Introduction: Asthma, a heterogeneous disease with variable age of onset, is likely the result of gene-by-environment interactions. Environmental tobacco smoke (ETS) exposure in early life is a known asthma risk factor. Yet, very few loci were found to interact with ETS exposure in asthma.

Objective: To identify new loci interacting with ETS exposure that influence time-to-asthma onset (TAO) in childhood.

Methods: We conducted a meta-analysis of five genome-wide interaction studies (GEWIS) of ETS exposure and TAO in childhood (total of 3,187 exposed (ETS+) and 5,086 non-exposed (ETS-) subjects of European ancestry) by using survival analysis techniques. Gene-set enrichment analysis (GSEA), based on the Gene Ontology (GO) database, was then applied to the GEWIS results.

Results: We found an interaction between the 13q21 locus and ETS exposure that met the genome-wide significance level (rs7334050 within KLHL1 gene, P=4.3x10^-8). Three other loci showed interactions at
P<5x10^{-6}: 20p12 (rs13037508 within MACROD2, P=4.9x10^{-7}), 14q22 (rs7493885 near NIN; P=2.9x10^{-6}) and 2p22 (rs232542 near CYP1B1; P=4.1x10^{-6}). All these SNPs show an opposite direction of effect in ETS^+ and ETS^- subjects. Functional annotations indicated co-localization of these SNPs with regulatory elements in blood or lung. Three GO categories were significantly enriched (FDR<1%) in genes interacting with ETS exposure: defense response to bacteria, oxidative phosphorylation, sterol metabolic process.

**Conclusion:** This study pointed out novel loci interacting with ETS exposure on time-to-asthma onset in childhood. Further epigenetic investigation may shed light on the underlying mechanisms.