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1 **Cohort profile: The national, longitudinal NASCITA Cohort study**

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21   **ABSTRACT**

22   **Purpose** The NASCITA Study, a national level, population-based, prospective cohort study,

23   was set up to better understand the early health status of Italian children, comprising their

24   physical, cognitive, and psychological development, and how it is affected by social and

25   health determinants, including nurturing care. NASCITA will also assess geographical

26   differences and disparities in health care.

27   **Participants** Participating family paediatricians from throughout Italy enrolled infants born

28   during the enrolment period (April 2019-July 2020). The 5054 newborns seen by the 139

29   paediatricians for at least two visits, including the first well-child visit, and for whom parental

30   consent was given, make up the baseline population.

31   **Findings to date** Mothers had a mean age at delivery of 33.1 years and tended to have a high

32   or medium level of education (42.5% university and 41.7% high school degrees) and to be

33   employed (69.7%). One third (36.1%) took folic acid supplementation appropriately, and

34   6.5% smoked or consumed alcohol (10.0%) during pregnancy.

35   One third (31.7%) of deliveries were caesarean deliveries.

36   Concerning the newborns, 5.8% had a low birthweight and 6.2% were born

37   prematurely. The majority (87.7%) slept in the supine position and 63.6% were exclusively

38   breastfed at one month, with a decreasing North to South prevalence (χ^2_t 52; p<0.001).

39   Significant North-South differences were found in all areas, including parental

40   education, behaviours in pregnancy, and hospital practices.

41   When compared with national level data, the cohort population's distribution, maternal

42   socio-demographic characteristics, and newborn physical characteristics reflect those of the

43   Italian population.

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44   **Future plans:** Data will continue to be collected during the well-child visits until the children

45   are 6 years old and multiple health outcomes will be studied, spanning child development and

46   illness, as well as potentially related factors including caregiving routines. The findings will

47   be used to develop specific interventions to improve children's health.

48   **Registration**: Clinicaltrials.gov: NCT03894566

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50   **Key words**: Cohort Studies; Child; Health; Infant, Newborn; Italy; Population

51   Characteristics; Public Health;

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53   **Strengths and limitations of this study**

54   • The NASCITA study is one of few involving the paediatricians directly as

55   protagonists in cohort design and data collection. The paediatricians' primary role

56   permits them to contribute first-hand to improving the cohort's functioning, to

57   implement the recommended changes in practice resulting from the findings, and to

58   achieve a "holistic" evaluation, including information on growth, health status, drug

59   prescriptions, diagnostic exams and specialist visits, data from clinical examinations

60   and screenings, integrated with information obtained from the parents.

61   • The newborn population is representative of the national newborn population in terms

62   of geographical distribution and characteristics.

63   • The population is restricted to the children assigned to the participating paediatricians,

64   and this may lead to a somewhat selected sample because many of the paediatricians

65   are part of the national Paediatricians' Cultural Association (ACP) and may have

66   joined it because they are more inclined to participate in research than others. The

67   geographic distribution of the paediatricians, however, is representative of Italy's

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68 North-Centre-South division, and the paediatricians do not choose which children to

69 follow, but receive those assigned to them by the local health unit.

70 • The newborn population reflects that of the newborn population normally followed by

71 family paediatricians in Italy, but not those with serious health problems who are

72 likely followed, at least in the first period of their lives, by hospital staff or specialists

73 and not by the family paediatrician.

74 • NASCITA does not collect biological samples due to the costs of data collection and

75 storage and will therefore not be able to evaluate genetic or immunological factors, for

76 example. Resources and efforts were utilized, however, to achieve the largest

77 population size possible in order to have enough power to study common child

78 exposures and outcomes.

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INTRODUCTION

Infancy and childhood are periods of rapid growth and development and contribute

significantly to well-being, health status, and behaviour throughout life.[1] In fact, many

common diseases and challenges in adult life can be traced back to early childhood,[2,3] but

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 is still poorly understood. Interactions between these health determinants also need to

be investigated.[4,5]

Prospective birth cohort studies are studies that follow a group of newborns for an

extended period of time and permit the collection of accurate information about exposures,

outcomes, and several covariates.[6] Many birth cohorts have been set up worldwide,[7,8]

some as early as 1921 in Europe,[9] and have contributed to knowledge in numerous areas,

from medical to social ones.[10–12]

Cohort characteristics vary greatly from one cohort to another, as do their objectives,

with some cohorts focused on one specific area, such as environmental factors and their effect

on health, and others on multiple areas. Some cohorts collect data retrospectively, others

prospectively. Some collect only written data, others also biological samples.

Two reviews of cohorts in Europe have been carried out, one from 2013 that gave a general

description of birth and pregnancy cohorts in Europe[7] and the second, from 2020, that gave

a more detailed description of cohorts that recruited at birth and not during pregnancy.[13]

These reviews showed that many cohorts have been set up in northern and western Europe

and that the study areas, and their range, varied greatly. The more recent review[13] showed

that many of the cohorts are relatively recent, with half of the 111 European cohorts

beginning after 2000, and that their methodologies differed significantly. This review also

showed that few, relatively recent cohorts focused on family context (nurturing care) and its

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117   impact. Nurturing care refers to the environment created by caregivers that is attentive to

118   children's health and nutritional and social needs and has been shown to positively influence

119   children's health, growth, and development.[2] Nurturing care is a central issue;[14] it offers

120   possibilities for interventions to promote maximum health, social, and cognitive development,

121   and should be a priority study area.

122   In Italy, the population is becoming more heterogeneous, and sociodemographic and

123   geographic differences, such as education and migrant status, have been associated with

124   health disparities.[15,16] Italy, in fact, has a public, universal healthcare system that should

125   pose no legal or financial barriers to subgroups of the population, but considerable health

126   inequalities exist[15] and arise from differences in health behaviour, exposure, environment,

127   genes, etc.

128   Various cohorts have been carried out in Italy, most with general aims and with data

129   collection limited in time or to specific geographical contexts.[17–25] Nine prospective

130   cohorts have been set up in Italy,[17,20,22,23,25–28] starting from 2000, some of which

131   recruited in pregnancy and some at birth. All these cohorts began data collection at

132   recruitment, through clinical visits, questionnaires, in-person or telephone interviews, and

133   medical records. The largest of these cohorts, the NINFEA, recruited participants online. The

134   population sizes of these cohorts ranged from 274-7500. The oldest cohort, the Genetic and

135   Environment: Prospective Study on Infancy in Italy (GASPII), began in 2005, and the newest,

136   the Neonatal Environmental and Health Outcomes (NEHO), in 2018. One cohort,

137   MUBICOS, specifically enrolled twins, and recruited them at in eight participating Italian

138   hospitals. The MUBICOS cohort is the only one currently recruiting. Only three of these

139   cohorts aimed to be representative of the Italian geographical context, North, Centre, and

140   South: the NINFEA, ICON, and MUBICOS cohorts.

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141   The NASCITA study (*NAscere e creSCere in ITAlia*), a longitudinal, prospective,

142   national level, population-based birth cohort, was set up in 2019 to improve the understanding

143   of the early health status of Italian children and how it is affected by social and health

144   determinants, including nurturing care. Like many other cohorts, it addresses multiple

145   research questions.[29,30] The central role of the paediatrician in data collection on overall

146   health and growth and in interaction with patients is a unique quality of NASCITA, however,

147   and is possible in Italy because primary care for children is guaranteed by the family

148   paediatrician, unlike in many other countries.[31] The data will be based on the

149   paediatrician's assessment and diagnosis of health status and outcomes instead of on parental

150   recounting or medical records, leading to more accurate data and avoiding possible cultural

151   and socio-demographic influences on data recall.[32] NASCITA will be able to collect data

152   from throughout the national context and will therefore be able to assess regional differences

153   and disparities in health behaviours and healthcare.

154   The main aim of the NASCITA cohort is to build a national observatory, starting from

155   the paediatricians' office, to evaluate physical, cognitive, and psychological development, and

156   health status and health resource use during the first six years of life in a group of newborns,

157   and to evaluate potentially associated factors. The findings will be used to develop specific

158   prevention measures and interventions to improve the health status of children, contributing to

159   the life-course approach being increasingly prioritized world-wide.[33]

160   This cohort profile paper describes the rationale behind the NASCITA Cohort, the

161   study design, and characteristics of the population of enrolled newborns, and those of their

162   families.

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3   **COHORT DESCRIPTION**
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6   In Italy, health care is provided free or at a minimal charge. Children are assigned to a family
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8   paediatrician by the Local Health Unit and receive care from that paediatrician until they are
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11   at least six years old. Seven well-child visits are scheduled by the paediatrician in the first six
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13   years of a child's life to monitor growth and development and offer preventive care.
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15   Additional visits are organized when needed. The NASCITA cohort was set up by the
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18   Laboratory for Mother and Child Health of the Istituto di Ricerche Farmacologiche Mario
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20   Negri IRCCS in Milan in collaboration with the national Paediatric Cultural Association
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22   (ACP) and was designed to be embedded in Italian paediatric primary care practice. Data are,
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24   in fact, collected directly by the paediatrician and mostly during the well-child visits. The
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27   study was approved by the Fondazione IRCCS Istituto Neurologico "Carlo Besta" ethics
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29   committee on 6 February 2019 (Verbale n 59).
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32   Paediatrician participation is voluntary and no compensation is given. Paediatricians
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34   who chose to participate provided initial information, such as contact information and area of
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36   residence, through an online form. A total of 139 paediatricians from throughout Italy,
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38   representing all geographic areas of the country, agreed to participate. Enrolment took place
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41   between April 2019 and July 2020 and, within this time frame, each paediatrician enrolled,
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43   for a 1-year period, all newborns presenting for their first visit (which routinely takes place in
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45   the first 45 days of life in Italy) and whose parents gave informed consent. No other inclusion
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47   or exclusion criteria were present for enrolment.
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50   Only children who were seen by the paediatricians for at least two visits, including the
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52   first well-child visit, were considered for the baseline population. Children who had not had a
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54   second visit were excluded in order to avoid including those seen by the paediatrician only in
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57   a transitory manner. Newborns will be followed-up until they are at least six years old.
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189   Multiple health outcomes will be studied in the NASCITA Cohort, including the

190   relationship between child development and nurturing care.[34] Specific factors that will be

191   evaluated are disease prevention and treatment actions, nutrition (breastfeeding and diet),

192   caregiving routine, home opportunities to explore and learn, parental adherence to the

193   recommendations for better child care and development, and how all these things relate to

194   child growth and development. Some maternal and paternal periconceptional characteristics

195   will also be evaluated, considering their role in offspring health. The influence of

196   geographical settings in educational and socialization opportunities available for young

197   children and in the care provided by the family paediatricians and by the national health

198   service will also be evaluated.

199   Paediatricians collected data on the newborns during the well-child visits held so far

200   through online forms. These forms were created for each of the planned well-child visits,

201   based on the foreseen age range,[34] and revised by a group of paediatricians and other

202   participants (pharmacists, educators, parents), who make up the technical-scientific

203   committee. The data collected vary as the children grow, with age-appropriate measures (e.g.

204   breastfeeding, neurodevelopmental parameters). An additional form is available online to

205   paediatricians to also collect data during any caregiver-paediatrician telephone contact or

206   extra visits. The children's records can be accessed at any time to complete any missing data.

207   Efforts are being made to reduce the amount of missing information, such as emailing or

208   calling paediatricians and implementing a system that notifies the paediatricians about

209   incomplete data. The more technological aspects of the NASCITA study, such as the web

210   portal and online platform for data input and modification, have been described in detail in a

211   separate article.[35]

212   Data is continuously being monitored and cleaned, and is analysed periodically. The

213   Kruskall-Wallis test was used to analyse continuous variables, and the chi-squared test was

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214   used for the categorical variables. All p-values <0.05 were considered statistically significant

215   and were labelled with an asterisk in the tables. Additional details on the NASCITA Cohort

216   are described in the protocol.[34] The NASCITA study's website is available at

217   https://coortenascita.marionegri.it.

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219   **FINDINGS TO DATE**

220   **Characteristics of study participants**

221   The cohort population consists of 5054 newborns, recruited by 139 paediatricians. The

222   paediatricians enrolled an average of 76.2% of the newborns assigned to them by the local

223   health unit.

224   The demographic characteristics of the parents are reported in Table 1. *Missing data*

225   *were excluded from the percentages in all tables because they were limited to <2,5% for all*

226   *the main variables, except maternal pregnancy body mass index (BMI) (limited to <5%).* The

227   mean age of the mothers at delivery was 33.1 years (median 33). If only primiparas are

228   considered, average maternal age was 32.3 years (range 16-54 years). The majority of

229   mothers and fathers was born in Italy (86.6% and 88.7%, respectively). A higher rate of both

230   parents born abroad was found for families in the North compared to the South of Italy.

231   Mothers tended to have a high or medium level of education (42.5% had a university degree

232   and 41.7 a high school degree), and to be employed (69.7%). Fewer fathers had a high level

233   of education (26.7% university degree), but the majority was employed (96.1%). In general,

234   there were higher levels of maternal and paternal education in the Centre, and lower levels of

235   maternal and paternal employment in the South.

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238 **Table 1.** Maternal and paternal characteristics

	North *n* (%)	Centre *n* (%)	South *n* (%)	Total *n* (%)	*P value*
Average maternal age at delivery, yrs; SD	32.9; 5.2	33.7; 5.3	32.9; 5.6	33.1; 5.4	0.0005*
Median maternal age at delivery, yrs; min-max	33.0; 18-51	34; 17-54	33; 16-51	33; 16-54	
Maternal age class at delivery, yrs					0.0034*
<25	142 (6.1)	46 (4.8)	118 (7.1)	306 (6.2)	
25-29	436 (18.9)	136 (14.3)	328 (19.7)	900 (18.2)	
30-34	836 (36.2)	353 (37.0)	582 (34.9)	1771 (35.9)	
35-39	667 (28.9)	309 (32.4)	462 (27.7)	1438 (29.2)	
40+	229 (9.9)	110 (11.5)	179 (10.7)	518 (10.5)	
Mother born in Italy	1894 (81.1)	837 (86.5)	1626 (93.9)	4357 (86.6)	<0.0001*
Father born in Italy	1950 (83.9)	841 (87.5)	1646 (95.8)	4437 (88.7)	<0.0001 *
Both parents born abroad	305 (13.1)	87 (9.1)	38 (2.2)	430 (8.6)	<0.0001 *
Maternal education					<0.0001 *
Elementary/Middle school	365 (15.8)	95 (9.8)	331 (19.4)	971 (15.8)	
Highschool	1020 (44.0)	337 (34.9)	725 (42.4)	2082 (41.7)	
University	933 (40.3)	535 (55.3)	655 (38.3)	2123 (42.5)	
Maternal employment	1740 (74.8)	747 (76.5)	1009 (58.8)	3496 (69.7)	<0.0001 *
Paternal education					<0.0001 *
Elementary/Middle school	547 (23.7)	137 (14.3)	471 (27.8)	1155 (23.3)	
Highschool	1191 (51.8)	454 (47.5)	826 (48.8)	2471 (50.0)	
University	561 (24.4)	364 (38.1)	394 (23.3)	1319 (26.7)	
Paternal employment	2281 (98.4)	929 (96.2)	1586 (93.1)	4796 (96.1)	<0.0001 *
Maternal civil status					<0.0001 *
Married/living together	2222 (96.0)	897 (93.0)	1653 (96.9)	4772 (95.7)	
Single/separated/divorced/widow	92 (4.0)	68 (7.0)	53 (3.1)	213 (4.3)	
Child living with both parents	2305 (98.6)	957 (98.0)	1687 (97.6)	4949 (98.2)	0.0550

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241 Many mothers (19.2%) had a chronic disease, such as hyper- or hypothyroidism, or asthma

242 (40.1% and 10.2% of mothers with a chronic disease, respectively) (Table 2). The presence of

243 chronic diseases in the mothers, and in the families in general, was more frequent in southern

244 Italy.

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253 **Table 2.** Pregnancy characteristics

	North n (%)	Centre n (%)	South n (%)	Total n (%)	P value
Natural conception	2204 (94.4)	912 (93.2)	1594 (94.7)	4710 (94.2)	0.229
Parity: Primiparous	1235 (53.0)	594 (60.9)	962 (55.6)	2791 (55.4)	0.0002 *
No previous pregnancies (*primigravida*)	1033 (44.3)	477 (49.0)	824 (47.8)	2334 (46.4)	0.0180 *
n previous pregnancies (2697 women)					0.0986
1	708 (54.8)	285 (58.0)	467 (52.6)	1460 (54.7)	
2	389 (30.1)	151 (30.8)	274 (30.9)	814 (30.5)	
>2	195 (15.1)	55 (11.2)	146 (16.5)	396 (14.8)	
Pre-pregnancy BMI					<0.0001 *
Underweight	208 (9.3)	80 (8.6)	94 (5.6)	382 (7.9)	
Normal weight	1.489 (66.5)	653 (70.2)	1.098 (65.4)	3.240 (66.8)	
Overweight	362 (16.2)	145 (15.6)	339 (20.2)	846 (17.5)	
Obese	179 (8.0)	52 (5.6)	149 (8.9)	380 (7.8)	
Gestational weight gain					0.3498
Inadequate	804 (36.2)	344 (37.1)	609 (36.7)	1.757 (36.6)	
Optimal	876 (39.5)	378 (40.8)	628 (37.9)	1.882 (39.2)	
Excessive	538 (24.3)	204 (22.0)	422 (25.4)	1.164 (24.2)	
Healthy pregnancy	1992 (85.2)	839 (85.9)	1497 (86.5)	4328 (85.8)	0.4839
Chronic disease in mother	397 (17.0)	188 (19.2)	387 (22.3)	972 (19.2)	0.0001 *
Folic acid taken appropriately*	910 (39.5)	400 (41.0)	496 (28.6)	1806 (36.1)	<0.0001 *
Vaccination in pregnancy	1121 (49.1)	278 (28.9)	229 (13.4)	1628 (32.8)	<0.0001 *
Most common vaccines					
DTaP	1076 (21.3)	267 (5.3)	199 (3.9)	1542 (30.5)	<0.0001 *
Influenza	239 (4.7)	89 (1.8)	73 (1.4)	401 (7.9)	<0.0001 *
If current smoker					
Any smoke during pregnancy	163 (7.0)	64 (6.7)	97 (5.7)	324 (6.5)	0.2238
Occasionally	58 (36.0)	22 (34.4)	36 (37.5)	116 (36.1)	
Daily	103 (64.0)	42 (65.6)	60 (62.5)	205 (63.9)	
If DAILY, how much					
Little (≤10/day)	91 (88.3)	38 (90.5)	49 (81.7)	178 (86.8)	0.4055
Moderate (11-19/day)	10 (9.7)	2 (4.8)	9 (15.0)	21 (10.2)	
A lot (1 pack/day)	2 (1.9)	2 (4.8)	2 (3.3)	6 (2.9)	
If alcohol use in pregnancy					<0.0001 *
Any alcohol during pregnancy	335 (14.8)	63 (6.6)	96 (5.6)	494 (10.0)	
Occasionally	325 (97.0)	61 (96.8)	94 (97.9)	480 (97.2)	0.9208
Daily	10 (3.0)	2 (3.2)	2 (2.1)	14 (2.8)	

254 * Folic acid supplementation was considered appropriate if folic acid was taken from at least one month before, and
255 throughout, at least the first trimester of pregnancy. It was classified as "inappropriate" if folic acid was taken only once
256 the pregnancy began, even if throughout the pregnancy, or if it was taken, but data were missing as to how and when.

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259 **Pregnancy**

260 The pregnancy characteristics, reported in Table 2, revealed a 94.2% rate of natural

261 conception. In all, 14.2% of mothers had a gestational disorder, in 35.0% of whom it was

262 gestational diabetes. Concerning maternal behaviours in pregnancy, folic acid

263 supplementation was often inappropriate (3043 mothers, 60.8%), or not present at all (160,

264 3.2%), and vaccination rates in pregnancy were low (1628, 32.8%), involving mostly DTaP

265 (94.8%). In terms of geographical differences, there were lower rates of proper folic acid

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266   supplementation and vaccination in the South. A total of 324 (6.5%) mothers smoked during

267   pregnancy, 63.9% of whom smoked daily. Alcohol was consumed by 494 (10.0%) mothers,

268   14 of whom drank it on a daily basis. The rate of alcohol consumption during pregnancy was

269   higher in the North. Maternal pre-pregnancy BMI showed that one fourth (25.3%) of mothers

270   was overweight or obese, with a higher in southern Italy compared to the North and Centre. In

271   general, one fourth of mothers (24.2%) gained an amount of weight greater than that

272   recommended by the US Institute of Medicine (IOM).

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274   **Delivery**

275   Concerning the birth characteristics (Table 3), almost all births were in-hospital (4980,

276   98.8%), 4895 (97.1%) were singleton births, and 1600 (31.7%) were caesarean births.

277   Hospitals provided skin to skin contact in three fourths of cases (3676, 73.8%), provided

278   intramuscular vitamin K prophylaxis at birth (4644, 92.9%), and gave newborns artificial

279   milk (1987, 40.1%), sugared water (215, 4.3%), or water (17, 0.3%). The rate of exclusive

280   breastfeeding at discharge was 69.6% (3509 mothers). In terms of national-level differences,

281   in the South caesarean births were more common, and rates of use of formula milk and

282   sugared water during hospital stay were higher. The rate of exclusive breastfeeding at

283   discharge was lower in the South (62.1% compared to 73.7% and 72.8% in the North and

284   Centre, respectively).

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286   **Newborns**

287   Table 3 reports the newborns' characteristics. In all, 2471 (48.9%) were female. Birthweight

288   ranged from 635 to 5885 grams (median 3270 grams), with 294 (5.8%) low birthweight

289   (<2500 grams) newborns and 234 (4.6%) weighing >4000 grams. A total of 315 (6.2%)

290   newborns were born prematurely (22-36 weeks gestational age (GA)), five (1.6%) of whom

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were extremely preterm (<28 weeks GA). Concerning weight and GA, 525 (10.5%) infants

were small for gestational age (SGA) and 452 (9.0%) were large for gestational age (LGA). In

all, 161 (3.2%) newborns needed resuscitation at birth, 161 (3.2%) were born with birth

defects, and 398 (7.9%) were born with a neonatal disease. The most common diseases were

jaundice (106 newborns), respiratory distress (59), and neonatal hypoglycaemia (47).

Furthermore, 16.5% of newborns had to be admitted to a neonatal care ward and 4.3% to a

neonatal intensive care unit.

Table 3. Delivery, in-hospital, breast feeding, and newborn characteristics

	North n (%)	Centre n (%)	South n (%)	Total n (%)	P value
Mean gestational age at birth, wks; SD	39.0; 1.7	39.0; 1.6	38.9; 1.8	39.0; 1.7	0.0158 *
Gestational age category (weeks)					0.0009 *
22-36	124 (5.3)	50 (5.1)	141 (8.1)	315 (6.2)	
37-41	2197 (93.9)	923 (94.3)	1571 (90.8)	4691 (92.9)	
42-44	18 (0.8)	6 (0.6)	19 (1.1)	43 (0.9)	
Birth in hospital	2323 (99.4)	966 (98.9)	1691 (98.0)	4980 (98.8)	0.0003 *
Single vs twin births					<0.0001 *
Single birth	2294 (98.2)	954 (97.5)	1647 (95.3)	4895 (97.1)	
Twins	42 (1.8)	23 (2.4)	82 (4.7)	147 (2.9)	
Birth type					<0.0001 *
Spontaneous	1639 (70.0)	608 (62.1)	993 (57.3)	3240 (64.1)	
Caesarean	575 (24.6)	328 (33.5)	697 (40.2)	1600 (31.7)	
Instrumental birth	126 (5.4)	43 (4.4)	44 (2.5)	213 (4.2)	
Skin to skin contact immediately after birth	1880 (82.1)	778 (80.1)	1018 (59.2)	3676 (73.8)	<0.0001 *
Intramuscular Vitamin K at birth	2204 (95.2)	940 (96.7)	1500 (87.7)	4644 (92.9)	<0.0001 *
Breast feeding in hospital	2098 (91.4)	906 (93.0)	1.476 (87.7)	4480 (90.5)	<0.0001 *
Exclusively breastfed upon hospital discharge	1720 (73.7)	713 (72.8)	1076 (62.1)	3509 (69.6)	<0.0001 *
NEWBORNS					
Female	1116 (47.7)	515 (52.6)	843 (48.6)	2474 (49.0)	0.0361 *
Mean birthweight, gr; SD	3278.0; 483.8	3250.3; 487.5	3225.8; 501.4	3254.7; 491.1	0.0055 *
Median birthweight, gr; min-max	3290.0; 635 - 4850	3250.0; 1.155 - 4750	3250.0; 1160 - 5885	3270.0; 635.0 - 5885.0	
Birthweight class, gr					0.0589
<2.500	124 (5.3)	53 (5.4)	117 (6.8)	294 (5.8)	
2.500-4.000	2098 (89.7)	874 (89.3)	1552 (89.6)	4524 (89.5)	
>4.000	118 (5.0)	52 (5.3)	64 (3.7)	234 (4.6)	
Weight for gestational age					0.8335
Small for gestational age (SGA)	236 (10.1)	97 (10.0)	192 (11.2)	525 (10.5)	
Appropriate for gestational age (AGA)	1884 (80.9)	785 (80.8)	1373 (79.9)	4042 (80.5)	
Large for gestational age (LGA)	210 (9.0)	89 (9.2)	153 (8.9)	452 (9.0)	
Mean length, cm; SD	49.7; 2.5	49.8; 2.3	49.5; 2.4	49.6; 2.4	0.0018 *
Malformation at birth	80 (3.4)	28 (2.9)	53 (3.1)	161 (3.2)	0.6565
Disease at birth	172 (7.4)	77 (7.9)	149 (8.6)	398 (7.9)	0.3466
Admitted to Neonatal Unit	398 (17.4)	181 (18.7)	241 (14.0)	820 (16.5)	0.0019 *
Admitted to Neonatal Intensive Care Unit	84 (3.6)	34 (3.5)	97 (5.6)	215 (4.3)	0.0030 *

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300   **First visit with the family paediatrician**

301   The average age of the newborns at their first out-of-hospital visit was 25.7 days, with a

302   median of 24.0 days (table 4). A total of 3187 (63.6%) newborns were being exclusively

303   breastfed at the time of their first visit, while, of the remaining newborns, over one third

304   (35.9%) was receiving formula milk and two thirds (64.1%) was receiving a mixed feeding

305   regimen.

306

307   **Table 4.** Characteristics at first visit with paediatrician (7-45 days old)

	North n (%)	Centre n (%)	South n (%)	Total n (%)	P value
Mean age, days; SD				25.7; 24.9	
Breast feeding					< 0.0001 *
Exclusive	1577 (67.9)	639 (65.5)	971 (56.7)	3187 (63.6)	
Mixed breast feeding	476 (20.4)	252 (25.8)	440 (25.6)	1168 (64.1)	
Artificial formula only	270 (11.6)	84 (8.6)	300 (17.5)	654 (35.9)	
Usual sleep position					<0.0001 *
Supine	2069 (90.3)	849 (87.3)	1444 (84.5)	4362 (87.7)	
Side	92 (4.0)	65 (6.7)	215 (12.6)	372 (7.5)	
Prone	130 (5.7)	59 (6.1)	50 (2.9)	239 (4.8)	
Vitamin D prophylaxis ongoing/initiated at visit	2.297 (98.7)	942 (96.3)	1.642 (95.6)	4881 (97.4)	<0.0001 *
Drug prescribed at visit (excluding vitamin D)	108 (4.6)	27 (2.8)	41 (2.4)	176 (3.5)	<0.0001 *

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309

310   The prevalence of exclusive breastfeeding at the first well-child visit decreased from

311   North to South (χ^2_t 52; p<0.001). In the South of Italy, 17.5% of newborns received only

312   formula, versus 11.6% in the North and 8.6% in the Centre.

313   Concerning sleeping position, the majority of newborns slept in the supine position

314   (87.7%), while 4.8% slept in the prone position. There were geographical differences in

315   sleeping position as well: the percentage of supine position was higher in the North (90.3%)

316   and lower in the South (84.5%) (χ^2_t31.2; p<0.001).

317   Concerning prophylaxis, 97.4% were receiving vitamin D prophylaxis at their first

318   visit. A total of 176 (3.5%) newborns received a drug prescription during their visit and the

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3   319   drugs most commonly prescribed were simethicone (17%), nystatin (14%), and ophthalmic
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5   320   tobramycin (10%).
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8   321   The results of the screening procedures for normal development (Table 4) show that
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10   322   most of the newborns had positive developmental assessment results. Very few were found to
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12   323   have problems with motor (9 newborns) or sensory and social (7) skills.
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15   324   The distribution of the cohort population reflects that of the Italian population, based
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17   325   on the ISTAT data from 2019,[36] which report that 46% of the national population resides in
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19   326   the North, 20% in the Centre, and 34% in the South/islands. The socio-demographic
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21   327   characteristics of the mothers also reflect national level data, where the mothers' average age
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23   328   at birth of the first child is 32.1 years, as reported in the 2019 Eurostat data for Italy,[37]
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25   329   compared to 32.3 in the NASCITA cohort. The main characteristics at birth of mothers and
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27   330   newborns in the NASCITA cohort and in the national reference data, the Ministry of Health's
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29   331   Certificato di assistenza al parto (CeDAP) 2019 data,[38] are listed in Table 5. The maternal
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31   332   level of education is higher in NASCITA compared to national level data (42.5% compared to
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33   333   31.2% of mothers have a university degree),[38] while the percentage of foreign-born mothers
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35   334   on the other hand, is lower in NASCITA (13.4% *vs* 21%), with both results likely to be due to
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37   335   language barriers that preclude recruitment and to the more frequent transfers to other
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39   336   areas/paediatricians on the part of families with parents who were born abroad. These
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41   337   differences are also true when NASCITA cohort data are compared with those of the Italian
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43   338   NINFEA[22] and PiccoliPiù[39] cohorts, i.e., the general population characteristics are
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45   339   similar, while the maternal level of education is higher in NASCITA and the percentage of
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47   340   foreign-born parents is lower. The distribution of the newborns' anthropometric measures is
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49   341   also comparable with that of the national data.[40]
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344 **Table 5.** Main characteristics at birth of mothers and newborns in the NASCITA cohort and
345 in the national reference data (CeDAP)

	NASCITA % population	CeDAP % population
MOTHERS		
Mother born in Italy	86.6	79
Mother's age, yrs		
≤29	24.4	25.3
30-39	65.1	63.5
40+	10.5	11.2
Maternal education		
Elementary/Middle school	23.3	25.9
Highschool	50.0	42.9
University	42.5	31.2
Maternal employment	69.7	55.0
Healthy pregnancy	85.8	85.2
Natural conception	94.2	96.9
Caesarean section	31.7	31.8
NEWBORNS		
Twins	2.9	1.6
Birthweight		
<1500 gr	0.5	0.9
1500-2499 gr	5.3	6.2
2500-3999 gr	89.5	87.6
>4000 gr	4.6	5.2
Gestational age at birth / Preterm birth		
22-36 weeks	6.2	6.8
37-41	92.9	92.7
>41	0.9	0.5
Malformation at birth	3.2	1.3

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348   Newborns participating in the NASCITA cohort, and their families, are representative

349 of the Italian population in terms of geographical distribution and sociodemographic

350 characteristics. The analysis of the characteristics during pregnancy and at birth confirms the

351 existence of large geographical differences in attitudes, in particular concerning folic acid

352 intake, immunization, caesarean birth, and exclusive breastfeeding prevalence.

353   One fourth of the NASCITA cohort mothers (25.3%) were overweight or obese,

354 although this rate seems to be lower than the European rate of 30%-50%.[41] The rate of

355 caesarean births in the NASCITA cohort, involving almost one in three births, confirms

356 Italy's standing as one of the countries with the highest rate in Europe. Large regional

357 differences exist, with much higher rates in the South.[42]

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3   358   Concerning aspects related to nurturing care and good practices, to be implemented
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5   359   from before pregnancy to the first few months of life and beyond, such as folic acid intake,
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8   360   smoke and alcohol avoidance, and breastfeeding, the data collected on these behaviours show
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10   361   that more must be done. Concerning exclusive breastfeeding, for example, the rates in Italy at
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13   362   hospital discharge were already low, represented by just over two thirds of mothers (69.6%),
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15   363   and the rate decreased to 63.6% at the first visit with the paediatrician. Concerning folic acid
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17   364   supplementation, only about one third of mothers took it in an appropriate manner, with an
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19   365   even worse situation in the South. Concerning smoking and alcohol use, the NASCITA data
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22   366   showed that 6.5% of mothers continued to smoke during pregnancy and that one in ten drank
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24   367   alcohol during pregnancy.
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26   368   Geographical differences in the health status and in the care of mother and newborns
27
28   369   are striking, in particular when looking southern Italy. Pregnant women living in southern
29
30   370   Italy were less compliant with folic acid prophylaxis and with recommended vaccinations.
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32   371   They were also at greater risk of being overweight or obese at the beginning of the pregnancy.
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34   372   A greater rate of caesarean delivery was reported, neonates were less frequently exposed to
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36   373   skin-to-skin contact with their mothers at birth, and were less likely to be breastfed at
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39   374   discharge from the hospital, and consequently, also at the first well-child visit. Differences in
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41   375   the exclusive breastfeeding rate at hospital discharge after delivery between the South and
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43   376   other geographic areas of Italy persist also when excluding preterm or low birthweight
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45   377   newborns, or newborns with congenital malformations (data not shown).
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51   379   **Strengths and limitations**
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54   380   The NASCITA study is one of the few involving the paediatricians directly as protagonists in
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56   381   cohort design and data collection. The paediatricians' direct role in data collection is a major
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58   382   strength in that it permits a "holistic" evaluation, including information on growth, health
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383   status, drug prescriptions, diagnostic exams and specialist visits, data from clinical

384   examinations, and screenings integrated with information obtained from the parents. Another

385   strength of this study is that the newborn population is representative of the national newborn

386   population in terms of geographical distribution and characteristics. Furthermore, strategies

387   were implemented to maintain paediatrician participation and to minimize loss to follow-

388   up,[62] involving, for example, maintaining contact with the paediatricians through periodic

389   emails providing updates on the progress of the cohort, providing paediatricians with timely

390   email assistance with data input, and sending periodic newsletters listing recent publications

391   on other cohort studies. Similarly, strategies were implemented to maintain parental

392   participation and minimize loss to follow-up of the newborns, such as providing information

393   dedicated to parents on the NASCITA study's web portal on common childhood diseases.

394   Another strength of the NASCITA study is that efforts were made to retrospectively collect

395   data on the mothers and fathers from before, and during, the pregnancy.

396   The limitations of this study are, first, that the population is restricted to the children

397   assigned to the participating paediatricians, and this may lead to a somewhat selected sample

398   because many of the paediatricians are part of the national Paediatricians' Cultural

399   Association (ACP) and may have joined NASCITA because they are more inclined to

400   participate in research than others. The geographic distribution of the paediatricians, however,

401   is representative of Italy's North-Centre-South division, and the paediatricians do not choose

402   which children to follow, but receive those assigned to them by the local health unit.

403   A second limit is that the newborn population reflects that of the newborn population

404   normally followed by family paediatricians in Italy, which includes all newborns who do not

405   have serious health problems that would prevent them from being regularly followed, at least

406   in the first period of their lives, by a family paediatrician. Newborns with serious health

407   problems are usually followed by hospital staff or specialists, and would therefore not likely

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408 have been taken to the first well-child visit within the first 45 days of life (when paediatricians

409 enrolled newborns in the study).

410 The third limit of the NASCITA cohort is that it does not collect biological samples due to the

411 costs of data collection and storage. It will therefore not be able to evaluate genetic or

412 immunological factors, for example. Resources and efforts were utilized, however, to achieve

413 the largest population size possible in order to have enough power to study common child

414 exposures and outcomes.

415

PATIENT AND PUBLIC INVOLVMENT

417 Patients were indirectly involved in the development of the research questions and

418 questionnaires in that the technical-scientific committee that was set up to supervise the study,

419 and that collaborates in creating and revising the questionnaires, involves professionals (e.g.,

420 paediatricians, pharmacists, educators) who are also parents. The public is involved through

421 the dissemination of cohort results and information on childhood diseases or conditions to

422 parents and the general public on the study's website.

423

COLLABORATION

425 Data from the NASCITA study will be available upon reasonable request, after approval by

426 NASCITA's technical-scientific committee, and for non-commercial purposes. We encourage

427 collaboration between different cohorts, for example to merge, or compare, data on chosen

428 topics of study.

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433 **FURTHER DETAILS**

434 **Competing interests**

435 None declared.

436

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441

442 **Patient consent for publication**

443 Not required.

444

445 **Ethics approval and consent to participate**

446 Newborns were enrolled only if parental consent was given. The study was approved by the

447 Fondazione IRCCS Istituto Neurologico "Carlo Besta" ethics committee on 6 February 2019

448 (Verbale n 59).

449

450 **Provenance and peer review**

451 Not commissioned; externally peer reviewed.

452

453 **Data availability statement**

454 The datasets used and/or analysed during the current study are available from the

455 corresponding author upon reasonable request and approval by the technical-scientific

456 committee, and only for non-commercial purposes.

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461

Author contributions

MB designed the Study. MB and AC directed the study's implementation. AC and MC

designed the analytical strategy. MC carried out the statistical analyses. AC and MC helped to

interpret the findings. CP conducted the literature review and was a major contributor in

writing the manuscript. All authors contributed to, and revised, the article. All authors read

and approved the final manuscript.

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516   Luisa Zuccolo. Roberto Cionini and Giuseppa Scornavacca unfortunately passed away.

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Cohort profile: the national, longitudinal NASCITA birth cohort study to investigate the health of Italian children and potential influencing factors

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1 **Cohort profile: the national, longitudinal NASCITA birth cohort study to investigate the**

2 **health of Italian children and potential influencing factors**

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ABSTRACT

Purpose The NASCITA Study, a national level, population-based, prospective cohort study, was set up to better understand the early health status of Italian children, comprising their physical, cognitive, and psychological development, and how it is affected by social and health determinants, including nurturing care. NASCITA will also assess geographical differences and disparities in health care.

Participants Participating family paediatricians from throughout Italy enrolled infants born during the enrolment period (April 2019-July 2020). The 5054 newborns seen by the 139 paediatricians for at least two visits, including the first well-child visit, and for whom parental consent was given, make up the baseline population.

Findings to date Mothers had a mean age at delivery of 33.1 years and tended to have a high or medium level of education (42.5% university and 41.7% high school degrees) and to be employed (69.7%). One third (36.1%) took folic acid supplementation appropriately, and 6.5% smoked or consumed alcohol (10.0%) during pregnancy. One third (31.7%) of deliveries were caesarean deliveries. Concerning the newborns, 5.8% had a low birthweight and 6.2% were born prematurely. The majority (87.7%) slept in the supine position and 63.6% were exclusively breastfed at one month, with a decreasing North to South prevalence (χ^2_t 52; p<0.001). Significant North-South differences were found in all areas, including parental education, behaviours in pregnancy, and hospital practices. When compared with national level data, the cohort population's distribution, maternal socio-demographic characteristics, and newborn physical characteristics reflect those of the Italian population.

Future plans: Data will continue to be collected during the well-child visits until the children are 6 years old and multiple health outcomes will be studied, spanning child development and

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illness, as well as potentially related factors including caregiving routines. The findings will

be used to develop specific interventions to improve children's health.

Study registration number: ClinicalTrials.gov, NCT03894566.

Keywords: Cohort Studies; Child; Health; Infant, Newborn; Italy; Population Characteristics; Public Health

Strengths and limitations of this study

- The NASCITA study is one of few involving paediatricians directly as protagonists in cohort design and data collection.

- The newborn population involved is representative of the national newborn population in terms of geographical distribution and characteristics.

- The population is restricted to the children assigned to the participating paediatricians, which might lead to a somewhat selected sample because many of the paediatricians are part of the national Paediatricians' Cultural Association (ACP) and may have joined because they are more inclined to participate in research than others; however, paediatricians do not choose which children will be placed in their care since children they are assigned to them by the local health unit.

- The newborn population reflects that of the newborn population normally followed by family paediatricians in Italy, but not those with serious health problems who are likely followed, at least in the first period of their lives, by hospital staff or specialists.

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67   •   NASCITA does not collect biological samples due to the costs of data collection and

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69   example.

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INTRODUCTION

Infancy and childhood are periods of rapid growth and development and contribute

significantly to well-being, health status, and behaviour throughout life.[1] Research carried

out worldwide has shown that many common diseases and challenges in adult life can be

traced back to early childhood and that health and social determinants in early life play a

strong role.[2,3] Specifically, certain social factors, socioeconomic status, living conditions,

parental and stakeholder care, and attitudes influence the well-being of children and lead to

health inequalities among children. In a developed region of the world such as Europe, most

children are healthy, but inequalities between and within member states, lack of access to

quality services, and unhealthy lifestyles negatively affect health in children and adolescents

also in Europe[4] In order to be able to set up the most effective interventions, tailored to

those who would benefit the most, it is important to identify the existing inequalities and

health determinants in specific countries. In Italy, research has been carried out on health

determinants and on their interactions,[5] with similar findings compared to other European

countries.[6] Low socioeconomic status, lower parental education, and employment status

were found to be associated with lower health and development outcomes. Despite complex

interaction between exposure variables found,[7] some determinants, such as promotion of

autonomy in the home environment, were found to play a crucial role in child neurocognitive

development. A 2019 review of inequalities in child health[8] found that behavioural

determinants, however, are not as influential as socioeconomic status and living conditions. It

would be useful to further investigate such influences in Italy. Interactions between health

determinants are complex and also need to be investigated.[8-10]

Prospective birth cohort studies are studies that follow a group of newborns for an

extended period of time and permit the collection of accurate information about exposures,

outcomes, and several covariates.[11] Many birth cohorts have been set up worldwide,[12,13]

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116   some as early as 1921 in Europe,[14] and have contributed to knowledge in numerous areas,

117   from medical to social ones.[15-17]

118   Cohort characteristics vary greatly from one cohort to another, as do their objectives,

119   with some cohorts focused on one specific area, such as environmental factors and their effect

120   on health, and others on multiple areas. Some cohorts collect data retrospectively, others

121   prospectively. Some collect only written data, others also biological samples.

122   Two reviews of cohorts in Europe have been carried out, one from 2013 that gave a

123   general description of birth and pregnancy cohorts in Europe[12] and the second, from 2020,

124   that gave a more detailed description of cohorts that recruited at birth and not during

125   pregnancy.[18] These reviews showed that many cohorts have been set up in northern and

126   western Europe and that the study areas, and their range, varied greatly. The more recent

127   review[18] showed that many of the cohorts are relatively recent, with half of the 111

128   European cohorts beginning after 2000, and that their methodologies differed significantly.

129   This review also showed that few, relatively recent cohorts focused on family context

130   (nurturing care) and its impact. Nurturing care refers to the environment created by caregivers

131   that is attentive to children's health and nutritional and social needs and has been shown to

132   positively influence children's health, growth, and development.[2] Nurturing care is a central

133   issue;[19] it offers possibilities for interventions to promote maximum health, social, and

134   cognitive development, and should be a priority study area.

135   In Italy, the population is becoming more heterogeneous, and sociodemographic and

136   geographic differences, such as education and migrant status, have been associated with

137   health disparities.[20,21] Italy, in fact, has a public, universal healthcare system that should

138   pose no legal or financial barriers to subgroups of the population, but considerable health

139   inequalities exist and arise from differences in health behaviour, exposure, environment,

140   genes, etc.[20] Many of these inequalities are well-known and relate to regional differences,

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141   with southern Italy often resulting at the greatest disadvantage due to cultural and economic

142   factors.[22]

143   Various cohort studies have been carried out in Italy, most with general aims and with

144   data collection limited in time or to specific geographical contexts.[23-31] Nine prospective

145   cohorts have been set up in Italy,[23,26,28-34] starting from 2000, some of which recruited in

146   pregnancy and some at birth. All these cohorts began data collection at recruitment, through

147   clinical visits, questionnaires, in-person or telephone interviews, and medical records. The

148   largest of these cohorts, the NINFEA, recruited participants online. The population sizes of

149   these cohorts ranged from 274-7500. The oldest cohort, the Genetic and Environment:

150   Prospective Study on Infancy in Italy (GASPII), began in 2005, and the newest, the Neonatal

151   Environmental and Health Outcomes (NEHO), in 2018. One cohort, MUBICOS, specifically

152   enrolled twins, and recruited them in eight participating Italian hospitals. The MUBICOS

153   cohort is the only one currently recruiting. Only three of these cohorts aimed to be

154   representative of the Italian geographical context, North, Centre, and South: the NINFEA,

155   ICON, and MUBICOS cohorts.

156   The NASCITA study (*NAscere e creSCere in ITAlia*), a longitudinal, prospective,

157   national level, population-based birth cohort, was set up in 2019 to improve the understanding

158   of the early health status of Italian children and how it is affected by social and health

159   determinants, including nurturing care. Like many other cohorts, it addresses multiple

160   research questions.[35,36] The central role of the paediatrician in data collection on overall

161   health and growth and in interaction with patients is a unique quality of NASCITA, however,

162   and is possible in Italy because primary care for children is guaranteed by the family

163   paediatrician, unlike in many other countries.[37] The data will be based on the

164   paediatrician's assessment and diagnosis of health status and outcomes instead of on parental

165   recounting or medical records, leading to more accurate data and avoiding possible cultural

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166 and socio-demographic influences on data recall.[38] The synergy between the paediatrician's

167 central role and this cohort study's focus on nurturing care make NASCITA different from

168 most Italian and European cohort studies. NASCITA will also be able to collect data from

169 throughout the national context and will therefore be able to better assess the regional

170 differences and disparities in health behaviours and healthcare that exist in Italy.

171   The main aim of the NASCITA cohort is to build a national observatory, starting from

172 the paediatricians' office, to evaluate physical, cognitive, and psychological development, and

173 health status and health resource use during the first six years of life in a group of newborns,

174 and to evaluate potentially associated factors. The findings will be used to develop specific

175 prevention measures and interventions to improve the health status of children, contributing to

176 the life-course approach that is being increasingly prioritized world-wide.[39]

177   This cohort profile paper describes the rationale behind the NASCITA Cohort, the

178 study design, and characteristics of the population of enrolled newborns, and those of their

179 families. In particular, as region of residence is known to be strongly associated with both

180 healthcare quality and behaviour, geographic differences were analysed.

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COHORT DESCRIPTION

183 In Italy, health care is provided free or at a minimal charge. Children are assigned to a family

184 paediatrician by the Local Health Unit and receive care from that paediatrician until they are

185 at least six years old. Seven well-child visits are scheduled by the paediatrician in the first six

186 years of a child's life to monitor growth and development and offer preventive care.

187 Additional visits are organized when needed. The NASCITA cohort was set up by the

188 Laboratory for Mother and Child Health of the Istituto di Ricerche Farmacologiche Mario

189 Negri IRCCS in Milan in collaboration with the national Paediatric Cultural Association

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190 (ACP) and was designed to be embedded in Italian paediatric primary care practice. Data are,

191 in fact, collected directly by the paediatrician and mostly during the well-child visits. The

192 study was approved by the Fondazione IRCCS Istituto Neurologico "Carlo Besta" ethics

193 committee on 6 February 2019 (Verbale n 59).

194   Paediatrician participation is voluntary and no compensation is given. Recruitment

195 details have been explained previously.[40] Briefly, locally representative paediatricians were

196 identified, initially through the national Paediatric Cultural Association (APC), after which

197 paediatricians identified in each geographic area were asked to identify additional

198 paediatricians from their area for invitation. Other paediatric and scientific societies were also

199 contacted for collaboration. Paediatricians who chose to participate provided initial

200 information, such as contact information and area of residence, through an online form. A

201 total of 139 paediatricians from throughout Italy, representing all geographic areas of the

202 country, agreed to participate.[41] Enrolment took place between April 2019 and July 2020

203 and, within this time frame, each paediatrician enrolled, for a 1-year period, all newborns

204 presenting for their first visit (which routinely takes place in the first 45 days of life in Italy)

205 and whose parents gave informed consent. No other inclusion or exclusion criteria were

206 present for enrolment.

207   Only children who were seen by the paediatricians for at least two visits, including the

208 first well-child visit, were considered for the baseline population. Children who had not had a

209 second visit (n. 112) were excluded in order to avoid including those seen by the paediatrician

210 only in a transitory manner. Newborns will be followed-up until they are at least six years old.

211   Multiple health outcomes will be studied in the NASCITA Cohort, including the

212 relationship between child development and nurturing care.[40] Nurturing care, which, as

213 mentioned above, refers to those behaviours put in place by parents and caregivers that create

214 an optimal environment for children to thrive, and involves factors to be implemented from

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215   before pregnancy to the first few months of life and beyond, such as folic acid intake, smoke

216   and alcohol avoidance, and breastfeeding. Specific factors that will be evaluated in this cohort

217   are disease prevention and treatment actions, nutrition (breastfeeding and diet), caregiving

218   routine, home opportunities to explore and learn, parental adherence to the recommendations

219   for better child care and development, and how all these things relate to child growth and

220   development. Some maternal and paternal periconceptional characteristics will also be

221   evaluated, considering their role in offspring health. The influence of geographical settings in

222   educational and socialization opportunities available for young children and in the care

223   provided by the family paediatricians and by the national health service will also be

224   evaluated.

225   Paediatricians collected data on the newborns and on parental socio-demographic and

226   lifestyle characteristics such as employment status, educational level, and smoking habits,

227   during the well-child visits held so far through online forms. These forms were created for

228   each of the planned well-child visits, based on the foreseen age range,[40] and were revised

229   by a group of paediatricians and other participants (pharmacists, educators, parents), who

230   make up the technical-scientific committee. The data collected vary as the children grow, with

231   age-appropriate measures (e.g. breastfeeding, neurodevelopmental parameters) and include

232   questions to ask parents during the visits on their habits and parenting behaviours. Most data

233   are already collected by paediatricians using routine data collection forms and checklists.

234   Additional data collected were integrated with validated tools for recording data of particular

235   interest (e.g. the CDC checklist for developmental milestones).[42] An additional form is

236   available online to paediatricians to also collect data during any caregiver-paediatrician

237   telephone contact or extra visits. The children's records can be accessed at any time to

238   complete any missing data. Efforts are being made to reduce the amount of missing

239   information, such as emailing or calling paediatricians and implementing a system that

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240   notifies the paediatricians about incomplete data. The more technological aspects of the

241   NASCITA study, such as the web portal and online platform for data input and modification,

242   have been described in detail in a separate article.[41]

243   Data is continuously being monitored and cleaned, and is analysed periodically. The

244   Kruskall-Wallis test was used to analyse continuous variables, and the chi-squared test was

245   used for the categorical variables. All p-values <0.05 were considered statistically significant

246   and were labelled with an asterisk in the tables. Additional details on the NASCITA Cohort

247   are described in the protocol.[40] The NASCITA study's website is available at

248   https://coortenascita.marionegri.it.

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FINDINGS TO DATE

251   **Characteristics of study participants**

252   The cohort population consists of 5054 newborns, recruited by 139 paediatricians. The

253   paediatricians enrolled an average of 76.2% of the newborns assigned to them by the local

254   health unit.

255   The demographic characteristics of the parents are reported in Table 1. Missing data

256   were excluded from the percentages in all tables because they were limited to <2,5% for all

257   the main variables, except maternal pregnancy body mass index (BMI) (limited to <5%). The

258   mean age of the mothers at delivery was 33.1 years (median 33). If only primiparas are

259   considered, average maternal age was 32.3 years (range 16-54 years). The majority of

260   mothers and fathers were born in Italy (86.6% and 88.7%, respectively). A higher rate of both

261   parents born abroad was found for families in the North compared to the South of Italy.

262   Mothers tended to have a high or medium level of education (42.5% had a university degree

263   and 41.7 a high school degree), and to be employed (69.7%). Fewer fathers had a high level

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264   of education (26.7% university degree), but the majority were employed (96.1%). In general,

265   there were higher levels of maternal and paternal education in the Centre, and lower levels of

266   maternal and paternal employment in the South.

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268   **Table 1. Maternal and paternal characteristics**

	Total n (%)	North n (%)	Centre n (%)	South n (%)	P value
Average maternal age at delivery, yrs; SD	33.1; 5.4	32.9; 5.2	33.7; 5.3	32.9; 5.6	0.0005*
Median maternal age at delivery, yrs; min-max	33; 16-54	33.0; 18-51	34; 17-54	33; 16-51	
Maternal age class at delivery, yrs					0.0034*
<25	306 (6.2)	142 (6.1)	46 (4.8)	118 (7.1)	
25-29	900 (18.2)	436 (18.9)	136 (14.3)	328 (19.7)	
30-34	1771 (35.9)	836 (36.2)	353 (37.0)	582 (34.9)	
35-39	1438 (29.2)	667 (28.9)	309 (32.4)	462 (27.7)	
40+	518 (10.5)	229 (9.9)	110 (11.5)	179 (10.7)	
Mother born in Italy	4357 (86.6)	1894 (81.1)	837 (86.5)	1626 (93.9)	<0.0001*
Father born in Italy	4437 (88.7)	1950 (83.9)	841 (87.5)	1646 (95.8)	<0.0001 *
Both parents born abroad	430 (8.6)	305 (13.1)	87 (9.1)	38 (2.2)	<0.0001 *
Maternal education					<0.0001 *
Elementary/Middle school	971 (15.8)	365 (15.8)	95 (9.8)	331 (19.4)	
Highschool	2082 (41.7)	1020 (44.0)	337 (34.9)	725 (42.4)	
University	2123 (42.5)	933 (40.3)	535 (55.3)	655 (38.3)	
Maternal employment	3496 (69.7)	1740 (74.8)	747 (76.5)	1009 (58.8)	<0.0001 *
Paternal education					<0.0001 *
Elementary/Middle school	1155 (23.3)	547 (23.7)	137 (14.3)	471 (27.8)	
Highschool	2471 (50.0)	1191 (51.8)	454 (47.5)	826 (48.8)	
University	1319 (26.7)	561 (24.4)	364 (38.1)	394 (23.3)	
Paternal employment	4796 (96.1)	2281 (98.4)	929 (96.2)	1586 (93.1)	<0.0001 *
Maternal civil status					<0.0001 *
Married/living together	4772 (95.7)	2222 (96.0)	897 (93.0)	1653 (96.9)	
Single/separated/divorced/widow	213 (4.3)	92 (4.0)	68 (7.0)	53 (3.1)	
Child living with both parents	4949 (98.2)	2305 (98.6)	957 (98.0)	1687 (97.6)	0.0550

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270

271   Many mothers (19.2%) had a chronic disease, such as hyper- or hypothyroidism, or asthma

272   (40.1% and 10.2% of mothers with a chronic disease, respectively) (Table 2). The presence of

273   chronic diseases in the mothers, and in the families in general, was more frequent in southern

274   Italy.

275

276

277   **Table 2. Pregnancy characteristics**

	North n (%)	Centre n (%)	South n (%)	Total n (%)	P value

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Natural conception	2204 (94.4)	912 (93.2)	1594 (94.7)	4710 (94.2)	0.229
Parity: Primiparous	1235 (53.0)	594 (60.9)	962 (55.6)	2791 (55.4)	0.0002 *
No previous pregnancies (*primigravida*)	1033 (44.3)	477 (49.0)	824 (47.8)	2334 (46.4)	0.0180 *
n previous pregnancies (2697 women)					0.0986
1	708 (54.8)	285 (58.0)	467 (52.6)	1460 (54.7)	
2	389 (30.1)	151 (30.8)	274 (30.9)	814 (30.5)	
>2	195 (15.1)	55 (11.2)	146 (16.5)	396 (14.8)	
Pre-pregnancy BMI					<0.0001 *
Underweight	208 (9.3)	80 (8.6)	94 (5.6)	382 (7.9)	
Normal weight	1.489 (66.5)	653 (70.2)	1.098 (65.4)	3.240 (66.8)	
Overweight	362 (16.2)	145 (15.6)	339 (20.2)	846 (17.5)	
Obese	179 (8.0)	52 (5.6)	149 (8.9)	380 (7.8)	
Gestational weight gain					0.3498
Inadequate	804 (36.2)	344 (37.1)	609 (36.7)	1.757 (36.6)	
Optimal	876 (39.5)	378 (40.8)	628 (37.9)	1.882 (39.2)	
Excessive	538 (24.3)	204 (22.0)	422 (25.4)	1.164 (24.2)	
Healthy pregnancy	1992 (85.2)	839 (85.9)	1497 (86.5)	4328 (85.8)	0.4839
Chronic disease in mother	397 (17.0)	188 (19.2)	387 (22.3)	972 (19.2)	0.0001 *
Folic acid taken appropriately*	910 (39.5)	400 (41.0)	496 (28.6)	1806 (36.1)	<0.0001 *
Vaccination in pregnancy	1121 (49.1)	278 (28.9)	229 (13.4)	1628 (32.8)	<0.0001 *
Recommended vaccines					
DTaP	1076 (46.0)	267 (27.2)	199 (11.5)	1542 (30.5)	<0.0001 *
Influenza	239 (10.2)	89 (9.1)	73 (4.2)	401 (7.9)	<0.0001 *
Any smoke during pregnancy	163 (7.0)	64 (6.7)	97 (5.7)	324 (6.5)	0.2238
Occasionally	58 (36.0)	22 (34.4)	36 (37.5)	116 (36.1)	
Daily	103 (64.0)	42 (65.6)	60 (62.5)	205 (63.9)	
If DAILY, how much					
Little (≤10/day)	91 (88.3)	38 (90.5)	49 (81.7)	178 (86.8)	0.4055
Moderate (11-19/day)	10 (9.7)	2 (4.8)	9 (15.0)	21 (10.2)	
A lot (1 pack/day)	2 (1.9)	2 (4.8)	2 (3.3)	6 (2.9)	
Any alcohol during pregnancy	335 (14.8)	63 (6.6)	96 (5.6)	494 (10.0)	
Occasionally	325 (97.0)	61 (96.8)	94 (97.9)	480 (97.2)	0.9208
Daily	10 (3.0)	2 (3.2)	2 (2.1)	14 (2.8)	

278 * Folic acid supplementation was considered appropriate if folic acid was taken from at least one month before, and
279 throughout, at least the first trimester of pregnancy. It was classified as "inappropriate" if folic acid was taken only once
280 the pregnancy began, even if throughout the pregnancy, or if it was taken, but data were missing as to how and when.
281

282 **Pregnancy**

283 The pregnancy characteristics, reported in Table 2, revealed a 94.2% rate of natural

284 conception. In all, 14.2% of mothers had a gestational disorder, in 35.0% of whom it was

285 gestational diabetes. Concerning maternal behaviours in pregnancy, folic acid

286 supplementation was often inappropriate (3043 mothers, 60.8%), or not present at all (160,

287 3.2%), and vaccination rates in pregnancy were low (1628, 32.8%), involving mostly DTaP

288 (94.8%). In terms of geographical differences, there were lower rates of proper folic acid

289 supplementation and vaccination in the South. A total of 324 (6.5%) mothers smoked during

290 pregnancy, 63.9% of whom smoked daily. Alcohol was consumed by 494 (10.0%) mothers,

291 14 of whom drank it on a daily basis. The rate of alcohol consumption during pregnancy was

292 higher in the North. Maternal pre-pregnancy BMI showed that one fourth (25.3%) of mothers

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293 was overweight or obese, with a higher in southern Italy compared to the North and Centre. In

294 general, one fourth of mothers (24.2%) gained an amount of weight greater than that

295 recommended by the US Institute of Medicine (IOM).

296

Delivery

298 Concerning the birth characteristics (Table 3), almost all births were in-hospital (4980,

299 98.8%), 4895 (97.1%) were singleton births, and 1600 (31.7%) were caesarean births.

300 Hospitals provided skin to skin contact in three fourths of cases (3676, 73.8%), provided

301 intramuscular vitamin K prophylaxis at birth (4644, 92.9%), and gave newborns artificial

302 milk (1987, 40.1%), sugared water (215, 4.3%), or water (17, 0.3%). The rate of exclusive

303 breastfeeding at discharge was 69.6% (3509 mothers). In terms of national-level differences,

304 in the South caesarean births were more common, and rates of use of formula milk and

305 sugared water during hospital stay were higher. The rate of exclusive breastfeeding at

306 discharge was lower in the South (62.1% compared to 73.7% and 72.8% in the North and

307 Centre, respectively).

308

Newborns

310 Table 3 reports the newborns' characteristics. In all, 2474 (48.9%) were female. Birthweight

311 ranged from 635 to 5885 grams (median 3270 grams), with 294 (5.8%) low birthweight

312 (<2500 grams) newborns and 234 (4.6%) weighing >4000 grams. A total of 315 (6.2%)

313 newborns were born prematurely (22-36 weeks gestational age (GA)), five (1.6%) of whom

314 were extremely preterm (<28 weeks GA). Concerning weight and GA, 525 (10.5%) infants

315 were small for gestational age (SGA) and 452 (9.0%) were large for gestational age (LGA),

316 Italian Neonatal Study (INeS) charts.[43]

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317   In all, 161 (3.2%) newborns needed resuscitation at birth, 161 (3.2%) were born with

318   birth defects, and 398 (7.9%) were born with a neonatal disease. The most common diseases

319   were jaundice (106 newborns), respiratory distress (59), and neonatal hypoglycaemia (47).

320   Furthermore, 16.5% of newborns had to be admitted to a neonatal care ward and 4.3% to a

321   neonatal intensive care unit.

322

323   **Table 3. Delivery, in-hospital, breast feeding, and newborn characteristics**

	North n (%)	Centre n (%)	South n (%)	Total n (%)	P value
Mean gestational age at birth, wks; SD	39.0; 1.7	39.0; 1.6	38.9; 1.8	39.0; 1.7	0.0158 *
Gestational age category (weeks)					0.0009 *
22-36	124 (5.3)	50 (5.1)	141 (8.1)	315 (6.2)	
37-41	2197 (93.9)	923 (94.3)	1571 (90.8)	4691 (92.9)	
42-44	18 (0.8)	6 (0.6)	19 (1.1)	43 (0.9)	
Birth in hospital	2323 (99.4)	966 (98.9)	1691 (98.0)	4980 (98.8)	0.0003 *
Single vs twin births					<0.0001 *
Single birth	2294 (98.2)	954 (97.5)	1647 (95.3)	4895 (97.1)	
Twins	42 (1.8)	23 (2.4)	82 (4.7)	147 (2.9)	
Birth type					<0.0001 *
Spontaneous	1639 (70.0)	608 (62.1)	993 (57.3)	3240 (64.1)	
Caesarean	575 (24.6)	328 (33.5)	697 (40.2)	1600 (31.7)	
Instrumental birth	126 (5.4)	43 (4.4)	44 (2.5)	213 (4.2)	
Skin to skin contact immediately after birth	1880 (82.1)	778 (80.1)	1018 (59.2)	3676 (73.8)	<0.0001 *
Intramuscular Vitamin K at birth	2204 (95.2)	940 (96.7)	1500 (87.7)	4644 (92.9)	<0.0001 *
Breast feeding in hospital	2098 (91.4)	906 (93.0)	1.476 (87.7)	4480 (90.5)	<0.0001 *
Exclusively breastfed upon hospital discharge	1720 (73.7)	713 (72.8)	1076 (62.1)	3509 (69.6)	<0.0001 *
<u>NEWBORNS</u>					
Female	1116 (47.7)	515 (52.6)	843 (48.6)	2474 (49.0)	0.0361 *
Mean birthweight, gr; SD	3278.0; 483.8	3250.3; 487.5	3225.8; 501.4	3254.7; 491.1	0.0055 *
Median birthweight, gr; min-max	3290.0; 635 - 4850	3250.0; 1155 - 4750	3250.0; 1160 - 5885	3270.0; 635.0 - 5885.0	
Birthweight class, gr					0.0589
<2.500	124 (5.3)	53 (5.4)	117 (6.8)	294 (5.8)	
2.500-4.000	2098 (89.7)	874 (89.3)	1552 (89.6)	4524 (89.5)	
>4.000	118 (5.0)	52 (5.3)	64 (3.7)	234 (4.6)	
Weight for gestational age					0.8335
Small for gestational age (SGA)	236 (10.1)	97 (10.0)	192 (11.2)	525 (10.5)	
Appropriate for gestational age (AGA)	1884 (80.9)	785 (80.8)	1373 (79.9)	4042 (80.5)	
Large for gestational age (LGA)	210 (9.0)	89 (9.2)	153 (8.9)	452 (9.0)	
Mean length, cm; SD	49.7; 2.5	49.8; 2.3	49.5; 2.4	49.6; 2.4	0.0018 *
Malformation at birth	80 (3.4)	28 (2.9)	53 (3.1)	161 (3.2)	0.6565
Disease at birth	172 (7.4)	77 (7.9)	149 (8.6)	398 (7.9)	0.3466
Admitted to Neonatal Unit	398 (17.4)	181 (18.7)	241 (14.0)	820 (16.5)	0.0019 *
Admitted to Neonatal Intensive Care Unit	84 (3.6)	34 (3.5)	97 (5.6)	215 (4.3)	0.0030 *

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325   **First visit with the family paediatrician**

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3   326   The average age of the newborns at their first out-of-hospital visit was 25.7 days, with a
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5   327   median of 24.9 days (Table 4). A total of 3187 (63.6%) newborns were being exclusively
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7   328   breastfed at the time of their first visit, while, of the remaining newborns, over one third
8
9   329   (35.9%) were receiving formula milk and two thirds (64.1%) were receiving a mixed feeding
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11   330   regimen.
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13   331
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16   332   **Table 4. Characteristics at first visit with paediatrician (7-45 days old)**

	North n (%)	Centre n (%)	South n (%)	Total n (%)	P value
Breast feeding					< 0.0001 *
Exclusive	1577 (67.9)	639 (65.5)	971 (56.7)	3187 (63.6)	
Mixed breast feeding	476 (20.4)	252 (25.8)	440 (25.6)	1168 (23.3)	
Artificial formula only	270 (11.6)	84 (8.6)	300 (17.5)	654 (13.1)	
Usual sleep position					<0.0001 *
Supine	2069 (90.3)	849 (87.3)	1444 (84.5)	4362 (87.7)	
Side	92 (4.0)	65 (6.7)	215 (12.6)	372 (7.5)	
Prone	130 (5.7)	59 (6.1)	50 (2.9)	239 (4.8)	
Vitamin D prophylaxis ongoing/initiated at visit	2.297 (98.7)	942 (96.3)	1.642 (95.6)	4881 (97.4)	<0.0001 *
Drug prescribed at visit (excluding vitamin D)	108 (4.6)	27 (2.8)	41 (2.4)	176 (3.5)	<0.0001 *

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335   The prevalence of exclusive breastfeeding at the first well-child visit decreased from

336   North to South (χ^2_t 52; p<0.001). In the South of Italy, 17.5% of newborns received only

337   formula, versus 11.6% in the North and 8.6% in the Centre.

338   Concerning sleeping position, the majority of newborns slept in the supine position

339   (87.7%), while 4.8% slept in the prone position. There were geographical differences in

340   sleeping position as well: the percentage of supine position was higher in the North (90.3%)

341   and lower in the South (84.5%) (χ^2_t31.2; p<0.001).

342   Concerning prophylaxis, 97.4% were receiving vitamin D prophylaxis at their first

343   visit. A total of 176 (3.5%) newborns received a drug prescription during their visit and the

344   drugs most commonly prescribed were simethicone (17%), nystatin (14%), and ophthalmic

345   tobramycin (10%).

16

346   The results of the screening procedures for normal development (Table 4) show that

347   most of the newborns had positive developmental assessment results. Very few were found to

348   have problems with motor (9 newborns) or sensory and social (7) skills.

349   The distribution of the cohort population reflects that of the Italian population, based

350   on the ISTAT data from 2019,[44] which report that 46% of the national population resides in

351   the North, 20% in the Centre, and 34% in the South/islands. The socio-demographic

352   characteristics of the mothers also reflect national level data, where the mothers' average age

353   at birth of the first child is 32.1 years, as reported in the 2019 Eurostat data for Italy,[45]

354   compared to 32.3 in the NASCITA cohort. The main characteristics at birth of mothers and

355   newborns in the NASCITA cohort and in the national reference data, the Ministry of Health's

356   Certificato di assistenza al parto (CeDAP) 2019 data,[46] are listed in Table 5. The maternal

357   level of education is higher in NASCITA compared to national level data (42.5% compared to

358   31.2% of mothers have a university degree),[46] while the percentage of foreign-born mothers

359   on the other hand, is lower in NASCITA (13.4% *vs* 21%), with both results likely to be due to

360   language barriers that preclude recruitment and to the more frequent transfers to other

361   areas/paediatricians on the part of families with parents who were born abroad. These

362   differences are also true when NASCITA cohort data are compared with those of the Italian

363   NINFEA[28] and PiccoliPiù[47] cohorts, i.e., the general population characteristics are

364   similar, while the maternal level of education is higher in NASCITA and the percentage of

365   foreign-born parents is lower. The distribution of the newborns' anthropometric measures is

366   also comparable with that of the national data.[48]

367

368   **Table 5. Main characteristics at birth of mothers and newborns in the NASCITA cohort**
369   **and in the national reference data (CeDAP)**

	NASCITA % population	CeDAP % population
MOTHERS		
Mother born in Italy	86.6	79
Mother's age, yrs		

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≤29	24.4	25.3
30-39	65.1	63.5
40+	10.5	11.2
Maternal education		
Elementary/Middle school	23.3	25.9
Highschool	50.0	42.9
University	42.5	31.2
Maternal employment	69.7	55.0
Healthy pregnancy	85.8	85.2
Natural conception	94.2	96.9
Caesarean section	31.7	31.8
NEWBORNS		
Twins	2.9	1.6
Birthweight		
<1500 gr	0.5	0.9
1500-2499 gr	5.3	6.2
2500-3999 gr	89.5	87.6
>4000 gr	4.6	5.2
Gestational age at birth / Preterm birth		
22-36 weeks	6.2	6.8
37-41	92.9	92.7
>41	0.9	0.5
Malformation at birth	3.2	1.3

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371

372   Newborns participating in the NASCITA cohort, and their families, are generally

373 representative of the Italian population in terms of geographical distribution[41] and

374 sociodemographic characteristics, with the exception of the lower prevalence of foreign-born

375 mothers, as reported above. The analysis of the characteristics during pregnancy and at birth

376 confirms the existence of large geographical differences in attitudes, in particular concerning

377 folic acid intake, immunization, caesarean birth, and exclusive breastfeeding prevalence.

378   One fourth of the NASCITA cohort mothers (25.3%) were overweight or obese,

379 although this rate seems to be lower than the European rate of 30%-50%.[49] The rate of

380 caesarean births in the NASCITA cohort, involving almost one in three births, confirms

381 Italy's standing as one of the countries with the highest rate in Europe. Large regional

382 differences exist, with much higher rates in the South.[50]

383   Concerning aspects related to nurturing care and good practices, the data collected on

384 these behaviours show that more must be done. When considering exclusive breastfeeding,

385 for example, the rates in Italy at hospital discharge were already low, represented by just over

18

386 two thirds of mothers (69.6%), and the rate decreased to 63.6% at the first visit with the

387 paediatrician. Concerning folic acid supplementation, only about one third of mothers took it

388 in an appropriate manner, with an even worse situation in the South. Concerning smoking and

389 alcohol use, the NASCITA data showed that 6.5% of mothers continued to smoke during

390 pregnancy and that one in ten drank alcohol during pregnancy.

391 Geographical differences in the health status and in the care of mother and newborns

392 are striking, in particular when looking southern Italy. Pregnant women living in southern

393 Italy were less compliant with folic acid prophylaxis and with recommended vaccinations.

394 They were also at greater risk of being overweight or obese at the beginning of the pregnancy.

395 A greater rate of caesarean delivery was reported, neonates were less frequently exposed to

396 skin-to-skin contact with their mothers at birth, and were less likely to be breastfed at

397 discharge from the hospital, and consequently, also at the first well-child visit. Differences in

398 the exclusive breastfeeding rate at hospital discharge after delivery between the South and

399 other geographic areas of Italy persist also when excluding preterm or low birthweight

400 newborns, or newborns with congenital malformations (data not shown). Geographical

401 differences have been already documented by previous studies[20,36] and according to our

402 findings, little has changed in the meantime. Several factors can be associated with these

403 differences (organisation of the healthcare system at the local level, physicians' attitudes, and

404 cultural and socioeconomic factors), and multifaceted interventions are needed. Even after

405 adjusting for sociodemographic variables (e.g. maternal age at delivery, educational level,

406 employment status, Italian nationality, parity, etc.) compliance with good practices remained

407 low in southern Italy (data not shown). Differences in socioeconomic status may have a role,

408 but other variables are likely involved. Moreover, the fact that the exclusive breastfeeding rate

409 at hospital discharge was 62.1% may suggest that there is a need for educational interventions

410 for health professionals involved in assistance at delivery and for organisational changes with

411 the aim to support mothers who desire to breastfeed.

412

Strengths and limitations

414 The NASCITA study confirms what is known about national level and regional level

415 differences in health care practices and behaviours from other studies, such as smoking and

416 alcohol data, but it is also the first study capable of assessing, at the national and regional

417 levels, other variables such as pertussis vaccination in pregnancy. Furthermore, the NASCITA

418 cohort is one of the few studies involving the paediatricians directly as protagonists in cohort

419 design and data collection. The paediatricians' direct role in data collection is a major strength

420 in that it permits a "holistic" evaluation, including information on growth, health status, drug

421 prescriptions, diagnostic exams and specialist visits, data from clinical examinations, and

422 screenings integrated with information obtained from the parents. Another strength of this

423 study is that the newborn population is representative of the national newborn population in

424 terms of geographical distribution and characteristics. Furthermore, strategies were

425 implemented to maintain paediatrician participation and to minimize loss to follow-up,[41]

426 involving, for example, maintaining contact with the paediatricians through periodic emails

427 providing updates on the progress of the cohort, providing paediatricians with timely email

428 assistance with data input, and sending periodic newsletters listing recent publications on

429 other cohort studies. Similarly, strategies were implemented to maintain parental participation

430 and minimize loss to follow-up of the newborns, such as providing information dedicated to

431 parents on the NASCITA study's web portal on common childhood diseases. A further

432 strength of the NASCITA study is that efforts were made to retrospectively collect data on the

433 mothers and fathers from before, and during, the pregnancy.

20

434   The limitations of this study are, first, that the population is restricted to the children

435   assigned to the participating paediatricians, and this may lead to a somewhat selected sample

436   because many of the paediatricians are part of the national Paediatricians' Cultural

437   Association (ACP) and may have joined NASCITA because they are more inclined to

438   participate in research than others. The geographic distribution of the paediatricians, however,

439   is representative of Italy's North-Centre-South division, and the paediatricians do not choose

440   which children to follow, but receive those assigned to them by the local health unit.

441   A second limitation is that the newborn population reflects that of the newborn population

442   normally followed by family paediatricians in Italy, which includes all newborns who do not

443   have serious health problems that would prevent them from being regularly followed, at least

444   in the first period of their lives, by a family paediatrician. Newborns with serious health

445   problems are usually followed by hospital staff or specialists, and would therefore not likely

446   have been taken to the first well-child visit within the first 45 days of life (when paediatricians

447   enrolled newborns in the study).

448   A third limit of the NASCITA cohort is that it does not collect biological samples due to the

449   costs of data collection and storage. It will therefore not be able to evaluate genetic or

450   immunological factors, for example. Resources and efforts were utilized, however, to achieve

451   the largest population size possible in order to have enough power to study common child

452   exposures and outcomes.

453

PATIENT AND PUBLIC INVOLVEMENT

455   Patients were indirectly involved in the development of the research questions and

456   questionnaires in that the technical-scientific committee that was set up to supervise the study,

457   and that collaborates in creating and revising the questionnaires, involves professionals (e.g.,

458   paediatricians, pharmacists, educators) who are also parents. The public is involved through

21

459 the dissemination of cohort results and information on childhood diseases or conditions to

460 parents and the general public on the study's website.

461

462 **COLLABORATION**

463 Data from the NASCITA study will be available upon reasonable request, after approval by

464 NASCITA's technical-scientific committee, and for non-commercial purposes. We encourage

465 collaboration between different cohorts, for example to merge, or compare, data on chosen

466 topics of study.

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Data availability statement

The datasets used and/or analysed during the current study are available from the

corresponding author upon reasonable request and approval by the technical-scientific

committee, and only for non-commercial purposes.

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MB designed the Study. MB and AC directed the study's implementation. AC and MC

designed the analytical strategy. MC and RC carried out the statistical analyses. AC, MC, RC,

and CP helped to interpret the findings. CP drafted the manuscript. MB, AC, MC, RC, and CP

contributed to, and revised, the article., MB, AC, MC, RC, and CP read and approved the

final manuscript, and agree to be accountable for all aspects of the work.

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543 Luisa Zuccolo. Roberto Cionini and Giuseppa Scornavacca unfortunately passed away.

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STROBE Statement—Checklist of items that should be included in reports of *cohort studies*

	Item No	Recommendation	Page n
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	5-8
Objectives	3	State specific objectives, including any prespecified hypotheses	8
Methods			
Study design	4	Present key elements of study design early in the paper	8-11
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	8-11
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	9,10
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed	N/A
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	9,10
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	*9,10*
Bias	9	Describe any efforts to address potential sources of bias missing data	10
Study size	10	Explain how the study size was arrived at	N/A (explained to reviewer)
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	11
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding PAG DESCR STATISTICS STUFF	11
		(*b*) Describe any methods used to examine subgroups and interactions NONE	N/A
		(*c*) Explain how missing data were addressed PAG	11
		(*d*) If applicable, explain how loss to follow-up was addressed	N/A
		(*e*) Describe any sensitivity analyses	N/A
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	9
		(b) Give reasons for non-participation at each stage	N/A
		(c) Consider use of a flow diagram	N/A
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	12,15
		(b) Indicate number of participants with missing data for each variable of interest	N/A
		(c) Summarise follow-up time (eg, average and total amount)	N/A

Outcome data	15*	Report numbers of outcome events or summary measures over time	
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	12,13,15,16
		(*b*) Report category boundaries when continuous variables were categorized	12,13,15,18
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	N/A
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	N/A
Discussion			
Key results	18	Summarise key results with reference to study objectives	11-19
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	21
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	19,20
Generalisability	21	Discuss the generalisability (external validity) of the study results	17,18
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	22

*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at http://www.strobe-statement.org.