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ORIGINAL RESEARCH

Exploring a Potential Interaction Between the Effect of Specific Maternal Smoking Patterns and Comorbid Antenatal Depression in Causing Postpartum Depression

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Purpose: To explore a potential interaction between the effect of specific maternal smoking patterns and the presence of antenatal depression, as independent exposures, in causing postpartum depression (PPD).

Methods: This case–control study of participants with singleton term births (N = 51220) was based on data from the 2017–2018 Pregnancy Risk Assessment Monitoring System. Multivariable log-binomial regression models examined the main effects of smoking patterns and self-reported symptoms of antenatal depression on the risk of PPD on the adjusted risk ratio (aRR) scale and tested a two-way interaction adjusting for covariates selected in a directed acyclic graph (DAG). The interaction effects were measured on the additive scale using relative excess risk due to interaction (RERI), the attributable proportion of interaction (AP), and the synergy index (SI). Causal effects were defined in a counterfactual framework. The E-value quantified the potential impact of unobserved/unknown covariates, conditional on observed covariates.

Results: Among 6841 women in the sample who self-reported PPD, 35.7% also reported symptoms of antenatal depression. Out of 3921 (7.7%) women who reported smoking during pregnancy, 32.6% smoked at high intensity (≥10 cigarettes/day) in all three trimesters and 36.6% had symptoms of antenatal depression. The main effect of PPD was the strongest for women who smoked at high intensity throughout pregnancy (aRR 1.65; 95% CI: 1.63, 1.68). A synergistic interaction was detected, and the effect of all maternal smoking patterns was augmented, particularly in late pregnancy for *Increasers* and *Reducers*.

Conclusion: Strong associations and interaction effects between maternal smoking patterns and co-occurring antenatal depression support smoking prevention and cessation interventions during pregnancy to lower the likelihood of PPD.

Keywords: maternal smoking patterns, antenatal depression, postpartum depression, interaction, directed acyclic graph, DAG

Introduction

Between 7% and 20% of women in the United States with a recent live birth reported symptoms of depression during pregnancy (antenatal depression),[1] and nearly 13% (1 in 7) reported symptoms of depression after giving birth (postpartum depression).[1,2] Moreover, evidence from longitudinal studies indicated that about 40% of women who experience antenatal depression had postpartum depression (PPD) and 47% of those with PPD had antenatal depression.[1–3] Antenatal depression can compromise fetal growth and negatively influence birth outcomes and is one of the strongest risk factors for PPD.[4] PPD can last between two weeks and up to a year and if not detected and not treated it can severely impair maternal functioning, child development, and parenting.[1–5] Research finds a strong association between maternal smoking, antenatal depression and PPD.[1–3,6,7] Despite an overall decline in smoking rates in the US general population from 20.9% in 2005 to 12.5% in

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2020, about 6.5% of women smoked in the last trimester of pregnancy and 8.8% smoked in postpartum.[8] A decline in smoking can be in part because some women switch to e-cigarette use upon recognition of pregnancy.[9] Adverse birth outcomes related to tobacco use during pregnancy are also well documented.[10–12] Pregnancy and postpartum periods increase maternal vulnerability to depression[3] and smoking is over four times more common among pregnant women with depression than without depression.[6,7] Maternal survey data show a substantial variability in smoking patterns during pregnancy and in early postpartum, when women typically change their smoking habit to minimize potential risks.[13,14] Fluctuation in smoking and quitting attempts can trigger symptoms of depression due to acute nicotine withdrawal. Self-medication with smoking helps reduce negative affect.[15,16] Heavy and nonpersistent moderate smokers reported higher level of antenatal depression, compared to light smokers,[13] and were also more likely to have symptoms of PPD.[12,17] However, Mendelian randomization studies did not support causal association between high-intensity smoking and anxiety and depression.[18–20] Antenatal depressive symptoms are as common as symptoms of postnatal depression.[5,21,22] The presence of antenatal depression is considered a predictor of PPD,[5,21] yet, a proportion of women develop PPD regardless of antenatal depression.[23] It is important to identify modifiable risk factors that contribute to PPD, such as smoking, to help develop targeted interventions and protect health of the mothers and families.

Hence, our study interest is to investigate how the joint effect of maternal smoking and antenatal depression, as independent exposures, can potentially influence PPD. Our research question is whether the effect of specific maternal smoking patterns in causing PPD can be amplified in the presence of co-occurring antenatal depression. This is an exploratory study, and we are unaware of any other studies that have investigated these relationships. We utilized a directed acyclic graph (DAG) as a tool to capture relations among variables and to guide regression model specifications on identified potential confounding. Evidence based on significant effect estimates obtained from the statistical models allowed drawing conclusions on causal inference in line with current epidemiological research practices.[24–29]

Materials and Methods

Study Population and Study Design

This case–control study was based on data from the 2017–2018 Pregnancy Risk Assessment Monitoring System (PRAMS).[30,31] The PRAMS is an ongoing state- and population-based survey system designed to monitor behaviors and experiences before, during, and after pregnancy among women in the US who recently (within 2–6 months) gave birth to a liveborn infant.[30,31] Data collected between March 2017 and February 2018 implemented the Phase 8 version of the PRAMS questionnaire with an overall response rate of 61%. Details on the PRAMS survey data collection and sampling design representative of each site's birth population are described elsewhere.[30,31] PRAMS data sets are deidentified and available to researchers upon request. In this retrospective case–control study, data were restricted to participants with live singleton term births (37–41 completed weeks gestation) to ensure a similar duration of exposure to smoking and antenatal depression across pregnancy and to avoid bias. About 14% of data involved one or more missing variables and were deleted, leaving complete-case data for the analyses. (Figure 1).

The Exposure and Outcome Variables

For the purpose of this study, there were two exposures affecting the outcome independently of one another. The primary exposure consisted of six unique and mutually exclusive maternal smoking patterns created based on self-reported variability in smoking intensity in early (first and second trimester) and late (third trimester) pregnancy, as described in a prior study,[14] and included: (1) *Quitters-Low* (1st and 2nd trimester, 1–9 cigarettes/day); (2) *Quitters-High* (1st and 2nd trimester, ≥10 cigarettes/day); (3) *Maintainers-Low* (all trimesters, 1–9 cigarettes/day); (4) *Maintainers-High* (all trimesters, ≥10 cigarettes/day); (5) *Reducers* (1st and 2nd trimester ≥10 cigarettes/day, and 3rd trimester 1–9 cigarettes/day); (6) *Increasers* (1st and 2nd trimester 1–9 cigarettes/day, and 3rd trimester ≥10 cigarettes/day); and (7) *Nonsmokers* (reference). The secondary exposure was antenatal depression status, a dichotomous variable that was self-reported in the PRAMS as "yes" or "no" by asking the following question: "During your most recent pregnancy, did you have depression?"[30]

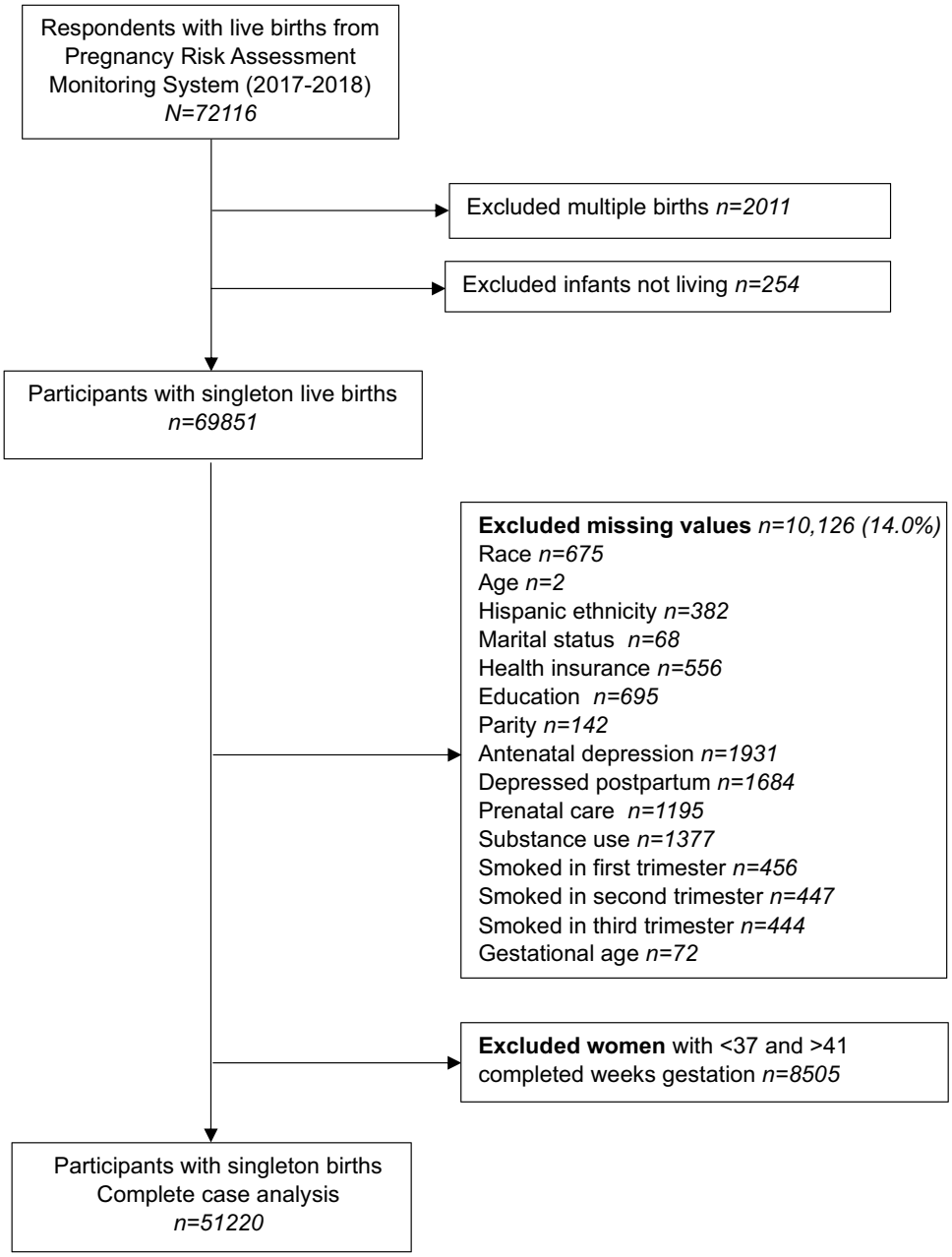

Figure 1 Flow diagram of the study population.

The outcome variable was PPD, a dichotomous variable that was self-reported in the PRAMS as "yes" or "no" using a modified version of the Patient Health Questionnaire-2 (PHQ-2) that consisted of two questions: "Since your new baby was born, have you felt down, depressed, or hopeless?" and since your new baby was born, have you had little interest or little pleasure in doing things? [30] A mother's response was "yes" to both questions.

Covariates

Covariates were selected based on prior research[1–3,5,6] and on availability in the dataset and included race categories (ie, non-Hispanic White, non-Hispanic Black, Asian, American Indian/Alaska Native, Native Hawaiian, Pacific Islander or mixed race) and Hispanic ethnicity, age categories (<20, 20–29, 30–34, and ≥35 years old), educational attainment (high school or less, some college, bachelor's degree or higher), prenatal care (inadequate or adequate/intermediate), marital

status (married, unmarried), health insurance (Medicaid, private insurance, none/self-pay, other), parity (1 or ≥2), smoking and substance use (Yes, No).

Statistical Analysis

SAS software version 9.4 (SAS Institute Inc., Cary, NC, USA) was used in all statistical analyses accounting for the complex sampling design in the PRAMS. Statistical significance was set at α=0.05. The percentages of women who self-reported PPD (cases) and who did not report PPD (controls) were calculated, and the prevalence of each smoking pattern was estimated across maternal sociodemographic characteristics. The DAG approach was utilized to identify potential covariates that were common causes for the exposure and outcome to be used for adjustment in the logistic regression models.[24,26,32] The structure of a DAG provided a graphical representation of the "backdoor" criterion[24] with several paths by which the effect of exposure to smoking during pregnancy and the presence of antenatal depression may be causally related to PPD (Figure 2). We assumed that all essential paths to common effects and common causes, including observed and unobserved/unmeasured confounding, were identified in the DAG to guide statistical model specifications for valid effect estimates. Multivariable log-binomial regression models examined the adjusted risk ratios (aRRs) and their 95% confidence intervals (CIs) for the individual (main) effects of all smoking patterns and the antenatal depression status. Separate regression models tested two-way interaction effects. The interaction effects were assessed on the additive scale using measures of the relative excess risk due to interaction (RERI), the attributable proportion of interaction (AP), and the synergy index (SI).[28,33,34] The RERI was calculated using the formula: [RR11 – RR10 – RR01 + 1], the AP was calculated using the formula: [RERI/RR11], the SI was calculated using the formula: [(RR11 – 1)]/[(RR10 – 1) + (RR01 – 1)], and their 95% CIs were based on the delta method.[35] It was expected that when a synergistic interaction occurs, the effect of the two exposures will be greater than the sum of their individual effects.[28,33,34] Additionally, the percentages and their corresponding 95% CIs of the total effect attributable to the interaction were computed for *Increasers* and *Reducers* who had the highest effect estimates. The following formulas were used to calculate the contribution of smoking alone: [RR10-1/RR11-1], of antenatal depression alone: [RR01-1/RR11-1], and the contribution of their joint effect: [RERI/RR11-1].[34,36] Causal effects were defined in a counterfactual framework.[37] Variables with missing values of more than 1.9% were imputed using multiple imputation by chained equations (MICE) and fitting regression models with variables from the primary complete-case analysis[38] following the 3-step Rubin's rule.[39] PROC MI and PROC MIANALYZE in SAS version 9.4 were employed in the analyses. The

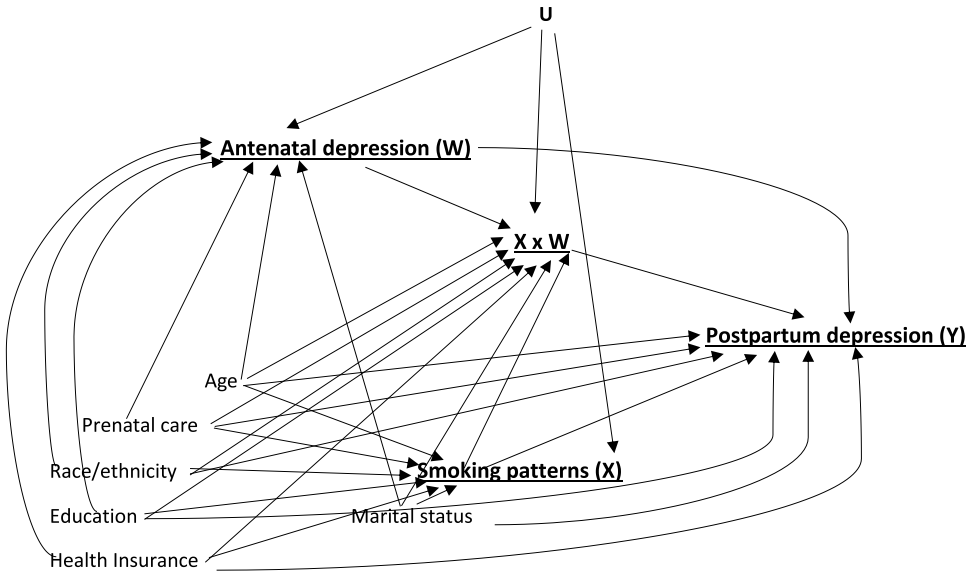

Figure 2 Directed acyclic graph (DAG). Primary exposure (X): smoking patterns; Secondary exposure (W): antenatal depression; Outcome (Y): postpartum depression; Interaction term (XxW): smoking x antenatal depression; Confounding variables: age, race/ethnicity, education, prenatal care, health insurance, and marital status. (U) other measured and unobserved/unmeasured confounders.

impact of unobserved/unmeasured confounding was assessed in a sensitivity analysis using the E-value for interaction based on the adjusted risk ratios and the upper or lower 95% CIs.[40–42] The E-value represents a minimum strength of association that unobserved/unmeasured confounders would need to have with the exposure and the outcome to explain away the observed association, conditional on measured covariates. This was a secondary analysis of deidentified data, and the study did not require approval by the Mercer University Institutional Review Board.

Results

Out of 51,220 women in the study, 6,841 women self-reported PPD and among them 35.7% reported antenatal depression (Table 1). Among 3,921 (7.7%) women who reported smoking during pregnancy, the most prevalent smoking patterns were: high-intensity smoking (more than 10 cigarettes/day) (*Maintainers-High*) and low-intensity smoking (less than 10 cigarettes/day) (*Maintainers-Low*) in all three trimesters (Table 2). The prevalence of antenatal depression and PPD was

Table 1 Participants with Live Singleton Term Births Who Reported (Cases) and Did Not Report (Controls) Postpartum Depression (Total *N = 51220*) (Unweighted N, Weighted %)

Characteristics	Postpartum Depression n=6841 (13.4%)	No Postpartum Depression n=44,379 (86.6%)	*P*-value
	n (%)	n (%)	
Race/ethnicity			<0.0001
Non-Hispanic White	2674 (39.1)	21,801 (49.1)	
Non-Hispanic Black	1642 (24.1)	7512 (16.9)	
Hispanic	1117 (16.3)	8536 (19.3)	
Other race/ethnicity [a]	1408 (20.5)	6530 (14.7)	
Age (years)			<0.0001
<20	555 (8.1)	1927 (4.3)	
20–29	3782 (55.3)	21,161 (47.7)	
30–34	1619 (23.7)	13,409 (30.2)	
≥35	885 (12.9)	7882 (17.8)	
Education			<0.0001
High school or less	3184 (46.6)	15,194 (34.2)	
Some college	2061 (30.1)	12,697 (28.6)	
Bachelor's or higher	1596 (23.3)	16,488 (37.2)	
Marital status			<0.0001
Married	3310 (48.4)	27,484 (61.9)	
Unmarried	3531 (51.6)	16,895 (38.1)	
Health Insurance			<0.0001
Medicaid	3872 (56.6)	18,268 (41.2)	
Private	2545 (37.2)	22,907 (51.6)	
None/Self-pay	185 (2.7)	1397 (3.1)	
Other [b]	239 (3.5)	1807 (4.1)	

(*Continued*)

Table 1 (Continued).

Characteristics	Postpartum Depression n=6841 (13.4%)	No Postpartum Depression n=44,379 (86.6%)	*P*-value
Prenatal care [c]			<0.0001
Inadequate	972 (14.2)	4695 (10.6)	
Adequate/Intermediate	5869 (85.8)	39,684 (89.4)	
Parity			0.7833
Parity 1	2604 (38.1)	17,114 (38.6)	
Parity ≥2	4237 (61.9)	27,265 (61.4)	
Substance use [d]			0.3023
Yes	5573 (81.5)	36,081 (81.3)	
No	1268 (18.5)	8298 (18.7)	
Smoking			<0.0001
Yes	826 (12.1)	3095 (7.0)	
No	6015 (87.9)	41,284 (93.0)	
Antenatal depression			<0.0001
Yes	2442 (35.7)	4365 (9.8)	
No	4399 (64.3)	40,014 (90.2)	

Notes: [a]Asian, American Indian/Alaska Native, Native Hawaiian, Pacific Islander or mixed race; [b] Government insurance, Tricare; [c] Inadequate: late care and ≤10 visits and Adequate/Intermediate: early care and >10 visits; [d] Any use of alcohol, marijuana, opiates, cocaine, amphetamines.

Table 2 Prevalence of Smoking Patterns During Pregnancy Among Study Participants (Total Smokers *N = 3921; 7.7%)* (Unweighted N, Weighted %)

Characteristics	Non-smokers n=47,299 (92.3%)	Quitters - Low n=606 (15.5%)	Quitters - High n=228 (5.8%)	Maintainers - Low n=1265 (32.3%)	Maintainers - High n=1280 (32.6%)	Reducers n=528 (13.5%)	Increasers n=14 (0.3%)	*P*-value
Race/ethnicity								<0.0001
Non-Hispanic White	22,216 (47.0)	271 (44.7)	136 (59.7)	590 (46.7)	922 (72.0)	331 (62.7)	9 (64.3)	
Non-Hispanic Black	8513 (18.0)	122 (20.1)	32 (14.0)	299 (23.6)	121 (9.5)	64 (12.1)	3 (21.4)	
Hispanic	9399 (19.9)	63 (10.4)	19 (8.3)	95 (7.5)	47 (3.7)	29 (5.5)	1 (7.1)	
Other race/ethnicity[a]	7171 (15.1)	150 (24.8)	41 (18.0)	281 (22.2)	190 (14.8)	104 (19.7)	1 (7.1)	
Age (years)								<0.0001
<20	2268 (4.8)	41 (6.8)	18 (7.9)	83 (6.6)	44 (3.4)	26 (4.9)	2 (14.2)	
20–29	22,550 (47.7)	384 (63.4)	148 (64.9)	777 (61.4)	745 (58.2)	333 (63.1)	6 (42.9)	
30–34	14,126 (29.9)	131 (21.6)	35 (15.4)	289 (22.8)	321 (25.1)	120 (22.7)	6 (42.9)	
35+	8355 (17.7)	50 (8.2)	27 (11.8)	116 (9.2)	170 (13.3)	49 (9.3)	0 (0.0)	

(*Continued*)

Table 2 (Continued).

Characteristics	Non-smokers n=47,299 (92.3%)	Quitters - Low n=606 (15.5%)	Quitters - High n=228 (5.8%)	Maintainers - Low n=1265 (32.3%)	Maintainers - High n=1280 (32.6%)	Reducers n=528 (13.5%)	Increasers n=14 (0.3%)	*P*-value
Education								<0.0001
High school or less	15,827 (33.5)	354 (58.4)	119 (52.2)	870 (68.8)	849 (66.3)	349 (66.1)	10 (71.4)	
Some college	13,527 (28.6)	210 (34.6)	95 (41.7)	363 (28.7)	395 (30.9)	165 (31.3)	3 (21.4)	
Bachelor's or higher	17,945 (37.9)	42 (6.9)	14 (6.1)	32 (2.5)	36 (2.8)	14 (2.6)	1 (7.2)	
Marital status								<0.0001
Married	29,771 (62.9)	144 (23.8)	62 (27.2)	297 (23.5)	383 (29.9)	135 (25.6)	2 (14.3)	
Unmarried	17,528 (37.1)	462 (76.2)	166 (72.8)	968 (76.5)	897 (70.1)	393 (74.4)	12 (85.7)	
Health Insurance								<0.0001
Medicaid	19,141 (40.5)	427 (70.5)	155 (68.0)	994 (78.6)	998 (78.0)	415 (78.6)	10 (71.4)	
Private	24,713 (52.2)	149 (24.6)	58 (25.4)	215 (17.0)	221 (17.3)	93 (17.6)	3 (21.4)	
None/Self-pay	1517 (3.2)	6 (1.0)	2 (0.9)	26 (2.0)	22 (1.7)	8 (1.5)	1 (7.2)	
Other[b]	1928 (4.1)	24 (3.9)	13 (5.7)	30 (2.4)	39 (3.0)	12 (2.3)	0 (0.0)	
Prenatal care[c]								<0.0001
Inadequate	5144 (10.9)	122 (20.1)	91 (39.9)	246 (19.4)	263 (20.5)	122 (23.1)	2 (14.3)	
Adequate/Intermediate	42,155 (89.1)	484 (79.9)	137 (60.1)	1019 (80.6)	1017 (79.5)	406 (76.9)	12 (85.7)	
Parity								<0.0001
Parity 1	18,585 (39.3)	228 (37.6)	100 (43.9)	359 (28.4)	287 (22.4)	153 (29.0)	6 (42.8)	
Parity ≥2	28,714 (60.7)	378 (62.4)	128 (56.1)	906 (71.6)	993 (77.6)	375 (71.0)	8 (57.2)	
Substance use[d]								<0.0001
Yes	38,172 (80.7)	525 (86.6)	211 (92.5)	1143 (90.3)	1124 (87.8)	465 (88.1)	14 (100.0)	
No	9127 (19.3)	81 (13.4)	17 (7.5)	122 (9.7)	156 (12.2)	63 (11.9)	0 (0.0)	
Antenatal depression								<0.0001
Yes	5578 (11.8)	148 (24.4)	65 (28.5)	363 (28.7)	468 (36.6)	173 (32.8)	5 (35.7)	
No	41,721 (88.2)	458 (75.6)	163 (71.5)	902 (71.3)	812 (63.4)	355 (67.2)	9 (64.3	
Postpartum depression								<0.0001
Yes	6015 (12.7)	116 (19.1)	47 (20.6)	261 (20.6)	289 (22.6)	110 (20.8)	3 (21.4)	
No	41,284 (87.3)	490 (80.9)	181 (79.4)	1004 (79.4)	991 (77.4)	418 (79.2)	11 (78.6)	

Notes: Quitters-Low (1st + 2nd trimester, 1–9 cigarettes/day); (2) Quitters-High (1st + 2nd trimester, ≥10 cigarettes/day); (3) Maintainers-Low (all trimesters, 1–9 cigarettes/day); (4) Maintainers-High (all trimesters, ≥10 cigarettes/day); (5) Reducers (1st + 2nd trimester ≥10 cigarettes/day and 3rd trimester 1–9 cigarettes/day); (6) Increasers (1st + 2nd trimester 1–9 cigarettes/day and 3rd trimester ≥10 cigarettes/day; [a] Asian, American Indian/Alaska Native, Native Hawaiian, Pacific Islander or mixed race; [b] Government insurance, Tricare; [c] Inadequate care: late and ≤10 visits and Adequate/Intermediate care: early and >10 visits; [d] Any use of alcohol, marijuana, opiates, cocaine, amphetamines;

highest among *Maintainers-High* (36.6% and 22.6%, respectively), followed by *Increasers* (ie, low-intensity smoking in the first and second trimesters and high-intensity smoking in the third trimester) (35.7% and 21.4%, respectively), and *Reducers* (ie, high-intensity smoking in the first and second trimesters and low-intensity smoking in the third trimester) (32.8% and 20.8%, respectively). The main effect on PPD was highest among *Maintainers-High* (aRR 1.65, 95% CI:

1.63, 1.68) and among *Quitters-Low* (ie, low-intensity smoking in first and second trimester only) (aRR 1.22, 95% CI: 1.18, 1.25), whereas among *Increasers* the main effect was 42% lower (aRR 0.58, 95% CI: 0.45, 0.74), compared to nonsmokers (Table 3). A synergistic interaction was detected for all maternal smoking patterns in the presence of antenatal depression, and the effect was strongest among *Increasers* (aRR 5.19; 95% CI: 1.67, 16.10) and *Reducers* (aRR 3.69, 95% CI: 2.93, 4.65) (Table 4). Among *Increasers*, the RERI was 2.84 (95% CI: 1.74, 3.93), the AP was 55% (95% CI: −0.54, 1.64) (not significant), and the SI was 3.10 (95% CI: 2.01, 4.20) (Table 5). Likewise, among *Reducers*, the RERI was 0.59 (95% CI: 0.41, 0.77), the AP was 16% (95% CI: −0.02, 0.34) (not significant), and the SI was 1.28 (95% CI: 1.10, 1.46) (Table 5). Regarding the attributable effect, among *Increasers* very little effect (−21%) was attributed to

Table 3 Multivariable Log Binomial Regression Models for the Main Effects

Variables	aRR	95% CI
Smoking patterns		
Nonsmoker (ref.)	1.00	1.00
Quitters-Low	1.22	1.18, 1.25
Quitters-High	1.21	1.17, 1.26
Maintainers-Low	1.17	1.15, 1.19
Maintainers-High	1.65	1.63, 1.68
Reducers	1.13	1.10, 1.17
Increasers	0.58	0.45, 0.74
Antenatal depression		
Reported	3.28	3.12, 3.45
Not reported (ref.)	1.00	1.00

Notes: Adjusted for: race/ethnicity, age, education, prenatal care, health insurance, and marital status.
Abbreviations: aRR, adjusted relative risk ratios; CI, confidence interval.

Table 4 Log-Binomial Regression Model for the Interaction Effects

Interaction terms	Adjusted model	
	aRR	95% CI
Nonsmokers*without antenatal depression (ref.)	1.00	1.00
Nonsmokers*with antenatal depression	3.25	3.08, 3.44
Quitters-Low *without antenatal depression	0.92	0.69, 1.21
Quitters-Low*with antenatal depression	3.64	2.84, 4.65
Quitters-High*without antenatal depression	0.71	0.43, 0.99
Quitters-High*with antenatal depression	3.06	2.08, 4.51
Maintainers-Low*without antenatal depression	0.74	0.61, 0.86
Maintainers-Low*with antenatal depression	3.15	2.65, 3.73

(*Continued*)

Table 4 (Continued).

Interaction terms	Adjusted model	
	aRR	95% CI
Maintainers-High*without antenatal depression	1.09	0.89, 1.34
Maintainers-High*with antenatal depression	3.61	3.12, 4.20
Reducers*without antenatal depression	0.85	0.61, 1.19
Reducers*with antenatal depression	3.69	2.93, 4.65
Increasers*without antenatal depression	0.10	0.06, 0.18
Increasers*with antenatal depression	5.19	1.67, 16.10

Notes: Adjusted for: race/ethnicity, age, education, prenatal care, health insurance, and marital status.
Abbreviations: aRR, adjusted risk ratio; CI, confidence interval.

Table 5 Additive Scale Measures for Interaction

Interaction terms	Additive scale measures		
	RERI (95% CI)	AP (95% CI)	SI (95% CI)
Quitters-low and antenatal depression	0.47 (0.28, 0.66)	0.12 (−0.06, 0.32)	1.21 (1.03, 1.40)
Quitters-high and antenatal depression	0.10 (−0.18, 0.38)	0.03 (−0.25, 0.31)	1.05 (0.77, 1.33)
Maintainers-low and antenatal depression	0.16 (0.03, 0.28)	0.05 (−0.07, 0.17)	1.08 (0.95, 1.20)
Maintainers-high and antenatal depression	0.27 (0.15, 0.39)	0.07 (−0.04, 0.19)	1.11 (1.00, 1.23)
Reducers and antenatal depression	0.59 (0.41, 0.77)	0.16 (−0.02, 0.34)	1.28 (1.10, 1.46)
Increasers and antenatal depression	2.84 (1.74, 3.93)	0.55 (−0.54, 1.64)	3.10 (2.01, 4.20)

Abbreviations, CI, confidence interval; RERI, the relative excess risk due to interaction; AP, the attributable proportion of interaction; SI, synergy index.

smoking alone in the absence of depression; 54% of the effect was attributed to depression alone in the absence of smoking; and 68% (95% CI: −0.42, 1.77) of effect was attributed to interaction. Similarly, among *Reducers*, very little effect (−5%) was attributed to smoking alone in the absence of depression; 84% was attributed to depression alone in the absence of smoking; and 22% was attributable to interaction. The repeated analysis using multiply-imputed data showed negligible differences (data not shown). The E-value was assessed for *Increasers* and *Reducers* because their interaction effects with the presence of antenatal depression were the strongest (Table S1). For *Increasers* the E-value was 9.85 and for *Reducers* was 6.84 indicating that the association of unobserved/unmeasured confounder with an exposure and outcome will have to be at least a 10-fold and a 7-fold stronger, respectively, to explain away observed risk ratio estimates in the presence of antenatal depression, compared to the absence of antenatal depression. This suggested that even if the assumptions are violated, the estimates remain robust and valid to infer causality.

Discussion

To our knowledge, there are no prior studies that explore the joint effect of diverse patterns of smoking in pregnancy and antenatal depression in causing PPD. Our findings reveal that the effect of smoking patterns could be amplified in a synergistic interaction with co-occurring antenatal depression. Despite a very little effect from smoking alone among *Increasers* and *Reducers*, the interaction effect was strongest and statistically significant, which could potentially be attributed to a high prevalence (17%) of depression in late pregnancy reported in prior studies.[43,44] Increasing variability

in smoking patterns and a rising level of antenatal depression toward the end of pregnancy may likely trigger an interaction and amplification of smoking effects.

Given that causal relations cannot be fully established using observational data, we followed a systematic process by combining structural, counterfactual and graphical approaches, making several assumptions, and using interaction methodology to raise the probability of obtaining estimates valid for causal inference. It was assumed that both exposures (smoking and antenatal depression) are independent of one another; one exposure does not influence the probability of the other to occur; both exposures have a causal (not preventive) effect on the outcome; the effect on the outcome is amplified by a potential interaction between exposures and is unconfounded.[29,34] Attia et al[45] proposed that in addition to the outcome arising from each of two individual exposures, there is also a common exposure effect represented by an interaction term that directly influences the outcome. The authors suggested that for clarity the main effects and the interaction term node in the causal pathway should all be displayed in a single DAG (as shown in Figure 2). The interaction term in a DAG specifies a probabilistic causal relationship between parents/ancestors (X and W) and a child/descendant (XxW) and can be conceptualized as a potential collider and a mediator. A DAG provides theoretical basis to causal associations between variables and helps identify potential confounding by blocking the "backdoor" path and facilitating the process of causal inference.[24,25] This approach has been used in epidemiology to identify a set of confounding factors (a minimal sufficient adjustment set) under hypothesized causal relationships.[24,25,32] Adjustment in the regression model for common effects of exposures and the outcome, such as a potential collider and a mediator, can open a backdoor path and introduce bias. Adjusting for a mediator can additionally decompose and decrease the total effect. However, an adjustment made for common causes will remove their effects (confounding) from the final estimates.[34] A counterfactual (or potential outcomes) framework clarified causal relationships observed when all individuals in the population are equally exposed and unexposed, assuming no unmeasured confounding conditional on observed covariates and allowing to interpret estimates as causal effects at the population level.[29,34,46,47]

From a biological perspective, both smoking during pregnancy and antenatal depression can contribute to PPD. Pregnancy is an immunomodulatory state with significant immune and inflammatory activity across trimesters and postpartum.[48] Smoking-prompted release of inflammatory mediators can lead to systemic inflammation.[49] An inflammatory response has been suggested as a mechanism in the signaling pathway underlying the effects of stress and depression.[50] Elevated levels of immune biomarkers in maternal serum in the final trimester of pregnancy were found to be associated with symptoms of antenatal depression.[51] Provided that smoking, antenatal depression and the immune system share a common physiological inflammatory pathway, it is plausible that they are likely to contribute to PPD.

This study is based on observational data and has some limitations that should be considered. First, although the PRAMS database is relatively standardized, self-reported survey data on smoking and depression are prone to under-reporting, recall, social-desirability bias, and potential misclassification error. However, in a previously published validation study,[52] self-reported information in the PRAMS was found to be in high agreement with clinical records. Second, small sample sizes imply low statistical power and findings have to be interpreted with caution. Nonetheless, despite a small sample size for the *Increasers* category, the joint effect of smoking and co-occurring depression was amplified and statistically significant. Third, other risk factors (eg, alcohol, drugs) have been linked to PPD and their effect needs to be investigated. Fourth, no information was available in the dataset regarding temporal associations between the occurrence of depression and the severity of antenatal and postnatal depression. Fifth, as assumptions cannot be fully tested statistically, background knowledge and existing evidence are essential in drawing causal inferences.[29,34,53] Additionally, these findings require further replication in a larger sample considering relationships between the occurrence, measures, and severity of both antenatal and postnatal depression. Finally, there are also limitations inherent to DAGs. While DAGs can identify possible sources of bias, they do not provide measures of bias. Even in correctly specified models, residual confounding may be present due to measurement error.[54–56] More information about the limitations of using DAGs can be found in prior research.[24,29,34,55–57] Despite these limitations, our study findings add supportive evidence about the effect of maternal smoking in causing PPD amplified by the presence of antenatal depression, and inform future research on causal inference using observational data.

Conclusions

This study provides new insight into complex associations between diverse maternal smoking patterns and comorbid antenatal depression in causing PPD. Strong associations and interaction effects support smoking prevention and cessation interventions in pregnant women to lower the risk of PPD.

Data Sharing Statement

A PRAMS analytic data set is available to researchers upon request from the CDC after completion of a short application with a brief research proposal summary.

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Disclosure

Dr Jennifer Barkin has a copyrighted (but not patented) instrument (the Barkin Index of Maternal Functioning) that is broadly relevant to maternal child health. The authors report no other conflicts of interest in this work.

References

1. Underwood L, Waldie K, D'Souza S, Peterson ER, Morton S. A review of longitudinal studies on antenatal and postnatal depression. *Archives of Women's Mental Health*. 2016;19(5):711–720. doi:10.1007/s00737-016-0629-1
2. Vliegen N, Casalin S, Luyten P. The course of postpartum depression: a review of longitudinal studies. *Harvard Review of Psychiatry*. 2014;22(1):1–22. doi:10.1097/HRP.0000000000000013
3. Curry SJ, Krist AH, Owens DK, et al. Interventions to prevent perinatal depression: US preventive services task force recommendation statement. *JAMA*. 2019;321(6):580–587. doi:10.1001/jama.2019.0007
4. Accortt EE, Cheadle AC, Schetter CD. Prenatal depression and adverse birth outcomes: an updated systematic review. *Maternal and Child Health*. 2015;19(6):1306–1337. doi:10.1007/s10995-014-1637-2
5. Milgrom J, Gemmill AW, Bilszta JL, et al. Antenatal risk factors for postnatal depression: a large prospective study. *Journal of Affective Disorders*. 2008;108(1–2):147–157. doi:10.1016/j.jad.2007.10.014
6. Guintivano J, Manuck T, Meltzer-Brody S. Predictors of postpartum depression: a comprehensive review of the last decade of evidence. *Clinical Obstetrics and Gynecology*. 2018;61(3):591–603. doi:10.1097/GRF.0000000000000368
7. Goodwin RD, Cheslack-Postava K, Nelson DB, et al. Smoking during pregnancy in the United States, 2005–2014: the role of depression. *Drug Alcohol Depen*. 2017;179:159–166. doi:10.1016/j.drugalcdep.2017.06.021
8. Centers for Disease Control and Prevention (CDC). Smoking and Tobacco Use; 2022. Available from: https://www.cdc.gov/tobacco/. Accessed March 26, 2024.
9. Oncken C, Ka R, Kuo CL, Dornelas E, Hr K, Hz S. Correlates of electronic cigarettes use before and during pregnancy. *Nicotine and Tobacco Research*. 2017;19(5):585–590. doi:10.1093/ntr/ntw225
10. Kondracki AJ, Hofferth SL. A gestational vulnerability window for smoking exposure and the increased risk of preterm birth: how timing and intensity of maternal smoking matter. *Reproductive Health*. 2019;16:43. doi:10.1186/s12978-019-0705-x
11. Kondracki AJ. Low birthweight in term singletons mediates the association between maternal smoking intensity exposure status and immediate neonatal intensive care unit admission: the E-value assessment. *Pregnancy and Childbirth*. 2020;20:341. doi:10.1186/s12884-020-02981-1
12. Liu B, Xu G, Sun Y, et al. Maternal cigarette smoking before and during pregnancy and the risk of preterm birth: a dose–response analysis of 25 million mother–infant pairs. *Public Lib Sci Med*. 2020;17(8):e1003158. doi:10.1371/journal.pmed.1003158
13. Eiden RD, Homish GG, Colder CR, Schuetze P, Gray TR, Huestis MA. Changes in smoking patterns during pregnancy. *Substance Use and Misuse*. 2013;48(7):513–522. doi:10.3109/10826084.2013.787091
14. Kondracki AJ. Prevalence and patterns of cigarette smoking before and during early and late pregnancy according to maternal characteristics: the first national data based on the 2003 birth certificate revision, United States, 2016. *Reproductive Health*. 2019;16(1):142. doi:10.1186/s12978-019-0807-5
15. Munafò MR, Hitsman B, Rende R, Metcalfe C, Niaura R. Effects of progression to cigarette smoking on depressed mood in adolescents: evidence from the national longitudinal study of adolescent health. *Addiction*. 2008;103(1):162–171. doi:10.1111/j.1360-0443.2007.02052.x
16. Munafò MR, Araya R. Cigarette smoking and depression: a question of causation. *British Journal of Psychiatry*. 2010;196(6):425–426. doi:10.1192/bjp.bp.109.074880
17. Chen HL, Cai JY, Zha ML, Shen WQ. Prenatal smoking and postpartum depression: a meta-analysis. *Journal of Psychosomatic Obstetrics & Gynecology*. 2019;40(2):97–105. doi:10.1080/0167482X.2017.1415881

18. Skov-Ettrup LS, Nordestgaard BG, Petersen CB, Tolstrup JS. Does high tobacco consumption cause psychological distress? A Mendelian randomization study. *Nicotine Tob Res*. 2017;19(1):32–38. doi:10.1093/ntr/ntw186
19. Taylor AE, Fluharty ME, Bjørngaard JH, et al. Investigating the possible causal association of smoking with depression and anxiety using Mendelian randomisation meta-analysis: the CARTA consortium. *BMJ Open*. 2024;4(10):e006141. doi:10.1136/bmjopen-2014-006141
20. Gage SH, Smith GD, Zammit S, Hickman M, Munafò MR. Using Mendelian randomisation to infer causality in depression and anxiety research. *Depression and Anxiety*. 2013;30(12):1185–1193. doi:10.1002/da.22150
21. Yu J, Zhang Z, Deng Y, et al. Risk factors for the development of postpartum depression in individuals who screened positive for antenatal depression. *BMC Psychiatry*. 2023;23(1):557. doi:10.1186/s12888-023-05030-1
22. Yim IS, Tanner Stapleton LR, Guardino CM, Hahn-Holbrook J, Dunkel Schetter C. Biological and psychosocial predictors of postpartum depression: systematic review and call for integration. *Annu Rev Clin Psychol*. 2015;11:99–137. doi:10.1146/annurev-clinpsy-101414-020426
23. Wisner KL, Sit DKY, McShea MC, et al. Onset timing, thoughts of self-harm, and diagnoses in postpartum women with screen-positive depression findings. *JAMA Psychiatry*. 2013;70(5):490–498. doi:10.1001/jamapsychiatry.2013.87
24. Pearl J. Causal diagrams for empirical research. *Biometrika*. 1995;82(4):669–688. doi:10.2307/2337329
25. Greenland S, Pearl J, Robins JM. Causal diagrams for epidemiologic research. *Epidemiology*. 1999;10(1):37–48. doi:10.1097/00001648-199901000-00008
26. Greenland S. Interactions in epidemiology: relevance, identification, and estimation. *Epidemiology*. 2009;20(1):14–17. doi:10.1097/EDE.0b013e318193e7b5
27. VanderWeele TJ. The Interaction Continuum. *Epidemiology*. 2019;30(5):648–658. doi:10.1097/EDE.0000000000001054
28. Rothman KJ, Greenland S. *Modern Epidemiology*. Philadelphia, PA: Lippincott Williams & Wilkins; 2008.
29. Hernan MA, Robins JM Causal Inference: what if. boca raton: chapman & hall/CRC. 2020. Available from: https://cdn1.sph.harvard.edu/wpcontent/uploads/sites/1268/2021/03/ciwhatif_hernanrobins_30mar21.pdf.Accessed March 26, 2024.
30. Centers for Disease Control and Prevention (CDC). Pregnancy Risk Assessment Monitoring System (PRAMS); 2021. Available from: https://www.cdc.gov/prams/methodology.htm.Accessed 7, Oct, 2014.
31. Shulman HB, D'Angelo DV, Harrison L, Smith RA, Warner L. The Pregnancy Risk Assessment Monitoring System (PRAMS): overview of design and methodology. *Am J Public Health*. 2018;108(10):1305–1313. doi:10.2105/AJPH.2018.304563
32. Williamson EJ, Aitken Z, Lawrie J, Dharmage SC, Burgess JA, Forbes AB. Introduction to causal diagrams for confounder selection. *Respirology*. 2014;19(3):303–311. doi:10.1111/resp.12238
33. de Mutsert R, Jager KJ, Zoccali C, Dekker FW. The effect of joint exposures: examining the presence of interaction. *Kidney International*. 2009;75(7):677–681. doi:10.1038/ki.2008.645
34. VanderWeele TJ. *Explanation in Causal Inference: Methods for Mediation and Interaction*. New York, NY: Oxford University Press; 2015.
35. Assmann SF, Hosmer DW, Lemeshow S, Mundt KA. Confidence intervals for measures of interaction. *Epidemiology*. 1996;7(3):286–290. doi:10.1097/00001648-199605000-00012
36. VanderWeele TJ, Tchetgen Tchetgen EJ. Attributing effects to interactions. *Epidemiology (Cambridge, Mass*. 2014;25(5):711–722. doi:10.1097/EDE.0000000000000096
37. Rubin DB. Causal inference using potential outcomes. *J Am Stat Assoc*. 2005;100:322–331. doi:10.1198/016214504000001880
38. Sterne JA, White IR, Carlin JB, et al. Multiple imputation for missing data in epidemiological and clinical research: potential and pitfalls. *BMJ*. 2009;338:157–160. doi:10.1136/bmj.b239330
39. Db R. Multiple imputation after 18+ Years. *J Am Stat Assoc*. 1996;91(434):473–489.
40. Ding P, VanderWeele TJ. Sensitivity analysis without assumptions. *Epidemiology*. 2016;27(3):368–377. doi:10.1097/EDE.0000000000000457
41. VanderWeele TJ, Ding P. Sensitivity analysis in observational research: introducing the E-value. *Ann Intern Med*. 2017;167(4):268. doi:10.7326/M16-2607
42. Mathur MB, Smith LH, Yoshida K, Ding P, VanderWeele TJ. E-values for effect heterogeneity and approximations for causal interaction. *Int J Epidemiol*. 2022;51(4):1268–1275. doi:10.1093/ije/dyac073
43. Josefsson A, Berg G, Nordin C, Sydsjö G. Prevalence of depressive symptoms in late pregnancy and postpartum. *Acta Obstetricia et Gynecologica Scandinavica*. 2001;80(3):251–255. doi:10.1034/j.1600-0412.2001.080003251.x
44. Zhang L, Wang L, Cui S, Yuan Q, Huang C, Zhou X. Prenatal depression in women in the third trimester: prevalence, predictive factors, and relationship with maternal-fetal attachment. *Frontiers in Public Health*. 2021;8:602005. doi:10.3389/fpubh.2020.602005
45. Attia J, Holliday E, Oldmeadow C. A proposal for capturing interaction and effect modification using DAGs. *Int J Epidemiol*. 2022;51(4):1047–1053. doi:10.1093/ije/dyac126
46. Greenland S, Poole C. Invariants and non-invariants in the concept of interdependent effects. *Scandinavian Journal of Work, Environment & Health*. 1988;14(2):125–129. doi:10.5271/sjweh.1945
47. Höfler M. Causal inference based on counterfactuals. *BMC Medical Research Methodology*. 2005;5:28. doi:10.1186/1471-2288-5-28
48. Mor G, Cardenas I, Abrahams V, Guller S. Inflammation and pregnancy: the role of the immune system at the implantation site. *Ann NY Acad Sci*. 2011;1221(1):80–87. doi:10.1111/j.1749-6632.2010.05938.x
49. Nunes SO, Vargas HO, Brum J, et al. A comparison of inflammatory markers in depressed and nondepressed smokers. *Nicotine Tobacco Res*. 2012;14(5):540–546. doi:10.1093/ntr/ntr247
50. Galan D, Perry BI, Warrier V, et al. Applying Mendelian randomization to appraise causality in relationships between smoking, depression and inflammation. *Sci Rep*. 2022;12(1):15041. doi:10.1038/s41598-022-19214-4
51. Osborne LM, Yenokyan G, Fei K, et al. Innate immune activation and depressive and anxious symptoms across the peripartum: an exploratory study. *Psychoneuro-Endocrinology*. 2019;99:80–86. doi:10.1016/j.psyneuen.2018.08.038
52. Dietz P, Bombard J, Mulready-Ward C, et al. Validation of self-reported maternal and infant health indicators in the pregnancy risk assessment monitoring System. *Maternal Child Health J*. 2014;18(10):2489–2498. doi:10.1007/s10995-014-1487-y
53. VanderWeele TJ. Concerning the consistency assumption in causal inference. *Epidemiology*. 2009;20(6):880–883. doi:10.1097/EDE.0b013e3181bd5638
54. Ferguson KD, McCann M, Katikireddi SV, et al. Evidence synthesis for constructing directed acyclic graphs (ESC-DAGs): a novel and systematic method for building directed acyclic graphs. *Int J Epidemiol*. 2020;49(1):322–329. doi:10.1093/ije/dyz150

55. Greenland S. Limitations of individual causal models, causal graphs, and ignorability assumptions, as illustrated by random confounding and design unfaithfulness. *European Journal of Epidemiology*. 2015;30:1101–1110. doi:10.1007/s10654-015-9995-7
56. Hernán MA, Cole SR. Invited commentary: causal diagrams and measurement bias. *American Journal of Epidemiology*. 2009;170(8):959–964. doi:10.1093/aje/kwp293
57. Krieger N, Davey SG. The tale wagged by the DAG: broadening the scope of causal inference and explanation for epidemiology. *Int J Epidemiol*. 2016;45(6):1787–1808. doi:10.1093/ije/dyw114