Systematic Review and Meta-Analysis of Damage Associated Molecular Patterns HMGB1 and S100B in Schizophrenia

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Objective Immune system dysregulation is hypothesised to be central to the aetiopathogenesis of schizophrenia; however, the role of sterile inflammation remains unclear. Damage associated molecular patterns are key initiators of sterile inflammation and are detectable in peripheral blood.

Methods A defined systematic search of the Web of Science, PubMed, and Scopus was performed to identify adult case-control studies published between January 1990 and June 2022. Three studies consisting of 242 cases and 83 controls met inclusion for the systematic review and meta-analysis of HMGB1 while twenty-eight studies consisting of 1,544 cases and 1,248 healthy controls were included for S100B.

Results A significant standardised mean difference in peripheral S100B and HMGB1 concentrations was detected between cases and controls. S100B subgroup analysis determined the largest significant effect size for unmedicated individuals diagnosed with schizophrenia.

Conclusion This study provides evidence that peripheral S100B and HMGB1 concentrations are elevated in individuals diagnosed with schizophrenia when compared with healthy controls. These results should be interpreted with caution as significant heterogeneity was present during meta-analysis of S100B in the entire sample and in sub-group analysis. The persistence of significant heterogeneity throughout subgroup analysis indicates that the current diagnostic groupings may be a barrier to understanding human behaviours and emotions. **Psychiatry Investig 2022;19(12):981-990**

Keywords Schizophrenia; Inflammation; Danger associated molecular patterns; Meta-analysis.

INTRODUCTION

Schizophrenia is defined as a complex neuropsychiatric disorder affecting approximately 1% of the global population.[1] The disorder includes delusions, hallucinations, and disorganised speech as positive symptoms, while flattened affect, anhedonia, alogia, avolition, and deficits in social functioning are collectively termed negative symptoms.[2,3] Immune system alterations are intricately interlinked with neurodevelopmental,[4,5] neurodegenerative,[6,7] genetic,[8,9] and biopsychosocial models[10,11] of schizophrenia. Multiple meta-analyses have uncovered increases in pro-inflammatory gene

transcripts and protein levels including tumour necrosis factor α, interleukin 1β (IL-1β), IL-6 and C-reactive protein in the peripheral blood and post-mortem brain samples of individuals diagnosed with schizophrenia compared to healthy controls.[7,12] Maternal inflammation prior to birth,[13] or a history of autoimmune disorder[14] are associated with increased risk of developing schizophrenia. Inflammation can also occur in the absence of infection. Sterile inflammation is initiated when damaged or dying cells release endogenous molecules termed damage associated molecular patterns (DAMPs), that ligate with DAMP sensing receptors and activate the innate immune response.[15,16] High mobility group box 1 (HMGB1) and S100 calcium binding protein B (S100B) are well characterised DAMPs that serve diagnostic and prognostic functions in other disorders including cancer[17] and traumatic brain injury.[18]

S100B is a calcium binding protein localised in the cytosol of glial cells and astrocytes of the central nervous system,[19] and both immune and non-immune cells of the peripheral nervous system.[20] S100B is important for a plethora of homeostatic activities including cell cycle progression and dif-

ferentiation,[21,22] calcium homeostasis,[23] activation of calcium dependent enzymes,[24] and microtubule assembly and disassembly of the cytoskeleton.[25] S100B is released by damaged or dying cells and interacts with the receptor for advanced glycation end products (RAGE),[26] conferring neuroprotective or neurotoxic effects on neurons in a concentration dependent manner.[27] HMGB1 is a chromatin binding protein and key epigenetic regulator that modulates the binding ability of regulatory elements such as nucleosomes and transcription factors for some genes associated with inflammation.[28] HMGB1 is expressed in all nucleated cells and remains within the nucleus under physiological conditions.[29] Damaged and dying cells release HMGB1 when the structural integrity of cells is diminished.[30] Extracellular HMGB1 interacts with a plethora of receptors including triggering receptor in myeloid cells 1, RAGE, toll-like receptor 2 (TLR2), and TLR4 to execute a number of functions pertaining to pro-inflammatory cytokine release,[31] cell survival and cell death mechanisms.[32,33]

The sterile immune response is critical for physiological functioning; however, chronic and sustained levels of inflammation can result in altered cellular functioning, cellular damage and death, which is hypothesised to contribute to the symptomology of schizophrenia.[6] This research aimed to quantify differences in peripheral DAMP concentrations in adults diagnosed with schizophrenia and healthy controls by conducting a systematic review and meta-analysis.

METHODS

Search criteria

A systematic search of the Web of Science, PubMed, and Scopus databases was conducted to identify relevant papers that were published between January 1990 and June 2022 using a combination of the following key search terms: ("schizophrenia" OR "schizoaffective") AND ("HMGB1" or "high mobility Group Box 1" OR "high mobility group protein 1" OR "S100" OR "S-100" OR "S100B"). Additional articles were identified by searching bibliographical references from articles that were retrieved through the original search.

Study selection criteria

Studies identified by the initial search were screened and selected for inclusion according to the following criteria: 1) longitudinal or cross-sectional, peer-reviewed original articles, 2) article is written in English, 3) case-control studies, 4) quantitative measures of S100B and HMGB1 reported, 5) individuals diagnosed with schizophrenia in accordance with the Diagnostic and Statistical Manual of Mental Disorders, fourth or fifth edition, or World Health Organisations International Statistical Classification of Disease versions ten or

eleven, and 6) sample is isolated from peripheral blood. Studies were excluded if: 1) individuals were diagnosed with comorbid neuropsychiatric disorders, 2) individuals were diagnosed with a chronic inflammatory, neurological, or autoimmune disorder, 3) individuals under the age of 18 were included, and 4) arithmetic mean and standard deviation for measures of S100B and/or HMGB1 were not reported or could not be extracted from the article.

Data extraction

Data pertaining to age, sex, concentration of peripheral S100B and/or HMGB1, neuropsychiatric diagnostic method, quantitative assay used, sample location, medication usage, psychopathological state, and medical history were collected where applicable for both the control and schizophrenia cohorts. In the case of longitudinal studies that included repeated blood draws and quantitative measurement of S100B and HMGB1, the values reported from the initial blood draw were included. In the case where the same patient cohort samples were published in multiple journal articles, the first article to appropriately report relevant measures was included, with all other articles using identical samples excluded. When the sample cohort of individuals diagnosed with schizophrenia was further divided into subpopulations and no information for the entire schizophrenia group was reported, the data from the subpopulations was pooled to generate a pooled mean and standard deviation. Quantitative data that was reported in alternative units was converted to ng/L for S100B and ng/mL for HMGB1 to allow comparison. When the arithmetic mean and standard error (SE) of the mean was not reported, the following calculation as used to convert the SE of the mean to standard deviation: standard deviation=(SE of the mean)×(√n).[34] The online tool WebPlotDigitizer (Pacifica, CA, USA) was used to extract data reported in graphic form only.

Statistical analysis

A meta-analysis was conducted for the thirty studies included in the systematic review of S100B. The standardised mean difference between individuals diagnosed with schizophrenia and controls served as the main outcome measure, while the conservative random effects model was fitted to the data to account for inter-study variance.[35] The effect size was reported as Hedges' g value with 95% confidence intervals (CIs).[36] Statistical heterogeneity was measured using Hedges estimator and reported as tau^2,[36] the Q-test for heterogeneity,[37] and the I^2 statistic.[38] Subgroup analysis was performed to explore possible causes of heterogeneity. Publication bias was measured using the Fail-Safe N,[39] Begg and Mazumdar's rank correlation,[40] Egger's regression,[41] and trim and fill num-

ber of Studies.[42] The statistical analysis software jamovi (V1.6)[43] was employed to conduct all statistical analysis.

Data reporting

This systematic review and meta-analysis were conducted in accordance with the most recent version of the Preferred Reporting Items for Systematic reviews and Meta-Analyses guidelines.[44]

RESULTS

Characteristics of included studies

The literature search identified 555 potentially relevant publications, of which 30 articles satisfied the inclusion criteria (Figure 1). One article was applicable for inclusion in both S100B and HMGB1 analysis.[45] Two other articles were suitable for inclusion in the HMGB1 group[46,47] and 28 articles were applicable for inclusion in the S100B group which are systematically reported in Suppletmentary Table 1 (in the online-only Data Supplement). Quantitative analysis of HMGB1 concentration was performed on serum samples from participants using an ELISA assay for all three studies. Kozłowska et al.,[45] (2021), measured clinical symptom severity using the Scale for assessment of Negative Symptoms (SANS), and Calgary Depression Scale for Schizophrenia (CDSS), while Mousa et al.,[46] (2021) and Yilmaz et al.,[47] (2021) used the Positive and Negative Symptom Scale (PANSS).

In total twenty-eight studies consisting of 1,544 individuals diagnosed with schizophrenia and 1,248 healthy controls were included in the systematic review and meta-analysis of S100B. The characteristics of individuals included is illustrated in Figure 2 and reported in Supplementary Table 1 (in the online-only Data Supplement). Ten studies included individuals who were exclusively unmedicated, ten studies included both individuals who were medicated and individuals who were not medicated, while the remaining eight studies included individuals who were all actively taking medication. Twenty-one studies recruited inpatients exclusively, while only three studies recruited only outpatients. A further two studies recruited both inpatients and outpatients, while two studies did not mention if individuals were receiving inpatient or outpatient care. The psychopathological state of individuals was characterised using the PANSS in 22 studies, the Brief Psychiatric Rating Scale (BPRS)[48] in six studies, the SANS was used in three studies, the Scale for assessment of Positive Symptoms (SAPS)[49] in two studies, the Negative Symptom Rat-
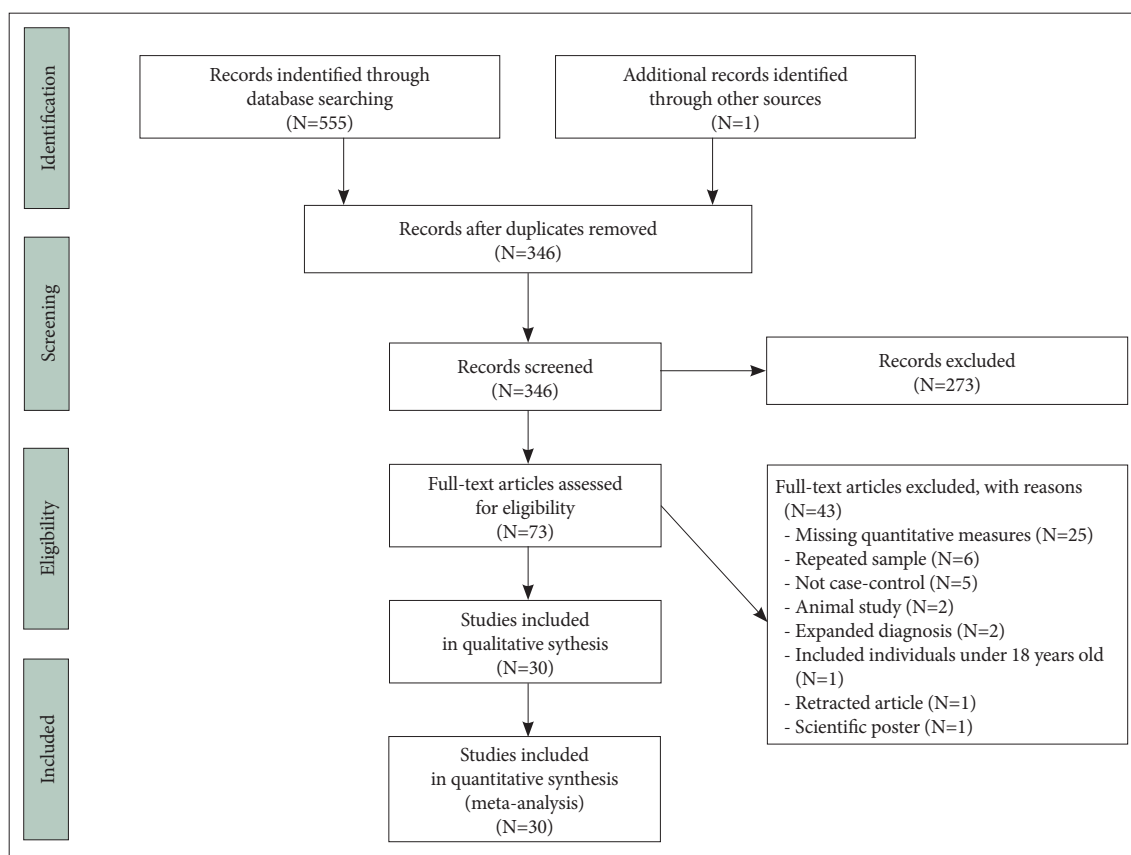

Figure 1. PRISMA flow diagram illustrating study selection process for the systematic review and meta-analysis in accordance with PRISMA guidelines.[72] PRISMA, Preferred Reporting Items for Systematic reviews and Meta-Analyses.
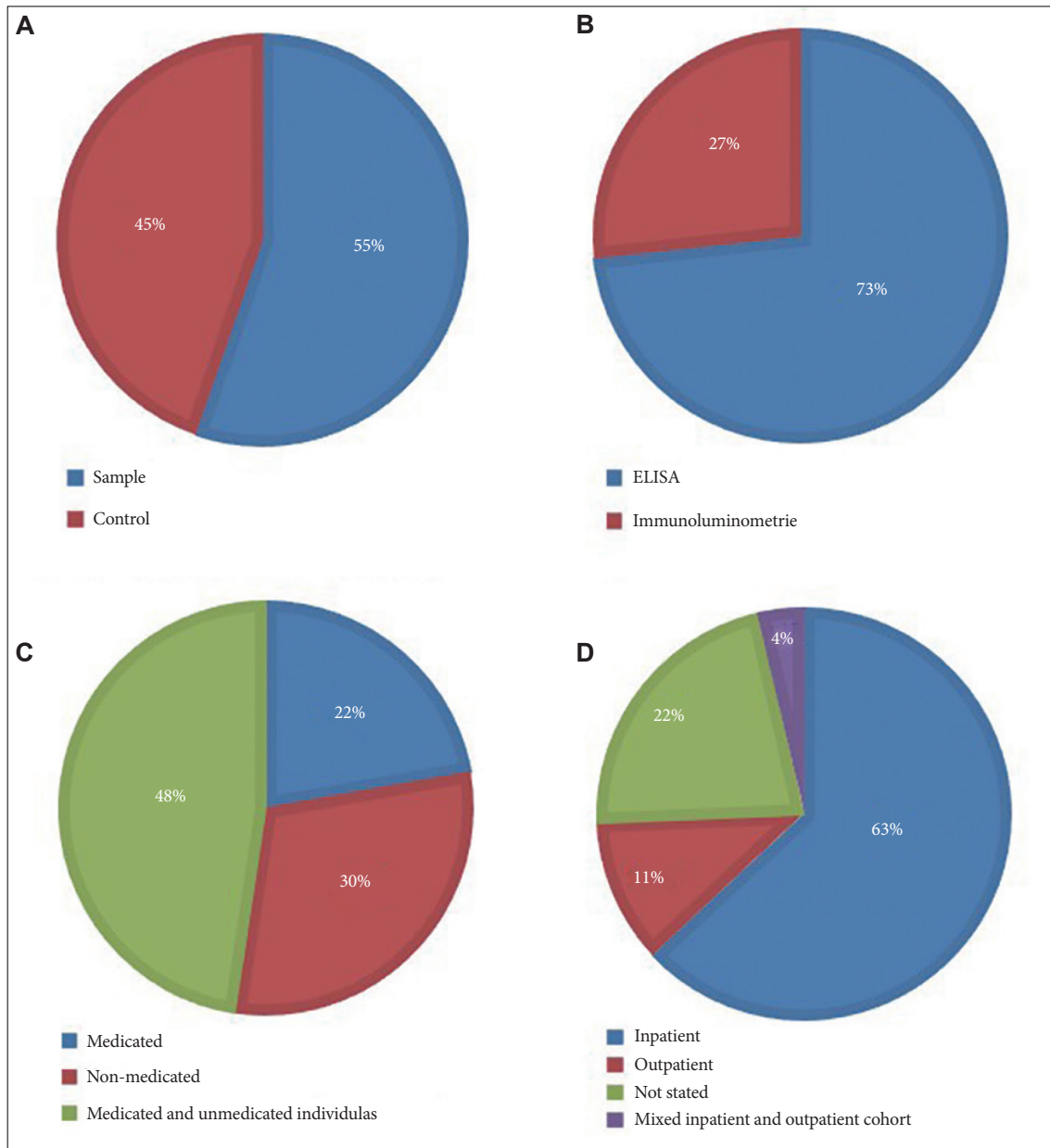
Figure 2. Pie charts illustrating characteristics of individuals included in the S100B systematic review and meta-analysis. A: Case and control. B: Assay. Pie charts A and B are representative of the whole population of individuals. C: Medication status. D: Patient setting. Pie charts C and D are exclusively representative of individuals diagnosed with schizophrenia. Unmedicated individuals described in pie chart C represents individuals who were not taking antipsychotic medication for at least one week prior to study commencement. ELISA, enzyme linked immunosorbent assay.

ing Scale (NSRS)[50] in one study and the CDSS in one study.

Meta-analysis of HMGB1

Individuals diagnosed with schizophrenia had significantly higher peripheral blood concentrations of HMGB1 compared to healthy controls. The observed standardised mean differences between the groups ranged from 0.2653 to 1.5697 with all the estimates having positive directionality (Figure 3). The estimated standardised mean difference between case and

control groups determined from the random effects model was g=0.9197, 95% CI (0.5181 to 1.3169) an effect size that differed significantly from zero (z=4.5030, p<0.001). Heterogeneity was measured using: Tau^2=0.0692 (SE=0.1252), I^2= 55.83% and Q=4.6331.656, p=0.098. Analysis of studentised residuals uncovered that all studies had a value smaller than ±2.3940. Publication bias was assessed and reported as: failsafe, n=51.00, p<0.001; Begg and Mazumdar rank correlation= -0.33, p>0.999; Egger's regression=-0.50, p=0.537; trim and fill

number of studies=0.00.

Whole group meta-analysis of S100B

Similarly, S100B concentrations were significantly higher in peripheral blood of individuals diagnosed with schizophrenia compared to healthy controls. The observed stan-

Figure 3. HMGB1 meta-analysis. This forest plot illustrates the whole group meta-analysis analysing peripheral HMGB1 concentrations in schizophrenia, with hedges g effect size and 95% CIs. CI, confidence interval.

dardised mean differences between the groups ranged from -0.5027 to 2.5247, with only three of the twenty-eight studies not reporting a positive effect (Figure 4). The estimated standardised mean difference between case and control groups determined from the random effects model was g=0.8695, 95% CI (0.5749 to 1.1641) with this effect size differing significantly from zero (z=5.7852, p<0.001). Heterogeneity was measured using: Tau^2=0.5580 (SE=0.172), I^2=91.79% and Q= 339.1195, p<0.001. Analysis of studentised residuals uncovered that all studies had a value smaller that ±3.1237. Publication bias was assessed and reported as: fail-safe, n=3,638.00, p<0.001; Begg and Mazumdar rank correlation=0.05, p= 0.710; Egger's regression=-0.03, p=0.978; trim and fill number of studies=5.00.

Subgroup meta-analysis of S100B

Subgroup analysis was performed to assess interstudy heterogeneity and determine the influence of potentially confounding factors on the standardised mean difference between cases and controls, through stratification of participants.
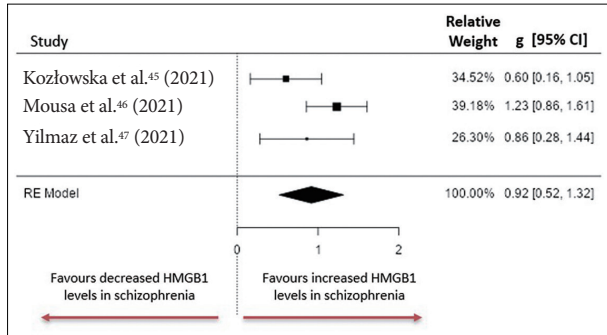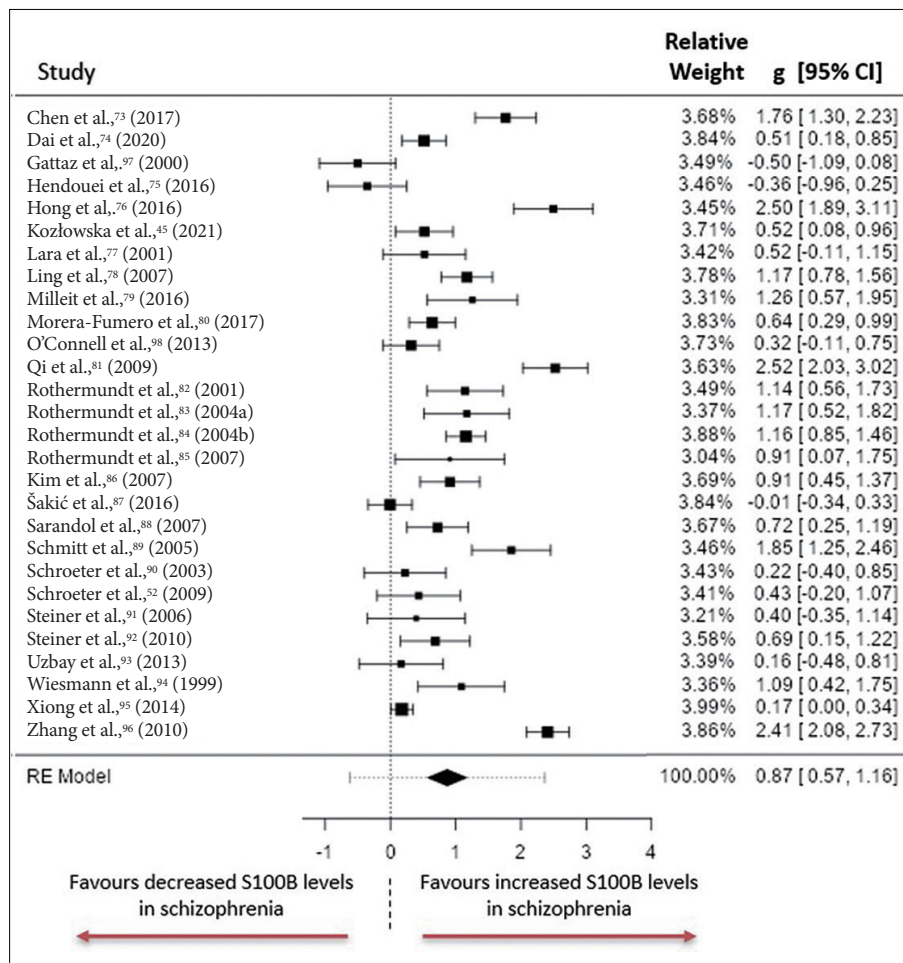

Figure 4. S100B meta-analysis. This Forest plot illustrates the whole group meta-analysis analysing peripheral S100B concentrations in schizophrenia, with hedges g effect size and 95% confidence intervals. CI, confidence interval.

Table 1. Summary of subgroup analysis

Cohort	Sample (N)	Control (N)	Sample	Effect size [CI]	I²	Fail-safe N
All individuals	1,544	1,248	Plasma and serum	0.87 [0.57, 1.16]	91.8%	3,638.00 (p<0.001)
Sample						
Serum measurement	1,385	1,093	Serum	0.87 [0.56, 1.17]	91.2%	2,566.00 (p<0.001)
Plasma measurement	159	155	Plasma	0.89 [-0.11, 1.88]	93.5%	89.00 (p<0.001)
Assay						
ELISA	1,144	902	Plasma and serum	0.91 [0.44, 1.39]	95.6%	1,449.00 (p<0.001)
Immunoluminometric	400	346	Plasma and serum	0.82 [0.49, 1.14]	75.5%	3,638.00 (p<0.001)
Medication status						
Medicated individuals	343	214	Plasma and serum	0.73 [0.01, 1.46]	92.9%	158.00 (p<0.001)
Non-medicated individuals	466	412	Plasma and serum	1.08 [0.68, 1.48]	86.2%	714.00 (p<0.001)
Medicated and unmedicated individuals	735	622	Plasma and serum	0.79 [0.25, 1.33]	92.3%	422.00 (p<0.001)
Patient setting						
Inpatient	970	781	Plasma and serum	0.99 [0.64, 1.34]	90.4%	2,458.00 (p<0.001)
Outpatient	174	112	Plasma and serum	0.21 [-0.42, 0.84]	83.3%	2.00 (p<0.001)
Mixed cohorts including outpatients and inpatients	60	55	Serum	N/A	N/A	N/A
Not stated	340	300	Serum	N/A	N/A	N/A

This table depicts the subgroup meta-analysis effect sizes based on sample source, assay conducted, medication status and patient setting. ELISA, enzyme linked immunosorbent assay; CI, confidence interval; N/A, not applicable

The sample (serum or plasma) used to quantitatively measure S100B, the assay used to measure S100B, the medication status of patients, and patient care status (inpatient or outpatient) were the subgroups used, with the standardised mean difference determined from the random effects model. The mean effect size was reported as hedges g with 95% CIs, and interstudy heterogeneity reported as I². Subgroup analysis is summarised in Table 1.

DISCUSSION

To our knowledge, this is the first meta-analysis to assess peripheral HMGB1 and the third such meta-analysis to compare peripheral S100B concentrations in adults diagnosed with schizophrenia and healthy controls.[51,52] This meta-analysis detected significantly elevated peripheral S100B and HMGB1 concentrations in adults diagnosed with schizophrenia compared to healthy controls. An overrepresentation of individuals diagnosed with schizophrenia using inpatient services (Figure 2) suggests that this study is more representative of individuals in an acute phase of illness compared to the whole population of individuals diagnosed with schizophrenia.

In agreement with previous meta-analyses, S100B concentrations are significantly elevated in the peripheral blood of adults diagnosed with schizophrenia compared with healthy controls.[51,52] Novel to this meta-analysis was differential S100B

concentrations detected in the peripheral blood of medicated and unmedicated subgroups of individuals diagnosed with schizophrenia. The subgroup of unmedicated individuals diagnosed with schizophrenia had the largest standardised mean difference between case and control populations, while medicated individuals diagnosed with schizophrenia did not report a statistically significant standardised mean difference between case and control groups. This suggests that antipsychotic medication may influence the immune system and partially elicit therapeutic effects through modulation of immune related pathways. At present, a distinct lack of clinical research examining the influence of antipsychotic medication on peripheral S100B concentrations exists. An in-vitro study has provided evidence that both typical and atypical antipsychotic medication can reduce S100B release from neuronal cell lines.[53] Further research is needed to understand if this effect translates to clinical populations. Studies on drug naïve individuals have reported significantly reduced IL-1β and IL-6 levels in the months following treatment with antipsychotic medication.[54,55] A consensus remains to be reached with longitudinal studies reporting that levels of pro-inflammatory cytokines return to their drug naïve baseline or even higher concentrations over time.[56-59]

The triangulation of available evidence suggests that elevated peripheral S100B and HMGB1 levels are characteristic of schizophrenia. Physiological concentrations of S100B and

HMGB1 are critical for homeostasis. However, sustained supraphysiological expression can induce altered cellular functioning, cellular damage and death, which is hypothesised to contribute to the symptomology of schizophrenia.[6,60,61] These DAMPs are also known to engage with pattern recognition receptors and therefore induce further inflammation.[16] Future longitudinal research exploring their potential causative or consequential roles in schizophrenia is required.

High levels of statistical heterogeneity were a major limiting factor of this study and were also noted in previous meta-analyses.[51] Understanding the sources of interstudy heterogeneity is of paramount importance as the validity of meta-analyses is dependent on this. Subgroup analysis was employed to assess potential contributors to the whole group heterogeneity but failed to reduce heterogeneity despite segregating participants based on potential effect modifiers and confounds including medication status, assay used, sample source and patient treatment status. It is possible that other potentially confounding factors that were not controlled for in this study including body mass index levels,[62] diet,[63] smoking habits,[64] and exercise levels[65] may have contributed to the observed heterogeneity.

Recent criticisms have highlighted the broad and heterogeneous grouping of individuals into diagnostic categories that encompass a vast number of overlapping symptoms, while failing to account for symptom severity.[66,67] Symptomology is hypothesised to more likely reflect neurobiological alterations as opposed to classical diagnostic groupings, indicating that heterogeneity introduced by clinical diagnosis is a barrier to understanding the neurobiological mechanisms underpinning dominant symptomology of neuropsychiatric disorders.[68] Efforts are underway to uncover and integrate neurobiological markers of neuropsychiatric disorders with more traditional diagnostic approaches.[69] Finally, the absence of an independent assessor or second person verification step may increase the risk of missing potentially relevant information.

The disparity between health of individuals diagnosed with schizophrenia and that of the general population has widened in recent decades, despite the advent of first and second generation antipsychotics and continuing research.[70,71] Understanding the role of current diagnostic groupings in contributing to clinical heterogeneity, and its validity as a conceptual model for which to study human thoughts, behaviours, and emotions should be a research priority as the gap between the health of individuals diagnosed with schizophrenia and the general population widens.

Supplementary Materials

The online-only Data Supplement is available with this article at https://doi.org/10.30773/pi.2022.0173.

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Supplementary Table 1. Systematic review of S100B and HMGB1 levels in patients with schizophrenia and healthy controls

Study		N	Sex (M/F)	Age (yr)	S100B concentration (ng/L)±SD	Diagnosis	Location	Assay	Psychopathological state	Sample medication	Sample characteristics	Illness duration (yr)	Control characteristics
S100B													
Chen et al.,[73] (2017)	Sample	62	24/38	35.31±11.61	226±80	DSM-4 (SCID)	Serum	ELISA	PANSS: 83.32±10.17	Drug naïve (N=34), drug (N=28)	All acute phase patients	3.9	Sex matched from local community
	Control	40	20/20	25.68±6.55	110±30								
Dai et al.,[74] (2020)	Sample	83	45/38	23.65±6.9	127.56±44.36	DSM-4 (SCID)	Serum	ELISA	PANSS: total not reported	All drug naïve	All first episode outpatients	0	Age and sex matched
	Control	60	32/28	24.6±3.6	107.41±29.84								
Gattaz et al.,[97] (2000)	Sample	23	16/7	36.0±9.0	440±270	DSM-4	Plasma	Luminometric assay	BPRS: 25.8±15.4, NSRS: 17.7±13.6	All medicated	All outpatients	17±7	NS
	Control	23	16/7	44±17.0	550±140								
Hendouei et al.,[75] (2016)	Sample	19	13/6	34.05±9.9	21.1±11.1	DSM-4-TR	Serum	ELISA	PANSS: 85.3±24	All medicated clozapine (N=6), risperidone (N=13)	All inpatients.	9.4±9.41	Age, gender, and BMI matched
	Control	25	18/7	34.2±8.30	26.4±16.8								
Hong et al.,[76] (2016)	Sample	41	18/23	37.0±11.30	303.09±34.76	ICD-10	Plasma	ELISA	PANSS: 80.29±29 9.22	All drug free ≥1 week prior to enrolment	All inpatients	11.6±8.93	Age and sex matched staff member and medical students
	Control	33	10/23	35.15±13.72	223±27.53								
Kozłowska et al.,[45] (2021)	Sample	68	45/23	38.5±10.7	308.4± 168.1	DSM-4 & ICD-10	Serum	ELISA	PANSS 65.20±15.80 CDSS: 2.76±3.38	All medicated: CAED: 746.5±642.2	All outpatients with chronic paranoid schizophrenia	NS	Age and sex matched from the local community
	Control	29	19/10	37.6±10.6	232.6±59.0								
Lara et al.,[77] (2001)	Sample	20	13/7	31±8	120±140	DSM-4	Serum	Luminometric assay	PANSS: 107±29	All drug free ≥1 week prior to commencement	Inpatients (N=14), outpatients (N=6)	NS	Age and sex matched
	Control	20	13/7	31±9	67±14								
Ling et al.,[78] (2007)	Sample	57	27/30	33.5±11.3	119±59	DSM-4 & ICD-10	Plasma	ELISA	PANSS: 77.8±13	All drug free ≥2 weeks prior to blood draw.	All inpatients	8.00±9.01	Age and sex matched volunteers from hospital staff
	Control	60	30/30	34.9±6.68	67±22								
Milleit et al.,[79] (2016)	Sample	17	6/11	33.9±9.7	85.8±21.7	DSM-4	Serum	Luminometric assay	PANSS: total NS	Drug naïve (N=10), unmedicated ≥4 days (N=7)	All inpatients	NS	NS
	Control	22	9/13	34.7±10.3	57±23								
Morera-Fumero et al.,[80] (2017)	Sample	65	36/29	36.7 ± 10.2	143.7 ± 210.7	DSM-4	Serum	ELISA	PANSS: total NS	Mostly medicated CAED: 757.7±400.0	All inpatients with acute psychotic relapse	12.3 ±10.0	Age and sex matched from research institute and colleagues.
	Control	65	46/19	39.6 ± 9.8	47.3 ± 23								
O'Connell et al.,[98] (2013)	Sample	97	68/29	45 ± 12.2	79.48 ± 39.8	DSM-4-TR	Serum	ELISA	BPRS: 31±9 SANS: 34±18	All medicated. CAED: 864 mg/d	All inpatients	NS	Age and sex matched from the same demographic
	Control	27	10/17	42.4 ± 10.3	67.78 ± 20.8								
Qi et al.,[81] (2009)	Sample	63	43/20	50.8 ± 6.8	359 ± 116	DSM-4	Serum	ELISA	PANSS: 59.8±13.1	All medicated. CAED:458±529 mg/d	All chronic schizophrenia inpatients	25.4±7.2	Age and gender matched from local community
	Control	50	29/21	49.6 ± 5.5	123 ± 50								
Rothermundt et al.,[82] (2001)	Sample	26	10/16	37.0±12.9	98±76	DSM-4	Serum	Luminometric assay	PANSS: 86.7±17.9	Drug free ≥6 months prior to commencement	All acute stage inpatients	9.96±10.35	Age and sex matched
	Control	26	10/16	37.0±12.9	34±17.5								
Rothermundt et al.,[83] (2004a)	Sample	21	17/4	32.5±13.0	65±31	DSM-4	Serum	Luminometric assay	PANSS: 97.7±25.6	Drug naïve (N=16), unmedicated ≥6 months (N=5)	All Inpatients. Acute episode inpatient (N=4)	NS	Age and sex matched from blood donation centre
	Control	21	17/4	32.2±11.8	38±8								
Rothermundt et al.,[84] (2004b)	Sample	98	56/42	42.1±11.1	73±32	ICD-10	Serum	Luminometric assay	PANSS: 82.5±17.1	Drug free ≥1 week prior to commencement	All chronic schizophrenia patients with primarily negative symptoms	NS.	Age and sex matched
	Control	98	56/42	42.1±11.1	44±15								
Rothermundt et al.,[85] (2007)	Sample	12	11/1	25.33±4.75	85±70	DSM-4 (SCID)	Serum	Luminometric assay	PANSS: 81±19.9	Drug naïve (N=9), Medicated (N=2)	All inpatients.	1.1 ± 1.3	Age and sex matched.
	Control	12	11/1	25.33±4.75	38±8								
Kim et al.,[86] (2007)	Sample	60	NS	37.0±3.5	140±84	DSM-4	Serum	Luminometric assay	PANSS: Total NS	Drug free (N=30) Medicated (N=30)	All inpatients.	15.0 ± 6.7	Age and sex matched.
	Control	30	13/17	37.0±3.5	76±18								
Šakić et al.,[87] (2016)	Sample	65	55/10	41.96±13.2	64.36±28.15	DSM-4-TR	Serum	ELISA	PANSS: 89.35±25.46	Drug naïve (N=12), Drug free ≥ 30 days (N=5), Medicated (N=48)	All inpatients.	1.7 ± 0.65	Age and sex matched
	Control	70	51/18	43.2±12.4	64.52±24.0								
Sarandol et al.,[88] (2007)	Sample	40	18/22	34.9±9.9	467±411	DSM-4	Serum	ELISA	SANS: 53.5±26.6, SAPS: 42.2± 21.3, BPRS: 42.2±21.3	Drug naïve (N=9), medication free ≥3 weeks prior to blood draw (N=31)	Inpatients (N=35) and outpatients (N=5)	6.73±6.3	Age and sex matched from hospital staff
	Control	35	17/18	33.5±9.2	235±152								
Schmitt et al.,[89] (2005)	Sample	41	24/17	63.3±7.0	132±43	DSM-4	Serum	Luminometric assay	SANS: 45.6±22.7, SAPS: 44.3±27.9, BPRS: 46.2±14.9	All medicated. CAED: 708±591.7	All inpatients with chronic schizophrenia	35.3±11.4	Age and sex matched
	Control	23	15/8	64.9±8	61±26								
Schroeter et al.,[90] (2003)	Sample	30	14/16	34.8±12.4	126.55±70.12	DSM-4 & ICD-10	Serum	Luminometric assay	BPRS: 43.5±12.6	Drug free (N=14), medicated (N=16) CAED: 363.1±248.8	All inpatients with chronic schizophrenia	8.9±8.8	Age and sex matched from hospital staff
	Control	15	8/7	34.2±5.6	112.8±31.8								
Schroeter et al.,[52] (2009)	Sample	20	9/11	34.6±12.7	73.4±72.1	DSM-4 & ICD-10	Serum	Luminometric assay	BPRS: 47.6±11.9	Drug free (N=5), medicated (N=15)	All inpatients	8.4±9.6	Age and sex matched from hospital
	Control	19	10/9	37.9±10.2	42.1±69.7								
Steiner et al.,[91] (2006)	Sample	12	7/5	24.0±7.0	90±30	DSM-4	Serum	Luminometric assay	PANSS: 87±15	Medicated (N=12)	All inpatients with first onset paranoid schizophrenia	1.75±0.9	Age and sex matched from cohort experiencing migraine
	Control	17	9/8	25.0±8.0	80±20								
Steiner et al.,[92] (2010)	Sample	26	17/9	34.7±11.3	72±38	DSM-4	Serum	ELISA	PANSS: 84.8±11.2	Medicated (N=15), medication free ≥6 weeks prior to enrolment (N=11)	All inpatients with acute onset schizophrenia	8±9	NS
	Control	32	20/12	34.4±10.8	52±18								
Uzbay et al.,[93] (2013)	Sample	18	11/7	37.4±3.0	7.81±10.6	DSM-4	Plasma	ELISA	PANSS: 87.17±3.13	All drug free ≥26 weeks	All inpatients: first episode inpatients (N=6)	9.83±2.37	NS
	Control	19	11/8	33.9±1.4	6.26±7.8								
Wiesmann et al.,[94] (1999)	Sample	20	8/12	35.7±10.7	165±138	DSM-4 & ICD-10	Plasma	Luminometric assay	PANSS: total NS	All medicated	All inpatients	8.3±1.1	Age and gender matched
	Control	20	NS	35.7±10.7	54±31								
Xiong et al.,[95] (2014)	Sample	278	170/108	34.2±10.5	20.02±9.95	DSM-4-TR	Serum	ELISA	PANSS: 70.6±15.8	Drug naïve (N= 84), medicated (N=194)	Commonest subtypes were paranoid (N=161) & residual (N=60)	1.8±2.1	Age, sex, and BMI matched
	Control	260	170/90	30.6±6.33	18.64±4.98								
Zhang et al.,[96] (2010)	Sample	162	99/63	40.1±8.3	445±164	DSM-4 (SCID)	Serum	ELISA	PANSS: 70.8	Drug naïve (N=80), medicated (N=82)	All inpatients. Early stage (N=80) and chronic, (N=82) disease courses	14.5±8.8	Recruited from local community
	Control	97	59/38	37.9±9.0	122±76								
HMGB1													
Kozłowska et al.,[45] (2021)	Sample	68	45/23	38.5±10.7	225.0±206.9	DSM-4 & ICD-10	Serum	ELISA	PANSS: 65.20±15.80, CDSS: 2.76±3.38	All medicated. CAED: 746.5±642.2	All outpatient with chronic, paranoid schizophrenia.	NS	Age and sex matched from the local community
	Control	29	19/10	37.6±10.6	116.0±83.3								
Mousa et al.,[46] (2021)	Sample	115	78/37	36.3±11.0	20.9±11.3	DSM-4-TR	Serum	ELISA	SANS: 73.1±14.7	All medicated. CAED: 761.0±267.1	55 partial responders to treatment, 60 non responders	NS	Recruited from local community
	Control	43	24/19	33.2±11.1	7.9±7.9								
Yilmaz et al.,[47] (2021)	Sample	59	40/19	38.0±7.7	2.23±0.52	DSM-5	Serum	ELISA	SANS: 19.3±7.9, BPRS: 13.5±7.8	All medicated	30 inpatients, 29 outpatients	10.6±6.0	Age and sex matched healthy controls
	Control	15	9/6	33.3±8.2	1.79±0.44								

This table depicts the patient characteristics, sample source, assays, medication and levels of DAMPs for each study listed. Age, age in years; BPRS, Brief Psychiatric Rating Scale; CAED, Chlorpromazine antipsychotic equivalent dose (mg/day); CDSS, Calagry Depression Scale for Schizophrenia; Control, healthy controls; DSM, Diagnostic and Statistics Manual of Mental Disorders; ELISA, enzyme linked immunosorbent assay; ICD, International Classification of Disease; Location, sample isolated from; NS, not stated; NSRS, Negative Symptom Rating Scale; PANSS, The Positive and Negative Symptom Scale; SANS, Scale for assessment of Negative Symptoms; SAPS, Scale for assessment of Positive Symptoms; SCID, Structured Clinical Interview for DSM; Sample, individuals diagnosed with schizophrenia; Sex M/F, number of males and females; TR, text revision; SD, standard deviation