Clinical significance of very high IgE levels (≥1000 IU/mL): Population-based study of 118,211 adults

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Background: Very high serum IgE (≥1000 IU/mL) is reported in atopic disorders. However, data on its significance in nonallergic disorders are limited.

Objective: We aimed to analyze the diagnostic value of very high IgE in adults.

Methods: A retrospective nationwide study was conducted using the electronic database of Clalit Health Services, covering adults (≥18 years) treated between 2002 and 2022. Subjects with IgE ≥ 1000 IU/mL were compared to the controls with IgE < 100 IU/mL across 3 age groups (18-30, 31-64, and ≥65 years). Outcomes included eosinophilic, autoimmune, autoinflammatory, and cardiovascular disorders (CVD), cancer, and inborn errors of immunity (IEI). A multivariable Cox regression model determined statistical significance ($P < .05$).

Results: The study included 118,211 subjects: 110,116 controls and 8635 with very high IgE levels. Excluding insect sting and drug allergies, very high IgE was more common across all tested allergic disorders, with asthma showing the highest rate (64.49%). Univariable analysis showed higher prevalence of CVD (3.88% vs 2.72%, $P < .001$), eosinophilic disorders (0.42% vs 0.06%, $P < .001$), and IEI (0.35% vs 0.20%, $P = .004$) in the very high IgE group. Multivariable analysis revealed age-dependent significant results: higher CVD risk in ages 31-64 (hazard ratio = 1.249; 95% confidence interval, 1.054-1.481; $P = .010$) and borderline IEI association in ages 18-30 (hazard ratio = 1.802; 95% confidence interval, 0.978-3.321; $P = .059$). Risk of eosinophilic disorders was increased across all age groups ($P < .001$).

Conclusions: Very high IgE level of ≥1000 IU/mL is associated with increased risks of CVD, IEI, and eosinophilic disorders. Physicians should consider further assessment for these conditions in nonallergic patients with very high IgE levels. (J Allergy Clin Immunol Global 2025;4:100403.)

Key words: *IgE, very high IgE, immunoglobulin E, population-based study*

IgE plays a pivotal role in the pathogenesis of various allergic disorders, including atopic asthma, allergic rhinitis, and atopic dermatitis. The differentiation of B cells into IgE-secreting plasma cells is triggered by IL-4, a T_H2 cytokine. On binding to the high-affinity IgE receptor, FcεRI, IgE initiates mast cell activation and degranulation, culminating in the release of histamine and other mediators that precipitate immediate hypersensitivity reactions.[1] Elevated IgE levels are also observed in nonallergic disorders, including helminth infections,[2,3] IgE multiple myeloma,[4] and autoimmunity.[5,6] Moreover, recent studies have linked heightened IgE levels to chronic inflammation, suggesting potential roles in allograft rejection and atherosclerosis.[5] A subset of patients with elevated total serum IgE exhibits very high levels, exceeding 1000 IU/mL. These levels can be found in various atopic conditions, such as food allergies and allergic bronchopulmonary mycosis.[7,8] In patients with asthma and very high IgE levels, increased rates of complications such as airway infections and rhinosinusitis are observed, while helminth infections or atopic dermatitis are less common.[9] However, very high IgE levels may also manifest as a distinct clinical entity of nonallergic origin. Hyper-IgE syndromes (HIES) represent a heterogeneous group of inborn errors of immunity (IEI) characterized by very high IgE levels, recurrent infections, and eczema.[10] Specific genetic variants, such as *STAT3* (signal transducer and activator of transcription 3) loss-of-function variants, differentiate HIES from other allergic conditions with increased IgE levels.[11] Additionally, autoimmune disorders like systemic lupus erythematosus may exhibit very high IgE levels due to self-reactive IgE autoantibodies driving detrimental immune responses.[12]

Given the various possible clinical implications of very high IgE levels, it is essential for practicing clinicians to have evidence-based guidelines for their assessment and management, particularly in screening for nonallergic etiologies, as well as possible consequences. However, the literature addressing very high IgE levels with nonallergic etiology remains

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Abbreviations used
CCI: Charlson comorbidity index
CHS: Clalit Health Services
CI: Confidence interval
CV: Cardiovascular
CVD: CV disorders
HIES: Hyper-IgE syndromes
HR: Hazard ratio
ICD-10: International Classification of Diseases, Tenth Revision
IEI: Inborn errors of immunity
SD: Standard deviation
SES: Socioeconomic status

limited, with scarce guidance on clinical management. In this nationwide study, our objective was to provide further insights into the clinical significance of very high IgE levels among adult patients. We comprehensively analyzed data on patients with serum IgE levels exceeding 1000 IU/mL, previously defined as very high IgE,[8,9,13] to elucidate their associations with nonallergic disorders. We aimed to furnish clinicians with additional evidence regarding the utility of very high IgE levels as a serum biomarker, guiding more informed clinical decisions to improve patient care.

METHODS

Study design and population

This retrospective population-based study was conducted using the electronic health record database of Clalit Health Services (CHS). CHS is Israel's largest health maintenance organization, covering over 4.5 million insured members and operating around 1500 primary care clinics and 14 medical centers.[14] Data were collected on adult patients (≥18 years) tested for serum IgE and treated by CHS between 2002 and 2022. Subjects with serum IgE levels of ≥1000 IU/mL were classified as having very high IgE, while those with serum IgE of <100 IU/mL served as controls for the study's analyses. Each subject was followed up for 5 years from the index date, which was the date of the maximum IgE test result. Adult patients having a history of any of study outcomes at baseline (index date) and patients lacking sufficient documented data in their medical records were excluded from the study. Data on demographics, baseline characteristics, and clinical outcomes were gathered and analyzed from the medical records. Data was extracted from CHS using the Clalit Research Data sharing platform powered by MDclone (www.mdclone.com).

Assays used for serum IgE testing in retrospective analysis

Regarding serum IgE testing methodology at CHS, different assays were utilized across the study period. Before 2007, CHS did not have a central laboratory, and IgE tests were outsourced to several small laboratories, none of which remains operational, making information on the specific assays used during this time unavailable. From July 1, 2007, to July 15, 2019, the ADVIA Centaur Immunoassay System was used. Since July 15, 2019, the Immulite system has been in use.

Clinical outcomes

Outcomes were identified from the CHS database for the period from January 2002 through December 2022 using the International Classification of Diseases, Tenth Revision (ICD-10), classification. ICD-10 codes for clinical outcomes and comorbidities are listed in Table E1 in this article's Online Repository available at www.jaci-global.org. Clinical outcomes were classified into 6 categories according to underlying mechanism: cancer, eosinophilic disorders, autoimmune disorders, autoinflammatory disorders, IEI, and cardiovascular disorders (CVD). Given that aging significantly affects the prevalence of cancer[15] and CVD,[16] as demonstrated in previous studies, we categorized the subjects into 3 age groups for analysis: young adults (18-30 years), middle-aged adults (31-64 years), and senior adults (65 years and older).

Statistical analysis

We examined the associations between the IgE group, baseline sociodemographic variables, Charlson comorbidity index (CCI), and clinical outcomes using univariable analyses, with Pearson chi-square test used for categorical variables and *t* test for continuous variables, as appropriate. Categorical variables are presented as frequencies and percentages of the total cohort; continuous variables are expressed as means ± standard deviations (SDs).

Kaplan-Meier survival analyses were performed to estimate the cumulative hazard of developing each clinical outcome after the index date. To further evaluate the potential association between very high IgE levels and the emergence of each clinical outcome, a series of Cox proportional hazards regression models were used. These models were stratified by age group at baseline (index date), defined as 18-30, 31-64, and ≥65 years. The Cox models were used to compute hazard ratios (HR) and the corresponding 95% confidence intervals (CIs), adjusting for sex, ethnicity, place of birth, socioeconomic status (SES) score, CCI, age, and the presence of any allergic disorder at baseline. For the outcome of CVD, the multivariable Cox regression model also included other risk factors such as diabetes, hypertension, hyperlipidemia, obesity, alcohol abuse, family history of ischemic heart disease, chronic kidney disease, and personal history of ischemic heart disease and stroke. Unfortunately, data on smoking and sedentary lifestyle were not available for analysis.

The proportional-hazards assumption for each variable was validated through visual inspection of the survival curves and the application of the Schoenfeld global test. Statistical significance was determined using a threshold of $P < .05$. All statistical analyses were conducted by SPSS v29.0 for Windows (IBM, Armonk, NY).

Ethical review

The study was approved by the CHS institutional review board (no. KMC-0005-23). The board granted a waiver from obtaining signed informed consent, given the retrospective nature of the study.

RESULTS

Baseline characteristics of study cohort subjects

Baseline characteristics of the subjects are presented in Table I. The study consisted of 118,211 subjects, of whom

TABLE I. Baseline characteristics of study cohorts

		IgE group						
		Control (IgE < 100 IU/mL)		Very high IgE (IgE ≥ 1000 IU/mL)		Total		
Characteristic	Parameter	No.	%	No.	%	No.	%	*P* value
No. of subjects		110116	100	8635	100	118211	100	
Sex	Female	76061	69.41	4592	53.18	80104	67.76	<.001*
	Male	33515	3.59	4043	46.82	38107	32.24	
Ethnicity	Jewish	74048	67.58	6421	74.36	80469	68.07	<.001*
	Arab	29914	27.30	1743	20.19	31657	26.78	
	Other	5614	5.12	471	5.45	6085	5.15	
Age (years) at index date	Mean ± SD	42.42 ± 16.26		42.32 ± 17.97		42.41 ± 16.39		.571
Age group at index date	18-30 years	33095	3.20	2984	34.56	36079	30.52	<.001*
	31-64 years	64363	58.74	4488	51.97	68851	58.24	
	≥65 years	12118	11.06	1163	13.47	13281	11.23	
SES	Very low	8039	7.3	440	5.1	8479	7.2	<.001*
	Low	30441	27.8	2889	33.5	33330	28.2	
	Medium	40693	34.3	3060	35.4	40693	34.4	
	High	25082	22.9	1759	20.4	26841	22.7	
	Very high	8381	7.6	487	5.6	8868	7.5	
Born in Israel	No	29044	26.51	3078	35.65	32122	27.17	<.001*
	Yes	80532	73.49	5557	64.35	86089	72.83	
CCI	Mean ± SD	1.04 ± 1.53		1.41 ± 1.75		1.07 ± 1.55		<.001*
IgE test counts	Mean ± SD	1 ± 1		2 ± 2		1 ± 1		<.001*
IgE test counts grouped	1	89227	81.43	5277	61.11	94504	79.95	<.001*
	2	14299	13.05	1864	21.59	16163	13.67	
	3+	6050	5.52	1494	17.30	7544	6.38	

*Statistically significant ($P < .05$).

110,116 were controls with serum IgE < 100 IU/mL, and 8635 had very high IgE levels (≥1000 IU/mL). The ratio between number of subjects in the control and very high IgE groups was 12.7:1. In both groups, most subjects were female (69.41% in the control group and 53.18% in the very high IgE group; $P < .001$) and Jewish (67.58% in the control group and 74.36% in the very high IgE group; $P < .001$). These percentages closely mirror the proportions of Jewish ethnicity in Israel. Importantly, all patients in Israel, irrespective of their ethnicity, are entitled by law to receive comprehensive medical services. Mean CCI was higher in the very high IgE group compared to the controls (1.41 ± 1.75 and 1.04 ± 1.53, respectively; $P < .001$). In addition, most patients in both cohorts were classified as medium SES and were born in Israel ($P < .001$ in both).

Mean ± SD ages of subjects from the control and very high IgE groups were comparable: 42.42 ± 16.26 and 42.32 ± 17.97, respectively ($P = .571$). Finally, subjects with very high IgE were significantly more frequently tested ≥3 times compared to the controls (17.30% vs 5.52% of subjects in the very high IgE and control groups, respectively; $P < .001$).

For serum IgE levels, mean ± SD (range) in the control group was 36.566 ± 26.746 (0-99.9) IU/mL and in the very high IgE group was 2600.801 ± 4075.830 (1000-142,000) IU/mL. The IgE levels at the 25th, 50th, and 75th percentiles were 14, 30, and 55.600 in the control group and 1246, 1653, and 2526 in the very high IgE group, respectively.

Prevalence of allergic disorders in subjects with very high IgE

To begin our analysis, we first examined the prevalence of allergic disorders in the very high IgE and control groups (Table II). Any allergic disorders, defined as the total sum of all disorders with an allergic etiology, were found to be more prevalent in the very high IgE group compared to the controls (69.57% vs 52.07%, $P < .001$). Additionally, increased rates of each allergic disorder category were observed in the very high IgE group compared to the controls, except for drug hypersensitivity and insect sting allergy. Among the allergic disorders, the highest percentage of subjects with IgE ≥ 1000 IU/mL was noted in asthma (64.49%). In relation to allergic bronchopulmonary mycosis, 9 patients were identified within the study cohorts; 8 of these patients had IgE ≥ 1000 IU/mL and were classified in the very high IgE group. Among the diagnosed patients, 8 were between the ages of 31 and 64, with none older than 65.

Univariable analysis reveals significant associations of very high IgE levels with CVD, eosinophilic disorders, and IEI

Next, we evaluated the prevalence of different nonallergic outcomes detected during follow-up in each IgE group for the 3 age categories (Table III). The outcomes represented disorders according to their underlying mechanisms: cancer, IEI, CVD, and autoimmune, autoinflammatory, and eosinophilic disorders. Of the 6 outcomes, only 3 were more prevalent in the very high IgE group: CVD (3.83% vs 2.36%, $P < .001$, for ages 31-64 years), eosinophilic disorders ($P < .001$, for all age groups), and IEI (0.44% vs 0.23%, $P = .027$, for ages 18-30 years). Frequencies of IEI in the study groups are presented in Table E2 in the Online Repository available at www.jaci-global.org. Interestingly, rates of cancer and autoimmune disorders were not increased in subjects with very high IgE.

TABLE II. Prevalence of allergic disorders recorded before index date among subjects with very high IgE compared to control group

		IgE group						
		Control (IgE < 100 IU/mL)		Very high IgE (IgE ≥ 1000 IU/mL)		Total		
Characteristic	Variable	No.	%	No.	%	No.	%	*P* value
Any allergic disorder	No	52521	47.93	2628	30.43	55149	46.65	<.001*
	Yes	57055	52.07	6007	69.57	63062	53.35	
Atopic dermatitis	No	102704	93.73	7223	83.65	109927	92.99	<.001*
	Yes	6872	6.27	1412	16.35	8284	7.01	
Asthma	No	52417	47.84	3066	35.51	55483	46.94	<.001*
	Yes	57159	52.16	5569	64.49	62728	53.06	
Anaphylaxis (any etiology)	No	108976	99.45	8541	98.91	117517	99.41	<.001*
	Yes	600	0.55	94	1.09	694	0.59	
Allergic rhinitis	No	78096	71.27	4740	54.89	82836	70.07	<.001*
	Yes	31480	28.73	3895	45.11	35375	29.93	
Drug hypersensitivity	No	101644	92.76	7975	92.36	109619	92.73	.163
	Yes	7932	7.24	660	7.64	8592	7.27	
Insect sting allergy†	No	109527	99.96	8631	99.95	118158	99.96	.946
	Yes	49	0.04	4	0.05	53	0.04	
Food allergy–induced anaphylactic shock	No	109212	99.67	8572	99.27	117784	99.64	<.001*
	Yes	364	0.33	63	0.73	427	0.36	
Allergic urticaria	No	68129	62.18	4563	52.84	72692	61.49	<.001*
	Yes	41447	37.82	4072	47.16	45519	38.51	
Allergic bronchopulmonary mycosis‡	No	109575	100.00	8627	99.90	118202	100	<.0001*
	Yes	1	0	8	0.10	9	0	

*Statistically significant ($P < .05$).
†Includes Hymenoptera and fire ant–related allergies.
‡Previously termed allergic bronchopulmonary aspergillosis.

Comparison between the very high IgE and control groups revealed that subjects in the very high IgE group had higher prevalence of all CVD risk factors, excluding obesity and personal histories of ischemic heart disease and stroke (see Table E3 in the Online Repository available at www.jaci-global.org).

In addition, we constructed Kaplan-Meier curves demonstrating cumulative risk for tested outcomes (Fig 1). Increased cumulative risks over the follow-up period of the study were observed by the univariable analysis for CVD, eosinophilic disorders, and IEI.

Multivariable analysis uncovers independent associations between very high IgE and increased risks of CVD, eosinophilic disorders, and IEI

To stratify our results, we used a multivariable Cox regression model. Each model evaluated a single clinical outcome from the 6 previously defined outcomes. Variables included the very high IgE group, sex, place of birth, ethnicity, SES, age on the index date, CCI, and any allergy noted during the pre–index date period. In addition, CVD outcome was adjusted to its specific risk factors, as detailed in Table E2. Each model was applied to 3 different age groups: 18-30, 31-64, and ≥65 years. Results are presented in Table IV.

As in the univariable analysis, the very high IgE group was associated with CVD and eosinophilic disorders, with borderline association with IEI. However, significant results varied across different age groups. Patients with very high IgE were more likely to develop CVD, but this association was limited to ages 31-64 years (HR = 1.249; 95% CI, 1.054-1.481; $P = .010$). In IEI, a borderline association with very high IgE was found in ages 18-30 (HR = 1.802; 95% CI, 0.978-3.321; $P = .059$), but not in older subjects. The only outcome that was characterized by a consistent risk of development across all age groups was eosinophilic disorders ($P < .001$ for each age group). However, even among subjects with eosinophilic disorders, the HR was most elevated in ages 18-30 years compared to other age groups (HR = 17.560; 95% CI, 5.510-55.964; HR = 4.118; 95% CI, 2.298-7.382; and HR = 6.266; 95% CI, 2.659-14.765 for 18-30, 31-64, and ≥65 years, respectively; $P < .001$ for each age group).

DISCUSSION

In this nationwide study, we found that adults with very high IgE levels are at an increased risk of being diagnosed with CVD, IEI, and eosinophilic disorders within 5 years of their index date IgE test. To our knowledge, to date, this is the largest published population-based cohort analyzed for the clinical significance of serum IgE ≥ 1000 IU/mL.

Very high IgE levels can be found in allergic disorders. Our results correlate with previously published studies describing associations of very high IgE levels with disorders involving type 2 inflammation, such as asthma, allergic rhinitis, and food allergy.[13] We observed an increased prevalence of very high IgE levels across all tested allergic disorders, with the exception of drug and insect bite allergies. Notably, drug and insect bite allergies are not genetically driven. This distinction offers further insights into the potential genetic mechanisms underlying very high IgE levels in atopic patients. Asthma is of special interest

TABLE III. Univariable analysis of outcomes measured in subjects with very high IgE and controls

			IgE group						
			Total		Controls (<100 IU/mL)		Very high IgE (≥1000 IU/mL)		
Age (years) at index date	Outcome	Variable	No.	%	No.	%	No.	%	*P* value
18-30	Cancer	No	35752	99.09	32796	99.10	2956	99.06	.847
		Yes	327	0.91	299	0.90	28	0.94	
	CVD	No	36018	99.83	33040	99.83	2978	99.8	.657
		Yes	61	0.17	55	0.17	6	0.20	
	Eosinophilic disorders	No	36065	99.96	33090	99.98	2975	99.70	<.001*
		Yes	14	0.04	5	0.02	9	0.30	
	Autoimmune disorders	No	33259	92.18	30494	92.14	2765	92.66	.311
		Yes	2820	7.82	2601	7.86	219	7.34	
	Autoinflammatory diseases	No	36001	99.78	33023	99.78	2978	99.80	.853
		Yes	78	0.22	72	0.22	6	0.20	
	IEI	No	35991	99.76	33020	99.77	2971	99.56	.027*
		Yes	88	0.24	75	0.23	13	0.44	
31-64	Cancer	No	66178	96.12	61844	96.09	4334	96.57	.106
		Yes	2673	3.88	2519	3.91	154	3.43	
	CVD	No	67162	97.55	62846	97.64	4316	96.17	<.001*
		Yes	1689	2.45	1517	2.36	172	3.83	
	Eosinophilic disorders	No	68786	99.91	64315	99.93	4471	99.62	<.001*
		Yes	65	0.09	48	0.07	17	0.38	
	Autoimmune disorders	No	63021	91.53	58897	91.51	4124	91.89	.347
		Yes	5830	8.47	5466	8.49	364	8.11	
	Autoinflammatory diseases	No	68704	99.79	64219	99.78	4485	99.93	.028*
		Yes	147	0.21	144	0.22	3	0.07	
	IEI	No	68730	99.82	64253	99.83	4477	99.75	.251
		Yes	121	0.18	110	0.17	11	0.25	
≥65	Cancer	No	11556	87.01	10539	86.97	1017	87.45	.644
		Yes	1725	12.99	1579	13.03	146	12.55	
	CVD	No	11718	88.23	10712	88.40	1006	86.50	.055
		Yes	1563	11.77	1406	11.60	157	13.50	
	Eosinophilic disorders	No	13256	99.81	12103	99.88	1153	99.14	<.001*
		Yes	25	0.19	15	0.12	10	0.86	
	Autoimmune disorders	No	11676	87.92	10634	87.75	1042	89.60	.066
		Yes	1605	12.08	1484	12.25	121	10.40	
	Autoinflammatory diseases	No	13255	99.80	12095	99.81	1160	99.74	.615
		Yes	26	0.20	23	0.19	3	0.26	
	IEI	No	13240	99.69	12083	99.71	1157	99.48	.182
		Yes	41	0.31	35	0.29	6	0.52	

*Statistically significant ($P < .05$).

because it was found to have the highest risk of being identified after a very high IgE test result. Indeed, increased rates of very high IgE levels were previously reported to be as high as 62% in asthmatic patients.[17] Notably, our cohort shows unusually low rates of allergic bronchopulmonary mycosis, with only 9 diagnosed cases. This contrasts with higher rates reported internationally, particularly among asthmatic patients, where rates average 2.5% (range, 0.72-3.5%[18]). In Israel, the prevalence is estimated to be similar and even higher among patients with cystic fibrosis (6.6%[19]). This discrepancy is likely due to underreporting or a lack of laboratory-based diagnosis of allergic bronchopulmonary mycosis by treating physicians.

However, our main findings concern nonallergic disorders. IgE has previously been implicated in the pathogenesis of atherosclerosis. Increased morbidity and mortality rates from atherosclerosis have been observed in IgE-mediated asthma and atopic dermatitis. The pathogenesis of atherosclerosis in these disorders is believed to be chronic inflammation, as well as hypertension and diabetes related to prolonged steroid treatment.[20] Additionally, a recent study described that IgE sensitization to food allergens, particularly cow's milk, is associated with increased cardiovascular (CV) mortality.[21] A common link between T_H2 immunity and CVD could be chronic mental stress, as recently described by our group.[22]

Pathogenesis has been illustrated in murine models. In a mouse model prone to atherosclerosis ($Apoe^{-/-}$ mice), IgE deficiency reduced atherosclerotic lesions, lipid deposition within these lesions, and macrophage accumulation.[23] IgE was shown to promote the proliferation of M1 macrophages, which produce TNF-α and IL-6, thereby contributing to foam cell formation and atherosclerosis through chronic inflammation. In $Apoe^{-/-}IgE^{-/-}$ mice, higher levels of M2 macrophages, which produce the anti-inflammatory cytokine IL-10, were observed.[23] Additionally, like elevated serum C-reactive protein, which has been previously linked to an increased risk of CVD,[24] very high IgE levels may also indicate a state of chronic systemic inflammation.

It is unclear why very high IgE levels increase the risk of CVD only among patients aged 31-64. We speculate, on the basis of our

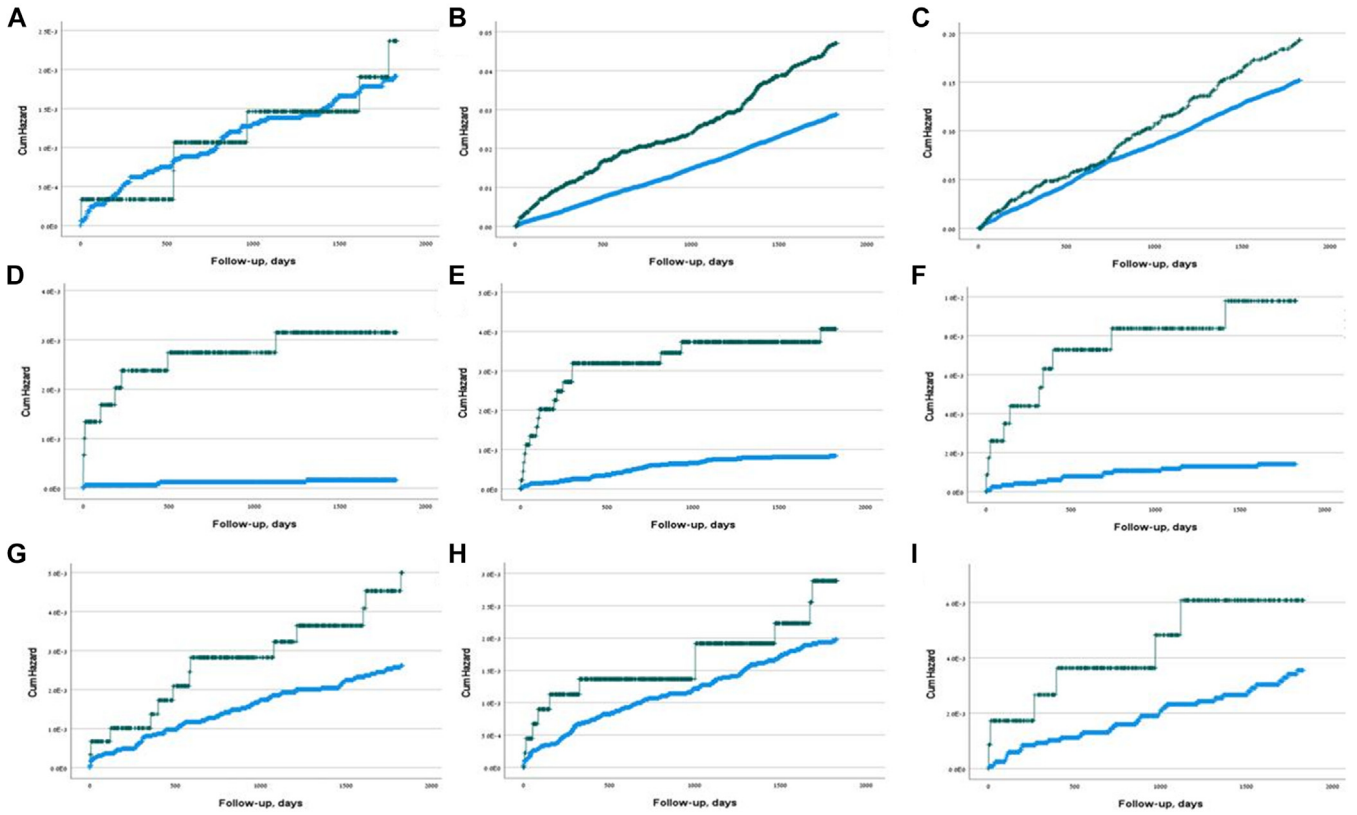

FIG 1. Kaplan-Meier curves illustrating cumulative risk of developing various outcomes in subjects with very high IgE levels compared to controls. Presented are Kaplan-Meier curves for outcomes demonstrating statistically significant associations in the univariable analysis. *Pale blue* indicates control group; *green,* very high IgE (≥1000 IU/mL) group. **(A-C)** Risk of developing CVD in age groups 18-30, 31-64, and ≥65 years, respectively. **(D-F)** Risk of developing eosinophilic disorders in age groups 18-30, 31-64, and ≥65 years, respectively. **(G-I)** Risk of being diagnosed with IEI in the age group of 18-30, 31-64, and ≥65 years, respectively.

current understanding of other CV risk factors, that traditional risk factors accelerate atherosclerosis primarily after prolonged exposure.[25] The present findings suggest that rising IgE levels may modestly modulate CV risk, potentially explaining why this effect has been overlooked until now. It is assumed that most patients experience prolonged exposure to elevated IgE levels and other abnormal immunological cascades, with similar distribution among different age groups. However, this assumption cannot be confirmed because of the retrospective nature of our study. On the basis of this cautious assumption, we hypothesize that patients younger than 30 may not have been exposed to very high IgE levels long enough to develop clinically significant CVD. In contrast, CVD is becoming more prevalent among individuals aged 31-64, and the increased morbidity observed in this group may be linked to longer exposure to elevated IgE levels. Conversely, in patients over 65, the prevalence of CV risk factors becomes much higher, resulting in overall CVD rates that may be too high to detect differences associated with modestly harmful risk factors, even after applying a multivariate correction approach. Of note, while examining CVD risk factors, we identified an increased rate of alcohol abuse in the very high IgE group compared to the controls, specifically in the 31-64-year age group. This observation corresponds with previous studies.[26,27] Various underlying mechanisms have been proposed for the elevation of IgE due to alcohol, including a shift toward T_H2 responses, direct induction of IgE class switching in B cells by alcohol, and the release of gut endotoxins associated with alcohol consumption.[27]

We also found an association between IgE levels ≥1000 IU/mL and IEI diagnosis. Skewing of T helper cells toward T_H2-mediated immunity is a recognized feature in several IEI. HIES exemplify increased T_H2 immunity and very high IgE levels. Gene variants in *STAT3, ZNF341, IL6R,* and *IL6ST* have all been implicated in HIES.[28] Additionally, primary immune regulatory disorders such as immune dysregulation, polyendocrinopathy, enteropathy, X-linked syndrome, and Wiskott-Aldrich syndrome are known to feature very high IgE levels, often without eosinophilia.[29] Treatment with omalizumab and dupilumab, monoclonal antibodies targeting, respectively, the IgE and IL-4/IL-13 receptor α subunit, has been successfully implemented to inhibit type 2 inflammation, thereby alleviating symptoms such as atopic dermatitis in patients with immune deficiencies.[30,31] Thus, we suggest that very high IgE levels in adult patients should raise suspicion of IEI and prompt further in-depth immune assessment for accurate diagnosis, specifically in the presence of other red flags for IEI, such as recurrent or severe infections.[32] This is crucial because some IEI are characterized by delayed diagnosis into adulthood as a result of phenotypic variation, delayed symptom onset, and reduced patient and physician awareness, among other factors.[33]

TABLE IV. Cox proportional hazards models predicting outcomes adjusted for various factors

		Age group at index date								
		18-30 years			31-64 years			≥65 years		
Outcome	Variable	HR	95% CI	*P*	HR	95% CI	*P*	HR	95% CI	*P*
Cancer	Very high IgE	1.017	0.681-1.520	.934	0.880	0.742-1.043	.140	0.887	0.736-1.069	.207
	Sex	0.584	0.450-0.757	<.001*	0.891	0.817-0.972	.009*	1.316	1.178-1.470	<.001*
	Born in Israel	0.809	0.604-1.084	.155	1.033	0.946-1.129	.466	0.957	0.848-1.080	.477
	Ethnicity (Jewish)	1.484	1.083-2.034	.014	1.429	1.264-1.616	<.001*	1.595	1.309-1.945	<.001*
	SES	1.105	0.969-1.259	.136	1.243	1.187-1.301	<.001*	1.219	1.152-1.291	<.001*
	Age at index date	1.093	1.059-1.129	<.001*	1.049	1.043-1.055	<.001*	1.006	0.996-1.015	.243
	CCI	1.845	1.635-2.083	<.001*	1.250	1.206-1.296	<.001*	1.092	1.054-1.132	<.001*
	Any allergy (before index visit)	0.744	0.593-0.934	.011	0.672	0.620-0.729	<.001*	0.772	0.695-0.857	<.001*
CVD	Very high IgE	1.210	0.506-2.897	.668	1.249	1.054-1.481	.010*	0.967	0.803-1.164	.722
	Sex	1.275	0.756-2.150	.362	2.332	2.106-2.582	<.001*	1.603	1.428-1.799	<.001*
	Born in Israel	0.790	0.384-1.622	.520	0.938	0.836-1.053	.278	0.998	0.875-1.137	.973
	Ethnicity (Jewish)	0.827	0.421-1.626	.583	0.867	0.754-0.996	.044*	0.903	0.754-1.080	.264
	SES	0.920	0.675-1.253	.596	0.918	0.864-0.975	.005*	1.029	0.968-1.093	.355
	Age at index date	1.063	0.991-1.141	.090	1.053	1.045-1.061	<.001*	1.018	1.008-1.028	<.001*
	CCI	1.151	0.738-1.794	.536	1.165	1.107-1.226	<.001*	1.128	1.076-1.182	<.001*
	Any allergy (before index visit)	0.790	0.465-1.343	.385	0.850	0.766-0.942	.002*	0.726	0.649-.813	<.001*
	DM	2.695	0.578-12.575	.207	1.660	1.448-1.903	<.001*	1.244	1.093-1.417	.001*
	Hypertension	4.873	1.834-12.946	.001*	1.753	1.562-1.967	<.001*	1.549	1.365-1.757	<.001*
	Hyperlipidemia	1.009	0.351-2.900	.986	1.364	1.218-1.526	<.001*	0.802	0.709-0.907	<.001*
	Obesity	0.778	0.339-1.785	.553	0.963	0.857-1.082	.521	0.989	0.875-1.118	.864
	Alcohol abuse	0	0	.997	2.114	1.378-3.241	.001*	1.025	0.533-1.972	.940
	Family history of IHD	0	0	.996	1.735	1.393-2.161	<.001*	1.538	1.102-2.146	.011*
	CKD	0	0	.997	1.115	0.825-1.507	.480	1.023	0.827-1.266	.831
	History of IHD	0	0	.999	1.171	0.790-1.737	.431	1.309	0.959-1.786	.090
	History of stroke	52.533	13.654-202.120	<.001*	3.304	2.241-4.870	<.001*	2.401	1.858-3.103	<.001*
Eosinophilic disorders	Very high IgE	17.560	5.510-55.964	<.001*	4.118	2.298-7.382	<.001*	6.266	2.659-14.765	<.001*
	Sex	1.259	0.430-3.682	.674	0.898	0.528-1.527	.690	1.857	0.812-4.246	.142
	Born in Israel	0.654	0.165-2.593	.545	0.886	0.510-1.539	.668	0.846	0.315-2.271	.739
	Ethnicity (Jewish)	0.439	0.109-1.763	.246	1.395	0.683-2.850	.360	3.677	0.430-31.427	.234
	SES	1.231	0.650-2.330	.524	0.868	0.645-1.168	.350	1.126	0.727-1.743	.595
	Age at index date	1.147	0.988-1.333	.072	1.013	0.982-1.045	.411	1.002	0.936-1.074	.946
	CCI	1.619	0.938-2.796	.084	1.350	1.134-1.606	.001*	1.025	0.781-1.344	.861
	Any allergy (before index visit)	1.320	0.389-4.476	.656	1.550	0.895-2.684	.118	0.559	0.249-1.258	.160
Autoimmune disorders	Very high IgE	0.946	0.817-1.096	.460	0.981	0.876-1.098	.733	0.910	0.745-1.112	.356
	Sex	0.781	0.716-0.851	<.001*	0.737	0.693-0.783	<.001*	0.781	0.690-0.883	<.001*
	Born in Israel	1.170	1.040-1.316	.009*	1.066	1.000-1.136	.050*	0.729	0.642-0.829	<.001*
	Ethnicity (Jewish)	1.559	1.400-1.737	<.001*	1.344	1.243-1.454	<.001*	1.014	0.842-1.223	.880
	SES	1.047	1.000- 1.097	.049*	1.051	1.018-1.086	.002*	1.149	1.084-1.218	<.001*
	Age at index date	1.017	1.006-1.028	.002*	1.003	1.000-1.007	.076	0.986	0.976-0.996	.007*
	CCI	1.147	1.064-1.236	<.001*	1.151	1.119-1.184	<.001*	1.049	1.010-1.091	.014*
	Any allergy (before index visit)	0.936	0.863-1.014	.106	0.900	0.851-0.951	<.001*	0.866	0.777-0.965	.009
Autoinflammatory diseases	Very high IgE	0.973	0.414-2.284	.949	0.339	0.107-1.070	.065	1.198	0.348-4.126	.774
	Sex	0.735	0.444-1.218	.232	0.774	0.537-1.116	.171	1.789	0.805-3.977	.154
	Born in Israel	4.269	1.330-13.698	.015	2.486	1.529-4.041	<.001*	0.574	0.206-1.602	.289
	Ethnicity (Jewish)	1.390	0.767-2.520	.278	1.170	0.753-1.821	.485	0.541	0.166-1.762	.308
	SES	0.848	0.647-1.112	.234	0.822	0.674-1.003	.053	0.834	0.540-1.290	.415
	Age at index date	0.986	0.927-1.048	.645	0.995	0.973-1.017	.636	1.027	0.957-1.103	.456
	CCI	1.148	0.739-1.784	.539	1.191	1.008-1.406	.039*	0.935	0.691-1.265	.663
	Any allergy (before index visit)	0.970	0.608-1.546	.897	0.726	0.520-1.014	.061	0.701	0.318-1.547	.379
IEI	Very high IgE	1.802	0.978-3.321	.059	1.403	0.744-2.646	.295	1.811	0.738-4.443	.194
	Sex	0.747	0.468-1.194	.223	0.721	0.478-1.087	.118	0.938	0.467-1.882	.856
	Born in Israel	2.290	1.045-5.021	.039	2.059	1.304-3.251	.002*	0.463	0.191-1.121	.088
	Ethnicity (Jewish)	1.855	1.007-3.417	.047*	3.609	1.959-6.649	<.001*	1.474	0.392-5.546	.566
	SES	1.041	0.811-1.335	.752	0.951	0.771-1.171	.634	1.040	0.740-1.463	.821
	Age at index date	1.029	0.970-1.090	.341	0.995	0.972-1.018	.664	0.966	0.910-1.025	.256
	CCI	1.365	0.990-1.882	.058	1.253	1.062-1.477	.007*	1.174	0.959-1.436	.120
	Any allergy (before index visit)	1.216	0.781-1.894	.386	1.189	0.819-1.727	.363	1.098	0.576-2.091	.777

CKD, Chronic kidney disease; *DM,* diabetes mellitus; *IHD,* ischemic heart disease.
*Statistically significant ($P < .05$).

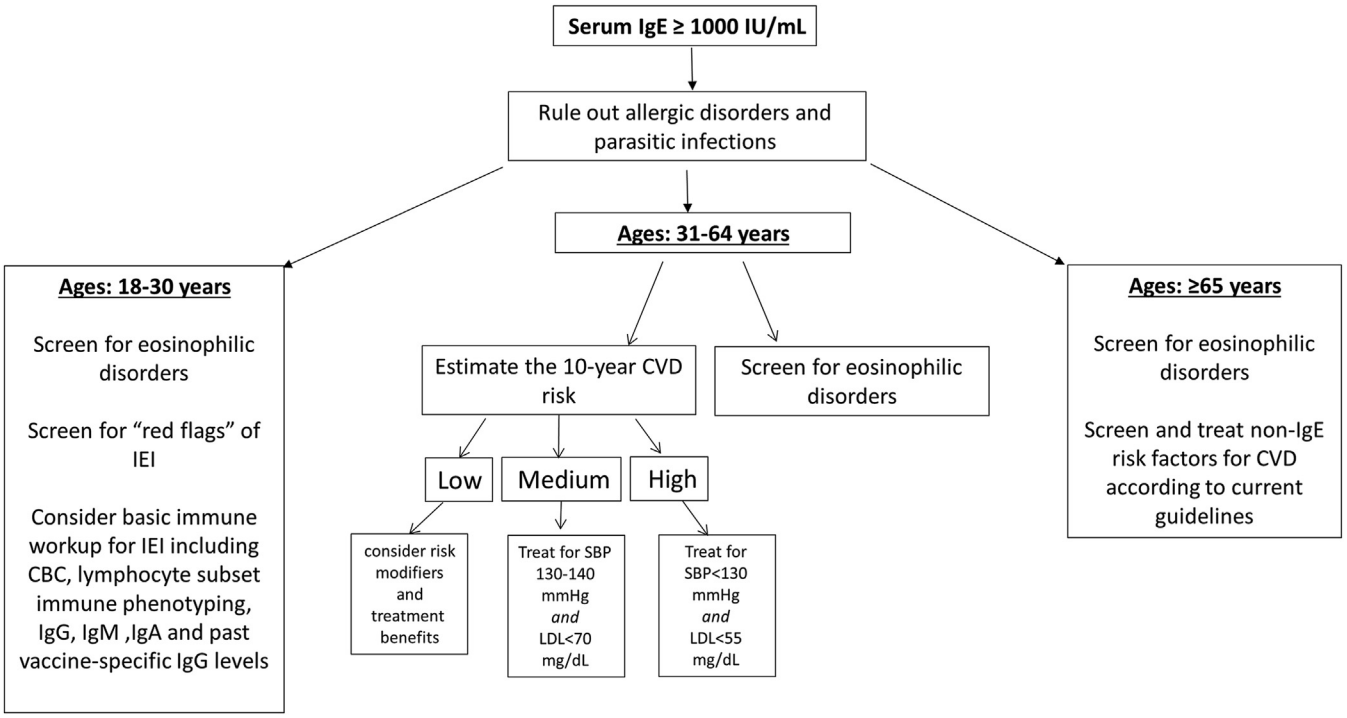

FIG 2. Suggested algorithm for clinical management of asymptomatic adult patients with serum IgE ≥ 1000 IU/mL. First, rule out allergic disorders such as atopic dermatitis and asthma, as well as parasitic infections. Management then depends on patient's age group. Screening for eosinophilic disorders, including CBC, should be conducted in all age groups. For young adults (18-30 years), investigate IEI by first looking for red flags,[32] then performing basic immune assessment. For patients aged 31-64 years with IgE ≥ 1000 IU/mL, follow guidelines for assessing 10-year CVD risk and treat other CVD risk factors accordingly.[35] *CBC,* Complete blood count; *LDL,* low-density lipoprotein; *SBP,* systolic blood pressure.

Finally, we found an increased risk of developing eosinophilic disorders among subjects with very high IgE levels. This outcome was consistently significant in the multivariable analysis across all age groups. Accordingly, very high IgE levels may indicate enhanced type 2 inflammation and can be observed in various eosinophilic disorders, such as eosinophilic granulomatosis with polyangiitis.[34]

Our findings should reassure physicians: no significant associations were identified between very high IgE levels and autoimmune, autoinflammatory, or malignant disorders. Moreover, although associations were observed with CVD, eosinophilic disorders, and IEI, the vast majority of patients with very high IgE levels were not diagnosed with these conditions (96.12%, 99.58%, and 99.65% of cases, respectively). Nevertheless, we recommend that treating physicians consider an assessment algorithm for the clinical management of asymptomatic, nonallergic patients with serum IgE levels ≥1000 IU/mL (Fig 2).

Regarding CVD risk, we suggest following the European Society of Cardiology guidelines by estimating the 10-year CVD risk in patients with IgE levels ≥1000 IU/mL. If the risk is low, risk modifiers and treatment benefits should be considered. If the risk is moderate to high, treatment should be initiated with the goal of achieving a systolic blood pressure of 130-140 mm Hg and a low-density lipoprotein cholesterol level of <70 mg/dL. If the risk is high, treatment should be targeted to achieve a systolic blood pressure of <130 mm Hg and a low-density lipoprotein level of <55 mg/dL.[35]

Furthermore, in patients with very high IgE levels, particularly those aged 31-64, who exhibit typical symptoms and possess other risk factors, a thorough assessment of the pretest probability of coronary heart disease should be conducted. For patients with suspected coronary disease, the initial evaluation should include a resting electrocardiogram, a resting transthoracic echocardiogram, and a carotid artery ultrasound.[36] For those with suspected coronary disease but a low likelihood of obstructive coronary artery disease, further evaluation may include coronary computed tomographic angiography.[36] Finally, patients with very high IgE levels and symptoms suggestive of cardiac ischemia should be treated in accordance with current CVD guidelines.[35]

Our study has several limitations. As a result of its retrospective design, we cannot establish a definitive cause-and-effect relationship between very high IgE levels and the observed clinical outcomes. Furthermore, the majority of participants in both the control and very high IgE groups were Jewish (67.58% and 74.36%, respectively). Our analysis did not involve a genetic examination of the subjects in the very high IgE group; this may pose challenges when attempting to generalize our findings to other genetically diverse populations globally. Additionally, as a result of the lack to genetic analysis, we cannot rule out genetic disorders that are more prevalent among the Jewish population and that manifest with very high IgE levels. Additionally, the subjects from each group were initially tested for IgE for specific reasons, which may introduce selection bias. One plausible reason for IgE testing in our subjects is related to the evaluation

of underlying allergic disorders. This is supported by the finding that most patients in the cohort had a diagnosis of allergic disorders (63,062, 53.35%, as shown in Table II). However, because of the large cohort size and the reliance on ICD-10 codes for data retrieval, it was not feasible to conduct an in-depth examination of patient records to determine the exact reason for IgE testing in each individual. Moreover, there are other unmeasured confounding variables, such as chronic receipt of medications, which were not included in the multivariable regression models as a result of data unavailability. Importantly, the IgE cutoff of ≥1000 IU/mL was derived from the existing literature[8,9,13,37] and is somewhat arbitrary. It is possible that similar associations might be observed within the 100-1000 IU/mL range; however, drawing conclusions from each subject with above-normal IgE levels is problematic. Another limitation resides in the interpretation of the Kaplan-Meier curves. These curves represent the univariable analysis with no stratification for independent variables. Thus, any conclusions arising from reading the curves should be viewed in light of the multivariable Cox regression models. It is also important to note that IgE antibodies play a crucial role in the immune response against parasites.[2,3] Despite our desire to include the diagnosis of parasitic infections in the outcomes analyzed for patients with very high IgE, we were unable to do so. This is because detecting parasitic infections often relies on laboratory tests that are not always performed. Additionally, some physicians do not consistently include parasitic infections as an ICD-10 code–based diagnosis. In terms of parasitic infections in the general adult Israeli population, a recently published population-based prospectively analyzed 144,859 stool samples of Israeli subjects in 2021. Parasites were identified in 9,861 adults, either through molecular testing or microscopy. The most frequently identified protozoa via PCR was *Blastocystis* spp (48.7%), followed by *Dientamoeba fragilis* (46.7%), then *Giardia lamblia* (3.9%) and *Cryptosporidium* spp (0.6%). Only 7 cases of *Entamoeba histolytica* (0.1%) and 3 cases of *Cyclospora* (0.03%) infection were detected. There were no regional differences in parasite distribution among laboratories.[38] However, we found no national study examining IgE levels in Israeli patients with parasitic infections, limiting our ability to assess the effect of such infections on our results. Finally, the risk of CVD increases with age, and the range in each tested age group is relatively broad, encompassing varying risk factors for CVD across this spectrum. Temporal bias can also be a result of changes in the diagnostic methods and criteria throughout the years of 2002 to 2022, which may have affected clinical outcome rates and levels of measured IgE. Given these limitations and confounders of our study, its retrospective design, the lack of evidence establishing causality, and the inability to assess the cost–benefit ratio of an extensive assessment for patients with very high IgE levels, further validation through large-cohort prospective studies is necessary before our recommendations can be applied in routine clinical practice.

In conclusion, IgE levels ≥1000 IU/mL are associated with increased risks of CVD, IEI, and eosinophilic disorders. Thus, very high IgE levels should be considered a serum biomarker for these disorders, especially when an allergic disorder has been excluded as the underlying cause. When encountering a nonallergic patient with a very high IgE test result, treating physicians should promote screening and further assessment to avoid delayed diagnosis and to offer better medical care for their patients.

DISCLOSURE STATEMENT

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Key messages

- **Very high serum IgE levels (≥1000 IU/mL) can be found in various atopic disorders, such as asthma.**
- **Very high IgE levels in adults are associated with increased risk of CVD, eosinophilic disorders, and IEI.**
- **Risk of eosinophilic disorders is found in every age group, but risk for CVD in adults with very high IgE is found specifically in ages 31-64.**
- **Physicians should consider further assessment for CVD, IEI, and eosinophilic disorders in nonallergic patients with very high IgE levels.**

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