Hypothesis

Association between Maternal Fever and Psychological/Behavior Outcomes: A Hypothesis

Stefan C. Dombrowski,[1]* Roy P. Martin,[2] and Matti O. Huttunen[3]

[1]Rider University, Graduate Education, School of Psychology Lawrenceville, New Jersey
[2]University of Georgia, Department of Educational Psychology Atlanta, Georgia
[3]University of Helsinki, Department of Psychiatry Helsinki, Finland

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BACKGROUND: This study is one of the first to investigate the association between maternal report of fever during middle to late pregnancy and psychological, behavioral, and educational outcomes in offspring. The hypothesis guiding this research was that maternal fever during the second trimester of pregnancy has an adverse effect on the development of the central nervous system (CNS) of the fetus, resulting in abnormalities of psychological development and behavior that can be observed in childhood. **METHODS:** Multivariate analyses of a birth cohort compared outcomes for children whose mothers never reported fever during pregnancy and those who reported fever in the second and third trimesters. Children were compared on measures of temperament, behavior, and academic performance in infancy and at five and 12 years of age. **RESULTS:** Associations were obtained for second-trimester fever and distress to novelty ($p < 0.05$) in infancy. Significant associations were also obtained for inhibition ($p < 0.01$), negative emotionality ($p < 0.05$), and lack of task persistence ($p < 0.01$) at age five. Furthermore, school achievement ($p < 0.05$) and task orientation ($p < 0.01$) at age 12 were associated with maternal reports of second-trimester fever exposure. **CONCLUSIONS:** Much of the gestation/hyperthermia research has focused on the relationship between hyperthermia exposure and profoundly teratogenic outcomes. In this study we investigated subtler psychological/behavioral associations that may not be observable until later in development. Although the current study was hampered by technical limitations, the results support the need for more rigorously controlled research into a possible association between gestational fever and psychological/behavioral outcomes. *Birth Defects Research (Part A) 67:905–910, 2003.* © 2003 Wiley-Liss, Inc.

Key words: gestational fever; pregnancy; child outcomes; temperament; behavior

INTRODUCTION

Maternal fever during pregnancy has been found to have adverse effects on the developing fetus (Hunter, 1984). An association has been reported in human studies between maternal first-trimester febrile episodes and later physical and neurological abnormalities, including neural tube defects, severe brain damage, facial dysmorphogeneses (e.g., micrognathia, cleft lip, midface hypoplasia, and external ear anomalies) and ophthalmological defects (Fraser and Skelton, 1978; Layde et al., 1980; Pleet et al., 1981; Shiota, 1982; Warkany, 1986; Milunsky et al., 1992; Lynberg et al., 1994; Edwards et al., 1997). While these studies demonstrated first-trimester teratogenic effects, there is some evidence that fever may have an adverse, albeit less profound, effect if it occurs during the second trimester of pregnancy. This evidence has accumulated in studies of second-trimester influenza infections. Epidemiological investigations reveal that influenza infection during the second trimester of pregnancy has been repeatedly associated with schizophrenia in progeny (Mednick et al., 1988; Kendall and Kemp, 1989; Barr et al., 1990; Rodrigo et al., 1992; Adams et al., 1993; Mcgrath and Castle, 1995). A secondary body of research has also provided epidemiological evidence that second-trimester influenza exposure may also be associated with affective disorders, including depression, bipolar disorder, and cycloid psychosis (Machon et al., 1997; Watson et al., 1999). Based on such evidence, some researchers have implicated fever as a possible teratogenic mechanism (Barr et al., 1990; Mehler and Kessler, 1999; Patterson, 2002). In these studies, it has been hypothesized that the developing fetus is vulnerable to environmental perturbations during the second trimester because this stage represents the beginning of a period of brain growth (Dobbing and Sands, 1979), and the time

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*Correspondence to: Stefan C. Dombrowski, 202 Memorial Hall, Rider University, Lawrenceville, NJ 08648. E-mail: sdombrowski@rider.edu

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when cell migration and other developmental phenomena of the central nervous system (CNS); (e.g., formation and connections of dendrites) are most active (Rakic, 1995). It has also been hypothesized that environmental disturbances, such as fever, may disrupt the timing of these processes and produce subtle malformations of the CNS that manifest in psychological outcomes (Machon et al., 1997; Patterson, 2002; Shi et al., 2003).

To date, however, no studies have investigated the effect of gestational fever exposure during pregnancy as it relates to later psychological and behavioral outcomes in the developing child. If fever exposure during pregnancy disturbs fetal brain development, then perhaps psychological and behavioral differences may be observable at later time periods during childhood. The purpose of the current study, therefore, was to investigate the impact of reports of maternal fever during the middle and late portions of pregnancy on psychological, behavioral, and academic outcomes in offspring at six months, five years, and 12 years of age. Specifically, it was hypothesized that maternal fever during the second trimester of pregnancy may result in psychological and behavioral outcomes at later stages of development.

MATERIALS AND METHODS

Participants

Participant data were obtained from the Helsinki Longitudinal Project, a prospective study of the antecedents and sequelae of early childhood temperament. The total sample consisted of all children (n = 6401) born between 1 July 1975 and 30 June 1976 in Helsinki, Finland, and the adjacent suburbs of Vantaa and Espo. The cohort size was adjusted by eliminating data for one twin of each twin pair. This adjustment resulted in a final cohort of 6388 children.

Two features of this study contribute to its uniqueness. First, the region from which the cohort was obtained is exceptionally homogeneous with regard to ethnicity: 90% are ethnic Finns, 7% are ethnic Swedes, 2% are from other Nordic countries, and only 1% are from non-Nordic countries. Second, the region was also homogeneous with regard to most indicators of social class. During the 1970s, Finland provided a strong social and economic support system for its citizens, including free health care and education. Thus, the socioeconomic status (SES) stratification that is common among many other industrialized countries was less evident in Finland during that time period. Wrede et al. (1980) reported that during the 1970s, 95% of mothers took part in prenatal care provided at government-supported clinics.

Expectant mothers at each prenatal visit to a government prenatal clinic were asked to complete a questionnaire describing their somatic and psychological health during the past month of pregnancy. Mothers were informed that participation was voluntary and for research purposes only. About 55% of the mothers chose to participate in the pregnancy questionnaire portion of the study. During each monthly prenatal visit, expectant mothers were asked to indicate whether or not they experienced fever during the past month. The fever questionnaire was a simple "yes/no" questionnaire, and it did not request information on either the magnitude or duration of a febrile episode.

Temperament data for the infant and preschool periods were collected at well-baby clinics. Visits at approximately six months and five years of age were part of the regularly scheduled pattern of visits of all mothers in the region. Assisted by attending nurses, mothers voluntarily completed questionnaires on their children's temperament at six months and five years of age. Data for the school-age period were compiled through an examination of academic performance and the voluntary completion of temperament and behavior ratings by the children's teachers. The following paragraphs describe the pregnancy questionnaire and the temperament and behavior rating forms.

Materials

Pregnancy questionnaire. At each prenatal visit, expectant mothers completed a 15-item questionnaire that asked about their somatic and mental health symptoms during the past month. The questionnaire included lists of symptoms of upper respiratory infection (e.g., fever, cough, rhinitis, and sore throat), and more general symptoms that might be related to pregnancy or other illnesses (e.g., nausea, diarrhea, fatigue, sleep problems, muscle pain, and headache). The questionnaire also contained lists of symptoms related to maternal mental health (e.g., anxiety/depression and mood lability). If fever was reported to have occurred at any time during the trimester, the mother was categorized as positive for the symptom during that trimester.

Infant temperament questionnaire. Mothers rated their infants on a 71-item version of the Carey Infant Temperament Questionnaire (Carey, 1970) when their children were six months of age. Based on an exploratory factor analysis using maximum likelihood factor extraction methods (Martin et al., 1997), five infant temperament factors were derived and used in this analysis: Biological Irregularity, Threshold, Distress to Novelty, Activity/Intensity, and Fussy/Demanding.

Preschool temperament questionnaire. Mothers also rated their preschoolers on a 72-item version of the Thomas, Chess, and Korn Parent Temperament Questionnaire (Thomas and Chess, 1977) when their children were five years of age. Based on an exploratory factor analysis, eight preschool temperament factors were derived (Martin et al., 1997) and used in the analysis: Negative Emotionality, Inhibition, Negative Persistence, Biological Irregularity, Emotional Intensity, Threshold, Activity Level, and Unhappy/Nonadaptive.

School-age temperament questionnaire. Teachers rated the 12-year-old children on the Keogh Teacher Temperament Survey. The following variables contained in this survey were used in the analysis: Task Orientation, Task Persistence, Inhibition, and Negative Emotionality.

Student grade reports. During the 1980s, Finnish elementary schools graded children on a 10-point scale, with a 10 indicating exceptional performance. One summative index of academic performance (Mean Academic Grade) was used in this study, which was the mean grade for all subjects, excluding physical education, art, music, practical skills, and behavior grade.

Methods

Because of the potentially confounding effects of maternal distress, gender, economic status, and maternal age, these variables in all subsequent analyses were controlled for statistically through the use of covariance procedures. Throughout all analyses, both multivariate logistic regression (MLR) and analysis of variance (ANOVA) procedures

Table 1
Number of Children in Each Sample

Sample	*n*	Percent of cohort	Percent with maternal pregnancy data[a]
Cohort	6388	100	
With pregnancy data	3489	54.5	
Infants sample	2001	31.2	
With pregnancy data	1291	20.2	64.5
Preschool (age 5) sample 1097			17.2
With pregnancy data	893	14.0	81.4
School age (age 12) sample	1289	20.2	
With pregnancy data	586	9.2	45.5

[a]Percent of the sub-sample for whom maternal pregnancy data were also available.

were used. MLR provides odds ratios (ORs) that are commonly seen in epidemiological/medical research, whereas ANOVAs enable the analysis of mean level differences and effect sizes, which are common in psychiatric/psychological research. Both statistical analyses were included to facilitate interpretation by a broader-based scientific population that often involves overlapping research interests.

RESULTS

The Helsinki Temperament Project was designed to sample the cohort at several different stages of development. Maternal temperament ratings were obtained for 2001 infants (50.2% male, 49.85% female) when they were approximately six months old. Temperament ratings were also obtained for 1097 of the children (54.2% male, 45.8% female) when they were five years old. Similarly, teacher behavioral and academic grade reports were obtained for 1289 of the children when they were 12 years old (51.8% male, 48.2% female). A summary of the cohort sample for which complete data were available is presented in Table 1. As shown in the table, fever and infant temperament data were available for 1291 children, fever and preschool temperament data were available for 893 children, and fever and 12-year school performance data were available for 586 children. Approximately 20% of the sample reported fever during middle or late pregnancy, with the majority reported as having occurred during the second trimester.

Since not all children of the cohort were studied, questions of ascertainment bias may arise. An extensive analysis of demographic variables, maternal mental health characteristics, smoking behavior, symptom patterns during pregnancy, and childhood temperament scores revealed few significant differences and no pattern indicative of ascertainment bias, with two exceptions. Children for whom infant temperament data were available were born approximately one month earlier during the cohort year, and represented approximately 9% more first-born children than the total cohort. It is likely that these differences reflect an initial eagerness on the part of the clinic staff and first-time mothers to participate in the study. The representativeness of the children assessed at five and 12 years of age was very similar to that of the children assessed in infancy.

Children assessed at ages five and 12 were not all the same children assessed at infancy. About one-third of the sample assessed at age five was also assessed in infancy, and a similar proportion of the 12-year participants were assessed in infancy. Thus, while all of the children were from the same birth cohort, only about one-third of the children were assessed at each assessment wave. Because of sample-size attrition, each child could not be tracked repeatedly across the three developmental stages.

Since only about 55% of the cohort mothers provided pregnancy questionnaire data, there was a chance that those who completed the pregnancy questionnaires were different from those who did not. Table 2 lists the demographic and family variables that were available in this study, and the frequencies and mean levels of the entire cohort are compared with those of the women who provided pregnancy questionnaire data. These data are consistent with the notion that the responders to the pregnancy questionnaire were not different from those in the cohort, at least with regard to the variables studied (gender distribution, maternal parity, socioeconomic status of the

Table 2
Comparison of Entire Cohort and That Portion of the Cohort for Whom Mothers Completed Symptom Questionnaires During Pregnancy

Characteristic	Cohort	Sub-sample with pregnancy data
Gender	52.7% male	53.0% male
Maternal parity	56.7% primipara	57.7% primipara
	43.3% multipara	42.3% multipara
Mean maternal age	27.26 years (s.d. = 4.51)	27.33 (4.30)
Mean paternal age	29.28 years (s.d. = 5.33)	29.17 (4.92)
Mean number of older siblings	.74 (s.d. = .92)	.68 (.84)
Mean socio-economic status	2.7 (SD = 1.41)	2.78 (SD = 139)

Table 3
Association Between Gestational Fever and Psychological/Behavior Outcomes*

Behavior characteristics	No fever	2nd only	3rd only	F-value	*p*-value	Effect size[a]
Infancy (6 months)						
Distress to novelty						
Mean	49.98	51.34	49.39	1.33	NS	—
SD	9.94	10.37	10.37			
Odds ratio	1.00	1.09[b]	0.99			
95% odds CI		(1.00–1.19)	(0.89–1.12)			
Preschool (age 5)						
Negative emotionality						
Mean	−0.02	0.10	0.06	1.36	NS	—
SD	1.03	0.93	1.04			
Odds ratio	1.00	0.93	1.45[b]			
95% odds CI		(0.70–1.24)	(1.03–2.04)			
Inhibition						
Mean	−0.06	0.35	−0.05	4.80	0.01	0.38
SD	0.96	1.17	0.94			
Odds ratio	1.00	1.31[c]	0.96			
95% odds CI		(1.02–1.69)	(0.68–1.35)			
Lack of task persistence						
Mean	−0.08	0.27	−0.09	4.65	0.01	0.36
SD	0.97	1.01	1.04			
Odds ratio	1.00	1.26[c]	1.13			
95% odds CI		(1.04–1.52)	(0.84–1.50)			
Age 12						
Mean academic grade						
Mean	7.94	7.72	7.91	3.10	0.05	0.32
SD	0.80	0.86	0.95			
Odds ratio	1.00	0.83[b]	0.89			
95% odds CI		(0.69–1.00)	(0.46–1.75)			
Task orientation						
Mean	41.20	37.72	41.45	6.87	0.01	0.34
SD	10.19	11.71	10.01			
Odds ratio	1.00	0.95[b]	0.99			
95% odds CI		(0.94–1.03)	(0.96–1.04)			

*Table includes results from both multivariate logistic regression and analysis of variance procedures. F-value, ES, and *p*-value relate to analysis of variance results. NS = not significant for analysis of variance procedures.
[a]Effect sizes (Cohen's) expressed in SD units.
[b]Significant at $p < .05$.
[c]Significant at $p < .01$.

mother [an occupation-based measure obtained from medical records], percentage of children with no sibling, and mean number of older siblings). Similarly, a comparison of hospitalization rates during pregnancy between pregnancy card responders and nonresponders did not reveal any significant difference. Although all of the previously listed temperamental, behavioral, and academic variables were investigated in the analysis, only those for which a significant result was obtained are presented in Table 3.

The results of an MLR indicated that maternal report of fever during the second trimester was associated ($p < 0.05$) with distress to novelty in infancy (OR, 1.09; 95% CI, 1.00–1.19). This means that infants whose mothers reported fever during the second trimester of pregnancy were distressed by novel situations or new individuals more easily than infants whose mothers did not report prenatal second-trimester fever. Similarly, maternal reports of fever during the second trimester of pregnancy significantly increased the risk that offspring would experience difficulties with Task Persistence (OR, 1.26; 95% CI, 1.03–1.52) and Inhibition (OR, 1.31; 95% CI, 1.02–1.69) at age five. Thus, preschool children (age five) whose mothers reported fever during the second trimester were less task-persistent (e.g., could not attend to play and learning materials as long as their peers), and were more socially inhibited in the presence of strange adults or children than children whose mothers did not report having fever during the second trimester. It is noteworthy that two other temperament characteristics (biological irregularity and emotional intensity) had effect sizes of approximately 0.25 of a standard deviation (SD), and that the association was clearest for the second-trimester fever for emotional intensity, but about equal for second- and third-trimester fever for biological irregularity. For Emotional Intensity and Biological Irregularity, the respective ORs for these two variables following second-trimester fever exposure were as follows: OR, 1.18; 95% CI, 0.90–1.53; and OR, 0.81; 95% CI, 0.63–1.02. An MLR indicated that fever during the third trimester of pregnancy was significantly associated ($p < 0.05$) with Negative Emotionality (OR, 1.45; 95% CI, 1.03–1.51) resulting in a 45% increase in the relative risk of experiencing negative emotionality following third-trimester fever exposure. At age 12, MLR revealed that fever during the second trimester of pregnancy was significantly associated with reduced academic performance (OR, 0.83; 95% CI, 0.69–1.00) and decreased ability to orient toward tasks

(OR, 0.95; 95% CI, 0.94–1.03). Thus, school-age children (age 12) whose mothers reported second-trimester fever exposure were less capable of focusing on tasks and were at greater risk for reduced academic achievement.

DISCUSSION

Although much of the fever/hyperthermia research has focused on the profound effects following first-trimester exposure, it is possible that fever exposure during the second trimester can also produce alterations in CNS structure that manifest later in life as psychological (i.e., temperament) or behavioral difficulties. In accord with this line of thinking, a body of research investigating the association between influenza during the second trimester of pregnancy and psychiatric outcomes in offspring indicates that fever is the mechanism by which fetal neurodevelopment is perturbed (Barr et al., 1990; Wright and Murray, 1996; Mehler and Kessler, 1999; Patterson, 2002). In these studies, associations were found with both psychiatric and cognitive outcomes, including schizophrenia, depression, autism, bipolar disorder, and mental retardation (Mednick et al., 1988; Jancar, 1994; Mcgrath and Castle, 1995; Takei et al., 1995; Shi et al., 2003).

The second-trimester results of our study are partially consistent with these studies, as well as with a neurodevelopmental hypothesis regarding fetal brain development. Research on the development of the cerebral cortex during gestation has shown that there are a variety of well-timed events that may represent periods of particular vulnerability for the developing fetus (Rakic, 1995). One such period occurs when cells begin to migrate from the zone of proliferation to their final location in the cortex. This period occurs midway through the second trimester of gestation. Another period occurs late in gestation, when the hypothalamic-pituitary-adrenal (HPA) axis and the right hemisphere of the brain begin a growth spurt. The HPA axis and the right hemisphere have been implicated in social/emotional functioning and the stress response (Schore, 2001). The right hemisphere is also considered important for the ability to pay attention (Sturm et al., 1999). The hypothesis derived from this line of thinking is that neurochemical or hyperthermic alterations of developing subcortical limbic-autonomic circuits during a critical prenatal period of gestational development could lead to later social emotional problems (e.g., social inhibition or negative emotionality) (Sturm et al., 1999). Thus, a disruption during critical gestational time periods may lead to the emotional/behavioral (e.g., inhibition, distress response to novelty, or lack of task persistence) and academic difficulties reported in this study.

The results of this study are also consistent with those found in the literature regarding gestational influenza. In particular, most of the significant associations occurred when mothers experienced fever during the second trimester of pregnancy. The associations with Distress to Novelty in infancy, and Inhibition and Negative Emotionality at age five are also connected to the influenza literature in another way. The epidemiological literature has associated second-trimester intrauterine influenza exposure with a later onset of affective disorders, including depression, anxiety, and mood lability. Furthermore, in the temperament literature an elevated level of distress to novelty in infancy has been considered a precursor to higher levels of inhibition and negative emotionality in childhood (Martin and Bridger, 1999). Moreover, elevated levels of negative emotionality and inhibition in children are thought to be precursors to certain psychiatric conditions in adulthood, including depression and anxiety (Kagan, 1997). Thus, both the influenza literature and the current study appear to support a possible link between second-trimester gestational hyperthermia and mood disorders.

The most important results of this study relate to the possible association between maternal reports of fever during the second trimester of pregnancy and child outcomes six months to 12 years later. Specifically, children whose mothers reported a febrile episode during the second trimester had greater distress to novelty during infancy, and lower task persistence and higher social inhibition at age five than children whose mothers experienced no fever. Third-trimester fever exposure was also associated with elevated ratings of negative emotionality at age five. In addition, evidence was found for an association between second-trimester maternal reports of fever and decreased academic performance and lower task orientation at age 12. Most statistically significant relationships were of sufficient size to have a practical significance as well, and most mean differences were in the range of one-third of an SD.

The results of this study must be considered in the light of several significant limitations. During monthly visits to the prenatal clinics, mothers reported whether they had or did not have fever since the last visit. This method of reporting did not allow for measurements of the duration or intensity of a febrile episode. Second, it was impossible to separate the related effects of infectious illness, fever, or the mother's immunological response that would be associated with symptoms of fever. Although emphasis in the current study was placed on the possible causative role of fever, other agents elicited by maternal infection are equally suitable causative factors. For instance, cytokines and corticosteroids induced by maternal infection can cross the placenta, and have been known to affect brain development (Patrick and Smith, 2002; Patterson, 2002). Therefore, we acknowledge the possibility that fever itself may only be a marker for the influence of other agents that might more directly perturb neurodevelopment. A third limitation is that fever was measured by maternal report. Therefore, it will be important in future studies to directly assess body temperature. Fourth, the conclusions would be more compelling if the results were more fully consistent across measures and ages. Because of attrition we did not have data on the same children across time periods, and thus we could not conduct a repeated analysis. The measures of temperament are also based on different scales for each period (e.g., infancy, age five, and age 12). Unfortunately, at the time of the study, and continuing to the present time, temperament measures that span the mentioned time periods still do not exist. Therefore, this article might be viewed conservatively as three separate studies (one per time period) aggregated into one. Fifth, the generalizability of these results might be constrained by the sampling attrition that occurred across the three time periods. Although we examined aspects of this issue by demonstrating the equivalency of the characteristics of mothers who completed the pregnancy questionnaire compared to those of mothers who did not (including hospitalization characteristics of pregnant mothers; Table 2), data regarding the equivalency of fever are unavailable. Given these

limitations, this study should be considered exploratory. In fact, it will be important in future research to replicate the results of this study in a much more rigorous and controlled fashion.

Despite the limitations of this study, the results are consistent with the broader hyperthermia literature that has provided evidence of the deleterious impact of fever during pregnancy. The current findings are also consistent with previous epidemiological studies on exposure to influenza and mental illness in adult offspring, and extend observations concerning the risk of exposure to a much younger age group. Thus, additional, more pointed research on the impact of maternal second-trimester gestational fever seems warranted, particularly as it relates to psychological/behavior outcomes. Our study represents a first step in such investigations by presenting preliminary data that links fever during the second trimester of pregnancy with psychological, behavioral, and academic outcomes in childhood. However, considering the technical limitations of this study, the results clearly should be viewed as tentative (albeit intriguing) until similar research can be replicated in a more rigorous and controlled fashion.

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