patients versus the non-NPSLE patient group, and patients with psychosis and/or mood disorder versus either the non-NPSLE patients or all other lupus patients. Finally, we evaluated the available data to compare active NPSLE versus non-NPSLE.

Eligible studies published in any language were retrieved during the stage of identification of pertinent articles and collaborating investigators, as described above. We updated the literature search of the 3 computerized databases in November 2004 to identify additional relevant studies published up to November 1, 2004. Meeting abstracts were not included because the results may not be final and may not have been subjected to formal peer review. Duplicate or overlapping data were counted only once. The inclusion criteria were similar to those of the collaborative meta-analysis, with no restriction on patient age or study location. Nevertheless, in these analyses, we did not use the stringent criteria regarding the method of antibody determination and classification of neuropsychiatric disease; studies were combined regardless of the assay used to detect anti-P antibodies and regardless of the criteria used to diagnose NPSLE.

Other sensitivity analyses. We also performed sensitivity analyses to assess the robustness of the quantitative estimates derived from the collaborative meta-analysis. These analyses were limited to studies that used the ACR criteria for NPSLE syndromes and limited to studies that specified blinding.

Software. Analyses were conducted with the use of the following software: SPSS, version 12.0 (SPSS, Chicago, IL), Meta-Test, version 0.6, New England Medical Center, Boston, MA, 1997 (Joseph Lau, Tufts–New England Medical Center, Boston, MA) and Meta-Analyst, version 0.991 (Joseph Lau, Boston, MA).

RESULTS

General characteristics. We sent inquiries to 104 investigators working on SLE. Of those 104 investigators, 65 did not reply, 18 did not have any data and could not produce such data for the project, and 4 declined to participate. Of the last group, 2 investigators had published studies that were included in the sensitivity analysis.

The collaborative meta-analysis considered 1,537 lupus patients from 14 teams of investigators. Of these, 1,295 patients underwent both anti-P antibody testing by immunoblotting or standard ELISA and evaluation for NPSLE according to the ACR case definitions. The median sample size per study was 91 patients (interquartile range [IQR] 48–162). Women accounted for 80–97% of each study population. Although more than one-half of the participants were of European descent, patients of other ancestries were also included (Table 1). The mean age of the patients at study entry ranged from 29.8 years to 41.6 years, and the median of the mean disease durations across study cohorts was 7.3 years (IQR 6.2–7.8).

Most studies used a solid-phase ELISA, with highly purified synthetic peptides of the carboxyl-terminal 22–amino acid sequence (n = 4), a multiple-antigen peptide format (n = 3), and purified native (n = 2) or recombinant (n = 3) proteins as coating antigen to detect anti-P antibodies. Seven studies designated a positive anti-P result as >2 SD (n = 1) or >3 SD (n = 6) above the mean value obtained in a normal population, whereas 5 studies reported results according to the suggested threshold for the commercial ELISA systems they used. Only 4 studies used Western blotting on cell extracts from various sources for the detection of this autoantibody specificity. A single study used a line immunoassay, which is an ELISA-based multianalyte assay (Table 1).

The median prevalence of anti-P antibodies was 18.2% (IQR 9.7–28.6%). These antibodies were more prevalent in lupus patients of Asian descent than among those of other racial ancestries. The study-specific frequencies of anti-P antibodies were 23.8–45.5% in 320 patients of Chinese, Japanese, Taiwanese, and Filipino ancestry and 6.4–25.4% in 1,212 patients of other ancestry.

Approximately one-third of the 1,537 lupus patients had NPSLE that manifested as syndromes described in the ACR case definitions (median prevalence 32% [IQR 12–42%]). In 1 study (Table 1), neuropsychiatric involvement was determined according to prespecified criteria other than the ACR case definitions. Eight research teams provided individual patient data; in these studies, 8% of patients had >1 neuropsychiatric disorder, but only 5% had both focal and diffuse presentations. The other 6 teams directly collected data on only the most prominent manifestation. More than one-half of the NPSLE patients presented with disorders reflecting diffuse cerebral involvement (median prevalence 54.5% [IQR 47.6–68.2%]). The median prevalence of psychosis, mood disorder, or both was 24.9% (IQR 17.1–38.4%). In most studies, NPSLE was diagnosed without knowledge of the anti-P antibody status, and test interpreters were blinded to the clinical condition of the patients (Table 1).

Diagnostic performance of anti-P antibody testing. Substantial heterogeneity was found in both the sensitivity and the specificity of anti-P antibody testing

Table 1. Characteristics of the studies and patient populations included in the collaborative meta-analysis*

Study ID	Investigator, country, year (ref.)	Study setting	No. of patients	% women	Ethnicity (%)†	Mean age, years	Mean disease duration, years	Anti-P antibody assay	Prevalence of NPSLE, %	NPSLE manifestation			Blinding‡
										Psychosis and/or mood disorder	Other diffuse manifestations	Focal events	
1	Doria A, Italy, 2004	University	101	88	Italian (98), African (2)	29.8	6.7	WB/ELISA	21	8	6	7	T, C
2	Morozzi G, Galeazzi M, Italy, 2004	University	20§	90	Italian (85), Chinese/Filipino (15)	35.7	7.6	ELISA	15	0	0	3	T, C
3	Afeltra A, Italy, 2004	University	43	88	Italian	41.6	8	ELISA	93	2	16	22	T, C
4	Mathieu A, Italy; Sanna G, UK, 2000 (24)	University	68¶	96	Italian	38.4	7.7	ELISA	49	7	9	17	T, C
5	Hoffman I, De Keyser F, Belgium, 2004 (14)	University	235#	88	Belgian, Dutch, Slovak, English	40	7.2	LIA	59	33	32	51	NS
6	Tzioufas A, Greece, 2000 (30)	University	185	96	Greek	34.7	4.3	ELISA	9	2	7	8	NS
7	Ambrozic A, Slovenia, 2003	University	150	91	Slovenian	38.1	7.8	WB	39	11	14	33	T, C
8	Inanc M, Turkey, 2004	University	218	89	Turkish	38.5	7.8	ELISA	23	20	5	26	T, C
9	Chang D-M, Taiwan, 2003	Community	80	91	Taiwanese	35	9.4	ELISA	6	1	3	1	NS
10	Mok CC, China, 2004	Community	33	97	Chinese	36.2	7	WB/ELISA	33	3	5	3	T, C
11	Hirohata S, Japan, 2003	University	50	80	Japanese	40.8	2.6	ELISA	32	5	7	4	T, C
12	Yoshio T, Japan, 2003 (35)	University	154**	90	Japanese	34.6	4.7	ELISA	40	14	24	24	T, C
13	Massardo L, Chile, 2002 (21)	University	141††	90	Chilean	33	7	WB/ELISA	9	5	1	6	T, C
14	Spindler AJ, Argentina, 2003	University	59	92	Argentinean	36	7.3	ELISA	44	11	4	11	T, C

* References and publication dates (when the contributed data were derived from published studies) are provided; otherwise, the year the data were collected and sent to the coordinating center are shown. See Patients and Methods for a full description of the 3 subgroups of neuropsychiatric systemic lupus erythematosus (NPSLE). Anti-P = anti–ribosomal P; WB = Western blotting; ELISA = enzyme-linked immunosorbent assay; LIA = line immunoassay.

† Percentages are given for studies that included patients of different ethnicities, when known.

‡ NPSLE was diagnosed without knowledge of the results of the anti-P antibody testing (T), and test interpreters were blinded to the clincial data (C). NS = not specified.

§ In this study, 3 patients had indeterminate results for anti-P antibodies and were not included in the quantitative synthesis.

¶ In this study, 5 patients who were not tested for anti-P antibodies were not included in the quantitative synthesis.

In this study, sufficient clinical information for NPSLE was available for 196 patients; the presence or absence of NPSLE was assessed using prespecified criteria other than the American College of Rheumatology case definitions (7); and data for disease duration were available for 197 patients.

** Only 44 patients were included in the published study.

†† In this study, 2 patients in addition to the ones listed under NPSLE manifestations had NPSLE, but the type of involvement was not known.

Table 2. Summary results of the collaborative meta-analysis*

Comparison	No. of studies	No. of subjects	Weighted sensitivity (95% CI)	Weighted specificity (95% CI)
NPSLE versus non-NPSLE	13	1,340	0.26 (0.15–0.42)	0.80 (0.74–0.85)
Psychosis and/or mood disorder versus non-NPSLE	12	1,024	0.27 (0.14–0.47)	0.80 (0.74–0.85)
Other diffuse neuropsychiatric manifestations versus non-NPSLE	12	1,034	0.24 (0.12–0.42)	0.80 (0.73–0.85)
Focal neurologic events versus non-NPSLE	13	1,110	0.29 (0.15–0.48)	0.80 (0.74–0.85)
All diffuse neuropsychiatric manifestations versus focal neurologic events	12	406	0.26 (0.14–0.43)	0.70 (0.50–0.84)
Psychosis and/or mood disorder versus other diffuse neuropsychiatric manifestations	12	228	0.28 (0.15–0.46)	0.75 (0.57–0.88)
Patients with psychosis and/or mood disorder versus all other lupus patients	12	1,322	0.27 (0.14–0.47)	0.80 (0.72–0.86)

* Weighted sensitivity and specificity were determined according to the random-effects model. Between-study heterogeneity was statistically significant for all comparisons ($P \ll 0.01$). 95% CI = 95% confidence interval; NPSLE = neuropsychiatric systemic lupus erythematosus.

using ELISA (Table 2). In the random-effects model, the overall weighted sensitivity and specificity estimates for the diagnosis of NPSLE were 26% (95% CI 15–42%) and 80% (95% CI 74–85%), respectively (Table 2).

Diagnostic performance for neuropsychiatric disease appeared to be somewhat better in studies that used Western blotting to detect anti-P antibodies (summary sensitivity 36% [95% CI 16–63%]; summary specificity 84% [95% CI 70–92%]), but significant between-study heterogeneity was still present (P = 0.0001 for heterogeneity in sensitivity estimates and P = 0.0007 for heterogeneity in specificity estimates), and data were too limited to be conclusive (4 studies; 424 patients). Test performance was poor for NPSLE in Asian patients (4 studies; 317 patients, yielding a summary sensitivity of 55% [95% CI 45–65%] and a summary specificity of 68% [95% CI 59–76%]). The weighted specificity tended to be higher in all other lupus patients, which were mostly of European descent, but there was low sensitivity (9 studies; 1,023 patients, yielding a summary sensitivity of 17% [95% CI 9–32%] and a summary specificity of 85% [95% CI 81–88%]).

SROC analyses suggested similar performance for identifying SLE-induced neuropsychiatric disease. Weighted and nonweighted curves were practically coincident (Figure 1A). Anti-P antibodies had an almost equally meager discriminating ability for the diagnosis of either psychiatric syndromes or other forms of neuropsychiatric involvement in SLE (Table 2). Weighted random-effects independent estimates stand very close to the weighted SROC curves for these comparisons (Figures 1B–D), suggesting that they are appropriate approximations of the overall diagnostic performance. Statistically significant asymmetry was found in all these curves (Figure 1), indicating that an improvement in specificity was accompanied by a disproportionately large decrease in sensitivity.

Within the group with NPSLE (Table 2), anti-P antibody testing could not accurately discriminate patients presenting with diffuse manifestations from those presenting with focal events (summary sensitivity 26%; summary specificity 70%) (Figure 2A) or patients presenting with psychiatric disorders from those presenting with any other diffuse symptom (summary sensitivity 28%; summary specificity 75%) (Figure 2B). Test characteristics remained unchanged for the identification of patients with psychiatric disorders compared with all other lupus patients (with or without neuropsychiatric dysfunction) (Table 2). Significant asymmetry was found in the corresponding SROC curve (Figure 2C), implying that an improvement in specificity was accompanied by an uneven, large decrease in sensitivity.

Findings of additional analyses. Our search of the 3 databases identified a total of 306 potentially relevant articles, of which 243 studies were excluded upon reading the titles and abstracts. Another 39 studies were excluded after reviewing the complete reports: 8 were editorials, comments without original data, or review articles, 11 were case reports, 7 studies presented duplicate or overlapping data, 8 evaluated anti-P antibody testing for other SLE manifestations or other autoimmune diseases, 3 focused on isolated neuropsy-

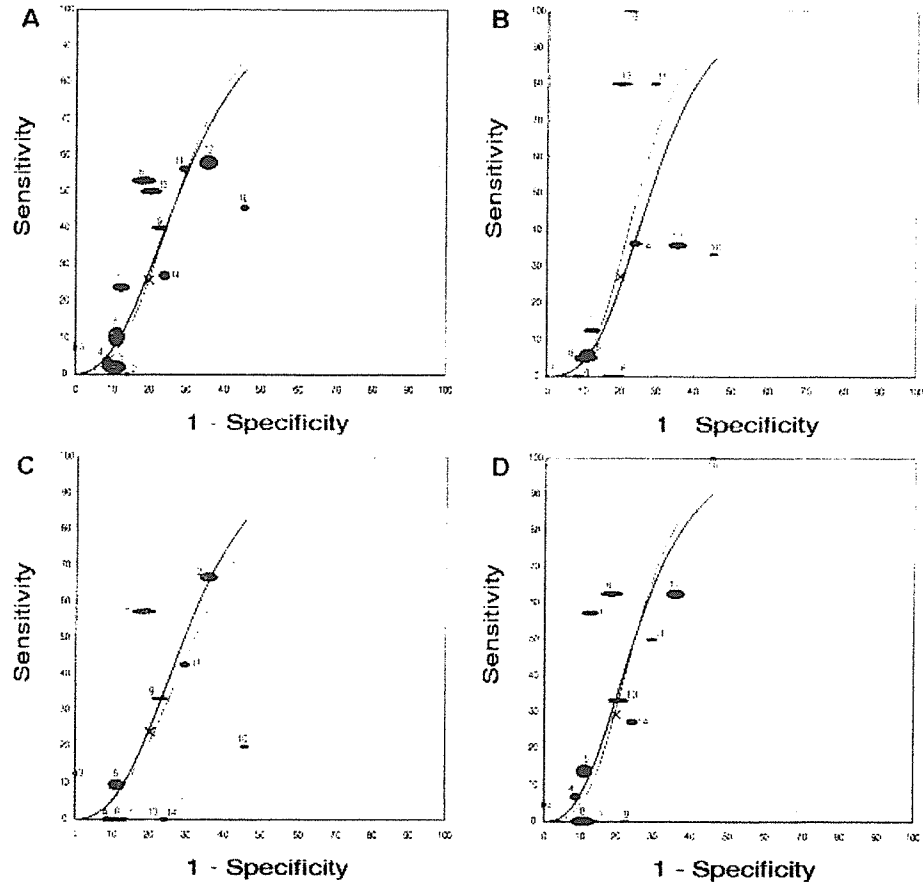

Figure 1. Summary receiver operating characteristic curves for the performance of antibodies to ribosomal P proteins in the diagnosis of various forms of neuropsychiatric systemic lupus erythematosus (NPSLE). Results are from the main analysis. Each ellipse corresponds to a study estimate of sensitivity and specificity; the area of each ellipse is proportional to the study size. Numbers beside the ellipses are study identification numbers and correspond to those shown in Table 1. Thin lines indicate nonweighted analyses; thick lines indicate weighted analyses. Shaded rectangles mark the 95% confidence intervals of the pooled sensitivity and pooled specificity obtained by random-effects calculations. × indicates exact estimates. **A,** NPSLE overall versus non-NPSLE. **B,** Psychosis and/or mood disorder versus non-NPSLE. **C,** Other diffuse neuropsychiatric manifestations versus non-NPSLE. **D,** Focal neurologic events versus non-NPSLE.

chiatric syndromes, and 2 provided insufficient data for calculating the sensitivity and specificity in any comparison considered.

Twenty-four additional publications (6,8–13,15–20,22,23,25–29,31–34) were retrieved from the database search, representing a total of 38 studies involving 3,713 lupus patients. Nevertheless, data for the comparison of NPSLE versus non-NPSLE groups were available in only 18 of the 24 additional studies; data for other comparisons were available in even fewer reports (Table 3). The results were consistent with those derived from the collaborative meta-analysis (Table 3 and Figure 3), but between-study heterogeneity was always considerable (Table 3). The overall weighted sensitivity and specificity estimates for identifying patients with NPSLE were 28% (95% CI 22–35%) and 80% (95% CI 75–85%), respectively. The SROC curve for this comparison was located very close to the diagonal, indicating poor diagnostic performance (Figure 3A). The overall sensitivity for psychosis, mood disorder, or both was slightly

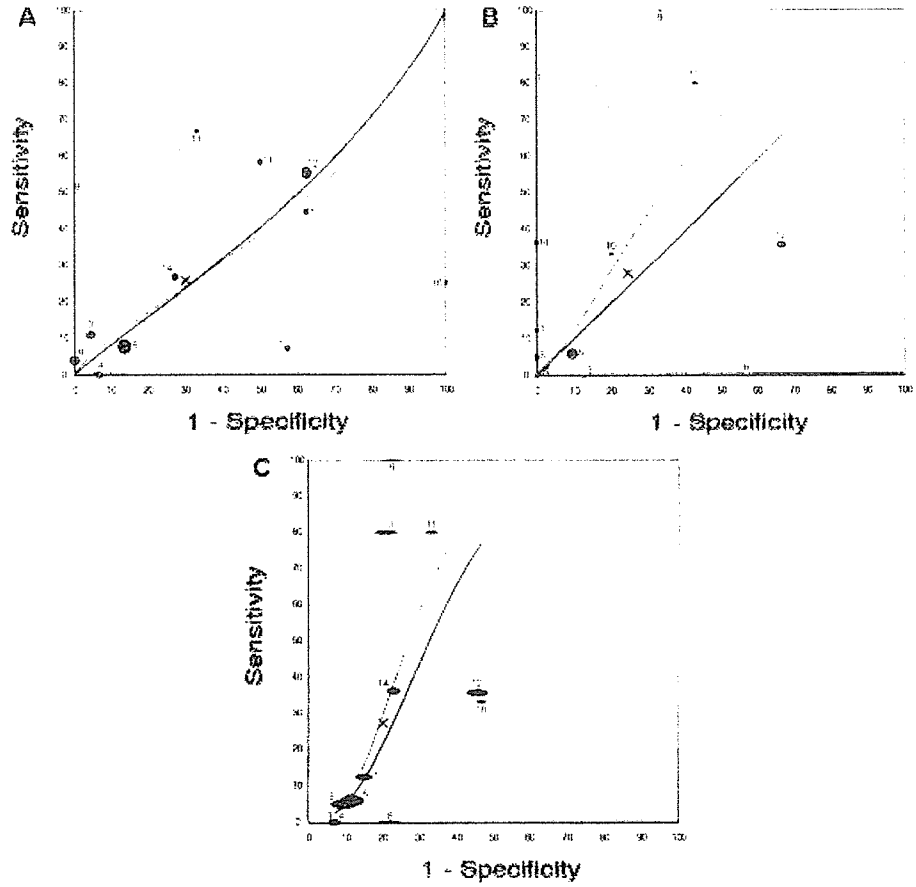

Figure 2. Summary receiver operating characteristic curves for the performance of antibodies to ribosomal P proteins in the diagnosis of various forms of neuropsychiatric systemic lupus erythematosus. Each ellipse corresponds to a study estimate of sensitivity and specificity; the area of each ellipse is proportional to the study size. Numbers beside the ellipses are study identification numbers and correspond to those shown in Table 1. Thin lines indicate nonweighted analyses; thick lines indicate weighted analyses. Shaded rectangles mark the 95% confidence intervals of the pooled sensitivity and pooled specificity obtained by random-effects calculations. × indicates exact estimates. **A,** All diffuse neuropsychiatric manifestations versus focal neurologic events. **B,** Psychosis and/or mood disorder versus other diffuse neuropsychiatric manifestations. **C,** Patients with psychosis and/or mood disorder versus all other lupus patients.

improved, but it was still suboptimal (42%), and the specificity remained essentially the same (81%). There was still significant asymmetry in the SROC curves for the diagnosis of psychiatric disorders (Figures 3B and C). Anti-P antibody testing was not more accurate when used to discriminate active NPSLE from non-NPSLE (Table 3 and Figure 3D). Weighted and nonweighted SROC curves were almost coincident in all these contrasts (Figure 3).

Findings of other sensitivity analyses. Analyses limited to studies that used the ACR criteria for NPSLE yielded similar results. The weighted sensitivity for NPSLE overall was 29% (95% CI 17–45%) and the weighted specificity was 79% (95% CI 73–84%). Analyses excluding studies that did not specify blinding yielded a sensitivity of 25% (95% CI 13–43%) for the diagnosis of NPSLE and a specificity of 79% (95% CI 70–86%). Likewise, the diagnostic performance of anti-

Table 3. Summary results of additional analyses that included published studies from database searches*

Comparison	No. of studies	No. of subjects	Weighted sensitivity (95% CI)	Weighted specificity (95% CI)
NPSLE versus non-NPSLE	32	2,861	0.28 (0.22–0.35)	0.80 (0.75–0.85)
Psychosis and/or mood disorder versus non-NPSLE	25	1,909	0.42 (0.30–0.53)	0.81 (0.76–0.85)
Patients with psychosis and/or mood disorder versus all other lupus patients	31	3,309	0.41 (0.31–0.52)	0.81 (0.77–0.85)
Active NPSLE versus non-NPSLE	10	1,025	0.34 (0.27–0.43)	0.82 (0.74–0.87)

* Data from the studies shown in Table 1 as well as from additional studies retrieved from a search of the Medline, EMBase, and Cochrane databases are included. Weighted sensitivity and specificity were determined according to the random-effects model. Between-study heterogeneity was statistically significant for all comparisons ($P < 0.01$). 95% CI = 95% confidence interval; NPSLE = neuropsychiatric systemic lupus erythematosus.

P antibodies was largely unaffected in all other comparisons (data not shown).

DISCUSSION

This meta-analysis demonstrated with large-scale evidence that the value of anti-P antibody testing for the diagnosis of NPSLE overall or for particular disease phenotypes is negligible. No large differences in diagnostic performance with ELISA measurements or with Western blotting were discerned. Serum anti-P antibodies are detected by ELISA in less than one-third of patients with NPSLE, while 15–25% of lupus patients without neuropsychiatric involvement have this autoantibody specificity. Testing for anti-P antibody is not useful in excluding disease-mediated psychosis or mood disorder with enough certainty, since more than 60% of cases are false negative. Also, a false-positive rate of ~20% militates against the dependence on this laboratory test for diagnosing psychiatric disorders in lupus patients.

Whereas nearly all studies suggested poor diagnostic performance, the exact test performance varied substantially. Variability beyond chance could be attributed to ethnic differences in the study patients, the clinical setting, the type of assay used, differences in test thresholds, and differences in therapy at the time of testing. Anti-P antibodies were more prevalent in Asian patients with lupus than among those of other racial ancestries. This finding is consistent with the observation that their production is influenced by certain class II major histocompatibility complex alleles (8). Despite the use of uniform criteria for defining neuropsychiatric disease, the prevalence of NPSLE differed across centers. This difference probably reflects varying referral patterns at the research sites, as well as varying practice patterns for performing anti-P antibody testing in lupus patients with possible NPSLE syndromes.

The immunoassays used for anti-P antibody determination often differed in terms of the antigenic source, the conditions of protein extraction and denaturation, the nature of the coating antigen, and the carrier proteins and coupling agents used for binding antigen to the plate. The selected cutoff value designating a positive result in enzyme immunoassays could also affect the sensitivity and specificity. Nevertheless, a standardization of anti-P antibody testing is essential to avoiding technical or analytical differences among centers. Treatment with immunosuppressive drugs at the time of testing might influence the antibody response and, therefore, could also account for the discrepancies in test performance. Heterogeneity stemming from all these sources is probably unavoidable, and it reflects actual clinical practice.

Our analysis addressed heterogeneity by using a random-effects model that incorporated the uncertainty arising from between-study differences. SROC curves, which correct for variation due to differences in test thresholds across studies, were also consistent with the independently weighted estimates, and accordingly, the results of the meta-analysis should be generalizable to diverse settings.

Specific design flaws of primary studies of diagnostic tests including lack of blinding, use of different reference tests according to the results of the experimental test, and insufficient description of the population under study can lead to biased, usually optimistic estimates of diagnostic accuracy (48). Our study had the methodologic advantage of using data from adequately described lupus cohorts in which a consistent application of standardized definitions of NPSLE syndromes, and

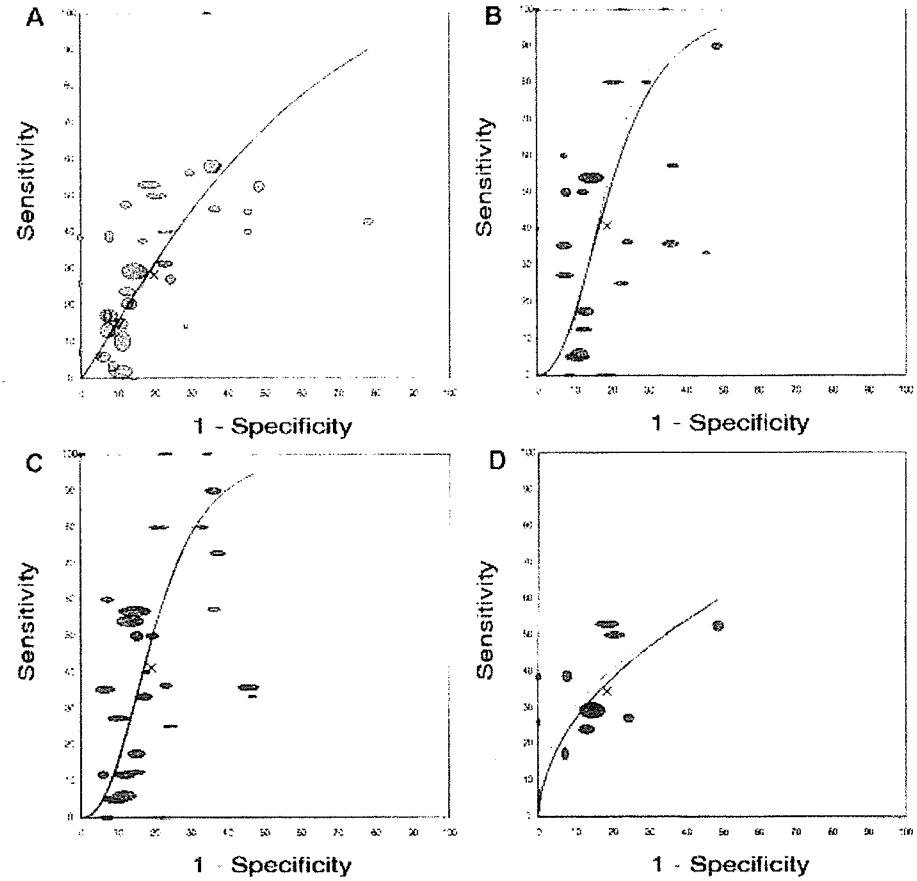

Figure 3. Summary receiver operating characteristic curves for the performance of antibodies to ribosomal P proteins in the diagnosis of various forms of neuropsychiatric systemic lupus erythematosus (NPSLE). Results are from sensitivity analyses that included additional published data. Each ellipse corresponds to a study estimate of sensitivity and specificity; the area of each ellipse is proportional to the study size. Thin lines indicate nonweighted analyses; thick lines indicate weighted analyses. Shaded rectangles mark the 95% confidence intervals of the pooled sensitivity and pooled specificity obtained by random-effects calculations. × indicates exact estimates. **A,** NPSLE overall versus non-NPSLE. **B,** Psychosis and/or mood disorder versus non-NPSLE. **C,** Patients with psychosis and/or mood disorder versus all other lupus patients. **D,** Active NPSLE versus non-NPSLE.

blinded interpretation of both the test results and the reference standard was ensured in most cases. In addition, the overall estimates did not materially change after we excluded the few studies that did not specify blinding or did not use the ACR case definitions for NPSLE.

We should acknowledge that the ACR criteria may not be a perfect reference standard for assessing the presence or absence of NPSLE syndromes in lupus patients. In fact, this classification system has been criticized for some lack of specificity; disorders such as headache, anxiety, mild cognitive dysfunction, mild depression, and polyneuropathy without electrophysiologic confirmation may not truly be NPSLE syndromes (1,49). Nevertheless, until revised criteria (49,50) are accepted and validated, the ACR case definitions constitute the best available tool with which to categorize neuropsychiatric events in SLE (4,51).

Another limitation of the study is that patients having both diffuse and focal NPSLE events were clas-

sified according to the predominant disorder. Such complex presentations might reflect a multifactorial pathogenic etiology with overlapping mechanisms (2,3,6), and therefore, we cannot completely exclude the possibility that some of these patients may have been misclassified. Nevertheless, this limitation is unlikely to have significantly affected the estimated performance, since anti-P antibodies had poor discriminating ability for all disease subtypes. Another possibility is that some patients who tested positive for anti-P antibodies could have been misclassified as non-NPSLE patients, because the disease phenotype may not have had adequate time to express itself. This seems implausible, since nervous system involvement occurs within the first 2 years of disease onset in most patients and rarely presents late (52). The median disease duration in the study population was 7.3 years. A further explanation for anti-P positivity in patients without neuropsychiatric involvement could be the presence of other manifestations that have been linked with these antibodies, such as liver or renal disease, but here, the evidence is far sparser than for NPSLE (53–56). Titers may also fluctuate with the course of the disease (53,55), making the appraisal of a positive or negative result even more difficult. Finally, the diagnostic ability of anti-P antibody in the cerebrospinal fluid needs further study, although it seems to be even more limited than the ability of serum autoantibodies to detect NPSLE (6,16,26,27).

The overall sensitivity of anti-P antibodies for identifying lupus patients with disease-associated psychosis, mood disorder, or both was slightly improved when further published studies were included in the analyses. However, these estimates have widely overlapping confidence intervals with those obtained from the collaborative meta-analysis. Yet, methodologic weaknesses frequently encountered in the relevant reports, such as the use of less strict definitions of psychiatric disorders and the lack of blinding during test or reference standard interpretation, might well have led to inflated sensitivity estimates.

Although the extent of publication bias in diagnostic studies is unknown, we should be aware that studies that failed to show a diagnostic value for anti-P antibodies may have remained unpublished. If this is so, the true diagnostic performance of anti-P antibodies may be even worse than what was demonstrated in this analysis.

There is increasing interest in synthesizing diagnostic information on tests used in autoimmune diseases (57–59). Based on the categorization standards adopted in meta-analyses conducted by the ACR Ad Hoc Committee on Immunologic Testing, the diagnostic performance of anti-P antibodies would be rated as "not useful" for most of the comparisons that we examined, since the observed sensitivity and specificity estimates would correspond to a positive likelihood of ratio <2 and a negative likelihood ratio of >0.5. Previous meta-analyses (57–59) have been based on published data, whereas in our meta-analysis, we made an effort to include the primary investigators and to obtain additional unpublished and prospectively accrued data. It is important to encourage such collaborations in an attempt to obtain large-scale unbiased evidence in the field.

In conclusion, anti-P antibody testing has negligible diagnostic utility for NPSLE overall or for particular neuropsychiatric presentations of SLE. A consortium approach with synthesis of standardized data through a comprehensive meta-analysis may offer a powerful method by which to rigorously evaluate diagnostic tests in SLE. Such an approach could limit health care costs by preventing unnecessary testing.

ACKNOWLEDGMENTS

We acknowledge the contributions of the other investigators of the collaborating study teams involved in this project, as follows: Borut Bozic, PhD, and Blaz Rozman, MD, University Medical Centre, Ljubljana, Slovenia; Nuray Gurel Polat, PhD, and Bahar Artim Esen, MD, Istanbul Medical Faculty, Istanbul University, Turkey; Eric Chan, MD, Queen Mary Hospital, Hong Kong, SAR, China; Takashi Sawada, MD, Teikyo University School of Medicine, Tokyo, Japan; and Veronica Bellomio, MD, Eleonora Lucero, MD, Alberto Berman, MD, and Silvia Presti, MD, School of Medicine, Universidad Nacional de Tucumán, Tucumán, Argentina.

REFERENCES

1. Hanly JG, McCurdy G, Fougere L, Douglas JA, Thompson K. Neuropsychiatric events in systemic lupus erythematosus: attribution and clinical significance. J Rheumatol 2004;31:2156–62.
2. Hermosillo-Romo D, Brey RL. Diagnosis and management of patients with neuropsychiatric systemic lupus erythematosus (NPSLE). Best Pract Res Clin Rheumatol 2002;16:229–44.
3. West SG. Neuropsychiatric lupus. Rheum Dis Clin North Am 1994;20:129–58.
4. Karassa FB, Ioannidis JP, Boki KA, Touloumi G, Argyropoulou MI, Strigaris KA, et al. Predictors of clinical outcome and radiologic progression in patients with neuropsychiatric manifestations of systemic lupus erythematosus. Am J Med 2000;109:628–34.
5. Rood MJ, Breedveld FC, Hulzinga TW. The accuracy of diagnosing neuropsychiatric systemic lupus erythematosus in a series of 49 hospitalized patients. Clin Exp Rheumatol 1999;17:55–61.
6. West SG, Emlen W, Wener MH, Kotzin BL. Neuropsychiatric

lupus erythematosus: a 10-year prospective study on the value of diagnostic tests. Am J Med 1995;99:153–63.
7. ACR Ad Hoc Committee on Neuropsychiatric Lupus Nomenclature. The American College of Rheumatology nomenclature and case definitions for neuropsychiatric lupus syndromes. Arthritis Rheum 1999;42:599–608.
8. Arnett FC, Reveille JD, Moutsopoulos HM, Georgescu L, Elkon KB. Ribosomal P autoantibodies in systemic lupus erythematosus: frequencies in different ethnic groups and clinical and immunogenetic associations. Arthritis Rheum 1996;39:1833–9.
9. Bonfa E, Golombek SJ, Kaufman LD, Skelly S, Weissbach H, Brot N, et al. Association between lupus psychosis and anti-ribosomal P protein antibodies. N Engl J Med 1987;317:265–71.
10. Chan EY, Ko OK, Lawton JW, Lau CS. The use of anti-ribosomal P antibodies in the diagnosis of cerebral lupus: superiority of western blotting over enzyme-linked immunosorbent assay. Hong Kong Med J 1998;4:145–50.
11. Conti F, Alessandri C, Bompane D, Bombardieri M, Spinelli FR, Rusconi AC, et al. Autoantibody profile in systemic lupus erythematosus with psychiatric manifestations: a role for anti-endothelial-cell antibodies. Arthritis Res Ther 2004;6:R366–72.
12. Corres Gonzalez JM, Rodriguez Hernandez C, Zea Mendoza AC, Sequi Navarro J, Sanchidrian Fernandez I. Anti-ribosomal antibodies in systemic lupus erythematosus. Rev Clin Esp 1995;195:16–21.
13. Gerli R, Caponi L, Tincani A, Scorza R, Sabbadini MG, Danieli MG, et al. Clinical and serological associations of ribosomal P autoantibodies in systemic lupus erythematosus: prospective evaluation in a large cohort of Italian patients. Rheumatology (Oxford) 2002;41:1357–66.
14. Hoffman IE, Peene I, Meheus L, Huizinga TW, Cebecauer L, Isenberg D, et al. Specific antinuclear antibodies are associated with clinical features in systemic lupus erythematosus. Ann Rheum Dis 2004;63:1155–8.
15. Isenberg DA, Garton M, Reichlin MW, Reichlin M. Long-term follow-up of autoantibody profiles in black female lupus patients and clinical comparison with Caucasian and Asian patients. Br J Rheumatol 1997;36:229–33.
16. Isshi K, Hirohata S. Association of anti-ribosomal P protein antibodies with neuropsychiatric systemic lupus erythematosus. Arthritis Rheum 1996;39:1483–90.
17. Johanet C, Andre C, Sibilia J, Baquey A, Oksman F, San Marco M, et al, and the Study Group on Autoimmunity (GEAI). Clinical significance of antiribosomal antibodies. Rev Med Interne 2000;21:510–6.
18. Jonsen A, Bengtsson AA, Nived O, Ryberg B, Truedsson L, Ronnblom L, et al. The heterogeneity of neuropsychiatric systemic lupus erythematosus is reflected in lack of association with cerebrospinal fluid cytokine profiles. Lupus 2003;12:846–50.
19. Kao CH, Ho YJ, Lan JL, Changlai SP, Liao KK, Chieng PU. Discrepancy between regional cerebral blood flow and glucose metabolism of the brain in systemic lupus erythematosus patients with normal brain magnetic resonance imaging findings. Arthritis Rheum 1999;42:61–8.
20. Mahler M, Kessenbrock K, Raats J, Williams R, Fritzler MJ, Bluthner M. Characterization of the human autoimmune response to the major C-terminal epitope of the ribosomal P proteins. J Mol Med 2003;81:194–204.
21. Massardo L, Burgos P, Martinez ME, Perez R, Calvo M, Barros J, et al. Antiribosomal P protein antibodies in Chilean SLE patients: no association with renal disease. Lupus 2002;11:379–83.
22. Nojima Y, Minota S, Yamada A, Takaku F, Aotsuka S, Yokohari R. Correlation of antibodies to ribosomal P protein with psychosis in patients with systemic lupus erythematosus. Ann Rheum Dis 1992;51:1053–5.
23. Press J, Palayew K, Laxer RM, Elkon K, Eddy A, Rakoff D, et al. Antiribosomal P antibodies in pediatric patients with systemic lupus erythematosus and psychosis. Arthritis Rheum 1996;39:671–6.
24. Sanna G, Piga M, Terryberry JW, Peltz MT, Giagheddu S, Satta L, et al. Central nervous system involvement in systemic lupus erythematosus: cerebral imaging and serological profile in patients with and without overt neuropsychiatric manifestations. Lupus 2000;9:573–83.
25. Sato T, Uchiumi T, Ozawa T, Kikuchi M, Nakano M, Kominami R, et al. Autoantibodies against ribosomal proteins found with high frequency in patients with systemic lupus erythematosus with active disease. J Rheumatol 1991;18:1681–4.
26. Schneebaum AB, Singleton JD, West SG, Blodgett JK, Allen LG, Cheronis JC, et al. Association of psychiatric manifestations with antibodies to ribosomal P proteins in systemic lupus erythematosus. Am J Med 1991;90:54–62.
27. Teh LS, Bedwell AE, Isenberg DA, Gordon C, Emery P, Charl[illegible] PJ, et al. Antibodies to protein P in systemic lupus erythemato[illegible] Ann Rheum Dis 1992;51:489–94.
28. Teh LS, Hay EM, Amos N, Black D, Huddy A, Creed F, e[illegible] Anti-P antibodies are associated with psychiatric and focal ce[illegible] bral disorders in patients with systemic lupus erythematosus. Br [illegible] Rheumatol 1993;32:287–90.
29. Teh LS, Lee MK, Wang F, Manivasagar M, Charles PJ, Nicholson GD, et al. Antiribosomal P protein antibodies in different populations of patients with systemic lupus erythematosus. Br J Rheumatol 1993;32:663–5.
30. Tzioufas AG, Tzortzakis NG, Panou-Pomonis E, Boki KA, Sakarellos-Daitsiotis M, Sakarellos C, et al. The clinical relevance of antibodies to ribosomal-P common epitope in two targeted systemic lupus erythematosus populations: a large cohort of consecutive patients and patients with active central nervous system disease. Ann Rheum Dis 2000;59:99–104.
31. Van Dam A, Nossent H, de Jong J, Meilof J, ter Borg EJ, Swaak T, et al. Diagnostic value of antibodies against ribosomal phosphoproteins: a cross sectional and longitudinal study. J Rheumatol 1991;18:1026–34.
32. Weiner SM, Otte A, Schumacher M, Klein R, Gutfleisch J, Brink I, et al. Diagnosis and monitoring of central nervous system involvement in systemic lupus erythematosus: value of F-18 fluorodeoxyglucose PET. Ann Rheum Dis 2000;59:377–85.
33. Williams RC Jr, Sugiura K, Tan EM. Antibodies to microtubule-associated protein 2 in patients with neuropsychiatric systemic lupus erythematosus. Arthritis Rheum 2004;50:1239–47.
34. Yalaoui S, Gorgi Y, Hajri R, Goucha R, Chaabouni L, Kooli C, et al. Autoantibodies to ribosomal P proteins in systemic lupus erythematosus. Joint Bone Spine 2002;69:173–6.
35. Yoshio T, Masuyama J, Ikeda M, Tamai K, Hachiya T, Emori T, et al. Quantification of antiribosomal P0 protein antibodies by ELISA with recombinant P0 fusion protein and their association with central nervous system disease in systemic lupus erythematosus. J Rheumatol 1995;22:1681–7.
36. Elkon K, Skelly S, Parnassa A, Moller W, Danho W, Weissbach H, et al. Identification and chemical synthesis of a ribosomal protein antigenic determinant in systemic lupus erythematosus. Proc Natl Acad Sci U S A 1986;83:7419–23.
37. Ghirardello A, Caponi L, Franceschini F, Zampieri S, Quinzanini M, Bendo R, et al. Diagnostic tests for antiribosomal P protein antibodies: a comparative evaluation of immunoblotting and ELISA assays. J Autoimmun 2002;19:71–7.
38. Mahler M, Kessenbrock K, Raats J, Fritzler MJ. Technical and clinical evaluation of anti-ribosomal P protein immunoassays. J Clin Lab Anal 2004;18:215–23.
39. Rayno K, Reichlin M. Evaluation of assays for the detection of autoantibodies to the ribosomal P proteins. Clin Immunol 2000;95:99–103.

40. Tan EM, Cohen AS, Fries JF, Masi AT, McShane DJ, Rothfield NF, et al. The 1982 revised criteria for the classification of systemic lupus erythematosus. Arthritis Rheum 1982;25:1271–7.
41. Owens DK, Holodniy M, Garber AM, Scott J, Sonnad S, Moses L, et al. Polymerase chain reaction for the diagnosis of HIV infection in adults: a meta-analysis with recommendations for clinical practice and study design. Ann Intern Med 1996;124:803–15.
42. Ioannidis JP. The value of meta-analysis in rheumatology research. Autoimmun Rev 2004;3 Suppl 1:S57–9.
43. Fleiss JL. The statistical basis of meta-analysis. Stat Methods Med Res 1993;2:121–45.
44. Mantel N, Haenszel W. Statistical aspects of the analysis of data from retrospective studies of disease. J Natl Cancer Inst 1959;22: 719–48.
45. Littenberg B, Moses LE. Estimating diagnostic accuracy from multiple conflicting reports: a new meta-analytic method. Med Decis Making 1993;13:313–21.
46. Moses LE, Shapiro D, Littenberg B. Combining independent studies of a diagnostic test into a summary ROC curve: data-analytic approaches and some additional considerations. Stat Med 1993;12:1293–316.
47. Irwig L, Macaskill P, Glasziou P, Fahey M. Meta-analytic methods for diagnostic test accuracy. J Clin Epidemiol 1995;48:119–30.
48. Lijmer JG, Mol BW, Heisterkamp S, Bonsel GJ, Prins MH, van der Meulen JH, et al. Empirical evidence of design-related bias in studies of diagnostic tests. JAMA 1999;282:1061–6.
49. Ainiala H, Hietaharju A, Loukkola J, Peltola J, Korpela M, Metsanoja R, et al. Validity of the new American College of Rheumatology criteria for neuropsychiatric lupus syndromes: a population-based evaluation. Arthritis Rheum 2001;45:419–23.
50. Hanly JG. ACR classification criteria for systemic lupus erythematosus: limitations and revisions to neuropsychiatric variables. Lupus 2004;13:861–4.
51. Afeltra A, Garzia P, Mitterhofer AP, Vadacca M, Galluzzo S, del Porto F, et al. Neuropsychiatric lupus syndromes: relationship with antiphospholipid antibodies. Neurology 2003;61:108–10.
52. Kovacs JA, Urowitz MB, Gladman DD. Dilemmas in neuropsychiatric lupus. Rheum Dis Clin North Am 1993;19:795–814.
53. Chindalore V, Neas B, Reichlin M. The association between anti-ribosomal P antibodies and active nephritis in systemic lupus erythematosus. Clin Immunol Immunopathol 1998;87:292–6.
54. Hulsey M, Goldstein R, Scully L, Surbeck W, Reichlin M. Anti-ribosomal P antibodies in systemic lupus erythematosus: a case-control study correlating hepatic and renal disease. Clin Immunol Immunopathol 1995;74:252–6.
55. Reichlin M, Broyles TF, Hubscher O, James J, Lehman TA, Palermo R, et al. Prevalence of autoantibodies to ribosomal P proteins in juvenile-onset systemic lupus erythematosus compared with the adult disease. Arthritis Rheum 1999;42:69–75.
56. Arnett FC, Reichlin M. Lupus hepatitis: an under-recognized disease feature associated with autoantibodies to ribosomal P. Am J Med 1995;99:465–72.
57. Kavanaugh AF, Solomon DH, and the American College of Rheumatology Ad Hoc Committee on Immunologic Testing Guidelines. Guidelines for immunologic laboratory testing in the rheumatic diseases: anti-DNA antibody tests. Arthritis Rheum 2002;47:546–55.
58. Solomon DH, Kavanaugh AJ, Schur PH, and the American College of Rheumatology Ad Hoc Committee on Immunologic Testing Guidelines. Evidence-based guidelines for the use of immunologic tests: antinuclear antibody testing. Arthritis Rheum 2002;47:434–44.
59. Benito-Garcia E, Schur PH, Lahita R, and the American College of Rheumatology Ad Hoc Committee on Immunologic Testing Guidelines. Guidelines for immunologic laboratory testing in the rheumatic diseases: anti-Sm and anti-RNP antibody tests. Arthritis Rheum 2004;51:1030–44.