Biologically Aged Females Present a Distinct Symptom and DNA Methylation Asthma Profile

K. D. Reddy[1], S. Buccholz[2], A. Bohnhorst[3], S. B. Biedermann[1], B. Schaub[4], G. Hansen[5], M. V. Kopp[6], E. Von Mutius[7], N. Maison[8], T. Bahmer[9], K. F. Rabe[10], C. B. Schmidt-Weber[11], C. A. Jakwerth[12], A.-M. Dittrich[13], T. Trojan[14], M. A. Alejandre Alcazar[15], R. Grychtol[13], F. Brinkmann[16], M. D. Weckmann[17];
[1]Forschungszentrum Borstel, Sülfeld, Germany, [2]Department of Paediatric Pneumology & Allergology, Lübeck, Germany, [3]University Hospital Schleswig-Holstein (UKSH), Lübeck, Germany, [4]University Childrens Hosp Munich, Munich 80337, Germany, [5]Medizinische Hochschule Hannover, Hannover, Germany, [6]University Lübeck, Lübeck, Germany, [7]Klinikum der Universitaet Muenchen, Muenchen, Germany, [8]Helmholtz Centre Munic, Munich, Germany, [9]University Hospital Schleswig-Holstein Campus Kiel, Kiel, Germany, [10]LungenClinic Grosshansdorf GmbH, Grosshansdorf, Germany, [11]Technische Universität and Helmholtz Centre Munich, Munich, Germany, [12]Klinikum rechts der Isar, Munich, Germany, [13]Hannover Medical School, Hannover, Germany, [14]University Hospital Cologne, Cologne, Germany, [15]University of Cologne, Cologne, Germany, [16]University Klinics Schleswig-Holstein (UKSH), Lübeck, Germany, [17]University Childrens Hospital Schleswig-Holstein, Luebeck, Germany

Corresponding author's email: karosham.reddy@uksh.de

Introduction Asthma is distinctly sexually dimorphic. Young males report higher asthma rates than females. This reverses at puberty, where females present increased incidence, reduced therapeutic effectiveness and worse asthma symptoms. The underlying molecular mechanisms causing this remain unknown. Biological DNA methylation (DNAm) clocks correlate with worse outcomes in chronic diseases such as asthma. The DNAm profile of males and females with asthma in the context of DNAm aging (DNAge) is yet to be explored. As such, we aimed to characterise and explore the DNA methylation profile associated with DNAge and biological sex in asthma. **Methods** Nasal brushings from the paediatric ALLIANCE cohort (n = 46F/74M; asthma = 73/ healthy = 31/ wheeze = 16; avg age = 11 yr range = 3 - 20 yr) were collected and DNAm processed and analysed by Illumina EPIC array using R software (*v4.1; watermelon, minfi*). DNAge was calculated using the established skinHorvath clock. The association between DNAge, sex, symptom severity or frequency of inhaled corticosteroid (ICS) use was analysed. Differential methylation analysis (DMA) comparing pathway enrichment analyses was completed using R packages (*limma, minfi, methylGSA*). Differential DNAm significance was determined at a false discovery rate (FDR) < 0.05. **Results** Highly symptomatic females with asthma are enriched for an accelerated DNAge compared to their male counterparts ($p = 0.03$). DNAge-accelerated females present increased asthma symptom frequency compared to DNAge-decelerated females and both male groups ($p < 0.0001$) despite equivalent ICS use. Focussing on highly symptomatic asthmatics, DMA comparing accelerated vs normal DNAged females and males revealed 459 differentially methylated sites (FDR < 0.05). Pathway analysis reported enrichment for Toll-like receptor, MAPK and Wnt signalling pathways as well as interferon type I, virus defence and mitochondrial response pathways (FDR < 0.05). **Conclusions** Here, we highlight a unique subset of female asthma patients who experience more asthma symptoms despite an equivalent use of ICS. In addition, this DNAged female sub-cohort carries a distinct DNAm profile from the male counterparts, with

enrichment for pathologically relevant signalling and cellular differentiation pathways. This may present a novel foundation and support for the use of the DNAge clock as a tool for the characterisation of asthma patient sub-groups.

This abstract is funded by: None