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Casey, Joan A
Goin, Dana E
Rudolph, Kara E
et al.

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Unconventional natural gas development and adverse birth outcomes in Pennsylvania: the potential mediating role of antenatal anxiety and depression

Joan A. Casey[1,2], **Dana E. Goin**[3], **Kara E. Rudolph**[4], **Brian S. Schwartz**[5,6,7], **Dione Mercer**[6], **Holly Elser**[3], **Ellen A. Eisen**[1], **Rachel Morello-Frosch**[8,9]

[1]Division of Environmental Health Sciences, School of Public Health, University of California, Berkeley, USA

[2]Department of Environmental Health Sciences, Mailman School of Public Health, Columbia University, New York, NY, USA

[3]Division of Epidemiology, School of Public Health, University of California, Berkeley, USA

[4]Department of Emergency Medicine, School of Medicine, University of California, Davis, Sacramento, CA, USA

[5]Department of Environmental Health and Engineering, Johns Hopkins Bloomberg School of Public Health, Baltimore, MD, USA

[6]Department of Epidemiology and Health Services Research, Geisinger, Danville, PA, USA

[7]Johns Hopkins School of Medicine, Department of Medicine, Baltimore, MD, USA

[8]Division of Community Health Sciences, School of Public Health, University of California, Berkeley, USA

[9]College of Natural Resources Department of Environmental Science, Policy, & Management, University of California, Berkeley, USA

Abstract

Background—Studies have reported associations between unconventional natural gas development (UNGD) and adverse birth outcomes. None have evaluated potential mediating mechanisms.

Objectives—To evaluate associations between (1) UNGD and antenatal anxiety and depression and (2) antenatal anxiety and depression and preterm birth (< 37 weeks gestation) and reduced term birth weight, (3) stochastic direct and indirect effects of UNGD on preterm birth and term birth weight operating through antenatal anxiety and depression, and (4) effect modification by family-level socioeconomic status.

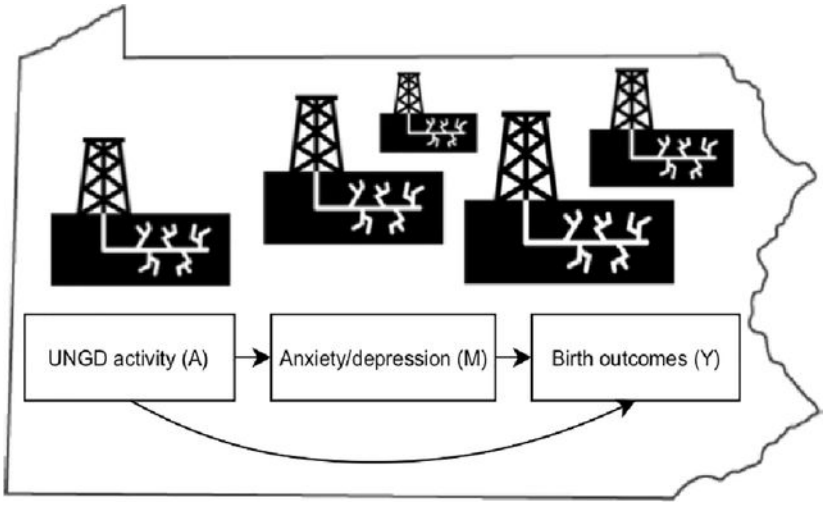
Corresponding author: Joan A. Casey, jac2250@columbia.edu, 722 W 168th St, RM 1206, New York NY 10032-327.

Methods—This retrospective cohort study included mothers without prevalent anxiety or depression at time of conception, who delivered at Geisinger in Pennsylvania between January 2009–January 2013. We assembled phase-specific UNGD activity data from public sources. Mothers were categorized as exposed (quartile 4) or unexposed (quartiles 1–3) based on average daily inverse distance-squared UNGD activity metric between conception and the week prior to anxiety or depression (cases) or the pregnancy-average daily metric (non-cases). We estimated associations with a doubly robust estimator (targeted minimum loss-based estimation) and adjusted for potential individual- and community-level confounding variables.

Results—Analyses included 8,371 births to 7,715 mothers, 12.2% of whom had antenatal anxiety or depression. We found 4.3 additional cases of antenatal anxiety or depression per 100 women (95% CI: 1.5, 7.0) under the scenario where all mothers lived in the highest quartile of UNGD activity versus quartiles 1–3. The risk difference appeared larger among mothers receiving Medical Assistance (indicator of low family income) compared to those who did not, 5.6 (95% CI: 0.5, 10.6) versus 2.9 (95% CI: −0.7, 6.5) additional cases of antenatal anxiety or depression per 100 women. We found no relationship between antenatal anxiety or depression and adverse birth outcomes and no mediation effect either overall or when stratifying by Medical Assistance.

Conclusion—We observed a relationship between UNGD activity and antenatal anxiety and depression, which did not mediate the overall association between UNGD activity and adverse birth outcomes.

Graphical Abstract



Keywords

Hydraulic Fracking; Maternal Health; Anxiety; Depressive Disorder; Social Class

1. INTRODUCTION

Recent advances in directional drilling and high-volume hydraulic fracturing have allowed unconventional natural gas development (UNGD) in previously inaccessible formations. UNGD operates on an industrial scale. It involves clearing land, building multi-well pads,

drilling both vertically and horizontally, and injecting millions of gallons of highly pressurized water combined with chemical additives and sand and/or silica into shale formations, which releases natural gas (Adgate et al. 2014; Finkel and Hays 2015). By 2017, shale gas accounted for nearly two-thirds of U.S. natural gas production (U.S. EIA 2019). Proponents point to lower energy costs and local economic benefits including increased tax revenue and job creation (Evensen and Stedman 2018; Feyrer et al. 2017; Kearney and Wilson 2018; Silva and Crowe 2015). Others caution that negative externalities may exist for populations living nearby in the form of reduced quality of life (Fisher et al. 2018; Jacquet et al. 2018; Perry 2013), migraine headache and fatigue (Tustin et al. 2017), asthma exacerbations (Rasmussen et al. 2016), and worse cardiovascular health (McKenzie et al. 2019). Studies in Colorado, Oklahoma, and Pennsylvania have found associations between residential proximity to UNGD and adverse birth outcomes (Casey et al. 2016; Currie et al. 2017; Hill 2018; Janitz et al. 2019; McKenzie et al. 2014; Stacy et al. 2015; Whitworth et al. 2018; Whitworth et al. 2017b). While Currie et al. 2017 and Hill et al. 2018 implemented analytic strategies designed to support causal inference, no large epidemiologic studies have attempted to disentangle the complex pathways that may link UNGD to adverse birth outcomes.

Health hazards attributable to UNGD–including air pollution from diesel equipment and trucks, fugitive emissions, secondarily-formed ozone, water contamination from spills and well casing failures, and noise pollution–could contribute to adverse birth outcomes (Balise et al. 2016; Elliott et al. 2017; Hays et al. 2017; Webb et al. 2014). Alternatively, anxiety and depression secondary to UNGD exposure (Hirsch et al. 2018) may mediate the association between UNGD and adverse birth outcomes. Past research documents community members' psychosocial stress related to traffic, safety, and unwelcome social and environmental change (Ferrar et al. 2013; Fisher et al. 2018; Sangaramoorthy et al. 2016; Willow et al. 2014), though perceptions of and reactions to UNGD vary (Howell et al. 2017; Lai et al. 2017; Thomas et al. 2017). A recent study in Pennsylvania found an association between proximity to more and larger wells and increased depressive symptoms (Casey et al. 2018b). Air pollution could lead to anxiety through systemic inflammation and oxidative stress (Hou et al. 2017) or exacerbation of other health conditions (Hayase et al. 2014). A recent study found an association between prenatal $PM_{2.5}$ exposures and postnatal anhedonia and depressive, but not anxiety symptoms (Sheffield et al. 2018). Nighttime noise can disrupt sleep (Basner and McGuire 2018), which in turn may harm mental health (Sygna et al. 2014). Noise may also independently activate the sympathetic nervous system and increase cortisol production, potentially leading to anxiety (Clark and Paunovic 2018).

UNGD may have unique psychologic consequences for women. The majority of UNGD-related jobs go to men (Jacquet et al. 2018) and, compared to men, women more often oppose UNGD (Boudet et al. 2014; Mayer 2016). In addition, pregnant women may perceive environmental exposures as riskier than non-pregnant women (Marie et al. 2016; Petersen et al. 2015) or men (Flynn et al. 1994). Concerns expressed by women about UNGD related to their family's health may be discounted in gendered ways (i.e., they are portrayed as hysterical) (McHenry 2017).

Further, pregnancy may represent a sensitive period for anxiety or depressive disorders. Prevalence estimates for antenatal anxiety or depressive disorders range from 10–15% (Bennett et al. 2004; Dennis et al. 2017). Few prior studies have evaluated environmental risk factors for antenatal anxiety or depression alone, more focus on the role of maternal mental health for offspring health (Ding et al. 2014; Field 2011). Psychosocial stress, anxiety, or depression during pregnancy may increase the risk of preterm birth and reduced birth weight by causing physiologic changes in the maternal hypothalamic-pituitary-adrenal axis (e.g., cortisol and corticotrophin-releasing hormone), oxidative stress, or changes in maternal health and social behaviors (Ding et al. 2014; Dunkel Schetter 2011; Staneva et al. 2015).

Mediation analyses can help uncover mechanisms of action that may explain the association between environmental exposures and perinatal health outcomes (Anthopolos et al. 2014; Ferguson et al. 2016; Rahman et al. 2017). In the present retrospective cohort study, we used stochastic direct and indirect effects (also called randomized interventional effects) (Rudolph et al. 2017; VanderWeele and Tchetgen Tchetgen 2017) to evaluate maternal mental health during pregnancy as a potential mediator of a previously observed relationship between UNGD and adverse birth outcomes in Pennsylvania (Casey et al. 2016). We hypothesized that UNGD could lead to worse maternal mental health and subsequently more adverse birth outcomes.

Certain sub-populations may be particularly vulnerable to UNGD, including pregnant women and individuals of low socioeconomic status (SES) (Hays and de Melo-Martin 2014). In the United States, individuals of lower SES tend to live in more polluted environments (Cushing et al. 2015). Consistent with prior perinatal epidemiologic research (Gray et al. 2014; Sealy-Jefferson et al. 2015; Vesterinen et al. 2017), we hypothesized that lower SES pregnant women might have a heightened response to UNGD activity due to co-exposure to other environmental and social stressors.

2. MATERIAL & METHODS

2.1 Sample

Geisinger is an integrated health system that provides primary care services in approximately 40 counties in central and northeast Pennsylvania, a region that sits atop large portions of the Marcellus shale. Pennsylvania is made up of county sub-divisions–townships, boroughs, and cities–that represent meaningful communities (Schwartz et al. 2011). During the study period, Geisinger had two labor and delivery facilities, the Geisinger Medical Center in Danville, PA and the Geisinger Wyoming Valley hospital in Wilkes-Barre, PA. The present study included women who gave birth to singletons free of serious birth defects (Table A.1) and of viable birth weight (≥ 500 g) and gestational age (≥ 22 weeks) at Geisinger between January 2009–January 2013 (Casey et al. 2016). We assigned these women to communities–townships, boroughs, and census tracts in cities–based on their geocoded addresses at the time of delivery. Consistent with our prior study (Casey et al. 2016), we excluded women with that only geocoded to the ZIP code centroid, including PO boxes. Prior work has found the Geisinger population to be representative of the general population in the region based on age, sex, and race/ethnicity (Casey et al. 2016), though this

does not generalize to the general U.S. population. The Institutional Review Boards at Geisinger and the University of California, Berkeley reviewed and approved this study (protocol numbers: 2017–0291 and 2016–12-9379).

2.2 Mediator: anxiety and depression during pregnancy

We used three methods to identify women with probable anxiety or depression during pregnancy: (1) an outpatient *International Classification of Diseases, Ninth Revision* (*ICD*-9) diagnosis (i.e., 293.84; 296.2–296.3; 296.82; 300.00–300.02; 300.09; 309.0–309.2; 311; 648.4, see Table A.2 for details); (2) an *ICD*-9 diagnosis for anxiety or depression that accompanied a medication order; or (3) a medication order for an anxiolytic or antidepressant (see Table A.3 for the list of medications). We defined anxiety or depression "during pregnancy" as meeting criteria (1), (2), or (3) between the date of conception until 3 days prior to delivery, the last 3 days of pregnancy excluded because anxiety or depression during these days could have been related to delivery. From criterion (3) we excluded women with a same-day diagnosis of tobacco use disorder, alcohol use or withdrawal, seizures or epilepsy, or fibromyalgia, conditions for which anxiolytics and antidepressants are also used (n = 168). We determined *a priori* that we would exclude women with more serious mental illnesses–i.e., schizophrenia or severe bipolar disorder–but no women had such diagnoses. The median (IQR) time under observation prior to conception was 1,735 days (301, 2,964), although 10% of women did not have a pre-conception healthcare visit. After excluding 1,669 women (17.8%) with probable anxiety or depression prior to conception, our final analytic sample included 7,715 mothers and 8,371 unique pregnancies (Figure A.1), of which 1,022 pregnancies (12.2%) met criteria 1, 2, or 3 for probable anxiety or depression during pregnancy (see Table A.4 for counts by criteria).

2.3 Outcomes: preterm birth and term birth weight

Geisinger clinicians determined gestational age based on patient-reported last menstrual period and 20-week ultrasound. In a prior analysis in the Geisinger population, we observed relationships between UNGD activity and preterm birth (< 37 weeks gestational age) and term (≥ 37 weeks) birth weight (Casey et al. 2016), and therefore evaluated these two variables as our outcomes of interest. While our original study included 9,384 mothers linked to 10,946 neonates, in the present study we limited our primary analysis to mothers without a diagnosis of or medication for anxiety or depression prior to conception, which brought our final sample size to 7,715 mothers linked to 8,371 neonates.

2.4 Exposure: Unconventional natural gas development

We obtained data on UNGD locations and times from the Pennsylvania Department of Environmental Protection, the Pennsylvania Department of Conservation and Natural Resources, the U.S. Department of Agriculture (aerial photographs), and SkyTruth (Shepherdstown, WV, skytruth.org). Based on well location, well-specific dates of well pad development, drilling, hydraulic fracturing, and production, and total well depth and volume of natural gas produced, we estimated weekly UNGD activity metrics using an inverse distance-squared method (Casey et al. 2016; Koehler et al. 2018; Rasmussen et al. 2016):

$$\text{Phase-specific metric for mother } j = \sum_{t=t}^{d} \sum_{i=1}^{n} \frac{s_i}{m_{ij}^2},$$

where t was the date of conception, d was the date of the indication of anxiety or depression minus 1 week or the child's date of birth for women without identified anxiety or depression, n was the number of wells in the given phase, m_{ij}^2 was the squared-distance in meters between well i and the home address for mother j, and s_i was 1 for well pad development and drilling phases, total well depth in meters of well i for the stimulation phase, and daily gas production volume in cubic-meters for well i during the production phase. We z-transformed the activity metrics for each phase of development and summed them to create a composite UNGD activity metric. The programming for the stochastic mediation method we used currently requires a binary exposure variable (Rudolph et al. 2017). Therefore, for analysis, we defined exposure to UNGD as living in the highest quartile of UNGD activity during pregnancy. Mothers in the highest quartile had, on average, 130 wells within 20km of their home, compared to 10 wells for mothers in quartiles 1–3.

2.5 Covariates

From the electronic health record, we extracted multiple *a priori* identified potential exposure-mediator, mediator-outcome, and exposure-outcome confounding variables: maternal age at delivery (mean-centered and squared); race/ethnicity (indicator variables for non-Hispanic Black and Hispanic mothers); Geisinger primary care provider status; smoking status during pregnancy (ever vs. never); pre-pregnancy body mass index based on Centers for Disease Control and Prevention z-score for mothers < 20 years of age and kg/m^2 otherwise (under-weight: z-score ≤ 2 SD below mean or < 18.5 kg/m^2; normal: z-score within 1 SD of mean or 18.5–24.9 kg/m^2; overweight: z-score 1–2 SD above mean or 25–29.9 kg/m^2; or obese: z score > 2 SD above mean or ≥30kg/m^2); parity (indicator for nulliparous); receipt of an antibiotic order during pregnancy (yes vs. no); receipt of Medical Assistance during pregnancy (yes vs. no), an income-based program used as a surrogate for low family SES (Casey et al. 2018a); season and year of conception; and gestational age (centered and squared for term birth weight models). Similarly, we included potential area-level confounding variables: distance to nearest major road in meters (quartiles) (Casey et al. 2016); community socioeconomic deprivation (quartiles) assigned based on each mother's community of residence at the time of birth (Liu et al. 2012); mean residential greenness within 1.25 km of mothers' homes during the 3 seasons prior to delivery based on satellite imagery (Solano et al. 2010); residential well water use (yes vs. no, assigned using Pennsylvania Department of Environmental Protection public water service areas); and decline in community-level housing value (yes vs. no). We calculated the latter using data from the 5-year American Community Surveys from 2005–2009, 2006–2010, 2007–2011, 2008–2012, 2009–2013, and 2010–2014. We defined trend in change in median housing value in each mother's community as positive (gained value) or negative (lost value) by subtracting values in two consecutive surveys. For example, for mothers who gave birth in 2013, we defined the trend by subtracting median housing value in 2009–2013 survey from

the 2010–2014 survey. We discuss two mediator-outcome confounders, receipt of an antibiotic order and change in housing value, in more detail in Methods A.1.

2.6 Overview of the mediation analysis

We aimed to investigate relationships between exposure to the highest quartile of UNGD activity (A), antenatal anxiety or depression (M), and preterm birth (Y_1) and reduced term birth weight (Y_2) (Figure 1). Mediation methods can allow one to consider the direct effect of $A \rightarrow Y$, not through M, as well as the indirect effect of A on Y operating through M (i.e., $A \rightarrow M \rightarrow Y$).

We estimated stochastic direct and indirect effects (Rudolph et al. 2017), which rely on contrasts of potential outcomes or counterfactual scenarios (Rubin 2005). Since each study participant received just one level of a binary exposure, we only observed one potential outcome in the data. To calculate stochastic direct and indirect effects, we estimated alternative potential outcomes by assigning mothers counterfactual values of the mediator that we drew from a distribution that corresponded to the exposure scenario of interest and the strata of covariates (Rudolph et al. 2017; VanderWeele and Tchetgen Tchetgen 2017). The stochastic direct effect provided an estimate of the population average of the difference in individual-level adverse birth outcomes contrasting if the mother was exposed to UNGD or not and in each case allowing her antenatal anxiety/depression status to be drawn from a distribution of antenatal anxiety/depression status among non-exposed mothers, conditional on baseline covariates. The stochastic indirect effect provided an estimate of the population average of the difference in individual-level adverse birth outcomes setting the mother exposed to UNGD and contrasting her antenatal anxiety/depression status from a distribution conditional on her being exposed versus unexposed, conditional on baseline covariates. For additional details, see Supplemental Methods A.1.

2.7 Statistical analysis

We used targeted maximum likelihood estimation (TMLE) to estimate the association between (1) UNGD activity and preterm birth and term birth weight; (2) UNGD activity and antenatal anxiety/depression; and (3) antenatal anxiety/depression and preterm birth and term birth weight. TMLE is a doubly robust substitution estimator that respects the bounds of the parameters of interest and is efficient if all models are correctly specified (Van der Laan and Rose 2011). If there was potential for mediation, based on non-null effects for (2) and (3) (Valeri and VanderWeele 2013), we next estimated stochastic direct and indirect effects using TMLE (Rudolph et al. 2017) (see Methods A.1 for more detail). All models included covariates identified *a priori* based on our conceptual model (Figure 1, and described above) as potential measured confounders of the A—M, M—Y, and A—Y relationships. Finally, we stratified each analysis by receipt Medical Assistance during pregnancy in order to assess differential associations by maternal socioeconomic vulnerability. We estimated parameters on the additive scale because absolute changes in risk may aid interpretation when estimating the impact of potential public health interventions (Vandenbroucke et al. 2007).

We imputed missing values for gestational age (n = 69 [0.8%) and pre-pregnancy body mass index category (n = 536 [6.4%]) generating 30 datasets by multiple imputation (Figure A.2) with chained equations (Buuren and Groothuis-Oudshoorn 2010). Within each imputation, we bootstrapped results 250 times to estimate standard errors while accounting for clustering of mothers within communities (Efron et al. 2001; Efron and Tibshirani 1986). Finally, we computed variance estimates using Rubin's combining rules (Buuren and Groothuis-Oudshoorn 2010; Rubin 2004). We conducted analyses using R version 3.5.1 (R Foundation for Statistical Computing).

2.7.1 Sensitivity analyses—We completed two sensitivity analyses related to anxiety or depression status. First, we explored receipt of a selective serotonin reuptake inhibitor (SSRI) during pregnancy as the mediator given prior evidence suggesting an association between SSRI use and preterm birth (Eke et al. 2016; Sujan et al. 2017). This relationship may operate through more severe depression or dysfunctional serotonin signaling. Second, while the main analysis excluded women with pre-pregnancy anxiety or depression we hypothesized that these women might have been particularly vulnerable to UNGD activity and thus we evaluated the overall effect (UNGD activity on preterm birth and term birth weight) among these women. We also restricted analyses to first births during the study period to eliminate within-woman correlation across multiple births.

3. RESULTS

3.1 Study population characteristics

The analysis included 7,715 mothers and 8,371 births that took place at Geisinger between January 2009–January 2013 (Table 1). Most women (n = 7,037, 91.9%) gave birth once during the study period, while 665 (7.9%) had two children, and 13 (0.2%) had three. In total, 49% of infants were girls. Median maternal age at delivery was 28 years (IQR: 23–32 years). One thousand twenty-two mothers (12.2%) had probable anxiety or depression during pregnancy. We observed a much higher prevalence of anxiety or depression among women receiving Medical Assistance during pregnancy vs. not (17.8% vs. 7.9%). Among mothers with probable antenatal anxiety or depression (vs. not), we observed a slightly higher unadjusted prevalence of preterm birth (11.3% vs. 10.6%) and lower unadjusted term birth weights (median = 3262 g [IQR = 2910–3608] vs. 3334 g [2978–3672]).

UNGD grew rapidly in Pennsylvania between 2009–2013, with production volume increasing annually and public interest, as measured by Google searches for "fracking," accelerating through 2013 (Figure A.3). During the study period, developers drilled 2,980 unconventional wells across 12 of the 31 counties that the majority (99%) of mothers resided in (Figure A.4). Exposed (highest quartile of UNGD activity) mothers lived a median distance of 11.2 km (IQR: 4.0, 18.0) from the nearest UNGD well, compared to 24.0 km (IQR: 17.0, 40.7) among mothers living in UNGD activity quartiles 1–3.

3.2 Effect of Exposure on Outcome

We first estimated the total effect of living in the highest quartile of UNGD activity on preterm birth and term birth weight. In adjusted models, comparing the scenario where all

pregnant women lived in the 4th quartile to the 1st-3rd, we found 4.3 additional preterm births per 100 women (95% CI: 1.1, 7.5), with very similar total effects for women receiving and not receiving Medical Assistance (Table A.5, Figure A.5). For term birth weight, we found no overall association. Babies born to mothers receiving Medical Assistance, however, weighed less, on average, −28g (95% CI: −76, 20) comparing the scenario where all pregnant women lived in the 4th vs. the 1st-3rd quartile of UNGD activity.

3.3 Effect of Exposure on Mediator

We estimated the adjusted association between UNGD activity and antenatal anxiety or depression. There were 4.3 additional cases of antenatal anxiety or depression per 100 women (95% CI: 1.5, 7.0) under the scenario where all mothers lived in the 4th quartile of UNGD activity versus all mothers lived in quartiles 1–3 (Figure 2 and Table A.6). The effect estimate was larger for mothers who received Medical Assistance during pregnancy compared to those who did not (RD = 5.6 per 100, 95% CI: 0.5, 10.6; vs. RD = 2.9, 95% CI: −0.7, 6.5). Descriptively, we also observed increasing prevalence of antenatal anxiety or depression across quartiles of UNGD activity: quartile 1 = 9.6%; quartile 2 = 10.9%; quartile 3 = 13.3%; and quartile 4 = 15.0%.

3.4 Effect of Mediator on Outcome

Next, we estimated the adjusted association between the mediator (i.e., antenatal anxiety or depression) and preterm birth and term birth weight. In overall models, we saw no association between antenatal anxiety or depression and adverse birth outcomes (Figure 3 and Table A7). Among mothers who received Medical Assistance versus not, we observed an indication of a protective association between antenatal anxiety or depression and preterm birth (RD = −1.5, 95% CI: −4.4, 1.5) and term birth weight (41 g, 95% CI: −5, 89).

3.5 Mediation analyses

Given the absence of association between the mediator and outcome in overall models, we focused on mediation analyses among those who did and did not receive Medical Assistance. We report results for overall models in the appendix (Figure A.5 and Table A.8). In adjusted analyses, we estimated the direct and indirect effects of living in the highest quartile of UNGD activity on preterm birth and term birth weight through antenatal anxiety or depression, among those who received Medical Assistance. As anticipated, given the weak association between the mediator and outcome, we found null indirect effect estimates (Figure 4 and Table A.8). This meant that antenatal anxiety or depression did not appear to be on the causal pathway between UNGD activity and preterm birth or reduced term birth weight, even among mothers who received Medical Assistance. Mothers who received Medical Assistance during pregnancy had a larger estimated direct effect (Figure 4 and Table A.8), 4.5 additional preterm births per 100 deliveries (95% CI: −0.9, 9.8), than mothers who did not receive Medical Assistance (RD = 1.2, 95% CI: −2.5, 4.9). The direct effect of the highest quartile of UNGD activity on term birth weight appeared protective for mothers who did not receive Medical Assistance and harmful for mothers who did receive Medical Assistance, but confidence intervals were wide (Figure 4 and Table A.8).

3.6 Sensitivity analyses

When we altered the definition of antenatal anxiety or depression to require the receipt of a SSRI order during pregnancy, we still observed no indirect effect between antenatal anxiety or depression and adverse birth outcomes (Figure A.6, Table A.9). Women who received and did not receive Medical Assistance had similar direct effects when we considered receipt of an SSRI as the mediator. We estimated direct effects of 4.4 additional preterm births per 100 deliveries (95% CI: 0.4, 8.5) and 4.2 additional preterm births per 100 deliveries (95% CI: 0, 8.4) among pregnant women receiving and not receiving Medical Assistance, respectively. When we assessed the association between UNGD activity and preterm birth and term birth weight among mothers with pre-existing anxiety or depression prior to conception (n = 2,125), we found no evidence of an association with either birth outcome and confidence intervals were very wide (Table A.10). In models restricted to first births during the study period (n = 7715), we observed comparable total, direct, and indirect effect estimates overall (Table A.11). The relationship between UNGD activity and antenatal anxiety or depression also appeared similar, if slightly stronger, in models restricted to first study period births (Table A.12).

4. DISCUSSION

In this retrospective cohort study, we used mediation analyses to evaluate a possible pathway that might explain a previously observed relationship between UNGD activity and preterm birth and reduced term birth weight among 7,715 mothers at Geisinger in Pennsylvania (Casey et al. 2016). Our findings revealed an association between living in the highest quartile of a cumulative metric of UNGD activity during pregnancy and increased risk of antenatal anxiety or depression. This increased risk, however, did not appear to mediate the observed association between UNGD activity and preterm birth or reduced term birth weight, as we found no relationship between antenatal anxiety or depression and these outcomes in our sample. For both preterm birth and term birth weight, we observed stronger direct effects of UNGD on adverse birth outcomes among mothers who received Medical Assistance during pregnancy. Sensitivity analyses restricted to first births during the study period showed comparable overall associations. In addition, the association between UNGD and antenatal anxiety or depression was slightly stronger for first pregnancies in the study period. Evidence regarding the association of parity and risk of antenatal depression and anxiety remains unclear and this relationship may also be influenced by past pregnancy delivery complications (Biaggi et al. 2016).

Our study indicates that maternal mental health, measured as antenatal anxiety or depression, did not act as a mediator of the relationship between UNGD activity and adverse birth outcomes. These results contrast with prior studies of community-level exposures that found that psychological distress mediated the relationship between acute environmental stressors (i.e., earthquake or ice storm) (Dancause et al. 2011; Torche 2011) and perceived adverse neighborhood conditions (Giurgescu et al. 2017) and preterm birth. Other studies, however, are consistent with our results. After Hurricane Katrina, Xiong et al. (2008) found an association between hurricane exposure and preterm birth, but also a lower prevalence of preterm birth among mothers with post-traumatic stress disorder.

In contrast to the substantial literature that reports risk factors for postpartum depression (O'hara and Swain 1996) and evaluates the association between maternal mental health and offspring health and development (Ding et al. 2014; Field 2011), relatively few epidemiologic studies have considered maternal stress, anxiety, or depression during pregnancy as an important endpoint alone. Positive neighborhood attributes like residential greenspace may be protective for pregnant women's mental health (McEachan et al. 2016), while neighborhood quality (Giurgescu et al. 2015) and nuisances like discarded furniture and construction debris (Messer et al. 2013) have been associated with higher Center for Epidemiological Studies-Depression (CES-D) scores. UNGD may likewise act as a community-level stressor that could lead to anxiety or depression. We found 4.3 additional cases of anxiety or depression per 100 pregnant women under the scenario that everyone lived in the highest quartile of UNGD activity vs. quartiles 1–3 and the risk difference reached 5.6 additional cases per 100 among women receiving Medical Assistance. The uncertain nature of small boom-bust cycles in UNGD activity related to fluctuations in natural gas prices may lead to stress (Fisher et al. 2018; Jacquet and Kay 2014). While UNGD in Pennsylvania may create jobs (Maniloff and Mastromonaco 2017; Paredes et al. 2015), this employment may be contract, temporary, and/or precarious (Sangaramoorthy et al. 2016). Individuals have reported other concerns, including destruction of the natural environment (Israel et al. 2015; Lai et al. 2017; Sangaramoorthy et al. 2016; Thomas et al. 2017), damage to way of life or community character (Evensen and Stedman 2018; Willow et al. 2014), increased traffic (Evensen and Stedman 2018; Fisher et al. 2018; Whitworth et al. 2017a), changing housing markets and prospect of moving away (Fisher et al. 2018; Jacquet et al. 2018), and worry about their own and their children's health (McDermott-Levy and Garcia 2016; McHenry 2017). Individuals have reported feeling lack of control over their environment (Jacquet et al. 2018) and over their ability to keep their children safe (Willow et al. 2014). Such perceived lack of control has been tied to anxiety and depression, with evidence that low control and low SES holds the highest risk (Griffin et al. 2002). Consistent with this theory, we found the greatest risk of anxiety or depression among low SES mothers living in the highest quartile of UNGD activity.

Prior studies have measured maternal mental health in a variety of ways: scales designed to capture objective and subjective reports of prenatal maternal stress (Dancause et al. 2011; Giurgescu et al. 2017; Kramer et al. 2009) and the Beck Depression Inventory and CES-D scores for depression (Brittain et al. 2015; Kramer et al. 2009). We used clinical diagnostic codes and medication orders from electronic health records of Geisinger patients to identify women with probable antenatal anxiety or depression. The different measures of maternal mental health across studies may explain the heterogeneity in findings related to mediating effects of antenatal mental health between acute and chronic community-level stressors and birth outcomes.

An individual's perception or opinion of UNGD likely affects their psychological response to this activity (Lai et al. 2017; McEvoy et al. 2017). For example, in Colorado, the true distance between an individual's home and UNGD did not predict risk perception, but individuals who perceived UNGD as located too close to their home reported lower quality of life (Mayer 2016). Conversely, some studies have found a PIMBY ("please in my backyard") effect where residents closer to UNGD reported increased support for such

activity (Dokshin 2016). In England, individuals who perceived UNGD as damaging to resources reported negative emotions, in contrast to those who felt they gained resources as a result of UNGD, who reported positive emotions (Lai et al. 2017). We could not assess these perceptual pathways as we lacked information on participants' feelings, opinions, beliefs, political leanings, and financial stakes in UNGD. Prior studies have found perceptual measures of neighborhood safety (Thayer 2017) and physical and social disorder (Giurgescu et al. 2017) were more strongly associated with maternal mental health outcomes than objective biologic or geographic measures. No studies have cataloged pregnant women's perception of UNGD; however, women tend to hold more negative views of UNGD than men (Boudet et al. 2014; Mayer 2016). Pregnant women may also judge environmental exposures as riskier than non-pregnant women (Marie et al. 2016), potentially exacerbating worries about the safety of UNGD in their community.

Cultural products, news, and social media may have influenced Pennsylvanian's psychological response to UNGD. For example, Josh Fox's documentary *Gasland*–showing Pennsylvanians in UNGD regions lighting the water from their household faucets on fire–premiered at Sundance in 2010 and received an Oscar nomination in 2011 (Mazur 2016). Twitter discourse related to "#fracking," calling for bans, and discussing water contamination issues (Hopke and Simis 2017) grew dramatically after *Gasland*'s nomination (Vasi et al. 2015). Similarly, in the wake of the 2011 Deepwater Horizon spill, the *New York Times* released a 10-part "Drilling Down" series, with headlines such as, "A Tainted Water Well, and Concern There May Be More," and "Insiders Sound an Alarm Amid a Natural Gas Rush" (Mazur 2016). This high-profile public debate regarding unconventional oil and natural gas extraction activities (Habib and Hinojosa 2017; Hopke and Simis 2017; Vasi et al. 2015), coupled with unsettled science about their health effects, and the lack of coherent public health messages, likely fueled broader uncertainty and concern about the safety of living near UNGD. During early Marcellus UNGD, community members sought to address the paucity of health data on UNGD (McDermott-Levy and Garcia 2016; Vasi et al. 2015) through "citizen science" projects, participatory mapping efforts, investigative reporting, and anti-fracking advocacy groups (Jacquet et al. 2018). Such efforts have filled key gaps on UNGD locations and potential community exposures but also likely shaped public perceptions of and concerns about UNGD activity.

Finally, while pregnant women in our study had a median of 14 prenatal visits, we likely underestimated the true prevalence of antenatal anxiety or depression as we only captured conditions explicitly recorded in the electronic medical record. The American College of Obstetricians and Gynecologists recommends postnatal, but not antenatal, screening for depression and anxiety (American College of Obstetricians and Gynecologists 2018). Gaps also exist between the proportion of women meeting definitions of anxiety or depressive disorders during pregnancy and those receiving diagnoses and treatment (Andersson et al. 2003; Goodman and Tyer-Viola 2010). Because common physical responses to pregnancy, like fatigue or trouble sleeping, overlap with symptoms of anxiety or depression, clinicians may have difficulty diagnosing these disorders during the antenatal period (Goodman and Tyer-Viola 2010). Pregnant women report fear of discussing mental health with their providers, stigma, cost of care, and hesitance to take pharmaceuticals during pregnancy as barriers to seeking care for mental health issues (Biaggi et al. 2016; Ko et al. 2012). While a

recent meta-analysis found associations between antidepressant medication use during pregnancy and several adverse birth outcomes (Ross et al. 2013), the authors cautioned that any treatment decisions should weigh the cost of untreated depression against the potential adverse effects of pharmaceuticals. We cannot know if the women in our study who received medication orders for antidepressants or anxiolytics actually took the medication.

4.1 Limitations

We observed an association between UNGD activity and antenatal anxiety and depression. While we hypothesized this relationship operated through psychosocial stress, it is possible that there are other more relevant factors for understanding the association between UNGD and mental health outcomes. For example, some recent studies report associations between air pollution and adverse mental health (Buoli et al. 2018), including among pregnant women (Sheffield et al. 2018). Our distance-based exposure metric precludes differentiating between multiple UNGD-related exposures, for example, psychosocial stress and air pollution. We attempted to assess a pathway operating through mental health in the association between UNGD and adverse birth outcomes, but future research could examine other potential mediators like air quality, noise, and light pollution. Timing of an environmental stressor may matter for maternal mental health and birth outcomes (Glynn et al. 2001) and while our exposure metric was time-varying, we were unable to assess the effects of trimester-specific exposures. Whitworth and colleagues (2018) recently examined trimester-specific and phase-specific associations between UNGD and risk of preterm birth in Texas, finding the strongest associations with exposures in the first and second trimesters. While we stratified analyses by receipt of Medical Assistance, an indicator of low family income, research suggests that risk factors for and vulnerability to poor antenatal mental health may differ by race/ethnicity (Biaggi et al. 2016; Mukherjee et al. 2016). However, the racially and ethnically homogenous composition of our study population precluded an assessment of racial/ethnic-specific associations. There may also have been differential patterns by maternal SES in participants articulating and providers diagnosing antenatal anxiety or depression that we could not assess. We observed an indication of an unexpected protective association between antenatal anxiety and depression and adverse birth outcomes among mothers receiving Medical Assistance. It is possible that the receipt of a mental health diagnosis or medication order indicated a closer patient-practitioner relationship, which may have supported improved birth outcomes. We only had access to maternal residential address at the time of delivery because Geisinger has not retained historical addresses. However, a prior analysis of the Geisinger patient population (Casey et al. 2016) showed fairly high residential stability with 80% of patients not moving over a 3-year period and of the 20% of movers, only 20% moved more than 16km from their original address. We excluded patients when their address only geocoded to the ZIP code centroid. This may have biased our results towards the null as rural addresses are less likely to geocode (McElroy et al. 2003), more UNGD takes place in rural communities, and, in our sample, the ZIP code centroid-only group had a higher prevalence of preterm birth (14%) compared to the included study population (11%).

Our UNGD activity measure integrated several elements, including distance from and number of wells, well phase and attributes of phase intensity: well depth for the stimulation

phase and production volume during the production phase. Nevertheless, this exposure assessment approach may have also led to heterogeneity within each exposure quartile and potential exposure misclassification; for example, mothers living within 1 kilometer from 2 wells with high production volume and mothers living within 10 kilometers from 10 wells with much lower production volume could both potentially be grouped within the same exposure quartile. In addition, we could not distinguish which environmental impacts associated with UNGD (e.g., well distance, production volume, noise and air pollution, light at night, increased truck traffic volume) might be the most important determinants of adverse birth outcomes. Despite this limitation, our UNGD activity measure provided a holistic and time-varying approach to characterizing prenatal exposures, considering exposure to the multiple phases of well development.

The mediation analyses in this study rely on several assumptions, including no unmeasured exposure-outcome confounding, no unmeasured exposure-mediator confounding, and no unmeasured mediator-outcome confounding (Rudolph et al. 2017). While our analysis controlled for many individual and area-level confounders, residual confounding may have remained, biasing our findings. Other assumptions for causal inference include positivity and the stable unit treatment value assumption (SUTVA). We evaluated positivity in the data and found no evidence of violations. SUTVA requires that one community's level of UNGD activity does not affect potential outcomes in another community. There may have been violations to this assumption if UNGD activity in one community increased traffic, air pollution, or other hazards in an adjacent community, which potentially could affect birth outcomes. SUTVA also requires a single version of the treatment (here, UNGD activity). We likely violated this assumption since mothers could arrive in the highest quartile of UNGD activity in many ways (e.g., one large well very nearby or many wells farther away).

4.2 Strengths

Although a growing number of studies report an association between UNGD activity and adverse birth outcomes, to our knowledge, this is the first study to use mediation analysis to elucidate potential pathways and mechanisms of effect. Our analytic approach toward evaluating the mediating effect of antenatal depression and anxiety on the association between UNGD activity and adverse birth outcomes allowed for the estimation of both direct and indirect pathways and for inclusion of post-exposure mediator-outcome confounders (Rudolph et al. 2017; VanderWeele and Tchetgen Tchetgen 2017). The inability to deal with such confounders is a limitation of other mediation methods.

This study also leveraged a rich source of electronic health record data that included assessing antenatal mental health outcomes with diagnostic codes, medications, birth outcome information and other key measures. To handle missing data, we conducted multiple imputation and applied a clustered bootstrap approach to derive standard errors in order to account for potential correlations among women living in the same communities.

5. CONCLUSION

In this retrospective cohort study of pregnant women in Pennsylvania, we applied novel mediation analyses to evaluate an antenatal mental health pathway that might have explained

the association between UNGD activity and adverse birth outcomes. Although our analysis suggested an association between living in proximity to more productive UNGD activity and an increased risk of antenatal anxiety and depression, this increased risk did not appear to mediate the association between UNGD and preterm birth or reduced term birth weight. Future research that integrates placed-based measures of UNGD intensity with individual-level perceptual measures of such activities, and improved capture of antenatal mental health status may better elucidate the extent to which psychological pathways mediate the relationship between UNGD and birth outcomes. Future work should also examine other potential mediators associated with UNGD activities such as air quality, noise, and light pollution. A better understanding of these mediating pathways can inform efforts to address any potential adverse effects of UNGD activity on vulnerable populations, such as pregnant women and their neonates.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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HIGHLIGHTS

- Unconventional natural gas development has been linked to adverse birth outcomes
- No studies have considered the role of antenatal mental health
- Unconventional natural gas development was associated with antenatal anxiety or depression
- This association did not mediate the original exposure-birth outcome relationship

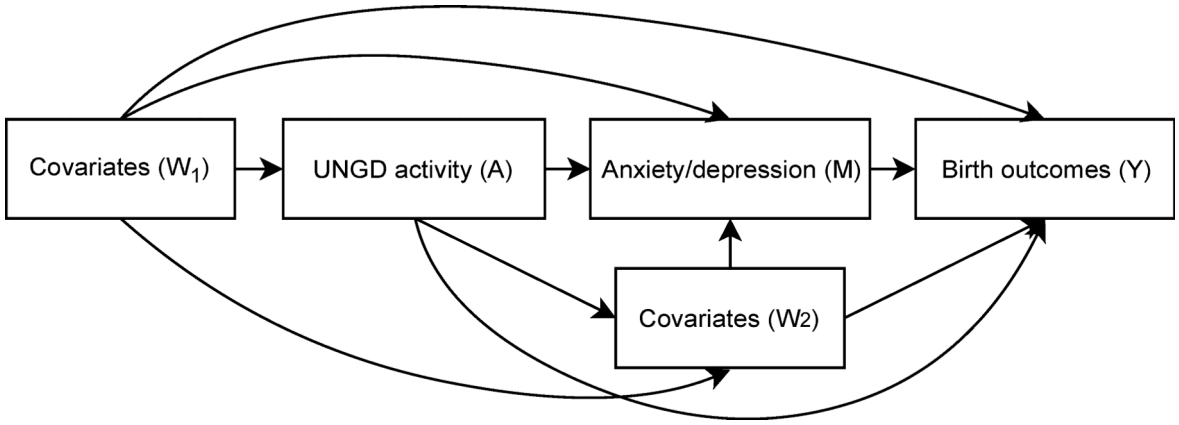

Figure 1:

Conceptual framework of a structural causal model of mediation of the relationship between unconventional natural gas development activity (A) and adverse birth outcomes by antenatal anxiety or depression during pregnancy. Antenatal anxiety or depression (M) was defined by a diagnosis of anxiety or depression or receipt of a medication used to treat anxiety or depression recorded in the Geisinger electronic health record during pregnancy. We evaluated two adverse birth outcomes (Y): preterm birth (< 37 weeks gestational age) and term (≥ 37 weeks) birth weight. In final models, W_1 included maternal age, race/ethnicity, Geisinger primary care provider status, smoking status during pregnancy, pre-pregnancy body mass index, parity, receipt of Medical Assistance during pregnancy, season and year of conception, distance to nearest major road, community socioeconomic deprivation, residential greenness and well water use, and, for birth weight models, gestational age. W_2 included receipt of an antibiotic order during pregnancy and decline in community-level housing value.

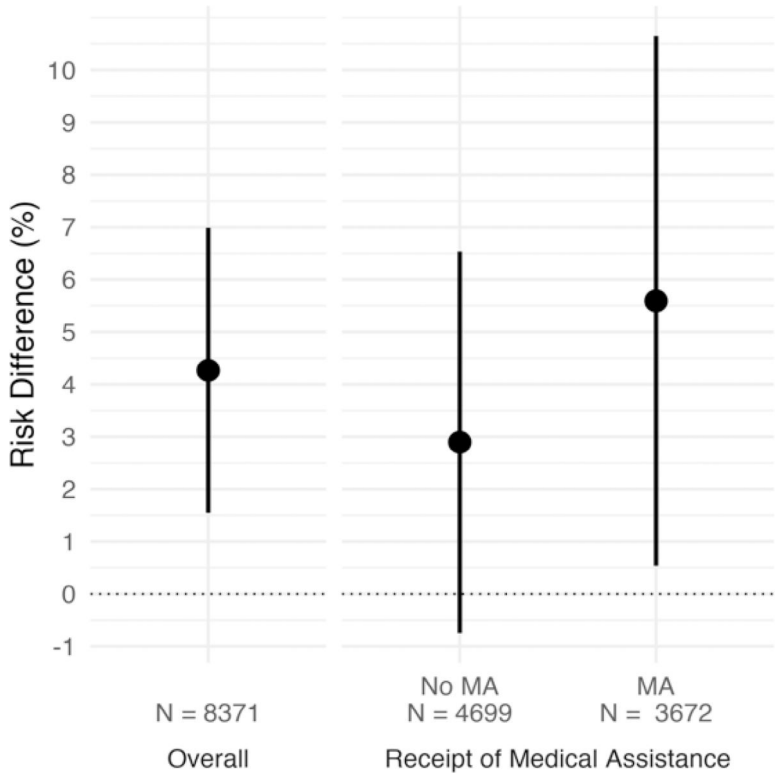

Figure 2:

Adjusted risk difference effect estimates and 95% confidence intervals of living in the highest quartile of UNGD activity on antenatal anxiety or depression overall and stratified by receipt of Medical Assistance during pregnancy, in Pennsylvania, January 2009–January 2013. We accounted for clustering of mothers in communities by bootstrapping results 250 times to estimate standard errors. Overall models were adjusted for maternal age at time of delivery (meancentered and mean-centered and squared terms), maternal race/ethnicity, season of conception and delivery, delivery hospital, primary care patient status, smoking status, parity, pre-pregnancy body mass index, receipt of Medical Assistance, antibiotic order during pregnancy, change in housing value, mean residential greenness during pregnancy, drinking water source, community socioeconomic deprivation quartile, and distance to nearest major road quartile.

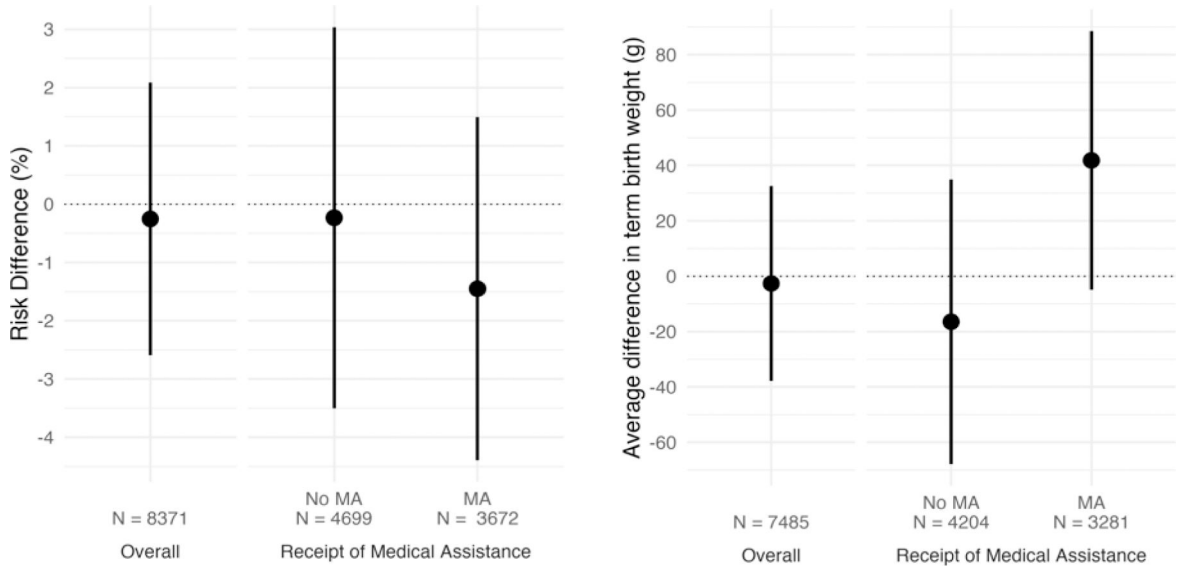

Figure 3:

Adjusted risk difference and mean difference effect estimates and 95% confidence intervals of the association between antenatal anxiety or depression and (A) preterm birth and (B) term birth weight, overall and stratified by receipt of Medical Assistance during pregnancy, in Pennsylvania, January 2009–January 2013. We accounted for clustering of mothers in communities by bootstrapping results 250 times to estimate standard errors. Overall models were adjusted for maternal age at time of delivery (mean-centered and mean-centered and squared terms), maternal race/ethnicity, season of conception and delivery, delivery hospital, primary care patient status, smoking status, parity, pre-pregnancy body mass index, receipt of Medical Assistance, antibiotic order during pregnancy, change in housing value, mean residential greenness during pregnancy, drinking water source, community socioeconomic deprivation quartile, and distance to nearest major road quartile.

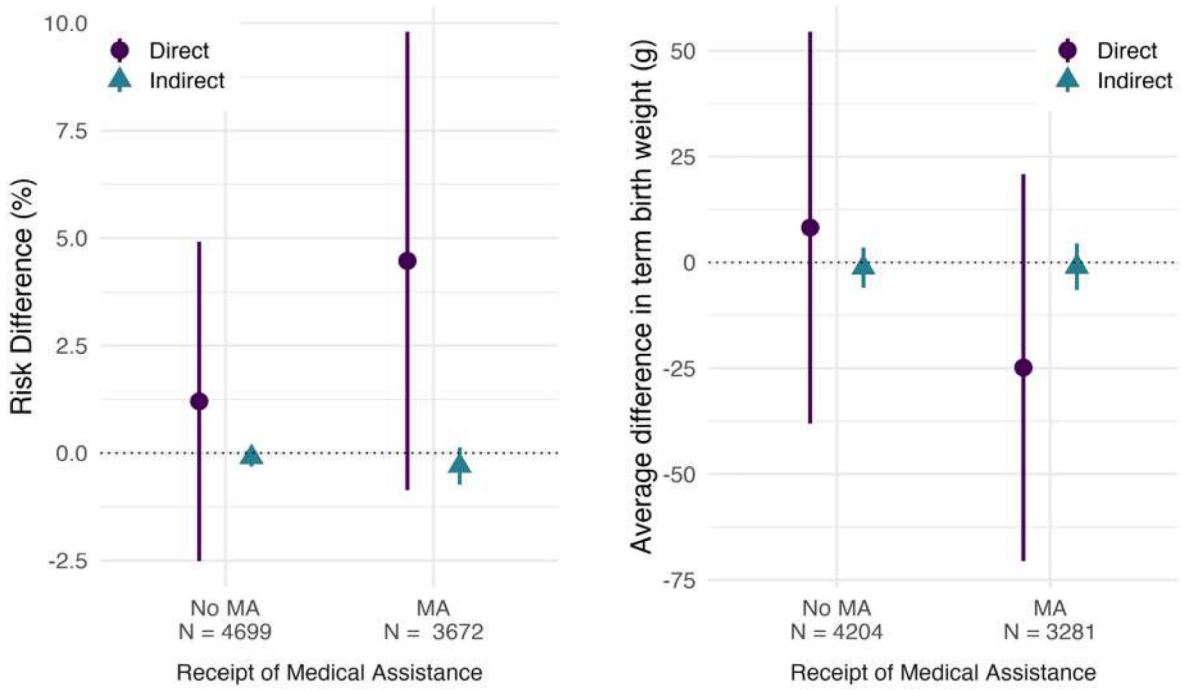

Figure 4:

Direct and indirect effect estimates and 95% confidence intervals considering antenatal anxiety or depression as the mediator of the relationship between unconventional natural gas development and (A) preterm birth and (B) term birth weight, stratified by receipt of Medical Assistance during pregnancy, in Pennsylvania, January 2009–January 2013. We accounted for clustering of mothers in communities by bootstrapping results 250 times to estimate standard errors. Models were adjusted for maternal age at time of delivery (mean-centered and mean-centered and squared terms), maternal race/ethnicity, season of conception and delivery, delivery hospital, primary care patient status, smoking status, parity, pre-pregnancy body mass index, antibiotic order during pregnancy, change in housing value, mean residential greenness during pregnancy, drinking water source, community socioeconomic deprivation quartile, and distance to nearest major road quartile. Term birth weight models additionally adjusted for gestational age (mean-centered and mean-centered and squared terms).

Table 1:

Distribution of study population characteristics among 7715 mothers without pre-pregnancy anxiety or depression and their 8371 neonates by UNGD activity quartile

	Overall cohort	UNGD activity quartile[a]	
	Total	1–3	4
N (%)	8371 (100)	6279 (75)	2092 (25)
Maternal characteristics			
Age at delivery, years, mean (SD)	27.7 (5.8)	27.7 (5.8)	27.8 (5.9)
Race/ethnicity, N (%)			
White	7323 (87)	5417 (86)	1906 (91)
Black	347 (4)	282 (4)	65 (3)
Hispanic	525 (6)	446 (7)	79 (4)
Other	139 (2)	102 (2)	37 (2)
Missing	37 (<1)	32 (<1)	5 (<1)
Season of conception, N (%)			
December-February	1972 (24)	1382 (22)	590 (28)
March-May	2071 (25)	1629 (26)	442 (21)
June-August	2212 (26)	1686 (27)	526 (25)
September-November	2116 (25)	1582 (25)	534 (26)
Primary care patient, %	3435 (41)	2579 (41)	856 (41)
Smoking status[b], %			
Never	4089 (49)	3019 (48)	1070 (51)
Former	1727 (21)	1306 (21)	421 (20)
Current	1341 (16)	1018 (16)	323 (15)
Conflicting or missing	1214 (15)	936 (15)	278 (13)
Pre-pregnancy body-mass index (kg/m^2), %			
<18.5	175 (2)	132 (2)	43 (2)
18.5–24.9	3107 (37)	2345 (37)	762 (36)
25–29.9	2260 (27)	1679 (27)	581 (28)
≥30	2293 (27)	1733 (28)	560 (27)
Missing[c]	536 (6)	390 (6)	146 (7)
Nulliparous, N (%)	3934 (47)	3296 (48)	2983 (45)
Pre-pregnancy healthcare visits, mean (SD)	14.5 (18.7)	14.3 (18.5)	15.0 (19.5)
Prenatal healthcare visits, mean (SD)	13.4 (6.5)	13.5 (6.5)	13.1 (6.6)
Antibiotic order during pregnancy, N (%)	2714 (32)	1970 (31)	743 (36)
Receipt of Medical Assistance, N (%)	3672 (44)	2743 (44)	929 (44)
Delivery hospital, N (%)			
Geisinger Medical Center	5638 (51)	3256 (52)	980 (47)
Geisinger Wyoming Valley	4858 (49)	3023 (48)	1112 (53)

	Overall cohort	UNGD activity quartile[a]	
	Total	1–3	4
Anxiety or depression during pregnancy, N (%)			
Yes	1022 (12)	708 (11)	314 (15)
Yes, via outpatient or medication diagnosis only	858 (10)	605 (10)	253 (12)
Yes, via SSRI	404 (5)	295 (5)	109 (5)
Distance to nearest major road, km, mean (SD)	2.8 (4.5)	2.2 (3.5)	4.7 (6.4)
Drinking water source, %			
Municipal water	5846 (70)	4649 (74)	1197 (57)
Well water	2525 (30)	1630 (26)	895 (43)
Community socioeconomic deprivation[d], %			
Quartile 1–least deprived	2129 (25)	1544 (25)	585 (28)
Quartile 2	2034 (25)	1417 (23)	617 (28)
Quartile 3	2128 (25)	1585 (25)	543 (26)
Quartile 4–most deprived	2080 (25)	1733 (27)	347 (17)
Change in community-level housing value (value in year of birth – value in year prior), N (%)			
Increase	4012 (48)	3034 (48)	978 (47)
Decrease	4359 (52)	3245 (52)	1114 (53)
Residential greenness, NDVI index, mean (SD)	0.54 (0.10)	0.53 (0.10)	0.55 (0.11)
Infant Characteristics			
Male, %	4256 (51)	3192 (51)	1064 (51)
Gestational age			
Weeks, mean (SD)	38.9 (2.3)	39.0 (2.2)	38.8 (2.3)
Missing,[c] N (%)	69 (1)	66 (1)	3 (1)
Preterm birth <37 weeks, N (%)	888 (11)	647 (10)	241 (12)
Term birth weight, grams, mean (SD)	3398 (462)	3399 (462)	3395 (463)
Birth year, %			
2009	1969 (24)	1923 (31)	46 (2)
2010	2051 (25)	1798 (29)	253 (12)
2011	2091 (25)	1615 (25)	476 (23)
2012	2122 (25)	906 (14)	1216 (58)
2013	138 (2)	37 (1)	101 (5)

Abbreviations: EHR, electronic health record; IQR, interquartile range; NDVI, normalized difference vegetation index; SSRI, selective serotonin reuptake inhibitors; UNGD, unconventional natural gas development.

[a]Quartiles 1–3: −0.62 to 0.18; Quartile 4: 0.18 to 142.57. UNGD activity quartile was assigned based on 4 z-transformed indicators using inverse-distance squared models that incorporated distance to the mother's home; dates and durations of the phases (well pad development, spudding, hydraulic fracturing, and production); and well characteristics (depth and production volume) during gestation, and is in standard deviation units. Percentages are rounded to whole numbers.

[b]Smoking status was reported during pregnancy in the EHR social history and problem list.

[c]Missing values were imputed using multiple imputation with chained equations (30 datasets)

[d]Community socioeconomic deprivation was assigned at the township, borough, or census tract level, based on 6 indicators derived from the U.S. Census American Community Survey 2012 5-year estimates: combined less than high school education, not in the labor force, in poverty, on public assistance, civilian unemployment, and does not own a car; a higher score represents a more deprived community.