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

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ABSTRACT

Background

Educational attainment is associated with well-being and health. Unfortunately, patients with schizophrenia achieve lower levels of education. Several effective interventions can ameliorate this. However, the magnitude of the education gap in schizophrenia and changes over time are unclear.

Methods

We performed a systematic review and meta-analysis including all studies reporting on patients with schizophrenia and describing their years of education, with or without healthy controls. There were no other design constraints on studies. 22 reviewers participated in retrieving data from a search in PubMed and PsycINFO (January 1st, 1970, to November 24th, 2020). We estimated the birth date of participants from their mean age and publication date, and meta-analyzed these data, focusing on educational attainment, the education gap, and changes over time. The protocol was registered in PROSPERO (CRD42020220546).

Outcomes

From 32,593 initial references, we included 3,321 studies reporting on 318,632 patients alongside 138,675 healthy controls (170,941 women and 275,821 men from studies describing gender; ethnicity was not collected). Patients' educational attainment increased over time mirroring the controls'. However, patients achieved 19 months less than patients, and this remained unchanged throughout the decades. Studies were biased to include more educated patients and controls than their respective larger population, but results were unchanged in studies with groups with similar parental education.

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.

Funding

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Keywords: schizophrenia, education, recovery, inequality

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 gap and changes over time would inform us on areas to improve. We searched PubMed (last search 8th November 2021) for meta-analyses examining the magnitude of the current education gap and changes in time. We used the terms (schizophrenia AND ("educational attainment" OR "academic achievement")) without language restrictions, with the filters Meta-Analysis, Systematic Review. Two references out of the 8 identified were related to schizophrenia and education, both focusing on pre-morbid educational achievement. One of them extended its analysis to the likelihood of entering higher education, including 22 studies from the last 20 years. It reported that patients were less likely (moderate effect size) to enter post-secondary education. This was interpreted as possibly being associated to the emergence of prodromal symptoms, without any mention of the possible effect of ameliorating strategies after the first episode. Changes in time were not examined, or 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 last century with a similar rate as healthy controls. We also found that, as suggested in previous studies, patients achieve fewer years of completed education. Importantly, we now show that this gap has remained stable in time across high-income countries, and has increased in low- and middle-income countries.

Implications of all the available evidence

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

INTRODUCTION

Education is a major determinant of a person's wellbeing. Although there is bidirectional causality, more educated people 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 Sustainable Development Goals of the United Nations[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 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 likely multifactorial. Some barriers predate the onset of symptoms. It has been well established that patients who develop schizophrenia have lower pre-morbid 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 and whether it has changed over time remains unclear. To shed light on these questions, we systematically reviewed the published literature of the last 50 years to reconstruct the trajectories of educational attainment in patients and if reported, on 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 characterizing the included participants. To explore changes over time, we used age-based educational attainment levels [21], where we imputed the patients' date of birth from the publication date and the reported average age of the participants. Thus, we incorporated data from people born throughout the 20th century. We hypothesized that the education gap (difference between educational attainment in patients and controls) would decrease in the last decades, particularly in high-income countries where a recovery approach has been implemented more widely.

METHODS

Protocol and Registration

This systematic review 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.

Information sources and search strategy

We searched PubMed and PsycINFO on the 24th November 2020 for studies published after the 1st January 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. Supplementary Information provides the search strategy used in both databases.

Eligibility criteria

We included all studies reporting on patients with schizophrenia, defined using clear diagnostic criteria (such as DSM or ICD), who were on average equal or older than 18 years old, and that reported years of education (alongside a measure of variance) and age of the participants. Studies only including patients with other schizophrenia spectrum disorders, such as schizoaffective disorder, were not included. However, schizophrenia studies frequently include subjects 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 also included. Studies not reporting educational attainment in completed years but in any other form, such as the percentage of completed high school/A-levels 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 this 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. If excluded, this might have biased our results. Their impact is assessed in a sensitivity analysis as described below.

Study selection

Initial hits 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 extracted included number of patients, years of education (with its standard deviation), mean age, sex composition, and country of the study. Ethnicity was not collected due to a lack of standardized groups across countries. When healthy controls were included as a comparator, all 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 duplicated (e.g., 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.

Data analysis

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

The main 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 criterion (a metric examining the trade-off between the goodness of fit of the model and its simplicity [23]). All of them used a random-effects model fitted with a maximum-likelihood estimator, and weighed the individual studies according to the inverse of the sampling variances of the reported years of education. Heterogeneity was quantified using the I^2 statistics [24].

The first model meta-analyzed 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 on a high-income country, or in a low- or middle-income country (LMIC) as defined by the World Bank in its 2020 classification [25], alongside the birth year, and their interaction. 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 performed a meta-analysis comparing education in patients compared to controls, restricting this analysis to studies that reported data on healthy participants. We used the same approach described above, comparing 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 to completing high school and 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 geographic 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.

Sensitivity analyses

Unlike traditional meta-analyses, the main 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, participants included might not be representative of the larger population in their defined group. We therefore compared the educational attainment from the healthy participants in the studies to reports of educational attainment in the general population from other sources [27]. We also reasoned that, if present, a bias towards including over- or under-educated participants would be larger in smaller studies, and performed meta-regression analyses exploring the effect of including sample size.

When examining the difference in educational attainment between groups, we performed three other sensitivity analyses. First, we only meta-analyzed 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 who were on average younger than 30 years old, as they might have not provided enough time for the implementation of strategies to resume education.

Role of the funding source

Study sponsors did not have any role in the study design, collection of the data, analysis, interpretation of the data, writing the report, or decision to submit the paper for publication.

RESULTS

From an initial 32,593 potential articles identified, 3,278 papers were included (Figure 1). The full list of references both included and excluded is described in the appendix. Some articles reported on more than one sample (for example, samples from different countries), giving a total of 3,321 individual studies that were the unit of analysis. These studies combined included 318,632 patients, who were on average 37.1 years old (standard deviation 9.04, Figure 2A), and 34.9% were female (108,455 women compared to 202,486 men in the 3,224 studies reporting gender). The imputed birth cohort to which these participants corresponded ranged from 1913 to 1998 (Figure 2B). Most of these studies were from the United States of America (1290, 39%), followed by China (446, 13%) and Japan (337, 10%) (Figure 2C). 2,002 studies (60.3%) 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 gender (R=0.73, 95% CI 0.7-0.75, 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 two terms, and a logarithmic growth in educational attainment (slowing its pace with time), was highly significant (omnibus test of moderators QM (degrees of freedom (df) = 3) = 1184.4, P < 0.0001, with an R^2 of 28.6%, but significant residual heterogeneity I^2 = 96.25%). Table S1 in the Supplementary Results compares this model with alternatives. 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 a low- or middle-income country the increment was larger and in a shorter period. The expected years of completed education for those born in 1950 was 7.8 years (an estimate for 1920 would be less precise due to fewer studies published before 1950), which increased to 12.8 for those born in 2000.

Changes in educational attainment in the healthy controls mirrored the patients' trajectory (Figure 3B). A meta-regression including a logarithmic increase with time, the country classification, and their interaction, fitted well the data (omnibus test of moderators QM (df = 3) = 781.0, $P < 0.0001$, with an R^2 of 29.8% and residual heterogeneity I^2 = 97.8%; see Table S2 for comparison to other models).

Comparing educational attainment in patients to controls, the model including a linear change with the imputed birth year, World Bank classification, and their interaction, best fit the data (test of moderators QM (df = 3) = 128.9, $P < 0.0001$, R^2 = 8.11%, I^2 =84.9%; see Table S3 for alternative models). As predicted, the educational attainment of patients with schizophrenia was lower than in controls, namely 1.6 years less for patients born in 1977 in a high-income country (95% confidence interval (CI) -1.66 to -1.53, $P < 0.0001$, equivalent to a Cohen's *d* of -0.56). That difference would imply an odds ratio of 2.58 for not completing 12 years of education for patients compared to controls. Remarkably, this difference between patients and controls was stable across the decades for high-income countries. The rate of change in number of total years of education in time was not significant (annual change of 0.0047, 95% CI -0.0005

to 0.0099 (*P* = 0.078)). For low- and middle-income countries, the education gap was significantly smaller (0.72 years less for those born in 1977, 95% CI 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, 95% CI -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 high-income countries (-1.83 years, 95% CI -1.93 to -1.72, P<0.001) with no significant changes in time (rate of change -0.002, P=0.72, Supplementary Figure 1). 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 (below average age of 30).

Examining the education gap in specific countries and regions showed consistent results compared to 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).

Plotting the healthy participants recruited in USA, China, Japan, and Australia compared to other sources of educational attainment [27] showed that controls included in the studies had

higher educational attainment (Figure S3A-C). This was in line with results examining the effect of samples size, showing that larger samples presented lower educational attainment, improving the fit of the model (Akaike's information criterion (AIC) 7628.3 compared to 7632.8, likelihood ratio test 6.47, P=0.011, Figure S4). For every 10 extra controls in the study, their average years of education decreased by 0.007 years (95% CI -0.013 to -0.002, P=0.011). For patients with schizophrenia, including size (*N*) of study as a moderator in the meta-regression model improved the fit of the model (AIC 11117.35 compared to 11184.16, likelihood ratio test 68.81, *P* <0.0001). For every 10 extra participants included, their mean years of education decreased by 0.01 years (95% CI -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. 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 significant disadvantage compared to 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 generation born in 1940 and 2000). It may 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 high school compared to healthy controls, which is among 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 significant impact particularly in vulnerable groups such as patients [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 [1] 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. A lingering 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 last five years. It is likely that we did not see an effect due to their recent implementation, or their lack of penetration in some geographical areas. Future studies will be needed to formally evaluate their impact. 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 go back to education [33].

The gap was narrower in low and middle-income countries. However, the rapid increase in educational attainment observed in China showed that this education gap resembled the

existing gap in high-income economies once the country reached high-income level of educational attainment. We did not have data to examine whether the education gap subsequently stabilized. This highlights a window of opportunity for preventing the development of this gap. Interventions supporting people with schizophrenia in low and middle-income countries should be developed to avoid falling behind with increasing levels of educational attainment in the general population.

The main limitation of our study is the restricted representativeness of participants included in research studies. Studies rarely describe their recruitment strategy, and many times appear to be including convenience samples both of patients and controls that may be subject to different biases. Our analyses comparing educational outcomes in healthy controls to other educational attainment databases, as well as the finding that smaller studies recruited healthy participants with higher education, suggest an over-representation 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. Considering that research centers 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 where groups were comparable 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 years obtained in

different qualifications (such as general and vocational secondary) 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 over world over time on the same metric. Our work analyzed 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 subject-level individual data will need to corroborate these results.

In conclusion, we here show 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, reevaluated, and increased.

Contributors

NAC designed the study. NAC and LMA did the data search. NAC, LMA, LC, DA, CPC, CD, BI, Carlos M, Cristian M, JPRM, AT, JV, LF, VM, CEH, CVU, GGC, LFKR, TMH, AGV, JU and AG selected the articles and extracted the data. NAC performed the analyses and drafted the article. All authors critically revised the article. 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

Nicolas Crossley has received personal fees from Janssen, outside the submitted work. Ary Gadelha has been a consultant and/or advisor to or has received honoraria from: Aché, Daiichi-Sankyo, Torrent, Bayer, Cristalia, Daiichi-Sankyo and Janssen. Celso Arango 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. None of the other authors has potential conflicts of interest to be disclosed. Christoph Correll has been a consultant and/or advisor to or has received honoraria from: AbbVie, Acadia, Alkermes, Allergan, Angelini, Aristo, Axsome, Damitsa, Gedeon Richter, Hikma, Holmusk, IntraCellular Therapies, Janssen/J&J, 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 Viatris. 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.

Data sharing

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

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REFERENCES

1 Lleras-Muney A. The relationship between education and adult mortality in the United States. *Rev Econ Stud* 2005; **72**: 189–221.

2 Davies NM, Dickson M, Smith GD, Van Den Berg GJ, Windmeijer F. The causal effects of education on health outcomes in the UK Biobank. *Nat Hum Behav* 2018; **2**: 117–25.

3 Day JC, Newburger EC. The Big Payoff: Educational Attainment and Synthetic Estimates of Work-Life Earnings. Special Studies. Current Population Reports. ERIC, 2002.

4 Ban K. Sustainable Development Goals. 2016.

5 Breslau J, Lane M, Sampson N, Kessler RC. Mental disorders and subsequent educational attainment in a US national sample. *J Psychiatr Res* 2008; **42**: 708–16.

6 Dalsgaard S, McGrath J, Østergaard SD, *et al.* Association of mental disorder in childhood and adolescence with subsequent educational achievement. *JAMA psychiatry* 2020; **77**: 797–805.

7 de Waal A, Dixon LB, Humensky JL. Association of participant preferences on work and school participation after a first episode of psychosis. *Early Interv Psychiatry* 2018; **12**: 959–63.

8 Iyer SN, Mangala R, Anitha J, Thara R, Malla AK. An examination of patient-identified goals for treatment in a first-episode programme in Chennai, India. *Early Interv Psychiatry* 2011; **5**: 360–5.

9 Dickson H, Hedges EP, Ma SY, *et al.* Academic achievement and schizophrenia: a systematic meta-analysis. *Psychol Med* 2020; **50**: 1949–65.

10 Isohanni I, Jones PB, Järvelin M-R, *et al.* Educational consequences of mental disorders

treated in hospital. A 31-year follow-up of the Northern Finland 1966 Birth Cohort. *Psychol Med* 2001; **31**: 339–49.

11 Annapally SR, Jagannathan A, Kishore T, Thirthalli J, Daliboina M, Channaveerachari NK. Barriers to academic reintegration in students with severe mental disorders: thematic analysis. *Asian J Psychiatr* 2019; **45**: 107–12.

12 van der Schans J, Vardar S, Çiçek R, *et al.* An explorative study of school performance and antipsychotic medication. *BMC Psychiatry* 2016; **16**: 1–8.

13 Killackey E, Allott K, Woodhead G, Connor S, Dragon S, Ring J. Individual placement and support, supported education in young people with mental illness: an exploratory feasibility study. *Early Interv Psychiatry* 2017; **11**: 526–31.

14 Rosenheck R, Mueser KT, Sint K, *et al.* Supported employment and education in comprehensive, integrated care for first episode psychosis: Effects on work, school, and disability income. *Schizophr Res* 2017; **182**: 120–8.

15 Nuechterlein KH, Subotnik KL, Ventura J, *et al.* Enhancing return to work or school after a first episode of schizophrenia: the UCLA RCT of Individual Placement and Support and Workplace Fundamentals Module training. *Psychol Med* 2020; **50**: 20–8.

16 Robson E, Waghorn G, Sherring J, Morris A. Preliminary outcomes from an individualised supported education programme delivered by a community mental health service. *Br J Occup Ther* 2010; **73**: 481–6.

17 National Institute for Health and Care Excellence (NICE). Psychosis and schizophrenia in adults: prevention and management. 2014.

18 Early Psychosis Guidelines Writing Group and EPPIC National Support Program,

Australian Clinical Guidelines for Early Psychosis, 2nd edition update, 2016, Orygen TNC of E in YMH. Australian Clinical Guidelines for Early Psychosis, Second Edition. 2016.

19 Bertolote J, McGorry P. Early intervention and recovery for young people with early psychosis: consensus statement. *Br J Psychiatry* 2005; **187**: s116–9.

20 iFEVR Group IFEVR (iFEVR). Meaningful lives: supporting young people with psychosis in education, training and employment: an international consensus statement. *Early Interv Psychiatry* 2010; **4**: 323–6.

21 OECD. Education at a glance 2011: OECD indicators. OECD Paris, 2011 DOI:http://dx.doi.org/10.1787/eag-2011-en.

22 Moher D, Liberati A, Tetzlaff J, Altman DG, Group P. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *PLoS Med* 2009; **6**: e1000097.

23 Akaike H. A new look at the statistical model identification. *IEEE Trans Automat Contr* 1974; **19**: 716–23.

24 Higgins JPT, Thompson SG. Quantifying heterogeneity in a meta-analysis. *Stat Med* 2002; **21**: 1539–58.

25 World Bank. World Development Indicators. 2020.

26 Alliende LM, Czepielewski LS, Aceituno D, *et al.* Gender, Age and Geographical Representation over the Past 50 Years of Schizophrenia Research. *Psychiatry Res* 2022; **307**.

27 Barro RJ, Lee JW. A new data set of educational attainment in the world, 1950–2010. *J Dev Econ* 2013; **104**: 184–98.

28 Czepielewski LS, Alliende LM, Castañeda CP, *et al.* Effects of socioeconomic status in cognition of people with schizophrenia: results from a Latin American collaboration network with 1175 subjects. *Psychol Med* 2021; : 1–12.

29 Brand JE, Xie Y. Who benefits most from college? Evidence for negative selection in heterogeneous economic returns to higher education. *Am Sociol Rev* 2010; **75**: 273–302.

30 McDaid D, Evans-Lacko S. The case for investing in the mental health and wellbeing of children. In: UNICEF State of the World's Children. United Nations Children's Fund, 2021.

31 Fleischhacker WW, Arango C, Arteel P, *et al.* Schizophrenia—time to commit to policy change. *Schizophr Bull* 2014; **40**: S165–94.

32 Saha S, Chant D, McGrath J. A systematic review of mortality in schizophrenia: is the differential mortality gap worsening over time? *Arch Gen Psychiatry* 2007; **64**: 1123–31.

33 Carter CS, Barch DM. Cognitive neuroscience-based approaches to measuring and improving treatment effects on cognition in schizophrenia: the CNTRICS initiative. *Schizophr Bull* 2007; **33**: 1131–7.

34 van Maarseveen R. The urban–rural education gap: do cities indeed make us smarter? *J Econ Geogr* 2021; **21**: 683–714.

35 Connelly R, Gayle V, Lambert PS. A review of educational attainment measures for social survey research. *Methodol Innov* 2016; **9**: 2059799116638001.

FIGURE LEGENDS

Figure 1. PRISMA flow-chart of studies.

Figure 2. Characteristics of the studies included. *(A) Histogram of mean age of patients in studies, and (B) their imputed average birth date calculated from the age and publication date. HIC= high-income country; LMIC= low- and middle-income country.*

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 classification, and their interaction.*

Figure 4. Pooled difference in educational attainment 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.*

Figure 5. Education gap in patients 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 the Supplementary Information. The education gap in European high-income countries can be found in Supplementary Figure 2. Solid line represents linear meta-regression for each country. Negative values on the Y-axis mean that the educational attainment reported was lower for patients than controls. Note that except from*

China, they all show no significant change in the education gap over time. LMIC = Lower and middle-income countries; HIC =High income countries.

Figure 1 editable form

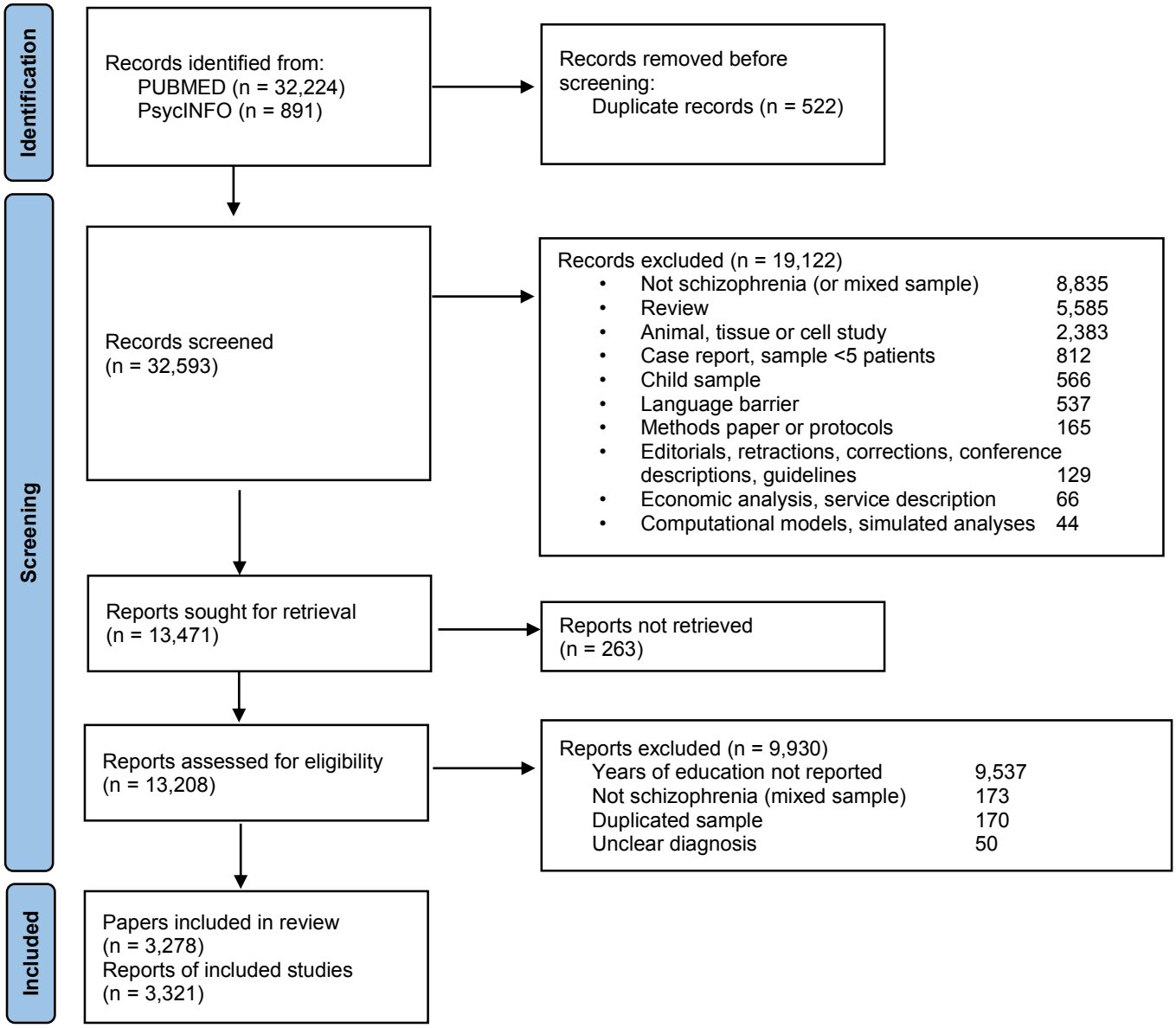


Figure 2

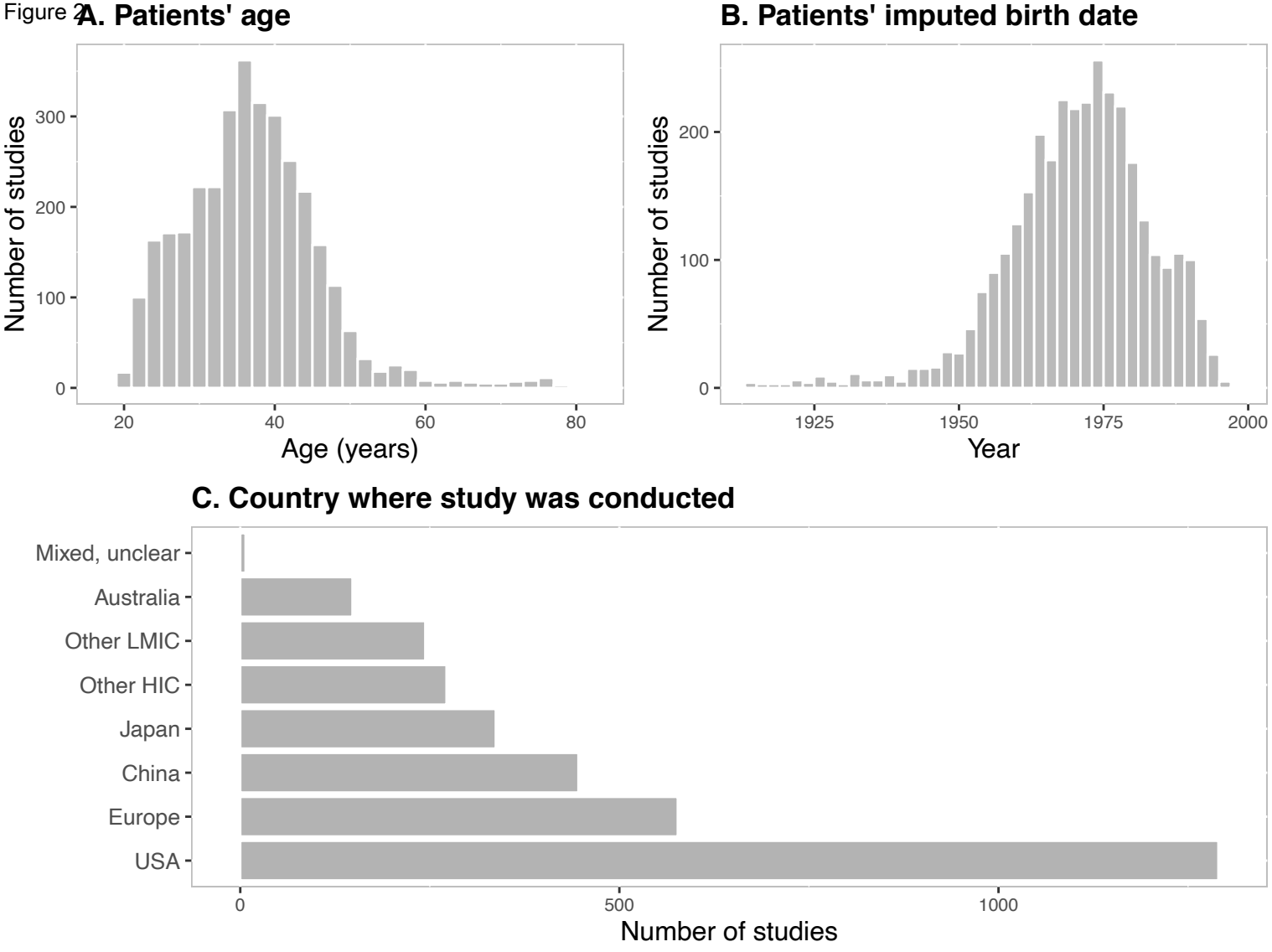

A. Patients' age
Number of studies
300
200
100
0
20
40
60
80
Age (years)
B. Patients' imputed birth date
Number of studies
200
100
0
1925
1950
1975
2000
Year
C. Country where study was conducted
Mixed, unclear
Australia
Other LMIC
Other HIC
Japan
China
Europe
USA
0
500
1000
Number of studies

Figure 3

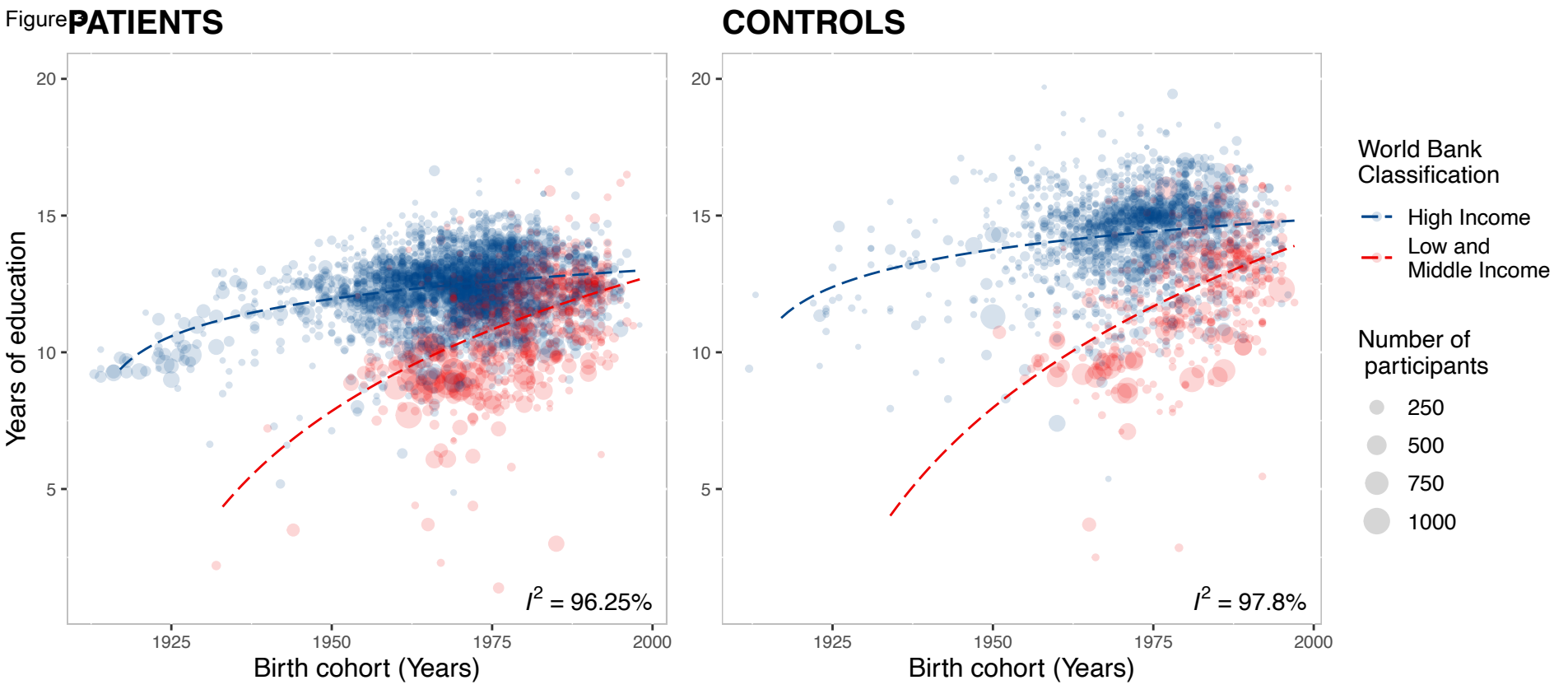

PATIENTS
CONTROLS
Years of education
Birth cohort (Years)
Birth cohort (Years)
20
15
10
5
1925
1950
1975
2000
I^2 = 96.25%
I^2 = 97.8%
World Bank Classification
High Income
Low and Middle Income
Number of participants
250
500
750
1000

Figure 2

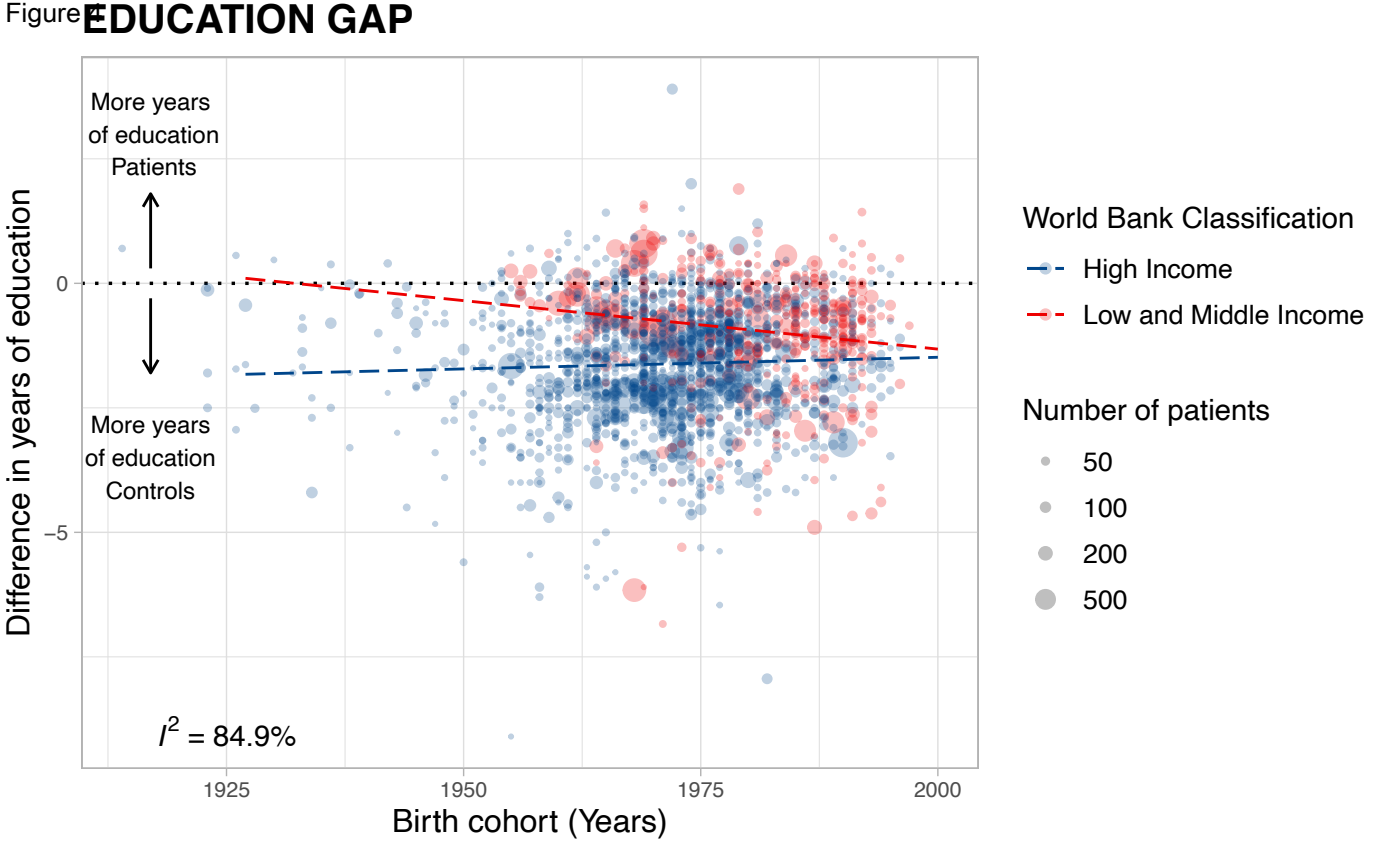
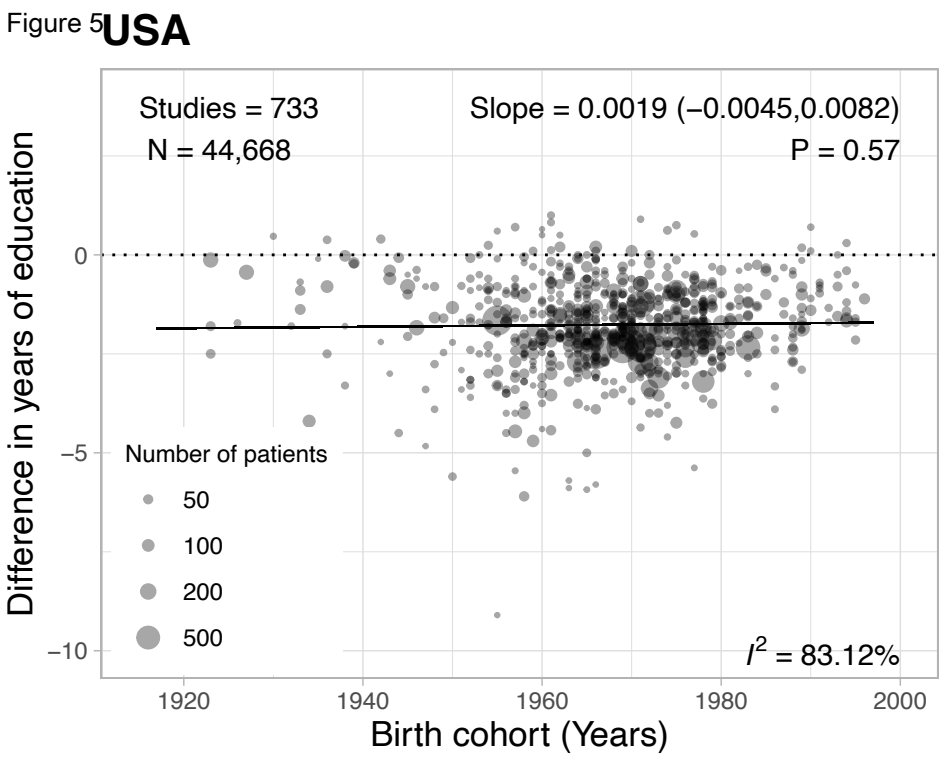
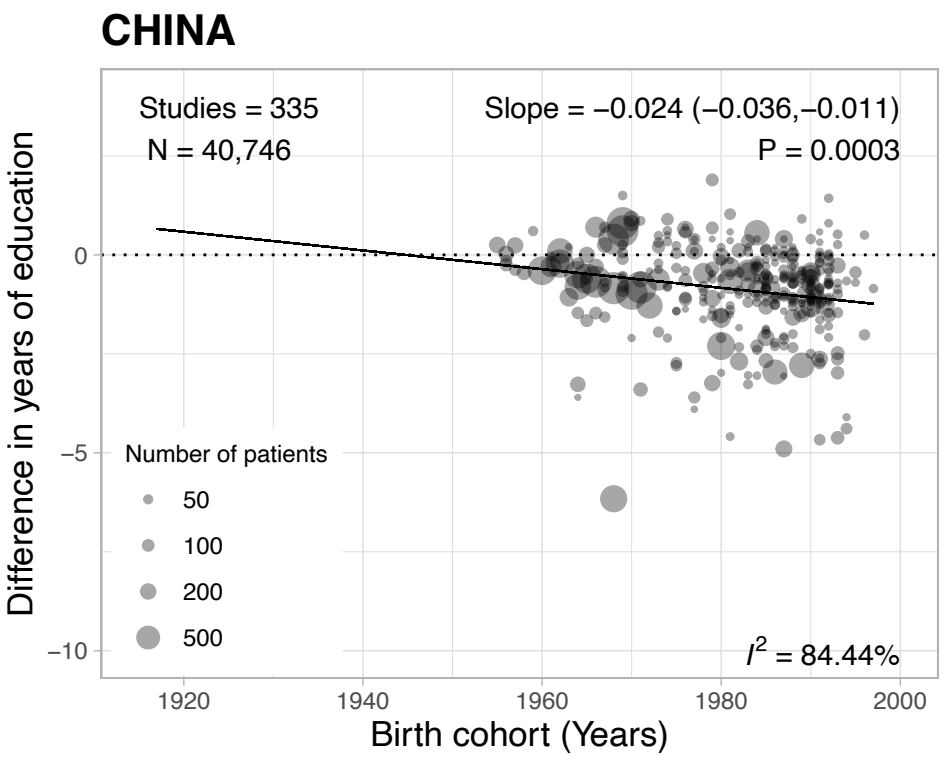
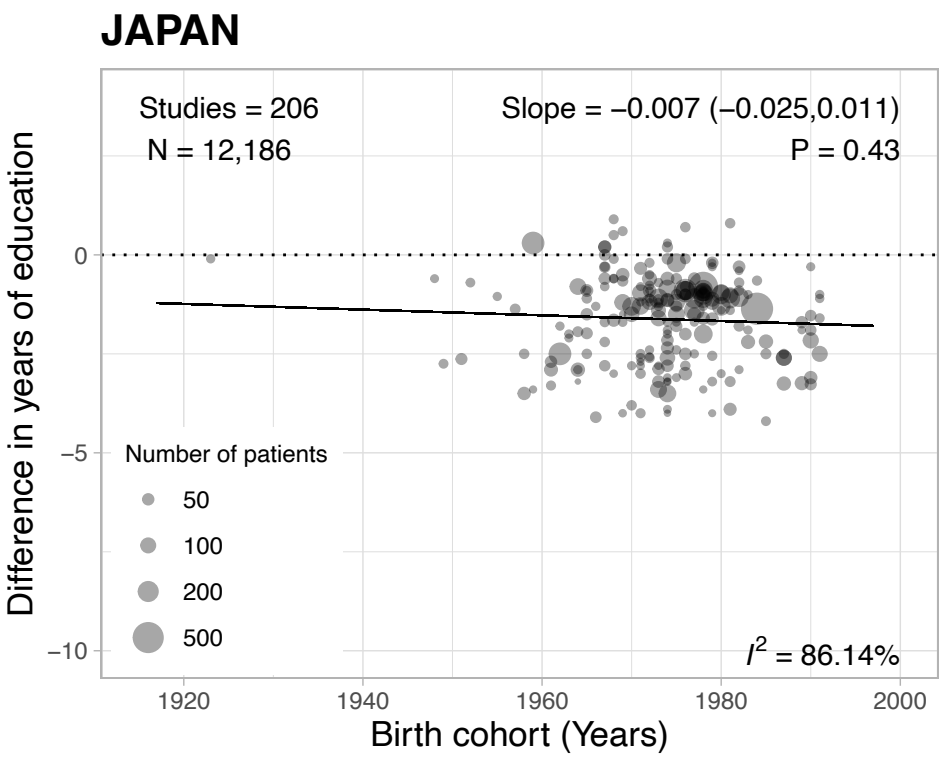
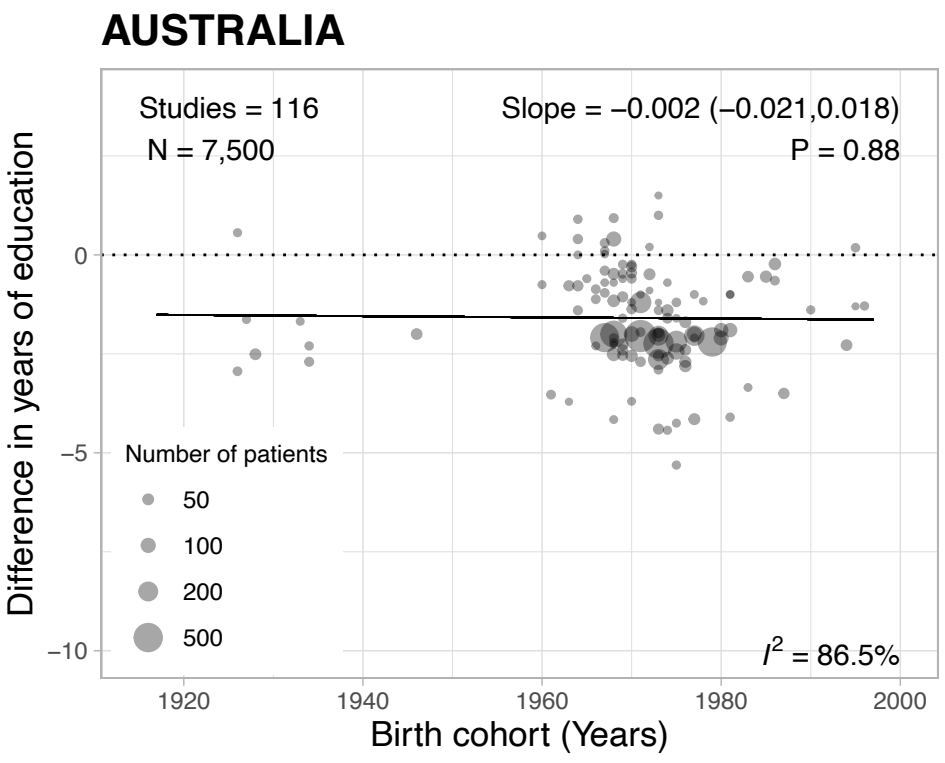

EDUCATION GAP
More years of education Patients
More years of education Controls
0
−5
Difference in years of education
I^2 = 84.9%
1925
1950
1975
2000
Birth cohort (Years)
World Bank Classification
High Income
Low and Middle Income
Number of patients
50
100
200
500

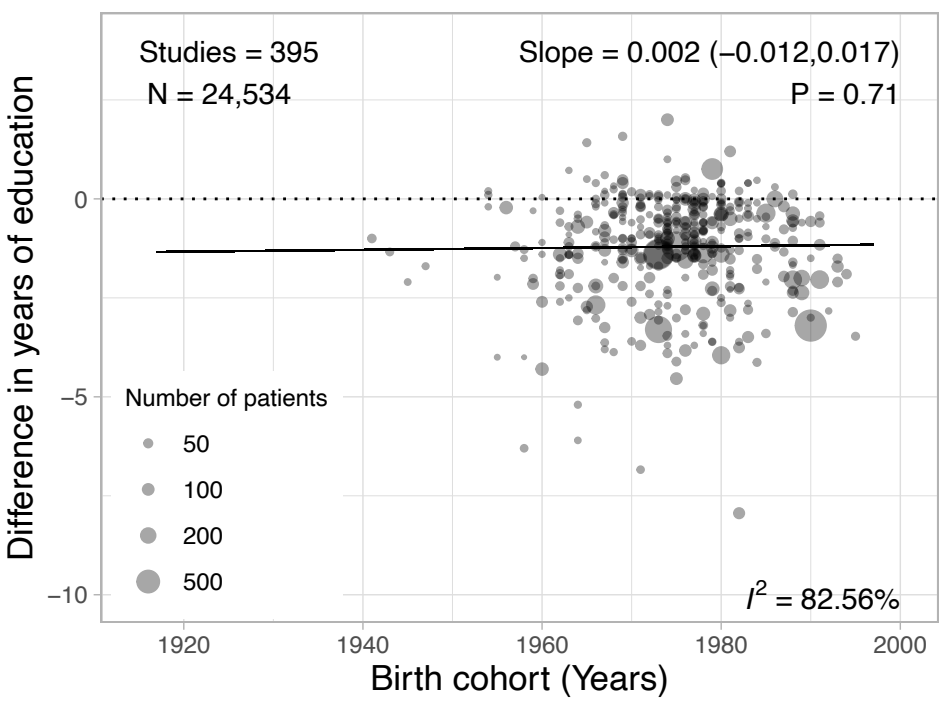
Figure 5

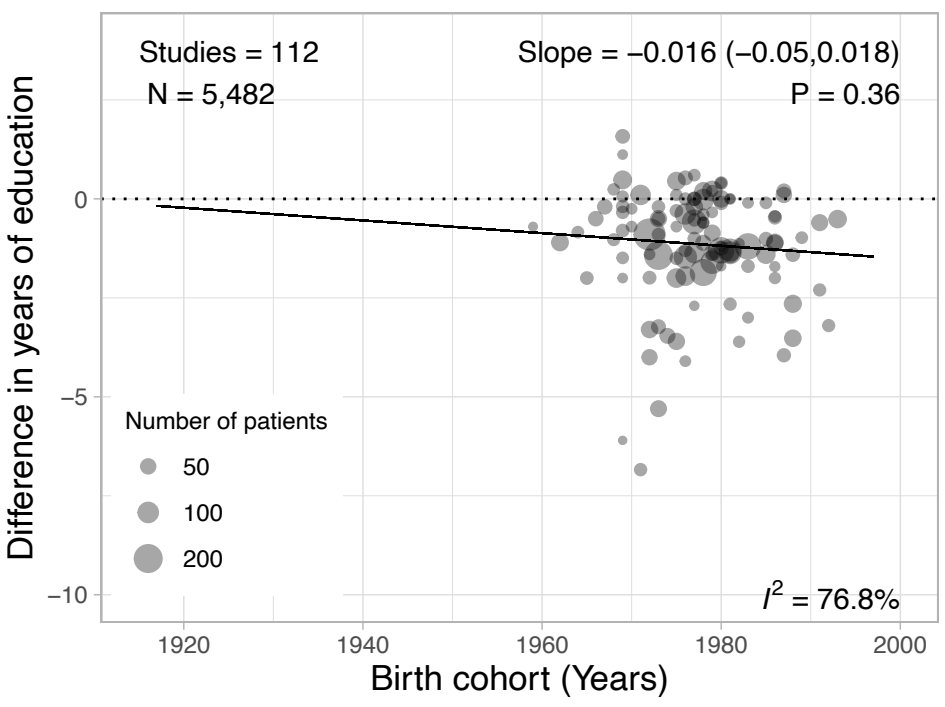

USA
Studies = 733
N = 44,668
Slope = 0.0019 (−0.0045,0.0082)
P = 0.57
Number of patients
50
100
200
500
I^2 = 83.12%
Difference in years of education
Birth cohort (Years)

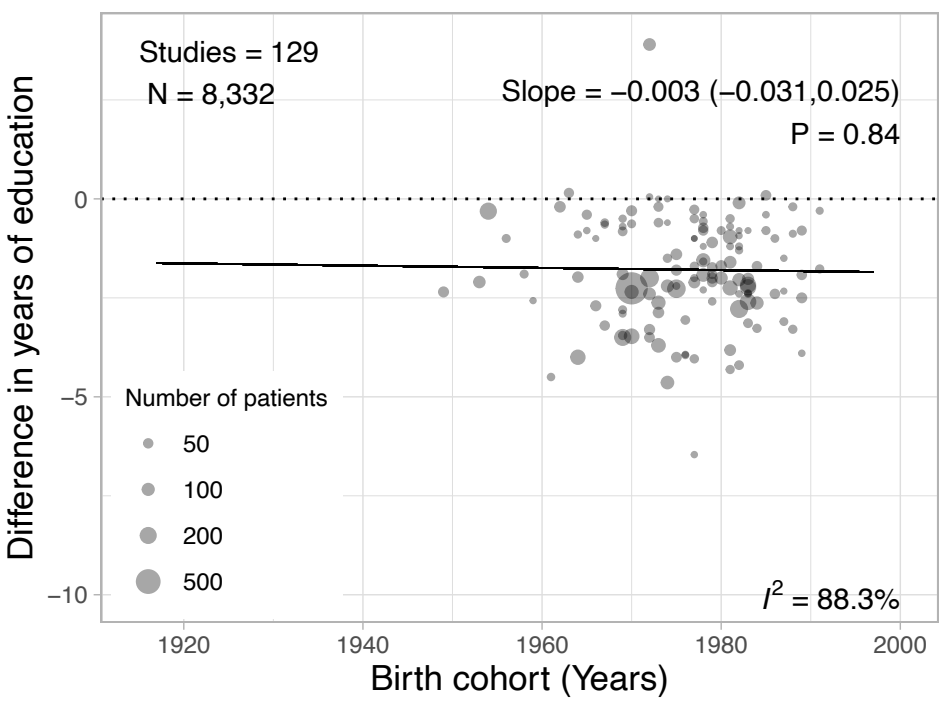

CHINA
Studies = 335
N = 40,746
Slope = −0.024 (−0.036,−0.011)
P = 0.0003
Number of patients
50
100
200
500
I^2 = 84.44%
Difference in years of education
Birth cohort (Years)


JAPAN
Studies = 206
N = 12,186
Slope = −0.007 (−0.025,0.011)
P = 0.43
Number of patients
50
100
200
500
I^2 = 86.14%
Difference in years of education
Birth cohort (Years)


AUSTRALIA
Studies = 116
N = 7,500
Slope = −0.002 (−0.021,0.018)
P = 0.88
Number of patients
50
100
200
500
I^2 = 86.5%
Difference in years of education
Birth cohort (Years)


EUROPE
Studies = 395
N = 24,534
Slope = 0.002 (−0.012,0.017)
P = 0.71
Number of patients
50
100
200
500
I^2 = 82.56%
Difference in years of education
Birth cohort (Years)


LMIC (not including China)
Studies = 112
N = 5,482
Slope = −0.016 (−0.05,0.018)
P = 0.36
Number of patients
50
100
200
I^2 = 76.8%
Difference in years of education
Birth cohort (Years)


OTHER HIC
Studies = 129
N = 8,332
Slope = −0.003 (−0.031,0.025)
P = 0.84
Number of patients
50
100
200
500
I^2 = 88.3%
Difference in years of education
Birth cohort (Years)