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Biological embedding of maternal postpartum depressive symptoms: The potential role of cortisol and telomere length

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ABSTRACT

Although maternal postpartum depressive symptoms (PDS) are associated with child behavior problems, the underlying biological mechanisms are poorly understood. Thus, the current study focused on 193 healthy mother-child dyads and investigated child cortisol and telomere length as potential mediating factors. At 3 and 6 months postpartum, mothers reported on PDS. At age 6, children provided saliva and buccal swab samples. At age 10, mothers and children reported on child behavior problems.

Structural equation modelling revealed (a) no association between PDS and child behavior problems and thus no possibility of mediation, but that (b) lower cortisol forecast more child-reported internalizing problems, and (c) shorter telomere length predicted more child-reported internalizing and externalizing problems. These findings raise mediational questions about the determinants of these biomarkers.

1. Introduction

Maternal postpartum depressive symptoms (PDS) are a major public health concern, affecting around 15 % of women worldwide (Pearlstein, Howard, Salisbury, & Zlotnick, 2009). Besides negative influences on affected women, associations between PDS and compromised child development are frequently reported (for a review, see Murray, Fearon, & Cooper, 2015). Because most prospective research is conducted in children up to preschool age, and in samples marked by high adversity, there is an uncertainty as to whether associations between PDS and compromised child development persist into late childhood in lower-risk samples. Here we address this is by examining, first, whether PDS predict child behavior problems at age 10 and then whether two potential biomarkers, child cortisol and telomere length, might mediate any detected effect.

1.1. PDS and child behavior problems

Research targeting high-risk samples chronicles marked differences in behavior of children with depressed mothers and well mothers. Depression is associated with more child internalizing (i.e., problems regarding psychological health, such as feelings of depression), as well as externalizing behavior (i.e., outward directed negative behavior, such as aggressive behaviors). Work on lower-risk samples typically does not reveal such adverse effects, even if disruptions in behavioral regulation have been observed in children up to preschool age (Murray, Fiori-Cowley, Hooper, & Cooper, 1996, 2015). The few studies that discern associations between PDS and more child and adolescent psychological difficulties focused mostly on mothers with depressive disorders (Halligan, Murray, Martins, & Cooper, 2007; Murray et al., 2011), or mothers stemming from high-risk samples (Fihrer, McMahon, & Taylor, 2009; Verkuijl et al., 2014). As such, the question remains whether long-term associations between PDS and adverse child outcomes also emerge in low-risk samples.

Notably, prior research on PDS heavily relied on maternal reports to assess child behavior problems. Given that PDS are likely to continue after the postpartum period in some mothers as for example, around a third of women with young children with initial elevated depressive symptoms continued to have elevated depressive symptoms at follow-

Abbreviations: PDS, postpartum depressive symptoms; HPA-axis, Hypothalamic-Pituitary-Adrenal axis

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up (i.e. one year later, Horwitz, Briggs-Gowan, Storfer-Isser, & Carter, 2009) the possibility that associations are an artefact of the mother's concurrent emotional state has to be acknowledged. It is therefore important to control for maternal depressive symptoms at the time of child assessment to increase confidence in conclusions regarding specific links to the postpartum episode (Pawlby, Hay, Sharp, Waters, & O'Keane, 2009). In general, research that includes both PDS and current maternal depression documents significant, though relatively small, effects of *postnatal* depression on child behavior, at least as reported by the mother (Murray et al., 2015). For a more independent assessment of child behavior, it is also important next to controlling for concurrent symptoms to include other informants of child behavior problems, including the child (Horwitz et al., 2009; Richters, 1992).

1.2. Biological embedding

Stress experienced early in life is known to carry risk for later compromised mental health, but the way early-life stress 'gets under the skin' and becomes biologically embedded is largely unknown. PDS is hypothesized to comprise such an early-life stress factor, as mothers suffering from depressive symptoms show lower quality of parenting, compromising the development of regulatory capacities and subsequent child mental health (Murray et al., 2015; Schore, 2001; Stein et al., 2014). Herein we investigate, in a low-risk sample, two potential biological mechanisms that may mediate the link between PDS and child behavior problems, cortisol and telomere length.

1.2.1. Cortisol

Cortisol is the primary hormonal product of the Hypothalamic-Pituitary-Adrenal (HPA) axis (Loman & Gunnar, 2010). According to the *Early-life Stress model,* adverse experiences in early life, such as maternal PDS, affect the development of the HPA-axis resulting in altered responses to stress and elevated cortisol production throughout the day. Only a few investigations have addressed cortisol responses to stress, with work by Waters et al. (2013) documenting reduced cortisol responsiveness to mild stressors in infants of depressed mothers. Research addressing basal cortisol measures in children exposed to PDS reveals elevations in children at 18 months, 3 years, and 4.5 years of age (Murray et al., 2015). Evidence for even longer-term effects emerged in a study chronicling links between exposure to postpartum maternal depressive disorder and elevated morning cortisol concentrations in 13-year-olds (Halligan, Herbert, Goodyer, & Murray, 2004). Elevated cortisol is thought to impair prefrontal cortex development, thereby resulting in problems regulating behaviour (Loman & Gunnar, 2010), and prospective research indeed indicated that elevated cortisol is predictive of future child problems (Adam et al., 2010; Shirtcliff & Essex, 2008). These findings invite the hypothesis, evaluated herein, that more PDS result in elevated diurnal cortisol, which in turn mediates the PDS-problems' association.

1.2.2. Telomeres

Telomeres are non-coding protective DNA-protein sequences appearing at the end of all chromosomes; they shorten with each cell division (Harley, Futcher, & Greider, 1990). When telomeres reach a critical short length, cellular senescence occurs. Short telomere length, therefore, has been associated with compromised adult all-cause mortality (Wang, Zhan, Pedersen, Fang, & Hägg, 2018) and morbidity, including physical disorders, such as gastric cancer and diabetes, as well as psychological disorders, such as depression (e.g. Desai et al., 2018; D'Mello et al., 2015; Gillis et al., 2019; Lin, Epel, & Blackburn, 2012; Ridout, Ridout, Price, Sen, & Tyrka, 2016; Smith et al., 2019).

Telomere length has also been proposed as a biological embedding mechanism by which early-life stress comes to be related to later behavior (Belsky & Shalev, 2016; Ridout et al., 2015; Shalev, 2012). The few studies on telomere length in childhood chronicled cross-sectional links in a similar fashion: shorter telomere length was related to more internalizing problems (Kroenke et al., 2011) and oppositional defiant behavior (Wojcicki et al., 2015). Hence, current theory and research suggest that telomere dynamics are receptive to early-life stress (Belsky, 2019; Burgin et al., 2019; Entringer, Buss, & Wadhwa, 2015; Willis, Reid, Calvo, Staudinger, & Factor-Litvak, 2018). For example, stressful events in childhood have been associated with shorter adult telomere length in multiple studies (Price, Kao, Burgers, Carpenter, & Tyrka, 2013). To date, almost all of this work has assessed relations between retrospective measures of early-life stressors and telomere length in adults. In children, however, Shalev et al. (2013) observed that exposure to violence was related to greater telomere shortening between age 5 and 10. Investigations of maternal depression chronicle associations between depression in the postpartum period and shorter child telomere length (e.g. Gotlib et al., 2015; Nelson, Allen, & Laurent, 2018; Wojcicki et al., 2015). Findings such as these invite the hypothesis that PDS affect telomere length and, thereby, mediate the PDS-problems' association.

1.3. Current study

This study addresses three questions: 1) Does greater PDS in a low-risk sample predict elevated cortisol and shorter telomeres at age 6, and more mother-reported and child-reported internalizing and externalizing problems at age 10? 2) Does elevated cortisol and/or shorter telomeres at age 6 predict greater child problems at age 10? 3) Does child cortisol and/or shorter telomeres mediate the anticipated association between PDS and child problems? We hypothesized 1) that PDS would predict elevated cortisol, shorter telomere length and more mother-reported and child-reported internalizing and externalizing problems; 2) that elevated cortisol and shorter telomere length would predict more child problems; and 3) that elevated cortisol and shorter telomere length would mediate detected effects of PDS on child problems association.

2. Methods

2.1. Participants

This study was part of a longitudinal project on psychobiological development in children (BIBO project; Basal Influences on Child Development). Ethical approval was obtained from the Social Science Ethical Committee (Radboud University), which follows the Helsinki Declaration. Pregnant women were recruited through midwife practices in and around Nijmegen, The Netherlands. Inclusion criteria were Dutch language fluency, no drug use, no physical or mental health problems, an uncomplicated singleton pregnancy with term delivery, and a 5-minute infant Apgar score of ≥ 7 (see Beijers, Jansen, Riksen-Walraven, & de Weerth, 2011). Of the 220 women who enrolled, 8 were excluded for medical reasons, such as preterm birth. Of the remaining 212 mothers, a further 19 discontinued the study during the first 3 postpartum months due to personal circumstances. This resulted in a final sample of 193 mothers and their infants, for whom the demographic characteristics are provided in Table 1. No differences in demographics were found between mothers who took part in the study and the 19 women who dropped out. Informed consent was given by all mothers.

2.2. Procedure

At 3 and 6 months after childbirth, mothers were asked to complete a depressive symptoms questionnaire. When the children were 6 years old, mothers collected saliva samples from their children on 2 consecutive days at home at 4 predefined time points. Additionally, during an afternoon school visit, researchers collected buccal cheek swab samples from the children. At age 10, child internalizing and externalizing problems were assessed by maternal reports and child reports during a home visit. Moreover, mothers reported on their current depressive symptoms.

Table 1
Overview of the demographic characteristics.

	Mean	SD	Range
Infant sex (% girls)	47.2%		
First born child (% yes)	41.0%		
Maternal marital status (% living with partner)	97.9%		
Maternal age at delivery	32.46	1.52	21.10-42.90
Maternal educational level			
Secondary education	20.4%		
College or university	75.8%		
Mother born in the Netherlands	95,8%		

2.3. Measures

2.3.1. Postpartum depressive symptoms (PDS)

PDS was measured at 3 and 6 months of infant age by the Edinburgh Postnatal Depression Scale (EPDS; Cox, Holden, & Sagovsky, 1987). The EPDS is a self-report questionnaire measuring depressive symptoms over the past week. The questionnaire consists of 10 items (4-point scale). An average total score was created to reflect PDS in the first 6 months after childbirth. If only one measurement was available, this was used.

2.3.2. Behavior problems

Behavior problems at age 10 were assessed using the child and parent version of the Strengths and Difficulties Questionnaire (SDQ; Goodman, 1997). It is comprised of 25 items (3-point scale). This study included the internalizing and externalizing subscales (Goodman, Lamping, & Ploubidis, 2010).

2.3.3. Cortisol

At child age 6, mothers collected 8 saliva samples from their child on two consecutive school-free days at 4 predefined time points (C1/C2/C3/C4: immediately after child awakening; 11:00; 15:00; 19:00). Saliva samples were collected with eye sponges (BD Visispeare, Waltham, MA; de Weerth, Jansen, Vos, Maitimu, & Lentjes, 2007). Mothers were instructed to note the exact sampling times, and to immediately store all saliva samples in their home freezer until transported to the university. Samples were analyzed in duplicate at the Laboratory of Endocrinology of the University Medical Center Utrecht. An in-house competitive radio-immunoassay employing a polyclonal anticortisol-antibody (K7348) and [1,2-3 H(N)]-Hydrocortisone (PerkinElmer NET396250UC) was used as a tracer. The lower detection limit was 1.0 nmol/L and inter-assay and intra-assay variations were < 10 %. To decrease fluctuations in cortisol due to sampling time, samples taken within the following time ranges were accepted (Beijers, Jansen, Riksen-Walraven, & de Weerth, 2010): C1 between 6:00 and 10:00, C2 between 10:00 and 12:00, C3 between 14:00 and 16:00, and C4 between 18:00 and 21:00. The window of 2 h was extended with one hour for C4 since diurnal cortisol fluctuation is less extreme at the end of the day (Edwards et al., 2001; Kirschbaum & Hellhammer, 1989). Illnesses, the use of medication, and biologically extreme values were also taken into account (Simons, Beijers, Cillessen, & de Weerth, 2015). Data was used to calculate the total amount of cortisol during the day, as reflected by the Area Under the Curve to the Ground (AUCg; Pruessner, Kirschbaum, Meinlschmid, & Hellhammer, 2003). After calculating the AUCg per day, an average score was calculated for the two days (Watamura, Donzella, Kertes, & Gunnar, 2004).

2.3.4. Telomere length

DNA was extracted from buccal epithelial cells collected at age 6 (M = 6 years and 20 days, SD = 67 days) using QIAamp DNA Mini Kit (Qiagen, Germany), and quantified using Quant-iT PicoGreen reagent (Thermo Fisher Scientific). DNA was stored at -80°C until telomere length assays. Telomere length assays were performed using a quantitative PCR protocol adapted from Cawthon (2002). Briefly, telomere length is expressed as a ratio of telomeric content (T) to a single-copy housekeeping gene (S). The single copy gene used in the assay is *36B4*. Separate PCR reactions using DNA from the same sample were conducted to quantify telomeric DNA content and *36B4* content. The cycling profile consists of denaturing at 95°C for 15 s and annealing/extending at 60°C for 1 min followed by fluorescence reading, 45 cycles. The final reaction mix for the telomeric DNA contains 1x SYBR Green Master Mix (Qiagen), 0.2U Uracil Glycosylase (Thermo Fisher Scientific), 0.1 u M forward primer, 0.1 u M reverse primer, and 3 ng DNA in a 20 u l reaction. The reaction mix for *36B4* contains 1x SYBR Green Master Mix, 0.2U Uracil Glycosylase, 0.3 u M forward primer, 0.5 u M reverse primer, and 3 ng DNA in a 20 u l reaction. The telomere primer sequences are: forward primer 5CGGTTTGTTTGGGTTTGGGT-TTGGGTTTGGGTTTGGGTT3; reverse primer 5GGCTTGCCTTACCCTTACCCTTAC-CCTTACCCTTACCCT3. The *36B4* primer sequences are: forward primer 5CAGCAAGTGG-GAAGGTGTAATCC3; reverse primer 5CCCATTCTATCATCAACGGGTACAA3. PCR amplifications used a robotic pipettor (QIAgility, Qiagen) to ensure maximum pipetting accuracy, and real-time qPCR was performed with a unique rotary design machine for sensitive and accurate optical performance (Qiagen's Rotor-Gene Q, Qiagen), which reduces well position effects.

The T/S ratio was calculated using the formula T/S = 2^(⟦Ct⟧ _36B4)/2^(⟦Ct⟧ _Telo), where Ct is the cycle at which the sample crosses a critical threshold of detection for the *36B4* and telomere reactions respectively. The same threshold was used for all assays (*36B4* and telomere). Samples were run in triplicate and the mean Ct across replicates was used for calculating the T/S ratio. When the Ct of one replicate deviated from the mean Ct by more than 15 % it was considered an outlier and the mean Ct was recalculated using two replicates.

To control for inter-assay variability, five controls samples were run on each plate. For each plate, the Ct value of each control DNA was divided by the average Ct value for the same DNA across all runs to get a normalizing factor for that sample on a given plate. This was done for all controls to get an average normalizing factor for that plate. In this manner the average intra-assay CV across all samples was less than 1 % and the average inter-assay CV was 1.1 %.

2.3.5. Covariate

As the EPDS (Cox et al., 1987) has been validated and used successfully beyond the postnatal period (e.g. Matijasevich et al., 2014; Matijasevich et al., 2015; Pearson et al., 2013), this same measure of maternal depression was used to control for maternal current depressive symptoms.

2.4. Data analyses

2.4.1. Data preparation

All variables were checked for violations of normality and outliers. All variables, except child-reported internalizing and externalizing problems, were subsequently log-transformed. Three variables contained one outlier. Since no outlier exceeded 4 SD, the outliers were included. Sensitivity analysis with only the cortisol variable log-transformed (as this variable proved to have the largest problems with non-normality), and with and without the outliers, revealed no differences in the pattern of significant effects to be reported.

2.4.2. Missing data

Of the 193 mother-child pairs, the data contained two complete missing cases. Of the 191 mothers and children comprising the analysis sample, the following data was complete: PDS at 3 and 6 months of infant age (N = 190), cortisol (N = 116), telomere length (N = 147), maternal-report of child problems (N = 156), child-report of child problems (N = 141). The TestMCARNormality function from the *MissMech* package (Jamshidian, Jalal, & Jansen, 2014) was used to test

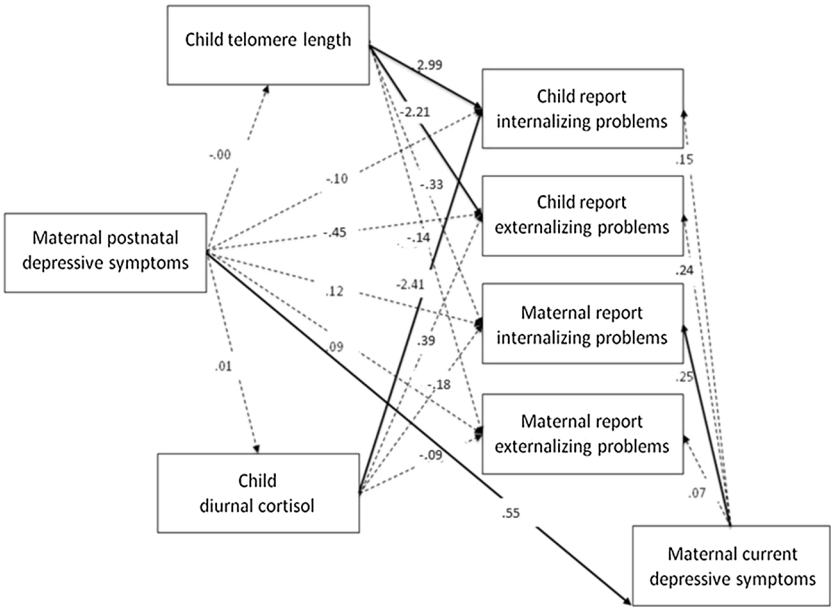

Fig. 1. Final SEM model describing the association between PDS and child behavior problems, as mediated by cortisol and telomere length. Significant paths are depicted in solid lines. Unstandardized estimates are presented.

whether missingness was missing completely at random (MCAR). The test revealed that there was not enough evidence to reject MCAR ($p > .05$). Provided that data is MCAR, multiple imputation gives unbiased estimates and standard errors (de Goeij et al., 2013), and was therefore used in order to retain sufficient power. In total, 304 imputations were done (22.5 %).

2.4.3. Primary analysis

Structural equation modelling (SEM) were conducted in R (Team, 2013). The SEM model depicted in Fig. 1 contained 18 regression paths, with PDS predicting cortisol, telomere length and the four child behavior variables (maternal-report and child-report on internalizing and externalizing problems). Moreover, four regression paths reflected the association between cortisol and the four child behavior variables, and four paths the association between telomere length and the four child behavior variables. Four additional regression paths reflected the association between maternal current depressive symptoms and the four child behavior variables. The final model is illustrated in Fig. 1.

The *Lavaan* statistical package (Rosseel, 2012) was used to test model fit. Because of the imputation strategy, standard errors could not be bootstrapped. Therefore, in a first step, a robust estimator (*MLR*) was used to calculate standard errors, and in a second step, bootstrapping was used to calculate bias-corrected confidence intervals. Based on modification indices, the initial model was adjusted 5 times to reach adequate model fit. For each adjusted model, the covariance with the highest modification index was included in the previous model to improve the model fit (see Table 2 for the fit indices). Regarding the final model, all goodness of fit measures indicated an adequate model fit as recommended by Kline (2005).

3. Results

3.1. Preliminary analysis

Descriptive statistics are presented in Table 3 (untransformed data). Most women in this low-risk sample reported minimal PDS, as illustrated by the 69.1 % of mothers with EPDS scores of less than 6. Mild postpartum depression (EPDS scores 7–13) was reported by 32.4 % of mothers, and moderate to severe depression (EPDS scores 14–30) by 1.5 % of mothers (severity cut-offs established by McCabe-Beane, Segre, Perkhounkova, Stuart, and O'Hara (2016).

Paired samples t-tests showed a difference between maternal reports and child reports of internalizing problems ($t(134) = 6.89$, $p < .001$), indicating that children generally reported more internalizing problems than their mothers. Children also reported more externalizing problems than their mothers ($t(130) = 8.91$, $p < .001$).

Spearman correlations between all variables are presented in Table 4. Higher PDS was associated with more mother-reported child internalizing problems, but not to child-reported problems. PDS was not significantly associated with cortisol or with telomere length. Lower cortisol was related to more child-reported internalizing problems. Also, shorter telomere length was related to more child-reported internalizing and externalizing problems. Furthermore, cortisol and telomere length were uncorrelated. Additionally, more mother-reported internalizing problems were related to more child-reported internalizing problems, and more mother-reported externalizing problems were related to more child-reported externalizing problems. Lastly, more PDS was related to more maternal depressive symptoms at child age 10.

3.2. Primary analysis

Parameter estimates and bootstrapped confidence intervals are summarized in Table 5. Given the simple-correlational results, it is not surprising that no significant direct paths emerged between PDS and child problems.[2] Moreover, PDS neither predicted child cortisol nor telomere length at age 6. In light of these null results, there was no evidence of any biological-embedding-related mediation.

It remains of interest, nevertheless, that the two biomarkers predicted child problems. Specifically, lower cortisol at age 6 forecast more child-reported internalizing problems at age 10 (b = .-2.41, 95 % CI [-4.20, -.62]) and shorter telomeres at the younger age predicted more child-reported internalizing problems (b = -2.98, 95 % CI [-5.18, -.79]) and externalizing ones at the older age(b = -2.24, 95 % CI [-4.07, -.41]). The former result, it should be recalled, proved to be exactly the

[2] When links between PDS and child problems were re-examined, this time not controlling for age 10 concurrent maternal symptoms, PDS did predict age 10 child internalizing problems, at least as reported by the mother (b = .242, 95% CI [.03,.46], p < .05).

Table 2
Goodness of fit indices of all models.

	CFI	SRMR	TLI	RMSEA	χ2
(1) Initial model	.459	.104	-.573	.164	$\chi2$ (9) = 55.22, $p < .001$
(2) First adjusted model	.863	.071	.520	.091	$\chi2$ (8) = 20.54, $p = .008$
(3) Second adjusted model	.923	.064	.691	.073	$\chi2$ (7) = 14.05, $p = .050$
(4) Third adjusted model	.947	.055	.754	.065	$\chi2$ (6) = 10.82, $p = .094$
(5) Fourth adjusted model	.969	.048	.824	.055	$\chi2$ (5) = 7.88, $p = .163$
(6) Final model	1.000	.029	1.098	.000	$\chi2$ (4) = 2.72, $p = .605$

Note. Covariances included in the models:
(1) Intitial model without Covariances.
(2) Initial model + Covariance between EP(child report) and EP(mother report).
(3) Covariances model 2 + Covariance between IP(child report) and IP(mother report).
(4) Covariances model 3 + Covariance between IP(child report) and EP(child report).
(5) Covariances model 4 + Covariance between IP(mother report) and EP(mother report).
(6) Covariances model 5 + Covariance between EP(child report) and IP(mother report).
EP = Externalizing problems; IP = Internalizing problems.

Table 3
Descriptive statistics of the study variables.

	M	SD	Range
PDS	5.06	3.29	0.00-21.00
Maternal current depressive symptoms	4.52	4.42	0.00-28.00
Telomere length (T/S-ratio)	1.11	0.56	0.30-3.42
Cortisol (AUCg; nmol/L)	4801.58	1440.03	2518.25-10801.13
Maternal-report internalizing problems	2.83	2.61	0.00-15.00
Maternal-report externalizing problems	3.96	3.23	0.00-16.00
Child-report internalizing problems	3.96	3.23	0.00-16.00
Child-report externalizing problems	4.56	2.84	0.00-15.00

opposite of what was anticipated (i.e., higher cortisol predicting more problems). Lastly, the results indicated that greater maternal depressive symptoms at age 10 were associated with greater child internalizing problems, as reported by mother herself (b = .25, 95 % CI [.081, .411]).

The final model explained 0 % of the variance in cortisol and telomere length, 12 % of the variance in mother-reported internalizing problems, and 1.8 % of the variance in mother-reported externalizing problems. Additionally, the model explained 11.8 % of the variance in child-reported internalizing problems, and 5.1 % of the variance in child-reported externalizing problems.

4. Discussion

We sought to evaluate whether, in a low-risk sample, PDS predicts child internalizing and externalizing behavior problems at age 10, as assessed by both maternal reports and child self-reports, and whether cortisol and telomere length at age 6 mediated any detected PDS-child problems' association. Recall that we hypothesized 1) that PDS would predict elevated cortisol, shorter telomere length, and more mother-reported and child-reported internalizing and externalizing problems; 2) that elevated cortisol and shorter telomere length would predict more child problems; and 3) that elevated cortisol and shorter telomere length would mediate the anticipated PDS and child problems' association. Results revealed no relation between PDS and later child cortisol, telomere length or behavior problems. As such, there was no evidence of any biological-embedding-related mediation. Nevertheless, findings indicated that variation in the two biomarkers forecast later behavior problems, such that lower cortisol was related to more internalizing problems and that shorter telomere length was related to more internalizing and externalizing problems, at least as reported by the child.

Several factors may explain why no associations were detected linking PDS with child cortisol, telomere length and behavior problems. First, our study was conducted in a low-risk community sample, with most mothers experiencing minimal or mild PDS. Although other studies of such low-risk samples have chronicled associations of the variables in question, most such work has focused on children younger than 10-year olds who were the focus of our inquiry. This observation raises the possibility that in low-risk, non-clinical samples, linkages between PDS and child problems may be relatively short lived, evident during the preschool years, but no longer so by middle childhood. Consistent with this possibility are the results of Closa-Monasterolo and associates' (2017) work which failed to document any association between PDS and behavior problems at age 8, and with two meta-analyses showing that the strength of the associations between PDS and child development tends to weaken as children age (Beck, 1998; Goodman et al., 2011). It is suggested that only prolonged maternal depressive symptoms, but not PDS alone, are associated with child well-being beyond the preschool years, at least in low-risk samples (Murray et al., 2015).

It also seems possible that the failure to discern an association

Table 4
Spearman correlations between all study variables.

	1	2	3	4	5	6	7	8
1. PDS								
2. Current depressive symptoms	.40***							
3. Telomere length	.00	-.03						
4. Cortisol	-.05	.02	.04					
5. Maternal-report internalizing problems	.22**	.27**	-.08	-.02				
6. Maternal-report externalizing problems	.09	.05	-.03	.02	.25**			
7. Child-report internalizing problems	-.03	.00	-.23*	-.22*	.19*	.12		
8. Child-report externalizing problems	-.06	.03	-.21*	-.03	.22**	.51***	.33***	

* $p < .05$.
** $p < .01$.
*** $p < .001$.

Table 5
Parameter estimates and bootstrapped Confidence Intervals for the final model.

	B	SE	Lower CI	Upper CI	ß
Regression paths					
Child telomere length					
PDS (a1)	.001	.039	-.075	.077	.002
Child diurnal cortisol (AUCg)					
PDS (a2)	.005	.047	-.087	.096	.010
Child report Internalizing Problems					
PDS (c1)	-.097	.482	−1.042	.849	-.019
TL (b1)	−2.989	1.123	−5.190	-.787	-.253
AUCg (b2)	−2.409	.914	−4.199	-.618	-.228
Child report Externalizing Problems					
PDS (c2)	-.448	.408	−1.248	.351	-.095
TL (b3)	−2.208	.934	−4.040	-.377	-.202
AUCg (b4)	.390	1.052	−1.672	2.451	.040
Maternal report Internalizing Problems					
PDS (c3)	.116	.119	-.117	.349	.094
TL (b5)	-.327	.218	-.754	.099	-.114
AUCg (b6)	-.181	.238	-.648	.285	-.071
Maternal report Externalizing Problems					
PDS (c4)	.088	.110	-.127	.304	.069
TL (b7)	-.140	.284	-.695	.416	-.047
AUCg (b8)	-.086	.245	-.566	.395	-.032
Maternal current depressive symptoms					
PDS	.553	.109	.340	.766	.410
Covariate					
Child report Internalizing Problems					
MCDS	.145	.331	-.503	.794	.039
Child report Externalizing Problems					
MCDS	.242	.369	-.481	.965	.069
Maternal report Internalizing Problems					
MCDS	.248	.084	.083	.413	.270
Maternal report Externalizing Problems					
MCDS	.072	.094	-.112	.256	.076
Indirect effects					
Mediator: Telomere length					
PDS→ TL→ CIP (a1 x b1)	-.002	.116	-.230	.226	.000
PDS→ TL→ CEP (a1x b3)	-.002	.086	-.170	.166	.000
PDS→ TL→ MIP (a1x b5)	.000	.013	-.025	.025	.000
PDS→ TL→ MEP (a1x b7)	.000	.005	-.011	.011	.000
Mediator: Diurnal cortisol					
PDS→ AUCg→ CIP (a2 x b2)	-.011	.112	-.231	.209	-.002
PDS→ AUCg→ CEP (a2x b4)	.002	.018	-.033	.037	.000
PDS→ AUCg→ MIP (a2x b6)	-.001	.009	-.017	.016	-.001
PDS→ AUCg→ MEP (a2x b8)	.000	.004	-.019	.008	.000

Note. $\chi 2$ (4) = 2.72, p = .605; CFI = 1.000; SRMR = .029; TLI = 1.098; RMSEA = .000.
Results based on N = 190. MLR estimator was used to calculate parameter estimates, bootstrapping to produce bias-corrected confidence intervals.
PDS = Maternal postpartum depressive symptoms; MCDS = Maternal current depressive symptoms; TL = Child telomere length; AUCg = area under the curve to the ground; CIP = Child report internalizing problems; CEP = Child report externalizing problems; MIP = Maternal report internalizing problems; MEP = Maternal report externalizing problems.

between PDS and later child problems was a result of controlling for concurrent maternal depressive symptoms at age 10, thereby making our inquiry really an investigation of the potential determinants of *change* in such symptoms over time. Notably, such an approach to illuminating the developmental sequelae of PDS is more the exception than the rule when evaluating PDS effects on child development (e.g., Grace, Evindar, & Stewart, 2003). This observation raises the possibility that in prior work adverse effects of concurrent depressive symptoms have been misattributed to PDS (Closa-Monasterolo et al., 2017; Gjerde et al., 2017).

To address this issue of misspecification of effects of PDS, we re-examined links between PDS and child problems, this time not controlling for age-10 concurrent maternal symptoms. The fact that under these analytic conditions PDS did predict age 10 child internalizing problems, at least as reported by the mother (b = .242, 95 % CI [.03, .46], p < .05), would seem to help explain why we failedin our primary analysesto detect any associations between PDS and later problems. In fact, the change in our results would seem to challenge interpretations of prior work linking PDS directly with later child problems without considering the stability of PDS over time.

In addition to any direct associations between PDS and child outcomes, we expected elevated cortisol to predict more child problems. To our surprise, it turned out that lower cortisol at age 6 forecast more child-reported internalizing problems at age 10. This finding is inconsistent with those of the few longitudinal studies which have generated the very results leading to our original cortisol-related prediction, including our mediational hypothesis (Saridjan et al., 2014; Shirtcliff & Essex, 2008). Our findings might be explained by the development of the HPA-axis during childhood in relation to co-occurring internalizing behavior problems. Ruttle et al. (2011) proposed that around the time when internalizing behaviors are first experienced, the stress system is *hyper*active, resulting in elevated cortisol concentrations. However, over a prolonged period of exposure to elevated cortisol, a down-regulation of the HPA-axis takes place. Such a process results in a *hypoactive* HPA-axis and thus lower cortisol concentrations (Miller, Chen, & Zhou, 2007).

From this perspective, had behavior problems preceded our cortisol measure, a shift from hyperactivity to hypoactivity of the HPA-axis could have been expected. In consequence, such hypoactivity might be expected to predict later behavior problems.

Needless to say, it will require future research to assess cortisol concentrations and internalizing problems simultaneously and repeatedly to clarify this matter. This future, longitudinal research could then also help clarify why no relation emerged between lower cortisol at age 6 and more externalizing problems at age 10. While the development of externalizing behavior has been associated with lower basal cortisol, this relation appeared smaller than previously thought and moderated by age; externalizing behavior was associated with higher basal cortisol in pre-schoolers, with lower basal cortisol in school-aged children, and not with basal cortisol in adolescents (Alink et al., 2008). If these age differences reflect developmental shifts in the link between externalizing behavior and cortisol, these shifts might explain our study non-findings between cortisol and externalizing behavior.

The result that did emerge as expected involved telomere length. Recall that shorter telomeres at age 6 predicted more child-reported internalizing and externalizing behavior problems at age 10. To our knowledge, this is the first such finding to be reported using longitudinal data, though the result is in line with those of two previous cross-sectional studies (Kroenke et al., 2011; Wojcicki et al., 2015). Importantly, causality cannot be assumed based on our research design, as shared sources of influence (e.g., shared genetic variance) might underlie both telomere length and behavior problems. The molecular pathways linking shorter telomere length to later behavior problems are unclear. Telomeres shorten with every cell division, and telomeres that are shortened past a critical length can become senescent (Harley et al., 1990). These senescent cells can exert harmful effects on the tissue micro-environment, including an increase in the secretion of pro-inflammatory cytokines (Davalos, Coppe, Campisi, & Desprez, 2010), which in turn could impact brain functioning and behavior (Flouri, Francesconi, Papachristou, Midouhas, & Lewis, 2019). Alternatively, as our present study did not include an earlier measure of behavior problems, it is also possible that telomeres do not contribute to the development, but are a result, of behavior problems. Many types of psychopathology, such as anxiety and depression, are related to telomere length and shortening, possibly due to mechanisms including elevated levels of glucocorticoids, oxidative stress, inflammation, mitochondrial dysfunction and telomerase regulation (Malouff & Schutte, 2017; Ridout et al., 2016; Shalev, 2012). Future prospective studies are needed to elucidate if and how molecular mechanisms relate telomere length to later internalizing and externalizing problems.

Interestingly, both cortisol and telomere length were only

associated with child reports, but not maternal reports, of problems. This is an important finding, considering that most studies solely rely on maternal reports of child problems. Once more there is evidence, then, that one set of reports cannot be presumed to reflect what would be detected with another set of reports, even though they are correlated to some extent (see Table 4). Particularly in regard to internalizing symptoms that may not be as readily observed by others compared to externalizing symptoms, it is possible that children are more accurate reporters of their internalizing symptoms. Future research on internalizing symptoms is encouraged to, whenever possible, also include child report.

Our study has several strengths, including its longitudinal design, assessments of behavior problems by two sets of respondents, and control for age 10 maternal depressive symptoms. We would be remiss if we did not highlight some limitations. Our study sample was rather privileged, with mostly highly educated women, living together with a partner. Though it is important to understand whether links between PDS and child outcomes are limited to at-risk samples, or also emerge in low-risk samples, the nature of our sample compromises the generalizability of our findings. The fact that we needed to rely on multiple imputation due to substantial missing data represents another weakness that must be highlighted.

Because the absence of evidence—in our case of biological embedding via cortisol or telomeres—is not evidence of absence, our results do not indicate that such embedding is not operative. Nor should they be read to discourage pursuit of other potential embedding mechanisms (e.g., inflammation, epigenetics). Conceivably, depressive symptoms during pregnancy, or PDS in combination with other early-life stressors (e.g., harsh parenting, single parenthood)—might still influence cortisol, telomeres or other physiological processes and, thereby, influence future behavior problems. Just as worthy of attention are factors that might buffer rather than amplify the effects of PDS when it comes to biological embedding, such as a supportive marital/partner relationship or sensitive fathering (Mezulis, Hyde, & Clark, 2004). These are avenues of inquiry that we look forward to seeing pursued.

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Declaration of Competing Interest

The authors report no conflicts of interest.

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