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Maternal infection and stress during pregnancy and depressive symptoms in adolescent offspring

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ABSTRACT

Maternal infection during pregnancy has been linked to increased risk of offspring depression. Additionally, maternal stress during pregnancy has been consistently linked with adverse offspring outcomes associated with depression. Relatedly, stress has been associated with increased risk of infection; however no study has investigated stress-infection interactions during pregnancy and risk for offspring depression. Participants were drawn from the Child Health and Development Studies (CHDS), a prospective, longitudinal study that enrolled pregnant women from 1959 to 1966. Maternal health and birth outcome information were collected, as well as open-ended interviews about worrisome events during pregnancy. The present study included participants from a subsample of women whose offspring (n = 1711) completed self-reports of depressive symptoms during adolescence. Results indicated that maternal infection during only the second trimester was associated with higher scores on adolescent offspring depressive symptoms, while controlling for maternal education at birth, adolescent age, and maternal depressive symptoms at adolescence. Maternal experiences of daily stress during pregnancy moderated this association, such that mothers diagnosed with second trimester infection and who experienced daily stress had offspring with significantly higher depression scores than mothers of adolescents diagnosed with an infection alone. Findings have potential implications for prevention and intervention strategies.

1. Introduction

Increasing evidence suggests that maternal infection during pregnancy is implicated in risk for offspring depression (reviewed in (Bilbo and Schwarz, 2009; Markham and Koenig, 2011; Simanek and Meier, 2015)). Specifically, two studies found associations between being pregnant during influenza epidemics and unipolar depression in adult offspring (Cannon et al., 1996; Machón et al., 1997). The first study, utilizing an Irish cohort, found that maternal self-report of influenza at any time during pregnancy was associated with a 1.59 times increased risk of a depressive disorder among adult offspring (Cannon et al., 1996). The second ecologic study, using a Finnish cohort, also found a significant increase in the proportion of psychiatric hospital admissions for unipolar major depressive disorder among individuals whose mothers were pregnant during the second trimester of an influenza epidemic (Machón et al., 1997). However, these studies were complicated by use of hospital admission data and/or familial report of offspring health to determine depression diagnoses. As such, findings from both studies may be representative of more severe mood disorders and lack generalizability to more moderate, but nonetheless clinically significant, diagnostic profiles of depression. However, a number of other studies have identified no associations between fetal exposure to maternal influenza and offspring depression (Brown et al., 1995; Mino et al., 2000; Morgan et al., 1997; Pang et al., 2009; Takei et al., 1993). Research findings utilizing a cohort of 3076 individuals born to mothers who were clinically diagnosed with various viral infections (e.g., influenza, rubella, mumps, measles, varicella, herpes zoster, hepatitis, cytomegalovirus) in the United Kingdom between 1946 and 1980 found no associations between individual viral infections and offspring depression (Pang et al., 2009). Surprisingly, this is the only study to our knowledge that has examined the link between maternal infection other than the influenza virus and offspring depression (Simanek and Meier, 2015). However, several studies in rodents using translational models of maternal immune activation (MIA) during pregnancy have

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demonstrated connections between prenatal infection and depressive-like alterations in offspring development (Bitanihirwe et al., 2010; reviewed in (Ronovsky et al., 2016)). Still, given the dearth of literature examining the role of prenatal infections in the etiology of depression, especially as it relates to adolescent psychopathology outcomes, further research is necessary.

Relatedly, emerging data indicate that maternal stress during pregnancy is implicated in risk for offspring depression. For instance, an ecologic study examining prenatal exposure to a severe earthquake in the city of Tangshan, China, in 1976 found that 18-year-old offspring whose mothers were pregnant during the earthquake had increased levels of severe depression and overall depressive symptoms compared to controls (Watson et al., 1999). Similarly, another ecologic study of prenatal exposure to the 1944–1945 Dutch "Hunger Winter," a period during World War II in which several cities in the Western Netherlands experienced famine, found that maternal exposure to famine during the second and third trimesters increased offspring risk of developing both unipolar and bipolar affective disorders in adulthood (Brown et al., 2000a, 2000b). However, the results likely reflect, at least in part, the adverse effects of long-term maternal malnutrition on offspring development. Moreover, both this study and that of Watson et al. (1999) are limited in their generalizability, given that "stress" was never measured but rather presumed based on severe life events. However, another study that prospectively followed mothers and their children for a period of more than 20 years, found that high levels of maternal depression, anxiety, and stress symptoms (assessed via a 4-item, self-report inventory) during pregnancy were associated with offspring internalizing behavior problems in adolescence (Betts et al., 2014) and adulthood (Betts et al., 2015). These results were consistent with findings from another prospective population-based cohort that demonstrated an association between maternal exposure to stressful life events during early pregnancy and an increased risk for depression and elevated depressive symptoms in 17 to 18-year-old offspring (Kingsbury et al., 2016).

Similarly, maternal stress during pregnancy has been related to childhood outcomes associated with later development of depression (Koenen et al., 2009). In particular, accumulating research suggests that maternal stress during pregnancy is related to childhood cognitive difficulties frequently seen in the histories of depressed populations (Hofstra et al., 2002; Wood et al., 2013), such as lower scores on tests of intellectual functioning and language abilities (Laplante et al., 2008; Slykerman et al., 2005), problems of attention/concentration (Brouwers et al., 2001; Gutteling et al., 2006), and difficultites in academic performance (Niederhofer and Reiter, 2004). Additionally, prenatal maternal stress has been associated with increases in offspring behavioral/emotional problems during childhood that are linked to risk of later depression (Zahn-Waxler et al., 2000), such as childhood anixety (Davis and Sandman, 2012; Loomans et al., 2011), parental report of behavioral maladjustment (Gutteling et al., 2005; O'Connor et al., 2002), internalizing problems (Howland et al., 2016; Park et al., 2014), and temperaments associated with increased frustration, crying, and negative reactivity (Davis et al., 2007; Gutteling et al., 2005; Werner et al., 2007). Evidence also suggests sex differences in fetal exposure to prenatal stress with females showing an increased risk for later affective problems compared to males, following fetal exposure to maternal stress (Quarini et al., 2016; Sandman et al., 2013). Further, there is substantial evidence that psychosocial stress is associated with increased risk of infection and increases in inflammation in both pregnant and non-pregnant populations (Coussons-Read et al., 2007, 2005; Culhane et al., 2001; Glaser and Kiecolt-Glaser, 2005; Wadhwa et al., 2001). Despite these findings, no studies have examined the potential interactions between maternal stress and infection during pregnancy and later risk for offspring depression.

Utilizing a prospectively collected, large birth cohort study with follow-up data through adolescence, the aim of the present study was to investigate whether maternal infection and/or stress during pregnancy was associated with risk of adolescent depression among offspring. Based on known associations between maternal infection and stress during pregnancy and negative developmental outcomes in offspring (reviewed in (Markham and Koenig, 2011; Richetto and Riva, 2014; Simanek and Meier, 2015)), we predicted that the presence of maternal infection and/or stress during pregnancy would be associated with higher scores on adolescents' self-reported ratings of current depressive symptomology. Gestational timing of infection also was examined, given evidence that insults during specific gestational time periods may confer increased risk for adverse offspring outcomes (Brown et al., 2004). Specifically, the second trimester of pregnancy has been hypothesized to be a critical period of time for the influence of maternal stress and infection on fetal neurodevelopment and risk of offspring depression (Brown, 2006; Ellman et al., 2008). Gestational timing of maternal stress could not be examined, as interviews were conducted primarily during the second trimester of pregnancy. The second important consideration in the present study was whether stress during pregnancy moderated the association between infection and offspring adolescent depressive symptoms, given the potential for stress to increase susceptibility to infection (Coussons-Read et al., 2007; Howerton and Bale, 2012). We hypothesized that mothers who reported experiences of daily stress during pregnancy and were diagnosed with an infection during pregnancy would have offspring with significantly higher depression scores than mothers of adolescents who experienced stress or infection alone.

2. Methods

2.1. Participants

Study procedures were approved by the following Institutional Review Boards: Columbia University, Public Health Institute, University of California-Los Angeles (UCLA) and Temple University. The Child Health and Development Studies (CHDS) is a prospective cohort study that enrolled pregnant women from 1959 to 1966 in Alameda County, California (van den Berg et al., 1988). The CHDS recruited almost all pregnant women receiving prenatal care through the Kaiser Foundation Health Plan (KFHP) at its clinics in the area (N = 19,044 live births; for review see van den Berg et al., 1988).

The Adolescent Study included offspring and mothers from the original CHDS cohort (who gave birth from 1960 to 1963, and resided in the San Francisco Bay Area). Offspring of the mothers (N = 2020) were followed from birth to adolescence. Mothers and offspring completed a series of interviews and questionnaires regarding health, health behaviors (e.g. exercise, smoking/drinking), and family relationships. Compared to the original CHDS cohort, the Adolescent subsample included a greater proportion of participants who were married and living with a husband at the original intake, who were white, and who were high school graduates; it also included a smaller proportion of first-born offspring (Keyes et al., 2011). Nevertheless, these differences were small and the demographic characteristics of the Adolescent Study still reflect a diverse and representative study sample (Keyes et al., 2011). Maternal interview data from pregnancy was available for 1976 of the 2020 adolescents (97.8%) participating in the study. As there were multiple offspring from the same mother in the sample, the present study randomly selected one member of each sibling set (n = 255) for removal to eliminate non-independent observations. An additional 10 participants had missing adolescent interview data, resulting in a final analytical sample of 1711 mothers (see Table 1 for demographic characteristics).

2.2. Prenatal exposure data

2.2.1. Maternal interviews and stress measurement

The maternal interviews in this study were conducted primarily during the second trimester of pregnancy (mean weeks gestation =

Table 1
Demographic characteristics of the sample (N = 1711).

Demographics	Overall sample (*n* = 1711)	
	N	**%**
Offspring sex		
Male	859	49.8
Female	852	50.2
Maternal race		
Caucasian	1304	76.2
African American	317	18.5
Asian	90	5.3
Maternal education		
Less than or equal to H.S.	782	45.8
Greater than H.S.	927	54.2
Maternal marital status		
Married	1684	98.4
Condition of newborn following delivery[a]		
Stillbirth	21	1.2
Spontaneous cry (good/excellent condition)	1564	91.9
Cried within 1–3 min	50	2.9
Cried within 3–5 min	32	1.9
Cried > 5 min or "other than good" condition	34	2.0
	Mean	**SD**
Birth weight (g)	3365.1	516.3
Gestational Age at Interview (Weeks)	15.3	6.8
Gestational Age at Birth (Weeks)	40.0	2.2
Maternal Age at Birth	29.0	6.0
Maternal Parity	2.14	2.0
Adolescent Age at Interview[b]	16.56	0.64
Adolescent Depressive Symptoms[b]	23.36	5.12
Maternal Depressive Symptoms at Adolescence	14.90	3.35

Note: The following variables had missing data: maternal education (n = 2); maternal marital status (n = 14); condition at birth (n = 10); GA at interview (n = 10); GA (n = 10); maternal age (n = 4); adolescent depression scores (n = 111); maternal depression scores (n = 191).

[a] Condition of newborn reflects time in minutes to sustained cry and respiration following delivery.

[b] Unadjusted values.

15.3, *SD* 6.8) and included comprehensive questions about the mother's behaviors, attitudes, and reproductive health history. Detailed sociodemographic information (age, ethnicity, education, occupation, place of birth) was collected for all mothers and their partners. Maternal psychosocial stress during pregnancy was measured using mothers' open-ended responses to the question "What kinds of things have been worrying you recently?" Responses often included detailed reports of financial and interpersonal stress, as well as stressful life events. Stress-related themes were extracted and coded from maternal narratives (Fineberg et al., 2016). Specific themes included: traumatic life events (TLEs), daily life stress, and pregnancy-specific anxiety (PSA), based on previous studies (Fineberg et al., 2016). These themes were chosen because these constructs previously have been associated with depression or obstetric/childhood risk factors associated with depression and have been successfully used in predicting risk of schizophrenia in the CHDS cohort (Betts et al., 2015, 2014; Brown et al., 2000a, 2000b; Buss et al., 2011; Da Costa et al., 1998; Huizink et al., 2003, 2002; Fineberg et al., 2016; Pritchard and Teo, 1994; Shah et al., 2011; Watson et al., 1999). Stress-related themes were operationally defined and coded based on well-established definitions of the constructs (e.g., (Cohen et al., 1997; Khashan et al., 2008; Serido et al., 2004)) and/or using a validated measure of the construct as a guide (e.g., (Cohen et al., 1983; Rini et al., 1999)).

TLEs were coded if there was actual or threatened death or serious injury, threat to physical integrity of self/others, and/or loss or diagnosis with cancer, acute myocardial infarction, or cerebrovascular accident of a close relative (Khashan et al., 2008). Daily life stress was coded if the mother reported discrete observable events that required adjustment in identity or routines (Cohen et al., 1997) or relatively minor events that disrupt daily life (Serido et al., 2004), such as marriage difficulties, moving, chronic (not life-threatening) illness of family member, and financial stress. Pregnancy-specific anxiety was coded if the mother reported worries or concerns about the pregnancy (e.g., fear of losing the baby) (Rini et al., 1999). Responses were coded according to a detailed coding manual by two trained independent raters blinded to offspring characteristics. Inter-rater reliability was achieved after coders reviewed 50 randomly selected maternal interviews from a distinct subset of the original CHDS cohort (mean ICC = 0.89 with ICCs ranging from 0.72 to 1.0). ICCs of 0.70 or above on the test cases were required before raters could proceed with review of maternal interviews from the Adolescent Study. In addition, 75 interviews from the current analytic dataset were selected at random and coded by both coders independently. ICCs for the second reliability check ranged from 0.76 to 1.0 (mean ICC = 0.81). Although interview coding documented the frequency with which women reported a stress theme (e.g., multiple mentions of daily stress within a single narrative), given the limited variability in the frequency of reporting one stress theme multiple times within an interview, stress variables were dichotomized to indicate presence or absence of the specific stress theme for the mother during pregnancy. Stress themes were coded using ATLAS.ti 6 (ATLAS.ti Scientific Software Development GmbH, Berlin, Germany).

2.2.2. Measures of maternal infection during pregnancy

Maternal medical events were abstracted in detail from women's Kaiser medical records. Records included virtually all medical events (diagnoses, special diagnostic procedures, hospitalizations, operations, routine check-ups, and prophylactic treatments) occurring six months prior to the women's last menstrual period until after delivery, including detailed information regarding the presence and timing of a variety of maternal infections during pregnancy. Individual infection diagnoses included poliomyelitis, measles, rubella, chicken pox, mumps, hepatitis, mononucleosis, rheumatic fever, tuberculosis, strep throat, sinusitis, laryngitis, pharyngitis, coryza, cold symptoms, tonsillitis, influenza, pneumonia, bronchitis, rhinitis, pleurisy, empyema, syphilis, gonorrhea, genital warts, venereal disease, endometritis, oophoritis, salpingitis, pelvic inflammatory disease (PID), cervicitis, vaginitis, trichomoniasis, monilia, and urinary tract infection. These infections were chosen, because they 1) have been associated with increased risk for other psychiatric disorders in offspring (Babulas et al., 2006; Brown et al., 2009a, 2000a, 2000b, 2009b; Parboosing et al., 2013); 2) caused clinically significant symptoms that warranted a doctor's visit, indicating the probability of an inflammatory response (Al-Adnani and Sebire, 2007; Mor and Cardenas, 2010; Racicot et al., 2014; Romero et al., 2007) and 3) mostly do not appear to cross the placenta, indicating that maternal immune responses may be a primary route by which the infection impacts the fetus (Kourtis et al., 2014; Patterson, 2009; Robbins and Bakardjiev, 2012; Shi et al., 2005; Van den Veyver et al., 1998). Infection variables were collapsed across categories and a single dichotomous infection variable was created to indicate presence or absence of infection in each trimester, similar to previous CHDS studies (Babulas et al., 2006; Brown et al., 2009a, 2000a, 2000b, 2009b; Parboosing et al., 2013). The presence of infection during specific trimesters also was explored.

2.3. Age 9–11 childhood visit

2.3.1. Maternal stress and disciplinarian style during childhood

At the 9–11 visit mothers were asked to provide yes/no responses to questions about whether finances, marital relations, employment, and/or health concerns that were worrying them recently. These four variables were included to account for the influence of postnatal stress on offspring development, as prenatal and postnatal environments can exert independent and interactive effects on mental and physical health outcomes (Entringer et al., 2015). Disciplinarian style, which was assessed via yes/no response to the questions "Would you consider

Table 2
Adolescent depression symptoms scale.

Overall how happy would you say you are nowadays?[a]
There is really no way I can solve some of the problems I have.
I can do just about anything I really set my mind to.[a]
I often feel helpless in dealing with problems in my life.
I have little control over the things that happen to me.
I feel that I'm a person of worth, at least on an equal plane with others.[a]
I feel that I have a number of good qualities.[a]
I am able to do things as well as most other people.[a]
I feel I do not have much to be proud of.
I take a positive attitude toward myself.[a]
Sometimes I think I am no good at all.
What happens to me in the future mostly depends on me.[a]
I feel that I can't do anything right.
I feel that my life is not very useful.

[a] Items were reversed scored.

yourself a strict disciplinarian?" and "Would you consider your husband a strict disciplinarian?," also was included to tap variables related to parenting behaviors during childhood as certain parenting styles (e.g., lack of warmth, authoritarian practices) have been associated with depression outcomes in offspring (Alloy et al., 2006; King et al., 2016).

2.4. Adolescent outcomes

2.4.1. Adolescent depression

Adolescents, ages 15–17, completed a 130-item self-administered questionnaire regarding different aspects of their lives and beliefs about themselves. Fifteen of these items addressed questions related specifically to current depressive symptomology (see Table 2). All adolescents responded to the same items on the depression scale using a 4-point Likert scale. Adolescent responses were summed and adolescent depression was examined as a continuous dimensional variable.

Analyses demonstrated high internal consistency of the depression scale (Cronbach's alpha = 0.81). Analyses also indicated that the scale had high predictive validity with semi-structured interviews conducted in 20–30 year follow-up studies. For instance, cohort members who received a Major Depressive Disorder (MDD) diagnosis in follow-up studies (n = 13 MDD, n = 39 controls overlapping with the adolescent cohort) using semi-structured interviews (First et al., 1994; Nurnberger et al., 1994) had significantly higher scores on the adolescent depression scale compared to those who received no depression diagnosis ($p = 0.04$, Cohen's $d = 0.62$).

Adolescent depression scores were also consistent with maternal assessment of their child's mood during adolescent interview. Mother's responses to the question "Overall, how happy would you say your child is?" with answers of "not too happy" or "very unhappy" had adolescents with significantly higher depression scores than adolescents of mothers who reported their child was "fairly happy" or "very happy" [$F(3, 1520) = 39.95$, $p < 0.001$].

2.4.2. Maternal depressive symptoms during adolescence

Mothers completed a self-report inventory of depressive symptoms that mirrored the self-report inventory completed by the adolescents at the same time point. The scale demonstrated high internal consistency (Cronbach's alpha = 0.76). As children of depressed mothers are at an increased risk for depression during childhood and adolescence (Beardslee et al., 1998), maternal depressive symptoms during adolescence were controlled for in statistical analyses. Furthermore, consideration of maternal depressive symptoms provided a crude assessment of genetic liability, given known genetic contributions of major depressive disorder (Fava and Kendler, 2000).

2.5. Data analysis

Adolescent depression was the main dependent variable. First, to rule out potential confounding variables, bivariate relationships were examined between the following variables and the main independent and dependent variables: infant sex, maternal race, maternal age at delivery, gestational length of the pregnancy, offspring birth weight, condition of the baby at birth (i.e., sustained cry and respiration), adolescent age, childhood parenting styles (parental perceptions of themselves as 'strict disciplinarians' when offspring were 9–11 years old), maternal depression at adolescence, and several variables attempting to tap into postnatal stress (e.g., maternal report of financial, marital, employment and health worries when offspring were 9–11 years old). Variables related to the main dependent and independent variables were added as covariates in statistical models; variables that were associated with the dependent variable were also included if they could influence the interpretation of findings (Keppel, 1991). Second, postnatal socioeconomic status (SES) was controlled for indirectly via maternal education at birth, as this variable has been strongly correlated with other measures of SES (e.g., income, employment) in related studies (Fineberg et al., 2016) and is frequently used in the literature as a proxy for postnatal adversity (Schlotz and Phillips, 2009). Moreover, the maternal education variable offered clearer delineation of SES compared to similarly related measures of SES (e.g., the family income data variable), which suffered from substantial missing data and issues of interpretability (i.e., incomes were from the 1960's). Further, maternal education was significantly associated with the main dependent and independent variables. First, separate ANCOVAs were conducted for infection analyses by trimester. Second, ANCOVAs were conducted for individual maternal stress themes during pregnancy (e.g., daily stress, TLE, PSA). Third, stress by infection interaction terms were added to ANCOVA analyses to determine whether stress moderated the relation between infection during pregnancy and offspring depression. These models were conducted separately for the first and second trimester of infection. Statistical analyses were conducted using SPSS version 22 software (Armonk, NY). All tests were two-tailed with $p < 0.05$ indicating significance.

3. Results

Results from the ANCOVA analyses are presented in Fig. 1 and Table 3. Maternal education was the only covariate that was significantly associated with the main dependent and independent variables. Adolescent age and maternal depressive symptoms at adolescence were also included as covariates, as these variables were significantly associated with adolescent depressive symptoms. There were no significant differences in depression scores for offspring prenatally exposed to infection in the first or third trimesters compared to unexposed offspring. Analyses indicated a significant difference in adolescent depression scores between offspring exposed prenatally to second trimester maternal infection and compared with unexposed offspring, while controlling for maternal education at birth, adolescent age, and maternal depressive symptoms at adolescence ($p = 0.02$, $d = 0.17$). While there were no significant differences in adolescent depression scores based on maternal experiences of any of the stress themes (see Table 3), there was a significant interaction between second trimester maternal infection and maternal experiences of daily stress during pregnancy ($p = 0.04$) controlling for maternal education, adolescent age, and maternal depression symptoms at adolescence. No other significant interactions were found between maternal stress themes and individual trimester maternal infections (see Table 3). Among mothers who reported experiences of daily stress during pregnancy, offspring exposed to maternal infection during the second trimester exhibited significantly higher depression scores compared with unexposed offspring, $F(1, 1421) = 9.78$, $p = 0.002$, $d = 0.31$, after controlling for maternal education at birth, adolescent age, and

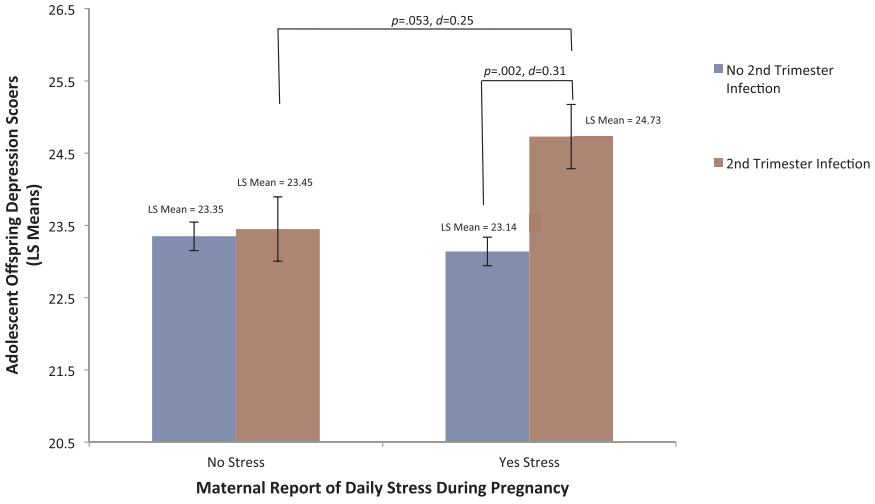

Fig. 1. Figure displays least square mean values for adolescent depression scores by maternal 2nd trimester infection and daily experiences of stress during pregnancy. All ANCOVA analyses controlled for maternal education at birth, adolescent age, and maternal depressive symptoms at adolescent interview (NS = nonsignificant at $p < 0.05$).

maternal depression symptoms at adolescence. Similarly, adolescent depression scores were higher in offspring who were exposed to both maternal experiences of daily stress during pregnancy and maternal infection during the second trimester compared to offspring only exposed to maternal second trimester infection, although this finding only approached significance, $F(1, 1421) = 3.76$, $p = 0.053$, $d = 0.25$, after controlling for maternal education at birth, adolescent age, and maternal depression symptoms at adolescence. In contrast, among mothers who did not report daily stress, there were no significant differences in offspring adolescent depression scores among offspring exposed and unexposed to maternal infection during the second trimester, $F(1, 1421) = 0.04$, $p = 0.85$ (see Fig. 1). Results for offspring were consistent in unadjusted analyses and analyses accounting for dependent observations (see Table 3 and Table S, respectively).

4. Discussion

This is the first study to find that maternal infection during the second trimester was significantly associated with higher scores on a measure of self-reported offspring depressive symptoms during adolescence in a population-based, prospectively collected longitudinal cohort. Although maternal report of daily stress during pregnancy did not independently predict adolescent depression scores, maternal daily stress during pregnancy moderated the association between second trimester maternal infection during pregnancy and adolescent depression scores. Specifically, our findings suggest that it is only in the context of maternal stress that prenatal infection portends increased risk for adolescent depressive symptoms. Fetal exposure to infection led to no significant increases in offspring depression among offspring with mothers who did not report daily stress during pregnancy. More specifically, the results indicate that the combination of maternal stress and infection during pregnancy may confer greater risk for offspring depressive symptomology than maternal stress or infection alone.

Support for these results comes from evidence from animal research suggesting that prenatal exposure to maternal infection during pregnancy may confer long-term consequences for offspring similar to the effects seen in depressed samples. Animal studies have repeatedly linked prenatal maternal infection to brain abnormalities and behaviors common in depressed populations and related disorders (e.g., schizophrenia), including deficits in social interaction, deficits in prepulse inhibition, deficits in open field and novel object exploration, impaired hippocampal functioning, hippocampal-related memory impairments,

Table 3
Maternal stress and infection ANCOVA analyses for risk of depression in adolescent offspring.

	Offspring with maternal exposure vs offspring without exposure, adjusted			Offspring with maternal exposure vs offspring without exposure, unadjusted		
Exposure	*F* (*df*)	*p*	Cohen's *d*	*F* (*df*)	*p*	Cohen's *d*
Infection						
1st Trimester	0.50(1, 1423)	0.48	− 0.06	0.48(1,1598)	0.49	− 0.05
2nd Trimester	5.56(1,1423)	0.02*	0.17	4.14(1,1598)	0.042*	0.14
3rd Trimester	0.01 (1,1423)	0.91	− 0.009	0.08(1,1598)	0.78	− 0.02
Maternal stress						
Daily stress	0.02(1,1423)	0.89	0.01	0.03(1,1598)	0.86	0.09
TLE	0.04(1, 1423)	0.83	− 0.02	0.63(1,1598)	0.43	− 0.08
PSA	1.16(1,1423)	0.28	− 0.08	1.39(1,1598)	0.24	− 0.08
1st Trimester × Daily stress	0.82 (1, 1421)	0.37	–	0.21(1, 1596)	0.65	–
2nd Trimester × Daily stress	4.24(1, 1421)	0.04*	–	4.36(1,1596)	0.037*	–
1st Trimester × TLE	2.66(1, 1421)	0.10	–	0.89(1,1596)	0.35	–
2nd Trimester × TLE	1.63(1, 1421)	0.20	–	1.92(1,1596)	0.17	–
1st Trimester × PSA	0.06(1, 1421)	0.81	–	0.08(1, 1596)	0.78	–
2nd Trimester × PSA	0.09(1,1421)	0.76	–	0.11(1,1596)	0.74	–

Note: Adjusted analyses controlled for maternal education at birth, adolescent age, and maternal depressive symptoms at adolescent interview (TLE = Traumatic Life Event; PSA = Pregnancy-Specific Anxiety). Least square mean values for adolescent depression scores were significantly different in offspring prenatally exposed to maternal second trimester infection ($M = 24.10$) compared to unexposed offspring ($M = 23.24$).

* $p < 0.05$.

alterations in hypothalamic pituitary (HPA) axis reactivity, long-term reductions in cortical gray matter, and depressive-like phenotypes (reviewed in (Bilbo and Schwarz, 2009; Markham and Koenig, 2011; Patterson, 2009; Patterson, 2002; Short et al., 2011)). Similar findings have been demonstrated in animal models using poly[I:C] and LPS, immune activating agents that mimic specific innate immune responses to viral or bacterial pathogens, respectively (reviewed in Ronovsky et al., 2016). These experiments suggest a link between maternal immune activation (MIA) during pregnancy and depression-related phenotypes in offspring, including increases in depressive-like behaviors in adult offspring (e.g., helplessness, anhedonia, behavioral despair), and brain abnormalities that have been associated with depression, such as reduced hippocampal cell proliferation and long-term potentiation (Babri et al., 2014; Depino, 2015; Graciarena et al., 2010; Khan et al., 2014; Lin and Wang, 2014; Zhang and van Praag, 2015). Both animal and human studies suggest that maternal timing of infection during mid-gestation (i.e., the second trimester) may be particularly relevant to the development of psychopathology in offspring (reviewed in (Boksa, 2010)). In rodents, experiments using poly[I:C] models of MIA suggest discrete windows of in utero exposure to infection may determine specificity of subsequent disorders in offspring with exposure at times corresponding to the second trimester in humans linked to depressive phenotypes, such as anhedonia and negative symptoms (Bitanihirwe et al., 2010; Labouesse et al., 2015).

Although a variety of studies have found that maternal stress during pregnancy is associated with adverse offspring outcomes similar to those found in depressed populations (Betts et al., 2015, 2014; Brown et al., 2000a, 2000b; Buss et al., 2011; Da Costa et al., 1998; Kingsbury et al., 2016; Pritchard and Teo, 1994; Shah et al., 2011; Watson et al., 1999), the present study did not find any independent associations between reported maternal stress during pregnancy and risk for offspring depression. Rather, the present study only found that maternal stress during pregnancy moderated the relation between infection during pregnancy and risk for offspring depression. These findings are consistent with a growing body of literature supporting an association between prenatal maternal stress and infection and increased risk for offspring depression. The link between psychosocial stress and infection has been repeatedly established in non-pregnant populations (Cohen et al., 1999; Cohen and Williamson, 1991), with emerging evidence suggesting that this association may be true of pregnant populations as well (Wadhwa et al., 2001). One study demonstrated that pregnant women experiencing high levels of chronic stress were significantly more likely to have bacterial vaginosis compared to those with low levels of stress, an effect which persisted even after controlling for relevant sociodemographic and behavioral risk factors (Culhane et al., 2001). Another study found individuals diagnosed with genitourinary infections during pregnancy had significant increases in cortisol during specific time periods of gestation (Ruiz et al., 2001). Importantly, data suggest that increases in prenatal stress are associated with higher levels of proinflammatory cytokines interleukin 6 (IL-6) and tumor necrosis factor (TNF-α), and with lower levels of anti-inflammatory cytokine IL-10 (Coussons-Read et al., 2005). Such changes are significant as most infections do not cross the placenta, but rather findings suggest that risk to the fetus may be related to maternal immune responses to infection (Fineberg and Ellman, 2013). Taken together, these studies present further support for stress-related changes in immune and endocrine functioning that may have meaningful consequences for pregnancy and offspring health.

While many women endorse occasions of stress and infection during pregnancy, the majority of mothers do not experience negative pregnancy outcomes as a result of exposure to these conditions on their own. This study provides preliminary results suggesting that stressful conditions during pregnancy may create a maternal environment in which infection may be more likely to influence fetal development. While it is unclear the specific mechanisms by which this occurs, there is some evidence to suggest that stress compromises the permeability of the placenta, potentially increasing fetal exposure to proteins (Aye and Keelan, 2013), such as proinflammatory cytokines, although this has not been well researched. While there is evidence that interleukin-6 (IL-6) can cross the placenta, there are a paucity of findings on cross-placental transfer of other immune proteins and whether maternal states during pregnancy increase permeability of a variety of cytokines across the placenta (Zaretsky et al., 2004). However, studies in rodents (Holmes et al., 2006; Mairesse et al., 2007) and humans (Glover et al., 2009) have shown associations between maternal stress and down-regulation of a placental enzyme responsible for converting cortisol to inactive cortisone, potentially allowing greater placental permeability to maternal cortisol, as well as other factors such as cytokines. Future animal and human studies are needed to investigate the specific pathways by which maternal stress and infection during pregnancy operate to influence fetal neurodevelopment.

Among the strengths of this study is the use of prospectively collected data specifically examining maternal and adolescent offspring health outcomes. Moreover, continual follow-up of offspring potentially allowed a more representative self-report measure of the whole spectrum of depressive symptoms and cases than previous cohort studies, which relied primarily on psychiatric hospital admission data. Another major strength is the access to detailed prospectively acquired information about maternal stress and experiences during pregnancy. However, a potential limitation of the scale used to measure adolescent depressive symptoms should be noted. Although the scale addressed several themes related to depressive symptomology (e.g., inadequacy, worthlessness, failure), the scale failed to assess common somatic symptoms of depression, such as issues with sleep, energy, appetite, and movement, symptoms of which have been linked to inflammation in depressed populations (Andréasson et al., 2007; Bower et al., 2002; Motivala et al., 2005). Therefore, it is possible that our findings would have been stronger and/or other trimesters would have been identified as portending risk if these additional symptoms were included in the depression scale. Future studies would benefit from standardized measures of depression, as this type of assessment would provide determination of whether prenatal infection is associated with clinical diagnoses of depression in offspring, as well as depression symptoms. Further, despite strict adherence to a detailed coding manual, measures of psychosocial stress were limited by available data (i.e., answers to the question “What kinds of things have been worrying you recently?”). Given the nature of the question, maternal narratives likely included disproportionately high reports of subjective stress (e.g., perceived stress) compared to objective stress (e.g., stressful life events). Importantly, the stress measures differed substantially from previous literature due to the qualitative nature of the assessment and unclear timing of the stress during pregnancy. It is possible that this contributed to the lack of findings regarding the main effect of stress or sex differences in offspring depressive symptoms, as these findings are inconsistent with other findings (Kingsbury et al., 2016; Sandman et al., 2013). Additionally, maternal interviews pertaining to reports of stressful experiences occurred predominantly in the second trimester; therefore, experiences of stress subsequent to the interview (i.e. in the third trimester) were not captured; however a number of studies have found decreases in reported maternal stress during the third trimester, potentially minimizing this concern (Blair et al., 2011; Davis et al., 2011; Glynn et al., 2008). Furthermore, given the multiple tests conducted in this study without adjusting p values for multiple comparisons, it possible that some of the findings were subject to Type 1 error. However, results related to the second trimester analyses were consistent with a priori hypotheses, reducing the probability of spurious findings. Another limitation included the use of multiple infections, as well as clinical diagnosis to determine infection status and timing, as serological information would be preferable. With respect to the former, future studies are necessary to determine whether there are differential influences of specific infections during pregnancy on risk for offspring depression. Nevertheless, many infections do not appear to

cross the placenta; therefore there may be common mechanisms related to risk to the fetus (e.g., inflammation, reviewed in (Fineberg and Ellman, 2013)). A final limitation concerns the small effect size associated with the study's findings. As a result, the magnitude and clinical significance of these findings should be interpreted with caution, although small effect sizes may have larger influences on disorders with high base rates in the population, such as depression (Kessler et al., 2005).

The current study has the potential to further our understanding of the role of prenatal maternal stress and infection and risk of depression in adolescent offspring. Results indicate that stress during pregnancy may increase the susceptibility women have to infection during pregnancy and/or exacerbate underlying infection symptoms during pregnancy as a result of prolonged stress, subsequently portending risk of adverse neurodevelopmental outcomes in offspring. It is also possible that prenatal infection and stress may leave offspring more susceptible to later insult (e.g., trauma, stress), creating a latent vulnerability to depressive symptoms in adolescence via a “multiple-hit” model (reviewed in Nabeshima and Kim, 2013). Preliminary evidence from research in mice suggests that combined exposure to prenatal inflammation and postnatal psychological stress in adolescence is associated with behavioral and neurochemical abnormalities consistent with those seen in neuropsychiatric disorders, highlighting the possibility of synergistic environment factors in the development of psychopathology (Giovanoli et al., 2013, 2014). A recent study in humans provides similar support, finding joint effects of exposure to prenatal infection and offspring psychological trauma in the development of schizophrenia (Debost et al., 2017). Such findings imply that prenatal exposure to maternal environmental factors, such as prenatal stress and infection, may influence fetal growth and development, resulting in long-term health consequences for offspring. Future directions for research include consideration of postnatal risk and resilience measures (e.g. parenting behaviors) that may impact offspring depression among mothers who experience stress and infection during pregnancy. Consideration of cognitive and behavioral outcomes during earlier developmental time periods (e.g., childhood) also warrant further study, as these factors may uniquely contribute to depressive symptomatology in adolescence. Finally, future studies should consider the possibility of suppressor effects in order to determine more precise prediction of how developmental risk factors influence the onset of depression. Overall, results from the present study may provide a first step that could help inform maternal healthcare practices and lead to more effective interventions during pregnancy, as well as contribute to improvements in overall offspring health.

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Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at http://dx.doi.org/10.1016/j.psychres.2017.07.025.

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