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Title: DNA methylation in asthma and allergy related genes is influenced by farm exposure and time trends in early childhood

Mr. Sven 10346 Michel michel.sven@mh-hannover.de ^{1,*}, Ms. Florence 10347 Busato busato@cng.fr ², Dr. Jon 10348 Genuneit jon.genuneit@uni-ulm.de MD ³, Prof. Dr Juha 10349 Pekkanen juha.pekkanen@thl.fi MD ⁴, Prof. Dr Charles 10350 Dalphin jean-charles.dalphin@univ-fcomte.fr MD ⁵, Prof. Dr Josef 10352 Riedler josef.riedler@kh-schwarzach.at MD ⁶, Mr. Nicolas 10353 Mazaleyrat nmaza@cng.fr ², Prof. Dr Erika 10355 von Mutius erika.von.mutius@med.uni-muenchen.de MD ⁷, Dr. Juliane 10356 Weber Juliane.Weber@med.uni-muenchen.de MD ⁷, Prof. Dr Charlotte 10357 Braun-Fahrländer C.Braun@unibas.ch MD ^{8,9}, Prof. Dr Roger 10358 Lauener Roger.Lauener@hgk.ch MD ^{10,11}, Prof. Dr Michael 10359 Kabesch kabesch.michael@mh-hannover.de MD ^{1,*}, Dr. Jörg 10360 Tost tost@cng.fr ² and 12177 the PASTURE study group Nicola.Korherr@med.uni-muenchen.de . ¹ Department of Pediatric Pneumology, Allergy and Neonatology, Hannover Medical School, Hannover, Germany ; ² Laboratory for Epigenetics, Centre National de Génotypage, CEA–Institut de Génomique, Evry, France ; ³ Institute of Epidemiology and Medical Biometry, Ulm University, Ulm, Germany ; ⁴ National Institute for Health and Welfare, THL Kuopio, Kuopio, Finland ; ⁵ Department of Respiratory Disease, Université de Franche-Comté, Besancon, France ; ⁶ Children's Hospital Schwarzach, Children's Hospital Schwarzach, Schwarzach, Austria ; ⁷ University Children's Hospital, LMU, Munich, Germany ; ⁸ Institute of Social and Preventive Medicine, Swiss Tropical and Public Health Institute, Basel, Switzerland ; ⁹ University of Basel, University of Basel, Switzerland ; ¹⁰ Children's Hospital and Christine Kühne-Center for Allergy, University of Zürich, Switzerland and ¹¹ Christine Kühne-Center for Allergy Research and Education, Hochgebirgsklinik Davos, Davos-Wolfgang, Switzerland .

Body: Genes and environmental influences are crucial for the development of asthma and atopic diseases. These factors may act upon each other through epigenetic mechanisms. We studied the rural birth cohort PASTURE (Protection against allergy: study in rural environments) to investigate if (a) epigenetic patterns in asthma candidate genes are influenced by farm exposure in general and (b) change over the first years of life and (c) whether these changes may contribute to the development of asthma. DNA was extracted from cord blood and whole blood at age 4.5 in 48 samples per time point. We analyzed DNA methylation of 23 regions in ten asthma and allergy candidate genes (ORMDL1, ORMDL2, ORMDL3, CHI3L1, RAD50, IL13, IL4, STAT6, FOXP3 and RUNX3) by pyrosequencing and compared differences between strata. In cord blood, regions in ORMDL1 and STAT6 showed a hypomethylation while regions in RAD50 and IL13 were hypermethylated when DNA from farmers was compared to non-farmers (lowest p-value 0.001 for STAT6). Only small associations between asthma status and methylation were observed in our population. Changes

in methylation over time occurred in 14 out of 23 gene regions investigated (lowest p-value for IL13, $p=1.57 \times 10^{-8}$). Interestingly, these differences clustered in the genes highly associated with asthma (ORMDL family) and IgE regulation (RAD50, IL13 and IL4) but not in the T-regulatory genes (FOXP3, RUNX3). Our study indicates that DNA methylation changes significantly in early childhood in specific asthma and allergy related genes in peripheral blood cells while also early exposure to farm life seems to influence methylation patterns in certain genes.