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XXXVI CICLO DEL DOTTORATO DI RICERCA IN

Scienze della Riproduzione e dello Sviluppo

EPINICU (Empowering Parents of newborns in the NICU). A Multicountry Project to identify sustainable models of interventions in different settings: findings from Italy and 3 scoping reviews.

Settore scientifico-disciplinare: **MED/38**

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INDICE

1. INTRODUCTION

The EPINICU study

My PhD project is part of an ongoing multicenter multicountry before and after study called **EPINICU (Empowering Parents of newborns In the NICU)** involving 4 countries (Italy, Tanzania, Brazil and Sri Lanka), 8 different hospitals and different partners: Doctors with Africa - Collegio Universitario Aspiranti Medici Missionari (CUAMM), Instituto de Medicina Integral Professor Fernando Figueira (IMIP) and the World Health Organization (WHO) Head Quarters of Geneva.

The WHO Collaborating Center of the Institute for Maternal and Child health, IRCSS Burlo Garofolo coordinates the study, and Prof. Marzia Lazzerini, responsible of the Trieste WHO Collaborating Center, is the Principal Investigator of the Project and supervisor of this PhD thesis.
The whole research team included over 40 collaborators in the four countries (**Figure 1a**).

Figure 1a. Institutions, hospitals and collaborators participating in the EPINICU study.

Institution	Coordination	Collaborators
WHO CC	**PI: Dr Marzia Lazzerini** Project Manager Brazil: Dr Emanuelle Pessa Valente	Data analysts: dr Paolo Dalena, Dr Ilaria Mariani
ITALY 	**IRCSS Burlo Garofolo** **Coordinator and PhD Student: Dr Jenny Bua**	Neonatology Director f.f.: Drssa Laura Travan Data collector and data entry: Dr Martina Girardelli Dr Murphy Tomadin Psicologists: Dr Stefano Bembich, Drssa Sabrina Plet Nurse component: Francesca Marrazzo, Barbara Albertacci, Luisa Bulzis, Maddalena Ermacora, Ursula Manzon Pediatrics Director: Prof Egidio Barbi Statistician: Ilaria Mariani Other collaborators: Silvia Panunzi, Cecilia Vuillard, Domenica Giglia, Cristina Tuminelli
TANZANIA 	Tosamaganga Hospital Coordinator: Dr Gaetano Azzimonti > Dr Paolo Berardi	Head of Planning CUAMM: Dr Giovanni Putoto Country manager: Dr Giovanni Torelli Data Collector: Emmanuel Ndile
BRASIL 	IMIP Coordinator: Dr Geisy Maria de Souza Lima (Neonatology unit coordinator at IMI OTHER 5 HOSPITALS In RECIFE Hospital das Clínicas - Barão de Lucena - CISAM - Agamenon Magalhães - Maria Lucinda Coordinator: Dr Waldemar Brandão Neto (Nursing professor Pernambuco University)	IMIP Dr Dafne Barcala - data collection coordinator IMIP – NICU, PhD student at IMIP Juliana Barradas - data collection coordinator IMIP – Kanguroo unit Bruna Malta Castro - data collector, medical student Vanessa Tenório Rodrigues - data collector, medical student Maria Luísa de Oliveira Maximino Pessoa - data collector, medical student Joana Beatriz Ribeiro Silva dos Santos - data collector, physioteraphy student Dr Vivian Farias- data collector, Neonatology medical resident at IMIP Carolina Ramos de Oliveira data insertion at database, Neonatology medical resident at IMIP Eduarda Medeiros Cisneiros - data insertion at database, Neonatology medical resident at IMIP OTHER 5 HOSPITALS In RECIFE Dr Giselle Paiva - data collection coordinator NICU- Dr Lorena Freitas- data collector, Neonatology medical resident Dr Walkyria Campos - data collector, Neonatology medical resident Núbia Dantas – data collector, nursing student Pernambuco University Renata Araújo - data collector, nursing student Pernambuco University Maria Eduarda Fraga - data collector, nursing student Pernambuco University
SRI LANKA 	De Soysa Maternity Hospital, Colombo Coordinator: Dr Mohamed Rishard Coordinator: Dr Hemantha Senanayake	Neonatology Director: Nalin Gamaathige Data collectors: tbc

Main focus of my PhD was the coordination of the project at the Italian site, the reporting of the Italian data while collaborating with the ongoing multicountry project.

1.1 Background

The first 28 days of life – the neonatal period – represent the most vulnerable time for a child's survival. In 2016, 2.6 million deaths, roughly 46% of all under-five deaths, occurred during this period

(Soon, 2012). According to the most recent global estimates, preterm births, infections and congenital anomalies are currently the leading causes of death in children under 5 years of age (Liu et al., 2015). Additionally, the implications of being born too soon, to have a congenital anomaly or to acquire an infection or another complication early in life often extend beyond the neonatal period and throughout the whole life cycle. These babies face greater risks of serious health problems, including cerebral palsy, intellectual impairment, chronic lung disease, and vision and hearing loss (Soon, 2012). The psychosocial, emotional and economic impact of these conditions for the families, the health system and the whole society is tremendous.

Babies with special needs (such as pre-term, small for gestational age, congenital anomalies, post-natal complications such as infections, severe jaundice and others) are usually hospitalized, for a medium to long term period, in neonatal intensive care units (NICUs) or semi-intensive care units. If, from one side, parents of babies in NICUs or semi-intensive care units suffer a high degree of psychophysical distress (Al Maghaireh et al., 2016; Provenzi & Santoro, 2015), on the other hand, they have a crucial role in supporting the health and neurological (including emotional) development of their babies, both during hospitalization and after discharge. Indeed, evidence show that middle and long-term developmental outcomes (ie, after 36 months of age) of these babies are closely related to aspects of their early social environment, such as parents' ability to provide an environment conducive to resilience (Soon, 2012). Consequently, effective interventions for strengthening the copying strategies of the parents, increasing their nurturance capacity, their knowledge and skills on how to take care for the baby and mutual collaboration with hospital staff, are desperately needed.

In high income countries, different models for parents' empowerment have been proposed. As best-known examples, the Newborn Individualized Developmental Care and Assessment Program (NIDCAP) (http://nidcap.org/en/) promotes an individualized, relationship-based, family-integrated model of care (Westrup, 2005) . The Creating Opportunities for Parents Empowerment (COPE) program, developed in US, helps parents understand the workings of the NICU and encourages their active engagement with NICU staff, teaching them how to interact with their preterm infant (http://www.copeforhope.com/nicu.php) (Melnyk et al., 2006a). However, both NIDCAP and COPE programs imply quite expensive and long training, difficult to access in low resources settings (http://www.copeforhope.com/nicu.php; Westrup, 2005). Several similar other strategies have been described in literature, with studies describing different combinations of interventions such as: information sessions, educational booklet, psychosocial support, organized support groups, environmental changes, home support, web-based information, telemedicine (Beheshtipour et al., 2014; Brett et al., 2011; Dol et al., 2017; Melnyk et al., 2006a; Melnyk & Feinstein, 2009; O'Brien et al., 2018a). Overall, most interventions aimed at teaching emotional coping skills, active problem-solving, and evidenced-based practices relevant to the care of pre-term babies.

Overall, the existing literature suggest that interventions for empowering families of pre-term babies may have major impact on the health and wellbeing of pre-term babies, their parents, and on the health system. Studies have showed that interventions for empowering families of pre-term babies improve newborn health outcomes (such as weight at discharge, hospitalization and length of stay), decrease parental negative symptoms (such as anxiety, stress and depression), improve parent-infant

and parent-health worker interaction during hospital, improve parental satisfaction and reduce costs for the health systems (Beheshtipour et al., 2014; Brett et al., 2011; De Bernardo et al., 2017; Melnyk et al., 2006a; Melnyk & Feinstein, 2009). Given its beneficial effects, family-centered care (FCC) is now recognized as one of the European Standards of Care for newborn health (https://newborn-health-standards.org/).

However, still there is limited experience in this field, and the practice of providing practical support to families of pre-term babies- in terms of a specific, individualized, comprehensive, family-integrated model of care, is not wide-spread among facilities, even in high income countries, such as Italy. In low resources settings, where the burden of premature children is higher, and their outcomes are generally worst, almost no experience exists in translating and testing these models of parental empowerment. Training opportunities for both health professionals (staff of NICU or Semi-Intensive Care units/Special Care Nurseries) and parents are also very limited (as an example, NIDCAP training sites are located only in US, Canada, Europe, Australia and Argentina). In few words, these interventions are lacking, where they are actually most needed.

Developing and testing culturally acceptable, effective and sustainable models of interventions to empower parents of NICU babies in different settings is crucial for babies, families, health workers, policy makers and researchers.

1.2 Objective

The *primary objective* of the EPINICU project is to develop and test low cost, context-specific models of interventions for empowering families of babies in NICUs or semi-intensive care units in the following settings: Italy, Tanzania, Brazil, Sri Lanka.

The *ultimate aim* is to improve the quality of care provided to families of babies in neonatal units, and therefore, improve their survival, health and development.

Specific objectives of EPINICU are as follows:

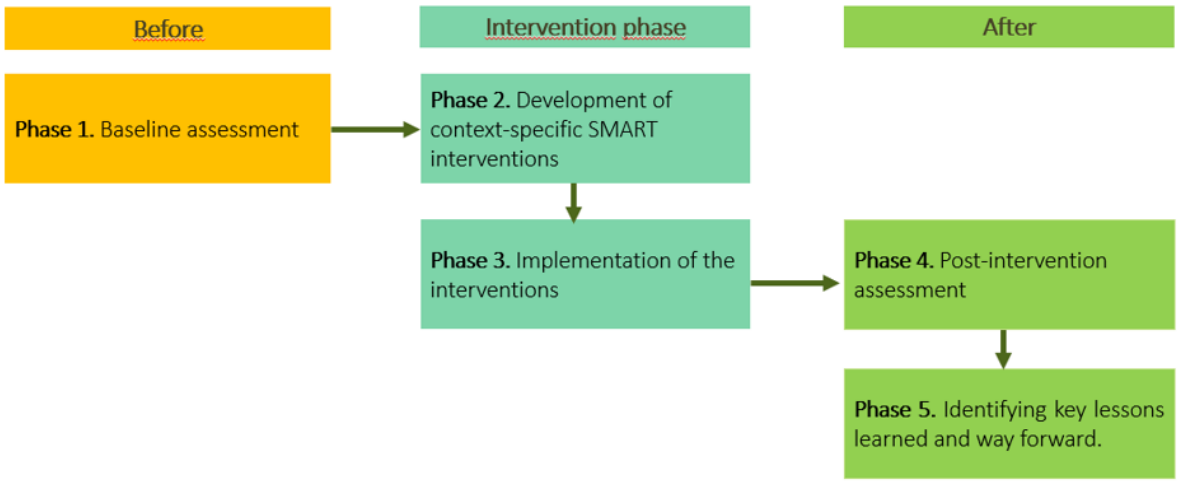
- To conduct a baseline assessment and evaluate in a systematic way and in different contexts the degree of parental participation in the care of infants. The study will also evaluate the parental mental distress by measuring parental stress, depression and anxiety.
- To develop context specific strategies for the empowerment of families of infants with feasible and SMART (Specific, Measurable, Achievable, Realistic, Time-definite) characteristics (SMART, 1981a) with a minimum local budget.
- To facilitate the exchange of experiences and acquired knowledge through local and an international technical workshop and to create an international network of experts.
- To reassess the degree of parental participation in newborn care and mental distress after the implementation of interventions.

1.3 Study design

The EPINICU study has a before and after intervention design, including 5 different phases **(Figure 1b):**

- **Phase 1.** Baseline assessment aimed at assessing systematically, in the different contexts (Italy, Brazil, Sri Lanka, Tanzania) the quality of care for babies hospitalized in NICUs or semi-intensive care units, using selected key indicators specifically: parental stress/anxiety/depression and the degree of parental participation in care.
- **Phase 2.** Collaborative development of context-specific interventions for the empowerment of NICU families with SMART (Specific, Measurable, Achievable, Realistic, Time-definite) characteristics(SMART, 1981a) with a minimum local budget.
- **Phase 3.** Implementation of the local SMART identified interventions
- **Phase 4.** Post-intervention assessment collecting data on the same indicators as Phase 1.
- **Phase 5.** Identifying key lessons learned and way forward: during this phase key lessons learned will be discussed. Recommendations for future research, as well as for policy makers will be made. In this phase a final workshop will be organized, with the participation of all teams from each site. Lessons learned will be described in appropriate communication material, targeting both the scientific audience (i.e. "Consensus paper: lessons learned and ways forward") and policy makers (i.e. video, evidence brief summary).

Figure 1b. Phases of the pre-post EPINICU Study



1.4 Study sites

EPINICU is a multicountry multicentered study involving 8 different hospitals in 4 countries.
The different study sites are detailed below.

ITALY

Neonatology Unit of the IRCCS Burlo Garofolo, Trieste. IRCSS Burlo is a third level referral university centre, currently the only Institute of Research in Maternal and Child Health in Italy, which is leading a research network of Pediatrics IRCCS in Italy (IDEA network, https://www.burlo.trieste.it/nasce-idea-rete-che-unisce-irccs-pediatrici-italiani). The Neonatology Unit of IRCCS Burlo is a regional referral center for newborn care, and well-established research site with around 1700 births/year.

BRAZIL

Six different hospitals of Recife are involved in the study with Instituto de Medicina Integral Professor Fernando Figueira (IMIP, Pernambuco, Brazil) being the Brazilian coordinator hospital.

IMIP, is a well-known philanthropic institute, tertiary referral centre for maternal and child health, with about 6000 births per year. Founded in 1960, IMIP operates in the areas of medical-social assistance, education, research, and community outreach. The IMIP Hospital Complex is recognized as one of the most important hospital structures in Pernambuco, serving as a reference center in various medical specialties. With over a thousand beds, IMIP handles more than 600,000 annual visits in its services. For premature infants, the hospital has 50 ICU beds, including 18 NICU beds and 32 semi-intensive care beds. (http://www1.imip.org.br/imip/home/index.html)

The other five neonatology units come all from five different hospitals of the city of Recife: Hospital das Clínicas (HC), Hospital Barão de Lucena (HBL), Centro Integrado de Saúde Amaury de Medeiros (CISAM), Hospital Agamenon Magalhães (HAM) and Hospital Maria Lucinda (HML) and are all coordinated by IMIP.
HC is part of the Federal University of Pernambuco, currently administered by the Brazilian Company of Hospital Services (EBSERH). The hospital conducts an average of 5,600 outpatient consultations, 748 hospitalizations, and 123 deliveries per month with 24-hour service. The Neonatal Intensive Care Unit (UTIN) has a total of 10 neonatal beds.
HBL was inaugurated in 1958. It is a high-complexity general hospital with a focus on maternal and child care, counting 340 beds. In the two emergency departments (obstetric and pediatric), an average of two thousand visits is made monthly. The surgical block conducts an average of 300 deliveries per month and has 18 NICU beds.
CISAM is considered the largest maternity hospital in Pernambuco in terms of the number of services provided, it is a reference hospital for high-risk pregnancy care. It has a total of 12 neonatal beds.
HAM has 425 beds, and its high-risk maternity is another important reference area contributing significantly to the State's Maternal-Child Network. With over 230 deliveries per month, the unit also has a milk bank to feed premature babies and a total of 15 NICU beds.
HML is a philanthropic institution with over 88 years of service to the people of Pernambuco. Currently, the hospital is maintained by the Manoel da Silva Almeida Foundation. It has a 24-hour

pediatric emergency service, an emergency care service for trauma and orthopedic injuries, and a specialty outpatient clinic.

TANZANIA

Tosamaganga Hospital is a regional referral centre with about 3000 births per year and a training site for local health professionals and community health workers. The hospital is supported since 1982 by Doctors with Africa CUAMM. (https://www.mediciconlafrica.org/)

The Neonatology Unit has recently been renewed, and staff has previous experience in quality improvements initiatives, as well in conducting research. The current practices of data collection system, and the familiarity with the Ethical Review Committee allow for a local coordination of studies. Junior Project officers (JPO) are routinely available on a rotation basis. Logistic is fully supported by the local CUAMM country office. CUAMM has been collaborating with the WHO CC of the IRCCS Burlo, and with other units the IRCCS Burlo for the last 25 years. More information on Tosamaganga Hospital can be found at https://www.mediciconlafrica.org/blog/cosa-stiamo-facendo/inafrica/ospedale-di-tosamaganga-tanzania/.

SRI LANKA

De Soysa Hospital in Colombo is one of the first maternity hospital in Asia (funded in 1879 by the philanthropist Charles Henry de Soysa) and is the major maternity unit in the country, with about 9000 births per year. The hospital is the site of the Faculty of Medicine, the second oldest faculty in Asia (Bengal Medical College a Calcutta) and as such is a training site for doctors, nurses and midwives, through the University of Colombo. De Soysa Hospital has been collaborating with the WHO CC of the IRCCS Burlo, and with other units the IRCCS Burlo for the last 15 years. More information on De Soysa Hospital can be found at http://www.dmh.health.gov.lk/home.

Although included in the EPINICU study, no data from Sri Lanka will be presented in the current thesis as due to the COVID pandemic and subsequent economic crisis, Sri Lanka site, at the time of the writing of this PhD thesis, had not yet started data collection.

The *WHO Collaborating Centre in Maternal and Child Health (WHO CC)*, IRCCS Burlo coordinates the project and it has over 25 years of experience in coordinating projects in maternal and newborn care in low resources settings, with a focus on projects aiming at improving the quality of hospital care. The WHO CC has supported WHO and other UN agencies in developing assessment tools, indicators, guidelines, manuals, and policies relevant to maternal and newborn care, and has long-term experiences in supporting a wide range of countries in implementing WHO recommendations. More information on products of the WHO CC Trieste can be found at https://www.burlo.trieste.it/content/who-collaborating-centre-maternal-and-child-health.

Partner of EPINICU project is the *World Health Organization Head quarter (WHO HQ) Geneva* which has the mandate within WHO of developing technical guidance, political strategies and supporting country implementation and research. More information on the WHO MNCA Health department can be found at http://www.who.int/maternal_child_adolescent/en/

The study sites were selected based on the following criteria:

- providing care to preterm newborns;
- geographical distribution in three different continents - Africa, Asia, and Latin America;
- large size (over 3000 births/year)
- existing commitment in improving the quality of care in their own facility;
- training site for health professionals, favoring diffusion of good practices;
- leading capacity enabling diffusing good practices to other facilities within the country;
- previous successful collaboration with the World Health Organization Collaborating Centre in Maternal and Child Health (WHO CC) of the Institute of Research in Maternal and Child Health Burlo Garofolo (IRCCS Burlo), Trieste Italy.

The study sites were intentionally selected in order to represent "model case study" of referral hospitals with different characteristics (eg, equipment and supplies, human resources, current practices, patients' empowerment, regulations etc) across different contexts. The multi-country nature of the project aimed at maximizing exchanges of experience and ideas.

1.5 Study population

Mother, fathers and other caregivers of newborns who have been hospitalized in the NICU or semi-intensive care for at least 24 hours (in Brazil) and 48 hours (in Italy and Tanzania), with an age of at least 18 years, able to understand the local language (Portuguese in Brazil, Italian in Italy and Swahili in Tanzania) were approached for inclusion and enrolled prospectively. Data collection times differed from sites due to organizational choices. Parents with previously diagnosed mental disorders or cognitive difficulties, parents of newborns dead at birth or during hospitalization, maternal deaths, and parents not providing consent were excluded.

The same population characteristics will be applied in Sri Lanka though data collection, as previously explained, has not yet started.

1.6 Outcomes, data collection tools and methods

Parental stress, depression, anxiety and parental participation in care were the main outcomes of the study, with parental stress as the primary outcome of the study. Validated questionnaires were used to measure them.

Table 1b. provides an overview of the study outcomes and data collection tools with their main characteristics.

Table 1b. Key characteristics of questionnaires used for data collection of EPINICU outcomes

Outcome	Questionnaire	Number of domains and questions	Period to which questions refer to	Score range	Cut-offs recommended in literature
Stress	PSS:NICU Parental Stressor Scale for NICU	26 questions in 3 domains - Sights and Sounds (6 items) - Infant Behaviour and Appearance (13 items) - Parental Role Alteration (7 items). - A final question about overall stress during NICU hospitalization.	Unspecific	1 to 5 for each question (Total: 1 to 5)	No reference in literature
Depression	EPDS Edinburgh Postnatal Depression Scale	10 questions	Last 7 days	0 to 3 for each question (Total: 0 to 30)	For diagnosis of depression: ≥12 Italy ≥13 Brazil and Tanzania
State Anxiety	STAY Y1 State Anxiety Inventory	20 questions	In the last 24/48 h	1 to 4 for each question (Total 20 to 80)	>40: anxiety. Anxiety level 41-50: mild anxiety 51-60: moderate anxiety >60: severe anxiety
Trait Anxiety	STAY Y2 Trait Anxiety Inventory	20 questions	Unspecific (describe how you generally feel)	1 to 4 for each question (Total 20 to 80)	>40: anxiety. Anxiety level 41-50: mild anxiety 51-60: moderate anxiety >60: severe anxiety
Participation in Care	IPP-NICU Index of Parental Participation	30 questions in 4 domains -Daily Living (6 items) -Providing Comfort (7 items) -Advocating for newborn health (7 items); -Technical Tasks (10 items).	Previous 24 hours	0 to 1 (yes or no) for each question (Total 0 to 30, different maximum	No reference in literature

				scores for each subdomain)	

Specifically, stress was measured with the *Parental Stressor Scale for NICU* (PSS:NICU) (Miles et al., 1993), which is a scale specific to parental stress related to NICU. The scale has been properly validated in Italy (Montirosso et al., 2012) and Brazil (Souza et al., 2012). Studies on the PSS:NICU are lacking from Africa (Caporali et al., 2020), therefore for use in our project in Tanzania the PSS:NICU questionnaire was translated and back translated in Swahili by expert mother tongue researchers, according to The Professional Society for Health Economics and Outcomes Research (ISPOR) guidelines (Wild et al., 2005).

PSS:NICU includes 26 statements divided in three sections: stress due to "Sights and Sounds" (6 items), to "Infant Behaviour and Appearance" (13 items) and to "Parental Role Alteration" (7 items). In PSS:NICU, questions do not refer to a specific time period. Answers for each question are on a Likert scale from 1 point for "not at all stressful", 2 points for "mild stress", 3 points for "fairly moderate stress", 4 points for "very stressful" and 5 points for "extreme/severe stress". Total PSS:NICU scores are calculated according to author instructions (Miles et al., 1993), using two methods: a) the Stress Occurrence Level (SOL) is calculated including only experienced items; b) the Overall Stress Level (OSL) is calculated scoring "not applicable items" with one point. According to author's instructions, SOL should be used when the focus is the parent as it captures better their experience, while OSL when the focus on the NICU environment (Miles et al., 1993).

Parental depression was measured with the *Edinburgh Postnatal Depression Scale (EPDS)*, which is the most widely instrument for screening postnatal depression. It has been validated in many countries, including in Italy in mothers and fathers (Benvenuti et al., 1999; Loscalzo et al., 2015), and Brazil (Santos et al., 2007); it has been translated in Swahili (Kumar et al., 2015)and used in several African countries, including Tanzania (Holm-Larsen et al., 2019; Mbarak et al., 2019; Rogathi et al., 2017; Rwakarema et al., 2015). The scale includes 10 questions which evaluate the emotional state of the last 7 days, with four possible answers each (points ranging from 0 to 3), and a total score ranging from 0 to 30. The cut off values considered more accurate for the diagnosis of depression are: a value >= 12 both for female and males in Italy (Benvenuti et al., 1999; Loscalzo et al., 2015), and a cut off >= 13 in Brazil(Santos et al., 2007) and Tanzania(Holm-Larsen et al., 2019; Mbarak et al., 2019; Rogathi et al., 2017; Rwakarema et al., 2015), although other studies from Africa (Tsai et al., 2013)used a lower cut-off (>= 12).

Anxiety was measured by the *State-Trait Anxiety Inventory (STAI)*, which include two complementary sub-scales: i) the State Anxiety Scale (STAI-Y1) evaluates the current state of anxiety, asking how respondents feel "right now", using 20 items each with a scale from 1 (not symptoms) to 4 (very much so); ii) the Trait Anxiety Scale (STAI-Y2) evaluates "anxiety proneness," by assesses frequency of

feelings “in general”, including general states of calmness, confidence, and security (Spielberger et al., 1983). The Trait Anxiety Scale has been suggested to capture not exclusively trait anxiety but rather a higher-order trait such as negative affectivity/neuroticism that characterizes both anxiety and depression (Knowles & Olatunji, 2020; Spielberger et al., 1983). The STAI has been validated in Italy (Ilardi et al., 2021; Santangelo et al., 2016), Brazil (Delgado et al., 2016; Gorenstein & Andrade, 1996), and widely used in Africa (Redinger et al., 2020; Ukpong & Owolabi, 2004). Each scale includes 20 items with a score ranging each from 1 (almost never) to 4 (almost always), thus for each scale, the total score can range from 20 to 80. Although slightly different cut offs for STAI have been used in literature, in general scores over 40 are considered indicative of anxiety, scores in between 41-50 indicating mild anxiety, 51-60 moderate anxiety and >60 severe anxiety (Barisone et al., 2004; Julian, 2011; Polloni et al., 2021).

Parental participation was measured with the *Index of Parental Participation (IPP)* to pediatric care (Melnyk, 1994), which was previously used in context with low resources (Abdelkader et al., 2016). For the use in the NICU setting, the IPP was adapted by a team of senior neonatologists and epidemiologists, changing few items. This adapted version of the IPP (IPP-NICU) was approved by Dr Melnik, the author of the original instrument (Melnyk, 1994). The IPP-NICU questionnaire was translated and back translated for use in the project in Brazil and Tanzania, following the ISPOR guidelines (Wild et al., 2005). The IPP-NICU includes 4 subdomains: activities related to Daily Living (6 items); Providing Comfort (7 items); Advocating for newborn health (7 items); Technical Tasks (10 items). Questions refers to the previous 24 hours. The total number of items is 30, with a dichotomous (yes/no) answering. The total score ranges from 0 to 30, with different maximum scores for each subdomain, and higher scores indicating higher parental participation in care.

A structured form, developed in dialogue with partners and field tested before use, was utilized to collect key newborns and parental characteristics, according to predefined case-definitions. Data from parents were collected from parents, data on newborns were collected from the patients’ files and from parents.

The questionnaires were self-administered in Italy and Brazil. In Tanzania, due to the high rate of maternal illiteracy, data were collected with an oral interview, carried forward by ad hoc trained researcher not involved in case management or in data analysis. To reduce the burden of data collection the assessment of anxiety (2 questionnaires) was not performed in Tanzania, and performed in a subsample of parents in the other two countries. In Brazil depression, parental state and trait anxiety and participation in care were assessed only in one facility (IMIP), while in the other five hospitals only data on stress were prioritized.

Delays have been experienced by all study sites due to the COVID-19 pandemic between 2020 and 2021. In Sri Lanka, due not only to COVID pandemic but also to its subsequent strains on the hospital services and the severe economic crisis, data collection has not yet started. At the time of writing of this PhD thesis Sri Lanka is starting organizing phase 1 of the EPINICU study.

1.7 Study ethical approval and funding

The study was approved in all countries: in Italy, it was approved by the by the Institutional Review Board of Friuli Venezia Giulia Region (Prot.31633, October 22, 2019); in Tanzania, by the National Institute for Medical Research (Reference Number NIMR/HQ/R.8a/Vol.IX/3295); In Brazil, by the "Comissão Nacional de Ética em Pesquisa" (National Research Ethics Committee) (Number: 3.931.201, CAAE: 17362919.0.0000.5201, 24/03/2020), Fundação Universidade de Pernambuco - UPE (Number: 3.847.757, CAAE 27526919.6.0000.5192, 19/02/2020), Centro Integrado de Saúde Amaury de Medeiros - CISAM/UPE (3.889.399 CAAE 27526919.6.3001.5191 28/02/2020), Empresa Brasileira de Servicos Hospitalares – EBSERH (Hospital das Clínicas da Universidade Federal De Pernambuco - HC/UFPE (Number: 3.905.586 CAAE: 27526919.6.3004.8807, 09/03/2020), Instituto de Medicina Integral Professor Fernando Figueira - IMIP/PE (Number: 3.910.660 CAAE: 27526919.6.3003.5201, 11/03/2020), and Hospital Agamenon Magalhães (Number: 3.949.213, CAAE 27526919.6.3002.5197, 01/04/2020).

The study has been awarded, through a competitive call, a "Chiesi Foundation research grant in Neonatology" in 2019.

2. OBJECTIVES of the PhD

Main focus of my PhD from 2020 until 2023 was the coordination of the project at the Italian site, the reporting of the Italian data while collaborating with the ongoing multicountry project and the contribution to 3 scoping reviews on Infant and Family Centered Developmental Care (IFCDC).

Three were my primary objectives:

2.1 PhD Objective 1: to coordinate and conduct the baseline assessment (Phase 1) in Italy and to contribute in comparing findings across EPINICU countries.

Specific objectives within this 1st objective were:

- To coordinate the data collection, analysis and reporting of the baseline assessment on parental participation in care and mental distress in Italy.
- To compare the data from Phase 1 of EPINICU study from Italy with that from the other countries participating in the study.

2.2 PhD Objective 2: to contribute to formative research.

In particular:

- To actively participate in a set of three scoping reviews of randomized controlled trials (RCTs) on Infant and Family Centered Developmental Care interventions. These scoping reviews had the aim to inform all EPINICU partners in a systematic manner on possible IFCDC interventions and their characteristics, hence being of support for the intervention phase (Phase 2-3) of EPINICU study.

2.3 PhD Objective 3: to coordinate the quality improvement phase in Italy (Phase 2-3) and contribute to a community of good practices

Specific objectives were:

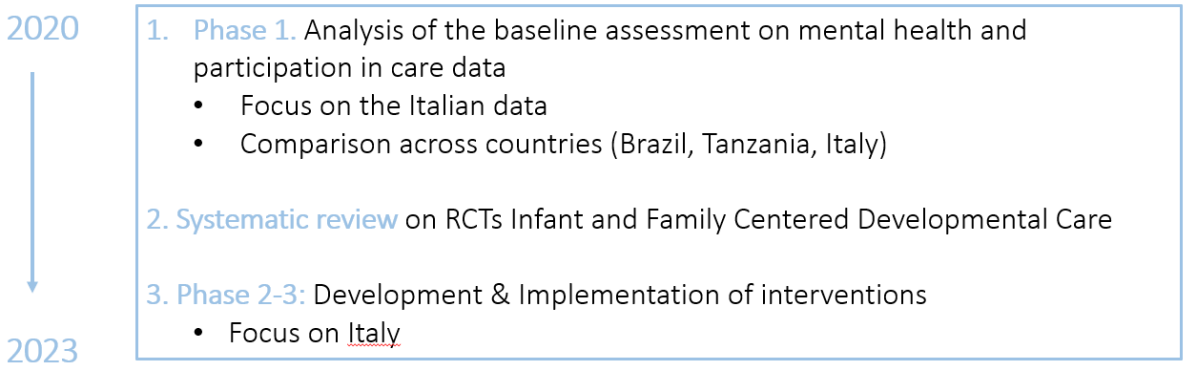
- To disseminate the results from the Italian phase 1 to all the Italian NICU staff in order to inform phase 2-3 of the project
- To coordinate the meetings of phase 2 of EPINICU study in my Unit in order to identify SMART interventions to empower parents in our NICU
- To help with the development of the chosen interventions
- To coordinate phase 3 helping with and coordinating the implementation and maintenance of the chosen interventions.
- To coordinate the monitoring meetings of the EPINICU project in our NICU
- To participate to the EPINICU multicountry meetings in order to contribute to a community of good practices.

3. RESULTS AND ACADEMIC PRODUCTS

Synthesis of overall achievements

During the 3 years of my PhD program starting from 2020 until 2023, and reflecting the above objectives, I achieved the results summarized in **Figure 3a.**

Figure 3a. Overview of my PhD results



Results can be detailed as follows:

1. **Phase 1. Analysis and report of the Italian baseline assessment on parental mental health and participation in care.**

In particular:

- As EPINICU study started just before the COVID-19 pandemic, it became an opportunity to generate evidence exploring study outcomes in Italy over different phases of the COVID-19 pandemic (published paper, detailed in **Results 3.1.1**)
- Italian baseline data was compared to Brazil and Tanzania data (detailed in **Results 3.1.2**)
- As in Italy, a much higher proportion of fathers participated to the baseline assessment, compared to Tanzania and Brazil where study populations included almost only mothers, differences of mental distress and participation in care between mothers and fathers were described (see **Results 3.1.3**)

2. **Formative research. A set of three scoping systematic reviews on RCTs of IFCDC interventions.**

I actively participated in the scoping systematic review process of randomized controlled trials (RCTs) on IFCDC interventions, resulting in 3 scoping reviews describing:

- the general characteristics of the identified RCTs (**Results 3.2.1**);
- the IFCDC interventions tested in RCTs developing a menu of interventions (**Results 3.2.2**);
- the specific outcomes evaluated in the RCTs, their category, the populations in which the outcomes were measured and the specific tools and timings used to measure such outcomes (**Results 3.2.3**).

3. Phase 2-3. Development and implementation of SMART interventions to empower parents in the NICU in Italy (Phase 2-3).

This step was fundamental in starting an important qualitative improvement process in our Unit, which led to several ongoing interventions in our NICU (**Results 3.3**).

Results from objectives 2.1 and 2.2 led to some academic products (scientific articles), detailed in **Table 3a**. One manuscript has been already published (Bua et al., 2021), while the other 5 have been finalized and agreements have been taken to be submitted as a journal supplement.

Table 3a. Academic products

Papers	
1. Parental stress, depression and participation in care before and during the COVID-19 pandemic: a prospective observational study in an Italian Neonatal Intensive Care Unit	Bua et al, 2021
2. Parental stress, depression, anxiety and participation to care in Neonatal Intensive Care Units: multi-country cross-sectional study across different settings	Under submission
3. Parental stress, depression, anxiety and participation in care in an Italian Neonatal Intensive Care Unit: a cross-sectional study comparing mothers versus fathers	Under submission
4. Infant and family's centered developmental care interventions in neonatal intensive and semi-intensive units: a scoping review to identify characteristics of randomised controlled trials	Under submission
5. Interventions to implement infant and family's centered developmental care in neonatal intensive and semi-intensive units: a scoping review of randomised controlled trials	Under submission
6. Outcomes and measurements methods to evaluate infant and family's centered development care interventions in NICUs and semi-intensive newborn units: a scoping review of randomised controlled trials	Under submission

3.1 Results on PhD objective 1: Analysis and report of the baseline assessment data (Phase 1) on parental mental health and participation in care in Italy and in comparison, across EPINICU countries.

3.1.1 Parental stress, depression and participation in care before and during the COVID-19 pandemic: a prospective observational study in an Italian Neonatal Intensive Care Unit

Background

Research has indicated that, in ordinary times, the experience of a neonatal intensive care unit (NICU) hospitalization is a distressing and potentially traumatic event for parents (Roque et al., 2017). During the current COVID-19 pandemic, multiple studies reported increased stress, anxiety, and depression among the general population and women around childbirth (Hessami et al., 2022; Kotlar et al., 2021). Parents of newborns hospitalized in the NICU may be particularly exposed to stressors associated with COVID-19, such as increased worries about newborn health, need for physical distancing, restrictions in NICU visitation, overall reorganization of health services, and reduced social and family support (Hessami et al., 2022; Kotlar et al., 2021; Roque et al., 2017). Family-centered care is essential to mitigating mental distress of NICU parents and improving the health and well-being of their infants, and several authors have called for monitoring and support of NICU parents' well-being during the COVID-19 pandemic (Erdei & Liu, 2020; Lemmon et al., 2020).

No study has explored how the COVID-19 pandemic affected parental stress, depression, and participation in care of their neonates admitted to the NICU. This study aimed at exploring whether, in an Italian NICU, parental stress, depression, and participation in care changed significantly over three time periods: before the pandemic, and during the pandemic and during periods of low and high COVID-19 incidence.

Specific Methods

This was a descriptive cross-sectional study, and the Strengthening the Reporting of Observational Studies (STROBE) in Epidemiology guidelines were applied (Vandenbroucke et al., 2007)

Outcomes of this study were parental stress, depression and participation in care measured by the validated questionnaires, respectively PPS:NICU, EPDS and IPP detailed in section 1.6.

Data were collected over three time periods: pre-pandemic (25th November 2019-1st March 2020, T_0); summertime just after the first Italian wave characterised by low incidence of COVID-19 cases (1st May-31st August 2020, T_1); autumn with high COVID-19 incidence (1st September-30th November 2020, T_2) as documented by the official statics from the Italian National Institute of Health (EpiCentro. Available online at: https://www.epicentro.iss.it/coronavirus/sars-cov-2-sorveglianza-dati). The study was temporarily interrupted at the very beginning of the pandemic and of the Italian lockdown (i.e., between 2nd March to 30th April) as the hospital priority was to react to the emergency and organize specific COVID-19 dedicated paths both for newborns, children and pregnant women, while most research activities were suspended.

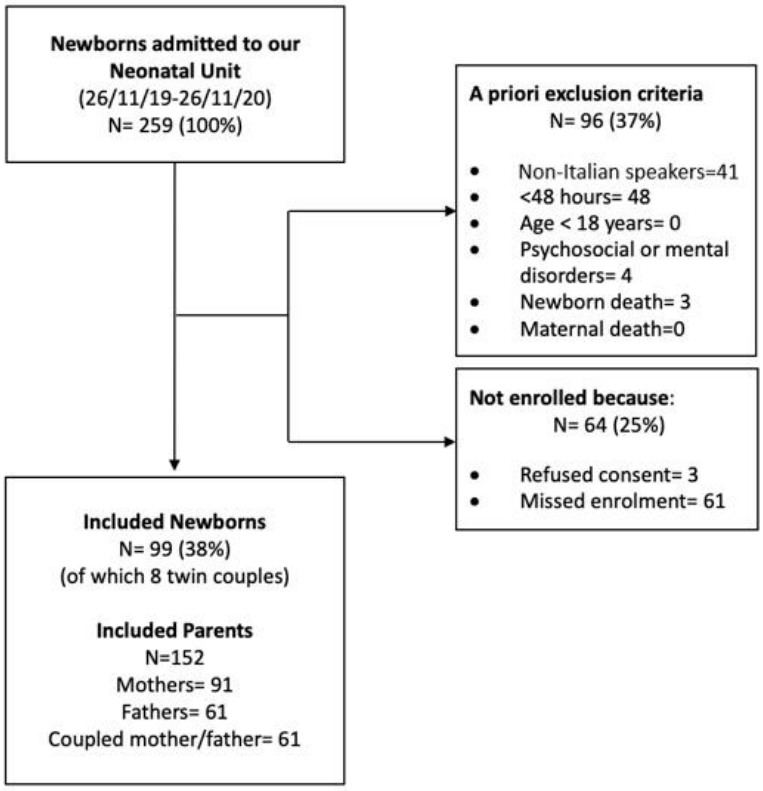
A sample of 108 parents, 34 for each time period, was estimated to be adequate to detect a difference in PSS:NICU stress occurrence level score (SOL; see below for definition) of 1.25 points between time periods, deemed to be clinically relevant and assuming an overall type I error of 0.05, 99% power and a conservative standard deviation of 1 (Miles et al., 1993) and using a Wilcoxon-Mann Whitney test.

Due to deviation from parametric model assumptions, to estimate score differences among periods a non-parametric analysis was performed using the Kruskal-Wallis test. Bonferroni adjusted p-values were calculated for multiple comparisons among time periods tested with the Wilcoxon-Mann Whitney. A subgroup analysis by periods was performed to evaluate whether parental outcomes differed according to unit of admission of their newborn (NICU vs semi-intensive) using a Wilcoxon-Mann Whitney test. Correlation between scores was analysed using Spearman rank correlation coefficients.

Results

Of the 259 newborns admitted to our Neonatal Unit during the study period (26/11/2019 – 26/11/2020), 96 (37%) were excluded as they did not meet the inclusion criteria. Parents of 64 (25%) newborns refused to participate (3/64) or were not approached for enrolment (61/64). Overall, we included 152 parents (91 mothers, 61 fathers) (Fig. 3.1.1a).

Figure 3.1.1a Flow chart of newborns enrolled in the study.



Newborns of included parents (N=99) did not differ from those whose parents were not enrolled (N=64) except for having a lower birthweight (2450.0 [1890.0, 3260.0] g vs 2880.0 [2385.0, 3535.0] g, p=0.004), a longer length of stay (14.0 [8.0, 23.5] days vs 5.0 [4.0, 11.0], p<0.001) and higher frequency of ventilation at birth (21.2% vs 4.7%, p=0.003).

Parental (Table 3.1.1a) and newborn (Table 3.1.1b) characteristics did not differ significantly between the parents' groups in the three study periods, except for a higher percentage of female babies (T_0 50%, T_1 46.2%, T_2 80%, p=0.034), and of infants admitted to the NICU compared to the semi-intensive unit in T_2 (T_0 15%, T_1 46.2%, T_2 60%, p=0.001) (Table 3.1.1b).

Table 3.1.1a Parents' characteristics during three COVID-19 pandemic periods.

	Overall *n (%)*	Pre-pandemic (T_0) *n (%)*	Low COVID-19 incidence (T_1) *n (%)*	High COVID-19 incidence (T_2) *n (%)*	*p-value*
N	152	62	56	34	
Age *Median [IQR]*	35.0 [31.0, 39.0]	35.0 [32.0, 39.0]	35.0 [30.0, 40.0]	34.0 [29.8, 38.0]	0.581
Role					
Father	61 (40.1)	25 (40.3)	21 (37.5)	15 (44.1)	0.824
Mother	91 (59.9)	37 (59.7)	35 (62.5)	19 (55.9)	0.824
Education					
Lower secondary	24 (15.8)	11 (17.7)	8 (14.3)	5 (14.7)	0.845
Upper secondary	65 (42.8)	25 (40.3)	23 (41.1)	17 (50.0)	0.670
Higher	61 (40.1)	24 (38.7)	25 (44.6)	12 (35.3)	0.675
Working status					
Working	129 (84.9)	51 (82.3)	48 (85.7)	30 (88.2)	0.709
Un-employed	19 (12.5)	9 (14.5)	7 (12.5)	3 (8.8)	0.737
Missing	4 (2.6)	2 (3.2)	1 (1.8)	1 (2.9)	1.000
Marital status					
Married	67 (44.1)	27 (43.5)	29 (51.8)	11 (32.4)	0.197
Un-married	85 (55.9)	35 (56.5)	27 (48.2)	23 (67.6)	0.197
Parity (recorded only for mothers)					
1	50 (32.9)	21 (33.9)	18 (32.1)	11 (32.4)	0.924
2	26 (17.1)	13 (21.0)	10 (17.9)	3 (8.8)	0.330
>2	14 (9.2)	3 (4.8)	6 (10.7)	5 (14.7)	0.167
Missing	1 (0.7)	0 (0.0)	1 (1.8)	0 (0.0)	0.593

Table 3.1.1b Newborns' characteristics during three COVID-19 pandemic periods.

	Overall n (%)	Pre-pandemic (T_0) n (%)	Low COVID-19 incidence (T_1) n (%)	High COVID-19 incidence (T_2) n (%)	*p-value*
N	99	40	39	20	
Sex					
Female	54 (54.5)	20 (50.0)	18 (46.2)	16 (80.0)	0.034
Male	45 (45.5)	20 (50.0)	21 (53.8)	4 (20.0)	0.034
Gestational age, weeks					
<=27	3 (3.0)	1 (2.5)	1 (2.6)	1 (5.0)	1.000
28-33	14 (14.1)	6 (15.0)	7 (17.9)	1 (5.0)	0.424
34-36	43 (43.4)	20 (50.0)	14 (35.9)	9 (45.0)	0.444
37-41	39 (39.4)	13 (32.5)	17 (43.6)	9 (45.0)	0.510
Unit of admission					
NICU	36 (36.4)	6 (15.0)	18 (46.2)	12 (60.0)	0.001
Semi-intensive care	63 (63.6)	34 (85.0)	21 (53.8)	8 (40.0)	0.001
Length of stay, days (Median [IQR])	14.0 [8.0, 23.5]	15.0 [9.0, 28.5]	14.0 [8.0, 23.5]	9.0 [6.5, 18.8]	0.327
Birthweight, grams	2450.0 [1890.0, 3260.0]	2294.5 [1731.0, 3242.5]	2320.0 [2057.5, 3333.5]	2944.5 [2437.5, 3289.8]	0.253
Birthweight					
<1000 g	5 (5.1)	2 (5.0)	2 (5.1)	1 (5.0)	1.000
1000-1499 g	8 (8.1)	4 (10.0)	4 (10.3)	0 (0.0)	0.355
1500-2499 g	38 (38.4)	18 (45.0)	15 (38.5)	5 (25.0)	0.339
≥2500 g	48 (48.5)	16 (40.0)	18 (46.2)	14 (70.0)	0.084
Weight at discharge, grams (Median [IQR])	2700.0 [2240.0, 3380.0]	2465.0 [2100.0, 3290.0]	2670.0 [2370.0, 3410.0]	3120.0 [2685.0, 3462.5]	0.083
Outborn	21 (21.2)	8 (20.0)	10 (25.6)	3 (15.0)	0.624
Apgar at 5 min <7	2 (2.0)	0 (0.0)	1 (2.6)	1 (5.0)	0.686
Ventilation at birth	21 (21.2)	10 (25.0)	8 (20.5)	3 (15.0)	0.697
Intubation	14 (14.1)	7 (17.5)	4 (10.3)	3 (15.0)	0.654
RDS	12 (12.1)	6 (15.0)	5 (12.8)	1 (5.0)	0.664
Any respiratory distress	45 (45.5)	21 (52.5)	19 (48.7)	5 (25.0)	0.117
Sepsis	11 (11.1)	7 (17.5)	2 (5.1)	2 (10.0)	0.243
Neurological event*	2 (2.0)	1 (2.5)	1 (2.6)	0 (0.0)	1.000
Major birth trauma**	1 (1.0)	1 (2.5)	0 (0.0)	0 (0.0)	1.000
Major malformation***	7 (7.1)	4 (10.0)	2 (5.1)	1 (5.0)	0.785

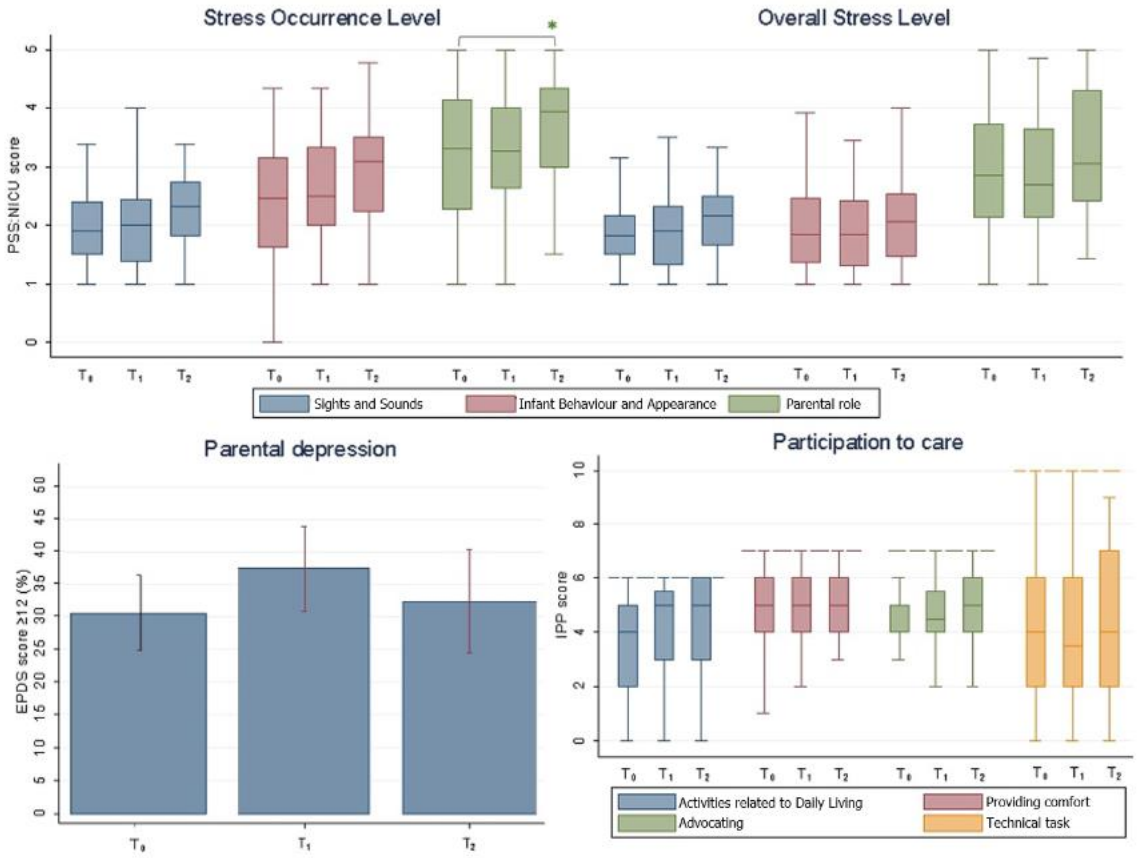
*Defined as convulsions, intraventricular haemorrhage, periventricular leukomalacia.
**Defined as fractured clavicle or humerus or fracture at any other site; brachial plexus paralysis and subgaleal hematoma.
***Defined for head and craniofacial structures: Anencephaly, encephalocele, holoprosencephaly, hydrocephaly, microphthalmia, anophthalmia, colobomas, microtia, cleft lip, cleft palate, severe micrognathia, macro and macroglossia. Neck: cystic hygroma. Chest: pectus excavatum, absent or hypoplastic clavicles. Back: meningomyelocele, spina bifida. Abdomen: omphalocele, gastroschisis. Genitalia: ambiguous genitalia. Extremities: absent or limb deficiencies, polydactyly, complete syndactyly, polysyndactyly, absent digits, ectrodactyly. Cardiovascular and great vessels: tetralogy of Fallot, truncus arteriosus, hypoplastic left heart, ventricular or atrial septal defect, transposition of the great vessels, interrupted aortic arch type B, total anomaly of pulmonary venous return, hypoplasia or coarctation of the aorta.
Abbreviations: IQR, interquartile range; RDS, respiratory distress syndrome.

Overall, moderate to high levels of stress (median PSS:NICU=3 [3.0-4.0]) were observed in our population, with 34% of parents scoring ≥ 12 at EPDS (**Table 3.1.1c**). No significant differences in the percentage of EPDS ≥12 and in median PSS:NICU and IPP scores were observed in the three periods (Fig. 3.1.1b), with the exception of a slight increase in the PSS:NICU parental role sub-score in T_2, when the score was calculated as SOL (T_0 3.3 [2.3-4.1] vs T_2 3.9 [3.1-4.3], adjusted p=0.038) (**Table 3.1.1c**). Difference in median PSS:NICU score was due to a single question measuring stress related to separation from the newborn (T_0 4.0 [4.0-5.0] vs T_2 5.0 [4.0-5.0], p=0.008) (**Table 3.1.1d**).

Table 3.1.1c PSS-NICU, EPDS and IPP median scores in three COVID-19 pandemic periods.

	Overall *Median [IQR]*	Pre-pandemic (T_0) *Median [IQR]*	Low COVID-19 incidence (T_1) *Median [IQR]*	High COVID-19 incidence (T_2) *Median [IQR]*	*p-value*	Multiple comparisons *Adjusted p value*		
						T_0-T_1	T_0-T_2	T_1-T_2
PSS: NICU	N=152	N=62	N=56	N=34				
SOL								
Sights and sounds	2.0 [1.5, 2.6]	1.9 [1.5, 2.4]	2.0 [1.4, 2.4]	2.3 [1.8, 2.7]	0.083	1.00	0.132	0.147
Treatments	2.6 [1.9, 3.4]	2.5 [1.6, 3.2]	2.5 [2.0, 3.3]	3.1 [2.3, 3.5]	0.142	0.818	0.201	0.692
Parental role	3.5 [2.6, 4.1]	3.3 [2.3, 4.1]	3.3 [2.7, 4.0]	3.9 [3.1, 4.3]	**0.028**	1.00	**0.038**	0.083
Total score	8.2 [6.4, 9.8]	7.5 [5.6, 9.3]	7.7 [6.5, 9.3]	9.4 [7.3, 10.2]	**0.031**	1.00	**0.037**	0.100
OSL								
Sights and sounds	1.9 [1.5, 2.3]	1.8 [1.5, 2.2]	1.9 [1.3, 2.3]	2.2 [1.7, 2.5]	0.132	1.00	0.202	0.232
Treatments	1.9 [1.4, 2.5]	1.8 [1.4, 2.4]	1.8 [1.3, 2.4]	2.1 [1.5, 2.5]	0.467	1.00	1.00	0.720
Parental role	2.9 [2.1, 3.7]	2.9 [2.1, 3.7]	2.7 [2.1, 3.6]	3.1 [2.5, 4.2]	0.141	1.00	0.241	0.210
Total score	6.9 [5.4, 8.5]	6.7 [5.2, 8.2]	6.6 [5.2, 8.3]	7.2 [5.9, 8.8]	0.165	1.00	0.357	0.185
Final PSS:NICU question on overall stress	3.0 [3.0, 4.0]	3.0 [2.2, 4.0]	3.0 [3.0, 4.0]	3.0 [2.2, 4.0]	0.831	1.00	1.00	1.00
EPDS	N=150	N=60	N=56	N=34				
Total score	9.0 [5.2, 13.0]	8.0 [4.8, 13.0]	8.5 [6.0, 13.2]	9.0 [6.0, 12.8]	0.615	1.00	1.00	1.00
score ≥12, *n (%)*	51 (34.0)	19 (31.7)	21 (37.5)	11 (32.4)	0.782	1.00	1.00	1.00
IPP	N=152	N=62	N=56	N=34				
Activities related to daily living	4.0 [3.0, 5.2]	4.0 [2.0, 5.0]	5.0 [3.0, 5.2]	5.0 [3.0, 5.8]	0.421	0.616	1.00	1.00
Providing comfort	5.0 [4.0, 6.0]	5.0 [4.0, 6.0]	5.0 [4.0, 6.0]	5.0 [4.0, 5.8]	0.631	1.00	1.00	1.00
Advocating	5.0 [4.0, 5.2]	5.0 [4.0, 5.0]	4.5 [4.0, 5.2]	5.0 [4.0, 6.0]	0.878	1.00	1.00	1.00
Technical task	4.0 [2.0, 6.0]	4.0 [2.0, 6.0]	3.5 [2.0, 6.0]	4.0 [2.0, 6.8]	0.806	1.00	1.00	1.00
Total score	18.0 [14.0, 21.2]	18.0 [15.0, 21.8]	18.0 [15.0, 21.2]	18.0 [13.2, 21.0]	0.957	1.00	1.00	1.00

Figure 3.1.1b Stress (PSS:NICU), depression (EPDS) and participation in care (IPP) during three COVID-19 pandemic periods.



IPP and EPDS total scores did not differ between the three periods (Table 3.1.1c). Increased parental participation in care was observed in T_2 for two specific aspects regarding the change of clothes and diapers (Table 3.1.1e).

Table 3.1.1d Median (IQR) scores for each specific PSS:NICU (Parental Stressor Scale in the NICU) answer in three COVID-19 pandemic periods.

	Overall	Pre-pandemic (T_0)	Low COVID-19 incidence (T_1)	High COVID-19 incidence (T_2)	*p-value*
N	152	62	56	34	
Presence of monitors and equipment	2.0 [1.0, 3.0]	2.0 [1.0, 3.0]	2.0 [1.0, 3.0]	2.0 [2.0, 3.0]	0.102
Constant noises of monitors and equipments	2.0 [2.0, 3.0]	2.0 [1.2, 3.0]	2.0 [1.0, 3.0]	2.0 [2.0, 3.0]	0.954
Sudden noises of monitor alarms	3.0 [2.0, 4.0]	3.0 [2.0, 3.8]	3.0 [2.0, 4.0]	3.0 [2.0, 4.0]	0.461
Other sick babies in the room	1.0 [1.0, 2.0]	1.0 [1.0, 2.0]	1.0 [1.0, 2.0]	1.0 [1.0, 2.8]	0.313
Large number of nurses and doctors in NICU	1.0 [1.0, 1.0]	1.0 [1.0, 1.0]	1.0 [1.0, 1.0]	1.0 [1.0, 1.0]	0.558
Having a ventilator to breathe for baby	1.0 [0.0, 2.0]	1.0 [0.0, 2.8]	1.0 [0.0, 2.0]	0.0 [0.0, 2.0]	0.403
Tubes and equipments on or near my baby	2.0 [1.0, 3.0]	2.0 [1.2, 3.0]	2.0 [1.0, 3.0]	2.0 [1.0, 3.8]	0.972
Bruises, cuts or incisions on my baby's body	1.0 [0.0, 3.0]	1.0 [0.0, 2.0]	0.0 [0.0, 3.0]	1.0 [0.0, 3.8]	0.771
Unusual color of my baby	1.0 [0.0, 3.0]	1.0 [0.0, 2.0]	1.0 [0.0, 2.2]	0.0 [0.0, 3.0]	0.891
Unusual or abnormal breathing patterns of my baby	1.0 [0.0, 3.2]	1.0 [0.0, 3.0]	1.0 [0.0, 3.0]	1.5 [0.0, 4.0]	0.405
Small size of my baby	1.0 [0.0, 2.0]	2.0 [0.0, 3.0]	0.5 [0.0, 2.0]	1.0 [0.0, 2.0]	0.072
Wrinkled appearance of my baby	0.0 [0.0, 1.0]	1.0 [0.0, 1.0]	0.0 [0.0, 1.0]	0.5 [0.0, 1.0]	0.189
Seeing needles and tubes being put on my baby	3.0 [1.0, 4.0]	3.0 [2.0, 4.0]	2.0 [0.0, 3.0]	3.0 [1.0, 4.0]	0.168
Baby fed by tube or intravenous line	2.0 [0.0, 3.0]	2.0 [2.0, 3.0]	2.0 [0.0, 4.0]	2.0 [0.0, 3.8]	0.975
Seeing my baby in pain	3.0 [0.0, 4.0]	2.0 [0.0, 4.0]	2.0 [0.0, 3.0]	3.5 [0.2, 4.0]	0.091
Seeing my baby to be sad	1.0 [0.0, 3.0]	2.0 [0.0, 3.0]	0.0 [0.0, 3.0]	1.0 [0.0, 4.0]	0.554
The limp or weak appearance of my baby	1.0 [0.0, 2.2]	2.0 [0.0, 2.8]	0.0 [0.0, 2.0]	1.0 [0.0, 3.0]	0.171
Jerky movements of my baby	2.0 [0.8, 3.0]	1.5 [0.2, 3.0]	2.0 [0.0, 3.0]	1.5 [1.0, 3.0]	0.805
Baby not crying like other babies	0.0 [0.0, 0.2]	0.0 [0.0, 0.0]	0.0 [0.0, 1.0]	0.0 [0.0, 0.0]	0.925
Being separated from my baby *	4.0 [3.0, 5.0]	4.0 [3.0, 5.0]	4.0 [4.0, 5.0]	5.0 [4.0, 5.0]	**0.008**
Not feeding my baby myself	2.0 [1.0, 4.0]	2.0 [1.0, 4.0]	2.0 [0.8, 4.0]	3.0 [1.0, 4.0]	0.395
Not being able to care for my baby myself	2.0 [0.0, 3.0]	2.0 [1.0, 3.0]	2.0 [0.0, 3.0]	2.5 [0.0, 4.0]	0.281

Not being able to hold my baby when I want	3.0 [2.0, 4.0]	3.0 [1.0, 4.0]	3.0 [2.0, 4.0]	4.0 [2.2, 5.0]	0.234
Feeling helpless and unable to protect my baby from painful procedures	3.0 [1.0, 5.0]	3.0 [1.0, 5.0]	3.0 [0.8, 5.0]	4.0 [2.0, 5.0]	0.691
Feeling helpless about how to help my baby during this time	4.0 [2.0, 4.2]	3.0 [1.2, 4.8]	3.0 [2.0, 4.0]	4.0 [3.0, 4.8]	0.345
Not having time to be alone with my baby	2.0 [0.0, 3.0]	2.0 [0.0, 3.0]	2.0 [1.0, 3.0]	3.0 [1.2, 3.8]	0.134

Table 3.1.1e Frequencies of IPP (Index of Parental Participation) positive answers in three COVID-19 pandemic periods.

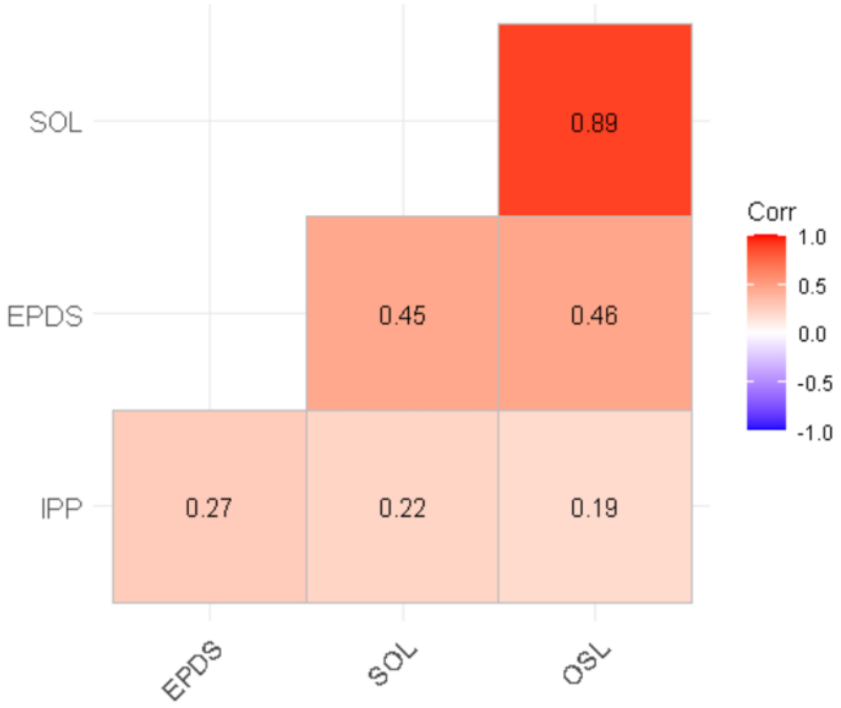
	Pre-pandemic (T_0)		Low COVID-19 incidence (T_1)		High COVID-19 incidence (T_2)		*p-value*
	N=62		N=56		N=34		
IPP question	Yes	%	Yes	%	Yes	%	
Activities related to daily living							
Fed the baby with breast milk	38	61.3	42	75.0	25	73.5	0.19
Fed the baby with formula milk	30	48.4	27	48.2	16	47.1	0.96
Changed clothes	**26**	**41.9**	**35**	**62.5**	**21**	**61.8**	**0.048**
Changes nappies	**41**	**66.1**	**49**	**87.5**	**25**	**73.5**	**0.025**
Helped with cleaning	46	74.2	39	69.6	24	70.6	0.849
Settled for sleep or nap	55	88.7	48	85.7	30	88.2	0.877
Providing confort							
Comforted baby when upset	50	80.6	54	96.4	29	85.3	0.066
Comforted baby during a painful procedure	20	32.3	14	25.0	13	38.2	0.381
Spent quiet time interacting with baby	57	91.9	54	96.4	33	97.1	0.435
Stroked baby/rubbed back	60	96.8	55	98.2	34	100.0	0.55
Talked to the baby	61	98.4	56	100.0	33	97.1	0.477
Skin to skin contact with the baby for at least 1 hour	32	51.6	29	51.8	15	44.1	0.738
Any form of play	17	27.4	21	37.5	9	26.5	0.365
Advocating							
Asked physician for baby's condition	58	93.5	54	96.4	29	85.3	0.292
Asked nurses for baby's condition	60	96.8	56	100.0	31	91.2	0.213
Asked staff about provided baby's care	60	96.8	48	85.7	29	85.3	0.138
Asked staff to explain something that you did not understand	42	67.7	39	69.6	29	85.3	0.087

Told staff about something your baby needed	43	69.4	30	53.6	21	61.8	0.253
Told staff about what your baby like/dislike of the daily routine	16	25.8	18	32.1	10	29.4	0.741
Suggested to the staff a different way or time for doing something that you thought would be better for your baby	9	14.5	11	19.6	9	26.5	0.321
Technical tasks							
Helped the baby feeding with nasogatric tube or by cup	35	56.5	33	58.9	21	61.8	0.734
Changed position to the baby	41	66.1	41	73.2	20	58.8	0.449
Helped nurses to give oral medications	14	22.6	8	14.3	5	14.7	0.451
Helped nurse in doing other procedures	29	46.8	16	28.6	12	35.3	0.123
Kept track of the baby intake (feeding and fluids) and tell the nurse	27	43.5	29	51.8	16	47.1	0.717
Kept track of how often the baby urinates and tell the nurse	19	30.6	18	32.1	13	38.2	0.7
Kept track of how often the baby defecates and tell the nurse	27	43.5	21	37.5	14	41.2	0.832
Kept track if the baby had regurgitation/vomiting and tell the nurse	26	41.9	19	33.9	19	55.9	0.092
Helped detecting changes in color of your baby, respiratory patter, body temperature	21	33.9	18	32.1	13	38.2	0.721
Helped detecting changes tone, movements, reactions, sleep/awake cycles	22	35.5	17	30.4	12	35.3	0.767

The subgroup analysis showed that in the three analysed periods there were no significant differences in parental PSS:NICU, EPDS and IPP scores according to unit of admission (data not shown).

The correlation between participation and stress score (r=0.19-022), and between participation and depression scores (r=0.27) were weak, while among depression and stress, a moderate positive correlation was found (r=0.45-0.48) (Figure 3.1.1c)

Figure 3.1.1c Correlation between IPP, EPDS and PSS:NICU SOL and OSL scores.



Discussion and conclusions

In our study, we found that parental stress, an EPDS value ≥12, and participation in care in an Italian NICU did not change significantly during the COVID-19 pandemic when compared with the period immediately before.

It is well documented that NICU parents are at increased risk of stress and depression (Roque et al., 2017). Studies are difficult to compare as they use different cut-off values for the same mental health scale, they include different populations (mothers and/or fathers) and explore parental wellbeing at different times during hospitalization (Alkozei et al., 2014; Caporali et al., 2020; Pace et al., 2016). Nonetheless, the rates of stress and depressive symptoms in our study resulted to be in line with the existent literature. A recent longitudinal study in parents of infants with lower gestational age at birth (<30 weeks) than our population showed that up to 40-50% had depressive symptoms, and, although rates decreased with time, they still remained above expected levels even after 12 weeks from admission (Pace et al., 2016). Alkozei reported that few days after NICU admission, mothers of preterm babies reported rates of stress comparable to those reported by our parents (mean PSS:NICU stress score: 2.99±0.85), while 38% of them had an EPDS ≥ 10 (Alkozei et al., 2014). As previously reported (Caporali et al., 2020), we found that parental stress was consistently higher in the domain of the parental role (Fig. 1). A recent meta-analysis on PSS:NICU confirmed that across different countries, the parental role is the greatest source of stress for both mothers and fathers in the NICU, while perceived stress seems to be independent from neonatal and clinical characteristics (Caporali et al., 2020).

There are no data in the literature to compare our findings on parental participation in care in the NICU. According to the IPP scoring system, parental participation resulted to be medium-to-high in our study, and it was higher for activities related to daily living, comfort provision and advocacy rather than technical tasks, which in our NICU setting are usually carried out by nurses (Table 3.1.1e).

In our study we did not find changes in parental stress, depression, or participation in care during the COVID-19 pandemic. A lot of concern has been raised recently because the added burden of the COVID-19 pandemic may negatively impact the already vulnerable psychosocial health of NICU families (Erdei & Liu, 2020; Lemmon et al., 2020). A cross-sectional survey of 277 NICUs mostly from the USA highlighted profound restrictions in NICU visitation practices, such as a significant decrease in 24-hours parental presence, and in parental participation in clinical rounds (Darcy Mahoney et al., 2020).

During the study period, visiting restrictions were applied but other organisational changes were enacted to mitigate the impact of these restrictions on families. Starting from T_1, universal SARSCoV-2 testing with nasopharyngeal swabs and quantitative polymerase chain reaction tests was introduced for parents every 2 weeks and, since September 2020, every week. Despite visits were restricted to one parent per baby at the time, parents were allowed to enter as frequently and as long as they liked for a maximum of 2 per room in the semi-intensive unit. There was neither a decrease in the psychological support (two psychologists) nor in the medical and nursing staff. Psychologists were present in our NICU from Monday to Saturday and offered parental support also outside the unit by phone, as they did before COVID pandemic. During T_1 and T_2, all NICU staff had to wear a facial mask (surgical or FFP2), environmental cleaning procedures were intensified but no other major changes in care occurred. When parents were not present, daily updates on the baby's clinical condition were provided through video-calls by unit psychologists or the director. Recently telehealth has been advocated as a potential low-cost strategy in order to keep patients and providers safe, while emphasizing family-centered care (Gaulton et al., 2020).

All these aspects may have contributed in our NICU to ensure constant parental participation in care and stabilize stress and depressive symptoms, although our study was not designed as an intervention study to test this hypothesis.

We did observe higher SOL stress scores during T_2, with separation from the baby deemed as the most stressful aspect. The higher percentage of babies in the NICU in T_2 did not account for this difference. This result may well reflect a real difficulty related to the pandemic. As suggested by other authors (Bembich et al., 2021; Cena et al., 2021), the uncertainty feelings due to the pandemic may have boosted the emotional distress due to the separation from the baby. More so, as only one parent per baby at the time was allowed, the absence of the partner support during the NICU visits may have contributed to increase this feeling (Bembich et al., 2021).

When exploring the correlation between scores, we found weak to moderate positive correlations between them. Evidence from RCTs showed that increased parental participation in care can reduce

parental distress(Melnyk et al., 2006; O'Brien et al., 2018) . However, our study was not conceived as an interventional or longitudinal study. Data were collected cross-sectionally, hence we do not know whether and how participation affected stress/depression at different time points. It may have occurred that parents showing higher stress were invited to participate more in the care of their baby and in our study, we found that in T_2, when Parental Role SOL was significantly higher, there was a significant increase in changing clothes and diapers when compared to T_0. However, the IPP questionnaire may not capture some aspects of the quality of parental participation in care, although it contains several items on relationship with staff and advocacy (Melnyk, 1994). Finally, depression and self-perception of stress can have many other underlying causes, such as personality traits, history of depression and reported substance abuse (Roque et al., 2017) which were not investigated in our study.

Limitations of this study include that it was not designed to test any specific intervention, nor to look specifically at the associations between parental characteristics, participation in care, stress, and depression. Gender differences in stress and depression in NICU parents are reported(Caporali et al., 2020; Roque et al., 2017) but our sample size did not allow us to stratify data further. Sociodemographic characteristics of included parents could not be directly compared with those of not enrolled ones, as these data are not registered in the neonatal clinical records. However, newborns of included parents needed more intensive and longer clinical care than those of not enrolled parents, hence underestimating stress in our study population seems unlikely. We acknowledged the lack of data related to the start of the pandemic (ie, 2nd March-30th April), however we believe this does not affect our findings related to T_2, as it was a period characterised by a higher COVID-19 incidence.
Findings of our study cannot be directly generalized to other NICUs. More investigations on parental participation in care, in parallel with parental stress, anxiety and depression in different settings and over time, shall further contribute to generate evidence on this often-neglected topic.

Further studies are also needed to evaluate specific interventions to mitigate the additional psychological burden of COVID-19, such as telematic approaches including telephone helplines, video calls, video tutorials and conferencing to see the hospitalized baby and to communicate with NICU staff (Cena et al., 2021; Gaulton et al., 2020).

Compared to other existing evidence, our study suggests that stress and depression levels of parents with infants admitted to NICU may remain unchanged even during peaks of the COVID-19 pandemic, and that parental participation in care can be maintained in these settings.

This first study, detailed in 3.1.1, has been already published (Bua et al, 2021). (Annex 6.1)

3.1.2 Parental stress, depression, anxiety and participation in care in Neonatal Intensive Care Units: a multi-country cross-sectional study across different settings

Background

Ensuring that all newborns receive the best care in NICU is critically important, and is recognized as a key aspect of human rights. Over the last decades, there has been increasing awareness on the importance of quality of care provided in NICU, as well as on the stressful nature of the NICU environment, both for infants and for parents (Caporali et al., 2020; Roque et al., 2017; Staver et al., 2021)).

A recent systematic review, including 53 studies, underscored that a high frequency of parental stress related to NICU admission has been documented by all studies exploring this topic, independently from timing of hospitalisation or newborn characteristics, and with parental role alteration being the greatest source of stress (Caporali et al., 2020). However, the review highlighted that very few studies have been conducted in Asia and South America, and none in Africa (Caporali et al., 2020).

Other reviews (Roque et al., 2017; Staver et al., 2021) looking at a wider range of mental health conditions- including depression, anxiety and others- in parents of newborns in NICU, suggested a high frequency of these conditions, across diverse ethnocultural groups and countries (Roque et al., 2017; Staver et al., 2021). However, again, several gaps in existing evidence were noted, such as: inconsistency in the use of measurement instruments and timing of measurement; lack of data on fathers (most studies included only mothers); availability of variables, such as parents' and newborns' characteristics, to identify high risk subgroups (Baldoni et al., 2021; Roque et al., 2017; Staver et al., 2021). Although in the very recent years a routine screening of mood and anxiety disorders for parents of newborn in NICU has been proposed by several authors (Baldoni et al., 2021; Caporali et al., 2020; Roque et al., 2017; Staver et al., 2021), yet this is not a reality in most settings, limiting staff awareness on the problem, as well as actions to mitigate mental distress in parents of newborn in NICU.

Similarly, although parents' participation in care has been recognised as one of the core pillars of family centred care and its benefit for parental and newborn health – including newborn weight gain, breastfeeding rate, decreasing length of stay and parental stress and anxiety- have been documented by several randomised controlled studied (RCTs) (Committee On Hospital Care and Institute For Patient- And Family-Centered Care, 2012; Gooding et al., 2011; Harrison, 1993; North et al., 2022), yet in most NICU settings parental participation in care is not actively promoted nor implemented. In high-income countries, programs such as the Newborn Individualized Developmental Care and Assessment Program (NIDCAP) (http://nidcap.org/en/) and the Creating Opportunities for Parents Empowerment (COPE) promote an individualized, relationship-based, family-integrated model of care, by teaching to parents how to interact with their preterm infant (http://www.copeforhope.com/nicu.php). However, both NIDCAP and COPE imply quite expensive and long individual training courses, which may be difficult to access for most professionals both in low and in high income countries. Little is known on the level of parents' participation in newborn care in many NICU settings, especially in low- and middle-income countries. Moreover, evidence is lacking on how, in different settings, different levels of participation in care correlates with different

levels of mental distress. A better understanding of the level of parents' participation in newborn care in countries with low income, when compared to countries with middle- and high-income, as well its correlation with mental health, would benefit both policy makers, health professionals, and researchers at different levels, and shall help identifying locally tailored approaches to improve mental health and wellbeing of parent of newborns in NICU.

This study, based on the baseline assessment data (Phase 1) of EPINICU study, aimed at documenting three mental health conditions- NICU related stress, depression and anxiety (both state and trait)- along with participation in newborn care, among parents of newborns in three different NICU settings: high-income (Italy), upper middle-income (Brazil) and low-income (Tanzania), to identify key differences and communalities. We also explored the association between NICU related parental stress, depression, anxiety- and other variables describing newborns and parental characteristics.

Methods

A sample of 166 parents was needed for each country based on an estimated prevalence of stress in parents of newborns in NICU, based on existing literature (Caporali et al., 2020; Roque et al., 2017; Staver et al., 2021) , of 50%±10%, with a confidence level of 99%

Outcomes and outcome cut-offs have been already detailed in section 1.6.
Data collection in Tanzania it started in Dec 2019 and ended in August 2020. In Italy it started in November 2019 to February 2020, and from May 2020 to November 2020. In Brazil it started in May 2020 and ended in December 2021. Since 2022 in all the 3 countries above, the intervention phase started with the implementation of local interventions.
As in Tanzania STAI was not used, we compared anxiety in the 3 countries by considering the EPDS-Anxiety subscale (EPDS-A) which allows to identify individuals with high anxiety with a subset of 3 questions from the EPDS (Brien et al., 2019).

For calculating frequencies of all conditions, we used as a sample the subgroup of parents for whom all the scores of interests were available. To analyses overlap between groups of parents identified with different conditions, the SOL score was used for stress, while both the STAI state and the EPDS-A scores were used for anxiety.

Additionally, we conducted univariate and multivariate logistic regression models for each country, considering the presence of mental health conditions under analysis as binary outcome variables and demographic (i.e., for parents: age, marital status, residence, financial situation, working status, role, education; for newborns: sex, twin) and clinical characteristics (i.e, for parents: stress, depression, anxiety, participation; for newborns: gestational age, weight at birth, malformation, surgery, intubation, COVID-19, length of stay, unit of stay) of parents and newborns as explanatory variables. For these analyses, we used the same cut-off used as for the descriptive analysis. Frequencies, odds ratios (OR) and adjusted odds ratios (adjOR) were calculated, with 95% confidence intervals (CI) and p-values of significance. For the analyses on the Brazilian sample, different models were calculated

considering the total Brazilian sample (327 parents) and the subsample of parents for whom all scores were available (106 parents). For the present thesis, only multivariate analyses from Italy will be presented as the analyses from the other countries are being finished.

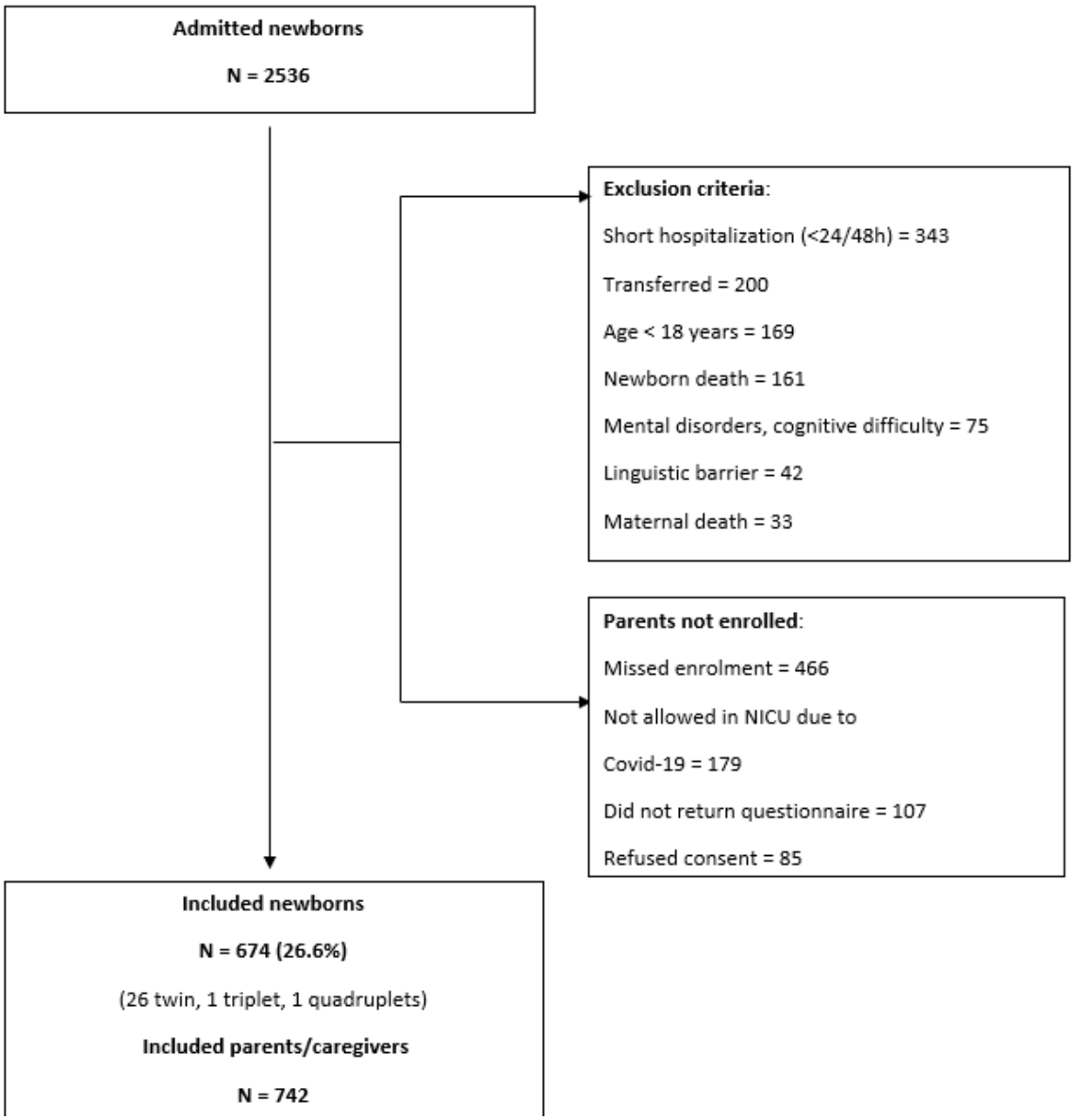
To assess differences between two values, we employed the two-proportions z-test (for proportions) and the Mood's median test (for medians). When comparing three proportions, we conducted multiple comparisons using the z-test. For three or more medians, we utilized the Asymptotic K-Sample Brown-Mood Median Test. All the tests were two-tailed.

Results

Population characteristics

Of the 2536 newborns admitted to the eight NICUs during the study period, 1511 (59.6%) met the inclusion criteria. Among these, 837 (55.4%) were not enrolled, with only few (5.6%) refusing consent (**Figure 3.1.2a**). Overall, we included 674 newborns and 742 parents/caregivers (Brazil = 327, Italy = 191, Tanzania = 224). Fathers were mostly represented in the Italian sample (N=19, 79 and 4 fathers in Brazil, Italy and Tanzania, respectively).

Figure 3.1.2a Flow diagram of the multicountry population



Both parental (Table 3.1.2a) and newborn (Table 3.1.2b) characteristics significantly differed among the three countries.

Table 3.1.2a Parental characteristics in the 3 countries

	Brazil	Italy	Tanzania	p-value
	N=327	N=191	N=224	
	n (%)	n (%)	n (%)	
Parental age (Median [IQR])	27 [22, 32]	37 [34, 41]	25 [21, 30]	< 0.0001
Missing	3 (0.9)	0	0	
Working status				
Housewife/Unemployed	198 (60.6)	20 (10.4)	40 (17.9)	< 0.0001
Working	127 (38.8)	167 (87.4)	183 (81.7)	
No data	2 (0.6)	4 (2.1)	1 (0.4)	
Marital status				
Married	114 (34.9)	89 (46.6)	164 (73.2)	
Un-married	135 (41.3)	5 (2.6)	57 (25.4)	< 0.0001
Unmarried living together	74 (22.6)	97 (50.8)	2 (0.9)	
Missing	4 (1.2)	0	1 (0.4)	
Education ISCED *				
0-1 *(No schooling or Primary ed.)*	4 (1.2)	0	145 (64.7)	
2-3 *(Lower secondary ed. or Upper secondary ed.)*	288 (88.1)	108 (56.5)	72 (32.1)	< 0.0001
4-5-6 *(Higher ed. and post graduation)*	35 (10.7)	81 (42.4)	7 (3.1)	
Missing	0	2 (1)	0	
Parity *(data collected only for mothers)*				
1	161 (49.2)	63 (56.3)	51 (22.8)	
2	82 (25.1)	28 (25)	16 (7.1)	0.003
>2	59 (18)	20 (17.9)	38 (17.0)	
Missing	25 (7.6)	1 (0.9)	113 (50.4)	

*ISCED CLASSIFICATION.(Statistics, 2012)

Table 3.1.2b Newborn characteristics in the 3 countries

	Brazil	Italy	Tanzania [2]	p-value
	N=327	N=123	N=224	
	n (%)	n (%)	n (%)	
Sex				
Female	160 (48.9)	63 (51.2)	114 (50.9)	0.916
Male	163 (49.8)	60 (48.8)	109 (48.7)	
Missing	4 (1.2)	0	1 (0.4)	
Gestational age at birth (weeks)				
≤27	21 (6.4)	6 (4.9)	8 (3.6)	**< 0.0001**
28-33	165 (50.5)	29 (23.6)	33 (14.7)	
34-36	69 (21.1)	41 (33.3)	26 (11.6)	
37-41	70 (21.4)	47 (38.2)	138 (61.6)	
≥42 *	0	0	19 (8.5)	
Unit				
NICU	219 (67.0)	60 (48.8)	160 (71.4)	**< 0.0001**
Semi-intensive care	103 (31.5)	63 (51.2)	63 (28.1)	
Missing	4 (1.2)	0	1 (0.4)	
Apgar at 5th minute <7	26 (8.0)	3 (2.4)	53 (23.7)	**< 0.0001**
Bag mask ventilation at birth	145 (44.3)	28 (22.8)	84 (37.5)	**0.031**
Any respiratory distress[1]	156 (47.7)	58 (47.2)	121 (54.0)	0.749
Intubation	95 (29.1)	24 (19.5)	0 (0.0)	NA
Sepsis	85 (26.0)	16 (13)	43 (19.2)	0.113
Jaundice	235 (71.9)	24 (19.5)	145 (64.7)	**< 0.0001**
Major malformation	47 (14.4)	8 (6.5)	12 (5.4)	0.064
Surgery	44 (13.5)	12 (9.8)	5 (2.2)	**0.020**
Total hospitalization, days *(Median [IQR])*	29 [18, 47]	15 [8.5, 26]	7 [5, 12]	**< 0.0001**
Missing	18 (5.5)	0	1 (0.4)	

Notes: * - For the chi-squared test comparing the different proportions, 'missing' levels were not considered because they have almost zero values; 1 – both clinical and radiological signs; 2 – second level hospital

Abbreviations: IQR = interquartile range.

Differences among parents included caregiver age, working status, marital status, educational level (all p-values <0.0001), and women parity (p = 0.003) Most of newborns' characteristics, such as Apgar score at 5th minute and frequency of associated medical conditions and related treatments (i.e., surgery, ventilation support at birth) were significantly different across countries (p-values < 0.05). Out of the total sample of 674 newborns, 400 (59.3%) were preterm (gestational age at birth < 37 weeks), with a higher frequency in Brazil (78.6%) and Italy (61.7%) when compared to Tanzania (29.9%, p < 0.001). The median length of stay in NICU for Brazil (29 days) was significantly higher than the one recorded in Italy (14 days, p <0.0001) and Tanzania (7 days, p <0.0001).

Frequency of stress, depression, and anxiety

The frequencies of depression, anxiety and stress were high in all the three countries under analysis (**Table 3.1.2c, Figure 3.1.2a**), with an overall frequency of any of the conditions of 65.1%, 52.9% and 58.0% in Brazil, Italy, Tanzania respectively (all p-values of multiple comparisons > 0.05).

The detected frequency of all three conditions simultaneously was also high in all countries: 16.0%, 11.5% and 1.8% in Brazil, Italy, Tanzania respectively, when considering EPDS-A for detecting anxiety. Depression was significantly more frequent in Tanzania (52.3%) when compared with both Brazil (35.8%) and Italy (33.3%) – (both p-values < 0.001)

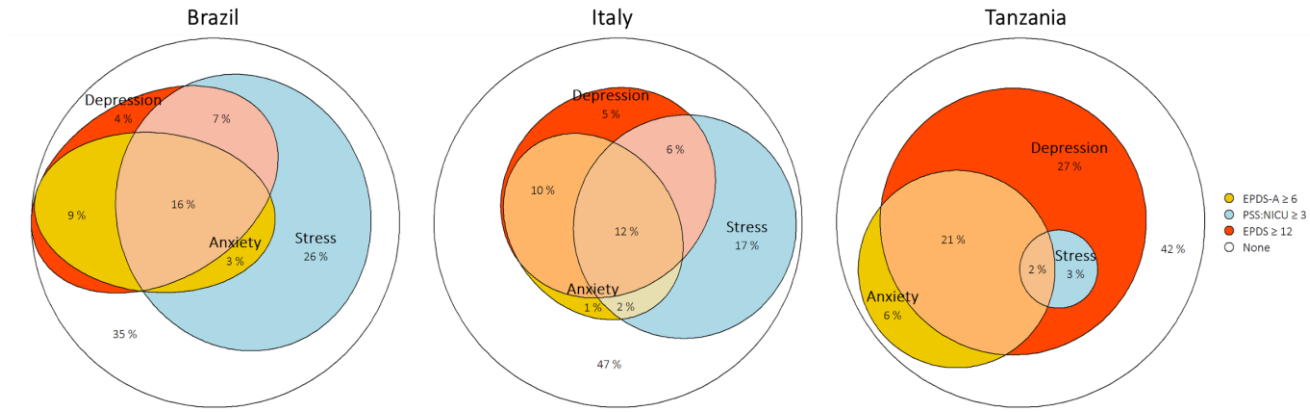
The three countries had different patterns of overlaps across populations. (**Figure 3.1.2a**)

Table 3.1.2c Frequency of parental depression, anxiety (EPDS-A) and stress

		At least one condition		All at once	
		Frequency N	*%*	*Frequency N*	*%*
Italy	Total sample (N = 191)	101	**52.9**	22	**11.5**
Brazil	Comparison sample (N= 106)	69	**65.1**	17	**16.0**
	Total sample (N = 327)	225	68.8		5.2
Tanzania	Total sample (N = 224)	130	**58.0**	4	**1.8**

Notes: cut-off predefined were as follow: Depression: EPDS ≥ 12 for Italy and ≥ 13 for Brazil and Tanzania; Anxiety: EPDS-A ≥ 6; Stress: SOL ≥ 3. Abbreviations: EPDS = Edinburgh Postnatal Depression Scale; EPDS-A = Edinburgh Postnatal Depression Scale for Anxiety; SOL = Stress Occurrence Level.

Figure 3.1.2a Frequency of parental depression, anxiety (EPDS-A score) and stress and intersections among identified populations



Notes: For PSS:NICU, the SOL score (Stress Occurrence Level) was used. : Depression cut-offs: EPDS ≥ 12 for Italy and ≥ 13 for Brazil and Tanzania. Abbreviations: EPDS=Edinburgh Postnatal Depression Scale; PSS:NICU=Parental Stressor Scale in NICU; STAI= State-Trait Anxiety Inventory

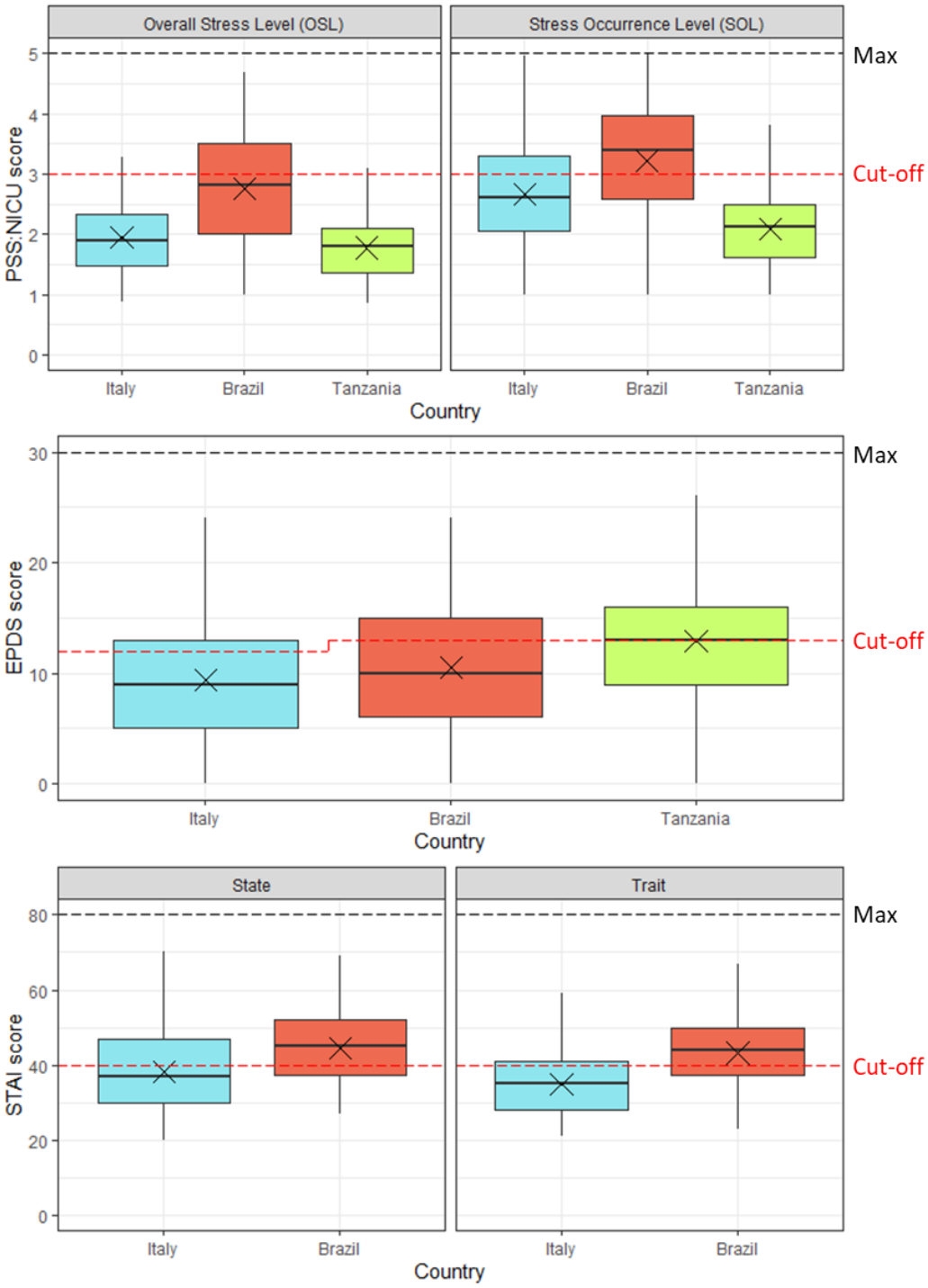
Severity of stress, depression, and anxiety

In all countries the scores of stress, depression, and anxiety had a wide variability, and reached very high values: the maximum value of the EPDS score was a score of 24 in Italy and Brazil, 26 in Tanzania; the maximum of the PSS:NICU SOL was 5 in Italy and Brazil and 4 in Tanzania; STAI state reached a score of 70 for Italy and 69 for Brazil; EPDS-A reached the maximum value (9) in each country. (**Figure 3.1.2b**).

Parents in Tanzania had significantly higher median scores for depression (EPDS median equal to 13, IQR [9; 16]) when compared to other countries (**Figure 3.1.2b**).

Parents in Brazil had higher median scores for anxiety and stress (STAI state median equal to 45 and SOL median equal to 3.4) than the other countries under analysis (p-value = 0.002 for STAI state, p-value < 0.001 for SOL); frequency of severe stress (PSS:NICU- SOL≥ 4) was also significantly higher in Brazil (22.6%) compared to Italy (4.69%, p-value < 0.001) and Tanzania (0%, p-value < 0.001). (**Figure 3.1.2b)**

Figure 3.1.2b Severity of stress, depression and anxiety (median scores)



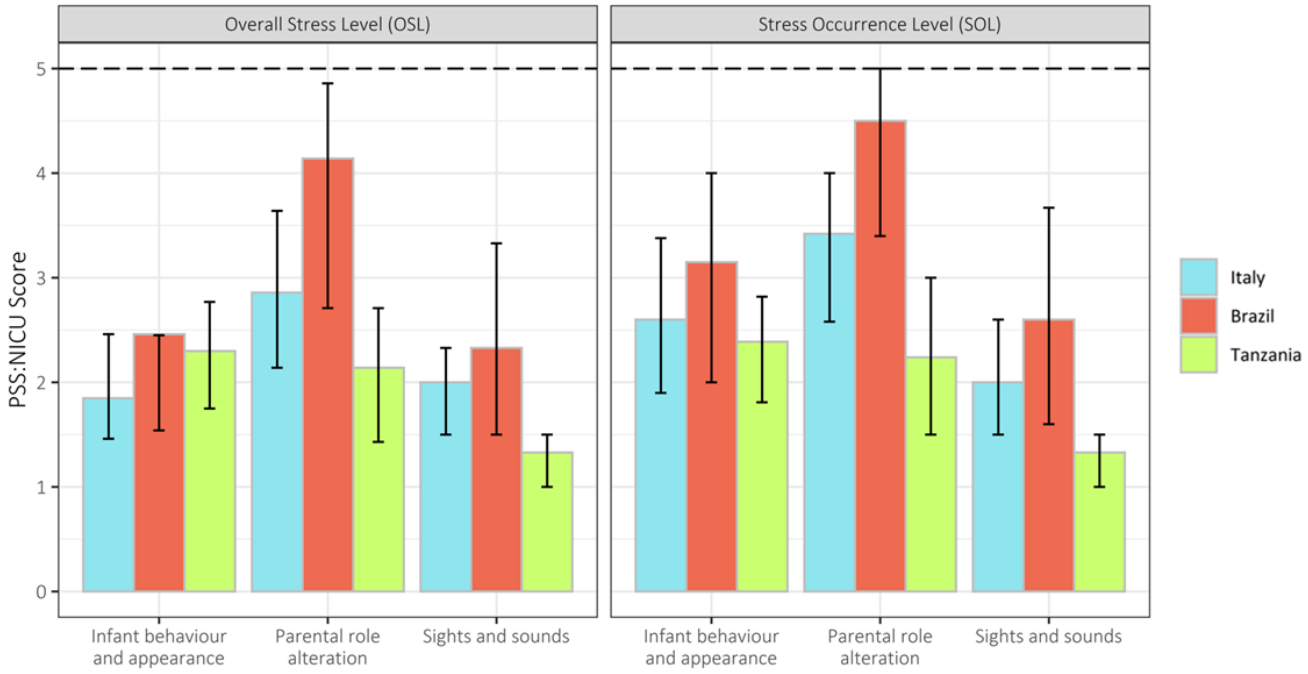
Note: the figure shows the median, the mean (represented by a "X") and the interquartile range of each score. Abbreviations: EPDS=Edinburgh Postnatal Depression Scale; PSS:NICU=Parental Stressor Scale in NICU; STAI= State-Trait Anxiety Inventory

Stress scores by domains

Sights and sounds was the domain perceived as least stressful, when compared to the other domains, in all three countries under analysis (**Figure 3.1.2c**).

For both Italian and Brazilian parents, the domains where the higher scores of parental stress were reported was the paternal role alteration (SOL median 3.4 and 4.5 for Italy and Brazil, respectively), while for Tanzanian parents it was the infant behavior and appearance (SOL median 2.38) (**Figure 3.1.2c**).

Figure 3.1.2c. Median stress scores in the three countries, by domain



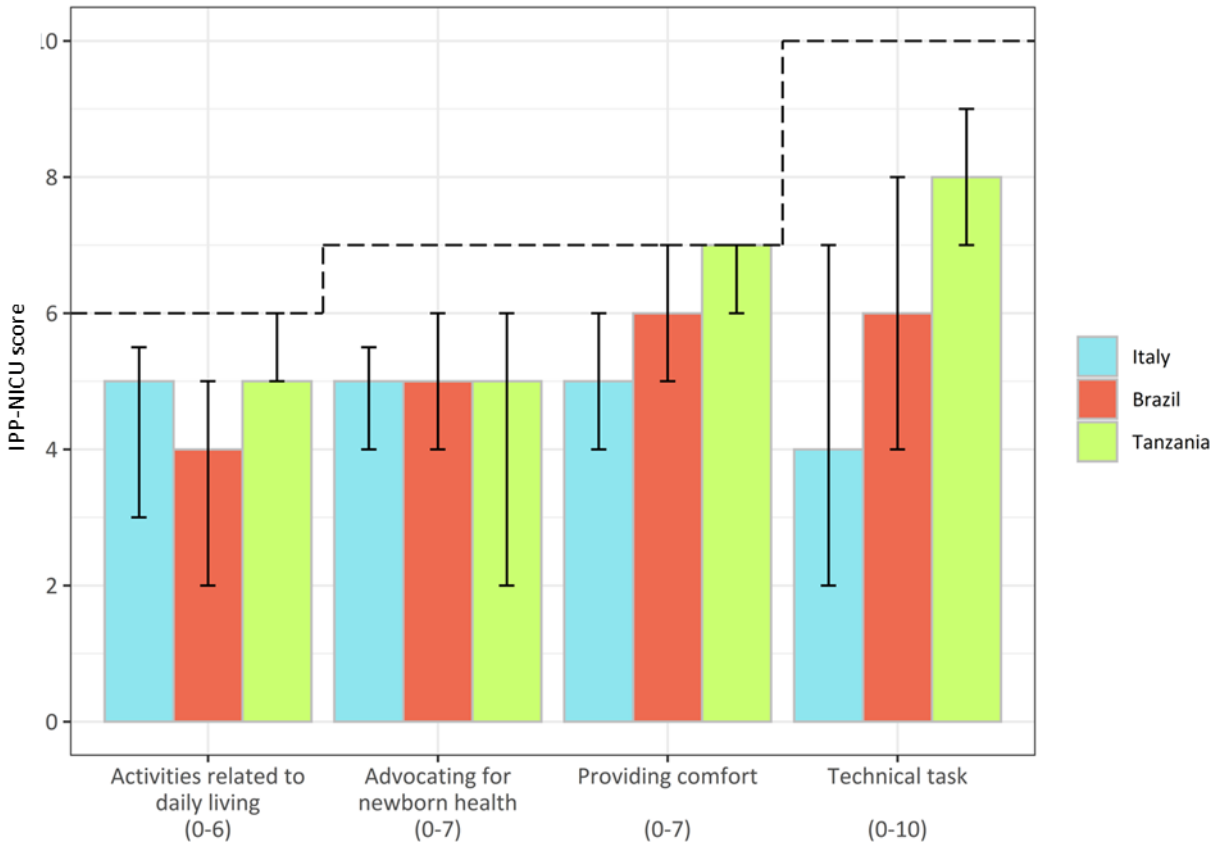
Note: the figure shows the median and the interquartile range of the PSS:NICU Abbreviations: IQR=interquartile range; PSS:NICU=Parental Stressor Scale in NICU.

Parental participation in care

In none country parental participation in care score reached its possible maximum value, with the largest gap in all countries being on "technical tasks" (**Figure 3.1.2d**).

In general, Tanzanian parents had the highest participation scores (median IPP-NICU score equal to 24, IQR [21; 26]), even in the domain of technical task (median 8 out of 10, IQR [7; 9] versus Brazil (median 6, IQR [4; 8]) and Italy (median 4, IQR [2; 7]) – p-value < 0.001). Italian parents reported the lowest scores (median IPP-NICU score equal to 18, IQR [12;22]). In Brazil, there was a medium-high level of participation (median 21, IQR [15; 24.8] (**Figure 3.1.2d**).

Figure 3.1.2c. Median parental participation scores in the three countries, by domain



Note: the figure shows the median and the interquartile range of the IPP-NICU. Abbreviations: IPP-NICU = Index of Parental Participation in NICU

Multivariate analyses

Below we report multivariate analyses regarding Italy, as at the time of PhD writing we are reviewing multivariate analyses from Brazil and Tanzania.

Italy

Several factors resulted significantly associated with mental health outcomes, as follows.

Stress: Being graduated and having a STAI state score > 40 resulted as significant risk factors (adjOR respectively equal to 2.53, 95% CI 1.04-6.41, p-value=0.043, and 2.44, 95% CI 1.00-6.12, p-value = 0.052) (Table 3.1.2d)

Depression: being a mother (adjOR 3.17, 95% CI 1.22-8.82, p-value = 0.021) and having scores above the cut-off for anxiety (adjOR 4.11, 95% CI 1.60-11.28, p-value = 0.004) were risk factors significantly associated with an EPDS score indicating depression. Being the parent of a newborn who was intubated compared to mothers of those not intubated decreased the odds of depression (adjOR 0.23, 95% CI 0.06-0.83, p-value = 0.032) (Table 3.1.2e).

Anxiety (evaluated with STAI state): being graduated (adjOR 3.21, 95% CI 1.28-8.56, p-value = 0.015) and having scores above the cut-off for stress (adjOR 3.08, 95% CI 1.13-8.90, p-value = 0.031), depression (adjOR 5.13, 95% CI 1.89-15.16, p-value = 0.002) and participation (adjOR 0.31, 95% CI 0.11-0.82, p-value = 0.022) resulted as significant risk factors for developing also anxiety. Being employed (adjOR 0.20, 95% CI 0.04-0.82, p-value = 0.036) resulted as a protective factor (Table 3.1.2f).

Table 3.1.2d. Logistic regression models – neonatal and parent's demographic factors associated to stress in Italy

Dependent: SOL ≥ 3		Not Stressed	Stressed	OR (univariable)	OR (multivariable)
Sex	*Female*	50 (73.5)	18 (26.5)	-	-
	Male	45 (62.5)	27 (37.5)	1.67 (0.82-3.46, p=0.164)	1.52 (0.67-3.55, p=0.320)
Gestational weeks	*<29*	12 (75.0)	4 (25.0)	-	-
	29-34	22 (81.5)	5 (18.5)	0.68 (0.15-3.21, p=0.615)	1.10 (0.04-12.83, p=0.946)
	>34	61 (62.9)	36 (37.1)	1.77 (0.57-6.71, p=0.352)	5.22 (0.15-111.57, p=0.300)
Weight	*<1500 g*	19 (79.2)	5 (20.8)	-	-
	≥ 1500 g	76 (65.5)	40 (34.5)	2.00 (0.74-6.39, p=0.199)	1.30 (0.08-38.83, p=0.859)
Intubation	*No*	74 (67.9)	35 (32.1)	-	-
	Yes	21 (67.7)	10 (32.3)	1.01 (0.42-2.32, p=0.988)	2.58 (0.62-11.53, p=0.196)
Length of stay	*≤ 14 days*	44 (64.7)	24 (35.3)	-	-
	> 14 days	51 (70.8)	21 (29.2)	0.75 (0.37-1.54, p=0.438)	1.26 (0.46-3.40, p=0.650)
Education	*Not graduated*	61 (77.2)	18 (22.8)	-	-
	Graduated	34 (55.7)	27 (44.3)	**2.69 (1.31-5.66, p=0.008)**	**2.53 (1.04-6.41, p=0.043)**
Parental age	*≥ 35 years*	66 (70.2)	28 (29.8)	-	-
	< 35 years	29 (63.0)	17 (37.0)	1.38 (0.65-2.90, p=0.394)	2.25 (0.84-6.27, p=0.111)
Working status	*Unemployed*	8 (61.5)	5 (38.5)	-	-
	Employed	87 (68.5)	40 (31.5)	0.74 (0.23-2.56, p=0.610)	2.17 (0.57-9.13, p=0.268)
Role	*Father*	48 (80.0)	12 (20.0)	-	-
	Mother	47 (58.8)	33 (41.2)	**2.81 (1.32-6.27, p=0.009)**	2.15 (0.86-5.52, p=0.104)
Depression	*EPDS < 12*	69 (73.4)	25 (26.6)	-	-
	EPDS ≥ 12	26 (56.5)	20 (43.5)	**2.12 (1.01-4.47, p=0.046)**	1.54 (0.60-4.02, p=0.373)
Participation	*IPP < 20*	53 (68.8)	24 (31.2)	-	-
	IPP ≥ 20	42 (66.7)	21 (33.3)	1.10 (0.54-2.25, p=0.785)	0.91 (0.38-2.14, p=0.831)
Anxiety	*STAI state ≤ 40*	65 (77.4)	19 (22.6)	-	-
	STAI state > 40	30 (53.6)	26 (46.4)	**2.96 (1.44-6.25, p=0.004)**	2.44 (1.00-6.12, p=0.052)

Notes: variable *twin* has been removed because of extreme results. Abbreviations: EPDS = Edinburgh Postnatal Depression Scale; STAI = State-Trait Anxiety Inventory; PSS:NICU = Parental Stressor Scale in NICU; SOL = Stress Occurrence Level.

Table 3.1.2e. Logistic regression models –factors associated to depression in Italy

Dependent: EPDS ≥ 12		Not depressed	Depressed	OR (univariable)	OR (multivariable)
Sex	*Female*	52 (76.5)	16 (23.5)	-	-
	Male	42 (58.3)	30 (41.7)	**2.32 (1.13-4.90, p=0.024)**	2.00 (0.79-5.23, p=0.149)
Twin	*No*	72 (65.5)	38 (34.5)	-	-
	Yes	22 (73.3)	8 (26.7)	0.69 (0.27-1.64, p=0.417)	0.40 (0.10-1.49, p=0.184)
Intubation	*No*	68 (62.4)	41 (37.6)	-	-
	Yes	26 (83.9)	5 (16.1)	**0.32 (0.10-0.83, p=0.030)**	**0.23 (0.06-0.83, p=0.032)**
Total stay	*≤ 14 days*	41 (60.3)	27 (39.7)	-	-
	> 14 days	53 (73.6)	19 (26.4)	0.54 (0.26-1.11, p=0.095)	0.76 (0.29-1.98, p=0.577)
Education	*Not graduated*	52 (65.8)	27 (34.2)	-	-
	Graduated	42 (68.9)	19 (31.1)	0.87 (0.42-1.77, p=0.705)	0.51 (0.19-1.30, p=0.170)
Parental age	*≥ 35 years*	69 (73.4)	25 (26.6)	-	-
	< 35 years	25 (54.3)	21 (45.7)	**2.32 (1.11-4.88, p=0.026)**	2.33 (0.89-6.30, p=0.087)
Working status	*Unemployed*	4 (30.8)	9 (69.2)	-	-
	Employed	90 (70.9)	37 (29.1)	**0.18 (0.05-0.60, p=0.007)**	0.53 (0.12-2.18, p=0.393)
Role	*Father*	50 (83.3)	10 (16.7)	-	-
	Mother	44 (55.0)	36 (45.0)	**4.09 (1.88-9.58, p=0.001)**	**3.17 (1.22-8.82, p=0.021)**
Stress	*SOL < 3*	69 (72.6)	26 (27.4)	-	-
	SOL ≥ 3	25 (55.6)	20 (44.4)	**2.12 (1.01-4.47, p=0.046)**	1.03 (0.37-2.85, p=0.957)
Participation	*IPP-NICU < 20*	56 (72.7)	21 (27.3)	-	-
	IPP-NICU ≥ 20	38 (60.3)	25 (39.7)	1.75 (0.86-3.60, p=0.122)	**2.87 (1.09-7.99, p=0.037)**
Anxiety	*STAI state ≤ 40*	65 (77.4)	19 (22.6)	-	-
	STAI state > 40	29 (51.8)	27 (48.2)	**3.19 (1.54-6.71, p=0.002)**	**4.11 (1.60-11.28, p=0.004)**

Notes: variables *gestational weeks* and *weight* have been removed because of extreme results. Abbreviations: EPDS = Edinburgh Postnatal Depression Scale; STAI = State-Trait Anxiety Inventory; PSS:NICU = Parental Stressor Scale in NICU; OSL = Overall Stress Level; SOL = Stress Occurrence Level; IPP-NICU = Index of Parental Partecipation in NICU.

Table 3.1.2f. Logistic regression models –factors associated to anxiety in Italy

Dependent: STAI state > 40		Not anxious	Anxious	OR (univariable)	OR (multivariable)
Sex	*Female*	43 (63.2)	25 (36.8)	-	-
	Male	41 (56.9)	31 (43.1)	1.30 (0.66-2.58, p=0.448)	0.98 (0.38-2.46, p=0.966)
Twin	*No*	64 (58.2)	46 (41.8)	-	-
	Yes	20 (66.7)	10 (33.3)	0.70 (0.29-1.60, p=0.402)	1.81 (0.47-7.18, p=0.391)
Gest. weeks at birth	*<29*	7 (43.8)	9 (56.2)	-	-
	29-34	22 (81.5)	5 (18.5)	**0.18 (0.04-0.68, p=0.014)**	0.11 (0.00-1.19, p=0.103)
	>34	55 (56.7)	42 (43.3)	0.59 (0.20-1.72, p=0.338)	0.31 (0.01-7.10, p=0.483)
Weight at birth	*<1500 g*	14 (58.3)	10 (41.7)	-	-
	≥ 1500 g	70 (60.3)	46 (39.7)	0.92 (0.38-2.30, p=0.855)	0.60 (0.03-19.08, p=0.736)
Intubation	*No*	65 (59.6)	44 (40.4)	-	-
	Yes	19 (61.3)	12 (38.7)	0.93 (0.40-2.10, p=0.868)	0.78 (0.17-3.23, p=0.731)
Length of stay	*≤ 14 days*	36 (52.9)	32 (47.1)	-	-
	> 14 days	48 (66.7)	24 (33.3)	0.56 (0.28-1.11, p=0.099)	0.73 (0.24-2.21, p=0.573)
Education	*Not graduated*	56 (70.9)	23 (29.1)	-	-
	Graduated	28 (45.9)	33 (54.1)	**2.87 (1.44-5.84, p=0.003)**	**3.21 (1.28-8.56, p=0.015)**
Parental age	*≥ 35 years*	54 (57.4)	40 (42.6)	-	-
	< 35 years	30 (65.2)	16 (34.8)	0.72 (0.34-1.48, p=0.379)	0.48 (0.15-1.40, p=0.186)
Working status	*Unemployed*	3 (23.1)	10 (76.9)	-	-
	Employed	81 (63.8)	46 (36.2)	**0.17 (0.04-0.59, p=0.010)**	**0.20 (0.04-0.82, p=0.036)**
Role	*Father*	41 (68.3)	19 (31.7)	-	-
	Mother	43 (53.8)	37 (46.2)	1.86 (0.93-3.78, p=0.083)	0.99 (0.38-2.54, p=0.990)
Stress	*SOL < 3*	65 (68.4)	30 (31.6)	-	-
	SOL ≥ 3	19 (42.2)	26 (57.8)	**2.96 (1.44-6.25, p=0.004)**	**3.08 (1.13-8.90, p=0.031)**
Participation	*IPP-NICU < 20*	42 (54.5)	35 (45.5)	-	-
	IPP-NICU ≥ 20	42 (66.7)	21 (33.3)	0.60 (0.30-1.19, p=0.147)	**0.31 (0.11-0.82, p=0.022)**
Depression	*EPDS < 12*	65 (69.1)	29 (30.9)	-	-
	EPDS ≥ 12	19 (41.3)	27 (58.7)	**3.19 (1.54-6.71, p=0.002)**	**5.13 (1.89-15.16, p=0.002)**

Abbreviations: EPDS = Edinburgh Postnatal Depression Scale; STAI = State-Trait Anxiety Inventory; PSS:NICU = Parental Stressor Scale in NICU; SOL = Stress Occurrence Level.

Discussion and conclusions

This study filled some of the gaps highlighted by recent systematic reviews (Caporali et al., 2020; Roque et al., 2017; Staver et al., 2021), by documenting three major outcomes of mental health-NICU related stress, depression and anxiety (both state and trait)- along with participation in newborn care, among parents of newborns in three different NICU settings in Italy, Brazil and Tanzania. The study contributed in generating new evidence, including many communalities across different settings, which call for immediate action.

Specifically, the very high frequency detected in this study of NICU related stress, depression and anxiety, with a high prevalence of severe conditions across parents of newborns in NICU call for urgent action to promote parents' and newborns' health and wellbeing. Study findings strongly support previous recommendations on the need of routine screening for mood, anxiety disorders and stress in parents of newborn in NICU (Baldoni et al., 2021; Caporali et al., 2020; Murthy et al., 2021; Roque et al., 2017; Staver et al., 2021). The feasibility of screening for mood and anxiety disorder has been positively evaluated by a recent systematic review (Murthy et al., 2021).

Prevention and support/treatment to parents with mental distress can be provided through psychological and social services, but also through many other innovative ways. Existing systematic reviews of interventions to reduce parental depressive and anxiety symptoms identified many effective interventions, including, beside cognitive behavioural therapy (Mendelson et al., 2017); educational interventions on a wide range of topics- such as newborn attachment, newborn growth and development, NICU environment, how to manipulate and nurture the baby, how to observe infant's behaviours and provide positive stimulation and relaxation, home care, training on problem solving strategies, and on how to deal with own emotions, and information existing resources (Maleki et al., 2022; Mendelson et al., 2017; Sabnis et al., 2019) ; parent's centered support communication (Maleki et al., 2022); parents' groups, fathers involvement in care, parents dairy to process emotions and experiences and music (Sabnis et al., 2019); emotional support (Maleki et al., 2022); relaxation techniques (breathing, muscle relaxation, guided imagery (Maleki et al., 2022; Sabnis et al., 2019); massage (Sabnis et al., 2019); environmental interventions such as family rooms (Maleki et al., 2022)and noise reduction (Almadhoob & Ohlsson, 2015).

Such interventions clearly require involvement of all NICU staff, including nurses, as highlighted by a recent systematic review (Maleki et al., 2022). Therefore, as a first step, there is the need to increase staff awareness, which cannot be given for granted, on the very high frequency of mental distress among parents of newborns in NICU. Secondly, competences of both doctors and nurses in mitigating at best on a routine basis parental mental distress need to be strengthened, with the aim of protecting both parents and staff. This study suggests that, based on the observed prevalence of mental distress among parents of newborn in NICU, related competences should be incorporated in the core curriculum of all NICU key staff. Evidence suggests that gaps in communication is one of the key areas reported by mothers as substandard (Lazzerini, Covi, Mariani, Drglin, et al., 2022; Lazzerini, Covi, Mariani, Giusti, et al., 2022), therefore competences to effectively establish, on a routine basis, effective communication, and a collaborative relationship with parents, even those with severe

mental distress, considering that they may be a not negligible proportion, appear to be one of the key core competencies needed for staff working in NICU. All these changes require a culture of family centered developmental care, where both family and staff needs are considered comprehensively (including psychological needs), in a proactive manner (taking action).

Study findings, with Tanzanian mothers compared to Italian and Brazilian parents reporting higher frequency of depression, despite higher participation to newborn care, are not in contradiction with existing RCTs, summarized by a recent systematic review, showing the many benefits of participation to care for newborns and parents' health (North et al., 2022). Moreover, in Tanzania, where the nurse/patient ratio is very low, maternal higher participation in care may indicate task shifting rather than effective family centred care policies hence explaining this finding. Post-partum depression, as shown by a recent metanalysis (Dadi et al., 2020), is frequent in African mothers and it is associated with a wide range of risk factors, that our study did not aim at exploring – such as poor obstetric condition, history of adverse birth and infant health outcomes, a previous history of mental health disorders, low economic status, poor social support and intimate partner violence (Dadi et al., 2020). Plausibly, when participation in care is promoted in the right environment and through parents' empowerment it brings a benefit, while when mothers are left alone with their children without support, it may be not associated with good mental outcomes. The most appropriate level of parental participation in newborn care in different settings has not been established yet. We believe that such an evaluation should take into consideration, beside the context readiness (e.g., existing resources, risk of infection etc), both views of parents and staff, their level of empowerment, their cultural expectations, and the existence of other existing support systems (e.g. staff and parental training, policies to favour parental participation to care).

We acknowledge limitations of this study. First, the cross-sectional nature of the study did not aim at testing any causal relationships among different study variables. In the lack of other previous multi-country assessments, this study was conceived as descriptive. It has the merit of documenting key mental health conditions together with participation in care, allowing comparison across countries, and providing data critical to develop context-specific interventions, as expected for the subsequent phases of the EPINICU project. Subgroup analyses looking at differences in study outcomes by sex of parents, as well as results of the subsequent phases of the EPINICU project will be reported in separate publications.

Second, data collection, occurring mostly during the COVID-19 pandemic may have overestimated the frequency of parental mental distress. It is difficult to estimate how slightly different time periods of data collection across the three countries may have affected our findings. However, detected frequency of stress, anxiety and depression aligns with those reported in studies in the pre-pandemic period (Caporali et al., 2020; Roque et al., 2017; Staver et al., 2021). Since the early phase of the pandemic evidence showed that COVID-19 mostly causes mild disease in children (Lazzerini et al., 2020), thus not justifying *per se* high levels of parental distress. Moreover, an analysis of the Italian dataset across different time periods (pre-pandemic, low and high COVID-19 incidence), showed that prevalence of stress, anxiety and depression did not change significantly over time (Bua et al., 2021). Future studies shall document to which extent parental mental distress in NICU was affected from

COVID-19, or persist beyond them.
Third, this study was conducted in one single referral facility per country, except for Brazil; more studies (or even better, data from screening programs) should aim at documenting the prevalence of parental mental distress in other settings.
Fourth, previous studies suggest that the severity of parental mental distress may change during the course of hospitalization (Pace et al., 2016). Our study did not aim at documenting such changes. More evidence and lessons on this topic shall be derived from a desirable routine practice of screening mental distress in parents of newborn in NICU.
Fifth, a potential population selection bias cannot be ruled out as a high proportion of parents were not included. However, non-selected parents were mainly due to missed enrolment due to organizational aspects rather than refusal to consent.
Lastly, the questionnaire used may have their intrinsic limitations: they collect data which are based on a self-assessment and on different time periods (table 1b); cultural appropriateness of EPDS in Africa is still debated (Tsai et al., 2013) and the same may apply to the concept of stress; IPP-NICU questionnaire does not capture parental satisfaction with participation to newborn care. Nevertheless, the questionnaire used in this study is the most widely validated and utilized in literature (section 1.6)

In conclusion, our study highlighted that regardless of the setting, high rates of depression, stress and anxiety are very common among NICU parents, regardless of a medium to high level of parental participation in care. The high rates of mental distress in NICU parents need to be acknowledged and call for urgent tailored context-specific interventions to promote parents' and newborns' health and wellbeing.

3.1.3 Parental stress, depression, anxiety and participation in care in an Italian Neonatal Intensive Care Unit: a cross-sectional study comparing mothers versus fathers

Background

Having a baby hospitalised in a neonatal intensive care unit (NICU) is a distressing and traumatic experience for parents (Caporali et al., 2020; Johnson Rolfes & Paulsen, 2022; Roque et al., 2017; Schappin et al., 2013; Woodward et al., 2014). A growing body of literature shows that, compared to parents of well babies, NICU parents are at higher risk to suffer from several mood and mental disorders, ranging from post-traumatic stress disorder, acute-stress disorder, depression and anxiety (Caporali et al., 2020; Johnson Rolfes & Paulsen, 2022; Roque et al., 2017; Schappin et al., 2013; Woodward et al., 2014). When NICU parents are distressed or depressed, their interactions with their infants may be less sensitive and attuned to their infant's needs. This in turn may interfere with the social, emotional, cognitive and physical development of these already vulnerable infants (Johnson Rolfes & Paulsen, 2022).

However, several gaps exist on the current evidence on the mental health and wellbeing of NICU parents. For a long time, most of the studies on psychological indicators of parents of newborns in NICU focused exclusively on mothers (Staver et al., 2021; Woodward et al., 2014). It is only in recent years that a few authors raised attention to the essential role of fathers in the NICU and to their specific needs (Baldoni et al., 2021; Holm et al., 2022; Merritt et al., 2022). Studies comparing mental health and wellbeing of mothers versus fathers while assessing multiple indicators are still limited (Caporali et al., 2020; Ionio et al., 2016; Matricardi et al., 2013; Schappin et al., 2013). Generally, in the few existing studies which explored this topic, NICU mothers were reported to be more stressed than fathers (Caporali et al., 2020; Ionio et al., 2016; Matricardi et al., 2013), although this difference was not always consistent (Schappin et al., 2013) .

Awareness of parental psychological distress is a first essential step in order to promote parental well-being. A routine screening of mood and anxiety disorder for parents in the NICU has been proposed by several authors (Baldoni et al., 2021; Caporali et al., 2020; Committee Opinion No, 2018; Murthy et al., 2021; Staver et al., 2021). Yet this did is not implemented in most neonatal units, limiting staff awareness on the problem, as well as actions to contain such distress. Gender differences need to be acknowledged in order to deliver tailored support for fathers and mothers, and to promote collaboration with the family of vulnerable newborns (Baldoni et al., 2021).

In parallel, evidence showed that family centred care and support to parents' participation in newborn care can be effective not only to promote parental wellbeing but also to help NICU hospitalised babies to better thrive and develop (Committee On Hospital Care and Institute For Patient- And Family-Centered Care, 2012; Gooding et al., 2011; North et al., 2022). However, little is known on the level of parents' participation in newborn care in most NICU settings.

Given these gaps in the literature, our study aimed at comparing the levels of stress, anxiety, depression, and participation in care among mothers and fathers of infants in the NICU of an Italian tertiary hospital.

Methods

Data were collected before and during the COVID-19 pandemic (from November 2019 to December 2020) based on a preliminary study on a subsample of the current sample (N=151), showing that parental stress, depression and participation in care did not change significantly during the COVID-19 pandemic compared to the pre-pandemic period (Bua et al), and data were not further divided by pandemic phases.

In the present study we reported new data compared to the previous publication (Bua et al., 2021), by comparing study outcomes in mothers versus fathers, and by analysing a larger sample of parents.

A sample of 154 parents (77 for each sub-group) was calculated based on an expected difference of 0.3 points in the PSS:NICU (SOL) total score and a standard deviation of 0.5, using a Wilcoxon-Mann-Whitney test with 95% confidence and a power of 95%.

Firstly, a descriptive analysis of parents and newborn characteristics was conducted.

For all scores, the differences between mothers and fathers were analysed by considering the medians and the percentages of observations over the cut-offs presented in section 1.6. The median test (also known as Mood's median test) and the two proportions Z-test were used respectively.

We also analysed the concurrently presence of stress, depression and anxiety on the subgroup of parents who contributed to the study providing data for all the related scores. For this analysis, we included only those parents with all 3 scores for mental distress (N=130, 75 mothers and 55 fathers) and we used the STAI state score (STAI-Y1) for anxiety, defining “any state anxiety” by a score > 40.

Results

Population characteristics

Of the 272 newborns admitted to our Neonatal Unit during the study period, 188 met the inclusion criteria. Among these, 65 (34%) were not enrolled, with only very few refusals to participate (online supplemental figure 1). Overall, we included 123 newborns and 191 parents (112 mothers, 79 fathers).

Characteristics of parents are summarised in **table 3.1.3a**, with the only statistical differences between groups being both the working status, despite being very high in both mothers (87%) and fathers (97%, $p<0.0001$) and the age of parents with fathers being significantly older than mothers (39 years vs 36, $p<0.003$).

Characteristics of newborns are detailed in **table 3.1.3b**. Overall, the newborn population was heterogenous in all clinical characteristics. About half of them were admitted to the intensive unit while the other half to the semi-intensive one.

Table 3.1.3a. Characteristics of mothers and fathers

	Overall N=191		Mothers N=112		Fathers N=79		p-value
	n	%	N	%	N	%	
Age, *median [IQR]*	37	[34, 41]	36	[32, 39]	39	[36, 43.5]	**0.003**
Education [1]							
Primary education	24	12.57	10	8.93	14	17.72	0.113
Lower secondary education	80	41.88	45	40.18	35	44.3	0.674
Upper secondary education	4	2.09	4	3.57	0	0	0.236
Bachelor's or more	81	42.41	52	46.43	29	36.71	0.234
Missing	2	1.05	1	0.89	1	1.27	NA
Working status							
Working	167	87.43	90	80.36	77	97.47	**0.001**
Un-employed	20	10.47	19	16.96	1	1.27	**0.001**
Missing	4	2.09	3	2.68	1	1.27	NA
Maritial status							
Married	186	97.38	108	96.43	78	98.73	0.601
Un-married	5	2.62	4	3.57	1	1.27	NA
Parity (only women)							
1	-	-	63	56.25	-	-	NA
2	-	-	28	25	-	-	NA
>2	-	-	20	17.86	-	-	NA
Missing	-	-	1	0.89	-	-	NA

Notes:

[1] ISCED CLASSIFICATION: Primary education – ISCED 1; Lower secondary education- ISCED 2; Upper secondary education – ISCED 3; Bachelor's or equivalent – ISCED 6.(Statistics, 2012)

NA= not applicable

Table 3.1.3b. Newborn characteristics

	N	%
Sex		
Female	63	51.22
Male	60	48.78
Gestational age, weeks		
<=27	6	4.88
28-33	29	23.58
34-36	41	33.33
37-41	47	38.21
Length of stay- days (Median, [IQR])	15	[8.5, 26]
Birthweight		
<1000 g	7	5.69
1000-1499 g	13	10.57
1500-2499 g	47	38.21
>=2500 g	56	45.53
Outborn	3	2.44
Apgar at 5 min <7	3	2.44
Ventilation at birth	28	22.76
Intubation	24	19.51
RDS	21	17.07
Any respiratory distress	58	47.15
Sepsis	16	13.01
Surgery	12	9.76
Neurological event [1]	5	4.07
Major birth trauma [2]	1	0.81
Major malformation [3]	8	6.50
Admission at		
Newborn intensive care unit	60	48.78
Semi-intensive care unit	63	51.22

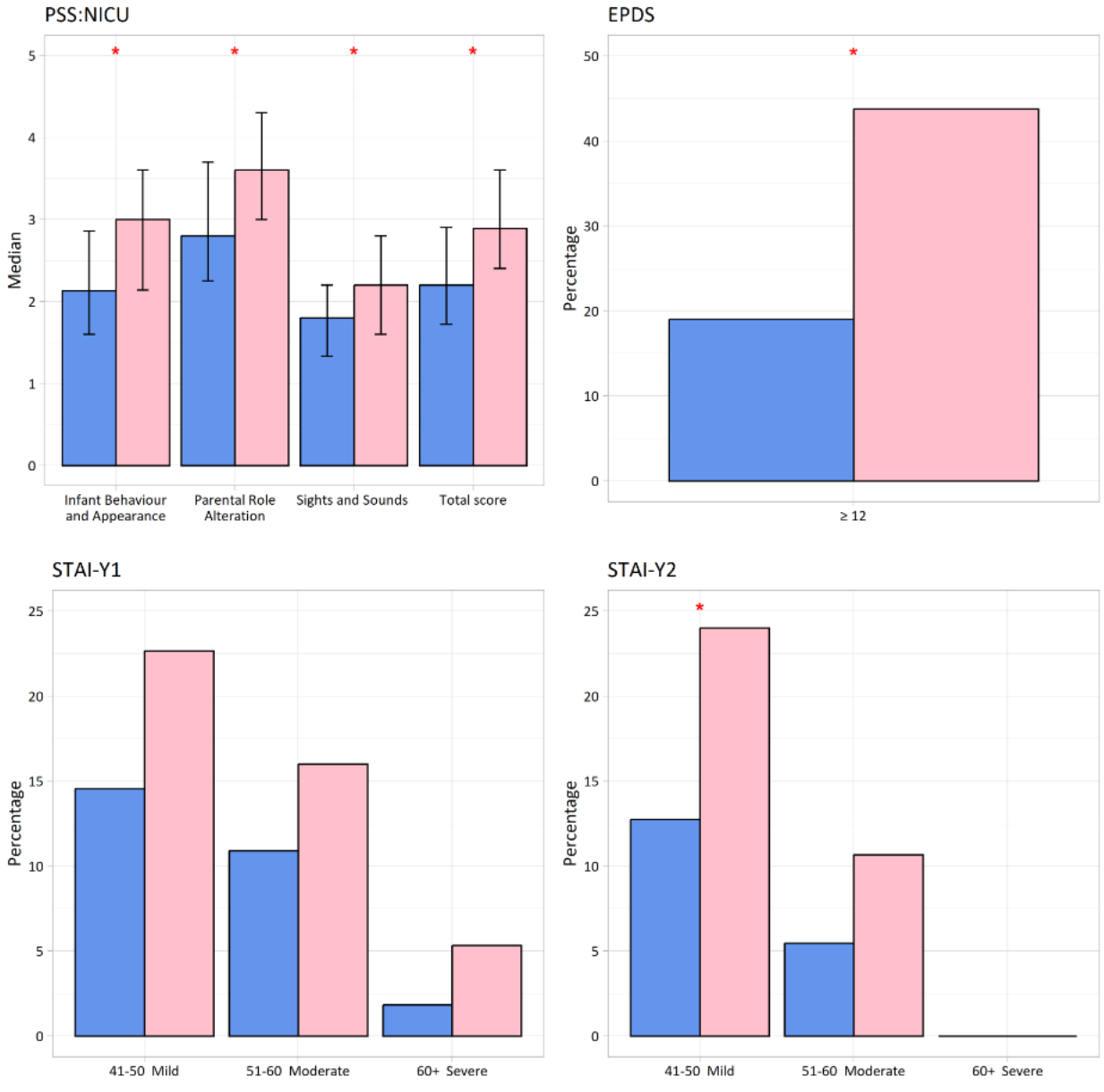
Notes: Among the 123 newborns under analysis, 23 are twins.

[1] Defined as convulsions, intraventricular haemorrhage, periventricular leukomalacia. [2] Defined as fractured clavicle or humerus or fracture at any other site; brachial plexus paralysis and subgaleal hematoma. [3] Defined for head and craniofacial structures: Anencephaly, encephalocele, holoprosencephaly, hydrocephaly, microphthalmia, anophthalmia, colobomas, microtia, cleft lip, cleft palate, severe micrognathia, macro and macroglossia. Neck: cystic hygroma. Chest: pectus excavatum, absent or hypoplastic clavicles. Back: meningomyelocele, spina bifida. Abdomen: omphalocele, gastroschisis. Genitalia: ambiguous genitalia. Extremities: absent or limb deficiencies, polydactyly, complete syndactyly, polysyndactyly, absent digits, ectrodactyly. Cardiovascular and great vessels: tetralogy of Fallot, truncus arteriosus, hypoplastic left heart, ventricular or atrial septal defect, transposition of the great vessels, interrupted aortic arch type B, total anomaly of pulmonary venous return, hypoplasia or coarctation of the aorta.

Stress, depression and anxiety

As shown by **figure 3.1.3a and table 3.1.3c**, mothers compared to fathers showed significantly higher median scores for stress and depression, and higher frequency of both state and trait anxiety, though a statistically significant difference was identified only for mild trait anxiety.

Figure 3.1.3a Differences of stress, depression and anxiety between mothers and fathers



Specifically, PSS:NICU median scores were 2.9 (IQR 2.4-3.6) in mothers compared to 2.2 (IQR 1.7-2.9) in fathers ($p<0.001$), with all sub-scores for stress being significantly higher in mothers. Parental role alteration was the highest source of stress for both mothers (3.6, IQR 3.0-4.3) and fathers (2.8, IQR 2.3-3.7) (**table 3.1.3c**). "High stress" was present in 45.54% of mothers compared to 24.05% of fathers ($p=0.004$).

Median EPDS scores were 10 (IQR 6.5-15) in mothers compared to 7 (IQR 3-10) in fathers (p<0.001) (table 3.1.3c). Almost half of mothers had an EPDS suggestive of clinical depression, compared to one father out of five (respectively 43.75% vs 18.99%, p<0.001) (table 3.1.3d).

Table 3.1.3c Parental stress, depression, anxiety and participation in care, median scores

	Overall		Mothers		Fathers		p-value
	Median	IQR	Median	IQR	Median	IQR	
PSS:NICU, N=191							
Stress Occurrence Level (SOL)							
Sights and Sounds	2	[1.5, 2.6]	2.2	[1.6, 2.8]	1.8	[1.3, 2.2]	0.022
Infant Behaviour and Appearance	2.6	[1.9, 3.4]	3	[2.1, 3.6]	2.1	[1.6, 2.9]	0.008
Parental Role Alteration	3.4	[2.6, 4]	3.6	[3.0, 4.3]	2.8	[2.3, 3.7]	<0.001
Total score	2.6	[2.1, 3.3]	2.9	[2.4, 3.6]	2.2	[1.7, 2.9]	<0.001
EPDS, N=191							
Total score	9	[5, 13]	10	[6.5, 15]	7	[3, 10]	<0.001
STAI, N = 130 (mothers = 75, fathers = 55)							
State Anxiety Scale (Y1)							
Total score	37	[30, 46.8]	38	[32, 48.5]	34	[27.5, 41.5]	0.068
Trait Anxiety Scale (Y2)							
Total score	35	[28, 41]	37	[30, 43]	32	[27, 37.5]	0.004
IPP, N=191							
Activities related to daily living	5	[3, 5.5]	5	[4, 6]	4	[2, 5]	<0.001
Providing comfort	5	[4, 6]	5	[4, 6]	4	[4, 5]	<0.001
Advocating	5	[4, 5.5]	5	[4, 6]	4	[3, 5]	0.053
Technical task	4	[2, 7]	5	[3, 7]	3	[1, 5]	0.001
Total score	18	[14, 22]	19	[16, 23]	15	[11, 20]	<0.001

Abbreviations: PSS:NICU = Parental Stressor Scale in NICU; EPDS = Edinburgh Postnatal Depression Scale; STAI = State and Trait Anxiety Scale; IPP = Index of parental participation.

No significant differences between mothers and fathers were found in state anxiety median scores (STAI Y1), while mothers were more likely to have a higher score for trait anxiety (STAI Y2) (median score 37 vs 32, p=0.004) (table 3.1.3c).

When analysed by frequency, state and trait anxiety was more frequent among mothers versus fathers though the difference was not statistically significantly (44% vs 27.27%, p=0.076; 34.67% vs 18.18%, p=0.061) with mild trait anxiety being significantly more frequent in mothers compared to fathers (24% vs 12.73%, p=0.042) (table 3.1.3d, figure 3.1.3b).

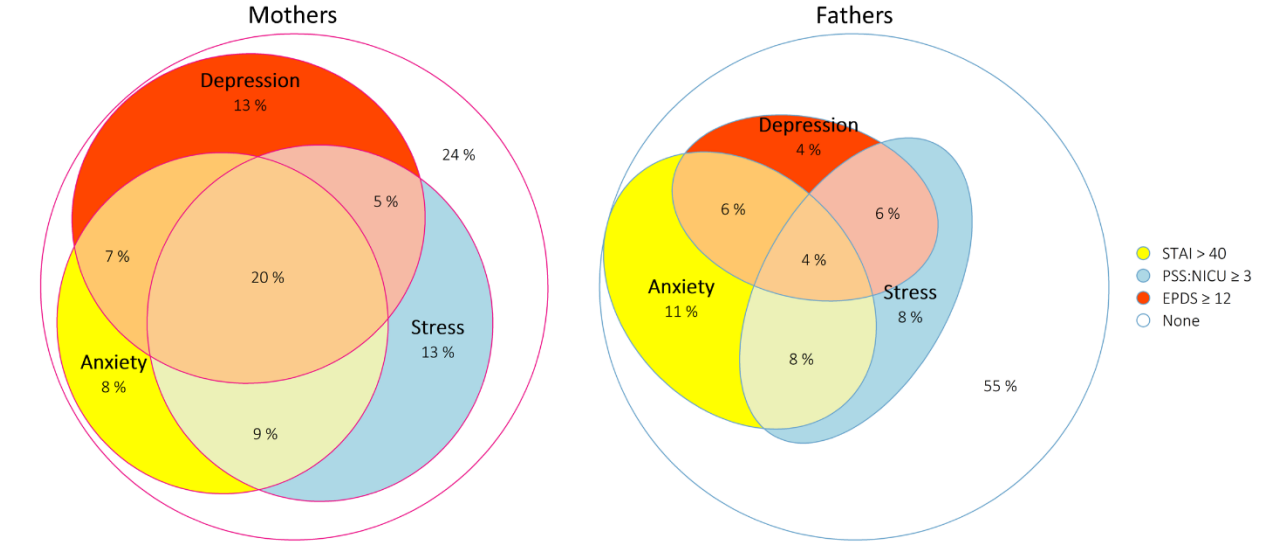
Table 3.1.3d Parental stress, depression, anxiety and participation in care, frequency by predefined cut-off

	Overall		Mothers		Fathers		p-value
	N	%	n	%	n	%	
PSS:NICU (SOL), N = 191							
< 3	121	63.35	61	54.46	60	75.95	0.004
≥ 3 Stress	70	36.65	51	45.54	19	24.05	0.004
EPDS, N=191							
< 12	127	66.49	63	56.25	64	81.01	<0.001
≥ 12 Depression	64	33.51	49	43.75	15	18.99	<0.001
STAI, N = 130 (mothers = 75, fathers = 55)							
State Anxiety Scale (Y1)							
≤ 40	82	63.08	42	56.00	40	72.73	0.076
> 40 Any anxiety	48	36.92	33	44.00	15	27.27	0.076
41-50 Mild	25	19.23	17	22.67	8	14.55	0.451
51-60 Moderate	18	13.85	12	16.00	6	10.91	0.566
> 60 Severe	5	3.85	4	5.33	1	1.82	0.570
Trait Anxiety Scale (Y2)							
≤ 40	94	72.31	49	65.33	45	81.82	0.061
> 40 Any anxiety	36	27.70	26	34.67	10	18.18	0.061
41-50 Mild	25	19.23	18	24.00	7	12.73	0.042
51-60 Moderate	11	8.46	8	10.67	3	5.45	0.462
> 60 Severe	0	0.00	0	0.00	0	0.00	-

Abbreviations: PSS:NICU = Parental Stressor Scale in NICU; EPDS = Edinburgh Postnatal Depression Scale; STAI = State and Trait Anxiety Scale.

When investigating whether mothers and fathers suffered from more than one condition among stress, depression and anxiety, mothers were suffering from all three conditions more frequently than fathers (20% vs 3.8%, p=0.016), with the vast majority of mothers (76%) suffering from at least one condition compared to less than half of fathers (45.3%, p<0.001). Patterns of overlap among conditions varied from mothers and fathers were relatively similar (**Figure 3.1.3b**).

Figure 3.1.3b Differences in pattern of overlaps among conditions between mothers and fathers

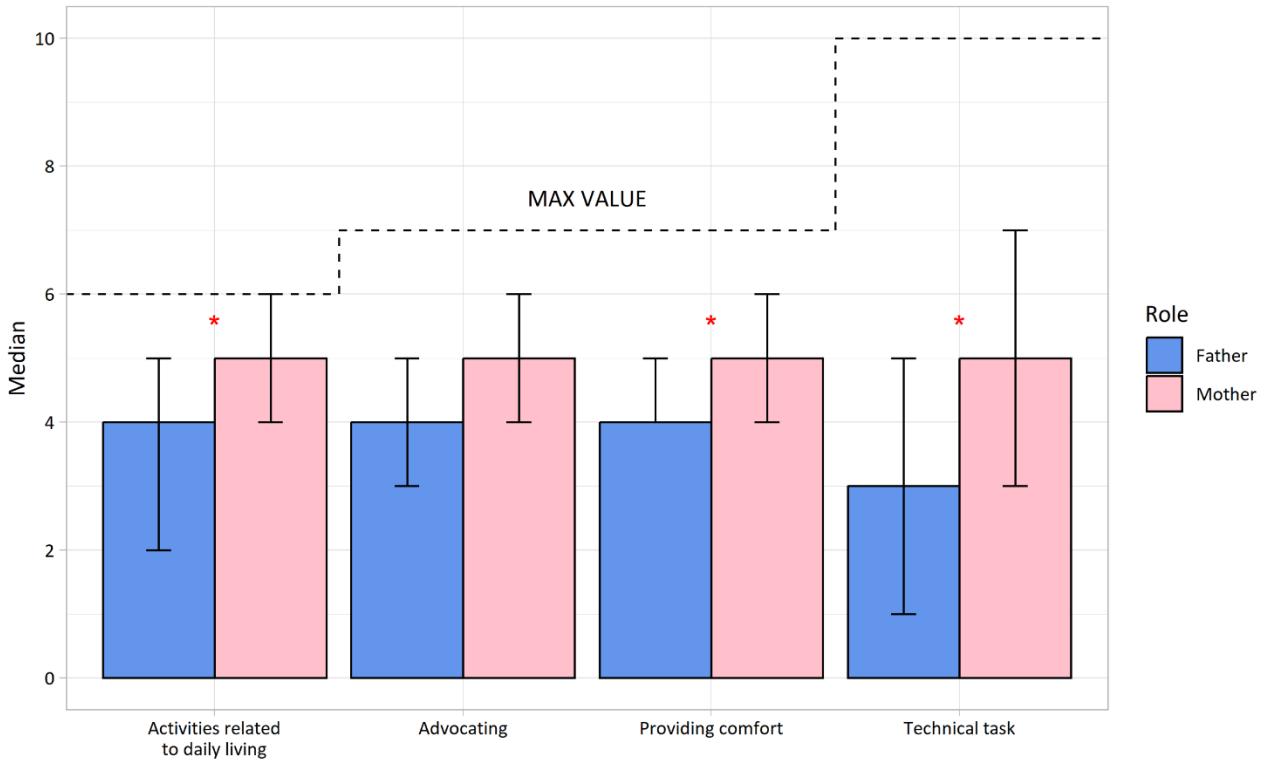


Abbreviations: PSS:NICU = Parental Stressor Scale in NICU; EPDS = Edinburgh Postnatal Depression Scale, STAI = State Anxiety Scale.
Notes: For anxiety, STAI state score was considered. Sample size = 75 (mothers), 55 (fathers).

Participation in care

With regard to participation in care, mothers showed significantly higher median sub-scores in all areas of participation investigated (5 vs 4 for fathers for activities related to daily living and providing comfort, 5 vs 3 for fathers for technical tasks, all p-values < 0.01) except for activities related to the advocacy for their baby (5 vs 4 for fathers, p=0.053) (**figure 3.1.3c, table 3.1.3c**).

Figure 3.1.3c IPP median sub-scores in mothers and fathers

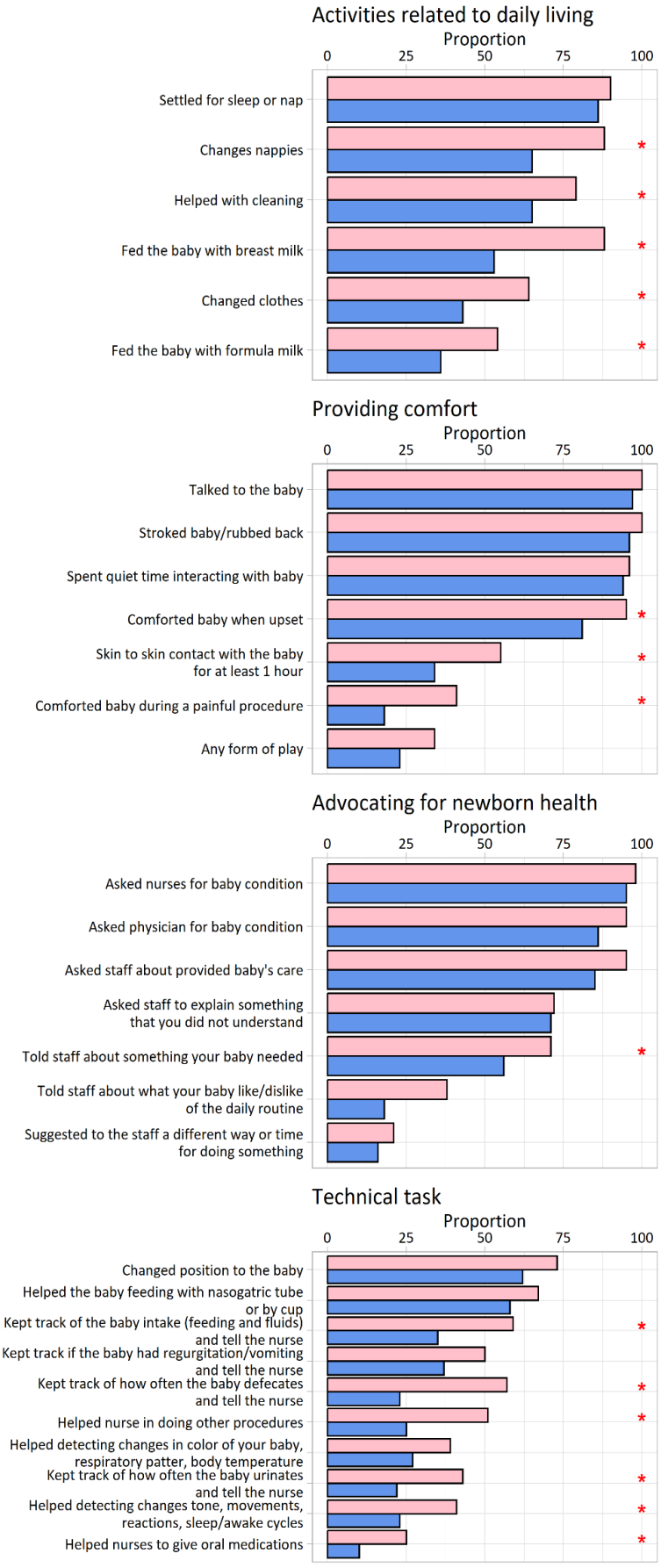


Abbreviations: IPP = Index of Parental Partecipation. Note: Red asterisk = significant difference between mothers and fathers ($p<0.05$). Sample size = 191.

When single IPP items were analysed (**figure 3.1.3d**), the only advocacy activity which was reported more frequently among mothers was to have actively told staff what her newborn needed (37.5% mothers vs 17.7% fathers, p=0.005). Mothers were more likely than fathers to comfort their newborns when upset or during painful procedures (94.6% vs 79.7%, p=0.003) and to do skin-to-skin for at least one hour (55.4% vs 34.2%, p=0.006).

Participation in the area of technical tasks showed the lower scores for both mothers and fathers, though it was higher among mothers who helped staff in keeping track of some clinical parameters (42.0% vs 21.5%, p=0.005, for urine and 56.2% vs 22.8%, p<0.001, for faeces) and in helping giving oral medication (25.0% vs 10.1%, p=0.016).

Figure 3.1.3d Single items in IPP questionnaire in mothers and fathers



Discussion and conclusions

This is one of the few studies exploring more than one mental health indicators in mothers versus fathers of newborns in the NICU, and, to the best of our knowledge the only study exploring multiple indicators of mental health together with a measure of participation in care.

In the NICU where this study was conducted, we found that self-reported stress, depression symptoms and mild trait anxiety were very frequent, confirming previous studies (Caporali et al., 2020; Johnson Rolfes & Paulsen, 2022; Roque et al., 2017; Schappin et al., 2013; Woodward et al., 2014) and significantly higher in mothers compared to fathers. Overall, our findings suggest that more attention should be given to the mental health of NICU parents, particularly to mothers, who are more directly involved in newborn care. This includes the need for more studies, to better describe differences in mental health indicators and participation in care among mothers and fathers in different settings and to describe tailored interventions, both in support of parents and staff.

Our study adds on the existing literature, which mainly focused on parental stress, showing that generally, though not consistently so, mothers and fathers differ in terms of their reactions to having a NICU hospitalized infant (Caporali et al., 2020; Matricardi et al., 2013; Schappin et al., 2013). A 2013 metanalysis of 38 studies describing parents of preterm and low birth weight infants found that differences in stress between mothers and fathers were clinically negligible (Schappin et al., 2013). Conversely, in line with our results, an updated 2020 metanalysis of 53 studies by Caporali et al focused on parental stress measured by PSS:NICU, found that mothers are significantly more stressed than fathers, with parental role alteration being the greatest source of stress for both NICU mothers and fathers (Caporali et al., 2020). In our setting we found that this difference was relevant with almost one in two mothers suffered from high stress compared to one in five fathers.

When looking at depression and anxiety, results of our study showed that both conditions were more frequent in mothers, though significantly so for depression and trait anxiety. These results are to a large extent aligned with previous studies, although again literature is not fully consistent. Garfield et al studied the trajectories in self-rated depression evaluated with EPDS in a Chicago NICU, showing that at admission and at discharge mothers were significantly more likely to be depressed than fathers but, interestingly, while mothers showed a reduction over time in their EPDS scores, fathers essentially remained the same(Garfield et al., 2021). In a study in New Zealand, where NICU parents were compared with parents of full-term infants not requiring admission to the NICU, using the Hospital Anxiety and Depression Rating Scale (HADS), anxiety and depression scores were higher among mothers than fathers in both groups of parents (Carter et al., 2005). However, in a prospective study of parents of newborns born less than 30 weeks of gestational age based in an Australian NICU, Pace et al. found that fathers had a frequency of clinically significant symptoms of depression and anxiety comparable with those of mothers and in both populations these symptoms declined over time with a similar pattern (Pace et al., 2016).

While it is plausible that differences among fathers and mothers are to some extent setting specific, and therefore need to be estimated for each setting, gender differences in psychological distress as

well as the role of father in newborn care need to be acknowledged by all NICU staff and taken into account during daily clinical work. Although in our study fathers experienced less frequently stress, anxiety and depressive symptoms, they were far to be immune from them. It is only in recent years that awareness on paternal psychological suffering in the NICU context has been raised (Baldoni et al., 2021; Holm et al., 2022; Merritt et al., 2022). Taking care of the psychological needs of fathers appears pivotal, as fathers play an essential role in promoting the early father-baby attachment relationship, in having positive effects on the psychological and somatic development of the newborn, and on the health of the mother and whole family (Baldoni et al., 2021; Holm et al., 2022; Merritt et al., 2022)(7-9).

Many scientific societies and authors are calling for a routine screening of mood and anxiety disorders for NICU parents (Baldoni et al., 2021; Caporali et al., 2020; Committee Opinion No, 2018; Murthy et al., 2021; Staver et al., 2021), as their psychological suffering may have short- and long-term negative effects not only on their health but also on the future health of their babies. It is critical to consider both mothers and fathers, and, when appropriate, other care-takers, when implementing these recommendations. Taking care of caregivers' mental health together with the promotion and support of a parent responsive and attuned care are among those fundamental "nurturing care" practices, which are advocated by World Health Organisation and by several paediatric societies, as they actively reduce "toxic stress", buffer adversity and help infants to flourish (Garner et al., 2021; https://www.who.int/teams/maternal-newborn-child-adolescent-health-and-ageing/child-health/nurturing-care).

To the best of our knowledge, we found no data to compare our findings on differences in participation in care in the NICU between mothers and fathers. Our findings, with mothers participated more than fathers in all areas investigated, may be due to the fact that a high percentage of fathers in our study population (97%) were employed. However, also a very high percentage of mothers in our study were employed (80%), thus suggesting that family support polices such as parental leave, together with local culture, may actually play a bigger role than employment status itself in affecting who is acting as primary care-taker for the newborn. In Italy parental leave is different between mothers and fathers, with a recognized paid paternity leave of 10 days compared to 5 months for government employed working mothers (https://ec.europa.eu/social/main.jsp?catId=1116&langId=en&intPageId=4618). This difference is confirmed by our clinical real-life experience as mothers are usually present in our NICU for longer time compared to fathers, giving them more opportunities to actively participate in care of their newborns. However, in the advocacy area these differences were not so evident, showing similar participation between fathers and mothers. Again, this finding emphasizes the key role that fathers play in the NICU. Importantly, since data were self-reported, they may also mirror self-perception of mothers and fathers, who may be another relevant area for further research.

Several limitations of our study need to be acknowledged. First, its cross-sectional nature cannot test any causal relationships among different study variables. However, it gives a valuable picture on differences among mothers and fathers psychological distress and participation in care. This new evidence generated is fundamental to start a quality improvement process to better take care of

parental mental health and to empower parents in the NICU, as the EPINICU study aims at. Secondly, frequency of parental mental distress may have been overestimated as study data was mainly collected during COVID-19 pandemic. However, a previous analysis on a smaller sample of our NICU parents across different time periods (pre-pandemic, low and high COVID-19 incidence), showed that prevalence of stress and depression did not change significantly in our setting with COVID-19 compared to the pre-pandemic period (Bua et al., 2021). Third, the intrinsic limitations of the questionnaires need to be taken into account. The collected data are based on self-assessment and not on clinical interviews, hence giving a picture of self-perceptions and of the risks for the conditions rather than representing a clinical diagnosis. The IPP questionnaire focus on activities in the last 24 hours and does not capture parental satisfaction during participation in newborn care. Nevertheless, these questionnaires are validated and widely utilized in the existing literature (Caporali et al., 2020; Committee Opinion No, 2018). Fourth, as anticipated, findings of this study are not directly generalizable to other settings; however, they contribute to fill a gap in evidence and they highlight the need to replicate similar studies in different settings.

In conclusion, our study confirmed that in NICU parents stress, depression and anxiety were very frequent, and significantly more frequent in mothers, whilst mothers participated in care more than fathers did. Routine screening of mental distress among parents of infants in NICU is warranted, while capacities of staff to prevent as much as possible and to cope with NICU challenging environment (i.e., to effectively support parents without risking burn-out), need to be strengthened and be part of NICU staff curriculum. More studies are warranted in order to explore how parental participation in care is associated with parental mental distress in different contexts.

3.2 Results on PhD objective 2: Formative research. A set of three scoping systematic reviews on RCTs of IFCDC interventions.

Background

Family-centered care in pediatrics is an approach that has been promoted since the late 1940s (Committee On Hospital Care and Institute For Patient- And Family-Centered Care, 2012; Gooding et al., 2011; Shields et al., 2012), and since then it has been supported by several strong advocates (Brazelton & Nugent, 1995; Harrison, 1993; Shelton, 1987) including the World Health Organization (WHO), the Institute for Patient- and Family-Centered Care, and the European Foundation for the Care of Newborn Infants (EFCNI)(Bergman & Westrup, 2018; *Institute for Patient- and Family-Centered Care. Frequently Asked Questions.*, n.d.; World Health Organization, 2016, 2019). Its importance has been recognized by governments, such as the UK government (Department of Health, 2003) and by scientific societies, such as the American Academy of Paediatrics (Committee On Hospital Care and Institute For Patient- And Family-Centered Care, 2012). Family-centered care is advocated based on a patient-rights perspective, and on increasing evidence showing that it can improve patient and family health outcomes, experience of care as well as healthcare professionals' satisfaction and effective use of health care resources (Committee On Hospital Care and Institute For Patient- And Family-Centered Care, 2012).

However, family-centered care is a concept in continuous development, for which slightly different definitions have been provided by different authors/groups (Committee On Hospital Care and Institute For Patient- And Family-Centered Care, 2012; Gooding et al., 2011; Moore et al., 2012; Ramezani et al., 2014; Shields et al., 2012). Specific to neonatology, infant- and family-centered developmental care (IFCDC) has been defined as a framework of newborn care that incorporates the theories and concepts of neurodevelopment, neurobehaviour, parent-infant interaction, parental involvement, breastfeeding promotion, environmental adaptation, and change of hospital systems (Bergman & Westrup, 2018). The core pillars of IFCDC are sensitive and responsive care to infant cues, parent engagement and wellbeing, and customized adaptations of the NICU environment and of the hospital system as a whole (Committee On Hospital Care and Institute For Patient- And Family-Centered Care, 2012).

Although standards of IFCDC have been developed (Bergman & Westrup, 2018), previously published systematic reviews on IFCDC interventions are both not comprehensive and not updated (Benzies et al., 2013; Brecht et al., 2012; Brett et al., 2011; Ding et al., 2019; McAndrew et al., 2022; Sabnis et al., 2019; Segers et al., 2019; Shields et al., 2012; Yu & Zhang, 2019). Shields et al., in a Cochrane review, published in 2012 and since then not updated, focused on the broad topic of family-centered care in children (Shields et al., 2012). Other existing reviews either focused on specific approaches- such as parents' engagement (McAndrew et al., 2022) or communication (Brett et al., 2011) – or specific timing of the intervention (Benzies et al., 2013) or on specific populations – such as preterm or low birth weight infants (Brecht et al., 2012; Ding et al., 2019; Yu & Zhang, 2019) – or on specific outcomes (Maleki et al., 2022; Sabnis et al., 2019; Segers et al., 2019). Moreover, in the last few years, new studies have been conducted and were not included in the previous reviews (Benzies et al., 2013;

Brecht et al., 2012; Brett et al., 2011; Ding et al., 2019; McAndrew et al., 2022; Sabnis et al., 2019; Segers et al., 2019; Shields et al., 2012; Yu & Zhang, 2019)..

In the context of EPINICU study, we decided to conduct a set of three scoping reviews of high-quality research (i.e. including only randomized controlled trials [RCTs]) on interventions to promote IFCDC in different settings, including low- and middle-income countries, each one with a different and complementary aim:

- systematically describe the characteristics of the identified studies (see section 3.2.1);
- provide a detailed description of the identified IFCDC interventions tested in RCTs, develop a menu of interventions and describe the populations involved in the intervention itself (section 3.2.2);
- describe, classify the specific outcomes evaluated in the RCTs, the populations where these outcomes were measured and the specific tools and timings used to measure such outcomes (section 3.2.3).

A scoping review approach was chosen due to the broad nature of IFCDC, the number of existing trials, and the need to first identify and categorize interventions and outcomes (The Joanna Briggs Institute, 2015). This set of three scoping reviews may be of interest for both researchers, by providing a synthesis relevant to the design of new studies, and for policy makers and for EPINICU collaborators, by providing a synthesis of IFCDC interventions which can be relevant to the decision on implementation and to inform Phase 3 of EPINICU study.

Methods of the scoping reviews

Study design

The three scoping reviews – including the present study - were conducted following the same methodology, using The Joanna Briggs Institute methodology (Peters et al., 2015, 2020; The Joanna Briggs Institute, 2015) and the Arksey's framework for scoping reviews and subsequent updates (Arksey & O'Malley, 2005; Levac et al., 2010). A protocol for the review was agreed before starting the screening of the studies, and it was further optimised after testing the inclusion and exclusion criteria.

The PRISMA Extension for Scoping Reviews (PRISMA-ScR) (Tricco et al., 2018) was followed for reporting.

Identifying the research question

The research question was developed including all domains of "the PCC" (population, concept, and context), as recommended by Peters et al. (Peters et al., 2020). The population consisted on infants admitted to NICU or semi-intensive units and their families; the concept included all IFCDC interventions, as further defined in the following paragraph "study selection"; the context was research, specifically RCTs, conducted in NICU or semi-intensive units.

Identifying relevant articles: Search strategy

We searched for all relevant studies published until January 31, 2022 in four electronic databases, i.e., PubMed, EMBASE, Web of Science and the Cochrane library, with no language restrictions. To develop the search strategy, we first tabulated and compared the search strategies used in previous existing reviews (Benzies et al., 2013; Ding et al., 2019; Ramezani et al., 2014; Segers et al., 2019). Secondly, the search strategy was improved, by adding missing terms, and optimising the use of Boolean operators. Third, the search strategy was tested, to assess whether it retrieved all relevant studies including those resulting from previous reviews. For each database, the full final search strategy is shown in Table 3.2a. In addition, we hand-searched reference lists of included studies to ensure inclusion of all relevant studies. All records were imported into Mendeley software and duplicates removed.

Table 3.2a Search strategy

1. PUBMED
((((((((((((((((((((((((((("Family"[Mesh]) OR (famil*)) OR ("Nuclear Family"[Mesh])) OR ("Fathers"[Mesh])) OR (father*)) OR (paternal)) OR ("Mothers"[Mesh])) OR (mother*)) OR (maternal)) OR ("Parents"[Mesh])) OR (parent*)) OR ("Siblings"[Mesh])) OR (sibling*)) OR (sister*)) OR (brother*)) OR ("Caregivers"[Mesh])) OR (caretaker*)) OR (caregiver*)) OR ("Legal Guardians"[Mesh])) OR ("legal custodian*")) OR ("legal tutor*")) OR ("legal guardian*")) OR (guardian*)) OR ("spouses"[MeSH Terms])) OR (spouses)) OR (couple*)) OR (marital)) OR (partner)) OR (partners)) OR (kins)) OR (relatives)) AND ((((((((((("Infant, Newborn"[Mesh]) OR ("Infant, Newborn, Diseases"[Mesh])) OR (newborn*)) OR (new-born*)) OR (neonat*)) OR (infant*)) OR (baby)) OR (babies)) OR (prematur*)) OR (preterm*)) AND ((((((((((((("Intensive Care Units"[Mesh]) OR ("Intensive Care Units, Neonatal"[Mesh])) OR ("intensive care")) OR (ICU)) OR (ICUs)) OR (NICU)) OR ("special care")) OR (SCBU)) OR ("neonatal unit*")) OR ("neonatal unit*")) OR ("Critical Care"[Mesh])) OR ("critical care")) OR ("kangaroo unit*")) OR ("semi-intensive"))) AND ((intervention*) OR (environment*)) OR ("Health Facility Environment"[Mesh])) OR (Health Facility Environment)) OR (Health Care Environment)) OR (reorganis*)) OR (reorganiz*)) OR ("Parent-Child Relations"[Mesh])) OR (interact*)) OR ("Policy"[Mesh])) OR (policy)) OR (policies)) OR ("Family Nursing"[Mesh])) OR (family nursing)) OR (integrat*)) OR (centred)) OR (centered)) OR (participat*)) OR (involv*)) OR (engage*)) OR (decision making)) OR (care decision)) OR ("partnership")) OR ("care delivery")) OR ("Patient Participation"[Mesh])) OR (collaborat*)) OR ("Communication"[Mesh])) OR (communicat*)) OR ("Education"[Mesh])) OR (educat*)) OR (lesson*)) OR ("Social Support"[Mesh])) OR (support*)) OR ("parent-to-parent")) OR ("Peer to peer") OR (empower*)) OR ("Personal Satisfaction"[Mesh])) OR ("Patient Satisfaction"[Mesh])) OR (satisf*)) OR (bond*)) OR ("Stress Disorders, Traumatic"[Mesh])) OR (Stress*)) AND ((((((((((((("Randomized Controlled Trial" [Publication Type]) OR ("Randomized Controlled Trial*")) OR ("Randomised Controlled Trial*")) OR (RCT)) OR (RCTs)) OR (randomized)) OR (randomised)) OR (randomly)) OR ("Controlled Clinical Trial*")) OR ("Controlled Clinical Trial" [Publication Type])) OR ("randomized Trial*")) OR ("randomised Trial*")) OR ("randomised clinical trial*") OR ("randomized clinical trial*")) Filter: humans

2. EMBASE
("Family"/exp OR famil* OR "Father"/exp OR father* OR paternal OR "Mother"/exp OR mother* OR maternal OR parent* OR sibling* OR sister* OR brother* OR "Caregiver"/exp OR caretaker* OR caregiver* OR "Legal Guardian"/exp OR "legal custodian*" OR "legal tutor*" OR "legal guardian*" OR guardian* OR spouses OR couple* OR marital OR partner OR partners OR kins OR relatives) AND (("Infant"/exp OR newborn* OR new-born* OR neonat* OR infant* OR baby OR babies OR prematur* OR preterm*) AND ("Intensive Care"/exp OR "intensive care" OR ICU OR ICUs OR NICU OR "special care" OR SCBU OR "neonatal unit*" OR "neonatal unit*" OR "critical care" OR "kangaroo unit*" OR "semi-intensive")) AND (intervention* OR environment* OR Health Facility Environment OR Health Care Environment OR reorganis* OR reorganiz* OR "child parent relation"/exp OR interact* OR "Policy"/exp OR policy OR policies OR "Family Nursing"/exp OR family nursing OR integrat* OR centred OR centered OR participat* OR involv* OR engage* OR decision making OR care decision OR "partnership" OR "care delivery" OR "Patient Participation"/exp OR collaborat* OR " interpersonal communication"/exp OR communicat* OR "Education"/exp OR educat* OR lesson* OR "Social Support"/exp OR support* OR "parent-to-parent" OR "Peer to peer" OR empower* OR "Satisfaction"/exp OR satisf* OR bond* OR "physiological Stress"/exp OR Stress*) AND ("Randomized Controlled Trial"/exp OR "Randomized Controlled Trial*" OR "Randomised Controlled Trial*" OR RCT OR RCTs OR randomized OR randomised OR randomly OR "Controlled Clinical Trial*" OR "Controlled Clinical Trial"/exp OR "randomized Trial*" OR "randomised Trial*" OR "randomised clinical trial*" OR "randomized clinical trial*")
3. COCHRANE LIBRARY
(famil* OR father* OR paternal OR mother* OR maternal OR parent* OR sibling* OR sister* OR brother* OR caretaker* OR caregiver* OR "legal custodian*" OR "legal tutor*" OR "legal guardian*" OR guardian* OR spouses OR couple* OR marital OR partner OR partners OR kins OR relatives) AND ((newborn* OR new-born* OR neonat* OR infant* OR baby OR babies OR prematur* OR preterm*) AND ("intensive care" OR ICU OR ICUs OR NICU OR "special care" OR SCBU OR "neonatal unit*" OR "neonatal unit*" OR "critical care" OR "kangaroo unit*" OR "semi-intensive")) AND (intervention* OR environment* OR “Health Facility Environment” OR “Health Care Environment” OR reorganis* OR reorganiz* OR "child parent relation" OR interact* OR policy OR policies OR “family nursing” OR integrat* OR centred OR centered OR participat* OR involv* OR engage* OR “decision making” OR “care decision” OR "partnership" OR "care delivery" OR collaborat* OR communicat* OR educat* OR lesson* OR support* OR "parent-to-parent" OR "Peer to peer" OR empower* OR satisf* OR bond* OR Stress*) AND ("Randomized Controlled Trial*" OR "Randomised Controlled Trial*" OR “RCT” OR “RCTs” OR randomized OR randomised OR randomly OR “Controlled Clinical Trial*” OR "randomized Trial*" OR "randomised Trial*" OR "randomised clinical trial*" OR "randomized clinical trial*")
4. WEB OF SCIENCE
famil* OR father* OR paternal OR mother* OR maternal OR parent* OR sibling* OR sister* OR brother* OR caretaker* OR caregiver* OR "legal custodian*" OR "legal tutor*" OR "legal guardian*" OR guardian* OR spouses OR couple* OR marital OR partner OR partners OR king OR relatives (All Fields) and

((newborn* OR new-born* OR neonat* OR infant* OR baby OR babies OR prematur* OR preterm*) AND ("intensive care" OR ICU OR ICUs OR NICU OR "special care" OR scab OR "neonatal unit*" OR "neonatal unit*" OR "critical care" OR "kangaroo unit*" OR "semi-intensive")) (All Fields) and

intervention* OR environment* OR “Health Facility Environment” OR “Health Care Environment” OR reorganis* OR reorganiz* OR "child parent relation" OR interact* OR policy OR policies OR “family nursing” OR integrat* OR centred OR centered OR participat* OR involv* OR engage* OR “decision making” OR “care decision” OR "partnership" OR "care delivery" OR collaborat* OR communicat* OR educat* OR lesson* OR support* OR "parent-to-parent" OR "Peer to peer" OR empower* OR satisf* OR bond* OR Stress* (All Fields) and

"Randomized Controlled Trial*" OR "Randomised Controlled Trial*" OR “RCT” OR “RCTs” OR randomized OR randomised OR randomly OR “Controlled Clinical Trial*” OR "randomized Trial*" OR "randomised Trial*" OR "randomised clinical trial*" OR "randomized clinical trial*" (All Fields)

Study selection

For these scoping reviews we included RCTs and extension studies of RCTs, reporting on interventions which took place or initiated in the hospital setting, in a NICU or in a semi-intensive newborn care unit, when the intervention was pertinent to IFCDC. Specifically, we adapted the five categories of interventions defined in the most recent Cochrane review on paediatric family centered care (Shields et al., 2012) with more precise definitions relevant to newborns, as further detailed below.

- Environmental interventions: defined as any intervention including a change in the physical structure or in their use, specifically aiming at providing an environment that maximized parental involvement and enhanced newborn recovery and/or convalescence, such as for example family rooms or privacy areas.
- Family-centered policies: defined as any intervention including an explicit change in written policies, specifically aiming at supporting IFCDC, such as for example change in visiting hours for siblings or extended family members, hospital guidelines/procedures to increase parent participation in newborn care (e.g., baby feeding or bathing).
- Communication interventions: defined as any intervention aiming at improving communication between parents and staff, such as for example parental presence and participation at daily interdisciplinary ward rounds and family meetings to plan future care, developing collaborative care pathways where both parents and health workers documented newborn and parental issues and progress, re-organization of health care to provide caregiver involvement (such as primary nursing), shared medical records, local hospital-based interpreters.
- Educational interventions: defined as any intervention including training of parents and/or staff specifically aiming at building knowledge and/or skills to provide IFCDC, such as for example structured educational sessions for parents, education programs for staff to provide care within a family-centered framework, in any format including video sessions.
- Family support interventions: defined as any intervention aiming at providing tangible support to families of newborns, such as social support, economic support (e.g., flexible charging schemes for poor families), psychological support, peer-to-peer parent support.

Studies exploring the following more focused (or specific or restrained) interventions already evaluated in other systematic reviews were excluded:

- breastfeeding and/or skin-to-skin and/or kangaroo mother care (KMC) as single interventions, for which there is already strong evidence on their benefits (Conde-Agudelo & Díaz-Rossello, 2016; Moore et al., 2012; Shah et al., 2012);
- parental presence during health care procedures as single intervention (e.g., management of procedural pain during routine examinations), summarized in other reviews (Francisco et al., 2021; Hatfield et al., 2019);
- maternal voice, maternal singing, mother's lullaby, musical therapy, sound reduction alone, or "Sleep Programs" as single interventions, evaluated in previous reviews (Almadhoob & Ohlsson, 2015; Costa et al., 2022; Provenzi et al., 2018; van den Hoogen et al., 2017; Williamson & McGrath, 2019);
- maternal massage, either alone or in combination with KMC, covered by other reviews (Álvarez et al., 2017; Lu et al., 2020; Mollà-Casanova et al., 2023);
- purely mental health interventions, including screening or prevention of maternal depression, when administered alone, or without other specific category of IFCDC, since already evaluated elsewhere (Caporali et al., 2020; Cherak et al., 2021; Mendelson et al., 2017; Roque et al., 2017; Sabnis et al., 2019; Staver et al., 2021);

Additionally, we excluded studies exploring the following interventions:

- praying or religious support of families/mothers;
- physical therapy interventions such as Yakson touch, M-technique methods and others kinaesthetic stimulation techniques, or physical therapy interventions specifically focusing on a specific function alone, e.g., head control;
- studies aiming at reducing parental bereavement alone;
- studies reporting on laboratory parameters (e.g., cortisol) as sole outcomes;
- studies where data of newborns in the NICU could not be separated from data of other populations, such as the general population of children in intensive care unit.

To minimise risk of selection bias, two reviewers, organised in couples independently screened all study titles and abstracts using the online Abstrackr tool (*Software for Semi-Automatic Citation Screening. 2012.*, n.d.). Discrepancies were resolved through group discussion with all authors. The full text articles of all relevant abstracts were assessed by 3 researchers to determine eligibility; any disagreement was resolved by consensus or with a fourth expert reviewer.

Data extraction

The following data were extracted from included studies: authors, year of publication, type of RCT design, study setting (i.e., country, World Bank country classification by income level (bank, n.d.), type and number of facilities involved), population involved in the study and samples, e.g., number of newborns and parents, gestational age at birth and newborn birth weight (when available), intervention's categories as specified above. A data extraction form was developed through an

iterative process from previous reviews forms (McAndrew et al., 2022), pre-piloted on a total of 10 studies and further optimised until considered satisfactory. Data extraction was performed by two authors, organised in couples. To ensure alignment in data extraction and tabulation across couples of authors, regular discussion sessions were held. Disagreements were resolved by either consensus or through further discussion with another senior author.

This being a scoping review, it did not aim at assessing risk of bias and effectiveness of different interventions.

Data synthesis

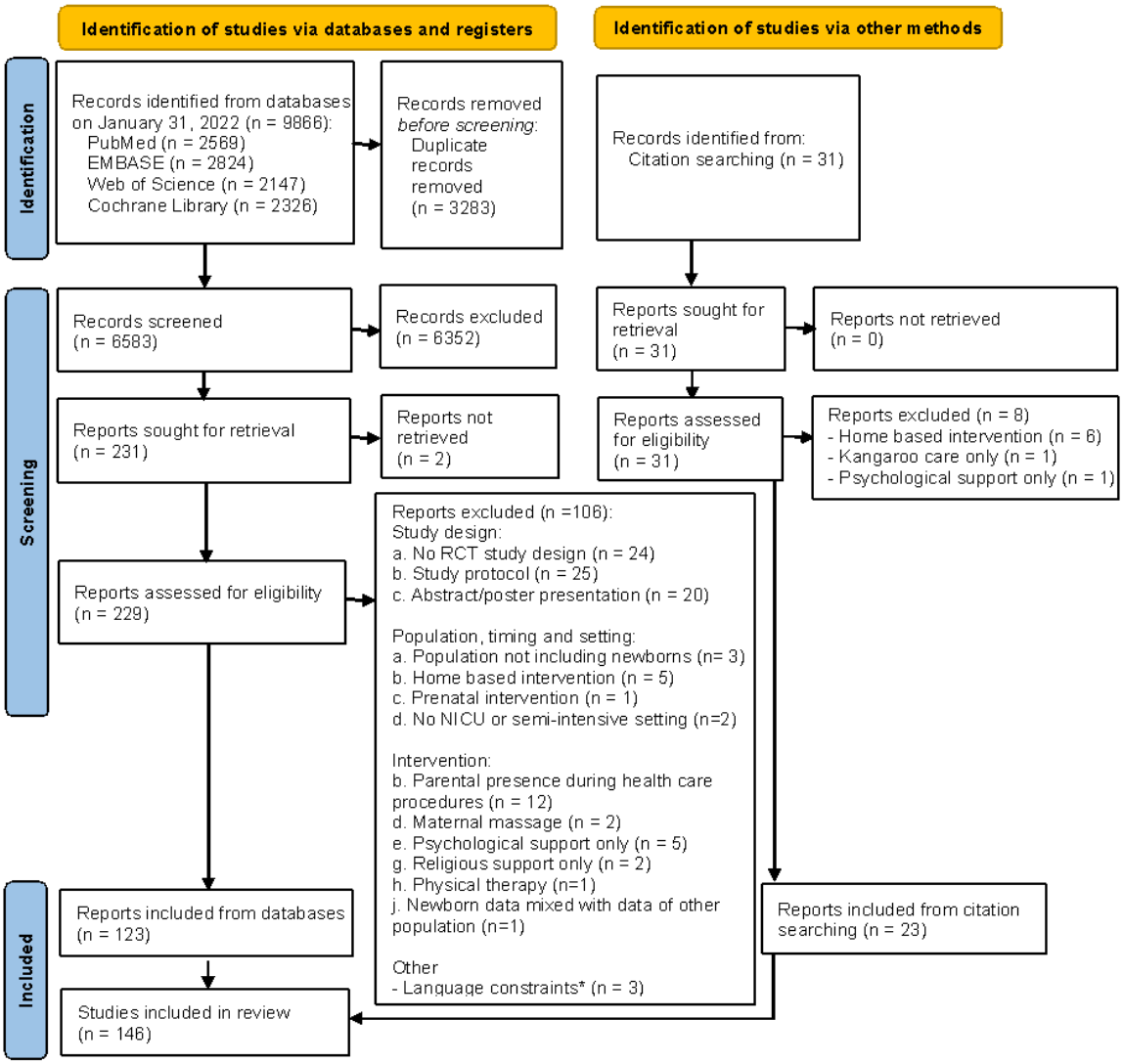
We summarised studies' characteristics, interventions and outcomes in tables and graphs. Data were reported as absolute numbers and percentages. Specific methods relative to each scoping review is detailed in the following sections (3.2.1, 3.2.2 and 3.2.3). To better explore if most recent RCTs differed from past ones, we reported RCTs characteristics by subgrouping them by publication date (up to 2016 vs after 2016). This data was chosen to describe whether RCTs characteristics changed in the last 5-6 years. For the 2nd and 3rd systematic review we also compared whether there were significant differences among RCTs published in high income countries with upper- and lower- middle income countries as per the World Bank categorization (bank, n.d.). No comparison was performed with low-income economies because no study was conducted in that setting. Findings were compared between groups with a binomial test.

Two-tailed tests were performed and a p-value <0.05 was considered as statistically significant. Statistical analyses were performed using Stata/SE version 14.0 (Stata Corporation, College Station, TX, USA) and R version 4.1.1 (R Foundation for Statistical Computing, Vienna, Austria. URL https://www.R-project.org/).

Results of the study selection

The searches yielded 9866 records (PubMed 2569, EMBASE 2824, Web of Science 2147, Cochrane Library 2326) and a total of 6583 records were identified for screening, after excluding duplicates. Additional 31 records were identified by hand searching of reference lists. After abstracts' review, 260 full-text articles were assessed for eligibility. A total of 146 RCTs studies were included in the three scoping reviews, 23 of which from citation searching (**Figure 3.2a**).

Figure 3.2a PRISMA flow diagram



3.2.1 Infant and family's centered developmental care interventions in neonatal intensive and semi-intensive units: a scoping review to identify characteristics of randomised clinical trials

Results

Study characteristics

Table 3.2.1a shows the principal characteristics of included studies. All but one study were parallel RCTs, the remaining one was a crossover RCT. There were 9 (6.2%) cluster RCTs, 8 of these published after 2016 (p=0.001).

Around two thirds (62.3%, n=91) of RCTs were single-centred, while 47 (32.2%) studies were multicenter with two studies being multicountry, both conducted in three high income countries (Canada, Australia, New Zealand). As shown in both Table 3.2.1a and Figure 3.2.1a, 80.8% of studies (n=118) were conducted in high-income countries (HIC), with countries with the higher numbers of studies being: United States of America (39.0%, n=57), Norway (9.6%, n=14), Australia (6.2%, n=9), Canada (7.6%, n=11), and the Netherlands (5.5%, n=8). Lower-middle income countries (LMIC) contributed with 13.0% of studies (n=19), mainly from Iran (10.3%, n=15), while 6.2% (n=9) RCTs were conducted in upper-middle income countries (UMIC), with the most frequent being China (2.7%, n=4). No studies were conducted in low-income countries.

Almost all studies were held only in the NICU ward (97.9%, n=143).

The majority of RCTs included ≤300 caregivers (72.6%, n=106) and ≤300 newborns (81.5%, n=119). Mothers were the caregivers more frequently involved (77.4%, n= 113), whereas fathers were involved only in 27.4% (n= 40) of the studies, mostly with mothers, with only one RCT (0.7%) studying fathers alone. About one out of five RTCs did not specify the type of caregiver involved (20.5%, n=30). Siblings were included in only two out of 146 studies. Among the 127 RCTs (87%) reporting on gestational age, 92.9% (n=118) included very preterm newborns (28-31+6 weeks), 74.8% (n=95) extremely preterm (<28 weeks) and 68.5% (n=87) moderate preterm (32-33+6 weeks). Information on birth weight was available for 49 studies, in which very low birth weight (1000-1499 g) and extremely low birth weight (<1000 g) were the most common categories involved (each n=40, 81.6%).

Table 3.2.1a Characteristics of included studies (N=146)

	Overall N=146	RCTs published up to 2016 N=93	RCTs published after 2016 N=53	
	n (%)	n (%)	n (%)	p-value
RCT design				
Parallel RCTs	136 (93.2)	91 (97.8)	45 (84.9)	0.005
Parallel cluster RCTs	9 (6.2)	1 (1.1)	8 (15.1)	0.001
Crossover RCTs	1 (0.7)	1 (1.1)	0 (0)	>0.99
Other information related to RCT design				
Long term extension RCTs	27 (18.5)	21 (22.6)	6 (11.3)	0.092
Self-identified as “pilot” RCTs	9 (6.2)	5 (5.4)	4 (7.5)	0.724
Secondary analysis of RCTs	2 (1.4)	1 (1.1)	1 (1.9)	>0.99
Setting				
Type of ward				
Only NICU	143 (97.9)	92 (98.9)	51 (96.2)	0.298
NICU and neonatal ward	2 (1.4)	0 (0.0)	2 (3.8)	0.130
NICU and semi-intensive	1 (0.7)	1 (1.1)	0 (0.0)	>0.99
Number of NICUs involved				
1	91 (62.3)	57 (61.3)	34 (64.2)	0.732
2	27 (18.5)	20 (21.5)	7 (13.2)	0.214
≥3	20 (13.7)	11 (11.8)	9 (17.0)	0.455
Not specified	8 (5.5)	5 (5.4)	3 (5.7)	>0.99
World Bank country classification by income level				
High income country	118 (80.8)	87 (93.5)	31 (58.5)	**<0.001**
Upper middle-income country	9 (6.2)	1 (1.1)	8 (15.1)	**0.001**

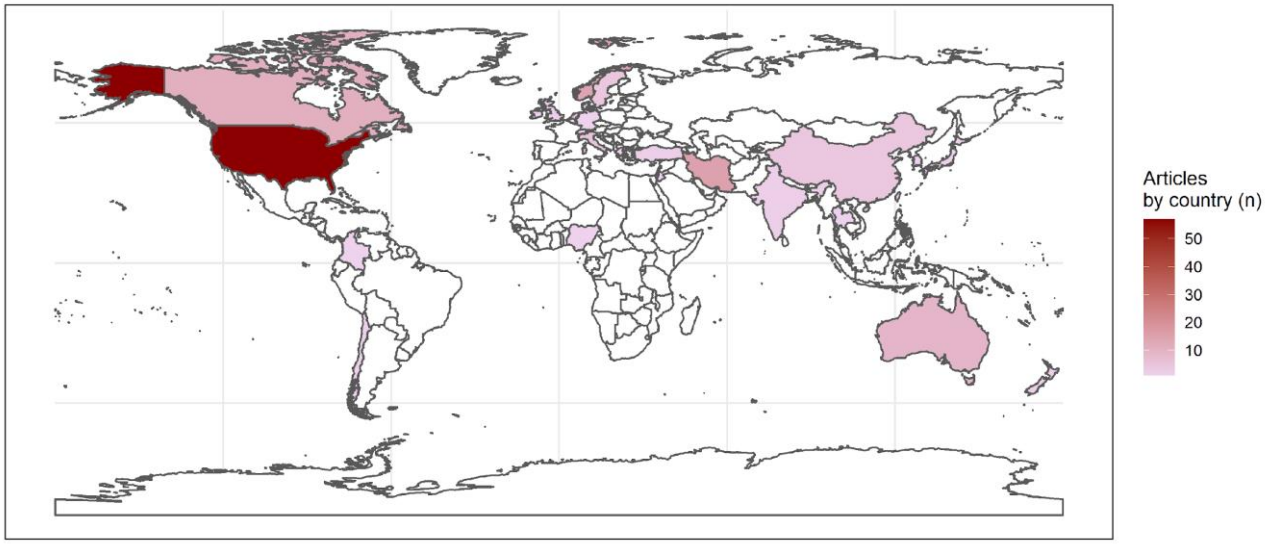
Lower middle-income country	19 (13)	5 (5.4)	14 (26.4)	**0.001**
Low-income country	0	0	0	-
Multicountry RCTs	2 (1.4)	0 (0)	2 (3.8)	0.130
Characteristics of randomised caregivers				
Number of randomised caregivers				
≤50	27 (18.5)	17 (18.3)	10 (18.9)	0.930
51-100	31 (21.2)	16 (17.2)	15 (28.3)	0.115
101-200	38 (26)	26 (28)	12 (22.6)	0.482
201-300	10 (6.8)	10 (10.8)	0 (0)	**0.014**
>300	7 (4.8)	1 (1.1)	6 (11.3)	**0.009**
Not specified	33 (22.6)	23 (24.7)	10 (18.9)	0.415
Type of caregiver				
Mothers only	74 (50.7)	41 (44.1)	33 (62.3)	**0.035**
Both mothers and fathers	37 (25.3)	27 (29)	10 (18.9)	0.175
Mothers and fathers and other caregivers (grandparents, relatives other)	2 (1.4)	1 (1.1)	1 (1.9)	>0.99
Siblings only	2 (1.4)	2 (2.2)	0 (0.0)	0.534
Fathers only	1 (0.7)	1 (1.1)	0 (0.0)	>0.99
Not specified	30 (20.5)	21 (22.6)	9 (17)	0.421
Characteristics of randomised newborns				
Number of randomised newborns				
≤50	34 (23.3)	23 (24.7)	11 (20.8)	0.585
51-100	28 (19.2)	15 (16.1)	13 (24.5)	0.215
101-200	45 (30.8)	33 (35.5)	12 (22.6)	0.106
201-300	12 (8.2)	10 (10.8)	2 (3.8)	0.140
>300	8 (5.5)	2 (2.2)	6 (11.3)	0.027
Not specified	19 (13)	10 (10.8)	9 (17)	0.282
Classification by gestational age *	**N=127**	**N=77**	**N=50**	
Term (≥37 weeks)	9 (7.3)	6 (7.8)	3 (6.4)	0.535

Late preterm (34-36+6 weeks)	53 (41.7)	35 (45.5)	18 (36.0)	0.291
Moderate preterm (32-33+6 weeks)	87 (68.5)	53 (86.8)	34 (68.0)	0.922
Very preterm (28-31+6 weeks)	118 (92.9)	72 (93.5)	46 (92.0)	0.747
Extremely preterm (<28 weeks)	95 (74.8)	61 (79.2)	34 (68.0)	0.155
Classification by birth weight *	**N=49**	**N=38**	**N=11**	
Low birth weight (1500-2500g)	25 (51.0)	18 (47.4)	7 (63.6)	0.342
Very low birth weight (1000-1499 g)	40 (81.6)	32 (84.2)	8 (72.7)	0.386
Extremely low birth weight (<1000 g)	40 (81.6)	33 (86.8)	7 (63.6)	0.179

Note: * A subset of studies provided the information, specifically, gestational age was available for 127 studies and birth weight for 49 studies; each RCT can include more than one category gestational age/birth weight category; classifications by gestational age and by birth weight are taken from UpToDate®, available at https://www.uptodate.com/contents/image?imageKey=PEDS%2F119362 (accessed on 10 May 2023)

Abbreviations: NICU = neonatal intensive care unit; RCT=randomised controlled trial.

Figure 3.2.1a. Countries where RCTs on IFCDC were conducted (N=146)



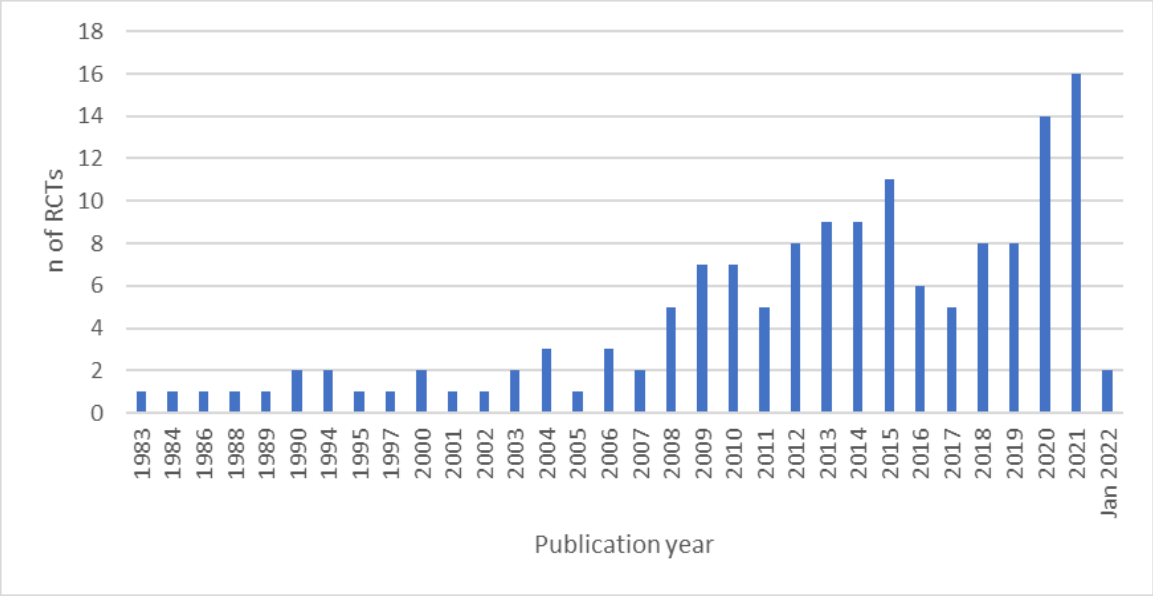
Abbreviations: RCT=randomised controlled trial; IFCDC= infant- and family-centred developmental care.

Study characteristics over time

Included RCTs were published between 1983 and January 2022, with an increasing publications' trend from 2008, most recent years accounting for the highest number of studies (**Figure 3.2.1b**). Specifically, 82.2% (n=120) RCTs were published after 2008, and 21.9% (n=32) in 2020-2022.

Most studies' characteristics did not significantly change over time (**Table 3.2.1a**). However, after 2016, RCTs in lower-and upper-middle income countries were more frequent (LMIC: 5.4% up to 2016 vs 26.4% after 2016, p=0.001, UMIC: 1.1% up to 2016 vs 15.1% after 2016, p=0.001). Moreover, the majority of RCTs including more than 300 caregivers (6 RCTs out of 7) were published after 2016 (p=0.009).

Figure 3.2.1b Number of RCTs on IFCDC published by year (N=146)



Abbreviations: RCT=randomized controlled trial; IFCDC= infant- and family-centred developmental care.

Category of intervention tested

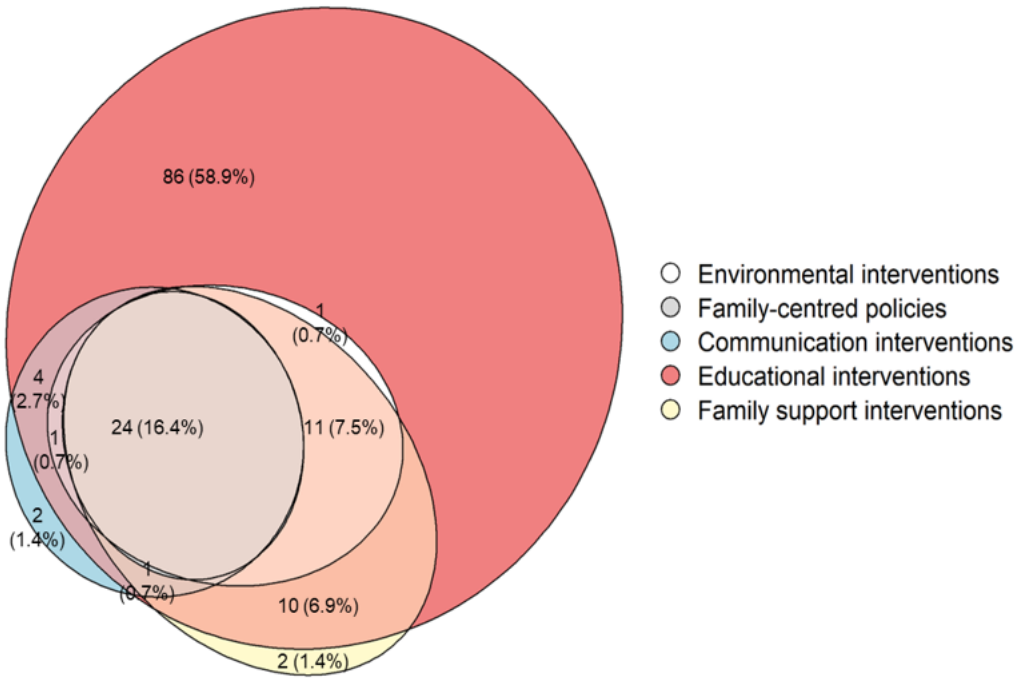
When interventions were classified into the five categories of IFCDC modified from Shields et al (Shields et al., 2012)(**Figure 3.2.1c**), educational interventions resulted the most common intervention type (138 RCTs, 94.5%), followed by family support interventions (48 RCTs, 32.9%), environmental interventions (39 RCTs, 26.7%) and communication interventions (32 RCTs, 21.9%). Family-centred policies had in general a low frequency with only 26 RCTs (17.8%).

The majority of RCTs reported single category interventions (94 RCTs, 64.4%) but one out of three were multi-category IFCDC interventions (52 RCTs, 35.6%).

More than half of the included RCTs (n=86, 58.9%) tested educational interventions as single intervention (**Figure 3.2.1c**) while all the other categories were rarely tested alone (each one in 2

studies, 1.4%) and all multi-category interventions tested included an educational component. Of all RCTs testing multi-category interventions nearly half (24 out of 52, 46.2%) included all five IFCDC categories, representing 16.4% of total RCTs.

Figure 3.2.1c Categories of IFCDC interventions studied in RCTs (146 RCTs)



Notes: in addition to the RCTs shown in the figure, 2 RCTs (1.4%) tested environmental interventions as single interventions and 2 RCTs (1.4%) tested family-centred policies as single category interventions.

Abbreviations: RCT=randomized controlled trial; IFCDC= infant- and family-centred developmental care.

Discussion

This first scoping review updates and expands on previous existing reviews (Benzies et al., 2013; Brecht et al., 2012; Brett et al., 2011; Ding et al., 2019; McAndrew et al., 2022; Ramezani et al., 2014; Segers et al., 2019; Shields et al., 2012; Yu & Zhang, 2019). It identifies 146 RCTs which is a much larger number compared to previously published systematic reviews (Benzies et al., 2013; Brecht et al., 2012; Brett et al., 2011; Ding et al., 2019; McAndrew et al., 2022; Ramezani et al., 2014; Segers et al., 2019; Shields et al., 2012; Yu & Zhang, 2019), and so represents an important body of evidence on possible interventions to promote IFCDC. Moreover, the increasing number of RCTs on IFCDC identified in the last years indicates an increasing interest in this topic, recognizing the pivotal role of IFCDC in promoting health in both newborns and caregivers.

This review provides important information for both researchers and policy-makers. The most relevant gap in current research on IFCDC interventions appears to be the lack of RCTs in low-income countries. Secondly, very few studies included fathers, especially alone, and siblings. The recent

EPINICU multicountry survey revealed that fathers of newborns hospitalized in the Italian NICU frequently suffered from mental distress and they may benefit from a more individualized approach and involvement in newborn care (Baldoni et al., 2021). Similarly, evidence suggests that siblings perceive as stressful the NICU hospitalization of their brother or sister and therefore would benefit to be more actively involved in IFCDC interventions (Aita et al., 2021; Greisen et al., 2009; Savanh et al., 2020). Thirdly, included RCTs focused primarily on very preterm and very/extremely low birthweight infants even though infants with gestational age above 34 weeks and birth weight ≥2000 g represent the most common NICU population in many settings (Braun et al., 2020).

Notably, the large number of monocentric RCTs with a small sample size identified by this systematic review seems to suggest constraints in conducting large studies on IFCDC, though after 2016 we found a significant increase in studies involving more than 300 caregivers. As a matter of a fact, several characteristics of the IFCDC interventions make it questionable if, at the current stage, the ideal study design to generate evidence in support of IFCDC interventions is an RCT. In fact, interventions to promote IFCDC are characterized by: 1) high complexity (multicategory); 2) high need to be tailored to the local setting, and therefore low directness; 3) high operator-dependence (e.g., motivation, human factor) therefore low reproducibility; 4) in principle, high plausibility for a benefit, if key principles of IFCDC are followed (e.g., sensitive and responsive care, parent engagement, customized adaptations of the NICU environment and of the hospital system) (Committee On Hospital Care and Institute For Patient- And Family-Centered Care, 2012). IFCDC interventions require multiple changes at multiple levels – structure, organization of care, technical skills and attitudes, and multiple resources, including a lot of staff, for a long time, in already very busy clinical departments such as NICUs. They also represent a major cultural shift (Cuttini M et al., 2020). A recent study identified as major factors affecting the implementation of IFCDC the following aspects: intervention source, cost, peer pressure, external policy and incentives, staff needs and resources, structural characteristics, organizational incentives and rewards, and knowledge, beliefs and attitudes (Zanoni et al., 2021). Actually, some of what may be among the key drivers of success of these interventions, such as good leadership capacity among different staff cadres, team attitude and good human dynamics, may need years to be established and evaluated.

Therefore, rather than investing in complex-design studies such as RCTs, which may suffer from both "study setting bias" as well as reporting bias, we believe that middle and long-term implementation research projects should be prioritised at this stage. Translating evidence into practice turns out to be particularly important considering that, despite in theory the principles of IFCDC have been widely accepted and advocated (Angelmar & Berman, 2007; Sumner et al., n.d.; World Health Organization, 2016), practical initiatives to translate these principles in actual care continue to be sporadically implemented (Ding et al., 2019; Gooding et al., 2011). Evidence shows that parent involvement in the care of newborns is still limited, while gaps remain in many aspects of newborn routine care, such as physician-parent communications, even in high income countries (Hagen et al., 2019; *Health Resources and Services Administration. National Survey of Children with Special Health Care Needs. Chartbook 2005–2006.*, n.d.). High rates of psychological distress among NICU parents (Caporali et al., 2020; Roque et al., 2017; Schappin et al., 2013)and lifelong medical and neurodevelopmental problems among many preterm and low birth weight infants (United Nations Inter-agency Group for

Child Mortality & IGME, 2021)further call for the urgent need to translate the IFCDC principles into actual policies, procedures, and culture.

Therefore, our recommendation for the future is for policy makers to work together with researchers and health workers to make available good documentation of implementation research projects. As recommended for implementation research, future studies should report more information on measures of acceptability, adoption, cost, penetration and sustainability (Wolfenden et al., 2021). More resources, including research funding opportunities, should also be made available to promote IFCDC as a human key right of newborns and their families.

Limitations of our scoping review included the possible presence of data collection bias. However, a broad comprehensive search strategy was used, based on the Cochrane review's definitions of IFCDC interventions (Shields et al., 2012), and on existing guidelines (Peters et al., 2015, 2020; The Joanna Briggs Institute, 2015). Multiple databases were searched without language barrier and hand-searching was also performed. Assessment of the risk of bias of included studies was not performed as not strictly recommended in scoping reviews (Peters et al., 2020). More details on the interventions and on the outcomes measured (number and type of tools used specifically for caregivers and infants) are provided in the two other reviews detailed in section 3.2.2 and 3.2.3.

3.2.2 Interventions to implement infant and family's centered developmental care in neonatal intensive and semi-intensive units: a scoping review of randomised controlled trials

Specific methods

As described in the methods section 3.2, from each included study we extracted the first author's name, year of publication, RCT design, study setting, categories of the intervention as specified above in an *ad-hoc* developed Excel spreadsheet. Additionally, specifically for this review, a REDCap 8.5.21- © 2021 Vanderbilt University- form was developed to collect details of IFCDC interventions such as: the name of the intervention, when available; the type of health professional involved in the intervention and whether the intervention prolonged after discharge. Furthermore, for each IFCDC category we extracted respectively type of: a) environmental interventions for improving NICU environment; b) policy and policy level for family-centred policies; c) interventions for improving communication and teamwork between parents and staff; d) interventions for supporting families. Since educational interventions could involve both parents and staff, we extracted independently for both groups data related to participants, format and setting, frequency and duration, training topic and delivery methods of each educational intervention.

The REDCap data extraction form was developed through an iterative process from previous reviews forms (McAndrew et al., 2022), pre-piloted and further optimised until considered satisfactory. Data extraction was independently performed by 3 authors. To ensure alignment in data charting and solve disagreements, regular discussion sessions were planned. Disagreements were solved through discussion or involvement of a fourth expert reviewer.

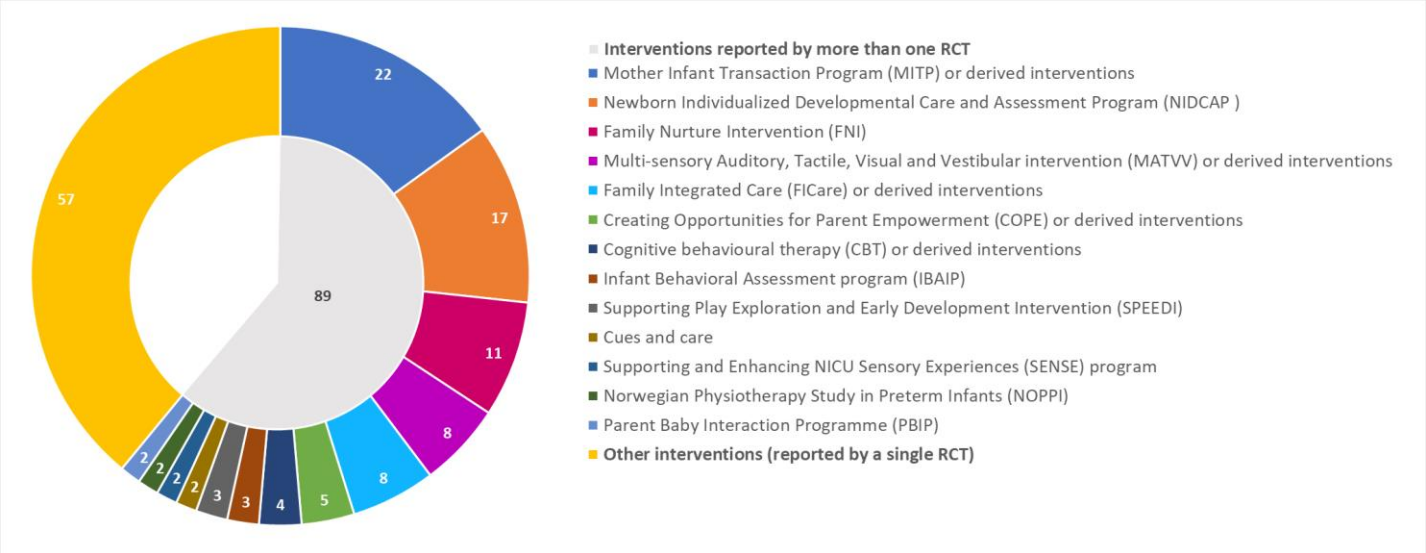
Data collected in both Excel spreadsheet and REDCap form were imported on R version 4.1.1 (R Foundation for Statistical Computing, Vienna, Austria. URL https://www.R-project.org/) and summarised in tables and figures to provide a menu of IFCDC interventions.

Results

Types of IFCDC interventions

In 146 RCTs identified we identified two groups of interventions were identified (figure 3.2.2a). The first group, covered by 89 RCTs (61.0% of the total RCTs), included 13 interventions for each of which several RCTs were available. The interventions, together with their derived ones, described in more than five published RCTs included: the Mother Infant Transaction Program (MITP) (22 RCTs, 15.1%), the Newborn Individualized Developmental Care and Assessment Program (NIDCAP) (17 RCTs, 11.6%), the Family Nurture Intervention (FNI) (11 RCTs, 7.5%), the Multi-sensory Auditory, Tactile, Visual and Vestibular intervention (MATVV) (8 RCTs, 5.5%), the Family Integrated Care (FICare) (8 RCTs, 5.5%), and the Creating Opportunities for Parent Empowerment (COPE) (5, 3.4%). The second group included 57 interventions, each one reported by a single RCT (39%).

Figure 3.2.2a Frequency of different types of IFCDC interventions (n=146 RCTs)

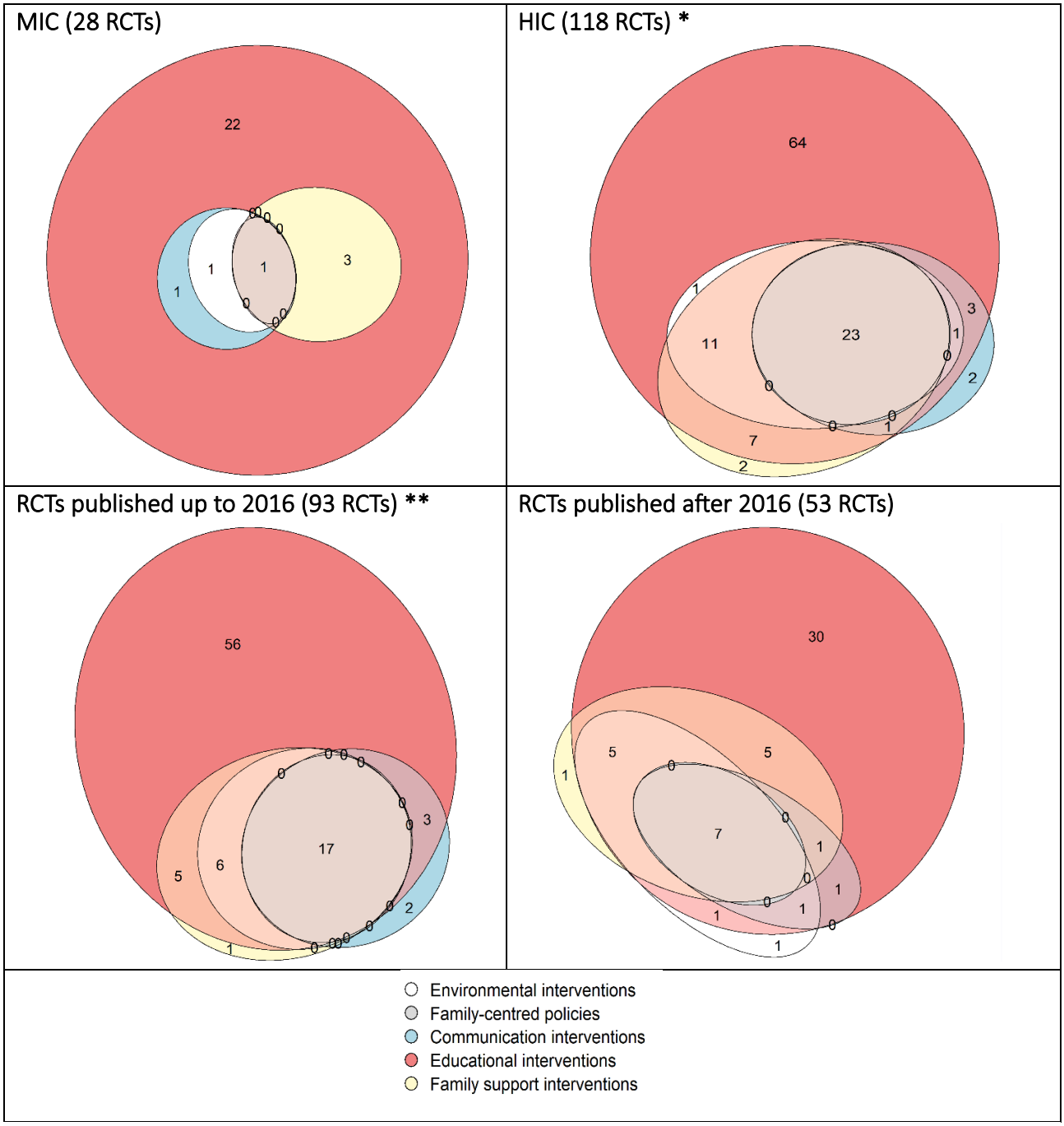


Note: Interventions classified as modified MITP, PremieStart and Early Parent Interaction program based on PremieStart were included as interventions derived from MITP; Hospital-Home Transition: Optimizing Prematures' Environment (H-HOPE) was included as intervention derived from MATVV; Alberta FICare FICare was included as intervention derived from FICare; interventions classified as modified COPE were included as interventions derived from COPE; interventions classified as modified CBT were included as interventions derived from CBT.

Subgroup analyses

Educational interventions were the most common intervention category (138 RCT, 94.5%), tested as single intervention in 86 RCTs while 52 were multi-category. In the subgroup analysis (**figure 3.2.2b**), family support interventions and environmental interventions were significantly more frequent in HICs compared to MICs (37.3% vs 14.3%, p=0.035; 31.4% vs 7.1%, p=0.018 respectively). The same tendency was also found for family-centred policies (21.2% vs 3.6%, p= 0.055). No difference in intervention categories was found by time period, however a post-discharge extension of the intervention was more common in RCTs published up to 2016 rather than after 2016 (50.5 % vs 26.4%, p=0.008).

Figure 3.2.2b Frequency of different categories of IFCDC interventions by subgroups (n=146 RCTs)



Notes: * in addition to the RCTs shown in the figure, 2 RCTs tested environmental interventions as single intervention and 2 RCTs tested family-centred policies as single component interventions; ** in addition to the RCTs shown in the figure, 2 RCTs tested family-centred policies as single intervention.

Abbreviations: HIC = high income country; IFCDC = infant- and family-centred developmental care; MIC = middle income country; RCT= randomised clinical trial.

Characteristics of IFCDC interventions

The menu of the interventions available for each of the 5 IFCDC categories is depicted in **figure 3.2.2c.**

Educational interventions targeted either mothers (55 RCTs, 37.7%) or both parents (82 RCTs, 56.2%) while no educational intervention was dedicated to fathers only. Only a minority involved other family members different from parents (e.g., siblings, grandparents) (16 RCTs, 11%).

One-to-one (106 RCTs, 72.6%) and practical sessions (121 RCTs, 82.9%) organised in mini-courses (67 RCTs, 45.9%) including more than three sessions (92 RCTs, 63%) were the most reported format of the educational interventions for parents, with oral (118 RCTs, 80.8%) and/or written (66 RCTs, 45.2%) as the most frequent delivery methods. Only few interventions included digital technologies such as apps (3 RCTs, 2.1%) or digital/online resources (19 RCTs, 13.0%).

The most frequent educational topics were: infant behaviours (116 RCTs, 79.5%) focusing mainly on infant cues (114 RCTs, 78.1%); parenteral role and interaction with the baby (127 RCTs, 87%) especially with regard to parent response to infant cues (106 RCTs, 72.6%) and touch stimulation (96 RCTs, 65.8%) (figure 3.2.2c and 3.2.2d). Parental mental wellbeing and transition to home were also frequent topics (65 and 63 RCTs, 44.5% and 43.2%, respectively) and they mainly focused on, respectively, parent-staff discussion of parental emotional issues related to pregnancy, NICU environment or infant health condition (46 RCTs, 31.5%) and infant and family's special care needs at discharge (35 RCTs, 24%).

Educational interventions for staff were reported by 81 RCTs (55.5%). However, details on the format, frequency, duration and delivery method were not specified in most of the cases (figure 3.2.2c).

The most frequent family support interventions were peer-to-peer support (26 RCTs, 17.8%) and socio-psychological support (e.g., referral to social services/psychologists) (16 RCTs, 11%) (figure 3.2.2c). Economical supports (10 RCTs, 6.8%) consisted on parking or public transport vouchers (7 RCTs in HIC and 1 in China), parking pass (one RCT from Canada), money transfer- $200-$600 per week- (one RCT from US).

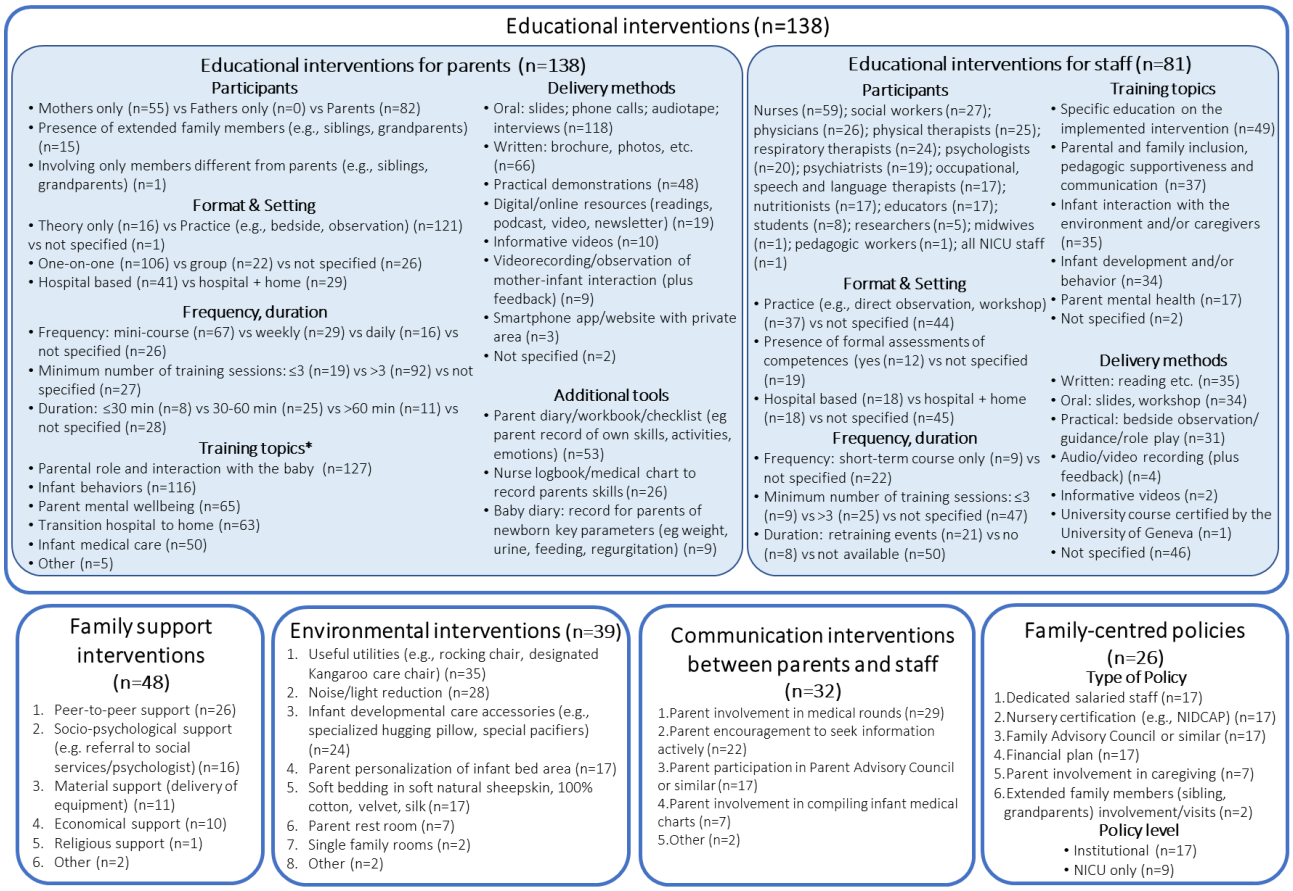
Environmental interventions included either interventions requiring low efforts, such as reducing noise/light (28 RCTs, 19.2%) or parent personalization of infant bed area (17 RCTs, 11.6%) or IFCDC accessories (e.g., specialized hugging pillow, special pacifiers) (24 RCTs, 16.4%), or high efforts such as special ward physical structure, e.g., providing useful utilities (e.g., rocking chair, designated Kangaroo care chair) (35 RCTs, 24%) or implementation of parent rest rooms (7 RCTs, 4.8%) or single family rooms (2 RCTs, 1.4%) (figure 3.2.2c).

The most common communication interventions included parent involvement in medical rounds (29 RCTs, 19.9%) and parent encouragement to seek information actively (22 RCTs, 15.1%).

Dedicated salaried staff (17 RCTs, 11.6%), nursery certification (e.g., NIDCAP) (17 RCTs, 11.6%), a financial plan (17 RCTs, 11.6%), and Family Advisory Council or similar (17 RCTs, 11.6%) were the most frequent family-centred policies implemented at institutional or NICU level (17 RCTs, 11.6% and 9 RCTs, 6.2%, respectively).

Figure 3.2.2d. describes all the training topics of the educational interventions on parents.

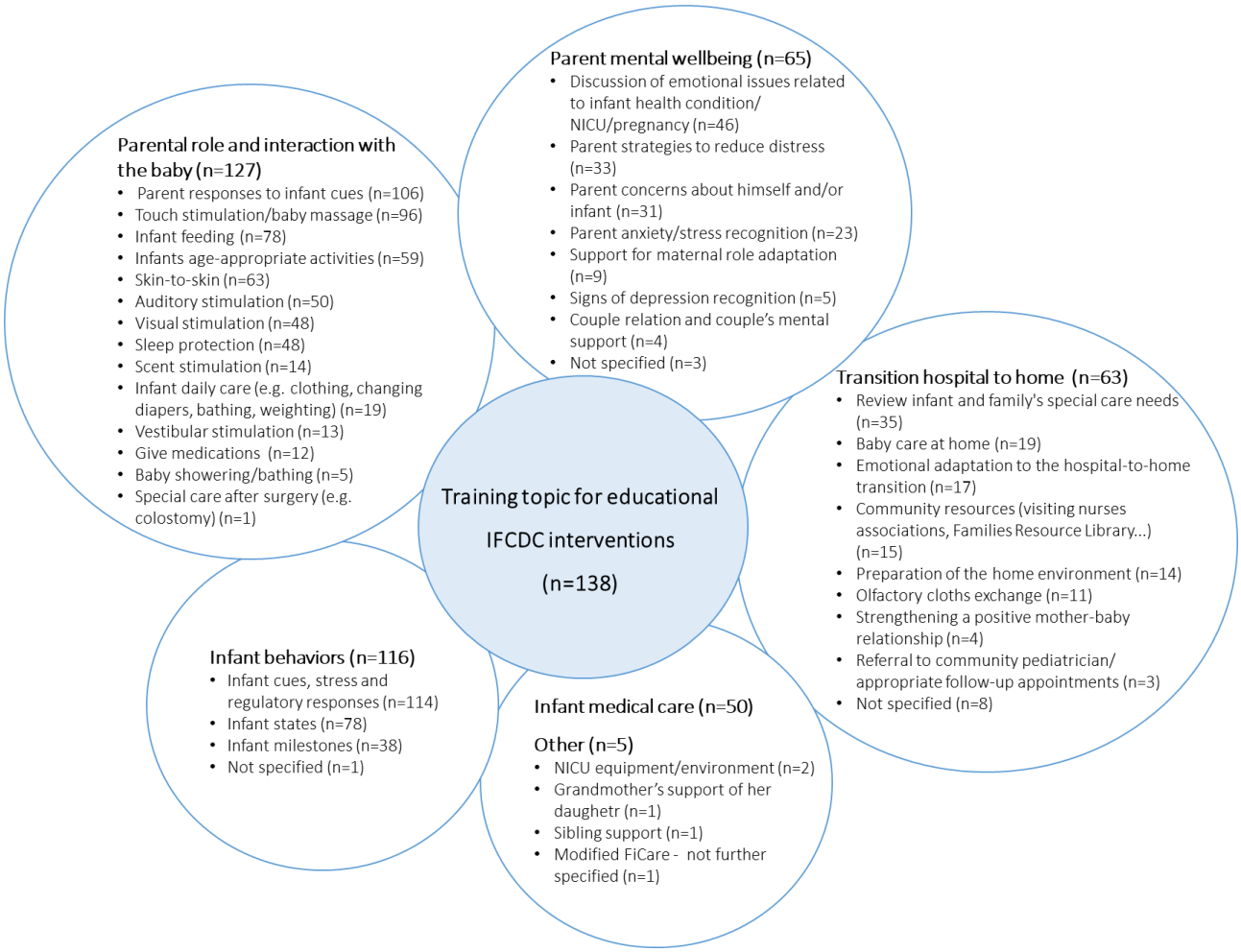
Figure 3.2.2c Menu of IFCDC interventions by categories (n=146 RCTs)



Notes: * Training topics are further detailed in Figure 3.2.2d.

Abbreviations: IFCDC = infant- and family-centred developmental care.

Figure 3.2.2d. IFCDC educational interventions for parents (n=146 RCTs)

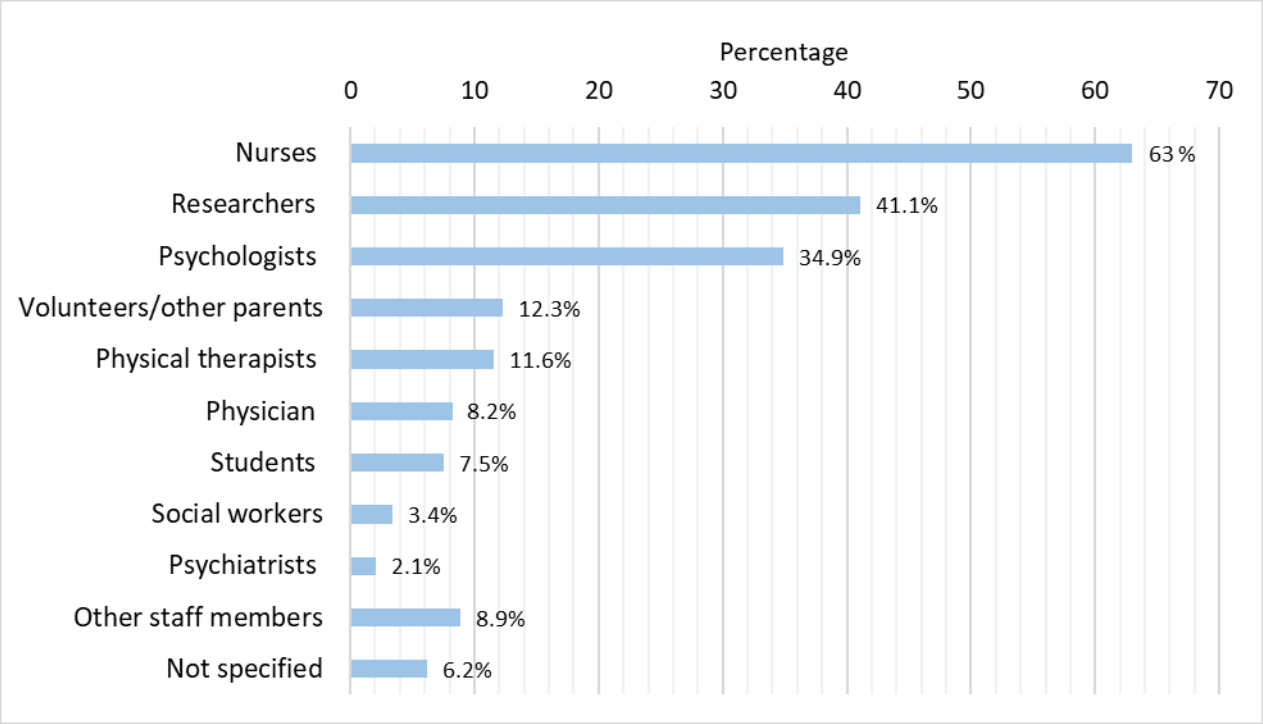


Abbreviations: IFCDC = infant- and family-centred developmental care.

Population involved in the intervention

Across the 146 RCTs identified, the two populations most frequently involved in the interventions were nurses (92 RCTs, 639%), researchers (60 RCTs, 41.1%) and psychologists (51 RCTs, 34.9%), followed by volunteers and physical therapists (**Figure 3.2.2e**). Physicians were reported to be involved in an intervention only in 8.2% of RCTs (12 RCTs) while in 9 RCTs (6.2%) the type of involved health professional was not specified.

Figure 3.2.2e Type of health professionals involved in IFCDC intervention (n=146 RCTs)



Note: Volunteers/other parents did not include health professionals; other staff members included lactation consultant, dietician, pharmacist, respiratory therapist, pharmacist, respiratory therapists, midwife software engineer, pedagogic workers or all NICU staff.
Abbreviations: IFCDC = infant- and family-centred developmental care.

Discussion

This scoping review summarises IFCDC interventions described in the 146 included RCTs in a synthetic menu of interventions that can facilitate identifying research gaps, choosing what interventions to implement as more feasible and appropriate in each setting, and developing new interventions either as stand-alone or a combination of different intervention categories. Although the majority of the included RCTs focused on a set of predefined IFCDC interventions such as NIDCAP, MITP and FNI, 57 (39%) RCTs reported another 57 IFCDC interventions, confirming that there is a very wide range of possible IFCDC interventions.

Interestingly, no IFCDC intervention was conducted in low-income countries where newborn mortality rate is higher (United Nations Inter-agency Group for Child Mortality & IGME, 2021), indicating that further research is needed to explore interventions tailored in low resource settings. Differences between HIC and MIC mainly in family support and environmental interventions, and secondarily in family-centred policies, may be explained by a different availability of resources and different priorities. Providing a psychological or economical support (Franck et al., 2022; Hall, Cross, et al., 2015; Hall et al., 2019) or single-family rooms (O'Callaghan et al., 2019; Soni et al., 2022) may be challenging, even in some HIC settings.

The most frequent IFCDC interventions were educational, thus calling for more documentation on the other intervention categories. Family-centred policies were the less frequently described, though policies are fundamental in establishing and reinforcing the commitment of the single unit or hospital in implementing IFCDC. Educational interventions addressing mothers or parents were often described in detail in the included RCTS. In their systematic review, Ding et al. identified education as the first step for implementing IFCDC (Ding et al., 2019)and other reviews recognised it as critical to the successful implementation of the IFCDC (Abukari & Schmollgruber, 2023; Shields et al., 2012). From our study education on parental role and on recognition of infant behaviour and responsive interaction emerged as the main parental educational topics, reflecting on the core pillars of IFCDC. Similarly, for Ding et al. education needed to provide parents skills and knowledge of newborn care (Ding et al., 2019). However, parental mental wellbeing was addressed less frequently although its potential effect on both short- and long-term outcomes of infants is well known (Huhtala et al., 2012; Lean et al., 2018). Similarly, addressing issues related to discharge to home was described in 25% of educational interventions, even if transition hospital-to-home can represent a stressful and delicate event for the family (Purdy et al., 2015; Smith et al., 2013).

Another key research gap was the lack of educational interventions entirely dedicated to fathers and of a comprehensive reporting on the educational interventions of staff. Other studies highlighted lower fathers' participation (Separation and Closeness Experiences in Neonatal Environment (SCENE) research group, 2016). To overcome possible barriers such as influence of society and staff on father's role (Mprah et al., 2023), targeted interventions on fathers, such as the "father-friendly NICU" developed in a recent quasi-experimental study (Risanger et al., 2023), may be developed and tested, also including staff education component to encourage their NICU involvement. Since staff education is recognised as a key component to implement IFCDC (Abukari & Schmollgruber, 2023; Hall, Cross, et al., 2015; Mprah et al., 2023; Soni & Tscherning, 2021), detailed reporting on educational interventions for staff is mandatory.

Nurses were the health professionals mostly involved in the interventions. Although nurses are frequently identified as IFCDC facilitators and key professionals for strengthening parental competencies thanks to parent-staff co-creation of knowledge and negotiation of roles (Brødsgaard et al., 2019; Dittman & Hughes, 2018), a more comprehensive staff involvement is warranted when implementing IFCDC interventions. Physicians apparently were the less involved, although they are key actors in the communication with the families and in their empowerment. The low frequency of physician involvement however might be explained if part of them were included in the "researchers" group.

Digital technologies (e.g., video, apps, online resources) were described and used in few interventions only. In their systematic app review, Richardson et al. confirmed a paucity of research on app quality and benefits and identified credibility and usability issues and low informational quality as main problems of the retrieved apps targeting NICU parents (Richardson et al., 2019). Multiple other mobile health interventions (e.g., daily SMS, WhatsApp messages) were recently developed but their impact on parent or newborn outcomes is still limited (Dol et al., 2017; Riskin et al., 2022).

The analysis of studies published before and after2016 highlighted no main changes in IFCDC interventions, except that interventions including an extension after discharge were more frequently described before 2016, suggesting a possible lack of resources to support long term interventions.

Despite the wide range of interventions supporting IFCDC, many barriers for IFCDC implementation can be encountered (Franck & O'Brien, 2019). A transition from experimental to implementation studies is needed to integrate IFCDC interventions in NICU policies and routine care. The participation of stakeholders, policy-makers and managers at this process is fundamental to create a culture of information promoting IFCDC. Our menu of interventions may guide policy-makers in implementing the best IFCDC intervention in a specific local setting. The wide range of interventions analysed should encourage to develop also *ad hoc setting-specific* interventions.

3.2.3 Outcomes and measurements methods to evaluate infant and family's centered developmental care in neonatal intensive and semi-intensive units: a scoping review of randomised controlled trials

Specific methods

For this review a specific ad-hoc Excel spreadsheet was developed to collect data related to study outcomes. Firstly, for each included study we tabulated the *measured outcomes*, and identified the *population* in which the outcome was measured (i.e., parents, infants, other). To simplify reporting, outcomes measuring the parent-infant interaction were classified under the population of "parent" although in reality they involved both infants and parents.

Secondly, we divided outcomes by *categories*. Given the lack of pre-existing categories of IFCDC outcomes, and the high heterogeneity in the wording used to describe similar outcomes, we developed a list of categories by identifying and tabulating keywords used in the full text paper of identified RCTS to describe each outcome. Keywords were then grouped in categories by two senior neonatologists and three expert researchers. For example, "neurobehavioural", "behaviour", "development", "cognitive" were terms used to identify similar outcomes, and these were grouped in the infant "neurobehavioural and developmental" category. The list of categories of outcomes together with the keywords is shown in Table 3.2.3a.

Table 3.2.3a List of categories of outcomes and relative keywords

CATEGORIES OF OUTCOMES	KEYWORDS USED IN RCTS TO DESCRIBE EACH OUTCOMES
Outcomes measured on parents	
1. Mental disorders	
•Stress	stress, salivary cortisol
•Anxiety	Anxiety
•Depression	Depression
•Post traumatic stress disorder	post-traumatic stress disorder
•Other mental disorders	mental health, emotional coping, wellbeing, psychopathology
2. Participation/ interaction/ attachment	participation (maternal visits to hospitalized infants, KMC periods, time spent by attendant), maternal awareness and sensitivity, involvement, interaction, bonding, behavior, copying strategy
3. Perceptions and beliefs on self-efficacy/ confidence in caregiving	self-efficacy, beliefs in parenting competencies, confidence in caregiving, knowledge on infant behaviours and characteristics, sense of competence, maternal adaptation, attitude, worry about child health, perception of vulnerability, knowledge of infant development
4. Parent satisfaction	parent opinion, satisfaction (about staff, care and support)
5. Staff-parent interaction	perception of health workers support, staff-parent interaction or partnership, content and quality of patient-physician communication
Outcomes measured on infants	
1.Neurobehavioural and developmental outcomes	neurobehavioural, behaviour, development, cognitive, language, fine motor, gross motor, motor, impairment, disability, temperament, neurologic, psychomotor, executive function, visual attention, communication, reaching skills, problem-solving behaviour, functioning, intellectual, socio-emotional and behavioural problems, social relatedness, temperament
2. Neurophysiological outcomes	neurophysiologic, “brain development”
3. Neurostructural outcomes	Neurostructure
4. Any health outcomes	
• growth	weight gain, growth, weight, height, head circumference, physical development, anthropometric indices, extrauterine growth restriction

• Infection	sepsis/nosocomial infection
• Nutrition	gavage, feeding, nutrition, breast, bottle-feeds, enteral, parenteral
• Retinopathy of prematurity	retinopathy of prematurity,
• Bronchopulmonary dysplasia	bronchopulmonary dysplasia, chronic lung disease
• Pneumothorax	Pneumothorax
• Necrotizing enterocolitis	necrotizing enterocolitis
• Patent ductus arteriosus	patent ductus arteriosus
• Intraventricular hemorrhage	intraventricular hemorrhage
• Periventicular leukomalacia	periventicular leukomalacia
• Mortality	Mortality
• Others	morbidity, medical outcomes, autonomic function, heart rate, methylation levels, visual function, cerebral palsy, quality of life, skin to skin
5. Healthcare outcomes	
• Any respiratory support	oxigen, O2, Mechanical ventilation, continuous positive airway pressure (CPAP)
• Hospitalization information	hospitalization, days in hospital, length of stay, age at discharge, number of days in intensive care unit, readmissions, access to emergency department
• Other	indomethacin administration, antibiotic use
6. Cost	hospital charges, medical expenditures, hospitalization charges
Outcomes measured on siblings	
Perception, beliefs, emotions and behaviours	perception, beliefs, emotions, reaction, behaviour, emotional impact
Outcomes measured on health workers	
Health worker satisfaction	opinion, satisfaction (about staff, care and support)

Thirdly, we extracted number, name and *type of measurement tools* used for outcome assessment (when available) according to four main types: 1. parent/self-completed questionnaire; 2. clinical/medical data/costs; 3. instrumental measures; 4. videos, interviews, tests or observations conducted by specialists.

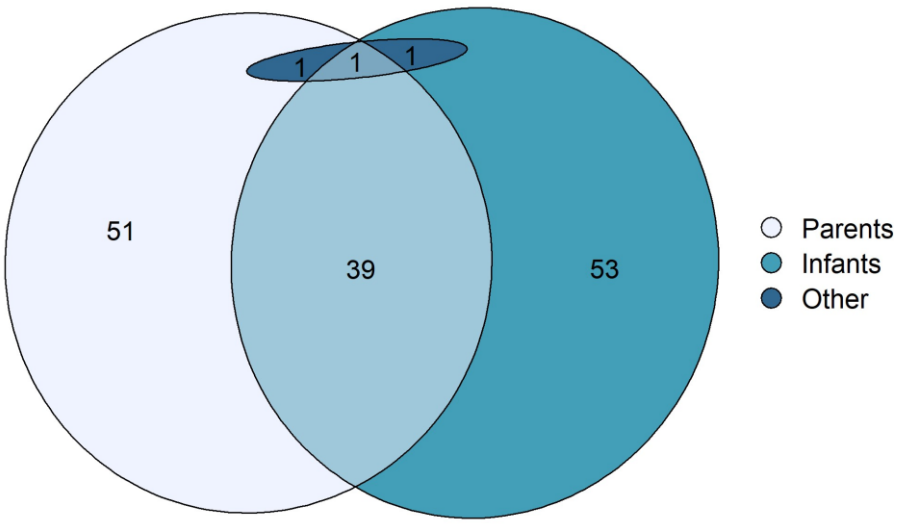
Lastly, we extracted information related to the *timings* when outcome was measured, registering the presence of multiple outcome assessments (yes/no); the presence of (at least one) intra-hospital assessments (yes/no) and timings of the last follow up assessment when performed (≤3 months after birth, 4-11 months, 12-23 months, ≥24 months).

Results

Number of outcomes and populations

Among the 146 included RCTs, 359 outcomes were retrieved with an average of two outcomes per RCT (SD=1.6, median=2; IQR= 1-3) and a wide range (range 1-8). In terms of measurement population, outcomes were mostly measured on infants only (53 RCTs, 36.3%), on parents only (51 RCTs, 34.9%), or on both infants and parents (39 RCTs, 26.7%) (**Figure 3.2.3a**). Among parents, mothers were the most represented (60 RCTs, 41.1% of the total RCTs), 32 RCTs (21.9%) reported on both parents, while only 1 focused only on fathers. No outcome was measured on caretakers other than parents. Two studies reported outcomes measured on siblings while outcomes measured on health workers were reported only in one RCT.

Figure 3.2.3a Populations in which IFCDC outcomes were measured across included RCTs



Notes: "Other" identifies two RCTs with outcomes measured on siblings, and one on health workers. Abbreviations: IFCDC = infant and family's centered developmental care; RCT = randomised controlled trial

Categories of outcomes

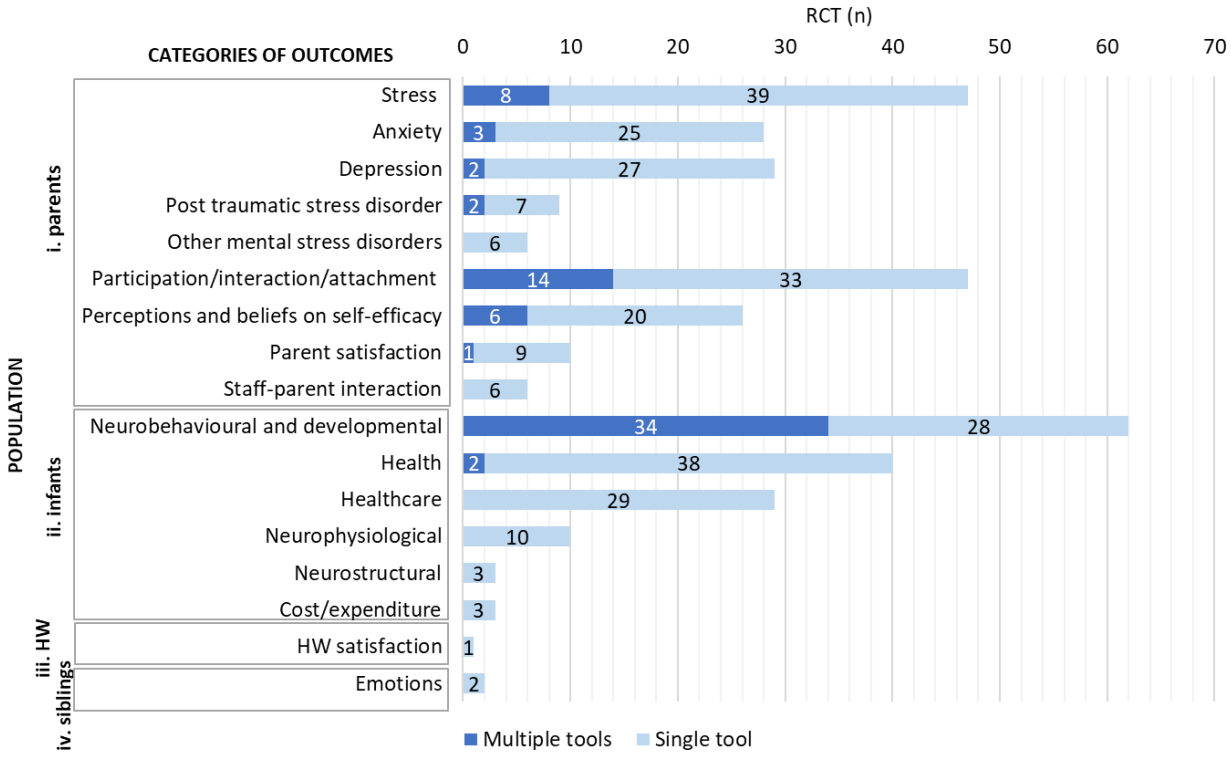
Figure 3.2.3b provide a list with frequency of outcomes used, by category and population. Category of outcome assessed varied by population (**Figures 3.2.3b**). In parents the two most frequent categories of outcomes were: 1) parental mental health conditions (61 RCTs), in particular stress (47

RCTs, 32.2% of total RCTS), depression (29 RCTs, 19.8%) and anxiety (28 RCTs, 19.2%); and 2) participation/interaction/attachment (47 RCTs, 32.2%).

In newborns the most frequent category of outcomes measured was the neurobehavioural and developmental (62 RCTs, 42.5%), followed by health outcomes (**Figure 3.2.3b**).

In health workers, satisfaction was the only outcome described in only one RCT, while in siblings (2 RCTs) the outcome described was emotions.

Figure 3.2.3b List and frequency of outcomes, by categories and population



Measurement tools

Overall, we listed 151 distinct outcome measurement tools, used in the 146 RCTs, detailed in **Figure 3.2.3c** and **Figure 3.2.3d**. Among these, 85 tools were used for parents **Figure 3.2.3c**, 79 for infants **Figure 3.2.3d**, two for siblings and one for health workers. Among parents, the category of outcomes with the higher number of measurement tools was participation/interaction/attachment (33 distinct tools), while among newborn it was neurobehavioural and developmental category (61 distinct tools). The majority of the RCTs used already developed tools while 24 (16.4%) RCTs for parents and 7 for infants developed ad hoc tools for the study, such as ad hoc questionnaires, or used unspecified tools, such as video assessments.

For the categories of outcomes most frequently reported among parents (stress, anxiety, depression), the *Parental Stressor Scale* (PSS:NICU) (27 RCTs, 18.5%) and *Parenting Stress Index* (15 RCTs, 10.3%) were the most common tools used to assess stress, while the *Edinburgh Postnatal Depression Scale* (9 RCTs, 6.1%) and the *Self-Trait Anxiety Inventory* (20 RCTs, 13.7%) were the most frequent for depression and anxiety respectively.

Participation/interaction/attachment category was evaluated with a heterogeneity of parent-completed questionnaires (22 RCTs, 15.1%) or assessments conducted by specialists such as videos, tests or observations (27 RCTs, 18.5%). Perceptions/beliefs on parent self-efficacy was evaluated in 26 RCTs (17.8%), mostly with parent-completed questionnaires. Ad hoc questionnaires were used in 9 out of 11 RCTs assessing parent satisfaction while the health workers' support was measured in 5 RCTs (3.4%) either with questionnaires (4 RCTs, 2.7%) (i.e., *Nurse Parent Support Tool, Pediatric Nurse-Parent Partnership Scale, Arizona Social Support Interview*) or audio records of daily rounds.

Figure 3.2.3c List of measurement tools used to assess outcomes in parents, by categories of outcomes

Participation/interaction/attachment (47 RCTs)

Self/parents completed questionnaires (22 RCTs)
1.Family Environment Scale (FES) (2 RCTs)
2.Index of Parental Participation/Hospitalized Infant (IPP-HI) (2 RCTs)
3.Maternal-Infant Interaction Scale (MIIS) (2 RCTs)
4.Maternal Postnatal Attachment Scale (MPAS) (2 RCTs)
5.Postpartum Bonding Questionnaire PBQ (2 RCTs)
6.Ways of coping questionnaire (WAYS) (2 RCTs)
7.Knowledge of Preterm Infant Behavior (KPIB) scale (1 RCT)
8.Maternal Attachment Inventory (MAI) (1 RCT)
9.Maternal Participation in Caring for Preterm Infant's Checklist (MPCPI) (1 RCT)
10.Missouri Behavioral Checklist (MBCL) (1 RCT)
11.Mother-to-Infant Bonding Scale (MIBS) (1 RCT)
12.My baby and I (MBI) (1 RCT)
13.Quality of Maternal Caregiving Behavior (MCB) (1 RCT)
14.Yale Inventory of Parental Thoughts and Actions (YIPTA) (1 RCT)
Tools developed ad-hoc for the study or unspecified
15. Diary (6 RCTs)
16. Ad hoc questionnaires (1 RCT)
Video, interview, tests or observation conducted by specialists (27 RCTs)
1.Home Observation for Measurement of the Environment (HOME) (5 RCTs)
2.Nursing Child Assessment Feeding Scale (NCAFS) (4 RCTs)
3.Nursing Child Assessment Satellite Training (NCAST) (3 RCTs)
4.Dyadic Mutuality Code (DMC) (2 RCTs)
5.Nursing Child Assessment Teaching Scale (NCATS) (2 RCTs)
6.Avant's attachment behavior checklist (AVANT) (1 RCT)
7.Behavioral observation checklist (1 RCT)
8.Index of Parental Behaviour-NICU (IPB) (1 RCT)
9.Interaction With Infant-NICU (VAS-I) Involvement in Infant Care-NICU
Sensitivity to Needs of Infant-NICU (VAS-S) (1 RCT)
10.Maternal Behavioral Q-Set (MQB) (1 RCT)
11.Monash Mother-Infant Interaction Scale (1 RCT)
12.Mother–Infant/Toddler Play Scale (1 RCT)
13.Nursing notes (1 RCT)
14.Price Assessment of Infant-Mother Empathy Scale (1 RCT)
15.Relationship Competencies Assessment observation (RCA) (1 RCT)
Tools developed ad-hoc for the study or unspecified
16. Video assessment (13 RCTs)
Clinical/medical data (5 RCTs)

Perceptions/beliefs on parent self-efficacy (26 RCTs)

Self/parents completed questionnaires (23 RCTs)
1. Parental Beliefs Scale - NICU (PBS) (4 RCTs)
2. Mother and Baby Scales (MABS) (2 RCTs)
3. Parenting Sense of Competence Scale (PSOC) (2 RCTs)
4. Perceived maternal parenting self-efficacy (PMP-SE) (3 RCTs)
5. Worry Index (2 RCTs)
6. Broussard Degree of Bother Inventory (DBI) (1 RCT)
7. Broussard Neonatal Perception Inventory (NPI) adapted for parents of prematures (1 RCT)
8. Child-Rearing Practices Report (CRPR) (1 RCT)
9. Hereford scores (1 RCT)
10. Knowledge of infant development inventory (KIDI) (1 RCT)
11. Maternal Confidence Questionnaire (MCQ) (1 RCT)
12. NICU-modified maternal role adaptation questionnaire (MRA:NICU) (1 RCT)
13. Maternal Self-Efficacy Scale (MSES) (1 RCT)
14. Maternal Self-Report Inventory (MSRI) (1 RCT)
15. Mother's View of the Child (MVC) (1 RCT)
16. Parenting Stress Index (PSI) (subset scale) (1 RCT)
17. Press-Ganey discharge questionnaire (1 RCT)
18. Quality of life 5-dimensions 5-levels (EURO QoL5D-5L) (1 RCT)
19. Seashore scores (1 RCT)
20. Vulnerable Child Scale (1 RCT)
Tools developed ad-hoc for the study
21. Ad hoc questionnaire (3 RCTs)
Interview conducted by specialists (1 RCT)

Mental health disorders (61 RCTs)

i. Stress (47 RCTs)

Self completed questionnaires (47 RCTs)
1. Parental Stressor Scale Neonatal Intensive Care (PSS:NICU) (27 RCTs)
2. Parenting Stress Index (PSI) (15 RCTs)
3. Perceived stress scale (PSS) (3 RCTs)
4. Stanford Acute Stress Reaction Questionnaire (SASRQ) (3 RCTs)
5. Davidson Trauma Scale (DTS) (1 RCT)
6. Margaret inventory (1 RCT)
7. Nijmegen Parenting Stress Index (NOSIK) (1 RCT)
8. Perinatal Post-Traumatic Stress Disorder Questionnaire (PPQ) (1 RCT)
9. Post Traumatic Stress Disorder (PTSD) Checklist 5 (PCL-5) (1 RCT)
10. Traumatic Events Questionnaire (TEQ) (1 RCT)
11. Zung self-assessment instrument (SAS) (1 RCT)
Clinical/medical data (3 RCTs)

ii. Depression (29 RCTs)

Self/parents completed questionnaires (27 RCTs)
1.Edinburgh Postnatal Depression Scale (EPDS) (9 RCTs)
2.Beck Depression Inventory (BDI) (7 RCTs)
3.Center for epidemiological studies depression scale (CESD) (5 RCTs)
4.Profile of Mood States (POMS) (3 RCTs)
5.Depression Adjective Checklists (DACL) (1 RCT)
6.Hospital anxiety and depression scale (HADS) (1 RCT)
7.Panic Disorder Severity Scale (PDSS) (1 RCT)
8.Questionnaires of Goldberg General Health (GHQ) (1 RCT)
Video, interview, tests or observation conducted by specialists (4 RCTs)

iii. Anxiety (28 RCTs)

Self/parents completed questionnaires (28 RCTs)
1.State-Trait Anxiety Inventory (STAI) (20 RCTs)
2.Beck Anxiety Inventory (BAI) (3 RCTs)
3.Profile of Mood States (POMS) (3 RCTs)
4.Goldberg General Health (GHQ) (1 RCT)
5.Hospital anxiety and depression scale (HADS) (1 RCT)
6.Zung self-assessment instrument (SAS) (1 RCT)
Interviews conducted by specialists (3 RCTs)

iv. Post traumatic stress disorder (9 RCTs)

Self/parents completed questionnaires (9 RCTs)
1.Perinatal PTSD Questionnaire (PPQ) (5 RCTs)
2.Davidson Trauma Scale (DTS) (3 RCTs)
3.Impact Event Scale-Revised (IES-R) (1 RCT)
Interviews conducted by specialists (2 RCTs)

v. Other mental stress disorders (7 RCTs)

Self/parents completed questionnaires (6 RCTs)
1. Profile of Mood States (POMS) (3 RCTs)
2. Questionnaires of Goldberg General Health (GHQ) (1 RCT)
3. Self-report Social Adjustment Scale (SAS-SR) (1 RCT)
4. Behavioral Inhibition System and Behavioral Activation System (BISBAS) (1 RCT)
Video, interview, tests or observation conducted by specialists (1 RCT)

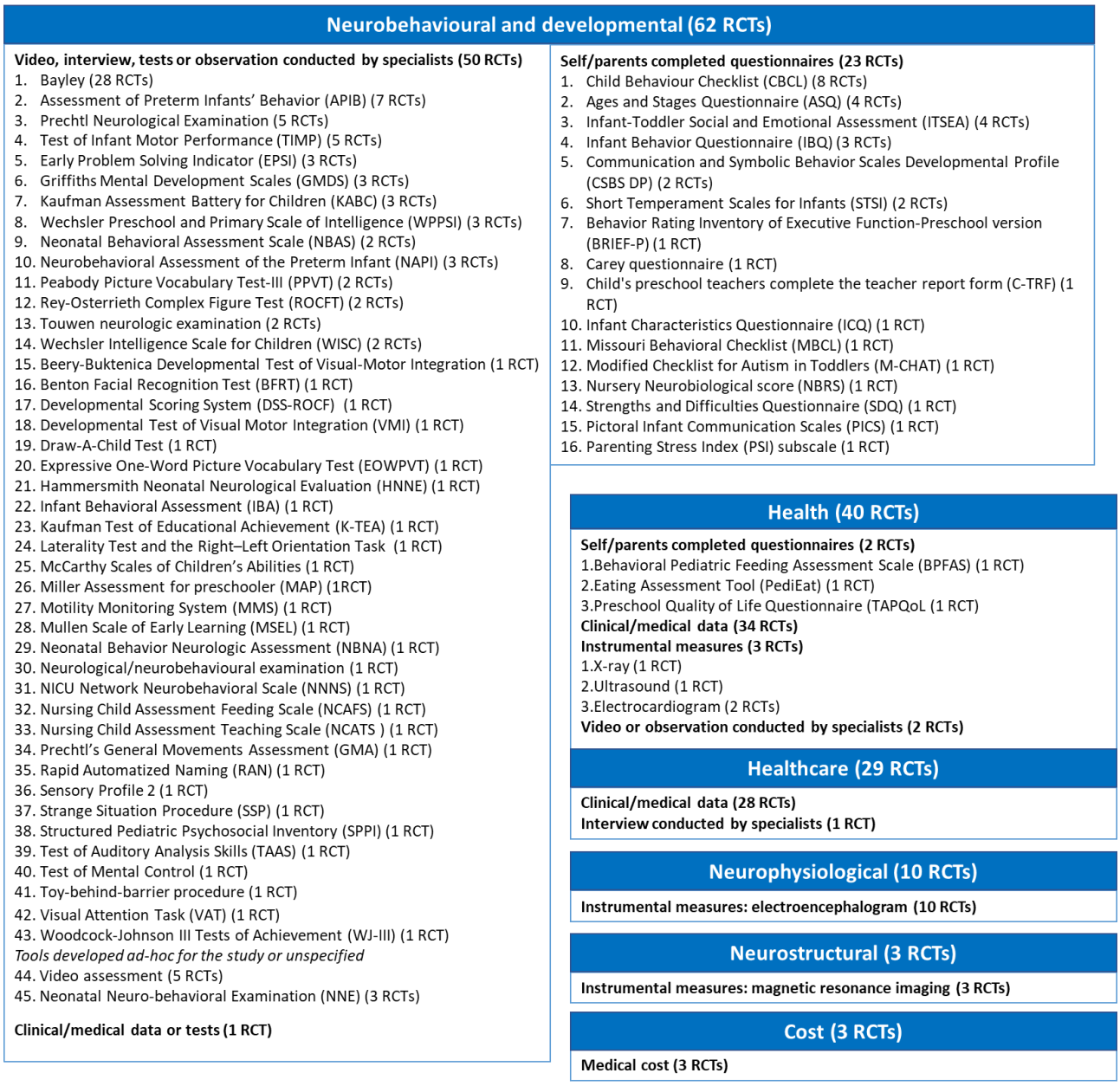
Satisfaction (11 RCTs)

Self/parents completed questionnaires (9 RCTs)
1.Family Inventory of Needs–Pediatrics (FIN-PED) (1 RCT)
Tools developed ad-hoc for the study
2. Survey/ad hoc questionnaire (9 RCTs)
Interview conducted by specialists (2 RCTs)

HW support (5 RCTs)

Self completed questionnaires (4 RCTs)
1. Nurse Parent Support Tool (NPST) (2 RCTs)
2. Pediatric Nurse-Parent Partnership Scale (1 RCT)
3. Arizona Social Support Interview (1 RCT)
Audio records of daily rounds (1 RCT)

Figure 3.2.3d List of measurement tools used to assess outcomes in infants, by categories of outcomes



Note: no distinction in reporting was made between the use of original version, updated versions, short-versions or subscale of questionnaires (e.g., Bayley Scales of Infant Development original version, second and third edition were presented as "Bayley"); 36 RCTs measuring outcomes on infants used multiple tools.

Timings of outcome measurements

56 RCTs (38.4%) included multiple time assessments (Table 3.2.3a). Outcomes were measured during hospitalization in 104 RCTs (71.2%), while 93 RCTs (63.7%) included post-discharge measurements. Of these latter, the most frequent post-discharge follow-up measurement was short with 70 RCTs out of 93 (75.3%) reporting a follow up less than 1 year. (Table 3.2.3a).

Table 3.2.3a Timings of outcome measurements

	Total RCTs N=146 n (%)	RCTs conducted in HICs N=118 n (%)	RCTs conducted in MICs N=28 n (%)	*p-value*	RCTs published up to 2016 N=93 n (%)	RCTs published after 2016 N=53 n (%)	*p-value*
Multiple time-point assessments	56 (38.4)	52 (44.1)	4 (14.3)	***0.004***	45 (48.4)	11 (20.8)	***0.001***
During hospitalization	104 (71.2)	77 (65.3)	27 (96.4)	***<0.001***	61 (65.6)	43 (81.1)	***0.046***
Post discharge outcome assessment	93 (63.7)	79 (66.9)	14 (50.0)	*0.094*	67 (72.0)	26 (49.1)	***0.005***
Post discharge follow up:							
≤ 3 months from birth	26/93 (27.9)	15/79 (19.0)	11/14 (78.6)	***0.001***	16/67 (23.9)	10/26 (38.5)	*0.160*
4-11 months from birth	25/93 (26.9)	24/79 (30.4)	1/14 (7.1)	*0.102*	23/67 (34.3)	2/26 (7.7)	***0.009***
12-23 months from birth	19/93 (20.4)	17/79 (21.5)	2/14 (14.3)	*0.727*	12/67 (17.9)	7/26 (26.9)	*0.999*
≥ 24 months from birth	23/93 (24.7)	23/79 (29.1)	0/14 (0.0)	***0.018***	16/67 (23.9)	7/26 (26.9)	*0.760*
Timings not specified	2 (1.4)	2 (1.7)	0 (0)	*>0.99*	2 (2.2)	0 (0)	*0.534*

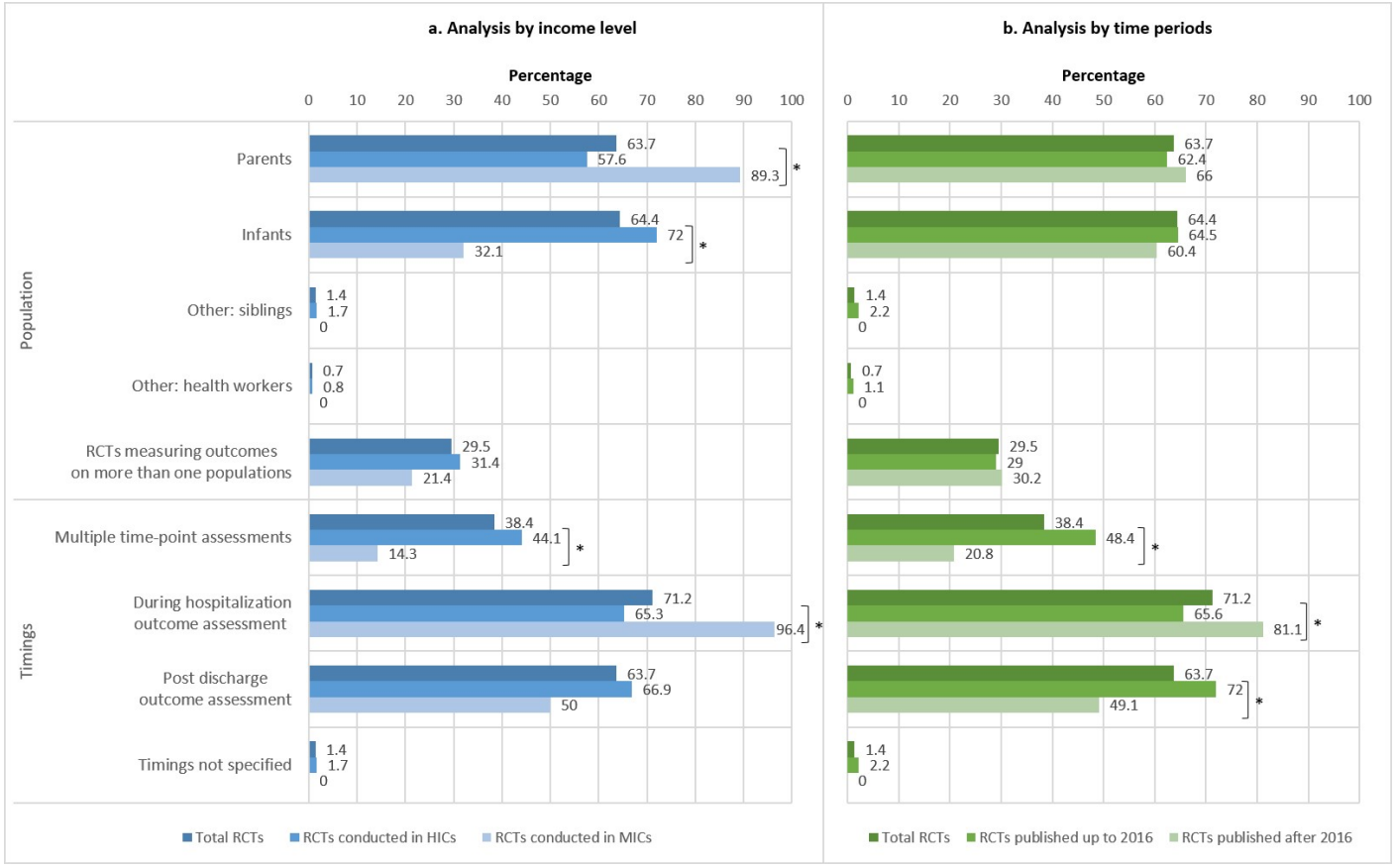
Subgroup analyses

Results of the comparison of studies in HICs (118 RCTs, 80.8%) vs MICs (28 RCTs, 19.2%) and studies published up to 2016 (93 RCTs, 63.7%) vs after 2016 (53 RCTs, 36.3%) are shown in **Figure 3.2.3e** and **Table 3.2.3a.** In MICs, outcomes were often measured on parents (25 RCTs in MICs, 89.3% vs 68 RCTs in HICs, 57.6% vs; p=0.002), in particular on mothers only (22 RCTs in MICs, 78.6% vs 38 RCTs in HICs, 32.2%; p<0.001). RCTs in MICs had less multiple time assessments than RCTs in HICs (vs 4 RCTs in MICs, 14.3% vs 52 RCTs in HICs, 44.1%; p=0.004) and a higher frequency of outcomes measured

during hospitalisation (27 RCTs in MICs, 96.4% vs 77 RCTs in HICs, 65.3%; p<0.001) or in the first three post discharge months (78.6% in MICs vs 19.0% in HICs; p=0.001). No follow-up later than 2 years after discharge was evaluated in MICs.

Populations in which IFCDC outcomes were measured were similar by time period with a slight difference in the number of outcomes measured on mothers only (28 RCTs after 2016, 52.8% vs 32 RCT up to 2016, 34.4%; p=0.017). Multiple time assessments less frequent in RCTs published after 2016 (11 RCTs after 2016, 20.8% vs 45 RCTs up to 2016, 48.4%; p=0.001).

Figure 3.2.3e



Discussion

This third scoping review provided a synthesis of category of outcomes, populations, measurements tools and timings used to measure such outcomes. We found that a very large number of outcomes (358) were measured in the 146 RCTs included with a median of 2 outcomes per RCT, underlining the lack of standardisation. Outcomes were mostly evaluated among mothers and infants, with the most frequent outcome categories being mental health disorders and participation/interaction/attachment in parents and neurobehaviour and development in infants. Again, a considerable number of tools were used to measure such outcomes, with up to 62 different tools to measure infant's

neurobehaviour and development and 32 for parental mental health disorders. Given this large number of identified tools we provided two detailed lists of all possible outcome tools used in the RCTs, stratified for parents and infants. The identified lists of outcomes and measurement tools can be relevant for both researchers and policy makers to favour implementation and to better standardise research methods.

Interestingly, although the concept of IFCDC highlights the importance of the involvement of the family as a whole and the recognition of its fundamental role for the thriving of the hospitalised baby (Craig et al., 2015; Gooding et al., 2011; Larocque et al., 2021), one of the main gaps identified by our scoping review was the scarcity of RCTs that measured outcomes in fathers only (1 RCT) and in siblings (2 RCTs). This aligns with finding of the second of our scoping reviews documented that only very few interventions targeted fathers alone, while the current review adds that, even when the intervention targeted both parents, outcomes were rarely measured in fathers only. It is only recently that, several authors recognised the fundamental role of fathers in the NICU (Baldoni et al., 2021; Holm et al., 2022). In clinical practice, fathers are often the first to see and to receive the information on their NICU hospitalised infant and they have the extremely delicate role to pass this information to the mother or the other family members (Baldoni et al., 2021). Although mental distress is often described to be more frequent in mothers (Caporali et al., 2020; Ionio et al., 2016; Matricardi et al., 2013), fathers are not immune from it, with some studies describing that almost one father out of two suffers from any condition among anxiety, depression and stress, as described in our NICU (see 3.1.3). NICU staff needs to be aware of the high prevalence of mental distress both in mothers and in fathers of newborns in NICU.

Similarly, having a brother or a sister in the NICU can be very challenging and stressful for older siblings. Again, as reported by several authors, even when a family-centered care approach is declared to be applied in the NICU, siblings are yet not directly involved during the hospitalisation of their preterm or sick brothers or sisters (Gooding et al., 2011; Savanh et al., 2020). Papers describing interventions to involve siblings in the NICU are still scarce although overall they showed benefits for both siblings and parents (Savanh et al., 2020).

Another identified gap is the lack of measured outcomes on health workers, with only one RCT reporting on health workers' satisfaction. As already noted, a family-centered approach requires a global change in culture requiring the involvement of the entire multi-professional NICU staff team (Hall, Cross, et al., 2015). IFCDC cannot exist if staff is not actively involved, motivated, educated and supported. IFCDC requires in fact educating all NICU staff and giving them tools to understand family's and infant's needs while enhancing their communication skills. At the same time, as NICUs are very stressful environments for staff, all NICU health workers should be provided with psychological, emotional and physical support in order to reduce the risk of burnout, fatigue and secondary traumatic stress disorder (Hall, Cross, et al., 2015). In turn, these investments on NICU staff would be beneficial both decreasing mental distress and increasing satisfaction of NICU families.

In the present review the observed differences at the subgroup analysis between HICs compared to MICs, highlighting that RCTs in HICs described outcomes significantly more with multiple time

assessments, and with a longer follow-up, may reflect a difference in the economic resources in conducting RCTs in these different settings. Again, the significant reduction in the frequency in multiple time assessments and length of post discharge follow-up measurements in RCTs published after 2016, may indicate economic constraints in conducting RCTs on IFCDC in more recent years.

In conclusion, our scoping review suggests that implementation research should focus on some “forgotten” populations, namely fathers, siblings and health workers. The lists of outcomes and outcome tools provided in this review may be helpful to further standardise research methods and promote implementation.

3.3 Results on PhD objective 3: Development and implementation of SMART interventions to empower parents in the NICU in Italy (Phase 2-3).

Process for the development of SMART interventions

By February 2022, transition to EPINICU Phase 2 (Development of context specific SMART interventions) took place in our NICU. In a quality-improvement perspective, the first step was to disseminate the results from the Italian Phase 1 of the project in order to inform on the baseline assessment of the frequency of parental mental distress and participation in care of the parents in our NICU and identify gaps and priorities to work on.

In order to achieve this, I coordinated four informative meetings from February to April 2022. During these meetings, results of the analyses shown in **section 3.1** of this thesis were presented to key local people which included all NICU staff (doctors, nurses, health care assistants, psychologist and physiotherapist), representatives of our local Parents' Association (*Scricciolo*) and the hospital directions with representatives of the General, Sanitary and Nurse directions.

After sharing, dissemination and discussion of the results of Phase 1, during the following months a series of meetings were held to stimulate brain storming in a participatory manner in order to identify possible SMART interventions (SMART, 1981) to empower parents in our NICU.

First of all, we identified the priorities to tackle in our NICU to better empower our parents. We then discussed the causes and barriers underpinning the potential identified gaps, which helped to identify concrete actions to be developed and implemented in our NICU. For each identified action a responsible person or a small group of persons and a timeline were identified. **Figure 3.3a** shows the template we used during the first brainstorming meetings.

Figure 3.3a Template used for guiding brainstorming during Phase 2 of EPINICU

Identified Priority	Causes/Barriers	Actions	Responsible person/ Timing

During Phase 2, five main intertwined priorities were identified by group discussions

- To increase participation of parents in the care of their newborns and to inform them on the benefits of their active participation in newborn care
- To facilitate communication with parents
- To increase psychological support of parents in order to ensure their well being
- To train NICU staff on IFCDC

- To create a more family friendly environment.

Direct results achieved in Italy: implemented SMART interventions

Starting from the identified priorities, we identified several interventions which are all summarized in **Table 3.3a**. The table shows also the identified barriers and the present state of implementation of each intervention.

All interventions were started to be implemented in October 2022.

Table 3.3a

Identified priorities and implemented interventions to empower parents in our NICU			
Identified priority	**Identified barriers/costraints**	**Interventions**	**State***
To increase the participation in care of parents and to inform them on the benefits of their active participation	High staff turnover Young staff feeling less comfortable in involving parents in care Some health workers not comfortable with parents involved in technical tasks Time of most therapy prescriptions at 8:00, when parents are often not present in the NICU Lack of parental awareness on the benefits of their active participation in newborn care Presence of non-Italian speakers parents	1.The *Baby Daily Diary* to be completed by parents and shared with NICU personnel to keep track of newborn feedings, sleeping, kangaroo/holding, passing of urine/feces in the semi-intensive unit area 2.Posters and parchments/handouts to inform on what activities parents can do with their babies during the NICU stay (present both in the NICU, semi-intensive unit, lactarium and disseminated via the *parents' whatsapp*) 3.*Reading in the NICU* project (Italian and silent books) 4.Change the time of oral prescriptions of vit D and Iron from 8:00 to 12:00 to allow and invite parents to give these drugs to their babies. 5.Video promoting skin to skin with the lived experiences and photos of parents from our NICU (created for the Kangaroo Care week)	**+/-** **+** **+** **+** **+**

To facilitate communication with parents	Work overload Staff shortage Time constraints to reinforce the importance of parental participation and IFCDC with parents	1.A "*parents' whatsapp group*" in which parents choose to participate in order to disseminate information on the NICU organization, parent meetings, educational materials such as posters and parchement/handouts. The administrators are the psychologist, 2 dedicated nurses and a NICU doctor . 2.A *Parents' Bulletin Board* in the NICU entrance area.	+/- +
To increase psychological support for parents	Stop of parents meetings during Covid pandemic Presence of only a part-time (8:30-14 am) clinical psychologist paid by *Scricciolo*.	1.*Parents-meeting*s with the NICU psychologist and the local NICU Parent Association (*Scricciolo*) every 15 days 2.A *Peer to Peer support* between NICU parents and parents of babies previously admitted to the NICU 3.A poster with the feelings of parents during their NICU stay in the lactarium 4.A «structured» psychological individual approach – 6 meetings 5.EPDS screening to all parents in our NICU	+ + + +/- -
To train NICU staff on Family-Centered-Care	High staff turnover Young staff with no experience in IFCDC Loss of staff "champions" in IFCDC Covid "long-term" effects	1. NICU staff training courses on IFCDC and communication skills 2. A Communication Skills Table, disseminated to all staff	+ +

To create a more family friendly NICU environment	Perception of a chaotic environment by staff and parents	1.Refurbishment and painting of the NICU access area 2.A *Parents' Bulletin Board* information/educational purposes in the NICU access area 3.To create a showcase with all NICU staff photos, names and roles.	. + + -

* **+** = ongoing
+/- =needing improvement
- =not implemented yet

Identified actions included some very simple concrete actions such as the change of time prescription of vitamin D and iron supplements from 8 am to 12 am, as it was noted that parents were often not present in our NICU, though open 24/24 hours, at 8 am. The change in drug prescription was shared with all NICU staff during the meetings and reinforced by email to recall all staff to invite parents to actively give the supplements to their babies during their NICU stay. This was one of the first interventions chosen in our NICU as it was perceived as simple and quick to implement and as technical tasks (such as drugs administration by parents) was the area in which our parents resulted to participate less. (detailed in section 3.1.3)

Other identified actions were more complex needing first the development of informative materials and then their implementation. This was the case for the posters and handouts/parchments dedicated to inform and motivate parents in actively participating to the care of their newborns (see below) and for the "*Baby Daily Diary*" (Figure 3.3b). This latter was entirely conceived and realized by two nurses together with a health assistant, in order to help parents to keep track of their activities and to share this information with the nurses, with the aim to improve parent-staff collaboration, communication and co-participation in the care of the newborn.

In the occasion of the Kangaroo Care Day (15th May), a video both explaining the importance and methods of kangaroo care and the emotional experiences of some of our parents was developed and shared in the *parents' whatsapp* group (see below)

Figure 3.3b The *Baby Daily Diary*

Concept idea of U. Manzon, B. Albertacci, L. Bulzis. Designed by V. Filippi

Posters and handouts/parchments were developed by a multi-professional team and harmonized together. The poster put the baby's views at the center by representing a baby who invited parents to actively participate in her/his care and explaining "*What you can do with me*" as shown in Figure 3.3.c.

Figure 3.3.c Poster developed in our NICU

Seven main topics were highlighted in the poster and included kangaroo/skin to skin; parent care activities; newborn cues/language; the availability of the psychology support in the NICU; the parents' right to have information; the presence of a 24 hours open NICU and the importance of reading in the NICU. Posters were hanged both in the entrance of the NICU, in all semi-intensive care rooms above the changing tables and in the "lactarium" room.

For each speech bubble of the main poster a different colour was chosen and repeated in a parchment/handout of the same colour which has been thought as a "deepening pill" of the topic presented in the Poster. Figure 3.3d shows as an example the handout of parents' activities in the NICU (pink). Some of the handouts referred to other materials developed during Phase 2 of the project such as the *Baby Daily Diary*. (Figure 3.3c)

The poster and all the relative parchments developed are included as Annex 6.2

Figure 3.3d Example of parchment/handout developed in our NICU

Among the parchments, one was dedicated to the *Reading in the NICU* project. Shared early book reading is known to be a nurturing activity as it simulates optimal patterns of brain development in a very sensitive critical window for child development, and consequently builds language, literacy, and social-emotional skills that may last a lifetime (Childhood et al., 2014; Jain et al., 2021) . A recent review found that parental shared book reading in the NICU is feasible and well accepted, and seems to have positive effects both on reducing parental stress and strengthening the parent-infant bonding and on short and long-term outcomes of NICU infants, such as more stability in their physiological parameters and better language and cognitive development (Boissel et al., 2022). Thanks to *Scricciolo* donations we were able to create a small library in our NICU shown in Figure 3.3e and promote early reading among our parents. The library includes some silent books.

Figure 3.3e NICU library for the *Reading in the NICU* project

The poster and parchments were used to create a small booklet to be left in the entrance area of the NICU, in the *lactarium* room so that mothers when expressing milk could read it or in *Scricciolo* room where the psychologist held the individual meetings with parents and to be shown on the *Parents Bulletin Board* at the entrance of the NICU.

To facilitate communication and dissemination of the above materials and information, a *parents' whatsapp group* was created. Parents were invited to join the *whatsapp group* during the first meeting with the NICU psychologist. The *whatsapp group* allows only administrators to post relevant information such as the informative materials, the parents meetings dates and *Scricciolo* activities. The *whatsapp group* is administered by a doctor, two dedicated nurses and the psychologist of our NICU.

Several actions were implemented to increase psychological support in our Unit. As before Covid pandemic, *parents group meetings* are now being held again every 15 days on Wednesdays with our psychologist moderating them. In each meeting a brief presentation of cross-cutting themes in the NICU is held at the beginning by an expert (i.e. understanding newborn cues, skin to skin, parental participation in care) in order to help the sharing of experiences among parents. In all meetings a *Scricciolo* representative is present to disseminate the activities of the association and the possibilities *Scricciolo* association offers to support the families in our NICU.

Moreover, a *Peer-to-Peer support*, which has been recommended recently in the literature (Hall, Ryan, et al., 2015), has started thanks to *Scricciolo*. Parents of "ex" NICU preterm or surgical babies, discharged home since now some years, come to the NICU every 15 days on Fridays to meet parents directly in the ward and to share their experiences and emotions.

Our psychologist developed and is now implementing a structured psychological approach to be offered during the individual meetings with parents, including 6 different meetings each one with a specific objective, the number and order of which can be tailored according to parents' needs. The six meetings have the following objectives:

1. to provide a brief introduction to the NICU and to newborn development and needs, to offer the participation and eventually acquire the informed consent for the *whatsapp group*, to hand out and briefly present the Baby Daily Diary, to offer a baseline assessment of parental mental distress

2. to offer tools and support for a "cognitive reconstruction" after the potential trauma of having a baby hospitalized in the NICU

3. to support the recognition of stress and triggers and to offer tools for self-care and stress-relieving activities

4. to facilitate a cognitive re-elaboration of the trauma

5. to recognize guilt and regret feelings and to give value to past experiences

6. to prevent hyper-protective parenting and to facilitate home discharge.

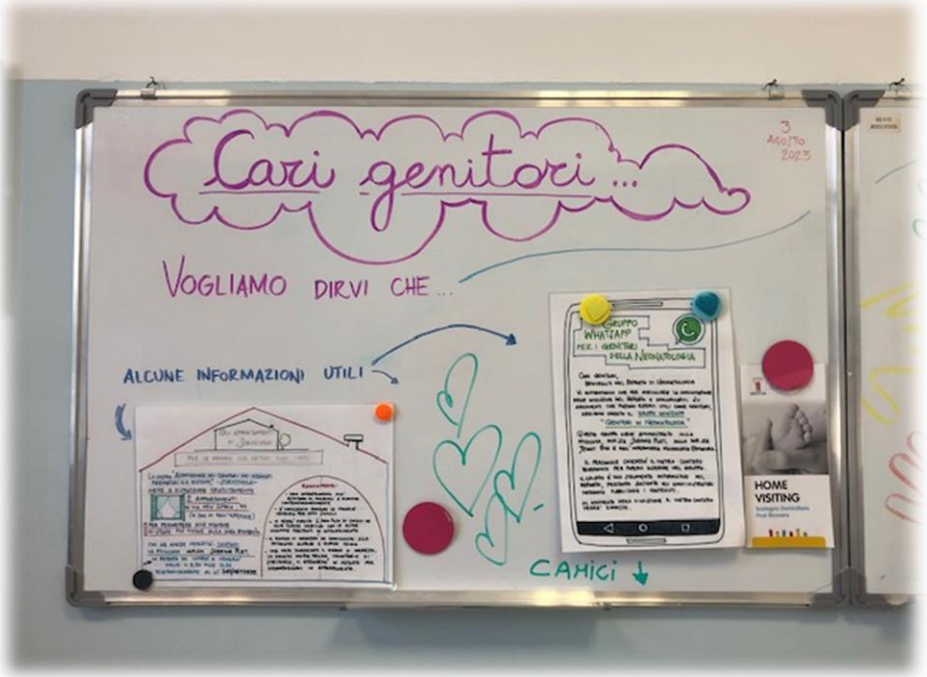
Finally, to improve knowledge on IFCDC among NICU staff, internal courses on IFCDC principles and communication were regularly held and are programmed to be held regularly in our Unit. Last year a course on the importance and the evidence of the benefits of reading in the NICU (Boissel et al., 2022) was held and was highly appreciated by all NICU staff.

Thanks to the economical contribution of the hospital, the entrance of the NICU has been refurbished with two comfortable armchairs and lockers for the parents' valuables (Figure 3.3d). Moreover, a *Parents Bulletin Board* (Figure 3.3e) has been created to welcome parents and disseminate relevant information.

To facilitate the communication with parents it was also felt and decided during the meetings to create a showcase with all the photos of the NICU staff, roles and names. However, due to economical restraints the showcase has not yet been implemented.

Figure 3.3d The refurbished NICU entrance

Figure 3.3e The *Parents Bulletin Board*



Indirect results achieved in Italy

The Phase 2-3 of EPINICU study in our Unit occurred just after the COVID pandemic, after which in our Unit there was a high staff turnover and shortage especially among nurses. The project and the process of Phase 2-3 contributed to team building as the SMART interventions were chosen in a participatory manner by the NICU staff all together, and in the development of the majority of the interventions, small working groups of responsible persons were created including different professions. Moreover, it was the occasion for the new staff to be exposed to the principles of IFCDC and reinforce the efforts of the entire Unit in empowering families.

The project offered the occasion to strengthen the existing collaboration between our Unit and the local parent association *Scricciolo.* This facilitated a better understanding of the needs of our parents as *Scricciolo* not only offered a parent perspective but also, thanks to the *Peer-to-Peer project* helped in gathering the parents' feedbacks. At the same time helped *Scricciolo* to better reach our NICU parents and to be more efficient in the offered support.

Community of good practices

The multicountry nature of the study was stimulating and fruitful and helped creating a community of good practices. At the time of the writing of this thesis, we held 5 international online meetings sharing the progress of the EPINICU project in all sites involved, which were occasions for learning from other experiences, for discussing local barriers and confronting on solutions and for taking inspiration from the ideas of the other partners.

The sharing of experiences among the EPINICU "community" helped raising new questions and new ideas for further research activities. As an example, a common experience among EPINICU partners was that the ideal level of participation in care of parents in the NICU is not really known and should really consider, in a quality-of-care perspective, the opinions and perceptions of parents and health workers. In Brasil, at IMIP, a pilot focus group study was undertaken during the parents meeting to explore the parental views on what were the care activities they wished to be actively involved in and those in which not. The same focus group was held with health workers exploring which were their views regarding their desired parental level of participation. This explorative experience showed some discrepancies among parents and health workers opinions and triggered the idea to conduct a more structured qualitative study in the different settings to explore parents and health workers views on participation in care. The drafting of the qualitative study is ongoing.

Barriers, mitigation actions and facilitators encountered

As detailed in Table 3.3a, several barriers/constraints were identified for each objective/action of the project during group discussion in our NICU.

Among the main identified barriers there are:

- the staff shortage and the high turnover in our NICU nursing staff with newly employed personnel with no experience nor training on IFCDC and communication and with the necessity to be informed and trained on the ongoing activities of the EPINICU project.

- the presence of one clinical part-time psychologist, who can dedicate her time to support parents only in the mornings.
- the time constraints and the work overload perceived by all staff, which in turn has an effect on the personnel motivation and active participation in the project itself. Moreover, Burlo Garofolo is a Research Institute and there are several ongoing research projects in our neonatology department diverting resources and focus on the present project.
- the need of continuous monitoring of the chosen interventions as some tended to be "forgotten" along the way.
- The difficulties in reaching non-Italian speaking parents.
- The effects of Covid pandemic, especially in the second year of the project, affecting staff shortage and the recovery of all the training activities without restrictions.

In order to overcome these barriers, some mitigation actions were put in place.
Monitoring monthly meetings were instituted. Every second Monday of the month we invited all NICU staff together with *Scricciolo* representatives in order to monitor EPINICU activities, to keep high the attention and the motivation of the staff on the project, to discuss solutions in the identified barriers of each identified activity and to share the feedbacks given by NICU parents to our psychologist and *Scricciolo* representatives during the *parents'* and *peer-to-peer meetings*. These monitoring meetings helped in facing the above constraints.

Moreover, since last year, these meetings are part of the Monday Update Neonatology Meetings, which are recognized by Burlo Garofolo as an Institutional field training course and by attending which staff (both doctors and nurses) can gain ECM credits (Educazione Continua in Medicina), compulsory for Italian health workers. This may have helped in increasing participation and motivation of staff.

Even in the presence of a hospital mediating and translating service, reaching non-Italian speaking families was and is certainly a barrier for EPINICU to reach parents without disparities. The materials developed for EPINICU were in Italian and due to economical constraints have not yet been translated. A partially mitigation action was taken with regard to the *Reading in the NICU* project which now includes some silent books which can be read in any language. Likewise, the *Baby Daily Diary* (Figure 3.3b), being simple and with very "intuitive" drawings, can be easily explained and used by non-Italian speaking parents.

On the other hand, the presence of a few "champions" among the nursing staff acted as a facilitator in the project. These "champions" have not only a strong longstanding training in IFCDC and communication skills but also enthusiasm and motivation in supporting the ongoing EPINICU activities and acting as a driving force for the entire group. In order to fully recognize their efforts and work, their participation in the project will be and has been acknowledged (Bua et al., 2021) in scientific publications.

Other potential facilitators of EPINICU in our settings may have been the fact that our NICU is open 24/24 hours and has a longstanding tradition of infant developmental care. Since 2020, Burlo Garofolo hospital joined the Baby Friendly Initiative and is now in the 2nd phase of the project (https://www.unicef.it/italia-amica-dei-bambini/insieme-per-allattamento/ospedale-amico-bambini/). This initiative, which has been strongly advocated by our neonatology Unit, may contribute to the hospital general culture and approach towards family centered care.

4. NEXT STEPS

4.1 Overall lessons learned

As a whole, I believe EPINICU project in our NICU has achieved some successes.
First of all, it generated new evidence. We learned that NICUs are highly stressful environments for parents regardless of the setting, that gender differences among mothers and fathers exist and need to be taken into account, that even during pandemics parental mental distress can be contained and participation in care can be ensured. The scoping systematic reviews highlighted that IFCDC interventions were not conducted in low-income countries; that several IFCDC interventions have been tested in the literature though the majority were educational; that there is a very poor reporting on the educational interventions dedicated to staff; that most of the interventions involved mothers, while fathers and siblings and other family members are often not included neither as participants nor when measuring outcomes; that there is a plethora of outcomes and outcome tools described in the literature though health workers opinions are almost always forgotten.

Secondly, it helped to start a local quality improvement project leading to some tangible interventions we hope can contribute to empower our NICU parents. The participatory process for the development of the interventions contributed to both team-building and to the dissemination of the principles and culture of IFCDC among staff. However, we learned that a constant monitoring is needed to keep the interventions going, the participation and awareness of staff focused and that systems to reward involved health workers are needed to motivate them to actively participate in the project. We learned that some barriers such as staff shortage and work overload are very difficult to balance, and that quality improvement projects are time and energy consuming and need to rely on the entire team and not on single health workers.

Thirdly, EPINICU was well received by staff, parents and the parents' local association, reinforcing the collaboration between these three actors, contributing in exchanging opinions and feedbacks, and improving the entire quality improvement process. This reinforced collaboration is pivotal both in the context of family-centered care and in ensuring quality of care.

Fourthly, the multi-centred, multi country and multi-professional nature of the project contributed to the creation of a community of good practice leading to a fruitful exchange of experiences and ideas and hence to new research ideas.

4.2 Next expected steps

The first expected step, from the academical point of view, is the publication of the papers submitted as a supplement and detailed in Table 3b. in order to disseminate the results from the baseline assessment and the scoping reviews in the scientific community.

Secondly, we aim to conduct a multi-centered qualitative study on the ideal level of participation in care exploring parental and health workers views in Italy, Brasil and Sri Lanka. The design of the project is being drafted to seek ethical approval in all three centers.

Thirdly, building on the evidence and implementation experience generated by Phase 1-3 of EPINICU, counting on the EPINICU existing multi country team of professionals and on the experience of the WHO CC of Trieste in the development of Quality Assessment and Improvement (QA&QI) tools, we aim to start a new project with the aim to develop a QA&QI for Family Centered Care for Newborns. As definitions of Family Centered Care for Newborns are not homogenous (EFCNI, n.d.; O'Brien et al., 2018; Shields et al., 2012) first we are planning to conduct a scoping review with the aim to uniform existing definitions, categories and setting-specific implementation models.

Lastly, from the implementation point of view of the project, local regular monitoring meetings are planned in order to sustain the implemented interventions in time, being conscious that quality improvement projects take long time for changes to root. Moreover, phase 4 (the post intervention assessment phase) will be started as the multi-country EPINICU team is about to discuss.

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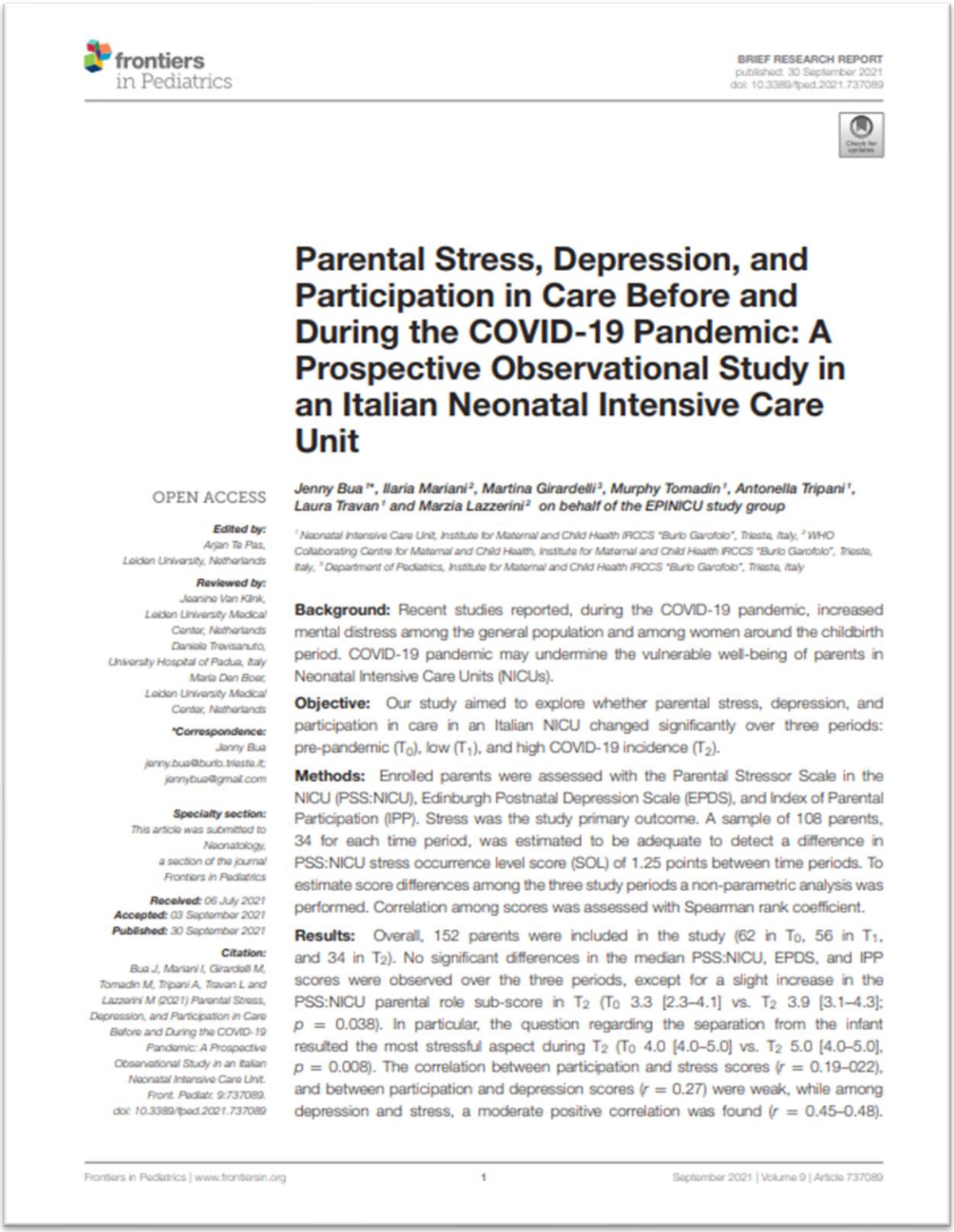
6. APPENDIX

6.1 Published paper (title page)



frontiers in Pediatrics

BRIEF RESEARCH REPORT
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Parental Stress, Depression, and Participation in Care Before and During the COVID-19 Pandemic: A Prospective Observational Study in an Italian Neonatal Intensive Care Unit

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Background: Recent studies reported, during the COVID-19 pandemic, increased mental distress among the general population and among women around the childbirth period. COVID-19 pandemic may undermine the vulnerable well-being of parents in Neonatal Intensive Care Units (NICUs).

Objective: Our study aimed to explore whether parental stress, depression, and participation in care in an Italian NICU changed significantly over three periods: pre-pandemic (T_0), low (T_1), and high COVID-19 incidence (T_2).

Methods: Enrolled parents were assessed with the Parental Stressor Scale in the NICU (PSS:NICU), Edinburgh Postnatal Depression Scale (EPDS), and Index of Parental Participation (IPP). Stress was the study primary outcome. A sample of 108 parents, 34 for each time period, was estimated to be adequate to detect a difference in PSS:NICU stress occurrence level score (SOL) of 1.25 points between time periods. To estimate score differences among the three study periods a non-parametric analysis was performed. Correlation among scores was assessed with Spearman rank coefficient.

Results: Overall, 152 parents were included in the study (62 in T_0, 56 in T_1, and 34 in T_2). No significant differences in the median PSS:NICU, EPDS, and IPP scores were observed over the three periods, except for a slight increase in the PSS:NICU parental role sub-score in T_2 (T_0 3.3 [2.3–4.1] vs. T_2 3.9 [3.1–4.3]; $p = 0.038$). In particular, the question regarding the separation from the infant resulted the most stressful aspect during T_2 (T_0 4.0 [4.0–5.0] vs. T_2 5.0 [4.0–5.0], $p = 0.008$). The correlation between participation and stress scores ($r = 0.19$–022), and between participation and depression scores ($r = 0.27$) were weak, while among depression and stress, a moderate positive correlation was found ($r = 0.45$–0.48).

6.2 Other tangible products: Poster and parchments

TIN aperta H 24

significa che tu, genitore o caregiver, potrai stare con il tuo o i tuoi cuccioli senza limitazioni di orario in reparto.

In questo modo avrai un ruolo centrale e attivo nell'accudimento e cura del tuo scricciolo.

Non ci sono cure e attenzioni migliori di quelle che puoi dare tu!

Ogni neonato parla, anche senza l'uso della parola!

Il personale ti aiuterà a osservare la tua bambina o il tuo bambino e a riconoscerne il linguaggio ed i suoi segnali.

Se non ti è già stato proposto, chiedi una copia del libricino "Il neonato ci parla", una piccola guida per avvicinarsi al linguaggio del tuo piccolo in Terapia Intensiva Neonatale.

L'obiettivo di questo strumento è fornirti informazioni riguardanti le caratteristiche dello sviluppo del neonato pretermine per aiutarti ad accompagnare la sua crescita e a svilupparne le potenzialità dai primi giorni di vita fino al momento della dimissione.

Kangaroo Care e pelle a pelle:

Che benefici ha?

Aiuta il tuo scricciolo a mantenere stabile
la temperatura,
la frequenza cardiaca
l'attività respiratoria
e lo aiuta a dormire meglio.

Migliora il suo sviluppo cerebrale

Riduce il dolore
quando vengono fatte delle procedure invasive

Aiuta a tollerare meglio il tuo ed il suo stress

Rinforza il vostro legame

Favorisce l'avvicinamento e
l'allattamento

La Family Centered Care è una modalità di assistenza che riconosce la centralità della famiglia, coinvolgendo attivamente genitori e/o caregivers lungo tutto il percorso di cura.

Attraverso questa modalità di assistenza che ti coinvolge attivamente nelle cure, sperimenterai un minore livello di ansia e di stress, rafforzerai il legame con il tuo bambino e stimolerai il suo sviluppo cerebrale.

Il cambio del pannolino, il bagnetto, l'offerta dei pasti, la somministrazione delle terapie (ad es. vitamina D e ferro), il contenimento durante le procedure sono occasioni per stare con il tuo bambino e crescere insieme!

Non sarai solo: il personale ti accompagna, ti sostiene e ti coinvolge nella cura del tuo piccolo fin dall'arrivo in Reparto. Se non ti è già stato proposto, chiedi una copia del Baby Daily Diary.

Prima di andare a casa – se le condizioni del Reparto lo permettono – avrai la possibilità di stare insieme nella family room

La famiglia ha il diritto e la responsabilità di collaborare al processo decisionale riguardante il percorso di cura del suo bambino. Ciò significa che genitori e caregivers hanno diritto ad essere informati sulla salute del loro piccolo.

Non abbiate timore di chiedere notizie: cercheremo di coinvolgervi nelle decisioni riguardanti il vostro cucciolo, in un rapporto di collaborazione e di rispetto reciproco.

Se lo ritenete necessario potete chiedere un colloquio dedicato che verrà concordato con i neonatologi e gli infermieri.

I genitori ed i caregivers sono parte integrante e imprescindibile della salute e dello sviluppo del proprio bambino. Il nostro reparto si fonda su questa consapevolezza. Per questo motivo in reparto è presente una psicologa che vi aiuta ad affrontare le difficoltà di una nascita prematura o della malattia del vostro piccolo.

Lo psicologo offre uno spazio di parola volto ad entrare in contatto con le vostre emozioni e ad elaborarle in un momento che può essere difficile. È disponibile quando siete vicino al vostro bambino, ma anche in colloqui individuali.

La psicologa propone anche riflessioni sulla genitorialità, in modo da favorire la costruzione di uno stile genitoriale responsivo e funzionale alla crescita del vostro bambino e anche alla vostra!

Inoltre ogni due settimane è previsto un incontro con tutti i genitori per condividere domande ed esperienze e ad un rappresentante dell'associazione dei genitori "Scricciolo".

Al tuo piccolo piace moltissimo stare vicino al tuo cuore ed essere cullato dal suono della tua voce.

E' ampiamente documentato che l'ascolto di letture ha grandi benefici sullo sviluppo cognitivo e linguistico del neonato. Potrai leggere un libro al tuo bambino, cantargli ninne nanne e recitargli filastrocche in ogni momento, anche mentre fai canguro o il pelle a pelle. Comunicherai al tuo piccolo un messaggio importante: «sono qui, ti sostengo, puoi contare su di me».

Potrai portare un tuo libro o sceglierne uno tra i tanti donati da *Scricciolo*, l'Associazione dei genitori del nostro reparto. Grazie a questo dono prezioso partecipiamo al progetto "Libri che divertono, che crescono, che curano" promosso dall'Associazione Culturale Pediatri e dal Centro per la Salute del Bambino.

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"*No one can whistle a symphony. It takes a whole orchestra to play it*"

HE Luccock.

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