

## Meta-analysis of anti-ribosomal P antibodies in lupus psychosis

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### Abstract

**AIM:** To perform a meta-analysis of the prevalence of anti-ribosomal P (aRP) antibodies in lupus psychosis, and the odds of psychosis in aRP-positive subjects.

**METHODS:** We identified articles by searching PubMed, PsychInfo, and ISI, and the reference lists of identified studies.

**RESULTS:** Twenty-four studies met the inclusion criteria. Positive aRP antibodies were found in 51% (91 of 179 total cases) of cases of lupus psychosis. There was an almost 3.5-fold increased odds of psychosis in aRP-positive patients (OR = 3.46, 95%CI: 1.97-6.09,  $P < 0.001$ ). The population attributable risk percentage was 36% for aRP antibodies.

**CONCLUSION:** aRP antibodies are common in lupus psychosis, although the potential mechanism(s) underlying this association remain unclear. Given the overlap

between the clinical presentation and risk factors for lupus psychosis and schizophrenia, further investigation of aRP antibodies in schizophrenia is warranted.

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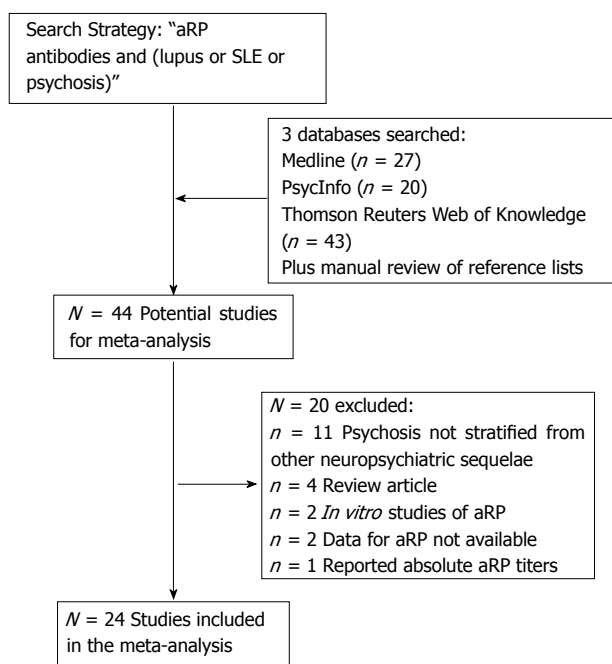
**Key words:** Systemic lupus erythematosus; Psychosis; Autoantibodies; Anti-ribosomal P antibodies; Meta-analysis

**Core tip:** In a meta-analysis of twenty-four studies, positive anti-ribosomal P (aRP) antibodies were found in 51% (91 of 179 total cases) of cases of lupus psychosis. There was an almost 3.5-fold increased odds of psychosis in aRP-positive patients (OR = 3.46, 95%CI: 1.97-6.09,  $P < 0.001$ ). The population attributable risk percentage was 36% for aRP antibodies. aRP antibodies are common in lupus psychosis, although the potential mechanism(s) underlying this association remain unclear. Given the overlap between the clinical presentation and risk factors for lupus psychosis and schizophrenia, further investigation of aRP antibodies in schizophrenia is warranted.

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### INTRODUCTION

Neuropsychiatric manifestations occur in about half of patients with systemic lupus erythematosus (SLE)<sup>[1]</sup>. Psychosis is a rare, but well-documented neuropsychiatric sequelae of SLE. A systematic review of 9 studies, comprised of 1422 subjects with SLE, found a 5% point prevalence of lupus psychosis<sup>[2]</sup>. Lupus psychosis is de-



**Figure 1** Flowchart of the study selection process. aRP: Anti-ribosomal P.

defined as a severe disturbance in the perception of reality characterized by delusions and/or hallucinations<sup>[3]</sup>. The diagnostic criteria require that the disturbance (1) includes either delusions or hallucinations without insight; (2) causes clinical distress or impairment in social, occupational, or other relevant areas of functioning; (3) does not occur exclusively during the course of a delirium; and (4) is not better accounted for by another mental disorder. A primary psychotic disorder unrelated to SLE (*e.g.*, schizophrenia), substance- or drug-induced psychosis, and a psychologically medicated reaction to SLE (*e.g.*, brief reactive psychosis with a major stressor) are exclusionary to the diagnosis of lupus psychosis.

The clinical presentation of lupus psychosis may mimic that of schizophrenia. Schizophrenia is a heterogeneous psychotic disorder that requires the presence of two or more characteristic symptoms—delusions, hallucinations, disorganized speech, grossly abnormal psychomotor behavior (such as catatonia), or negative symptoms (*i.e.* restricted affect or avolition/asociality<sup>[4]</sup>). At least one of these two characteristic symptoms should include delusions, hallucinations, or disorganized speech. There is significant impairment in one or more major areas of functioning, including work, interpersonal relations, and self-care. It must also be established that the disturbance is not better accounted for by a primary mood disorder, schizoaffective disorder, substance intoxication or withdrawal, or another general medical condition.

A recent study found that 2 of 85 subjects hospitalized for a first-episode of schizophrenia had positive anti-nuclear (ANA) antibody titers and subsequently were found to have neuropsychiatric SLE<sup>[5]</sup>. Importantly, neither subject had signs or symptoms suggestive of rheumatologic disease, and presented only with psychiatric complaints.

A number of previous studies have found an asso-

ciation between anti-ribosomal P (aRP) antibodies and lupus psychosis<sup>[6-11]</sup>. aRP antibodies target P0, P1 and P2 proteins on the ribosomal sub-unit, and are capable of penetrating cells and inducing apoptotic changes. A previous meta-analysis investigated the accuracy of aRP antibody testing for the diagnosis of neuropsychiatric SLE<sup>[1]</sup>; however, this study did not consider psychosis separately from other neuropsychiatric manifestations of SLE, such as mood disorders and seizures. The purpose of the present study was to perform a meta-analysis of the prevalence of aRP antibodies in lupus psychosis, and the odds of psychosis in aRP-positive subjects.

## MATERIALS AND METHODS

### Study design

Studies of aRP antibodies in lupus psychosis were systematically searched using Medline (PubMed, National Center for Biotechnology Information, United States National Library of Medicine, Bethesda, Maryland), PsycInfo (*via* Ovid, United States Psychological Association, Washington, DC), and Thomson Reuters (formerly ISI) Web of Knowledge (Science Citation Index and Social Sciences Citation Index, Thomson Reuters, Charlottesville, Virginia) in October 2011 and again in March 2013. The primary search strategy was “anti-ribosomal P antibodies and (lupus or SLE or psychosis).” Limiting results to studies in English, this search resulted in 27 citations from Medline, 20 from PsycInfo, and 43 from ISI. From these citations, as well as a manual review of their reference lists, we identified 44 potential studies, which are described in Table 1<sup>[1,6-48]</sup>.

The inclusion criteria were (1) cross-sectional studies of the proportion of subjects with SLE positive for aRP antibodies, stratified by the presence or absence of psychosis; (2) cross-sectional studies of the proportion of subjects with lupus psychosis and positive aRP antibodies; or (3) longitudinal studies of aRP antibodies at multiple time points in subjects with lupus psychosis. The exclusion criteria were: (1) studies in which there were no cases of lupus psychosis; (2) studies which did not stratify psychosis from other neuropsychiatric sequelae of SLE, such as seizures and mood disorders; and (3) *in vitro* studies of aRP antibodies.

After independent searches, review of the study methods by two authors (BJM and KL) 24 studies met the inclusion criteria. There was universal agreement on the independent studies. 20 studies were excluded due: psychosis not stratified from other neuropsychiatric sequelae ( $n = 11$ ), review articles ( $n = 4$ ), *in vitro* studies of aRP ( $n = 2$ ), data for aRP not available ( $n = 2$ ), and reported absolute aRP titers ( $n = 1$ ). A flow chart summarizing the study selection process is presented in Figure 1. For each of the 16 case-control studies identified, we also extracted descriptive data on subject age, gender, and illness duration.

### Statistical analysis (prevalence of anti-ribosomal P antibodies)

For all 24 studies, we calculated the prevalence of positive

**Table 1** Studies of anti-ribosomal P antibodies in systemic lupus erythematosus

Study	Assay method	Location	Included	Comment
Abdel-Nesser 2008	ELISA	Egypt	Yes	Case-control study
Almeida 2002	ELISA	Spain	Yes	
Arnett 1996	ELISA	United States	Yes	Case-control study
Bonfa 1987	Immunoblotting, RIA	United States	Yes	
Briani 2009	Immunoblotting	Italy	Yes	Case-control study
Caponi 2002	ELISA	Italy	Yes	Case-control study
Chan 1998	ELISA, Western blot	China	No	Psychosis not stratified from other neuropsychiatric sequelae
Conti 2004	ELISA	Italy	No	Psychosis not stratified from other neuropsychiatric sequelae
Derksen 1990	ELISA	Netherlands	Yes	
Ebert 2005	N/A		No	Review article
Ghirardello 2001	N/A		No	Review article
Haddouk 2009	Immunodot assay	Tunisia	Yes	Case-control study
Hanly 2008	ELISA	Canada	Yes	Case-control study
Hanly 2011	ELISA, Lupus anticoagulant	Canada	Yes	Case-control study
Hoffman 2004	N/A	Europe	No	Data for aRP not available
Isshi 1996	ELISA	Japan	Yes	Case-control study
Isshi 1998	ELISA	Japan	No	Reported absolute titers
Jonsen 2003	Immunoassays	Sweden	Yes	
Kao 1999	N/A	China	Yes	
Karassa 2005	N/A	Multicenter	No	Psychosis not stratified from other neuropsychiatric sequelae
Magalhaes 2007	ELISA	Brazil	No	Psychosis not stratified from other neuropsychiatric sequelae
Mahler 2003	Indirect immunofluorescence		No	Review article
Massardo 2002	Double immune diffusion, or Western blot and ELISA	Chile	Yes	Case-control study
Munoz 1999	N/A	Spain	Yes	
Nagai 2005	Flow cytometry	Japan	No	In vitro study
Nagai 2011	ELISA	Japan	No	In vitro study
Nojima 1992	western blot	Japan	Yes	Case-control study
Press 1996	ELISA	Canada	Yes	Case-control study
Sanna 2000	N/A	Italy	No	Data for aRP not available
Sato 1991	FIEA	Japan	No	Psychosis not stratified from other neuropsychiatric sequelae
Schneebaum 1991	ELISA	United States	Yes	Case-control study
Showman 2006	ELISA	Israel	Yes	Case-control study
Teh 1992	ELISA	United Kingdom	Yes	Case-control study
Teh 1993	ELISA	United Kingdom	No	Psychosis not stratified from other neuropsychiatric sequelae
Teh 1993b	ELISA	United Kingdom	No	Psychosis not stratified from other neuropsychiatric sequelae
Toubi 2007	N/A		No	Review article
Tzioufas 2000	Western blot	Israel	No	Psychosis not stratified from other neuropsychiatric sequelae
Van Dam 1991	ELISA, Immunoblotting	Netherlands	Yes	Case-control study
Watanabe 1996	ELISA	Japan	No	Psychosis not stratified from other neuropsychiatric sequelae
Weiner 2000	Not specified	Germany	No	Psychosis not stratified from other neuropsychiatric sequelae
West 1995	ELISA	United States	Yes	
Williams 2004	Western blot	United States	Yes	
Yalaoui 2002	N/A	Tunisia	No	Psychosis not stratified from other neuropsychiatric sequelae
Yoshio 1995	ELISA	Japan	Yes	Case-control study

aRP: Anti-ribosomal P; FIEA: Fluoro-immuno-enzymatic assay; RIA: Radioimmunoassay.

aRP antibodies in lupus psychosis by dividing the number of subjects with psychosis and positive aRP antibodies by the total number of subjects with psychosis.

### Meta-analysis

For each of the 16 case-control studies, we calculated odds ratios (OR) and 95% confidence intervals (95%CI) for psychosis in aRP-positive patients, with odds set equal to 1.00 for psychosis in aRP-negative patients. We then performed a meta-analysis to estimate pooled OR (and 95%CI) for psychosis in aRP-positive patients, again with risk = 1.00 for psychosis in aRP-negative patients. Random effects pooled estimates and 95%CI were calculated using the method of DerSimonian and Laird. Random ef-

fects models yield their actual first error rate while fixed effect models tend to inflate their first error rate. CIs obtained by fixed effect models are also biased and their actual coverage rate is smaller than their nominal coverage rate<sup>[49]</sup>. *P*-values were considered statistically significant at the  $\chi^2 = 0.05$  level. A funnel plot and Egger's test were generated to assess for publication bias. In case of significant heterogeneity in the overall result, we performed subgroup analysis and meta-regression, to explore possible reasons for the heterogeneity. The subgroup analysis included assay methodology (ELISA *vs* other). We conducted meta-regression analyses of four variables, year of publication, age, the proportion of female subjects, and illness duration. The statistical analyses were performed

**Table 2** Effect of anti-ribosomal P antibody status on psychosis risk

Study	Total (N)	Mean age (yr)	Female (%)	Mean illness duration (yr)	aRP(+) (n)	aRP(-) (n)	Psychosis (n)	Psychosis and aRP(+) (n)	No psychosis and aRP(+) (n)	Psychosis and aRP(-) (n)	No psychosis and aRP(-) (n)	OR	95%CI
Abdel-Nesser 2008	32	25.0	87.5	3.9	7	25	1	1	6	0	25	8.33	0.25-278.68
Arnett 1996	364				63	301	17	8	55	9	292	4.72	1.74-12.76
Briani 2009	219	28.0	84.5		45	174	1	1	44	0	174	7.91	0.26-239.58
Caponi 2002	149	37.1	93.3	9.3	18	131	1	0	18	1	130	0.07	0-2.6 × 10 <sup>7</sup>
Haddouk 2009	200	30.5	86.5		47	153	3	1	46	2	151	1.64	0.15-18.51
Hanly 2008	214	34.9	87.4	0.4	17	197	7	3	14	4	193	10.34	2.10-50.82
Hanly 2011	991	35.2	89.1	0.5	91	900	14	4	87	10	890	4.09	1.26-13.32
Isshi 1996	75				21	54	19	10	11	9	45	4.55	1.49-13.88
Massardo 2002	141	33.0	90.1	5.0	21	120	2	2	19	0	120	25.26	1.10-581.69
Nojima 1992	91		80.0		38	53	10	9	29	1	53	16.45	1.98-136.36
Press 1996	79				16	63	13	5	11	8	55	3.13	0.86-11.37
Schneebaum 1991	269				51	218	29	13	38	16	202	4.32	1.92-9.71
Shovman 2006	44				6	38	1	1	5	0	38	15.2	0.45-513.80
The 1992	116				18	98	13	3	15	10	88	1.76	0.43-7.15
Van Dam 1991	38				12	26	1	1	11	0	26	4.73	0.15-151.50
Yoshio 1995	70	31.9	94.3		41	29	10	3	38	7	22	0.25	0.06-1.06
Total	3093				512	2581	142	65	447	77	2504		

aRP: Anti-ribosomal P; OR: Odds ratios; CI: Confidence interval.

using Stata 10.0 (StataCorp LP, College Station, TX). The meta-analysis procedure also calculates a  $\chi^2$  value for the heterogeneity in effect size (ES) estimates, which is based on Cochran's Q-statistic<sup>[50]</sup>. Between-study heterogeneity  $\chi^2$  was considered significant for  $P < 0.10$ <sup>[51]</sup>.

## RESULTS

### Prevalence of anti-ribosomal P antibodies

Positive aRP antibodies were found in 51% (91 of 179 total cases) of cases of lupus psychosis.

### Meta-analysis

As described in Table 2, the case-control studies included a total of 3093 subjects. Table 2 and Figure 2 present the estimates of OR with 95% CIs from the meta-analysis. There was an almost 3.5-fold increased odds of psychosis in aRP-positive patients (OR = 3.46, 95%CI: 1.97-6.09,  $P < 0.001$ ). There was significant heterogeneity in this effect size estimate,  $\chi^2 = 26.43$ ,  $P = 0.03$ . In a post-hoc sensitivity analysis, the heterogeneity was no longer significant ( $\chi^2 = 12.63$ ,  $P = 0.55$ ) and the association was stronger (OR = 4.29, 95%CI: 2.90-6.36,  $P < 0.001$ ) after excluding one study (Yoshio). A funnel plot showed no evidence of publication bias (Figure 3; Eggers test,  $P = 0.99$ ).

In the subgroup analysis, there was no change in the association when studies using ELISA to measure aRP antibodies were considered separately (OR = 3.00, 95%CI: 1.60-5.59,  $P < 0.001$ ). In meta-regression analyses, year of publication ( $P = 0.55$ ), age (0.55), and illness duration ( $P = 0.27$ ) were unrelated to the association between aRP antibodies and lupus psychosis. However, there was a significant association with gender (slope = -0.31, 95%CI: -0.55 to -0.08,  $P = 0.02$ ), with a stronger association in studies with a higher proportion of males

(Figure 4).

We also estimated the population attributable risk percentage (PAR%) for aRP-positivity. The PAR% is the prevalence of the outcome (psychosis) in all subjects, minus the prevalence of the outcome among the unexposed (defined here as aRP negative patients), divided by the prevalence of outcome in the total population, and multiplied by 100%. The population PAR% was 36% for aRP antibodies.

## DISCUSSION

Although psychosis is a rare neuropsychiatric manifestation of SLE, we found that more than half of subjects with lupus psychosis had positive aRP antibodies. Furthermore, there was an almost 3.5-fold increased odds of psychosis in aRP-positive patients. The association was not moderated by year of publication, age, or illness duration, but there was a significant association with gender. The PAR% was 36% for anti-ribosomal P antibodies.

An important strength of our study is that we included data from all case-control studies of this association. A previous meta-analysis aRP antibodies in SLE did not consider psychosis separately from other neuropsychiatric manifestations of SLE<sup>[1]</sup>. Our analysis differed from this study in several ways. First, we focused on psychosis as the outcome, rather than the broader category of neuropsychiatric SLE. Second, we were able to calculate the odds of psychosis in aRP-positive subjects, as well as the PAR% for aRP-positivity. Although we were able to perform subgroup and meta-regression analyses, an important limitation of the present study was that data on a number of potential confounding factors, including age, sex, and illness duration, were available for only a portion of studies. We were not able to control for other potential confounding factors including smoking status,

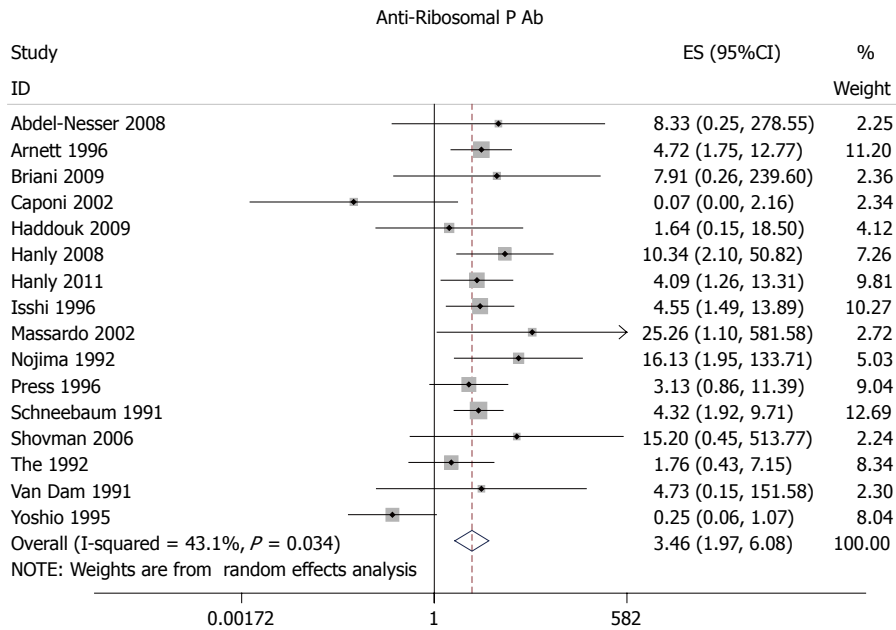


Figure 2 Forest plot of risk of psychosis in anti-ribosomal P antibody-positive subjects.

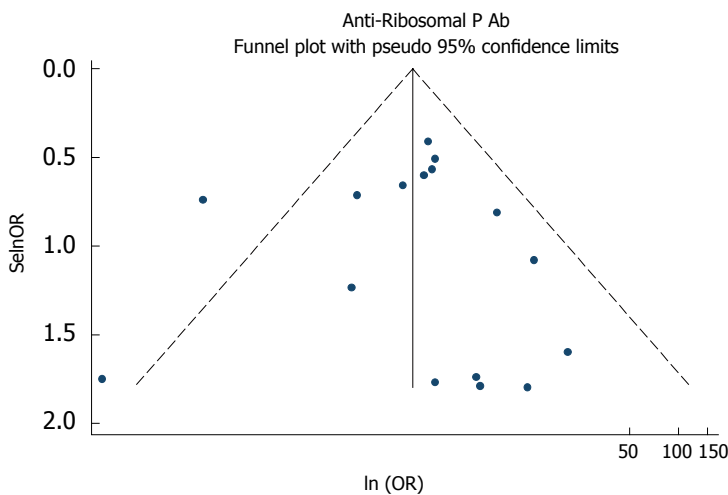


Figure 3 Funnel plot of studies of anti-ribosomal P antibodies in lupus psychosis.

rheumatologic symptoms, stage of illness (*e.g.*, active *vs* inactive SLE), and medications.

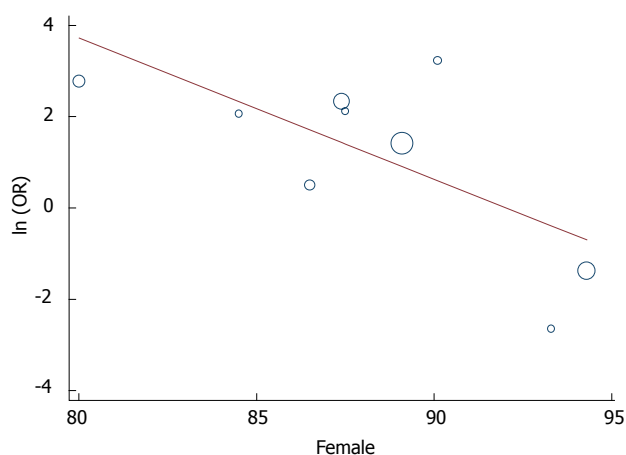
We found a population attributable risk percentage (PAR%) of 36% for aRP-positivity. As the PAR% varies with both the risk (*i.e.* OR) associated with an exposure (*i.e.* aRP-positivity) and its prevalence, caution must be exercised in the interpretation of this result. The PAR% refers to a family of concepts. Greenland and Robins<sup>[52]</sup> distinguished between the etiologic and excess fraction. The etiologic fraction is the proportion of cases that the exposure had played a causal role in its development. The excess fraction is the proportion of cases among the exposed population that is in excess in comparison with the unexposed. Our results describe the excess fraction for aRP-positivity, as it is not possible to establish the causality of this association.

One longitudinal study found that IgA and IgM classes of aRP antibodies were elevated at the onset of psychosis, and titers decreased following a remission of

psychosis<sup>[43]</sup>. Another longitudinal study of aRP activity in two patients with psychosis revealed that aRP levels increased before and during the active phases of psychosis<sup>[15]</sup>. This could possibly help predict efficacy of treatment and warrants further investigation into the possibility of monitoring disease activity by aRP titers.

The mechanism(s) underlying this association remain unclear and warrant further investigation. One possibility is that aRP antibodies may directly cross-react with central nervous system antigens, resulting in acute psychosis. Autoantibodies are also associated with increases in pro-inflammatory cytokines, such as interleukin-6 (IL-6) which can directly modulate dopaminergic neurotransmission<sup>[53]</sup>, or indirectly modulate glutamatergic neurotransmission through tryptophan catabolism<sup>[54]</sup>, which can also result in acute psychosis. Consistent with the latter, increased cerebrospinal fluid IL-6 is also associated with lupus psychosis, although the relationship with aRP antibodies is unknown<sup>[55]</sup>.





**Figure 4** Meta-regression analysis of the effect of the proportion of female subjects on the association between anti-ribosomal P antibodies and psychosis.

A previous study found 2 of 85 subjects presenting with first-episode schizophrenia were subsequently diagnosed with neuropsychiatric SLE, and neither subject had other signs or symptoms of rheumatologic disease<sup>[5]</sup>. A systematic quantitative review also found an increased prevalence of autoantibodies associated with limbic encephalitis (NMDA receptor antibodies) in subjects with first-episode schizophrenia, in the absence of other neurologic signs or symptoms<sup>[56]</sup>. To our knowledge, only one previous study has measured aRP antibodies in subjects with schizophrenia<sup>[57]</sup>. Among 59 patients in this study, aRP antibody titers were below cutoff levels in 58 patients and borderline in 1 patient. One possibility for the negative finding is that the prevalence of potentially pathogenic central nervous system autoantibodies in schizophrenia is low, and this study was underpowered to detect an association. Another possibility is that serum autoantibodies are only present earlier in the course of the disorder.

In addition to overlapping clinical presentations, there are also shared risk factors for lupus psychosis and schizophrenia. There is bidirectional evidence for an association between schizophrenia and autoimmune disorders<sup>[58-60]</sup>. Single nucleotide polymorphisms in genes in the major histocompatibility complex on chromosome 6q, which are critical to immune system function and associated with autoimmune disorders, are also risk factors for schizophrenia<sup>[61-63]</sup>. Patients with schizophrenia may also have abnormal absolute levels of antibody-producing B-lymphocytes<sup>[64-66]</sup>. Thus, as identification of patients with autoantibody-mediated psychosis (*vs* schizophrenia) has important treatment-related implications, these findings suggest that future studies of aRP antibodies in patients with schizophrenia are warranted.

In conclusion, aRP antibodies are highly prevalent and significant predictors of lupus psychosis. Future studies of these antibodies will be important to an improved understanding of the pathophysiology of psychosis. Further investigation of these autoantibodies in patients with

schizophrenia, which has largely been unexplored, are warranted.

## ACKNOWLEDGEMENTS

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## COMMENTS

### Background

Neuropsychiatric manifestations occur in about half of patients with systemic lupus erythematosus (SLE). Psychosis is a rare, but well-documented neuropsychiatric sequelae of SLE. A number of previous studies have reported an association between anti-ribosomal P (aRP) antibodies and lupus psychosis.

### Research frontiers

The purpose of the present study was to perform a meta-analysis of the prevalence of aRP antibodies in lupus psychosis, and the odds of psychosis in aRP-positive subjects.

### Innovations and breakthroughs

A previous meta-analysis investigated the accuracy of aRP antibody testing for the diagnosis of neuropsychiatric SLE; however, this study did not consider psychosis separately from other neuropsychiatric manifestations of SLE, such as mood disorders and seizures. In a meta-analysis of 24 studies, we report that positive aRP antibodies were found in 51% (91 of 179 total cases) of cases of lupus psychosis. There was an almost 4-fold increased odds of psychosis in aRP-positive patients (OR = 3.75, 95%CI: 2.23-6.30,  $P < 0.001$ ). The population attributable risk percentage was 36% for aRP antibodies.

### Applications

aRP antibodies are common in lupus psychosis. Schizophrenia is associated with increased prevalence of autoantibodies and autoimmune disease. Given these associations, aRP warrants further investigation in schizophrenia.

### Terminology

**aRP antibodies:** Autoantibodies are immune molecules (proteins) that are directed against the body's own tissues. aRP antibodies target proteins on the ribosome, and are capable of penetrating cells and inducing apoptosis, or programmed cell death.

**Psychosis:** Psychosis is a potential neuropsychiatric complication that occurs in some patients with systemic lupus erythematosus. Psychosis is a neuropsychiatric disorder that includes abnormalities in thinking, behavior, mood, and cognition. Common symptoms of psychosis included hallucinations, delusions, disorganized speech and behavior, and negative symptoms.

### Peer review

This is a very good study that supports a potential role for anti-ribosomal P antibodies in lupus psychosis. Findings strengthened previous reports in the literature about this association. The topic is up-to-date and the results are of high interest for other researchers.

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