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Autoimmunity in the Neuropsychological Manifestations of 22q11.2 Deletion Syndrome

By

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Degree to be awarded: Master of Public Health

Department: Epidemiology

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Committee Chair

Autoimmunity in the neuropsychological manifestations of 22q11.2 deletion syndrome

By

Hidayat Ogunsola

MBBS
Gulf Medical University
2012

Thesis Committee Chair: [Dr. Bradley Pearce, PhD]

An abstract of
A thesis submitted to the Faculty of the
Rollins School of Public Health of Emory University
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2023

Abstract

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The 22q11.2 deletion syndrome (22q11DS) is a chromosomal microdeletion disorder that presents with multiple congenital anomalies and immune conditions. Most of newly identified patients with 22q11DS have de-novo deletions. Development of autoimmunity in patients with 22q11.2 deletion can possibly be due to various mechanisms including infections, molecular mimicry, and bystander activation of autoreactive T lymphocytes by inflammatory cytokines.
Cognitive deficits occur among individuals with 22q11DS, and there is a high rate of autism spectrum disorders as well as psychotic disorders (in particular, schizophrenia).

We hypothesized that there is an association between immune biological factors and neuropsychological manifestations in patients with 22q11DS. By using the existing SERPh22 database comprising of 778 individuals with 22q11DS, leukocyte cell counts (CD3+ CD4+ CD8+ CD19+ CD56+) and immunoglobulin levels (IgA, IgG, IgM) were extracted from the database. I then examined a subset of 23 children from this group to test the association between the immunological factors on record and scores on the Communication and Symbolic Behavior Scales-Developmental Profile Infant-Toddler Checklist (CSBS-DP ITC) and Child Development Inventory profile (CDIP). On regression analysis, IgG was associated with significantly greater impairment in the CSBS-DP ITC Social scale ($B=0.5851$, $SE=0.2299$, $p<0.05$), in models adjusted sex, age at blood work, and age at the behavioral assessment (adjusted $R^2=0.424$). IgA levels were associated with worst outcomes on the CDIP sub-scale, Expressive Language, ($B=0.07177$, $SE=0.0476$, $p<0.05$), in models adjusted for the same covariates (adjusted $R^2=0.514$). Prior studies in other pediatric conditions have found elevated IgG in autoimmunity, through there is little information on its relationship to neurobehavioral parameters. A limitation of this study was the small sample size and multiple comparisons since multiple immune factors were analyzed. Conducting this research in a larger cohort will be beneficial in better understanding the association between immune biological factors and neuropsychological manifestations among patients with 22q deletion syndrome.

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information on its relationship to neurobehavioral parameters. A limitation of this study was the small sample size and multiple comparisons since multiple immune factors were analyzed. Conducting this research in a larger cohort will be beneficial in better understanding the association between immune biological factors and neuropsychological manifestations among patients with 22q deletion syndrome.

Goal of this project

The overarching goal of my thesis is to investigate the relationship between autoimmunity and neuropsychological indices in patients with 22q11 deletion syndrome. To this end, I am relying on an existing database of over 700 individuals with this syndrome that was created by Dr. Pearce and colleagues (termed the SERph22 database).

My original plan was to supplement this database with new data by marshaling and coding the prevalence of specific autoimmune diseases among the individuals in the database. Although we received IRB approval, and my proposal and data request were approved through CHOA, including the division head, the complete data set is not yet available for this thesis.

Fortunately, the SERph22 is a rich data source with extensive immune data relevant to autoimmune disease, especially biological factors such as immune cell counts and the presence or absence of the thymus, and immunoactive hormones (e.g., T3, T4, TSH). The analysis for my thesis is focused on the relationship between immune indices and select neuropsychological outcomes.

INTRODUCTION

Characteristics of the 22q11 deletion syndrome.

22q11.2 deletion syndrome is the most common microdeletion syndrome. The 22q11.2 region of the chromosome is a highly unstable region due to non-homologous meiotic recombination. The misalignment of segmental duplications of this region leads to the deletion of chromosome 22.q11.2.(Hacıhamdioğlu, Hacıhamdioğlu, & Delil, 2015). T-box protein 1 (TBX1) is a gene located on the long arm of chromosome 22, and it is the main gene deleted in 22q11.2 deletion syndrome. Various literature suggests that T-box protein 1 (*TBX1)* is predominantly responsible for the physical malformations seen in patients with 22q11.2 deletion syndrome. (Yagi et al., 2003).

Patients with 22q11.2 deletion syndrome exhibit dysmorphic features including low set ears, micrognathia, cleft palate resulting in feeding difficulties, and defects in the heart(conotruncal), thymus, and parathyroid glands. This is due to the impaired migration of neural crest cells during embryogenesis.(McLean-Tooke, Spickett, & Gennery, 2007). In the 1960s, 22q11.2 deletion syndrome was characterized by the clinical triad of congenital heart defect, immunodeficiency, and hypoparathyroidism. Now, it is known that the condition has heterogenous presentation including autoimmune diseases, gastrointestinal involvement, renal abnormalities, cognitive delays, and psychiatric conditions. (McDonald-McGinn et al., 2015).

Immune abnormalities in autoimmunity in 22q11DS.

Autoimmune conditions occur due to abnormalities in the immune system. The presence of self-reactive B cells and/or T cells results in chronic inflammatory process within target organs, disrupting the normal function of tissues. Immunological tolerance is a process of inhibiting the immune system from mounting responses against self-antigens. (Romagnani, 2006). It is however important to note that healthy individuals exhibit autoreactive T cells and autoreactive B cells. Such T cells and B cells are kept under control by regulatory mechanisms. Autoimmunity develops when there is loss of tolerance to self-antigens. The thymus plays a key role in immune tolerance, in part through regulatory T-cells (Treg cells), which are essential for maintaining self-tolerance. (McLean-Tooke et al., 2007). Patients with 22q11.2 deletion syndrome have abnormal thymic development resulting in decreased frequency of Treg cells and potential disruption of tolerance.

Prior studies on 22q.11.2 deletion syndrome has proposed different mechanisms for the development of autoimmunity. Evidence shows that infections play a role in autoimmunity through the release of sequestered antigens from damage to tissues. Inflammatory cytokines released from infiltrating monocytes and macrophages cause activation of autoreactive T cells. Molecular mimicry is also implicated in the development of autoimmunity when microbial products share structural similarity with endogenous peptides. (McLean-Tooke et al., 2007). Prior studies have been small-scale since the prevalence of 22q.11.2 deletion syndrome is approximately 1/4000 births.

Neuropsychological manifestations in 22q.11.2

Neuropsychological manifestations in 22q.11.2 deletion syndrome include autism spectrum disorders, intellectual disability, and schizophrenia. Studies have also shown that some individuals with this syndrome also have and increased rate of attention-deficit/hyperactivity disorder (ADHD), anxiety and emotional instability compared to the general population. (Niklasson, L et al., 2001).

For my thesis I achieved the following aims:

Aim 1. Construct a table of all the available literature on autoimmune disorders in 22q11DS.

Aim 2. Download deidentified data on leukocyte cell counts and immunoglobulin levels, and cross index this with the availability of individual data (scores) on psychometric tests.

Aim 3. Examine the characteristics of this data, such as normality and redundancy, and develop a modeling strategy.

Aim 4. Use regression analysis to investigate the association between levels of these immune parameters and psychological outcomes.

METHODS:

Sample

The study population include over 778 individuals with 22q.11DS from the SERph22 database maintained by Dr. Pearce. Biologic factors relevant to autoimmune disease such as counts in peripheral blood of T-cells (CD3+, CD4+, CD8+), B-cells (CD19+), and Natural Killer (NK) cells (CD56+) along with the immunoglobulins A, G and M were extracted from the SERph22 database. Behavioral assessments with sufficient data were also extracted for cross-correlation and linear regression analysis. As described below, CSBS-DP and CDIP data were selected to be included in the study. Behavioral assessment data were derived from questionnaires from participants at the 22q Specialty Clinic at Children's Healthcare of Atlanta between October 2006 to December 2017.

Literature Review Search strategy and selection criteria:

I searched PubMed, Embase, Web of Knowledge, SCOPUS, and CINAHL, and Google Scholar electronic database from Jan 1, 1997, to Jan 1, 2023, for studies reporting autoimmune diseases among patients with 22q.11DS. After consultation with an expert librarian, the search strategy was developed. I limited the search to humans and language to English. I used the following search terms, adapted for each database when appropriate: "chromosome 22 microdeletion 22 q11", "22q11 Deletion Syndrome", "22q11*", "digeorge", AND "Autoimmune Diseases", "autoimmune", and "autoimmunity". In addition to literature searches, I conducted gathered data on ICD codes related to autoimmune disease.

Data from Psychological Assessment Instruments

The CSBS-DP is used in patients 6-24 months of age, while the CDIP is used in pediatric age group between 15 months to 6 years of age.(Wetherby, Prizant, & Barry, 1990) The best predictor of a developmental delay in a child may be their degree of communication skills. When major medical conditions or physical disabilities are absent, a child's delay in language development may be the first obvious sign that anything is wrong with their development. Language delays could be the main issue, or they could be caused by delays in other areas.

The CSBS-DP has two goals: first, it identifies children who already have a communication deficit or who are at risk of developing one, and second, it tracks changes in a child's expressive speech, communication, and symbolic behavior through time. The Checklist has 24 questions totaling 57 points that fall between 2 and 4 points in each of the 7 Clusters.

The scores are then classified in Concern or No Concern. If the criteria levels are more than 1.25SD below the mean for the particular age of the child being tested, participants were labeled as "Concern". The classification determines whether the children are classified as communicating appropriately for their age or as needing to be referred for a developmental review.

A communication composite score of 8–26 for infants who are 6 months old is considered normal, while a score of 0–7 raises concerns. When the score is between 0 and 1, the expressive speech

composite is of concern, but not when it is between 2 and 14. Finally for symbolic, a score of 3-17 is of no concern whereas, a score of 0-2 is of concern.

The CDI is for the assessment of children 15 months to six years of age and for older children who are judged to be functioning in the one to six-year range. It is a standardized method in which parents complete the instrument to assess the child's development. The child's social maturity is reflected in the Social Scale results and also by the presence or absence of behavioral problems included in the CDI Problems items. For the CDIP test, the scales to evaluate are social (S), self-help (SH), gross motor (GM), fine motor (FM), expressive language (EL), language comprehension (LC), letters (L), numbers (N) and general development (GD), which is a summary of all the previous scales. The scores will be compared to the expected scores by age in each of the scales, which are based on a sample of 568 children one to six years old. If the child's score is less than 30% below the age limit, the child's development is below expectation.

The Self-Help Scale and Social Scale work together to define how well a child has mastered independent living tasks like eating, dressing, washing, and using the restroom. These abilities are partly developed as a result of the child's desire for independence, which is demonstrated by the phrase "I want to do it myself."

The development of the child's physical abilities is described by the two motor scales, Gross Motor and Fine Motor. They include the development of more refined eye-hand coordination as well as big muscle or whole-body coordination. One could argue that children's knowledge of their own developing physical skills serves as their initial sense of mastery and foundation for self-esteem.

Parental recognition of the child's developing skills, most visibly demonstrated by the child's walking, then serves to reinforce this sense of competence.

Expressive language, as well as the child's growing language comprehension enhance their connection to the outside world. The ability to comprehend language and, in particular, to comprehend concepts, gives a child a whole new set of skills for adapting to new situations and addressing problems. There is growing evidence that early intervention has a bigger influence on outcomes for children and families than assistance offered to students in school.

For the behavioral assessments, CSBS-DP test was for the sub-scales social, expressive speech, and symbolic composite while CDIP test was for the social (S), gross motor (GM), fine motor (FM), expressive language (EL), and language comprehension (LC) sub-scales. The test scores were correlated with immunological factors –cell counts CD3+, CD4+, CD8+, CD19+, CD56+, and immunoglobulins IgA, IgG and IgM to examine the characteristics of this data, such as normality and redundancy, and develop a modeling strategy.

Statistical Analysis:

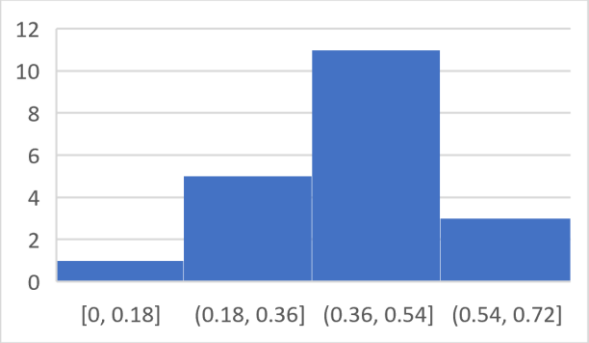
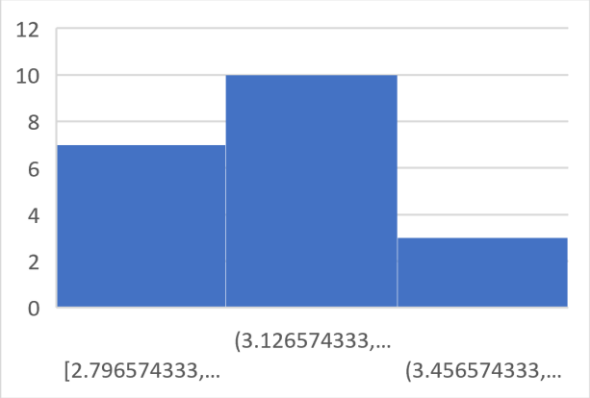
To determine if cell counts CD3+, CD4+, CD8+, CD19+, CD56+, and immunoglobulins IgA, IgG and IgM predicted CSBS-DP ITC and CDIP assessment scores. Normality test was done for predictor variables and did log transformation of the ones that are not normal. Regression models were used with the CD3+, CD4+, CD8+, CD19+, CD56+, and immunoglobulins IgA, IGG and

IgM levels as the exposure variable and scores on each of the three CSBS-DP ITC and five of the CDIP composites as the outcomes. To control for possible confounding factors, models were run with age at blood draw for the immunological tests, age at CSBS-DP ITC and CDIP assessment as covariates. Sex as recorded in the medical record was also a covariate. Statistical tests were implemented in SAS Version 9.4 software (SAS Institute Inc., Cary, NC).

Results:

Tables 1 and 2 show normality check for the cell counts and psychological outcomes.

Table 1: Normality check for predictor variables

	Log 10 Transformation
CD4	
CD3	

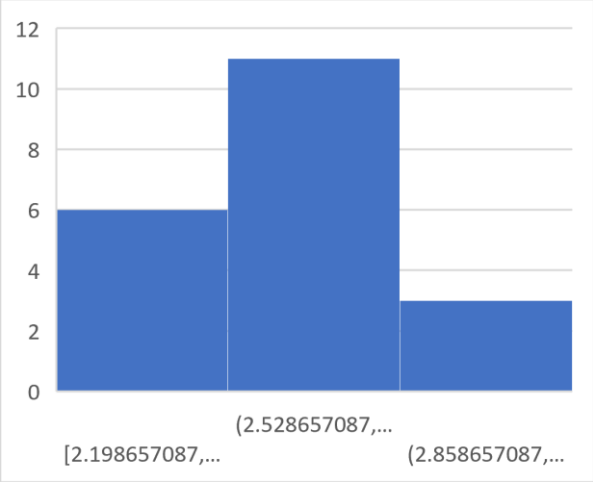
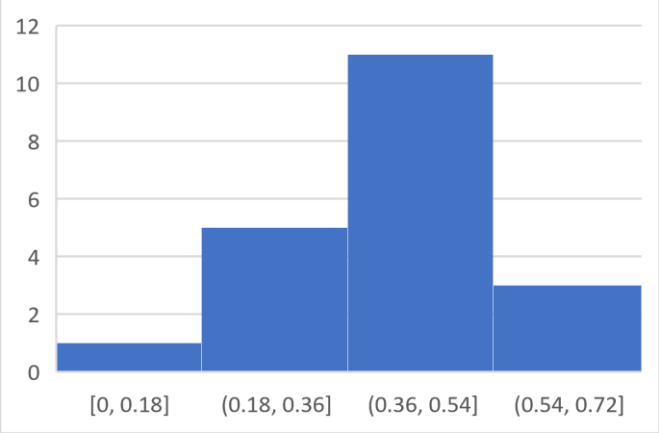
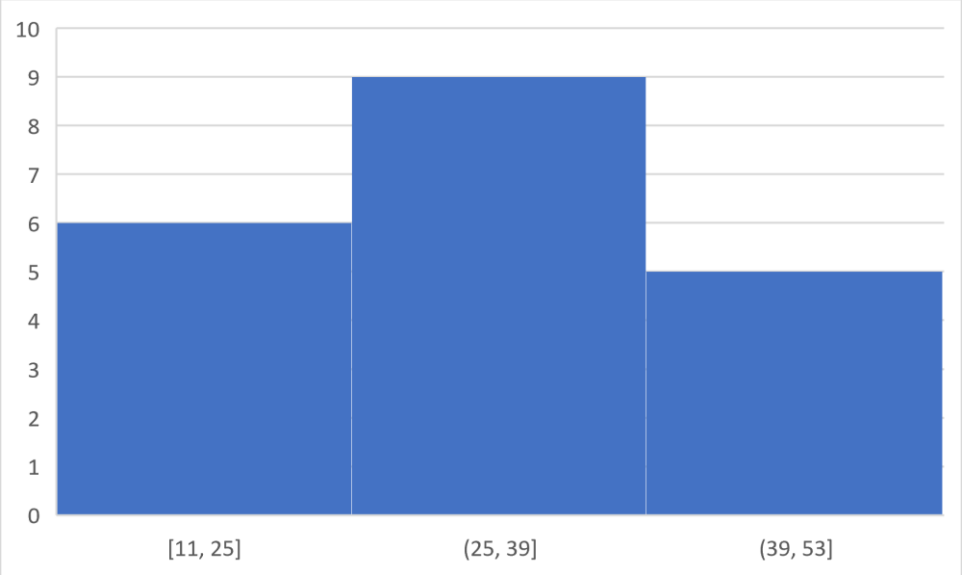
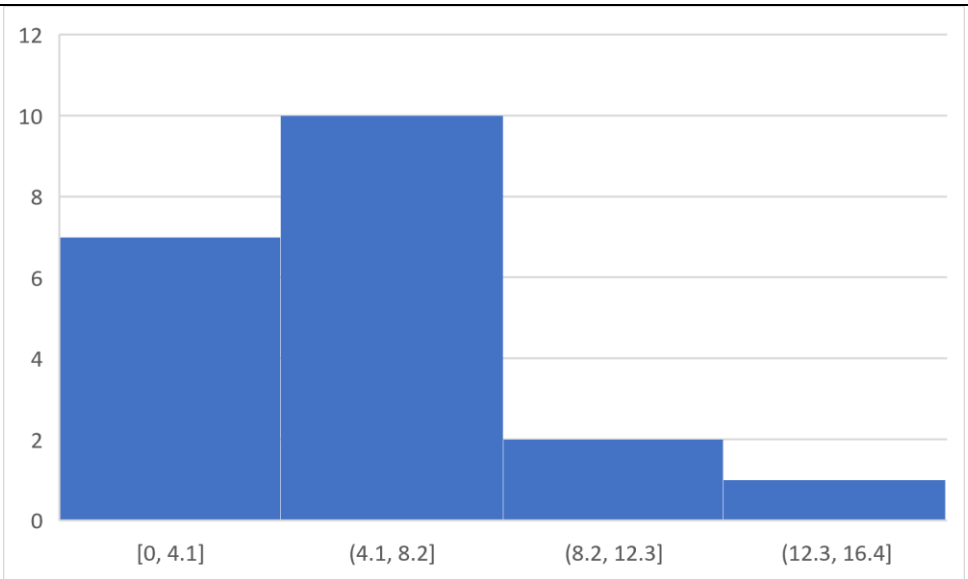
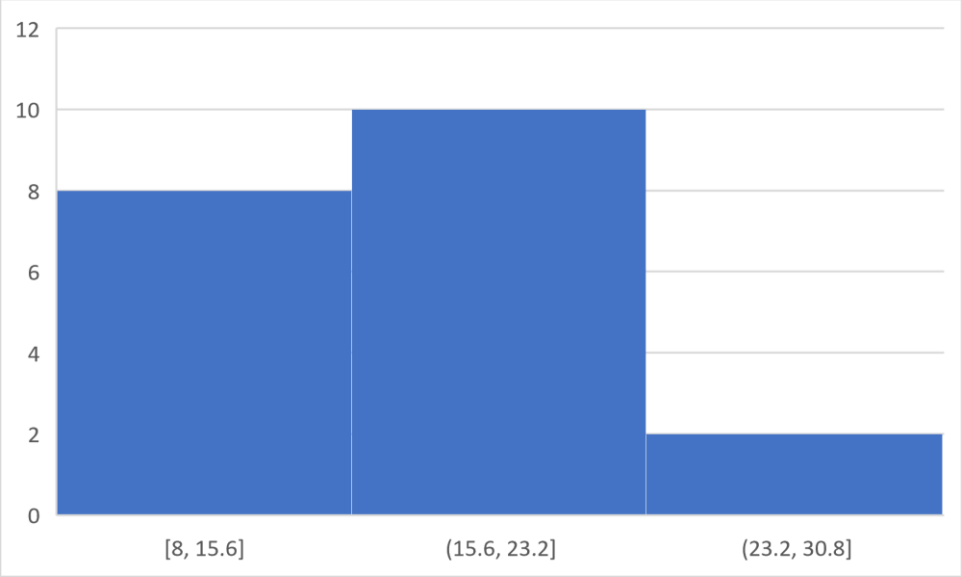
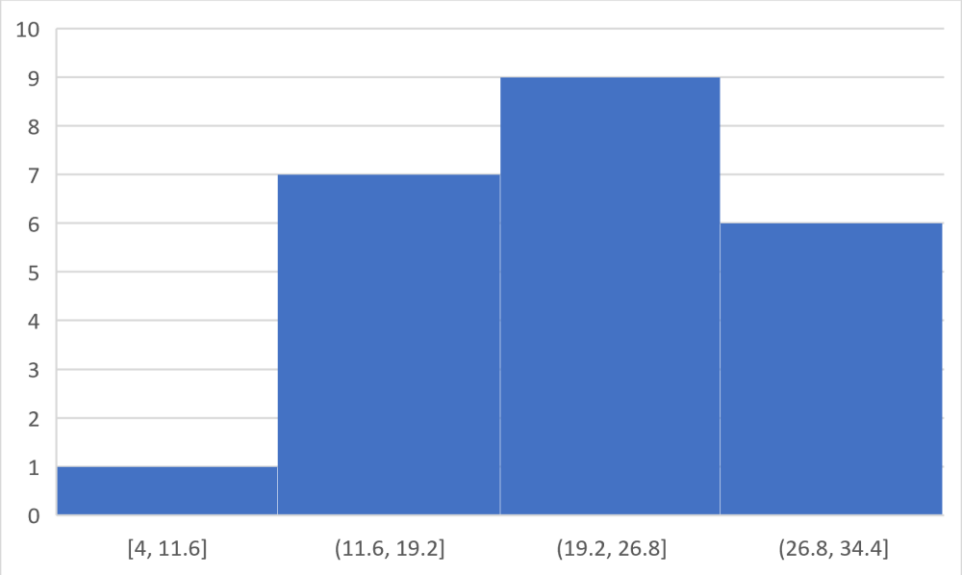
CD8	 12 10 8 6 4 2 0 [2.198657087,... (2.528657087,... (2.858657087,...
CD4/CD8	 12 10 8 6 4 2 0 [0, 0.18] (0.18, 0.36] (0.36, 0.54] (0.54, 0.72]

Table 2: Normality check for psychological outcome variables.

CSBS total	
Speech	

Social	
Gross Motor	

Tables 3 and 4 show collection of ICD information (ICD 9&10) and literature search.

Table 3: Shows the information from ICD code books 9 and 10. This covered the timeframe for our study from 1997 till date.

	Autoimmune diseases	ICD–9-CM	ICD-10-CM	Keywords
1	Acquired aplastic anemia	284.9	D61. 9	Anemia, aplastic anemia
2	Acquired hemophilia	286.52	D68. 311	autoantibodies against FVIII, bleeding symptoms
3	Agammaglobulinemia, primary	279.00	D80. 0	Antibody deficiency, Immunoglobulins.
4	Alopecia Areata	704.01	L63	hair loss
5	Ankylosing spondylitis	720.0	M45.0-M45.9	Spine, arthritis
6	Anti-NMDA receptor encephalitis	323?	*G04.90*	*Autoimmune encephalitis*

7	Anti-phospholipid syndrome	286.53	D68. 61	lupus anticoagulants, anti-cardiolipin, anti-beta-2-glycoprotein I, vascular thrombosis, pregnancy complication
8	Autoimmune Addison's disease	255.41	E27.1	Autoimmune adrenalitis
9	Autoimmune autonomic ganglionopathy	337.9	G90. 9	Autoimmune dysautonomia
10	Autoimmune encephalitis/acute disseminated encephalomyelitis	323.81	G04. 81	antibody; autoimmune; encephalitis; paraneoplastic.
11	Autoimmune gastritis	535.10	K29. 40, K29. 50	Iron deficiency, Vitamin B 12 deficiency, Autoimmune gastritis
12	Autoimmune Hemolytic anemia	283.0	D59. 10	Cold agglutinin disease; Microvesicles
13	Autoimmune hepatitis	571.42	K75. 4	Liver-related autoantibodies

14	Autoimmune polyglandular syndrome	258.1	*E31.0*	
15	Behcet's disease	136.1	M35. 2	HLA-B*51; systemic vasculitis; immunosuppressive therapy; anti- inflammatory therapy
16	Bullous Pemphigoid	694·5	L12. 0, L12. 9	Antibodies, Autoimmunity, Hemidesmosomes.
17	Celiac disease	579.0	K90. 0	Celiac sprue; Gee-Herter-Heubner disease; Gluten sensitive enteropathy; GSE; Nontropical sprue.
18	Churg-Strauss Syndrome	446.4	M30. 1	ANCA-associated vasculitis; Asthma; Eosinophilic granulomatosis with polyangiitis; Hypereosinophilic syndromes;
19	CREST syndrome	*701.0*	M34.1	systemic sclerosis, dystrophic calcinosis, CREST syndrome, telangiectasia, Raynaud's phenomenon, sclerodactyly.

20	Dermatitis herpetiformis	694.0	L13. 0	autoimmune; bullous; celiac disease; dermatitis herpetiformis; disease monitoring; pruritis.
21	Dermatomyositis	710.3	M33. 1	Cutaneous manifestations; Muscle weakness, Rash
22	Diabetes, type 1	250.93	E10.9	insulin- dependent diabetes
23	Discoid Lupus	695.4, 710.8, 710.9	L93. 0	cutaneous lupus erythematosus
24	Evans Syndrome	287.32	D69. 41	auto-immune haemolytic anaemia (AIHA), autoimmune cytopenias.
25	Glomerulonephritis	580.0	M32. 14, N05.2	Glomerular Lesion; ANA; Autoimmune disease; C3 glomerulonephritis; C3 glomerulopathy; ds-DNA..
26	Good pasture's syndrome	446.21	M31.0	ANCAs; Anti-GBM antibodies; Anti-GBM disease; Crescentic glomerulonephritis;

				Goodpasture syndrome; Pulmonary-renal syndrome.
27	Glomerulomatosis with polyangiitis/Wegener's granulomatosis	446.4	M31. 3	Granulomatosis with polyangiitis; necrotizing vasculitis; ANCA-associated vasculitis;
28	Graves' disease	242.0	E05. 00	autoimmune thyroid disease; hyperthyroidism;
29	Guillain Barre Syndrome	357.0	G61. 0	Campylobacter jejuni; Guillain–Barré syndrome; acute inflammatory demyelinating polyneuropathy; acute motor axonal neuropathy;
30	Hashimoto's thyroiditis	245.2	E06. 3	Hashimoto's thyroiditis; autoimmune diseases; autoimmune thyroid disorders; autoimmune thyroiditis; hypothyroidism;
31	Henoch Schonlein Purpura	287.0	D69.0	Abdominal pain; IgA vasculitis; arthralgia; arthritis; hematuria;

				palpable purpura; proteinuria; vasculitis.
32	IgA nephropathy	583.9	*N02.8*	chronic kidney disease · glomerulonephritis · IgA nephropathy · proteinuria.
33	Immune thrombocytopenia	287.3	D69. 3	immune, thrombocytopenia, Idiopathis Thrombocytopenic Purpura, platelets, thrombopoietin, splenectomy
34	Juvenile idiopathic arthritis	714.30	M08	*Juvenile arthritis*, rheumatoid arthritis, joints.
35	Lambert Eaton myasthenic syndrome	358.1	G70. 80	Autoimmunity; Lambert–Eaton myasthenic syndrome; Neuromuscular junction; Quality of life; Small cell lung carcinoma; Voltage-gated calcium channels.
36	Meniere’s disease	386.00	H81. 0	Vertigo; sensorineural hearing loss; tinnitus; vestibular disorders

37	Mixed connective tissue disease	----	M35.1	Dermatomyositis; Genetics; Interstitial pulmonary fibrosis; Mixed connective tissue disease; Myositis; Polymyositis; Pulmonary hypertension; Systemic lupus erythematosus; Systemic sclerosis; U1 small nuclear ribonucleoprotein.
38	Multiple Sclerosis	340	G35	Demyelination; Multiple sclerosis; Myelin; Oligodendrocyte
39	Myasthenia gravis	358.00	G70	B cells; T cells; acetylcholine receptor; autoantibodies; cytokines; myasthenia gravis
40	Paroxysmal nocturnal hemoglobinuria	283.2	D59.5	hemolytic anemia, bone marrow failure, thromboembolism;
41	PANS/PANDAS	----	D89.89	Autoimmune; Obsessive Compulsive disorder; Psychiatric; Tics.

42	Pemphigus Vulgaris	694.4	L10. 0	Pemphigus, paraneoplastic pemphigus, oral erosions, stomatitis, blistering disorder, acantholysis, rituximab
43	Pernicious Anemia	281.0	D51	cobalamin deficiency; macrocytic anemia; pernicious anemia; vitamin B12 deficiency.
44	POEMS syndrome	359.29	D47.7	Castleman disease; Chronic inflammatory polyradiculoneuropathy; Paraneoplastic; Plasma cell disorder.
45	Polyarthritis nodosa	446.0	M30. 0	Medium vessel vasculitis; Polyarteritis nodosa; Systemic necrotizing vasculitis; Vasculitis.
46	Polymyalgia Rheumatica	725.0	M35. 3	giant cell arteritis; polymyalgia rheumatica; temporal arteritis; treatment.
47	Polymyositis	710.4	M33. 2	Dermatomyositis; inclusion-body myositis; inflammatory

				myopathy; myositis-specific autoantibodies;
48	Primary Biliary Cirrhosis	571.6	K74. 3	Cholestatic liver disease; Cirrhosis; Liver transplantation; Primary biliary cirrhosis; Ursodeoxycholic acid.
49	Primary Sclerosing Cholangitis	576.1	K83. 01	Etiopathogenesis inflammatory bowel disease; Liver transplantation
50	Psoriasis	696.1	L40	inflammation, chronic skin disease
51	Pure Red Cell Aplasia	284.81	D61. 01	Dyserythropoiesis, *pure red cells aplasia*, reticulocytopenia
52	Raynaud's syndrome	443.0	I73. 0	Connective tissue disease; Digital ischemia; Raynaud's phenomenon; Scleroderma; Systemic sclerosis
53	Reactive arthritis/Reiter's syndrome	099.3	M02. 9	Rheumatic Disease; Chlamydia Trachomatis; Reactive Arthritis;

				Yersinia Enterocolitica; Joint Symptom.
54	Rheumatic fever	390 -392	100-102	arthritis; autoimmunity; rheumatic fever; rheumatic heart disease; streptococcus.
55	Rheumatoid Arthritis	714.0	M06.09	Arthritis; arthrology; autoimmune disease; immunopathology; inflammatory; joints; pannus
56	Sarcoidosis	135	D86.9	inflammatory disease; granulomas (small nodules of immune cells); lungs; lymph nodes.
57	Schmidt’s syndrome	258.1	*E31.9*	Polyglandular, Schmidt's syndrome, autoimmune, primary adrenal insufficiency, autoimmune hypothyroid,

				insulin dependent diabetes mellitus
58	Scleroderma	710.1	M34	Autoimmune; Skin, blood vessels, muscles and joints, gastrointestinal (GI) tract, kidneys, lungs and heart
59	Sjogren's syndrome	710.2	M35. 01	Autoimmune; keratoconjunctivitis sicca (dry eyes); and xerostomia (dry mouth*).*
60	Systemic Lupus Erythematosus	710.0, 695.4, 710.8	M32. 9	Systemic Lupus Erythematosus (SLE); cardiovascular disease (CVD); cerebrovascular accident (CVA); chronic kidney disease (CKD).
61	Subacute Bacterial Endocarditis	*421.0*	I33. 0	Streptococcus salivarius; bicuspid aortic valve; infective endocarditis; splenic infarction; subacute bacterial endocarditis.

62	Sydenham’s chorea	392	I02. 9	Sydenham's chorea*;* autoimmune movement disorders; acute rheumatic fever.
63	Sympathetic Ophthalmia	360.11	H44.1	Dalen–Fuchs nodule, granulomatous uveitis, immunosuppression, ocular trauma.
64	Takayasu’s disease	446.7	M31. 4	Takayasu disease, claudication, pulseless disease, granulomatous inflammatory vasculitis, transmural fibrous thickening
65	Ulcerative colitis	556.9	K51	Crohn's disease; Inflammatory bowel diseases
66	Vitiligo	709.01	L80	White or depigmented macules and patches

Table 4: Shows results of the literature search using the strategy explained in the methods.

Reference	**Title**	**Study Population**	**% Autoimmunity in cohort**
(A. R. Gennery, 2012)	Immunological aspects of 22q11.2 deletion syndrome.	N= 60	43 of 60 subjects alive (72%). 13 patients had autoimmune thyroid disease, 9 patients had lineage hematological cytopenia, and other patients had nephritic syndrome and autoimmune enteritis.
(A. Gennery et al., 2002)	Antibody deficiency and autoimmunity in 22q 11.2 deletion syndrome	N = 32	Of 32 patients identified, 26 (81%) had severe or recurrent infection,

			of which 13 (50%) had abnormal serum immunoglobulin measurements and 11/20 ≥4 years old (55%) had an abnormal response to pneumococcal polysaccharide. Ten of 30 patients (33%) had autoimmune phenomena; six (20%) were symptomatic.
(Di Cesare et al., 2015)	Autoimmunity and regulatory T cells in 22q11.2 deletion syndrome patients	N = 50	16 of 50 patients (32%) had recurrent infection. Higher frequency of autoimmunity 44% (7 out of 16) compared with those

			without recurrent infections (6%, 2 of 34).
(Ricci et al., 2022)	Characterization of Autoimmune Thyroid Disease in a Cohort of 73 Pediatric Patients Affected by 22q11.2 Deletion Syndrome	N = 73	16 of the 73 enrolled patients (21.9%) developed ATD before 18 years of age (mean age 12.92 ± 3.66 years). A total of 20.5% developed Hashimoto's Thyroiditis (HT), 50% required L-thyroxine treatment; 1.4% developed Graves' Disease.
(G. Giardino et al., 2019)	Clinical and immunological features in a cohort of patients with partial DiGeorge	N = 446	Autoimmune disease was diagnosed in 35/446 (7.84%) patients (Table 1). Autoimmune

	syndrome followed at a single center.		cytopenia was the most common manifestation observed (9/446). Five patients suffered from more than 1 autoimmune manifestation. Mean age at the onset of autoimmunity was 7.8 ± 5.5 years (range, 0.5-17).
(K. Lima et al., 2011)	Hypoparathyroidism and autoimmunity in the 22q11.2 deletion syndrome	N = 59	Out of 59 patients, 28 patients were positive for autoantibodies. Six (10%) persons developed an autoimmune disease.
(Montin et al., 2019)	Immunophenotype anomalies predict the	N = 358	The study population included 358

	development of autoimmune cytopenia in 22q11.2 deletion syndrome.		patients with a global prevalence of autoimmunity of 24%. Autoimmune cytopenia were seen in 8%.
(Tison et al., 2011)	Autoimmunity in a cohort of 130 pediatric patients with partial DiGeorge syndrome	N = 130	Eleven (8.5%)patients had an autoimmune disease, mean age of presentation of 5 years, 8 (72%) were females. Three patients had autoimmune hypothyroidism, 1 patient had monoarticular arthritis with a positive antinuclear antibody result, 1

			patient had juvenile idiopathic arthritis, 1 patient had vitiligo, 1 patient had psoriasis, 1 patient had autoimmune neutropenia, and 4 patients had ITP and AIHA.
(Jawad, McDonald-McGinn, Zackai, & Sullivan, 2001)	Immunologic features of chromosome 22q11.2 deletion syndrome	N = 195	Study of 195 patients with 22q11.2 deletion syndrome reported juvenile rheumatoid arthritis (n = 4), idiopathic thrombocytopenia (n = 8), autoimmune hemolytic anemia (n

			= 1), vitiligo (n = 1) and inflammatory bowel disease (n = 1).
(Hernández-Nieto, Yamazaki-Nakashimada, Lieberman-Hernández, & Espinosa-Padilla, 2011)	Autoimmune Thrombocytopenic Purpura in Partial DiGeorge Syndrome	N = 1	Autoimmune Thrombocytopenic Purpura in Partial DiGeorge Syndrome.
(Gottlieb, Li, Uzel, Nussenbla	Uveitis in DiGeorge syndrome: a case of autoimmune ocular	N = 1	A case of autoimmune ocular inflammation in a

tt, & Sen, 2010)	inflammation in a patient with deletion 22q11.2		patient with deletion 22q11.2
(Choi et al., 2005)	Endocrine Manifestations of Chromosome 22q11.2 Microdeletion Syndrome	N = 61	Hypocalcemia was found in 20 patients (32.8%), and overt hypoparathyroidism in 8 (13.1%). Two patients (3.3%) showed autoimmune thyroid diseases, 1 each with Graves' disease and Hashimoto thyroiditis.
(Kawamura et al., 2000)	Di- George syndrome with Graves' disease: A case report. Endocr J 47: 91-95	N = 1	Graves' disease reported an 18-year-old female with partial phenotype of Digeorge Syndrome

(Kawame et al., 2001)	Graves' disease in patients with 22q11.2 deletion.	N = 5	Graves' disease reported in four females and one male diagnosed between the ages of 27 months and 16 years.
(Elder, Kaiser-Rogers, Aylsworth, & Calikoglu, 2001)	Type I diabetes mellitus in a patient with chromosome 22q11.2 deletion syndrome.	N = 1	9-year-old boy with a history of glottic web, clubfoot, polyuria, polydipsia, weight loss, hyperglycemia, ketosis, serum insulin antibodies, and a low C-peptide level. The authors suggested that the presence of insulin antibodies in this patient indicate an autoimmune etiology for his

			diabetes mellitus type I.
(Brown, Datta, Browning, & Swift, 2004)	Graves' Disease in DiGeorge Syndrome: Patient Report with a Review of Endocrine Autoimmunity Associated with 22q11.2 Deletion"	N = 1	Case report: Graves' Disease in DiGeorge Syndrome.
(Xie et al., 2016)	Autoimmune disorder secondary to DiGeorge syndrome: a long-term follow-up case report and literature review	N = 1	A female born with congenital heart disease followed till 20 years. 6 years old, the blood routine test showed slight thrombocytopenia and 9 years Found to have anemia and severe thrombocytopenia.

(Kratz et al., 2003)	Evans Syndrome in a Patient with Chromosome 22q11.2 Deletion Syndrome: A Case Report	N = 1	Evans Syndrome in a Patient with Chromosome 22q11.2 Deletion Syndrome: A Case Report, Pediatric Hematology and Oncology.
(Chang et al., 2006)	Type III Mixed Cryoglobulinemia and Antiphospholipid Syndrome in a Patient With Partial DiGeorge Syndrome	N = 1	Type III Mixed Cryoglobulinemia and Antiphospholipid Syndrome in a Patient with Partial DiGeorge Syndrome
(Pongpruttipan, Cook, Reyes-Mugica, Spahr, & Swerdlow, 2012)	Pulmonary Extranodal Marginal Zone Lymphoma of Mucosa-Associated Lymphoid Tissue Associated with Granulomatous Inflammation in a Child with Chromosome 22q11.2 Deletion Syndrome (DiGeorge Syndrome)	N = 1	Pulmonary Extranodal Marginal Zone Lymphoma of Mucosa-Associated Lymphoid Tissue Associated with Granulomatous Inflammation in a

			Child with Chromosome 22q11.2 Deletion Syndrome
(Verloes et al., 1998)	Juvenile rheumatoid arthritis and del(22q11) syndrome: a non-random association. *Journal of Medical Genetics* 1998;35:943-947.	N = 3	Three children with the deletion and a chronic, erosive polyarthritis resembling idiopathic cases of juvenile rheumatoid arthritis (JRA)
(Sullivan et al., 1997)	Juvenile rheumatoid arthritis-like polyarthritis in chromosome 22q11.2 deletion syndrome	N = 80	Eighty patients with chromosome 22q11.2 deletion syndrome were tested arthropathy and all 3 patients with polyarthritis had evidence of more extensive

			immunoregulatory derangements.
(Bruno, Barbier, Lambilliotte, Rey, & Turck, 2002)	Auto-immune pancytopenia in a child with DiGeorge syndrome.	N = 1	Autoimmune pancytopenia in a child with DiGeorge syndrome
(Casimire, Golla, & Smith, 2011)	Sarcoidosis In A 43-Year-Old Woman With Digeorge Syndrome	N = 1	Sarcoidosis in a 43-year-old woman with Digeorge Syndrome
(Mahé et al., 2019)	Risk factors of clinical dysimmune manifestations in a cohort of 86 children with 22q11.2 deletion syndrome: A retrospective study in France	N = 86	Eleven patients (13%) developed an autoimmune disease; ATD, JIA, and ITP. the only risk factor was an antecedent of severe infection

			(OR: 4.1; 95% CI [1.099–15.573]).
(Ueda et al., 2017)	Graves' Disease in Pediatric and Elderly Patients with 22q11.2 Deletion Syndrome	N = 2	Two female patients (one child and an elderly) with Graves' disease
(Fishman et al., 2011)	Prevalence of thyroid disease in children with 22q11.2 deletion syndrome	N = 169	Overt thyroid disease was noted in 9.5% of 169 children with the syndrome. Hypothyroidism occurred in 7.7% and hyperthyroidism in 1.8%

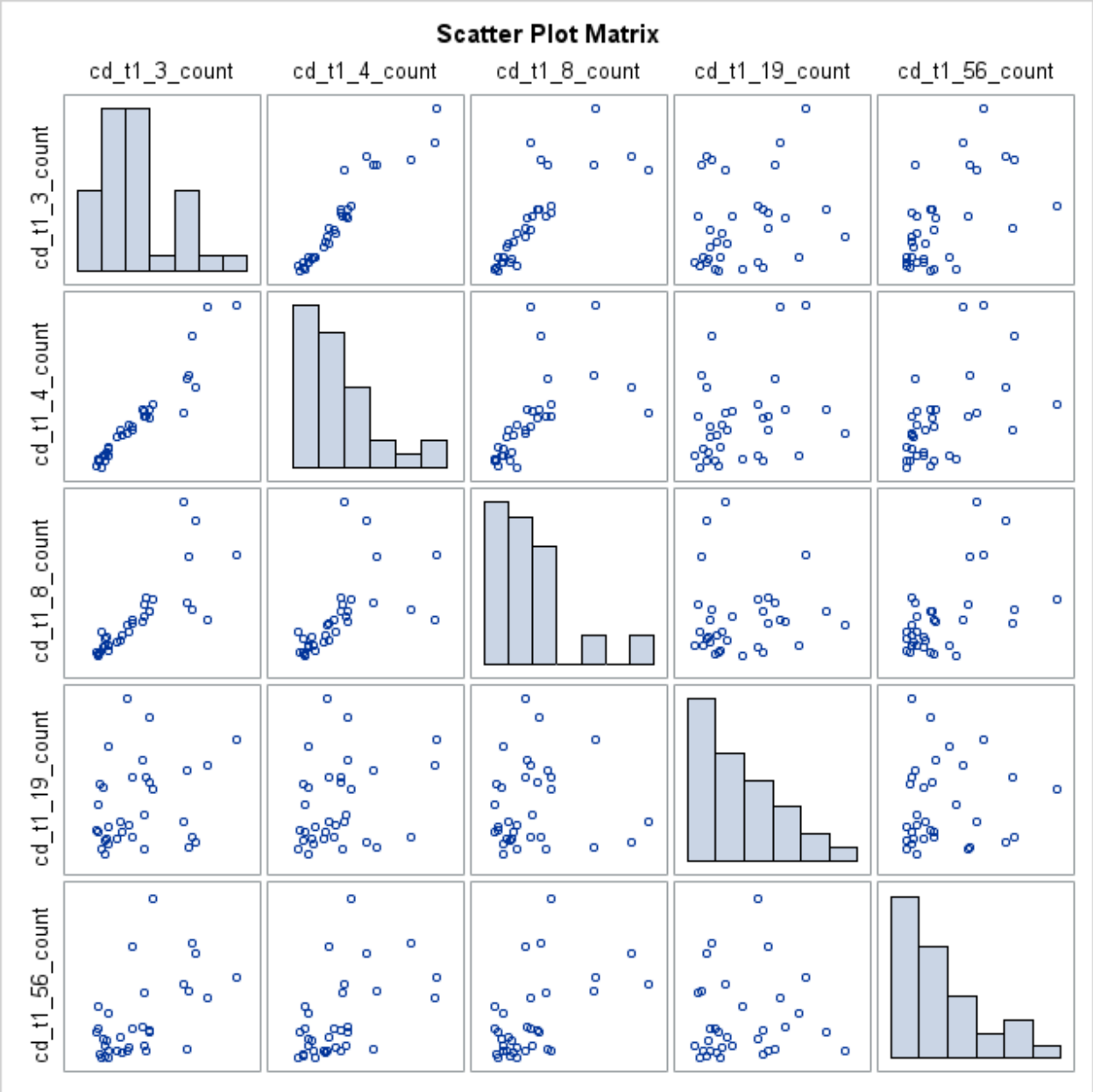
Table 5: Shows the large potential outcome variables that are in the SERph22 database. This table shows outcome variables that have a sufficient number of individuals that I chose to further analyze.

Data on outcome	CD3 count	CD4 count	CD8 count	CD19 count	CD56 count	IgA	IgG	IgM	IgE
Psych Diagnosis	N = 58	N = 59	N = 57	N = 58	N = 58	N= 31	N = 30	N= 31	N = 0
CSBS	N = 33	N = 33	N = 33	N = 33	N = 33	N = 20	N = 20	N = 20	N = 0
CDIP	N = 37	N = 37	N = 38	N = 38	N = 38	N = 17	N = 17	N = 17	N = 0
ADOS	N = 21	N = 21	N = 21	N = 21	N = 21	N = 20	N = 20	N = 20	N = 0
ADI	N = 21	N = 21	N = 21	N = 21	N = 21	N = 20	N = 20	N = 20	N = 0
ABC	N = 10	N = 10	N = 10	N = 10	N = 10	N = 10	N = 10	N = 10	N = 0
CBCL	N = 10	N = 10	N = 10	N = 10	N = 10	N = 13	N = 13	N = 13	N = 0
How many assessment did the participant have?	N = 56	N = 56	N = 56	N = 55	N = 55	N = 47	N = 48	N = 48	N = 0
Was the SCID-I/P ADMINISTERED?	N = 10	N = 10	N = 10	N = 10	N = 10	N = 10	N = 10	N = 10	N = 0
Was the ABAS assessment completed during the first evaluation?	N = 57	N = 57	N = 57	N = 56	N = 56	N = 49	N = 50	N = 50	N = 0
Was the CAARS assessment completed during the first evaluation?	N = 10	N = 10	N = 10	N = 10	N = 10	N = 10	N = 10	N = 10	N = 0
Was the Prodromal Questionnaire completed during the first evaluation?	N = 9	N = 9	N = 9	N = 9	N = 9	N = 6	N = 6	N = 6	N = 0
Was the Prodromal Questionnaire completed during the second evaluation?	N = 6	N = 6	N = 6	N = 6	N = 6	N = 6	N = 6	N = 6	N = 0
Autism Spectrum Disorder	N = 3	N = 3	N = 3	N = 3	N = 3	N = 5	N = 5	N = 5	N = 1
ADHD	N = 4	N = 4	N = 4	N = 4	N = 4	N = 4	N = 4	N = 4	N = 1

Table 6: This table shows outcome variables that had insufficient number of individuals for analysis.

Data on outcome	CD3 count	CD4 count	CD8 count	CD19 count	CD56 count	IgA	IgG	IgM	IgE
Was the Prodromal Questionnaire completed during the first evaluation?	N = 9	N = 9	N = 9	N = 9	N = 9	N = 6	N = 6	N = 6	N = 0
Was the Prodromal Questionnaire completed during the second evaluation?	N = 6	N = 6	N = 6	N = 6	N = 6	N = 6	N = 6	N = 6	N = 0
Autism Spectrum Disorder	N = 3	N = 3	N = 3	N = 3	N = 3	N = 5	N = 5	N = 5	N = 1
ADHD	N = 4	N = 4	N = 4	N = 4	N = 4	N = 4	N = 4	N = 4	N = 1

Figure 1: Matrix plot of CD3+, CD4+, CD8+, and CD19+ for CSBS scale

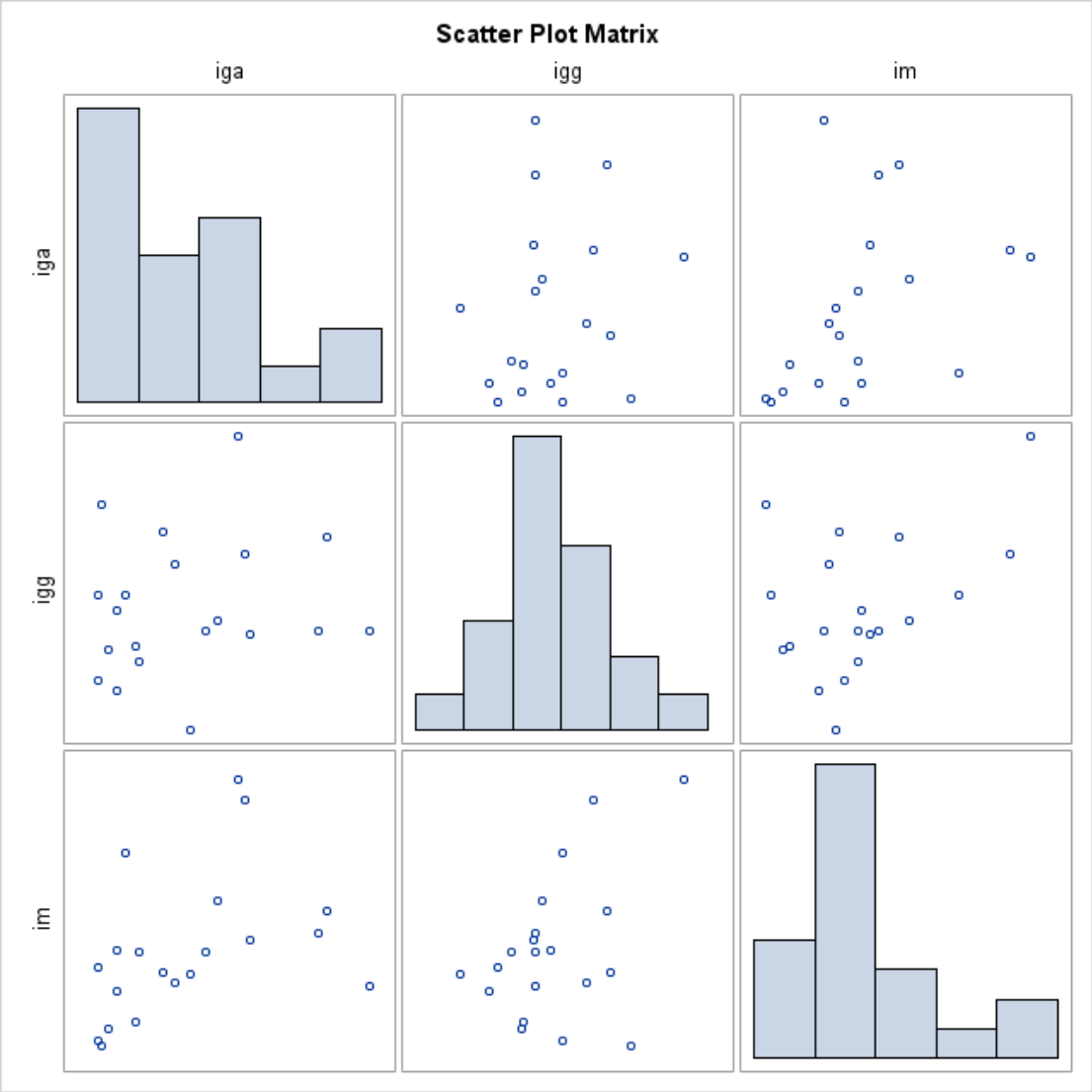


Leukocyte counts expressing markers: CD3+CD4+ CD8+ CD19+ CD56+: measured cubic millimeter (cells/mm^3) of blood.

The histograms indicate an overall lack of a normal distribution, and as expected CD3-- a marker of T cells-- is correlated with Tcell subsets CD4 and CD8

Simple Statistics						
Variable	**N**	**Mean**	**Std Dev**	**Sum**	**Minimum**	**Maximum**
CD3+	33	1981	1230	65383	626.00000	5266
CD4+	33	1343	845.39666	44335	402.00000	3680
CD8+	33	582.33333	466.85314	19217	118.00000	2045
CD19+	33	1142	850.95448	37685	148.00000	3338
CD56+	33	447.75758	334.28067	14776	131.00000	1466

Figure 2: Matrix plot of IgA, IgG, IgM

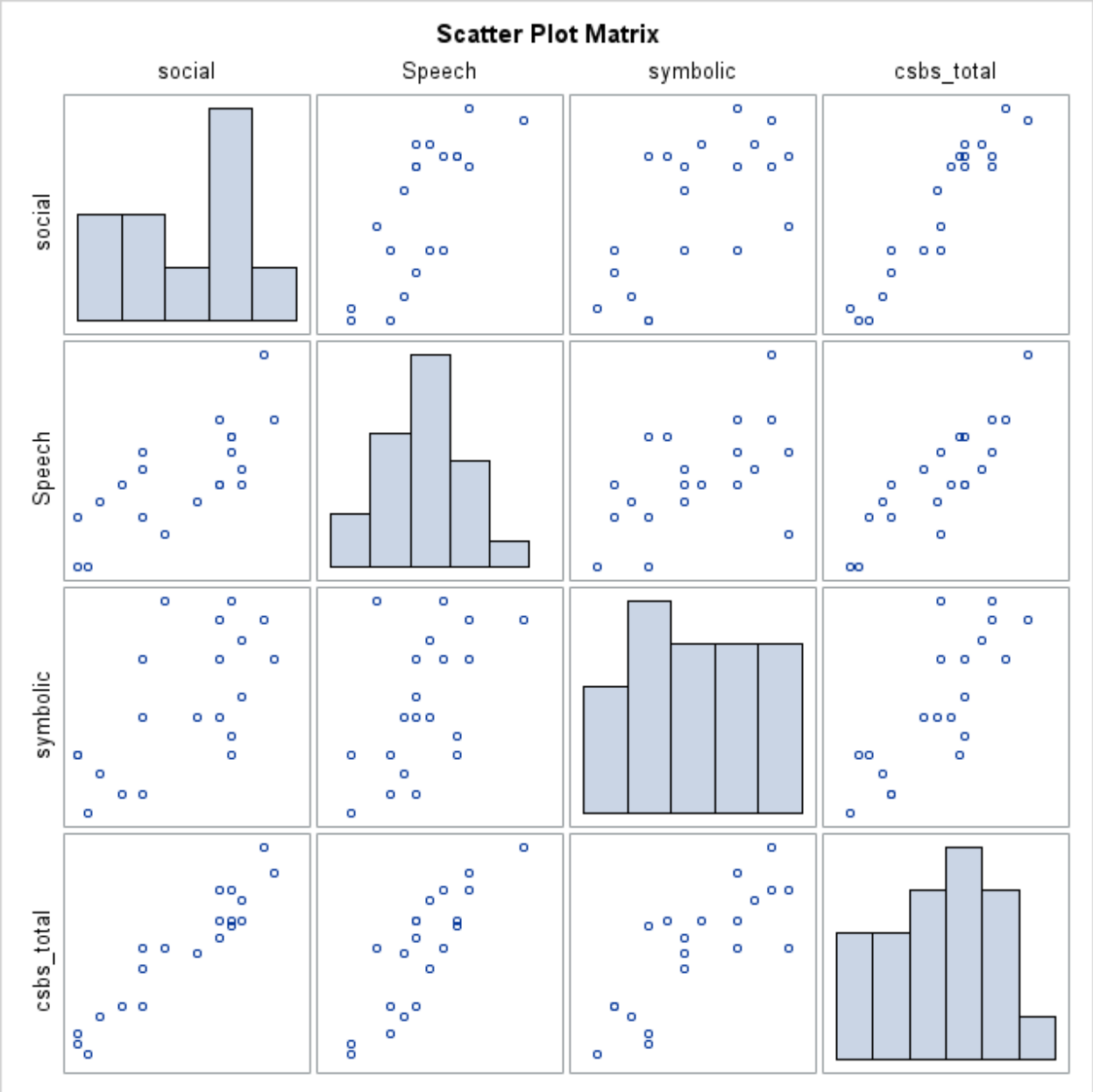


IgG: Immunoglobulin G IgA: Immunoglobulin A IgM: Immunoglobulin M measured in mg/100 ml

There is a slight correlation between the immunoglobulins.

Simple Statistics						
Variable	**N**	**Mean**	**Std Dev**	**Sum**	**Minimum**	**Maximum**
IgA	20	36.00000	27.16228	720.00000	7.00000	96.00000
IgG	20	566.40000	217.43926	11328	180.00000	1102
IgM	20	44.40000	29.56598	888.00000	5.00000	114.00000

Figure 3: Matrix plot of Social Speech Symbolic and CSBS total scales

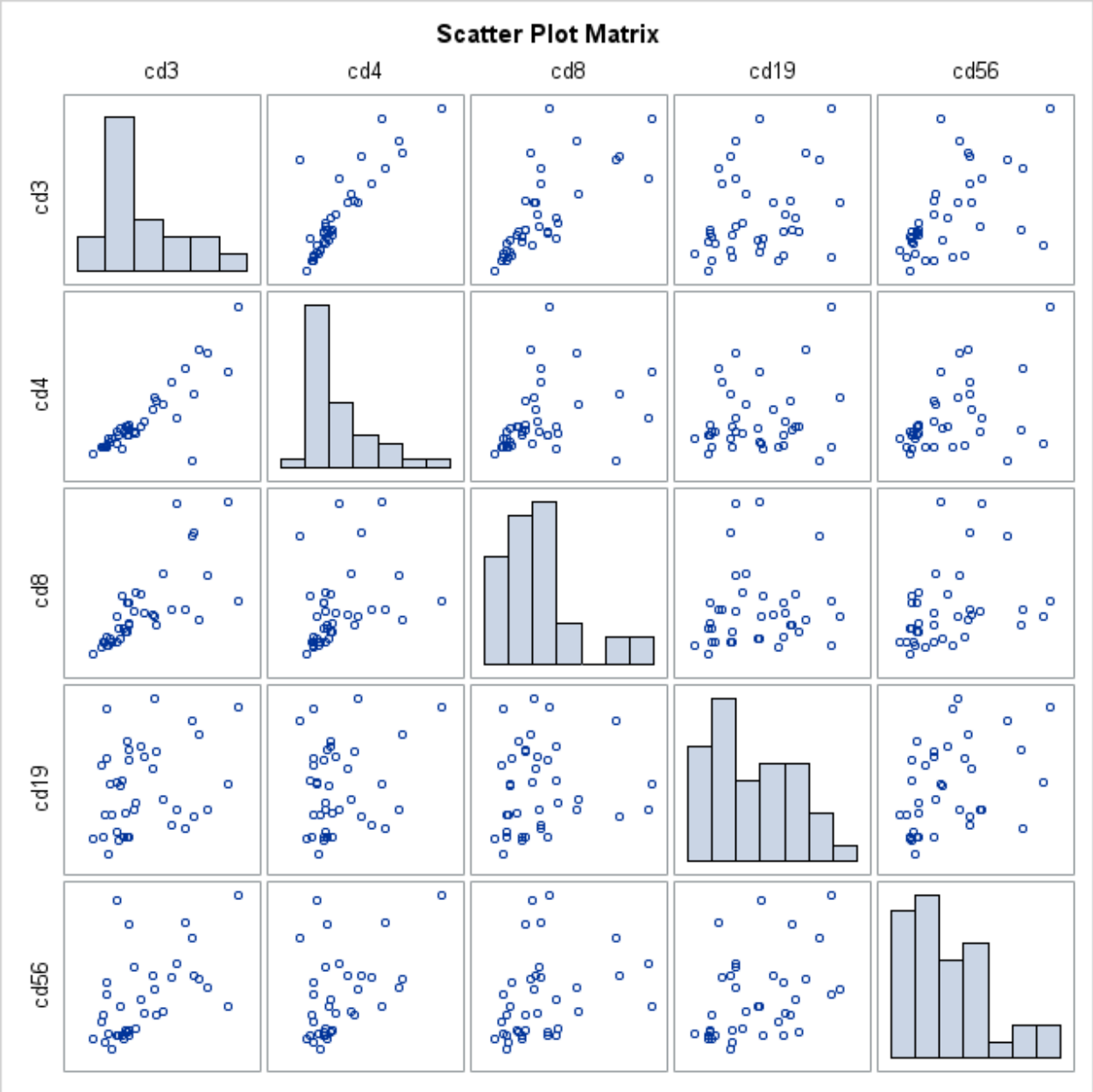


CSBS total: The total score of the sub-scales.

As shown in figure 3, there are correlations between the scales and CSBS total.

Simple Statistics						
Variable	**N**	**Mean**	**Std Dev**	**Sum**	**Minimum**	**Maximum**
social	20	17.50000	5.92497	350.00000	8.00000	26.00000
Speech	20	5.45000	3.15353	109.00000	0	13.00000
symbolic	20	7.65000	3.52846	153.00000	2.00000	13.00000
csbs_total	20	30.55000	11.18963	611.00000	11.00000	50.00000

Figure 4: Matrix plot of CD3+, CD4+, CD8+, and CD19+ for CDIP



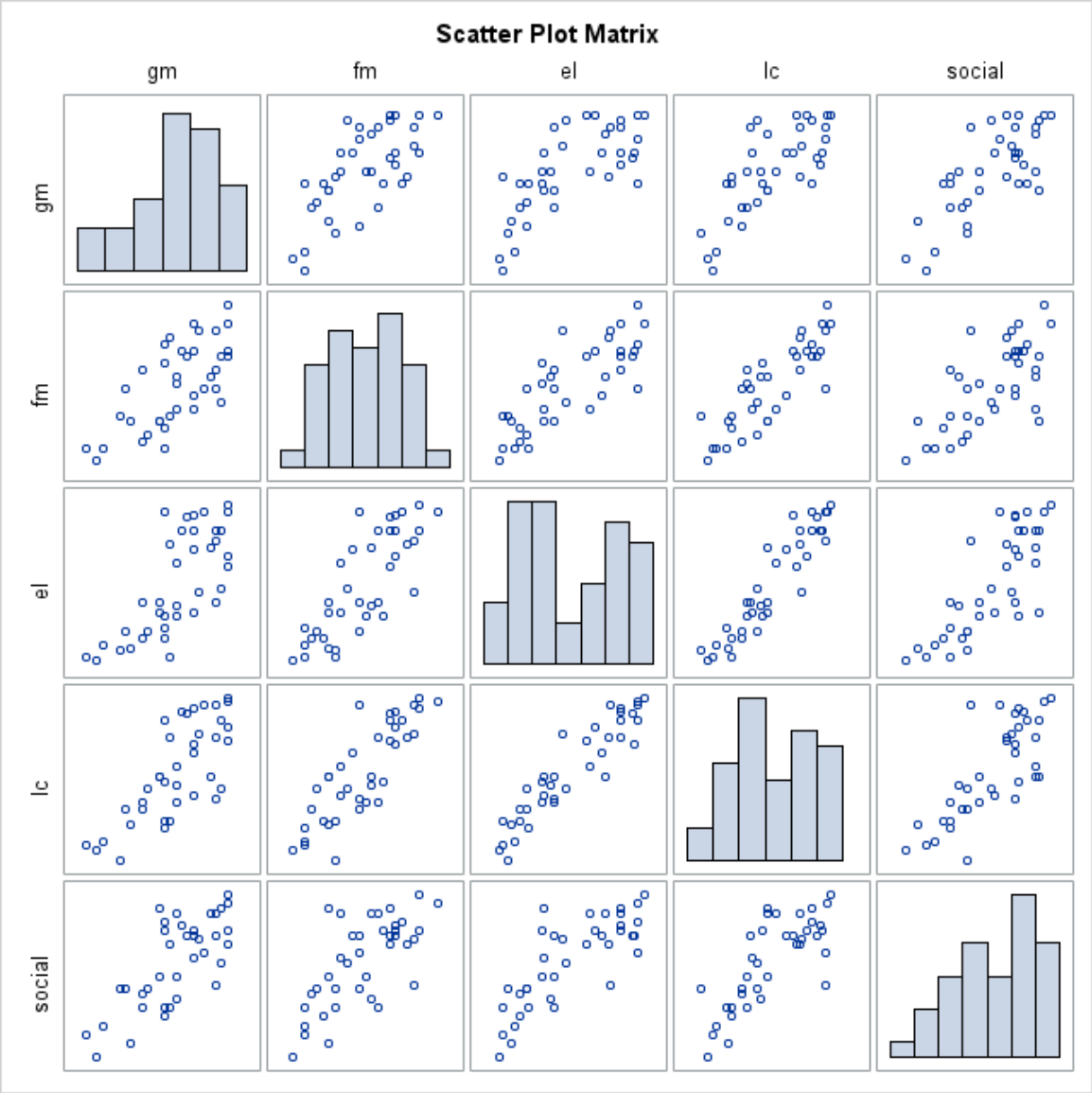
CD3+CD4+ CD8+ CD19+ CD56+: measured cubic millimeter (cells/mm^3) of blood.

As shown in figure 4, there are correlations between the immune parameters with each other.

The histograms indicate an overall lack of a normal distribution.

Variable	N	Mean	Std Dev	Sum	Minimum	Maximum
cd3+	38	2290	1313	87022	555.00000	5684
cd4+	38	1486	1018	56473	221.00000	4921
cd8+	38	688.78947	481.19132	26174	133.00000	2074
cd19+	38	1135	660.66542	43111	110.00000	2520
cd56	37	474.27027	330.17156	17548	69.00000	1309

Figure 5: Matrix plot of subscales for CDIP

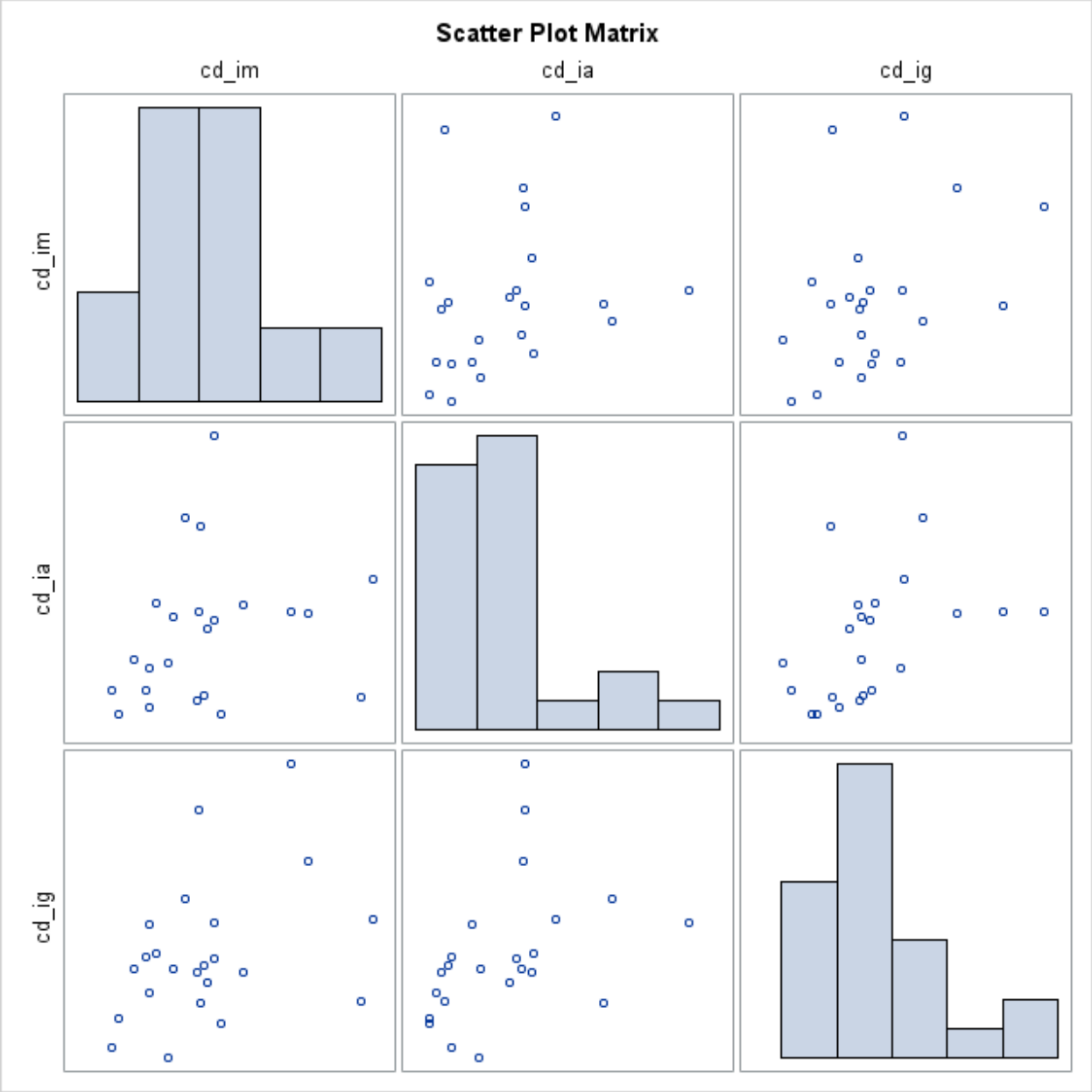


GM: Gross Motor FM: Fine motor EL: Expressive Language LC: Language Comprehension

As shown in figure 5, there are correlations between the CDIP scales.

Simple Statistics						
Variable	**N**	**Mean**	**Std Dev**	**Sum**	**Minimum**	**Maximum**
gm	38	20.00000	6.81017	760.00000	4.00000	29.00000
fm	38	17.60526	6.36519	669.00000	6.00000	30.00000
el	38	24.57895	15.71474	934.00000	1.00000	49.00000
lc	38	27.50000	14.80093	1045	0	50.00000
social	38	25.21053	9.67906	958.00000	4.00000	40.00000

Figure 6: Matrix plot of IgG, IgM, and IgA



Immunoglobulin levels IgM cd_ia:IgA cd_ig:IgG (Note code prefix cd is used as per variable name in the SERPh22 database but these are cluster differentiation markers)

The figure shows that there are some correlations between the immunoglobulins.

Simple Statistics						
Variable	**N**	**Mean**	**Std Dev**	**Sum**	**Minimum**	**Maximum**
IgM	23	63.08696	34.72347	1451	17.00000	146.00000
IgA	23	44.02609	32.53693	1013	7.00000	135.00000
IgG	23	654.91304	338.83435	15063	154.00000	1574

Regression analysis.

After eliminating samples lacking concurrent CD3+ CD4+ CD8+ CD19+ CD56+ IgA, IgG IgM with CSBS and CDIP, 20 individuals had data for CSBS, and 23 individuals had data for CDIP. I ran 45 regression models but however, majority of them were not significant fits. Therefore, I am showing the models that are only significant fit as shown in the tables 7 and 8.

Table 7: Shows my regression for significant CSBS predictor variables.

Model	Predictor variable	B	SE	P value	R^2	Adj R^2
1. Social				0.0456	0.6364	0.4244
	IGG	0.01528	0.00553	0.0172		
	Age at assessment	0.58513	0.22989	0.0257		
	Age at blood test	0.00510	0.00612	0.4209		
	Sex	-3.79270	2.35451	0.1332		

2. Total CSBS				0.0322	0.4845	0.3471
	Age at assessment	1.42539	0.49018	0.0108		
	Age at blood test	0.01072	0.01081	0.3371		
	Sex	-1.46131	4.43646	0.7464		
3. Symbolic				0.0462	0.4557	0.3105
	Age at assessment	0.44598	0.15884	0.0133		
	Age at blood test	-0.01070	0.00420	0.0201		
	Sex	-5.24301	5.28779	0.3346		

Table8: Shows my regression for significant CDIP predictor variables

Model	Predictor variable	B	SE	P value	R^2	Adj R^2
1. Gross motor				0.0063	0.5314	0.4273
	Age at assessment	0.22207	0.07600	0.0091		
	Age at blood test	-0.00147	0.00189	0.4459		
	Sex	2.92629	2.37772	0.2343		
2. Fine motor				0.0003	0.6704	0.5971
	Age at assessment	0.33277	0.05790	<.0001		
	Age at blood test	-0.00042958	0.00141	0.7637		
	Sex	-2.91790	1.95939	0.1538		
3.Language comprehension				0.0004	0.6601	0.5846

	Age at assessment	0.66076	0.12763	<.0001		
	Age at blood test	-0.00363	0.00310	0.2569		
	Sex	-0.76300	4.31893	0.8617		
4. Expressive language				0.0016	0.6023	0.5140
	Age at Assessment	0.70729	0.16902	0.0006		
	Age at blood test	-0.01070	0.00420	0.0201		
	Sex	-1.18511	5.66911	0.8372		
	IgA	-0.15481	0.07177	0.0476	0.7424	0.6221

We performed a regression analysis with CSBS as CDIP as dependent variables, age at assessment, age at blood drawn and sex as covariates and immunological parameters as predictors. Tables 7 and 8 show where the regression was significant. In table 7, we found a significant association of IgG with social outcome. The higher the IgG, the higher the score on

social scale. In Table 8, none of the models was significant except for IgA which shows that the higher the IgA, the higher the scores on expressive language. Results are in appendix.

Discussion and Conclusion:

In this study I examined the potential association between peripheral blood leukocyte subsets and two measures of childhood neuropsychological development (CSBS and CDIP), as preparation for future studies that will provide a more detailed analysis of autoimmune phenomena and these psychological factors. I likewise formed a similar analysis for immunoglobulins (IgM, IgG, IgA).

My regression analysis for CSBS shows that many of the model fits were not significant. However, both IgG and age at assessment were significant for the social sub-scale model. For the IgG exposure variable, the parameter estimate was 0.01528 and the p value was 0.0172 and the 95% confidence interval was (0.0032, 0.02733). IgG was positively associated with CSBS score meaning that higher IgG indicates worse functioning of the individual. Age at assessment was positively associated with CSBS score. Likewise, for total CSBS and symbolic subscales, age at assessment was also significant. The mean (SD, range) age at the blood draw and at the CSBS-DP assessment were 179.5 (215.97, 646) days and 14.4 (5.27, 19) months, respectively. The mean (SD) age at the blood draw and at the CDIP assessment were 462.65 (617.66, 1826) days and 48.394 (16.30, 47.11) months, respectively.

For CDIP model, IgA, age at assessment and age at blood test showed significant result for the Expressive Language sub-scale. This model indicated that infants with higher IgA will perhaps have poorer expressive language function. For the other sub-scales, only the age at assessment was significant.

I performed a detailed review of autoimmunity in 22q11.2DS. Autoimmunity in 22q11.2DS usually presents as hyper-hypothyroidism, juvenile idiopathic arthritis, and autoimmune cytopenia.(Giuliana Giardino et al., 2019) Viral respiratory infections are the most common type of infection in patients with 22q11.2DS and opportunistic infections are rare. Previous studies show varying degrees of autoimmune conditions among individuals with 22q11DS. According to Lima et al, 47%(28 patients) out of 59 patients among individuals with 22q.11DS had hypoparathyroidism. (Kari Lima et al., 2011). Kathleen E Sullivan recorded 24% of autoimmune conditions in the research on immune biomarkers of autoimmunity (Sullivan, 2019). Development of autoimmunity in patients with 22q11.2 deletion can be due to different mechanisms (Khandaker, Zimbron, Dalman, Lewis, & Jones, 2012). Infections, molecular mimicry, and bystander activation of autoreactive T lymphocyte by inflammatory cytokines are some of the mechanisms leading to autoimmunity. (Kuo, Signer, & Saitta, 2018)

Abnormal thymic development leading to partial immunodeficiency is also relevant to autoimmunity. About 1.5% of patients with 22q11DS) have complete athymia with signs and symptoms similar to severe combined immune deficiency (SCID). Therefore, absence of T

lymphocyte is due to athymia as opposed to intrinsic hematopoietic abnormalities inherent in SCID. (Giuliana Giardino et al., 2019) In addition, Regulatory T cells (Treg) play a crucial role in maintaining self-tolerance in humans. Individuals with 22q11DS have been reported to have decreased frequency of Treg cells. (Klocperk et al., 2014)

Prior studies have examined the correlation between leukocyte subsets and autoimmune phenomena, but data is generally lacking for 22q11.2DS. There is also no data in the literature on whether there is any correlation between these immune parameters and neurodevelopmental indices in this genetic condition. Therefore, the work in my thesis yielded some novel insights.

My study found an association between immunoglobulin levels and adverse neurobehavioral outcomes. Considering that elevated immunoglobulins has been associated with autoimmune disease (Mindy S. Lo et al), further studies are needed to examine this connection in 22q11DS.

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