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### Preterm birth

*Risk factors and treatment*

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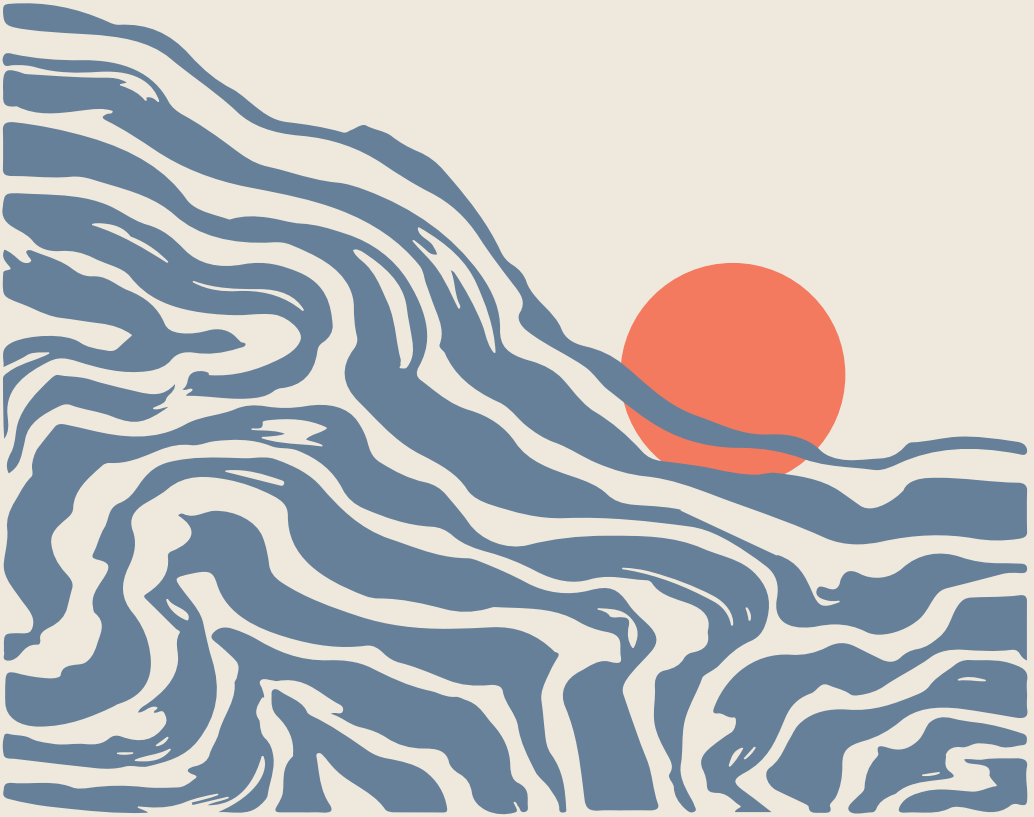
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# CHAPTER 4

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## Deprived neighborhoods and spontaneous preterm birth: a national cohort study

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## ABSTRACT

### Objective

Spontaneous preterm birth is the leading cause of infant morbidity and mortality in the developed world. Environmental socio-economic factors, such as neighborhood deprivation, are known to negatively affect birth outcomes, including overall preterm birth. However, the role of neighborhood deprivation in spontaneous preterm birth (SPTB) is unclear. The aim of the study is to 1) to determine the effect of neighborhood deprivation on SPTB birth and 2) to investigate the trend in rates of SPTB between 2010 and 2019 for each quintile of neighborhood deprivation.

### Study design

Based on the national perinatal registry, we included 1,584,225 singleton pregnancies resulting in a birth from 22 to 42 completed weeks of gestation between 2010 and 2019 in the Netherlands. Deprivation scores per neighborhood were derived from the Netherlands Institute of Social Research and were linked to the perinatal registry data, using the woman's home address. The scores were divided into quintiles (Q). Rates of SPTB were calculated, categorized into <37 weeks, <32 weeks and <28 weeks of gestation. We used logistic regression analysis to adjust for maternal age, parity and ethnicity.

### Results

Compared to the most affluent neighborhoods (Q1), women in all other quintiles had a statistically significant increased risk for SPTB. The largest effect was observed in the most deprived neighborhoods (Q5); adjusted odds ratio 1.16 (95% confidence interval 1.13 – 1.19). From 2010 to 2019, we observed an overall decrease of 0.21% in SPTB <37 weeks ( $p < 0.0001$ ). All quintiles showed a decrease in SPTBs <37 weeks, but only in Q1, Q2 & Q5 this decline in SPTB was statistically significant.

### Conclusions

Pregnant women in deprived neighborhoods in the Netherlands are more at risk for spontaneous preterm birth. From 2010 to 2019, the rate of spontaneous preterm birth decreased.

Efforts should be made by both governmental and medical professionals to develop intervention programs to reduce spontaneous preterm birth in more deprived neighborhoods.

## INTRODUCTION

Preterm birth (PTB), defined as birth before 37 weeks of completed gestation, is the leading cause of death worldwide for children below 5 years of age, and is strongly associated with childhood morbidity.<sup>1</sup> The estimated global PTB rate for 2014 was 10.6%, amounting to an estimated 14.84 million live preterm births.<sup>2</sup> Because of this high incidence, preterm birth comes with a substantial burden of disease in both the social and economic domain. The majority of PTB is of spontaneous origin, about 70 to 80 percent is due to preterm labor or preterm prelabor rupture of membranes.<sup>3</sup> Spontaneous PTB (SPTB) is a complex syndrome with multiple etiologies. Risk factors for SPTB include maternal age (adolescence or advanced age), history of preterm birth, multiple pregnancy, short inter-pregnancy interval, infections, medical conditions, poor nutrition, smoking and genetic predisposition.<sup>3-4</sup> Ideally, identification of risk factors will lead to interventions that help prevent SPTB.<sup>5</sup> Although a decline in the rate of SPTB was noted in the Netherlands,<sup>6-7</sup> we are still not able to prevent all SPTBs. A further reduction of the SPTB rate should be possible, especially by focusing on modifiable risk factors such as age and education.

The association between lower socioeconomic status and poorer health has been recognized for a long time.<sup>8</sup> One way to characterize the socioeconomic environment of a certain population is by dividing neighborhoods by level of deprivation; hence the term deprived neighborhoods. Deprived neighborhoods are known to be associated with adverse perinatal outcomes, such as perinatal mortality, intra uterine growth restriction, low birthweight and total preterm birth.<sup>9-10</sup> A review by Ncube et al. showed that neighborhood deprivation is associated with a 27% (95% confidence interval (CI): 1.16 - 1.39) higher rate of total PTB among the most disadvantaged compared with the least disadvantaged neighborhoods in the United States.<sup>11</sup> In a national cohort study in England, Jardine J et al. showed that socioeconomic inequalities were responsible for a substantial proportion of preterm births in England.<sup>12</sup>

Bertens et al. and Burgos Ochoa et al. illustrated a neighborhood deprivation effect on total PTB in the Netherlands.<sup>13-14</sup> Since most studies have investigated the effect on total PTB, the effect of neighborhood deprivation on SPTB is not known. By studying spontaneous PTB only, we can eliminate the strong intervention/care effect in iatrogenic births that influences the total preterm rate. An association with spontaneous preterm birth may provide an important lead for governmental and medical professionals to decrease the rate of spontaneous preterm birth and its consequences.

In this study, we subdivided all singleton pregnancies in the Netherlands into quintiles based on neighborhood deprivation scores. Furthermore, we analyzed trends in SPTB from 2010 to 2019 for each deprivation quintile to investigate whether rate differences by neighborhood quintile improve over time. We addressed the following research questions:

1. Are women living in deprived neighborhoods more at risk of spontaneous preterm birth?
2. What is the trend in the spontaneous preterm birth rate between 2010 and 2019?
3. How does this trend in spontaneous preterm birth over time relate to neighborhood deprivation?

## MATERIALS AND METHODS

### Study population

This study was performed in a nationwide cohort using The Netherlands Perinatal Registry (PERINED).<sup>15</sup> The registry consists of population-based data containing information on pregnancy, delivery and neonatal outcomes. The PERINED database is obtained by a validated linkage of three different registries: the midwifery registry, the obstetrics registry and the neonatology registry. The coverage of the PERINED registry is approximately 98% of all deliveries in The Netherlands.

All data contained in the PERINED are voluntarily recorded by the caregiver during prenatal care, delivery, and the neonatal period. For this study, we selected all singleton pregnancies resulting in birth between 22 weeks + 0 days and 42 weeks + 6 days of gestation, from January 1<sup>st</sup> 2010 to December 31<sup>st</sup> 2019. First, pregnancies with missing gestational age (GA) and missing postal code were excluded. Second, we excluded pregnancies with congenital abnormalities, since these pregnancies have an intrinsic high risk of preterm birth. Lastly, we excluded pregnancies with antepartum fetal death (are not considered preterm births).

### Deprivation index

Data on neighborhood socioeconomic status were obtained from The Netherlands Institute for Social Research (in Dutch: Sociaal Cultureel Planbureau, SCP).<sup>16</sup> The neighborhoods have an average of 4000 inhabitants and a size of 5.3 km<sup>2</sup>. Using the woman's 4 digit postal code, these SCP data could be linked to the perinatal registry file. The socioeconomic status score of a postal code is based on 4 variables: 1) mean income level, 2) the percentage of households with a low income, 3) the percentage of inhabitants without a paid job and 4) the percentage of households with on average a low education. With a factor analysis, these yearly measurements are combined to a national deprivation score. The socioeconomic status score can be seen as a deprivation index. The lower the status score, the higher the deprivation in this neighborhood.

For each year of birth, all births were categorized into socioeconomic deprivation quintiles, based on the score. This was done for each of the 10 years separately, and thereafter combined for the total of 10 years. The most affluent neighborhood (Q1) contains the highest socioeconomic status scores, the most deprived quintile (Q5) contains the lowest socioeconomic status scores.

### Outcomes

Preterm birth (PTB) was defined as birth before 37 completed weeks of gestation. Spontaneous preterm birth (SPTB) included all births after spontaneous onset of contractions with or without prelabor rupture of membranes (PROM). Iatrogenic preterm births were all births after induction of labor or elective caesarian section.

Gestational age was based on crown rump length measurement in early pregnancy. We categorized SPTB by duration of gestation into three subgroups of <37 weeks, <32 weeks and <28 weeks of gestation.

### **Characteristics**

Maternal age was used continuous in the baseline analysis and also categorized into <20, 20–24, 25–34, 35–39 and ≥40 years. Parity is categorized into 0 (first birth), 1 (second birth) and 2+ (third and higher birth). Maternal ethnicity, reported by the woman's care provider, is categorized into western, Mediterranean (including Moroccan, Turkish) and other non-western ethnicities (Africa, South Asian, mixed).

Information on smoking and BMI was not available from the PERINED data. Data on history of preterm birth, diabetes and/or hypertension during pregnancy are recorded in PERINED, but are known to be underreported by caregivers, and were therefore not taken into account in this analysis.

There were, because of the exclusion criteria, no missing values in the determinant (deprivation quintile) and in the outcome measurements SPTB. Less than 1% of data on maternal age, parity, ethnicity and birthweight were missing. These missing variables were imputed.

### **Statistical analysis**

Maternal and birth characteristics were tabulated per deprivation quintile (Q1-Q5) and tested with a chi-square for categorical variables and an ANOVA test for continuous variables.

Preterm birth rates were determined as the number of singleton births before 37 completed weeks of gestation a proportion of all birth and the result expressed per 100 births (%). SPTB rates in the 3 different gestational age groups (<37, <32 and <28 weeks of gestation) were also expressed per 100 births (%).

First, rates of SPTB were tabulated for each quintile of deprivation. Second, we used crude and multiple logistic regression modelling to derive odds ratio's (OR) for the effect of deprivation quintile on the outcome SPTB. The most affluent quintile (Q1) was set as the reference group.

We adjusted for maternal age (<20, 20-24, 25-29 (ref), 35-39, ≥40 years of age), parity (para 0, para 1 (ref), para 2+), ethnicity (western (ref), Mediterranean, other non-western), fetal sex (male (ref), female) and year of birth (2010 (ref), 2011, 2012, 2013, 2014, 2015, 2016, 2017, 2018, 2019).

Third, to take into account possible changes over time, we tested if there was interaction between deprivation quintile and year of birth. In addition, the analysis was stratified for two time periods (2010-2014 and 2015-2019).

Fourth, to visually assess the trends over time, absolute rates of SPTB in total and for each quintile were plotted. To investigate whether there was a trend in SPTB rate over time, we performed a Cochran-Armitage trend test, with the year as the independent variable and SPTB as the dependent variable. This was performed for SPTB <37 weeks, SPTB <32 weeks, SPTB <28 weeks, as well as total PTB <37 weeks.

Fifth, we calculated the Population Attributable Fraction (PAF) to assess the public health impact of the exposure (deprived neighborhood) in our population.<sup>17</sup>

Lastly, we conducted three sensitivity analyses:

1. We used the mid quintile Q3 as a reference group instead of the most affluent quintile Q1.
2. Instead of calculating the quintiles for each year separately and thereafter combining them, we calculated the quintiles for the 10 years together (alternative quintiles, Qa).
3. We excluded births with 22 and 23 weeks of gestation (22 weeks + 0 days to 23 weeks + 6 days) from the analysis.

All analyses were performed using SAS, version 9.4 and R statistics version 3.6.1. Permission for use and analysis of data for the purpose of the study was obtained from the Netherlands Perinatal Registry (data approval petition 18.09).

### **Details of ethics approval**

Anonymous registry data were used so no ethical approval was needed. Permission for use and analysis of data for the purpose of the study was obtained from the Netherlands Perinatal Registry (data approval petition 18.09).

## **RESULTS**

### **Study population**

In total, 1,662,687 singleton births with a known gestational age in the Netherlands were included over the 10-year study period. After excluding pregnancies with GA < 22 weeks or GA ≥ 43 weeks (1.3%) and pregnancies with missing postal code/deprivation score (1.1%), 1,621,709 singleton births remained. Lastly, pregnancies with congenital abnormalities (2.0%) and cases with antepartum fetal death (0.3%) were excluded, leaving 1,584,225 pregnancies for final analysis, see fig. 1 (flowchart).



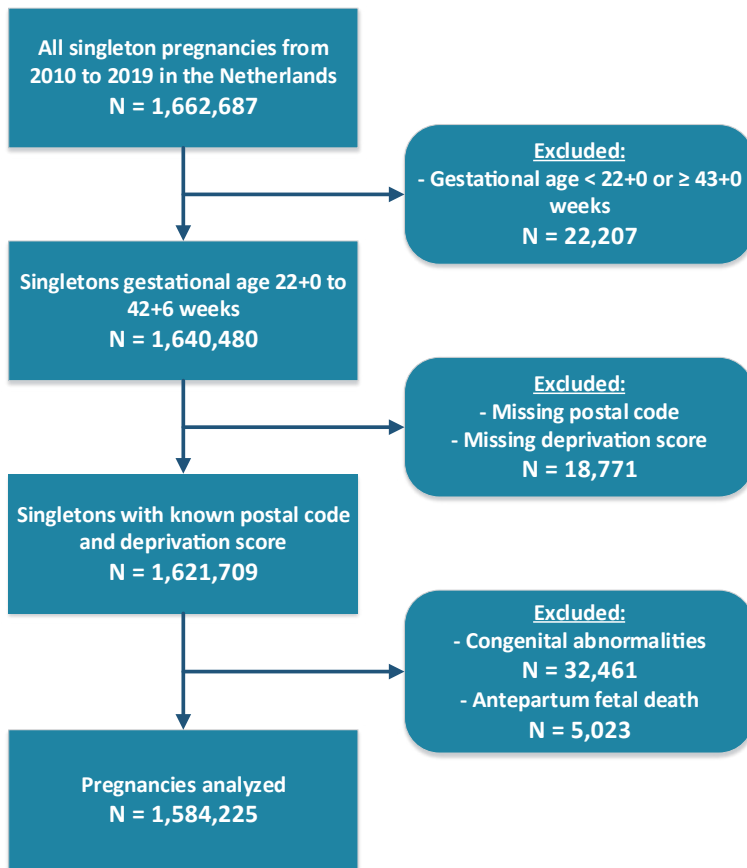


Figure 1. Study population flowchart

Baseline characteristics are presented in table 1. Women in the most deprived quintile Q5 had more teenage pregnancies (maternal age <20) than women in the affluent quintiles (1.9% vs. 0.5%). Women in Q5 were also more frequently pregnant of child 2 or more (Q5, 23% vs Q1, 17%,  $p < 0.001$ ). Older maternal age ( $\geq 40$  years) during pregnancy was seen more in the most affluent quintile Q1 than in the other quintiles. Furthermore, women in deprived neighborhoods are more likely to be non-western (39%) compared to Q1 (16%,  $p < 0.001$ ).

**Table 1.** Population characteristics by deprivation quintile

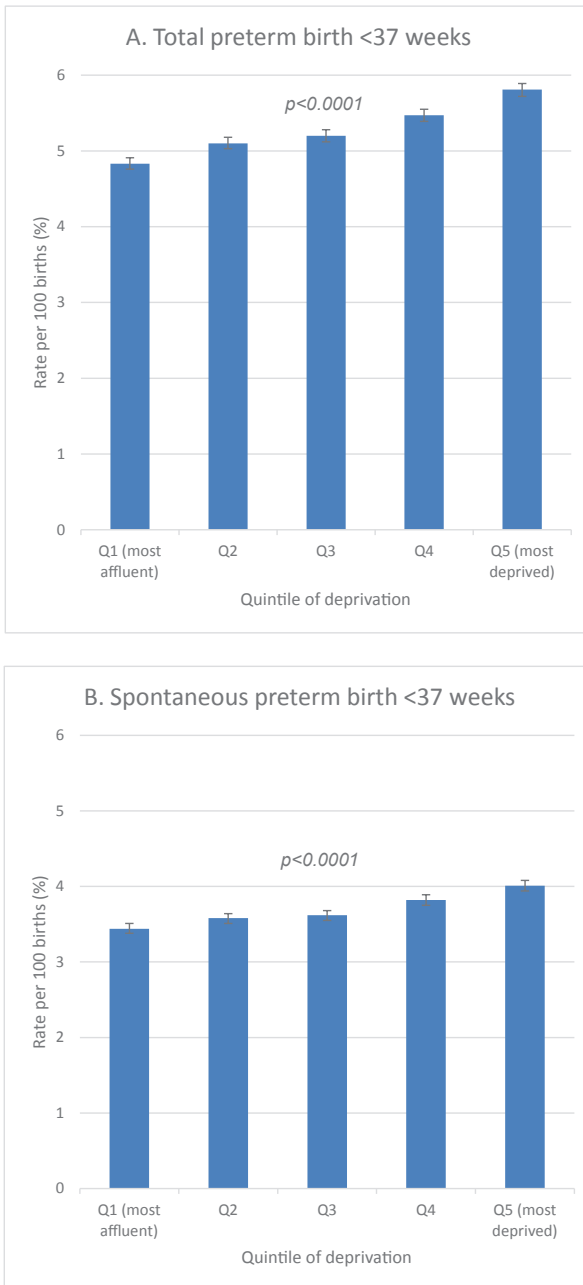
Characteristics	Deprivation quintile					Total	p-value
	Q1 (most affluent)	Q2	Q3	Q4	Q5 (most deprived)		
<b>N (%)</b>	319,552 (20.1)	316,147 (20.0)	317,323 (20.0)	316,335 (20.0)	314,868 (19.9)	<b>1,584,225</b>	
<b>Maternal age (y), SD</b>	31.8 (4.5)	30.8 (4.6)	30.4 (4.7)	30.2 (4.8)	29.7 (5.2)	<b>30.6</b>	<.0001
<b>Maternal age (%)</b>							<.0001
<20	0.5	0.8	1.0	1.2	1.9	<b>1.1</b>	
20-24	4.7	7.6	9.3	10.6	14.1	<b>9.3</b>	
25-34	67.4	70.5	70.5	69.2	65.7	<b>68.7</b>	
35-39	23.1	18.0	16.3	16.0	15.2	<b>17.7</b>	
≥40	4.2	3.2	2.9	3.0	3.2	<b>3.3</b>	
<b>Ethnicity (%)</b>							<.0001
Western	84.5	87.1	86.5	79.9	61.3	<b>79.9</b>	
Mediterranean	5.1	4.4	5.2	8.4	19.7	<b>8.6</b>	
Other non-Western	10.4	8.4	8.3	11.8	19.0	<b>11.6</b>	
<b>Parity (%)</b>							<.0001
P0	44.3	44.6	45.0	45.9	44.4	<b>44.8</b>	
P1	38.5	37.0	35.9	35.2	33.1	<b>35.9</b>	
P2+	17.2	18.5	19.2	18.9	22.5	<b>19.3</b>	
<b>Fetal Sex (%)</b>							0.27
Male	51.2	51.4	51.3	51.2	51.2	<b>51.3</b>	

P0: first birth, P1: second birth, P2+: third and higher birth, Q: deprivation quintile, SD: standard deviation

### Absolutes rates spontaneous preterm birth

Fig. 2 shows the absolute rates of PTB types per 100 births. The rate of total PTB <37 weeks for the whole cohort was 5.28% and 3.74% for spontaneous PTB <37 weeks.

For each of the preterm birth gestation groups <37, <32 and <28 weeks, the rate of SPTB increased with each quintile towards more deprivation, table 2. For instance, the rate of SPTB <37 weeks in most affluent quintile Q1 was 3.4%, where the rate in the most deprived quintile Q5 was 4.0%. The differences between the quintiles were statistically significant for all 3 spontaneous gestation groups, as well as for the iatrogenic and total PTB <37 weeks groups (table 2).



**Figure 2.** Rates of total and spontaneous preterm birth <37 weeks

Error bars represent the 95% confidence intervals

**Table 2.** Absolute rates of spontaneous, iatrogenic and total preterm birth per neighborhood deprivation quintile

Neighborhood deprivation	Spontaneous preterm birth			Iatrogenic PTB	Preterm birth
	SPTB <37 weeks (%)	SPTB <32 weeks (%)	SPTB <28 weeks (%)	IPTB <37 weeks (%)	Total PTB <37 weeks (%)
Q1 (most affluent)	3.44	0.42	0.17	1.39	4.83
Q2	3.58	0.45	0.19	1.51	5.10
Q3	3.62	0.43	0.18	1.58	5.20
Q4	3.82	0.48	0.22	1.64	5.47
Q5 (most deprived)	4.01	0.57	0.26	1.81	5.81
<b>Total</b>	<b>3.74</b>	<b>0.47</b>	<b>0.20</b>	<b>1.59</b>	<b>5.28</b>
p-value	<i>p</i> <.0001	<i>p</i> <.0001	<i>p</i> <.0001	<i>p</i> <.0001	<i>p</i> <.0001

Q: quintile of deprivation, STPB: spontaneous preterm birth

### Odds ratios

Odds ratios were calculated for the effect of neighborhood deprivation on SPTB <37 weeks using the most affluent quintile (Q1) as reference. It provides information on SPTB rates in Q2-Q5 relative to the SPTB rate in Q1.

All sequential quintiles were statistically significantly more at risk for SPTB compared to Q1, with increasing odds ratios with every quintile, resulting in an adjusted odds ratio (aOR) of 1.16 (95%CI 1.13-1.19) of Q5 compared to Q1; corresponding with a 16% higher rate of SPTB, see Table 3. The differences in risks between Q1 and Q5 were bigger for the more severe outcomes SPTB <32 weeks (aOR 1.27 (95% CI 1.18 – 1.36)) and SPTB <28 weeks (aOR 1.33 (95% CI 1.19 – 1.49)).

Using the PAF calculation, if all women lived in affluent neighborhoods (Q1), approximately 400 spontaneous preterm births could be prevented each year.

**Table 3.** Odds ratios for spontaneous preterm birth <37 weeks per neighborhood deprivation quintile

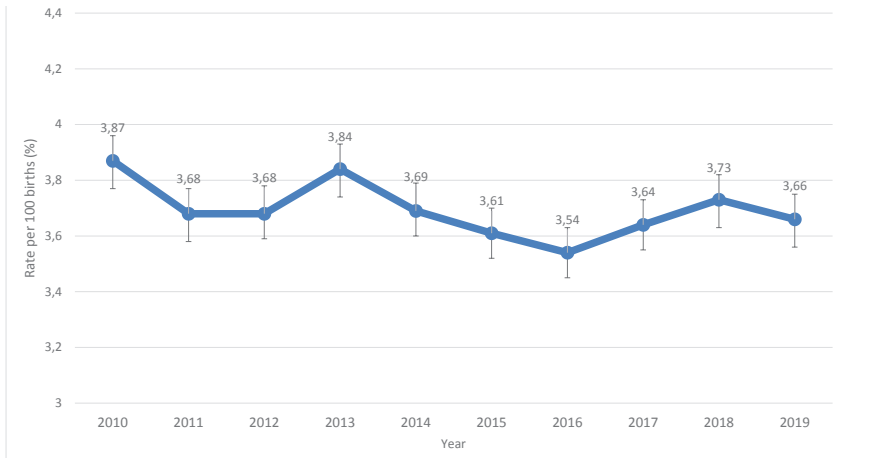
Neighborhood deprivation	SPTB <37 weeks				SPTB <32 weeks		SPTB <28 weeks	
	Unadjusted OR	95% CI	Adjusted OR*	95% CI	Adjusted OR*	95%CI	Adjusted OR*	95% CI
<b>Q1 (most affluent)</b>	<i>Reference</i>		<i>Reference</i>		<i>Reference</i>		<i>Reference</i>	
<b>Q2</b>	1.05	(1.02 – 1.07)	1.05	(1.02 – 1.08)	1.08	(1.00 – 1.17)	1.15	(0.98 – 1.24)
<b>Q3</b>	1.06	(1.03 – 1.09)	1.06	(1.03 – 1.09)	1.05	(0.97 – 1.13)	1.07	(0.95 – 1.20)
<b>Q4</b>	1.12	(1.09 – 1.15)	1.11	(1.08 – 1.14)	1.14	(1.06 – 1.22)	1.24	(1.11 – 1.39)
<b>Q5 (most deprived)</b>	1.17	(1.14 – 1.20)	1.16	(1.13 – 1.19)	1.27	(1.18 – 1.36)	1.33	(1.19 – 1.49)

CI: confidence interval, OR: odds ratio, Q: quintile of deprivation, SPTB: spontaneous preterm birth

\* Adjusted for maternal age, ethnicity, parity, fetal sex and year.

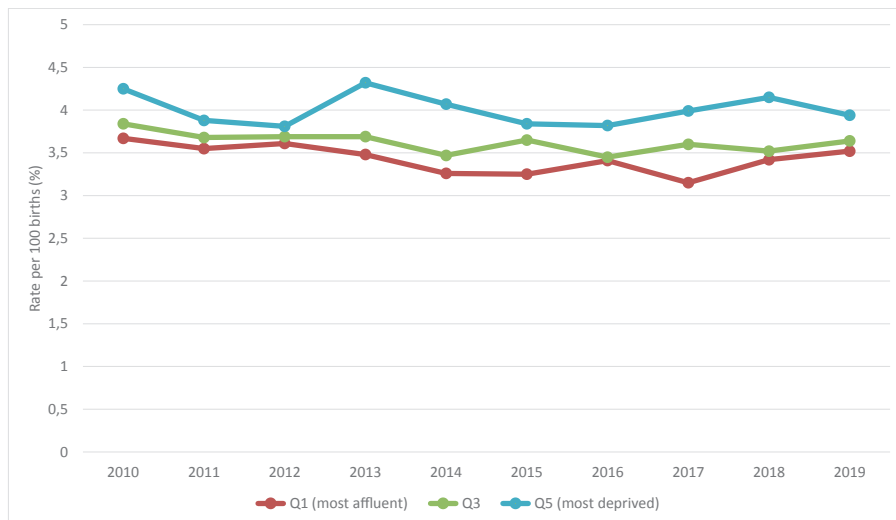
### Trends in SPTB between 2010 and 2019

The trend in SPTB <37 weeks from 2010 to 2019 is visualized in fig. 3. The graph shows that there has been a slight decline in SPTBs, from 3.9% to 3.7% ( $p < 0.0001$ ). Fig. 4 shows the trends from 2010 to 2019 per neighborhood deprivation quintile. We left Q2 and Q4 were left out for readability. All quintiles showed a decrease in SPTBs <37 weeks, but was only statistically significant in Q1, Q2 and Q5 ( $p < 0.004$ ,  $p = 0.032$  and  $p = 0.003$  respectively).



**Figure 3.** Trend in spontaneous preterm birth <37 weeks rates by year: 2010 - 2019

*Error bars represent the 95% confidence intervals*



**Figure 4.** Trends in SPTB <37 weeks rates per neighborhood deprivation quintile: 2010 -2019

*Quintiles 2 and 4 were left out for readability*

*Q1:  $p < 0.004$ ; Q2:  $p = 0.032$ ; Q3:  $p = 0.22$ ; Q4  $p = 0.37$ ; Q5:  $p = 0.003$*

The rate SPTB < 32 weeks and SPTB < 28 weeks showed a small increase over the years from 2010 to 2019 (SPTB < 32 weeks: from 0.44% to 0.56%;  $p < 0.0001$  and SPTB < 28 weeks from 0.19% to 0.25%,  $p < 0.0001$ , supplementary fig. 1 - 4).

To understand if the found association varied over time, we tested for interaction between neighborhood deprivation and year. The interaction term was not statistically significant ( $p = 0.053$ ). We repeated the main analysis for two five year periods: 2010-2014 and 2015-2019. Table 4 shows that the percentage of SPTB decreased from 3.75% in 2010-2014 to 3.63% in 2015-2019. The odds ratios of neighborhood deprivation quintiles Q2-Q5 in the last five years 2015-2019 were higher than in 2010-2014, indicating a relative increase of inequality of Q5 to Q2 compared to Q1 over time.

**Table 4.** Absolute rates and odds ratios for spontaneous preterm birth <37 weeks per neighborhood deprivation quintile for different time periods

Neighborhood deprivation	Spontaneous preterm birth <37 weeks					
	Period 1: 2010-2014			Period 2: 2015-2019		
	Rate (%)	Adjusted OR*	95% CI	Rate (%)	Adjusted OR*	95% CI
<b>Q1 (most affluent)</b>	3.52	<i>Reference</i>		3.45	<i>Reference</i>	
<b>Q2</b>	3.66	1.05	(1.01 – 1.09)	3.50	1.05	(1.01 – 1.09)
<b>Q3</b>	3.67	1.05	(1.01 – 1.08)	3.57	1.07	(1.03 – 1.11)
<b>Q4</b>	3.84	1.08	(1.04 – 1.12)	3.80	1.13	(1.09 – 1.17)
<b>Q5 (most deprived)</b>	4.6	1.14	(1.10 – 1.19)	3.95	1.18	(1.13 – 1.23)
<b>Total</b>	<b>3.75</b>			<b>3.63</b>		

OR: CI: confidence interval, Odds ratio, Q: quintile of deprivation, SPTB: spontaneous preterm birth

\* Adjusted for maternal age, ethnicity, parity, fetal sex and year.

Supplementary table 1 shows the absolute cases (%) for SPTB <37 weeks in the year 2010 compared to the year 2019 and the change between the rate in these two years. The biggest changes were observable in Q2 and Q5, where the rate decreased from 3.77% to 3.36% in Q2 and from 4.25% to 3.94% in Q5.

## Sensitivity analyses

The results from the three sensitivity analyses are displayed in supplementary tables 2 - 6.

First, when using the mid quintile Q3 as reference instead of Q1, crude ratio's showed an increased risk of SPTB <37 weeks the 2 more deprived quintiles Q4 and Q5 (both statistically significant) and a reduced risk for the 2 less deprived quintiles (Q1 statistically significant, Q2 non-statistically significant). After adjusting for risk factors, these associations remained.

Second, an alternative classification of the quintiles (Qa) resulted in the same SPTB <37 weeks rates per quintile and the same odds ratio's as in the main analyses.

Third, the exclusion of births with gestational age 22 weeks + 0 days to 23 weeks and 6 days, resulted in slightly lower rates of SPTB <37 weeks (overall SPTB rate 3.63%). The differences between the quintiles in SPTB remained.

## DISCUSSION

Our study suggests that women living in deprived neighborhoods are more at risk of spontaneous preterm birth than women from affluent neighborhoods. From 2010 to 2019, there was a significant decline in SPTB the Netherlands. However, the differences between deprived and affluent neighborhoods and SPTB increased over time.

A growing number of studies have revealed disparities in birth outcomes by neighborhood.<sup>9</sup> Despite the Netherlands being a prosperous country with a widely acknowledged equality in income and access to healthcare, i.e. mandatory health insurance and cost-free primary care, this study demonstrates a significant perinatal health inequality.

Only few studies reporting on neighborhood deprivation and preterm birth have differentiated between spontaneous and iatrogenic origin. Consistent with our results, Wood et al. (2001 to 2006, n=73,585) showed modest but significant differences in absolute rates between 5 quintile neighborhood categories in Alberta, Canada.<sup>18</sup> In another Canadian study, Joseph et al. reported that family income was associated with crude rates of SPTB, but adjusting for risk factors attenuated this effect.<sup>19</sup> In contrary, our findings suggest that - after adjusting for risk factors - even the second most affluent quintile Q2 has a higher risk of SPTB than the most affluent quintile Q1. These data show that even in a country where, in theory, access to health care is universal, the rate of SPTB in the most affluent neighborhood is the lowest, and is the highest in the most deprived neighborhood.

The overall decline in the rate of SPTB between 2010-2019 we demonstrated in this cohort follows an earlier decline from 2000 to 2007 in the Netherlands.<sup>7</sup> This decline might be the result of the introduction of preventive medical interventions, proven to be successful in reducing the risk of SPTB. For example, progesterone treatment as part of the national protocol 'prevention of recurrent spontaneous preterm birth', which started in 2007. In addition, screening for short cervical length in both low and high risk women has been introduced in the Netherlands in this time period. A nationwide policy program to reduce smoking across the whole population and restrictive law policies regarding smoking have been introduced in this time period, resulting in a lower percentage of women smoking during pregnancy.<sup>20</sup> This might also have contributed to a lower rate of SPTB.

The decline in SPTB rate compares favorably to other international SPTB rates, where most countries show a stable SPTB rate, and some countries show a small increase.<sup>21-22</sup>

The relative health inequality between the quintiles increased from 2010 to 2019. Although we demonstrated a decline in SPTB all 5 quintiles, the analysis in the two 5 year periods (2010-2014 vs. 2015-2019) indicates a widening of the gap between Q1 and Q5. Studies that focus on changing trends in inequalities in (spontaneous) preterm birth are limited. Gray et al. studied trends in overall preterm birth in Scotland from 1980 to 2003 and found increase in adjusted odds ratios between Q1 and Q5 over time, also indicating a widening of the equality gap.<sup>23</sup> Another study by Bertens et al, investigating the effect of neighborhood deprivation on adverse birth outcomes in the Netherland from 2003 to 2017, concluded that relative inequalities remained persistent over the observed period.<sup>13</sup> A study of Burgos et al. showed that for women living in a neighborhood where SES improved from low Q5 to medium Q3, the odds for preterm birth was still increased.. None of these studies differentiated between spontaneous and iatrogenic origin, which makes comparing results with our study difficult.

One could argue that the prevention programs health professionals have set up, both on community level as well as on individual medical level, more likely reach women in affluent neighborhoods with a low risk on preterm birth, and not the women with the highest risks. In our opinion, therefore, there is room for improvement, in both severe and medium deprived neighborhoods. In the Netherlands, a national program had been set up to improve birth outcomes and increase chances for an promising start (program "The first 1000 days").<sup>24</sup> These findings should be used by policy makers and health care professionals to strive for intervention programs to reduce the level of SPTB in all neighborhoods to the rate present in the most affluent Q1.

The underlying mechanisms by which neighborhood deprivation can increase the rate of SPTB cannot be explained by our study. Based on previous research, De Graaf et al. presented three non-mutually exclusive pathways of neighborhoods deprivation leading to SPTB.<sup>25-26</sup> First, the accumulation of risks at the individual level. Second, the provision of suboptimal care either through decreased access or lower performance. In the Netherlands, access to pregnancy health care is available for every woman at no additional costs, so in theory this should not provide a barrier for anyone. However, it is known that woman with lower healthcare skills, consult their health care providers at a later stage if problems arise. Third, exposure to environmental stressors and risk factors (e.g. crime, noise, air pollution), leading to psychosocial stress, ultimately leading tot SPTB.<sup>27-28</sup>

A major strength of the study is the nearly complete perinatal registry database of all births in the Netherland; the registry is almost 98% complete. Second, we focused only on singleton preterm births with spontaneous onset. This allowed us to investigate the association of neighborhood deprivation with SPTB, not blurred by the care-effect in iatrogenic preterm birth. Lastly, our data allowed us to observe trends in time over a recent 10 year period with more than 1.5 million cases.



The study also has some limitations. We used aggregate area-based scores to categorize women in deprivation quintiles, based on their place of residence. This means every woman from one neighborhood (4 digit postal code) falls into the same quintile, despite individual socioeconomic status. This may have led to an underestimation of the effect of severe deprivation as was also seen in other studies.<sup>12</sup>

The national perinatal registry does not contain reliable information on smoking, body mass index (BMI), drug use and the presence of a history of SPTB, all known risk factors for the outcome. Especially smoking and high BMI disproportionately impacts people in deprived communities. Not taking into account these factors in the adjustment analysis could have led to an overestimation of the effect of neighborhood deprivation on SPTB. Perined is putting effort into more reliable data collection, to enable more comprehensive analyses with these variables in the near future.

By definition, induction of labor and cesarean section after preterm PROM are considered as spontaneous onset. Caregivers however occasionally record these cases as iatrogenic onset, not taking the spontaneous rupture of membranes into account. This could have led to a slightly lower rate of SPTB, yet we believe that differences in reporting between the quintiles are unlikely.

Our study contributes to the current knowledge about risk factors for SPTB. This knowledge can improve efforts to reduce the risk for woman living in deprived neighborhoods. Although the odds ratios suggest small differences between the quintiles, the impact is substantial when assessed in terms of the numbers of preterm infants. For example, a difference of 270 spontaneous preterm births is seen between Q1 and Q5 in 2010 (Supplement B). Using the PAF calculation, if all women lived in affluent neighborhoods (Q1), approximately 400 spontaneous preterm births could be prevented each year; thereby influencing the lives of many families.

## CONCLUSION

Neighborhood deprivation is associated with a higher rate of spontaneous preterm birth. The higher the deprivation, the higher the rate of SPTB. Overall, the incidence of SPTB in the investigated time period gradually decreased. This study shows that there is room for improvement to further reduce SPTB rates, especially focusing on women in the more deprived neighborhoods.

## ACKNOWLEDGEMENTS

This study would not have been possible without registration in the national perinatal registry by all midwives, general practitioners, obstetricians and neonatologists in the Netherlands. PERINED ([www.perined.nl](http://www.perined.nl)) provided permission to analyze the anonymized dataset for the study objective (data approval petition 18.09).

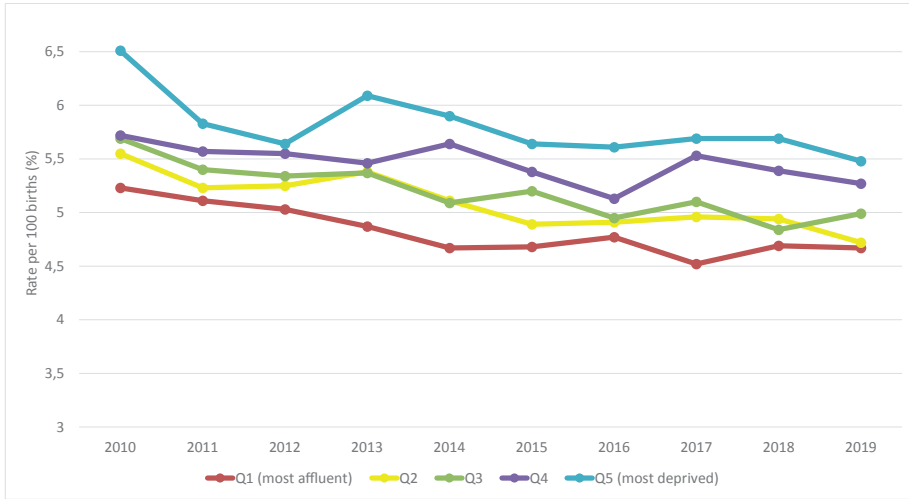
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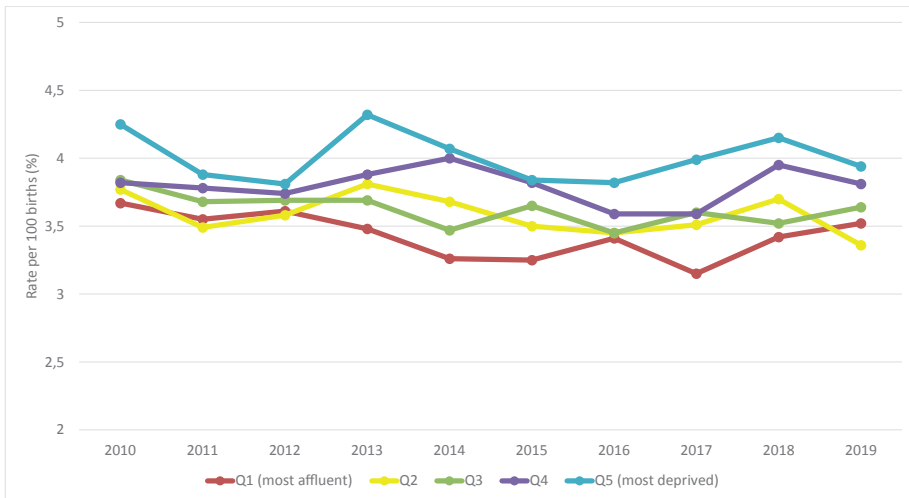
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## SUPPLEMENTS

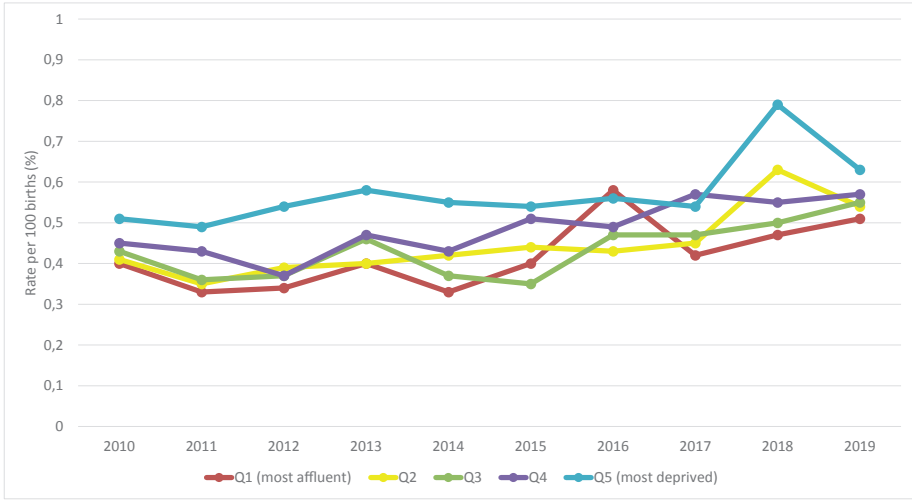
Supplementary figures 1 to 4: Trends in total preterm birth <37 weeks, and 3 groups of SPTB (<37 weeks, <32 weeks and <28 weeks) from 2010 to 2019 by neighborhood deprivation quintiles



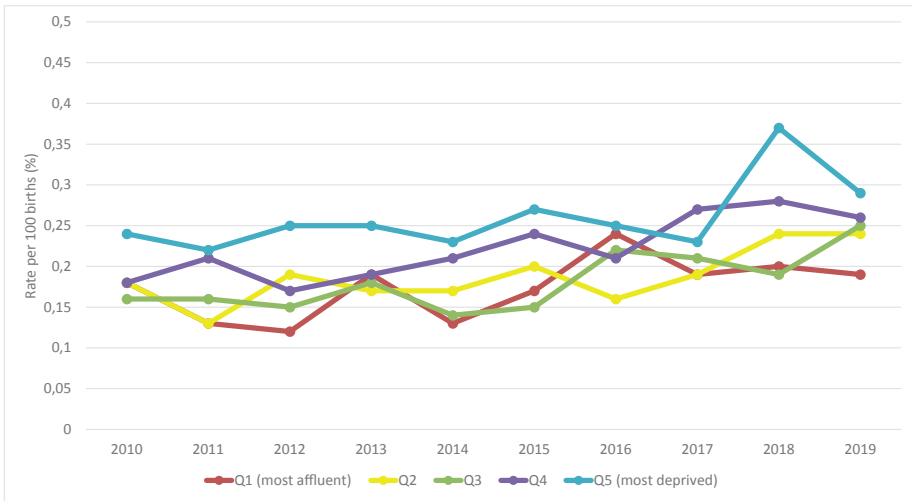
Supplementary figure 1. Trends in total preterm birth <37 weeks from 2010 to 2019 by neighborhood deprivation quintiles.



Supplementary figure 2. Trends in spontaneous preterm birth <37 weeks from 2010 to 2019 by neighborhood deprivation quintiles.



Supplementary figure 3. Trends in total spontaneous birth <32 weeks from 2010 to 2019 by neighborhood deprivation quintiles.



Supplementary figure 4. Trends in total preterm birth <28 weeks from 2010 to 2019 by neighborhood deprivation quintiles.

**Supplementary table 1.** Absolutes cases and rates for spontaneous preterm birth per neighborhood deprivation quintile in 2010 and 2019

Neighborhood deprivation	2010		2019		Difference	
	%	n	%	n	%	n
<b>Q1 (most affluent)</b>	3.67	1242	3.52	1097	-0.15	-145
<b>Q2</b>	3.77	1218	3.36	1037	-0.41	-181
<b>Q3</b>	3.84	1264	3.64	1127	-0.20	-137
<b>Q4</b>	3.82	1250	3.81	1206	-0.01	-44
<b>Q5 (most deprived)</b>	4.25	1399	3.94	1195	-0.31	-204
<b>Total</b>	<b>3.87</b>	<b>6373</b>	<b>3.66</b>	<b>5662</b>	<b>-0.21</b>	<b>-711</b>

Q: quintile of deprivation, SPTB=spontaneous preterm birth

**Supplementary table 2.** Sensitivity analysis I. Odds ratios for spontaneous preterm birth <37 weeks per neighborhood deprivation quintile with Q3 as reference

Neighborhood deprivation	Spontaneous preterm birth <37 weeks	
	Unadjusted OR	Adjusted OR*
<b>Q1 (most affluent)</b>	0.95 (0.92 – 0.97)	0.95 (0.92 – 0.97)
<b>Q2</b>	0.99 (0.96 – 1.02)	0.99 (0.96 – 1.02)
<b>Q3</b>	<i>Reference</i>	<i>Reference</i>
<b>Q4</b>	1.06 (1.03 – 1.09)	1.05 (1.02 – 1.07)
<b>Q5 (most deprived)</b>	1.10 (1.08 – 1.14)	1.10 (1.07 – 1.13)

OR: odds ratio, Q: quintile of deprivation

\* Adjusted for maternal age, ethnicity, parity, fetal sex and year

**Supplementary table 3.** Sensitivity analysis II. Absolute rates for spontaneous preterm birth and total preterm birth by neighborhood deprivation quintile, with an alternative subdivision into quintiles Qa

Neighborhood deprivation	SPTB <37 weeks (%)	SPTB <32 weeks (%)	SPTB <28 weeks (%)	Total PTB <37 weeks (%)
<b>Qa1 (most affluent)</b>	3.44	0.42	0.17	4.83
<b>Qa2</b>	3.58	0.44	0.19	5.09
<b>Qa3</b>	3.63	0.43	0.18	5.22
<b>Qa4</b>	3.83	0.48	0.22	5.47
<b>Qa5 (most deprived)</b>	3.99	0.58	0.27	5.79
<b>Total</b>	<b>3.69</b>	<b>0.47</b>	<b>0.20</b>	<b>5.28</b>
	<i>p</i> <.0001	<i>p</i> <.0001	<i>p</i> <.0001	<i>p</i> <.0001

Qa: alternative quintile of deprivation, SPTB: spontaneous preterm birth

**Supplementary table 4.** Sensitivity analysis II. Odds ratios for spontaneous preterm birth <37 weeks per neighborhood deprivation quintile with an alternative subdivision into quintiles Qa, Q1 as reference

Neighborhood deprivation	Spontaneous preterm birth <37 weeks	
	Unadjusted OR	Adjusted OR*
<b>Qa1 (most affluent)</b>	<i>Reference</i>	<i>Reference</i>
<b>Qa2</b>	1.04 (1.01 – 1.07)	1.04 (1.01 – 1.07)
<b>Qa3</b>	1.06 (1.03 – 1.09)	1.06 (1.03 – 1.09)
<b>Qa4</b>	1.12 (1.09 – 1.15)	1.10 (1.08 – 1.13)
<b>Qa5 (most deprived)</b>	1.17 (1.14 – 1.20)	1.16 (1.13 – 1.19)

OR: odds ratio, Qa: alternative quintile of deprivation

\* Adjusted for maternal age, ethnicity, parity, fetal sex and year

**Supplementary table 5.** Sensitivity analysis III. Absolute rates for spontaneous preterm birth and total preterm birth by neighborhood deprivation quintile (births 22+0 to 23+6 excluded)

Neighborhood deprivation	SPTB <37 weeks (%)	SPTB <32 weeks (%)	SPTB <28 weeks (%)	Total PTB <37 weeks (%)
<b>Q1 (most affluent)</b>	3.38	0.36	0.12	4.73
<b>Q2</b>	3.53	0.39	0.13	5.01
<b>Q3</b>	3.57	0.38	0.13	5.11
<b>Q4</b>	3.75	0.41	0.15	5.36
<b>Q5 (most deprived)</b>	3.93	0.49	0.18	5.69
<b>Total</b>	<b>3.63</b>	<b>0.41</b>	<b>0.14</b>	<b>5.18</b>
	<i>p&lt;.0001</i>	<i>p&lt;.0001</i>	<i>p&lt;.0001</i>	<i>p&lt;.0001</i>

Q: quintile of deprivation, SPTB: spontaneous preterm birth

**Supplementary table 6.** Sensitivity analysis III. Odds ratios for spontaneous preterm birth <37 weeks per neighborhood deprivation quintile (births 22+0 to 23+6 excluded) with Q1 as reference

Neighborhood deprivation	Spontaneous preterm birth <37 weeks	
	Adjusted OR*	Adjusted OR*
<b>Q1 (most affluent)</b>	<i>Reference</i>	<i>Reference</i>
<b>Q2</b>	1.05 (1.02 – 1.07)	1.05 (1.02 – 1.08)
<b>Q3</b>	1.06 (1.03 – 1.09)	1.06 (1.03 – 1.09)
<b>Q4</b>	1.11 (1.08 – 1.14)	1.10 (1.07 – 1.13)
<b>Q5 (most deprived)</b>	1.17 (1.14 – 1.20)	1.16 (1.13 – 1.19)

OR: odds ratio, Q: quintile of deprivation

\* Adjusted for maternal age, ethnicity, parity, fetal sex and year