



Early View

Original research article

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Preterm birth and asthma and COPD in adulthood: A nationwide register study from two Nordic countries

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Abstract

Preterm birth affects lungs in several ways but only few studies have follow-up until adulthood. We investigated the association of the entire spectrum of gestational ages with specialist care episodes for obstructive airway disease (asthma and chronic obstructive pulmonary disease, COPD) at age 18-50 years.

We used nationwide register data on 706 717 people born 1987-1998 in Finland (4.8% preterm) and 1 669 528 born 1967-1999 in Norway (5.0% preterm). Care episodes of asthma and COPD were obtained from specialised healthcare registers, available in Finland 2005-2016 and in Norway 2008-2017. We used logistic regression to estimate odds ratios (OR) for having a care episode with either disease outcome.

Odds of any obstructive airway disease in adulthood were 2-3-fold for those born <28 or 28-31 completed weeks, compared with those born full-term (39-41 completed weeks), persisting after adjustments. For individuals born at 32-33, 34-36 or 37-38 weeks, the odds were 1.1- to 1.5-fold. Associations were similar in the Finnish and the Norwegian data and among people aged 18-29 and 30-50 years. For COPD at age 30-50 years, the OR was 7.44 (95% CI 3.49-15.85) for those born <28 weeks, 3.18 (2.23-4.54) for those born 28-31 weeks, and 2.32 (1.72-3.12) for those born 32-33 weeks. Bronchopulmonary dysplasia in infancy increased the odds further for those born <28 and 32-31 weeks.

Preterm birth is a risk factor for asthma and COPD in adulthood. The high odds of COPD calls for diagnostic vigilance when adults born very preterm present with respiratory symptoms.

Keywords: preterm birth, asthma, COPD, register study

Introduction

One in ten babies worldwide is born preterm, before 37 completed weeks of gestation [1]. Preterm birth disrupts normal lung development, which can have lasting effects on lung function, in particular on airflow [2-4]. This is most evident in infants born very preterm (<32 weeks) who develop bronchopulmonary dysplasia (BPD), which is characterised by alveolar septal fibrosis and inflammation or by impaired alveolar growth [3,5,6].

Impaired airflow is the hallmark of the obstructive airway diseases asthma and chronic obstructive pulmonary disease (COPD). In 2017, the global prevalence of asthma was estimated at 3.6% and COPD at 3.9% [7]. The prevalence of asthma is the highest in childhood and, after a nadir in young adulthood, increases again with age, while the prevalence of COPD increases steadily with age from early midlife onwards. Although COPD is typically linked to smoking and indoor or outdoor air pollution, fetal and childhood factors that impair lung development and function, such as prematurity or allergy and bronchitis in childhood, have been recognised as risk factors both for asthma and COPD [3,8-11].

Studies of the risk of adult obstructive airway diseases among preterm born individuals show mixed findings. Many show an association between preterm birth and obstructive airway disease in younger ages, whereas most studies show no association in older ages [8,12-16]. However, there is evidence of a more prominent risk for asthma in preterm-born women [17], COPD in both women and men [5,6,18], and increased mortality from chronic lung diseases [19] in adulthood. A separate body of research has focused on those born very preterm (<32 weeks) or at very low birth weight (<1500 g) who have lower expiratory airflow as young adults than those born at term [18]. Airflow is even lower among those who have experienced neonatal BPD [5,6,18]. However, several gaps in the knowledge remain. So far, only few studies have had sufficiently long follow-up and adequate

statistical power to assess early life origins of COPD. Moreover, many studies have assessed infants born preterm as one group, not appreciating the wide variation in degree of immaturity or related traits such as being born small for gestational age (SGA).

In this population-based register study we investigated the association between the full range of gestational ages (GA), and obstructive airway disease (asthma and/or COPD) in early and mid-adulthood, using nationwide data from two Nordic countries. Additionally, we investigated whether the association differed in subgroups of individuals born preterm who were diagnosed with BPD or were born SGA.

Material and methods

Study population

The study populations, identified from the Medical Birth Registers (MBR), comprised all live births in Finland from 1987 to 1998 (N=750 733) and in Norway from 1967 to 1999 (N=1 904 600). More information of the MBR's can be found in the Methodological appendix. Data from the MBRs in Finland and Norway were linked with data from other national registers, using encrypted national identification codes provided to every citizen and permanent resident of Finland or Norway [20-24].

We excluded individuals who died (n=41 494, 1.6%) or emigrated (n=8 797, 0.3%) before the start of the follow-up, who had congenital anomalies (n=69 238, 2.6%), missing GA (n=123 109, 4.6%), GA <23+0 or >43+6 weeks or implausible GA and birth weight combinations (n=29 296, 1.1%), GA >33+6 completed weeks who had a diagnosis of BPD (n=33, 0.0%) and those with missing data on covariates, including triplets and quadruplets due to missing birth weight z-score (n=7 121, 0.3%) (Supplementary Figure 1).

In Finland, this study was approved by Research Ethics Board of the Finnish Institute for Health and Welfare (THL/1960/6.02.01/2018, §810), and in Norway, by the Central Norway Regional Committee for Medical Research Ethics (2018/32) and by the registries. Information on data permissions and waiver of informed consent is presented in the Methodological appendix.

Gestational age

GA in completed weeks was ascertained from the MBRs [23,24]. The duration of gestation has been confirmed by ultrasonography in Finland starting from late 1980s or early 1990s, and in Norway from December 1998. Prior to that, duration of gestation was estimated mainly based on data on last menstrual period, or by means of clinical examination [25,26]. GA was categorised as extremely preterm (23 to 27 weeks), very preterm (28 to 31 weeks), moderately preterm (32 to 33 weeks), late preterm (34 to 36 weeks), early term (37 to 38 weeks), full-term (39 to 41 weeks, reference) and post-term (42 weeks).

Obstructive airway disease outcomes

We started the follow-up at the earliest when the individuals turned 18 years: in Finland the study time frame extended from 2005 (the oldest Finnish individuals within the study population turned 18 years) to 2016 and in Norway from 2008 (national identity number was introduced in the Norwegian Patient Registry (NPR) allowing obtaining data at the individual level) to 2017 (Supplementary Figure 2). During these time periods, the Finnish Care Register for Health Care (CRHC) covered all specialist inpatient care and public hospital outpatient care episodes [21] and the NPR covered all publicly funded specialist inpatient and outpatient care episodes, [20] with care records using the 10th revision of International Statistical Classification of Diseases and Related Health Problems (ICD) codes. For asthma, we included diagnostic codes J45-J46 [27], and for

COPD diagnosis sub-groups of pulmonary emphysema (J43) other COPD (J41-J42, J44.0-J44.8), and unspecified COPD (J44.9) [17,28]. Individuals were considered as cases if they had an inpatient or outpatient hospital or specialist care episode with these codes as the main diagnosis, regardless of the number of records.

Covariates

As covariates we selected factors that are associated with preterm birth [29,30] and asthma [31] or COPD [9,32]. Information on sex, birth year, birth weight, single vs. twin birth, parity, Caesarean section, and mother's age were obtained from the MBRs. Birth weight z-scores (BWZ) were calculated using the Sankilampi growth references for singletons and twins born at GA 23-43 weeks [33]. Mother's asthma diagnosis was obtained from the CRHC in Finland and from the MBR in Norway. Information on mother's hypertensive disorders during pregnancy (chronic hypertension or gestational hypertension, and pre-eclampsia or eclampsia) was obtained from both CRHC and MBR in Finland and from the MBR in Norway. Data on highest attained education of the mother and father were obtained from Statistics Finland and Statistics Norway. Diagnosis of BPD was obtained from the CRHC and maternal smoking during pregnancy from the MBR in Finland. The methodological appendix provides details on the covariates and the directed acyclic graph presenting the assumed relationships between the variables used in this study.

Statistical analysis

In the main analyses we used logistic regression to estimate odds ratios (OR) and associated 95% confidence intervals (CIs) for having a care episode with diagnoses of obstructive airway disease in specialty care, across the seven GA categories with those born full-term as the reference. We investigated the association for all obstructive airway diseases combined, for asthma and COPD separately, and for the COPD sub-groups (in Norway only). In Finland, we included care episodes

at 18-29 years. In Norway, we included two age categories, ages 18-29 and 30-50 years, and the full follow-up at ages 18-50 years, and used Generalised Estimation Equations (PROC GENMOD in SAS) with exchangeable working correlation structure to account for intraindividual dependence of those participants who contributed to both of the two age categories [34]. We calculated the population attributable risk to estimate the risk of obstructive airway disease attributable to preterm birth and bronchopulmonary dysplasia (only available in the Finnish data) in the total population. Numbers of individuals included in the analyses, by age category and country, are presented in Supplementary Figure 1.

We constructed two models: Model 1 was adjusted for sex and birth year. Model 2 was additionally adjusted for BWZ, twin birth, parity, Caesarean section, mother's age, mother's hypertensive disorders during pregnancy, mother's asthma, and mother's and father's highest education (separate measures). In the Finnish data, we created sub-categories for the extremely, very, and moderately preterm groups with and without BPD diagnosis and compared them to the group born full-term (interaction for BPD*GA categories $p < 0.001$ for obstructive airway diseases combined). We also ran the models for ages 18-29 in both countries, in subgroups born SGA (BWZ < -2 SDs, standard deviation), appropriate for gestational age (AGA, BWZ -2 to $+2$ SDs), and large for gestational age (LGA, BWZ $> +2$ SDs), comparing categories of preterm born to those born full-term (interaction for birth weight groups*GA categories $p < 0.001$ in both countries).

As sensitivity analyses, in both countries, we ran the main analyses using care episodes only from 1) pulmonology speciality or 2) inpatient care, and 3) using completed weeks of GA as the exposure, with GA 40 weeks as the reference category, as well as running the analyses 4) separately by sex and 5) mother's parity, and 6) by excluding twin births. Additionally, using only data from Finland, we 7) constructed a model adjusting additionally for maternal smoking during pregnancy.

Further, to account for possible survival bias, we 8) calculated survival time from the beginning of the follow-up to the first care episode of obstructive airway disease, death, or emigration and estimated hazard ratios from Cox regression in Finland and Norway at age 18-29 years. Statistical analyses were conducted using SAS EG versions 7.13 and 7.15 (SAS Institute Inc., Cary, NC, USA).

Results

Study population

Selection of the study population is presented in Supplementary Figure 1. Of the 2 655 333 individuals born alive in Finland or Norway during the baseline period, 2 376 245 (89.5%) were included in the analyses (706 717 in Finland and 1 669 528 in Norway). Detailed characteristics of the study population by country are shown in Table 1 and by outcome groups in Supplementary Table 1. In total, 1.9% (n=45 624) of the participants had a specialised health care episode with diagnosis on obstructive airway disease during the follow-up (Supplementary Table 2). Of these individuals, 90.6% (n=41 332) had asthma only, 5.9% (n=2 706) COPD only, and 3.5% (n=1 586) had both diseases during the follow-up.

Main results

All groups born preterm had higher odds of obstructive airway disease in adulthood (Figure 1). ORs for both models are presented in Supplementary Table 3. We observed a graded association between gestational age at birth and the odds of having a care episode of obstructive airway disease in adulthood (p for trend <0.001 in both countries). In the Finnish dataset, the odds of obstructive airway disease at age 18-29 were the highest (OR: 2.77, 95% CI 1.91-4.02) in the extremely preterm group, compared to the full-term born group. The corresponding OR in the Norwegian dataset was 3.22 (95% CI 2.40-4.31). In Norway, estimates were only slightly lower at age 30-50

and 18-50 years (OR for extremely preterm: 2.96 (95% CI 1.98-4.43) and 3.12 (95% CI 2.42-4.03), respectively). Adjustment for covariates did not alter the direction or magnitude of the estimates. The odds of airway disease did not markedly differ between the full-term and post-term born individuals. Population attributable risk of preterm birth for obstructive airway disease was 1.2% (95% CI 0.7-1.7%) in Finland and 1.3% (95% CI 1.1-1.6) in Norway, and of BPD 0.3% (95% CI 0.2-0.5%) in Finland.

For asthma, the risk was higher in all groups born preterm, except for those born moderately preterm in Finland (Figure 2, panel A). The risk for COPD was higher in Norway in all groups born preterm, but not for those born early term while aged 18-29 years (Figure 2, panel B). In Finland, there were no COPD cases in the extremely or very preterm groups. The risk of COPD was markedly increased for the moderately preterm group (Figure 2, panel B). These associations attenuated only slightly after adjustment for covariates (Table 2, Supplementary Table 3). Odds ratios for COPD sub-groups in Norway are shown in Table 2. The highest odds in those born extremely preterm were for emphysema (OR at age 18-29: 31.09 (95% CI 7.54-128.14), OR at age 30-50: 16.66 (95% CI 4.13-67.12), and OR at age 18-50: 21.68 (95% CI 6.47-71.63) in the fully adjusted model).

Bronchopulmonary dysplasia

Data on neonatal BPD were available in Finland (Figure 3). Associations with GA were stronger among those with than those without a BPD diagnosis. With term-born individuals as the reference group, fully adjusted OR was 4.79 (95% CI 2.88 to 7.99) for those born extremely preterm with BPD, vs. 1.91 (95% CI 1.10 to 3.33) for those without BPD. The corresponding estimates for those born very preterm were 8.17 (95% CI 5.15 to 12.93) vs. 1.76 (95% CI 1.34 to 2.31).

Being born small for gestational age

In total, 4.0% of the participants were born SGA and 3.0% LGA. In Norway, individuals born extremely, very, and late preterm, and early term, and in Finland those born very preterm or early term had higher odds for obstructive airway disease compared to those born full-term, in both SGA and AGA categories (Figure 4). However, individuals born SGA in preterm groups had somewhat higher odds than those born AGA. For example, the fully adjusted OR was 2.36 (95% CI 1.58-3.52) in the SGA very preterm group and 1.92 (95% CI 1.57-2.34) in the AGA very preterm group in Norway. In Finland, the corresponding ORs were 2.80 (95% CI 1.64-4.78) in the SGA very preterm group and 2.22 (95% CI 1.71-2.88) in the AGA very preterm group. In general, no significant associations between gestational age and obstructive airway disease in the LGA groups were found although the point estimates were somewhat lower than in the AGA groups.

Sensitivity analyses

When GA was studied week by week, the highest odds were observed among individuals born before 28 weeks, whereafter the odds decreased gradually (Supplementary Figure 3). Restricting the outcomes to care episodes from pulmonology speciality (Supplementary Table 4) or from inpatient care (Supplementary Table 5) resulted in slightly higher odds, compared to using all episodes. However, in Finland where the number of inpatient episodes was much smaller, only individuals born very preterm had higher odds than those born full-term using model 1. There were no major differences between men and women in the associations of GA with the risk of obstructive airway diseases (Supplementary Figure 4) or between the first born or later born (Supplementary Figure 5). Excluding twins (Finland, n=17 679, 2.5%; Norway n=34 725, 2.1%) resulted in associations of similar magnitude as in the main analysis (Supplementary Table 6). In Finland, after adjusting model 2 additionally for maternal smoking, the odds for obstructive airway disease remained

essentially similar as in the main analysis (Supplementary Table 7). The associations also remained similar when using Cox regression to account for survival time (Supplementary Table 8).

Discussion

In this two-country register study of over two million people we found that preterm born individuals had higher risks of care episodes due to asthma and/or COPD in young adulthood and middle age than those born full-term. The risks at the lowest gestational ages were substantial, but the risks were observed across all gestational ages before full-term in a dose-response manner. Risk remained higher over young to mid-adulthood, also after adjusting for parity, Caesarean section, twin birth, mother's age, mother's asthma, and parents' education. The risk was further increased in preterm born individuals who were born SGA or who had a BPD diagnosis.

A key strength of our study derives from the large sets of individual-level data, with follow-up from birth up to the age of 50 years. Near-complete information of births and diagnoses received in specialised health care, both in Finland and in Norway, minimised the risk of bias from loss to follow-up. We were able to include many potential confounders by linking data from different registers. Large register data offered sufficient statistical power to study risk of obstructive airway disease across a wide spectrum of gestational ages.

An inherent limitation of a register study is that individual asthma and COPD diagnoses cannot be independently verified by assessing reversibility of obstructed airflow through clinical lung function measures. Nevertheless, asthma and COPD diagnoses in specialist care are typically based on thorough clinical history and paraclinical evaluations in the Nordic countries, and we evaluate any such misclassification most possibly non-differential and thus not likely to substantially bias to the main findings. We have also shown that our results remained similar when we restricted the

outcome only to care episodes from pulmonology or inpatient care. Importantly, we only included care episodes from specialist health care and had no data on primary care visits for the time period covered in our study. Thus, our results show the more severe end of asthma and COPD spectrum, and not the total prevalence of the conditions. It is possible that people born extremely or very preterm could be more likely to be treated for respiratory symptoms in specialist care, for example because of other chronic conditions. However, we believe that in adulthood this is unlikely to cause substantial bias [35]. In addition, pregnancy dating based on last menstrual period, which was a commonly used method in Norway up to the late 1980's, may have overestimated the length of gestation for some individuals in our dataset [29]. We would expect this to produce more conservative estimates, however, the associations of obstructive airway disease at age 30-50 years in Norway (born 1967-1987) were not weaker than at age 18-29 years (born 1979-1999). Based on previous research from Finland [36] and Norway [37] we expect preterm-born young adults to be less or as likely to smoke as term-born individuals. We were able to adjust for maternal smoking during pregnancy in Finnish data with negligible changes in the results. Nevertheless, it is possible that our findings have been influenced by residual confounding from unmeasured confounders. For example, register data offer only limited information on certain prenatal or early life factors, such as chorioamnionitis or respiratory tract infections, health behaviours and life-style factors, such as personal smoking and work-related exposure to dust particles, that could contribute to the associations.

Overall, the findings in the Finnish and Norwegian datasets were consistent across the sub-groups. However, the individuals in our study were born in 1967-1999, during a period of change in clinical care practices for preterm-born neonates [38], which has to be taken into account when interpreting the results. Some of the individuals, mainly from Norway, were born during the pre-surfactant era, before 1990 [18,38], whereas the individuals for whom we had information on BPD diagnosis were

born in Finland in 1987-1998. Most of the BPD is likely to be the “new” BPD, which is considered of a consequence of disrupted lung development, whereas the share of “classic” BPD caused by aggressive ventilation strategies was probably higher in the Norwegian sample where we have no information on BPD diagnoses [6]. The results may thus not be generalisable to preterm born individuals who received modern prenatal and neonatal care, individuals in other settings with different health care systems or with different measurement of duration of gestation.

Our findings on the association of gestational age and adult asthma are in line with previous research showing higher risk in young adulthood for those born preterm, compared to term born individuals [8,39]. We were also able to expand this investigation up to 50 years of age. Unlike previous research from Denmark, which reported higher risk among individuals born preterm for asthma medication purchases in childhood but not in young adulthood, [13] we found increased risk of asthma treated in specialist health care also in middle age, with a dose-response pattern in young adulthood similar to that observed by others [39].

Few studies have investigated COPD or obstructive airway diseases combined. In two Swedish studies, risk of obstructive airway disease was either similar [14] or higher only for women born preterm, compared to term-born women [17]. In an Australian study, the risk of COPD at age 53 was higher for individuals born at GA 28-33 weeks, but not for those born at 34-36 weeks [10]. We found higher risk for asthma and COPD combined, and COPD alone, in all groups born preterm, and both for men and women. The differences in the results may be due to the smaller sample size, differences in defining the outcome or the reference group, and regional, older cohorts with fewer extremely and very preterm survivors in the earlier studies. Our results support the hypothesis that preterm birth could increase the risk of COPD in adulthood, potentially via mechanisms relating to

impaired lung development and function among preterm born children, young people and adults [4,9,18,40].

Earlier research has found that airway obstruction is more marked with extremely preterm born individuals with history of BPD [41,42]. We can extend this finding to include very preterm born individuals with BPD, who in our study also had a markedly higher risk for a diagnosis of obstructive pulmonary disease in young adulthood compared to very preterm-born without BPD. We were also able to investigate the combined risk of being born both preterm and with SGA and found that SGA was associated with additionally higher risk for obstructive airway disease in some of the preterm categories.

Conclusion

Adults born preterm are more often treated in specialist care for obstructive airway diseases including both asthma and COPD, compared to individuals born full-term. The higher risk is extended to those born late preterm and early term and is higher for those who received a BPD diagnosis in infancy, or who were born SGA. Preterm birth should be recognised as a risk factor for obstructive airway diseases in adulthood, and full medical history for people presenting with respiratory symptoms should include key perinatal data such as birth weight, gestational age and key pregnancy conditions. High risk groups of preterm born individuals, such as extremely or very preterm or those with a history of BPD, could benefit from more systematic follow-up with specialized teams who have knowledge on risks, possible prevention strategies, early diagnosis, and treatment. In these groups, the excess risks are clinically significant and call for particular diagnostic vigilance when individuals born preterm present with respiratory symptoms.

Table 1 Characteristics of the study population

	Finland, born 1987-1998 (n=706 717)		Norway, born 1967-1999 (n=1 669 528)	
	n	%/SD/IQR	n	%/SD/IQR
Male, n (%)	360 028	50.9	852 867	51.1
Gestational age at birth, completed weeks, n (%)				
Extremely preterm (23-27)	850	0.1	1 359	0.1
Very preterm (28-31)	2 793	0.4	6 931	0.4
Moderately preterm (32-33)	4 048	0.6	10 880	0.7
Late preterm (34-36)	26 557	3.8	65 057	3.9
Early term (37-38)	125 648	17.8	218 145	13.1
Full-term (39-41)	515 608	73.0	1 153 153	69.1
Post-term (42)	31 213	4.4	214 003	12.8
Birth weight Z-score, mean (SD)	0.00	1.06	0.00	1.11
Small for gestational age, n (%)	17 958	2.5	77 405	4.6
Large for gestational age, n (%)	23 612	3.3	47 144	2.8
First born, n (%)	281 020	39.8	687 968	41.2
Singleton, n (%)	689 038	97.5	1 634 803	97.9
Caesarean section, n (%)	105 846	15.0	135 827	8.1
Bronchopulmonary dysplasia, n (%) ¹	616	0.1	N/A	N/A
Follow-up time in years, median (IQR)	6.0	3.2-8.9	10.0	7.5-10.0
Attained age, n (%)				
18-29 years	706 717	100.0	623 024	37.3
30-50 years	-	0.0	1 046 504	62.7
Mother's age at giving birth, mean (SD) years	29.0	5.18	27.4	5.24
Maternal smoking during pregnancy, n (%) ^{1,2}	108 184	15.6	N/A	N/A
Mother's history of asthma, n (%)	8 705	1.2	25 616	1.5
Mother's hypertensive disorders during pregnancy, n (%)				
No	668 333	94.6	1 595 953	95.6
Chronic or gestational hypertension	20 110	2.9	27 339	1.6
Pre-eclampsia or eclampsia	18 274	2.6	46 236	2.8
Mother's education				
Unknown	3 559	0.5	10 541	0.6
Low (ISCED classes 0 to 2)	71 668	10.1	408 046	24.4
Intermediate (ISCED classes 3 to 5)	464 997	65.8	770 949	46.2
High (ISCED classes 6 to 8)	166 493	23.6	479 992	28.8
Father's education				
Unknown	10 676	1.5	25 541	1.5
Low (ISCED classes 0 to 2)	128 028	18.1	372 900	22.3
Intermediate (ISCED classes 3 to 5)	426 067	60.3	836 690	50.1
High (ISCED classes 6 to 8)	141 946	20.1	434 397	26.0
Care episode at 18-29 years of age ³				
Obstructive airway disease ⁴	9 512	1.3	14 763	1.4
Asthma ⁵	9 412	1.3	14 418	1.4

COPD ⁶	147	0.0	582	0.1
Care episode at 30-50 years of age ^{3,7}				
Obstructive airway disease ⁴	N/A	N/A	22 271	2.1
Asthma ⁵	N/A	N/A	19 971	1.9
COPD ⁶	N/A	N/A	3 594	0.3
Care episodes from inpatient care				
Obstructive airway disease at 18-29 years of age ^{3,4}	520	0.1	987	0.1
Obstructive airway disease at 30-50 years of age ^{3,4,7}	N/A	N/A	2 091	0.2
Care episodes from pulmonology speciality				
Obstructive airway disease at 18-29 years of age ^{3,4}	6 398	0.9	8 811	0.8
Obstructive airway disease at 30-50 years of age ^{3,4,7}	N/A	N/A	15 975	1.5

COPD chronic obstructive pulmonary disease; GA gestational age; IQR interquartile range; ISCED the International Standard Classification of Education; N/A not available; SD standard deviation

¹ Information is not available in Norway

² Maternal smoking missing in Finland, n=14 028

³ Number contributed to analyses at different age categories in Norway: 18-29 years: 1 065 372, 30-50 years: 1 046 611

⁴ Obstructive airway disease comprises of both asthma and/or COPD.

⁵ ICD-10 codes for asthma: J45-J46

⁶ ICD-10 codes for COPD: J41-J44

⁷ Information not available in Finland

Table 2 Odds ratios (OR) with 95% confidence intervals (CI) for different obstructive airway diseases¹

	Finland			Norway								
	18-29 years			18-29 years			30-50 years			18-50 years		
	OR	95% CI		OR	95% CI		OR	95% CI		OR	95% CI	
Asthma, J45-J46												
Full-term ²	Ref			Ref			Ref					
Extremely preterm	2.90	2.00	4.21	3.10	2.29	4.20	2.71	1.73	4.25	2.96	2.26	3.88
Very preterm	2.26	1.80	2.85	2.04	1.71	1.44	1.83	1.51	2.21	1.94	1.70	1.70
Moderately preterm	1.24	0.96	1.60	1.42	1.20	1.69	1.41	1.20	1.66	1.41	1.25	1.25
Late preterm	1.17	1.05	1.30	1.28	1.18	1.38	1.25	1.17	1.34	1.26	1.20	1.20
Early term	1.12	1.06	1.18	1.13	1.08	1.19	1.10	1.05	1.15	1.11	1.08	1.08
Post-term	0.94	0.85	1.05	0.98	0.93	1.03	1.00	0.95	1.04	0.99	0.96	0.96
All COPD, J41-J44												
Full-term ²	Ref			Ref			Ref					
Extremely preterm ³				18.92	9.30	38.46	7.44	3.49	15.85	9.58	5.50	16.69
Very preterm ³				6.69	4.00	11.18	3.18	2.23	4.54	3.32	2.45	4.49
Moderately preterm	3.95	1.38	11.32	3.13	1.72	5.70	2.32	1.72	3.12	2.28	1.75	2.97
Late preterm	1.28	0.60	2.71	1.47	1.01	2.13	1.39	1.19	1.63	1.41	1.22	1.63
Early term	0.66	0.40	1.09	1.03	0.80	1.32	1.23	1.12	1.35	1.23	1.13	1.35
Post-term	0.61	0.22	1.65	1.08	0.85	1.38	1.03	0.93	1.14	0.97	0.88	1.08
Emphysema, J43												
Full-term ²	Ref			Ref			Ref					
Extremely preterm ³				31.09	7.54	128.14	16.66	4.13	67.23	21.68	6.47	71.63
Very preterm ³				9.54	3.09	29.45	2.60	0.83	8.18	4.06	1.86	8.90
Moderately preterm ³				6.28	1.95	20.17	1.84	0.68	4.98	2.62	1.23	5.58
Late preterm ³				1.09	0.34	3.44	1.16	0.70	1.93	1.15	0.72	1.81
Early term ³				0.62	0.27	1.46	1.13	0.84	1.52	1.04	0.79	1.38
Post-term ³				1.14	0.59	2.18	1.18	0.90	1.56	1.17	0.91	1.52
Other COPD, J41, J42, J44 (not J44.9)												
Full-term ²	Ref			Ref			Ref					
Extremely preterm ³				6.39	0.89	45.79	8.33	3.68	18.85	7.99	3.77	16.97
Very preterm ³				8.27	3.88	17.60	3.61	2.48	5.24	4.06	2.91	5.67
Moderately preterm ³				2.23	0.71	6.97	2.61	1.91	3.56	2.58	1.91	3.48
Late preterm ³				1.01	0.49	2.06	1.51	1.28	1.79	1.48	1.25	1.74
Early term ³				0.95	0.63	1.45	1.23	1.11	1.37	1.21	1.09	1.34
Post-term ³				1.22	0.84	1.77	1.04	0.93	1.16	1.05	0.94	1.17
Unspecified COPD, J44.9												
Full-term ²	Ref			Ref			Ref					
Extremely preterm ³				32.37	14.16	73.96	9.82	4.33	22.25	15.13	8.41	27.21
Very preterm ³				7.73	3.82	15.64	3.59	2.40	5.35	4.11	2.85	5.94
Moderately preterm ³				3.01	1.24	7.33	2.68	1.93	3.72	2.71	1.99	3.68
Late preterm ³				2.04	1.28	3.25	1.56	1.31	1.86	1.61	1.36	1.90
Early term ³				1.21	0.86	1.69	1.24	1.11	1.39	1.23	1.11	1.37
Post-term ³				0.97	0.68	1.40	1.04	0.93	1.17	1.04	0.93	1.16

¹ Models adjusted for sex, birth year birth weight z-score, multiple birth, parity, Caesarean section, mother's age, mother's hypertensive disorders during pregnancy, mother's asthma, and mother's and father's education.

² Extremely preterm: gestational age 23-27 completed weeks; very preterm: 28-31 weeks; moderately preterm: 32-33 weeks; late preterm: 34-36 weeks; early term: 37-38 weeks; full-term: 39-41 weeks; post-term: 42 weeks

³ Missing outcome values in Finland.

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Obstructive airway disease by country and age

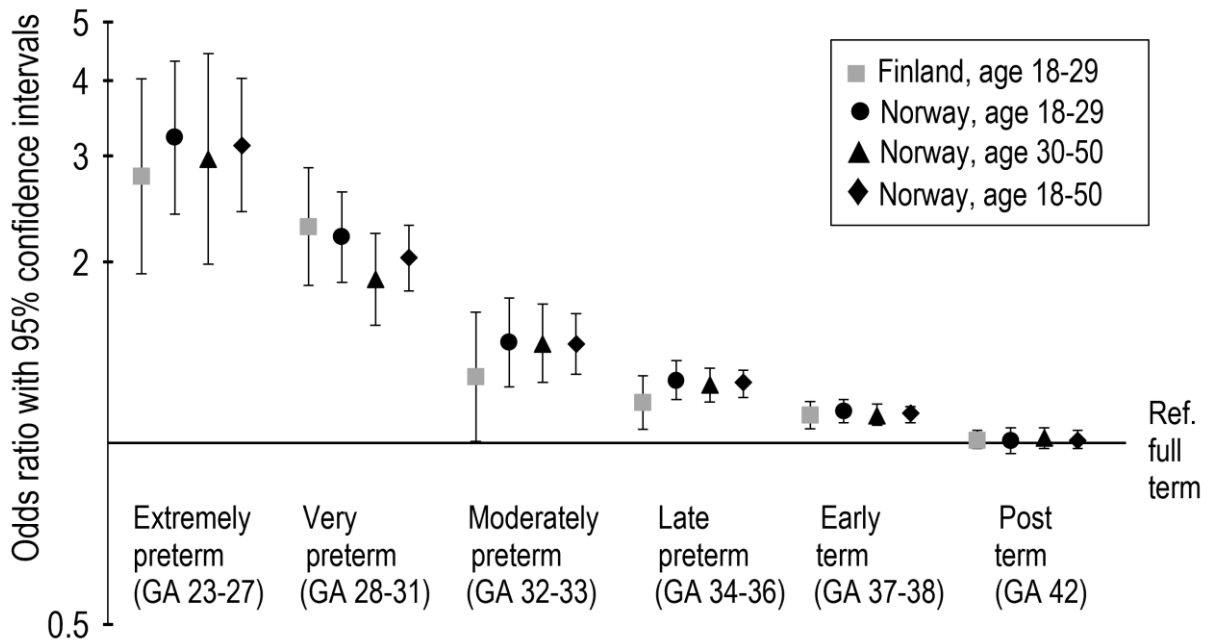
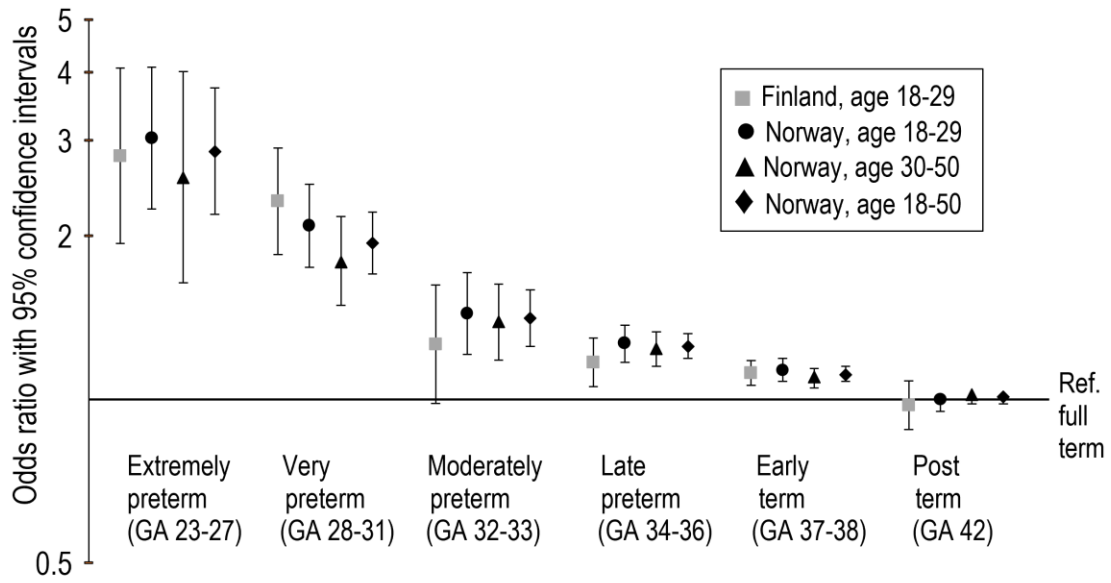


Figure 1. Associations between gestational age and any obstructive airway disease (asthma or chronic obstructive pulmonary disease), adjusted for sex and birth year. Footnote to Figure 1: GA, gestational age in weeks

A. Asthma by country and age



B. COPD by country and age

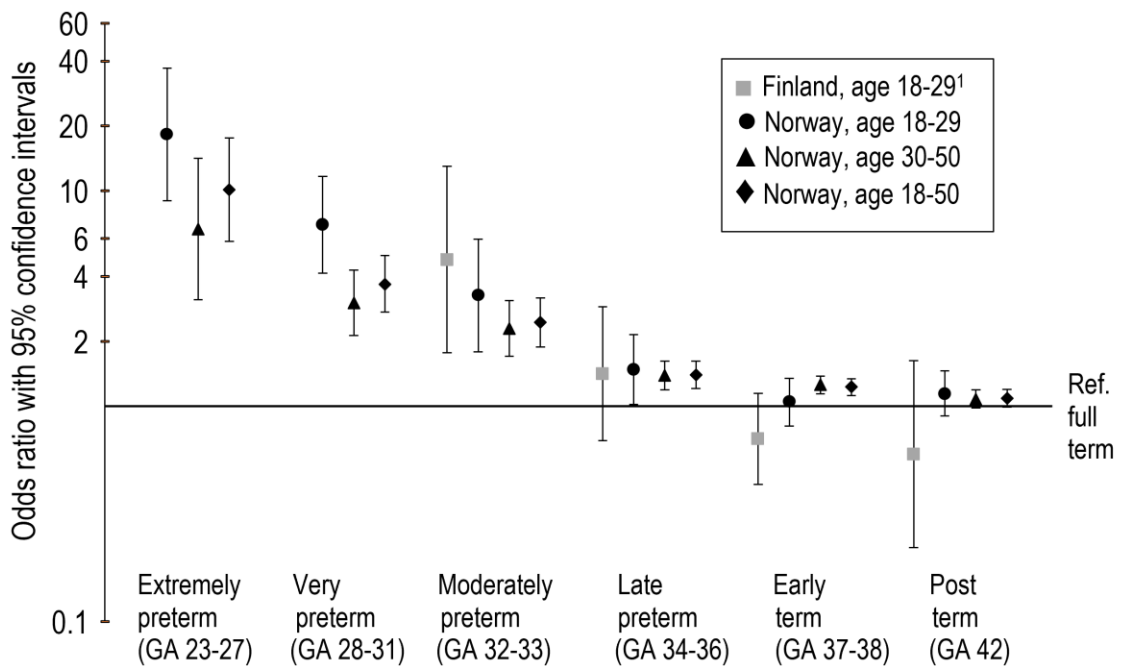


Figure 2. Associations between gestational age and asthma (panel A) and chronic obstructive pulmonary disease (COPD) (panel B), adjusted for sex and birth year

Footnotes to Figure 2: GA, gestational age in weeks 1 Missing outcome values for extremely and very preterm born in Finland

Obstructive airway disease by BPD diagnosis, Finland

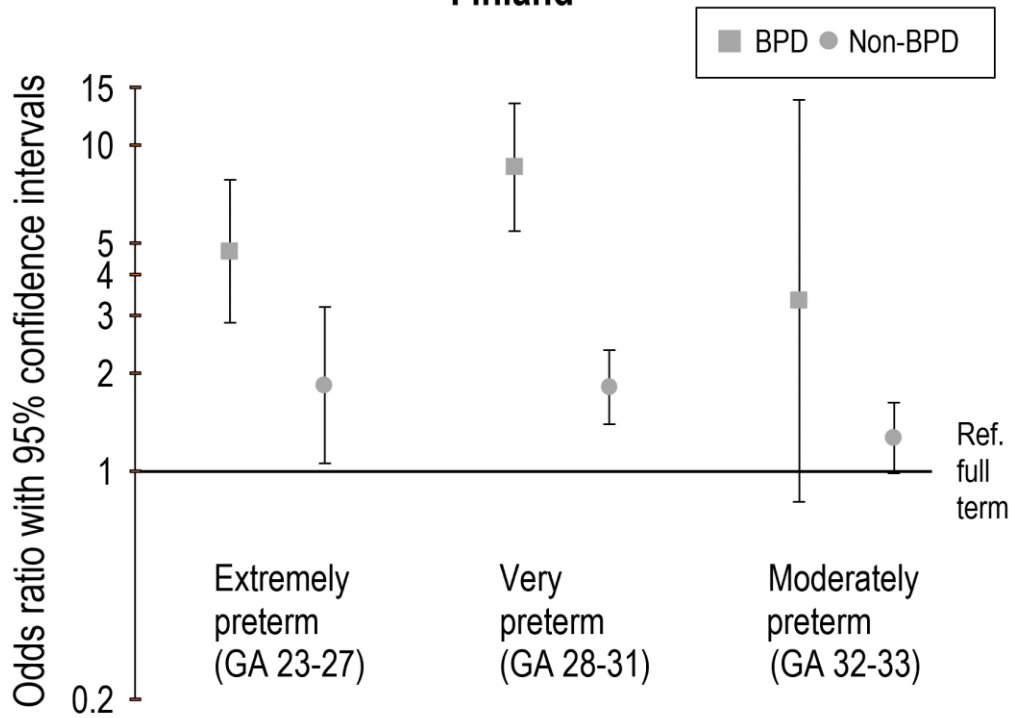


Figure 3. Associations between gestational age and obstructive airway disease (asthma or chronic obstructive pulmonary disease) at age 18-29 in children born preterm with or without a diagnosis of bronchopulmonary dysplasia (BPD). Models are adjusted for sex and birth year.

Footnote to Figure 3: GA, gestational age in weeks; BPD, bronchopulmonary dysplasia

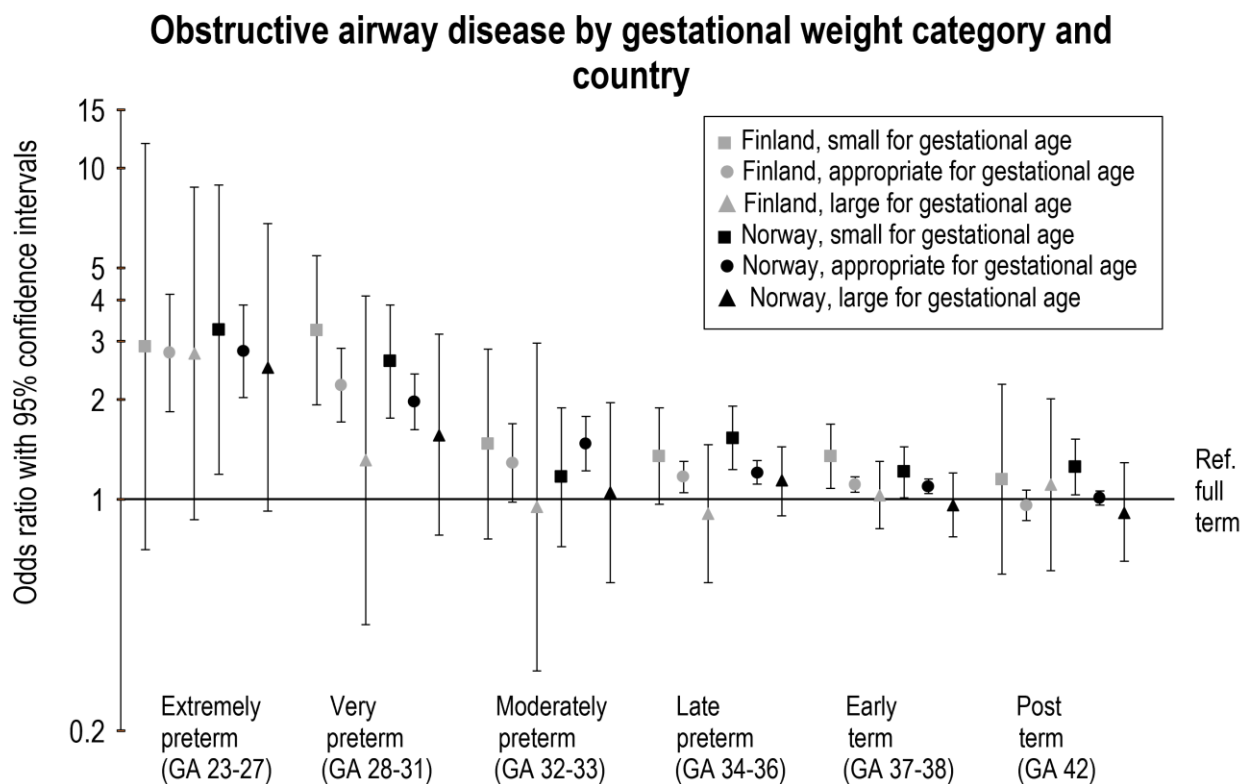


Figure 4. Associations between gestational age and obstructive airway disease (asthma or chronic obstructive pulmonary disease), at age 18-29 years in different birth weight groups. Models adjusted for sex and birth year.

Footnote to Figure 4: GA, gestational age in weeks

Preterm birth and asthma and COPD in adulthood: A nationwide register study from two Nordic countries

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Methodological appendix

Informed consent

In Finland, informed consent from the registered persons is not required for the use of pseudonymised register data for research purposes. In Norway, the Central Norway Regional Committee for Medical Research Ethics gave an exemption from the requirement to obtain informed consent from the study participants.

Permissions for register linkages

Data were linked with permissions from the Finnish Institute for Health and Welfare, Statistics Finland, and Digital and Population Data Services Authority in Finland, and the Norwegian Directorate of Health, Norwegian Institute of Public Health, and Statistics Norway in Norway.

Medical Birth Registers

Medical Birth Registers (MBR's) of both countries are based on compulsory notification of every birth [1,2]. The Finnish MBR was established in 1987 and includes information on all livebirths and stillborn infants with a birth weight of at least 500 grams, or a gestational age of 22 weeks or more [1]. The Norwegian MBR, established in 1967, includes information on every birth or late abortion from a gestational age 16 weeks onwards until 1998 [2] and from gestational age 12 weeks onwards from 1999 [3].

Covariates

Sex was defined as male vs. female, parity as number of previous live births 0 vs. ≥ 1 , Caesarean section (yes vs. no), and birth year in seven categories: 1967-1970, 1971-1975, 1976-1980, 1981-1985, 1986-1990, 1991-1995, and 1996-1999. Mother's age was obtained in full years. Mother's asthma was defined as an asthma diagnosis in the Care Register for Health Care before the birth of the child in Finland (ICD-10: J45-J46; ICD-9: 493; ICD-8: 493.00, 493.02, 493.08, 493.09) and from a pre-defined asthma variable in the MBR in Norway.

Information on mother's hypertensive disorders during pregnancy was categorised as no hypertension, chronic hypertension or gestational hypertension, and pre-eclampsia or eclampsia. This information was obtained from pre-defined variables in the MBR's of both of the countries. Additionally, in Finland, information on mother's hypertensive disorders during pregnancy was

identified from the Finnish Care Register for Health Care (CRHC) using the following diagnostic codes given during pregnancy:

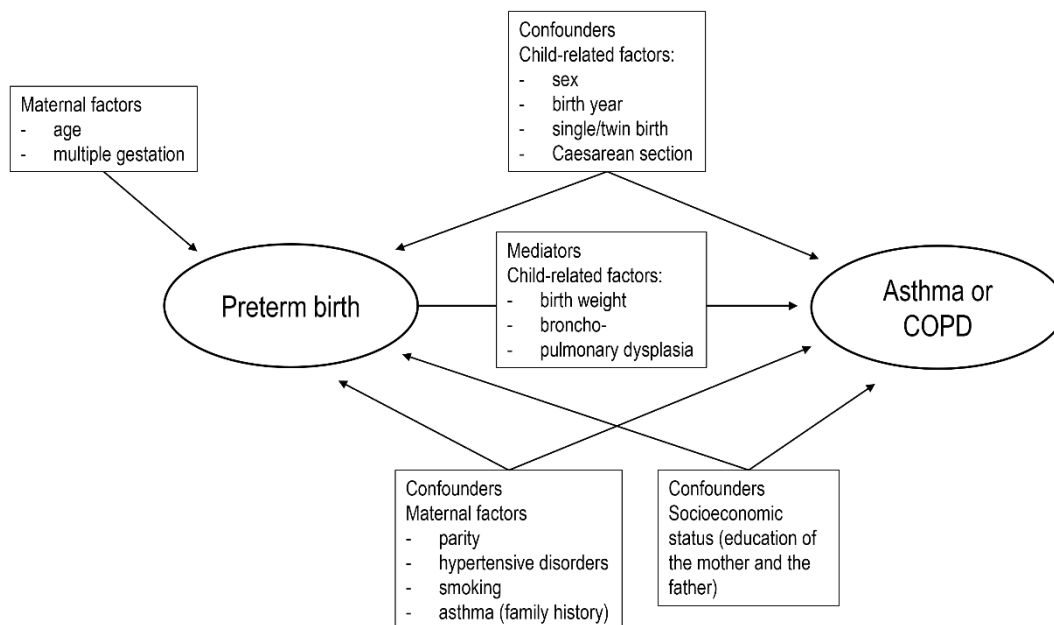
- Chronic hypertension or gestational hypertension: O10 and O13 (ICD-10) and 6420X, 6421X, 6422X, 6423A, 6423B, 6423C, 63701 (ICD-9).
- Pre-eclampsia or eclampsia: O11, O14 or O15 (ICD-10) and 6427A, 6427B, 6427C, 6424A, 6424B, 6424C, 6425A, 6425B, 6425C, 63703, 63704, 63709, 6426A, 6426B, 6426C, 63710 (ICD-9)

Data on the mother’s and father’s highest completed education during the study period were categorised according to the International Standard Classification of Education 2011 (ISCED) as low (ISCED classes 0 to 2), intermediate (ISCED classes 3 to 5), high (ISCED classes 6 to 8) or missing [4].

Of covariates only available in Finland, diagnosis of BPD was defined from the CRHC by diagnosis codes of P27.1 (ICD-10 revision) or 7707A (ICD-9 revision) during the first year of life, and maternal smoking during pregnancy was obtained from the Finnish MBR and coded as smoking, not smoking, or unknown.

Study concept

Directed acyclic graph showing the assumptions about the relationship between the variables used in this study:



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Supplementary Table 1a

Characteristics of the study population by outcome category, Finland

	No obstructive airway disease n=697 205		Obstructive airway diseases n=9 512		Asthma ¹ n=9 414		COPD ² n=147		Emphysema ³ n=39		Other COPD ⁴ n=96		Unspecified COPD ⁵ n=15	
Male, n (%)	355 709	51.0	4 319	45.4	4 269	45.4	68	46.3	20	51.3	44	45.8	4	26.7
Gestational age at birth, completed weeks, n (%)														
Extremely preterm (23-27)	821	0.1	29	0.3	29	0.3	-	0.0	-	0.0	0	0.0	0	0.0
Very preterm (28-31)	2 714	0.4	79	0.8	79	0.8	-	0.0	-	0.0	0	0.0	0	0.0
Moderately preterm (32-33) ⁶	3 983	0.6	65	0.7	63	0.7	4	2.7						
Late preterm (34-36) ⁶	26 160	3.8	397	4.2	393	4.2	8	5.4	6	15.4	22	22.9	3	20.0
Early term (37-38) ⁶	123 842	17.8	1 806	19.0	1 793	19.1	19	12.9						
Full-term (39-41) ⁷	508 862	73.0	6 746	70.9	6 666	70.8	112	76.2	33	84.6	71	74.0	12	80.0
Post-term (42) ⁷	30 823	4.4	390	4.1	389	4.1	4	2.7	0	0.0	3	3.1		
Birth weight Z-score, mean (SD)	0.00	1.05	-0.04	1.08	-0.04	1.1	-0.08	1.14	-0.22	1.07	0.06	1.12	-0.82	1.21
Small for gestational age, n (%)	17 654	2.5	304	3.2	304	3.2	4	2.7	<3	<7	<3	<7	<3	<20
Large for gestational age, n (%)	23 291	3.3	321	3.4	317	3.4	7	4.8	<3	<7	6	6.3	<3	<20
First born, n (%)	276 876	39.7	4 144	43.6	4 112	43.7	52	35.4	12	30.8	34	35.4	6	40.0
Singleton, n (%)	679 757	97.5	9 281	97.6	9 184	97.6	143	97.3	38	97.4	93	96.9	15	100.0
Caesarean section, n (%)	104 283	15.0	1 563	16.4	1 550	16.5	28	19.0	5	12.8	21	21.9	3	20.0
Bronchopulmonary dysplasia, n (%)	577	0.1	39	0.4	39	0.4	-	0.0	-	0.0	0	0.0	0	0.0
Follow-up time in years, median (IQR)	6.0	3.1-8.9	7.7	5.1-9.9	7.7	5.1-9.9	8.9	5.4-10.3	8.9	3.9-10.3	9.0	5.5-10.5	9.3	6.3- 10.7
Attained age, n (%)														
18-29 years	697 205	100.0	9 512	100.0	9 412	100.0	147	100.0	39	100.0	96	100.0	15	100.0
30-50 years	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Mother's age, mean (SD) years	28.87	5.18	28.29	5.16	28.28	5.16	28.67	5.42	28.38	6.08	28.71	5.01	29.60	6.70
Mother's smoking during pregnancy, n (%)	106 560	15.3	1 618	17.0	1 596	17.0	32	21.8	9	23.1	17	17.7	8	53.3

	No obstructive airway disease n=697 205		Obstructive airway diseases n=9 512		Asthma ¹ n=9 414		COPD ² n=147		Emphysema ³ n=39		Other COPD ⁴ n=96		Unspecified COPD ⁵ n=15	
Mother's hypertensive disorders during pregnancy														
No	659 363	94.6	8 970	94.3	8 878	94.3	134	91.2	34	87.2	90	93.8	13	86.7
Chronic or gestational hypertension	19 848	2.9	262	2.8	257	2.7	7	4.8	4	12.7	6	6.2	<3	<20
Pre-eclampsia or eclampsia	17 994	2.6	280	2.9	277	2.9	6	4.1						
Mother's history of asthma, n (%)	8 463	1.2	242	2.5	240	2.5	<3	<7	<3	<7	0	0.0	0	0.0
Mother's education ^{8,9}														
Unknown	3 506	0.5	53	0.6	53	0.6	27	18.4	8	20.5	0	0.0	0	0.0
Low	70 612	10.1	1 056	11.1	1 040	11.0					17	17.7	3	20.0
Intermediate	458 600	65.8	6 397	67.3	6 334	67.3	94	63.9	23	59.0	62	64.6	10	66.7
High	164 487	23.6	2 006	21.1	1 985	21.1	26	17.7	8	20.5	17	17.7	2	13.3
Father's education ^{8,9}														
Unknown	10 519	1.5	157	1.7	156	1.7	33	22.4	8	20.5	21	21.9	0	0.0
Low	126 158	18.1	1 870	19.7	1 851	19.7							5	33.3
Intermediate	420 279	60.3	5 788	60.8	5 721	60.8	92	62.6	26	66.7	59	61.5	7	46.7
High	140 249	20.1	1 697	17.8	1 684	17.9	22	15.0	5	12.8	16	16.7	3	20.0

COPD chronic obstructive pulmonary disease; GA gestational age; IQR interquartile range; N/A not available; SD standard deviation

¹ ICD-10 codes for asthma: J45-J46

² ICD-10 codes for COPD: J41-J44

³ ICD-10 code for emphysema: J43

⁴ ICD-10 codes for other COPD: J41-J42, J44.0-J44.8

⁵ ICD-10 code for unspecified COPD: J44.9

⁶ Figures for moderately preterm, late preterm and early term combined where n<3

⁷ Figures for full-term and post-term combined where n<3

⁸ Figures for unknown and low education combined where n<3

⁹ Figures for intermediate and high education combined where n<3

Supplementary Table 1b

Characteristics of the study population by outcome category, Norway

	No obstructive airway disease n=1 633 416		Obstructive airway diseases n=36 112		Asthma ¹ n=33 506		COPD ² n=4 145		Emphysema ³ n=479		Other COPD ⁴ n=1 219		Unspecified COPD ⁵ n=2 894	
Male, n (%)	836 844	51.2	16 023	44.4	14 477	43.2	2 281	55.0	262	54.7	590	48.4	1 668	57.6
Gestational age at birth, completed weeks, n (%)														
Extremely preterm (23-27) ⁶	1 293	0.1	66	0.2	59	0.2	14	0.3	3	0.6	19	1.6	12	0.4
Very preterm (28-31) ⁶	6 669	0.4	262	0.7	239	0.7	45	1.1	6	1.3			31	1.1
Moderately preterm (32-33)	10 571	0.6	309	0.9	278	0.8	56	1.4	7	1.5	14	1.1	42	1.5
Late preterm (34-36)	63 422	3.9	1 635	4.5	1 516	4.5	200	4.8	19	4.0	49	4.0	157	5.4
Early term (37-38)	213 216	13.1	4 929	13.6	4 564	13.6	589	14.2	60	12.5	165	13.5	418	14.4
Full-term (39-41)	209 361	12.8	4 642	12.9	4 300	12.8	550	13.3	71	14.8	165	13.5	381	13.2
Post-term (42)	1 128 884	69.1	24 269	67.2	22 550	67.3	2 691	64.9	313	65.3	807	66.2	1 853	64.0
Birth weight Z-score, mean (SD)	-0.21	1.11	-0.31	1.15	-0.30	1.15	-0.49	1.19	-0.44	1.20	-0.45	1.14	-0.54	1.22
Small for gestational age, n (%)	75 160	4.6	2 245	6.2	2 031	6.1	358	8.6	35	7.3	102	8.4	274	9.5
Large for gestational age, n (%)	46 197	2.8	947	2.6	885	2.6	93	2.2	19	4.0	16	1.3	67	2.3
First born, n (%)	672 665	41.2	15 303	42.4	14 370	42.9	1 514	36.5	158	33.0	451	37.0	1 054	36.4
Singleton, n (%)	1 599 400	97.9	35 403	98.0	32 848	98.0	4 063	98.0	472	98.5	1 192	97.8	2 837	98.0
Caesarean section, n (%)	132 987	8.1	2 840	7.9	2 725	8.1	198	4.8	31	6.5	71	5.8	110	3.8
Bronchopulmonary dysplasia, n (%)	-0.21	1.11	-0.31	1.15	-0.30	1.15	-0.49	1.19	-0.44	1.20	-0.45	1.14	-0.54	1.22
Follow-up time in years, median (IQR)	10	7.5- 10.0	10.0	10.0- 10.0	10.0	10.0- 10.0	10.0	10.0- 10.0	10.0	10.0- 10.0	10.0	10.0- 10.0	10.0	10.0- 10.0
Attained age, n (%)														
18-29 years	612 631	37.5	10 393	28.8	10 190	30.4	346	8.3	48	10.0	149	12.2	160	5.5
30-50 years	1 020 785	62.5	25 719	71.2	23 316	69.6	3 799	91.7	431	90.0	1 070	87.8	2 734	94.5
Mother's age, mean (SD) years	27.40	5.24	26.90	5.24	26.96	5.21	26.10	5.57	26.36	5.63	26.40	5.59	25.89	5.60
Mother's smoking during pregnancy, n (%) ^{1,2}	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A

	No obstructive airway disease n=1 633 416		Obstructive airway diseases n=36 112		Asthma ¹ n=33 506		COPD ² n=4 145		Emphysema ³ n=479		Other COPD ⁴ n=1 219		Unspecified COPD ⁵ n=2 894	
Mother's hypertensive disorders during pregnancy														
No	1 561 548	95.6	344 05	95.3	31 897	95.2	3 980	96.0	464	96.9	1 170	96.0	2 776	95.9
Chronic or gestational hypertension	26 731	1.6	608	1.7	569	1.7	63	1.5	9	1.9	16	1.3	40	1.4
Pre-eclampsia or eclampsia	45 137	2.8	1 099	3.0	1 040	3.1	102	2.5	6	1.3	33	2.7	78	2.7
Mother's history of asthma, n (%)	35 121	2.2	991	2.7	961	2.9	63	1.5	4	0.8	20	1.6	41	1.4
Mother's education ⁷														
Unknown	10 437	0.6	104	0.3	97	0.3	14	0.3	212	44.3	3	0.2	12	0.4
Low	397 911	24.4	10 135	28.1	9 008	26.9	1 768	42.7			501	41.1	1 275	44.1
Intermediate	754 409	46.2	16 540	45.8	15 390	45.9	1 837	44.3	200	41.8	532	43.6	1 289	44.5
High	470 659	28.8	9 333	25.8	9 011	26.9	526	12.7	67	14.0	183	15.0	318	11.0
Father's education														
Unknown	24 972	1.5	569	1.6	513	1.5	85	2.1	10	2.1	26	2.1	61	2.1
Low	363 972	22.3	8 928	24.7	7 947	23.7	1 524	36.8	176	36.7	424	34.8	1 106	38.2
Intermediate	818 584	50.1	18 106	50.1	16 890	50.4	1 972	47.6	232	48.4	579	47.5	1 378	47.6
High	425 888	26.1	8 509	23.6	8 156	24.3	564	13.6	61	12.7	190	15.6	349	12.1

COPD chronic obstructive pulmonary disease; IQR interquartile range; N/A not available; SD standard deviation

¹ ICD-10 codes for asthma: J45-J46

² ICD-10 codes for COPD: J41-J44

³ ICD-10 code for emphysema: J43

⁴ ICD-10 codes for other COPD: J41-J42, J44.0-J44.8

⁵ ICD-10 code for unspecified COPD: J44.9

⁶ Figures for extremely preterm, very preterm combined where n<3

⁷ Figures for unknown and low education combined where n<3

Supplementary Table 2

Number of deaths, emigrations, and outcomes in the gestational age categories

	Death during the follow-up	Emigration during the follow-up	Obstructive airway diseases	Asthma	COPD				
	n (%)	n (%)	n (%)	n (%)	Median (IQR) number of episodes	Median (IQR) age of the first care episode for asthma ¹	n (%)	Median (IQR) number of episodes	Median (IQR) age of the first care episode for COPD ¹
Finland (N=706 717)									
Extremely preterm (23-27)	9 (1.1)	9 (1.1)	29 (3.4)	29 (3.4)	4 (2-7)	18.7 (18.3-19.4)	(0.0)		
Very preterm (28-31)	26 (0.9)	39 (1.4)	79 (2.8)	79 (2.8)	3 (2-5)	18.8 (18.3-20.5)	(0.0)		
Moderately preterm (32-33)	30 (0.7)	68 (1.7)	65 (1.6)	63 (1.6)	2 (1-4)	18.8 (18.3-20.3)	4 (0.1)	1.5 (1-2)	(19.3) 19.0-19.9
Late preterm (34-36)	157 (0.6)	507 (1.9)	397 (1.5)	393 (1.3)	2 (1-4)	19.5 (18.4-21.8)	8 (0.03)	1 (1-1)	(21.6) 20.2-23.4
Early term (37-38)	675 (0.5)	2 530 (2.0)	1 806 (1.4)	1 793 (1.4)	2 (1-4)	19.6 (18.4-22.0)	19 (0.02)	1 (1-1)	(20.7) 18.6-23.8
Full-term (39-41)	2 581 (0.5)	10 586 (2.1)	6 746 (1.3)	6 666 (1.3)	2 (1-4)	19.6 (18.5-22.0)	112 (0.02)	1 (1-2)	(20.9) 19.2-23.9
Post-term (42)	154 (0.5)	682 (2.2)	390 (1.3)	389 (1.3)	2 (1-4)	19.4 (18.4-21.9)	4 (0.01)	1(1-1)	(19.9) 18.7-20.9
Norway (N=1 669 528)									
Extremely preterm (23-27)	9 (0.7)	14 (1.4)	68 (4.9)	61 (4.4)	2 (1-4)	24.7 (17.7-31.3)	14 (1.0)	1 (1-3)	(28.8) 19.3-37.2
Very preterm (28-31)	45 (0.7)	130 (1.9)	263 (3.7)	236 (3.4)	2 (1-3)	27.3 (20.3-38.3)	46 (0.7)	1 (1-3)	(35.9) 25.9-40.0
Moderately preterm (32-33)	87 (0.8)	209 (1.9)	312 (2.8)	281 (2.6)	2 (1-3)	30.8 (21.8-38.0)	56 (0.5)	2 (1-3)	(41.0) 34.3-44.8
Late preterm (34-36)	429 (0.7)	1 379 (2.1)	1 643 (2.5)	1 522 (2.3)	2 (1-3)	31.6 (22.4-39.7)	202 (0.3)	1 (1-2.5)	(41.4) 35.2-44.8
Early term (37-38)	1 327 (0.6)	4 623 (2.1)	4 929 (2.3)	4 564 (2.1)	2 (1-3)	31.7 (22.2-40.0)	589 (0.3)	1 (1-2)	(41.3) 35.7-44.8
Full-term (39-41)	6 490 (0.6)	24 502 (2.1)	24 277 (2.1)	22 556 (2.0)	2 (1-3)	32.9 (23.3-40.3)	2 693 (0.2)	1 (1-2)	(40.8) 35.4-44.7
Post-term (42)	1 303 (0.6)	4 680 (2.2)	4 716 (2.2)	4 370 (2.0)	2 (1-3)	33.3 (23.6-40.5)	556 (0.3)	1 (1-2)	(40.9) 35.3-44.6

¹ The age of the first care episode after age 18 in Finland after age 18 and year 2008 in Norway.

Supplementary Table 3

Associations between gestational age and obstructive airway diseases (asthma or chronic obstructive pulmonary disease), analogous to Figure 1.

	Finland			Norway			Age 30 to 50 years		Age 18 to 50 years			
	Age 18 to 29 years			Age 18 to 29 years			OR	95% CI	OR	95% CI	OR	95% CI
	OR	95% CI		OR	95% CI							
Model 1¹												
Full-term ²	Ref			Ref			Ref					
Extremely preterm	2.77	1.91	4.02	3.22	2.40	4.31	2.96	1.98	4.43	3.12	2.42	4.03
Very preterm	2.29	1.83	2.87	2.20	1.85	2.61	1.87	1.57	2.23	2.03	1.79	2.30
Moderately preterm	1.29	1.01	1.65	1.47	1.24	1.74	1.46	1.26	1.70	1.46	1.30	1.64
Late preterm	1.17	1.05	1.29	1.27	1.18	1.37	1.25	1.17	1.33	1.26	1.19	1.32
Early term	1.11	1.06	1.17	1.13	1.08	1.18	1.11	1.07	1.16	1.12	1.08	1.15
Post-term	0.97	0.87	1.07	1.01	0.96	1.06	1.02	0.98	1.06	1.01	0.98	1.05
Model 2³												
Full-term ²	Ref			Ref			Ref					
Extremely preterm	2.90	2.51	4.18	3.29	2.45	4.42	3.14	2.09	4.70	3.24	2.50	4.18
Very preterm	2.26	1.79	2.31	2.15	1.81	2.56	1.90	1.59	2.27	2.02	1.78	2.30
Moderately preterm	1.24	1.31	1.65	1.45	1.22	1.72	1.48	1.27	1.72	1.46	1.30	1.65
Late preterm	1.17	1.21	1.34	1.28	1.18	1.38	1.26	1.18	1.35	1.27	1.20	1.34
Early term	1.12	1.08	1.15	1.13	1.08	1.18	1.11	1.07	1.16	1.12	1.08	1.15
Post-term	0.99	0.96	1.02	0.98	0.94	1.04	1.00	0.96	1.04	0.99	0.96	1.02

¹ Model 1 is adjusted for sex and birth year.

² Extremely preterm: gestational age 23-27 completed weeks; very preterm: 28-31 weeks; moderately preterm: 32-33 weeks; late preterm: 34-36 weeks; early term: 37-38 weeks; full-term: 39-41 weeks; post-term: 42 weeks

³ Model 2 adjusted for sex, birth year, birth weight z-score, multiple birth, parity, Caesarean section, mother's age, mother's asthma, mother's hypertensive disorders during pregnancy, and mother's and father's highest education.

OR odds ratio; CI confidence interval

Supplementary Table 4

Associations between gestational age and diagnosis of obstructive airway diseases (asthma or chronic obstructive pulmonary disease) from a pulmonology specialist.

	Finland											
	18-29 years			18-29 years			30-50 years			18-50 years		
	OR	95% CI		OR	95% CI		OR	95% CI		OR	95% CI	
Model 1¹												
Full-term ²	Ref			Ref			Ref					
Extremely preterm	3.27	2.16	4.96	3.39	2.36	4.88	3.79	2.49	5.77	3.55	2.66	4.74
Very preterm	2.71	2.11	3.49	2.21	1.78	2.75	1.92	1.57	2.36	2.05	1.76	2.38
Moderately preterm	1.29	0.96	1.74	1.41	1.13	1.76	1.57	1.33	1.86	1.51	1.31	1.73
Late preterm	1.23	1.09	1.38	1.30	1.18	1.43	1.28	1.19	1.38	1.29	1.21	1.37
Early term	1.08	1.01	1.15	1.13	1.07	1.21	1.14	1.08	1.19	1.14	1.09	1.18
Post-term	0.91	0.80	1.04	1.00	0.94	1.07	1.02	0.97	1.07	1.01	0.97	1.05
Model 2³												
Full-term ²	Ref			Ref			Ref					
Extremely preterm	3.38	2.22	5.13	3.46	2.40	4.98	4.05	2.66	6.16	3.69	2.77	4.93
Very preterm	2.67	2.06	3.46	2.12	1.71	2.65	1.95	1.59	2.40	2.03	1.74	2.37
Moderately preterm	1.29	0.95	1.74	1.37	1.09	1.71	1.58	1.33	1.87	1.50	1.30	1.72
Late preterm	1.23	1.08	1.39	1.29	1.17	1.43	1.29	1.20	1.40	1.29	1.22	1.38
Early term	1.08	1.01	1.15	1.13	1.06	1.20	1.13	1.08	1.19	1.13	1.09	1.18
Post-term	0.89	0.78	1.01	0.98	0.91	1.04	0.99	0.95	1.04	0.99	0.95	1.03

¹ Model 1 is adjusted for sex and birth year.

² Extremely preterm: gestational age 23-27 completed weeks; very preterm: 28-31 weeks; moderately preterm: 32-33 weeks; late preterm: 34-36 weeks; early term: 37-38 weeks; full-term: 39-41 weeks; post-term: 42 weeks

³ Model 2 adjusted for sex, birth year, birth weight z-score, multiple birth, parity, Caesarean section, mother's age, mother's asthma, mother's hypertensive disorders during pregnancy, and mother's and father's highest education.

OR odds ratio; CI confidence interval

Supplementary Table 5

Associations between gestational age and inpatient diagnosis of obstructive airway diseases (asthma or chronic obstructive pulmonary disease).

	Finland											
	18-29 years			18-29 years			30-50 years			18-50 years		
	OR	95% CI		OR	95% CI		OR	95% CI		OR	95% CI	
Model 1¹												
Full-term ²	Ref			Ref			Ref					
Extremely preterm ³				4.35	1.63	11.63	4.29	1.38	13.35	4.37	2.08	9.18
Very preterm	2.62	1.08	6.34	2.72	1.50	4.94	2.59	1.58	4.25	2.65	1.79	3.93
Moderately preterm	1.09	0.35	3.41	1.96	1.11	3.47	2.63	1.83	3.80	2.39	1.74	3.29
Late preterm	0.74	0.44	1.27	1.12	0.82	1.54	1.52	1.25	1.85	1.38	1.17	1.63
Early term	1.13	0.91	1.41	1.07	0.88	1.29	1.18	1.04	1.34	1.14	1.02	1.27
Post-term	0.94	0.60	1.46	0.98	0.80	1.18	1.09	0.96	1.24	1.05	0.95	1.17
Model 2⁴												
Full-term ²	Ref			Ref			Ref					
Extremely preterm ³				4.24	1.59	11.29	4.61	1.47	14.40	4.47	2.13	9.36
Very preterm	2.62	1.08	6.34	2.32	1.28	4.23	2.58	1.57	4.24	2.49	1.67	3.72
Moderately preterm	1.09	0.35	3.41	1.71	0.96	3.07	2.55	1.76	3.68	2.25	1.63	3.10
Late preterm	0.74	0.44	1.27	1.06	0.78	1.46	1.49	1.22	1.82	1.34	1.13	1.59
Early term	1.13	0.91	1.41	1.03	0.86	1.25	1.15	1.01	1.31	1.12	1.00	1.24
Post-term	0.94	0.60	1.46	0.92	0.76	1.12	1.04	0.91	1.18	1.00	0.90	1.12

¹ Model 1 is adjusted for sex and birth year.

² Extremely preterm: gestational age 23-27 completed weeks; very preterm: 28-31 weeks; moderately preterm: 32-33 weeks; late preterm: 34-36 weeks; early term: 37-38 weeks; full-term: 39-41 weeks; post-term: 42 weeks

³ Not available for Finland

⁴ Model 2 adjusted for sex, birth year, birth weight z-score, multiple birth, parity, Caesarean section, mother's age, mother's asthma, mother's hypertensive disorders during pregnancy, and mother's and father's highest education.

OR odds ratio; CI confidence interval

Supplementary Table 6

Associations between gestational age and obstructive airway diseases (asthma or chronic obstructive pulmonary disease), excluding twins.

	Finland			Norway			Age 30 to 50 years		Age 18 to 50 years			
	Age 18 to 29 years			Age 18 to 29 years			OR	95% CI	OR	95% CI		
	OR	95% CI		OR	95% CI		OR	95% CI	OR	95% CI		
Model 1¹												
Full-term ²	Ref			Ref			Ref					
Extremely preterm	3.01	2.01	4.49	3.26	2.37	4.50	2.90	1.89	4.46	3.12	2.37	4.12
Very preterm	2.13	1.63	2.79	2.26	1.87	2.73	1.86	1.53	2.25	2.04	1.78	2.35
Moderately preterm	1.36	1.03	1.79	1.52	1.26	1.83	1.43	1.21	1.69	1.47	1.29	1.67
Late preterm	1.16	1.04	1.30	1.27	1.17	1.38	1.25	1.16	1.34	1.26	1.19	1.33
Early term	1.13	1.07	1.19	1.14	1.09	1.20	1.13	1.08	1.18	1.13	1.10	1.17
Post-term	0.96	0.87	1.07	1.00	0.96	1.06	1.02	0.98	1.06	1.01	0.98	1.05
Model 2³												
Full-term ²	Ref			Ref			Ref					
Extremely preterm	3.03	2.03	4.53	3.27	2.37	4.51	3.04	1.98	4.68	3.18	2.41	4.20
Very preterm	2.01	1.54	2.64	2.15	1.78	2.60	1.86	1.53	2.25	2.00	1.74	2.29
Moderately preterm	1.29	0.98	1.70	1.45	1.20	1.75	1.42	1.20	1.67	1.43	1.26	1.62
Late preterm	1.13	1.01	1.26	1.26	1.16	1.37	1.25	1.16	1.34	1.25	1.18	1.32
Early term	1.12	1.06	1.18	1.13	1.08	1.19	1.12	1.08	1.17	1.13	1.09	1.16
Post-term	0.94	0.84	1.04	0.98	0.94	1.04	1.00	0.96	1.04	0.99	0.96	1.02

¹ Model 1 is adjusted for sex and birth year

² Extremely preterm: gestational age 23-27 completed weeks; very preterm: 28-31 weeks; moderately preterm: 32-33 weeks; late preterm: 34-36 weeks; early term: 37-38 weeks; full-term: 39-41 weeks; post-term: 42 weeks

³ Model 2 adjusted for sex, birth year, birth weight z-score, multiple birth, parity, Caesarean section, mother's age, mother's asthma, mother's hypertensive disorders during pregnancy, and mother's and father's highest education.

OR odds ratio; CI confidence interval

Supplementary Table 7

Associations between gestational age and obstructive airway diseases (asthma or chronic obstructive pulmonary disease), at age 18-29 years in Finland. Model was adjusted for sex, birth year, birth weight z-score, multiple birth, parity, Caesarean section, mother's age, mother's asthma, mother's hypertensive disorders during pregnancy, and mother's and father's highest education, and maternal smoking during pregnancy.

	OR	95% CI	
Full-term (39-41)	Ref		
Extremely preterm (23-27)	2.78	1.91	4.03
Very preterm (28-31)	2.16	1.72	2.72
Moderately preterm (32-33)	1.22	0.95	1.57
Late preterm (34-36)	1.14	1.02	1.26
Early term (37-38)	1.11	1.05	1.17
Post-term (42)	0.94	0.84	1.04

OR odds ratio; CI confidence interval

Supplementary Table 8

Hazard ratios for associations between gestational age and obstructive airway diseases (asthma or chronic obstructive pulmonary disease).

	Finland			Norway		
	Age 18 to 29 years			Age 18 to 29 years		
	OR	95% CI		OR	95% CI	
Model 1¹						
Full-term ²	Ref			Ref		
Extremely preterm	2.75	1.91	3.96	2.94	2.27	3.81
Very preterm	2.28	1.82	2.84	2.06	1.77	2.39
Moderately preterm	1.29	1.01	1.65	1.39	1.20	1.61
Late preterm	1.17	1.06	1.29	1.23	1.15	1.31
Early term	1.11	1.06	1.17	1.12	1.07	1.16
Post-term	0.96	0.87	1.07	1.02	0.97	1.06
Model 2³						
Full-term ²						
Extremely preterm	2.85	1.97	4.11	3.01	2.32	3.91
Very preterm	2.22	1.77	2.79	2.02	1.73	2.35
Moderately preterm	1.27	0.99	1.62	1.37	1.18	1.60
Late preterm	1.16	1.05	1.29	1.24	1.15	1.32
Early term	1.12	1.06	1.18	1.12	1.07	1.17
Post-term	0.93	0.84	1.03	1.00	0.96	1.05

¹ Model 1 is adjusted for sex and birth year

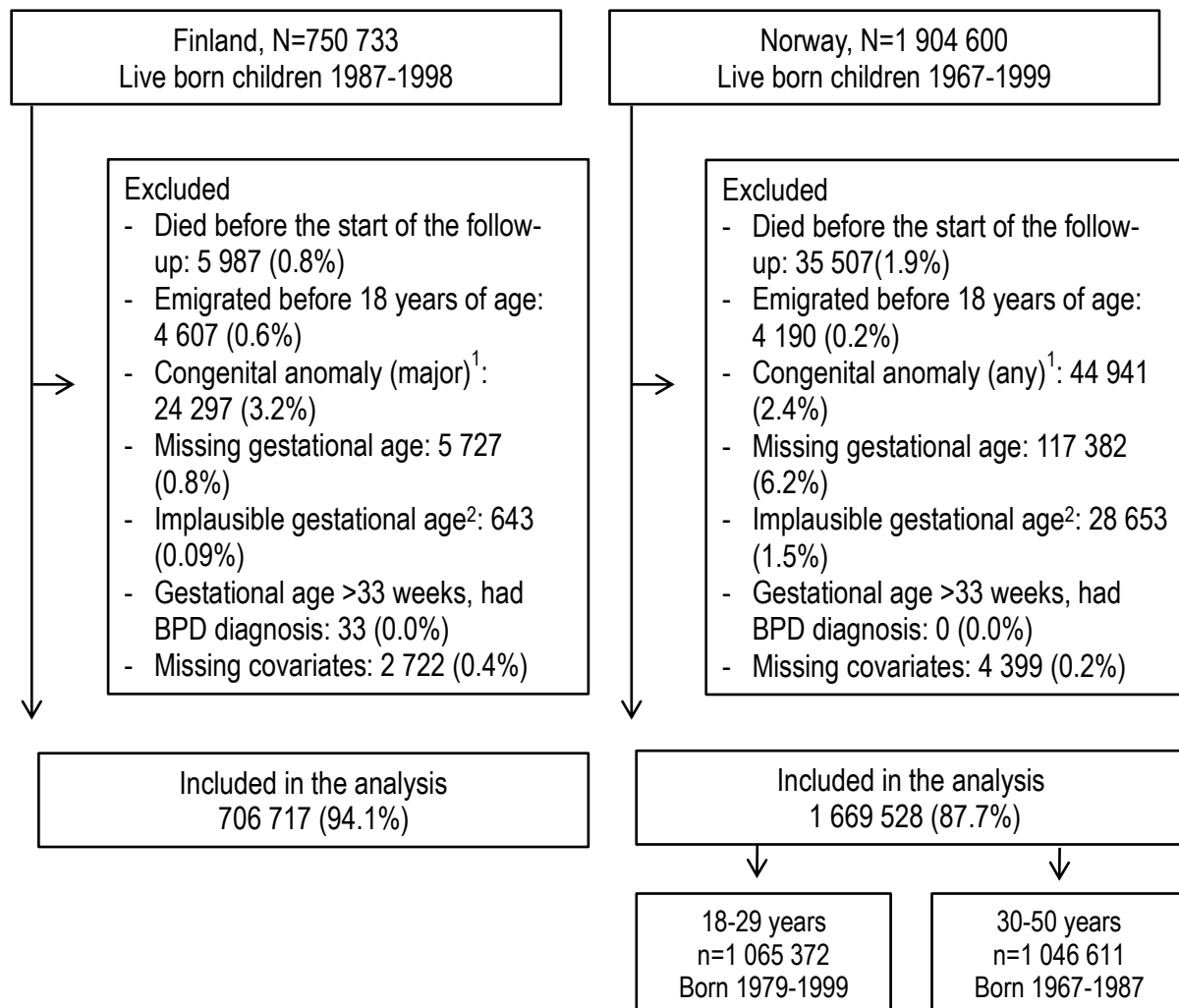
² Extremely preterm: gestational age 23-27 completed weeks; very preterm: 28-31 weeks; moderately preterm: 32-33 weeks; late preterm: 34-36 weeks; early term: 37-38 weeks; full-term: 39-41 weeks; post-term: 42 weeks

³ Model 2 adjusted for sex, birth year, birth weight z-score, multiple birth, parity, Caesarean section, mother's age, mother's asthma, mother's hypertensive disorders during pregnancy, and mother's and father's highest education.

HR hazard ratio; CI Confidence Interval

Supplementary Figure 1

Selection of study participants in Finland and Norway.

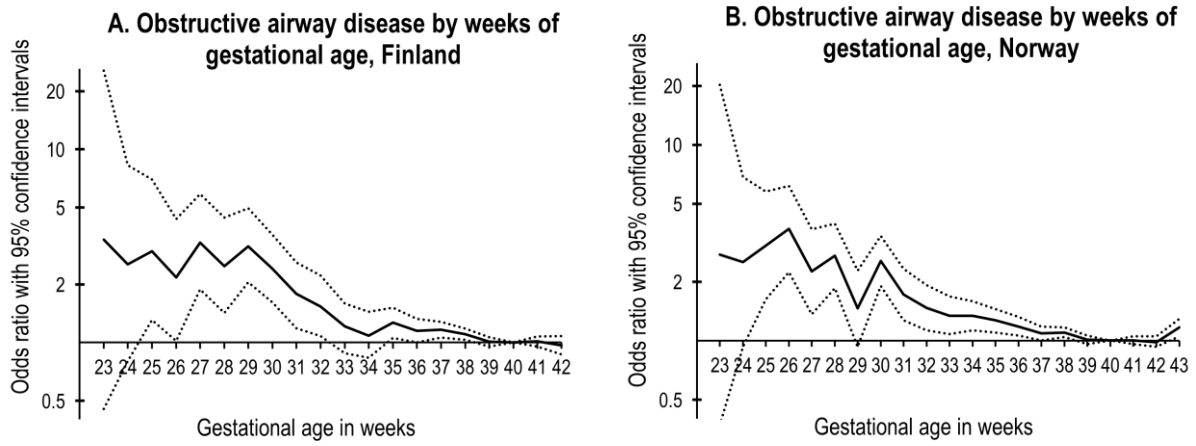


¹ In Finland, congenital anomalies were ascertained from the Register of Congenital Malformations (individuals with major congenital anomalies excluded) and in Norway from the Norwegian Medical Birth Register (individuals with any congenital anomaly at birth excluded)

² Implausible gestational age defined as birth weight z-score less than -6 SD, birth weight less than 300 grams, or GA less than 37+0 weeks and birth weight z-score larger than 4 SD.

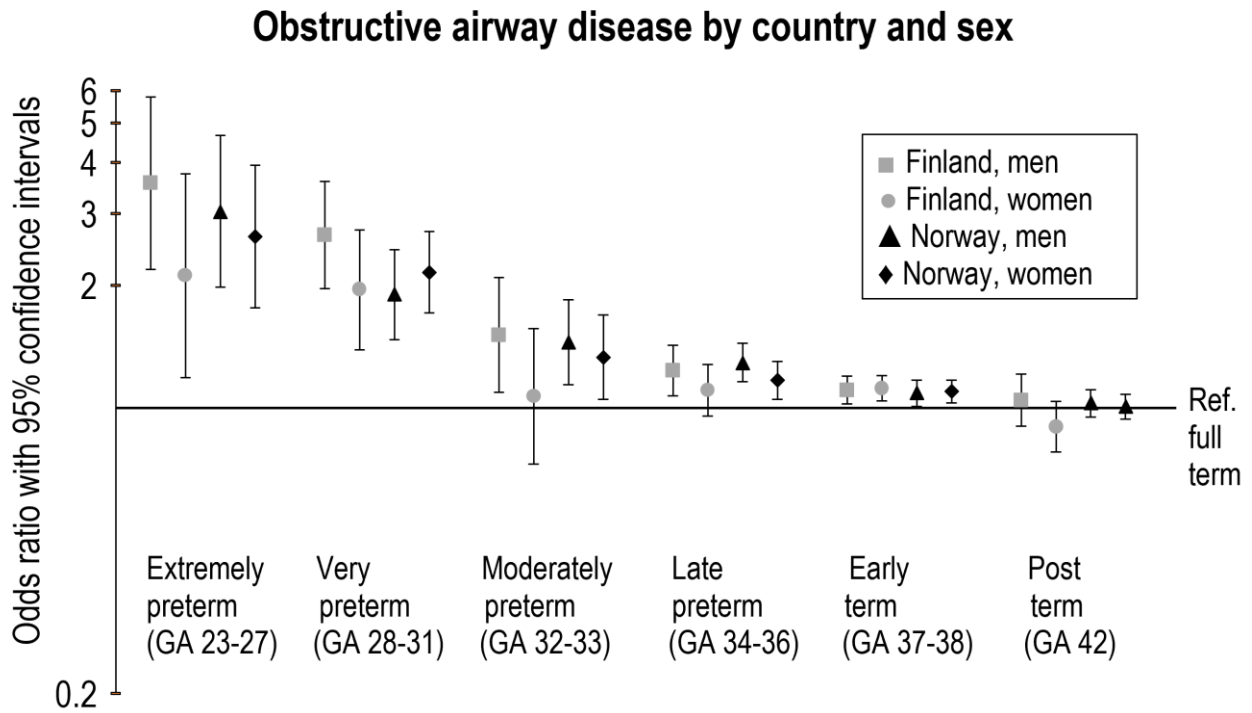
Supplementary Figure 3

Associations between gestational age in completed weeks and obstructive airway diseases (asthma or chronic obstructive pulmonary disease), at age 18-29 years. The models are adjusted for sex and birth year.



Supplementary Figure 4

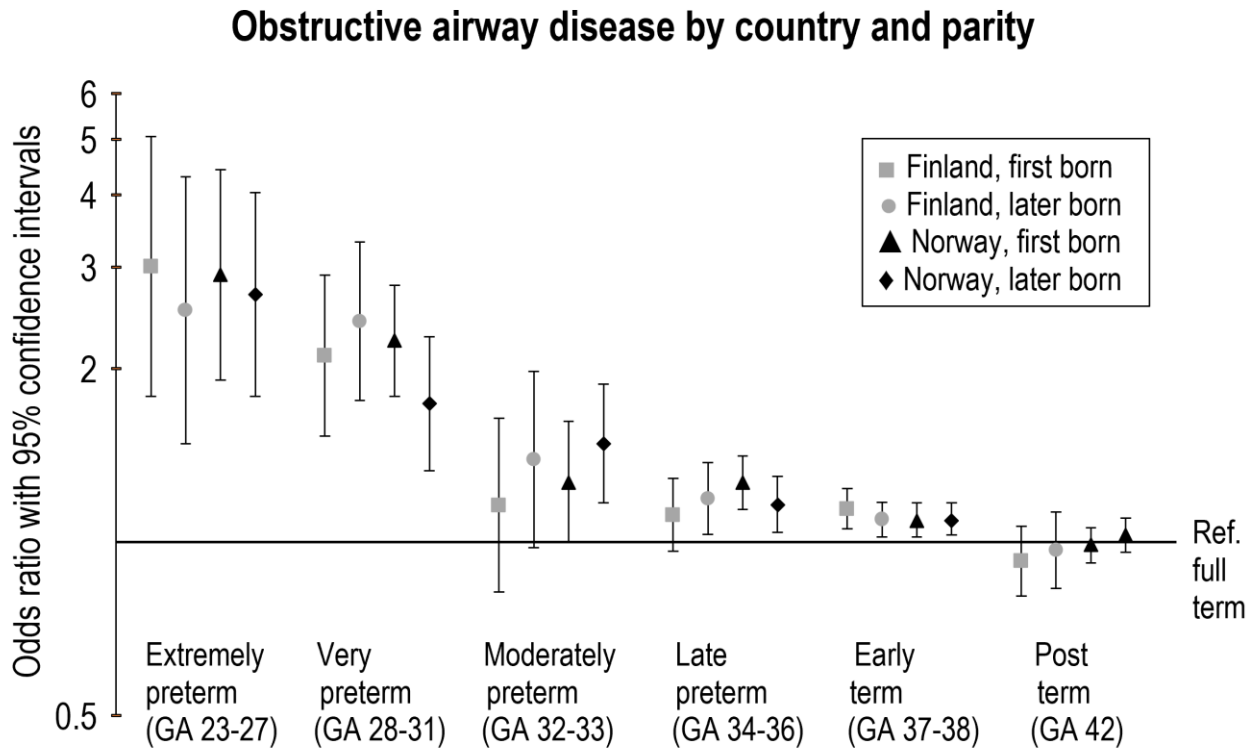
Associations between gestational age and obstructive airway diseases (asthma or chronic obstructive pulmonary disease) at age 18-29 by country and sex. Models are adjusted for sex and birth year.



GA, gestational age in weeks

Supplementary Figure 5

Associations between gestational age and obstructive airway diseases (asthma or chronic obstructive pulmonary disease) at age 18-29 by country and parity. Models are adjusted for sex and birth year.



GA, gestational age in weeks