# NEWSLETTER

**INDICE**                                                                                         **pag.**

*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.*

1. Sci Rep 2021;11(1):4467. doi:10.1038/s41598-021-84151-7
   **MATERNAL USE OF SEDATIVE DRUGS AND ITS EFFECTS ON PREGNANCY OUTCOMES: A FINNISH BIRTH COHORT STUDY.**
   *Björkstedt S-M, Kautiainen H, Tuomi U, et al.*

   Our aim was to evaluate maternal use of sedative drugs before, during, and after pregnancy and to assess the influence of use of these drugs on pregnancy outcomes. The study cohort (N = 6231) consists of all primiparous women, who lived in the city of Vantaa, Finland, and who delivered a singleton between 2009 and 2015. Data were obtained from Finnish national health registers. Of the women, 3.2% (n = 202) purchased at least once sedative drugs within 90 days before conception, during pregnancy and/or within 90 days after delivery. Sedative drug users were older, less likely to cohabitate, more often smokers, had lower educational attainment and had more mental diseases (for all p < 0.001) compared with non-users. Sedative drug users purchased more often antidepressants and drugs for the alimentary tract, musculoskeletal and nervous system than non-users (for all p < 0.001). No adverse birth or pregnancy outcomes were found in the group using sedative drugs compared with the non-users. Studies in larger cohorts are needed to confirm our study findings.

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2. Paediatr Perinat Epidemiol Published online May 6, 2021 doi:10.1111/ppe.12757
   **THE MATERNAL HEALTH STUDY: STUDY DESIGN UPDATE FOR A PROSPECTIVE COHORT OF FIRST-TIME MOTHERS AND THEIR FIRSTBORN CHILDREN FROM BIRTH TO AGE TEN.**
   *Brown SJ, Gartland D, Woolhouse H, et al.*

   **BACKGROUND**: Maternal health is critical to the health and well-being of children and families, but is rarely the primary focus of pregnancy and birth cohort studies. Globally, poor maternal health and the exposure of women and children to family violence contribute to the perpetuation and persistence of intergenerational health inequalities.
   **OBJECTIVES**: The Maternal Health Study was designed to investigate the contribution of social and obstetric risk factors to common maternal physical and psychological morbidities. Over time, our focus has expanded to include mother-child pairs and investigation of intergenerational trauma and family violence.
   **POPULATION**: A total of 1507 first-time mothers were recruited in early pregnancy from six public hospitals in Melbourne, Australia, in 2003-2005.
   **METHODS**: Women completed questionnaires or telephone interviews in early pregnancy (≤24 weeks); at 32 weeks' gestation; at three, six, nine, 12 and 18 months postpartum; and at four and ten years. At ten years, women and children were invited to participate in face-to-face interviews, which included

direct assessment of children's cognitive and language development. A wide range of obstetric, social and contextual factors have been measured, including exposure to intimate partner violence (IPV) (1-year, 4-year and 10-year follow-up).

**RESULTS**: 1507 eligible women were recruited at a mean gestation of 15 weeks. At one year, four years and ten years postpartum, 90.0%, 73.1% and 63.2% of the original cohort took part in follow-up. One in three women in the study (34.5%) reported exposure to IPV in the first ten years of motherhood: 19% in the first 12 months postpartum, 20% in the year prior to four-year follow-up and 18.3% in the year prior to ten-year follow-up.

**CONCLUSION**: The study affords a unique opportunity to examine patterns of maternal and child health and health service use associated with exposure to IPV.

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3. Prev Med 2021;147:106499. doi:10.1016/j.ypmed.2021.106499
**PRE-AND POSTNATAL MATERNAL SMOKING AND OFFSPRING SMOKING TRAJECTORIES: EVIDENCE FROM A 20-YEAR BIRTH COHORT.**
Chadi N, Ahun MN, Laporte C, et al.

Maternal smoking is associated with increased risk of smoking in the offspring. However, it remains unclear whether this association depends on the timing of exposure to maternal smoking. We investigated the association between prenatal and/or postnatal maternal smoking and offspring smoking during adolescence. Participants (N = 1661) were from the Québec Longitudinal Study of Child Development cohort. We identified longitudinal trajectories of maternal smoking from before pregnancy to child age 12 years using group-based trajectory modeling (GBTM). Adolescent (12-19 years) smoking trajectories were also identified using GBTM. Associations between maternal smoking and offspring smoking trajectories were estimated using multinomial logistic regressions. We used propensity score inverse probability weighting (IPW) to account for the differential distribution of maternal and familial characteristics across exposure groups. We identified four distinct groups for maternal smoking: no (66.1%), decreasing (5.6%), increasing (9.5%) and persistent (18.8%) smoking, and three adolescent smoking trajectories: abstinent, early-onset (before age 15) and late-onset (after age 15). In IPW-adjusted models, youth with mothers with decreasing, increasing and persistent smoking had higher risk of being early-onset smokers compared with youth with mothers in the non-smoking group. We also found that only youth whose mothers were persistent smokers had an increased risk of late-onset smoking. Regardless of timing, offspring exposure to maternal smoking is associated with increased risk of smoking during adolescence. More research is needed on how to create effective smoking cessation campaigns that span preconception, prenatal, and postnatal periods to help prevent intergenerational transmission of smoking behaviors.

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4. Clin Exp Allergy 2021;51(4):556-563. doi:10.1111/cea.13818
**BLOOD EOSINOPHILS ASSOCIATE WITH REDUCED LUNG FUNCTION GROWTH IN**

**ADOLESCENT ASTHMATICS.**

*Koefoed HJL, Gehring U, Vonk JM, Koppelman GH.*

**BACKGROUND AND OBJECTIVE**: Some children with asthma have low lung growth, putting them at increased risk for COPD later in life. However, it is currently not clear who will experience this adverse growth pattern. We therefore investigated the predictive role of blood eosinophils as a type 2 inflammation marker in lung growth, focusing on the presence and severity of asthma.

**METHODS**: We investigated blood eosinophils and lung function growth (percentage of predicted values) using linear mixed models in children and adolescents from two longitudinal cohorts. One cohort was hospital-based and consisted of asthmatic children at their first outpatient clinic visit after referral by the general practitioner (n = 133, mean age 9.8), while the second was a general population-based birth cohort (PIAMA, asthma n = 52 and non-asthma n = 433, mean age 8.1). The hospital-based cohort had not been treated with inhaled corticosteroids (ICS) before referral.

**RESULTS**: Subjects in the hospital-based asthma cohort had more severe asthma compared with the asthmatic subjects in the population-based cohort, defined by lower lung function levels and a higher prevalence of bronchial hyper-responsiveness. In the asthma cohort, higher blood eosinophil numbers were associated with less growth in FEV1 (estimated change in lung function per 1 unit increase in ln blood eosinophils (B): −0.66%/year (95% confidence interval (CI): −1.11 to −0.20, $p < .01$)) and FVC (B: −0.40%/year (95% CI: −0.75 to −0.05, $p = .025$)) during follow-up in adolescence (min 7, max 17 years). These associations were not observed in the general population-based birth cohort, regardless of asthma status during follow-up (age 8–16).

**CONCLUSIONS AND CLINICAL RELEVANCE**: Blood eosinophil counts in children with asthma not treated with ICS at referral were predictive of lower growth in FEV1 and FVC during follow-up in adolescence. Our findings indicate that this association is dependent on the degree of asthma severity. Future studies should address whether anti-eosinophilic treatments preserve lung function growth in children with asthma.

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**CARDIOMETABOLIC PROFILE OF DIFFERENT BODY COMPOSITION PHENOTYPES IN CHILDREN.**

*Ong YY, Huang JY, Michael N, et al.*

**CONTEXT**: Cardiometabolic profiles of different body composition phenotypes are poorly characterized in young children, where it is well established that high adiposity is unfavorable, but the role of lean mass is unclear. OBJECTIVE: We hypothesized that higher lean mass attenuates cardiometabolic risk in children with high fat mass.

**METHODS**: In 6-year-old children (n = 377) from the Growing Up in Singapore Towards healthy Outcomes (GUSTO) prospective birth cohort, whole-body

composition was measured by quantitative magnetic resonance, a novel validated technology. Based on fat mass index (FMI) and lean mass index (LMI), 4 body composition phenotypes were derived: low FMI-low LMI (LF-LL), low FMI-high LMI (LF-HL), high FMI-low LMI (HF-LL), high FMI-high LMI (HF-HL). MAIN **OUTCOME MEASURES**: Body mass index (BMI) z-score, fasting plasma glucose, insulin resistance, metabolic syndrome risk score, fatty liver index, and blood pressure.

**RESULTS**: Compared with the LF-HL group, children in both high FMI groups had increased BMI z-score (HF-HL: 1.43 units 95% CI [1.11,1.76]; HF-LL: 0.61 units [0.25,0.96]) and metabolic syndrome risk score (HF-HL: 1.64 [0.77,2.50]; HF-LL: 1.28 [0.34,2.21]). The HF-HL group also had increased fatty liver index (1.15 [0.54,1.77]). Girls in HF-HL group had lower fasting plasma glucose (-0.29 mmol/L [-0.55,-0.04]) and diastolic blood pressure (-3.22 mmHg [-6.03,-0.41]) than girls in the HF-LL group. No similar associations were observed in boys.

**CONCLUSION**: In a multi-ethnic Asian cohort, lean mass seemed to protect against some cardiometabolic risk markers linked with adiposity, but only in girls. The FMI seemed more important than lean mass index in relation to cardiometabolic profiles of young children.

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6. Pain 2021;162(5):1449-1456. doi:10.1097/j.pain.0000000000002141
**HEADACHE IN GIRLS AND BOYS GROWING UP FROM AGE 11 TO 20 YEARS: THE PREVENTION AND INCIDENCE OF ASTHMA AND MITE ALLERGY BIRTH COHORT STUDY.**
*Wijga AH, Gehring U, van de Putte EM, et al.*

The striking difference between men and women in headache prevalence is suggested to develop in adolescence. Although headaches are common and affect quality of life and daily functioning, the evidence needed to develop effective counselling and preventive approaches is still limited. Using data collected at age 11, 14, 17, and 20 years in the Dutch Prevention and Incidence of Asthma and Mite Allergy birth cohort study (n = 3064 with ≥ 1 questionnaire), we assessed headache prevalence and incidence in girls and boys and explored associations with early life, environmental, lifestyle, health, and psychosocial factors. Associations were analysed longitudinally with generalized linear mixed models and discrete time hazard models. From age 11 to 20 years, the prevalence of headache increased from 9.4% to 19.8% in girls and hardly changed in boys (7.6%-6.1%). Headache commonly co-occurred with other unfavorable health and psychosocial conditions. Eighty-eight percent of the girls and 76% of boys with headache also reported at least one of the following at age 17: sleeping problems, asthma, hay fever, musculoskeletal complaints, fatigue, low mental health, or worrying. Results suggest higher headache prevalence in adolescents following lower educational tracks, in those who skip breakfast ≥2 days per week, and in boys exposed to tobacco smoke in infancy. In girls, sleeping problems and musculoskeletal complaints were associated with higher odds of incident headache and residential greenness with lower odds of incident headache. The high prevalence and strong female predominance of headache, already in adolescence and often with

comorbidities, deserve recognition by professionals in (preventive) health care settings and schools.

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# COORTE NASCITA

### INFORMATICS METHODOLOGY USED IN THE WEB-BASED PORTAL OF THE NASCITA COHORT STUDY: DEVELOPMENT AND IMPLEMENTATION STUDY.
*Zanetti M, Clavenna A, Pandolfini C, et al.*

**BACKGROUND**: Many diseases occurring in adults can be pinned down to early childhood and birth cohorts are the optimal means to study this connection. Birth cohorts have contributed to the understanding of many diseases and their risk factors.

**OBJECTIVE**: To improve the knowledge of the health status of Italian children early on and how it is affected by social and health determinants, we set up a longitudinal, prospective, national-level, population-based birth cohort, the NASCITA study (NAscere e creSCere in ITAlia).

The main aim of this cohort is to evaluate physical, cognitive, and psychological development; health status; and health resource use in the first 6 years of life in newborns, and potential associated factors. A web-based system was set up with the aim to host the cohort; provide ongoing information to pediatricians and to families; and facilitate accurate data input, monitoring, and analysis. This article describes the informatics methodology used to set up and maintain the NASCITA cohort with its web-based platform, and provides a general description of the data on children aged over 7 months.

**METHODS**: Family pediatricians were contacted for participation in the cohort and enrolled newborns from April 2019 to July 2020 at their first well-child visit. Information collected included basic data that are part of those routinely collected by the family pediatricians, but also parental data, such as medical history, characteristics and lifestyle, and indoor and outdoor environment. A specific web portal for the NASCITA cohort study was developed and an electronic case report form for data input was created and tested. Interactive data charts, including growth curves, are being made available to pediatricians with their patients' data. Newsletters covering the current biomedical literature on child cohorts are periodically being put up for pediatricians, and, for parents, evidence-based information on common illnesses and problems in children.

**RESULTS**: The entire cohort population consists of 5166 children, with 139 participating pediatricians, distributed throughout Italy. The number of children enrolled per pediatrician ranged from 1 to 100. The 5166 enrolled children represent 66.55% (5166/7763) of the children born in all of 2018 covered by the same pediatricians participating in the cohort.

The number of children aged over 7 months at the time of these analyses, and for whom the most complete data were available upon initial analyses, was 4386 (2226/4381 males [50.81%] and 142/4370 twins [3.25%]). The age of the mothers at birth of the 4386 children ranged

from 16 to 54 years. Most newborns' mothers (3758/4367, 86.05%) were born in Italy, followed by mothers born in Romania (101/4367, 2.31%), Albania (75/4367, 1.72%), and Morocco (60/4367, 1.37%). Concerning the newborns, 138/4386 (3.15%) were born with malformations and 352/4386 (8.03%) had a disease, most commonly neonatal respiratory distress syndrome (n=52), neonatal jaundice (n=46), and neonatal hypoglycemia (n=45).

**CONCLUSIONS**: The NASCITA cohort is well underway and the population size will permit significant conclusions to be drawn. The key role of pediatricians in obtaining clinical data directly, along with the national-level representativity, will make the findings even more solid. In addition to promoting accurate data input, the multiple functions of the web portal, with its interactive platform, help maintain a solid relationship with the pediatricians and keep parents informed and interested in participating. TRIAL REGISTRATION: ClinicalTrials.gov NCT03894566; https://clinicaltrials.gov/ct2/show/NCT03894566.

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1. J Psychosom Res 2021;145:110488. doi:10.1016/j.jpsychores.2021.110488
   **ADVANCED GLYCATION END PRODUCTS MEASURED BY SKIN AUTOFLUORESCENCE ARE ASSOCIATED WITH MELANCHOLIC DEPRESSIVE SYMPTOMS - FINDINGS FROM HELSINKI BIRTH COHORT STUDY.**
   *Eriksson MD, Eriksson JG, Kautiainen H, et al.*

   **BACKGROUND**: Millions of people live with depression and its burden of disease. Depression has an increased comorbidity and mortality that has remained unexplained. Studies have reported connections between advanced glycation end products (AGEs) and various disease processes, including mental health. The present study evaluated associations between AGEs, depressive symptoms, and types of depressive symptoms.
   **METHODS**: From the Helsinki Birth Cohort Study, 815 participants with a mean age of 76 years were recruited for this cross-sectional study. Characteristics regarding self-reported lifestyle and medical history, as well as blood tests were obtained along with responses regarding depressive symptoms according to the Beck Depression Inventory (BDI) and Mental Health Inventory-5. Each participant had their AGE level measured non-invasively with skin autofluorescence (SAF). Statistical analyses looked at relationships between types of depressive symptoms and AGE levels by sex.
   **RESULTS**: Of women, 27% scored ≥10 on the BDI and 18% of men, respectively. Men had higher crude AGE levels (mean [standard deviation], arbitrary units) (2.49 [0.51]) compared to women (2.33 [0.46]) (p < 0.001). The highest crude AGE levels were found in those with melancholic depressive symptoms (2.61 [0.57]), followed by those with non-melancholic depressive symptoms (2.45 [0.45]) and those with no depressive symptoms (2.38 [0.49]) (p = 0.013). These findings remained significant in the fully adjusted model.
   **CONCLUSIONS**: The current study shows an association between depressive symptoms and higher AGE levels. The association is likely part of a multi-factorial effect, and hence no directionality, causality, or effect can be inferred solely based on the results of this study.

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2. Pain Med Published online March 13, 2021 doi:10.1093/pm/pnaa455
   **EPIDEMIOLOGY OF TRAUMA HISTORY AND BODY PAIN: A RETROSPECTIVE STUDY OF COMMUNITY-BASED AUSTRALIAN WOMEN.**
   *Flehr A, Coles J, Dixon JB, et al.*

   **OBJECTIVE**: To assess whether body pain was associated with different trauma histories (physical injury vs. interpersonal injury [IPI]) within Australian women,

along with body pain and trauma history associations with biological and psychological (biopsycho) confounders.

**METHODS**: A retrospective cross-sectional analysis was conducted on the Australian Longitudinal Study on Women's Health (ALSWH) 1973-1978 birth cohort wave 6 data. Relevant life events were categorized into two types of traumatic experience and included as exposure variables in a multinomial regression model for body pain subgroups. Also, subgroup analyses considered trauma and pain effects and interactions on biopsycho burden.

**RESULTS**: The unadjusted multinomial regression model revealed that a history of physical injury was found to be significantly associated with body pain severity, as was a history of IPI trauma. After the model was adjusted to include biopsycho confounders, the association between IPI and body pain was no longer significant, and post hoc analysis revealed the relationship was instead mediated by biopsycho confounders. Women with a history of IPI and body pain were also found to have the greatest biopsycho (physical functioning, stress, anxiety, and depression) burden.

**DISCUSSION**: The relationship between IPI and body pain was found to be mediated by biopsycho burden, whereas the relationship between physical injury and body pain was not. Also, a history of IPI was associated with a greater biopsycho burden than was a history of physical injury. These results suggest there is clinical value in considering the comprehensive trauma history of patients with pain when developing their biopsychosocial model of care.

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3.  J Hum Hypertens 2021;35(4):371-377. doi:10.1038/s41371-020-0339-z
    **BLOOD PRESSURE LOAD PER BODY SURFACE AREA IS HIGHER IN WOMEN THAN IN MEN.**
    *Korhonen PE, Palmu S, Kautiainen H, Eriksson JG.*

Many unexplained sex differences have been observed in blood pressure (BP) related morbidity. However, there has been little research about the most obvious difference between men and women-body size. Given that blood vessels are organs of tubular shape, we hypothesized that correction of BP for body surface area (BSA), a two-dimensional measurement of body size, would allow comparison of BP load between men and women. We assessed the relationship of 24-h ambulatory BP measurements and BSA in 534 participants (mean age 61 ± 3 years, 51% women) from the Helsinki Birth Cohort Study. The study subjects had no previous medication affecting vasculature or BP. When BP values were adjusted for age, smoking, physical activity, and body fat percentage, males had higher ambulatory daytime mean systolic BP (131 mmHg vs. 127 mmHg, $p < 0.001$), diastolic BP (83 mmHg vs. 78 mmHg, $p < 0.001$), and mean arterial pressure (100 mmHg vs. 96 mmHg, $p < 0.001$) than females. However, all BP components per unit of BSA were significantly lower in males: daytime mean systolic BP (65 mmHg vs. 71 mmHg, $p < 0.001$), diastolic BP (41 mmHg vs. 44 mmHg, $p < 0.001$), pulse pressure (24 mmHg vs. 28 mmHg, $p = 0.013$), and mean arterial pressure (49 mmHg vs. 54 mmHg, $p < 0.001$). The same phenomenon was observed in night-

time BP values. BP load per BSA is higher in women than in men, which may explain many reported sex differences in cardiovascular morbidity. Relatively small-sized individuals might benefit from a more aggressive therapeutic strategy.

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**CARDIOVASCULAR DISEASE IN PEOPLE BORN TO UNMARRIED MOTHERS IN TWO HISTORICAL PERIODS: THE HELSINKI BIRTH COHORT STUDY 1934-1944.**
*Mikkonen HM, Salonen MK, Häkkinen A, Osmond C, Eriksson JG, Kajantie E.*

**AIMS**: Socio-economic conditions in early life are important contributors to cardiovascular disease - the leading cause of mortality globally - in later life. We studied coronary heart disease (CHD) and stroke in adulthood among people born out of wedlock in two historical periods: before and during World War II in Finland.
**METHODS**: We compared offspring born out of wedlock before (1934-1939) and during (1940-1944) World War II with the offspring of married mothers in the Helsinki Birth Cohort Study. The war affected the position of unmarried mothers in society. We followed the study subjects from 1971 to 2014 and identified deaths and hospital admissions from CHD and stroke. Data were analysed using a Cox regression, adjusting for other childhood and adulthood socio-economic circumstances.
**RESULTS**: The rate of out-of-wedlock births was 240/4052 (5.9%) before World War II and 397/9197 (4.3%) during World War II. Among those born before World War II, out-of-wedlock birth was associated with an increased risk of stroke (hazard ratio (HR)=1.44; 95% confidence interval (CI) 1.00-2.07) and CHD (HR=1.37; 95% CI 1.02-1.86). Among those born out of wedlock during World War II, the risks of stroke (HR=0.89; 95% CI 0.58-1.36) and CHD (HR=0.70; 95% CI 0.48=1.03) were similar to those observed for the offspring of married mothers. The p-values for interaction of unmarried×World War II were (p=0.015) for stroke and (p=0.003) for CHD.
**CONCLUSIONS**: In a society in which marriage is normative, being born out of wedlock is an important predictor of lifelong health disadvantage. However, this may change rapidly when societal circumstances change, such as during a war.

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## EUROPEAN CHILD COHORT NETWORK'S

- Eur J Epidemiol 2021;36(5):565-580. doi:10.1007/s10654-021-00733-9
  **THE EU CHILD COHORT NETWORK'S CORE DATA: ESTABLISHING A SET OF FINDABLE, ACCESSIBLE, INTEROPERABLE AND RE-USABLE (FAIR) VARIABLES.**
  *Pinot de Moira A, Haakma S, Strandberg-Larsen K, et al.*

*The Horizon2020 LifeCycle Project is a cross-cohort collaboration which brings together data from multiple birth cohorts from across Europe and Australia to facilitate studies on the influence of early-life exposures on later health outcomes. A major product of this collaboration has been the establishment of a FAIR (findable, accessible, interoperable and reusable) data resource known as the EU Child Cohort Network. Here we focus on the EU Child Cohort Network's core variables. These are a set of basic variables, derivable by the majority of participating cohorts and frequently used as covariates or exposures in lifecourse research. First, we describe the process by which the list of core variables was established. Second, we explain the protocol according to which these variables were harmonised in order to make them interoperable. Third, we describe the catalogue developed to ensure that the network's data are findable and reusable. Finally, we describe the core data, including the proportion of variables harmonised by each cohort and the number of children for whom harmonised core data are available. EU Child Cohort Network data will be analysed using a federated analysis platform, removing the need to physically transfer data and thus making the data more accessible to researchers. The network will add value to participating cohorts by increasing statistical power and exposure heterogeneity, as well as facilitating cross-cohort comparisons, cross-validation and replication. Our aim is to motivate other cohorts to join the network and encourage the use of the EU Child Cohort Network by the wider research community.*

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## SEGNALAZIONI

## 33° Congresso Nazionale ACP

Il "mestiere" di pediatra dal presente al futuro (webinar)

23 ottobre 2021

Original Paper

# Informatics Methodology Used in the Web-Based Portal of the NASCITA Cohort Study: Development and Implementation Study

Michele Zanetti, BEng; Antonio Clavenna, MD; Chiara Pandolfini, PhD; Claudia Pansieri, PharmD; Maria Grazia Calati, HS; Massimo Cartabia, StatSc; Daniela Miglio, HS; Maurizio Bonati, MD

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## Abstract

**Background:** Many diseases occurring in adults can be pinned down to early childhood and birth cohorts are the optimal means to study this connection. Birth cohorts have contributed to the understanding of many diseases and their risk factors.

**Objective:** To improve the knowledge of the health status of Italian children early on and how it is affected by social and health determinants, we set up a longitudinal, prospective, national-level, population-based birth cohort, the NASCITA study (NAscere e creSCere in ITAlia). The main aim of this cohort is to evaluate physical, cognitive, and psychological development; health status; and health resource use in the first 6 years of life in newborns, and potential associated factors. A web-based system was set up with the aim to host the cohort; provide ongoing information to pediatricians and to families; and facilitate accurate data input, monitoring, and analysis. This article describes the informatics methodology used to set up and maintain the NASCITA cohort with its web-based platform, and provides a general description of the data on children aged over 7 months.

**Methods:** Family pediatricians were contacted for participation in the cohort and enrolled newborns from April 2019 to July 2020 at their first well-child visit. Information collected included basic data that are part of those routinely collected by the family pediatricians, but also parental data, such as medical history, characteristics and lifestyle, and indoor and outdoor environment. A specific web portal for the NASCITA cohort study was developed and an electronic case report form for data input was created and tested. Interactive data charts, including growth curves, are being made available to pediatricians with their patients' data. Newsletters covering the current biomedical literature on child cohorts are periodically being put up for pediatricians, and, for parents, evidence-based information on common illnesses and problems in children.

**Results:** The entire cohort population consists of 5166 children, with 139 participating pediatricians, distributed throughout Italy. The number of children enrolled per pediatrician ranged from 1 to 100. The 5166 enrolled children represent 66.55% (5166/7763) of the children born in all of 2018 covered by the same pediatricians participating in the cohort. The number of children aged over 7 months at the time of these analyses, and for whom the most complete data were available upon initial analyses, was 4386 (2226/4381 males [50.81%] and 142/4370 twins [3.25%]). The age of the mothers at birth of the 4386 children ranged from 16 to 54 years. Most newborns' mothers (3758/4367, 86.05%) were born in Italy, followed by mothers born in Romania (101/4367, 2.31%), Albania (75/4367, 1.72%), and Morocco (60/4367, 1.37%). Concerning the newborns, 138/4386 (3.15%) were born with malformations and 352/4386 (8.03%) had a disease, most commonly neonatal respiratory distress syndrome (n=52), neonatal jaundice (n=46), and neonatal hypoglycemia (n=45).

**Conclusions:** The NASCITA cohort is well underway and the population size will permit significant conclusions to be drawn. The key role of pediatricians in obtaining clinical data directly, along with the national-level representativity, will make the findings even more solid. In addition to promoting accurate data input, the multiple functions of the web portal, with its interactive platform, help maintain a solid relationship with the pediatricians and keep parents informed and interested in participating.

**Trial Registration:** ClinicalTrials.gov NCT03894566; https://clinicaltrials.gov/ct2/show/NCT03894566

## Introduction

It is well known that many diseases occurring in adults can be traced back to early childhood [1,2]. In fact, nearly all domains of later health experience, including cardiovascular and respiratory disease, cognitive decline, and psychological health, have been associated with early life exposures [3]. Many different factors in childhood play a role in future health inequalities between individuals, from socioeconomic status to parental care, to lifestyle factors, but the way they are related is uncertain.

Birth cohort studies are studies that follow a group of newborns for an extended period in order to assess possible associations between exposures in early life and later health. Northern Europe has a long-lasting tradition in birth cohorts [4,5], starting from as far back as 1921 [6]. Findings from these studies have led to important knowledge in different fields, contributing to the understanding of multiple diseases and their risk factors [7,8]. These studies have also set the basis of our positive daily health behaviors. The Avon Longitudinal Study of Parents and Children (ALSPAC), for example, showed that eating oily fish during pregnancy was associated with better eye and cognitive development in children [9].

Numerous large- and small-scale birth cohorts have been set up, also in the past decade, not only in Europe but all around the world [10]. Characteristics vary greatly from one cohort to another in terms of design, objectives, size, and duration of follow-up.

Since 2003, several cohorts have also been carried out in Italy. Most of them have general aims, with data collection limited in time or to specific geographical contexts [11-19]. Italy is a special country with a public, universal health care system that should be equally accessible to all, but considerable health inequalities exist [20,21]. Up to now, no national-level birth cohort has been set up that included a large sample of the pediatric population independent of socioeconomic status or other types of limitation, such as gestational age. The Piccolipiù cohort [17], for example, recruited newborns from northern and central Italy; the NINFEA cohort [16] population was limited to women who had enough knowledge of the internet to complete online questionnaires; and the ICON cohort [19] selected preterm newborns and enrolled additional newborns of later gestational age.

In order to improve the knowledge of the health status of Italian children early on and how it is affected by social and health determinants, we set up a longitudinal, prospective, national-level, population-based birth cohort, the NASCITA study (NAscere e creSCere in ITAlia) [22]. Like many other cohorts, it addresses multiple research questions [16,17]. NASCITA is unique, however, in terms of characteristics, methodology, and population size. 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.

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 6 years of life in a group of newborns, and to evaluate potential associated factors.

The peculiarity of NASCITA is that data collection is designated to the general pediatricians, fitting itself into the Italian public health care system, as data reported in NASCITA are part of those routinely collected by the family pediatricians at the well-child visits. Furthermore, the data are equally distributed throughout the Italian territory.

A website and web-based system [23] 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.

This article describes the informatics methodology used to set up and maintain the NASCITA cohort with its web-based platform, and provides a general description of the participant characteristics.

## Methods

### Cohort Organization

NASCITA is embedded in Italian pediatric primary care practice. Data collection for the NASCITA cohort occurs for the most part during the 7 well-child visits planned for each child. The majority of the participating pediatricians are part of the national Pediatric Cultural Association (ACP), an association with about 2000 members consisting mainly of family pediatricians and with which the coordinating center has collaborated over the years. Participation was proposed to the ACP and forms the basis of pediatrician participation in the study. Pediatrician participation was voluntary and for free. Collaboration was also expanded through contact with other pediatric scientific societies and associations. Meetings were held during 2018 to present the study to a group of pediatricians acting as local representatives. Each representative then asked other pediatricians working in their area (at the local health unit or regional levels) to participate. Pediatrician enrollment was monitored and discussed with the local representatives. A scientific committee was set up to supervise the project, and includes professionals and lay people from different fields of expertise.

At the start of the study, there were 7960 cities/towns in Italy. These were classified into 21 geographic clusters (Figure 1), identified based on geographic and administrative criteria used by the Italian National Statistics Institute (ISTAT) [24]. More specifically, these take into consideration geographic area (north, center, south), setting (urban, rural), and land characteristics

(plain, mountain, sea). Four cities were also selected (Milan, Rome, Bari, and Palermo), covering the different geographic areas and the islands.

Enrollment of newborns began in April 2019 and ended in July 2020. Recruitment of the newborns (and their parents) took place during the first routine well-child visit scheduled for all newborns in Italy within their first 45 days of life. All newborns assigned to the participating pediatricians were enrolled if parental consent was given. Pediatricians chose when to begin enrolling their newborns and continued to enroll for (at least) a 1-year period. Follow-up of the children will continue until at least the age of 6 years.

A minimum recruitment of 5000 newborns was calculated in order to have enough power to study common childhood exposures and outcomes.

In this article we present the characteristics of the children aged over 7 months at the time of analyses in order to provide more complete data, as pediatricians would have had time to fill in most missing data for these participants.

**Figure 1.** The 21 geographic clusters, identified based on ISTAT geographic and administrative criteria. ISTAT: Italian National Statistics Institute.
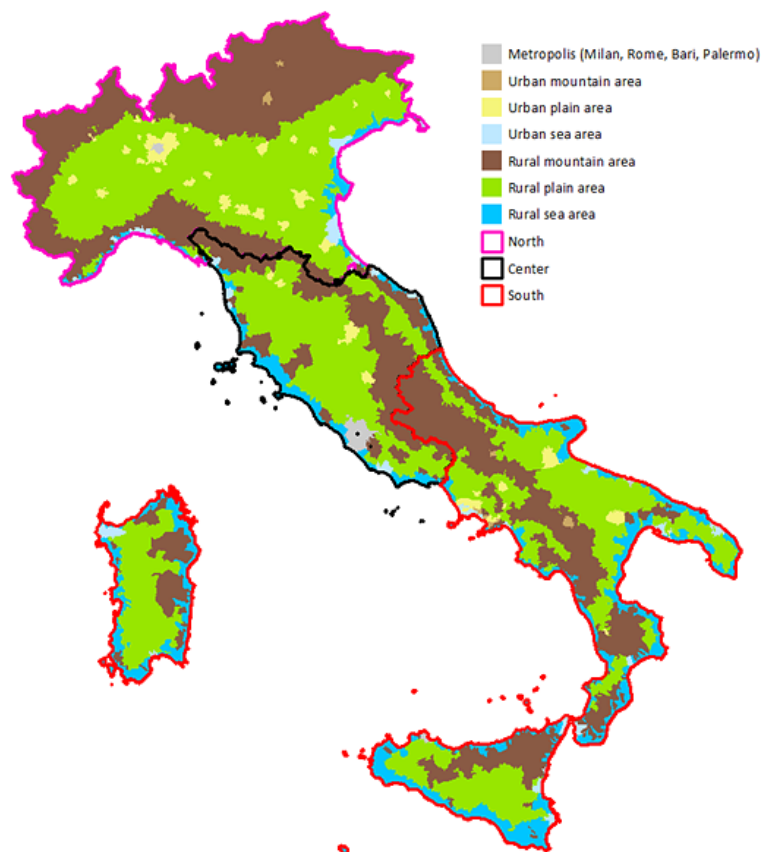


### Ethics

Parents were given oral and written information about the study and a consent form to sign if interested in participating. Pediatricians signed a consent form before participation as well. Withdrawal from the study was guaranteed at any time to both pediatricians and parents.

### Data Collection

Italian health care is provided free or at a nominal charge through a network of 148 local health units. The local health units assign children to a family pediatrician until they are 6 years old, after which the children can be registered with a general practitioner or remain with that pediatrician until they are 14 years old. In Italy there are about 7500 family pediatricians, for an average of 450,000 births/year [25], so about 60 newborns/year are assigned to each pediatrician. All children are scheduled 7 well-child visits at the pediatrician's office during their first 6 years of life to ensure necessary preventive care and monitor a child's growth and development.

Basic data are being collected and consist of data that are part of those routinely collected by the family pediatricians at the well-child visits. Some data will also be collected during each extra contact with the enrolled children. Data collection also involves parental data, such as medical history, characteristics and lifestyle, indoor and outdoor environment, and circumstances during pregnancy and around birth. Follow-up data on children will cover different fields, including physical and mental/cognitive development, nutrition and allergies, environmental exposures, and preventable infectious diseases. See Table 1 for a description of the main parts of the questionnaire. Questions were added to allow the project, in a second phase, to address specific areas such as nutrition, environment, and nurturing care.

**Table 1.** Main sections of the online questionnaires and description of the general data collected.

| Section | Description |
| --- | --- |
| Personal data | Name, place of birth, family data such as number of family members, sibling health, parental place of birth, allergies |
| Medical history | Mother's pregnancy data (including medicines, smoking and alcohol consumption, and reading out loud and listening to music), birth data (eg, newborn height, weight), perinatal medical history (eg, malformations, diseases, transfer to an intensive care unit), breastfeeding status at discharge |
| Visits 1-7 | Medicines taken, anthropometric measures; breastfeeding status/weaning/nutrition; sleep data; age-appropriate physical examination; vitamin D + K prophylaxis; psychomotor, neurologic, and cognitive development; general health; paternal depression; language development; family habits (eg, smoking, reading out loud, listening to music, nursery school, indoor and open-air activities); home proximity to traffic or to areas of intensive farming; screen time |
| Extra visits | Type of contact (office, phone, home visit), diagnosis, medicines/specialist visits/examinations prescribed |
| Vaccination compliance | Vaccines received and adverse reactions |
| Exiting the cohort | Reason for exit (transfer, pulled out of study, death) |

## Statistical Analysis

The analyses of the cohort data will evaluate specific research questions related to the overall aims of the study, such as the relationship between child development and the domains that affect nurturing care during the preschool period including health, nutrition, and caregiving routine; the association between the well-being of children and parental adherence to the recommendations for better child care and development; and the differences between geographical settings in educational and socialization opportunities available and in the care provided by the family pediatricians.

Data are presented as frequencies, percentages, and mean (SD) or median values. Percentages are based on denominators for which missing values have been excluded. All data management and analyses have been performed using SAS version 9.4 (SAS Institute) and ArcMap version 10.5 (ESRI). More detailed analyses will be performed, as specified in the protocol [22], and reported in future articles.

## Web Portal

A specific web portal for the NASCITA cohort study was developed [23] with reserved sections for the coordinating center, registered users, and participating pediatricians. The web portal serves to assist pediatricians with data collection and to provide findings and other information during the study period to 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 [26]. Selected sections of the portal have been translated into English. See Figure 2 for the functions of the web portal and its architecture.

Newsletters focused on child cohorts are periodically provided in the pediatrician's general area and contain bibliographic information of the current biomedical literature. In the private area, each participating pediatrician can access information including cohort documents; frequently asked questions; the study protocol; and pdf versions of the case report forms (CRFs); as well as patient data for input/modification; interactive data charts of his/her patients or of those of the entire cohort, including growth curves (Figure 3); and data concerning subsections of the cohort addressing areas such as nutrition and environment in which he/she participates. The pediatrician's section on the web portal, together with individual telephone calls with the pediatricians and online and in-person meetings on the study's progress and possible problems, serves to keep pediatricians engaged in the study.

The information for the parents section contains a growing series of cards, created in collaboration between health professionals and parents, that provide evidence-based information on the more common illnesses and 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 information pages.

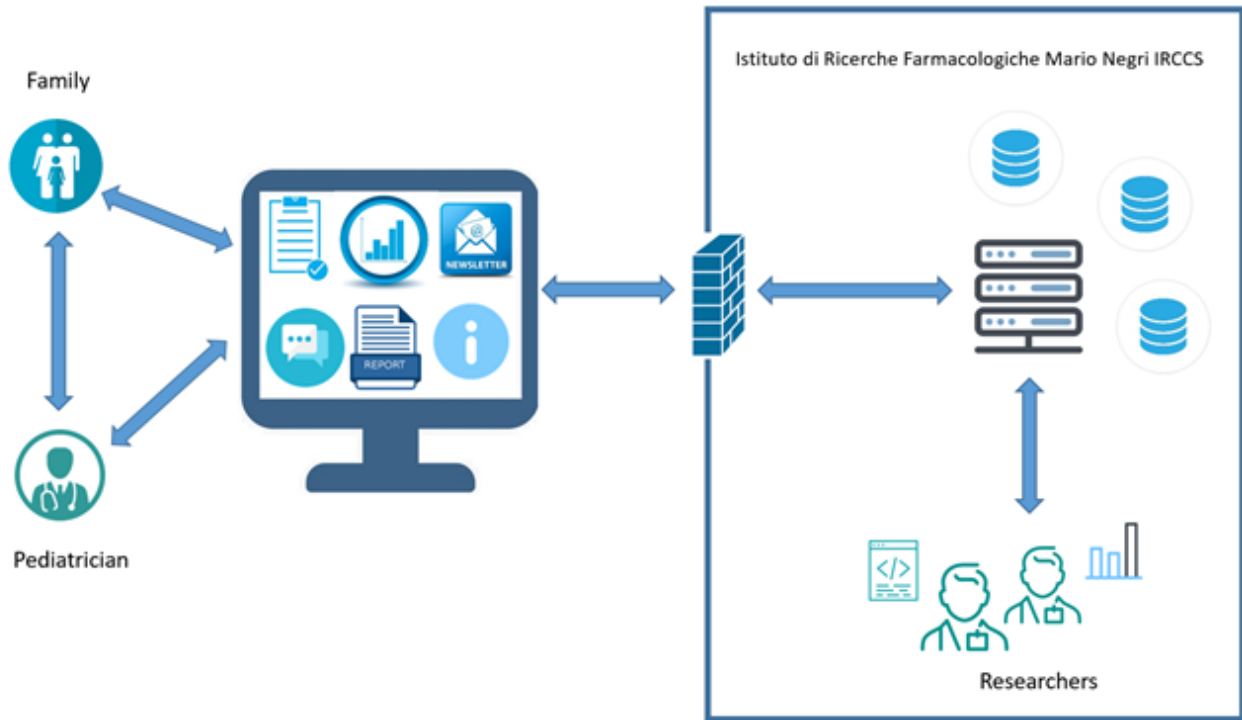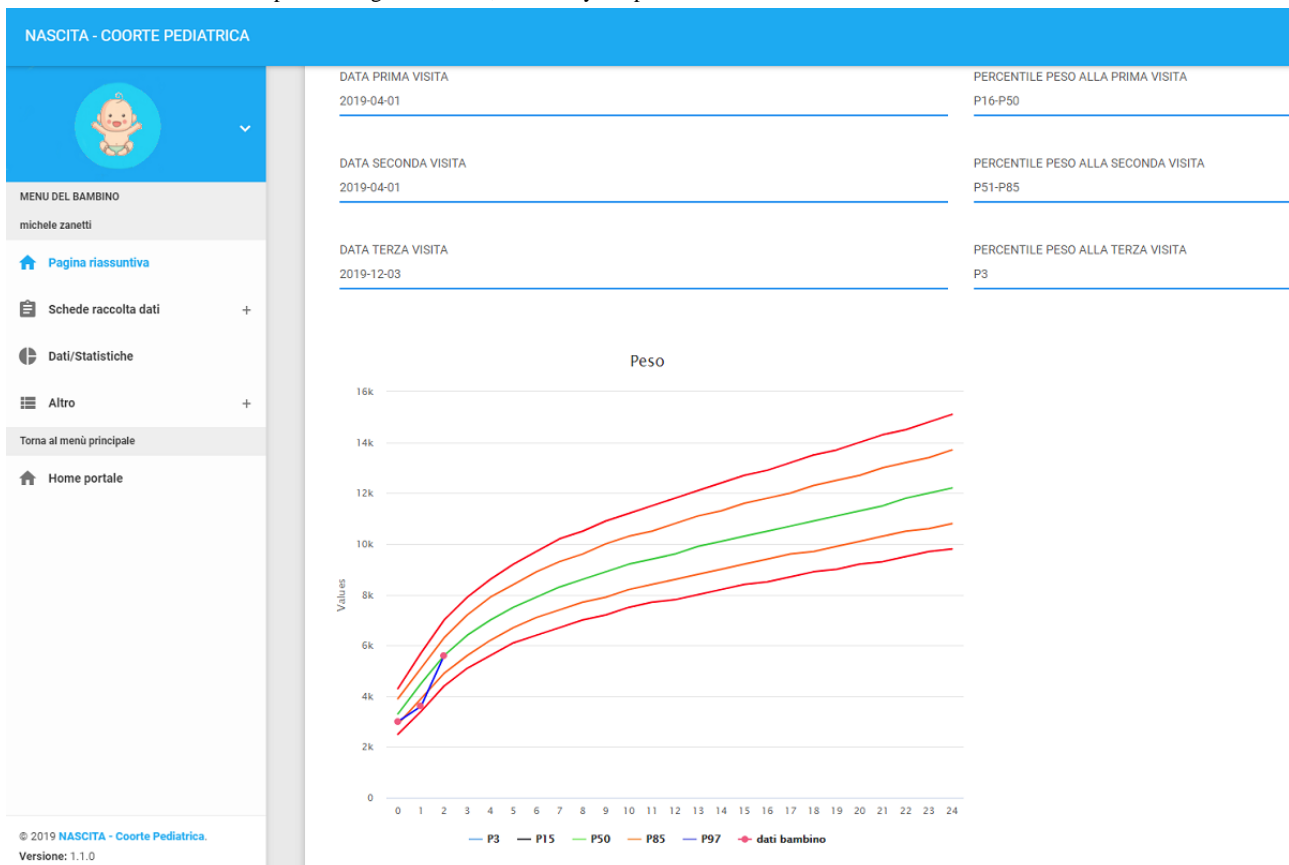**Figure 2.** Functions of the platform and its architecture.



**Figure 3.** Individual child's data plotted on growth curve, as seen by the pediatrician.



## Electronic Case Report Form

The CRF was created and tested together with a group of pediatricians. An electronic CRF (eCRF) was then set up and tested, again with the help of the pediatricians, before enrollment began. More specifically, the pediatricians were asked to register themselves and access the portal starting from January 2019 to test it. The eCRF (Figure 4) was set up in such a way as to facilitate the pediatricians' input of data for the study and to provide fast and efficient support for any problems or doubts about data input. A "chat" section was consequently included through which pediatricians can ask for support. The eCRF

includes consistency and range checks to prevent internal inconsistencies (eg, value ranges, fields with limited values, and time ranges). Data are, in any case, monitored continuously and irregularities resolved through email, chat, or phone contact with the pediatricians.

The eCRF has been structured in a way that will permit data collection to be expanded to cover the additional areas (eg, nutrition) more thoroughly in a second phase; the different data collection sections are, in fact, based on an XML definition that can easily be implemented and modified [27].

The development engine of the eCRF has been made available on Gitlab [28].

A test was performed with a group of pediatricians (including those with less experience in using the computer) to assess the additional amount of time it would take each pediatrician to enter data for a patient throughout the duration of the study. Entering data for the first follow-up visit took about 15 minutes. Multiplying this by the average number of newborns per pediatricians and, considering that after 3 months of the start of the study the subsequent regular check-ups would begin, an average of 3 hours a month in the first year was calculated, after which the amount of time necessary would decrease.

**Figure 4.** eCRF screenshots: input for second visit.



## Data Quality Control

A dashboard is dedicated to checking the completeness, or lack, of the visits and displays a table listing the children for whom data have been included by that pediatrician. Each column in the table represents a specific visit and shows a series of colored bells (green, yellow, or red) that indicate the completeness status of the visit (Figure 5). When a pediatrician opens the data on a specific visit, the system displays a list of the variables with missing information in order to facilitate data completion.

Frequent reports will automatically be created to monitor recruitment of pediatricians and children and the data inputted. Individual and group reports will also be created for the pediatricians and for the study's scientific committee.

**Figure 5.** eCRF dashboard for checking completeness of data on the visits for individual patients.



## Data Security

The private area is accessible only through authentication by pediatricians, who have been previously approved and enabled. A specific role is assigned to them, for example, *compiler*. Passwords must have at least eight characters and contain special and uppercase characters. Each pediatrician with a compiler role can insert their patients' data. Sensitive data, such as name and last name, are encoded and visible only to the compiler. Once the data are saved, they are transmitted via secure HTTPS protocol, and are stored in databases that can be accessed only by authorized project staff (IT, statisticians). Back-ups are kept for security and disaster recovery.

## Results

Enrollment in the NASCITA cohort began on April 1, 2019, and ended on July 31, 2020. The number of participating pediatricians is 139 and the total number of children enrolled is 5166. The pediatricians are distributed throughout Italy, with 68 in the north, 29 in the center, and 42 in the south. The 5166 children enrolled represent 66.55% (5166/7763) of the children born in all of 2018 covered by these same pediatricians.

The total number of children aged over 7 months at the time of these analyses was 4386. Of these children, excluding those with missing data, 2226/4381 (50.81%) were male and 142/4370 (3.25%) were twins. The children were distributed throughout Italy, with 2025/4386 (46.17%) in the north, 882/4386 (20.11%) in the center, and 1479/4386 (33.72%) in the south. Table 2 reports the distribution of the number of these 4386 children enrolled and the percentage of children born, by cluster and geographic area, based on ISTAT data [24], and shows that

there are minimal differences. The number of children enrolled per pediatrician ranged from 1 to 100 (mean 32 [SD 18.5]; median 30).

The age of the mothers at birth of the 4386 children ranged from 16 to 54 (mean 33 [SD 5.4] years; median 33 years, excluding 133 missing values), while the age of the fathers ranged from 17 to 69 (mean 36 [SD 6.3]; median 36, excluding 154 missing values). Most of the newborn's mothers (3758/4367, 86.05%) were born in Italy; the 3 next most common countries were Romania (101/4367, 2.31%), Albania (75/4367, 1.72%), and Morocco (60/4367, 1.37%). For two-thirds of children (2892/4320, 66.94%), the mothers were married or living in civil union; for 1233/4320 children (28.54%), the mother was living with the father; and for 167/4320 (3.87%), mothers were single. Most of the children's mothers had a university (1813/4320, 41.96%) or high-school degree (1800/4320, 41.66%), followed by a middle-school diploma (675/4320, 15.63%) and an elementary (30/4320, 0.69%) level of education. Family size (including the enrolled child) was grouped into 2, 3, 4, or >4 people, with half (2189/4311, 50.78%) of the families being made up of 3 people, followed by 1567/4311 (36.35%) made up of 4 people. Two-member families represented 1.43% (62/4311) of the total. Concerning the pregnancies, 3741/4363 (85.74%) were physiologic pregnancies, while in the remaining pregnancies gestational diabetes (203/622 mothers, 32.64%), gestational hypertension (90/622, 14.47%), and preeclampsia (41/622, 6.59%) were the most common diseases. Concerning the newborns, 139/4340 (3.20%) were born with malformations and 352/4335 (8.12%) had a disease, the 3 most common of which were neonatal respiratory distress syndrome (n=52), neonatal jaundice (n=46), and neonatal hypoglycemia (n=45).

**Table 2.** Distribution of the number of children and the number of children born in each cluster and geographic area.

| Distribution/Location | Children enrolled, n (N=4386) | Population enrolled, n (%) | Births per year in Italy[a], n (%) | Difference between the third and fourth columns, % |
|---|---|---|---|---|
| Metropolis: Milan | 184 | 184/4386 (4.20) | 11,267/467,640 (2.41) | 1.79 |
| Metropolis: Rome | 428 | 428/4386 (9.76) | 21,497/467,640 (4.60) | 5.16 |
| Metropolis: Bari | 70 | 70/4386 (1.60) | 2214/467,640 (0.47) | 1.13 |
| Metropolis: Palermo | 62 | 62/4386 (1.41) | 5578/467,640 (1.19) | 0.22 |
| North: urban mountain | __[b] | — | 2243/467,640 (0.48) | –0.48 |
| North: urban plain | 304 | 304/4386 (6.93) | 45,595/467,640 (9.75) | –2.82 |
| North: urban sea | 93 | 93/4386 (2.12) | 10,258/467,640 (2.19) | 0.07 |
| North: rural mountain | 228 | 228/4386 (5.20) | 25,274/467,640 (5.40) | –0.20 |
| North: rural plain | 1151 | 1151/4386 (26.24) | 112,824/467,640 (24.13) | 2.11 |
| North: rural sea | 60 | 60/4386 (1.37) | 5882/467,640 (1.26) | 0.11 |
| Center: urban plain | 61 | 61/4386 (1.39) | 6330/467,640 (1.35) | –0.04 |
| Center: urban sea | 1 | 1/4386 (0.02) | 5339/467,640 (1.14) | –1.12 |
| Center: rural mountain | 90 | 90/4386 (2.05) | 13,887/467,640 (2.97) | –0.92 |
| Center: rural plain | 233 | 233/4386 (5.31) | 31,997/467,640 (6.84) | –1.53 |
| Center: rural sea | 68 | 68/4386 (1.55) | 11,118/467,640 (2.38) | –0.83 |
| South: urban mountain | 8 | 8/4386 (0.18) | 4010/467,640 (0.86) | –0.68 |
| South: urban plain | 136 | 136/4386 (3.10) | 15,826/467,640 (3.38) | –0.28 |
| South: urban sea | 421 | 421/4386 (9.60) | 27,281/467,640 (5.83) | 3.77 |
| South: rural mountain | 98 | 98/4386 (2.23) | 21,932/467,640 (4.69) | –2.46 |
| South: rural plain | 421 | 421/4386 (9.60) | 47,026/467,640 (10.06) | –0.46 |
| South: rural sea | 255 | 255/4386 (5.81) | 40,262/467,640 (8.61) | –2.80 |
| Missing | 14 | — | — | — |

[a]Based on data on the newborn population residing in the cluster on January 1, 2017. ISTAT demographic statistics data [24] referring to December 31, 2016, were used for clusters with missing data.

[b]—: not available.

## Discussion

### Considerations

The NASCITA cohort is based on community-level pediatric practice, involving the family pediatricians directly, as very few European cohorts do [29]. With their clinical practice, pediatricians are most in contact with patients and can promote study and action. Their involvement in child cohorts permits the collection of prospective, community-level data and allows them to contribute to optimizing both the quality of the data collected and its re-investment back into the community as health promotion interventions. In fact, pediatricians play a key role both in educating families and in implementing curative and disease prevention interventions through their routine clinical practice. They are in the optimal position to influence public health in general because adult health also depends on habits embraced when young, and pediatricians can undoubtedly influence children and their parents to adopt healthy lifestyles. In order to give something back to the pediatricians participating in the cohort, we have attempted to provide the pediatricians with useful information and interesting data, such as the

interactive data charts of their patients. The system set up through which pediatricians can easily and quickly contact the cohort team for any questions or problems, and the periodic meetings organized to update pediatricians on the cohort's status and to discuss any current issues or suggestions are additional ways to show our appreciation for all their continuing efforts. During the latest meeting we had with the participating pediatricians, online in November 2020, we described the enrolled population as it was just after enrollment closure and the next steps. On this occasion several pediatricians provided additional suggestions for improving input, resulting in the message to all that their participation and efforts are ongoing and continue to be acknowledged by the research team.

Recruitment of newborns took place over a period of 1 year for each pediatrician. This time span permitted us to avoid introducing bias related to the period of recruitment, for example, by recruiting newborns born during one season as opposed to another. The sample of children aged over 7 months reflects the distribution of births in Italy in terms of both geographic area (north, center, and south) and 21 clusters, based on the ISTAT data. Collection of data at the national level will

permit the identification of differences in health care quality, such as those caused by socioeconomic inequalities present between the north and south of Italy [30], and of differences in family behaviors that influence child health status (eg, smoking or reading out loud to children). Better identifying health care–related inequalities will permit the channeling of resources where they are most needed [31]. If funding is obtained, the population enrolled could be expanded further.

As explained previously, the web portal has multiple functions and is fundamental for several reasons. The innovative aspects involve permitting the accurate input and monitoring of data through the use of a tool that creates data collection based on an xml definition, and providing pediatricians with interactive charts of current data to share with the children's parents.

This xml-based system allows a continuous and simple updating of the CRF, saving a lot of time in the development and testing phase. In addition, saving the data in the JavaScript Object Notation (JSON) format allows greater flexibility in the database structure which, therefore, does not need to be remodified at each CRF update [32].

Furthermore, our idea for the future is to interconnect the portal with apps for parents to use to access data and to provide additional information.

## Strengths and Limitations

This is one of a very limited number of child cohorts based on the participation of family pediatricians, permitting the collection of data by those directly involved with the children

and the implementation of findings to inform and help those directly involved (the children and their families). Furthermore, the large, representative population sample of newborns throughout the country, which allows stratified trends based on socioeconomic and geographic characteristics to be performed, and the use of standard measurements for anthropometric and neurocognitive parameters are among the strengths of this study.

A limit of the NASCITA cohort is that it does not collect biological samples due to the costs of data collection and storage, 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 in order to have enough power to study relatively common child exposures and outcomes. Another limitation is the potential bias in the pediatrician population because participation was voluntary and this may have led more motivated pediatricians to participate than others.

## Conclusions

The NASCITA cohort is well underway and its population size will permit significant conclusions to be drawn. The key role of pediatricians in obtaining clinical data directly, along with the national-level representativity, will make the findings even more solid. In addition to promoting accurate data, the multiple functions of the web portal, with its expanding, interactive platform, will help maintain a solid relationship with the pediatricians and keep parents informed and interested in participating.

## Authors' Contributions

MB, AC, and C Pansieri conceptualized the study, designed the web portal, and designed the CRF. AC, C Pandolfini, C Pansieri, and DM tested the CRF. MZ created the web portal, the eCRFs, and the interactive charts system. AC, MC, and C Pansieri coordinated and monitored data collection. MGC collaborated in assisting the pediatricians with data input problems and managed email and phone communication with pediatricians and with the technical and scientific committees. MC carried out the analyses. DM and C Pansieri were responsible for merging requests for modifications and corrections to the CRFs during testing, for re-testing them, and for creating the layout with data check and limit specifications for transformation into the electronic version. DM was responsible for website content and created the information cards for parents and the newsletters for the pediatricians. C Pandolfini wrote the first draft of the manuscript. All authors interpreted data and critically reviewed and revised the final manuscript as submitted. All authors agree to be accountable for aspects of their contribution to the work. MB is the guarantor.

## Conflicts of Interest

None declared.

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## Abbreviations

**ACP:** Pediatric Cultural Association
**CRF:** case report form
**eCRF:** electronic case report form
**ISTAT:** National Statistics Institute
**JSON:** JavaScript Object Notation
**NASCITA cohort:** NAscere e creSCere in ITAlia cohort

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