Geographical Differences in Preterm delivery rates in Sweden: A population-based Cohort Study

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Geographical differences in preterm delivery rates in Sweden: a population-based cohort study

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ABSTRACT

Introduction: Preterm delivery is a major global public health challenge. The objective of this study was to determine how the preterm delivery rates differ throughout a country of very high human-development index and to explore rural versus urban environmental and socio-economic factors which might be responsible for this variation. **Material and methods:** A population-based study was performed using data from the Swedish Medical Birth Register 1998 to 2013. Sweden was chosen as a model because of its validated routinely collected data and availability of individual social data. The total population comprised 1 335 802 singleton births. Multiple linear regression was used to adjust gestational age for known risk factors (maternal smoking, ethnicity, maternal education, maternal age, height, fetal gender, maternal diabetes, maternal hypertension and parity). A second and a third model were subsequently fitted allowing separate intercepts for each municipality (as fixed or random effects). Adjusted gestational ages were converted to preterm delivery rates and mapped to maternal residential municipalities. Additionally, the effects of six rural versus urban environmental and socio-economic factors on gestational age were tested using simple weighted linear regression. **Results:** The study population preterm delivery rate was 4.12%. Marked differences from the overall preterm delivery rate were observed (rate estimates ranged from 1.73% - 6.31%). Statistical significance of this heterogeneity across municipalities was confirmed by a chi-squared test ($p<0.001$). Around 20% of the gestational age variance explained by the full model (after adjustment for known variables described above) could be attributed to municipality-level effects. In addition, gestational age was found to be longer in areas with higher fraction of built upon land and other urban features.

Conclusions: After adjusting for known risk factors large geographical differences in rates of preterm delivery remain. Additional analyses to look at the effect of environmental and socio-economic factors on gestational age revealed an increased gestational age in urban areas. Future research strategies could focus on investigating the urbanity effect to try to explain the preterm delivery variation across countries with a very high human-development index.

Key words:

Preterm birth/ premature obstetric labor/ preterm infant/ premature/ epidemiology

Abbreviations

PTD – preterm delivery

Key Message:

Wide geographical differences exist in preterm delivery rates across Sweden even after adjustment for known socio-economic risk factors. Gestational length appears to be longer in urban areas in Sweden compared to rural areas.

Introduction

Globally preterm delivery (PTD), defined as delivery before 37 weeks of gestation, remains a major public health priority and is responsible for 1.1 million neonatal deaths each year(1). As well as being the most common single cause of infant and perinatal mortality it also causes increased neonatal morbidity as it affects approximately 15 million infants worldwide(2). The economic burden of PTD is therefore substantial given that it affects so many babies, and is estimated that it costs the US healthcare system $26 billion yearly (3,4). The WHO ‘born too soon’ report published in 2012 called for a 50% reduction in the mortality related to PTD in resource poor countries from 2010 - 2025(5). PTD rates are known to differ widely throughout the world even amongst countries with a very high human development index (ranging in 2010 from 5.3 per 100 live births in Latvia to 14.7 per 100 live births in Cyprus)(1). Sweden is a county with a very high human development index and had one of the lowest rates of PTD in 2010(1). Why such a variation between countries exists is largely unknown and Chang *et al.* went on to conclude that the implementation of interventions (smoking cessation, cervical cerclage, progesterone, reducing unnecessary iatrogenic PTD and avoiding multiple embryo transfers) would jointly produce a relative reduction in PTD of only 5% from 9.59% to 9.07%, thus highlighting the need for substantial further research to improve etiological understanding and guide development of interventions. A recent individual participant analysis of 4.1 million births from 5 countries with a very high human development index aimed to assess the contributions of risk factors and successful interventions(6). The study confirmed what has been found previously that prior PTD and pre-eclampsia were the strongest individual risk factors of PTD(7,8) but two thirds of the cases have no attributable causes, again highlighting the urgent need for further research into the etiology of PTD. This uncertainty in etiology is reflected in the fact that the best intervention for PTD prevention is still unclear(9).

Environmental factors have been described as having the potential to act as ‘pregnancy stressors’ resulting in adverse pregnancy outcomes (10). In particular, exposure to air pollution (released from dust, pollen or grinding operations) has been shown in a systematic review to increase the risk of PTD (odds ratio 1.03, 95% confidence interval 1.01 to 1.05) (11), as has exposure to carbon monoxide exposure (12). These environmental factors differ according to geographical area, in particular with regard to rural versus urban residence with higher rates of air pollution in urban areas.

The objective of this population-based study was to use Sweden as a model of a very high human-development index country (13) (with one of the lowest PTD rates, an accessible public healthcare system, free antenatal care with close to 100% of the pregnant population participating and a relatively homogenous population in terms of ethnicity and socio-economic status with almost 80% of the population having intermediate or high-level education) to determine if geographical differences in PTD rates exist throughout the country. The overall singleton PTD rate in Sweden was estimated at 4.4% in 2014 by Statistics Sweden (14). We hypothesized that similar to the international differences(1,6) wide geographical variations in PTD rates would exist. In addition, we used individual maternal and fetal risk factor adjusted gestational age to show that these differences should not be attributed to different distributions of PTD risk factors. To provide some possible causes of the observed geographic differences, we performed some further exploratory analysis on a number of environmental and socio-economic factors and gestational length.

MATERIAL AND METHODS

A population-based register study was performed using data from the Swedish Medical Birth Register from 1998-2013. The mandatory Swedish Medical Birth Register collects data prospectively from the first antenatal visit and has been maintained by the National Board for Health and Welfare since 1973. The information included in the register includes demographic data, reproductive history and complications during pregnancy, delivery and the neonatal period. All births are validated every year through individual record linkage to the Swedish Population Register, which is 99% accurate for all births in Sweden. The register is subject to quality control on an annual basis. The Swedish Medical Birth Register was complemented by linked data from Statistics Sweden to provide the individual level social data(15). A quality analysis of the register has been previously described and it is considered to be of high quality(16).

The Medical Birth Register data was merged with the maternal residence information using data from Statistics Sweden (SCB), indicating the municipality (kommun) of maternal residence at the time of pregnancy. The population of Sweden is around 10 million with 85% of the population residing in the three biggest urban areas, Stockholm, Gothenburg and Malmö. Municipality level information on median disposable household income, fraction of 16+ year old population employed, fraction of population living in urban areas, fraction of the land which is built upon and mean distance to protected nature areas were also obtained through Statistics Sweden. Information on violent crimes was obtained from the Swedish National Council for Crime Prevention.

The study period 1998-2013 was chosen as 1998 represented the introduction of the International Classification of Disease (ICD-10) coding system. Gestational age measurement is recorded in the Swedish Medical Birth Register by best available method for each infant. This variable has been described previously and is considered to be of high quality(17). In Sweden second trimester scanning has been used since the mid 1980s onwards for gestational age measurement, which is generally regarded as the gold standard for gestational age estimation in the country. By using this study period, we could therefore be sure our measurement of the outcome of interest (gestational age) was by the best available method. Only pregnancies with an accurate gestational age measurement were included in the study. Multiple pregnancies, stillbirths and pregnancies complicated by fetal anomalies were excluded, as these pregnancies are known to be at increased risk of PTD compared to the general population(18).

The type of onset of delivery has been recorded accurately in the registry since 1991. It is currently recorded as spontaneous or induced labor, or prelabor caesarean section. Induced labor and prelabor caesarean section were classified as iatrogenic deliveries. All analyses were repeated using only spontaneous, only iatrogenic, or all deliveries together.

Statistical analyses

Gestational age in days was adjusted for known individual maternal and fetal risk factors using multiple linear regression. The following variables were included in the multivariate model: maternal age at delivery (years categorized as <20, 20-29, 30-40, >40), maternal height (continuous variable), maternal smoking (categorized as non-smoker, smoking in pregnancy, smoking >10 cigarettes in pregnancy), ethnicity (binary variable categorized as Swedish born mother and other), parity (primigravida, para 1, para 2, para 3, ≥ para 4), maternal education (categorized in three levels, 1 = primary/secondary school completed, 2 = less than two years of higher education completed, 3 = at least two years of higher level education/higher degree/PhD), year of delivery, infant gender, pre-existing maternal diabetes, maternal hypertension, and gestational age measurement method. Missing covariate values were not included in the adjusted multivariate analyses. Municipality PTD rates were calculated from individual gestational age measurements in days (as percentage of deliveries at <37 weeks of gestation) and mapped across Sweden. When calculating risk-factor adjusted PTD rates, individual gestational age was replaced with the residual plus intercept from the corresponding regression model, and dichotomized as above.

A funnel plot was used to demonstrate the variability in the gestational age measurements by municipality size. To show the expected distribution of estimates under the null, we calculated 95% and 99.98% (95%, Bonferroni adjusted for 296 municipalities) confidence intervals as $\mu \pm Z_{1-\alpha/2}\sigma/\sqrt{n}$, where μ and σ are country-wide estimates and Z quartile function of standard normal distribution.

A second fixed effects linear regression model was fitted, allowing separate intercepts for each municipality. The variance explained by municipality-level effects was estimated by comparing the R-squared values of the models. The analysis was then repeated using municipality as a random effect. Overall significance of the added municipality-level effects was evaluated by the F-test between the nested models.

A binomial test was performed to test the PTD rates in each municipality against the overall PTD rate in the country to determine which municipalities were statistically different from the country-wide PTD rate. The chi squared test for homogeneity was used to measure the homogeneity of PTD rates in four ways: across all municipalities, only Stockholm municipalities, only Gothenburg municipalities and only Malmö municipalities.

All analyses were undertaken using the R language (version 3.4.1). The code used for the study is available at http://github.com/Perinatal Lab/SE_MFR_GEODATA.

We went on to investigate a number of different environmental and socio-economic factors to try to understand municipality differences in PTD rates. Each factor was tested in a simple weighted linear regression setting with mean adjusted gestational age in days as the outcome. Here we used gestational age in days rather than PTD rates in order to allow us to run linear models. Weights were proportional to the number of deliveries in the municipality. The additional factors investigated were median disposable household income (thousands of Swedish crowns, data from year 2011), fraction of 16+ year old population employed (year 2010), fraction of population living in urban areas (year 2010), fraction of the land which is built upon (year 2010), mean distance from residence to protected nature areas (year 2013) and violent crimes (against life and health, rate per capita, year 2010).

Ethical approval

The study was approved by the Regional Ethical Review Board in Gothenburg, Sweden (968-14). The national Board of Health and Welfare approved the use of the data from the Swedish Medical Birth Register and Statistics Sweden approved the use of the individual level social data.

RESULTS

The total population comprised 1 554 999 singleton births in Sweden registered in the Swedish Medical Birth register between 1998-2013, of which 1 335 802 met the inclusion criteria. There were 53 713 preterm infants born in the study population, giving an overall PTD rate of 4.12%. Of the PTDs 36 356 (67.69%) were spontaneous (Figure 1). The maternal characteristics related to all spontaneous deliveries and preterm (spontaneous and iatrogenic) deliveries are summarized in Table 1. Of the 53 713 mothers that delivered preterm, 87.96% (n = 47 247) were non-smokers (compared to 90.66%, n = 985 698, of all spontaneous deliveries) and 79.89% (n = 42 909) were Swedish born mothers (this was similar to all spontaneous deliveries, n = 863 953, 79.46%). 93.85% (n = 1 020 367) of the gestational age measurements in the cohort were by 2nd trimester ultrasound scanning, with the remainder (6.15%, n = 66 896) by best estimate dating by last menstrual period.

PTD was strongly associated with maternal geographical residence and differed significantly throughout the country (both adjusted and unadjusted) and within major regions (chi squared test of independence, all *p* values < 0.001). Figure 2 is a funnel plot showing the mean gestational age estimates according to municipality population size. A number of municipalities fall outside the 95% confidence area (136 out of 296 and 52 out of 296 after Bonferroni adjustment at 99.98%), indicating that they significantly deviate from the population mean. Wide variations (range 2.09% - 6.39%) in the crude spontaneous PTD rates based on municipality were observed (Supporting Information S1). After adjusting for potential confounding effects of maternal age, ethnicity, maternal height, smoking, parity, maternal education, baby gender, maternal hypertension and maternal diabetes, PTD rates were still widely diverse across the country (range 1.73% - 6.24%; Figure 3, for full area names see Supporting Information S1). The results of the multiple linear regression analysis are displayed in Table 2. Covariates accounted for approximately 1% of the variance of gestational age (R-squared 0.01); adjusted rates of spontaneous PTD were then generated which take these covariates into account. These adjusted rates were mapped across the country (and areas where they were statistically significantly different to the population mean were highlighted) and again a wide variation was observed (Figure 4, for full area names see Supporting Information S2). Unadjusted rates are shown in the Supporting Information S3. In supplementary analyses, we mapped spontaneous and iatrogenic rates separately (Supporting Information S4, S5). The spontaneous PTD rates showed a wide variation similar to all PTD rates. When the iatrogenic rates were mapped separately across the county the differences were even larger (range 2.29% to 12.40%) and did not match areas of high spontaneous PTD rates (Supporting Information S5).

When the second regression model was fitted allowing separate intercepts for each municipality the R-squared value of the model rose from 0.01 to 0.02 suggesting around 20% of the variance explained by the model can be attributed to municipality-level effects. The PTD rates that were significantly above and below the population mean (using false discovery rate (FDR) adjustment for multiple testing, q-value threshold 10%) were then mapped (Supporting Information S6). A third model with municipality as a random effect was fitted and the estimates from the second model were almost identical therefore no further mapping was undertaken (Supporting Information S7). In both fixed and random effect models, addition of municipality-level effects significantly improved the model fit (F test $p < 0.001$).

In the further analysis of urban versus rural environmental and socio-economic factors and their association with gestational length across Sweden, gestational age in days was significantly positively associated with several proxies for urbanity: fraction of population living in urban areas (p=0.005), fraction of population employed (p=0.02), fraction of land built upon (p<0.001) and number of violent crimes (p<0.001) (Figure 5). Municipality affluence (measured by median household income) was not associated with gestational age in days (p=0.99, Figure 5).

DISCUSSION

This large population based study comprising >1.3 million pregnancies reveals novel information on the association between maternal geographical residence and PTD rates. Using Sweden as a model of a very high human-development index country with one of the lowest PTD rates in the world and a public healthcare system with free antenatal care (particularly suited to this study because of its accurate and detailed routinely collected data), we have shown that PTD rates vary widely throughout the country in line with our hypothesis. Our study shows that the within country differences in PTD rates (1.40 – 5.73%) are almost as large as between country differences in PTD rates described previously (5-10% among live births in Europe (1,2,19), and many areas of the country significantly deviate from the overall PTD rate, despite the relatively homogeneous nature of the population and health care system. This wide variation is seen for spontaneous deliveries, iatrogenic deliveries, and both categories combined. Our study highlights what is demonstrated in previous studies(6,20), that currently known epidemiologic risk factors for PTD account for only a small proportion of the overall variation in PTD rates, evident from the small R-squared value of the multiple linear regression model in our analysis. Our study therefore highlights further the need to consider other factors, which may be driving this association between geographical residence and PTD.

The mechanism which underlies the strong association between maternal geographical residence and PTD rates remains unclear and indeed it is surprising that a cohort of largely non-smokers (91%) and Swedish born mothers (80%) with access to one of the most comprehensive healthcare systems in the world should show such a variation in PTD rates. In our further analysis of rural versus urban environmental and socio-economic factors we have shown an association between area urbanity (and proxy measures of it such as fraction of the population employed) and a longer gestational age. The association of an increased number of violent crimes and longer gestational age is not what would be expected if it was the main stressor - more likely, crime rate acts as a proxy measure of urbanity, which affects PTD rate through other factors. One hypothesis is that despite the public healthcare organization, more advanced healthcare practices exist within urban areas of the country. We plan to go on to look at the accessibility of specialized obstetric care providers in Sweden as previous research has showed this to be associated with pregnancy outcome (21). The role of other environmental factors, not shown here, such as levels of sunlight (given emerging evidence about vitamin D in pregnancy and its association with a reduction in PTD rates (22), longitude and latitude effects and the role of water and air pollution which have previously been shown to be associated with PTD could also be investigated to further determine this urban versus rural difference (rural areas may be have increased rates of pesticide use and therefore increased water pollution and CO emissions) (23). As well as investigating environmental stressors, maternal stressors such as maternal anxiety and depression have been shown to contribute to poor obstetric outcome and increased risks of preterm birth (25) and are important potential confounders we were unable to address in this study.

Our study has a number of strengths. Firstly the large sample size of >1.3 million pregnancies allowed us to report the PTD rates after reliably adjusting for the known risk factors for PTD. Using a full-population database reduces the risk of selection bias and the population is homogenous with a free public healthcare system. The main strength of our study lies in the accurate measurement of gestational age and the completeness of our dataset. 94% of our gestational age measurements were by ultrasound scan and pregnancies with inaccurate gestational age measurement were excluded. Gestational age measurement is often a reason for variations in PTD rates between countries but this variation is accounted for in our analysis (24). Gestational age is recorded in the Swedish dataset in days and this greatly reduces the measurement noise in all our analyses. Using unique individual patient IDs we were able to accurately link the Swedish Medical birth registry data to the Statistics Sweden data with a very high match rate. Using Sweden as a model of a very high human-development index Country we believe the results to be generalizable to other populations of similar development status.

A caveat to this population-based approach is the reliance on routinely collected data method for the analysis. Large datasets are at higher risk of containing coding errors, misclassification of exposure or outcome variables, and missing data. Although we did not formally assess the Swedish Birth Register data quality for this project, it has been shown in a previous study to be 99% accurate for all births in Sweden (17). There is potential selection bias resulting from the missing covariate values in the study, which caused samples to be excluded from the adjusted analyses. However, the similarity between adjusted and unadjusted results implies that the missing data should not have a strong effect on the observed PTD rates. Another limitation is regarding the use of municipality social and environmental data from 2010 or 2013 as this data was not available for the actual year of pregnancy/birth and may have changed over the course of the study period.

In conclusion PTD rates are rising and it remains difficult to treat because of its heterogeneity and the unknown components of the etiology. Our study has shown that risk factor adjustment alone only accounts for a small amount of the variation in gestational age seen throughout a country with a very high human-development index. We observe that gestational age is longer in urban areas. We believe that future research efforts should be directed at determining the role of environmental factors and explaining the effect of urbanity on PTD rates as targeting rural municipalities may be required to reduce PTD rates.

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References

1. Chang HH, Larson J, Blencowe H, et al. Preventing preterm births: analysis of trends and potential reductions with interventions in 39 countries with very high human development index. Lancet. 2013;381(9862):223–34.

2. Blencowe H, Cousens S, Oestergaard MZ, et al. National, regional, and worldwide estimates of preterm birth rates in the year 2010 with time trends since 1990 for selected countries: a systematic analysis and implications. Lancet. 2012;379(9832):2162–72.

3. Institute of Medicine (US) Committee on Understanding Premature Birth and Assuring Healthy Outcomes, Behrman RE, Butler AS. Preterm Birth: Causes, Consequences, and Prevention. Washington (DC): National Academies Press (US); 2007.

4. Henderson J. Economic implications of multiple births: inpatient hospital costs in the first 5 years of life. Arch Dis Child Fetal Neonatal Ed. 2004;89:F542-5.

5. World Health Organization. Born too soon: the global action report on preterm birth. Geneva : World Health Organization; 2012.

6. Ferrero DM, Larson J, Jacobsson B, et al. Cross-Country Individual Participant Analysis of 4.1 Million Singleton Births in 5 Countries with Very High Human Development Index

Confirms Known Associations but Provides No Biologic Explanation for 2/3 of All Preterm Births. Luo Z-C, editor. PLoS ONE; 2016;11(9):e0162506.

7. Goldenberg RL, Culhane JF, Iams JD, Romero R. Epidemiology and causes of preterm birth. Lancet. 2008;371(9606):75–84.

8. Räisänen S, Gissler M, Saari J, Kramer M, Heinonen S. Contribution of Risk Factors to Extremely, Very and Moderately Preterm Births – Register-Based Analysis of 1,390,742 Singleton Births. PLoS ONE. 2013;8(4):e60660.

9. Stock SJ, Ismail KMK. Which intervention reduces the risk of preterm birth in women with risk factors? BMJ. 2016;355:i5206.

10. Dibben C, Clemens T. Place of work and residential exposure to ambient air pollution and birth outcomes in Scotland, using geographically fine pollution climate mapping estimates. Environ Res. 2015;140:535–41.

11. Li X, Huang S, Jiao A, et al. Association between ambient fine particulate matter and preterm birth or term low birth weight: An updated systematic review and meta-analysis. Environ Pollut. 2017;227:596–605.

12. Liu SL, Krewski D, Shi YL, Chen Y, Burnett RT. Association between gaseous ambient air pollutants and adverse pregnancy outcomes in Vancouver, Canada. Environ Health Pers. 2003;111(14):1773–8.

13. Thérien J-P. The United Nations and Human Development: From Ideology to Global Policies. Global Policy. 2012;3(1):1–12.

14. Statistics SO. Pregnancies, deliveries and newborn babies. 2015. Available from: http://www.socialstyrelsen.se/Lists/Artikelkatalog/Attachments/20009/2015-12-27.pdf

15. Kernell K, Sydsjö G, Bladh M, Nielsen NE, Josefsson A. Congenital heart disease in men – birth characteristics and reproduction: a national cohort study. BMC Pregnancy Childbirth. 2014;14(1):187.

16. Cnattingius S, Ericson A, Gunnarskog J, Källén B. A Quality Study of a Medical Birth Registry. Scand J Soc Med. 1990;18(2):143–8.

17. Morken N-H, Källen K, Jacobsson B. Fetal growth and onset of delivery: a nationwide population-based study of preterm infants. Am J Obstet Gynecol. 2006;195(1):154–61.

18. Morken N-H, Källen K, Hagberg H, Jacobsson B. Preterm birth in Sweden 1973-2001: rate, subgroups, and effect of changing patterns in multiple births, maternal age, and smoking. Acta Obstet Gynecol Scand. 2005;84(6):558–65.

19. Zeitlin J, Szamotulska K, Drewniak N, et al. Preterm birth time trends in Europe: a study of 19 countries. BJOG. 2013;120(11):1356–65.

20. Di Renzo GC, Giardina I, Rosati A, et al. Maternal risk factors for preterm birth: a country-based population analysis. Eur J Obstet Gynecol Reprod Biol. 2011;159(2):342–6.

21. Bauer J, Groneberg DA, Maier W, Manek R, Louwen F, Brueggmann D. Accessibility of general and specialized obstetric care providers in Germany and England: an analysis of location and neonatal outcome. Int J Health Geogr. 2017;16(1):44..

22. De-Regil LM, Palacios C, Lombardo LK, Peña-Rosas JP. Vitamin D supplementation for women during pregnancy. Cochrane Database Syst Rev. 2016;1:CD008873.

23. Hao H, Chang HH, Holmes HA, et al. Air Pollution and Preterm Birth in the U.S. State of Georgia (2002–2006): Associations with Concentrations of 11 Ambient Air Pollutants Estimated by Combining Community Multiscale Air Quality Model (CMAQ) Simulations with Stationary Monitor Measurements. Environ Health Perspect. 2016;124(6):875-80.

24. Delnord M, Blondel B, Zeitlin J. What contributes to disparities in the preterm birth rate in European countries? Curr Opin Obstet Gynecol. 2015;27(2):133-42.

25. Ibanez G, Charles M-A, Forhan A, et al. Depression and anxiety in women during pregnancy and neonatal outcome: data from the EDEN mother-child cohort. Early Hum Dev. 2012;88(8):643–9.

Supporting information legends

Figure S1: Preterm delivery rates across Sweden adjusted for known risk factors from a multiple linear regression model (full place names).

Figure S2: Preterm delivery rates significantly higher or lower than the population mean preterm delivery rate (full place names).

Figure S3: Crude preterm delivery rates among live births in Sweden.

Figure S4: Spontaneous preterm delivery rates in Sweden adjusted for known risk factors.

Figure S5: Iatrogenic preterm delivery rates in Sweden adjusted for known risk factors.

Figure S6 (a): Preterm delivery (PTD) rates significantly higher or lower than the population mean PTD rate adjusted from a multivariate regression model with separate intercepts for each municipality (false discovery rate>10%). **(b):** PTD rates significantly higher or lower than the population mean PTD rate adjusted from a multivariable regression model with separate intercepts for each municipality (p<0.1).

Figure S7: Effect estimates compared by method of municipality modeling (fixed and random effects).

Legends of figures and tables

Figure 1: Cohort composition

Figure 2: Funnel plot of gestational age and population size plotted against the population mean gestational age

Figure 3: Preterm delivery rates across Sweden adjusted for known risk factors from a multiple linear regression model (both spontaneous and iatrogenic deliveries are included).

Figure 4: Preterm delivery rates significantly higher or lower than the population mean preterm delivery rate (binomial test p<0.1, no multiple testing adjustment).

Figure 5: Weighted linear regression plots of environmental and socio-economic municipality features and gestational age. Points represent municipalities, weighted by their number of deliveries (*n*).

Table 1: Baseline demographics of all the 1,087,263 singleton deliveries and in the Swedish population 1998 – 2013.

Table note: PTD, preterm delivery.

Table 2: Results of the multiple linear regression analysis of 1,023,142 pregnancies (64,121 removed due to missing covariates).

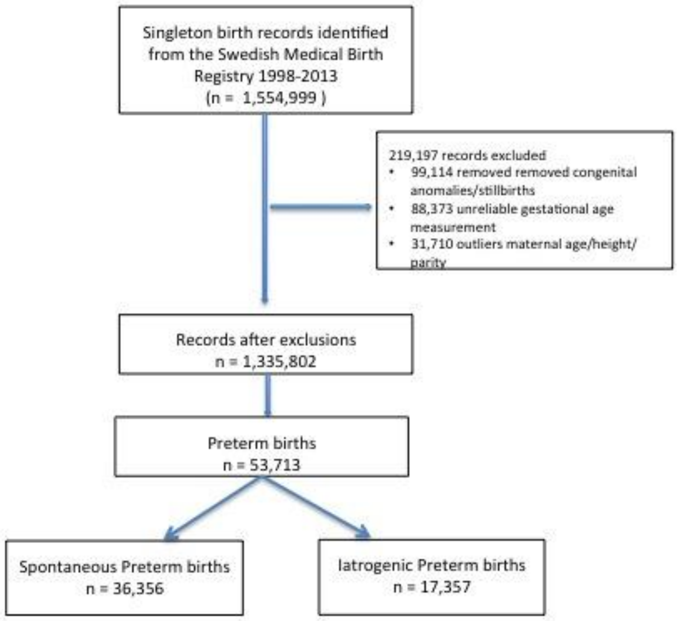
Table 1: Baseline demographics of all the 1 087 263 singleton deliveries in the Swedish population 1998 – 2013.

Characteristic	N of individuals within the demographic group (% of all spontaneous births)	N PTD (% PTD from all births within the demographic group)	
		Spontaneous	Iatrogenic
Maternal age (years)			
<20	18856 (1.73)	839 (4.45)	287 (1.52)
20-30	583093 (56.63)	20343 (3.49)	8297 (1.42)
31-40	468810 (43.11)	14533 (3.10)	8209 (1.42)
>40	16504 (1.52)	641 (3.88)	564 (3.42)
Missing	0	0	0
Maternal parity			
1	480827 (44.22)	21061 (4.38)	8960 (1.86)
2	408500 (37.57)	10102 (2.47)	4609 (1.23)
3	140990 (12.97)	3383 (2.40)	2334 (1.66)
4+	56946 (5.24)	1810 (3.18)	1454 (2.55)
Missing	0	0	0
Maternal smoking			
None	985698 (90.66)	32005 (3.25)	15242 (1.55)
<10	64957 (5.97)	2736 (4.21)	1274 (1.96)
10+	22646 (2.08)	1122 (4.95)	540 (2.38)
Missing	13972 (1.29)	493 (3.53)	301 (2.15)
Maternal Diabetes			
Yes	3040 (0.28)	444 (14.6)	694 (9.80)
No	1084223 (99.72)	35912 (2.39)	16663 (1.54)
Maternal Hypertension			
Yes	3103 (0.29)	154 (4.96)	427 (13.76)
No	1084160 (99.71)	36202 (3.34)	16930 (1.56)
Maternal Ethnicity			
Swedish	863953 (79.46)	28989 (3.36)	13920 (1.61)
Non-Swedish	223310 (20.54)	7387 (3.31)	3437 (1.54)
Maternal Education			
1	248058 (22.81)	9012 (3.63)	4830 (1.95)
2	447356 (41.15)	15160 (3.39)	7176 (1.60)
3	340987 (31.36)	10489 (3.08)	4592 (1.35)
Missing	50862 (4.68)	1695 (3.33)	759 (1.49)
Method of gestational age measurement			
Ultrasound	1020394 (93.85)	33991 (3.33)	16183 (1.59)
Best estimate using last menstrual period	66869 (6.15)	2365 (3.54)	1174 (1.75)
Fetal sex			
Male	550620 (50.64)	19740 (3.59)	9021 (1.64)
Female	536643 (49.36)	16616 (3.10)	8336 (1.55)
Missing	0	0	0

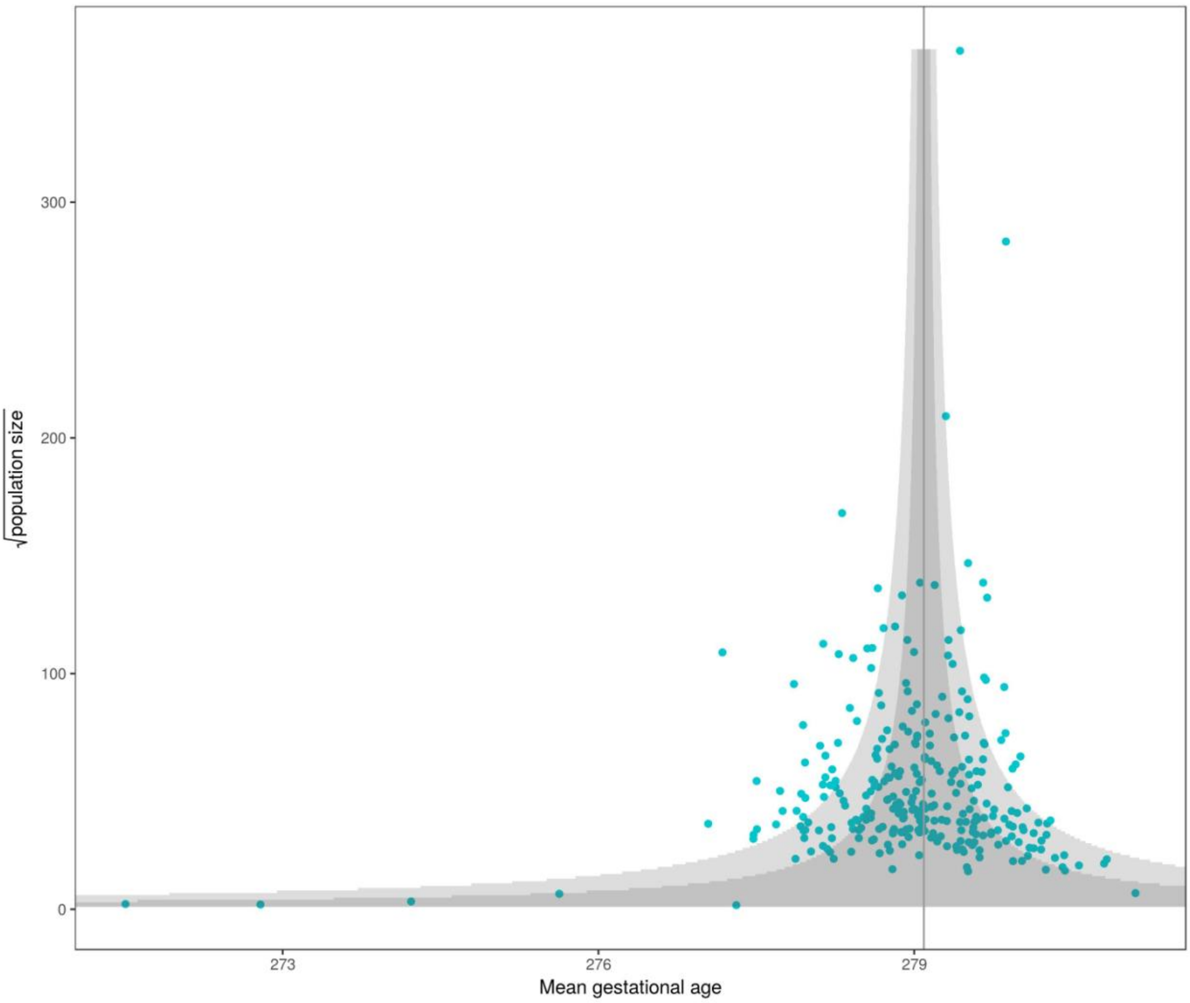
Table 2: Results of the multiple linear regression analysis of 1 258 038 pregnancies (77 608 removed due to missing covariates)

Variable	N	Estimate[a,b]	Standard Error (SE)	p value
Maternal age				
<20	17 393	-0.454	0.090	<0.0001
20-30	645 835	Ref		
31-40	571 353	0.064	0.022	<0.0001
>40	23 476	-1.011	0.078	0.004
Maternal Height	1 258 038	0.149	0.001	<0.0001
Smoking				
No smoking	1 155 513	Ref		
Smoking (<10)	75 790	-0.703	0.044	<0.0001
Smoking (>10)	26 754	-1.568	0.072	<0.0001
Parity				
Primigravida	556 768	Ref		
Para 1	469 844	-0.046	0.023	0.048
Para 2	167 782	-0.165	0.034	<0.0001
Para 3	43 503	-0.725	0.059	<0.0001
≥ para 4	20 160	-1.241	0.085	<0.0001
Ethnicity				
Swedish mother	1 044 070	Ref		
Non Swedish mother	213 987	-0.149	0.028	<0.0001
Maternal Education				
Category 1	306 215	Ref		
Category 2	539 853	0.235	0.027	<0.0001
Category 3	411 989	0.487	0.030	<0.0001
Fetal gender				
Male	642 620	-0.389	0.020	<0.0001
Female	615 437	REF		
Birth year	1 258 038	-0.032	0.002	<0.0001
Maternal diabetes				
Yes	6567	-9.379	0.142	<0.0001
No	1 251 490	Ref		
Maternal Hypertension				
Yes	5130	-4.244	0.161	<0.0001
No	1 252 927	Ref		
Gestational age measurem				
Ultrasound	1 182 104	Ref		<0.0001
Other	75 53	1.011	0.043	

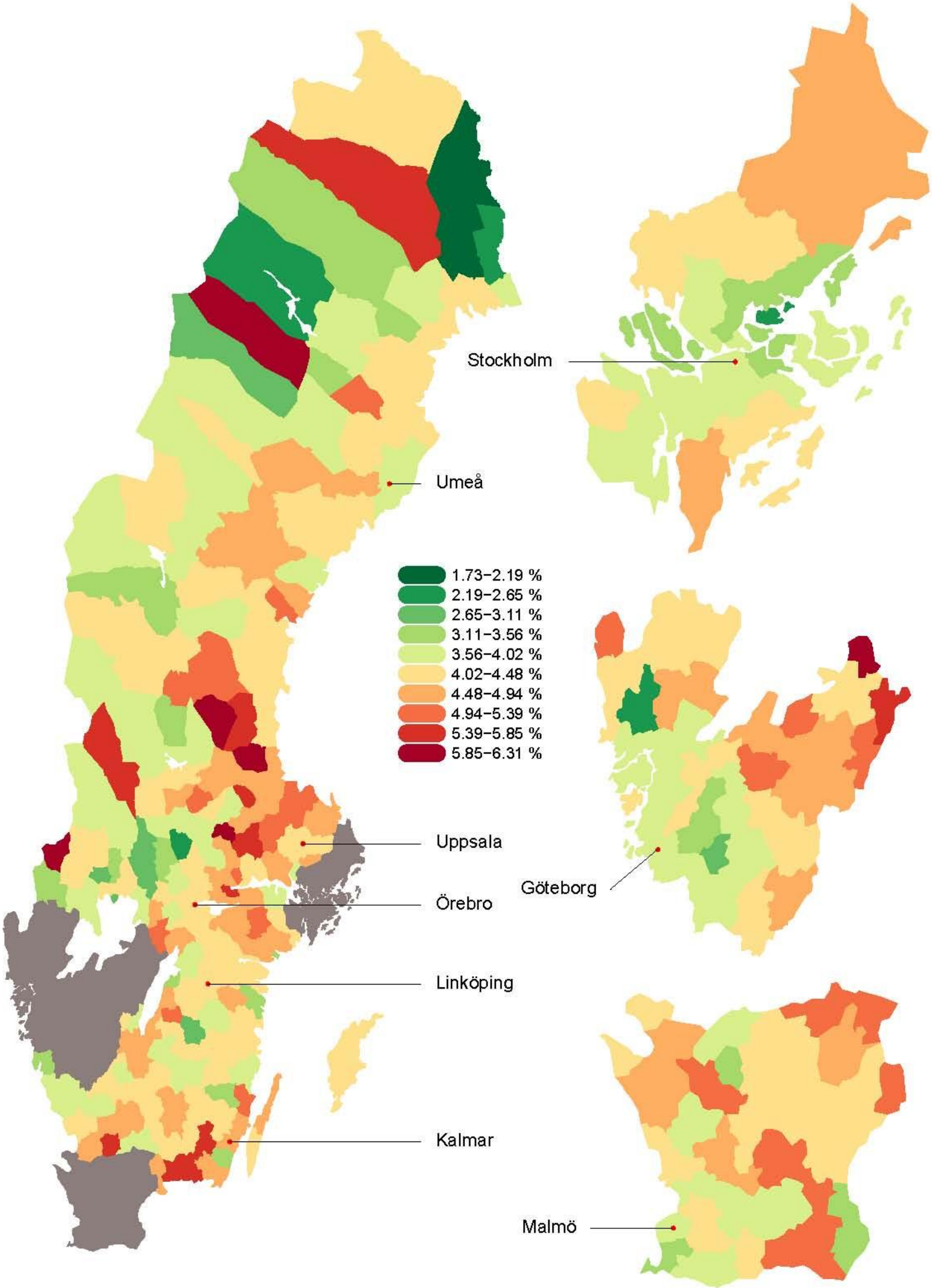
[a]Effect sizes correspond to the mean gestational age shift in days.
[b]Adjusted for all the variables in the table.

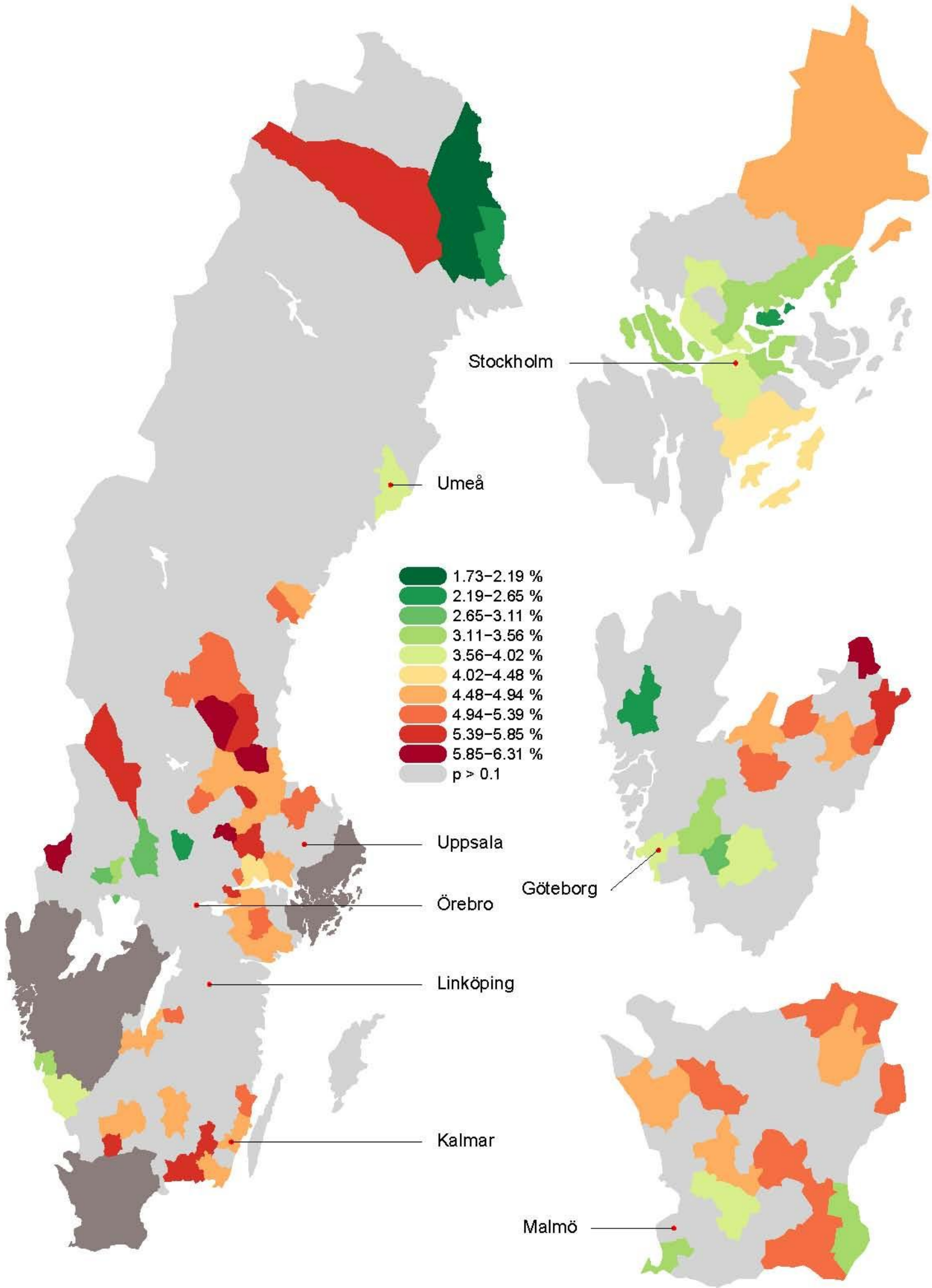


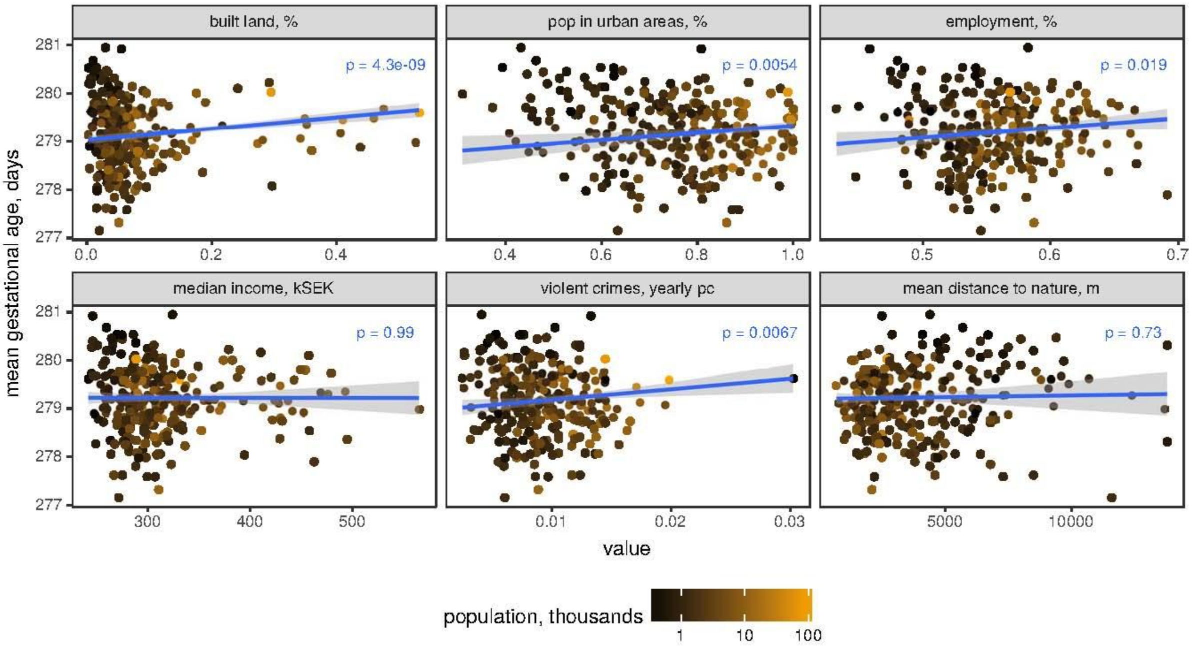
Singleton birth records identified from the Swedish Medical Birth Registry 1998-2013
(n = 1,554,999)
219,197 records excluded
• 99,114 removed removed congenital anomalies/stillbirths
• 88,373 unreliable gestational age measurement
• 31,710 outliers maternal age/height/parity
Records after exclusions
n = 1,335,802
Preterm births
n = 53,713
Spontaneous Preterm births
n = 36,356
Iatrogenic Preterm births
n = 17,357



300
200
100
0
√population size
273
276
279
Mean gestational age


Stockholm
Umeå
1.73–2.19 %
2.19–2.65 %
2.65–3.11 %
3.11–3.56 %
3.56–4.02 %
4.02–4.48 %
4.48–4.94 %
4.94–5.39 %
5.39–5.85 %
5.85–6.31 %
Uppsala
Örebro
Göteborg
Linköping
Kalmar
Malmö


Stockholm
Umeå
1.73−2.19 %
2.19−2.65 %
2.65−3.11 %
3.11−3.56 %
3.56−4.02 %
4.02−4.48 %
4.48−4.94 %
4.94−5.39 %
5.39−5.85 %
5.85−6.31 %
p > 0.1
Uppsala
Örebro
Göteborg
Linköping
Kalmar
Malmö


built land, %
pop in urban areas, %
employment, %
median income, kSEK
violent crimes, yearly pc
mean distance to nature, m
p = 4.3e-09
p = 0.0054
p = 0.019
p = 0.99
p = 0.0067
p = 0.73
mean gestational age, days
value
population, thousands
1
10
100