

ECOLE DOCTORALE PIERRE LOUIS DE SANTE PUBLIQUE A PARIS
ÉPIDÉMIOLOGIE ET SCIENCES DE L'INFORMATION BIOMÉDICALE

Directeur : Pierre-Yves Boëlle
Responsable pour l'Université Paris Cité : Isabelle Boutron

PROPOSITION DE SUJET DE THESE

SIGLE ET NOM DU LABORATOIRE : INSERM U1153, CENTER FOR EPIDEMIOLOGY AND STATISTICS (CRESS)

NOM DE L'EQUIPE: ÉPOPÉ – OBSTETRICAL, PERINATAL AND PEDIATRIC EPIDEMIOLOGY RESEARCH TEAM (EPOPÉ)

DIRECTEUR DE THESE: JENNIFER ZEITLIN

ADRESSE : MATERNITÉ PORT-ROYAL, 53 AVENUE DE L'OBSERVATOIRE, 75014 PARIS

TITRE DE LA THÈSE: GROWTH IN EARLY CHILDHOOD AFTER VERY PRETERM BIRTH IN EUROPE

CO-ENCADRANT EVENTUEL :

EQUIPE DU CO-ENCADRANT :

LABORATOIRE :

PRESENTATION DU SUJET

1. Scientific context of the project

Development in perinatal and neonatal medicine has led to an increase in the survival of infants born very preterm (<32 weeks of gestation, constituting about 1-2% of all births). It is important to investigate the long-term health outcomes of these children as they are more likely to have poor neurodevelopment and health problems in later life (1, 2). These consequences can have a major impact on the lives of individuals born preterm and their families, as well as the provision of health, educational and social services.

Optimizing early life nutrition may be one way to improve outcomes after very preterm birth. Preterm-born children face higher risks of sub-optimal growth. Preterm birth can be the result of fetal growth restriction; it is also associated with clinical factors that affect growth such as courses of postnatal corticosteroids and feeding difficulties (3). In many studies, suboptimal weight and growth in preterm infants have been linked with impaired neurodevelopmental outcomes, especially cognitive difficulties in early childhood (4, 5). This research indicates that improving growth during the postnatal period with adequate postnatal nutrition may be an effective strategy for promoting better cognitive outcomes in children born preterm (6, 7). However, a growing body of evidence suggests that nutritional supplements that provide rapid catch-up growth may increase the risk of future obesity and lead to metabolic disease later in life (8, 9). It should be noted that according to the Developmental Origins of Health and Disease (DOHaD) paradigm, these outcomes may also result from fetal growth restriction followed by rapid catch-up growth (10).

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In the EPICure cohort of extremely preterm infants in the United Kingdom, increased catch-up growth in early childhood has been associated with higher body mass index (BMI) and central systolic blood pressure in early adulthood (11). Fetal growth restriction and postnatal growth restriction (also called extrauterine growth restriction) are risk indicators of overweight and metabolic disorders in children born very preterm (12). A recent study using data from 16 general population-based cohorts reported that very preterm children had lower BMI scores in early childhood overall, but nonetheless increased risk of overweight in adolescence compared to their full-term peers which may be related to catch-up growth in this population (13).

Given these concerns, knowledge about how very preterm children grow in early life is important for understanding research in adulthood and linking growth during pregnancy or the postnatal hospitalization to later outcomes. Most of the previous research that studied physical growth in very preterm population focused on immediate postnatal growth or during the infancy period. Other limitations are inclusion of a limited number of factors of interest, for example, infant feeding or the socioeconomic context (14). However, the growth outcomes of children born very preterm in early childhood are influenced by a broad range of perinatal, social, and developmental risk factors. In particular, social factors may play a role in increasing the risk of being overweight in very preterm-born children. Social deprivation increases the risks of very preterm birth and disadvantaged families are over-represented in this population. For this reason, children born very preterm may be more at risk of being overweight than children in the general population because of the social context (15). There may also be interactions between the social environment and the effect of preterm birth on growth. A final important issue when assessing risks of being overweight among children born very preterm is their level of physical activity: these children may be more sedentary because of developmental motor problem which are highly prevalent (40-50%) and should be considered (16).

Considering the rise in the number of preterm-born survivors, a detailed investigation of their growth in early childhood can inform risk prediction and prevention and provide essential context for understanding later growth and risks for metabolic disease.

2. Research question

This doctoral project aims to:

- Describe the prevalence of under and overweight at 2 and 5 years of age among children born very preterm using data from the European multi-country area-based EPICE-SHIPS cohort, study the changes between these two time points and investigate differences in these outcomes among children who experienced fetal growth restriction and/or extrauterine growth restriction.
- Identify perinatal, sociodemographic, and developmental risk factors, including the presence of developmental motor problems, for under and overweight at 2 and 5 years of age and changes between 2 and 5 years.
- Verify the consistency of patterns of underweight and overweight in early childhood overall and by sociodemographic status and other risk factors in the countries participating in the EPICE-SHIPS cohort as well as in other very preterm cohorts federated on a European research platform (RECAP Preterm).

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3. *Data sources*

Study population

The EPICE-SHIPS cohort is a European cohort of children born very preterm which includes 6,792 children born before 32 weeks of gestation in 2011-2012 in 19 regions of 11 European countries and who survived to discharge home from the neonatal unit. After a first follow-up by parental questionnaire at 2 years, the SHIPS project followed up with children between 5 and 6 years old using a parental questionnaire for all children in the sample and clinical assessments of cognitive and motor function for children born <28 weeks of gestation.

Measurement of growth

At 2 and 5 years of age, anthropometric measurements were recorded (weight, height). Weight was measured at discharge from the neonatal unit, and at 2 and 5 years of age. Height was measured at 2 and 5 years of age. Measurements at 2 and 5 years are reported on the parental questionnaires. Parents indicate who measured the child (health provider or the parents' themselves) and the date of the measurement.

Measurement of perinatal, sociodemographic, and developmental factors

Clinical and perinatal factors which may be associated with postnatal growth (including maternal age, parity, gestational age, complications of pregnancy and neonatal morbidities) were collected from medical records in obstetrical and neonatal units using a standardized protocol.

Sociodemographic factors (maternal and paternal educational level, marital status, professional status, country of birth and language spoken at home) come from the parental questionnaires completed when the child was 2 and 5 years of age.

Several questions are also available on parent's concerns regarding the nutrition and growth of their children.

The RECAP Preterm Platform: An infrastructure allowing federated analysis of individual patient data from other very preterm cohorts

The RECAP preterm platform is a geographically diverse and multidisciplinary platform of national and European cohorts of very preterm and very low birthweight populations that were constituted over a 30-year time span.

In addition to data from the EPICE-SHIPS cohort which are on the platform, data regarding growth and anthropometric measurements during early childhood are available for 11 cohorts, birth years ranging from 1986 to 2015 with at least two anthropometric measurements during early childhood.

4. *Methods*

Objective 1

- A comprehensive literature search will be performed to document the evidence for choice of appropriate growth measurements for children born very preterm at the ages of 2 and 5, including: weight percentiles, weight for length Z scores, BMI, as well as for the selection of norms to identify underweight and overweight in this at-risk population.
- Descriptive statistics will be used to describe the prevalence of under and overweight and changes between 2 and 5 in these outcomes. We will compare the consistency of results by growth measure selected.

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- Finally, we will explore the association between early growth problems (fetal growth restriction and extra uterine growth restriction) and prevalence of under and overweight and changes in status from 2 to 5 years of age.

Objective 2

- A comprehensive literature search will be performed to identify perinatal, sociodemographic, and developmental risk factors associated with under and overweight at 2 and 5 years of age and potentially at-risk growth trajectories.
- We will select risk factors identified in the search and which are included in our data source, as well as characteristics shown to be associated with growth, health and development in previous EPICE-SHIPS publications. We will describe their association with under and overweight at 2 and 5 years and use multinomial logistic regression to produce relative risk ratios, with appropriate weight as a reference category. Adjustments will be based on a directed acyclic graph describing assumptions about the relationships between variables.
- These analyses will be informed by results from objective 1 linking early growth restriction with later growth.

Objective 3

- Growth patterns and risk factors will be assessed using RECAP Preterm platform in order to externally validate findings from the EPICE-SHIPS cohort related to growth patterns and risk factors. Analysis on the RECAP Preterm platform is done using DataSHIELD, an R-based software designed for federated platforms. Variables on anthropometric measurements will be harmonized on the platform based on results from objective 1. Risk factors will be selected from already harmonized variables, which include those associated with health and development and included in Core Outcome Sets for follow-up of children born very preterm.
- We will synthesize data on prevalence of underweight and overweight in all the cohorts in early childhood and on the relationships of the principal risk factors with growth. We will use meta-analytic techniques to derive pooled measures and to test for heterogeneity. A protocol will be developed and registered on PROSPERO after the completion of work in Objective 1 to define the most appropriate measure for defining underweight and overweight in the VPT population.

5. *Number of subjects/sample size*

In the EPICE-SHIPS cohort, 6,792 children survived to discharge from the neonatal hospitalization of which 4,426 were followed at 2 years and 3,687 were followed at 5 years (including 3,138 children followed at both time periods). Weight and height are recorded in this dataset with good completeness.

Given a total sample size of 3,500 with full data on BMI at 5 years of age and an estimated sample prevalence of overweight and obesity of 10%, we would be able to detect risk differences of at least 1.4 between children by risk factors with a sample prevalence starting at 20% (such as low educational level or fetal growth restriction) with a power of .8 (β) and a significance (α) of .05.

The RECAP Preterm cohorts are diverse in size, ranging from <100 live births included in the very early cohorts to 7,900 live births in the EPICE-SHIPS cohort. Sample sizes for our analysis will depend on follow-up rates in

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early childhood in the cohorts. However, most cohorts have over 200 children included in follow-up at early childhood and 5 have more than 500 children.

6. *Provisional schedule*

1 st semester	Literature review, analysis for the first article
2 nd semester	Completing analysis for the first article, drafting and submission of the first article
3 rd semester	Analysis and drafting of the second article, revisions of first article
4 th semester	Analysis for third article, revisions of second article
5 th semester	Writing and submission of third article, writing thesis
6 th semester	Revisions to third article, writing, finalization and submission of the thesis, defense

7. *Themes for three articles*

Paper 1: Growth outcomes of very preterm infants in early childhood

Paper 2: Sociodemographic, perinatal and developmental risk factors associated with underweight and overweight among children born very preterm in a European very preterm cohort

Paper 3: Patterns of growth in early childhood in very preterm children: an individual patient data meta-analysis of European cohorts

8. *References*

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PRÉREQUIS, FORMATION:

MASTER'S DEGREE IN PUBLIC HEALTH OR EPIDEMIOLOGY

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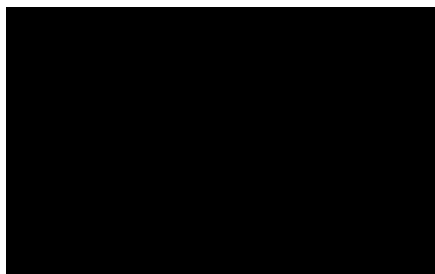
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