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Please cite the final published version:

Dreier, J. W., Berg-Beckhoff, G., Andersen, A-M. N., Susser, E., Nordentoft, M., & Strandberg-Larsen, K. (2017). Fever and infections during pregnancy and psychosis-like experiences in the offspring at age 11. A prospective study within the Danish National Birth Cohort. *Psychological Medicine*, 48(3), 426-436.
<https://doi.org/10.1017/S0033291717001805>

Publication metadata

Title:	Fever and infections during pregnancy and psychosis-like experiences in the offspring at age 11. A prospective study within the Danish National Birth Cohort
Author(s):	Dreier, J. W., Berg-Beckhoff, G., Andersen, A-M. N., Susser, E., Nordentoft, M., & Strandberg-Larsen, K.
Journal:	<i>Psychological Medicine</i>
DOI/Link:	10.1017/S0033291717001805
Document version:	Accepted manuscript (post-print)
Document license:	<i>[If the document is published under a Creative Commons, enter link to the license here]</i>

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Title page

Word count: 3871

Figures: 1

Tables: 4

E-table: 2

Manuscript title: Fever and infections during pregnancy and psychosis-like experiences in the offspring at age 11. A prospective study within the Danish National Birth Cohort

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Abbreviated title: Fever and infections during pregnancy and psychosis-like experiences in the offspring

Acknowledgements: The Danish National Birth Cohort was established with a significant grant from the Danish National Research Foundation. Additional support was obtained from the Danish Regional Committees, the Pharmacy Foundation, the Egmont Foundation, the March of Dimes Birth Defects Foundation, the Health Foundation and other minor grants. The DNBC Biobank has been supported by the Novo Nordisk Foundation and the Lundbeck Foundation.

Follow-up of mothers and children have been supported by the Danish Medical Research Council (SSVF 0646, 271-08-0839/06-066023, O602-01042B, 0602-02738B), the Lundbeck Foundation (195/04, R100-A9193), The Innovation Fund Denmark 0603-00294B (09-067124), the Nordea Foundation (02-2013-2014), Aarhus Ideas (AU R9-A959-13-S804), University of Copenhagen Strategic Grant (IFSV 2012), and the Danish Council for Independent Research (DFF – 4183-00594 and DFF - 4183-00152).

Financial support

This research received no specific grant from any funding agency, commercial or not-for-profit sectors.

Conflicts of interest

None

Abstract

Background

Maternal exposures to fever and infections in pregnancy have been linked to subsequent psychiatric morbidity in the child. This study examined whether fever and common infections in pregnancy were associated with psychosis-like experiences in the child.

Methods

A longitudinal study of 46,184 children who participated in the 11-year follow-up of the Danish National Birth Cohort was conducted. Pregnant women were enrolled between 1996 and 2002 and information on fever, genitourinary infections, respiratory tract infection, and influenza-like illness during pregnancy was prospectively collected in two interviews during pregnancy. Psychosis-like experiences were assessed using the seven-item Adolescent Psychotic-Like Symptom Screener in a web-based questionnaire completed by the children themselves at age 11.

Results

Psychosis-like experiences were reported among 11% of the children. Multinomial logistic regression models with probability weights to adjust for potential selection bias due to attrition suggested that maternal fever, genitourinary infections and influenza-like illness were associated with a weak to moderate increased risk of subclinical psychosis-like symptoms in the offspring, whereas respiratory tract infections were not. No clear pattern was observed between the strengths of the associations and the timing of exposure, or the type of psychosis-like symptom.

Conclusions

In this study, maternal exposures to fevers and common infections in pregnancy were generally associated with a subtle excess risk of psychosis-like experiences in the child. A more pronounced association was found for influenza-like illness under an a priori definition, leaving open the possibility that certain kinds of infections may constitute important risk factors.

Introduction

Fever and infection during pregnancy have been associated with a range of psychiatric conditions in the offspring, such as schizophrenia, depression and autism (Kim et al., 2015, Bale et al., 2010). These associations are evident for conditions in which it is unlikely that the fetus was directly infected. This raises the possibility that fetal brain development may be disrupted when the mother (but not the fetus) is exposed to an infectious agent, and that this disruption may ultimately contribute to psychiatric disorder in the child. Although the underlying mechanisms for such effects are poorly understood, some animal models and other lines of evidence have generated a plausible theory, that is, the maternal responses common for various infections in pregnancy, such as maternal inflammation or fever, may impact fetal neurodevelopment (Zhou, 2012, Flinkkila et al., 2016). Around 25% of pregnant women experience at least one episode of fever during pregnancy, and approximately 60% are exposed to infections (Collier et al., 2009, Werenberg Dreier et al., 2016). Given that these exposures are highly common in pregnancy, it is of interest to consider whether the reported associations with offspring psychiatric diagnoses are evident for other measures of psychiatric morbidity as well.

Psychosis-like experiences (PLEs), such as brief hallucinations, delusional ideas and unusual thought content are considered as early markers or sub-clinical expressions of psychosis (van Os et al., 2009). In comparison with clinical psychotic disorders, PLEs are expressed in a much larger part of the population. A meta-analysis of studies in non-clinical samples showed that the median prevalence of such symptoms among 9-12 year old children was 17% (Kelleher et al., 2012a). Although the prognostic value of PLEs is still to be fully understood, children exhibiting these symptoms are believed to be at increased vulnerability for psychiatric morbidity in later life (van Os and Linscott, 2012, Linscott and van Os, 2012, Kaymaz et al., 2012). Also, even in the absence of progression to clinical psychopathology, PLEs are strongly linked to poor psychosocial outcomes and self-harming behavior (Fonville et al., 2015, Nishida et al., 2010, Kelleher et al., 2012b).

One previous study in children from the Avon Longitudinal Study of Parents and their Children (ALSPAC) study showed an approximately 40% increased risk of PLEs at age 12 following exposure to any maternal infection in pregnancy (Zammit et al., 2009). The aim of this study was to add to this sparse literature by

examining whether fever and common infections during pregnancy increases the risk of PLEs at age 11 in the children from the Danish National Birth Cohort (DNBC). We focused on fever per se, and on genitourinary infections, respiratory infections, and influenza-like illness.

Methods

Study population

The DNBC is a nation-wide cohort of mother-child dyads (Olsen et al., 2001). Pregnant women were enrolled during 1996-2002 by their general practitioners at their first antenatal visit, which is scheduled to take place around gestational weeks 6-10. Inclusion criteria for enrollment into the DNBC were intention to carry the pregnancy to term, residency in Denmark, and sufficient Danish proficiency to participate in telephone-interviews. The women were interviewed twice during pregnancy (approximately at gestational week 16 and 30), and provided information about their health and lifestyle. Continuous follow up of their children is still ongoing (Statens Serum Institut, 2016). A total of 94 593 live-born children were eligible for inclusion in this study. The analyses are based on 46 184 children participating in the 11-year follow-up and not missing $\geq$ three PLE questions, see **Figure 1**. Written informed consent was obtained from all mothers at time of enrollment and this study has been approved by the Danish Data Protection Agency (Journal number: 2013-41-1431)

INSERT FIGURE 1

Psychosis-like experiences

Psychosis-like symptoms were assessed in a web-based questionnaire completed by the children themselves at age 11. A seven-item Adolescent Psychotic-Like Symptom Screener (Kelleher et al., 2011), partly based on the Diagnostic Interview Schedule for Children (Shaffer et al., 2000) was devised to address experiences of visual and auditory hallucinations, thought interference, receiving messages from the radio or television, being spied on, being controlled and grandiosity. The questions were generally phrased as “Have you ever heard voices or sounds that no one else can hear?” and they were able to answer “yes, definitely”, “yes, I think so” and “no”. PLEs were analyzed as a summarized variable according to the presence or absence of any definite symptoms. Children were subsequently grouped as having reported none, one or $\geq$ two definite

symptoms. If one or two responses were missing for the seven items (n=861), these missings were coded as the most common response to that particular item (“no”, for all items).

Maternal fever and infections

Maternal episodes of fever and infections during pregnancy were reported in the two pregnancy interviews. The questions for fever, for instance, were formulated as “In this pregnancy, have you had any episodes of fever?” A fetus was considered as exposed if the mother in any of the two interviews answered yes to that question. Exposure to genitourinary infections was defined by maternal report of cystitis, pyelonephritis or vaginal infections and respiratory tract infection was defined by prolonged cough. The woman could report multiple exposure episodes of fever and each infection and timing of each episode was reported in gestational weeks. For fever episodes, the maximum recorded temperature (in °C) was reported as well. Given that an influenza diagnosis is rarely confirmed and self-diagnosis has poor predictive value (Jutel et al., 2011), women were not asked directly about their exposure to influenza. Instead, we a priori decided to define a fever-episode accompanied by headache and muscle or joint pain as a case of influenza-like illness. While exposure to influenza-like illness was considered as a sub-group of women experiencing fevers, the other infections were defined independently of fever exposure.

Covariates

Inclusion of covariates was informed by existing literature and based on several sources of information. Maternal age at birth was extracted from the Danish Medical Birth Registry (Knudsen and Olsen, 1998), through linkage using the mother’s civil registration number. Maternal educational status was based on the highest level of completed education listed in the Population’s Education Register (Jensen and Rasmussen, 2011). If the mother was enrolled at an educational institution at the time of giving birth, the highest ongoing education was used. We extracted the household income in the year prior to the year of birth from the Income Statistics Register (Baadsgaard and Quitzau, 2011) and parental secondary mental health care was based on registered contacts to psychiatric departments between 1977 until 2010, extracted from the Danish Psychiatric Central Research Register (Mors et al., 2011). Maternal report of smoking during pregnancy and number of children in the household was assessed in the first pregnancy interview. If smoking status was missing (~4% of pregnancies) we used information from the Medical Birth Registry. In the Medical Birth

Registry, smoking habits in early pregnancy is recorded, based on the first consultation with a midwife, which usually takes place around gestational week 16-17. Finally, place of birth as listed in the Medical Birth Registry was divided into five levels of urbanization (capital, capital suburb, provincial city with more than 100,000 inhabitants, provincial towns with more than 10,000 inhabitants, and rural areas), as described elsewhere (Pedersen and Mortensen, 2001).

Other variables

In order to compare general rates of psychiatric morbidity among children who participated in the 11 year follow-up with children lost to follow-up, we additionally used the Danish Psychiatric Central Research Register to extract all contacts with the psychiatric system for all live-born children in the DNBC.

Statistical analyses

Multinomial logistic regression models were used to calculate adjusted relative risk ratios (RRR) and corresponding 95% confidence intervals (Cis) for the associations between exposures to fevers and infections in pregnancy and PLEs in the child at age 11. The children with no definite PLEs were considered the reference group in all models.

Initially, exposures to fever, genitourinary infections, respiratory infections, and influenza-like illness at any time during pregnancy were analyzed. Fever episodes were additionally analyzed according to the reported maximum temperature of the fever ($<39^{\circ}\text{C}$, $\geq 39^{\circ}\text{C}$, or unknown) in order to examine potential dose-response effects. Next, we considered the timing of exposures, according to trimester (1st trimester: gestational week 1-12 and 2nd trimester: gestational week 13-28). A woman was only included in the trimester-specific analyses if exposure information on the entire trimester of interest was available (i.e. the timing of her last interview exceeded the last gestational week in the trimester). Because the last interview was scheduled to take place at approximately gestational week 30, we did not estimate effects of third trimester exposure. To determine whether potential effects were similar across the different types of psychosis-like symptoms, we then examined how the prenatal exposures were associated with each specific PLE, for probable and definite symptoms, respectively. Finally, as a sensitivity analysis we furthermore examined alternative case-definitions of influenza-like illness.

In this study nearly half of the 94,593 eligible children did not participate in the 11-year follow-up. We expected that loss to follow-up was differential on several important characteristics. To evaluate to what extent such selection biased our results we compared the original analyses with analyses using weights to correct for loss to follow-up (Seaman and White, 2013). In essence, we estimated a weight for each child, proportional to the inverse probability that he or she participated in the follow-up, given the specified covariates. The rationale was that children remaining in the study, but with a low chance according to the model of doing so (for instance because they had a mental illness), were given a higher weight, so that they were not only representing themselves, but also children like them, that did not participate in the 11-year follow-up. The weights were estimated using a logistic regression model ($n= 94\,593$) and aimed to include all relevant variables that predicted follow-up status. The model was based on information on maternal age, maternal education, household income, parental and child secondary mental health care, maternal smoking in pregnancy, and urbanization.

All analyses were performed with Stata (StataCorp, College Station,Texas) and using robust standard errors to correct for the dependency between siblings in the sample.

Results

Prenatal exposures to episodes of fever and infections were relatively common among children participating in the 11-year follow-up of the DNBC. Twenty-seven percent of the children were prenatally exposed to fever, while influenza-like illness, genitourinary infections and prolonged cough occurred in 3.5%, 25.5% and 14.9% of the pregnancies, respectively (see **Table 1**). The frequency of these prenatal exposures did not differ substantially between children who participated in the 11-year follow-up and those who did not. Being lost to follow-up was however associated with young maternal age at birth, lower maternal education and income, higher maternal smoking, and whether parents or the child itself had any registered contacts to a psychiatric department.

INSERT TABLE 1

Prevalence of specific psychotic experiences among the children varied substantially, see **Table 2**. Auditory hallucinations and the feeling of being spied on were the two most common PLEs with around one in four children reporting that they definitely or probably had experienced such symptoms. Contrarily <3% reported having definitively or probably received messages from the television or radio and <7% reported that they were controlled by external forces. Generally, reporting of definite symptoms was much less frequent, than probable symptoms, and 89% of the children did not report any definite symptoms at all, while 7% reported one and 4% reported $\geq$ two definite symptoms.

INSERT TABLE 2

The multinomial logistic models showed that prenatal fevers and infections were generally associated with a low to moderate excess risk of PLEs in the children at age 11 (**Table 3**). Maternal fever was associated with a slightly elevated risk of PLEs in the child for one definite PLE (RRR: 1.13, 95% CI: 1.04-1.23), but not to a larger extent for $\geq$ two (RRR: 1.09, 95% CI: 0.97-1.21). High fevers showed a slightly stronger association with PLEs than low fevers, but the number of women with high fevers was small and neither of these associations were statistically significant. The association was strongest for unknown fever temperatures, but all associations were somewhat attenuated in the weighted analyses, suggesting that attrition may have biased these estimates somewhat upwards. Genitourinary infections were likewise marginally associated with the child's report of PLEs, with the association being slightly stronger for $\geq$ two definite PLEs (RRR: 1.15, 95% CI: 1.04-1.29), than for one, (RRR: 1.07, 95% CI: 0.98-1.16). No association was observed for respiratory tract infections, but influenza-like illness in pregnancy was associated with an approximately 40% increased risk of the child having experienced two or more PLEs at age 11. In the sensitivity analyses, where we examined the same association, but where influenza-like illness was defined using other combinations of fever and influenza symptoms, this associations was however reduced or entirely removed (**e-Table 1**).

INSERT TABLE 3

Further analyses revealed that the observed associations between PLEs following prenatal exposures to fever and the various infections did not seem to be strongly dependent on the trimester of exposure (**e-Table 2**). The point estimates did vary somewhat and tended to be highest for first-trimester exposure. However, none of these associations reached statistical significance.

When we considered each PLE independently, we observed that the associations found in the overall analyses were not limited to any particular symptom(s) (**Table 4**). Some PLEs (e.g. involving auditory hallucinations and feelings of paranoia) were, however, more consistently associated with the prenatal exposures of interest, than others (e.g. receiving messages from the radio/television and having their thoughts read). The strongest associations were generally found for prenatal exposure to influenza-like illness, but also exposure to fever, genitourinary infections and respiratory infections showed associations with several of the individual PLEs. Across most symptoms there were a tendency that associations were stronger for definite symptoms compared to probable symptoms, although this was not entirely consistent.

INSERT TABLE 4

Discussion

In this large prospective study among children at age 11, we found some evidence of a modest association between prenatal exposures to fever and common infections and the occurrence of PLEs during childhood. We found that maternal fever and genitourinary infections at any point in pregnancy were associated with a slightly increased risk of PLEs at age 11 (about 10-15%). Respiratory tract infections were not associated with PLEs in general, but was weakly associated with specific symptoms. Finally, our results suggested that under an a priori definition of influenza-like illness, there were a more substantial association with offspring PLEs, but these results were very sensitive, to how influenza-like illness was defined.

Our findings are somewhat, but not entirely in line with those reported from the ALSPAC study (Zammit et al., 2009). The authors found that a range of maternal infections were associated with PLEs (odds ratio: 1.44, 95% CI: 1.14-1.86), but found that influenza during any time of pregnancy was not associated more, or less, strongly with PLEs in the child, than having other non-influenza infections. These findings were consistent

with the theory that adverse effects of prenatal maternal infections may not be pathogen-specific, but rather, related to a maternal response that is seen in multiple infections. In our study, however, we found some indication that influenza during pregnancy, more so than other infections, was associated with the risk of sub-clinical psychotic symptoms during childhood, at least when our a priori definition of influenza-like illness was used. While the strength of the association with influenza-like illness was comparable to that found in the ALSPAC study, those found for fever and genitourinary infections were more modest. The different findings might be attributed to methodological differences, such as differences in sample size ($n = 5379$ vs. $n = 46,184$ in our study), different means of data collection for maternal exposures (postal questionnaire vs. telephone interview in our study), or differences in measurement of PLEs (the PLIKSi semi-structured interview vs. the web-based Adolescent Psychotic-Like Symptom Screener in ours).

To our knowledge, this is the first study that specifically addresses maternal fever in pregnancy in relation to childhood PLEs. While there is some evidence to suggest that elevated maternal body temperature during pregnancy may indeed cause neurodevelopmental impairment in the offspring (Dreier et al., 2014) and even psychosis (Jones et al., 1998, Torrey et al., 2000), our findings did not suggest that prenatal fever exposure constitute a substantial risk factor for childhood PLEs. In fact, given that we did not observe a clear dose-response relationship with fever temperature, might indicate that the underlying infection rather than the fever itself was responsible for the small excess risks that we did observe. Another potential explanation for the weak, but positive findings for fever and also genitourinary infections in this study, is that PLEs act as proxies for more severe mental illness. Under this scenario, effects would be expected to be small, because children exhibiting PLEs consists of a mix of children that will go on to develop an actual clinical psychiatric disorder and children that will not. It is consequently possible that the associations, may not represent actual causal effects for PLEs, but rather reflect stronger underlying associations with specific clinical disorders, associated with PLEs (for instance schizophrenia or depression). As the children in the DNBC reaches young adulthood in the years to come, this could be a priority for further studies.

In contrasts to what we expected, we did not find that the associations between prenatal infections and PLEs were dependent on the timing of exposure. Much of the literature linking prenatal infections to psychiatric morbidity have suggested that these effects were often trimester-specific, although both early and mid-

pregnancy has been proposed as the most critical period (Brown et al., 2004, Brown and Derkits, 2010, Meyer et al., 2007, Martin and Dombrowski, 2008). It is however, possible that we were not able to detect any variation in effect across pregnancy, given that the effects that we observed were relatively small and the statistical power in these analyses was limited.

In this study we examined seven different symptoms of sub-clinical psychosis, that were part of the Adolescent Psychotic-Like Symptom Screener. We found that a total of 11% of the children in the DNBC follow-up reported at least one definite PLE. Compared to population-based estimates, this is probably somewhat lower, given that children with mental health problems were less likely to participate in the 11-year follow-up. The prevalence of the seven different PLEs varied substantially, with auditory hallucinations being the most common phenomenon reported by the children with definite psychosis-like symptoms. These findings are similar to that reported in other studies (Polanczyk et al., 2010, Kelleher et al., 2011). No clear pattern was however found in how the prenatal exposures were associated with the specific symptoms of psychosis, although the more prevalent symptoms also showed more consistency in the link to the prenatal exposures.

The clinical relevance of PLEs in childhood has been widely debated and several issues has been raised. First of all, although the presence of PLEs may predict onset of psychiatric illness, in most children the symptoms will resolve, rather than evolve (Nelson et al., 2012). This suggests that PLEs do not generally constitute a persisting problem for a majority of the children affected. However increasing frequency and pervasiveness of the symptoms have been shown to be more strongly associated with progression to clinical psychopathology (Yung et al., 2009, Nelson et al., 2012). In this study we did, however, not have any information regarding the frequency of the symptoms or whether the child was distressed by the occurrences. A second issue, is the specificity of PLEs as markers of psychiatric disorders. Evidence suggest that, although PLEs are measures of mild or brief psychotic symptoms, they do not seem to be more strongly associated with subsequent development of psychotic disorders than with other psychiatric conditions (Kelleher et al., 2012a, Hanssen et al., 2003). Instead, they have been suggested to constitute a measure of general psychopathology (Nelson et al., 2012). Finally, some studies have questioned whether endorsement in screening instruments, such as the one used in this study, accurately predict actual psychosis-like symptoms, when not followed up by probing

questions, for instance in a clinical interview (Horwood et al., 2008, Laurens et al., 2007). To overcome this issue, at least in part, we focused primarily on the children reporting definite symptoms (rather than probable), and also distinguished between children with one or multiple PLEs, as any issues with misclassification is likely to be lower among these children. A recent validation study using clinical interviews did additionally conclude that the Adolescent Psychotic-like Symptom Screener did in fact provide good sensitivity and specificity in identifying young adolescents in the general population with PLEs (Kelleher et al., 2011).

Several important strengths of this study are worth noting. Given the comprehensiveness of the information that were available on fever and common infections in pregnancy, we were able to conduct detailed sub-analyses examining, for instance, the effects of exposure timing and temperature of fevers. Furthermore, as all information on maternal exposures were collected during pregnancy, any missing information or flawed recall was most likely independent of the future outcome in the child. A further strength of this study, was the ability to adjust all analyses for a host of potential confounders, including maternal sociodemographic characteristics, health-related conditions, as well as lifestyle during pregnancy.

Attrition was, however, relatively high. To correct for selective attrition, we conducted a range of weighted sensitivity analyses, which allowed us to assess the extent of any potential bias. One major advantage in the specification of these weights was the inclusion of an indicator for childhood secondary mental health care. This auxiliary variable was strongly associated with follow-up status as well as PLEs, which increases the accuracy of the corrected estimates in weighted models and make the missing at random assumption more plausible (National Research Council (US) Panel on Handling Missing Data in Clinical Trials, 2010). The measures of association were generally only slightly attenuated in the weighted analyses, suggesting that loss to follow-up did not bias our results in any substantial manner. This was most likely due to the fact that attrition seemed to be largely independent of prenatal exposure status.

Another important limitation was that all measures of exposures were based on maternal self-report. However, given that the assessments were carried out during pregnancy, the women only had to recall exposures that were 2-4 months back in time, which heightens the accuracy of recall. Use of serologic data on maternal levels of immunoglobulin M and G could nevertheless potentially improve exposure classification in future research.

Using hospital records to examine the influence of more severe infections during pregnancy could similarly improve our understanding of the possible link between these infections and PLEs in childhood. Finally, we examined the associations between many different exposures, and with PLEs individually and combined, resulting in large number of statistical tests. Thus, we cannot exclude that some of our positive findings are simply due to multiple testing.

In conclusion, in this large prospective study, fever and a range of common infections in pregnancy generally showed weak but positive associations with sub-clinical psychotic symptoms in the offspring. Our findings regarding influenza-like illness furthermore suggested that it may be especially relevant to further consider the role of prenatal influenza in future research on PLEs.

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Table 1: Characteristics of DNBC participants according to follow-up status at age 11.

Characteristics	Study population	Lost to follow-up	p-value
	<i>N</i> = 46 184 n (%)	<i>N</i> = 45 262 n (%)	
Maternal age at birth			< 0.001
≤24 years	4613 (10.0)	6969 (15.4)	
25-29 years	19 133 (41.4)	18 514 (40.9)	
30-34 years	16 543 (35.8)	14 863 (32.8)	
≥ 35 years	5895 (12.8)	4916 (10.9)	
Maternal education at birth			< 0.001
Primary education	3401 (7.4)	6932 (15.3)	
Secondary education	17 997 (39.0)	20 969 (46.3)	
Higher education	24 730 (53.6)	17 217 (38.0)	
Missing	56 (0.1)	144 (0.3)	
Household income in year prior to birth			< 0.001
Lowest quintile	8440 (18.3)	9738 (21.5)	
2 nd quintile	8567 (18.6)	9568 (21.1)	
Medium	9048 (19.6)	9169 (20.3)	
4 th quintile	9804 (21.2)	8383 (18.5)	
Highest quintile	10 080 (21.8)	8130 (18.0)	
Missing	245 (0.5)	274 (0.6)	
Maternal smoking in pregnancy			< 0.001
Nonsmokers	36 241 (78.5)	31 636 (69.9)	
Former smokers	4061 (8.8)	4245 (9.4)	
Light smokers (1-9 cigarettes/day)	3489 (7.6)	4858 (10.7)	
Heavy smokers (>10 cigarettes/day)	2341 (5.1)	4465 (9.9)	
Missing	52 (0.1)	58 (0.1)	
Children in household at birth			< 0.001
0	21 066 (45.6)	19 624 (43.4)	
1	16 304 (35.3)	16 551 (36.6)	
≥2	7069 (15.3)	7043 (15.6)	
Missing	1745 (3.8)	2044 (4.5)	
Urbanization			< 0.001
Copenhagen	6211 (13.5)	5225 (11.5)	
Sub-urban Copenhagen	5185 (11.2)	5228 (11.6)	
Provincial cities	6508 (14.1)	5635 (12.5)	
Provincial towns	13 329 (28.9)	13 306 (29.4)	
Rural areas	14 918 (32.3)	15 803 (34.9)	
Missing	33 (0.1)	65 (0.1)	
Parental secondary mental health care	4367 (9.5)	6601 (14.6)	< 0.001
Child secondary mental health care	1258 (2.7)	2393 (5.3)	< 0.001
Prenatal exposure			
Fever	12 475 (27.0)	12 541 (27.7)	0.013
Influenza-like illness ^a	1622 (3.5)	1653 (3.7)	0.240
Genitourinary infection	11 769 (25.5)	11 377 (25.1)	0.016
Prolonged cough	6895 (14.9)	6658 (14.7)	0.092

^a Influenza-like illness was defined a priori as episodes of fever with headache and muscle or joint pain

Table 2: Prevalence of psychosis-like experiences in 46 101 children in the 11-year follow-up of the DNBC

Psychosis-like experience	Yes, definitely	Yes, I think so	No
Having one's mind read	453 (1.0)	3286 (7.1)	42 445 (91.9)
Received messages from radio/TV	331 (0.7)	735 (1.6)	45 118 (97.7)
Being followed or spied on	2157 (4.7)	9484 (20.5)	34 543 (74.8)
Heard voices that no one else can hear	2779 (6.0)	7512 (16.3)	35 893 (77.7)
Being controlled by external forces	540 (1.2)	2511 (5.4)	43 133 (93.4)
Seen things that no one else can see	1293 (2.8)	3908 (8.5)	40 983 (88.7)
Having supernatural powers	884 (1.9)	3221 (7.0)	42 079 (91.1)

Table 3: Multinomial logistic regression of prenatal fever and infection exposures and reporting of definite psychosis-like experiences at age 11.^a Analyses of original and weighted data. DNBC, $n=46\,184$.

Prenatal exposure	n^b	Reporting of definite psychosis-like experiences			
		Original data (unweighted analyses)		Weighted analyses ^d	
		1 PLE	≥ 2 PLEs	1 PLE	≥ 2 PLEs
		RRR ^c (95 % CI)	RRR ^c (95 % CI)	RRR ^c (95 % CI)	RRR ^c (95 % CI)
Fever					
No	33 626	ref.	ref.	ref.	ref.
Yes	12 475	1.13 (1.04-1.23)	1.09 (0.97-1.21)	1.12 (1.03-1.22)	1.06 (0.95-1.19)
Max temperature during fever					
No fever	33 626	ref.	ref.	ref.	ref.
<39 °C	3460	1.02 (0.89-1.18)	0.90 (0.74-1.10)	1.02 (0.89-1.18)	0.91 (0.73-1.11)
≥ 39 °C	2772	1.10 (0.94-1.27)	1.14 (0.94-1.38)	1.07 (0.91-1.25)	1.12 (0.92-1.37)
Temperature unknown	6243	1.21 (1.09-1.34)	1.17 (1.01-1.34)	1.20 (1.08-1.34)	1.12 (0.97-1.29)
Genitourinary infection					
No	31 517	ref.	ref.	ref.	ref.
Yes	11 769	1.07 (0.98-1.16)	1.15 (1.04-1.29)	1.04 (0.95-1.13)	1.17 (1.04-1.31)
Respiratory tract infection					
No	36 790	ref.	ref.	ref.	ref.
Yes	6895	1.02 (0.92-1.13)	1.04 (0.91-1.19)	1.03 (0.93-1.15)	1.07 (0.93-1.23)
Influenza-like illness					
No	44 479	ref.	ref.	ref.	Ref.
Yes	1622	1.16 (0.96-1.39)	1.40 (1.12-1.76)	1.11 (0.92-1.34)	1.37 (1.09-1.73)

^a Reference category: Not having reported any definite psychosis-like experiences

^b Refers to numbers in crude analyses

^c Analyses are adjusted for maternal age, maternal education, household income, parental secondary mental health care, maternal smoking in pregnancy, children in the household at birth, and urbanization. Analyses of fever episodes are additionally adjusted for genitourinary and respiratory infection exposure and vice versa.

^d Inverse probability weights were based on a logistic regression model ($n=94\,593$) and included maternal age, maternal education, household income, parental and child secondary mental health care, maternal smoking in pregnancy, and urbanization. The number of children in the household at birth was not included in the construction of weights, due to the large proportion of missings.

Table 4: Multinomial logistic regressions of prenatal exposures and separate psychosis-like experiences. Probable and definite symptoms.

	Fever OR ^a (95 % CI)	Genitourinary infections OR ^a (95 % CI)	Respiratory infections OR ^a (95 % CI)	Influenza-like illness OR ^a (95 % CI)
Reading thoughts				
No	ref.	ref.	ref.	ref.
Probably, yes	1.07 (0.99-1.17)	1.06 (0.98-1.16)	1.04 (0.94-1.15)	1.09 (0.90-1.32)
Definitely yes	1.00 (0.79-1.25)	1.21 (0.97-1.50)	0.93 (0.70-1.23)	1.65 (1.09-2.50)
Received messages				
No	ref.	ref.	ref.	ref.
Probably, yes	1.05 (0.88-1.25)	1.02 (0.85-1.21)	0.98 (0.79-1.21)	0.88 (0.57-1.34)
Definitely yes	1.14 (0.88-1.48)	0.96 (0.74-1.24)	1.07 (0.78-1.47)	0.89 (0.47-1.68)
Being spied on				
No	ref.	ref.	ref.	ref.
Probably, yes	1.03 (0.98-1.09)	1.03 (0.98-1.10)	1.07 (1.00-1.15)	1.07 (0.95-1.21)
Definitely yes	1.12 (1.01-1.24)	1.14 (1.03-1.26)	1.08 (0.95-1.22)	1.35 (1.09-1.68)
Hearing voices				
No	ref.	ref.	ref.	ref.
Probably, yes	1.05 (0.99-1.11)	1.04 (0.98-1.10)	1.08 (1.00-1.16)	1.18 (1.04-1.35)
Definitely yes	1.15 (1.05-1.25)	1.10 (1.01-1.21)	1.06 (0.95-1.18)	1.36 (1.12-1.65)
Controlled by external forces				
No	ref.	ref.	ref.	ref.
Probably, yes	1.19 (1.08-1.30)	1.14 (1.04-1.25)	1.08 (0.96-1.21)	1.28 (1.05-1.56)
Definitely yes	1.03 (0.84-1.27)	1.29 (1.05-1.56)	0.92 (0.71-1.19)	1.14 (0.72-1.79)
Hallucinations				
No	ref.	ref.	ref.	ref.
Probably, yes	1.12 (1.04-1.21)	1.09 (1.01-1.17)	1.01 (0.92-1.11)	1.12 (0.94-1.33)
Definitely yes	1.13 (1.00-1.29)	1.12 (0.98-1.28)	1.09 (0.93-1.27)	1.17 (0.88-1.56)
Supernatural powers				
No	ref.	ref.	ref.	ref.
Probably, yes	1.06 (0.98-1.16)	1.19 (1.09-1.29)	1.11 (1.00-1.23)	1.10 (0.91-1.33)
Definitely yes	1.06 (0.90-1.24)	1.10 (0.94-1.28)	1.10 (0.91-1.33)	1.22 (0.87-1.71)

^a Analyses are adjusted for maternal age, maternal education, household income, parental secondary mental health care, maternal smoking in pregnancy, children in the household at birth, and urbanization. Analyses of fever episodes are additionally adjusted for genitourinary and respiratory infection exposure and vice versa.

Figure 1: Flowchart of the study population

e-Table 1: Multinomial logistic regression of prenatal exposure to influenza-like illness and reporting of definite psychosis-like experiences at age 11.^a Use of various influenza case-definitions. DNBC, *n*= 46 184.

Definition of influenza-like illness	<i>n</i> ^b	Presence of definite psychosis-like experiences	
		1 PLE	≥2 PLEs
		RRR ^c (95 % CI)	RRR ^c (95 % CI)
Fever and cough or sore throat			
No	42,984	ref.	ref.
Yes	3,117	1.09 (0.95-1.25)	0.96 (0.80-1.17)
Fever, and cough or sore throat, and headache or muscle pain			
No	44,660	ref.	ref.
Yes	1,441	1.03 (0.84-1.26)	0.98 (0.75-1.29)
Fever and at least two other symptoms of influenza ^d			
No	38,468	ref.	ref.
Yes	7,633	1.07 (0.98-1.18)	1.16 (1.03-1.31)

^a Reference category: Not having reported any definite psychosis-like experiences

^b Refers to numbers in crude analyses

^c Analyses are adjusted for maternal age, maternal education, household income, parental secondary mental health care, maternal smoking in pregnancy, children in the household at birth, and urbanization.

^d Included any combination of the following symptoms: common cold, cough, headache, joint pain, muscle pain, pain behind eyes, sore throat, or tiredness.

e-Table 2: Multinomial logistic regression of trimester specific exposures to prenatal fever and infection and reporting of definite psychosis-like experiences at age 11.^a DNBC, *n*= 46 184.

Prenatal exposure	Presence of definite psychosis-like experiences	
	1 PLE	≥2 PLEs
	RRR ^b (95 % CI)	RRR ^b (95 % CI)
Fever ^c		
1 st trimester	1.11 (0.99-1.25)	1.01 (0.87-1.19)
2 nd trimester	1.08 (0.97-1.21)	0.95 (0.81-1.11)
Genitourinary infection ^c		
1 st trimester	1.08 (0.91-1.27)	1.08 (0.86-1.36)
2 nd trimester	1.01 (0.91-1.13)	1.03 (0.88-1.19)
Respiratory tract infection ^c		
1 st trimester	1.22 (0.97-1.53)	1.10 (0.80-1.52)
2 nd trimester	0.98 (0.87-1.12)	1.04 (0.88-1.22)
Influenza-like illness ^c		
1 st trimester	1.32 (1.00-1.73)	1.32 (0.93-1.89)
2 nd trimester	1.11 (0.84-1.47)	1.42 (1.02-1.97)

^a Reference category: Not having reported any psychosis-like experiences

^b Analyses are adjusted for maternal age, maternal education, household income, parental secondary mental health care, maternal smoking in pregnancy, children in the household at birth, and urbanization. Analyses of fever episodes are additionally adjusted for genitourinary and respiratory infection exposure and vice versa.

^c Models are mutually adjusted for exposure in 1st and 2nd trimester. 3rd trimester exposures are not included in the analyses, as the last interview in pregnancy was conducted at approximately gestational week 30.