

**Understanding asthma phenotypes:
the World Asthma Phenotypes (WASP) international collaboration**

Lucy Pembrey¹, Mauricio L. Barreto^{2,9}, Jeroen Douwes³, Philip Cooper⁴⁻⁶, John Henderson⁷,
Harriet Mpairwe⁸, Cristina Ardura-Garcia⁶, Martha Chico⁶, Collin Brooks³, Alvaro A.
Cruz^{10,11}, Alison M. Elliott⁸, Camila A Figueiredo², Sinéad M. Langan¹, Beatrice Nassanga⁸,
Susan Ring⁷, Laura Rodrigues¹, Neil Pearce^{1,3}

¹London School of Hygiene and Tropical Medicine, United Kingdom

²Institute of Collective Health, Federal University of Bahia, Salvador, Brazil

³Centre for Public Health Research, Massey University, Wellington, New Zealand

⁴St George's University of London, United Kingdom

⁵Universidad Internacional del Ecuador, Quito, Ecuador

⁶Fundacion Ecuatoriana Para Investigacion en Salud, Quito, Ecuador

⁷Population Health Sciences, Bristol Medical School, University of Bristol, United Kingdom

⁸MRC/UVRI Uganda Research Unit on AIDS, Entebbe, Uganda

⁹Center for Data and Knowledge Integration for Health (CIDACS), Fiocruz, Bahia

¹⁰ProAR, Federal University of Bahia, Salvador, Brazil

¹¹Institute for Health Sciences, Federal University of Bahia, Salvador, Brazil

Correspondence:

Professor Neil Pearce

Department of Medical Statistics and Centre for Global Chronic Conditions

Faculty of Epidemiology and Population Health

London School of Hygiene and Tropical Medicine

Keppel Street

London WC1E 7HT

United Kingdom

neil.pearce@lshtm.ac.uk

Table S1: Selected studies identifying phenotypes based on clinical factors and on markers of airways inflammation

Clinical factors			
Study	Participants	Location	Phenotypes
Henderson et al (2008) [25]	Avon Longitudinal Study of Parents and Children (ALSPAC) participants assessed from birth to 7 years (n=6,265)	United Kingdom	1. Never/infrequent wheeze (59%) 2. Transient early wheeze (16%) 3. Prolonged early wheeze (9%) 4. Intermediate onset wheeze (3%) 5. Late onset wheeze (6%) 6. Persistent wheeze (7%)
Moore et al (2010) [26]	Severe Asthma Research Program cohort aged 6-80 years (n=726)	United States	1. Early onset atopic asthma with normal lung function treated with two or fewer controller medications and minimal health care utilization (15%) 2. Early-onset atopic asthma and preserved lung function but increased medication requirements and health care utilization (44%) 3. Obese women with late-onset non-atopic asthma, moderate reductions in FEV(1), and frequent oral corticosteroid use (8%) 4. Severe airflow obstruction with bronchodilator responsiveness, childhood onset, atopy (17%) 5. Severe airflow obstruction with bronchodilator responsiveness, female, later-onset, less atopy (16%)
Fitzpatrick et al (2011) [27]	Children in Severe Asthma Research Program aged 6-17 years (n=161)	United States	1. Normal lung function, less atopy (26%) 2. Lower lung function, more atopy, increased symptoms and medication use (32%) 3. Greater comorbidity, increased bronchial responsiveness, lower lung function (20%) 4. Lowest lung function, most symptoms and medication use (18%)
Siroux et al (2011) [28]	Adults in the European Community Respiratory Health Survey (n=1,895)	Europe	1. Active treated allergic childhood-onset asthma (36%) 2. Active treated adult-onset asthma (19%) 3. Inactive/mild treated allergic asthma (29%) 4. Inactive/mild untreated nonallergic asthma (16%)
Siroux et al (2011) [28]	Adults in the Epidemiological Study on the Genetics and Environment of Asthma	Europe	1. Active treated allergic childhood-onset asthma (35%) 2. Active treated adult-onset asthma (15%)

	(EGEA2) (n=641)		3. Inactive/mild untreated allergic childhood onset asthma (25%) 4. Inactive/mild untreated adult onset asthma (26%)
Savenije et al (2011) [29]	Children in Prevention and Incidence or Asthma and Mite Allergy (PIAMA) (n=2,810)	The Netherlands	1. Never/infrequent wheeze (75%) 2. Transient early wheeze (17%) 3. Intermediate onset wheeze (3%) 4. Late onset wheeze (2%) 5. Persistent wheeze (4%)
Weinmayr et al (2013) [30]	Children aged 8-12 years in cross-sectional studies in four centres (n>4,000); Spain	Spain	1. Cough during colds (22%) 2. Chronic cough and phlegm (5%) 3. Nocturnal breathlessness (6%) 4. Wheeze only with colds (5%) 5. Wheeze without colds, with cough (4%) 6. Wheeze without colds, without cough (2%)

Markers of airways inflammation

Study	Participants	Location	Phenotypes
Simpson et al (2006)[32]	93 adult non-smokers with asthma	Australia	1. Eosinophilic asthma (41%) 2. Neutrophilic asthma (20%) 3. Mixed granulocytic asthma (8%) 4. Paucigranulocytic asthma (31%)
Drews et al (2009)[22]	57 asthmatic children	Brazil	1. Atopic asthma (49%); 81% with sputum eosinophilia 2. Non-atopic asthma (51%); 24% with sputum eosinophilia
Wang et al (2011)[63]	51 adults with asthma (29 stable, 22 acute); 77 children with asthma (49 stable, 28 acute)	Australia	1. Eosinophilic asthma (17% adult stable, 0% adult acute, 29% children stable, 50% children acute) 2. Neutrophilic asthma (28% adult stable, 82% adult acute, 20% children stable, 7% children acute) 3. Mixed granulocytic asthma (4% adult stable, 18% adult acute, 2% children stable, 36% children acute) 4. Paucigranulocytic asthma (52% adult stable, 0% adult acute, 49% children stable, 7% children acute)
Brooks et al (2016)[14]	Asthmatic and non-asthmatic children aged 12-17 years	New Zealand	1. Eosinophilic asthma (46%) 2. Non-eosinophilic asthma (54%) (8% neutrophilic, 46% other)

Table S2 Skin prick test allergens to be used in each study centre

	Allergens to be tested:	Uganda	Wellington, NZ	Bristol, UK	Ecuador	Brazil
Standard panel	Dermatophagoides pteronyssinus (house dust mite)	✓ pteronyssinus & farinae mix	✓	✓	✓ pteronyssinus & farinae mix	✓
	tree pollen mix	✓	✓	✓		
	grass pollen mix	✓ weeds	✓	✓	✓	
	cat dander	✓	✓	✓	✓	✓
	dog dander	✓	✓	✓	✓	✓
	Alternaria tenuis (=Alternaria alternata)		✓	✓	✓	
	Penicillium mix		✓			
Other locally relevant allergens	Blomia tropicalis (dust mite)	✓				✓
	Dermatophagoides farinae (house dust mite)	✓				✓
	Mould mix	✓				
	Mixed fungi				✓	
	Aspergillus fumigatus			✓		✓
	Cladosporium		✓			✓
	Blatella germanica (German cockroach)	✓		✓		✓
	Periplaneta Americana (American cockroach)				✓	✓
	peanut	✓				
	Anisakis simplex (parasitic worm)	✓				

References

1. Edwards MR, Saglani S, Schwarze J, Skevaki C, Smith JA, Ainsworth B, Almond M, Andreakos E, Belvisi MG, Chung KF, Cookson W, Cullinan P, Hawrylowicz C, Lommatzsch M, Jackson D, Lutter R, Marsland B, Moffatt M, Thomas M, Virchow JC, Xanthou G, Edwards J, Walker S, Johnston SL, members of the EWPwg. Addressing unmet needs in understanding asthma mechanisms: From the European Asthma Research and Innovation Partnership (EARIP) Work Package (WP)2 collaborators. *Eur Respir J* 2017; 49(5).
2. Pavord ID, Beasley R, Agusti A, Anderson GP, Bel E, Brusselle G, Cullinan P, Custovic A, Ducharme FM, Fahy JV, Frey U, Gibson P, Heaney LG, Holt PG, Humbert M, Lloyd CM, Marks G, Martinez FD, Sly PD, von Mutius E, Wenzel S, Zar HJ, Bush A. After asthma: redefining airways diseases. *Lancet* 2017.
3. Douwes J, Gibson P, Pekkanen J, Pearce N. Non-eosinophilic asthma: importance and possible mechanisms.[comment]. *Thorax* 2002; 57(7): 643-648.
4. Pearce N, Pekkanen J, Beasley R. How much asthma is really attributable to atopy? *Thorax* 1999; 54(3): 268-272.
5. Pearce N, Douwes J, Beasley R. Is allergen exposure the major primary cause of asthma? *Thorax* 2000; 55(5): 424-431.
6. Douwes J, Boezen M, Pearce N. Chronic obstructive pulmonary disease and asthma. In: Detels R BR, Lansang MA, Gulliford M, ed. Oxford textbook of public health. 5 ed. Oxford University Press, Oxford, 2009; pp. 1021-1045.
7. Weinmayr G, Weiland SK, Bjorksten B, Brunekreef B, Buchele G, Cookson WOC, Garcia-Marcos L, Gotua M, Gratziou C, van Hage M, von Mutius E, Riikjarv MA, Rzehak P, Stein RT, Strachan DP, Tsanakas J, Wickens K, Wong GW. Atopic sensitization and the international variation of asthma symptom prevalence in children. *American Journal of Respiratory and Critical Care Medicine* 2007; 176(6): 565-574.

8. Barreto ML, Cunha SS, Fiaccone R, Esquivel R, Amorim LD, Alvim S, Prado M, Cruz AA, Cooper PJ, Santos DN, Strina A, Alcantara-Neves N, Rodrigues LC. Poverty, dirt, infections and non-atopic wheezing in children from a Brazilian urban center. *Respiratory Research* 2010; 11.
9. Wenzel SE. Asthma phenotypes: the evolution from clinical to molecular approaches. *Nature Medicine* 2012; 18(5): 716-725.
10. Pekkanen J, Lampi J, Genuneit J, Hartikainen AL, Jarvelin MR. Analyzing atopic and non-atopic asthma. *European Journal of Epidemiology* 2012; 27(4): 281-286.
11. Douwes J, Pearce N. The end of the hygiene hypothesis? *International Journal of Epidemiology* 2008; 37(3): 570-572.
12. Moncayo AL, Vaca M, Oviedo G, Erazo S, Quinzo I, Fiaccone RL, Chico ME, Barreto ML, Cooper PJ. Risk factors for atopic and non-atopic asthma in a rural area of Ecuador. *Thorax* 2010; 65(5): 409-416.
13. Simpson JL, Grissell TV, Douwes J, Scott RJ, Boyle MJ, Gibson PG. Innate immune activation in neutrophilic asthma and bronchiectasis. *Thorax* 2007; 62(3): 211-218.
14. Brooks CR, van Dalen CJ, Zacharasiewicz A, Simpson JL, Harper JL, Le Gros G, Gibson PG, Pearce N, Douwes J. Absence of airway inflammation in a large proportion of adolescents with asthma. *Respirology* 2016; 21(3): 460-466.
15. Hancox RJ, Cowan DC, Aldridge RE, Cowan JO, Palmary R, Williamson A, Town GI, Taylor DR. Asthma phenotypes: consistency of classification using induced sputum. *Respirology* 2012; 17(3): 461-466.
16. Fleming L, Tsartsali L, Wilson N, Regamey N, Bush A. Sputum inflammatory phenotypes are not stable in children with asthma. *Thorax* 2012; 67(8): 675-681.
17. Spycher BD, Silverman M, Kuehni CE. Phenotypes of childhood asthma: are they real? *Clinical and Experimental Allergy* 2010; 40(8): 1130-1141.

18. Haldar P, Pavord ID, Shaw DE, Berry MA, Thomas M, Brightling CE, Wardlaw AI, Green RH. Cluster analysis and clinical asthma phenotypes. *American Journal of Respiratory and Critical Care Medicine* 2008; 178(3): 218-224.
19. Spycher BD, Minder CE, Kuehni CE. Multivariate modelling of responses to conditional items: New possibilities for latent class analysis. *Statistics in Medicine* 2009; 28(14): 1927-1939.
20. Deliu M, Yavuz TS, Sperrin M, Belgrave D, Sahiner UM, Sackesen C, Kalayci O, Custovic A. Features of asthma which provide meaningful insights for understanding the disease heterogeneity. *Clin Exp Allergy* 2017.
21. Anto JM, Bousquet J, Akdis M, Auffray C, Keil T, Momas I, Postma DS, Valenta R, Wickman M, Cambon-Thomsen A, Haahtela T, Lambrecht BN, Lodrup Carlsen KC, Koppelman GH, Sunyer J, Zuberbier T, Annesi-Maesano I, Arno A, Bindslev-Jensen C, De Carlo G, Forastiere F, Heinrich J, Kowalski ML, Maier D, Melen E, Smit HA, Standl M, Wright J, Asarnoj A, Benet M, Ballardini N, Garcia-Aymerich J, Gehring U, Guerra S, Hohmann C, Kull I, Lupinek C, Pinart M, Skrindo I, Westman M, Smagghe D, Akdis C, Andersson N, Bachert C, Ballereau S, Ballester F, Basagana X, Bedbrook A, Bergstrom A, von Berg A, Brunekreef B, Burte E, Carlsen KH, Chatzi L, Coquet JM, Curin M, Demoly P, Eller E, Fantini MP, von Hertzen L, Hovland V, Jacquemin B, Just J, Keller T, Kiss R, Kogevinas M, Koletzko S, Lau S, Lehmann I, Lemonnier N, Makela M, Mestres J, Mowinckel P, Nadif R, Nawijn MC, Pellet J, Pin I, Porta D, Ranciere F, Rial-Sebbag E, Saeys Y, Schuijs MJ, Siroux V, Tischer CG, Torrent M, Varraso R, Wenzel K, Xu CJ. Mechanisms of the Development of Allergy (MeDALL): Introducing novel concepts in allergy phenotypes. *J Allergy Clin Immunol* 2017; 139(2): 388-399.

22. Drews AC, Pizzichini MMM, Pizzichini E, Pereira MU, Pitrez PM, Jones MH, Sly PD, Stein RT. Neutrophilic airway inflammation is a main feature of induced sputum in nonatopic asthmatic children. *Allergy* 2009; 64(11): 1597-1601.
23. Ye WJ, Xu WG, Guo XJ, Han FF, Peng J, Li XM, Guan WB, Yu LW, Sun JY, Cui ZL, Song L, Zhang Y, Wang YM, Yang TY, Ge XH, Yao D, Liu S. Differences in airway remodeling and airway inflammation among moderate-severe asthma clinical phenotypes. *J Thorac Dis* 2017; 9(9): 2904-2914.
24. Martinez FD, Wright AL, Taussig LM, Holberg CJ, Halonen M, Morgan WJ, Bean J, Bianchi H, Curtiss J, Ey J, Sanguineti A, Smith B, Vondrak T, West N, McLellan M. Asthma and wheezing in the first 6 years of life. *New England Journal of Medicine* 1995; 332(3): 133-138.
25. Henderson J, Granell R, Heron J, Sherriff A, Simpson A, Woodcock A, Strachan DP, Shaheen SO, Sterne JAC. Associations of wheezing phenotypes in the first 6 years of life with atopy, lung function and airway responsiveness in mid-childhood. *Thorax* 2008; 63(11): 974-980.
26. Moore WC, Meyers DA, Wenzel SE, Teague WG, Li HS, Li XN, D'Agostino R, Castro M, Curran-Everett D, Fitzpatrick AM, Gaston B, Jarjour NN, Sorkness R, Calhoun WJ, Chung KF, Comhair SAA, Dweik RA, Israel E, Peters SP, Busse WW, Erzurum SC, Bleecker ER, Natl Heart Lung Blood I. Identification of Asthma Phenotypes Using Cluster Analysis in the Severe Asthma Research Program. *American Journal of Respiratory and Critical Care Medicine* 2010; 181(4): 315-323.
27. Fitzpatrick AM, Teague WG, Meyers DA, Peters SP, Li XN, Li HS, Wenzel SE, Auja S, Castro M, Bacharier LB, Gaston BM, Bleecker ER, Moore WC, Natl Inst H, Natl Heart L, Blood Inst S. Heterogeneity of severe asthma in childhood: Confirmation by cluster analysis of children in the National Institutes of Health/National Heart, Lung, and Blood

Institute Severe Asthma Research Program. *Journal of Allergy and Clinical Immunology* 2011; 127(2): 382-U973.

28. Siroux V, Basagana X, Boudier A, Pin I, Garcia-Aymerich J, Vesin A, Slama R, Jarvis D, Anto JM, Kauffmann F, Sunyer J. Identifying adult asthma phenotypes using a clustering approach. *European Respiratory Journal* 2011; 38(2): 310-317.
29. Savenije OE, Granell R, Caudri D, Koppelman GH, Smit HA, Wijga A, de Jongste JC, Brunekreef B, Sterne JA, Postma DS, Henderson J, Kerkhof M. Comparison of childhood wheezing phenotypes in 2 birth cohorts: ALSPAC and PIAMA. *Journal of Allergy and Clinical Immunology* 2011; 127(6): 1505-U1285.
30. Weinmayr G, Keller F, Kleiner A, du Prel JB, Garcia-Marcos L, Batlles-Garrido J, Garcia-Hernandez G, Suarez-Varela MM, Strachan DP, Nagel G. Asthma phenotypes identified by latent class analysis in the ISAAC phase II Spain study. *Clinical and Experimental Allergy* 2013; 43(2): 223-232.
31. Pavord ID. Asthma Phenotypes. *Seminars in Respiratory and Critical Care Medicine* 2012; 33(6): 645-652.
32. Simpson JL, Scott R, Boyle MJ, Gibson PG. Inflammatory subtypes in asthma: Assessment and identification using induced sputum. *Respirology* 2006; 11(1): 54-61.
33. Haldar P, Pavord ID. Noneosinophilic asthma: A distinct clinical and pathologic phenotype. *Journal of Allergy and Clinical Immunology* 2007; 119(5): 1043-1052.
34. Shaw DE, Sousa AR, Fowler SJ, Fleming LJ, Roberts G, Corfield J, Pandis I, Bansal AT, Bel EH, Auffray C, Compton CH, Bisgaard H, Bucchioni E, Caruso M, Chanez P, Dahlen B, Dahlen SE, Dyson K, Frey U, Geiser T, Gerhardsson de Verdier M, Gibeon D, Guo YK, Hashimoto S, Hedlin G, Jeyasingham E, Hekking PP, Higenbottam T, Horvath I, Knox AJ, Krug N, Erpenbeck VJ, Larsson LX, Lazarinis N, Matthews JG, Middelveld R, Montuschi P, Musial J, Myles D, Pahus L, Sandstrom T, Seibold W, Singer F, Strandberg K,

Vestbo J, Vissing N, von Garnier C, Adcock IM, Wagers S, Rowe A, Howarth P, Wagener AH, Djukanovic R, Sterk PJ, Chung KF, Group UBS. Clinical and inflammatory characteristics of the European U-BIOPRED adult severe asthma cohort. *Eur Respir J* 2015; 46(5): 1308-1321.

35. Guiddir T, Saint-Pierre P, Purene-Denis E, Lambert N, Laoudi Y, Couderc R, Gouvis-Echraghi R, Amat F, Just J. Neutrophilic Steroid-Refractory Recurrent Wheeze and

Eosinophilic Steroid-Refractory Asthma in Children. *J Allergy Clin Immunol Pract* 2017; 5(5): 1351-1361 e1352.

36. Brooks CR, Van Dalen CJ, Harding E, Hermans IF, Douwes J. Effects of treatment changes on asthma phenotype prevalence and airway neutrophil function. *BMC Pulm Med* 2017; 17(1): 169.

37. Veres TZ, Rochlitzer S, Braun A. The role of neuro-immune cross-talk in the regulation of inflammation and remodelling in asthma. *Pharmacol Ther* 2009; 122(2): 203-

214.

38. Pearce N, Beasley R, Burgess C, J. C. *Asthma epidemiology*. Oxford University Press, New York, 1998.

39. Chaudhuri R, McMahon AD, McSharry CP, Macleod KJ, Fraser I, Livingston E, Thomson NC. Serum and sputum neurotrophin levels in chronic persistent cough. *Clin Exp Allergy* 2005; 35(7): 949-953.

40. Mostafa GA, Reda SM, Abd El-Aziz MM, Ahmed SA. Sputum neurokinin A in Egyptian asthmatic children and adolescents: relation to exacerbation severity. *Allergy* 2008; 63(9): 1244-1247.

41. Hilty M, Burke C, Pedro H, Cardenas P, Bush A, Bossley C, Davies J, Ervine A, Poulter L, Pachter L, Moffatt MF, Cookson WO. Disordered microbial communities in asthmatic airways. *PLoS One* 2010; 5(1): e8578.

42. Cowan DC, Cowan JO, Palmay R, Williamson A, Taylor DR. Effects of steroid therapy on inflammatory cell subtypes in asthma. *Thorax* 2010; 65(5): 384-390.
43. Demarche SF, Schleich FN, Henket MA, Paulus VA, Van Hees TJ, Louis RE. Effectiveness of inhaled corticosteroids in real life on clinical outcomes, sputum cells and systemic inflammation in asthmatics: a retrospective cohort study in a secondary care centre. *BMJ Open* 2017; 7(11): e018186.
44. Bacci E, Cianchetti S, Ruocco L, Bartoli ML, Carnevali S, Dente FL, Di Franco A, Giannini D, Macchioni P, Vagaggini B, Morelli MC, Paggiaro PL. Comparison between eosinophilic markers in induced sputum and blood in asthmatic patients. *Clin Exp Allergy* 1998; 28(10): 1237-1243.
45. Jatakanon A, Lim S, Barnes PJ. Changes in sputum eosinophils predict loss of asthma control. *Am J Respir Crit Care Med* 2000; 161(1): 64-72.
46. Sozanska B, Blaszczyk M, Pearce N, Cullinan P. Atopy and allergic respiratory disease in rural Poland before and after accession to the European Union. *Journal of Allergy and Clinical Immunology* 2014; 133(5): 1347-1353.
47. Boyd A, Golding J, Macleod J, Lawlor DA, Fraser A, Henderson J, Molloy L, Ness A, Ring S, Davey Smith G. Cohort Profile: the 'children of the 90s'--the index offspring of the Avon Longitudinal Study of Parents and Children. *Int J Epidemiol* 2013; 42(1): 111-127.
48. Juniper EF, Gruffydd-Jones K, Ward S, Svensson K. Asthma Control Questionnaire in children: validation, measurement properties, interpretation. *Eur Respir J* 2010; 36(6): 1410-1416.
49. Wickens K, Lane JM, Fitzharris P, Siebers R, Riley G, Douwes J, Smith T, Crane J. Farm residence and exposures and the risk of allergic diseases in New Zealand children. *Allergy* 2002; 57(12): 1171-1179.

50. Weiland SK, Bjorksten B, Brunekreef B, Cookson WOC, von Mutius E, Strachan DP, International Study Asthma A. Phase II of the international study of asthma and allergies in childhood (ISAAC II): rationale and methods. *European Respiratory Journal* 2004; 24(3): 406-412.
51. Amoah AS, Obeng BB, Larbi IA, Versteeg SA, Aryeetey Y, Akkerdaas JH, Zuidmeer L, Lidholm J, Fernandez-Rivas M, Hartgers FC, Boakye DA, van Ree R, Yazdanbakhsh M. Peanut-specific IgE antibodies in asymptomatic Ghanaian children possibly caused by carbohydrate determinant cross-reactivity. *J Allergy Clin Immunol* 2013; 132(3): 639-647.
52. Hamid F, Versteeg SA, Wiria AE, Wammes LJ, Wahyuni S, Supali T, Sartono E, van Ree R, Yazdanbakhsh M. Molecular diagnostics and lack of clinical allergy in helminth-endemic areas in Indonesia. *J Allergy Clin Immunol* 2017; 140(4): 1196-1199 e1196.
53. Gibson PG, Wlodarczyk JW, Hensley MJ, Gleeson M, Henry RL, Cripps AW, Clancy RL. Epidemiological association of airway inflammation with asthma symptoms and airway hyperresponsiveness in childhood. *Am J Respir Crit Care Med* 1998; 158(1): 36-41.
54. Paggiaro PL, Chanez P, Holz O, Ind PW, Djukanovic R, Maestrelli P, Sterk PJ. Sputum induction. *Eur Respir J Suppl* 2002; 37: 3s-8s.
55. Soto-Quiros M, Avila L, Platts-Mills TA, Hunt JF, Erdman DD, Carper H, Murphy DD, Odio S, James HR, Patrie JT, Hunt W, O'Rourke AK, Davis MD, Steinke JW, Lu X, Kennedy J, Heymann PW. High titers of IgE antibody to dust mite allergen and risk for wheezing among asthmatic children infected with rhinovirus. *J Allergy Clin Immunol* 2012; 129(6): 1499-1505 e1495.
56. Lawlor DA, Tilling K, Davey Smith G. Triangulation in aetiological epidemiology. *Int J Epidemiol* 2016; 45(6): 1866-1886.

57. Shen RL, Olshen AB, Ladanyi M. Integrative clustering of multiple genomic data types using a joint latent variable model with application to breast and lung cancer subtype analysis. *Bioinformatics* 2009; 25(22): 2906-2912.
58. McGrath KW, Icitovic N, Boushey HA, Lazarus SC, Sutherland ER, Chinchilli VM, Fahy JV, Asthma Clinical Research Network of the National Heart L, Blood I. A large subgroup of mild-to-moderate asthma is persistently noneosinophilic. *Am J Respir Crit Care Med* 2012; 185(6): 612-619.
59. Gibson PG, Simpson JL, Saltos N. Heterogeneity of airway inflammation in persistent asthma : evidence of neutrophilic inflammation and increased sputum interleukin-8. *Chest* 2001; 119(5): 1329-1336.
60. Pearce N, Aït-Khaled N, Beasley R, Mallol J, Mitchell E, Robertson C, ISAAC Phase Three Study group. Worldwide trends in the prevalence of asthma symptoms: Phase Three of the International Study of Asthma and Allergies in Childhood (ISAAC). *Thorax* 2007; 62: 757-765.
61. Muraro A, Lemanske RF, Jr., Hellings PW, Akdis CA, Bieber T, Casale TB, Jutel M, Ong PY, Poulsen LK, Schmid-Grendelmeier P, Simon HU, Seys SF, Agache I. Precision medicine in patients with allergic diseases: Airway diseases and atopic dermatitis-PRACTALL document of the European Academy of Allergy and Clinical Immunology and the American Academy of Allergy, Asthma & Immunology. *J Allergy Clin Immunol* 2016; 137(5): 1347-1358.
62. Custovic A, Ainsworth J, Arshad H, Bishop C, Buchan I, Cullinan P, Devereux G, Henderson J, Holloway J, Roberts G, Turner S, Woodcock A, Simpson A. The Study Team for Early Life Asthma Research (STELAR) consortium 'Asthma e-lab': team science bringing data, methods and investigators together. *Thorax* 2015; 70(8): 799-801.

63. Wang F, He XY, Baines KJ, Gunawardhana LP, Simpson JL, Li F, Gibson PG. Different inflammatory phenotypes in adults and children with acute asthma. *European Respiratory Journal* 2011; 38(3): 567-574.