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Increased risk of neonatal complications and infections in children of kidney-transplanted women: A nationwide controlled cohort study

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Abbreviations: DNBR – Danish National Birth Registry, **DNPR –** Danish National Patient Registry, **ICD –** International Classification of Diseases, **NRDT –** Danish National Registry of Regular Dialysis and Transplantation, **RKKP** – The Danish Clinical Registries

Abstract

Information related to short- and long-term risks of children born to kidney-transplanted women remains limited. With the aim of investigating the risk of neonatal complications, and the short- and long-term risk of infections in offspring of kidney-transplanted women, all children born to kidney-transplanted women in Denmark from 1964 to 2016 were identified in a nationwide retrospective matched cohort study. A total of 124 children of kidney-transplanted women were identified and matched on gender, birth year, and number of siblings at birth 1:10 with children born to non-transplanted women identified in the Danish general population. Prevalence of low birth weight (37.9%, RR=12.61[95%CI 8.5-18.5]), premature birth (46.0%, RR=11.32[95%CI 8.1-15.7]) and malformations (11.3%, RR=1.98[95%CI 1.2-3.4]) was increased in children of kidney-transplanted women compared with controls. Similarly, prevalence of hospitalization due to infection was increased during the first year of life (21.0%, RR=1.94[95% CI 1.3–2.8]), from age one to five (34.2%, RR=1.89[95%CI 1.4–2.5]), and overall (41.9%, RR=1.67[95%CI 1.3-2.1]). The risk of infection was also higher in children of kidney-transplanted mothers born preterm or with low birth weight compared with similar controls. In conclusion, risk of neonatal complications, malformations, and both early and late infection was increased in children born to kidney-transplanted women.

1. Introduction

Fertility improves within months in women following successful kidney transplantation.[1] Optimal timing of pregnancy following kidney transplantation remains debated. Historically, kidney-transplanted women have been advised to postpone pregnancy two years following transplantation due to concerns about rejection and allograft function.[2,3] A committee consensus from the American Society of Transplantation in 2003 recommended that pregnancy could be considered after one year following transplantation if the woman has had no rejection, had adequate and stable graft function, no risk of infections, no use of teratogenic medications and stable immunosuppressive treatment.[3,4] Potential risks of pregnancy in kidney-transplanted women include pregnancy-related complications (e.g. preeclampsia, cesarean section and preterm birth) and potential risk for fetal development due to the immunosuppressive treatment.[1–3] The risk of graft rejection during pregnancy are similar to non-pregnant women[4,5] with a rejection rate of approximately 9-14.5%.[4] To mitigate risk, guidelines advocate adjustment of maintenance immunosuppressive therapy in kidney-transplanted women prior to conception and during pregnancy[6], with current recommendations advocating a combination of azathioprine, maintenance prednisone, and either tacrolimus or cyclosporine.[7]

Knowledge regarding kidney-transplanted women and pregnancy outcomes is limited. Most studies reporting pregnancy outcomes in kidney-transplanted women are small, single-center based, and retrospective; additionally, existing studies have primarily reported on maternal complications and neonatal outcomes such as preterm birth, low birth weight, and malformations.[5,8,9] Only one study with 28 children of kidney-transplanted women has reported on risk of infections during the first year of life.[10] The aim of this nationwide controlled cohort study was to investigate the risk for neonatal complications and malformations with specific emphasis on the short- and long-term risk of infections in offspring of kidney-transplanted women.

2. Materials and Methods

2.1 Data sources

Numerous comprehensive and validated national registers exist in Denmark. All information regarding hospitalization, medication, morbidity and mortality is recorded in national databases (i.e. The Danish National Patient Register, The Danish National Prescription Registry, and The Civil Registration System) under a unique individual central person register number permitting cross-referencing of data between registers.

The validated Danish National Register on Regular Dialysis and Transplantation (NRDT) was established in 1990, but includes all patients with kidney transplantation since 1964.[11] The Danish National Patient Register (DNPR) contains information on the date, cause and type of all hospitalizations and surgical procedures in Denmark since 1977. All diagnoses from 1977 to 1994 are registered according to International Classification of Diseases (ICD), Eighth Revision, and those from 1994 onward according to ICD-10.[12,13]

The Danish Medical Birth Register (DMBR) was established in 1973, but contains data on all children born in Denmark and their parents from 1954 permitting cross-referencing of data between parents and children.[14] The register permits cross-referencing of information between siblings and extended family. Furthermore, the DMBR contains data on birth weight, gestational week and length. The validated Danish National Prescription Register contains information on all redemptions of prescriptions in Denmark.[15] Outpatient pharmacies are mandated by law to register information on all redeemed prescriptions, and the register has been shown to be of high-quality from 1995 and onward. Data are registered according to the Anatomical Therapeutic Chemical Classification System (ATC).[16]

2.2 Study population

All children born to kidney-transplanted women between 1964 (when the first kidney-transplantation was performed in Denmark) and 31st December 2016 were identified in the DMBR. Children of kidney-transplanted women were exact matched on gender, birth year, and number of siblings at birth in a ratio of 1:10 with children born to non-transplanted

women identified in the Danish general population. Subjects were included at birth and followed until the time of an event, emigration, death or the end of the study period (31st December 2017).

2.3 Study outcomes

Outcomes were defined based on administrative diagnosis codes identified in the DNPR and DMBR relating preterm birth (birth prior to gestational week 37), malformation (malformations in the nervous system, eyes, ears, face, neck, lip, palate, cardiovascular system, gastrointestinal system, genital system, urinary system, bones and tissue and chromosome anomalies), low birth weight (birth weight < 2500g) and hospitalization due to infections. Study outcomes relating to redemptions of a prescription for antibiotic treatment were identified in The Danish National Prescription Registry (ATC J01-04). An overview of all administrative codes employed is provided in Supplemental Table S1. Outcomes for both hospitalizations due to infections and redemption of a prescription for antibiotic treatment were evaluated overall (from birth to age 5 years), early (within the first year of life) and late (from age 1-5 years).

2.4 Statistical analyses

Continuous variables were compared with the Student's t-test, and discrete variables with $\chi 2$ test. Risk ratios (RR) were calculated for the binary outcomes premature birth, malformation, low birth weight, as well as for hospitalizations due to infections and redemptions of a prescription for antibiotic treatment within three age periods (0-1, 0-5 and 1-5 years). We calculated the difference between exposed and non-exposed children in relation to the average number of hospitalizations per child due to infection and the number of redeemed prescriptions for antibiotic treatment within the three age periods. Koopman's method was used for uncensored data[17] and appropriate methods were used to deal with censoring and competing risks where relevant.[18,19] Subgroup analyses were performed to study the effect of exposure within the population of infants with premature birth, low birth weight or born from a mother suffering from diabetes or hypertension. Subgroup analyses by time periods (< 1996, 1996-2010, > 2010) and by use of prednisone on risk of infection were also performed.

P-values < 0.05 were considered statistically significant. All analyses were performed using SAS Version 9.4 (SAS Institute, NC, USA) or R: A language and environment for statistical computing, version 1.1.447 (www.R-project.org The R Foundation).

2.5 Ethics

The project was approved by the Danish Data Protection Agency (Ref no. 2008-58-0028/2017-182). Use of the NRDT database was approved by The Danish Clinical Registries, (RKKP), (Ref no. DNSL-2017-11-17). Pseudo-anonymized data were made accessible at an individual level permitting cross-referencing across national registers. Retrospective register studies in Denmark do not require approval from ethics committees. All data are held by Statistics Denmark, which also has administrative rights of the data. Due to legislative restrictions in Denmark on the use of register-based health care data, we are unable to publicize results on 'microdata' i.e. aggregated data with < 4 cases.

3. Results

A total of 124 children born to kidney-transplanted women were identified between 1964 and 2016 (Supplemental Figure S1) and comprised the exposed cohort. A total of 1231 children of non-transplanted women identified in the Danish general population comprised the non-exposed cohort. The match was complete except for nine children. Baseline characteristics are shown in Table 1. Median follow-up time was approximately 14 years in both groups. The average birth weight was 2421 g in the exposed cohort compared to 3444 g in the non-exposed cohort. Supplemental Figure S2 illustrates the distribution curves over the birth weight.

Figure 1 shows the outcomes pertaining to neonatal complications. Prevalence and risk ratios of premature birth and low birth weight were increased in the exposed cohort. Of note, prevalence of premature birth and low birth weight in children of kidney-transplanted women were 46.0% (RR 11.3 [95%CI 8.1-15.7]) and 37.9% (RR 12.6 [95%CI 8.5-18.5]), respectively. The exposed children observed a significantly 1.98 (95% CI 1.2-3.4) increased risk of malformations compared with the non-exposed cohort. Fifty percent of the malformations in the exposed cohort were cardiovascular malformations, of these the

majority (6 cases) had malformations in relation to the septum (e.g. ventricular septal defect and atrial septal defect). No significant differences in infant mortality (death during the first year of life) were observed.

Risk ratios for hospitalization due to infection were increased for all periods as shown in Figure 2. No significant differences were observed regarding redemptions of prescription for antibiotic treatment.

During the first year of life a total of 26 cases (with 34 hospital contacts) were registered with hospitalization due to infections. Five cases had more than one hospitalization due to infection. The diagnosis included bacterial sepsis in newborn (6 hospital contacts), unspecific virus infection (6 hospital contacts), laryngitis (4 hospital contacts) and respiratory infection (e.g. pneumonia and bronchitis) (6 hospital contacts). The median of the hospitalization time was 2 days (IQR 1-10). For the control group the similar median hospitalization time was 2 days (IQR 2-6).

A total of 42 cases (with 77 hospital contacts) were registered with hospitalization due to infection from age 1-5. Nine cases had more than one hospitalization due to infection. The diagnosis included gastroenteritis (12 hospital contacts), pneumonia (8 hospital contacts), bronchitis (5 hospital contacts), acute obstructive laryngitis (8 hospital contacts), pharyngitis (5 hospital contacts), acute and chronic middle ear infection (6 and 8 hospital contacts) and urinary tract infection (e.g. pyelonephritis and cystitis) (5 hospital contacts). The median of the hospitalization time was 2 days (IQR 1-3). For the control group the similar median hospitalization time was 2 days (IQR 2-3).

Furthermore, the average number of hospitalizations due to infection was observed to be higher in the exposed cohort compared with the non-exposed cohort for all age periods as shown in Table 2. Additionally, the average number of antibiotic prescriptions filled between age one and five was also increased in exposed children (2.15 95%CI 1.65-2.65) compared with non-exposed children (1.49 95%CI 1.38-1.61).

Figure 3 illustrates the cumulative incidence of hospitalization due to infection over time in the exposed and non-exposed cohort. The cumulative incidence of severe infections was

higher in the exposed cohort and the difference between the two groups increased in relation to time.

3.1 Subgroup analyses

In subgroup analyses, outcomes in preterm children in the exposed cohort were compared with outcomes in preterm children of the non-exposed cohort. Results are provided in Supplemental Table S2. Risk ratios for late hospitalizations due to infections (RR 2.02, 95%CI 1.12-3.65) and the difference between average number pertaining to overall (RR 0.61, 95%CI 0.03-1.20) and late number of infections (RR 0.61, 95%CI 0.23-0.98) continued to be significantly increased. Similarly, in the subgroup analysis with children born with low birth weight (Supplemental Table S3), the difference regarding average number of hospitalizations due to late infections also observed a borderline significant increase (RR 0.43, 95%CI -0.01-0.88).

No significant differences were observed in a subgroup analysis of children to mothers with diabetes (Supplemental Table S4). In subgroup analyses comparing outcomes between different time periods (children born before 1996, from 1996 to 2010 and from 2010) (Supplemental Table S5, S6 and S7), results remained principally unchanged. No substantial differences were evident for hospitals employing a reduced prednisone compared with standard dose prednisone (Supplemental Table S8 and S9). No significant differences were observed in a subgroup analysis of children to mothers with hypertension (Supplemental Table S10). The most frequent anti-hypertensive treatment in our cohort of kidney-transplanted mothers was beta-blockers, calcium antagonists and methyldopa (Supplemental Table S11).

4. Discussion

The major new finding in this nationwide cohort study, was that children of kidney-transplanted women are at increased risk of early as well as late infection. In addition, our results confirm the increased prevalence of low birth weight, preterm birth, and malformation in these children reported in other studies.

The higher incidence of low weight children in the exposed cohort (37.9%) is similar to previous observations in other studies.[8,9] Similarly, our results confirm an increased incidence of preterm birth of 46.0%, analogous to the increased incidences previously observed in smaller studies.[5,8,9]

In a study from UK with 108 children of kidney-transplanted women, the prevalence of congenital anomaly was 5%.[9] In our study, the prevalence of malformations was 11.3%; however, the difference compared with Bramham et al. (2013) may reflect differences in definitions of the outcome. Nonetheless, the increased risk for malformations plausibly reflects the toxic effects of immunosuppressive treatment in fetal life. Additionally, a substantial proportion of kidney-transplanted women require antihypertensive treatment prior to and during pregnancy. In our cohort 71% (88/124) of the children in the kidney-transplanted cohort were exposed to maternal hypertension during pregnancy. As such, the exposure to hypertension could increase the risk for malformation, particularly in cases of unplanned pregnancy leading to delayed conversion of antihypertensive treatment to 'safe' medications.

A study from Brazil with 28 children of kidney-transplanted women showed a higher risk of hospital admission for infectious causes in the first year of life compared with controls (28.6% vs 3.6%, p=0.025).[10] However, the study was of limited size and did not report long-term risk of infection. We are not aware of other studies demonstrating the long-term risk for infections in offspring of kidney-transplanted women.

To evaluate the risk of infection, our study evaluated both hospitalizations due to infections, indicating severe infections, and the use of prescription for antibiotic treatment. The exposed cohort observed a higher prevalence of both early (21.0%) and late hospitalization due to infections (34.2%) compared with the non-exposed cohort; specifically, children of kidney-transplanted women observed a 94% and 89% increased risk of hospitalization for treatment of infection during the first year of life and from age one to five years, respectively, compared with non-exposed children. Of note, no differences were observed regarding prescription of antibiotic treatment; however, this may reflect an overriding general use of antibiotic treatment in the general population. To further assess the risk of infection, the

total number of hospitalizations due to infection and total number of prescriptions for antibiotics were also considered - thereby accounting for the possibility of repeated outcomes within the follow-up period.

As such, children of kidney-transplanted women observed more frequent hospitalization due to infection during the first year, between ages one and five years, and overall. No difference was observed regarding prescription of antibiotics within the first year and overall; however, children of kidney-transplanted women did observe a more frequent requirement of prescription antibiotics between ages one to five years.

To examine the impact of preterm birth and low birth weight on risk of infection, subgroup analyses were performed. Importantly, the subgroup analyses indicate that the increased risk ratios for infections, especially late infections, in children born by kidney-transplanted women remained independently of preterm birth and low birth weight. As such, our results indicate that risk of infection is at least somewhat independent of preterm birth and low birth weight.

Plausibly, the greater predisposition for infection in offspring of kidney-transplanted women could be mediated by exposure to immunosuppressive treatment in fetal life. Central immunologic tolerance develops in the thymus in fetal life and can be affected by various immunosuppressive drugs. Animal studies have reported that immunosuppressive drugs can affect both the positive selection (selection of T cells that can recognize self-MHC molecules) and the negative selection (T cells that bind too strong to self-MHC class are signaled to die) in thymus in fetal life[20]. It is possible that the immunosuppressive drugs affect the positive selection, which becomes too strong or unspecific leading to a lack of T-lymphocytes with specificity against bacterial antigens. Small studies in children exposed to immunosuppressive treatment in fetal life have shown lower numbers of T- and B-cells compared to controls.[21,22] Similarly, a recent study with 28 children of kidney-transplanted women reported lower numbers of CD4+ T-cell, natural killer cells and intense reduction of B cells.[10] This could perhaps explain the immunosuppressive effect on the immune system. Further research is needed to clarify the causation and possible mediation.

Additionally, kidney-transplanted mothers may infer possible inheritance of specific genetic dispositions, particularly with regard to immunology due to a predominance of a history of glomerulonephritis in young adults with end-stage renal disease. As such, the observed increase in risk of infection could also represent inherited immune vulnerability.

Exposure to immunosuppressive treatment in fetal life has in animal studies also been associated with an increased risk of autoimmune disease.[23] In addition, a case report described several autoimmune diseases in a daughter of a kidney-transplanted woman treated with immunosuppression with azathioprine and prednisone during pregnancy.[24] Children exposed to immunosuppressive treatment in fetal life may therefore be at increased risk for developing autoimmune diseases. We were not able to evaluate the risk for autoimmune diseases in our study because of too few cases. This could, however, be influenced by the follow-up time (median follow-up time was 14.5 years). Long-term follow-up is therefore necessary to explore the risk for autoimmune diseases in the offspring of kidney-transplanted women.

4.1 Strengths and weaknesses of the study

This nationwide controlled cohort study has several strengths. Most importantly, this may be the first study worldwide to investigate the long-term risk for infections in offspring of kidney-transplanted women. In addition, this study has the largest cohort of children born by kidney-transplanted women internationally with regard to infections.[10] Piccoli et al. reported outcomes of 189 children born by kidney-transplanted women but only with regard to neonatal complications.[8]

The study was not limited by selection- or recall bias as all offspring of all kidney-transplanted women in Denmark were included, and data was retrieved from excellently validated national registers and not through questionnaires or retrospective interviews. Prior register-based studies on pregnancy outcomes in kidney-transplanted women employ the National Transplantation Pregnancy Register in the US, which is a voluntary database representing only 1/3 of all available information reported on pregnancy outcomes in kidney-transplanted women.[5] The registries in Denmark are of high quality for epidemiological research. The DMBR is unique worldwide and it is exceptional that we can

connect parents and children.[13,14] Similarly, the NRDT is validated to be complete, of high quality and a good source for epidemiological studies.[11]

A limitation concerning the exact immunosuppressive treatment is that this medicine is delivered directly from the hospital and is therefore not registered in The Danish National Prescription Registry. However, all kidney-transplanted women have received and continue to receive immunosuppressive treatment in accordance with international guidelines and the treatment is standardized in Denmark. Additionally, tax-funded health care is provided by law to all Danish citizens, and all kidney-transplanted procedures and follow-up is provided via 14 nephrology departments at accredited public hospitals without exception. Nonetheless, the study is unable to assess the impact of specific immunosuppressive protocols on the risk of neonatal complications and early- and late infection.

Breast feeding in transplanted mothers on immunosuppressive treatment remains controversial. Transference of maternal antibodies and immunosuppressants via breast milk varies, and significance is uncertain.[3] The consensus opinion from the American Society of Transplantation in 2003 was however, that breastfeeding need not be viewed as absolutely contraindicated.[3] Data is however limited, and as breast feeding status remains unaccounted for in our cohort of kidney-transplanted mothers, our results remain unable to assess the impact of breast feeding.

It could be argued, that children born by kidney-transplanted women are more exposed to clinical examinations than children born by healthy mothers. However, the outcomes preterm birth and birth weight are independent and registered for all children born in Denmark. In generally, all prescriptions of antibiotics in Denmark require an individual medical examination. Since the knowledge about long-term risk after immunosuppressive treatment in fetal life is very limited, this information is not considered to be of great importance in the clinical examination and it is assumed that children of kidney-transplanted women are prescribed antibiotic drugs according to the same guidelines as other children.

4.2 Conclusions

Children born by kidney-transplanted women have an increased risk of neonatal complications and both early and late infections up to the age of five years. The increased risk for infections could be due to immunosuppressive exposure in fetal life; however, further research is needed to clarify the causation and possible mediation of specific treatment protocols for the increased risk of infections in offspring off kidney-transplanted women.

Data availability

It is not possible to share data due to the pseudo-anonymized data.

Acknowledgments

Nicholas Carlson, Christian Torp-Petersen, and Ole Bjarne Christiansen planned the study. Pia Egerup, Louise Bruun Oestergaard and Nicholas Carlson performed the data management. Pia Egerup, Nicholas Carlson and Paul Blanche completed the statistical analysis. Mads Hornum and James Scott contributed with relevant expect knowledge. The first author wrote the first draft on the manuscript. All authors contributed and approved the final manuscript.

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Disclosure

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Supporting Information

Additional supporting information by be found online in the Supporting Information section at the end of the article.

Table 1. Baseline characteristics of the children.

	Exposed (n=124)	**Non-exposed (n=1231)**
Birthday year, *n(%)*		
< 1990	31 (25%)	310 (25.2%)
1990-2000	26 (21%)	260 (21.1%)
> 2000	67 (54%)	661 (53.7%)
Sex, n(%)		
Boys	67 (54%)	670 (54.4%)
Girls	57 (46%)	561 (45.6%)
Number of siblings at birth, *n(%)*		
0	95 (76.7%)	950 (77.2%)
1	20 (16.1%)	200 (16.2%)
2	4 (3.2)	40 (3.2%)
≥ 3	5 (4.0%)	44 (3.6%)
Gestational age in days, *mean (SD)*	245.2 (22.6)	277.7 (22.6)
Birth weight in gram, *mean (SD)*	2421.6 (766.4)	3444.1 (569.1)
Birth length in cm, *mean (SD)*	45.5 (8.5)	51.0 (6.6)
Head circumference in cm, *mean (SD)*	28.5 (11.0)	33.9 (5.9)
Abdominal circumference in cm, *mean (SD)*	20.3 (14.6)	31.3 (8.8)
Weight of placenta in gram, *mean (SD)*	508.3 (191.5)	653.4 (181.7)

Apgar score at birth,		
10	71 (86.6%)	719 (91%)
8-9	11 (13.4%)	54 (6.8%)
< 8	0	17 (2.2%)
Follow-up time in years ***median (IQR)***	14.5 (7.1-22.8)	14.1 (6.6-2.4)

Table 2. Average number of infections leading to hospital admission/antibiotics per child in non-exposed and exposed children, respectively, and the difference between the two groups. Both outcomes were evaluated overall (from birth to age 5), early (within the first year of life) and late (from age 4-5).

	Average number of infections/antibiotics in non-exposed children (95%CI)	Average number of infections/antibiotics in exposed children (95%CI)	Difference (95%CI)
Overall infections	0.41 (0.36-0.46)	0.88 (0.61-1.15)	0.48 (0.20-0.75)
Early infections	0.14 (0.11-0.17)	0.28 (0.16-0.39)	0.14 (0.02-0.25)
Late infections	0.23 (0.20-0.27)	0.56 (0.37-0.74)	0.32 (0.13-0.51)
Overall antibiotics	2.24 (2.08-2.40)	2.88 (2.21-3.54)	0.64 (-0.05-1.32)
Early antibiotics	0.40 (0.35-0.45)	0.43 (0.27-0.59)	0.030 (-0.13-0.20)
Late antibiotics	1.49 (1.38-1.61)	2.15 (1.65-2.65)	0.66 (0.14-1.17)

Overall defined as age 0-5. Early defined as age < 1. Late defined as age 4-5.

Figure 1. Prevalences and Risk Ratios (RR) for neonatal complications.

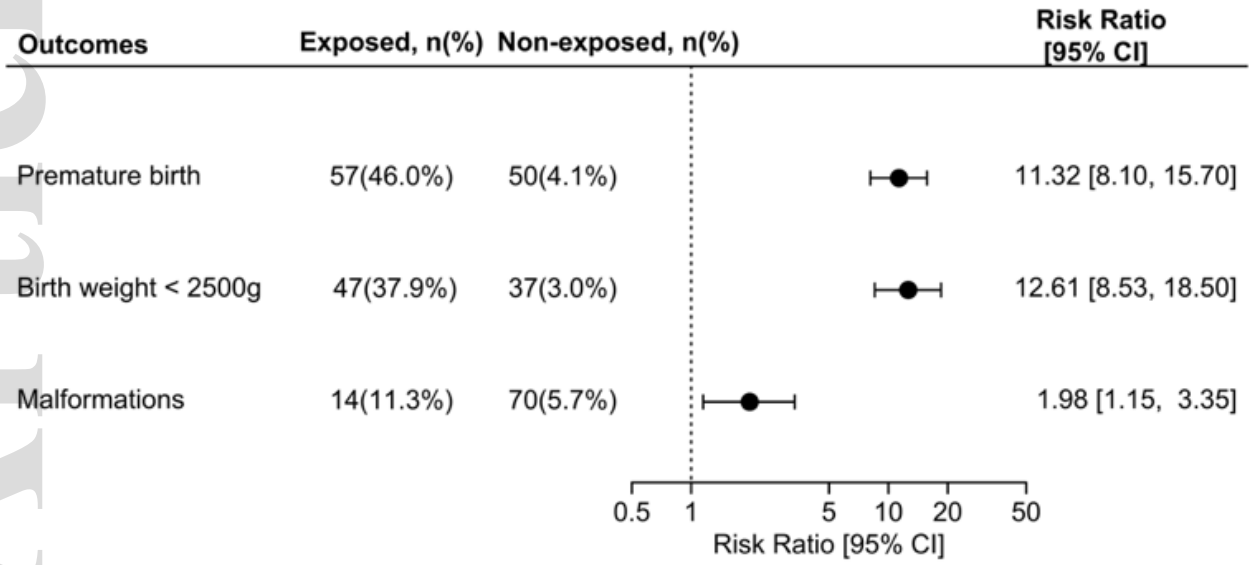
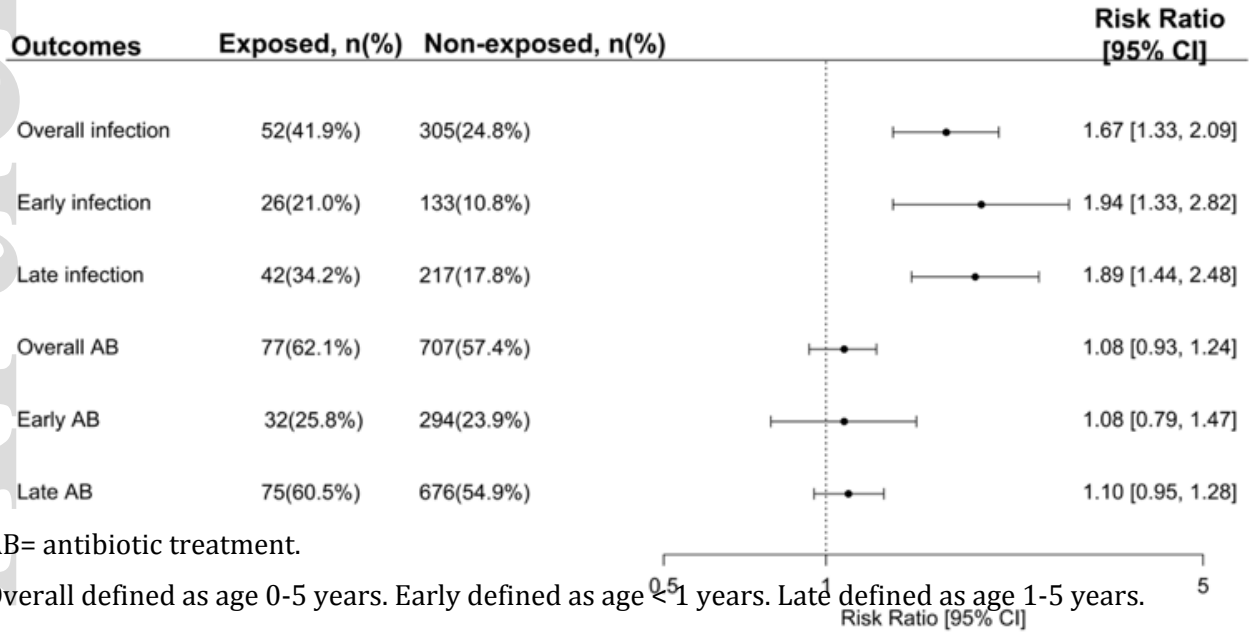


Figure 2. Prevalences and Risk Ratios for hospitalizations due to infections and redemptions of an antibiotic prescription.



AB= antibiotic treatment.

Overall defined as age 0-5 years. Early defined as age < 1 years. Late defined as age 1-5 years.

Figure 3. Cumulative incidence with 95% CI of first hospitalization due to infection over time in children of kidney-transplanted mothers and unexposed mothers.