Master of Public Health

Master de Santé Publique

Determinants of Health Care Use in Very Preterm-Born Children with Asthma at Five Years of Age in the French EPIPAGE-2 Cohort

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MPH, Year 2 - 2024-2025

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Acknowledgements

I would like to express my deepest gratitude to my supervisors, Dr. Anna-Veera Seppänen, Dr. Jennifer Zeitlin, and Prof. Florence Bodeau-Livinec for their invaluable guidance, support, and encouragement throughout the course of this thesis. Their expertise in perinatal epidemiology and thoughtful feedback were instrumental in shaping this work.

I am especially thankful to Dr. Anna-Veera Seppänen, who not only guided me through the research and analysis process with exceptional clarity and dedication, but also supported me through moments of doubt and difficulty. Her mentorship, analytical expertise, and unwavering belief in my abilities played a crucial role in the successful completion of this project. I am truly grateful for her generosity, patience, and the resilience she inspired in me.

I am also sincerely thankful to the entire OPPaLE team at the Centre for Research in Epidemiology and Statistics (CRESS), Inserm U1153, for providing a collaborative and intellectually stimulating environment during my internship.

Special thanks to Laetitia Marchand-Martin for her patient explanations and valuable statistical insights, and to all members of the EPIPAGE-2 study team whose rigorous work and commitment made this research possible.

Finally, I wish to thank my family and friends for their continuous support, encouragement, and belief in me throughout my studies.

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List of Acronyms

Acronym	Full Term
BPD	Bronchopulmonary Dysplasia
CI	Confidence Interval
DAG	Directed Acyclic Graph
ELFE	Étude Longitudinale Française depuis l'Enfance
ENT	Ears, Nose and Throat
EPIPAGE-2	Étude Épidémiologique sur les Petits Âges Gestationnels-2
ER	Emergency Room
FUP	Follow-up
GA	Gestational Age
GP	General Practitioner
RR	Relative Risk
SGA	Small for Gestational Age
VPT	Very Preterm

Abstract

Background and Objectives

Very preterm (VPT) children (<32 weeks of gestational age) are at increased risk for long-term respiratory complications, including asthma, compared to term-born children. Although healthcare use is high among VPT-born children, research suggests there may be unmet care needs in this population. We aimed to describe the healthcare use of VPT and term-born children with and without asthma, and identify determinants of respiratory-related care use among asthmatic VPT children, focusing on family sociodemographic factors, to assess potentially suboptimal care.

Methods

Data were drawn from the 5.5-year follow-up of the French prospective population-based cohort of preterm births, EPIPAGE-2, and a term-born reference sample from the ELFE cohort. Data was collected from medical records at birth and parental questionnaires and clinical exams at age 5. The analysis included descriptive, univariable analysis of healthcare use by gestational age and asthma status, and multivariable methods to assess associations between sociodemographic factors and respiratory healthcare use among asthmatic VPT children, adjusting for perinatal factors.

Results

Asthma prevalence at 5.5 years was over twice as high in VPT children compared to term-born children (28.7% vs. 12.6%). Respiratory healthcare use was higher in asthmatic children overall, with similar rates between VPT (36%) and term (30%) groups. Among VPT children with asthma, those who received respiratory-specific care had higher rates of bronchopulmonary dysplasia (BPD) (19% vs. 10%) and had greater use of other health services, including hospitalizations and Emergency Room (ER) visits. Adjusted analyses showed that BPD was the only factor associated with receiving respiratory care (aRR = 1.71).

Conclusions

BPD was the main factor linked to respiratory-specific care use in asthmatic children born VPT, and we found no association between care and sociodemographic factors after adjusting for covariates. Further research should explore if respiratory-specific care is associated with less avoidable hospitalizations and ER visits.

Key words: Very preterm birth, Asthma, Healthcare use, EPIPAGE-2, France

1. Introduction

1.1. Preterm Birth and Respiratory Sequelae

Very preterm (VPT) birth, defined as birth before 32 weeks of gestation, affects approximately 1–2% of infants (1). Children who survive very preterm birth are at higher risk for a range of long-term health complications compared to those born at term (37–41 weeks), including cerebral palsy, visual and auditory deficits, respiratory problems, and impaired motor and cognitive development (2–5). These health consequences, along with the associated care needs, impact not only the children themselves but also their families and society as a whole.

Among these complications, respiratory morbidity—particularly obstructive airway diseases such as asthma—is one of the most prevalent (6–8). The lungs of preterm infants, especially those born before 32 weeks, are structurally and functionally immature at birth (9), which can result in long-term lung function impairment (10). Several biological and environmental factors contribute to asthma risk in preterm infants, including smaller airway size, heightened immune response to viral infections or allergens, ongoing inflammation, and altered microbiome composition (10). Preterm children are more likely than their term-born peers to experience respiratory symptoms such as coughing and wheezing, not only during infancy but also into adolescence (2,11–14). By school age, up to one-third of children born VPT receive asthma medication (13–15). A meta-analysis of observational studies reported that VPT children have a threefold increased risk of wheezing disorders compared to their term-born counterparts (16). The prevalence of asthma among children born VPT has been estimated at between 20.6% to 33% in different studies (17–19).

1.2. Healthcare Use After Preterm Birth

1.2.1. Higher Use of Health Care Among Children Born Very Preterm

Due to their complex medical and developmental needs, children born VPT often require greater use of healthcare services, including hospital care, compared to their non-VPT peers in the general population during childhood (ages 1–9 years) (20). These needs often extend to specialized care, with evidence showing that children born VPT already exhibit high levels of specialist care use by age 2 (21). At age 5, a substantial proportion of VPT-born children in Europe still have high levels of health service utilization: 43% report high primary care use (primary care sick visits, ER visits, hospitalizations), and 48% have high specialist care use (22). Follow-up programme children born VTP or who have other risk factors for long-term

health outcomes aim to detect health developmental problems early, to enable timely intervention and care (23,24) to avoid hospitalizations and emergency visits (25).

1.2.2. Factors Associated with Health Care Use in the Pediatric Population

Perinatal factors such as male sex, lower gestational age, small for gestational age (SGA), bronchopulmonary dysplasia (BPD), and other neonatal morbidities are associated with increased healthcare use specifically hospitalizations, emergency room (ER) visits, and specialist care use, during the first two years of life (21,24) and at age 5 years (22).

Socioeconomic factors also have been associated with the use of health care services in the published literature; for instance, socioeconomic deprivation is linked to higher rehospitalization rates within the first year of life in infant born preterm (26) and in VPT born children (27). Maternal education level and parental employment status have been shown to influence healthcare service utilization; specifically, children of mothers with intermediate or low education, or of unemployed parents, were at higher risk of high outpatient and inpatient service use at age 5. This included more frequent visits to general practitioners, pediatricians, and emergency services (22). Furthermore, children of young parents, parents with lower educational level and foreign-born parents are more likely to never have participated in follow-up programs for children born VPT, after adjusting for perinatal risk factors (28)

1.2.3. Adequacy of Health Care Among Children Born VPT

Despite having high service utilization, studies suggest that there is unmet health care needs among children born VPT. Up to half of VPT children with developmental impairments are not receiving relevant care (3,29). Furthermore, despite the increased medical needs of this population, follow-up care practices vary across Europe (30), including within France (28) before 2020, there were no national guidelines for structured follow-up of health and development specifically for VPT infants throughout early childhood (31) in France. Regardless of the wide range of healthcare needs children born VPT have, the evidence suggesting that there may be unmet care needs in this population, there is a lack of studies that evaluate the adequacy of care received at school age. One of the principal difficulties of such research is determining care appropriateness (i.e., if received care is sufficient, insufficient, or potentially avoidable), due to the widely heterogeneous and complex health care needs of VPT-born children, and health service use being part of current classifications of complex health care needs (32). In this Master's project, the aim is to go further in assessing the appropriateness of care received by children born VPT: by investigating health

service use in a population with asthma for which care needs would be similar, and for which a defined set of health services can be associated. Regardless of respiratory conditions being a prevalent condition in children born VPT, to the best of our knowledge, no studies have assessed the adequacy of respiratory care in this population.

1.3. Aims and Objectives

This internship project is part of an interdisciplinary study between OPPaLE (Obstetric, Perinatal and Pediatric Lifecourse Epidemiology) and LIRAES (Interdisciplinary Group in Applied Health Economics and Management Research) at Université Paris Cité - the “Preterm Care at Five” study. The aim of Preterm Care at Five is to describe and assess the adequacy of health service use for very preterm-born children in France at five years of age, to investigate socio-economic and demographic inequities in health service use, and assess economic costs related to the use of these services. This internship project focuses on the first two aims - to assess the appropriateness of health care received by children born VPT, and to assess the determinants of health care use, by investigating health service use in children with respiratory morbidities - frequent long-term outcomes after very preterm birth, with important implications for health care use and hospitalizations.

1.3.1. Aims

This internship project aims to assess the determinants of health care use in children born very preterm by investigating factors associated with respiratory-related health service utilization in children with asthma, with focus on sociodemographic factors.

1.3.2. Objectives

The specific objectives are to:
1. Identify and describe the characteristics of very preterm and term-born children with and without asthma
2. Analyze their health service use and assess whether there is potential suboptimal use
3. Investigate the determinants of using respiratory-related care, focusing on whether suboptimal care is associated with family sociodemographic factors.

1.3.3. Hypothesis

1. Respiratory care use should be higher in VPT children with asthma compared to children without asthma and to children born at term, due to the higher rates of BPD and the more careful follow-up related to prematurity in this population.

2. If socioeconomic or demographic determinants are associated with not receiving respiratory-related care in VPT children with asthma, this may indicate potential suboptimal care in this population.

2. Methods

2.1. Data Source, Data Collection and Study Population

For this project, data from two cohorts were used: the Étude Épidémiologique sur les Petits Âges Gestationnels-2 (EPIPAGE-2) and Étude Longitudinale Française depuis l'Enfance (ELFE). EPIPAGE-2 is a French population-based prospective birth cohort study which includes all children born preterm between 22 and 34 weeks of gestation in 25 French regions from March to December 2011. The recruitment period varied according to gestational age (GA), as births at earlier gestational ages occurred less frequently. Births occurring at 22–26 weeks' GA were included over a period of eight months, those at 27–31 weeks' GA over a period of six months, and births at 32–34 weeks' GA were included over a shorter period of five weeks (33). However, this study focused on children born VPT, defined as birth before 32 weeks' gestational age.

Out of 7,804 births (stillbirths, live births and terminations of pregnancy) between 22-34 weeks' gestation included at baseline, 4,312 were discharged alive from the neonatal unit and eligible for follow-up in the cohort. At birth, data collection was conducted through several methods. Information on parental sociodemographic characteristics, and the child's perinatal health and birth-related data was collected from medical records, interviews with mothers while they were in the maternity units (33).

From 2011 to 2017, three follow-up steps were conducted at 1 year, 2 years, and 5.5 years of age. At 5.5 years of age data were collected from parental questionnaires, standardized medical examinations performed by physicians, and neuropsychological assessments performed by psychologists. The follow-up at five years of age collected data on the child's health, neurodevelopment and behavior, and health care use, as well as updated information on family socioeconomic and demographic characteristics, such as parental education level and insurance status (33). A control group of term-born children come from the ELFE cohort, a national French birth cohort study of children born at term in 2011 in a random sample of maternity units. To provide reference data for EPIPAGE-2 at 5.5 years, a subsample of 585 ELFE children was assessed using the EPIPAGE-2 protocol (34).

2.2. Data and Definitions

2.2.1. Data on Perinatal and Birth-Related Characteristics

Data on perinatal and birth-related characteristics collected at baseline included the child's sex (male or female); gestational age, which was categorized into three groups: <28 weeks, 28–29 weeks, and 30–31 weeks; multiple births (singleton, one surviving multiple, or multiples—twins, triplets, or quadruplets); Bronchopulmonary Dysplasia (BPD), defined at 36 weeks' postmenstrual age: no BPD; mild BPD (oxygen required for ≥28 days); moderate BPD (oxygen and spontaneous respiration in room air, or oxygen for ≥28 days with mechanical ventilation, CPAP, or FiO_2 >21%); and severe BPD (oxygen for ≥28 days with mechanical ventilation, CPAP, or FiO_2 = 30%) were used. Severe neonatal morbidities were defined as the presence of one or more of the following: severe intraventricular haemorrhage (grades III–IV), cystic periventricular leukomalacia based on ultrasound diagnosis, severe necrotising enterocolitis (Bell's stages 2–3), severe retinopathy of prematurity (stage >3), and/or late-onset sepsis (positive blood culture after 72 hours of life, associated with antibiotic administration for five days or more).

2.2.2. Data on Sociodemographic Characteristics

Maternal characteristics included country of origin (born in France or outside France), mother's age at birth (≤24 years, 25–34 years, or ≥35 years), level of education at the five-year follow-up, categorized as low (upper secondary education or lower, including short professional training), intermediate (post-secondary non-tertiary or short-cycle tertiary vocational training), and high (bachelor's degree or higher), as well as parity at birth (nulliparous or multiparous). Child-related variables at age 5 included health insurance status, classified as complete health insurance (social security/statutory health insurance [SHI] or Couverture Maladie Universelle [CMU] with complementary private insurance [mutuelle] or 100% coverage for chronic conditions [ALD]) versus incomplete or no insurance (Aide Médicale de l'État [AME], CMU only, SHI only, or no insurance). Definitions of these insurance schemes are as follows: SHI is statutory health insurance; mutuelle is private top-up insurance; CMU provides additional coverage for low-income individuals; ALD covers full health expenditures for certain chronic conditions; and AME offers emergency care coverage for uninsured foreigners. Additional family-related variables at age 5 were whether the child was living with two parents or a single parent (or other situation, such as with grand-parents) and parental occupational status, defined by whether both parents were working full-time or not (for instance, only one parent working full time, two part-time working parents, and single-parent households).

2.2.3. Data on Health Service Use at Five Years of Age

In the parent questionnaires at the five-year follow-up, the parents were asked : “Over the past 12 months, have you visited any of the following health care services with your child?” For each service, parents reported yes/no and the number of times visited. The list included general practitioners (GPs), pediatricians, ears, nose and throat (ENT) specialists, pulmonologists, respiratory physiotherapists, emergency room (ER) visits, and others (e.g., neurologists, psychiatrists). Parents could also specify other providers in a free-text response, such as allergologists. The main outcome variable was defined as any visits to respiratory-related health care providers over the past 12 months. These providers included pulmonologists, respiratory physiotherapists, and allergologists.

Hospitalization data were also collected from the parent-report questionnaires. Parents were asked: “Has your child been hospitalized over the past 12 months?” (yes/no), and if yes, were prompted to provide the reason for hospitalization, type of service, number of nights, and whether surgery was performed, for up to three hospitalizations.

Additionally, data on follow-up related to preterm birth were collected. Parents were asked whether their child had health examinations as part of a follow-up specifically for children born preterm (“Never / Not anymore / Yes, still (specify where...)”), with responses complemented by information from the physician-completed medical questionnaire. Parents were also asked whether the child was currently followed in a specialized centre (yes/no), with response options including CAMSP (Centre d’Action Médico-Sociale Précoce), CMP (Centre Médico-Psychologique), CMPP (Centre Médico-Psycho-Pédagogique), or other (with a space to specify). A variable was created for follow-up, defined as still seeing any of these services.

Using the information collected on health service use, two summary variables were created: the total number of different health care services consulted and the total number of visits across all services. A total of 32 distinct services were included in this count. Fourteen were listed directly in the questionnaire: pediatrician, general practitioner (GP), ophthalmologist, orthoptist, ENT specialist, pneumologist, neurologist, psychiatrist, osteopath, psychomotor therapist, physiotherapist, psychologist, speech therapist, and respiratory physiotherapist. An additional 18 services were identified from free-text responses: allergologist, cardiologist, dermatologist, endocrinologist, gastroenterologist, geneticist, haematologist, nephrologist, oncologist, orthopaedist, phoniatrist, rehabilitation physician, rheumatologist, urologist, ergotherapist, podiatrist, psychotherapist, and nutritionist.

2.2.4. Data on Child's Health at Five Years of Age

Data on child respiratory health were primarily collected during medical examinations at 5.5 years of age. Several respiratory variables were derived from responses to physician-reported questions to the parent regarding asthma symptoms. These included wheezing ever, assessed by the question: "Has the child ever had wheezing at any point in their life?"; wheezing in the past 12 months: "Has the child had wheezing in the last 12 months?"; wheezing after physical effort: "In the past 12 months, has the child experienced wheezing during or after exertion?"; and dry cough at night: "In the past 12 months, has the child had a dry cough at night when they did not have a cold or respiratory infection?"

The presence of an asthma diagnosis was also assessed during the medical exam, with questions including asthma diagnosis ever: "Has the child been diagnosed with asthma?"; infant asthma: if the answer to the previous question was yes, "Was the diagnosis made during infancy?"; asthma after 3 years of age: if asthma was diagnosed, "Was the diagnosis made after the age of 3?"; and asthma attacks: "Has the child ever had one or more asthma attacks?" The physician was asked to provide information on whether the child has other respiratory pathologies in free text, from which cases of asthmatic bronchiolitis were derived. For parents who did not participate in the medical exams with their child, a question was asked in the parental follow-up questionnaire about whether a physician or other health professional had diagnosed their child with asthma.

A separate question concerned whether or not the child had eczema or atopic dermatitis at five years of age. Finally, physicians were asked to provide information on any other health problems the child might have through a free-text question: "Does the child have other health problems? If yes, which ones?", from which cases of allergy were derived.

2.2.5. Data on Medications at Five Years of Age

During the medical exams at the five-year follow-up, physicians answered a free-text question regarding the child's current long-term treatments (Is the child currently undergoing long-treatment (medication or other)? If yes, mention treatments and indications). Asthma medications were then identified from these responses as part of the data cleaning process used to define asthma. Classification of asthma medication use followed the 2024 SP2A guidelines for managing asthma in children aged 6–12 years (35). The main medications of interest were the use of asthma medication, defined by the presence of short- and long-acting beta-agonists, inhaled corticosteroids, combination inhalers, and Montelukast.

2.3. Asthma Definition

In the published literature, there is variation in the definition of asthma, especially among very preterm populations. Common definitions include wheezing in the past 12 months (17,36,37), parent-reported diagnosis of asthma (18), use of asthma medication (19,38), or a combination of these (39,40) (Appendix Table A1). A commonly used epidemiological definition of asthma used in previous publications include the definition from the Mechanisms of the Development of Allergy (MeDALL) project, which considers a child to have asthma if they meet at least two of the following criteria: asthma diagnosis, wheezing in the past 12 months, or use of asthma medication (41). Another definition, used in the International Study of Asthma and Allergies in Childhood (ISAAC), defines asthma as the presence of both an asthma diagnosis and either wheezing or use of asthma medication in the past 12 months (42). However, these definitions rely on the child having received a diagnosis or medication for asthma, and therefore primarily include children who have already accessed health care services. As such, they are not appropriate for our objective, which is to assess potential underuse of care. Children with asthma symptoms who have not consulted a health professional would be excluded by definition, leading to an underestimation of unmet care needs.

After reviewing the various definitions in the literature and consulting with a French neonatologist and a pediatric pulmonologist, we decided to adopt the following definition of asthma: a child was considered to have asthma if they had any of the following — a diagnosis of asthma (excluding children with neonatal asthma only, i.e. diagnosed before age 3), current use of asthma medication, or wheezing in the past 12 months. This broad definition includes parent-reported symptoms that are not dependent on prior contact with a health professional (as is the case for diagnosis or medication), allowing us to assess potential suboptimal use of health care in children with asthma symptoms at 5 years of age.

2.4. Analytical Strategy

2.4.1. Directed Acyclic Graph (DAG)

A literature review was conducted to identify relevant variables associated with asthma and health service use, and a DAG (Figure 1) was constructed to identify potential confounders and guide variable selection for assessing the potential impact of sociodemographic factors on respiratory health care use at age 5 in VPT children. Factors associated with both the risk of developing respiratory problems and the likelihood of receiving health care include perinatal characteristics such as GA, SGA, multiplicity, and child sex, as well as socioeconomic and demographic factors. GA is also a criterion for inclusion in follow-up programs for VPT infants, which are designed to facilitate access to care. Socioeconomic

factors may influence the likelihood of having comprehensive health insurance, which in turn may affect access to care. Additionally, regional differences in the availability of care may further influence access. Finally, we hypothesize that receiving respiratory care is associated with subsequent use of hospital and emergency room (ER) services.

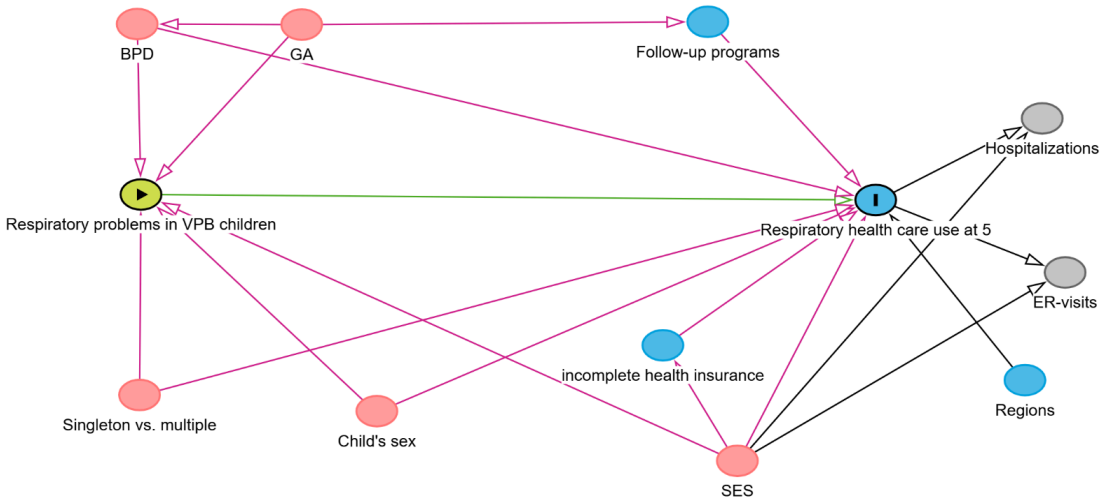

Figure 1: DAG

2.4.2. Descriptive and Univariable Analyses

The first analyses involved describing the inclusion into the VPT sample population, and comparing the perinatal and sociodemographic characteristics of VPT children followed up at five years of age, compared to those lost to follow-up. This analysis could not be done for the term population because full information on the baseline sample is not available. We then described the prevalence of asthma in VPT and term-born children, before describing the characteristics of children both with and without asthma, including their health care use, sociodemographic characteristics and perinatal characteristics. In a second set of analyses, we focused in more detail on the factors affecting the use of health services by children born VPT with asthma. Univariate analyses were performed using Chi² tests examining the perinatal and socioeconomic and demographic characteristics of VPT with asthma who received and did not receive respiratory related care and also to assess use of other related health services in these two groups.

Statistical weights were used in all our analyses to serve two primary purposes. First, they account for the sampling design of the Epipage-2 study, in which the recruitment period differed for births occurring at 22–26 weeks' GA compared to those at 27–31 weeks' GA. Second, they correct for selection bias by aligning the characteristics of the ELFE cohort with those of the general pediatric population of term births in France in 2011, due to initial non-participation and attrition over time. The ELFE weights are constructed using

information on the mother's and father's socioeconomic and demographic characteristics, lifestyle-related factors, the child's perinatal characteristics, and characteristics of maternity units (34). These weights have been previously applied in analyses involving the ELFE cohort, supporting their relevance and validity as a reference population for preterm children (3).

2.4.3. Multivariable Analyses

For the selection of variables potentially associated with receiving respiratory-related health care for the multivariable regression, covariates were selected based on the published literature. We used a Poisson regression model with a log link function to estimate relative risks (RRs) and 95% confidence intervals (CIs) for the association between sociodemographic factors and the outcome of respiratory-specific care among VPT children with asthma. To account for potential heteroskedasticity, we calculated robust standard errors using the heteroskedasticity-consistent (HC0) sandwich estimator. The exponentiated regression coefficients are presented as relative risks with corresponding 95% confidence intervals.

In Model 1, we estimated unadjusted RRs for receiving respiratory-specific care using a separate Poisson regressions model with a log link function for each socioeconomic status (SES) variable. Each model included one SES variable as the independent variable. In Model 2, we estimated the RR for receiving respiratory-specific care for each SES variable independently, adjusting for perinatal factors. Each model included one SES variable and all perinatal covariates. In Model 3, we estimated the RRs for receiving respiratory-specific care while adjusting simultaneously for all SES variables and perinatal factors and any preterm follow-up care variable. In Model 4, we included all SES variables, perinatal factors, and any preterm follow-up care variable, and additionally adjusted for fixed effects of all 25 regions. The aforementioned weights were used in all regression models. All analyses were conducted using R version 4.4.2 (R Core Team, 2024).

2.4.4. Sensitivity Analyses

We conducted a sensitivity analysis to assess the robustness of our asthma definition, by using an alternative definition of asthma, excluding children who reported wheezing in the past 12 months without diagnosis and without asthma medication, but had no other symptoms or concurrent asthma-related comorbidities, including dry cough at night, wheezing after physical effort, eczema, allergies or asthma attacks (Appendix Table A2). This approach was motivated by previous findings suggesting that wheezing alone,

especially in the absence of other indicators, is a poor marker for asthma in epidemiological studies (37). In this alternative definition, we also included children with a diagnosis of infant asthma (defined as an asthma diagnosis made before age 3) who did not have a diagnosis after age 3, nor wheezing in the past 12 months or medications, but who presented with persistent respiratory or allergic symptoms at age 5 (Appendix Table A3). These symptoms included dry cough at night, wheezing after physical effort, eczema, or allergies. Additionally, in this sensitivity analysis, we used an alternative variable for “respiratory care” in which all missing values for pulmonologist visits were coded as “no”. The complete multivariable model (Model 4) was compared to a model using the alternative asthma definition and respiratory care variable (Model 5).

2.5. Ethical Considerations

The EPIPAGE-2 study received approval from the French National Data Protection Authority (CNIL, DR-2016-290), the Consultative Committee on the Treatment of Data on Personal Health for Research Purposes (No. 16.263), and the Committee for the Protection of People Participating in Biomedical Research (2016-A00333-48). Written informed consent was obtained from the parents of all participants prior to inclusion in the study and prior to participating in the five-year follow-up.

3. Results

3.1. Study Population

Figure 2 presents the study population flowchart. A total of 3,964 live-born children born between 22 and 31 weeks' gestation (extremely or very preterm) were included in the EPIPAGE-2 cohort. After excluding early deaths and losses to follow-up, 2,262 children born at 24–31 completed weeks of gestation who survived to 5.5 years of age, were included in the study, representing 73% out of 3,099 children eligible at 5.5 years. Additionally, 585 term-born children (37–40 completed weeks of gestation) from the ELFE study who were assessed at 5.5 years of age were included.

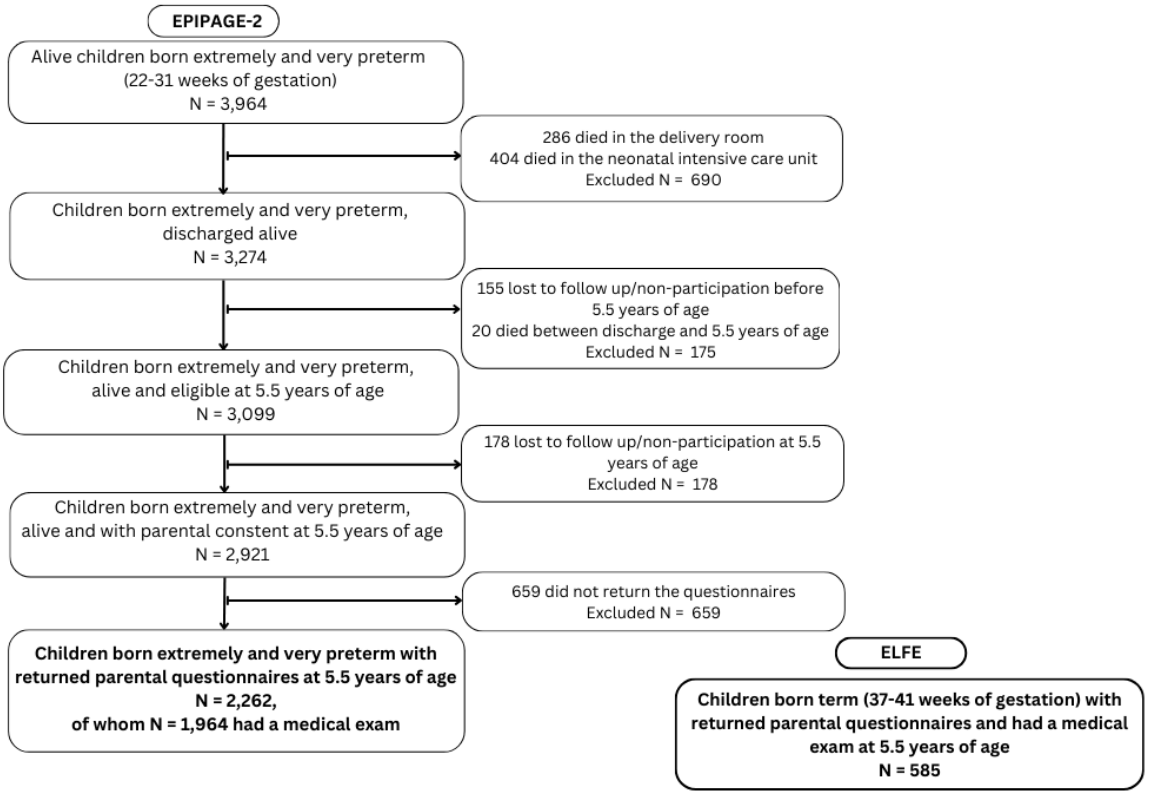

Figure 2: Study population flowchart

Compared to children lost to follow-up, the EPIPAGE-2 children included in the study were more likely to have mothers with higher educational levels, to be born to French-born mothers, have older mothers at delivery, and to be firstborn (Appendix Table A4).
When comparing children born VPT to those in the term comparison group, parents of term-born children had higher educational levels, more complete health insurance coverage, and were more likely to both be employed (Table 1).

3.2. Asthma Prevalence

The prevalence of asthma was 28.7% among VPT children, compared to 12.6% among term born children (Appendix Table A5). Asthma rates increased with decreasing GA: 33.5% in children born before 28 weeks, 28.4% in those born at 28–29 weeks, and 26.5% in those born at 30–31 weeks. Among children born VPT, 10% had asthma diagnosis, 10.2% had received asthma medication, and 22.7% experienced wheezing in the past 12 months, compared to 5.6%, 4.6% and 10.1% in term-born children, respectively. Out of the 531 VPT-born children with asthma, 212 (39.9%) had only wheezing in the past 12 months, 28 (5.3%) had only asthma medication, and 33 (6.2%) had only asthma diagnosis, whereas 70

(13.2%) had all three components of our asthma definition (Appendix Table A6). Proportions were similar for term-born children.

3.3. Characteristics of Children With and Without Asthma

Compared to VPT children without asthma, those with asthma were more often male (57.3% vs. 51.2%), born at lower gestational ages (28.1% vs 22.5% before 28 weeks), and more frequently singletons (72.2% vs. 65.4%) (Table 1). They also had slightly higher rates of moderate/severe BPD (13.4% vs. 11.9%) and other severe neonatal morbidities (29.5% vs. 26.6%). Children with asthma, both VPT and term-born, were more often born to native French mothers compared to those without asthma. There were no other major differences in sociodemographic characteristics between VPT children with and without asthma. Among term-born children, those with asthma more frequently had older mothers, siblings and had less often mothers with high educational level and were less often from single-parent households (Table 1).

Table 1. Descriptive Characteristics of Very Preterm and Term Children With and Without Asthma

	Very preterm		Term	
	Asthma N = 531 No. (%)	**No asthma** N = 1303 No. (%)	**Asthma** N = 62 No. (%)	**No asthma** N = 454 No. (%)
Perinatal characteristics				
Child's sex				
Male	302 (57.3)	668 (51.2)	35 (49.2)	239 (54.5)
Female	229 (42.7)	635 (48.8)	27 (50.8)	215 (45.5)
Gestational age				
<28	168 (28.1)	333 (22.5)		
28-29	150 (29.7)	379 (30.3)		
30-31	213 (42.2)	591 (47.2)		
SGA (percentiles)				
<3rd	110 (21.2)	313 (24.6)		
3 - 9th	55 (10.5)	173 (13.4)		
≥10th	366 (68.3)	817 (62.0)		
Multiple birth				
Singleton or one surviving multiple	383 (72.2)	852 (65.4)		
Multiples	148 (27.8)	451 (34.6)		
BPD				
No or mild	441 (86.6)	1,117 (88.1)		
Moderate or severe	71 (13.4)	167 (11.9)		
Severe neonatal morbidity[1]				
No	350 (70.5)	913 (73.4)		
Yes	160 (29.5)	350 (26.6)		
Sociodemographic characteristics				
Country of origin				
France	443 (83.5)	1,031 (79.5)	54 (89.3)	402 (79.4)

Outside France	88 (16.5)	265 (20.5)	7 (10.7)	50 (20.6)
Age at birth				
≤24 years	72 (13.6)	198 (15.1)	1 (6.5)	25 (13.7)
25-34 years	342 (64.8)	814 (62.2)	42 (65.5)	316 (67.8)
≥35 years	117 (21.5)	291 (22.6)	18 (27.9)	112 (18.5)
Education[2]				
Low	243 (45.8)	560 (43.1)	9 (39.2)	65 (37.1)
Intermediate	122 (23.2)	348 (26.6)	16 (25.2)	105 (22.3)
High	165 (30.9)	393 (30.2)	37 (35.6)	279 (40.6)
Parity				
Nulliparous	299 (56.8)	752 (58.1)	16 (29.3)	197 (45.3)
Multiparous	229 (43.2)	535 (41.9)	42 (70.7)	235 (54.7)
Insurance				
Complete	442 (83.8)	1084 (84.5)	60 (92.9)	433 (92.4)
Without or incomplete	84 (16.2)	200 (15.5)	2 (7.1)	15 (7.6)
Being single parent				
No	437 (82.2)	1095 (84.4)	59 (96.8)	420 (89.4)
Yes	94 (17.8)	203 (15.6)	3 (3.2)	33 (10.6)
Two full-time working parents				
No	328 (63.1)	785 (63.3)	29 (49.6)	214 (51.3)
Yes	189 (36.9)	456 (36.7)	33 (50.4)	240 (48.7)

SGA: Small for Gestational Age; BPD: Bronchopulmonary Dysplasia.

[1] Severe intraventricular haemorrhage (grades III-IV) OR cystic periventricular leukomalacia based on ultrasound diagnosis OR severe necrotising enterocolitis (Bell's stages 2-3) OR severe retinopathy of prematurity (stage >3) AND/OR late onset sepsis (positive blood culture after 72h of life, associated with antibiotic administration for five days or more). [2] Low (Upper secondary (lycée) or lower, including short professional training), Intermediate (Post-secondary, non tertiary (pre-university courses) or short cycle tertiary (vocational)), High (Bachelor degree or equivalent, or higher).

Respiratory health care use was higher in the children with asthma compared to children without asthma. A pulmonologist over the past year was most common in children with asthma (31.2% in VPT and 26.9% in term-born children) compared to those without asthma (<3%) (Table 2). Rates of respiratory physiotherapy were low overall, but highest among asthmatic term-born children (10.1%). Having at least one respiratory-related specialist visit over the past year was most frequent in children with asthma—35.5% among VPT and 30.3% in term-born children—compared to <6% in children without asthma. The mean number of visits was highest among VPT children with asthma across all respiratory care providers (Table 2).

Table 2 shows the majority of children had seen a GP regardless of asthma status and gestational age. Use of other related healthcare services differed across groups. Pediatrician visits were more frequent among VPT children (62.7% with and 52.2% without asthma) compared to term children (37.9% and 34.7% respectively). Preterm follow-up care was highest among VPT children with asthma (70.3%) and lower among those without asthma (60.6%). ENT specialist visits were slightly more common among children with asthma, particularly in the VPT group (30.2%) compared to their term counterparts (28.4%).

A total of 37.9% of VPT children with asthma had ER visits, compared to 20.5% of those without asthma. ER visit rates were similar between asthmatic VPT and term-born children (37.9% and 39.4%, respectively), as well as among non-asthmatic children in both groups (approximately 21%). Children with asthma, particularly those born VPT, had higher hospitalization rates (19.9%) compared to other groups (10.4% in non-asthmatic VPT, 12.6% in asthmatic term, and 5.4% in non-asthmatic term children) (Table 2).

Table 2. Health Service Use of Very Preterm and Term Children With and Without Asthma

	Very preterm		Term	
	Asthma N = 531 No. (%) *Mean (SD)* *Median [IQR]*	**No asthma** N = 1303 No. (%) *Mean (SD)* *Median [IQR]*	**Asthma** N = 62 No. (%) *Mean (SD)* *Median [IQR]*	**No asthma** N = 454 No. (%) *Mean (SD)* *Median [IQR]*
Respiratory health care use				
Pulmonologist (any visit)	137 (31.2)	29 (2.7)	12 (26.9)	7 (0.1)
Among children who saw a pulmonologist: number of visits	*1.7 (1.1)*	*1.3 (0.7)*	*1.1 (0.4)*	*1.1 (0.3)*
	1 [1-2]	*1 [1-1]*	*1 [1-1]*	*1 [1-1]*
Respiratory physiotherapist (any visit)	33 (6.2)	27 (2.1)	4 (10.1)	3 (0.3)
Among children who saw a respiratory physiotherapist: number of visits	*9.1 (17.5)*	*3.4 (4.2)*	*3.1 (1.8)*	*4.5 (2.4)*
	3 [1-10]	*1 [1-5]*	*3 [3-3]*	*5 [5-6]*
Allergologist[1] (any visit)	2	4	2	4
Respiratory care[2] (any visit)	155 (35.5)	60 (5.8)	15 (30.3)	14 (2.2)
Among children who had respiratory care[2]**:** number of visits	*3.5 (8.7)*	*2.2 (3.1)*	*2.5 (1.7)*	*1.8 (1.6)*
	2 [1-4]	*1 [1-3]*	*2 [1-5]*	*2 [1-2]*
Other related health care use				
GP visit (any visit)	461 (88.1)	1081 (84.2)	51 (89.6)	375 (85.6)
Among children who saw a GP: number of visits	*4.3 (6.2)*	*3.4 (4.9)*	*4.4 (3.1)*	*2.6 (1.8)*
	3 [1-5]	*2 [1-4]*	*3 [2-6]*	*2 [1-3]*
Pediatrician visits (any visit)	332 (62.7)	672 (52.2)	23 (37.9)	166 (34.7)
Among children who saw a pediatrician: number of visits	*2.5 (2.6)*	*1.8 (1.5)*	*2.7 (1.9)*	*2.1 (2.2)*
	1 [1-3]	*1 [1-2]*	*3 [1-3]*	*1 [1-2]*
Any preterm follow-up	374 (70.3)	797 (60.6)	3 (2.9)	23 (7.8)
ENT specialist (any visit)	159 (30.2)	343 (26.8)	14 (28.4)	99 (19.4)
Among children who saw an ENT specialist: number of visits	*1.6 (1.1)*	*1.7 (3.0)*	*1.4 (0.7)*	*1.7 (1.1)*
	1 [1-2]	*1 [1-2]*	*1 [1-2]*	*1 [1-2]*
ER visit (any visit)	197 (37.9)	262 (20.5)	22 (39.4)	92 (20.9)
Among children who visited the ER: number of visits	*1.8 (1.8)*	*1.6 (2.0)*	*1.3 (0.6)*	*1.3 (0.8)*

	1 [1-2]	*1 [1-2]*	*1 [1-2]*	*1 [1-2]*
Hospitalizations (any hospitalization)	104 (19.9)	135 (10.4)	8 (12.6)	31 (5.4)
Among children who were hospitalized: number of nights hospitalized	*2.9 (4.0)*	*1.7 (2.8)*	*4.4 (7.4)*	*1.0 (1.9)*
	1 [0-4]	*1 [0-2]*	*3 [2-3]*	*1 [0-1]*
Total number of health care services consulted[3]	*3.9 (2.2)*	*3.2 (2.0)*	*3.1 (1.7)*	*2.4 (1.4)*
	3 [2-5]	*3 [2-4]*	*3 [2-4]*	*2 [1-3]*
Total number of health care visits[3]	*22.8 (38.1)*	*19.5 (39.7)*	*8.6 (8.3)*	*11.3 (26.2)*
	8 [4-20]	*6 [3-13]*	*6 [4-12]*	*4 [2-8]*

GP: General Practitioner; ENT: Ears, Nose and Throat; ER: Emergency Room.

[1] "Allergologist" is derived from free-text responses where only affirmative mentions were recorded. [2] Respiratory care includes any visit or the total number of visits to a pulmonologist, respiratory physiotherapist, or allergologist.

[3] Total number of services and visits includes 32 services (see Methods for full list)

3.4. Factors Associated With Receiving vs. Not receiving Respiratory-Specific Care Among VPT Children With Asthma

Table 3 compares VPT children with asthma who received respiratory-specific care (n = 155) to those who did not (n = 279) across perinatal and sociodemographic characteristics. Although no statistically significant differences were observed between the two groups, a higher proportion of children who received respiratory-specific care were born at lower GA (before 30 weeks) (61.8% vs. 53.8%) and had mothers aged 35 years or older at the time of birth (25.2% vs. 17.8%). Additionally, these children's mothers tended to have higher educational levels (32.8% vs. 26.4%) and more often had complete health insurance coverage (85.7% vs. 81.5%).

Table 3. Comparison of Perinatal and Sociodemographic Characteristics Between VPT Children With Asthma Using vs. Not Using Respiratory Health Care

	No respiratory-specific care N = 279 No. (%)	Received respiratory-specific care N = 155 No. (%)	p-value
Perinatal characteristics			
Child's sex			0.4
Male	152 (54.8)	90 (58.7)	
Female	127 (45.2)	65 (41.3)	
Gestational age			0.3
<28	85 (26.8)	53 (30.3)	
28-29	71 (26.8)	46 (31.5)	
30-31	123 (46.4)	56 (38.3)	
SGA (percentiles)			0.7
<3rd	58 (21.1)	36 (24.3)	

3 - 9th	29 (10.5)	13 (8.5)	
≥10th	192 (68.4)	106 (67.2)	
Multiple birth			0.5
Singleton or one surviving multiple	204 (73.2)	109 (70.3)	
Multiples	75 (26.8)	46 (29.7)	
BPD			< 0.01
No or mild	244 (89.9)	116 (81.0)	
Moderate or severe	31 (10.1)	31 (19.0)	
Severe neonatal morbidity[1]			0.5
No	188 (71.6)	97 (68.1)	
Yes	81 (28.4)	50 (31.9)	
Maternal and sociodemographic characteristics			
Country of origin			0.9
France	231 (83.0)	128 (82.4)	
Outside France	48 (17.0)	27 (17.6)	
Age at birth			0.1
≤24 years	45 (16.2)	19 (12.3)	
25-34 years	183 (66.0)	96 (62.5)	
≥35 years	51 (17.8)	40 (25.2)	
Education[2]			0.4
Low	140 (50.3)	70 (44.7)	
Intermediate	64 (23.3)	34 (22.5)	
High	75 (26.4)	50 (32.8)	
Parity			0.8
Nulliparous	153 (55.7)	84 (54.5)	
Multiparous	124 (44.3)	70 (45.5)	
Health insurance status			0.3
Complete	225 (81.5)	132 (85.7)	
Without or incomplete	50 (18.5)	22 (14.3)	
Being single parent			0.5
No	224 (80.0)	128 (82.4)	
Yes	55 (20.0)	27 (17.6)	
Two full-time working parents			0.5
No	171 (61.7)	99 (65.0)	
Yes	105 (38.3)	52 (35.0)	

SGA: Small for Gestational Age; BPD: Bronchopulmonary Dysplasia.

[1]Severe intraventricular haemorrhage (grades III-IV) OR cystic periventricular leukomalacia based on ultrasound diagnosis OR severe necrotising enterocolitis (Bell's stages 2-3) OR severe retinopathy of prematurity (stage >3) AND/OR late onset sepsis (positive blood culture after 72h of life, associated with antibiotic administration for five days or more). [2]Low (Upper secondary (lycée) or lower, including short professional training), Intermediate (Post-secondary, non tertiary (pre-university courses) or short cycle tertiary (vocational)), High (Bachelor degree or equivalent, or higher)

Table 4 compares the use of other health care services between VPT children with asthma who received respiratory-specific care and those who did not. While GP and pediatrician consultations were similar between the groups, statistically significant differences were found for ENT specialist consultations and hospitalizations. Children who did not receive

respiratory-specific care had lower rates of ENT visits (56.5% vs. 75.3%) and hospitalizations (72.1% vs. 83.3%).

Table 4. Comparison of Health Service Use Between Very Preterm Children With Asthma Using vs. Not Using Respiratory Health Care

	No respiratory-specific care, N = 279 No. (%)	Received respiratory-specific care, N = 155 No. (%)	p-value
Related health care use			
GP visits (any visit)			0.8
No	33 (11.4)	19 (12.3)	
Yes	244 (88.6)	134 (87.7)	
Pediatrician visits (any visit)			0.4
No	108 (39.0)	52 (34.6)	
Yes	169 (61.0)	102 (65.4)	
ENT specialist (any visit)			< 0.001
No	204 (75.3)	84 (56.5)	
Yes	68 (24.7)	67 (43.5)	
ER visit (any visit)			0.1
No	178 (63.5)	82 (55.2)	
Yes	99 (36.5)	68 (44.8)	
Hospitalizations (any hospitalization)			< 0.01
No	227 (83.8)	108 (72.1)	
Yes	44 (16.2)	42 (27.9)	
Any preterm follow-up			0.3
No	89 (31.9)	41 (27.0)	
Yes	190 (68.1)	114 (73.0)	

GP: General Practitioner; ENT: Ears, Nose and Throat; ER: Emergency Room.

3.5. Multivariable Analysis: Factors Associated With Receiving Respiratory-Specific Care Among VPT Children With Asthma

When adjusting for perinatal factors only (Model 2), both BPD and maternal age were significantly associated with respiratory care use (Table 5). Children with BPD had a 48% higher likelihood of receiving respiratory care compared to those without BPD (aRR = 1.48; 95% CI: 1.04–2.09), and children of older mothers also had a higher likelihood (aRR = 1.34; 95% CI: 1.00–1.81). However, the association with maternal age was no longer significant after adjusting for additional sociodemographic factors and follow-up participation in Model 3. In contrast, the association with BPD remained significant and even slightly stronger (aRR = 1.52; 95% CI: 1.05–2.19).

In the final multivariable model (model 4) adjusting for sociodemographic and perinatal factors as well as participating in preterm follow-up and regions, moderate/severe BPD was the only factor significantly associated with receiving respiratory-specific care at 5 years of

age. In the fully adjusted model, children with moderate/severe BPD had a 71% higher probability of receiving such care compared to those without BPD (aRR: 1.71, 95% CI: 1.17-2.49) (Table 5).

Other sociodemographic variables such as maternal age, parental education, and health insurance status were not significantly associated with respiratory care use in the fully adjusted models, although the children born to mothers aged ≥35 years showed a non-significant tendency toward higher care use (aRR: 1.27, 95% CI: 0.93–1.75), and those with incomplete insurance had slightly lower use (aRR: 0.80, 95% CI: 0.51–1.26), for instance.

Table 5: Relative Risks of Respiratory Health Care Use at 5 Years of Age Among VPT-Born Children with Asthma, by Sociodemographic, Perinatal, and Follow-up Characteristics

	Model 1 Unadjusted RR [95% CI]	**Model 2** Adjusted RR for all Perinatal factors [95% CI]	**Model 3** Adjusted RR for all SES, perinatal factors, and Any FUP [95% CI]	**Model 4** Adjusted RR for all SES, perinatal factors, any FUP, and Regions [95% CI]
Sociodemographic Factors				
Mother's Country of Origin (ref: born in France)				
Born outside France	1.01 [0.72-1.41]	1.10 [0.79-1.54]	1.15 [0.82-1.60]	1.17 [0.82-1.66]
Mother's Age at Birth (ref: 25-34 years)				
≤24 years	0.86 [0.57-1.3]	0.74 [0.46-1.18]	0.79 [0.48-1.29]	0.78 [0.48-1.26]
≥35 years	1.28 [0.96-1.70]	1.34 [1.00-1.81]	1.29 [0.94-1.76]	1.27 [0.93-1.75]
Mother's Education[1] (ref: intermediate)				
Low	0.96 [0.69-1.34]	0.97 [0.68-1.37]	1.00 [0.69-1.45]	0.94 [0.65-1.35]
High	1.15 [0.82-1.63]	1.16 [0.80-1.68]	1.16 [0.80-1.70]	1.03 [0.71-1.48]
Parity (ref: nulliparous)				
Multiparous	1.02 [0.79-1.31]	1.12 [0.86-1.45]	1.03 [0.77-1.38]	1.03 [0.77-1.36]
Health insurance status (ref: complete)				
Without or incomplete insurance	0.83 [0.57-1.20]	0.83 [0.56-1.23]	0.86 [0.55-1.36]	0.80 [0.51-1.26]
Parental occupational status (ref: not both parents full-time workers)				
Two full-time working parents	0.98 [0.77-1.25]	0.99 [0.72-1.33]	0.96 [0.71-1.31]	0.88 [0.65-1.20]
Perinatal Factors				
Child's sex (ref: male)				
Being female		0.89 [0.68-1.16]	0.91 [0.69-1.20]	0.91 [0.69-1.20]
Gestational age		0.96 [0.89-1.04]	0.97 [0.90-1.05]	0.99 [0.92-1.07]
SGA (ref: percentiles ≥10th)				
Percentiles <3rd		1.02 [0.73-1.42]	1.02 [0.73-1.41]	0.97 [0.70-1.36]
Percentiles 3 − 9th		0.81 [0.48-1.36]	0.80 [0.46-1.39]	0.73 [0.42-1.25]
Multiple birth (ref: singleton or one surviving multiple)				
Multiples		1.21 [0.91-1.61]	1.23 [0.92-1.65]	1.18 [0.86-1.59]
BPD (ref: no or mild)				
Moderate or severe		1.48 [1.04-2.09]	1.52 [1.05-2.19]	1.71 [1.17-2.49]

Presence of severe neonatal morbidity	0.98 [0.73-1.33]	1.00 [0.74-1.36]	1.05 [0.78-1.41]
Follow-up and Regions			
Any preterm follow-up		1.10 [0.80-1.51]	1.16 [0.84-1.61]
Regions			Not shown*

[1] Low (Upper secondary (lycée) or lower, including short professional training), Intermediate (Post-secondary, non tertiary (pre-university courses) or short cycle tertiary (vocational)), High (Bachelor degree or equivalent, or higher)

[2] 25 Region fixed effects were included in the model but individual coefficients are not presented.

We performed sensitivity analyses, using an asthma definition excluding 60 children who had wheezing in the past 12 months but no other asthma-related symptoms or comorbidities at age 5, and including 66 children who had been diagnosed with infant asthma and presented with persistent asthma-related symptoms or comorbidities at age 5. To address missing data on pulmonologist visits, we also coded missing values as ”No”. There were 570 missing values for pulmonologist (20% missing values), similar rates in both Epipage-2 and ELFE, while for the other services, missing values are 2-3%. Using these updated criteria in the adjusted multivariable models (model 5), the results remained consistent with the main findings (Appendix Table A7).

4. Discussion

In this large population-based cohort study of children born VPT in France and a contemporaneous reference group of children born at term, asthma prevalence was more than twice as high in VPT children compared to term-born children (28.7% vs. 12.6%). Asthmatic versus non-asthmatic children were more likely to see respiratory specialists, but there was little difference between VPT and term children: 35.5% of VPT and 30.3% of term children with asthma had respiratory healthcare use over the past year. No differences were observed between term and VPT children in ER visits, but differences were found in hospitalization rates across GA groups, with the highest rates observed among VPT children with asthma. There were no observed differences in perinatal and sociodemographic characteristics between VPT children with asthma who did and did not receive respiratory-specific care, except for higher rates of BPD among those who received care (19% vs. 10%). Differences were also found in service use: VPT children with asthma who did not receive respiratory care, had lower rates of other relevant health care use too, including lower rates of ENT visits, ER visits and hospitalizations. Adjusted analyses showed that moderate to severe BPD was the only factor associated with receiving respiratory-specific care at 5 years of age, with a 71% higher likelihood of receiving such

care compared to those without BPD. These results suggest that the VPT children with asthma, especially those with BPD, may have more severe health conditions, leading to greater need for specialised care and hospitalisation, and provide no evidence that the family's socioeconomic characteristics affect access to care.

4.1. Strengths and Limitations

A major strength of this study is the use of large, national prospective birth cohorts (EPIPAGE-2 and ELFE), which allowed for a detailed comparison of respiratory health use in VPT versus term children. The use of an asthma definition based on the published literature and using data derived primarily from the parental questionnaires as well as an assessment by a physician during a medical visit, provides a comprehensive assessment of disease prevalence. The availability of a reference population of term-born children enabled us to contextualize our findings and confirm that asthma was more prevalent among children born VPT. These results, from a large population with follow-up at 5, provides an important new data point for researchers investigating asthma in the VPT population.

However, several limitations should be considered when interpreting the results. First, loss to follow-up may have led to an underestimation of asthma prevalence, especially if children with more severe outcomes were less likely to participate. Although BPD and other perinatal risk factors for respiratory sequelae did not differ between those lost to follow-up and those retained, attrition was more common among some families with lower maternal education, maternal age, born outside France and multiparous. This may lead to an underrepresentation of socially disadvantaged groups, potentially underestimating associations between socioeconomic factors and asthma outcomes.

Second, data on health service use came from parent-report, which may be subject to recall bias, potentially leading to an underestimation of respiratory health service use. Additionally, some missing values, for example, in pulmonologist consultations, may reflect lack of awareness about what a pulmonologist is among parents who had not accessed such care. As part of our sensitivity analyses, we therefore coded missing values for pulmonologist visits to 'no use, which did not have any impact on our main results.

Third, although the overall sample was large, our population of most interest, VPT children with asthma, were a smaller subset of this group. Missing data reduced the sample size further for the multilevel analyses. The sample size was insufficient to reliably assess regional differences in care, which may affect the availability of providers. However, we did adjust for regions in our multivariate analyses.

Finally, we were unable to determine the reasons for health care visits based on the available parental questionnaire data. We were therefore not able to know whether children had visited a pediatrician specifically for respiratory issues, and could not assess the adequacy of respiratory care by pediatricians in the primary care setting.

4.2. Asthma Definition and Prevalence

We observed a higher prevalence of asthma at 5.5 years of age in VPT compared to term-born children – 28.7% versus 12.6%, respectively– indicating a prevalence more than twice as high in the VPT group. Our findings are consistent with previous studies showing that asthma is more prevalent in children born VPT (10,19,36,38,43). However, reported asthma rates in preterm populations vary widely ranging from 9.5% to 44%, often due to differing definitions, most commonly based on wheezing symptoms ever or past 12 months (17,36,39,43). Other European cohorts and studies have reported slightly lower asthma rates depending on gestational age and criteria used. In a longitudinal prospective study, where asthma was defined as wheezing in the past 12 months, asthma rate was reported 23.2% in preterm born children aged 7–8 years (36). In a retrospective population-based study based on the Korean National Health Insurance claims database, asthma was defined as prescription of asthma medication at least twice per year and asthma prevalence in VPT born children was reported as 21.2% at 5 years of age (19) (Appendix Table A1 for more details).

We used a definition based on data from medical visits (presence of diagnosis, and asthma medication use), including parent-reported symptoms (wheezing), which allows us to take into account potential cases of asthma in children who have not consulted any relevant health care professional over the past year. However, this definition has limitations. In our population of VPT children with asthma, 39.9% had wheezing in the past 12 months without having a diagnosis or current medication. While wheeze and asthma frequently go hand-in-hand, wheeze alone is not necessarily sufficient for the diagnosis of asthma (44), and can also be a symptom of acute respiratory infection, for instance. Data on other respiratory symptoms and comorbidities showed that the majority (76%) of the children in our study with wheezing in the past 12 months, but no diagnosis and no medication, had other symptoms or comorbidities consistent with asthma (dry cough at night without having a respiratory infection, wheezing after physical effort, asthma attacks, eczema or allergies) (Appendix Table A6), supporting that wheezing reflects underlying asthma in our population. Furthermore, it is possible that children who have infant asthma and persistent symptoms or associated comorbidities at age 5 may have asthma. We performed sensitivity analyses

with an alternative definition of asthma excluding children with wheezing in the past 12 months only without other symptoms or comorbidities, and including children with infant asthma with concurrent symptoms or comorbidities at age 5. These analyses yielded similar results. (Appendix Table A7)

4.3. Health Care Use in VPT Born Children With Asthma

Among children with asthma, 35.5% of those born VPT and 30.3% of those born at term had seen a respiratory-specific care provider in the past year. As expected, rates were lower among children without asthma; however, somewhat surprisingly, rates did not differ much between VPT and term-born children. We could have expected more respiratory service use in VPT, because of the higher rates of respiratory morbidities in the neonatal period, and the more thorough and frequent health check-ups they receive through follow-up programs, which are supposed to facilitate timely identification and management of health issues. VPT children with asthma had more frequent respiratory care visits and saw slightly more ENT specialists and pediatricians, which could suggest greater severity of respiratory conditions compared to term-born children. Therefore, VPT children might require more intensive respiratory care and follow-up compared to term-born children.

The literature on children with asthma shows that risk factors such as not being followed up by physicians, more frequent use of short-acting beta-agonists (reflecting not proper care), and poor asthma control are linked to increased rates of both ER visits and hospitalizations (45). In our study, ER visit rates were higher among children with asthma, compared with children without asthma in line with this previous research. However, rates were similar between asthmatic VPT and term-born children, as well as among non-asthmatic children in both groups, regardless of gestational age. Furthermore, VPT born children with asthma who had respiratory care use had higher rates of ENT visits, ER use, and hospitalizations. We did not find higher rates of ER visits, and we did not find more hospitalizations as a consequence of not having respiratory care, as hypothesized. Instead, our results probably reflect higher severity of asthma, or potentially the presence of other comorbidities, among children who are using respiratory care, leading to more health service use overall, but we did not have data available on severity. For the group of asthmatic children not using respiratory care-related services, it is possible that their asthma is less severe and sufficiently well managed in primary care to avoid specialist use and emergency care. It would be important to explore ER visits and hospitalizations specifically in children who did not receive respiratory-specific care, did not have any pediatrician visits, or whose asthma

was managed exclusively with short-acting beta-agonists, as this may reflect suboptimal asthma care.

4.4. Factors Associated with Receiving Respiratory-Related Care

Among VPT children with asthma, those with moderate to severe BPD were more likely to receive respiratory-specific care: rates of moderate to severe BPD were significantly higher in the group who received respiratory care (19%) compared to the group that did not (10%). This association remained significant in adjusted analyses, even after controlling for perinatal and sociodemographic factors. This finding is expected, as BPD is one of perinatal factors associated with increased respiratory healthcare use. It is possible that VPT children with BPD have more thorough respiratory-specific follow-up and monitoring throughout childhood compared to VPT children without BPD, as it is a known risk factor for respiratory sequelae. These results may also reflect differences in asthma severity between asthmatic children with and without BPD, which we were not able to assess in our study.

In contrast, no statistically significant associations were observed between sociodemographic factors and respiratory-specific care use. While some SES indicators (e.g., higher maternal education and insurance coverage) showed tendencies in the expected direction (towards less use of respiratory-specific services) in bivariate and unadjusted analyses, these associations were no longer significant after adjustment for perinatal factors. Results remained similar after adjusting for participation in preterm follow-up and region, in addition. One possible explanation is that the sample size in the subgroup of VPT children with asthma was too small to detect such effects. Additionally, since those lost to follow-up were more socially deprived, this may have weakened associations between sociodemographic factors and respiratory care use in our analyses. Although, reassuringly, we found no significant associations with sociodemographic factors, this does not rule out the presence of social inequalities. A larger sample and the use of weights accounting for study attrition related to sociodemographic characteristics may be needed to better detect such differences, alternatively, to confirm that social inequities in respiratory care are not present in this population.

4.5. Implications for Further Research

The high prevalence of asthma among VPT children, and its gradient with gestational age, are in line with previous studies suggesting that prematurity plays a crucial role in long-term respiratory health. The health service use data further demonstrate the clinical and economic burden of asthma in both VPT and term born children. For example, pulmonologist and ER

visits were significantly more frequent in this group, demonstrating a need for both structured respiratory care and acute care in children with asthma.

Future analyses should apply multiple imputation techniques to address missing values in respiratory care variables, improving the robustness of the findings and reducing bias. Furthermore, analyses using inverse probability weighting or other statistical methods to adjust for loss to follow-up are needed to ensure the generalizability of results, and reduce bias, especially given the lower participation of the most vulnerable children. As a next step, new inverse probability weights, which are currently being developed within the research team, will be used to take into account initial non-inclusion, and non-response at the 5-year follow-up, in addition to taking into account the sampling design. Future research should explore whether use of respiratory care services (e.g., pulmonologist consultations, prescription treatments) is associated with downstream health outcomes such as hospitalizations and ER visits, after adjusting for perinatal risk factors and socioeconomic status.

Finally, continuing follow-up of this cohort into later childhood or adolescence could help determine whether asthma symptoms persist, remit, or evolve into other respiratory or allergic conditions, and whether the progression of asthma is related to the use of respiratory health specialists.

5. Conclusion

Children born VPT remain at higher risk for asthma compared to children born at term, with the prevalence increasing with decreasing gestational age; almost one-third of all VPT-born children had asthma at five years of age, compared to 12.6% among children born at term. Among children with asthma 36% of VPT children and 30% of term-born children had seen a respiratory-specific care provider over the past year. These children had greater use of other health services, including hospitalizations and ER visits. Reassuringly, we found no association with sociodemographic factors and receiving respiratory care once adjusting for perinatal factors. The principal factor associated with receiving respiratory-specific care was BPD. Further studies are needed to assess whether receiving respiratory care is associated with avoidable hospitalizations and ER visits.

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Appendix

Table A1. Literature review on asthma definition and prevalence in preterm and term born children

Population Definition	Country	Year of Birth	Data Source	Study design	Asthma Definition	Asthma prevalence
Born very preterm, (N=234)(18)	Western Australia, King Edward Memorial Hospital in Perth	1997 - 2015 (10.7-18.9 years)	Two previously published studies	Retrospective analysis	**Had been diagnosed** *via* a physician **reported by parents** or guardians Objective diagnosis (ERS*)	33% physician-diagnosed asthma 20% met the ERS diagnostic criteria 16.1% met both ERS and had been diagnosed *via* a physician
Born preterm (N=99,139) compared to term (N=500,546)(19)	Korea	2002 - 2018 (0-17 years)	Korean National Health Insurance (NHI) claims database	Retrospective population-based	**Asthma medication** prescriptions at least twice per year	**20.6%** in very preterm 21.2% in preterm at 5 years age
Born very preterm, (N=74) Moderately-late preterm, (N=74)(17)	Spain (two hospitals)	2003 & 2004 (13–14 years)	The study collected medical history and clinical measurements	cross-sectional	“Have you had **wheezing** episodes over **the last 12 months**?”	**21.6**% in very preterm 9.5% in moderately-late preterm
Preterm infants, (N= 116) compared to term infants (N=116)(36)	Spain (Hospital Clínico Universitario)	2006 - 2008 (7–8 years)	The study collected medical history and clinical measurements	Longitudinal prospective	"Have you had any **wheezing in the past 12 months**?"	23.3% in preterm 6.9% in term
Born very preterm (N = 304) and term (N=47)(43)	France (four regions)	1997 (5 and/or 8 years)	EPIPAGE cohort and its follow-up study, EPIPAGEADO	Prospective birth cohort	“Have you had **wheezing or whistling** in the chest **in the past 12 months**?”	**42.8%** preschool wheeze **16.5%** school age asthma

Preterm infants 0–5 years (N = 2,540), and 6–9 years (N = 1,072)(39)	The United States (Boston Medical Center)	2003 - 2013 (5.0 ± 2.8 years)	The study utilized electronic medical record data on physician diagnoses and prescriptions	Prospective birth cohort	**Diagnosis and medication**	Preterm With ever asthma (>=1) 32%, with ever wheezing (>=1) 25%, Medication 44%
Preterm infants compared to term infants (N=44,173)(38)	Finland (Kuopio University Hospital)	1989 - 2008 (0-19 years)	Social Insurance Institution of Finland	Retrospective case-control	reimbursement claims for **asthma medication**	Very and moderately preterm **17.8**% Late preterm 9% Term 5.5%
Term (N=18,329)(46)	France	2011	ELFE cohort	National birth cohort	parental reporting of "**asthma ever**" or "**wheezing in the past 12 months**" at Age 5	20.6% in ELFE
Term (N=10,603)(40)	Sweden, Germany, and the Netherlands	1990 - 1999	Pooled data from five birth cohorts (BAMSE(SE), GINIplus(DE), MAS(DE), PIAMA(NL), and LISA plus(DE))	Prospective birth cohort	**MedALL definition**	8% at 4y in BAMSE 7.1% at 5y in PIAMA 7.4% at 6y in GINIplus 6.4% at 6y in LISA 7.1% at 6y in MAS

*European Respiratory Society (ERS) clinical practice guidelines for the diagnosis of asthma in children aged 5–16 years, asthma definition: have at least two abnormal measurements, abnormal spirometry and a positive BDR, with or without elevated FENO

Table A2. Other asthma symptoms and asthma-related morbidities in the subgroup of children with wheezing in past 12 months only

	Children with wheezing in past 12 months only N = 250[1] n (%[2])
Wheezing after physical effort in past 12 months	48 (19%)
Dry cough at night without having cold or infection, in past 12 months	92 (37%)
Eczema at age 5	60 (24%)
Allergy at age 5	10 (4%)
Asthma attacks ever	111 (44%)
At least one of the above	183 (73%)
None of the above	67 (27%)
None of the above, also excluding 7 children with newborn asthma	60 (24%)[3]

[1]Children with wheezing but no medication and no diagnosis (N=236), or with wheezing but data on medication or diagnosis is missing (N=14). [2]Proportions have not been weighted [3]10% of all 593 children with asthma

Table A3. Other asthma symptoms and concurrent asthma-related morbidities in the subgroup of children with newborn asthma only, not considered to have asthma at age 5

	Children with newborn asthma N = 225 n (%[1])
Wheezing after physical effort in past 12 months	7 (3%)
Dry cough at night without having cold or infection in past 12 months	30 (13%)
Dry cough at night or wheezing after physical effort	34 (15%)
Eczema at age 5	38 (17%)
Allergy at age 5	3 (1%)
At least one of the above	66 (29%)

[1]Proportions have not been weighed.

Table A4. Comparison of children characteristics included and lost to follow-up at the 5-year follow-up in the EPIPAGE-2 study

	Children **lost to follow-up** at 5-year follow up N = 992		Children **included** at 5-year follow up N = 2,262		
	n	% weighted	n	% weighted	P-value
Gestational age, completed weeks					
<28	262	23.0	610	23.7	0.2568
28-29	257	27.1	636	29.4	
30-31	473	49.9	1,016	46.9	

Total	992	100.0	2,262	100.0	
SGA (percentiles)					
<3rd	219	22.7	520	23.5	0.6161
3 - 9th	109	11.1	268	12.0	
≥10th	664	66.2	1,474	64.5	
Total	992	100.0	2,262	100.0	
BPD					
No	695	76.3	1,530	72.9	0.2256
Mild	142	14.2	358	15.6	
Moderate	32	3.0	88	3.7	
Severe	68	6.5	183	7.7	
Total	937	100	2,159	100	
Severe neonatal morbidity[1]					
No	650	70.2	1,475	69.4	0.4913
Yes	302	29.8	702	30.6	
Total	952	100.0	2,177	100.0	
Child sex					
Male	520	52.4	1,164	51.5	0.8206
Female	472	47.6	1,098	48.5	
Total	992	100.0	2,262	100.0	
Multiple birth					
Singleton or one surviving multiple	694	69.9	1,506	66.6	0.1437
Multiples (twins, triplets or quadruplets)	298	30.1	756	33.4	
Total	992	100.0	2,262	100.0	
Maternal educational level at birth[2]					
Low	555	67.2	1,051	48	< 0.001
Intermediate	136	16.3	518	23.7	
High	134	16.5	620	28.3	
Total	825	100.0	2,189	100.0	
Maternal age at delivery					
≤24 years	269	27.0	339	15.0	< 0.001
25-34 years	508	51.3	1,415	62.5	
≥35 years	215	21.7	508	22.5	
Total	992	100.0	2,262	100.0	
Maternal country of birth					
Outside France	307	31.7	455	20.1	< 0.001
France	657	68.3	1,799	79.9	
Total	964	100.0	2,254	100.0	
Parity					
Nulliparous	476	48.6	1,270	56.6	< 0.001
Multiparous	503	51.4	969	43.4	
Total	979	100.0	2,239	100.0	

SGA: small for gestational age; BPD: bronchopulmonary dysplasia; VPT: very preterm. [1] Intraventricular hemorrhage grades III-IV, cystic periventricular leukomalacia, retinopathy of prematurity stages III-V or necrotizing enterocolitis requiring surgery. [2] Low (Upper secondary (lycée) or lower, including short professional training), Intermediate (Post-secondary, non tertiary (pre-university courses) or short cycle tertiary (vocational)), High (Bachelor degree or equivalent, or higher)

Table A5. Respiratory health in very preterm and term-born children

	Very preterm N = 2,262 N (weighted %)	**Term** N = 585 N (weighted %)
Asthma diagnosis after age 3 years	200 (10.0)	31 (5.6)
Asthma medication (currently)	194 (10.2)	19 (4.6)
Wheezing past 12 months	448 (22.7)	54 (10.1)
Asthmatic bronchiolitis*	9	2
Asthma (any of the above)	**531 (28.7)**	**62 (12.6)**
Asthma diagnosis ever (including infant asthma)	584 (29.8)	74 (14.2)
Wheezing after physical effort in past 12 months	184 (9.4)	10 (2.6)
Dry cough at night without having cold or infection, In past 12 months	358 (18.6)	63 (14.1)
Asthma attacks ever	545 (29.6)	68 (13.2)

*Freetext answers only

Table A6. Proportions of wheezing in past 12 months, asthma diagnosis after age 3 and current asthma medication among very preterm and term-born children with asthma

	Very preterm N = 531 N (%*)	**Term** N = 62 N (%*)
Wheezing only (no medication, no diagnosis)	212 (39.9)	24 (38.7)
Medication only (no wheezing, no diagnosis)	28 (5.3)	2 (3.2)
Diagnosis only (no wheezing, no medication)	33 (6.2)	4 (6.5)
Wheezing + diagnosis (no medication)	67 (12.6)	12 (19.4)
Wheezing + medication (no diagnosis)	77 (14.5)	4 (6.5)
Diagnosis + medication (no wheezing)	17 (3.2)	2 (3.2)
Wheezing + diagnosis + medication	70 (13.2)	11 (17.7)
Missing 1 or 2 composition	27 (5.1)	3 (4.8)
Total number* (wheezing or diagnosis or medication)	531 (100.0)	62 (100.0)

*Proportions have not been weighted

Table A7. Assessing the association between asthma in VPT born children and respiratory health care use at 5 years of age: A sensitivity analysis

	Model 5 aRR [95% CI]
Sociodemographic Factors	
Mother's Country of Origin (ref: born in France)	
Born outside France	1.18 [0.82-1.69]
Mother's Age at Birth (ref: 25-34 years)	
≤24 years	0.84 [0.53-1.35]
≥35 years	1.33 [0.96-1.84]
Mother's Education[1] (ref: intermediate)	
Low	0.94 [0.65-1.37]
High	0.94 [0.65-1.37]
Parity (ref: nulliparous)	
Multiparous	1.01 [0.75-1.35]
Health insurance status (ref: complete)	
Without or incomplete insurance	0.85 [0.53-1.36]
Parental occupational status (ref: not both parents full-time workers)	
Two full-time working parents	0.95 [0.69-1.31]
Perinatal Factors	
Child's sex (ref: male)	
Being female	0.97 [0.74-1.27]
Gestational age	0.97 [0.90-1.06]
SGA (ref: percentiles ≥10th)	
Percentiles <3rd	1.15 [0.83-1.61]
Percentiles 3 − 9th	0.94 [0.58-1.51]
Multiple birth (ref: singleton or one surviving multiple)	
Multiples	1.25 [0.91-1.71]
BPD (ref: no or mild)	
Moderate or severe	1.71 [1.17-2.49]
Presence of severe neonatal morbidity	0.95 [0.69-1.31]
Follow-up and Regions	
Any preterm follow-up	1.26 [0.90-1.77]
Regions	Not shown[2]

[1] Low (Upper secondary (lycée) or lower, including short professional training), Intermediate (Post-secondary, non tertiary (pre-university courses) or short cycle tertiary (vocational)), High (Bachelor degree or equivalent, or higher)

[2] 25 Region fixed effects were included in the model but individual coefficients are not presented.

Résumé

Déterminants du recours aux services de santé à l'âge de cinq ans chez les enfants nés grands prématurés et atteints d'asthme dans la cohorte française EPIPAGE-2

Contexte et objectifs

Les enfants nés grands prématurés (<32 semaines de gestation) présentent un risque accru de complications respiratoires à long terme, notamment d'asthme, par rapport aux enfants nés à terme. Bien que le recours aux services de santé soit élevé chez les enfants grands prématurés, des études suggèrent qu'il peut exister de besoins de soins non satisfaits dans cette population. Nos objectifs étaient de décrire le recours aux services de santé chez les enfants grands prématurés et à terme, avec et sans asthme, et d'identifier les déterminants du recours aux services liés à la santé respiratoire chez les enfants grands prématurés asthmatiques, en nous concentrant sur les facteurs sociodémographiques familiaux, afin d'évaluer une éventuelle prise en charge sous-optimale.

Méthodes

Les données utilisées proviennent de la cohorte longitudinale nationale EPIPAGE-2 - l'étude épidémiologique sur les petits âges gestationnels, ainsi que d'un échantillon témoin d'enfants nés à terme issus de la cohorte ELFE. Les données ont été recueillies à partir des dossiers médicaux à la naissance et de questionnaires parentaux et examens cliniques à l'âge de 5,5 ans. L'analyse a inclus des statistiques descriptives, des analyses univariées du recours aux services de santé selon l'âge gestationnel et le statut asthmatique, et des modèles multivariés pour étudier les associations entre les facteurs sociodémographiques et le recours aux services de santé respiratoires chez les enfants asthmatiques grands prématurés , en ajustant sur les facteurs périnataux.

Résultats

La prévalence de l'asthme à 5,5 ans était plus de deux fois plus élevée chez les enfants grands prématurés que chez ceux nés à terme (28,7% vs 12,6%). Le recours aux services de santé respiratoire était plus élevé chez les enfants asthmatiques dans l'ensemble, avec des taux similaires entre les groupes d'enfants nés grands prématurés (36%) et à terme (30%). Parmi les enfants asthmatiques grands prématurés, ceux ayant bénéficié de services liés à la santé respiratoire présentaient des taux plus élevés de dysplasie bronchopulmonaire (DBP) (19% vs 10%) et avaient un recours accru à d'autres services de santé, y compris les hospitalisations et les passages aux urgences. Les analyses ajustées

ont montré que la DBP était le seul facteur associé à l'utilisation de services de santé respiratoire (aRR = 1,71).

Conclusions

La DBP était le principal facteur lié au recours à des services de santé respiratoire chez les enfants asthmatiques nés grands prématurés. Aucune association n'a été observée avec les facteurs sociodémographiques après ajustement. Des recherches supplémentaires sont nécessaires pour déterminer si les services de santé respiratoire sont associés à une réduction des hospitalisations et passages aux urgences évitables.

Mots-clés : Naissances grands prématurées, Asthme, Recours aux services de santé, EPIPAGE-2, France