

Maternal depression alters stress and immune biomarkers in mother and child

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Background: Exposure to maternal depression bears long-term negative consequences for children's well-being. Yet, no study has tested the joint contribution of maternal and child's hypothalamic pituitary axis and immune systems in mediating the effects of maternal depression on child psychopathology.

Methods: We followed a birth cohort over-represented for maternal depression from birth to 10 years ($N = 125$). At 10 years, mother and child's cortisol (CT) and secretory immunoglobulin A (s-IgA), biomarkers of the stress and immune systems, were assayed, mother-child interaction observed, mothers and children underwent psychiatric diagnosis, and children's externalizing and internalizing symptoms reported.

Results: Depressed mothers had higher CT and s-IgA levels and displayed more negative parenting, characterized by negative affect, intrusion, and criticism. Children of depressed mothers exhibited more Axis-I disorders, higher s-IgA levels, and greater social withdrawal. Structural equation modeling charted four paths by which maternal depression impacted child externalizing and internalizing symptoms: (a) increasing maternal CT, which linked with higher child CT and behavior problems; (b) augmenting maternal and child's immune response, which were associated with child symptoms; (c) enhancing negative parenting that predicted child social withdrawal and symptoms; and (d), via a combined endocrine-immune pathway suppressing symptom formation.

Conclusions: Our findings, the first to test stress and immune biomarkers in depressed mothers and their children in relation to social behavior, describe mechanisms of endocrine synchrony in shaping children's stress response and immunity, advocate the need to follow the long-term effects of maternal depression on children's health throughout life, and highlight maternal depression as an important public health concern.

KEY WORDS

child psychopathology, cortisol, immunity, maternal depression, mother-child relationship, salivary IgA, stress

1 | INTRODUCTION

Maternal depression is a global public health concern and women of childbearing age are at a particularly high risk to suffer from depression, with many experiencing undiagnosed and untreated depression

throughout their child's early years (Bernard-Bonnin, 2004; Kessler & Bromet, 2013). Rates of maternal depression vary from 10% in the United States and up to 74% in developing countries (Ertel, Rich-Edwards, & Koenen, 2011; Norhayati, Hazlina, Asrennee, & Wan Emilin, 2015), indicating that millions of children across the globe are reared by mothers who suffer depression and are exposed to its toxic effects on their physical and emotional health.

Maternal depression has been repeatedly linked with negative child outcomes, including increased psychopathology (Apter-Levi, Feldman, Vakart, Ebstein, & Feldman, 2013; Goodman et al., 2011),

Abbreviations: CRP, C-reactive protein; CBCL, Child Behavior Checklist; CFI, comparative fit index; CI, confidence interval; CIB, Coding Interactive Behavior; CT, cortisol; ELS, early life stress; HPA, hypothalamic pituitary axis; IL-6, interleukin 6; MDD, major depressive disorder; PCLOSE, p of close fit; RMSEA, root mean square error of approximation; s-IgA, secretory immunoglobulin A; TLI, Tucker-Lewis index

poor socioemotional adaptation (Comaskey et al., 2017; Cummings & Davies, 1994), externalizing and internalizing symptoms (Betts, Williams, Najman, & Alati, 2014; Lyons-Ruth, Easterbrooks, & Lyons-Ruth, 1997), emotion dysregulation (Harden et al., 2017), and conduct problems (Chronis et al., 2007; Elgar, McGrath, Waschbusch, Stewart, & Curtis, 2004). In addition, maternal depression is related to poor physical health throughout life (Buka & Gortmaker, 2009). For instance, prenatal maternal depressive symptoms were associated with poor physical health across early childhood, which, in turn, predicted health-related stress and diminished social functioning at age 20 (Raposa, Hammen, Brennan, & Najman, 2014). These findings suggest that maternal depression functions as a distinct early life stress (ELS) that shapes children's stress response and physical health in ways that require much further research.

ELS increases the risk for disease in adulthood (Carr, Martins, Stingel, Lemgruber, & Juruena, 2013; Ferraro, Schafer, & Wilkinson, 2016; Murphy, Cohn, & Assistant, 2016) and one mechanism proposed to account for the long-term effects of ELS on health is the disruption to the developing stress response caused by chronic early stress, including both the hypothalamic pituitary axis (HPA) and the immune system (Dhabhar, 2014; Elwenspoek, Kuehn, Claude, & Turner, 2017; Lovallo, 2011), which maintain ongoing crosstalk among them (Padgett & Glaser, 2003). Studies have shown that prenatal maternal stress alters the development of adaptive immune response in the infant (O'Connor et al., 2013) and newborns of prenatally stressed mothers showed deficient cytokine levels (Andersson, Li, Mills, Ly, & Chen, 2016). These early effects of stress on immunity are long-lasting and prenatal maternal depression has been shown to predict offspring inflammation at 25 years (Plant, Pawlby, Sharp, Zunszain, & Pariante, 2016). Yet, the specific pathways by which maternal depression creates a distinct ELS constellation that negatively impacts both the HPA-axis and the immune system in their offspring and how such disruptions lead to child psychopathology has not been studied. Thus, the overarching goal of the current study is to test how maternal depression impacts stress and immune biomarkers in mother and child and interact with social behavior to shape behavior problems in the children.

Depression has been associated with abnormalities in HPA-axis functioning, expressed in higher baseline cortisol (CT), blunted CT response, slower CT recovery from stress, flat diurnal patterns, or abnormal CT awakening response (Adam et al., 2010; Jarcho, Slavich, Tylova-Stein, Wolkowitz, & Burke, 2013; Wichmann, Kirschbaum, Clemens, & Petrowski, 2017). Depressed mothers similarly exhibit higher baseline CT and slower CT recovery (Feldman et al., 2009; Harris et al., 2000), abnormal CT reactivity (Burke, Davis, Otte, & Mohr, 2005; Stetler & Miller, 2005), and flatter diurnal CT curves (Pratt, Goldstein, Levy, & Feldman, 2017; Taylor, Glover, Marks, & Kammerer, 2009). In parallel, children of depressed mothers show the same HPA-axis abnormalities as their mothers, including greater CT levels (Essex, Klein, Cho, & Kalin, 2002; Feldman et al., 2009; Vreeburg et al., 2010), augmented CT response (Bouma, Riese, Ormel, Verhulst, & Oldehinkel, 2011; Dougherty, Klein, Rose, & Laptook, 2011; Laurent, 2017), flat CT reactivity (Van den Bergh, Van Calster, Smits, Van Huffel, & Lagae, 2008), and flatter diurnal curves (Apter-Levi et al., 2016; Groer & Morgan, 2007). Such aberrant CT patterns have been linked

with increased psychopathology (Heim, Newport, Mletzko, Miller, & Nemeroff, 2008; Shea, Walsh, MacMillan, & Steiner, 2004), externalizing and internalizing symptoms (Alink et al., 2008; Apter-Levi et al., 2016; Brummelte et al., 2011), emotion dysregulation (Feldman et al., 2009; Kiel & Kalomiris, 2016), difficult temperament (Dougherty et al., 2011), school problems (Sohr-Preston & Scaramella, 2006), social withdrawal (Granger et al., 1998; Smider et al., 2002), and low executive functions (Gonzalez, Jenkins, Steiner, & Fleming, 2012; Plamondon et al., 2015), indicating that CT alterations may mediate the effects of maternal depression on child social withdrawal and psychopathology.

HPA-axis dysfunction in children of depressed mothers has been linked with the depressed mother's rigid and insensitive parenting, including higher intrusiveness (Lovejoy, Graczyk, O'Hare, & Neuman, 2000), less consistent parenting (Field, 2010), more negative affect (Webster-stratton & Hammond, 1988), and less warmth (Feldman et al., 2009). As positive parenting and the expression of the species-typical maternal behavior shape maturation of children's stress response and predict psychopathology (Kuhlman, Olson, & Lopez-Duran, 2014; Silk et al., 2007), the reduction in positive parenting can impact child symptom formation as mediated by HPA-axis dysfunction. Furthermore, through mechanisms of "adrenocortical synchrony" (Feldman, 2016; Pratt, Apter-Levi, et al., 2017) or "CT linkage" (Saxbe et al., 2017), the concordance between maternal and child's CT levels, the depressed mother's HPA-axis dysfunctions are transferred to the child. CT linkage is found across development, in infancy (Tarullo, Moore, John, & Meyer, 2017), childhood (Williams et al., 2013), and adolescence (Papp, Pendry, & Adam, 2009) and is related to sensitive parenting that mediates the child's CT response (Feldman, Gordon, Influs, Gutbir, & Ebstein, 2013; Pratt, Apter-Levi, et al., 2017; Saxbe et al., 2017; Thompson & Trevathan, 2008). This suggests that maternal CT levels should be considered when testing the mediating role of child CT on risk and resilience.

HPA-axis dysfunction has been linked with disruptions to the immune system, which, in turn, may exacerbate psychopathology in children of depressed mothers. Depression is related to immune system abnormalities partly mediated by HPA hyperactivity (Furtado & Katzman, 2015), which may lead to production of proinflammatory cytokines (Kiecolt-Glaser & Glaser, 2002), including interleukin 6 (IL-6) and C-reactive protein (CRP; Raison, Capuron, & Miller, 2006). Patients with major depression show chronic activation of inflammatory responses (Berk et al., 2013; Miller, Maletic, & Raison, 2009) and studies describe links between stress, maternal depression, and immunosuppression during pregnancy (Christian, 2012). These studies suggest that the mutual influences between the two systems in the mother may transfer to the child via mechanisms of endocrine synchrony, potentially impacting the child's immunity and risk for psychopathology.

Secretory immunoglobulin A (s-IgA) is the most prevalent antibody in mucosal tissues and serves as an immunological barrier for pathogenic penetration (De Almeida, Grégo, Machado, De Lima, & Azevedo, 2008; Stone, Cox, Valdimarsdottir, & Neale, 1987). S-IgA serves many immunomodulatory and anti-inflammatory roles (Ben Mkaddem, Rossato, Heming, & Monteiro, 2013; Russell, Sibley, Nikolova, Tomana, & Mestecky, 1997) and studies have utilized

s-IgA as a biomarker of the immune system. Whereas acute psychological stress is typically associated with reduced s-IgA levels (Deinzer, Kleineidam, Stiller-Winkler, Idel, & Bachg, 2000; Ng et al., 2004), chronic stress is linked with increased s-IgA (Bosch, Ring, de Geus, Veerman, & Amerongen, 2002), albeit results are inconsistent (Segerstrom & Miller, 2004) and the relations between s-IgA and stress are complex and context dependent (Mouton, Fillion, Tawadros, & Tessier, 1989). Higher s-IgA in breast milk has been linked with maternal negative emotions (Thibeau & D'Apolito, 2012), depression (Hart et al., 2004), anger (Groer, Humenick, & Hill, 1994), and perceived stress (O'Connor, Schmidt, Carroll-Pankhurst & Olness, 1998), while lower s-IgA correlates with maternal satisfaction (Groer et al., 1994). Mothers and children exposed to chronic trauma showed higher s-IgA levels and endocrine synchrony between maternal and child's s-IgA, highlighting the associations between chronic stress and immune system functionality in mother and child. Moreover, higher s-IgA levels correlated with less sensitive maternal behavior and greater prevalence of child anxiety disorders, charting a pathway from chronic early stress to child symptoms as mediated by s-IgA system functionality and relational behavior (Ulmer-Yaniv et al., 2018).

As such, the current study aims to examine the effects of maternal depression on mother and child's stress and immune system biomarkers and social behavior and how these mediate the effects of maternal depression on child psychopathology. We utilized a birth cohort of depressed mothers and matched controls who were otherwise of low-risk background, making maternal depression the only risk factor in order to tease apart the effects of maternal depression as such from frequently occurring comorbidities (e.g., poverty, single parenthood, teenage mothering, substance abuse, prematurity). At 10 years, mothers and children underwent psychiatric diagnosis, CT and s-IgA were assayed in both partners, mother-child interaction was coded for maternal negative parenting and child social withdrawal, the two relational behaviors previously linked with CT disruptions (Apter-Levi et al., 2016), and children's externalizing and internalizing symptoms were reported. Using structural equation modeling we examined paths leading from maternal depression to child symptoms as mediated by HPA-axis, immune system, and maternal and child's social behavior.

Three global hypotheses were formulated. First, as to mean-level differences, we expected children of depressed mothers to exhibit more Axis-I psychiatric disorders and more externalizing and internalizing symptoms. We expected higher CT and s-IgA levels in depressed mothers and their children. Similarly, we expected depressed mothers to be more negative, including greater intrusion, negative affect, criticism, and hostility, and their children to be more socially withdrawn, exhibiting less positive affect and engagement (Pratt et al., 2015). Second, we expected endocrine synchrony in the two systems; between maternal and child CT and between maternal and child s-IgA. Finally, for a full conceptual model on the effects of maternal depression on child symptom formation as mediated by the three pathways (CT, s-IgA, and social behavior), we built a path model linking maternal depression to child internalizing and externalizing symptoms as mediated by three pathways, related to maternal and child's CT, maternal and child's s-IgA, and maternal and child's social behavior. We hypothesized that disruptions to both the stress-immune axis and the parent-child

relationship would mediate the effects of maternal depression on children's externalizing and internalizing symptoms.

2 | METHODS

2.1 | Participants

2.1.1 | Birth and first year

The initial cohort included 1,983 women recruited on the second post-birth day in three maternity wards who completed measures of anxiety and depression. Inclusion criteria were: healthy mothers, high school graduates, age over 21 years, marriage or cohabitation, income above poverty line, and infants that were born healthy, in term and singleton. Women in the high Beck depression inventory ($BDI \geq 11$; Beck, Ward, Mendelson, Mock, & Erbaugh, 1961) and low ($BDI < 9$) ends of the depressive symptoms continuum completed measures of anxiety and depression at 6 months ($N = 900$ approached, $N = 680$ responded: 75.5%) and again at 9 months ($N = 350$ approached, $N = 254$ responded; 72.5%), excluding high anxiety symptoms (State-Trait Anxiety Inventory Score > 43). Of responding mothers at 9 months, 192(75.5%) were clinically diagnosed and observed in their homes when the infant was approximately 9 months.

2.1.2 | Six years

Of the 192 families visited at 9 months, 156 (81.2%) were revisited at 6 years (child age 6.33 ± 1.25 , mothers' age 38.66 ± 4.4). Of these, 80% of parents had college degree, 91.4% were married, and 89% of mothers were employed. Forty-six mothers (29.6%) were defined as chronically depressed. These mothers showed high depressive symptoms ($BDI > 11$) at birth, 6, and 9 months, received major depressive disorder (MDD) diagnosis at 9 months and 6 years and reported being depressed throughout the child's first 6 years. Similarly, 103 mothers (66%) were defined as controls, showed no elevated symptoms at any time-point, and did not receive any Axis-I diagnosis. Seven mothers were excluded due to clinical anxiety ($n = 3$) or subclinical depression ($n = 4$).

2.1.3 | Ten years

Of the families visited at 6 years, 125 (81.1%) were located and revisited at 10 years (child age $M = 9.63 \pm 0.65$, mothers' age $M = 39.06 \pm 5.64$). Attrition was mainly related to inability to locate families. There were no significant demographic or psychopathologic differences between those who dropped out and those who continued at 6 and 10 years. Of the 125 families revisited at 10 years, 35 were from the depressed group and 90 were from the control group at age 6. At 10 years, all mothers underwent a psychiatric diagnosis (see details below). The maternal depression group was defined as mothers receiving MDD diagnosis at 6 years, 10 years, or both (42.8%). Antidepressant intake was coded as a study variable and only 2 mothers in the maternal depression group were taking antidepressants (Escitalopram) and one from the control group was taking Methylphenidate. Controlling for medication intake results remained unchanged.

3 | PROCEDURE AND MEASURES

Families were visited at home in between 4:00 and 7:00 p.m. to control for diurnal hormonal variability and visits included maternal and child psychiatric diagnosis, testing, hormonal collection, and age-appropriate mother-child interactions. *Ethical considerations:* All participants received detailed explanations before study and signed informed consent. Study procedures were conducted according to ethical guidelines. Participants received a small gift for participation. The study was approved by the university's institutional review board.

3.1 | Maternal psychiatric diagnosis

The Structured Clinical Interview for DSM-IV Axis I Disorders (SCID-I; First, Spitzer, Gibbon, & Williams, 1996). At 10 Years, 15 of the depressed mothers at 6 years (42.8%) were still diagnosed with MDD, while 20 (57.1%) were not. Of the controls, 83 mothers (92.2%) remained without diagnosis, while 7 (7.7%) received MDD diagnosis.

3.2 | Child behavior problems

The Child Behavior Checklist 4–16 years (CBCL; Achenbach & Edelbrock, 1983) is a parent self-report measure of child behavior problems clustered into internalizing, externalizing, and total scores. The CBCL is the most widely used instrument for assessing behavior problems in children with established reliability and validity (Dutra, Campbell, & Westen, 2004).

3.3 | Mother–child interaction

Mothers and children interacted in two well-validated paradigms for 7 min each: first discussing typical conflict in their relationship, second planning a “the best day ever” to spend together. Interactions were coded using the Coding Interactive Behavior Manual (CIB; Feldman, 1998, pp. 1–54). The CIB is a well-validated rating system for social interactions in infants, children, adolescents, and adults that includes multiple scales for parent, child, and dyad, aggregated into theoretically derived composites with good psychometric properties (Feldman, 2012). Coding was conducted by trained coders, blind to other information, and reliability on 20% of the interactions exceeded 93% and 90% on all codes ($k = 0.84$, range 0.78–0.95 and $k = 0.82$, range = 0.78–0.96), at 6 and 10 years, respectively.

Two constructs were used:

Maternal negativity: Included mother codes of intrusiveness, negative affect, anger, hostility, and criticizing.

Child withdrawal: Included child codes of negative emotionality, avoidance, withdrawal, and emotional lability.

3.4 | Saliva samples collection and measuring

Three salivary samples were collected by child/mother. Subjects were asked to place a roll of cotton-salivette (Sarstedt, Rommelsdorf, Nürnberg, Germany), in their mouths, chew it for a minute until it became saturated. Three samples were collected during the visit; (a) baseline (after 10 min of acquaintance (T1), (b) after testing (T2 80 min from

baseline), and (c) after mother–child interactions (T3, 75 min from T2). Participants were asked not to eat for 1 hr and did not drink for 30 min prior to the saliva collection. Samples were stored at –20°C until centrifuged twice at 4°C at 1500 × g for 30 min.

3.4.1 | Salivary CT

CT levels were assayed using a commercial ELISA kit (ENZO, New York, NY). Measurements were performed according to the kit's instructions. In order to correlate between plate and different periods, three in-house controls were included in each plate (250, 900, 1200 pg/ml). CT levels were calculated by using MATLAB 7 according to relevant standard curves. The intra-assay and inter-assay coefficient of controls was less than 5.6%, and intra-assay and inter-assay coefficients for samples were less than 14.9%.

3.4.2 | Secretory immunoglobulin A

Determination of s-IgA was performed using a commercial s-IgA ELISA kit (EUROIMMUN AG: 23560, Luebeck, Germany). The kit provides quantitative in vitro assay for s-IgA in human saliva. On day of assay, samples were thawed completely and diluted 1:201 in sample buffer and further measured according the kit's instructions. Measurements were performed in duplicate and the concentrations of samples were calculated by using MATLAB 7 according to relevant standard curves. The intra-assay coefficient of samples and controls was 8.1%, and inter-assay coefficients for samples and controls were less than 11.6%.

3.4.3 | Statistical analysis

CT and s-IgA were measured, consistent with prior research, by computing area under the curve with respect to the ground (Pruessner, Kirschbaum, Meinlschmid, & Hellhammer, 2003), to measure maternal and child's hormonal levels across the evening period of the home visit. Chi-square and t-tests were used to compare study variables in children of depressed/nondepressed mothers, and Pearson correlations tested relationships among variables. For a comprehensive model on the direct and mediated paths from maternal depression to children's internalizing and externalizing symptoms, we conducted path analysis using lavaan 0.5–23.1097 package (Rosseel, 2012) in R 3.3.2 (RC Team, 2017; RStudio, 2015). Path analysis was based on maximum likelihood estimations and indicators of model fit were: chi-square values, root mean square error of approximation (RMSEA), comparative fit index (CFI), with Tucker–Lewis index (TLI) values >0.95 considered good fit (Hu & Bentler, 1999). To assess significance of the mediation effects, we used a procedure recommended by Hayes (2013) and calculated the 95% confidence intervals (CI) of 5,000 bias-corrected and accelerated bootstrapping analyses (Bakar, Mahmood, & Ismail, 2015; MacKinnon, Lockwood, & Williams, 2004). In cases where the value zero is not included in the CI, this indicates significant effect at $\alpha < 0.05$.

4 | RESULTS

As a first step, we measured the prevalence of child Axis-I disorders in children of depressed and nondepressed mothers. Children to depressed mothers were more likely to present a full-blown

TABLE 1 Means and SD for study variables by maternal depression

	Nondepressed		Depressed		t	Cohen's D
	M	SD	M	SD		
Mother CT	32,325.98	16,423.39	43,310.84	17,855.96	$t_{(60)} = -2.36, P < 0.05$.64
Child CT	26,583.84	12,179.57	25,017.93	10,894.13	$t_{(49)} = 0.47, P > 0.05$.14
Mother s-IgA	1,614,394.95	829,997.90	2,164,092.72	748,543.05	$t_{(47)} = -2.24, P < 0.05$.70
Child s-IgA	1,288,544.08	469,387.57	1,893,060.31	451,841.17	$t_{(40)} = -3.13, P < 0.01$	1.31
Maternal negativity	1.37	0.43	1.60	0.55	$t_{(106)} = -2.25, P < 0.05$.45
Child withdrawal	1.70	0.56	1.95	0.50	$t_{(96)} = -2.03, P < 0.05$.47
Child Behavior Checklist						
Internalizing symptoms	2.76	2.22	3.94	3.30	$t_{(100)} = -2.13, P < 0.05$.42
Externalizing symptoms	4.16	3.06	5.94	4.59	$t_{(107)} = -2.38, P < 0.05$.46

Note. For t-tests Cohen's D were calculated as effect sizes. Values in the same row not sharing the same subscript are significantly different at $P < 0.05$. CT: cortisol; M: mean; s-IgA: secretory immunoglobulin A; SD: standard deviation.

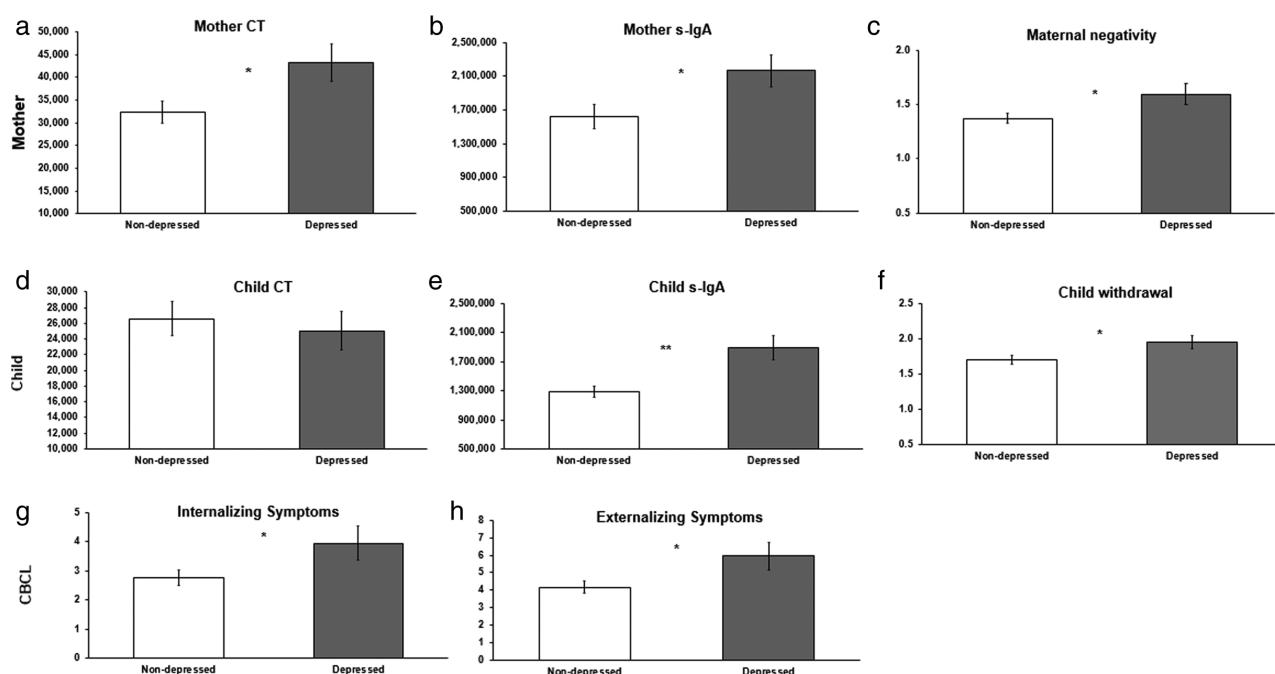


FIGURE 1 Cortisol (CT), secretory immunoglobulin A (s-IgA), and relational behavior in depressed and nondepressed mothers and children (a) depressed mothers showed significantly higher salivary CT and s-IgA (b) levels, (c) depressed mothers showed more negative behaviors toward their children, (d) children of depressed mothers showed no significant different in CT levels, but significantly higher s-IgA levels (e) and more withdrawal behaviors, (f) children of depressed mothers showed more internalizing (g) and externalizing (h) symptoms compared to children whose mothers were not depressed

Note. * $P < 0.05$; ** $P < 0.01$. Significant differences were examined using t-tests.

psychiatric disorder compared to control children; $\chi^2_{(1)} = 5.72$, $P < 0.05$. We next compared all study variables among children exposed to maternal depression at 6 or 10 years and found no differences on any study variable ($P > 0.05$) and thus, the two groups were collapsed into a maternal depression group.

t-Tests on study variables with maternal depression as independent variable were examined, and significant differences were found for all variables except child CT ($P > 0.05$). As seen in Table 1 and Figure 1, depressed mothers had higher CT and s-IgA levels, and were more negative toward their children. In addition, children of depressed mothers had higher s-IgA levels, presented more withdrawal behaviors, and had more internalizing and externalizing symptoms.

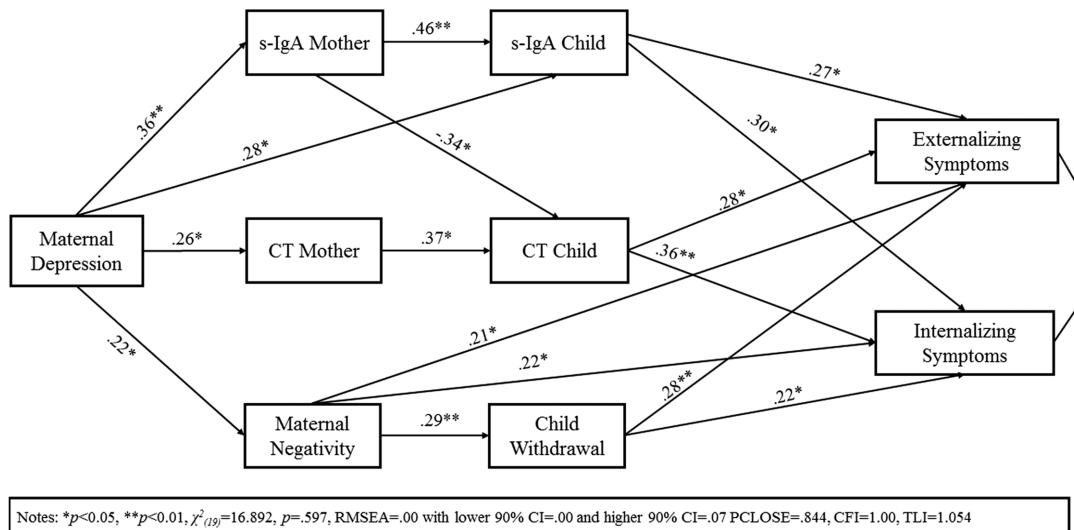
Pearson correlations appear in Table 2 and show associations between mother and child hormonal, behavioral, and pathological variables and endocrine synchrony for both CT and s-IgA; mothers' CT levels were associated with children's CT and mothers' IgA was associated with child's IgA levels as well as with lower child CT levels. Mothers' negativity correlated with children's withdrawal. Children's internalizing and externalizing symptoms were associated with children's CT, maternal negativity, children's withdrawal, and s-IgA levels.

Finally, we used path analysis to test our model on the paths leading from maternal depression to child externalizing and internalizing symptoms as mediated by maternal and child's behavior, CT, and s-IgA (Figure 2). The overall model provided an excellent fit to the

TABLE 2 Pearson correlations among CT, s-IgA, relational behavior, and child symptoms

Variable	1	2	3	4	5	6	7
1. Child CT							
2. Mother CT	0.54**						
3. Child s-IgA	-0.02	-0.09					
4. Mother s-IgA	-0.60**	0.01	0.60**				
5. Maternal negativity	0.05	0.05	0.18	-0.09			
6. Child withdrawal	0.12	0.10	0.06	0.08	0.26*		
Child Behavior Checklist							
7. Internalizing symptoms	0.44**	-0.02	0.46**	0.10	0.34**	0.32**	
8. Externalizing symptoms	0.47**	-0.13	0.45**	0.07	0.29**	0.31**	0.55**

Note. * $P < 0.05$; ** $P < 0.01$. CT: cortisol; s-IgA: secretory immunoglobulin A.



Notes: * $p < 0.05$, ** $p < 0.01$, $\chi^2_{(19)} = 16.892$, $p = .597$, RMSEA = .00 with lower 90% CI = .00 and higher 90% CI = .07 PCLOSE = .844, CFI = 1.00, TLI = 1.054

FIGURE 2 Path-analysis linking maternal depression with child externalizing and internalizing symptoms at 10 years via hypothalamic pituitary axis (HPA)-axis, immune system, and relational behavior

Note. Coefficients represent standardized regression weights. The overall model provided an adequate fit to the data: $\chi^2_{(19)} = 16.892$, $P = 0.597$, root mean square error of approximation (RMSEA) = 0.00 with lower 90% confidence interval (CI) = 0.00 and higher 90% CI = 0.07 p of close fit (PCLOSE) = 0.844, comparative fit index (CFI) = 1.00, Tucker–Lewis index (TLI) = 1.054. * $P < 0.05$; ** $P < 0.01$.

data: $\chi^2_{(19)} = 16.892$, $P = 0.597$, RMSEA = 0.00 with lower 90% CI = 0.00 and higher 90% CI = 0.07 p of close fit (PCLOSE) = 0.844, CFI = 1.00, TLI = 1.054.

We identified four paths leading from maternal depression to internalizing and externalizing symptoms. (a) The *behavioral pathway*: Maternal depression linked with higher maternal negativity, which predicted greater child withdrawal, which was associated with higher internalizing and externalizing symptoms. Test of mediation indicates that these indirect paths were significant (95% CI = 0.000, 0.015 and 95% CI = 0.000, 0.017, respectively).

(b) The *HPA-axis pathway*: Maternal depression was associated with higher maternal CT, which correlated with higher child CT, and finally related to more internalizing and externalizing symptoms (95% CI = 0.001, 0.158 and 95% CI = 0.001, 0.118, respectively).

(c) The *immune pathway*: Linking maternal depression with an increase in mother and child s-IgA levels, which linked with increased internalizing and externalizing symptoms (95% CI = 0.000, 0.061 and 95% CI = 0.000, 0.062, respectively).

Finally, the last path (d) A *hormonal-immune pathway*: It starts with maternal depression, which predicted higher maternal s-IgA, associated with reduced child CT, which was related to increased internalizing and externalizing symptoms (95% CI = -0.198, -0.001 and 95% CI = -0.144, -0.002, respectively).

To provide further evidence for our model on the dual stress-immune pathway in mediating the effects of maternal depression on child symptoms, we compared it to an alternative model that eliminated the effects of s-IgA on internalizing and externalizing symptoms (Supporting Information Figure S1). Thus, our alternative model was built from maternal depression, mother and child behaviors and CT levels only. This model provided a less adequate fit to the data ($\chi^2_{(10)} = 14.139$, $P = 0.167$, RMSEA = 0.06 with lower 90% CI = 0.00 and higher 90% CI = 0.12 PCLOSE = 0.365, CFI = 0.95, TLI = 0.848) and the path from maternal depression to mother CT was not significant ($P > 0.05$). The main paths from mother depression to externalizing and internalizing symptoms in this model were significant only through the behavioral path (95% CI = 0.002, 0.061 and 95% CI = 0.002,

0.057, respectively) and the CT path ($95\% \text{ CI} = 0.001, 0.123$ and $95\% \text{ CI} = 0.001, 0.142$, respectively), suggesting that the HPA and immune system provide a joint biological pathway mediating the effects of maternal depression on child symptoms.

5 | DISCUSSION

Results of the current study are the first, to our knowledge, to show that HPA-axis and immune system biomarkers integrate with maternal and child's social behavior to chart three mediating pathways linking maternal depression with child externalizing and internalizing symptoms. In an attempt to specify how maternal depression impacts children's hormonal and behavioral stress response and consequently shape child psychopathology, we assessed evening CT, s-IgA, relational behavior, and psychiatric diagnosis in depressed mothers and their 10-year-old children. Consistent with much research indicating that exposure to maternal depression negatively impacts children's development (Goodman et al., 2011), we found that depressed mothers had higher CT and s-IgA evening levels and their parenting was characterized by higher negativity, intrusion, and hostility. Children of depressed mothers had higher s-IgA levels, exhibited greater social withdrawal during interaction with their mothers, had more Axis-I disorders, and displayed more externalizing and internalizing symptoms. Finally, using structural equation modeling, we found that stress and immune biomarkers jointly mediated the effects of maternal depression on child symptoms via four independent paths: by augmenting maternal and child's CT production, by increasing s-IgA levels, by impairing maternal and child relational behavior, and via a mixed hormonal-immune pathway by which maternal s-IgA impacts child CT levels. Overall, our results provide evidence for the pervasive effects of maternal depression on child stress and immune systems intactness and social repertoire, increasing child vulnerability, reducing resilience, and rendering children more susceptible to psychopathology. It is important to note, however, that our findings describe a pattern of associations and in no way imply causality and such intercorrelations may be impacted by other unmeasured variables, such as genetic and epigenetic influences.

HPA dysregulation and hypercortisolism have been described in individuals with major depression disorder (Bhagwagar, Hafizi, & Cowen, 2005; Dougherty et al., 2013) and in depressed mothers (Feldman et al., 2009; Glynn, Davis, & Sandman, 2013; Harris et al., 2000; Iliadis, Comasco, Sylvén, Hellgren, & Sundström, 2015; Nierop, Bratsikas, Zimmermann, & Ehlert, 2006). Our findings corroborate previous research and show that depressed mothers had higher CT levels during the evening hours, when CT levels are typically at their lowest, as compared to nondepressed mothers. These higher evening CT levels were linked with parenting behavior characterized by negativity, hostility, anger, and criticism toward the child. The associations between maternal depression, lower maternal sensitivity, and negative maternal care is well established and studies have repeatedly described the adverse outcomes of such parenting, including insecure attachment and child behavior problems (Feldman et al., 2009; Newland, Parade, Dickstein, & Seifer, 2016); yet, most research on

the relationship between maternal depression and negative parenting had focused on infants and young children. Our findings show similar patterns in 10-year-old children, indicating that the reduction in positive parenting and increased negativity are not limited to prelinguistic and is also observed in late childhood, a period when little observational research has been conducted. We show that the increased CT observed in depressed mothers was associated with negative maternal behavior and mediated the effects of maternal depression on the development of behavioral symptoms.

In addition to HPA-axis dysregulation, higher s-IgA evening levels were found in both depressed mothers and their children. High s-IgA levels have been associated with chronic stress, such as occupational stress (Henningsen et al., 1992; Kugler, Reintjes, Tewes, & Schedlowski, 1996; Zeier, Brauchli, & Joller-Jemelka, 1996), military assignments (Kvietkauskaitė, Vaicaitienė, Girkontaite, & Labeikyte, 2014), and sport competitions (Mazdarani, Khaledi, & Hedayati, 2016). As children of depressed mothers were found to display more externalizing problems (Foster, Garber, & Durlak, 2008; Marchand, Hock, & Widaman, 2002) and anti-social behavior (Kim-Cohen, Moffitt, Taylor, Pawlby, & Caspi, 2005), it is possible that the child's difficulty, lack of engagement, and dysregulated behavior function as a source of continuous stress to the mother, increasing her immune response. Prior studies have indicated that patients suffering from major depression show increased inflammatory response characterized by increased expression of pro-inflammatory cytokines, such as IL-6 and CRP (Raison et al., 2006; Sluzewska et al., 1996). HPA-axis hyperactivity and inflammation may be part of the same pathophysiological process inducing glucocorticoid resistance, which has been linked with major depression (Dowlati et al., 2010; Zunszain, Anacker, Cattaneo, Carvalho, & Pariante, 2011). Moreover, research has shown that various components of the immune system can induce neuropsychological symptoms (Miller et al., 2009). For instance, treatment with interferon-alpha is associated with initiation of depression and anhedonia (Capuron et al., 2002) and inflammatory response can induce depressive symptoms (Dantzer, O'Connor, Freund, Johnson, & Kelley, 2008). It is thus possible that the increased immune response in the mother reflects her chronic stress in the maternal role, which through endocrine synchrony is related to child's immune system activations and greater vulnerability.

Our theoretical model demonstrate a two-pronged hormonal-immune pathway linking maternal depression with child psychopathology as mediated by increased CT and s-IgA levels in mothers, which, via mechanisms of endocrine synchrony passed on to their children, possibly interfering with their ability to manage physiological stress. Such two-pronged model was found to provide a better fit to the data as compared to a model containing only HPA-axis biomarkers. Rodents studies indicate that following stress, increases in s-IgA were associated with a rise in plasma levels of corticosterone (Jarillo-Luna et al., 2015). Regarding the HPA-pathway, we found that maternal depression linked with higher maternal CT, which correlated with child CT and more externalizing and internalizing problems. Our model is consistent with research suggesting that exposure to maternal depression at any time-point across childhood impacts children's stress response (Ashman, Dawson, Panagiotides, & Yamada, 2002; Brennan et al., 2008; Corwin & Pajer, 2008). In pregnancy, prenatal exposure

to increased third trimester maternal depressed mood was associated with increased salivary CT stress responses at 3 months and with negative infant temperament (Davis et al., 2007); in childhood, higher maternal depression was linked with flat CT reactivity during the evening (Apter-Levi et al., 2016); and during adolescence, morning CT secretion mediated an association between maternal post-natal depression and depressive symptoms (Halligan, Herbert, Goodyer, & Murray, 2007). Thus, while most research has focused on the negative effects of maternal depression during pregnancy or the first months of life on children's physiology and behavior, our findings show that exposure to maternal depression at any time-point in childhood bears negative consequences for children's immunity and emotional well-being. Of note, while we found correlations between maternal and child's CT levels, no main effects of depression was observed in child CT levels, suggesting that in some children of depressed mothers evening CT levels are not affected and further research is required to tease apart those with and without higher CT levels.

Our study attempted to provide an ecological study on sequelae of maternal depression; we observed mother and child in the home ecology and under typical evening conditions and observed their typical daily social behavior, and thus, we did not include a predetermined lab stressor. We chose to examine evening CT levels to ensure high subject compliance and cooperation but also to measure CT at the time when it is typically low. Our results address only one aspect of the HPA system, which has a complex, multifactorial activity. Much further research is needed to understand whether the elevated evening CT levels in the depressed mothers is a consequence of chronic stress in the maternal role, result from genetic vulnerability or epigenetic alterations, or their combination. Yet, our study is the first to include long-term follow-up of depressed mothers and their 10-year-old children from birth, assess biomarkers of the HPA-axis and immune system in mother and child, and integrate these biomarkers with careful assessment of social behavior in the home ecology.

The second path from maternal depression to child outcomes charts an immune system pathway. Depression was associated with higher maternal s-IgA, which correlated with higher child s-IgA and linked with higher symptoms. Such pathway describes the disruptions to the immune system in depressed mothers and their children and shows its relation to psychopathology in children. However, higher maternal s-IgA was also associated with reduction in child CT, which in turn was related to lower externalizing and internalizing symptoms. In rodent studies, restraint stress was followed by intestinal s-IgA decrease that was modulated by glucocorticoid receptors (Campos-Rodríguez et al., 2013; Jarillo-Luna et al., 2007), suggesting that our findings may also be associated with an HPA-immune modulation mechanism. In some studies, high s-IgA levels were associated with pleasant stimuli and humor (McClelland & Cherrif, 1997; Watanuki & Kim, 2005), perhaps the high maternal s-IgA levels changed the maternal behavior (though it was not shown in our observation) and the result was a reduction in child CT levels. It is thus possible that maternal s-IgA may lead to either increased risk, via elevating the child's immune response, or resilience, via suppressing its effects on child CT levels, and these differential effects are probably linked with a physiological, genetic, or behavior variable not measured here and our study

should lead to much further research on the associations between the HPA and immune system in mothers and children under various ELS conditions.

The results showing that maternal s-IgA is associated with both child s-IgA and CT levels suggest a cross-system linkage of the stress and immune systems, both of which are sensitive to ELS. Yet, the exact mechanisms of HPA-immune crosstalk require much further research. An important limitation of our study is that we did not measure other immune biomarkers. Generally, s-IgA is relevant to inflammation in the sense that the endocrine and sympathetic nervous systems are connected to the immune system, but it is not a direct biomarker of inflammation as it is associated with both pro-inflammatory (Wu et al., 2007) and anti-inflammatory (Ben Mkaddem et al., 2013; Russell et al., 1997) processes. Another limitation is that we did not measure fathers' CT and s-IgA, as fathering can exert a mitigating effect on child psychopathology in the context of maternal depression (Vakrat et al., 2018).

Interestingly, the rate of antidepressants intake in our sample was very low: only 1.6% of the women were taking antidepressants. There are several possible explanations for this low use. First, In Israel, the percentage of psychiatric medications intake is substantially lower compared to Europe and the United States (Grinshpoon, Marom, Weizman, & Ponizovsky, 2007), due to stigmas and low public awareness. Second, our study was initiated 17 years ago when public awareness of postpartum depression and the provision of community-based treatments were minimal. In the last decade we see that following studies like ours, psychiatric treatments have become more common and in parallel, the public awareness and acceptance of psychiatric illness increased. We specifically chose to recruit a community cohort of women of otherwise low risk, not a clinical sample. Our results, therefore, should raise concern and suggest that when mothers experience other adversities, such as single parenting, poverty, food insecurity, premature birth, or substance abuse, the effects of depression on mother and child's physiology, behavior, well-being, and physical health are likely to be much greater. Much future research is required to test the effects of maternal depression on children's stress and physical well-being throughout life, directing much needed public attention and resources to conducting longitudinal studies and developing targeted interventions for depressed mothers and their children and treating maternal depression as one of the major public health issues.

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