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Early environment and major depression in young adults: A longitudinal study

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Abstract

Post-natal incubator care represents an early specific environment that may affect the risk for major depression later in life. A subsample of 1212 young adults from the French-speaking general population of the region of Quebec were selected from an ongoing longitudinal study that started during their kindergarten years. Information on peri-natal condition, obstetrical complications and incubator care was collected by consulting hospital medical records. Participants were evaluated using DSM III-R based psychiatric assessment when they were 15 and 21 years old. Incubator care predicted an approximate two- to three-fold decreased risk for depressive disorder at age 21. Results from three different logistic models adjusting for family adversity and for maternal depression confirmed this relationship. Analyses were replicated for depression at age 15, showing the same association in female adolescents. This study suggests that post-natal incubator care may paradoxically decrease the occurrence of major depression later in life. This protective effect might be direct (through optimized biological, physiological and sensory parameters) or indirect (induction of specific parent–child interactions due to the perception of their infant's vulnerability). This study could enhance understanding of the links between early post-natal environment and affective disorders later in life.

Keywords: Major depression; Incubator care; Post-natal environment; Resilience

1. Introduction

Emerging evidence from epidemiological studies (Essex et al., 2002; Jaffee et al., 2002; Heim et al., 2002; Gale and Martyn, 2004; Pruessner et al., 2004) has shown that the exposure of a newborn to early stressors might affect his development by promoting affective disorders later in life.

Recent animal studies suggest that early mother–infant interactions, including post-natal handling in the first week of life, have favorable consequences on the behavioural and endocrine responses to stress over the lifespan (Liu et al., 1997; Weaver et al., 2004; Zhang et al., 2006).

In the field of evolutionary medicine, the fetal origins hypothesis, or Barker's hypothesis, suggesting a correlation between conditions around the time of birth and risk

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of chronic disease later in life (Ellison, 2005), has attracted considerable attention.

Development is essentially a process of adaptation to adversity that may result both in vulnerability or resilience to the emergence of illness later in life (Zhang et al., 2006). Trials in the 1950s showed that optimizing the post-natal environment improves survival for low birthweight and pre-term infants. Neo-natal incubator care is now one of the most common post-natal interventions in developed countries (about one third of all births). This is a potential model of early maternal separation which can increase stress vulnerability and later depression-like behaviour.

In the present study, using data from a large, longitudinal population-based sample of 21-year-old participants and their mothers, we tested whether being treated in an incubator during the neo-natal period could be associated with an increased incidence of depression at ages 15 and 21.

A range of obstetrical and peri-natal parameters were carefully selected because they were associated with incubator care and were entered in several regression models as adjustment variables. In addition, subsequent adjustments on family adversity and maternal depression were performed (Kramer et al., 2000), as well as between incubator care and levels of maternal depression (Feldman et al., 2002).

2. Methods

2.1. Participants and data collection

Participants ($n=1212$) were part of an ongoing longitudinal study (Cote et al., 2002) that started in1986, when, at 6 years of age, they attended one of the French-speaking public schools in 1986–1987 (Brezo et al., 2006; Cote et al., 2002; Tremblay and Schaal, 1996).

The sample ($n=1903$) comprised 957 boys and 946 girls randomly selected from schools representative of urban and rural Quebec. To reduce cultural heterogeneity, only children whose parents were born in Canada and whose mother tongue was French were included in this cohort. The majority of children (89%) were Whites. The remainder reported being of Native Indian, Asian, Black, and White Hispanic origin. The attrition rate was 36.3%. Previous attrition tests of non-participating and participating members of the original cohort suggested no differences in childhood behaviours at ages 6 and 12 years or psychiatric diagnoses at age 15 (Brezo et al., 2006). Nevertheless, the non-participants had significantly higher early socio-economic adversity (including poorer childhood living arrangements and lower parental socio-economic status, age, or education). The proportion of infants having being treated with incubator care was not significantly different in participants who completed the study and in those who did not (16.5% vs. 17.8%, Pearson's $r=0.49$, $P=0.4$).

The study was approved by the research ethics boards of the University of Montreal. Written informed consent was obtained from all subjects.

2.2. Measures

2.2.1. Peri-natal condition and obstetrical complications

Information on obstetrical complications was collected by consulting hospital medical records. Obstetrical and peri-natal parameters included birthweight, gestational age, irregular position, umbilical cord prolapse, twin birth, and physical anomalies. Peri-natal and post-natal medical interventions were also studied and included use of forceps, cesarean section and incubator care. Table 1 shows that the most frequent conditions associated with incubator care were C-section, pre-maturity and low birthweight.

2.2.2. Diagnoses of major depressive disorder

Psychiatric diagnoses of major depressive disorders at age 15 were based on the Diagnostic Interview

Table 1
Comparing sex, age, race, family adversity, peri-natal condition and obstetrical complications in participants according to their antecedents of incubator care

Incubator care	Yes, $n=201$; 16.5%	No, $n=1011$; 83.5%	Chi^2/t
Sex	94M/107F	468M/623F	1.03
Age	20.82+0.8	20.80+0.8	0.04
Race Caucasian	176 (88%)	933 (92%)	4.07
Family adversity	0.30±0.18	0.27±0.19	− 1.96[a]
Obstetrical parameters			
Gestational age	34±5.1	36±3.6	39.8[b]
Birthweight	2893±728	3354±478	125.2[b]
C-section $n=220$	98 (48%)	117 (11.5%)	176[b]
Pre-maturity $n=265$	77 (38.3%)	188 (18.5%)	46.2[b]
Birthweight<2500g $n=98$	63 (31%)	35 (3.4%)	188[b]
Irregular position $n=111$	34 (16.9%)	74 (7.3%)	24.6[b]
Forceps $n=226$	29 (14.4%)	190 (18.7%)	0.73
Umbilical cord prolapse $n=104$	20(9.9%)	83 (8.2%)	1.49
Twin birth $n=23$	12 (6%)	11 (1.08%)	24[b]
Physical anomalies $n=30$	12 (6%)	18 (1.7%)	14.1[b]

[a] $P<0.05$.
[b] $P<0.01$.

Schedule for Children (DISC 2; Shaffer et al., 1996) and at age 21 on the 2005 version of the Diagnostic Interview Schedule (DIS) http://epi.wustl.edu/dis/dishome.htm), using DSM-III-R criteria. Mothers were also assessed for DSM major depression with the DIS when their children were 15 years old. Each interviewer received one day's training followed by a practice session and an additional half-day of training. Interviewers were blind to the antecedents of neo-natal incubator care.

2.2.3. Family adversity

Seven socioeconomic indices were used to create an index of family adversity (Tremblay et al., 1991). This was a composite index of family adversity ranging from 0 to 4, including the following: (1) the parents' ages when the first child was born, (2) the parents' levels of education, (3) the family socioeconomic status, and (4) the family living arrangement (e.g., living with biological parents). Families at or below the 30th percentile in one of these areas (or non-intact families) were coded as having one adversity point. Higher scores indicated lower age of the parents at the birth of the first child, lower education, lower income, or separated parents. Kindergarten family adversity was used because most of the variables in this index are either very stable in time (e.g., parents' education) or invariable in time (e.g., parents' ages at the birth of the first child). Information on these indices was collected during a telephone interview with the mother at the end of the child's kindergarten year. Occupational prestige represents a socioeconomic job index for Canadians, whereas family integrity indicated whether both biological parents were still living with the child. The accumulation of these different variables has been shown to increase the risk of emotional and behavioural disorders by creating stressful rearing conditions (Rutter, 1985). Because it was hypothesized that environmental conditions have their major impact early in life, only the age-6 measure of family adversity was used on the grounds that it represented the earliest index of the socioeconomic conditions in which the children grew up. The scores were standardized. This index does not take into account child maltreatment, which represents an important predictor of major depressive disorder.

2.3. Statistical analysis

We used univariate tests (Chi^2 and *t*-tests) to compare sex, age, race, family adversity, peri-natal condition and obstetrical complications in participants according to their antecedents of incubator care.

For major depression DSM diagnostic, we first focused on the age-21 data and not the age-15 data because the prevalence of the disorder at age 21 was most important and thus provided a better statistical model. Logistic regression analyses were performed to test the association between incubator care and major depression at age 21 (Model I), adjusted for sex, birthweight, and obstetrical complications. Then, we tested the same association by reestimating Model I after entering a measure indexing family adversity (Model II). Next, we tested the maternal transmission hypothesis by reestimating Model II after entering the diagnostic of mother's lifetime major depressive disorder (Model III). Finally, we repeated these analyses, using Model III to predict the diagnostic of major depression at age 15.

As several independent variables of the model were highly inter-correlated (i.e. incubator care and low birthweight), raising the problem of multicollinearity, we performed a set of supplemental analyses, introducing a single binary variable for obstetrical problems. This variable was coded 0 for "no obstetrical variable" and 1 for "any obstetrical problem". Multicollinearity between the independent variables was evaluated by the variance inflation factor (VIF) and the condition index (CI), applying SPSS procedures.

3. Results

3.1. Is there an association between incubator care and major depression at age 21, controlling for family adversity and maternal depression?

Based on the DIS, 112 subjects (8.6%) fulfilled criteria for lifetime major depression at age 21, according to DSM-IV criteria. Within the entire sample, 15.5% ($n=201$) had antecedents of incubator care (Table 1); in this subgroup, 11 suffered from major depression (5.4%), whereas in subjects without antecedents of incubator care ($n=1091$), 101 were diagnosed with major depression (9.25%).

Logistic regression was used to examine the relationship between incubator care and major depressive disorder (adjusted odds ratio = 0.34 [0,14–0.83]; $P=0.018$), adjusting for peri-natal condition and obstetrical problems (birthweight, gestational age, C-section, umbilical cord prolapse, forceps and irregular position).

In order to test the hypothesis that early environmental factors have a direct effect on major depressive disorder later in life, the model was further adjusted for family adversity and for maternal depression (Table 2).

In the three models, incubator care during the early post-natal period appeared as a significant factor decreasing the risk of major depression in young adults,

Table 2
Association between major depression at age 21 and antecedents of incubator care (adjusted odds ratio and range), controlling for sex, perinatal condition and obstetrical complications (Model I); plus family adversity (Model II); plus maternal diagnostic of lifetime major depressive disorder (Model III)

	Model I: Baseline	Model II: Family adversity	Model III: Maternal depressive disorder
Incubator care	0.3 [0.1–0.7] [a]	0.3 [0.1–0.7] [a]	0.3 [0.1–0.9] [b]
C-section	1.3 [0.6–2.6]	1.3 [0.7–2.5]	1.7 [0.4–7.7]
Birthweight	1.0 [1.0–1.0]	1.0 [1.0–1.0]	1.4 [0.6–3.5]
Gestational age	0.9 [0.6–1.7]	1.1 [0.6–1.7]	1.2 [0.6–2.6]
Twins	1.6 [0.3–7]	1.7 [0.3–8]	1.4 [0.2–7.2]
Irregular position	1.3 [0.6–2.8]	1.3 [0.6–2.7]	1.2 [0.7–2.0]
Sex	0.4 [0.2–0.6] [b]	0.4 [0.2–0.7] [b]	0.4 [0.3–0.7] [b]
Family adversity		3.7 [1.0–13.2] [b]	0.9 [0.4–1.7]
Maternal depression			3.0 [1.7–5.1] [b]

[a] $P<0.05$.
[b] $P<0.01$.

even after adjustment on various dependent variables. The effect of sex was significant and the risk for major depressive disorder was increased in female participants. High family adversity scores significantly increased the risk for major depressive disorder (Model II). But in Model III, with the addition of maternal depression, which was associated with the risk for major depressive disorder, the effect of family adversity was no longer significant.

There was no significant interaction between sex and the antecedents of incubator care on the risk of major depression (adjusted odds ratio [AOR]=1.4, $P=0.7$) nor on the number of symptoms of depression ($P=0.3$).

3.2. Is there an association between incubator care and major depression at age 15, controlling for family adversity and maternal depression?

Using the last regression model (Model III), we tried to replicate this result with an earlier measure of depression (at age 15, the participants were evaluated with the DISC-2.25) and results were marginal but in the same direction as findings with age-21 depression diagnosis (AOR=0.4; $P=0.07$).

We conducted the same analysis separately in the male and female groups. Incubator care antecedents significantly decreased the risk of major depression at age 15 in female participants (AOR=0.3; [0.1–0.9]; $P=0.03$) but not in male participants (AOR=0.6 [0.1–3.2]; $P=0.5$).

3.3. Is there still an association between incubator care and major depression at age 21, when using a simplified model avoiding multicollinearity between dependent variables?

To confirm the validity of these results in a model not biased by multicollinearity between independent variables, another regression model predicting major depression at age 21 was tested, by entering only two binary independent variables: “incubator care” and “any obstetrical problem”. Incubator care was still a significant predictor of major depression in this model ($P=0.049$). By contrast, the other independent variable “any obstetrical problem” was not significant ($P=0.74$).

The VIF (1.081) and CI (values of 2.29 and 12.35 for dimensions 2 and 3, respectively) were small compared with the values considered as a real concern for collinearity.

4. Discussion

This study explored for the first time the longitudinal relationships between post-natal incubator care and major depression at ages 15 and 21. Surprisingly, we found that incubator care significantly decreased the risk of major depression, even after multiple adjustments of potential confounders. The average AOR ranged between 0.32 and 0.33 in three different regression models. Using an earlier measure of major depression at age 15, we confirmed this result, but only in female participants (with a similar AOR=0.3), probably because major depression is less common boys, especially during middle adolescence.

To explain how post-natal incubator care intervention may reduce the risk of depression, we speculate that it could act through both direct and indirect pathways:

1) Incubator care allows adjustment of several key ambient parameters, improving thermal regulation and brain oxygenation and reducing heat loss and environmental noise, factors that may have an important impact on neurodevelopmental outcomes.
2) Having a baby placed in an incubator may have modified mother–child interactions; the maternal perception of the infant’s vulnerability may have led to specific long-term parenting styles or attitudes. Indeed, babies placed in an incubator just after birth may experience differential mother–child interactions due to the fact that the maternal perception of her baby’s vulnerability may modify her parenting style (Eiser et al., 2005).

Although any number of factors could account for variations of stress resilience, early life experiences and relationships, and particularly those with parents, may contribute to the development of appropriate styles of coping, which, in turn, influence affective responses in the face of stressors encountered later in life (Matheson et al., 2005).

On the other hand, recent research has documented that incubator traditional care intervention in premature infants, compared with skin-to-skin care, results in higher stress response in both mother and child (Morelius et al., 2005). Such studies show that incubator care impairs the infant's motor and cognitive development during the first months of life (Feldman et al., 2002) and affects parent–child interactions (Feldman et al., 2002; Tessier et al., 1998). Environmental adversity is known to affect the quality of parent–offspring interactions (Champagne et al., 2003; Smith et al., 2004) and it has been previously shown that the families of pre-term infants who are placed in an incubator immediately after birth experience the stress of physical separation (Klaus et al., 1972).

3) Finally, our results might be understood in a more comprehensive framework, in the light of recent findings from epigenetic studies: development is essentially a process of adaptation to adversity that may lead to increased vulnerability or resilience toward the emergence of multiple forms of illnesses (Zhang et al., 2006). For instance, early maternal care effects on gene expression and phenotypic variation in response to stress in rats appear to be associated with alteration in DNA methylation of relevant promoter sites (Weaver et al., 2004). Interestingly, the maternal care effect seems to occur only during the first week of life in rodents, which corresponds in terms of developmental stage to the prenatal period in humans. In examinations of the relation between maternal care and the development of behavioural and endocrine response to stress in rats, plasma ACTH and corticosterone responses to acute stress were decreased in adult offspring of high licking–grooming and arched-back nursing mothers (Champagne et al., 2003). These findings, as well as findings from clinical studies (Muris et al., 2001; Radziszewska et al., 1996), suggest that early care may have a protective effect on stress-related disorders. Because of evidence that the effect of early environment on the development of neural systems that underlie the expression of behavioural and endocrine response to stress may be mediated by parental rearing (Liu et al., 1997; Meaney, 2001; Weaver et al., 2004; Zhang et al., 2006), pleasure in mother–child interactions should be investigated as a potential mediator between incubator neo-natal care and major depression later in life.

There are limitations to this study. The main limitation was the sample attrition between the childhood and adult assessments. The attrition analyses suggested that attrition was higher among the children most at risk. The replication of the results using attrition weights indicates that the findings are not explained by attrition.

The association between post-natal incubator care and major depression could be mediated by other potential confounding variables that we failed to control for, including maternal pre- and post-natal stress (O'Connor et al., 2002; Van den Bergh et al., 2005), medications — corticosteroid treatment for pre-term children may have induced dysfunctions in the hypothalamic-pituitary-adrenal axis (Swaab et al., 2005) — and early nutrition (Horwood et al., 2001; Slykerman et al., 2005) — breast feeding is far less frequent for babies with neo-natal incubator care intervention. But all these variables are known to potentially increase the risk of cognitive and emotional disorders later in life, not to reduce the risk of major depression. Thus they might have decreased the strength of the association between incubator care antecedents and the risk of major depression.

Another limitation is the fact that we had no data on the association of incubator care with blue-light phototherapy, usually used for treating neo-natal jaundice. Indeed, it has been previously shown that phototherapy increases the cerebral blood flow velocity (Benders et al., 1998) and nitric monoxide (NO) production in newborns (Ergenekon et al., 2002) which might result in brain changes in terms of monoaminergic system development (McLeod et al., 2001). Future research should directly test these potential mediators.

To conclude, the present study represents, to date, the first evidence that incubator care may decrease the risk of major depression later in life, controlling for a range of confounding variables, in a representative cohort from childhood to adulthood. However, the replicability of the present results among other population samples strongly deserves to be investigated. It is essential to emphasize that instead of considering incubator care as the main cause, we favour the interpretation that it acts as a trigger for a complex process, which may involve a chain of biological and/or emotional events. Understanding the causal processes will have important implications for designing interventions aimed at preventing major depression.

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