SOCIAL OBSTETRICS

ADDRESSING INEQUALITIES IN PERINATAL HEALTHCARE

JACQUELINE LAGENDIJK

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ADDRESSING INEQUALITIES IN PERINATAL HEALTHCARE

SOCIALE VERLOSKUNDE
AANPAKKEN VAN ONGELIJKHEDEN IN DE PERINATALE GEZONDHEIDSZORG

Proefschrift

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PROMOTIECOMMISSIE

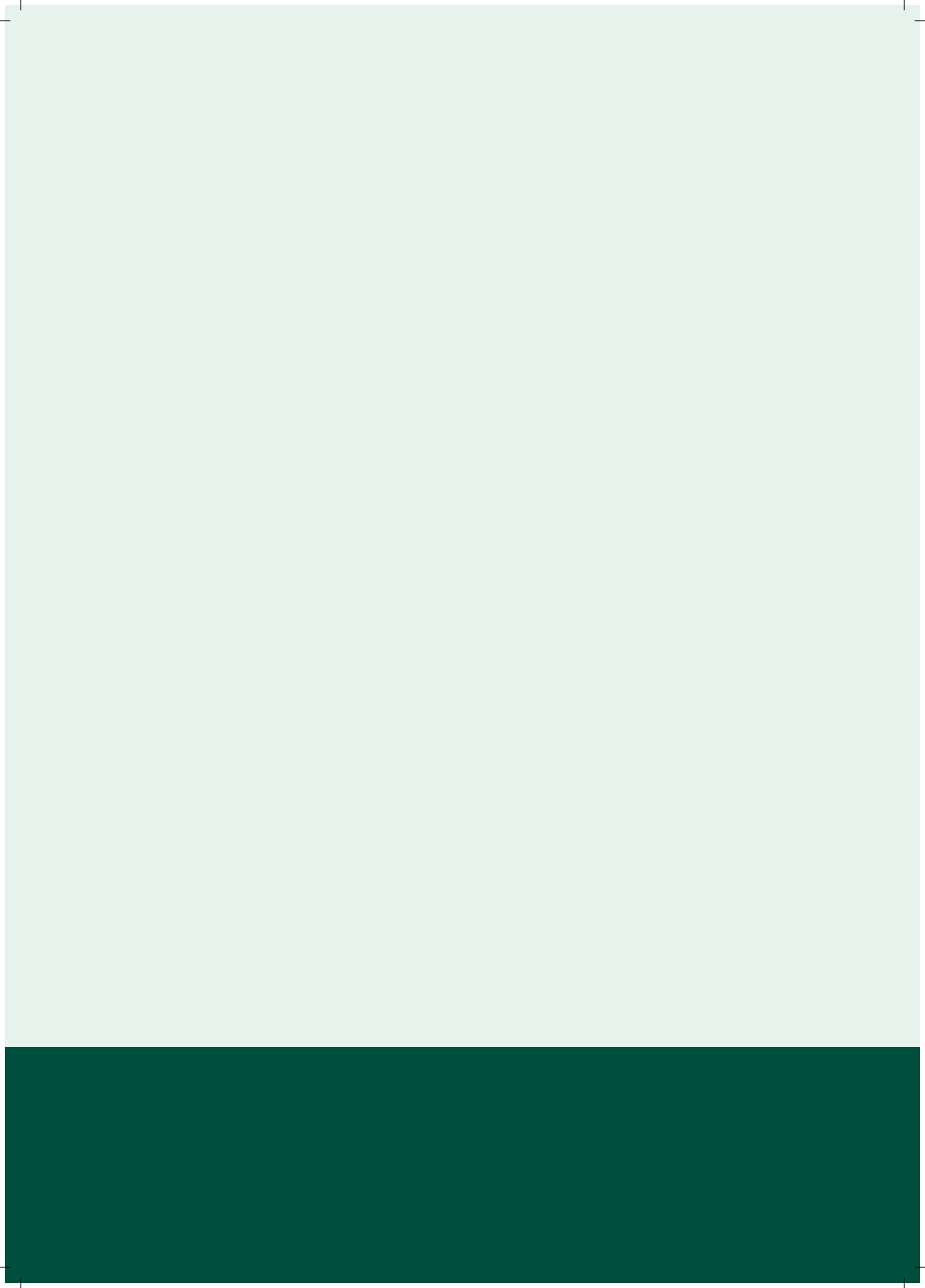|	
Promotor:	Prof. dr. E.A.P. Steegers
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Paranimfen

Drs. V.E.E.G. Ritfeld

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"If we cannot now end our differences,
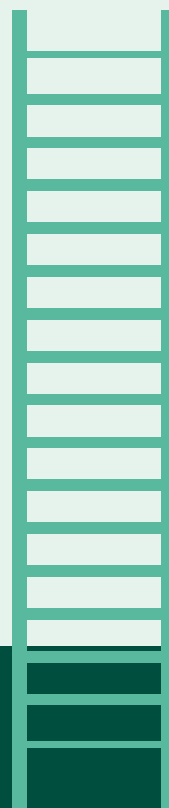*at least we can help make the world safer for diversity"*
John F. Kennedy

CONTENTS

CHAPTER 1

Introduction

Substantial evidence exist that health status diminishes continually with social status; a phenomena called the social gradient in health: the lower a person's socioeconomic status, the higher the incidence of health problems, disease, and premature death [1-11]. Children with a lower socioeconomic status are more likely to be in poor health at birth, partly because their mothers are less able to provide a healthy fetal environment [2 5 6 12 13]. Poor health at birth is associated with poorer adult health outcomes, which in turn provide less than optimal conditions for the next generation.

Causal pathways for health inequalities can be related to factors that partly determine socioeconomic status (e.g. a person's income or educational attainment) or by a bigger concept of self-control or self-efficacy [2 4 5 10]. For example, income can be considered as a way of acquiring more possessions that are material and as a way of keeping one's social position and one's social value, hereby increasing a person's sense of control. Geographical inequalities in health are also present in the Netherlands, where perinatal mortality ranges from 5.3 to 10.2 per 1000 births between non-deprived and deprived neighbourhoods, respectively [3 9 11]. Perinatal mortality includes both neonatal deaths in the first week of life and fetal deaths (stillbirths). The underlying reasons for these negative associations are not completely clear [2 6]. Possible explanations include: worse nutritional status, increased frequency of cigarette smoking, lower and later use of antenatal care, and higher levels of adverse psychological factors.

The strong position of primary care in the Netherlands, which includes easy access of care for the mother and her (unborn) child from pregnancy onwards, provides potential to promote equity in maternal and infant health [2]. In order to develop effective approaches to reduce existing inequalities, a better understanding of the determinants of the uptake of primary care is required. Additionally, professionals should screen for these determinants and institute effective strategies that address these risks and diminish their negative impact on health [2 14 15]. The evaluation of these novel interventions should consider health-related outcomes (e.g. neonatal morbidities) along with measurements of self-efficacy (e.g. a person's empowerment), as both are associated with a person's socioeconomic status [13 15].

Social determinants of health may be at least as important as major biological and genetic risk factors in determining perinatal health outcomes. The reproductive healthcare system that includes preconception, antenatal and postpartum care, is an excellent starting point since what mothers do even before they are pregnant may have profound consequences for on an individual's life course health [2 6].

AIM OF THE THESIS

The overarching aim of this thesis is to investigate the effectiveness of preventive strategies to reduce adverse perinatal health outcomes and low empowerment particularly among women with a low socioeconomic status and their offspring. These strategies will be implemented during the preconception -, prenatal -, postpartum -, and early childhood period, in order to establish comprehensive care beyond the boundaries of the separate social and medical domains of care.

OBJECTIVES PER PART

Part I: The effectiveness of strategies aimed at improving neonatal health outcomes
- To evaluate the impact of the "Ready for a baby" program on perinatal mortality, preterm birth and small for gestational age births in Rotterdam (chapter 2).
- To evaluate the effectiveness of the intervention embedded in the national "Healthy Pregnancy 4 All-1" C-RCT in reducing the incidence of babies being born preterm and/or small for gestational age (chapter 3).
- TTo validate the prognostic model of the R4U-scorecard and improve its functionality in antenatal risk-surveillance (chapter 4).

Part II: The rationale for strategies aimed at improving the provision and the content of postpartum care to increase maternal and child well-being
- TTo describe the rationale for expanding risk-guided care beyond the pregnancy period to maternity care and Preventive Child Health Care (chapter 5).
- TTo determine whether inequity exists in postpartum care provision in the Netherlands and whether a lack of postpartum care is associated with subsequent healthcare expenditure (chapter 6).
- TTo describe the rationale of a C-RCT evaluating the effectiveness of client-tailored, risk-based maternity care to increase maternal empowerment postpartum (chapter 7).
- TTo evaluate the effectiveness of the intervention embedded in the national "Healthy Pregnancy 4 All-2" C-RCT in reducing the incidence of a low maternal empowerment score in the early postpartum period (chapter 8).

OUTLINE OF THE THESIS

This thesis has two parts, each of which draws evidence from different programmes and datasets.

Part one describes an evaluation of the effectiveness of different strategies to improve neonatal health outcomes through the local "Ready for a Baby" programme and the national "Healthy Pregnancy 4 All-1" program. In addition, the validity of the R4U (Rotterdam Reproductive Risk Reduction) scorecard, used to identify pregnant women at risk during their first antenatal visit, is reported and an updated version is presented.

The **'Ready for a Baby' program (2008-2012)** aimed to improve communication and collaboration between caregivers in the obstetric healthcare chain. Health researchers established a collaboration with municipal policymakers in order to develop a comprehensive program aimed at improving perinatal health in the city [16]. Multiple interventions including organisational, service delivery and non-medical service interventions were implemented in parallel in an attempt to improve health outcomes.

Stemming from this experience, the **'Healthy Pregnancy 4 All-1' program (2011-2015)** was initiated to evaluate the effectiveness of two interventions in either the preconception period or the antenatal period to reduce adverse neonatal outcomes [17][18]. Accordingly, two sub-studies were specified: a population-based prospective cohort study focussing on the effectiveness of customised preconception care [19] and a Cluster-Randomised Controlled Trial (C-RCT) focussing on early identification of groups at risk for adverse neonatal outcomes using the Rotterdam Reproductive Risk Reduction (R4U) scorecard [18]. The R4U scorecard assesses a pregnant women's risk of adverse pregnancy outcomes based on multiple medical, obstetric, and other non-medical determinants.

Part two describes the rationale for expanding the scope of these strategies from pregnancy and childbirth towards the postpartum period and early childhood, leading to the development of the national follow-on "Healthy Pregnancy 4 All-2" program. The effectiveness of the embedded C-RCT, which aimed to improve maternal empowerment and reduce early adversity during the postpartum period, is reported. Furthermore, the current degree of inequalities in uptake of postpartum care and its association with healthcare expenditure in the year following childbirth is outlined.

The **'Healthy Pregnancy 4 All-2' program (2014-2017)** aimed to improve the care for young children and their mothers by extending the continuum for risk selection and tailored care from the preconception and prenatal period towards the postpartum, early childhood and interconception period [3]. Three sub-studies were specified: 1) a C-RCT focussing on

a structured risk assessment during pregnancy and tailored maternity care to increase maternal empowerment postpartum (this thesis), a prospective cohort study aiming to identify children with a high risk of growth and development problems through extended risk surveillance in Preventive Child Health Care (PCHC) services, and a prospective cohort study aiming to implement and evaluate interconception care in PCHC centres [3].

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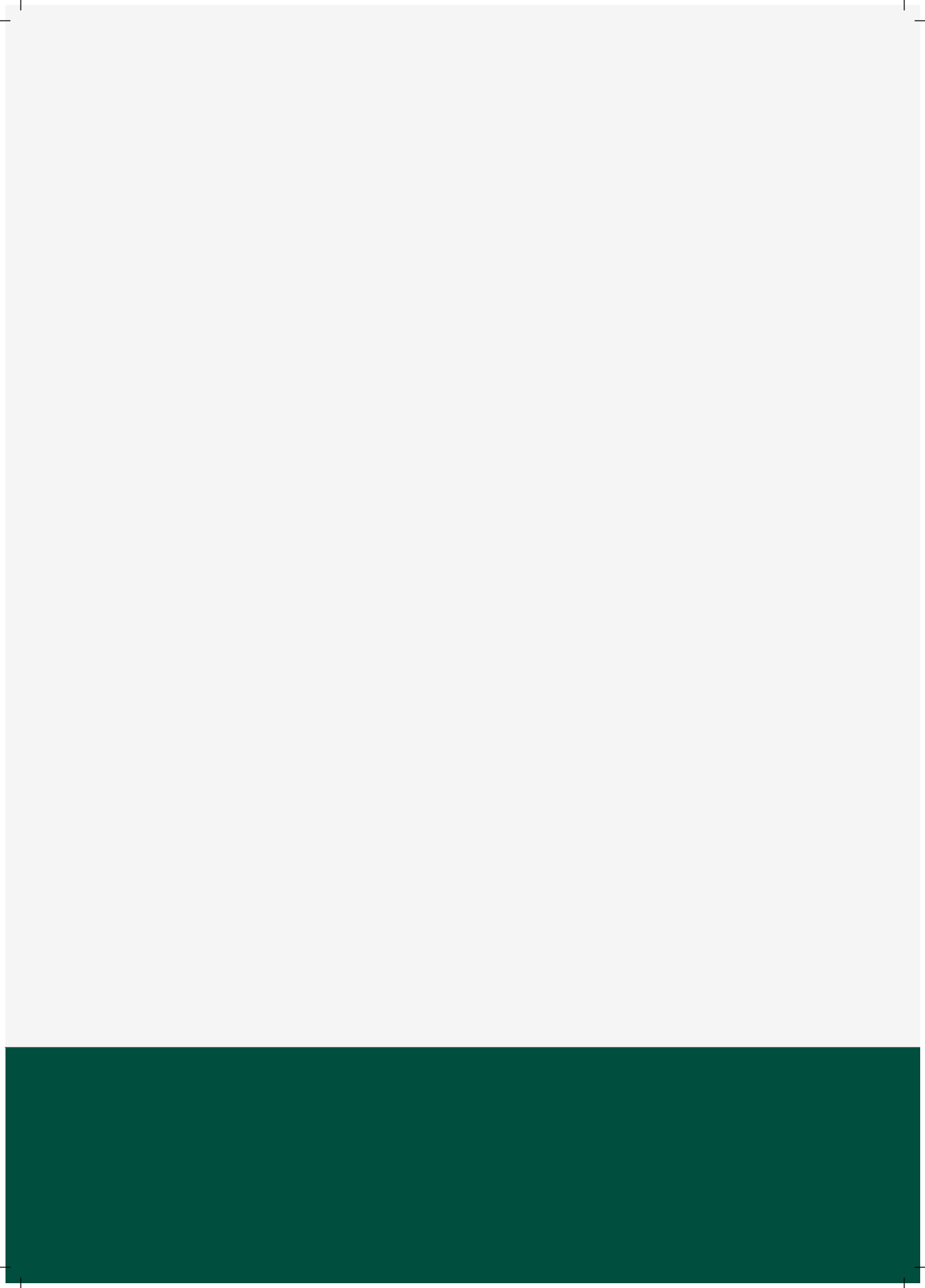
PART I

Impact of public health strategies on perinatal health inequalities

CHAPTER 2

**Did an urban perinatal health programme in Rotterdam, the Netherlands, reduce adverse perinatal outcomes?
A register-based retrospective cohort study.**

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ABSTRACT

Objectives
to study the effect of an urban perinatal health programme in Rotterdam, the Netherlands, on perinatal outcomes.

Design
A retrospective cohort study with difference-in-differences analysis using individual-level perinatal outcome data from the Dutch Perinatal Registry 2003-2014 linked to Central Bureau of Statistics data of migration background and individual disposable household income.

Intervention
The programme consisted of perinatal health promotion, risk selection and risk-guided pregnancy care, and a new primary care child birth centre. The programme was implemented during 2009-2012.

Primary outcome measures
We compared trends in perinatal mortality, preterm delivery, and small for gestational age births between targeted urban neighbourhoods in Rotterdam (n=61,415) and all other urban neighbourhoods in the Netherlands (n=881,202). The effect of the programme was modelled as a change in trend of each perinatal outcome in the treatment group post-intervention compared to the control population from January 2010 onwards. All analyses were adjusted for maternal age, parity, ethnicity, and individual-level low socio-economic status. We also conducted a stratified analysis by SES.

Results
During 2003-2014 downward trends in perinatal mortality (adjusted odds ratio (aOR) 0.9439 per year, 95% confidence interval (CI) 0.9362-0.9517), preterm birth (aOR 0.9970 per year, 95% CI 0.9944-0.9997), and small for gestational age births (aOR 0.9809 per year, 95% CI 0.9787-0.9831) in the entire study population were observed. No demonstrable changes in these trends were found in the intervention group after the programme had started. The stratified analyses by socio-economic status showed no changes in trends post-intervention in both strata either.

Conclusions
The programme had no demonstrable effects on perinatal outcomes. The intervention may not have reached a sufficient proportion of the population or has provided too little contrast to the widespread attention for inequalities in pregnancy outcomes occurring simultaneously in the Netherlands.

INTRODUCTION

In the 2000s the Netherlands had a relatively high perinatal mortality, ranking third highest among 26 European countries in 2004 and sixth highest in 2010 [1-3]. Considerable regional inequalities in perinatal outcomes were reported within the Netherlands [4]. In Rotterdam, the second largest city in the Netherlands, perinatal mortality was markedly higher than nationally, most notably in its deprived neighbourhoods [5]. In a child-birth cohort study, these neighbourhood differences in various perinatal outcomes could largely be attributed to the increased prevalence of medical, as well as, social risk factors [6].

In response to these findings, the Erasmus MC in collaboration with the Municipal Health Service Rotterdam-Rijnmond initiated an urban perinatal health programme, called "Ready for a Baby", with the aim to improve perinatal outcomes in Rotterdam. The programme consisted of several intervention components across the pregnancy care chain: preconception health promotion, improved risk selection and risk guided care during pregnancy, and the establishment of a primary care birth centre. These components were gradually introduced in the period 2009-2012, and, depending on the component, reached nearly city wide coverage (preconception health promotion) or only specific neighbourhoods (e.g. primary care birth centre) [7].

Perinatal mortality in the Netherlands has gradually reduced over the past two decades. Favourable trends in risk factors may have contributed, including a reduction in smoking by pregnant women, less multiple births, increased use of ultrasonography at 20 weeks gestation for detection of congenital abnormalities, and improved care for very premature babies [8]. The introduction of the "Ready for a Baby" programme in Rotterdam was conceptualised as a natural experiment [9]. In order to evaluate whether this programme has had an additional impact on the secular trends of decline in unfavourable perinatal outcomes, the Difference-in-Differences (DiD) method was considered the appropriate approach to evaluate the effects of an intervention in an observational study. In this method the change in health in the intervention group before and after the introduction of the intervention (difference) can be distinguished from changes in health over time in both the intervention and control groups (differences) [10]. Therefore, the aim of this study was to determine the influence of the urban perinatal health programme "Ready for a Baby" on adverse perinatal health outcomes.

METHODS

Study design and population

We conducted a retrospective cohort study on routinely collected birth data from the Dutch Perinatal registry, enriched with national registers with personal information to evaluate the influence of a community intervention with a difference-in-difference analysis. The start in year 2003 was determined by individual information on socio-economic status (SES) becoming available in national registers. The year 2014 was the last year with complete information available at time of this study. The study population consisted of all singleton deliveries in urban neighbourhoods in the Netherlands during the study period, comprising approximately 45% of all deliveries in the Netherlands. A neighbourhood was defined as a postal code area and an urban neighbourhood as a postal code area with more than 1500 houses per square kilometre [11]. The intervention group consisted of all deliveries in all 51 urban neighbourhoods in 10 out of 14 boroughs in Rotterdam, where at some point in time during the intervention period a component of the urban perinatal health programme was implemented. The control group comprised all deliveries in other urban postal code areas in the Netherlands, including six untargeted urban neighbourhoods in Rotterdam.

Programme description

The "Ready for a Baby" programme had three components: health promotion in preconception care, improved risk selection and risk guided care, and establishment of a primary care birth centre in the university medical centre. The content of the programme has been published in detail before and will be described here briefly [7].

The first component of the programme aimed to promote preconception health by three strategies. The first strategy aimed to collectively increase awareness of the importance of preconception health through mass media campaigns (including flyers, posters, editorials, and advertisements in local Dutch and Turkish newspapers, on busses and trams, at offices of health care providers, pharmacists, retailers, and at churches and mosques). Besides increasing awareness, these campaigns aimed to promote favourable attitudes and behaviours for a healthy pregnancy, such as the use of folic acid and the cessation of smoking and alcohol use. This strategy targeted all citizens in Rotterdam and was not confined to the intervention group. The second strategy used peer education to increase preconception-related health literacy and motivation to attend preconception care consultations, especially amongst low SES and migrant groups [12]. Peer educators recruited about 2,300 participants during the course of the programme for peer education group sessions through their existing network and community meeting places (e.g. mosques and schools). The sessions were interactive, often in multiple languages, and provided participants information on the influence of lifestyle changes on pregnancy outcomes, and additionally advised on where to obtain individual consultations. The third strategy in targeted neighbourhoods was the

provision of individual preconception care consultations by general practitioners (GPs) and community midwives. At least 43 couples attended an individual consultation after receiving tailored health promotion from a web-based preconception health assessment "Preconceptiewijzer.nl" [12 13].

The second component of the programme aimed to improve risk selection and risk guided care by use of the Rotterdam Reproductive Risk Reduction (R4U) scorecard along with the Shared-Care model in the targeted neighbourhoods [14-16]. The R4U scorecard is a systematic risk assessment in the first trimester of pregnancy focussing on medical and non-medical risk factors related to adverse pregnancy outcomes, including for example migration background and low household income [15 16]. The Shared-Care model is an approach to risk guided care that has three elements: 1) continuity of care (e.g. a case manager is assigned to high risk women who need care from different professionals, care pathways are defined for risks identified in the R4U), 2) patient centeredness (e.g. through fostering of self-management, and efforts to combine appointments to different care providers), and 3) interprofessional collaboration (e.g. through formulating a joint set of aims and ambitions for collaboration including care pathways, training in team work, and interprofessional education) [14].

The R4U-scorecard guided the care pathways in the Shared-Care model through templates describing the consecutive steps a professional was advised to take to reduce the potential contribution of identified risk factors for adverse perinatal health outcomes. In order to enhance the efficiency and quality of the local antenatal health care, all details of instruments and templates were discussed during meetings with community midwives, obstetricians, and social workers under guidance of a member of the "Ready for a Baby" programme. Since midwives are usually the first point of contact of a pregnant woman, the vast majority (n=46) of all community midwives in the intervention area were trained to use and integrate the R4U scorecard along with the Shared-Care model into their daily practice. In three selected boroughs the programme supported the use of care pathways in midwifery practices and hospitals with multidisciplinary meetings to follow up on high risk cases.

The third component of the programme was the establishment of a primary care birth centre (PCBC) in the Erasmus University Medical Centre in Rotterdam. The PCBC is a separate facility led by community midwives, where women can deliver at their own discretion if a hospital delivery is not medically indicated but social factors make a home delivery less preferable [17]. The PCBC aimed to provide risk-directed care by assessing the risk status of each woman at different intervals (e.g. upon arrival at the PCBC, during labour, and postpartum). Figure 1 shows how the different parts of the intervention were introduced from July 2009 until December 2012. The first component of the programme, preconception health promotion, targeted primarily women in selected neighbourhoods, but by nature of the

instrument the mass media approach had a reach in all neighbourhoods in Rotterdam. The second component, the risk selection and shared care, was implemented in the selected neighbourhoods. The third component, the new birth centre, primarily served pregnant women from the community midwife practices around Erasmus MC. So the different components were introduced at different moments in time and in different neighbourhoods.

Figure 1. A graph showing the different parts of the intervention "Ready for a Baby" that were introduced from July 2009 until December 2012.
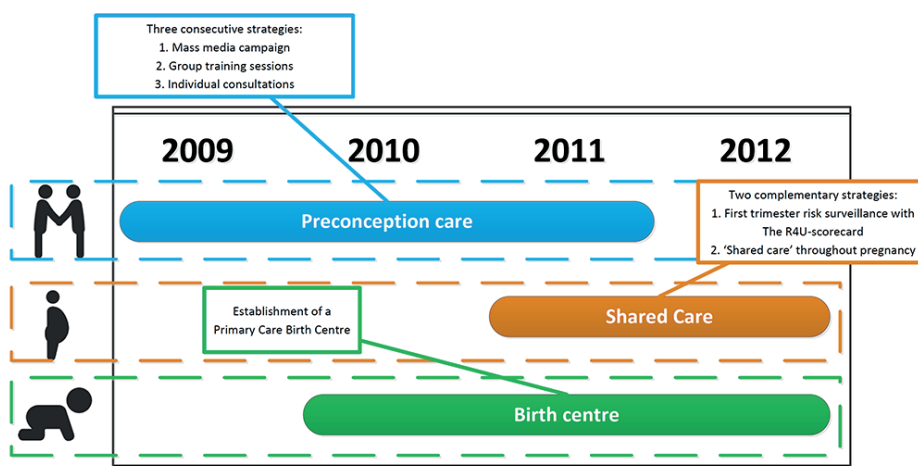
Data

We used data from the Dutch Perinatal Registry 2003-2014 (Perined, https://www.perined.nl). The Dutch Perinatal Registry is a registry with information provided by midwives, gynaecologists, paediatricians, and general practitioners and contains demographic characteristics, medical risk factors, obstetric history, and pregnancy and neonatal outcomes. Through individual-level linkage the Dutch Perinatal Registry was enriched with two nationwide registries from Statistics Netherlands. Household income from the Integral Household Income (IHI) register, based on tax information from 2003 onwards, was used to define low socio-economic status by lowest 20% disposable household income. The second, the Dutch population register, provided information on migration background.

A trusted third party (an in-house service at Statistics Netherlands) merged these datasets using four-digit postal code, birth date of the mother and birth date of the child after which the identifying variables were removed. The merged one-way coded dataset was made available in a secure research environment at Statistics Netherlands for analysis.

Results were rigorously checked for identifiability by Statistics the Netherlands before they were released from the secure research environment for publication. This procedure is in accordance with Dutch legislation and the Dutch Code of Conduct for Medical Research for use of anonymous data for research purposes without an explicit informed consent. Deliveries with less than 24 completed weeks of gestation from the dataset were excluded, because most of these deliveries will end in stillbirth. These stillbirths aren't registered in the population registry according to Dutch law so can't be linked to household income and migration background data, which were required for the statistical analysis. Records with other missing covariates for the statistical analysis were also excluded.

Outcomes

Our primary outcomes were: perinatal mortality, preterm birth, and small for gestational age (SGA) birth. Perinatal mortality was defined as the number of stillbirths from 24 completed weeks of gestation or early neonatal deaths (i.e. death of a live born baby within the first seven days of life) per 1,000 singleton births. Preterm birth was defined as birth before 37 completed weeks of gestation per 1,000 singleton livebirths. SGA was defined as any baby that was smaller than the 10th centile, corrected for gestational age in weeks and sex, according to the Visser curve, per 1,000 singleton livebirths [18].

Statistical analysis

A DiD analysis was conducted with logistic regression models for perinatal mortality, preterm birth, and SGA as dichotomous dependent variables. Each model has three key independent variables and several confounders. The first variable is the year of birth as continuous variable, which captures the trend over time and is expressed by the odds ratio (OR) for trend per year that represents the yearly increase or decrease in likelihood of perinatal outcome. The second variable is a dummy variable with value 1 for the intervention group and value 0 for the control group. This dummy variable reflects differences in perinatal health between intervention and control groups at baseline. The third variable is an interaction term between years since start of the programme as continuous variable and intervention group status. This term corresponds to the DiD estimate, as it presents differences in perinatal health trends between intervention and control groups post-intervention over and above the underlying temporal trends (15). It is important to note that this DiD estimate presents the change in slope of the trend for the intervention group post-intervention. Thus, we did not model the invention as an immediate effect (step function) that introduces a constant difference between intervention and control group from start of the programme until 2014. The programme was gradually introduced from July 2009 onwards and, given the duration of pregnancy, we assumed that the intervention could take effect first from 2010 onwards. Therefore, an DiD analysis on change in the trend per year in the intervention group after 2010 was considered most appropriate. A crucial assumption in the DiD analysis is the parallel trend assumption, i.e. that pre-

intervention trends were similar in intervention and control groups over the period 2003-2009. This assumption was assessed with graphs of the perinatal outcomes per year 2003-2009 (supplementary file 1-3). The assumption was also tested with a regression model on the pre-intervention period 2003-2009 with an interaction between intervention and a dummy variable for year of birth 2003-2009, which indicates whether the baseline difference between intervention and control group changed per year. The graphs and regression model showed that the parallel trend assumption was not violated for any of the perinatal outcomes (supplementary file 4).

We included four major risk factors that were targeted in the intervention (SES, ethnicity, parity and age) as confounders. This step was taken to improve the comparability of the intervention and control groups in the analysis. SES is associated with perinatal outcomes and was differently distributed in the intervention and control groups, therefore lowest 20 percentile household income was used as indicator of SES. As the intervention targeted particularly low-SES women, we also conducted stratified analyses according to SES. Ethnicity is associated with perinatal outcomes and with urbanisation, and hence was included as confounder. Non-Dutch ethnicity was defined as any person who was born in another country than the Netherlands (first generation migration background) or had at least one parent born in another country (second generation migration background). We also included parity and age at delivery as potential confounders.

We conducted several sensitivity analyses for lagged programme effects, adjustment for covariate imbalance and the individual program component effects. Lagged programme effects were studied with a regression model with an interaction of the intervention and a dummy variable for each year in the period 2010-2014. Adjustment for covariate imbalance in our main analysis was handled by ordinary regression analysis, which is appropriate given the number of observations [19]. Propensity score matching as alternative approach was conducted as a sensitivity analysis [20]. For the propensity score model we used the same set of variables for matching as in the main analysis (age, parity, migration background, household income). Matching was done per year of delivery using the nearest neighbour algorithm. We evaluated the balance as sufficient by inspecting a table with the distribution of the outcomes and covariates. As a final sensitivity analysis, we studied a possible intervention effect in the boroughs that were targeted by these interventions, compared to the control population, using the same difference-in-difference model as in the main analysis.

Patient and public involvement
This research was done without patient or public involvement. However, the research question was proposed by the Municipal Health Service Rotterdam as part of their legal task of monitoring population health (Dutch Public Health Law).

RESULTS

Study population

From 2003-2014, a total of 2,116,226 deliveries was available in the Dutch Perinatal Registry, encompassing 96.6% of all deliveries in the Netherlands in that period [20-21]. A total of 1,031,683 deliveries was registered within an urban neighbourhood of the intervention and control group, thus representing 49% of all deliveries in the Netherlands (figure 2). We excluded all deliveries before 24 weeks of completed gestation and all multiple births, which were 38,931 deliveries (3.8% of all deliveries) of which 3,704 perinatal deaths (39% of all perinatal deaths (Supplementary File 5)). In addition, we excluded deliveries that could not be matched to Statistics Netherlands data (household income or migration background) (16,319 deliveries, 1.6%) or lacked information on any other confounder (33,819 deliveries, 3.3%). Thus, the total study population comprised 942,614 deliveries (figure 2).

Figure 2. A flow chart displaying how the study population was generated from the Perined data for the Netherlands, 2003-2014.
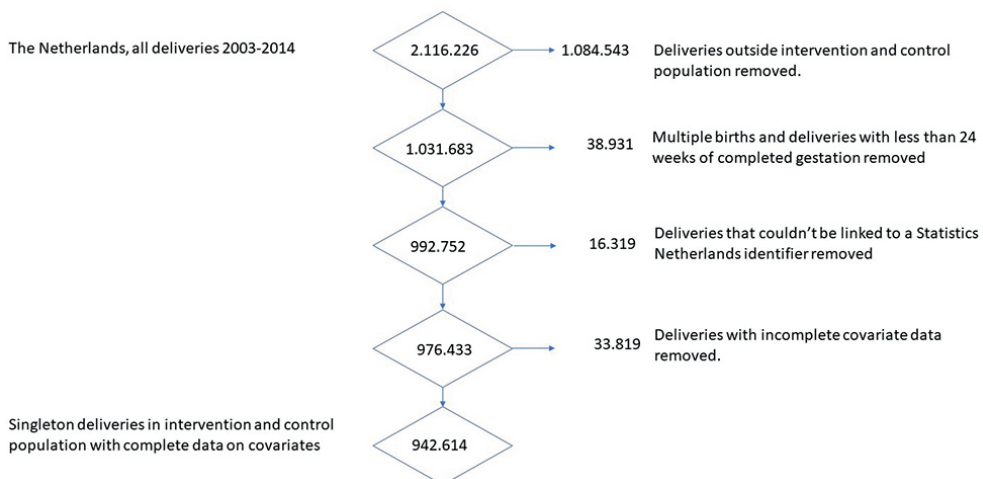
In the intervention group 83% of all deliveries took place in deprived urban neighbourhoods, whereas in the control group the corresponding figure was 39% (table 1). Women delivering in the intervention group were more often younger, multiparous, non-Dutch, and more often had a household income below the 20th percentile. The percentage of women with more than one of these risk factor was considerably higher in the intervention population (59%) than in the control population (34%). In addition, in deprived neighbourhoods in the intervention group pregnant women had a higher prevalence of risk factors than pregnant women in deprived neighbourhoods of the control group, specifically non-Dutch background

(73% vs. 49%) and low dispensable household income (46% vs. 35%). The incidence rates for perinatal mortality, preterm birth and for SGA were higher in the intervention group than in the control group, both in deprived as well as non-deprived neighbourhoods.

Differences-in-differences analysis

Table 2 shows that the likelihood of perinatal mortality decreased during 2003-2014 by about 6% per year across all urban neighbourhoods in the Netherlands (adjusted odd ratio (aOR) 0.9439/year (95% confidence interval (CI) 0.9362-0.9517)). SGA decreased by 2% per year (aOR 0.9809 (95% CI 0.9787-0.9831)) and preterm birth decreased by 0.3% per year (aOR 0.9970 (95% CI 0.9944-0.9997)). Small differences in annual trends between the intervention and the control group were observed, albeit not statistically significant. The DiD analysis on the effect of the urban perinatal health programme showed that during the post-intervention period in the intervention group perinatal mortality (aOR 1.0535 (95% CI 0.9889-1.1223) increased slightly each year, whereas preterm birth (aOR 0.9809 (95% CI 0.9619-1.0004) and SGA (aOR 0.9928 (95% CI 0.9772-1.0086)) showed modest improvements.

The analysis showed that for the pre-intervention period, after adjustment for important confounders, perinatal mortality was 14% lower in the intervention population than in the control population (aOR 0.8601, 95% CI 0.7534-0.9819). Preterm birth (aOR 1.0962 (95% CI 1.0505-1.1440)) and SGA (aOR 1.1313 (95% CI 1.0935-1.1703)) were higher in the intervention population than in the control population.

The stratified analysis by socio-economic status of the pregnant woman showed very similar results for pregnant women with low SES and pregnant women with higher SES. The intervention had no demonstrable influence on trends in any of the perinatal outcomes post-intervention (table 3).

The sensitivity analysis for lagged programme effects did not indicate any lagged programme effect (supplementary file 6). The sensitivity analysis using propensity score matching gave similar results to the main analysis (supplementary file 7). No intervention effects were observed for individual programme components (supplementary file 8).

Table 1: Socio-demographic characteristics, presence of risk factors, and perinatal mortality, preterm birth, and small-for-gestational age over the period 2003-2014 in intervention group (targeted urban neighbourhoods in Rotterdam) and control group (other urban neighbourhoods in the Netherlands), stratified by deprivation of postal code area.*

	Intervention area			Control areas		
	All	Deprived	Non-deprived	All	Deprived	Non-deprived
Total no. of deliveries	61,415	50,727	10,688	881,202	340,914	540,288
Parity						
Nulliparous	48% / 29,308	46% / 23,180	57% / 6,128	47% / 418,074	47% / 160,270	48% / 257,804
1-2	44% / 26,880	45% / 22,716	39% / 4,164	47% / 417,538	46% / 156,892	48% / 260,646
3+	9% / 5,227	10% / 4,831	4% / 396	5% / 45,590	7% / 23,752	4% / 21,838
Ethnicity (non Dutch)	68% / 41,702	73% / 36,951	44% / 4,751	37% / 321,950	49% / 167,943	29% / 154,007
Age of mother						
<25	20% / 12,423	22% / 11,319	10% / 1,104	13% / 110,465	18% / 60,191	9% / 50,274
25-29	30% / 18,361	31% / 15,679	25% / 2,682	28% / 250,322	31% / 105,834	27% / 144,488
30-34	31% / 18,917	29% / 14,522	41% / 4,395	37% / 327,361	33% / 111,349	40% / 216,012
35-39	16% / 9,616	15% / 7,491	20% / 2,125	19% / 164,403	16% / 53,252	21% / 111,151
>=40	3% / 2,098	3% / 1,716	4% / 382	3% / 28,651	3% / 10,288	3% / 18,363
Socio-economic status						
lowest 20% disposable household income	42% / 25,919	46% / 23,431	23% / 2,488	24% / 212,405	35% / 120,488	17% / 91,917
More than 1 risk factor†	59% / 36,139	63% / 29,638	43% / 6,501	34% / 299,727	49% / 129,418	27% / 170,309
Perinatal mortality (/1,000 stillbirths & live singleton births)						
2003-2009	6.5 / 223	6.7 / 202	4.8 / 21	6.2 / 3,173	7.1 / 1,436	5.7 / 1,737
2010-2014	5.1 / 136	5.7 / 116	3.2 / 20	4.5 / 1,667	5.2 / 725	4.0 / 942
Preterm birth rate (/1,000 live singleton births)						
2003-2009	63 / 2,166	64 / 1,917	57 / 249	56 / 28447	60 / 12,066	54 / 16,381
2010-2014	60 / 1,611	61 / 1,254	57 / 357	55 / 20376	59 / 8,098	53 / 12,278
SGA rate (/1,000 live singleton births)						
2003-2009	109 / 3,756	113 / 3,377	87 / 379	84 / 42,505	96 / 19,330	76 / 23,175
2010-2014	94 / 2,513	98 / 2,007	80 / 506	76 / 28,249	86 / 11,898	70 / 16,351

* Deprivation is defined as the lowest quintile of postal codes by status score, an area level composite index of individual household income, education and employment status calculated every four years by the Netherlands Institute of Social Research. † The following risk factors are considered: nulliparous, non Dutch ethnicity, age of the mother <25 year, lowest 20% disposable household income

Table 2. Logistic regression models with difference-in-differences analyses of the effect of the urban perinatal health programme on perinatal mortality, preterm birth and SGA.

	Perinatal mortality			Preterm birth			SGA		
	OR	95% CI		OR	95% CI		OR	95% CI	
trend per year	0.9439	0.9362	0.9517	0.9970	0.9944	0.9997	0.9809	0.9787	0.9831
difference intervention and control group	0.8601	0.7534	0.9819	1.0962	1.0505	1.1440	1.1313	1.0935	1.1703
programme effect	1.0535	0.9889	1.1223	0.9809	0.9619	1.0004	0.9928	0.9772	1.0086
low SES	1.3761	1.2917	1.4660	1.2017	1.1764	1.2275	1.4417	1.4170	1.4668
ethnicity non Dutch	1.2690	1.3462	1.1963	1.0068	1.0264	0.9876	1.2927	1.3134	1.2722
parity 0 (reference)	1.0000			1.0000			1.0000		
parity 1-2	0.7560	0.7120	0.8026	0.6114	0.5998	0.6232	0.5340	0.5254	0.5427
parity 3+	1.2823	1.1541	1.4248	0.8218	0.7894	0.8554	0.4871	0.4687	0.5062
age <25 (reference)	1.0000			1.0000			1.0000		
age 25-34	0.9401	0.8654	1.0212	0.9786	0.9529	1.0050	0.8554	0.8377	0.8735
age >=35	1.2238	1.1112	1.3479	1.0762	1.0423	1.1111	0.9339	0.9100	0.9585
baseline rate*	8.6	7.8	9.4	71	69	74	155	151	159

Perinatal mortality is defined as still birth from 24 weeks onwards plus early neonatal mortality. The total number of observations for the perinatal mortality model is 942,614. Preterm is defined as born before a gestational age of 37 weeks and SGA is defined as a birth weight below the 10th percentile corrected for gestational age and sex. The total number of observations for the preterm birth and SGA models is 937,639. * for perinatal mortality per 1,000 live and stillbirths, for preterm birth and SGA per 1,000 live births

Table 3. Stratified analysis by socio-economic status of the mother with logistic regression models with difference-in-differences analyses of the effect of the urban perinatal health programme on perinatal mortality, preterm birth and SGA.

Lowest quintile household income	Perinatal mortality			Preterm birth			SGA		
	OR	95% CI		OR	95% CI		OR	95% CI	
trend per year	0.9516	0.9380	0.9654	1.0008	0.9958	1.0059	0.9864	0.9825	0.9903
difference intervention and control group	0.8209	0.6786	0.9929	1.1677	1.0957	1.2444	1.1296	1.0749	1.1871
programme effect (change in trend per year from 2010 onwards)	1.0673	0.9761	1.1670	0.9767	0.9481	1.0062	0.9947	0.9718	1.0181
ethnicity non Dutch	1.3668	1.5181	1.2307	0.8716	0.9024	0.8418	1.0167	1.0450	0.9893
parity 0 (reference)	1.0000			1.0000			1.0000		
parity 1-2	0.7392	0.6652	0.8214	0.7826	0.7545	0.8117	0.6258	0.6084	0.6438
parity 3	1.0544	0.8960	1.2407	1.0134	0.9539	1.0766	0.5605	0.5308	0.5918
age <25 (reference)	1.0000			1.0000			1.0000		
age 25-34	1.0666	0.9478	1.2004	0.9566	0.9188	0.9960	0.8914	0.8647	0.9190
age >=35	1.2893	1.1082	1.4999	1.1172	1.0597	1.1778	0.9334	0.8947	0.9737
baseline rate*	11.2	9.8	12.7	70	67	74	181	175	188

Household income above 20th percentile	Perinatal mortality			Preterm birth			SGA		
	OR	95% CI		OR	95% CI		OR	95% CI	
trend per year	0.9402	0.9308	0.9497	0.9961	0.9930	0.9992	0.9787	0.9761	0.9813
difference intervention and control group	0.9084	0.7553	1.0926	1.0472	0.9884	1.1094	1.1500	1.0978	1.2046
intervention effect (change in trend per year from 2010 onwards)	1.0294	0.9403	1.1270	0.9841	0.9585	1.0103	0.9876	0.9663	1.0093
ethnicity non Dutch	1.2108	1.3017	1.1262	1.0665	1.0913	1.0423	1.4399	1.4678	1.4126
parity 0 (reference)	1.0000			1.0000			1.0000		
parity 1-2	0.7592	0.7057	0.8166	0.5592	0.5467	0.5721	0.4956	0.4859	0.5056
parity 3+	1.4987	1.3058	1.7201	0.7298	0.6905	0.7713	0.4446	0.4206	0.4700
age <25 (reference)	1.0000			1.0000			1.0000		
age 25-34	0.8417	0.7489	0.9461	0.9544	0.9206	0.9894	0.8185	0.7950	0.8427
age >=35	1.1253	0.9880	1.2816	1.0446	1.0024	1.0886	0.9142	0.8835	0.9459
baseline rate*	9.2	8.1	10.4	80	76	83	179	173	185

Perinatal mortality is defined as still birth from 24 weeks onwards plus early neonatal mortality. The total number of observations for the perinatal mortality model is 238,226 for low SES and 704,388 for high SES. Preterm is defined as born before a gestational age of 37 weeks and SGA is defined as a birth weight below the 10th percentile corrected for gestational age and sex. The total number of observations for the preterm birth and SGA models is 236,737 for low SES and 701,524 for high SES. Low SES was defined as the lowest 20 percentile by disposable household income per year. * for perinatal mortality per 1,000 live and stillbirths, for preterm birth and SGA per 1,000 live births

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DISCUSSION

In this study, the influence of an urban perinatal health programme in Rotterdam on perinatal health outcomes was evaluated by a DiD approach, an analytical technique for natural experiment evaluation in an observational setting. The DiD analysis could not demonstrate that the introduction of the programme influenced trends in perinatal mortality, preterm birth, or small-for-gestational age birth in the post-intervention years in the intervention group.

Strengths of this study include the large study population and the available information on important confounders. The nationally representative sample of almost a million pregnancies during the period 2003-2014 had a good discriminatory power to estimate the effect of the programme on a rare outcome like perinatal mortality. The linkage across three routinely collected data registries provided pregnancy outcomes and socioeconomic data, allowing adjustment for important medical and social determinants in the statistical analysis. The modelling was checked for robustness by several sensitivity analyses. Our study also has several limitations pertaining to data availability, and to the DiD analysis. Availability of data was dictated by the registers used. SES is an important determinant of perinatal health, but in our analysis only disposable household income was available. Highest educational attainment based on certified diploma registers had a high percentage of missing values, and could therefore not be included as a covariate in our study. Using only a one-dimensional representation of SES might not fully adjust for residual differences between the intervention and the control group.

The DiD analysis applied in this study has several limitations. First, a crucial assumption is that trends in outcome in intervention and control groups in the years before the intervention are parallel, i.e. have a constant difference, captured in the DiD logistic regression model by the difference at baseline (table 2). Evaluation showed that this assumption was not violated. The DiD analysis accounts for time-invariant differences between the intervention and control groups, as well as any factors that equally change over time in both groups. The descriptive information showed that in the intervention neighbourhoods in Rotterdam there is much higher accumulation of risk factors among pregnant women, and that a much larger proportion of women lived in deprived neighbourhoods. In our analysis we adjusted for these risk factors to ensure comparability of intervention and control groups. However, it cannot be discarded that women in Rotterdam have experienced less favourable trends in other, unobserved, risk factors during the observation period of this study, which may have attenuated any potential effect of the intervention. Second, the DiD makes the strong assumption that the precise timing of the intervention is completely at random, creating exogenous variation that allows causal inference. This assumption cannot be formally tested, but it must be acknowledged that the urban perinatal health programme was designed and

implemented in response to the relatively high perinatal mortality in the Netherlands and opportunities for improvement in prevention and child health care in Rotterdam.

At the start of the "Ready for a Baby" programme, adjusted for risk factors, perinatal mortality was lower in Rotterdam than in other urban areas in the Netherlands. This favourable position of Rotterdam might be partly attributed to the large concentration of hospitals in Rotterdam and attention in the local child health care system for high-risk women since they constitute a relatively large part of all pregnant women. Therefore, the DiD analysis may have not been able to capture additional change in an already decreasing trend in perinatal mortality in the intervention group. A linked issue is that improvements in perinatal health care may have occurred also in other neighbourhoods. These co-interventions may have biased the comparisons between intervention and control groups.

It is important to consider that this study evaluates the possible influence of a population intervention rather than the effects of an intervention at individual level. The content of the complex intervention comprises universal primary prevention and changes in quality and delivery of child health care, which are notoriously difficult to evaluate at individual level. Also, the different components of the intervention were introduced gradually during the intervention period and had varying coverage: from nearly city wide to certain neighbourhoods only. In the analysis, all pregnant women in the targeted urban neighbourhoods with the intervention were considered to be exposed to the intervention, whether or not these women were actually reached by activities within the complex intervention. This might have attenuated observed associations, when a substantial number of women would not have been included in components of the programme. Only 43 couples attended an individual preconception consultation by a general practitioner in all of Rotterdam, which is too small to expect any effect on population level. In contrast, the majority of midwifes was trained to use the R4U scorecard and Shared Care method, resulting in a large uptake of the second component of the programme. However, we lack information on compliance of the implementation of the R4U and Shared Care in daily practice.

A fair question to ask is whether the DiD evaluation of the programme "Ready for a Baby" sufficiently reflects the underlying improvements. The programme had several interacting components of universal and high-risk prevention embedded in improvements in quality of child health care and can therefore be characterized as a complex intervention. Complex interventions usually develop in phases from series of pilots to fully scaled up programs and should preferably be tested using a phased approach, starting with a series of pilot studies and moving on to an exploratory and then a definitive evaluation [21]. The programme "Ready for a Baby" could be described as the first phase in the development of a programme to reduce inequalities in perinatal outcomes and the lessons learnt from the programme were included in the next phase, the "Healthy Pregnancy 4 All" programme [22]. Therefore, the

results of the evaluation of the first programme "Ready for a Baby" should be interpreted with care. Other studies and other research methods are needed to better understand the underlying mechanisms of reach, uptake and effectiveness of specific programme activities (e.g. action research to understand the dynamics of the developing pilots).

In conclusion, in this DiD analysis we could not demonstrate an influence of the urban perinatal health "Ready for a baby" on perinatal outcomes. Epidemiological evidence of inequalities in adverse pregnancy outcomes is compelling enough to justify continued efforts to develop a health care system that can properly deal with social risk factors. It is advised to evaluate such a system when it has been brought to scale and matured sufficiently to have a discernible impact [23]. The "Ready for a Baby" programme generated a lot of attention both locally and nationally for the relevance of social determinants of pregnancy outcomes and for the development of methods to integrate obstetric care and the social domain, which is a valuable outcome in itself.

SUPPLEMENTARY INFORMATION

Supplementary file 1. Perinatal mortality by year for the control (blue line) and intervention area (red line). Perinatal mortality is defined as still birth from 24 weeks onwards plus early neonatal mortality per 1,000 births.
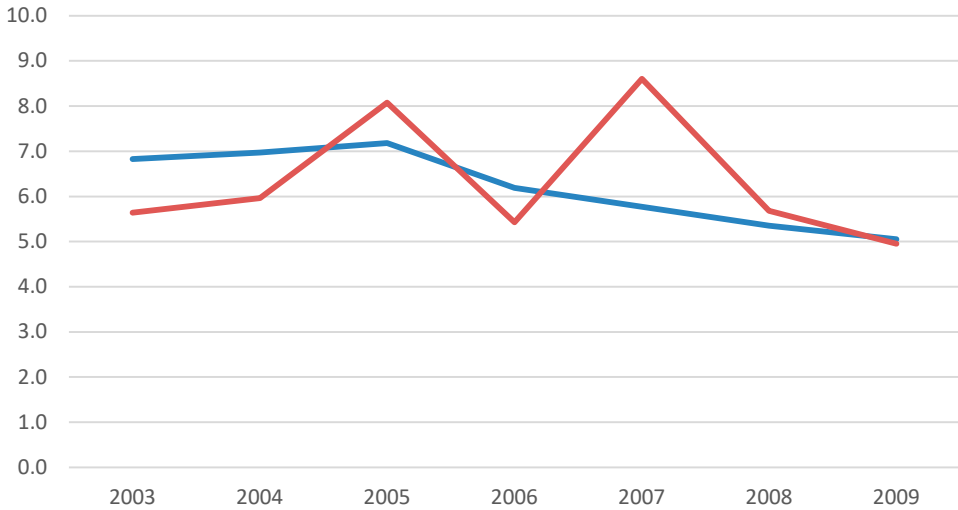
Supplementary file 3. Small for gestational age (SGA) for the control (blue line) and intervention area (red line). SGA is defined as a birth weight below the 10th percentile for gestational age per 1,000 live births.
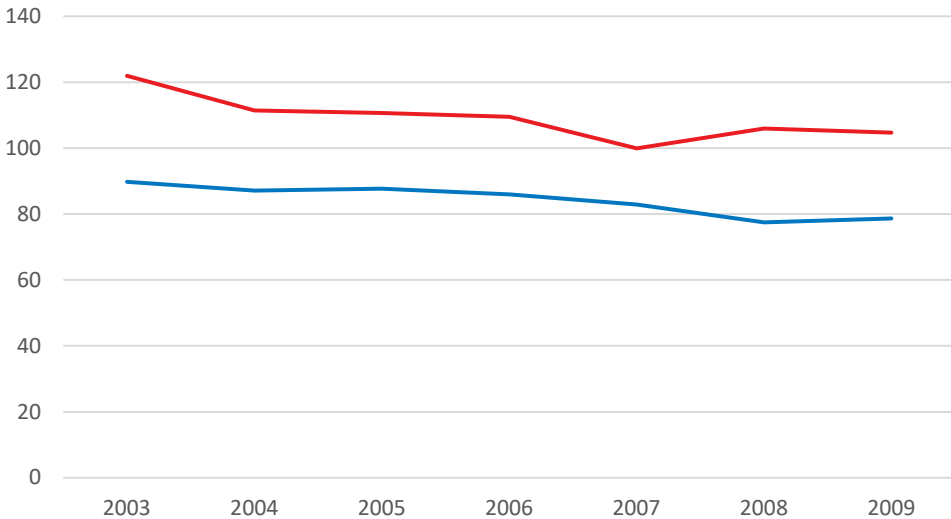
Supplementary file 4. Logistic regression models that test the parallel trend assumption for perinatal mortality, small for gestational age and preterm birth during the preintervention period 2003-2009. Perinatal mortality is defined as still birth from 24 weeks onwards plus early neonatal mortality. Preterm is defined as born before a gestational age of 37 weeks. SGA is defined as a birth weight below the 10th percentile for gestational age. The time trend is defined as a continuous variable per year with 2003 as reference. Possible deviations from the time trend are defined as interactions between time dummies (reference 2003, per year) * intervention. The total number of observations is 542,824 for perinatal mortality and 539,909 for SGA and preterm birth.

independent variables	Perinatal mortality			SGA			Preterm birth		
	OR	95% CI		OR	95% CI		OR	95% CI	
Time (years, 2003-2009, reference 2003, continuous variable)	0.942	0.926	0.959	0.975	0.970	0.979	1.004	0.998	1.010
difference intervention and control	0.654	0.452	0.948	1.184	1.086	1.291	0.976	0.865	1.101
*interaction time (dummy)*intervention (reference 2003)*									
2004	1.127	0.672	1.889	0.933	0.825	1.056	1.195	1.015	1.407
2005	1.620	1.002	2.621	0.958	0.846	1.084	1.069	0.905	1.263
2006	1.158	0.679	1.975	0.980	0.865	1.111	1.203	1.021	1.419
2007	1.938	1.193	3.148	0.910	0.799	1.037	1.060	0.893	1.257
2008	1.376	0.812	2.334	0.999	0.879	1.134	1.149	0.973	1.357
2009	1.272	0.740	2.185	1.018	0.897	1.155	1.064	0.900	1.258
poverty	1.318	1.218	1.425	1.432	1.400	1.464	1.189	1.157	1.223
dutch	0.783	0.728	0.842	0.794	0.778	0.811	0.985	0.960	1.010
parity (n=2)	0.737	0.684	0.794	0.533	0.522	0.544	0.606	0.591	0.621
parity (n=3+)	1.292	1.133	1.473	0.492	0.467	0.517	0.804	0.762	0.848
age 25-34	0.893	0.809	0.987	0.845	0.823	0.868	0.971	0.939	1.005
age >=35	1.179	1.049	1.325	0.912	0.882	0.943	1.055	1.012	1.099

Supplementary file 5: the number and percentage of low SES pregnant women that are poor by year and the threshold of disposable household income that defines poverty.

Year	No. of deliveries				No. of low SES deliveries				% low SES deliveries			
	Total	NL - other	Control	Intervention	Total	NL - other	Control	Intervention	Total	NL-other	Control	Intervention
2003	187,578	99,171	82,431	5,976	37,749	15,196	19,858	2,695	20%	15%	24%	45%
2004	178,146	93,027	79,504	5,615	35,847	14,253	19,138	2,456	20%	15%	24%	44%
2005	175,231	90,968	78,604	5,659	35,238	13,793	18,983	2,462	20%	15%	24%	44%
2006	174,501	90,425	78,608	5,468	35,080	13,575	19,103	2,401	20%	15%	24%	44%
2007	171,618	88,861	77,465	5,292	34,482	13,275	18,901	2,306	20%	15%	24%	44%
2008	175,762	90,093	80,095	5,574	35,342	13,731	19,335	2,276	20%	15%	24%	41%
2009	178,213	90,717	81,587	5,909	35,789	13,981	19,408	2,401	20%	15%	24%	41%
2010	175,533	88,461	81,501	5,571	35,227	13,623	19,310	2,294	20%	15%	24%	41%
2011	175,346	87,821	81,488	6,037	35,189	13,283	19,357	2,549	20%	15%	24%	42%
2012	172,888	85,136	81,474	6,278	34,695	12,561	19,541	2,593	20%	15%	24%	41%
2013	166,248	81,786	78,553	5,909	33,389	12,331	18,672	2,387	20%	15%	24%	40%
2014	170,837	83,752	81,056	6,029	34,276	12,540	19,372	2,364	20%	15%	24%	39%

Supplementary file 6: Lagged treatment effect post intervention (dummies 2010-2014). Perinatal mortality is defined as still birth from 24 weeks onwards plus early neonatal mortality. Preterm is defined as born before a gestational age of 37 weeks. SGA is defined as a birth weight below the 10th percentile for gestational age. The total number of observations is 542,824 for perinatal mortality and 539,909 for SGA and preterm birth.

independent variables	Perinatal mortality			SGA			Preterm birth		
	OR	95% CI		OR	95% CI		OR	95% CI	
difference intervention and control before intervention	0.874	0.761	1.004	1.143	1.103	1.185	1.079	1.031	1.129
change in control area year 1 post intervention (2010)	0.807	0.725	0.897	0.911	0.885	0.938	1.017	0.984	1.051
change in control area year 2 post intervention (2011)	0.716	0.640	0.802	0.898	0.873	0.925	0.973	0.940	1.006
change in control area year 3 post intervention (2012)	0.758	0.679	0.847	0.876	0.851	0.902	0.944	0.912	0.976
change in control area year 4 post intervention (2013)	0.650	0.577	0.733	0.897	0.871	0.924	0.977	0.944	1.011
change in control area year 5 post intervention (2014)	0.608	0.538	0.687	0.891	0.865	0.917	0.957	0.925	0.991
intervention effect year 1 post intervention	1.169	0.786	1.740	0.955	0.860	1.060	1.081	0.956	1.221
intervention effect year 2 post intervention	0.724	0.442	1.188	0.983	0.888	1.087	1.020	0.902	1.153
intervention effect year 3 post intervention	1.074	0.717	1.608	0.925	0.835	1.025	0.932	0.821	1.058
intervention effect year 4 post intervention	1.254	0.825	1.905	0.964	0.870	1.068	0.920	0.809	1.047
intervention effect year 5 post intervention	1.465	0.980	2.189	0.947	0.854	1.050	0.956	0.842	1.086
poverty	1.377	1.292	1.467	1.442	1.417	1.467	1.202	1.176	1.228
dutch	0.790	0.745	0.838	0.774	0.762	0.787	0.993	0.974	1.012
parity (n=2)	0.756	0.712	0.802	0.534	0.525	0.543	0.612	0.600	0.623
parity (n=3+)	1.284	1.156	1.427	0.487	0.469	0.506	0.822	0.790	0.856
age 25-34	0.937	0.862	1.018	0.854	0.836	0.872	0.979	0.953	1.005
age >=35	1.214	1.103	1.337	0.931	0.907	0.956	1.076	1.042	1.111

Supplementary file 7: Propensity score matching. Perinatal mortality is defined as still birth from 24 weeks onwards plus early neonatal mortality. Preterm is defined as born before a gestational age of 37 weeks. SGA is defined as a birth weight below the 10th percentile for gestational age. The total number of observations is 122,766 for perinatal mortality and 122,133 for SGA and preterm birth.

independent variables	Perinatal mortality OR	95% CI		SGA OR	95% CI		Preterm birth OR	95% CI	
linear time	0.970	0.945	0.995	0.983	0.975	0.990	0.997	0.988	1.006
difference intervention and control	0.920	0.775	1.091	1.254	1.197	1.312	1.207	1.140	1.279
intervention effect - slope change	1.003	0.929	1.084	0.990	0.970	1.010	0.982	0.958	1.006
poverty	1.287	1.103	1.502	1.316	1.263	1.372	1.239	1.176	1.305
dutch	0.654	0.544	0.786	0.718	0.686	0.752	1.020	0.965	1.078
parity (n=2)	0.876	0.744	1.032	0.577	0.553	0.603	0.762	0.722	0.804
parity (n=3+)	1.353	1.056	1.733	0.489	0.449	0.533	0.989	0.902	1.084
age 25-34	0.985	0.811	1.195	0.845	0.805	0.886	0.898	0.844	0.956
age >=35	1.132	0.885	1.448	0.858	0.803	0.917	0.965	0.889	1.047

Supplementary file 8: The intervention effect (slope change per year) of three interventions in selected boroughs (peer education, care pathways and birth centre) compared to the control population, using the same difference-in-difference model as in the main analysis. Perinatal mortality is defined as still birth from 24 weeks onwards plus early neonatal mortality. Preterm is defined as born before a gestational age of 37 weeks. SGA is defined as a birth weight below the 10th percentile for gestational age. The analyses are adjusted for time (year), difference between intervention and control group at t=0 (2003), age, parity, migration background and household income.

	perinatal mortality OR	95% CI		SGA beta	95% CI		preterm birth OR	95% CI	
peer education	1.1826	1.0393	1.3457	0.9825	0.9489	1.0171	0.9634	0.9226	1.0059
care pathways	1.1165	0.9512	1.3104	0.9951	0.9552	1.0366	0.9855	0.9364	1.0372
birth centre	1.0583	0.9606	1.1659	0.9896	0.7054	1.0139	0.9706	0.9414	1.0008

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2

CHAPTER 3

Antenatal non-medical risk assessment and care pathways to improve pregnancy outcomes: a cluster randomised controlled trial

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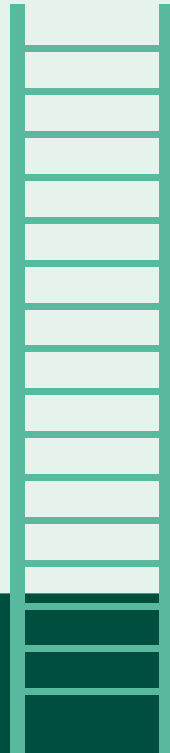
ABSTRACT

Background

Social deprivation negatively affects health outcomes but receives little attention in obstetric risk selection. We investigated whether a combination of (1) risk assessment focused on non-medical risk factors, lifestyle factors, and medical risk factors, with (2) subsequent institution of risk-specific care pathways, and (3) multidisciplinary consultation between care providers from the curative and the public health sector reduced adverse pregnancy outcomes among women in selected urban areas in the Netherlands.

Methods

We conducted a cluster randomised controlled trial in 14 urban municipalities across the Netherlands. Prior to the randomisation, municipalities were ranked and paired according to their expected proportion of pregnant women at risk for adverse outcomes at birth. The primary outcome was delivery of a preterm and/or small for gestational age (SGA) baby, analysed with multilevel mixed-effects logistic regression analysis adjusting for clustering and individual baseline characteristics.

Findings

A total of 33 community midwife practices and nine hospitals participated throughout the study. Data from 4302 participants was included in the Intention To Treat (ITT) analysis. The intervention had no demonstrable impact on the primary outcome: adjusted odds ratio (aOR) 1.17 (95% CI 0.84 to 1.63). Among the secondary outcomes, the intervention improved the detection of threatening preterm delivery and fetal growth restriction during pregnancy (aOR 1.27 (95%CI 1.01 to 1.61)).

Interpretation

Implementation of additional non-medical risk assessment and preventive strategies into general practices is feasible but did not decrease the incidence of preterm and/or SGA birth in the index pregnancy in deprived urban areas.

Trial registration

Netherlands National Trial Register (NTR-3367).

INTRODUCTION

Social deprivation negatively affects health outcomes. This association is already apparent before birth and extends into early childhood [1-4]. In addition to the negative impact of medical and obstetric risk factors, multiple studies have shown a strong association between non-medical risk factors and adverse pregnancy outcomes. Key examples of such risk factors include low socioeconomic status (SES), living in a deprived neighbourhood, ineffective social integration into society, smoking, and psychosocial stressors [5-8]. The increased prevalence of non-medical risk factors and the accumulation of such factors are responsible for at least part of the overrepresentation of adverse pregnancy outcomes in deprived urban areas within high-income countries [7][9]. Risk assessment and subsequent implementation of preventive measures in antenatal health care with the aim to reduce adverse pregnancy outcomes should, therefore, take both medical and non-medical risk factors into account. However, current risk selection during pregnancy mainly focuses on medical risks, and integration between the curative and public health sector is scarce [10].

In the Netherlands, obstetric risk selection is based on the 'List of Obstetric Indications'(LOI), which specifies manifest conditions that define a low, medium, or high-risk pregnancy. These conditions are single medical or obstetric risk factors, that indicate whether a patient's care during pregnancy or parturition is to be supervised by a community midwife or an obstetrician [11].

The R4U scorecard is a comprehensive risk assessment tool which can, in addition to the LOI, be used by obstetric care providers to identify psychological, social, lifestyle, obstetric and non-obstetric care related factors [12]. The total R4U score is strongly associated with adverse pregnancy outcomes and shows a clear gradient across categories of SES and ethnicity [13].

We conducted a cluster randomised controlled trial (C-RCT) to assess the effectiveness of using the R4U scorecard in conjunction with institution of appropriate care pathways and multidisciplinary consultations, to reduce the incidence of adverse pregnancy outcomes. The study was conducted among pregnant women in selected urban areas in the Netherlands with an overrepresentation of adverse pregnancy outcomes [14-16]. This study is part of the 'Healthy pregnancy 4 All' (HP4All) programme, a nationwide study evaluating strategies to improve pregnancy outcomes, in particular among deprived populations [14].

METHODS

Trial design

We conducted a C-RCT in 14 municipalities in the Netherlands. The Daily Board of the Medical Ethics Committee Erasmus MC approved the study (METC 2012-322). The study protocol was peer-reviewed and published, and was registered at the Netherlands National Trial Register (NTR-3367)[17]. Municipalities were selected based on multiple criteria: 1) size (having more than 70,000 inhabitants), 2) disproportionally high prevalence of risk factors for adverse pregnancy outcomes (high and/or low maternal age, primiparity, non-western ethnicity, and low SES), 3) a high incidence of adverse pregnancy outcomes (delivery of a small for gestational age baby (SGA), preterm delivery, and perinatal mortality (mortality from the 22th week of gestation until 7 days postnatally)), and 4) a higher than average case-fatality rate [14]. The case-fatality rate is the proportion of perinatal mortality amongst neonates with a so-called 'BIG4' condition: congenital anomalies, preterm birth, SGA, and/or an Apgar score below seven at five minutes after birth.[18] A more detailed description of the selection process of municipalities has been published before.[14] All community midwife practices and hospitals located in the participating municipalities were invited to participate in the trial.

Participants

The 14 selected municipalities were divided into ten clusters; five municipalities in the northern part of the Netherlands were merged into one cluster due to the intended formation of a so called 'obstetric collaborative network' in that area [17]. An obstetric collaborative network is an inter-professional care system in which community midwives, obstetricians, and maternity care providers share local guidelines and protocols. All women with a singleton pregnancy living in a selected municipality and booking their first antenatal visit at one of the participating community midwife practices or at a participating hospital were eligible for this trial. Exclusion criteria included an obstetric emergency situation or being in labour during the initial visit.

Intervention

In the intervention clusters, participating obstetric care providers used the R4U scorecard as a risk assessment tool at the first antepartum visit. They did so in addition to their conventional risk assessment approach (LOI-based). The R4U scorecard guided coordination of antepartum care through systematic risk assessment for medical and non-medical risk factors for adverse pregnancy outcomes (Online Resource 1). To increase uniformity in questioning within the R4U, a 'script' text was formulated for each separate item as a literal text. A positive response indicated presence of the risk factor. Risk factors were selected after a broad literature search and complemented with detailed epidemiological information of prevalence and risk estimates derived from well-documented large birth cohort studies [17]. Risk factors were weighted based on their relative risk for adverse pregnancy outcomes [12].

Scores for individual risk factors were added up to form a total score (range R4U 0-98). A predefined cut-off score was based on data from a pilot study in the Netherlands from 2010 to 2011; a score of 16 points or higher was selected to identify women in the upper 20% of risk scores [19]. In the current study, a cumulative R4U score of ≥16 points implied a follow-up action via a case-based discussion in a multidisciplinary setting. In addition, the institution of appropriate individual care pathways was guided by particular single, or a set of multiple, risk factors (figure 1).

Case-based multidisciplinary consultations involved community midwives, obstetricians and other healthcare professionals, such as paediatricians or social workers. With this approach optimal linkage was sought between the public health sector and the curative care sector. The aim of the meeting was to agree on a customised antepartum policy for each individual patient [17]. Obstetric care providers were in addition allowed to discuss participants in these discussions to their own discretion, independently of the cumulative R4U score. As a result, participants with relevant individual risk factors could also be discussed when the cumulative score was below 16 (figure 1).

Prior to start of the study, 28 templates of care pathways were developed based on the medical and non-medical risk factors incorporated in the R4U. These templates consisted of a set of steps a healthcare professional was advised to take in an attempt to reduce the potential contribution of one or more risk factors to developing an adverse pregnancy outcome. As such, each care pathway could, for example, direct the user to a specific health care provider, or to a health care organisation, public health care organisation, or an office for legal or financial support. When there was existing evidence for interventions to address modifiable risk factors this was used for the contents of the pathway. To enhance the efficiency of the care provided, care pathways are explicit as to which caregiver will be responsible. To facilitate local adaptation of this new way of organising antenatal care, details of the care pathways were discussed during meetings with community midwives, obstetricians, social workers, and a city council representative. In these meetings the templates for the pathways were complemented with the availability of local facilities and health insurance agreements, and refined through direct interaction with relevant local health care providers, and organisations. In addition, the introduction of organized meetings to customize care pathways induced a change in the mutual professional relationship between care providers of different echelons. An example of a care pathway, in this case for psychosocial risk factors, is added in the Online Resource 2.
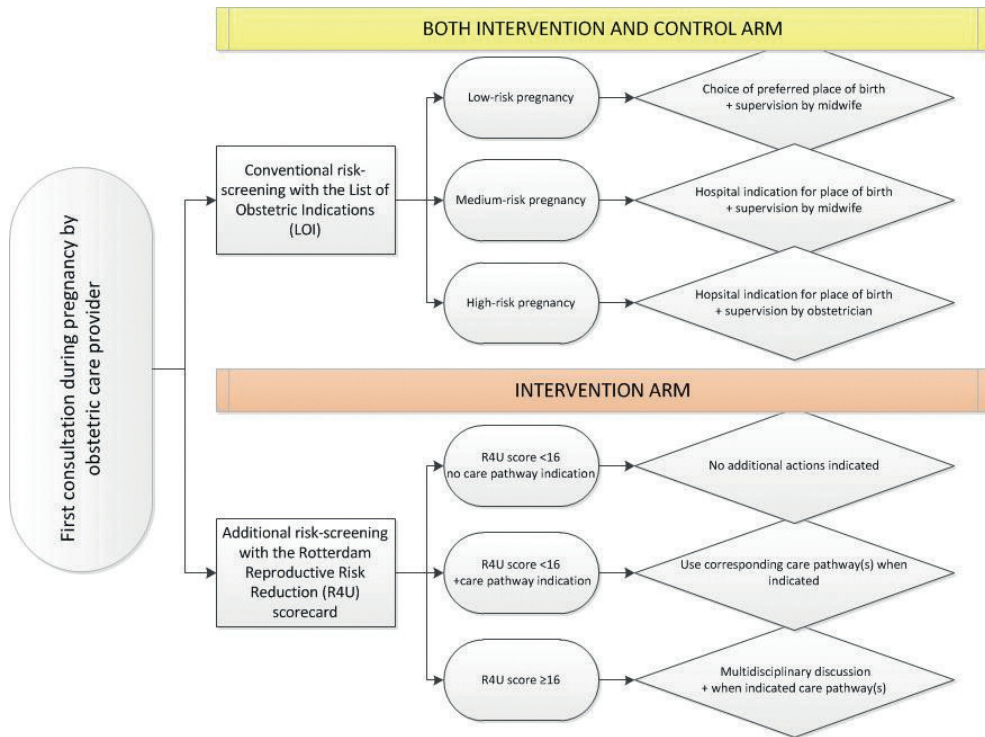
Controls

In the control clusters, an existing screening instrument (LOI), which focuses on identification of single, manifest obstetric and medical risks, was used, combined with individual care according to local protocols. The LOI distinguishes between a low, medium, or a high risk pregnancy based on anticipated third trimester and labour complications [11]. Low risk indications allow women to choose the preferred place of delivery (i.e. home birth, birth centre, hospital birth), which is supervised by an independent community midwife. Women with medium risk pregnancies should deliver in a hospital supervised by a midwife, whereas women with high risk pregnancies are supervised by an obstetrician during pregnancy and hospital delivery [11]. If the risk changes from a low or medium risk to a high risk, the woman is referred from primary to secondary or tertiary care, even during labour (figure 1).

Outcomes

Baseline characteristics were collected via a questionnaire that was filled out by participants after the first antepartum visit, generally around ten to 12 weeks of gestational age. The following characteristics were collected: maternal age at inclusion, parity, ethnicity (western versus non-western based on maternal country of birth and classified according to Statistics Netherlands), single motherhood, maternal SES (based on the classification by

the Netherlands Institute of Social Research to all postal code areas, and divided into three centile groups: low <20, medium 20-80, and high >80) [20], maternal BMI prior to conception (categorised into low <20, normal 20-29, and high 30 and more), maternal education ((highest completed education categorised into low: primary school, special education, pre-vocational (secondary) education, junior general secondary education; middle: senior general secondary education, pre-university education, senior secondary vocational education; and high: higher professional education, university education)), smoking during pregnancy (yes/no), and risk factors derived from the obstetric history (previous SGA baby, previous preterm delivery).

Perinatal outcome data was collected by a member of the research team six weeks after a participant gave birth from medical charts of community midwives and obstetricians.

All predefined outcomes regarding the effectiveness of this intervention pertain to the participant level. The primary study outcome was: delivery of a preterm (i.e. before 37 weeks of gestation) and/or SGA baby (birth weight below the 10th centile adjusted for parity, gestational age, and gender, based on the Dutch reference curves[21]) together referred to as 'BIG2'. Secondary outcomes were: the detection of fetal growth restriction during pregnancy (defined as fetal growth below the 10th centile for gestational age) and/or threatening preterm birth during pregnancy (defined by the detection of, and any action taken by an obstetric care provider, after suggestive symptoms of preterm labour), any referral to non-obstetric health care providers during pregnancy used as a proxy for involvement (regardless of referral within the care pathways), any referral to preventive care organisations during pregnancy used as a proxy for involvement (regardless of referral within the care pathways), maternal mortality, unexpected SGA (babies born SGA under supervision of a community midwife), unexpected preterm birth (babies born preterm under supervision of a community midwife), birth asphyxia (an Apgar score below seven at five minutes after birth was used as a proxy), neonatal admission to an intensive care unit, and perinatal mortality (mortality from the 22th week of gestation until seven days postnatally). Two secondary outcome measures, as defined in the initial protocol were not analysed, as these outcomes were not considered to be potentially sensitive to a postconceptional intervention. These were: 'prevalence of general risk factors' (defined as: pre-existing chronic disease, folic acid use, and medication use) and 'congenital anomalies'. Among a sub-cohort we assessed participants' and health care providers' satisfaction, and efficacy of implementation of the intervention; these findings are reported elsewhere [22].

Sample size
Calculation of sample size was based on the presumed effect of the intervention on the primary outcome, and a two-group comparison based on the combined prevalence of preterm birth and SGA in the Netherlands. The intervention was implemented at the municipality

level (cluster), while the intervention effect was measured at the participant level. To account for clustering of participants within municipalities, the sample size was multiplied by a Variance Inflation Factor (VIF) of 2.06, calculated with the formula of Donner et al [23]. In the selected clusters the average incidence of the primary outcome before start of the study (2000-2008) was 16.7%; we hypothesised that the intervention would lead to a decline towards 13% [17]. At an alpha of 0.05 and 80% power, we required 700 participants per cluster, or 3500 participants in each arm. The pre-defined stopping rule was based on the end of the HP4All study period (July 2015).

Randomisation

We randomised at the level of the clusters. Before the randomisation procedure, municipalities were ranked according to their expected percentage of pregnant women at risk for a 'BIG2' outcome at birth. Expected proportions were based on incidence rates from 2000-2008 derived from the Netherlands Perinatal Registry. Municipalities were then paired based on this ranking. The random number generator in R version 2.7.1 was used to assign one of the municipalities in each pair to the intervention arm. The other municipality of that pair was then assigned to the control arm. An independent statistician, who was not involved in executing the study, carried out the randomisation process. The randomisation at cluster level, instead of the randomisation of midwife practices or hospitals, was necessary to avoid contamination as community midwives and obstetricians generally work closely together in obstetric collaborative networks. Obstetric care providers within each cluster were informed and educated with knowledge of the outcome of the randomisation process. Blinding of obstetric care providers was not possible given the nature of the intervention. Allocation concealment of participants was set out by exclusively foreseeing in study information about the situation that was assigned to a specific cluster. As a result, participants were unaware of the randomised design of the study.

Statistical methods

The impact of the intervention on the primary and secondary outcomes was analysed using multilevel mixed-effects logistic regression analysis (with an assumed random effect for each cluster). Multiple imputation using chained equations was used to account for missing data in baseline characteristics. Both predictor and outcome variables were included to inform the multiple imputation process, forming 15 datasets. Results across the sets were combined using Rubin's Rules [24]. No interim analysis was performed. Analyses were performed according to the ITT principle. We included the following covariates in our models: age, ethnicity, BMI prior to pregnancy, SES, single motherhood, smoking during pregnancy, and obstetric history (previous SGA baby and/or previous preterm delivery). To account for over-fitting we only analysed secondary outcomes when there were more than ten events in the two groups. Statistical analysis was performed using Stata SE (version 14). Statistical significance was accepted at $p<0.05$ (two-sided).

Sensitivity analyses
Per protocol analysis
During the trial not all participants in the intervention clusters were screened using the R4U. Therefore, a sensitivity analysis was performed using a per protocol approach to investigate whether this affected the effect estimates.

Enrichment of the control clusters
During the study, there was a substantial lag in participant recruitment in the control clusters. Following an ad-hoc study group meeting, a decision was made to 'enrich' the control arm with pregnancies included retrospectively from participating practices to a total of 700 participants per cluster. Retrospective pregnancy data was extracted from digital medical charts in participating community midwife practices. Inclusion criteria were identical to the prospective inclusion. Demographic characteristics of the prospectively and retrospectively included participants in the control arm were compared and the potential differences between the groups were explored.

RESULTS

Participant flow
Five clusters, including eight hospitals and 20 community midwife practices, were included in the intervention arm, and five clusters (eight hospitals and 16 community midwife practices) served as controls (figure 2). Complete data regarding baseline characteristics was available for 2486 of 2872 (86.8%) participants in the intervention arm and 2227 of 2424 (91.9%) participants in the control arm (figure 2). We excluded participants who had a miscarriage (125 and 72, for the intervention and control group, respectively). Primary outcome data was unavailable for 92 (3.2%) participants in the intervention arm and 122 (5.0%) participants in the control arm (figure 2). Accordingly, 4302 participants were included in the ITT analyses.

In the intervention arm, 77.3% of participants were actually screened using the R4U. Of all participants screened 7% had a sum score of 16 or higher, and 50% of participants with an R4U cut-off score above 16 had a registered multidisciplinary consultation.

Baseline data
Table 1 presents the maternal and pregnancy characteristics at the individual level of all prospectively included participants, by treatment allocation. Online Resource 3, presents the same characteristics at cluster level. Participants in the control arm had a higher income per month, a higher educational level and a higher SES as compared to those in the intervention arm. Participants who did not have data on the primary outcome did not differ importantly from those included in the ITT analysis (Online Resource 4).

Figure 2: Flow diagram according to CONSORT statement

Assessed for eligibility (n=10 municipalities)

Randomised (n=10 municipalities)

Allocation

Assessed for participation (n=5 municipalities, n=28 practices
(9 hospitals and 19 midwife practices))
Received allocated intervention (n=5 municipalities;n=24 practices
(8 hospitals and 16 midwife practices))
(n=2424 patients, median (min-max) per cluster 499 (302-769))

Assessed for participation (n=5 municipalities, n=29 practices
(8 hospitals and 21 midwife practices))
Received allocated intervention (n=5 municipalities, n=28 practices
(8 hospitals and 20 midwife practices))
(n=2872 patients, median (min-max) per cluster 454 (112-1312))

Follow-Up

Lost to follow-up (n=0 municipalities; n=0 practices)
Discontinued intervention (n=0 municipalities; n=4 practices
(3 hospitals and 1 midwife practice)
Lost to follow-up; outcome questionnaire not available (n=197
patients)
(n=2227 patients, median (min-max) per cluster 410 (288-749))

Lost to follow-up (n=0 municipalities; n=0 practices)
Discontinued intervention (n=0 municipalities; n=6 practices
(4 hospitals and 2 midwife practices))
Lost to follow-up; outcome questionnaire not available (n=386
patients)
(n=2486 patients, median (min-max) per cluster 328 (101-1176))

Analysis

Analysed (n=5 municipalities; n=20 practices)
Excluded from analysis (n=0 municipalities; n=0 practices)
Excluded from analysis; miscarriage (n=72), primary outcome data
not available (n=122)
(n=2033 patients, median (min-max) per cluster 370 (255-673);
per practice 53 (1-377))

Analysed (n=5 municipalities; n=22 practices)
Excluded from analysis (n=0 municipalities; n=0 practices)
Excluded from analysis; miscarriage (n=125), primary outcome data
not available (n=92)
(n=2269 patients, median (min-max) per cluster 298 (99-1059);
per practice 39 (1-395))

Table 1. Baseline characteristics of participants

		Intervention (n=2269)		Control (n=2033)	
Maternal characteristics					
Age category (years)		N	%	N	%
	<20	16	0.71	17	0.89
	20-35	1685	74.33	1431	71.08
	>35	566	24.97	565	28.10
	Missing	2	0.09	20	0.98
Ethnic origin					
	Western	2020	89.70	1736	85.77
	Non-western	232	10.30	288	14.24
	Missing	17	0.75	9	0.44
Smoking during pregnancy					
	No	1230	81.35	1294	87.79
	Yes	282	18.65	182	8.99
	Missing	757	33.36	557	27.40
Single mother					
	No	1967	95.35	1439	87.14
	Yes	96	4.65	46	3.10
	Missing	206	9.08	548	26.98
Family income net (euros/month)					
	<1000	116	7.89	106	7.37
	1000-1499	233	15.85	176	12.23
	1500-1999	203	13.81	160	11.12
	2000-2499	228	15.51	195	13.55
	2500-2999	239	16.26	204	14.18
	>3000	451	30.68	598	41.56
	Missing	799	35.21	594	29.22
Educational level					
	Low	199	13.17	179	12.30
	Medium	672	44.47	463	31.80
	High	640	42.36	814	55.91
	Missing	758	33.41	577	28.38
Socioeconomic status					
	Low (<P20)	1485	72.79	862	46.59
	Medium (P20 - P80)	457	22.40	731	39.51
	High (>P80)	98	4.80	257	13.89
	Missing	229	10.09	183	9.00
BMI at start pregnancy					
	BMI <25	1021	45.20	1098	54.30
	BMI 25-35	943	41.74	736	36.40
	BMI >35	295	13.06	188	9.30
	Missing	10	0.44	11	0.54
Prior pregnancy characteristics					
Previous SGA baby					
	Nulliparous	1079	47.55	985	48.50
	No	700	36.12	860	92.18
	Yes	159	8.20	73	7.82
	Missing	331	14.59	115	10.97
Previous preterm delivery					
	Nulliparous	1079	47.55	985	48.50
	No	824	41.78	883	93.94
	Yes	69	3.50	57	6.06
	Missing	297	13.09	108	10.31
Pregnancy characteristics					
	Parity				
	Nulliparous	1079	47.55	985	48.50
	Multiparous	1190	52.45	1048	51.60
	Missing	0	0	0	0

Values are expressed as numbers (first) and percentage (second).
Percentages of categorised values are percentages of non-missing cases.
Missing percentages are percentages of total cases.

Table 2. Primary and secondary outcomes at individual level

		Intervention (n=2269)		Control (n=2033)	
		n	%	n	%
Primary outcome					
BIG2					
	Yes	371	16.35	269	13.23
Secondary outcomes					
Maternal					
Referral to non-obstetric health care providers					
	Yes	523	26.02	568	29.82
	Missing	259	11.41	128	6.30
Referral to preventive care organisations					
	Yes	129	6.59	74	4.34
	Missing	311	13.71	327	16.08
BIG2 detected during pregnancy					
	Yes	220	10.59	150	7.69
	Missing	192	8.46	83	4.08
Delivery					
Unexpected SGA (delivery of SGA baby in first tier)					
	Yes	44	1.95	35	1.73
	Missing	7	0.31	11	0.54
Unexpected preterm (preterm delivery in first tier)					
	Yes	4	0.18	3	0.15
	Missing	10	0.44	13	0.64
Neonatal					
Preterm delivery					
	Yes	165	7.28	94	4.63
Small for gestational age					
	Yes	229	10.09	186	9.15
Perinatal mortality					
	Yes	15	0.67	8	0.40
	Missing	35	1.54	10	0.49

Primary and secondary outcomes at individual level, categorised in primary (delivery of a preterm and/or a SGA baby, referred to as 'BIG2') and secondary outcomes (maternal, delivery, and neonatal). Values are expressed as numbers (first) and percentage (second). Percentages of categorised values are percentages of non-missing cases. Missing percentages are percentages of total cases.

Impact of the intervention on primary and secondary outcomes

The combined primary outcome delivery of a preterm and/or a SGA baby (BIG2) occurred in 16.3% of participants in the intervention arm and in 13.2% of participants in the control arm (unadjusted odds ratio OR 1.34 (95% CI 0.92 to 1.94); table 2 and Online Resource 5. The intervention had no demonstrable impact on the primary outcome in multivariable analysis: adjusted odds ratio (aOR) 1.17 (95% CI 0.84 to 1.63) (table 3). The intervention improved the detection of threatening preterm delivery and fetal growth restriction during pregnancy compared to the control arm: aOR 1.27 (95%CI 1.01 to 1.61), but had no significant impact on any other secondary outcomes (table 3).

Table 3. Impact of intervention on primary and secondary outcomes

Primary outcomes	OR (95% CI)	
	unadjusted	adjusted
BIG2 (n=4002)	1.34 (0.92-1.94)	1.17 (0.84-1.63)
Secondary outcomes		
Referral to non-obstetric health care providers (n=3748)	0.82 (0.54-1.24)	0.79 (0.51-1.23)
Referral to preventive care organisations (n=3568)	1.17 (0.43-3.21)	0.96 (0.36-2.54)
Fetal growth restriction/preterm birth detected in pregnancy (n=3830)	1.40 (1.03-1.92)	1.27 (1.01-1.61)
Unexpected SGA (n=3989)	1.21 (0.69-2.13)	1.28 (0.63-2.62)
Perinatal mortality (n=3975)	1.70 (0.72-4.02)	1.33 (0.51-3.44)

Numbers are aOR and 95% confidence interval.

Sensitivity analyses

Demographic characteristics differed significantly between the prospectively and retrospectively included participants in the control arm (Online Resource 6). Prospectively included participants were more often of western ethnic origin, had a higher educational level, and a higher SES. Due to this important heterogeneity we decided not to conduct any additional analyses including data from the retrospectively included participants.

Per protocol analysis

The effect estimates did not change materially when performing a per protocol analysis as compared to the intention to treat analysis (table 4).

Table 4. Per protocol sensitivity analysis primary and secondary outcome variables.

Per protocol analysis	
Primary outcomes	aOR (95% CI)
BIG2 (n=3564)	1.10 (0.77-1.57)
Secondary outcomes	
Referral to non-obstetric health care providers (n=3438)	0.79 (0.51-1.22)
Referral to preventive care organisations (n=3282)	0.95 (0.37-2.42)
fetal growth restriction/preterm birth detected in pregnancy (n=3618)	1.32 (0.96-1.80)
Unexpected SGA (n=3618)	1.04 (0.48-2.29)
Perinatal mortality (n=3539)	1.29 (0.47-3.53)

Numbers are aOR and 95% confidence interval.

DISCUSSION

By introducing one single tool for additional risk assessment in all tiers of the Dutch obstetric care system we achieved uniformity in risk assessment among 33 community midwife practices and nine hospitals in 14 urban municipalities in the Netherlands [25]. The combination with subsequent institution of care pathways and multidisciplinary consultations further promoted uniformity in a more proactive and preventive approach regarding medical and non-medical risk factors during pregnancy. Hereby the traditional risk assessment during pregnancy, aimed at recognising primarily medical risk factors for complications during labour, shifted towards the first trimester and created a larger window of opportunity for prevention. However in this C-RCT, this combined intervention had no demonstrable impact on preterm and/or SGA birth.

Health inequalities depend on a person's social, economic, and political environment. These environments are shaped by policies, which makes them amenable to change [26]. Our trial is part of the overall HP4All research programme designed to evaluate the effectiveness of interventions, and their associated preventive strategies, in decreasing health inequalities in pregnancy outcomes [14]. To accomplish implementation of such a programme, interventions should contain a flexible approach that allows for adaptation. Such adaptations stimulate the implementation process and increase sustainability[18]. However, the same flexibility may also have influenced our results. For example, all participating caregivers, including those belonging to the control arm, were educated prior to the start of the program about the importance of non-medical risk factors in relation to adverse pregnancy outcomes. Such adaptations may have resulted in an unintended spill over of intervention effects in the control arm.

This study also has other limitations. Firstly, the intended inclusion of 7000 participants was not achieved within the study's time frame, and there was a wide variation in sample size among clusters. Secondly, despite the fact that the HP4All programme was set out in the most deprived neighbourhoods of the Netherlands, the participants in this study had an educational level and family income above the national average, suggesting a substantial degree of selection bias. As a result, whereas based on previous research we expected 20% of participants to have an R4U score of 16 or higher, only 7% fulfilled this criterion in the final sample. Thirdly, our results show that not all participants received the intervention as intended. In the intervention arm, 77.4 % of all participants were assessed using the R4U scorecard. Of participants with a cut-off score higher than 16, only 50% had a registered multidisciplinary consultation. In addition, the process evaluation of this study, based on Saunders' 7-step method, showed that only half of the participating municipalities met the criteria for full implementation of the risk assessment program [22]. The combination of not achieving the intended sample size, having fewer participants with a high-risk score

according to the pre-defined cut-off, and the above mentioned dilution of the intervention, reduced the power of this study to identify effectiveness.

Fourthly, there were differences in demographic characteristics between participants in the intervention arm and participants in the control arm (table 1). Participants in the intervention arm had a lower income per month, a lower educational level and a lower SES as compared to those in the control arm. This heterogeneity could be explained by a selection bias, which is a well-recognised phenomenon in C-RCTs [27] [28]. Participants were recruited after the clusters had been randomised. Obstetric care providers had knowledge of whether participants belonged to the intervention or the control arm and this could have affected the types of participants they recruited. Health care providers in the intervention arm may have included more participants with a higher risk for adverse pregnancy outcomes, or in other terms, participants more suitable for 'active management'. In the control arm this selection likely led to an inclusion of participants with a favourable risk profile. This is further substantiated by the observation that prospectively included participants were more often of western ethnic origin, had a higher educational level, and a higher SES than retrospectively included participants, who were more likely to represent an unbiased sample (Online Resource 6). Although in our analysis we adjusted for known potential confounders, unmeasured confounders could have been imbalanced too and as such may have influenced the results of our analysis.

Despite careful theoretical planning, cluster randomised controlled trials are known to be vulnerable to risk of bias, specifically, bias in selection of participants [27] [29] [30]. Our experience has implications for designing similar trials in the future. The observed inclusion bias in this trial is mostly based on a recruitment bias. Blinding the recruiter of participants for allocation could potentially have diminished this bias. In our trial, participants were recruited by their health care providers, who were also responsible for subsequent pregnancy care, making blinding impossible. This may be addressed by separating participant inclusion from participant care in future studies. Moreover, researchers of C-RCTs may consider conducting an interim analysis, which could potentially have detected the differences in baseline characteristics between the intervention and the control arm. Such an analysis would potentially also have been able to detect the additional issues that eventually caused a dilution of the intervention effect, allowing these to be addressed during the course of the trial.

Despite the above-mentioned limitations, our study shows that implementation of additional non-medical risk assessment and preventive strategies into general practices are feasible. It did, however, not decrease the incidence of adverse perinatal outcomes in the index pregnancy in deprived urban areas.

Extended screening for populations at risk, together with improved collaboration between the curative and public health sector in patient-tailored care, is a start in establishing equity-oriented strategies during pregnancy. However, an intensive research programme as HP4All should ultimately seek to serve pregnant women. Serving in these interventions means detecting those with the greatest health needs, and help them to find the power to direct resources towards those needs. In this perspective, future research in this field should elucidate what empowers pregnant women and which specific resources they need to address their health needs. Effectiveness in this regard, could include value based outcome measures, rather than focusing merely on health outcomes.

SUPPLEMENTARY MATERIAL

Supplementary figure 1: R4U-scorecard

Name						Study ID			G:	P:	Date of Birth			
Name of practice				Zip Code			Date of booking visit			Due date		□ LMP	□ US	□ IVF

SOCIAL			action	GENERAL HISTORY			action
Social situation	YES	NO		**Disorders**	YES	NO	
Single mother				Chronic maternal illness (as described in script)			
Relationship problems > 3 months				Annual consultation GP or physician			
Experience of inadequate social support				Hemoglobinopathy			
Domestic violence				Refuses blood transfusion (Jehovah's Witness)			
Previous referral to children's social services							
				Medication	YES	NO	
Work and income	YES	NO		Prescribed medication			
Unemployed (> 3 months)				Over-the-counter drugs			
Standing labour				No preconceptional folic acid use			
Working hours > 32 and stressful							
Netto family income < 1000 euro				**Infectious diseases**	YES	NO	
Irredeemable Financial debts				(Treated for) sexually transmitted disease last year			
Partner unemployed				Promiscuity			
				At risk for Toxoplasmosis			
Education	YES	NO		At risk for Rubella			
Low education level (< 7 years) or illiterate							
				Psychiatry	YES	NO	
Neighbourhood	YES	NO		History of psychiatric admission / positive family history (1st degree)			
Housing problems				Current use of psychiatric medication			
Deprived neighbourhood*				Current psychiatric problems			
(*ZIP code classification present in script)							
				OBSTETRIC HISTORY			
ETHNICITY				**History**	YES	NO	
Ethnicity	YES	NO		Nulliparous			
Surinamese - Hindo				Recurrent miscarriage (2 or more)			
Surinamese - Creole				Interpregnancy interval < 6 months			
Surinamese - Javanese				Preterm birth (< 37 weeks)			
Antillean / Aruban				Low Apgarscore < 7 after 5 minutes			
Cape Verdian				Small for gestational age (<p10)			
Turkish				Previous child with major congenital anomalies			
Maroccan				Stillbirth (22 weeks - 7 days postpartum)			
Non-Western other				Shoulder dystocia			
Language / communication	YES	NO		Instrumental delivery			
Language barrier (limited Dutch or English)				Caeserean section			
Exclusively communication by interpreter				Gestational diabetes			
Mentally disabled				Manual placental removal / postpartum haemorrhage			
REPRODUCTIVE FACTORS				Placental abruption			
General	YES	NO		(Pre)eclampsia or HELLP syndrome			
Uninsured							
				Family	YES	NO	
Family planning / age	YES	NO		Major congenital anomaly in first degree relative			
Unwanted pregnancy				Other (as described obstetric indication list)			
Unplanned, but wanted pregnancy							
Assisted reproduction (ICSI/IVF/IUI/oocyte donation)				**Result booking bloods**	POS	NEG	
Teenage pregnancy (≤ 18 yeas)				Irregular antibodies			
Advanced maternal age (≥ 40 jaar)				Hepatitis B			
				HIV			
Obstretical	YES	NO		Lues			
Start antenatal care 12 - 14 weeks							
Late start antenatal care > 14 weeks				**Preconception consult**			
				□ Yes midwife □ Yes GP □ No			
LIFESTYLE				date (mm/yy): date (mm/yy):			
Intoxication	YES	NO					
Preconceptional smoking (past 6 months)							
Smoking during first trimester				**Plus factor**			
Smoking during second trimester							
Preconceptional alcohol use (past 6 months)							
Alcohol use during first trimester							
Alcohol use during second trimester				**Result**			
Preconceptional illicit drug use (past 6 months)				**Domain**		**Score**	
Illicit drug use during first trimester				Social			
Illicit drug use during second trimester				Ethnicity			
				Care			
Nutrition	YES	NO		Life style			
Vegetarian, vegan or macrobiotic diet				General history			
No daily vegetable intake				Obstetrical history			
No daily fruit intake				Lab results booking bloods			
				CUMULATIVE score			
Body weight	YES	NO					
BMI < 18				**Time start consult (hh:mm)**			
BMI 30 - 35				**Time end consult (hh:mm)**			
BMI > 35							

Supplementary figure 2: care pathway
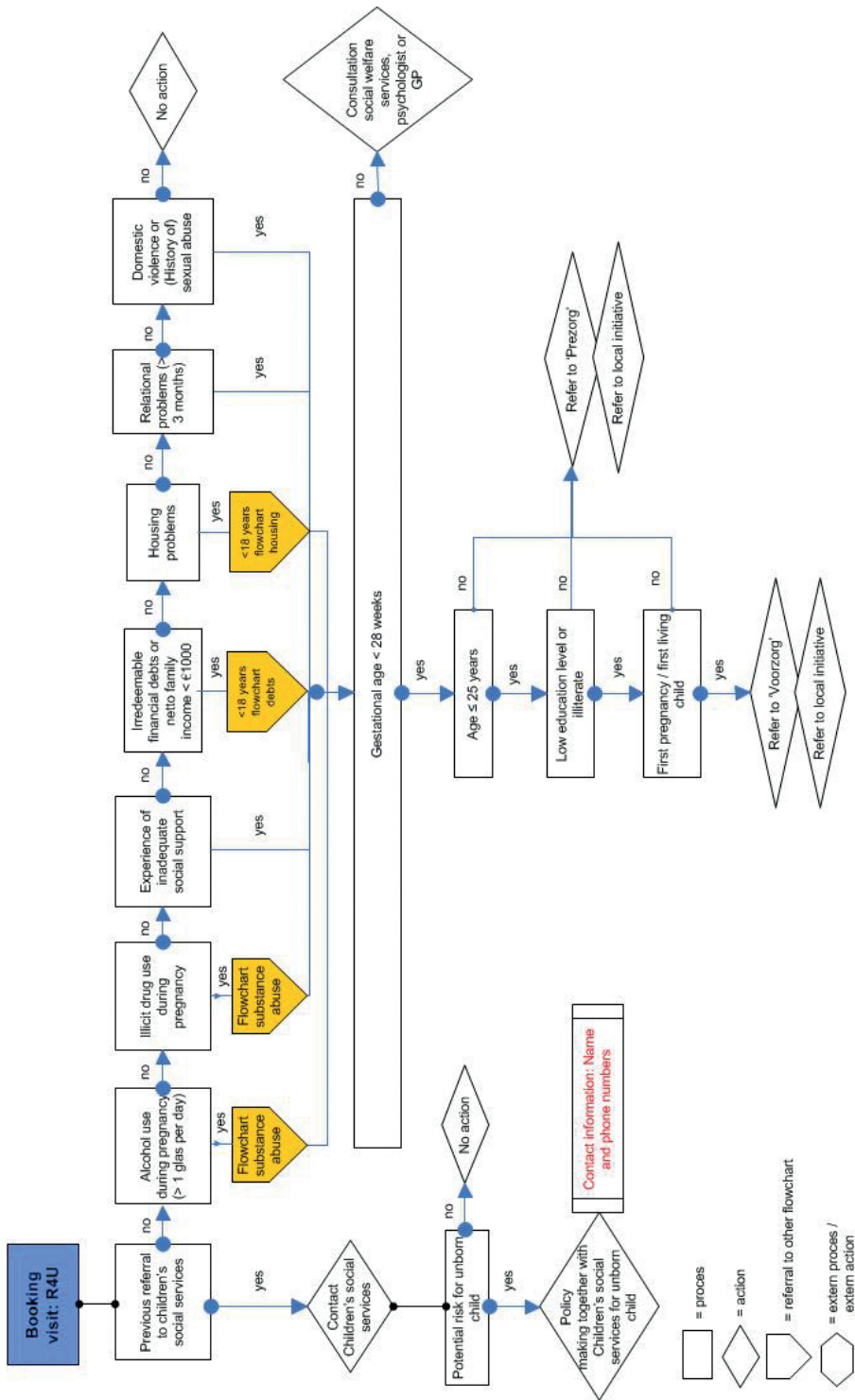
Supplementary tables (Online Resources)

Appendix 3 Baseline characteristics of participants at cluster level

	Intervention (n=2269)												Control (n=2033)											
Cluster level	1 (n=298)	%	2 (n=258)	%	3 (n=99)	%	4 (n=555)	%	5 (n=1059)	%	total	%	6 (n=370)	%	7 (n=457)	%	8 (n=278)	%	9 (n=673)	%	10 (n=255)	%	total	%
Maternal characteristics																								
Age in category																								
<20	2	0.67	0	0.00	1	1.01	5	0.90	8	0.76	16	0.71	0	0.00	4	0.88	1	0.36	0	0.00	12	5.06	17	0.85
20-35	191	64.09	165	63.95	79	79.80	415	75.05	835	78.85	1685	74.33	286	77.51	316	69.15	206	74.37	442	65.68	181	76.37	1431	71.16
>35	105	35.23	93	36.05	19	19.19	133	24.05	216	20.40	566	24.97	83	22.49	137	29.98	70	25.27	231	34.32	44	18.57	565	28.10
Missing	0	0.00	0	0.00	0	0.00	2	0.36	0	0.00	2	0.09	1	0.27	0	0.00	1	0.36	0	0.00	18	7.06	20	0.98
Ethnic origin																								
Western	158	53.74	248	97.25	91	91.92	504	91.80	1019	96.59	2020	89.70	328	89.62	307	67.62	246	88.81	617	91.82	237	92.94	1736	85.86
Non-western	136	46.26	7	2.75	8	8.08	45	8.20	36	3.41	232	10.30	38	10.38	147	32.38	31	11.19	55	8.18	17	6.67	288	14.24
Missing	4	1.34	3	1.16	0	0.00	6	1.08	4	0.38	17	0.75	4	1.08	3	0.66	1	0.36	1	0.15	0	0.00	9	0.44
Smoking during pregnancy																								
No	169	83.66	161	84.29	64	90.14	299	78.89	537	80.27	1230	81.35	221	89.47	313	85.05	130	87.84	468	93.04	162	77.14	1294	87.79
Yes	33	16.34	30	15.71	7	9.86	80	21.11	132	19.73	282	18.65	26	10.53	55	14.95	18	12.16	35	6.96	48	22.86	182	12.35
Missing	96	32.21	67	25.97	28	28.28	176	31.71	390	36.83	757	33.36	123	33.24	89	19.47	130	46.76	170	25.26	45	17.65	557	27.42
Single mother																								
No	219	80.22	254	99.61	96	96.97	508	96.95	890	97.59	1967	95.35	243	97.98	20	5.41	146	98.65	495	97.83	205	96.24	1439	97.03
Yes	54	19.78	1	0.39	3	3.03	16	3.05	22	2.41	96	4.65	5	2.02	350	94.59	2	1.35	11	2.17	8	3.76	46	3.10
Missing	25	8.39	3	1.16	0	0.00	31	5.59	147	13.88	206	9.08	122	32.97	87	19.04	130	46.76	167	24.81	42	16.47	548	26.98
Family income net (euros/month)																								
<1000	49	17.07	4	2.13	1	1.39	27	7.46	35	5.30	116	7.89	9	3.67	44	12.57	13	9.09	16	3.25	24	11.54	106	7.38
1000-1499	52	18.12	10	5.32	12	16.67	43	11.88	116	17.58	233	15.85	20	8.16	73	20.86	17	11.89	30	6.09	36	17.31	176	12.25
1500-1999	30	10.45	18	9.57	9	12.50	46	12.71	100	15.15	203	13.81	26	10.61	56	16.00	20	13.99	30	6.09	28	13.46	160	11.13
2000-2499	24	8.36	24	12.77	8	11.11	57	15.75	115	17.42	228	15.51	41	16.73	51	14.57	14	9.79	59	11.97	30	14.42	195	13.57
2500-2999	9	3.14	39	20.74	8	11.11	59	16.30	124	18.79	239	16.26	43	17.55	37	10.57	25	17.48	65	13.18	34	16.35	204	14.20
>3000	24	8.36	93	49.47	34	47.22	130	35.91	170	25.76	451	30.68	106	43.27	89	25.43	54	37.76	293	59.43	56	26.92	598	41.61
Missing	110	36.91	70	27.13	27	27.27	193	34.77	399	37.68	799	35.21	125	33.78	107	23.41	135	48.56	180	26.75	47	18.43	594	29.25

3

Appendix 3 *continued*

Educational level

	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%
Low	50	25.13	11	5.70	6	8.45	50	13.26	82	12.22	199	13.17	25	10.12	66	18.38	15	10.20	21	4.25	52	24.41	179	12.31
Medium	86	43.22	52	26.94	31	43.66	160	42.44	343	51.12	672	44.47	92	37.25	151	42.06	53	36.05	64	12.96	103	48.36	463	31.84
High	63	31.66	130	67.36	34	47.89	167	44.30	246	36.66	640	42.36	130	52.63	142	39.55	79	53.74	409	82.79	54	25.35	814	55.98
Missing	99	33.22	65	25.19	28	28.28	178	32.07	388	36.64	758	33.24	123	33.41	98	21.44	131	47.12	179	26.60	42	16.47	577	28.41

Social-economic status

	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%
Low (<P20)	260	95.24	153	59.77	66	66.67	407	77.52	599	67.45	1485	72.79	38	12.75	227	58.66	95	34.42	291	44.56	211	89.41	862	46.65
Medium (P20 - P80)	12	4.40	63	24.61	27	27.27	91	17.33	264	29.73	457	22.40	140	46.98	106	27.39	155	56.16	305	46.71	25	10.59	731	39.56
High (>P80)	1	0.37	39	15.23	6	6.06	27	5.14	25	2.82	98	4.80	120	40.27	54	13.95	26	9.42	57	8.73	0	0.00	257	13.91
Missing	25	8.39	3	1.16	0	0.00	30	5.41	171	16.15	229	10.09	72	19.46	70	15.32	2	0.72	20	2.97	19	7.45	183	9.01

BMI start pregnancy

	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%
BMI <25	110	37.29	144	55.81	49	49.49	272	49.10	446	42.36	1021	45.20	187	50.82	193	42.60	153	55.04	446	66.27	119	46.67	1098	54.06
BMI 25-35	134	45.42	107	41.47	45	45.45	231	41.70	426	40.46	943	40.49	149	41.74	178	39.29	112	40.29	199	29.57	98	38.43	736	36.24
BMI >35	51	17.29	7	2.71	5	5.05	51	9.21	181	17.19	295	8.70	32	13.06	82	18.10	13	4.68	28	4.16	33	12.94	188	9.26
Missing	3	1.01	0	0.00	0	0.00	1	0.18	6	0.57	10	0.54	2	0.44	4	0.88	0	0.00	0	0.00	5	1.96	11	0.54

Prior pregnancy characteristics

Previous SGA baby

	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%
No	97	37.60	101	41.06	42	43.30	185	38.14	275	32.28	700	36.12	167	46.91	210	51.22	116	43.45	254	39.38	118	49.17	860	44.89
Yes	49	18.99	26	10.57	4	4.12	32	6.60	48	5.63	159	8.20	17	4.78	16	3.90	13	4.87	18	2.79	9	3.75	73	3.81
Missing	40	13.42	12	4.65	2	2.02	70	12.61	207	19.55	331	14.59	14	3.78	47	10.28	11	3.96	28	4.16	15	5.88	115	5.66

Previous preterm delivery

	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%
No	152	53.90	121	49.39	41	42.27	203	41.18	307	35.91	824	41.78	173	48.32	216	50.94	115	44.40	267	41.27	112	47.26	883	45.92
Yes	18	6.38	5	2.04	5	5.15	22	4.46	19	2.22	69	3.50	13	3.63	24	5.66	6	2.32	7	1.08	7	2.95	57	2.96
Missing	16	5.37	13	5.04	2	2.02	62	11.17	204	19.26	297	13.09	12	3.24	33	7.22	19	6.83	26	3.86	18	7.06	108	5.32

Pregnancy characteristics

Parity

	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%
Nulliparous	112	37.58	119	46.12	51	51.52	268	48.29	529	49.95	1079	47.55	172	46.49	184	40.26	138	49.64	373	55.42	118	46.27	985	48.50
Multiparous	186	62.42	139	53.88	48	48.48	287	51.71	530	50.05	1190	52.45	198	53.51	273	59.74	140	50.36	300	44.58	137	53.73	1048	51.60
	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00

Values are expressed as numbers (first) and percentage (second). Percentages of categorised values are percentages of non-missing cases. Missing percentages are percentages of total cases. Prior pregnancy characteristics are presented for multiparous participants.

Appendix 4 baseline characteristics of participants with outcome data and participants without outcome data

	Participants with outcome data (n=4714)		Participants without outcome data (n=604)	
	n	%	n	%
Maternal characteristics				
Age in category				
<20	41	0,88	21	3,55
20-35	3399	72,74	430	72,64
>35	1233	26,39	141	23,82
Missing	41	0,87	12	1,99
Ethnic origin				
Western	4120	87,98	460	77,31
Non-western	563	12,02	135	22,69
Missing	31	0,66	9	1,49
Smoking during pregnancy				
No	2713	84,54	376	87,04
Yes	496	15,46	56	12,96
Missing	1505	31,93	172	28,48
Single mother				
No	3666	96,02	486	93,64
Yes	152	3,98	33	6,36
Missing	896	19,01	85	14,07
Family income (euros/month)				
<1000	246	7,88	59	14,71
1000-1499	442	14,15	74	18,45
1500-1999	394	12,62	52	12,97
2000-2499	453	14,51	50	12,47
2500-2999	475	15,21	53	13,22
>3000	1113	35,64	113	28,18
Missing	1591	33,75	203	33,61
Educational level				
Low	419	13,14	67	15,62
Medium	1219	38,24	173	40,33
High	1550	48,62	189	44,06
Missing	1526	32,37	175	28,97
Social-economic status				
Low (<P20)	2532	60,14	354	62,21
Medium (P20 - P80)	1289	30,62	165	29,00
High (>P80)	389	9,24	50	8,79
Missing	504	10,69	35	5,79
Pregnancy characteristics				
Parity				
Nulliparous	2273	48,29	52	44,07
Multiparous	2434	51,71	66	55,93
Missing	7	0,15	486	80,46
Prior pregnancy characteristics				
Previous SGA baby				
No	1662	39,68	73	34,76
Yes	251	5,99	7	3,33
Missing	526	11,16	394	65,23
Previous preterm delivery				
No	1828	43,13	69	30,13
Yes	135	3,19	3	1,31
Missing	476	10,10	375	62,09

Values are expressed as numbers (first) and percentage (second). Percentages of categorised values are percentages of non-missing cases. Missing percentages are percentages of total cases. Prior pregnancy characteristics are presented for multiparous participants.

Appendix 5 Primary and secondary outcomes at cluster level

Cluster level	Intervention (n=2269)												Control (n=2033)											
	1 (n=298)	%	2 (n=258)	%	3 (n=99)	%	4 (n=555)	%	5 (n=1059)	%	total	%	6 (n=370)	%	7 (n=457)	%	8 (n=278)	%	9 (n=673)	%	10 (n=255)	%	total	%
Primary outcome																								
BIG2																								
Yes	87	29.19	37	14.34	15	15.15	89	16.04	143	13.50	371	16.35	57	15.41	70	15.32	33	11.87	70	10.40	39	15.29	269	13.23
Secondary outcomes																								
Maternal																								
Referral to non-obstetric health care providers																								
Yes	82	28.08	108	43.03	19	19.19	90	16.42	224	27.32	523	26.02	88	27.76	133	29.30	84	31.34	195	29.02	68	35.05	568	29.82
Missing	6	2.01	7	2.71	0	0.00	7	1.26	239	22.57	259	11.41	53	14.32	3	0.66	10	3.60	1	0.15	61	23.92	128	6.30
Referral to non-obstetric health care organisations																								
Yes	47	16.15	6	2.46	1	1.01	25	4.58	50	6.43	129	6.59	14	4.75	21	6.84	25	9.54	8	1.19	6	3.49	74	4.34
Missing	7	2.35	14	5.43	0	0.00	9	1.62	281	26.53	311	13.71	75	20.27	150	32.82	16	5.76	3	0.45	83	32.55	327	16.08
BIG2 detected during pregnancy																								
Yes	40	14.18	23	9.20	10	10.64	46	8.91	101	10.80	220	10.59	17	4.83	42	9.77	24	9.30	41	6.18	26	10.53	150	7.69
Missing	16	5.37	8	3.10	5	5.05	39	7.03	124	11.71	192	8.46	18	4.86	27	5.91	20	7.19	10	1.49	8	3.14	83	4.08
Delivery																								
SGA baby in first tier																								
Yes	11	3.72	8	3.10	0	0.00	12	2.18	13	1.23	44	1.95	9	2.45	5	1.11	3	1.08	14	2.08	4	1.58	35	1.73
Missing	2	0.67	0	0.00	0	0.00	5	0.90	0	0.00	7	0.31	2	0.54	6	1.31	1	0.36	0	0.00	2	0.78	11	0.54
Preterm in first tier																								
Yes	1	0.34	0	0.00	0	0.00	0	0.00	3	0.28	4	0.18	1	0.27	1	0.22	0	0.00	1	0.15	0	0.00	3	0.15

	Missing	2	0.67	0	0.00	0	0.00	6	1.08	2	0.19	10	0.44	2	0.54	7	1.53	1	0.36	0	0.00	3	1.18	13	0.64
Neonatal																									
Preterm delivery																									
	Yes	39	13.09	11	4.26	9	9.09	43	7.76	63	5.96	165	7.28	19	5.14	30	6.58	14	5.04	20	2.97	11	4.33	94	4.63
Small for gestational age																									
	Yes	58	19.46	26	10.08	6	6.06	49	8.83	90	8.50	229	10.09	40	10.81	42	9.19	20	7.19	54	8.02	30	11.76	186	9.15
Perinatal mortality																									
	Yes	3	1.03	0	0.00	1	1.02	5	0.91	6	0.57	15	0.67	3	0.81	1	0.22	1	0.36	2	0.30	1	0.39	8	0.40
	Missing	7	2.35	6	2.33	1	1.01	8	1.44	13	1.23	35	1.54	1	0.27	5	1.09	2	0.72	2	0.30	0	0.00	10	0.49

Supplementary table 3 Primary and secondary outcomes at cluster level, categorised in primary and secondary outcomes (maternal, delivery, and neonatal). Values are expressed as numbers (first) and percentage (second). Percentages of categorised values are percentages of non-missing cases. Missing percentages are percentages of total cases.

Appendix 6 baseline characteristics of prospective and retrospective participants in the control arm

	Prospective participants (n=2033)		Retrospective 'participants' (n=917)	
	n	%	n	%
Maternal characteristics				
Age in category				
<20	17	0.84	5	0.55
20-35	1431	71.09	637	69.47
>35	565	28.07	275	29.99
Missing	20	0.98	0	0.00
Ethnic origin				
Western	1736	85.77	492	59.71
Non-western	288	14.23	332	40.29
Missing	9	0.44	93	10.14
Smoking during pregnancy				
No	1294	87.67	726	81.66
Yes	182	12.33	163	18.34
Missing	557	27.40	28	3.05
Single mother				
No	1439	96.90	852	94.77
Yes	46	3.10	47	5.23
Missing	548	26.96	18	1.96
Family income (euros/month)				
<1000	106	7.37		
1000-1499	176	12.23		
1500-1999	160	11.12		
2000-2499	195	13.55		
2500-2999	204	14.18		
>3000	598	41.56		
Missing	594	29.22		
Educational level				
Low	179	12.29	53	17.61
Medium	463	31.80	150	49.83
High	814	55.91	98	32.56
Missing	577	28.38	616	67.18
Social-economic status				
Low (<P20)	862	46.59	307	45.48
Medium (P20 - P80)	731	39.51	271	40.15
High (>P80)	257	13.89	97	14.37
Missing	183	9.00	242	26.39
BMI start pregnancy				
BMI <25	1098	54.30	443	48.63
BMI 25-35	736	36.40	369	40.50
BMI >35	188	9.30	99	10.87
Missing	11	0.54	6	0.65
Pregnancy characteristics				
Parity				
Nulliparous	985	48.45	437	47.66
Multiparous	1048	51.55	480	52.34
Missing	0	0.00	0	0.00

Prior pregnancy characteristics					
Previous SGA baby					
	No	860	44.84	415	45.70
	Yes	73	3.81	56	6.17
	Missing	115	5.66	9	0.98
Previous preterm delivery					
	No	883	45.07	440	48.78
	Yes	57	2.91	25	2.77
	Missing	74	3.64	15	1.64

Values are expressed as numbers (first) and percentage (second). Percentages of categorised values are percentages of non-missing cases. Missing percentages are percentages of total cases. Prior pregnancy characteristics are presented for multiparous participants.

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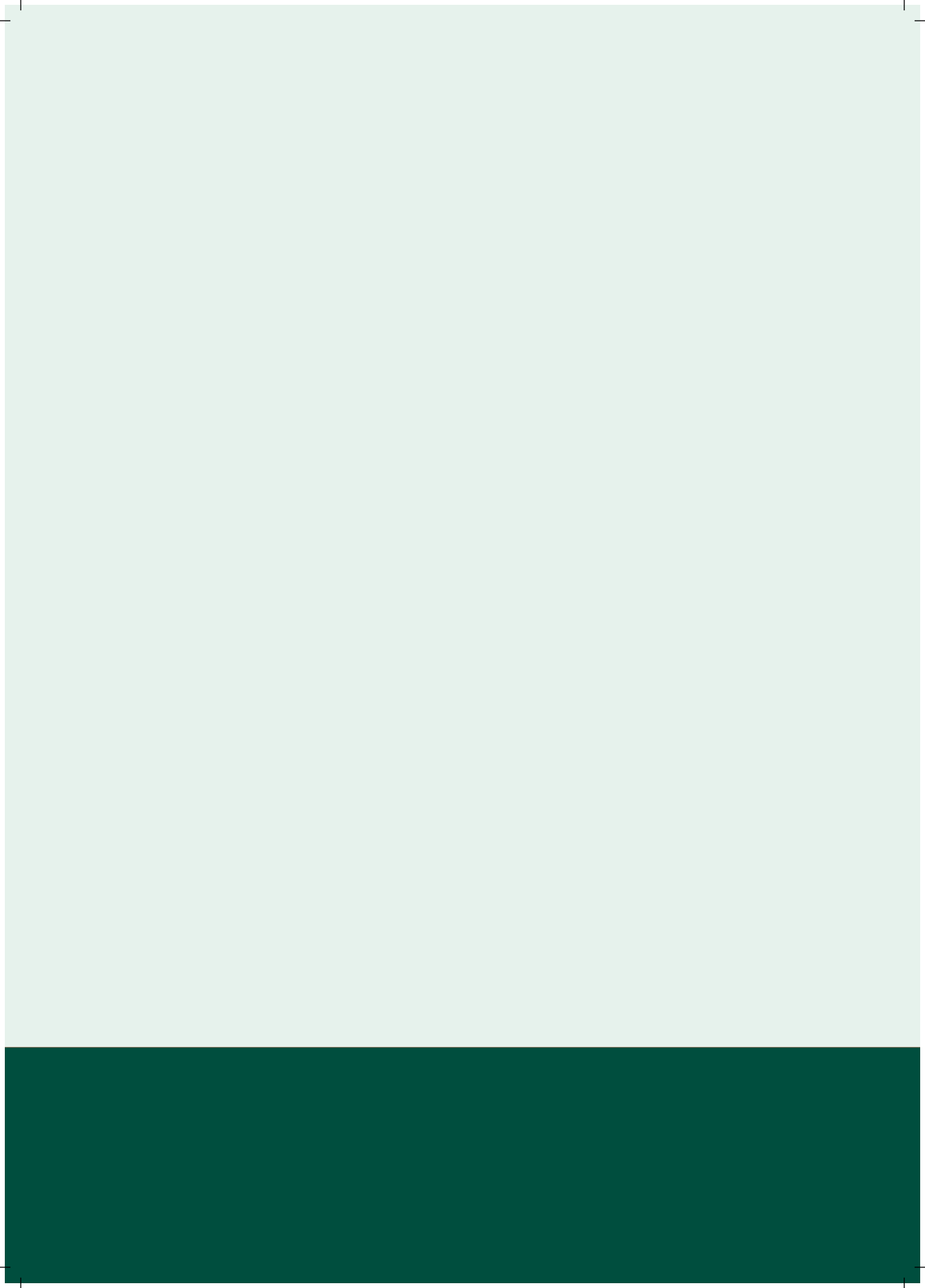
CHAPTER 4

Validation of a prognostic model for adverse perinatal health outcomes

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ABSTRACT

There is a strong association between social deprivation and adverse perinatal health outcomes, but related risk factors receive little attention in current antenatal risk selection. To increase awareness of healthcare professionals for these risk factors, a model for antenatal risk surveillance and care was developed in the Netherlands, called the 'Rotterdam Reproductive Risk Reduction' (R4U) scorecard. The aim of this study was to validate the R4U-scorecard.

This study was conducted using external, prospective data from thirty-two midwifery practices, and fifteen hospitals in the Netherlands. The main outcome measures were the discrimination of the prognostic models for the probability of a pregnant woman developing adverse pregnancy outcomes (babies born preterm or small for gestational age), and calibration. We performed cross-validation and updated the model using statistical re-estimation of all predictors.

1752 participants were included, of whom 282 (16%) had one of the predefined adverse outcomes. The discriminative value of the original scoring system was poor (area under the curve (AUC) of 0.58 (95% CI 0.53-0.64)). The model showed moderate calibration. The updated R4U-scorecard showed good generalisability to the validation set but did not alter the predictive value (AUC 0.61 (95% CI 0.56-0.66).

By using external data and by updating the prognostic model, we have provided a comprehensive evaluation of the R4U-scorecard. Further improvement in classification of high-risk pregnancies is important considering the necessity of early risk detection for healthcare professionals to take appropriate actions to prevent these risks from becoming manifest problems.

INTRODUCTION

There is a strong association between social deprivation and adverse perinatal health outcomes. This association is already present during pregnancy and extends into adulthood, with potentially severe long-term health consequences.[1-5] In the Netherlands, risk surveillance in antenatal health care traditionally mainly focuses on single medical or obstetric risk factors.[6] Psychosocial (non-medical) risk factors generally receive little attention. To increase awareness among health care professionals for these risk factors, a model for antenatal risk surveillance and care was developed in 2008 in the Netherlands.[7] This model, implemented as the 'Rotterdam Reproductive Risk Reduction (R4U)' scorecard (supplementary figure 1), estimates the probability that a pregnant woman is at increased risk of adverse pregnancy outcomes based on multiple medical, obstetric, and non-medical factors (i.e. risk factors related to a person's socioeconomic status and environment). Additionally, the R4U-scorecard is accompanied by recommended decisions for clinicians, such as prioritisation of risk factors, risk-specific care pathways, and multidisciplinary consultations.[8]

Following its development, the R4U-scorecard was used in the national Healthy Pregnancy 4 All-1 (HP4All-1) programme, a Cluster Randomized Controlled Trial (C-RCT). This trial investigated the effectiveness of systematic risk detection and preventive strategies to reduce adverse perinatal health outcomes in antenatal healthcare.[8-10] The implementation of the R4U-scorecard into routine care, along with risk-guided care throughout pregnancy, was feasible. Moreover it had a positive impact on physicians' behaviour by improving awareness of one of the most common adverse perinatal health outcomes during pregnancy, namely intra-uterine growth restriction.[7]

We aimed to conduct a comprehensive evaluation of the R4U. We hereto included cross-validation of the prognostic model underlying the scorecard and suggest directions for improvement by updating the model.[11,12]

METHODS

Using external data from a national Cluster-Randomised Controlled Trial (C-RCT),[7] we performed cross-validation of the R4U-scorecard with re-consideration of the additional effect of all predictors included in the scorecard. We then derived an updated version of the R4U-scorecard.

Derivation cohort the Healthy Pregnancy 4 All-1 programme

The national HP4All-1 programme was conducted in the Netherlands from 2011 through 2014.[9] Two sub-studies within the programme combined public health and epidemiologic research. The first evaluated the effectiveness of programmatic preconception care, and the second evaluated the effectiveness of antenatal risk assessment with consecutive risk-guided care throughout pregnancy.[8,13]

The antenatal risk assessment sub-study

The antenatal risk assessment sub-study was conducted as a C-RCT aiming to reduce adverse pregnancy outcomes by implementing a complex intervention.[7] The complex intervention consisted of three parts; 1) a first trimester risk surveillance using the R4U-scorecard, assessing both medical and non-medical risk factors known to be associated with adverse perinatal health outcomes (supplementary figure 1); 2) subsequent application of risk-specific care pathways; and 3) multidisciplinary consultation between care professionals from different echelons to discuss high-risk cases (e.g. health care organisations, public health care organisations, the office for legal or financial support).

Randomisation in this study took place at the level of the clusters, consisting of community midwifery practices or obstetric departments in hospitals. In the intervention arm, identification of specific risk factors implied a follow-up action such as tailoring care using risk-specific care pathways. In the control clusters, conventional obstetric care was provided. This consisted of screening by means of the 'list of obstetric indications' (LOI), which focuses on identification of single, manifest obstetric and medical risks, combined with individual care according to local protocols of obstetric care givers[6].

The data from this C-RCT was used as external data to update the R4U-scorecard that was originally piloted in several hospitals and midwifery practices in Rotterdam from 2010 until 2011.[14]

The R4U-scorecard

The primary basis for the R4U-scorecard was a simple scoring system in which all components had been selected and scores assigned both subjectively by expert consensus and objectively using available scientific literature, as described previously.[10]

Seventy-nine medical and non-medical dichotomised variables were incorporated in the R4U-scorecard, of which 76 pertain to the first trimester (supplementary figure 1). Key examples of non-medical risk factors include: low socioeconomic status, living in a deprived neighbourhood, ineffective social integration into society, and smoking.

Two types of variables were included in the first trimester risk surveillance: predictors and awareness items.[7] The first type of factor was incorporated in the R4U-scorecard as predictive factor and will be referred to as 'predictors' (50 items). The original weighing of each predictor was based on the relative risk for adverse pregnancy outcomes (e.g. babies born preterm and/or SGA). The scores of the individual items ranged from 0-3 points and these were added up to form a cumulative score (range 0-98 points). The cumulative score of the R4U-scorecard was developed using a simple approach assuming that all features are conditionally independent of each other given the class, based on Bayes' rule.[15] The initial cut-off score was based on data from a pilot study; a score of 16 points or higher was selected to identify women in the upper 20% of risk scores.[8,16] A score above this cut-off implied a follow-up action via a multidisciplinary consultation between involved care professionals guided by a particular single, or a set of multiple, risk factors.[7]

Awareness items were incorporated to increase awareness for factors that could mediate the association between risk factors and adverse pregnancy outcomes, or to factors that are considered to be 'red flags' (26 items).[10,16] All awareness items are indications for additional consideration or evaluation, and these items do not have a score. Examples of potential mediators are: 'irredeemable financial debts', and 'previous referral to youth social services', and an example of a red flag is 'having no health care insurance'.

Participants
Participants in the intervention arm of the HP4All-1 risk screening C-RCT were included in the current study if the following data was available; 1) a completed R4U-scorecard and 2) pregnancy outcome data collected in the follow-up period.

Step 1. Data management and dealing with missing values
The primary outcome measure in the C-RCT was neonatal morbidity, defined as the combination of preterm birth (i.e. a delivery before 37 completed weeks of gestation), and/or having a SGA baby (i.e. a birth weight below the 10th centile adjusted for parity, gestational age, and gender, based on the Dutch reference curves).[17] We compared maternal, pregnancy, and prior-pregnancy predictors in uncomplicated pregnancies with pregnancies followed by perinatal morbidity (table 1).

Seven percent of the participants had at least one missing value within the predictor items, and complete case analysis would have reduced the total sample by 19 percent. A multiple

imputation approach was therefore used to account for missing values in predictors.[18] Predictor variables and outcome variables were included to inform the process, forming 20 datasets using multiple imputations with chained equations.[19] Fifteen predictors with a low incidence were excluded from the multiple imputation process since this might have resulted in computational instability and unreliable estimates. We defined a low incidence as an incidence below 2% of the total sample size. The imputed data was then used to update the original prognostic model (step 3).

Step 2. Cross-validation of the original prognostic model

Cross-validation was based on the inclusion date of participants within the HP4All-1 programme.[11] Participants before September 2014 were included in the development set and participants from September onward were included in the validation set. This date was chosen based on a second training session provided to all health care providers that implemented the R4U-scorecard in routine practice. Domain validation was performed first on complete cases to test the generalisability of the prognostic model across different domains, including participants from different health care settings (i.e. community midwifery practices, secondary and tertiary hospital care).[20] Validation was assessed with calibration plots and by computing the area under the receiver operating characteristic curve (AUC) with a 95% confidence interval (CI).[21,22] Calibration was defined as the agreement between the probabilities of neonatal morbidity, as predicted by the prognostic model, and the observed frequencies. Discrimination was defined as the ability of the original model to distinguish between women who will have a preterm and/or SGA baby and those who will not. Sensitivity and specificity were calculated at the pre-specified cut-off R4U score of 16 points.

Step 3. Updating of the original prognostic model

The process of updating the original prognostic model consisted of four steps. The multiple imputed data was used to re-estimate the effect of each predictor in the model for updating.[23] The development set was used to update the prognostic model. The validation set was used to test generalisability.

In the first step we determined which predictors were to be re-estimated by assessing their additional predictive value on top of the cumulative R4U-score. Predictors that were assessed separately in the second trimester of pregnancy were not evaluated (three items) and predictors that related to prior pregnancy characteristics were evaluated in multiparous women only (five items). A reference model was based on a univariate logistic regression model describing the association of the cumulative R4U-score with perinatal morbidity. Separate bivariate logistic regression models were constructed adding single predictors one at a time. Each nested, bivariate logistic regression model was tested separately against the reference model. Predictors were categorised as 'candidate predictors' if the p-value

of their association with adverse pregnancy outcomes independent of the total R4U score was below 0.20, with reference to the Wald test. Final selection of all candidate variables for the fully updated model was based on backward elimination of variables with a p-value above 0.20.

In the second step a heuristic shrinkage factor was added to adjust β-coefficients of all included predictors for overfitting and to avoid extreme predictions when applied to new participants.[23-25]
The shrinkage factor was estimated as follows:[25]

$$\frac{\text{Model } X^2 - (\text{degrees of freedom} - 1)}{\text{Model } X^2}$$

The number of degrees of freedom in this case is the total number of degrees of freedom that is considered in the process of selecting from all predictors, plus all covariates fitted in the model.

The third step consisted of an evaluation of the obtained multivariable model by exploring the β-coefficients and their corresponding sign and size. Because all predictors were initially incorporated in the R4U-scorecard based on their *positive* association with adverse pregnancy outcomes, a *negative* sign of the β-coefficient in the current multivariable model was considered counterintuitive. Counterintuitive signs observed in multivariable models can be explained by correlations between predictors and therefore careful evaluation of the model obtained is necessary.[25] External information from recent literature and expert opinion was sought if a sign was counterintuitive in both univariate and multivariable analyses to finalise the model selection.

In the fourth and final step, we determined the additional effect of each predictor. Hereto we divided the β-coefficients obtained from the fully updated model, by the value of the coefficient corresponding with one point increase in the cumulative R4U-score, after shrinkage and evaluation of the sign had been accounted for.

Step 4. Assessing generalisability in the validation set using the updated model
To assess the predictive value of the updated model we used the validation set. Validation was assessed with calibration plots and by computing the area under the receiver operating characteristic curve. Sensitivity and specificity of the original and update score were compared in the validation set.

RESULTS

Of the 2269 women who originally participated in the intervention arm of the C-RCT embedded in the HP4All-1 programme [7], 1752 women (77%) were included in this study. The other participants were excluded because, despite being in the intervention arm, they did not undergo antenatal risk surveillance with the R4U-scorecard. Among the included pregnancies, 282 (16%) had one of the predefined adverse perinatal health outcomes (i.e. baby born preterm or small for gestational age (SGA)). Women with an adverse outcome were more often smokers, single mothers, and more often had a net household income below 1000 euros per month (table 1).

The median R4U-score was 6 (IQR 4-9). An R4U-score above 16 points (n=90), was associated with substantially higher odds of having an adverse pregnancy outcome (OR 3.2 (95% CI 2.1-4.8)). In the development set for the cross validation, the median R4U score was the same as observed in the complete dataset. A high score (above 16 points) resulted in a higher odds of having an adverse pregnancy outcome in the development set (OR 4.2 (95% CI 2.1-8.1).

The original scoring system had an AUC of 0.58 (95% CI 0.53-0.64) in the validation set. The model showed moderate calibration as evidenced by the calibration plot (figure 1).

Figure 1: calibration plot of the original model and the updated model
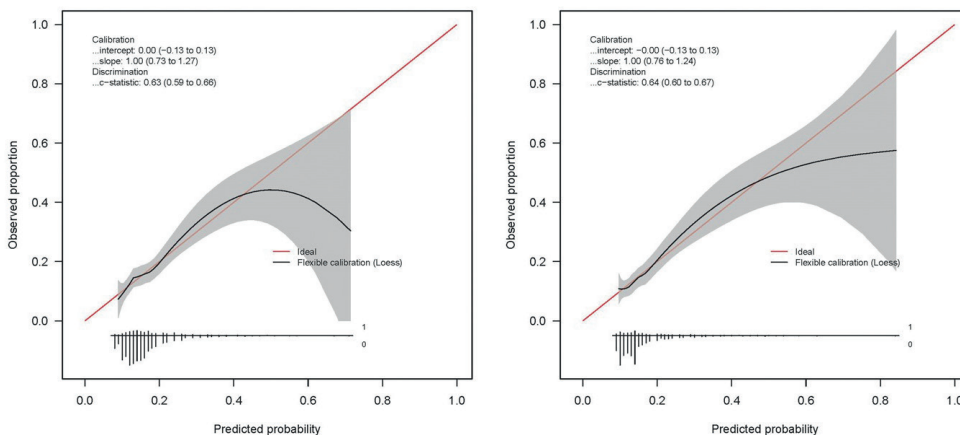
Calibration curve comparison between the original and the updated model for neonatal morbidities with 95% confidence interval in grey. The y-axis represents the observed proportion of high-risk scores (above 16 points). The intercept and slope of the logistic regression model are presented together with the c-statistic, indicating the discriminative ability. The diagonal red 45-degree line represents perfect prediction by an ideal model. The distribution of participants is indicated with spikes at the bottom of the graph, stratified by endpoint (those with neonatal morbidities above the x-axis and those without adverse outcomes below the x-axis). Graph: xlim=c(0,.45).

Table 1. Patient characteristics, comparing women with and without an adverse pregnancy outcome

		Women with adverse pregnancy outcomes (n=282)		Women without adverse pregnancy outcomes (n=1470)		
		N	%	N	%	P –value[A]
Maternal characteristics						
Age category (years)						
	<20	0	0	13	0.9	0.267
	20-35	206	73.0	1079	73.4	
	>35	76	27.0	378	25.7	
Ethnic origin						
	Western	243	86.2	1301	88.5	0.089
	Non-western	39	13.8	156	10.6	
	Missing	0	0.0	13	0.9	
Smoking during pregnancy						
	Yes	70	24.8	248	16.9	0.005
	No	210	74.5	1202	81.8	
	Missing	2	0.7	20	1.4	
Single mother						
	Yes	32	11.3	76	5.2	0.001
	No	250	88.7	1392	94.7	
	Missing	0	0.0	2	0.1	
Low household income						
	Yes	36	12.8	113	7.7	0.013
	No	245	86.9	1343	91.4	
	Missing	1	0.4	14	1.0	
BMI at start pregnancy						
	BMI <25	22	7.8	67	4.6	0.073
	BMI 25-35	195	69.1	1040	70.7	
	BMI >35	65	23.0	363	24.7	
Pregnancy characteristics						
Parity						
	Nulliparous	128	45.4	672	45.7	0.920
	Multiparous	154	54.6	798	54.3	

[A] P-value based on chi-square analysis for categorical variables.
SGA= Small for Gestational Age.

[B] Western versus non-western origin based on maternal country of birth and classified according to Statistics Netherlands.

[C] Low net income defined as a household income below 1000 euro's/month.

Update of the original model in the development set

We selected seven predictors for which the R4U score would be updated (figure 2). The heuristic shrinkage factor was calculated as 0.45 (assuming 43 degrees of freedom). One point increase in R4U-score corresponded with a β-coefficient of 0.06.

Two of the seven predictors, i.e. 'illicit drug use during the preconception period' and 'recurrent miscarriages', had a counterintuitive sign (i.e. a protective effect) and were therefore excluded from the model (figure 2).

Figure 2; updating steps of the prognostic model

STEPWISE UPDATE OF THE PREDICTION MODEL

Step 1: selection of seven predictors after backward modelling:
'illicit drug use during the preconception period', 'recurrent miscarriages (2 or more)', 'insufficient social support', 'single mother', 'experience of inadequate social support'. Additionally, two candidate predictors were selected in multiparous women, namely: 'SGA baby obstetric history', and 'preterm baby obstetric history'.

Step 2: calculating of the shrinkage factor
The heuristic shrinkage factor was calculated as 0.44 and this factor was multiplied with the obtained beta's in step 4.

Step 3: evaluation of the regression coefficient signs
The predictor 'illicit drug use during the preconception period' and the predictor 'recurrent miscarriages' had a counterintuitive protective effect and were excluded from the model.

Step 4: Update of the score of the remaining five predictors
Additional scores from highest to lowest and with increased score and final score in updated R4U-model in brackets: 'SGA baby obstetric history' 13 points (16 points), 'preterm baby obstetric history' 5 points (8 points), 'experience of inadequate social support' 6 points (7 points), 'Netto family income <1000 euro' 5 points (7 points), and 'Single mother' 5 points (6 points).

Predictive value of the updated model in the validation set

Updating of the prognostic model with regard to the remaining five predictors showed a similar discriminative ability of the R4U score in the validation set (AUC 0.61 (95% CI 0.56-0.66) compared to the development set. The updated prognostic model improved calibration (figure 1). Sensitivity increased from 11% to 23%.

DISCUSSION

We present an updated R4U-scorecard that is applicable in the first trimester of pregnancy to estimate the risk of adverse perinatal health outcomes, based on a comprehensive set of medical, obstetric, and non-medical risk factors (supplementary figure 1). By using a large external dataset and by applying a stepwise statistical approach to update the prognostic model and perform cross-validation, we have provided a comprehensive evaluation of this diagnostic tool.[12,20,23]

Our large multicentre prospective cohort included both low- and high-risk pregnancies derived from a population in which the model is aimed to be used. We applied domain validation. This is considered to be the broadest form of validation, leading to the strongest evidence that the prediction model can be generalised to new patients over time. The generalisability was underlined by the predictive value of the model in the validation set. A scorecard that is generalizable to new patients makes the subsequent institution of preventive strategies more relevant. We present a detailed description of the methodology used to update the prognostic model in several distinct steps. Validation studies of antenatal risk surveillance tools that include non-medical risk factors, such as a person's socioeconomic status, are to our knowledge non-existent. The steps we present could be considered as a framework, and can be applied in other fields of study based on the elaborate description provided.

There are also several limitations that merit discussion. First, predictors are interconnected making it difficult to establish their independent contribution. For example, having a low household income might induce changes in one or more other risk factors such as housing conditions, but risk factors such as chronic diseases may also reduce labour supply and earnings.[26-28] In view of these complex relationships, our estimates and the resulting cumulative score, which assumes unidirectional causal associations, should be interpreted with caution.

Second, the development and validation of the models originated from a prospective cohort in the Netherlands, potentially limiting the generalisability outside the Dutch antenatal health care system. Additionally, the previously reported degree of selection bias in the C-RCT,[7] also applies to the results presented. A generally healthy population was included with a lower incidence of adverse pregnancy outcomes than the Dutch national average. Importantly, this bias is likely to cause underestimation of the discriminating power of the model.

Thirdly, we made some simplifications for easy clinical application of the R4U-scorecard. For example, all predictors and the outcome were dichotomised.

Both calibration and discrimination are useful aspects of a prediction model. However, in general discrimination is insensitive to errors in calibration, and considers the situation of classification in a pair of participants with and without the endpoint.[29] By applying the stepwise statistical approach in order to update the predictors in the scorecard we primarily intended to improve calibration.

To further improve clinical decision making with the updated scorecard, a range of thresholds for high and low-risk participants could be considered to optimise the discriminative value. It is usually difficult to define an optimum threshold as empirical evidence for the relative weights of benefits and harms is often lacking. In our example considerations should weigh

the potential of early identification of pregnant women at risk and the possibility to introduce preventive strategies early in the first trimester of pregnancy, against the potential harms of 'over-treatment'.

Moreover, to create a valuable decision tool for antenatal risk surveillance and preventive strategies, a prognostic model alone is not sufficient. Consecutive preventive strategies (e.g. care-pathways) prioritised at addressing risk factors with a high relative risk for adverse health outcomes together with comprehensive guidelines for preventive strategies for individual risks, need to be available and updated regularly to fit changes in daily clinical practices. Also, updating of the R4U prognostic scoring system may be needed to meet the local population.

Implementation of accurate prognostic models early in pregnancy provides room for preventive strategies and embodies potential to change daily practices and reduce early adversity in health outcomes. By updating the R4U-scorecard we have amended a clinical tool to guide these actions. Furthermore, we presented a framework for updating of a prognostic model with new information while keeping the prior information. This framework is relevant for wider implementation of prognostic models in clinical practice.

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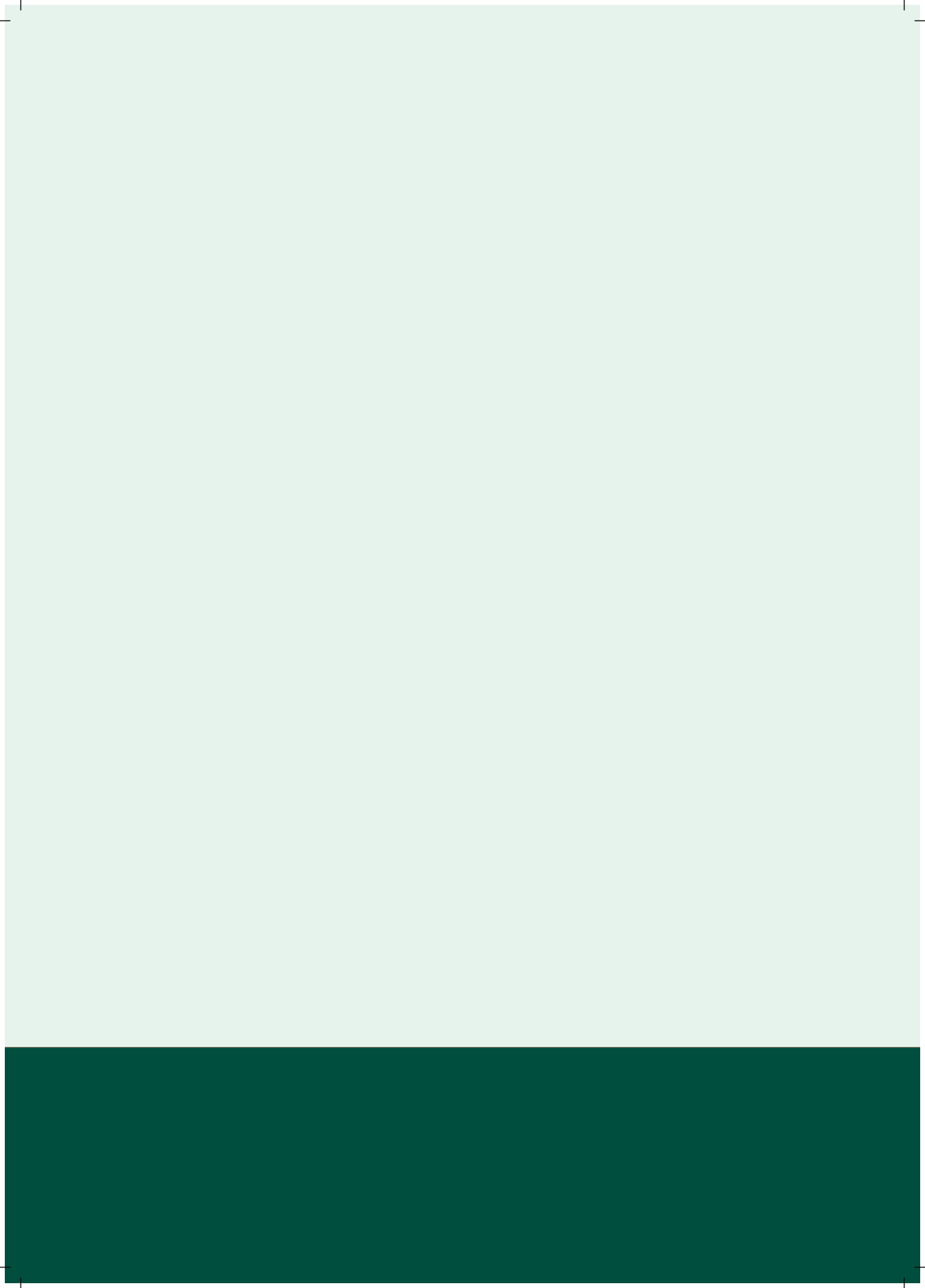
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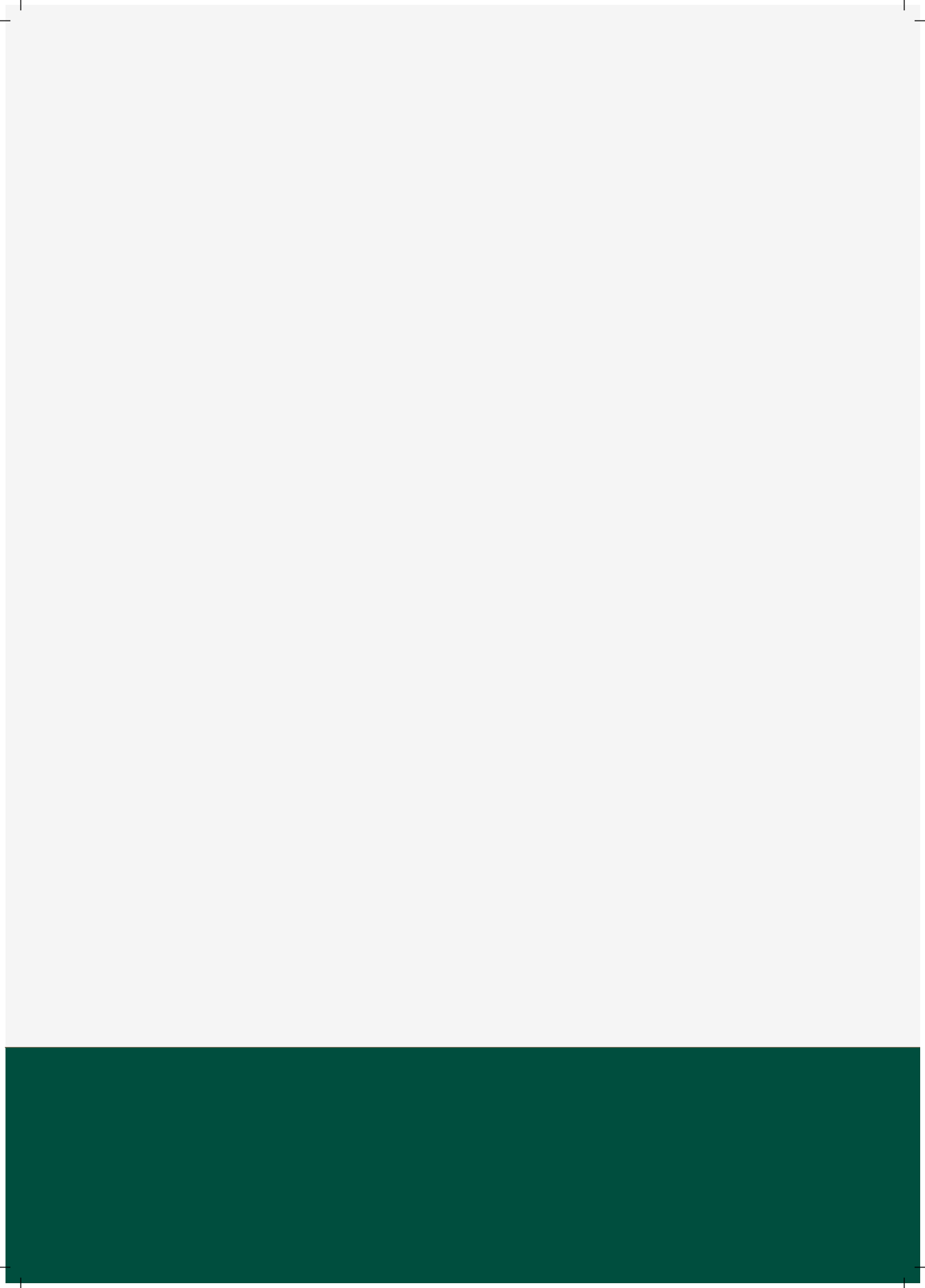
PART II

Addressing postpartum care to reduce inequalities in maternal and child health

CHAPTER 5

Geographical differences in perinatal health and child welfare in the Netherlands: rationale for the healthy pregnancy 4 all-2 program.

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ABSTRACT

Background
Geographical inequalities in perinatal health and child welfare require attention. To improve the identification, and care, of mothers and young children at risk of adverse health outcomes, the HP4All-2 program was developed. The program consists of three studies, focusing on creating a continuum for risk selection and tailored care pathways from preconception and antenatal care towards 1) postpartum care, 2) early childhood care, as well as 3) interconception care. The program has been implemented in ten municipalities in the Netherlands, aiming to target communities with a relatively disadvantageous position with regard to perinatal and child health outcomes. To delineate the position of the ten participating municipalities, we present municipal and regional differences in the prevalence of perinatal mortality, perinatal morbidity, children living in deprived neighbourhoods, and children living in families on welfare.

Methods
Data on all singleton births in the Netherlands between 2009 and 2014 were analysed for the prevalence of perinatal mortality and morbidity. In addition, national data on children living in deprived neighbourhoods and children living in families on welfare between 2009 and 2012 were analysed. The prevalence of these outcomes were calculated and ranked for 62 geographical areas: the 50 largest municipalities and the 12 provinces, to determine the position of the municipalities that participate in HP4All-2.

Results
Considerable geographical differences were present for all four outcomes. The municipalities that participate in HP4All-2 are among the 25 municipalities with the highest prevalence of perinatal mortality, perinatal morbidity, children living in deprived neighbourhoods, or children in families on welfare.

Conclusion
This study illustrates geographical differences in perinatal health and/or child welfare outcomes and demonstrates that the HP4All-2 program targets municipalities with a relative unfavourable position. By targeting these municipalities, the program is expected to contribute most to improving the care for young children and their mothers at risk, and hence to reducing their risks and health inequalities.

INTRODUCTION

Suboptimal health before birth and in early life has long term consequences for children, their families, and next generations [1]. Moreover, substantial (perinatal) health inequalities are present between, and within, high-income countries. In the Netherlands, perinatal mortality rates are higher than in many other European countries [2], and these rates differ widely between regions and even between neighbourhoods [3-5].

Living in a deprived region is acknowledged as an important risk factor for adverse birth outcomes, such as preterm birth and small-for-gestational age birth [3 6 7]. In deprived regions the prevalence of risk factors, single or in combination, is higher than in non-deprived regions [8 9]. Not only medical risks, but also non-medical risk factors are involved, often related to poverty, such as low socioeconomic status, substance abuse including smoking, and psychological distress [9].

Since 2008, in response to the awareness about the high prevalence of adverse perinatal outcomes in the Netherlands, much effort has been invested into improving perinatal health.[10] This has led to research and policy programs that aim to increase attention for risk assessment and risk reduction before and during pregnancy. One such program, 'Ready for a Baby' (2008-2012), was initiated with the aim to improve perinatal health in Rotterdam, the second largest city in the Netherlands, especially in its deprived neighbourhoods [11 12]. Strengthening of the inter-professional collaboration between curative and the public health professionals and reaching-out to a more vulnerable population, consisting of low-educated and/or immigrant groups, were the stepping stones to reach this goal.

In 2011, building on the insights of the 'Ready for a Baby' program, we launched the Healthy Pregnancy 4 All (HP4All-1) program in 14 municipalities that had higher rates of adverse perinatal outcomes than the national average [4]. The HP4All-1 program focused on: a) the implementation of preconception care via different recruitment strategies, and b) the introduction of systematic antenatal risk assessment (considering both medical and non-medical risk factors) with the antenatal Rotterdam Reproductive Risk Reduction (R4U) scorecard, followed by tailored multidisciplinary care pathways [13 14]. Again, optimal linkage between the curative and the public health domain was sought on preconception, prenatal and perinatal care.

Since 2014, this approach has been extended to cover postpartum care, early childhood care and interconception care in the Healthy Pregnancy for All 2 (HP4All-2) program.

HP4All-2 program
The HP4All-2 program focuses on creating a continuum of risk selection, followed by tailored (multidisciplinary) care pathways, from the preconception and prenatal period towards the

postpartum and early childhood period. The rationale for this focus is that certain risk factors before and during pregnancy, such as neighbourhoods and individual social characteristics, often continue to exist after delivery, affecting both maternal and offspring health [6,15]. Moreover, perinatal health status in itself is an important determinant of child health and health in later life [1]. For example, high birth weight is positively associated with childhood overweight and low birth weight is negatively associated with developmental outcomes [16] [17]. To translate this knowledge into practice, comprehensive care beyond the boundaries of the separate social and medical domains of care is needed in the preconception, prenatal, postpartum and early childhood period [18].

Therefore, HP4All-2 aims to introduce integrated, risk-guided care, beyond separate domains of antenatal care, maternity care and Preventive Child Health Care (PCHC). In the Netherlands, professional maternity care is provided at home by maternity care assistants, who have completed a specialisation of 'personal health care assistant' at the level of secondary vocational education and are being supervised by community midwives [19]. PCHC organizations promote children's health up to the age of 19 years by providing immunisations, monitoring growth and development, offering health advice, and referring to specialised care if needed [20,21].

Maternity care and PCHC are used as the main settings for three risk assessment interventions that are studied within the HP4All-2 program. These three intervention studies are being implemented in ten municipalities that agreed to participate in one or more of the studies (table 1).

Table 1. An overview of the participation of municipalities in the HP4All-2 program, and its studies

Municipality	Maternity care study [a]	PCHC study [b]	Interconception care study [c]
Amsterdam*		X	X
Rotterdam*	X	X	X
Den Haag*			X
Utrecht*	X		
Tilburg*			X
Groningen*	X		X
Almere*	X		X
Arnhem	X		
Dordrecht		X	
Schiedam*	X		X

a) Structured risk assessment during pregnancy and customised maternity care study; b) Optimizing postnatal risk assessment in PCHC study; c) Interconception care study through PCHC; * selection based on their participation in earlier programs ('Ready for a Baby' or HP4All-1)

Study 1: Structured risk assessment during pregnancy and customised maternity care
Aim This study aims to timely plan customised maternity care to the individual needs of women at high risk for adverse pregnancy and child outcomes.

Rationale Previous research indicates that high risk women benefit more from intensive postpartum care than women with low risks [22] [23]. This yields the need for a structured risk assessment during pregnancy in conjunction with custom fit maternity care.

Study design This study is a cluster randomised controlled trial in six municipalities in the Netherlands. Within a municipality, two clusters are formed in the same geographical area; one intervention and one control cluster. Two municipalities were merged together to account for enough participants, resulting in a total number of 10 clusters. A cluster may consist of one or more maternity care organisations. The intervention under study is a systematic risk assessment during pregnancy of medical and non-medical risk factors for adverse maternal and child outcomes, in conjunction with client-tailored care during pregnancy and the postpartum period. In the control clusters this systematic risk assessment is introduced during pregnancy as well, yet is followed by conventional maternity care during pregnancy and in the postpartum period. All pregnant women cared for by participating maternity care organisations, who have a scheduled home visit during pregnancy, are invited to take part in the trial.

Outcomes Primary outcome is maternal empowerment assessed between day six and 14 postpartum. Secondary outcome measures include maternal health outcomes, maternal health behaviour and health care utilisation in the first months postpartum. In addition, we will assess the determinants of successful implementation by questionnaires addressed to managers of maternity care organisations and to maternity care assistants.

Study 2: Optimising postnatal risk assessment in Preventive Child Health Care
Aim This study aims to identify and reduce the risk of growth and developmental problems in children before the age of 18 months, during their postnatal visits to the PCHC centre.

Rationale Within PCHC centres, care is provided to all children and families free of charge, with population coverage of 95% during the first year of life. Therefore, it seems to be the ideal setting for early risk screening and indicating appropriate care for vulnerable families at risk of adverse child health outcomes. To ensure structured risk assessment, the 'postnatal R4U' has been developed (comparable to the 'antenatal R4U' [13]). This risk assessment instrument scores both medical and non-medical risk factors and combines information already documented by the PCHC, obstetric data and newly screened items. All items of the 'postnatal R4U' are based on an extensive literature search and expert consultations by

focus group interviews. In summary, the items were categorised into six domains: the social [24-26], ethnicity [17 27], care status [28], lifestyle [29-31], obstetric [32 33] and medical domains [34 35].

Study design In this prospective cohort study, the 'postnatal R4U' is introduced in the participating PCHC centres in three municipalities. All children aged zero to eight weeks old will be assessed with this instrument and, in case of detected risks, integrated care pathways will be offered to reduce the detected risks. A historical control group of children in the same four-digit postal code area will be constructed for comparison of the study outcomes.

Outcomes Primary outcomes are growth problems (defined as overweight, obesity and catch-up growth) and developmental problems in children until the age of 18 months. Developmental problems will be assessed using the 'Van Wiechen Scheme', a Dutch instrument for monitoring motor, language, cognitive and psychosocial development which is routinely applied from birth onward at visits to the PCHC centre.[36]

Study 3: Interconception care through Preventive Child Health Care
Aim This study aims to implement and evaluate interconception care in PCHC centres.

Rationale Interconception care, also referred to as preconception care between pregnancies, aims to facilitate optimal preparation for pregnancy and minimise risk factors for an adverse pregnancy outcome. Delivery of interconception care is still uncommon [37]. A valuable opportunity to deliver interconception care can be through PCHC centres, since almost all parents and their young children visit PCHC centres regularly for routine well-child visits [38].

Study design In this prospective cohort study, interconception care is implemented in participating PCHC centres in seven municipalities. PCHC professionals are instructed to inform women about the possibility of an interconception care consultation in case of a (future) pregnancy wish. They discuss this possibility with women who attend for a routine visit at their child's age of six months. Subsequently, women can make an appointment for a separate interconception care consultation. In three municipalities women are offered this consultation by the PCHC centre, in the other four municipalities they are referred to local midwives or general practitioners. Decisions on which approach was applied, were made in mutual agreement with stakeholders within the municipalities.
Professionals are requested to record each time they discuss the possibility of an interconception care consultation with women, as well as when they provide the actual consultation.

Outcomes Primary outcome is the effectiveness of the implementation of interconception care in PCHC, measured as the proportion of eligible women who were informed about

an interconception care consultation. Secondary outcomes include determinants of the implementation, effectiveness and utilisation of interconception care, studied by surveying women with a (future) pregnancy wish and PCHC professionals.

The HP4All-2 program is currently implementing these studies, aiming to target municipalities with a relatively disadvantageous position on perinatal and child health outcomes. In 2014 we presented data on regional perinatal health outcomes in the Netherlands during the period 2000-2008, based on which municipalities were invited to participate in the HP4All-1 program [4]. To delineate the recent position of the ten currently participating municipalities relative to other regions in the Netherlands, we now present the municipal and regional prevalence of perinatal mortality and morbidity over the period 2009-2014. Additionally, given the focus of the HP4All-2 program on postnatal care in continuum with antenatal care, proxies for socioeconomic risk factors for adverse child health are included in our analyses, being the prevalence of children living in deprived neighbourhoods and of children living in families on welfare over the period 2009-2012.

METHODS

Data sources
National data on all singleton births from 22 weeks of gestation onwards between 2009 and 2014 were obtained from Perined (www.perined.nl) in April 2016. Perined contains information on more than 97% of all pregnancies in the Netherlands. Pregnancy, delivery, and neonatal data are routinely collected by midwives, gynaecologists and paediatricians [39]. A detailed description of the linkage procedures can be found on the Perined website (www.perined.nl).

Small area-level data on the proportion of children living in deprived neighbourhoods and of children living in families on welfare between 2009 and 2012, were provided by the 'Defense for Children' (www.defenseforchildren.nl), a Dutch non-governmental Coalition for Children's Rights. This coalition monitors data on child well-being, based on 'Kid's Count', a method used in the USA [40][41]. The data of both outcomes applied to the age group 0 up to and including 17 years, and were available per four-digit postal code per year. Details on the definitions of these outcomes are available at the website (www.defenseforchildren.nl).

Data from Statistics Netherlands (CBS, www.CBS.nl) were used to identify the 50 largest municipalities of the Netherlands, based on the number of inhabitants in January 2015 (all above 70,000 inhabitants).

The four-digit postal code from the Perined database was used to assign each pregnancy to one of these 50 municipalities or to one of the 12 provinces (excluding the 50 previously selected municipalities). In the same way, the data on children living in deprived neighbourhoods and living in families on welfare were assigned to one of these 62 geographical areas.

Data on socioeconomic status (SES) were based on an area-level SES indicator by four-digit postal code, constructed by the Netherlands Institute for Social Research (SCP, www.scp.nl) over the year 2014. The SES indicator had been composed by a principal component analysis of the following items: 1) mean annual income per household, 2) percentage of households with low income, 3) percentage of households with low education and (4) percentage of unemployed inhabitants [42].

The SES data were linked to the data on pregnancies using the four-digit postal code.

Outcomes
Perinatal mortality: was defined as death occurring between 22 weeks of gestational age and 7 days after birth. This determinant includes foetal mortality, intrapartum mortality and early neonatal mortality.

BIG2: was defined as small for gestational age (SGA) and/or preterm birth. SGA was defined as a birth weight below the 10th centile adjusted for ethnicity, parity, gestational age, and gender [43]. Preterm birth was defined as any birth occurring before 37+0 weeks of gestational age.

Proportion children living in deprived neighbourhoods: was defined as the number of children, in the age group zero up to and including 17 years, living in deprived neighbourhoods per municipality, divided by the total number of children of that age living in that municipality.

Proportion children living in families on welfare: was defined as the number of children in the age group 0-17 years, living in families on welfare per municipality, divided by the total number of children of that age living in that municipality.

Determinants
Ethnicity: the mothers' ethnicities were categorised into Western and non-Western. Western consisted of Dutch and other European nationalities. Non-western consisted of all other (i.e. non-European) ethnicities. Socioeconomic status: the SES-scores where categorised into three groups: 'Low', a SES-score below the 20th centile; 'Medium', from the 20th up to and including the 80th centile; and 'High', above the 80th centile. Parity: the mothers' parity

was dichotomised into 2 categories: 'Primiparity' including all first time pregnancies; and 'Multiparity', including all subsequent pregnancies.

Missing data

The amount of missing data varied across determinants and ranged between 0.01% (parity) and 1.6% (ethnicity). In the data provided, there were no missing data on perinatal mortality, BIG2, children living in deprived neighbourhoods, and children living in families on welfare. Each determinant was assessed on unlikely or contradictory values. These unlikely values were found in the determinants 'age of the mother' (values below 10 years of age), and 'postal code' (if area code was officially labelled as uninhabited). Unlikely values were considered as missing data. Missing data were not imputed, as the determinants containing missing data were only used to describe the population and there were no missing data for each of the outcomes.

Statistical analyses

Firstly demographic characteristics (i.e. age , ethnicity, parity, and SES) of all singleton births, as well as perinatal outcomes and child welfare outcomes were tabulated according to whether these occurred in one of the four largest cities of the Netherlands (Amsterdam, Rotterdam, The Hague, and Utrecht (the G4)), in analogy to Denktaş et al [4].

Secondly, to delineate the recent position of the participating HP4All-2 municipalities relative to other regions in the Netherlands, each birth was assigned to one of the 62 selected geographical areas (50 largest municipalities and 12 provinces), and the geographical prevalence (per 1000 births) of perinatal mortality, BIG2, children living in deprived neighbourhoods, and children living in families on welfare was calculated. Maps were constructed to graphically illustrate these distributions.

Thirdly, the calculated prevalence per geographical area for all four outcomes was used to construct a ranking of the geographical areas. For each outcome, rank 1 was assigned to the geographical area with the highest prevalence and rank 62 to the area with the lowest prevalence.

Finally, the prevalence of known socio-demographic risk factors for adverse perinatal outcomes for which we had data (i.e. age of mother below 20, non-Western ethnicity, primiparity, and low SES) were tabulated against the 62 geographical areas.

The analyses were based on non-blinded data, since we based our analyses on national registry data independent of the HP4All-2 program. Analyses were performed using R version 3.2.3 (2016, The R Foundation for Statistical Computing) and ArcGIS 9.3, a geographical information system (release NL-16m07).

RESULTS

Of the 1 027 556 births in the Netherlands registered with Perined over the period 2009 – 2014, 1 009 687 (98%) were singleton pregnancies, and used for the analyses. In table 2 characteristics of these pregnancies are tabulated by whether women lived in one of the four largest cities or in the rest of the Netherlands (The Netherlands minus the four largest cities).

Table 2. Population characteristics of the singleton births between 2009 and 2014 and child welfare outcomes between 2009 and 2012, stratified by location in the four largest cities (G4) or in the rest of the Netherlands.

	G4-cities	The Netherlands minus G4-cities	Total
Singleton births	174,989	834,698	1,009,687
Parity			
Primiparous	49.0	45.2	45.9
Multiparous	51.0	54.8	54.1
Ethnicity			
Western	65.1	89.7	85.5
Non- Western	34.9	10.3	14.5
Maternal age			
< 20 years	1.6	1.2	1.2
20-24 years	10.5	10.1	10.2
25-29 years	25.1	31.7	30.6
30-34 years	37.1	37.1	37.1
≥ 35 years	25.7	19.8	20.9
Socioeconomic status score			
Low (< p20)	39.5	16.0	20.1
Middle (p20 – p80)	32.3	65.7	59.9
High (> p80)	28.2	18.3	20.0
Perinatal outcomes			
Congenital anomalies	2.3	2.7	2.7
Preterm birth	6.2	6.1	6.1
Small for gestational age	10.2	8.3	8.7
Apgar score <7 (5min after birth)	2.3	1.9	1.9
Any BIG2[*]	15.7	13.9	14.2
Fetal mortality	0.32	0.30	0.30
Intrapartum mortality	0.20	0.17	0.18
Early neonatal mortality	0.34	0.29	0.30
Perinatal mortality†	0.86	0.76	0.78
Children 0-17 years (4 years)**	1,692,985	12,339,094	14,032,079
Child welfare outcomes			
Children living in deprived neighbourhoods	43.8	13.7	17.3
Children living in families on welfare	13.4	4.2	5.3

Data are presented as percentages. * = Individual BIG2 morbidities (combination of SGA and/or premature births) do not add up to 'Any BIG2' as newborns can have >1 BIG2 morbidity. † = Total of foetal (from 22 weeks gestational age), intrapartum, and neonatal mortality (up to 7 days after birth) ** Sum of Children 0-17 years in 2009, 2010, 2011 and 2012.

Regarding the total number of the births in the Netherlands, the median age of the mother was 30 years (interquartile range: 27 – 40) and the mothers' ethnicity was predominantly Western (86%).The overall perinatal mortality over the period between 2009 and 2014 was 7.8 per 1000 births. Perinatal morbidity, represented by BIG2, was 142 per 1000 births.

In the four largest cities, considerably more mothers were of non-Western ethnicity (35% vs. 10%) and had low SES (40% vs. 16%) compared to the mothers in the rest of the Netherlands. Perinatal mortality and morbidity (i.e. BIG2) per 1000 was also higher in the four largest cities: 8.6 vs. 7.6 per 1000, and 157 vs. 139 per 1000, respectively.

The national prevalence of children living in deprived neighbourhoods and living in families on welfare were 173 and 53 per 1000 children in the Netherlands, respectively. Again, both were higher in the four largest cities; 438 vs. 137 per 1000 for children living in deprived neighbourhoods and 134 vs. 42 per 1000 for children living in families on welfare.

In table 3 the prevalence of perinatal mortality, BIG2, children living in deprived neighbourhoods, and children living in families on welfare are shown for each of the 62 geographical areas. Between geographical areas, perinatal mortality ranged from 5.3 – 10.2 per 1000 births, and perinatal morbidity ranged between 117 and 195 per 1000 births. The prevalence of children living in deprived neighbourhoods ranged between 0 and 895 per 1000, and for children living in families on welfare between 23 and 174 per 1000. The prevalence of all four outcomes in the 62 geographical areas is illustrated in figures 1a to 1d. In supplementary table 1 the prevalence of maternal age below 20 years, parity, non-Western ethnicity, and low SES tabulated for each of 62 geographical areas are presented.

Table 3. Prevalence (per 1000) of perinatal mortality, morbidity (BIG2), between 2009 and 2014, and children living in deprived neighbourhoods, and children living in families on welfare between 2009 and 2012, for the Netherlands and the selected 62 geographical areas.

	Perinatal mortality	BIG2 *	Children in deprived neighbourhoods	Children in families on welfare
The Netherlands	7.8	141.7	173.1	53.4
50 largest municipalities				
Amsterdam	8.8	151.2	450.7	144.3
Rotterdam	8.9	173.4	595.0	174.4
Den Haag	8.7	165.5	373.5	105.8
Utrecht	7.6	132.5	206.9	74.0
Eindhoven	8.8	156.5	304.1	80.8
Tilburg	8.7	170.8	246.0	78.5
Groningen	9.1	138.8	325.2	120.8
Almere	8.9	163.6	65.7	70.6
Breda	6.5	146.9	160.5	58.2
Nijmegen	7.3	145.5	337.1	93.3
Apeldoorn	8.9	136.1	35.3	43.4
Enschede	8.7	164.0	563.6	103.1
Haarlem	7.4	133.2	193.8	47.8
Arnhem	6.7	146.9	360.1	106.8
Amersfoort	6.3	127.6	35.9	45.2
Zaanstad	8.6	151.7	262.6	49.0
Den Bosch	7.8	152.5	179.4	51.7
Haarlemmermeer	8.4	133.5	0.0	24.8
Zwolle	7.3	118.2	122.2	56.4
Zoetermeer	10.2	151.8	68.6	73.1
Leiden	6.9	137.5	122.7	71.1
Maastricht	9.7	174.1	354.0	83.2
Dordrecht	7.1	146.0	261.5	71.8
Ede	6.0	117.2	0.0	37.5
Alphen a/d Rijn	6.9	120.3	10.2	36.1
Leeuwarden	9.7	136.6	291.9	98.9
Alkmaar	7.3	134.9	80.3	43.9
Emmen	6.8	145.6	650.6	68.9
Westland	7.1	121.5	2.9	23.6
Delft	8.1	144.7	308.3	95.1
Venlo	9.5	149.7	373.7	72.7
Deventer	6.8	147.8	261.7	49.4
Sittard-Geleen	7.2	160.8	384.9	72.3
Helmond	8.9	158.3	316.3	64.5
Oss	7.4	157.2	186.8	33.6
Amstelveen	7.4	139.8	0.0	25.5
Hilversum	8.9	139.4	154.5	37.3
Heerlen	9.3	195.0	895.4	124.6
Nissewaard	6.3	166.1	18.5	62.4
Sudwest Fryslan	6.7	118.2	280.0	42.2
Hengelo	5.3	137.6	380.9	56.5
Purmerend	7.5	156.0	113.8	38.1
Schiedam	8.0	167.1	328.3	101.2

Roosendaal	10.2	167.4	38.4	44.2
Lelystad	9.5	166.6	245.3	67.0
Leidschendam-Voorburg	6.5	132.5	133.6	61.2
Almelo	5.9	154.2	557.1	72.9
Hoorn	6.0	132.8	0.0	44.3
Middelburg	7.4	124.8	147.9	57.7
Vlissingen	7.4	160.2	182.2	75.5
12 Provinces (minus 50 largest municipalities)				
Groningen	8.9	139.0	462.2	49.8
Friesland	7.9	125.8	377.8	37.3
Drenthe	7.5	121.9	241.6	40.8
Overijssel	7.2	124.6	80.9	23.1
Gelderland	7.5	132.1	48.4	28.6
Utrecht	6.7	123.6	17.9	27.9
Noord-Holland	6.6	124.7	29.6	27.7
Zuid-Holland	7.1	131.1	55.4	32.3
Zeeland	7.7	137.6	83.9	27.2
Noord-Brabant	7.5	146.4	38.5	26.5
Limburg	8.3	159.1	136.2	44.2
Flevoland	8.8	125.6	112.1	35.0

Data are presented as promille (1 per 1000). Perinatal mortality and morbidity over the period 2009-2014 and children in deprived neighbourhoods and living in families on welfare over the period 2009-2012. Ordering of the 50 largest municipalities is based on the number of inhabitants per municipality, with the largest municipality displayed first. * = BIG2 combination of SGA and/or premature births.

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Table 4 shows the relative ranking of the ten participating municipalities in HP4All-2 for each of the four outcomes presented in table 3.

Table 4. Ranking of the ten participating HP4All-2 municipalities on perinatal mortality, BIG2, children living in deprived neighbourhoods, and children living in families on welfare.

	Perinatal mortality	BIG2*	Children in deprived neighbourhoods	Children in families on welfare
Amsterdam	15	23	7	2
Rotterdam	9	3	3	1
Den Haag	18	9	12	6
Utrecht	29	46	29	16
Tilburg	19	4	26	14
Groningen	8	36	17	4
Almere	13	11	47	23
Arnhem	52	27	13	5
Dordrecht	44	29	25	21
Schiedam	25	6	16	8

Data represent the relative ranking of the prevalence of each outcome for the ten participating HP4All-2 municipalities in the Netherlands. Rank 1 corresponds to the highest prevalence of that outcome, while rank 62 represents the lowest prevalence of that outcome.

Higher rankings correspond to higher prevalence for the corresponding outcome. Seven of the ten HP4All-2 municipalities are ranked in the top 10 for one or more of the outcomes, and all of them are placed in the top 25 for at least one of the outcomes.

Figure 1a-d: The prevalence of all four outcomes in the 62 geographical areas is illustrated

a

	< 5.9
	5.9 - 7.2
	7.2 - 8.4
	8.4 - 9.6
	> 9.6

b

	110 - 131
	131 - 152
	152 - 173
	> 173

c

	< 74.0
	74.0 - 296.3
	296.3 - 520.3
	> 520.3

d

	< 26.9
	26.9 - 67.1
	67.1 - 107.6
	> 107.6
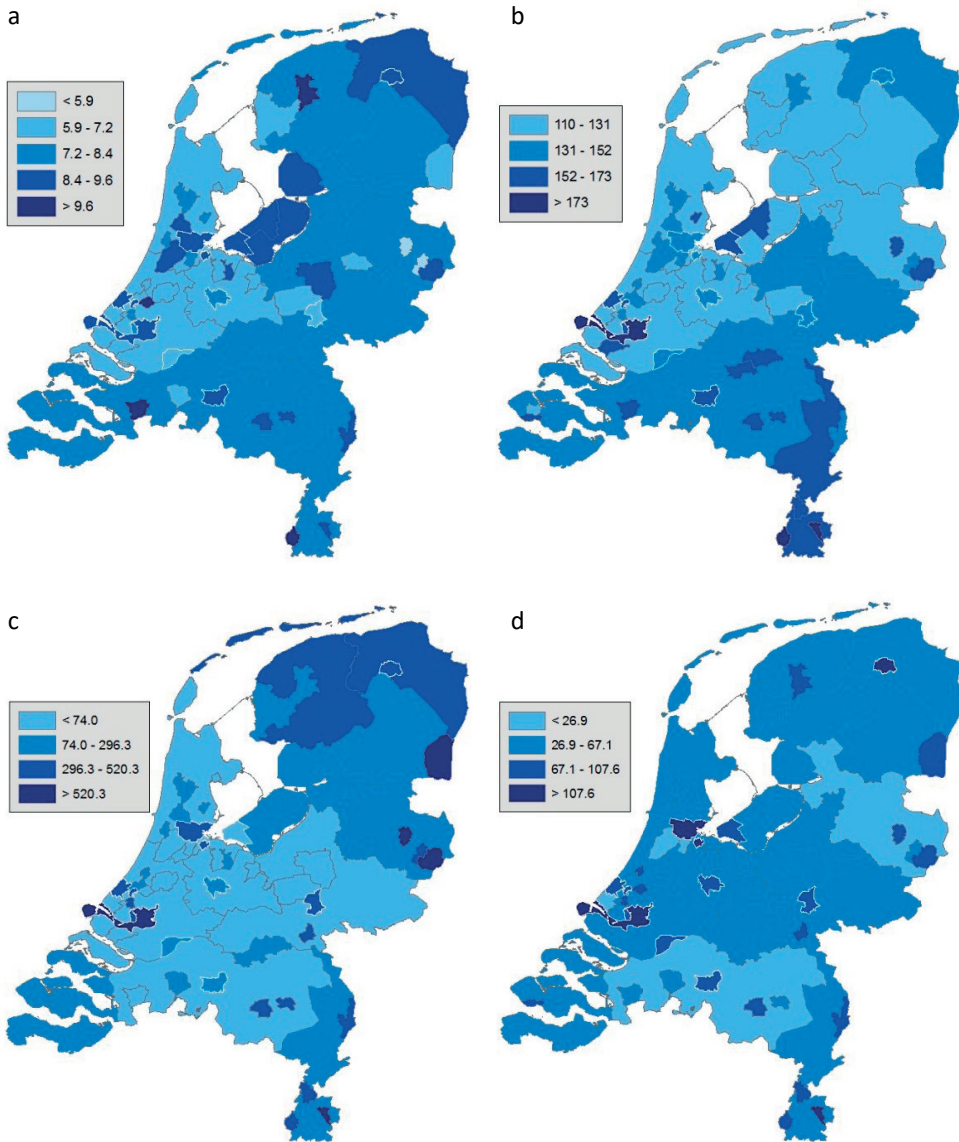
a. Perinatal mortality
b. Perinatal morbidity (BIG2)
c. Children in deprived neighbourhoods
d. Children in families on welfare

DISCUSSION

We identified considerable variation between geographical areas within the Netherlands for perinatal mortality and morbidity, and the prevalence of children living in deprived neighbourhoods and children living in families on welfare (table 3). This study shows that even in a high-income country such as the Netherlands, important geographical inequalities in perinatal and child health exist. The results of this study also suggest associations between adverse perinatal health and socio-economic disadvantage of children. Furthermore, when relating area-level SES (supplementary table 1) with the outcomes (table 3) it appears that the municipalities with a higher prevalence of the study outcomes also have a higher proportion of births occurring in women from a low SES area (statistically significant positive correlation; analysis not shown). The importance of area SES and deprivation in relation to poor health outcomes in general, and more specifically perinatal and child mortality has been recognised with regards to other western countries as well [7 15 44 45]. In addition to area SES and individual-level risk indicators, other area characteristics could contribute to explaining the geographical differences found in this study, such as environmental factors or population density (i.e. air pollution, minority density and distance to health care) [46-48]. Although the aim of the analyses was not to unravel the potential causes of the geographical differences, it highlights the urgency to reduce these inequalities.

The municipalities that were approached and have agreed to participate in the HP4All-2 program are among the municipalities with the most unfavourable perinatal health and/or child welfare outcomes. In the predecessor program HP4All-1, similar types of analyses were performed to identify those municipalities that had the highest rates of adverse (birth) outcomes.[4] The selection of HP4All-2 municipalities was not guided by formal analyses. Instead, selection of municipalities was guided by 1) participation in HP4All-1 and 'Ready for a Baby', and 2) interest shown by municipalities in the topic addressed in the program. A reason for selecting municipalities this way was that in the predecessor programs close collaboration with the participating municipalities had been established, which presumably facilitates the implementation of the HP4All-2 program studies. In these municipalities, the health care professionals, local government, and local public health services were already committed to improve perinatal outcomes via a broad multidisciplinary network.[10] Both newly selected municipalities (Dordrecht and Arnhem) have improving care for more vulnerable women and children high on the political agenda. The selection was thus merely based on effective implementation of the program in those municipalities, which we expected to have a relatively unfavourable position, not on the actual position. Nevertheless, our analyses demonstrate that most of our selected municipalities are among the worst performing in the Netherlands, with the exception of Dordrecht with a highest ranking of 21.

The intention to target high-risk municipalities with the HP4All-2 program has been based on the assumption that geographical areas with a relatively large population being at risk of adverse perinatal and child health outcomes will benefit most from interventions aimed at reducing those adverse outcomes. Sharing knowledge on how to support the most vulnerable families in the society with all involved parties is crucial, but challenging [18]. Therefore, the implementation of the HP4all-2 program, and its studies, is also expected to be challenging. Along with partnership with local parties, training sessions to share the required knowledge are being offered to health care professionals involved to help the implementation of the program.

CONCLUSION

The ten participating municipalities in HP4All-2 all had a relatively unfavourable position regarding perinatal health and/or child welfare outcomes prior to the start of the program. In these municipalities, HP4All-2 aims to improve the care for young children and their mothers by extending the continuum for risk selection and tailored care from the preconception and prenatal period towards the postpartum, early childhood and interconception period, beyond the boundaries of separate domains of health care. By implementing and evaluating this enhanced risk management in high-risk populations, HP4All-2 aims to contribute to the reduction of (perinatal and childhood).

SUPPLEMENT

Supplementary table 1. Demographic characteristics of the singleton pregnancies for each of the 62 selected geographical areas.

	Maternal age < 20 years	Primiparous	Non-Western ethnicity	Low SES
The Netherlands	1.3	45.8	14.2	20.0
50 largest municipalities				
Amsterdam	1.3	50.0	35.5	38.2
Rotterdam	2.5	48.6	38.2	57.41
Den Haag	1.7	47.1	36.9	37.04
Utrecht	0.6	49.8	20.9	17.22
Eindhoven	1.2	48.9	20.9	20.81
Tilburg	1.6	48.6	17.9	36.49
Groningen	1.6	51.9	9.9	39.3
Almere	2.1	44.2	34.5	4.74
Breda	1.5	48.5	12.9	21.08
Nijmegen	1.1	49.5	11.4	28.45
Apeldoorn	1.4	45.6	9.6	9.52
Enschede	2.2	46.8	15.2	56.99
Haarlem	0.9	49.4	12.7	16.09
Arnhem	1.2	49.2	18.6	41.91
Amersfoort	1.0	44.3	13.7	12.14
Zaanstad	1.2	44.6	23.6	20.06
Den Bosch	0.9	49.3	11.9	29.53
Haarlemmermeer	0.5	44.1	13.1	0
Zwolle	1.4	45.9	7.3	19.17
Zoetermeer	1.8	45.6	18.9	6.65
Leiden	0.9	49.6	15.2	9.82
Maastricht	2.4	50.5	11.8	38.44
Dordrecht	2.0	46.7	18.4	39.32
Ede	1.6	40.4	7.8	0
Alphen a/d Rijn	0.7	45.7	10.7	0
Leeuwarden	2.2	49.0	10.5	33.2
Alkmaar	1.3	48.6	15.2	9.65
Emmen	2.1	45.9	6.6	67.88
Westland	0.7	43.7	5.4	0.42
Delft	1.6	49.5	21.0	14.65
Venlo	1.4	46.3	14.0	39.69
Deventer	1.4	46.3	10.2	32.65
Sittard-Geleen	1.8	49.0	8.8	50.08
Helmond	1.3	45.8	13.1	38.31
Oss	1.0	48.1	11.1	14.02
Amstelveen	0.3	45.1	22.9	0
Hilversum	1.3	48.1	14.4	4.26
Heerlen	2.9	50.2	11.0	88.62
Nissewaard	2.1	48.5	12.2	0
Sudwest Fryslan	1.4	41.9	2.8	31.75
Hengelo	1.5	46.3	10.7	42.74

Purmerend	1.3	48.2	16.1	8.78
Schiedam	2.1	47.1	37.3	34.81
Roosendaal	1.5	55.2	16.4	54.67
Lelystad	2.6	41.6	21.1	25.57
Leidschendam-Voorburg	1.1	48.5	16.1	8.86
Almelo	2.1	44.3	12.8	69.55
Hoorn	1.3	48.7	14.4	12.15
Middelburg	1.4	42.7	9.8	16.9
Vlissingen	2.2	46.2	9.7	19.0
12 Provinces (minus 50 largest municipalities)				
1. Groningen	2.0	44.0	5.6	46.9
2. Friesland	1.4	42.7	3.9	35.0
3. Drenthe	1.4	41.6	4.0	21.0
4. Overijssel	0.8	41.9	2.9	5.3
5. Gelderland	1.2	44.1	5.6	7.0
6. Utrecht	0.9	42.9	9.6	2.6
7. Noord-Holland	1.0	44.3	8.4	2.1
8. Zuid-Holland	1.0	43.8	10.9	5.2
9. Zeeland	1.5	42.3	4.8	2.3
10. Noord-Brabant	0.8	45.8	6.2	4.9
11. Limburg	1.2	48.1	6.9	17.2
12. Flevoland	1.6	41.1	3.9	2.2

Data are presented as percentiles (1 per 100, %). Ordering of the 50 largest municipalities is based on the number of inhabitants per municipality, with the largest municipality displayed first.

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CHAPTER 6

Inequity in postpartum healthcare provision at home and its association with subsequent healthcare expenditure

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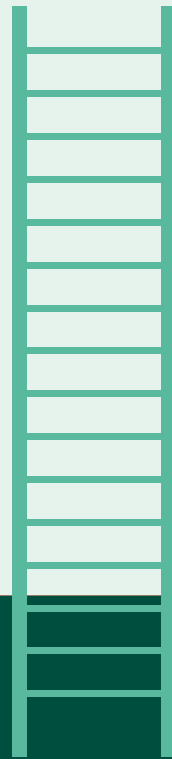
ABSTRACT

Background
Provision of postpartum care can support new families in adapting to a new situation. We aimed to determine whether various determinants of socioeconomic status (SES) were associated with utilisation of postpartum care. Also, to stress the relevance of increasing postpartum care uptake among low SES-groups, an assessment of the potential (cost-) effectiveness of postpartum care is required.

Methods
National retrospective cohort study using linked routinely collected healthcare data from all registered singleton deliveries (2010-2013) in the Netherlands. Small-for-gestational age and preterm babies were excluded. The associations between SES and postpartum care uptake, and between uptake and health care expenditure were studied using multivariable regression analyses.

Results
Of all 569 921 deliveries included, 1.2% did not receive postpartum care. Among women who did receive care, care duration was below the recommended minimum of 24 hours in 15.3%. All indicators of low SES were independently associated with a lack in care uptake. Extremes of maternal age, single parenthood, and being of non-Dutch origin were associated with reduced uptake independent of SES determinants.

No uptake of postpartum care was associated with maternal healthcare expenses in the highest quartile: aOR 1.34 (95%CI 1.10-1.67). Uptake below the recommended amount was associated with higher maternal and infant healthcare expenses: aOR 1.09 (95%CI 1.03-1.18) and aOR 1.20 (95%CI 1.13-1.27), respectively.

Conclusion
Although uptake was generally high, low SES women less often received postpartum care, this being associated with higher subsequent healthcare expenses. Strategies to effectively reduce these substantial inequities in early life are urgently needed.

INTRODUCTION

The postpartum period is a critical transitional period not only for babies but also in the lives of new mothers[1]. Adequate care provision during this period by skilled maternity care professionals enables an optimal start for the new family. A healthy start following childbirth may be of substantial short and long term benefit for maternal and child wellbeing, and as such has the potential to reduce healthcare associated costs[2, 3].

The uptake of healthcare overall and the incidence of adverse health outcomes during the postpartum period are closely linked to different determinants of one's socioeconomic position; persons with a lower socioeconomic position tend to make less use of routine or preventive healthcare[4, 5], and have a higher incidence of adverse health outcomes[3, 6-10]. Although a number of studies examined this relationship, the association between SES and use of postpartum care has not been investigated previously.

The strong position of primary care in the Netherlands, which includes easy access to postpartum care at home during the early postpartum period (figure 1), provides considerable potential to promote equity in maternal and infant health. This study seeks to describe the patterns of utilisation of postpartum care services using a national population-based study, assessing: 1. whether different determinants of SES – represented by individual level, household level, and area-level indicators – were associated with uptake of postpartum care, and 2. whether any inequalities translated in uptake of care translated into differences in subsequent healthcare expenditures for mother and child in the first year after childbirth, as an estimate of potential (cost-)effectiveness.

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> **Box 1. Postpartum care in the Netherlands**
>
> In the Netherlands, postpartum care professionals provide care in a family's home during the postpartum period. This care is initially delivered for six to eight hours a day, tapering to fewer hours per day towards the end of the care period, which usually consist of eight consecutive days following childbirth. The purpose of this postpartum care is to provide maternal and infant care by giving informational and emotional support, by providing comprehensive care for the mother and child dyad, and by enhancing maternal empowerment. The duration of postpartum care is indexed in advance for each woman individually during a scheduled home visit during the second or third trimester of pregnancy. The minimal amount of postpartum care is set at 24 hours (i.e. three hours per day for eight consecutive days after childbirth). The recommended amount of care is set at 49 hours, and the maximum amount of care is 80 hours depending on specific indications, for example an (imminent) mastitis or symptoms of psychological illness. When a mother and child dyad is hospitalised after childbirth (for example when an infant is born preterm or SGA) the indexed amount of postpartum care at home is reduced for every day that they remain in the hospital. Skilled nurses who have a lower secondary education degree for postpartum care provide this care. The costs for postpartum care are covered within the basic package of health insurance, which is obligatory for Dutch citizens, with exception of an out-of-pocket payment per hour of care received (i.e. € 4.30 in 2018) (http://www.digitalezorg.nl/digitale/uploads/2015/03/netherlands.pdf).

METHODS

We conducted a national population-based retrospective cohort study of women living in the Netherlands who delivered a live singleton baby between 1 January 2010 and 31 December 2013. Routinely collected healthcare and claims data were linked at the individual level across various national databases. First we studied the association between different determinants of low SES and the uptake of postpartum care. Second, we studied the association between the uptake of postpartum care and healthcare expenditures for mother and child in the following year. We used the RECORD statement to guide reporting of our findings (supplementary file 1) [11].

Study design and setting

Population-based retrospective cohort study from 1 January 2010 through 31 December 2013 using routinely collected healthcare data from Statistics Netherlands (translated Dutch name: 'Central Bureau of Statistics', abbreviation 'CBS').

Participants

All registered pregnancies among women living in the Netherlands who delivered a live singleton baby at 24 or more completed gestational weeks between 2010 and 2013.

Exposure variables

For the first part of this study, multiple determinants of SES including individual, household, and area-level SES indicators constituted the exposures of interest. Disposable household income was used as an individual SES indicator, defined as the sum available from the household income for final consumption and savings (i.e. net income), and divided into quartiles. Mother's highest educational qualification, based on the International Standard Classification of Education (ISCED) (http://uis.unesco.org/sites/default/files/documents/international-standard-classification-of-education-isced-2011-en.pdf), was considered a second individual SES indicator. Three groups were considered: lower education (pre-primary, primary, and lower secondary education), intermediate education (upper secondary education, post-secondary non-tertiary education), and higher education (first stage of tertiary education, second stage of tertiary education). Home ownership was considered a household indicator of SES and was dichotomized into owner-occupiers and no-owners (i.e. renters and others). Neighbourhood deprivation was considered an area-level SES indicator and was based on the Neighbourhood Deprivation Index (NDI) formulated by NIVEL in 2012[12]. Deprivation was defined at an NDI of 5.5% (i.e., 885 000 people).

In the second part, the exposure was the uptake of any postpartum care, and – in a secondary analysis – the uptake of postpartum care above the recommended minimum (i.e. 24 hours) among those who did receive postpartum care.

Covariates

Covariates were selected based on their association with the outcome variables or both the outcome and the exposure variables: maternal age, parity, country of origin, parenthood household status, level of urbanisation, and small-for-gestational age and preterm babies. Details are presented in supplementary file 2.

Outcomes

Determinants of low SES and uptake of postpartum care

Uptake of postpartum care was derived from data regarding healthcare expenditures. Expenditures were provided per annum; therefore pregnancies from women who gave birth

more than once within one year were excluded for all analysis. The amount of postpartum care was calculated by dividing the total postpartum care expenditures within one year by the eligible compensation per hour of care, which differed per year[13]. Uptake of postpartum care was dichotomized into 'No', and 'Yes' (any amount of postpartum care). The secondary outcome was postpartum care uptake above the minimum (i.e. 24 hours), as assessed among all women who did make use of postpartum care. The uptake of the minimum amount of care was dichotomized.

Uptake of postpartum care and healthcare expenditures
Annual total healthcare expenditures were obtained separately for mother and child. Quartiles of annual healthcare expenditures were formed for each and dichotomized into 'low' (expenses within the first three quartiles) and 'high' (expenses in the fourth quartile). Healthcare expenditure data were only available at an aggregated level per annum. We were therefore able to reliably evaluate health care costs in the year post-delivery only among those women delivering close to closing of the year. As such, we pragmatically considered total healthcare costs in the subsequent year following delivery in December a reasonable estimate of healthcare expenditure in the year post-delivery, and excluded deliveries in January to November from these analyses. Healthcare expenditures are subdivided based on a combination of diagnosis and treatment codes enabling us to exclude all healthcare expenses that were labelled as pregnancy-related. In addition, we excluded women with more than one pregnancy during the study period (i.e. 2010-2013) because having consecutive pregnancies over a two-year period could influence healthcare expenditures at the annual level.

Data sources and linkage
The available data for this study was linked across different national registries by CBS using the unique citizen service number (BSN) or the identification number of the Dutch Population Register (Dutch: A-number). Linkage with this information is feasible in 98-100% of all procedures undertaken by CBS. Details about the individual-level linkage across various routinely collected datasets are presented in supplementary file 2.

Potential for bias
The data in this study is based on routinely collected healthcare data. There was a reasonably high proportion of missing values in some registries that could have introduced different biases. We applied multiple imputation using chained equations to account for this missing data in baseline characteristics. Multiple predictor variables were included to inform the multiple imputation process, forming 10 datasets. Results across the sets were combined using Rubin's Rules[14].

Statistical methods

We analysed the two associations under study using logistic regression analysis. Infants born preterm or SGA and their mothers tend to remain in the hospital during most of the time that the mothers would otherwise be amendable to receiving postpartum care in the home situation (figure 1). Therefore, we excluded deliveries with these outcomes for all analyses because postpartum care uptake would otherwise be underestimated due to prolonged hospital admission.

Determinants of low SES and the uptake of postpartum care

The association between various determinants of low SES and postpartum care uptake (first), and uptake above the minimum (second) was analysed. All indicators of SES as exposure variables, and the predefined covariates were included in the analysis to minimize potential confounding.

Uptake of postpartum care and healthcare expenditures

The second model analysed the association between postpartum care uptake and healthcare expenditures for mother and child. We accounted for all SES indicators and all covariates included in the first model.

Sensitivity analyses

Consecutive pregnancies within the same mother have more characteristics in common than pregnancies between women. To assess whether this dependency of data affected our findings, we reran the model that analyses the first association with additional accounting for clustering at the individual level.

To assess whether the multiple imputed data was biased, we reran the two models on complete cases only.

Accessibility of protocol and programming code

Upon request all programming codes and the study protocol are available with the principal investigator.

Details of Ethics Approval

According to Dutch law, formal ethical assessment of the study protocol was not needed as the study did not involve an intervention and data from CBS is anonymized (based on guidance from the Central Committee on Research Involving Human Subjects (WMO) and the Dutch Personal Data Protection Act).

CBS collects and produces population statistics, referred to as non-public microdata, for all registered Dutch citizens. Under strict conditions, these data are accessible for scientific

research. The research board of CBS has reviewed and approved the study protocol (project number 7883).

RESULTS

Participants

During the study period, 683 163 deliveries were registered with CBS. After applying the pre-specified exclusion criteria, the final sample included 569 921 deliveries (supplementary figure 1). For investigation of the association between postpartum care uptake and healthcare expenditures we additionally excluded deliveries in January through November, and consecutive pregnancies within individual women during the study period. The final sample for this analysis contained 44 458 deliveries (supplementary figure 1).

Determinants of low SES and uptake of postpartum care
Univariable associations

Table 1 presents the descriptive statistics for the study sample, by uptake of postpartum care. Of all deliveries included, 1.2% did not receive any postpartum care. Data on the uptake of postpartum care was missing for 4.8% of all deliveries. Women who did not use postpartum care were more often: multiparous (67.9% versus 54.2%), single parents (20.1% versus 7.7%), born outside the Netherlands (2.9% versus 0.6%), and they more often lived in deprived neighbourhoods (19.1% versus 6.8%; table 1). Among women who did receive postpartum care, care duration was below the recommended minimum of 24 hours in 15.3% (supplementary table 1). These deliveries were also associated with indicators of low SES when compared to deliveries with postpartum care uptake above the minimum amount (supplementary table 1).

Multivariable associations

All indicators of low SES were consistently and strongly associated with no uptake of postpartum care after mutual adjustment (table 2). Similarly, among mothers who did receive postpartum care, low SES indicators were associated with care uptake below the minimum (table 2). Extremes of maternal age, single parenthood, and being of non-Dutch origin were associated with reduced uptake of postpartum care independent of individual and area-level SES.

Table 1: Descriptive statistics of all deliveries by uptake of postpartum care (yes, no, missing)

			Postpartum care uptake					
	Total population		Yes		No		Missing	
	n=569 921	%	n=535 470	%	n=6833	%	n=27 618	%
Maternal age								
<20	6837	1.2	6231	1.2	237	3.5	369	1.3
20-40	552 753	97.0	519 882	97.1	6325	92.6	26 546	96.1
>40	10 331	1.8	9357	1.7	271	4.0	703	2.5
Parity								
Primiparous	259 330	45.5	245 298	45.8	2196	32.1	11 836	42.9
Multiparous	310 591	54.5	290 172	54.2	4637	67.9	15 782	57.1
Country of origin								
the Netherlands	414 243	72.7	393 408	73.5	2 544	37.2	18 291	66.2
Morocco	24 726	4.3	22 920	4.3	980	14.3	826	3.0
Turkey	18 985	3.3	17 989	3.4	515	7.5	481	1.7
Suriname	13 802	2.4	12 864	2.4	372	5.4	566	2.0
Netherlands Antilles	6 503	1.1	5 864	1.1	189	2.8	450	1.6
Other Non-Western	36 253	6.4	32 077	6.0	1 216	17.8	2 960	10.7
Other Western	55 409	9.7	50 348	9.4	1 017	14.9	4 044	14.6
Parenthood status								
Single parent	44 576	7.8	41 130	7.7	1377	20.2	2069	7.5
Two parents	521 140	91.4	491 138	91.7	5184	75.9	24 818	89.9
Other	4197	0.7	3195	0.6	272	4.0	730	2.6
Missing	8	0.0	7	0.0	0	0.0	1	0.0
Urbanized area								
Yes	163 610	28.7	155 696	29.1	1247	18.2	6667	24.1
No	406 311	71.3	379 774	70.9	5586	81.8	20 951	75.9
SES indicators								
Education								
Lower education	74 984	13.2	70 317	13.1	2052	30.0	2615	9.5
Intermediate education	163 305	28.7	156 371	29.2	1438	21.0	5496	19.9
Higher education	197 725	34.7	184 817	34.5	955	14.0	11 953	43.3
Missing	133 907	23.5	123 965	23.2	2388	34.9	7554	27.4
Low disposable income								
Yes	131 290	23.0	122 207	22.8	3445	50.4	5638	20.4
No	416 580	73.1	393 035	73.4	2993	43.8	20 552	74.4
Missing	22,051	3.9	20,228	3.8	395	5.8	1,428	5.2
Home ownership								
No-owners	146,307	25.7	135,846	25.4	3,984	58.3	6,477	23.5
Owner-occupiers	401,563	70.5	379,396	70.9	2,454	35.9	19,713	71.4
Missing	22,051	3.9	20,228	3.8	395	5.8	1,428	5.2
Neighbourhood deprivation								
Yes	39,526	6.9	36,248	6.8	1,305	19.1	1,973	7.1
No	530,395	93.1	499,222	93.2	5,528	80.9	25,645	92.9

Values are presented as numbers and percentage.

Table 2. Multivariable models of the association between SES indicators and 1) postpartum care uptake, and 2) uptake above the minimum (i.e. 24 hours).

	Postpartum care uptake (n=569,921)		Uptake above the minimum amount (n=535,470)	
	aOR (95% CI)	p-value	aOR (95% CI)	p-value
Covariates				
Maternal age				
< 20 years	0.70 (0.61-0.81)	< 0.001	0.57 (0.54-0.60)	< 0.001
20-40 years (ref)		1		1
> 40 years	0.53 (0.47-0.60)	< 0.001	0.78 (0.73-0.82)	< 0.001
Parity				
Primiparous (ref)		1		1
Multiparous	0.59 (0.55-0.62)	< 0.001	0.99 (0.98-1.01)	0.601
Parenthood				
Single parent	0.82 (0.76-0.88)	< 0.001	0.82 (0.80-0.84)	< 0.001
Two parents (ref)		1		1
Other	0.22 (0.19-0.25)	< 0.001	0.40 (0.37-0.43)	< 0.001
Country of origin				
The Netherlands (ref)		1		1
Morocco	0.37 (0.34-0.40)	< 0.001	0.23 (0.22-0.24)	< 0.001
Turkey	0.44 (0.40-0.49)	< 0.001	0.26 (0.25-0.27)	< 0.001
Suriname	0.46 (0.41-0.51)	< 0.001	0.29 (0.28-0.30)	< 0.001
Net. Antilles	0.50 (0.43-0.58)	< 0.001	0.32 (0.30-0.34)	< 0.001
Other Non-Western	0.40 (0.37-0.43)	< 0.001	0.22 (0.22-0.23)	< 0.001
Other Western	0.41 (0.41-0.48)	< 0.001	0.41 (0.40-0.42)	< 0.001
SES indicators				
Individual				
Education				
Lower education	0.62 (0.57-0.66)	< 0.001	0.65 (0.64-0.67)	< 0.001
Inter. education (ref)		1		1
Higher education	1.21 (1.12-1.32)	< 0.001	1.39 (1.36-1.42)	< 0.001
Low disposable income				
Yes	0.72 (0.68-0.77)	< 0.001	0.69 (0.68-0.71)	< 0.001
Household				
Home ownership				
No-owners	0.55 (0.52-0.59)	< 0.001	0.51 (0.50-0.52)	< 0.001
Owner-occupiers (ref)		1		1
Area-level				
Neighbourhood deprivation				
Yes	0.80 (0.75-0.85)	< 0.001	0.79 (0.77-0.81)	< 0.001

Presented are adjusted odds ratios (aOR) and their 95% confidence intervals (95%CI). All p-values are two-sided. Results for the uptake of care and the minimum uptake of care are presented separately.

Sensitivity analyses

Consistent results were obtained in all sensitivity analyses for robustness checks, including those accounting for clustering of pregnancies at the individual level, and those analysing complete cases only (supplementary table 2).

Uptake of postpartum care and healthcare expenditures

Univariable associations

Descriptive statistics for the subgroup of 44 458 deliveries in December, were similar to those of all deliveries (supplementary table 3). The prevalence of low SES indicators increased steadily across the four quartiles of maternal healthcare expenditure, with the highest quartile having the highest prevalence of low SES indicators: lowest educational level 23.0% in the highest quartile versus 17.3% across the other quartiles, low disposable income 30.0% versus 25.2%, no home-ownership 34.4% versus 27.7%, and living in a deprived neighbourhood 9.0% versus 7.1% (supplementary table 3). This tendency was not seen across the four quartiles of infant healthcare expenditure, were the prevalence of low maternal SES indicators in the highest quartile was comparable with the prevalence across the other quartiles (data not presented). The percentage of women who did not receive postpartum care was highest in the fourth quartile of maternal healthcare expenses (2.1% in the highest quartile versus 1.2% across the other quartiles; supplementary table 3).

Multivariable associations

Not receiving postpartum care, or having postpartum care uptake below the minimum, was associated with a significantly higher odds of having maternal healthcare expenditure within the highest quartile in the year following child birth: aOR 1.34; 95% CI 1.10 to 1.67; P 0.004, and aOR 1.09; 95% CI 1.03 to 1.18; P 0.005, respectively (table 3). Deliveries followed by postpartum care uptake below the minimum were in addition associated with infant healthcare expenditure within the highest quartile in the first year after birth (aOR 1.20; 95% CI 1.13 to 1.27; P <0.001) (table 3).

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Table 3. Multivariable model of the association between the uptake of postpartum care and the lack in uptake and maternal and infant healthcare expenses within the highest quartile.

	Maternal health care expenditures highest quartile		Infant health care expenditures highest quartile	
	aOR (95% CI)	p-value	aOR (95% CI)	p-value
Primary analyses				
Maternity care uptake (n=44 458)				
No	1.34 (1.10-1.67)	0.004	1.12 (0.94-1.35)	0.205
Yes (ref)	1		1	
Maternity care >24 hours (n=41 583)				
No	1.09 (1.03-1.18)	0.005	1.20 (1.13-1.27)	<0.001
Yes (ref)	1		1	

Presented are adjusted odds ratios (aOR) and their 95% confidence intervals (95%CI). All p-values are two-sided. Results are presented separately for maternal and infant healthcare expenditures, adjusted for maternal age, parity, country of origin, parenthood status, and all indicators of SES (i.e. educational level, disposable income, home ownership, and neighborhood poverty).

Sensitivity analyses

The associations between no uptake of postpartum care and maternal healthcare expenses during the first year after childbirth was consistent in the sensitivity analysis on complete cases only (aOR 1.54 (95% CI 1.23 to 1.92; P <0.001)).

DISCUSSION

Using a national linked dataset of over half a million singleton pregnancies, we found that all indicators of low SES were associated with no uptake of postpartum care and with uptake of care below the recommended minimum. This lack of postpartum care uptake was associated with higher healthcare expenses in the first year after childbirth. For the first time, we demonstrate that postpartum care may be a cost-effective tool but is least provided to those who are most likely to benefit from it.

Strengths of this study include the very large and nationally representative sample and the use of a unique individual-level linkage across various routinely collected datasets of relevant medical and socioeconomic data. The relationship between low SES and lack of uptake of postpartum care was highly consistent across the various SES indicators. Although at the population level the proportion of women not receiving postpartum care is very small, we have shown that these women represent a marginalized group and may therefore benefit from efforts to improve their care.

Also, associations between low SES and postpartum care uptake as well as between postpartum care uptake and subsequent healthcare expenditure showed a dose-response association. The largest differences were present between women who did not receive postpartum care and those who received care above the minimum amount. The findings

of both analyses were furthermore highly robust in sensitivity analyses. In the absence of major changes to the system used for indicating the amount of postpartum care and of the health care insurance system in the Netherlands, the data used in this study (from 2010-2013) may be considered generalizable to the current day.

Our study also has limitations. First, some of the national registries from Statistics Netherlands have a reasonably high percentage of missing values. For example, the percentage of missing values on a woman's highest educational qualification was as high as 30%. Upward educational-attainment biases could have influenced the registered data. To minimize bias within the imputed data, we had all SES indicators and outcome variables inform the imputation process. Sensitivity analyses on complete cases only showed similar results to the main analyses, supporting validity of the imputation and robustness of the findings. Second, we lacked information on medical conditions of women and infants. Having a medical condition that requires inpatient treatment could directly affect the uptake of postpartum care, as this care is provided only in the primary care setting (i.e. at home or in a primary care birth centre). A third limitation is that the provided postpartum care is expressed in total expense rather than days of care received, making derivation necessary. Also we did not have information on the number of days spent in the hospital prior to receiving postpartum care, which may have biased our findings. Somewhat related to this point is that healthcare expenditures were only available at the annual level. We pragmatically addressed this by only assessing deliveries in December when exploring the association between postpartum care uptake and healthcare expenditure. Although this substantially reduced sample size, statistically significant and clinically relevant associations were still observed.

Our findings stress the need to further explore how equity in care uptake may be promoted. Obstetric healthcare providers should include the social determinants of health in their medical records, and in the referral to postpartum care organisations [2, 15-17]. Provision of postpartum care should be tailored according to these determinants to reach poor and other marginalized subpopulations[18, 19]. When striving to reduce inequalities in uptake of postpartum care additional determinants, besides those related to a person's SES, should be considered. For example, our results showed that immigrant populations were less likely to receive postpartum care, even when accounting for SES indicators (table 2). This suggests that interventions targeting high-risk groups to increase postpartum care uptake should consider ethnic background in addition to SES-related factors. Cultural factors are likely to explain at least part of this inequity, but this requires further study. Mixed-methods research is needed to assess the facilitators and barriers to receiving postpartum care among low-SES women and those with an immigrant background.

Our results are in line with those observed in other reports; there is a consistent inequity in primary care provision, where more care is provided to the well-off, who need it less, than

to the more disadvantaged [2, 4, 5, 16-18, 20]. In the Netherlands, a possible barrier to postpartum care uptake is the additional co-payment required for each hour of care. To ensure equitable, universal coverage, policy-makers and health insurers should consider waiving this co-payment, particularly for low SES groups. Furthermore, our study provides evidence to suggest that postpartum care may help reduce subsequent healthcare expenditure, providing an additional incentive for stakeholders to invest in increasing the uptake of care. There is a need to further assess whether explicit resource allocation and priority setting to those in greatest need, perhaps in conjunction with approaches to reduce unnecessary care provision resulting in the over-payment in other sectors may help improve cost-effectiveness of postpartum care provision.

Given the observational nature of this study it is important that findings are reproduced in other settings or using different methodological approaches (i.e. prospective or randomized studies). Future research should focus on further analysing the (cost-)effectiveness of postpartum care; not only its effectiveness in achieving equity in care provision, but also its ability to prevent illness and associated healthcare needs. An in-depth economic evaluation taking into account all expenses made by postpartum care organisations and the potential benefits (e.g. health benefits or value based health measures) gained by mothers and their children could strengthen a renewed allocation for care provision.

SUPPLEMENT

Supplementary file 1 "RECORD checklist".
Available upon request.

Supplementary file 2 "Definition variables and data linkage".
Definition and categorisation of all exposure variables and covariates
Covariates
Maternal age at delivery was calculated as date of delivery minus mother's date of birth and categorized in three categories (<20 years, 20-40 years, >40 years of age). Parity was defined as the number of previous deliveries of each mother and dichotomized into primiparous and multiparous women. Country of origin was defined by birthplace of the woman according to the Dutch Population Register and categorized according to the largest subgroups into: the Netherlands, Morocco, Turkey, Suriname, Netherlands Antilles, other non-Western, and other Western. Parenthood household status was categorized into single parent household, two parent household, and other, the latter including institutionalized women and households not further specified. The level of urbanization, based on address density within a radius of one kilometre around an address, divided by the area of the circle, was dichotomized into 'rural' (<1000 addresses), and 'urban' (≥1000 addresses).

In addition, two perinatal characteristics were defined: preterm delivery defined as a delivery before 37 completed weeks of gestation, and delivery of a small for gestational age baby (SGA), defined as a birth weight below the 10th centile for parity, gestational age, and gender [21].

Data sources and linkage
The available data for this study was linked across different national registries by CBS using the citizen service number (BSN) or the identification number of the Dutch Population Register (Dutch: A-number). Alternatively, a person's gender, date of birth, postal code, and year of address registration is used for linkage.

Pregnancy data was obtained from the Dutch medical birth registry ('Perined'), which includes data of pregnancies, including stillbirths, of 22 or more completed gestational weeks, of all women registered in the Dutch Register of Population. Approximately 97% of all births in The Netherlands are registered with Perined [22].

We obtained information on maternal and neonatal deaths by using the Cause of Death register, which includes information on all deaths in the Netherlands (https://www.cbs.nl/-/media/cbs%20op%20maat/microdatabestanden/documents/2016/30/do.pdf).

Diagnoses and causes of death are coded according to the Dutch version of the International Classification of Diseases, tenth Revision (ICD-10).

Data regarding participants' educational level was collected from the central registry for application into tertiary education (Dutch abbreviation 'CRIHO') and the registry for exam results for secondary education (Dutch abbreviation 'ERR'). To complement the data of these two registries, an annual survey assessing a person's educational skills is conducted by Statistics Netherlands (https://www.cbs.nl/-/media/cbs%20op%20maat/microdatabestanden/documents/2016/37/hoogsteopltab.pdf). The educational data covers approximately 70% of the adult Dutch population.

Income data was collected from the Dutch Tax Service registry (https://www.cbs.nl/-/media/cbs%20op%20maat/microdatabestanden/documents/2016/51/integraal%20persoonlijk%20inkomen.pdf). Data regarding a woman's residency based on postal codes, her parental status, and home ownership was obtained from the Dutch Population Register. Registering oneself in the Dutch Population Register is obligatory, except for North Atlantic Treaty Organization (NATO)-soldiers, diplomats, and residents who remain in the Netherlands for less than four months within a period of six months (https://www.government.nl/binaries/government/documents/leaflets/2017/01/19/brochure-brp-engelstalig/Brochure+BRP+-+Engelstalig+-+def+versie+voor+publicatie+lowres.pdf). An important group missing in the Dutch population Register are illegal immigrants (estimated percentage of the total Dutch population in 2001: 0.29-0.72%)[23]. The Dutch index of deprivation (abbreviation in Dutch language: NIVEL) is an area-based measure of deprivation that ranks small geographical areas (i.e. based on postal codes) on the basis of multiple aspects of deprivation identified in administrative data [12]. This index was used to identify deprived areas. We assessed the level of urbanization based on a woman's postal code. Postal codes obtained from Dutch Population Register were linked with the date of delivery to obtain precise information with regard to maternal living condition at the time of childbirth. The level of urbanization was based on address density per area.
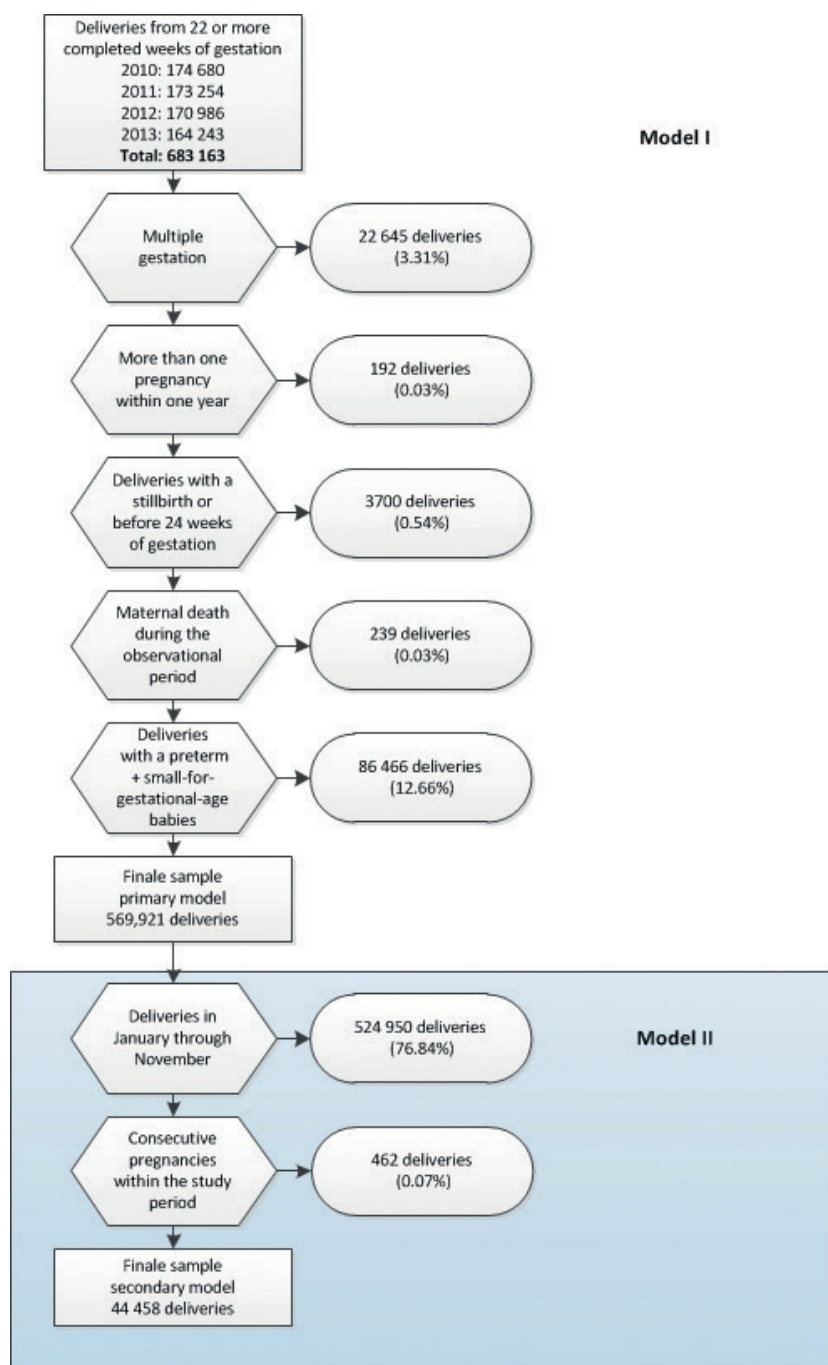
Vektis is a private organization that collects costs made by everyone with a basic package of health insurance at annual level. Data regarding health expenditures covers approximately 95% of the Dutch population (https://www.cbs.nl/-/media/cbs%20op%20maat/microdatabestanden/documents/2017/27/zvwzorgkostentab.pdf). Health care expenditures are subdivided based on a combination of diagnosis and treatment. Information regarding the uptake of maternity care is based on a subdivision of expenses made during pregnancy and the postpartum period. Individual-level data on health care expenditures were available aggregated per year from 2011-2014. Health care costs can be invoiced with a delay, to obtain an accurate number for expenditures per annum; expenses were therefore calculated with data across seven quarters of a year (i.e. four quarters of the actual year and the first three quarters of the subsequent year) according to the standardized method of Statistics Netherlands. For women delivering

in December the health care costs from the following year were considered a reasonable estimate of the costs made in the first year after childbirth.

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Supplementary figure 1: flowchart

Model I: analysing the association between different dimensions of low SES and the uptake of maternity care.
Model II: analysing the association between the uptake of maternity care and health care expenditures for mother and child in the following year (i.e. the first year after childbirth) within mothers delivering in December

Supplementary table 1: Descriptive statistics by uptake of postpartum care above the recommended minimum.

| | Total population | | Postpartum care uptake above minimum amount | | | |
| | | | Yes | | No | |
	n=535 470	%	n=453 762	%	n=81 708	%
Maternal age						
<20	6231	1,2	3509	0,8	2722	3,3
20-40	519 882	97,1	442 757	97,6	77 125	94,4
>40	9357	1,7	7496	1,7	1861	2,3
Parity						
Primiparous	245 298	45,8	208 914	46,0	36 384	44,5
Multiparous	290 172	54,2	244 848	54,0	45 324	55,5
Country of origin						
the Netherlands	393 408	73.5	361 802	79.7	31 606	38.7
Morocco	22 920	4.3	12 235	2.7	10 685	13.0
Turkey	17 989	3.4	11 034	2.4	6 955	8.5
Suriname	12 864	2.4	8 146	1.8	4 718	5.8
Netherlands Antilles	5 864	1.1	3 534	0.8	2 330	2.9
Other Non-Western	32 077	6.0	18 040	4.0	14 037	17.2
Other Western	50 348	9.4	38 971	8.6	11 377	13.9
Parenthood status						
Single parent	41 130	7,7	26 148	5,8	14 982	18,3
Two parents	491 138	91,7	425 631	93,8	65 507	80,2
Other	3195	0,6	1978	0,4	1217	1,5
Missing	7	0,0	5	0,0	2	0,0
Urbanized area						
Yes	155 696	29,1	143 085	31,5	12 611	15,4
No	379 774	70,9	310 677	68,5	69 097	84,6
SES indicators						
Education						
Lower education	70 317	13,1	46 009	10,1	24 308	29,7
Intermediate education	156 371	29,2	134 850	29,7	21 521	26,3
Higher education	184 817	34,5	172 643	38,0	12 174	14,9
Missing	123 965	23,2	100 260	22,1	23 705	29,0
Low disposable income						
Yes	122 207	22,8	84 011	18,5	38 196	46,7
No	393 035	73,4	354 035	78,0	39 000	47,7
Missing	20 228	3,8	15 716	3,5	4512	5,5
Home ownership						
No-owners	135 846	25,4	90 553	20,0	45 293	55,4
Owner-occupiers	379 396	70,9	347 493	76,6	31 903	39,0
Missing	20 228	3,8	15 716	3,5	4512	5,5
Neighbourhood deprivation						
Yes	36 248	6,8	22 004	4,8	14 244	17,4
No	499 222	93,2	431 758	95,2	67 464	82,6

Values are presented as numbers and percentage.

Supplementary table 2: sensitivity analyses of the association between SES indicators and maternity care uptake (first) and uptake above the recommended minimum (second) (model I).

	Addition of clustering on individual level				Complete cases			
	Maternity care uptake (n=569,921)		Minimum uptake of care (n=535,470)		Maternity care uptake (n=399,529)		Minimum uptake of care (n=395,329)	
	aOR (95% CI)	p-value	aOR (95% CI)	p-value	aOR (95% CI)	p-value	aOR (95% CI)	p-value
Socioeconomic indicators								
Individual								
Education								
Lower education	0.61 (0.57-0.66)	<0.001	0.65 (0.64-0.67)	<0.001	0.62 (0.57-0.67)	<0.001	0.57 (0.56-0.59)	<0.001
Intermediate education (ref)	1		1		1		1	
Higher education	1.21 (1.11-1.32)	<0.001	1.39 (1.36-1.42)	<0.001	1.26 (1.16-1.38)	<0.001	1.59 (1.55-1.63)	<0.001
Low disposable income								
Yes	0.72 (0.68-0.77)	<0.001	0.69 (0.67-0.71)	<0.001	0.68 (0.63-0.74)	<0.001	0.73 (0.71-0.74)	<0.001
No (ref)	1		1		1		1	
Household								
Home ownership								
No-owners	0.56 (0.52-0.60)	<0.001	0.51 (0.50-0.52)	<0.001	0.58 (0.53-0.63)	<0.001	0.51 (0.49-0.52)	<0.001
Owner-occupiers (ref)	1		1		1		1	
Area-level								
Neighbourhood deprivation								
Yes	0.80 (0.75-0.86)	<0.001	0.78 (0.77-0.81)	<0.001	0.80 (0.73-0.87)	<0.001	0.77 (0.74-0.79)	<0.001
No (ref)	1		1		1		1	

Presented are adjusted odds ratios (aOR) and their 95% confidence intervals (95%CI). All p-values are two-sided. Results for the uptake of care and the minimum uptake of care are presented separately. Adjusted for maternal age, parity, country of origin, parental status, and urbanised area.

Supplementary table 3: Descriptive statistics of all deliveries in December (model II) by quartiles of maternal health care expenditures.

	Total population		Quartiles of maternal health care expenditures with percentages							
	n=44 458		Q1 (n=10 551)		Q2 (n=12 079)		Q3 (n=12 278)		Q4 (n=9550)	
Maternal age (years)										
<20	585	1,3	78	0,7	156	1,3	198	1,6	153	1,6
20-40	43 060	96,9	10 295	97,6	11 718	97,0	11 848	96,5	9199	96,3
>40	813	1,8	178	1,7	205	1,7	232	1,9	198	2,1
Parity										
Primiparous	21 583	48,5	5159	48,9	5968	49,4	5884	47,9	4572	47,9
Multiparous	22 875	51,5	5392	51,1	6111	50,6	6394	52,1	4978	52,1
Country of origin										
the Netherlands	31 724	71.4	7 884	74.7	8 704	72.1	8 640	70.4	6 496	68.0
Morocco	2 044	4.6	296	2.8	537	4.5	643	5.2	568	6.0
Turkey	1 563	3.5	285	2.7	408	3.4	473	3.9	397	4.2
Suriname	1 188	2.7	204	1.9	315	2.6	370	3.0	299	3.1
Netherlands Antilles	512	1.1	98	0.9	145	1.2	161	1.3	108	1.1
Other Non-Western	2 938	6.6	613	5.8	756	6.3	863	7.0	706	7.4
Other Western	4 489	10.1	1 171	11.1	1 214	10.1	1 128	9.2	976	10.2
Parenthood status										
Single parent	3851	8,7	648	6,1	904	7,5	1207	9,8	1092	11,4
Two parents	40 245	90,5	9836	93,2	11 100	91,9	10 960	89,3	8349	87,4
Other	362	0,8	67	0,6	75	0,6	111	0,9	109	1,1
Urbanized area										
Yes	12 651	28,5	3497	33,1	3454	28,6	3274	26,7	2426	25,4
No	31 807	71,5	7054	66,9	8625	71,4	9004	73,3	7124	74,6
Education										
Lower education	6382	18,6	1111	13,7	1653	17,5	1938	20,3	1680	23,0
Intermediate education	13 077	38,0	2976	36,7	3522	37,4	3770	39,5	2809	38,4
Higher education	14 922	43,4	4022	49,6	4245	45,1	3825	40,1	2830	38,7
Missing	10 077	22,7	2442	23,1	2659	22,0	2745	22,4	2231	23,4
Low disposable income										
Yes	11 194	26,3	2323	22,9	2828	24,5	3299	28,0	2744	30,0
No	31 435	73,7	7810	77,1	8721	75,5	8497	72,0	6407	70,0
Missing	1829	4,1	418	4,0	530	4,4	482	3,9	399	4,2
Home ownership										
No-owners	12 417	29,1	2514	24,8	3129	27,1	3626	30,7	3148	34,4
Owner-occupiers	30 212	70,9	7619	75,2	8420	72,9	8170	69,3	6003	65,6
Missing	1829	4,1	418	4,0	530	4,4	482	3,9	399	4,2
Neighbourhood deprivation										
Yes	3327	7,5	590	5,6	868	7,2	1005	8,2	864	9,0
No	41 131	92,5	9961	94,4	11 211	92,8	11 273	91,8	8686	91,0
Maternity care uptake										
No	582	1,4	138	1,3	140	1,2	145	1,2	159	2,1
Yes	41 583	98,6	10 297	98,7	11 832	98,8	12 008	98,8	7448	97,9
Missing	2293	5,2	116	1,1	109	0,9	125	1,0	1943	20,3

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6

CHAPTER 7

Client-tailored maternity care to increase maternal empowerment: cluster randomized controlled trial protocol; the Healthy Pregnancy 4 All-2 program

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ABSTRACT

Background

The postpartum period is an important period for preventive strategies as common maternal and child health risks may become manifest. Women with a lower socioeconomic status tend to have lower maternal empowerment, increasing their risks of adverse maternal and child health outcomes. This study aims to assess the effectiveness of a primary care level intervention, delivered to maternity care assistants, aiming to increase maternal empowerment postpartum.

Methods

This study is part of the Dutch nationwide "Healthy Pregnancy 4 All-2" (HP4All-2) program, which aims to identify vulnerable mothers and young children at risk of adverse health outcomes, with subsequent improvement of care. This program targets women from deprived neighborhoods.

A pragmatic cluster randomized controlled trial will be undertaken with 12 maternity care organizations. Maternity care organizations in urban municipalities (i.e. the clusters) will be randomized to either a systematic risk assessment during pregnancy with emphasis on identification of non-medical risk factors for adverse maternal and neonatal health outcomes, and subsequent adaptation of care towards a client-tailored approach during pregnancy and the postpartum period, or solely the systematic risk assessment. The primary outcome is the prevalence of a low maternal empowerment score postpartum. Secondary maternal outcomes cover health-related quality of life, postnatal depression, smoking, alcohol consumption, illicit drug use. Finally, maternal and neonatal health care utilization postpartum are recorded. All outcomes will be analyzed according to the intention-to-treat principle, using multi-level mixed effects models.

Discussion

The study will contribute to evidence regarding the effectiveness of client-tailored, risk-based maternity care in increasing maternal empowerment postpartum.

Ethics and trial registration

The Daily Board of the Medical Ethics Committee Erasmus MC approved the study (METC 2015-156). Netherlands Trial Registry (NTR) 6311, registered 05-24-2017.

INTRODUCTION

The postpartum period, defined by the World Health Organization (WHO) as the period from childbirth to the 42nd day following delivery, is an important period for preventive strategies as common maternal and child health problems become apparent. Health problems include maternal and neonatal infections, postpartum hemorrhage, neonatal respiratory and feeding problems, and psychological problems of varying severity [1]. The purpose of maternity care provided during this period is manifold; 1) to promote physical health of the mother and her baby, 2) to promote coping of parents with the new situation through providing support, and 3) to promote parental empowerment in handling their baby [1 2]. To achieve this, maternity care consists not only of medical care, but also of psychosocial care, support, and education. Maternity care assistants (MCAs) provide care following delivery at home on a daily basis for over a week (see box 1).

Women with a lower socioeconomic status (SES) are more at risk of developing adverse maternal and child health outcomes within both western and non-western countries. The resulting inequity in maternal and child health outcomes already starts before birth and extends into early childhood [3-7]. In addition, women with a lower SES tend to have a lower empowerment as compared to women with a higher SES [8]. The WHO defined empowerment as a process through which people gain greater control over decisions and actions affecting their health [9]. Maternal empowerment is a valuable outcome per se, but also an important predictor of maternal and child health and increased health care utilization [10-13]. Thus, the already increased risk of adverse health outcomes among women with a low SES may be further augmented by insufficient maternal empowerment.

In the Netherlands, a national protocol is used during pregnancy to assess the need for maternity care postpartum, expressed in hours of care [14]. This Dutch national maternity care indication protocol (abbreviated by 'LIP' in Dutch) is in line with the assessment by midwives and obstetricians, and mostly focuses on medical risk factors (box 1). This protocol, however, insufficiently acknowledges the relevance of non-medical risk factors, including those associated with low SES, for health outcomes around birth and the associated additional need for maternity care. Our study amended the existing risk assessment with non-medical risk factors, and introduced tailored care adaptations according to the risk profile. The intensive and preventive structure of maternity care along with the opportunities for maternity care assistants (MCAs) to tailor care from pregnancy onwards creates a window of opportunity for patient-tailored care (see box 2). We hypothesize that the delivery of client-tailored, risk-guided maternity care could improve maternal empowerment and thereby reduce the probability of risk factors developing into manifest problems [15 16].

This study is part of the Dutch nationwide "Healthy Pregnancy 4 All-2" (HP4All-2) program, which aims to improve the identification of and care for mothers and young children at risk of adverse health outcomes [17]. HP4All-2 particularly targets women from deprived neighborhoods. In the current cluster randomized controlled trial (C-RCT) we aim to specifically address health inequalities during the postpartum period by 1) systematically improving identification of non-medical risk factors during pregnancy, and 2) using this risk profile to provide client-tailored care during pregnancy and the postpartum period.

METHODS

We designed a pragmatic C-RCT in six municipalities in the Netherlands to assess the effectiveness of a complex intervention to promote maternal empowerment in the postpartum period. The intervention under study consists of a systematic risk assessment during pregnancy, with emphasis on identifying non-medical risk factors for adverse maternal and neonatal health outcomes, in conjunction with client-tailored care during pregnancy and the postpartum period based on the obtained risk profile. We used the SPIRIT statement for clinical trial protocols to guide reporting of our protocol [18].

There are around 120 maternity care organizations in the Netherlands that function as independent enterprises. Women can sign up during pregnancy with any maternity care organization that provides care in their neighborhood. On average, 95% of all women make use of some amount of maternity care.

During pregnancy a MCA will assess a woman's expected care requirements during a scheduled home visit around 25-37 weeks of gestation. For primiparous women this intake is scheduled as a home visit, whereas for multiparous women this intake is conducted per telephone. Compensation from health insurers to maternity care organizations differs according to this policy. The intensity of care provision during the postpartum period is based on the indications denoted in the Dutch national indication protocol (abbreviated by LIP in Dutch). Examples of indications that add to the intensity of care are: not being physically self-sufficient, having a psychological illness, and having other children under the age of four years. An example of an indication that will downscale the intensity of care is planning to bottle feed rather than breastfeed the newborn.

> **Box 1. Dutch perinatal care system**
>
> Antenatal care in The Netherlands is based on the concept that pregnancy, childbirth, and the postpartum period are fundamentally physiologic processes. Obstetric risk selection is performed by community midwives or obstetricians and is based on the 'List of Obstetric Indications' (LOI), which specifies manifest conditions that define a low, medium, or high-risk pregnancy. An obstetrician will care for women with a high-risk pregnancy whereas a community midwife may provide care to women with a low or a medium risk.
>
> Based on the LOI approximately 30% of all pregnant women are considered to have a low risk throughout their pregnancy and delivery. In 2015, 13.1% of all births in the Netherlands were home births (https://www.perined.nl/producten/publicaties/jaarboeken). In case of an uncomplicated institutional delivery the mother will usually be discharged home within a few hours. Regardless of the risk indication based on the LOI, the community midwife will be responsible for care of the mother when discharged home during the postpartum period.
>
> Maternity care is provided by maternity care assistants (MCAs) and will start at home, or – less frequently – in a primary care birth center, under supervision of the community midwife. Following delivery, a MCA visits and supports the family at home on a daily basis for the first eight to ten consecutive days. Initially maternity care covers six to eight hours a day but this is tapered off towards the end of the care period. If a mother is hospitalized after delivery for a longer duration, the provided care by MCAs is reduced. However, based on specific indications (see box 2) the care provision by MCAs may be expanded.

The minimum volume of care at home is set at 24 hours over eight days, the recommended volume is set at 49 hours, and its maximum amount is set at 80 hours, depending on specific indications, spread out over eight to ten days. Maternity care is covered by the general health care insurance (which is mandatory for every Dutch inhabitant) with exception of an out-of-pocket payment of €4.30 per hour (2017).

Study setting

This study is embedded in the HP4All-2 program that aims to reduce perinatal health inequalities and to improve the care for young children and their mothers [17]. Six out of ten participating municipalities within the overall HP4All-2 program participate in this trial. A detailed description of the selection process of municipalities has been published before [17]. We designed a two-arm C-RCT in six municipalities, including 12 maternity care organizations (figure 1). Two adjacent municipalities were merged to ensure that enough eligible women could be expected to be included during the study period. The resulting five

participating municipalities were each subdivided into an intervention cluster and a control cluster, resulting in a total number of ten clusters. Each cluster consisted of one or more distinct maternity care organizations, depending on the expected number of eligible women within each organization (figure 1). Clustering at the level of the maternity care organization was chosen to avoid contamination of the intervention, which includes education of MCAs, between MCAs within maternity care organizations and between mother-baby dyads cared for by the same MCA. Outcomes will be assessed at the individual level.

Figure 1: trial profile
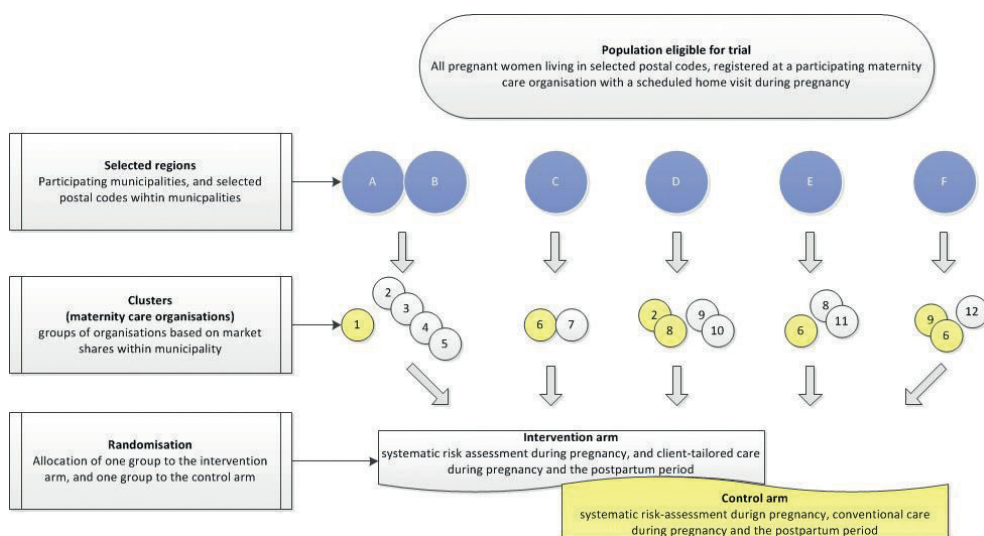
Eligibility criteria

Criteria for maternity care organizations

Participation of maternity care organizations is based on several factors: their willingness to participate, their capacity (defined as the expected number of eligible women to be cared for during the study period), and their ability to allow a sufficient number of MCAs to participate throughout the study period (sufficiency is based on the expected number of participants included). To increase cooperation of the participating organizations in the study, we aligned our protocol with their standard working schedules. Such an alignment for example would allow that the timing of our intervention, which starts during a scheduled home visit, differs regarding weeks of gestation.

Criteria for health care professionals

MCAs from the participating organizations will act as local researchers after completing the training sessions. They will inform potential participants about the study and obtain written informed consent. They also serve as the main point of contact between the research

team and the participants, and have a key role in sustaining participant recruitment and participant participation throughout the study period.

Exclusion criteria for maternity care organizations
Inability to conduct a scheduled home visit for all participants.

Inclusion criteria participants
All pregnant women to be cared for by participating maternity care organizations, with a scheduled home visit during pregnancy, are eligible and invited to take part in the study.

Exclusion criteria participants
Unwillingness to sign a written informed consent form.

Intervention
Intervention at the level of the participant
The intervention consists of two dimensions: 1) a systematic risk assessment during pregnancy with emphasis on identification of non-medical risk factors for adverse maternal and neonatal health outcomes, and 2) subsequent adaptation of maternity care towards a client-tailored approach during pregnancy and the postpartum period.

The first part is based on an electronic risk assessment questionnaire and covers six different domains related to individual level SES and psychological factors. All assessed factors are known to be associated with adverse health outcomes during pregnancy, childbirth or early childhood. The assessment consists of three main components: 1) the validated Mind2Care (M2C) tool [19], 2) the Maternal Empowerment Questionnaire (MEQ) [20] with slight modifications, and (3) eight additional questions regarding a person's financial situation, whether they have health care insurance, and their use of health care in the year prior to pregnancy. Two out of five domains of the MEQ were omitted for this assessment after consulting the authors (i.e. domains "the future" and "maternity care") as being not applicable. All other questions were grammatically adjusted for application during pregnancy, rather than after childbirth.

The MCA will review and discuss the identified risk factor(s) upon completion of the electronic assessment by the participant. Specific risk factors are linked to specific care pathways, which guide the MCA into taking appropriate action, and organize client-tailored care during pregnancy and the postpartum period. Care pathways consist of different steps a MCA can take to initiate a risk-guided provision of care in collaboration with professionals from different echelons. These steps can include communication with an involved community midwife or obstetrician but also with professionals from the public health sector. Care pathways are tailored in order to accommodate practice variations within maternity care organizations to fit local protocols and habits.

Aspects relevant to both intervention and control arms

Three large health insurers in the Netherlands agreed to additional fund a home risk intake (instead of per telephone call) for all study participants rather than for primiparous women alone. Prior to inclusion of participants, MCAs from both the intervention and the control arm will be trained extensively to use the renewed risk assessment. Each pair of clusters within a municipality will be trained together. The training consists of two sessions of three hours and will be led by a well-established Dutch educational agency together with the executing investigator (JL). For each cluster, the first training will take place at the start of the study and the second refresher training will be scheduled three months after the start.

The training program is focused on providing various communication skills for health care professionals that will build their confidence to address risks within a participant's social situation and lifestyle (the non-medical risk component). The following key topics were covered during the training program: creating opportunities for constructive conversations, empowering women to take control and manage their personal situation, and asking additional questions to identify the need of a participant regarding her health care provision. In addition, this training program covers group exercises to enhance effective and respectful engagement, in order to correctly include participants in a research trial, and in order to answer participants' questions regarding the study protocol effectively.

The second training was set up to refresh the knowledge and skills obtained in the first training and to evaluate the feasibility of the study protocol. If deemed necessary by the investigator team, minor adjustments in study protocol may be made to address any issues raised. Prior to the start of the study, all staff working in the administrative or the management sector of every participating organization receives training by the executing investigator of the research team (JL). This training focuses on the study protocol and all administrative tasks related to participant engagement with the study (i.e. sending the study flyer prior to the intake, scheduling the intake and informing eligible women on the study; see "participant timeline").

Intervention on the level of the MCA and the level of maternity organizations

Prior to the start of the intervention during the postpartum period, all MCAs working for maternity care organizations allocated to the intervention arm receive an additional three-hour training session directed towards the subsequent step of a tailored care approach, once the risk profile is known. This training session is led by another well-established Dutch educational agency together with the executing investigator of the research team (JL).

The content of this training includes the rationale for the study; background information highlighting the importance of the social gradient in perinatal and postpartum health, a group conversation of the contribution of the risk factors evaluated to this gradient, and

skills training. Skills training is focused on different topics: shaping knowledge of the social gradient in health to create and encourage a preventive approach in care, creating confidence to address a participant's social situation and lifestyle, and skills to increase practical and emotional social support. In addition, the timing of the obtained skills during the early postpartum period and the subsequent preventive approaches will be discussed in-group exercises. The obtained skills should strengthen a participant's own capabilities in taking care of herself, her baby, and her family, thereby increasing maternal empowerment.

Control situation

To adequately compare the intervention and the control group with regard to their medical and non-medical risk factors during pregnancy, the risk assessment during pregnancy is performed in both study arms. The MCA in the control arm is however instructed not to discuss the detected risks with the participant upon completion of the risk assessment or to discuss the findings with other health care professionals. One exception to this blinding of participants is made for the risk factor "suicidal thoughts", given the severity of this risk identification. In the control group the risk assessment will be followed by conventional care during pregnancy and the postpartum period.

Outcomes

Primary outcome

The primary outcome is the prevalence of a low maternal empowerment score postpartum, defined as a score beneath the 20th centile of all empowerment scores within the control arm (table 1). Maternal empowerment will be assessed via the MEQ at the last day of the provided maternity care, usually at day eight after childbirth, and will be defined as the median score across four out of five domains within the MEQ (i.e. scores from the domain 'Maternity care' will not be considered for the primary outcome (table 1)) [20].

Secondary outcomes

Secondary outcome measures address maternal health-related quality of life, maternal depression, maternal smoking, alcohol consumption, drug use, and maternal and neonatal health care utilization postpartum. All individual outcome measures are summarized in table 1 with used definitions and timing of assessment.

The adherence to the study protocol within the intervention arm will be assessed quantitatively using questionnaires filled out by the MCAs who provided the care in the early postpartum period. This questionnaire will be filled out for each participant separately and assesses the MCAs' knowledge of the maternal risk factors obtained during pregnancy and

Table 1: Primary and all secondary outcomes at the individual level with definitions and timing of assessment

Outcomes	Postpartum period	
	Early (1-2 weeks after childbirth)	Late (6-12 weeks after childbirth)
Primary	*Maternal empowerment*	
Definition	Low empowerment score (no/yes) defined as a score beneath the 20th centile within the control group	
Assessment	Maternal Empowerment Questionnaire (MEQ). Overall scoring based on the median score across the following four domains; "Looking after yourself", "My baby", "My family", "The future". Values per question: 1 "Never" 2 "Sometimes", 3 "Usually", and 4 "Always".	
Secondary	*Maternal health related quality of life*	*Maternal depression (postnatal depression)*
Definition	Continuous outcome ranging from zero (dead) to one (full health).	Dichotomous outcome based on the sum score: "No" sum score <13 and "Yes" sum score >12.
Assessment	5-level EQ-5D (EQ-5D-5L). Each dimension within the questionnaire has 5 levels: 1 "no problems", 2 "slight problems", 3 "moderate problems", 4 "severe problems", and 5 "extreme problems". Resulting in health profiles ranging from "11111" through "55555". Continuous score calculated with the obtained profiles of the questionnaire with the validated EQ-5D-5L calculator.	Edinburgh Postnatal Depression Scale (EPDS). Ten item scale. Responses are scored 0, 1, 2 and 3 based on the seriousness of the symptom. Range 0-30.
	Maternal perceived health	*Maternal health care utilization*
Definition	Continuous outcome ranging from zero (the worst health possible) to 100 (the best health possible).	Categorical outcome: "No additional care", "One visit to the A and E department, GP, or GP out-of-hours service", "Multiple visits", and "Admission in a hospital"
Assessment	EuroQol-visual analogue scales (EQ-VAS) represented by a 20 cm vertical scale.	Q1: Since your baby was born, have you had any symptoms for which you have been to the accident and emergency (A and E) department, GP or out-of-hours GP service? Q2: Have you been admitted to hospital since your baby was born?
		Neonatal health care utilization
Definition		Categorical outcome ranging from: "No additional care", "One visit to the A and E department, GP, or GP out-of-hours service", "Multiple visits", and "Admission in a hospital"
Assessment		Q1: Have you been to the accident and emergency (A and E) department, GP or out-of-hours GP service for your baby since he or she was born? Q2: Has your baby been admitted to hospital since he or she was born?
	Maternal cigarette use	*Maternal cigarette use*
Definition	Dichotomous outcome (no/yes): "Yes" defined as any usage	Dichotomous outcome (no/yes): "Yes" defined as any usage
Assessment	Q: Do you smoke?	Q: Do you smoke?
	Maternal alcohol use	*Maternal alcohol use*
Definition	Dichotomous outcome (no/yes): "Yes" defined as any usage	Dichotomous outcome (no/yes): "Yes" defined as any usage
Assessment	Q: Do you drink alcohol?	Q: Do you drink alcohol?

	Maternal drugs use	*Maternal drugs use*
Definition	Dichotomous outcome (no/yes): "Yes" defined as any usage	Dichotomous outcome (no/yes): "Yes" defined as any usage
Assessment	Q: Do you use drugs? Marijuana, hash and weed are drugs too.	Q: Do you use drugs? Marijuana, hash and weed are drugs too.

their knowledge of the applied client-tailored care during pregnancy and the postpartum period.

In addition we will assess the effectiveness of the implementation process and the adherence to the study protocol in both arms. The effectiveness of the implementation process within maternity care organizations will be assessed quantitatively with a questionnaire addressed to professionals working in the administrative or management sector of each maternity care organization.

Participant timeline

Potentially eligible women receive a study flyer when registering with one of the participating maternity care organizations. During a scheduled home visit (i.e. the intake), the participant will fill out the structured risk assessment electronically. At the end of the standard maternity care provision period, a second questionnaire will be filled out assessing the primary outcome and a number of secondary outcomes (table 1). A third electronic questionnaire will be sent to participants during the late postpartum period (i.e. six weeks after they gave birth). This questionnaire will assess multiple secondary outcomes (table 1).

Sample size

Calculation of sample size is based on the presumed effect of the intervention on the primary outcome at the individual level. The intervention is considered to be effective when the prevalence of a low empowerment score, is reduced by 50%; in other words, our sample size is calculated to determine a proportion difference from a low empowerment score at the 20th centile towards the 10th centile.

A previous study using the MEQ, in an unselected population of 2675 women in the postpartum period, showed a mean score over four domains of 3.70, with a left-skewed distribution (25th centile 3.46 and 75th centile 3.88) [20]. We hypothesize that the intervention will lead to a decline of an empowerment score of <3.38 (i.e. the 20th centile) by 50%. At an alpha of 0.05 and 80% power, we will require 196 participants per arm and as such 392 participants in total.

The intervention will be implemented at the cluster level (i.e. (groups of) maternity care organizations), while the intervention effect will be assessed at the participant level. We expect a small variance in provided care between clusters as is common in primary care

practices [21]. The Intraclass Correlation Coefficient (ICC) is therefore set at 0.05. The Variance Inflation Factor (VIF), calculated with the formula of Donner et al [22], is calculated to be 2.91.

We account for a lost to follow-up of 33% (i.e. from inclusion to assessment of primary outcome). The target sample size is therefore set at 856 (i.e. 1.5*(2.91*196)) participants per arm.

Recruitment
To achieve adequate participant enrolment, an inclusion target per month will be set for each organization. Monitoring of this target will be communicated on monthly bases with all local researchers. Not achieving this target is seen as the impediment of effective recruitment and action will be taken to improve the effectiveness in recruiting eligible participants. An example of such action would be evaluating the barriers for participant inclusion, evaluating engagement barriers, and providing additional support for MCAs.

Randomization and allocation
We will perform allocation by clusters, with the maternity care organization(s) as the randomization unit, to minimize possible contamination effects among professionals. Each cluster was randomized to the intervention arm or the control arm by a statistician not involved in the implementation of the trial and blind to the identity of the clusters and the incorporated maternity care organizations.

Blinding
Maternity care organizations agreed to participate, and to accept any allocation, prior to the randomization procedure.
Study information to participants strictly contains information related to the allocated arm, without mentioning the randomized design of the trial or the changes in the provided care during pregnancy and the postpartum period.

Data collection
No interim analyses are planned, and all outcomes will be analyzed following data collection.

Statistical methods
All analyses will be performed according to the intention-to-treat principle. Descriptive statistics will be presented, and formal inference will be based on hypothesis testing with two-sided statistical significance assessed at the 5% level. Multiple imputation using chained equations will be used to account for missing data in baseline characteristics. We will analyze the effect of the intervention on our primary and secondary outcome measurements using multilevel mixed-effects linear or logistic regression analyses with an assumed random effect for each cluster.

Data monitoring

A data monitoring committee (DMC) is not installed, as the ethics committee deemed it as unnecessary, because the risks for participants are negligible. All aspects of the intervention fall within the scope of conventional maternity care. The funding source has no role in the design of the study, and neither in the collection and management of the data.

DISCUSSION

With this C-RCT we aim to systematically increase the identification of non-medical risk factors during pregnancy, and use the obtained risk profile for improved client-tailored care during the postpartum period. We envisage that this intervention creates an additional opportunity for MCAs to empower women during the postpartum period. Increased maternal empowerment has the potential to enhance their self-efficacy, their quality of life, and their child's well-being during the postpartum period [10][13].

To our knowledge this is the first multicenter trial of client-tailored, risk-guided maternity care, creating a unique opportunity to investigate its potential to improve maternal empowerment. In concordance with the overall aim of the HP4All-2 program, this study targets women from deprived neighborhoods, aiming to reduce adverse maternal and neonatal outcomes of those who are at greatest risk.

There are several challenges in the execution of this complex C-RCT that merit discussion. This C-RCT is embedded in a complex existing collaborative setting involving multiple municipalities and maternity care organizations and their professionals. Particular challenges include maintaining engagement in 17 sites spread across the country, engaging staff groups employed by different organizations, and motivating MCAs from different organizations to change their routine working practices and adapt to a more risk-guided provision of care. In addition, there is an unequivocal registration of the personalized care undertaken by maternity care professionals during the postpartum.

To conclude, this C-RCT is the first trial in the Netherlands aiming to empower women during the postpartum period. Providing a risk assessment, with emphasis on non-medical risks related to SES and psychopathology, facilitates client-tailored care and may contribute to prevention of adverse health outcomes for mother and child.

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7

CHAPTER 8

Enhancing maternal empowerment postpartum: a cluster randomised controlled trial

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ABSTRACT

Objective
To investigate whether a structured inquiry during pregnancy of medical factors and social factors associated with low socioeconomic status, and subsequent patient-centred maternity care could increase maternal empowerment.

Design
Cluster-randomised controlled trial.

Setting
This study was conducted among pregnant women in selected urban areas in the Netherlands. This study was part of the nationwide Healthy Pregnancy 4 All-2 programme.

Population
Pregnant women listed at one of the sixteen participating maternity care organisations between July 1, 2015, and Dec 31, 2016.

Methods
All practices were instructed to provide a systematic risk assessment during pregnancy. Practices were randomly allocated to continue usual care (seven practices), or to provide a patient-centred, risk-guided approach to addressing any risks (nine practices) identified via the risk assessment during pregnancy.

Main Outcome Measures
Low postpartum maternal empowerment score.

Results
We recruited 1579 participants; 879 participants in the intervention arm, and 700 participants in the control arm. The prevalence of one or more risk factors during pregnancy was similar between the two arms: 40% and 39%, respectively. In our intention-to-treat analysis, the intervention resulted in a significant reduction in the odds of having a low empowerment score [i.e. the primary outcome; adjusted OR 0.69 ((95% CI 0.47; 0.99), P 0.046)].

Conclusions
Implementation of additional risk assessment addressing both medical and social factors and subsequent tailored preventive strategies into maternity care reduced the incidence of low maternal empowerment during the postpartum period. Introducing this approach in routine maternity care may help reduce early adversity during the postpartum period.

INTRODUCTION

Maternity care refers to the safe and high quality health care given in relation to pregnancy and delivery of an infant. The purpose of maternity care is manifold: providing information and emotional support, providing adequate care for mother and child, and enhancing maternal empowerment (1, 2). Empowerment is defined as achieving self-efficacy, and it reflects the process through which people gain greater control over decisions and actions affecting their health (3).

Women with a lower socioeconomic status (SES) tend to have lower self-efficacy than women with a higher SES (4-7). This lower self-efficacy of women with a low SES may further augment their already increased risk of developing adverse maternal and child health outcomes (8-13). As such, building women's sense of autonomy and control may help reduce inequalities in maternal and child health outcomes resulting from factors related to a person's SES (10, 12, 14-18).

Unfortunately, missed opportunities occur in daily practice as SES indicators and factors related to a person's self-efficacy are insufficiently acknowledged or taken into account in the provision of maternity care (19). Moreover, there is a consistent inequity in postpartum care provision in the Netherlands, where more care is provided to women with a higher SES, who need it less, than to women who are disadvantaged (20). We hypothesised that a structured inquiry of medical factors and social factors associated with low SES, and subsequent patient-centred maternity care tailored to these factors during pregnancy and the postpartum period, would increase postpartum maternal empowerment.

MATERIALS AND METHODS

We conducted a cluster-randomised controlled trial (C-RCT) in six municipalities in the Netherlands to assess the effectiveness of a complex intervention to advance maternal empowerment in the postpartum period (21, 22). The intervention consisted of a systematic risk assessment including both medical and social factors, and a patient-centred, risk-guided approach to address risks identified during pregnancy and the postpartum period.

This C-RCT was embedded in the national Healthy Pregnancy 4 All-2 (HP4All-2) programme (21), a successor to the HP4All-1 programme (23). Both programmes aimed to improve perinatal health by reducing health inequalities during pregnancy and childbirth. Poor neighbourhoods in the Netherlands were the main location to reach women with a lower SES (21). We used the CONSORT statement for C-RCTs to guide reporting of our findings (24).

Trial design

The study design and rationale are briefly outlined below; a detailed study protocol was previously published (22). The study was registered in the Netherlands Trial Registry (NTR: 6311). A two-arm, parallel, pragmatic C-RCT was conducted with 12 independent maternity care organisations, which were geographically spread over the Netherlands with 16 offices (figure 1).

Six out of ten municipalities within the HP4All-2 programme participated in this trial. Each municipality was divided into an intervention and a control cluster, to minimise the influence of geographical variation on the outcome measures. To avoid contamination between maternity care assistants (MCAs) working within the same maternity care organisation we allocated the intervention at the level of the maternity care organisation(s) per municipality rather than at the individual MCA or participant level. As such, a cluster could consist of multiple maternity care organisations.

Figure 1: C-RCT Design with Intervention Details
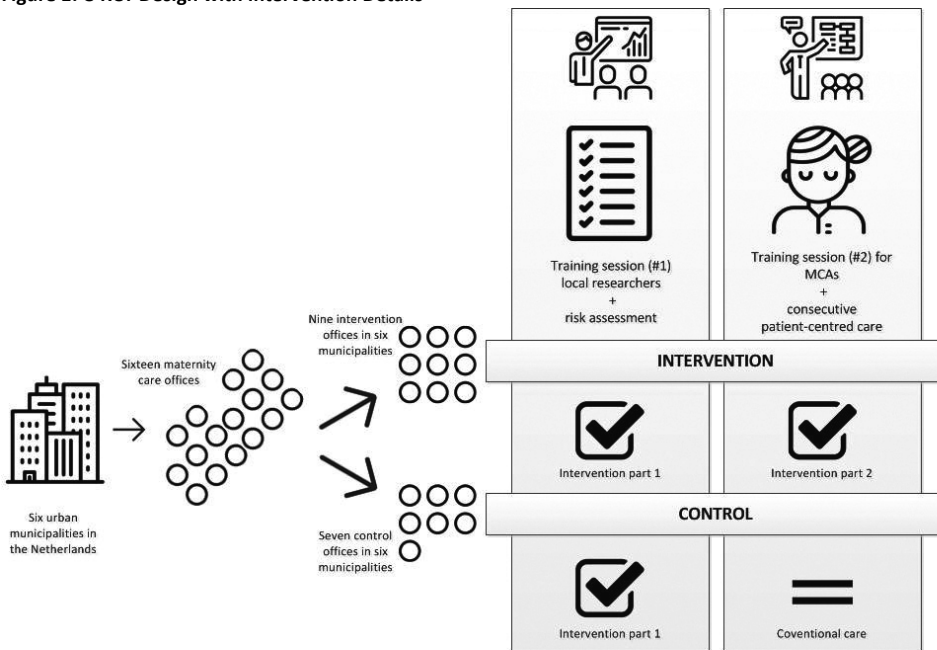
*Within the six urban municipalities, 16 maternity care offices were randomised in clusters with one or more offices. Nine offices were assigned to the intervention arm. They received the first part of the intervention which consisted of a systematic risk assessment and the second part that consisted of patient-centred, risk-guided care, along with the consecutive training sessions. The seven remaining offices were assigned to the control arm and they solely implemented the first part (i.e. the risk assessment) along with training session number one. Care provision in the control arm was based on conventional care.

Participants

All pregnant women cared for by participating maternity care organisations with a scheduled home visit during pregnancy were eligible to take part in the study. Eligible participants were informed about the study and written informed consent was obtained prior to inclusion. Participants were enrolled between July 2015 and December 2016. Follow-up data was collected until July 2017.

Intervention and control conditions

The study included two practice changes: 1) implementation of a systematic risk assessment during pregnancy to identify medical, social and non-medical risk factors associated with adverse maternal health (control and intervention arm); and 2) provision of patient-centred care throughout pregnancy and the post-partum period by MCAs, as informed by their risk profile (intervention arm only) (22). Participants were followed up until they were 12 weeks postpartum.

The systematic risk assessment was included in the standard home intake that is scheduled by maternity care organisations in the third trimester of pregnancy. The assessment was an electronic questionnaire and covered domains related to socioeconomic and psychological factors. The questionnaire consisted of the following components: 1) the Mind2Care (M2C) tool (a validated third trimester risk screening tool frequently used to assess psychological and psychosocial problems (https://www.mind2care.nl/Home)); 2) the Maternal Empowerment Questionnaire (MEQ; a validated postpartum tool based on the World Health Organization (WHO) Responsiveness model used to assess the performance of maternity care based on clients' experiences (25)) with slight adjustments; and 3) additional questions regarding socioeconomic status.

To properly carry out the risk assessment, professionals were trained in two separate sessions, each three hours long, referred to as 'Training Session 1a and 1b' (Figure 1). The first and core training was held prior to the start of participant enrolment and focused on effective use of the risk assessment tool and on building communication skills (Training 1a). The second training, after the first month of participant enrolment, was aimed at refreshing the obtained knowledge and providing a platform for discussing possible implementation issues that were encountered during patient enrolment (Training 1b). An established national educational organisation ("Kersten & van de Pol") assisted the research team in providing these training sessions (22). Maternity care professionals who completed both Training Session number 1a and number 1b, and who enrolled participants in the study, are henceforth referred to as 'local researchers'. For the second part (i.e. the actual intervention under study), the provision of patient-centred risk-tailored maternity care during the postpartum period, training sessions were held for all MCAs in the intervention arm prior to the start of the study (Training Session number 2). This training session covered knowledge and skills enabling MCAs to provide

advice for additional care, to tailor maternity care provision to the individual needs and the existing resources of a participant, and to strengthen participants' own capabilities. Another established national educational organisation, ("Voorlichters Gezondheid"), assisted the research team in delivering Training Session 2. In addition to this accredited training session, templates were introduced to guide an MCA into taking appropriate action once a risk factor was identified. As such, each template served as a care pathway by directing the MCAs to, for example, a specific health care provider (i.e. midwife, obstetrician, or general practitioner), a public health care organisation, or an office for legal or financial support. As an example, the template for addressing the risk factor 'irredeemable financial debts' guided the local researcher into taking the following actions during pregnancy: creating awareness among involved health care professionals (e.g. community midwife, general practitioner, MCAs) and applying for local funds that supply free postpartum packages consisting of, among other things, nappies and sanitary pads. In the control arm, professionals were blinded for the outcome of the risk assessment and they provided conventional care during pregnancy and the postpartum period (figure 1).

Outcomes

We hypothesised that our intervention would reduce the proportion of women with a low empowerment score postpartum. As such, the primary outcome was a low maternal empowerment score in the early postpartum period, between one to two weeks after childbirth, as assessed by the validated MEQ (26). A low empowerment score was defined as a MEQ-score beneath the 20th centile (rounded at one decimal) of empowerment scores in the control arm. Secondary outcome measures pertain to maternal health-related quality of life, maternal perceived health, maternal psychological health, maternal and neonatal health care utilisation postpartum, maternal smoking behaviour, and alcohol consumption during the late postpartum period, up and until twelve weeks after childbirth (Table S1).

MCAs in the intervention arm filled out a questionnaire during the participant's early postpartum period. This questionnaire assessed the MCAs' understanding of the participant's obtained risk profile during pregnancy, and the relevance of the detected risk-profile for the care that they provided during the postpartum period. All MCAs filled out the Measurement Instrument for Determinants of Innovations (MIDI); an instrument that measures determinants of innovations (27) at the end of the study period to assess the delivery of the intervention.

Randomisation, implementation, and blinding

Figure S1 summarises the chronology of events, blinding, and any differences between the two arms (28). The timeline cluster diagram is complementary to the CONSORT-flowchart for C-RCTs (Figure 2) (24). At the start of the study, maternity care organisations were identified and recruited. Clusters were formed and consisted of one or more distinct

maternity care organisations, depending on the expected number of eligible women within each organisation. Randomisation was then performed at the cluster level. A statistician who was not involved in the implementation of the trial and who was blinded to the identity of the clusters performed the randomisation procedure. After randomisation of the clusters, all eligible women received study information at first contact with a maternity care organisation and prior to the scheduled home visit. Hence, participants were blinded for allocation because they were unaware of the randomised design of the study, and as such of the alternative strategy. Blinding of MCAs and local researchers was not feasible due to the training related to our intervention. Therefore, recruitment of participants, the following baseline assessment, execution of the experimental intervention during pregnancy and the postpartum period, as well as outcome assessments in the postpartum period were partially blinded; the participant was unaware of the randomised design but the MCA was aware of the outcome of allocation.
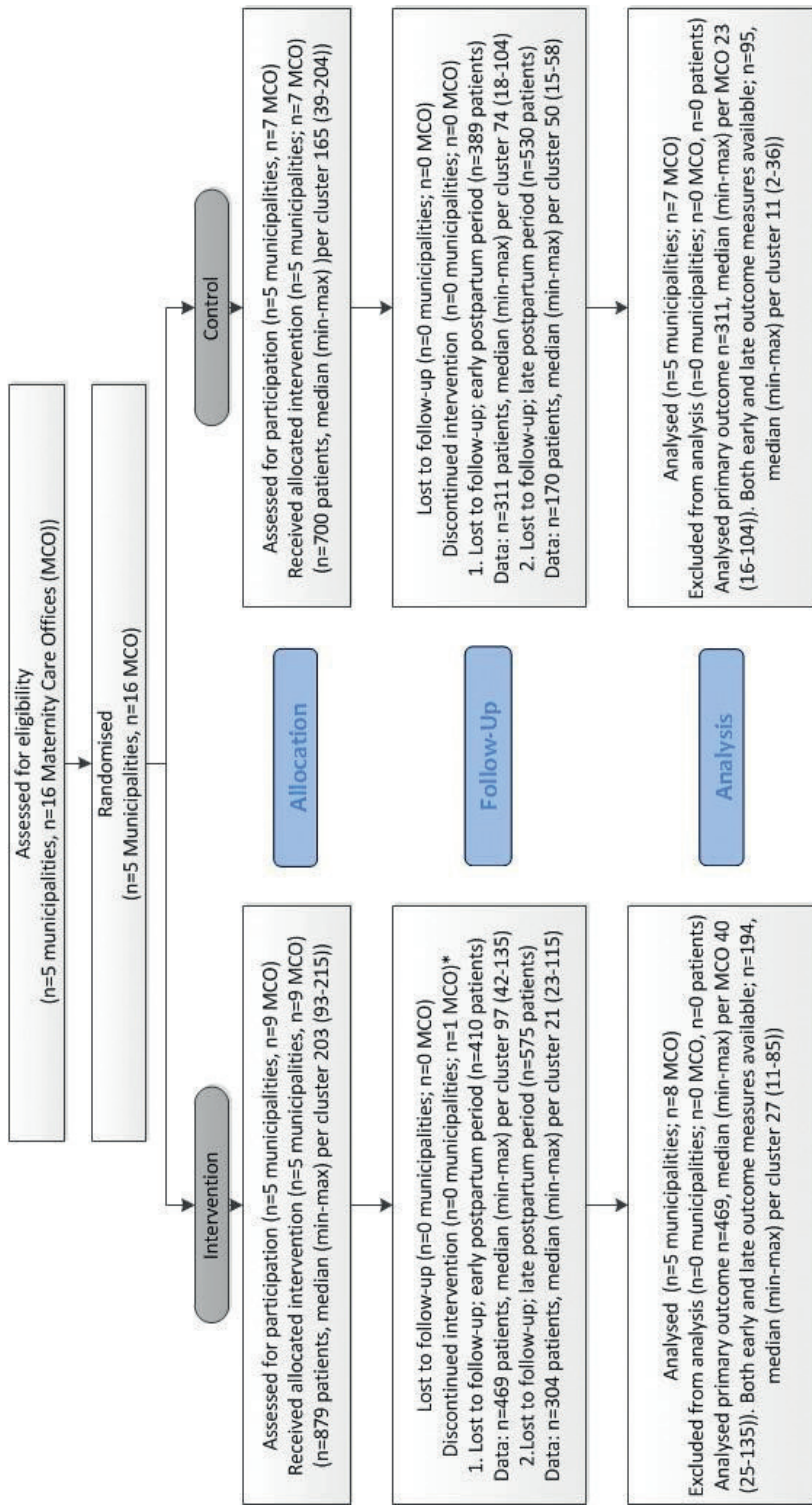
Sample size

An initial sample size of 1711 participants was calculated using an alpha of 0.05, a power of 80%, and assuming a lost to follow-up of 33% (22). To adjust for clustering, an Intraclass Correlation Coefficient (ICC) of 0.05 was assumed in this sample size calculation, as is common in studies involving primary care practices (29, 30).

Statistical methods

Impact of the intervention

Descriptive data were compared to identify major differences between the two arms in baseline characteristics, pregnancy outcomes, and in uptake of maternity care. Mixed-effects models were used to adjust for clustering within the (clusters of) maternity care organisations. Analyses were conducted with random effect for clusters only ('unadjusted models'), and additionally adjusted for selected covariates ('adjusted models'). Selection of covariates was based on a stepwise backward elimination using the Wald test and keeping a p value of 0.20 as a threshold for elimination. 'Parity' (multiparous vs primiparous), and 'single parenthood' (living without a partner) were fixed prior to the stepwise modelling as these variables are incorporated in the national protocol for determining the amount of postpartum care provision and as such may affect maternal empowerment postpartum (19). Multilevel mixed-effects logistic regression was used for binary outcomes, multilevel mixed-effects linear regression was used for continuous outcomes, and multilevel mixed-effects ordered regression was used for categorical outcomes. The main analyses were undertaken on an intention-to-treat (ITT) basis. The observed intraclass correlation coefficient was calculated using the adjusted model for the primary outcome.

Figure 2: CONSORT diagram showing flow of municipalities, maternity care organisations, and participants

Assessed for eligibility
(n=5 municipalities, n=16 Maternity Care Offices (MCO))

Randomised
(n=5 Municipalities, n=16 MCO)

Intervention

Assessed for participation (n=5 municipalities, n=9 MCO)
Received allocated intervention (n=5 municipalities, n=9 MCO)
(n=879 patients, median (min-max) per cluster 203 (93-215))

Allocation

Control

Assessed for participation (n=5 municipalities, n=7 MCO)
Received allocated intervention (n=5 municipalities; n=7 MCO)
(n=700 patients, median (min-max))per cluster 165 (39-204))

Lost to follow-up (n=0 municipalities; n=0 MCO)
Discontinued intervention (n=0 municipalities; n=1 MCO)*
1. Lost to follow-up; early postpartum period (n=410 patients)
Data: n=469 patients, median (min-max) per cluster 97 (42-135)
2.Lost to follow-up; late postpartum period (n=575 patients)
Data: n=304 patients, median (min-max) per cluster 21 (23-115)

Follow-Up

Lost to follow-up (n=0 municipalities; n=0 MCO)
Discontinued intervention (n=0 municipalities; n=0 MCO)
1. Lost to follow-up; early postpartum period (n=389 patients)
Data: n=311 patients, median (min-max) per cluster 74 (18-104)
2. Lost to follow-up; late postpartum period (n=530 patients)
Data: n=170 patients, median (min-max) per cluster 50 (15-58)

Analysed (n=5 municipalities; n=8 MCO)
Excluded from analysis (n=0 municipalities; n=0 MCO, n=0 patients)
Analysed primary outcome n=469, median (min-max) per MCO 40
(25-135)). Both early and late outcome measures available; n=194,
median (min-max) per cluster 27 (11-85))

Analysis

Analysed (n=5 municipalities; n=7 MCO)
Excluded from analysis (n=0 municipalities; n=0 MCO, n=0 patients)
Analysed primary outcome n=311, median (min-max) per MCO 23
(16-104)). Both early and late outcome measures available; n=95,
median (min-max) per cluster 11 (2-36))

*One maternity care organisation discontinued the intervention before participant enrollment due to self-reported time constraints, and the inability to work with an electronic device for risk assessment during pregnancy

Subgroup analysis

To assess whether there was a differential effect of the intervention on maternal empowerment according to whether risk factors had been identified during pregnancy, a subgroup analysis on participants with at least one identified factor was performed.

Post-hoc analysis

A higher-than-anticipated attrition rate was observed during the trial. In an attempt to address this we applied multiple imputation using chained equations, creating 20 unique datasets, to account for loss to follow-up and missing information (31). Both predictor and outcome variables were included to inform the multiple imputation process and results across the sets were combined using Rubin's Rules (32). A post-hoc sensitivity analysis using the multiple imputed data was performed to check whether this attrition rate affected the effect estimates of the primary outcome. For all analyses, nominal significance level was 5%; with no adjustment for multiple testing. Analyses were performed using Stata version 15.

Determinants of the delivery of the intervention

To evaluate the delivery of the intervention in the postpartum period, MCAs were asked to indicate if they were aware that a risk factor had been identified during pregnancy, and if they agreed that this detected risk had indeed been present throughout the postpartum period. To evaluate the determinants of implementation all local researchers were asked to fill out the MIDI questionnaire. The response scale consisted of a five point scale; 'totally disagree', 'disagree', 'neither agree nor disagree', 'agree', and 'totally agree'. All outcomes regarding these determinants of implementation are reported as frequencies and percentages.

RESULTS

Cluster and participant flow

Sixteen maternity care offices from 12 independent maternity care organisations were recruited. In the intervention group, one maternity care office discontinued the intervention before participant enrolment due to difficulties with using electronic questionnaires (Figure 2). A total of 76 professionals from maternity care offices in both arms were recruited and trained extensively completing both Training Session 1a and 1b. All local researchers participated throughout the study period. Additionally, in the intervention arm, 385 MCAs were trained in Session number 2 and participated in the provision of patient-centred, risk-based maternity care during pregnancy and the postpartum period.

Together, the 15 maternity care offices that participated throughout the study period included 1579 participants: 879 participants in the intervention arm, and 700 participants in the control arm. Enrolment of participants stopped after December 2016 according to protocol (22).

Follow-up data from the early postpartum period, between one to two weeks after childbirth, was available for 469 participants (53%) in the intervention arm and 311 (44%) in the control arm. For all participants with follow-up data from the early postpartum period, data from the consecutive late postpartum period, six through twelve weeks after childbirth, was available for 304 participants (64%) in the intervention arm and 170 participants (54%) in the control arm (figure 2).

Participants who were lost to follow-up during the early and late follow-up period more often: were first or second generation immigrants (early: 40% versus 24%; late: 37% versus 21%), had a low disposable household income (early 17% versus 7%; late 15% versus 6%), and were without a paid job during pregnancy (early follow-up 26% versus 17%; late follow-up 26% versus 12%) (Table S2).

Participant characteristics
Baseline characteristics assessed during pregnancy were similar for participants in the intervention and the control arm (Table 1); this similarity was also observed between clusters (Table S3). The percentage of participants who had one or more risk factor(s) identified during pregnancy was similar between both arms: 40% and 39% in the intervention and the control arm, respectively (Table S4). The most frequent risk factors were: fear for upcoming delivery (intervention 37%; control 34%); a self-reported concern about being prepared for care provision for the baby (intervention 27%; control 27%); and inadequate health literacy (intervention 17%; control 20%). Data regarding pregnancy outcomes and uptake of maternity care were available for 1445 participants (92%). There were no relevant differences in pregnancy outcomes or in the provided amount of maternity care between the intervention arm and the control arm (table 2).

Impact of the intervention
A low empowerment score in the early postpartum period was observed in 19.2% and 25.4% of all participants in the intervention and control arm, respectively. The intervention resulted in a significant reduction in the odds of having a low empowerment score [unadjusted OR 0.69 ((95% CI 0.48;0.99), P 0.047); adjusted OR 0.69 ((95% CI 0.47; 0.99), P 0.046)] (table 3).

Analyses of predefined secondary outcomes showed no significant effects of the intervention on maternal health-related quality of life, perceived health, psychological health, maternal- and neonatal health care utilisation postpartum, and maternal smoking behaviour and alcohol consumption during the postpartum period (table 3).

Table 1: Individual-level baseline characteristics assessed during pregnancy

	Intervention (n=879)		Control (n=700)	
	Mean	**SD**	**Mean**	**SD**
Maternal age*	31.5	4.8	31.7	4.4
	N	**%**	**N**	**%**
Parity				
Primiparous	446	50.7%	360	51.4%
Multiparous	433	49.3%	340	48.6%
Parenthood				
Single	20	2.3%	31	4.4%
Living together	859	97.7%	669	95.6%
Immigrant status				
Non-immigrant	595	68.7%	468	67.1%
First generation	135	15.6%	97	13.9%
Second generation	136	15.7%	132	18.9%
Missing	13	1.5%	3	0.4%
Health insurance				
No	1	0.1%	1	0.1%
Yes	878	99.9%	699	99.9%
Education				
Lower	50	5.7%	43	6.1%
Intermediate	538	61.2%	428	61.1%
High	291	33.1%	229	32.7%
Net household income (euro/month)				
<1500	95	10.8%	95	13.6%
1500-3000	338	38.5%	260	37.1%
>3000	446	50.7%	345	49.3%
Paid job during pregnancy				
No	201	22.9%	145	20.7%
Yes	678	77.1%	555	79.3%
Neighbourhood deprivation				
No	517	58.8%	370	52.9%
Yes	362	41.2%	330	47.1%
Smoking during pregnancy				
No	762	86.7%	602	86.0%
Yes	117	13.3%	98	14.0%
Alcohol use during pregnancy				
No	693	78.8%	565	80.7%
Yes	186	21.2%	135	19.3%
Drug use during pregnancy				
No	867	98.6%	689	98.4%
Yes	12	1.4%	11	1.6%
Risk factors detected				
No	527	60.0%	424	60.6%
Yes	352	40.0%	276	39.4%
Indicated hours of maternity care				
24-49 hours	691	82%	571	84%
>49 hours	153	18%	106	16%
Missing	34	4%	23	3%

Mean* with SD or number with % (presented as percentage of non-missing values). Missing value percentage of total.

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Subgroup analysis

The impact of the intervention on the incidence of a low maternal empowerment score was mainly attributable to its impact among participants with one or multiple identified risks during pregnancy (n=412): aOR 0.61 ((95% CI 0.38; 0.98), P 0.043). There was no demonstrable effect of the intervention in the subgroup of women without identified risks during pregnancy (n=368): aOR 0.78 ((95% CI 0.43; 1.41), P 0.407).

Post-hoc sensitivity analysis

Following imputation of missing data, the incidence of a low empowerment score was 20% and 23% in the intervention and control group, respectively. The estimated proportions of all predefined outcomes were more alike between the two arms in the imputed data than in the observed data (table 3).

Within the post-hoc analysis using imputed data, the impact of the intervention was smaller than in the complete dataset and no longer statistically significant [OR 0.83 ((95% CI 0.61; 1.12); P 0.228); aOR 0.82 (95% CI 0.60; 1.10); P 0.182)].

Table 2: Pregnancy outcomes and maternity care uptake postpartum.

	Intervention (n=812)		Control (n=633)	
	N	%	N	%
Gender newborn				
Male	423	52.1%	303	47.9%
Female	389	47.9%	330	52.1%
Caesarean section				
No	704	86.7%	541	85.5%
Yes	108	13.3%	92	14.5%
Preterm delivery				
No	783	96.4%	609	96.2%
Yes	29	3.6%	24	3.8%
Low birth weight (<2500 grams)				
No	773	96.0%	601	95.7%
Yes	32	4.0%	27	4.3%
Missing	7	0.9%	5	0.8%
Provided hours of postpartum care				
<24 hours	69	8.7%	43	6.9%
24-49 hours	476	59.8%	391	62.4%
>49 hours	251	31.5%	193	30.8%
Missing	16	2.0%	6	0.9%

Number with % (presented as percentage of non-missing values). Missing value percentage of total.

Table 3: Impact of the intervention on primary and secondary outcomes

Primary and secondary outcomes		N	Proportions		OR (95% CI)	aOR (95% CI)
			Intervention	Control		
Complete cases						
Early postpartum period						
Primary outcome						
Low empowerment score	Yes	711	0.19	0.25	0.69 (0.48; 0.99)	0.69 (0.47; 0.99)
Secondary outcomes						
Maternal health related quality of life, cont.	mean (SE)	763	0.82 (0.13)	0.83 (0.13)	-0.01 (-0.03; 0.14)	-0.01 (-0.04; 0.11)
Maternal perceived health, cont.	mean (SE)	775	76.80 (13.1)	76.43 (12.0)	0.35 (-2.06; 2.76)	-0.07 (-1.99; 1.84)
Late postpartum period						
Secondary outcomes						
Maternal psychological health	EPDS>12	474	0.05	0.05	0.90 (0.35; 2.30)	0.85 (0.31; 2.38)
Maternal health care utilisation		413				
One visit			0.21	0.34	0.63 (0.32; 1.22)	0.68 (0.35; 1.32)
Multiple visits			0.10	0.05		
Hospital admission			0.03	0.03		
Neonatal health care utilisation		428				
One visit			0.12	0.12	1.29 (0.89; 1.89)	1.32 (0.89; 1.94)
Multiple visits			0.28	0.30		
Hospital admission			0.06	0.07		
Smoking late postpartum period	Yes	447	0.06	0.05	1.13 (0.49; 2.56)	0.96 (0.40; 2.28)
Alcohol late postpartum period	Yes	300	0.39	0.32	1.34 (0.91; 2.00)	1.40 (0.94; 2.10)

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Table 3: *continued*

Subgroup analysis: at least one risk factor in assessment

	N				
Low empowerment score	412				
		Yes	0.21	0.30	0.64 (0.40; 1.01)	0.61 (0.38; 0.98)

Post-hoc analysis: imputed dataset

	N				
Low empowerment score	711				
		Yes	0.20	0.23	0.83 (0.61; 1.12)	0.82 (0.60; 1.10)

Number of complete cases per outcome (N) with proportions of primary and secondary outcomes; presented by early and late postpartum period (column: first) and by primary and secondary outcomes (second). Results from the multilevel mixed-effects logistic regression and multilevel mixed-effects ordered logistic regression are presented as (unadjusted) OR with 95% CI (first), and adjusted OR (aOR) with 95% CI (second). Results from multilevel mixed-effects linear regression are marked as cont. (continuous) and presented as β with 95% CI. Adjustment for parity, parenthood, household income, and educational attainment.

Determinants of the delivery of the intervention

Delivery of the intervention during the postpartum period

Of all participants in the intervention arm for whom follow-up data were available, 90% (n=420) had a response from the MCA who provided maternity care to them. Of these participants, 55% (n=233) had one or multiple identified risk factor(s) during pregnancy. The response from the MCAs indicated that they were aware of these risks in only 30% (n=70) of all care provisions. Among those aware, 79% (n=55) agreed that this risk factor had influenced the content of their care. This low awareness of MCAs was mostly due to lack of communication between MCAs responsible for care during pregnancy and those responsible for the postpartum period, as reported in the MIDI instrument.

Determinants of implementation of the intervention

At the end of the study period, 52 out of 76 trained local researchers (68%) filled out the MIDI questionnaire assessing the determinants of implementation of the intervention. Local researchers reported an overall positive feeling regarding the intervention. Sixty-seven percent of all local researchers agreed that the procedural clarity of the intervention was good, 56% agreed that the intervention was based on factually correct knowledge (i.e. the correctness of the intervention itself), and 57% reported a good compatibility of the intervention with their values and standard working patterns. When asked if they believed that the intervention was relevant for their client, only 8% disagreed. However, the evaluated determinants that were associated with themselves, as the adapting person, were scored less positively. Twenty-one percent of all local researchers reported little to no personal gain from the intervention with regard to improving their standard working patterns. Only 30% agreed with the following statement: "with this innovation I achieved risk-based, patient-centred care during pregnancy and the postpartum period".

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DISCUSSION

This pragmatic C-RCT indicates that a structured risk assessment, including social and other non-medical determinants of health, followed by patient-centred maternity care may help reduce the incidence of low maternal empowerment during the postpartum period. This effect was particularly seen among high-risk women, as detected by the assessment during pregnancy.

This trial has several strengths. It contains several positive key characteristics of pragmatic trials: 1) comparison of a clinically relevant alternative to current practice; 2) a diverse and representative population of study participants; 3) heterogeneous practice settings similar to those where the aspired preventive care is to be set out; and 4) collection of data on a broad range of health outcomes (33, 34). Furthermore, with this large scale randomised

trial we are the first to evaluate the effectiveness of risk-guided, patient-centred care in increasing maternal self-efficacy.

In addition, analysis of determinants of implementation showed that the different intervention components were acceptable by local researchers from participating maternity care organisations. The combination of the good acceptability from health care professionals and the possibility of reducing low maternal empowerment scores, supports the potential for introducing this approach. Given that low maternal empowerment is associated with an increased risk of developing adverse maternal and child health, this intervention has the potential to reduce persisting inequalities in maternal and child health outcomes

When interpreting our findings, a number of limitations also need to be taken into account. First, there was a considerable and selective loss to follow-up that has introduced a bias in our data. The loss to follow-up rate was particularly high among the less advantaged participants (Table S2), a phenomenon that is often observed in clinical trials (35-37). To address the resulting amount of missing data, including missing outcomes, we used multiple imputation. Baseline characteristics that were related to the loss to follow-up were included to inform the imputation model. However, concerns about validity persist because multiple imputation does not work well when data is missing not at random, hence producing biased estimates (38). This complicated interpretation of the contrasting findings of the analyses of the imputed versus the original data, as both could be biased.

Second, the calculated sample size of 1711 participants was not achieved, possibly reducing the accuracy of our results. Formulas for calculating appropriate sample size in C-RCTs traditionally include inflation with the Variance Inflation Factor (VIF). This factor is calculated by multiplying the number of participants per cluster with the ICC (29, 30). For our initial sample size calculation we anticipated an ICC of 0.05 (22). However, the observed ICC from our primary model was negligible (ICC= 3.21 e-15), and as such the correlation between clusters was much less than expected. Sample size calculations using the observed rather than the anticipated ICC, together with the higher than expected attrition rate would have resulted in a lower required sample size (i.e. a total of 784 participants).

Third, the observed fidelity of our intervention was low, which might have affected its effectiveness (39). We had intended to have MCAs tailor their maternity care to the identified risk factors in pregnancy. However, in only 40% of all postpartum care provisions that involved participants in whom risk factors had been identified during pregnancy, the MCA reported to be aware of these risks. Nevertheless, due to the extensive training prior to the start of the intervention, all MCAs were accustomed with the importance of risk assessment and centring their care to meet these risks and the participants' own resources and capabilities.

Fourth, although the reduction in low empowerment scores in the intervention arm was statistically significant, it may not reflect a clinically important difference. Overall, women had a strong sense of self efficacy during the initial assessment , and the difference in median scores between the two groups was small. Although the validity and reliability of the MEQ have been reported before as good (26), the questionnaire has not been tested on its responsiveness to change and the size of what may be considered a clinically meaningful difference has not been established.

Research has shown that it is challenging to show benefit of universally provided home visits regarding the wellbeing of mothers and babies, as underlined by the review of Yonemoto and colleagues (40). They concluded that interventions aiming to improve maternal health outcomes in the postnatal period might be effective if subpopulations with a higher risk would be targeted (40). It is in this regard important to note that we have previously demonstrated that low-SES women are less likely to receive postpartum care in the Netherlands, at the same time showing that lack of maternity care is associated with increased subsequent health care costs (20). Hence, we intended to address a specific subpopulation of high-risk women during pregnancy, to enhance empowerment in those at overall greater risk of adverse health outcomes. Although study participants had a relatively high educational level, a high net income, and were more often non-immigrants compared to the general Dutch population, still 40% had one or more risk factors amendable to tailored care identified. Furthermore, the effect of the intervention was greatest in this subgroup of women with one or multiple risk factors.

Future research should consider alternative designs to analyse the effectiveness of complex interventions into routine maternity care. Quasi-experimental studies or stepped-wedge trials may be better suited to assess impact of novel care adaptations. Alternatively, future research should include focus groups and interviews with women to hear from their perspective the challenges they face and the supports they need. Letting them be part of the design of the interventions could help reduce attrition and improve outcomes.

With this study, we have provided evidence that it is feasible to amend routine maternity care by introducing patient-centred care based on predefined medical and non-medical risk factors, and that this may improve maternal empowerment in the postpartum period. Additional work is needed to assess how early identification of women at risk for adverse pregnancy and postpartum outcomes along with patient-centred, risk-reducing strategies may help minimise early adversity and existing inequalities in postpartum care.

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SUPPLEMENT

Supporting Tables

Supplementary table 1 (table S1): Outcome measures at participant level with definitions

	Early (1-2 weeks after childbirth)	Late (6-12 weeks after childbirth)
Primary	*Maternal empowerment*	
	Low empowerment score (no/yes) defined as a MEQ-score beneath the 20th centile within the control group	
Secondary	*Maternal health related quality of life*	*Maternal depression (postnatal depression)*
	Continuous score ranging from zero (dead) to one (full health) based on the validated EQ-5D-5L calculator	Dichotomous outcome based on the EPDS-sum score: "No" sum score <13 and "Yes" sum score >12.
	Maternal perceived health	*Maternal health care utilisation*
	Continuous score ranging from zero (the worst health possible) to 100 (the best health possible) based on the EuroQol-visual analogue scales (EQ-VAS)	Categorical outcome ranging from "No additional care" to "Admission in a hospital", based on a single question
		Neonatal health care utilization
		Categorical outcome ranging from: "No additional care" to "Admission in a hospital", based on a single question
	Maternal cigarette use	*Maternal cigarette use*
	Dichotomous outcome based on a single question	Dichotomous outcome based on a single question
	Maternal alcohol use	*Maternal alcohol use*
	Dichotomous outcome based on a single question	Dichotomous outcome based on a single question
	Maternal drugs use	*Maternal drugs use*
	Dichotomous outcome based on a single question	Dichotomous outcome based on a single question

Supplementary table 2 (table S2): Baseline characteristics for participants who were lost to-follow up by timing of follow-up (early and late postpartum period)

		Missing information participants						
		Early postpartum period				Late postpartum period		
		No (n=799)		Yes (n=780)		No(n=1,105)		Yes (n=474)	
Maternal age		31.27	(4.7)	31.87	(4.5)	31.21	(4.8)	32.38	(4.1)
Parity									
	Primiparous	411	51.4%	395	50.6%	548	49.6%	258	54.4%
	Multiparous	388	48.6%	385	49.4%	557	50.4%	216	45.6%
Cohabitation partners									
	Single	39	4.9%	12	1.5%	41	3.7%	10	2.1%
	Living together	760	95.1%	768	98.5%	1,064	96.3%	464	97.9%
Immigrant status									
	Non-immigrant	472	59.8%	591	76.4%	695	62.9%	368	77.6%
	First generation	138	17.5%	94	12.1%	191	17.3%	41	8.6%
	Second generation	179	22.7%	89	11.5%	210	19.0%	58	12.2%
	Missing	10	1.3%	6	0.8%	9	0.8%	7	1.5%
Health insurance									
	No	0	0.0%	2	0.3%	0	0.0%	2	0.4%
	Yes	799	100.0%	778	99.7%	1,105	100.0%	472	99.6%
Education									
	Lower	54	6.8%	39	5.0%	77	7.0%	16	3.4%
	Intermediate	533	66.7%	433	55.5%	705	63.8%	261	55.1%
	High	212	26.5%	308	39.5%	323	29.2%	197	41.6%
Household income (euro/month)									
	<1500	132	16.5%	58	7.4%	164	14.8%	26	5.5%
	1500-3000	317	39.7%	281	36.0%	433	39.2%	165	34.8%
	>3000	350	43.8%	441	56.5%	508	46.0%	283	59.7%
Paid job during pregnancy									
	No	211	26.4%	135	17.3%	288	26.1%	58	12.2%
	Yes	588	73.6%	645	82.7%	817	73.9%	416	87.8%
Neighbourhood deprivation									
	No	432	54.1%	455	58.3%	619	56.0%	268	56.5%
	Yes	367	45.9%	325	41.7%	486	44.0%	206	43.5%
Smoking									
	No	681	85.2%	683	87.6%	942	85.2%	422	89.0%
	Yes	118	14.8%	97	12.4%	163	14.8%	52	11.0%
Alcohol									
	No	656	82.1%	602	77.2%	884	80.0%	374	78.9%
	Yes	143	17.9%	178	22.8%	221	20.0%	100	21.1%
Drugs									
	No	783	98.0%	773	99.1%	1,084	98.1%	472	99.6%
	Yes	16	2.0%	7	0.9%	21	1.9%	2	0.4%

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Supplementary table 3 (table S3): Baseline characteristics, presented by cluster and by intervention allocation

| | Cluster 1 | | | | Cluster 2 | | | | Cluster 3 | | | | Cluster 4 | | | | Cluster 5 | | | |
| | Intervention | | Control | | Intervention | | Control | | Intervention | | Control | | Intervention | | Control | | Intervention | | Control | |
	N	%	N	%	N	%	N	%	N	%	N	%	N	%	N	%	N	%	N	%
Maternal age	31.2	5.5	31.0	3.7	30.2	5.3	30.4	5.0	32.6	4.2	32.8	3.6	31.5	4.7	31.8	4.9	32.0	4.0	31.5	4.2
Parity																				
Primiparous	36	38.7%	34	87.2%	110	54.2%	50	48.1%	107	49.8%	95	50.5%	108	52.7%	92	55.8%	85	52.1%	89	43.6%
Multiparous	57	61.3%	5	12.8%	93	45.8%	54	51.9%	108	50.2%	93	49.5%	97	47.3%	73	44.2%	78	47.9%	115	56.4%
Cohabitation partners																				
Single	4	4.3%	1	2.6%	9	4.4%	11	10.6%	3	1.4%	4	2.1%	2	1.0%	4	2.4%	2	1.2%	11	5.4%
Living together	89	95.7%	38	97.4%	194	95.6%	93	89.4%	212	98.6%	184	97.9%	203	99.0%	161	97.6%	161	98.8%	193	94.6%
Immigrant status																				
Non-immigrant	56	60.2%	30	78.9%	103	51.2%	29	28.2%	142	67.9%	132	70.6%	162	79.0%	107	64.8%	132	83.5%	170	83.3%
First generation	17	18.3%	3	7.9%	59	29.4%	21	20.4%	32	15.3%	29	15.5%	17	8.3%	25	15.2%	10	6.3%	19	9.3%
Second generation	20	21.5%	5	13.2%	39	19.4%	53	51.5%	35	16.7%	26	13.9%	26	12.7%	33	20.0%	16	10.1%	15	7.4%
Missing	0	0.0%	1	2.6%	2	1.0%	1	1.0%	6	2.8%	1	0.5%	0	0.0%	0	0.0%	5	3.1%	0	0.0%
Health insurance																				
No	0	0.0%	0	0.0%	1	0.5%	0	0.0%	0	0.0%	0	0.0%	0	0.0%	0	0.0%	0	0.0%	1	0.5%
Yes	93	100.0%	39	100.0%	202	99.5%	104	100.0%	215	100.0%	188	100.0%	205	100.0%	165	100.0%	163	100.0%	203	99.5%
Education																				
Lower	8	8.6%	2	5.1%	16	7.9%	9	8.7%	13	6.0%	7	3.7%	11	5.4%	17	10.3%	2	1.2%	8	3.9%
Intermediate	77	82.8%	31	79.5%	138	68.0%	81	77.9%	95	44.2%	75	39.9%	145	70.7%	115	69.7%	83	50.9%	126	61.8%
High	8	8.6%	6	15.4%	49	24.1%	14	13.5%	107	49.8%	106	56.4%	49	23.9%	33	20.0%	78	47.9%	70	34.3%
Household income (euro/month)																				
<1500	16	17.2%	1	2.6%	27	13.3%	34	32.7%	17	7.9%	9	4.8%	17	8.3%	22	13.3%	18	11.0%	29	14.2%
1500-3000	43	46.2%	18	46.2%	90	44.3%	47	45.2%	83	38.6%	62	33.0%	72	35.1%	61	37.0%	50	30.7%	72	35.3%
>3000	34	36.6%	20	51.3%	86	42.4%	23	22.1%	115	53.5%	117	62.2%	116	56.6%	82	49.7%	95	58.3%	103	50.5%
Paid job (pregnancy)																				
No	31	33.3%	6	15.4%	64	31.5%	37	35.6%	38	17.7%	26	13.8%	40	19.5%	42	25.5%	28	17.2%	34	16.7%
Yes	62	66.7%	33	84.6%	139	68.5%	67	64.4%	177	82.3%	162	86.2%	165	80.5%	123	74.5%	135	82.8%	170	83.3%

		n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%
Neighbourhood deprivation																					
	No	88	94.6%	39	100.0%	99	48.8%	44	42.3%	94	43.7%	68	36.2%	135	65.9%	76	46.1%	101	62.0%	143	70.1%
	Yes	5	5.4%	0	0.0%	104	51.2%	60	57.7%	121	56.3%	120	63.8%	70	34.1%	89	53.9%	62	38.0%	61	29.9%
Smoking																					
	No	76	81.7%	33	84.6%	167	82.3%	84	80.8%	196	91.2%	177	94.1%	180	87.8%	136	82.4%	143	87.7%	172	84.3%
	Yes	17	18.3%	6	15.4%	36	17.7%	20	19.2%	19	8.8%	11	5.9%	25	12.2%	29	17.6%	20	12.3%	32	15.7%
Alcohol																					
	No	77	82.8%	33	84.6%	170	83.7%	91	87.5%	163	75.8%	147	78.2%	170	82.9%	140	84.8%	113	69.3%	154	75.5%
	Yes	16	17.2%	6	15.4%	33	16.3%	13	12.5%	52	24.2%	41	21.8%	35	17.1%	25	15.2%	50	30.7%	50	24.5%
Drugs																					
	No	91	97.8%	39	100.0%	201	99.0%	98	94.2%	214	99.5%	187	99.5%	204	99.5%	162	98.2%	157	96.3%	203	99.5%
	Yes	2	2.2%	0	0.0%	2	1.0%	6	5.8%	1	0.5%	1	0.5%	1	0.5%	3	1.8%	6	3.7%	1	0.5%
Risk detected during pregnancy																					
	No	45	48.4%	24	61.5%	112	55.2%	51	49.0%	143	66.5%	123	65.4%	125	61.0%	89	53.9%	102	62.6%	137	67.2%
	Yes	48	51.6%	15	38.5%	91	44.8%	53	51.0%	72	33.5%	65	34.6%	80	39.0%	76	46.1%	61	37.4%	67	32.8%
Indicated hours of maternity care																					
	24-49 hours	57	61.3%	30	85.7%	156	80.3%	53	51.0%	180	87.4%	163	87.6%	168	87.0%	144	90.0%	131	81.9%	181	94.3%
	>49 hours	36	38.7%	5	14.3%	37	19.2%	51	49.0%	26	12.6%	23	12.4%	25	13.0%	16	10.0%	29	18.1%	11	5.7%
	Missing	0	0.0%	4	10.3%	10	4.9%	0	0.0%	9	4.2%	2	1.1%	12	5.9%	5	3.0%	3	1.8%	12	5.9%

8

Supplementary table 4 (table S4): Self-reported identified risk factors(s), by intervention allocation

	Intervention (n=879)		Control (n=700)	
	N	%	N	%
Risk detected during pregnancy				
No	527	60.0%	424	60.6%
Yes	352	40.0%	276	39.4%
Risk factors				
Low empowerment sum-score	52	15%	64	23%
Alcohol during pregnancy	186	53%	135	49%
Smoking during pregnancy	117	33%	98	36%
Drugs during pregnancy	12	3%	11	4%
Use of medication	3	1%	2	1%
Combined alcohol, cigarette, and drugs use during the preconception period	5	1%	5	2%
Expected low empowerment regarding the baby	96	27%	75	27%
Anxiety disorders / depression	96	27%	68	25%
Fear for childbirth	130	37%	93	34%
Chronic disease unknown to obstetrician	1	0%	0	0%
Health literacy	59	17%	56	20%
Financial problems	34	10%	35	13%
Housing problems	15	4%	14	5%
No health insurance	1	0%	1	0%
Physical or emotional abuse	1	0%	1	0%
Problems family members	4	1%	4	1%

Supporting Figures

Supplementary figure 1 (figure S1): The timeline cluster diagram
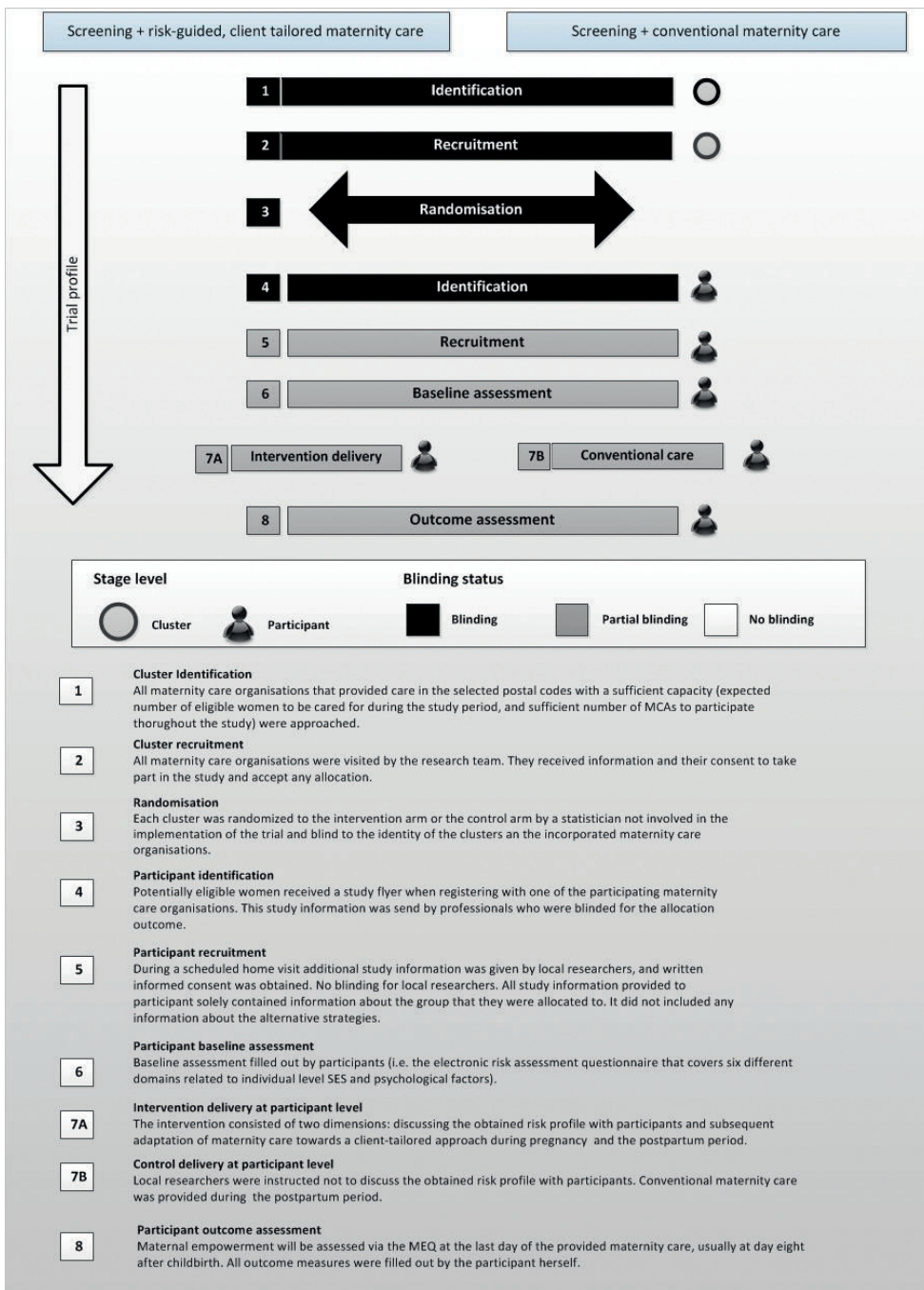
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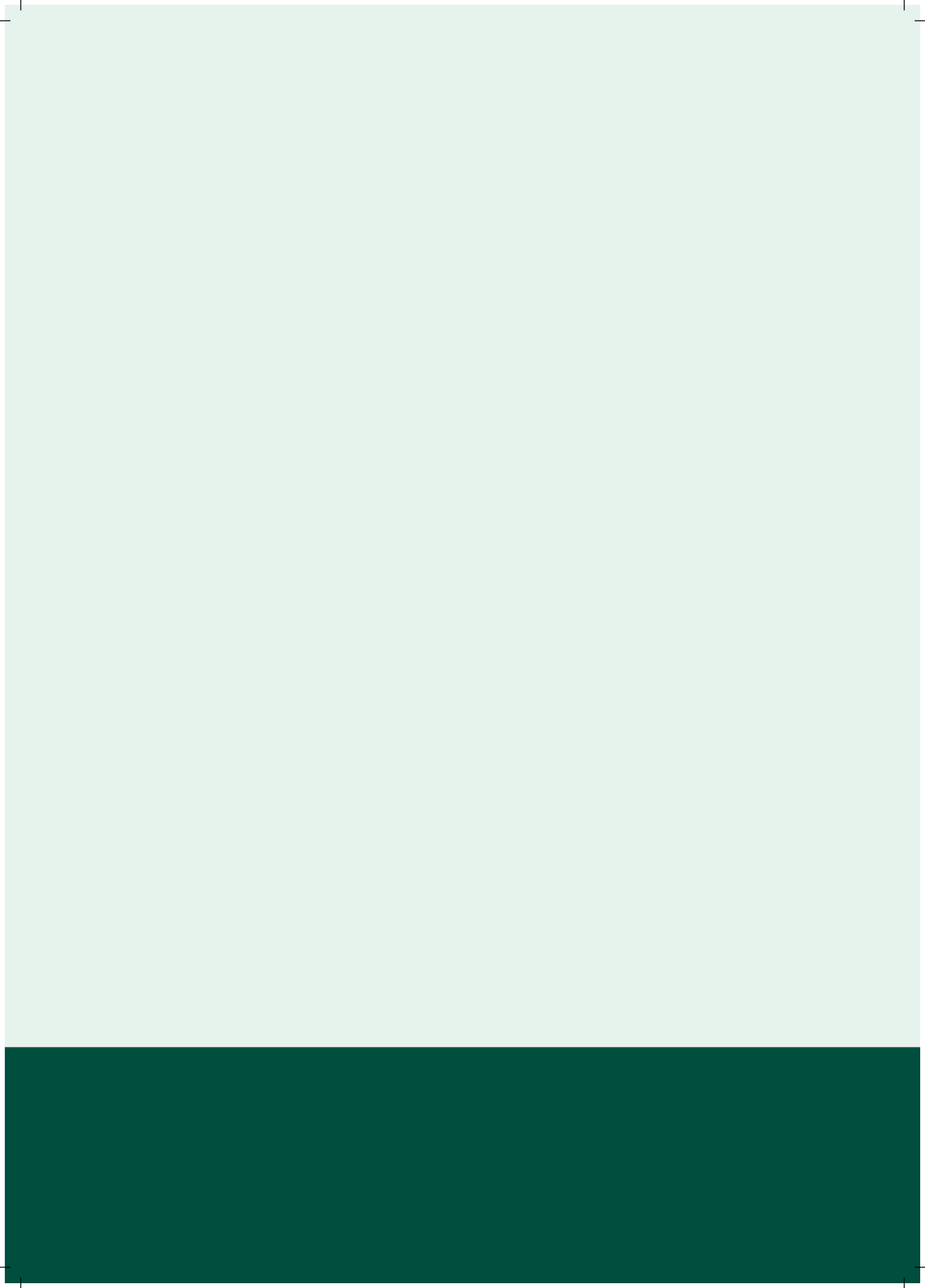
CHAPTER 9

General discussion

In this thesis preventive strategies during the preconception, antenatal, and postpartum period are described along with their effectiveness in reducing inequalities in perinatal health.

These strategies were implemented around the intersection of municipal social health and welfare provisions. It follows increased understanding that social and economic conditions profoundly impact perinatal health, and that the health of the population should be a matter of significant political and societal concern. Better knowledge of the social determinants of health will not only provide a better understanding of the causal pathways to negative health outcomes, but may also help the development of new preventive strategies and stimulate local and national changes in health policies. Therefore, in the following paragraphs the clinical implications of our findings, and future research directions will be discussed.

Inequalities in perinatal health in the Netherlands

Socioeconomic inequalities in perinatal health concern systematic variations in health status between different socioeconomic groups [1]. These variations in health status are socially and economically determined making them theoretically modifiable [2-6]. Striving to promote health equity includes increasing awareness for health disparities among professionals and effective policy and healthcare strategies [2 7]. Inequalities in maternal and child health also exist in the Netherlands as illustrated by the higher prevalence of poor perinatal health outcomes in more deprived areas [1 8-10]. These inequalities could be partially attributed to the births occurring in women from a lower socioeconomic status (**chapter 5**).

In addition, women with a lower socioeconomic position tend to make less use of routine or preventive healthcare, further increasing their already augmented risk [11 12]. We confirmed this consistent inequity in primary care uptake in the Netherlands by showing that indicators of low socioeconomic status, at the individual level, the household level, and the area level, were associated with a lack in uptake of postpartum care (**chapter 6**). For postpartum care uptake specifically, additional determinants, besides those related to a person's socioeconomic status, play a role in the uptake of care. For example, immigrant populations were less likely to receive maternity care, even when accounting for socioeconomic status (**chapter 6**).

Preventive strategies throughout reproductive healthcare

We have provided a brief summary of three large research programmes initiated by the Erasmus MC in the last decade. All three research programmes were initiated in collaboration with the Ministry of Health, Welfare and Sports. For the implementation of the programmes collaboration was sought with the board of all participating municipalities and other healthcare professionals, and stakeholders.

The local 'Ready for a Baby' programme and the two national 'Healthy Pregnancy 4 All' programmes subsequently tested the effectiveness of implementing a continuum for risk selection and tailored care during the preconception, the prenatal, the postpartum, and the interconception period (**chapter 2,3 and 5**). The programmes focussed on achieving a greater awareness of health inequalities and their drivers by educating (healthcare) professionals, and by creating and evaluating interventions that could be implemented in routine care. The investments made with these programmes have helped shape the field of reproductive health in the Netherlands to a discipline in which social obstetrics now plays an important role. Largely inspired by these programmes, the national programme "Kansrijke Start" was introduced in September 2018. This action programme strives to provide more children with a promising start. The action programme is organised through local coalitions ,supported by a specialised team and managed by a steering group. It is currently being rolled out across 127 of 355 municipalities in the Netherlands. Local coalitions for this national programme are formed by a board member of a local municipality, a representative from a health care insurance company, several medical doctors (a general practitioner and a gynaecologist) , a midwife, a health care professional from child health care services and from a maternity care company, and other relevant local partners.

The *'Ready for a Baby'* programme, implemented in Rotterdam, provided the foundations for the field of social obstetrics by incrementally implementing a complex intervention consisting of various preventive strategies. The Ready for a Baby programme had three components: 1. health promotion in preconception care, 2. improved risk selection and risk-guided care, and 3. establishment of a primary care birth centre in the Erasmus MC [13]. This programme encouraged professionals from different echelons to work together and jointly shape new health policies. The difference-in-difference analysis used to evaluate this intervention could not demonstrate that the programme significantly influenced trends in perinatal mortality, preterm birth, or small-for-gestational age births in the post-intervention years in the intervention group (**chapter 2**). This lack of demonstrable intervention effect may be partly attributed to the gradually implementation of the different components of the intervention during the study period and the variety in coverage. All pregnant women in the targeted urban neighbourhoods were considered to be exposed to the intervention, whether or not these women were actually reached by activities within the complex intervention. This might have attenuated observed associations, when a substantial number of women would not have been included in components of the programme.

The local 'Ready for a Baby' programme inspired the ministry of Health, Welfare and Sports to sponsor the national *'Healthy Pregnancy 4 All-1' (***chapter 3***)*. This programme evaluated strategies to improve pregnancy outcomes, in particular among deprived populations. It consisted of, among other interventions, implementation of a tool for risk assessment during pregnancy that could be used in all tiers of the Dutch obstetric care system [14][15].

This risk assessment instrument, called the 'Rotterdam Reproductive Risk Reduction' (R4U) scorecard, serves as an important extension to the currently used, mostly medically orientated, risk assessment by including non-medical risk factors (**chapter 4**). Non-medical risk factors for adverse pregnancy outcomes include lifestyle factors, psychosocial factors, and other factors related to a person's socioeconomic status.

The implementation of the intervention (i.e. the R4U-scorecard together with risk-specific care pathways, and multidisciplinary consultations) promoted uniformity in risk surveillance. The intervention further increased care professionals' awareness during pregnancy of the two most frequently observed neonatal morbidities at birth (i.e. babies born preterm and small for gestational age) (**chapter 3**).

After completing the first Healthy Pregnancy 4 All programme, the prediction model underlying this scorecard was validated. We performed a commonly used step in prediction research and updated the model [16] [17]. A reconsideration of the additional effect of all predictors incorporated in the model was performed resulting in an updated version of the scorecard (**chapter 4**). The updated version increased sensitivity to predict the incidence of adverse pregnancy outcomes by 11%.

The implementation of additional non-medical risk assessment and preventive strategies into general practices was shown to be feasible. Extended screening for pregnant women at risk, together with improved collaboration between the curative and public health sector in patient-tailored care, was considered a valuable step in establishing equity-oriented strategies throughout reproductive health care.

The *'Healthy Pregnancy 4 All-2'* programme extended the screening for women at risk along with consecutive tailored care from pregnancy towards the postpartum period and the early years of life (**chapter 5 & 7**) as illustrated in figure 1.

The Healthy Pregnancy 4 all -2 programme combined three sub studies aiming to implement integrated, risk guided care, beyond the separate domains of antenatal care, postpartum care and Preventive Child Health Care (PCHC). The vast majority of parents with young children attend routine visits to PCHC services. This provides an ideal opportunity to implement personalised, risk-based care from PCHC professionals to promote interconception care. The cluster randomised controlled trial embedded in this programme showed that maternal empowerment could be increased in the postpartum period through the extension of tailored care from pregnancy onwards (**chapter 8**). Furthermore, the R4U-scorecard that was used in the Ready For a Baby programme and later in the first Healthy Pregnancy 4 All programme (**chapter 2-4**) was adapted to enable its use by PCHC professionals (**chapter 5**) [18].

Together, all three programmes provided tools for comprehensive risk screening and for risk-guided care. The implementation of these tools enabled awareness of healthcare professionals to be increased regarding the importance of initiating personalised care for every woman as early as possible in order to prevent risks from becoming manifest health problems (**chapter 3 & 7**).

Reflection on the obtained results

The interventions during the preconception period and during pregnancy showed improved detection of the two most frequently observed adverse outcomes during pregnancy, intra-uterine growth restriction and imminent preterm birth (**chapter 2 and 3**). In addition, outreach strategies amongst the general population were demonstrated to promote the uptake of preconception care consultations [19]. The expansion of risk surveillance and tailored care towards the postpartum period proofed to be feasible and effective in improving maternal empowerment in the first week after childbirth (**chapter 8**). The collaboration with different maternity care organisations to implement this large-scale randomised trial marked the first steps for the Dutch postpartum care to become involved in the field of medical research.

The interventions described in **chapter 2 and 3** did not, however, have a demonstrable effect on the predefined primary health outcomes. This may be related to the type of outcome itself, the timing of assessment to show effects, or to both.

Preterm birth, defined as delivery prior to 37 completed weeks of gestation, was defined as an important indicator of effectiveness for both programmes as it is the leading cause of perinatal mortality and long-term morbidity worldwide [20-23]. Preterm birth may result from different disorders, implicating maternal and/or fetal disease and others of which the cause is unknown [21,22]. Moreover, a substantial proportion of preterm deliveries is iatrogenic (i.e. labour induction or caesarean delivery for maternal or fetal indications) whilst others occur spontaneously [21,22]. These complex and possibly inter-related causal pathways lead to the assumption that, using currently available preventive measures, 95% of all preterm births may not be preventable [24]. Considering this, the choice for preterm birth as a primary outcome measure for the presented interventions, may in retrospect have been overly optimistic. As an alternative, patient reported outcome measures may be considered to illustrate effectiveness of these preventive interventions. The cluster randomised controlled trial in **chapter 8** showed effectiveness by assessing postpartum maternal empowerment, providing an example of a patient reported outcome measure. Besides these considerations on defining outcome measures, the timing of assessment should be taken into account. Reducing inequalities in health outcomes by increasing awareness and by reallocation of existing healthcare resources, is a challenging goal and evidence of impact may take years to emerge.

The majority of preventive strategies presented in this thesis were implemented at the level of the healthcare professional instead of that of the individual participants. As outlined in **chapter 2, 3, and 7**, healthcare professionals were trained extensively in all three research programmes to adhere to different aspects of the often complex interventions. They were made aware of the potential they have to initiate risk-specific interventions. The effect that these training sessions for professionals had - together with the implementation of the intervention into routine care - should be considered the backbone of the intervention, and the effects on the individual participant as a derivative. Primary outcome measures could then shift towards process and implementation measures with the underlying assumption that a more equipped healthcare professional ultimately leads to improved healthcare, and hopefully improved individual health outcomes after the initial study period. Effectiveness of these interventions on important health outcomes could then be addressed by designing a natural experiment with a pre-intervention and post-intervention measurement overtime. Alternatively different groups of individuals could be exposed in the same time interval.

Methodological considerations

The studies in this thesis comprise different data sources and study designs. Two cluster randomised controlled trials are reported (**chapter 3 and 8**). Both interventions could be labelled as pragmatic and complex. In contrast to explanatory trials, which are performed under ideal and controlled conditions, pragmatic trials measure the effect of an intervention in real clinical practice. The main benefit of pragmatic trials is that the produced results can be generalised and applied in routine practice settings.

Cluster randomised controlled trials are commonly used to evaluate pragmatic interventions; this design has, however, certain challenges for researchers [25-27]. The similarity among participants within pre-existing clusters reduces the variability of responses in a clustered sample, which reduces the power to detect an intervention effect [28]. To account for this greater similarity the sample size is inflated, resulting in an increase in the required sample size. In both cluster randomised controlled trials, the required sample size was not achieved within the predefined timeframe of the trial. The reduced sample size, although including respectively 4302 and 780 participants, decreased the probability to detect true effects of the intervention. Cluster randomised trials have a recognised risk of introducing selection bias [25-27 29]. A frequently observed risk of bias lies in inadequate concealment of the treatment allocation through insufficient blinding of professionals who identify or recruit eligible participants [26 27]. Selection bias appeared to be present in both randomised trials reported on in this thesis. In the trial embedded in the Healthy Pregnancy 4 All-1 programme (**chapter 3**), this bias likely led to an inclusion of participants with a fairly favourable risk profile compared to the general Dutch population. This contrasted with the aim of the trial to primarily reach out to high-risk populations. In the second trial, embedded in the second Healthy Pregnancy 4 All-2 programme (**chapter 8**), a similar bias was found. Participants

more often had a higher educational level, a higher net income, and were more often non-immigrants as compared to the general Dutch population. Because all preventive strategies reported in this thesis were aimed at participants who are among the more socially disadvantaged, this bias may have influenced the possible effectiveness of the interventions. All interventions were designed to screen for and reduce the impact of risk factors, when fewer risks are present the effectiveness of the preventive intervention might decrease. To reduce the impact of the methodological challenges presented above another study design could be considered. Alternatives to a randomised design are studies with a non-random assignment of treatment, such as a quasi-experiment [30][31]. Quasi-experimental studies are a potentially valuable and valid tool to evaluate the impact of population-level policies on health outcomes or health inequalities [31]. These experiments can be conducted when a straightforward assignment to either treatment or control is lacking. For example, when a new or alternative health intervention is assigned to different geographical locations [32]. We applied a quasi-experimental study design in the evaluation of the Ready for a Baby programme (**chapter 2**).

In **chapter 3, 4, and 6** multiple imputation techniques were applied to account for missing data under the missing (completely) at random assumption. Missing data almost invariably occurs in medical research. Missing data can reduce the power and efficiency of a study but may also lead to systematic and unpredictable bias that may influence the obtained results [33-35]. Multiple studies have shown that application of a multiple imputation technique is superior to complete case analysis and simple imputation techniques such as 'overall mean imputation' and 'last observation carried forward' [34-38]. In this thesis sensitivity analyses were performed to formally check the missing at random assumption. The importance of formally analysing the pattern underlying missing data is illustrated in **chapter 8**. The substantial loss to follow-up in this trial was likely to have been selective, leading to missingness that was not at random. In this case there is no universal method of handling the missing data properly [34]. In every situation, prevention is the best way to handle missing data, so more effort needs to be put into avoiding missing data at the design and conduct stage of the trial.

Future perspectives and recommendations

Many perinatal health disparities are preventable, but not inevitable. The inequity in postpartum care provision, presented in **chapter 6**, illustrates inequity in care provision and may inform social policies directed toward reducing social inequalities in health. The results presented in that chapter suggest that postpartum care may help reduce subsequent healthcare expenditure, providing a possible incentive for stakeholders, such as healthcare insurers, to invest in increasing the uptake of care among those with a lower socioeconomic status who currently, as we have shown, receive less postpartum care. Choices in resource allocation are complex, difficult, and morally problematic. Further research is needed to evaluate if a dose-response effect is present in postpartum care, and to evaluate the current reasoning for postpartum care uptake below the recommended minimum.

Finding an appropriate balance in universal healthcare coverage on the one hand and allocating healthcare to those most in need on the other in order to create an equitable distribution, is challenging and is fraught with controversy. However, the current way of providing preconception, antenatal, and postpartum care achieves less equity in health than it may be capable of doing. More could be achieved through commitments to explicit resource allocation and priority setting to reduce unnecessary care provision resulting in the over-payment in some sectors at the dispense of others.

Collaboration between professionals from the medical sector, the social sector, the public health sector and local governments needs further exploration to increase its potential in tackling health inequalities. In Dutch policy programs the role of municipal governments is stressed in facilitating these cross-sectoral collaborations. The '*Healthy Pregnancy 4 All-3*' program that started in 2018 and will run through 2020, aims to identify and develop ways to institutionally embed social obstetrics into policy programs and actions. The '*Healthy Pregnancy 4 All*' programmes helped form a basis for the formation of a national program called '*Promising Start*'. Promising start runs from 2018 and is initiated and financed by the Dutch government to improve early life health outcomes. Participating municipalities receive financial support to enable implementation of existing approaches which are aimed at tackling health inequalities before, during and after pregnancy.

As part of the '*Healthy Pregnancy 4 All*' programmes, the work presented in this thesis has helped shape current practices in reproductive health care towards a multidisciplinary, preventive way of thinking. Several limitations regarding the design, the outcomes, and the analysis of these studies have been discussed. It is important to also consider the change in perception of involved health care professionals after the implementation of our interventions. Health care professionals are the backbone of our health care system, and through them changes in care will be possible and progress can be made.

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CHAPTER 10

Summary

Samenvatting

SUMMARY

The overarching aim of this thesis was to investigate the effectiveness of preventive strategies, implemented during different phases in reproductive healthcare, to reduce adverse perinatal health outcomes and low empowerment particularly among women with a low socioeconomic status and their offspring.

In part one the effectiveness of different strategies to improve neonatal health outcomes was described along with a validation study of the R4U-scorecard.

The results of the 'Ready for a Baby' programme that ran from 2009 to 2012 in Rotterdam are presented in **chapter 2**. In this study, the influence of an urban perinatal health programme in Rotterdam on perinatal health outcomes was evaluated by a difference in difference approach, an analytical technique for natural experiment evaluation in an observational setting. The difference in difference analysis could not demonstrate that the introduction of the programme influenced trends in perinatal mortality, preterm birth, or small-for-gestational age birth in the post-intervention years in the intervention group.

In **chapter 3** the results of the national C-RCT embedded in the 'Healthy Pregnancy 4 All-1' programme are described. The implementation of an extended risk assessment during pregnancy, and subsequent institution of care pathways and multidisciplinary consultations, showed to be feasible. The traditional risk assessment during pregnancy, mainly focussing on apparent medical risk factors, shifted towards the first trimester and created a larger window of opportunity for prevention. However, the intervention did not decrease the incidence of adverse neonatal health outcomes at birth.

Chapter 4 consists of a comprehensive evaluation of the 'Rotterdam Reproductive Risk Reduction' (R4U) scorecard, used in the 'Healthy Pregnancy 4 All-1' programme. An updated R4U-scorecard was presented that can be used in the first trimester of pregnancy to estimate the risk of adverse neonatal health outcomes. By updating the model we increased the sensitivity of the scorecard by 11%. This improved classification of high-risk pregnancies is especially important considering the feasible function of the R4U-scorecard as a diagnostic tool guiding clinicians into taking appropriate preventive follow-up actions.

In part two the current degree of inequalities in care provision and child health outcomes were reported. Furthermore, the effectiveness of extending the application of preventive strategies from pregnancy towards the postpartum period and early childhood was evaluated.

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Chapter 5 presents the protocol for the "Healthy Pregnancy 4 All-2" programme. The results presented in this chapter underlie the considerable variation between geographical areas within the Netherlands for perinatal mortality and morbidity, and the prevalence of children living in deprived neighbourhoods and children living in families on welfare. The results of this study also suggest associations between adverse perinatal health and socio-economic disadvantage of children, hereby reinforcing the importance of extending the continuum for risk selection and tailored care pathways from preconception and antenatal care towards postpartum care, early childhood care, and interconception care.

In **chapter 6** the existing inequity in postpartum care provision in the Netherlands is presented using a national population-based retrospective cohort study with routinely collected healthcare data. The results illustrated that women of low socioeconomic status are much less likely to receive postpartum care, and that low uptake of postpartum care was associated with higher health care expenditure after childbirth. Furthermore, the results of this study showed that substantial inequities in postpartum care provision exist according to immigration status.

The protocol for a pragmatic C-RCT embedded in the 'Healthy Pregnancy 4 All-2' programme is presented in **chapter 7**. Six urban municipalities and twelve independent maternity care organisations participated in this study that evaluates the effectiveness of a complex intervention to promote maternal empowerment in the postpartum period. The intervention under study consisted of a structured risk assessment during pregnancy, focussing on identifying non-medical risk factors for adverse maternal and neonatal health outcomes. Consecutive risk-guided tailored care was instituted throughout pregnancy and the postpartum period.

Chapter 8 presents the results of the study described in chapter 7. The implementation of the structured risk assessment during pregnancy followed by client-tailored maternity care showed to reduce the incidence of low maternal empowerment during the postpartum period. This large-scale randomised trial was the first to amend routine maternity care with tailored care and to evaluate its effectiveness. Moving forward to early identification of women at risk along with tailored, risk-reducing strategies that decrease the odds of having a low empowerment score might minimise early adversity and existing inequalities in postpartum care.

SAMENVATTING

Het overkoepelende doel van dit proefschrift was het onderzoeken van de effectiviteit van preventieve strategieën, geïmplementeerd tijdens verschillende fases in de reproductieve gezondheidszorg, om ongunstige perinatale gezondheidsuitkomsten en lage zelfredzaamheid te verminderen, vooral bij vrouwen met een lage socio-economische status en hun nakomelingen.

In deel één werd de effectiviteit van verschillende strategieën voor het verbeteren van neonatale gezondheidsuitkomsten beschreven, samen met een validatieonderzoek van de R4U-scorecard.

De resultaten van het 'Klaar Voor Een Kind' programma, dat van 2009 tot 2012 in Rotterdam werd uitgevoerd, staan beschreven in **hoofdstuk 2**. In deze studie werd de invloed van een stedelijk perinataal gezondheidsprogramma in Rotterdam op perinatale gezondheidsresultaten geëvalueerd door middel van een 'Difference-in-Difference' analyse. De uitkomst van deze analyse kon niet aantonen dat de introductie van het programma de trends in perinatale sterfte, vroeggeboorte of geboorte in de kleintjes in de post-interventiejaren beïnvloedde.

In **hoofdstuk 3** werden de resultaten beschreven van de een nationale cluster gerandomiseerde studie ingebed in het 'Healthy Pregnancy 4 All-1' programma. In deze studie bleek het implementeren van een uitgebreide risicoscreening tijdens de zwangerschap en daaropvolgende risicogerichte zorgpaden en multidisciplinaire consulten haalbaar. De traditionele risicoscreening tijdens de zwangerschap, voornamelijk gericht op bestaande, medische risicofactoren, verschoof naar het eerste trimester en creëerde hiermee meer ruimte voor preventie. De samengestelde interventie had geen effect op de primaire uitkomstmaat aangezien het de incidentie van ongunstige neonatale gezondheidsuitkomsten bij de geboorte niet verlaagde.

Hoofdstuk 4 bestaat uit een uitgebreide evaluatie van de 'Rotterdam Reproductive Risk Reduction' (R4U) scorecard, die gebruikt werd in de studie beschreven in hoofdstuk 3. Er werd een bijgewerkte R4U-scorecard gepresenteerd die in het eerste trimester van de zwangerschap kan worden gebruikt om het risico op ongunstige neonatale gezondheidsresultaten te schatten. Door het model bij te werken verhoogden we de sensitiviteit van de screening met 11%. Deze verbeterde classificatie van risicovolle zwangerschappen is vooral belangrijk gezien de haalbare functie van de R4U-scorecard als diagnostisch hulpmiddel dat clinici begeleidt bij het nemen van preventieve vervolgacties.
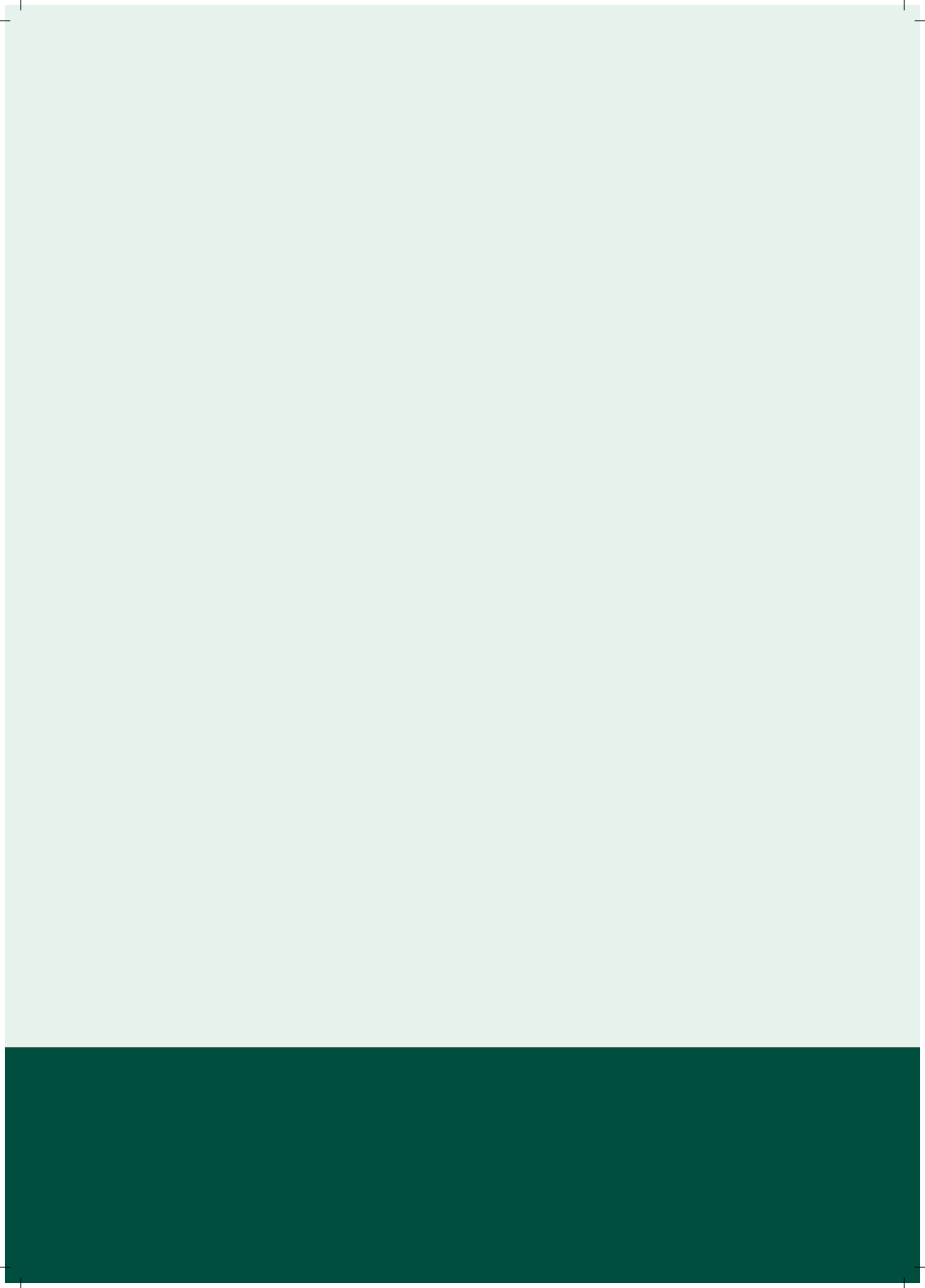
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In deel twee werden de huidige ongelijkheden in zorgvoorziening gerapporteerd alsmede de ongelijkheden in gezondheidsuitkomsten voor kinderen. Daarnaast werd de effectiviteit geëvalueerd van het uitbreiden van de toepassing van preventieve strategieën vanuit de zwangerschap naar de postpartumperiode en vroege kinderjaren.

Hoofdstuk 5 presenteerde het protocol voor het programma "Healthy Pregnancy 4 All-2". De resultaten in dit hoofdstuk bevestigde de aanzienlijke verschillen tussen geografische gebieden in Nederland met betrekking tot perinatale sterfte en morbiditeit. De resultaten van dit onderzoek suggereren ook associaties tussen ongunstige perinatale gezondheid en sociaaleconomische achterstand van kinderen, en versterken hiermee het belang van uitbreiding van het continuüm voor risicoselectie en op maat gemaakte zorgpaden van preconceptie en prenatale zorg tot postpartumzorg, kinderopvang en interconceptie zorg.

In **hoofdstuk 6** werd de bestaande ongelijkheid in de Nederlandse kraamzorg gepresenteerd met behulp van een nationale, populatie brede, retrospectieve cohortstudie bestaande uit routinematig verzamelde gezondheidsgegevens van het CBS. De resultaten illustreren dat vrouwen met een lage socio-economische status veel minder gebruik maken van kraamzorg en dat een lage opname van kraamzorg geassocieerd is met hogere zorgkosten na de bevalling. Bovendien hebben de resultaten van deze studie aangetoond dat er aanzienlijke verschillen bestaan in kraamzorg afname naar een vrouw haar migratiestatus.

Het protocol voor de pragmatische C-RCT ingebed in het programma 'Healthy Pregnancy 4 All-2' werd gepresenteerd in **hoofdstuk 7**. Zes stedelijke gemeenten en twaalf onafhankelijke kraamzorgorganisaties namen deel aan dit onderzoek, dat de effectiviteit evalueerde van een complexe interventie om een moeder haar zelfredzaamheid te bevorderen. De geëvalueerde interventie bestond uit een gestructureerde risicoscreening tijdens de zwangerschap, met de nadruk op het identificeren van niet-medische risicofactoren voor ongunstige gezondheidsuitkomsten voor moeders en pasgeborenen. Daarop volgens werd risico gestuurde, op maat gemaakte zorg ingesteld tijdens de zwangerschap en de periode na de bevalling teneinde te voorkomen dat risico's manifeste problemen werden.

In **Hoofdstuk 8** werden de resultaten van de studie uit hoofdstuk 7 beschreven. De implementatie van de gestructureerde risicoscreening tijdens de zwangerschap, gevolgd door op de klant toegesneden kraamzorg, toonde aan dat de incidentie van een lage zelfredzaamheid gedurende de kraamperiode verminderde. Deze grootschalige gerandomiseerde studie was de eerste om routine kraamzorg aan te passen met op maat gemaakte zorg en om de effectiviteit ervan te evalueren. Vooruitgang naar vroege identificatie van risico's, samen met op maat gemaakte risico verminderende strategieën, heeft de potentie om vroege tegenslagen en bestaande ongelijkheden in kraamzorg te verminderen.
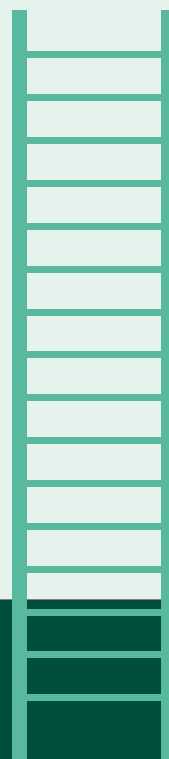
CHAPTER 11

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PHD PORTFOLIO

Erasmus MC Department	Obstetrics & Gynaecology
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PhD period	May 2014 - August 2018
Promotor(s)	Prof. dr. E.A.P. Steegers
Co-promotor	Dr. J.V. Been

1. PhD training	Year	Workload (ECTS)
General and specific courses		
BROK (Basiscursus Regelgeving Klinisch Onderzoek)	2014	1.0
Center for Patient-Oriented research (CPO) course, Erasmus MC	2014	0.2
Integrity in Science, Erasmus MC	2015	0.3
Biomedical English Writing and Communication, Erasmus MC	2015-2016	3.0
Master's degree Health Sciences – specialization Epidemiology, NIHES	2015-2017	70
International conferences		
10th World Congress Developmental Origins of Health and Disease (DOHaD), Rotterdam, the Netherlands: *oral presentation*	2017	1
10th European Public Health Conference, Stockholm, Sweden: *workshop presentation*	2017	1
65th Annual Scientific Meeting of the Society for Reproductive Investigation (SRI), San Diego, USA: o*ral presentation*	2018	1
National conferences		
Healthy Pregnancy 4 All symposium, The Hague	2014	0.2
3rd Symposium Urban Perinatal Health, Rotterdam	2015	0.2
4th Symposium Urban Perinatal Health, Rotterdam - *oral presentation*	2017	0.2
2nd "Academische Werkplaats Kraamzorg in Geboortezorg" najaarscongres, Utrecht – *oral presentation*	2017	0.2
1st "Geboortezorg Plus" congress, Utrecht – *oral presentation*	2018	0.2
Seminars, workshops and research meetings		
Workshop on Work-related risks and pregnancy, RIVM, Utrecht	2014	0.1
Expert meeting on preconception care, zonMW, The Hague	2014	0.1
Workshop media contact for researchers, Erasmus MC	2015	0.1
Erasmus MC PhD day	2015	0.2
Weekly and biweekly obstetric research meetings of the Department of Obstetrics and Gynaecology, Erasmus MC	2014-2018	5.0
Three-monthly research meetings Rotterdam Gynaecologists Teaching Hospitals (RGOC)	2015-2018	0.5
Annual RGOC award meeting: 'Wladimiroff symposium'	2015-2018	0.3
Reports and other writing		
Contributed to writing of the report for the Dutch Ministry of Health on Healthy Pregnancy 4 All		
Contributed to writing of the report for the Dutch Ministry of Health on Healthy Pregnancy 4 All-2		

2. Teaching	Year	Workload (ECTS)
Lecturing Lecture on antenatal risk surveillance for master students - Physician Assistants, Hogeschool Rotterdam	2015-2017	1.5
Tutoring / training Training maternity care professional on risk surveillance and tailored care (within the Healthy Pregnancy 4 All program) – 650 maternity care assistants and 70 maternity care professionals for a 3 hour training	2014-2016	10.0
Supervising Master's theses Supervising master thesis of Joske Moscou, medical student, Erasmus MC. Title: *'Review and Renewal of the R4U in Search of Improved Antenatal Risk Screening'.*	2015	2.0
Supervising master thesis of Jacqueline Lu, medical student, Erasmus MC. Title: '*A comparison of the maternal empowerment during pregnancy and in the postpartum period'.*	2017	2.0
Partly supervising master thesis of Leonie Daalderop, medical student, Maastricht University. Title: *'Evaluating Antenatal Risk Surveillance: Update of the Rotterdam Reproductive Risk Reduction Scorecard'.*	2018	1.0
3. Personal grants 65th Annual Meeting Society for Reproductive Investigation (SRI) – *oral presentation* Juriy Waldimiroff research day – *oral presentation*		

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ABOUT THE AUTHOR

Jacqueline Lagendijk was born on November 2nd, 1986 in Rotterdam, the Netherlands. As one of an identical twin, sister Mirelle Lagendijk, she grew up in Barendrecht where she completed both elementary school and high school. During medical school, Jacqueline worked in different medical student-teams within the Erasmus Medical Center, Rotterdam, the Netherlands. Following the completion of her regular internships, her interest in obstetrics and gynaecology originated which resulted in a possibility to work as a resident at the Amphia hospital, in Breda, the Netherlands (dr. M.G.K. Dijksterhuis). With a lot of enthusiasm, this period was followed by a period of 10 months in which Jacqueline worked as a resident in the Erasmus MC, in Rotterdam, the Netherlands (dr. M.J. ten Kate – Booij). Directly after she started working at the Erasmus MC Sophia Children's hospital as a fulltime PhD-candidate from June 2014 until August 2018 (dr. J.V. Been, prof. dr. E.A.P. Steegers). During her PhD traineeship, she finished her master's degree Health Sciences – specialization Epidemiology in August 2017. Jacqueline started her obstetrics and gynaecology residency training per November 2018 in the Amphia hospital, in Breda, the Netherlands (dr. M.G.K. Dijksterhuis, Dr. D.J. Hendriks).

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