Investigation into IgE Deficiency as a Predictive Marker of Hypogammaglobulinemia

Thomas Makin, MD
Allergy and Immunology Fellow
University of Virginia

Research Mentors: Monica Lawrence MD, Jeffrey Wilson MD, PhD, Larry Borish MD

Overarching Hypothesis:

IgE deficiency serves as a sentinel marker for a defect in humoral immunity. It represents an early marker of evolving common variable immunodeficiency (CVID).

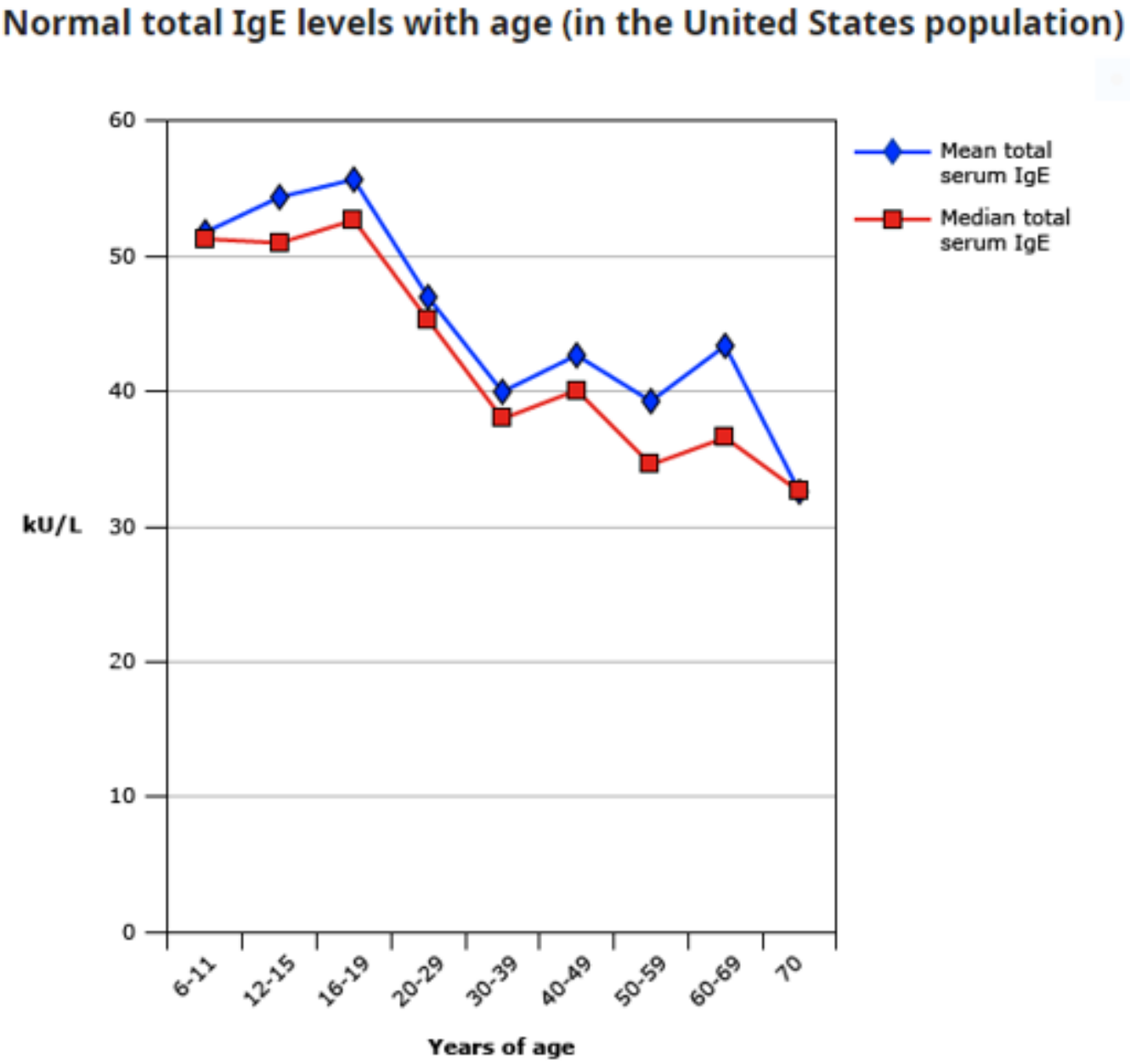
IgE deficiency

UVA lab IgE Reference Range:

- <18 y.o.: 8-144 IU/ mL
- >18 y.o.: 10-180 IU/mL

IgE deficiency: Definitions vary in literature: <2.5 IU/ mL, <2.0 IU/mL, or below lower limit of detection (LLOD)

Prevalence of IgE below LLOD in the general population is estimated to be **3.3%**



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IgE deficiency

Clinical significance remains controversial

Not included in consensus classification of Primary Immunodeficiency Diseases

IgE deficiency has been poorly studied.

- Past studies are **retrospective** and have a persistent **confounding variable** of studying patients who had an IgE ordered by a physician for some reason
  - (e.g. IgE ordered due to concern for malignancy, immunodeficiency, or atopy)

Associations with IgE deficiency

In retrospective studies, IgE deficiency has been associated with numerous conditions (many of which are also commonly seen with CVID):

- Infections (sinopulmonary infections, otitis media, H. pylori infection)
- Non-allergic airway disease
- Autoimmunity
- Malignancy
- Cardiovascular disease

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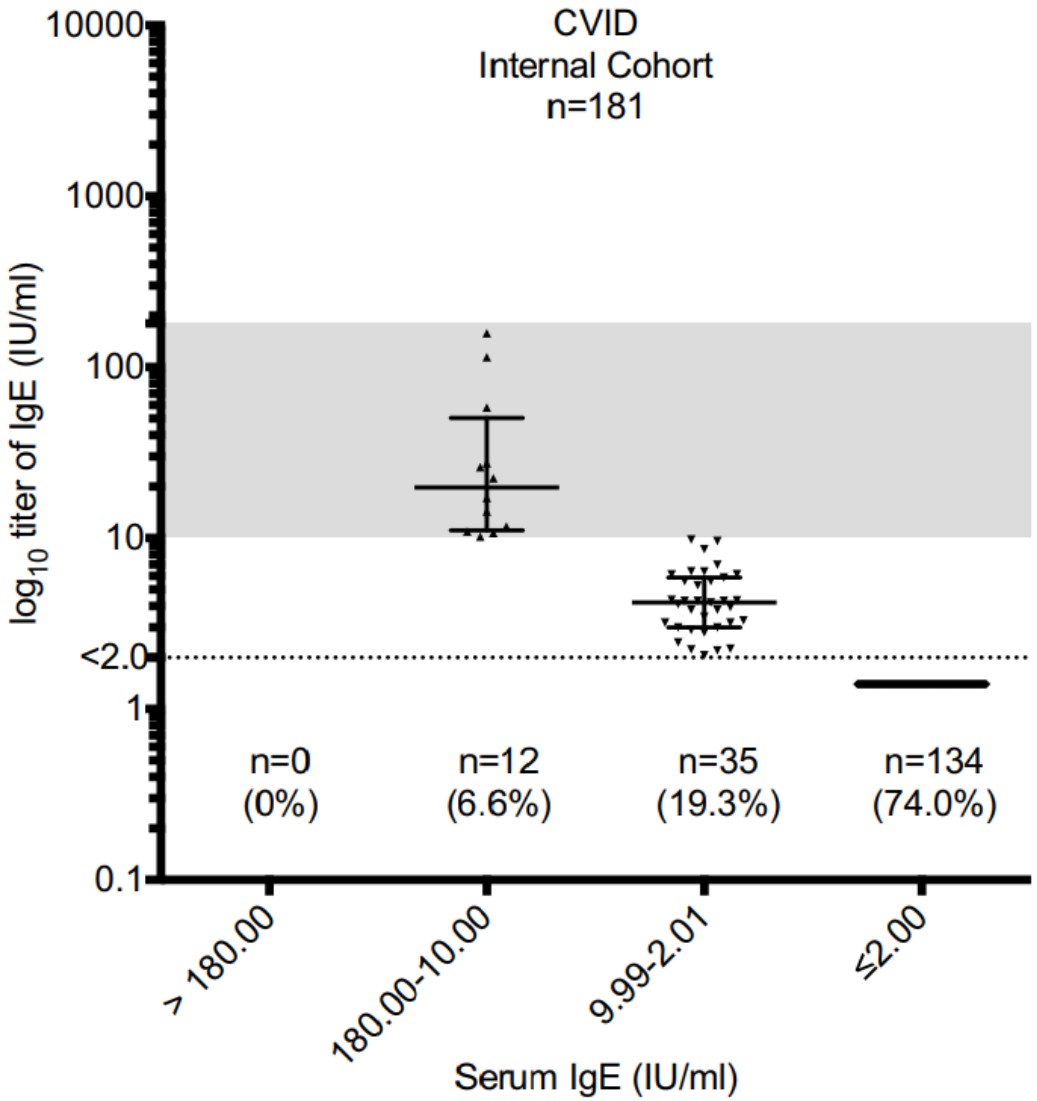
IgE deficiency association with CVID

In patients with CVID (n=607):

- IgE <2 IU/mL in 76%

Using a cutoff of IgE< 2 IU/mL for the diagnosis of CVID :

- Sensitivity is 63%
- Specificity is 96%



Lawrence, M. G. et al. (2018). Low serum IgE is a sensitive and specific marker for common variable immunodeficiency (CVID). *Journal of clinical immunology*, *38*(3), 225-233.

IgE deficiency as a marker for hypogammaglobulinemia

An Immunology laboratory in Chertsey, UK performed reflex measurement of other immunoglobulin classes on patients with IgE deficiency (<2 IU/mL) over a 2.5 year period

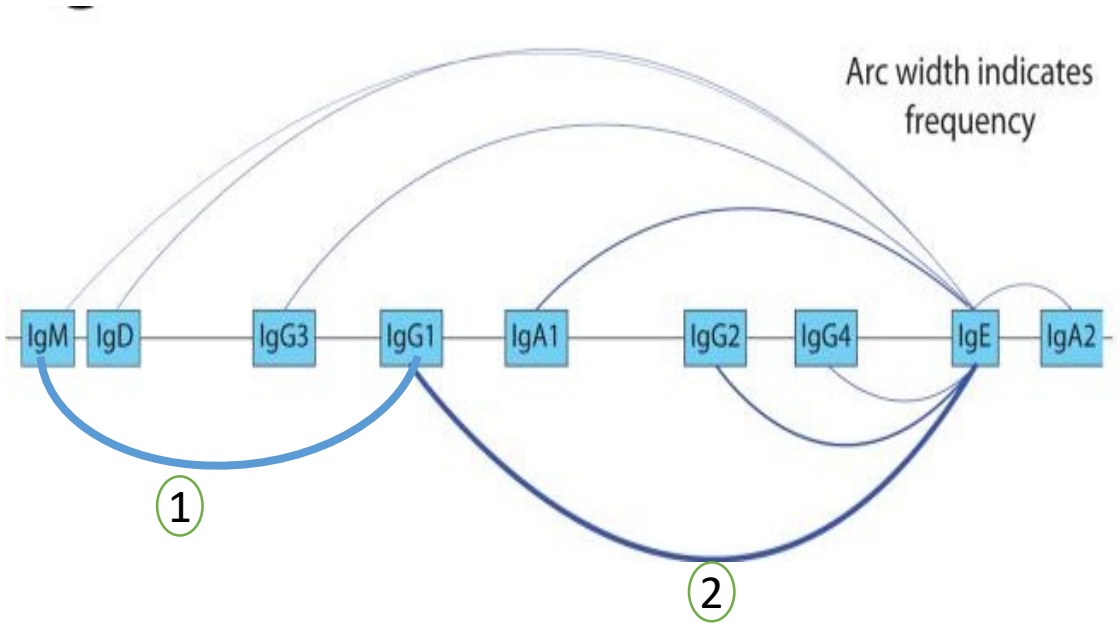
3% (336/11,268) of patients had IgE deficiency

- 10% (25/253) of IgE deficient patients had low IgG levels
  - New diagnoses: CVID (2), hypogammaglobulinemia unclear cause (3), lymphoma (2)

Campisi, L. et al. (2018). Reflex Testing of Immunoglobulins in Patients with Total Serum IgE< 2 kU/L. Journal of clinical immunology, 38(5), 550-552.

IgE deficiency pathophysiology

- IgE production typically occurs through a process requiring 2 class switch recombination (CSR) events
- CVID (broadly) represents a defect in CSR
- If an impairment develops in CSR (I.e. CVID), then IgE production may be affected before other immunoglobulin classes that only require a single CSR event
- IgE deficiency may therefore represent a sentinel marker of an evolving failure of CSR and humoral immunity



Looney, T. J. et al (2016). Human B-cell isotype switching origins of IgE. Journal of Allergy and Clinical Immunology, 137(2), 579-586.

Research Plan

Study questions:

Is IgE deficiency associated with hypogammaglobulinemia?

Does IgE deficiency predict the development of hypogammaglobulinemia?

In this study, we related IgE levels and IgG levels at two points in time in a cohort of 3000 military personnel who had serum biobanked in the Department of Defense serum biorepository

This cohort was originally designed to study the prevalence of alpha-gal sensitization in different geographic areas

- This study population avoided the bias of studying patients who had an IgE level drawn for a clinical indication

Research Plan

Total IgE was measured by ImmunoCAP in a cohort of 3000 military personnel as part of an alpha-gal research study

Subjects with IgE deficiency (IgE < 2 IU/mL) at baseline were identified.

A similar number of sex-matched control subjects with IgE >10 IU/mL at baseline were randomly selected.

For both groups, total IgG was measured by ImmunoCAP at time of enlistment and a second time point, ~3.5 years later.

Hypotheses

1) Subjects with IgE deficiency (IgE < 2 IU/mL) will demonstrate lower levels of IgG at baseline and at the second time point relative to subjects with IgE > 10 IU/mL

2) Subjects with IgE deficiency will demonstrate increased incidence of hypogammaglobulinemia

3) Subjects with IgE deficiency (IgE < 2 IU/mL) will demonstrate a decline in IgG over the assessed time interval (roughly 3.5 years)

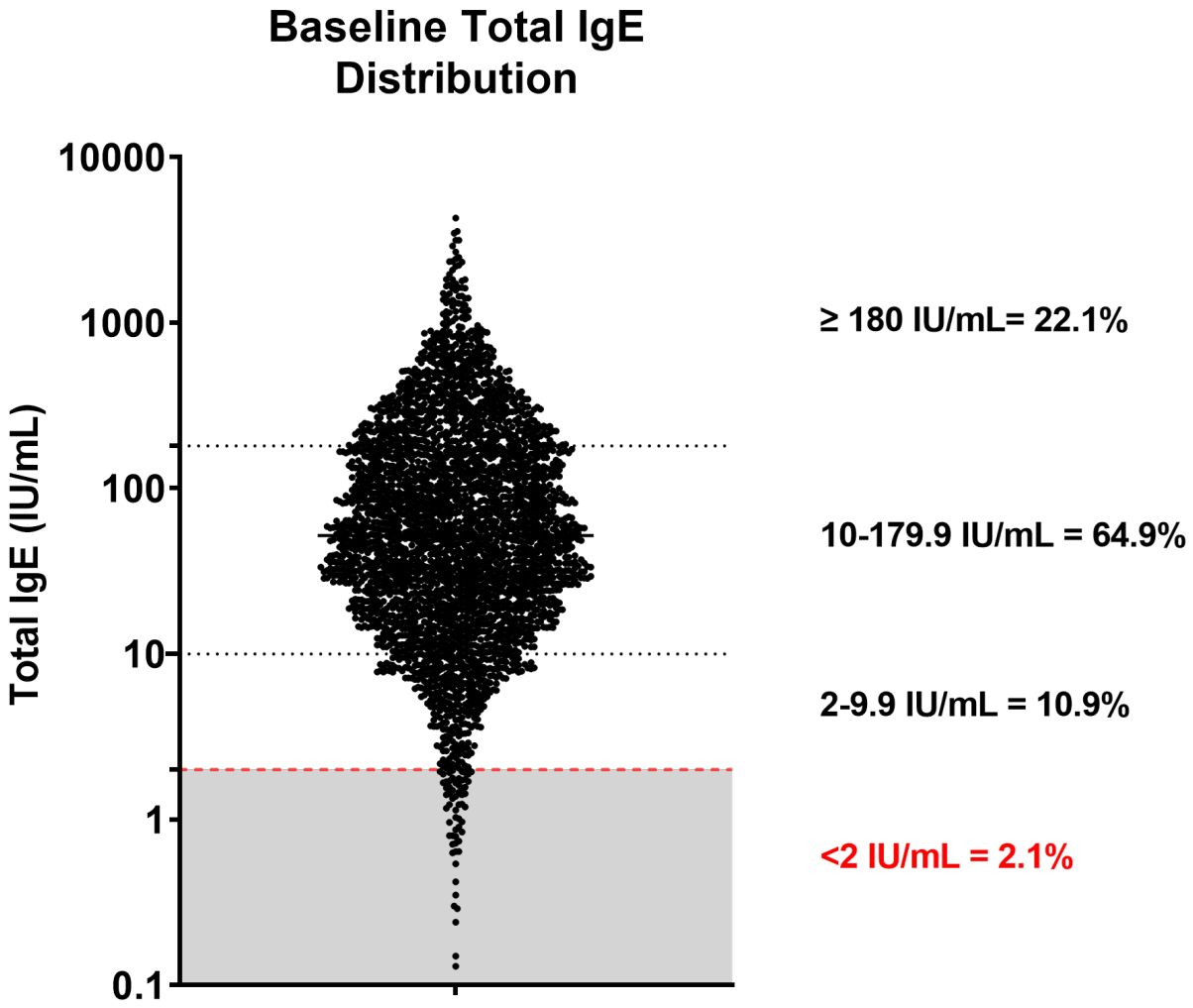
Demographics

	Entire Cohort (n=3000)	IgE <2 IU/mL Group (n=64)	IgE >10 IU/mL Control Group (n=75)
Sex, female (%)	544 (18.1)	18* (28)	21 (28)
Median Age (range)	19 (18-48)	20 (18-41)	19 (18-34)

**P* value= 0.049 comparing IgE<2 IU/mL group with entire cohort

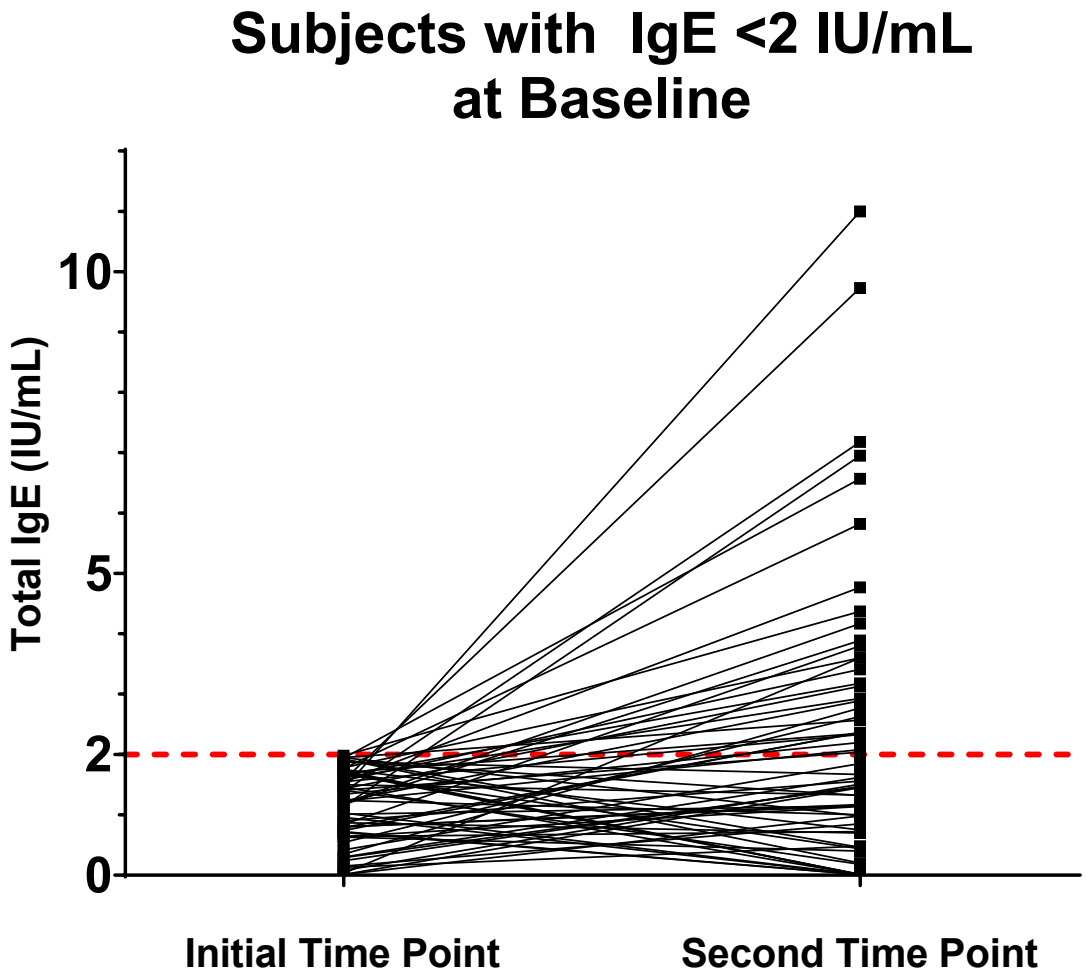
- Study population consisted of 3000 military recruits with sera stored in the Department of Defense BioRepository
- Subjects had sera available at two separate time points with a median interval of 3.4 years apart (range of 3-4 years)
- Females were over-represented among the IgE deficient group

Baseline IgE distribution



	Entire Cohort (n=3000)	IgE <2 IU/mL Group (n=64)	IgE >10 IU/mL Control Group (n=75)
Median Baseline total IgE (IU/mL) (range)	51.8 (0.01-4268)	1.23 (0.01-1.98)	67.6 (10.3- 1821)

IgE Trend among IgE deficient cohort



64 subjects had IgE deficiency at baseline.

Amongst this group at the second time point:

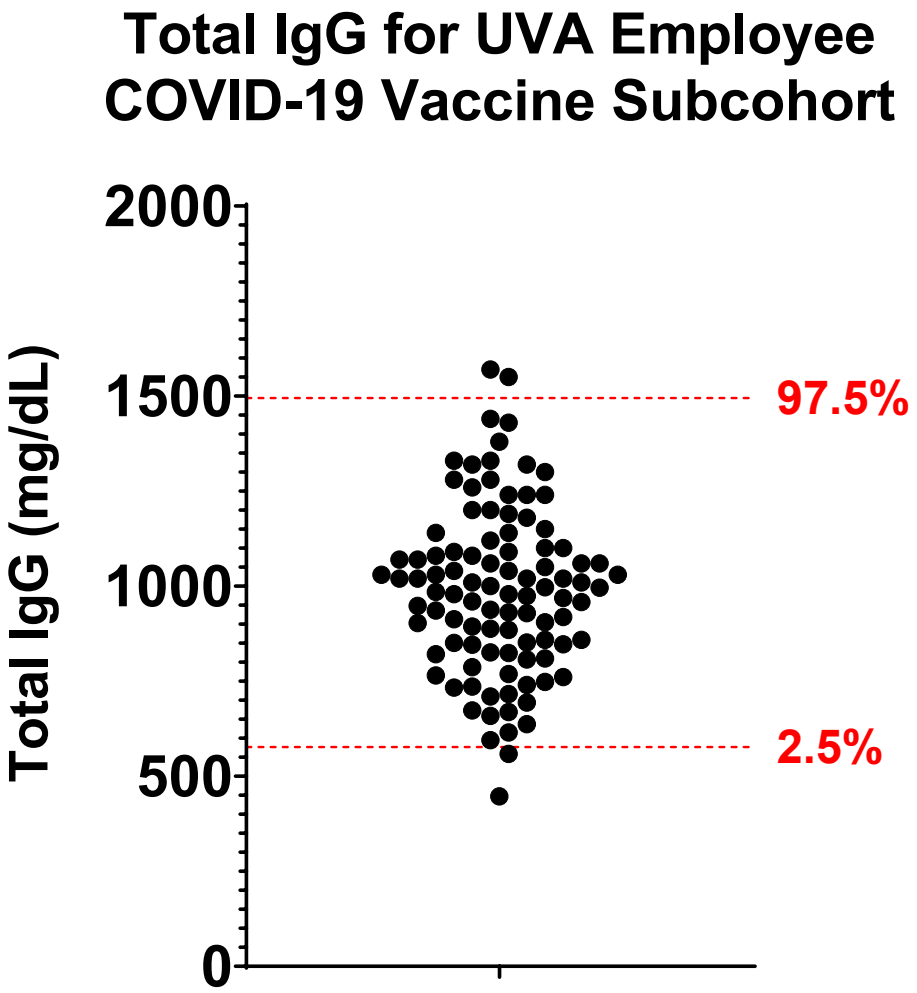
- **55% (35/64)** had IgE <2 IU/mL
- **45% (29/64)** had IgE >2 IU/mL (range 2.1-11)

13 subjects developed new onset IgE deficiency at the second time point (not depicted here)

IgG Reference Range

- A universal reference range for total IgG does not exist
- Each lab creates their own reference range typically by defining the 2.5^{th}- 97.5^{th} percentile IgG values of a sample population
- We established a reference range for total IgG using a University of Virginia employee cohort
  - This cohort was originally designed to study immune responses to COVID-19 vaccination and COVID-19 infection

IgG Reference Range

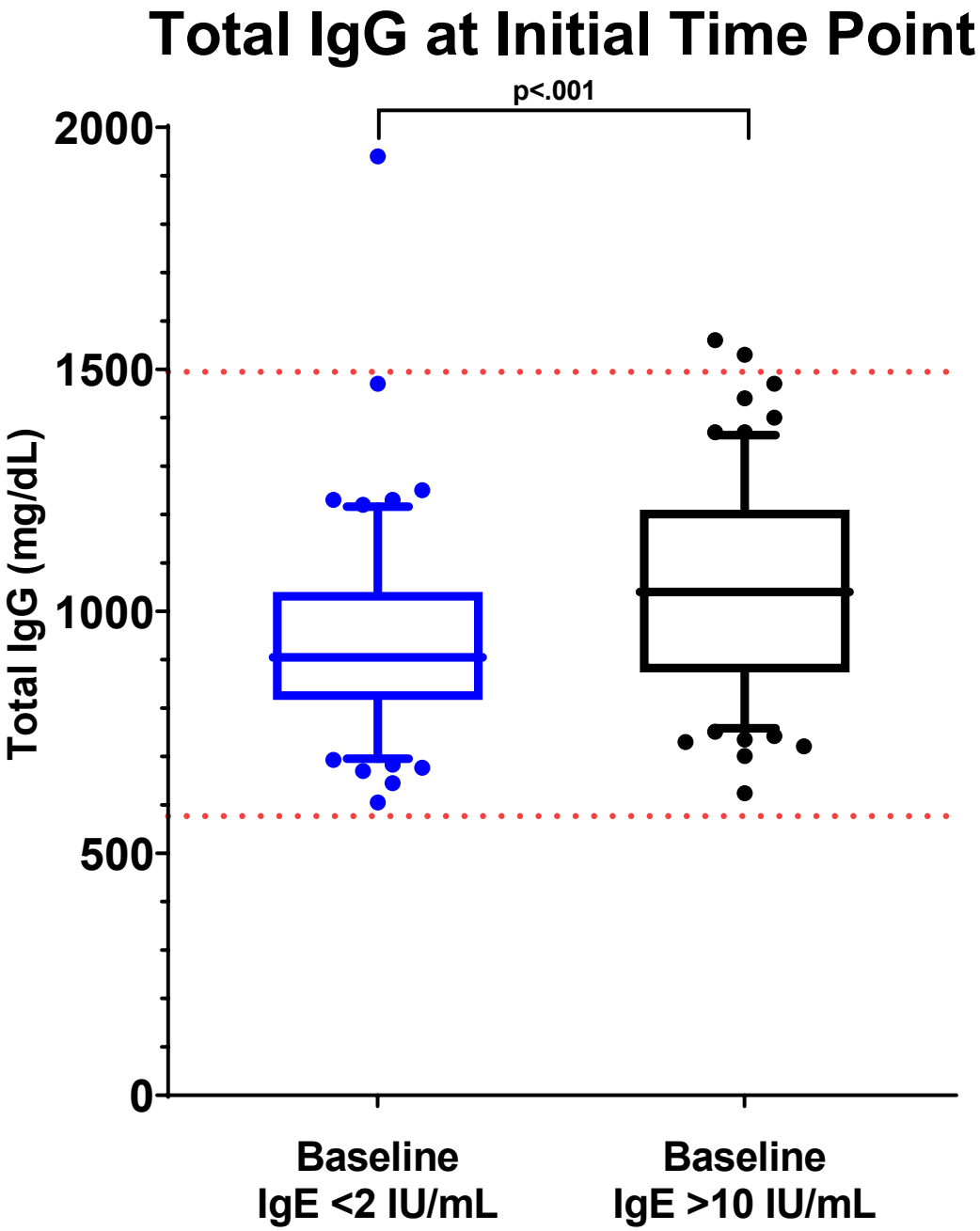


Reference population:

- 50 males and 49 females enrolled in a UVA employee cohort
- Median age= 36 years old
- Serum samples were excluded if the subject had received a COVID-19 vaccine in the preceding 3 months

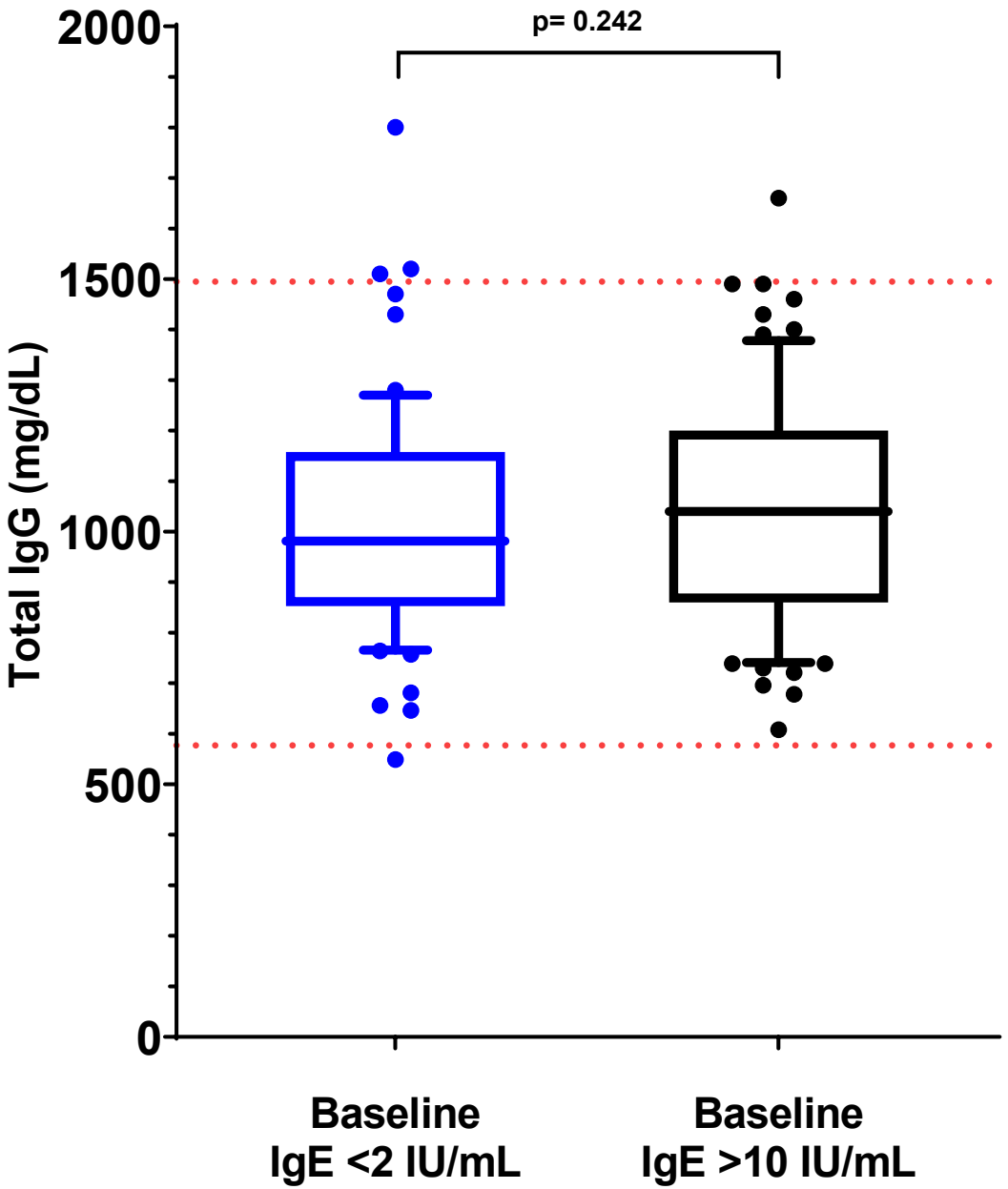
RR (2.5^{th}- 97.5^{th} percentile) =

577-1495 mg/dL



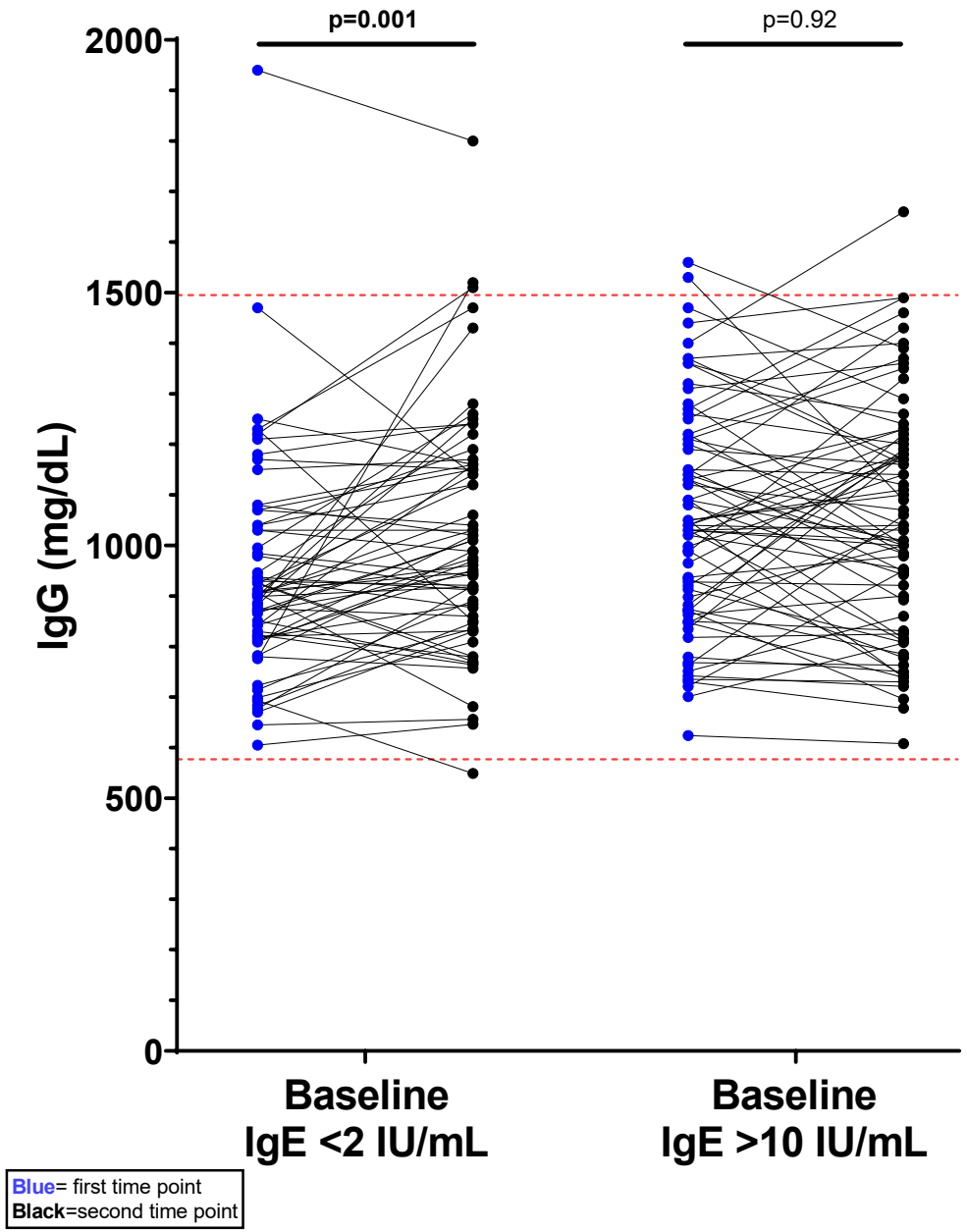
	IgE <2 IU/mL Group (n=64)	IgE >10 IU/mL Control Group (n=75)	*p*-value (Mann-Whitney U test)
Median IgG (mg/dL) (range)	905 (605-1940)	1040 (624-1560)	**P<0.001**

Total IgG at Second Time Point



	IgE <2 IU/mL Group (n=64)	IgE >10 IU/mL Control Group (n=75)	*p*-value (Mann-Whitney U test)
Median IgG (mg/dL) (range)	982 (549-1800)	1040 (608- 1660)	*p*=0.242

Change in Total IgG Over Time (~3.5 years)



	IgE <2 IU/mL Group (n=64)	IgE >10 IU/mL Control Group (n=75)
Median Change in IgG	Increase of 64 mg/dL	Decrease of 10 mg/dL
***p*-value (Wilcoxon matched-pairs signed rank test)**	0.001	0.915

Frequency of hypogammaglobulinemia

	IgE <2 IU/mL Group (n=64)	IgE >10 IU/mL Control Group (n=75)	*p*-value (Fisher's exact test)
Number of subjects with hypogammaglobulinemia at any time point (%)	1 (2)	0 (0)	P=0.46

Results Summary

- IgE deficient subjects had significantly lower IgG levels then non-IgE deficient subjects at baseline; there was not a significant difference between the two groups at the second time point

- 1 subject with IgE deficiency had hypogammaglobulinemia compared to 0 control subjects

- A decline in IgG levels was not observed among IgE deficient patients over the assessed time interval (~3.5 years).

Discussion

Strengths/ novel contributions:

- This study had a large sample size (N=3000)
- We were able to follow the relationship between IgE and IgG in our cohort over two time points
- This study did not have the same selection bias as past studies of IgE deficiency (past studies examined patients who had an IgE ordered by a physician for some reason)

Limitations:

- The time interval in this study was relatively short (3.5 years). IgE deficient patients probably need to be studied over a longer period of time to detect evolving hypogammaglobulinemia
- This study had its own selection bias as the study population consisted of young (median age=19), predominantly male, and presumably healthy military recruits. This affects generalizability.
- The independent cohort used to define the IgG reference range skewed older (median age= 36) than the study population (median age=19). We may not have established an adequate reference range for our younger study population

Discussion

- The association between IgE deficiency and hypogammaglobulinemia was inconsistent in this study

- It’s possible there is only a weak association and only a very small subset of patients are at risk of an evolving humoral immunodeficiency
  - Stronger associations reported in past studies may be due to selection biases (studying patients with a clinical indication to have an IgE drawn)

- It’s possible a strong association exists but limitations of this study prevented its detection

Clinical Implications

- More work is needed to understand the clinical significance of IgE deficiency
- When IgE deficiency is incidentally discovered, it may be prudent to screen patients for a history of recurrent infections and consider checking other immunoglobulin classes
- Based on the findings in this study, hypogammaglobulinemia is unlikely to develop over 3-4 years in IgE deficient patients; repeat screening for hypogammaglobulinemia could be considered every 5 years

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[1]*Division of Allergy & Immunology, University of Virginia, Charlottesville, VA*

[2]*Uniformed Services University of the Health Sciences, Bethesda, MD*

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