confounder and subfertility as an unmeasured confounder. We denote subfertility as an unmeasured confounder in the broadest sense when, in fact, subfertility may serve as a marker for an underlying condition that results in both conception delay and preeclampsia should a conception occur.

CP, cerebral palsy; *PE*, preeclampsia.

Ananth. Intermediate variables in interpreting observational studies. Am J Obstet Gynecol 2017.

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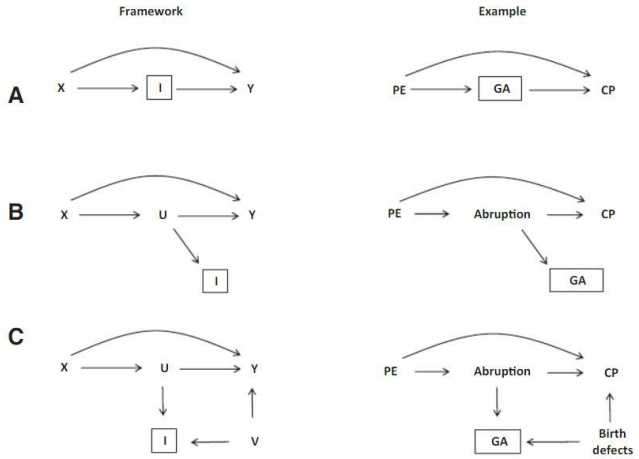
FIGURE 2
DAGs representing three scenarios for variables acting as intermediates



The left panels show the framework for an intermediate variable, and the right panels show illustrations of how an intermediate variable, GA, may affect the PE and CP association, with placental abruption as an unmeasured intermediate (U). V is another unmeasured confounder, for example, birth defects.

CP, cerebral palsy; *GA*, gestational age; *PE*, preeclampsia.

Ananth. Intermediate variables in interpreting observational studies. Am J Obstet Gynecol 2017.

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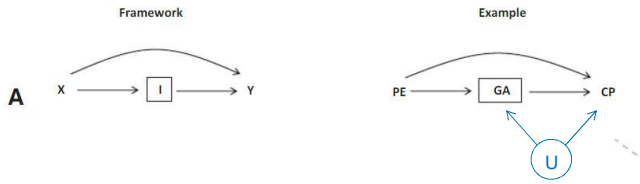
FIGURE 2
DAGs representing three scenarios for variables acting as intermediates



Ananth page 169:
However, if control is made for the intermediate variable I, then the total causal effect of the X →Y association cannot be consistently estimated.

But OK if proper mediator analysis is used?

Not OK if there is some unmeasured confounder U.

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Ananth page 169:
If one controls for the variable I in Figure 2B, which is a proxy for the variable U (on the causal pathway between exposure and outcome), the total causal effect of the X →Y association again cannot be consistently estimated. To clarify, if an intermediate such as gestational age is adjusted on the preeclampsia-cerebral palsy association, the total effect will be underestimated.

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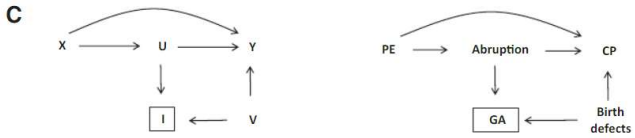
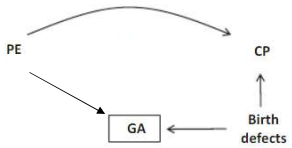


Ananth page 169:
If one does adjust for gestational age or preterm delivery in the presence of an unmeasured confounder between gestational age and cerebral palsy, the preeclampsia – cerebral palsy estimate will be rendered biased, a bias called collider stratification bias.

Also the case for this simplified model?



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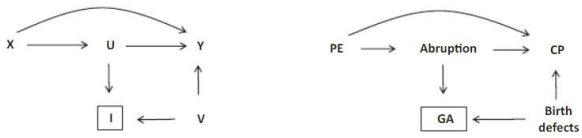

Ananth page 169:
If one does adjust for gestational age or preterm delivery in the presence of an unmeasured confounder between gestational age and cerebral palsy, the preeclampsia – cerebral palsy estimate will be rendered biased, a bias called collider stratification bias.

Ananth page 170:
However, not adjusting for gestational age avoids the collider and will yield an unbiased estimate of the total effect. …
Adjusting on such a common effect (ie a collider) can result in selection bias. In the preeclampsia – cerebral palsy example, gestational age is a collider.

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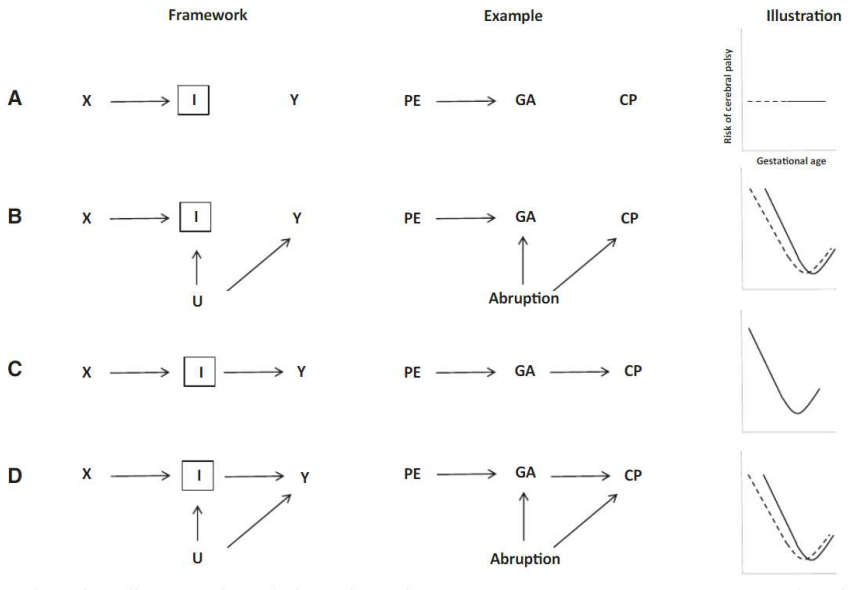
FIGURE 3
DAGs representing collider stratification bias with three illustrations for each scenario

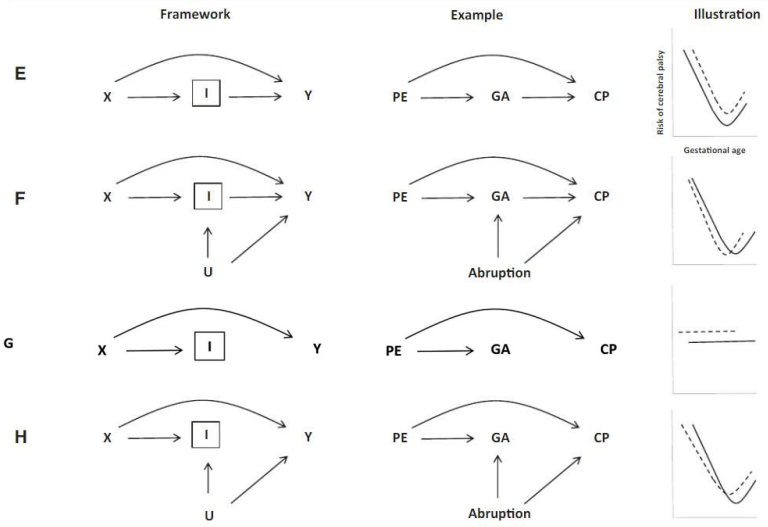


Ananth. Intermediate variables in interpreting observational studies. Am J Obstet Gynecol 2017.

(continued)

FIGURE 3
(*Continued*)

Note: G has been corrected for a typo pointed out by Ananth, March 2018.



The left panels show the theoretical framework for an intermediate variable, the middle panels show illustrations of how adjusting for an intermediate variable, I, depicted in a box and labeled a collider with GA as the intermediate, will induce bias of the PE and CP association. The right panels show the risks of cerebral palsy on the y-axis by gestational age on the x-axis, among women with (*solid line*) and without preeclampsia (*dashed line*). Placental abruption is assumed to be an unmeasured variable.

CP, cerebral palsy; *GA*, gestational age; *PE*, preeclampsia.

Ananth. Intermediate variables in interpreting observational studies. Am J Obstet Gynecol 2017.

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Er det galt å justere for gestasjonsalder i epidemolologisk årsaksforskning?

- Kanskje nyttig å skiller mellom to typer studier:
  - Prediksjon eller prognose
  - Årsaksanalyse (analytiske studier)
- DAG, confounders, mediation etc er bare relevant innen siste type studier(?)
- Avhengig av forskningsspørsmål, vil den ene eller andre typen studie være relevant.

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