Incidence of and risk factors for small vulnerable newborns in north India: a secondary analysis of a prospective pregnancy cohort

Ramachandran Thiruvengadam, Ayushi, Deepika Rathna Murugesan*, Bapu Koundinya Desiraju, Sumit Misra, Dharmendra Sharma, Suresh Somi Subbaian, Umesh Mehta, Alka Singh, Sunita Sharma, Ashok Khurana, Pratima Mittal, Harish Chellani, Rekha Bharti, Reva Tripathi, Shailaja Sopory, Pallavi Kshetrapal, Dinakar M Salunke, Uma Chandra Mouli Natchu, Siddarth Ramji, GARBH-Ini study team†, Nitya Wadhwa‡, Shinjini Bhatnagar‡*

Summary

Background Globally, recent estimates have shown there have been 3·6 million stillbirths and neonatal deaths in 2022, with nearly 60% occurring in low-income and middle-income countries. The Small Vulnerable Newborn Consortium has proposed a framework combining preterm birth (<37 weeks of gestation), small for gestational age (SGA) by INTERGROWTH-21st standard, and low birthweight (<2500 g) under the category small vulnerable newborns (SVN). Reliable data on SVN from sub-Saharan Africa, central Asia, and south Asia are sparse. We aimed to estimate the incidence of SVN and its types, and quantify risk factors, both overall and trimester-specific, from a pregnancy cohort in north India.

Methods In the GARBH-Ini (Interdisciplinary Group for Advanced Research on Birth Outcomes—DBT India Initiative) pregnancy cohort, 8000 participants were enrolled with less than 20 weeks' gestation between May 11, 2015, and Aug 8, 2020, at a secondary-care hospital in north India. The cohort was followed up across the antenatal period for a detailed study on preterm birth. We conducted a secondary analysis of cohort data for the outcome of SVN, classified into its types: preterm-SGA, preterm-nonSGA, and term-SGA. We estimated the relative risk and population attributable fraction of candidate risk factors for SVN (modified Poisson regression) and its types (multinomial regression).

Findings 7183 (89·9%) of 7990 participants completed the study. Among 6206 newborns included for analysis, the incidence of SVN was 48·4% (35·1% term-SGA newborns [n=2179], 9·7% preterm-nonSGA newborns [n=605], and 3·6% preterm-SGA newborns [n=222]). Compared with term-nonSGA newborns, proportions of stillbirths and neonatal deaths within 72 h of birth among SVN were three times and 2·5 times higher, respectively. Preterm-SGA newborns had the highest incidence of stillbirth (15 [6·8%] of 222) and neonatal deaths (six [4·2%] of 142). Low body-mass index (BMI <18·5 kg/m²) of participants at the start of pregnancy was associated with higher risk for preterm-SGA (adjusted relative risk [RR] 1·61 [95% CI 1·17–2·22]), preterm-nonSGA (1·35 [1·09–1·68]), and term-SGA (1·44 [1·27– 1·64]), with population attributable fraction ranging from 8·7% to 13·8%. Pre-eclampsia (adjusted RR 1·48 [95% CI 1·30–1·71]), short cervical length (1·15 [1·04–1·26]), and bacterial vaginosis (1·13 [0·88–1·45]) were other important antenatal risk factors.

Interpretation In a comprehensive analysis of SVN and its types from north India, we identified risk factors to guide prioritisation of interventions. Complemented with risk-stratification tools, this focused approach will enhance antenatal care, and accelerate achievement of Sustainable Development Goals—namely, to end preventable deaths of newborns and children younger than 5 years by 2030 (target 3·2).

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For the Hindi translation of the abstract see Online for appendix 1

*Contributed equally as second authors

†Members listed at the end of the Article

‡Contributed equally as last authors

Translational Health Science and Technology Institute, Faridabad, India (R Thiruvengadam PhD, Ayushi MSc, D R Murugesan MDS, B K Desiraju PhD, S Misra MBBS, D Sharma MCA, S S Subbaian MSc, S Sopory PhD, P Kshetrapal PhD, U C M Natchu MD, N Wadhwa MD, Prof S Bhatnagar PhD); **Pondicherry Institute of Medical Sciences, Puducherry, India** (R Thiruvengadam); **Gurugram Civil Hospital, Gurugram, India** (U Mehta MD, A Singh MD, S Sharma MD); **The Ultrasound Lab, Defence Colony, New Delhi, India** (A Khurana MD); **Amrita Institute of Medical Sciences & Research Centre, Faridabad, India** (P Mittal MS); **Vardhman Mahavir Medical College & Safdarjung Hospital, New Delhi, India** (P Mittal, H Chellani MD, R Bharti MD); **Society for Applied Studies, New Delhi, India** (H Chellani, U C M Natchu); **Sitaram Bhartia Institute of Science and Research, New Delhi, India** (R Tripathi MD); **Maulana Azad Medical College, New Delhi, India** (R Tripathi, S Ramji MD); **International Centre for Genetic Engineering and Biotechnology, New Delhi, India** (D M Salunke PhD)

Introduction

Globally, preventable stillbirths and newborn deaths remain alarmingly high. As per the most recent WHO report on maternal and newborn health, there were 4·5 million deaths in 2022, of which 1·9 million were stillbirths and 2·3 million were neonatal deaths.[1] The global progress in reducing perinatal deaths has plateaued over the past decade and the improvements observed between 2000 and 2010 have not been sustained, with more than 50 countries projected to fall short of meeting the targets of Sustainable Development Goals (SDGs), specifically SDG target 3.2, for neonatal and child mortality.[2] Sub-Saharan Africa, central Asia, and south Asia continue to have the highest numbers of these deaths. Within these regions there are ten countries, topped by India, which are responsible for 60% of global maternal, fetal, and newborn deaths.[1]

Correspondence to:
Prof Shinjini Bhatnagar,
Translational Health Science and Technology Institute,
Faridabad 121001, India
shinjini.bhatnagar@thsti.res.in

Research in context

Evidence before this study

Reports from WHO have highlighted the slow progress made in achieving the Sustainable Development Goal targets of reducing neonatal and infant mortality despite global commitments since 1990. This outcome is essentially because efforts towards primary prevention have focused either on neonates born too small or too soon or with low birthweight. This focus is largely due to the absence of an integrated approach to address all newborns with high risk of perinatal mortality. In a 2023 Series in *The Lancet*, a novel conceptual framework was suggested, combining preterm birth and infants born too small under the term small vulnerable newborns (SVN), with the aim to guide preventive strategies in a more comprehensive and standardised manner. We searched PubMed for studies published from database inception to Sept 16, 2023, with the search terms "small vulnerable newborn," or "preterm SGA" or "preterm AGA" or "term SGA" or "born too small or too soon" and "risk factors" [MeSH], or "determinants, epidemiologic" [MeSH], and identified 1401 articles. The estimated global prevalence of SVN for 195 countries and territories for the year 2020, using secondary data from 41 countries, was reported as 26·2% (1·1% preterm small for gestational age (SGA) newborns; 8·8% preterm-nonSGA newborns; and 16·3% term-SGA newborns). The results highlighted the substantial proportion of SVN in regions such as south Asia, necessitating urgent and targeted interventions. However, there was a clear knowledge gap in terms of well designed prospective studies on the rates of SVN and the crucial risk factors from low-income and middle-income settings.

Added value of this study

To the best of our knowledge, we have reported for the first time the prevalence estimates of SVN, its types, and their risk factors across pregnancy from a prospective cohort in north India. Almost every other newborn in our setting was an SVN. The proportion of preterm-SGA newborns in our population was 3·6%, which was much higher than the global estimates. Maternal undernutrition before and during pregnancy emerged as a prominent risk factor of SVN, with a population attributable fraction of 30%. Pre-eclampsia, short cervical length, and bacterial vaginosis were associated with higher risk of SVN.

Implications of all the available evidence

The critical overall and trimester-specific risk factors for SVN and its types will guide prioritisation of interventions. A focused approach targeted to pregnant individuals at risk will enhance care for the most vulnerable newborns and accelerate efforts towards reduction of neonatal and infant mortality.

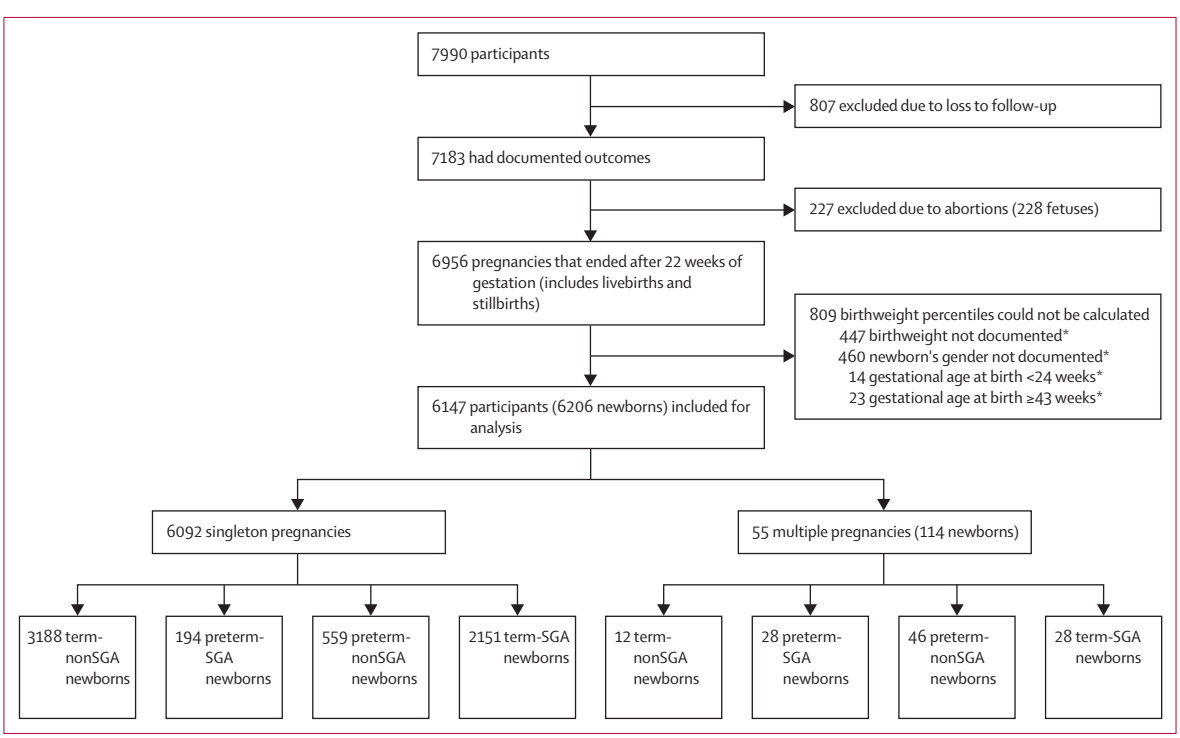

Figure 1: **Study profile**
*Each of the 809 newborns satisfied one or more criteria.

Infants born preterm, small for gestational age (SGA), or with low birthweight have a significantly higher risk of perinatal and child mortality.[3] These newborns are also at a higher risk of short-term and long-term morbidities, impacting their development and also their families.[3] Although there have been promising interventions to

	Study population
Maternal age, years	23·7 (3·9)
Gestational age at enrolment, weeks + days	12 + 4 (3 + 6)
Education status*	
Illiterate	1602 (20·1%)
Primary school	687 (8·6%)
Middle school or high school	2666 (33·4%)
College or higher	3035 (38·0%)
Occupation†	
Unemployed	7336 (91·8%)
Unskilled work	428 (5·4%)
Skilled work	202 (2·5%)
Professional	23 (0·3%)
Ever consumed alcohol‡§	6 (0·1%)
Smoking	
Ever smoked§¶	8 (0·1%)
Second-hand exposure to tobacco smoke§‖	1504 (18·8%)
Smokeless tobacco§¶	54 (0·7%)
Religion	
Hindu	7315 (91·6%)
Muslim	573 (7·2%)
Sikh	27 (0·3%)
Christian	64 (0·8%)
Other	11 (0·1%)
Nuclear family**	4442 (55·6%)
Overcrowding††‡‡	5122 (64·1%)
Monthly family income (USD)§§¶¶	220·5 (148·0–338·1)
Proportion below poverty line§§‖‖	183 (2·3%)
Residing in unengineered house***	682 (8·5%)
Biomass fuel use for cooking†††	623 (7·8%)
Access to safe drinking water†‡‡‡	7809 (97·7%)
Access to safe toilet (flush, pour flush toilet, dry toilet)§§§	7812 (98·3%)

(Table 1 continues in next column)

(Continued from previous column)

	Study population
Nulliparous	4042 (50·6%)
History before preterm birth¶¶¶	414 (10·8%)
History of ≥2 abortions‖‖‖	562 (11·5%)
Interpregnancy interval <18 months****	746 (32·4%)
Body-mass index at enrolment (categorised per WHO 2000), kg/m²††††	
Underweight (<18·5)	2150 (27·0%)
Normal (18·5–24·9)	4881 (61·1%)
Overweight (25–29·9)	819 (10·3%)
Obese (≥30)	133 (1·7%)

Data are mean (SD), n (%), and median (IQR). *As per modified Kuppuswamy scale. †Of 7989 included participants with data available. ‡Of 7968 included participants with data available. §As reported by participant. ¶Of 7982 included participants with data available. ‖Of 7981 included participants with data available. **Family unit comprising participant, their spouse, and dependent children. ††Of 7986 included participants with data available. ‡‡Overcrowding has been ascertained based on family size and number of rooms in the house according to Park's criteria. A participant's home was considered overcrowded if the number of people within the household exceeds two, three, five, seven, or ten for a house with one, two, three, four, or five rooms, respectively. For homes with more than five rooms, the overcrowding threshold was calculated as (5+X)×2, where X represents the number of rooms beyond five. §§Of 7974 included participants with data available. ¶¶The average conversion rate for the study period (2015–20) was 1 USD=68·03 INR. ‖‖Poverty line was adapted from the report from New Delhi Planning commission, 2014, as monthly per capita income below 1407 INR (USD 20·6). ***The walls or roof of which are made of material such as un-burnt bricks, bamboos, mud, grass, reeds, thatch, or loosely packed stones. †††Biomass fuel use refers to use of non-petroleum gas fuel sources for cooking. ‡‡‡Piped water, public tap, tube well, or borehole; or hand pump, closed well, tanker truck, or bottled water as considered safe sources of drinking water. §§§Of 7950 included participants with data available. ¶¶¶Of 3832 included participants as this item was estimated only in participants with parity ≥1; 116 participants answered "don't know". ‖‖‖Of 4873 included participants as this item was estimated only in participants with multigravida. ****Of 2304 included participants as this item was estimated only in multiparous participants. ††††Of 7983 included participants with data available.

Table 1: **Descriptive characteristics of the GARBH-Ini cohort (n=7990)**

prevent SGA and preterm birth, delivery of such interventions has been challenging for health-care practitioners.[3] A 2023 collaborative effort by the Small Vulnerable Newborn Consortium has proposed a new framework bringing together preterm birth, SGA, and low birthweight under the term small vulnerable newborn (SVN).[3,4] This framework, for the first time, estimates the global prevalence of SVN and encourages the identification of determinants of SVN and accelerated implementation of interventions to prevent them.[3,5] Most of the data for these estimates are from national health information systems, such as hospital information management systems, civil registration, and medical birth registries, which have limitations on the accurate classification of these groups. There is paucity of data on the prevalence of and risk factors for SVN from low-income and middle-income countries (LMICs);[6] it is imperative to have more primary data emerging from these countries. In this secondary analysis of a cohort study, we aimed to estimate the incidence of SVN and its types, and quantify risk factors, both overall and trimester specific, from a pregnancy cohort in north India.

Methods

Study design and participants

The GARBH-Ini (Interdisciplinary Group for Advanced Research on Birth Outcomes—DBT India Initiative) programme is a prospective cohort study of pregnant individuals attending the antenatal clinic of a secondary-care hospital in north India.[7] The study was initiated with the hypothesis that time-series data collected on multidimensional characteristics—including clinical, imaging, environmental, genomic, epigenomic, meta-genomic, and proteomic data—during pregnancy will identify individuals at high risk of delivering preterm (<37 completed weeks of gestation). We enrolled 8000 pregnant individuals with less than 20 weeks' gestation based on ultrasound between May 11, 2015, and Aug 8, 2020, with longitudinal assessments of clinical, imaging, and biological parameters throughout the antenatal period and up to 6 months after delivery. The

enrolled participants were scheduled for three or four follow-up antenatal visits (during weeks 11–14, weeks 18–20, weeks 26–28, and weeks 30–32) at the secondary-level care hospital depending on the gestational age at enrolment; an additional visit was scheduled between 6 weeks and 6 months after delivery. Further details are provided elsewhere.[7] In our cohort, ultrasound-based dating (crown rump length in first trimester and fetal biometry in second trimester) was done by sonologists according to standardised procedures (GE Voluson E8 Expert; General Electric Healthcare, Chicago, IL, USA) at enrolment. Full details of the cohort methods have been reported in the GARBH-Ini cohort study design.[7]

Institutional ethics committees of all the collaborating institutions (Translational Health Science and Technology Institute, Faridabad; Gurugram Civil Hospital, Haryana; and Vardhman Mahavir Medical College & Safdarjung Hospital, New Delhi) approved the GARBH-Ini programme. Written informed consent was obtained from an eligible female individual after they had read and understood the participant information sheet. If an eligible participant was illiterate, the study was explained in the presence of a literate impartial witness. A thumb impression was taken from the participant after ensuring that they had understood and stated their consent verbally; a literate impartial witness signed the consent form.

See Online for appendix 2

	Number of exposed participants with outcomes/number of exposed	Adjusted relative risk (95% CI)*	p value	Population attributable fraction (95% CI)
Baseline				
Education of participant†				
Illiterate	608/1164	Reference	..	..
College	1061/2371	0·89 (0·82–0·96)	0·0018	NA
School	1235/2557	0·94 (0·87–1·00)	0·058	NA
Occupation of participant†				
Unemployed	2691/5590	Reference	..	..
Professional	2/17	0·24 (0·06–0·93)	0·04	NA
Skilled work	63/154	0·87 (0·72–1·06)	0·16	NA
Unskilled work	148/331	0·92 (0·81–1·04)	0·19	NA
Education of head of family†				
Illiterate	589/1139	Reference	..	..
College	900/2032	0·85 (0·79–0·92)	<0·0001	NA
School	1415/2921	0·94 (0·88–1·00)	0·058	NA
Occupation of head of family†	410/817	Reference	..	..
Unemployed	..	..	..	..
Professional	19/44	0·96 (0·67–1·36)	0·80	NA
Skilled	584/1265	0·98 (0·89–1·08)	0·66	NA
Unskilled	1891/3966	0·98 (0·91–1·06)	0·63	NA
Type of house				
Residing in engineered house	2644/5572	Reference	..	..
Residing in unengineered house‡	260/520	1·03 (0·94–1·13)	0·27	NA
Cooking fuel				
Petroleum gas fuel	2655/5629	Reference	..	..
Biomass fuel use for cooking§	249/463	1·15 (1·05–1·26)	0·0024	1·12 (0·98–1·26)
Smoke exposure status				
No exposure to passive smoke	2359/4958	Reference	..	..
Exposure to passive smoke¶	543/1129	1·01 (0·94–1·08)	0·85	NA
Maternal height, cm				
≥145 cm	2607/5609	Reference	..	..
<145 cm	295/481	1·32 (1·22–1·42)	<0·0001	2·46 (2·21–2·71)

(Table 2 continues on next page)

Procedures and outcome

In the secondary analysis reported here, we considered all female participants enrolled in the GARBH-Ini cohort. We excluded participants who had abortions or medical termination of the current pregnancy and who were lost to follow-up. Our primary outcome was SVN, described as any neonate born too soon (preterm birth) or too small (SGA). Preterm birth was defined as any birth before 37 completed weeks of gestation, and SGA was defined as birthweight for gestational age and sex below the 10th percentile according to INTERGROWTH-21st standards.[3,8] SVN was classified into three types: preterm-SGA, preterm-nonSGA, and term-SGA.

We documented candidate risk factors at baseline, such as socioeconomic status, body-mass index (BMI) measured up to 20 weeks of gestation, and obstetric details from the past (eg, history of abortions and previous preterm birth) and during the antenatal period (eg, vaginal bleeding and bacterial vaginosis). Antenatal factors, such as anthropometry (weight and height), physiological parameters (eg, cervical length and blood pressure), and medical conditions during pregnancy (eg, infections and pathological events) were documented. Full details and definitions of risk factors are provided in appendix 2 (pp 1–2).

Statistical analysis

The sample size for the GARBH-Ini cohort study was originally estimated to identify risk factors for preterm birth.[7] To demonstrate an effect size with a relative risk of at least 2·1 between two groups (exposed or unexposed to a risk factor) in the cohort, with 80% power and 5% significance level, we estimated that data on 400 participants were required in each group. In a cohort design, some exposures might occur in as few as 5% of participants, necessitating enrolment of 8000 pregnant participants. For the current analysis of SVN and its risk factors, we considered the entire cohort for analysis (N=8000).[7] We expected adequate statistical power to identify risk factors of SVN at an incidence of 40–50%.

We described baseline characteristics of the cohort using median (IQR) or mean (SD) for quantitative variables and frequencies, with percentages for categorical variables. The incidence of SVN and its types were estimated for all cohort participants and expressed

as percentages. We estimated the proportion of stillbirth and mortality within 72 h of birth for SVN and its types. Candidate risk factors were assessed for two distinct analyses. The first analysis identified risk factors that occurred at any time during the antenatal period, whereas the second specifically evaluated them based on their occurrence in individual trimesters. We evaluated risk factors of SVN among singleton pregnancies and excluded a priori those that were multiple (≥2; eg, twins or triplets) as numbers were very small. Simple regression analysis for SVN among singleton pregnancies was performed on all candidate risk factors documented in the GARBH-Ini cohort, with term-nonSGA newborns used as reference. Risk factors associated with SVN with an a priori decided p value of 0·2 or less were considered for multivariable analysis to estimate the effect sizes adjusted for confounding. For each exposure, directed acyclic graphs were constructed to show the inter-relationships between each candidate risk factor, covariates, and SVN outcome (appendix 2 pp 3–6); this guided the selection of minimal sufficient adjustment sets for estimating the total effect of each candidate risk factor on the outcome (appendix 2 pp 1–6). A separate multivariable model was constructed for each exposure of interest. Adjusted effect estimates were reported with their 95% CIs. Three modelling strategies were used. First, to derive the adjusted effect estimates of the association between an exposure and SVN outcome, we used modified Poisson regression models with robust error variance adjusting for the identified confounders.[9] To evaluate the proportion of SVN in our study population that can be attributed to a specific risk factor, we calculated the population attributable fraction.[8] Population attributable fraction was defined as the fraction of all cases of SVN in our population that was attributable to a specific risk factor, assuming a causal and independent relationship between the two, and was calculated using the formula

$$\text{Population attributable fraction (\%)} = P_c\left(1-\left[\frac{1}{\text{adjusted relative risk}}\right]\right)\times 100$$

where P_c represents prevalence of exposure among cases.[10] Second, to estimate the unadjusted and adjusted effect estimates for each type of SVN, we applied multinomial regression analyses to identify risk factors for types of SVN, considering term-nonSGA newborns as the reference class using the radiant model package in R. Finally, we evaluated the non-linear relationship between continuous exposures (early pregnancy BMI and gestational weight gain) and outcomes using restricted cubic splines implemented with the rms package in R and visualised the predicted probability of SVN and its types, as determined through logistic and multinomial regression models.[11]

To evaluate interaction between risk factors, we estimated relative excess risk due to interaction using the formula

	Number of exposed participants with outcomes/number of exposed	Adjusted relative risk (95% CI)*	p value	Population attributable fraction (95% CI)
(Continued from previous page)				
BMI (categorised by WHO 2000)				
Normal (18·5 to 24·9 kg/m²)	1732/3737	Reference	..	..
Overweight or obese (≥25 kg/m²)	283/765	0·82 (0·74–0·91)	<0·0001	NA
Underweight (≤18·5 kg/m²)	887/1588	1·19 (1·13–1·26)	<0·0001	5·41 (5·14–5·68)
Pregnancy type				
Parity ≥3	112/233	1·06 (0·92–1·22)	0·45	NA
Parity 1–2	1237/2773	Reference	..	..
Nulliparous	1555/3086	1·13 (1·07–1·20)	<0·0001	NA
Interpregnancy interval status				
Normal (≥18 months)	543/1211	Reference	..	..
Short (<18 months)‖	270/550	1·09 (0·98–1·21)	0·13	NA
Abortion history among the individuals with multigravida				
<2 abortions	1494/3262	Reference	..	..
Repeated abortions	193/430	1·01 (0·90–1·12)	0·89	NA
Caesarean section				
No history of caesarean section	1057/2391	Reference	..	..
Previous caesarean section¶	292/614	1·09 (0·99–1·2)	0·060	NA
Previous term birth among the multiparous who could recall the event				
Yes	1187/2694	Reference	..	..
No	167/314	1·23 (1·10–1·38)	0·0003	NA
Antenatal (anytime during pregnancy)				
Gestational weight gain				
Adequate	289/828	Reference	..	..
Inadequate (IOM 2009)**	1310/2552	1·49 (1·34–1·64)	<0·0001	26·94 (26·31–27·58)
Weight-gain-for-gestational-age††				
≥10th percentile	1414/3057	Reference	..	..
<10th percentile	185/323	1·24 (1·12–1·38)	<0·0001	2·24 (1·97–2·57)
Anaemia status‡‡				
No anaemia	25/73	Reference	..	..
Anaemia	2856/5974	1·38 (1·01–1·90)	0·046	27·3 (27·20–27·38)
Pre-eclampsia status§§				
No pre-eclampsia	1022/2203	Reference	..	..
Pre-eclampsia	79/132	1·48 (1·30–1·71)	<0·0001	2·33 (1·84–2·84)
Placental position (as diagnosed by sonologist)				
Normal	2415/5073	Reference	..	..
Low lying	16/30	1·12 (0·8–1·57)	0·51	NA
Change in mean uterine artery pulsatility index¶¶				
Adequate	1534/3259	Reference	..	..
Inadequate	273/520	1·05 (0·92–1·19)	0·51	NA
Cervical length according to radiologist				
Normal (≥2·5 cm)	2606/5539	Reference	..	..
Short (<2·5 cm)	210/384	1·15 (1·04–1·26)	0·0049	0·97 (0·85–1·10)
Bacterial vaginosis status‖‖				
No bacterial vaginosis	969/2107	Reference	..	..
Bacterial vaginosis	223/484	1·13 (0·88–1·45)	0·35	NA

(Table 2 continues on next page)

	Number of exposed participants with outcomes/number of exposed	Adjusted relative risk (95% CI)*	p value	Population attributable fraction (95% CI)
(Continued from previous page)				
Vaginal bleeding status				
No vaginal bleeding	2646/5632	Reference	..	..
Vaginal bleeding¶	258/460	1·16 (0·93–1·43)	0·18	NA
Vaginal discharge status				
No vaginal discharge	1998/4156	Reference	..	..
Vaginal discharge¶	906/1936	0·92 (0·8–1·06)	0·28	NA
Exanthematous fever status				
No exanthematous fever	2819/5912	Reference	..	..
Exanthematous fever (rash with fever)	85/180	0·99 (0·85–1·16)	0·89	NA
Respiratory tract infection status				
No respiratory tract infection	2676/5597	Reference	..	..
Respiratory tract infection (cough with fever lasting >2 days)	228/495	0·96 (0·87–1·06)	0·46	NA
Urinary tract infection status				
No urinary tract infection	1920/4096	Reference	..	..
Urinary tract infection (burning micturition with change in frequency of urination lasting >2 days)	981/1989	1·05 (0·99–1·11)	0·075	NA
Jaundice status				
No jaundice	2865/6033	Reference	..	..
Jaundice	39/59	1·38 (1·14–1·68)	0·0008	0·37 (0·26–0·50)
First trimester				
Vaginal bleeding status				
No vaginal bleeding	2781/5864	Reference	..	..
Vaginal bleeding¶	74/139	1·09 (0·71–1·67)	0·69	NA
Vaginal discharge status				
No vaginal discharge	2218/4647	Reference	..	..
Vaginal discharge¶	370/807	0·9 (0·73–1·11)	0·34	NA
Exanthematous fever status				
No exanthematous fever	2881/6045	Reference	..	..
Exanthematous fever (rash with fever)	14/27	1·09 (0·76–1·57)	0·65	NA
Respiratory tract infection status				
No respiratory tract infection	2807/5896	Reference	..	..
Respiratory tract infection (cough with fever lasting >2 days)	55/111	1·04 (0·86–1·26)	0·68	NA
Urinary tract infection status				
No urinary tract infection	2506/5283	Reference	..	..
Urinary tract infection (burning micturition with change in frequency of urination lasting >2 days)	196/426	0·97 (0·87–1·08)	0·56	NA
Second trimester				
Cervical length according to radiologist				
Normal (≥2·5 cm)	2395/5005	Reference	..	..
Short (<2·5 cm)	50/81	1·32 (1·1–1·58)	0·0031	0·5 (0·35–0·64)

(Table 2 continues on next page)

$$\text{Relative excess risk due to interaction} = RR_{11} - RR_{10} - RR_{01} + 1$$

where RR_{11} represents relative risk when both risk factors are present, and RR_{10} and RR_{01} when only first and second risk factors are present, respectively.[12] Absolute excess risk due to interaction was calculated using the formula

$$\text{Absolute excess risk due to interaction} = R_{11} - R_{10} - R_{01} + R_{00}$$

where R_{11} represents absolute risk when both risk factors are present; R_{10} with only the first; R_{01} with only the second; and R_{00} with neither (appendix 2 pp 25–26).

We evaluated potential bias in the effect estimates. Early pregnancy BMI was assessed at enrolment (up to 20 weeks of gestation). To evaluate a possible bias of BMI's dependence on gestational age at enrolment, we estimated the association between underweight BMI (<18·5 kg/m²) and SVN in participants of two strata (<14 weeks of gestation and 14–20 weeks of gestation; appendix 2 p 8).[13] Inadequate gestational weight gain was defined based on the Institute of Medicine 2009 (IOM 2009) definition.[14] This definition considers total gestational weight gain irrespective of gestational duration. Therefore, participants who delivered preterm would have lower gestational weight gain due to shorter gestation. To overcome this bias, we redefined inadequate gestational weight gain as those participants who gained weight less than the 10th percentile for the gestational duration (appendix 2 p 11). Participants who had missing delivery outcomes were excluded from the analyses. All statistical analyses were performed using R (version 4.2.0).

Role of the funding source

The funders of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report.

Results

Among 8000 participants enrolled between May 11, 2015, and Aug 8, 2020, data from 7990 were used for this analysis (ten participants withdrew consent). 7183 (89·9%) of 7990 enrolled participants completed the study. After exclusions such as loss to follow-up, abortions, and missing data, 6147 participants (6206 newborns) were considered for analysis (figure 1). Mean age of the cohort participants was 23·7 years (SD 3·9) and the mean gestational age at enrolment was 12 weeks and 4 days (SD 3 weeks and 6 days; median 12 weeks and 5 days [IQR 9 weeks and 1 day to 15 weeks and 6 days). 2150 (27·0%) of 7983 participants had a BMI less than 18·5 (underweight) at enrolment, and 4042 (50·6%) were nulliparous. The median monthly family income was USD 220·5 (IQR 148·0–338·1). Among those enrolled, 623 (7·8%) participants used biomass fuel for cooking in their households and 1504 (18·8%) had second-hand

exposure to tobacco smoke (table 1). The characteristics of participants who were excluded from the analysis due to reasons such as loss to follow-up were similar to those included (appendix 2 p 7).

The incidence of SVN in this cohort was 48·4% (3006 of 6206 participants; almost twice as high among multiple births compared with singletons). Incidence of SVN types was 35·1% among term-SGA (n=2179; 2151 singleton and 28 twins), 9·7% among preterm-nonSGA (n=605; 559 singletons and 46 twins), and 3·6% among preterm-SGA (n=222; 194 singleton and 28 twins).

The proportion of perinatal deaths among SVN was higher compared with term-nonSGA newborns; nearly a three times higher proportion of stillbirth and 2·5 times higher proportion of neonatal death within 72 h of birth was observed among SVN compared with term-nonSGA newborns. Among the SVN types, preterm-SGA newborns had the highest incidence of stillbirth (6·8%) and neonatal death (4·2%) within 72 h of birth (appendix 2 p 9). Among term-SGA newborns, stillbirth proportions were 0·4% (six of 1451) and 0·5% (five of 1070) among those with a birthweight less than 5th percentile and less than 3rd percentile, respectively. Median gestational age among the preterm-SGA and preterm-nonSGA newborns was 35·71 weeks (IQR 34·75–36·43) and 35·57 weeks (34·14–36·43), respectively. Among other characteristics, SVN had a lower median birthweight (2486 [IQR 2179–2618] g) than did term-nonSGA newborns (3019 [2867–3300] g).

Table 2 depicts the risk factors for singleton SVN (n=6092). Maternal preconception and antenatal nutrition emerged as a prominent risk factor for SVN. Female participants who were underweight (BMI <18·5 kg/m²) at the start of pregnancy were at higher risk (adjusted relative risk 1·19 [95% CI 1·13–1·26]) of SVN compared with those with normal BMI (18·5-24·9 kg/m²), with a population attributable fraction of 5·41% (95% CI 5·14–5·68). The adjusted relative risk estimate of underweight BMI on SVN was nearly 30% higher among female participants enrolled between 14 and 20 weeks of gestation compared with those enrolled at less than 14 weeks (appendix 2 pp 10–11). Risk of SVN decreased with an increase in early pregnancy BMI, more precisely in the range of 15–45 (figure 2A). When evaluated against individual types of SVN, an increase in BMI decreased the risk of term-SGA (protective effect). However, increased BMI, particularly in the range of above 25, increased the risk of preterm-nonSGA (figure 2A). Maternal short stature (<145 cm) was associated with a significantly increased risk for SVN (adjusted relative risk 1·32 [95% CI 1·22–1·42]). In the range of 5–15 kg, an increase in gestational weight gain was associated with decreased risk of SVN and its types (figure 2B; appendix 2 p 9). Participants with inadequate gestational weight gain (IOM 2009) had an increased risk of SVN (adjusted relative risk 1·49 [95% CI 1·34–1·64]) compared with those with adequate weight gain.

	Number of exposed participants with outcomes/number of exposed	Adjusted relative risk (95% CI)*	p value	Population attributable fraction (95% CI)
(Continued from previous page)				
Bacterial vaginosis status‖‖				
No bacterial vaginosis	874/1893	Reference	..	..
Bacterial vaginosis	188/419	1·11 (0·84–1·47)	0·45	NA
Vaginal bleeding status				
No vaginal bleeding	2796/5887	Reference	..	..
Vaginal bleeding¶	86/161	1·03 (0·79–1·35)	0·82	NA
Vaginal discharge status				
No vaginal discharge	2400/5030	Reference	..	..
Vaginal discharge¶	469/999	1 (0·89–1·12)	0·99	NA
Gastroenteritis status				
No gastroenteritis	2766/5842	Reference	..	..
Gastroenteritis (diarrhoea lasting >2 days)	105/190	1·16 (1·02–1·33)	0·022	0·5 (0·41–0·60)
Urinary tract infection status				
No urinary tract infection	1740/3764	Reference	..	..
Urinary tract infection (burning micturition with change in frequency of urination lasting >2 days)	670/1296	1·12 (1·05–1·19)	0·0005	2·98 (2·78–3·16)
Jaundice status				
No jaundice	2873/6047	Reference	..	..
Jaundice	23/32	1·5 (1·21–1·86)	0·0002	0·26 (0·16–0·39)
Third trimester				
Anaemia status‡‡				
No anaemia	115/282	Reference	..	..
Mild anaemia	1092/2308	1·15 (0·99–1·34)	0·058	NA
Moderate anaemia	487/1046	1·14 (0·97–1·33)	0·11	NA
Severe anaemia	9/15	1·46 (0·95–2·24)	0·09	NA
Cervical length according to radiologist				
Normal (≥2·5 cm)	1846/3993	Reference	..	..
Short (<2·5 cm)	99/169	1·22 (1·06–1·41)	0·0068	0·92 (0·75–1·09)
Retroplacental blood collection status				
No retroplacental blood collection	1919/4096	Reference	..	..
Retroplacental blood collection	32/87	0·82 (0·62–1·09)	0·17	NA
Vaginal bleeding status				
No vaginal bleeding	2775/5876	Reference	..	..
Vaginal bleeding ¶	111/184	1·13 (0·92–1·39)	0·23	NA
Vaginal discharge status				
No vaginal discharge	2689/5653	Reference	..	..
Vaginal discharge¶	203/424	1·03 (0·88–1·20)	0·73	NA
Exanthematous fever status				
No exanthematous fever	2859/6006	Reference	..	..
Exanthematous fever (rash with fever)	33/71	0·97 (0·76–1·25)	0·83	NA
Respiratory tract infection status				
No respiratory tract infection	1946/4105	Reference	..	..
Respiratory tract infection (cough with fever lasting >2 days)	65/142	0·97 (0·81–1·16)	0·71	NA

(Table 2 continues on next page)

	Number of exposed participants with outcomes/number of exposed	Adjusted relative risk (95% CI)*	p value	Population attributable fraction (95% CI)
(Continued from previous page)				
Jaundice status				
No jaundice	2878/6055	Reference	..	..
Jaundice	14/22	1·52 (1·16–2·00)	0·0026	0·17 (0·08–0·26)

Reference: term-nonSGA. Relative risk quantifies the magnitude of an association between exposure and outcome, indicating how much more (relative risk >1) or less (relative risk <1) probable the outcome is in the exposed group versus the unexposed group. NA for population attributable fraction if the factor is not statistically significant or protective or non-modifiable. Baseline factors such as nuclear family, overcrowding, unsafe source of drinking water, unsafe toilet, alcohol consumption, chewing tobacco, underage (age <18 years), and overage (age >35 years); antenatal factors such as low-lying placenta, retroplacental blood collection, and gastroenteritis assessed anytime during pregnancy; first trimester anaemia (mild, moderate, or severe), short cervical length, bacterial vaginosis, gastroenteritis, and jaundice; second trimester anaemia (mild, moderate, or severe), retroplacental blood collection, exanthematous fever, and respiratory tract infection; and third trimester gastroenteritis and urinary tract infection were excluded from adjusted analysis as the p value from the simple regression analysis was more than 0·2.
The estimates of the unadjusted analysis and the covariates adjusted are detailed in appendix 2 (pp 12–15). NA=not applicable. SGA=small for gestational age. SVN=small vulnerable newborns. *Adjusted for covariates in appendix 2 (pp 1–2). †As per modified Kuppuswamy scale. ‡The walls or roof of which are made of material such as un-burnt bricks, bamboos, mud, grass, reeds, thatch, or loosely packed stones. §Biomass fuel use refers to use of non-petroleum gas fuel sources for cooking. ¶As reported by participant. ||Among the individuals with multigravida excluding those whose previous outcome was abortion. **Gestational weight gain (weight gained between enrolment and just before the birth of the neonate) below the IOM 2009 criteria. ††Detailed definition in appendix 2 (pp 10–11). ‡‡Classified as per WHO criteria for anaemia during pregnancy as mild (haemoglobin <11 g/dL and ≥9 g/dL), moderate (haemoglobin <9 g/dL and ≥7 g/dL), or severe (haemoglobin <7 g/dL) based on the lowest haemoglobin measurement in each trimester. §§Female participants with hypertension at least two time points (≥140 mm systolic or ≥90 mm diastolic during pregnancy) and proteinuria (dipstick test ≥1) at the same visit as high blood pressure, or female participants with ≥160 mm systolic blood pressure or ≥110 mm diastolic blood pressure on one occasion and proteinuria (dipstick test ≥1) at different visit as blood pressure. ¶¶If difference between index visit and previous visit was zero or positive it was considered adequate. ||||Bacterial vaginosis diagnosed by microbiologist from the high vaginal swab collected by a qualified gynaecologist during the antenatal visits.

Table 2: **Risk factors for SVN in female participants with singleton pregnancy (n=6092)**

Participants whose weight gain for gestational age was less than 10th percentile had an increased risk of SVN (adjusted relative risk 1·24 [95% CI 1·12–1·38]). Additionally, use of biomass fuel, short cervical length, maternal jaundice, and pre-eclampsia at any timepoint in pregnancy was associated with an increased risk of SVN (table 2). 7195 (95·1%) of 7566 female participants had anaemia 49·7% mild, 44·9% moderate, and 0·4% severe) at the outset of pregnancy. Anaemia diagnosed anytime during pregnancy was associated with an increased risk of SVN (adjusted relative risk 1·38 [95% CI 1·01–1·90]), with a population attributable fraction of 27·3% (95% CI 27·20–27·38).

As SVN were not a homogenous group, a separate analysis of risk factors for its types was done (table 3). Underweight BMI was associated with higher risk for all three types of SVN with the population attributable fraction ranging from 8·67 (95% CI 7·58–9·74) for preterm-nonSGA newborns to as high as 13·84 (95% CI 11·12–16·47; table 3) for preterm-SGA newborns. Urinary tract infection in the second trimester of pregnancy was a significant risk factor associated with all three types of SVN, with the strongest association with preterm-SGA newborns (population attributable fraction 13·49 [95% CI 10·45–16·23]). The risk of specific types of SVN, particularly term-SGA, was high in participants with anaemia. Short interpregnancy interval (<18 months) posed a significant risk (adjusted relative risk 1·59 [95%CI 1·14–2·21]) for preterm-nonSGA. As expected, preterm-SGA emerged as the SVN type with the strongest associations for certain unique risk factors: bacterial vaginosis (adjusted relative risk 4·54 [95% CI 1·30–15·93]) and pre-eclampsia (6·92 [3·45–13·86]) attributed to 11·27% (5·63–17·52) and 14·63% (7·55–22·22) of preterm-SGA newborns, respectively. Short cervical length both in the second trimester (adjusted relative risk 6·03 [95% CI 2·63–13·85]) and the third trimester (3·09 [1·53–6·23]), and vaginal bleeding in the third trimester (3·41 [1·54–7·55]) emerged as significant trimester-specific risk factors of preterm-SGA. The unadjusted and adjusted estimates of all risk factors evaluated are provided in appendix 2 (pp 12–14). Risk factors of SVN showed synergistic interactions that were not statistically significant. Specifically, excess risk due to two exposures—namely, poverty and indoor air pollution—occurring together was 8 percentage points absolute excess risk due to interaction 0·08 [95% CI –0·08 to 0·26]) greater than the sum of individual risks with each exposure acting alone (appendix 2 p 26).

Discussion

A high incidence of SVN (48·4%) was observed in the GARBH-Ini cohort enrolled from a secondary-level care setting in north India. The most prevalent type was term-SGA (35·1%), followed by preterm-nonSGA and preterm-SGA. Preterm-SGA newborns had the worst outcomes, with 11 times and seven times higher risk of stillbirth and neonatal death within 72 h of birth, respectively, compared with term-nonSGA newborns (nonSVN). Maternal underweight BMI and inadequate gestational weight gain were important risk factors for all types of SVN. In addition to the trimester-specific risk factors for SVN, some risk factors were unique for each type (eg, bacterial vaginosis particularly increases risk for preterm-SGA, anaemia for term-SGA, and jaundice for preterm-nonSGA).

The incidence of SVN in the present study is high and similar to modelled estimates reported from south Asia.[3,15] The high incidence of preterm-SGA documented in the GARBH-Ini cohort is worrisome as it has the highest associated proportion of mortality in the first 72 h of the neonatal period. The proportion of stillbirth among preterm-SGA newborns in our study was high (6·8%), although this finding was lower than the global modelled estimate of 11·3%.[3,16] This high incidence of SVN and its types is possibly attributed to biological and socio-demographic risk factors. We believe the high SVN incidence is a matter of concern and must be highlighted in north India. This documentation will enable tracking of SVN burden in the future as we implement preventive interventions.

The most prominent risk factors for SVN in our cohort are related to maternal nutrition, such as low early

pregnancy BMI and inadequate gestational weight gain. Interestingly, BMI has a contrasting relationship with the types preterm-nonSGA and term-SGA newborns. With increasing BMI, risk of term-SGA decreases whereas that of preterm-nonSGA increases. This finding emphasises that SVN is biologically heterogeneous; nutritional interventions to reduce SVN should be cautiously designed and go beyond just dietary supplementation. A well designed package of health, nutrition, psychosocial care, and water and sanitation and hygiene interventions delivered during preconception and pregnancy has shown to improve maternal outcomes and reduce the risk of low birthweight.[17] Delivery of such interventions must be scaled up in LMICs. We used the IOM 2009 recommendations to classify participants as having inadequate gestational weight gain because there is an absence of global recommendations with representation from LMICs. The alternative was to use population-specific gestational weight gain percentiles as derived in our cohort. This absence of globally relevant recommendations for optimal gestational weight gain is a major knowledge gap. The recent effort from WHO to consolidate such data to inform guidelines for monitoring gestational weight gain globally ensuring wider representation is encouraging.[18,19] Since anaemia is an important marker for maternal nutrition,[20] we evaluated its association with SVN in our cohort. The high prevalence of anaemia and its association with SVN despite the implementation of an iron-folic acid supplementation programme is of concern and needs urgent attention.

As preterm-SGA is the most severe type of SVN, interventions need to be prioritised. The modifiable risk factors with large population attributable fraction for this SVN type are pre-eclampsia, short cervical length starting from the second trimester, and bacterial vaginosis. Preventing these conditions will be an effective strategy to reduce the risk of stillbirth and neonatal mortality. Although SVN are susceptible to adverse clinical outcomes, some risk factors are specific for either preterm birth or SGA. For example, cervical length, bacterial vaginosis, and vaginal bleeding are risk factors that are associated with the preterm birth types of SVN. Interventions targeted against these factors will reduce the incidence of the specific types. Individuals at risk of pre-eclampsia have shown nearly 25% reduction in births before 34 weeks of gestation when started on low-dose aspirin before 14 weeks of gestation.[21,22] A sustainable screening programme for pre-eclampsia in LMICs is an emergent need. Given the significant benefits of vaginal progesterone in prevention of preterm birth in individuals with short cervical length, early detection is crucial.[23] The strong association of bacterial vaginosis with preterm-SGA newborns suggests that vaginal dysbiosis could be a mechanistic pathway. Vaginal microbiome evaluation in the GARBH-Ini cohort has demonstrated variations in

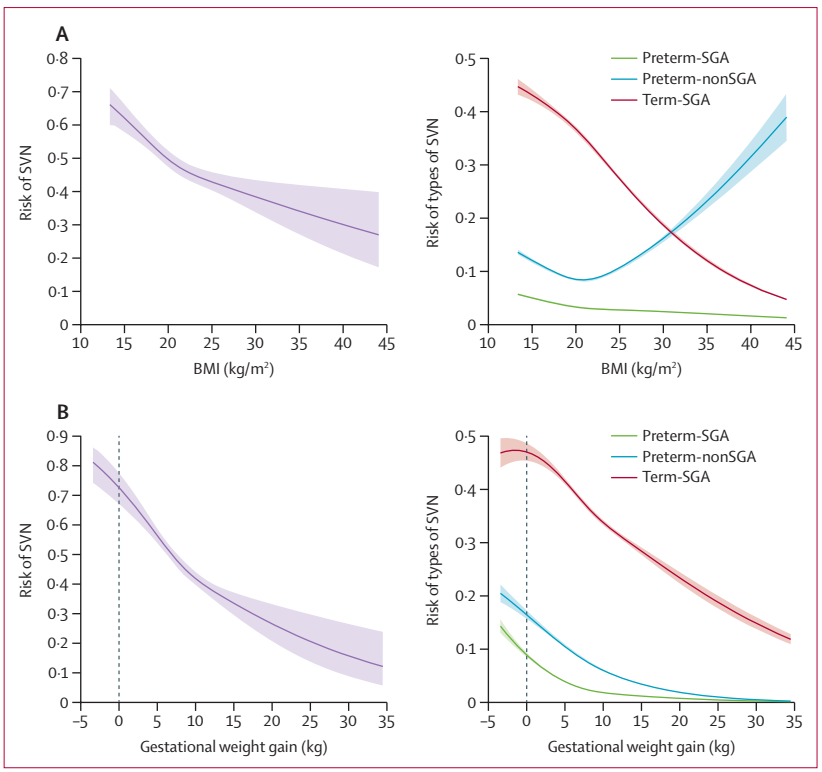

Figure 2: **Association of continuous exposures with probability of SVN**
(A) Association of early pregnancy BMI with probability of SVN (n=6090); adjusted for diabetes, parity, short interpregnancy interval, passive smoking, and participant's age. (B) Association of gestational weight gain with probability of SVN (n=3380); adjusted for overcrowding, fever, and BMI. The y-axis represents the predicted probability (or risk) of the SVN (logistic regression) and its types (multinomial regression) using restricted cubic splines. Solid line represents predicted probability of outcome across the range of gestational weight gain. Shaded area bound by dashed line represents 95% CI. Given that weight gain during pregnancy could be influenced by the weight of the newborn, we also evaluated the association of gestational weight gain after subtraction of birthweight (appendix 2 p 27). BMI=body-mass index. SGA=small for gestational age. SVN=small vulnerable newborns.

Lactobacillus species in individuals delivering preterm birth, compared with term birth.[24,25] An opportunity exists to develop effective probiotic-based interventions to correct this dysbiosis, thereby reducing the incidence of preterm-SGA births. Further, we identified risk factors for specific SVN types across trimesters—namely, biomass fuel, jaundice, and symptoms suggestive of urinary tract infection. Notably, biomass fuel and urinary tract infection have been previously reported as risk factors for SGA and preterm birth, respectively.[26,27] In our study, these exposures were collected as qualitative variables using a questionnaire. There is a need to quantitatively assess these exposures, for example, measure the concentration of particulate matter that is 2·5 µm or smaller in diameter in the air (to quantify the exposure of biomass fuel) and quantify serum bilirubin and bacteriological load (to assess the presence and severity of urinary tract infections).

The incidence of SVN is very high and it will be challenging to deliver universally preventive interventions to all pregnant individuals. Even within SVN, some who were born at the lowest ends of the weight or gestational

	Preterm-SGA (n=194)				Preterm-nonSGA (n=559)				Term-SGA (n=2151)			
	Number of exposed participants with outcomes/ number of exposed	Adjusted RR (95% CI)*	p value	PAF (95% CI)	Number of exposed participants with outcomes/ number of exposed	Adjusted RR (95% CI)*	p value	PAF (95% CI)	Number of exposed participants with outcomes/ number of exposed	Adjusted RR (95% CI)*	p value	PAF (95%CI)
Baseline												
Education of participant†												
Illiterate	48/604	Reference	..	..	113/669	Reference	..	..	447/1003	Reference	..	..
College	61/1371	0·62 (0·41–0·94)	0·024	NA	206/1516	0·82 (0·62–1·06)	0·13	NA	794/2104	0·80 (0·68–0·94)	0·008	NA
School	85/1407	0·77 (0·53–1·12)	0·17	NA	240/1562	0·91 (0·71–1·17)	0·48	NA	910/2232	0·88 (0·75–1·02)	0·087	NA
Occupation of participant†												
Unemployed	186/3085	Reference	..	..	522/3421	Reference	..	..	1983/4882	Reference	..	..
Professional	0/15	..	..	NA	1/16	0·35 (0·04–2·81)	0·32	NA	1/16	0·10 (0·01–0·76)	0·026	NA
Skilled work	1/92	0·21 (0·03–1·50)	0·12	NA	11/102	0·68 (0·36–1·28)	0·23	NA	51/142	0·86 (0·60–1·22)	0·39	NA
Unskilled work	7/190	0·58 (0·27–1·26)	1·26	NA	25/208	0·75 (0·49–1·16)	0·20	NA	116/299	0·91 (0·72–1·16)	0·45	NA
Education of head of family†												
Illiterate	46/596	Reference	..	..	111/661	Reference	..	..	432/982	Reference	..	..
College	48/1180	0·49 (0·32–0·74)	0·0008	NA	177/1309	0·77 (0·59–0·99)	0·049	NA	675/1807	0·76 (0·65–0·89)	0·0007	NA
School	100/1606	0·78 (0·54–1·12)	0·18	NA	271/1777	0·89 (0·70–1·14)	0·35	NA	1044/2550	0·88 (0·76–1·03)	0·10	NA
Occupation of head of family†												
Unemployed	35/442	Reference	..	..	83/490	Reference	..	..	292/699	Reference	..	..
Professional	1/26	0·69 (0·09–5·42)	0·73	NA	4/29	0·94 (0·31–2·81)	0·91	NA	14/39	0·94 (0·48–1·86)	0·86	NA
Skilled	27/708	0·57 (0·33–0·99)	0·045	NA	122/803	0·97 (0·7–1·35)	0·88	NA	435/1116	0·99 (0·81–1·22)	0·98	NA
Unskilled	131/2206	0·81 (0·54–1·22)	0·31	NA	350/2425	0·87 (0·66–1·14)	0·32	NA	1410/3485	1·01 (0·85–1·19)	0·94	NA
Type of house												
Residing in engineered house	172/3100	Reference	..	..	517/3445	Reference	..	..	1955/4883	Reference	..	..
Residing in unengineered house‡	22/282	1·31 (0·82–2·09)	0·26	NA	42/302	0·89 (0·63–1·26)	0·52	NA	196/456	1·08 (0·89–1·32)	0·43	NA
Cooking fuel												
Petroleum gas fuel	175/3149	Reference	..	..	502/3476	Reference	..	..	1978/4952	Reference	..	..
Biomass fuel use for cooking§	19/233	1·48 (0·90–2·44)	0·12	NA	57/271	1·51 (1·11–2·05)	0·009	3·44 (2·65–4·28)	173/387	1·26 (1·02–1·55)	0·033	1·66 (1·44–1·89)
Smoke exposure status												
No exposure to passive smoke	151/2750	Reference	..	..	437/3036	Reference	..	..	1771/4370	Reference	..	..
Exposure to passive smoke¶	43/629	1·24 (0·87–1·77)	0·23	NA	122/708	1·19 (0·95–1·48)	0·13	NA	378/964	0·95 (0·82–1·10)	0·47	NA
Maternal height, cm												
≥145 cm	180/3182	Reference	..	..	507/3506	Reference	..	..	1920/4922	Reference	..	..
<145 cm	14/200	1·25 (0·71–2·2)	0·44	NA	51/237	1·62 (1·17–2·23)	0·0037	3·5 (2·61–4·46)	230/416	1·95 (1·59–2·39)	<0·0001	5·21 (4·59–5·84)

(Table 3 continues on next page)

	Preterm-SGA (n=194)				Preterm-nonSGA (n=559)				Term-SGA (n=2151)			
	Number of exposed participants with outcomes/ number of exposed	Adjusted RR (95% CI)*	p value	PAF (95% CI)	Number of exposed participants with outcomes/ number of exposed	Adjusted RR (95% CI)*	p value	PAF (95% CI)	Number of exposed participants with outcomes/ number of exposed	Adjusted RR (95% CI)*	p value	PAF (95%CI)
(Continued from previous page)												
BMI (categorised by WHO 2000)												
Normal (18·5–24·9 kg/m²)	113/2118	Reference	..	..	312/2317	Reference	..	..	1307/3312	Reference	..	..
Overweight or obese (≥25 kg/m²)	16/498	0·63 (0·37–1·09)	0·089	NA	94/576	1·29 (0·99–1·67)	0·058	NA	173/655	0·58 (0·48–0·71)	<0·0001	NA
Underweight (<18 kg/m²)	65/766	1·61 (1·17–2·22)	0·0037	13·84 (11·12–16·47)	152/853	1·35 (1·09–1·68)	0·0058	8·67 (7·58–9·74)	670/1371	1·44 (1·27–1·64)	<0·0001	10·36 (9·71–11·02)
Parity												
Parity ≥3	8/129	1·19 (0·56–2·53)	0·65	NA	32/153	1·36 (0·90–2·06)	0·14	NA	72/193	1·02 (0·75–1·38)	0·92	NA
Parity 1–2	79/1615	Reference	..	..	294/1830	Reference	..	..	864/2400	Reference	..	..
Nulliparous	107/1638	1·38 (1·02–1·86)	0·038	NA	233/1764	0·79 (0·66–0·95)	0·014	NA	1215/2746	1·42 (1·27–1·59)	<0·0001	NA
Interpregnancy interval status												
Normal (≥18 months)	33/701	Reference	..	..	110/778	Reference	..	..	400/1068	Reference	..	..
Short (<18 months)‖	13/293	0·92 (0·48–1·79)	0·81	NA	73/353	1·59 (1·14–2·21)	0·006	NA	184/464	1·08 (0·86–1·35)	0·52	NA
Abortion history among the individuals with multigravida												
<2 abortions	90/1858	Reference	..	..	335/2103	Reference	..	..	1069/2837	Reference	..	..
≥2 abortions	20/257	1·71 (1·03–2·84)	0·037	NA	39/276	0·88 (0·61–1·25)	0·47	NA	134/371	1·00 (0·8–1·26)	0·997	NA
Caesarean section												
No history of caesarean section	66/1400	Reference	..	..	214/1548	Reference	..	..	777/2111	Reference	..	..
Previous caesarean section¶	21/343	1·41 (0·85–2·34)	0·19	NA	112/434	2·22 (1·71–2·88)	<0·0001	NA	159/481	0·88 (0·71–1·08)	0·22	NA
Previous term birth among the multiparous who could recall the event												
Yes	66/1573	Reference	..	..	256/1763	Reference	..	..	865/2372	Reference	..	..
No	17/164	2·74 (1·55–4·82)	0·0005	NA	68/215	2·76 (2·01–3·8)	<0·0001	NA	82/229	1·02 (0·77–1·35)	0·90	NA
Antenatal (anytime during pregnancy)												
Gestational weight gain												
Adequate	15/554	Reference	..	..	36/575	Reference	..	..	238/777	Reference	..	..
Inadequate (IOM 2009)**	84/1326	2·34 (1·31–4·17)	0·0039	48·59 (43·96–52·54)	225/1467	2·99 (2·04–4·39)	<0·0001	57·38 (54·54–60·1)	1001/2243	1·73 (1·44–2·08)	<0·0001	34·09 (33·17–35·04)
Weight gain for gestational age††												
≥10th percentile	85/1728	Reference	..	..	232/1875	Reference	..	..	1097/2740	Reference	..	..
<10th percentile	14/152	2·27 (1·25–4·13)	0·01	7·91 (4·12–11·95)	29/167	1·51 (0·99–2·32)	0·057	3·87 (3·29–4·44)	142/280	1·74 (1·36–2·24)	<0·0001	4·87 (4·14–5·6)
Anaemia status‡‡												
No anaemia	1/49	Reference	..	..	6/54	Reference	..	..	18/66	Reference	..	..
Anaemia	193/3311	2·88 (0·39–21·03)	0·30	NA	549/3667	1·24 (0·53–2·93)	0·62	NA	2114/5232	1·85 (1·07–3·20)	0·027	45·56 (45·38–45·73)

(Table 3 continues on next page)

	Preterm-SGA (n=194)				Preterm-nonSGA (n=559)				Term-SGA (n=2151)			
	Number of exposed participants with outcomes/ number of exposed	Adjusted RR (95% CI)*	p value	PAF (95% CI)	Number of exposed participants with outcomes/ number of exposed	Adjusted RR (95% CI)*	p value	PAF (95% CI)	Number of exposed participants with outcomes/ number of exposed	Adjusted RR (95% CI)*	p value	PAF (95%CI)
(Continued from previous page)												
Pre-eclampsia status§§												
No pre-eclampsia	63/1244	Reference	..	..	167/1348	Reference	..	..	792/1973	Reference	..	..
Pre-eclampsia	13/66	6·92 (3·45–13·86)	<0·0001	14·63 (7·55–22·22)	10/63	1·45 (0·71–2·97)	0·31	NA	56/109	2·3 (1·52–3·47)	<0·0001	3·73 (2·86–4·67)
Placental position (as diagnosed by sonologist)												
Normal	160/2818	Reference	..	..	440/3098	Reference	..	..	1815/4473	Reference	..	..
Low lying	0/14	NA	NA	NA	5/19	2·24 (0·80–6·30)	0·12	NA	11/25	1·14 (0·52–2·53)	0·74	NA
Change in mean uterine artery pulsatility index¶¶												
Adequate	95/1820	Reference	..	..	276/2001	Reference	..	..	1163/2888	Reference	..	..
Inadequate	18/265	1·75 (0·92–3·3)	0·086	NA	56/303	1·17 (0·76–1·78)	0·48	NA	199/446	1·01 (0·77–1·33)	0·93	NA
Cervical length according to radiologist												
Normal (≥2·5 cm)	165/3098	Reference	..	..	481/3414	Reference	..	..	1960/4893	Reference	..	..
Short (<2·5 cm)	23/197	2·28 (1·43–3·62)	0·0005	6·87 (4·29–9·72)	62/236	2·16 (1·59–2·94)	<0·0001	6·13 (4·78–7·59)	125/299	1·04 (0·82–1·32)	0·75	NA
Bacterial vaginosis status||||												
No bacterial vaginosis	71/1209	Reference	..	..	195/1333	Reference	..	..	703/1841	Reference	..	..
Bacterial vaginosis	12/273	4·54 (1·30–15·93)	0·018	11·27 (5·63–17·52)	36/297	0·88 (0·29–2·74)	0·83	NA	175/436	1·24 (0·65–2·36)	0·52	NA
Vaginal bleeding status												
No vaginal bleeding	164/3150	Reference	..	..	485/3471	Reference	..	..	1997/4983	Reference	..	..
Vaginal bleeding¶	30/232	1·71 (0·58–5·06)	0·34	NA	74/276	2·12 (1·06–4·23)	0·033	6·99 (5·55–8·46)	154/356	1·12 (0·67–1·88)	0·67	NA
Vaginal discharge status												
No vaginal discharge	134/2292	Reference	..	..	346/2504	Reference	..	..	1518/3676	Reference	..	..
Vaginal discharge¶	60/1090	1·33 (0·68–2·6)	0·40	NA	213/1243	1·05 (0·66–1·66)	0·84	NA	633/1663	0·78 (0·59–1·04)	0·09	NA
Exanthematous fever status												
No exanthematous fever	184/3277	Reference	..	..	541/3634	Reference	..	..	2094/5187	Reference	..	..
Exanthematous fever (rash with fever)	10/105	1·77 (0·91–3·45)	0·094	NA	18/113	1·08 (0·65–1·81)	0·76	NA	57/152	0·88 (0·63–1·23)	0·47	NA
Respiratory tract infection status												
No respiratory tract infection	170/3091	Reference	..	..	517/3438	Reference	..	..	1989/4910	Reference	..	..
Respiratory tract infection (cough with fever lasting >2 days)	24/291	1·54 (0·99–2·4)	0·058	NA	42/309	0·89 (0·63–1·24)	0·48	NA	162/429	0·89 (0·73–1·09)	0·27	NA
Urinary tract infection status												
No urinary tract infection	118/2294	Reference	..	..	373/2549	Reference	..	..	1429/3605	Reference	..	..
Urinary tract infection (burning micturition with change in frequency of urination lasting >2 days)	76/1084	1·39 (1·03–1·87)	0·030	10·99 (9·00–12·88)	186/1194	1·07 (0·89–1·30)	0·46	NA	719/1727	1·08 (0·97–1·22)	0·17	NA

(Table 3 continues on next page)

	Preterm-SGA (n=194)				Preterm-nonSGA (n=559)				Term-SGA (n=2151)			
	Number of exposed participants with outcomes/ number of exposed	Adjusted RR (95% CI)*	p value	PAF (95% CI)	Number of exposed participants with outcomes/ number of exposed	Adjusted RR (95% CI)*	p value	PAF (95% CI)	Number of exposed participants with outcomes/ number of exposed	Adjusted RR (95% CI)*	p value	PAF (95%CI)
(Continued from previous page)												
Jaundice status												
No jaundice	191/3359	Reference	..	..	549/3717	Reference	..	..	2125/5293	Reference	..	..
Jaundice	3/23	2·85 (0·83–9·82)	0·098	NA	10/30	3·36 (1·54–7·34)	0·0023	1·26 (0·54–2·06)	26/46	1·83 (0·98–3·4)	0·058	NA
First trimester												
Vaginal bleeding status												
No vaginal bleeding	185/3268	Reference	..	..	524/3607	Reference	..	..	2072/5155	Reference	..	..
Vaginal bleeding¶	7/72	1·42 (0·18–11·35)	0·74	NA	22/87	1·07 (0·23–4·92)	0·93	NA	45/110	1·19 (0·47–2·98)	0·72	NA
Vaginal discharge status												
No vaginal discharge	145/2574	Reference	..	..	411/2840	Reference	..	..	1662/4091	Reference	..	..
Vaginal discharge¶	32/469	2·11 (0·95–4·71)	0·067	NA	84/521	0·79 (0·40–1·56)	0·50	NA	254/691	0·73 (0·48–1·11)	0·14	NA
Exanthematous fever status												
No exanthematous fever	192/3356	Reference	..	..	554/3718	Reference	..	..	2135/5299	Reference	..	..
Exanthematous fever (rash with fever)	2/15	2·53 (0·57–11·31)	0·22	NA	3/16	1·32 (0·37–4·64)	0·67	NA	9/22	1·03 (0·44–2·41)	0·95	NA
Respiratory tract infection status												
No respiratory tract infection	184/3273	Reference	..	..	540/3629	Reference	..	..	2083/5172	Reference	..	..
Respiratory tract infection (cough with fever lasting >2 days)	7/63	2·10 (0·94–4·66)	0·069	NA	12/68	1·22 (0·65–2·3)	0·53	NA	36/92	0·95 (0·62–1·45)	0·82	NA
Urinary tract infection status												
No urinary tract infection	158/2935	Reference	..	..	486/3263	Reference	..	..	1862/4639	Reference	..	..
Urinary tract infection (burning micturition with change in frequency of urination lasting >2 days)	21/251	1·61 (1·00–2·59)	0·049	4·44 (2·64–6·35)	36/266	0·89 (0·62–1·28)	0·54	NA	139/369	0·90 (0·72–1·12)	0·34	NA
Second trimester												
Cervical length according to radiologist												
Normal (≥2·5 cm)	158/2768	Reference	..	..	438/3048	Reference	..	..	1799/4409	Reference	..	..
Short (<2·5 cm)	8/39	6·03 (2·63–13·85)	<0·0001	4·02 (1·49–7·15)	10/41	1·95 (0·86–4·4)	0·11	NA	32/63	1·56 (0·88–2·78)	0·13	NA
Bacterial vaginosis status‖‖												
No bacterial vaginosis	62/1081	Reference	..	..	180/1199	Reference	..	..	632/1651	Reference	..	..
Bacterial vaginosis	11/242	5·12 (1·43–18·3)	0·012	12·13 (5·96–18·78)	31/262	1·08 (0·34–3·43)	0·89	NA	146/377	1·09 (0·53–2·28)	0·81	NA
Vaginal bleeding status												
No vaginal bleeding	183/3274	Reference	..	..	524/3615	Reference	..	..	2089/5180	Reference	..	..
Vaginal bleeding¶	6/27	1·09 (0·26–4·65)	0·91	NA	25/100	2·33 (1·18–4·62)	0·015	2·6 (1·71–3·63)	55/130	0·72 (0·38–1·36)	0·31	NA
Vaginal discharge status												
No vaginal discharge	161/2791	Reference	..	..	444/3074	Reference	..	..	1795/4425	Reference	..	..
Vaginal discharge¶	29/559	1·11 (0·61–2·02)	0·74	NA	101/631	1·50 (1·06–2·12)	0·02	6·18 (5·08–7·33)	339/869	0·87 (0·69–1·11)	0·27	NA

(Table 3 continues on next page)

	Preterm-SGA (n=194)				Preterm-nonSGA (n=559)				Term-SGA (n=2151)			
	Number of exposed participants with outcomes/ number of exposed	Adjusted RR (95% CI)*	p value	PAF (95% CI)	Number of exposed participants with outcomes/ number of exposed	Adjusted RR (95% CI)*	p value	PAF (95% CI)	Number of exposed participants with outcomes/ number of exposed	Adjusted RR (95% CI)*	p value	PAF (95%CI)
(Continued from previous page)												
Gastroenteritis status												
No gastroenteritis	178/3254	Reference	..	..	531/3607	Reference	..	..	2057/5133	Reference	..	..
Gastroenteritis (diarrhoea lasting >2 days)	11/96	2·21 (1·16–4·23)	0·016	3·19 (1·35–4·98)	21/106	1·42 (0·87–2·32)	0·16	NA	73/158	1·28 (0·93–1·76)	0·13	NA
Urinary tract infection status												
No urinary tract infection	109/2133	Reference	..	..	296/2320	Reference	..	..	1335/3359	Reference	..	..
Urinary tract infection (burning micturition with change in frequency of urination lasting >2 days)	56/682	1·66 (1·19–2·32)	0·0029	13·49 (10·45–16·23)	136/762	1·49 (1·19–1·86)	0·0005	10·35 (8·88–11·87)	478/1104	1·16 (1·01–1·33)	0·036	3·64 (3·39–3·90)
Jaundice status												
No jaundice	189/3363	Reference	..	..	550/3724	Reference	..	..	2134/5308	Reference	..	..
Jaundice	2/11	4·00 (0·85–18·78)	0·079	NA	6/15	4·05 (1·43–11·45)	0·008	0·81 (0·27–1·52)	15/24	2·41 (1·05–5·53)	0·038	0·41 (0·22–0·65)
Third trimester												
Anaemia status‡‡												
No anaemia	5/172	Reference	..	..	22/189	Reference	..	..	88/255	Reference	..	..
Mild anaemia	72/1288	1·95 (0·77–4·89)	0·16	NA	187/1403	1·11 (0·69–1·78)	0·66	NA	833/2049	1·30 (0·99–1·71)	0·059	NA
Moderate anaemia	35/594	2·04 (0·79–5·32)	0·14	NA	73/632	0·92 (0·55–1·53)	0·74	NA	379/938	1·30 (0·97–1·75)	0·076	NA
Severe anaemia	1/7	5·53 (0·55–55·12)	0·15	NA	2/8	2·37 (0·45–12·55)	0·31	NA	6/12	1·89 (0·59–6·06)	0·28	NA
Cervical length according to radiologist												
Normal (≥2·5 cm)	108/2255	Reference	..	..	291/2438	Reference	..	..	1447/3594	Reference	..	..
Short (<2·5 cm)	13/83	3·09 (1·53–6·23)	0·0017	7·27 (3·85–11·28)	38/108	3·65 (2·30–5·79)	<0·0001	8·39 (6·05–10·89)	48/118	0·97 (0·64–1·46)	0·87	NA
Retroplacental blood collection status												
No retroplacental blood collection	119/2296	Reference	..	..	320/2497	Reference	..	..	1480/3657	Reference	..	..
Retroplacental blood collection	2/57	0·38 (0·05–2·8)	0·34	NA	9/64	1·34 (0·65–2·77)	0·43	NA	21/76	0·60 (0·35–1·02)	0·061	NA
Vaginal bleeding status												
No vaginal bleeding	173/3274	Reference	..	..	520/3621	Reference	..	..	2082/5183	Reference	..	..
Vaginal bleeding¶	17/90	3·41 (1·54–7·55)	0·0025	6·32 (3·45–9·31)	31/104	1·72 (0·89–3·33)	0·10	NA	63/136	0·98 (0·60–1·60)	0·94	NA
Vaginal discharge status												
No vaginal discharge	178/3142	Reference	..	..	491/3455	Reference	..	..	2020/4984	Reference	..	..
Vaginal discharge¶	12/233	0·96 (0·40–2·25)	0·92	NA	61/282	1·82 (1·18–2·81)	0·01	4·98 (3·91–6·21)	130/351	0·88 (0·63–1·22)	0·43	NA
Exanthematous fever status												
No exanthematous fever	186/3333	Reference	..	..	542/3689	Reference	..	..	2131/5278	Reference	..	..
Exanthematous fever (rash with fever)	4/42	1·78 (0·63–5·04)	0·28	NA	10/48	1·53 (0·76–3·09)	0·24	NA	19/57	0·73 (0·42–1·27)	0·27	NA

(Table 3 continues on next page)

	Preterm-SGA (n=194)				Preterm-nonSGA (n=559)				Term-SGA (n=2151)			
	Number of exposed participants with outcomes/ number of exposed	Adjusted RR (95% CI)*	p value	PAF (95% CI)	Number of exposed participants with outcomes/ number of exposed	Adjusted RR (95% CI)*	p value	PAF (95% CI)	Number of exposed participants with outcomes/ number of exposed	Adjusted RR (95% CI)*	p value	PAF (95%CI)
(Continued from previous page)												
Respiratory tract infection status												
No respiratory tract infection	123/2282	Reference	..	..	349/2508	Reference	..	..	1474/3633	Reference	..	..
Respiratory tract infection (cough with fever lasting >2 days)	11/88	2·50 (1·30–4·83)	0·006	4·93 (2·34–7·71)	10/87	0·80 (0·41–1·56)	0·52	NA	44/121	0·84 (0·58–1·22)	0·36	NA
Jaundice status												
No jaundice	188/3365	Reference	..	..	548/3725	Reference	..	..	2142/5319	Reference	..	..
Jaundice	2/10	7·83 (1·40–43·64)	0·019	0·92 (0–2·3)	4/12	4·46 (0·99–20·03)	0·051	0·56 (0·13–1·14)	8/16	2·39 (0·70–8·18)	0·17	NA

Reference: term-nonSGA. RR quantifies the magnitude of an association between exposure and outcome, indicating how much more (RR >1) or less (RR <1) probable the outcome is in the exposed group versus the unexposed group. NA for population attributable fraction if the factor is not statistically significant or protective or non-modifiable. Baseline factors such as nuclear family, overcrowding, unsafe source of drinking water, unsafe toilet, alcohol consumption, chewing tobacco use, underage (age <18 years), and overage (age >35 years); antenatal factors such as low-lying placenta, retroplacental blood collection, and gastroenteritis assessed anytime during pregnancy; first trimester anaemia (mild, moderate, or severe), short cervical length, bacterial vaginosis, gastroenteritis, and jaundice; second trimester anaemia (mild, moderate, or severe), retroplacental blood collection, exanthematous fever, and respiratory tract infection; and third trimester gastroenteritis and urinary tract infection were excluded from adjusted analysis as the p value from the simple regression analysis was more than 0·2. The estimates of the unadjusted analysis and the covariates adjusted are detailed in appendix 2 (pp 16–23). NA=not applicable. PAF=population attributable fraction. RR=relative risk. SGA=small for gestational age. SVN=small vulnerable newborns. *Adjusted for covariates in appendix 2 (pp 1–2). †As per modified Kuppuswamy scale. ‡The walls or roof of which are made of material such as un-burnt bricks, bamboos, mud, grass, reeds, thatch, or loosely packed stones. §Biomass fuel use refers to use of non-petroleum gas fuel sources for cooking. ¶As reported by participant. ||Among the individuals with multigravida excluding those whose previous outcome was abortion. **Gestational weight gain (weight gained between enrolment and just before the birth of the neonate) below the IOM 2009 criteria. ††Detailed definition in appendix 2 (pp 10–11). ‡‡Classified as per WHO criteria for anaemia during pregnancy as mild (haemoglobin <11 g/dL and ≥9 g/dL), moderate (haemoglobin <9 g/dL and ≥7 g/dL), or severe (haemoglobin <7 g/dL) based on the lowest haemoglobin measurement in each trimester. §§Female participants with hypertension at at least two timepoints (≥140 mm systolic or ≥90 mm diastolic during pregnancy) and proteinuria (dipstick test ≥1) at the same visit as high blood pressure, or female participants with ≥160 mm systolic blood pressure or ≥110 mm diastolic blood pressure on one occasion and proteinuria (dipstick test ≥1) at different visit as high blood pressure. ¶¶If difference between index visit and previous visit was zero or positive it was considered adequate. ||||Bacterial vaginosis diagnosed by microbiologist from the high vaginal swab collected by a qualified gynaecologist during the antenatal visits.

Table 3: **Risk factors for types of SVN in female participants with singleton pregnancy**

age spectrum are likely to have a worse prognosis than others. There is an urgent need for accurate risk-stratification tools to enable efficient delivery targeted to those who are at risk of SVN. Such prediction tools can be developed by integrating clinical, molecular, and imaging sciences.[7,28] We have discovered novel molecular markers that can be combined with clinical and imaging predictors to accurately stratify pregnant individuals at risk of preterm birth.[29,30] Such an approach can be adopted for SVN.

The major strength and novelty of our study is the comprehensive evaluation of overall and trimester-specific risk factors from a rigorously followed prospective cohort analysed using robust methods. We used population attributable fraction to identify risk factors that need urgent intervention. Further, the accurate estimation of gestational age using ultrasound (done in either the first trimester or early second trimester) adds to the reliability of our outcomes. Importantly, the recent *Lancet* series[3–6] highlighted data scarcity from south Asia compared with other regions, and our study significantly contributes to filling this gap. To the best of our knowledge, this study is the first available analysis of SVN after this framework was suggested.

There are two limitations that need to be noted of our study. The study was based in a secondary-level care district hospital and not at the community level. However, the inferences are representative of the population in the region as this hospital assumes the role of a primary-care centre when it caters to pregnant individuals. Another important limitation is that the study was conducted in a single north Indian centre. Similar analyses from other regions within India and south Asia are needed to improve the generalisability of our findings.

In conclusion, we identified crucial trimester-specific risk factors for SVN and its types based on their effect sizes and attributable fractions to be able to prioritise interventions. Addressing preconception and antenatal maternal undernutrition; communicating the risks of short time periods between pregnancies; and preventing and managing pre-eclampsia, bacterial vaginosis, and urinary tract infections are priority areas for public health interventions for SVN. These interventions should be complemented with use of risk-stratification tools. Such a concerted effort will improve care for the most vulnerable newborns and accelerate the achievement of Sustainable Development Goals (specifically sustainable development target 3.2).

GARBH-Ini study team
Shinjini Bhatnagar, Nitya Wadhwa, Uma Chandra Mouli Natchu, Bhabatosh Das, Pallavi S Kshetrapal, Shailaja Sopory, Ramachandran Thiruvengadam, Sumit Misra, Dharmendra Sharma, Kanika Sachdeva, Amanpreet Singh, Balakrish G Nair, Satyajit Rath, and Vineeta Bal (Translational Health Science and Technology Institute, Faridabad, Haryana, India); Alka Sharma, Sunita Sharma, Umesh Mehta, and Brahmdeep Sindhu (Gurugram Civil Hospital, Gurugram, India); Pratima Mittal, Rekha Bharti, Harish Chellani, Rani Gera, Jyotsna Suri, Pradeep Debata, and Sugandha Arya (Vardhman Mahavir Medical College & Safdarjung Hospital, New Delhi, India); Arindam Maitra (National Institute of Biomedical Genomics, Kalyani, India); Tushar K Maiti (Regional Centre for Biotechnology, Faridabad, India); Dinakar M Salunke (International Centre for Genetic Engineering and Biotechnology, New Delhi, India); Nikhil Tandon, Yashdeep Gupta, Alpesh Goyal, Smriti Hari, Aparna Sharma K, and Anubhuti Rana (All India Institute of Medical Sciences, New Delhi, India); Siddarth Ramji and Anju Garg (Maulana Azad Medical College, New Delhi, India); Ashok Khurana (The Ultrasound Lab, Defence Colony, New Delhi, India); Reva Tripathi (Sitaram Bhartia Institute of Science and Research, New Delhi, India); Rakesh Gupta and Partha P Majumder (Government of India); Himanshu Sinha and Raghunathan Rengasamy (Indian Institute of Technology Madras, Chennai, India); Vineeta Bal (Indian Institute of Science Education and Research, Pune, India); Pratima Mittal (Amrita Institute of Medical Sciences & Research Centre, Faridabad, India); Uma Chandra Mouli Natchu and Harish Chellani (Center for Health Research and Development, Society for Applied Studies, New Delhi, India); and Ramachandran Thiruvengadam (Pondicherry Institute of Medical Sciences, Puducherry, India).

Contributors
SB conceived, designed, and led the GARBH-Ini programme; SB, RaT, and NW conceived the research question and designed the analysis; SB, NW, RaT, SM, UM, AS, SuS, AK, ShS, PK, PM, HC, RB, SR, ReT, UCMN, DMS, and the GARBH-Ini study team conducted the GARBH-Ini cohort study and acquired the data; DS and SSS managed the data and prepared it for analysis; A, DRM, BKD, and RaT analysed data; SB, SR, NW, BKD, and RaT guided and provided feedback on the analysis and interpretation of results; SB, RaT, NW, A, DRM, BKD, and SR wrote the manuscript. All authors critically reviewed and approved the final manuscript. All authors had access to all the data in the study and had final responsibility for the decision to submit for publication. SB, RaT, NW, A, DRM, BKD, DS, and SSS have accessed and verified the data.

Declaration of interests
We declare no competing interests.

Data sharing
Data described in the manuscript will be made available upon request to the corresponding author pending approval. Analysis code will be made available upon request with the objective of use.

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