TITLE: Association between neonatal homecare for preterm infants and incidence of postpartum depression in mothers.

INTRODUCTION

Preterm birth is a major risk factor for maternal postpartum depression.[1] Maternal postpartum depression has consequences for mothers and infants as it negatively affects the mothers' psychological health, quality of life and interactions with their infant and partner.[2] The infants seems to have more physical health concerns, decreased cognitive development and higher degrees of emotional disorders.[2]

Annually ~ 15 million infants are born prematurely, defined as birth prior to 37 weeks of gestation.[3] Preterm infants require treatment in the Neonatal Intensive Care Unit (NICU) due to increased morbidity[4] and mortality.[5] They are highly dependent on treatment from specialists, but they benefit from their parent's presence.[6] The duration of NICU admission varies from days to months depending on gestational age and the infant's complications.[7] Prolonged hospitalization of preterm infants may cause parental stress, which is expressed through anxiety and depression.[8,9]

Parents experience stress caused by uncertainty regarding the prognosis and an unfamiliar and intimidating NICU environment[10] and mothers strive to conduct normal parenthood.[11] The mothers battle feelings of guilt of not caring independently for their infant.[12] Further, the mothers have to navigate between expectations from clinicians[11] and doubts of their own maternal competences.[12]

Neonatal homecare was developed by NICU to optimize conditions for the families during the last weeks of the admission and is a well-established and safe discharge program for families with clinically stable infants. Neonatal homecare implies that parents manage the care and tube feeding parallel to breastfeeding or bottle establishment in the home supported by nurses from the NICU.[7,13] Close contact between the NICU and the parents is essential to monitor infant growth,

breastfeeding status, tube weaning and family well-being. Neonatal homecare facilitates family cen-tered care while it supports the families during transition from the NICU to home.[14,15]

Previous research had found that neonatal homecare increases breastfeeding rates, parent self-esteem and shortens hospitalization at NICU.[15,16] Low self-esteem and long hospitalization at NICU are associated with depression episodes[17], but the relationship between neonatal homecare and the incidence of postpartum depression is unknown. We aimed to investigate whether the implementa-tion of neonatal homecare was associated with a change of the incidence of postpartum depression among mothers of preterm infants.

METHODS

Study population

We assessed nationwide Danish population registers[18], including Medical Birth Register, Psychiat-ric Central Research Register[19], Danish National Prescription Registry[20], National Patient Register, and Statistics Denmark. Our population included all Danish mothers giving birth prematurely be-tween 1994 and 2017, whose infants were live born and with at least one night spent in the NICU.

Assessment of postpartum depression

The outcome of postpartum depression was established within Psychiatric Central Research Regis-ter as diagnostic codes F32, F33, F34.1, F38.8, F39, and F43 (ICD-10). Supplemented with infor-mation on redeemed antidepressant medication as identified in Danish National Prescription Regis-try as ATC-codes N06A.[20] The mothers were classified with postpartum depression if they had been admitted to a psychiatric hospital with a diagnosis of postpartum depression or redeemed a pre-scribed antidepressant medication within the first six months after giving birth. We defined the postpartum period as 0-6 months after giving birth, which is a period of increased vulnerability.[21] We conducted sensitivity analyses using both a more narrow period of 0-3 months (suggested as a

more homogenous phenotype) and 0-12 months (clinically used to identify the postpartum period).[22]

Study design

The mothers were followed from the day of delivery until the first day of following events: postpartum depression, death, emigration from Denmark or the infant's six months birthday in the main analyses. In the sensitivity analyses the follow-up times were the infant's three- or twelve-months birthday. We obtained data concerning the implementation dates of neonatal homecare by sending all Danish NICUs an online survey. The NICUs which lacked answering the survey were called by the first author. Answers from all NICUs were conducted. The implementation of neonatal homecare varied among the NICUs (1997-2015) and two out of 19 NICUs did not provide neonatal homecare. Sometimes mothers and infants were transferred from one NICU to another due to the infants' conditions. Therefor in our analyses the mothers were connected to the NICU which their infants were finally discharge from.

Statistical analysis

We performed an interrupted time series analysis to determine the development of postpartum depression, and whether the implementation of neonatal homecare affected the development. An interrupted time series analysis is a statistical procedure to estimate the impact of natural interventions, e.g. when an intervention lacks investigation in the context of a randomized clinical trial. The association between postpartum depression and neonatal homecare was analyzed with Poisson regression with robust standard errors and the natural logarithm of observation time included as offset. Because of the different implementation years throughout Denmark, we used time before or after implementation as the underlying time scale, rather than calendar time.

Results are presented with incidence rate ratio (IRR) and 95% confidence intervals (95% CI). We conducted sensitivity analyses to investigate if any of the following variables were confounders affecting the results: mother's age, length of stay at NICU, parity, gestational age and depression during pregnancy. We based P values on likelihood ratio tests (P<0.05 was considered statistically significant), and 95% confidence intervals were calculated by Wald test. This study was approved by the Danish Data Protection Agency. All analyses were conducted in STATA/MP 15.1.

RESULTS

Population characteristics

A total of 49,315 mothers fulfilled the inclusion criteria; however, 2,859 mothers were discharged from a NICU without neonatal homecare and therefor excluded. Total study population was 46,456 mothers. The median age of the mothers was 30 years with an interquartile range from 27-34 years. 20 % of the mothers were discharged from a NICU with neonatal homecare at the time of discharge; these mothers were included in the part of the analysis after the implementation of neonatal homecare. Hereby about 80% of the mothers were discharged from a NICU before neonatal homecare; these mothers were included in the part of the analysis before the implementation. Results are shown in table 1.

Postpartum depression among mothers

The primary analysis investigated postpartum depression within the first six months after giving birth prematurely. We found a significant increase in the incidence rate of postpartum depression before the implementation of neonatal homecare; (IRR=1.05 [CI: 1.04-1.06] every half year, p<0.001). The implementation made a significant level change where the IRR was reduced with 45 % (IRR=0.55 [CI: 0.45-0.67], p<0.001). The percentage of mothers with postpartum depression was 10 % in the period (six months) before neonatal homecare, this number dropped to 5 % in the

period (six months) after the implementation of neonatal homecare. The implementation significantly changed the development of the incidence of postpartum depression (p=0.001). After the implementation the incidence of postpartum depression was stabilized (IRR=1.00 every half year [CI: 1.00-1.02], p=0.83). Results are shown in figure 1 and table 2.

Sensitivity analyses

The results, from the analyses with changed follow-up time (3 and 12 months), did not differ markedly from the main analysis (Table 2). The incidence of postpartum depression increased before the implementation of neonatal homecare in both analyses. Further the implementation also reduced and stabilized the incidence of postpartum depression in both analyses. (Table 2)

Additional sensitivity analyses were conducted with the following variables: Mothers age, gestation age, parity and length of stay in NICU. The follow-up time in these sensitivity analyses were six months. Depending on gestational age, the incidence rate of postpartum depression was reduced to varying degrees. The implementation had the least reducing effect on the group of mothers of extremely preterm infants (GA<28 weeks), the incidence was reduced with 39 % but this was not statistical significant (p-value=0.070). Among the groups of very preterm (28<GA<32) and moderate preterm (GA>37) the implementation reduced the incidence rate of postpartum depression with 51 % (p-value=0.005) and 45 % (p-value<0.001), respectively.

Further the implementation had less reducing effect on mothers of twins than mothers of singletons. Another variable differed from the main analysis, if we excluded all mothers who were depressed during their pregnancy, the incidence rate before the implementation increased more slowly with only 3 % every half year compared with 5 % from the main analysis. Thus the incidence still got reduced with 47 % and was also stabilized after the implementation as well as in the main analysis. Results are graphed in figure 2. The association between neonatal homecare and reduced incidence of postpartum depression was more uncertain in the group of mothers who were

depressed during their pregnancy. The incidence of postpartum depression was only reduced with 17 % but the reduction was not statistical significant (p=0.11). The rest of the variables did not differ markedly form the main analysis. Results from the sensitivity analyses are shown in table 2.

In total, 3.2%, 4.5% and 6.3% were diagnosed with postpartum depression within the first three, six and twelve months after giving birth respectively.

DISCUSSION

The main finding was a reduction of the incidence rate of postpartum depression after the implementation of neonatal homecare. The reduction was 45 % and afterwards the incidence rate ratio was stabilized. Additionally, we found the incidence rate was increasing with 5 % every half year in the period toward the implementation of neonatal homecare. A possible association between neonatal homecare and reduction in incidence rate of postpartum depression would provide more knowledge about mothers' mental health.

To the best of our knowledge this was the first study to investigate if the neonatal homecare influenced the incidence rate of postpartum depression in a nationwide population. The results from this study showed a possible association between the implementation of neonatal homecare and a reduction of the incidence rate of postpartum depression among the mothers of preterm infants. However many factors should be considered in the connection to a reduction of the incidence rate of postpartum depression.

Assuming the association is causal, the reduced incidence of postpartum depression if likely mediated through a number of factors. Earlier studies have found positive effects of neonatal homecare, including a reduction of risk factors and an increase of protective factors linked to postpartum depression. Neonatal homecare reduces the time of hospitalization, and a long hospitalization increases the levels of stress or anxiety which both are risk factors for postpartum depression among mothers of preterm infants.[23] Further a study has showed that neonatal homecare do not in-

crease the levels of stress and anxiety.[8] Neonatal homecare also increase parents' self-efficacy[15] and the feeling of attachment to the infant which both are protective factors against postpartum depression among mothers of preterm infants. [12,26]

However, non-causal mechanisms should also be considered. Family-Centered-Care is acknowledged as the golden standard at the NICUs. The Institute for Patient- and Family-Centered Care was established In the 1990s to support family-centered-care in paediatrics.[25] They present four concepts in family-centered-care compiling; respect and dignity, information sharing, participation and collaboration.[25] An increased focus on family-centered care has played a central role at the NICUs within the last 20 years. The increased focus on family-centered care has most likely also affected the incidence rate of postpartum depression positively as well as the implementation of neonatal homecare. Other risk factors for postpartum depression, e.g. infant mortality, have probably decreased over time in parallel with the introduction of neonatal homecare. However, interrupted time series are quite robust to such phenomena, as long as they are not dramatically influenced by something else happening at the exact same time as neonatal homecare. We are not aware of any such other interventions taking place at the same time as the introduction of neonatal homecare, and thus consider this unlikely to influence our results.

A total of 4.5 % of the mothers had a postpartum depression within the first six months after giving birth which is considerably less than other studies with rates upward 40% in specific subgroups.[26] A major reason to this discrepancy is most likely how depression was defined in the individual studies. Most reported postpartum depression with self-reported surveys[26]. In our study we defined postpartum depression if the mothers redeemed a prescription of antidepressant medication or if the mothers were admitted in a psychiatric hospital, as we believed that medication prescription was a more consistent approach than answering a survey. Further the extremely good perinatal care at the Danish NICUs, where methods to improve early parent-infant attachment are acknowl-

edged and practiced, could also be a reason to the discrepancy in the percentage of mothers with postpartum depression[27].

Strengths and limitation

A major strength of this study was the usage of nationwide registries with cross linkages between registries trough unique personal identification numbers given at birth in Denmark and thereby minimizing selection biases and information bias related to use of self-reports. Furthermore, the nationwide registers enable investigation of a whole population through many years. Lastly, this study included a large population whilst many NICUs offered neonatal homecare to the families, which therefore enabled a large cohort of mothers in our analysis.

Some limitations should be considered. First, this study was not a randomized controlled study, but a register-based study with the inherent limitations related to this study design. However, a randomized study would have a decreased validity caused by the presence of confounding by indication due to the selection of mothers offered neonatal homecare. It would be impossible to randomize the mothers because the families offered neonatal homecare were chosen by the health professionals. The health professionals chose on the basis of their perception of the families' ability to manage the responsibility associated with neonatal homecare. Some of the NICUs reported that if the mothers were vulnerable, anxious or stressed they would maybe be considered as "not ready" for neonatal homecare, but the criteria for neonatal homecare varies between NICUs. Vulnerable mothers would more likely be grouped in the group without neonatal homecare and probably have a higher risk for postpartum depression. Such a randomized study design would most likely overestimate the true effect of neonatal homecare at the incidence rate of postpartum depression. We avoided this by using the retrospective register-based study design.

Second, due to the register we were not able to include the mothers with a postpartum depression who were neither hospitalized nor treated with antidepressant medication. Hereby, milder postpartum depressions or adjustment behavior were excluded, which may had resulted in an under-diagnosis of postpartum depression. This was, however, equally likely to be the case before and after implementation of neonatal homecare. Furthermore, we may have included women who have been taking antidepressant medication for anxiety and not depression.

Third, the NICUs various time of implementation of neonatal homecare made it impossible to make a calendar-based timeline in our analyses. We used time before or after implementation as the underlying time scale. The non-year-based timeline do have a limitation; other societal tendencies different districts.

Lastly, the awareness and identification of postpartum depression have probably increased through the years; this may had resulted in an under-diagnosis of postpartum depression in the first statistical periods in our analysis. An under-diagnosing in the first periods would make the increasing incidence of postpartum depression before neonatal homecare look bigger than actual. The increasing incidence of postpartum depression before neonatal homecare was comparable to the background population consumption of antidepressant medication. In general the consumption of antidepressant medication has increased from 2000 to 2010 and from 2010 to 2017 the consumption has slowly decreased.[28,29] This probably affected our graph and could be a secondary reason to the reduction of the incidence rate of postpartum depression among the mothers.

CONCLUSION

We found a possible association between the implementation of neonatal homecare and a reduction in the incidence rate of postpartum depression among mothers of preterm infants. Future research

on the association between neonatal homecare and postpartum depression should be conducted to verify the association and its potentially additional positive derivatives.

TABLES AND FIGURES

Table 1. Description of the mothers of preterm infants between 1997 and 2017 (N=46,456)	
Age in years, median (interquartile range)	30 (27-34)
<27 years (%)	12,767 (27.5)
Between 27 and 35 years (%)	13,878 (29.9)
> 35 years (%)	14,119 (30.4)
Unknown (%)	5,692 (12.3)
Gestation Age in weeks, median (interquartile range)	34.3 (32.3-35.6)
Extremely preterm = GA<28 weeks (%)	3,036 (6.5)
Very preterm = 28<GA>32 (%)	7,943 (17.1)
Moderate preterm = 32<GA>37 (%)	35,477 (76.4)
Length of stay at NICU in nights, median (interquartile range)	19 (11-34)
<14 nights (%)	16,765 (36.1)
Between 14 to 30 nights (%)	16,202 (34.9)
>30 nights (%)	13,486 (29.1)
Parity = number of completed pregnancies, defined as > = 22 weeks	
1 (%)	22,468 (48.4)
2 (%)	11,136 (24.0)
3 (%)	4,359 (9.4)
≥4 (%)	2,224 (4.8)
Unknown (%)	6,269 (13.5)
Civil status	
Married (%)	23,117 (49.8)
Registered partner (%)	103 (0.2)
Cohabitants (%)	18,545 (39.9)
Single (%)	4,601 (9.9)
Unknown (%)	90 (0.2)
Type of pregnancy	
Singleton (%)	37,031 (79.7)
Twins (%)	9,425 (20.3)
Neonatal homecare available at NICU	
Yes (%)	9,685 (20.9)
No (%)	36,771 (79.2)

Table 2. The incidence rate ratio of postpartum depression in three different periods in relation to the implementation of neonatal homecare: The period before, the time of implementation and the period after

Variable	Cohort size	1. Increase per half-year in the incidence rate of PPD before NH		2. The IRR of comparing the incidence of PPD just after NH versus just before NH		Interaction of NH	3. Increase per half-year in the incidence rate of PPD after NH	
	N	IRR [95%CI]	p-value	IRR [95%CI]	p-value	p-value	IRR [95%CI]	p-value
The main analysis:								
All mothers between 1994-2017, who gave birth to a preterm live born infant and with at least one night spent at NICU	46,456	1.05 [1.04-1.06]	<0.001	0.55 [0.45-0.67]	<0.001	=0.001	1.00 [1.00-1.02]	=0.83
The sensitivity analyses:								
Follow-up time								
3 months	46,456	1.06 [1.05-1.07]	<0.001	0.56 [0.45-0.70]	=0.001	<0.001	1.00 [1.00-1.02]	=0.08
12 months	46,456	1.04 [1.04-1.05]	<0.001	0.57 [0.47-0.69]	<0.001	<0.001	1.00 [0.99-1.01]	=0.53
Age in years (mothers)								
<27 years	9,976	1.05 [1.03-1.06]	<0.001	0.49 [0.33-0.70]	<0.001	=0.009	1.01 [0.99-1.03]	=0.20
Between 27 and 35 years	24,308	1.05 [1.04-1.06]	<0.001	0.54 [0.42-0.69]	<0.001	<0.001	1.00 [0.99-1.01]	=0.24
> 35 years	6,480	1.04 [1.02-1.05]	<0.001	0.64 [0.44-0.92]	=0.018	=0.004	1.00 [0.98-1.02]	=0.78
Gestation Age in weeks								
Extremely preterm (GA<28 weeks)	3,036	1.06 [1.04-1.08]	<0.001	0.61 [0.36-1.04]	=0.070	=0.001	1.00 [0.97-1.02]	=0.80
Very preterm (28<GA>32)	7,943	1.05 [1.04-1.07]	<0.001	0.49 [0.30-0.80]	=0.005	=0.009	1.01 [0.99-1.04]	=0.32
Moderate preterm (32<GA>37)	35,477	1.05 [1.04-1.06]	<0.001	0.55 [0.44-0.69]	<0.001	<0.001	1.00 [1.00-1.02]	=0.12
Length of stay at NICU in nights								
<14 nights	16,765	1.06 [1.05-1.07]	<0.001	0.49 [0.37-0.64]	<0.001	<0.001	1.01 [1.00-1.02]	=0.04
Between 14 and 30 nights	16,205	1.05 [1.04-1.06]	<0.001	0.50 [0.39-0.64]	<0.001	<0.001	1.00 [0.99-1.02]	=0.66
>30 nights	13,486	1.05 [1.03-1.06]	<0.001	0.69 [0.50-0.96]	=0.026	<0.001	0.99 [0.98-1.02]	=0.77
Parity (number of completed pregnancies, defined as > = 22 weeks)								
Primipara	22,468	1.05 [1.04-1.06]	<0.001	0.61 [0.47-0.79]	<0.001	<0.001	1.00 [0.99-1.02]	=0.25
Multipara	17,719	1.05 [1.04-1.06]	<0.001	0.48 [0.37-0.61]	<0.001	<0.001	1.00 [1.00-1.02]	=0.12
Depression during pregnancy								
No	43,906	1.03 [1.02-1.04]	<0.001	0.53 [0.40-0.68]	<0.001	=0.005	1.00 [0.99-1.02]	=0.32
Yes	1,922	1.02 [1.01-1.03]	<0.001	0.83 [0.66-1.04]	=0.116	=0.045	1.00 [0.98-1.01]	=0.87
Type of pregnancy								
Singleton	37,031	1.05 [1.04-1.06]	<0.001	0.52 [0.42-0.65]	<0.001	<0.001	1.00 [0.99-1.02]	=0.11
Twins	9,425	1.06 [1.04-1.07]	<0.001	0.66 [0.41-1.05]	=0.085	<0.001	1.00 [0.97-1.02]	=0.97
Abbreviations: IRR= incidence rate ratio, PPD= postpartum depression, NH= neonatal homecare, CI= confidence interval, GA= gestation age								

Figure 1 – Interrupted time-series analyses of the association between implementation of neonatal homecare and incidence of postpartum depression among all included mothers (N= 45,456).
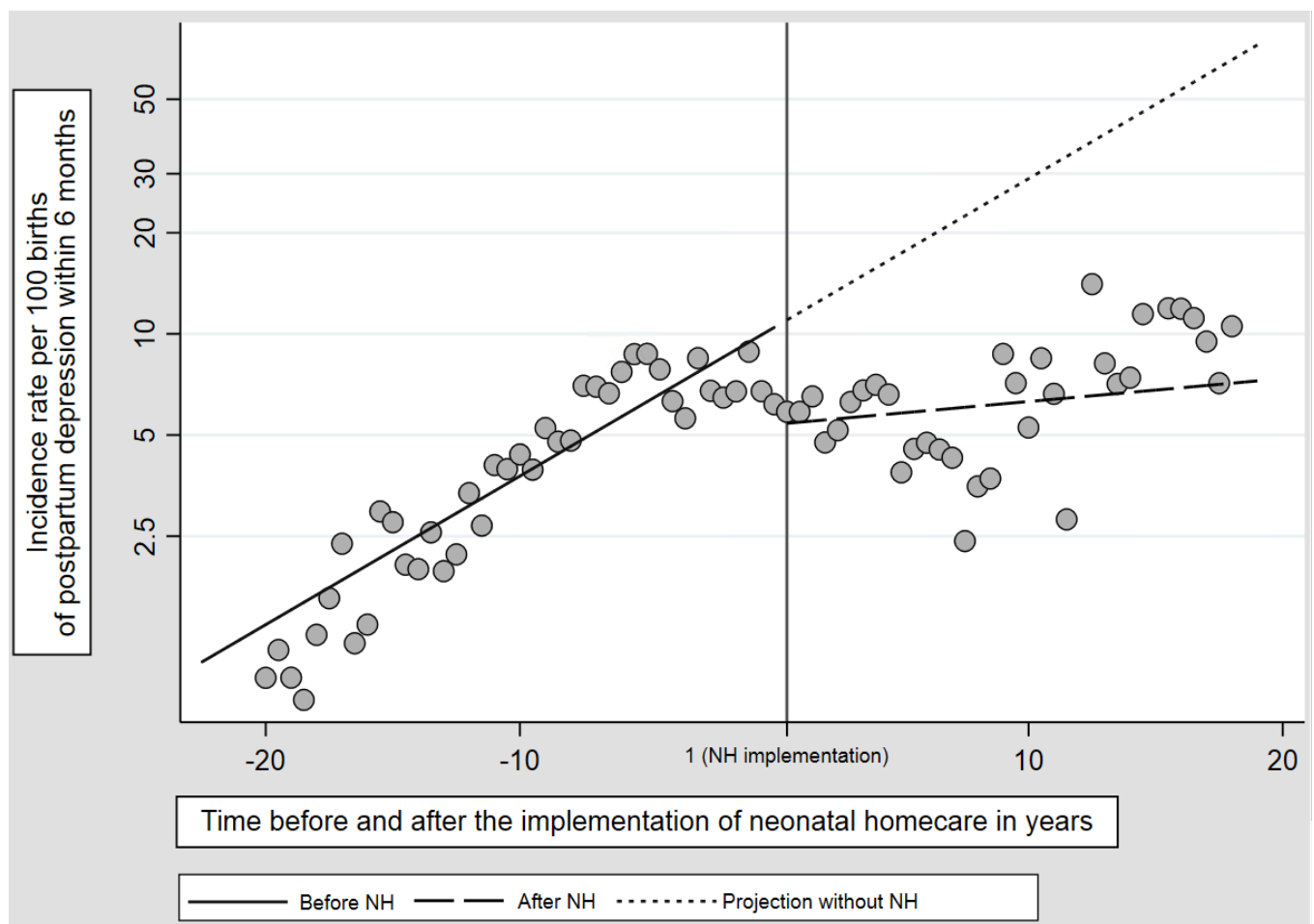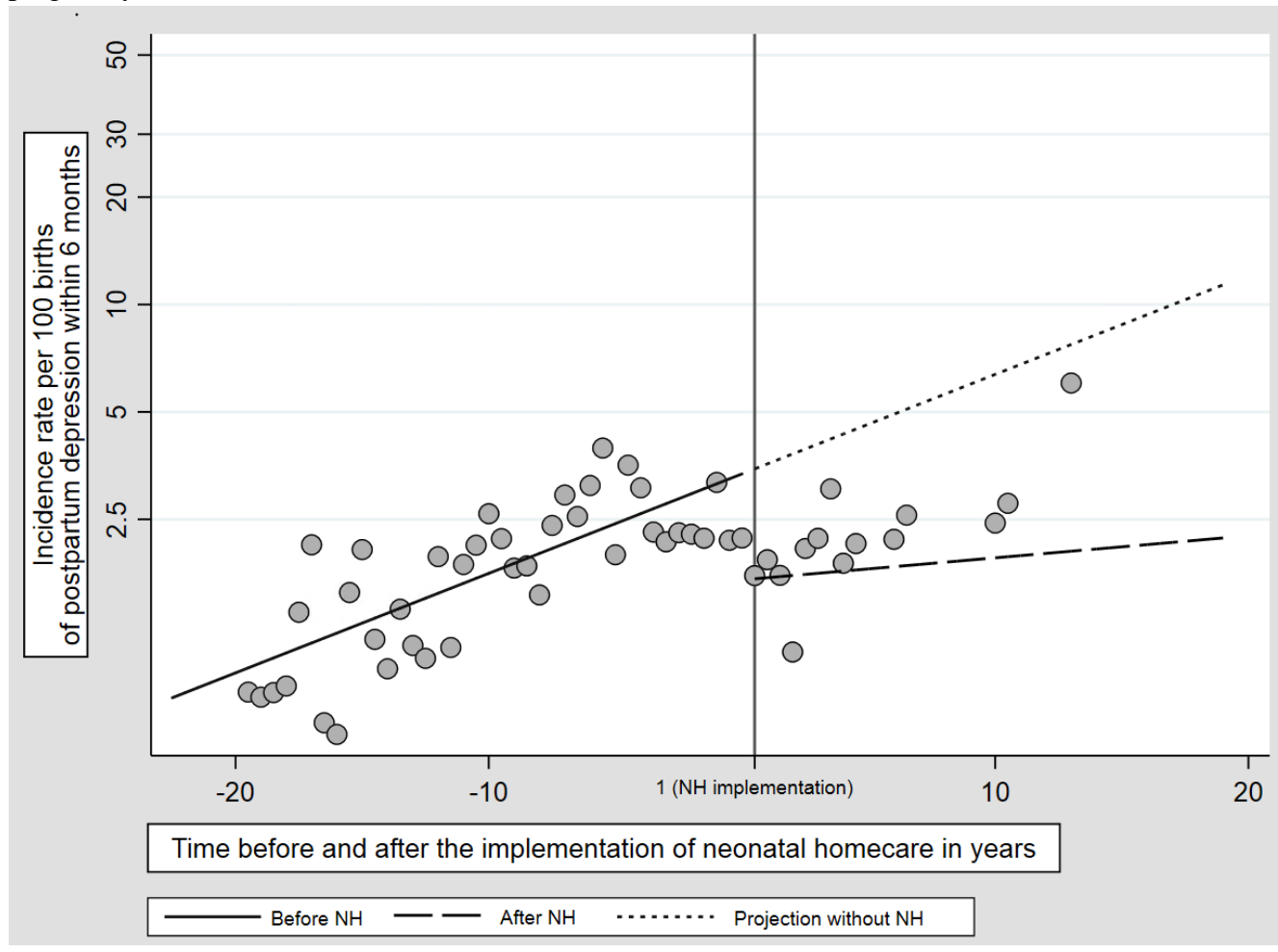
Figure 2 – Interrupted time-series analyses of the association between implementation of neonatal homecare and incidence of postpartum depression among mothers with no depression during their pregnancy.

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