Attention deficit/hyperactivity disorder in children following in utero fever exposure
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Background
Fever is a very common event during pregnancy, with around 1 in 5 women being affected. Neurodevelopmental impairment has been reported in children following in utero exposure to fever, but no studies have considered attention deficit/hyperactivity disorder (ADHD). Since the fetal brain undergoes a rapid development throughout the pregnancy we wanted to investigate how fever exposure in different gestational periods was related to the offspring risk of ADHD.

Methods
The study was conducted within the Danish National Birth Cohort, using data on 89,146 pregnancies enrolled during 1996–2002. Fever exposure was assessed using computer-assisted interviews conducted on approximately gestational weeks 12 and 30. A register-based follow-up in three nationwide patient and prescription registers was used to determine ADHD status, by linkage with the child’s civil registration number. Stratified Cox regressions were used to calculate adjusted hazard ratios of ADHD occurrence.

Results
We found that fever in the late part of 1st trimester (gestational weeks 9–12) was associated with a slightly increased rate of ADHD (aHR: 1.33, 95% CI: 1.12–1.58). For the remaining part of the pregnancy fever did not seem to have any strong association with ADHD. A similar pattern was observed when the analyses were restricted to women reporting no use of antipyretic medication, suggesting that the finding was not explained by any potential harmful effects associated with acetaminophen exposure.

Conclusions
The analyses indicate that fever exposure in gestational weeks 9–12 may increase risk of ADHD in the offspring. We did not have any a priori assumption that this specific period of the pregnancy would constitute a critical developmental period for subsequent ADHD occurrence, so further studies needs to clarify whether this in fact is the case.

Key messages
- ADHD occurrence may be associated with in utero fever exposure
- Timing-specific analyses of exposures are important to capture variation in vulnerability across the pregnancy