

Survey of Neonates in Pomerania (SNIp): Study design and cohort update

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Abstract

Background: The health status of newborns is a major concern for parents and medical personnel. Recent studies have provided increasing evidence that factors from the foetal and perinatal periods of life influence health later in life. The “Follow-up of the Survey of Neonates in Pomerania” (SNIp-I-Follow-up) is the first follow-up of the population-based birth cohort study, SNIp-I, established in north-east Germany. **Objectives:** The primary aim of SNIp-I-Follow-up study was the collection of longitudinal data on children and adolescents. The associations will be analysed between risk factors in pregnancy and the perinatal period and health status in infancy and later childhood.

Population: The population-based cohort study SNIp-I was conducted in Pomerania in north-east Germany between February 2002 and November 2008. All mothers from the SNIp-I birth cohort were recontacted when their children were from 9 to 15 years of age.

Design: The SNIp-I-Follow-up study was carried out between December 2016 and August 2017 and is a questionnaire-based survey.

Methods: Physical development, health status, and social behaviour (school and leisure behaviour) of children were analysed using a questionnaire comprising medical, epidemiological, and socio-economic data, associated health care risk factors, and life circumstances of newborns, children, and their parents.

Preliminary results: Out of 5725 children invited to participate in the SNIp-I-Follow-up study between December 2016 and August 2017, 29% (n = 1665) children participated in the SNIp-I-Follow-up study, providing data on 1665 mothers-child dyads. Responders had higher socio-economic status, especially in relation to maternal education status.

Conclusion: As a longitudinal birth cohort from rural Germany, the SNIp cohort will be a resource to address urgent research needs and contribute to overall population health.

Kantorczyk and Domanski are equally contributed to this study.

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KEYWORDS

child health, population-based birth cohort, SNIp, study design, Survey of Neonates in Pomerania

1 | BACKGROUND

There is increasing evidence showing the importance of the foetal and perinatal period for health later in life. Risk factors with adverse effects on the child's future health are alcohol consumption¹ and smoking during pregnancy,^{2,3} high pre-pregnancy BMI,⁴ low social status and low educational level of the mother,^{5,6} and maternal infectious diseases.⁷ These factors increase the risk of diabetes, metabolic syndrome, and cardiovascular diseases in adolescence or adulthood.⁸ Therefore, improving population health requires the early identification of vulnerable groups and preventative health care and policies during pregnancy and in early infancy and childhood. Longitudinal population-based multipurpose birth cohort studies are an essential tool for researchers aiming to understand and mitigate the impact of early life circumstances on later health.

The Survey of Neonates in Pomerania (SNIp) is a population-based cohort study conducted in Pomerania in north-east Germany starting in 2002. The baseline assessment, carried out between February 2002 and November 2008, generated representative medical, epidemiological, and socio-economic data concerning public health, associated health care risk factors, and life circumstances of newborns, children, and their parents.⁹⁻¹¹ The broad spectrum of data on the prenatal, perinatal, and postnatal periods has allowed multiple data analyses focusing on clinically relevant topics, including preventive medical check-ups during pregnancy,^{12,13} health and health-related risk factors with regard to socio-economic background,¹⁴ and health risk factors and their associated outcome in infancy.^{15,16}

The SNIp-I-Follow-up study collects information on this cohort in childhood and adolescence in order to investigate the associations between biological, clinical, social, and health care factors in pregnancy and the perinatal period and later health. Also, given the paucity of data on the health of children and adolescents, in contrast to vast amounts of data available on adult health,¹⁷ the study aimed to provide data on the physical development, health status, and social behaviour (school and leisure behaviour) of children in the study area. This paper updates the study design and cohort profile after the first follow-up study of children aged 9-15 years from the original SNIp-I cohort using a comprehensive questionnaire.

2 | METHODS

The SNIp-I study recruited participants starting in February 2002 and continuing until November 2008. The study area comprised the

Synopsis**Study question**

The primary aim of SNIp-I-Follow-up study was the collection of longitudinal data on children and adolescents to analyse associations between risk factors in pregnancy and the perinatal period and their health status in infancy and later childhood.

What's already known

There is increasing evidence that risk factors in the foetal and perinatal periods influence health later in life.

What this study adds

The Follow-up of the Survey of Neonates in Pomerania (SNIp-I-Follow-up) is the first follow-up of the SNIp-I population-based birth cohort study in north-east Germany. We observed a bias towards higher socio-economic status among responders, especially in relation to maternal education status. These data will enable research on the Developmental Origins of Health and Disease (DOHaD) hypotheses in a rural part of Germany.

entire region of "Ostvorpommern" (Figure 1),⁹ a geographic area of 1962 km² with 162 500 residents and approximately 1250 births per year. The region included three maternity hospitals (Anklam, Wolgast, and Greifswald) and is located in north-east Germany within the federal state of Mecklenburg-West Pomerania that belonged formerly to the German Democratic Republic. All mothers who were permanent residents in the study area at the time of delivery and gave birth during the study period in one of these three maternity units were included in the study. Home births comprised <5% of all births. With a registration of 95% and a first-participation rate of 75% of all deliveries in the study area, the collected data are population-based and described in detail the population in north-eastern Pomerania.⁹

Data collected in the SNIp-I study at the time of birth come from questionnaires administered to mothers, medical files, and biological samples. Mothers provided information using self-administered questionnaires or were interviewed by study staff in a standardised face-to-face interview. In addition, data from the mothers' and newborns' medical records, prenatal booklets, mothers' delivery records,

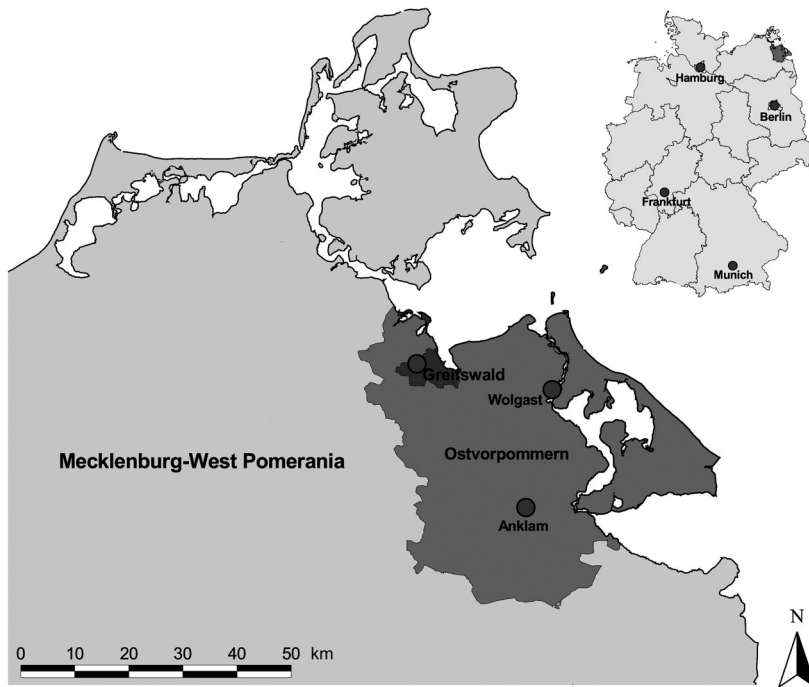


FIGURE 1 Study region of “Ostvorpommern” with the location of paediatric hospitals (from Ebner et al⁹). The study area was defined by zip codes 17389-17999

and newborn hospital records were included in the database. Biological samples included cord blood and DNA, as well as placental tissue specimens. Other details regarding the SNIp-I cohort have been previously described.⁹

3 | SNIp-I-FOLLOW-UP

The SNIp-I-Follow-up study was carried out between December 2016 and August 2017. Data were collected by a self-administered questionnaire that could be answered electronically using a Web-based application or via paper-based questionnaire. Invitation letters were sent to mothers who participated in the SNIp-I study and agreed to be contacted for any follow-up study. Each questionnaire contained the same 140 questions in the same sequence. There was only a single questionnaire to be filled in. The average time needed to complete a questionnaire by respondents was estimated to be about 20 minutes. At the end of the form, participants were invited to provide short feedback about the time needed to fill out the questionnaire and questions that they felt uncomfortable answering. Neither linked data from medical records nor biospecimens were collected during the SNIp-I-Follow-up.

Table 1 summarises the topics that were included in the questionnaire with relevant definitions. These included the development, growth, and health status of the child; the environmental, social, and economic factors influencing the child's development; and the family environment and mother's satisfaction with her current life situation.

The questionnaire was harmonised with the German Health Interview and Examination Survey for Children and Adolescents Study (KiGGS) in order to enable comparative data analyses.¹⁷ According to the original paper describing the design of the

KiGGS-Study,¹⁷ the KiGGS-Study interview and examination survey was conducted from May 2003 to May 2006 by the German Ministry of Health (Robert Koch Institute). We received permission to use selected questions from the KiGGS questionnaires regarding the child's development and socio-economical parameters.

3.1 | Ethics approval

The design of the baseline SNIp-I study was reviewed and approved by the Ethics Committee at the University Medicine Greifswald (Reg.-Nr III UV 20/00). Written informed consent was obtained from all women who agreed to participate in the study. Additional permission for future contact and data linkage was sought from all study participants at the time of initial consent. In cases of legally minor mothers (ie age <18 years), additional signatures were required from the newborn's and mother's legal caregivers. The content and design of the SNIp-I-Follow-up study was reviewed and approved by the Ethics Committee at the University Medicine Greifswald (BB 020/16).

3.2 | Acquisition of participants

First invitation letters were sent to participants from the baseline cohort ($n = 5725$) between December 12 and 20, 2016 (Figure 2). The number of participants ($n = 4783$) published in the original paper by Ebner⁹ included participants from the main phase of the SNIp-I study from March 2003 to November 2008, while we also included participants from the pilot phase lasting from May 2002 to February 2003.

TABLE 1 Detailed information on the content of the questionnaire sent to participants of the SNiP-I-Follow-up

Topic	Content	Further definition
Child		
Child's growth and development from the birth until survey*	Medical screening examinations	Participation in preventive examinations (U1-J1), according to recommended schedule, including its date, but without recording any medical findings
	Medical consultations within last 12 mo (other than dentist)	If child got a medical consultation within last 12 mo
	Weight and height	Actual child's weight and height used further to calculate secondary variables, for example BMI, percentiles for weight and height, etc
Child's health status*	Visual aids	If child uses any visual aids, and since when
	Hearing impairment	Does child suffer from any hearing losses
	ADHD	Does child suffer from attention disorder and hyperactivity
	Headache	Occurring of headache during last three months, type of applied therapy
	Allergies	Whether child suffers from any allergy or not, and if, what kind of allergy (hay fever, atopic eczema, allergic asthma, allergy to animal hairs, drugs or other substances)
	Faint	Whether child was unconscious within last 12 mo or not
	Heart diseases	Whether child suffers from cardiac murmur, ventricular septal defect, atrial septal defect
	Chronic diseases	Information asked here is a checklist, not official diagnoses according to ICD-10 system, for example coeliac disease, anorexia nervosa, diabetes mellitus, hypertension, epilepsy
	Accident(s) with last 12 mo	Whether child was involved in any accident (home, school, leisure time) or not
	Dental hygiene	Frequency of daily dental hygiene, type of used toothpaste, frequency of visit by a dentist
Estimation of the child's well-being*	Child's physical well-being	Perception of physical well-being during last seven days, like filling sick, tired, or having power and endurance (assessment done by mother)
	Child's mental well-being	Perception of mental well-being, like (assessment done by mother)
	Child's self-esteem	(assessment done by mother)
	Child's relations within the family	(assessment done by mother)
	Child's friendship	(assessment done by mother)
	Child's perception of the school	(assessment done by mother)
School*	Type of school attended by child	Elementary school, secondary school (Hauptschule, Realschule, or Gymnasium), other type of school, incl. Waldorf school or schools for children with mental or physical disabilities
	Child's performance at school	Skipping or repeating a grade
Child's recreational activity*	Sport	School mark for sport, satisfaction of parents with child's sport performance
	Outdoor activities	Frequency of exercising sport in or outside a sport association
	Indoor activities	Time spent watching TV, playing computer, videogames, game console, using smartphone
Contact with animals*	Pets	Type of pet kept at child's home (dogs, cats, birds, aquatic animals, reptiles, others)
	Farm animals	Contact with farm animals during last 12 mo (horses, cattle, pigs, poultry, others)
Nutrition*	Breast feeding	Whether child was breast fed, and if, for how long
	Infant food and infant milk	When mother started to give infant food and infant milk
	Special nutrition	Whether child receive currently a special nutrition, for example vegetarian, no eggs, no beef, poultry, or pork meat
	School meal	Participation in and satisfaction from school dinner

(Continues)



TABLE 1 (Continued)

Topic	Content	Further definition
Smoking and alcohol consumption*	Smoking	Child's smoking behaviour (yes/no), smoking in the presence of child (passive smoking)
	Alcohol consumption	Child's alcohol consumption (yes/no)
Life circumstances*	Place of residence of the child	Living with their parents/grandparents/single parent/ foster parents
Mother/father or cohabitee		
Health status*	Allergies ^V	Whether mother suffers from any allergy or not, and if, what kind of allergy (hay fever, atopic eczema, allergic asthma, allergy to animal hairs, drugs, or other substances)
	Weight and height ^V	Actual mother's weight and height used further to calculate secondary variables, for example BMI
Social environment*	Support received by mother during pregnancy	List of usual support offered in Germany to mothers during pregnancy, incl. visits of local midwife, participation in antenatal classes
	Support received by mother after delivery	List of usual support offered in Germany to mothers after delivery, incl. postnatal visits of local midwife, postnatal physical exercises, early support to child, financial support offered to mother, affirmation as mother by family, and friends
	Childcare before school	Child care before entering school, for example exclusively within family, nanny, kindergarten, other forms
	Smoking ^V	Smoking behaviour (daily, occasionally, never); indoor smoking in the presence of child
	Sleeping quality ^V	Assessed for last 4 wk; reasons for bad sleep: lack of comfortable breathing, too low or too high temperature, bad dreams, pain; using sleep inducing drugs
Life circumstances*	Marital status ^V	Mode of partnership
	Housing situation	Size of house/flat, mould in house/flat
	Number of persons in household	Family size of household
	Life satisfaction	Satisfaction with family, health, relationship, professional status, income (question from SOEP using a 7-level Likert scale)
Socio-economic data*	Graduation level ^V	Highest graduation level obtained by parents
	Professional position ^V	Occupation held by parents
	Household income ^V	Total available monthly income, taxes, and social security contributions excluded
	Type of employment ^V	Full time/part time; participation in standby duty and shift work
Resume	Uncomfortable questions	Questions that may be unsavoury to or unpleasant to be answered by a respondent
	Comments	Any additional information provided by parents (free text)
	Effort needed to fill in the questionnaire	Opinion on the burden connected with participation in the study

Note: All information was collected from a single questionnaire. Information regarding the perinatal period was asked retrospectively. Parents were invited to fill in the questionnaire together with their children.

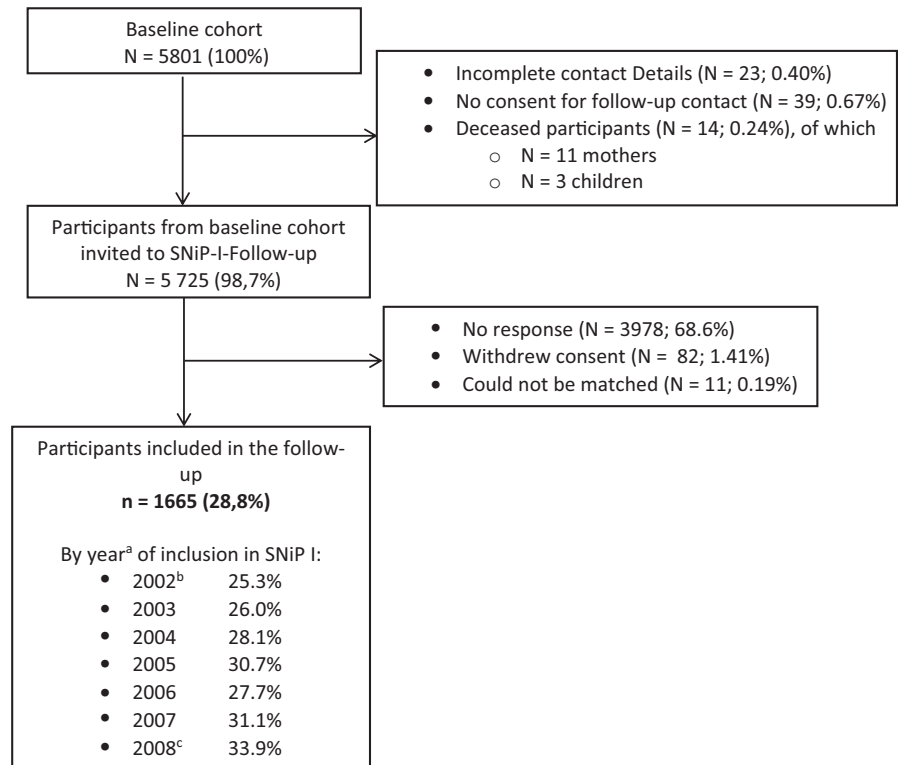
*Topics harmonised with KiGGS survey.

^VQuestions also related to child's father or mother's cohabitee. It was left to mother's discretion who has answered questions regarding child's father or cohabitee.

Each participant received a cover letter that included log-in details to access an online questionnaire, a printed questionnaire, detailed information about the study, and a consent form. In March 2017, 12 weeks after the first invitation, a reminder was sent to all persons who did not return a completed questionnaire, to fill out a questionnaire online, or withdraw their written consent from the SNIPI study. People who did not respond to the original invitation or the first reminder by the end of March 2017 or whose

letters were undeliverable were phoned by study staff in April 2017 and invited to participate in the follow-up study. The telephone call consisted of a short introduction of the person calling and the reason for the call (ie no previous participation or letter undeliverable due to incorrect address), followed by a request to participate. If the answer was positive, the mother's address and name were checked and corrected, if necessary. If the mother decided against participating, she was marked as a non-participant

FIGURE 2 Selection process and participant enrolment during the SNIp-I-Follow-up study. We have included not only participants from the main phase of the SNIp-I study (from March 2003 to November 2008), but also from the pilot phase (from May 2002 to February 2003). Therefore, the number of participants in our study is larger the number presented by Ebner et al.⁹ ^aData are the percentage of participants from the SNIp-I baseline who completed the SNIp-I-Follow-up survey. ^bFebruary 2002–December 2002. ^cJanuary 2008–November 2008



in the database. No telephone interviews were conducted. A final reminder was sent in July 2017 to participants who had not responded to the first invitation or the first reminder. We assumed that any study-related material sent in December 2016 was thrown away; therefore, we sent a cover letter that included log-in details, an information leaflet about the study, and another printed questionnaire.

To increase participation rates and to increase knowledge about the study and its visibility, SNIp-I-Follow-up study was accompanied by advertising efforts in the local newspapers, on the Internet, and on social media. Information about the progress and importance of the study was provided at regular intervals, in both the regional newspapers and Internet-based media. Information booklets and posters about SNIp-I-Follow-up were also displayed by resident paediatricians across the study area. As an incentive, we also held a drawing for five high-end tablet computers among all participants.

3.3 | Statistical analysis

Data from the SNIp-I and SNIp-I-Follow-up studies were stored in separate databases to ensure non-traceability of the data. To conduct statistical analyses, the individual data records were matched using an identifier common to both databases. Out of the total records, 11 could not be matched and were excluded from the statistical analysis, leaving 5714 individual data records (Figure 2).

For the description of the baseline and follow-up samples, continuous data were reported as the median with 25th and 75th

percentiles; categorical data were expressed as the absolute number and percentage. Chi-square tests were used to compare frequencies and the Wilcoxon test to compare medians. All analyses were carried out in Stata 14.1 (Stata Corporation).

4 | RESULTS

The scheme of the SNIp-I-Follow-up study, including number of participants at baseline and follow-up, is given in Figure 2. From the SNIp-I baseline cohort, surviving participants who had provided consent for further contact at the time of enrolment and for whom contact details were available were eligible to be recontacted or a total of 5725 children between 9 and 14 years of age and their mothers. The response rate was 28.8%, based on the total number of participants of the original SNIp-I study. The term non-responders describes people who received invitations and did not return the questionnaire as well as people for whom invitations could not be delivered. Non-responders could be divided into two main groups: those who did not answer ($n = 3980$) and those who withdrew their written consent ($n = 82$). The distribution of response rates varied across individual study years (Figure 2). Mothers from the early years of SNIp-I participated less frequently in the SNIp-I-Follow-up. Only one-fourth women recruited in 2002 participated in the SNIp-I-Follow-up, whereas one-third recruited in 2008 participated. The year 2006 represents the only exception from this pattern, with a lower response than for the previous years. All invited participants had a choice to respond using a paper-based or Web-based version of the survey. A vast majority, more than 80%, answered by paper survey.



4.1 | Responder and non-responder analysis of SNIp-I-Follow-up

Detailed results of the responder and non-responder analysis of the SNIp-I-Follow-up study at baseline are given in Table 2. Out of four neonatal parameters selected for comparison, only one, admission to neonatal care unit, differed between participants and non-responders. Neither birthweight, nor sex nor the rate of preterm birth (<37 weeks) differed significantly between participants and non-responders. No differences were observed for mothers pre-pregnancy BMI or prevalence of GDM, but other maternal characteristics differed: mothers of participants in the SNIp-I-Follow-up study were older, had higher available monthly income and educational status, were less likely to smoke during pregnancy, and had more frequently declared their intentions to breast feed compared to mothers of non-responders.

Table 3 shows demographic data of the SNIp-I-Follow-up sample. Mothers taking part in the SNIp-I-Follow-up study were 40 years old (median), and their children were 12 years old. In line with increased maternal age, we observed increases in their BMI from 22.4 to 24.2 at the median age of 29 and 40 years, respectively (Tables 2 and 3). Equivalent net income was higher by 262 Euros by the time of the SNIp-I-Follow-up study, roughly reflecting the inflation rate between 2006 and 2017. We observed substantial changes in maternal marital status. The percentage of married women increased from about 37% (SNIp baseline) to almost 69% (SNIp-I-Follow-up). At the same time, the fraction of single women decreased from 58% (SNIp baseline)⁹ to 7% (SNIp-I-Follow-up). The smoking rate increased from 8.8% of women at the SNIp baseline (Table 2) to more than 23% for women taking part in the SNIp-I-Follow-up study.

4.2 | Biospecimen collection rate at baseline

Biospecimens were collected only during the baseline study. The biobank includes samples of EDTA plasma (n = 4794; 82.6% of all children) and DNA (n = 4839; 83.4% of all children) isolated from cord blood and samples of placental tissue (n = 4657; 80.3% of all children). Those biospecimens collected at baseline were available for 78% (EDTA plasma n = 1300, child DNA n = 1300) and 71% (placental tissue, n = 1183) of the participants who completed the SNIp-I-Follow-up. Recently, we prepared a series of analyses of plasma derived from the EDTA-cord blood using a 1H-NMR-based measurements: lipoprotein profiling (Apo-A1, Apo-A2, Apo-B, LDL particle, cholesterol) and metabolic profiling (amino acids and derivatives, selected drugs and vitamins, keto acids, purines, pyridines, pyrimidines and their derivatives, selected sugars and their derivatives).

4.3 | Data access

Data and biospecimens are available upon request and free of charge. The full data are not freely available to respect the

confidentiality of the participants, ensure data integrity, and avoid scientific overlap between projects. However, this data repository allows any researcher to register and apply for access. Research proposals will be subjected to review by the Community Medicine Steering Committee and approval by institutional research ethics boards. Additional details and contact information are available on the study website at http://www2.medizin.uni-greifswald.de/kind_med/index.php?xml:id=759. The website provides a data dictionary and online application tools for accessing the data.

5 | COMMENT

5.1 | Principal findings

Of the original baseline cohort, 28.8% participated in the SNIp-I-Follow-up study. Participants in the follow-up study had higher educational levels, higher available incomes, and were older at the time of their enrolment in the baseline study. This shift in socio-economical parameters was also reflected in behavioural variables, such as smoking or alcohol consumption. Higher socio-economical status was connected with higher rate of alcohol consumption but lower rate of smoking. Surprisingly, we observed a significant increased of smoking women, a local trend being in opposition to continuously decreasing number of smokers in the general population. It is not clear whether this is a data bias or a local anomaly. While the response rate of 28.8% may seem low, it is comparable with rates reported for many other cohort studies. For instance, approximately 10 years from the start of the study, the coverage rates in the Ulm SPATZ¹⁸⁻²⁰ and Odense Child^{21,22} studies were roughly 20%, while the Generation R study had a higher coverage rate of 43%-48%.²³ The comparisons of responders and non-responders also confirmed the general bias towards participants with higher socio-economic status observed in most of follow-up studies.²⁴⁻²⁷

5.2 | Strengths of the study

A strength of the SNIp-I and SNIp-I-Follow-up studies is their high population coverage at baseline. The main reason for the high baseline participation rate was that large parts of the SNIp-I-study was embedded in clinical care. This created confidence in physicians and nurses who were in charge of the mother and infant with respect to clinical care and recruitment for the cohort study. Population-based data covering perinatal and child health in rural populations are unique in Germany.² Finally, the study has substantial geographic overlap with one of Europe's largest and most comprehensive, prospective studies of health in an adult sample, the "Study of Health in Pomerania (SHIP),"²⁸ that is allowing comparison of health and risk factors of pregnant women on the background of the representative sample of the local population.

TABLE 2 Comparison of selected parameters for participants in SNiP-I and SNiP-I-Follow-up

Indicator	SNiP-I (n = 5714)	Participants of SNiP-I-Follow-up (n = 1665)	Non-responders of SNiP-I-Follow-up (n = 4049)	(Risk ratios for categorical variables and B coefficients for continuous variables) (95% confidence interval) ^{a,b}
Children				
Sex: male, %	52.9 (n = 3003)	52.9 (n = 872)	52.5 (n = 2131)	0.98 (0.88, 1.10)
Birthweight, g, mean (SD)	3306 (n = 5714)	3326 (n = 1665)	3299 (n = 4049)	27.2 (-11.4, 65.9)
Admission to neonatal care unit, %	23.3 (n = 1331)	21.5 (n = 353)	24.1 (n = 978)	0.86 (0.75, 0.99)
Preterm birth (<37 wk), %	11.5 (n = 655)	11.5 (n = 189)	11.5 (n = 466)	1.01 (0.83, 1.24)
Mothers				
BMI (overall), kg/m ²	22.5 (n = 5070)	22.4 (n = 1563)	22.5 (n = 3507)	-0.28 (-0.56, 0.01)
BMI classes				
Underweight (BMI < 18.5), %	7.08 (n = 359)	6.14 (n = 96)	7.50 (n = 263)	0.76 (0.60, 0.97)
Normal weight (BMI ≥ 18.5 and <25.0), %	65.7 (n = 3333)	69.0 (n = 1079)	64.3 (n = 2254)	1.00 Reference
Overweight (BMI ≥ 25.0 and <30.0), %	17.8 (n = 903)	17.1 (n = 268)	18.1 (n = 635)	0.88 (0.75, 1.03)
Obesity (BMI ≥ 30.0), %	9.37 (n = 475)	7.68 (n = 120)	10.1 (n = 355)	0.71 (0.57, 0.88)
GDM, %	4.97 (n = 284)	4.85 (n = 80)	5.02 (n = 204)	1.07 (0.81, 1.41)
Age, years, mean (SD)	27.5 (5.48) (n = 5705)	28.9 (5.10) (n = 1646)	26.9 (5.53) (n = 4059)	1.99 (1.68, 2.30)
Equivalent net income, €, mean (SD)	1128 (680) (n = 2606)	1318 (679) (n = 929)	1023 (658) (n = 1677)	295 (242, 249)
Education level < 10 y, %	15.3 (n = 765)	7.72 (n = 112)	18.9 (n = 653)	0.41 (0.33, 0.51) ^e
Education level > 10 y, %	32.1 (n = 1602)	42.7 (n = 657)	27.3 (n = 945)	1.68 (1.47, 1.91) ^e
Any alcohol consumption during pregnancy, %	21.1 (n = 1107)	24.0 (n = 372)	21.0 (n = 735)	0.84 (0.73, 0.97)
Smoking in the last 4 wk of pregnancy, %	19.0 (n = 935)	8.75 (n = 143)	23.6 (n = 801)	0.31 (0.26, 0.38)
Intent to breast feed, %	90.8 (n = 1870)	93.0 (n = 602)	89.8 (n = 1268)	1.52 (1.07, 2.15)

Note: In this paper, we did not analyse the dose effect of tobacco and alcohol consumption on pregnancy outcomes. Therefore, we did not differentiate the cohort by the amount of alcohol consumed or tobacco smoked. Instead, we used a simple dichotomous classification: “smoker/non-smoker” and “drinker/non-drinker.” A woman was classified as a smoker if she declared that she smoked during the last 4 wk before delivery. Similarly, a woman was classified as a drinker if she continued to drink alcohol during pregnancy, regardless of the amount and time period of consumption. “Available monthly equivalent income” was calculated by dividing the household’s income by the weighted number of members in the household.³⁴ Babies and their mothers were left at the maternity ward as long as conditions allowed. For the purposes of the study, “admission to neonatal care” included both neonatal intensive care and special care with respect to the newborn’s condition and needs.

Abbreviation: SD, standard deviation.

^aMeans for categorical data (child’s sex, admission to neonatal care unit, preterm birth, GDM, mother’s education level, alcohol consumption, smoking, breast feeding) or medians for continuous data (child’s birthweight, mother’s BMI, age, available monthly income).

^bRisk ratios for categorical data and β -coefficients for continuous data.

^cEducation level = 10 y as reference group.

**TABLE 3** Selected demographic data of the SNiP-I-Follow-up sample

Indicator	SNiP-I-Follow-up (n = 1665)
Child age, years ^a	12 (10, 13; n = 1650)
Maternal age, years ^a	40 (37, 45; n = 1646)
Maternal BMI, kg/m ^{2a}	24.2 (21.80, 27.82; n = 1633)
Equivalent net income, € ^a	1588 (1122, 2020; n = 1168)
Maternal marital status, %:	
• Married, living together with partner	65.9 (n = 1098)
• Married, but living in separation	2.46 (n = 41)
• Unmarried, but living in partnership	18.3 (n = 304)
• Single	7.08 (n = 118)
• Divorced	4.86 (n = 81)
• Widowed	0.42 (n = 7)
Smoking, %	23.4 (n = 386)

^aMedian, 25th and 75th percentile, and sample size, respectively (in parentheses); differences between sample size for an individual parameter and the sample size of the SNiP-I-Follow-up are a measure of missing data.

5.3 | Limitations of the data

The retention of participants in longitudinal cohort studies, especially when they are population-based, is a recognised and common problem. A Cochrane review²⁹ identified incentives that contribute to increasing response rates for postal questionnaires, improving the quality of the research and minimising potential bias, including (a) monetary incentives, especially when these are not conditional on response, (b) using short and personalised questionnaires, (c) sending by certified delivery, (d) using stamped return envelopes, (e) providing non-respondents with a second copy of the questionnaire, and (f) contacting participants before and during the survey. These strategies have been followed by many previous and recent cohort studies,^{23,30,31} and many of these incentives were adopted in the SNiP-I-Follow-up. Regardless of our efforts, several additional factors may have decreased the participation rate in the SNiP-I-Follow-up study. The long time lag (8-13 years) between the initial recruitment and time of the contact may have reduced the participation rate, as seen by the lower response rates by year of baseline recruitment. The low population density was also a challenge. There is no large city located in the study area and the straight-line distance between the study centre (Greifswald) and distant towns and villages are up to as much as 50 km. Therefore, logistic aspects related to the promotion and implementation of the SNiP-I-Follow-up study required much more effort than studies carried out in large towns or cities. Finally, Greifswald and the surrounding area have a high percentage of students (~20%) who move after their studies are completed; participation in local programmes, such as a local health study, may then lose importance.

5.4 | Interpretation

The SNiP-I-Follow-up study is a questionnaire-based survey addressing all mothers and children from the SNiP-I birth cohort when the children are 9-14 years of age. A total of 1665 maternal-child dyads were included which will allow evaluation of the physical development, health status, and social behaviour of children, maternal support and well-being and associations with risk factors from pregnancy and the perinatal period. The detailed and comprehensive questionnaire covers a wide range of health and social issues. Furthermore, a high proportion of biospecimen availability for participants in the SNiP-I-Follow-up study (more than 70%) allows for the combination of clinical and biochemical data to provide more detailed and precise outcome predictions; combining these has been shown to have more predictive power for pregnancy outcomes than either clinical or biochemical markers alone.^{32,33}

While some variables did not differ between responders and non-responders, some maternal and neonatal characteristics differed. In particular, there was a higher rate of loss to follow-up in mothers with lower levels of education, low net income, and young age at delivery. This bias towards higher socio-economic status, especially in relation to maternal education status, has been observed for other birth cohorts.²³⁻²⁷ However, baseline data from the SNiP study can be used to reduce this bias in future analysis by calculating the inverse probability drop-out weights or by using statistical techniques to impute missing data.

6 | CONCLUSIONS

The SNiP cohort is now a longitudinal birth cohort and serves as a resource to understand the origins of perinatal poor outcomes by characterising the social, environmental, and genetic factors from the pregnancy period and to contribute to overall population health. The SNiP birth cohort encourages researchers to access the data and biospecimens and incorporate their own research questions (subject to review and approval). Current studies, based on data acquired during the SNiP-I and SNiP-I-Follow-up studies, focus on pregnancy and neonatal outcome after complications, such as gestational diabetes, low maternal pre-pregnancy BMI < 18.5 kg/m², and in cooperation with Sophia's Children's Hospital in Rotterdam, the Netherlands, the association of concentrations of tryptophan and kynurenine pathway metabolites with the risk of intrauterine growth restriction, pre-eclampsia, and subsequent neonatal diseases. Recruitment of a second birth cohort (SNiP-II, 2013-2017) in the same area was completed 10 years after SNiP-I. Follow-up of children in SNiP-II is currently in progress with a modified questionnaire at 2-5 years of age in two waves in 2018 and 2019.

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