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Appendix 1. Methods Notes

A. Validation of Outcome Measure: Spontaneous Preterm Birth

Spontaneous cases of preterm birth (as opposed to medically indicated/induced) were deemed most relevant to evaluating direct contribution of posttraumatic stress to premature delivery; they also have the advantage of being most reliably identified in the maternal data. Cases were identified by International Classification of Diseases, 9th Revision, Clinical Modification (ICD-9) diagnosis code 644.2 (“spontaneous onset of delivery before 37 weeks”) in the maternal delivery claim. Maternal claim summaries lack detailed gestational age for offspring, and for our analysis dataset we did not have access to infant records or birth certificates to confirm gestational age. Instead, we performed external validation of this ICD-9 using a similar non-VA database of over 500,000 maternal discharge claims which did have linkage to infant birth certificates data,¹ and found in our validation set that maternal ICD-9 644.2 was associated with a median gestational age of 35 weeks, and 98% specific to birth prior to 37 weeks gestation.

B. Military Sexual Trauma Screening

Mandatory screening for military sexual trauma (MST) has been in place at the VA since 2002 via a brief validated screening instrument (**Box 1**).² Patients are considered positive for MST if either response is affirmative. We linked each delivery to the veteran’s MST status, using cumulative screening results through fiscal year 2012.

Box 1. Military Sexual Trauma Screening Questions²

While you were in the military:

- (a) Did you receive uninvited and unwanted sexual attention, such as touching, cornering, pressure for sexual favors, or verbal remarks?;*
- (b) Did someone ever use force or threat of force to have sexual contact with you against your will?*

C. Handling of Missing Race Data

Race, a well-established predictor of preterm birth, is inconsistently available in the VA,³ therefore we looked across 4 different variables containing mixed self- and third-party reported data and used the most recently reported race for each veteran; the 11% without data (i.e. those who declined to answer and those with no recorded data) were included in our primary model with race categorized as “missing.” In sensitivity analysis, we tested excluding those deliveries with race categorized as “missing” from analysis, and our main findings were unchanged (**Table A3**).

Appendix 2. Sensitivity Analysis

We performed several additional analyses to test the sensitivity of our primary finding to assumptions made in building the model (**Tables A3 – A5**). Specifically, our sensitivity analyses revisited key covariates dropped in our iterative development of the primary model, and examined additional obstetric factors, potential temporal trends, and possible impact of changes in the threshold for PTSD diagnosis. Under all of these various models the effect size for active PTSD remained robust, and essentially unchanged, with an adjusted odds ratio (aOR) consistently in the range of 1.3–1.4.

Table A3, Model 1 shows our primary adjusted model (which includes adjustment for age, race, deployment history, and twins/higher order births) as a reference. **Model 2** demonstrates that adding back MST to the model, which was originally dropped for reasons of parsimony as it showed no evidence of confounding, makes no difference in the observed effect of PTSD. **Model 3** adds back marital status, which was likewise dropped, and similarly finds no notable change in the results. **Model 4** adjusts for reported income to evaluate if socio-economic status confounds the observed association of PTSD and preterm delivery; while limited to the 2/3rds of the sample that had income data, adjusting for income did not alter the pattern of association for PTSD and preterm birth. **Model 5** limits the analysis cohort to those with known race, to evaluate for any suggestion of bias introduced by our handling of missing race (included categorically as “missing race”) in our base model; reassuringly, the primary finding remains unchanged when the analysis is restricted to those with complete race data.

Models 6 to 9 (Table A4) explore various obstetrical indicators. Twins/higher order births account for relatively few cases in our sample, but are very strongly associated with preterm birth. In our primary model we include and adjust for such births as a covariate, reasoning that these high-risk pregnancies would be similarly susceptible to the abnormal stress of PTSD; in **Model 6**, we take the alternate approach, and exclude such pregnancies from our analysis, and find the association of PTSD and preterm birth remains largely unchanged. **Model 7** limits our analysis to a single delivery (the first) for all subjects in our sample. By excluding 2300 repeat deliveries it also altered the appropriate statistical

methodology, obviating the need to account for within-subject correlation and allowed use of logistic regression (instead of generalized estimating equations adjusting for repeated measures); even with this loss of sample size and alternate method of modeling, the findings were replicated. **Model 8** attempts to approximate and adjust for maternal parity (i.e. what number delivery it is for each mother), but is limited by our lack of data prior to the year 2000, as well as our inability to rule out prior deliveries not captured within VA data. Nonetheless, by the best approximation possible with the data available, adjusting for number of prior deliveries showed no evidence of altering the results. With similar limitations, **Model 9** accounts for history of preterm delivery, adjusting explicitly (beyond the adjustment inherent in our statistical methods of clustering by individual, which accounts for within-subject correlation for mothers with multiple deliveries) by introducing a binary indicator of prior spontaneous preterm birth; the results are unchanged. **Model 10** adjusts for history of cesarean delivery, which was evaluated but dropped for parsimony from the original model. Although it has potential to be a confounding covariate—as it is known to predict a high chance of subsequent cesarean delivery, and such deliveries are potentially less likely to be recorded as spontaneous preterm births, even when the onset of preterm labor was spontaneous—the findings are no different when it is included.

Models 11-14 (Table A5) explore for evidence that temporal trends and/or changes in criteria for diagnosing PTSD might affect the findings. Adjusting for the year of the delivery (and thus the time period in which the active prenatal PTSD diagnosis occurred) in **Model 11**, made little difference. Nor did adjusting for delivery year show evidence of a temporal trend in the risk of preterm birth over the 13-year study period. **Model 12** restricts the cohort to deliveries after year 2007, by which time the VA had fully implemented a clinical reminder and standardized tool to ensure universal screening for PTSD; despite this system-wide change, which potentially increased PTSD detection, the pattern of association between active PTSD and preterm birth remained unaltered. Finally, as a single occurrence of a diagnostic code in a medical record may sometimes reflect a clinician recording a 'probable' or 'rule-out' diagnosis, we also explored using a more rigorous standard to identify PTSD—i.e., requiring that the ICD-9 code occur at least twice. In **Model 13** we assume that 222 (11.6%) of the active PTSD cases (and 362 of the historical cases) that only have a single occurrence of the ICD-9 recorded are putative at best and

exclude them from analysis; even with this decimation of our active PTSD sample, the association remains highly significant and of similar magnitude, aOR 1.31 (CI 1.09 to 1.58). **Model 14** tests a narrower definition of “active” PTSD in the antepartum period, defined by presence of an encounter diagnosis within 9 months prior to delivery (instead of 12 months); this results in 242 (12.6%) of PTSD cases being reassigned from active PTSD to historical PTSD, however the effect size remains essentially unchanged for historical PTSD, with and only a slight increase in the effect size for active PTSD observed, aOR 1.41 (CI 1.18 – 1.69).

Appendix 3. Tables

Table A1. Association of Military Sexual Trauma (MST) and Spontaneous Preterm Birth
(n=15,520; preterm delivery events=1,197)

Parameter			Unadjusted			Multivariate Model ^a		
			Odds Ratio	(95% CI)	P Value	Adjusted Odds Ratio	(95% CI)	P Value
MST			1.08	(0.94 - 1.24)	0.3	0.99	(0.84 - 1.15)	0.8
PTSD	No History	(n=13,285)				1	Reference	
	Historical	(n= 1,128)				1.06	(0.84 - 1.35)	0.6
	Active	(n= 1,921)				1.35	(1.12 - 1.63)	0.002
Maternal Age	19-25					1	Reference	
	25-29					0.97	(0.80 - 1.17)	0.7
	30-34					1.12	(0.92 - 1.36)	0.3
	35-39					1.14	(0.91 - 1.44)	0.3
	≥ 40					1.16	(0.83 - 1.62)	0.4
Race	White					1	Reference	
	Black or African American					1.49	(1.29 - 1.71)	<0.001
	Asian					1.30	(0.84 - 2.01)	0.2
	American Indian/Alaskan Native					2.07	(1.19 - 3.59)	0.01
	Hawaiian/Pacific Islander					1.39	(0.87 - 2.22)	0.2
	Missing/Not Reported					1.11	(0.90 - 1.38)	0.3
Twins/Higher-order Gestation						6.74	(5.30 - 8.57)	<0.001
Deployed (OEF/OIF/OND)						0.69	(0.60 - 0.80)	<0.001

MST = Military Sexual Trauma; PTSD = Posttraumatic Stress Disorder;

OEF/OIF/OND = Operations Enduring Freedom, Iraqi Freedom, and New Dawn

^a Generalized estimating equations with logit linkage and clustered by unique individual using exchangeable correlation matrix for repeat deliveries. Independent variables are those listed.

Table A2. Association of PTSD Status and Spontaneous Preterm Birth, Adjusted for Potential Intermediaries^a

		Model 1: Base Model			Model 2: Include Chronic Disease			Model 3: Include Substance Use			Model 4: Include Alternative Mental Health Disorders ^b		
Parameter		OR	(95% CI)	P Value	OR	(95% CI)	P Value	OR	(95% CI)	P Value	OR	(95% CI)	P Value
PTSD	No History	1	Reference		1	Reference		1	Reference		1	Reference	
	Historical	1.06	(0.84 - 1.34)	0.6	1.05	(0.83 - 1.33)	0.7	1.05	(0.83 - 1.33)	0.7	1.01	(0.79 - 1.29)	0.9
	Active	1.35	(1.14 - 1.61)	<0.001	1.32	(1.11 - 1.58)	0.002	1.29	(1.08 - 1.55)	0.005	1.30	(1.07 - 1.58)	0.009
Hypertension					1.71	(1.40 - 2.09)	<0.001						
Diabetes					1.21	(0.90 - 1.62)	0.2						
Asthma					1.09	(0.89 - 1.34)	0.4						
Drug Abuse/Dependence								1.38	(1.03 - 1.85)	0.03			
Alcohol Abuse/Dependence								1.16	(0.79 - 1.70)	0.5			
Tobacco Use								1.03	(0.85 - 1.25)	0.7			
Depressive Disorder	No History										1	Reference	
	Historical										1.02	(0.85 - 1.23)	0.8
	Active										0.95	(0.80 - 1.13)	0.6
Anxiety Disorder	No History										1	Reference	
	Historical										1.09	(0.90 - 1.32)	0.4
	Active										1.18	(0.97 - 1.45)	0.1
Adjustment Disorder	No History										1	Reference	
	Historical										1.04	(0.84 - 1.28)	0.7
	Active										1.00	(0.75 - 1.32)	0.99
Bipolar Disorder	No History										1	Reference	
	Historical										0.81	(0.55 - 1.20)	0.3
	Active										1.26	(0.94 - 1.68)	0.1
Personality Disorder	No History										1	Reference	
	Historical										1.13	(0.83 - 1.55)	0.4
	Active										0.92	(0.62 - 1.37)	0.7

PTSD = Posttraumatic Stress Disorder. OEF/OIF/OND = Operations Enduring Freedom, Iraqi Freedom, and New Dawn

^aAll models use generalized estimating equations with logit link, clustered by unique individual using an exchangeable correlation matrix for repeat deliveries. All models also control for age, race, twin or higher-order pregnancy, and deployment history, in addition to the covariates listed. QIC (quasi-likelihood information criterion for GEE) indicate Model 2 and 3 to have better fit relative to the baseline model, and Model 4 to have poorer fit.

^bGiven the high levels of co-occurrence of mental health diagnoses, we evaluated the degree of multi-collinearity of all variables in this model (placing them within an ordinary least squares model [not shown]) and found no suggestion of problematic levels of collinearity: variance inflation factors and conditions indices were all ≤ 3 .

Table A3. Sensitivity Tests of Model Assumptions – Demographics

PTSD Status	Model 1: Base Model	Model 2: Include MST	Model 3: Include Marital Status	Model 4: Include Income^a	Model 5: Exclude Deliveries with Missing Race^b
Active PTSD, aOR	1.35**	1.35**	1.34**	1.40**	1.35**
Historical PTSD, aOR	1.06 ns	1.06 ns	1.03 ns	1.10 ns	1.04 ns
No PTSD	ref	ref	ref	ref	ref

** p <0.01, * p <0.05, ns= p>0.05;

PTSD = posttraumatic stress disorder, aOR = adjusted odds ratio, MST = military sexual trauma

All models also adjusted for age, race, deployment, and twins/higher-order gestation.

^a Excludes 31% with missing income data

^b Excludes 11% with race categorized as “missing” (i.e. declined to answered or no data available)

Table A4. Sensitivity Tests of Model Assumptions – Obstetric Factors

PTSD Status	Model 6: Exclude Twin / Higher Order Births	Model 7: Restrict to First Delivery in Cohort	Model 8: Include Delivery Count^a	Model 9: Include History of Prior Spontaneous Preterm Birth	Model 10: Include History of Cesarean
Active PTSD, aOR	1.32**	1.37**	1.34*	1.35*	1.36**
Historical PTSD, aOR	0.96 ns	0.97 ns	1.00 ns	1.08 ns	1.06 ns
No PTSD	ref	ref	ref	ref	ref

** p <0.01, * p <0.05, ns= p>0.05;

PTSD = posttraumatic stress disorder, aOR = adjusted odds ratio, MST = military sexual trauma;

All models also adjusted for age, race, deployment, and twins/higher-order gestation (except as otherwise noted).

^a Model restricted to deliveries from 2003 onwards to permit 3-year lead-time to capture all recent prior VA-covered deliveries, as the available data only includes deliveries reimbursed by the VA since 2000, and can not account for non-VA or pre-2000 deliveries.

Table A5. Sensitivity Tests of Model Assumptions – PTSD Diagnosis

PTSD Status	Model 11: Include Delivery Year^a	Model 12: Restrict to Years After 2007^b	Model 13: Restrict to “Confirmed” PTSD Diagnoses^c	Model 14: Redefine “Active” PTSD as within 9 Months Prior^d
Active PTSD, aOR	1.37**	1.36**	1.31**	1.41**
Historical PTSD, aOR	1.07 ns	0.98 ns	1.00 ns	1.05 ns
No PTSD	ref	ref	ref	ref

** p <0.01, * p <0.05, ns= p>0.05;

PTSD = posttraumatic stress disorder, aOR = adjusted odds ratio, MST = military sexual trauma;

All models also adjusted for age, race, deployment, and twins/higher-order gestation.

^aYear modeled as categorical variable; it was also tested as a continuous variable, with similar findings, and p for trend was non-significant (0.2).

^bYear in which electronic-reminder for PTSD screening implemented in VA .

^cConfirmed cases are those with ≥2 instances of the PTSD ICD-9 recorded in encounters; model excludes 222 unconfirmed Active PTSD and 362 unconfirmed Historical PTSD cases, i.e., 19% of the total PTSD cases included in the base model.

^dRedefining the diagnosis window designated “active” in the prenatal period to 9 months prior to delivery (instead of 12 months) reassigns 242 (12.6%) of previously “active” PTSD to be “historical” PTSD.

References

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3. Long JA, Bamba MI, Ling B, Shea JA. Missing race/ethnicity data in Veterans Health Administration based disparities research: a systematic review. *J Health Care Poor Underserved*. 2006 Feb;17(1):128–40.