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The Development and Running of an Italian Birth Cohort for an In-Depth Evaluation of Child Health Status and Health Care Utilization in the First Years of Life

Thesis

Pansieri Claudia

Personal identifier: F3156262

Programme of study: Master of Philosophy (MPhil)

Discipline: Life and biomolecular science

Thesis title:

The development and running of an Italian birth cohort for an in-depth evaluation of child health status and health care utilization in the first years of life.

October 2020

ABSTRACT

Background: The first 1,000 days of life are a unique period for the brain architecture. The development of perceptual, sensorimotor, social and language systems depend crucially on environmental stimulation. Multiple factors influence the acquisition of competencies, including health, nutrition, security and safety, responsive caregiving, and early learning. All are necessary for nurturing care and evolve through bi-directional interactions.

Following children from born since adulthood researchers can identify individual trajectories through the different stages of growth that develop in function of the social and the historical context.

Aim: The thesis aims to describe the development and running of a national birth cohort aiming to understand how the influences of environmental and nurture factors, that include also the social context, can affect child health.

Methods: We performed an extensive review aiming for the identification of all the European Birth Cohorts focusing on those that started data collection at birth.

All the information gathered from this review has been essential to defining and running NASCITA (NAscere e CREscere in ITAlia) a national birth cohort officially started on the 1st of April 2019. In this thesis, I will present the protocol, the management and the organization of this birth cohort and some preliminary results.

Results:

The enrollment of newborns began on April 1st, 2019. After six months from the start, the number of participating pediatricians was 160 and the number of children enrolled 2264. Most of the mothers (84%) were born in Italy and had a healthy pregnancy. The anthropometric measures of the newborns were showing an

average of 3792 grams at birth and 59% of them were also breastfed at 6 months.

Discussion: The only way to understand the epidemiology of diseases and to address related needs is through large epidemiological studies. In NASCITA we aim to perform an in-depth study of child development and health and the impact on them of nurturing care.

Acknowledgment

I would first of all thank Dr Maurizio Bonati for his guidance and for gave me the possibility to achieve this important personal objective. I would also like to thank Prof Imti Choonara for his trust in me and the help over these years.

A special thanks to Chiara Pandolfini for her daily assistance and for the knowledge she passed on to me. Thanks to Antonio Clavenna for his professionalism and expertise.

Thanks to Daniela Miglio and Massimo Cartabia for the valuable work done over these years and in these last weeks. Thanks to Maria Grazia Calati and Michele Zanetti for the daily assistance in the NASCITA project. Thanks also to all the other components of the staff that help me in these years.

Last but not least I would also like to thank my family. My children, Beatrice and Edoardo, that are the essence of my life and that gave me every day a reason to do, and to be, better. Thanks to my husband that supports me all over the PhD period and in the professional decisions of my life. Thanks to my mother and father for the help over these years. Without all of them, I could never have reached this important turning point in my life and in my career.

LIST OF TABLES AND FIGURES

LIST OF ABBREVIATIONS

ACP: Associazione Culturale Pediatri

CRF: Case Report Form;

DOHaD: Developmental Origins of Health and Disease eCRF:

Electronic Case Report Form

FP: Family pediatrician

GP: general practitioner

GBD: Global Burden of Diseases

ICD: international classifications of diseases

LHU: Local Health Unit

MMR: measles-mumps-rubella

NASCITA: NAscere e creSCere in ITAlia

NCD: non-communicable diseases

NHS: National Health System

NIP: national immunisation plan

OR: odds ratio

 RCT: Randomized Controlled Trial

RR: The relative risk

WHO: World Health Organization

I. INTRODUCTION

A. The first thousand days of life and the child's health.

The time between conception and second birthday, well known as the first 1,000 days of life, is a unique period of opportunity and vulnerability. Studies conducted over the past twenty years have shown how the architecture of the brain depends on the mutual influences of genetics, environment, and experiences.

Brains are built over time and the basic architecture is constructed through an ongoing process that begins before birth and continues into adulthood. Early experiences affect the quality of that architecture by establishing either a robust or a fragile foundation for the learning, health and behaviour that follow. According to the well-evidenced Developmental Origins of Health and Disease concept (originally the 'Barker hypothesis'), a disadvantage in fetal life and early childhood influences health in adulthood [Barker 2004; Barker et al. 1989].

In the first few years of life, 700 new neural connections (called synapses) are formed every second [Bourgeois 1997; Singer 1995]. After this period of rapid proliferation, these connections are reduced through a process called pruning, so that brain circuits become more efficient. Sensory pathways, like those for basic vision and hearing, are the first to develop followed by early language skills and later by higher cognitive functions (Figure 1 and Figure 2) [Nelson et al 2000; National Scientific Council on the Developing Child, 2007].

Figure 1.   Synapse formation in the developing brain
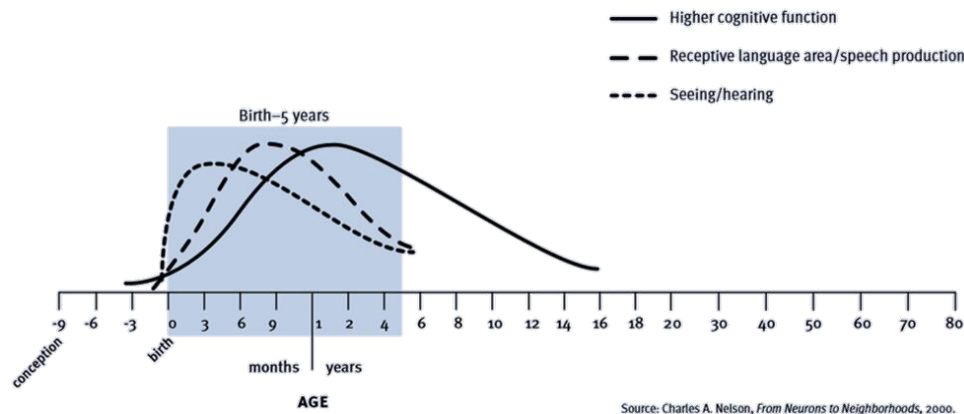
Source: Charles A. Nelson, *From Neurons to Neighborhoods*, 2000.

Early environments and experiences have an exceptionally strong influence on brain architecture. Developmental changes may occur in different "critical periods" of the prenatal (germinal, embryonic and fetal) and of the post-natal development. Complex epigenetic mechanisms are activated, regulating and programming the expression of our gene pool in response to several influences, mainly: maternal factors (e.g. physical and psychological health, lifestyle) and environmental factors [Barker et al. 1986; Jaakkola et al. 2004].

The period of exceptional sensitivity to the effects of environment and experience is called a "*sensitive period*" for that circuit. This sensitive period is a constrained window of time when the environment most impacts brain function via experience-expectant mechanisms with a residual plasticity after the period ends such that experiences may continue to affect brain function [Nelson et al. 2020]. Some examples of behavioral capacities that are affected by sensitive periods of underlying circuitry include vision, hearing, and language (Figure 2) [National Scientific Council on the Developing Child, 2007].

Figure 2.   Sensitive periods in early brain development
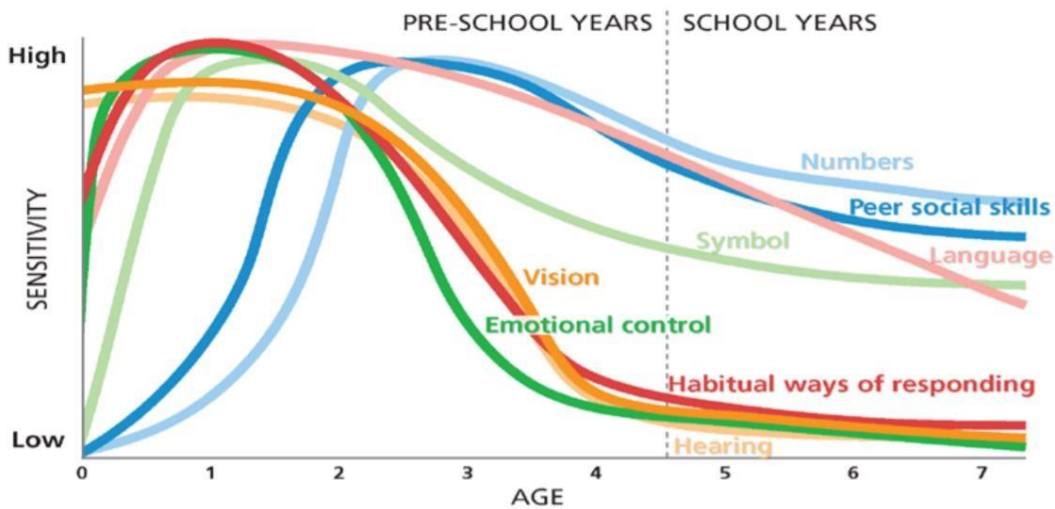
Graph developed by **Council for Early Child Development** (ref: Nash, 1997; *Early Years Study*, 1999; Shonkoff, 2000.)

A.1 Nurturing care and Social Determinant that support children's developmental health

The nervous system is especially sensitive to certain stimuli and the development of certain perceptual, sensorimotor, social and language systems depends crucially on environmental stimulation [Fox et al. 2010] .

Children's early development is characterised by sensitive periods for development related to maturation and genetic–environmental interactions, the effect of interventions varies based on sensitive periods related to specific experiences or environmental conditions. [Black et al. 2017; Wachs et al 2014]. In this context resaerchers demonstrate how the timing of nutrient provision or deficiency determines how the structure develops and ultimately how it functions. A given nutrient deficit at one age may result in quite different developmental effects than the same nutrient deficit at another age. These findings imply that critical/sensitive

windows exist for many of these systems and that these windows are tightly linked to periods of rapid regional brain growth and differentiation. [Wachs et al 2014]

Multiple factors interact with each other and can be mutually reinforcing through the process of development and influence the acquisition of competencies. Nurturing care is characterised by good health, adequate nutrition, safety and security, responsive caregiving and opportunities for early learning and occur through bidirectional interactions, initiated by both children and caregivers, and sustained by their environments. [Black et al 2017] It is also linked to a home environment that is sensitive to children's health and nutritional needs, responsive, emotionally supportive, and developmentally stimulating and appropriate, with opportunities for play and exploration and protection from adversities. Positive associations between nurturing care and children's health, growth, and development have been demonstrated worldwide, supported by neuroscientific evidence that nurturing care during early childhood attenuates the detrimental effects of low socioeconomic status on brain development [Black et al. 2017; Britto et al. 2017].

Among the environmental stimuli that influences children healthy developments and neurodevelopment there are several factors: socioeconomic, interpersonal and/or family, and nutritional [Bick et al. 2016].

Researchers show that the family (defined as any group of people who eat and participate in other daily, home-based activities together) quality of care, activities and socialization, play an important role since is the primary environmental influence on children's development [Cornish et al. 2005]. The most salient features of the family are its social and economic resources. Social resources include

parenting skills and education, cultural practices and approaches, intra-familial relations, and the health status of family members [Houweling et al. 2005].

Stable, responsive, nurturing relationships and rich learning experiences in the earliest years provide lifelong benefits for learning, behavior and both physical and mental health. In contrast, research on the biology of stress in early childhood shows how chronic stress caused by major adversity, such as extreme poverty can weaken developing brain architecture and permanently set the body's stress response system on high alert, thereby increasing the risk for a range of chronic diseases [National Scientific Council on the Developing Child, 2005; Darling et al. 2020].

Lancet series in 2013 added support for a focus on the first 1000 days as previously called in the 2008 Maternal and Child Undernutrition Lancet [Bhutta et al. 2008] The subsequent 2013 Lancet Series on Maternal and Child Nutrition further demonstrated early undernutrition as a serious hidden cause of child mortality and increased risk of adult chronic diseases. [Bhutta et al. 2013] On the contrary, evidence has continued to mount that in high-income countries, nutrition in the first 1000 days (including maternal nutrition, obesity during pregnancy, breastfeeding and early diet) has a powerful impact on later risk of obesity (Hu et al. 2020)

Breastfeeding is important for infants as it helps protect against infections [Renfrew et al. 2012]. It is also thought that breastfeeding contributes to cognitive development, reduced risk of developing obesity and Type 2 diabetes [Victora et al. 2016]. For these reasons breastfeeding is recommended exclusively for up to 6 months.

It is important that weight in early childhood is recorded, monitored and maintained at a healthy level since overweight children are likely to present other health and wellbeing problems and are likely to become overweight adults. Since children aged <4 years have frequent contact with their general practitioner (GP) or family pediatrician (FP), primary care is perfectly positioned to collect this early childhood weight data and deliver effective early intervention. Integration of electronic growth charts and centile calculators into GP health systems would support this commitment and benefit both health professionals and the children they care for.

A.2 Non-communicable diseases

Several studies have been conducted to understand which influential factors occurring during the early stage of development affect the risk of going encountering non-communicable diseases, often much later in life. The "developmental origins of health and disease" (DOHaD) is a concept that has emerged over the past 50 years, linking the state of health and risk from the disease in later childhood and adult life with the environmental conditions of the early life. The first 1,000 days of life, thus, represents the ideal target of any primary prevention program for non-communicable disease. Policies, plans and services for the prevention and control of noncommunicable diseases need to take account of health and social needs at all stages of the life-course, starting with maternal health, including preconception, antenatal and postnatal care, maternal nutrition and reducing environmental exposures to risk factors, and continuing through proper infant feeding practices, including promotion of breastfeeding and health promotion for children, adolescents and youth followed by promotion of a healthy

working life, healthy ageing and care for people with noncommunicable diseases in later life.

(http://www.salute.gov.it/imgs/C_17_pubblicazioni_2087_ulterioriallegati_ulterior eallegato_0_alleg.pdf)

Non-communicable diseases (NCD), represent today the most important health problem in both advanced and developing countries. [GBD 2017] This epidemic situation, probably linked to the profound lifestyle changes, has serious implications on the quality of life of the population but also an equally important socioeconomic impact, that is often underestimated.

Health promotion and prevention of NCDs in the early ages of life must necessarily be based on a wider intervention that has the aim of promoting a healthy lifestyle throughout the reproductive age, therefore right from school. Generally, on the adoption of healthy lifestyles and essentially on a more balanced diet, on the promotion of physical activity and the promotion of an ecosystem free of pollutants. Improving family health requires addressing the social determinants of health and inequities (ex: infant mortality reduction comes from improved women education).

B.   The Italian health system framework

Italian healthcare is provided free or at a nominal charge through a network of 20 Regions and 101 Local Health Units (LHUs). Every Italian resident is registered with a family (pediatric or general) practitioner. Children are assigned to a FP until they are 6 years old; afterward, the parents can choose to register a child with a GP.

Pharmaceutical prescriptions that are issued by the FP or by the GP, In Italy, are collected in a national formulary that is available for researchers and in which

drugs are categorised into three classes: class A includes essential drugs that patients do not have to pay for, class C contains drugs not covered by the National Health System (NHS), and class H contains drugs administered only to inpatients that are fully reimbursed. Italian outpatients receive class A prescriptions from FPs, GPs, or other specialists and then get medications free of charge from retail pharmacies. Outpatients receiving prescriptions in community pharmacies and get the medicines free of charge through

GP prescriptions. Each local pharmacy provides these prescriptions to the Regional Health Authority to get reimbursed.

B.1   Databases for healthcare research

While administrative data are not designed for research, have limitations, are often difficult to access, and the linkage required between certain databases may be unfeasible, yet they retain a great research potential. The Administrative Data Taskforce identified the following items of value associated with the use of administrative [Connelly et al. 2016].

• The data already exists. There are no additional data collection costs associated with research use;

• The data are typically large datasets, permitting more detailed research to be undertaken than would otherwise be the case;

• The data records a process, which can be documented and understood;

• The linkage between data relating to different periods can create longitudinal resources;

- Linkage to other data sources (e.g. surveys) can enhance these resources. Additionally, health databases can provide data on diagnosed diseases through hospital admission and surgical procedures codes. The information on prescribed drugs, with appropriate techniques and integrations, can be used to estimate the prevalence of certain diseases, also in the outpatients.

The Italian healthcare system can exploit with small differences between regions, three different databases.

B.2   Reimbursed prescription database

The database contains reimbursable prescriptions (class A) routinely acquired for administrative and reimbursement reasons. The database stores all community (i.e. outside hospital) prescriptions issued to individuals living in a specific region. Within this system, a unique patient code prevents double counting of individuals who have been prescribed drugs by more than one physician. Each prescription is associated with a unique code identifying the medicine prescribed (including dosage and formulation). Other information available is: the prescription date, the number of boxes prescribed, and the prescriber and his/her characteristics.

B.3   Hospital discharge form database

Besides prescription data, this database contains the hospital admissions of patients classified according to the ICD-9 system (hiips://www.cdc.gov/nchs /icd/index.htm) [Centers for Disease Control and Prevention, 2020]. The relevant information available is concerning the patients' vital statistics (age, sex, and address of residence); characteristics of the hospital stay (institute, ward and unit, type of admission, length of stay, priority) and clinical characteristics (primary diagnosis,

other secondary diagnoses, diagnostic and therapeutic procedures, date of admission, discharge, or in-hospital death). Drugs administered during the hospital stay are not included in this database.

B.4 Specialist visits database

Information about the outpatient specialist visits, in particular: prescriptions for diagnostic tests, specialist visits, and rehabilitation performed in outpatient ambulatories are recorded for each resident patient.

Since these three databases share the same unique patient identifier - through the Patient Record Database (which contains each patient's vital statistics) - prescriptions, hospital admissions and specialist visits can be linked

straightforwardly.

The availability of these data depends on single projects. For each project, a specific authorisation should be requested at competent authorities.

For example, in our laboratory (Laboratory for Mother and Child Health) a pharmacoepidemiologic project called EPIFARM was running since 2003 in agreement with the Regional Health Ministry of the Lombardy Region [EPIFARM, 2003]. The quality and accuracy of data are routinely checked and validated each year ensuring high standards. The anonymity of each patient is granted by a third party society, that is not involved in any way in the analyses of the data, and that provide the laboratory with the data already encrypted within the unique patient identifier.

B.5 CEDAP: Certificate of Delivery Assistance

Implemented by the Ministry of Health into law in 2001, the Certificate of Delivery Assistance, or CEDAP, is the national source for vital birth information. Information collected and added to the birth certificate includes basic data relating to births, stillbirths, and newborns with congenital malformations. The questionnaire included at the end of the document is divided into sections: the general personal data and socio-demographic characteristics of the parents; conditions of the pregnancy; circumstances of the delivery and the health of the newborn; the causes of stillbirth where applicable; and the presence of congenital malformations if present. There are also tables of the most common malformations and causes of stillbirths [Regione Lombardia, 2019].

C.   Strength and limitations of these databases and available data

The main advantage of monitoring the prescriptions dispensed by all the physicians to an entire population in a specific region is that data are available for a long period and easily available for longitudinal research.

Moreover, there is no bias for the exclusion of children with different familiar socioeconomic status, or concerning the prescription of more costly drugs, like is the case in other countries.

The main limits related to the use of these health care databases are that over-the-counter drugs, and drugs not reimbursed by the national health service, are not included. Other limitations are that the therapeutic indication is lacking and that it is not possible to know if the patient took the drug. Moreover, information concerning the socio-economic status or the educational level of the individuals is not available. To overcome this issue usually in some studies, average annual income at the area level was used as a proxy to the socio-economic status of individuals and families. Another way to overcome these limitations could be the design of a longitudinal prospective study in which all this information is collected.

D.   Organization of pediatric's care and health visits

The Italian Health System provides, thanks to the collaboration with the family pediatricians, for all children and adolescents a routine health check system called "Bilanci di salute" or "filter visits" with contents agreed and defined at the regional level occurring at pre-established times from the first month of life to 14 years old. They are guaranteed in the context of primary pediatric care and are a valid dynamic and prospective tool that accompanies the child's growth. Since the "filter visits" are based on specific protocols, are important in the early evaluation of some disorders (ex: neuropsychiatric disorders).. Through these visits, pediatricians have a unique opportunity to identify and address important social, developmental, behavioral, and health issues that could have significant and long-lasting effects on children's lives as adults, early and intensive visits are important for early childhood development and unfavorable outcomes prevention. [Shah et al. 2016]

According to the WHO definition: "Health is not only a state characterized by the absence of disease but by the achievement of a state of physical, mental and social well-being." In the context of primary pediatric care, In Italy, the Presidential Decree number 613/96 for the first time explicitly recognized the importance of prevention and health education thought the well-child visits guaranteed .

In this context, the FP establishes a continuous and privileged contact with the family. In this particular setting disease prevention, health education and correct lifestyles, health improvement and patient empowerment activities can be

23.

developed and implemented, which represent an added value to normal care activities for acute and chronic pathology.

In recent years, social and cultural changes and rapid scientific-technological progress have changed the health needs of the pediatric population, in particular, we can observe: development of diseases resulting from poverty and foodstuffs (e.g. overweight and obesity); the increase of diseases linked to environmental factors etc…

The main objectives of the "filter visits" are:

• assess the child's health status to identify and prevent the appearance of secondary complications;

• provide indications of health education, anticipating as far as possible the problems related to the natural history of the pathology responsible for disability;

• implement specific prevention interventions;

• understand the health needs and discomforts of the family, interacting closely with basic medicine and psycho-social services.

D.1   Scientific research in the pediatric setting

Since 2001 in Italy, as in the rest of Europe, was adopted the European Clinical Trials Directive (2001/20/CE) that simplified and harmonized the controlled clinical assessment in general and pediatric practice. Under the clinical governance, the FP's daily work became an opportunity for the development and running of a scientific research.

In particular the well-child care visits, also called "bilanci di salute" represents a unique opportunity for the collection of epidemiological data. In this context, they

are essential for identifying specific health problems and to identify any difference in the Italian setting, as well as useful for developing research in the field of primary care.

A useful observation arises from previous experiences occurring in my laboratory, "Laboratorio per la salute materno infantile", in collaboration with the family pediatricians, shows how, in the first year of the child's life, there is a high use of health resources (access to the emergency room, number of specialist visits) and a high prescription of drugs (antibiotics and not ..) with important differences between the north, center and southern Italy. (Bianchi et al 2013; Putignano et al 2019; Clavenna et al 2014; Piovani et al 2013)

E.   The evidence-based medicine

In medical science, routinely collected data is a valuable resource for use in epidemiological studies [Vandenbroucke 2004] and is an important tool for evidence-based medicine. Evidence-based medicine has been described as 'the conscientious, explicit and judicious use of current best evidence in making decisions about the care of individual patients [Sackett et al. 1996]. The first and earliest principle of evidence-based medicine indicated that not all evidence is the same but a hierarchy of evidence exists. Various versions of the evidence pyramid have been described, but all of them focused on showing weaker study designs in the bottom (basic science and case series), followed by case–control and cohort studies in the middle, then randomised controlled trials (RCTs), and at the very top, systematic reviews and meta-analysis (Figure 3).

Figure 3.   The pyramid of evidence
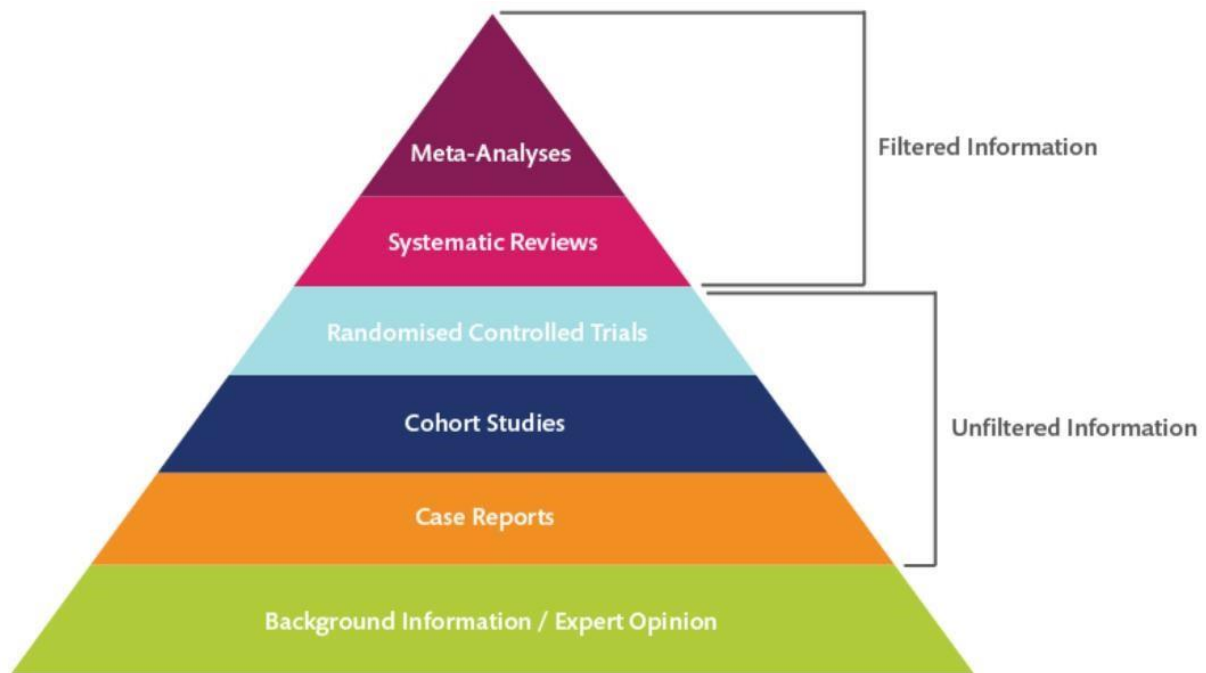
The randomised controlled trial is the principal research design in the evaluation of medical interventions. However, aetiological hypotheses, for example, those relating common exposures to the occurrence of disease—cannot generally be tested in randomised experiments. Analyses of observational data also have a role in medical effectiveness research [Egger et al. 1998].

E.1   Cohort studies

The most efficacious study design to detect possible correlation within several factors are longitudinal studies: Cohorts studies. In longitudinal studies, the word *cohort* describes a group of people who share a common experience or condition. *Cohort studies* are studies in which subsets of a defined population are identified. These groups may, or may not, be exposed to factors hypothesized to influence the probability of the occurrence of a particular disease or other outcomes. Cohorts are

defined populations that, as a whole, are followed in an attempt to determine distinguishing subgroup characteristics.

Prospective birth cohort studies are amongst the strongest observational study designs. *Birth cohorts* are observational longitudinal studies that follow participants (parents and their children) from the intrauterine period, birth or shortly after, through childhood into adolescence and sometimes adulthood. The main advantages are that risk factors and health outcomes of subjects may be monitored continuously, or they may be assessed repeatedly at specified time intervals and the data permits researchers to calculate relative risks of individual or cumulative factors and gain insight into the aetiology of disease processes. Therefore, as observational studies, they do not involve any experiments or any other interventions by researchers. The primary purpose of these studies is to identify and examine the relationship between suspected or known risk factors or exposures with the prevalence of disease as an outcome. This permits hypotheses about these risk factors, such as cigarette smoke exposure, to be tested by comparing the prevalence or incidence of disease in various groups that are identified as being at different levels of risk for disease.

However, there are limitations of this study design. To obtain sufficient data, it is necessary to study a large number of individuals over an extended period. The prolonged period of follow-up involved in this study design accounts for the larger attrition rates associated with this study design. The loss to follow-up may result in incomplete data sets this limiting the statistical power of the study. This is why a large number of participants is required by researchers wishing to conduct research

using this study design. It also usually requires considerable logistical effort to coordinate recruitment and subsequent follow up of participants.

Despite the efforts required to conduct these studies, to date, there have been several birth cohort studies that have demonstrated results that justify the effort required. Historical birth cohorts launched after the Second World War analysed the lives of thousands of babies from birth through life in staggering detail, from records of birth weights and ages of weaning to reading skills and employment in later life. Results from these studies firstly birth to analyse the educational and socioeconomic effects on child growth currently looking for the effect of aging. Or the Framingham Heart Study that began in 1948 and is now on its fourth generation of participants thanks to which much of the now-common knowledge concerning heart diseases, such as the effects of diet, exercise, and common medications such as aspirin, is based on this longitudinal study [Mahmood et al. 2013]. A detailed description of current and historical will be presented in the next chapter. Following children from birth into adulthood, and in some cases throughout all lives, researchers can identify individual trajectories towards the different stages of growth that change in function of social and the historical context. [Halfon et al. 2014]

E.1.1 Statistical analysis for cohort studies

Health indicators are commonly used to estimate population health. In a longitudinal study, subjects are followed over time with continuous or repeated monitoring of risk factors or health outcomes, or both. Most examine associations between exposure to known or suspected causes of disease and subsequent morbidity or mortality. The common definitions given assume that rates in an "exposed" population are being compared with those in "unexposed" people. The exposure might be to "risk factors" suspected of causing the disease (for example, being bottle-fed or owning a cat) or of protecting against it (for example, immunisation). (https://www.bmj.com/about-bmj/resources-readers/publications/epidemiology-uninitiated/3-comparing-disease-rates)

The relative risk (RR) that is usually calculated in this kind of study, defined the ratio of the disease rate in exposed persons to that in unexposed people and is the measure of association most often used. Closely related to relative risk is the odds ratio (OR), defined as the odds of disease in exposed persons divided by the odds of disease in unexposed persons. Most complex statistical analysis, like regression analysis, a set of statistical processes for estimating the relationships between a dependent variable (often called the 'outcome variable') and one or more independent variables (often called 'predictors', 'covariates', or 'features'), can be applied in function of the specific study protocol and the specific associations that should be investigated.

The statistical testing of longitudinal data necessitates the consideration of numerous factors.

Central amongst these are:

(I) the linked nature of the data for an individual, despite separation in time;

(II) the co-existence of fixed and dynamic variables;

(III) potential for differences in time intervals between data instances;

(IV) the likely presence of missing data.

Whatever the study type, study planning and procedure, must always avoid the various forms of bias, such as systematic errors (for example, selection of study population) and confounding factors [Vandenbroucke 2004].

It is defined as bias any systemic error (design, data collection, analysis or reporting of a study) in epidemiological study that results in incorrect estimation of the association between exposure and outcome. Investigators can introduce bias into a study as a result of the procedures for identifying and enrolling subjects or from the procedures for collecting or analysing information.

Type of bias:

- *Selection bias*: Selection bias can result when the selection of subjects into a study or their likelihood of being retained in the study, leads to a result that is different from what you would have gotten if you had enrolled the entire target population.

  This form of selection bias could be more common in a retrospective cohort study. Factors affecting the enrolment of subjects into a prospective cohort study would not be expected to introduce selection bias. The reason is that, in prospective cohort studies, subjects are enrolled before they have experienced the outcome of

  interest.

- *Information bias*: The method of gathering information is inappropriate and yields systemic errors in the measurement of exposure or outcome. For example, the recall bias. When people interviewed with a particular outcome or exposure may remember events more clearly than others. Or the reporting bias, when participants can collaborate with researchers and give answers in the directions they perceive are of interest. Or loss to follow up. Those that are lost through follow-up or who withdrawn from the study may be different from those who are followed for the entire study.

- *Confounding*: Confounding is one type of systematic error that can occur in epidemiologic studies. It is the distortion of the association between an exposure and health outcome by an extraneous, third variable called a confounder. It is a very important issue because if present, it can cause an over- or underestimate of the observed association between exposure and health outcome. The distortion introduced by a confounding factor can be large, and it can even change the apparent direction of an effect.

Confounding should be of concern when:

- Evaluating an exposure-health outcome association.

- Quantifying the degree of association between an exposure and health outcome.

- Multiple causal pathways may lead to the health outcome.

The confounding is the only type of bias that could be controlled at different stages: during the study design or later in the analysis stage. To avoid the confounding bias during the study design is possible to apply:

- Restriction: subjects are restricted to only those possessing a narrow range of characteristics, to equalize important extraneous factors.

- Matching: for each patient in one group there are one or more patients in the comparison group with the same characteristics, except for the factor of interest. (Es: matching done for age, sex, race, etc…)

- Randomization: subjects of study are randomly selected to even out unknown confounders.

The possible confounding could be avoided also later in the analysis stage applying:

- Stratification: The process of separating a sample into several sub-sample according to specific criteria such as age group, socioeconomic status, etc.

- Multivariate analysis: the statistical analysis of data collected on more than one variable (es: people age, weight, body fats…) [Smith & Phillips 1992; Hemkens et al. 2018].

E.2 Data collection methods

Longitudinal research can utilize either data collected by a researcher from first-hand sources (primary data), or data gathered from studies that have been run by other people or for other research (secondary data).

For both the options: the most common data collection methods can include:

- responses to survey questions;

- direct clinical measurements such as height, weight that are carried out by trained personnel as part of a face-to-face interview;

- clinical samples, for example, blood, hair or saliva;

- linking study results to administrative data from government records. (See the section on the Italian health system framework).

Data should be collected using a structured form. First of all, it is important to ensure that all the Case Study Report (CRF) are optimally designed, and protocol-driven. Besides the methods of data collection preferred, all the longitudinal studies need a structured and safe informatic data collection [Zanetti et al. 2019]. To structure data longitudinally, information on visits and contacts must be organized that, in turn, can be linked over time to individuals, a "patient log-list". In European Nordic countries where there is a comprehensive registration of data for a high proportion or all of the population, government-administered patient registries may include hospital encounters, diagnoses and procedures, such as the Norwegian Patient Registry, the

Danish National Patient Registry or the Swedish National Patient Register.

F. Strength and limitations of longitudinal cohort

Strength of longitudinal cohort include:

- The ability to identify and relate events to particular exposures, and to further define these exposures with regards to presence, timing and chronicity;

- Establishing sequence of events.

- Following change over time in particular individuals within the cohort.

- Excluding recall bias in participants, by collecting data prospectively and prior to knowledge of a possible subsequent event occurring.

Disadvantages are implicit in the study design, particularly by virtue of this occurring over protracted time periods:

- Incomplete and interrupted follow-up of individuals, and attrition with loss to follow-up over time.

- Difficulty in the separation of the reciprocal impact of exposure and outcome, in view of the potentiation of one by the other; and particularly wherein the induction period between exposure and occurrence is prolonged.

- The potential for inaccuracy in conclusion if adopting statistical techniques that fail to account for the intra-individual correlation of measures.

- Generally increased temporal and financial demands associated with this approach.

G.   Gap of knowledge

Research has shown that there are key building blocks that serve as a foundation of children's developmental health. These determinants may be considered under three general themes: Care, Support and Opportunity. In most industrialized societies, is highly dependent on two enabling conditions: Family time and resources (that is, time to care personally for children, adequate income/financial resources and educational skills, knowledge and access to information); and universally accessible community services such as high-quality education, care, health programs and services. It is in this context that we decide to develop this thesis with the aim to understand how the influences of environmental factors and nurture, that include also the social context, can affect the process of child development and health, and its changes across time.

To address these questions, the most suitable and complete methodology designs are the longitudinal studies and the prospective birth cohort studies.

In the first part of my thesis, I concentrate my efforts on the identification of all the European Birth Cohort and perform an in-depth analysis of the ones that starting recruitment at birth or shortly after birth.

With this review, we aim to understand the European birth cohort's panorama, their aims and general structure and also the methodology used. All the information gathered from this observation have been essential to define and launch NASCITA (NAscere e CREscere in ITAlia) a national birth cohort officially started on the 1st of April 2019. In this thesis, I will present the protocol, management and organization of these birth cohorts and some preliminary results.

II.   AIMS

I.   To identify all the European Birth Cohort and to perform an in-depth analysis of the ones that starting recruitment at birth or shortly after birth. To understand the European birth cohort's panorama, their aims and general structure and also the methodology used.

II.   To provide input for those creating collaborations and laying out guidelines aimed at unifying cohort methodologies to enable merging of data and maximise knowledge acquisition.

III.   All the information gathered from this observation has been essential to define and launch NASCITA (NAscere e CREscere in ITAlia) a national birth cohort officially started on the 1st of April 2019.

IV.   The main aim of the NASCITA cohort is to evaluate physical, cognitive, and psychological development, and health status, and health resource use during the first six years of life in a group of newborns, and to evaluate potential associated factors.

V.   To evaluate differences between geographical settings in educational and socialization opportunities available for young children and in the care provided by the family pediatricians and by the National Health Service for the same needs.

VI.   To evaluate the association between the well-being of children and parental adherence to the recommendations for better childcare and development.

VII. To understand how the influences of environmental factors and nurture, which also include the social context, can affect the process of child development and health, and its changes across time.

III.   STEPS (Methods)

A.   Step 1: An inventory of the existing European Birth Cohorts

A.1   Background

Cohort studies collect data on a group of people in order to identify and quantify the relationship between exposure and outcome. They can be prospective or retrospective.

In prospective cohort studies, the population is recruited regardless of exposure or outcome status and is followed for a set period until the disease or outcomes of interest occur [De Groot et al. 2017; Klebanoff et al. 2018]. In retrospective cohort studies the population and its medical events or outcomes are examined by looking at the past. The limitations of this kind of study are linked to the limited control that the investigator has over data collection, increasing the risk of incomplete, inaccurate or inconsistent data [Song et al., 2010].

The increasing use of electronic health records has facilitated the development of a number of registries within large health plans.   Registries can also be used to collect data prospectively and continuously, as in the collection of medical record data, reflecting clinical practice. [Sessler et al. 2015] Both cohorts and registries can be started at different times, based on their aims, can be used for different scopes, and can collect data at different time points. There are different types of registries, from patient registries based on a disease or exposure, which collect data on patients with that characteristic, to those simply listing patients with specific diseases, e.g., rare diseases, but are not used for evaluating outcomes [Gliklich et al. 2014]. A cohort is more malleable and can be designed to identify causality between risk or exposure factors in early life and health in later life. Birth cohorts, which start from pregnancy or birth and follow newborns for a period of time, often into adolescence

or adulthood, are carried out especially with this aim, for example, to assess the impact of environmental exposure during development and its effects on adult health. Substantial evidence about this link has been found in recent years [Balbus et al. 2013], and increased attention is being placed on the prospective, longitudinal collection of data from participants throughout. Longitudinal cohorts permit the repeated collection of data and the study of various factors contemporaneously. These diverse factors range from those involved in nurturing care [Britto et al. 2017; Maggi et al. 2010], i.e., family structure, social and physical environment, schooling, and health and nutritional behavior, to exposure to environmental toxins such as air pollution, allergens, metals, pesticides, and smoking [Gehring et al. 2013]. All these factors have increasingly been acknowledged as having a significant impact on adult health [Lawlor et al. 2009] and birth cohorts are fundamental in understanding the extent of their effects. Scientific evidence has shown how simple actions involving the reduction of exposure to risk factors or the promotion of protective factors in the first few years of life can prevent significant health problems in children and adults.[Balbus et al. 2013; Barker 1998; Barouki et al. 2012; World Health Organization Regional Office for Europe 2013]

Many birth cohorts have been carried out around the world and many are currently ongoing [Batty et al. 2007; Vrijheid et al. 2012; Larsen et al. 2013]. Europe, especially Northern Europe, has been particularly active. In this context, we reviewed European birth cohorts to analyze where they are based, the current enrolment status, their objectives, areas addressed, and age periods covered, with a focus on cohorts that started enrolment at birth and not in pregnancy. We aimed to generate a panorama of the current birth cohorts' research topics and design and to provide

input for those creating collaborations and laying out guidelines aimed at unifying cohort methodologies emerging of data and maximize knowledge acquisition. We also aimed to understand how many birth cohorts address the impact of the family context (nurturing care) and the impact of the pediatricians' care on child health and growth, to provide input for future cohort studies.

A2. Materials and Methods

Between January and July 2019, we performed a narrative review of the European birth cohorts taking into consideration multiple sources.

A.2.1 Search strategy

The search strategy is described in detail in Annex A. Inclusion criteria were: Birth cohorts that were based in a European country and collected longitudinal and prospective data on the babies. In order not to exclude pertinent publications, however, we chose search strategies with high specificity and low sensitivity and had to limit results via individual ascertainment. We searched PubMed and Embase with the last update on 1 July 2019, limiting the results to the 20th of May 2019, with no restriction on past publication years. We excluded randomized controlled trials and articles focusing on vaccines or genes or gene expression. Data were reported using the flow diagram proposed by the PRISMA statement for reporting Systematic Review and Meta-Analysis [Liberati et al. 2009].

Records found were downloaded in the Reference Manager 12 software (Thomson Research Soft, Carlsbad, CA, USA).

A.2.2 Data extraction

The records were reviewed and, for each one, the name of the cohort it involved was noted. When this information was not available in the records' abstracts, the articles were retrieved when possible. We also searched online birth cohort inventories to see if any additional cohorts could be found. In particular, we consulted the web-based database (http://www.birthcohorts.net), created as part of the Children Geno Network (a European FP5 Research Program) in 2005, and improved and redesigned within the European FP7 Program CHICOS project (http://www.chicosproject.eu). We also searched the cohorts listed by two EU-funded research projects: The ENRIECO project [Chase et al. 1998] and the EUCCONET Network [Piler et al. 2017]. Exclusion criteria were: Vaccine studies, case-control studies designed within existing cohorts, studies that applied gene analysis or other criteria in sample selection, or cohort studies focusing only on the parents or on pregnancy outcomes, that were exclusively retrospective, that collected data from registries, or that did not involve a follow-up. The European definition used was the UN definition [Doyle & Golding, 2009].

We performed more detailed analyses on the subgroup of cohorts that began recruitment at birth and not during pregnancy. Cohorts that began collecting data after a few months of birth, even though patients were enrolled at birth, were included. For the more detailed analyses it was often necessary to search for additional scientific publications resulting from the single cohorts, in addition to the cohorts' websites, to limit the amount of missing data. Two authors (Claudia Pansieri and Chiara Pandolfini) worked on different parts of the data extraction

process as well as on certain overlapping parts, and all cases of uncertainty, discrepancy, or missing data were resolved through discussion, searches for additional data sources, and consensus.

The type of funding received by the cohorts was classified into four types: Public (ministries of health, hospitals, including university hospitals, etc.), Foundation, University, and Industry.

A.3   Results

A.3.1 Identification of the Cohorts

A total of 8572 articles were found through the internet-based bibliographic literature databases consulted, after the exclusion of duplicates as illustrated in the PRISMA flow diagram (Figure 4). Of these, 5444 articles referred to 111 birth cohorts, while 3128 articles were not pertinent mostly because they referred to case-control studies and retrospective studies (Figure 5).

Figure 4. Literature selection from the two databases: Medline and Embase
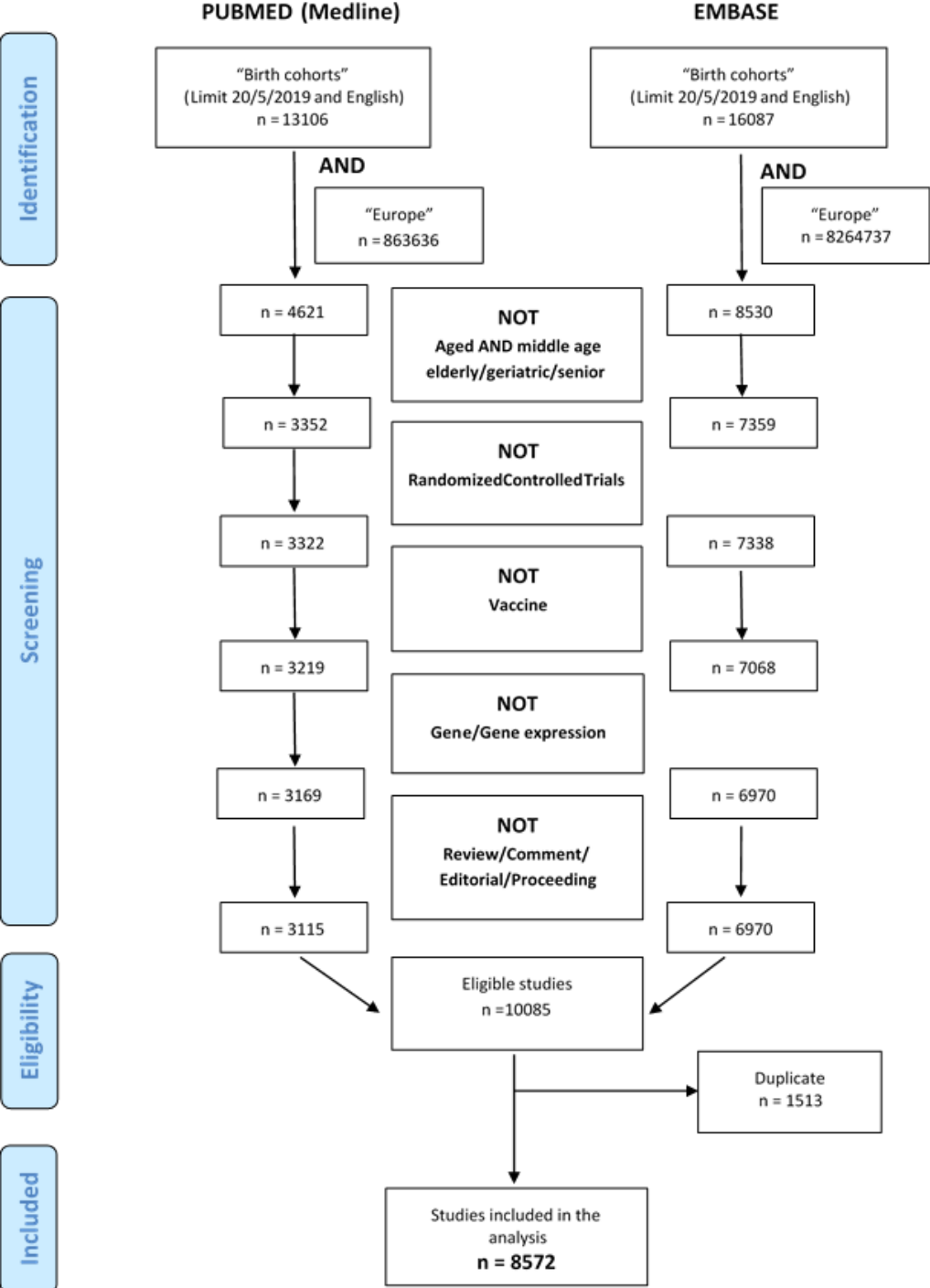
Figure 5.   Selection of articles and number of related cohort
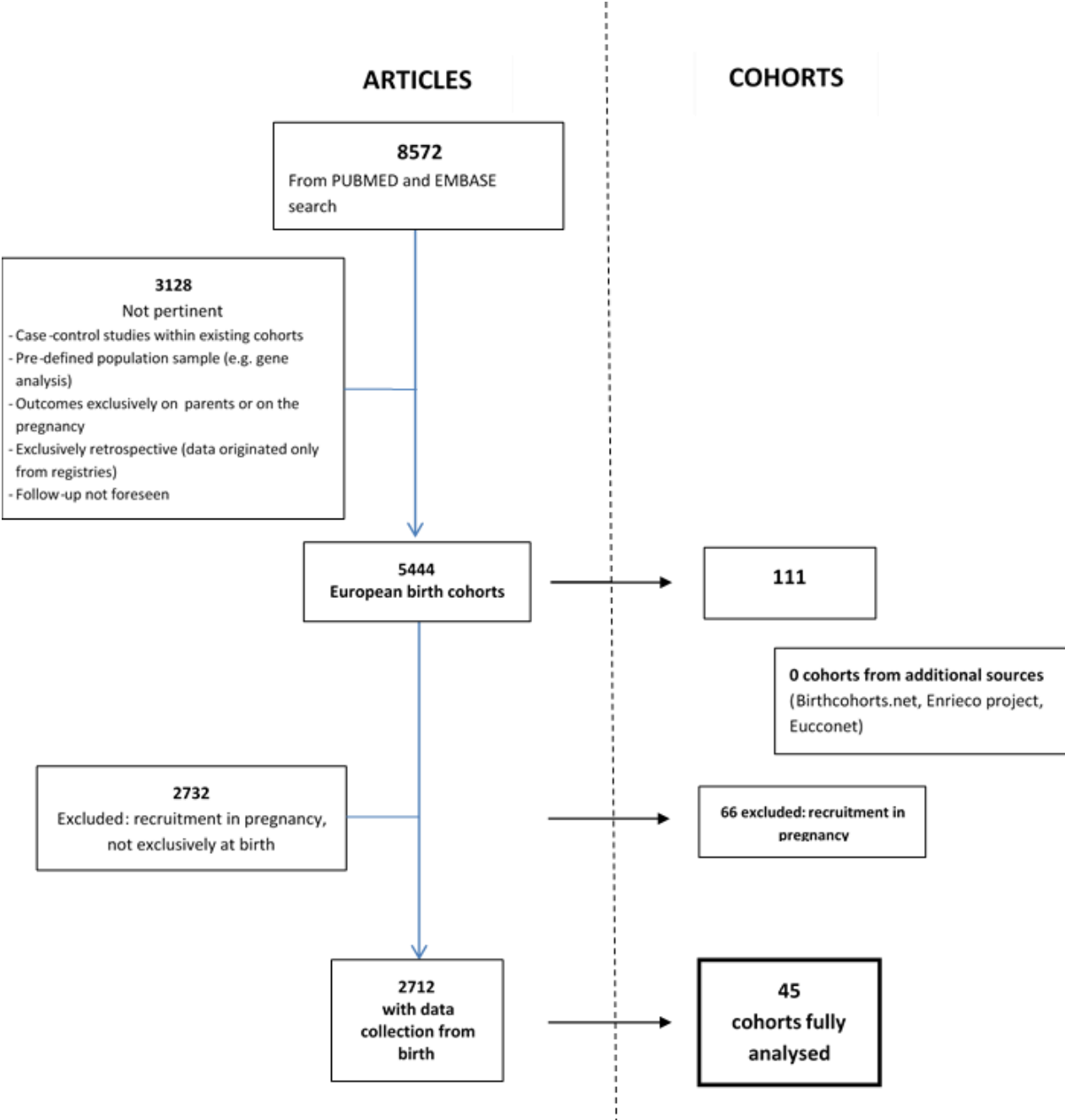
The large proportion of non-pertinent articles, since no specific indexed term exists

in Medline or Embase for birth cohorts, led to the need for individual assessment of

a large portion of abstracts or full-texts. Other cohorts, such as NCCGP North

Cumbria Community Project [Pearson 2015], were also excluded because of a lack of

basic information such as the enrolment period and the number of patients included

or expected and the consequent lack of any useful information. When the online birth cohort databases were searched for additional European cohorts, none were found. A total of 111 European birth cohorts were identified. Of these, 66 began enrolment in pregnancy (2 of which in pre-pregnancy) and 45 at birth or shortly afterward. References of articles referring to the 45 cohorts found are listed in Supplementary Material, Table 2.

Table 1. List of the 45 birth cohort
(Details)

Nation	Cohort full name	Acronym	Reference
Belgium	FLEHS-I Flemish Environment and Health Study	FLEHS-1	Den Hond, et al. 2009
Belgium	ENVIRONAGE	ENVIRONAGE	Hogervorst, et al. 2019
Czech Republic	CzECH-Czech Early Childhood Health	CzECH	Dejmek, et al. 2000
Denmark	CCC2000-Copenhagen Child Cohort	CCC2000	Skovgaard, et al. 2005
Denmark	DARC-The Danish Allergy Research Centre	DARC	Kjaer, et al. 2008
Finland	NFB C8586-The Northern Finland Birth Cohort 1985/1986	NFB C8586	Paananen & Gissler, 2012
France	ELFE- Etude Longitudinale Francaise depuis l'Enfance	ELFE	Vandentorren, et al. 2009
France	AuBE	AuBE	Patural, et al. 2014
France	Epifane survey	Epifane	Boudet-Berquier, et al. 2017
France	EPIPAGE 2	EPIPAGE 2	Regional coordination, 2013
France	PARIS- Pollution and Asthma Risk: an Infant Study	PARIS	Clarisse, et al. 2007
Germany	DONALD- Dortmund Nutritional and Anthropometric Longitudinally Designed study	DONALD	Kroke, et al. 2004
Germany	GINIplus- German Infant Study on the Influence of Nutrition Intervention	GINIplus	Heinrich, et al. 2017
Germany	LISA PLUS- Influence of lifestyle factors on the development of the immune system and allergies in East and West Germany	LISA PLUS	Zutavern, et al. 2007
Germany	MAS-90-Multizentrische Allergie studie	MAS-90	Nickel, et al. 2002
Germany	Ulm SPATZ Health Study	SPATZ	Braig, et al. 2017
Germany	KUNO-Kids birth cohort	KUNO	Brandstetter, et al. 2019
Germany	UBCS-Ulm birth cohort study	UBCS	Christiansen, et al. 2017
Italy	GASPII -The Gene And Environment Prospective Study Of Infancy In Italy	GASPII	Porta, et al. 2007
Italy	MUBICOS- Multiple Births Cohort Study	MUBICOS	Brescianini, et al. 2013
Italy	Piccolipiu'	Piccolipiù	Farchi, et al. 2014
Italy	ITA-Neonatologie Multicenter Italian Birth cohort	ITAL NEONAT	Lanari, et al. 2015
Multicenter	Europrevall	Europrevall	McBride, et al. 2012
Norway	HUMIS-The Norwegian Human Milk Study	HUMIS	Eggesbø, et al. 2009
Norway	ECA-Environment and Childhood Asthma	ECA	Lødrup Carlsen, 2002
Portugal	G21-The Generation XXI Study	G21	Correia, et al. 2014
Slovakia	PCB Cohort- Early Childhood Development and PCB exposure in Slovakia	PCB	Jusko, et al. 2010
Slovakia	Slovak multicentric prospective mother-child cohort PRENATAL	PRENATAL	Dunlop, et al. 2006

Sweden	ABIS- The All Babies In Southeast Sweden Study	ABIS	ABIS study, 1997
Sweden	BAMSE-Children (Barn), Allergy, Milieu, Stockholm, Epidemiological study	BAMSE	Lannerö, et al. 2002
Sweden	H2GS-Halland Health and Growth Study (H2GS)	H2GS	Roswall, et al. 2016
The Netherlands	WHISTLER-Wheezing Illnesses Study in Leidsche Rijn	WHISTLER	Katier, et al. 2004
The Netherlands	The Terneuzen Birth Cohort	TERNEUZEN	de Kroon, 2011
The Netherlands	Dutch cohort	Dutch	Veldwijk, et al. 2011
The Netherlands	LucKi birth cohort	LucKi	de Korte-de Boer, et al. 2015
Turkey	ADAPAR- Adana Pediatric Allergy Research	ADAPAR	Dogruel, et al. 2016
UK	1921 Aberdeen birth cohort	ABERDEEN	Baxter-Jones, et al. 1999
UK	EPICure	EPICure	Costeloe, et al. 2000
UK	GEMINI-Health and Delopment in twins	GEMINI	van Jaarsveld, et al. 2010
UK	GMS (Gateshead Millenium Cohort Study)	GMS	Parkinson, et al. 2011
UK	GUS -Growing Up in Scotland	GUS	Growing up in Scotland, 2004
UK	LRC- The Leicester Respiratory Cohorts	LRC	Kuehni, et al. 2007
UK	TEDS-Twins early development study	TEDS	TEDS, 1994
UK	FAIR cohort-Food Allergy and Intollerance Research	FAIR	FAIR, 2001
Finland	1982- TURKU	TURKU	Piekkala, et al. 1987

48.

A.3.2 The European Panorama

The 111 European cohorts represented 27 different countries, including three countries represented only in the four multinational cohorts (Austria, Iceland, and Slovenia). The countries most commonly involved, in 16 cohort searches, were Germany and the UK, followed by the Netherlands (15). The number of children recruited in the different cohorts ranged from 107 to 10.8500 (median 1924). The starting year of enrolment in the different cohorts ranged from 1921 to 2016 (median 2002) and the duration of enrolment, excluding 10 with currently ongoing enrolment, and one with missing data, ranged from 1 to 23 years (median 2) (rounded to whole years). Concerning the follow-ups, 62 have ongoing follow-ups, of which 22 are lifelong and the rest of which have a duration of 1 to 31 years. The median could not be calculated because of the general nature of the description of follow-up duration for several cohorts (e.g., young adulthood).

A.3.3 The 45 Cohorts Starting Recruitment at Birth

When only the subset of cohorts that began recruitment at birth was selected, 45 cohorts were present (Table 2), representing 19 European countries, 7 (37%) of which are located in Northern Europe, and 11 (58%) in Northern or Western Europe (Figure 6). Only the Europrevall cohort was multinational and involved 9 countries.

Table 2. The 45 European birth cohorts analysed

Nation	Acronym	N. children	Enrolment start	Follow up status	Data collection[1]	Data origin[2]	Genetic analysis	Biological samples (if taken)
Belgium	ENVIRONAGE	1080	2010	Ongoing	Q, PV	SR	Yes	Cord blood
Belgium	FLEHS-I	1196	2002	Closed	Q, PV	SR	Yes	Blood, Cord blood, Exhaled breath condensate, Meconium, Saliva
Czech Republic	CzECH	7577	1994	Closed	Q, PV	SR/PED	Yes	Cord blood, Urine
Denmark	CCC2000	6090	2000	Closed	PV	PED	No	
Denmark	DARC	562	1998	Closed	Q, PV	SR/GYN-HCP/PED	No	Blood
Finland	NFB C8586	9479	1985	Closed	Q	SR	No	*Info missing*
Finland	TURKU	5356	1981	Closed	PV	GYN-HCP/PED	No	
France	AuBE	302	2009	Closed	Q	SR	No	Colostrum
France	ELFE	18326	2011	Ongoing	Q	SR	No	Cord blood, Hair, Urine
France	Epifane	3368	2012	Closed	Q	SR	No	
France	EPIPAGE 2	5567	2011	Ongoing	Q, PV	SR/GYN-HCP	No	
France	PARIS	3840	2003	Ongoing	Q, PV	SR/PED	No	Serum
Germany	DONALD	1300	1985	Ongoing	Q, PV	PED	No	Urine
Germany	GINIplus	5991	1995	Ongoing	Q, PV	PED	Yes	Cord blood, Serum
Germany	KUNO	2515+	2015	Ongoing	Q, PV	SR/PED	Yes	Buccal swab, Cord blood, Gingival smears, Hair, Skin swab, Stool, Urine
Germany	LISA PLUS	3097	1997	Closed	Q	-	Yes	Serum
Germany	MAS-90	1314	1990	Closed	Q, PV	GYN-HCP/PED	Yes	Blood, Cord blood, Urine
Germany	SPATZ	1006	2012	Ongoing	Q	SR	No	Blood, Breast milk, Hair, Urine
Germany	UBCS	1022	2000	Closed	Q	SR	Yes	Breath test, Serum
Italy	ITAL NEONAT	697	2009	Closed	Q, PV	PED	No	*Info missing*
Italy	GASPII	708	2003	Ongoing	Q, PV	PED	Yes	Blood, Cord blood, Serum
Italy	MUBICOS	800	2009	Ongoing	Q	SR	No	Saliva

Nation	Acronym children	N. children	Enrolment start	status	Follow up collection₁	Data origin / analysis ²	Genetic	Biological samples (if taken)
Italy	Piccolipiù	3328	2011	Ongoing	Q, PV	SR/PED	Yes	Blood, Cord blood, Urine
Multicenter	Europrevall	12049	2005	Ongoing	Q	SR	Yes	Blood, Cord blood,
Norway	ECA	3754	1992	Closed	Q, PV	SR/PED	Yes	Cord blood
Norway	HUMIS	2000	2003	Ongoing	Q	SR	No	Breast milk, Cord blood
Portugal	G21	8647	2005	Ongoing	Q	-	No	Cord blood, Serum
Slovakia	PCB	1134	2002	Closed	Q, PV	SR/GYN-HCP/PED	No	Cord blood
Slovakia	PRENATAL	1990	1997	Closed	Q, PV	GYN-HCP	Yes	
Sweden	ABIS	16058	1997	Closed	Q, PV	PED	Yes	Blood, Breast milk, Serum
Sweden	BAMSE	4089	1994	Ongoing	Q	SR	Yes	Blood, Plasma, Urine
Sweden	H2GS	2026	2007	Closed	Q, PV	SR/PED	No	
The Netherlands	Dutch	236	1990	Closed	Q, PV	SR/GYN-HCP/PED	No	
The Netherlands	LucKi	5000	2006	Ongoing	Q, PV	SR/GYN-HCP	No	Meconium
The Netherlands	TERNEUZEN	2604	1977	Closed	Q, PV	-	No	
The Netherlands	WHISTLER	2923	2003	Ongoing	Q	-	No	
Turkey	ADAPAR	1377	2010	Closed	Q, PV	SR/PED	No	Cord blood, Serum
UK	ABERDEEN	668	1921	Closed	Q, PV	GYN-HCP	No	
UK	EPICure	308	1995	Ongoing	Q	-	No	
UK	FAIR	969	2001	Closed	Q	SR	No	
UK	GEMINI	2402	2007	Closed	Q	SR	No	
UK	GMS	1029	1999	Ongoing	Q, PV	SR	Yes	Blood, Saliva
UK	GUS	5217	2004	Ongoing	Q	SR	No	
UK	LRC	10350	1985	Ongoing	Q	SR	No	Saliva
UK	TEDS	21000	1994	Ongoing	Q	SR	Yes	*Info missing*

1. Q: questionnaire, PV: Patient visit.

2. SR: Self-reported questionnaire by parent; GYN-HCP: Medical information directly from gynaecologists or other health care practitioner, not pediatricians; PED: Medical information directly from pediatricians/hospital-based pediatricians.

Figure 6. Location of the countries participating in the 45 birth cohorts
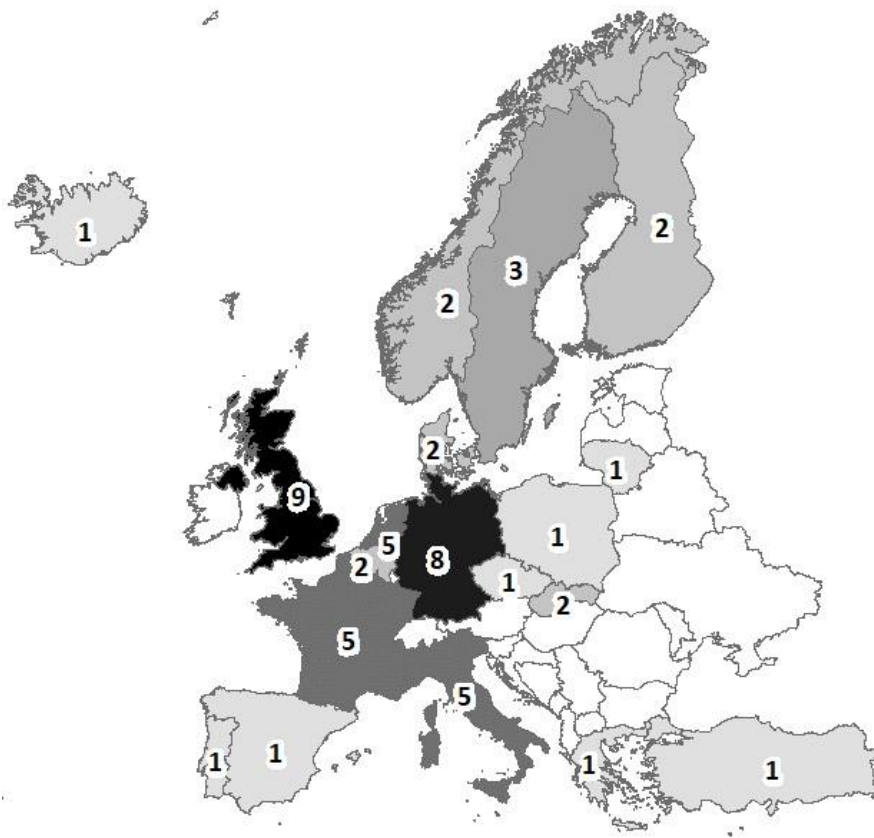
The starting years of these cohorts ranged from 1921 to 2015 (median 2002). More than half of the cohorts began in 2000 or later and 8 after 2010. The sample size of each cohort varied considerably, from 236 of the 1990 Dutch cohort to more than 21000 children of the TEDS-Twins early development study, with a mean of 4230 (median 2515). The two largest birth cohorts are located in the UK (TEDS-Twins early development study, with 21000 children enrolled) and in FRANCE (ELFE- Etude Longitudinale Francaise depuis l'Enfance, with 18326 children enrolled).

The oldest of the 45 cohorts enrolled participants in 1921 (the 1921 Aberdeen Birth Cohort) and the youngest began enrolment in 2015 (the German KUNO-Kids birth cohort) (Figure 7). As of January 2020, the majority of cohorts were closed to

recruitment since they completed the enrolment of child participants. Five cohorts are currently still recruiting: DONALD (begun in 1985), GUS -Growing Up in Scotland (2004), KUNO-Kids (2015), the LucKi birth cohort (2006), and MUBICOS (2009). Concerning the follow-up, 49% (22/45) of the cohorts are still undergoing follow-up, while the rest are definitively closed. Concerning the more recent cohorts, fifteen of the 26 (58%) cohorts set up from 2000 on, and 6 of the 8 (75%) from 2010 on, are currently ongoing. The duration of the follow-ups ranged from 1 year to life-long (Figure 7).

Figure 7. Cohorts' enrolment period, follow-up status (Ongoing/Closed), and duration (years)
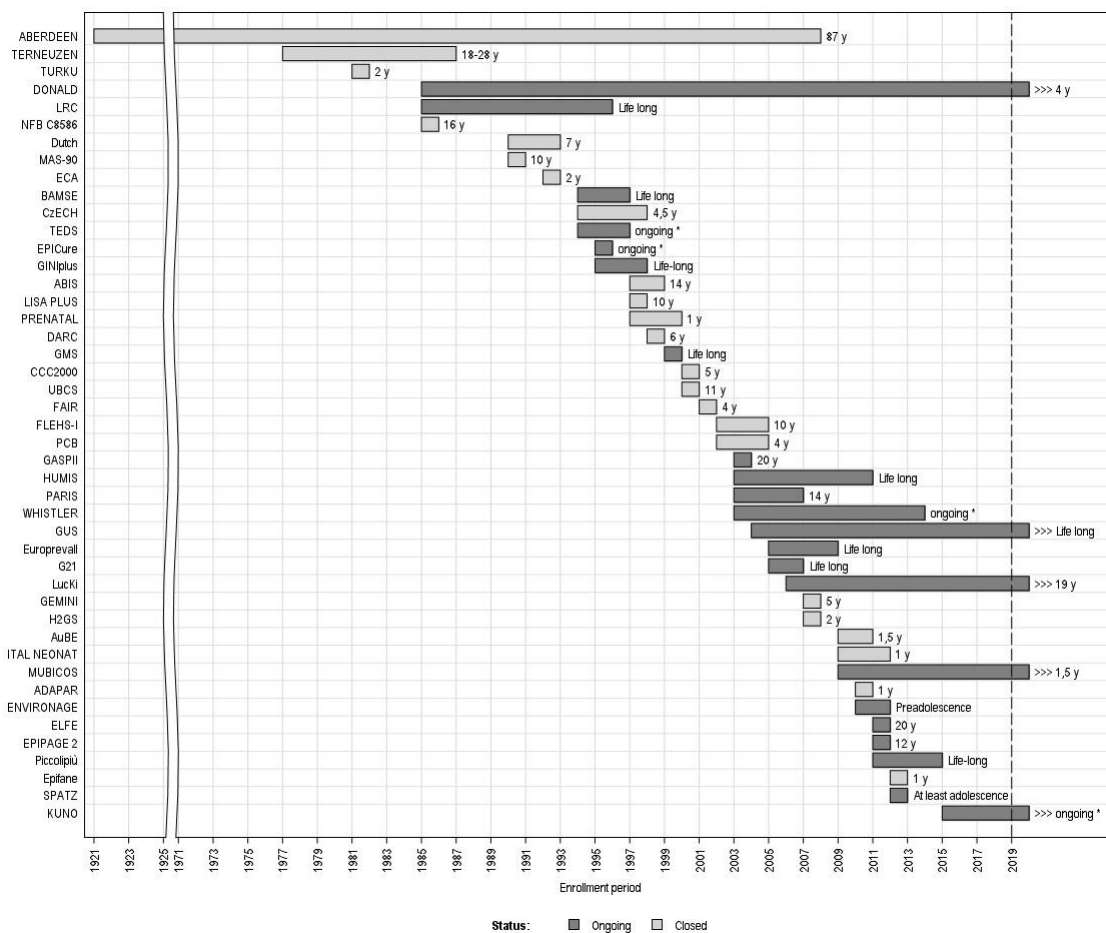
The aims behind the creation of the cohorts are various and cover a broad range of aspects of child health. The most frequently studied individual topics included: allergic diseases (14 cohorts), environmental exposure (12), and growth (intended as physical growth, 10), although several cohorts (28) addressed multiple areas and were designed to test a wide range of hypotheses (Figure 8). Allergic diseases were most often studied in terms of their association with environmental exposures and asthma, but also with autoimmune diseases, lifestyle exposure, nutrition, and obesity. The environmental exposure was also studied together with genes, lifestyle exposure, neurocognitive development, and twin development, but also with asthma, autoimmune disease, growth, and nutrition. Growth was also studied together with nutrition, but also with health, neurocognitive development, and prematurity.

Figure 8. Frequency of scientific areas addressed by the cohorts
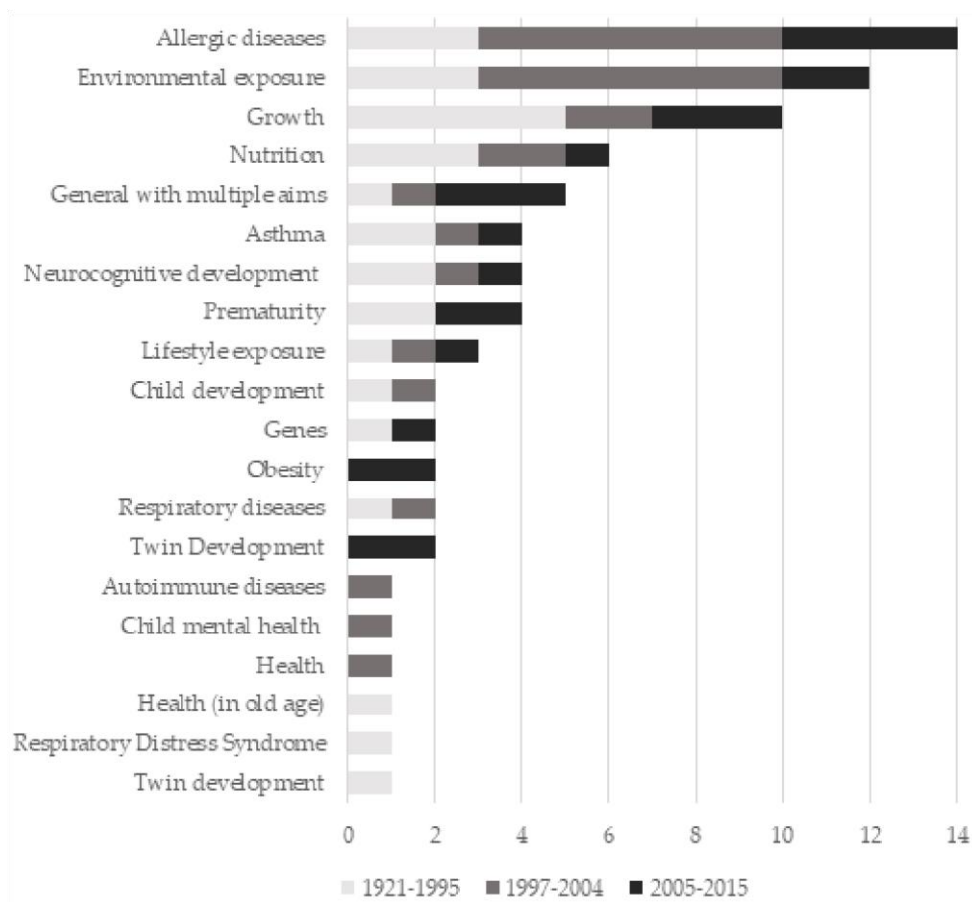
When divided into three groups based on the age of the cohorts to see if, over time, the priorities studied changed, allergic diseases and environmental exposure were more recent priorities. Both were initially studied to a limited extent. Allergic diseases resulted as a priority area among the cohorts for the first time in 1990 and environmental exposure in 1992. More specifically, in the 1921-1995 period, growth (5 cohorts) and allergic diseases, environmental exposure, and nutrition (3 each) were the most commonly addressed areas, between 1997-2004, they were, allergic diseases and environmental exposure (7 cohorts each), and in 2005-2015 they were allergic diseases (4), and growth and general areas with multiple aims (3 each). Only three cohorts addressed the impact of the family context (nurturing care) to a

certain extent among their goals, the ELFE, Epifane, and GUS cohorts. All three of these cohorts were relatively recent (2011, 2012, and 2004, respectively).

A.4   Discussion

In this review, we provide up to date information on birth cohorts in Europe with a focus on those that began data collection at birth.

The fact that more than half of the cohorts began in 2000 or later and that many are still ongoing in terms of follow-up of participants suggests that there is a current, active interest in newborns, although with the involvement of only 9 countries, and with different aims.

The number of participants included varied largely, although the average was only just over 4000. With larger sample sizes, aided by the use of standard measures in the pooling of cohorts, and the joining of data from large epidemiological studies from other countries, it is possible to understand the epidemiology of diseases [Piler et al. 2017]. A long follow-up period is fundamental to assess the impact of different factors on adult health and to be able to identify possible corrective interventions. A powerful limiting factor in setting up, and running, large cohorts over large periods is the cost [Doyle & Golding 2009]. Two very large studies in the UK and US have, in fact, recently been cancelled also due to budgetary issues. [Pearson 2015; Cernansky 2017]

More than a third of the European cohorts were established in northern Europe, where this kind of study has a long-lasting tradition. Health surveillance (perinatal and not) in this area of the world is often of high quality also because of the use of record linkage between health, civil and administrative data [Furu et al. 2010]. Two-

thirds of the cohorts were established in Northern or Western Europe, and high-income countries in all except one case. These data are similar to those of Larsen et al, which included pregnancy cohorts as well, and whose cohorts were limited to those of greater entity and limited to 2013 [Larsen et al. 2013].

Unlike the work carried out by Larsen and colleagues [Larsen et al. 2013], we limited the analysis to European cohorts starting enrolment of the babies after birth. This was done because we wished to focus our study on child development in general and on the impact of nurturing care. We, however, reported in the data the cases in which the cohorts included retrospective pregnancy data.

The main areas addressed by the cohorts were allergic diseases and environmental exposure, both of which have become priority study areas more recently. The numerous cohorts addressing environmental exposure reflect increasing attention to the negative effects of pollution on health. Growth was studied more by the older cohorts, while obesity is a new research area, although all of the areas currently remain topics of interest for research, expansion of knowledge, and appropriateness of interventions. Many cohorts were designed to test a wide range of hypotheses, such as the Spatz cohort [Braig et al. 2017]. This approach addresses the identification of many risk factors for disorders thought to have a perinatal/early life aetiology such as birth defects, respiratory conditions, and childhood cancer [Golding et al. 2017;

Guyatt et al. 2015]. Other cohorts were more focused on specific topics, such as respiratory diseases (e.g. the LRC cohort) [Kuehni et al. 2007]. Exposure to a pattern of adverse early-life stressors, in specific age windows, influence health throughout the life cycle. The scientific evidence currently available shows how even events

occurring shortly after conception and up until the time a baby is delivered may lead to diseases and morbid events. These may be either present at birth or may manifest themselves later in life, in early childhood and or in adult age [Barker 1998; Barouki et al. 2012; Barker 2004; Latzin et al. 2009]. Several stressors have already been identified through the exploration of data from historical birth cohorts [Power & Elliott 2006]. The early-life stressors that recently reached scientific attention are socioeconomic circumstances, migration, urban environment as well as lifestyle-related determinants [Lynch & Smith 2005].

The research results show that few cohorts have followed in detail child development as well as neurodevelopment. In general, child health is a product of biological factors and diverse sets of environmental influences, including intrauterine and social ones

[Lawlor et al. 2009; Barker 1998; Barouki et al. 2012; World Health Organization Regional Office for Europe, 2013; Batty et al. 2007; Vrijheid et al. 2012; Prado et al. 2019]. This implies that high-quality measures of multiple dimensions of both sets of influences need to be taken during appropriate developmental periods. Epigenetic and phenotypic measures and their associations with health outcomes since conception and/or birth are increasing aims of prospective cohort studies [Corley et al. 2019]. The collection of biological samples, conducted by the majority of the ongoing cohorts, has increasingly become part of routine data collection [Bailey et al. 2017] given its importance in studying the biological mechanisms of disease, and also permitting the measuring of biomarkers of environmental exposures. Biological samples, in fact, allow researchers to study how social and environmental factors

leave biological imprints, independent of, or in combination with, genetic background [Richmond et al. 2014].

The cohorts were supported mostly by public funds. Setting up and running cohorts, especially over long periods of time, is very important but is also extremely costly. More economic support would be useful for setting up cohorts in all countries, and for making it possible to collect enough information, and in a suitable format, to make the cohorts comparable enough to merge their data with that of other cohorts. The industry had a limited presence in the cohorts described in this review.

The limited funds available for running cohorts inevitably influence the type of data collection employed. While most of the cohorts collected data via predefined questionnaires and face-to-face interviews, which are less costly, patient visits involving clinical assessment were carried out in just over half the cohorts. The Nordic countries often draw patient data from different inter-related registries, facilitating the collection of also clinical data, and reducing costs [Cernansky 2017; Sørensen 1997]. The cohorts also used hospital records to obtain data on the mothers, the pregnancies, and the births, facilitating the collection of sufficient data from which to calculate correlations with subsequent events. The use of web-based questionnaires in assessing perinatal outcomes has also been found to be a valid way to collect data while limiting costs [van Gelder et al. 2017].

The lack of commonly acknowledged guidelines on the use of common measures for data collection, along with the various data sources used by cohorts, leads to the extreme difficulty in merging or comparing data from different cohorts, a process that would permit more far-reaching, significant conclusions from the research. This is a well-recognized issue and different groups are working to address it.

Few cohorts also focused on family context (nurturing care) and its impact among their research areas. Family context is a fundamental issue [Britto et al. 2017] and should be a priority study area.The cohorts that at least partly investigated the family context was relatively recent and were set up around the years when the Lancet series addressing the evidence linking early childhood development with adult health and wellbeing began [Jones 2018].

Few cohorts involved the general pediatrician (or the general practitioner) as the person delegated to collect data, highlighting the fact that primary care is a neglected resource for research [Bhutta et al. 2008]. With their clinical practice, pediatricians are most in contact with patients and can promote study and action. Pediatricians can play a role both in the education of parents and other caregivers, and in the implementation of curative, preventive, and health-promoting interventions through their professional practice. They can work together with other professionals in the development and execution of research with special attention to child growth and development, child mental health, and, in general, to the well-being of future generations.

Our aim was to describe the birth cohorts' research topics and design, to understand their interest in the impact of the family context (nurturing care) and the general pediatricians' role in child care and data acquisition, and to provide input for future cohort studies and for those working towards universally acknowledged guidelines for unifying cohort methodologies to enable data merging and the consequent maximum acquisition of knowledge. The results of this study show that a limited number of countries participates in multinational birth cohort studies and that adequate, universally recognized methodological aspects (e.g.,

sample size, data collection, and follow-up duration), and common health priorities, are needed to permit the comparison and merging of cohort data. Such an expanded amount of comparable data would permit researchers to draw more solid conclusions and stakeholders to implement the knowledge in initiatives aimed at improving people's health.

To our knowledge, this is the first inventory of birth cohorts, both at the European and worldwide level, starting recruitment after birth. Considering pregnancy and birth cohorts together, inventories have been produced in Canada [Joly et al 2012] and Asia [Kishi et al. 2017]. Several collaborations addressing specific research questions including several worldwide birth cohorts, however, were set up in the last few years, such as the Environment and Child Health International Birth Cohort Group

(ECHIBCG) [Nakayama et al. 2019] and the CODATwins Project [Silventoinen et al. 2019]. The only indispensable tool that can easily be searched and that accepts registration from pregnancy and birth cohorts established all over the world is www.birthcohorts.net. Potential limits of this study exist. It is possible that we did not identify all the European birth cohorts, but we attempted to use the most rigorous and extensive search strategy for identifying the cohorts, so we expect that a potential percentage gap would be small. This review is descriptive; we did not contact the principal investigators of the cohorts but searched for information only via web, and this may have limited the completeness of data or led to partial data, since data found in one publication may be different from those in other publications referring to the same cohort. Furthermore, classifying the cohorts' aims into individual scientific areas was difficult given the overlap between areas (e.g.

lifestyle and environmental exposures), but the distinction was useful to provide a general description of the cohorts and to show their differences. For example, the four remaining cohorts labelled as addressing general areas with multiple aims were not classifiable because their aims were so widespread. The strengths of this study are that it reports on a large number of active initiatives whose role is to look ahead, starting from birth, to monitor the development of European newborns. The findings of these cohort studies can be useful for stakeholders in allocating resources towards appropriate endeavours in order to work towards improving the health of citizens from birth.

A.5. Conclusions

The continuing follow-up of existing cohorts is the most efficient way to detect areas of improvement and windows of collaboration. Longitudinal data investments need to be directed at capturing the circumstances of tomorrow's children and adults, i.e. current cohorts must be able to answer upcoming research questions considering several aspects: genetic and biological, psychological/social environments, medical care and medications, and lifestyle and environmental parameters. In this regard, new cohorts are periodically being set up to address the more pressing issues, such as child health and pollution.

We also believe that primary care should be supported, exploited and valued in public health research. Future studies should involve close collaboration with family pediatricians, or physicians caring for children, since in this new vision their role will no longer be limited to the treatment of diseases, but will involve the global

assistance of the child and family. The present study reveals the involvement of only a few countries. Shortly, more countries should be involved in multinational birth cohort studies, with adequate, universally recognized methodological aspects (e.g., sample size, data collection, and follow-up duration), with common health priorities. The role of the European Commission, in addition to supporting the setup of such multinational cohorts, is to promote, and eventually require, the implementation of commonly acknowledged parameters to allow for comparison of cohorts and data merging to maximise the acquisition of knowledge from such studies.

A.6 A view on major extra Europe longitudinal studies and initiatives

In a recent review, Waleska and colleagues [Waleska et al. 2018] identified around 84 cohorts all around the world.

Of the 84 cohorts identified, 41 were birth cohorts, 41 were prenatal cohorts, and 2 were preconception cohorts. Of this 64 have a prospective design with longitudinal data collection.

Of the 84 cohorts identified, 40 were in Europe, 4 in Africa, 13 in the Americas, 15 in Asia, and 12 in Oceania. See Figure 9.

The size of each marker is proportional to the initial membership of each cohort, and the colours of the markers indicate whether the study involved a preconception, prenatal, or birth cohort [Waleska et al. 2018].

Figure 9. Map of the world showing the location of the preconception, prenatal, and birth cohorts identified.
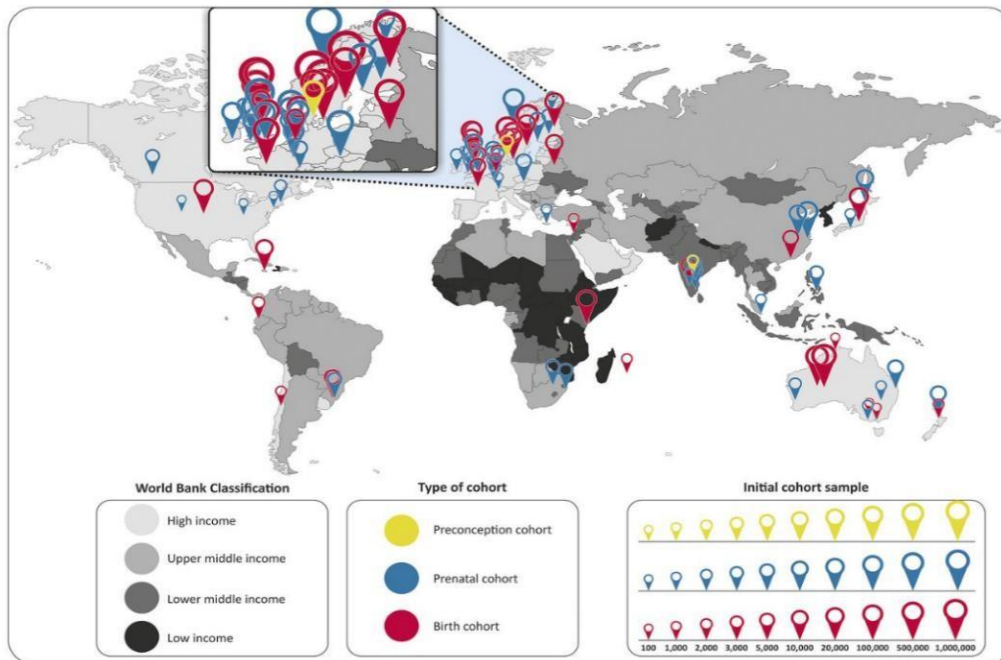
AFRICA

The most complete overview of the birth cohort studies conducted in Africa (Figure 1) was reported by Campbell and Rudan around 10 years ago [Campbell et al. 2011].

Figure 10. Location of the African birth cohorts
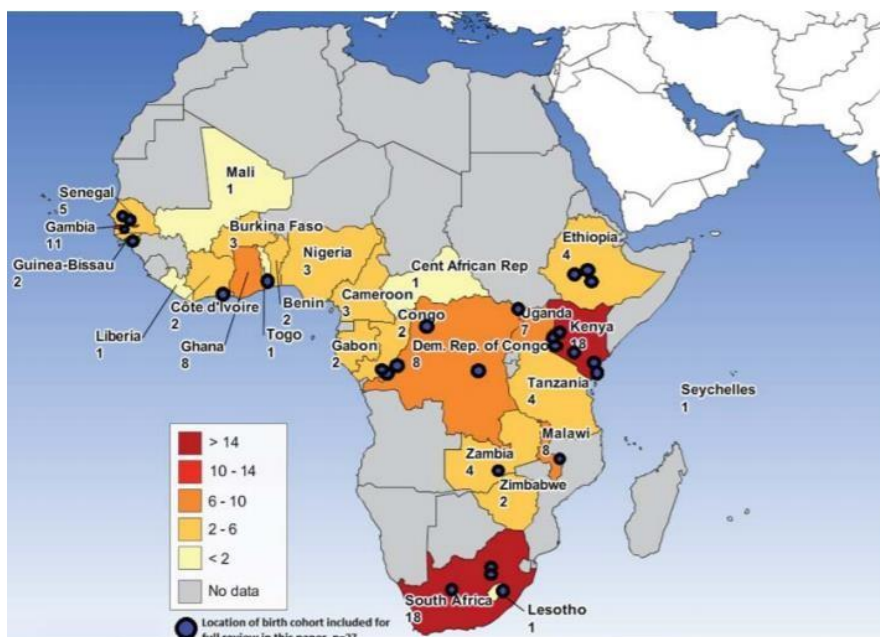
UNITED STATES

No systematic review on birth cohorts established in the United States were found.

The biggest birth cohort in the United States is the National Children's Study (NCS or Study) This study aimed to recruit a nationally representative longitudinal cohort study of 100,000 children from before birth through age 21 to examine the effects of a broad range of environmental and biological factors on children's health and development. It was closed in December 2014.

CANADA

An inventory of Pregnancy and Birth Cohort Studies in Canada was performed in 2009 by Joly and colleagues [Joly et al. 2012].

They identified 46 birth cohort studies. (Figure 11) The details of data collected have been uploaded on the website of IHDCYH: hiip://www.cihr -irsc.gc.ca/e/40753.html.

Figure 11. Percent of birth cohort studies conducted by province and territory in Canada
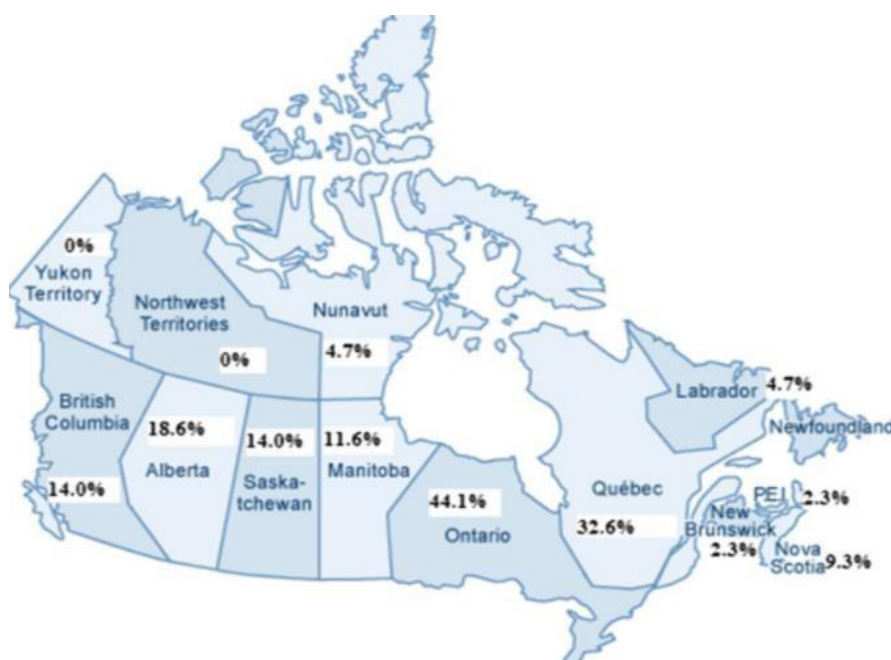
AUSTRALIA AND NEW ZEALAND

Townsend and colleagues in 2016 performed a systematic review collecting birth cohorts from Australia and New Zealand. The studies undertaken in these developed regions are characterised by particular social ecologies and policy environments that differ from other countries, with the populations eligible for universal and quality health care and education, living in clean environments with less defined class based society and diverse cultural backgrounds.

They identified 23 studies, he 83% of studies identified are of prospective longitudinal birth cohort design. Authors reported an increasing interest and acknowledgment of the value in collecting detailed data on parents and grandparents, not just the index child [Townsend et al. 2016].

ASIA

The Birth Cohort Consortium of Asia (BICCA)

BICCA includes 27 birth cohorts with approximately 80,000 study subjects that were conducted in 13 Asian countries and provides an information exchange platform for birth cohort in Asian countries [Kishi et al. 2017].

SOUTHEAST ASIA AND EASTERN MEDITERRANEAN

McKinnon and colleagues performed a Systematic Review of birth cohort studies in South East Asia and Eastern Mediterranean Regions in 2011 (Figure 12). They detected 120 studies in total located mainly in the SEA region (n = 83) compared to the EM region (n = 37). An overview of studies revealed large diversity in their methodologies, most of the studies that declare collection on biologic samples are prospective [McKinnon & Campbell 2011].

Figure 12. Location of the asian birth cohorts

MIDDLE EAST

No systematic review on birth cohorts established in the Middle East has been detected. One of the principal birth cohorts is The Mother-Infant Study Cohort (MISC) that is an ongoing two-year prospective cohort study which recruited Arab pregnant women in their third trimester from prenatal clinics in Dubai, Sharjah and Ajman [Radwan et al.

2018].

INTERNATIONAL INITIATIVES

The Global Longitudinal Research Initiative (GLORI 2.0)

The Global Longitudinal Research Initiative (GLORI 2.0) is a research network of longitudinal researchers working on topics relevant for children, an initiative promoted by the UNICEF aiming to tracks longitudinal research projects looking at child development trends and trajectories around the world. Set up in 2014, the network has members working in over 30 countries. (Figure 13) This is a developing community of practice seeking to: Add to the evidence base through a coordinated

approach; Create an inventory of resources and harmonise tools in some areas; Document and share best practice; Develop mechanisms to strengthen institutional capacity and local ownership; [UNICEF, 2013].

Figure 13. GLORI 2.0 - Currently Studies country
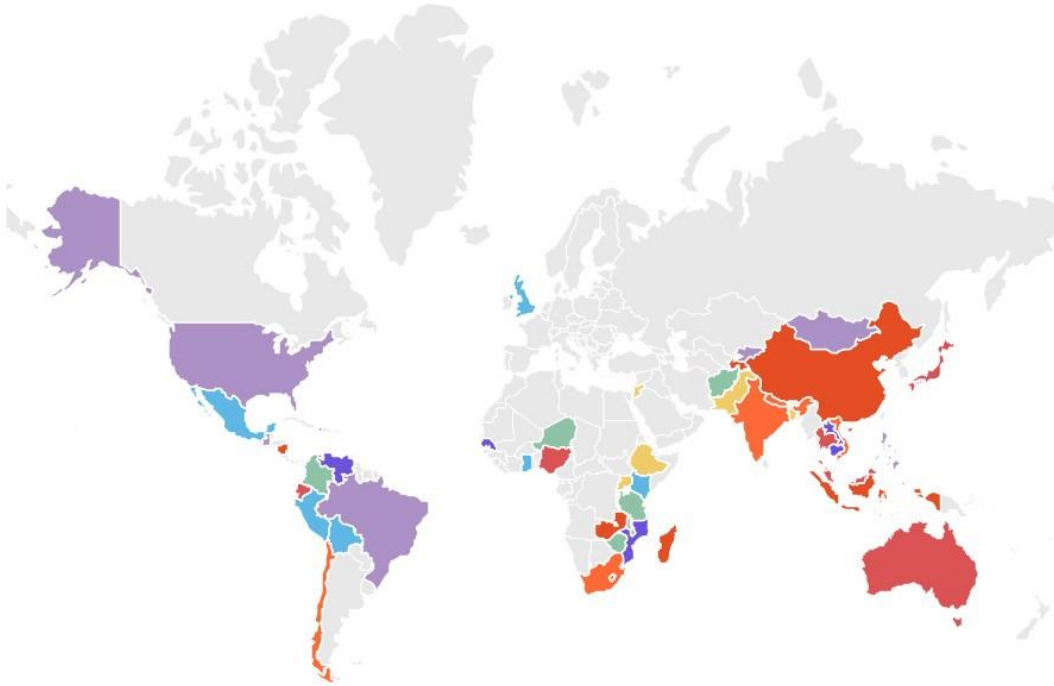
ReACH - The Research Advancement through Cohort Cataloguing and Harmonization

The Research Advancement through Cohort Cataloguing and Harmonization (ReACH) initiative was formally established in 2016. ReACH initiative is funded through a CIHR Operating Grant for the Canadian DoHaD Cohort Registry (2016-2021).

ReACH initiative will provide resources in the form of a comprehensive web-based catalogue and a harmonization platform to optimize and expand the use of Canadian pregnancy and birth cohorts data and biological samples.

Figure 14. Homepage of Research Advancement through Cohort Cataloguing website
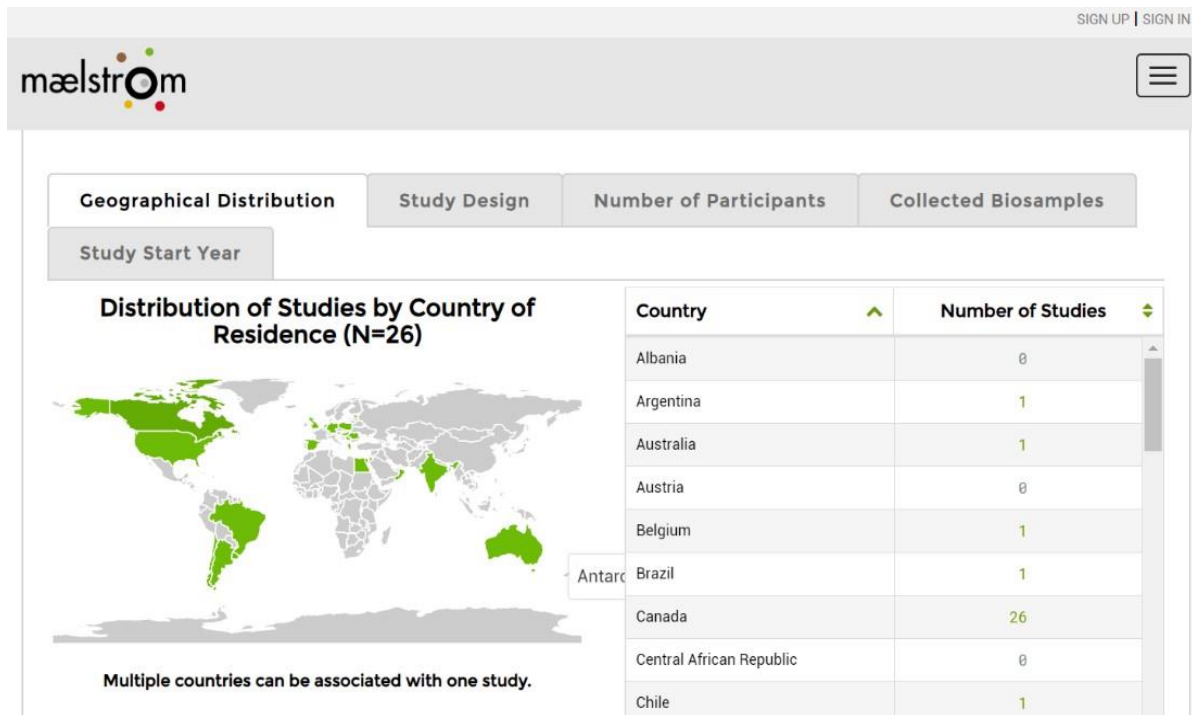
The Consortium of Health-Oriented Research in Transitioning Societies

The Consortium of Health-Oriented Research in Transitioning Societies, encompassing 5 of the largest birth cohorts located in low- and middle-income countries (Brazil, Guatemala, India, the Philippines, and South Africa), with the fundamental objective of providing high-quality scientific data on the early origins of chronic diseases and human capital, has evaluated data related to approximately 22,840 children [Richter et al. 2012].

B. Step 2: NASCITA (NAscere e creSCere in ITAlia) a new birth cohort

B.1. The protocol

B.1.1 Background: Nurturing care

Childhood development is a maturational process resulting in an ordered progression of perceptual, motor, cognitive, language, socio-emotional, and self-regulation skills. The acquisition of skills throughout the life-cycle, therefore, builds on the foundational capacities established in early childhood. [Black et al. 2017]. Multiple factors influence the acquisition of competencies and skills, including health, nutrition, security and safety, responsive caregiving, and early learning. All are necessary for nurturing care [Black et al. 2017; Lancet's Series 2016]. Nurturing care reduces the detrimental effects of disadvantage on brain structure and function which, in turn, improves children's health, growth, and development [Black et al. 2017; Meuter et al. 2015]. Nurturing care is characterized by a home environment that is sensitive to children's health and nutritional needs, responsive, emotionally supportive, and developmentally stimulating and appropriate, with opportunities for play and exploration and protection from adversities [Black et al. 2017; Singla et al. 2015]. Nurturing care extends beyond families to include community caregivers for families [Black et al. 2017; Lancet's Series 2016; Meuter et al. 2015; Singla et al. 2015; Bellman & Vijeratnam 2012]. The environmental, social, economic, political, climatic, and cultural contexts can therefore affect nurturing care and early childhood development. Infancy and childhood are characterized by rapid growth and development, and are considered critical periods of development in life that strongly contribute to health status, well-being, and behaviour across the

lifespan [Lancet's Series, 2016]. Many common diseases and challenges in adult life can be traced back to early childhood [Black et al. 2017; Barouki et al. 2012].

B.1.2 The Italian context

The heterogeneity of the population in Italy is increasing, and sociodemographic and factors (e.g., in education and migrant status) associated with health disparities have been increased [Bonati et al. 2005; Landi et al. 2018]. In this context to adequately describe public health in Italy, epidemiological studies enrolling participants from all population groups and settings are therefore needed. Although Italy has a public, universal healthcare system that should pose no legal or financial barriers to subgroups of the population, considerable health inequalities exist [Corsello et al. 2016]. Differences arise from differences in factors such as health behaviour, exposure, environment, genes, etc. Life-course approaches show that a considerable part of these inequalities is determined by exposure, health status, and development in utero and early childhood [Black et al. 2017; Barouki et al. 2012]. Moreover, in early childhood, children are particularly vulnerable to the influence of different factors and their interactions. While this fact is well documented, underlying mechanisms remain unclear. It is still poorly understood how specific social factors, socioeconomic status, living conditions, parental and stakeholder care, and attitudes act on the well-being of children or in creating health inequalities among children. Moreover, interactions between these factors need to be investigated [Pillas et al. 2014; Andrea et al. 2017; Christian et al. 2015].

As well described in the introduction, birth cohort studies are a powerful study design for medical and social research because they are designed to observe the

impact of early exposures prospectively and at multiple time points during child development [Lawlor et al. 2009]. Several birth cohort studies have been carried out [Larsen et al. 2013], also in Italy [Richiardi et al. 2018; Farchi et al. 2014], with different aims and sizes.

The overall aim of the NASCITA study (NAscere e creSCere in ITAlia) is to improve the understanding of the health status of Italian children early on and how it is affected by social and health determinants. Like many other cohorts, it will address multiple research questions [Richiardi et al. 2018; Farchi et al. 2014]. The findings will add important evidence, in terms of epidemiological data, for the development of specific prevention measures and interventions to improve the health status of children, in particular more vulnerable ones.

B.1.3 Hypothesis and significance

We hypothesize that:

• differences due to environmental, sociodemographic, and parental determinants, as well as to child characteristics and physician attitudes, exist between geographic areas in a population's health and the use of health resources in the first few years of life;

• differences exist in the appropriateness of care provided by the National Health Service at different levels (regional, local, family pediatrician);

• differences exist in parental attitudes toward the recommendations concerning children's health care and these differences may be a determinant of child development and well-being and health resource

  utilization;

- the existing differences between locations in the opportunities for children to access educational/ socialization experiences (e.g. day-care centers) may have an impact on development.

B.1.4 Aims

The main aim of the NASCITA cohort is to evaluate physical, cognitive, and psychological development, health status and health resource use during the first six years of life in a group of newborns, and to assess associations between factors. The specific research topics are:

- the relationship between child development and the domains that affect nurturing care during the preschool period: health (disease prevention and treatment), nutrition (breastfeeding and dietary approach), safety and security (care and early intervention for vulnerable children), responsive caregiving (caregiving routine), and early learning (home opportunities to explore and learn);

- the association between the well-being of children and parental adherence to the recommendations for better child care and development;

- the potential factors influencing child well-being and growth and development, including the acquisition of competencies;

- the differences between geographical settings in educational and socialization opportunities available for young children and in the care provided by the family pediatricians and by the National Health Service for the same needs.

B.2. Methods

B.2.1 Study area and setting

Italy is located in southern Europe and comprises the long, boot-shaped Italian peninsula, the southern side of the Alps, the large plain of the Po Valley and some islands including Sicily and Sardinia. Almost 40% of the Italian territory is mountainous, and there is a coastline of 7600 km on the Adriatic Sea, Ionian Sea, Tyrrhenian Sea, Ligurian Sea, Sea of Sardinia and Strait of Sicily. Italy is subdivided into 20 regions and is further divided into 14 metropolitan cities and 96 provinces, which in turn are subdivided into 7960 municipalities. A gaping North-South divide and can be noted by the huge difference in income between the northern and southern regions and municipalities [Eurostat 2017]. Twenty-two geographic clusters were identified as representative of the country based on locations and socio-economic characteristics and administrative divisions, using the National Statistics Institute definitions for each town/city [ISTAT 2020].

See Figure 15 for the geographical distribution of the NASCITA cohort. Pediatricians and newborns of all the 22 identified clusters have been involved in the study.

Figure 15. Geographical distribution of NASCITA birth cohort

Italian healthcare is provided free or at a nominal charge through a network of Local

Health Units (LHU). Each LHU consists of a number of healthcare districts, which are

population-based territorial entities that aggregate different municipalities. Every

Italian resident is registered with a family (pediatric or general) practitioner.

Children are assigned to a pediatrician until they are 6 years old; afterward, the

parents can choose to register a child with a general practitioner. All adolescents

>13 years old are assigned to a general practitioner. In Italy, there are about 7500 family pediatricians, for an average of 450.000 births/year [Corsello et al. 2016]. About 60 newborns/year are therefore assigned to each pediatrician. All children are

scheduled 7 well-child visits during their first 6 years of life (within 45 days of life and at 3, 6, 12, 24, 36, and 72 months of age). This list includes the recommended age for each well-child visit by the family pediatrician to ensure necessary preventive care, monitor a child's growth and development, and establish a relationship between the child and his/her parents and the pediatrician.

B.2.2 Study design

NASCITA is an ongoing, dynamic, prospective, population-based birth cohort study. From the start of 1st April, 2019 newborns will be continuously included in the study for (at least) an entire one-year period chosen by each participating family pediatrician and will be followed prospectively until at least the age of 6years. Given the ongoing character of the study, no maximum number of inclusions has been set.

B.2.3 Participants characteristics

The study population of the NASCITA cohort study consists of all Italian children born during (at least) one year starting from the 1st April 2019, who will be followed by participating pediatricians until the age of 6 years and whose parents agree to participate. Data on all newborns, including those with special conditions or disabilities, e.g., congenital malformations, will be collected and reported. The

77.

characteristics of the population with special condition will be evaluated separately in the analyses and a differential report will be produced.

B.2.4 Inclusion and exclusion criteria

The inclusion criteria for participating in NASCITA are:

• To be born in Italy.

• Date of birth > 1ˢᵗ April 2019 or during the period chosen by each pediatrician participating in the cohort study. That, in any case, could not be previous of this data.

• Parents' consent to participate signing the informed consent.

Exclusion criteria:

• Children born outside Italy

• Children whose parents do not agree to participate, or decide to withdraw, will be excluded from the study.

The recruitment embedded in Italian pediatric primary care practice. The coordination center has collaborated over the years with a network of hundreds of family pediatricians, as documented by numerous collaborative publications [Clavenna et al. 2014; Piovani et al. 2014; Cazzato et al. 2001; Nova et al. 2008], which represents the first interlocutor to whom we proposed participation in the study. The basis of this network is the national Pediatric Cultural Association (ACP), with around 2000 members consisting mainly of family pediatricians.

To have as large a sample as possible we therefore used the already existing network to begin the first identification of the locally representative pediatricians, who were then asked to identify additional pediatricians, not necessarily belonging to the ACP, in their areas for participation. Other pediatric scientific societies and

associations have been contacted to expand collaboration and the number of participating pediatricians. In this regard, detailed information concerning the study will be disseminated through national pediatric journals and internet-based resources to increase recruitment. Recruitment was based on the voluntary participation of interested by pediatricians who, however, can guarantee seven years of professional activity so that they can follow the enrolled newborns for the whole study period. This approach to enrolling pediatricians can be defined as a mixed-method using also non-probability sampling techniques (convenience and purposive sampling) applied to choose a sample of subjects/units from a population [Palinkas et al. 2015].

B.2.5 Pilot phase

The already existing network of ACP members was contacted to begin the first identification of the locally representative pediatricians. Ideally one for each region. The project was firstly discussed with the president of the ACP. A group of family pediatrician participated in the pilot phase in which examples of case report forms were discussed and tested. In this phase was also tested the time needed to fill the forms. The time was recorded by each participant and difficulties or doubts were reported to the coordinating centre. The participants in the pilot phase assured the coordinating team that the data collection was feasible.

B.2.6 Recruitment

There were double steps of recruitment one dedicated to the family pediatrician and one to the newborns.

Pediatrician recruitment: Firstly, regional coordinators were identified, contacted and trained. Then they were asked to identify additional pediatricians, not necessarily belonging to the ACP, in their areas for participation. Other pediatric scientific societies and associations have been contacted to expand collaboration and the number of participating pediatricians. In this regard, detailed information concerning the study will be disseminated through national pediatric journals and internet-based resources to increase recruitment.

Then we asked to start the recruitment of the newborns. Pediatricians could choose independently when to start the recruitment within a period comprised between the 1st April 2019 and the 30th September.

Newborns recruitment: Recruitment of the newborns (and their parents) take place during the first routine well-child visit scheduled for all newborns within their first 45 days of life at the office of the pediatrician assigned to them by the LHU to which they belong. Parents received oral and written information about the purpose and methods of the study and have been invited to participate. If they agree to participate, they have been asked to sign an informed consent. Recruitment of newborns will begin in April 2019.

B.2.7 Study population size

The NASCITA cohort is sized to have enough power to study relatively common child exposures and outcomes. Table 3 reports the national prevalence of certain health characteristics of Italian children and the expected number of cases for different enrolling scenarios to obtain a minimum number of participants that would permit all these characteristics to be sufficiently represented.

The aim is to recruit no less than 5000, and hopefully at least 10,000, newborns with complete information collected throughout the study. We hypothesize that, given the fact that the data collection is based on routine visits by the pediatrician, attrition in NASCITA will be irrelevant for at least the first two years. Considering the previous experience of other Italian cohorts, NINFEA [Richiardi et al. 2019] and PiccoliPiù [Farchi et al. 2014], we estimate a 20% loss to follow-up after the first two years. With an expected minimum of 5000 newborns, representing about 1% of the newborns in Italy, and with an estimated 20% loss to follow-up, the resulting sample size of 4000 children will still give NASCITA enough power to study common childhood exposures and outcomes [Farchi et al. 2014]. With the parents' consent, data on children withdrawing after 12 months of age will be considered in the analysis for the relevant time period of participation (e.g. rate of exclusive breastfeeding, reading out loud, SIDS prevention, etc.). Data will be deleted upon parents' request.

Table 3. National prevalence of certain health characteristics of the Italian children and the expected cases for different enrolling scenarios in the NASCITA cohort study

Characteristics	Italian prevalence (%)	5.000 enrollments (n°)	10.000 enrollments (n°)	15.000 enrollments (n°)
Sex (% male)	51.3	2565	5130	7695
Gestational age at birth				
• < 37 weeks	6.9	345	690	1035
• 37–40 weeks	92.3	4615	9230	1385
• > 40 weeks	0.9	45	90	135
Twins/multiple birth	1.7	85	170	255
Live birth rate after medically assisted procreation	2.14	107	214	321
Birth defects	2.0	100	200	300
Language disorders Age 3.5 years	7.5	375	750	1125
Maternal smoking during pregnancy	7	350	700	1050
Breastfeeding (exclusive)				
• Until age 6 months	42.7	2135	4270	6405
• 6–12 months	5.5	275	550	825
Parental history of atopy	22–37	1100–1850	2200–3700	3300–5550
Eczema prevalence Age 36 months-5 years	21.0	1050	2100	3150
Wheezing prevalence Age 36 months-5 years	25.2	1260	2520	3780
Overweight prevalence Age 2–6 years	16	800	1600	2400

B.3 Training and tutorial activities

As described above, before the start of the study, family pediatricians have been involved in training activities. Local coordinators have been trained by the research team, and they have been responsible for the training of their peers at the local level. A case report form (CRF) was created in an online form with the contribution of local representatives of family pediatricians and scientific committee participants. During an initial phase (Pilot phase), a group of family pediatricians tested the electronic CRF (eCRF), leading to improvements and adding the necessary questions to achieve an eCRF that would allow a more complete and simple collection of data. The eCRF has been made available online before the start of the enrollment period to let participating family pediatricians familiarize themselves with the information that needs to be collected.

Central and local monitoring of the study have been scheduled with the aim to guarantee follow-up of the infants and the quality of data collected.

B.4   Data collection

Data considered for the basic CRF are part of those routinely collected by the family pediatricians at the 7 standard well-child care visits scheduled for all children during their first 6 years of life, and data collected during each contact with the enrolled children.

In the Italian setting small differences exist in numbers (from 5 to 9) of well-child care visits, to standardize the number of visits in NASCITA we fixed at 7 collections of data requested for all the Italian territory. See Figure 16 for the timeline of data collection, follow-up, and milestones in the NASCITA Study.

In addition to the routinely collected data (basic data) fully descript in the next section, questions were added to allow the project to address specific areas such as nutrition, environment, and nurturing care.

Figure 16. Timeline of data collection, follow up, and milestones in the NASCITA

Study
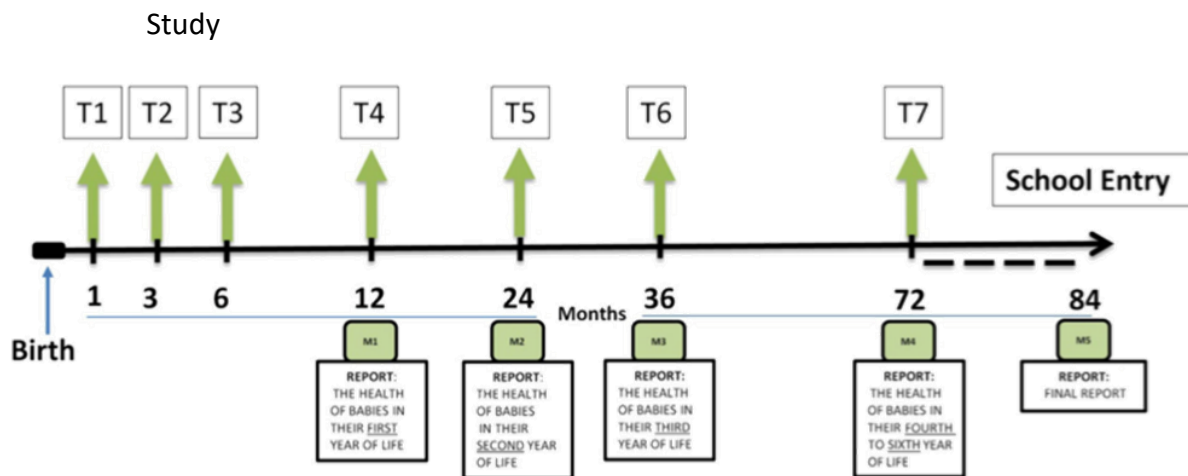
Some questions are already proposed during the seven well-child visits. The eCRFs were consequently structured in a way that will permit us to expand data collection and analysis in these areas in a second phase. In order to enhance the quality of the data, the eCRF includes consistency and range checks to prevent internal inconsistencies, although the continuing review of collected data is guaranteed by the coordinating centre and, in case of inconsistencies, pediatricians are contacted. The administrators of the website (the coordinating centre) can view the completed forms also in a graphic format that is periodically updated.

B.4.1 Baseline data

The baseline data collected during the first visit, which should happen within 45 days of life of the newborn, parents are asked about parental medical history, characteristics and lifestyle, indoor and outdoor environment, and circumstances during pregnancy and around birth. Pregnancy and perinatal data are collected also through hospital discharge documents following delivery.

All the baseline data collected, which includes also retrospective data concerning information on the mother and the family and the delivery, are important to gather information about the broader aspect of the child's health.

In detail, we collected subjective information concerning the family history from parent interviews but also chart and medical records. Past Medical History; medications in pregnancy and allergies from mother or father. History related to the *current need* for care or treatment were also collected.

B.4.2 Follow-up and outcomes

The primary outcomes of the study are measures of the health of the newborns/children from birth until (at least) the age of 6 years. Health outcomes of children aged 0–6 years will cover different fields including: physical development, mental/cognitive development, nutrition and allergies, environmental exposures, and preventable infectious diseases.

The physical exams "Head to Toe assessment" (mostly objective information) includes information of:

• Vital Signs (Es: pulse).

• Inspection, Head, Ears, Eyes, Nose, Throat, and colors of lips and moistness.

• Auscultation.

• Percussion.

• Palpation.

• Neurological evaluation (developmental status...).

• MSK (motor skills, some neuro).

• Genitalia.

Some other Subjective information reported by parents is collected.

Table 4 provides an overview of data sources and collection at the different follow-up stages.

Table 4.   Overview of outcome measures collected by follow up stage

Phase	Measurements
Baseline, T1 (within 45 days of life)	Demographic, socioeconomic, and health status of parents, details of pregnancy and perinatal routine, well-being of newborn, breast feeding/breast milk substitutes, living and social environment. Metabolic screening (notification). Anthropometric evaluation and physical examination. Immunization coverage. Infectious diseases. Dental health.
T2 (3 months of life)	Anthropometric evaluation and physical examination. Breast feeding/breast milk substitutes, child health, sleep. Hip ultrasound (notification). Vaccines (notification). Infectious diseases. Dental health.
T3 (6 months of life)	Anthropometric evaluation and physical examination. Neuromotor development assessment (Brazelton). Boel test. Breastfeeding status/Nutrition Vaccines (notification). Infectious diseases. Dental health.
T4 (1 year of life)	Child health, physical and psychological development, sleep, language development. Vaccines (notification). Breastfeeding status/Nutrition. Neurodevelopment evaluation. Infectious diseases. Dental health.
T5 (2 years of life)	Physical and cognitive development of child, child health, sleep, language development, and spoken language at home, media use. Language development. Breastfeeding status/Nutrition. Neurodevelopment evaluation. Vaccines (notification). Infectious diseases. Dental health.
T6 (3 years of life)	Anthropometric evaluation and physical examination. Child nutrition. Hearing check. Language development. Neurodevelopment evaluation. Vaccines (notification). Infectious diseases. Dental health.
T7 (4-6 years of life)	Physical and cognitive development of child, child health. Child nutrition. Neurodevelopment evaluation. Visual acuity examination. Vaccines (notification). Infectious diseases. Dental health.

The analysis plan for the NASCITA cohort entails the investigation of several exposures and outcomes to address numerous research questions. The main independent variables that will be tested are:

- Maternal/paternal age. Education level. Employment. Marital status. Parental health status. Parental lifestyle habits (smoking, alcohol). A few examples of the dependent variables are Vaccination in pregnancy. Folic acid prophylaxis.

- Birthweight. Duration of breastfeeding. Reading out loud. Sleep position. Overweight and obesity. Neurocognitive development. Nursery school attendance.

- Prescription prevalence and appropriateness.

A few of these variables will be tested as both independent and dependent variables based on the kind of analyses (e.g., reading out loud will be the dependent variable while testing the influence of maternal age or educational level, but will be considered an independent variable when possible factors influencing children's development are tested).

Examples of the NASCITA study's research questions are:

- the relationship between mothers' age, education level, and geographic area (independent variables) and vaccination in pregnancy (Influenza and Tdap vaccines) (dependent variable);

- the association between maternal smoking in pregnancy (independent variable) and birth weight (dependent variable);

- the relationship between pregnancy, perinatal, and newborn growth

characteristics and occurrence of adverse outcomes (i.e., obesity, hypertension, wheezing, eczema, hay fever, and asthma);

• the relationship between parents' educational level (independent variable) and duration of breastfeeding (at discharge from hospital and at 3 and 6months) (dependent variable);

• the relationship between parents' educational level (independent variable) and children's weight and BMI/ percentage of overweight/obese status (dependent variable);

• the association between lifestyle factors and health inequalities and the trajectory of health in the preschool period;

• the association between geographical setting and nursery school attendance;

• the association between geographical setting and quality of care in terms of prevalence and appropriateness of drug prescriptions.

In all of the analyses, the effect of the geographic and environmental setting will be evaluated. This type of general objective, involving numerous research questions, is similar to the goals of two Italian cohorts, the NINFEA [Richiardi et al. 2019] and the PiccoliPiù [Farchi et al. 2014], as stated in their protocols.

Some populations will be evaluated separately and included in special subgroup analyses such as migrant newborns, very low and low birth weight newborns.

B.4.3 Statistical analysis

Categorical variables will be summarized using proportions and associations tested using chi-square or Fisher's exact test, where applicable. Continuous variables will be summarized using means and standard deviations for normally distributed data,

while skewed data will be summarized using medians. One-way ANOVA (F-value) will be used to test the difference of means for normally distributed continuous variables and the Mann-Whitney U test for skewed continuous variables. Statistical significance will be evaluated using a 95% confidence interval and a two-tailed p-value of <0.05. Multivariate analyses will also be performed based on the study designs and outcomes to be evaluated.

The ad-hoc analysis will also be performed based on the different research questions.

B.5   Organization framework

The coordination of the NASCITA study is provided by the team of the Laboratory for Mother and Child Health of the Mario Negri Research Institute that integrates different expertise and competence with a long-standing experience in multicenter clinical research. The coordinating center has multiple tasks: design and wrote the draft of the project, create the family pediatrician network, also carry out data collection, storage, management, and analysis.

A network of local contacts (contact person per area) between pediatricians has been set up so that each node, representative of a setting, will act as a bridge to the coordinating center in conducting the study. An additional group of individual pediatricians has been identified to act as specialists in their area of expertise, e.g., environment, nutrition, and neurodevelopment.

An independent scientific committee consisting of representatives of different disciplines and realities (including laypeople) that monitor the development and results of the project.

B.6. Ethics and dissemination

The study was approved by the Fondazione IRCCS Istituto Neurologico Carlo Besta's Ethics Committee (6 February 2019, Verbale n.59). In the Appendix B I have reported the list of documents needed for the application. A consent form for participation has been signed by the pediatricians upon their first access to the web site. A paper consent form will be signed by parents at the first visit. This form includes the consent to data collection at each contact with the pediatrician during the six-year study period (first 6 years of the child's life). The filled-in consent form will be stored by the pediatrician for ten years. Withdrawal from the study is guaranteed at any time both to pediatricians and parents. When consent is withdrawn, the child's data collected up to that point will be kept in the analyses, but no further data will be collected. Standard procedures for the protection of confidential individual information will be applied according to national and international ethical recommendations and guidelines as well as national legal regulations. Data will be pseudonymized and all analyses will be conducted with fully anonymized data sets. A newsletter report will periodically be sent to the pediatricians and uploaded on the web site. During the study, different tools will be used to update the participating families.

Ad-hoc information material will be created and will be disseminated to families through newsletters and the website. Collected data will be periodically analyzed according to the aims of the project, and findings reported to laypeople and the scientific community.

The coordinating centre will provide the information, but the pediatricians will also be able to provide the families with information deriving from the cohort during

their visits. When the enrolled children reach the age of 6years, if not decided otherwise in the meantime, their files will no longer be updated but will be kept for another 10 years in the database.

NASCITA proposes to be a resource for the research community, so data will be available to public researchers outside the NASCITA research group upon request for collaborative research initiatives, after approval by the scientific committee.

B.7   Application of study results

The information gathered by the NASCITA birth cohort study will be valuable for child health care and public health policymaking. Information concerning the children will be collected at specific ages that coincide with routine contact moments, so findings from NASCITA that can be translated into parental advice or other preventive measures can directly be incorporated into routine protocols and reach a large group of children and their parents at once. Furthermore, study results on (modifiable) risk factors, disease prognosis, and medication use may also be relevant for family pediatricians.

Moreover, NASCITA findings may aid policy and decision-makers, who need scientific evidence to develop and implement prevention and intervention strategies. NASCITA will progressively build on a database containing policy-relevant information on a broad range of determinants and health outcomes that may be beneficial in responding to certain public health issues. NASCITA results may also contribute to the evidence towards the need to build up a permanent national observatory on child health and development.

B.8   Strengths and limitations of this study

NASCITA is entirely embedded in the child health care practice foreseen by the National Health Service and provided by family pediatricians. Recruitment and follow-up coincide with routine contact moments, so broad participation and follow-up rates are expected. Collaboration with other cohorts is foreseen. The NASCITA cohort data will be linkable and integrable with other data sources, such as routinely collected health data or as part of future scientific collaborations. High participation rates would allow an appropriate description and evaluation of all the different national-territorial clusters. Moreover, NASCITA will provide opportunities to initiate new, experimental studies in subgroups of the cohort, and will contribute relevant information on determinants and health outcomes to policy and decision-makers. Since the loss to follow-up is always a cause for concern in cohort studies and should be minimized, efforts have been made to establish a close and trust-based relationship with all participants. These efforts involve the creation of ad-hoc information material, the website, and newsletters to keep in touch with the study participants and to apply health promotion measures within the cohort. The estimated 20% loss to follow-up would, in any case, lead to a sample size that is large enough to be able to study common childhood exposures and outcomes. With the parents' consent, data on children withdrawing after 12 months of age will be considered in the analysis. One of the proposed benefits of distributing research questionnaires online, in contrast to postal methods was cost-effectiveness.

A limit of the NASCITA study (as with any observational study) is the possibility of selection bias in the study population. The pediatricians recruited represent a cooperative sample, not a random sample, and should not be considered to be

representative of the population of family pediatricians. The pediatricians, for example, could be more sensitive to better care practices or recommendations and could influence the parents accordingly, promoting, for example, reading out loud to children. The target population of the study, however, will be the newborns (and their families) who are assigned to the pediatricians by the LHU based on places that have been freed up with those pediatricians reducing. The rising number of migrant patients means increasing potential language barriers in the communication between a healthcare practitioner and a patient who speaks a different language, and miscommunication may occur in healthcare settings [Singla et al. 2015]. Non-italian speaking parents, in particular recent immigrants, may decide not to participate in the study and this may create a minimal selection bias.

C. Step 3: Engagement and Dissemination activities of NASCITA project

An Engagement Strategy, essential to increase the number of participants and to achieve the expected number of enrollments [Lucas et al. 2013] has been implemented for family pediatricians and families in NASCITA project.

Within the Engagement activities undertaken we:

• Developed and maintained the study web-site where it is also present a space for feedback, questions and requests.

• E-mail alerts and bulletins to interest list (e-mail list). The email list has been regularly "cleaned" to ensure that any redundant e-mail addresses are removed and that family pediatricians not interest in the study were removed.

- Social media (Facebook) have been created to communicate directly and for sharing information.

- Presentations at conferences and to smaller groups (by request).

- Conference and Journal articles.

Within the dissemination activities that have already be taken, we:

- Regularly provide information on a wide range of topics the families taking part in the studies: Family circumstances and experiences, Child health, development and Parenting not necessarily linked to the cohort's main topic.

- Writing Newsletter dedicated to family pediatricians.

- Targeted briefings to particular groups of family pediatrician

- Presented the project at conferences and events.

- Publication of articles.

C.1   The Web portal

A specific web portal for the NASCITA cohort study was developed (*hiips://coortenascita.marionegri.it*), with reserved sections for the coordinating centre, registered users, and participating pediatricians. The web portal was built to permit data collection and to provide findings and other information during the study period for parents and pediatricians, also with the use of graphics for the analyses and data collected, based on a successful approach already reported by the coordinating center.[Reale et al. 2017; Bonati et al.2019; Zanetti et al. 2019]

Selected sections of the portal have been translated into English.

In Figure 17 are reported the screenshot of the different sections of the web portal.

Figure 17. Sections of the web portal

Area Pediatra

In questa pagina potete trovare materiale informativo per i pediatri relativo alle coorti nascita e ai loro risultati, e informazioni sull'andamento e i risultati della Coorte NASCITA.

Accedi all'area privata

Newsletter

Clicca qui per iscriverti alla newsletter di NASCITA oppure per visualizzare le passate newsletter.

Iscriviti alla Newsletter

Newsletter Precedenti

Buone Pratiche Per Mamma E Papà

La Febbre

Le Vitamine

Le Curve di Crescita

I Vaccini

Allattamento e farmaci

Le Coliche

Parlare di COVID

Link e Numeri Utili

📞 112 Numero Unico di Emergenza

📞 02 66101029 - CENTRO ANTIVELENI Milano

📞 800 88 33 00 - CENTRO ANTIVELENI E TOSSICOLOGIA Bergamo

The information for parents section contains a growing series of cards, created in collaboration between health professionals and parents, that provides evidence-based information on the more common illnesses or problems in young children as well as answers to common questions that parents have on child care. This section

also contains links to useful emergency telephone numbers and useful links. In the pediatrician's general area, newsletters covering the current biomedical literature pertinent to child cohorts are available. In Annex E, the first newsletter was produced.

The website provides also a link to the public website ClinicalTrials.gov where the study has been registered to answer the request on data sharing (Figure 18) [NASCITA, 2019].

Figure 18. NASCITA in ClinicalTrials.gov
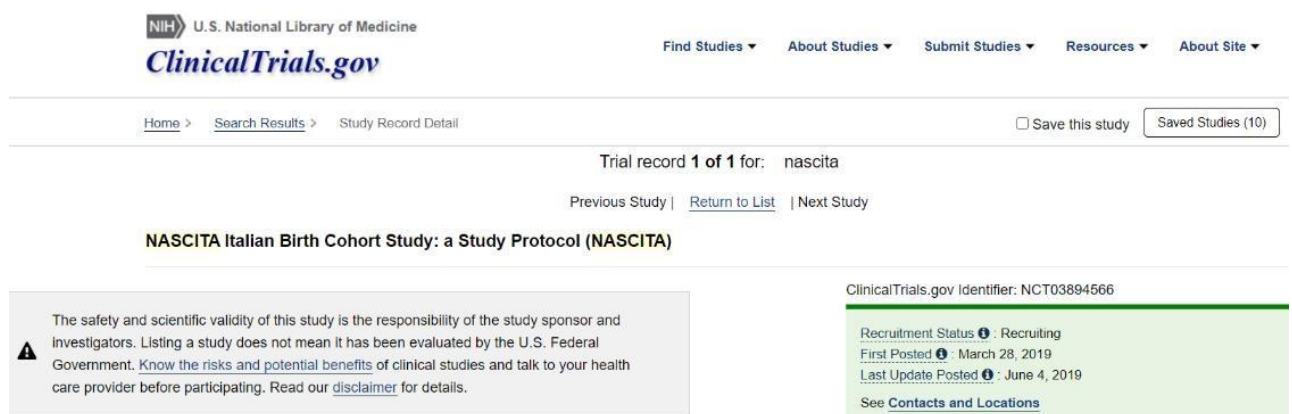
C.2 Family pediatricians area: The Electronic case report form

A specific web portal for the NASCITA cohort study was developed to collect data, through a web-based form, and to provide findings and other information during the study period, also with the use of graphics on the analyses and data collection based on a successful approach already reported by the coordinating centre.

To facilitate the pediatricians' input of data for the NASCITA study, as well as provide fast and efficient support for any problems or data input doubts, an

electronic case report form (eCRF) was tested and set up (see Figure 19) and includes a "chat" section through which pediatricians can ask for support. The eCRF was structured in a way that will permit data collection to be expanded to more thoroughly cover the additional areas (e.g., nutrition) in a second phase. The eCRF includes consistency and range checks to prevent internal inconsistencies. In any case, data are continuously monitored and irregularities will be resolved through email or phone contact with the family pediatricians participants.

In the private area, each participating pediatrician can access information such as: cohort documents, frequently asked questions, study protocol, and pdf versions of the eCRFs. Pediatricians can also input/modify patient's data, interactive data charts of his/her patients or of those of the entire cohort, including growth curves, and data concerning subsections of the cohort.

Figure 19. eCRF screenshots

Reports will be automatically generated to monitor the recruitment of pediatricians and children. Individual and group reports will also be created for the pediatricians and the scientific committee set up for the study. The administrators of the website (the coordinating center) will also be able to view the data in a graphic format.

C.3 Materials produced

A range of dissemination materials have been produced to date (Figure 20 to 23)

Figure 20. Leaflets
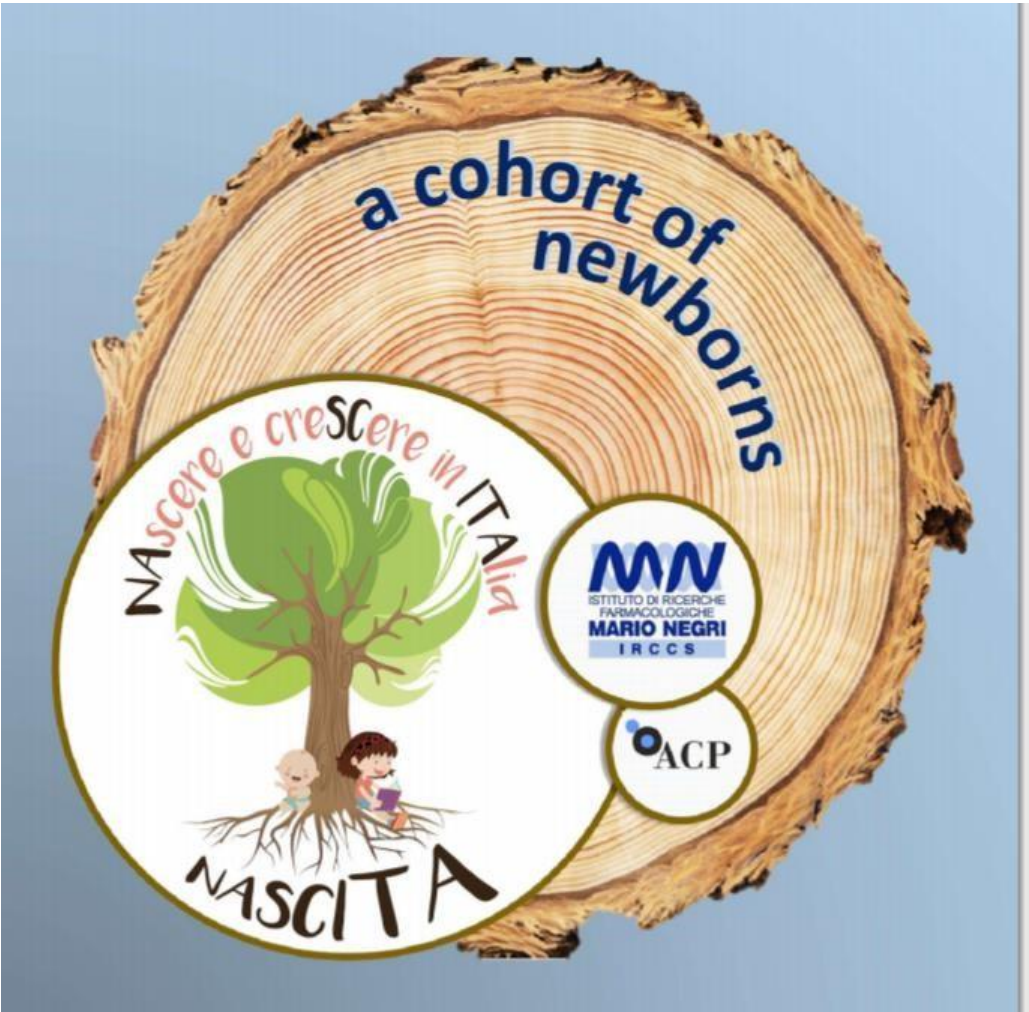
WITH WHOM?

The **newborns**, with the **parents**' collaboration, will be enrolled during their first visit with the **family paediatrician**.

HOW?

Essential prenatal, health, and life-context information will be provided by the parents at the time of their child's enrollment (anamnesis). The postnatal information will be collected by the family paediatricians and will also be provided by the parents at various times during the child's growth.

WHEN?

From birth through the preschool period, with a special focus on the first two years of life.

WHERE?

In Italy: in the North, Centre, and South; along the coasts, in the plains and in the mountains; in the city centres and the suburbs; in urban and rural areas.

WHY?

- To build a national observatory starting from the paediatrician's office.
- To describe, follow up over time, and assess the children's development, growth, and care and educational pathways in the different home and care settings.
- To identify and measure the health needs (also social needs), disorders (e.g. in neurocognitive development, obesity), and diseases (e.g. diabetes, asthma), attempting to identify the possible causes and the interventions to reduce them.

WITH WHICH TOOLS?

With computer based tools that simplify the creation of study material, make participation easier, and allow greater diffusion of the information collected and analysed. More specifically, with a dedicated website containing information on the study status, the results, and the topics addressed by the study, with newsletters, and with dedicated meetings involving family paediatricians and parents.

https://coortenascita.marionegri.it

Figure 21. Conference leaflets
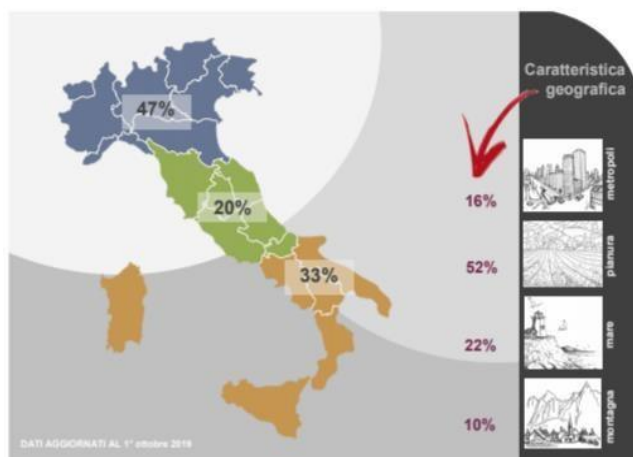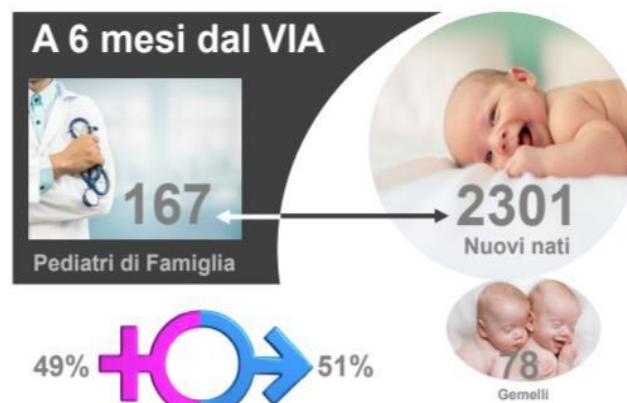
Figure 22. Conference posters and press
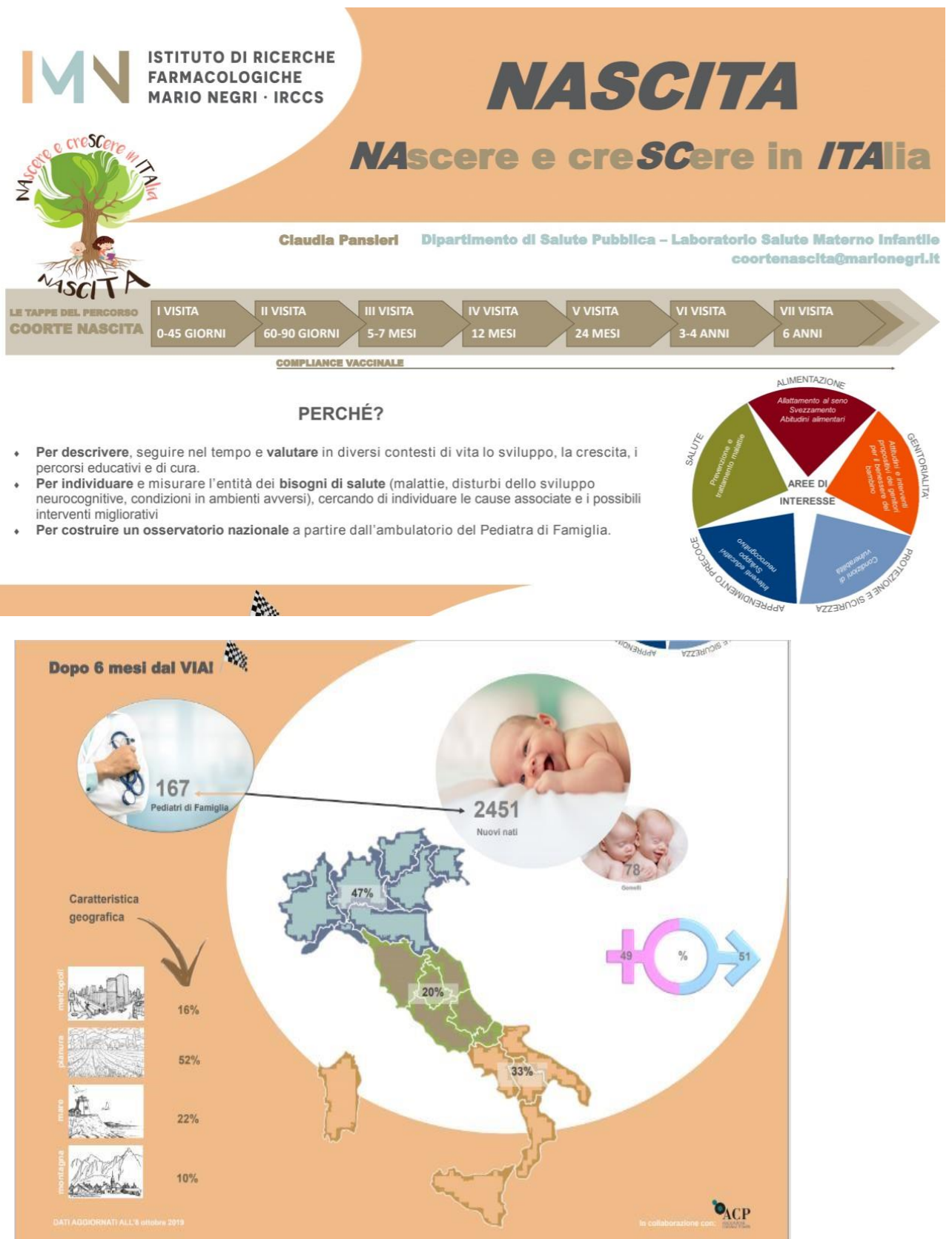
FARMACISTE
Carlotta Franchi
Unità di Farmacoepidemiologia nell'anziano – Dipartimento di Neuroscienze
Daria Putignano
Unità di Farmacoepidemiologia – Dipartimento di Salute Pubblica
Claudia Pansieri
Laboratorio Salute Materno Infantile - Dipartimento Salute Pubblica

#STEMA in the City

L'USO DEI FARMACI DA 0 A 99 ANNI

QUALE RICERCA

FARMACOEPIDEMIOLOGIA ramo dell'epidemiologia che si occupa dell'utilizzo e dell'effetto di farmaci in popolazioni specifiche. Studia le relazioni tra pazienti, malattie e farmaci.

APPROPRIATEZZA PRESCRITTIVA DEI FARMACI si verifica quando essi sono prescritti per patologie per le quali esiste l'indicazione terapeutica nella scheda tecnica e al dosaggio indicato.

PERCHE'?

Per rispondere a quesiti in merito a:
> Efficacia clinica
> Sicurezza
> Qualità delle cure

Agenzie   Servizi   Professionisti   Pazienti

IN QUALI POPOLAZIONI?

> Fragili
> Non rappresentate nei trial clinici
> Più esposte a rischi di presentare reazioni avverse da farmaci

BAMBINI   ANZIANI

AREE E...

ANTIBIOTICI
Appropriatezza d'uso, rischio di antibiotico-resistenza

ASMA
Appropriatezza d'uso e qualità delle cure

EPILESSIA
Percorsi di cura

PSICOFARMACI
Bisogni trascurati/inevasi

SIM-AF
(SIMulation-based technologies to improve the appropriate use of hospitalized elderly patients with Atrial Fibrillation).
- Intervento di formazione basato sulla simulazione rivolto a medici ospedalieri per promuovere l'uso degli anticoagulanti orali nei pazienti anziani ospedalizzati, spesso sottotrattati.
- Bando di ricerca internazionale 2015- Bristol Meyer Squibb-Pfizer.

LAPTOP-PPI
(Evaluation of the effectiveness of a low-cost informative intervention to improve the appropriate prescription of proton pump inhibitors in older people in primary care: a cluster-randomized controlled study).
- Intervento di formazione rivolto a medici di base per promuovere l'uso appropriato dei gastroprotettori nei pazienti anziani.
- Bando della Ricerca Finalizzata 2016 - Giovani Ricercatori finanziata dal Ministero della Salute.

PROGETTI DI RICERCA

NASCITA
per monitorare l'appropriatezza prescrittiva e di uso dei farmaci e delle risorse sanitarie in una coorte di nuovi nati nel corso dei primi 6 anni di vita.

Con la collaborazione di 230 pediatri per 5000 bambini

DALLA RICERCA...

...ALLA DIVULGAZIONE

Lo sai mamma?

Servizio di Informazione sul Farmaci

02-3570319

104.

Figure 23. Spread of information through social network (Twitter and Facebook)
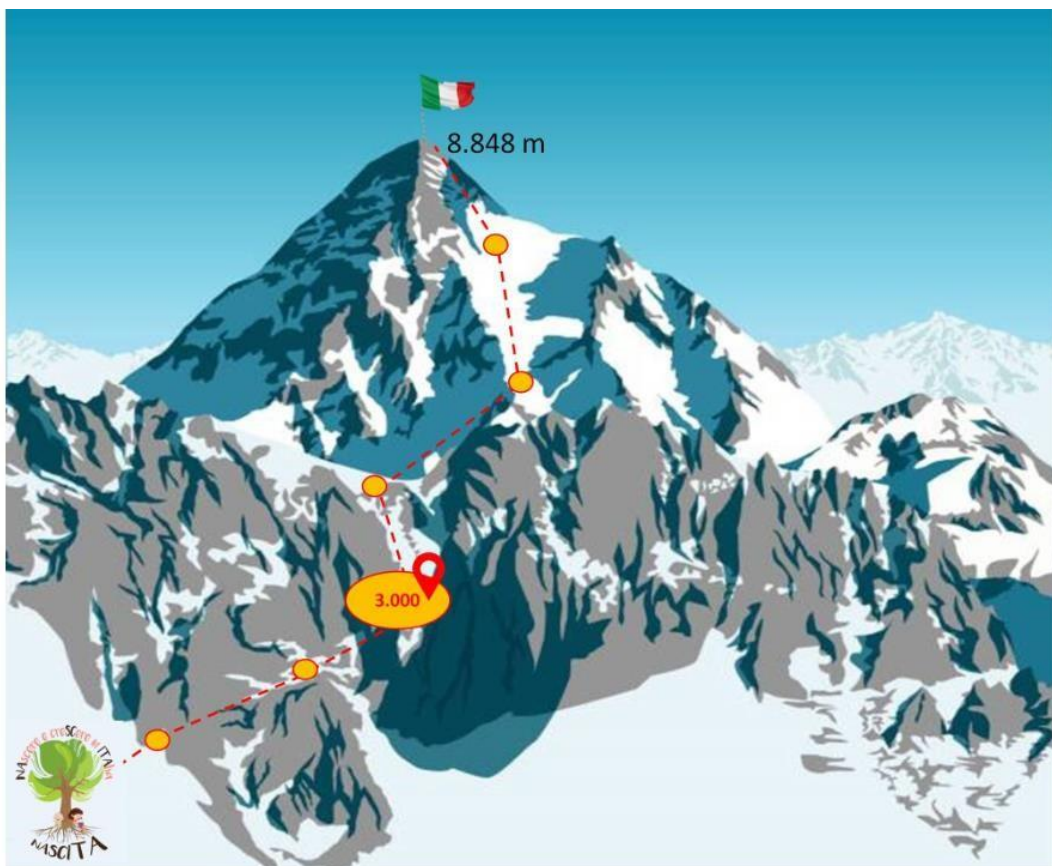
D. Step 4: Study Recruitment Data from NASCITA

D.1 Family pediatricians' enrollment

Enrollment of the family pediatricians participating in the NASCITA cohort began on

January 1st and by September 30th, 2019. As previously described, the pediatrician's

enrollment followed two phases: Initially, we have identified the representatives of each

geographical area within the ACP members. After agreeing to participate,

they were asked to share the invitation to all the ACP members in their area (Figure

24) (Figure 25).

Figure 24. Localisation North Center and South Italy of the ACP members
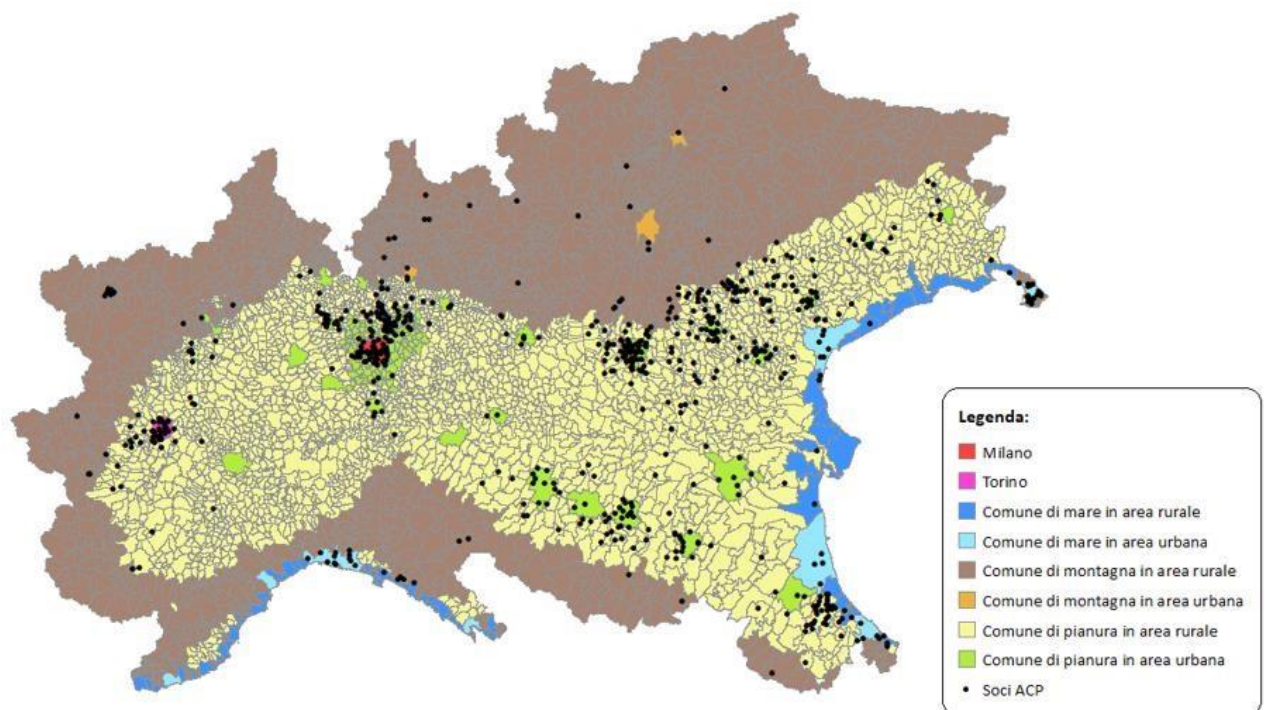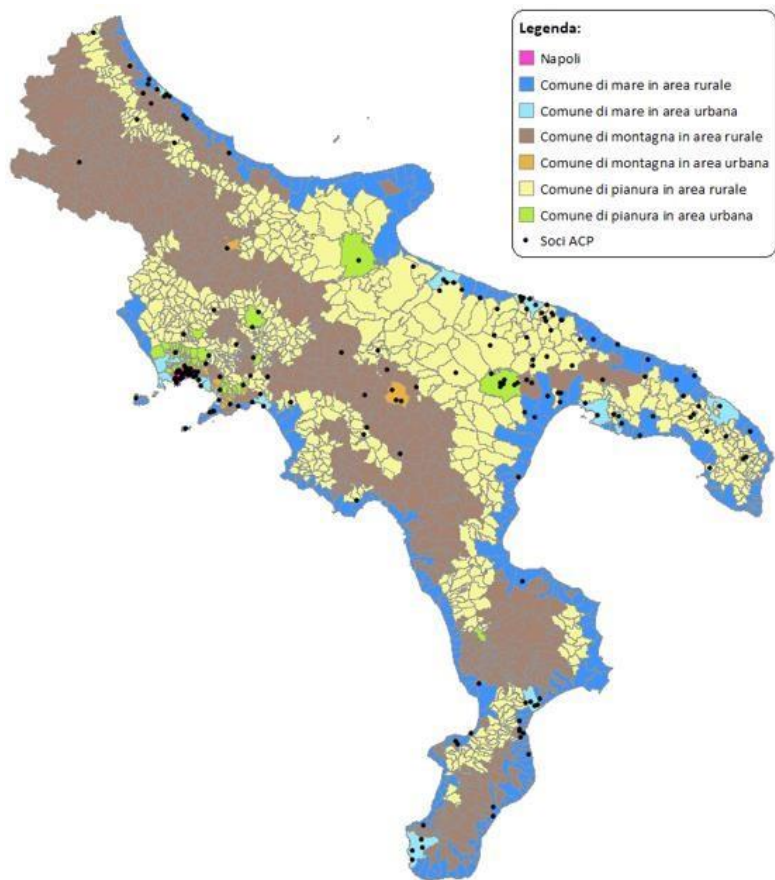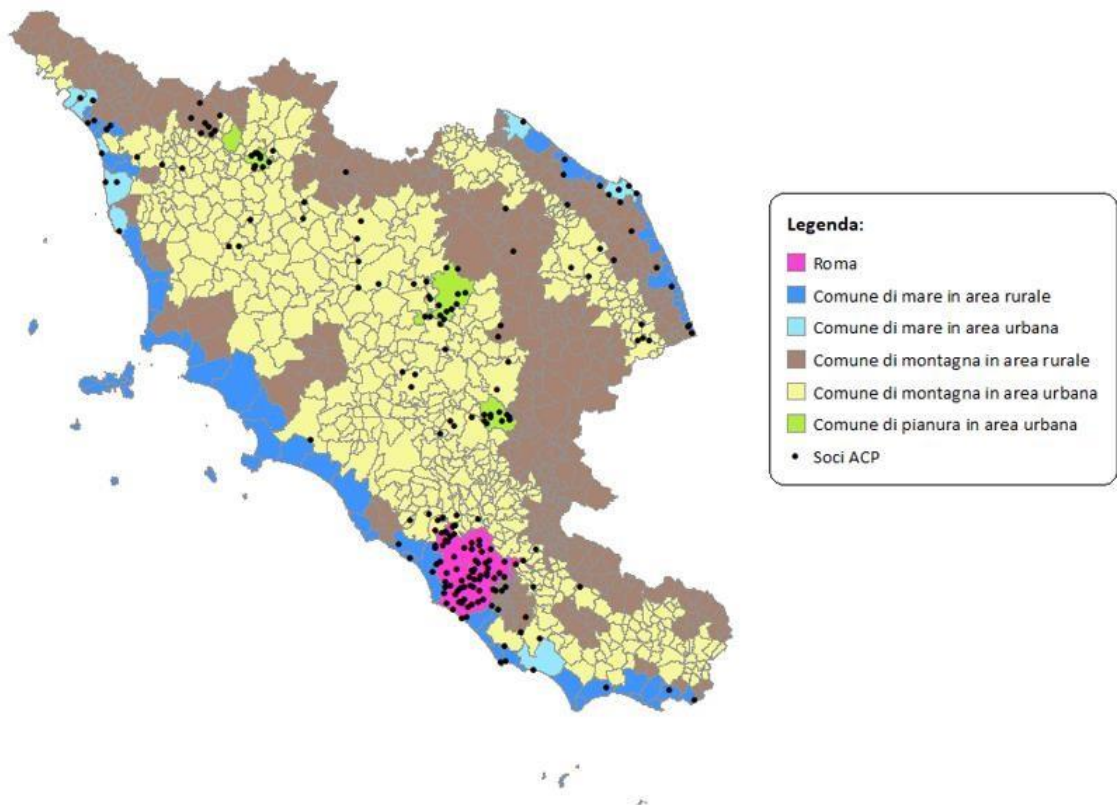
Legenda:
- Roma
- Comune di mare in area rurale
- Comune di mare in area urbana
- Comune di montagna in area rurale
- Comune di montagna in area urbana
- Comune di pianura in area urbana
- Soci ACP

Legenda:
- Napoli
- Comune di mare in area rurale
- Comune di mare in area urbana
- Comune di montagna in area rurale
- Comune di montagna in area urbana
- Comune di pianura in area rurale
- Comune di pianura in area urbana
- Soci ACP

108.
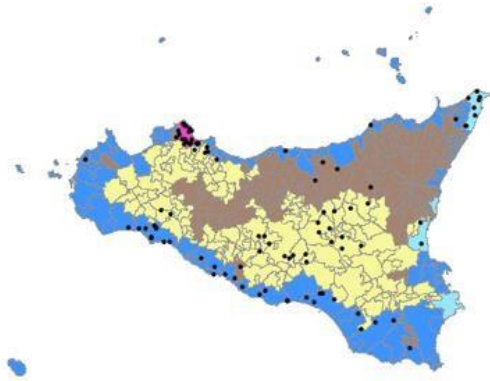
Figure 25. Family pediatricians enrollment strategy
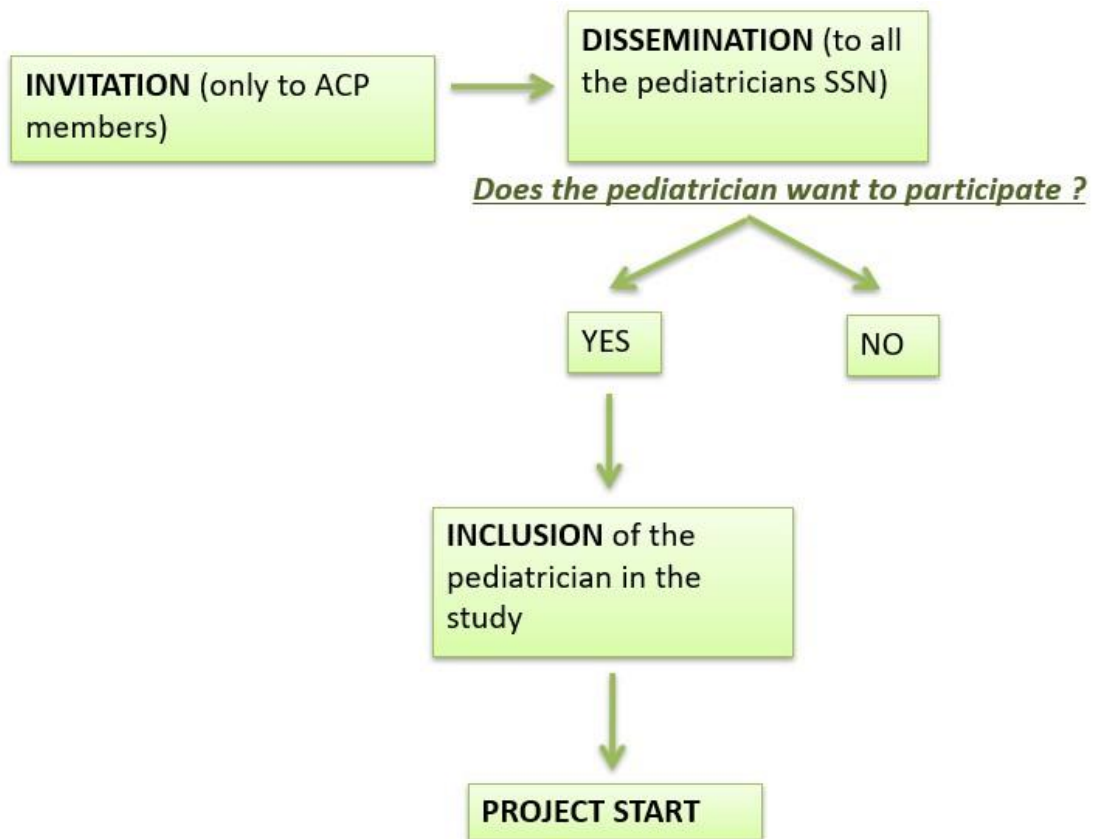
On 29 November 2019, a total of 193/247 requested pediatricians accessed the website and made the preliminary registration. Of these 80.5% practice in the North of Italy, the 81.8% in the center, and 65.6% in the South of Italy.

At the end of July 2020, the number of pediatricians that actively participate in the project include at least one child in the cohort is 160. The pediatricians were distributed throughout Italy, with 82 in the north, 31 in the center, and 47 in the south.

D.2 Newborns enrollment

Enrollment of newborns in the NASCITA cohort began on April 1st, 2019 and by September 30th, after six months, the number of participating pediatricians was 160 and the number of children enrolled 2264 (Figure 26). The children enrolled (51% male) were distributed in the north (46%), center (21%), and south (33%). The number of children enrolled after 6 months represented 24% of those born in 2018 and covered by those same pediatricians. Excluding pediatricians who had enrolled no children, each pediatrician recruited between 1 and 45 babies.

Figure 26. Number of enrolled newborns
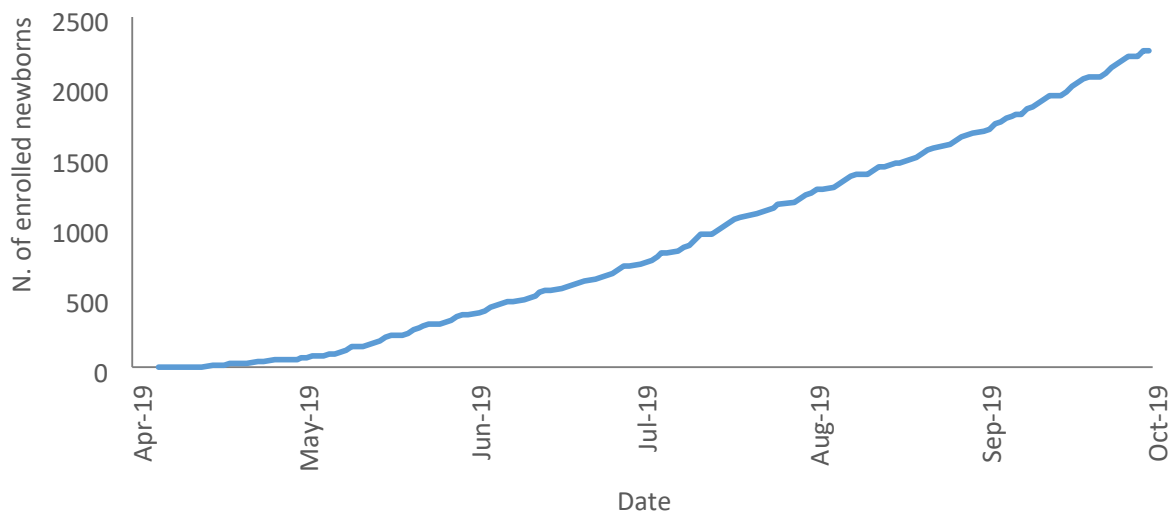
D.3 Preliminary data on family

Most of the mothers (84%) were born in Italy; the three next most common countries were Albania and Romania (2% each), and Morocco (1%). Family size, that included the newborn, ranged from 2 to 10 people, with almost half (48%) of families being made up of 3 people, followed by 38% made up of 4 people. Two-member families represented 2% of the total.

D.4   Preliminary data on pregnancy and labour

Concerning the pregnancies, 86% were, while gestational diabetes (88 mothers), gestational hypertension (38 mothers), and preeclampsia (17 mothers) were the most common diseases in the remaining pregnancies. Concerning the newborns, 3% were born with malformations and 8% had a disease, the 3 most common of which were neonatal respiratory distress syndrome (21 cases), neonatal jaundice (19), and neonatal hypoglycemia (15).

D.5 Preliminary data on some data collected during the first 6 months of life

The following are examples of follow-up data collected during the first three routine visits covered in the first 6 months of the cohort. The anthropometric measures taken during the first visit (held within 45 days of life), showed that weight ranged from 500 to 7000 grams (3792 average), height 40 to 69 cm (52.5 average), and head circumference 26 to 43.5 cm (35.9 cm average). The second routine visit (held within the first 60-90 days of life) collected breastfeeding data, among other information. Considering the children who had already undergone this visit after 6 months of the start of the study, about half (59%) were still being exclusively breastfed. Of the 41% of mothers who were no longer exclusively breastfeeding, a majority (59%) were giving formula milk and 41% breast and formula milk. The weaning data collected during the third visit (held between 5-7 months of life), considering the children who had undergone this visit, showed that over one half (56%) were being weaned, two thirds (63%) of whom in a classic manner and one third (37%) with the baby-led weaning method.

IV. DISCUSSION

Early environments and experiences have an exceptionally strong influence on brain architecture. The basic principles of neuroscience indicate that providing supportive conditions for early childhood development is more effective and less costly than attempting to address the consequences of early adversity later [Black et al. 2017; Campbell et al. 2014]. After birth, experiences play an increasingly important role in shaping the architecture of developing neural circuits so that they function optimally for each individual. Childhood development is a maturational and interactive process, resulting in an ordered progression of perceptual, motor, cognitive, language, socio-emotional, and self-regulation skills (Figure 27) [National Scientific Council on the Developing Child, 2007].

Figure 27. Childhood development: Interconnections
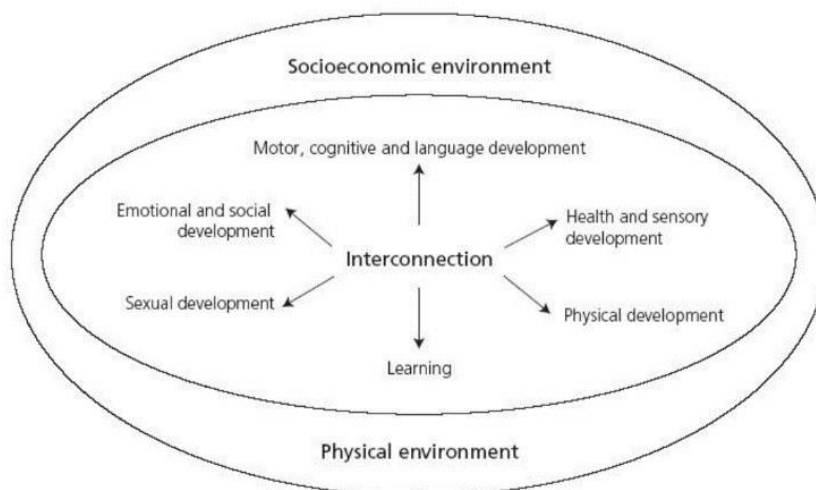
Good health (of both mother and child), good nutrition, good parenting, strong social supports and stimulative interaction with others outside the home all combine to provide the best chance of success. Since neglecting investment in any

one of these areas reduces the value of investment in other areas, investments to improve pre- and post-conception health of the future mother are a crucial input to early childhood development (ECD) [Black et al. 2017; Campbell et al. 2014].

Healthy early child development, which includes the physical, social/emotional, and language/cognitive domains of development, strongly influences well-being, obesity/stunting, mental health, heart disease, competence in literacy and numeracy, criminality, and economic participation throughout life.

The social determinants of health are the conditions in which people are born, grow, live, work and aged. These circumstances are shaped by the distribution of money, power and resources at global, national and local levels. The social determinants of health are mostly responsible for health inequities - the unfair and avoidable differences in health status seen within and between countries.

(hiips://www.who.int/social_determinants/sdh_definition/en/)

Child health is also determining by the parenting resources (the attachment, guidance, and supervision accorded to children, as well as the quality of the schools, neighbourhoods, and hospitals surrounding them). Such early efforts promote schooling, reduce crime, foster workforce productivity, reduce teenage pregnancy, and develop healthy behaviours [Conti & Heckman 2013].

Evidence has shown that early interventions in childhood, is far more effective than later remediation [Conti & Heckman 2013] and will create healthier adult populations and significantly reduce public health spending in the medium- and long-term (Marmot 2010). Demographic changes in the age structure of the European population are also going to have an important effect on absolute numbers of disease events even assuming no major changes in age-specific

incidence rates. The financial costs associated with treating chronic diseases are extremely high and given that the average age of the European population is increasing, chronic diseases will continue to place an important pressure on the national budget [Brennan et al. 2017].

The birth cohorts are composed of individuals whose common event is birth at a given place and time. In these studies, data related to prenatal exposures are collected retrospectively. The birth cohort studies are the best methodologic approach to find any possible correlation affecting child health since allow the collection of accurate information about exposures, outcomes and several covariates as well as biological material which is not usually included in retrospective studies. The results from these studies have contributed significantly to our knowledge of the determinants of health during childhood, as well as the effects in later life. One concern is the lack of commonly acknowledged guidelines on the use of common measures for data collection, along with the various data sources used by cohorts, which lead to the extreme difficulty in merging or comparing data from different cohorts. This is a well-recognized issue and different groups are working to address it [O'Neill et al. 2019]. A huge amount of work has been done in this sense by the CLOSER initiatives linking all together with data from different UK birth cohorts. In this context, very recently they published a guide to the cognitive measures in five British birth Cohort studies [Moulton et al. 2020].

With larger sample sizes, aided by the use of standard measures in the pooling of cohorts, and the joining of data from large epidemiological studies from other countries, it is possible to understand the epidemiology of diseases [Pileret al.

2017]. We also hope that this initiative leading the way for similar workgroup all around the countries, as the Life-Cycle Project aims to do [The lifecycle, 2020).

Observational studies based on population-based administrative data sources are increasingly being used to provide evidence and support quality improvement for pediatrics. Real-world data originating from a variety of sources are to support healthcare and policy decision-making [Corrao & Cantarutti 2018; Canova 2020]. Health surveillance (perinatal and not) in Northern Europe of the world is often of high quality also because of the use of record linkage between health, civil and administrative data [Furu et al. 2010]. And it is in this part of the world that we have count more birth cohorts' studies [Pansieri et al. 2020].

The risk factors that can affect the good child and lately adult health and can be analysed through these kinds of studies are categorized into two main groups: genetic and environmental.

The genetic risk factors are defined as changes in the base pair sequence of the human genome and do not change during life. The environmental risk factors however are experienced throughout life of course. They vary from life events to exposure to lifestyle factors (diet, smoking, physical activity), to air pollution and medical interventions (drugs, surgery, psychological consultations, etc.)

These environmental factors are (thought to be) modifiable and often used in clinical practice and intervention studies. In contrast, other environmental risk factors are more or less 'fixed', like past environmental experiences (intra-uterine environment; exposures at day care center, school and occupation) and macro-environmental exposures (air pollution).

The systematic review that we performed at the beginning of this research shows an active "recent" interest. More than half of the European cohorts that we identified began in 2000 or later and many are still ongoing in terms of follow-up of participants suggesting a growing interest in longitudinal studies in particular on environmental factors that affecting child wellbeing. The main areas addressed by the cohorts were allergic diseases and environmental exposure, both of which have become priority study areas more recently and the numerous cohorts addressing environmental exposure reflect increasing attention to the negative effects of pollution on health. The child growth was studied more by the older cohorts, while obesity is a new research area. Many cohorts were designed to test a wide range of hypotheses, such as the Spatz cohort [Braig et al. 2017].

Once identified the Italian and the European birth cohort's panorama, we defined the general structure and the protocol of our own birth cohort: NASCITA. The planning and the execution of NASCITA took a lot of time and involve the meticulous planning

of all its stages:

1) the definition of the study objectives;

2) selection of the study population;

3) the selection of the exposures and outcomes that will be investigated;

4) creation of instruments for data collection and measurement;

5) development of strategies to avoid losses to follow-up;

6) execution of a pilot study before beginning definitive data collection,

7) the data analysis plan after completion of the follow-up.

Considering the gap in knowledge identified by our European birth cohorts review.

NASCITA has been set up to have general aims with a focus on family context (nurturing care) and neurodevelopment. This approach addresses the identification of many risk factors for disorders thought to have a perinatal/early life etiology such as birth defects, respiratory conditions, and childhood cancer [Golding et al. 2017; Guyatt et al. 2015]. Genetic and environmental factors are collected and some of them will be added in the future when a dedicated area will be created. In this way, we will have the possibility to generate more hypotheses and trying to answer each of them.

Clear aims and objectives should be agreed upon to facilitate direction and efficient methodology. Data may be used to test future hypotheses, and so as much information should be gathered as concisely as possible. The Aberdeen cohort [Lawlor et al. 2006] has been criticised for having no information on smoking in households, despite making detailed social observations, since this was before the association between maternal smoking and low birth weight had been established [Ong et al. 2002].

To minimize the risk of confounding we will include as many possible questions, however in remain the risk of unmeasured confounding, especially when new relationships are investigated. To avoid this risk we will perform sensitivity analyses aimed to evaluate the robustness of the results to the omission of relevant factors in the analysis [Canova & Cantarutti 2020].

The use of contemporary technology is hoped to improve compliance and retention of participants. Evidence suggests that using web-based support for epidemiological research can increase response rates, and improve the quality of data [Truell et al. 2002; Golding 1990]. However, the recall accuracy efficacy using these resources is

still unknown [Ley et al. 2019]. To perform adequate statistical analysis, the number of participants should be as high as possible a drop out rats should be as low as possible. Thanks to the strength collaborations with clinicians, informaticians and statisticians, instruments for data collection and measurement have been developed. Specifically a website and web-based system were set up in order to host the cohort, provide ongoing information to pediatricians and to families, and facilitate data input on the part of the pediatricians. The system was also designed to optimize data accuracy, minimize missing data, and permit data monitoring, analysis, and reporting throughout the duration of the cohort.

To facilitate the pediatrician's work, any document uploaded on the web based system has been converted and made printable. Every step from the selection of the clinical report form passing through the logo, the images and themes and choice within the dropdown menus or the single or multiple-choice buttons, were built with careful analysis.

Within the strategy to avoid losses to follow up of the participating pediatricians, the private area was improved with a private chat to provide instant support. A large amount of our work was devoted to responding the queries responsive that we regularly received. Queries are mainly concerning the tasks and obligations (during the engagement phase) or problem on the use of the web portal or to doubtes on clinical question proposed in our questionnaire. All the pediatricians participating in NASCITA are informed of the overall status of the cohort through frequent email.

NASCITA is an ambitious project and will contribute to a better understanding of children's development and health in the first year of life. A longitudinal study on this scale has never been done before in Italy.

The NASCITA cohort is based on community-level pediatric practice, involving the family pediatricians directly. No participation fees have been allocated to the pediatricians, each of them. Both pediatricians and families participate voluntarily. With their clinical practice, pediatricians are the most frequent healthcare contact with patients. Pediatricians play a key role in both educating families and in implementing health protection and health promotion. Their involvement in child cohorts permits the collection of prospective, community-level data.

A.   Future directions

Priorities for the next phase of research are:

IMMUNISATION: This is among the most cost-effective health interventions for public health. In Italy, vaccination is actively offered to target population groups and administered free of charge by public immunisation services. In 2017, vaccinations against pertussis, measles-mumps-rubella (MMR), varicella and Haemophilus influenza type b (Hib) were added to the list of already mandatory vaccines (diphtheria, tetanus, hepatitis B and polio) in the national immunisation plan (NIP). Normally, by 12 months of age, babies should have received several vaccinations, including three doses of the 5-in-1 vaccination (diphtheria, tetanus, whooping cough, polio and Haemophilus influenzae type b (Hib)). The current rate range of the 5-in-1 vaccination is from 88.6% and 98.4% [D'Ancona et al. 2019].

INEQUALITIES: Evidence suggests that socioeconomic disadvantages in early-life can affect child health and have long-term effects also on adult health [Cantarutti et al. 2017; Kuh et al. 2004]. Better identifying these inequalities will permit the channeling of resources where they are most needed. Collection of data at the national level will permit the identification of differences in health care quality, for example, caused also by socio-economic inequalities present between the north and south of Italy, differences in family behaviors that influence child health status, e.g. smoking or reading out loud to children, will also be examined.

MEDICATIONS: Reviews of pediatric prescriptions in the community setting have quantified off-label use to reach 52 % and unlicensed use to reach 17 % [Ellul et al. 2016]. Most drugs (75-80%) were not labeled as safe and effective for infants and children and off label use was the norm for these therapeutic orphans [Waller 2000; Conroy et al. 2000].

LOW BIRTHWEIGHT: Low birthweight represents an important public health issue since it is associated with profound short term and long term consequences. [Khan et al. 2015; Rüdiger et al. 2019].

A possible focus could be also put on medication use during pregnancy and its impact on maternal and fetal health, which is a growing public health concern. [Lynch et al. 2018]. The use of any medication including over-the-counter drugs, during pregnancy is estimated at 94%. However, studies have shown that less than 10% of medications approved from 1980 to 2010 have sufficient evidence to determine fetal risks deriving from in utero exposures.

In this field, a specific attention could be also put to medication use among women who breastfed their children. [Canova & Cantarutti 2020].

B.   Strengths and weaknesses

A strength of this thesis is the updated overview of the European birth cohorts that is important, and should be frequently updated, to highlight the current scenario, the gaps of knowledge, and to improve national and international collaboration that is essential to understand the epidemiology of diseases. The major weaknesses of this project were: highlighted the questions to be addressed, such as difficulties with long-term follow-up, advantages and drawbacks of different collection methods, funding, logistics, ethical questions and dissemination of data to the research community.

A strength of NASCITA is the participation of family pediatricians, permitting the collection of data by those directly involved with the care of children and their families.

The large representative sample of newborns from across the country, allows stratified trends based on socioeconomic and geographic characteristics to be performed.

Among the strengths of this study is the use of standard measurements for anthropometric and neurocognitive parameters.

A limit of the NASCITA cohort is that the longitudinal collection of data start after birth. Cohort studies that begin in pregnancy and those that begin in the preconception period permit to identify fetal and preconception exposures in real-time. However, the gathering of information related to pregnant women requires

greater logistical planning and incurs higher costs than maternal/newborn data assessed at birth.

NASCITA does not collect biological samples which has increasingly become part of routine data collection in similar cohorts [Bailey et al. 2017] so it will not be able to evaluate genetic or immunological factors, for example. Resources and efforts were utilized, however, to achieve the largest population size possible to have enough power to study relatively common child exposures and outcomes.

In general, the set up and management of a birth cohort study requires a considerable amount of time and resources [Canova & Cantarutti 2020].

Two very large studies in the UK and US have, in fact, recently been cancelled also due to budgetary issues [Doyle & Golding 2009; Pearson 2015]. This pragmatic cohort, building on existing resources to collect data, is an important attempt to recruit a large cohort at reduced cost.

V. CONCLUSION

For the WHO (World Health Organization) health is not only a state described by the absence of disease but by the achievement of a state of physical, mental and social well-being. From pregnancy through early childhood, all of the environments in which children live and learn, and the quality of their relationships with adults and caregivers, have a significant impact on their cognitive, emotional and social development. What happens to the child in the early years of life is critical for the child's developmental trajectory and life time health.

Longitudinal birth cohort studies are considered the gold standard to investigate the causes of disease and to establish links between risk factors and health outcomes

and very large birth cohort studies provide a unique opportunity to validate or confirm findings reported from smaller and more focused epidemiological studies. Their results significantly contributed to inform governments and allowed a wide range of policies implemented to protect and promote health in childhood including those directed toward early care and education.

There is a consensus among leading scientific and political organizations that a national longitudinal study of a representative birth cohort, particularly one designed to examine disparities in health outcomes related to inequality of health care and sociodemographic diversity, has a unique value for major advancements in our understanding of how children grow into healthy, successful, and happy adults. NASCITA is the first Italian birth cohort built with these purposes and to explore how nurturing care, pediatricians and families decisions are connected with newborns and child health.

Our preliminary systematic review of European birth cohort's shows that few cohorts have followed in detail child development as well as neurodevelopment.

NASCITA, moreover, is one of the rare cases in which the family pediatricians are directly involved and leading scientific research, considering it a pioneering approach.

The European cohort list identified in the systematic review, provides a reseources for future work and collaboration. It will also be useful to search for connection, tools and to answer upcoming research questions, as on the outcomes of the recent COVID pandemia. The very recent COVID situation highlights the power of the existing longitudinal studies to understand the immediate and long-term impacts of the pandemic on individuals, families, households, and society. The consequences

of the COVID-19 pandemic for individuals, families and society will be deep and long-lasting. Due to the unique nature of longitudinal studies, it will also be possible to track the longer-term consequences and impacts for years to come, the cohorts that are currently recruiting patients should take into consideration this important aspect.

Thanks to this unique "adventure" that enriches my knowledge in terms of research and methodology (bibliographic, epidemiologic and biostatistics…), and encourage closer cross-disciplinary collaboration (clinicians, informatics and statistical). I found this experience an important point of intersection between epidemiological and public health research.

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VII. APPENDIX

Appendix A. Embase and PubMed search strategies.

Embase

('birth cohort'/exp OR 'birth cohort':ti,ab) AND (bulgaria:ad OR andorra:ad OR austria:ad OR austrian:ad OR albania:ad OR albanian:ad OR bosnia:ad OR bosnian:ad OR bulgarian:ad OR croatia:ad OR croatian:ad OR czechoslovakian:ad OR hungary:ad OR hungarian:ad OR poland:ad OR polish:ad OR kosovo:ad OR kosovian:ad OR greece:ad OR greek:ad OR luxembourg:ad OR norway:ad OR norwegian:ad OR iceland:ad OR icelanders:ad OR sweden:ad OR swedish:ad OR finland:ad OR finnish:ad OR uk:ad OR england:ad OR scotland:ad OR scottish:ad OR ireland:ad OR irish:ad OR denmark:ad OR danish:ad OR belarus:ad OR estonia:ad OR latvia:ad OR lithuania:ad OR germany:ad OR german:ad OR france:ad OR french:ad OR switzerland:ad OR swiss:ad OR belgium:ad OR belgian:ad OR dutch:ad OR netherlands:ad OR spain:ad OR spains:ad OR italy:ad OR italian:ad OR portugal:ad OR portuguese:ad OR slovakia:ad OR slovakian:ad OR slovenia:ad OR slovenian:ad OR ukraine:ad OR ukrainian:ad OR bulgaria:ff OR 'europe'/exp OR 'european'/exp

OR andorra:ff OR austria:ff OR austrian:ff OR albania:ff OR albanian:ff OR bosnia:ff OR bosnian:ff OR bulgarian:ff OR croatia:ff OR croatian:ff OR czech OR czechoslovakian:ff OR hungary:ff OR hungarian:ff OR poland:ff OR polish:ff OR kosovo:ff OR kosovian:ff OR greece:ff OR greek:ff OR luxembourg:ff OR norway:ff OR norwegian:ff OR iceland:ff OR icelanders:ff OR sweden:ff OR swedish:ff OR finland:ff OR finnish:ff OR uk:ff OR england:ff OR scotland:ff OR scottish:ff OR ireland:ff OR irish:ff OR denmark:ff OR danish:ff OR belarus:ff OR estonia:ff OR latvia:ff OR lithuania:ff OR germany:ff OR german:ff OR france:ff OR french:ff OR switzerland:ff OR swiss:ff OR belgium:ff OR belgian:ff OR dutch:ff OR netherlands:ff OR spain:ff OR spains:ff OR italy:ff OR italian:ff OR portugal:ff OR portuguese:ff OR slovakia:ff OR slovakian:ff OR slovenia:ff OR slovenian:ff OR ukraine:ff OR ukrainian:ff) NOT ('aged'/exp OR 'middle aged'/exp) NOT ('controlled clinical trial (topic)'/exp OR 'controlled clinical trial':ti,ab) NOT ('vaccination'/exp OR vaccine:ti,ab) NOT 'gene expression'/exp NOT ([conference review]/lim OR [editorial]/lim OR [review]/lim OR proceedings) AND [english]/lim AND [1-71960]/sd NOT [21-5-2019]/sd

Medline (PubMed)

((((((("birth cohort"[tiab] AND ((Poland[Affiliation] OR Germany[Affiliation] OR France[Affiliation] OR Switzerland[Affiliation] OR Belgium[Affiliation] OR Netherlands[Affiliation] OR Spain[Affiliation] OR Italy[Affiliation] OR Portugal[Affiliation] OR Slovakia[Affiliation] OR Slovenia[Affiliation] OR Ukraine[Affiliation] OR Finland[Affiliation] OR UK[Affiliation] OR Scotland[Affiliation] OR Ireland[Affiliation] OR Denmark[Affiliation] OR Belarus[Affiliation] OR Estonia[Affiliation] OR Latvia[Affiliation] OR Lithuania[Affiliation] OR

Poland[Affiliation] OR Kosovo[Affiliation] OR Greece[Affiliation] OR
Luxembourg[Affiliation] OR Norway[Affiliation] OR Iceland[Affiliation] OR
Sweden[Affiliation] OR Austria[Affiliation] OR Albania[Affiliation] OR
Bosnia[Affiliation] OR Bulgaria[Affiliation] OR Croatia[Affiliation] OR Czech
Republic[Affiliation] OR Hungary[Affiliation] OR Andorra[Affiliation]) AND
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Republic"[tiab] OR czechoslovakian[tiab] OR "hungary"[tiab] OR hungarian[tiab] OR
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OR "italy"[tiab] OR Italian[tiab] OR "portugal"[tiab] OR portuguese[tiab] OR
"slovakia"[tiab] OR slovakian[tiab] OR "slovenia"[tiab] OR Slovenian[tiab] OR
"ukraine"[tiab] OR ukrainian[tiab]))) AND English[lang]) NOT
("Aged"[Mesh] OR "Middle Aged"[Mesh])) NOT (((ELDERLY[Title/Abstract] OR
ELDER[Title/Abstract]) OR GERIATRIC[Title/Abstract]) OR SENIOR[Title/Abstract]))
NOT ("Randomized Controlled Trial"[Publication Type] OR "Randomized Controlled Trials
as Topic"[Mesh]) NOT ("Vaccination"[Mesh] OR (vaccine[Title/Abstract] OR
vaccine'[Title/Abstract] OR vaccine's[Title/Abstract] OR vaccine1[Title/Abstract] OR
vaccine13[Title/Abstract] OR vaccine2014[Title/Abstract] OR
vaccinea[Title/Abstract] OR vaccineand[Title/Abstract] OR vaccineas[Title/Abstract]
OR vaccineassociated[Title/Abstract] OR vaccineatd[Title/Abstract] OR
vaccinecad[Title/Abstract] OR vaccinechallenged[Title/Abstract] OR
vaccined[Title/Abstract] OR vaccineda[Title/Abstract] OR vaccinedelivery[Title/Abstract]
OR vaccinediluent[Title/Abstract] OR
vaccinee[Title/Abstract] OR vaccinee'[Title/Abstract] OR vaccinee's[Title/Abstract] OR
vaccinees[Title/Abstract] OR vaccinees'[Title/Abstract] OR vaccinefor[Title/Abstract] OR
vaccineforme[Title/Abstract] OR vaccineformis[Title/Abstract] OR
vaccinefrom[Title/Abstract] OR vaccinein[Title/Abstract] OR
vaccineinduced[Title/Abstract] OR vaccinelike[Title/Abstract] OR
vaccinelymph[Title/Abstract] OR vaccinemediated[Title/Abstract] OR
vaccinemia[Title/Abstract] OR vaccineontology[Title/Abstract] OR
vaccineotherapy[Title/Abstract] OR vaccinepreventable[Title/Abstract] OR
vaccinerate[Title/Abstract] OR
vaccines[Title/Abstract] OR vaccines'[Title/Abstract] OR vaccines''[Title/Abstract] OR
vaccines4kids[Title/Abstract] OR vaccinesafety[Title/Abstract] OR
vaccinesagainst[Title/Abstract] OR vaccinesan[Title/Abstract] OR
vaccineselection[Title/Abstract] OR vaccineshoppe[Title/Abstract] OR
vacciness[Title/Abstract] OR vaccinessummary[Title/Abstract] OR

vaccinesthe[Title/Abstract] OR vaccinetherapy[Title/Abstract] OR
vaccineurin[Title/Abstract] OR vaccinex[Title/Abstract])) NOT ("Gene
Expression"[Mesh] OR "Genes"[Mesh]) NOT (Comment[sb] OR Editorial[ptyp] OR
Review[ptyp]) NOT proceedings[All Fields] AND English[lang])) AND (
"0001/01/01"[PDat] : "2019/05/20"[PDat]))

Appendix B. Ethics application

List of the documents requested by the Servizio Ricerca e Sviluppo Clinico Fondazione I.R.C.C.S. Istituto Neurologico Carlo Besta – Milano:

a) Sinossi dello studio, versione 2.0 del 9 gennaio 2019

b) CRF della prima Visita (See Appendix C)

c) Informativa dello studio, versione 2.0 del 9 gennaio 2019

d) Informativa sulla privacy e modulo di consenso informato al trattamento dei dati personali destinati ai genitori, versione 2.0 del 9 gennaio 2019

a) Sinossi dello studio, versione 2.0 del 9 gennaio 2019

Lo sviluppo in salute dei bambini nei primi anni di vita dipende dalla "nurturing care" che garantisce un buono stato di salute, un'alimentazione adeguata, un atteggiamento genitoriale "responsivo", protezione e sicurezza e opportunità di apprendimento precoce. I primi anni di vita sono caratterizzati da uno sviluppo fisico, motorio, cognitivo e relazionale estremamente rapido, che influenza in gran parte lo stato di salute e di benessere nel corso della vita. L'individuazione dei fattori di rischio modificabili e di fattori prognostici in periodi critici dell'esistenza possono contribuire allo sviluppo di strategie efficaci di prevenzione e di intervento. A questo riguardo è stata ideata l'iniziativa NASCITA (NAscere e creSCere in ITAlia) con lo scopo di monitorare lo sviluppo fisico/cognitivo/psicologico, lo stato di salute e benessere e il consumo di risorse sanitarie in una coorte di nuovi nati nel corso dei primi 6 anni di età e di valutare i potenziali fattori che possono influenzarli.

NASCITA è un'iniziativa nazionale per la costituzione di un database/registro che raccoglierà informazioni (dati correnti dell'attivita' del pediatra di famiglia) che coinvolgerà una coorte di almeno 5000 nuovi nati (birth cohort) a partire dal 2019, in 23 cluster geografici rappresentativi della realtà italiana.

L'arruolamento dei bambini avverrà nel corso della prima visita (bilancio di salute) effettuata dal pediatra di famiglia prevista in Italia entro i primi 45 giorni di vita.

I dati raccolti nel corso delle 7 visite dei bilanci di salute previste nei primi 6 anni di vita dai pediatri di famiglia partecipanti saranno inseriti in una scheda di raccolta dati elettronica (web-based). Inoltre, saranno raccolti i dati riguardanti tutti i contatti tra il pediatra e il bambino/la famiglia (p.es. visite in ambulatorio e domiciliari, consulti telefonici, trasmissioni di informazioni relative a visite specialistiche, ospedalizzazioni). Saranno valutati la crescita staturo-ponderale, lo sviluppo psicomotorio, i percorsi educativi/di socializzazione, l'alimentazione (p.es. durata dell'allattamento al seno, età e modalità di svezzamento…), le vaccinazioni effettuate, eventuali malattie (in particolare le condizioni di cronicità), la prescrizione di farmaci, visite specialistiche ed esami diagnostici, gli accessi in Pronto Soccorso e i ricoveri ospedalieri. L'analisi dei dati consentirà di descrivere lo stato di salute della popolazione partecipante e consentirà anche di valutare p. es: eventuali associazioni tra determinanti prenatali, contesto di vita (ambiente), alimentazione, buone pratiche genitoriali, opportunità di apprendimento precoce e di socializzazione e l'incidenza di eventi avversi intesi come malattie croniche, sovrappeso/obesità, disturbi dello sviluppo cognitivo/psicomotorio.

L'iniziativa sarà coordinata dal Laboratorio per la Salute Materno Infantile dell'Istituto di Ricerche Farmacologiche Mario Negri IRCCS, Milano, in collaborazione con l'Associazione Culturale Pediatri (ACP). L'iniziativa sarà monitorata da un comitato scientifico indipendente e multidisciplinare, rappresentativo di differenti competenze e professionalità e con il coinvolgimento di cittadini e genitori. Ai fini organizzativi, sono stati individuati 23 referenti allo scopo di fungere da coordinatori locali e da tramite fra i pediatri partecipanti e il centro di coordinamento.

La raccolta e l'analisi dei dati da parte dei ricercatori dell'Istituto di Ricerche Farmacologiche Mario Negri IRCCS avverrà in forma criptata anonimizzata e i ricercatori non avranno accesso all'identità dei bambini e

dei genitori partecipanti. Ai genitori sarà richiesto il consenso a fornire i dati personali propri e del/della

figlio/a per le finalità dello studio.

b) CRF della prima Visita (See Appendix C)

c) **Informativa dello studio, versione 2.0 del 9 gennaio 2019**

Caro mamma, caro papà,

siamo ricercatori e ricercatrici che lavorano nel Laboratorio per la Salute Materno Infantile dell'Istituto di

Ricerche Farmacologiche Mario Negri IRCCS di Milano. In collaborazione con il Vostro pediatra e

l'Associazione Culturale Pediatri (ACP) vogliamo condurre uno studio dal nome NASCITA (NAscere e

creSCere in ITAlia) che vuole seguire nel tempo, per sei anni almeno fino all'ingresso nella scuola

dell'obbligo, lo stato di salute di un gruppo (coorte) di bambini sin dalla nascita.

Per questo studio abbiamo bisogno del Vostro (mamma, papà, bambino/a) aiuto.

Questo modulo intende fornirVi tutte le informazioni necessarie affinché possiate decidere se far

partecipare Vostro/a figlio/a a questo studio. Per qualsiasi dubbio o domanda potete, comunque, in ogni

momento rivolgerVi al pediatra di Vs figlio/a.

PERCHÉ?

Per creare un registro nazionale che raccoglierà i dati di Vostro/a figlio/a insieme a quelli di moltissimi altri

bambini allo scopo di descrivere, controllare e valutare nel tempo e nei diversi contesti di vita, lo sviluppo,

la crescita, i percorsi educativi e di cura dei bambini, e quali fattori possono incidere sul loro benessere.

L'analisi dei dati di questo registro permetterà di individuare alcuni fattori "critici" che possono

compromettere la salute e il benessere dei bambini. Solo attraverso la valutazione delle informazioni

riguardanti tanti bambini e' possibile intraprendere azioni concrete di intervento o prevenzione.

Grazie a questo registro sarà possibile:

valutare quale è la frequenza e la durata dell'allattamento al seno, con quali tempi e modalità avviene lo svezzamento e quali sono i fattori associati a una maggiore attitudine all'allattamento al seno

 descrivere la crescita (statura, peso, indice di massa corporea) dei bambini italiani, stimare quale è la percentuale di bambini con sovrappeso o obesità e valutare i fattori di rischio di sovrappeso/obesità

stimare quanto sono frequenti alcune malattie nella popolazione pediatrica (per esempio bronchite asmatica, allergie, diabete, epilessia) e valutare quali sono i fattori che aumentano il rischio di sviluppare queste malattie

 stimare quanti sono i bambini con bisogni speciali e quali sono le attenzioni e le risposte fornite nei differenti contesti geografici

 valutare in che misura sono garantiti ai bambini e alle loro famiglie nei differenti contesti geografici i percorsi di socializzazione ed educativi

Con questo studio, il pediatra avra' un ulteriore strumento che gli permettera' di evidenziare precocemente quelle situazioni che richiedono percorsi di cura specifici in modo da indirizzare al meglio le famiglie.

CON CHI?

Tanti nuovi nati, con la collaborazione dei genitori, sono coinvolti al momento della prima visita dal Pediatri di Famiglia (PdF).

Il Vostro coinvolgimento non implica nessun impegno. Semplicemente, accettando di partecipare, alcuni dei dati normalmente raccolti dal Vostro pediatra saranno analizzati, insieme a quelli degli altri bambini, in forma criptata anonimizzata che non permetterà al ricercatore di risalire direttamente all'identità di Vostro figlio, se non presso il Vostro pediatra.

QUANDO?

I bambini saranno seguiti dalla nascita fino all'ingresso della scuola primaria.

DOVE?

In Italia: al nord, al centro e al sud; in territori costieri, di pianura e montani; nel centro e nelle periferie delle metropoli; in comuni urbani e in quelli rurali.

COME?

Lo studio non prevede di fare alcuna visita, esame o trattamento in più o differente di quanto avverrà per la cura di Vostro figlio/a. Le informazioni essenziali riguardanti lo sviluppo, la crescita e la salute dei bambini e la salute dei genitori sono quelle raccolte

normalmente dal pediatra durante le visite e i controlli che avrà con Voi e Vostro figlio/a e che registrerà come di norma nella cartella clinica.

Suo figlio/a sarà identificato/a con un codice per la trasmissione dei dati al Laboratorio per la Salute Materno Infantile dell'Istituto di Ricerche Farmacologiche Mario Negri IRCCS di Milano. I ricercatori non potranno, quindi, conoscere la vostra identità né quella di Vostro/a figlio/a.

CON QUALI STRUMENTI?

Partecipando a questo studio avrete la possibilità di accedere alle informazioni sulla crescita e lo sviluppo di Vostro/a figlio/a, collegandoVi al sito https://coortenascita.marionegri.it. Potrete consultare queste informazioni direttamente sul sito o scaricando e stampando un "diario" cartaceo. Solo Voi e il Vostro pediatra potrete generare e consultare questo "diario". I dati da noi analizzati sono criptati e non ci e' possibile risalire alle Vostre identità. Sullo stesso sito sarà disponibile materiale informativo per i genitori, come supporto e aiuto nella gestione dei più frequenti problemi di salute e suggerimenti su buone pratiche per una sana crescita.

Sarete periodicamente aggiornati dal Vostro pediatra e/o attraverso il sito sull'andamento dello studio e sui risultati ottenuti.

Se accettate di partecipare, Vi chiediamo gentilmente di acconsentire al trattamento dei dati personali Vostri e di Vostro/a figlio/a, leggendo l'informativa che il pediatra Vi ha consegnato e firmando il modulo di consenso. La partecipazione allo studio è volontaria, il rifiuto non compromette in nessun modo la qualita'

delle cure fornite dal vostro pediatra. E in quasiasi momento potrete ritirarVi. Non saranno raccolti ulteriori dati che Vi riguardano, ferma restando l'utilizzazione di quelli eventualmente già raccolti per conseguire, senza alterarli, i risultati della ricerca.

d) Informativa sulla privacy e modulo di consenso informato al trattamento dei dati personali destinati ai genitori, versione 2.0 del 9 gennaio 2019

INFORMATIVA PER IL TRATTAMENTO DEI DATI PERSONALI

Titolo dello studio: Coorte NASCITA- NAscere e creSCere in ITALIA (anche lo "Studio")

Promotore:

- Istituto di Ricerche Farmacologiche Mario Negri IRCCS, Via Giuseppe La Masa 19, 20156, Milano; (anche "Promotore")

Titolare e Responsabile della Protezione dei dati

Il Promotore che ha commissionato lo Studio (inclusi suoi partner di ricerca, designati e rappresentanti che collaborano allo Studio) e il pediatra di Suo/a figlio/a, in qualità di Titolari del Trattamento, ciascuno per gli ambiti di propria competenza e in accordo alle responsabilità previste dalle norme di Buona Pratica Clinica (D.L. 211/2003), dal Regolamento UE 2016/679 del Parlamento e del Consiglio Europeo relativo alla protezione delle persone fisiche con riguardo al trattamento dei dati personali, nonché alla libera circolazione di tali dati (di seguito GDPR), dall'Autorizzazione generale n.9/2016 al trattamento dei dati personali effettuato a scopi di ricerca scientifica del 15 dicembre 2016, e successive modifiche, tratteranno i dati personali, Suoi e di suo figlio/a, soltanto nella misura in cui sono indispensabili in relazione all'obiettivo dello Studio e per le finalità di seguito indicate.

La informiamo che i Titolari, ai sensi dell'articolo 37 del GDPR EU 2016/679, hanno proceduto ad

individuare e nominare il Responsabile della Protezione dei dati (anche "Data Protection Officer" o "DPO"):

Daniele Gervasio, Via D. Piccinini 2, Cap 24122, Bergamo. Tel: 035-3889611

Categorie di dati oggetto del trattamento

Il presente trattamento avrà ad oggetto i Suoi dati personali e quelli di Suo figlio/a, di seguito meglio

specificati:

a) Dati identificativi: Nome, Cognome, Data e Comune di Nascita di Suo figlio/a e dei genitori, Comune di

residenza del nucleo famigliare.

b) Dati particolari ex art. 9 GDPR relativi a:

- Andamento della gravidanza (tipo di concepimento, problemi di salute della mamma insorti durante la

gravidanza);

- Parto (tipo di parto, età gestazionale, peso alla nascita, lunghezza, circonferenza cranica, punteggio

APGAR);

- Andamento dell'accrescimento (peso, altezza) e dello sviluppo neurologico, psicomotorio e relazione

del/della bambino/a;

- Tipo di allattamento e alimentazione del bambino; Malattie acute e croniche del/della bambino/a,

prescrizione di farmaci ed eventuali ricoveri o accessi in Pronto Soccorso;

- Eventuali malattie croniche ed ereditarie presenti in famiglia (genitori, nonni);

Tutti i dati sopra citati, sono quelli raccolti normalmente dal pediatra nel corso delle visite e registrati nella

cartella clinica e da lui/lei utilizzati "per l'esercizio dell'attività di prevenzione, diagnosi e cura dello stato di

salute del bambino/a, nonché per gli adempimenti di legge, per gli adempimenti previsti dalla normativa in

tema di servizio sanitario nazionale e per finalità gestionali e statistiche", e per cui Lei ha già espresso il

consenso al trattamento.

Nel caso in cui i ricercatori decidessero di avviare studi specifici, le potrebbero essere richieste altre informazioni. In tal caso, la Sua partecipazione resterà volontaria e le sarà sottoposto un ulteriore modulo di consenso informato.

Finalità del trattamento

I dati sopra descritti verranno trattati per consentire lo svolgimento dello Studio in parola e di tutte le relative operazioni ed attività strettamente connesse allo stesso (intendendosi – a titolo esemplificativo e non esaustivo, le analisi statistiche con lo scopo di valutare l'influenza di determinanti ambientali, sociali, famigliari, sullo sviluppo e sullo stato di salute del bambino.

Base giuridica del trattamento

Il consenso informato costituisce la base giuridica per il trattamento dei Suoi dati e di Suo/a figlio/a per gli scopi descritti nella scheda informativa. In assenza di consenso firmato non potremo utilizzare i Suoi dati e quelli di Suo/a figlio/a per la conduzione e le analisi dello Studio.

Potrà interrompere la partecipazione di Suo/a figlio/a in qualsiasi momento e senza fornire alcuna motivazione; in tal caso, i Vostri dati verranno trattati come descritto nella scheda informativa dello Studio. A seguito di ciò, non saranno raccolti ulteriori dati che Vi riguardano, ferma restando l'utilizzazione di quelli eventualmente già raccolti per conseguire, senza alterarli, i risultati della ricerca.

Natura del conferimento dei dati

La partecipazione allo Studio avviene su base volontaria, pertanto, il conferimento dei dati personali è assolutamente volontario, nel senso che Lei può decidere di non conferire i Suoi dati personali e quelli di Suo figlio/a, quindi, di non partecipare allo Studio.

Modalità di Trattamento dei dati

Le finalità sopra indicate prevedono lo svolgimento del trattamento dei dati personali mediante strumenti manuali e informatici con logiche strettamente correlate alle finalità stesse e, comunque, in modo da garantire la sicurezza e la riservatezza dei dati stessi.

159.

I dati raccolti per i fini dello Studio verranno gestiti in forma codificata: Suo figlio/a sarà identificato/a con un codice che non permetterà di risalire direttamente alla Sua identità, se non presso il Suo pediatra. I ricercatori avranno a disposizione dati contraddistinti unicamente dal codice segreto che impedisce loro qualsiasi possibilità di associare i dati delle indagini scientifiche con la Vostra identità.

I dati che La riguardano, raccolti nel corso dello Studio, ad eccezione del Suo nominativo e di quello di Suo figlio/a, saranno trasmessi al Promotore e dallo Stesso registrati, elaborati e conservati.

Soltanto il pediatra, potrà collegare questo codice ai vostri nominativi quando necessario.

Ambito di comunicazione dei dati

La diffusione dei dati scientifici risultanti dalle analisi dei dati dello Studio, potrà avvenire solo in forma anonima e per sole finalità scientifiche. In pratica, i risultati delle ricerche scientifiche, potranno essere presentati in forma aggregata nell'ambito di Convegni o pubblicati su riviste specializzate senza mai permettere la precisa identificazione dei singoli pazienti.

I Suoi dati personali potranno essere trasferiti a Centri esterni per avvalersi della collaborazione di soggetti terzi per le finalità previste dal protocollo, espressamente designati dai Titolari quali "Responsabili del trattamento".

Potrà conoscere l'elenco aggiornato dei Responsabili del Trattamento, inviando una comunicazione ai riferimenti sopra riportati.

Trasferimento dei dati ad un Paese terzo o a un'organizzazione internazionale

Sebbene lo Studio non preveda che i Suoi dati personali codificati vengano trasferiti e trattati in Paesi al di fuori dell'Area Economica Europea (European Economic Area (EEA)), deve sapere che qualora ciò si dovesse rendere necessario, per ragioni tecniche non prevedibili fin da subito, avverrà esclusivamente per finalità di archiviazione/memorizzazione dei dati presso data centers. In tal caso, saranno comunque adottate tutte le misure di sicurezza appropriate per salvaguardare i Suoi diritti in materia di riservatezza dei dati.

Politica in materia di conservazione dei dati personali

I dati personali raccolti nell'ambito di questo Studio verranno conservati presso il pediatra, e il Promotore, per un periodo minimo di 10 anni dopo la conclusione dello Studio o per un periodo più lungo, se necessario, in base ad ulteriori requisiti di legge.

Diritti dell'Interessato:

Diritto di accesso ai dati

Può chiedere di consultare le informazioni che sono state raccolte su Suo figlio/a o su di Lei. Tuttavia, per salvaguardare l'integrità scientifica dello Studio, potrebbe non essere possibile accedere ad alcuni dati prima della conclusione dello Studio stesso.

Diritto di rettifica ai dati

Può richiedere la modifica dei dati che vi riguardano, qualora fossero errati o incompleti. Durante la valutazione di tale richiesta, ha il diritto di limitare il trattamento dei dati che La riguardano.

Diritto di portabilità dei dati

Può richiedere il trasferimento dei dati che La riguardano a Lei stesso o a qualcun altro in un formato comunemente utilizzato (cartaceo o elettronico).

Diritto di cancellazione dei dati

Può ritirare il consenso in qualsiasi momento senza darne motivazione alcuna. Può ritirare il consenso per il trattamento dello Studio e/o il follow up successivo, anche senza ritirare il consenso per il trattamento dei dati. Qualora cambiasse idea sul trattamento dei Suoi dati e di quelli di suo figlio/a, non sarà possibile rimuovere le informazioni personali già elaborate per lo Studio prima del Suo ritiro (coperte dal consenso originale). In seguito, al ritiro del consenso al trattamento dei Suoi dati non verrebbero acquisite ulteriori informazioni che La riguardano.

Diritto di reclamo

Può presentare un reclamo presso l'autorità incaricata della protezione dei dati:

Garante della privacy, E-mail: garante@garanteprivacy.it, Sito web: http://www.garanteprivacy.it/

In merito all'esercizio di tali diritti, potrà rivolgersi direttamente al Suo pediatra o, per il suo tramite, al Responsabile della protezione dei dati del Promotore.

Consenso al trattamento dei dati personali

ai sensi del GDPR UE 2016/679

Preso atto dell'informativa di cui all'art. 13 del GDPR UE 2016/679, il

sottoscritto_____, nato a_____, il_____, in qualità di:

Interessato e:

Esercente la potestà di **Genitore** del minore (nome e cognome)_____

nato/a a_____ il_____

residente a _____ in Via _____

□ Congiuntamente all'altro genitore (nome e cognome) _____

nato a _____ il_____

residente a_____ in via_____

□ Presente

□ Assente, ma è INFORMATO e AUTORIZZA a procedere per il minore

□ Disgiuntamente dall'altro genitore in forza del seguente Provvedimento_____

n_____ in data _____ repertorio/registro _____

Autorità _____ di _____

□ **Genitore unico**

□ Dà il proprio consenso □ Nega il proprio consenso

al trattamento dei dati del minore per le finalità relative allo studio osservazionale sopra citato

□ Dà il proprio consenso □ Nega il proprio consenso

al trattamento dei propri dati per le finalità relative allo studio osservazionale sopra citato

Data ..../........./........ Firma leggibile del dichiarante ………………………………

Appendix C. Data collected in the first visit

1° - ANAGRAFICA DEL BAMBINO

Nome ……………………………………………………………..

Cognome …………………………………………………

Sesso   □ M   □ F

Data di nascita   □□□□□□□□ □□□□□□□□ □□□□□□□□□□□□□□□
                            giorno   *mese*   *anno*

Regione di nascita ………… ………… (lista)

Provincia di nascita ………… ………… (lista)

Comune di nascita ………… ………… (lista)

Regione di residenza ………… ………… ………… (lista)

Provincia di residenza ………… ………… ………… (lista)

Comune di residenza ………… ………… (lista)

2° - NUCLEO FAMIGLIARE

1.   Tipologia del nucleo famigliare   □ eterogenitoriale

                                                                    □ omogenitoriale

2.   Componenti del nucleo famigliare *(compreso il bambino)*   Numero
       □□□□□□□□□

3.   Il bambino vive con entrambi i genitori?   □ SI □ NO

4.   Figlio unico?   □ SI □ NO

       Gemello?   □ SI □ NO

Se NO, Specificare il numero di figli, fratelli che vivono con il bambino (compreso il bambino) □□□□□□□□□

Se NO, i fratelli sono portatori di malattie croniche?   □ SI □ NO

    Se SI, quali malattie   □ Diabete
                                                      □ Epilessia
                                                      □ Asma
                                                      □ Ipertensione
                                                      □ Altro, specificare

    …………….… (ELENCO)

5.   Animali domestici?   □ SI □ NO
        Se SI, specificare   □ Cane
                                                         □ Gatto
                                                         □ Coniglio
                                                         □ Altro, specificare

    ……………………………..

-

3° ANAGRAFICA della MADRE

Data di nascita   □□□□□□□□   □□□□□□□□   □□□□□□□□□□□□□□
                      giorno   *mese*   *anno*

6. E' nata in Italia? □ SI □ NO

   Se NO, specificare nazione …………………………………………………… (lista)

   Se *SI*,   Regione di nascita ………… ………… ………… (lista)
                 Provincia di nascita ………… ………… ………… (lista)
                 Comune di nascita ………… ………… ………… (lista)

7. Mamma nata in Italia da famiglia straniera? □ SI □ NO

8. Durante la gravidanza, la residenza era la stessa di quella registrata per il neonato? □ SI □ NO

   Se NO: La residenza durante la gravidanza era in Italia? □ SI □ NO

        Se NO, Nazione …………………..

       Se *SI*, Regione di residenza ………… ………… ………… (lista)

                  Provincia di residenza ………… ………… ………… (lista)

                  Comune di residenza ………… ………… (lista)

9. Primo Figlio   □ SI □ NO

10. Stato civile   □ Nubile

                                             □ Coniugata/Unita

    Civilmente

                                             □ Separata/Divorziata
                                             □ Convivente
                                             □ Vedova

11. Titolo di studio conseguito   □ Scuola Primaria
    (elementare)

    grado (medie)
                                             □ Scuola Secondaria di I

    grado (superiori)
                                             □ Scuola Secondaria di II

                                             □ Laurea (università)
                                             □ Nessuno

12. Condizione professionale   □ Studentessa

□ Occupata
□ Disoccupata
□ Casalinga

Se occupata, specificare posizione professionale   □ Libero professionista
□ Imprenditrice

□ Impiegata   □ Dirigente

□ Operaia
□ Insegnante/educatrice
□ Altro

13. Soffre di malattie croniche? □ SI □ NO
    Se SI, specificare   □ Diabete
□ Epilessia
□ Asma
□ Ipertensione
□ Altro, specificare ………………

14. Soffre di atopia?   □ SI □ NO
    Se SI, specificare   □ Asma
□ Rinite allergica
□ Eczema
□ Altro specificare …………………

15. Vi sono malattie croniche/ereditarie in famiglia (genitori, fratelli/sorelle, materni)?   □ SI □

    NO   □ Non note

    Se SI, specificare ……………………………

4°   ANAGRAFICA del PADRE

Data di nascita   □□□□□□□□ □□□□□□□□ □□□□□□□□□□□□□□□□
                      giorno   *mese*   *anno*

16. E' nato in Italia?   □ SI □ NO

    Se NO, specificare nazione ………… ………… ………… (lista)

-

Se *SI*,   Regione di nascita ………… ………… ………… (lista)

                Provincia di nascita ………… ………… ………… (lista)

                Comune di nascita ………… ………… ………… (lista)

17.   Stato civile   □ Celibe

                                      □ Coniugato/Unito

Civilmente

                                      □ Separato/Divorziato
                                      □ Convivente
                                      □ Vedovo

18.   Titolo di studio conseguito   □ Scuola Primaria (elementare)

                                      □ Scuola Secondaria di I

grado (medie)

                                      □ Scuola Secondaria di II

grado (superiori)

                                      □ Laurea (università)
                                        □ Nessuno

19.   Condizione professionale   □ Studente

                                      □ Occupato
                                      □ Disoccupato
                                      □ Pensionato
                                      □ Casalingo

   Se occupato, specificare posizione professionale   □ Libero professionista
                                      □ Imprenditore
                                      □ Impiegato
                                      □ Dirigente
                                      □ Operaio
                                      □ Insegnante/educatore
                                      □ Altro

Compilare le domande 19-20-21 solo se il tipo di nucleo famigliare è eterogenitoriale

20.   Soffre di malattie croniche?   □ SI □ NO
       Se SI, specificare   □ Diabete
                                      □ Epilessia
                                      □ Asma

□ Ipertensione

□ Altro, specificare

……………… (ELENCO)

21. Soffre di atopia?　　　□ SI □ NO

    Se SI, specificare　　　　　　　　□ Asma

    □ Rinite allergica

    □ Eczema

    □ Altro specificare

    …………………

22. Vi sono malattie croniche/ereditarie in famiglia (genitori, fratelli/sorelle, paterni)?　□ SI □ NO

    □ Non note

    Se SI, specificare ……….…………………

5° ANAMNESI OSTETRICA

Gravidanza

23. Concepimento naturale?　　　□ SI □ NO

24. Gravidanza con decorso fisiologico? □ SI □ NO

    Se NO, specificare la patologia intercorsa durante la gravidanza □ Diabete gravidico

    □ Ipertensione gravidica

    □ Pre-eclampsia

    □ Altro, specificare

    ……………

25. Assunzione di acido folico? □ SI □ NO *Se SI*, specificare il periodo di assunzione:

    □ almeno 1 mese prima della gravidanza e per tutto il I° trimestre

-

        □ almeno 1 mese prima della gravidanza e per tutta la gravidanza

        □ solo nel I° trimestre (non prima della gravidanza) □ a partire del I° trimestre e oltre

26. Assunzione continuata di farmaci (non integratori) con modalità croniche/subcroniche (per oltre 3 settimane in modo continuativo), prescritti dal medico durante la gravidanza? □ SI □ NO

    Se SI, quali …………………… (lista ATC)

27. E' stata vaccinata in gravidanza? □ SI □ NO

    Se SI, specificare la vaccinazione   □ Antinfluenzale

            □ dTpa (Difterite, tetano, pertosse)   sett. gestazione

    □□□□□□□□□

            □ Altro, specificare ……………………………………..

28. Fumatrice (sigarette)? □ SI

            □ NO, Mai fumato
            □ Ho smesso prima della gravidanza
            □ Non risponde

    Se SI, durante la gravidanza?   □ Occasionalmente
            □ Giornalmente

    Se giornalmente, quanto?   □ Poco (□10/die)
            □ Moderato (□11-19/die)
            □ Tanto (1 pacchetto/die)

29. Assunzione di Alcol?   □ SI

            □ NO, Astemia
            □ Ho smesso prima della gravidanza
            □ Non risponde

    Se SI, durante la gravidanza?

            □ Occasionalmente
            □ Giornalmente

    Se giornalmente, quanto?   Numero di unità alcoliche al giorno
    □□□□□□□□□
    (1 unità corrisponde a birra 330 ml oppure 1 bicchiere di vino 125 ml)

30. Peso inizio (kg) □□□□□□□□□□□□□□□□ Peso fine (kg) □□□□□□□□□□□□□□□□

Aumento ponderale percentuale durante la gravidanza (kg) _____
(calcolato in automatico)

31. Altezza (cm) □□□□□□□□□□□□□

BMI (indice di massa corporea) a inizio gravidanza _____ *(calcolato in automatico)*

BMI (indice di massa corporea) a fine gravidanza _____ *(calcolato in automatico)*

Sottopeso = <18,5
Normopeso = tra 18,5 e 24,9
Sovrappeso = tra 25,0 e 29,9
Obeso = ≥ 30

GRAFICO IN AUTOMATICO

32. Gravidanze precedenti? □ SI □ NO

Se SI, specificare numero di gravidanze □□□□□□□□□□

33. Durante la gravidanza ha mai letto un libro ad alta voce? □ Mai
□ 1-2 volte
□ Più di 2 volte

34. Durante la gravidanza hai praticato dell'ascolto musicale rivolto al tuo bambino? ☐

Mai

☐

1-2 volte

☐

Più di 2 volte

Parto

35.   Età gestazionale alla nascita (settimane)   □□□□□□□□□

36.   Ha partorito in ospedale?   □ SI □ NO

37.   Parto singolo? □ SI □ NO

       Se NO, specificare il numero di nati □□□□□□□□□

38.   Modalità del parto: □ Spontaneo
                              □ Cesareo
                              □ Forcipe
                              □ Ventosa

39.   Subito dopo il parto c'è stato contatto pelle a pelle "mamma-
       neonato"? □ SI □ NO

6° - ANAMNESI NEO-PERINATALE

40. Punteggio APGAR   (valori da 0 a 10)   1' □□□□□□□□□   5'

    □□□□□□□□□

41. Peso alla nascita (gr)   □□□□□□□□□□□□□□□□□

42. Lunghezza (cm)   □□□□□□□□□□□□□

43. Circonferenza cranica (cm)   □□□□□□□□□□□□

44. Rianimazione cardiopolmonare?   □ SI □ NO

45. Malformazioni?   □ SI □ NO

    Se SI, specificare la malformazione ……………………. (ELENCO)

46. Patologia neonatale? □ SI □ NO

    Se SI, specificare la patologia ……………………. (ELENCO)

47. Ricovero in Unità Operativa di Neonatologia (Nido)**?   □ SI   □
    NO

48. Ricovero in Unità di Terapia Intensiva Neonatale (UTIN)?   □ SI □ NO

    Se SI, specificare il numero giorni di ricovero   □□□□□□□□□□□□

        Diagnosi alla dimissione ……………………. (ELENCO)

49. Durante la degenza in ospedale* (*nascita-dimissione)
    al neonato è stato somministrato: □ Latte materno
                                                 □ Latte artificiale
                                                 □ Acqua
                                                 □ Acqua zuccherata
                                                 □ Tè
                    □ Tisane   □ Succhi

50. Alla dimissione il bambino era allattato ESCLUSIVAMENTE al seno?   □
    SI □ NO

T1 – PRIMA VISITA PEDIATRA-BAMBINO

Nel primo mese di vita (1-45 giorni)

51. Data della visita   □□□□□□□□   □□□□□□□□   □□□□□□□□□□□□□□□□
      giorno   mese   anno

52. Alla dimissione al bambino è stata prescritta qualche terapia farmacologica? □ SI □ NO
      Se SI, specificare ………………………………… (LISTA ATC)

CONTROLLO AUXOLOGICO

VALUTAZIONE ANTROPOMETRICA   *(con i valori COMPARE IL GRAFICO PERCENTILI)*

53. Peso (gr)   □□□□□□□□□□□□□□□□   _____
      (calcolato in automatico)

54. Lunghezza (cm)   □□□□□□□□□□□□   _____
      (calcolato in automatico)

55. Circonferenza cranica (cm)   □□□□□□□□□□□□   _____
      (calcolato in automatico)

BMI (indice di massa corporea) _____ *(calcolato in automatico)*

ALIMENTAZIONE E SONNO

56. Attualmente il bambino riceve esclusivamente* latte materno?

□ SI □ NO

Se NO, specificare   □ Artificiale   □ Misto

Il latte artificiale quando è stato introdotto? (giorni del bambino)

175.

□□□□□□□□□□□□□□

57. Nelle ultime 24 ore, il bambino ha assunto altre bevande oltre al latte?

□ SI □ NO

Se SI, specificare
□ Acqua
□ Acqua zuccherata
□ Tè
□ Tisane
□ Succhi

58. Postura abituale del sonno   □ Prono   □ Supino   □   di Fianco

ESAME OBIETTIVO

(campo di testo libero)

59. Fontanella anteriore normale? □ SI □ NO   *Se NO*, specificare: ……………………

60. Cute Normale?   □ SI □ NO   *Se NO*, specificare: ……………………

61. Cuore normale? □ SI □ NO   *Se NO*, specificare: ……………………

62. Torace normale?   □ SI □ NO   *Se NO*, specificare: ……………………

63. Organi ipocondriaci normali?   □ SI □ NO   *Se NO*, specificare: ……………………

64. Genitali normali?   □ SI □ NO   *Se NO*, specificare: ……………………

65. Alvo normale?   □ SI □ NO   *Se NO*, specificare: ……………………

66. Colore delle feci normale?   □ SI □ NO   *Se NO*, specificare: ……………………

67. Valutazione ortopedica normale? □ SI □ NO

   Se NO, specificare: □ Piede torto congenito
   □ Piede talo valgo

                         □ Metatarso varo riducibile
                         □ Metatarso varo non riducibile
                         □ Frattura della clavicola
                         □ Lesione del plesso brachiale
                          □ Displasia evolutiva dell'anca (dopo aver eseguito la manovra di
   Ortolani-Barlow)
                         □ Plagiocefalia
                         □ Torcicollo

PROCEDURE CLINICO-STRUMENTALI E TERAPEUTICHE

68. Profilassi vitamina K alla nascita?   □ SI □ NO

177.

Se SI, ancora in corso?   □ SI □ NO

69. Profilassi vitamina D in corso?   □ SI □ NO

     Se NO, è stata prescritta in questa visita?   □ SI □ NO

70. Altre supplementazioni: □ SI □ NO
     Se SI   □ Ferro
                       □ Luteina
                       □ Multivitaminico
                       □ Altro, specificare _____

71. Screening neonatale esteso effettuato? □ SI □ NO

72. Otoemissioni (verifica esecuzione)?   □ SI □ NO

73. Riflesso rosso normale?   □ SI □ NO

     Se NO, specificare □ Cataratta parziale   □
     Cataratta totale
                         □ Retinoblastoma

VALUTAZIONE DELLO SVILUPPO NEUROLOGICO E PSICOMOTORIO

MOTRICITÀ

74. Movimenti ricchi, variabili, fluidi, compreso mani e piedi □ Normale □ Da rivalutare a breve
     □ Patologico
75. Controllo del capo su tronco (in braccio, prono, alla trazione)   □ Normale □ Da rivalutare a

     breve   □ Patologico

 76. Arti sulla linea mediana (mani alla bocca)   □ Normale □ Da rivalutare a

     breve   □ Patologico

RELAZIONE

77. Sguardo (fissa e segue il volto o un oggetto)   □ Normale □ Da rivalutare a

     breve   □ Patologico

78. Ascolto (reagisce, presta attenzione e si orienta ai suoni)   □ Normale □ Da rivalutare a

     breve   □ Patologico

79. Mimica (qualità e variabilità espressiva)   □ Normale □ Da rivalutare a

     breve   □ Patologico

80. Pianto e consolabilità (si calma con voce, contenimento, suzione)   □ Normale □ Da rivalutare a
     breve   □ Patologico

PRESCRIZIONI

81. Nel corso di questa visita al bambino è stato prescritto qualcosa? □ SI □ NO, sta bene

Suggerito

Se SI, specificare □   Terapia farmacologica:

□

farmaco (ATC) …………………………………………. **+**

motivo (ICD) …………………………………………. **+**

□   Visita specialistica, specificare …………………………………………..

□

□   Esami di laboratorio

□

□ Esami diagnostici

□ Ecografia, specificare sede

…………………………………………… □

□ Radiografia, specificare sede

…………………………………………… □

□ Tac, specificare sede

…………………………………………………… □

□ Risonanza, specificare sede

…………………………………………… □

□ Elettrocardiogramma □

□ Elettroencefalogramma □

□ Polisonnografia □

□ Altro, specificare

………………………………………………………… □

179.

Appendix D. Data collected in the second visit

T2 – SECONDA VISITA

(60-90 giorni di vita)

82. Data della visita ⬚⬚⬚⬚⬚⬚⬚⬚ ⬚⬚⬚⬚⬚⬚⬚⬚ ⬚⬚⬚⬚⬚⬚⬚⬚⬚⬚⬚⬚⬚⬚⬚⬚
    giorno   *mese*   *anno*

CONTROLLO AUXOLOGICO VALUTAZIONE ANTROPOMETRICA

(con i valori COMPARE IL GRAFICO PERCENTILI)

83. Peso (gr) ⬚⬚⬚⬚⬚⬚⬚⬚⬚⬚⬚⬚⬚⬚⬚ _____
    (calcolato in automatico)

84. Lunghezza (cm) ⬚⬚⬚⬚⬚⬚⬚⬚⬚⬚⬚⬚⬚ _____
    (calcolato in automatico)

85. Circonferenza cranica (cm) ⬚⬚⬚⬚⬚⬚⬚⬚⬚⬚⬚⬚ _____
    (calcolato in automatico)

BMI (indice di massa corporea) _____ *(calcolato in automatico)*

ALIMENTAZIONE E SONNO

86. Attualmente il bambino riceve esclusivamente* latte materno? □ SI □ NO *Se NO*, specificare □ Artificiale □ Misto

87. Nelle ultime 24 ore, il bambino ha assunto altre bevande oltre al latte? □ SI □ NO

    Se SI, specificare
    - □ Acqua
    - □ Acqua zuccherata
    - □ Tè
    - □ Tisane □ Succhi

88. Postura abituale nel sonno □ Prono □ Supino □ Di fianco

89. Dove dorme in prevalenza? □ Culla □ "Next to me" □ Lettone

90. Presenza di disturbi del sonno? □ SI □ NO *Se SI* □ Difficoltà ad addormentarsi
    □ Risvegli frequenti
    □ Dorme poco
    □ Altro, specificare _____

> **TOOLTIP**
> ** il consumo di latte umano senza aggiunta di supplementi di alcun genere, fatta eccezione per vitamine, minerali e farmaci.*

91. Il genitore riporta coliche? □ SI □ NO

92. Il genitore riporta altri disturbi? □ SI □ NO
    Se SI, specificare _____

ESAME OBIETTIVO

(campo di testo libero)

93. Fontanella anteriore normale? □ SI □ NO *Se NO*, specificare:
    _____

94. Cute normale? □ SI □ NO *Se NO*, specificare:
    _____

95. Orofaringe normale? □ SI □ NO *Se NO*, specificare:
    _____

96. Cuore normale? □ SI □ NO *Se NO*, specificare:
    _____

97. Torace normale? □ SI □ NO *Se NO*, specificare:
    _____

98. Addome normale? □ SI □ NO *Se NO*, specificare:
    _____

99. Ombelico nomale? □ SI □ NO *Se NO*, specificare:
    _____

100. Apparato genitale normale? □ SI □ NO *Se NO*, specificare:
    _____

VALUTAZIONE DELLO SVILUPPO NEUROLOGICO E PSICOMOTORIO

CONTROLLO DELL'UDITO

101. Il bambino gira gli occhi e/o la testa verso la fonte di un suono? □ SI □ NO □ Da rivalutare a breve

102. Cambia espressione al suono di una campanella o di un sonaglio fatti tintinnare al di fuori del
campo visivo? □ SI □ NO □ Da rivalutare a breve

MOTRICITÀ

	Normale	Da rivalutare a breve
Patologico		
103. Si muove bene e in modo simmetrico	□	□
(movimenti ricchi, variabili, fluidi, compreso mani e piedi)	□	
104. Controllo assiale capo e tronco	□	□
(in braccio, prono, alla trazione)	□	
105. Arti sulla linea mediana	□	□
(piedi e mani)	□	
106. Sostegno sugli arti superiori – Da prono apre le mani	□	□
	□ (iniziale)	
107. Attività occhio-mano-bocca	□	□
(si guarda le mani, le porta in bocca, tocca gli oggetti)	□	

RELAZIONE

108. Sguardo (fissa e segue il volto o un oggetto)	□	□
	□	
109. Ascolto (reagisce, presta attenzione e si orienta ai suoni)	□	□
	□	

110. Mimica (espressivo, sorride e poi ride, vocalizza)   □   □

                                                           □

111. Pianto e consolabilità (si calma con voce, contenimento, suzione)   □   □

                                                           □

PROCEDURE CLINICO-STRUMENTALI E TERAPEUTICHE

112. Profilassi vitaminica in corso: Vitamina D   □ SI □ NO

                                       Vitamina K   □ SI □ NO

113. Altre supplementazioni (vitamine o integratori)?   □ SI □ NO

    Se SI: □ Ferro
                    □ Luteina
                    □ Multivitaminico
                    □ Altro, specificare _____

114. Riflesso rosso normale?   □ SI □ NO   *Se NO*, specificare:
    _____

115. Manovra di Ortolani-Barlow? □ Positiva   □ Negativa

116. Ecografia delle anche effettuata?   □ SI □ NO

    Se SI: tipizzazione dell'anca destra secondo Graf _____ (lista)

    tipizzazione dell'anca sinistra secondo Graf _____ (lista) *Se NO*:

    E' stata prenotata? □ SI □ NO

CONTESTO FAMIGLIARE

117. I genitori fumano?   □ NO
                              □ Solo la madre
                              □ Solo il padre
                              □ Entrambi

118. *La madre, fuma la sigaretta elettronica?* □ SI □ NO

119. *Il padre, fuma la sigaretta elettronica?*   □ SI □ NO

120. Nelle ultime 2 settimane avete letto al bambino un libro ad alta voce? □ SI □ NO

183.

121. Nelle ultime 2 settimane avete intenzionalmente fatto ascoltare musica al bambino?

□ SI □ NO

122. Il bambino frequenta l'asilo nido?   □ SI □ NO

123. Quanto spesso il bambino sta all'aria aperta?   □ Saltuariamente
□ meno di 1 ora al giorno
□ da 1 a 3 ore al giorno
□ oltre 3 ore al giorno

124. Il bambino risiede in una via ad <u>alto traffico</u>[*]?   □ SI □ NO

125. Il bambino risiede in <u>prossimità</u>[**] di <u>coltivazioni intensive</u>[***]?   □ SI □ NO

Tooltip:
[*] Presenza di almeno 2 linee di autobus o passaggio di autocarri sulla strada dell'abitazione

[**] Se la distanza tra la casa e i campi è inferiore a 300 metri

[***] Grandi estensioni di terreno con piante tutte uguali trattate con sostanze chimiche

---

PRESCRIZIONI

126. Nel corso di questa visita al bambino è stato prescritto qualcosa?   □ SI □ NO

Suggerito

Se SI, specificare   □   Terapia farmacologica:

□

farmaco (ATC) …………………………………………. **+**

motivo (ICD) …………………………………………. **+**

□   Visita specialistica, specifica ………………………………….

□

□   Esami di laboratorio

☐

☐ Esami diagnostici

    ☐ Ecografia, specificare sede

    …………………………………………… ☐

    ☐ Radiografia, specificare sede

    …………………………………………… ☐

    ☐ Tac, specificare sede

    ………………………………………………..…… ☐

    ☐ Risonanza, specificare sede

    …………………………………………… ☐

☐ Elettrocardiogramma ☐

☐ Elettroencefalogramma ☐

☐ Polisonnografia ☐

    ☐ Altro, specificare

    ……………………………………………………… ☐

Appendix E. Data collected in the third visit

T3 − TERZA VISITA

Tra il 5° e il 7° MESE (180gg +/- 30gg)

127. Data della visita ☐☐☐☐☐☐☐☐ ☐☐☐☐☐☐☐☐ ☐☐☐☐☐☐☐☐☐☐☐☐☐☐
giorno   *mese*   *anno*

CONTROLLO AUXOLOGICO

VALUTAZIONE ANTROPOMETRICA

128. Peso (gr) ☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐

129. Lunghezza (cm) ☐☐☐☐☐☐☐☐☐☐☐☐

130. Circonferenza cranica (cm) ☐☐☐☐☐☐☐☐☐☐☐☐

BMI (indice di massa corporea) _____ *(calcolato in automatico)*

ALIMENTAZIONE/SVEZZAMENTO

131. Il bambino è allattato al seno? ☐ SI ☐ NO

Se SI, quante volte al giorno? ☐☐☐☐☐☐☐☐

Se NO, a che età è stato interrotto l'allattamento esclusivo al seno? ☐☐☐☐☐☐☐☐☐

(mesi)

132. Il bambino è già stato svezzato? ☐ SI ☐ NO *Se SI*, specificare a quanti mesi ☐☐☐☐☐☐☐☐

133. Come viene svezzato/si intende svezzare il bambino? ☐ Svezzamento classico per gradi

☐ Autosvezzamento

Se Autosvezzamento: Mangia lo stesso cibo dei genitori? ☐ SI ☐ NO

186.

134. A casa, con chi mangia solitamente il bambino?   □ Mamma

                                                     □ Papà

                                                     □ Nonni

                                                     □ Altri famigliari

                                                     □ Tata

135. Il cibo che viene dato al bambino, solitamente è: □ "Industriale" (pappe pronte)

                                                     □ Preparato a casa

136. Ci sono difficoltà nel proporre i cibi solidi?   □ Nessuna

                                                     □ Abbastanza

                                                     □ Molta

137. L'appetito del bambino è: □ Scarso

                                                     □ Normale

                                                     □ Eccessivo

138. C'è preoccupazione riguardo la sua crescita?   □ SI □ NO

139. Il bambino sta seguendo una dieta speciale?   □ SI □ NO

    Se SI, quale?   □ Vegetariana

                                                    □ Senza glutine

                                                    □ A basso contenuto di lattosio

                                                    □ Altro, specificare: _____

SONNO

140. Postura abituale nel sonno: □ Prono   □ Supino   □ Di fianco

141. La sera, dove si addormenta abitualmente?   □ Nel suo lettino

                                               □ Nel lettone

                                               □ In una stanza diversa da quella dove dorme

142. Dove dorme abitualmente?   □ Tutta la notte nel suo lettino

                                             □ Tutta la notte nel lettone

                                             □ In entrambi ma in prevalenza nel suo lettino

                                             □ In entrambi ma in prevalenza nel lettone

143. Dorme in camera da solo?   □ SI □ NO
    Se NO; dorme in camera con fratelli?   □ SI □ NO

144. Presenza di disturbi del sonno?   □ SI   □ NO
    Se SI,   □ Difficoltà ad addormentarsi
                 □ Risvegli frequenti
                 □ Dorme poco
                 □ Altro, specificare _____

    Se Risvegli frequenti:
    Nell'ultima settimana quante volte si è svegliato in media per notte?
    □□□□□□□□□ *(numero)*

ESAME OBIETTIVO

                                                    (campo di testo libero)

145. Fontanella anteriore normale?   □ SI □ NO   *Se NO*, specificare:
    _____

146. Cute normale?   □ SI □ NO   *Se NO*, specificare:
    _____

147. Orofaringe normale?   □ SI □ NO   *Se NO*, specificare:
    _____

148. Cuore normale?   □ SI □ NO   *Se NO*, specificare:
    _____

149. Torace normale?   □ SI □ NO   *Se NO*, specificare:
    _____

150. Addome normale?   □ SI □ NO   *Se NO*, specificare:
    _____

151. Ombelico nomale?   □ SI □ NO   *Se NO*, specificare:
    _____

152. Apparato genitale normale?   □ SI □ NO   *Se NO*, specificare:
    _____

153. Dentizione?   □ SI □ NO

Se SI, Il bambino presenta: □ Incisivi inferiori □ Incisivi superiori

□ Incisivi lato inferiori □ Incisivi lato superiori
□ 1° Molare inferiore □ 1° Molare superiore
□ Canini inferiori □ Canini superiori

VALUTAZIONE DELLO SVILUPPO NEUROLOGICO E PSICOMOTORIO

CONTROLLO DELLA VISTA

154. Riflesso rosso normale? □ SI □ NO *Se NO*, specificare:

_____

155. Riflessi pupillari e corneali normali? □ SI □ NO *Se NO*, specificare:

_____

156. Movimenti oculari normali? □ SI □ NO *Se NO*, specificare:

_____

157. Strabismo? □ SI □ NO

158. E' stata fatta diagnosi di cataratta congenita? □ SI □ NO

MOTRICITÀ

	Patologico	Normale	Da rivalutare a breve
159. Si muove bene e in modo simmetrico	□	□	□
(movimenti ricchi, variabili, fluidi, compreso mani e piedi)			
160. Controllo assiale capo e tronco	□	□	□
(seduto con appoggio)			
161. Spostamenti	□	□	□
(si mette sul fianco, rotola, si sposta di lato facendo perno sull'ombelico)			
162. Manipolazione	□	□	□
(afferra gli oggetti, sia con la destra che la sinistra, con presa globale e poi con pinza inferiore, li porta alla bocca)			

189.

RELAZIONE

163. Qualità globale dell'attenzione ☐ ☐

☐

(guarda e segue, si orienta verso i suoni, espressivo, interessato agli
eventi famigliari, anticipa eventi conosciuti)

164. Comportamento diversificato verso estranei ☐ ☐

☐

e ambienti nuovi (inizio)

165. Comunicazione verbale (vocalizzi, gorgheggi, inizio lallazione) ☐ ☐

☐

166. Gioco/libro (curiosità, esplorazione dell'oggetto, presta attenzione) ☐ ☐

☐

PROCEDURE CLINICO-STRUMENTALI E TERAPEUTICHE

167. Profilassi con Vitamina D in corso? ☐ SI ☐ NO

168. Altre supplementazioni (vitamine o integratori)? ☐ SI ☐ NO
   Se SI, ☐ Ferro ☐ Fluoro ☐ Altro, specificare _____

169. Ecografia delle anche effettuata? ☐ SI ☐ NO ☐ Ho già risposto nella II°

   visita

   Se SI, tipizzazione dell'anca destra secondo Graf _____ (lista)

   tipizzazione dell'anca sinistra secondo Graf _____ (lista)

CONTESTO FAMIGLIARE

170. La madre ha sofferto di depressione post-parto? ☐ SI ☐ NO

171. Il padre ha sofferto di depressione post-parto? ☐ SI ☐ NO

172. I genitori fumano? ☐ NO
   ☐ Solo la madre
   ☐ Solo il padre ☐ Entrambi

173. *La madre, fuma la sigaretta elettronica?* ☐ SI ☐ NO

190.

174. *Il padre, fuma la sigaretta elettronica?* □ SI □ NO

175. Nelle ultime 2 settimane avete letto al bambino un libro ad alta voce? □ SI □ NO

Se SI: Qual'è il libro preferito dal bambino? specificare

_____

176. Nelle ultime 2 settimane avete intenzionalmente fatto ascoltare musica al bambino?

□ SI □ NO

177. Quando è sveglio, trascorre del tempo a pancia in giù *(Tummy time)*? □ SI □ NO

Se SI, per quanto tempo nell'arco della giornata?   □ meno di 15 minuti
□ da 15 a 30 minuti
□ da 30 minuti a 1 ora
□ oltre 1 ora

Quando è sveglio e tranquillo dove passa la maggior parte del tempo?
□ per terra (su un tappeto o coperta)
□ nella sdraietta/seggiolina
□ in braccio ad un adulto
□ altro (palestrina, tappeto gioco, box, girello...)

178. Il bambino frequenta l'asilo nido?   □ SI □ NO

179. Quanto spesso il bambino sta all'aria aperta?   □ Saltuariamente
□ meno di 1 ora al giorno
□ da 1 a 3 ore al giorno
□ oltre 3 ore al giorno

PRESCRIZIONI

180. Nel corso di questa visita al bambino è stato prescritto qualcosa?   □ SI □ NO

Suggerito

Se SI, specificare □ Terapia farmacologica:

□

farmaco (ATC) ……………………………………….. **+**

motivo (ICD) ……………………………………….. **+**

191.

☐   Visita specialistica, specifica …………………………………………..

☐

☐   Esami di laboratorio

☐

☐   Esami diagnostici

    ☐ Ecografia, specificare sede

      ………………………………………………   ☐

    ☐ Radiografia, specificare sede

      ………………………………………………   ☐

    ☐ Tac, specificare sede

      …………………………………………….……   ☐

    ☐ Risonanza, specificare sede

      ………………………………………………   ☐

  ☐ Elettrocardiogramma   ☐

  ☐ Elettroencefalogramma   ☐

  ☐ Polisonnografia   ☐

  ☐ Altro, specificare

      …………………………………………………………   ☐

APPENDIX F. Newsletter

NEWSLETTER

Per la ricerca degli articoli pubblicati nella letteratura scientifica nel trimestre in esame sono state consultate le banche dati Medline, Embase, utilizzando le seguenti parole chiave (o i loro sinonimi): 'Birth Cohort', 'Primary Care', 'Infant', 'Child', 'Human', 'Newborn', 'Pediatrician', 'General pratice'. Sono qui riportate le referenze considerate rilevanti e pertinenti.

VIII. PUBLICATION ARISED FROM THE PROJECT

Pansieri C, Pandolfini C, Clavenna A, Choonara I, Bonati M.: An Inventory of European Birth Cohorts. Int J Environ Res Public Health 2020;17(9):3071.

Pansieri C, Clavenna A, Pandolfini C, Zanetti M, Calati MG, Miglio D, Cartabia M, Zanetto F, Bonati M. NASCITA Italian birth cohort study: a study protocol. *BMC Pediatr* 2020;20:80. doi.org/10.1186/s12887-020-1961-1

Zanetti M, Clavenna A, Pandolfini C, Pansieri C, Calati MG, Cartabia M, Miglio D, Bonati M. Informatics Methodology Used in the Web-Based Portal of the NASCITA Cohort Study: Development and Implementation Study. J Med Internet Res. 2021 Mar 12;23(3):e23087. doi: 10.2196/23087. PMID: 33709930; PMCID: PMC7998320.