

The Po River Delta epidemiological survey: Reference values of total serum IgE levels in a normal population sample of North Italy (8–78 yrs)

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Abstract. The aim of this paper was to define, for the first time in Italy, normal levels of total serum IgE in a general population sample of North Italy. Total serum IgE in 1905 subjects, living in Po Delta area (near Venice), were measured by PRIST method. Normal values were derived from 558 subjects without asthma and/or asthmatic/rhinitic symptoms, noncurrent smokers, skin prick-test negatives ('normals'). Cut-off values to differentiate 'normals' from the remaining part of the sample ('others'), from asthmatic, and from rhinitic subjects, were established with the IgE value midway between the upper limit of the 95% confidence intervals (CI) of the geometric mean for 'normals' and the lower limit for 'others', asthmatics, and rhinitics, respectively. Geometric mean of normal children–adolescents was

45 kU/L (SD: 2.6; 95% CI: 38–63). In normal adults geometric mean was 29 kU/L (SD: 3.3; 95% CI: 25–40) in males and 19 kU/L (SD: 3.8; 95% CI: 16–22) in females. The diagnostic sensitivity of IgE test was low, while the specificity was very high. A good positive predictive value in discriminating 'normals' from 'others' was found, on the contrary, we found a good negative predictive value in discriminating 'normals' from asthmatics or from rhinitics. In conclusion, our results confirm that it is necessary to provide separate total serum IgE reference values for what concerns age in children–adolescents and in adults, and gender, in adults. Low serum IgE are helpful to exclude allergic asthma or rhinitis level of total.

Key words: Atopy, Diagnostic efficiency, Epidemiological survey, Reference values, Total serum IgE

Introduction

Allergic diseases are a major problem in industrialized countries, because they affect about one-third of people under 30 yrs of age [1]. The prevalence of asthma, one of the most common diseases associated with allergy, has increased worldwide [2].

Diagnosis of allergy (i.e. diagnosis of rhinitis, eczema, and asthma) is largely based on clinical findings [3]. However, some markers, such as skin test reactivity to common aeroallergens or total and specific IgE, histamine basophil degranulation, eosinophil cationic protein, are increasingly used to confirm clinical suspect of allergy [4].

The knowledge of total IgE level helps to define atopic status; in fact, increased IgE levels have been observed in most atopic subjects, such as subjects with positive skin test reaction, or in subjects with allergic rhinitis and/or asthma [5, 6]. However, the interpretation of IgE levels is not always simple, because there is a widespread overlapping between the IgE distributions in atopic and nonatopic subjects [5, 7]. Moreover, there are a lot of confounding factors,

such as age, sex, cigarette smoking [3, 8], that may influence IgE levels. Finally, other disorders not related to allergy (e.g. parasitic diseases) can also produce elevated IgE levels [5]. Thus, it is very difficult to define a 'normal sample' for providing a normal range of total serum IgE [9].

In the evaluation of diagnostic validity of IgE test, it is helpful to know the method of computation of the positivity threshold (cut-off to discriminate pathologic from nonpathologic condition), because the sensitivity of IgE test decreases with the increasing of the cut-off (while specificity moves in the opposite direction) [10]. The literature contains several different reference ranges of total serum IgE for both adults [6, 11, 12] and adolescents [5, 13], but no one regards the Italian population. In the last 10 yrs, several studies have pointed out the importance of accounting for gender and age in the determination of reference values [10, 14].

The aim of this paper is to assess the distribution of total serum IgE and to provide upper reference limits from a normal sample of the general population living in an area of North Italy.

Materials and methods

During the second phase (1988–1991) of a longitudinal epidemiological survey [15] on a representative general population sample ($n = 2841$, 8–78 yrs), living in the Po River Delta area (near Venice), 2649 subjects underwent skin prick test (ST) to 12 common local aeroallergens (Pharmaceutical Laboratory LOFARMA S.r.l., Milan, Italy); pollens (Graminaeae mix, Compositae mix, *Parietaria officinalis*, and *Olea*); house dust mites (*Dermatophagoides pteronyssinus* and *D. farinae*); animal danders (dog, cat, horse, cow epithelium); molds (*Aspergillus fumigatus* and *Alternaria tenuis*). A detailed description of the methods is reported in the paper by Baldacci et al. [16]. A ST index was computed by summing up the minimum (min) and maximum (max) diameters of the wheal for each allergen (A) as follows [17]:

$$\begin{aligned} \text{ST index} = & \text{sum}[(\min_{A1} + \max_{A1}) - (\min \text{ negative control} \\ & + \max \text{ negative control})] + [(\min_{A2} + \max_{A2}) \\ & - (\min \text{ negative control} + \max \text{ negative control})] \\ & + \dots + [(\min_{A12} + \max_{A12}) \\ & - (\min \text{ negative control} \\ & + \max \text{ negative control})]/12 \end{aligned}$$

Subjects with ST index > 0 were considered skin prick test positive (ST+), otherwise they were considered skin prick test negative (ST-).

On 1946 subjects the level of total serum IgE was also determined. No difference was observed between subjects with and without IgE determination in regard to sex, respiratory symptoms/diagnosis, asthma, and passive smoking exposure. Subjects with IgE determination were older (39.5 vs. 34.2 yrs) and showed a greater prevalence of ex-current smokers (29.4 vs. 24.1%) and of ST+ (40.3 vs. 35.5%), when compared to subjects without IgE determination. Analyses were performed on 1905 subjects (whole sample = 67% of original population; 915 males, 990 females), who had both the IgE determination and the result of ST. IgE determination was performed by direct paper radioimmunosorbent test (PRIST, Pharmacia Diagnostics AB Uppsala, Sweden, detection limit of about 0.1 kU/L). Each determination was performed in duplicate and the average of two values was recorded. When the coefficient of variation between duplicate measurements was greater than 10%, the determination was repeated. Total serum IgE were reported as kU/L, where one unit is approximately 2.4×10^{-9} g [18]. A detailed description of the method is reported in the paper by Sapigni et al. [17].

Information on respiratory symptoms/diseases and risk factors were obtained by a standardized interviewer-administered questionnaire, developed by the National Research Council (CNR), following that of National Heart, Lung and Blood Institute (NHLBI) [19]. Subjects who were smoking at least one cigarette

per day were defined as 'current smokers'. 'Occasional smokers' were those who were currently smoking less than one cigarette a day. 'Ex-smokers' were those who had quitted smoking habit for at least 6 months. 'Never smokers' were the subjects who had never smoked. 'Rhinitics' were those subjects who answered affirmatively to the question: 'Have you ever had hay fever, runny or stuffy nose, out of common colds?', and to whom the diagnosis of rhinitis was confirmed by a physician. Subjects were classified as 'asthmatics', when they answered affirmatively to the questions: 'Have you ever had bronchial asthma or asthmatic bronchitis?', and 'was the diagnosis of asthma confirmed by a physician?'

Reference group

The selection of the reference group was performed taking into account the following factors [20]:

1. pre-analytical factors: season and hour of blood collection, fasting/nonfasting state, drugs/alcohol/coffee/tea intakes, dietary regimen, menopause, physical exercise;
2. diseases and risk factors responsible of known deviation of IgE (i.e. asthma, bronchitis, rhinitis, asthmatic/bronchitic/rhinitic symptoms, ST+ reaction, smoking habit, food allergy, familial asthma and other familial allergies, eczema).

Pre-analytical factors did not result to influence IgE levels. Previous analyses on the same population sample [17] showed that ST+ reaction, current smoke, asthma, and/or asthmatic/rhinitic symptoms increased significantly IgE levels. On the contrary, chronic bronchitis, emphysema, cough/phlegm out of common cold, food allergy, familial asthma/other allergies, and eczema were not associated with a significant increase of total IgE. Subjects having conditions which were significantly associated to increased IgE levels were excluded from the selection of the reference group. Thus, subjects of the reference group ('normals', $n = 558$) were defined as: ST-, noncurrent smokers, without asthma/rhinitis or asthmatic/rhinitic symptoms. Subjects ST+ and/or current smokers and/or subjects with asthma/rhinitis and/or with asthmatic/rhinitic symptoms were defined as 'others'.

Statistical analyses

Statistical analyses were performed using the Statistical Package for the Social Sciences (SPSS-X) [21]. The used routines were: Kolmogorov–Smirnov non-parametric test for normality, one-way and multi-factorial analysis of variance (ANOVA), χ^2 test, multiple stepwise regression analysis. IgE values were not normally distributed, thus a $\log_{10}$ transformation was performed. The IgE mean levels were reported both as $\log_{10}$ mean and geometric mean. Upper ref-

erence limits were defined as the values corresponding to the 97.5 percentile of the frequency distribution of IgE.

The parameters of the IgE test to discriminate separately 'normals' from 'others', 'normals' from asthmatics and from rhinitics, were computed as following [22]:

$$\text{sensitivity} = [\text{TP}/(\text{TP} + \text{FN})] \times 100$$

$$\text{specificity} = [\text{TN}/(\text{TN} + \text{FP})] \times 100$$

$$\text{positive predictive value} = [\text{TP}/(\text{TP} + \text{FP})] \times 100$$

$$\text{negative predictive value} = [\text{TN}/(\text{TN} + \text{FN})] \times 100$$

$$\text{diagnostic efficiency} = [(\text{TP} + \text{TN})/(\text{TP} + \text{TN} + \text{FP} + \text{FN})] \times 100,$$

where TP = true positives, FP = false positives, TN = true negatives, FN = false negatives. TP + FN represented the cases (i.e. 'others' or asthmatics or rhinitics, separately), whereas TN + FP represented the controls.

For these computations, we used a positive threshold (cut-off-I), established as the IgE value midway between the upper limit of the 95% CI of the geometric mean in 'normals' and the lower limit of the 95% CI of the geometric mean in 'others' (subjects who remained after selection of normals), in asthmatics, and in rhinitics, respectively [6]. This method of cut-off computation provides a cut-off very similar to the optimal cut-off found on the ROC curves by the inspection of the graph. In fact, both the cut-off-I and the optimal cut-off by the ROC curve, offer the best compromise between the highest sensitivity and specificity [3]. For comparison with other authors [13], a second type of cut-off was

computed as the product of IgE geometric mean and 2SD in 'normals' (cut-off-II).

The level of statistical significance was $p = 0.05$.

Results

Table 1 shows characteristics of the whole sample and of 'normals'. In the whole sample, about 40% of subjects were ST+ and 5–6% of subjects reported to have asthma; men were more frequently current smokers, but they presented a double proportion of ex-smoking habit than women.

Normal subjects showed significantly lower IgE values than 'others', in both sexes (males: 29.5 vs. 60.3 kU/L; females: 19.5 vs. 35.5 kU/L), even if a large overlapping of the IgE distributions in 'normals' and 'others' was shown (Figure 1).

In normal adults, total serum IgE levels ranged from 1.2 to 635 kU/L in males, and from 4.2 to 714 kU/L in females; in children–adolescents, IgE values ranged from 6.5 to 426 kU/L. Table 2 shows IgE geometric means and upper limits in both normal children–adolescents and adults. Children–adolescents had significantly greater IgE values than adults. In the latter, males showed significantly higher IgE values than females. Stratifying by age, significant differences between genders remained in the age groups 25–34, 45–54, and 65+ yrs.

Figures 2 and 3 show how cut-off-I were very similar to the optimal thresholds provided by ROC curves. With the ROC curve, by plotting the false positives (i.e. 1-specificity) against the true positives (i.e. sensitivity), we found the optimal threshold by measuring the closest distance from the ideal point (sensitivity = 1 and specificity = 1, that corresponds to 1-specificity = 0) on the curve, by inspection of the graph. On the contrary, cut-off-II offers a greater specificity, but a very low sensitivity.

Table 1. Characteristics of studied subjects

Whole sample N = 1905	Males N = 915	Females N = 990
Age (yrs ± SD)	39.3 ± 15.9	39.5 ± 16.4
Smokers (%)	37.3	24.0
Ex-smokers (%)	36.1	17.7
Never smokers (%)	26.6	58.3
ST+ (%)	40.7	40.0
Asthma (%)	5.9	5.3
Rhinitis (%)	17.7	18.1
Wheeze (%)	24.3	15.1
Normals N = 588	Males N = 241	Females N = 347
Age (yrs ± SD)	40.0 ± 16.5	38.9 ± 17.4
Ex-smokers (%)	56.2	25.1
Never smokers (%)	43.8	74.9

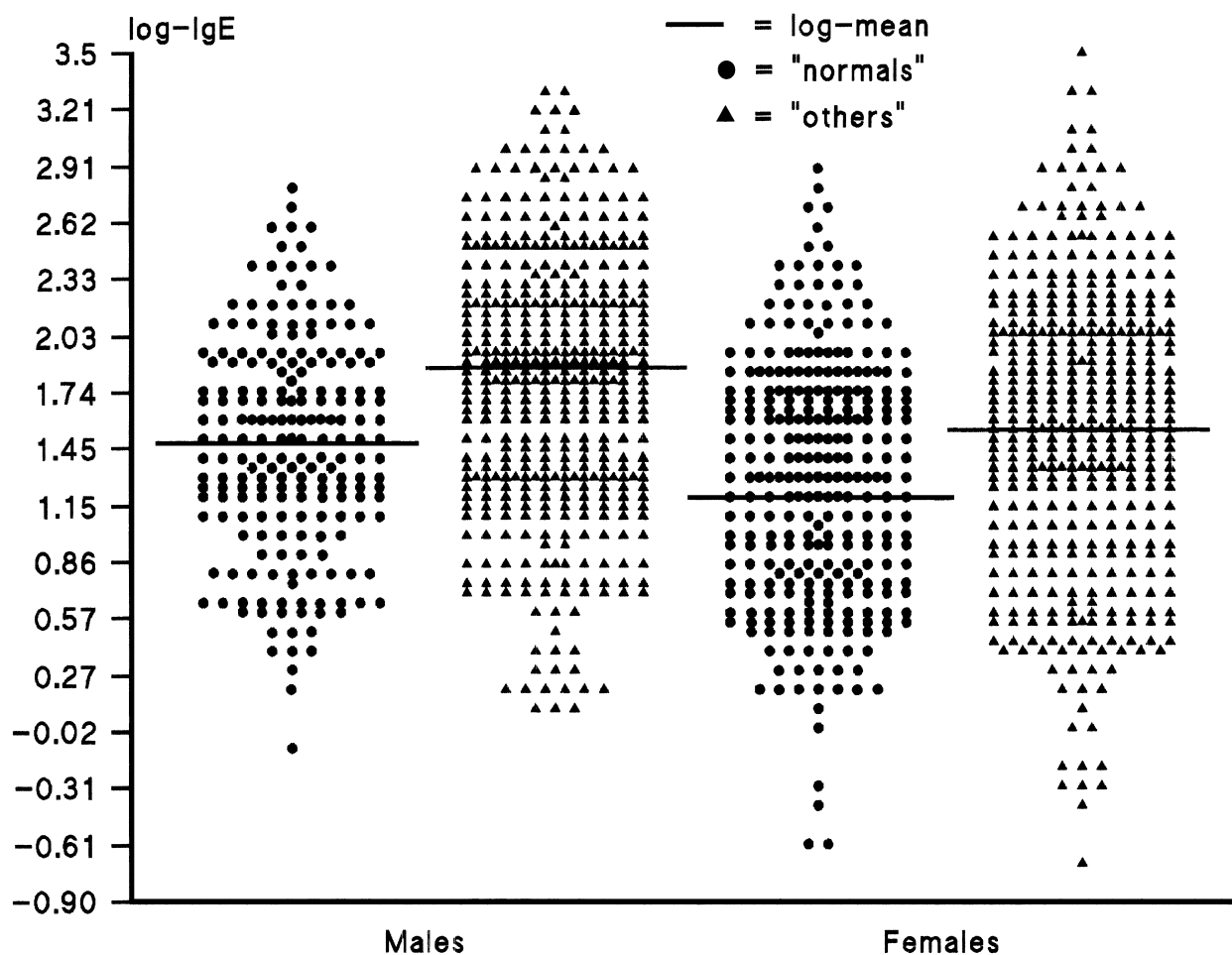


Figure 1. Log-IgE distribution was significantly lower in 'normals' (ST-, noncurrent smokers, without asthma or asthmatic/rhinitic symptoms) than in 'others', in both genders ($p < 0.001$ by ANOVA).

Although sensitivity of the test (Table 3) in discriminating 'normals' from 'others' of both sexes, was low, good positive predictive values with both cut-off-I (74–84%) and cut-off-II (85–94%) were found. On the contrary, good negative predictive values were shown in discriminating 'normals' from asthmatics (71–86%) and 'normals' from rhinitics (77–81%). With cut-off-II (that was higher than cut-off-I), the specificity was very high (98%). The greatest diagnostic efficiency (81%) was found in females for the discrimination of 'normals' from asthmatics with cut-off-II.

Discussion

Our results showed a large overlapping of total serum IgE distributions in 'normals' and 'others', thus confirming the findings of other authors [6, 12].

'Normals' showed significantly higher IgE levels in adult males than in adult females, confirming the findings of other authors [7, 10]. Holford-Strevens [12] reported that the difference between genders disappeared in normals subjects (i.e. ST-/asymptomatic/nonsmoker subjects), thus he explained the difference between genders as due to the presence of a greater prevalence of smokers in men. However, we used the same criteria in selecting 'normals' and, even if current smokers were excluded, the significant difference between males and females remained, confirming that current smoking habit is not the only factor responsible of the higher IgE level in males [9].

In children-adolescents, as also reported by Backer et al. [13] and Lindberg and Arroyave [5], we did not find differences between males and females; however, we provided separated reference values also in this age group (8–14 yrs), to allow comparisons with other studies (Table 4). In accordance with other authors [10], significantly higher IgE levels in children-adolescents than in adults were found. In adults (15+ yrs) there was no significant age related difference of IgE values, even if a nonsignificant trend to decrease with aging was confirmed [1, 6, 12, 14]. Thus, we did not provide age related reference levels, except for children-adolescents and adults, in disagreement with Klink et al. [9], who suggested providing reference levels in different decades of age.

Table 2. Reference values of total serum IgE levels in 'normals'

	N	Geometric mean (kU/L)	95% CI of geometric mean	Upper limit ^a	95% CI of 97.5th percentile
Children-adolescents (8-14 yrs)					
Males + Females	31	45	38-63	291	164-518
Adults (15+ yrs)					
Males	226	29	25-40 ^b	297	228-387
Females	331	19	16-22	257	201-330

^a 95% interfractile reference interval (97.5th percentile) = $\text{antilog}_{10} [\text{mean log}_{10} \text{IgE} + (1.96 \times \text{SD log}_{10} \text{IgE})]$.

^b $p < 0.001$ between sexes by ANOVA.

In Table 4 we report a comparison of IgE reference values by different authors [6, 10, 12-14], who used similar study methods. In each study the PRIST method was used, and 'normals' were selected as ST-subjects without asthma and/or asthmatic/allergic symptoms, except for the Backer et al. [13] study, in which 'normals' were only ST-subjects. Holford-Strevens [12] excluded, as we did, current smokers,

too. Our upper limits of 'normality' were in the range of the published data, confirming the consistency of these first Italian values. In children-adolescents, the upper limits were very similar to those of a Danish study [13] (303 vs. 305 kU/L), and even our normal children-adolescents were very few ($n = 31$). In adults, our upper limits were similar to those by Grigoreas et al. [14] in a Greek study (297 vs.

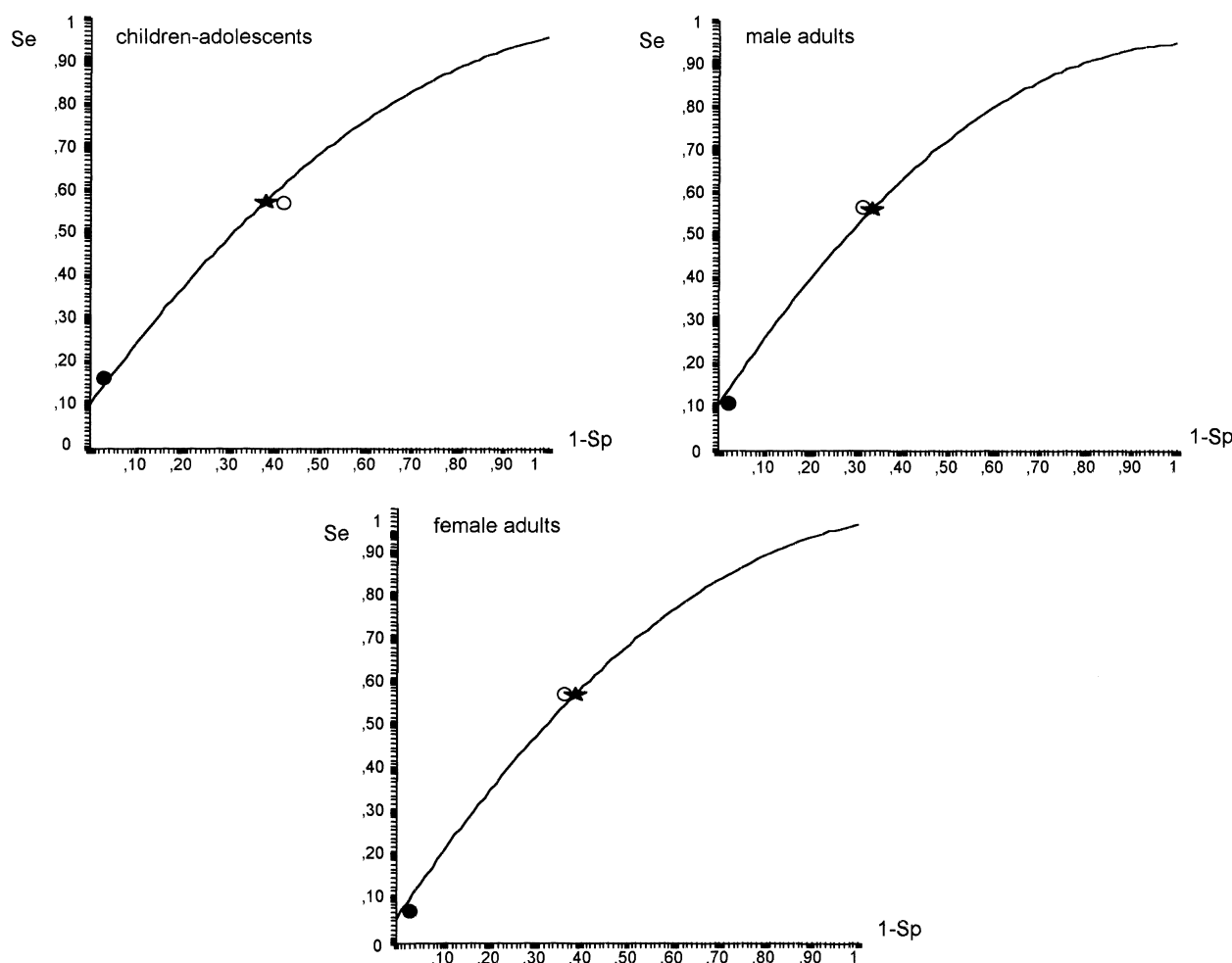


Figure 2. ROC curves. 'Normals' vs. 'others'. The IgE level, which provides both sensitivity (Se) and specificity (Sp) equal to 1 ($1 - \text{Sp} = 0$), represents the ideal point. The optimal cut-off (star) provides the best compromise between Se and Sp and it is the closest point on the curve to the ideal point. In this figure and in Figure 3, the optimal cut-off (star) on ROC curves were determined by inspection of the graphs. The empty circles correspond to cut-off-I, while the full circles represent cut-off-II.

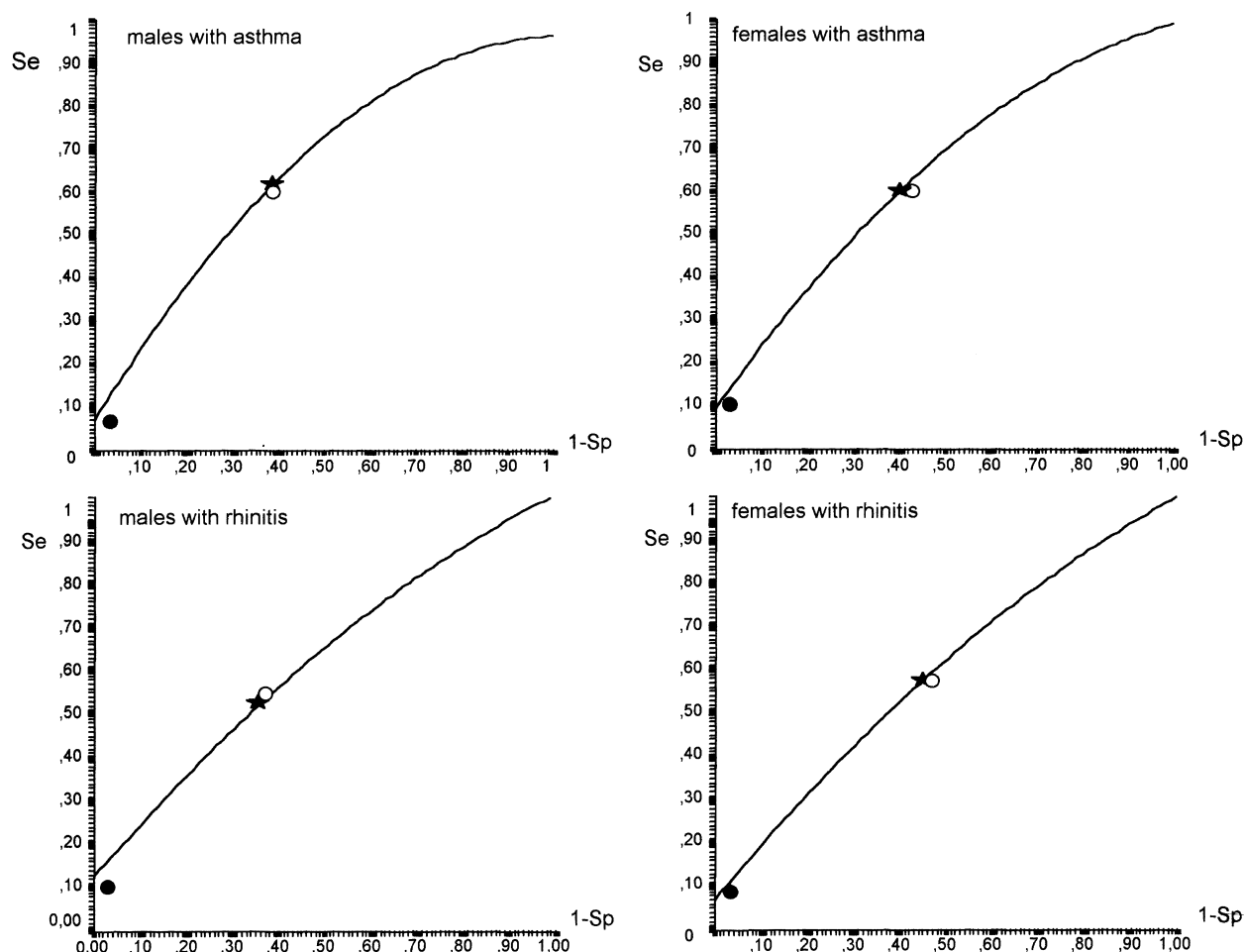


Figure 3. ROC curves. 'Normals' vs. asthma. 'Normals' vs. rhinitis. Se = sensitivity; Sp = specificity.

290 kU/L in males, and 257 vs. 255 kU/L in females). Klink et al. [9], in an American study, found IgE values higher than ours, except for adult females. The Canadian study by Holford-Strevens [12] showed IgE levels lower than ours in adults. The only apparent difference was that the Canadian sample was older than our sample (20+ vs. 15+ yrs). However, IgE values by Grigoreas et al. [14] were similar to ours, even if the same difference of age was present. It is to point out that the differences among the results of different studies may be due to chance, or produced by either the kind of investigated population (e.g. differences in sampling criteria, representativeness of a general population, sample size, age range, etc.), or the technical variability (e.g. differences in laboratory procedures, manufacture and batch of IgE kit, etc.).

The method of computation of the positive cut-off is very important to provide the indices of the test performance. If the cut-off is too low, the sensitivity increases, but the specificity decreases, with the consequent increase in the number of false positive subjects.

With regard to the discrimination between 'normals' and 'others', in adults, cut-off-II produced a higher specificity (98% in both sexes) than cut-off-I

(68% in males, 63% in females), whereas the positive predictive value was quite good with both cut-off-II (94% for males and 85% for females) and cut-off-I (84% for males, 74% for females). The clinical consequence, independently from the used cut-off, was a low number of false positive subjects (and a consequent high number of true negative subjects).

In children-adolescents, we found a low sensitivity with the cut-off-II (16%), consequent with a low number of false positive subjects (3%), to confirm the finding by Backer et al. (4%) [13].

The negative predictive values in the discrimination of 'normals' from asthmatics or from rhinitics, was quite high, particularly in discriminating 'normals' from asthmatic females. It seemed that the probability of finding an asthmatic or a rhinitic subject with low IgE level was very low. The diagnostic efficiency was low with cut-off-I, whereas, with cut-off-II, it was quite high in discriminating 'normals' from asthmatic or 'normals' from rhinitic subjects.

Our results confirm that it is necessary to provide reference values separately for children-adolescents and adults, and distinction of sexes among adults.

There was not a single cut-off that would discriminate 'normals' from 'others' with a good diagnostic

Table 3. Parameters of total IgE test performance in discriminating 'normals' from diseased by two different types of cut-off

	Cut-off-I						Cut-off-II					
	Value (kU/L)	Se (%)	Sp (%)	PPV (%)	NPV (%)	DE (%)	Value (kU/L)	Se (%)	Sp (%)	PPV (%)	NPV (%)	DE (%)
'Normals' vs. 'others'												
<i>Children-adolescents</i>	59	57	58	68	46	58	303	16	97	89	42	48
Males + females (31/49)												
<i>Adults</i>												
Males (226/648)	48	57	68	84	36	60	316	11	98	94	28	34
Females (331/620)	30	57	63	74	44	59	269	7	98	85	36	38
'Normals' vs. only asthmatics												
<i>Adults</i>												
Males (226/97)	42	60	63	41	78	62	316	6	98	55	71	70
Females (331/79)	25	60	57	25	86	58	269	10	98	53	82	81
'Normals' vs. only rhinitics												
<i>Adults</i>												
Males (226/67)	40	54	60	28	81	58	316	10	98	58	79	78
Females (331/104)	23	56	55	28	80	55	269	9	98	56	77	77

^a Midway value between the upper limit and the lower limit of the 95% CI of the geometric mean in 'normals' and diseased, respectively.

^b Geometric mean $\times$ antilog₁₀ ($\times 2SD$).

Se = sensitivity; Sp = specificity; PPV = positive predictive value: $(TP/TP + FP) \times 100$; NPV = negative predictive value: $(TN/TN + FN) \times 100$; DE = diagnostic efficiency: $(TP + TN/\text{all subjects}) \times 100$.

efficiency. On the contrary, the diagnostic efficiency in discriminating normal adults from asthmatics or from rhinitics was good with cut-off-II.

Unfortunately, there is no single test that can be used as a 'gold standard' for atopic allergy, but the total IgE test is helpful for evaluating the presence of allergic diseases in subjects with high IgE values, and, consequently, to evaluate the exclusion of asthma or rhinitis in subjects with low levels.

A possible limitation of this study, could be the lack of data on the presence of parasitosis, that is known to increase the level of total IgE. However, we think that, in a general population sample like ours, living in an area of North Italy, the prevalence of parasitosis should not be so high to lead to a modification of the reported results. Another limitation could be the exclusion of bronchial hyperresponsiveness (BHR) from analyses. In fact, BHR could play a role in the increase of IgE levels. However, as all studies reported in Table 4 on IgE reference values, did not take into account BHR in the selection of the reference population sample, we too, did not consider this variable, for a better comparison. Moreover, only 16 subjects in the normal sample showed bronchial hyperreactivity, and IgE values in these subjects did not result higher than in subjects without bronchial hyperreactivity.

Even if it has been difficult to determine a precise role for IgE in the pathogenesis of asthma [23], it is undeniable that total IgE levels have been shown to be strongly associated with the risk of developing asthma in large population samples [24]. Moreover, in the Tucson epidemiological survey, no physician-

diagnosed asthma was reported in subjects with very low IgE levels [25]. In the usual management of asthma, before and after the medical treatment, one of the first step is the determination of IgE serum values, along with blood eosinophils. All clinical laboratories provide a range of normality for IgE values which, however, are seldom based on general population samples. It is even more important to know the reference values in epidemiological studies, for comparison among the population samples of different countries. Total IgE values, as well as all biological parameters, may differ for race, geographical area, diet. Moreover, because these ranges may change with time, a periodic re-evaluation would be suitable.

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Table 4. Comparison of total serum IgE levels in 'reference populations' of different studies

	Kind of population	Method	Manufacturer	N		Age (yrs)	Mean (SD) (log ₁₀)		97.5th centile ^a (kU/L)		95th centile ^b (kU/L)		
				M	F		M	F	M	F	M	F	
Children-adolescents													
Klink et al. [9]	Random stratified residents in Tucson (Arizona)(ST ⁻ , no current asthma/asthmatic symptoms)	PRIST	Pharmacia, Piscataway (NJ)	69	71	6-14	1.61 (0.65)	1.61 (0.52)	766	426	474	290	
Backer et al. [13]	Random (ST ⁻)	PRIST	Pharmacia, Copenhagen (DK)	M + F	= 199	8-15	1.25 (0.63)		305		192		
Po Delta	Random stratified residents in a rural area (ST ⁻ , non current smokers, no allergic or asthmatic symptoms, no asthma)	PRIST	Pharmacia, Sweden	15	16	8-14	1.60 (0.46)	1.70 (0.37)	323	266	245	174	
Adults													
Holford-Strevens [12]	Resident in a rural Canadian area (83% eligible) (non smokers, ST ⁻ , no symptoms of allergy, no asthma)	PRIST	Pharmacia, Canada	130	242	≥20	1.10 (0.48)	1.07 (0.49)	110	107	77	75	
Klink et al. [9]	Random stratified residents in Tucson (Arizona) (ST ⁻ , no current asthma /asthmatic symptoms)	PRIST	Pharmacia, Piscataway (NJ)	643	786	≥15 ^c	1.31 (0.69)	1.09 (0.66)	460	246	276	149	
Zetterström [6]	Subjects participating in a health survey in Sweden (RAST ⁻ , no allergic symptoms)	PRIST	Pharmacia, Sweden	M + F	= 175	≥17	1.21 (0.47)		109		96		
Grigoreas et al. [14]	Ground personnel of the Greek Airforce (ST ⁻ , no symptoms of allergy)	PRIST	Pharmacia, Sweden	536	276	≥20	1.58 (0.45)	1.47 (0.48)	290	255	208	181	
Po Delta	Random stratified residents in a rural area (ST ⁻ , non current smokers, no allergic or asthmatic symptoms, no asthma)	PRIST	Pharmacia, Sweden	226	331	≥15	1.46 (0.52)	1.27 (0.58)	297	257	231	179	

^a Upper limit of interfractile reference interval 95% = antilog₁₀ [log₁₀ mean + (1.96 log₁₀ SD)] [24].^b Upper limit of interfractile reference interval 90% = antilog₁₀ [log₁₀ mean + (1.64 log₁₀ SD)] [24].^c Average of reported age group means.

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