*Title:*

Urban metabolic and airway immune profiles increase the risk of infections in early childhood

*Abstract:*

**Background**

Infections in early childhood remain a leading global cause of child mortality where environmental exposures seem crucial. We sought to investigate whether an urbanized environment at birth was associated with risk of infections and explore underlying mechanisms.

**Methods**

Children (n=633) from the COPSAC2010 mother-child cohort were monitored daily with symptom diaries of infection episodes during the first 3 years and prospectively diagnosed with asthma until age 6 years. Rural and urban environments were based on the CORINE land cover database. Child airway immune profile was measured at age 4 weeks. Maternal and child metabolomics profiling were assessed at pregnancy week 24 and at birth, respectively.

**Results**

We observed a mean (SD) total number of infections of 16.3 (8.4) consisting mainly of upper respiratory infections. Urban vs rural living increased infection risk (17.1 (8.7) vs 15.2 (7.9), adjusted incidence rate ratio; 1.15 (1.05-1.26), p=0.002) and altered the child airway immune profile, which increased infection risk (principal component 1 (PC1): 1.03 (1.00-1.06), p=0.038 and PC2: 1.04 (1.01-1.07), p=0.022). Urban living also altered the maternal and child metabolomic profiles, which also increased infection risk. The association between urbanicity and infection risk was partly mediated through the maternal metabolomic and child airway immune profiles. Finally, urbanicity increased the risk of asthma by age 6 years, which was mediated through early infection load (pACME<0.001).

**Conclusions**

This study suggests urbanicity as a risk factor for early infections partly explained by changes in the early metabolic and immunological development with implications for later risk of asthma.