Accepted Manuscript

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

Joan A. Casey, Dana E. Goin, Kara E. Rudolph, Brian S. Schwartz, Dione Mercer, Holly Elser, Ellen A. Eisen, Rachel Morello-Frosch

PII: S0013-9351(19)30395-0

DOI: https://doi.org/10.1016/j.envres.2019.108598

Article Number: 108598

Reference: YENRS 108598

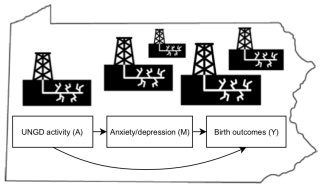
To appear in: *Environmental Research*

Received Date: 18 March 2019

Revised Date: 18 July 2019

Accepted Date: 19 July 2019

Please cite this article as: Casey, J.A., Goin, D.E., Rudolph, K.E., Schwartz, B.S., Mercer, D., Elser, H., Eisen, E.A., Morello-Frosch, R., Unconventional natural gas development and adverse birth outcomes in Pennsylvania: The potential mediating role of antenatal anxiety and depression, *Environmental Research* (2019), doi: https://doi.org/10.1016/j.envres.2019.108598.



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], 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

Corresponding author: Joan A. Casey

jac2250@columbia.edu

722 W 168th St, RM 1206

New York NY 10032-327

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.

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.

KEYWORDS

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

Acknowledgements: This project was funded, in part, through a National Institute of Environmental Health Sciences grant K99ES027023 to J.A.C., a National Institute on Drug Abuse R00DA042127 to K.E.R., and a National Institutes of Health Environmental Influences on Child Health Outcomes (ECHO) Program UG3 OD023272, a UH3 OD023272, and a National Institute of Environmental Health Sciences grant P42ES04705 to R.M.F.

The authors declare they have no actual or potential competing financial interests. Dr. Brian Schwartz has served as an informal advisor to the Post Carbon Institute (PCI). He has received no payment for this role and his research is entirely independent of PCI, and is not motivated, reviewed, or funded by PCI.

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

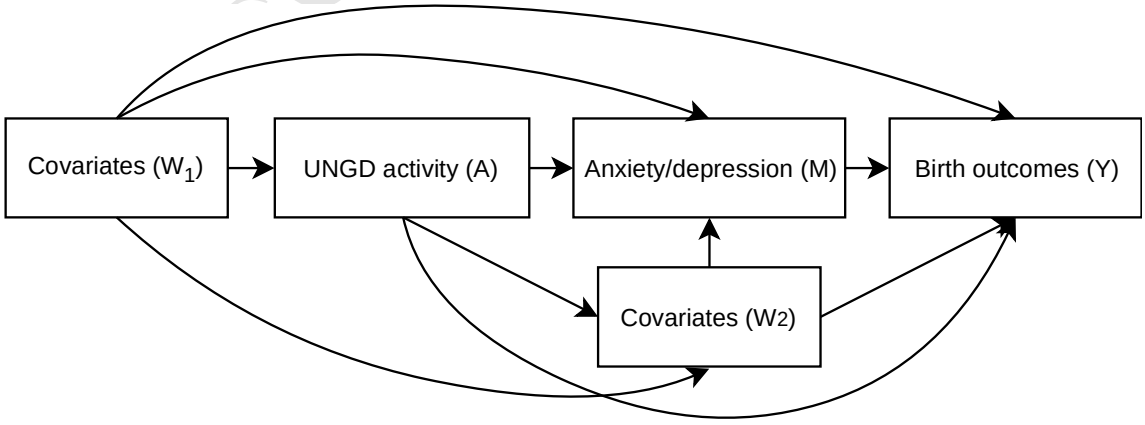
From the electronic health record, we extracted multiple *a priori* identified potential exposure-mediator, mediator-outcome, and exposure-outcome confounding variables: maternal age at delivery (mean-centered and squared); race/ethnicity (indicator variables for non-Hispanic Black and Hispanic mothers); 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 $\leq$ 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,

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.



as well as the indirect effect of *A* on *Y* operating through *M* (i.e., *A* → *M* → *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 estimated the relationship between UNGD activity and antenatal anxiety or depression among nulliparous women to test for differences by birth order.

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 4^{th} quartile to the 1^{st}-3^{rd}, 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 4^{th} vs. the 1^{st}-3^{rd} 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%.

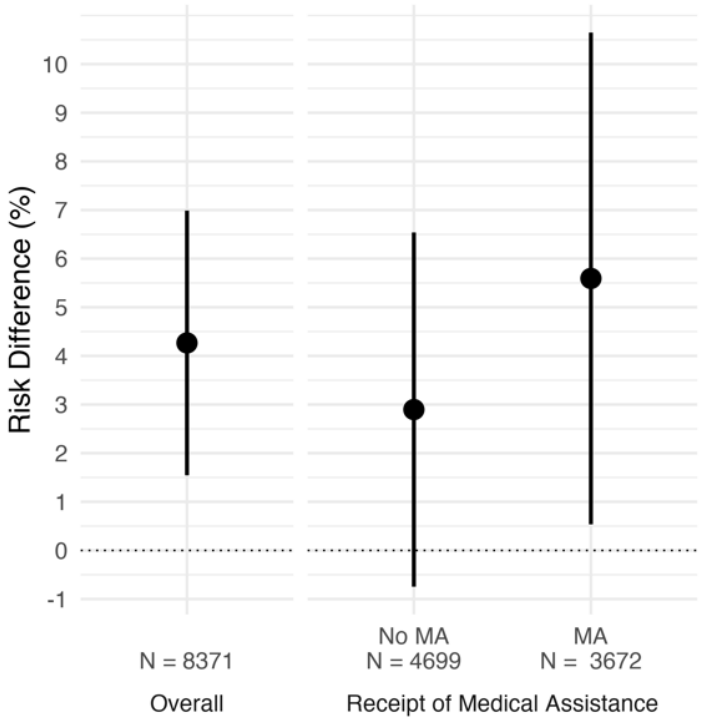


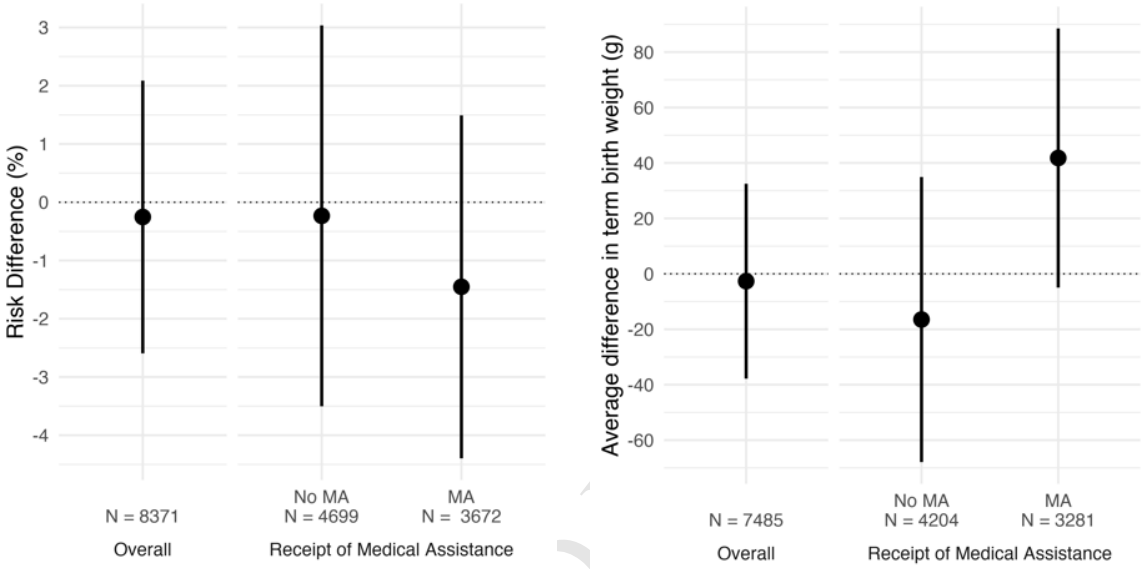
Figure 2: Adjusted risk difference effect estimates and 95% confidence intervals of living in the highest quartile of UNGD activity on antenatal anxiety or depression overall and stratified by receipt of Medical Assistance during pregnancy, in Pennsylvania, January 2009–January 2013. We accounted for 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 (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.

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

313 antenatal anxiety or depression and adverse birth outcomes (**Figure 3 and Table A7**). Among mothers
314 who received Medical Assistance versus not, we observed an indication of a protective association
315 between antenatal anxiety or depression and preterm birth (RD = -1.5, 95% CI: -4.4, 1.5) and term birth
316 weight (41 g, 95% CI: -5, 89).

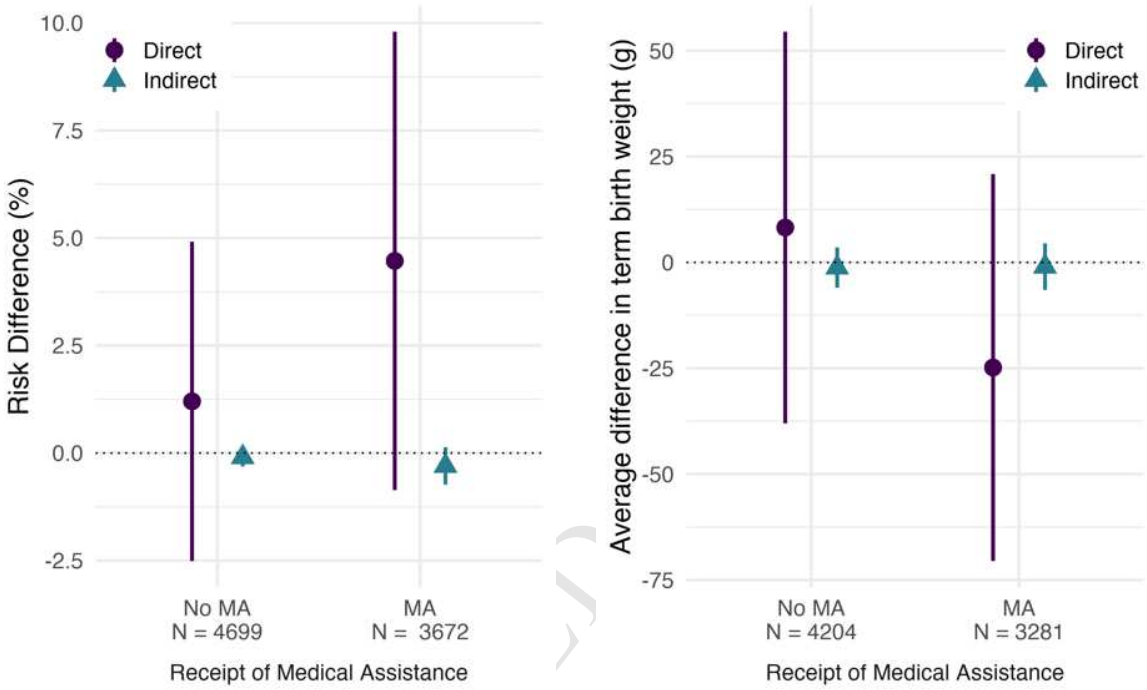
Figure 3: Adjusted risk difference and mean difference effect estimates and 95% confidence intervals of the association between antenatal anxiety or depression and (A) preterm birth and (B) term birth weight, overall and stratified by receipt of Medical Assistance during pregnancy, in Pennsylvania, January 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.



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

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).



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 nulliparous women showed comparable overall

associations. In addition, we found that nulliparous women had a lower prevalence of antenatal anxiety or depression compared to multiparous women. 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.

REFERENCES

Adgate JL, Goldstein BD, McKenzie LM. 2014. Potential public health hazards, exposures and health effects from unconventional natural gas development. Environ Sci Technol 48(15):8307-8320. 10.1021/es404621d.

American College of Obstetricians and Gynecologists. 2018. ACOG Committee Opinion No. 757. Screening for perinatal depression. Obstet Gynecol(132):e208-212.

Andersson L, Sundström-Poromaa I, Bixo M, Wulff M, Bondestam K, Åström M. 2003. Point prevalence of psychiatric disorders during the second trimester of pregnancy: a population-based study. Am J Obstet Gynecol 189(1):148-154.

Anthopolos R, Kaufman JS, Messer LC, Miranda ML. 2014. Racial residential segregation and preterm birth: built environment as a mediator. Epidemiology 25(3):397-405.

Balise VD, Meng C-X, Cornelius-Green JN, Kassotis CD, Kennedy R, Nagel SC. 2016. Systematic review of the association between oil and natural gas extraction processes and human reproduction. Fertil Steril 106(4):795-819.

Basner M, McGuire S. 2018. WHO environmental noise guidelines for the European region: a systematic review on environmental noise and effects on sleep. Int J Environ Res Public Health 15(3). 10.3390/ijerph15030519.

Bennett HA, Einarson A, Taddio A, Koren G, Einarson TR. 2004. Prevalence of depression during pregnancy: systematic review. Obstet Gynecol 103(4):698-709. 10.1097/01.AOG.0000116689.75396.5f.

Biaggi A, Conroy S, Pawlby S, Pariante CM. 2016. Identifying the women at risk of antenatal anxiety and depression: a systematic review. J Affect Disord 191:62-77.

Boudet H, Clarke C, Bugden D, Maibach E, Roser-Renouf C, Leiserowitz A. 2014. "Fracking" controversy and communication: Using national survey data to understand public perceptions of hydraulic fracturing. Energ Policy 65:57-67.

561 Brittain K, Myer L, Koen N, Koopowitz S, Donald KA, Barnett W, et al. 2015. Risk factors for antenatal
562 depression and associations with infant birth outcomes: results From a South African birth cohort study.
563 Paediatr Perinat Epidemiol 29(6):505-514. 10.1111/ppe.12216.
564 Buoli M, Grassi S, Caldiroli A, Carnevali GS, Mucci F, Iodice S, et al. 2018. Is there a link between air
565 pollution and mental disorders? Environ Int 118:154-168.
566 Buuren Sv, Groothuis-Oudshoorn K. 2010. mice: Multivariate imputation by chained equations in R. J
567 Stat Softw:1-68.
568 Casey JA, Pollak J, Glymour MM, Mayeda ER, Hirsch AG, Schwartz BS. 2018a. Measures of SES for
569 electronic health record-based research. Am J Prev Med 54(3):430-439. 10.1016/j.amepre.2017.10.004.
570 Casey JA, Savitz DA, Rasmussen SG, Ogburn EL, Pollak J, Mercer DG, et al. 2016. Unconventional natural
571 gas development and birth outcomes in Pennsylvania, USA. Epidemiology 27(2):163-172.
572 10.1097/EDE.0000000000000387.
573 Casey JA, Wilcox HC, Hirsch AG, Pollak J, Schwartz BS. 2018b. Associations of unconventional natural gas
574 development with depression symptoms and disordered sleep in Pennsylvania. Sci Rep 8(1):11375.
575 10.1038/s41598-018-29747-2.
576 Clark C, Paunovic K. 2018. WHO environmental noise guidelines for the European region: A systematic
577 review on environmental noise and quality of life, wellbeing and mental health. Int J Environ Res Public
578 Health 15(11). 10.3390/ijerph15112400.
579 Currie J, Greenstone M, Meckel K. 2017. Hydraulic fracturing and infant health: New evidence from
580 Pennsylvania. Sci Adv 3(12):e1603021.
581 Cushing L, Morello-Frosch R, Wander M, Pastor M. 2015. The haves, the have-nots, and the health of
582 everyone: the relationship between social inequality and environmental quality. Annu Rev Public Health
583 36:193-209. 10.1146/annurev-publhealth-031914-122646.

584 Dancause KN, Laplante DP, Oremus C, Fraser S, Brunet A, King S. 2011. Disaster-related prenatal
585 maternal stress influences birth outcomes: project Ice Storm. Early Hum Dev 87(12):813-820.
586 10.1016/j.earlhumdev.2011.06.007.
587 Dennis CL, Falah-Hassani K, Shiri R. 2017. Prevalence of antenatal and postnatal anxiety: systematic
588 review and meta-analysis. Br J Psychiatry 210(5):315-323. 10.1192/bjp.bp.116.187179.
589 Ding XX, Wu YL, Xu SJ, Zhu RP, Jia XM, Zhang SF, et al. 2014. Maternal anxiety during pregnancy and
590 adverse birth outcomes: a systematic review and meta-analysis of prospective cohort studies. J Affect
591 Disord 159:103-110. 10.1016/j.jad.2014.02.027.
592 Dokshin FA. 2016. Whose backyard and what's at issue? Spatial and ideological dynamics of local
593 opposition to fracking in New York state, 2010 to 2013. Am Sociol Rev 81(5):921-948.
594 10.1177/0003122416663929.
595 Dunkel Schetter C. 2011. Psychological science on pregnancy: stress processes, biopsychosocial models,
596 and emerging research issues. Annu Rev Psychol 62(1):531-558. 10.1146/annurev.psych.031809.130727.
597 Efron B, Rogosa D, Tibshirani R. 2001. Resampling methods of estimation. In: International Encyclopedia
598 of the Social & Behavioral Sciences, Vol. 11. Amsterdam.
599 Efron B, Tibshirani R. 1986. Bootstrap methods for standard errors, confidence intervals, and other
600 measures of statistical accuracy. Stat Sci 1(1):54-75.
601 Eke A, Saccone G, Berghella V. 2016. Selective serotonin reuptake inhibitor (SSRI) use during pregnancy
602 and risk of preterm birth: a systematic review and meta-analysis. BJOG 123(12):1900-1907.
603 Elliott EG, Ettinger AS, Leaderer BP, Bracken MB, Deziel NC. 2017. A systematic evaluation of chemicals
604 in hydraulic-fracturing fluids and wastewater for reproductive and developmental toxicity. J Expo Sci
605 Environ Epidemiol 27(1):90-99. 10.1038/jes.2015.81.
606 Evensen D, Stedman R. 2018. Fracking': Promoter and destroyer of 'the good life. J Rural Stud 59:142-
607 152.

608 Ferguson KK, Chen Y-H, VanderWeele TJ, McElrath TF, Meeker JD, Mukherjee B. 2016. Mediation of the
609 relationship between maternal phthalate exposure and preterm birth by oxidative stress with repeated
610 measurements across pregnancy. Environ Health Perspect 125(3):488-494.
611 Ferrar KJ, Kriesky J, Christen CL, Marshall LP, Malone SL, Sharma RK, et al. 2013. Assessment and
612 longitudinal analysis of health impacts and stressors perceived to result from unconventional shale gas
613 development in the Marcellus Shale region. Int J Occup Environ Health 19(2):104-112.
614 10.1179/2049396713Y.0000000024.
615 Feyrer J, Mansur ET, Sacerdote B. 2017. Geographic dispersion of economic shocks: Evidence from the
616 fracking revolution. Am Econ Rev 107(4):1313-1334.
617 Field T. 2011. Prenatal depression effects on early development: A review. Infant Behav Dev 34(1):1-14.
618 https://doi.org/10.1016/j.infbeh.2010.09.008.
619 Finkel ML, Hays J. 2015. Environmental and health impacts of 'fracking': why epidemiological studies are
620 necessary. J Epidemiol Community Health:jech-2015-205487.
621 Fisher MP, Mayer A, Vollet K, Hill EL, Haynes EN. 2018. Psychosocial implications of unconventional
622 natural gas development: Quality of life in Ohio's Guernsey and Noble Counties. J Environ Psychol 55:90-
623 98. https://doi.org/10.1016/j.jenvp.2017.12.008.
624 Flynn J, Slovic P, Mertz CK. 1994. Gender, race, and perception of environmental health risks. Risk Anal
625 14(6):1101-1108.
626 Giurgescu C, Zenk SN, Templin TN, Engeland CG, Dancy BL, Park CG, et al. 2015. The impact of
627 neighborhood environment, social support, and avoidance coping on depressive symptoms of pregnant
628 African-American women. Womens Health Issues 25(3):294-302. 10.1016/j.whi.2015.02.001.
629 Giurgescu C, Zenk SN, Templin TN, Engeland CG, Kavanaugh K, Misra DP. 2017. The impact of
630 neighborhood conditions and psychological distress on preterm birth in African-American women. Public
631 Health Nurs 34(3):256-266. 10.1111/phn.12305.

632 Glynn LM, Wadhwa PD, Dunkel-Schetter C, Chicz-DeMet A, Sandman CA. 2001. When stress happens
633 matters: Effects of earthquake timing on stress responsivity in pregnancy. Am J Obstet Gynecol
634 184(4):637-642. 10.1067/mob.2001.111066.
635 Goodman JH, Tyer-Viola L. 2010. Detection, treatment, and referral of perinatal depression and anxiety
636 by obstetrical providers. J Womens Health (Larchmt) 19(3):477-490. 10.1089/jwh.2008.1352.
637 Gray SC, Edwards SE, Schultz BD, Miranda ML. 2014. Assessing the impact of race, social factors and air
638 pollution on birth outcomes: a population-based study. Environ Health 13(1):4. 10.1186/1476-069X-13-
639 4.
640 Griffin JM, Fuhrer R, Stansfeld SA, Marmot M. 2002. The importance of low control at work and home on
641 depression and anxiety: do these effects vary by gender and social class? Soc Sci Med 54(5):783-798.
642 Habib S, Hinojosa MS. 2017. Representation of fracking in mainstream American newspapers. Environ
643 Pract 18(2):83-93. 10.1017/s1466046616000089.
644 Hayase M, Shimada M, Seki H. 2014. Sleep quality and stress in women with pregnancy-induced
645 hypertension and gestational diabetes mellitus. Women and Birth 27(3):190-195.
646 https://doi.org/10.1016/j.wombi.2014.04.002.
647 Hays J, de Melo-Martin I. 2014. Ethical concerns surrounding unconventional oil and gas development
648 and vulnerable populations. Rev Environ Health 29(4):275-276. 10.1515/reveh-2014-0071.
649 Hays J, McCawley M, Shonkoff SBC. 2017. Public health implications of environmental noise associated
650 with unconventional oil and gas development. Sci Total Environ 580:448-456.
651 10.1016/j.scitotenv.2016.11.118.
652 Hill EL. 2018. Shale gas development and infant health: Evidence from Pennsylvania. J Health Econ
653 61:134-150.

654 Hirsch JK, Smalley KB, Selby-Nelson EM, Hamel-Lambert JM, Rosmann MR, Barnes TA, et al. 2018.
655 Psychosocial impact of fracking: a review of the literature on the mental health consequences of
656 hydraulic fracturing. Int J Ment Health Addict 16(1):1-15.
657 Hopke JE, Simis M. 2017. Discourse over a contested technology on Twitter: A case study of hydraulic
658 fracturing. Public Underst Sci 26(1):105-120. 10.1177/0963662515607725.
659 Hou R, Garner M, Holmes C, Osmond C, Teeling J, Lau L, et al. 2017. Peripheral inflammatory cytokines
660 and immune balance in Generalised Anxiety Disorder: Case-controlled study. Brain Behav Immun
661 62:212-218.
662 Howell EL, Li N, Akin H, Scheufele DA, Xenos MA, Brossard D. 2017. How do US state residents form
663 opinions about 'fracking'in social contexts? A multilevel analysis. Energ Policy 106:345-355.
664 Israel AL, Wong-Parodi G, Webler T, Stern PC. 2015. Eliciting public concerns about an emerging energy
665 technology: The case of unconventional shale gas development in the United States. Energy Res Soc Sci
666 8:139-150.
667 Jacquet J, Kay DL. 2014. The Unconventional Boomtown: Updating the impact model to fit new spatial
668 and temporal scales. J Rural Stud 9(1).
669 Jacquet JB, Junod AN, Bugden D, Wildermuth G, Fergen JT, Jalbert K, et al. 2018. A decade of Marcellus
670 Shale: Impacts to people, policy, and culture from 2008 to 2018 in the Greater Mid-Atlantic region of the
671 United States. Extr Ind Soc 5(4):596-609. 10.1016/j.exis.2018.06.006.
672 Janitz AE, Dao HD, Campbell JE, Stoner JA, Peck JD. 2019. The association between natural gas well
673 activity and specific congenital anomalies in Oklahoma, 1997-2009. Environ Int 122:381-388.
674 10.1016/j.envint.2018.12.011.
675 Kearney MS, Wilson R. 2018. Male earnings, marriageable men, and nonmarital fertility: Evidence from
676 the fracking boom. Rev Econ Stat 100(4):678-690.

677 Ko JY, Farr SL, Dietz PM, Robbins CL. 2012. Depression and treatment among U.S. pregnant and
678 nonpregnant women of reproductive age, 2005–2009. J Womens Health 21(8):830-836.
679 10.1089/jwh.2011.3466.
680 Koehler K, Ellis JH, Casey JA, Manthos D, Bandeen-Roche K, Platt R, et al. 2018. Exposure assessment
681 using secondary data sources in unconventional natural gas development and health studies. Environ Sci
682 Technol 52(10):6061-6069. 10.1021/acs.est.8b00507.
683 Kramer MS, Lydon J, Seguin L, Goulet L, Kahn SR, McNamara H, et al. 2009. Stress pathways to
684 spontaneous preterm birth: the role of stressors, psychological distress, and stress hormones. Am J
685 Epidemiol 169(11):1319-1326. 10.1093/aje/kwp061.
686 Lai P-H, Lyons KD, Gudergan SP, Grimstad S. 2017. Understanding the psychological impact of
687 unconventional gas developments in affected communities. Energ Policy 101:492-501.
688 Liu AY, Curriero FC, Glass TA, Stewart WF, Schwartz BS. 2012. Associations of the burden of coal
689 abandoned mine lands with three dimensions of community context in Pennsylvania. ISRN Public Health
690 2012:1-11. 10.5402/2012/251201.
691 Maniloff P, Mastromonaco R. 2017. The local employment impacts of fracking: A national study. Resour
692 Energy Econ 49:62-85. https://doi.org/10.1016/j.reseneeco.2017.04.005.
693 Marie C, Cabut S, Vendittelli F, Sauvant-Rochat M-P. 2016. Changes in cosmetics use during pregnancy
694 and risk perception by women. Int J Environ Res Publ Health 13(4):383.
695 Mayer A. 2016. Risk and benefits in a fracking boom: Evidence from Colorado. Extr Ind Soc 3(3):744-753.
696 Mazur A. 2016. How did the fracking controversy emerge in the period 2010-2012? Public Underst Sci
697 25(2):207-222. 10.1177/0963662514545311.
698 McDermott-Levy R, Garcia V. 2016. Health concerns of northeastern Pennsylvania residents living in an
699 unconventional oil and gas development county. Public Health Nurs 33(6):502-510.

McEachan R, Prady S, Smith G, Fairley L, Cabieses B, Gidlow C, et al. 2016. The association between green space and depressive symptoms in pregnant women: moderating roles of socioeconomic status and physical activity. J Epidemiol Community Health 70(3):253-259.

McElroy JA, Remington PL, Trentham-Dietz A, Robert SA, Newcomb PA. 2003. Geocoding addresses from a large population-based study: lessons learned. Epidemiology 14(4):399-407.

McEvoy J, Gilbertz SJ, Anderson MB, Ormerod KJ, Bergmann NT. 2017. Cultural theory of risk as a heuristic for understanding perceptions of oil and gas development in Eastern Montana, USA. Extr Ind Soc 4(4):852-859. https://doi.org/10.1016/j.exis.2017.10.004.

McHenry KA. 2017. Fracking women: A feminist critical analysis of hydraulic fracturing in Pennsylvania. Int J Fem Approaches Bioeth 10(2):79-104.

McKenzie LM, Crooks J, Peel JL, Blair BD, Brindley S, Allshouse WB, et al. 2019. Relationships between indicators of cardiovascular disease and intensity of oil and natural gas activity in Northeastern Colorado. Environ Res 170:56-64.

McKenzie LM, Guo R, Witter RZ, Savitz DA, Newman LS, Adgate JL. 2014. Birth outcomes and maternal residential proximity to natural gas development in rural Colorado. Environ Health Perspect 122(4):412-417. 10.1289/ehp.1306722.

Messer LC, Maxson P, Miranda ML. 2013. The urban built environment and associations with women's psychosocial health. J Urban Health 90(5):857-871.

Mukherjee S, Trepka MJ, Pierre-Victor D, Bahelah R, Avent T. 2016. Racial/ethnic disparities in antenatal depression in the United States: A systematic review. Matern Child Health J 20(9):1780-1797. 10.1007/s10995-016-1989-x.

O'hara MW, Swain AM. 1996. Rates and risk of postpartum depression—a meta-analysis. Int Rev Psychiatry 8(1):37-54.

723 Paredes D, Komarek T, Loveridge S. 2015. Income and employment effects of shale gas extraction
724 windfalls: Evidence from the Marcellus region. Energy Economics 47:112-120.
725 http://dx.doi.org/10.1016/j.eneco.2014.09.025.
726 Perry SL. 2013. Using ethnography to monitor the community health implications of onshore
727 unconventional oil and gas developments: examples from Pennsylvania's Marcellus Shale. New Solut
728 23(1):33-53. 10.2190/NS.23.1.d.
729 Petersen I, McCrea RL, Lupattelli A, Nordeng H. 2015. Women's perception of risks of adverse fetal
730 pregnancy outcomes: a large-scale multinational survey. BMJ Open 5(6):e007390. 10.1136/bmjopen-
731 2014-007390.
732 Rahman ML, Valeri L, Kile ML, Mazumdar M, Mostofa G, Qamruzzaman Q, et al. 2017. Investigating
733 causal relation between prenatal arsenic exposure and birthweight: Are smaller infants more
734 susceptible? Environ Int 108:32-40.
735 Rasmussen SG, Ogburn EL, McCormack M, Casey JA, Bandeen-Roche K, Mercer DG, et al. 2016.
736 Association between unconventional natural gas development in the Marcellus Shale and asthma
737 exacerbations. JAMA Intern Med 176(9):1334-1343. 10.1001/jamainternmed.2016.2436.
738 Ross LE, Grigoriadis S, Mamisashvili L, VonderPorten EH, Roerecke M, Rehm J, et al. 2013. Selected
739 pregnancy and delivery outcomes after exposure to antidepressant medication: A systematic review and
740 meta-analysis. JAMA Psychiatry 70(4):436-443. 10.1001/jamapsychiatry.2013.684.
741 Rubin DB. 2005. Causal inference using potential outcomes: Design, modeling, decisions. J Am Stat Assoc
742 100(469):322-331.
743 Rubin DB. 2004. Multiple imputation for nonresponse in surveys: John Wiley & Sons.
744 Rudolph KE, Sofrygin O, Zheng W, van der Laan MJ. 2017. Robust and flexible estimation of stochastic
745 mediation effects: a proposed method and example in a randomized trial setting. Epi Methods.

Sangaramoorthy T, Jamison AM, Boyle MD, Payne-Sturges DC, Sapkota A, Milton DK, et al. 2016. Place-based perceptions of the impacts of fracking along the Marcellus Shale. Soc Sci Med 151:27-37. 10.1016/j.socscimed.2016.01.002.

Schwartz BS, Stewart WF, Godby S, Pollak J, DeWalle J, Larson S, et al. 2011. Body mass index and the built and social environments in children and adolescents using electronic health records. Am J Prev Med 41(4):e17-e28. Doi 10.1016/J.Amepre.2011.06.038.

Sealy-Jefferson S, Giurgescu C, Helmkamp L, Misra DP, Osypuk TL. 2015. Perceived physical and social residential environment and preterm delivery in African-American women. Am J Epidemiol 182(6):485-493. 10.1093/aje/kwv106.

Sheffield PE, Speranza R, Chiu Y-HM, Hsu H-HL, Curtin PC, Renzetti S, et al. 2018. Association between particulate air pollution exposure during pregnancy and postpartum maternal psychological functioning. Plos One 13(4):e0195267.

Silva TJ, Crowe JA. 2015. The hope-reality gap: rural community officials' perceptions of unconventional shale development as a means to increase local population and revitalize resource extraction. Community Dev 46(4):312-328.

Solano R, Didan K, Jacobson A, Huete A. 2010. MODIS vegetation index user's guide (MOD13 Series) version 2.00. Tucson: the University of Arizona. Available: http://vip.arizona.edu/documents/MODIS/MODIS_VI_UsersGuide_01_2012.pdf [accessed 2014 Jan 7].

Stacy SL, Brink LL, Larkin JC, Sadovsky Y, Goldstein BD, Pitt BR, et al. 2015. Perinatal outcomes and unconventional natural gas operations in Southwest Pennsylvania. Plos One 10(6):e0126425. 10.1371/journal.pone.0126425.

Staneva A, Bogossian F, Pritchard M, Wittkowski A. 2015. The effects of maternal depression, anxiety, and perceived stress during pregnancy on preterm birth: A systematic review. Women and Birth 10.1016/j.wombi.2015.02.003. 10.1016/j.wombi.2015.02.003.

770 Sujan AC, Rickert ME, Öberg A, et al. 2017. Associations of maternal antidepressant use during the first
771 trimester of pregnancy with preterm birth, small for gestational age, autism spectrum disorder, and
772 attention-deficit/hyperactivity disorder in offspring. JAMA 317(15):1553-1562. 10.1001/jama.2017.3413.
773 Sygna K, Aasvang GM, Aamodt G, Oftedal B, Krog NH. 2014. Road traffic noise, sleep and mental health.
774 Environ Res 131:17-24. 10.1016/j.envres.2014.02.010.
775 Thayer ZM. 2017. Dark shadow of the long white cloud: neighborhood safety is associated with self-
776 rated health and cortisol during pregnancy in Auckland, Aotearoa/New Zealand. SSM Popul Health 3:75-
777 80.
778 Thomas M, Partridge T, Harthorn BH, Pidgeon N. 2017. Deliberating the perceived risks, benefits, and
779 societal implications of shale gas and oil extraction by hydraulic fracturing in the US and UK. Nat Energy
780 2(5). 10.1038/nenergy.2017.54.
781 Torche F. 2011. The effect of maternal stress on birth outcomes: exploiting a natural experiment.
782 Demography 48(4):1473-1491. 10.1007/s13524-011-0054-z.
783 Tustin AW, Hirsch AG, Rasmussen SG, Casey JA, Bandeen-Roche K, Schwartz BS. 2017. Associations
784 between unconventional natural gas development and nasal and sinus, migraine headache, and fatigue
785 symptoms in Pennsylvania. Environ Health Perspect 125(2):189-197. 10.1289/EHP281.
786 U.S. Energy Information Administration. 2019. U.S. Crude Oil and Natural Gas Proved Reserves, Year-end
787 2017. Available: https://www.eia.gov/naturalgas/crudeoilreserves/ accessed [16 Jan 2019].
788 Valeri L, VanderWeele TJ. 2013. Mediation analysis allowing for exposure–mediator interactions and
789 causal interpretation: theoretical assumptions and implementation with SAS and SPSS macros. Psychol
790 Methods 18(2):137.
791 Van der Laan MJ, Rose S. 2011. Targeted learning: causal inference for observational and experimental
792 data: Springer Science & Business Media.

793 Vandenbroucke JP, von Elm E, Altman DG, Gotzsche PC, Mulrow CD, Pocock SJ, et al. 2007.
794 Strengthening the Reporting of Observational Studies in Epidemiology (STROBE): explanation and
795 elaboration. PLoS Med 4(10):e297. 10.1371/journal.pmed.0040297.
796 VanderWeele TJ, Tchetgen Tchetgen EJ. 2017. Mediation analysis with time varying exposures and
797 mediators. J R Stat Soc Series B Stat Methodol 79(3):917-938.
798 Vasi IB, Walker ET, Johnson JS, Tan HF. 2015. “No fracking way!” Documentary film, discursive
799 opportunity, and local opposition against hydraulic fracturing in the United States, 2010 to 2013. Am
800 Sociol Rev 80(5):934-959.
801 Vesterinen HM, Morello-Frosch R, Sen S, Zeise L, Woodruff TJ. 2017. Cumulative effects of prenatal-
802 exposure to exogenous chemicals and psychosocial stress on fetal growth: Systematic-review of the
803 human and animal evidence. Plos One 12(7):e0176331. 10.1371/journal.pone.0176331.
804 Webb E, Bushkin-Bedient S, Cheng A, Kassotis CD, Balise V, Nagel SC. 2014. Developmental and
805 reproductive effects of chemicals associated with unconventional oil and natural gas operations. Rev
806 Environ Health 29(4):307-318. 10.1515/reveh-2014-0057.
807 Whitworth KW, De LaRosa E, Mackay T, Hernandez A, Martin MK, Lopez J, et al. 2017a. Exploring
808 perceptions of fracking and environmental health in a 3-county population in South Texas. J Epidemiol
809 Res 3(1):61.
810 Whitworth KW, Marshall AK, Symanski E. 2018. Drilling and production activity related to
811 unconventional gas development and severity of preterm birth. Environ Health Perspect 126(3).
812 Whitworth KW, Marshall AK, Symanski E. 2017b. Maternal residential proximity to unconventional gas
813 development and perinatal outcomes among a diverse urban population in Texas. Plos One
814 12(7):e0180966. 10.1371/journal.pone.0180966.
815 Willow AJ, Zak R, Vilaplana D, Sheeley D. 2014. The contested landscape of unconventional energy
816 development: a report from Ohio's shale gas country. J Environ Stud Sci 4(1):56-64.

817 Xiong X, Harville EW, Mattison DR, Elkind-Hirsch K, Pridjian G, Buekens P. 2008. Exposure to Hurricane
818 Katrina, post-traumatic stress disorder and birth outcomes. Am J Med Sci 336(2):111-115.
819 10.1097/MAJ.0b013e318180f21c.
820
821

822 **Table 1**: Distribution of study population characteristics among 7715 mothers without pre-pregnancy

823 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)
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)

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

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

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

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

834 [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.

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