

Antenatal and postnatal maternal mental health as determinants of infant neurodevelopment at 18 months of age in a mother–child cohort (Rhea Study) in Crete, Greece

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Abstract

Purpose A growing body of evidence links poor maternal mental health with negative outcomes on early child development. We examined the effect of antenatal and postnatal maternal mental health on infant neurodevelopment at age 18 months in a population-based mother–child cohort (Rhea Study) in Crete, Greece.

Methods Self-reported measures of maternal depression (EPDS), trait anxiety (STAI-Trait) and personality traits (EPQ-R) were assessed in a sample of women during pregnancy and at 8 weeks postpartum ($n = 223$). An additional sample of 247 mothers also completed the EPDS scale at 8 weeks postpartum ($n = 470$). Neurodevelopment at 18 months was assessed with the use of Bayley Scales of Infant and Toddler Development (3rd edition).

Results Multivariable linear regression models adjusted for confounders revealed that antenatal depressive symptoms ($EPDS \geq 13$) were associated with decrease in cognitive development independently of postnatal depression. High trait anxiety and extraversion were associated with decrease and increase, respectively, in social–emotional development. Also, high trait anxiety and neuroticism had a positive effect on infants' expressive communication. Finally, postpartum depressive symptoms ($EPDS \geq 13$) were associated with decrease in cognitive and fine motor development independently of antenatal depression.

Conclusions These findings suggest that antenatal and postnatal maternal psychological well-being has important consequences on early child neurodevelopment.

Keywords Antenatal maternal mental health · Postpartum depression · Infant neurodevelopment

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Introduction

There is a growing body of evidence that links maternal emotional distress during pregnancy with poor child development in the cognitive, emotional, and behavioral domains (for literature review see [1]). Recent studies have reported that stress experienced by the mother during pregnancy is associated with increased risk for many adverse long-term effects on the child, including neurodevelopment [2–4]. The increased risk for child cognitive and behavioral problems is found with moderate elevations of anxiety and in non-selected samples [5], and is independent of postnatal anxiety and depression [5]. Prenatal programming of fetal stress reactivity is the most often suggested mechanism responsible for this association.

Perinatal maternal depression affects 10–15 % of women [6], and as such, represents a considerable public health problem affecting women and their families. Prospective studies investigating the impact of postpartum depression on later child cognitive and language development have reported inconsistent findings [7–9]. Some studies have shown lasting adverse effects of depression in the first postnatal year, with no additional impact of later depression [10], others report no lasting impact on cognitive development [7], yet others conclude that adverse developmental outcomes are related to chronicity and severity of maternal depression [11, 12]. Recently, Evans and his associates [13] in a longitudinal assessment of maternal depression on child cognitive development found that the postnatal period is not a sensitive one for exposure to maternal depression and that antenatal occurrence of depression might be more important than depression at other times. This is consistent with previous findings indicating that the antenatal period may be more important than the postnatal one for several aspects of child development [14, 15].

The majority of the studies evaluating the role of maternal mental health on infant neurodevelopment included school-age children and adolescents, while there are only few epidemiological studies, with inconsistent results, that have focused on infant and toddler neurodevelopment [12, 14, 16, 17]. Within the context of a population-based mother–child cohort study in Crete, Greece (Rhea Study), we investigated the association of antenatal (3rd trimester) versus postnatal maternal depression (at 8 weeks postpartum) on the one hand and predisposing personality characteristics on the other hand with infant neurodevelopment at 18 months of age. A secondary aim was to evaluate in a larger sample whether postpartum depressive symptoms alone would be associated with infant neurodevelopment at 18 months of age and how any such findings would compare to the conflicting literature. This is the first study evaluating the effect of maternal mental characteristics on child neurodevelopment in a Greek population and is among the few similar studies evaluating simultaneously antenatal and postnatal mental health.

Methods

The mother–child cohort in Crete (Rhea Study)

The Rhea Cohort Study is a prospective mother–child study which examines a population-based cohort of pregnant women and their children at the prefecture of Heraklion, Crete [18]. Female residents (Greek and immigrants) who had become pregnant during the

12-month period starting from February 2007 have been contacted at four maternity clinics in Heraklion and asked to participate in the study. To be eligible for inclusion in the study, women had to have a good understanding of the Greek language and be older than 17 years of age. The first contact was made before week 15 of gestation, at the time of the first major ultrasound examination. Women were informed about the study protocol by trained nurses and midwives and asked to participate in the study. Women were then contacted again at 28th–32nd week of gestation, at birth, at 8 weeks, 6 and 18 months postpartum and currently the children are being followed up at 4 years of child's age. Face-to-face structured interviews, together with self-administered questionnaires and medical records, were used to obtain information on several psychosocial, dietary, and environmental exposures during pregnancy and early childhood. The study was conducted according to the guidelines laid down in the Declaration of Helsinki and all procedures involving human subjects were approved by the ethical committee of the University Hospital in Heraklion, Crete, Greece. Written informed consent was obtained from all women participating in the study.

Detailed characteristics of the study population have been described elsewhere [18]. During the study recruitment period 1,765 eligible women were approached, 1,610 (91 %) agreed to participate, and 1,388 (86 %) were followed up until delivery. Women were asked to complete self-reported instruments for antenatal psychological assessment at 28–32 weeks of gestation at home and they were asked to return them by mail. Postnatal assessment at 8 weeks postpartum took place by telephone interview, where women were invited by trained interviewers to provide information about symptoms of postpartum depression in the EPDS scale. A random sample of 828 mothers was contacted by telephone at the 18-month follow-up, and 599 (73 %) agreed to participate in the neurodevelopmental assessment [19]. In total, 502 (84 % of the total study population with neurodevelopmental assessment) mother–child pairs were eligible for inclusion in the present analysis, having complete information on postpartum depressive symptoms and neurodevelopmental assessment at 18 months of age. We included only women with singleton pregnancies, thus multiple pregnancies were excluded ($n = 26$). We also excluded six infants due to incomplete examination ($n = 1$), signs of pervasive developmental disorders (PDD) ($n = 1$), plagiocephalus ($n = 1$), brain tumor ($n = 1$), microcephalus ($n = 2$). Hence, a cohort of 470 mother–child pairs (77 % of the total study population) with neurodevelopmental assessment was available for this analysis. For a sub-sample of this cohort ($n = 223$, 47.4 %) self-reported measures of antenatal depression, trait anxiety and personality traits were available.

Psychological assessment during pregnancy and at the postpartum period

Maternal anxiety was measured at 28–32 weeks of gestation using the State-Trait Anxiety Inventory (STAI) [20]. It is a 40-item scale made up of two 20-item subscales (one state and one trait), and has been widely used to assess anxiety not only in clinical but also in non-clinical samples. Only the STAI-Trait subscale was used for the purposes of the present study. Trait anxiety reflects relatively stable individual differences in anxiety proneness. Each item of the trait subscale is scored on a 4-point scale ranging from 1 (almost never) to 4 (almost always). The STAI is a widely used index of anxiety symptoms and has considerable validity, reliability, and clinical utility. The STAI has been translated and validated in Greek by Liakos and Giannitsi [21].

Maternal depressive symptoms were assessed—antenatally at 28–32 weeks of gestation and postnatally at 8 weeks postpartum—using the Edinburgh Postnatal Depression Scale (EPDS) [22]. The EPDS is a widely used 10-item self-reported questionnaire providing an indication of the severity of mother's mood during the past 7 days. Items are rated on a 4-point Likert scale ranging from 0 (not at all) to 3 (most of the time) and refers to depressed mood, anhedonia, guilt, anxiety, and suicidal ideation. The EPDS is the only rating scale for depression validated during both the antenatal and the postnatal period [23]. One Greek study has shown that an EPDS cutoff score of 11/12 may be an effective screening for minor depression postnatally in a small ($n = 81$) and non-representative Greek sample [24], while another one has shown that a cutoff score of 8/9 may be an effective screening for self-reported depressive symptoms postnatally [25]. Since none of the two Greek studies validated the EPDS against a rigorous clinical interview, in the present study we adopted a cutoff score of 13 or greater as recommended by Cox et al. [22] which appeared to be an effective screening for probable clinical depression in numerous studies. This cutoff is also consistent with previous work in our cohort [26], and it has been shown to achieve high sensitivity (95 %) and specificity (93 %) when compared with clinical psychiatric interview in a subsample of our cohort. Thus, in the present analysis, EPDS was used as a continuous variable and as a categorical variable with EPDS ≥ 13 indicating high levels of postpartum depressive symptoms. We used the same cutoff score for antenatal depression in order to obtain comparable data.

The Eysenck Personality Questionnaire—Revised (EPQ-R) [27] was used for the assessment of maternal personality characteristics during pregnancy at 28–32 weeks of gestation. The 106-item self-reported questionnaire provides a convenient measure of three key dimensions of

personality: psychoticism (P), extraversion (E), neuroticism (N). A lie scale (L) is also included, along with supplementary measures of predisposition to addiction and criminality. Extraversion includes such attributes as sociability, liveliness, assertiveness, being active, and sensation seeking. Neuroticism includes anxiety, low mood, feelings of guilt, and low self-esteem. Psychoticism describes characteristics of coldness, aggression, cruelty, and predisposition to antisocial behavior rather than the current concept of the disturbance of mind found in disorders such as schizophrenia. The fourth scale, lie, measures dissimulation and the tendency for respondents to adjust their responses so that they are more socially acceptable. Each score is a sum of the responses of agreement or disagreement (yes/no) for each dimension or scale.

Neurodevelopmental assessment at 18 months

The children's mental and psychomotor development was assessed at 18 months (± 6 weeks) using the Bayley Scales of Infant and Toddler Development—Third Edition (Bayley-III) [28]. The Bayley-III is an individually administered instrument that assesses the developmental functioning of infants and young children between 1 and 42 months of age. Its primary purposes are to identify children with developmental delay and to provide information for intervention planning.

The Bayley-III assesses infant and toddler development across three domains: (1) The cognitive scale (COG) includes items that assess sensorimotor development, exploration and manipulation, object relatedness, concept formation, memory, and other aspects of cognitive processing. (2) The language scale is composed of the receptive communication (RC) and the expressive communication (EC) subtest. The RC subtest includes items that assess preverbal behaviors, vocabulary development, vocabulary related to morphological development, and understanding of morphological markers, children's social referencing and verbal comprehension; the EC subtest includes items that assess preverbal communication, vocabulary development, and morpho-syntactic development. (3) The motor scale is divided into the fine motor (FM) and the gross motor (GM) subtest. In the FM subtest are included fine motor skills associated with prehension, perceptual-motor integration, motor planning, and motor speed. The GM subtest primarily measures the movement of the limbs and torso.

For each scale, the child's score was determined by the number of items for which credit was received. We analyzed raw scores instead of scaled scores and composite score equivalents because the United States reference sample may not be appropriate for children outside United States. Raw scores were standardized to a mean of 100 with

a standard deviation of 15 to homogenize all the scales [19].

We also used the self-reported Social–Emotional Scale (SE) of Bayley-III. The scale assesses the acquisition of social and emotional milestones in infants and young children. It identifies the major developmental milestones that should be achieved by certain ages. It includes items that assess the child’s mastery of functional emotional skills, communication needs, the child’s ability to engage others and establish relationships, use emotions in an interactive, purposeful manner, and use emotional signals or gestures to solve problems. The cross-cultural adaptation of the Social–Emotional Scale was performed according to internationally recommended methodology, using the following guidelines: forward translation, backward translation, cognitive debriefing process, and pretesting [19].

Neurodevelopmental assessments were conducted by three trained psychologists, who completed the formal training course in the use, administration and interpretation of Bayley-III [28]. All testing was done at the Medical School of the University of Crete, two public hospitals in Heraklion, and Medical Health Centers in the provinces, always in the presence of the mother. Total administration time was approximately 90 min. The examiners, also, noted critical comments about the difficulties or special conditions of the neurodevelopmental assessment so as to evaluate the “quality of assessment” such as no difficulties, difficulties due to physical problems (e.g. physical illness, tiredness, asleep, etc.), difficulties due to behavior problems (e.g. nervousness, shyness, etc.).

Mothers were re-contacted by mail and given feedback on their child’s performance at the test within 1 month of the neurodevelopmental assessment.

Potential confounders

Potential confounders evaluated included children’s and mothers’ characteristics that have an established or potential association with children’s neurodevelopment and/or maternal psychosocial stress. Children’s characteristics included child’s gender (boy vs. girl), quality of assessment (non-difficulties, infants participated in the reliability study, difficulties due to physical status, difficulties due to behavioral problems), delivery type (cesarean vs. vaginal delivery), gestational age (completed weeks), breastfeeding duration (months), and child care until 18th month (nursery care vs. no nursery care). Maternal characteristics included maternal age at delivery, maternal education (low level: ≤ 9 years of school, medium level: ≤ 12 years of school and > 9 years of school, and high level: some years in university or university degree, ref: low level), maternal origin (Greek vs. non-Greek), parity (multiparous vs.

primiparous), and mother’s employment status at the 18th month (working vs. not-working).

Statistical analysis

Reliability

Twelve children participated in the reliability study of the neurodevelopmental assessment. Each of the psychologists conducted four interviews in turn as examiner, in order to achieve exchangeability, where the other two were simultaneously scoring the Bayley’s test for COG, RC, EC, FM and GM scales as observers. Their ratings were used to evaluate the reliability of the assessment. The intra-class correlation coefficient (ICC) was used to measure the inter-rater reliability for absolute agreement between scores in a two-way random model.

Standardization of scores

Raw scores were standardised for psychologist and child’s age at test administration using a parametric method for the estimation of age-specific reference intervals [29]. The parameters of the distribution are modeled as fractional polynomial (FP) function of age and estimated by maximum likelihood (ML). Standardised residuals were then typified having a mean of 100 points with a 15 SD to homogenize the scales (parameters conventionally used in psychometrics for assessing IQs).

Statistical analysis

Descriptive statistics were used to summarize the baseline characteristics of participants. The main outcome variables are neurodevelopmental scores in the six scales of Bayley-III of infants at 18 months. In the main sample of 223 mother–infant pairs, the primary exposures of interest were antenatal depressive symptoms, personality traits (i.e. trait anxiety, neuroticism, psychoticism and extraversion) and postpartum depressive symptoms. In the larger cohort of 470 mother–infant pairs, the primary exposure of interest was maternal postpartum symptoms of depression at 8 weeks postpartum. The EPDS was used as a continuous variable and as a categorical variable with EPDS ≥ 13 indicating high levels of postpartum depressive symptoms [22].

Bivariate associations between categorical independent (predictors) and continuous dependent variables (outcomes) were studied using Student *t* test. Bivariate associations between categorical independent (predictors) and dependent variables (outcomes) were studied using Pearson’s χ^2 test. Spearman’s rho correlation coefficient was used to estimate the strength of the association between two

continuous variables. Multivariable linear regression models were fit to estimate the associations of psychological measures and neurodevelopmental outcomes after adjusting for confounders, as well. Potential confounders related with either the outcomes or the exposure of interest in the bivariate associations with a p value <0.2 were included in the multivariable models, as well as *a priori* selected potential confounders such as child's sex, maternal age, maternal education, gestational age, quality of assessment, and breastfeeding duration. Separate multivariable models were built having as an outcome each one of the six neurodevelopmental scales. Estimated associations are described in terms of β -coefficients (beta) and their 95 % confidence intervals (CI). All hypothesis testing was conducted assuming a 0.05 significance level and a two-sided alternative hypothesis.

All statistical analyses were performed using PASW Statistics 18 software (SPSS Inc, Chicago, IL, USA).

Results

Reliability

Overall, the inter-rater reliability for all measures was excellent. Specifically, the inter-rater reliability for the cognitive scale was found to be $ICC_{COG} = 0.990$ ($p < 0.001$), for receptive communication $ICC_{RC} = 0.996$ ($p < 0.001$), for expressive communication $ICC_{EC} = 0.994$ ($p < 0.001$), for fine motor $ICC_{FM} = 0.924$ ($p < 0.001$), and finally for gross motor $ICC_{GM} = 0.972$ ($p < 0.001$).

Sample characteristics

Table 1 presents the maternal and infant characteristics of the study samples (223 women with full pre- and post-natal data and 470 women with postnatal EPDS only). There were no significant differences between each sample and the entire cohort or between the two samples. Most mothers were of Greek origin (97.0 %), 255 (56.4 %) were multiparous, 50.3 % had medium level of education and 57.6 % were working during pregnancy. Participants' mean age at birth was 30.09 years ($SD = 4.53$). The mean age of infants at the time of assessment was 18.1 months ($SD = 0.7$) and the mean gestational age was 38.3 ($SD = 1.3$) weeks. Among infants, 256 (54.5 %) were males, 10.5 % were born prematurely (<37 weeks of gestation), and 239 (51.2 %) of the deliveries were cesarean in line with previous reports in Crete [30] and elsewhere in Greece [31] (Table 1).

Table 1 Socio-demographic characteristics of the study population

	$n = 470$		$n = 223$	
	n	%	n	%
Maternal education				
Low	58	(12.6)	22	(9.9)
Medium	232	(50.3)	110	(49.3)
High	171	(37.1)	91	(40.8)
Origin				
Greek	455	(97.0)	217	(97.3)
Non-Greek	14	(3.0)	6	(2.7)
Working during pregnancy				
Yes	266	(57.6)	133	(59.6)
No	196	(42.4)	90	(40.4)
Marital status				
Married	419	(90.3)	222	(99.6)
Other	45	(9.7)	1	(0.4)
Parity				
Primiparous	197	(43.6)	91	(42.7)
Multiparous	255	(56.4)	122	(57.3)
Smoking during pregnancy				
Smoker	85	(18.5)	40	(17.9)
Ex smoker	99	(21.5)	49	(22.0)
Non-smoker	276	(60.0)	134	(60.1)
Child Sex				
Male	256	(54.5)	125	(56.1)
Female	214	(45.5)	98	(43.9)
Delivery type				
Normal	228	(48.8)	111	(49.8)
Cesarean	239	(51.2)	112	(50.2)
Prematurity				
Non-preterm	418	(89.5)	199	(91.3)
Preterm	49	(10.5)	19	(8.7)
		Mean (SD)	Mean (SD)	
Maternal age (years)		30.09 (4.5)	30.31 (4.1)	
Gestational age (weeks)		38.3 (1.3)	38.4 (1.3)	
Birthweight (grams)		3187.9 (415.5)	3229.3 (425.8)	
Breastfeeding duration (months)		4.38 (4.4)	4.53 (4.2)	
Infant age (months)		18.1 (0.7)	18.1 (0.7)	

Antenatal maternal mental health and infant neurodevelopment at 18 months

Table 2 shows the relationship between antenatal maternal mental health and child neurodevelopment at age 18 months. Multivariable analysis revealed that high levels of antenatal maternal depressive symptoms (antenatal EPDS score ≥ 13) were associated with 5.5 units decrease in the scale of cognitive development (β coefficient -5.45 , 95 % CI: -10.44 , -0.46). Because of a positive association between

Table 2 Association of antenatal maternal mental health and infants' neurodevelopmental outcomes at age 18 months (RHEA Study, Crete, Greece, 2007–2012)

	Cognitive ^a		Receptive communication ^a		Expressive communication ^a		Fine motor ^a		Gross motor ^a		Social-emotional ^a	
	β -coeff	95 % CI	β	95 % CI	β	95 % CI	β	95 % CI	β	95 % CI	β	95 % CI
Crude models ^a (<i>n</i> = 223)												
STAI-trait (per 5 unit increase)	-0.88	(-1.96, 0.19)	0.03	(-0.99, 1.04)	1.15	(0.16, 2.14)*	-0.32	(-1.40, 0.76)	-0.14	(-1.16, 0.88)	-1.43	(-2.61, -0.25)*
EPQ												
Neuroticism	-0.27	(-0.65, 0.11)	-0.06	(-0.42, 0.30)	0.37	(0.02, 0.72)*	-0.01	(-0.39, 0.36)	-0.08	(-0.44, 0.28)	-0.17	(-0.59, 0.25)
Extraversion	-0.13	(-0.57, 0.32)	-0.13	(-0.55, 0.29)	0.29	(-0.13, 0.70)	-0.27	(-0.71, 0.17)	-0.05	(-0.48, 0.38)	0.52	(0.02, 1.01)*
Psychoticism	-0.64	(-1.38, 0.09)	-0.56	(-1.25, 0.14)	-0.38	(-1.06, 0.30)	-0.73	(-1.46, 0.00)	0.08	(-0.62, 0.78)	-0.39	(-1.20, 0.42)
EPDS antenatal	-0.35	(-0.74, 0.03)	-0.11	(-0.47, 0.26)	0.16	(-0.20, 0.52)	-0.07	(-0.46, 0.32)	-0.16	(-0.54, 0.20)	-0.40	(-0.83, 0.03)
EPDS antenatal ≥ 13	-5.75	(-10.85, -0.65)*	-0.16	(-5.03, 4.70)	2.11	(-2.65, 6.88)	-0.61	(-5.76, 4.53)	-1.82	(-6.69, 3.05)	-5.06	(-10.73, 0.62)
EPDS postnatal	-0.40	(-0.80, -0.01)*	-0.05	(-0.42, 0.33)	0.15	(-0.22, 0.52)	-0.11	(-0.51, 0.28)	0.14	(-0.24, 0.52)	-0.38	(-0.82, 0.06)
EPDS postnatal ≥ 13	-5.25	(-11.16, 0.66)	-0.26	(-5.87, 5.36)	2.85	(-2.64, 8.35)	-1.17	(-7.10, 4.76)	4.90	(-0.69, 10.49)	-2.59	(-9.19, 4.00)
Adjusted models ^b (<i>n</i> = 223)												
STAI-trait (per 5 unit increase)	-0.82	(-1.88, 0.25) ^c	0.12	(-0.89, 1.12)	1.13	(0.15, 2.11)* ^c	-0.17	(-1.23, 0.88)	0.05	(-0.98, 1.07)	-1.43	(-2.63, -0.23)*
EPQ												
Neuroticism	-0.13	(-0.52, 0.25) ^d	-0.06	(-0.42, 0.29)	0.38	(0.03, 0.72)* ^e	0.05	(-0.33, 0.42)	-0.08	(-0.45, 0.29) ^d	-0.19	(-0.61, 0.24)
Extraversion	-0.06	(-0.50, 0.39) ^d	-0.05	(-0.47, 0.36)	0.36	(-0.04, 0.77) ^e	-0.20	(-0.63, 0.24)	-0.09	(-0.52, 0.35) ^d	0.54	(0.04, 1.04)*
Psychoticism	-0.73	(-1.49, 0.04) ^d	-0.61	(-1.29, 0.07)	-0.35	(-1.02, 0.31) ^e	-0.68	(-1.40, 0.03)	-0.03	(-0.77, 0.70) ^d	-0.47	(-1.29, 0.35)
EPDS antenatal	-0.29	(-0.67, 0.10)	-0.06	(-0.43, 0.30)	0.23	(-0.12, 0.59)	0.01	(-0.38, 0.39)	-0.11	(-0.48, 0.26)	-0.44	(-0.87, 0.00)
EPDS antenatal ≥ 13	-5.45	(-10.44, -0.46)*	0.09	(-4.66, 4.84)	2.21	(-2.41, 6.83) ^f	-0.04	(-5.03, 4.94)	-1.53	(-6.38, 3.32)	-4.92	(-10.61, -0.78)
EPDS postnatal	-0.44	(-0.83, -0.05) ^{g,*}	-0.11	(-0.49, 0.28)	0.09	(-0.29, 0.46)	-0.15	(-0.53, 0.24)	0.11	(-0.27, 0.49)	-0.39	(-0.84, 0.05)
EPDS postnatal ≥ 13	-5.80	(-11.65, -0.05) ^{g,*}	-1.07	(-6.70, 4.57) ^h	2.67	(-2.80, 8.15) ^b	-1.76	(-7.57, 4.05) ^g	4.15	(-1.49, 9.80) ^g	-2.96	(-9.64, 3.72)

* $p < 0.05$ ^a β -coefficients and 95 % CI of β retained from linear regression. All models adjusted for child sex, quality of assessment and gestational age^b β -coefficients and 95 % CI of β retained from linear regression. All models adjusted for maternal age, maternal education, gestational age, quality of assessment, child sex and breastfeeding duration^c Also adjusted for maternal origin^d Also adjusted for delivery type and mother's employment status at 18th months^e Also adjusted for parity^f Also adjusted for delivery type^g Also adjusted for mother's employment status at the 18th month^h Also adjusted for mother's employment status at the 18th month and mother's child care until 18th month

antenatal/postnatal EPDS ($p = 0.420$, $p < 0.001$) we repeated this analysis after exclusion of 27 women with postnatal EPDS ≥ 13 in order to rule out a possible confounding effect of postnatal depression on infant neurodevelopment. This sensitivity analysis revealed that the relationship between antenatal depressive symptoms and reduction in cognitive development was remarkably robust (β coefficient -5.94 , 95 % CI: -11.83 , -0.05).

A per 5 unit increase in the STAI-Trait score was associated with 1.4 units decrease (β coefficient -1.43 , 95 % CI: -2.63 , -0.23), while a per unit increase in the EPQ extraversion scale was associated with 0.5 increase (β coefficient 0.54 , 95 % CI: 0.08 , 1.00) in the scale of social-emotional development at 18 months of age. We also found that higher scores of maternal trait anxiety (β coefficient 1.13 , 95 % CI: 0.15 , 2.11) and neuroticism (β coefficient 0.38 , 95 % CI: 0.03 , 0.72) were estimated to have a positive effect on infants' expressive communication scores. A per 5 unit increase in the STAI-Trait scale and a per unit increase in the EPQ extraversion were related to 1.1 and 0.4 units increase, respectively, in the scale of expressive communication.

Maternal postpartum depression and infant neurodevelopment at 18 months

High levels of postpartum depressive symptoms (postnatal EPDS score ≥ 13) were associated with 5.8 units decrease in the scale of cognitive development (β coefficient -5.80 ,

95 % CI: -11.65 , -0.05) (Table 2). The latter relationship proved remarkably robust when sensitivity analysis was conducted after exclusion of 36 women with antenatal EPDS ≥ 13 to explore the possible impact of antenatal depression (β coefficient -7.51 , 95 % CI: -15.46 , 0.44). These results were confirmed in the larger sample of 470 women with postnatal EPDS. Table 3 presents the unadjusted and adjusted associations between maternal postnatal mental health and infant neurodevelopment at 18 months of age. In the multivariable analysis, a per unit increase in maternal postpartum depressive symptoms was found to be associated with lower cognitive (β coefficient -0.33 , 95 % CI: -0.58 , -0.08) and fine motor scores (β coefficient -0.29 , 95 % CI: -0.55 , -0.03) in infants. High levels of maternal postpartum depression (defined with a cutoff EPDS score ≥ 13) were associated with 5.6 units decrease in the scale of cognitive development (β coefficient -5.64 , 95 % CI: -9.56 , -1.72) and 5 units decrease in the scale of fine motor development (β coefficient -4.90 , 95 % CI: -8.92 , -0.88) at 18 months of age.

Discussion

We found that high levels of maternal antenatal depressive symptoms, independent of postpartum depressive ones and after controlling for adverse birth outcomes and other established confounders were associated with adverse

Table 3 Association of postnatal maternal mental health and infants' neurodevelopmental outcomes at age 18 months (RHEA Study, Crete, Greece, 2007–2012)

	Cognitive ^a		Receptive communication ^a		Expressive communication ^a		Fine motor ^a		Gross motor ^a		Social-emotional ^a	
	β -coeff	95 % CI	β	95 % CI	β	95 % CI	β	95 % CI	β	95 % CI	β	95 % CI
Crude models ^b ($n = 470$)												
EPDS postnatal	-0.39	(-0.65, -0.13) *	0.22	(-0.47, 0.04)	-0.06	(-0.33, 0.21)	-0.36	(-0.63, -0.10) *	0.07	(-0.19, 0.34)	-0.31	(-0.59, -0.03)
EPDS postnatal ≥ 13	-6.25	(-10.25, -2.24) *	-2.82	(-6.70, 1.07)	-0.76	(-4.94, 3.42)	-5.35	(-9.40, -1.30) *	0.22	(-3.88, 4.33)	-2.10	(-6.44, 2.23)
Adjusted models ^c ($n = 470$)												
EPDS postnatal	-0.33	(-0.58, -0.08) * ^d	-0.16	(-0.40, 0.08)	-0.04	(-0.30, 0.22)	-0.29	(-0.55, -0.03) * ^d	0.10	(-0.17, 0.37)	-0.28	(-0.57, 0.00) *
EPDS postnatal ≥ 13	-5.64	(-9.56, -1.72) * ^d	-2.37	(-6.12, 1.38) ^e	-0.71	(-4.73, 3.31) ^e	-4.90	(-8.92, -0.88) * ^d	0.71	(-3.45, 4.87) ^d	-1.84	(-6.22, 2.54)

* $p < 0.05$

^a Based on standardised values

^b β -coefficients and 95 % CI of β retained from linear regression. All models adjusted for child sex, quality of assessment and gestational age

^c β -coefficients and 95 % CI of β retained from linear regression. All models adjusted for maternal age, maternal education, gestational age, quality of assessment, child sex, and breastfeeding duration

^d Also adjusted for mother's employment status at 18th months

^e Also adjusted for mother's employment status at 18th months and mother's child care until 18th months

cognitive development and high levels of maternal antenatal anxiety with poor social–emotional development at 18 months of age. We also found an unexpected positive association between higher levels of maternal trait anxiety and neuroticism with advanced infants' expressive communication, while extraversion was positively related to infants' social–emotional development. Finally, for the first time in a Greek population, previous findings on the detrimental effects of maternal depressive symptomatology at 8 weeks postpartum, on infants' cognitive and fine motor development were supported, even though some studies have not found this association.

Compared to postpartum depression, fewer studies have addressed the potential impact of maternal antenatal depression and personality traits on infant's neurodevelopment. Our main set of findings that antenatal depression impacts on infant's cognitive development as early as age 18 months is in line with two previous studies [14, 17]. We also replicated previous findings [9, 12, 32] on the impact of postpartum depression on infants' cognitive and fine motor development. Caution is required, however, in the interpretation of this finding, since maternal depression was assessed only at 8 weeks postpartum. Hence, information on maternal mood throughout the 18-month period and at the time of infants' assessment, which might have affected neurodevelopmental outcomes, is missing. Importantly, we showed that the effects of antenatal and postpartum depression are not necessarily attributed to each other, although this requires replication in a larger sample with complete antenatal/postnatal dataset. This finding is consistent with the literature which suggests that antenatal and postpartum depression may not necessarily affect offspring's neurodevelopment in identical ways. The effect of antenatal depression is probably mediated by maternal stress hormones such as cortisol [33], which may disturb fetal brain development, dysregulating the HPA-axis [34], limbic and prefrontal connectivity, thus increasing the risk of high stress reactivity and emotional/behavioral problems in childhood and adolescence [16, 35]. Moreover, mothers who are stressed or depressed during pregnancy may be more likely to practice unhealthy behaviors, such as alcohol consumption [36] and smoking [37] which might affect child development. In contrast, postpartum depression is not thought to be associated with elevated mid-pregnancy cortisol levels [33]. Postpartum depression has been associated with negative effects on infant care practices and maternal involvement with the baby [38], as well as negative maternal attitudes which may interfere with secure attachment, maternal coping and caregiving [39] thus indirectly increasing the risk for delayed cognitive development and child behavior problems [8, 40].

Personality determines the appraisal of external stressors and the nature, availability and efficiency of coping

mechanisms, as well as utilization of personal and social support systems. We found, according to prediction, that adverse and beneficial personality profile may have adverse or beneficial effects on neurodevelopmental outcomes, respectively. Indeed, high levels of trait anxiety, a stable and enduring tendency for anxious worrying [20], were associated with adverse effects on offspring's social–emotional development. This is in line with previous associations between high maternal anxiety and children's temperamental difficulties at 4 and 6 months of age [41], 27 months [42] or behavioral/emotional problems at age 4 years [5]. In contrast, extraversion which refers to positive emotionality, energy, sociability and assertiveness, predicted a higher level of offspring's social–emotional development. Mothers high on extraversion may be expected to be more sensitive to their children's cues because people high on extraversion tend to be affectionate, optimistic, talkative, energetic, and enjoy social interactions including interactions with children. Indeed, extraversion is associated with responsive care and expressiveness which has been associated with children's social–emotional development [43]. However, it must be emphasized here that the social–emotional domain is the only domain of Bayley Scales which is scored by the mother; therefore, caution is required in the interpretation of these findings, as they may reflect anxious versus optimistic mother's attitudes and appraisals of their children's social/emotional behavior rather than genuine effects of personality on offspring's neurodevelopmental outcome.

Maternal neuroticism is a stable and enduring tendency to experience distress frequently [44, 45] which predisposes mothers to internalizing psychiatric conditions i.e. anxiety and depression [46]. Our group has recently shown that maternal neuroticism is associated with adverse birth outcomes [47]. It is therefore surprising and contrary to our prediction that higher levels of maternal trait anxiety and neuroticism were associated with higher expressive communication of the infant, which is a beneficial neurodevelopmental outcome. However, this finding is in line with a previous report for a positive association between higher (but non-clinical) levels of antenatal anxiety, stress and depression and advanced motor and mental development at age 2 years [17]. It may be that high maternal anxiety and neuroticism may act as motivating factors for maternal care giving rise to infants higher expressive communication. If this finding is replicated, certainly more research is required with specifically designed studies to explore this relationship.

Maternal personality was assessed only in late pregnancy and a possible moderating effect of pregnancy per se on the self-rating of personality traits cannot be entirely ruled out; however, empirical evidence suggests that personality traits are reasonably stable in adulthood [48]. Enduring personality characteristics of mothers may

account for the putative causal—and compromising— influence of antenatal stress on children’s development. It is not difficult to imagine, in fact, that personality traits specifically related to stress reactivity and sensitivity, such as trait anxiety and neuroticism, may influence a pregnant woman’s reporting and/or experiencing of antenatal stress. If this is so, it would compromise any causal interpretation of associations linking antenatal stress with postnatal child well-being [49].

The strengths of the present study include the population-based, prospective follow-up design and the multi-scale measures of infant neurodevelopment at 18 months of age. The Bayley Scales of Infant and Toddler Development (third edition) are recognised internationally as one of the most comprehensive tools to provide a valid and reliable measure of a child’s abilities from as young as 1-month-old. In the last revised version of Bayley Scales cognitive and language development are assessed separately as compared to the previous versions (e.g. BSID-II) which provided a total Mental Developmental Index (MDI) for the intellectual development of the child. Furthermore, the exclusion of women who gave birth to twins as well as adjustment for several socio-demographic variables reduced the likelihood of confounding. The study population included women followed up since early pregnancy, providing the opportunity to account prospectively for the effect of exposures during pregnancy. We did not observe any substantial differences between the crude and the adjusted models. Thus, it is unlikely that over-adjustment affected our findings. Participants were unaware of the hypothesis being tested, so, misclassification of mental health scores estimated by the questionnaires is likely to be random with respect to neurodevelopmental outcomes. Breastfeeding rates in Greece are relatively low as compared to other European countries, although breastfeeding duration in our study among those breastfed was found to be relatively long ($M = 4.38$, $SD = 4.42$). The beneficial effects of breastfeeding on child neurodevelopment have been shown in other populations [50] and for this reason we have adjusted all postnatal analyses for breastfeeding duration.

There are several limitations in the present study that deserve acknowledgement. We assessed antenatal and postpartum depressive symptoms with the self-administered EPDS scale and trait anxiety with the self-administered STAI-Trait scale, rather than definite cases of depression and anxiety based on clinician-administered structured diagnostic interview. However, this an epidemiological study assessing risk for antenatal/postpartum depression and trait anxiety, and EPDS and STAI-Trait scores are established and widely used screening tools with high specificity and sensitivity [51]. Another possible limitation was the low participation rate (47.4 %) in the

analysis of antenatal maternal mental health. This, however, could have affected the prevalence of anxiety and depression symptoms in our population but not the direction of the association between antenatal maternal mental health and infants’ neurodevelopment found in our study. Taking into account that attrition is inevitable in longitudinal studies, we compared women with antenatal psychological assessment (participants) with those with no data in psychological measures (non-participants) in the present study to determine if there were significant socio-demographic differences between the two groups. Although non-significant differences were found, we cannot exclude bias due to this non-participation rate within this population-based study, thus this possibility should be taken into account when considering study findings. Finally, although we incorporated extensive information on potential social and environmental factors that are associated with children’s neurodevelopment, there may be other unidentified factors linked both with infant neurodevelopment and maternal mental health that could explain this association.

In summary, in this first report from a Greek population (Rhea mother–child cohort), we found that antenatal and postpartum depression are independently of each other associated with delays in offspring neurodevelopment as early as 18 months of age after adjusting for a large number of confounders. We also detected adverse effects of trait anxiety on the one hand and beneficial effects of maternal extraversion on the other hand, on children’s social–emotional development at age 18 months, which could reflect maternal attitudes and appraisal of children’s behavior rather than primary effects on neurodevelopment. Finally, we found a positive association between higher levels of maternal antenatal trait anxiety and neuroticism with advanced infants’ expressive communication, an interesting finding that requires replication and further study.

Our findings add to the growing body of research, suggesting that antenatal and postnatal maternal psychological well-being has important consequences for early child neurodevelopment. It may be that the presence of maternal anxiety or depression is actually a marker for some genetic influence, and if so, then mere psychological therapy or medication for maternal depression during pregnancy or postpartum might have little if any effects on infant outcomes. On the other hand, the opposite may also be true at least in a subset of maternal anxious/depressed phenotypes. Consequently, more research is required on early screening and therapy of ante- and postnatal maternal anxiety and depression in specialist settings in collaboration with perinatal psychiatry using longitudinal designs. This may be of major importance for prevention of deficient infant’s neurodevelopment and may prove greatly beneficial for public health.

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Conflict of interest The authors have no conflicts of interest to declare.

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