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Using fathers as a Negative Control Exposure to test the Developmental Origins of Health and Disease Hypothesis: A case study on maternal distress and offspring asthma using Swedish register data.

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Short title: A model for Negative Control paternal exposures to test fetal programming hypotheses.

Abstract

Background: Developmental Origins of Health and Disease Hypothesis (DOHaD) studies are often observational in nature and are therefore prone to biases from loss to follow-up and unmeasured confounding. Register-based studies can reduce these issues since they allow almost complete follow-up and provide information on fathers that can be used in a negative control analysis to assess the impact of unmeasured confounding.

Aim: To propose a causal model for testing DOHaD using paternal exposure as a negative control, and its application to maternal distress in pregnancy and offspring asthma.

Methods: A causal diagram including shared and parent-specific measured and unmeasured confounders for maternal (fetal) and paternal exposures is proposed. The case-study consisted of all children born in Sweden from July 2006 to December 2008 (n=254 150). Information about childhood asthma, parental distress and covariates was obtained from the Swedish National health registers. Associations between maternal and paternal distress during pregnancy and offspring asthma at age 5 years were assessed separately and with mutual adjustment for the other parent's distress measure, as well as for shared confounders.

Results: Maternal distress during pregnancy was associated with offspring asthma risk; mutually adjusted Odds Ratio (OR) 1.32 (95% CI 1.23, 1.43). The mutually adjusted paternal distress-offspring asthma analysis (OR 1.05 95% CI 0.97, 1.13) indicated no evidence for unmeasured confounding shared by the mother and father.

Conclusions: Using paternal exposure in a negative control model to test the robustness of fetal programming hypotheses can be a relatively simple extension of conventional observational studies but limitations need to be considered.

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Introduction

The Developmental Origins of Health and Disease (DOHaD) theory hypothesizes that chronic disease risk is influenced by variation in environmental exposures *in utero* that alter fetal programming [1]. Many exposures implicated in fetal programming cannot be investigated in randomized controlled trials for practical and/or ethical reasons. Thus, most DOHaD research on human samples is observational. Observational studies based on recruitment of participants are prone to bias from several sources including selection bias, recall bias, loss to follow-up and confounding [2]. Studies that use population-based registers have the ability to minimize many of these sources of bias since they rely on nation-wide systematic recording of data.

Confounding is typically addressed by adjusting for measured variables that are considered determinants of both the exposure and the outcome. However, unmeasured confounding has the potential to bias results [3], including those from population-based register studies. One method that can test for the possibility of unmeasured confounding is to use a negative control study [4, 5]. The negative control can be either another outcome or another exposure that ideally shares the same measured and unmeasured confounders as the exposure of interest [4]. Additionally, a control outcome should not be caused by the exposure of interest, and a control exposure should not cause the outcome of interest [4].

Negative Control Paternal Exposure studies testing DOHaD

In studies of fetal programming, the impact of unmeasured confounding can be examined by using measurement of paternal exposure to a trait of interest during the pregnancy term as the negative control exposure, based on the assumptions that there is no direct association between the father's exposure during the pregnancy period and the child's outcome, and that the shared confounders are equally associated with the mother and the father's exposures [4]. Although negative control analyses using paternal exposures are becoming more common [2, 6-8] a specific causal diagram for this theoretical framework has not been proposed to date. An important consideration for paternal exposure as a negative control is the potential for paternal exposure to directly affect maternal exposure. In previous studies this has been addressed by mutually adjusting for the other parent's exposure [6, 9, 10]. We wished to explore the scope and issues of these designs

further and propose a causal diagram for negative control exposure studies testing the DOHaD hypothesis in Figure 1.

According to Figure 1, an association between maternal exposure in pregnancy and an outcome of interest (adjusted for shared measured confounders –L1 and maternal-specific measured confounders-L2) could be due to a causal effect or due to unmeasured confounding from U1 or U2. Additionally, if the paternal exposure directly affects the maternal exposure, e.g. by behavior modification, then there is a possible third pathway linking maternal exposure and the outcome via paternal-specific measured and unmeasured confounders- L3 and U3 respectively. Mutually adjusting the maternal exposure-outcome association for paternal exposure B can remove the confounding bias by U3 and L3.

An observed association between paternal exposure and child's outcome after adjusting for measured confounders L1 and L3 could be due to unmeasured confounding from U1 or U2 and/or the direct effect of paternal exposure on maternal exposure. Adjusting the paternal exposure model for maternal exposure (and L2) blocks the causal pathway through A (direct and back door through U1) but could also introduce bias from the maternal-specific confounders (collider bias). If no (or a very weak) association is observed between the paternal exposure and outcome then the implication is that the total of unmeasured confounding bias (U1, U2 and U3) is having no (or a very weak) impact on the association of maternal exposure and outcome, assuming each parental-specific confounding biases are of comparable magnitudes. Thus, this scenario reduces the possibility of residual confounding and adds evidence for fetal programming. However, if an association of the paternal exposure with the outcome is found, the interpretation is more difficult. It could mean that there is unmeasured confounding of the maternal exposure-child association and therefore less likelihood of fetal programming, but it could also mean that the association is due to paternal-specific unmeasured confounding by U3 thus not ruling out the possibility of fetal programming. However, the importance is that it brings awareness to the researcher of the possibility of residual confounding and the need for further investigation [4].

Case Study. Maternal distress during pregnancy and childhood asthma

The following worked example will help to illuminate the proposed model using real data from the Swedish national registers.

Background

Several cohort studies have found that maternal depression and anxiety (distress) during pregnancy are associated with offspring developing asthma, possibly due to fetal programming [10, 11]. Given that distress and asthma are often comorbid [12, 13] it seems plausible that this association could be confounded by other unmeasured factors. The objective is to investigate whether the association between maternal distress in pregnancy and offspring asthma risk is potentially biased by unmeasured confounding using paternal distress measured during pregnancy as a negative control exposure.

Methods

The study sample consisted of children born between 1 July 2006 and 31 December 2008 identified in the Swedish Medical Birth Register (n=254 150) [14]. Linkage to the Multi-Generation Register allowed identification of fathers. Maternal and paternal distress were defined as medication for, or a diagnosis of, an anxiety or depressive disorder during the mother's pregnancy (Appendix I) [15]. Offspring asthma at age 5 was defined as: 1) an asthma diagnosis in the year after turning 5, or 2) an asthma medication prescription OR diagnosis between ages 1 and 6, AND an asthma medication prescription in the year after turning 5 [16]. Maternal and paternal history of asthma was defined as: any history of asthma self-reported at the first antenatal appointment, or any register-recorded asthma diagnosis, or at least two prescriptions for an asthma medication before the child's birth. Highest level of parental education attained when the child was born, and parity (number of older siblings) were taken from the Swedish registers (Appendix I).

Statistical Analysis: Multivariable logistic regression was used to determine the associations between maternal or paternal distress during pregnancy with offspring asthma risk. Analyses were adjusted for parity and parental education attainment: measured confounders shared by maternal and paternal exposures (denoted L1 in Figure 1). The separate maternal and paternal models also included adjustment for history of maternal and paternal asthma respectively: measured parent-specific confounders (denoted L2 and L3 in Figure 1). Subsequent models were mutually adjusted for the other parent's distress during pregnancy as paternal distress was found to be associated with maternal distress (adjOdds Ratio (OR) 2.6 95% CI 2.4, 2.8). Due to the potential for collider bias (illustrated in Figure 1), the paternal mutually adjusted model was also adjusted for history of maternal asthma. SAS Enterprise Guide 7.1 was used for statistical analysis.

Ethics: The study was approved by the regional ethics review board in Stockholm, Sweden.

Results

Maternal distress during pregnancy was associated with risk of asthma at age 5 (adjusted OR 1.33, 95% CI 1.24, 1.43) which reduced negligibly when mutually adjusted for paternal distress (Table I). Paternal distress during the mother's pregnancy was marginally associated with asthma at age 5 after confounding adjustment (adjusted OR 1.06, 95% CI 0.99, 1.15). The paternal association was similarly weak in the mutually adjusted model (OR 1.05 95% CI 0.97, 1.13).

Discussion

We have presented a negative control causal diagram using paternal exposure during pregnancy to test the DOHaD hypothesis. The specific case study found that the association of maternal distress during pregnancy with offspring asthma risk did not appear to be strongly biased by unmeasured confounding shared by the mother and father.

The main strength of this study is that, by using linked register data, we were able to obtain both maternal and paternal exposure data during pregnancy as well as data for many confounders, hence reduce the potential for unmeasured confounding as well as being able to use a negative control exposure to test for residual existence of this confounding. In addition, we had a very large sample size made possible by the use of the Swedish national registers. The main limitation of the specific case-study is that distress measurement lacked sensitivity. This is because our data only represented distress for those who had received treatment or had a diagnosis for such from a specialist, rather than from primary care or undiagnosed distress.

An issue of this worked example in relation to the causal model for negative control exposures is that if the paternal exposure during pregnancy in part determines the maternal exposure, then this violates the assumption of the ideal negative control study that the negative control exposure is not affecting the outcome via influence on the exposure of interest. In addition, it also introduces potential bias from unmeasured paternal-specific confounding between the paternal exposure and the outcome. In our case study, an example of this specific confounding would be genetic variants that affect both proneness to distress and asthma, and which offspring inherit from fathers. This confounding might be similar in nature and magnitude to confounding unique to the maternal exposure-outcome association, and thus the comparison of exposure and negative control exposure associations with outcomes remains warranted. However, this could vary for

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different examples, for example personality differences. Mutual adjustment helps mitigate (but not solve) this issue, by blocking the paternal-specific unmeasured confounding when mutually adjusting for paternal exposure in the maternal model. In the paternal model mutually adjusting for maternal exposure blocks the direct and backdoor pathways through maternal exposure and opens the pathway for U1 and U2 by collider bias. In our case study odds only changed from 1.06 to 1.05 with mutual adjustment which could either suggest that the collider bias is negligible, or that the collider bias balances out the direct and backdoor effects in the original model, it is not possible to tell. . Secondly, if the outcome is measured postnatally, the possibility of a direct effect of the paternal exposure on the outcome after fetal life should be considered, as this would invalidate its use as a negative control [17]. For example, if paternal distress during pregnancy tracks as distress during the child's life time, concomitant changes in paternal behavior (such as proneness to smoking) could affect offspring asthma risk. In our example, this seems unlikely, given a null finding for the paternal exposure in pregnancy in association with offspring asthma. However, if an association of negative control with outcome is found in this context, its meaning may be more difficult to interpret.

In conclusion, using paternal information in a negative control model to test the robustness of fetal programming hypotheses can be a relatively simple extension of conventional observational studies and is feasible within register-linked data. However, we recommend careful consideration and interpretation of findings by those wishing to use this methodology, given the various strengths and limitations of these applications.

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Caption for Figure 1:

Causal diagram for an ideal negative control exposure study testing in utero programming effects. A represents fetal exposure in utero to the maternal environment, Y is the outcome in the offspring. B represents paternal exposure during the pregnancy term. L1, L2 and L3 make up measured confounders, shared (L1) and parent-specific (L2, L3) . U1, U2 and U3 make up the unmeasured confounders, shared (U1) and parent-specific (U2, U3).

Table I. Distress during pregnancy and offspring asthma

Exposure during Pregnancy	Children with asthma N= 19 468 n (%)	Children without asthma N= 234 682 n (%)	Unadjusted (OR and 95% CI)	Adjusted[a] (OR and 95% CI)	Mutual adjustment[b] (OR and 95% CI)
Maternal Distress	853 (4.4)	7184 (3.1)	1.45 (1.35, 1.56)***	1.33 (1.24, 1.43)***	1.32 (1.23, 1.43)***
Paternal Distress	800 (4.1)	8618 (3.7)	1.12 (1.04, 1.21)**	1.06 (0.99, 1.15)	1.05 (0.97, 1.13)

*** p< 0.0001 **p< 0.01   * p≤ 0.05

a.   adjusted model = maternal (parity, maternal asthma, parental education), paternal (parity, parental education, paternal asthma)

b.   mutual adjustment = maternal (parity, maternal asthma, parental education, paternal distress during pregnancy) , paternal (parity, parental education, maternal distress during pregnancy, maternal asthma, paternal asthma)
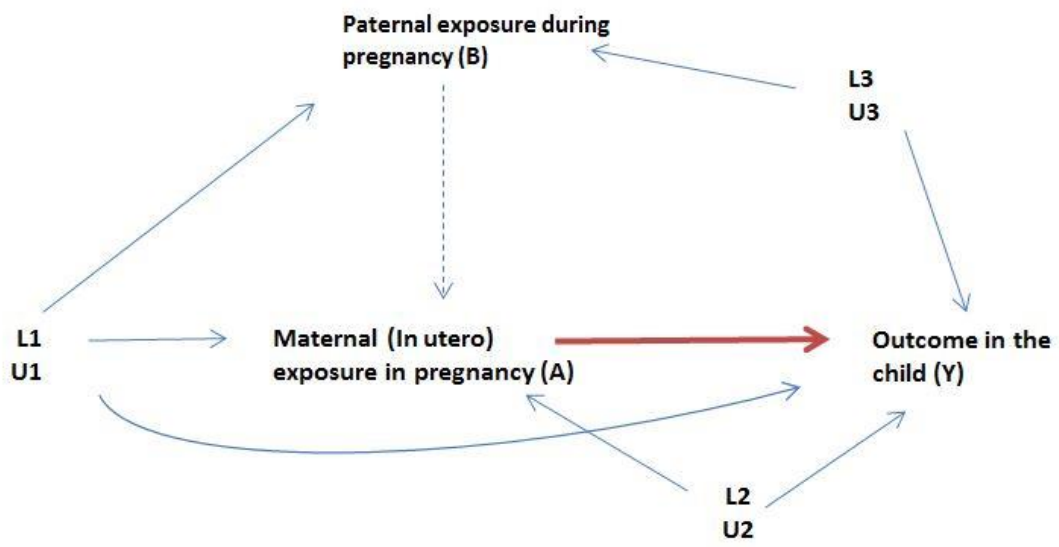
Image 1

Appendix

Variables, codes and registers used for Exposures, Outcomes and Covariates.

	Variable	CODES ATC (medication) or ICD-10 codes (diagnosis)	Register
Distress exposure	Antidepressant Medication	N05B	Prescribed Drug Register
	Anxiolytic medication	N06A	Prescribed Drug Register
	Depressive disorder diagnosis	F30-34, F38-39	National Patient Register
	Anxiety disorder diagnosis	F40-F45, F48	National Patient Register
Offspring Asthma outcome	Asthma diagnosis	J45	National Patient Register
	Asthma medication	R03BA R03DC R03AK R03AC	Prescribed Drug Register
Covariates	Parity		Medical Birth Register
	Parental Highest Education level attained		Longitudinal Integration database for Health Insurance and Labour Market Studies
	Maternal asthma -self report		Medical Birth Register
	Maternal or Paternal Asthma -diagnosis	J45	National Patient Register
	Maternal or Parental Asthma -medication	R03BA R03DC R03AK R03AC	Prescribed Drug Register