PERINATAL MORTALITY

-System Related and Environmental Factors-

Virender Jashvant John Poeran

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PhD thesis, Erasmus University Rotterdam, The Netherlands

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"*The Dutch Vasa Previa Foundation is a non-profit organization whose primary objective is the reduction of infant mortality or permanent injury due to vasa previa. Some activities to achieve this are drawing attention to the risk of vasa previa within the relevant professional groups and aiming for adjustment of medical protocols, which are important for diagnosis and management of vasa previa. In addition, the foundation offers support and advice to anyone who is experiencing or has experienced vasa previa*."

Perinatal Mortality

– System Related and Environmental Factors –

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en omgevingsgebonden factoren

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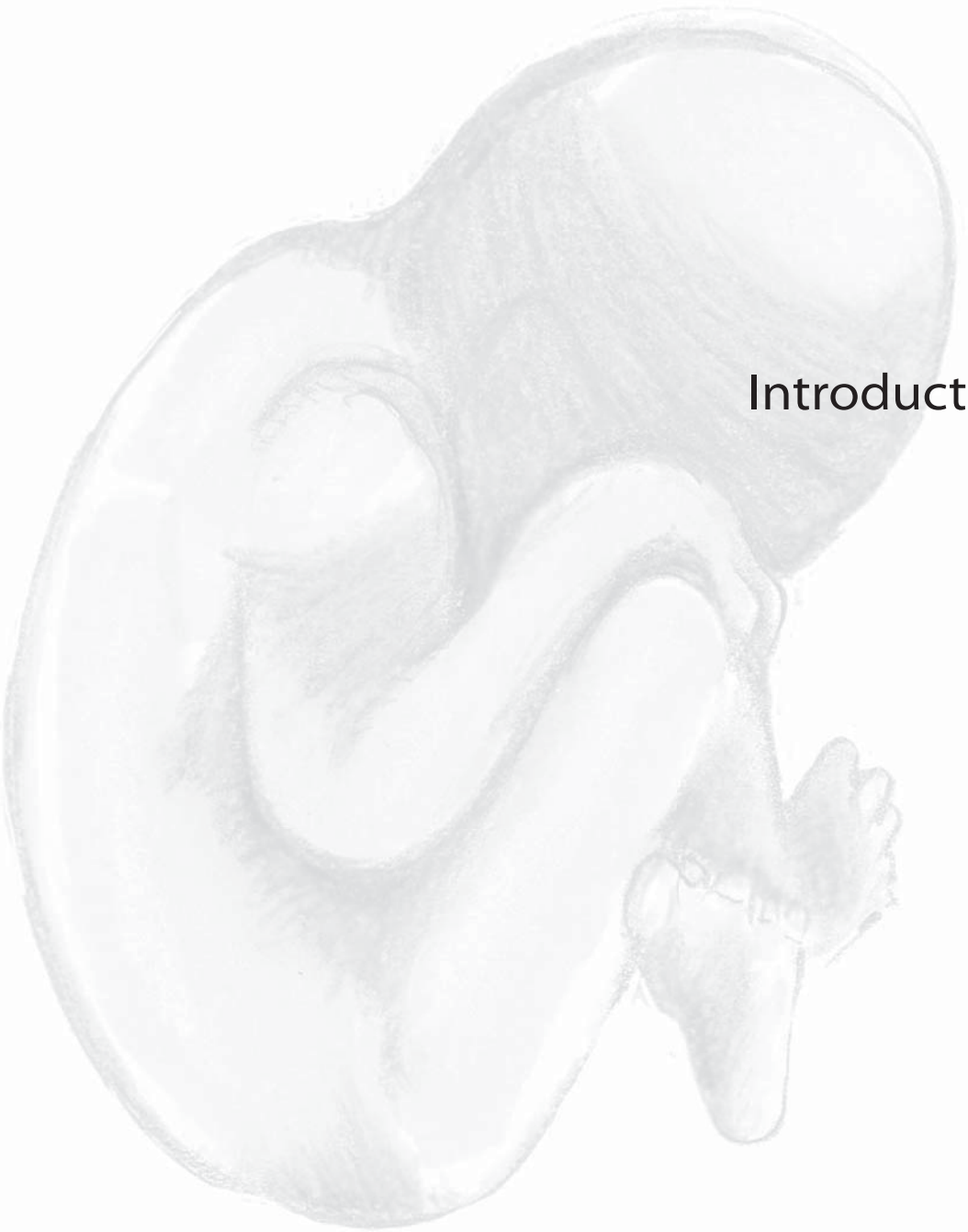
Introduction



In The Netherlands perinatal mortality rates exceed the European average.[1-3] On a second geographic level of comparison, i.e., within The Netherlands, adverse perinatal outcome rates are much higher in the four largest cities ('G4', i.e., Amsterdam, Rotterdam, The Hague, Utrecht).[4,5] Again, on a third level, i.e., within the G4-cities, adverse perinatal outcomes are overrepresented in socially deprived areas on the borough- and neighbourhood level.[6-9]

For long, population factors such as the high age of mothers at first childbirth, the high prevalence of multiple pregnancies (as a consequence of either assisted reproduction or high maternal age), and the increasing prevalence of non-Western pregnant women were held responsible for the high perinatal mortality.[1,2] However, these explanations were challenged as perinatal mortality remains high in analyses after exclusion of these risk groups.[10] Recent studies have thus addressed the potential role of other factors, in particular healthcare related factors and geographic (e.g., neighbourhood, environment) factors. Healthcare related factors put forward the unique system of Dutch obstetric care with independently practicing community midwives[11,12], travel time to hospital[13], and organisational characteristics of hospitals[14]. Candidate environmental factors are physical factors (e.g., air pollution[15,16] and ambient noise pollution[17]), and aggregate social factors like urban deprivation[4,7,8,18].

As stated, three geographic levels of inequalities in perinatal health are present, i.e., (1) The Netherlands vs. Europe, (2) regions and G4-cities vs. the remainder of the Netherlands, and (3) deprived vs. non-deprived neighbourhoods and boroughs within these G4-cities. The causal factors of perinatal inequalities may differ between the three geographic levels. An important cause (e.g., social deprivation) at one level may play an insignificant role at another level. Furthermore, as the majority of studies only deliver relative effect measures[5,6,8,11-14,19] with or without adjustment such as odds ratios, there is insufficient information on the importance of risk factors for perinatal mortality in absolute terms on the population level (e.g., population attributable risks), and the effect size of interdependence (interaction) between these risk factors. An estimate of attribution, including interaction, is critical to prioritise among options available to tackle perinatal mortality.

Finally, the definition of perinatal mortality has to be taken into account: death from 22 weeks of gestational age until 7 days postpartum. This definition combines stillbirth and neonatal mortality; hence, perinatal mortality differences may rest on different underlying patterns of these two components. Organisational studies within the Netherlands focus on intrapartum and neonatal mortality[14], but international comparison shows that in particular (term) stillbirth mainly contributes to the poor Dutch position on perinatal health.[1-3]

In response to the high perinatal mortality, the Dutch Minister of Health issued several measures[20] in 2008, of which two were deemed most important: (1) the appointment of an advisory board on pregnancy and birth, and (2) the request for a national report on priority setting of perinatal research. The advisory board proposed several recommendations in their final report ('A good beginning') in 2010.[20,21] Two important recommendations refer to (1) targeting pregnancy and deprivation (particularly in urban areas), and (2) universal access within 15 minutes to 'qualified professionals' (midwives, gynaecologists, paediatricians, anaesthesiologists, and operating theatre staff) to guarantee the quality of 24*7 acute obstetric care.

Most recommendations from the advisory group report were also mentioned in the research topics proposed in the ZonMw (The Netherlands Organisation for Health Research and Development) *Signalement* study, which provided the quantitative background to some of the aforementioned recommendations.[22] In this study, the unique Dutch system of obstetric care was addressed on patient, environment and healthcare related risk factors of perinatal mortality and morbidity. Also, the concept of 'Big4' was introduced; 'Big4' refers to four adverse pregnancy outcomes (perinatal morbidities) which precede perinatal mortality in 85% of cases.[22] 'Big4' morbidities were defined as the presence (single or combined) of congenital anomalies (list defined), preterm birth (<37th week of gestation), small for gestational age (SGA, birthweight below the 10th percentile for gestational age[23]) or low Apgar score (<7, 5 minutes after birth). Mostly, the first three 'Big4' morbidities offer some interventional opportunities in terms of diagnosis, preventive actions or treatments when timely detected. Figure 1.1 illustrates in a Venn diagram the relationship between (combinations of) 'Big4' morbidities and perinatal mortality. Mainly, the presence of more than one 'Big4' morbidity poses a significant risk for perinatal mortality, e.g., a low Apgar score combined with preterm birth occurs in 30.3% of all cases of perinatal mortality.[22]

The *Signalement* study proposed a 'stepwise' model to represent the causal chain to perinatal mortality.[22,24] The occurrence of 'Big4' morbidities ('step 1') and their progression to perinatal mortality ('step 2') is influenced by the accumulation[18] and interaction of patient, environment and healthcare related risk factors. This 'stepwise' model not only offers different windows for intervention, but also implies different ways to intervene in each step.

In addition to national policy measures to increase perinatal health, local and regional projects were launched. One comprehensive regional project is the 'Ready for a Baby' programme in the multi-ethnic city of Rotterdam.[25,26] This public health programme was instituted by the municipal council of Rotterdam, with collaboration of the local public health

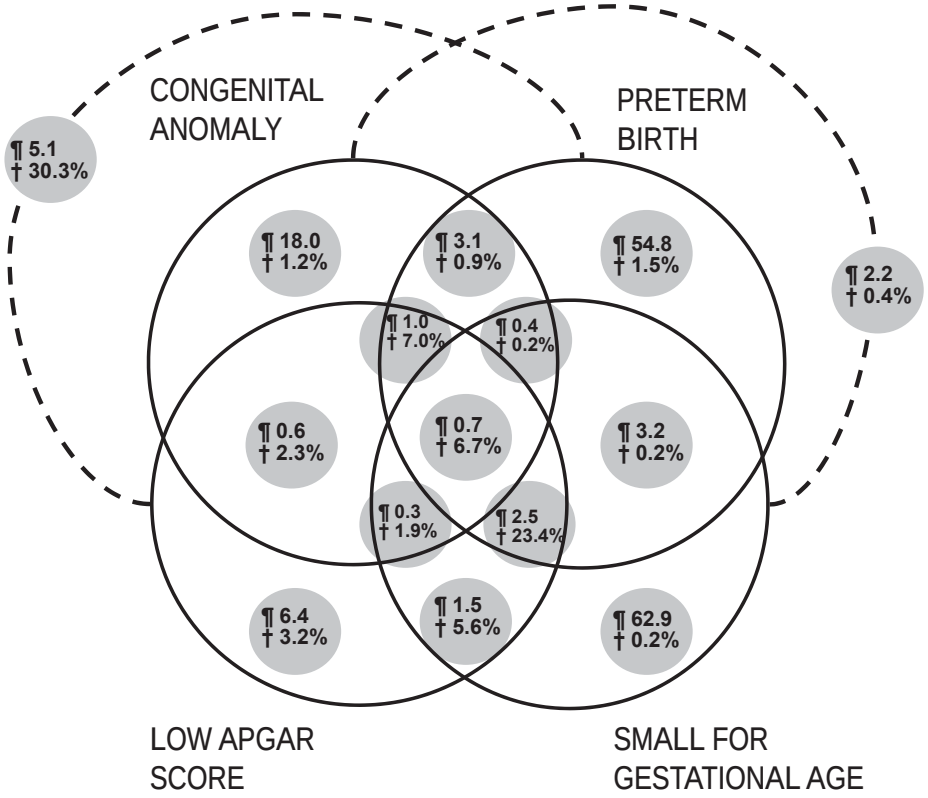


Figure 1.1 Venn diagram with the prevalence per 1,000 births (¶) of separate and combined 'Big4' morbidities and their contribution to all cases of perinatal mortality († in %); this adds up to 85% of all cases of perinatal mortality.

authorities (GGD Rotterdam Rijnmond), the university medical centre (Erasmus MC) and the healthcare professionals (e.g., gynaecologists, midwives, youth healthcare physicians). The main object of this 10-year programme is to improve perinatal health and to reduce perinatal mortality in all districts of Rotterdam to at least the current national average.[25,26] Key elements include: (1) better understanding of the large health differences between women living in deprived and non-deprived urban areas[5,6], (2) improving cooperation between healthcare professionals in the chain of obstetric healthcare[27], (3) developing improved methods for risk selection before and during pregnancy, and (4) methods to reach low educated and immigrant groups. Baseline measurement and continuous monitoring of the effect of interventions in the 'Ready for a Baby' programme are vital in this process.

AIM OF THIS THESIS

The aim of this thesis is to investigate the main contributing factors in adverse perinatal outcomes on the three geographic levels. In particular the relative role of patient-, environment- and healthcare related risk factors is studied in order to select rational health policies and to decrease gaps in perinatal health.

This thesis has two parts, each of which draws evidence from different sources. Part I describes results from the regional 'Ready for a Baby' programme, and part II contains studies on the national level, either ordered by 'ZonMw' (The Netherlands Organisation for Health Research and Development) concerning the '*Signalement*' study, 'SAZ' hospitals (a co-operative institution of circa 40 small general hospitals in The Netherlands), or the Ministry of Health, Welfare and Sport (regarding the national programme 'Healthy Pregnancy 4 All'). These studies will guide the reader through the eight research questions, the first two questions being addressed in part I (Rotterdam), and questions three to eight being addressed in part II (The Netherlands).

Part I. Rotterdam

1. How are perinatal mortality and morbidity distributed within the city of Rotterdam?
2. To what extent are determinants of social deprivation pertinent to differences in perinatal mortality and morbidity?

Part II. The Netherlands

3. What is the contributing role of patient (maternal and child) and non-patient (healthcare organisation, environment) risk factors in perinatal mortality on the population level?
4. What is a rational method to select priority areas for improved prevention of adverse perinatal outcome?
5. Is the Dutch system of risk selection adequate in separating low risk pregnancies from high risk pregnancies?
6. Can the unique feature of home birth in Dutch obstetric care still be offered as a safe option to a selected group of women?
7. Is centralisation of acute obstetric care an effective intervention, on the healthcare organisational level, to improve perinatal outcome?
8. Do climatological factors provide an additional explanation for inequalities in perinatal outcome?

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PART I

Perinatal health in Rotterdam

2

Urban perinatal health inequalities

J. Poeran, S. Denktaş, E. Birnie, G.J. Bonsel, E.A.P. Steegers

Journal of Maternal-Fetal and Neonatal Medicine. 2011;24:643-646.

ABSTRACT

Objective Large urban areas have higher perinatal mortality rates. In attaining a better understanding, we conducted an analysis on a neighbourhood level in Rotterdam, the second largest city of The Netherlands.

Methods Perinatal outcome of all single pregnancies (50,000) was analysed for the period of 2000-2006. The prevalences of perinatal mortality and perinatal morbidity were determined for every neighbourhood.

Results Large perinatal health inequalities exist between neighbourhoods in the city of Rotterdam with perinatal mortality rates as high as 37 per 1,000 births. The highest risks were observed in deprived neighbourhoods.

Conclusion We observed high levels of perinatal health inequalities in the city of Rotterdam which have not been previously described in the Western world. Accumulation of medical risk factors as well as socio-economic and urban risk factors seems to be a likely contributor.

INTRODUCTION

Health inequalities pose a complex problem in the field of public health, consisting of medical, social and socio-economic aspects. Considering the substantial long term effects, adverse perinatal health outcomes, along with perinatal health inequalities, are of particular interest.[1,2]

In The Netherlands, perinatal mortality exceeds the European average despite a high standard of mother and child healthcare.[3,4] A recent national study showed an increased risk of 12% on adverse perinatal outcomes in large urban areas; for non-Western women this additional risk was 26%.[3] The largest risk was observed in deprived neighbourhoods where ethnicity was expected to be a key etiologic factor.[3] However, the effect of living in deprived neighbourhoods, as compared to living elsewhere, was most prominent among Western women with an increased risk of 24%.[3] In attaining a better understanding of this complicated matter, we conducted an analysis on the neighbourhood level in the second largest city of The Netherlands, i.e., the city of Rotterdam where socio-economic inequalities are most obvious.

METHODS

The Netherlands Perinatal Registry contains population-based information of 96% of all pregnancies in The Netherlands. Source data are collected by 95% of midwives, 99% of gynaecologists and 68% of paediatricians (including 100% of Neonatal Intensive Care Unit paediatricians).[5] From this registry we selected perinatal outcome data of the city of Rotterdam (587,161 inhabitants in 2009) for the period of 2000-2006 (50,000 singleton pregnancies). The prevalence of adverse perinatal outcomes was determined for every neighbourhood using the 4-digit zip codes as recorded in The Netherlands Perinatal Registry, and municipal neighbourhood boundaries. Adverse perinatal outcome was defined as the occurrence of either perinatal mortality or perinatal morbidity. Perinatal mortality was defined as death from 22 weeks of gestational age until 7 days postpartum; perinatal morbidity was defined as the presence (single or combined) of congenital anomalies (list defined), small for gestational age (SGA, birthweight below the 10th percentile for gestational age[6]), preterm birth (<37th week of gestation) or low Apgar score (< 7, 5 minutes after birth). The prevalences of adverse perinatal outcomes were illustrated on a map of Rotterdam making use of separate colours per stratum.

RESULTS

Table 2.1 shows recent socio-demographic characteristics of the Rotterdam population in 2009 along with characteristics of the pregnant population from 2000-2006. During the study period (2000-2006) there were 50,000 singleton pregnancies in the city of Rotterdam. In almost half of these cases (49%) the mother had a non-Western background; almost half (48%) of women were primiparous. Teenage pregnancies accounted for 4% of all pregnancies. The geographic distribution of prevalences of perinatal mortality and perinatal morbidity is illustrated in figure 2.1. The neighbourhood-specific perinatal mortality rates varied from 2 to 34 per 1,000 births, for congenital anomalies from 10 to 91 per 1,000 births, for SGA from 38 to153 per 1,000 births, for preterm birth from 34 to 157 per 1,000 births and for low Apgar score from 4 to 37 per 1,000 births. The highest mortality rates were observed in deprived neighbourhoods.

Table 2.1 Socio-demographic characteristics of the Rotterdam population (2009, top) and characteristics of the Rotterdam pregnant population along with perinatal outcomes (2000-2006, bottom)

	Absolute number	Percentage
General population		
Ethnicity		
Western	373,115	64%
Non-Western		
Surinamese	52,206	9%
Antillean	20,261	3%
Turkish	46,203	8%
Moroccan	38,158	6%
Cape Verdean	15,103	3%
Non-Western, other	42,115	7%
Socioeconomic characteristics		
Having a job	300,236	51%
Dependent on social security	29,504	5%
Debt settlement	4,747	1%
Composition of household		
Living alone	139,367	24%
Couple without children	133,681	23%
Couple with children	216,874	37%
One-parent household	80,543	14%
Other	16,696	3%

Table 2.1 continues on next page.

Table 2.1 *Continued*

	Absolute number	Percentage
Pregnant population		
Total number of single pregnancies	50,000	100%
Neighbourhoods with <500 births	32	40%
Neighbourhoods with 500-1,000 births	27	33%
Neighbourhoods with >1,000 births	22	27%
Ethnicity		
Western	25,544	51%
Non-Western	24,456	49%
General characteristics		
Primiparity	24,050	48%
Teenage pregnancy	2,231	4%
Maternal age >36 years	1,548	3%
	Absolute number	**Per 1,000 births**
Perinatal outcomes		
Perinatal mortality	600	12
Top 5 best neighbourhoods	2	2
Top 5 worst neighbourhoods	53	23
Congenital abnormalities	1,333	27
Top 5 best neighbourhoods	44	13
Top 5 worst neighbourhoods	80	63
Small for gestational age	4,704	94
Top 5 best neighbourhoods	92	47
Top 5 worst neighbourhoods	378	118
Preterm birth	3,865	77
Top 5 best neighbourhoods	84	47
Top 5 worst neighbourhoods	204	119
Apgar score <7, 5 minutes after birth	1,221	24
Top 5 best neighbourhoods	9	5
Top 5 worst neighbourhoods	145	36

DISCUSSION

Impressive geographic perinatal health inequalities between neighbourhoods were observed in the second largest city of The Netherlands. In several neighbourhoods perinatal mortality and morbidity exceeded national levels observed well before the 1960s. The highest risks of adverse perinatal outcomes were seen in deprived neighbourhoods, supporting the theory of neighbourhood context as an individual risk factor for adverse

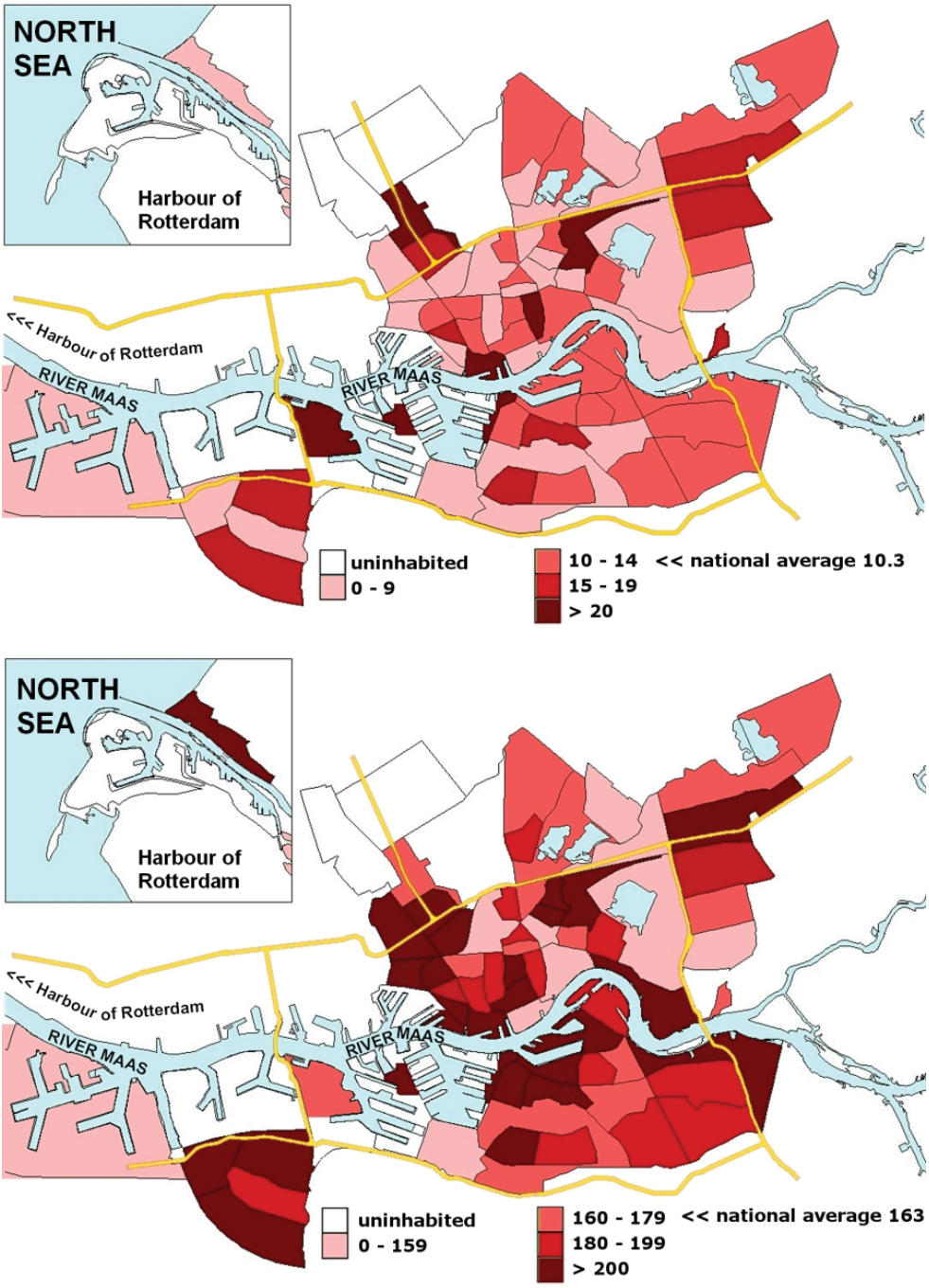

Figure 2.1 Neighbourhood inequalities in perinatal health in Rotterdam: perinatal mortality rates (top) and adverse perinatal outcome rates (bottom), both per 1000 births (2000-2006); yellow lines indicate highways.

perinatal outcomes. This may be due to various reasons (single or combined), e.g., stress due to unsafety or noise, environmental hazards (petrochemical industry, traffic pollution), and/or healthcare deficits (restricted healthcare access and insufficient healthcare performance).[3,7,8]

Ethnicity is an important risk factor for adverse perinatal outcomes.[9,10] However, to understand perinatal health patterns in large cities, urban and socio-economic risk factors should also be considered.[7] In particular, the accumulation of risk factors in urban communities may explain such perinatal health inequalities as studied in large cohort studies in the cities of Rotterdam ('Generation R')[10] and Amsterdam ('ABCD')[7,9]. Medical and non-medical risk factors may synergistically increase the risk of adverse perinatal outcomes to a far greater extent than can be explained by their individual etiologic contributions.

Some methodological issues should be discussed. The high number of pregnancies in the 7-year study period minimises the effect of yearly fluctuation of neighbourhood prevalences of adverse perinatal outcomes. As the risk of perinatal outcomes differs significantly between multiple and singleton pregnancies, only singleton pregnancies were studied. The Netherlands Perinatal Registry has a high degree of coverage of all pregnancies in The Netherlands (96% of all pregnancies are registered), another factor which augments the validity of our findings.

The usage of 4-digit zip codes allowed a clear illustration of the perinatal health inequalities between neighbourhoods. The disadvantage of using 4-digit zip codes is the great variety in neighbourhood size, expressed in geographical size as well as the number of inhabitants. Consequently, there is a risk of overestimating or underestimating the prevalence of rare adverse perinatal outcomes in small neighbourhoods. To minimise this effect we aggregated neighbourhood prevalences into two large groups of outcomes: perinatal mortality and perinatal morbidity.

To our knowledge, the observed degree of perinatal health inequalities has not been previously described in other Western cities. Considering the substantial long term health effects of perinatal morbidity for individuals and generations to come, we feel that these findings warrant further investigation and also should be given priority on the public health agenda as it is very likely that similar problems exist in comparable settings.

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3

Pregnancy and birth in Rotterdam: a local health report

J. Poeran, S. Denktaş, E. Birnie, H.J. van der Weg, A.J.J. Voorham, E.A.P. Steegers, G.J. Bonsel

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(Article in Dutch, translated into English for this thesis)

ABSTRACT

Within The Netherlands, the city of Rotterdam has high rates of perinatal mortality and morbidity (congenital anomalies, preterm birth, small for gestational age, low Apgar score: so-called 'Big4' morbidities). Following this observation, the municipality of Rotterdam initiated an elaborate public health initiative to reduce perinatal mortality and morbidity. This initiative, 'Ready for a Baby', is a collaboration between the municipality, the academic medical centre (Erasmus MC) and the local public health authorities (GGD Rotterdam Rijnmond). The main target is to decrease perinatal mortality and 'Big4' morbidities in Rotterdam. An important first step was the measuring of baseline perinatal health in the city of Rotterdam. Data were derived from The Netherlands Perinatal Registry for the period 2000-2007 (n=56,443 singleton pregnancies). We looked at prevalences, absolute and standardised (for parity, maternal age, ethnicity and socioeconomic status), of perinatal mortality and 'Big4' morbidities within the several boroughs of Rotterdam. Additionally, we looked at socio-demographics and healthcare related factors. Large differences in perinatal mortality and morbidity exist between boroughs in the city of Rotterdam, with most likely different causes per borough. In some boroughs healthcare related factors and environmental factors play an important role while in other boroughs characteristics of the pregnant women, e.g., lifestyle or ethnicity are more important causes. These data are crucial in the development of policies specifically targeted to the several boroughs to decrease perinatal morbidity and mortality within the city of Rotterdam.

INTRODUCTION

A recent Dutch study showed women in the four largest cities of The Netherlands to be at increased risk for perinatal mortality and related perinatal morbidity.[1,2] In particular, Rotterdam has high rates of perinatal mortality and preceding perinatal morbidity, the most important being congenital anomalies, preterm birth (<37 weeks' gestation), small for gestational age (SGA, birthweight <p10) and a so-called low Apgar score, 5 minutes after birth.[3] Due to their importance in perinatal mortality (they precede 85% of perinatal mortality) we refer to these four precursor morbidities as 'Big4'. In 2008, following the observations in the city of Rotterdam, the municipal authorities started an elaborate public health initiative in collaboration with the academic medical centre (Erasmus MC) and the local public health authority (*GGD Rotterdam Rijnmond*): the 'Ready for a Baby' programme (in Dutch: *Klaar voor een Kind*, see www.klaarvooreenkind.nl). The aim of this 10-year initiative is to reduce perinatal mortality and perinatal morbidity in the city of Rotterdam to the national level.[4,5]

The first step in this initiative was to thoroughly record perinatal mortality, morbidity, and their attributing factors in Rotterdam. These attributing factors can pertain to the pregnant women (e.g., smoking, folic acid use or ethnicity), their environment (e.g., neighbourhood social quality or environmental pollution), or they can be related to healthcare (e.g., access to care or availability of facilities). However, as these factors are not registered as such, we defined several indicators (which could be derived from existing data) to approximate the separate role of patient, healthcare and environment related risk factors for adverse perinatal outcome.[3] Depending on the role of these specific indicators, neighbourhood- and risk factor-specific policy will be possible within the city of Rotterdam.[6,7] This approach is analogous to the national 'Public Health Forecast' reports ('*VTV*') by the National Institute for Public Health and the Environment ('*RIVM*').[8] This manuscript describes the used methods and includes a small selection from the Rotterdam borough reports on perinatal health. These reports have been discussed in the Rotterdam municipal council in 2011 as well as the borough councils, and are now publicly available.[6]

METHODS

The Netherlands Perinatal Registry

Data regarding the indicators (socio-demographics, healthcare related and perinatal outcome) were derived from The Netherlands Perinatal Registry (www.perinatreg.nl),

containing complete population-based information of >97% of all pregnancies in The Netherlands. Source data are routinely collected by 94% of midwives, 99% of gynaecologists and 68% of paediatricians including 100% of Neonatal Intensive Care Unit paediatricians. Data were available for 2000-2007; only singleton pregnancies were included.

Indicators

Perinatal outcome

The most important outcome indicators were perinatal morbidity and perinatal mortality. The former comprised the 'Big4' morbidities (congenital anomalies, SGA, preterm birth and low Apgar score). Congenital anomalies are recorded postpartum and classified through a standard coding system by organ system (8 categories, 71 subcategories, see www.perinatreg.nl). Preterm birth is defined as birth before 37 weeks of gestational age; small for gestational age (SGA) is defined as a birthweight below the 10th percentile for gestational age. An Apgar score is a 0-10 score based on complexion, pulse rate, reflex irritability, muscle tone and breathing; a low Apgar score is defined as <7, 5 minutes after birth. Perinatal mortality is the sum of fetal mortality (intrauterine death from 22 weeks of gestational age) and early neonatal mortality (death in the first 7 days after birth).

Healthcare related indicators

Healthcare related indicators included in the borough reports refer to: (1) the proportion of women with a late first antenatal booking visit (after 14 weeks of gestational age), and (2) the level of care at start of labour (primary care under supervision of a community midwife, or secondary/tertiary care under supervision of an obstetrician). Women with a late antenatal booking visit will not fully benefit from healthy lifestyle advices during pregnancy, concerning an optimal pregnancy outcome. Moreover, due to their gestational age, these women are not able to participate in first trimester screening for chromosomal anomalies, mainly Down syndrome. Also, ultrasound determination of gestational age is less precise after the first trimester; this will result in a less precise due date and the definition of a possible preterm birth.[3,9] The second indicator refers to the unique system of obstetric care in The Netherlands. This system is characterised by risk-based levels of care: primary care for low risk pregnancies, provided by independently practicing community midwives, and secondary/tertiary care for high risk pregnancies provided by obstetricians. Through risk selection, this distinction between assumed low risk and high risk pregnancies is made by primary care community midwives. Therefore, the proportion of women starting labour in primary care (supposedly low risk) is an important healthcare related indicator.

We used the prevalence of 'Big4' as an indicator of high risk pregnancy. Based on the 'Big4' prevalence per borough, an estimation can be made on the expected proportion of women starting labour in primary care and the degree to which high risk pregnancies are detected and referred, e.g., high 'Big4' prevalence with low proportion of women starting labour in primary care may refer to adequate risk selection.

Demographics

Demographic indicators pertain to ethnicity (Western, non-Western), and maternal age (<20 years, >35 years). Non-Western women are at increased risk for adverse pregnancy outcome including perinatal mortality.[1] This increased risk also regards pregnant women outside the range of maternal age 20-35 years.[10,11]

Other

The other indicators refer to parity (primiparous / multiparous) and the environment of the pregnant woman (neighbourhood social quality as measured by a composite indicator). Both indicators are associated with perinatal outcome, including perinatal mortality.[1,3] 'Deprived neighbourhood' was defined as having a 'Social Index' score of <6. The 'Social Index' (SI) is a composite 0-10 measure indicating neighbourhood social quality as annually determined by the Rotterdam Centre for Research and Statistics (see www.cos.rotterdam.nl). The SI is only available for the city of Rotterdam, but is preferred over the less refined national 'yes / no deprived neighbourhood' variable based on 4-digit zip codes and an official public list of 40 deprived zip code based neighbourhoods.[12,13] Moreover, this national variable indicates some Rotterdam neighbourhoods as 'non-deprived' while their Social Index score indicates otherwise.

Geographics

In the study period, the city of Rotterdam consisted of 13 boroughs (in March 2010, a 14th was added, *Rozenburg*). These boroughs were defined based on 4-digit postal code areas, the lowest level of aggregation in The Netherlands Perinatal Registry. Next to using crosstabs, we also illustrated outcomes per borough on a map of Rotterdam, using shades of red to indicate outcome levels (figure 3.1, the darker the shade the more negative the outcome). Maps were constructed using ESRI® ArcGIS version 9.3 (Environmental Systems Research Institute, Inc., USA). Geographic information was obtained from the Rotterdam municipal services. Due to the availability of data from 8 years (2000-2007) we could avoid too small numbers of pregnancies per geographic area.

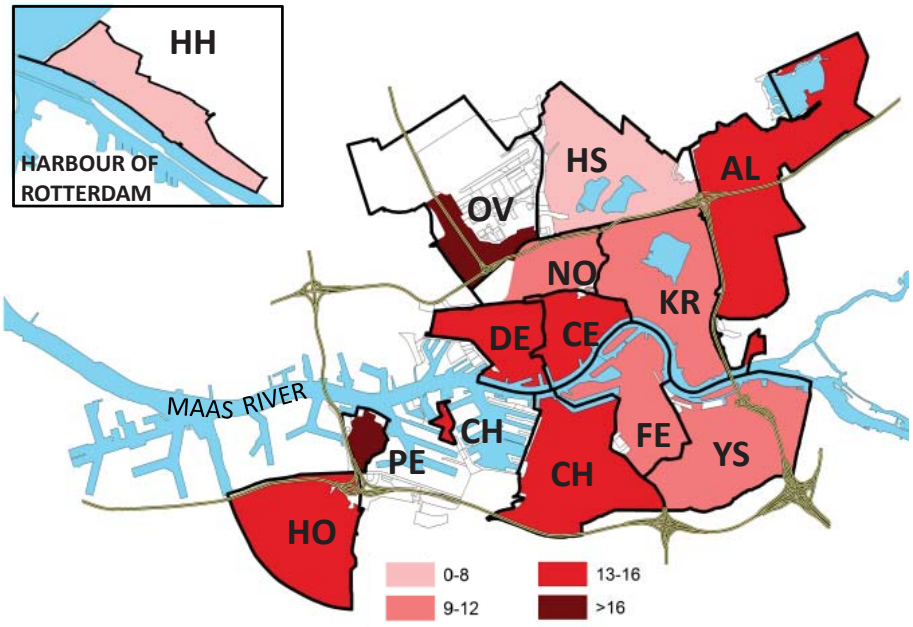

Figure 3.1 Perinatal mortality (per 1,000 births) in the 13 boroughs of Rotterdam. Rotterdam average 11.5 per 1,000 births. National average 9.7 per 1,000 births. Names of boroughs are abbreviated: HH *Hoek van Holland*, OV *Overschie*, HS *Hillegersberg-Schiebroek*, AL *Prins Alexander*, NO *Noord*, DE *Delfshaven*, CE *Stadscentrum*, KR *Kralingen-Crooswijk*, HO *Hoogvliet*, PE *Pernis*, CH *Charlois*, FE *Feijenoord*, YS *IJsselmonde*.

Standardisation

In comparing indicators between the 13 boroughs, differences in socio-demographics have to be taken into account as they have an effect on perinatal outcome, e.g., a borough with a high number of non-Western women, a high number of teenage pregnancies, or women from neighbourhoods with a low Social Index, will generally have a higher prevalence of adverse perinatal outcomes. To make an 'honest' comparison between the boroughs, differences in socio-demographics have to be accounted for. Standardisation is a method to account for this. With 'direct standardisation' the 'expected' outcome levels per borough are calculated for the scenario that the concerning borough has the same socio-demographic composition (by maternal age, parity, Social Index and ethnicity) as the whole city of Rotterdam. Persisting differences in outcome after standardisation, may be attributable to

other factors (than socio-demographics) such as quality of healthcare or local health policies. The most important limitation of standardisation is that it implies that the standardisation factors (in this case maternal age, parity, Social Index and ethnicity) are non-modifiable. In other words: the effect of these four standardisation factors is disregarded when looking only at standardised figures. Another important limitation refers to boroughs differing greatly (compared to the whole city of Rotterdam) in socio-demographic composition, with accompanying large expected differences in perinatal outcomes. Standardisation might moderate these significant differences seen in absolute outcomes. Therefore, both crude and standardised outcomes are important to observe. The technique of direct standardisation is described in more detail elsewhere.[14]

Selection from the borough reports

As the borough reports are extensive we included only a selection in this manuscript to illustrate the most important conclusions. Both crude and standardised rates are included in the borough reports.[6] The selection for this manuscript pertains to:

- crude (absolute, unstandardised) perinatal mortality and 'Big4' prevalence per borough (table 3.1);
- crude perinatal mortality per borough visualised on a map of Rotterdam (figure 3.1);
- crude and standardised indicator rates compared for two boroughs (*Hoogvliet* and *Overschie*, table 3.2). These boroughs were chosen to illustrate that factors attributing to perinatal mortality (increased in both boroughs) are thought to differ for each borough.

RESULTS

Overview

There were 56,443 singleton pregnancies in the study period (2000-2007) in the city of Rotterdam. Table 3.1 and figure 3.1 illustrate crude perinatal mortality (per 1,000 births) for each borough. Additionally, table 3.1 shows crude 'Big4' prevalence per borough. Perinatal mortality varies from 3.4 (*Hoek van Holland*) per 1,000 births to 21.1 (*Pernis*) per 1,000 births. 'Big4' prevalence varied from 140.6 (*Hillegersberg-Schiebroek*) per 1,000 births to 205.7 (*Charlois*) per 1,000 births.

Table 3.1 Perinatal mortality (†) and 'Big4' per 1,000 births, for The Netherlands, Rotterdam and the Rotterdam boroughs

Geographic area	†	'Big4'
The Netherlands	9.7	152.7
Rotterdam	11.5	181.1
Boroughs		
Charlois	13.3	205.7
Delfshaven	13.3	192.8
Feijenoord	11.3	181.1
Hillegersberg-Schiebroek	7.6	140.6
Hoek van Holland	3.4	181.8
Hoogvliet	12.5	203.5
IJsselmonde	10.3	184.4
Kralingen-Crooswijk	12.0	178.6
Noord	8.9	174.3
Overschie	16.3	185.7
Pernis	21.1	165.7
Prins Alexander	12.8	168.6
Stadscentrum	13.1	171.3

Rotterdam compared to The Netherlands

Table 3.2 provides an overview of the indicators for The Netherlands, Rotterdam, and two boroughs (*Hoogvliet* and *Overschie*). The first two columns ('A' and 'B') compare the indicators for The Netherlands with Rotterdam. Columns 3 to 6 refer to the borough of *Hoogvliet*; columns 7 to 10 refer to the borough of *Overschie*.

The first two columns illustrate a higher perinatal mortality for Rotterdam compared to The Netherlands (11.5 compared to 9.7 per 1,000 births, respectively). Also, 'Big4' prevalence is higher in Rotterdam (181.1 compared to 152.7 per 1,000 births in The Netherlands). Rotterdam also has a higher proportion of women with a late antenatal booking visit (36.1% compared to 20.7% for The Netherlands), and a higher proportion of non-Western women (48.7% compared to 16.2%).

Comparing boroughs: *Hoogvliet*

Column 3 ('C') from table 3.2 shows crude rates for the borough of *Hoogvliet*. The proportional change compared to the crude rates for Rotterdam ('B') is shown in the 4th column ('C-B'). In particular preterm birth (+38.3%) and low Apgar score (+34.0%) are increased in the

Table 3.2 Indicators listed for two boroughs, *Hoogvliet* and *Overschie*. Strongly deviating levels are coloured to enhance interpretation*.

			Borough of Hoogvliet				Borough of Overschie			
Indicator	NLDS A	RDAM B	ABS C	CRU Δ% C-B	STN D	STN Δ% C-D	ABS E	ABS Δ% E-B	STN F	STN Δ% E-F
Perinatal outcome (per 1,000)										
Congenital anomalies	27.0	26.4	21.4	-19.0%	25.8	-17.1%	27.6	4.8%	27.0	2.2%
Preterm birth	61.5	69.2	95.7	38.3%	67.9	41.0%	75.8	9.5%	70.5	7.6%
Small for gestational age	71.5	93.1	89.9	-3.4%	82.6	8.9%	93.6	0.5%	91.1	2.6%
Low Apgar score	11.5	15.0	20.0	34.0%	13.0	54.5%	14.2	-5.2%	14.6	-2.7%
Total 'Big4' morbidities	152.7	181.1	203.5	12.4%	169.3	20.2%	185.7	2.5%	180.9	2.7%
Perinatal mortality	9.7	11.5	12.5	8.4%	10.3	20.9%	16.3	41.8%	11.3	44.2%
Fetal mortality	6.9	8.3	8.5	2.5%	7.3	16.6%	13.5	63.1%	8.1	66.5%
Early neonatal mortality	2.8	3.2	4.0	23.6%	3.1	31.3%	2.8	-12.6%	3.2	-11.8%
Healthcare related (%)										
Antenatal booking at >14 weeks	20.7%	36.1%	36.0%	-0.3%	27.5%	31.0%	23.8%	-34.1%	32.6%	-27.1%
Start labour in primary care	49.0%	47.6%	20.3%	-57.4%	46.1%	-56.0%	57.4%	20.4%	47.0%	22.1%
Pregnant population (%)										
Non-Western women	16.2%	48.7%	36.6%	-24.9%	N/A	N/A	36.8%	-24.4%	N/A	N/A
Western teens	1.2%	2.9%	2.9%	-0.5%	N/A	N/A	1.7%	-40.6%	N/A	N/A
Non-Western teens	4.3%	5.8%	6.9%	18.7%	N/A	N/A	5.2%	-11.1%	N/A	N/A
Western 35+ years old	20.4%	22.0%	17.8%	-19.1%	N/A	N/A	22.9%	3.8%	N/A	N/A
Non-Western 35+ years old	16.6%	14.8%	15.1%	2.3%	N/A	N/A	12.5%	-15.1%	N/A	N/A
Other (%)										
Primiparous women	46.1%	48.0%	44.6%	-7.1%	N/A	N/A	49.2%	2.4%	N/A	N/A
Neighbourhood Social Index < 6.0	N/A	58.3%	0.0%	-100.0%	N/A	N/A	49.7%	-14.8%	N/A	N/A

-5% to -10% | more than -10% | more than +10%
+5% to +10% | +10% to +15%

* Shades of green represent a positive deviation; yellow, orange and red represent a negative deviation. Colour coding is not used for 'the proportion of women starting labour in primary care' as there is no negative or positive judgment possible without taking into account other factors such as antenatal risk load ('Big4').

borough of Hoogvliet (compared to Rotterdam). On the other hand, congenital anomalies are decreased (-19.0%). The perinatal mortality rate (12.5 per 1,000 births) is increased compared to Rotterdam (+8.4%); mainly due to an increase in early neonatal mortality (+23.6%). Another notable finding is that there is a smaller proportion of women starting labour in primary care under the supervision of a primary care community midwife (-57.4%). Also, the *Hoogvliet* population differs greatly from the Rotterdam population with less non-Western pregnant women (-24.9%) in *Hoogvliet*, but an increased proportion of non-Western pregnant teens (+18.7%). There are no neighbourhoods with a low Social Index score (<6) in this borough.

Column 5 ('D') shows standardised rates for *Hoogvliet*; column 6 ('C-D') shows the comparison between the crude ('C') and standardised ('D') rates. Except for congenital anomalies (-17.1%) all adverse perinatal outcomes have a higher prevalence than expected based on standardisation, in particular preterm birth (+41.0%), low Apgar score (+54.5%) and early neonatal mortality (+31.3%). Furthermore, the proportion of women with a late antenatal first booking is higher (+31.0%) than would be expected based on standardisation. By contrast, the proportion of women starting labour in primary care is lower (-56.0%) than expected.

Comparing boroughs: *Overschie*

Analogous to the rates for *Hoogvliet*, columns 7 ('E') and 8 ('E-B') from table 3.2 show crude rates for the borough of *Overschie* (column 7) and the proportional difference with the crude Rotterdam rates (column 8). Crude differences with Rotterdam are relatively small for separate 'Big4' prevalences with a maximum difference of +9.5% for preterm birth. However, relative perinatal mortality is increased (+41.8%), mainly due to an increased fetal mortality (+63.1%). The proportion of women with a late antenatal booking visit is lower (-34.1%) compared to Rotterdam. However, a greater proportion of women start labour in primary care (+20.4%). Also notable is the decreased proportion of non-Western pregnant women in *Overschie* (-24.4%), and also less pregnant women living in a neighbourhood with a low Social Index (<6, -14,8%). Columns 9 ('F') and 10 ('E-F') show standardised rates and their comparison with crude rates, respectively. Standardised 'Big4' rates do not differ much compared to the crude rates for this borough, similar to the crude differences with Rotterdam as shown in the 'E-B' column. Again, perinatal mortality is higher (+44.2%), the proportion of women with a late antenatal booking is lower (-27.1%), and the proportion of women starting labour in primary care is higher (+22,1%).

DISCUSSION

In Rotterdam, large differences exist in crude and standardised perinatal mortality and 'Big4' rates between boroughs. Next to differences in outcome, there are also large differences in socio-demographics and healthcare related factors. The Rotterdam borough reports on perinatal health provide possible explanations on borough-specific backgrounds on increased perinatal mortality or 'Big4' prevalence, e.g., maternal or child factors such as primiparity or having a SGA baby, healthcare related factors such as a suboptimal selection (and referral) of high risk pregnancies, or environment related factors such as living in a deprived neighbourhood.

The comparison between the boroughs of *Hoogvliet* and *Overschie* showed an increased perinatal mortality in both boroughs, however, with large differences in 'Big4' prevalence, healthcare related factors and the proportion of non-Western pregnant women. What particularly stands out is the highly increased perinatal mortality without an expected increased 'Big4' prevalence (as precursors of perinatal mortality) in *Overschie*. This suggests a small role of 'Big4' morbidities in the increased perinatal mortality shifting the focus to other causes such as healthcare related factors or environment related factors. The borough of *Hoogvliet* has relatively high 'Big4' rates accompanied by a strongly increased perinatal mortality. This suggests a high antenatal risk level, caused by precursors of 'Big4', e.g., smoking during pregnancy. In addition, the high early neonatal mortality (death after a live birth) suggests suboptimal healthcare related factors around birth.

The differences between crude and standardised rates indicate different backgrounds on perinatal health per borough. These differences are more pronounced in the borough reports on perinatal health as all boroughs are described and compared.[6] In some boroughs healthcare related factors and environment are the main contributors, while in other boroughs mainly characteristics of the pregnant women are the main contributors (e.g., ethnicity or lifestyle factors such as smoking).

Comparable initiatives

'Urban perinatal health' is a relatively new field within Obstetrics and Public Health, gaining a lot of attention in The Netherlands. This is readily illustrated by a comparable urban perinatal health report for the city of Amsterdam.[15] The Amsterdam report also concludes that effects of risk factors for perinatal mortality differ per borough, advising differential policies per borough. An important difference, compared to the Rotterdam report, is the absence of standardisation.

International initiatives pertaining to urban or inner-city perinatal health also exist.[16-18] Even though these initiatives are comparable on some points with the Rotterdam and Amsterdam initiatives, there are mostly large differences. In the United Kingdom, for example, there are more (reliable) data available on smoking during pregnancy, one of the most important lifestyle factors in the context of adverse perinatal outcome.[19] Data from The Netherlands Perinatal Registry underestimate the actual smoking prevalence as this is poorly registered by the caregivers. In addition, the UK studies use larger geographical areas, with also outcomes being studied per practice or hospital.[16-18] Another important to mention difference refers to the unique system of obstetric care in The Netherlands which significantly differs from systems in other Western countries.

Cumulation of risks

An important subject in the UK reports is the connection between adverse perinatal outcome and social deprivation, a specific characteristic of large urban areas.[16-18] Indeed, a large body on literature exists on the association between social deprivation and adverse perinatal outcome.[20-22] Mostly, the effect of social deprivation on low birthweight / SGA, preterm birth and perinatal mortality is described.[20-22] Also, de Graaf et al. describe an increased perinatal mortality and 'Big4' in socially deprived neighbourhoods in the context of The Netherlands.[1] A particular finding in this study is that specifically Western women appeared at increased risk in socially deprived neighbourhoods. In Rotterdam, this translated into a 24% increased risk for adverse perinatal outcome for Western women compared to non-Western women in socially deprived neighbourhoods.[1]

Another Dutch study in this context was conducted by Timmermans and colleagues.[22] They used data from the Rotterdam 'Generation R' cohort and concluded that deprived neighbourhoods are characterised by a cumulation of risk factors which drives the adverse perinatal outcomes in these neighbourhoods.[22] Numerous risk factors may be responsible for affecting perinatal health, specific for deprived areas are factors such as feelings of stress due to unsafety or noise pollution, physical environment (e.g., industry, traffic), or problematic (access to) healthcare.[7,20,22-25] In order to gain insight in the background of urban perinatal health and specific intervention policies in this context, the full range of urban perinatal risk factors has to be taken into account; medical as well as non-medical (deprivation, psychosocial, etc.) risk factors.[20,26] Large cohort studies such as 'Generation R' in Rotterdam[27] and 'ABCD' in Amsterdam[20,28] have resulted in knowledge on numerous risk factors. Outcomes of these studies are crucial in understanding perinatal health in the city of Rotterdam.

The 'Ready for a Baby' programme

The large differences in borough profiles suggest borough-specific policies in which collaborations between caregivers are crucial. Spread out across the country there are currently numerous regional 'obstetric collaborations' between midwives and obstetricians in the same region. At-risk pregnant women are systematically discussed in these collaborations. Next to just midwives and obstetricians, it is also crucial to collaborate with other caregivers in the chain of obstetric healthcare (e.g., youth healthcare physicians, paediatricians or maternity care professionals).

In the municipal public health programme 'Ready for a Baby' experiments in healthcare are conducted aimed to improve communication and collaboration between caregivers in the chain of obstetric healthcare (see www.klaarvooreenkind.nl).[4,5,29] One of the most important projects is the so called 'R4U' project. 'R4U' stands for Rotterdam Reproductive Risk Reduction; it is a scorecard which scores medical and non-medical (e.g., psychosocial) risk factors in a standardised way at first antenatal booking visit. This project goes beyond just screening and subsequently links care pathways to specific risk factors, thus enhancing collaboration. Other initiatives within the 'Ready for a Baby' programme are:

- implementation of and research with a new instrument ('GyPsy')[29] to screen for psycho-pathology during pregnancy;
- the construction of within-hospital birth centres (opening in October 2009 and March 2011), a place where women can deliver in a safe home-like primary care setting under supervision of a primary care community midwife;
- extensive education on preconception care aimed at specific groups at risk, e.g., ethnic minorities;
- strategies to improve communication in the transfer of care from obstetric care to youth healthcare.

The effect of these initiatives will become apparent in the coming years by continuous monitoring of perinatal health in the city of Rotterdam.

Conclusion

Within the city of Rotterdam, large differences in perinatal mortality and morbidity ('Big4') exist between boroughs in the city of Rotterdam, with most likely different causes per borough. In some boroughs healthcare related factors and environmental factors play

an important role while in other boroughs characteristics of the pregnant women, e.g., lifestyle or ethnicity are more important causes. These data are crucial in the development of policies specifically targeted to the several boroughs and aimed at decreasing perinatal morbidity and mortality within the city of Rotterdam.

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4

Social deprivation and adverse perinatal outcomes among Western and non-Western pregnant women in a Dutch urban population

J. Poeran, A.F.G. Maas, E. Birnie, S. Denktaş, E.A.P. Steegers, G.J. Bonsel

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ABSTRACT

Social deprivation is considered a key factor in adverse perinatal outcomes. Rotterdam, the second largest city in The Netherlands, has large inequalities in perinatal health and a high number of deprived neighbourhoods. Social deprivation is measured here through a composite variable: 'Social Index' (SI). We studied the impact of the SI (2008-2009; 5 categories) in terms of perinatal mortality, congenital anomalies, preterm birth, small for gestational age (SGA) and low 5-minute Apgar score as registered in The Netherlands Perinatal Registry (Rotterdam 2000-2007, n=56,443 singleton pregnancies). We applied ethnic dichotomisation as Western (European/North-American/Australian) vs. Non-Western (all others) ethnicity was expected to interact with the impact of SI. Tests for trend and multilevel regression analysis were applied. Gradually decreasing prevalence of adverse perinatal outcomes was observed in Western women from the lowest SI category (low social quality) to the highest SI category (high social quality). In Western women the low-high SI gradient for prevalence of spontaneous preterm birth (per 1,000) changed from 57.2 to 34.1, for iatrogenic preterm birth from 35.2 to19.0, for SGA from 119.6 to 59.4, for low Apgar score from 10.9 to 8.2, and for perinatal mortality from 14.9 to 7.6. These trends were statistically confirmed by Chi2-tests for trend ($p<0.001$). For non-Western women such trends were absent. These strong effects for Western women were confirmed by significant odds ratios for almost all adverse perinatal outcomes estimated from multilevel regression analysis. We conclude social deprivation to play a different role among Western vs. non-Western women. Our results suggest that improvements in social quality may improve perinatal outcomes in Western women, but alternative approaches may be necessary for non-Western groups. Suggested explanations for non-Western 'migrant' groups include the presence of 'protective' effects through knowledge systems or intrinsic resilience. Implications concern both general and targeted policies.

INTRODUCTION

In The Netherlands perinatal mortality exceeds the European average despite a high standard of mother and child healthcare with free access.[1] Perinatal health in the larger cities is even worse, with the highest rates of perinatal mortality and morbidity being observed in deprived neighbourhoods.[2] The high prevalence of ethnic minority groups and disseminated social deprivation in urban areas are generally put forward as key aetiologic factors.[2-6] Social deprivation is a very broad term and can be defined as 'reduction or prevention of culturally normal interaction with the rest of society'. Indeed, aspects of social deprivation such as material poverty and lack of social cohesion are both related to ill health, and also strongly connected; the combined reinforcing presence of these factors might be particularly important for perinatal ill health.[7-9] Numerous studies have shown ethnicity and social deprivation to be strongly related to adverse perinatal outcomes such as preterm birth and small for gestational age.[3,4,10-14] However, many recent studies have been conducted in the United States and Canada where ethnic minorities differ considerably from those in Europe and, more specifically, The Netherlands.[2-6,11,13,15,16] In the United States the majority of ethnic minorities either comprise African-Americans or Hispanics; in Europe they mainly originate from former colonies (for example in the United Kingdom or The Netherlands) or they result from the 1960's labour migration from countries such as Turkey or Morocco (for example in Germany and France, respectively). Findings from these studies do not necessarily apply to European countries.

Another motivation for our study pertains to findings from a recent Dutch study which showed Western (European/North-American/Australian) women in deprived neighbourhoods to have an increased risk of adverse perinatal outcomes as opposed to non-Western women.[2]

Rotterdam, the second largest city of The Netherlands, has the highest proportion of non-Western inhabitants as well as the highest number of deprived neighbourhoods, and the highest rate of adverse perinatal outcomes, creating a suitable population in which to study the effect of social deprivation on perinatal outcomes.[2] In continuation of previous work, we investigated the background and the association of social deprivation with adverse perinatal outcomes, for Western and non-Western women separately, as we hypothesise differential effects. We used a composite variable, the so called 'Social Index' (SI) as deprivation indicator at the neighbourhood level in the city of Rotterdam. As social deprivation is considered an important metric of neighbourhood quality policy makers have created the SI and its underlying domains to measure this. It is used to measure the effectiveness of efforts to reduce area-based social deprivation. The SI conceptually resembles the less detailed

Scottish Carstairs index.[17] We use the unaltered SI values to facilitate communication of study results to policy-makers.

METHODS

Outcome data

Data from all single pregnancies in Rotterdam over the period 2000-2007 were derived from The Netherlands Perinatal Registry. This registry contains population-based information of 97% of all pregnancies in The Netherlands.[18] Source data are collected by 94% of midwives, 99% of gynaecologists and 68% of paediatricians, including 100% of Neonatal Intensive Care Unit paediatricians.[18] The mission of The Netherlands Perinatal Registry is to improve the quality of healthcare by giving insight into the perinatal care process and outcomes (see also www.perinatreg.nl).

The Netherlands Perinatal Registry provided individual-level information on adverse perinatal outcomes, along with the four-digit zip codes of the mothers' places of residence. The number of pregnancies per zip code area (neighbourhood) ranged from 127 to 2,611. Adverse perinatal outcome was defined as the occurrence of either perinatal mortality or perinatal morbidity. Perinatal mortality was defined as death from 22 weeks of gestational age until 7 days postpartum. We also defined four outcome variables of perinatal morbidity: congenital anomalies (list defined), small for gestational age (SGA, birthweight below the 10th percentile for gestational age[19], preterm birth (<37th week of gestation) or low 5-minute Apgar-score (<7). As previously described[4], preterm birth was subdivided into spontaneous and iatrogenic preterm birth, the latter being defined as birth <37th week of gestation and an elective caesarean section or induction of labour. The remainder of births <37th week of gestation were classified as spontaneous preterm birth. We assume iatrogenic preterm birth and low Apgar score to be related to both maternal factors as well as peripartum healthcare factors, whereas the remaining morbidity conditions are assumed to be primarily related to individual (maternal) characteristics.

Social Index

Neighbourhood social quality was assessed making use of a combined variable, the so-called 'Social Index' (SI). This index was created in 2008 and is calculated annually for the Rotterdam municipal authorities by the Centre for Research and Statistics Rotterdam (COS-Rotterdam,

www.cos.nl) as a policy measure. All underlying data are empirical. The SI is a composite multidimensional variable indicating neighbourhood social quality on a 1-10 scale. As is depicted in figure 4.1 the SI sum score combines scores from 4 'domains': (1) (personal) capacities, (2) living environment, (3) participation and (4) neighbourhood commitment ('social cohesion'). In turn, these 'domain' scores are a sum of 'item' scores which are based on a combination of registration data and questionnaire data. The questionnaire data are obtained from respondents from a random sample of the Rotterdam population. Per neighbourhood 900 persons were sampled, proportionally stratified for age group, sex and ethnicity. The number of inhabitants per neighbourhood ranged from 1,579 to 21,200. The aim was to have 175 respondents (who completed the questionnaire) per neighbourhood. The initial format was an online questionnaire; if response was not sufficient, respondents were approached with a paper and pencil questionnaire or by telephone. Overall, response was 52% online, 21% by paper and pencil, and 27% by telephone.

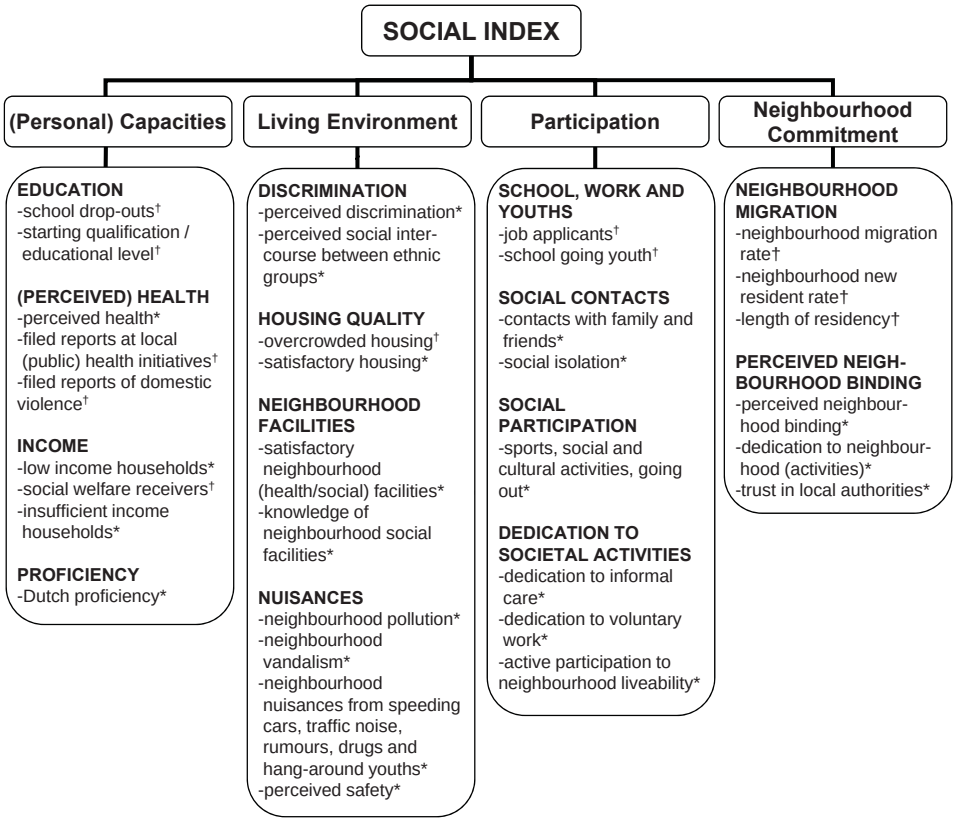

Figure 4.1 Composition of the SI: four SI 'domains' with corresponding 'items' extracted from questionnaire data (*) and from registration data (†).

The SI and its underlying domains are considered important metrics of the effectiveness of policy makers' efforts to reduce area-based social deprivation. More in-depth information on the Social Index and its construction is provided in the online appendix file. In this study, we used the average SI for 2008 and 2009 as a proxy for neighbourhood social quality, both as a continuous measure and as an ordinal measure (5 categories) with the following 'COS-Rotterdam' thresholds:

<3.9 highest social deprivation (I);
3.9-4.9 problematic social deprivation (II);
5.0-5.9 moderate social deprivation (III);
6.0-7.0 adequate social quality (IV);
>7.0 high social quality (V).

Ethnicity

Dutch law does not permit the routine utilisation or registration of ethnicity data. As yet, The Netherlands Perinatal Registry is exempt from this restriction. The ethnic classification in this professional-based registry recognises seven possible categories: Western Dutch, Western other (including women from other European countries, Australia and the US), Mediterranean, (East) Asian, African, South Asian, or other non-Western. The African and South Asian group mainly comprises women from the former Dutch colonies Suriname and The Netherlands Antilles. The group of East Asian women mainly originate from Indonesia, also a former Dutch colony.

Classification of clients is done by the healthcare professional with an absence of strict coding rules in applying the category labels. Current classification is therefore crudely based on a mixture of self-declared ethnicity, race and known country of birth of the woman or her parents. The registry does not contain information on first/second generation migrants, nor on their length of stay in Rotterdam or The Netherlands.

Therefore, the current system as devised by the professional organisations may introduce some classification error, in particular within 'migrant' (non-Western) categories. We dichotomised ethnic groups as Western vs. non-Western for two reasons: (1) to compare our results with previous studies, and (2) in view of the hypothesis generating nature of our study which may lead to more detailed investigation of specific ethnic groups in future studies. The first two classes of the original classification were combined into Western and the remainder into non-Western women.[2]

Analysis

Individual-level data on pregnancy outcomes as registered in The Netherlands Perinatal Registry were linked to the 2008-2009 neighbourhood SI making use of 4-digit zip codes. Simple crosstabs were created illustrating the proportion of Western and non-Western women, mean age, and prevalence rates of adverse perinatal outcomes for each SI category. Mean age and adverse outcome were separately illustrated for Western and non-Western pregnant women. One-way tests for trend were carried out for the association of ethnicity, age and adverse perinatal outcomes and the SI categories (ANOVA for age, Chi-square for dichotomous variables).

Analogous to the above, we also compared average SI domain scores for Western women with scores from non-Western women in each SI category. A one-way ANOVA test was used to test for the difference in mean SI domain scores.

Multilevel logistic regression models were used to estimate adjusted odds ratios (aOR) to further asses the association between the 2008-2009 mean neighbourhood SI (continuous measure) and adverse perinatal outcomes (dichotomous outcomes) for Western and non-Western women. We specified hierarchical random-intercept models that allow for the incorporation of both individual-level and neighbourhood-level characteristics, as well as the adjustment for clustering of individuals within their neighbourhoods. SAS version 9.2 (SAS Institute Inc., Cary, NC) was used to run the random intercept multilevel models with the GLIMMIX procedure. Crude and aORs (for parity; primiparous/multiparous) are reported. The significance was set at alpha=0.05, two tailed.

RESULTS

A total of 56,443 singleton pregnancies were analysed. Characteristics of the study population are shown in table 4.1.

Patient characteristics per SI category

The association of ethnicity and mean maternal age with SI category is described in table 4.2 (upper part). There are no neighbourhoods in Rotterdam in category I (SI <3.9). The proportions of Western women and non-Western women respectively increase (from 24.0 to 89.5%) and decrease (from 76.0 to 10.5%) with increasing SI (a higher SI stands for a neighbourhood with higher social quality). Mean maternal age increases for both Western

Table 4.1 Characteristics of the study population and perinatal outcomes (Rotterdam, 2000-2007)

	N	Percentage
No. of singleton pregnancies during study period	56,443	100.0%
Parity[a]		
Primiparous	27,105	48.0%
Multiparous	29,333	52.0%
Gestational age[a]		
< 37 weeks	3,900	7.0%
37-42 weeks	51,591	92.9%
> 42 weeks	71	0.1%
Maternal age[a]		
≤ 19 years	2,445	4.3%
20-24 years	10,378	18.4%
25-29 years	15,800	28.0%
30-34 years	17,368	30.8%
≥ 35 years	10,437	18.5%
Ethnicity		
Western	28,972	51.3%
Non-Western	27,471	48.7%
Social Index		
>3.9	0	0.0%
3.9-4.9	6,138	10.9%
5.0-5.9	26,760	47.4%
6.0-7.0	16,611	29.4%
>7.0	6,934	12.3%
	Absolute number	**Per 1,000 births**
Perinatal outcomes[b]		
Congenital anomalies	1,489	26.4
Preterm birth	3,908	69.3
Small for gestational age	5,255	93.1
Apgar score <7 (5 minutes after birth)	844	15.0
Any Big4[b]	10,222	181.2
Fetal mortality[c]	466	8.3
Early neonatal mortality[d]	183	3.2
Perinatal mortality[e]	649	11.5

[a] Totals do not add up due to missing values (parity 5 missings, gestational age 881 missings, maternal age 15 missings).
[b] Number and proportion of pregnant women with at least one 'Big4' morbidity.
[c] From 22 weeks of gestational age.
[d] 0-7 days postpartum.
[e] Total of fetal, intrapartum and neonatal mortality.

Table 4.2 Mean age, ethnicity and prevalence rates of adverse perinatal outcomes for Western and non-Western women per SI category

	Ethnicity	Total	SI category					p[a]
			I	II	III	IV	V	
		n=56,443	n=0	n=6,138	n=26,760	n=16,611	n=6,934	
Pregnancies (%)	Western	51.3	0	24.0	38.0	67.0	89.5	<0.001
	Non-Western	48.7	0	76.0	62.0	23.0	10.5	
Mean age (years)	Western	30.3	0	27.7	29.7	30.3	32.1	<0.001
	Non-Western	28.0	0	27.4	28.0	28.3	30.0	<0.001
Congenital anomalies (per 1,000)	Western	25.9	0	23.8	26.4	23.5	30.0	0.249
	Non-Western	26.9	0	20.8	28.8	26.4	24.6	0.219
Preterm birth (per 1,000)								
Spontaneous	Western	44.5	0	57.2	49.1	44.4	34.1	<0.001
	Non-Western	45.2	0	46.6	44.8	45.9	42.0	0.757
Iatrogenic	Western	26.4	0	35.2	25.3	30.3	19.0	0.009
	Non-Western	24.5	0	23.6	23.4	27.5	33.6	0.056
Small for gestational age (per 1,000)	Western	84.2	0	119.6	99.1	79.9	59.4	<0.001
	Non-Western	103.4	0	103.3	102.5	106.0	106.1	0.593
Low Apgar score (per 1,000)	Western	12.5	0	10.9	13.5	14.3	8.2	0.050
	Non-Western	17.5	0	18.6	18.0	15.5	13.7	0.139
Perinatal mortality (per 1,000)	Western	10.3	0	14.9	11.1	10.5	7.6	0.008
	Non-Western	12.7	0	12.0	13.3	12.4	6.8	0.576

[a] Chi-square test for trend was used for ethnicity and prevalence rates of adverse outcomes. For the mean age a one-way ANOVA was used.

and non-Western women with increasing SI (27.7-32.1 and 27.4-30.0 years, respectively). Both mean age (for Western and non-Western women) and ethnicity show significant p-values ($p<0.001$) when testing for trend.

Outcomes in Western women per SI category

The lower part of table 4.2 shows a decreasing trend for rates of spontaneous and iatrogenic preterm birth (range: 57.2-34.1 and 35.2-19.0 per 1,000, respectively), small for gestational age (119.6-59.4 per 1,000) and perinatal mortality (14.9-7.6 per 1,000) with better SI values. This is also verified by the significant p-values when testing for trend (range: <0.001-0.009). When comparing SI category II with category V, the congenital anomaly rate increases (23.8-30.0 per 1,000), and the low Apgar score rate decreases (10.9-8.2 per 1,000).

Outcomes in non-Western women per SI category

When comparing SI category II with category V, congenital anomalies, iatrogenic preterm birth and small for gestational age increase (from 20.8 to 24.6, 23.6-33.6 and 103.3-106.1 per 1,000, respectively). Conversely, rates of spontaneous preterm birth, low Apgar score and perinatal mortality decrease (46.6-42.0, 18.6-13.7 and 12.0-6.8 per 1,000, respectively). Trends, however, were not statistically significant.

SI domains

Table 4.3 depicts mean SI domain scores per SI category for Western and non-Western women. Western women almost always have significantly higher mean SI domain scores compared with non-Western women, except for SI domains 'participation' and 'neighbourhood commitment' in SI category II. The latter being the only domain score for which non-Western women have a significantly higher score compared with Western women.

Multilevel logistic regression models

Table 4.4 shows the crude and adjusted odds ratio (OR and aOR adjusted for parity) of the impact of the mean 2008-2009 neighbourhood SI (on a continuous 1-10 scale) on adverse perinatal outcomes, for Western and non-Western women. For Western as well as non-Western women congenital anomalies show non-significant effects of SI. For Western women significant negative associations with SI were shown for spontaneous and iatrogenic preterm birth, small for gestational age, low Apgar score and perinatal mortality. For non-

Western women a positive association was demonstrated for iatrogenic preterm birth and a negative association for low Apgar score. The largest protective effect of higher SI was seen in Western women for small for gestational age (aOR 0.78; CI 0.73-0.83).

Table 4.3 Mean SI domain scores per SI category for Western and non-Western women

		SI category				
		I	II	III	IV	V
Domain	Ethnicity	n=0	n=6,138	n=26,760	n=16,611	n=6,934
Capacities	Western	0	3.94[a]	4.86[a]	6.44[a]	8.13[a]
	Non-Western	0	3.93[a]	4.69[a]	6.33[a]	8.03[a]
Living environment	Western	0	5.13[a]	5.88[a]	6.71[a]	7.61[a]
	Non-Western	0	5.10[a]	5.78[a]	6.64[a]	7.55[a]
Participation	Western	0	5.03	5.77[a]	6.34[a]	7.37[a]
	Non-Western	0	5.04	5.72[a]	6.29[a]	7.32[a]
Neighbourhood commitment	Western	0	4.85[a]	5.71[b]	6.62[a]	7.41[a]
	Non-Western	0	4.93[a]	5.72[b]	6.56[a]	7.32[a]

[a] Western vs. non-Western women, ANOVA p<0.001.
[b] Western vs. non-Western women, ANOVA p<0.05.

Table 4.4 Multilevel hierarchical random-intercept logistic regression models: crude (OR) as well as adjusted (aOR, adjusted for parity) odds ratios including 95% confidence intervals (CI) of the associations between mean 2008-2009 neighbourhood SI and adverse perinatal outcomes for Western and non-Western women

	Ethnicity	OR[a] (CI[c])	aOR[b] (CI[c])
Congenital anomalies	Western	1.02 (0.90-1.16)	1.02 (0.90-1.17)
	Non-Western	1.02 (0.91-1.15)	1.02 (0.91-1.15)
Preterm birth			
Spontaneous	Western	0.86 (0.80-0.92)[d]	0.87 (0.80-0.93)[d]
	Non-Western	1.01 (0.92-1.11)	1.00 (0.91-1.10)
Iatrogenic	Western	0.88 (0.78-0.98)[e]	0.88 (0.78-0.99)[e]
	Non-Western	1.15 (1.03-1.28)[e]	1.15 (1.03-1.28)[e]
Small for gestational age	Western	0.77 (0.72-0.82)[d]	0.78 (0.73-0.83)[d]
	Non-Western	1.02 (0.96-1.08)	1.01 (0.95-1.07)
Low Apgar score	Western	0.83 (0.73-0.95)[e]	0.84 (0.74-0.96)[e]
	Non-Western	0.87 (0.75-1.00)	0.86 (0.74-1.00)[e]
Perinatal mortality	Western	0.83 (0.72-0.96)[e]	0.84 (0.72-0.97)[e]
	Non-Western	0.96 (0.82-1.13)	0.96 (0.82-1.12)

[a] OR: crude odds ratio
[b] aOR: adjusted odds ratio (for parity)
[c] CI: confidence interval
[d] p-value <0.001
[e] p-value <0.05

DISCUSSION

Principal findings

This study is one of the few European studies to address the effect of a combined social deprivation measure on adverse perinatal outcomes and applying multilevel modelling.[20] In the large, multi-ethnic city of Rotterdam the impact of social deprivation on adverse perinatal outcomes plays a key role with a striking ethnicity-related effect. In the most deprived neighbourhoods, perinatal outcomes were universally poor with a tendency for even worse figures for Western women compared to non-Western women. With decreasing deprivation, a strong gradient for improvement exists for almost all perinatal outcomes in Western women. For every point increase of the Social Index (higher is better), adjusted perinatal mortality in Western women shows a 16% decrease. As a similar gradient in perinatal outcomes is absent in non-Western women, an ethnicity related perinatal outcome gap emerges, with impressive perinatal health inequalities in neighbourhoods with the lowest deprivation.

Other studies

Our finding that social deprivation has a stronger negative effect on Western women than non-Western women has been sparsely described in the literature.[13,21] Fang et al. used New York City birth records to show that foreign born women of African and Caribbean descent had more favourable birth outcomes compared with that for whites, particularly in the poorest neighbourhoods.[21] O'Campo et al. studied the effect sizes for non-Hispanic whites and non-Hispanic blacks for the relation between neighbourhood deprivation and preterm birth.[13] For whites, the effect size was larger compared to blacks indicating that this group appears to be less affected by neighbourhood deprivation than whites.[13] Furthermore, one previous study by De Graaf et al., conducted in The Netherlands also supports the current findings.[2] They found that the effect of living in deprived neighbourhoods, as compared to living elsewhere, was most prominent among Western women with an increased risk of adverse perinatal outcomes of 24%.[2]

Possible underlying mechanisms

It is challenging to interpret the observed ethnicity-related effect by one underlying mechanism. A first explanation takes into account the density of migrant subgroups in the neighbourhood population.[22] Previous studies have suggested that the risk of poor health

outcomes for a minority individual is inversely related to the density of his or her racial/ethnic group in the local community, i.e., greater numbers of migrants/non-Western populations in deprived neighbourhoods, and that living in neighbourhoods with a high migrant density may be beneficial specifically for migrant (here non-Western) women, such that fewer negative effects of deprivation in these neighbourhoods may be experienced. This hypothesis has been validated for various adverse health outcomes ranging from psychiatric conditions to rates of heart disease.[7,8,23,24] The presumed mechanisms include health protection through increased participation in social networks or knowledge systems, and a more extensive repertoire of positive coping behaviours.[7,8,23,24] When applied to our study context, these protective effects may result in less feelings of stress during pregnancy and may stimulate healthy behaviour. In Rotterdam, this could be valid for the non-Western women in deprived areas (lowest SI) as they generally tend to have better outcomes than Western women in these areas. However, we also observed a lack of improvement in adverse perinatal outcomes with increasing SI for non-Western women. This 'net neutral effect' may be (partly) explained by the combination of a decrease in potentially protective migrant/non-Western density when SI and its positive effects increase. A second explanation may rest on lifestyle epidemiology concerning factors such as smoking which is known to have a profound effect on perinatal outcome.[25] Previous studies have shown that smoking behaviour differs among ethnic and socio-economic groups.[26] Our data could reflect healthier lifestyle behaviour for Western women with increasing SI, this gradient may be absent in non-Western women.

Another explanation of our study results pertains to healthcare related factors. This may pertain to general thresholds to healthcare or density of facilities which is lower in deprived areas. Western women might profit more from this effect due to better health literacy and informal networks.[9] We assumed iatrogenic preterm birth and low Apgar score to be partially related to peripartum healthcare factors. However, different patterns were observed for low Apgar score and iatrogenic preterm birth in Western and non-Western women. Thus, it is unclear to what extent healthcare related factors have affected the observed ethnic disparities. The perinatal healthcare process still needs careful analysis as little is known on its dynamics in a multicultural setting.[27]

A sociobiological explanation of our study results may involve the presence of epigenetic effects in some groups of non-Western women, particularly those of African descent, that limit the potential for positive effects on perinatal outcomes when SI increases.[28,29] This phenomenon has been demonstrated by Collins et al. in a three generation linked dataset of African Americans in Illinois.[30] Their study showed rates of low birthweight to be associated with worsening maternal grandmothers' residential environments during her pregnancy

with her daughter that years later delivered a low birthweight neonate. This association was independent of the living conditions of the daughter during her pregnancy with the infant with low birthweight.[30] Further research is needed to investigate if this phenomenon among African Americans also applies to other non-Western populations.

Finally, instead of the above so-called 'causation' options, one may think of 'selection'. Western and non-Western women may differ in their motive to move to a deprived neighbourhood or differ in the potential for 'upward mobility'. As previously described, ethnic minorities tend to cluster, usually in poor urban areas. This 'ethnic concentration' may be maintained by both its residents and newly arriving migrants because of the amenities and organisations feeding on this ethnic concentration. That is why residents stay in these neighbourhoods even when they have the financial means to move out.[31,32] Western women in deprived neighbourhoods are thought to represent a negative selection as the above mechanism may not apply to them.[31,32] The latter is supported by our finding that the only SI domain for which Western women have a significantly lower score than non-Western women is for 'neighbourhood commitment' (social cohesion) in the lowest SI category in Rotterdam, i.e., Western women are thought to have less commitment to these neighbourhoods.[32]

Strengths and weaknesses

The major strengths of the current study include the use of a validated registry with a high coverage over a long period of time; The Netherlands Perinatal Registry, currently 2000-2007.[18] As social quality and social deprivation are multidimensional concepts, the usage of a neighbourhood-specific combined social deprivation variable adds strength to the estimates and, in case of the Social Index, it also allows to draw conclusions regarding a more specific dimension of social deprivation.[33] Neighbourhood-specific social deprivation indices are generally constructed with factor or principal component analysis.[16,33] Such an approach rests on selecting the most efficient items to represent 1 or more underlying constructs. The SI intentionally was composed by municipal policymakers, selecting items which in their view represented best observable and direct interpretable information on social deprivation; herewith, statistical overlap was accepted to allow for political communication. Hence, the Social Index was designed for policy monitoring purposes as an outcome in the first place, rather than for research purposes as a determinant. What also adds strength to our findings is that initial results were cross-validated by additional analyses of the effect of neighbourhood house price quintiles on adverse perinatal outcomes (data available in the online appendix file). A particular strength of the current study pertains to

the differentiation between iatrogenic and spontaneous preterm birth as they may differ in aetiological or causal pathways.[34] The majority of previous retrospective studies on the effect of social deprivation and preterm birth do not take this difference into account.[10,12,15,20,34,35]

The limitations associated with this study should also be noted. Firstly, area based indices such as the SI may not correspond to individual socioeconomic status ('ecological fallacy') and do not reflect heterogeneity among the individuals within a neighbourhood. A possible way to triangulate would be to interview a sample of the women. However, the strict national privacy regulations which apply to The Netherlands Perinatal Registry, do not allow identification of individuals for subsequent active approach. Multilevel modelling to estimate effects based on a neighbourhood-level measure may partially bypass this problem. The advantage of this approach is that it allows for the incorporation of both individual-level and neighbourhood-level characteristics. Moreover, it adjusts for clustering of individuals within neighbourhoods, thereby increasing the validity of the effect sizes compared to conventional logistic regression analysis.[36] As parity was one of the few individual-level factors we could adjust for, and as we did not have information on individual-level socioeconomic status, we could not fully benefit from the theoretical advantages of multilevel modelling over conventional logistic regression. An advantage of the usage of neighbourhood specific indices is that they provide complementary information to individual measures of social quality and may be particularly useful in studies concerning pregnancy outcomes. Determination of social class is known to be problematic in such studies as not only the mother's socioeconomic characteristics have to be taken into account, but also the father's.[37] Additionally, the use of area based deprivation indices is well supported in the literature.[3,10-13,15,16,20,37]

Another limitation refers to the use of the mean 2008-2009 SI in assessing the effect on perinatal outcomes from 2000-2007. This discrepancy was due to the unavailability of data. Consequently, our analysis does not take into account the variability of neighbourhood SI between 2000 and 2007. The variability between 2008 and 2009 was small (data available in the online appendix file). Moreover, it is generally expected to take a long period of time for possible changes in neighbourhood social quality to take effect (data available in the online appendix file). Therefore, the discrepancy in the years of available data between the exposure variable and outcome variables is expected to play a marginal role. Also, the current study lacks data on lifestyle, in particular smoking, one of the main risk factors for adverse perinatal outcomes.[25] This could have resulted in possible overestimation of the impact of SI on adverse pregnancy outcomes. However, previous studies have shown that socioeconomic status remains significantly associated with adverse perinatal outcomes

such as preterm birth, even after taking smoking into account.[13,20] Finally, one could argue against the grouping of all non-Western women as this is a very heterogeneous group, disregarding among others any differences in races, cultures, first or second generations, or migrants' length of stay. However, the main objective of our study follows from a previous study which suggested that specifically Western women were at risk for adverse pregnancy outcomes in deprived areas.[2] To further study and reconfirm this effect, we chose to group non-Western women as we were specifically interested in Western women.

Possible implications

The SI is associated with adverse perinatal outcomes to the extent that both general and targeted policies seem relevant. In the context of social deprivation, social policy should continue to aim to serve Western as well as non-Western women equally. General policies, in particular preventive policies, show higher average benefits (compared to targeted policies) if applied on the population level. However, they do so while increasing health gaps as their effects rely on competences and resources which are unequally distributed, this is called the 'prevention paradox'.[38] Therefore, complementary priority programs are justified, dedicated to specific 'worst off' subgroups.

The observed increased risk of adverse perinatal outcomes in Western women in the most deprived neighbourhoods justifies additional attention in antenatal care. This approach could include intensified prevention from existing health promoting programs in combination with targeted social welfare. It is, however, difficult to extend this recommendation to non-Western women, as our data and those of others do not show a straightforward relation between social deprivation and perinatal outcome beyond the effect of being an ethnic minority itself. Perhaps the 'Western' conventional deprivation indicators do not cover the subtle ethnic specific pathways for adverse perinatal outcomes.

Non-Western women did not improve in perinatal outcome with increasing SI, but showed an advantage over Western women in deprived neighbourhoods, possibly due to 'protective' knowledge systems. Future research could tap into these knowledge systems to evaluate whether they can contribute to improvement in outcome with increasing SI in non-Western women.

In addition, we also recommend more studies on this subject in European settings as most studies on social deprivation and adverse perinatal outcomes have been conducted in either the US or Canada which makes it unclear to what extent observations are valid for European populations.

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PART II

Perinatal health in The Netherlands

5

Population attributable risks of patient, child and organisational risk factors for perinatal mortality

J. Poeran, G.J.J.M. Borsboom, J.P. De Graaf, E. Birnie,
E.A.P. Steegers, G.J. Bonsel

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ABSTRACT

Objective Estimate the contributing role of maternal, child, and organisational risk factors in perinatal mortality by calculating their population attributable risks (PAR).

Methods The primary dataset comprised all (n=1,020,749) singleton hospital births from ≥22 weeks' gestation (The Netherlands Perinatal Registry 2000-2008). PARs for single and grouped risk factors were estimated in four stages: (1) creating a duplicate dataset for each PAR analysis in which risk factors of interest were set to the most favourable value (e.g., all women assigned 'Western' for PAR calculation of ethnicity); (2) in the primary dataset an elaborate multilevel logistic regression model was fitted from which (3) the obtained coefficients were used to predict perinatal mortality in each duplicate dataset; (4) PARs were then estimated as the proportional change of predicted- compared to observed perinatal mortality. Additionally, PARs for grouped risk factors were estimated by using incremental values in two orders: after PAR estimation of grouped maternal risk factors, the resulting PARs for grouped child, and grouped organisational factors were estimated, and vice versa.

Results The combined PAR of maternal, child and organisational factors is 94.4%, i.e., when all factors are set to the most favourable value perinatal mortality is expected to be reduced with 94.4%. Depending on the order of analysis, the PAR of maternal risk factors varies from 1.4-13.1%, and for child- and organisational factors 58.7-74.0% and 7.3-34.3%, respectively.

Conclusion The PAR of maternal, child and organisational factors combined is 94.4%. Optimisation of organisational factors may achieve a 34.3% decrease in perinatal mortality.

INTRODUCTION

In The Netherlands perinatal mortality rates exceed the European average.[1,2] For long, population factors such as the high maternal age at first childbirth, the high number of multiple pregnancies, and the increasing proportion of non-Western pregnant women were held responsible.[1,2] These explanations were challenged as perinatal mortality remains high after exclusion of these risk groups.[3] Recent studies have thus addressed the contribution of non-patient factors like the system of Dutch obstetric care with independently practicing community midwives[4], travel time to a hospital[5], organisational characteristics of hospitals[6], and geographic factors, in particular urban deprivation[7-9]. However, of these studies neither established the relative importance of the patient and non-patient risk factors, nor the magnitude of the effect when unfavourable patient and non-patient risks coincide. A valid estimate of attribution of these is essential to prioritise among available policy options to reduce perinatal mortality. Our study aims to disentangle the contribution of patient and non-patient risk factors to perinatal mortality, applying the population attributable risk (PAR) concept to a comprehensive (2000-2008) national perinatal dataset. The PAR concept is attractive as it generally quantifies the separate impact of a risk factor in terms of proportion of total mortality (or other relevant outcome) accounted for by that factor. The standard PAR approach assumes risk factors to act independently, and applies straightforward formulae.[10] The concept is considerably more complex if risk factors interact, in a non-additive, conditional or time-dependent fashion. For convenience such interaction effects are often ignored, or risk groups are excluded[11], at the cost of conflicting or invalid estimations of the impact of risk factors (in the perinatal context).

Our approach particularly accounts for interactions between the organisational features of care provision and the fetal-maternal risk level. E.g., we account for the effect that travel time to hospital[5] for women referred during parturition may strongly depend on fetal morbidity and maternal features: under perfect fetal-maternal conditions, travel time effects may be minimal, while the effect may be sizable if the rate of unexpected transfers is high. Likewise, we account for interaction between staffing level during out-of-office hours and fetal-maternal characteristics.

We introduce a four-stage computational framework to estimate the relative importance of interacting patient- and non-patient risk factors for perinatal mortality.

METHODS

Patient data

In this retrospective cohort study we derived data on maternal factors, child factors and outcomes from The Netherlands Perinatal Registry. This registry contains complete population-based information of >97% of all pregnancies in the Netherlands.[12] On behalf of the respective professional societies, source data are routinely collected by 94% of midwives, 99% of gynaecologists and 68% of paediatricians including 100% of Neonatal Intensive Care Unit paediatricians.[12] (See website for detailed description: www.perinatreg.nl). The registry contains 1,620,126 birth records for the period of 2000-2008.

We excluded multiple pregnancies (n=35,326), births with unknown gestational age (n=17,768), births with unknown or erroneous zip code (n=20,804), and births supervised exclusively by primary care midwives (n=525,479) as we assume hospital organisational features to be of little or no importance in births under the exclusive supervision of primary care midwives. Intra-uterine deaths (stillbirths, n=7,661) were excluded as their delivery differs from normal cases.[13]

The final patient database consisted of 1,013,088 records.

Geographical data

Travel time to hospital was calculated as the travel time between a pregnant woman's 4-digit zip code and the hospital's zip code; zip code covers an average of 4,000 inhabitants. Travel time data were derived from a commercially available geographic information system package acquired from the Geodan company (www.geodan.nl). We assume travel time to hospital only to have an impact on women with unplanned births who were transferred from home to hospital during parturition. Thus, hospital travel time was set to zero for women with planned births, i.e., induction of labor (n=467,071) or a planned (primary) caesarean section (n=98,135).

Hospital data

Hospital organisational data were collected separately from this study by one of the investigators (JPDG), with the full support of the Dutch Society of Obstetricians and Gynaecologists using a standardised (structured) interview for all (n=99) maternity units. Response was 100%.[6] Collected data consisted of 24 variables (table 5.1) with inevitable

Table 5.1 Overview of hospitals' organisational data

Organisational feature	Remarks
General	
teaching hospital	categorised into yes / no
Gynaecology department	
duration of daytime shifts	categorised into durations of 10-12 hours and 7-9 hours
duration of evening / night shifts and the highest level of the professional who is attending these shifts	categorised into durations of ≤14 hours and ≥15 hours with professional levels categorised into two groups: (1) gynaecologist / gynaecologist in training and (2) non-in-training physician / midwife / nurse
the highest level of the professional who is attending the evening and night shifts during the week	categorised into five groups: (1) gynaecologist, (2) in-training and non-in-training resident gynaecology, (3) general emergency physician, (4) midwife and (5) nurse
the highest level of the professional who is attending the daytime shifts during weekends	categorised into five groups: (1) gynaecologist, (2) in-training and non-in-training resident gynaecology, (3) general emergency physician, (4) midwife and (5) nurse
the highest level of the professional who is attending the evening and night shifts during weekends	categorised into five groups: (1) gynaecologist, (2) in-training and non-in-training resident gynaecology, (3) general emergency physician, (4) midwife and (5) nurse
permitted to sleep during attending shifts	categorised into yes / no
gynaecologist on backup call during shifts	categorised into yes / no
professional doing rounds during weekends	categorised into four groups: (1) gynaecologist, (2) in-training and non-in-training resident gynaecology, (3) general emergency physician, (4) midwife and (5) nurse
in-hospital presence of the emergency operating theatre team	categorised into three groups: in-hospital presence during (1) 24 hours, (2) presence during daytime and evening and on-call during the night, (3) presence during daytime and on-call during the evening and night
in-hospital presence of an anesthaesiologist	categorised into three groups: in-hospital presence during (1) 24 hours, (2) presence during daytime and evening and on-call during the night, (3) presence during daytime and on-call during the evening and night
the total number of obstetric caregivers (specialists, physicians, midwives, nurses)	a continuous number
annual number of deliveries	continuous as well as grouped into three categories: (1) <1000, (2) 1000-2000, (3) >2000
combination of the annual number of deliveries with the gynaecologist:other obstetric caregiver ratio	categorised into six groups: (1) <1000 and ≤1:4, (2) <1000 and 1:4-1:6, (3) <1000 and >1:6, (4) 1000-2000 and ≤1:4, (5) 1000-2000 >1:4, (6) >2000 and all ratios
minimum duration of attending shift during weekends	a continuous number (range 12-72 hours)

Table 5.1 continues on next page.

Table 5.1 *Continued*

Organizational feature	Remarks
average travel time in minutes from home to hospital for an on-call gynaecologist	a continuous number
maximum travel time in minutes from home to hospital for an on-call gynaecologist	a continuous number
number of caregivers present during attending shifts on weekday evenings and nights	a continuous number
number of caregivers present during attending shifts on weekends during the day	a continuous number
number of caregivers present during attending shifts on weekends during the evening and the night	a continuous number
Paediatrics department	
level of care for newborns	categorised into four groups: (1) Neonatal Intensive Care Unit (NICU), (2) post-NICU or incubator from 30 weeks of gestational age, (3) incubator from 32 weeks of gestational age, (4) initially first aid for neonate with suboptimal start with subsequent referral to a hospital with a higher level of care
the highest level of the professional at the paediatrics department who is attending the shifts outside office hours	categorised into six groups: (1) fellow neonatologist, (2) paediatrician, (3) in-training paediatrician, (4) non-in-training resident paediatrics, (5) general emergency physician, (6) no professional present but on-call
the lowest level of the professional at the paediatrics department who is attending the shifts outside office hours	categorised into six groups: (1) fellow neonatologist, (2) paediatrician, (3) in-training paediatrician, (4) non-in-training resident paediatrics, (5) general emergency physician, (6) no professional present but on-call
professional on-call at the paediatrics department	categorised into four groups: (1) no one on-call, (2) paediatrician on-call, (3) fellow neonatologist on-call, (4) other professional on-call

partial overlap. For that reason we used principal component analysis (PCA) as an accepted technique to reduce the high number of interrelated explanatory variables to a limited number of so-called principal components. PCA summarises the net information content of overlapping data into a small number of independent, non-overlapping constructed variables. Such a constructed variable consists of a weighted sum of the scores of the observed variables, where each weight reflects the added informative value of each observed variable to the constructed variable. The background and the technique itself are described in more depth elsewhere.[14] In the best case, 50% or more of all variability in the original variables is covered by a limited number of (usually two or three) constructed variables. The removal of overlap increases the power of the constructed variables as

determinants in explanatory regression analysis. Note that the PCA technique is descriptive only: it can not be used for predictive analysis.

In our analysis the 24 organisation variables were summarised into two principal components, factor 1 and factor 2, with a computed numerical score for each hospital. Factor 1 can be interpreted as 'scale size of the hospital' as it primarily combines original variables pointing to hospital size and the number of obstetric caregivers: the lower the factor value, the larger the hospital and the higher the number of obstetric caregivers. Factor 2 can be interpreted as '24-hour equality of service level'. This factor combines original variables pointing to around-the-clock availability of qualified professionals from various backgrounds. The two factors together cover about 70% of the information (variability) contained in the original 24 variables.

We additionally computed a 'hospital-specific intervention policy' variable defined as the hospital-specific percentage of primary caesarean sections for term breech presentation. A low 'primary-caesarean-section- for-term-breech' percentage represents hospitals with a more expectative approach in obstetric policy whereas a high percentage stands for hospitals with a more proactive obstetric policy.

Outcome measures and risk factors

The main outcome was intrapartum or early neonatal death within 7 days after live birth, for convenience further referred to as perinatal mortality.[6] Risk factors were grouped into maternal and child factors (patient factors) and organisational factors (non-patient factors). Maternal factors were ethnicity (Western / non-Western of African descent / other non-Western), parity (0 / 1-2 / >2) and maternal age (<25 / 25-29 / 30-34 / 35-39 / ≥40 years). Child factors were gestational age (thirteen categories)[6], congenital anomalies (yes / no), small for gestational age (SGA: birthweight >10th / 2.3-10th / <2.3rd percentile)[15,16] and fetal presentation (cephalic / breech / transverse or other / unknown). Congenital anomalies are recorded postpartum and classified through a standard coding system by organ system (8 categories, 71 subcategories).[17]

Travel time to the hospital was expressed in minutes (continuous). Other organisational factors were: day and time of delivery (Saturday / Sunday / weekday, each subdivided into three time slots 00:00-07:59 / 08:00-17:59 / 18:00-00:00), emergency referral during parturition (yes / no), the two principal component factors, and the 'primary-caesarean-section-for-term-breech' percentage. Emergency referral during parturition was defined according to the caregiver providing delivery information in the registry.

Population attributable risk

The aim of this study is to estimate the population attributable risk (PAR) of maternal, child and organisational risk factors for perinatal mortality. The PAR of a risk factor is the amount of perinatal mortality that can be attributed to that particular risk factor among individuals with the risk factor compared to those without.[10] The standard PAR calculation is as follows: PAR%=[(P*(RR−1))/(1+(P*(RR−1)))]*100. From this formula PAR estimations are expressed as 'the percentage or proportion of outcome accounted for' by the risk factor involved. RR stands for relative risk, and P for the prevalence of the risk factor in the studied population.

As said, PAR estimates from the above formula are subject to limitations if risk factors or their effects interact. First, the formula is not additive if multiple risk factors act dependently: a simple one-factor-at-a-time computation then leads to an unrealistic sum of PARs being >100%. Second, computational complexity increases rapidly with more independent factors, e.g., requiring simulation studies. Confounding adds to the complexity.

Logistic regression analysis enables to address several risk factors at a time, and indeed has been used in some PAR studies.[18] The resulting adjusted odds ratios (OR) are, however, difficult to interpret, as the reference risk is unclear, and as this approach has no solution for conditionally dependent factors.[18] The method we present in this study addresses the interaction problem. It only requires the researcher to be explicit on the presumed causal priority of the related explanatory variables under study.[11]

Estimation of PARs

The PAR for single risk factors and groups of risk factors were estimated with a four-stage approach (figure 5.1). In stage one, multiple duplicate datasets were created. In the duplicate dataset the risk factor(s) of interest were eliminated by setting their values uniformly to the most favourable value in terms of outcome. E.g., in the duplicate dataset used for the PAR analysis of the single risk factor 'ethnicity', all women were assigned 'Western'. The most favourable value (categorical or continuous) was obvious in most variables. E.g., in case of travel time to hospital, this value was zero; for the principal component factors 1 and 2, we used the average value of the academic hospitals as optimum. For the primary-caesarean-section-for-term-breech' policy we replaced the observed percentage of primary caesarean sections in term breech in a specific hospital by the national average, in those hospitals where the observed percentage was lower than this average. Thus, a specific duplicate dataset underlies each specific PAR estimate.

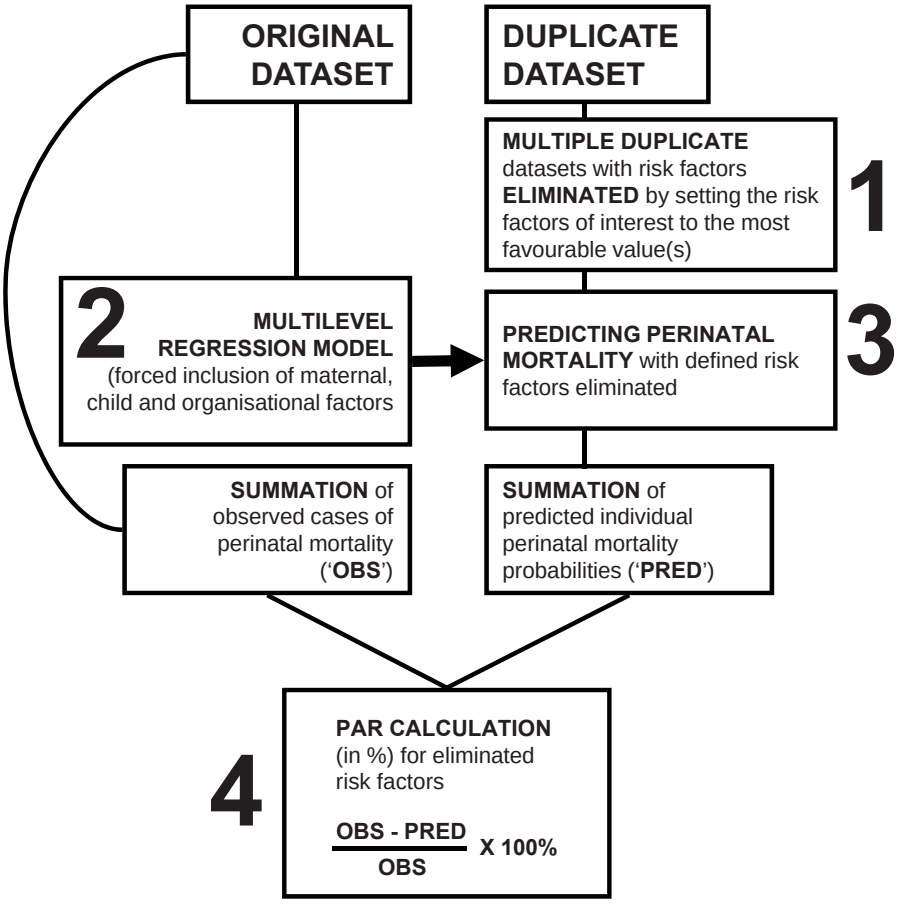

Figure 5.1 Four-stage procedural scheme for the estimation of PARs.

In stage two, a multilevel multivariable logistic regression model with perinatal mortality as dependent variable was fitted using the original (unchanged) dataset. All determinants mentioned above (=independent variables) were forced into the model, including predefined interactions. Because of the multilevel structure of the data (individuals are grouped per hospital) we used a multilevel logistic regression model which adjusts for the possible clustering of particular individuals within hospitals (random intercept).

In stage three, the estimated beta-coefficients obtained in the multilevel model with the original dataset, were used to predict -on the individual level- the probability of perinatal mortality ('PRED' in figure 5.1) once a specific factor was eliminated. In each duplicate dataset

the role of one or more risk factors was eliminated by setting the value to the optimum. The individual perinatal mortality probabilities were then summed to obtain a total predicted perinatal mortality for each duplicate dataset with one or more risk factors eliminated. For example, the predicted number of cases of perinatal mortality in a hypothetical world with Western mothers only, all other factors equal, was estimated by applying the parameter estimates from the multilevel model to the duplicate dataset in which all women were assigned 'Western'.

In stage four, PARs were calculated. The total predicted (by definition: lower) perinatal mortality of each duplicate dataset was compared to the observed ('OBS' in figure 5.1) total mortality of the original dataset. The PAR was then conventionally calculated as the proportional change of the perinatal mortality (in %): e.g., if predicted mortality was 78% of the observed mortality, the PAR was 22%. We did so for all single risk factors and groups of risk factors (maternal, child, and organisational factors). If sets of risk factors were defined cumulative, this allowed for an incremental analysis. E.g., if we start with estimating the PAR of ethnicity, followed by the PAR of ethnicity and maternal age combined, the difference between these two PARs provides a PAR of maternal age conditional on a population with only Western women.

The magnitude of the contribution of risk factors to perinatal mortality as computed by this four-stage approach is presented in three ways:

1. the 'univariable contribution', where only the risk factor(s) at stake are set to the most favourable values, leaving all other variables to their original level;
2. a 'descending order contribution', where we used a cumulative approach starting with maternal, followed by child, and organisational factors, respectively. Note that in this case the organisational PAR is estimated, assuming both maternal and child factors to be optimal. For this method of calculation, the PAR of maternal factors is the same as the 'univariable contribution' PAR.
3. 'ascending order' contribution' with the reversed order of appearance of risk factors: first organisational, then child, and finally maternal factors.

It can be expected that starting with organisational factors ('ascending order'), leaving the original level of mother and child risks unaltered, provides an equal or higher PAR, compared to estimating the PAR of organisational factors conditional on a hypothetically perfect mother-child population ('descending order'). The comparison of results from (2) the descending vs. (3) ascending order may thus be thought of as a policy choice to start with either improvement of maternal and child factors vs. improvement of organisational factors.

SAS version 9.2 (SAS Institute Inc., Cary, NC) was used, with the GLIMMIX procedure to run the random intercept multilevel models which were also used to calculate the predicted values of perinatal mortality. Syntax can be obtained from the authors.

RESULTS

In our study population (table 5.2) most women are of Western origin (83.3%), primiparous (52.9%) and 30-34 years old (38.3%). Preterm birth (<37 weeks' gestation) was seen in 8.6%, congenital anomaly in 3.0%, SGA in 10.6%, and a non-cephalic presentation was seen in 8.1% of cases. Almost 15% of women had to travel 15 minutes or more to the hospital where they gave birth, most children (42.4%) were born on a weekday between 08:00 and 17:59, 32.4% of women were referred during parturition, and 12.5% of women gave birth in a hospital with a 'primary-caesarean-section- for-term-breech' percentage of 75% or more. All academic hospitals showed principal component factor values in the 'best' quartile (data not shown).

Table 5.2 Characteristics of the study population

	N	Percentage
Study population	1,013,088	100,0%
Maternal factors		
Ethnicity		
Western	844,340	83.3%
Non-Western African descent	27,617	2.7%
Non-Western other	141,131	13.9%
Parity		
Primiparous (P0)	535,641	52.9%
Multiparous (P1-P2)	425,288	42.0%
Multiparous (P>2)	52,159	5.1%
Maternal age		
< 25 years	122,769	12.1%
25-29 years	290,524	28.7%
30-34 years	387,942	38.3%
35-39 years	181,738	17.9%
≥ 40 years	30,115	3.0%
Child factors		
Gestational age		
22-27.6 weeks	4,876	0.5%
28-31.6 weeks	8,417	0.8%
32 weeks	4,238	0.4%

Table 5.2 continues on next page.

Table 5.2 *Continued*

	N	Percentage
33 weeks	6,733	0.7%
34 weeks	11,157	1.1%
35 weeks	18,119	1.8%
36 weeks	33,707	3.3%
37 weeks	63,848	6.3%
38 weeks	155,400	15.3%
39 weeks	212,947	21.0%
40 weeks	242,565	23.9%
41 weeks	176,094	17.4%
≥ 42 weeks	74,987	7.4%
Congenital anomalies		
No	982,273	97.0%
Yes	30,815	3.0%
Small for gestational age (SGA)		
No SGA	905,919	89.4%
Birthweight P2.3-P10	80,697	8.0%
Birthweight < P2.3	26,472	2.6%
Fetal presentation		
Cephalic	930,785	91.9%
Breech	72,313	7.1%
Transverse or other	9,036	0.9%
Unknown	954	0.1%
Organisational factors		
Travel time to hospital		
< 15 minutes	865,105	85.4%
≥ 15 minutes	147,983	14.6%
Day and time of delivery		
Saturday 00:00-07:59	33,625	3.3%
Saturday 08:00-17:59	55,509	5.5%
Saturday 18:00-23:59	28,743	2.8%
Sunday 00:00-07:59	33,750	3.3%
Sunday 08:00-17:59	54,880	5.4%
Sunday 18:00-23:59	28,434	2.8%
Weekdays 00:00-07:59	173,463	17.1%
Weekdays 08:00-17:59	429,398	42.4%
Weekdays 18:00-23:59	175,286	17.3%
Referral during parturition		
No	684,495	67.6%
Yes	328,593	32.4%
Hospital 'elective-caesarean-section- for-term-breech' percentage		
< 75%	886,893	87.5%
≥ 75%	126,195	12.5%

Multivariable multilevel logistic regression model using the original dataset

Effect estimates from the multivariable multilevel logistic regression model are shown in table 5.3. For maternal factors, only parity is significantly associated with perinatal mortality, with the highest risk for multiparous (P>2) women (OR 1.57; CI 1.38-1.78). All child factors are significantly associated with perinatal mortality. Gestational ages <37 weeks have the highest risks for perinatal mortality (OR range 3.71 to >1,000); the highest risk for term pregnancies is seen for 37 weeks of gestation (OR 2.35; CI 2.01-2.75). Infants with congenital anomalies have an 11 times increased risk (OR 11.05; CI 10.25-11.91), and a birthweight < P2.3 has an almost 7 times increased risk (OR 6.79; CI 6.10-7.56) for perinatal mortality. Increased risks are also observed for non-cephalic fetal presentations (OR range 1.53-2.20). For organisational factors only the principal component factors are

Table 5.3 Multivariable multilevel logistic regression model

	aOR	CI		P-value
Maternal factors				
Ethnicity				0.083
Western **[ref]**	1.00			
Non-Western African descent	1.10	0.94	1.28	
Non-Western other	1.10	1.01	1.20	
Parity				
Primiparous (P0) **[ref]**	1.00			<.0001
Multiparous (P1-P2)	1.31	1.23	1.40	
Multiparous (P>2)	1.57	1.38	1.78	
Maternal age				0.085
< 25 years	1.05	0.95	1.16	
25-29 years **[ref]**	1.00			
30-34 years	1.07	0.99	1.16	
35-39 years	1.13	1.03	1.24	
≥ 40 years	0.96	0.81	1.15	
Child factors				
Gestational age				<.0001
22-27.6 weeks	>1,000	>1,000	>1,000	
28-31.6 weeks	43.38	37.28	50.48	
32 weeks	16.68	13.52	20.59	
33 weeks	12.42	10.22	15.09	
34 weeks	7.35	6.07	8.91	

Table 5.3 continues on next page.

Table 5.3 *Continued*

	aOR	CI		P-value
35 weeks	5.54	4.64	6.62	
36 weeks	3.71	3.14	4.37	
37 weeks	2.35	2.01	2.75	
38 weeks	1.36	1.18	1.57	
39 weeks	1.05	0.91	1.21	
40 weeks **[ref]**	1.00			
41 weeks	1.34	1.16	1.54	
≥ 42 weeks	1.35	1.12	1.63	
Congenital anomalies				<.0001
No **[ref]**	1.00			
Yes	11.05	10.25	11.91	
Small for gestational age (SGA)				
No SGA **[ref]**	1.00			<.0001
Birthweight P2.3-P10	2.41	2.18	2.65	
Birthweight < P2.3	6.79	6.10	7.56	
Fetal presentation				<.0001
Cephalic **[ref]**	1.00			
Breech	1.53	1.41	1.66	
Transverse or other	1.54	1.29	1.83	
Unknown	2.20	1.26	3.86	
Organisational factors				
Travel time to hospital	1.00	0.99	1.00	<.0001
Day and time of delivery				<.0001
Saturday 00:00-07:59	1.49	1.27	1.75	
Saturday 08:00-17:59	1.11	0.97	1.29	
Saturday 18:00-23:59	1.34	1.12	1.60	
Sunday 00:00-07:59	1.40	1.19	1.64	
Sunday 08:00-17:59	1.31	1.14	1.50	
Sunday 18:00-23:59	1.16	0.96	1.39	
Weekdays 00:00-07:59	1.42	1.31	1.55	
Weekdays 08:00-17:59 **[ref]**	1.00			
Weekdays 18:00-23:59	1.29	1.19	1.41	
Referral during parturition				<.0001
No **[ref]**	1.00			
Yes	1.24	1.14	1.34	
Hospital 'elective-caesarean-section-for-term-breech' percentage	0.99	0.98	0.99	<.0001
Hospital organisational features				
Principal component (factor 1)	1.01	0.91	1.11	0.915
Principal component (factor 2)	0.98	0.89	1.09	0.752
Principal component (factor 1) ^2	0.86	0.77	0.97	0.012
Principal component (factor 2) ^2	0.99	0.95	1.04	0.746

not significantly associated with perinatal mortality (OR 1.01; CI 0.91-1.11 and OR 0.98; CI 0.89-1.09 for factor 1 and 2, respectively). Births on Saturday nights and weekday nights have a >40% increased risk for perinatal mortality (OR 1.49; CI 1.27-1.75 and OR 1.42; CI 1.31-1.55, respectively), referral during parturition has an almost 25% increased risk (OR 1.24; CI 1.14-1.34). The hospital 'primary-caesarean-section- for-term-breech' percentage is also significantly associated with perinatal mortality (0.99; CI 0.98-0.99). For every percentage increase in 'primary-caesarean-section- for-term-breech', perinatal mortality decreases with 1%. Thus, a hospital with a higher percentage of primary caesarean sections on average has a lower rate of perinatal mortality adjusted for other factors.

PAR results

Table 5.4 lists PARs of single risk factors (upper part) and groups of risk factors ('univariable contribution'; lower part). Of all maternal factors, parity has the highest univariable PAR (8.9%). In other words: if all women in our dataset would be primiparous perinatal mortality would be reduced by 8.9%, all other things equal. Of all child factors, gestational age (72.2%) and congenital anomalies (22.7%) have the highest univariable PAR. Hospital organisational factors captured in the 'primary-caesarean-section- for-term-breech' percentage and the principal component factors have the highest univariable PAR (13.2% and 16.4%, respectively) of the organisational factors. If every hospital is set to the between-hospital average 'primary-caesarean-sections-for-term-breech' percentage, perinatal mortality would decline with 13.2%. If all hospitals are set to the most favourable principal component

Table 5.4 Observed and predicted perinatal mortality with subsequent PAR estimations of single risk factors (upper part) and groups of risk factors (lower part)

	N	OBS-PRED	PAR (%)
Observed cases of perinatal mortality	6,269	-	100,0%
Predicted cases of perinatal mortality			
Maternal factors			
Ethnicity			
Everyone Western	6,184	85	1.4%
Parity			
Everyone nulliparous	5,711	558	8.9%
Maternal age			
Everyone 25-29 years	6,047	222	3.5%

Table 5.4 continues on next page.

Table 5.4 *Continued*

	N	OBS-PRED	PAR (%)
Child factors			
Gestational age			
Everyone 40 weeks	1,740	4,529	72.2%
Congenital anomalies			
No congenital anomalies	4,848	1,421	22.7%
Small for gestational age (SGA)			
No SGA	5,554	715	11.4%
Fetal presentation			
Everyone cephalic	5,881	388	6.2%
Organisational factors			
Travel time to hospital			
Everyone no travel time	6,458	-189*	*
Day and time of delivery			
Everyone on weekdays 08:00-17:59	5,564	705	11.2%
Referral during parturition			
No referrals	6,076	193	3.1%
Hospital 'elective-caesarean-section- for-term-breech' percentage			
Every hospital the average %	5,444	825	13.2%
Principal component factors			
All principal component factors set to the most favorable value	5,240	1,029	16.4%
Groups of factors			
All maternal factors set to the most favorable value	5,450	819	13.1%
All child factors set to the most favorable value	1,004	5,265	84.0%
All organisational factors set to the most favorable value	4,120	2,149	34.3%
All mother and child factors set to the most favorable value	811	5,458	87.1%
All child and organisational factors set to the most favorable value	438	5,831	93.0%
All maternal, child and organisational factors set to the most favorable value	352	5,917	94.4%

* In table 5.3 'travel time to hospital' has an OR of 0.995 representing a 0.5% decreased risk of perinatal mortality for every minute of extra travel time. Therefore, predicted mortality > observed mortality when everyone in the duplicate dataset is assigned a 0 for travel time. This would result in a negative PAR according to our calculation method.

factor value, perinatal mortality would be reduced with 16.4%. According to the 'univariable contribution' estimation method, the estimated PAR of all maternal factors combined is 13.1%. Univariable contribution of the child factors combined and the organisational factors combined is 84.0% and 34.3%, respectively. The PAR of all maternal, child and organisational factors together is 94.4%. In other words: when all factors are set to the most favourable

Table 5.5 PARs of groups of risk factors estimated by two methods: 'descending order contribution' (left) and 'ascending order contribution' (right)

	↓		
MATERNAL FACTORS	**13.1%**	**94.4%**	**MATERNAL FACTORS**
↓	+74.0%	+1.4%	↑
CHILD FACTORS	**87.1%**	**93.0%**	**CHILD FACTORS**
↓	+7.3%	+58.7%	↑
ORGANISATIONAL FACTORS	**94.4%**	**34.3%**	**ORGANISATIONAL FACTORS**
		↑	

value the perinatal mortality is expected to be reduced with 94.4%, pointing to a high explanatory power of the complete set of variables in this analysis.

Table 5.5 compares results from the 'descending order contribution' vs. the 'ascending order contribution'. The former estimation method results in a PAR of 13.1%, 74.0% and 7.3% for maternal, child and organisational factors, respectively. The latter estimation method results in a PAR of 34.3%, 58.7% and 1.4% for organisational, child and maternal factors, respectively. Hence, depending on the estimation method, the PAR of maternal factors varies from 1.4 to 13.1%; for child factors from 58.7 to 74.0%, and for organisational factors from 7.3 to 34.3%.

DISCUSSION

Principal findings

Combining a multilevel logistic regression approach with a specific 'what-if' framework, we were able to estimate the impact of maternal, child and organisational risk factors on perinatal mortality. We estimated the combined population attributable risk (PAR) of

patient- (maternal and child) and non-patient (organisational) factors to be 94.4%. Thus, almost all perinatal mortality could be explained statistically. Gestational age showed the highest single contribution (PAR of 72.2%), but also organisational factors as single factors ranked high (PAR of 34.3%). In estimating the risk attributions for combined maternal, child and organisational factors, results depended on the causal priority given on the various risk groups. By selecting a 'descending order' the PARs of maternal, child and organisational factors are 13.1%, 74.0% and 7.3%, respectively. The reverse order provides PARs of 34.3%, 58.7% and 1.4%, which can be translated into the following: optimising organisational factors with the current pregnant population has a potential of a one third decrease in perinatal mortality.

Also, our data showed the overriding importance of decreasing preterm births, and a distinct >200% risk of a birth at 37.0-37.6 weeks of gestation (table 5.3, OR 2.35), considered 'at term'[6]. This finding suggests reconsidering the threshold of 'term' pregnancy from 37 weeks to 38 weeks.[19,20]

Other PAR studies

Previous studies describing PARs for perinatal mortality have used multivariable regression models with the resulting adjusted odds ratio (OR) replacing the relative risk (RR) in the conventional PAR formula (depicted in the methods section).[18,21-23] Two previous studies have used data from The Netherlands Perinatal Registry to calculate PARs for perinatal mortality, however with each a different approach.[11,22] Ravelli and colleagues calculated adjusted PARs for perinatal mortality (stillbirths included) through multivariable regression and adjusted odds ratios (see above). Focusing on maternal factors only, they showed nulliparity to have the highest PAR for perinatal mortality (14.8%), considerably more than e.g. maternal age (PAR 1.4-3.6%), ethnicity (PAR 6.6%), and gender of the child (PAR 3.6%).[22] The difference with our PARs arises from the absence of child and organisational factors, the different computational procedure (see Methods), and the inclusion of stillbirths. Gijsen et al. used a method comparable to our multilevel and 'observed-expected' method in estimating perinatal mortality attributable to the effect of an off-hours delivery.[11] They found an overall PAR of 12.5% of evening and night time deliveries for intrapartum and early neonatal mortality. A limitation of this study is the exclusion of several groups at risk for intrapartum and early neonatal mortality, e.g., small for gestational age infants and severe congenital anomalies which most likely are more vulnerable to suboptimal care.

Strengths and weaknesses

An important strength of our study is the usage of a validated national database (The Netherlands Perinatal Registry) with complete coverage of all deliveries over a long period of time (2000-2008). Second, compared to previous studies, our explanatory model included more detailed information on organisational factors from all Dutch hospitals, built on a previous study on hospital related effects.[6,11,22] Third, we used a novel method to calculate PARs in a multivariable context, and demonstrated a strong effect of the researcher's choice of explanatory variables ('ascending and 'descending order contribution') and on the order of including these variables in computing PARs.

Provided that appropriate choices are made, we assume the resulting multivariable PARs to be more accurate compared to PAR estimations from the conventional PAR-formula which is unsuitable in case of interacting variables.[18] Generally, a multivariable PAR provides additional information beyond measures on the strength of association.[4-6,8,9,24-26] For example: a placental abruption may have a high OR for perinatal mortality; however, on the population level its attributable risk is limited as the condition is very rare; PARs account for this.[10]

This study also has limitations. First, the lack of detailed data on maternal lifestyle factors in The Netherlands Perinatal Registry, in particular smoking, may contribute to a too small PAR of maternal factors.[27] By including SGA and gestational age in our study model part of this maternal smoking effect is switched to these child factors. Still, in view of the low PAR of maternal factors, our study suggests that in the perinatal mortality context, casemix adjustment for maternal factors is of less value than often assumed.[1-3] A second limitation refers to the modifiability of risk factors, which is not addressed by our method. In public health, PARs are generally calculated for modifiable risk factors only as the concept is used to judge priorities for intervention programs. Some risk factors in our study obviously are non-modifiable (e.g., parity or ethnicity), and others only partially. Still, the small PARs on parity and ethnicity may serve the discussion on relevance and prioritisation. Finally, we by intent excluded births under supervision of independently practicing midwives (n=525,479 from a total of 1,620,126). Our results only pertain to hospital births; as in most Western countries births take place in hospital this selection may account for international generalisability of our results.

Possible implications

In assuming organisational factors to be modifiable at least partially on the long term, our study suggests a major decrease in perinatal mortality (PAR of 34%) after these factors have

been optimised. Possible policies include ensuring (e)quality of obstetric care during off-hours, and a proactive approach in obstetric policy. Centralisation of obstetric care may be deemed necessary in optimising organisational factors ensuring 24-hour high level obstetric, anaesthesia, and optimal neonatal resuscitation coverage.[28] Next to organisational factors, the PAR estimations of child factors suggest substantial reduction of perinatal mortality on the population level through measures decreasing preterm birth rates. Foremost, methods to improve detection of (risks for) preterm are needed which may be achieved through standardised antenatal risk scoring systems, or prediction algorithms for preterm birth.[29,30] The threshold of term may be shifted to 38 weeks gestational age.

Conclusion

We quantified the overall impact on in-hospital perinatal mortality of maternal, child, and organisational risk factors, adjusting for their mutual dependencies. The so-called population attributable risk (PAR) of these three groups of factors combined is 94.4%, where gestational age has the highest single impact. The PARs of risk factors separately vary by the method of estimation, in particular the order of adjustment which in turn depends on the intended use. Focusing on the role of hospital organisational factors, the PAR results suggest that a change towards the theoretical organisation optimum with an otherwise unchanged pregnant population provides a 34.3% decrease in in-hospital perinatal mortality.

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6

The 'Healthy Pregnancy 4 All' Study: design and cohort profile

S. Denktaş, J. Poeran, L.C. de Jong-Potjer, S.F. van Voorst, A.A. Vos, A.J.M. Waelput, E. Birnie, G.J. Bonsel, E.A.P. Steegers

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ABSTRACT

The design of a national study designated as 'Healthy Pregnancy 4 All' (HP4All) is presented. This study combines epidemiologic and health services research to evaluate the effectiveness of two obstetric interventions: (1) programmatic preconception care (PCC) provision to reduce the risks and risk load related adverse pregnancy outcome in a population-based prospective cohort study; (2) a score card-based antenatal risk assessment in a cluster randomised controlled trial for medical and non-medical risks related to adverse pregnancy outcome, followed by patient-tailored multidisciplinary care pathways. Altogether, 14 municipalities/regions were selected to participate according to socio-demographic data (high risk load), perinatal outcome data (high adverse outcome prevalence), and some specific data for either PCC or antenatal risk assessment. In total, 839 women need to be included in the preconception care study and 7,000 women need to be included in the antenatal risk assessment study. Data are collected by physical examinations, questionnaires, interviews, and biological samples. Preparations started in the spring of 2011. Participant recruitment and complete data collection started in the fall of 2012.

INTRODUCTION

Perinatal mortality rates in the Netherlands are high and decline slowly compared to other European countries.[1-3] More risks and a higher risk load for adverse outcomes were found for women living in socially deprived areas.[4] With the support of the Ministry of Health and Welfare a nationwide study, called 'Healthy Pregnancy 4 All' (HP4All), was developed to provide evidence based strategies at an early stage to improve pregnancy outcome. Several municipal pilot studies in the city of Rotterdam provided the framework for this national study.[5]

Main objectives

The main HP4All study objective is to evaluate the effectiveness of two interventions and their associated preventive strategies in either the preconception period or the antenatal period to reduce adverse pregnancy outcome. Accordingly, two sub-studies are specified: a population-based prospective cohort study focusing on the effectiveness of customised preconception care (PCC) and a cluster randomised trial focusing on the early identification of groups at risk for adverse pregnancy outcomes (in particular, preterm birth and small for gestational age) and the related effectiveness of score-card based early antenatal risk assessment with the so-called 'R4U' (Rotterdam Reproductive Risk Reduction) score card.

Rationale

The rationale of the PCC sub-study originates from increasing evidence showing the critical influence of embryonic development and placentation during early pregnancy on pregnancy outcome.[6-8] Risks influencing this early pregnancy phase are optimally modified in the preconception period.[6,9,10] The Dutch Health Council recommended (2007) to integrate general PCC in the health care system.[11] The Minister of Health, however, advised to first evaluate the utilisation and effectiveness of PCC for high risk groups in the HP4All study, before the nationwide implementation of PCC in Dutch obstetric care can be considered.

The rationale of the second sub-study on early antenatal risk assessment originates from the unique Dutch system of obstetric care which has three risk-based levels of care: primary care for low risk pregnancies and deliveries, provided by independently practicing community midwives, and secondary/tertiary care for high risk pregnancies provided by obstetricians.[12] As the level of care depends on the distinction between assumed low risk and high risk pregnancies, antenatal risk assessment by primary care community midwives is an important

part of Dutch obstetric care.[12] Although social deprivation has been shown to contribute to adverse perinatal health in the Netherlands, standard risk assessment does not include the assessment of social risks of perinatal health.[4,5,13,14] In addition, subsequent patient-tailored social care pathways are lacking. Therefore, in the new antenatal risk assessment tool ('R4U') explicitly social and medical risk factors are taken into account as part of the HP4All study.

Population-based cohort studies, e.g., the Generation R[15] and ABCD[16] studies have contributed to our knowledge of various health problems in pregnancy and childhood and their lasting impact on health in later life. Moreover, studies using a large national Dutch database (The Netherlands Perinatal Registry) showed increased adverse pregnancy outcome in large urban areas, in particular in deprived neighbourhoods.[13,17] Also, four specific morbidities appear to precede perinatal mortality in 85% of cases, the so-called 'Big4' morbidities.[18,19] These are: congenital anomalies (list defined), preterm birth (<37th week of gestation), small for gestational age (SGA, birth weight <10th percentile for gestational age) or low Apgar score (<7, 5 minutes after birth). Taking advantage of knowledge from these cohort studies, the HP4All study will study the effectiveness of newly introduced evidence-based care strategies for early identification and customised care provision to women at risk.

Below, we first describe the selection of geographical areas most suitable for the interventions. Next, we describe the designs of the preconception care and the antenatal risk assessment studies.

SELECTION OF THE PARTICIPATING MUNICIPALITIES/ REGIONS

The first step in HP4All was the identification of the geographical unit in which the aforementioned sub-studies would preferably be carried out. We used a national geographic information system (GIS) to divide The Netherlands into 62 municipalities/regions, being the 50 cities with > 70,000 inhabitants and the 12 provinces (excluding the 50 previously selected cities). The second step involved the selection of municipalities/regions in which to carry out the sub-studies, based on multiple criteria which are relevant to either the preconception care sub-study, to the enhanced antenatal risk assessment sub-study, or to both. The final step dealt with additional conditions and the final selection of the participating municipalities/regions which is elaborated on below.

Selection criteria

Initially, we selected municipalities/regions according to socio-demographic parameters associated with high risk load (maternal age, parity, ethnicity, and socioeconomic status) and perinatal outcome data (overall 'Big4' and perinatal mortality prevalence). Before the municipalities/regions could be selected, specific parameters relevant to either sub-study PCC or antenatal risk assessment were added.

For the PCC sub-study these criteria were (1) proportion of women having their first antenatal booking visit at ≥14 weeks of gestational age, and prevalences of (2) congenital anomalies and of (3) SGA. A timely first antenatal booking is important because the opportunities for prenatal screening and interventions (i.e., lifestyle advice and changes) as well as the effectiveness of those interventions are larger in an early fetal stage. Congenital anomaly and SGA prevalences are considered to be indicative for a region's periconceptional health status.

For the antenatal risk assessment sub-study, additional criteria were (1) overall perinatal mortality rates, (2) perinatal mortality amongst women with 'Big4' pregnancies, and (3) prevalence of SGA and prematurity.

Data sources

The division of The Netherlands into 62 municipalities/regions was based on 4-digit postal codes areas. Data were provided by the Falk company (www.falk.nl), the National Public Health Authority, and the Statistics Netherlands organisation (CBS, www.cbs.nl). Information on socioeconomic status (SES, determined in 2006) per postal code area was obtained from the Social and Cultural Planning Office (SCP, www.scp.nl). Data on pregnancy and perinatal outcome were derived from The Netherlands Perinatal Registry (2000-2008), containing information of more than 97% of all pregnancies in The Netherlands.[20] These data are routinely collected by 94% of midwives, 99% of gynaecologists and 68% of paediatricians including 100% of Neonatal Intensive Care Unit paediatricians.[20] Table 6.1 shows the demographic characteristics of the so-called 'G4-cities', i.e., the four largest cities: Amsterdam, Rotterdam, The Hague, Utrecht, and the rest of the Netherlands. Compared to the rest of The Netherlands, the 'G4'-cities have a larger proportion of non-Western women (43% vs. 11.3%), more teenage pregnancies (2.8% vs. 1.5%), and more women in low SES neighbourhoods (59.2% vs. 19.0%). Considerably more women live in deprived neighbourhoods (32.5% vs. 1.3%) and the overall adverse perinatal outcome is worse in 'G4-cities', as illustrated by a 'Big4' prevalence of 20.5% compared to 18.1%.

Table 6.1 Demographic characteristics of the study population by yes/no 'G4-cities' (the four largest cities) with percentages in brackets

	G4-cities	Netherlands minus G4-cities	Total
No. of pregnancies during study period	245,445 (100.0)	1,338,420 (100.0)	1,583,865 (100.0)
Parity			
Primiparous	121,592 (49.5)	607,953 (45.4)	729,545 (46.1)
Multiparous	123,853 (50.5)	730,467 (54.6)	854,320 (53.9)
Ethnicity			
Western	139,786 (57.0)	1,186,772 (88.7)	1,326,558 (83.8)
Non-Western	105,659 (43.0)	151,648 (11.3)	257,307 (16.2)
Maternal age			
< 20 years	6,987 (2.8)	19,861 (1.5)	26,848 (1.7)
20-24 years	34,864 (14.2)	127,013 (9.5)	161,877 (10.2)
25-29 years	61,354 (25.0)	395,138 (29.5)	456,492 (28.8)
30-34 years	85,444 (34.8)	535,927 (40.0)	621,371 (39.2)
≥ 35 years	56,796 (23.1)	260,481 (19.5)	317,277 (20.0)
Socioeconomic 'status score'			
<p20	145,367 (59.2)	254,607 (19.0)	399,974 (25.3)
p20-p80	58,641 (23.9)	853,074 (63.7)	911,715 (57.6)
>p80	41,437 (16.9)	230,739 (17.2)	272,176 (17.2)
Neighbourhood			
Non-deprived	165,658 (67.5)	1,320,392 (98.7)	1,486,050 (93.8)
Deprived	79,787 (32.5)	18,028 (1.3)	97,815 (6.2)
Perinatal outcomes**			
Congenital anomalies	5,233 (2.1)	33,159 (2.5)	38,392 (2.4)
Preterm birth	15,673 (6.4)	81,646 (6.1)	97,319 (6.1)
Small for gestational age	27,724 (11.3)	125,175 (9.4)	152,899 (9.7)
Apgar score <7 (5 minutes after birth)	3,385 (1.4)	14,818 (1.1)	18,203 (1.1)
Any Big4**	50,267 (20.5)	242,697 (18.1)	292,964 (18.5)
Fetal mortality†	1,478 (0.6)	6,718 (0.5)	8,196 (0.5)
Intrapartum mortality	458 (0.2)	2,126 (0.2)	2,584 (0.2)
Neonatal mortality††	761 (0.3)	3,547 (0.3)	4,308 (0.3)
Perinatal mortality‡	2,697 (1.1)	12,391 (0.9)	15,088 (1.0)

** Individual 'Big4' morbidities do not add up to 'any Big4' as women can have >1 'Big4' morbidity.
† From 22 weeks of gestational age.
†† 0-7 days postpartum.
‡ Total of fetal, intrapartum and neonatal mortality.

Perinatal mortality and 'Big4' prevalence

Figures 6.1 and 6.2 illustrate the geographical distribution of perinatal mortality rates, and the prevalence rate of 'Big4' (per 1,000) respectively. Various shades of red represent the different prevalence classes, the darker the shade the more prevalent the adverse outcome. The classes are based on the distribution of the rates: the middle three classes comprise 95% (2 standard deviations) of the outcome levels; the middle class comprises 68%. Both figures show large geographical inequalities in adverse perinatal outcomes on the national level.

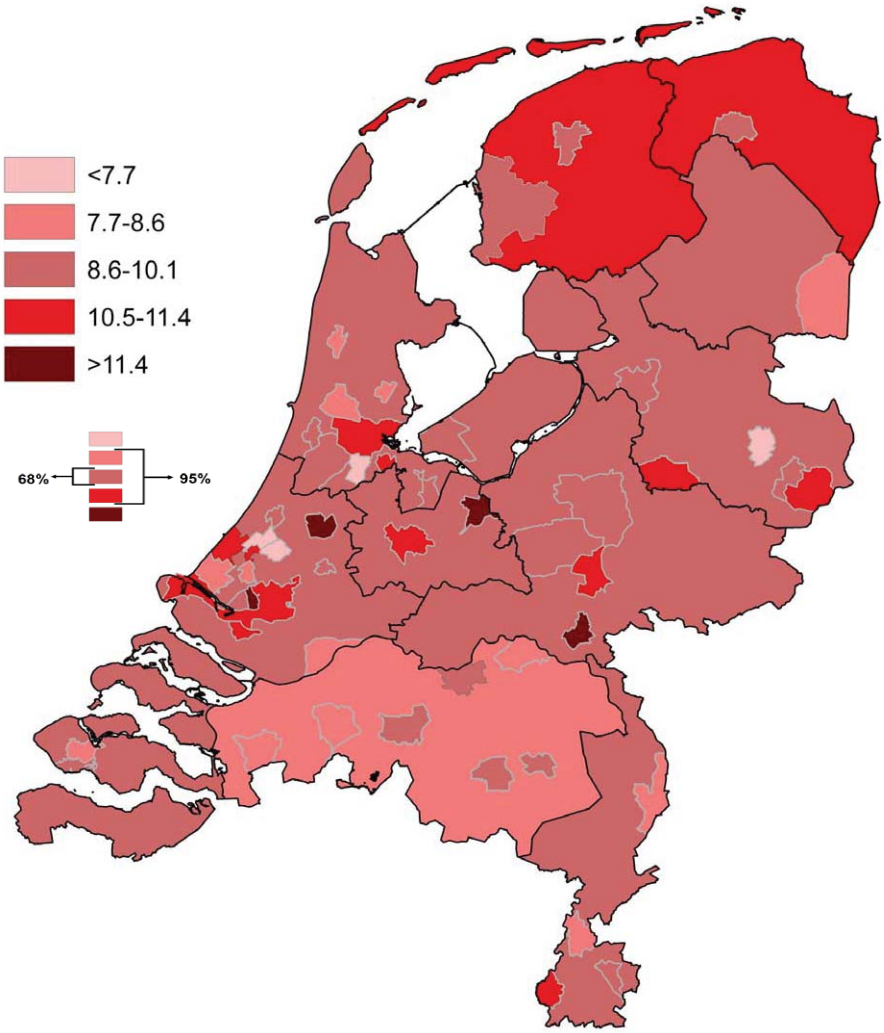

Figure 6.1 Absolute prevalence of perinatal mortality per 1,000 births.

Comparison municipalities/regions

We additionally compared these outcomes across regions after direct standardisation[21] for population differences by maternal age, parity, ethnicity, and SES. Standardisation is needed because a region with, e.g., a high number of non-Western women or a high number of teenage pregnancies will generally have a higher prevalence of adverse perinatal outcomes.

Tables 6.2 and 6.3 show the socio-demographic parameters and the specific criteria for the PCC and the antenatal risk assessment sub-studies. For each specific indicator we present

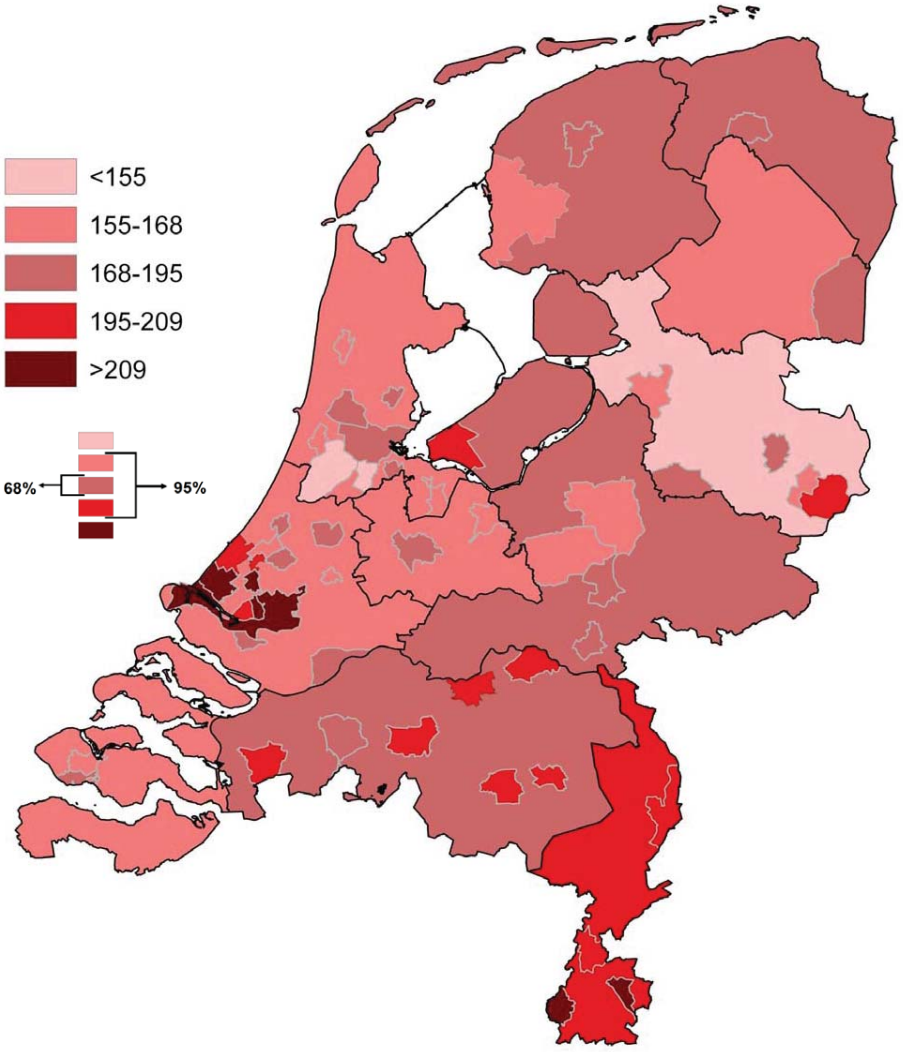

Figure 6.2 Absolute prevalence of 'Big4' morbidities per 1,000 births.

Table 6.2 Selection criteria* for the preconception care experiment with scoring in deciles; the higher deciles represent a more likely qualification for inclusion

#		Demographics				1st antenatal booking ≥14W			Congenital anomalies			SGA			Rank
		% PREG	AGE <20	NW ETHN	LOW SES	ABS	STND	INEQ	ABS	STND	INEQ	ABS	STND	INEQ	
	Cities														
1	Amsterdam	10	8	10	10	10	10	3	3	2	7	8	6	9	96
2	Rotterdam	10	10	10	10	10	10	3	6	7	4	10	9	6	105
3	Den Haag	9	10	10	10	10	10	2	9	8	4	10	9	8	109
4	Utrecht	9	3	10	6	10	10	4	10	10	7	3	2	7	91
5	Eindhoven	8	7	9	7	9	9	6	8	9	8	9	9	5	103
6	Tilburg	8	8	9	9	5	4	10	4	4	5	10	10	3	89
7	Almere	8	7	10	3	10	9	1	7	7	6	9	8	8	93
8	Groningen city	7	9	5	9	2	2	5	2	2	4	5	3	5	60
9	Breda	7	6	6	5	3	1	9	9	9	3	6	7	4	75
10	Nijmegen	7	5	6	9	3	3	9	4	5	6	8	8	6	79
11	Enschede	6	8	8	10	4	4	2	5	5	3	9	7	6	77
12	Apeldoorn	6	5	3	2	6	7	4	1	1	9	5	4	10	63
13	Haarlem	7	3	7	6	8	7	3	1	2	7	4	4	7	66
14	Arnhem	6	9	9	8	8	5	7	6	6	3	7	7	5	86
15	Zaanstad	6	4	8	6	7	7	1	2	3	2	5	4	8	63
16	Amersfoort	7	2	7	4	9	9	7	5	6	6	3	2	4	71
17	Haarlemmermeer	7	1	4	1	4	5	4	1	1	2	2	2	7	41
18	's-Hertogenbosch	5	3	3	4	1	2	10	9	9	4	8	8	4	70
19	Zoetermeer	5	6	8	3	1	1	6	4	4	1	7	6	10	62
20	Zwolle	6	7	3	4	2	3	7	2	1	7	2	1	10	55
21	Maastricht	4	9	4	6	4	3	10	10	10	10	10	10	1	91

Table 6.2 continues on next page.

Table 6.2 *Continued*

#		Demographics				1st antenatal booking ≥14W		Congenital anomalies		SGA		Rank
		% PREG	AGE <20	NW ETHN	LOW SES	ABS	STND	ABS	STND	ABS	STND	INEQ	
22	Dordrecht	6	10	9	7	9	8	3	2	1	3	8	80
23	Leiden	5	4	7	6	8	8	6	8	7	10	6	5	3	83
24	Emmen	4	6	1	10	4	5	10	2	2	7	6	4	9	70
25	Ede	5	6	3	5	5	6	6	7	8	2	1	1	5	60
26	Venlo	3	7	8	7	3	2	8	6	6	5	9	10	1	75
27	Westland	4	1	1	1	5	7	6	10	10	8	1	1	10	65
28	Deventer	5	6	6	8	7	8	7	7	7	2	7	7	2	79
29	Delft	3	7	9	9	7	5	7	10	10	10	5	5	6	93
30	Sittard-Geleen	3	8	3	7	1	2	10	5	4	4	9	8	1	65
31	Leeuwarden	4	10	4	9	5	4	8	8	8	2	5	3	10	80
32	Alkmaar	4	4	6	5	6	6	8	5	5	10	2	2	2	65
33	Heerlen	2	10	5	10	3	4	8	10	10	3	10	10	2	87
34	Helmond	5	5	7	6	6	5	4	8	8	5	9	10	1	79
35	Hilversum	1	5	5	3	9	9	1	1	1	8	3	5	1	52
36	Súdwest Fryslân	3	5	1	8	2	2	9	2	2	10	1	1	3	49
37	Amstelveen	2	1	8	2	8	8	1	1	1	10	2	1	10	55
38	Hengelo	4	6	4	7	5	6	1	4	3	1	4	4	5	54
39	Purmerend	2	4	6	4	9	10	1	3	5	1	4	6	9	64
40	Roosendaal	2	5	9	1	2	1	8	9	9	8	8	10	1	73
41	Oss	2	2	4	3	1	1	7	5	4	9	10	10	2	60
42	Schiedam	1	10	10	10	10	10	2	7	6	4	10	9	7	96
43	Spijkenisse	1	9	7	4	3	2	5	3	3	1	6	9	4	57

44	Leidschendam-Voorburg	2	2	7	3	8	7	5	5	4	9	3	5	5	65
45	Alphen a/d Rijn	1	2	5	1	4	4	9	7	8	1	4	4	6	56
46	Almelo	3	8	5	8	2	3	1	1	1	9	7	6	1	55
47	Vlaardingen	1	8	10	5	7	4	8	6	5	9	8	8	4	83
48	Gouda	3	3	8	8	3	1	9	1	3	3	4	3	3	52
49	Middelburg	1	9	4	7	6	6	4	8	6	6	4	3	3	67
50	Vlissingen	1	10	6	5	8	6	5	6	8	1	8	9	3	76
	Provinces														
51	Groningen	8	7	2	9	7	9	5	3	2	8	5	6	7	78
52	Friesland	9	4	1	8	9	9	3	10	10	8	2	3	9	85
53	Drenthe	9	3	1	5	6	8	6	4	4	2	3	5	8	64
54	Overijssel	9	1	1	2	5	7	2	3	3	6	1	2	9	51
55	Gelderland	10	2	2	2	1	3	3	10	9	9	2	3	6	62
56	Utrecht	10	1	3	1	2	3	5	9	9	5	1	1	7	57
57	Noord-Holland	10	1	2	2	7	8	2	6	6	5	1	1	8	59
58	Zuid-Holland	10	2	2	1	4	5	4	8	7	7	1	2	9	62
59	Zeeland	8	3	1	3	10	10	2	4	5	1	3	5	4	59
60	Noord-Brabant	10	1	2	1	1	1	9	7	7	5	6	7	2	59
61	Limburg	9	4	2	2	1	1	10	9	10	6	7	8	2	71
62	Flevoland	8	9	5	4	6	6	6	3	3	9	6	6	7	78

10% HIGEST SCORE

10%-20% HIGHEST SCORE

10% LOWEST SCORE

* '% PREG': % pregnant women in the general population / 'AGE <20': % teenage pregnancies / 'NW ETHN': % non-Western pregnant women / 'LOW SES': % women in neighbourhoods with a socioeconomic status score <p20 / 'ABS': Absolute % / 'STND': Standardised % / 'INEQ': Inequality as measured by the relative risk of prevalences between women from neighbourhoods with socioeconomic status score <p20 compared to >p80.

Table 6.3 Selection criteria* for the risk selection experiment with scoring in deciles; the higher deciles represent a more likely qualification for inclusion

#		Demographics					Perinatal mortality / all women			Perinatal mortality / BIG4 morbidities			Perinatal mortality / start labour in primary care			Rank
		% PREG	AGE <20	PRIMI	NW ETHN	LOW SES	ABS	STND	INEQ	ABS	STND	INEQ	ABS	STND	INEQ	
	Cities															
1	Amsterdam	10	8	10	10	10	8	6	9	8	7	7	7	5	8	113
2	Rotterdam	10	10	7	10	10	10	10	3	6	7	3	10	9	5	110
3	Den Haag	9	10	7	10	10	9	8	7	6	7	4	10	8	9	114
4	Utrecht	9	3	9	10	6	9	9	2	9	10	2	7	6	5	96
5	Eindhoven	8	7	9	9	7	5	5	4	2	2	2	9	8	6	83
6	Tilburg	8	8	7	9	9	8	8	6	4	5	8	9	9	3	101
7	Almere	8	7	4	10	3	8	10	3	5	8	3	6	7	7	89
8	Groningen	7	9	10	5	9	7	9	1	8	9	3	2	1	7	87
9	Breda	7	6	6	6	5	3	4	7	2	4	6	7	8	3	74
10	Nijmegen	7	5	8	6	9	10	10	4	10	10	2	6	6	7	100
11	Enschede	6	8	5	8	10	9	9	4	8	6	3	9	8	3	96
12	Apeldoorn	6	5	4	3	2	8	8	8	9	8	8	3	4	10	86
13	Haarlem	7	3	9	7	6	4	6	8	5	6	9	3	2	7	82
14	Arnhem	6	9	10	9	8	9	4	9	9	6	8	5	2	8	102
15	Zaanstad	6	4	6	8	6	2	1	1	2	1	4	5	6	4	56
16	Amersfoort	7	2	6	7	4	10	10	5	10	10	7	1	1	8	88
17	Haarlemmermeer	7	1	5	4	1	4	3	7	7	6	7	1	1	6	60
18	's-Hertogenbosch	5	3	10	3	4	6	5	3	4	4	5	6	7	5	70
19	Zoetermeer	5	6	6	8	3	1	1	2	1	1	1	6	7	10	58
20	Zwolle	6	7	6	3	4	6	2	5	8	4	2	4	1	10	68
21	Maastricht	4	9	8	4	6	8	7	8	3	2	6	10	9	6	90
22	Dordrecht	6	10	4	9	7	2	1	3	2	1	5	7	4	10	71

23	Leiden	5	4	10	7	6	4	2	9	3	2	9	4	5	3	73
24	Emmen	4	6	4	1	10	2	2	1	3	3	1	8	6	10	61
25	Ede	5	6	1	3	5	7	4	9	9	5	10	1	3	2	70
26	Venlo	3	7	5	8	7	3	2	10	3	1	10	10	10	2	81
27	Westland	4	1	1	1	1	1	2	8	1	1	8	8	7	9	53
28	Deventer	5	6	6	6	8	9	9	3	7	5	4	9	10	3	90
29	Delft	3	7	8	9	9	1	1	5	1	1	1	10	10	8	74
30	Sittard-Geleen	3	8	9	3	7	3	1	7	1	1	9	9	9	1	71
31	Leeuwarden	4	10	9	4	9	5	5	10	5	5	10	5	5	5	91
32	Alkmaar	4	4	7	6	5	2	2	10	4	3	10	3	4	1	65
33	Heerlen	2	10	10	5	10	7	8	6	1	2	8	10	10	4	93
34	Helmond	5	5	4	7	6	5	4	8	4	3	10	8	8	2	79
35	Hilversum	1	5	10	5	3	7	5	2	10	8	6	3	3	4	72
36	Súdwest Fryslân	3	5	2	1	8	7	7	10	10	10	10	1	1	7	82
37	Amstelveen	2	1	3	8	2	1	1	10	7	5	9	1	1	10	61
38	Hengelo	4	6	3	4	7	5	7	5	6	6	7	4	4	4	72
39	Purmerend	2	4	8	6	4	2	3	9	5	4	9	7	9	5	77
40	Roosendaal	2	5	5	9	1	2	5	2	1	2	5	9	10	1	59
41	Oss	2	2	5	4	3	3	4	7	1	2	7	8	7	6	61
42	Schiedam	1	10	9	10	10	10	10	9	6	4	8	5	1	4	97
43	Spijkenisse	1	9	8	7	4	10	8	6	9	8	4	6	7	7	94
44	Leidschendam-Voorburg	2	2	7	7	3	1	1	10	4	3	10	2	3	8	63
45	Alphen a/d Rijn	1	2	8	5	1	10	10	1	10	10	5	4	3	5	75
46	Almelo	3	8	3	5	8	1	3	2	2	5	1	6	6	1	54
47	Vlaardingen	1	8	7	10	5	7	10	3	6	10	3	10	10	2	92
48	Gouda	3	3	1	8	8	6	3	10	7	6	9	2	2	3	71
49	Middelburg	1	9	1	4	7	1	3	1	3	4	2	2	2	2	42
50	Vlissingen	1	10	4	6	5	6	9	1	4	7	1	8	10	1	73

Table 6.3 continues on next page.

Table 6.3 *Continued*

#		Demographics					Perinatal mortality / all women			Perinatal mortality / BIG4 morbidities			Perinatal mortality / start labour in primary care			Rank
		% PREG	AGE <20	PRIMI	NW ETHN	LOW SES	ABS	STND	INEQ	ABS	STND	INEQ	ABS	STND	INEQ	
#	**Provinces**															
51	Groningen	8	7	3	2	9	9	8	6	10	9	6	5	5	4	91
52	Friesland	9	4	2	1	8	10	9	5	9	9	4	4	6	9	89
53	Drenthe	9	3	2	1	5	6	6	2	8	8	2	4	5	9	70
54	Overijssel	9	1	1	1	2	5	7	4	8	9	1	1	3	9	61
55	Gelderland	10	2	1	2	2	5	6	4	5	7	4	3	4	6	61
56	Utrecht	10	1	2	3	1	4	5	4	6	7	3	3	4	6	59
57	Noord-Holland	10	1	3	2	2	4	6	7	7	9	6	1	2	8	68
58	Zuid-Holland	10	2	2	2	1	4	6	1	5	8	1	2	2	9	55
59	Zeeland	8	3	2	1	3	8	7	8	10	10	5	2	3	1	71
60	Noord-Brabant	10	1	3	2	1	3	3	6	3	3	7	7	8	2	59
61	Limburg	9	4	5	2	2	3	4	5	2	3	6	8	9	1	63
62	Flevoland	8	9	1	5	4	6	7	6	7	9	5	5	5	10	87

10% HIGEST SCORE

10%-20% HIGHEST SCORE

10% LOWEST SCORE

* '% PREG': % pregnant women in the general population / 'AGE <20': % teenage pregnancies / 'PRIMI': % primiparous women / 'NW ETHN': % non-Western pregnant women / 'LOW SES': % women in neighbourhoods with a socioeconomic status score <p20 / 'ABS': Absolute % / 'STND': Standardised % / 'INEQ': Inequality as measured by the relative risk of prevalences between women from neighbourhoods with socioeconomic status score <p20 compared to >p80.

the absolute rate (ABS), the standardised rate (STND) and the inequality-rate (INEQ), the latter being expressed as the relative risk of the outcome for low SES pregnant women compared to high SES pregnant women, after direct standardisation for maternal age, parity and ethnicity.[17] Next, to facilitate comparisons, we assigned decile scores to regions, varying from one (the region is one of the 10% areas with best outcomes) to 10 (the region belongs to the 10% worst outcomes). The sum of the decile scores for the various indicators by region is shown in the last column ('RANK'); higher scores imply unfavourable ranking. For clarity, colors are used to differentiate between favourable and unfavourable outcomes: green represents the first decile (with the best outcome), pink the 10th decile (10% with the most adverse outcomes), amber the 10th-20th decile. Based on the sum of the decile scores for the PCC sub-study (table 6.2), the pink and amber municipalities/regions have the most adverse outcomes, i.e., 1. The Hague; 2. Rotterdam; 3. Eindhoven; 4. Amsterdam; 5. Schiedam; 6. Almere ; 7. Delft; 8. Utrecht; 9. Maastricht; 10. Tilburg; 11. Heerlen; 12. Arnhem; 13. Friesland. According to the sum of the decile score for the risk assessment sub-study (table 6.3) the following municipalities/regions show the most adverse outcomes: 1. The Hague; 2. Amsterdam; 3. Rotterdam; 4. Arnhem; 5. Tilburg; 6. Nijmegen; 7. Schiedam; 8. Utrecht; 9. Enschede; 10. Spijkenisse; 11. Heerlen; 12. Vlaardingen; 13. Groningen; 14. Leeuwarden.

Additional to the identified municipalities, the province of Friesland best qualified for the PCC sub-study and the province of Groningen for the risk assessment sub-study.

Final selection municipalities/regions

After the theoretical selection of the candidate municipalities/regions in the previous step, the next step elaborated on the practical aspects of sub-study implementation in candidate municipalities/regions, e.g., willingness to participate of local authorities and caregivers. The candidate municipalities/regions were first presented to the Ministry of Health, after which the Aldermen of these candidate municipalities/regions were consulted, which resulted in a final selection. The participating municipalities/regions are (figure 6.3): in the province of Groningen Appingedam/Delfzijl/Menterwolde/Pekela and Groningen city, the municipalities of Enschede, Nijmegen, Heerlen, Tilburg, Schiedam, Utrecht, The Hague, Amsterdam, and Almere.

All municipalities decided to participate in both sub-studies either as study or control. As a separate municipal program on reducing perinatal mortality was already being carried out in Rotterdam[5], this city was not selected for participation in the HP4All study.

Figure 6.3 Participating municipalities in the 'Healthy Pregnancy 4 All' project.

DESIGN OF THE PRECONCEPTION CARE SUB-STUDY

In this population-based prospective cohort study with a pre-post design for the measurement of effectiveness of PCC, we approach all women in the fertile age (18-42 years) and invite them to visit Preconception Care Consultations if they contemplate pregnancy. This sub-study consists of two consultations provided by midwives or general practitioners (GP), the second consultation takes place three months after the first. During

the first consultation, PCC risks are assessed and a tailored management plan is composed. At the second consultation, reduction of the PCC risk load is measured, and if required, the management plan is adapted.

Sample size calculation

The statistical design is based on a pre-post comparison with paired data. The primary outcomes used for the sample size calculation are overall preconceptional folic acid supplementation use and smoking cessation amongst smokers, as changes in these behavioral risk factors have a major impact on perinatal health and can be measured by biomarkers.[22-24]

The sample size was based on the following criteria:

1. *Self-reported folic acid supplementation use*. To reject the null hypothesis (H0: $\Delta \leq 20\%$, defined as the PCC program leading to a ≤ 20% increase of folic acid users in women that were not already using folic acid supplements at baseline) a total sample size of n= 839 is needed. Assumptions for the power calculation were (1) the smallest clinically relevant difference ('Δ') is a 20% increase of folic acid use in non-users at baseline, (2) the proportion of women using folic acid at baseline is 30% ($\pi 0=30\%$), (3) a-select drop-out rate of 10%, (4) results are pairwise analysed, (5) a statistical significance level $\alpha < 0.025$ (1-sided, correction for multiple testing due to two primary outcome measures), and (6) a power (1-β) of 0.80.
2. *Smoking cessation*. (1) To reject the null hypothesis (H0: $\Delta \leq 5\%$, defined as smoking cessation occurring in ≤ 5% of women that smoked at baseline) a total sample size of n=687 is needed. Assumptions for the power calculation were (2) the smallest clinically relevant difference ('Δ') is a 5% decrease of smoking compared to baseline, (3) the proportion of smoking women at baseline is 30% ($\pi 0=30\%$), (4) the a-select drop-out rate is 10%, (5) the results are pairwise analysed, (5) the significance level is $\alpha < 0.025$ (1-sided, correction for multiple testing due to two primary outcome measures), and (6) the power (1-β) is 0.80.

Enrollment

Women are actively approached by: (1) an invitational letter from the municipal public health service or municipality, and/or (2) an invitational letter from their GP, and/or (3) referral by a youth healthcare physician or nurse, and/or (4) referral by a peer educator in perinatal

health. The precise mode of approach depends on specific local collaborative agreements with the municipal authorities, the local public health authorities and the local caregivers. In addition, participating GPs and midwives can recruit women regularly attending their care. Furthermore, women within the community are informed about the PCC consultations by flyers and posters. Each woman, including the method that they were recruited by, is registered when a PCC visit at participating GP or midwife practices is scheduled. Women are sent participant information leaflets with an informed consent form before they are approached by telephone for inclusion. If women agree to participate they hand in the informed consent form before their consultation.

Logistics and data collection

The logistics of the PCC sub-study are carried out in close collaboration with local project coordinators and certified clinical laboratories in the 14 participating municipalities. The PCC risk assessment is performed by the client prior to each consultation individually at a convenient moment using the web-based validated '*ZwangerWijzer*' (translated 'Preparing for pregancy') internet questionnaire (www.zwangerwijzer.nl).[25] GPs and midwives during the consultations are supported professionally by the '*Preconceptiewijzer*' (translated 'Preparing for preconception care') tool (www.preconceptiewijzer.nl)., '*Preconceptiewijzer*' presents identified risk factors from '*ZwangerWijzer*'.This tool further provides GPs and midwives both with protocols on management of PCC risk factors and with information leaflets to hand out to the client.

Before the first PCC visit takes place, additional information will be collected from participating women: data on basic characteristics (e.g., educational level), general health (e.g., medical history), details on risk factors and health behaviours (primarily: folic acid use, alcohol consumption, smoking, drug use, diet, preventive behaviours regarding Listeria/ Toxoplasmosis prevention, weight) , and attitudes towards PCC are collected by a digital or on request by a paper - questionnaire (table 6.4). This questionnaire also includes a cardiovascular risk score (My Life Check, American Heart association, online: http://mylifecheck.heart.org/) and a risk score for diabetes (FINDRISK).[26] To measure alterations after the first PC consultation, clients are sent a digital or paper questionnaire regarding their health behaviours (risk reduction or elimination) 3 months after the first consultation. The same health behaviours are addressed as in the first questionnaire.

Additionally, protocol-based anthropometric measurements are performed (BMI, blood pressure, waist- and hip circumference), and biomarkers are collected at both consultations.

Table 6.4 Planned assessments in the preconception care experiment: parameters, biomarkers, questionnaires and outcome

Parameter	Biomarker	Questionnaire	Outcome
Folic acid suppletion	Erytrocyte folate, after both consultations	Self-reported folic acid use	• Prevalence: folic acid use measured at baseline with erytrocyte folate and self-reported use. • Effectiveness of preconception care: increase in number of women using folic acid (self-reported and increase of erytrocyte folate compared to baseline).
Smoking cessation	Serum cotinine level, after both consultations	Self-reported smoking, smoking cessation and smoking reduction.	• Prevalence: number of smokers at baseline based on self-report and serum cotinine. • Effectiveness preconception care: number of women reporting to have stopped smoking or have reduced smoking.
Alcohol intake cessation	% CDT[a] and Gamma GT, after both consultations	Self-reported alcohol consumption, before each consultation.	• Prevalence: number of women using alcohol and have been binge drinking, or classified as heavy drinkers (self-reported use),% CDT and Gamma GT at baseline. • Effectiveness of preconception care: change in number of women using alcohol preconceptionally (self-report). Decrease in % CDT and Gamma GT, normalizing for heavy drinkers after abstinence/ decreased use.
Drugs	Tox screening urine[b], after both consultations	Questionnaire and measure before each consultation	• Prevalence: number of women using hard- and softdrugs at baseline based on self-report and urine screening. • Effectiveness of preconception care: number of women who stopped drug use based on self-report and urine screening

Table 6.4 continues on next page.

Table 6.4 *Continued*

Parameter	Biomarker	Questionnaire	Outcome
Vitamine D	25-OH Calcidiol, after the first consultation	–	• Prevalence of vitamin D deficiency based on 25-OH Calcidiol level measured at the start of the preconception care consultation. • Questions regarding prognostic factors
Nutrition	Not applicable	Self reported diet, before each consultation	• Avoidance of vitamin A, no raw products and properly washed vegetables: self-reported at baseline. • Increase in number of women with a healthy diet, avoiding vitamin A and raw products, vegetables properly washed: self-reported during second consultation compared to baseline.
Adjustment medication regime	Not applicable	Self reported medication use, before each consultation.	• Prevalence: preconceptional medication use and types of medication. • Effectiveness: safe medication policy evaluation by the health care provider ([1] referral from midwife to GP for medication policy, [2] number of cases in which cessation/replacement/no cessation/continuation of medication is chosen, based on 'Teratology Information Service' advice, [3] patient adherence to medication policy
Pursuing a healthy bodyweight	–	Anthropometrics in both consultations	• Prevalence of overweight (BMI 25-30), obesity (BMI >30), and underweight (BMI <18.5) • Effectiveness of preconception care: number of women with overweight BMI >25 losing weight, and underweight BMI <18.5% gaining weight.

Adherence to personalized advice	–		• Adherence to advice regarding specific detected risk factors according to the caregiver.
Pregnancy outcome	–	Retrospective from national database (The Netherlands Perinatal Registry)	• Number of births adverse outcomes defined as (1) perinatal mortality, (2) congenital anomalies, (3) preterm birth (<37th week of pregnancy), (4) small for gestational age (birthweight <10th percentile), (5) low Apgar score (<5, 5 minutes after birth).
Booking visit <12th week of gestation	–	Retrospective from The Netherlands Perinatal Registry, self-reported at first consultation	• Gestational age at first antenatal booking visit
Cardiovascular risk score according to 'My Life Check'[c]	Cholesterol, Glucose	Measured blood pressure, BMI, questionnaire items regarding dietary habits and physical activity	• Prognostic value of cardiovascular risk score and prevalence of: hypertensive disease in pregnancy, congenital anomalies, preterm birth, small for gestational age, low Apgar score.
FINDRISK diabetes score	Cholesterol, Glucose	Blood pressure, BMI, waist and hip circumference, questionnaire items regarding family history, abnormal glucose measurement	• Prognostic value diabetes risk score and prevalence of: gestational diabetes, hypertensive disease in pregnancy, perinatal mortality, macrosomia, congenital anomalies, preterm birth, small for gestational age, low Apgar score.

[a] CDT: Carbohydrate-deficient transferrin, laboratory test to detect (heavy) alchohol consumption.
[b] screens for amfetamines, barbiturates, benzodiazepines, cocaine, ecstasy, metamfetamine, methadon, opiates, PCP, cannabis.
[c] http://mylifecheck.heart.org.

Blood samples are collected either by the caregiver or by an outpatient-testing facility of the local laboratory. Initial analysis of the samples (hemoglobin, mean corpuscular volume, fasting glucose at baseline) and refrigeration (between -20 and -80 degrees Celsius) will occur within 24 hours after sample collection at the local laboratory. Only deviant vitamin D, glucose, cholesterol and hemoglobin results are communicated to the participant's GP if she has requested so in the informed consent form. Regarding primary outcomes: erytrocyte folate – as biomarker for folic acid use), serum cotinin – as biomarker for cigarette smoking, carbohydrate dehydrogenase (CDT) – as biomarker for outcome for heavy drinking and urinary drugs tests – as biomarker for soft and hard-drug use; are measured.

Study preparation

Before study onset, the participating midwives and GPs receive training in PCC, including implementation of the '*Preconceptiewijzer*' tool. Additionally, the participating caregivers and their staff are given a preparatory tutorial at baseline on relevant procedures within the HP4All study. These procedures include anthropometric and blood pressure measurements and paper and web-based data registration.

Recruitment for the PCC sub-study was set up to the extent that was agreed upon with the local project coordinators. Firstly, the municipality or Municipal Health Service (which ever was chosen locally) selected women by the municipal population registry to mail the invitational letter. An invitational letter was provided by the project, and letters were adapted locally to fit the local situation. Secondly, local youth service was provided with flyers and posters- with local practices offering consultations - to disseminate amongst their youth healthcare physicians and nurses. Furthermore, GPs were supported logistically in selecting women registered in their practice. Women with evident contraindications for such invitation, both medically (such as terminal illness, with a hysterectomy or sterilisation in the past) or socially (widow, in detention) were excluded. They sent out a locally adapted basic letter provided by the project. Perinatal Health Educators were trained and provide perinatal health education sessions to self-recruited women contemplating pregnancy.

DESIGN OF THE ANTENATAL RISK ASSESSMENT SUB-STUDY

In this cluster randomised trial midwifery practices in participating municipalities ('clusters') were randomly assigned to either the use of a score-card ('R4U') based antenatal risk

assessment, care pathways and multidisciplinary consultation (intervention group) or conventional risk assessment (control group). Score-card based systematic risk assessment will be performed with the 'R4U' score-card at the first antenatal booking visit followed by, if necessary, a specific referral to, e.g., higher level obstetric care (gynaecologist), psychosocial care in case of medical or non-medical high risk using risk-specific care pathways. Additionally, these women at increased risk will be reviewed in a multidisciplinary team of caregivers concerning tailored antenatal care. Exclusion criteria include a medical emergency situation during the booking visit (e.g., ectopic pregnancy), or women being in labour.

The 70-item 'R4U' score-card consists of six risk domains (social status, ethnicity, care, lifestyle, medical history and obstetric history). Corresponding care pathways to both medical and non-medical services will support health care professionals to encounter complex (non-) medical risk factors. A predefined weighted sum risk threshold, based on weighted single risk factors, is derived from the 'R4U' score-card. If a pregnant woman's individual sum risk score exceeds the threshold, her case will be assessed in a multidisciplinary setting with community midwives, obstetricians, and other care providers.

Pregnant women's risk status in the control group is assessed conventionally, i.e., according to the elaborate so-called 'List of Obstetric Indications' (in Dutch: *Verloskundige Indicatie Lijst*)[12] which lists all conventional (>140) high risk indications (for referral or consultation). In each control region care 'as usual' will be provided until 700 participants have been included or until 2/3 of the study period (2 years) has passed. After that moment, the implementation of the risk assessment intervention will start.

Primary outcomes are the prevalence of preterm birth and SGA, and the efficacy of 'R4U' implementation (measured by the number of 'R4U' score-cards completed by the health care professional against the number of booking visits, the development and use of care pathways following 'R4U' scores, actually performed multidisciplinary consultations, and patient and healthcare professional satisfaction). Secondary outcomes are perinatal mortality (from 22 weeks' gestation until 7 days postpartum), undetected SGA and unexpected preterm birth, measured as onset of childbirth in primary care, prevalence and accumulation of medical and non-medical risk factors, and the number of women referred to secondary care through either R4U score-card based or conventional risk assessment.

Randomisation procedure and sample size calculation

In January 2011 randomisation took place by an independent statistician. In order to study the need for matching, we stratified the adverse perinatal outcomes ('Big4' and perinatal mortality) in each cluster by SES and ethnicity. Since clusters were not considerably different in terms of these characteristics, matching of clusters for SES and ethnicity was considered unnecessary.

Sample size in this study is based on the effectiveness of the 'R4U' risk assessment and resulting care pathways intervention in early pregnancy on the likelihood of SGA and preterm birth. In this cluster-randomised trial, sample size depends on: (1) the average risk of SGA and preterm birth without the intervention ($\pi 0$); (2) the expected effect of the intervention ($\pi 1$); (3) the inflation factor reflecting the partial similarity/dependency of women's outcomes or responses within the same cluster[27]); and (4) the α and (5) power (1-β) of the test. Using data from the 2000-2008 Netherlands Perinatal Registry for the selected postal code regions[20], we estimated $\pi 0$ at 16.7% (summation of preterm birth and SGA), the expected effect of the intervention ($\pi 1$) at 13% and the inflation factor at 2.06, based on formulas on Donner et al.[27] With 10 clusters, five municipalities in the control and five in the intervention group, and an alpha of 0.05 (two-sided), 7,000 participants (3,500 per arm) should provide power in excess of 80%. This means that 700 women per cluster should be included in the analysis.

Logistics and data collection

As with the PCC sub-study, the logistics of this sub-study are carried out in close collaboration with participating local project coordinators, midwives, obstetricians, and, if available, research midwives in the 14 participating municipalities. Midwives and obstetricians inform pregnant women about the HP4All study at the booking visit and hand out an information package.

All pregnant women at their first antenatal booking visit with a midwife or obstetrician located in the areas are eligible if she meets the inclusion criteria. In intervention municipalities, the 'R4U' score-card will be filled out during the first antenatal visit. For the 'R4U' score-card a web-based registration form is used in which women are registered, coded with a study identification number. Depending on the detected risk factors, care pathways can be used to modify these risk factors. If a pregnant woman's weighted sum risk score exceeds the predefined threshold, multidisciplinary consultation will be advised. In control municipalities, pregnant women in the control group will receive regular antenatal health care. Table 6.5 provides an overview of the planned assessments within the risk assessment sub-study including variables, methods and outcomes.

Table 6.5 Planned assessments in the risk selection experiment: variables, methods and outcomes

Variables	Methods	Outcomes
Patients		
1. INTERVENTION GROUP *Non-medical risk factors*: 39 items from the risk score card, categorized into the domains social, ethnicity, care, and lifestyle. *Medical risk factors*: 30 items from the risk score card, categorized into the domains general history and obstetric history *Baseline characteristics*: Age, zip-code, ethnicity, onset of care, household composition, family income, employment, education level, smoking, alcohol, drugs, folic acid use, medication use, pre-existing chronic diseases, sexually transmitted diseases.	R4U score card + registration form 'Obstetric history' Questionnaire 'Baseline characteristics' Case Record Form 'pregnancy and delivery data'	Primary outcomes: - Preterm birth - SGA Secondary outcomes: - Undetected SGA and unexpected preterm births (babies born in primary care) - Prevalence of risk factors - Risk accumulation - Involved healthcare professionals during pregnancy - Detection and prevention of impaired growth and preterm birth during pregnancy - Perinatal mortality - Congenital anomalies - Mode of delivery - Place of delivery - Asphyxia - Neonatal admission - Maternal morbidity (e.g., pre-existing chronic disease, pregnancy complications), and maternal mortality.
2. CONTROL GROUP *Baseline characteristics*: Age, zip-code, ethnicity, onset of care, household composition, family income, employment, education level, smoking, alcohol, drugs, folic acid use, medication use, pre-existing chronic diseases, sexually transmitted diseases.	Registration form 'Obstetric history' Questionnaire 'Baseline characteristics' Case Record Form 'pregnancy and delivery data'	
Patient satisfaction *in both groups*	Questionnaire 'Patient experiences during the first antenatal visit'	- Which topics were discussed (10 examples)? - What was your experience? - Do you think this was important to ask?
Care providers		
General characteristics participating midwifery practices and hospitals *in both groups*	Interview-based questionnaire	- Current number of patients and employees - Use of risk selection instruments - Collaboration with hospitals and (other) midwifery practices - Work processes (e.g., counselling for prenatal screening, or ultrasound facilities).
Care provider satisfaction *in both groups*	Questionnaire	- Feasibility - Efficacy of implementation - Collaboration - Continuation of intervention

Study preparation

In municipalities allocated to the intervention group, midwives and obstetricians will use the 'R4U' score-card during the first antenatal visit of all women (provided that informed consent is given). Participating midwives and obstetricians receive personal instructions in planned sessions by the project team for the practical use of the web-based 'R4U' score-card. Besides, an e-learning program is available for all caregivers. The project team has developed 28 templates of care pathways for all risk factors in the 'R4U' score-card. Together with local healthcare professionals in perinatal care, municipal services, community health services, and other services, these templates will be adapted in organised meetings to local setting, taking the availability of local facilities, agreements, and guidelines into consideration. We aim to assess 20% of all pregnant women in this multidisciplinary setting in order to determine a cut-off score per municipality.

INFORMED CONSENT, DATA QUALITY, CONTROL, MANAGEMENT AND TIME SCHEDULE FOR BOTH SUB-STUDIES

Informed consent

The HP4All study has been approved by the Medical Ethical Committee of the Erasmus Medical Centre Rotterdam (Preconception Care sub-study: MEC 2012-425; Antenatal risk assessment trial: MEC 2012-322), and by the management of all participating care providers. Pregnant and non-pregnant women, depending on the sub-study, will receive written and oral information about the study.

Participation in either sub-study is voluntary and informed consent must be obtained. PCC consultations are currently not covered by health care insurances; PCC providers will receive reimbursement from the HP4All project. The participating practices in the antenatal risk sub-study receive no financial compensation.

Data quality, control and management

For logistic reason, data are collected and coded with a study identification number. Otherwise we will not be able to link data from the initial visit to birth records. The research team and participating caregivers have access to the key that links study identification

number to record data. Data analysis and storage will take place on an anonymised dataset. Access to this anonymised data is only available to the research team. All data and biomaterials are stored 15 years after inclusion.

Time schedule

The HP4All study was initiated in April 2011. Full participant recruitment and complete data collection started in December 2012. A cohort of 839 women for the PCC sub-study is expected to be completed by the beginning of 2014. For the risk assessment sub-study, 7,000 women are also expected to be included by the beginning of 2014.

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The effectiveness of risk selection in the Dutch obstetric care system

J. Poeran, J. van der Kooy, E. Birnie, S. Denktaş, E.A.P. Steegers, G.J. Bonsel

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ABSTRACT

Objective To quantify if risk selection in Dutch obstetric care (by midwives) results in a true low risk population in primary care at the end of pregnancy. This is an essential quality of care indicator as a distinction is made between primary care for low risk pregnancies by independently practicing community midwives, and secondary/tertiary care for high risk pregnancies by obstetricians.

Methods All singleton pregnancies (≥22 weeks' gestation, 2000-2007, n=1,407,387) from The Netherlands Perinatal Registry were selected. We defined high risk pregnancy as the presence of ≥1 'Big4' morbidities, the main precursors of perinatal mortality: congenital anomalies, preterm birth, small for gestational age (SGA), or low Apgar score. Referral patterns of high risk pregnancies were studied during pregnancy and parturition; adequate risk selection implies no high risk pregnancies in primary care. Additionally, we applied a diagnostic test framework to study effectiveness of SGA selection (and referral) by defining true positives (referral of SGA), false positives (referral of non-SGA), false negatives (non-referral of SGA), and true negatives (non-referral of non-SGA). Sensitivity, specificity, negative predictive value (NPV), negative likelihood ratio (LR-), and false negative rate (FN) were determined for eight patient subgroups.

Results 59% of 'Big4' were referred during pregnancy, 19% during parturition; 22% remained in primary care. SGA 'test' characteristics differed considerably for subgroups (sensitivity 15%-59%, specificity 54%-87%, NPV 89%-97%, LR- 0.69-1.05, FN 3%-11%).

Conclusion Risk selection in Dutch obstetric care does not realise its aim of a true low risk group in primary care at the end of pregnancy. Methods for improvement are warranted.

INTRODUCTION

In The Netherlands perinatal mortality exceeds the European average.[1] The unique Dutch system of obstetric care has been regarded as a potential contributing factor.[2-4] This system is characterised by three risk-based levels of care. Primary care for low risk pregnancies is provided by independently practicing community midwives and a small percentage of general practitioners (GPs). Assumed low risk pregnant women can either opt for a home birth or a short-stay hospital birth under supervision of a community midwife. Secondary/ tertiary care for assumed high risk pregnancies is provided by obstetricians in hospitals.

Currently, approximately 80% of pregnant women start antenatal care in primary care.[5] Whenever risk factors (for adverse perinatal or maternal outcome) are present before pregnancy or arise during pregnancy or parturition, women shift from low risk to high risk and are referred to secondary care or from secondary to tertiary care, also during parturition. This ongoing risk assessment *during pregnancy* and *during parturition* is called 'risk selection'. In formal terms, the aim of risk selection is to identify and refer high risk pregnancies in order to obtain a true low risk group of pregnant women (expressed as high negative predictive value of risk selection) in the primary care setting.[5,6] Thus, risk selection adequacy is an essential quality of care indicator of the Dutch obstetric care system.

Although the effectiveness of risk selection in Dutch primary obstetric care has been studied, a nationwide systematic evaluation on the performance of the risk selection process is still absent.[3,4,6-11] The present nationwide retrospective study quantifies the performance of risk selection (*during pregnancy* and *during parturition*) by community midwives in terms of its ability to achieve a true low risk population at the end of pregnancy.

METHODS

Netherlands Perinatal Registry

We selected data from all singleton pregnancies for the period 2000-2007 as registered in The Netherlands Perinatal Registry, which is subject to Dutch law regulations regarding confidentiality. In agreement with the World Health Organization (WHO) reporting guidelines, only pregnancies with a gestational age of ≥22 weeks were included.[12] The registry contains population-based information of >97% of all pregnancies in The Netherlands.[13] Source data are collected by 94% of midwives, 99% of gynaecologists and 68% of paediatricians (including 100% of Neonatal Intensive Care Unit paediatricians) as part

of their routine medical dossier; see website for detailed description www.perinatreg.nl.[13] The board of The Netherlands Perinatal Registry granted permission to use the anonymous registry data for this study. The Netherlands Perinatal Registry has been extensively described and used in several recent studies.[1,2,4,10,13-15]

Assignment of high risk

In Dutch obstetric care a pregnancy is considered a valid high risk, justifying referral, if an adverse perinatal outcome, adverse maternal outcome or combination of both is present or is to be expected. Indications for referral are listed in the so-called 'List of Obstetric Indications' (in Dutch: *Verloskundige Indicatie Lijst*).[5] Community midwives are trained in the use of the 'List of Obstetric Indications' to detect (expected) high risks.

Judgment of adequacy of high and low risk assignment

As a retrospective measure to judge whether assumed low risk women truly were low risk, we used the prevalence of so-called 'Big4' morbidities as an indicator of risk status (***gold standard***).[2,15] From a detailed analysis of The Netherlands Perinatal Registry we know that four specific morbidities precede perinatal mortality in 85% of cases, the so-called 'Big4' morbidities.[2,15] These are: congenital anomalies (list defined), preterm birth (<37th week of gestation), small for gestational age (SGA, birthweight <10th percentile for gestational age[16]) or low Apgar score (<7, 5 minutes after birth). Congenital anomalies are registered postpartum through a standard coding system with eight different organ systems, and further distinction into 51 specific and 20 more global categories. By using remnant 'Big4' morbidity among assumed low risk women as yard stick we focus on undetected risks which are relevant to perinatal mortality. This focus by definition does not include any unexpected adverse maternal outcome in low risk women.

Effectiveness of risk selection

The primary outcome in quantifying the effectiveness of risk selection is the 'Big4' (high risk) prevalence at the end of pregnancy in primary care. In the theoretical perfect case 'Big4' morbidity is absent in assumed low risk pregnancies.

From this starting point, we utilise three methods to quantify effectiveness of risk selection:

Method 1. with a flow chart approach describing the proportional shift of women from primary care to secondary/tertiary care over the course of pregnancy, distinguishing

between two referral moments (*during pregnancy* and *during parturition*); risk selection should preferably take place *during pregnancy*;

Method 2. by comparing eight, mutually exclusive, patient subgroups in terms of the level of care at first antenatal booking (primary, secondary/tertiary care) and subsequent referral, where 'Big4' prevalence and perinatal mortality are observed in the various subgroups; preferably, perinatal mortality is only increased in the secondary/tertiary care group with referral of 'Big4' pregnancies *during parturition* being a rare event.

The eight subgroups were defined according to parity (primiparous/multiparous), ethnicity (Western/non-Western), and living in a deprived neighbourhood (yes/no, based on 4-digit zip codes and an official public list of 40 deprived zip code based neighbourhoods).[17] The eight groups presumably differ according to 'Big4' prevalence and care characteristics.

Method 3. by formal analysis of diagnostic performance of selection and referral of one 'Big4' category, i.e., SGA. The theoretical goal is to obtain a SGA-free population in the primary care setting, which is studied for the same eight patient subgroups as before. If the subgroup SGA prevalence matches the subgroup variation in test characteristics, then, the selected patient subgroup factors (parity/ethnicity/neighbourhood) are likely to be responsible for the between subgroup differences in test characteristics. However, if there is a discrepancy, other factors may explain the subgroup test characteristics variation factors, e.g., system related factors.

SGA was chosen as, together with congenital anomalies, it can be detected the easiest in the antenatal phase. Moreover, there is general consensus on (improving) detection of SGA because of the inherent increased risk for adverse outcome[18], and most congenital anomalies are now detected by routine ultrasound (introduced in 2007) at 20 weeks of gestational age.

Referral categories

To describe the referral process we defined five mutually exclusive categories:

I. First antenatal booking in secondary/tertiary care, no referral by definition, birth in hospital in secondary/tertiary care.

II. First antenatal booking in primary care, referral *during pregnancy*, birth in hospital in secondary/tertiary care;

III. First antenatal booking in primary care, referral *during parturition*, birth in hospital in secondary/tertiary care;

IV. First antenatal booking in primary care, no referral, home birth in primary care;

V. First antenatal booking in primary care, no referral, short-stay hospital birth in primary care.

Diagnostic performance of SGA referral and selection

For the third quantification of effectiveness of risk selection we applied a diagnostic test framework in which SGA selection (and referral) *during pregnancy* and *during parturition* are treated as a positive 'test result', whereas the presence of SGA at birth is regarded as the 'gold standard' outcome. The related 2x2 table is illustrated in table 7.1: 'A' represents true positives (referral of SGA), 'B' false positives (referral of non-SGA), 'C' false negatives (non-referral of SGA), and 'D' true negatives (non-referral of non-SGA).

The following five diagnostic test characteristics were determined applying method 3[19-21]:

- Sensitivity [A/(A+C)], the proportion of SGA cases referred;
- Specificity [D/(B+D)], the proportion of non-SGA cases which are not referred;
- Negative predictive value (NPV) [D/(C+D)], the proportion of non-referred women without a SGA baby;
- Negative likelihood ratio (LR-), [1-sensitivity/specificity], determines whether a negative 'test' result, i.e., no referral, decreases the probability of having a SGA baby for women who are not referred. A negative likelihood ratio ranging from 0 to <1 implies diagnostic value of the test, a value of 1 represents a test without diagnostic value ('similar to flipping a coin') regarding SGA selection and referral. The lower the LR-, the higher the diagnostic value, i.e., non-referral being associated with absence of SGA;
- SGA false negative rate (FN) [1-NPV], i.e., the proportion of non-referred women with a SGA baby (false negative).

Table 7.1 Main 2x2 table with actual referral to secondary/tertiary care treated as a positive 'test result' and the presence of SGA (small for gestational age) at birth treated as the 'gold standard' outcome

		SGA present at birth	
		Yes	No
Referral	Yes	A	B
	No	C	D

A: True positive / B: False positive / C: False negative / D: True negative

The NPV, LR- and FN can be considered the most important test characteristics. These characteristics pertain to the least desirable situation, i.e., a woman with a high risk (e.g., SGA) pregnancy giving birth in primary care which is only intended for low risk pregnancies.

RESULTS

Process of risk selection

A total of 1,407,387 single pregnancies were analysed. Figure 7.1 displays the selection and referral of 'Big4' pregnancies by referral category in a flowchart; 15% of all pregnancies are 'Big4' pregnancies. The dark grey area represents the 'Big4' proportion in primary care (above the dashed line) and in secondary/tertiary care (below the dashed line). The dark grey area above the dashed line diminishes in width if 'Big4' pregnancies are referred from primary care to secondary/tertiary care *during pregnancy* or *during parturition*. Over the course of pregnancy, the proportion of 'Big4' pregnancies in primary care decreases from 14% at first antenatal booking to 6% in women giving birth at home and to 9% among women with a short-stay hospital delivery under the supervision of a community midwife.

Table 7.2 displays demographics and outcomes in the overall study population by the referral categories. Most women are multiparous (54%), between the ages of 20-35 years (84%), of Western origin (84%) and living in a non-deprived neighbourhood (94%). The largest referral group is the group of women referred during pregnancy (group II, n=466,415). In the group referred *during parturition* (group III), 70% of women are primiparous compared to 48% of women referred *during pregnancy* (group II). Group IV has the lowest risks, the group with the highest risk is group I.

Method 2: 'Big4' and perinatal mortality prevalence by patient subgroup and referral category

Table 7.3 shows the 'Big4' and perinatal mortality (overall 9.8 per 1,000) prevalence for the different subgroups in the five referral categories. Late 'Big4' referral, i.e., 'Big4' prevalence in women referred *during parturition* is not rare with a range of 14-19%; perinatal mortality, however, is relatively low ranging from 3.5 to 8.3 per 1,000 births.

Overall, there are large differences in perinatal mortality and 'Big4' prevalence between subgroups and referral categories: in all referral categories, primiparous women have

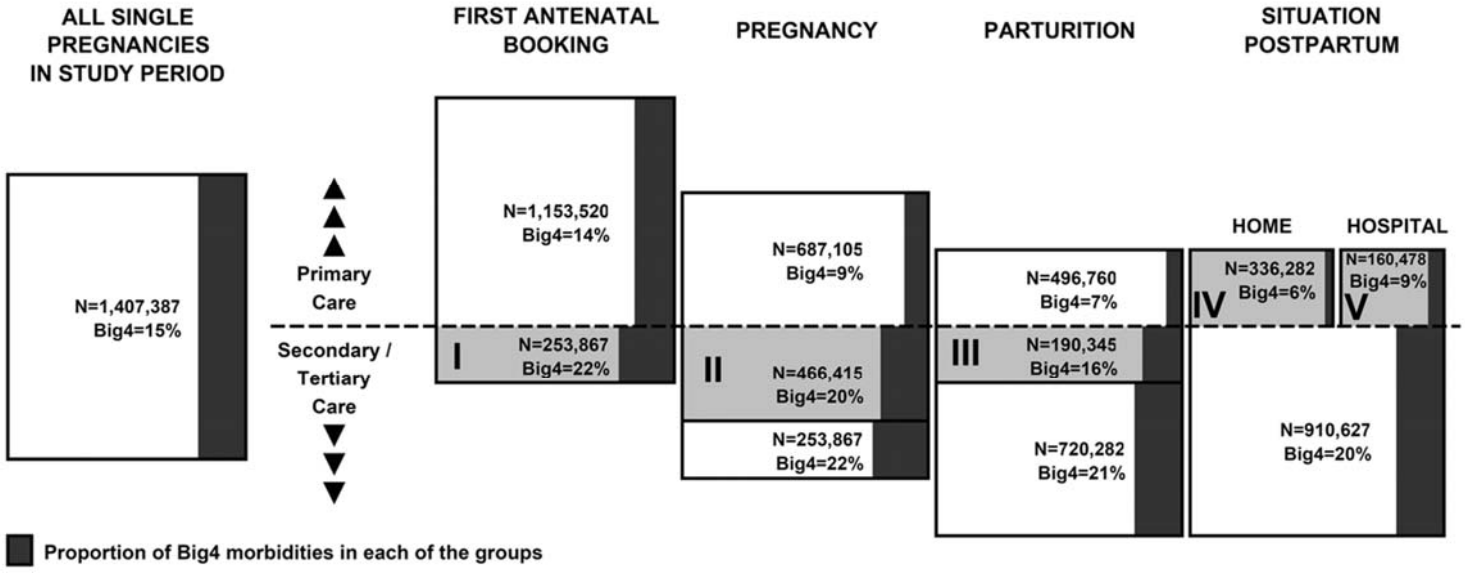

Figure 7.1 Referral and risk selection in Dutch obstetric care in absolute numbers; effectiveness of risk selection is illustrated as the proportion of 'Big4' pregnancies in dark grey. The different referral categories are light grey; from left to right referral categories I to V.

Table 7.2 Demographics and outcome in the study population by the five different referral categories

	Referral categories					
Referral category	I	II	III	IV	V	Total
First booking	Secondary/ Tertiary care	Primary care	Primary care	Primary care	Primary care	
Birth	Secondary/ Tertiary care	Secondary/ Tertiary care	Secondary/ Tertiary care	Primary care: home	Primary care: hospital	
Referral	No referral	During pregnancy	During parturition	No referral	No referral	
N	253,867	466,415	190,345	336,282	160,478	1,407,387
Parity*						
Primiparous (%)	121,066 (48)	226,133 (48)	134,102 (70)	1044,88 (31)	63,567 (40)	649,356 (46)
Multiparous (%)	132,794 (52)	240,121 (52)	56,193 (30)	231,719 (69)	96,826 (60)	757,653 (54)
Maternal age*						
<20 years (%)	4,725 (2)**	7,539 (2)	4,333 (2)	2,820 (1)	4,637 (3)	24,054 (2)
20-35 years (%)	206,984 (82)**	382,195 (82)	166,938 (88)	290,442 (86)	136,418 (85)	1,182,977(84)
>35 years (%)	42,158 (17)**	76,681 (16)	19,074 (10)	43,020 (13)	19,423 (12)	200,356 (14)
Ethnicity						
Western (%)	214,332 (84)	387,985 (83)	157,245 (83)	308,425 (92)	112,775 (70)	1,180,762 (84)
Non-Western (%)	39,535 (16)	78,430 (17)	33,100 (17)	27,857 (8)	47,703 (30)	226,625 (16)

Table 7.2 continues on next page.

Table 7.2 *Continued*

	Referral categories					
Referral category	I	II	III	IV	V	Total
First booking	Secondary/ Tertiary care	Primary care	Primary care	Primary care	Primary care	
Birth	Secondary/ Tertiary care	Secondary/ Tertiary care	Secondary/ Tertiary care	Primary care: home	Primary care: hospital	
Referral	No referral	During pregnancy	During parturition	No referral	No referral	
Neighborhood						
Non-deprived	237,836 (94)	437,358 (94)	177,652 (93)	324,477 (96)	143,699 (90)	1,321,022 (94)
Deprived	16,031 (6)	29,057 (6)	12,693 (7)	11,805 (4)	16,779 (10)	86,365 (6)
Congenital anomalies						
No (%)	245,554 (97)	447,192 (96)	185,515 (97)	332,647 (99)	158,329 (99)	1,369,237 (97)
Yes (%)	8,313 (3)	19,223 (4)	4,830 (3)	3,635 (1)	2,149 (1)	38,150 (3)
Preterm birth						
No (%)	223,946 (88)	426,324 (91)	177,404 (93)	334,920 (100)	157,945 (98)	1,320,539 (94)
Yes (%)	29,921 (12)	40,091 (9)	12,941 (7)	1,362 (0)	2,533 (2)	86,848 (6)
Small for gestational age						
No (%)	231,494 (91)	425,522 (91)	178,062 (94)	321,107 (95)	150,532 (94)	1,306,717 (93)
Yes (%)	22,373 (9)	40,893 (9)	12,283 (6)	15,175 (5)	9,946 (6)	100,670 (7)

* Totals do not always add up due to missing values (parity 378 missings, maternal age 284 missings).
** Percentages add up to 101% because of rounding

Table 7.3 Prevalence of 'Big4' morbidities and perinatal mortality by the five referral categories in different subgroups (based on parity, ethnicity and neighbourhood). Total number of pregnancies (N=1,407,009) does not include 378 parity missings.

		Referral categories																	
Referral category		I			II			III			IV			V			Total		
First booking		Secondary/Tertiary care			Primary care			Primary care			Primary care			Primary care					
Birth		Secondary/Tertiary care			Secondary/Tertiary care			Secondary/Tertiary care			Primary care: home			Primary care: hospital					
Referral		No referral			During pregnancy			During parturition			No referral			No referral					
		N	Big4*	†**	N	Big4*	†**	N	Big4*	†**	N	Big4*	†**	N	Big4*	†**	N	Big4*	†**
Subgroups																			
Primiparous																			
Western	Non-deprived	101,876	25%	20.3	188,323	24%	13.8	110,669	16%	3.7	94,435	9%	0.8	44,882	12%	5.9	540,185	19%	10.0
	Deprived	3,284	28%	26.5	6,379	27%	16.3	3,719	18%	3.5	2,597	8%	0.8	2,063	15%	3.4	18,042	21%	11.8
Non-Western	Non-deprived	12,293	30%	34.2	24,570	27%	17.6	15,316	18%	5.3	5,947	12%	1.7	12,302	14%	5.1	70,428	22%	14.3
	Deprived	3,613	30%	39.6	6,861	29%	18.4	4,398	19%	5.5	1,509	13%	2.7	4,320	14%	2.8	20,701	23%	14.9
Multiparous																			
Western	Non-deprived	106,312	18%	19.6	188,639	15%	11.7	41,725	14%	6.2	208,150	5%	0.6	63,800	6%	3.6	608,626	11%	8.1
	Deprived	2,858	27%	33.9	4,522	20%	13.0	1,097	16%	7.3	3,179	6%	1.9	1,993	8%	2.0	13,649	16%	12.7
Non-Western	Non-deprived	17,348	23%	31.5	35,683	18%	15.6	9,897	15%	7.0	15,876	7%	0.6	22,640	7%	2.5	101,444	15%	12.2
	Deprived	6,276	25%	33.5	11,277	20%	17.0	3,474	15%	8.3	4,514	6%	0.9	8,393	8%	1.4	33,934	15%	13.2
Total		253,860	22%	22.3	466,254	20%	13.5	190,295	16%	4.7	336,207	6%	0.7	160,393	9%	4.0	1,407,009	15%	9.8

* 'Big4' morbidities in percentage of the total amount of pregnancies in that subgroup.
** Perinatal mortality (from 22 weeks of gestational age until 7 days postpartum) per 1,000 births.

higher 'Big4' prevalences compared to multiparous women (range 8-30% versus 5-27% for multiparous women). Perinatal mortality, however, is lower in primiparous women referred *during parturition* compared to multiparous women (3.5-5.5 vs. 6.2-8.3 per 1,000 births, respectively). In almost all subgroups and referral categories, non-Western women have higher 'Big4' and perinatal mortality prevalences; outcome differences between living in a non-deprived versus living in a deprived neighbourhood are smaller.

Method 3: SGA selection *during pregnancy*

Table 7.4 shows the SGA prevalence before and after selection (and subsequent referral), and diagnostic test characteristics for SGA selection and referral *during pregnancy* and *during parturition*. Of all women exposed to the selection and referral process *during pregnancy* (referral categories II to V), non-Western primiparous women in deprived neighbourhoods have the highest SGA prevalence (13%). For all subgroups, SGA prevalence is lower after selection compared to before. Sensitivity and specificity of SGA selection *during pregnancy* ranges from 49% to 59% and from 58% to 63% respectively. The range of NPV is 89-97%. The negative likelihood ratio (LR-) ranges from 0.69 to 0.85, indicating that that the SGA prevalence decreases (after the selection / 'test') in the group of women who are not referred *during pregnancy*. However, the values are close to 1 (which would imply a test without diagnostic value) which implies a modest discriminating value. The FN ranges from 3-11% depicting the percentage of non-referred women having SGA babies.

Method 3: SGA selection *during parturition*

Of all women exposed to the selection and referral process *during parturition* (referral categories III to V) primiparous non-Western women have the highest SGA prevalence (11%). For all subgroups, there is no difference in SGA prevalence before and after selection. Sensitivity and specificity of SGA selection *during parturition* range from 15% to 45% and from 54% to 87%, respectively. For primiparous women the sensitivity is higher than for multiparous women. Specificity, on the other hand, is higher for multiparous women than for primiparous women. The NPV is similar to that for the SGA selection process *during pregnancy* 89-97%. The LR- ranges from 0.97 to 1.05 implying no diagnostic value of risk selection for SGA *during parturition*. The FN ranges from 3-11%.

Table 7.4 Subgroup SGA prevalence before ('SGA% BF') and after ('SGA% AF') selection, and diagnostic test characteristics*; both for selection and referral of SGA pregnancies *during pregnancy* and *during parturition*

		Selection during pregnancy							Selection during parturition						
		SGA% BF	SGA% AF	SENS	SPEC	NPV	LR-	FN	SGA% BF	SGA% AF	SENS	SPEC	NPV	LR-	FN
Subgroups															
Primiparous															
Western	Non-deprived	9%	7%	53%	58%	93%	0.82	7%	7%	7%	42%	56%	93%	1.05	7%
	Deprived	11%	9%	53%	58%	91%	0.80	9%	9%	9%	44%	56%	91%	1.01	9%
Non-Western	Non-deprived	12%	11%	50%	59%	89%	0.85	11%	11%	11%	45%	54%	89%	1.01	11%
	Deprived	13%	11%	49%	61%	89%	0.83	11%	11%	11%	44%	57%	89%	0.99	11%
Multiparous															
Western	Non-deprived	4%	3%	52%	63%	97%	0.76	3%	3%	3%	15%	87%	97%	0.98	3%
	Deprived	7%	5%	59%	59%	95%	0.69	5%	5%	5%	18%	83%	95%	0.99	5%
Non-Western	Non-deprived	6%	5%	53%	58%	95%	0.81	5%	5%	5%	23%	80%	95%	0.97	5%
	Deprived	7%	5%	52%	60%	95%	0.79	5%	5%	5%	21%	79%	95%	1.00	5%
Total		7%	5%	52%	60%	95%	0.79	5%	5%	5%	33%	73%	95%	0.93	5%

* SENS: sensitivity, SPEC: specificity, NPV: negative predictive value, LR-: negative likelihood ratio, FN: SGA false negative rate.

DISCUSSION

Principal findings

To our knowledge, this is the largest study on the effectiveness of risk selection in Dutch primary obstetric care. The main focus was to examine whether risk selection realises its aim of a true low risk group of pregnant women by identifying and referring high risk pregnancies. Even though many 'Big4' pregnancies are referred, our results demonstrate that a true low risk population is never attained, with a 'Big4' prevalence of up to 15% in primary care (table 7.3), intended for low risk pregnancies only. Also, 'Big4' prevalence among late referrals (*during parturition*) was still substantial, ranging from 14% to 19%.

We further observed a suboptimal discrimination of SGA and non-SGA pregnancies (low sensitivity, LR- close to 1 in all subgroups) with a SGA prevalence of 3% to 11% still being born in primary care.

Moreover, we observed a discrepancy in the subgroup SGA prevalence and the subgroup variation in SGA selection test characteristics (table 7.4). This implies other factors to be responsible for the suboptimal test characteristics instead of the selected patient factors, e.g., system related factors. One may think of differences in availability of SGA screening methods.

Home birth versus short-stay hospital birth

In primary care, short-stay hospital births showed higher 'Big4' prevalence compared to home births (9% vs. 6%). This may reflect an unintentional selection process by either the midwife or self-selection by pregnant women, i.e., more healthy women appear to opt for home birth. This has also been observed in other studies.[22]

Preventability

From our results, the question arises whether the birth of a 'Big4' baby in a primary rather than secondary care setting is a preventable situation. As stated, congenital anomalies and SGA are better predictable than (spontaneous) preterm birth and a low Apgar score. In accepting that a NPV of 100% is not attainable, we actually state that 'Big4' deliveries in a primary care are to some extent inevitable in a system with different risk-based settings.

The subsequent question then refers to the observed 'setting safety' of a primary care setting. Both general consensus and the 'List of Obstetric Interventions' agree that a neonate with a 'Big4' morbidity is better off in a hospital setting under the care of an obstetrician/paediatrician.[23] The benefit of this so-called 'setting safety' may be related to availability of neonatological expertise, continuous fetal heart rate monitoring or advanced resuscitation equipment.[4,10]

As we showed less optimal SGA selection, and more referrals *during parturition* for primiparous women, we believe that all primiparous women should deliver in a hospital environment, either under supervision of a midwife (birth centre) or an obstetrician. This also follows from unequivocal evidence from previous studies[24-26], where others generally waive the primary care option.[24]

Strengths and limitations

The strengths of the current study include the nationwide approach and high coverage of pregnancies in The Netherlands Perinatal Registry over a long period of time. In addition, the use of 'Big4' morbidities, as the major precursors of perinatal mortality, allows for an easy-to-comprehend proxy measure of high risk pregnancy.[2,15] Also, the application of a diagnostic test framework allows the results to be interpreted objectively in a standardised way; comparisons with other diagnostic test studies can be easily made. Another strength pertains to the use of subgroups. It is interesting at the very least to see a discrepancy between the level of subgroup differences for SGA prevalence compared to the smaller subgroup differences in test characteristics.

This study also has limitations. Firstly, it is not possible to determine the exact indication for why women were referred because of the retrospective nature of The Netherlands Perinatal Registry. For our study objective, the effect of this limitation is limited as we focused on high risk births taking place in primary care, which is intended for low risk births. Our estimate of prevalence of high risk births in primary care is conservative as it is likely to be higher, providing it would have been possible to take into account all referral indications. Another possible limitation is that with the 'Big4' approach, maternal and other non-'Big4' related risks are disregarded. This problem also appears to be limited as the majority of referral indications according to the 'List of Obstetric Interventions' pertain to fetal/neonatal risks alone.[5] Finally, the impact of routine ultrasound examination at 20 weeks of gestational age (introduced in 2007) on congenital abnormality rates and perinatal mortality rates due to second trimester abortions cannot be evaluated in our 2000-2007 dataset.

Previous studies on risk selection in the Dutch system

Our findings contradict most previous studies on the effectiveness of risk selection in Dutch primary obstetric care, stating that risk selection is effective.[6-9] In contrast with our study, these studies took into account maternal morbidity and obstetric interventions (e.g., caesarean section). However, these studies have been conducted some time ago, are restricted to smaller study groups, specific regions or did not evaluate the risk selection process systematically.[6-9] Another limitation of previous studies is that they defined the effectiveness of risk selection not only as prevention of adverse perinatal outcomes but also as prevention of obstetric interventions such as a caesarean section.[7-9] While we recognise that the assessment of risk selection must be weighed against the risk of possibly unnecessary obstetric interventions, the primary goal of adequate risk selection and subsequent referral is to prevent adverse perinatal and/or maternal outcomes, the prevention of (unnecessary) obstetric interventions being an important secondary goal.[6,9,27]

Several reports have expressed concern on the effectiveness of risk selection in Dutch primary obstetric care.[2,4,10] A recent Dutch study revealed that in 43% of Neonatal Intensive Care Unit (NICU) admissions the pregnancy had been indicated as low risk, and thus parturition had started in primary obstetric care.[10] Furthermore, infants of pregnant women at supposedly low risk whose labor started in primary care had a significantly higher delivery related perinatal mortality risk than the infants of assumed high risk women whose labor started in secondary care (relative risk 2.33, confidence interval 1.12-4.83).[4] Infants of women who were referred *during parturition* had a 3.66 times higher risk of delivery related perinatal mortality than infants of women who started labor in secondary care, and a 2.5-fold higher risk of NICU admission.[4] These studies emphasise that the level of healthcare provision could be improved for a proportion of supposedly low risk pregnant women at the onset of labor. Whether the delay in referral is related to late diagnosis (no continuous fetal heart rate monitoring *during parturition* in primary care), transport to hospital or assessment ('primary care is supposedly low risk'), is yet unclear.[4,10]

Possible implications

Our results demonstrate that the aim of risk selection in Dutch primary obstetric care is suboptimally attained. We propose some directions of improvement. As stated in the 'List of Obstetric Interventions', risk selection is currently exclusively done by primary care community midwives. Possible improvements could be the increase of midwives' competence and capabilities, or introduction of a checklist-based standardised risk

selection strategy at first antenatal booking. However, we believe that the required pace of change is more likely to be achieved through a combination of the latter with 'shared care': better cooperation between midwives and obstetricians who are jointly responsible for the determination of a woman's risk status, thereby joining their expertise which is either physiology-based (midwives) or pathology-based (obstetricians).[28] Shared obstetric care has already been implemented in some form in other Western countries such as Australia and the United Kingdom.[29-31] One study demonstrated a 27% increase in the detection rate of intrauterine growth restriction for women receiving shared obstetric care as opposed to conventional obstetric care.[32] For more generalisable results however, a study to evaluate different shared care strategies has to be conducted in The Netherlands because of the unique system of obstetric care. We believe that our recommendation for shared care also applies to countries which are considering or already have an obstetric care system with features similar to the Dutch system, such as Canada.[33-36]

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8

Planned home compared with planned hospital births in The Netherlands: intrapartum and early neonatal death in low-risk pregnancies

J. van der Kooy, J. Poeran, J.P. de Graaf, E. Birnie,
S. Denktaş, E.A.P. Steegers, G.J. Bonsel

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ABSTRACT

Objective The purpose of our study was to compare the intrapartum and early neonatal mortality rate of planned home birth vs. planned hospital birth in community midwife-led deliveries, after case mix adjustment.

Methods Perinatal outcome of 679,952 low-risk women was obtained from the Dutch Perinatal Registry (2000-2007). This group represents all women who had a choice between home and hospital birth. Two different analyses were performed; natural prospective approach (intention-to-treat like analysis) and perfect guideline approach (per-protocol like analysis). Unadjusted and adjusted odds ratios were calculated. Case mix was based on the presence of at least one of the following: congenital abnormalities, small for gestational age, preterm birth, or low Apgar score. We also investigated the potential risk role of intended place of birth. The technique used was multivariable stepwise logistic regression.

Results Intrapartum and neonatal death 0-7 days was observed in 0.15% of planned home vs 0.18% in planned hospital births (crude RR 0.80 95%CI 0.71-0.91). After case mix adjustment, the relation is reversed, showing non-significant increased mortality risk of home birth (OR 1.05 95%CI 0.91-1.21). In certain subgroups additional mortality may arise at home if risk conditions emerge at birth (up to 20% increase).

Conclusion Home birth, under routine conditions, is generally not associated with increased intrapartum and early neonatal death, yet in subgroups additional risk cannot be excluded.

INTRODUCTION

The debate on the safety of home births continues in the literature as recently addressed in the Lancet.[1] In the Netherlands, approximately 50% of women give birth under the supervision of a community midwife. The community midwives are independent health care professionals in the Netherlands, operating either solely or in group practices. The proportion of home birth deliveries in the Netherlands has steadily decreased over the last decade but is currently stable at 25% of all births. Several Anglo-Saxon countries are considering the reintroduction of home births, based on recent claims of sufficient safety.[2] The reverse trend is observed in the Netherlands, where the debate has intensified since the national perinatal mortality rate showed to be one of the highest in Europe.[3]

In the Dutch system, independently operating community midwives provide care for low- and medium-risk pregnant women (primary healthcare). High-risk pregnant women are referred to the gynaecologist for remaining ante- and intrapartum care. If no or only a few risk factors are present, women can stay with the midwife and decide where the delivery will take place: at home or in the hospital, both supervised by the community midwife. For pregnant women with so called 'medium-risk' delivery in hospital is obligatory but can still be under the supervision of the community midwife. A strict definition of medium risk, created and agreed upon by midwives and gynaecologists together, is defined in the Dutch guidelines.[4] The claimed benefits of planned home births include the reduction of maternal-fetal morbidity, a lower risk for unjustified medical interventions, and psychosocial advantages for the mother. These benefits may be counterbalanced by the disadvantages associated with a high intrapartum referral rate and an increased perinatal mortality, morbidity and long term negative effects.[5-11]

This paper re-addresses the Dutch evidence focusing on two critical features of previous analyses. First, previous studies compared outcomes after exclusion of pregnant women who in view of the delivery guidelines should have been referred to a gynaecologist. Second, previous studies did not apply case mix analysis, assuming risk equivalence of home and hospital groups.[5,9,12-18] Case mix may, however, differ across planned place of delivery, due to self selection or due to the midwife's proposal, with the healthiest and most affluent women receiving home birth (confounding the comparison by indication bias).[5 6,7,11,19-21]

The purpose of our study was to compare the intrapartum and early neonatal mortality rate of planned home birth vs. planned hospital birth in community midwife-led deliveries, after case mix adjustment. We compared a natural prospective approach without ex post exclusion of unsuitable midwife cases (intention-to-treat like), with the conventional

approach based on a theoretical midwife population under perfect guideline adherence (per-protocol like). We hypothesised that while in general no difference may exist between home and hospital outcomes, for specific risk groups the hospital setting is protective as obstetrical and neonatal expertise and clinical facilities are directly available (so-called "setting safety").

METHODS

Data

The Netherlands Perinatal Registry (PRN) contains population-based information of 96% of all pregnancies in The Netherlands. Source data are collected by 95% of midwives, 99% of gynaecologists and 68% of paediatricians (including 100% of Neonatal Intensive Care Unit paediatricians).[3,22] (See website for detailed description: www.perinatreg.nl). We selected the records of all singleton pregnant women, under supervision of a community midwife at the onset of labour between 2000-2007 (693,592 women). The onset of labour was defined as spontaneous contractions or the spontaneous rupture of membranes by the PRN. Two subsets of pregnant women were further excluded from the original set of 693,592 women. First, 13,384 women with so called 'medium risk', for example women with a history of postpartum haemorrhage or obesity (BMI>30). Dutch guidelines prescribe a hospital delivery for these women which may be supervised by the community midwife. Secondly we excluded records were the data was incomplete (n=256).

The remaining women (n=679,952) were categorised according to intended place of birth, which usually is concordant with the observed place of birth either home or hospital. For some women the place was not decided until the onset of labour. This could be due to indifference on the part of the woman; or delayed antepartum care. The intended place was then coded 'unknown'. This yielded 3 intention groups: home, hospital, and, unknown.

Outcome measures, maternal and neonatal risk factors

Outcome was defined as intrapartum and early neonatal mortality , i.e. (I) intrapartum death, (II) neonatal death up to 24 hrs, and (III) neonatal death up from 1 day to 7 days post partum. In our low risk group under midwife supervision, mortality beyond 8 days is rare, and regarded to be unrelated to place of delivery. The PRN does not include long term child outcomes for example psychomotor development and behavioural function.

Maternal risk factors were parity (nulliparous vs. multiparous), age, ethnicity (Western/non-Western; based on a more refined classification in the registry), and living in a deprived neighbourhood (yes/no, based on 4-digit zip-codes and a public list of deprived, zip-code based, neighbourhoods issued by the Dutch government).

Detailed risk information is unavailable in national registries. Case mix of any defined group of women was primarily represented by the prevalence (single or combined) of 'Big4' conditions (see below). From detailed analysis of the complete perinatal dataset of the same Netherlands Perinatal Registry (PRN), years 2000-2007, (1.25 million records)[23], it appeared that the presence of any of 4 conditions preceded perinatal mortality in 85% of cases. These conditions were defined as; congenital abnormalities (list defined), small for gestational age (SGA, birth weight below the 10th percentile for gestational age, gender and parity specific), preterm birth (< 37th week of gestation) or low Apgar score (< 7, measured 5 minutes after birth). We will continue to refer to these 4 conditions as the 'Big4'. The main results of this detailed analysis are found in figure 8.1.

In our current analysis these so called 'Big4' represent an objective estimate of the risk challenge at birth. The preventability of their occurrence, either antenatally or during delivery, is not at issue. Here we intentionally use it as a risk indicator, an explanatory factor at onset. By doing so, we ignore differential management effects of setting on the emergence of these Big4, in particular low Apgar, should they exist.

Data analysis

As primary analysis we present the results of the natural prospective approach (NPA), resembling an intention-to-treat analysis. For comparison we added a perfect guideline approach (PGA), resembling a per-protocol analysis. The NPA approach establishes, within observational constraints, the intrapartum and early neonatal death of planned home versus planned hospital births. It stems from the viewpoint of a pregnant woman starting birth under supervision of a midwife (the denominator is n=679,952). The natural approach thus includes spontaneous preterm labour since to some extent this group was not referred to the gynaecologist during labour or was referred late during (home) delivery. Therefore a direct setting effect (admission to hospital at the onset of labour) may be visible to the advantage of the hospital. Furthermore indirect setting effects may be present, for example the timing of referral.

PGA includes the subset of women within the NPA population, who *in retrospect* were compliant with the guidelines which define low risk at the onset of labour and therefore allowed to choose between a home or hospital birth under supervision of a midwife.

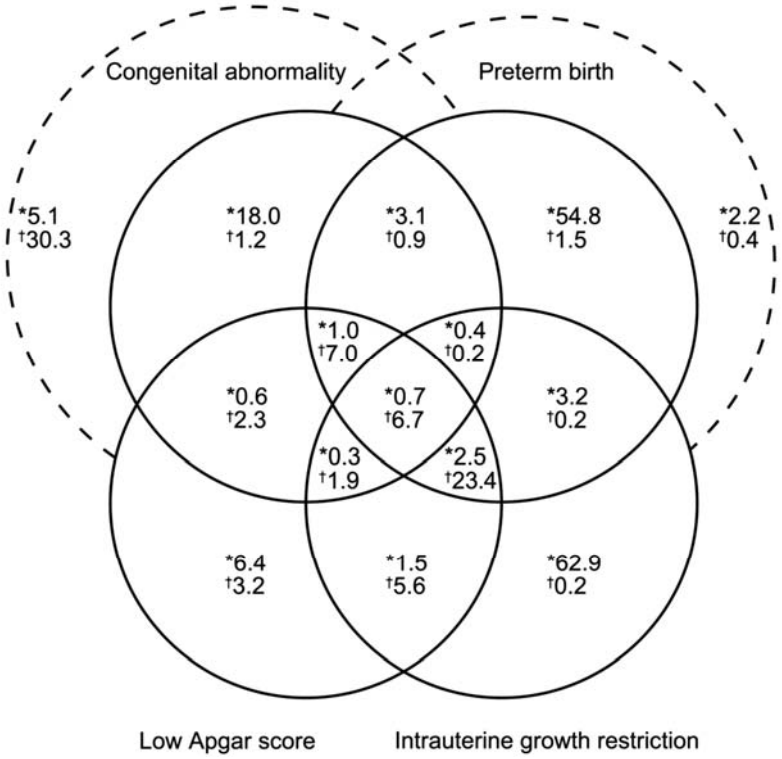

Figure 8.1 Perinatogram illustrating in a Venn diagram the relationship between (combinations of) Big 4 morbidities and perinatal mortality defined as death from 22 weeks of gestational age until 7 days postpartum. In 85% of all cases of perinatal mortality, one or more Big4 morbidities are present; for instance, a low Apgar score combined with preterm birth occurs in 30.3% of all cases of perinatal mortality. *Prevalence per 1,000 births of separate and combined Big 4 morbidities and their contribution to all cases of perinatal mortality (†percentage); this adds up to 85% of all cases of perinatal mortality. The dashed circles connect low Apgar score with preterm birth and congenital abnormality with intrauterine growth restriction.

Non-compliance exists if a high risk condition was already detectable at the onset of labour. These conditions applied to women with a gestational age <37 or >41 weeks, prolonged rupture of membranes (>24hr) and intrauterine death with unclear timing relative to onset of labour (see figure 8.2). PGA (n=602,331) still included undetected SGA and congenital malformations that emerge at birth, as detection failure cannot be regarded as non-compliance from the viewpoint of current guidelines.

First we compared characteristics of the NPA and PGA populations by intended place of birth (t-tests for comparisons). Then we investigated the potential risk role of intended place

of birth by a set of predefined nested multivariable logistic regression models (stepwise analysis; inclusion $p<0.05$; exclusion $p>0.10$) where we added maternal and neonatal (case mix) explanatory variables. For these variables, hospital birth was set as the reference. All stepwise analyses were repeated with a forward and backward approach, and finally forced inclusion of predictive variables ($p<0.05$). Risk factor coefficients were only shown

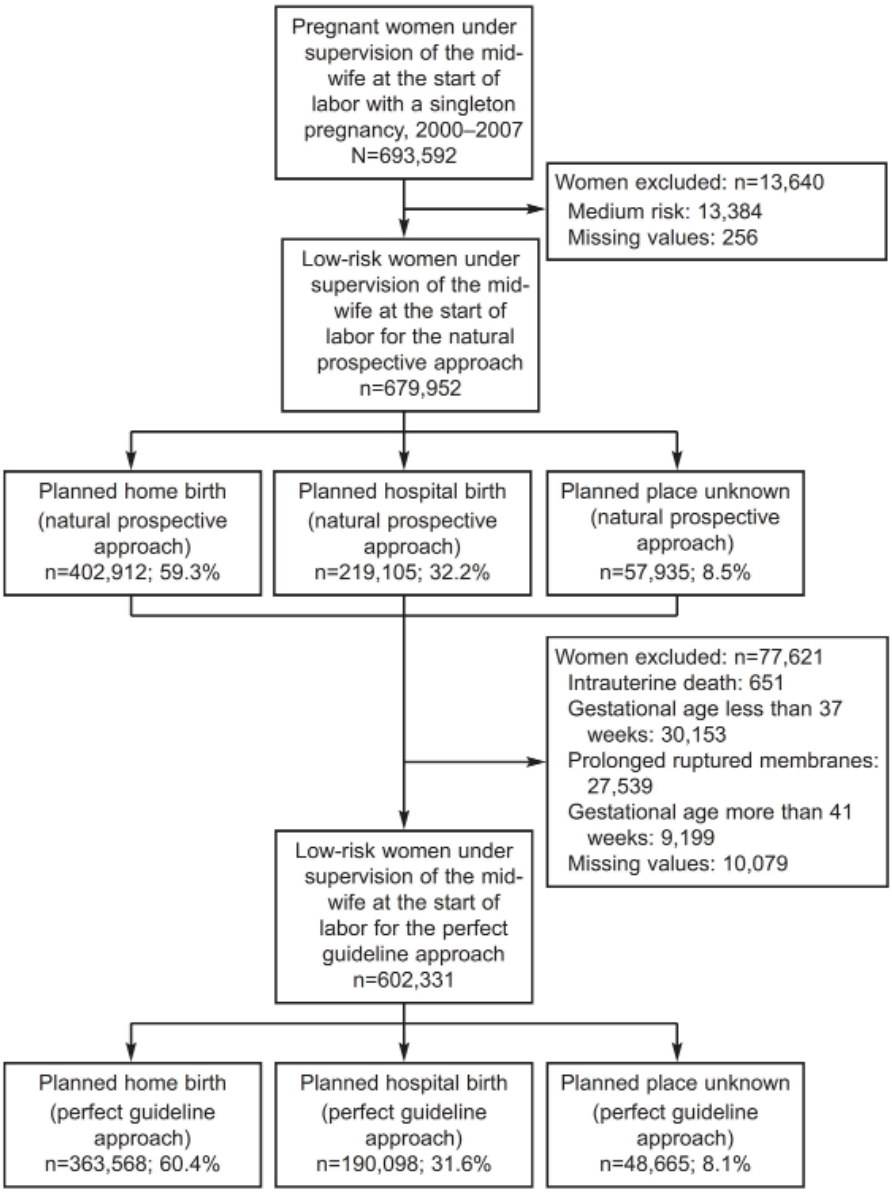

Figure 8.2 Flow of women through the study.

in case of significance $p<0.05$. Results across the three approaches were similar unless stated otherwise.

We graphically described the crude mortality of the planned home and planned hospital population, for the series of populations which result from successive exclusion of women meeting a criterion for non-compliance (figure 8.3; dotted lines). This successive exclusion through non-compliance criteria gradually transforms the NPA population into the PGA population. If the mortality rate of a non-compliance group is average, home and hospital mortality rates do not change on its exclusion. If the rates decrease at a different gradient (e.g. hospital steeper than home, as after exclusion of pregnancy duration < 36 weeks) this may point to either differential prevalence of the non-compliance factor (as here), or to differential case fatality by setting where the largest mortality decrease is observed in the setting with the highest case fatality (interpretable as lowest setting safety).

To support this interpretation, we first divided the crude mortality of the home and hospital group by the respective prevalence of Big4 conditions to obtain case mix adjustment. This assumes Big4 prevalence to be a suitable risk indicator at the group level. Subsequent division of the resulting home/Big4 mortality ratio by the hospital/Big4 mortality yields an index (Big4 adjusted homebirth mortality index; figure 8.3; black line). If this index is 100%, then relative mortality in home births and hospital births is equal. If the index is for example 120%, then home births have 20% excess mortality taking our case mix differences into account. Combining crude mortality changes with index changes allows for tentative interpretation of setting effects.

RESULTS

Table 8.1 describes the baseline characteristics of both the NPA and PGA populations (n=679,952 vs. 602,331).

In both the NPA and PGA populations about 60% of women planned a home delivery and about 32% planned a hospital delivery. Compared to women who planned birth in the hospital or with unknown location, the women with planned home birth were more likely to be multiparous, 25 years or older, of Dutch origin and to live in a privileged neighbourhood (all of which are favourable conditions). In home birth women, neonatal case mix compared also favourably. Premature delivery was less common, as was the prevalence of a Big4 condition (NPA home birth 8.7% vs. hospital 10.8% vs. unknown 10.5%; PGA home birth 6.5% vs. hospital 8.2% vs. unknown 7.5%; $p<0.001$ in both cases).

Intrapartum and early neonatal mortality was 1099/679,952=1.62 ‰ in the NPA women and 551/602,331=0.91‰ in PGA women. Mortality was lower in women who were multiparous, between 24-34 year, of Dutch origin, or living in a privileged neighbourhood (both NPA and PGA), see table 8.1. Within the group with intrapartum and early neonatal mortality, Big4 conditions were found in 792 of the 1099 deaths (72.1%) in the NPA women, compared to 290 out of 551 deaths (52.6%) in the PGA group.

In the NPA population, crude mortality risk was significantly lower for women who planned to give birth at home (RR 0.80 95%CI 0.71-0.91) and for women with unknown intention (RR 0.96 95%CI 0.77-1.19) compared to those who intended to give birth in hospital (P<0.05) (see table 8.2). All maternal and neonatal risk factors, except living in a deprived neighbourhood, showed significant effect sizes in agreement with the expected direction. Mortality was significantly increased in infants with a Big4 outcome, especially in infants with multiple Big4 conditions (RR 168.9 95%CI 148.9-191.4).

The nested multivariable logistic regression analysis showed that in the presence of adjusting maternal factors only (model 2), the intended place of birth had no significant impact on outcome. The maternal factors showed risks similar to the univariable (crude) analysis. The addition of Big4 case mix adjustment (model 3) showed the intended place of birth to be a significant co-variable, yet the contrast of planned home birth (OR 1.05 95%CI 0.91-1.21) vs. hospital birth (reference=1) turned out to be non-significant. The effect of maternal risk factors was affected to a limited degree by the introduction of Big4 case mix.

We repeated the analysis for the PGA population (table 8.3). The results of the crude analysis were close to the NPA analysis. However, the effect of ethnic background was considerably stronger in the PGA population. In all analyses the intended place of birth showed a consistent significant impact on intrapartum and early neonatal mortality, yet the contrast between home and hospital birth never reached statistical difference. After Big4 case mix adjustment home birth showed a non-significant increased risk (OR 1.11 95%CI 0.93-1.34).

Figure 8.3 describes the crude mortality risk (left Y-axis) and the Big4 adjusted home birth mortality index (right Y-axis), where each dot represents the mortality risk results after the group listed on the X-axis has been excluded from the population.

The crude mortality (dotted lines) initially shows a difference in favour of home delivery (home: 0.18% vs. hospital: 0.22%), which converges towards a much lower average level if premature births are excluded. Further exclusions lower the crude mortality rate, leaving the small difference almost unaffected. The mortality index (black line) shows a distinct change from an initial level of about 100% towards about 120% after exclusion of the pregnancy

Table 8.1 Characteristics and outcomes of women in primary care at the onset of labour (natural prospective approach and perfect guideline approach)*

Variable	Planned home birth		Planned hospital birth		Planned place unknown		Intrapartum and early neonatal death	
	NPA	PGA	NPA	PGA	NPA	PGA	NPA	PGA
Parity†	402,912 (59.3)	363,568 (60.4)	219,105 (32.2)	190,098 (31.6)	57,935 (8.5)	48,665 (8.1)	679,952	602,331
Primiparous	171,986 (42.69)	148,082 (40.73)	104,249 (47.58)	88,110 (46.35)	26,254 (45.32)	21,047 (43.25)	614 (0.20)	283 (0.11)
Multiparous	230,926 (57.31)	215,486 (59.27)	114,856 (52.42)	101,988 (53.65)	31,681 (54.68)	27,618 (56.75)	485 (0.13)	268 (0.08)
Maternal age (y)†								
Younger than 19	4,036 (1.00)	3,502 (0.96)	6,713 (3.06)	5,770 (3.04)	1,190 (2.05)	910 (1.87)	42 (0.35)	13 (0.13)
20-25	34,661 (8.60)	30,787 (8.47)	32,617 (14.89)	28,669 (15.08)	6,823 (11.78)	5,611 (11.53)	133 (0.18)	65 (0.10)
25-34	296,128 (73.50)	267,408 (73.55)	142,597 (65.08)	124,071 (65.27)	39,526 (68.22)	33,583 (69.01)	693 (0.14)	348 (0.08)
Older than 35	68,087 (16.90)	61,871 (17.02)	37,178 (16.97)	31,588 (16.62)	10,396 (17.94)	8,559 (17.59)	231 (0.20)	125 (0.12)
Ethnic background†								
Western	364,796 (90.54)	329,677 (90.68)	143,677 (65.57)	124,144 (65.31)	45,205 (78.03)	38,508 (68.80)	880 (0.16)	452 (0.09)
Non Western	38,116 (9.46)	33,891 (9.32)	75,428 (34.43)	65,954 (34.69)	12,730 (21.97)	17,461 (31.20)	219 (0.17)	99 (0.08)
Neighbourhood†								
Privileged neighbourhood	388,089 (96.32)	350,346 (96.36)	196,659 (89.76)	170,366 (89.62)	53,823 (92.90)	45,425 (93.34)	1,031 (0.16)	518 (0.09)
Underprivileged neighbourhood	14,823 (3.68)	13,222 (3.64)	22,446 (10.24)	19,732 (10.38)	4,112 (7.10)	3,240 (6.66)	68 (0.16)	33 (0.09)

Gestational age (wk)†								
Less than 34	2,409 (0.60)		1,702 (0.78)		583 (1.01)		370 (7.88)	
35-36	6,510 (1.62)		4,064 (1.85)		1,206 (2.08)		65 (0.55)	
37	15,203 (3.77)	13,622 (3.75)	9,603 (4.38)	8,468 (4.45)	2,497 (4.31)	2,187 (4.49)	56 (0.21)	51 (0.21)
38-41	368,926 (91.56)	349,946 (96.25)	193,816 (88.46)	181,630 (95.55)	49,585 (85.59)	46,478 (95.51)	548 (0.09)	500 (0.09)
More than 41	9,864 (2.45)		9,920 (4.53)		4,064 (7.01)		60 (0.25)	
Big4†								
Small for gestational age	18,786 (4.66)	17,089 (4.70)	13,114 (5.99)	11,604 (6.10)	3,081 (5.32)	2,665 (5.48)	71 (0.20)	59 (0.19)
Premature	8,090 (2.01)		5,117 (2.34)		1,547 (2.67)		92 (0.62)	0.00
Low Apgar score	1,692 (0.42)	1,483 (0.41)	1,180 (0.54)	959 (0.50)	289 (0.50)	228 (0.47)	97 (3.07)	86 (3.22)
Congenital abnomality	4,874 (1.21)	4,366 (1.20)	2,941 (1.34)	2,531 (1.33)	778 (1.34)	655 (1.35)	74 (0.86)	60 (0.79)
Combination Big4	1,648 (0.41)	693 (0.19)	1,279 (0.58)	453 (0.24)	391 (0.67)	92 (0.19)	458 (13.80)	85 (6.87)
Total Big4	35,090 (8.71)	23,631 (6.50)	23,631 (10.79)	15,547 (8.18)	6,086 (10.50)	3,640 (7.48)	792 (1.22)	290 (0.68)

NPA, natural prospective approach; PGA, perfect guideline approach.
Data are n (%).
* Totals may not add up to 100 because of rounding error.
† P<.001.

Table 8.2 Intrapartum and neonatal death 0-7 days in women who are in primary care at the onset of labour (natural prospective approach)

				Model 1			Model 2			Model 3		
	Total	Mortality	p	Crude RR	95% CI	p	Adjusted OR	95% CI	p	Adjusted OR	95% CI	p
Intended place of birth			<.05			<.05						<.05
Home	402,912	594 (0.15)		0.80	0.71–0.91		nie			1.05	0.91–1.21	
Hospital [ref]	219,105	403 (0.18)		1						1		
Unknown	57,935	102 (0.18)		0.96	0.77–1.19		nie			0.77	0.61–0.97	
Parity			<.001			<.001			<.001			
Primiparous	302,489	614 (0.20)		1.58	1.40–1.78		1.67	1.47–1.89		nie		
Multiparous [ref]	377,463	485 (0.13)		1			1					
Maternal age (y)			<.001			<.001			<.001			<.001
Younger than 19	11,939	42 (0.35)		2.43	1.78–3.31		1.80	1.31–2.48		1.67	1.17–2.38	
20-25	74,101	133 (0.18)		1.24	1.03–1.49		1.03	0.85–1.24		0.92	0.75–1.13	
25-34 [ref]	478,017	693 (0.14)		1			1			1		
Older than 35	115,661	231 (0.20)		1.38	1.19–1.60		1.56	1.34–1.81		1.44	1.23–1.68	
Ethnic background			<.001			<.001			<.05			<.05
Western [ref]	571,185	880 (0.15)		1			1			1		
Non-Western	108,767	219 (0.20)		1.31	1.13–1.52		1.32	1.14–1.54		1.21	1.02–1.45	

Neighbourhood						<.05				
Privileged neighbourhood [ref]	638,571	1,031 (0.16)		1						
Underprivileged neighbourhood	41,381	68 (0.16)		1.02	0.80–1.30		nie		nie	
Gestational age (wk)			<.001			<.001				<.001
Less than 34	4,694	370 (7.88)		88.08	77.44–100.18				15.74	12.56–19.72
35-36	11,780	65 (0.55)		6.17	4.77–7.97				2.11	1.56–2.86
37	27,303	56 (0.21)		2.29	1.74–3.02				2.26	1.71–2.99
38-41 [ref]	612,327	548 (0.09)		1					1	
More than 41	23,848	60 (0.25)		2.81	2.15–3.67				2.10	1.60–2.77
Big4			<.001			<.001				<.001
SGA	34,910	71 (0.20)		1.27	1.00–1.62				3.64	2.82–4.69
Prematurity	14,754	92 (0.62)		12.49	9.90–15.76					
Low apgar	3,161	97 (3.07)		21.35	17.28–26.38				53.41	42.55–67.04
Congenital abnomality	8,593	74 (0.86)		5.68	4.48–7.20				14.53	11.30–18.67
Combination Big4	3,318	458 (13.80)		168.85	148.94–191.41				68.17	55.27–84.08
No Big4	615,145	307 (0.05)		1						

RR, relative risk; CI, confidence interval; OR, odds ratio; nie, not in equation.
Data are n or n (%) unless otherwise specified.
Model 1: crude RR. Model 2: adjusted for maternal factors including intended place of birth, parity, age, ethnic background, and neighborhood. Model 3: adjusted for maternal factors and child factors; model 2 + gestational age and presence of Big4.

Table 8.3 Intrapartum and neonatal death 0-7 days in women who are in primary care at the onset of labour (perfect guideline approach)

			Model 1			Model 2			Model 3		
	Total (n)	Mortality	Crude RR	95% CI	p	Adjusted OR	95% CI	p	Adjusted OR	95% CI	p
Intended place of birth					<.05			<.05			<.05
Home	363,568	344 (0.09)	0.99	0.83–1.18		1.02	0.85–1.23		1.11	0.93–1.34	
Hospital [ref]	190,098	182 (0.10)	1			1			1		
Unknown	48,665	25 (0.05)	0.54	0.35–0.81		0.54	0.36–0.83		0.57	0.37–0.86	
Parity					<.001			<.001			
Primiparous	257,239	283 (0.11)	1.42	1.20–1.67		1.52	1.28–1.82		nie		
Multiparous [ref]	345,092	268 (0.08)	1			1					
Maternal age (y)					<.001			<.001			<.05
Younger than 19	10,182	13 (0.13)	1.56	0.90–2.71		1.31	0.75–2.30		1.29	0.73–2.26	
20-25	65,067	65 (0.10)	1.22	0.94–1.59		1.11	0.84–1.45		1.08	0.83–1.41	
25-34 [ref]	424,915	348 (0.08)	1			1			1		
Older than 35	102,018	125 (0.12)	1.50	1.22–1.84		1.66	1.34–2.04		1.50	1.22–1.85	
Ethnic background											
Western [ref]	507,063	452 (0.09)	1								
Non-Western	94,717	99 (0.10)	1.17	0.94–1.46		nie			nie		

Neighbourhood									
Privileged neighbourhood [ref]	566,137	518 (0.09)	1						
Underprivileged neighbourhood	36,194	33 (0.09)	1.00	0.70–1.42		nie	nie		
Gestational age (wk)					<.001				<.001
37	24,277	51 (0.21)	2.43	1.82–3.24			2.51	1.87–3.37	
38-41 [ref]	578,054	500 (0.09)	1				1		
Big3					<.001				<.001
SGA	31,358	59 (0.19)	4.03	3.04–5.35			4.28	3.22–5.68	
Low apgar	2,670	86 (3.22)	69.05	54.28–87.84			71.52	55.87–91.56	
Congenital abnomality	7,552	60 (0.79)	17.03	12.88–22.53			16.76	12.64–22.23	
Combination Big3	1,238	85 (6.87)	147.19	115.97–186.80			159.49	123.86–205.38	
No Big3	559,513	261 (0.05)	1				1		

RR, relative risk; CI, confidence interval; OR, odds ratio; nie, not in equation.
Model 1: crude RR. Model 2: adjusted for maternal factors including intended place of birth, parity, age, ethnic background, and neighborhood. Model 3: adjusted for maternal factors and child factors; model 2 + gestational age and presence of Big 4.

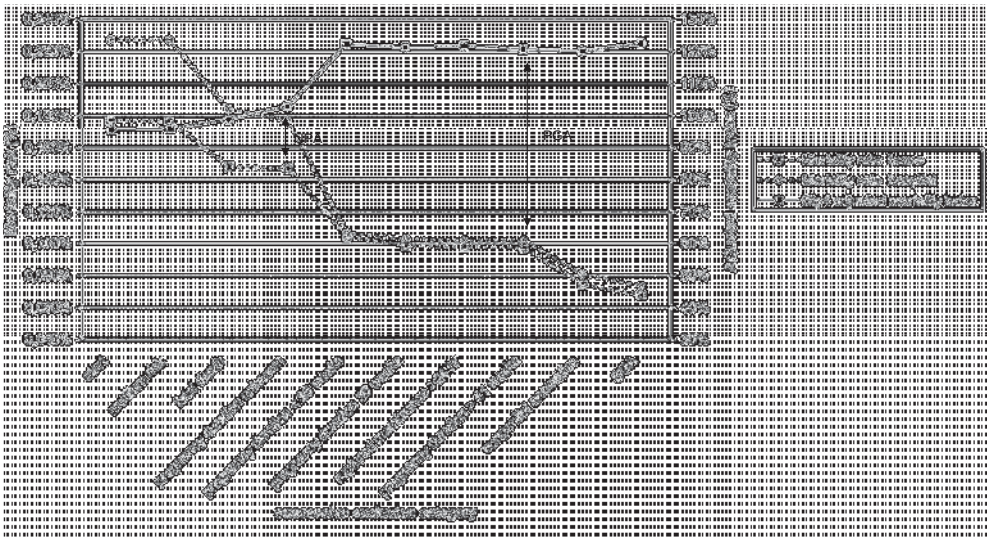

Figure 8.3 'Big4' adjusted mortality index of home birth (hospital based birth under midwife supervision=100%).

duration <36 weeks. Combined with the similar crude mortality rates of home and hospital delivery from then onwards, this suggests setting safety for the risk groups still included i.e. all groups right to the exclusion label 'pregnancy duration <36 weeks'. For example after exclusion of pregnancy duration > 41 weeks (PGA group), the adjusted mortality index is 120%, which is slightly larger than the non significant regression result of 111% (table 8.3).

DISCUSSION

Planned home birth within the Dutch maternity care system has a lower crude mortality rate compared to a community midwife led planned hospital birth. However, after case mix adjustment, the relation is reversed, showing a non-significant increased perinatal mortality rate of home birth. Excess setting dependent mortality may arise at home if risk conditions are present or emerge at birth, yet remnant confounding by indication effect (Big4 conditions are more prevalent in hospital) and low mortality prevalence limits statistical proof. Authors favouring a comparison of settings among 'suitable' home births only (PGA), usually exclude risk conditions with a potential setting effect. This mechanism may explain the apparently contradictory results from previous studies.[1,5,7,10-15,17,18]

A strength of this study was the size of the study population, which reflects the complete Dutch experience from 2000-2007. The amount of missing explanatory data is negligible, mortality data have been shown to be complete. No annual trends are observed in the relations shown, except for a minimal gradual decrease in total perinatal mortality.[3]

Our case mix adjustment proved to be essential. The assumption of comparability across home vs. hospital populations appeared not to be justifiable judging from the unequal prevalence of Big4 conditions. These primarily have their origin in early negative fetal conditions and disadvantaged genetic background of the parents. Only in the case of low Apgar, one may argue that the midwifery management during labour might influence it's occurrence, while a management role in SGA, spontaneous prematurity, and congenital anomalies at that stage is unlikely. We decided to include low Apgar cases assuming the role of management to be small compared to the disadvantage of the home setting once a child with persistent low Apgar is born. Thus, our point of departure starts from the risk challenge represented by Big4 at the onset of labour, and investigates whether setting matters in terms of prognosis. The mechanisms underlying the apparent favourable selection for home birth are still to be elucidated. Self selection by the pregnant women can coincide with implicit or explicit selection by the midwife who may tend to 'refer' to hospital if she feels uncomfortable with the risk level at home. The difference in the ratio home:hospital community midwifery led deliveries among the four largest Dutch cities suggests the presence of substantial professional and setting effects. In Amsterdam and Utrecht the ratio is 2:1, and in Rotterdam and the Hague it is 1:2.

Several study limitations merit discussion. While an improvement compared to previous studies, our case mix control is still incomplete because Big4 is unrelated to 15% of deaths. In the PGA population this proportion is even 48%. Thus we cannot rule out remnant confounding by indication as little is known on the factors underlying choice of setting.

RCT would be the superior design to address our research question. However when home birth was part of a trial, participation hampered[24] and introduced selective participation which limited generalisability. Moreover if following one's choice impacts outcome, estimates of setting effects are also biased.[24-26] Despite their shortcomings, in particular when considering the difficulty to overcome the confounding by indication phenomenon, observational studies as ours are therefore invaluable. A comparison with a 100% gynaecologist hospital-based system is not included. The data from an otherwise very similar country as Flanders[27] suggest that more favourable results may be expected in low risk women in general from a hospital-based system. In Flanders perinatal mortality is about 33% less than in the Netherlands, while the caesarean section rates show little difference.

This study primarily focuses upon the disadvantages and neglects the claimed benefits when comparing planned home versus planned hospital births. However studies accessing mother's opinion show that preventing these disadvantages easily outweighs the claimed benefits.[28]

Our results appear compatible with most other reports even though previous studies show conflicting results. Planned home births attended by registered professional attendants are not associated with an increased risk of adverse perinatal outcomes in cohort studies in North America[7,12], the United Kingdom[14], Europe [5,11,15,17], Australia[29] and New Zealand[30]. In contrast, other cohort studies have shown a higher risk of perinatal mortality in planned home births compared to planned hospital births.[10,13,16,18,30] All studies are limited by voluntary submission of data[7,8,11-14,17,31,32], non representative sampling[5,13], lack of appropriate comparison groups[7,12,15,29], or insufficient statistical power[5,17,29,32]. A critical factor, as our study shows, is the in retrospect exclusion of unplanned and unsuitable home births from analysis.[18]

Our results partly agree with those of Kennare at al.[30] who found higher standardised perinatal mortality ratios among planned home deliveries after limited adjustment (birth weight, gestational age). Our results also partly agree with the meta-analysis by Wax et al.[9]: differences in the prevalence of SGA, premature births and congenital anomalies seem equally present in planned home vs. hospital births. They reported a twofold higher neonatal mortality rate but no increase in perinatal mortality. These results are in agreement with figure 8.3 where the fetal death subgroup does not benefit from setting safety. It should be noted that the study of Wax et al. received methodological criticisms[33-36] most notably the inclusion of the study of Pang and the exclusion of the study of De Jonge. Our conclusions apparently contradict those of De Jonge et al. who concluded equal intrapartum and early neonatal outcome of planned home birth vs. hospital birth in apparently the same population.[15] However, the point of departure is not the same. Of our two comparisons of home delivery vs. hospital delivery, one parallels the approach of De Jonge. Our principal approach (NPA) compares neonatal mortality in the actual populations delivering at home vs. hospital, while the approach of De Jonge compares neonatal mortality in a hypothetical group resembling our PGA population. Our adjustment procedure however goes further than the maternal factor adjustment of De Jonge.[15]

From our study we conclude that planned home birth, under routine conditions, is not associated with a higher intrapartum and early neonatal mortality rate. However in subgroups additional risk cannot be excluded.

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9

Does centralisation of acute obstetric care reduce perinatal mortality? An empirical study of over 1 million births in The Netherlands

J. Poeran, G.J.J.M. Borsboom, J.P. de Graaf, E. Birnie,
E.A.P.Steegers, J.P. Mackenbach, G.J. Bonsel

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ABSTRACT

Objective Estimating outcome of hypothetical closure of 10 small hospitals (out of 99) and centralisation of acute obstetric care in larger hospitals in order to assess whether this would lower perinatal mortality in The Netherlands.

Design Hypothetical analysis using retrospective cohort data.

Setting The Netherlands

Population Selected were all (n=1,160,708) singleton hospital births from ≥22 weeks' gestation as recorded in The Netherlands Perinatal Registry 2000-2008 with exclusion of (1) unknown gestational age, (2) unknown or no travel time to hospital and (3) fetal mortality.

Main outcome measures Predicted perinatal (intrapartum and first-week) mortality for several patient subgroups for two simulated centralisation scenarios: (1) closure of the 10 smallest hospitals, and (2) closure of the 10 smallest hospitals, but avoiding adjacent closures. Women who delivered in hypothetically closed hospitals were assigned the next-nearest hospital with travel time and hospital features changed accordingly. Predictions followed from regression coefficients from a multilevel logistic regression model with a forced casemix control (maternal and child factors) and a set of hospital organisational features with perinatal mortality as outcome.

Results Scenario 1 resulted in doubled travel time, and 10% increased mortality (0.34% vs. 0.38%). In scenario 2 perinatal mortality showed little change (0.33% vs. 0.32%) with less effect on travel time. Heterogeneity in hospital organisational features caused simultaneous improvement and deterioration of predicted perinatal mortality depending mainly on the features of the newly assigned next-nearest hospital. Consequences vary for subgroups: pregnant women at increased risk suffer more from increased travelling, and gain more if a (specialised) 'perinatal centre' or a better performing hospital is nearby.

Conclusion In The Netherlands, centralisation of acute obstetric care according to the 'closure-of-the-smallest-rule' yields suboptimal outcomes. In order to develop an optimal strategy for centralisation one would need to consider all positive and negative effects: heterogeneity in organisational features of closed and surviving hospitals, financial aspects, differential effects for patient subgroups, increased travel time and adequate antenatal risk selection.

INTRODUCTION

Dutch perinatal mortality exceeds the European average.[1,2] Structural inadequacies in the provision of care were discovered as major contributors.[3] In response, a national Steering Group on Pregnancy and Birth -on behalf of the Dutch Ministry of Health-, issued several recommendations.[4] One recommendation addressed the observed inadequate availability of 7*24h acute obstetric care stating availability within 15 minutes of 'qualified professionals' (midwives, gynaecologists, paediatricians, anaesthesiologists, and operating theatre staff; 'qualified' in terms of seniority).[4,5] However, small hospitals reported to be unable to satisfy these demands with existing on-call coverage schemes. Moreover, larger hospitals were unwilling to do so as the current financial system explicitly excludes any reimbursement of so-called 'availability (standby) costs'. Consequently, centralisation of acute obstetric care services was considered, implying a reduction of acute services in about half of all hospitals with a parallel redistribution of qualified professionals from small local to nearby larger hospitals. While the advantages are obvious (e.g., increase in continuity of care, and a likely volume related performance improvement), the disadvantages of centralisation should be acknowledged too (e.g., increased travel time and organisational disutilities regarding non-obstetric services).[4-9] Centralisation may also critically affect paediatric, emergency room, and acute anaesthesia services in the reduced hospitals.[8]

The key question is whether direct effects of centralisation on patient outcomes are to be expected. An overall positive outcome would more easily justify the above disutilities. In this study we estimated the direct effects on intrapartum and first-week mortality when 10 small hospitals (out of 99 providing obstetric care) would hypothetically be closed according to two plausible centralisation scenarios. The effects of closing were estimated by a redistribution of patient flow (depending on their zip code of residency) to the next-nearest hospital, taking into account (1) detailed information of maternal and child characteristics, (2) acute referral status, (3) travel time in normal and (in retrospect) high risk cases, and hospital related factors such as (4) day and time of birth, (5) the hospital's organisational 7*24h characteristics, and (6) any additional non-specific hospital effects not accounted for by the previously mentioned factors. The net consequences were then calculated for all individual women redistributed from the hypothetically closed hospitals to the remaining hospitals, to allow for a trade-off of positive and negative effects.

METHODS

General approach

This study was issued by the so-called society of SAZ-hospitals, which represents the interests of about 40 small general hospitals in The Netherlands. These hospitals are located throughout The Netherlands, either within the 'Randstad' conurbation (the densely populated western part of the Netherlands) or outside. Centralisation of care primarily will affect SAZ hospitals.

Our general approach was as follows. In step 1, we estimated the impact of maternal, child, and hospital's organisational characteristics in terms of intrapartum and first-week (perinatal) mortality, using multilevel logistic regression analysis. Next, in step 2, we identified all pregnant women who would need to change hospital as the consequence of a defined centralisation scenario. We distinguished two centralisation scenarios: closure of the 10 smallest hospitals (scenario 1) and closure of the 10 smallest hospitals, while avoiding simultaneous closure of two adjacent hospitals (scenario 2). The women involved were assumed to deliver in the next-nearest hospital in terms of estimated travel time. In step 3, we estimated the individual intrapartum and first-week mortality risk after closure. We did so by applying to each individual woman the regression coefficients (obtained in step 1) to the characteristics of her situation after centralisation. Finally, in step 4, we compared the current observed total mortality among women affected by closure, with the expected total mortality by adding the estimated probabilities.

Data collection

Data on maternal factors, child factors and outcomes were obtained from The Netherlands Perinatal Registry. This registry contains population-based information of 97% of all pregnancies in the Netherlands.[10] On behalf of the respective professional societies, source data are routinely collected by 94% of midwives, 99% of gynaecologists and 68% of paediatricians including 100% of Neonatal Intensive Care Unit (NICU) paediatricians (see website for detailed description: www.perinatreg.nl).[10] The professional board of The Netherlands Perinatal Registry granted permission to use the anonymous registry data for this study. The registry contains 1,620,126 records for the period 2000-2008. We excluded multiple pregnancies (n=35,326), births with unknown gestational age (n=17,278), births with an unknown or erroneous zip code (n=23,736), births in hospitals which had not participated in the registry >2 years (n=6,535), homebirths (n=368,672), and stillbirths (n=7,871).

We excluded homebirths since centralisation of care, travel distance, and hospital's organisational features are of little or no importance in homebirths. Stillbirths were excluded as delivery decisions are subject to different considerations.[11]

Analysed were 1,160,708 births which additionally were combined with data from two sources: travel time data and individual hospital's organisational characteristics. Travel times to the closed and next-nearest hospitals were calculated making use of the hospital's zip code and pregnant women's zip code (these 4-digit zip codes cover on average 4,000 inhabitants). Travel times (not: distances) between zip codes were derived from a commercially available geographic information system (www.geodan.nl). We distinguished planned from unplanned births as we assume travel time to hospital only to have an impact on women with unplanned births who were transferred from home to hospital during parturition. Thus, hospital travel time was set to zero for women with planned births, i.e., induction of labour or a planned (primary) caesarean section.

Data on hospital's organisational characteristics including data pertinent to 7*24 hour services were collected separately from this study, with the support of the Dutch Society of Obstetricians and Gynaecologists using a standard questionnaire for all 99 Dutch maternity units (response: 100%).[3]

Table 9.1 displays these collected 24 variables with inevitable overlap of data. We used principal component analysis (PCA) to summarise the original 24 variables into two principal components, factor 1 and factor 2, with a computed numerical score for each hospital. Factor 1 can be interpreted as 'hospital's scale size' as it primarily combines original variables pointing to hospital size and the number of obstetric caregivers: the lower the factor value the larger the hospital and the higher the number of obstetric caregivers. Factor 2 can be interpreted as '24-hour equality of service level'. This factor combines original variables pointing to around-the-clock availability of the various qualified professionals: the higher the factor value the more the 24-hour equality of service level (in terms of seniority). These two factors jointly explained almost 70% of variance of the original 24 variables, i.e., the two constructed variables contain 70% of the available information.

PCA is a 'data reduction' technique commonly used in datasets with a high number of related explanatory variables. It essentially summarises the net information content of overlapping data into a small number of independent constructed variables. The background and the technique itself are described in more depth elsewhere.[12]

Table 9.1 Overview of hospitals' organisational data

Organisational feature	Remarks
General	
Teaching hospital	categorised into yes / no
Gynaecology department	
Duration of daytime shifts	categorised into durations of 10-12 hours and 7-9 hours
Duration of evening / night shifts and the highest level of the professional who is attending these shifts	categorised into durations of ≤14 hours and ≥15 hours with professional levels categorised into two groups: (1) gynaecologist / gynaecologist in training and (2) non-in-training physician / midwife / nurse
The highest level of the professional who is attending the evening and night shifts during the week	categorised into five groups: (1) gynaecologist, (2) in-training and non-in-training resident gynaecology, (3) general emergency physician, (4) midwife and (5) nurse
The highest level of the professional who is attending the daytime shifts during weekends	categorised into five groups: (1) gynaecologist, (2) in-training and non-in-training resident gynaecology, (3) general emergency physician, (4) midwife and (5) nurse
The highest level of the professional who is attending the evening and night shifts during weekends	categorised into five groups: (1) gynaecologist, (2) in-training and non-in-training resident gynaecology, (3) general emergency physician, (4) midwife and (5) nurse
Permitted to sleep during attending shifts	categorised into yes / no
Gynaecologist on backup call during shifts	categorised into yes / no
Professional doing rounds during weekends	categorised into four groups: (1) gynaecologist, (2) in-training and non-in-training resident gynaecology, (3) general emergency physician, (4) midwife and (5) nurse
In-hospital presence of the emergency operating theatre team	categorised into three groups: in-hospital presence during (1) 24 hours, (2) presence during daytime and evening and on-call during the night, (3) presence during daytime and on-call during the evening and night
In-hospital presence of an anaesthesiologist	categorised into three groups: in-hospital presence during (1) 24 hours, (2) presence during daytime and evening and on-call during the night, (3) presence during daytime and on-call during the evening and night
The total number of obstetric caregivers (specialists, physicians, midwives, nurses)	a continuous number
Annual number of deliveries	continuous as well as grouped into three categories: (1) <1000, (2) 1000-2000, (3) >2000

Combination of the annual number of deliveries with the gynaecologist:other obstetric caregiver ratio	categorised into six groups: (1) <1000 and ≤1:4, (2) <1000 and 1:4-1:6, (3) <1000 and >1:6, (4) 1000-2000 and ≤1:4, (5) 1000-2000 >1:4, (6) >2000 and all ratios
Minimum duration of attending shift during weekends	a continuous number (range 12-72 hours)
Average travel time in minutes from home to hospital for an on-call gynaecologist	a continuous number
Maximum travel time in minutes from home to hospital for an on-call gynaecologist	a continuous number
Number of caregivers present during attending shifts on weekday evenings and nights	a continuous number
Number of caregivers present during attending shifts on weekends during the day	a continuous number
Number of caregivers present during attending shifts on weekends during the evening and the night	a continuous number
Paediatrics department	
Level of care for newborns	categorised into four groups: (1) Neonatal Intensive Care Unit (NICU), (2) post-NICU or incubator from 30 weeks of gestational age, (3) incubator from 32 weeks of gestational age, (4) initially first aid for neonate with suboptimal start with subsequent referral to a hospital with a higher level of care
The highest level of the professional at the paediatrics department who is attending the shifts outside office hours	categorised into six groups: (1) fellow neonatologist, (2) paediatrician, (3) in-training paediatrician, (4) non-in-training resident paediatrics, (5) general emergency physician, (6) no professional present but on-call
The lowest level of the professional at the paediatrics department who is attending the shifts outside office hours	categorised into six groups: (1) fellow neonatologist, (2) paediatrician, (3) in-training paediatrician, (4) non-in-training resident paediatrics, (5) general emergency physician, (6) no professional present but on-call
Professional on-call at the paediatrics department	categorised into four groups: (1) no one on-call, (2) paediatrician on-call, (3) fellow neonatologist on-call, (4) other professional on-call

Outcome and determinants of hospital performance

The main outcome was intrapartum or first-week mortality after live birth, for convenience further referred to as perinatal mortality. Determinants with their optimal categorisation were selected for their proven effect on perinatal mortality.[3,7,13-17] We distinguished maternal and child factors (casemix) and organisational factors. Maternal factors were parity and age category combined (primiparous / multiparous, <25 / 25-29 / 30-34 / 35-39 / ≥40 years), and ethnicity (Western / non-Western). Child factors were gestational age (thirteen categories[3]), congenital anomalies (yes / no), small for gestational age (SGA: birthweight >10th / 2.3-10th / <2.3rd percentile) and fetal presentation (cephalic / breech / transverse or other / unknown). Congenital anomalies are recorded postpartum and classified through a standard coding system by organ system (8 categories, 71 subcategories).[18]

Organisational factors were travel time to the hospital in minutes (continuous), the two principal components (factor 1 and factor 2), day and time of delivery (Saturday / Sunday / weekday, each subdivided into three time slots 00:00-07:59 / 08:00-17:59 / 18:00-00:00), and emergency referral during parturition (yes / no). We assumed the hospitals' performance according to principal component factor 1 and 2 did not to change after the hypothetical closure of the 10 small hospitals. Emergency referral during parturition was defined by using information from both the caregiver during pregnancy (midwife, obstetrician) and the caregiver responsible at start of labour (midwife or obstetrician).

Analysis

For presentational purposes only, we grouped hospitals into small size SAZ hospitals (1) within and (2) outside the Randstad conurbation, (3) academic hospitals and (4) other general hospitals.

The different steps in the analysis are illustrated in figure 9.1. First, a comprehensive multilevel multivariable logistic regression model ('hospital performance model') was fitted using the primary dataset (step 1). All determinants mentioned above were entered into the model. The principal component factors were included in the model as both their actual value as well as their quadratic value as we presumed linear effects as well as effects of extremes (e.g., the largest hospitals' performance to be comparable to the smallest hospitals in which quality in the former is ensured by the total staffing levels ['quantity'] and in the latter by the level of obstetric staff [mostly gynaecologists, not residents on duty, 'quality'])

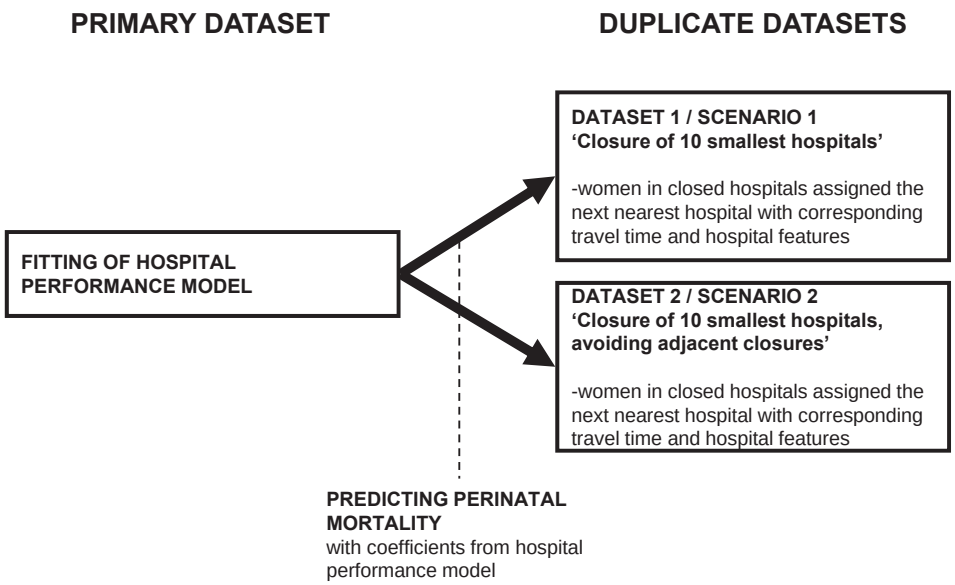

Figure 9.1 Overview of computational model.

We predefined an additional interaction term relating travel time to clinical condition of the child, as previous studies have suggested a poorer condition to be associated with a larger adverse impact of extended travel time.[19] Clinical condition was represented by the single or combined presence of so-called 'Big4'[20] morbidities: congenital anomalies, preterm birth (<37th week of gestation), SGA (birthweight <10th percentile for gestational age) or low Apgar score (<7, 5 minutes after birth). As the presence of any of the 'Big4' morbidities precedes perinatal mortality in 85% of cases, we assume this to be an appropriate risk indicator.[20] Because of the multilevel structure of the data (individuals are grouped per hospital) we used multilevel logistic regression analysis which adjusts for the possible clustering of individuals within hospitals, and unspecified effects at the hospital level. In step 2 women who delivered in the hypothetically closed hospitals were assigned the next-nearest hospital. Finally, the estimated coefficients obtained from step 1 were used to predict perinatal mortality for each scenario (step 3) taking into account (1) the features of the new hospital, (2) the associated travel distance and (3) the specific interaction term of 'Big4'*travel time for those referred. The overall observed and predicted mortality before vs. after the closure of the hospitals were then compared. Predicted mortality was the sum of all individually recalculated mortality probabilities for women affected by centralisation.

Presentation was for all women together, and for several subgroups based on planned or unplanned birth, referral during parturition, deliveries within 'office hours', parity, and presence of morbidities. The statistical software package SAS version 9.2 (SAS Institute Inc., Cary, NC) was used, with the GLIMMIX procedure to run random intercept multilevel models.

RESULTS

Table 9.2 shows the study population characteristics by type of hospital. Most women are multiparous and 30-34 years (20.2-22.8%), and of Western origin (79.0-90.4%). Preterm birth (<37 weeks' gestation) was observed in 0.6-3.8%, congenital anomalies in 1.8-5.0%, SGA in 9.4-11.3%, and a non-cephalic presentation in 7.2-9.2%. Of all women 2.1-12.9% had to travel more than 20 minutes to the hospital where they gave birth. SAZ hospitals all fell in the ≥ P25 value range of factor 1 ('hospital scale size, number of obstetric caregivers', a lower value represents larger hospitals) while academic hospitals all fell in the <P25 value range. This confirms the SAZ hospitals to be relatively small with smaller numbers of obstetric caregivers compared to the larger academic hospitals. Factor 2 ('24-hour equality of service level' a higher factor value represents more 24-hour equality of service level in terms of seniority) was distributed more evenly across type of hospital. The majority of women delivered in hospitals in the ≥ P25 value range illustrating most women to deliver in hospitals with the highest level of 24-hour equality of service. Most deliveries were on a weekday between 08:00 and 17:59 (37.9-43.9%); 22.2-29.9% of women were referred during parturition. 'Big4' risk prevalence did not differ much between SAZ hospitals (17.3-19.2%) and other non-academic hospitals (19.0%). For academic hospitals prevalence is 27.3%.

Hospital performance

Effect estimates from the multilevel multivariable logistic regression model ('hospital performance model') are shown in table 9.3. All casemix variables are significantly associated with perinatal mortality. The highest risks are seen for multiparous women of 35-39 years (OR 1.51 CI 1.30-1.75), non-Western women (OR 1.15 CI 1.04-1.28), gestational ages <37 (OR range 2.97->1000), congenital anomalies (OR 10.11 CI 9.14-11.19), birthweight <p2.3 (OR 6.46 CI 5.67-7.35), and transverse or other fetal presentation (OR 2.06 CI 1.60-2.65).

For organisational factors only principal component factor 1, 2 and quadratic factor 2 are not significantly associated with perinatal mortality. Travel time (in minutes) to hospital has an OR of 0.98, implying a 2% decreased risk of perinatal mortality for every extra minute of

Table 9.2 Characteristics of the study population per hospital group

	SAZ hospitals within Randstad conurbation		SAZ hospitals outside Randstad conurbation		Academic hospitals		Other hospitals	
	N	%	N	%	N	%	N	%
Casemix variables								
Parity & age category								
Primiparous & <25 years	9,600	9.2%	22,737	9.6%	13,654	9.0%	67,324	10.1%
Primiparous & 25-29 years	18,477	17.7%	47,239	19.9%	23,546	15.5%	118,197	17,7%
Primiparous & 30-34 years	19,113	18.3%	37,042	15.6%	25,826	17.0%	116,589	17.5%
Primiparous & ≥35 years	7,462	7.1%	10,945	4.6%	11,755	7.7%	42,888	6.4%
Multiparous & <25 years	2,582	2.5%	6,805	2.9%	4,814	3.2%	21,252	3.2%
Multiparous & 25-29 years	10,270	9.8%	29,148	12.3%	15,829	10.4%	71,636	10.7%
Multiparous & 30-34 years	21,067	20.2%	54,102	22.8%	31,184	20.5%	135,850	20.4%
Multiparous & 35-39 years	13,551	13.0%	25,978	10.9%	21,153	13.9%	79,350	11.9%
Multiparous & ≥40 years	2,369	2.3%	3,631	1.5%	4,232	2.8%	13,511	2.0%
Ethnicity								
Western	83,865	80.3%	214,887	90.4%	120,036	79.0%	529,076	79.4%
Non-Western	20,626	19.7%	22,740	9.6%	31,957	21.0%	137,521	20.6%
Gestational age								
22-27.6 weeks	127	0.1%	348	0.1%	3,190	2.1%	1,317	0.2%
28-31.6 weeks	119	0.1%	393	0.2%	6,605	4.3%	1,421	0.2%
32 weeks	248	0.2%	713	0.3%	1,296	0.9%	2,051	0.3%
33 weeks	539	0.5%	1,361	0.6%	1,280	0.8%	3,653	0.5%
34 weeks	944	0.9%	2,363	1.0%	1,804	1.2%	6,238	0.9%

Table 9.1 continues on next page.

Table 9.2 *Continued*

	SAZ hospitals within Randstad conurbation		SAZ hospitals outside Randstad conurbation		Academic hospitals		Other hospitals	
	N	%	N	%	N	%	N	%
35 weeks	1,556	1.5%	3,967	1.7%	2,517	1.7%	10,363	1.6%
36 weeks	2,949	2.8%	7,255	3.1%	4,641	3.1%	19,611	2.9%
37 weeks	6,771	6.5%	15,563	6.5%	9,487	6.2%	39,044	5.9%
38 weeks	16,342	15.6%	38,814	16.3%	21,784	14.3%	97,357	14.6%
39 weeks	23,157	22.2%	52,262	22.0%	30,917	20.3%	147,476	22.1%
40 weeks	27,052	25.9%	58,970	24.8%	35,281	23.2%	170,672	25.6%
41 weeks	18,582	17.8%	41,370	17.4%	24,171	15.9%	119,727	18.0%
≥ 42 weeks	6,105	5.8%	14,248	6.0%	9,020	5.9%	47,667	7.2%
Congenital anomalies								
No	102,648	98.2%	229,997	96.8%	144,320	95.0%	651,150	97.7%
Yes	1,843	1.8%	7,630	3.2%	7,673	5.0%	15,447	2.3%
Small for gestational age (SGA)								
No SGA	94,585	90.5%	214,312	90.2%	134,787	88.7%	596,671	89.5%
Birthweight P2.3-P10	7,663	7.3%	17,706	7.5%	12,936	8.5%	53,289	8.0%
Birthweight < P2.3	2,243	2.1%	5,609	2.4%	4,270	2.8%	16,637	2.5%
Fetal presentation								
Cephalic	97,009	92.8%	218,010	91.7%	137,933	90.7%	618,148	92.7%
Breech	5,873	5.6%	15,360	6.5%	10,822	7.1%	40,099	6.0%
Transverse or other	720	0.7%	1,839	0.8%	1,510	1.0%	5,033	0.8%
Unknown	889	0.9%	2,418	1.0%	1,728	1.1%	3,317	0.5%

Organisational factors								
Travel time to hospital								
≤ 20 minutes	102,320	97.9%	217,048	91.3%	132,426	87.1%	627,186	94.1%
> 20 minutes	2,171	2.1%	20,579	8.7%	19,567	12.9%	39,411	5.9%
Hospital organisational features								
Principal component (factor 1)								
≥ P25	104,491	100.0%	237,627	100.0%	0	0.0%	539,523	80.9%
< P25	0	0.0%	0	0.0%	151,993	100.0%	127,074	19.1%
Principal component (factor 2)								
≥ P25	87,162	83.4%	237,627	100.0%	151,993	100.0%	400,368	60.1%
< P25	17,329	16.6%	0	0.0%	0	0.0%	266,229	39.9%
Day and time of delivery								
Saturday 00:00-07:59	3,432	3.3%	7,704	3.2%	5,985	3.9%	24,195	3.6%
Saturday 08:00-17:59	5,485	5.2%	13,177	5.5%	8,248	5.4%	37,169	5.6%
Saturday 18:00-23:59	2,846	2.7%	6,458	2.7%	4,397	2.9%	19,358	2.9%
Sunday 00:00-07:59	3,386	3.2%	7,814	3.3%	5,977	3.9%	24,464	3.7%
Sunday 08:00-17:59	5,736	5.5%	12,846	5.4%	8,259	5.4%	37,118	5.6%
Sunday 18:00-23:59	2,768	2.6%	6,209	2.6%	4,447	2.9%	19,329	2.9%
Weekdays 00:00-07:59	17,600	16.8%	39,607	16.7%	30,296	19.9%	125,363	18.8%
Weekdays 08:00-17:59	45,837	43.9%	103,152	43.4%	57,544	37.9%	266,601	40.0%
Weekdays 18:00-23:59	17,401	16.7%	40,660	17.1%	26,840	17.7%	113,000	17.0%
Referral during parturition								
No	76,046	72.8%	171,325	72.1%	118,186	77.8%	467,602	70.1%
Yes	28,445	27.2%	66,302	27.9%	33,807	22.2%	198,995	29.9%
Big4 Category								
No Big4	86,454	82.7%	192,103	80.8%	110,463	72.7%	539,708	81.0%
Only one Big4	16,724	16.0%	41,741	17.6%	33,636	22.1%	116,160	17.4%
More than one Big4	1,313	1.3%	3,783	1.6%	7,894	5.2%	10,729	1.6%

Table 9.3 Hospital performance model

	aOR	CI		P
Casemix variables				
Parity & age category				<.0001
Primiparous & <25 years	1.09	0.93	1.28	
Primiparous & 25-29 years [ref]	1.00			
Primiparous & 30-34 years	1.09	0.95	1.26	
Primiparous & ≥35 years	1.32	1.11	1.58	
Multiparous & <25 years	0.88	0.68	1.14	
Multiparous & 25-29 years	1.32	1.13	1.55	
Multiparous & 30-34 years	1.45	1.27	1.65	
Multiparous & 35-39 years	1.51	1.30	1.75	
Multiparous & ≥25 years	1.51	1.16	1.97	
Ethnicity				0,009
Western [ref]	1.00			
Non-Western	1.15	1.04	1.28	
Gestational age				<.0001
22-27.6 weeks	>1,000	>1,000	>1,000	
28-31.6 weeks	68.41	55.92	83.67	
32 weeks	14.64	11,18	19.17	
33 weeks	11.94	9.52	14.97	
34 weeks	6.23	4.95	7.84	
35 weeks	4.88	3.96	6.00	
36 weeks	2.97	2.44	3.61	
37 weeks	2.16	1.82	2.58	
38 weeks	1.18	1.00	1.39	
39 weeks	1.05	0.90	1.22	
40 weeks [ref]	1.00			
41 weeks	1.38	1.18	1.60	
≥ 42 weeks	1.37	1.11	1.69	
Congenital anomalies				<.0001
No [ref]	1.00			
Yes	10.11	9.14	11.19	
Small for gestational age (SGA)				<.0001
No SGA [ref]	1.00			
Birthweight P2.3-P10	2.51	2.24	2.83	
Birthweight < P2.3	6.46	5.67	7.35	
Fetal presentation				<.0001
Cephalic [ref]	1.00			
Breech	1.65	1.46	1.85	
Transverse or other	2.06	1.60	2.65	
Unknown	1.48	1.02	2.13	

Table 9.3 continues on next page.

Table 9.3 *Continued*

	aOR	CI		P
Organisational factors				
Travel time (to hospital, in minutes)	0.98	0.97	0.99	<.0001
Hospital organisational features				
Principal component (factor 1)	0.99	0.87	1.13	0,893
Principal component (factor 2)	1.08	0.92	1.27	0,356
Principal component (factor 1) ^2	0.85	0.72	1.00	0,048
Principal component (factor 2) ^2	1.04	0.92	1.18	0,510
Day and time of delivery				<0.001
Saturday 00:00-07:59	1.50	1.22	1.85	
Saturday 08:00-17:59	1.17	0.97	1.40	
Saturday 18:00-23:59	1.41	1.12	1.78	
Sunday 00:00-07:59	1.31	1.06	1.63	
Sunday 08:00-17:59	1.46	1.24	1.73	
Sunday 18:00-23:59	1.33	1.05	1.68	
Weekdays 00:00-07:59	1.35	1.21	1.51	
Weekdays 08:00-17:59 [ref]	1.00			
Weekdays 18:00-23:59	1.40	1.25	1.56	
Referral during parturition				<0.001
No [ref]	1.00			
Yes	1.28	1.17	1.41	
Interaction				<.0001
No Big4*travel time [ref]	1.00			
Only one Big4*travel time	0.99	0.98	0.99	
More than one Big4*travel time	1.02	1.01	1.02	

aOR: adjusted odds ratio, CI: confidence interval.

travel time. Deliveries on Saturday nights have a 50% increased risk for perinatal mortality (OR 1.50; CI 1.22-1.85), referral during parturition has a 28% increased risk (OR 1.28; CI 1.17-1.41). The interaction term Big4*travel time is 'protective' in case of one 'Big4' morbidity (OR 0.99; CI 0.98-0.99), but complex 'Big4' morbidity adds to the travel risk (RR 1.02; CI 1.01-1.02). The random coefficient for hospital varied (data not shown) which is suggestive of differences in hospital performance in terms of perinatal mortality.

Effects of centralisation scenarios

Table 9.4 and table 9.5 list the predicted results of the centralisation scenarios 1 and 2. The left side of the table ('before closure') depicts the observed situation while the right side ('after closure') depicts the predicted effects for the defined subgroups.

Scenario 1

Following scenario 1 (table 9.4), a total number of 61,578 (5.3%) women will have to deliver in other hospitals as their hospital of (actual) delivery will be hypothetically closed. Perinatal mortality is expected to increase with 21 (10%) cases: from 210 cases (0.34%) observed before closure to 231 cases (0.38%) predicted after closure. In absolute numbers, expected perinatal mortality after closure is higher than the observed mortality before closure for almost all subgroups except for unplanned hospital births (from 124 to 116 mortality cases)

Table 9.4 Predicted results after hypothetical closure of 10 hospitals according to scenario 1

Group	Before closure			After closure		
	N	† N	† %	N	† N	† %
All pregnant women	61,578	210	0.34%	61,578	231	0.38%
Planned hospital birth (primary caesarean section/induced labour)	26,431	86	0.33%	26,431	115	0.44%
Unplanned hospital birth	35,147	124	0.35%	35,147	116	0.33%
Referral during parturition from home	6,775	19	0.28%	6,775	22	0.32%
Referral during parturition from hospital	7,599	20	0.26%	7,599	25	0.33%
Deliveries within 'office hours'	26,618	75	0.28%	26,618	79	0.30%
Deliveries outside 'office hours'	34,960	135	0.39%	34,960	152	0.43%
Primiparous women	30,664	102	0.33%	30,664	113	0.37%
Multiparous women	30,914	108	0.35%	30,914	118	0.38%
No Big4 morbidities	49,247	30	0.06%	49,217	58	0.12%
Only one Big4 morbidity	11,175	91	0.81%	11,175	89	0.80%
More than one Big4 morbidities	1,156	89	7.70%	1,156	84	7.27%
		Minutes	95% CI	Minutes	95% CI	
Average travel time in unplanned hospital births		12.7	3.2-22.2	23.7	12.5-34.9	
Travel time >20 minutes in hospital births		6,077	9.9%	20,201	32.8%	
Hospital size (deliveries per year)			N	N		
<750 per year			61,578	23,884		
750-1,250 per year			0	28,273		
1,250-1,750 per year			0	9,400		
>1,750 per year			0	21		

†: perinatal mortality.

and the presence of one (from 91 to 89 mortality cases) or more (from 89 to 84 mortality cases) 'Big4' morbidities. The largest difference in observed versus predicted perinatal mortality is for the group of planned hospital births (from 86 to 115 mortality cases). In addition, average travel time to hospital will increase from 12.7 to 23.7 minutes with almost one third (32.8%) of women having to travel more than 20 minutes after closure. Less than half of women (23,884 of 61,578) will deliver in an alternative hospital that is of the same size group (<750 annual deliveries) as before closure.

Table 9.5 Predicted results after hypothetical closure of 10 hospitals according to scenario 2

Group	Before closure			After closure		
	N	† N	† %	N	† N	† %
All pregnant women	81,852	268	0.33%	81,852	259	0.32%
Planned hospital birth (primary caesarean section/induced labour)	39,172	124	0.32%	39,172	122	0.31%
Unplanned hospital birth	42,680	144	0.34%	42,680	137	0.32%
Referral during parturition from home	11,113	28	0.25%	11,113	29	0.26%
Referral during parturition from hospital	11,037	22	0.20%	11,037	28	0.25%
Deliveries within 'office hours'	36,285	95	0.26%	36,285	95	0.26%
Deliveries outside 'office hours'	45,567	173	0.38%	45,567	164	0.36%
Primiparous women	42,085	131	0.31%	42,085	119	0.28%
Multiparous women	39,767	137	0.34%	39,767	140	0.35%
No Big4 morbidities	67,233	52	0.08%	67,233	86	0.13%
Only one Big4 morbidity	13,488	99	0.73%	13,488	94	0.70%
More than one Big4 morbidities	1,131	117	10.34%	1,131	79	6.98%
		Minutes	95% CI	Minutes	95% CI	
Average travel time in unplanned hospital births		10.8	4.2-17.3	15.8	10.3-21.4	
Travel time >20 minutes in hospital births		3,106	3.8%	9,167	11.2%	
Hospital size (deliveries per year)			N	N		
<750 per year			81,852	9,089		
750-1,250 per year			0	69,204		
1,250-1,750 per year			0	3,533		
>1,750 per year			0	26		

†: perinatal mortality.

Scenario 2

According to scenario 2 (table 9.5), a total number of 81,852 (7.1%) women will have to deliver in other hospitals with the relocation resulting in a negligible effect on perinatal mortality (from 268 to 259 cases). For most subgroups, expected perinatal mortality after closure is lower than the observed mortality before closure, except for referral during parturition from home (from 28 to 29 cases) or hospital (from 22 to 28 cases), deliveries within 'office hours' (95 cases before and after closure), multiparous women (from 137 to 140 cases), and no 'Big4' morbidities (from 52 to 86 cases). In addition, average travel time to hospital will increase from 10.8 to 15.8 minutes. Note that a minority of women (9,089 of 81,852, 11.1%) will deliver in an alternative hospital of the same size group (<750 annual deliveries) as before closure.

DISCUSSION

Principal findings

In this national study with retrospective cohort data we predicted outcome effects for two centralisation scenarios for acute obstetrical care by using a comprehensive empirical model. Combined with increased travel time to hospital for both scenarios, scenario 1 resulted in a 10% overall increased perinatal mortality, while scenario 2 resulted in a negligible effect on perinatal mortality. In scenario 2 >85% of women in hypothetically 'closed' hospitals were 'transferred' to higher volume hospitals. Rather than just increased travel time, the effects of centralisation appear to be determined by heterogeneity of hospitals' organisational characteristics which in turn increase or decrease predicted perinatal mortality. These changes appeared to depend more on the features of the newly assigned next-nearest hospital rather than that of the initial hypothetically closed hospital. Indirectly and by their quality factor scores, the data demonstrate that small hospitals perform reasonably well. The picture is subtle: risk groups, e.g., women with one or more 'Big4' morbidities benefit from both centralisation scenarios as their predicted perinatal mortality is lower than observed perinatal mortality before closure, Conversely, centralisation appears to be detrimental for the small subset of women who are referred during parturition.

Other studies

Centralisation of acute obstetric care services has been considered in other countries as well, mostly relying on theoretical reasoning alone.[21-23] Furthermore, previous studies at best used an ecological study design, were descriptive rather than comparative, and were heterogeneous in design and results.[9,19,22-24] Most studies conclude a strong pro- or against-centralisation policy comparing risk-adjusted outcome in small (low level care) hospitals versus outcome in large (high level care) hospitals, without modelling hospital performance itself.[9,19,22-25] In Norway, Moster et al. performed a population-based study using data on 1.7 million births from The Norwegian Medical Birth Registry.[24] Neonatal mortality was compared between several geographical areas characterised by the volume of the majority of the maternity units. Overall neonatal mortality was 1.2-2.2 times higher in areas with the majority of women giving birth in small scale maternity units (500 or less births annually) compared to areas with the majority of births in large scale units (>3,000 births annually). As this study lacked risk and casemix adjustment, its conclusion in favour of centralisation may be biased in the presence of area related risk differences as shown in other studies.[24]

Some studies focus on either high risk or low risk patient groups.[9,19,23,25] Bartels et al.[25] and Phibbs et al.[19] studied the effect of NICU level on neonatal mortality for high risk infants, both showing (up to 94%) higher (adjusted) neonatal mortality in smaller and lower level NICUs favouring centralisation. Finally, two studies which focused on low risk patients show conflicting results.[9,23]

Strengths and weaknesses

An important strength of our study is the usage of a validated national database as virtually all pregnancies over 9 years were included (2000-2008). Additionally, our analysis included detailed information on organisational characteristics of all Dutch hospitals, lacking in other studies.[9,19,22-25] Other strengths include the detailed casemix adjustment and the multilevel approach which adjusts for the possible clustering of individuals within hospitals. The hospital performance model combined with our scenario approach enables detailed effect estimations of different hypothetical centralisation scenarios going beyond mortality impact estimations only.[9,19,22-25] Studies based on reasoning can account less easily for the mix of perinatal mortality effects, and the subdivision of effects into effects in different patient groups. Based on these strengths, our study goes beyond similar previous studies' methodology providing empirical evidence on differential effects of centralisation schemes. We believe our framework to be beneficial for other countries also considering

centralisation of acute obstetric care. In the United Kingdom, for example, the Royal College of Obstetricians and Gynaecologists recently cautioned the widespread belief that centralisation will always result in better patient outcome by stating 'localised where possible, centralised where necessary'.[21]

This study has limitations. Maternal lifestyle factors, in particular smoking, were unavailable and not included in the casemix adjustment[26] By including SGA and gestational age in the model the effects of this limitation (in the context of this study) are reduced as they, if combined, act as a proxy for smoking. Smoking has little effect beyond its effect on birth weight and gestational age at delivery. Furthermore, we based our estimations on the assumption that women in the hypothetically closed hospitals would deliver in the next-nearest hospital. While this strategy is generally valid, individual preferences may decide otherwise.[27] Also, we assumed no change in performance and organisational features of remaining hospitals after centralisation. As conflicting study results illustrate[9,19,22-24], it is unclear in what direction these features will change after centralisation. Additional research is needed.

Finally, we only included perinatal mortality, travel time and volume of destination hospitals as effect measures of the centralisation scenarios to illustrate the differential effects of two different centralisation scenarios. Future research with additional outcomes such as NICU-admission or intervention rates may further specify the effects of centralisation.

Arguments pro and con centralisation

Common arguments in favour of centralisation are: volume-related better care provision, access to rapid intervention during delivery, quick resuscitation of the newborn, and rapid identification and management of newborn infants with unexpected morbidities (e.g., congenital anomalies) in large and higher level hospitals.[24] An important reason opposing centralisation is the increased travel time to hospital, with inherent increased risk for adverse perinatal outcome, especially for high risk women or out-of-hospital delivery.[22] Ravelli et al. showed a 17-52% increased risk for perinatal mortality with travel time to hospital of 20 minutes or more.[7] Another reason against centralisation is that in high risk oriented hospitals, low risk births are expected to be less 'natural' with an increased risk for (obstetric) interventions and corresponding increased costs.[28] Moreover, financial aspects of centralisation policy need to be considered, e.g., resource distribution costs or education and salary costs for consultants (obstetrics, paediatrics, anaesthesiology, etc.).[29] The inter-dependency of acute obstetric care services with, e.g., paediatric / neonatal services and

anaesthesiology services should also be considered. These services may be at risk of collapse as the number of physicians required to sustain on-call coverage may be no longer available in small hospitals after acute obstetric care has been centralised.[8] Finally, particularly for The Netherlands where about 20% of births still occur at home under supervision of a midwife[10], increased travel time to hospital will compromise these (low risk) women in their choice to opt for a birth at home.

Conclusion

In The Netherlands, centralisation of obstetric care according to the 'closure-of-the-smallest-rule' yields suboptimal outcomes in terms of perinatal mortality and increased travel time to hospital. In order to develop an optimal strategy for centralisation one would need to consider all positive and negative effects: heterogeneity in organisational features of closed and surviving hospitals, financial aspects, differential effects for patient subgroups, increased travel time and adequate antenatal risk selection. Current heterogeneity in organisational features, where the smallest hospitals on average perform remarkably well, contradicts a simple size related closure strategy. Differential effects of hospital quality, travel time and antenatal risk selection should all be taken into account.

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10

The impact of extremes in outdoor temperature and sunshine exposure on birthweight

J. Poeran, E. Birnie, E.A.P. Steegers, G.J. Bonsel

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ABSTRACT

Background With the advent of the 'fetal origins of adult disease' hypothesis, environmental determinants of birthweight regained interest. However, studies are heterogeneous in design with conflicting results. We developed and applied a detailed spatial-time exposure model for the most likely climatological factors affecting fetal growth: seasonality, temperature and sunshine

Methods Daily climatological data (29 weather stations) were linked to all 1,460,401 term singleton births (The Netherlands Perinatal Registry 2000-2008). An individual exposure matrix for each pregnancy was computed for five exposure windows: (1) periconceptional, (2) first / (3) second / (4) third trimester, and (5) day of delivery. Next, linear regression models were specified with birthweight (in grams) as outcome and seasonality, minimum and maximum ambient temperature, cumulative sunshine exposure, and maternal and child factors as determinants. The final model enabled to quantify climatological contribution to existing spatial variations in birthweight.

Results In The Netherlands, substantial regional differences exist in temperature extremes and sunshine, with less temperature extremes and more sunshine in coastal areas. Our exposure model explained existing irregular and modest seasonal birthweight effects as a combined effect of season, temperature and sunshine with biologically plausible exposure effects. A seasonal birthweight pattern emerged, modified by short and long term temperature and sunshine effects. Summer is associated with an almost 20 gram significantly decreased birthweight. Short term minimum and maximum temperature exposures are significantly associated with higher and lower birthweight, respectively, with effect sizes dependent on their timing during pregnancy. Also, higher cumulative sunshine exposure during pregnancy increases birthweight. On the population level, we demonstrated spatial differences in birthweight (range -11 to +25 grams) attributable to the cumulative climatological effects, with lowest birthweights in inland areas.

Conclusion Birthweight is associated with the combined effect of season and exposure to temperature extremes and cumulative exposure to sunshine, in particular during critical reproductive exposure windows in pregnancy. The demonstrated negative birthweight effects of maximum temperature exposure confirm results from animal studies. Consequently, a climate footprint is visible in the regional birth weight differences.

INTRODUCTION

Over 2,000 years ago, Hippocrates already postulated effects of 'warm and cold winds, seasons and changes in weather' on health.[1] Indeed, a large body of evidence exists on the effects of seasonality, ambient temperature and sunshine exposure on adult health.[2-4] With the advent of the 'fetal origins of adult disease' hypothesis[5], many studies have also focused on exposure to climatological factors in the intrauterine period.[6] In particular, the determinants of birthweight are of renewed interest in the search to identify modifiable factors which may prove useful for the development of strategies that prevent possible disease in later life.[6-10]

Seasonality, ambient temperature and sunshine appear the most likely factors to influence birthweight and have been previously studied.[6-10] However, these studies show inconsistent results, due to differences in methodology and study size, little or no adjustment for known confounders, and considerable differences in exposure definitions.[6-10] So far, no universal exposure concept has emerged, distinguishing between peak exposure and cumulative exposure effects, and taking varying exposure windows during pregnancy into account. Most studies use mean temperature during pregnancy as exposure measure[6-10], while in particular extremes during heat and cold waves are of interest as they increase cardiovascular mortality in adult deaths through blood flow changes.[11] Regarding sunshine, cumulative rather than peak exposure is of interest as it is thought that its effect runs mainly through vitamin D.[12]

Here, we study the impact of peak temperature and cumulative sunshine on birthweight, distinguishing between five exposure windows: periconceptionally, in the first, second and third trimesters of pregnancy, and the day of delivery. We obtained geographically detailed climatological data which permitted us to compute day-to-day individual exposure patterns. The impact of climatological factors on birthweight was then studied using an individual exposure model, taking into account the association between temperature and sunshine exposure, and the competing impact of other known endogenous and exogenous factors influencing birthweight.[13] The resulting temporal-spatial relations were mapped, to demonstrate the contribution of the selected climatological factors to existing regional differences in birthweight.

METHODS

Patient data

In this retrospective cohort study we derived data on maternal factors, child factors and birthweight from The Netherlands Perinatal Registry. This registry contains complete population-based information of >97% of all pregnancies in the Netherlands.[14] On behalf of the respective professional societies, source data are routinely collected by 94% of midwives, 99% of gynaecologists and 68% of paediatricians including 100% of Neonatal Intensive Care Unit paediatricians.[14] (See website for detailed description: www.perinatreg.nl). The board of The Netherlands Perinatal Registry granted permission to use the anonymous registry data for this study. The registry contains data on 1,620,126 births for the period of 2000-2008. We excluded multiple pregnancies (n=35,326), births with gestational age < 37 weeks or unknown (n=116,139), births with unknown parity or neonate's sex (n=353 and n=433, respectively), and unknown or erroneous zip code (n=7,474). The final database consisted of 1,460,401 births.

Climatological data

Daily maximum and minimum temperatures (in degrees Celsius) and sunshine (in hours) were derived from 29 temperature stations throughout The Netherlands (figure 10.1). The catchment area of each temperature station was based on 2-digit zip code with an average population of 182,228 per zip code area. Data were obtained from the Royal Netherlands Meteorological Institute (see website for detailed description: www.knmi.nl/index_en.html).

Exposure concept

From past evidence and biological considerations (critical reproductive windows) [6-10], we derived five non-overlapping exposure windows (figure 10.2):

- from 3 days before to 3 days after conception, periconceptional (E1);
- from conception to 91 days after conception, first trimester (E2);
- from 92 days to 182 days after conception, second trimester (E3);
- from 183 days to 273 days after conception, third trimester (E4);
- day of birth (E5).

Climatological exposure was defined as follows: seasonality (captured by month of birth), the minimum and maximum temperature, individually calculated for each exposure window (E1-E5), and total sunshine exposure (in hours) individually calculated for windows E2-E4.

The computation of exposure started with determining date of conception, which was estimated from recorded information on gestational age at birth and date of delivery.

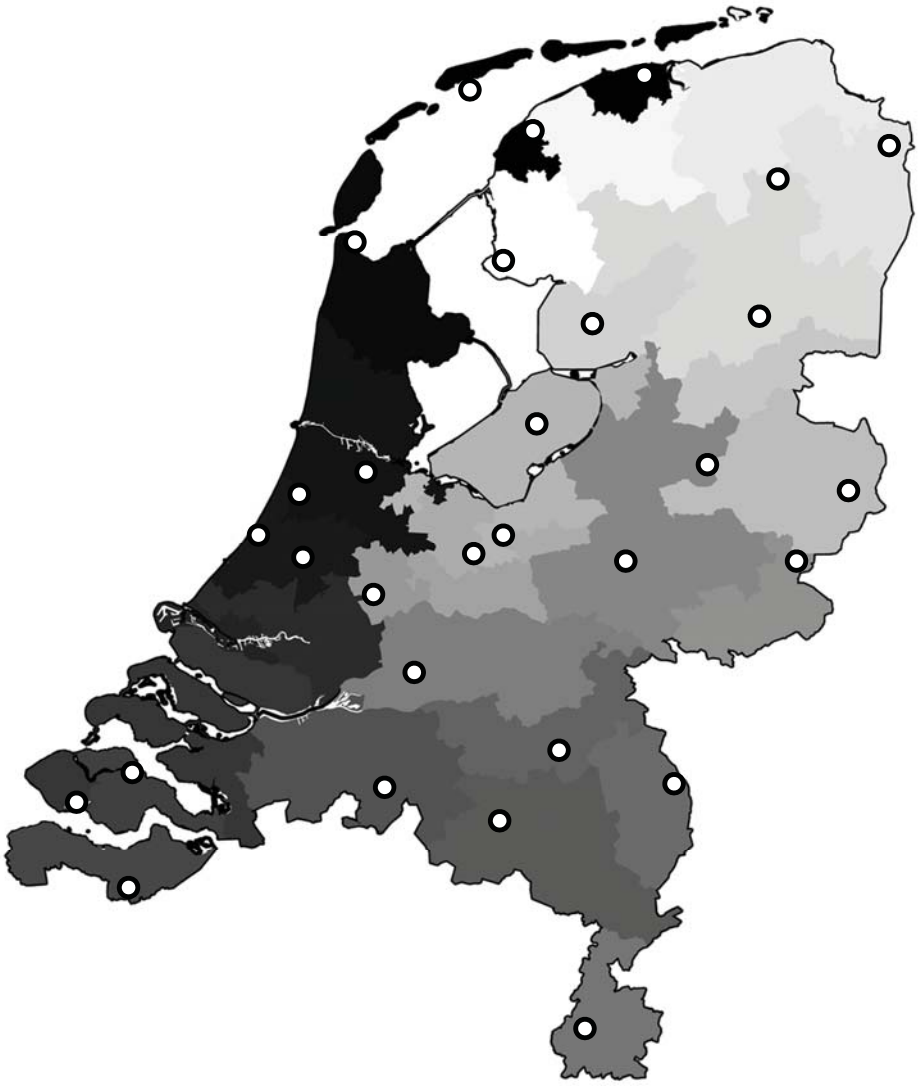

Figure 10.1 Map of The Netherlands with the 29 temperature stations and their catchment areas in shades of grey.

	MEASURE OF EXPOSURE		
WINDOW OF EXPOSURE	Minimum temperature	Maximum temperature	Total sunshine exposure in hours
E1: 3 days before to 3 days after conception	X	X	
E2: from conception to 91 days after conception	X	X	X
E3: from 92 days to 182 days after conception	X	X	X
E4: from 183 days to 273 days after conception	X	X	X
E5: day of birth	X	X	

Figure 10.2 Exposition model with different windows of exposure and the selection of exposure measures included the regression model. C = conception, C-3 = conception minus 3 days, C+91/182/273 = conception plus 91/182/273 days, E1-E5 = windows of exposure.

The climatological exposure information was subsequently projected on each pregnancy individually for E1 to E5, providing an individual exposure profile for each woman. Climate data were linked to individual records using the zip code. Date of delivery (a consecutive number from 1 to 3,288 for every day in the study period) was used as variable to capture the secular trend of increasing birthweight.[8]

Definition of outcome and maternal and child factors

The main outcome was birthweight in grams. Known maternal and child factors affecting birthweight were also included. Maternal factors were parity (primiparous / multiparous), ethnicity (Western / non-Western), maternal age (continuous), and socioeconomic status (SES) score based on zip code of residence. Since the effect of maternal age on birthweight appears to be inverse U-shaped (lower birthweight for the youngest and oldest mothers), we used the quadratic value of maternal age as determinant. As a proxy for neighbourhood

SES we used zip code specific (publicly available) SES scores, which are made available by the National Statistics Office (website in Dutch: www.scp.nl/Organisatie/Onderzoeksgroepen/Wonen_Leefbaarheid_Veiligheid/Lopend_onderzoek_van_WLV/Statusscores). These SES scores are zip code based and use individual data on e.g., income, taxes, hours of work, and educational level. The scores are approximately normally distributed at the neighbourhood level, where a negative score represents a high SES.

Child factors were gestational age (six categories), presence of congenital anomalies (yes / no), and neonate's sex (male / female). In The Netherlands Perinatal Registry, congenital anomalies are recorded postpartum and classified through a standard coding system by organ system (8 categories, 71 subcategories).

Analysis

Linear regression models were specified in a predefined order. First, all maternal and child factors and consecutive number of day of birth were included as determinants (model 0). Next, season (month of birth) was added (model 1). In model 2 and 3, the temperature and sunshine exposure measures were subsequently added. Models' goodness of fit was compared by the adjusted R-squared (R2) statistic.

Subsequently, we aimed to study regional differences in mean birthweight attributable to our climatological exposure measures. We did so by studying the birthweight difference between a dataset in which we allowed for the actual regional climatological differences (original dataset) and a dataset in which we (hypothetically) 'eliminated' this regional difference by substituting the minimum and maximum temperature, and sunshine exposition by the national average, all other things equal (duplicate dataset). We used coefficients obtained from model 3 to predict mean birthweight in this duplicate dataset. The resulting regional differences (in grams) between observed mean weight (including the effect of climatological factors) and predicted mean weight (excluding the effect of climatological factors) are attributable to climatological factors and were illustrated on a map of The Netherlands per 2-digit zip code. Because of the cancellation of the effect of climatological factors in the duplicate dataset, the difference in mean weight between the original and duplicate dataset represents the regional differences in birthweight attributable to the selected climatological factors.

The linear regression models were fitted using SPSS version 20 (IBM Corporation, Somers, NY, USA). SAS version 9.2 (SAS Institute Inc., Cary, NC) was used, with the GLM procedure to run model 3 and use its coefficients to predict birthweight in a duplicate dataset. Maps

were constructed using ESRI ArcGIS version 9.3 (Environmental Systems Research Institute, Inc., USA).

Table 10.1 Study group characteristics: subgroup sizes, subgroup mean birthweight differences with overall mean birthweight, and subgroup SGA prevalence (%)

	N	Mean subgroup BW-mean overall BW[a]	SD	% SGA
Maternal factors				
Parity				
Primiparous	660,797	-88	485	9.7%
Multiparous	799604	73	500	9.8%
Maternal age				
<20 years	23,594	-197	469	14.1%
20-35 years	1,226,233	-2	497	9.6%
>35 years	210,574	32	516	10.3%
Ethicity				
Western	1,225,392	18	500	9.0%
Non-Western	235,009	-92	490	13.5%
Socioeconomic status[b]				
Low (<p20)	365,558	-56	504	12.2%
Medium (p20-p80)	842,290	15	499	9.2%
High (>p80)	252,553	33	490	8.2%
Child factors				
Gestational age				
37 weeks	87,505	-473	488	9.8%
38 weeks	221,349	-237	468	9.8%
39 weeks	361,621	-67	450	9.8%
40 weeks	428,778	85	453	9.7%
41 weeks	281,509	210	466	9.8%
≥42 weeks	79,639	282	476	9.7%
Congenital anomalies				
No	1,430,003	2	498	9.6%
Yes	30,398	-97	581	16.1%
Sex				
Male	746,603	67	505	9.7%
Female	713,798	-70	485	9.8%
Year of birth				
2000-2002	501,459	-14	501	10.3%
2003-2005	488,010	5	501	9.7%
2006-2008	470,932	9	497	9.1%

[a] Mean overall BW = 3,522 gram, with SD = 500 gram.
[b] Status scores were cut off at the 20th (low SES) and 80th percentile (high SES).

RESULTS

Table 10.1 illustrates study population characteristics, differences between subgroup mean birthweight and overall mean birthweight, and small for gestational age prevalence per subgroup (SGA, birthweight <10th percentile). Subgroups with a significantly lower mean birthweight are: (1) women who are primiparous (-88 grams), <20 years (-197 grams), non-Western origin/background (-92 grams), with a low socioeconomic status (-56 grams); and children who are born between 37 and 39 weeks of gestational age (-473 to -67 grams), who have congenital anomalies (-97 grams), and are female (-70 grams). SGA prevalence was highest in teenage pregnancies (maternal age <20 years, 14.1%), non-Western women (13.5%), low socioeconomic status women (12.2%), and children born with a congenital anomaly (16.1%).

Differences in temperature and sunshine exposure by region

Table 10.2 illustrates the regional and within-year variation in temperature and sunshine exposure in The Netherlands. For convenience we listed temperature and sunshine exposure overall, and for three temperature stations separately: 'de Kooy', 'de Bilt', and 'Maastricht' located in the north, middle and south of The Netherlands, respectively. As expected, temperatures are highest in summer (peaks in July / August, average 17.9 and 17.7 degrees Celsius), and lowest in winter (nadirs in December / January, average 4.0 and 4.2 degrees Celsius). Sunshine exposure is highest in May / June (average 7.2 and 7.3 hours per day), and lowest in December / January (average 2.2 and 1.9 hours per day).

There is a difference of 1 degree Celsius between the northern (higher in January) and the southern temperature stations (higher in July). In the north, the temperature extremes appear less, with more sunshine, particularly in July with a difference of almost an hour per day (7.4 - 6.6 = 0.8 hours).

Linear regressions

Table 10.3 lists the linear regressions with beta coefficients, their 95% confidence intervals (CI), and the adjusted R2 values for each model. In model 0 all determinants have a significant contribution to the model with the largest beta coefficients for primiparous women (-169.8, CI -171.3;-168.4), children born at 37 weeks (-552.3, CI -555.5;-549.1) and 38 weeks (-324.1, CI -326.4;-321.9), and female sex (-145.8, CI -147.2;-144.3). In model 1, month of birth was added which did not alter the beta coefficients of maternal and child factors.

Table 10.2 Monthly differences of temperature and sunshine; overall and for three temperature stations separately: 'de Kooy', 'de Bilt', and 'Maastricht' located in the north, middle and south of The Netherlands, respectively

	Mean day temperature	Minimum day temperature	Maximum day temperature	Mean day sunshine hours
Temperature station: all				
Month				
January	4.2	-16.8	15.9	2.2
February	4.2	-15.4	18.0	3.5
March	6.2	-20.7	22.2	4.4
April	9.6	-7.9	29.7	6.4
May	13.6	-1.5	32.6	7.2
June	16.1	0.9	34.7	7.3
July	17.9	3.7	37.1	6.8
August	17.7	4.4	37.8	6.0
September	15.3	0.5	31.3	5.3
October	11.2	-8.5	24.0	4.0
November	7.4	-7.2	19.4	2.2
December	4.0	-17.0	16.3	1.9
Temperature station: 'De Kooy'				
Month				
January	4.8	-8.5	12.2	2.3
July	17.5	8.4	30.2	7.4
Temperature station: 'De Bilt'				
Month				
January	4.3	-10.6	14.1	2.1
July	18.1	6.4	35.7	6.6
Temperature station: 'Maastricht'				
Month				
January	3.9	-11.7	15.5	2.2
July	18.5	7.2	36.3	6.6

Most months showed significant, yet small effects on birthweight with beta coefficients ranging from 3.7 (September) to 6.7 (May) compared to January. No clear pattern in beta coefficients of month of birth was observed. Temperature exposure measures were added in model 2. A clear pattern in months emerged with a highly significant birthweight nadir in summer: >18 grams lower birthweight in July (-18.4) and August (-18.5). Beta coefficients for temperature exposure measures were small. For minimum temperature only exposures during first, second and third trimester were significant with beta coefficients ranging

Table 10.3 Linear regression models with regression coefficients with (95% confidence intervals)

	(adjusted R^2)	Model 0 (0.21)	Model 1 (0.21)	Model 2 (0.21)	Model 3 (0.21)
		Beta coefficient	Beta coefficient	Beta coefficient	Beta coefficient
Constant		3903.9 (3900.9;3907.0)*	3900.0 (3896.1;3903.8)**	4049.2 (4035.7;4062.6)*	4019.0 (4004.0;4033.9)*
Maternal factors					
Parity					
Primiparous		-169.8 (-171.3;-168.4)*	-169.8 (-171.3;-168.3)*	-169.9 (-171.4;-168.4)*	-169.9 (-171.4;-168.4)*
Multiparous		Reference	Reference	Reference	Reference
Maternal age^2		-0.17 (-0.18;-0.16)*	-0.17 (-0.18;-0.16)*	-0.17 (-0.18;-0.16)*	-0.17 (-0.18;-0.16)*
Ethicity					
Western		Reference	Reference	Reference	Reference
Non-Western		-90.0 (-92.1;-87.9)*	-90.0 (-92.1;-87.9)*	-91.0 (-93.1;-88.9)*	-91.4 (-93.5;-89.3)*
Socioeconomic status score		-17.9 (-18.6;-17.1)*	-17.9 (-18.6;-17.1)*	-18.1 (-18.8;-17.3)*	-18.0 (-18.7;-17.2)*
Child factors					
Gestational age					
37 weeks		-552.3 (-555.5;-549.1)*	-552.3 (-555.5;-549.0)*	-552.2 (-555.4;-549.0)*	-552.2 (-555.4;-549.0)*
38 weeks		-324.1 (-326.4;-321.9)*	-324.1 (-326.4;-321.8)*	-324.1 (-326.4;-321.8)*	-324.1 (-326.4;-321.8)*
39 weeks		-152.5 (-154.4;-150.5)*	-152.5 (-154.4;-150.5)*	-152.4 (-154.4;-150.4)*	-152.4 (-154.4;-150.5)*
40 weeks		Reference	Reference	Reference	Reference
41 weeks		127.7 (125.6;129.8)*	127.7 (125.6;129.8)*	127.6 (125.5;129.8)*	127.6 (125.5;129.7)*
≥42 weeks		218.4 (215.0;221.8)*	218.4 (215.0;221.8)*	218.5 (215.1;221.8)*	218.4 (215.1;221.8)*
Congenital anomalies					
No		Reference	Reference	Reference	Reference
Yes		-74.6 (-79.6;-69.5)*	-74.6 (-79.6;-69.5)*	-74.3 (-79.4;-69.3)*	-74.3 (-79.3;-69.2)*

Table 10.3 continues on next page.

Table 10.3 *Continued*

(adjusted R2)	Model 0 (0.21)	Model 1 (0.21)	Model 2 (0.21)	Model 3 (0.21)
	Beta coefficient	Beta coefficient	Beta coefficient	Beta coefficient
Sex				
Male	Reference	Reference	Reference	Reference
Female	-145.8 (-147.2;-144.3)*	-145.8 (-147.2;-144.3)*	-145.7 (-147.2;-144.3)*	-145.7 (-147.2;-144.3)*
Climatological factors				
Day of birth: consecutive number in study period	0.010 (0.009;0.010)*	0.010 (0.009;0.010)*	0.010 (0.010;0.011)*	0.009 (0.009;0.010)*
Month of birth	Not in equation			
January	-			
February	-	2.4 (-1.2;6.0)	-1.3 (-5.4;2.8)	-0.3 (-4.4;3.8)
March	-	4.0 (0.5;7.5)***	-4.4 (-9.3;0.6)	-2.0 (-7.1;3.1)
April	-	5.6 (2.0;9.1)**	-6.0 (-12.0;-0.1)***	-1.5 (-7.7;4.7)
May	-	6.7 (3.2;10.2)*	-8.3 (-15.0;-1.6)***	-1.3 (-8.4;5.7)
June	-	5.2 (1.7;8.8)**	-16.1 (-23.3;-8.9)*	-7.5 (-15.2;0.2)
July	-	6.2 (2.8;9.7)*	-18.4 (-25.5;-11.2)*	-9.3 (-17.0;-1.5)***
August	-	3.0 (-0.5;6.5)	-18.5 (-25.5;-11.4)*	-11.1 (-18.7;-3.6)**
September	-	3.7 (0.2;7.2)***	-15.1 (-21.6;-8.6)*	-10.5 (-17.3;-3.6)**
October	-	4.1 (0.6;7.6)***	-6.1 (-11.6;-0.6)***	-3.5 (-9.3;2.3)
November	-	5.9 (2.3;9.4)**	3.5 (-1.3;8.3)	5.4 (0.4;10.4)***
December	-	0.4 (-3.1;4.0)	-0.4 (-4.6;3.8)	0.3 (-4.0;4.5)

Minimum temperature: window of exposure	Not in equation	Not in equation		
E1: periconceptional	-	-	0.3 (0.0;0.6)	0.2 (-0.1;0.6)
E2: first trimester	-	-	-0.6 (-1.1;-0.2)**	-0.3 (-0.8;0.1)
E3: second trimester	-	-	0.6 (0.3;1.0)**	0.4 (0.0;0.8)***
E4: third trimester	-	-	1.5 (1.3;1.8)*	1.5 (1.2;1.7)*
E5: day of birth	-	-	0.1 (-0.2;0.4)	0.1 (-0.2;0.4)
Maximum temperature: window of exposure	Not in equation	Not in equation		
E1: periconceptional	-	-	-0.6 (-0.9;-0.3)*	-0.4 (-0.8;-0.1)**
E2: first trimester	-	-	-1.6 (-1.9;-1.2)*	-2.1 (-2.4;-1.7)*
E3: second trimester	-	-	-2.2 (-2.5;-1.9)*	-2.4 (-2.8;-2.0)*
E4: third trimester	-	-	-2.0 (-2.3;-1.7)*	-2.1 (-2.5;-1.8)*
E5: day of birth	-	-	-0.4 (-0.7;-0.2)**	-0.4 (-0.6;-0.1)**
Cumulative sunshine in hours: window of exposure	Not in equation	Not in equation	Not in equation	
E2: first trimester	-	-	-	0.052 (0.039;0.065)*
E3: second trimester	-	-	-	0.025 (0.011;0.038)**
E4: third trimester	-	-	-	0.023 (0.010;0.036)**

* p<0.0001, ** p>0.0001 and p<0.01, *** p>0.01 and p<0.05.

from -0.6 to 1.5. For maximum temperature all exposure windows had significant beta coefficients ranging from -0.4 (day of birth) to -2.2 (second trimester). After adding sunshine exposure to model 3, the summer nadir remained significant, but with moderation of beta coefficients to -9.3 for July and -11.1 for August. Sunshine exposure demonstrated small, yet significant effects with beta coefficients ranging from 0.023 to 0.052. As opposed to

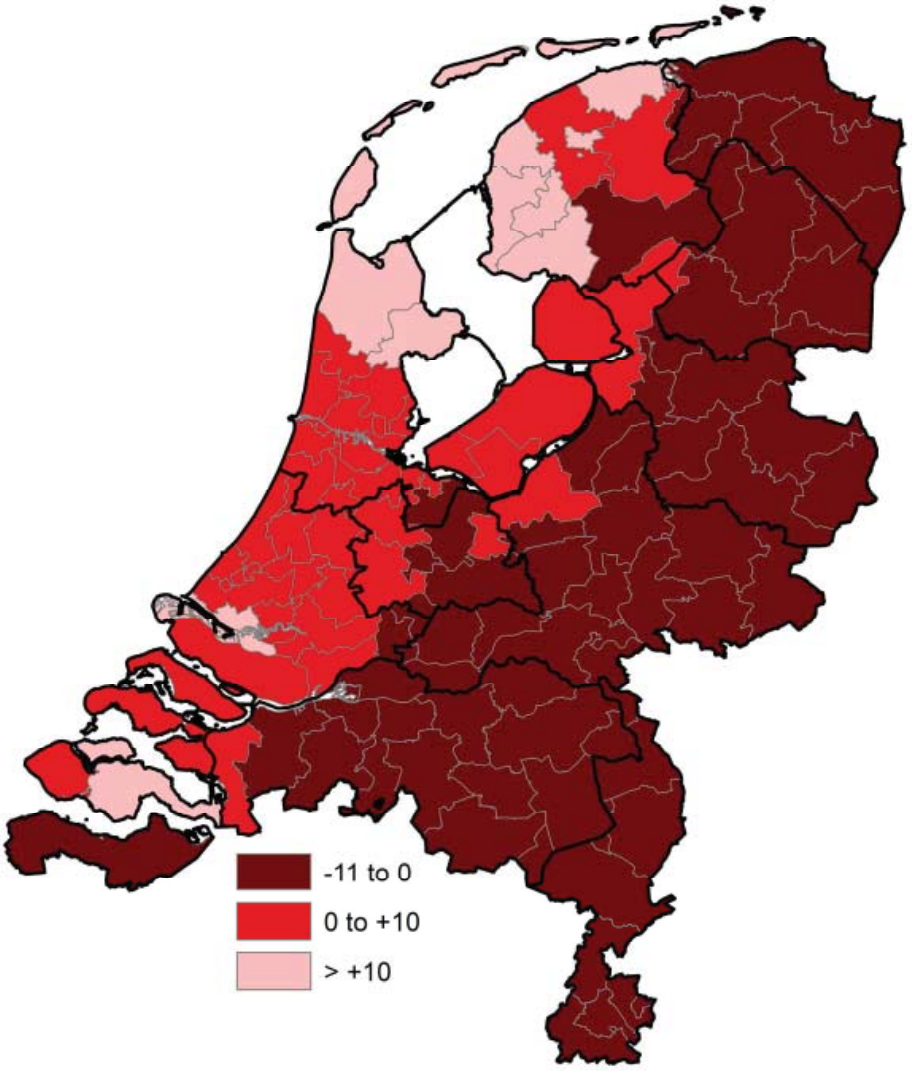

Figure 10.3 Regional birthweight differences (per 2-digit zip code) attributable to difference in exposure to temperature extremes and sunshine (adjusted for maternal factors, child factors, and day and month of birth).

the emerging pattern of seasonality in model 2, there was no difference in adjusted R2 (0.21) between the models, implying combined (interacting) effects of temperature and sunshine with seasonality.

Regional birthweight differences

The regional birthweight differences range from -11 to +25 grams due to the selected climatological exposures, with moderation of these effects (i.e., higher birthweights) in coastal areas (figure 10.3).

DISCUSSION

Birthweight is associated with the combined effect of season and exposure to temperature extremes and cumulative exposure to sunshine, in particular during critical reproductive exposure windows in pregnancy. We demonstrated small, yet consistent effects on top of known maternal and child factors. The effects of seasonality alone were initially modest (table 10.3, model 1) but most likely hided interacting effects of temperature and sunshine, illustrated by the clear pattern in seasonality after inclusion of temperature and sunshine in the model (table 10.3, model 2 and 3). The result was an almost 20 gram significantly decreased birthweight in summer compared to January. We found minimum temperature exposure in the second and third trimester to be associated with higher birthweight, maximum temperature exposure for all exposure windows to be associated with lower birthweight, and cumulative sunshine exposure to be associated with higher birthweight. On the population level, there are significant regional differences in birthweight, attributable to the selected climatological exposure measures, ranging from -11 to +25 grams (relative to the observed birthweight). The detrimental effect of maximum temperature in particular, appears to be moderated in coastal areas where there are less temperature extremes and more sunshine hours. The superposition of the observed effects with differential timing of exposure explains the hitherto unexplained or contradictory patterns in previous papers.[6]

Other studies

Previous studies on the relationship between climate and birthweight are heterogeneous in design and outcome.[6-10] In an Australian large cohort study in the Perth region, Pereira et al. investigated the effect of seasonal variation, temperature and sunshine on birthweight, adjusted for sociodemographic, biological, and environmental exposures (e.g., air pollutants,

temperature and sunshine).[7] Effects were studied separately by trimester. Analogous to our findings, they report a 2% significantly increased risk of SGA by higher temperatures sustained over pregnancy; this risk for lower birthweight was particularly observed for exposition during the third trimester. The main differences compared to our study include the use of only maximum temperature, exposure data from just two temperature stations, and the inclusion of births from 33 weeks of gestational age, leading to incomplete exposure windows for the third trimester.[7]

Although an inverse relation of heat stress on birthweight has been observed in several studies[7,9,15], the opposite (i.e., heat stress causing increased birthweight) has also been demonstrated.[8,9] Probably due to heterogeneity in study design, most of these studies did not find consistent directions of effect measures for all exposure windows, e.g., one study found a negative effect of first trimester temperature exposure on birthweight (beta coefficient -5.4, 95% CI -7.9;-2.9), and a positive effect of third trimester temperature exposure on birthweight (beta coefficient 1.3, 95% CI 0.5-2.1).[9]

Animal studies provide a biological explanation for part of our findings as they show heat stress during pregnancy to be associated with reduced placental weight, decreased uterine and umbilical blood flow and consequent reduction in offspring birthweight.[16] Galan et al. exposed pregnant ewes to heat stress during pregnancy for 55 days (mean birthweight 1,841 grams) and 80 days (mean birthweight 882 grams).[17] They observed a significant reduction in fetal and placental weights compared with a control group (mean birthweight 3,391 grams).[17] In terms of the 'fetal origins of adult disease' hypothesis[5], our findings, combined with findings from these animal studies may demonstrate some form of adaptation mechanism regarding the expected outdoor climate after birth.

Possible mechanisms

Several theories exist on the background of our observed results. According to one, fetal growth is influenced by the rate of uteroplacental blood flow. Extremes of temperature, in particular heat, are known to affect human blood flow with excess cardiovascular deaths occurring in heat waves.[11] It is therefore plausible that maternal blood flow and, hence, fetal nutrition will be affected by these extremes in different stages of pregnancy. It is also possible that outdoor temperature during pregnancy or seasonality is linked to maternal behaviours including smoking, diet and physical activity. In particular smoking may have contributed to the summer decrease in birthweight as it has a profound negative effect on birthweight, and tobacco consumption in general has been shown to peak in summer.[18,19]

Inherent to sunshine, vitamin D has also been mentioned as a possible causal factor. Its production depends primarily on the action of sunlight on the skin, and therefore, it is strongly associated with the duration of sunshine.[12,20] A 2010 Dutch study found women with deficient vitamin D levels in early pregnancy (median 13 weeks' gestation) to be at increased risk for an infant with lower birthweight (-114.4 gram, 95% CI -151.2;-77.6) and SGA.[20] Vitamin D deficiency is more prevalent during the winter months. Women with the end of first trimester in winter will deliver during late spring and summer, and, according to this hypothesis, will have lower birthweight children as demonstrated in our results.

Strengths and limitations

An important strength of our study is the usage of a validated national database (The Netherlands Perinatal Registry) with an almost complete coverage of all pregnancies over a long period of time (2000-2008), and detailed climatological data from a nationwide network of 29 temperature stations, increasing the precision and generalisability of our results. Additionally, in comparison with previous studies, our study model included an individual exposition model covering the whole duration of pregnancy including the periconceptional period.[3,6-10] Other strengths include the use of sunshine exposure, as most studies do not include this in their model, and the adjustment for socioeconomic status. The latter is important because in current times it is relatively easy to keep a home and a person in a temperate ambient, but this is less likely the case if socioeconomic status is low and housing quality is poor.

One of the study limitations, similar to most previous studies, is that outdoor temperature does not reflect the true exposition as a significant amount of time is spent indoors, especially at time of extreme temperatures. Another potential source of error is a person's mobility as climatological data linked to a person's zip code of residence may compromise the exposure estimate. Inaccuracy resulting from the first underestimates the individual exposure to temperature extremes with underestimation of the true peak temperature effect. The second inaccuracy may yield an under- or overestimation on the individual level without obvious systematic effect in general. Despite this error and the generally temperate Dutch climate, a consistent effect remains. A last limitation is the lack of data on maternal lifestyle factors, in particular smoking. However, by excluding preterm births and taking into account socioeconomic status, both strongly related to maternal smoking, we attempted to minimise the effects of this limitation.

Implications

Climatological factors impact birthweight on the individual level, the effect of which emerges as regional differences in birthweight on the population level. For healthy babies born at term the demonstrated differences appear small and effects on health later in life are unlikely. More detrimental effects may emerge for vulnerable subgroups (e.g., women carrying growth restricted babies) implying future research in these groups. The birthweight effects on the population level may be also more sizeable in countries where the population is truly exposed to extremes.

The World Health Organization recommends an indoor temperature of 18 degrees Celsius, or 21 degrees Celsius for vulnerable people[21]; as it is impossible to change the climate, improving housing quality to moderate exposure to extremes in temperature appears a realistic implication for vulnerable subgroups.

Conclusion

Birthweight is associated with the combined effect of season and exposure to temperature extremes and cumulative exposure to sunshine, in particular during critical reproductive exposure windows in pregnancy. The effect of seasonality appears to be mediated by interacting effects of temperature and sunshine, resulting in an almost average 20 gram significantly decreased birthweight in summer compared to January. On the population level, significant regional differences in birthweight exist, most likely attributable to particularly maximum temperatures, with moderation of the effect in coastal areas. For healthy babies born at term these differences in birthweight appear small; however, more severe detrimental effects may emerge for vulnerable subgroups, e.g., women carrying growth restricted babies.

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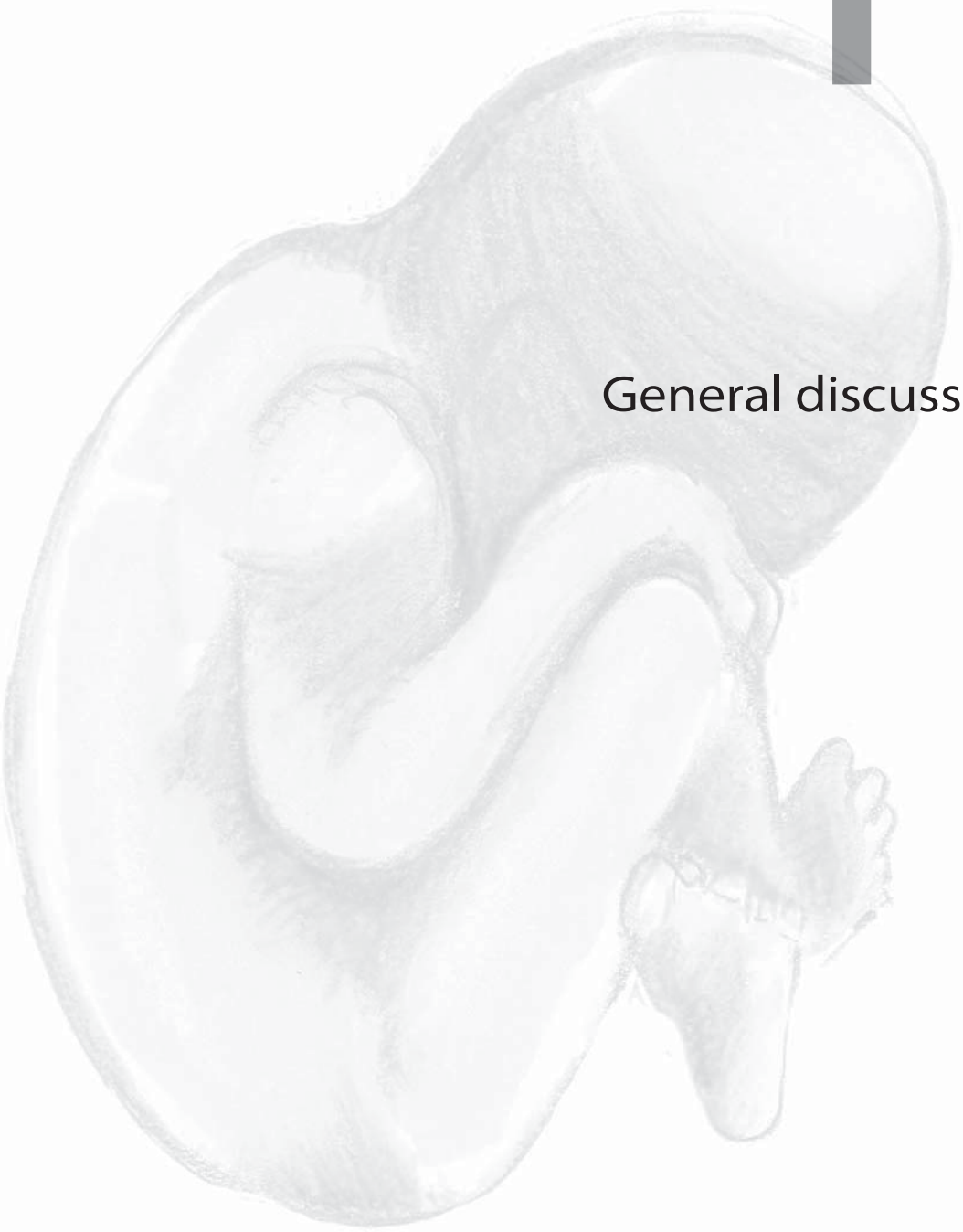
11

General discussion



AIM OF THIS THESIS

The aim of this thesis was to investigate the main contributing factors in adverse perinatal outcomes on the three geographic levels (international, national, regional). The role of patient, environmental, and healthcare related factors was studied, in particular their relative importance. Such information may guide to select and to prioritise among policies to decrease gaps in perinatal health.

Our results are presented in two parts. Part I contains three studies from the regional 'Ready for a Baby' programme; part II contains six studies on the national level, either ordered by 'ZonMw' (The Netherlands Organisation for Health Research and Development), 'SAZ' hospitals (a co-operative institution of about 40 small general hospitals in The Netherlands), or the Ministry of Health, Welfare and Sport. All studies draw on data from The Netherlands Perinatal Registry.

PRINCIPAL FINDINGS

Part I

We demonstrated that large differences exist in absolute perinatal mortality and morbidity rates between neighbourhoods within the city of Rotterdam (**chapter 2**). The magnitude of these inner-city inequalities in perinatal health had not been previously described in developed countries. The inequalities were somewhat reduced by accounting for socio-demographic population differences ('standardisation' for maternal age, parity, ethnicity, neighbourhood social quality) between the Rotterdam boroughs, yet substantial differences remained (**chapter 3**). The municipal report on perinatal health as described in **chapter 3** shows how such an analysis allows to differentiate between patterns of possible causes per borough, implying the necessity of different policy measures per borough. We believe that the mechanisms in deprived neighbourhoods work through the accumulation of heterogeneous risks (maternal, child, organisational, environmental). These risks are more abundant in these neighbourhoods and underlie the generally high level of adverse pregnancy outcomes.[1]

Another important factor influencing urban perinatal health is social deprivation (**chapter 4**). Deprivation points both to the above described higher risk level, and the lack of personal and family resources to counter ill-health. We demonstrated differential effects of social deprivation on Western and non-Western women in the city of Rotterdam. Better

neighbourhood social quality (expressed in the Social Index) was clearly associated with better perinatal outcomes for Western women. This trend was absent for non-Western women as they showed small changes in prevalence of adverse pregnancy outcome with better neighbourhood social quality. Policy recommendations in this context may refer to (1) risk management and intensified care, and (2) empowerment, improving resources and care access. For Western women, the latter is more important as our results show that improved social quality is associated with perinatal outcome improvement in this group. While this may also benefit non-Western women, tailored change requires better understanding of the underlying patterns first. Suggested explanations for non-Western 'migrant' groups include the presence of 'protective' effects through knowledge systems ('resource availability') or intrinsic resilience ('high risk level').[2-4] The suggestion of knowledge systems follows from the so-called 'ethnic density' hypothesis which suggests the risk of poor health outcomes for a minority individual to be inversely related to the density of his or her racial/ethnic group in the local community.[5-8] The presumed mechanisms include health protection through increased participation in social networks or knowledge systems, and a more extensive repertoire of positive coping behaviours.[5-9] Additional etiological research in this multi-ethnic urban setting is mandatory. Possibly, risk assessment tools and social measures such as the Social Index capture features through a 'Western perspective', e.g., rather than household income greater family income may be a more important measure for non-Western groups.

Part II

The population attributable risks (PAR[10]) of maternal, child and organisational risk factors for perinatal mortality are demonstrated in **chapter 5**. Adapting a new multivariable method to compute PARs, the results showed to vary according to methodological choices. For example, a PAR of maternal factors can be estimated with and without taking into account the PAR of child and organisational factors. Maternal factors, long put forward as a crucial determinant for the national perinatal mortality rate[11-13], appeared to attribute to only 1.4% to 13.1% of perinatal mortality in a multivariate context. PARs of child and organisational factors were 58.7-74.0% and 7.3-34.3%, respectively, where the range reflects different priority (for that factor) in the adjustment procedure. Focusing on the role of hospital organisation factors, the PAR results suggest that a change towards the theoretical organisation optimum, with an otherwise unchanged pregnant population, provides a 34.3% decrease of in-hospital perinatal mortality.

The highest PAR for a single risk factor was observed for gestational age (72.2%), i.e., if all women would deliver at 40 weeks of gestational age - all other things equal - , the perinatal mortality is expected to be reduced with 72.2%. Moreover, being born at 37-37.6 weeks of gestation (considered at term) reflects a 200% increased risk for perinatal mortality (compared to 40 weeks), which questions the definition of 'term pregnancy' and suggests a change of the lower threshold from 37 weeks to 38 weeks of gestation.[14,15]

Results from the PAR study are in support of policy measures aimed at (1) improving organisational factors in obstetric healthcare[16-19], and (2) improved prevention of preterm birth.

Next to targeting specific risk factors, also regional policy measures may be implemented to improve perinatal health. **Chapter 6** reported on epidemiological methods to select priority regions in which to study the implementation of intensified preconception care and uniformal antenatal risk selection for the 'Healthy Pregnancy 4 All' project. Crude as well as standardised rates are used in this selection process. Depending on the goal of the intervention, i.e., improvement of preconception care or antenatal risk selection, different indicators are needed to prioritise among regions. These indicators are related to perinatal mortality, morbidity and healthcare factors. Both strategies of selection point out the four largest cities ('G4', i.e., Amsterdam, Rotterdam, The Hague, Utrecht) as a priority region, thus, illustrating the multifactorial effects on and the complexity of urban perinatal health.

Chapters 7, **8** and **9** address the unique Dutch system of obstetric care. This system is characterised by three risk-based levels of care.[20,21] Primary care for assumed low risk pregnancies is provided by independently practicing community midwives. Assumed low risk pregnant women can either opt for a home birth or a short-stay hospital birth under supervision of a community midwife.[20,21] Secondary/tertiary care for assumed high risk pregnancies is provided by obstetricians in hospitals. Whenever risk factors of adverse perinatal or maternal outcome are present before pregnancy or arise during pregnancy or parturition, women shift from low risk to high risk and are referred to secondary care or from secondary to tertiary care, also during parturition. This ongoing risk assessment during pregnancy and during parturition is called 'risk selection', an essential quality of care indicator of the Dutch obstetric care system.[20-22] Risk selection in the Netherlands is the exclusive responsibility of primary care community midwives.[22] In formal terms, the aim of risk selection is to identify and refer high risk pregnancies from an undifferentiated group at onset of pregnancy, in order to obtain a true low risk group of pregnant women (expressed as high negative predictive value of risk selection) for delivery in the primary care setting.[20,21]

Indications for referral and definitions of high and low risk pregnancy are listed in the 'List of Obstetric Indications' (in Dutch: *Verloskundige Indicatie Lijst*).[20,22] These indications, however, are not fully registered as such in The Netherlands Perinatal Registry, and not always defined unequivocally. For our analysis of risk selection effectiveness we therefore defined a high risk pregnancy based on the presence of a 'Big4' morbidity.[23]

Our study showed that current risk selection does not result in a true low risk population in primary care at the end of pregnancy. Furthermore, a considerable part of high risk women is referred during parturition (**chapter 7**). Several mechanisms may be responsible for suboptimal risk selection. First, primary care community midwives are oriented towards low risk pregnancies. This 'risk experience' may cause high risk women not being detected as such in primary care. By a similar mechanism low risk women who might deliver under a midwife's supervision may not always be detected in secondary/tertiary care. Second, the availability of tools to detect high risk pregnancies in primary care may also play a role, e.g., standardised checklist-based risk screen methods in the first trimester or ultrasound examination in the second and third trimester. Standardised checklist-based antenatal risk selection is currently evaluated in a national public health programme: 'Health Pregnancy 4 All' (HP4All).[24] The instrument being used, the 'R4U' (Rotterdam Reproductive Risk Reduction), screens on medical as well as social risk factors for adverse perinatal outcome.[24]

Financial incentives are a third mechanism which may influence risk selection effectiveness. Assigning a high risk level implies referral, which directly affects professional income. For example, midwives receive the full fee for delivery care, independent of the duration of labour. If the patient is referred just after (artificial) rupture of membranes, this does not affect the fee. Similarly, no surplus is provided in time consuming deliveries. This incentive promotes a policy in which pregnant women stay under care of the primary care community midwife until just after the start of delivery. Similarly, gynaecologists receive a fee independent from the stage of delivery. The two aforementioned incentives together may be responsible for high referral rates during parturition.

We believe that a successful effort in increasing risk selection effectiveness depends on optimal collaboration between midwives and obstetricians with a joint responsibility for the determination of a woman's risk status, i.e., 'shared care'. Shared obstetric care has already been implemented in some form in other Western countries such as Australia and the United Kingdom.[25-27] One study demonstrated a 27% increase in the detection rate of intrauterine growth restriction for women receiving shared obstetric care as opposed to conventional obstetric care.[28]

Chapter 8 addresses the safety of home birth. Under routine conditions, home birth is generally not associated with increased intrapartum and early neonatal mortality. The mortality risk of home birth compared to planned hospital birth in low risk pregnancies is non-significantly increased (OR 1.05, 95% CI 0.91–1.21). In subgroups, additional risk cannot be excluded. Moreover, a recent report, which presents an overview of evidence concerning safety of home birth, advocates hospital based delivery for all women. The evidence in their view supports professional responsibility to be more important than a consumer's choice, i.e., the home birth option for low risk women.[29]

In this thesis we frame the policy choice involving the home birth option along two key questions. The first is whether risk selection is adequate, i.e., is the group starting delivery under a midwife's supervision truly a low risk group of women, who consequently can be offered the choice to deliver at home? A 6% prevalence of perinatal morbidities in home births - even after referral of high risks during parturition and pregnancy - suggests a negative reply to this answer (**chapter 7**). The second question refers to the outcome difference in the home environment vs. in the hospital environment in unanticipated perinatal morbidities. We assume that neonates with morbidities are likely to benefit from being in the hospital setting at onset, as this decreases delay in specialised care provision.[30,31]

In-hospital midwife-led birth centres provide a possible alternative to provide a home-like environment during delivery without delay if referral to the hospital is deemed necessary.[32] While home birth perhaps may be considered for a group of selected low risk multiparous women, one can argue that all primiparous women should deliver in an in-hospital environment, either under supervision of the midwife (birth centre) or a gynaecologist.[29,33]

The study in **chapter 9** was set up because of current policy proposals in favour of centralisation acute obstetric care. The goal of centralisation is to ensure 7*24h availability of 'qualified professionals' (midwives, gynaecologists, paediatricians, anaesthesiologists, and operating theatre staff; 'qualified' in terms of seniority) within 15 minutes.[16,34]

Centralisation is also under consideration in other countries.[17-19] Recently, the Royal College of Obstetricians and Gynaecologists (RCOG) stated in their 'Working Party Report' it is adamant that obstetric care delivery has qualified specialists available at all times, 24 hours a day, 7 days a week as more than half of all births, after all, take place 'out of hours'.[17] However, also taking into account the possible drawbacks of centralisation they caution this recommendation by stating 'localised where possible, centralised where necessary'.[17]

The main reasons mentioned in the literature in favour of centralisation are: (1) better care and access to rapid intervention during delivery, resuscitation of the newborn, and

identification and management of newborn infants with unexpected morbidities (e.g., congenital anomalies) in large and higher level hospitals.[35] However, this 'bigger-is-better' mantra is mainly based on theoretical reasoning, and empirical evidence from centralisation studies in the context of (complex) surgical procedures.[36] Moreover, in the context of acute obstetric care, evidence-based data are scarce, and most studies on this subject are ecological or of a descriptive nature, heterogeneous in design and have contradictory results.[18,19,35,37,38] One important argument against centralisation is increased travel time to hospital, with inherent increased risk for adverse perinatal outcome (especially for high risk women) or out-of-hospital delivery.[39] Furthermore, as around 20% of births in The Netherlands still occur at home under supervision of a midwife[40], increased travel time to hospital will compromise some low risk women in their choice to opt for a birth at home. Finally, centralisation of acute obstetric care fits into a broader change of Dutch hospitals towards merging, strongly advocated by health insurance companies who prefer larger institutions for management reasons.

We provided an empirical framework to study the effects of centralisation of acute obstetric care (**chapter 9**). Two hypothetical centralisation scenarios are defined, both representing fairly small changes affecting 6-7% of patients: (1) closure of the 10 smallest hospitals, and (2) closure of the 10 smallest hospitals, but avoiding adjacent closures. As only 10 small hospitals were hypothetically closed we assumed no system effects. Our results demonstrated that closing the small hospitals (scenario 1 and 2) does not necessarily result in distinct better outcomes on the population level. Outcome strongly depended on the organisational features of the hospital receiving the patients from the closed hospitals.[41] Multiple factors have to be taken into account regarding centralisation of acute obstetric care, e.g., the organisational features of the closing hospital, the characteristics of the women 'shifting' to the next nearest hospital (are they low risk or high risk), the quality of risk selection (are there many 'unexpected' high risk women who need to be transferred); thus, also additional travel time is an essential feature. Moreover, short term and long term economic aspects of centralisation and 'side' effects on paediatric and anaesthesiology services also need to be evaluated.

In line with the results from **chapter 5**, showing a 30% decrease in perinatal mortality to be expected from optimising hospital organisational factors alone, we think centralisation, on average, to be effective in improving perinatal health. However, centralisation should be carried out bearing (organisational) information on the specific hospitals in mind. In particular rural regions may not benefit at all from centralisation. We therefore support the RCOG's statement 'localised where possible, centralised where necessary'.[17]

In **chapter 10** we studied the effect of climatological factors, i.e., seasonality, extremes in temperature and cumulative sunshine exposure, on birthweight. For this purpose we specified an elaborate exposition model taking into account the whole course of pregnancy from conception to birth. Our aim was to identify critical phases and the type of exposure to demonstrate the strongest effects on birthweight.

We found all measures of exposure to be significantly associated with birthweight, where the modest effects of season alone hided interacting effects of temperature and sunshine. In a multivariable context, we found minimum temperature exposure in the second and third trimester to be associated with higher birthweight, maximum temperature exposure for all exposure windows to be associated with lower birthweight, and cumulative sunshine exposure to be associated with higher birthweight. The greatest single effect was observed for seasonality, in particular after correction for temperature and sunshine effects. Unlike most previous studies[42], we demonstrated a regular seasonal pattern after this correction, resulting in a spring/summer nadir with an almost 20 gram significantly decreased birthweight in summer. Our results partially correspond with results from animal studies in which maximum temperature exposures are consistently significantly associated with lower birthweight.[43,44]

On the population level and combining all seasons, we demonstrated significant regional differences in birthweight, attributable to the studied measures of minimum and maximum temperature, and cumulative sunshine exposure. Maximum temperatures appear to attribute most to these regional effects, with moderation in coastal areas. For healthy babies born at term these differences appear small; however, more severe detrimental effects may emerge for vulnerable subgroups, e.g., women carrying growth restricted babies. Regarding the effect of climatologic factors on birthweight, the population level is too small to expect a contribution to the national problem of increased perinatal mortality.

METHODOLOGICAL ISSUES

The Netherlands Perinatal Registry

In all studies described in this thesis data from The Netherlands Perinatal Registry are used. This medical registry contains complete population-based information of >97% of all pregnancies in The Netherlands.[40] Source data are routinely collected by 94% of midwives, 99% of gynaecologists and 68% of paediatricians including 100% of Neonatal Intensive Care Unit paediatricians.[40] (See website for detailed description: www.perinatreg.nl).

In general, medical registries such as The Netherlands Perinatal Registry try to capture particular actions in healthcare systems (e.g., admissions, billing, drug prescriptions), while research registries usually try to capture details on one specific disease or research question. The use of medical registries for research purposes may be challenged by the limited amount and the quality of the information. Quality concerns include the classification of the health outcome, the limited amount of detailed clinical information (e.g., existing health status of the patient), the limited amount of information on events occurring before the health event (e.g., information on past exposures) and information on events after the health event (e.g., follow-up information).[45]

While useful for the studies described in this thesis, The Netherlands Perinatal Registry's quality is challenged in different ways. Health events and disease states are not always clearly classified, e.g., presence of pre-eclampsia. Its quality is also challenged by the limited amount of information before and after birth (the health event), on former pregnancies, on risk factors (such as smoking, educational level, etc.), on process information of hospital admission and referrals (e.g., indication for referral and treatment in such cases). Secondly, about 70% of the paediatricians and 100% of NICU paediatricians participate. While the percentage of participating paediatricians is increasing, partial and selective participation challenges completeness of short term neonatal outcome. Thirdly, the registry does not contain long term follow up outcome of newborns. This information is registered separately by, e.g., care providers in youth healthcare. While these shortcomings may be true in general, our studies primarily suffer from the unavailability of detailed information on former pregnancies and risk factors, since these may lead to residual confounding. To some extent they also suffer from missing data on referrals and hospital admissions, since these may provide insight in the possible underlying mechanisms of adverse outcome. Most importantly, the legal environment and user costs should be evaluated to ensure access to and continuing improvement of The Netherlands Perinatal Registry as our studies show the value of this registry for our research purposes.

Adjustment techniques

In the observational context of the studies presented in this thesis different adjustment techniques are indispensible. We used multivariable regression techniques and (direct) standardisation techniques.[46-49] Advantages of direct and indirect standardisation include computational simplicity, and relatively fewer statistical assumptions. Standardisation can be regarded as the preferred adjustment technique if one is more interested in the overall

effect instead of the influence of separate determinants.[46-48] Moreover, standardisation requires a researcher's selection of adjustment variables prior to outcome analysis, which forces thought and plausible rationale from the researcher. In our research, standardised rates provided useful summary measures, especially when outcomes are rare and specific rates display wide random variability. However, any summary measure can hide patterns that might have important public health implications. Standardisation rates put more emphasis on less prevalent groups.[46-48]

Adjustment by regression (forced entry of adjusters), is more convenient for statistical tests for interactions and group differences (the individual effect of different determinants). Therefore, when many determinants are present, adjustment by means of multivariable regression analysis is more convenient.[47-49] However, when applying this technique more statistical assumptions have to be made (particularly when continuous variables are used), such as linear correlation of adjustment variables with outcome effects, equal effects for everyone, and all combinations of parameters being possible (including biological implausible combinations).[47-49] Moreover, in regression adjustment variables are less restricted as they can be, e.g., nominal, ordinal or interval variables; adjustment variables in standardisation, however, require strata to be created. Adjusted rates in regression are based on the most prevalent groups. Also, regression can either require a researcher's selection of adjustment variables (forced entry) or this can be determined statistically (stepwise) which may compromise plausibility.

In **chapters 4**, **5**, and **9** we use multilevel modelling to adjust for clustering of individuals within their neighbourhoods (**chapter 4**) or hospitals (**chapters 5**, **9**). The advantage of this approach is that it allows for the incorporation of both individual-level and neighbourhood-level or hospital-level characteristics. Moreover, it increases the validity of the effect sizes compared to conventional logistic regression analysis.[50] In **chapter 9** we observed great variation in random effects per hospital suggesting differences in hospital performance in terms of perinatal mortality.

Due to lacking information in The Netherlands Perinatal Registry, in particular individual-level socioeconomic status, we, however, could not fully benefit from the theoretical advantages of multilevel modelling over conventional logistic regression.

'Big4' morbidities

From detailed analysis of the complete perinatal dataset of The Netherlands Perinatal Registry, it appeared that the presence of a so-called 'Big4' morbidity precedes perinatal

mortality in 85% of cases.[23] These 'Big4' morbidities are: congenital anomalies, preterm birth, small for gestational age, and low Apgar score. Risk status of pregnancies could be insufficiently established due to lacking data in The Netherlands Perinatal Registry, especially due to lacking registration of referral indications. Due to their attribution to perinatal mortality, we used the presence of one or more 'Big4' morbidities as a proxy measure of high risk pregnancy in several studies in this thesis.

A limitation from this proxy measure may refer to 'preventability'. From this retrospective dataset no conclusions can be drawn on the preventability of 'Big4' morbidities in primary care would they have been referred to secondary/tertiary care. However, congenital anomalies and SGA are the most predictable in the antenatal phase. Most congenital anomalies are now detected by routine ultrasound (introduced in 2007) at 20 weeks of gestational age. Furthermore, there is general consensus on (improving) detection of SGA which holds an increased risk for adverse perinatal outcome.[51]

Most important, however, is that, again, both general consensus and the 'List of Obstetric Interventions' agree that a neonate with a 'Big4' morbidity is better off in a hospital setting under the care of an obstetrician/paediatrician.[52] Thus, the more important issue concerns the adequate level of care for a high risk pregnancy (optimal risk selection) and not the preventability of 'Big4'. Recent Dutch reports have expressed concerns on the effectiveness of risk selection in Dutch primary obstetric care.[23,30,31] Results from these studies emphasise that the level of healthcare provision is inadequate for a proportion of supposedly low risk pregnant women at the onset of labour. Whether the delay in referral is related to late diagnosis (no continuous fetal heart rate monitoring during parturition in primary care), transport to hospital or assessment ('primary care is supposedly low risk'), is yet unclear and needs to be additionally studied.[30,31]

RECOMMENDATIONS

From the above discussion the following recommendations can be given.

Recommendations Part I

- Within the city of Rotterdam, neighbourhood and borough-specific policies are mandatory on tackling the high degree of perinatal health inequalities between neighbourhoods and boroughs. These recommendations most likely will extend to other large cities.

- In particular Western women in socially deprived neighbourhoods are entitled to intensified antenatal care. This approach could include intensified prevention from existing health promoting programs in combination with targeted social welfare. Also, risk assessment should be modernised, regarding both the tools used for antenatal risk screening and the approach of risks detected ('shared care'). To enhance sustainability of the joint responsibility of both obstetric and social caregivers in high risk pregnancies, a combined financial remuneration system with adequate incentives should be advocated.
- Additional research is needed on (1) the differential effects of deprivation on Western and non-Western pregnant women, (2) the risk accumulation phenomenon, and (3) the consequences of adverse pregnancy outcomes in childhood. Concerning (1), the sources of differential effects are important for tailored improvement programmes. Concerning (2), the generalisability of the risk accumulation phenomenon is important to support national antenatal screening instruments like the 'R4U' checklist. Concerning (3), investigating long term consequences of adverse pregnancy outcomes is essential in general, but more particular to check whether the same differential outcomes can be observed (i.e., do the ethnicity related differential effects continue after birth). A remote consequence of the research proposed under 1 to 3 could be different risk assessment tools and strategies for different population strata.
- The financial remuneration structure should take into account the considerable regional risk differences in the perinatal context; if regional budgeting is aimed at, adjusting for maternal characteristics only is insufficient.

Recommendations Part II

- Improvement of hospital organisation deserves priority. Multiple factors appear modifiable, e.g., 7*24h organisation including the timing of (planned) deliveries in a fashion that problems most likely will emerge during daytime hours. Also, proactive obstetric policy should be advocated, at least in the Dutch context. We expect policies to already change towards a more proactive approach; however, no recent data are available to substantiate this.
- Centralisation of acute obstetric care services should take local configuration and measured hospital organisational features into account. Apart from the academic perinatal centres, hospital size is not a decisive factor in this regard. Side effects of centralisation may exceed the intended benefits.

- Studies aimed at the prevention of preterm birth are expected to grossly affect perinatal mortality. Rigorous anti-smoking policies combined with organisational and financial support for active antenatal prevention are justified. Also, the 'term' threshold should change from 37.0 to 38.0 weeks.
- In prioritising regions for public health interventions, crude and standardised outcome both need to be made available.
- Home birth as an option should be restricted to low risk multiparous women, but is only a sustained option if risk selection throughout pregnancy considerably improves.

General recommendations

- Risk factors should be detected in a consistent way (possibly through a standardised checklist based approach) during antenatal risk selection preferably through a joint effort by primary care community midwives and obstetricians.
- Mandatory information on lifestyle factors such as smoking should be incorporated in detail in The Netherlands Perinatal Registry and the registration process.
- Data from medical and administrative registries should be conditionally made available for research and care improving purposes, without prior individual consent, similar to, e.g., the Nordic countries. Additionally, quality assurance should be a regular part, and an intensive collaboration between registry authorities and hospitals and IT-stakeholders for hospital administration systems is mandatory to respond to change.

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12

English and Dutch summary

ENGLISH SUMMARY

In The Netherlands perinatal mortality rates exceed the European average. Also, within The Netherlands inequalities in perinatal health are present, mainly in the four largest cities ('G4') and deprived neighbourhoods. We state three levels of inequalities: (1) The Netherlands vs. Europe, (2) regions and G4-cities vs. the remainder of The Netherlands, and (3) deprived vs. non-deprived neighbourhoods and boroughs within these G4-cities. The causal factors for perinatal inequalities may differ between the three geographic levels.

In response to the high perinatal mortality, the Dutch Minister for Health as well as the municipality of Rotterdam issued several measures and research topics. This thesis reports on local (PART I) and national (PART II) initiatives in the context of improving perinatal health in The Netherlands. The aim is to investigate the main contributing factors in adverse perinatal outcomes on the three geographic levels (international, national, regional). Throughout this thesis, the concept of 'Big4' is applied. 'Big4' refers to four adverse pregnancy outcomes (perinatal morbidities) which precede perinatal mortality in 85% of cases: congenital anomalies, preterm birth (<37th week of gestation), small for gestational age (SGA, birthweight below the 10th percentile for gestational age) or low Apgar score (<7, 5 minutes after birth).

On the first geographic level, i.e., The Netherlands vs. Europe, the Dutch system of obstetric care significantly differs from those in other Western countries, with a high percentage of homebirths (around 20%), and an independent role for primary care community midwives. Most important, however, is the risk-based level of care: primary care for low risk pregnancies provided by independently practicing community midwives, and secondary/ tertiary care for high risk pregnancies provided by obstetricians in hospitals. Due to the distinction between assumed low risk and high risk pregnancies, antenatal risk selection is an essential indicator of the adequacy of the Dutch obstetric care system. We demonstrate an insufficient separation of low risk pregnancies from a mix of low and high risk pregnancies with a considerable part of this selection and subsequent referral taking place even during parturition (**chapter 7**).

Home birth, as another unique feature, is generally not associated with increased intra-partum and early neonatal mortality, under routine conditions (**chapter 8**). However, the safety of home births is dependent on antenatal risk selection as only assumed low risk women can be offered the choice of a birth at home. However, as antenatal risk selection still results in 6% to 9% of high risk ('Big4') women in primary care, intended for low risk pregnancies, improvement is mandatory (**chapter 7**).

Chapters 5, **6**, **9** and **10** pertain to perinatal health inequalities on the second geographic level, i.e., regions and G4-cities vs. the remainder of the Netherlands. In **chapter 5** we demonstrate that an over 30% decrease in perinatal mortality is expected on the national level through optimisation of (hospital) organisational features. This optimisation may be achieved through centralisation of acute obstetric care services. However, hospitals appear very heterogeneous in organisational features affecting perinatal outcome. Therefore, in centralisation, these organisational features need to be taken into account as well as the full scope of negatively (e.g., increased travel time) and positively (e.g., better 7*24h access to specialised care) influencing factors (**chapter 9**). Due to the complexity of this matter we agree with the statement from the Royal College of Obstetricians and Gynaecologists: 'localised where possible, centralised where necessary'.

Chapter 6 reports on the selection of priority regions in which to implement intensified preconception care and uniform antenatal risk selection. This selection was based on indicators related to perinatal mortality, morbidity and healthcare factors. Both selecting strategies (regarding to risk selection and preconception care) point out the four largest cities ('G4', i.e., Amsterdam, Rotterdam, The Hague, Utrecht) as a priority region, thus illustrating the increased risk for adverse perinatal outcome in large urban areas. G4-cities surfacing in both selecting strategies emphasises the multifactorial effects on and the complexity of urban perinatal health.

In **chapter 10** we demonstrate the effect of climatological factors, i.e., seasonality, extremes in temperature and cumulative sunshine exposure, on birthweight. Minimum temperature exposure in the second and third trimester was associated with higher birthweight, maximum temperature exposure for all exposure windows was associated with lower birthweight, and cumulative sunshine exposure was associated with higher birthweight. On the population level, significant regional differences in birthweight exist, most likely attributable to particularly maximum temperatures, with moderation of the effect in coastal areas. For healthy babies born at term these differences in birthweight appear small; however, more severe detrimental effects may emerge for vulnerable subgroups, e.g., women carrying growth restricted babies.

Chapters 2, **3** and **4** pertain to perinatal health inequalities on the third geographic level, i.e., deprived vs. non-deprived neighbourhoods and boroughs within G4-cities, in particular Rotterdam. We demonstrate large differences in absolute perinatal mortality and perinatal morbidity rates between neighbourhoods within the city of Rotterdam with perinatal mortality rates as high as 37 per 1,000 births (**chapter 2**). These inequalities remain after

standardisation, also implying differences in possible causes per borough with subsequent different policy measures per borough (**chapter 3**). Common mechanisms of adverse perinatal outcome in deprived neighbourhoods are thought to be social deprivation and accumulation of risks for perinatal mortality and morbidity. In **chapter 4** we demonstrate differential effects of social deprivation on Western and non-Western women in Rotterdam. Improvement in neighbourhood social quality causes improvement in perinatal outcomes for Western women only. Policy measures aimed at improving social quality for Western women may improve outcome in Western women, however, alternative approaches may be necessary for non-Western groups.

The most important recommendations for improvement of perinatal health on the first geographic level include improvement of risk selection (possibly through a standardised checklist based approach) and 'shared care' as the success of improvement strategies depends on a joint collaboration of midwives and obstetricians. Important recommendations on the second geographic level of perinatal health inequalities include a sensible policy on centralisation of acute obstetric care and additional research and more public health awareness for the complex issue of urban perinatal health. On the third geographic level of perinatal health, we propose additional research on the differential effects of social deprivation on Western and non-Western women. Our results imply strategies to improve social quality for in particular for Western women and more focus on alternative approaches for non-Western groups; these alternative approaches may be based on results from additional research. Furthermore, neighbourhood, and borough specific policies are mandatory on tackling urban perinatal health inequalities.

NEDERLANDSE SAMENVATTING

Nederland kent een van de hoogste perinatale sterftecijfers in Europa met ook binnen Nederland ongelijkheid in perinatale gezondheid waarbij de meest ongunstige uitkomsten gezien worden in de vier grootste steden (G4: Amsterdam, Rotterdam, Den Haag, Utrecht) en achterstandswijken. De ongelijkheid in perinatale gezondheid kan onderverdeeld worden naar drie niveaus gebaseerd op geografie: (1) Nederland tegenover Europa, (2) de G4 en regio's binnen Nederland, en (3) achterstandswijken tegenover niet-achterstandswijken. De oorzaken voor de ongelijkheid in perinatale gezondheid verschillen hoogstwaarschijnlijk per niveau.

De hoge perinatale sterfte in Nederland werd zowel voor de landelijke als regionale politiek een prioriteit met voorstellen van de minister van Volksgezondheid en de gemeente Rotterdam tot onderzoek en beleidsmaatregelen. Dit proefschrift rapporteert over regionale (DEEL I) en landelijke initiatieven (DEEL II) ter verbetering van de perinatale sterfte in Nederland. Hoofddoel van het proefschrift is dan ook de belangrijkste factoren te identificieren die bijdragen aan de slechte perinatale gezondheid in Nederland betreffende de drie geografische niveaus (internationaal, nationaal, regionaal). Het concept van '*Big4*' aandoeningen speelt een belangrijke rol in de stukken behorend bij dit proefschrift. '*Big4*' staat voor de vier ongunstige zwangerschapsuitkomsten die voorafgaan aan 85% van alle gevallen van perinatale sterfte: aangeboren afwijkingen, vroeggeboorte (vóór 37 weken zwangerschap), te laag geboortegewicht voor de zwangerschapsduur (geboortegewicht <p10), en een lage Apgarscore (<7, 5 minuten na de geboorte).

Voor de vergelijking op het eerste geografische niveau (Nederland tegenover de rest van Europa) speelt het unieke systeem van verloskundige zorg in Nederland een belangrijke rol; uniek in die zin dat, in vergelijking met andere Westerse landen, in Nederland een hoog percentage van de zwangere vrouwen thuis bevalt (rond de 20%). Een ander verschil met andere Westerse landen is de belangrijke rol van de eerstelijns verloskundige. Het belangrijkste verschil is echter het intrinsieke verschil tussen hoogrisico- en laagrisicozwangerschappen met daarbij behorende risicogeleide zorg in de verloskunde: eerstelijns zorg voor laagrisicozwangerschappen verleend door verloskundigen, en tweede-/derdelijns zorg voor hoogrisicozwangerschappen in ziekenhuizen verleend door gynaecologen. Door dit onderscheid en de specifieke bijbehorende zorgconsequenties speelt antenatale risicoselectie een belangrijke rol in het Nederlandse systeem en kan dan ook gezien worden als een belangrijke kwaliteitsindicator: 'hoe goed worden laagrisico- en hoogrisicozwangerschappen van elkaar onderscheiden'. In dit proefschrift tonen wij aan dat deze twee groepen

suboptimaal kunnen worden onderscheiden van elkaar in de periode vóór de bevalling. Daarnaast wordt ook een substantieel deel van de zwangere vrouwen gedurende de baring aangeduid zijnde hoogrisico en daarop doorverwezen naar het ziekenhuis (**hoofdstuk 7**).

De thuisbevalling is een ander uniek kenmerk van het Nederlandse verloskundige systeem. Onder normale omstandigheiden is deze niet geassocieerd met een verhoogde sterftekans tijdens de baring of in de eerste week na de bevalling (**hoofdstuk 8**). Echter, de veiligheid van thuisbevallingen hangt sterk af van herkenning en selectie van risico's vóór de start van de baring omdat alleen vrouwen die geacht worden laagrisico te zijn de keus wordt geboden om thuis te bevallen. Door suboptimale risicoselectie bevalt nog steeds een niet onbelangrijk deel van de hoogrisico ('Big4') vrouwen in de eerste lijn: 6% tot 9%. Het is van cruciaal belang dit percentage omlaag te krijgen aangezien eerstelijns zorg uitsluitend toegerust is op een laagrisicozwangerschap en -bevalling (**hoofdstuk 7**).

Hoofdstukken 5, **6**, **9** en **10** behandelen verschillen in perinatale gezonheid op het tweede geografische niveau: de G4 en regio's binnen Nederland. In **hoofdstuk 5** tonen wij aan dat door optimalisatie van ziekenhuisorganisatie de perinatale sterfte met mogelijk meer dan 30% zou kunnen dalen. Een veelgenoemde beleidsmaatregel in dit kader is centralisatie van acute verloskundige zorg, wat geacht wordt organisatieaspecten van ziekenhuizen te verbeteren door het aantal ziekenhuizen dat acute verloskundige zorg biedt sterk te verminderen. Dit impliceert sluiting van kleinere ziekenhuizen waarbij er een geringer aantal grotere ziekenhuizen overblijft. Er bestaan echter grote verschillen tussen ziekenhuizen voor wat betreft organisatieaspecten met op hun beurt een positief of negatief effect op de perinatale sterfte. Dit is een belangrijke factor waar rekening mee gehouden moet worden bij een beleid van centralisatie van acute verloskundige zorg. Een verstandig centralisatiebeleid houdt verder rekening met het hele spectrum van factoren die zowel een positief (bijvoorbeeld 7*24 toegang tot specialistische zorg) als negatief (bijvoorbeeld een toegenomen reistijd naar het ziekenhuis) effect kunnen hebben op de perinatale gezondheid (**hoofdstuk 9**). Het centralisatievraagstuk is erg complex; wij ondersteunen dan ook het standpunt van de Britse *Royal College of Obstetricians and Gynaecologists: 'localised where possible, centralised where necessary'*.

In **hoofdstuk 6** wordt ingegaan op twee selectiestrategieën ter identificatie van hoogrisicogebieden in Nederland met als doel hier intensieve preconceptiezorg of uniforme antenatale risicoselectie toe te passen. Deze selectie is gebaseerd op indicatoren gerelateerd aan perinatale sterfte, morbiditeit en zorgfactoren. De selectiestrategieën identificeerden de G4 als hoogrisico voor zowel preconceptiezorg als antenatale risicoselectie; hierbij werd nog

eens bevestigd dat er een verhoogd risico bestaat op ongunstige zwangerschapsuitkomsten in de G4. Daarnaast was dit ook een bevestiging van de complexiteit en multifactoriële oorzaken van perinatale gezondheid in de grote steden.

In **hoofdstuk 10** tonen wij effecten van het klimaat, te weten seizoen, temperatuurextremen en cumulatieve blootstelling aan zonlicht, op geboortegewicht. Blootstelling aan minimum temperaturen in het tweede en derde trimester van de zwangerschap was geassocieerd met een hoger geboortegewicht; blootstelling aan maximum temperaturen gedurende de periconceptionele periode, alle trimesters van de zwangerschap en op de dag van geboorte was geassocieerd met een lager geboortegewicht; cumulatieve blootstelling aan zonlicht gedurende alle trimesters was geassocieerd met een hoger geboortegewicht. Ook bleken er binnen Nederland substantiële klimaatgerelateerde regionale verschillen te bestaan in geboortegewicht die waarschijnlijk voor het belangrijkste deel toegeschreven kunnen worden aan de blootstelling aan maximum temperaturen. Voor gezonde á terme zuigelingen lijken deze verschillen klein; echter, de effecten kunnen ernstiger zijn voor risicogroepen zoals vrouwen die zwanger zijn van groeivertraagde baby's.

Hoofdstukken 2, **3** en **4** omvatten verschillen in perinatale gezondheid op het derde geografische niveau: achterstandswijken tegenover niet-achterstandswijken binnen de G4, in het bijzonder Rotterdam. Er bestaan grote verschillen in absolute perinatale sterfte en perinatale morbiditeit tussen verschillende wijken binnen de stad Rotterdam met perinatale sterftecijfers oplopend tot 37 per 1.000 geboorten (**hoofdstuk 2**). Dat deze verschillen ook na standaardisatie aanhouden impliceert dat er verschillende oorzaken bestaan per deelgemeente waarbij deelgemeente-specifiek beleid is geïndiceerd (**hoofdstuk 3**). Veelgenoemde mechanismen van ongunstige zwangerschapsuitkomsten in achterstandswijken zijn sociale achterstand en cumulatie van risico's gerelateerd aan perinatale sterfte en morbiditeit. In **hoofdstuk 4** tonen wij differentiële effecten van sociale achterstand op Westerse en niet-Westerse zwangere vrouwen in Rotterdam. Met verbetering van sociale kwaliteit in de buurt verbetert ook de perinatale gezondheid van Westerse vrouwen; een verband dat niet gezien werd voor niet-Westerse vrouwen. Beleidsmaatregelen gericht op verbetering van sociale kwaliteit, in het bijzonder gericht op Westerse vrouwen in achterstandssituaties, zal waarschijnlijk ook de perinatale gezonheid in deze groep ten goede komen. Voor niet-Westerse vrouwen is waarschijnlijk een alternatieve aanpak nodig.

Verbetering van perinatale gezondheid op het eerste geografische niveau zal waarschijnlijk vooral bewerkstelligd kunnen worden door verbetering van antenatale risicoselectie (mogelijk door een checklist-gebaseerde aanpak) en zogenaamde *shared care* waarbij

risicoselectie een gemeenschappelijke verantwoordelijkheid is van zowel verloskundigen als gynaecologen. Belangrijke aanbevelingen op het tweede geografische niveau omvatten een verstandig beleid van centralisatie van acute verloskundige zorg, en nader onderzoek naar het complexe thema van grootstedelijke perinatale gezondheid met meer focus op de maatschappelijke gezondheidszorg. Voor wat betreft het derde geografische niveau is de belangrijkste aanbeveling het nader onderzoek naar differentiële effecten van sociale achterstand op Westerse en niet-Westerse vrouwen. Onze studieresultaten impliceren een beleid ter verbetering van sociale kwaliteit voor met name Westerse vrouwen met een focus op alternatieve maatregelen voor niet-Westerse vrouwen. Deze alternatieve maatregelen zullen moeten volgen uit resultaten van nader onderzoek. Een andere belangrijke aanbeveling op dit niveau is buurt- en deelgemeente-specifiek beleid voor wat betreft verbetering van grootstedelijke perinatale gezondheid.

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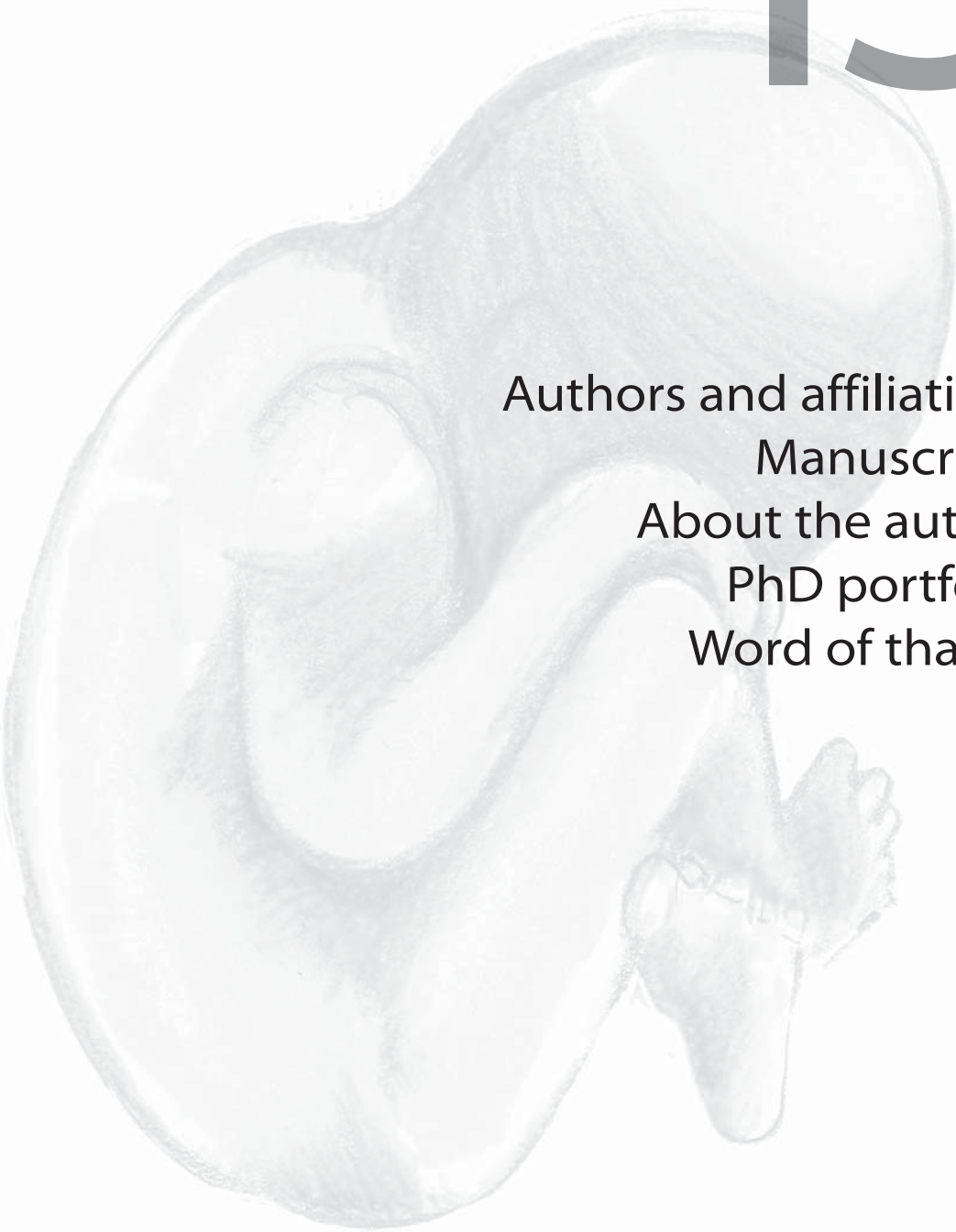

Authors and affiliations
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AUTHORS AND AFFILIATIONS

From the Department of Obstetrics and Gynaecology, Division of Obstetrics and Prenatal Medicine, Erasmus MC, University Medical Centre Rotterdam, The Netherlands

Semiha Denktaş, Eric A.P. Steegers, Gouke J. Bonsel, Arno F.G. Maas, Johanna (Hanneke) P. de Graaf, Adja J.M. Waelput, Lieke C. de Jong-Potjer, Sabine F. van Voorst, Amber A. Vos, Jacoba van der Kooy

From the Department of Public Health, Erasmus MC, University Medical Centre Rotterdam, The Netherlands

Gouke J. Bonsel, Gerard J.J.M. Borsboom, Johan P. Mackenbach

From the Midwifery Academy, Rotterdam University of Applied Sciences, Rotterdam, The Netherlands

Gouke J. Bonsel

From the Institute of Health Policy and Management, Erasmus University, Rotterdam, The Netherlands

Erwin Birnie

From the Municipal Public Health Authority 'GGD Rotterdam Rijnmond', Rotterdam, The Netherlands

H.J. (Ernie) van der Weg, A.J.J. (Toon) Voorham

MANUSCRIPTS

Manuscripts related to this thesis

Chapter 2

J. Poeran, S. Denktaş, E. Birnie, G.J. Bonsel, E.A.P. Steegers. Urban perinatal health inequalities. Journal of Maternal-Fetal and Neonatal Medicine 2011;24:643-6.

Chapter 3

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Chapter 4

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Chapter 5

J. Poeran, G.J.J.M. Borsboom, J.P. de Graaf, E. Birnie, E.A.P. Steegers, G.J. Bonsel. Population attributable risks of patient, child and organisational risk factors for perinatal mortality. Manuscript submitted for publication.

Chapter 6

S. Denktaş, **J. Poeran**, A.J.M. Waelput, L.C. de Jong-Potjer, S.F. van Voorst, A.A. Vos, G.J. Bonsel, E.A. P. Steegers. The 'Healthy Pregnancy 4 All' Study: Design and cohort profile. Manuscript submitted for publication.

Chapter 7

J. Poeran, J. van der Kooy, E. Birnie, S. Denktaş, E.A.P. Steegers, G.J. Bonsel. The effectiveness of risk selection in the Dutch obstetric care system. Manuscript submitted for publication.

Chapter 8

J. van der Kooy, **J. Poeran**, J.P. de Graaf, E. Birnie, S. Denktaş, E.A.P. Steegers, G.J. Bonsel. Planned home compared with planned hospital births in The Netherlands: intrapartum and early neonatal death in low-risk pregnancies. Obstetrics and Gynecolology 2011;118:1037-46.

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Chapter 10

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Other manuscripts

Scientific journals

S.J.A.L. Hemelaar, **J. Poeran**, E.A.P. Steegers, W.I. van der Meijden. Neonatal herpes infections in The Netherlands in the period 2006-2011. Manuscript submitted for publication.

J. de Graaf, J. Schutte, **J. Poeran**, J. Van Roosmalen, G.J. Bonsel, E.A.P. Steegers. Regional differences in Dutch maternal mortality. BJOG. 2012;119:582-8.

J.P. de Graaf, J.M. Schutte, **J. Poeran**, J. Van Roosmalen, G.J. Bonsel, E.A. Steegers. Regional differences in maternal mortality in the Netherlands. Ned Tijdschr Geneeskd. 156:A4952. (in Dutch with English abstract)

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J. Poeran, H. Wildschut, M. Gaytant, J. Galama, E.A.P. Steegers, W. van der Meijden. The incidence of neonatal herpes in The Netherlands. J Clin Virol. 2008;42:321-5.

Health reports

G.J. Bonsel, **J. Poeran**, G.J.J.M. Borsboom, J.P. de Graaf, E. Birnie, E.A.P. Steegers. '*Populatie attributieve risico's van moeder-, kind- en organisatie factoren voor perinatale sterfte*' The population attributable risk of mother-, child- and organisational factors for the perinatal mortality in The Netherlands 2000-2008. Rotterdam: Erasmus MC, 2012. (Report for 'ZonMw' The Netherlands Organisation for Health Research and Development, report in Dutch with English abstract)

G.J. Bonsel, **J. Poeran**, J.P. de Graaf, G.J.J.M. Borsboom, E. Birnie, E.A.P. Steegers, J.P. Mackenbach. '*De effecten van concentratie van verloskundige zorg*' Merging hospitals with acute obstetric care in The Netherlands: effects on perinatal mortality in a system with high intrapartum referral rates and heterogeneous hospitals. Rotterdam: Erasmus MC, 2012. (Report for a group of 40 small and medium sized hospitals in The Netherlands which was presented to the Dutch Minister for Health, report in Dutch with English abstract)

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G.J. Bonsel, E. Birnie, S. Denktaş, **J. Poeran**, E.A.P. Steegers. '*Signalementstudie: lijnen in de perinatale sterfte*' National report on priority topics in perinatal health improvement in The Netherlands. Rotterdam: Erasmus MC, 2010. (Report for 'ZonMw' The Netherlands Organisation for Health Research and Development, presented to the Dutch Minister for Health, report in Dutch with English abstract)

ABOUT THE AUTHOR

As the mother of the author, I am very honoured in helping him write this piece for his PhD-thesis. **Virender Jashvant John Poeran** was born at a gestational age of 38 weeks on March 21st, 1983 in the *Diakonessen* hospital in Paramaribo, Suriname. Labour progressed fast, and early in the morning at exactly 06:40 AM he came into this world in vertex presentation with a birthweight of 3,560 grams, over 500 grams heavier than his older brother. His height was 49 centimetres with a head circumference of 36.5 centimetres. Right after birth, this already attention seeking baby started crying loudly after which the midwife gave him an Apgar score of 10/10. During my whole pregnancy I had expected a girl and I even came up with the name 'Sheila'. Having the nurse yelling 'it's a boy!' made me adjust my reality a bit, but I soon fell in love with that beautiful smile. The most important thing I remember about his childhood is that he was the naughtiest of my three children. I could not leave him alone for one second. He was always up to doing something and always busy bullying his little sister.

Jashvant's first career choices involved being a magician, a pilot and an astronaut. It wasn't until his late teens he started thinking of going to **medical school** for which he was accepted in the summer of 2001. During his medical training he stumbled upon the path of **research** in which he was guided by **professor Steegers** from the department of Obstetrics and **dr. van der Meijden** from the department of Dermatology. At the end of medical school he more or less made the decision to pursue a career in **Obstetrics and Gynaecology**. He finished two clinical internships abroad (Thailand and Suriname) and one in the **Albert Schweitzer hospital** in Dordrecht. After obtaining his **medical degree in 2008** he worked a short period as a physician at the department of **Obstetrics and Gynaecology at the Albert Schweitzer hospital in Dordrecht**.

Six months later Jashvant was accepted for a **PhD-program in Perinatal Epidemiology** under guidance of **professors Bonsel and Steegers at Erasmus MC**. This municipal program in the city of Rotterdam had been initiated to reduce the high perinatal mortality in the city. He was additionally granted the possibility to obtain a Master's degree in Epidemiology, which he finished in August 2012. It was during his PhD-period that Jashvant was extensively re-thinking his career choices and decided to pursue a career in **Psychiatry** instead of Obstetrics and Gynaecology. At the end of his PhD-research he therefore worked as an **emergency physician in Psychiatry at the Parnassia Bavo Group**, a large suburban mental hospital in the Rotterdam area.

Always the adventurer and a big traveller, at the end of his PhD-period Jashvant fell in love with the city of **New York**. After several meetings with his future boss and mentor **dr.**

Mazumdar he decided to pursue his career in the United States instead of The Netherlands. In April 2013 he started working as a **postdoctoral associate of Epidemiology at Weill Cornell Medical College** in New York under guidance of **dr. Mazumdar and dr. Memtsoudis**. He is currently studying for his medical degree to be recognised in the United States and may someday enter clinical medicine again. Being in New York, he has also signed up to run the **New York City Marathon** on November 3, 2013, for which he will raise money for charity. Although I sometimes cannot follow his choices in life I try to support him wherever I can; in the end, I truly can say I am a proud mother.

Chandra Kirpal, Jashvant's mother

PHD PORTFOLIO

Summary of PhD training and teaching activities

Name PhD candidate:	Virender Jashvant John Poeran
Erasmus MC Department:	Obstetrics & Gynaecology
Research school:	Netherlands Institute for Health Sciences (NIHES)
PhD period:	August 2009 - December 2012
Promotors:	Prof. dr. Gouke J. Bonsel Prof. dr. Eric A.P. Steegers
Copromotors:	Dr. Erwin Birnie Dr. Semiha Denktaş

	Year	Workload (ECTS)
1. PHD TRAINING		
General and specific courses		
Master of Science in Epidemiology, Netherlands Institute for Health Sciences, Rotterdam, The Netherlands (NIHES)	2010-2012	35
Introduction in 'R' programming	2012	0.1
Introduction in SPSS Data Entry	2010	0.3
International conferences		
Symposium 'How Maternity Care Develops in a Multi-Ethnic Urban Society', Rotterdam, The Netherlands: **oral presentation** *Urban perinatal health in Rotterdam*	2012	1.5
59th Annual Meeting of the Society for Gynecologic Investigation, San Diego, USA: **poster presentation** *Social deprivation and adverse perinatal outcomes among Western and non-Western pregnant women in a Dutch urban population*	2012	1
58th Annual Meeting of the Society for Gynecologic Investigation, Miami, USA: **poster presentation** *The effectiveness of risk selection in the Dutch obstetric care system*	2011	1
11th Congress of the European Society of Contraception and Reproductive Health, The Hague, The Netherlands: **oral presentation** *Unexpected large perinatal health inequalities in an urban, multi-ethnic population in the Netherlands*	2010	1.5
57th Annual Meeting of the Society for Gynecologic Investigation, Orlando, USA: **poster presentation** *Unexpected high levels of perinatal health inequalities in an urban multi-ethnic population in The Netherlands*	2010	1
National conferences		
Symposium 'Urban Perinatal Health' (in Dutch: 'Grootstedelijke Perinatale Gezondheid'), Rotterdam, The Netherlands: **oral presentation** *The Social Index and Urban Perinatal Health in Rotterdam* (Assisted in organising this symposium)	2011	3
NCVGZ Dutch Annual Public Health Conference (In Dutch: 'Nationaal Congres Volksgezondheid'), Amsterdam, The Netherlands: **oral presentation** *The Social index and perinatal outcomes in the city of Rotterdam*	2011	2
NCVGZ Dutch Annual Public Health Conference (In Dutch: 'Nationaal Congres Volksgezondheid'), Rotterdam, The Netherlands: **oral presentation** *Large perinatal health inequalities within the city of Rotterdam*	2010	2

	Year	Workload (ECTS)
Seminars, workshops, research meetings		
The Netherlands Perinatal Registry Annual Meetings *('PRN Contactdag')*, Utrecht, The Netherlands	2009-2012	0.8
Attending weekly and quarterly research meetings of the Department of Obstetrics and Gynaecology (and Urology) with three **oral presentations**, Rotterdam, The Netherlands	2009-2012	5
Attending the annual meetings of the Collaboration of Rotterdam Regional Gynaecologists' Teaching Hospitals (in Dutch: RGOC) 'Wladimiroff Symposium with one **oral presentation**, Rotterdam, The Netherlands	2010-2012	2
Attending the symposium on behalf of the 2.5 year anniversary of the 'Sophia Birth Centre', Rotterdam, The Netherlands	2012	0.2
Attending the symposium 'Home Birth or Hospital Birth', Maastricht, The Netherlands	2012	0.3
Visit from professor Eileen Hutton and staff, VU Medical Centre, Amsterdam, The Netherlands; **oral presentation**	2012	0.5
Visit from professor Lucilla Poston and staff, King's College, London, United Kingdom; **oral presentation**	2011	0.5
Regional Obstetric Collaboration meeting ('*VSV*'), Schiedam, The Netherlands with one **oral presentation**	2010	1
Other: Grant proposal assistance		
Assisted in the writing of several grant proposals for 'ZonMw' The Netherlands Organisation for Health Research and Development	2009-2012	5
Other: writing of municipal and national (public) health reports		
(Assisted in) writing of several national and municipal health reports for local and national (health) authorities: (1) 'ZonMw', (2) a collaboration of 40 small hospitals, (3) the Ministry of Health, (4) the Municipality of Rotterdam	2009-2012	15
2. TEACHING ACTIVITIES		
Lecturing		
Lectures and practicals on 'Perinatal Health' in The Netherlands and Rotterdam for Medical students; minor 'Circle of Life'	2011-2012	5
Lectures on 'Perinatal Health and Policy Implications' for Clinical Midwives aspiring to obtain a Master's degree as Physician Assistant	2011-2012	2
Lecture on 'Ethnicity and Perinatal Health' for NIHES Master's candidates; course 'Urban Perinatal Health and Health Care'	2012	1
Lecture for students doing their research electives from the Rotterdam University of Applied Sciences on 'The Dutch System of Obstetric Healthcare'	2011	1
Tutoring		
Tutoring first-year Medical students in the first four months of their studies, also preparing them for an academic environment	2012	1
Supervising (Master's) theses		
Medical student Arno F.G. Maas, title: 'The Social Index and Adverse Perinatal Outcomes in Rotterdam'	2010	2
Medical student Elva Hinborch, title: 'Environmental Factors Influencing Perinatal Health'	2010	1
Medical student Rénuka S. Birbal, title: 'Congenital Anomalies in the Borough of Hoek van Holland'	2011	2
Medical student Steffannie J.A.L. Hemelaar, title: 'The Incidence of Neonatal Herpes in The Netherlands 2005-2012'	2012	2

WORD OF THANKS

Dat ik hier vandaag sta, de laatste dag als promovendus, heb ik aan meerdere personen te danken. Ik heb mijn promotie-onderzoek ervaren als een tijd waarin ik een enorme persoonlijke en professionele groei heb doorgemaakt. Wetenschap bleek mij meer te trekken dan ik aanvankelijk had durven denken, en ik kreeg er nog betaald voor ook. Ondanks dat ik mijn toekomst al langere tijd zag als gynaecoloog, heb ik meerdere moeilijke keuzes durven nemen met een enorme impact op mijn toekomstbeeld, maar die mij uiteindelijk wel gelukkiger hebben gemaakt.

Allereerst wil ik iedereen bedanken die in een bepaalde vorm heeft bijgedragen aan de totstandkoming van dit proefschrift, in het bijzonder mijn promotoren **prof. dr. Gouke Bonsel** en **prof. dr. Eric Steegers**.

Gouke, ik herinner me onze eerste ontmoeting nog heel goed, je had heel wat te vertellen over ene 'Signalementstudie', omdat ik net uit een nachtdienst kwam is het meeste langs me heen gegaan. Dat was gelukkig niet het geval toen ik ook daadwerkelijk onder jouw hoede op de afdeling kwam. Het is niet te meten hoeveel ik van je heb geleerd over epidemiologie, statistiek, algemene wetenschap, en de meest actuele (maar ook de minder actuele) roddels. De manier waarop je altijd het onderste uit de kan wil halen, altijd nieuwsgierig bent naar hoe dingen in elkaar zitten, heeft erg inspirerend gewerkt. Ik ben erg blij dat jij mijn promotor bent geweest, dank voor de inspirerende jaren.

Beste Eric, na mijn onderzoek als student geneeskunde bleef ik je per e-mail stalken omdat ik graag gynaecoloog wilde worden en wilde promoveren op jouw afdeling. Dat laatste heb ik inmiddels bereikt en voor wat betreft dat eerste heb ik een van de moeilijkste gesprekken uit mijn leven met jou gevoerd. Dank voor de voortdurende steun, het begrip, maar vooral ook het getoonde vertrouwen. Ik hoop dat we in de toekomst nog zullen samenwerken.

Mijn eerste copromotor **dr. Erwin Birnie**. Beste Erwin, een man van initieel weinig woorden, maar wel de juiste. Jouw altijd scherpe commentaren op mijn manuscripten waren altijd een motivator om mezelf te blijven verbeteren en altijd kritisch te blijven; dit waardeer ik enorm. Iets waar ik altijd aan zal terugdenken zijn de 'soep-momenten' en later de 'vis-momenten' waar altijd weer de nieuwste roddels werden uitgewisseld.

Mijn tweede copromotor **dr. Semiha Denktaş**. Beste Semiha, ook met jou is het altijd prettig samenwerken geweest; met name de informele sfeer heb ik erg gewaardeerd. Ik kon met alles naar je toe komen, je bood altijd een luisterend oor en je gaf ook altijd advies hoe te handelen in moeilijke situaties. Ik heb erg veel respect voor hoe jij bent

gepromoveerd, een groot gemeentelijk programma hebt geleid, een groot landelijk programma leidt en daarnaast nog eens een moeder van twee kinderen bent. Ook aan jouw doorzettingsvermogen en multifunctionaliteit hoop ik me eens te meten.

Dit hele promotietraject was niet mogelijk geweest zonder financiële ondersteuning van de Gemeente Rotterdam in de vorm van het initialiseren van het programma 'Klaar voor een Kind'. Rotterdam heeft met dit project nog maar eens bewezen vooral te 'doen' en te 'durven' in plaats van te 'dralen'. In dit kader ben ik ook de GGD Rotterdam Rijnmond erg erkentelijk voor de samenwerking binnen dit programma, in het bijzonder **drs. H.J. (Ernie) van der Weg** en **dr. A.J.J. (Toon) Voorham**.

Bij de realisatie van dit proefschrift is voornamelijk gebruik gemaakt van gegevens uit de Perinatale Registratie Nederland (PRN). Graag wil ik dan ook bedanken het **PRN bestuur**, **drs. G. de Winter** en natuurlijk **dr. ir. C.W.P.M. (Chantal) Hukkelhoven**.

Graag wil ik ook bedanken de overige leden van de leescommissie voor hun kritische blik op mijn proefschrift: **prof. dr. ir. A. Burdorf**, **prof. dr. A.J. van der Heijden** en **prof. dr. A.P. Verhoeff**.

Ook de leden van de **grote commissie** wil ik hierbij bedanken voor hun tijd, hun kritische blik en de discussie over de inhoud van mijn proefschrift.

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- de Gemeente Rotterdam en het 'Klaar voor een Kind' programma (www.klaarvooreenkind.nl)
- J.E. Jurriaanse Stichting
- Medical Dynamics
- Mpluz
- Danone
- BMA-Mosos
- Goodlife Pharma
- AbbVie BV
- Nutricia
- Vasa Previa Foundation (www.vasaprevia.nl)

"*De Nederlandse Vasa Previa Foundation is een non-profit organisatie met als hoofddoel het terugbrengen van babysterfte of blijvend letsel als gevolg van vasa previa. Enkele activiteiten om dit te bereiken zijn het onder de aandacht brengen van het gevaar van vasa previa binnen de relevante beroepsgroepen en het aansturen op aanpassing van de medische protocollen, die belangrijk zijn voor diagnose en management van vasa previa. Daarnaast biedt de stichting een luisterend oor en advies voor iedereen die vasa previa meemaakt of heeft meegemaakt.*"

Virender Jashvant John Poeran was born at a gestational age of 38 weeks on March 21st, 1983 in the Diakonessen hospital in Paramaribo, Suriname, at exactly 6:40 AM. He came into this world in vertex presentation with a birthweight of 3560 grams, a height of 49 centimetres and a head circumference of 36.5 centimetres. The attending midwife granted him an Apgar score of 10/10.

At the age of 8 he moved to The Netherlands where he finished middle and high school. In the summer of 2001 he was accepted for **medical school** at **Erasmus University,** Rotterdam. During his medical training he stumbled upon the path of **research** in which he was guided by **professor Steegers** from the department of Obstetrics and **dr. van der Meijden** from the department of Dermatology. After obtaining his **medical degree** in **2008** he worked as a physician at the department of **Obstetrics and Gynaecology** at the **Albert Schweitzer hospital** in Dordrecht.

In 2009 he was accepted for a **PhD-program in Perinatal Epidemiology** under guidance of **professors Bonsel and Steegers** at **Erasmus MC**. He was additionally granted the possibility to obtain a **Master's degree in Epidemiology**, which he finished in August 2012, the same year in which he decided to pursue a career in **Psychiatry** instead of Obstetrics and Gynaecology. At the end of his PhD-research he therefore worked as an **emergency physician in Psychiatry** at the **Parnassia Bavo Group**. However, in the fall of 2012 he fell in love with the city of **New York** and is currently working as a **postdoctoral associate of Epidemiology** at **Weill Cornell Medical College** in New York.