Published in final edited form as:
Mayo Clin Proc. 2013 August ; 88(8): 813–821. doi:10.1016/j.mayocp.2013.05.021.

Asthma and Risk of Selective IgA Deficiency or Common Variable Immunodeficiency: A Population-Based Case-Control Study

Sang-Hwa Urm, MD, Ph.D.[1,2], **Hyun Don Yun, MD**[1,3], **Yilma A. Fenta, MD**[1], **Kwang Ha Yoo, MD, Ph.D.**[4], **Roshini S. Abraham, Ph.D.**[5], **John Hagan, MD**[6], and **Young J. Juhn, MD, MPH**[1]

[1]Department of Pediatric and Adolescent Medicine, Mayo Clinic, Rochester, MN

[2]Department of Preventive Medicine, Medical College, Inje University, Busan, South Korea

[3]Department of Medicine, Harbor Hospital, Baltimore, MD

[4]Department of Internal Medicine, Konkuk University School of Medicine, Seoul, South Korea

[5]Division of Clinical Biochemistry and Immunology, Mayo Clinic, Rochester, MN

[6]Division of Allergic Diseases, Mayo Clinic, Rochester, MN

Abstract

Objectives—To determine the association between a prior history of asthma and diagnosis of sIgAD/CVID.

Methods—The study was designed as a population-based case-control study, which included sIgAD/CVID cases who met the PAGID/ESID diagnostic criteria from the residents of Olmsted County, MN, in January 1, 1964 through December 31, 2008. Each case had 4 age- and gender-matched controls (two from the community and two from a list of individuals who had undergone an immune work up). We ascertained asthma status by applying predetermined criteria for asthma.

Results—We identified 39 sIgAD/CVID cases; 26 (66.7%) had sIgAD and the remaining cases had CVID. Of the 39 cases, 51.3% were male and 97.1% were Caucasians. The mean age at the index date (time when one met the criteria) of sIgAD/CVID was 34.2 years. Of the 39 cases, 9 (23%) had a history of asthma prior to index date of sIgAD/CVID; whereas of the 156 controls, 13 (10%) had a history of asthma prior to index date (OR: 2.77, 95%CI: 1.09-7.06, *P=.03*). A history of asthma (before or after the index date of sIgAD/CVID) was more prevalent among sIgAD/CVID cases (31%) than matched controls (12%) (OR: 3.57, 95%CI: 1.50-8.51, *P=.01*).

Conclusions—Asthmatics are more likely to have a diagnosis of sIgAD/CVID compared to non-asthmatics. This association may potentially account for increased risks of bacterial infections among some individuals with asthma.

Corresponding Author: Young J. Juhn, M.D., MPH, Department of Pediatric and Adolescent Medicine, 200 First St. SW, Rochester, MN 55905, Telephone: 507-538-1642, Fax: 507-538-1852, Juhn.Young@mayo.edu.

Conflict of interest statement
Declaration of all sources of funding:

Keywords

Asthma; selective IgA deficiency; common variable immunodeficiency; primary immunodeficiency; case-control study; epidemiology; risk

Asthma is the most common chronic illness in childhood and a major cause of morbidity in adults, affecting 9.6-13% of children,[1,2] 7.7-10.1% of adults in the US,[2,3] and 300 million people globally.[4] Individuals with asthma have an increased risk of serious pneumococcal disease,[5,6] and we have also shown this association with Streptococcus pyogenes,[7] otitis media,[8] and Bordetella pertussis infections.[9] The Advisory Committee on Immunization Practices of the US now recommends that all adult asthmatics (19-64 years) receive a single dose of 23-valent pneumococcal vaccine to prevent serious pneumococcal disease.[10] The mechanisms underlying the increased risk of microbial infections among asthmatics are unknown. Previous studies have shown that individuals with asthma or other atopic conditions have impaired innate[11-15] and adaptive immunity,[16-20] which may result in increased risk of microbial infections.

Another potential hypothesis, other than global immune incompetence for the increased risk of microbial infections in asthmatics, is the presence of an underlying primary immune deficiency (PID) such as selective IgA deficiency (sIgAD) or Common Variable Immunodeficiency (CVID), which in the latter case is frequently associated with sinopulmonary infections may be disproportionately overrepresented among patients with asthma due to unrecognized yet shared immunogenetic mechanisms. The etiopathogenesis of both sIgAD and CVID, which are the two most common PID, is multifactorial. The exact causal mechanism underlying selective IgA deficiency is an area of ongoing investigation. With a reported twenty percent of selective IgAD patients having detectable autoantibodies, most whom have not previously received exogenous immunoglobulin, recent evidence has suggested probable causes to include autoimmune mechanisms along with probable defects in the maturation of B cells into IgA-producing plasma cells (e.g., isotype switching defect or post-switch defect).[21-23] There may be other causes for sIgAD that have not been fully elucidated.[21] CVID is probably an oligogenic PID in the majority of patients with a monogenic etiology in a minority.[24,25] Some authors have regarded these two conditions as part of a spectrum of immunodeficiency with varying severity ranging from IgA deficiency to panhypogammaglobulinemia,[26-30] with a common molecular etiology, at least in some cases. Examples would include the reported mutations in the *TNFRSF13B* gene encoding the TACI protein (TACI gene-transmembrane activator and calcium-modulator and cyclophilin ligand interactor), which is involved in isotype class-switching to IgA, or the MHC genes).[30-32]

Indeed, there have been many cross-sectional studies that show a higher prevalence of asthma or other atopic conditions in patients with sIgAD[33-41] or CVID suggesting a potential association.[42-44] However, little is known about whether patients with asthma or other atopic conditions are predisposed to (i.e., asthma as a preceding factor) development of diagnosis of sIgAD or CVID over time or whether asthma or atopy could be a phenotypic marker for a subgroup of sIgAD/CVID patients. To date, there is no a population-based study that has evaluated whether or not asthma represents a predisposing risk factor for diagnosis of sIgAD or CVID. Given the potential delay in diagnosis of sIgAD (mean duration of 10.5 years)[45] and CVID (median duration of 5.8 years)[46] and the increased risk of microbial infections among asthmatics, this information may be useful for early identification of a subgroup of asthmatics with sIgAD or CVID to better manage risk of infections and other conditions. We hypothesized that a prior history of asthma is more

prevalent among individuals with a diagnis of sIgAD or CVID than matched controls without sIgAD or CVID.

METHODS

The study was approved by both the Institutional Review Boards at Mayo Clinic and Olmsted Medical Center. This is a population-based, retrospective case-control study with 39 cases and 156 controls from Olmsted County, MN, 1964 through 2008, designed to assess if asthma is associated with the incidence of sIgAD/CVID.

Study Population and Setting

Characteristics of the Olmsted County populations were similar to those of the U.S. Caucasian population, with the exception of a higher proportion of the working population employed in the health care industry.[47] If a patient grants the authorization (95% compliance), under the auspices of the Rochester Epidemiology Project (REP),[48,49] each patient is assigned a unique identifier; all clinical diagnoses are electronically indexed, and information from every episode of care is contained within detailed patient-based medical records; essentially, all medical care settings and providers are linked. Using REP resources, we previously demonstrated that incidence rates of asthma for this community are similar to other communities. The incidence rate of asthma in Rochester was 238 cases per 100,000 persons, which is comparable to those in other communities such as Tecumseh, Michigan, (250/100,000) during the study period.[50]

Study Design

This study was designed as a population-based, cumulative incidence, case-control study in which cases occurring during the study period (1964-2008) were included, but controls were selected from among individuals who, at the end of the study period, had not developed sIgAD or CVID. In this study we included both sIgAD and CVID patients due to the relative frequency of these PIDs compared to others.[26-30] Controls were matched to cases with regard to birthday (within 1 year), gender, and clinic registration year (within 1 year) and clinic visit date within 1 year of index date of case. Thus, cases and controls had similar follow-up duration. We then compared the frequency of a history of asthma prior to index date of sIgAD/CVID and a history of ever having had asthma (regardless of index date of sIgAD or CVID) between cases and controls. Data abstraction from chart review was conducted by a physician (HDY) who was blinded throughout the entire study period with regard to the study hypothesis and status of case and control for each study subject.

Subject Selection

Case ascertainment—To identify all potential sIgAD/CVID cases among both adults and children, we utilized three different data sources: 1) the REP database listing all Olmsted County, MN, residents with a unique identifier (ICD codes used: 279.01, 279.06, 279.03, and 279.0), 2) a clinical immunology laboratory database listing all individuals who had undergone immunology work up between 1984-2008, and 3) a previous study database for primary immunodeficiency.[51] Merging all these data sources, we identified a total of 228 potential sIgAD/CVID cases.

Subsequently, we applied the Pan-American Group for Immunodeficiency (PAGID) and European Society for Primary Immunodeficiency (ESID) criteria for sIgAD/CVID. [52] Briefly, the criteria for complete sIgAD includes: 1) IgA level < 7mg/dL AND normal IgG and IgM, 2) age greater than 4 years, and 3) other causes of hypogammaglobulinemia were ruled out. The criteria for probable sIgAD included: 1) IgA level at least less than 2 standard deviation below normal for age with normal IgG and IgM, 2) age greater than 4 years, and

3) other causes of hypogammaglobulinemia were ruled out. We included both definite and probable sIgAD cases in this study. The criteria for probable CVID included: 1) low IgG and/or low IgA/low IgM, 2) absence of functional antibody responses to protein or polysaccharide antigens (Diphtheria toxoid, Tetanus toxoid, *Haemophilus influenzae* B (HiB), pneumococcal vaccines, isohemagglutinins), or IgG levels less than 400mg/dL,[53] 3) age greater than 2 years, and 4) recurrent sinopulmonary infections. The criteria for possible CVID included: 1) either low IgG, low IgA or low IgM, 2) absence of antibody response to peptide or polysaccharide antigens (Diphtheria, Tetanus toxoid, Hib, Pneumovax) and/or absence isohemagglutinin or IgG level less than 400mg/dL, 3) subjects must be older than 2 years of age, and 4) recurrent sinopulmonary infections.[54] In this study, we included both probable and possible CVID cases. The criteria for recurrent infection were based on the Jeffrey Modell Foundation Medical Advisory Board's 10 warning signs for PID.[54]

Our exclusion criteria included: 1) subject who did not meet the PAGID/ESID criteria for sIgAD/CVID (e.g., <2 year of age for CVID and <4 years of age for sIgAD), 2) people without research authorization for using medical records for research, 3) non-Olmsted County, MN, residents (to exclude referral patients from elsewhere), 4) individuals with documented hypogammaglobulinemia due to primary or secondary immune deficiency suggested by PAGID and ESID: i) drug-induced conditions (e.g., immunosuppressants and high-dose systemic corticosteroid), ii) genetic disorders (e.g., ataxia telangiectasia), iii) infectious diseases (e.g., human immunodeficiency virus infection), iv) malignancy (e.g., chronic lymphocytic leukemia), v) other systemic diseases (e.g., protein losing enteropathy), and vi) chromosomal anomalies (e.g., chromosome 18q-syndrome), vii) reported PID other than sIgAD/CVID,[55] and viii) conditions listed in Table I, which made ascertainment of asthma difficult.

Identification of controls—After eligible cases were identified, to address detection bias (i.e., asthma status may influence a likelihood of sIgAD/CVID), we identified two sets of controls. Controls were matched to cases with regard to birthday (within 1 year), gender, clinic registration date, and clinic visit date within 1 year of index date of sIgAD/CVID. One set of controls was two controls (per case, i.e., 1:2 matching) randomly selected from the REP database (i.e., Olmsted County, MN, residents without sIgAD/CVID) who met the matching criteria. Another set of controls included two controls selected from an immunology database listing all Olmsted County, MN, residents who had undergone immunologic workup and had normal results and who met the matching criteria. Therefore, one case had four controls (two controls from the community and two controls from immunology lab database). The exclusion criteria for controls were the same as those for cases.

Exposure ascertainment (asthma status)—For ascertaining asthma status of all cases and controls, we conducted comprehensive medical record reviews to apply predetermined criteria for asthma. The criteria are delineated in Table 1. These criteria have been extensively used in research for asthma epidemiology and were found to have high reliability.[47,56-65] We included both definite and probable asthma because most probable asthmatics become definite over time.[47,65] Given the difficulty to determine the accurate time of development of sIgAD/CVID, in our study, we determined whether asthma status by predetermined criteria might precede the diagnosis of sIgAD/CVID instead of actual development of sIgAD/CVID.

Data Analysis

The primary analysis was to compare the frequency of a history of asthma prior to index date (diagnosis date) of sIgAD/CVID between sIgAD/CVID cases and their matched

controls. The secondary analysis was to compare the frequency of a history of ever having asthma between sIgAD/CVID cases and their matched controls. In the analysis, we combined sIgAD and CVID cases since each category had a small sample size and could be considered part of a spectrum of humoral immunodeficiency conditions. Matched analysis was carried out using a conditional logistic regression model to calculate odds ratios and their corresponding 95%CI. First, we calculated the odds ratio for the association between asthma and sIgAD/CVID using cases and all controls combined (1:4 matching). Subsequently, we carried out analysis using cases and their matched controls from the community and the immunology lab database separately (i.e., 1:2 matched analysis for cases and their community controls, and 1:2 matched analysis for cases and their immunology lab controls). All analysis was performed using SAS 9.1 (SAS Institute Inc., NC).

RESULTS

Study Subjects

Initially, we identified 228 potential sIgAD/CVID cases from three different data sources, and 189 subjects were excluded based on the exclusion criteria. The reasons for exclusion included: 1) failure to meet the PGID/ESID criteria (n=86), 2) no research authorization (n=12), 3) non-Olmsted County, MN, residency (n=22), and 4) secondary immunodeficiency (n=69, 39 subjects for leukemia or malignant lymphoma, 16 for immunosuppressive drugs, and 14 subjects for renal failure). Thus, a total of 39 sIgAD/CVID cases were enrolled in this study, of whom 26 (67%) had sIgAD, and the remaining cases were CVID. Of these 39 cases, 51.3% were male and 97.1% were Caucasians. The mean age at the index date of sIgAD/CVID was 34.2 years. Characteristics of the study subjects are summarized in Table 2.

Association between asthma and sIgAD/CVID—Overall, of the 39 cases, 9 (23%) had a history of asthma prior to index date (diagnosis) of sIgAD/CVID; whereas of the 156 controls, 16 (10%) had a history of asthma prior to index date (diagnosis) (OR: 2.77, 95%CI: 1.09-7.06, *P=.03*). A history of ever having asthma was more prevalent among sIgAD/CVID cases (31%) than matched controls (12%) (OR: 3.57, 95%CI: 1.50-8.51, *P=.01*) (Table 3).

In a separate analysis using the control group from the community alone (see Table 3),the association between a history of asthma prior to index date and the incidence of sIgAD/CVID remained significant (OR: 3.52, 95%CI: 1.05-11.75, *P=.04*), and this was true for the association between a history of ever having asthma and the diagnosis of sIgAD/CVID (OR: 4.98, 95%CI: 1.58-15.71, *P=.01*). If we limit the analysis to the cases and the laboratory controls, the association between a history of asthma prior to index date and the diagnosis of sIgAD/CVID was not statistically significant (OR: 2.46, 95%CI: 0.84-7.17, *P=.10*), but the association between a history of ever having asthma and the diagnosis of sIgAD/CVID was significant (OR:3.02, 95%CI: 1.09-8.35, *P=.03*). Of the 39 cases, 9 developed asthma prior to index date of sIgAD/CVID; and of these 9 asthmatics, only 1 subject was on systemic corticosteroid within 3 months of index date of sIgAD/CVID (1 subject was started on systemic corticosteroid, 13mg prednisone-equivalent dose, 4 days prior to index date of CVID), and 3 subjects were on inhaled corticosteroid or nasal topical steroid.

DISCUSSION

Our study results show that both a prior history of asthma and a history of ever having had asthma are associated with an increased diagnosis of sIgAD/CVID compared to those without such histories (OR: 2.46-4.98). Unlike previous studies, since our study is a population-based study, it is less susceptible to selection (or susceptibility) bias. However,

detection bias is a major concern in investigating the association since exposure status (asthma) might potentially affect a likelihood of detection of outcomes (sIgAD/CVID). Because of this concern, we enrolled two sets of control groups (i.e., community controls and laboratory controls). We limited the analysis to the cases vs. the laboratory controls (who had normal immunology work-up) because the laboratory control group is likely to share similar clinical history (e.g., frequent infections) and access to medical care for evaluation. The results showed the association was still significant and consistent with the exception of the association between a prior history of asthma and sIgAD/CVID, which approached to statistical significance due to limited statistical power. Because we matched clinic registration year and index date between cases and controls ensuring similar follow-up duration, a differential follow-up duration between asthmatics and non-asthmatics within case-control pair is unlikely to explain the association. Also, both exposure status (asthma) and outcomes (sIgAD/CVID) were ascertained by predetermined criteria, and the data abstractor was blinded to the hypothesis and the status of case and control. Thus, performance bias is unlikely. Of 39 sIgAD/CVID cases, only 1 asthmatic subject was on low-dose systemic corticosteroid (13 mg prednisone equivalent dose) at index date of sIgAD/CVID. Hence, exposure to corticosteroid (susceptibility bias) is also unlikely to account for the association. We also conducted a subgroup analysis for definite vs. probable sIgAD/CVID. The association of asthma with definite (OR:15.4, 95%CI: 1.76-135, p=0.014) and probable CVID (OR:13.5, 95%CI:1.51-125, p=0.02) appears to be consistent, although the confidence interval is large due to a small sample size. Also, asthma was consistently associated with development of definite (OR:2.24, 95%CI0.79-6.31, p=0.128) and probable sIgAD (OR:5.04, 95%CI:0.82-30, p=0.081) but they only approached statistical significance due to the limited sample size. Taken together, asthmatics are more likely to represent patients with the sIgAD/CVID diagnosis compared to non-asthmatics over time. Given the potential delay in diagnosis of sIgAD (mean duration of 10.5 years)[45] and CVID (median duration of 5.8 years)[46] and the increased risk of microbial infections among asthmatics, asthmatics may be an important target population with sIgAD/CVID.

Most previous studies assessed the prevalence of asthma or other atopic conditions among patients with sIgAD (15% to 83%).[33,34,36,41] However, there are few longitudinal studies which have assessed whether asthmatics are at a higher risk of developing sIgAD or CVID over time. A few cross-sectional studies showed that IgA levels tend to be lower or deficient among asthmatics than non-asthmatics.[66,67] At present, the role of asthma or atopy in the diagnosis and prognosis of sIgAD or CVID is unknown. To our knowledge, this is the first population-based study investigating the epidemiologic relationship between asthma and sIgAD/CVID by predetermined criteria for both asthma and sIgAD/CVID.

However, given the difficulty to determine the accurate time of the incidence of sIgAD/CVID due to its asymptomatic nature of the disease, it is plausible that sIgAD or CVID might precede asthma. If this is true, our study findings still provide an important insight into the potential role of sIgAD/CVID in development of asthma. For example, it could be hypothesized that patients with sIgAD/CVID would lose part of the capacity to block the entry of allergens through the mucosa, and they would induce sensitization predisposing to development of asthma.

The mechanisms for the association between asthma and sIgAD/CVID are unknown and therefore, we can only speculate based on previously published data. *TNFRSF13B* variants have been suggested as a potential molecular defect associated with sIgAD and CVID, respectively;[30,31] although they only accounted for 6.25% of sIgAD and 8-21% of CVID patients,[30,68] suggesting a role for other genetic defects in the etio-pathogenetisis of sIgAD/CVID. Although little is known about the role of *TNFRSF13B* gene mutations in development of asthma or atopy, a recent study showed that Swedish children with

TNFRSF13B mutations had a 2-fold increased risk of wheezing at 2 and 4 years of age and a 2.5-fold increased risk of asthma at 4 years of age independent of IgE levels.[69] Further studies unraveling the mechanisms underlying this association are needed.

Our study has inherent limitations as a retrospective study. Our study is susceptible to bias intrinsic to retrospective study such as selection or detection bias. A prospective longitudinal study is needed to replicate our study findings. However, a population-based study approach may minimize this concern. Also, the study approach with the laboratory control reduced detection bias. The low prevalence of sIgAD/CVID (a small number of cases) resulted in limited statistical power. However, we were able to detect the association between asthma and sIgAD/CVID. Our study subjects were predominantly Caucasians, which may limit the broad application or generalization of our study findings.

CONCLUSION

Asthma is associated with sIgAD/CVID in certain individuals. Because asthma is heterogeneous, it would be important to examine the phenotype of asthma associated with the immune conditions and to assess if the association can be further specified in a way to identify a subgroup of asthmatics with the immune conditions. Further studies are needed to replicate our study findings.

Acknowledgments

We are grateful for administrative support from Elizabeth Krusemark and Denise Chase and research support from the staff of the Pediatric Asthma Epidemiology Research Unit. We thank Drs. Avni Joshi and Brian Brennan for their support. This work was supported by a grant from the T. Denny Sanford Collaborative Research Fund, a partnership between Sanford Health and Mayo Clinic. This study was made possible by the Rochester Epidemiology Project (grant number R01-AG034676; Principal Investigators: Walter A. Rocca, MD, and Barbara P. Yawn, MD, MSc).

This work was supported by a grant from the T. Denny Sanford Collaborative Research Fund, a partnership between Sanford Health and Mayo Clinic. The work was made possible by the Rochester Epidemiology Project (R01-AG034676) from the National Institute on Aging.

Abbreviations Used

sIgAD	Selective IgA Deficiency
CVID	Common Variable Immunodeficiency
PID	Primary Immune Deficiency
PAGID	Pan-American Group for Immunodeficiency
ESID	European Society for Immunodeficiencies
OR	Odds ratio
CI	Confidence interval

REFERENCES

1. Valet RS, Gebretsadik T, Carroll KN, et al. High asthma prevalence and increased morbidity among rural children in a Medicaid cohort. Annals of Allergy, Asthma & Immunology. 2011 In Press, Corrected Proof.
2. Centers for Disease Control and Prevention. Vital signs: asthma prevalence, disease characteristics, and self-management education: United States, 2001--2009. MMWR Morb Mortal Wkly Rep. 2011; 60:547–552. [PubMed: 21544044]

3. Lethbridge-Cejku M, Vickerie J. Summary of Health Statistics for US Adults: National Health Interview Survey, 2003. National Center for Health Statistics. 2005; 10(225):2005.
4. WHO. Fact Sheet for Asthma. In: Center, WM., editor. Fact Sheet for Asthma N307. Vol. 2006. WHO Media Center; 2005.
5. Talbot TR, Hartert TV, Mitchel E, et al. Asthma as a risk factor for invasive pneumococcal disease. The New England journal of medicine. 2005; 352:2082–2090. [PubMed: 15901861]
6. Juhn YJ, Kita H, Yawn BP, et al. Increased risk of serious pneumococcal disease in patients with asthma. J Allergy Clin Immunol. 2008; 122:719–723. [PubMed: 18790525]
7. Frey DM, Li X, Weaver AL, Jacobson RM, Poland GA, Juhn YJ. Increased Risk of Group A Streptococcal Upper Respiratory Infections in Pediatric Asthmatics. The Journal of Allergy and Clinical Immunology. 2008; 121:S23.
8. Bjur KA, Lynch RL, Fenta YA, et al. Assessment of the association between atopic conditions and tympanostomy tube placement in children. Allergy and asthma proceedings: the official journal of regional and state allergy societies. 2012; 33:289–296. [PubMed: 22584196]
9. Capili CHA, Rigelman-Hedberg N, Fink L, Boyce T, Juhn Y. Increased Risk of Pertussis in Patients with Asthma. Journal of Allergy & Clinical Immunology. 2012; 129:957–963. [PubMed: 22206778]
10. The Advisory Committee on Immunization Practices; the Center for Disease Control and Prevention (CDC). ACIP Provisional Recommendations for Use of Pneumococcal Vaccines. 2008; 2009
11. Ingo M, Tamara K, Anja B, et al. An interaction between filaggrin mutations and early food sensitization improves the prediction of childhood asthma. The Journal of allergy and clinical immunology. 2009; 123:911–916. [PubMed: 19348926]
12. Weidinger S, O'Sullivan M, Illig T, et al. Filaggrin mutations, atopic eczema, hay fever, and asthma in children. Journal of Allergy & Clinical Immunology. 2008; 121:1203–1209. e1201. [PubMed: 18396323]
13. Contoli M, Message SD, Laza-Stanca V, et al. Role of deficient type III interferon-lambda production in asthma exacerbations. Nature Medicine. 2006; 12:1023–1026.
14. Wark PA, Johnston SL, Bucchieri F, et al. Asthmatic bronchial epithelial cells have a deficient innate immune response to infection with rhinovirus. Journal of Experimental Medicine. 2005; 201:937–947. [PubMed: 15781584]
15. Habibzay M, Saldana JI, Goulding J, Lloyd CM, Hussell T. Altered regulation of Toll-like receptor responses impairs antibacterial immunity in the allergic lung. Mucosal Immunol. 2012; 5:524–534. [PubMed: 22549744]
16. Strannegard IL, Lindholm L, Strannegard O. T lymphocytes in atopic children. International Archives of Allergy & Applied Immunology. 1976; 50:684–692. [PubMed: 1083835]
17. Grove DI BT, Wellby ML, Ford RM, Forbes IJ. Humoral and cellular immunity in asthma. Journal of Allergy & Clinical Immunology. 1975; 55:152–163. [PubMed: 1089697]
18. Grove DI RJ, Forbes IJ. Humoral and cellular immunity in atopic eczema. British Journal of Dermatology. 1975; 92:611–618. [PubMed: 1101939]
19. Schneider LC, Weinberg A, Boguniewicz M, et al. Abnormal Immune Response to Varicella Vaccine in Subjects with Atopic Dermatitis Compared to Non-atopic controls. Journal of Allergy and Clinical Immunology. 2008; 121:S272–S273.
20. Yoo KH, Agarwal K, Butterfield M, Jacobson RM, Poland GA, Juhn YJ. Assessment of humoral and cell-mediated immune response to measles-mumps-rubella vaccine viruses among patients with asthma. Allergy and asthma proceedings. 2010; 31:499–506. [PubMed: 21708062]
21. Cerutti, Andrea. Regulation of IgA class switching. Nat Immunol Review. 2008; 8:421–434.
22. Ferreira RC, Pan-Hammarstrom Q, Graham RR, et al. Association of IFIH1 and other autoimmunity risk alleles with selective IgA deficiency. Nature Genetics. 2010; 42:777–780. [PubMed: 20694011]
23. Wang, Ning NS.; Vyse, Timothy J.; Anand, Vidya; Gunnarson, Iva; Sturfelt, Gunnar; Rantapaa, Solbritt; Elvin, Kerstin; Truedsson, Lennart; Andersson, Bengt A.; Dahle, Charlotte; Ortqvist, Eva; Gregersen, Peter K.; Behrens, Timothy W.; Hammarstrom, Lennart. Selective IgA deficiency in autoimmune diseases. Molecular Medicine. 2011; 17:1383–1396. [PubMed: 21826374]

24. Yong PFTF, Grimbacher B. “A rose is a rose is a rose,” but CVID is Not CVID common variable immune deficiency (CVID), what do we know in 2011? Adv Immunol. 2011; 111:47–107. [PubMed: 21970952]
25. Orange JS GJ, Resnick E, Sulivan KE, Lucas M, Ferry B, Kim CE, Hou C, Wang F, Chiavacci R KS, Sleasman JW, Baldassano R, Perez E, Chapel H, Cunningham-Rundles CHH. Genome-wide association identifies diverse causes of common variable immunodeficiency. The Journal of allergy and clinical immunology. 2011; 127:1360–1367. [PubMed: 21497890]
26. Espanol T, Catala M, Hernandez M, Caragol I, Bertran JM. Development of a common variable immunodeficiency in IgA-deficient patients. Clin Immunol Immunopathol. 1996; 80:333–335. [PubMed: 8811056]
27. Johnson ML, Keeton LG, Zhu ZB, Volanakis JE, Cooper MD, Schroeder HW Jr. Age-related changes in serum immunoglobulins in patients with familial IgA deficiency and common variable immunodeficiency (CVID). Clin Exp Immunol. 1997; 108:477–483. [PubMed: 9182895]
28. Aghamohammadi A, Mohammadi J, Parvaneh N, et al. Progression of selective IgA deficiency to common variable immunodeficiency. Int Arch Allergy Immunol. 2008; 147:87–92. [PubMed: 18520152]
29. Litzman J, Burianova M, Thon V, Lokaj J. Progression of selective IgA deficiency to common variable immunodeficiency in a 16 year old boy. Allergol Immunopathol (Madr). 1996; 24:174–176. [PubMed: 8939274]
30. Castigli E, Wilson SA, Garibyan L, et al. TACI is mutant in common variable immunodeficiency and IgA deficiency.[see comment]. Nature Genetics. 2005; 37:829–834. [PubMed: 16007086]
31. Rachid R, Castigli E, Geha RS, Bonilla FA. TACI mutation in common variable immunodeficiency and IgA deficiency. Current Allergy & Asthma Reports. 2006; 6:357–362. [PubMed: 16899196]
32. Volanakis JE, Zhu ZB, Schaffer FM, et al. Major histocompatibility complex class III genes and susceptibility to immunoglobulin A deficiency and common variable immunodeficiency. Journal of Clinical Investigation. 1992; 89:1914–1922. [PubMed: 1351062]
33. Edwards E, Razvi S, Cunningham-Rundles C. IgA deficiency: clinical correlates and responses to pneumococcal vaccine. Clin Immunol. 2004; 111:93–97. [PubMed: 15093556]
34. Aghamohammadi A, Cheraghi T, Gharagozlou M, et al. IgA deficiency: correlation between clinical and immunological phenotypes. J Clin Immunol. 2009; 29:130–136. [PubMed: 18683032]
35. Papadopoulou A, Mermiri D, Taousani S, Triga M, Nicolaidou P, Priftis KN. Bronchial hyper-responsiveness in selective IgA deficiency. Pediatr Allergy Immunol. 2005; 16:495–500. [PubMed: 16176396]
36. Grumach AS, Jacob CM, Pastorino AC. [IgA deficiency: clinical and laboratory evaluation of 60 patients from the “Instituto da Crianca”]. Rev Assoc Med Bras. 1998; 44:277–282. [PubMed: 9852646]
37. Calvo M, Grob K, Bertoglio J, Marin F, Denis R. Secretory IgA deficiency in pediatric patients: clinical and laboratory follow-up. Allergol Immunopathol (Madr). 1990; 18:149–153. [PubMed: 2251975]
38. Michel FB, Guendon R, d’Hinterland LD, Pinel AM, Preault M. [Role of (serum and secretory) IgA deficiency in chronic respiratory disorders. A proposal 21 cases]. Nouv Presse Med. 1975; 4:327–331. [PubMed: 48232]
39. Cunningham-Rundles C. Physiology of IgA and IgA deficiency. Journal of Clinical Immunology. 2001; 21:303–309. [PubMed: 11720003]
40. van de Kant, K.; Jobsis, Q.; deJongste, J.; van Schayck, P.; Muris, J.; Dompeling, E. The 2008 Annual European Respiratory Congress. Berlin, Germany: 2008. Feasibility of noninvasive methods for an early asthma diagnosis in preschool children.
41. De Laat PC, Weemaes CM, Gonera R, Van Munster PJ, Bakkeren JA, Stoelinga GB. Clinical manifestations in selective IgA deficiency in childhood. A follow-up report. Acta Paediatr Scand. 1991; 80:798–804. [PubMed: 1957599]
42. Ogershok PR, Hogan MB, Welch JE, Corder WT, Wilson NW. Spectrum of illness in pediatric common variable immunodeficiency. Ann Allergy Asthma Immunol. 2006; 97:653–656. [PubMed: 17165275]

43. Agondi RC, Barros MT, Rizzo LV, Kalil J, Giavina-Bianchi P. Allergic asthma in patients with common variable immunodeficiency. Allergy. 65:510–515. [PubMed: 19839975]
44. Thickett KM, Kumararatne DS, Banerjee AK, Dudley R, Stableforth DE. Common variable immune deficiency: respiratory manifestations, pulmonary function and high-resolution CT scan findings. Qjm. 2002; 95:655–662. [PubMed: 12324637]
45. Van der Meer, V.; Bakker, M.; Rabe, K., et al. The 2008 Annual European Respiratory Congress. Berlin, Germany: 2008. Improved quality of life by internet-based self-management versus usual care in asthma: a randomized controlled trial.
46. Urschel S, Kayikci L, Wintergerst U, Notheis G, Jansson A, Belohradsky BH. Common variable immunodeficiency disorders in children: delayed diagnosis despite typical clinical presentation. J Pediatr. 2009; 154:888–894. [PubMed: 19230900]
47. Yunginger JW, Reed CE, Connell EJ, Melton LJ 3rd, O'Fallon WM, Silverstein MD. A community-based study of the epidemiology of asthma. Incidence rates, 1964-1983. The American review of respiratory disease. 1992; 146:888–894. [PubMed: 1416415]
48. Sauver JL, Grossardt BR, Yawn BP, Melton LJ, Rocca WA. Use of a Medical Records Linkage System to Enumerate a Dynamic Population Over Time: The Rochester Epidemiology Project. American Journal of Epidemiology. 2011; 173:1059–1068. [PubMed: 21430193]
49. Rocca WA, Yawn BP, Sauver JL, Grossardt BR, Melton LJ. History of the Rochester Epidemiology Project: Half a Century of Medical Records Linkage in a US Population. Mayo Clinic proceedings. Mayo Clinic. 2012; 87:1202–1213. [PubMed: 23199802]
50. Broder I, Higgins MW, Mathews KP, Keller JB. Epidemiology of asthma and allergic rhinitis in a total community, Tecumseh, Michigan. IV. Natural history. The Journal of Allergy and Clinical Immunology. 1974; 54:100–110. [PubMed: 4851886]
51. Joshi AY, Iyer VN, Hagan JB, Sauver JL, Boyce TG. Incidence and temporal trends of primary immunodeficiency: a population-based cohort study. Mayo Clinic Proceedings. 2009; 84:16–22. [PubMed: 19121249]
52. Conley ME, Notarangelo LD, Etzioni A. Diagnostic criteria for primary immunodeficiencies. Representing PAGID (Pan-American Group for Immunodeficiency) and ESID (European Society for Immunodeficiencies). Clin Immunol. 1999; 93:190–197. [PubMed: 10600329]
53. Cunningham-Rundles C, Bodian C. Common variable immunodeficiency: clinical and immunological features of 248 patients. Clinical Immunology. 1999; 92:34–48. [PubMed: 10413651]
54. The Jeffrey Modell Foundation Medical Advisory Board. 10 Warning Sings of Primary Immunodeficiency. 2006; 2011
55. Geha RS, Notarangelo LD, Casanova JL, et al. Primary immunodeficiency diseases: an update from the International Union of Immunological Societies Primary Immunodeficiency Diseases Classification Committee. Journal of Allergy & Clinical Immunology. 2007; 120:776–794. [PubMed: 17952897]
56. Beard CM, Yunginger JW, Reed CE, O'Connell EJ, Silverstein MD. Interobserver variability in medical record review: an epidemiological study of asthma. Journal of clinical epidemiology. 1992; 45:1013–1020. [PubMed: 1432015]
57. Hunt LW Jr. Silverstein MD, Reed CE, O'Connell EJ, O'Fallon WM, Yunginger JW. Accuracy of the death certificate in a population-based study of asthmatic patients. JAMA: the journal of the American Medical Association. 1993; 269:1947–1952. [PubMed: 8464126]
58. Silverstein MD, Reed CE, O'Connell EJ, Melton LJ 3rd, O'Fallon WM, Yunginger JW. Long-term survival of a cohort of community residents with asthma. The New England journal of medicine. 1994; 331:1537–1541. [PubMed: 7969322]
59. Bauer BA, Reed CE, Yunginger JW, Wollan PC, Silverstein MD. Incidence and outcomes of asthma in the elderly. A population-based study in Rochester, Minnesota. Chest. 1997; 111:303–310. [PubMed: 9041973]
60. Silverstein MD, Yunginger JW, Reed CE, et al. Attained adult height after childhood asthma: effect of glucocorticoid therapy. The Journal of allergy and clinical immunology. 1997; 99:466–474. [PubMed: 9111490]

61. Juhn YJ, Qin R, Urm S, Katusic S, Vargas-Chanes D. The influence of neighborhood environment on the incidence of childhood asthma: a propensity score approach. The Journal of allergy and clinical immunology. 2010; 125:838–843. e832. [PubMed: 20236695]

62. Juhn YJ, Sauver JS, Katusic S, Vargas D, Weaver A, Yunginger J. The influence of neighborhood environment on the incidence of childhood asthma: a multilevel approach. Social Science & Medicine. 2005; 60:2453–2464. [PubMed: 15814171]

63. Juhn YJ, Weaver A, Katusic S, Yunginger J. Mode of delivery at birth and development of asthma: A population-based cohort study. Journal of Allergy and Clinical Immunology. 2005; 116:510–516. [PubMed: 16159617]

64. Yawn BP, Yunginger JW, Wollan PC, Reed CE, Silverstein MD, Harris AG. Allergic rhinitis in Rochester, Minnesota residents with asthma: frequency and impact on health care charges. The Journal of Allergy and Clinical Immunology. 1999; 103:54–59. [PubMed: 9893185]

65. Juhn YJ, Kita H, Lee LA, et al. Childhood asthma and measles vaccine response. Annals of allergy, asthma & immunology: official publication of the American College of Allergy, Asthma, & Immunology. 2006; 97:469–476.

66. Grundbacher FJ, Massie FS. Levels of immunoglobulin G, M, A, and E at various ages in allergic and nonallergic black and white individuals. The Journal of allergy and clinical immunology. 1985; 75:651–658. [PubMed: 4008794]

67. Estrella L, Patel C, Forbes L, Cunningham-Rundles C. Asthma and Steroid use in 462 Survey Respondents with Primary Immune Deficiency on IVIg. The Journal of allergy and clinical immunology. 2008; 121:S83.

68. Salzer U, Bacchelli C, Buckridge S, et al. Relevance of biallelic versus monoallelic TNFRSF13B mutations in distinguishing disease-causing from risk-increasing TNFRSF13B variants in antibody deficiency syndromes. Blood. 2009; 113:1967–1976. [PubMed: 18981294]

69. Janzi M, Melen E, Kull I, Wickman M, Hammarstrom L. Rare mutations in TNFRSF13B increase the risk of asthma symptoms in Swedish children. Genes Immun. 2012; 13:59–65. [PubMed: 21850030]

Table 1

Definition of Asthma

Patients were considered to have *definite* asthma if a physician had made a diagnosis of asthma and/or if each of the following 3 conditions were present, and they were considered to have *probable* asthma if only the first 2 conditions were present:

1 History of cough, dyspnea, and/or wheezing, OR history of cough and/or dyspnea plus wheezing on examination,

2 Substantial variability in symptoms from time to time or periods of weeks or more when symptoms were absent, and

3 Two or more of the following:

- Sleep disturbance by nocturnal cough and wheeze
- Nonsmoker (14 yrs or older)
- Nasal polyps
- Blood eosinophilia higher than 300/uL
- Positive wheal and flare skin tests OR elevated serum IgE
- History of hay fever or infantile eczema OR cough, dyspnea, and wheezing regularly on exposure to an antigen
- Pulmonary function tests showing one FEV1 or FVC less than 70% predicted and another with at least 20% improvement to an FEV1 of higher 70% predicted OR methacholine challenge test showing 20% or greater decrease in FEV1
- Favorable clinical response to bronchodilator

Patients were excluded from the study if any of these conditions were present:

- Pulmonary function tests that showed FEV1 to be consistently below 50% predicted or diminished diffusion capacity
- Tracheobronchial foreign body at or about the incidence date
- Wheezing occurring only in response to anesthesia or medications
- Bullous emphysema or pulmonary fibrosis on chest radiograph
- PiZZ alpha1-antitrypsin
- Cystic fibrosis
- Other major chest disease such as juvenile kyphoscoliosis or bronchiectasis

Table 2

Characteristics of sIgAD/CVID Cases and Their Matched Controls

Variables	Case (n=39)	All Controls (n=156)	*P* value	Community Controls (n=78)	*P* value	Lab Controls (n=78)	*P* value
Male (%)	20 (51.3)	80 (51.3)	>.99	40 (51.3)	>.99	40 (51.3)	>.99
Age at Disease Occur (year) Mean±SD[†] Median	34.2±24.2 32.0	34.2±23.9 32.5	.99	34.2±24.0 32.0	>.99	34.2±23.9 33.0	.99
Caucasians (%)[§]	33 (97.1)	133 (91.7)	.28	65 (91.6)	.29	68 (91.9)	.31
Educational level [¶] (%)							
≤ High School degree	24 (61.5)	109 (69.9)	.33	63 (80.8)	.08	46 (59.0)	.61
Some college	4 (10.3)	22 (14.1)		7 (9.0)		15 (19.2)	
College degree	7 (18.0)	14 (9.0)		4 (5.1)		10 (12.8)	
Graduate school degree	4 (10.3)	11 (7.1)		4 (5.1)		7 (9.0)	
Asthma prior to index date, n (%)	9 (23.1)	16 (10.3)	.03	7 (9.0)	.04	9 (11.5)	.10
Asthma ever, n (%)	12 (30.8)	18 (11.5)	.01	7 (9.0)	.01	11 (14.1)	.03
Comorbid conditions	9 (23.1)	18 (11.5)	.06	10 (12.8)	.16	8 (10.3)	.06

[†]SD: standard deviation;

[§]: 16 subjects were missed (5 subjects from case, 7 subjects from community control and 4 subjects from lab control);

[¶]: Chisquare test for trend; Lab: Controls selected from the Immunology Lab. Database

Table 3

Association between Asthma and sIgAD/CVID Stratified by Different Control Groups Based on Matched Analysis

	All Controls		Community Control		Laboratory Control	
	OR matched (95%CI)	***P* value**	**OR matched (95%CI)**	***P* value**	**OR matched (95%CI)**	***P* value**
Asthma prior to index date	2.77 (1.09-7.06)	.03	3.52 (1.05-11.75)	.04	2.46 (0.84-7.17)	.10
Asthma ever	3.57 (1.50 - 8.51)	.01	4.98 (1.58 - 15.71)	.01	3.02 (1.09 - 8.35)	.03

CI: confidence interval