



# A Scoping Review on Biological Factors Associated with Interpersonal Violence in Adults with Severe Mental Illness

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## Abstract

**Introduction:** Knowledge about the biological basis of violence in people with severe mental illness is needed to formulate strategies in the management of violence. The aim of this study was to identify and describe the biological factors associated with interpersonal violence in adults with severe mental illness.

**Methods:** This scoping review was written with reference to the Preferred Reporting Items for Systematic reviews and Meta-Analyses extension for Scoping Reviews (PRISMA-ScR) Checklist. The literature search was conducted in MEDLINE (via PubMed), PsycINFO, SciELO, ProQuest and Epistemonikos until October 2020. Primary and Secondary studies in English or Spanish were included without restrictions as to date of publication. The information charted during the process included: authors; publication year; country; type of research; study population; biological factors; outcomes and key findings.

**Results:** Twenty-eight articles were included after the selection process. The most widely-studied population was people with schizophrenia. The biological factors studied in the articles are categorized into six groups: Serotonin function, genes, hormones, neuroactive steroids, brain function and anatomy, and immune factors. Several studies showed a relationship between different biological factors and interpersonal violence in people with severe mental illness.

**Conclusion:** This scoping review describes current research, and provides evidence on a biological basis. Nevertheless, further studies are needed to carry out research into biological factors associated with interpersonal violence in people with severe mental illness.

## Keywords

Mental disorders (MeSH), Aggression, Violence, Biological factors

## Introduction

Aggressive behavior is a complex phenomenon, sustained throughout evolution in most species including humans [1].

Evidence shows a higher prevalence of serious crime among people with schizophrenia and increased rates of convictions for violence [2,3]. In addition, it has been found that people with severe mental illness had perpetrated higher rates of violence and there is an increased risk for homicide in individuals with psychosis compared with the general population [4,5].

Despite the prevalence of victimisation being higher than violence in people with severe mental illness, society has a negative, dangerous perception of people with mental illness and violence. Moreover, a study found that 5.3% of the estimated total social cost of violence was related to people with severe mental illness in England and Wales in 2015-16 [6-8].

There are different factors related to psychiatric in-patient aggression, such as being younger, male, being involved

in involuntary admissions, having a greater number of previous admissions, a diagnosis of schizophrenia, a history of violence, a history of self-destructive behavior and a history of substance abuse [9]. In addition, some modifiable risk factors are associated with violence in psychosis, such as hostile behavior, recent drug, substance or alcohol misuse, non-adherence to psychological therapies, poorer impulse control scores, and non-adherence with pharmacological treatment [10].

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With regard to biological basis, various studies suggest biological factors have an effect on people with severe mental illness and aggressive behavior. Several studies have reported an association between gene polymorphisms and violence in people with schizophrenia, such as the Catechol-O-methyltransferase (COMT) polymorphism, the Methylenetetrahydrofolate reductase (MTHFR) gene polymorphism or functional polymorphisms of the dopamine receptor D4 (DRD4) and monoamine oxidase A (MAO-A) genes. Li, et al. found a relationship between Th17-related cytokine levels and the severity of schizophrenia and aggressive behavior. In addition, some studies found differences in gray matter volume, cortical morphology, and hippocampal volume in people with schizophrenia and violence [11-19].

Notwithstanding the existence of several studies on this topic, no scoping review has been found related to the biological basis of people with severe mental illness and aggressive behavior.

## Rationale

The complexity of violence and its relationship with people with severe mental illness, its economic impact, the existence of evidence related to the role of biological factors in aggressive behavior and the absence of a scoping review on this topic calls for a study to provide knowledge on the biological basis of violence in this population that will help health practitioners to formulate strategies for the management of violence.

## Objective

The aim of this study was to identify and describe the biological factors associated with interpersonal violence in adults with severe mental illness.

## Methodology

### Study design and protocol registration

This study was written with reference to the Preferred Reporting Items for Systematic reviews and Meta-Analyses extension for Scoping Reviews (PRISMA-ScR) Checklist [20]. The protocol was registered with the Open Science Framework (<https://osf.io/pw3a9/>). This study did not require ethical approval as no patients or other participants were involved in this study.

### Identifying the research question

This scoping review was conducted to answer the following research question: What are the biological factors associated with interpersonal violence in people with severe mental illness described in the literature?

### Information sources and search

The literature search was conducted in the following databases: MEDLINE (via PubMed), PsycINFO, SciELO, ProQuest and Epistemonikos until October 2020. The systematic literature searches were conducted using a designed search strategy, and the search strategy used on Pubmed is given in [Supplementary File 1](#) as an example. The combinations of keywords and search terms were adapted in other databases with no restriction as to year of publication. Zotero was

used to import all studies and manage the references from the search.

### Study selection and screening process

**Eligibility criteria:** The studies had to consider biological factors in interpersonal violence in people with severe mental illness in order to be included and violence had to include physical or verbal aggression.

The outcomes/measures of interest were:

- Biological factor: Any biological determination or analysis.
- Interpersonal violence: Physical or verbal aggression.

The inclusion criteria for severe mental illness was adults with a diagnosis of severe mental illness or any condition included in severe mental illness [21]: Schizophrenic disorder, schizoaffective disorder, schizotypal disorder, persistent or induced delusional disorder, bipolar disorder, obsessive-compulsive disorder, major depressive episode with psychotic features, recurrent major depressive disorders, atypical psychosis or other non-organic psychoses (according to international classification systems: Diagnostic and Statistical Manual of Mental Disorders or International Classification of Diseases). No restrictions were placed on the setting.

This scoping review included quantitative studies (primary original research) and systematic reviews/meta-analyses of quantitative studies (secondary research). When quantitative studies were present in a systematic review/meta-analysis, the review was selected instead of the primary study. All studies had to be published in Spanish or English. No restrictions were applied as to date of publication. The following study design was excluded from the scoping review: Narrative reviews.

### Study screening, selection and data extraction process

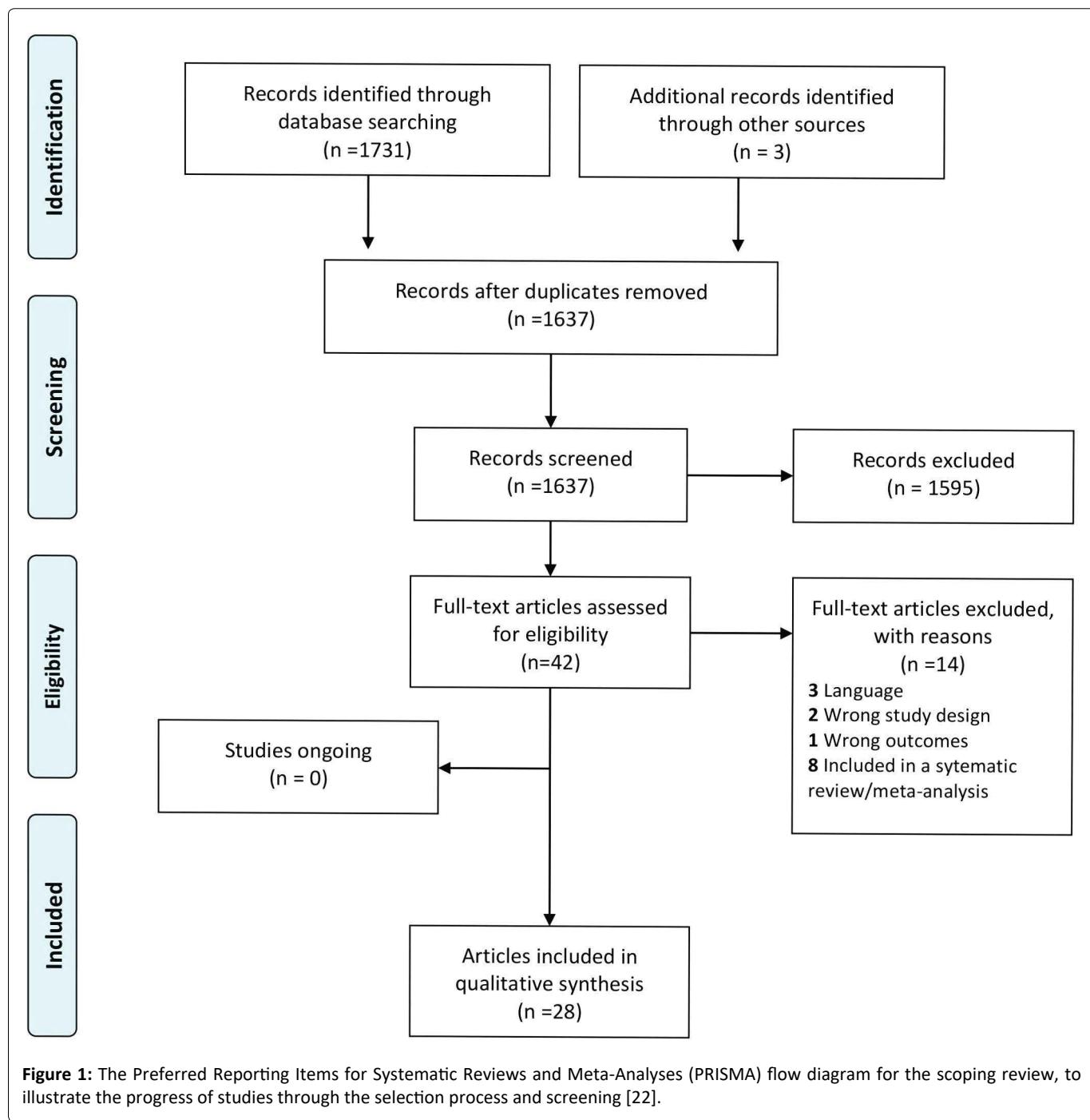
The titles and abstracts of studies retrieved using the search strategy were screened to identify studies that meet the inclusion criteria and full texts were assessed for final inclusion/exclusion. Additionally, the reference list of articles was reviewed to identify other relevant studies. All relevant data was included to answer the scoping review questions. The information charted during the process included: authors; publication year; country; type of research; study population; biological factor; outcomes and key findings. In accordance with scoping review methodology, the quality of individual studies was not assessed.

## Results

A total of 1734 articles were identified in the search, and 28 articles were included after the selection process ([Figure 1](#)). The selected studies were primary and secondary research from different states and the most widely studied population was people with schizophrenia [22].

### Biological factors associated with interpersonal violence

The summary of the main results of twenty-eight articles



**Figure 1:** The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram for the scoping review, to illustrate the progress of studies through the selection process and screening [22].

are presented in a descriptive table (Table 1). The biological factors studied in the articles are categorized into six groups: (1) Serotonin function, (2) Genes, (3) Hormones, (4) Neuroactive steroids, (5) Brain function and anatomy, and (6) Immune factors.

### Serotonin function

Maguire, et al. found no significant difference between aggressive and non-aggressive schizophrenic patients in the constant  $K_d$  or  $B_{max}$  for platelet [ $^3$ H] paroxetine binding. Nevertheless, Modai, et al. found differences for  $B_{max}$  of [ $^3$ H] paroxetine binding in the platelets of aggressive schizophrenic patients [23,24].

Moreover, Barkan, et al. showed differences in the  $V_{max}$

of [ $^3$ H] 5-HT to fresh lymphocytes and in the  $K_m$  values of the 5-HT to the transporter in currently aggressive patients with schizophrenia, and Chou, et al. found a significant association between aggressive behavior with serotonin transporter availability in the midbrain in bipolar disorder II patients [25,26].

### Genes

**Catechol-O-methyl transferase (COMT) gene polymorphism:** A meta-analysis (Bhakta, et al.) reported that the Met158 allele of the COMT gene was associated with higher risk for violence in schizophrenia. In addition, Singh, et al. showed that male patients with schizophrenia who carry the low activity Met allele of the Val158Met polymorphism of the

COMT gene had an elevated risk of violence [12,14].

**Brain-derived neurotrophic factor (BDNF) Val66Met functional gene polymorphism:** Chung, et al. and Guan, et al. found no significant difference in the genotype distribution or allelic frequency of the BDNF Val66Met polymorphism between the schizophrenic groups. Nonetheless, Spalletta, et al. observed that the BDNF Val66Met gene polymorphism is associated with a different level of aggressiveness in schizophrenic patients [27-29].

**D-amino acid oxidase (DAO) and D-amino acid oxidase activator (DAOA) gene polymorphisms:** Chung, et al. showed no significant differences in genotype distributions and allele frequencies of DAO and DAOA genes between groups [30].

**Methylenetetrahydrofolate reductase (MTHFR) gene polymorphism:** Dong, et al. suggested an association between the T-allele polymorphism of rs1801133 and the T-C haplotype of the MTHFR gene and susceptibility to aggressive behavior [13].

**Dopamine receptor D4 (DRD4) and monoamine oxidase A (MAO-A) genes polymorphisms:** Fresan, et al. found a significant association between patients with schizophrenia and aggressive behavior and the DRD4 gene, but no association between the MAO-A gene and aggressive behavior. However, there was a significant difference between the MAO-A/4R allele and verbal aggression [11].

**Serotonin gene polymorphisms:** Hong, et al. showed no significant difference in serotonin 1B Receptor (A-161T) gene polymorphism and Tsai, et al. found no significant difference in genotype or allele frequencies for serotonin 5-HT6 (C267T) polymorphism [31,32].

**Tryptophan hydroxylase 1 (TPH1) A218C polymorphism:** Kim, et al. found no significant association for TPH1 A218C polymorphism [33].

**The T-cell receptor beta variable chain (TRBV):** Li, et al. observed a significantly higher frequency of TRBV2 in the violent schizophrenia group [34].

## Hormones

Das, et al. found a statistically significant correlation between cortisol variability and aggression [35].

## Neuroactive steroids

Spalletta, et al. showed that increased aggressiveness was associated with increased 3 $\alpha$ ,5 $\alpha$ - tetrahydroprogesterone (3 $\alpha$ ,5 $\alpha$ -THP) plasma levels [36].

## Brain function and anatomy

Two systematic reviews (Fjellvang, et al. and Widmayer, et al.) found volume differences in some areas such as pre-frontal regions, temporal lobe, hippocampus, thalamus and cerebellum, lateral ventricles, amygdala, and putamen, and Tesli, et al. showed differences in hippocampal subfields and amygdala nuclei volumes in violent patients with schizophrenia [16,19,37]. In addition, Storverstre, et al. showed differences in cortical folding and cortical thickness in different cor-

tex areas in violent schizophrenia patients and Schoretsanitis, et al. found differences of gray matter (GM) volume in the left inferior frontal gyrus [17,18]. Moreover, Garcíá-Martí, et al. showed significant focal hyperactivations in patients with a greater association with violent behavior and Wong, et al. found a reduced [18F] fluorodeoxyglucose (FDG) uptake in the left anterior inferior temporal (LAIT) in violent patients [38,39].

## Inimmune factors

Li, et al. found that the Th17-related cytokine levels were related to the severity of schizophrenia and aggressive behavior and Zhang, et al. showed positive correlations between C-reactive protein (hsCRP) and interleukin (IL)-10 and aggression in patients with schizophrenia [15,40]. In addition, Das, et al. suggested that cytokines IFN-G and IL10 are both significantly associated with aggression and psychosis [41].

## Discussion

The Catechol-O-methyl transferase (COMT) gene polymorphism and differences in brain function and anatomy were the most widely studied factors. These biological factors were evaluated by secondary research (systematic reviews and meta-analyses), which are at the top of the evidence pyramid, and the evidence shows a relationship between these factors and interpersonal violence.

Few studies found an association between the dopamine receptor D4 (DRD4) and monoamine oxidase A (MAO-A) gene polymorphisms, methylenetetrahydrofolate reductase (MTHFR) gene polymorphism, T-cell receptor beta variable chain (TRBV), cortisol, 3 $\alpha$ ,5 $\alpha$ - tetrahydroprogesterone (3 $\alpha$ ,5 $\alpha$ -THP), Th17-related cytokines, C-reactive protein (hsCRP), interleukin (IL)-10 and aggressive behavior. On the other hand, the results on the brain-derived neurotrophic factor (BDNF) Val66Met functional gene polymorphism differ between studies and there is no evidence regarding D-amino acid oxidase (DAO) and D-amino acid oxidase activator (DAOA) gene polymorphisms, serotonin gene polymorphisms, tryptophan hydroxylase 1 (TPH1) A218C polymorphism and violent behavior. Not many studies have been found on these factors and all of them were primary studies, so it is still necessary to continue research in this area.

Despite the fact that the results derived from this scoping review are limited due to absence of evidence about some factors, the evidence shows the existence of an association between some biological factors and violent behavior in people with severe mental illness.

Regarding the limitations, as a scoping review, this study contributes to identifying biological factors in interpersonal violence in people with severe mental illness but does not assess the quality of the evidence. In addition, this study considered only studies published in English and Spanish, and it was carried out by one author. Notwithstanding, important data sources were searched and references of included studies were analysed to be included in this scoping review. It is important to consider the presence of primary study overlap in the included reviews and meta-analysis as a potential bias.

Nonetheless, this scoping review describes current research and provides information that could help researchers in future studies on this topic.

A better understanding of the biological factors could help in developing strategies for managing violence, so further studies are needed to investigate biological factors associated with interpersonal violence in people with severe mental illness.

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## Competing Interests

None declared.

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## Additional file 1:

### The search strategy used on Pubmed:

((("mental disorders"[MeSH Terms] OR ("mental"[All Fields] AND "disorders"[All Fields]) OR "mental disorders"[All Fields] OR ("severe"[All Fields] AND "mental"[All Fields] AND "disorder"[All Fields]) OR "severe mental disorder"[All Fields] OR ((("sever"[All Fields] OR "severe"[All Fields] OR "severed"[All Fields] OR "severely"[All Fields] OR "severer"[All Fields] OR "severes"[All Fields] OR "severing"[All Fields] OR "severities"[All Fields] OR "severity"[All Fields] OR "severs"[All Fields]) AND ("mental disorders"[MeSH Terms] OR ("mental"[All Fields] AND "disorders"[All Fields]) OR "mental disorders"[All Fields] OR ("mental"[All Fields] AND "illness"[All Fields]) OR "mental illness"[All Fields])) OR ("schizophrenia"[MeSH Terms] OR "schizophrenia"[All Fields] OR "schizophrenias"[All Fields] OR "schizophrenia s"[All Fields]) OR ("psychotic disorders"[MeSH Terms] OR ("psychotic"[All Fields] AND "disorders"[All Fields]) OR "psychotic disorders"[All Fields] OR "psychosis"[All Fields]) OR 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