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The Development of Preterm Infants from Low SES Families: The Combined Effects of Melatonin, Autonomic Nervous System Maturation and Psychosocial Factors (ProMote)

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INTRODUCTION

The Developmental Origins Theory was proposed to explain the observations linking early life events, such as prematurity, with later adult pathology (Barker, 2002, 2007). A 'preterm behavioral phenotype' is characterized by increased risk for symptoms and disorders associated with anxiety, social difficulties, behavioral and developmental delays and an increased prevalence of autism spectrum disorders (Johnson & Marlow, 2011).

Biological, psychological and sociological risks interact in a way that threatens the family's ability of low SES to respond to the physical, social, and emotional needs of its members (Maurer & Smith, 2013). Socioeconomic disadvantage and risk factors are associated with preterm birth (van der Hulst, 2022). Antenatal anxiety and postpartum depression are more prevalent in women of low compared to high SES (Cena, 2020; Goyal, 2010; Kozhimannil, 2011). Low SES is associated with more stressful family life situations (Reiss, 2019). Lack of social relations constitutes one of the stressors faced by low SES families compared to high SES families (Leahy-Warren, 2020; Weyers, 2008). Due to preterm birth, early mother–infant intersubjective interactions may be compromised (Carrulo, 2022). The absence of intersubjective communication in spontaneous mother–infant interaction interferes with the development of socio-emotional competences associated to neuro-developmental disorders (Trevarthen & Aitken, 2001). Gestational age in preterm infants significantly correlates with heart rate variability (HRV) parameters, the lower is gestational age, the higher is mean HR for longer time and lower HRV. Melatonin in human milk is important for normal neurodevelopment, it plays an important role in newborn synchronization with the mother's rhythm, it entrains rhythms in the cardiovascular system that are essential to neonatal homeostasis and function and may contribute to better growth and development with long-term outcomes (Gombert & Codoñer-Franch, 2021). Nutritional deficiencies can impact circadian rhythmicity in human milk composition (Italianer, 2020) but it is unclear to what extent socioeconomic status variation (Italianer, 2020; Samuel, 2020).

AIMS AND OBJECTIVES

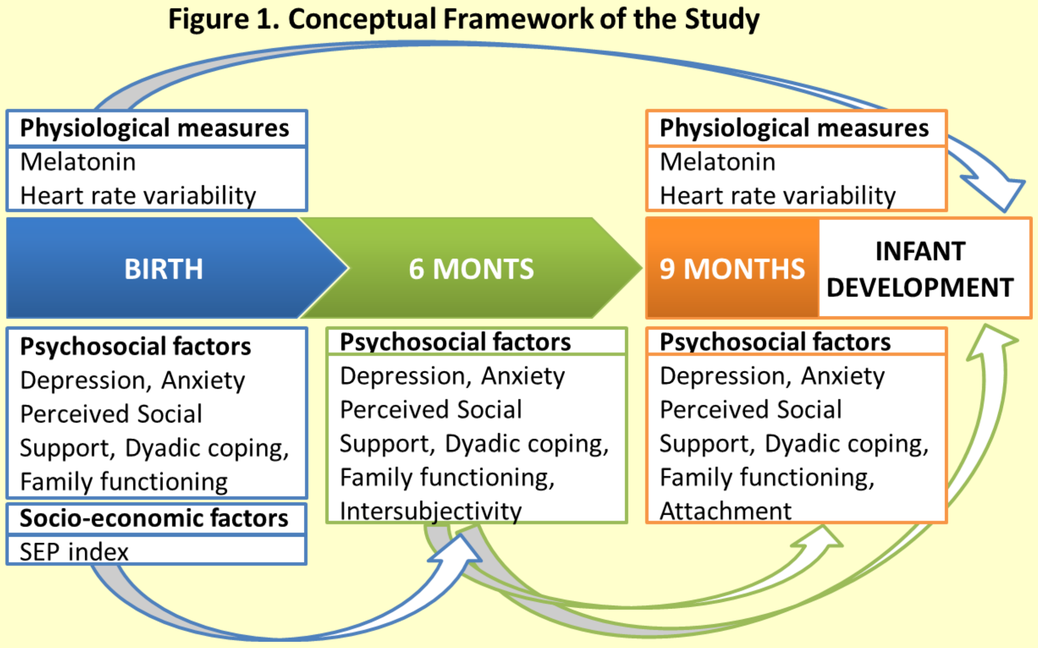
The main aim of this study is to investigate the association of certain psychosocial and biological factors across the first year of life of preterm infants' development, with focus on low socio-economic status families.

- **Objective 1:** To explore the way psychosocial factors, such as maternal mental health, maternal perception of infant's intersubjectivity and attachment, across the first year of preterm birth are related with infants' emotional and cognitive development at 9 months (corrected age). Further, we will explore whether this association varies between infants from low and high SES. In addition, we will investigate whether other characteristics (family functioning, perceived social support and dyadic coping) may be related to these associations and if these characteristics can moderate for the risks posed by low socio-economic status.
- **Objective 2:** To assess the way physiological factors, such as autonomic nervous system maturation, measured according to heart rate variability (HRV), is associated with premature infants' emotional and cognitive development at 9 months (corrected age) and whether this association varies between low and high SES. Further, we will explore whether maternal derived-melatonin through breastfeeding intervenes this association.

METHODOLOGY AND IMPLEMENTATION

Study population: The study will include preterm neonates (<37 weeks) hospitalized in the Neonatology Department/NICU of the University Hospital of Heraklion and their mothers. The conceptual framework of the described work is summarized in the following figure:

Figure 1. Conceptual Framework of the Study



Questionnaires: The well-validated *Edinburgh Postnatal Depression Scale* (EPDS, Cox, 1987) will be used to screen possible depressive symptoms in new mothers at birth. *The Beck Depression Inventory-II* (BDI-II; Beck, 1996) will be used to screen maternal symptoms of depression experienced at 6 and 9 months. The *Spielberger State-Trait Anxiety Inventory for Adults* (STAI, Spielberger, 1983) will be used to measure maternal anxiety. The *Family Adaptability and Cohesion Evaluation Scales IV Package* (FACES IV; Olson, 1979; Olson, 2019) will be used to assess perceived family functioning. The *Multidimensional Scale of Perceived Social Support* (MSPSS, Zimet, 1988) will be used to assess the perception of social support mothers receive from three sources, each corresponding to a subscale: family, friends, and significant other. *The Dyadic Coping Inventory* (DCI, Bodenmann, 2008; Ledermann, 2010) will be used to measure dyadic coping behaviors. The *Maternal Perception of Infant's Intersubjectivity Questionnaire* (MPIIQ, Carrulo, 2022) will be used to assess maternal perception of the infant's intersubjectivity. The *Maternal Postnatal Attachment Scale* (MPAS, Condon & Corkingdale, 1998) will be used to assess mother's subjective feelings of attachment to her infant via maternal self-reported feelings, cognitions and behaviour in relation to their infant.

Breastmilk melatonin concentrations: Mothers of preterm neonates will be asked to collect 5-10ml of breastmilk with the use of an electrical pump between 01:00-05.00 at three specific time points: 3rd-5th day (colostrum), 10th-14th day (transitional milk) and 20th-28th day (mature milk). An umbilical cord blood sample of 1-2ml will be collected at every preterm delivery or caesarean section, in order to measure the melatonin level at the time of birth. Blood samples from the preterm neonate will be collected for premature infants >33 weeks, at 4th-7th day of life and 10th-14th day, and for premature neonates <33 weeks, 3 samples will be collected (4th-7th day of life, 10th-14th day and at a date that will coincide with a gestational age of 35-36 weeks).

Neonates' and infants' and maternal ECG will be obtained at 2 successive time intervals (neonatal period and 9 months after the birth) and the HRV by measuring short-term variability which provides important information about the maturation of the ANS in newborns (Lavanga, 2021; Longin, 2006).

Infant development: At 9 months, the social and cognitive development of infants will be assessed at hospital by the administration of the *Bayley Scales of Infant and Toddler Development, 3rd Edition* (Bayley, 2006).

EXPECTED OUTCOMES

According to the above-mentioned objectives:

1.We expect that associations between maternal mental health, maternal perception of infant's intersubjectivity, attachment and infant development at 9 months will vary according to SES. Psychosocial factors such as family functioning, perceived social support and dyadic coping will be related to these associations.

2.HRV will be associated with premature infant development at 9 months. Maternal derived melatonin will intervene the association between HRV and premature infant development.

The findings of this study may highlight the need for future community-based prevention efforts and may convince policy makers and government to increase evidence-based interventions and family-focused care targeted on the promotion of perinatal mental health-care of mothers and preterm infants' development from low SES.

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