Parental infections during pregnancy as risk factors for mental disorders in childhood and adolescence – a nationwide Danish study

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INTRODUCTION

Infections during pregnancy are common and approximately 40% of all pregnant women in Denmark are exposed to infections treated with antibiotics during pregnancy.[1] Over the last decades, maternal infections and inflammatory responses during pregnancy have increasingly been suggested to affect the fetal developing brain elevating the risk of mental disorders in the offspring. The majority of studies have focused on psychosis and schizophrenia.[2–16] Maternal infections during pregnancy with rubella,[2] *Toxoplasma gondii*,[3] herpes simplex virus type 2,[4,5] influenza[6,7] and bacterial infections during the first trimester[8] have been associated with an increased risk of schizophrenia in the offspring. However, the findings have not been consistent[3,9–11,17,18] and few epidemiological studies have investigated other mental disorders such as autism[19–24] and affective disorders.[3,25–29] Most prior studies have had several limitations, e.g. few cases,[2,3,9] infections based on maternal self-report[12,20,21] or ecological study design.[6,7] In the larger studies, exposure has mainly been based on infections requiring hospital contacts[11,13,19] thus disregarding the more commonly occurring infections treated by general practitioners. Finally, the majority of studies have not taken potentially important confounders into account, e.g. parental psychiatric diagnoses[8,21] or socioeconomic factors.[3,13,19]

Several pathways have been suggested for the abovementioned associations. Although the infection itself could impact the developing fetal central nervous system (CNS) directly,[2,3] it is also likely that maternal immune activation in response to infections plays a significant part[16,30,31] as similarly increased risks of mental disorders have been found across a wide range of infections and in relation to fever[12,20,21,32] and elevated acute phase reactants.[23,33] Maternal immune activation is thought to influence the fetal microglia, which play a pivotal role in neural circuit formation and

other neurodevelopmental processes.[30] However, one previous study found that parental hospitalizations for infections before, during and after pregnancy similarly increased the risk of schizophrenia.[13] This has led to the question of whether the proposed relationship between infections and mental disorders is rather a shared genetic susceptibility to infections and mental disorders, which could also extend to other mental disorders.

We aimed to investigate the association between all treated parental infections during pregnancy and the offspring's risk of being diagnosed with any mental disorder. We included comparison between maternal and paternal infections before, during and after the pregnancy period to examine if a possible association was confined to maternal infections during pregnancy or if it was merely a generally increased susceptibility to infections among the parents as suggested by a previous study.[13] Additionally, we investigated the risk of specific mental disorders, dose-response relationships and associations with timing of infection exposure based on pregnancy trimester.

MATERIAL AND METHODS

Study population

The present study is a nationwide, register-based cohort study covering the entire Danish population. We included all children born in Denmark between July 1, 1996, and December 31, 2011, utilizing the Danish Civil Registration System.[34] We excluded children with missing parental information establishing a cohort of 987,667 individuals. All individuals were followed from first birthday to first outcome (see below), emigration, death or end of study period on July 31, 2013, whichever came first.

Exposure – assessment of infections

We identified all treated maternal and paternal infections via 1) prescribed anti-infective agents and 2) diagnosed infections requiring hospital contacts. Data on anti-infective agents were obtained through the National Prescription Registry,[35] which contains information on all redeemed prescriptions since January 1, 1995. Infections requiring hospital contacts were identified via the National Patient Register,[36] which has registered all diagnoses given in Danish somatic hospitals since 1977, including information on all outpatient contacts since January 1, 1995. Infections were divided into bacterial infections and other infections, i.e. viral, parasitic and mycotic.

Exposure periods

The abovementioned infections were identified before, during and after the pregnancy period. We defined the pregnancy period as the 40 weeks before date of birth. This period was subdivided into trimesters; week 0-12 (1^{st} trimester), week 13-28 (2^{nd} trimester), week 29-40 (3^{rd} trimester). The pre-pregnancy and post-pregnancy periods were defined as the 40 weeks prior to the pregnancy period and the 40 weeks following date of birth, respectively.

Outcome - assessment of mental disorders

The Danish Psychiatric Central Research Register[37] includes all hospitalizations in psychiatric hospitals since 1969 and outpatient treatment and emergency room contacts since January 1,

1995. We identified mental disorders within the cohort from first birthday to the end of study on July 31, 2013. We only included the main diagnosis of the first psychiatric hospital contact. Our main outcome was any mental disorder defined as a diagnosis of F20-99 according to the International Classification of Diseases, 10th edition (ICD-10). Our secondary outcomes were specific diagnoses depending on category according to ICD-10 (F20-29, F30-39, F40-49, F50-59, F60-69, F70-79, F80-89 & F90-99).

Covariates

Sex and birth year were derived from the Danish Civil Registration System.[34] Birth year was categorized into three groups (1996-2000, 2001-2005, 2006-2011). Parental age at childbirth was categorized into five categories: <25 years, 25-29 y, 30-34 y, 35-39 y and ≥40 y. Information on parental education was obtained from the Danish Education Registers[38] and was defined as the highest level of education at childbirth divided into six categories (primary school, secondary school, vocational education, short higher education, medium higher education and long higher education). Parental psychiatric history was defined as any diagnosis (ICD-10: F00-F99 and ICD-8: 290-315) prior to childbirth since 1969.[37] The risk of spread of an infection from one parent to the other was handled by adjusting the analyses for concurrent infection (either treated with anti-infective agents or hospitalization) in the other parent. Parental infections outside the time period was defined as one or more maternal or paternal infection in other time periods i.e. pre-pregnancy, post-pregnancy and 1st and 3rd trimester, when analyzing 2nd trimester etc.

Statistical analyses

The primary analysis compared individuals who had been exposed to maternal infections treated with anti-infective agents or resulting in hospital contact before, during or after the pregnancy period with non-exposed individuals during the specific period regarding the risk of any mental disorder. We performed the same analyses for paternal infections.

Secondly, we investigated potential vulnerable periods for maternal or paternal infections during pregnancy depending on trimester.

Thirdly, we investigated the risk of specific mental disorders in the offspring and lastly, we investigated potential dose-response relationships between the number of infections treated with anti-infective agents and risk of mental disorders.

All analyses were performed with Stata version 13.1. We conducted Cox regression analyses with age as the underlying timescale and present results as hazard ratios (HR) with 95%-confidence intervals (95%CI). All analyses were stratified for sex and adjusted for birth year, parental age at childbirth, parental educational level at childbirth, any parental mental diagnosis before childbirth, concurrent infection in the other parent and parental infections outside the time period. We adjusted for multiple comparisons using Bonferroni correction.

RESULTS:

The cohort consisted of 987,667 children born July 1, 1996 to December 31, 2011 with 7,948,772 person-years of follow-up from July 1, 1997 to July 31, 2013. A total of 449,904 (45.6%) of the children were exposed to maternal infections treated with anti-infective agents during pregnancy,

while 10,498 (1.1%) were exposed to maternal infections requiring hospital contacts during pregnancy (see Table 1 for all exposures before, during and after pregnancy).

Parental infections before, during and after pregnancy and the risk of mental disorders in the child

In the fully adjusted model, we found that children exposed to maternal infections treated with anti-infective agents during pregnancy had an increased risk of any mental disorder with a HR of 1.14 (95%CI: 1.11-1.16) compared to children not exposed to maternal infections treated with anti-infective agents during pregnancy (Table 2). Exposure to maternal infections requiring hospital contacts during pregnancy increased the risk of mental disorders with a HR of 1.38 (95%CI: 1.28-1.50). We found no difference in the increased risk of mental disorders after maternal infections of bacterial or other origin (data not shown).

In comparison, paternal infections treated with anti-infective agents during pregnancy conferred a HR of 1.01 (95%CI: 0.99-1.04), whereas infections resulting in hospitalization increased the risk with a HR of 1.24 (95%CI: 1.10-1.39). Most parental infections in the pre- or post-pregnancy period showed similarly increased risk estimates for any mental disorder as the parental infections during pregnancy (Table 2).

When performing Wald's test comparing the risk of mental disorders after maternal and paternal infections, we found that the risks after maternal infections treated with anti-infective agents were significantly higher than for paternal infections (all $p<0.001$), but found no difference for parental infections resulting in hospitalization (all $p>0.12$).

Infections based on trimester and the risk of mental disorders

We found a similarly increased risk of mental disorders after exposure to maternal infections across all three trimesters of pregnancy (Table 3). Paternal infections only showed a significantly increased risk after hospitalization during the third trimester. We found no difference across trimesters in the increased risk depending on bacterial or other origin of maternal infection (Table 4).

Risk of specific mental disorders

The most elevated risk of specific mental disorders in the child was observed for schizophrenia spectrum disorders (F20-29), where maternal hospitalizations with infections during pregnancy showed an increased risk in the offspring with a HR of 3.22 (95%CI: 1.70-6.10; N=10 cases) (Table 5). There were no increased risks of mood disorders (F30-39), behavioral syndromes (F50-59), personality disorders (F60-69) or of mental retardation (F70-79) (data not shown). We found an increased risk of anxiety disorders (F40-49) and of behavioral and emotional disorders (F90-99) after primarily maternal infections before, during and after pregnancy.

Only maternal infections were associated with an increased risk of developmental disorders (F80-89) with a HR of 1.13 (95%CI: 1.08-1.18) after maternal infections treated with anti-infective agents during pregnancy, while maternal infections resulting in hospital contacts during pregnancy and post-pregnancy showed a HR 1.43 (95%CI: 1.23-1.67) and 1.48 (95%CI: 1.29-1.71), respectively. The estimates specifically for autism (ICD-10: F84.0, 84.1, 84.5, 84.8, 84.9) were

similar with HR of 1.11 (95%CI: 1.07-1.16), 1.41 (95%CI: 1.20-1.66) and 1.50 (95%CI: 1.29-1.74), respectively.

Dose-response associations

Figure 1 indicates that the risk for any mental disorder increased in a dose-response relationship depending on the number of maternal prescriptions before, during and after pregnancy (all $p<0.001$). We found no dose-response associations with paternal prescriptions or the number of maternal or paternal hospital contacts.

DISCUSSION

Our nationwide study is the largest to date investigating the association between parental infections during pregnancy and risk of mental disorders in the offspring, covering all treated infections in the primary and secondary healthcare sector. We showed that maternal infections during pregnancy increased the risk of mental disorders in the child with 14% for infections treated with anti-infective agents and with 38% for infections requiring hospitalization. Maternal infections during pregnancy treated with anti-infective agents displayed a higher risk than paternal infections, whereas there was no significant difference for infections requiring hospital contact. Furthermore, the risk estimates after maternal infections outside of the pregnancy period were similarly elevated compared to the risk after maternal infections during pregnancy. Maternal infections treated with anti-infective agents increased the risk with a dose-response relationship

both during pregnancy and outside the pregnancy period, whereas no dose-response relationships were observed for paternal infections.

Previous studies have shown conflicting results,[3,9–11,17,18] with some studies indicating that maternal infections during pregnancy could increase the risk of particularly schizophrenia[2–8,13] and autism;[19,20,22–24] however, this is the first study to investigate the risk of any mental disorder in the offspring. Bacterial infections during the first trimester have been associated with schizophrenia,[8] but a study by Nielsen et al.[13] found that the risk of schizophrenia in the child was similarly increased after maternal and paternal infections requiring hospital contacts before, during or after pregnancy. In addition, Blomström et al.[11] found an increased risk of psychosis associated with maternal infections requiring hospitalization five years prior to pregnancy and with maternal infections during pregnancy for mothers with mental disorders. Regarding the risk of autism, increased risks have been observed after viral infections during first trimester and bacterial infections during second trimester.[19] Furthermore, Zerbo et al.[22] found that maternal infection diagnosed during hospitalization in the pregnancy period was associated with autism spectrum disorders by an odds ratio of 1.48 (95%CI: 1.07-2.04). Our larger study found no vulnerable period depending on the timing of the parental infection based on pregnancy trimesters nor did we find a difference in the risk depending on bacterial or other origin of the infection. Although we also found similar risk estimates before, during and after pregnancy, we found maternal infections to increase the risk of mental disorders more than paternal infections treated in the primary sector. Specifically for schizophrenia spectrum disorders we only found maternal infections requiring hospitalization during pregnancy to increase the risk (Table 5).

Our findings as well as others[11,13] suggest that the associations between parental infections and higher risks of mental disorders in the offspring are not only due to a possible effect of the infections, inflammation or pregnancy complications due to infections, but could also partly be explained by shared genetic susceptibility to infections and mental disorders due to the similar risk estimates after infections outside the pregnancy period. Nevertheless, it could also be an epiphenomenon due to reduced immunity of the parents with poor living conditions, psychological stress,[39,40] lifestyle factors or medical-seeking behavior. However, all analyses were adjusted for parental level of education and parental psychiatric diagnoses capturing many important socioeconomic factors. Moreover, our investigation did not look into specific infections that during specific vulnerable periods potentially could influence the fetal neurodevelopment.

Strengths and limitations

This study is a nationwide register-based cohort study with the advantages of complete follow up and is not subject to recall bias. We had a large cohort yielding statistical power to investigate infections in specific vulnerable time periods, such as on a trimester basis. Furthermore, we were able to adjust for important confounders. However, untreated infections could not be included. Hence, we cannot exclude the consequences of untreated infections, as most viruses such as influenza are only rarely treated with anti-infective medications. Furthermore, we were not able to separate the treatment from the infection itself, so it is possible that the risk of mental disorders is associated with the medication rather than the infection. However, we found similarly increased risks before, during and after pregnancy indicating that the use of anti-infective agents during pregnancy is as safe as the use outside of the pregnancy period in regard to the future

mental health of the child. Lastly, our cohort was fairly young so the mental disorders were mainly within the spectrum of childhood and adolescence mental disorders, as the children were followed until a maximum age of 17 years. Hence, the estimates for the development of e.g. schizophrenia was based on a small subpopulation with early onset compared to the general population of individuals with schizophrenia and should therefore be interpreted with caution.

Conclusion and perspectives

We found similarly increased risks of mental disorders in the offspring after exposure to maternal infections both before, during and after pregnancy - indicating that the pregnancy period was not a period of particular risk. The risk of mental disorders was generally higher for maternal infections and for infections resulting in hospital contact. We found no vulnerable period depending on the timing of the parental infection based on pregnancy trimesters. Future studies need to investigate specific immune components during pregnancy together with shared genetic factors between infections and mental disorders.

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Image on front page: http://www.thimetis.com/learn-about-psychiatry/ (29.10.2017)

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TABLES AND FIGURES

Table 1: Maternal and paternal infections before, during or after pregnancy among 987,667 individuals. Numbers based on one or more prescription for anti-infective agents or hospital discharge diagnoses for infections pr. individual during the designated period. Number of individuals (%)

	Before pregnancy	*During pregnancy*	*After pregnancy*
		Maternal infections	
Prescriptions	443,673 (44.9)	449,904 (45.6)	467,643 (47.4)
Bacterial	382,990 (38.8)	414,762 (42.0)	415,805 (42.1)
Other	148,845 (15.1)	92,367 (9.4)	137,043 (13.9)
Hospitalizations	7,869 (0.8)	10,498 (1.1)	11,354 (1.2)
Bacterial	5,030 (0.5)	6,554 (0.7)	8,995 (0.9)
Other	3,133 (0.3)	4,283 (0.4)	2,634 (0.3)
		Paternal infections	
Prescriptions	278,044 (28.2)	280,824 (28.4)	285,548 (28.9)
Bacterial	230,758 (23.4)	233,709 (23.7)	243,014 (24.6)
Other	76,652 (7.8)	77,161 (7.8)	71,526 (7.2)
Hospitalizations	4,696 (0.5)	4,755 (0.5)	4,849 (0.5)
Bacterial	2,288 (0.2)	2,411 (0.2)	2,425 (0.3)
Other	2,549 (0.3)	2,483 (0.3)	2,610 (0.3)

Table 2: Risk of any mental disorder in offspring by maternal and paternal infections before, during or after pregnancy.

	Pre-pregnancy period		During pregnancy		Post-pregnancy period	
	No. cases	Fully adjusted HR (95% CI)[1]	No. cases	Fully adjusted HR (95% CI)[1]	No. cases	Fully adjusted HR (95% CI)[1]
Maternal infection treated with anti-infective agents						
No infection	16,074	1.00 (ref)	16,529	1.00 (ref)	15,684	1.00 (ref)
≥1 infection	17,538	**1.11** (1.09-1.13)*	17,083	**1.14** (1.11-1.16)*	17,928	**1.09** (1.07-1.11)*
Maternal infection requiring hospital contact						
No infection	33,133	1.00 (ref)	32,959	1.00 (ref)	32,976	1.00 (ref)
≥1 infection	479	**1.20** (1.09-1.31)*	653	**1.38** (1.28-1.50)*	636	**1.27** (1.17-1.38)*
Paternal infection treated with anti-infective agents						
No infection	23,423	1.00 (ref)	23,335	1.00 (ref)	22,963	1.00 (ref)
≥1 infection	10,189	1.01 (0.99-1.04)	10,277	1.01 (0.99-1.04)	10,649	**1.04** (1.02-1.07)*
Paternal infection requiring hospital contact						
No infection	33,347	1.00 (ref)	33,330	1.00 (ref)	33,335	1.00 (ref)
≥1 infection	265	1.19 (1.06-1.35)	282	**1.24** (1.10-1.39)*	277	1.18 (1.05-1.33)

[1]Adjusted for sex, birth year, concurrent infection in the other parent, parental infections outside the time period, parental level of education at childbirth, parental age at childbirth, any parental psychiatric diagnoses at childbirth (ICD-10: F00-F99).

* = Significant after adjustment for multiple comparisons

Table 3: Risk of any mental disorder in offspring by maternal and paternal infections during 1st, 2nd and 3rd trimester of pregnancy.

	First trimester		Second trimester		Third trimester	
	No. cases	Fully adjusted HR (95% CI)[1]	No. cases	Fully adjusted HR (95% CI)[1]	No. cases	Fully adjusted HR (95% CI)[1]
Maternal infection treated with anti-infective agents						
No infection	26,159	1.00 (ref)	25,392	1.00 (ref)	25,205	1.00 (ref)
≥1 infection	7,453	**1.07** (1.04-1.09)*	8,220	**1.12** (1.09-1.14)*	8,407	**1.10** (1.08-1.13)*
Maternal infection requiring hospital contact						
No infection	33,458	1.00 (ref)	33,398	1.00 (ref)	33,292	1.00 (ref)
≥1 infection	154	**1.28** (1.09-1.50)*	214	**1.42** (1.24-1.62)*	320	**1.37** (1.23-1.53)*
Paternal infection treated with anti-infective agents						
No infection	29,621	1.00 (ref)	29,157	1.00 (ref)	29,255	1.00 (ref)
≥1 infection	3,991	1.02 (0.99-1.06)	4,455	1.01 (0.98-1.04)	4,357	0.99 (0.95-1.02)
Paternal infection requiring hospital contact						
No infection	33,525	1.00 (ref)	33,513	1.00 (ref)	33,504	1.00 (ref)
≥1 infection	87	1.20 (0.97-1.49)	99	1.18 (0.97-1.44)	108	**1.33** (1.10-1.61)*

[1]Adjusted for sex, birth year, concurrent infection in the other parent, parental infections outside the time period, parental level of education at childbirth, parental age at childbirth, any parental psychiatric diagnoses at childbirth (ICD-10: F00-F99).

* = Significant after adjustment for multiple comparisons

Table 4: Risk of any mental disorder in offspring by maternal and paternal infections divided into bacterial or other infections during 1st, 2nd and 3rd trimester of pregnancy.

	First trimester		Second trimester		Third	
	No. cases	Fully adjusted HR (95% CI)[1]	No. cases	Fully adjusted HR (95% CI)[1]	No. cases	Fully adjusted HR (95% CI)[1]
Maternal						
Prescription Antibacterial	6,498	**1.06** (1.03-1.09)*	7,498	**1.12** (1.09-1.15)*	7,652	**1.10** (1.07-1.13)*
Prescription Other	1,599	**1.09** (1.04-1.15)*	1,324	**1.07** (1.01-1.13)	1,357	**1.11** (1.05-1.17)*
Hospital contact Bacterial	90	**1.28** (1.04-1.57)	121	**1.51** (1.26-1.80)*	234	**1.42** (1.25-1.62)*
Hospital contact Other	69	**1.31** (1.03-1.66)	96	**1.28** (1.04-1.56)	90	1.23 (1.00-1.51)
Paternal						
Prescription Antibacterial	3,303	**1.05** (1.01-1.09)	3,620	1.01 (0.98-1.05)	3,606	1.01 (0.98-1.05)
Prescription Other	908	0.95 (0.89-1.01)	1,105	1.00 (0.94-1.07)	1,019	**0.93** (0.87-0.99)
Hospital contact Bacterial	42	1.14 (0.84-1.55)	42	0.97 (0.72-1.32)	53	1.25 (0.95-1.63)
Hospital contact Other	47	1.25 (0.94-1.66)	59	**1.40** (1.09-1.81)	55	**1.37** (1.05-1.79)

Reference (HR=1.00) is children with no maternal/paternal infection treated with anti-infective agents/requiring hospital contacts during the specified time period.

[1]Adjusted for sex, birth year, concurrent infection in the other parent, parental infections outside the time period, parental level of education at childbirth, parental age at childbirth, any parental psychiatric diagnoses at childbirth (ICD-10: F00-F99).

* = Significant after adjustment for multiple comparisons

Table 5: Risk of specific categories of mental disorders in the offspring after exposure to maternal or paternal infections before, during or after pregnancy.[a,b]

	No. cases	Schizophrenia disorders F20-29	No. cases	Anxiety disorders F40-49	No. cases	Developmental disorders F80-89	No. cases	Behavioural and emotional disorders F90-99
Total no. cases		245		4,756		9,875		15,489
Before pregnancy								
Maternal *Prescriptions*	131	1.05 (0.81-1.36)	2639	**1.15*** (1.08-1.22)	4692	0.99 (0.95-1.03)	8347	**1.19*** (1.15-1.23)
Hospital contacts	-	-	87	**1.60*** (1.29-1.98)	128	1.32 (1.11-1.57)	224	1.21 (1.06-1.38)
Paternal *Prescriptions*	66	0.81 (0.61-1.08)	1532	1.05 (0.99-1.13)	2838	0.98 (0.94-1.03)	4760	1.02 (0.99-1.06)
Hospital contacts	-	-	42	1.33 (1.00-1.85)	73	1.32 (1.05-1.67)	117	1.15 (0.96-1.37)
During pregnancy								
Maternal *Prescriptions*	121	1.05 (0.81-1.36)	2448	**1.13*** (1.06-1.20)	4843	**1.13*** (1.08-1.18)	8031	**1.15*** (1.12-1.19)
Hospital contacts	10	**3.22*** (1.70-6.10)	92	**1.46*** (1.19-1.80)	171	**1.43*** (1.23-1.67)	328	**1.48*** (1.33-1.66)
Paternal *Prescriptions*	84	1.25 (0.95-1.65)	1523	1.05 (0.99-1.12)	2840	0.96 (0.92-1.01)	4881	1.05 (1.01-1.08)
Hospital contacts	-	-	38	1.27 (0.92-1.74)	70	1.21 (0.96-1.54)	150	**1.43*** (1.21-1.68)
After pregnancy								
Maternal *Prescriptions*	134	1.07 (0.82-1.38)	2681	**1.15*** (1.08-1.22)	4923	1.01 (0.97-1.06)	8451	**1.14*** (1.10-1.17)
Hospital contacts	6	1.77 (0.78-3.98)	82	1.23 (0.98-1.53)	194	**1.48*** (1.29-1.71)	301	**1.31*** (1.17-1.47)
Paternal *Prescriptions*	76	0.99 (0.75-1.31)	1596	1.11 (1.04-1.18)	2964	1.00 (0.96-1.05)	4983	1.05 (1.02-1.09)
Hospital contacts	-	-	37	1.14 (0.83-1.58)	73	1.25 (0.99-1.58)	139	1.32 (1.11-1.55)

[a]Adjusted for sex, birth year, concurrent infection in the other parent, parental level of education at childbirth, parental age at childbirth, any parental psychiatric diagnoses at childbirth (ICD-10: F00-F99).

[b]Reference (HR=1.00) is children with no maternal/paternal infection treated with anti-infective agents/requiring hospital contacts during the specified time period.

- = Risk estimate not available due to few cases

* = p<0.001, significance-level after adjustment for multiple comparisons.

Figure 1A: Risk of any mental disorder in the child depending on the number of parental infections treated with anti-infective agents during pregnancy

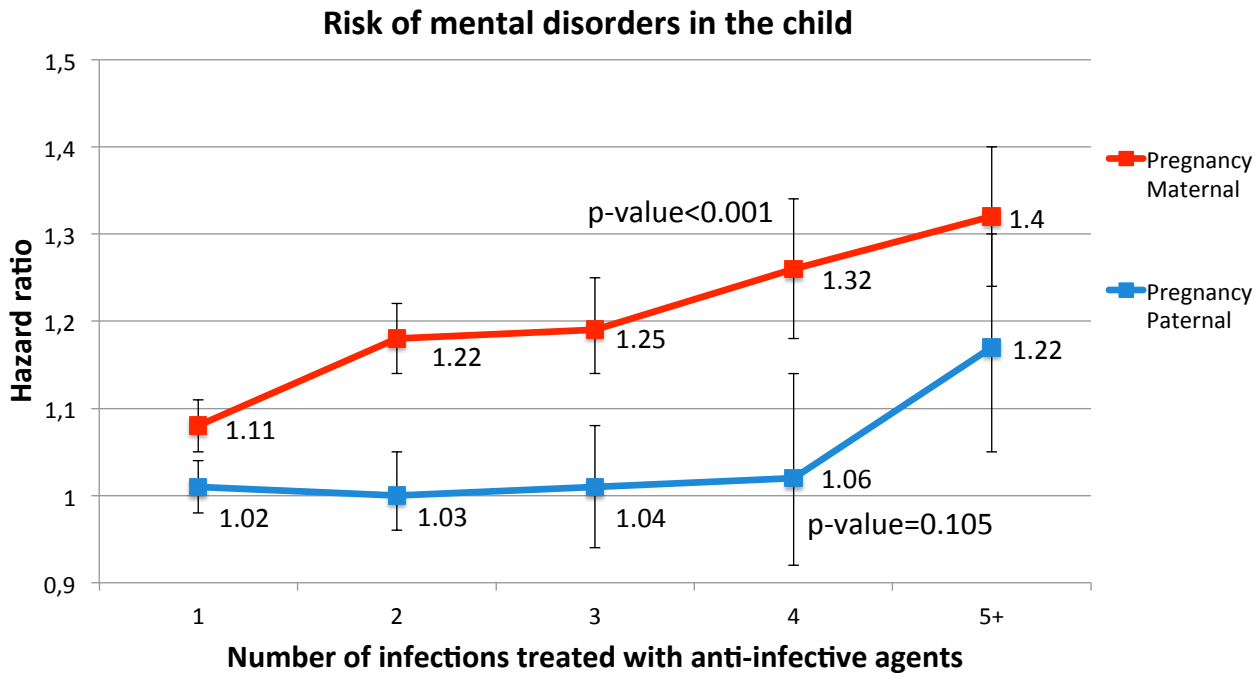

Figure 1B: Risk of any mental disorder in the child depending on the number of parental infections treated with anti-infective agents before, during or after pregnancy.