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ASSOCIATION BETWEEN PRETERM BREASTMILK MELATONIN CONCENTRATION AND PSYCHOSOCIAL FACTORS AT BIRTH (ProMote)

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Melatonin and infant development

- **Melatonin** is a neurohormone synthetized mainly by the **pineal gland** and, to a lesser extent, by extra-pineal tissues such as the **placenta** (Joseph et al., 2024).
- Besides regulating the **circadian rhythm**, melatonin has a wide range of biological functions, including **antioxidation**, **anti-inflammatory**, **anti-apoptosis**, **immunomodulatory**, and **gut microbiota formation**, making it a potent bioactive molecule with long-term **cardiovascular health effects**, especially in infants (Qin et al., 2019; Gombert & Codoñer-Franch, 2021).

Rhythm of melatonin levels during gestation

- **Maternal serum melatonin levels increase** gradually from 24 weeks after implantation, reaching a peak in the third trimester, at 32 weeks, and a maximum at term. In the third trimester, melatonin maternal levels are around 3-fold higher than in the first trimester though daytime levels of melatonin do not increase accordingly.
- Fetal circadian rhythms can be observed in utero from 30 weeks gestation, coupled to the maternal rhythm, but synchronize to the external environment only after birth. Meanwhile, during the first 3 months approximately the infant will experience a transient deficiency in melatonin, due to suboptimal melatonin production and immature circadian rhythmicity. This property has special importance in **preterm newborns**, since they are **not exposed to the final stage of pregnancy** when **maternal melatonin** supply to the fetus is **the highest** (Chen et al., 2012; Ejaz et al., 2021; Häusler et al., 2024; Joseph et al., 2024; McCarthy et al., 2019).

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Early-Life Melatonin Supply Through Breastfeeding

- Because endogenous melatonin production is minimal in the neonatal period, **breast-milk** is the principal physiologic source of melatonin early in life (Attanasio et al., 1986; Kennaway et al., 1992).
- **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).
- **Preterm breast-milk** has a higher concentration of melatonin than term breast-milk, suggesting that breast-milk may provide a protective tool to compensate for the lack of melatonin due to premature birth (Qin et al., 2019).

Premature birth, melatonin, maternal mental health and family functioning

- Both **anxiety and depression** during pregnancy have been associated with **preterm birth** (Adhikari, 2020) but also **stress of parents of preterm infants** is high and they may face additional challenges (Enlow, 2017).
- Families of **preterm infants** are **disproportionately burdened** by **stress** and mothers experience significant anxiety in the perinatal period (Enlow, 2017). One of the coping that can potentially affect how couples adapt to the transition to parenthood is the **family sense of coherence** (Ngai & Ngu, 2016), that is the emotional bond that family members have towards one another (Olson, 2019). Couples with a strong family sense of coherence probably share a common goal in bringing up a child and are motivated to mobilize all available resources to deal with the parental demands (Ngai and Ngu, 2016).

Contradictory evidence on the association between melatonin and maternal mental health and the gap in relation to family functioning

- Maternal **postpartum stress** and **negative mood** have been associated with **higher melatonin in milk samples** (Groër et al., 2005), or **laughter increased** the levels of **breastmilk melatonin** in healthy mothers (Kimata, 2007).
- An indirect effect between melatonin and family environment is implied only by limited evidence showing that interventions to improve sleep of ASD children had also a benefit on family functioning (Malow, 2014).

The aim and objectives of this study (ProMote)

- **Aim**: Explore the association between **psychosocial factors and breastmilk melatonin** concentration after **preterm birth**.
- **Objectives**:
  - To investigate the correlation between **breastmilk melatonin** and **maternal mental health (depression and anxiety)** in the first days after **premature birth**,
  - To study the correlation between **breastmilk melatonin** and **family functioning** in the first days after **premature birth**.

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The importance of this study (ProMote)

- Prematurity has been associated with **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).
- The role of **melatonin for preterm infant development** is **unclear** (Tauman, 2002) and **under-investigated**.
- In Greece, **multiproblem families** have been said to be on the rise due to the financial crisis of the last decade (Papadakaki, 2021) while the pandemic affected adversely the mental health of Greeks (Parlapani, 2020; Vatavali, 2020).
- **Preterm births** constitute a **major public health issue** in Greece. This emphasizes an urgent need for preventive interventions to be implemented (Vlachadis, 2013). The national preterm birth rate in Greece more than quadrupled during 1991-2022 (Vlachadis et al., 2024, 2025).
- **Perinatal mental health problems** are a **major public health concern** globally (Tripathy, 2020). Maternal perinatal mental health disorders have persistent effects on behavioural, physiological and immunological functioning **throughout the lifespan** and may even be evident **across generations** (Coussons-Read, 2013).

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Study Population

- **In total, 112 mothers** agreed to participate in the Promote study
  - Of which, 20 gave birth to twins.
- **Breast milk:** 106 (94.6%) mothers provided at least one sample of night-time breast-milk (between 01:00-05.00 a.m.):
  - 84 mothers provided colostrum (3rd-5th day),
  - 83 transitional milk (10th-14th day) and
  - 73 mature milk (20th-28th day).
- Psychometric scales: 106 (94.6%) mothers completed at least one of the questionnaires on Anxiety (94), Depression (102) and Family functioning (99)

Maternal Characteristics

	N	%	Mean	SD
Maternal age (*years*)	91		34.3	6.8
Marital status				
Married	71	78		
Other	20	22		
Educational level				
Compulsory	6	6.6		
Secondary	26	28.6		
Tertiary	59	64.8		
Working Status				
Employed/Self-employed	74	82.2		
Unemployed, looking for work	11	12.2		
Not working	5	5.6		

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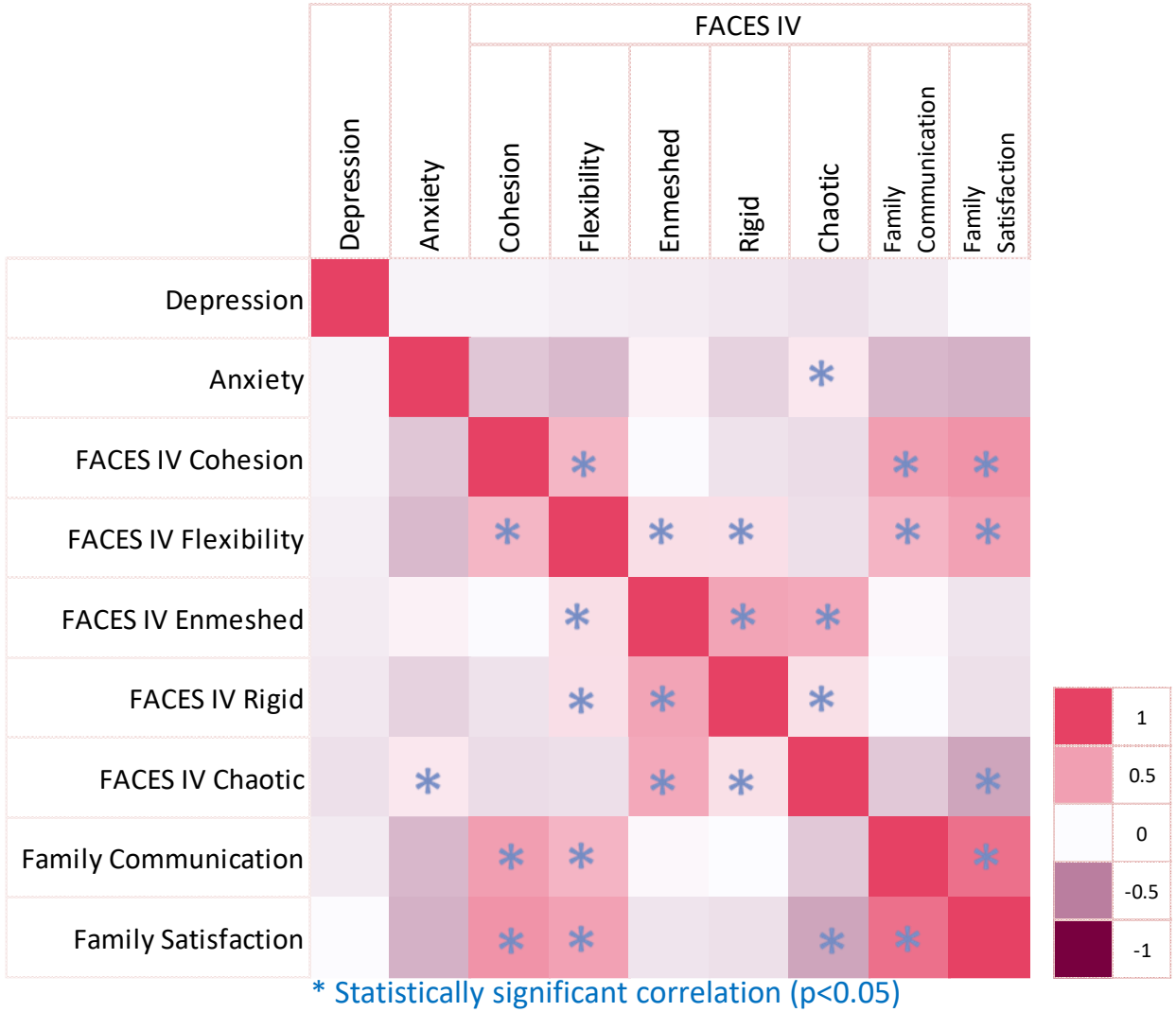
Perinatal Information

	N	%	Mean	SD
Gestational age (*weeks*)	92		33.4	2.3
Prematurity				
Extremely preterm	3	3.3		
Very preterm	13	14.1		
Moderate to late preterm	76	82.6		
Multiple pregnancy				
Singletons	76	82.6		
Twins	16	17.4		
Urgent delivery				
Yes	52	56.5		
No	40	43.5		
Complications at delivery				
Yes	70	80.5		
No	17	19.5		

Psychosocial scales

	N	Mean	SD
Depression (*EPDS*)	87	13.2	2.2
Anxiety (*STAI-Trait*)	79	36.2	8.7
FACES IV Cohesion	85	29.6	2.8
FACES IV Flexibility	87	26.5	3.6
FACES IV Enmeshed	88	17.0	4.2
FACES IV Rigid	88	17.8	4.0
FACES IV Chaotic	87	15.3	4.5
Family Communication	89	42.0	5.4
Family Satisfaction	79	39.3	6.6



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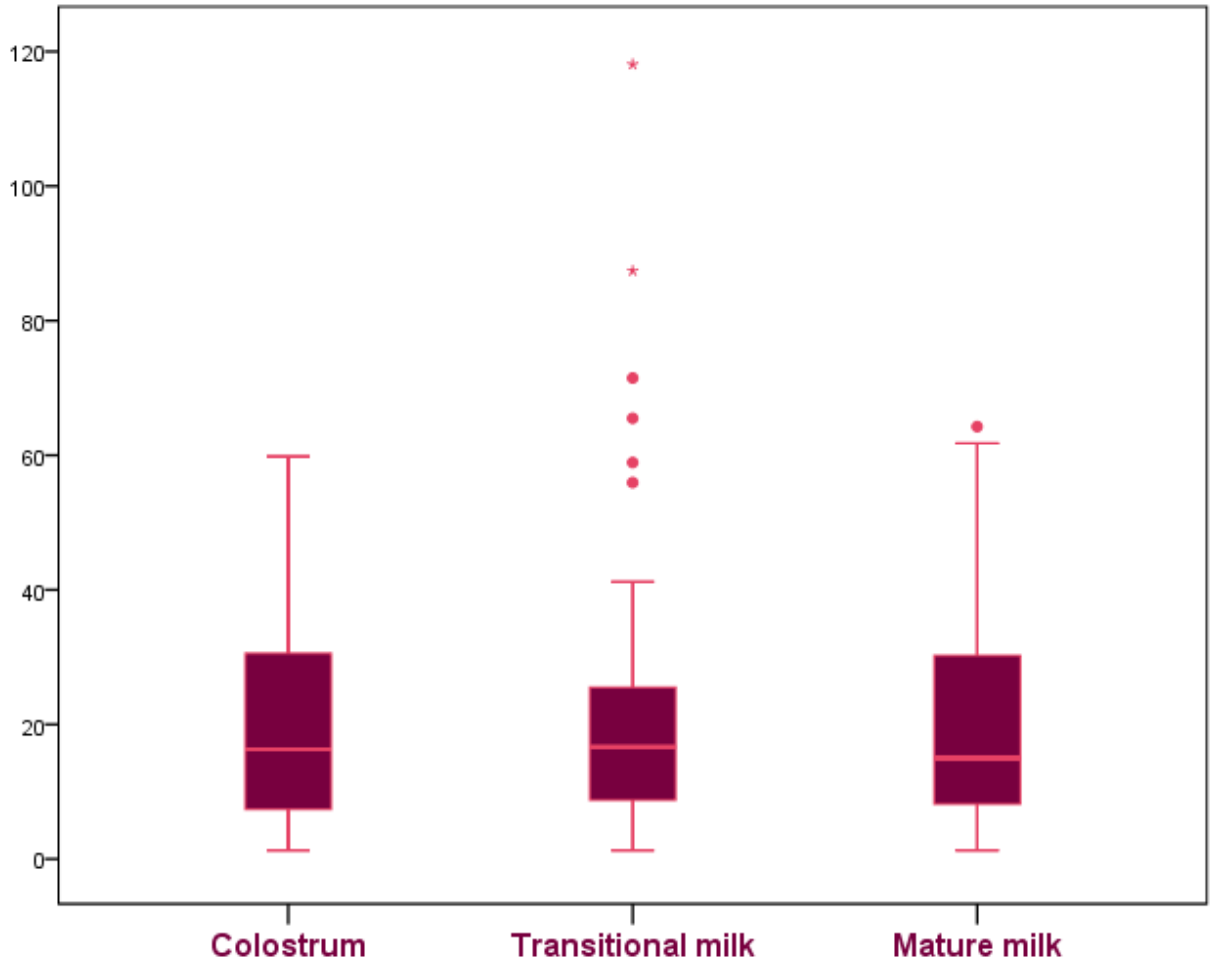
Breast milk melatonin concentration (pg/ml)



	N	Mean	SD	% below LOD
Colostrum	75	20.4	15.8	1.3
Transitional milk	74	22.0	19.9	1.4
Mature milk	65	21.0	18.1	6.2

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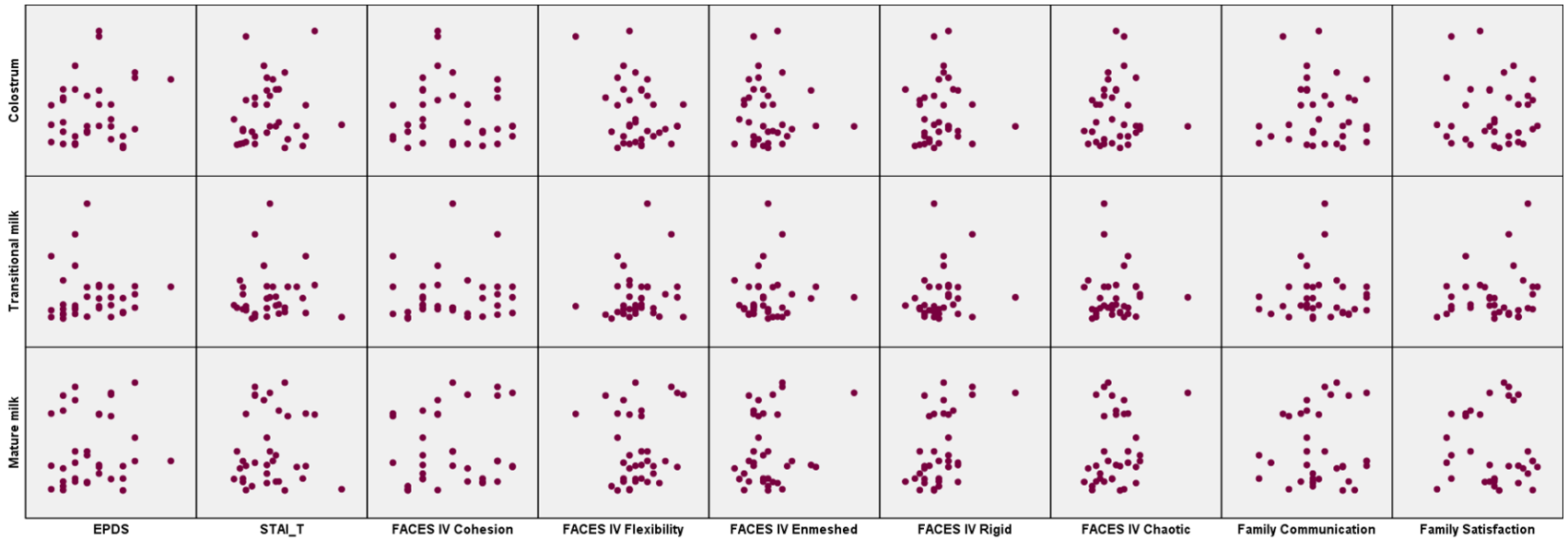
Breast milk melatonin concentration (pg/ml)

	Mean difference	Std. Error	P-value
Pair 1: Colostrum-Transitional milk	-3.3	3.1	0.281
Pair 2: Colostrum -Mature milk	-2.1	2.8	0.459
Pair 3: Transitional milk - Mature milk	1.2	3.0	0.687

Correlations

r = Pearson's correlation coefficient

	Colostrum			Transitional milk			Mature milk		
	N	r	P-value	N	r	P-value	N	r	P-value
Depression	73	0.169	0.153	69	0.043	0.726	62	0.101	0.436
Anxiety	65	0.125	0.321	61	0.102	0.433	56	0.044	0.746
FACES IV Cohesion	**72**	**-0.315**	**0.007**	68	0.048	0.698	63	0.060	0.639
FACES IV Flexibility	**72**	**-0.298**	**0.011**	69	0.143	0.241	62	-0.021	0.872
FACES IV Enmeshed	73	-0.017	0.885	70	0.042	0.729	63	0.107	0.403
FACES IV Rigid	73	-0.032	0.786	70	0.005	0.969	63	0.229	0.071
FACES IV Chaotic	72	0.068	0.572	69	-0.077	0.531	62	0.209	0.103
Family Communication	74	-0.196	0.094	71	0.019	0.873	64	-0.148	0.242
Family Satisfaction	64	-0.169	0.181	64	0.201	0.111	58	-0.082	0.543



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Association estimates

		Colostrum		Transitional milk		Mature milk	
		B-coeff	95% CI	B-coeff	95% CI	B-coeff	95% CI
Depression	Crude	1.15	(-0.44 ;2.74)	0.40	(-1.87 ;2.68)	0.83	(-1.29 ;2.96)
	Adjusted	1.70	(0.09 ;3.32)	0.87	(-1.49 ;3.23)	1.19	(-0.99 ;3.37)
Anxiety	Crude	0.26	(-0.26 ;0.77)	0.24	(-0.37 ;0.85)	0.09	(-0.45 ;0.63)
	Adjusted	0.37	(-0.15 ;0.90)	0.35	(-0.29 ;0.99)	0.00	(-0.57 ;0.57)
FACES IV Cohesion	Crude	-1.78	(-3.05 ;-0.50)	0.35	(-1.45 ;2.15)	0.46	(-1.48 ;2.39)
	Adjusted	-1.96	(-3.28 ;-0.63)	0.32	(-1.60 ;2.23)	0.99	(-1.04 ;3.02)
FACES IV Flexibility	Crude	-1.29	(-2.28 ;-0.30)	0.86	(-0.59 ;2.32)	-0.11	(-1.48 ;1.26)
	Adjusted	-1.18	(-2.19 ;-0.18)	0.86	(-0.59 ;2.32)	0.12	(-1.26 ;1.50)
FACES IV Enmeshed	Crude	-0.06	(-0.91 ;0.78)	0.19	(-0.90 ;1.28)	0.44	(-0.60 ;1.47)
	Adjusted	-0.08	(-0.98 ;0.82)	0.32	(-0.85 ;1.48)	0.12	(-0.95 ;1.19)
FACES IV Rigid	Crude	-0.12	(-1.00 ;0.76)	0.02	(-1.20 ;1.24)	1.08	(-0.10 ;2.25)
	Adjusted	-0.13	(-1.05 ;0.79)	-0.08	(-1.37 ;1.21)	0.73	(-0.48 ;1.95)
FACES IV Chaotic	Crude	0.23	(-0.58 ;1.04)	-0.35	(-1.46 ;0.76)	0.84	(-0.18 ;1.86)
	Adjusted	0.20	(-0.67 ;1.07)	-0.39	(-1.57 ;0.78)	0.47	(-0.59 ;1.52)
Family Communication	Crude	-0.57	(-1.24 ;0.10)	0.08	(-0.88 ;1.03)	-0.58	(-1.57 ;0.40)
	Adjusted	-0.62	(-1.33 ;0.08)	-0.02	(-1.00 ;0.95)	-0.59	(-1.57 ;0.40)
Family Satisfaction	Crude	-0.39	(-0.96 ;0.19)	0.67	(-0.16 ;1.49)	-0.28	(-1.18 ;0.63)
	Adjusted	-0.40	(-0.99 ;0.19)	0.66	(-0.17 ;1.49)	-0.09	(-0.98 ;0.81)

B-coefficients and corresponding 95% Confidence intervals (CI) obtained from linear regression models; crude and adjusted for gestational age at delivery, maternal age, education, marital and working status

Discussion (1)

Summary of main results:

Psychosocial Factors (maternal mental health and family functioning)

Positive association between **maternal anxiety** and **chaotic family functioning**

Negative association between **family satisfaction and chaotic family functioning**

Positive associations between:

- Family cohesion – family satisfaction, family cohesion- family communication,
- Family flexibility – family satisfaction, family flexibility - family communication

Breastmilk melatonin and Family Functioning

Negative correlation between:

- Colostrum melatonin – family cohesion
- Colostrum melatonin – family flexibility

Discussion (2)

- **Positive association** between **maternal anxiety - chaotic family functioning, family cohesion – family satisfaction / family communication**, **family flexibility – family satisfaction / family communication** as well as **negative association** between **family satisfaction and chaotic family functioning** are in accordance to **Olson's framework** addressing **family functioning** (Olson et al., 2019).
- **Better-functioning families** tend to have members with **fewer** instances of depression and **emotional distress**. **Cohesion** involves fostering strong emotional bonds between family members, and its **decrease** is associated with an **increased** risk of **emotional distress** in family members. **Flexibility** is the measure of the family system **balance** between stability and change; it enables families to cope with change and reduces the impact of negative events on family members' mental health. Effective family communication serves to reduce conflict and increase adaptability and cohesion (Urbanska-Crosz et al., 2024).

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Discussion (3)

There were **no correlations** between night-time breastmilk **melatonin** and **maternal mental health. Mothers** of this sample showed **depressive symptoms** with a mean score at the **threshold** and **low levels of anxiety**.

In our sample, the wide between-neonate variation of morning serum melatonin (Kokkinaki et al., 2025, under review) may imply also **individual variability between night-time mothers' breastmilk melatonin.** Also, we **did not control for the exact time of milk pumping** apart from the wide time-window between 01:00-05:00 a.m.

Taken these together, they may be associated with **wide differences in melatonin onset / offset times** and / or **lower strength of the hypothalamic circadian pacemaker** that regulates melatonin secretion in women with depressive symptoms. Alternatively, as early morning light suppresses melatonin, causing an earlier offset, these women may have **an increased sensitivity to early morning light**, or may experience more light in the morning due to early morning awakening that occurs in depression (Parry et al., 2008). The combination of all these did not permit capturing significant correlations or monotonic changes between night-time **breastmilk melatonin** and **maternal mental health.**

Discussion (4)

Though we did not evidence correlations between breastmilk melatonin and maternal mental health, our findings on the **negative association** between **breastmilk melatonin** and **family cohesion/flexibility** *indirectly* **confirm** relevant evidence:

- **maternal fatigue** during the early postpartum, which is a predictor of **perceived stress,** appear to be related to **higher melatonin levels** in maternal morning milk (Groër et al., 2005) though here we collected night-time breastmilk.
- **mothers of preterm infants** who reported **less total sleep** and fewer sleep bouts had **higher daytime salivary melatonin levels** (McMillen et al., 1993), but others have not found an effect of sleep deprivation on melatonin (von Treuer, Norman, & Armstrong, 1996).
- **Plasma nocturnal melatonin concentrations**, especially in the morning hours, were lower in depressed pregnant (major depression), but **elevated in depressed postpartum women**, compared with healthy comparison women (Parry et al., 2008).

Discussion (5)

Our findings on the **negative association** between **breastmilk melatonin** and **family cohesion/flexibility** may be explained by the **intervening role** of certain **psychosocial factors**, such as **social support (1)** or life events, or **biological factors (2)**:

(1) e.g., **in instances of low family cohesion / flexibility** the provision of **social support may protect and promote maternal mental health** thus **reinforcing night-time breastmilk melatonin secretion.**

(2) Alternatively, it may be that mothers with depressed symptoms coming from low level family cohesion / flexibility may be **less sensitive** to the effects of **estradiol or progesterone** on **melatonin receptors,** e. g. the declining levels of estradiol and progesterone would decrease melatonin in healthy women but may result in higher melatonin levels in mothers with depressed symptoms (Parry et al., 2008).

Further investigation is needed.

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Implications

- 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.

Limitations

- Longitudinal studies with larger sample size comparing relevant psychosocial and biological factors and the development of both preterm and full-term neonates are necessary.
- Melatonin in human milk needs to be measured according to breastfeeding duration given the reduction of melatonin concentration at the end of feeding compared to the pre-breastfeeding period.
- Future research needs to address respective issues in relation to women's way of birth (vaginal delivery vs cesarean section) given the relevant contradictory evidence.
- Further, cortisol measurements need to be added since the fetal circadian rhythm is synchronized to maternal cortisol and melatonin levels. Pregnant women experience changes in circadian regulated plasma cortisol and melatonin concentration.

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Thank you very much for your attention!

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