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Mother's anxiety and depression and associated risk factors during early pregnancy: effects on fetal growth and activity at 20–22 weeks of gestation

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Abstract

To examine effects of mother's anxiety and depression and associated risk factors during early pregnancy on fetal growth and activity. Repeated measures of mother's anxiety (State-Anxiety Inventory (STAI-S)) and depression (Edinburgh Postnatal Depression Scale (EPDS)) and related socio demographics and substance consumption were obtained at the 1st and 2nd pregnancy trimesters, and fetus' ($N = 147$) biometric data and behavior was recorded during ultrasound examination at 20–22 weeks of gestation. Higher anxiety symptoms were associated to both lower fetal growth and higher fetal activity. While lower education, primiparity, adolescent motherhood, and tobacco consumption predicted lower fetal growth, coffee intake predicted lower fetal activity. Vulnerability of fetal development to mother's psychological symptoms as well as to other socio-demographic and substance consumption risk factors during early and mid pregnancy is suggested.

Keywords: *Anxiety, depression, pregnancy, fetal growth, fetal activity*

Introduction

The study of human development usually considers childbirth as the starting point. However, several research studies have suggested that psychological development begins during the gestational period, and prenatal influences can explain a significant part of the child's behavioral and developmental variability.

Fetal growth and fetal activity have been widely analyzed to describe normal development across pregnancy and to identify potential risk factors. Fetal movements have been found to reflect the integrity and activity of the central nervous system (CNS), as the more frequent movement patterns follow a clear developmental course [1] and abnormal movement patterns have been observed in fetuses with motor disorders related to CNS development, such as cerebral palsy [2]. With increasing gestational age, fetal movements, eye movements and heart rate patterns get organized into specific behavioral states that resemble those Prechtl described in the neonate [3].

Results of longitudinal studies involving the assessment of fetal behavior in early pregnancy using 2D sonographic scanning revealed that different movements have diverse incidences and assume distinctive patterns [4,5], as well as a decrease in overall fetal activity from the 20 weeks of gestation until delivery [6]. These findings are in line with new data provided by the recent studies involving 4D sonographic scanning [7,8].

Due to the higher sensitivity of fetal brain early in gestation, fetuses are especially vulnerable to small changes in the intra-uterine physiological environment, induced by internal and/or external factors. Both animal and human studies have shown that prenatal influences can have long lasting effects on development and health. Maternal nutrition, for instance, is associated with coronary heart disease

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and non-insulin dependent diabetes in adulthood, whereas maternal depression and anxiety are associated with problems in infant biobehavioral development [9,10]. Hormones of the hypothalamic–pituitary–adrenal (HPA) axis and sex hormones have been found to have programming effects and were pointed out as possible explanations to such long-term effects [11]. A number of risk factors have been identified which may account for abnormal growth and activity including maternal socio-demographic, substance consumption and psychological symptoms. Considering socio-demographic risk factors, social class was clearly related to several measures of early child morbidity and mortality [12], and high-intensity occupational activity and high demanding physical tasks at work have been associated with adverse pregnancy outcomes, such as preterm delivery [13]. Reported developmental effects of race and sex [14], parity [15–18], maternal age [19,20], nutritional status [21–23], and maternal anthropometrics [24–26] include the increased incidence of fetal and neonatal mortality, intrauterine growth retardation, low birth weight, premature delivery and several neonatal morbidities, although the direction of these effects, as well as the mutual interplay of the risk factors awaits further elucidation.

Studies examining the association between maternal substance consumption and early infant development have mostly suggested the potential short and long term teratogenic and neurodevelopmental consequences of nicotine [27,28], caffeine [29–31], and alcohol use during pregnancy [32], mostly when in the presence of high doses and chronic exposure. Reported development effects include a significant fetal growth reduction [33–37], low birth weight and preterm delivery [26,38,39], more time spent in a low fetal heart rate variation pattern and decrement of fetal activity both in high and low fetal heart rate variation periods [40], delayed onset of response to the maternal voice in fetuses less than 37 weeks gestational age [41] and fetal death [42]. Some animal and human studies also revealed a combined effect of the use of several substances by the same women, which increases the risk of obstetric and fetal/neonatal complications [43,44].

There is conflicting data regarding the effect of maternal psychological distress on fetal growth and activity. Recent empirical evidence suggests that the nature of adverse life events [45], as well as the moment of exposure [46,47] are important determinants of these disparities. Some researchers who found an impact of psychological distress on fetal growth observed a growth delay in fetuses of mothers who presented prenatal anxiety [48] and/or depression [49]; others studies only found a growth reduction after exposure to severe life events in premature born before 32 weeks of gestation [50]. The same effect is found for fetal activity, with fetuses of anxious [51,52] and/or depressed [53] mothers being more active than fetuses of non-anxious and/or non-depressed mothers. Moreover, fetuses of anxious mothers spend more time in passive sleep and show more indiscriminate movements when they are in active sleep [54,55].

Several others did not find this effect, neither for fetal growth [56–58] nor for fetal behavior [59]. DiPietro et al. [60] suggest that mild to moderate levels of psychological distress may enhance fetal maturation in healthy populations, as higher levels of prenatal anxiety, non-specific stress, and depressive symptoms can be associated to greater motor and mental development in children at age two.

Despite a number of prenatal influences having been identified for infant development, the mutual interplay of the range of such risk factors is complex and not yet fully understood. Thus, the purpose of this study was to explore the effects of mothers' anxiety and depression and associated risk factors during early pregnancy on fetal growth and activity at 20–22 weeks of gestation, namely by (1) examining group differences concerning mothers' anxiety (State-Trait Anxiety Inventory-State (STAI-S) < 45 *versus* STAI-S ≥ 45) and depression (Edinburgh Postnatal Depression Scale, EPDS < 10 *versus* EPDS ≥ 10) at the 1st and 2nd trimesters across fetal growth and movement patterns; and (2) analyzing possible effects of mothers' anxiety and depression at the 1st and 2nd trimesters on fetal growth and activity at 20–22 weeks of gestation. The effect of mothers' socio demographics and substance consumption and fetus' gender were also analyzed.

Methods

After approval from the Ethical Committee, participants were recruited at the antenatal Obstetric Unit (Júlio Dinis Maternity Hospital, Porto, Portugal). Medical records were consulted and all identified women up to 14 weeks of gestation were contacted, except those with multiple gestations and with medical and/or obstetric complications. After informed consent, which included permission for recording fetal behavior, mother's socio-demographics were collected. Repeated measures of anxiety (STAI-S) and depression (EPDS) were obtained at the 1st and 2nd pregnancy trimesters. At the 2nd pregnancy trimester, fetus's biometrical data were collected from clinical reports and in a subsample of 47 fetuses with gestational ages (menstrual age) greater than or equal to 20 weeks and lower to 23 weeks, a video tape of the fetal behavior was made by the research team's obstetrician, during ultrasound examination.

Information about demographic factors, such as age, ethnicity, nationality, employment and occupation, marital status, household arrangements,

educational attainment, medical and obstetrical history, psychological status, and substance consumption (tobacco consumption measured by number of cigarettes per day and coffee consumption measured by number of espressos per day), was obtained through a standardized interview.

The Spielberger [61] STAI was used to measure anxiety symptoms. The STAI is a self-report questionnaire consisting of two subscales, the *state anxiety* subscale and the *trait anxiety* subscale, each containing 20 items. Only the state anxiety subscale (STAI-S), which measures anxiety at the moment of scoring, was used in the analyses. The scores in this subscale range from 20 to 80 and higher scores indicate higher state anxiety (conceptualized as a transient emotional condition of the individual, characterized by subjectively experienced feelings of tension, together with a heightened activity of the autonomous nervous system). This scale has been used in several studies implemented during pregnancy and the postpartum period [62,63]. The Portuguese version of the STAI showed good internal consistency (State and Trait Cronbach's α in women = 0.88 and 0.87, respectively) and construct validity demonstrated by substantial differences in scores obtained under stressful and neutral conditions [64]. Authors suggest a cutoff of 45 for high anxiety.

The Portuguese version of the EPDS [65,66], a self-report questionnaire composed by 10 items in a likert scale of four points (0–3), was used to assess depressive symptoms. Psychometric studies of the EPDS Portuguese version showed good internal consistency (Cronbach $\alpha = 0.85$), test–retest reliability (Spearman Correlation = 0.75), and external validity with the Schedule for Affective Disorders and Schizophrenia (SADS psychiatric interview) ($r = 0.86$) [67]. A score higher than 10 indicates the probable presence of a major depressive episode with a sensitivity of 29% and specificity of 96% [68]. This questionnaire has been used in several studies with pregnant and postpartum women [63,69], some of which in Portugal [66–68,70].

Fetal growth and activity were assessed during the morphological ultrasound of the 2nd trimester of pregnancy. Fetal growth measures included biparietal distance (BPD), head circumference (HC), abdominal circumference (AC), and femur length (FL). These measures were obtained by the obstetrician of the research team, using standard clinical measurement protocols [71–73].

The spontaneous motor activity of fetuses, which reflects the activity of the CNS [1], was video recorded during the 2nd trimester of pregnancy real-time ultrasound (General Electric, model Voluson c730 expert) following the same procedures and fetal activity categories used in previous research [53,74–76]. Since the nature and pattern of fetal movements can be determined by gestational age, mother's feeding and circadian rhythm [77], conditions for fetal movements' assessment were standardized. All fetuses had gestational ages between 20 and 22 weeks. All video recordings were performed in the afternoon, between 2:30 p.m. and 4:00 p.m., with the mother in a semi supine position. Women shouldn't have had food intake, coffee, tea, smoking, or alcohol consumption for 1 h and 30 min before the recording. For the fetal movements assignment, the obstetrician positioned the ultrasound transducer to obtain a lateral view of the fetus, including visualization of the head, trunk, and limbs. Taking into account the high percentage of time in which some of the fetuses were not accurately viewable, leading to the repositioning of the transducer (which induced non spontaneous fetal behavior), a maximum period of three consecutive minutes of good viewing of the fetus, achieved in all participants, was selected for fetal behavior scoring. The 3-min period of video recording was subdivided into 3-s ''windows'', in which observers should signal the occurrence of the following fetal activity categories including: (a) Single limb movement (isolated arm, leg or head movement, without movements in other body parts); (b) Multiple limb movement (movement which implies changes in position of the limb segments towards each other, with limb joints being active and moving simultaneously); and (c) Gross body movement (movement involving the whole body and/or limbs of the fetus lasting a variable period of time). *No movement* classification should be coded when no fetal movements occurred for a period of 3 s. Two consecutive bursts of fetal movements were considered as independent when a complete absence of movements was observed between them. For the data analyses, the percentage of time (% time) the fetus engaged in total movement, as well as in each movement category, was calculated.

Records of five fetuses were used in the training of three observers. Final coding of these records was reached after the achievement agreement between the three observers. The remaining records were rated by two observers, with the achievement of excellent inter-observers reliability (Kappa of Cohen greater than or equal to 0.75) in 20 fetal assessments and good agreement (Kappa of Cohen between 0.40 and 0.75) in 22 fetal assessments. In this case, a third observer was used in order to obtain the final quotation.

Multivariate analyses of variance (MANOVA) were used to examine mothers' 1st and 2nd trimester's anxiety (STAI-S < 45 *versus* STAI-S ≥ 45) and depression (EPDS < 10 *versus* EPDS ≥ 10) group differences across the fetal growth measures (BPD, HC, AC, and FL; dependent variables) and fetal activity categories (no movements, single limb movement, multiple limb movement

and gross body movement; dependent variables) at the 2nd pregnancy trimester. Multiple regression analyses were applied to examine the role of mothers' 1st and 2nd trimester's anxiety (STAI-S total scores) and depression (EPDS total scores) in the prediction of fetal growth measures and activity categories, respectively, at the 2nd trimester of pregnancy. Data were analyzed using the Statistical Package for the Social Sciences (SPSS), version 15.0.

Results

The sample involved 147 fetuses (49% females and 51% males) with gestational ages of 20 (44.9%), 21 (34.7%), and 22 (20.4%) weeks (M = 21.05; SD = 0.77). The mean of each biometric parameter (BPD, HC, AC, and FL) was within the normative range of values expected for the same menstrual age. Information on fetal outcome is available for 130 fetuses (88.4%). Most of these infants were born after a normal (86.2%) full-term gestation (96.9%; M = 38.91, SD = 1.27, Min = 35.00, Max = 42.00), not needing reanimation procedures (94.6%). More than half of the deliveries were dystocic (51.5%; 40.8% with cesarean section and 10.7% deliveries by forceps/ventouse), and used anesthetic procedures (90.0%). At time of birth, newborns' HC s ranged between 24.0 and 45.5 cm (M = 34.66, SD = 2.66), most of them (93.1%) had birth weight equal or higher than 2500 g (M = 3191.72, SD = 462.04, Min = 1830.00, Max = 4415.00), birth length equal or higher than 47 cm (83.8%; M = 48.70, SD = 2.21, Min = 42.00, Max = 55.50), Ponderal index equal or higher than 2.50 (82.3%; M = 2.75, SD = 0.26, Min = 2.15, Max = 3.79), and Apgar Index equal or higher to 7 at the 1st (92.9%) and 5th (99.2%) minute.

Mothers were primíparous (53.7%) and multíparous (46.3%), Portuguese (88.4%), and Caucasian (93.2%). Most mothers (89.1%) were older than 19 (M = 27.04, SD = 5.90; Min = 15; Max = 41), had completed high school (9–12 years of study) and were employed. A large percentage of women lived with their partners (86.4%), and the household included other elements from the extended family in 23.8% of cases. From the 147 mothers-to-be, 19 (12.9%) reported tobacco use (14 women with $\geq 3 \cap < 10$ cigarettes/day and 5 women = 10 cigarettes/day; M = 2.42, SD = 6.79; Min = 3; Max = 10 cigarettes per day) and 39 (26.5%) espresso coffee intake (37 women with 1 or 2 espressos/day and 2 women with 3 or 4 espressos/day (Min = 1 ($\pm$75 mg) – Max = 4 ($\pm$300 mg) cups of coffee per day), but none reported alcohol or drug consumption during pregnancy (cf. Table I).

Table I. Mother's socio-demographics ($N = 147$).

		%
Education (years of school)	<9	29.9
	≥9 and ≤12	50.4
	Graduate	19.7
Occupational status	Employed	69.4
	Unemployed	21.8
	Household	2.0
	Student	6.8
Marital status	Married	59.2
	Co-habitation	27.2
	Single/Divorced	13.6
Household arrangement	Living with partner (and children)	74.1
	Living with partner and extended family	12.2
	Living with extended family without partner	11.6
	Living without extended family and without partner	2.1

Multivariate analyses of variance (MANOVA) were used to examine mothers' 1st and 2nd trimester's anxiety (STAI-S < 45 *versus* STAI-S ≥ 45) and depression (EPDS < 10 *versus* EPDS ≥ 10) group differences across the fetal growth measures (BPD, HC, AC, and FL; dependent variables). No significant group differences were found across the independent variables of anxiety (STAI-S) at the 1st trimester (Wilks' $\lambda = 0.977$; $F(4, 142) = 0.834$; $p = 0.506$), depression (EPDS) at the 1st trimester (Wilks' $\lambda = 0.981$; $F(4, 142) = 0.693$; $p = 0.598$), anxiety (STAI-S) at the 2nd trimester (Wilks' $\lambda = 0.984$; $F(4, 142) = 0.594$; $p = 0.668$) and depression (EPDS) at the 2nd trimester (Wilks' $\lambda = 0.980$; $F(4, 142) = 0.716$; $p = 0.582$).

Different forced entry multiple regression analyses were performed to identify mother and fetus socio-demographics and substance consumption potential predictors ($p < 0.150$) of each fetal growth measure (BPD, HC, AC, and FL) at the 2nd pregnancy trimester.

Parity appeared as a potential socio-demographic predictor of BPD ($\beta = 0.171$; $p = 0.054$), HC ($\beta = 0.228$; $p = 0.009$), AC ($\beta = 0.150$; $p = 0.083$) and FL ($\beta = 0.210$; $p = 0.017$). Education and maternal age appeared as potential socio-demographic predictors of HC ($\beta = 0.134$; $p = 0.117$) and AC ($\beta = 0.231$; $p = 0.027$), respectively. Mother's smoking during pregnancy emerged as a potential substance consumption predictor of BPD ($\beta = 0.194$; $p = 0.021$).

In a final hierarchical regression analysis (blockwise entry), each fetal growth measure (dependent variable) was regressed on mothers' anxiety (STAI-S total scores) and depression (EPDS total scores) at the 1st and 2nd trimesters (Block 1), followed by previously identified socio-demographic and substance consumption potential predictors (Block 2).

As shown in Table II, mothers' anxiety (STAI-S total scores) and depression (EPDS total scores) at the 1st and 2nd trimesters (Block 1) did not significantly predict or explain the variance of fetal growth measures, with the exception of FL (BPD, $F(4, 141) = 0.947$, $p = 0.439$; HC, $F(4, 141) = 1.046$, $p = 0.386$; AC, $F(4, 142) = 1.154$, $p = 0.334$).

When tobacco consumption and parity variables were added to the final regression model of BPD (Block 2), 8.6% of the variance in this dependent variable was explained, $\Delta R^2 = 0.060$, $\Delta F(2, 139) = 4.564$, $p = 0.012$, with tobacco consumption emerging as a significant predictor and STAI-S and EPDS at both trimesters and parity not contributing significantly. Mother's smoking during pregnancy significantly predicted higher fetus' BPD (cf. Table II).

When education and parity were added to the final regression model of HC (Block 2), 12% of the variance in this dependent variable was explained, $\Delta R^2 = 0.091$, $\Delta F(2, 139) = 7.217$, $p = 0.001$, with STAI-S at the 2nd trimester, education and parity significantly predicting HC, while STAI-S at the 1st trimester and EPDS at both trimesters did not

Table II. Predictors of fetal growth at 20–22 weeks: multiple hierarchical regression (final model), Blockwise entry ($N = 147$).

Dependent variables	Independent variables	R^2	ΔR^2	F	β	t
BPD	Step 1					
	STAI-S 2nd trim				−0.249	−1.893
	EPDS 2nd trim				0.111	0.856
	STAI-S 1st trim				0.149	1.094
	EPDS 1st trim	0.026	–	0.947	−0.002	−0.018
	Step 2					
	STAI-S 2nd trim				−0.247	−1.921
	EPDS 2nd trim				0.060	0.474
	STAI-S 1st trim				0.156	1.173
	EPDS 1st trim				0.003	0.019
	Tobacco use				0.168	2.048*
	Parity	0.086	0.060	2.184*	0.163	1.952
HC	Step 1					
	STAI-S 2nd trim				−0.255	−1.939
	EPDS 2nd trim	0.029	–	1.046	0.058	0.449
	STAI-S 1st trim				0.159	1.170
	EPDS 1st trim				0.032	0.238
	Step 2					
	STAI-S 2nd trim				−0.306	−2.410*
	EPDS 2nd trim				0.017	0.139
	STAI-S 1st trim				0.168	1.288
	EPDS 1st trim				0.067	0.506
	Education				0.212	2.557*
	Parity	0.120	0.091	3.165**	0.276	3.312**
AC	Step 1					
	STAI-S 2nd trim				−0.172	−1.313
	EPDS 2nd trim				−0.005	−0.037
	STAI-S 1st trim				0.166	1.221
	EPDS 1st trim	0.031	–	1.154	0.106	0.789
	Step 2					
	STAI-S 2nd trim				−0.202	−1.585
	EPDS 2nd trim				−0.012	−0.097
	STAI-S 1st trim				0.146	1.107
	EPDS 1st trim				0.126	0.962
	Maternal age				0.222	2.685**
	Parity	0.101	0.070	2.621*	0.111	1.331
FL	Step 1					
	STAI-S 2nd trim				−0.324	−2.501*
	EPDS 2nd trim				0.192	1.509
	STAI-S 1st trim				0.217	1.616
	EPDS 1st trim	0.048	–	1.777	−0.045	−0.334
	Step 2					
	STAI-S 2nd trim				−0.336	−2.633**
	EPDS 2nd trim				0.155	1.235
	STAI-S 1st trim				0.230	1.736
	EPDS 1st trim				−0.050	−0.381
	Parity	0.085	0.038	2.632*	0.199	2.411*

**$p < 0.01$; *$p < 0.05$.

contribute significantly. High mother's anxiety at the 2nd trimester, lower education and primiparity significantly predicted lower fetus' HC (cf. Table II).

When maternal age and parity were added to the final regression model of AC (Block 2), 10.1% of the variance in this dependent variable was explained, $\Delta R^2 = 0.070$, $\Delta F(2, 140) = 5.412$, $p = 0.005$, with maternal age emerging as a significant predictor of AC, while STAI-S and EPDS at both trimesters and parity did not contribute significantly: lower maternal age (adolescent motherhood) significantly predicted lower fetus's AC (cf. Table II).

In the final hierarchical regression analysis (block-wise entry) of FL, the model with mother's anxiety (STAI-S total scores) and depression (EPDS total scores) at the 1st and 2nd trimesters (Block 1) was not significant, although STAI-S at the 2nd pregnancy trimester emerged as a significant predictor, $F(4, 142) = 1.77$, $p = 0.137$. When parity was added to the model, 8.5% of the variance in FL was explained, $\Delta R^2 = 0.038$; $\Delta F(1, 141) = 5.812$, $p = 0.017$, with STAI-S at the 2nd trimester and parity as significant predictors, while STAI-S at the 1st trimester and EPDS at either trimester did not contribute significantly. High mother's anxiety at the 2nd trimester and primiparity significantly predicted lower fetus's FL (cf. Table II).

As can be seen in Table III in this sample the presence and absence of fetal movements occupied, on average, the same percentages of the time, and during the active periods, Gross body movement was the most prevalent category of fetal activity.

Multivariate analyses of variance (MANOVA) were used to examine mother's 1st and 2nd trimester's anxiety (STAI-S < 45 *versus* STAI-S ≥ 45) and depression (EPDS < 10 *versus* EPDS ≥ 10) group differences across the fetal activity categories (No movement, Single limb movement, Multiple limb movement, and Gross body movement) No significant group differences were found across the independent variables of anxiety (STAI-S) (Wilks' $\lambda = 0.898$; $F(4, 42) = 1.187$; $p = 0.330$) and depression (EPDS) (Wilks' $\lambda = 0.974$; $F(4, 42) = 0.275$; $p = 0.892$) at the 1st trimester.

MANOVA multivariate tests did not show significant group differences across any fetal activity categories taking into account the independent variable depression (EPDS) at the 2nd pregnancy trimester (Wilks' $\lambda = 0.844$; $F(4, 42) = 1.942$; $p = 0.121$), but MANOVA univariate tests showed that fetuses of depressed mothers spent significantly more time in Single limb movements at the 2nd pregnancy trimester than fetuses of non-depressed mothers at the time (cf. Table IV).

Significant group differences were found across the fetal activity categories taking into account the independent variable of anxiety (STAI-S) at the 2nd trimester of pregnancy (Wilks' $\lambda = 0.788$; $F(4, 42) = 2.831$; $p = 0.036$): fetuses of anxious mothers spent significantly more time in Single limb movements at the 2nd pregnancy trimester than fetuses of non-anxious mothers at the time (cf. Table IV).

As for fetal growth measures, different forced entry multiple regression analyses were performed to identify mothers' and fetus's socio-demographics and substance consumption potential predictors ($p < 0.150$) for each fetal activity category (no movements, single limb movement, multiple limb movement and gross body movement) at the 2nd pregnancy trimester.

Table III. Fetal activity at 20–22 weeks ($N = 47$).

	Min–Max	Mean (DP)	25th–75th Percentile
No movement (% time)	1.70–98.30	54.20 (25.17)	33.30–75.00
Single limb movement (% time)	0.00–30.00	8.96 (7.85)	3.30–15.00
Multiple limb movement (% time)	0.00–16.70	3.39 (4.38)	0.00–6.65
Gross body movement (% time)	1.70–96.70	33.45 (22.85)	13.30–45.00

Table IV. Mother's anxiety and depression (2nd trimester of pregnancy): MANOVA for fetal activity categories at 20–22 weeks ($N = 47$).

		No movement		Single limb movement		Multiple limb movement		Gross body movement	
	N	Mean (SD)	*F*(1,45)	Mean (SD)	*F*(1,45)	Mean (SD)	*F*(1,45)	Mean (SD)	*F*(1,45)
STAI-S									
<45	35	52.84 (25.92)	0.397	7.62 (6.34)	4.257*	2.86 (3.66)	2.053	36.68 (23.57)	2.847
≥45	12	58.18 (23.43)		12.85 (10.53)		4.94 (5.97)		24.03 (18.34)	
EPDS									
<10	35	54.98 (25.04)	0.130	7.43 (6.32)	5.730*	2.74 (3.60)	3.144	34.85 (23.70)	0.506
≥10	12	51.92 (26.52)		13.41 (10.25)		5.29 (5.94)		29.38 (20.55)	

*$p < 0.05$.

Mothers' coffee intake during pregnancy emerged as a potential substance consumption predictor of time spent by the fetus in Single limb movements ($\beta = -0.334$; $p = 0.024$) and Multiple limb movements ($\beta = -0.253$; $p = 0.095$). No socio-demographics and substance consumption potential predictors were found to the remaining fetal activity categories.

In a final hierarchical regression analysis (blockwise entry), each fetal activity category (dependent variable) was regressed on mother's anxiety (STAI-S total scores) and depression (EPDS total scores) at the 1st and 2nd trimester (Block 1), followed by previously identified socio-demographic and substances consumption potential predictors (Block 2).

As can be seen in Table V, mother's anxiety (STAI-S total scores) and depression (EPDS total scores) at the 1st and 2nd trimester (Block 1) didn't significantly predict or explain the variance observed in the time spent in any of the fetal activity categories, except for Multiple limb movement (No movement, $F(4, 42) = 0.855$, $p = 0.499$; Single movements, $F(4, 42) = 1.681$, $p = 0.172$; Gross body movements, $F(4, 42) = 1.556$, $p = 0.204$).

When coffee intake was added to the final regression model of single limb movement, 25.5% of the variance was explained, $\Delta R^2 = 0.117$, $\Delta F(1, 41) = 6.420$, $p = 0.015$, with coffee intake predicting significantly less time spent in Single limb movements while STAI-S and EPDS at both trimesters did not contribute significantly (cf. Table V).

Although STAI-S at the 1st trimester emerged as a significant predictor of multiple limb movement, the model with mother's anxiety (STAI-S total scores) and depression (EPDS total scores) at the 1st and 2nd trimesters (Block 1) was not significant, $F(4, 42) = 1.623$, $p = 0.186$. The addition of coffee intake to the model did not contribute significantly to predict multiple limb movement, $\Delta R^2 = 0.073$; $\Delta F(1, 41) = 3.766$, $p = 0.059$, even though STAI-S at the 1st trimester remained a significant predictor. Higher mother's anxiety at the 1st trimester significantly predicted more time spent in Multiple limb movements (cf. Table V).

Discussion

The focus of the present study was to examine the effects of mothers' anxiety and depression and

Table V. Predictors of fetal activity categories at 20–22 weeks: multiple hierarchical regression (final model), Blockwise entry ($N = 47$).

Dependent variables	Independent variables	R^2	ΔR^2	F	β	t
No movement	Step 1					
	STAI-S 2nd trim				0.214	0.729
	EPDS 2nd trim				−0.282	−1.064
	STAI-S 1st trim				0.172	0.659
	EPDS 1st trim	0.075	–	0.855	−0.193	−0.804
Single limb movement	Step 1					
	STAI-S 2nd trim				0.062	0.219
	EPDS 2nd trim				0.010	0.039
	STAI-S 1st trim				0.318	1.267
	EPDS 1st trim	0.138	–	1.681	−0.006	−0.026
	Step 2					
	STAI-S 2nd trim				0.007	0.024
	EPDS 2nd trim				0.015	0.062
	STAI-S 1st trim				0.341	1.442
	EPDS 1st trim				0.010	0.044
	Coffee intake	0.255	0.117	2.802*	−0.343	−2.534*
Multiple limb movement	Step 1					
	STAI-S 2nd trim				−0.459	−1.618
	EPDS 2nd trim				0.280	1.089
	STAI-S 1st trim				0.566	2.246*
	EPDS 1st trim	0.134	–	1.623	−0.166	−0.712
	Step 2					
	STAI-S 2nd trim				−0.503	−1.824
	EPDS 2nd trim				0.283	1.140
	STAI-S 1st trim				0.584	2.391*
	EPDS 1st trim				−0.153	−0.679
	Coffee intake	0.207	0.073	2.137	−0.271	−1.941
Gross body movement	Step 1					
	STAI-S 2nd trim				−0.168	−0.592
	EPDS 2nd trim	0.129	–	1.556	0.253	0.984
	STAI-S 1st trim				−0.407	−1.611
	EPDS 1st trim				0.247	1.057

*$p < 0.05$.

associated risk factors during early pregnancy on fetal growth and activity at 20–22 weeks. In line with previous epidemiological studies, present results also observed the vulnerability of fetal development to mother's psychological symptoms, as well as to other socio-demographic and substance consumption risk factors during early and mid pregnancy. In addition, current analyses made new contributions to the study of prenatal determinants of fetal development. First, present findings associate higher anxiety symptoms, more than depression symptoms, to both lower fetal growth and higher fetal activity, although more significant for fetal behavior. Second, a differential impact of each risk factor on fetal growth and activity was pointed out. While lower education, primiparity, adolescent motherhood, and tobacco consumption predicted lower fetal growth, coffee intake predicted lower fetal activity. Finally, the mutual interplay of the range of risk factors shows its relevance in the understanding of the course of early infant development.

A lack of support was found for the independent effect of mothers' anxiety and depression early in pregnancy on fetal growth measures at 20–22 weeks of gestation, except for femur length (affected by mothers' anxiety at the 2nd trimester of pregnancy). These findings are consistent with previous studies which also suggest subtle disruptions in normative development provoked by maternal psychological symptoms [56–58]. Even so, when the effects of mothers' socio-demographic and substance consumption risk factors was explored in association to psychological symptoms, maternal education, age, parity, tobacco consumption during pregnancy and anxiety symptoms at the 2nd trimester appeared as significant predictors of fetal growth, suggesting the relevance of the mutual interplay of the range of antenatal risk factors in determination of fetal development [78].

Reported developmental effects of lower education, such as preterm delivery, have already been referred by other studies focused on prenatal determinants of neonatal outcomes [78]. Although several mechanisms were proposed to explain the way socio-demographic factors, such as education, can operate, namely by the observed correlation of these factors with adverse life events [79], more clinical research is needed to further understand the causal pathways, specifically related to the impact on fetal growth.

Primiparity was associated in the present study to lower fetal growth. Similarly, primiparity has been previously identified as an independent risk factor for intrauterine growth retardation [17], small-for-gestational-age [18], or birth weight [17,80]. There is still an ongoing debate regarding the possible underlying mechanisms by which parity affects early human development [for a revision see 15,16].

The same debate exists when the developmental effects of maternal age are analyzed. Young maternal age (adolescent motherhood) was associated in the present study to lower fetal growth, as observed in previous researches for obstetric [19,20] and neonatal outcomes [21–23]. Maternal nutrition, associated not only to inadequate or marginal nutritional status during pregnancy, but also to the hierarchy of nutrient partitioning in order to promote simultaneously for fetal growth and the growth of the maternal body [21–23], poor socio-economic status and gynecological immaturity [81], and maternal somatic features and anthropometrics [24–26] are some of the factors pointed out as possible mediators of this effect [for a deeply knowledge of the debate around the mediation role of these different aspects see 25].

As mentioned previously, an effect of tobacco consumption on fetal growth was found in the present study. Fetuses of mothers who smoked during pregnancy had higher BPDs than those of non-smoking mothers. Despite the small number of women in this sample who reported tobacco consumption, this result it is consistent with previous findings of Lampl et al. [82], who observed that smoke exposure was significantly associated with early growth acceleration in head and abdominal diameters at 20–27 weeks, followed by altered head shape (a significantly smaller biparietal to occipital frontal diameter ratio at 32 weeks), and a proximal/distal growth gradient as proportionately long arms (at 27 and 32 weeks) and short legs were apparent by 32 weeks, with a significant reduction in the tibia/femur ratio. According to these researchers, the greater early gestational upper body growth with preferential growth of head dimensions, upper limb length, and abdominal size with smoke exposure may reflect an upregulation of normal cellular growth mechanisms, which can be a sign of an evolutionary adaptive response strategy. This strategy would function under conditions of energy restriction, such as those involved in fetal smoke exposure during gestation, to preserve fetal development. Through selective growth restriction and augmentation the fetus is capable of adjusting its own growth to match available resources. However, as Lampl et al. [82] alert, these adaptive strategies may not be entirely beneficial in the long term, as there may be side effects of the upregulated cellular functions, which can cause abnormal, compensatory growth of structures. Compensatory growth changes the normal biological design of developing organs and an altered cellular histology, which leaves the organism at risk for subsequent functional sequels. This hypothesis was also sustained by the results of Jaddoe et al. [27] who found, in a population-based prospective cohort study, associations between maternal smoking during pregnancy, mainly from late pregnancy onwards, and

impaired growth in fetal HC and AC. As the present study did not focus fetal development near the end of gestation, we cannot assess the validity of this hypothesis, although preliminary non-published results obtained with the same sample, associate lower birth weight in newborns of mothers who smoked during pregnancy. Further investigation in this domain, namely in the effect of prenatal anxiety and depression early in gestation in these growth patterns is, thus, recommended.

An association between mothers' anxiety and depression and higher fetal activity was observed in the present study, similarly to what previous researches aimed to analyze the effect of maternal psychological symptoms on fetal behavior have found. For instance, Dieter et al. [53] also showed that fetuses of depressed mothers were more active than those of non-depressed mothers at the 5th, 6th, and 7th months of pregnancy. DiPietro et al. [51] verified, in a sample of 52 mothers and fetuses, assessed at 24, 30, and 36 weeks of gestation, that the fetuses of more emotional women, assessing their lives as more stressful and signalizing more difficulties during pregnancy, were more active, than those of mothers who perceived their pregnancy with positive emotionality. Mediation mechanisms involving stress hormones, the HPA axis and role of the placenta have been proposed to explain the association between maternal psychological symptoms and fetal behavior [83,84].

Although there is a growing awareness that quantitative assessment of fetal activity seems to be more valuable to demonstrate trends in the variance of activity than for identifying individual fetuses at high risk [85], it is also true that the inhibition is a hallmark of neurological development and, consequently, a decrement in fetal activity should be found during gestation [86,87]. In the same way, a gradual increment in coordination of motor activity is expected [88], as both aspects are signs of central nervous development [1]. Due to that, and despite the fact some cautions should be taken when general conclusions are proposed, higher fetal activity, especially of less coordinate single limb movements, found in fetus of anxious/depressed mothers when compared to non-anxious/non-depressed mothers, can be taken as a sign of higher immaturity of the nervous system in these fetuses.

Espresso is one of the most popular beverages in Portugal, being widely consumed. Almost a quarter of the pregnant women of the sample reported espresso consumption. Thus, the understanding of the mutual interplay of the range of risk factors in the determination of early infant development, proposed as one of the major aims/contributions of the present study, requires the analysis of the effect of coffee intake on fetal growth and activity. An effect of mothers' coffee intake during pregnancy on fetal activity was found, with fewer single movements being observed in fetuses whose mothers consumed coffee during gestation, when compared to mothers without this consumption. Although evaluation of the human developmental risks of caffeine is difficult and findings are inconsistent, as already suggested in previous reports, it is also true that the medical literature contains many distinct references that appear to indicate that human adverse reproductive/developmental effects are produced by caffeine [29]. The fact that many caffeine users are subject to multiple confounding factors and, the considerable variation in caffeine content of foods and beverages, may interfere with the attainment of valid interpretations [29]. Even so, according to a few epidemiological studies it is assumed that one espresso contains 70–80 mg of caffeine, which was sufficient, according to some studies, to explain several reported effects in fetal development [for a revision see 29,89]. The mechanisms through which this impact can be observed may include the acknowledged association between coffee intake and the consumption of other substances, such as alcohol and tobacco [29,90].

The major limitations of the present study were related to the small size of the sub-sample involved in the assessment of fetal behavior and to the small period of 3 min for observation of motor activity, when compared to previous studies developed in this domain [59,91]. These limitations resulted from institutional constraints to the implementation of the present research which imposed the assessment of fetal movements by the obstetrician during the morphological ultrasound routine. Due to that a maximum period of 10 min was allowed by the maternity hospital for video recording of fetal activity. The exclusive interest in fetal spontaneous' behavior established the use of a period maximum of 3 consecutive minutes of good viewing of the fetus, achieved by all participants, for fetal behavior scoring, taking into account the high percentage of time in which some of the fetuses were not accurately viewable (which, in turn, determined the need for repositioning of the transducer). Even so, the similar distribution of the presence and absence of the different fetal movement patterns, when compared with results of previous studies, which aimed at the quantitative aspects of fetal motor activity [5,86], suggest that the 3 min observation can be considered as representative of fetal behavior in mid gestation, even though some critics can be addressed to the assessment of fetal behavior, in consequence of the evolution of ultrasound machines.

Despite these limitations, the current findings support previous research indicating a detrimental effect of maternal psychological distress during pregnancy on fetal development. Mainly when different risk factors, such as mothers' psychopathological symptoms, sociodemographic disadvantage

and substance consumption are combined. The investigation of the impact of both anxiety and depression symptoms on fetal growth and behavior, and the deep understanding of the mutual interplay of the range of risk factors in the determination of early infant development appear, in this way, the major contributions of the present study. The results of the current research also suggest the differential impact that these diverse risk factors can have on fetal growth and activity and the importance of the moment of exposure in determining the course of this impact. Interdisciplinary interventions, which should begin early in gestation and take into account the bio psychosocial reality of the families, were recommended. The examination of present findings in larger samples, namely taking into account the multiple relationships that can exist between different risk factors, is advised, in that the deep knowledge of the pathway by which each prenatal factor affects child development will allow health professionals to establish more efficient preventive interventions.

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Current knowledge on this subject

- Psychological development begins during the gestational period, and prenatal influences can explain a significant part of the child's future behavioral and developmental variability.
- Psychosocial distress, socio-demographic disadvantage, and substance consumption have been suggested as risk factors of fetal development.
- Non consensual results related to the effects of maternal anxiety and depression during pregnancy on fetal growth and activity was obtained.

What this study adds

- Support for the previous findings suggesting the vulnerability of fetal development to maternal psychological distress (anxiety and depression) during pregnancy, mainly when associated with other risk factors such as socio-demographic disadvantage, tobacco use and coffee intake.
- The differential impact of the diverse risk factors on fetal growth and activity.
- The importance of the moment of exposure in determination of the course of this impact.