Chlamydia trachomatis during pregnancy and childhood asthma-related morbidity: a population-based prospective cohort

Evelien R. van Meel[1,2], Marina Attanasi[1,2], Vincent W.V. Jaddoe[1,3], Irwin K.M. Reiss[4], Henriëtte A. Moll[3], Johan C. de Jongste[2] and Liesbeth Duijts[2,4]

Affiliations: [1]The Generation R Study Group, Erasmus MC, University Medical Center Rotterdam, Rotterdam, The Netherlands. [2]Dept of Pediatrics, Division of Respiratory Medicine and Allergology, Erasmus MC, University Medical Center Rotterdam, Rotterdam, The Netherlands. [3]Dept of Pediatrics, Erasmus MC, University Medical Center Rotterdam, Rotterdam, The Netherlands. [4]Dept of Pediatrics, Division of Neonatology, Erasmus MC, University Medical Center Rotterdam, Rotterdam, The Netherlands.

Correspondence: Liesbeth Duijts, Erasmus MC, University Medical Center Rotterdam, Sp-3435, PO Box 2060, 3000 CB Rotterdam, The Netherlands. E-mail: l.duijts@erasmusmc.nl

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***Chlamydia trachomatis* infection during pregnancy is associated with increased odds of wheezing and asthma, and impaired lung function in childhood, and may be a target for prevention strategies focused on improving offspring respiratory health** https://bit.ly/34fSXda

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ABSTRACT

Introduction: *Chlamydia trachomatis* is the most commonly reported sexually transmitted disease and although infection during pregnancy is associated with neonatal complications, long-term respiratory consequences are unknown. We aimed to determine whether *C. trachomatis* infection during pregnancy is associated with asthma-related symptoms across childhood

Methods: This study among 2475 children and their mothers was embedded in a population-based prospective cohort study. Maternal urine samples were tested for *C. trachomatis* infection during pregnancy. Questionnaires provided information on childhood physician-attended lower respiratory tract infections and wheezing, and current asthma at age 10 years. Lung function was measured by spirometry at age 10 years.

Results: The prevalence of *C. trachomatis* infection during pregnancy was 3.2% (78 out of 2475). *C. trachomatis* infection during pregnancy was not associated with lower respiratory tract infections until age 6 years, but was associated with a higher odds of wheezing in children until age 10 years (OR 1.50 (95% CI 1.10–2.03)). *C. trachomatis* infection during pregnancy was associated with an increased odds of asthma (OR 2.29 (95% CI 1.02–5.13)), and with a lower forced expiratory volume in 1 s/forced vital capacity and forced expiratory flow at 75% of forced vital capacity (z-score difference −0.28 (95% CI −0.52–−0.04) and −0.24 (95% CI −0.46–−0.01), respectively) in children at age 10 years. The observed associations were only partly explained by mode of delivery, gestational age at birth or birthweight.

Conclusions: *C. trachomatis* infection during pregnancy is associated with increased odds of wheezing, asthma and impaired lung function. The causality of the observed associations and potential underlying mechanisms need to be explored.

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Introduction

Chlamydia trachomatis is the most commonly reported sexually transmitted disease in Western countries [1–3]. It is hypothesised that *C. trachomatis* during pregnancy could affect childhood respiratory health through direct or indirect effects. *C. trachomatis* during pregnancy could directly lead to placental inflammation, potentially leading to altered immune and atopic development, and persistent risks of respiratory morbidity of the child [4, 5]. *C. trachomatis* infection during pregnancy is known to be associated with a 1.3- to 4-fold increased risk of neonatal complications such as perinatal mortality, pre-term birth, low birthweight and pneumonia [4, 6–10]. Pre-term birth, low birthweight and neonatal respiratory disease are known to predispose to respiratory morbidity at later ages [11–13]. Therefore, *C. trachomatis* during pregnancy might also be associated with respiratory health in later life indirectly through these altered birth characteristics. Previous small-sample-sized observational studies focused mostly on the association of *C. trachomatis* infection in children with their respiratory health and suggested that an infection in infancy is associated with adverse respiratory health [14, 15]. Only one prospective cohort study was performed, studying the association between *C. trachomatis* and asthma in a subanalysis only, and reported that treatment for *C. trachomatis* during pregnancy was associated with a 3-fold increased risk of asthma in the offspring at age 7 years [16]. However, no studies have examined the association of *C. trachomatis* during pregnancy with respiratory health or with objective lung function measurements later in childhood.

We hypothesise that *C. trachomatis* during pregnancy leads to fetal respiratory and immunological developmental adaptations, predisposing children to long-term asthma-related morbidity. We examined in a population-based prospective cohort study the associations of *C. trachomatis* infection during pregnancy with the odds of lower respiratory tract infections, wheezing, asthma and impaired lung function in children. We also examined whether any associations were explained by mode of delivery, gestational age at birth or birthweight.

Methods

Design

This study was embedded in the Generation R Study, a population-based prospective cohort from early fetal life onwards in Rotterdam in the Netherlands, comprising 9901 children and their mothers [17]. The study has been approved by the Medical Ethical Committee of the Erasmus MC (University Medical Center Rotterdam, Rotterdam, The Netherlands; MEC-2012-165). Written informed consent was obtained from mothers, parents or legal representatives of all children. The *C. trachomatis* substudy was performed between February 2003 and January 2005, and comprised 4055 mothers and children [6]. Non-singleton or non-live-born children and children without information on at least one of the respiratory outcomes were excluded, which left a total of 2475 children and their mothers for the current analysis. The flowchart of participants included for analysis is given in figure 1.

C. trachomatis *infection during pregnancy*

Women provided a first-void urine specimen to test for *C. trachomatis* at enrolment, as described previously [6]. In summary, urine samples were stored at 4°C, transported the same or following working day and processed within 24 h of receipt by the laboratory. DNA was isolated from five pooled urine specimens using the MagNA Pure LC Bacterial DNA Isolation Kit III (Roche Molecular Systems, Alameda, CA, USA) and amplified by PCR (Cobas Amplicor, Roche Molecular Diagnostics, Branchburg, NJ, USA). Urine samples from positive pools were individually re-tested and reported as negative or positive. Due to the observational nature of this study and the fact that screening for *C. trachomatis* during pregnancy was not part of standard care, results were not reported back to the women.

Asthma and asthma-related morbidity in childhood

We obtained information on lower respiratory tract infections (physician-attended pneumonia, bronchitis or bronchiolitis) by annual questionnaires from birth to age 4 years and at age 6 years. Information on wheezing was obtained at similar ages and at age 10 years. Information on asthma medication use in the past 12 months was obtained during the visit at the research centre (median age 9.8 years; 5–95% range 9.5–10.4 years). Asthma was defined as ever-diagnosis of asthma, obtained by questionnaire at age 10 years, with either wheezing or medication use in the past 12 months. All questions on wheezing and asthma were based on the International Study on Asthma and Allergy in Childhood (ISAAC) questionnaire [18].

We performed spirometry according to the American Thoracic Society (ATS)/European Respiratory Society (ERS) recommendations during the visit at the research centre at age 10 years. Children (n=154) with a >5% deviation in forced expiratory volume in 1 s (FEV_1) or forced vital capacity (FVC) but with at least one blow with adequate reach and duration of plateau according to ATS/ERS criteria were additionally included [19, 20]. Lung function measures included FEV_1, FVC, FEV_1/FVC and forced

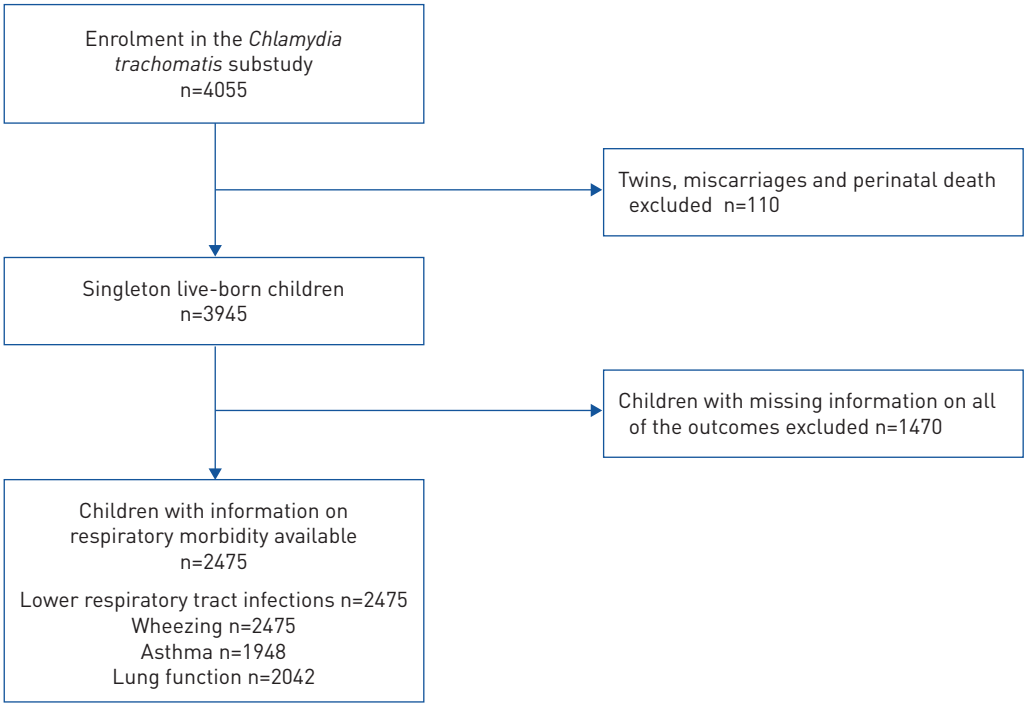

FIGURE 1 Flowchart of participants included for analysis.

expiratory flow at 75% of FVC ($FEF_{75\%}$), and were converted into sex-, height-, age- and ethnicity-adjusted z-scores according to the Global Lung Initiative reference data [21].

Covariates

Information on maternal age, educational level, risk behaviour including ever-treatment for sexually transmitted diseases and multiple sexual partners in the year before pregnancy, psychiatric symptoms, smoking during pregnancy, and alcohol use during pregnancy was obtained by multiple questionnaires during pregnancy [17]. Midwife and hospital registries provided information on mode of delivery, child's sex, gestational age at birth and birthweight [17]. Child's ethnicity was based on questionnaires during pregnancy. Questionnaires after birth provided information about child's breastfeeding and day care attendance.

Statistical analysis

First, we performed a loss-to-follow-up analysis by comparing characteristics of children included in our study and those lost to follow-up by using independent samples t-tests, Mann–Whitney *U*-tests and Pearson's Chi-squared tests. Second, we used generalised estimating equation models to examine the associations of *C. trachomatis* infection during pregnancy with the odds of lower respiratory tract infections and wheezing of the child until age 6 and 10 years, respectively. These models take the correlations between repeated measurements of either lower respiratory tract infections or wheezing within the same subject into account. Both an unstructured and first-order autoregressive correlation structure was tested, and the difference between these matrices was assessed by means of the quasilikelihood under the independence model criterion (QIC) statistic [22, 23]. Given that both correlation structures yielded similar results, but with a lower QIC for the first-order autoregressive correlation structure, this structure was used in the final model. Third, we used logistic and linear regression models to examine the associations of *C. trachomatis* infection during pregnancy with the odds of asthma and lung function measures, respectively. All multivariable analyses were adjusted for maternal age, educational level, psychiatric symptoms, and smoking and alcohol use during pregnancy, and child's ethnicity, breastfeeding and day care attendance in the first year of life (confounder model). Confounders were selected from literature first, and were subsequently tested for their association with both the determinant and the outcome, or a change of the unadjusted effect estimates of ⩾10% when added to the univariate model [24–28]. A directed acyclic graph was created to visualise the relationship between exposure, outcome and possible covariates (supplementary figure S1). Confounders were included in the final model if they were either associated with determinant and outcome, and not in the causal pathway, or if the effect estimate changed by ⩾10% when they were included. To address potential residual confounding related to *C.*

trachomatis infection during pregnancy, we additionally examined whether risk behaviour including ever-treatment for a sexually transmitted disease (yes/no) and multiple sexual partners in the year before pregnancy (yes/no) differed among women with and without *C. trachomatis* during pregnancy by means of Fisher's exact test.

We examined if the associations of *C. trachomatis* during pregnancy with respiratory morbidity were explained by mode of delivery, gestational age or birthweight by additionally adjusting for these variables (full model). We assessed the change in effect estimates after additional adjustment for these variables, by using the following formulas for percentage change:

$$100 \times (\text{Effect estimate}_{\text{full model}} - \text{Effect estimate}_{\text{original model}})/(\text{Effect estimate}_{\text{original model}} - 1)$$

for categorical lower respiratory tract infections, wheezing and asthma, and

$$100 \times (\text{Effect estimate}_{\text{full model}} - \text{Effect estimate}_{\text{original model}})/(\text{Effect estimate}_{\text{original model}})$$

for continuous lung function measures [11]. Additionally, we tested possible effect modification by gestational age at urine sampling for *Chlamydia* diagnosis by adding an interaction term to the model. Missing data in covariates, and in repeated measures of lower respiratory tract infections and wheezing, were imputed by the multiple imputation method using chained equations to select the most likely value for a missing response [29], creating 10 new datasets. Since we observed no major differences in the magnitude or direction of the effect estimates between analyses with imputed missing data and complete cases only, we only present the results based on imputed datasets. All measures of association are presented as odds ratios or z-score differences and their corresponding 95% confidence intervals. Statistical analyses were performed using SPSS version 24.0 for Windows (IBM, Armonk, NY, USA), SAS version 9.4 for Windows (SAS Institute, Cary, NC, USA) and R version 3.4.1 (https://cran.r-project.org).

Results

Subject characteristics

Maternal and child characteristics are presented in table 1. The prevalence of *C. trachomatis* infection during pregnancy was 3.2% (78 out of 2475). The prevalence of childhood lower respiratory tract infections decreased after age 2 years, while the prevalence of childhood wheezing decreased gradually until age 10 years. Among the children born to mothers without *versus* with *C. trachomatis* during pregnancy, the prevalence of asthma at age 10 years was 5.3% (101 out of 1893) *versus* 14.5% (eight out of 55) ($p_{difference}$=0.004). Main results of the loss-to-follow-up analysis showed that children not included in the study had a mother who more often had *C. trachomatis* during pregnancy, and had a lower gestational age at birth and birthweight (supplementary table S1).

C. trachomatis, *asthma and asthma-related morbidity*

None of the children with a lower respiratory tract infection at age 6 months were born to a mother with *C. trachomatis* infection during pregnancy and therefore only lower respiratory tract infections from age 1 year onwards were included in the model. *C. trachomatis* infection during pregnancy was not associated with annual or overall odds of lower respiratory tract infections in childhood (figure 2). Compared with children born to mothers without *C. trachomatis* infection during pregnancy, those born to mothers with *C. trachomatis* infection during pregnancy had an increased odds of wheezing until age 10 years (OR 1.50 (95% CI 1.10–2.03)) (figure 2) and an increased odds of asthma (OR 2.29 (95% CI 1.02–5.13)) (table 2). Additionally, these children had a lower FEV_1/FVC (z-score difference −0.28 (95% CI −0.52–−0.04)) and $FEF_{75\%}$ (z-score difference −0.24 (95% CI −0.46–−0.01)) at age 10 years, but not a lower FEV_1 or FVC (table 2). The proportion of women ever treated for a sexually transmitted disease did not differ between the groups with and without *C. trachomatis* infection during pregnancy (12.1% *versus* 11.6%; p=0.84). The proportion of women having multiple sexual partners in the year before pregnancy in the group with *C. trachomatis* during pregnancy was lower than in the group without (0% *versus* 7.6%; p=0.02).

Additional adjustment for mode of delivery, gestational age at birth or birthweight did not materially change the effect estimates of the association of *C. trachomatis* infection during pregnancy with childhood respiratory health (table 2 for asthma and lung function, and supplementary tables S2 and S3 for lower respiratory tract infections and wheezing, respectively). The percentages change in the association of *C. trachomatis* during pregnancy with lung function and asthma after additional adjustment for birth characteristics ranged from −6.2% to 1.1% (table 2) and were nonsignificant. The percentage changes for the overall odds of lower respiratory tract infection and wheezing were –2.7% (95% CI −156–175%) and −5.0% (95% CI −24.7–−0.2%), respectively. There was no effect modification by gestational age at diagnosis for associations of *C. trachomatis* with respiratory health ($p_{interaction}$=0.434–0.887).

TABLE 1 Characteristics of children and their mothers

	Full group	*Chlamydia*-negative	*Chlamydia*-positive
Subjects	2475	2397	78
Maternal characteristics			
Age years	30.76±4.8	30.86±4.7	27.58±6.2
Caesarean section	361 (14.6)	309 (12.9)	12 (15.4)
Low/middle education level	1218 (49.2)	1161 (48.4)	56 (71.8)
Maternal psychiatric symptoms	0.16 (0.07–0.37)	0.15 (0.06–0.31)	0.27 (0.12–0.45)
Smoking during pregnancy	611 (24.7)	589 (24.6)	23 (29.5)
Alcohol use during pregnancy	1417 (57.3)	1373 (57.3)	44 (56.4)
Chlamydia trachomatis infection during pregnancy	78 (3.1)	NA	NA
Child's characteristics			
Female sex	1230 (49.7)	1193 (49.8)	37 (47.4)
Gestational age at birth weeks	40.1 (39.3–41.0)	40.1 (39.3–41.0)	40.0 (39.1–41.0)
Birthweight g	3446±546	3450±545	3327±627
European ethnicity	1556 (62.9)	1591 (67.3)	30 (41.0)
Ever breastfeeding	2301 (93.0)	2229 (93.0)	71 (91.0)
Day care attendance first year	1350 (54.5)	1325 (55.3)	25 (32.1)
Lower respiratory tract infections			
Age 1 year	210 (8.5)	202 (8.4)	8 (10.2)
Age 2 years	317 (12.8)	310 (12.9)	7 (9.0)
Age 3 years	203 (8.2)	193 (8.1)	10 (12.8)
Age 4 years	159 (6.4)	149 (6.2)	10 (12.8)
Age 6 years	145 (5.8)	139 (5.8)	6 (7.6)
Wheezing			
Age 1 year	773 (31.2)	741 (30.9)	32 (41.0)
Age 2 years	541 (21.9)	519 (21.7)	22 (28.2)
Age 3 years	377 (15.2)	354 (14.8)	23 (29.5)
Age 4 years	381 (15.4)	363 (15.1)	18 (23.1)
Age 6 years	294 (11.9)	281 (11.7)	13 (16.7)
Age 10 years	162 (6.5)	152 (6.3)	11 (14.1)
Asthma[#]	109 (5.6)	101 (5.3)	8 (14.5)
Lung function measures[#]			
FEV_1 L	2.02 (0.30)	2.03 (0.30)	1.97 (0.32)
FVC L	2.34 (0.37)	2.34 (0.37)	2.27 (0.39)
FEV_1/FVC %	86.94 (5.68)	86.9 (5.7)	85.9 (5.1)
$FEF_{75\%}$ $L{\cdot}s^{-1}$	1.16 (0.35)	1.16 (0.35)	1.04 (0.32)

Data are presented as n, mean±SD, n (%) or median (interquartile range). NA: not applicable; FEV_1: forced expiratory volume in 1 s; FVC: forced vital capacity; $FEF_{75\%}$: forced expiratory flow at 75% of FVC. [#]: data were missing and not imputed for asthma (n=527) and lung function measures (n=433).

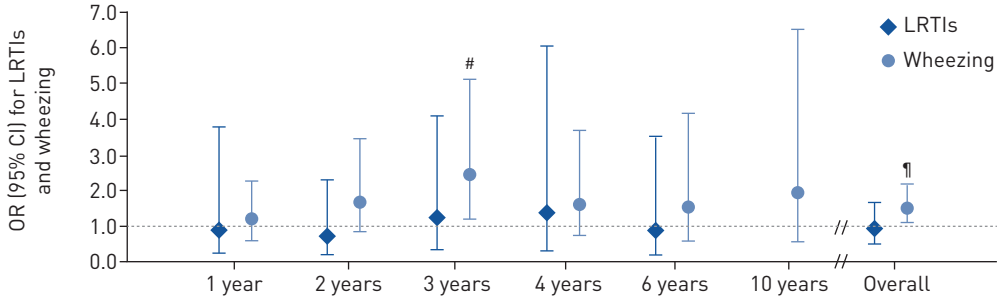

FIGURE 2 Associations of *Chlamydia trachomatis* infection during pregnancy with lower respiratory tract infections (LRTIs) from age 1 to 6 years and wheezing from age 1 to 10 years. Odds ratios with 95% confidence intervals from generalised estimating equation models. Models are adjusted for maternal age, educational level, psychiatric symptoms, and smoking and alcohol use during pregnancy, and child's ethnicity, breastfeeding and day care attendance in the first year of life. [#]: p=0.028; [¶]: p=0.013.

TABLE 2 Associations of *Chlamydia trachomatis* infection during pregnancy with lung function and asthma

	n	FEV_1 z-score difference (95% CI)	FVC z-score difference (95% CI)	FEV_1/FVC z-score difference (95% CI)	$FEF_{75\%}$ z-score difference (95% CI)	Asthma OR (95% CI)
Subjects n		2402	2402	2402	2402	1948
Infection during pregnancy (yes *versus* no)						
Crude model	2475	−0.16 (−0.39–0.08)	−0.04 (−0.27–0.18)	−0.24 (−0.47–−0.10)	−0.15 (−0.37–0.07)	3.02 (1.39–6.56)
p-value		0.198	0.700	0.041	0.176	0.005
Confounder model[#]	2475	−0.23 (−0.47–0.01)	−0.11 (−0.34–0.12)	−0.28 (−0.52–−0.04)	−0.24 (−0.46–−0.01)	2.29 (1.02–5.13)
p-value		0.059	0.366	0.021	0.040	0.045
Full model[¶]	2475	−0.23 (−0.47–0.02)	−0.11 (−0.34–0.13)	−0.27 (−0.51–−0.02)	−0.23 (−0.45–−0.00)	2.27 (1.01–5.15)
p-value		0.070	0.359	0.032	0.049	0.049
Percentage change %[+]		−3.9 (−28.8–51.4)	1.1 (−160.5–208.1)	−6.2 (−35.5–16.5)	−3.3 (−42.1–31.0)	−0.6 (−47.8–53.3)

Data are presented are changes in z-score or odds ratio, derived from linear and logistic regression models, respectively. FEV_1: forced expiratory volume in 1 s; FVC: forced vital capacity; $FEF_{75\%}$: forced expiratory flow at 75% of FVC. [#]: adjusted for maternal age, educational level, psychiatric symptoms, and smoking and alcohol use during pregnancy, and child's ethnicity, breastfeeding and day care attendance in the first year of life; [¶]: additionally adjusted for mode of delivery, gestational age at birth and birthweight; [+]: percentage change (95% CI) is between the full model and the confounder model.

Discussion

We observed that children of mothers with a *C. trachomatis* infection during pregnancy had increased odds of wheezing, asthma and impaired lung function in childhood. These observed associations with asthma and lung function were not explained by mode of delivery, gestational age at birth or birthweight, while the associations with overall wheezing were partly explained by these birth characteristics. *C. trachomatis* infection during pregnancy was not associated with lower respiratory tract infections across childhood.

Strengths and limitations

The major strength of this study is that it is embedded in a large prospective population-based cohort with longitudinal measurement of multiple respiratory outcomes and adjustment for relevant confounders. Additionally, we used a highly sensitive microbiological method to diagnose *C. trachomatis* [30]. The study was performed in a low-risk population, which increases generalisability to the general population.

Some limitations need to be discussed. As in most prospective cohorts, loss to follow-up might have led towards selection of a more healthy population. The prevalence of *C. trachomatis* infection during pregnancy was higher in those lost to follow-up, which most likely might have led to an underestimation of the observed associations. The low absolute numbers of *C. trachomatis* infection during pregnancy and of specific diagnoses of lower respiratory tract infections might have led to a lack of power to show associations. A previous study did observe a prevalence of 7% of *C. trachomatis* in children until age 6 months with respiratory tract infections [31]. However, the study population comprised children presenting with respiratory complaints to a specialised university medical centre, which is not comparable to our general, more healthy study population. Our results might suggest that the risk of overall wheezing is driven by the significant association of *C. trachomatis* with wheezing at age 3 years. However, the effect estimates for wheezing at all other ages are also taken into account and were moderate to strong (effect estimate 1.22–2.06). Their lack of significance was most probably due to a low prevalence of *C. trachomatis*. The confidence intervals of the percentage change due to mediators were large, which could be due to the large confidence intervals of the original effect estimates. Information on lower respiratory tract infections, wheezing and asthma was obtained by questionnaire, which might have led to reporting bias. For wheezing and asthma, however, validated and frequently used ISAAC questionnaires were used. Last, we did not observe increased risk behaviour, such as multiple sexual partners or treatment for previous sexually transmitted diseases of women with *C. trachomatis* infection during pregnancy. Although we took various potential confounders and mediators into account, residual confounding might be an issue, as in any observational study. As our study was largely focused on subclinical *C. trachomatis* infection, we assume the large majority of women were not treated with antibiotics.

Comparison with previous studies

C. trachomatis infection during pregnancy is associated with neonatal complications such as pre-term birth and neonatal respiratory morbidity [5, 7, 8]. Only one prospective birth cohort study among 8088

mothers and children demonstrated that treatment for *Chlamydia* during pregnancy, as reported by the mother as treatment for a gynaecological infection, was associated with a 3-fold increased risk of asthma in the offspring at age 7 years [16]. These women were most likely symptomatic, while due to non-selective urine screening women in our study were most likely asymptomatic. Additionally, in this study treatment for *Chlamydia* was self-reported and studied in a subanalysis only, which could have led to bias. Our findings suggest that *C. trachomatis* infection during pregnancy is also associated with asthma in later childhood and impaired lung function measurements reflecting airflow limitation and obstruction in the small airways. To the best of our knowledge, the current study is the first to examine the associations of *C. trachomatis* infection during pregnancy with various types of respiratory morbidity and objective lung function measurements in childhood.

Other studies focused on the associations of chlamydial infections in infancy with childhood outcomes. An observational study compared 18 children hospitalised for chlamydial pneumonia with 19 controls and reported that infants with chlamydial pneumonia were more likely to have asthma at age 7 years, and more often had impaired lung function and bronchial hyperreactivity [14]. Findings from another study comparing 40 children hospitalised for pneumonia or bronchitis in infancy with 71 healthy controls suggested that the association of chlamydial infection in infancy with respiratory diseases is not solely explained by respiratory tract infections [15]. Children with chlamydial lower respiratory tract infections in infancy had an increased risk of cough and were more likely to have an abnormal functional residual capacity until age 5 years than children with non-chlamydial lower respiratory tract infections. Overall, we did not observe associations of *C. trachomatis* infection during pregnancy with lower respiratory tract infections. This might be due to the low prevalence of lower respiratory tract infections in this general, non-hospital-based population. These findings suggest that *C. trachomatis* infection during pregnancy specifically predisposes children for asthma-related symptoms, but not to general respiratory tract infections.

Explanation and implications of the findings

Because of the observational design of the study, we cannot draw conclusions on the underlying causality and mechanisms. *In vitro* studies have elucidated possible direct mechanisms underlying the association between *C. trachomatis* and respiratory health. An *in vitro* study among neonatal and adult mice showed that mice infected as neonates with *Chlamydia muridarum*, the murine biovar of *C. trachomatis*, were not able to clear the infection, had *C. muridarum*-specific IgE in bronchoalveolar fluid and serum, and had an increased production of interleukin (IL)-4 and IL-10, while this was not observed for mice infected in adulthood [32]. Both IgE and IL-4 are of importance in asthma pathogenesis, which might explain our observed association with asthma. Additionally, a related *in vitro* study demonstrated that alveolar diameter was increased in mice that were infected in the neonatal period, but not in mice infected in infancy or adulthood, which might imply that *C. trachomatis* directly affects the lungs [33]. These findings suggest that chlamydial infection during early life specifically might lead to developmental lung and immune system adaptations, and consequently an increased risk of wheezing, asthma and lower lung function in later life, but not lower respiratory tract infections. We did not observe any modifying effect of gestational age at diagnosis of *C. trachomatis* on respiratory health. However, *C. trachomatis* could have been asymptomatically present for a longer duration of time [34, 35]. *C. trachomatis* infection during pregnancy may lead to chorioamnionitis [5, 6]. Chorioamnionitis itself is associated with an increased risk of asthma or impaired lung function especially in children born pre-term [36–39], possibly through immune changes in the child as a result of the chorioamnionitis [40]. In our study, the associations of *C. trachomatis* infection during pregnancy with school-age lung function and asthma were not explained by pre-term birth, while the association with childhood wheezing was. This might imply that this mediation has only short-term effects. Further studies are needed to assess whether chorioamnionitis explains the observed associations. Lastly, co-infections during pregnancy might play a role in the association of *C. trachomatis* with respiratory health. Previous studies demonstrated that *C. trachomatis* can co-occur with, for example, *Neisseria gonorrhoeae* and *Trichomonas vaginalis*, mostly in high-risk populations, but their association with respiratory health is unclear [41–44].

Our findings are important from both an aetiological and population health perspective. They suggest that a *C. trachomatis* infection during pregnancy leads to fetal developmental adaptations, which predispose children to asthma-related morbidity, rather through lower lung function than susceptibility for lower respiratory tract infections. Population attributable fractions (calculated as prevalence of exposure among cases×(1−1/relative risk)) of *C. trachomatis* for asthma and overall wheezing in this study were 4.2% and 1.2%, respectively [45]. We only observed associations of *C. trachomatis* on FEV_1/FVC and $FEF_{75\%}$, and not the other lung function measures. Although the effect sizes are important from an aetiological perspective, they should be carefully considered from a clinical perspective. *C. trachomatis* infections are

common and infections are mostly asymptomatic. Screening of pregnant women for *C. trachomatis* is recommended in the USA for all women under age 25 years or women with risk factors for a sexually transmitted disease [46, 47]. According to local practice, screening for *C. trachomatis* is not routine practice, although it has been suggested to be cost-effective [48]. *C. trachomatis* can be treated easily and effectively with a single-dose therapy of azithromycin, even during pregnancy [46, 49]. Implementation of screening and treatment of pregnant women in the USA has led to a decrease of *C. trachomatis* infection of the newborn, and morbidity such as pre-term rupture of the membranes and pre-term birth [47, 50]. Additionally, prevention due to vaccination could be considered in the future [51–53]. Replication of these findings would be of interest, and future studies should focus on the effects of treatment during pregnancy on intra-uterine transmission, chorioamnionitis and long-term offspring health.

Conclusions and future research

Our results suggest that *C. trachomatis* infection during pregnancy is associated with increased odds of wheezing, asthma and impaired lung function across childhood. The causality of the observed associations and potential underlying biological mechanisms need to be explored.

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