Influence of methodological and patient factors on serum NMDAR IgG antibody detection in psychotic disorders: a meta-analysis of cross-sectional and case-control studies

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**Research in context**

**Evidence before this study**

Over the past decade, there has been a surge of interest in the role that *N*-methyl-D-aspartate receptor (NMDAR) antibodies may play in the onset of psychotic disorders. This interest followed the discovery that these neuronal surface antibodies can trigger an autoimmune encephalitis syndrome characterised by prominent psychotic symptoms, that is treatable with immunotherapy. An early meta-analysis reported that 1·5% of psychosis patients are seropositive for NMDAR antibodies of the IgG subclass, and that these antibodies are more common in psychosis populations than healthy individuals. However, subsequent studies have yielded conflicting findings, possibly due to differences in methodological approaches and patient characteristics. These inconsistencies have led clinicians to ask whom, if anyone, might benefit from serum testing and which methods should be used for detection. We thus sought to investigate the effect of study factors on heterogeneity. Web of Science and Ovid (Medline and PsycINFO) were searched for articles published between January 2000 and May 2019 using the following keywords ((schiz\*) Or (Psychotic disorders) OR (Bipolar) OR (Depression)) AND ((Antibod\*) AND ((NMDAR) OR (N-methyl-D-aspartate receptor) OR (GABAA) OR (GABAB) OR (AMPA) OR (VGKC) OR (Lgi1) OR (Caspr2) OR (DPPX) OR (mGluR5) OR (D2R))) NOT (retina)).

**Added value of this study**

This is first study to use meta-regression to assess the impact of study factors on heterogeneity. We provide robust evidence that the live cell-based assay leads to higher detection of NMDAR IgG antibodies in psychosis patients compared to the fixed cell-based assay (2·97% vs. 0·36%), and that studies using the live method show significant differences between patients and controls (OR 4·43, 95% CI 1·73–11·36). In addition, we find that prevalence is elevated in patients with first-episode illness (although this was not confirmed in case-control studies) and that low-quality case-control studies yield higher odds ratios.

**Implications of all available evidence**

Clinicians should be aware that NMDAR IgG antibodies are rare, but detectable, among psychosis patients, and that it may be useful to selectively test patients who have recently experienced their first psychotic episode[A: In discussion section, this point seems more nuanced. Can you make this more clear here as currently it reads as if limiting serum testing FEP patients might be called for.]. In both clinical and research settings, we strongly recommend that the live cell-based assay is employed. As we found that many studies lacked information regarding the representativeness and characteristics of patient samples, and that very few performed complementary CSF testing, future studies should:

* Include a clear statement regarding steps taken to ensure a representative sample.
* Use a validated diagnostic tool and describe illness phase, stage, and mode of onset.
* Report full demographic details, personal and family history of autoimmune disease, current symptoms (using a validated scale), medication details, and treatment response.
* Characterise seronegative as well as seropositive individuals.
* Include paired serum-CSF testing where practicable or perform CSF testing in all seropositive subjects and a randomly-selected group of seronegative subjects.

# Summary

**Background:** Antibodies targeting the N-methyl-D-aspartate receptor (NMDAR) have been detected in psychosis patients. However, studies measuring the IgG subclass in serum have provided variable estimates of prevalence, and it is unclear whether these antibodies are more common in patients than controls. As these inconsistencies may be driven by methodological approaches and patient characteristics, we aimed to investigate the effect of these factors on heterogeneity.

**Methods:** We searched Web of Science and Ovid (Medline and PsycINFO) for cross-sectional and case-control studies published between January 2000 and May 2019 reporting NMDAR IgG antibody seropositivity in psychosis patients. Pooled proportions and odds ratios (OR) were derived using random-effects models. Meta-regression was used to investigate the effect of study factors on heterogeneity. Our protocol was registered on PROSPERO (CRD42018099874).

**Findings:** NMDAR IgG antibodies were detected in 0·73% (95% CI 0·09%–1·38%, I2=56%) of patients with psychosis in cross-sectional studies (N=14); however, case-control studies (N=14) showed that psychosis patients were not significantly more likely to be seropositive than healthy individuals (OR 1·58, 95% CI 0·78-3.17, I2=15%). Meta-regression analyses indicated significant effects of assay type, illness stage, and study quality/risk of bias on heterogeneity (p < 0.05 for all). Compared to those using a fixed cell-based assay, cross-sectional and case-control studies using the live method yielded higher pooled prevalence estimates (0·36% vs. 2·97%) and ORs (0·65 vs 4·43), respectively, in cross-sectional studies only, the prevalence was higher in exclusively first-episode samples (2·18% vs. 0·16%), and in case-control studies, higher ORs were reported in low quality studies (3·81 vs. 0·72).

**Interpretation:** Higher estimates of NMDAR IgG antibody prevalence are obtained with the live cell-based assay, and studies using this method find seropositivity is more common in patients than controls. Effects of illness stage and study quality/risk of bias on heterogeneity were not consistent across study designs, and we provide clear recommendations for clinicians and researchers regarding interpreting these findings.

# Introduction

The discovery of an encephalitic syndrome driven by antibodies targeting the *N*-methyl-D-aspartate receptor (NMDAR, specifically, the NR1 subunit) in which psychotic symptoms feature prominently,1-3 has prompted questions as to whether these neuronal surface antibodies are also present in psychosis patients with no accompanying encephalopathic illness. Whilst the detection of these antibodies in cerebrospinal fluid (CSF) is the gold-standard required for a diagnosis of NMDAR autoimmune encephalitis, lumbar puncture is rarely undertaken in routine psychiatric care as it is impractical to do so (particularly as the majority of patients are treated in community settings). As such, in psychiatry, this line of investigation has focused largely on NMDAR antibodies in serum, with an early meta-analysis indicating that these can be detected in 8% of psychosis patients, falling to 1·5% when restricted to the IgG subclass.4 However, findings vary considerably, with some large-scale investigations failing to detect NMDAR antibodies in any psychosis patients,5-7 yet others reporting that seropositivity (for any Ig class) is reasonably high in both psychosis patients (9·4%) and healthy controls (8·5%).8 This variability is likely due to the fact that some studies include IgA and IgM subclasses, which appear to be more common than IgG, and are of uncertain aetiological relevance.9 Moreover, multiple methods for detecting neuronal antibodies exist,10 and even within the more common cell-based assay (CBA) approaches, the use of ‘live’ or ‘fixed’ cells may yield different results.11 In addition to these methodological factors, patient samples range from acutely-unwell, first-episode psychosis (FEP) patients,12 to those with chronic schizophrenia.5 Whilst we suspect that these factors contribute to heterogeneity, earlier meta-analyses did not investigate this.4,13 To this end, we used meta-analysis and meta-regression to answer: (1) what proportion of patients with psychosis are seropositive for NMDAR IgG antibodies? (2) are psychosis patients more likely to be seropositive than healthy individuals? and (3) what impact do study factors (assay method, illness phase and stage, study quality/risk if bias) have on heterogeneity?

# Methods

## Search strategy and selection criteria

Our meta-analysis followed the recommendations of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement.14 The study protocol was prospectively registered with PROSPERO ([CRD42018099874](https://www.crd.york.ac.uk/prospero/display_record.php?RecordID=99874)).

Cross-sectional and case-control studies were eligible for inclusion; data from the former were used to estimate the proportion of psychosis patients seropositive for NMDAR IgG, with data from the latter used to compare the odds of seropositivity in patients and healthy controls. Psychosis groups from case-control studies were not included in the former analysis as such studies are rarely designed to estimate prevalence.

Original studies, published between January 2000 and May 2019, that met the following criteria were eligible: (1) number screening positive for NMDAR IgG antibodies in serum reported, (2) inclusion of at least one patient group with psychotic disorder, and (3) article published in a peer-reviewed English-language journal. Case-control studies also required a healthy control group. Searches were performed in Web of Science and Ovid (Medline and PsycINFO) using the following keywords ((schiz\*) Or (Psychotic disorders) OR (Bipolar) OR (Depression)) AND ((Antibod\*) AND ((NMDAR) OR (N-methyl-D-aspartate receptor) OR (GABAA) OR (GABAB) OR (AMPA) OR (VGKC) OR (Lgi1) OR (Caspr2) OR (DPPX) OR (mGluR5) OR (D2R))) NOT (retina)), where the latter was included to remove any study of retinal NMDAR cells. Full details of the searches performed in each database can be found in Supplementary Material[A: Supplementary material should be called “Appendix” as per Lancet style, and a specific page number in the Appendix pointing to the referenced information provided (ie Appendix pg XX) Please do this for all places in the manuscript where “Supplementary Material is mentioned]. Reference lists of review articles were also manually searched.

Titles and abstracts of all articles were screened independently by two researchers (E P-C & TP) to exclude clearly irrelevant studies. Full-texts of potentially relevant articles were then independently assessed for eligibility by two members of the research team (E P-C, SV, MH, HC[A: Which two authors did the full text assessments?]), conflicts were resolved by joint review and discussion with the senior author (BL). The full-text review identified two case-control studies from the same group with overlapping participant samples,15,16 as the second publication included both a reanalysis of the original samples (using an ‘up-to-date’ commercial assay, rather than the in-house laboratory procedure implemented previously) and an analysis of newly-collected samples, it was jointly agreed that this publication superseded the first. We therefore retained the second publication only in the meta-analysis.

## Data analysis

Data extraction was performed independently by three authors (E P-C, TP, AEC), any discrepancies were resolved following a joint review of the primary publication. The following were extracted for all eligible studies: year of publication, study design, diagnosis, illness phase, illness stage, size of psychosis group, antibodies measured, assay type, and number of seropositive psychosis patients; for case control studies, the control group size and number of seropositive controls was also extracted. Study authors were contacted where these details were unclear,17 with clarification subsequently provided. Two binary variables indexing illness phase (active/acute vs. stable phase and mixed samples) and illness stage (first-episode vs. multi-episode and mixed samples) were coded independently by two authors (AEC, BL). Samples were classified as comprising active/acute phase patients if (a) this was explicitly stated, (b) blood samples were acquired upon admission to an inpatient setting, or (c) study inclusion criteria specified that only patients with above-threshold scores on a measure of symptoms were eligible. For illness stage, samples were classified as first-episode if it was explicitly noted that all patients were in their first-episode or had recent-onset illness. If there was no indication that patients were in an active/acute phase or that all were first-episode, we classified samples as ‘stable phase and mixed’ and ‘multi-episode and mixed’, respectively; where there was ambiguity regarding illness phase or stage, further details were provided by study authors.6,18,19

Study quality/risk of bias was assessed independently by three authors (AEC, E P-C, TP, disagreements resolved by discussion) using modified versions of the Newcastle-Ottawa Scales (NOS) for quality assessment of cross-sectional studies and case-control studies (see Supplementary Material).20 For meta-regression analyses, we derived binary variables (low study quality/high bias vs. high study quality/low bias) defined using the median NOS value within each study design.

Analyses were performed using Stata version 16. Pooled proportions and odds ratios (OR) were derived from random-effects models (as we assumed that the true effect estimated in each study varied due to differences in patient characteristics and assay types) using metaprop21 and metan,22 respectively. For both analyses, a continuity correction of 0·5 was applied to cells with zero counts, and the DerSimonian and Laird method was used to estimate between-study variance (τ2), where the estimate of heterogeneity is taken from the inverse-variance fixed-effect model. Heterogeneity was assessed via the τ2 (estimated variance of the true effects) and I2 (proportion of observed variance due to heterogeneity) statistics.23 For both effect sizes (proportion and OR) we then performed univariable random-effects meta-regression with metareg24 to determine the effect of study factors on heterogeneity, with the adjusted R2 value indicating the proportion of between-study variance explained by the study factor (negative values indicating that the variable explains less variance than would be expected by chance). To maintain consistency with the meta-analytic models, we used the method-of-moments (approximating the DerSimonian and Laird method) to estimate between-study heterogeneity without the Knapp-Hartung variance estimator modification.24 Within each of the four study variables, we then performed stratified meta-analyses (using the same meta-regression model options, but estimating the constant term only) to derive pooled effect sizes (proportion and ORs) for each strata. Small sample bias (aka publication bias) was assessed visually (funnel plots), as is recommended for studies with binary outcome variables and substantial heterogeneity.25

As some publications reported effect sizes for more than one patient sample, we conducted additional analyses to account for the hierarchical structure within the data (i.e., effect sizes nested within a larger cluster, in this instance, publication).26 Robust variance estimation (RVE) with hierarchical weights was performed to derive the unconditional overall effect size (proportion or OR) by estimating the constant term only.27 As it was not possible to perform meta-regression or stratified meta-analyses with RVE due to the small number of studies,28 and we were keen to maintain consistency between these models and the main meta-analyses, RVE was employed for sensitivity analyses only.

## Role of funding source

There was no funding source for this study.

# Results

The search yielded 1276 articles (Figure 1). In total, 14 cross-sectional studies 5-7,11,17-19,29-35 and 14 case-control studies 8,12,15,36-46 were eligible for inclusion. Study characteristics are provided in Table 1. Two cross-sectional studies,5,6 and one case-control study,41 included more than one patient group, a further cross-sectional study 17 used both a live CBA (29 patients) and a fixed CBA (96 patients): these were counted as separate samples bringing the total number of cross-sectional and case-control samples to 18 and 15, respectively.

**[Insert Figure 1 and Table 1 here]**

Cross-sectional studies provided data on 1953 patients with psychosis, where there was considerable variation in sample size (range: 17 to 319). Age and sex/gender data were reported for 13 and 12 samples, respectively: of those with available data, all included adult patients (mean age 33·.6 years [SD 7·6], mean age range 24·1–46·1 years), and both males and females (mean percentage male 58% [SD 18%], range of percentage male 34-85%). Diagnoses included psychosis,7,11,17,19,29-31,34,35 schizophrenia,5,6,18,32,33 schizoaffective disorder,6,18 and schizophreniform disorder;5,6 details of illness phase and stage are provided in Table 1, although these were not reported in a substantial number of studies.5-7,17,19,30,32,33 Total NOS scores, shown in Table 1, ranged from one to 10 (mean 5·6 [SD 2·6]), full details are provided in Supplementary Material. In brief, less than half of the samples exceeded 100 participants, few were deemed to be highly representative, and response rates were reported for only three. Antibody assays were described in high- or moderate-detail in most studies; however, in five samples it was not clear that all results were reported.

The 14 case-control studies included 2428 psychosis patients (range 7 to 1378) and 2717 healthy controls (range 3 to 1703) in total. All except one44 examined adults; the mean age (reported in all studies) was similar in psychosis (mean age 30·5 years [SD 6·9], range of mean age 15·0–39·4 years) and healthy control groups (mean age 31·5 years [SD 5·5], range of mean age 22·7–38·4 years). Participant sex/gender was available for all studies although one did not provide this information for control participants: males were somewhat over-represented in the psychosis group (mean percentage male 58% [SD 19%], range of percentage male 0-79%) but under-represented in controls (mean percentage male 42% [SD 24%], range of percentage male 0-75%). Patient diagnoses included psychosis,12,36,38,40-42,44 schizophrenia,8,15,39,40,43,45,46 schizoaffective disorder,8 schizophreniform disorder,43 and post-partum psychosis;37 details of illness phase and stage were lacking for several studies.8,38,42,45,46 Total NOS scores (Table 1) ranged from one to eight (mean 4·5 [SD 2·3]). As detailed in Supplementary Material, there were particular concerns with regards to sample size (patient and control groups both exceeded 150 participants in only two studies), representativeness of patient and control groups, and potential for selection bias. Matching on potential confounders was performed in less than half of the studies and only three noted that antibody assays were performed blind to case/control status.

**[Insert Table 2 here]**

Table 2 provides the results of meta-analyses performed using standard approaches (random-effects models) and sensitivity analyses employing RVE (hierarchical models) to account for non-independence of effects. The random-effects model performed on cross-sectional data (Figure 2), indicated that NMDAR IgG antibodies were detected in 0·73% (95% CI 0·09%–1·38%) of psychosis patients, which was significantly different to zero (p=0·026). There was moderate heterogeneity in observed effects (I2=56%), although the estimated variance of ‘true effects’ was small (τ2=0·01). As expected, given that the pooled prevalence was extremely close to the lower possible limit (i.e., zero), the funnel plot was asymmetric (Supplementary Material): visual inspection revealed that proportions reported in larger studies tended to cluster around zero, suggesting the presence of small sample bias. In contrast, the random-effects model performed on case-control data (Figure 3) indicated that psychosis patients were no more likely than controls to screen positive for NMDAR IgG (OR 1·58, 95% CI 0·78-3.17). There was little evidence of heterogeneity (τ2= 0·26, I2=15%); however, the funnel plot (Supplementary Material) showed a cluster of small studies reporting negative effects (ORs < 1). RVE models yielded a slightly higher pooled prevalence to the standard model (1·43% 95% CI 0·01%- 2·84%), whilst the pooled OR was consistent with the standard model (1·63, 95% CI 0·91-2·93).

**[Insert Figures 2 and 3 here]**

Univariable meta-regression analyses indicated significant effects of assay type and illness stage on prevalence estimates from cross-sectional studies (Table 3). Figure 4 provides the results of individual meta-analyses stratified by each study factor, performed to further explore the pattern of effects across strata.[A: Owing to a higher-than-usual workload for our Production team, we need to limit the number of Tables and Figures in the main manuscript to 6 plus the Research in Context panel. I would recommend we move Figures 4 and 5 into the Appendix and rewrite this sentence as follows: We stratified each study factor for individual meta-analysis to further explore the pattern of effects across strata (Appendix pg XX, where Figure 4 will be)] For assay type, these analyses yielded a pooled prevalence of 0·36% (95% CI -0·23%–0·95%) when a fixed CBA was used and 2·97% (95% CI 0·70%–5·25%) when a live CBA was used; when stratified by illness stage, pooled estimates of 0·16% (95% CI -0·31%–0·63%) in multi-episode and mixed samples and 2·18% (95% CI 0·25%–4·12%) in FEP samples were observed. Similarly, meta-regression analyses performed on case-control study data indicated significant effects of assay type and study quality/bias on heterogeneity (Table 3). In stratified meta-analyses (Appendix pg XX), a pooled OR of 0·65 (95% CI 0·33–1·29) was found in samples where a fixed CBA had been employed and 4·43 (95% CI 1·73–11·36) when a live CBA was used; when stratified by study quality/bias, a pooled OR of 3·81 (95% CI 1·47–9·84) was observed in studies with low quality/high bias and 0·72 (95% CI 0·36–1·42) in high quality/low bias studies.

**[Insert Table 3 and Figures 4 and 5 here]**

# Discussion

In the largest meta-analysis, and the first to investigate sources of heterogeneity, we find that (1) NMDAR IgG antibodies are detectable in 0·73% of patients with psychosis, an estimate slightly lower than that found previously (1·5%),4 (2) in contrast to earlier reviews,4,13 patients are no more likely to be antibody positive than controls, and (3) heterogeneity is associated with assay type, illness stage, and study quality/risk of bias.

As variability of effect sizes was expected, we sought to gain a better understanding of the factors driving these differences with a view to (a) enabling clinicians to selectively identify patients in whom screening of serum might be beneficial, and (b) informing future research in this field. The effect of assay type was consistent across cross-sectional and case-control studies. Compared to the fixed CBA, the live CBA was associated with significantly increased prevalence of NMDAR IgG positive cases in psychosis patients (0·36% vs. 2·97%) and significantly higher ORs when comparing patients and controls (0·65 vs 4·43). Indeed, the null effect that we observed in our overall meta-analysis of case-control studies might be partially attributable to the prominent effect of assay type (i.e., cancelling effects). Of note, different assays were used in the two studies with largest weights (17%39 and 29%8), the former employing the live CBA and finding a strong positive association (OR=7·7) with the latter using the fixed CBA and showing a strong negative association (OR=0·49). Whilst one interpretation is that the live CBA yields false positive results, we would expect these to be equally prevalent in patient and control groups (i.e., inconsistent with the case-control findings). Moreover, a previous study of FEP patients found that antibodies detectable with a live, but not a fixed CBA, disrupted the surface dynamics of the NMDAR in live cultured neurons,11,47 suggesting that these antibodies indeed have functional relevance. Thus, we conclude that the live CBA leads to improved detection of NMDAR IgG antibodies in serum, and that the significantly increased odds of IgG positivity in psychosis patients relative to controls observed when using this method is genuine. It should be noted, however, that comparing pooled estimates derived from different samples cannot provide definite evidence for the superiority of the live assay; studies directly comparing the fixed and live CBA (when applied to the same samples) are needed to confirm this finding.

In cross-sectional studies, IgG was more commonly detected in exclusively FEP samples (2·18% vs. 0·16%). However, the two highest prevalence estimates were observed in a mixed sample comprising first- and multi-episode patients (10%)29 and a sample of treatment-refractory, multi-episode schizophrenia patients (7%).18 Furthermore, there was no effect of illness stage on heterogeneity in case-control studies. So, whilst our analyses of cross-sectional study data suggest that serum-testing in clinical settings might be more beneficial in FEP patients, the fact that this pattern was not observed in case-control studies suggests that further work is needed to support this approach. It is important to note, however, that these analyses do not directly compare first-episode and chronic illness as the reference group (not FEP) included mixed samples of first- and multi-episode patients,5,6,29 and samples where illness phase was not reported.7,17,32,33 As a related issue, poor reporting of illness phase might explain why we observed no effect of acute/active phase of illness in either analysis. Moreover, we were unable to examine the impact of mode of onset due to inadequate information, which is particularly important given that the recently proposed diagnostic criteria for ‘autoimmune psychosis’ requires an abrupt illness onset (rapid progression < three months).9 Future studies must provide full details of illness stage, phase, and mode of onset to allow more robust investigations into the impact of these factors. Nevertheless, as our analyses of the available data show no consistent effect of either illness phase or illness stage across cross-sectional and case-control studies, our findings indicate that it would be a mistake for clinicians to dismiss the possibility of autoimmune involvement in some patients simply because they are not acutely unwell or have chronic illness.

Our finding that low quality case-control studies yielded significantly higher odds ratios than high quality studies (3·81 vs. 0·72) is concerning. Although a similar pattern was detected in cross-sectional studies (low quality studies reported higher proportions), this difference was not statistically significant; moreover, two large cross-sectional studies with very high NOS scores detected IgG antibodies in 4-5% of patients.11,34 Overall, the quality of case-control studies was poor: only 2/15 patient samples and 5/14 control samples were likely representative, no studies reported response rates, and in six studies (including two samples in which the highest ORs were reported)39,41 it was unclear how patients had been selected for inclusion, therefore serum testing might have been performed in patients with more unusual presentations. However, in most cases, low scores were awarded due to a lack of information (particularly as many studies were published abstracts or letters) as opposed to there being clear evidence of bias. Full reporting of all recruitment methods and procedures is therefore vital if we hope to derive more robust and trustworthy estimates of effect and assess the true impact of bias.

We examined NMDAR IgG antibodies measured in serum, an approach which is controversial as the pathogenicity of these markers is unclear.48 Indeed, CSF testing is required for the definitive diagnosis of NMDAR encephalitis,49 and, as recently proposed, for identifying cases of autoimmune psychosis.9 However, only five studies also performed CSF testing, implying that, at present, CSF testing is uncommon in the field. Moreover, the approach was highly variable: one study examined CSF for all seropositive cases (3/4 were CSF-positive),34 others tested CSF in only a subset of seropositive cases,12,36,39 and another performed CSF testing in all patients and it was not clear that the one seropositive case was also CSF-positive.17 Whilst our results are limited by the lack of comparison with CSF findings, our intention was to pool the results of serum investigations, quantify the degree of variability, and identify sources of heterogeneity; these results may lead researchers and clinicians to further question the value of serum-only testing.

Further limitations should be noted. First, we did not examine NMDAR IgA and IgM isotypes, largely because the aetiological relevance of these subclasses is unclear, but in addition these were only reported in 5/28 studies.7,8,15,30,44 As a related point, we did not include the full spectrum of neuronal autoantibodies (e.g., those targeting LGI1, AMPAR or CASPR2) associated with autoimmune encephalitis.9 Whilst these other (non-NMDAR) autoantibodies were reported in several papers eligible for inclusion,5,7,8,12,17,31,34,35,38,40,44 it was beyond the scope of our review to examine these data in meta-analyses. Second, we examined antibody positivity as a discrete/binary outcome, that may mask important differences in the absolute values of antibody titre in patients and controls.13 This is particularly relevant given that threshold values for positivity have changed over time; reporting absolute values would avoid this issue. Third, the small number of studies included in the review limited our ability to assess small sample bias and meant that we were unable to use RVE for meta-regression or perform multivariable meta-regression analyses. The latter is important as study factors may not be independent of each other: for example, 6/7 cross-sectional studies using a live CBA were rated as low quality/high bias compared to 4/11 studies using the fixed CBA; thus, low study quality might have contributed to the increased prevalence observed in studies employing the live CBA. However, as study quality was not significantly associated with heterogeneity in cross-sectional studies, and the effect of assay type was also observed in case-control studies, this is unlikely to fully account for this effect. Finally, we performed multiple meta-regression analyses without applying corrections to reduce the risk of type 1 error. However, we restricted our analyses to study factors that we nominated *a priori*: indeed, we did not examine the influence of participant age and sex/gender as we had no strong rationale for investigating these factors (although this may be an avenue for future research, particularly as patients with psychosis and healthy controls appeared to differ on the latter

These limitations notwithstanding, our findings have important implications for clinicians. We show that when tested in serum samples, which can be routinely collected in clinical practice, approximately 1 in 100 patients are positive for NMDAR IgG antibodies. Of note, these may not be the only neuronal antibodies present and the underlying causes of any inflammatory/immunological disturbances must be investigated, including the presence of an autoimmune disorder (which are more common among individuals with psychosis).50 As recommended in the recent consensus guidelines, seropositive cases should be followed up with CSF testing, electroencephalography and MRI, and, when probable or definite autoimmune psychosis is indicated (which includes the presence of IgG antibodies in CSF), treatments should be undertaken to remove circulating antibodies.9 It is important to note, however, that whilst a seropositive result should flag to clinicians that there is increased probability of active CNS autoimmune involvement, a negative serum test does not provide definitive evidence that this is not the case, therefore CSF testing should always be performed (not only for antibodies, but also for other indications of CNS inflammation) if clinically indicated.

With regards to research implications, we strongly recommend that future studies (a) make efforts to obtain large, representative patient samples, in which illness phase, stage, and mode of onset are accurately classified, which may necessitate the development of national registries, (b) use a live CBA for serum testing, and perform CSF testing (including cell count, serum-paired oligoclonal bands and IgG index where possible) for all seropositive cases and a random sample of seronegative cases, and report the sensitivity, specificity, and positive predictive value of serum results for CSF abnormalities as a minimum, and (c) provide mean absolute titre values for patient and control groups, in addition to positive/negative test status, to facilitate comparison of mean differences.

# Contributors

BL, E P-C & TP conceived the idea of the study, BL, E P-C SV, MH, HC & TP developed the search strategy. Article screening was completed by E P-C, SV, MH, HC. Data extraction and quality ratings were performed by AEC, E P-C & TP. All data analyses were planned and performed by AEC who produced a first draft of the manuscript. All authors contributed to the final version of the manuscript and approved content.

# Declaration of interest

All authors declare no conflict of interest.

# Role of funding source

None.

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# Figure captions

**Figure 1**: Study selection

**Figure 2**: Prevalence of NMDAR IgG antibody seropositivity in patients with psychosis derived from case control studies

**Figure 3**: Odds of NMDAR IgG antibody seropositivity in psychosis patients and healthy controls derived from case-control studies

**Figure 4**: Distribution of prevalence estimates by study factor

**Figure 5**: Distribution of odds ratios by study factor

# Figure legends

**Figure 2**: NOS: Newcastle-Ottawa Scale score; Sz: schizophrenia; SzAff: schizoaffective disorder; SzPF: schizophreniform disorder; FE: first-episode; FCB: fixed cell-based assay; LCB: live cell-based assay; n: number seropositive for NMDAR IgG; N: total sample size; ES: effect-size; CI: confidence interval; RE: random-effects model.

**Figure 3**: NOS: Newcastle-Ottawa Scale score; Sz: schizophrenia; SzAff: schizoaffective disorder; SzPF: schizophreniform disorder; FE: first-episode; FCB: fixed cell-based assay; LCB: live cell-based assay; n: number seropositive for NMDAR IgG; N: total sample size; OR: odds ratio; CI: confidence interval.

**Figure4**: Plot of prevalence estimates obtained in individual samples where marker size represents the study weighting in random-effects model. Subgroup proportions obtained via stratified random-effects meta-analysis.

**Figure 5**: Plot of odds ratios obtained in individual samples where marker size represents the study weighting in random-effects model. Subgroup odds ratios obtained via stratified random-effects meta-analysis.

***Table 1*: Characteristics of cross-sectional and case-control studies included in meta-analyses by study design**

|  |  |  |  |  |  |  | Participant characteristics (psychosis / controls) | NOS score /max |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
| Author | Country | Recruitment setting (psychosis / controls) | Diagnosis | Illness phase | Illness stage | Assay type | N | Mean age, yrs a | % Male |
| Cross-sectional studies |  |  |  |  |  |  |  |  |  |  |
| Ando et al (2016) | Japan | Psychiatry and neurology inpatient departments | Psychosis | Active/acute | Mixed  | LCB | 59 | 42·0 | 39 | 3/11 |
| Beck et al (2015) | UK | Treatment-refractory psychosis clinic | Sz/SzAff | Active/acute | Multi-episode | FCB | 43 | 40·3 | 74 | 4/11 |
| Chen et al (2017c1) | Taiwan | Research project | Sz/SzPF | Active/acute | First-episode | FCB | 78 | 24·1 | 41 | 5/11 |
| Chen et al (2017c2) | Taiwan | Hospitals and mental health research centres | Schizophrenia | NR | Multi-episode | FCB | 234 | 46·1 | 43 | 7/11 |
| de Witte et al (2015c1) | Belgium | Inpatients and outpatients in contact with psychiatric centre | Sz/SzAff/SzPF | NR | Mixed | FCB | 110 | 26·2 | 85 | 6/11 |
| de Witte et al (2015c2) | Netherlands | Consecutively admitted patients | Sz/SzAff/SzPF | Active/acute | First-episode or recent-onset | FCB | 46 | 27·4 | 80 | 7/11 |
| de Witte et al (2015c3) | Netherlands | Research project (GROUP) | Sz/SzAff/SzPF | NR | Mixed | FCB | 319 | 30·6 | 77 | 9/11 |
| Endres et al (2015)  | Germany | Tertiary care hospital clinic | Psychosis | Active/acute | NR | FCB | 96 | NR | NR | 5/11 |
| Endres et al (2015)  | Germany | Tertiary care hospital clinic | Psychosis | Active/acute | NR | LCB | 29 | NR | NR | 5/11 |
| Hara et al (2018) | Spain | Regional psychiatric centre  | Psychosis | NR | First-episode | LCB | 50 |  |  | 6/11 |
| Haussleiter et al (2012) | Germany | NR | Psychosis | Active/acute | Mixed | FCB | 50 | 43·8 | 34 | 3/11 |
| Heresco-Levy et al (2015) | NR | NR | Schizophrenia | NR | NR | Live | 17 | NR | NR | 1/11 |
| Jézéquel et al (2017a) | International multi-centre | Research project (OPTiMiSE)  | Psychosis | Stable  | First-episode | FCB | 298 | 26·1 | 66 | 9/11 |
| Kelleher et al (2015) | Ireland | Inpatient and outpatient | Psychosis | NR | First-episode | LCB | 85 | 37·0 | 58 | 3/11 |
| Nakagami et al (2017) | Japan | Inpatient and outpatient hospital clinic | Schizophrenia | NR | NR | LCB | 136 | NR | NR | 5/11 |
| Schou et al (2016) | Norway | Inpatient psychiatry department in hospital  | Psychosis | Active/acute | NR | FCB | 144 | 32·0 | NR | 10/11 |
| Scott et al (2018) | Australia | Hospital inpatient | Psychosis | Active/acute | First-episode | FCB | 113 | 26·2 | 58 | 9/11 |
| Zandi et al. (2011) | UK | Early intervention service | Psychosis | Stable | First-episode | LCB | 46 | NR | NR | 3/11 |
| Case-control studies |  |  |  |  |  |  |  |  |  |  |
| Arboleya et al (2016) | Spain | Inpatient new-onset programme / general population | Psychosis | Active/acute | First-episode | FCB | 61 / 47 | 24·5 / NR | 59 / NR | 6/12 |
| Bergink et al (2015) | Netherlands | Mother-Baby inpatient unit / postpartum women from obstetrics and gynaecology department | Post-partum psychosis | Active/acute | Mixed | FCB | 96 / 65 | 31·2 / 32·8 | 0 / 0 | 4/12 |
| Dahm et al (2014) | Germany | Research project (multisite) / blood donors, students, hospital staff | Sz/SzAff | NR | NR | FCB | 1378 / 1703 | 39·0 / 37·8 | 65 / 58 | 8/12 |
| Gaughran et al (2018) | UK | Inpatient and outpatient / local general population | Psychosis | NR | First-episode | LCB | 96 / 98 | 32·7 / 32·2 | 51 / 50 | 8/12 |
| Jézéquel et al (2017b) | France | NR / clinical investigation centre | Schizophrenia | Mixed  | Mixed | LCB | 48 / 104 | 36·0 / 37·4 | 79 / 44 | 4/12 |
| Lennox et al (2009) | UK | Inpatient and outpatient / general population | Schizophrenia | Stable | Multi-episode | LCB | 22 / 23 | 38·6 / NR | 68 / 22 | 2/12 |
| Lennox et al (2009) | UK | Early intervention team / general population | Psychosis | Stable | First-episode | LCB | 16 / 23 | 24·2 / NR | 63 / 22 | 2/12 |
| Lennox et al (2017) | UK | Early intervention community team and mental health inpatient / general population  | Psychosis | Active/acute | First-episode | LCB | 228 / 105 | 24·3 / 23·8 | 62 / 64 | 5/12 |
| Mantere et al (2018) | Finland | NR / Population register centre | Psychosis | Active/acute | First-episode | FCB | 70 / 34 | 26·3 / 28·8 | 66 / 56 | 6/12 |
| Masdeu et al (2012) | Spain | Regional psychiatric centre / NR | Psychosis | NR | First-episode | FCB | 80 / 40 | 29·4 / 30·7 | 72 / 62 | 3/12 |
| Masopust et al (2015) | Czech Republic | Hospital psychiatry department / hospital staff | Sz/SzPF | Active/acute | First-episode | FCB | 50 / 50 | 27·4 / 27·0 | 58 / 58 | 5/12 |
| Pathmanandavel et al (2015) | Australia | Paediatric hospital / NR | Psychosis | Active/acute | First-episode | LCB | 43 / 17 | 15·0 / NR | 49 / NR | 2/12 |
| Rhoads et al (2011) | USA | NR / NR | Schizophrenia | NR | NR | FCB | 7 / 3 | 39·4 / 22·7 | 43 / 33 | 2/12 |
| Steiner et al (2014) | Germany | Scientific biobank from university psychiatric department | Schizophrenia | Active/acute | Mixed | FCB | 184 / 357 | 34·0 / 35·0 | 60 / 50 | 8/12 |
| Timucin et al (2016) | Turkey | Medical centre / NR | Schizophrenia | Mixed  | NR | LCB | 49 / 48 | 35·9 / 38·4 | 73 / 75 | 3/12 |

NR: not reported; Sz: schizophrenia; SzAff: schizoaffective disorder; SzPF: schizophreniform disorder; LCB: life cell-based; FCB: fixed cell-based; NOS: Newcastle-Ottawa Scale score. a Age at time of serum collection.

***Table 2*: Meta-analyses of prevalence of NMDAR IgG antibody positivity derived from cross-sectional studies and odds of IgG antibody positivity in psychosis patients and healthy controls derived from case control studies**

|  |  |  |
| --- | --- | --- |
|  | Prevalence of NMDAR IgG in patients with psychosis a | Odds of NMDAR IgG in patients relative to controls |
| Model | **Ns** | **Nc** | **Prevalence (95% CI)** | **p value** | **τ2** | **I2** | **Ns** | **Nc** | **Odds ratio (95% CI)** | **P value** | **τ2** | **I2** |
| Random effects model | 18 | – | 0·73 (0·09–1·38) | 0·026 | 0·01 | 56% | 15 | – | 1·58 (0·78–3·17) | 0·202 | 0·26 | 15% |
| Hierarchical effects model  | 18 | 14 | 1·43 (0·01–2·84) | 0·049 | 0·00 | – | 15 | 14 | 1·63 (0·91–2·93) | 0·093 | 0·00 | – |

Ns: Number of samples contributing to analysis; Nc: number of clusters (publications) included in analyses; CI: confidence interval; τ2: tau-squared (estimate of between-study variance); I2: % variation in effect size due to heterogeneity. For random-effects model, τ2 estimated using the DerSimonian and Laird method. Hierarchical effects model performed using robust variance estimation (RVE) with hierarchical weights. a To aid interpretation, all values reported for prevalence analyses are presented as percentages rather than proportions.

***Table 3*: Meta-regression analyses examining the influence of methodological and patient factors on heterogeneity**

|  |  |  |
| --- | --- | --- |
|  | Prevalence of NMDAR IgG in patients with psychosis a | Odds of NMDAR IgG in patients relative to controls |
| Predictor variable | **Ns** | **Prevalence (95% CI)** | **p value** | **τ2** | **I2** | **Adj R2** | **Ns** | **Odds ratio (95% CI)** | **p value** | **τ2** | **I2** | **Adj R2** |
| Assay type (fixed CBA vs. live CBA) | 18 | 1·85 (0·11–3·58) | 0·037 | 0·01 | 50% | 24·3% | 15 | 6·81 (2·12–21·84) | 0·001 | 0·00 | 0% | 100·0% |
| Illness phase (stable or mixed vs. acute/active) | 18 | -0·25 (-1·64–1·14) | 0·723 | 0·01 | 58% | -23·3% | 15 | 1·87 (0·43–8·18) | 0·408 | 0·24 | 13% | 7·7% |
| Illness stage (multi-episode or mixed vs. first-episode) | 18 | 1·50 (0·11–2·88) | 0·034 | 0·00 | 48% | 27·6% | 15 | 1·71 (0·39–7·52) | 0·477 | 0·27 | 14% | -0·6% |
| Study quality (low quality/high bias vs. high quality/low bias) | 18 | -0·73 (-2·11–0·66) | 0·303 | 0·01 | 56% | -1·3% | 15 | 0·19 (0·06–0·61) | 0·005 | 0·00 | 0% | 100·0% |

Ns: Number of samples contributing to analysis; CI: confidence interval; τ2: tau-squared (estimate of between-study variance); I2: % variation in effect size due to heterogeneity; Adj R2: Adjusted R2 indicating % of between study variance explained by study factor (negative values indicate study factor explains less variation than expected by chance); CBA: cell-based assay. All models employ random-effects with τ2 estimated using the method of moments approach. a To aid interpretation, all values reported for prevalence analyses are presented as percentages rather than proportions.