



The enduring gap in educational attainment in schizophrenia according to the past 50 years of published research: a systematic review and meta-analysis

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Summary

Background Educational attainment is associated with wellbeing and health, but patients with schizophrenia achieve lower levels of education than people without. Several effective interventions can ameliorate this situation. However, the magnitude of the education gap in schizophrenia and its change over time are unclear. We aimed to reconstruct the trajectories of educational attainment in patients with schizophrenia and, if reported, their healthy comparator controls.

Methods We did a systematic review and meta-analysis including all studies reporting on patients with schizophrenia (of mean age ≥ 18 years) and describing the number of years of education of the participants, with or without healthy controls. There were no other design constraints on studies. We excluded studies that included only patients with other schizophrenia spectrum disorders and studies that did not specify the number of years of education of the participants. 22 reviewers participated in retrieving data from a search in PubMed and PsycINFO (Jan 1, 1970, to Nov 24, 2020). We estimated the birth date of participants from their mean age and publication date, and meta-analysed these data using random-effects models, focusing on educational attainment, the education gap, and changes over time. The primary outcome was years of education. The protocol was registered on PROSPERO (CRD42020220546).

Findings From 32 593 initial references, we included 3321 studies reporting on 318 632 patients alongside 138 675 healthy controls (170 941 women and 275 821 men from studies describing sex or gender; data on ethnicity were not collected). Patients' educational attainment increased over time, mirroring that of controls. However, patients with schizophrenia in high-income countries had 19 months less education than controls (-1.59 years, 95% CI -1.66 to -1.53 ; $p < 0.0001$), which is equivalent to a Cohen's d of -0.56 (95% CI -0.58 to -0.54) and implies an odds ratio of 2.58 for not completing 12 years of education (ie, not completing secondary education) for patients compared with controls. This gap remained stable throughout the decades; the rate of change in number of total years of education in time was not significant (annual change: 0.0047 years, 95% CI -0.0005 to 0.0099 ; $p = 0.078$). For patients in low-income and middle-income countries, the education gap was significantly smaller than in high-income countries (smaller by 0.72 years, 0.85 to 0.59 ; $p < 0.0001$), yet there was evidence that this gap was widening over the years, approaching that of high-income countries (annual change: -0.024 years, -0.037 to -0.011 ; $p = 0.0002$).

Interpretation Patients with schizophrenia have faced persistent inequality in educational attainment in the last century, despite advances in psychosocial and pharmacological treatment. Reducing this gap should become a priority to improve their functional outcomes.

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Introduction

Education is a major determinant of a person's wellbeing. Although there is bidirectional causality, people who are more educated live longer and happier lives.^{1,2} Education is also linked to better employment prospects and higher lifetime earnings.³ Ensuring equitable

quality education is one of the UN Sustainable Development Goals.⁴ Mental health problems, particularly those that present early in life, are associated with disruption in schooling.⁵ Among them, schizophrenia has some of the poorest educational outcomes.⁶ Moreover, people with psychosis regard education as

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Research in context

Evidence before this study

Schizophrenia is associated with lower educational attainment. Improving this situation is an important goal of current services and is widely supported by patients. Examining the magnitude of this education gap and its changes over time would inform the psychiatric community on areas to improve. We searched PubMed from database inception (last search Nov 8, 2021) for meta-analyses examining the magnitude of the current education gap and changes over time. We used the terms (schizophrenia AND (“educational attainment” OR “academic achievement”)) without language restrictions, with the filters Meta-Analysis, Systematic Review. Two of the eight references identified were related to schizophrenia and education, both focusing on premorbid educational achievement. One of them extended its analysis to the likelihood of entering higher education, including 22 studies from the past 20 years. It reported that patients were less likely (moderate effect size) to enter post-secondary education. This was interpreted as possibly being associated with the emergence of prodromal symptoms, without any mention of the possible effect of ameliorating

central to their process of recovery, ranking it more important than symptomatic remission.^{7,8}

The reason why schizophrenia is associated with lower educational attainment is probably multifactorial. Some barriers pre-date the onset of symptoms. It has been well established that individuals who develop schizophrenia have lower premorbid academic achievement.⁹ Other barriers present after the onset of the first episode.¹⁰ Symptoms (including cognitive deficits), medication, the time demands of clinical care (hospital admission, outpatient appointments), and stigma might all have a role in preventing patients from going back to education after a psychotic episode.^{11,12} Promoting a prompt return to education after the onset of psychosis is a feasible and important goal of early intervention,^{13–16} as recommended by many guidelines.^{17,18} The importance of returning to education has been highlighted by at least two international calls for action.^{19,20}

Despite its acknowledged importance, the magnitude of the existing gap in education and whether it has changed over time remain unclear. To shed light on these questions, we systematically reviewed the published literature of the past 50 years to reconstruct the trajectories of educational attainment in patients with schizophrenia and, if reported, their healthy comparator controls. We included different types of studies in which educational attainment was reported, irrespective of whether education was its central focus, or reported as secondary information characterising the included participants. To explore changes over time, we used age-based educational attainment levels,²¹ for which we imputed the patients’ date of birth from the publication

strategies after the first episode. Changes in time were not examined, and nor were differences across countries.

Added value of this study

We here present evidence that educational attainment in people with schizophrenia, expressed as years of completed education, has increased in the past century at a similar rate to that of healthy controls. We also found that, as suggested in previous studies, patients achieve fewer years of completed education than healthy controls. Importantly, we now show that this gap has remained stable over time across high-income countries and has increased in low-income and middle-income countries.

Implications of all the available evidence

People with schizophrenia have faced persistent inequality in educational attainment in the past century, despite the development of psychosocial and pharmacological interventions, and a widespread agreement that this problem needs to be tackled. There is a need for urgent action to improve this situation.

date and the reported mean age of the participants. Thus, we incorporated data from people born throughout the 20th century. We hypothesised that the education gap (difference in educational attainment between patients and controls) would decrease in the past decades, particularly in high-income countries where a recovery approach has been implemented more widely.

Methods

Search strategy and selection criteria

This systematic review and meta-analysis was conducted following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.²² A protocol was registered in the International Prospective Register of Systematic Reviews (PROSPERO), registration number CRD42020220546.

We searched PubMed and PsycINFO on Nov 24, 2020, for studies published after Jan 1, 1970. We kept our search strategy broad, combining terms related to schizophrenia alongside education (including “years of education” or “schooling”). Studies in English, Spanish, Portuguese, German, and French were considered. The search strategy used in both databases is outlined in appendix 1 (p 2).

We included all studies reporting on patients with schizophrenia, defined using clear diagnostic criteria (such as DSM or ICD), with a mean age of 18 years or older, and that reported years of education (alongside a measure of variance) and age of the participants. All types of study design were considered. Studies including only patients with other schizophrenia spectrum disorders, such as schizoaffective disorder, were not included.

However, schizophrenia studies frequently include patients with these disorders within the schizophrenia group, without necessarily reporting them separately or describing their numbers. Therefore, studies including patients with schizoaffective or schizophreniform disorder among the patients with schizophrenia were included. Studies not reporting educational attainment in completed years but in any other form, such as the percentage of participants who completed secondary education or higher education, were not included. We did not exclude studies reporting no significant differences in education between groups, which sometimes was referred to as “matched”. It was frequently not clear whether describing a study as matched was the result of a specific recruitment strategy or a post-hoc description of a non-significant difference found in generally small groups due to random sampling. The exclusion of these studies might have biased our results. Their effect is assessed in a sensitivity analysis as described later.

The initial results of the search were subdivided, and considering their large number, their abstracts were reviewed by 22 researchers. Studies considered eligible were subsequently reviewed by two independent reviewers, including the data extraction. Disagreements were resolved by a third party.

Data analysis

Data extracted included number of patients, years of education (plus standard deviation), mean age, sex or gender composition, and country of the study. Ethnicity was not collected due to a lack of standardised groups across countries. When healthy controls were included as a comparator, all of this information was also retrieved from them. We excluded data reported in another publication that was already included. To do this we searched the title of publications reporting on known big studies that were likely to be duplicated (eg, CATIE or EUFEST). We also searched for duplicates in the extracted data looking for studies reporting the same sample size and years of education. After identifying such possible duplicates, original studies were again retrieved and examined if they reported the same data, keeping the one published first that reported the full sample.

For all analyses, we imputed the participants' year of birth from the publication date minus their reported mean age. Considering that there is a delay from recruitment in the study (when age is recorded) to its final publication, we subtracted 3 years from the estimated year of birth. Given that this is a constant applied to all studies, most of the analyses described herein would be unaffected if this parameter were changed. Ideally, we would have used the actual date when the data were collected in our estimate. However, this date is seldom reported, leaving us without enough studies to examine temporal trends as described in this report.

The primary outcome of our analyses was years of education, which was first addressed separately for patients and controls. As a general approach, we built three models examining our outcome, which were then compared using Akaike's information criterion (AIC; a metric examining the trade-off between the goodness of fit of the model and its simplicity²³). All of them used a random-effects model fitted with a maximum-likelihood estimator, and they weighted the individual studies according to the inverse of the sampling variances of the reported years of education. Heterogeneity was quantified using the I^2 statistic.²⁴

The first model meta-analysed the years of education with no other explanatory variables. The second model added the year of birth of participants. A third model included whether the study was based in a high-income country or in a low-income or middle-income country (LMIC), as defined by the World Bank in its 2020 classification,²⁵ alongside the birth year, and the interaction between birth year and country income status. We also examined whether a linear change with time would fit the data better than a logarithmic change (a faster initial increase in years of education but slowing down with time).

We then did a meta-analysis comparing education in patients with controls, restricting this analysis to studies that reported data on healthy participants. We used the same approach described in the previous paragraph, comparing the three models but looking at the difference in educational attainment reported within studies.

To express the results as effect sizes (Cohen's d), we calculated the weighted mean variance of healthy controls and expressed the differences in this pooled variance. Similarly, we used the weighted mean variance of healthy controls and patients to translate the different distributions in years of education to the proportion of participants achieving a specific milestone. Considering the socioeconomic importance associated with completing secondary education, and to facilitate comparison with other studies, we focused on the odds of completing 12 years of education.

Changes in the characteristics of the included studies over time, particularly the geographical location of studies, the proportion of women included, and age of the participants, are described in a separate report.²⁶

All analyses were performed in R (version 4.0.2) using the metafor package. The R script and data used are included in the supplementary material (appendix 2 and appendix 3).

Sensitivity analyses

Unlike traditional meta-analyses, the primary outcome of our study (years of education) was usually not the main outcome reported in the primary studies. This reduces the likelihood of publication bias. However, the participants included might not be representative of the larger population in their defined group. We therefore

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For the protocol see https://www.crd.york.ac.uk/prospero/display_record.php?RecordID=220546

See Online for appendix 1

See Online for appendices 2 and 3

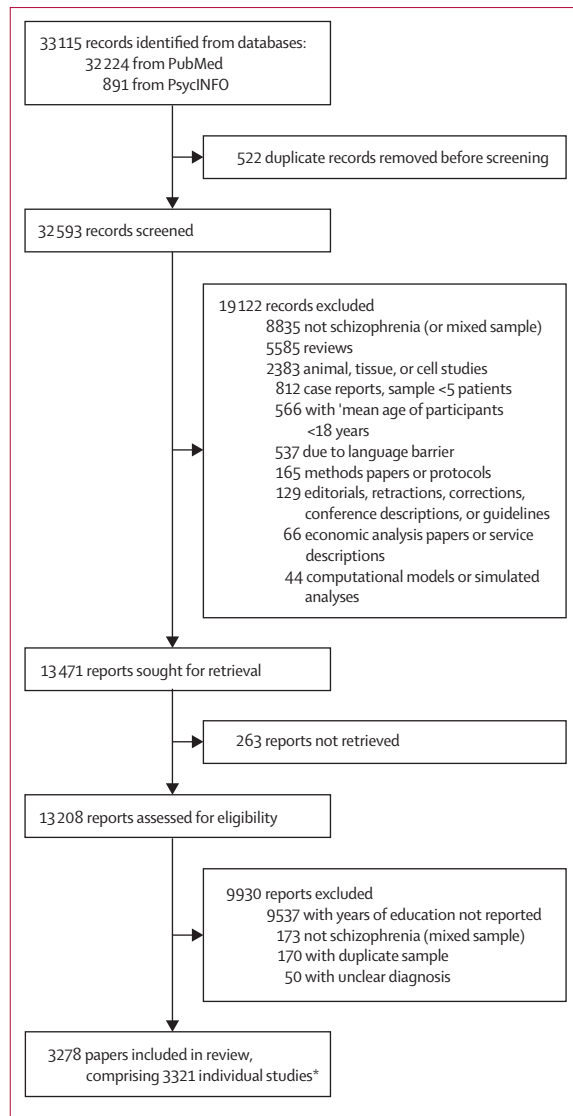


Figure 1: PRISMA flowchart of studies
 *3278 papers were included; of these, some reported on more than one sample (eg, samples from different countries), giving a total of 3321 individual studies that were the unit of analysis. All 3321 studies were included in the meta-analysis of the trajectories of educational attainment in patients. For the meta-analysis comparing educational attainment in patients with controls, only the 2002 studies with healthy comparator controls were included.

compared the educational attainment from the healthy participants in the studies with reports of educational attainment in the general population from other sources.²⁷ We also reasoned that, if present, a bias towards including overeducated or undereducated participants (relative to the general population) would be larger in smaller studies, and we performed meta-regression analyses exploring the effect of including sample size.

When examining the difference in educational attainment between groups, we did three other

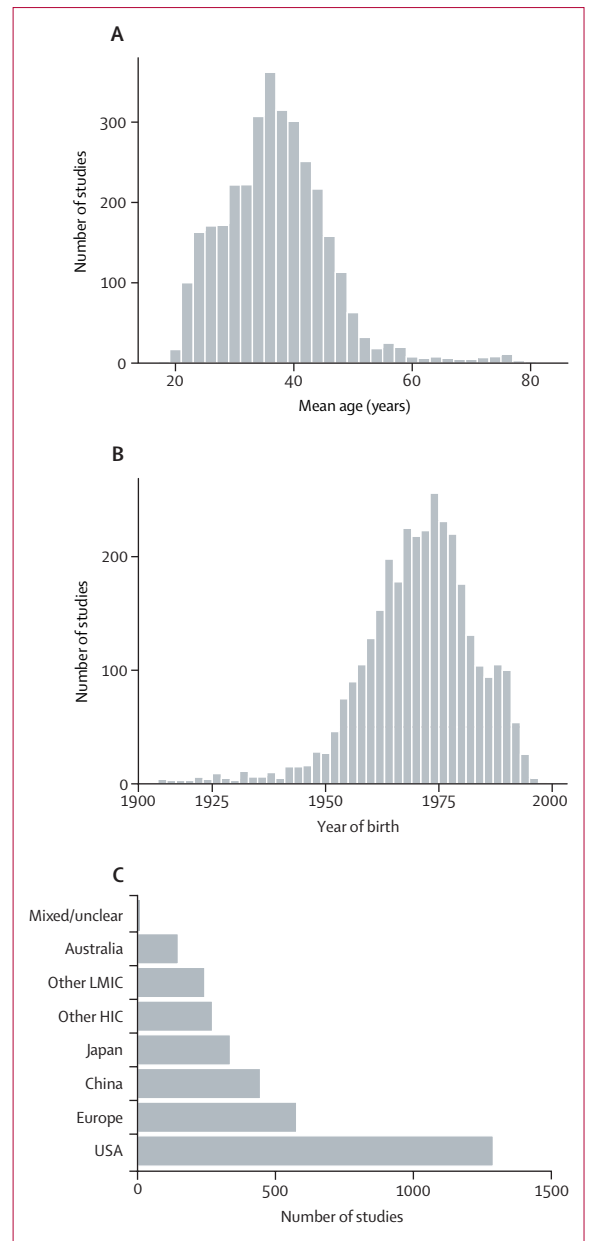


Figure 2: Characteristics of the included studies
 (A) Mean age of patients in studies. (B) Imputed mean birth date of patients calculated from their age and the publication date of the study. (C) Country where study was conducted. HIC=high-income country. LMIC=low-income or middle-income country.

sensitivity analyses. First, we only meta-analysed studies reporting similar parental education in the two groups. A second analysis excluded all studies that reported that healthy controls were not different in education to patients. Finally, we excluded studies reporting on patients whose mean age was younger than 30 years, because they might have not provided enough time for the implementation of strategies to resume education.

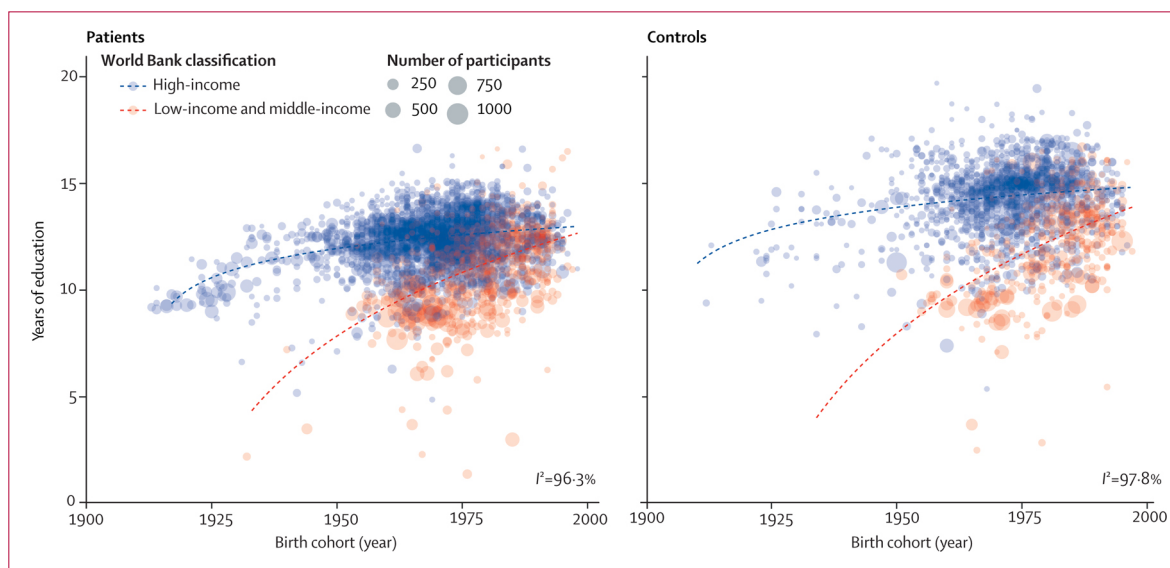


Figure 3: Patients' and controls' educational attainment in completed years of education over the decades

Dashed lines in figures are the meta-regression fit including a logarithmic increase over years, World Bank country income classification, and the interaction between birth year and country income status.

Role of the funding source

The funder of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report.

Results

From an initial 32 593 potential articles identified, 3278 papers were included (figure 1). The full list of references both included and excluded is described in appendix 2. Some articles reported on more than one sample (eg, samples from different countries), giving a total of 3321 individual studies that were the unit of analysis. These studies combined included 318 632 patients, whose mean age was 37.1 years (SD 9.04; figure 2A), and of whom 35% were female (108 455 women and 202 486 men in the 3224 studies reporting sex or gender). The imputed birth cohort to which these participants corresponded ranged from 1913 to 1998 (figure 2B). Most of these studies were from the USA (1290 [39%]), followed by China (446 [13%]) and Japan (337 [10%]; figure 2C). 2002 studies (60%) also included healthy controls as comparisons, with a total of 138 675 healthy participants (62 486 women and 73 335 men). Controls in each study were well balanced with the patients in age (correlation coefficient $r=0.89$, 95% CI 0.88–0.90; $p<0.0001$) and to a lesser extent in sex ($r=0.73$, 95% CI 0.70–0.75, $p<0.0001$).

Patients' educational attainment increased over the years as depicted in figure 3A. The model including imputed birth cohort, World Bank classification for the included countries, the interaction between the birth year and country income classification (model 3), and a logarithmic growth in educational attainment (slowing its pace with time), was highly significant (omnibus test of

moderators QM [3 degrees of freedom]=1184.4, $p<0.0001$, with an r^2 of 28.6%, but substantial residual heterogeneity, $I^2=96.3\%$). Appendix 1 (p 3) compares this model with alternatives. According to this model, a patient born in the year 2000 in a high-income country would be expected to achieve 13 years of education, in contrast to 10 years for a patient born in 1920. For a patient born in an LMIC, the increase in years of education was larger and over a shorter period; the expected years of completed education for a patient born in 1950 was 7.8 years (an estimate for 1920 would be less precise because fewer studies were published before 1950), which increased to 12.8 years for a patient born in 2000.

Changes in educational attainment in the healthy controls mirrored the patients' trajectory (figure 3B). A meta-regression including year of birth, country income classification, and their interaction, using a logarithmic increase with time, fitted the data well (omnibus test of moderators QM [3 degrees of freedom]=781.0, $p<0.0001$, with an r^2 of 29.8% and residual heterogeneity, $I^2=97.8\%$; see appendix 1 [p 3] for comparison with other models).

Comparing educational attainment of patients with that of controls (figure 4), the model including a linear change with the imputed birth year, World Bank classification, and the interaction between birth year and country income status, best fitted the data (test of moderators QM [3 degrees of freedom]=128.9, $p<0.0001$, $r^2=8.11\%$, $I^2=84.9\%$; see appendix 1 [p 4] for alternative models). As predicted, the educational attainment of patients with schizophrenia was lower than in controls. It was 1.59 years (19 months) less for patients born in 1977 (the median birth year of patients, used to centre the model) in a high-income country (95% CI -1.66 to -1.53 ;

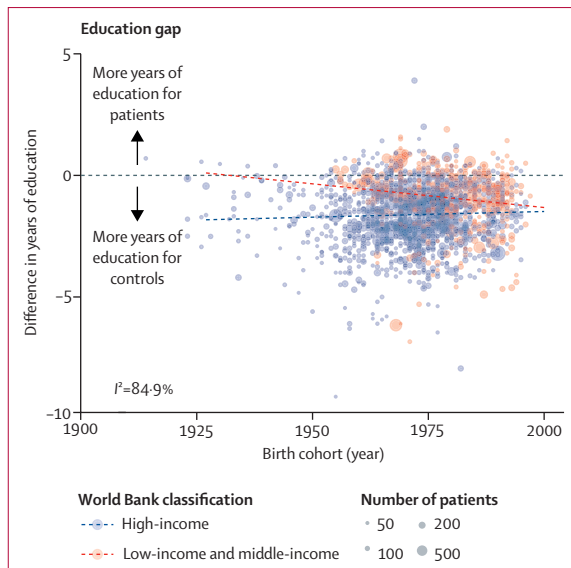


Figure 4: Pooled difference in educational attainment between patients and controls over the decades

Analysis includes the effect of type of economy (World Bank classification) in blue and red, with their respective meta-regression estimate represented with a dashed line.

$p < 0.0001$, equivalent to a Cohen's d of -0.56 , 95% CI -0.58 to -0.54). That difference would imply an odds ratio of 2.58 for not completing 12 years of education for patients compared with controls. Remarkably, this difference between patients and controls was stable across the decades for high-income countries (figure 4). The rate of change, in the number of total years of education over time, was not significant (annual change of 0.0047 years, -0.0005 to 0.0099 ; $p = 0.078$). For LMICs, the education gap for patients born in 1977 was significantly smaller than in high-income countries (smaller by 0.72 years, 0.85 to 0.59; $p < 0.0001$), yet there was evidence that this gap was widening over the years, approaching that of high-income countries (annual change of -0.024 years, -0.037 to -0.011 ; $p = 0.0002$).

A subgroup analysis of studies in which groups were similar in parental education (259 studies) showed a slightly larger difference in years of education in high-income countries (-1.83 years, 95% CI -1.93 to -1.72 ; $p < 0.001$) with no significant changes in time (annual change of -0.002 years, -0.01 to 0.01 , $p = 0.72$; appendix 1 [p 5]). Excluding studies that reported recruiting controls matched by education (430 studies excluded) resulted in the rate of change in high-income countries becoming significant ($p = 0.039$). However, this model included a very low magnitude of change—namely, a yearly decrease of 0.006 years in the gap, and a larger estimate of the difference between groups to overcome (1.78 years for the cohort of 1977 in high-income countries). Results remained the same when excluding 530 studies focused on younger patients (younger than mean age of 30 years; appendix 1 [p 6]).

Examining the education gap in specific countries and regions showed consistent results compared with our main analysis (figure 5). The only exception was China, where there was an increase in time in the education gap (patients completing 0.24 years less than controls every 10 years; $p = 0.0003$).

Comparing the educational attainment of the healthy participants recruited in studies based in the USA, China, Japan, and Australia with that of the general population of those countries²⁷ showed that the controls included in the studies had higher educational attainment than the general population (appendix 1 [p 8]). This finding was in line with results examining the effect of sample sizes, showing that larger samples presented lower educational attainment, improving the fit of the model (AIC 7628.3 vs 7632.8 [for the full model including sample size compared with the model not including sample size, respectively], likelihood ratio test 6.47, $p = 0.011$; appendix 1 [p 9]). For every ten extra controls in the study, their mean years of education decreased by 0.007 years (95% CI -0.013 to -0.002 ; $p = 0.011$). For patients with schizophrenia, including the sample size of the study (number of patients) as a moderator in the meta-regression model improved the fit of the model (AIC 11117.35 vs 11184.16, likelihood ratio test 68.81; $p < 0.0001$). For every ten extra participants included, their mean years of education decreased by 0.01 years (-0.013 to -0.008 , $p < 0.0001$). The effect of sample size was no longer significant when included as a covariate in the analysis of differences in educational attainment between groups ($p = 0.14$), without any other substantial differences from the main analysis.

Discussion

By pooling data from the published literature of the last 50 years, we found that, overall, people with schizophrenia have increased their years of completed education in the last century, to a similar extent as healthy controls have. However, there remains a significant gap in educational attainment between patients and controls. Strikingly, there was no evidence that the gap has changed during this last century. Despite the international efforts to decrease this education gap, and the development of a broad range of interventions, patients with schizophrenia remain at substantial disadvantage compared with their unaffected peers.

How meaningful is a gap of 19 months, which perhaps does not appear initially very large? Notably, this period is equivalent to the gains in education after three generations in healthy controls included in studies from high-income countries (the difference between the generations born in 1940 and 2000). It can also be seen as a moderate effect size in terms of a Cohen's d of -0.56 . This difference can also be translated to an odds ratio of 2.58 for not graduating from secondary school in patients compared with healthy controls, which is among

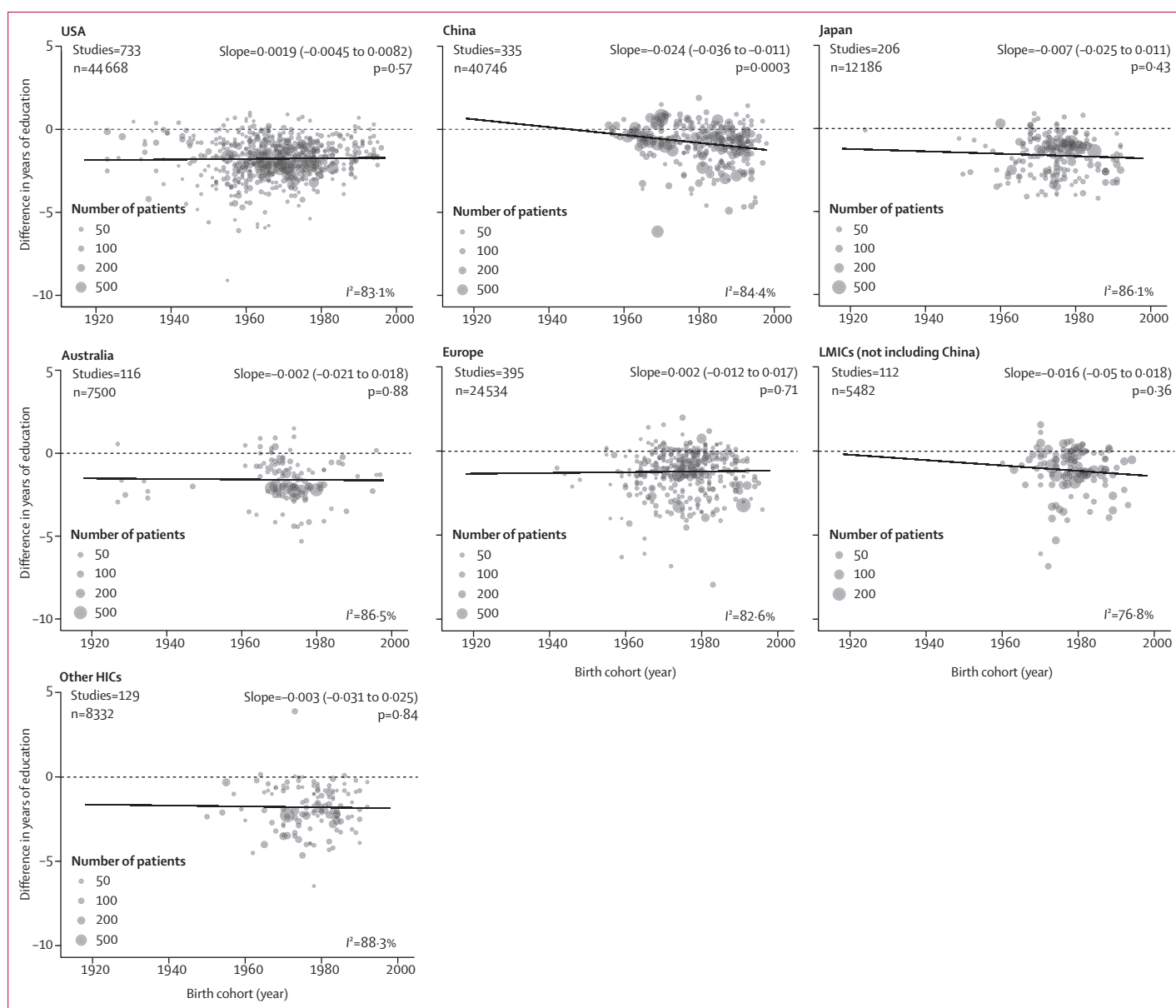


Figure 5: Education gap in patients and controls across the decades in different countries and regions

Countries and regions examined are those including more than 100 studies. Individual countries listed in each group can be found in appendix 1 (p 2). The education gap in European HICs can be found in appendix 1 (p 7). The slope of each line is the annual change in the difference in years of education between patients and controls (eg, a slope of 0.0019 means an annual decrease in the education gap of 0.0019 years); the numbers in parentheses are 95% CIs. Note that apart from China, all countries show no significant change in the education gap over time. HICs=high-income countries. LMICs=low-income and middle-income countries.

the highest reported for mental health disorders using comparable milestones.⁵

The implications of this enduring education gap for patients with schizophrenia are potentially wide-reaching. Higher educational attainment is strongly associated with work opportunities and higher lifetime earnings.³ An extra year in education could have a considerable effect, particularly in vulnerable groups such as patients with schizophrenia.^{28,29} There is a strong economic argument to ameliorate this disadvantaged

position of people with schizophrenia.^{30,31} We could also note the parallels between the education gap and the mortality gap between patients with schizophrenia and healthy controls.³² The causes of the mortality gap are likely to be complex. Nevertheless, acknowledging the possible link between education and survival rates' could mean that improving patients' education might also improve the enduring mortality gap. Alongside all these potential implications, we should highlight that education is frequently reported as a central outcome in

the process of recovery from the patients' perspectives. An ongoing question is whether this problem has received enough attention from the research community, service providers, and policy makers.

Our data show that the gap is present across high-income countries. We expected to see a reduction in countries with widespread implementation of early intervention services such as Australia, since these services highlight return to education and promote effective interventions. However, even in that pioneering country, these changes have been implemented nationwide only in the past 5 years. It is likely that we did not see an effect due to their recent implementation, or their lack of penetration into some geographical areas. Future studies will be needed to formally evaluate their effect. This enduring gap also highlights the importance of understanding the neurobiology of cognition in schizophrenia, and the development of interventions that could ameliorate its deficits, which could eventually help patients to return to education.³³

The educational attainment gap was narrower in LMICs. However, the rapid increase in educational attainment observed in China showed that this education gap resembled the existing gap in high-income economies once China reached a high-income level of educational attainment. We did not have data to examine whether the education gap subsequently stabilised. This observation highlights a window of opportunity for preventing the development of this gap. Interventions supporting people with schizophrenia in LMICs should be developed to avoid falling behind as the levels of educational attainment in the general population increase.

The main limitation of our study is the restricted representativeness of participants included in research studies. Studies rarely describe their recruitment strategy, and in many cases appear to be including convenience samples both of patients and controls that might be subject to different biases. Our analyses comparing educational outcomes in healthy controls with other educational attainment databases, as well as the finding that smaller studies recruited healthy participants with higher education, suggest an overrepresentation of highly educated controls. The data displayed a similar sampling bias in patients, and examining its effect on the observed education gap suggested that they cancel each other out. Considering that research centres are usually based in cities, the urban–rural gap seen in many countries might explain why both groups were more educated than their respective larger population.³⁴ The finding of a similar temporally stable difference between patients and controls in studies in which groups were similar in parental education supports the idea that our results are not due to a sampling bias only. We also acknowledge the limitation of using years of education as a measure of educational attainment. Finishing a year of education

does not necessarily provide information about the level of proficiency acquired. Furthermore, it assumes that the years of education in different educational settings (such as general and vocational secondary education) are the same, although they provide different competencies and have a different value in the labour market.³⁵ Nevertheless, years of education is a widely reported metric across countries, allowing us to compare many samples from diverse regions of the world over time on the same metric. Our work analysed data at the aggregate (group) level, so we cannot rule out that some of the group-based inferences do not apply to the individual patients. Future studies on patient-level individual data will need to corroborate these results.

In conclusion, we have shown that there is an enduring deficit in educational attainment associated with schizophrenia, which has not decreased in the last century despite an increase in educational attainment in all participants. Educational efforts targeted specifically at people with schizophrenia need to be developed, deployed, re-evaluated, and increased.

Contributors

NAC designed the study. NAC and LMA did the data search. NAC, LMA, LSC, DA, CPC, CD, BI, CaM, CrM, JPR-M, AT, JV, LF, VM, CEH, CV-U, GG-C, LFK-R, TM-H, AG-V, JU, and AG selected the articles and extracted the data. NAC did the analyses and drafted the manuscript. All authors critically revised the manuscript. NAC and AG accessed and verified the data. All authors had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Declaration of interests

NAC has received personal fees from Janssen, outside the submitted work. AG has been a consultant and/or advisor to or has received honoraria from Aché, Daiichi-Sankyo, Torrent, Bayer, Cristalia, Daiichi-Sankyo and Janssen. CA has been a consultant to or has received honoraria or grants from Acadia, Angelini, Biogen, Boehringer, Gedeon Richter, Janssen Cilag, Lundbeck, Minerva, Otsuka, Pfizer, Roche, Sage, Servier, Shire, Schering Plough, Sumitomo Dainippon Pharma, Sunovion, and Takeda. DMB has received consulting fees from Boehringer-Ingelheim. SE-L has received consulting fees from Janssen. CUC has been a consultant and/or advisor to or has received honoraria from AbbVie, Acadia, Alkermes, Allergan, Angelini, Aristo, Axsome, Damitsa, Gedeon Richter, Hikma, Holmus, IntraCellular Therapies, Janssen/Johnson & Johnson, Karuna, LB Pharma, Lundbeck, MedAvante-ProPhase, MedInCell, Medscape, Merck, Mitsubishi Tanabe Pharma, Mylan, Neurocrine, Noven, Otsuka, Pfizer, Recordati, Relmada, Rovi, Seqirus, Servier, SK Life Science, Sumitomo Dainippon, Sunovion, Supernus, Takeda, Teva, and Viatrix. He provided expert testimony for Janssen and Otsuka. He served on a Data Safety Monitoring Board for Lundbeck, Relmada, Rovi, and Teva. He has received grant support from Janssen and Takeda. He received royalties from UpToDate and is also a stock option holder of LB Pharma. All other authors declare no competing interests.

Data sharing

The data used in this paper and an accompanying R script with all the analyses are included in the appendices.

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