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## Self-stigma in schizophrenia: a systematic review and meta-analysis of 40 studies from 25 high- and low-tomiddle income countries

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Article

Keywords: mental health, psychiatry, schizophrenia, psychotic disorders, depressive disorders, stigma

Posted Date: August 31st, 2022

DOI: https://doi.org/10.21203/rs.3.rs-1949952/v1

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## Abstract

In schizophrenia, it is currently thought that stigma experience is increased by psychotic and depressive symptomatology, exposure to stigma at the workplace, and that self-stigma levels vary across countries without knowing the factors explaining these variations. The aim of the present meta-analysis was to synthetize the data of observational studies comprehensively exploring multiple self-stigma dimensions and associated factors. A systematic literature search without language or time restrictions was conducted in Medline, Google Scholar and Web of Science for studies, last 09/2021. Eligible studies that included  $\geq$  80% of patients diagnosed with schizophrenia-spectrum disorders and used a validated scale measuring self-stigma dimensions were metaanalyzed using random-effects models, followed by subgroup and meta-regression analyses. Study registration: PROSPERO CRD42020185030. Across 40 studies (n = 7,717) from 25 countries (5 continents), with 20 studies conducted in high-income countries, published between 2007 and 2020 using two scales with total scores ranging 1-4. The mean estimate of perceived stigma was 2.76 [95% confidence interval (CI) = 2.60-2.94], experienced stigma 2.29 [95%CI = 2.18,2.41], alienation 2.40 [95%CI = 2.29,2.52], stereotype endorsement 2.06 [95%CI = 1.88,2.26], social withdrawal 2.28 [95%CI = 2.17,2.39] and stigma resistance: 2.53 [95%CI = 2.43,2.63]). Self-stigma levels did not reduce over time. Living outside urban areas, low income, singleness, unemployment, high antipsychotic dose and low functioning were associated with different stigma dimensions. Some stigma dimensions were lower in studies carried out in Europe compared to other regions. Most studies published since 2007 report that self-stigma is a particular concern for a specific subgroup of patients. This subgroup is characterized by singleness, unemployment, repeated psychiatric hospitalizations and is also probably more depressed, but data are imprecise to confirm this point. We identified important other missing factors that should be explored to improve the effectiveness of public policies and personalized interventions to reduce self-stigma. Importantly, classical illness severity indices (psychotic severity, age at illness onset, illness duration) and sociodemographic variables (age, sex and education) were not associated with self-stigma, moderating previous findings.

### Introduction

Self-stigma is the status loss and discrimination triggered by negative stereotypes[1]. The self-stigma associated with mental illness adds to the public health burden of mental illness itself by eroding individuals' social networks, self-esteem and social status, all of which contribute to unemployment, isolation, delayed treatment-seeking, treatment-refractory symptoms, prolonged illness course and avoidable hospitalizations [2]. Anti-stigma initiatives have been established to decrease stigmatizing attitudes in the society as a whole[3]. During the 2000s, a better understanding of the self-stigma or "internalized stigma" process -i.e. the internalization of public stigma [4]- has shifted the attention from public stigma to the subjective experience of stigmatized people. People with schizophrenia may report perceived stigma (thinking or being afraid of being the target of public stigma) or experienced/"objective" self-stigma. Experienced stigma has emotional (alienation /shame), cognitive (stereotype endorsement) and behavioural (social withdrawal) consequences[2]. In reaction to self-stigma, "stigma resistance", is defined as the ability to challenge or deflect self-stigmatizing beliefs[5].

Several individual and illness characteristics have been identified as factors influencing self-stigmatization[6]. A systematic review carried out almost 10 years ago reported weighted percentage of approximately 49.2% of people with schizophrenia experiencing AL and 26.8% SE[7]. This systematic review also reported that positive symptoms, depression and general psychopathology were "associated with stigma in the majority of cases", however we lack quantitative analyses to definitely conclude this [7]. The authors also reported "ambiguous associations" with illness duration, negative symptoms, treatment compliance and social functioning[7]. Labour force has been associated

with lower self-esteem in a recent large-scale cohort of outpatients with schizophrenia[8], which may play a role in stigma. We need to know if other factors, like the age at illness onset and antipsychotic treatments, may play a role in stigma experience. Stigma resistance has been shown to be associated with advanced stages of recovery in schizophrenia[5], but has been inconsistently associated with sociodemographic variables (age, sex, educational level, employment, marital status, income, and source of income)[5].

In summary, while self-stigma dimensions have been conceptualized fairly well in schizophrenia, to our knowledge, a quantitative synthesis of the data has not been conducted for a decade. Our objective was to synthetize in a quantitative meta-analysis the mean estimates of self-stigma dimensions and to analyse sociodemographic and illness-related associated factors.

## Methods

## Literature search strategy

This meta-analysis was conducted following the Preferred Reporting Items for Systematic reviews and Meta-Analysis guidelines [9]. Systematic bibliographic searches were carried out according to the Cochrane methodology. This project was registered in PROSPERO (reference number CRD42020185030).

The search paradigm was based on the Mesh terms of the Medline® database and adapted for Google Scholar® and Web of Science®: ("schizophrenia" OR "schizoaffective disorder" OR "psychotic disorders") AND ("stigma" OR "stigmatization"). The last search was carried out on September 30th, 2021. The reference lists of relevant reviews and articles were manually searched for additional eligible articles. If needed, the corresponding authors were asked to provide additional data not included in the original publications and any unpublished results.

# Eligibility

The inclusion criteria were as follows: 1. Any language and date of publication; 2. Original research papers;  $3. \ge 80\%$  of patients diagnosed with schizophrenia-spectrum disorders (schizophrenia, schizoaffective disorder, schizophreniform disorder); 4. Use of a validate scale that measures self-stigma and/or its domains.

The exclusion criteria were: use of non-validated scales (e.g. questionnaire created for the purpose of the study) or validated scales used in three studies or less, absence of results separately for participants with schizophrenia and other mental disorders, or crude scores reported without dividing these scores by the number of items.

MV and MJ carried out the selection of included studies. In case of a non-consensus for the inclusion of a study, a third author (GF) made the final decision.

## Self-stigma dimensions and associated factors

The following variables were extracted into a pre-defined form:

- Stigma scores (continuous): Perceived stigma, Experienced stigma, Alienation, Stereotype Endorsement, Social Withdrawal, Stigma Resistance scores
- Sociodemographic factors (continuous): age, percentage of males, percentage of participants with high education level, percentage of single / unemployed / White or Caucasian / African-American / Black / Latino / Asian / Urban / Living alone / low-income participants;

- Illness characteristics (continuous): mean age at illness onset (years), mean illness duration (years), mean duration of untreated psychosis (years), percentage of patients with lifetime psychiatric hospitalizations, percentage of participants with schizoaffective disorder, psychotic symptomatology measured by the Positive symptoms (measured with the Positive and Negative Syndrome Scale for schizophrenia (PANSS)[10] positive factor), Negative symptoms (PANSS negative factor), Total psychotic symptoms (PANSS total score), depression (Calgary score)[11], insight into illness (Birchwood Insight Scale score)[12], Lifetime number of psychiatric hospitalizations, percentage of patients with tobacco/alcohol/cannabis/substance use disorder, mean antipsychotic daily dose (calculated in chlorpromazine equivalents[13], continuous), percentage of patients treated with second-generation or first-generation antipsychotics, Global Assessment of Functioning (GAF)[14] score.
- Study characteristics (binary): Regions: Asia vs other regions, Europe vs. other regions, High income country vs Lower to middle income countries as defined by the World Bank classification[15], Small sample size (< 100) vs. large sample size (>/=100), Multicentric vs. monocentric recruitment, Outpatient vs. mixed out- and/or inpatient recruitment), study published before 2016 (median year) vs. ≥2016.

Two researchers (MV and MJ) extracted data from the included studies in a systematic manner using a predesigned extraction form, which was based on the Joanna Briggs Institute Data Extraction Form for Prevalence and Incidence Studies[16]. Additional items relevant to the current study were also added. GF examined each discrepancy in data extraction to reach consensus.

## **Quality assessment**

Study quality analysis was performed using the NIH Study Quality Assessment Tools of case–control studies[17]. This tool was chosen to address the limits of the Newcastle-Ottawa scale[18].

# Statistical analyses

Using the inverse-variance weighting method, a random-effects model was used to calculate the pooled estimate of each self-stigma dimension and its 95% confidence interval (95% CI) [19] [20]. Heterogeneity between studies was quantified with the I<sup>2</sup> statistic[21]. Q and I<sup>2</sup> were calculated to assess heterogeneity across all studies and within subaroups, with  $l^2 \ge 50\%$  indicating significant heterogeneity[22]. Sensitivity analyses were conducted using the leave-one-out method[23]. Subgroup analyses for binary variables (all variables) and univariate meta-regression analyses for continuous variables were carried out when they were reported in  $\geq$  4 studies. All binary variables were explored, as well as the following continuous variables: Mean sample age, percentage of males, percentage of highly educated participants, percentage of unemployed participants, percentage of participants living in an urban area, percentage of low-income participants, percentage of single participants, lifetime number of psychiatric hospitalizations, age at illness onset, illness duration, total psychotic symptoms (PANSS total score), positive symptoms (measured with PANSS[10] positive factor), negative symptoms (PANSS negative factor), daily antipsychotic dose (calculated by the chlorpromazine equivalent method), functioning measured by the Global Assessment of Functioning score (GAF)[14]). The other factors were reported in < 4 studies and were therefore not analysed. Publication bias was assessed graphically with a funnel plot and statistically with Egger's test when  $\geq 10$ studies were included in the meta-analysis[24]. All analyses and graphs were carried out using R software (version 3.1.1; R Foundation, Vienna, Austria) with the meta package.

## Results

# **Study Characteristics**

Overall, 40 studies, published 2017–2020, exploring self-stigma dimensions in schizophrenia (n = 7,717 across 25 countries, 16 in Asia[4, 25–36], 13 in Europe[37–49], three in Latin-America[50], three in Middle-Eastern (Turkey)[51–53], two in Africa[54, 55], one in North-America (US)[56], one in Indonesia[57] and one in 20 European countries[58]) were included in the random-effects meta-analysis (Flow chart **Fig. 1**). The characteristics of the included studies are presented in Table 1 and study quality in **Supplementary Table 2**. Twenty studies (50.0%) were carried out in high-income countries. Altogether, 36 studies (90.0%) used different versions (10-29 items) of the Internalized Stigma of Mental Illness (ISMI)[2], with items ranging from a score of 1-4. The remaining four studies (10.0%) used the 12-item Perceived Devaluation and Discrimination toward mental illness scale (PDD)[59], with items ranging from a score of 1-4.

| First author               | Publication<br>Year | Country           | Ν    | Stigma<br>Scale | Age (mean),<br>years | SD    | Percentage of men |
|----------------------------|---------------------|-------------------|------|-----------------|----------------------|-------|-------------------|
| Vauth                      | 2007                | Switzerland       | 172  | PDD12           | 39.6                 | 11    | 60.5              |
| Staring                    | 2009                | Netherlands       | 114  | PDD12           | 38.3                 | 11.5  | 71                |
| Brohan                     | 2010                | 20<br>countries*  | 1229 | ISMI24          | 39.8                 | 10.7  | 52.6              |
| Sibitz                     | 2011                | Austria           | 157  | ISMI24          | 37.3                 | 11.9  | 54.5              |
| Lu                         | 2012                | China             | 92   | ISMI24          | 26.1                 | 7.5   | 58.7              |
| Ow                         | 2012                | Singapore         | 80   | PDD12           | 43.4                 | 10.6  | 52.5              |
| Mosanya                    | 2013                | Nigeria           | 256  | ISMI24          | 39.5                 | 10.6  | 52                |
| Sarisoy                    | 2013                | Turkey            | 109  | ISMI29          | 35.48                | 10.56 | 47.4              |
| Schrank                    | 2013                | Austria           | 284  | ISMI24          | 39.9                 | 12.6  | 58.1              |
| Campellone                 | 2014                | US                | 51   | ISMI24          | 45.92                | 10.6  | 52.9              |
| Hasson-Ohayon              | 2014                | Israel            | 80   | ISMI29          | 44                   | 11.3  | 54                |
| Bouvet                     | 2015                | France            | 62   | ISMI29          | 38.71                | 0.43  | 75                |
| Horsselenberg              | 2016                | Netherlands       | 102  | ISMI29          | 39.1                 | 11.3  | 75.5              |
| Lien                       | 2016                | Taiwan            | 170  | ISMI24          | 44.4                 | 10.1  | 55                |
| Singh                      | 2016                | India             | 100  | ISMI24          | 36.8                 | 12.1  | 54                |
| Vidovic                    | 2016                | Croatia           | 149  | ISMI29          | NR                   | NR    | 71.8              |
| Wang                       | 2016                | China             | 146  | PDD12           | NR                   | NR    | 47.3              |
| Grover                     | 2017                | India             | 707  | ISMI24          | 33.79                | 10.73 | 57.3              |
| Hsiao                      | 2017                | Taiwan            | 111  | ISMI24          | 45.59                | 10.06 | 65.8              |
| Li                         | 2017                | China             | 384  | ISMI29          | 39.96                | 7.69  | 51.3              |
| Picco                      | 2017                | Singapore         | 74   | ISMI24          | 43                   | 10.4  | 51.4              |
| Feldhaus                   | 2018                | Germany           | 81   | ISMI29          | 38.35                | 13    | 54.3              |
| Kondratova                 | 2018                | Czech<br>Republic | 133  | ISMI10          | 42.3                 | 11    | 52.6              |
| Morgades-bamba             | 2018                | Spain             | 216  | ISMI13          | 43.93                | 9.28  | 71.76             |
| Caqueo-Urizar<br>(Bolivia) | 2019                | Bolivia           | 83   | ISMI29          | 33.7                 | 11    | 75.9              |
| Caqueo-Urizar<br>(Chili)   | 2019                | Chili             | 85   | ISMI29          | 37.9                 | 15.3  | 68.2              |

Table 1

PDD: Perceived Devaluation and Discrimination toward mental illness scale. ISMI: Internalized Stigma of Mental Illness (ISMI). The number is the number of items. E.g. ISMI29: 29 items.

| First author            | Publication<br>Year | Country        | Ν   | Stigma<br>Scale | Age (mean),<br>years | SD     | Percentage of men |
|-------------------------|---------------------|----------------|-----|-----------------|----------------------|--------|-------------------|
|                         |                     |                |     |                 |                      |        |                   |
|                         |                     |                |     |                 |                      |        |                   |
| Caqueo-Urizar<br>(Peru) | 2019                | Peru           | 85  | ISMI29          | 35.2                 | 10.3   | 50.5              |
| Grover (group 1)        | 2019                | India          | 34  | ISMI29          | 28.61                | 9.08   | 64.7              |
| Grover (group 2)        | 2019                | India          | 56  | ISMI29          | 36.75                | 9.55   | 44.6              |
| Hofer                   | 2019                | Austria        | 54  | ISMI24          | 43.9                 | 10.5   | 50                |
| Lim                     | 2019                | Singapore      | 66  | ISMI10          | 40.29                | 10.552 | 45.5              |
| Morgades-bamba          | 2019                | Spain          | 167 | ISMI13          | 44.38                | 9.69   | 73.6              |
| Park                    | 2019                | South<br>Korea | 116 | ISMI29          | 41.08                | 9.11   | 65.5              |
| Tanriverdi              | 2019                | Turkey         | 46  | ISMI29          | NR                   | NR     | NR                |
| Amore                   | 2020                | Italy          | 921 | ISMI29          | 40.2                 | 10.7   | 69.6              |
| Fadipe                  | 2020                | Nigeria        | 370 | ISMI29          | NR                   | NR     | 48.9              |
| Komatsu                 | 2020                | Japan          | 127 | ISMI24          | 46.5                 | 13.8   | 49.6              |
| Li                      | 2020                | Hong Kong      | 48  | ISMI29          | NR                   | NR     | NR                |
| Pribadi                 | 2020                | Indonesia      | 300 | ISMI29          | 37.1                 | 10.7   | 61.3              |
| Singla                  | 2020                | India          | 100 | ISMI29          | 37.1                 | 12.1   | 65                |
|                         |                     |                |     |                 |                      |        |                   |

PDD: Perceived Devaluation and Discrimination toward mental illness scale. ISMI: Internalized Stigma of Mental Illness (ISMI). The number is the number of items. E.g. ISMI29: 29 items.

## Self-stigma dimensions' score estimates

The forest plots of the mean scores for the different self-stigma dimensions are presented in Fig. 2A-F. The mean estimate of perceived stigma was 2.76 [95%CI = 2.60,2.94], experienced stigma: 2.29 [95%CI = 2.18,2.41], alienation: 2.40 [95%CI = 2.29,2.52], stereotype endorsement: 2.06 [95%CI = 1.88,2.26], social withdrawal: 2.28 [95%CI = 2.17,2.39], and stigma resistance: SR 2.53 [95%CI = 2.43,2.63]).

# Source of heterogeneity

All estimates were associated with high heterogeneity (I<sup>2</sup> > 96% for all self-stigma dimensions, **Supplementary Fig. 1**). The leave-one-out method did not identify a specific study that was responsible for heterogeneity (**Supplementary Table 3**).

The significant factors associated with self-stigma dimensions are presented in Table 2. Higher Experienced Stigma and Social Withdrawal were associated with the same factors: higher daily antipsychotic dose (B = 0.0017 [95%Cl = 0.0009, 0.0024], p < 0.0001 and B=-0.0058[95%Cl=-0.0104, -0.0012], p = 0.0135 respectively) and lower functioning (B

= 0.017[95%Cl = 0.0009,0.0026], p < 0.001 and B=-0.0079[95%Cl=-0.0127, -0.0030], p = 0.0015, respectively). Higher Alienation and Stereotype Endorsement were reported in samples with lower percentage of participants living in urban areas (B=-0.0026[95%Cl=-0.0049, -0.0004], p = 0.0216 and B=-0.0057[95%Cl=-0.0107, -0.0008], p = 0.0226) and lower percentage of low-income participants (B=-0.0033[95%Cl=-0.0066, -0.0001], p = 0.0465 and B=-0.0046[95%Cl=-0.0087, -0.0005], p = 0.0278). Higher Perceived Stigma and lower Alienation were also reported in samples with higher percentage of single participants (B = 0.0116[95%Cl=-0.0057, 0.0176], p = 0.0001, B=-0.0030[95%Cl=-0.0054, -0.0006], p = 0.0147) while higher Perceived Stigma was associated with higher percentage of unemployed participants (B = 0.0034[95%Cl = 0.0017, 0.0051], p = 0.0001) and higher Stereotype Endorsement with higher lifetime number of psychiatric hospitalizations (B = 0.189[95%Cl = 0.0833, 0.2947], p = 0.0005).

|   | Factors associated with self-stigma dimensions: metaregression analyses |                     |                     |                           |                      |                      |  |  |  |
|---|---|---------------------|---------------------|---------------------------|----------------------|----------------------|--|--|--|
| Factors   | Perceived<br>stigma   | Experienced stigma  | Alienation          | Stereotype<br>endorsement | Social<br>withdrawal | Stigma<br>resistance |  |  |  |
| Global mean<br>estimate [95%<br>confidence<br>interval]       | 2.76[2.60,2.94]   | 2.29<br>[2.18,2.41] | 2.40<br>[2.29,2.52] | 2.06<br>[1.88,2.26]       | 2.28<br>[2.17,2.39]  | 2.53[2.43,2.63]      |  |  |  |
| Heterogeneity<br>(I <sup>2</sup> )                            | 95%   | 95%                 | 96%                 | 98%                       | 94%                  | 96%                  |  |  |  |
| Moderators  |   |                     |                     |                           |                      |                      |  |  |  |
| Mean sample<br>age  | ns  | ns                  | ns                  | ns                        | ns                   | ns                   |  |  |  |
| Percentage of males   | ns  | ns                  | ns                  | ns                        | ns                   | ns                   |  |  |  |
| Percentage of<br>highly educated<br>participants              | Insufficient<br>data  | ns                  | ns                  | ns                        | ns                   | ns                   |  |  |  |
| Percentage of<br>unemployed<br>participants                   | 0.0034***   | ns                  | ns                  | ns                        | ns                   | ns                   |  |  |  |
| Percentage of<br>participants<br>living in an<br>urban area   | Insufficient<br>data  | ns                  | -0.0026*            | -0.0057*                  | ns                   | ns                   |  |  |  |
| Percentage of<br>low-income<br>participants                   | Insufficient<br>data  | ns                  | -0.0033*            | -0.0046*                  | ns                   | 0.0027***            |  |  |  |
| Percentage of<br>single<br>participants                       | 0.0116***   | ns                  | -0.0030*            | ns                        | ns                   | ns                   |  |  |  |
| Lifetime<br>number of<br>psychiatric<br>hospitalizations      | Insufficient<br>data  | ns                  | ns                  | 0.189***                  | ns                   | ns                   |  |  |  |
| Age at illness<br>onset                                       | Insufficient<br>data  | ns                  | ns                  | ns                        | ns                   | ns                   |  |  |  |
| Illness duration  | Insufficient<br>data  | ns                  | ns                  | ns                        | ns                   | 0.0151*              |  |  |  |
| Percentage of<br>patients with<br>schizoaffective<br>disorder | Insufficient<br>data  | ns                  | ns                  | ns                        | ns                   | ns                   |  |  |  |

Table 2 actors associated with self-stigma dimensions: metaregression analyses

Only significant associations (p < 0.05) are presented. \* p < 0.05. \*\*p < 0.01. \*\*\*p < 0.001. ns: non-significant(p  $\ge$  0.05). N: number of studies reporting the outcome (the first number is for the four first stigma dimensions, which are always reported concomitantly in the results, the second one is for stigma resistance which may be reported separately and more frequently). Factors associated with perceived stigma were not explored due to the small number of studies (n = 6).

| Factors   | Perceived<br>stigma  | Experienced stigma | Alienation | Stereotype<br>endorsement | Social<br>withdrawal | Stigma<br>resistance |
|---|----------------------|--------------------|------------|---------------------------|----------------------|----------------------|
| Positive<br>symptoms  | Insufficient<br>data | ns                 | ns         | ns                        | ns                   | 0.0500*              |
| Negative<br>symptoms  | Insufficient<br>data | ns                 | ns         | ns                        | ns                   | ns                   |
| Total psychotic<br>symptoms   | Insufficient<br>data | ns                 | ns         | ns                        | ns                   | ns                   |
| Daily<br>antipsychotic<br>dose  | Insufficient<br>data | 0.0017***          | ns         | ns                        | 0.017**              | ns                   |
| Functioning   | Insufficient<br>data | -0.0058*           | ns         | ns                        | -0.0079**            | ns                   |
| Only significant associations ( $p < 0.05$ ) are presented. * $p < 0.05$ . ** $p < 0.01$ . *** $p < 0.001$ . ns: non-significant( $p \ge 0.05$ ). N: number of studies reporting the outcome (the first number is for the four first stigma dimensions, which |                      |                    |            |                           |                      |                      |

Only significant associations (p < 0.05) are presented. \* p < 0.05. \*\*p < 0.01. \*\*\*p < 0.001. ns: non-significant( $p \ge 0.05$ ). N: number of studies reporting the outcome (the first number is for the four first stigma dimensions, which are always reported concomitantly in the results, the second one is for stigma resistance which may be reported separately and more frequently). Factors associated with perceived stigma were not explored due to the small number of studies (n = 6).

Experienced Stigma, Stereotype Endorsement and Social Withdrawal scores were significantly lower in studies conducted in Europe compared to other regions. We found no other significant association (all p > 0.05). Subgroup analyses were not carried out for Perceived Stigma due to insufficient number of studies (n = 6).

# **Publication bias**

The funnel plots are presented in **Supplementary Fig. 2**. The visual examination and Egger's test[60] did not suggest a publication bias (all Egger's tests p > 0.05) except for Social Withdrawal (Egger's test = 0.0296).

## Discussion

This work adds important insight to a previous comprehensive systematic review published on self-stigma in schizophrenia in 2013[7]. First, we have reported for the first time quantitatively the mean self-stigma scores and its different dimensions that can be used to inform future evaluations of self-stigma in schizophrenia. For example, the participants in the meta-analyzed studies reported lower Stereotype Endorsement scores (mean 2.06) and higher Alienation scores (mean 2.40), suggesting that the emotional dimension of Alienation of self-stigma in schizophrenia is more marked than the cognitive dimension of Stereotype Endorsement. Exploring the role of depression seems therefore a priority, as depression may impact both emotional and cognitive processes of self-stigma or be influenced negatively by self-stigma, but we lacked sufficient data to confirm that depressed patients reported higher self-stigma levels. The high heterogeneity ( $\geq$  95% for all dimensions) also suggest that stigma is not a uniform phenomenon concerning all patients with schizophrenia to a similar degree.

We found that the origin of study participants in urban areas and low-income countries was associated with the emotional dimension of alienation and the cognitive dimension of stereotype endorsement of self-stigma. This result suggests that these parameters may influence the emotional and cognitive dimensions of stigma more than the objective/observable aspects and consequences of stigma. In HIV studies, stigma has been repeatedly shown to be lower in urban areas, due to better knowledge about the illness[61–63], and the same phenomenon has been shown in schizophrenia, for example in India [64] China [65] and Ethiopia[66, 67]. The percentage of participants

living in urban vs. rural areas was reported in 12 studies for this analysis, which makes our result robust, while the percentage of participants living in low-income countries was only reported in four studies. However, only six studies included a mix of participants living in urban and rural areas. These studies were carried out only in Turkey (one study[51]) and India (five studies[32, 33, 34, 34, 53]), which limits the generalizability of this result. The association between lower self-stigma and lower income may also in part be due to the fact that in lower income areas and strata the expectation of functioning and success is lower and therefore the delta smaller that may affect self-stigma.

Our results indicate that the participants of European studies reported lower rates of stigma compared to other regions, suggesting that the region of the study may also play a role. Most of these studies were carried out in Western Europe. Contrary to what could have been expected, our results suggest that the lower self-stigma level is not explained by the high-income country status alone. It may be hypothesized that these countries may have disseminated public health policies to lower the public stigma of mental illness, or that social interventions to protect people with mental disabilities may reduce self-stigma experience in those countries[8]. It should be noted that we did not find an obvious decrease in the level of stigma over time despite the implementation of public and individual interventions to reduce stigma over 20 years of high-profile national campaigns (e.g., Time to Change in England; Beyond Blue in Australia, Schizophrénie, bonheur et Cie in France, StigmaFree in the US)[68]. However, the oldest eligible study was published in 2007, and public online interventions are relatively recent. A recent systematic review of interventions carried out in low-to-middle-income countries has highlighted that most of interventions aimed at decreasing stigma were disseminated during the last 5 years[69]. As two recent meta-analyses have confirmed their effectiveness, web-based interventions should be promoted in countries with high internet access[70, 71]. The evidence for the effectiveness of interventions aiming to reduce personal stigma was recently synthetized in a meta-analysis of 21 randomized clinical trials [72]. The results were in favour of group self-assertiveness training and psychoeducation programs but with a low level of confidence in the guality of the trials[72].

We found that single patients with schizophrenia reported higher Perceived Stigma and lower Alienation scores compared to non-single patient. These results were provided by studies including middle-aged participants, and age and sex were not associated with personal stigma. However, this discrepancy should be interpreted with caveats, as the studies assessing Perceived Stigma (using the PDD scale) were not the same that those assessing Alienation (using the ISMI scale), and were therefore not carried out in the same countries nor at the same time. Future studies should therefore administer both PDD and ISMI scales to explore the relationships between Perceived Stigma and other stigma dimensions. Although requiring replication, these results suggest that promoting intimate relationships may help people with schizophrenia coping with the negative emotions associated with stigma but that an intimate relationship may also play a role in the fear of stigma. Including spouses in interventions targeting stigma may therefore improve their effectiveness. The fear of stigma was also higher in unemployed patients, which suggests that promoting work rehabilitation may improve Perceived Stigma in schizophrenia[73].

We further found that a higher number of previous psychiatric hospitalizations was associated with higher Stereotype Endorsement. While the mental healthcare system should help patients dealing with self-stigma, repeated full-time hospitalization may favour the internalization of public stigma by the patients. The studies reporting this association were carried out in miscellaneous countries (Israel [53], Taiwan[4], China[30], Germany [45] and Indonesia [57]), suggesting that this phenomenon was not associated with one particular healthcare system. The caregivers working in public mental health departments may have a pessimistic view of the schizophrenia prognosis by a selection bias. The patients with the more severe form of schizophrenia are more often hospitalized, leading to a vicious circle. It has been shown for example that Japanese nurses working in mental health departments reported high levels of stigma about schizophrenia[74]. Another explanation is that the psychiatric hospitalization itself is a source of stigmatization [75]. That's why specific anti-stigma interventions have been developed for professionals and health students and with positive results[76–79]. Promoting anti-stigma interventions in healthcare professionals working in inpatient departments should be therefore recommended as part of routine care[80].

Moreover, we found that lower functioning and higher antipsychotic daily dose were associated with higher Experienced Stigma and Social Withdrawal, i.e. the external consequences of stigma. We may hypothesize that both poorer functioning and daily antipsychotic dose may result in more visible functional handicap that may result in more objective/external consequences of stigma. However these results should be interpreted with caution, as functioning was only explored in two Indian studies published by the same team [33, 81] and one study carried out in China[30]. Antipsychotic dose was calculated in two Indian studies [33, 81] and one German study[45]. Therefore, these results need replication to be confirmed.

Finally, the important aspect of Stigma Resistance has received insufficient attention. In this meta-analysis living in a low-income country reduced Stigma Resistance, while longer illness duration and more positive symptoms were associated with increased Stigma Resistance. Living in a low-income country may reduce access to internal and external resources to deal with the illness burden, including self-stigma. Conversely, having had more time to come to terms with the illness and "surviving" it, not being pulled into the cycle of self-stigma, depression and suicidality[82], as well as having remaining symptoms that may be related to impaired illness insight (that was insufficient captured in the meta-analyzable studies) may be protective. In any case, the multifaceted topic of resilience requires more research in severe mental disorders, including schizophrenia. A recent meta-analysis on resilience in schizophrenia identified that overall resilience was related to lower levels of self-stigma and higher self-estem[83].

The results of this meta-analysis need to be interpreted within its limitations. Altogether, we have identified a strikingly low number of sociodemographic and illness factors explaining the heterogeneity identified in self-stigma and its dimensions. This finding suggests that most studies failed to assess in detail the factors influencing selfstigma. The absence of sufficient data to explore the role of depression is a major limitation in the field. Major depression is identified in about one third of people with schizophrenia[84, 85] and predicts multiple poor outcomes, including impaired guality of life[86]. It is highly probable that depression would play a role in at least the emotional and cognitive dimensions of self-stigma[41]. Better illness insight and better cognition have also been associated with a greater likelihood of depression and lower quality of life in schizophrenia[87–89] and may also play a role in self-stigma[41]. However, these factors were insufficiently reported to be included in our analyses. The list of insufficiently explored factors is extremely long but includes for example: immigrant status, history of incarceration or homelessness, parenting status, parental/caregiver insight and stigma, self-perception of clinical severity, perceived and observed cognitive dysfunction, attributions of personal responsibility, shame proneness, avoidant or self-defeating personality traits, attachment style, self-compassion, all different quality of life dimensions, metacognitive abilities, social network/functioning/power, psychological flexibility, fear of negative evaluation, coping strategies, treatment alliance and adherence, mental health and reading/writing literacy, and cultural factors (e.g. attributing mental illness to supernatural causes and loss of face in Eastern countries).

### Conclusion

This comprehensive meta-analysis found that most studies published since 2007 report a moderate perceived stigma and a mild overall self-stigma level in patients with schizophrenia, but with high heterogeneity across

studies, suggesting that the level of self-stigma varies across specific subgroups of patients. The subgroup with the highest risk of self-stigma is characterized by singleness, unemployment, repeated psychiatric hospitalizations and is also probably more depressed, but we lack data to confirm this point. We identified important other missing factors that should be explored to improve the understanding of moderators of self-stigma and, thus, the effectiveness of more targeted public and personalized interventions. An important message is that classical illness severity indices (e.g., psychotic severity, age at illness onset, illness duration) and sociodemographic variables (age, sex and education) were not significantly associated with stigma, moderating previous findings. However, since study of origin and other patient population and study design features can influence the findings, clearly, more studies are needed to better understand the frequency, severity and determinants of self-stigma in patients with schizophrenia.

### Declarations

#### Funding

This work was funded by the FondaMental Foundation, Assistance Publique – Hôpitaux Marseille (APHM) and Aix-Marseille University (AMU).

#### **Author Contributions**

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#### **Declaration of interests**

CU Correll has been a consultant and/or advisor to or has received honoraria from: AbbVie, Acadia, Alkermes, Allergan, Angelini, Aristo, Boehringer-Ingelheim, Cardio Diagnostics, Cerevel, CNX Therapeutics, Compass Pathways, Darnitsa, Gedeon Richter, Hikma, Holmusk, IntraCellular Therapies, Janssen/J&J, Karuna, LB Pharma, Lundbeck, MedAvante-ProPhase, MedInCell, Merck, Mindpax, Mitsubishi Tanabe Pharma, Mylan, Neurocrine, Newron, Noven, Otsuka, Pharmabrain, PPD Biotech, Recordati, Relmada, Reviva, Rovi, Seqirus, SK Life Science, Sunovion, Sun Pharma, Supernus, Takeda, Teva, and Viatris. He provided expert testimony for Janssen and Otsuka. He served on a Data Safety Monitoring Board for Lundbeck, Relmada, Reviva, Rovi, Supernus, and Teva. He has received grant support from Janssen and Takeda. He received royalties from UpToDate and is also a stock option holder of Cardio Diagnostics, Mindpax, LB Pharma and Quantic. Marco Solmi received honoraria/has been a consultant for Angelini, Lundbeck, Otsuka. All other authors declare no competing interests.

#### Data sharing

This study does not contain individual original data.

ACKNOWLEDGMENTS: We thank the following authors for answering our inquiries about their work: H. Komatsu, T.Feldhaus, R.Lencer, B.Aukst-Margetic, Yli.Wong, Y.Mizuno, H.Uchida, Abp.Staring, M. Van Der Gaag, M. Van Den Berge, H.J. Duivenvoorden, C.L. Mulder, C.Brain, Rc.Kessler, S.Galderisi, C.Hippman, Jc.Austin, P. Yanos, D.Kamarodova, J.Dubreucq, W.Gaebel, Wt. Chieng, E.Abdisa, D.Quinn, S. De Jong, O.Esan, Aa. Hasan, A.Lasalvia, M.Sajatovic, N.Thomas, Fhn.Chio, Wws.Mak, V.Vass, L.Violeau, J.Harangozo, B.Reneses, A.Üçok, Ac.Watson, Yw.Lau.

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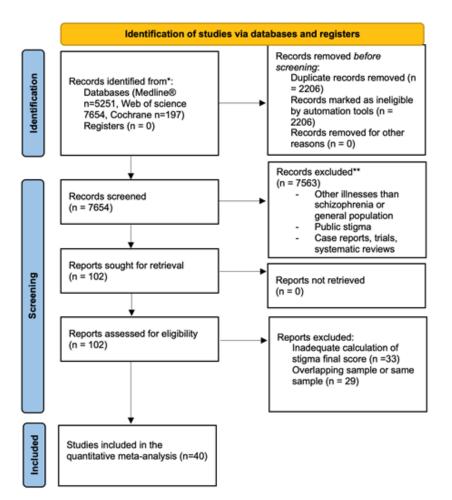
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### **Figures**

PRISMA 2020 flow diagram for new systematic reviews which included searches of databases and



#### Figure 1

Flow chart

#### Figure 2

Forest plot of studies exploring stigma dimensions (experienced stigma, alienation, stereotype endorsement, social withdrawal and stigma resistance) in schizophrenia

### **Supplementary Files**

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