General Psychiatry

Understanding the educational inequalities in suicide attempts and their mediators: a Mendelian randomisation study

Jiahao Zhu,[1] Houpu Liu,[1] Rui Gao,[1] Lilu Ding,[1] Jing Wang,[1] Ye Yang,[1] Dan Zhou,[2,3] Yingjun Li [1]

To cite: Zhu J, Liu H, Gao R, *et al*. Understanding the educational inequalities in suicide attempts and their mediators: a Mendelian randomisation study. *General Psychiatry* 2024;**37**:e101369. doi:10.1136/gpsych-2023-101369

► Additional supplemental material is published online only. To view, please visit the journal online (http://dx.doi.org/10.1136/gpsych-2023-101369).

JZ and HL contributed equally.

JZ and HL are joint first authors.

Received 28 September 2023
Accepted 27 December 2023

For numbered affiliations see end of article.

Correspondence to
Dr Yingjun Li;
2016034036@hmc.edu.cn

Dr Dan Zhou;
danzhou@zju.edu.cn

ABSTRACT

Background Educational inequalities in suicide have become increasingly prominent over the past decade. Elucidating modifiable risk factors that serve as intermediaries in the impact of low educational attainment on suicide has the potential to reduce health disparities.

Aims To examine the risk factors that mediate the relationship between educational attainment and suicide attempts and quantify their contributions to the mediation effect.

Methods We conducted a two-sample Mendelian randomisation (MR) analysis to estimate the causal effect of educational attainment on suicide attempts, utilising genome-wide association study summary statistics from the Integrative Psychiatric Research (iPSYCH; 6024 cases and 44 240 controls) and FinnGen (8978 cases and 368 299 controls). We systematically evaluated 42 putative mediators within the causal pathway connecting reduced educational attainment to suicide attempts and employed two-step and multivariable MR to quantify the proportion of the mediated effect.

Results In the combined analysis of iPSYCH and FinnGen, each standard deviation (SD) decrease in genetically predicted educational attainment (equating to 3.4 years of education) was associated with a 105% higher risk of suicide attempts (odds ratio (OR): 2.05; 95% confidence interval (CI): 1.81 to 2.31). Of the 42 risk factors analysed, the two-step MR identified five factors that mediated the association between educational attainment and suicide attempts. The respective proportions of mediation were 47% (95% CI: 29% to 66%) for smoking behaviour, 36% (95% CI: 0% to 84%) for chronic pain, 49% (95% CI: 36% to 61%) for depression, 35% (95% CI: 12% to 59%) for anxiety and 26% (95% CI: 18% to 34%) for insomnia. Multivariable MR implicated these five mediators collectively, accounting for 68% (95% CI: 40% to 96%) of the total effect.

Conclusions This study identified smoking, chronic pain and mental disorders as primary intervention targets for attenuating suicide risk attributable to lower educational levels in the European population.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ In the last decade, inequalities in suicide rates linked to educational level have notably intensified.

⇒ Identifying modifiable risk factors that mediate the relationship between lower educational levels and increased suicide risk is critical for reducing health inequalities.

WHAT THIS STUDY ADDS

⇒ Utilising the Mendelian randomisation methodology, this study established that a 3.4-year decrease in educational attainment is causally associated with a 105% higher risk of suicide attempts.

⇒ Within the assessed range of potential mediators, the proportion of mediation was the most significant for depression (49%), followed by smoking (47%), chronic pain (36%), anxiety disorders (35%) and insomnia (26%).

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ Our findings highlight that interventions aimed at diminishing suicide disparities attributable to lower educational attainment should strategically target the reduction of smoking behaviour and management of chronic pain and mental health disorders.

INTRODUCTION

Suicide is a leading cause of global mortality, with annual deaths approximating one million.[1] In recent decades, the global suicide rate has decreased by 26%; however, the disparity in suicide rates across different socioeconomic strata has intensified.[2] Education, a pivotal aspect of socioeconomic status, exerts considerable influence on other socioeconomic indicators, including income and occupational standing. Despite numerous studies demonstrating an inverse association between educational attainment and suicide,[2–4] the mediators bridging educational disparities and suicide are not fully understood. Previous studies have suggested a correlation between educational level, a spectrum of health behaviours (eg, smoking) and clinical outcomes (eg, depression),[5 6] which

may, in turn, influence the risk of suicide.[7 8] Discerning the causal nature of these factors and their mediating influence on the relationship between lower educational attainment and elevated suicide risk is imperative for crafting targeted interventions to alleviate these disparities. This is particularly crucial, considering the practical challenges inherent in direct intervention in education.

The ascertainment of causal linkages using conventional observational studies is challenging because of the potential for residual confounding, reverse causality and measurement errors. Mendelian randomisation (MR) was developed as a methodologically robust alternative to overcome these challenges.[9] Using genetic variants randomly allocated at conception as instrumental variables, MR estimates the causal effect of an exposure on an outcome in a manner akin to a quasi-experimental design.[9] Recent methodological developments have expanded the applicability of MR to mediation analyses, enriching our aetiological understanding.[10] Using data from large-scale genome-wide association studies (GWASs), this study aimed to evaluate the causal impact of educational attainment on suicide attempts using a standard MR framework (figure 1). Concurrently, we conducted a mediation analysis to investigate the roles of common socioeconomic and behavioural factors, clinical indicators, and mental and physical health conditions in the association between educational attainment and suicide risk.

METHODS

Data sources

This MR study used publicly accessible summary-level data from GWASs. Since no additional individual-level data were used, ethical approval and informed consent were not required. The data selection process was governed by a set of predefined criteria. We prioritised summary statistics that (1) originated from the largest GWASs available, conducted on studies composed entirely or predominantly of individuals of European ancestry; (2) were derived from populations with balanced gender distributions, thereby excluding sex-specific phenotypes such as breast cancer; (3) were not adjusted for heritable covariates, such as body mass index, in order to circumvent collider bias; (4) represented continuous variables rather than dichotomised forms (eg, the continuum of blood pressure vs the binary classification of hypertension), to uphold the suitability of the MR assumptions and enhance the statistical power. In most GWAS data sets, genetic associations were adjusted for age, sex and principal components of genetic ancestry. Detailed statistical descriptors for each phenotype are presented in online supplemental table 1.

Educational attainment

In this study, educational attainment was the focal exposure. Summary statistics for this exposure were sourced from the latest GWAS meta-analysis conducted by the Social Science Genetic Association Consortium (N=3 037 499).[11] The educational attainment phenotype was constructed by mapping the highest level of education attained by individuals at a minimum age of 30 years, congruent with the International Standard Classification of Education System (1997). This classification facilitated the conversion to an equivalent number of years of full-time education. The mean educational duration was 15.4 years with a standard deviation (SD) of 3.4 years.

Suicide attempts

This study examined suicide attempts, the most important predictor of completed suicide, as the primary outcome of interest. To minimise potential bias due to sample overlap, particularly given that measures of educational attainment and some proposed mediators were partially or entirely derived from the UK Biobank cohort, we utilised GWAS summary statistics for suicide attempts that did not include the UK Biobank data. Summary statistics were collated from two independent GWASs: the Lundbeck Foundation Integrative Psychiatric Research (iPSYCH) based in Denmark (6024 cases and 44 240 controls)[12] and the FinnGen conducted in Finland (8978 cases and 368 299 controls).[13] Within the iPSYCH data set, the case definition was contingent on clinical diagnoses of suicide attempts as codified by the 10th edition of the International Classification of Diseases (ICD-10) criteria (X60-X84) through the Danish Psychiatric Central Research Register. A broader inclusion criterion was adopted, wherein individuals presented with a primary mental disorder diagnosis (ICD-10: F chapter) in conjunction with secondary diagnoses indicative of self-harm, poisoning by pharmaceutical substances or other means or injuries localised to the hand, wrist or forearm (ICD-10: T36-T50, T52-T60, S51, S55, S59, S61, S65, S69). Conversely, FinnGen identified cases exclusively based on suicide attempt diagnoses (ICD-10: X60-X84) via national medical registries. The control groups in both studies were population-based participants with no recorded instances of suicide attempts.

Mediators

The identification of putative mediators was guided by four stringent criteria: (1) evidence from the extant literature or scientific rationale should suggest that the mediator contributes to the causal pathway between educational attainment and suicide; (2) the mediator should be modifiable through lifestyle modifications or clinical interventions; (3) the mediator should be sufficiently widespread to imply significant public health relevance in the context of suicide and (4) accessible and well-powered GWAS summary statistics meet the standards necessary for inclusion in the analysis. Following these criteria, we identified 42 candidate mediators that were subsequently stratified into four domains: 11 socioeconomic and behavioural factors, 11 biological indicators, 7 mental health disorders and 13 physical health diseases (online supplemental table 1). A comprehensive

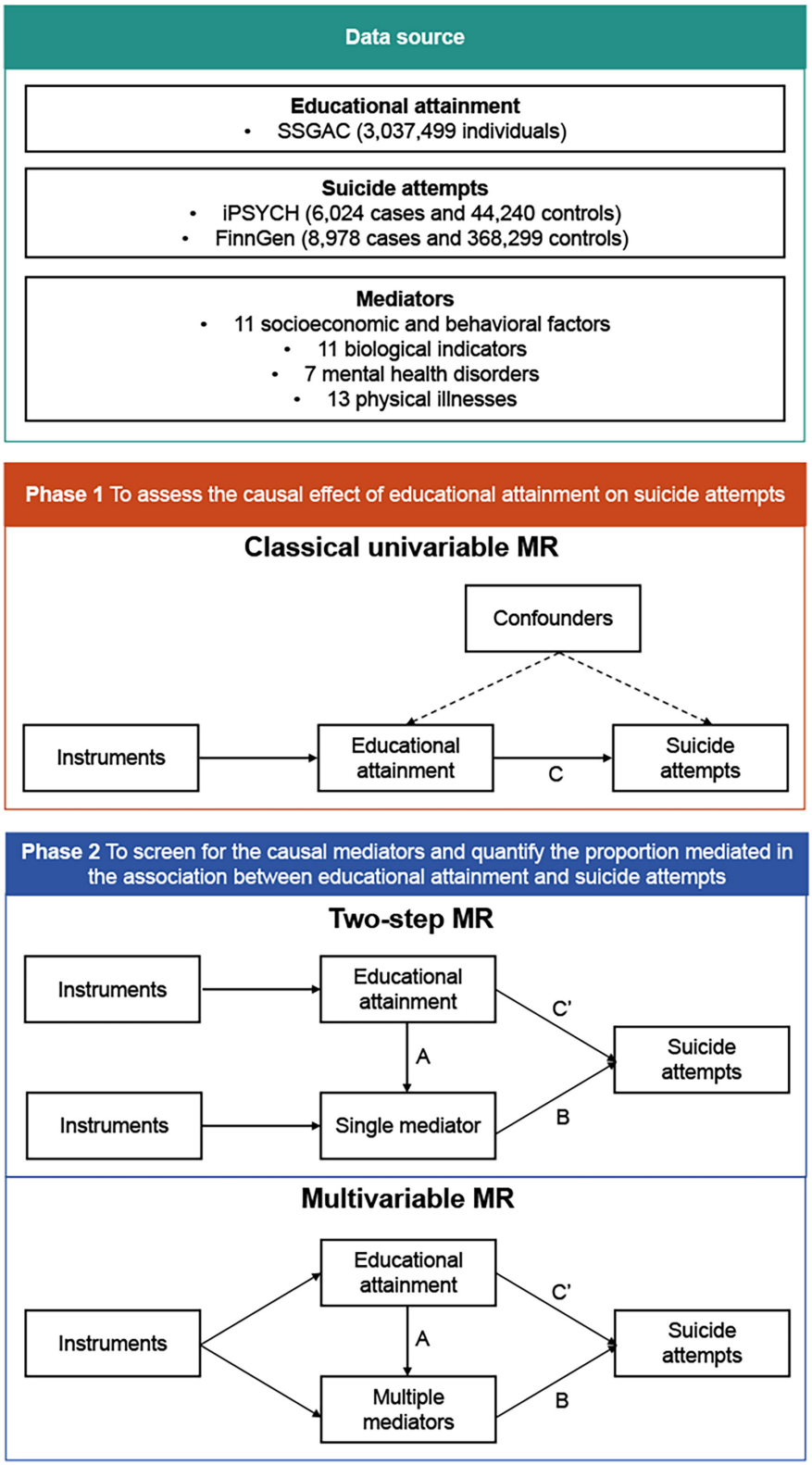

Figure 1 Overview of the study design. In this study, two analytical phases were involved. In phase 1, we assessed the total effect (C) of educational attainment on suicide attempts using classical univariable Mendelian randomisation (MR). In phase 2, 42 potential mediators were screened, and two-step MR and multivariable MR were used to estimate the effect of individual mediators and multiple mediators combined, respectively. In two-step MR, the effect of education on the mediator (A) and the mediator on suicide attempts (B) were estimated separately by employing the separate sets of instruments for both education and the mediator. The indirect effect was then computed by multiplying these two estimates together (A*B), akin to the product method. Conversely, in multivariable MR, the direct effect (C') was estimated using a composite set of instruments for education and mediators. This direct effect was then subtracted from the total effect to derive indirect effect (C-C'), akin to the difference method. iPSYCH, Integrative Psychiatric Research; SSGAC, Social Science Genetic Association Consortium.

discussion of the selected mediators, including their respective data sources, is provided in online supplemental methods 1.

Statistical analysis

Statistical analyses were performed using the 'TwoSampleMR', 'MendelianRandomization', 'MRPRESSO' and 'RadialMR' packages within the R V.4.1.1 software.

Instrument selection

In adherence to conventional norms for instrument selection, our study used a genome-wide significance threshold ($p<5\times10^{-8}$) to extract single-nucleotide polymorphisms (SNPs) with a minor allele frequency >0.01. The extracted SNPs were subjected to a clumping procedure to ensure allelic independence by linkage disequilibrium ($r^2<0.001$, with a clumping distance of 10 000 kb), using the European reference panel. To align the SNP effects between the exposure and outcome data sets and avoid strand mismatches, we executed a harmonisation process. The strength of the instruments was appraised using the F-statistic, where values >10 denoted a sufficiently strong instrument.

Primary analysis

The Wald ratio was computed for individual SNPs to estimate the unbiased effect of exposure on the outcome. Wald ratios for singular SNPs were combined using a random-effects inverse variance-weighted (IVW) approach, applicable to both univariable and multivariable MR analyses.[14] Under the assumptions of instrument validity and balanced horizontal pleiotropy, the IVW method yielded the most precise and robust estimates. The random-effects model further accounted for the inherent heterogeneity of the instruments.

Mediation analysis

Mediation analysis progressed with the inclusion of candidate mediators that conformed to the pre-established selection criteria (figure 2). Within this mediation paradigm, the total effect of exposure (educational attainment) on the outcome (suicide attempts) was divided into direct (unmediated) and indirect (mediated) components (figure 1). We employed a two-step MR strategy (also known as the product of the coefficient approach) for the individual assessment of the mediators.[15] The first step was to estimate the effect of educational attainment on the mediator via univariable MR. The second step was to evaluate the effect of the mediator on suicide attempts, adjusting for educational attainment, within a multivariable MR model. The indirect effect was deduced by multiplying the estimates from both analytical steps. To ascertain the collective effect of mediators, a multivariable difference-in-coefficients (MR) method was conducted, where the direct educational effect was separated by adjusting for all mediators under consideration. The mediated proportion was determined as the ratio of the indirect effect to the total effect. The 95% confidence intervals (CIs) were calculated using the propagation-of-error method.

Sensitivity analysis

To assess the potential bias due to horizontal pleiotropy, a spectrum of alternative univariable MR methods was employed, including the weighted median estimator, weighted mode estimator and MR-Egger regression.[14] For the same purpose, the median-based and MR-Egger approaches were extended to a multivariable MR analysis. These methods are valid under certain assumptions. Cochran's Q statistic was used to evaluate instrument heterogeneity, and the MR-Egger intercept was calculated to detect the presence of horizontal pleiotropy. The pleiotropy residual sum and outlier (MR-PRESSO) outlier test, radial MR and leave-one-out analysis were used to identify and mitigate the influence of outlying SNPs.[14]

Given the substantial correlation among education, intelligence and cognitive performance, we investigated the independent effects of educational attainment on suicide attempts. Multivariable MR was implemented with adjustments for intelligence and cognitive performance metrics, individually and in combination. Summary statistics for intelligence were sourced from a GWAS meta-analysis of 14 cohorts (N=269 867).[16] Summary statistics for cognitive performance were obtained from a meta-analysis of the UK Biobank and Cognitive Genomics Consortium (N=257 841).[17]

Third, Steiger filtering was applied to validate the directionality of the posited relationships.[14] This technique eliminates instrumental SNPs that exhibit greater variance in outcomes relative to exposure. Additionally, reverse-direction MR analyses were conducted using instrumental variables as mediators to elucidate putative causal effects on educational attainment. To assess the causal influence of suicide attempts on mediators and educational attainment, we constructed instruments for suicide attempts using SNPs satisfying a less stringent significance threshold ($p<1\times10^{-6}$), with a similar procedure for clumping because of the absence of genome-wide significant SNPs associated with suicide attempts.[12] A comparable relaxation of the significance threshold was applied to anxiety and other candidate mediators encountering a paucity of SNPs reaching genome-wide significance to boost the statistical power. Additionally, an MR Robust Adjusted Profile Score method was introduced to mitigate the potential weak instrumental bias arising from the utilisation of the relaxed significance threshold.

Finally, to recognise the substantial sample overlap between GWASs of educational attainment and specific mediators (such as smoking) attributable to UK Biobank contributions, we employed genetic associations ascertained from an earlier GWAS of educational attainment, one that did not include UK Biobank data, to facilitate validation.[18]

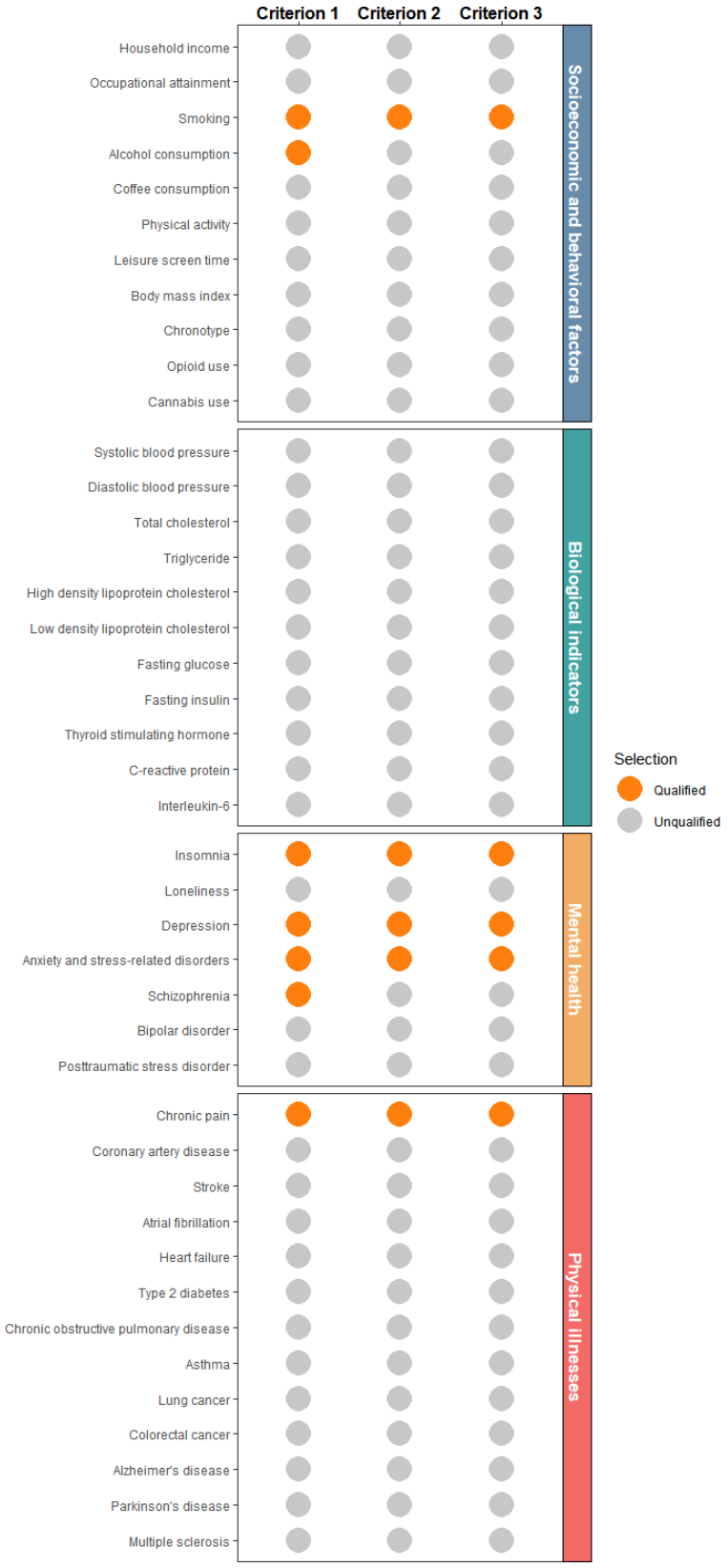

Figure 2 Selection process for mediators of the causal effect of education on suicide attempts. Criterion 1. The mediator should have a causal effect on suicide attempts. Criterion 2. Education should exert a causal effect on the mediator. Criterion 3. The education-mediator association and the mediator-suicide attempts association should be in the same direction. Among the 42 candidate mediators, seven demonstrated causal relationships with suicide attempts through univariable Mendelian randomisation (MR). Alcohol consumption and schizophrenia were then excluded due to a lack of causal association with educational attainment. Five mediators met all three predefined criteria and were thus retained for the final step of the mediation analysis. These encompassed smoking, chronic pain, insomnia, depression, and anxiety and stress-related disorders.

Interpretation of findings

This study's reporting and interpretation align with the Strengthening the Reporting of Observational Studies in Epidemiology using MR guidelines.[19] The results are reported as odds ratios (ORs) with 95% CIs for each SD change in continuous exposure (such as educational level) and per unit change in the log odds scale for dichotomous exposure (such as depression). Considering the traditional overreliance on p values for interpretive validity, our study incorporates a tripartite evaluative framework: (1) association robustness: assessment of the association's statistical significance and its replicability; (2) MR assumption suitability: scrutiny for minimal evidence of horizontal pleiotropy and (3) directional consistency: uniformity of effect directions across different studies and analytical methods.

To explore the relationship between educational attainment and suicide attempts, associations that achieved a nominal significance level ($p<0.05$) via the IVW approach in both the iPSYCH and FinnGen studies and satisfied the latter two evaluative criteria were considered credible. For the 42 putative mediators, we heightened the stringency of the first evaluative criterion: associations were required to exceed the Bonferroni-corrected significance threshold ($p<1.19\times10^{-3}$) in at least one study and simultaneously attain nominal significance ($p<0.05$) in another.

RESULTS

Instrument statistics

In total, 602 independent SNPs were identified as instrumental variables for educational attainment, explaining 2.78% of the variance. The mean F-statistic was 83 (range, 28–576). Detailed statistics for the genetic instruments corresponding to the mediators are presented in online supplemental table 2.

Effect of educational attainment on suicide attempts

Employing univariable MR to assess the total effect, the IVW method results indicated that each SD decrease (equivalent to 3.4 years) in genetically predicted educational attainment was associated with a 1.93-fold (95% CI: 1.60 to 2.33; $p<0.001$) higher risk of suicide attempts in the iPSYCH study and 2.13-fold (OR: 2.13; 95% CI: 1.82 to 2.49; $p<0.001$) in the FinnGen study. The combined analysis of these studies showed an OR of 2.05 (95% CI: 1.81 to 2.31; $p<0.001$) for suicide attempts.

Mediation analysis

Following stringent selection processes, five mediators from the initial 42 candidates were incorporated into the final stage of the mediation analysis (figure 2). In univariable MR analysis, genetically predicted lower educational attainment was associated with increased smoking exposure (beta: 0.40; 95% CI: 0.37 to 0.43; $p<0.001$), a greater number of chronic pain sites endured (beta: 0.30; 95% CI: 0.27 to 0.33; $p<0.001$) and higher risks of insomnia (beta: 0.38; 95% CI: 0.32 to 0.44; $p<0.001$), depression (beta:

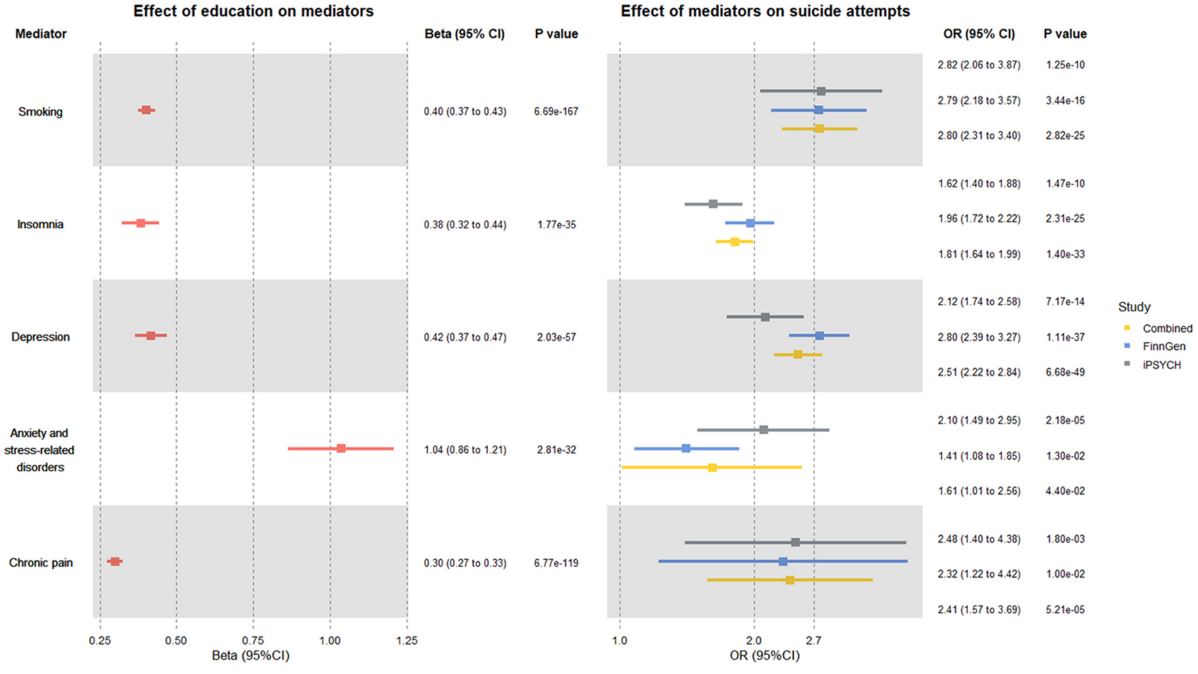

Figure 3 Two-step Mendelian randomisation (MR) results for the causal effect of educational attainment on each mediator (left) and the causal effect of each mediator on suicide attempts (right). MR estimates were derived from the inverse-variance weighted method. The squares represent odds ratios (ORs) or beta coefficients, with the error bars indicating 95% confidence intervals (CIs). The estimates from the Integrative Psychiatric Research (iPSYCH) and FinnGen datasets were combined using the fixed-effects model when no heterogeneity was detected ($p>0.05$); otherwise, the random-effects model was used.

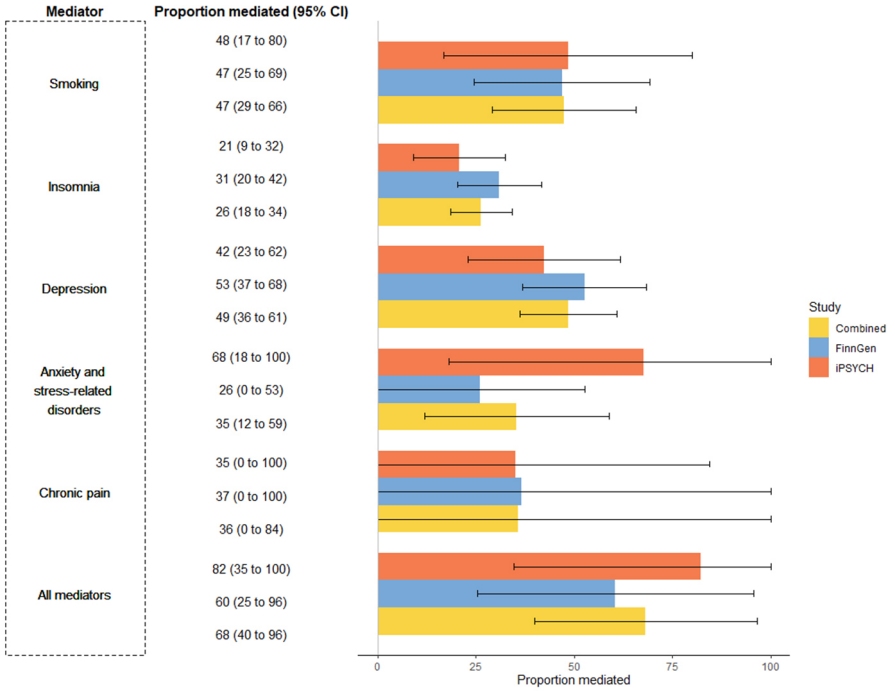

Figure 4 Proportions mediated by each mediator and all mediators combined in the causal association between educational attainment and suicide attempts. The bars represent proportions, with the error bars indicating 95% confidence intervals (CIs). The estimates from the Integrative Psychiatric Research (iPSYCH) and FinnGen datasets were combined using the fixed-effects model when no heterogeneity was detected (p>0.05); otherwise, the random-effects model was used.

0.42; 95% CI: 0.37 to 0.47; p<0.001) and anxiety (beta: 1.04; 95% CI: 0.86 to 1.21; p<0.001) (figure 3). These five mediators demonstrated consistent causal effects on suicide attempts using data from the iPSYCH and FinnGen studies. The combined analysis yielded ORs for suicide attempts of 2.80 (95% CI: 2.31 to 3.40; p<0.001) for increased genetically predicted smoking exposure, 2.41 (95% CI: 1.57 to 3.69; p<0.001) for a higher number of chronic pain sites, 1.81 (95% CI: 1.64 to 1.99; p<0.001) for genetic liability to insomnia, 2.51 (95% CI: 2.22 to 2.84; p<0.001) for genetic liability to depression and 1.61 (95% CI: 1.01 to 2.56; p=0.044) for genetic liability to anxiety (figure 3).

In the combined analysis of iPSYCH and FinnGen, both smoking (proportion mediated: 47%; 95% CI: 29% to 66%) and depression (proportion mediated: 49%; 95% CI: 36% to 61%) alone mediated nearly half of the effect of educational attainment on suicide attempts, followed by anxiety (proportion mediated: 35%; 95% CI: 12% to 59%), chronic pain (proportion mediated: 36%; 95% CI: 0% to 84%) and insomnia (proportion mediated: 26%; 95% CI: 18% to 34%) (figure 4). In multivariable MR, these five mediators together explained 68% (95% CI: 40% to 96%) of the total effect of educational attainment on suicide attempts.

Sensitivity analysis

The primary IVW results were consistent with the alternative pleiotropy-robust methods, both in terms of the direction and magnitude of the effect, except for MR-Egger regression because of its lower efficiency and susceptibility to outliers (online supplemental tables 3 and 4). There was significant heterogeneity in most analyses, as suggested by Cochran's Q statistic; however, the MR-Egger intercept did not indicate evidence of horizontal pleiotropy (online supplemental table 5). Leave-one-out analysis revealed no specific SNP that significantly affected the results (online supplemental table 5). After excluding outliers detected through the MR-PRESSO outlier test and radial MR, the results remained consistent, and heterogeneity was no longer observed (online supplemental table 6). After controlling for intelligence and cognitive performance via multivariable MR, the effect of lower genetically predicted education on the risk of suicide attempts remained largely unchanged (online supplemental table 7). Steiger filtering yielded similar results after controlling for possible reverse causation (online supplemental table 8). In reverse-direction MR, there was evidence of a possible effect of genetically predicted smoking on education (online supplemental table 9), and this association might be driven by directional pleiotropy (p for MR-Egger intercept <0.001). The results also indicated that genetic liability for depression, chronic pain and suicide attempts could lead to lower educational attainment, with no indications of pleiotropy. Comparable results were obtained using summary statistics from a smaller educational GWAS without the UK Biobank (online supplemental table 10).

DISCUSSION

Main findings

Using a methodologically robust MR framework to enhance causal inference, this study indicated that a decrement of 3.4 years in educational attainment is causally associated with an approximately two-fold increased risk of suicide attempts. Our study also elucidates that smoking, chronic pain and mental health disorders collectively mediate a substantial proportion, estimated at 70%, of the association between educational attainment and the risk of suicide attempts.

Previous MR analyses utilising the iPSYCH data set have consistently reported that for each SD decrease in educational attainment, the risk of suicide attempts nearly doubled .[20 21] This study corroborates these findings by employing genetic instruments for educational attainment derived from the most comprehensive GWAS to date, which are approximately three times the size of those used in previous studies and fortified by additional data procured from FinnGen. In contrast to the pronounced impact of educational attainment, our study does not substantiate the putative role of other socioeconomic indices such as household income and occupational class. These results partially support the observation that a low educational level is a more robust predictor of suicidal behaviour and broader health outcomes than income level.[22 23] Educational attainment, reflective of the material and intellectual resources accrued from one's family of origin and typically acquired during the early stages of life, is moderated by accessibility to education and intellectual capacity and potentially exerts influence on an individual's cognitive abilities, thus shaping opportunities to adopt health-enhancing behaviours. Significantly, our multivariable MR analysis showed that the link between genetically predicted educational attainment and suicide attempts was not mitigated on adjustment for intelligence and cognitive performance, indicating the presence of mechanisms that act independently of these intermediary phenotypes.

To date, few studies have attempted to dissect the potential mediating pathways between low educational attainment and elevated suicide risk. Taylor *et al*, utilising data from the Australian National Survey, found that the prevalence of suicide attempts diminished marginally (from 2.9% to 2.5% in men and from 4.3% to 3.6% in women) within the lowest category of educational attainment after adjusting for psychiatric disorders.[24] Using data from a representative health survey in Korea, Ki *et al* deployed a structured equation model to appraise the mediating roles of problematic drinking and mental and physical disorders.[25] Their findings indicated that the impact of educational attainment on suicide attempts was mediated through physical illnesses (proportion mediated: 26%) and problem drinking (proportion mediated: 2%) but not through mental disorders characterised by anxiety or depression. Both studies employed cross-sectional designs, which inherently limited causal deductions because of temporal ambiguity. Our MR investigation supported the possibility of a bidirectional causal relationship between educational attainment and chronic pain, depression and suicide attempts. In a previous MR study, Rosoff *et al* reported that the magnitude of the association between genetically predicted education and suicide attempts remained largely unchanged in a multivariable MR framework, even after adjusting for smoking, alcohol consumption and psychiatric disorders.[20] Nonetheless, that study was limited by its low power and did not formally implement a mediation analysis to quantify the mediating effects. In contrast, the current study leveraged the largest GWAS data sets available to scrutinise the mediating effects of a broad array of risk factors by employing rigorous MR methodologies, including both two-step MR and multivariable MR, to facilitate a comprehensive mediation analysis. Our findings suggest that smoking, chronic pain, insomnia, depression and anxiety contribute to over a quarter of the risk of suicide attempts, which is attributable to lower educational attainment.

In the present analysis, approximately 30% of the educational effect on suicide attempts remains unexplained. While alcohol consumption is a significant risk factor implicated in suicide[26] and has been posited as a potential explanatory mechanism underlying the educational influence, the current study yields no substantial evidence to support the causal relationship between educational attainment and the total amount of weekly drinks. This is in alignment with a preceding MR study.[27] Given the complex and diverse correlations between educational attainment and various patterns of alcohol consumption as well as alcohol-related consequences,[28] the mediation effect by alternate alcohol use behaviours, such as binge drinking or alcohol dependency, remains a viable hypothesis that necessitates further investigation. Moreover, educational attainment has been connected to a spectrum of clinical outcomes that may increase the risk of suicide.[21] The current study suggests that, except for chronic pain, no clinical markers (including blood pressure, lipidemic profiles, glycaemic traits, thyroid hormones and inflammatory cytokines) or physical illnesses (neoplastic, cardiometabolic, chronic respiratory and neurological diseases) demonstrate significant causal relationships with suicide attempts. These null results contrast with those of numerous observational studies, which may have been limited by uncontrolled confounders such as poor socioeconomic conditions, long treatment histories and the presence of comorbid mental health conditions and pain.[29]

Limitations

This study has several limitations. First, as with all MR analyses, avoiding the influence of pleiotropy is a salient challenge. Although multiple sensitivity analyses yielded consistent results and the MR-Egger intercept indicated minimal pleiotropic bias, the possibility of underlying pleiotropy cannot be completely excluded, particularly given the predominantly uncertain biological functions of the instrumental SNPs involved. Furthermore, the

application of MR in mediation analyses presupposes additional assumptions such as the absence of interaction between the exposure and mediator, the absence of time-varying effects of the exposure and mediator and the linear impact of the exposure or mediator on the outcome.[15] By nature, these assumptions are untestable with summary-level data, potentially rendering mediation estimates susceptible to bias. Despite this, two-step MR continues to serve as a credible approach for assessing the causal null hypothesis in the context of mediation analysis. The study also has the limitation of statistical power, particularly for certain mediators such as physical activity, where genetic variants explain only a minimal proportion of the variance. The possibility that some mediators have small-to-moderate effects on suicide attempts cannot be excluded. Additionally, the identification of suicide attempts via hospital records may omit cases that did not seek or receive medical care. Furthermore, despite known sexual dimorphism in suicide, the study design did not permit sex-stratified analysis because of the unavailability of sex-specific GWAS data. Similarly, the effect of age could not be distinguished. Finally, the study was based on data from individuals of predominately European ancestry, which limits the generalisability of the findings across diverse ethnic groups. This is exemplified by a quasi-experimental study indicating that higher educational attainment confers protection against suicide attempts in non-Hispanic White populations but not in Black populations.[30]

Implications

Historical policies aimed at prolonging mandatory education have yielded health improvements, and such efforts must be perpetuated. However, direct interventions targeting education may pose challenges without the accompanying social and political reforms. The findings of this study suggest that strategies to mitigate disparities in suicide attributable to lower educational levels should prioritise the reduction of smoking prevalence and management of chronic pain and mental health disorders. It is imperative that future research endeavours aim to identify additional mediators and elucidate the interactions among them to effectively address and reduce social disparities.

Author affiliations
[1]Department of Epidemiology and Health Statistics, School of Public Health, Hangzhou Medical College, Hangzhou, Zhejiang, China
[2]Vanderbit Genetics Institute, Vanderbilt University Medical Center, Nashville, Tennessee, USA
[3]School of Public Health and the Second Affiliated Hospital, Zhejiang University School of Medicine, Hangzhou, Zhejiang, China

Contributors JZ contributed to the analysis and interpretation of data and drafted the manuscript. HL contributed to data analysis and visualisation. All authors participated in revisions and approved the final version. YL is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Funding This study was supported by the Key Discipline of Zhejiang Province in Public Health and Preventative Medicine (First Class, Category A) at the Hangzhou Medical College, China.

Competing interests None declared.

Patient consent for publication Not applicable.

Ethics approval This investigation used publicly available datasets from previously published studies that do not include any individual-specific information. The original studies had obtained ethical approval and informed consent from the relevant ethics review committees. As a result, the Institutional Board of Hangzhou Medical College exempted this study from further review. Participants gave informed consent to participate in the study before taking part.

Provenance and peer review Not commissioned; externally peer-reviewed.

Data availability statement Data are available in a public, open access repository. Summary statistics for suicide attempts are publicly available in the Lundbeck Foundation Initiative for Integrative Psychiatric Research (iPSYCH) at https://ipsych.dk/forskning/downloads, reference [12] and in the FinnGen study at https://finngen.gitbook.io/documentation/data-download, reference [13].

ORCID iD
Yingjun Li http://orcid.org/0000-0001-8899-916X

REFERENCES

1 Turecki G, Brent DA. Suicide and suicidal behaviour. *Lancet* 2016;387:1227–39.
2 Lorant V, de Gelder R, Kapadia D, *et al*. Socioeconomic inequalities in suicide in Europe: the widening gap. *Br J Psychiatry* 2018;212:356–61.
3 Phillips JA, Hempstead K. Differences in U.S. suicide rates by educational attainment, 2000-2014. *Am J Prev Med* 2017;53:e123–30.
4 Kim M-H, Jung-Choi K, Jun H-J, *et al*. Socioeconomic inequalities in suicidal ideation, parasuicides, and completed suicides in South Korea. *Soc Sci Med* 2010;70:1254–61.
5 Allen L, Williams J, Townsend N, *et al*. Socioeconomic status and non-communicable disease behavioural risk factors in low-income and lower-middle-income countries: a systematic review. *Lancet Glob Health* 2017;5:e277–89.
6 Shahbazi F, Shahbazi M, Poorolajal J. Association between socioeconomic inequality and the global prevalence of anxiety and depressive disorders: an ecological study. *Gen Psychiatr* 2022;35:e100735.
7 Beghi M, Butera E, Cerri CG, *et al*. Suicidal behaviour in older age: a systematic review of risk factors associated to suicide attempts and completed suicides. *Neurosci Biobehav Rev* 2021;127:193–211.
8 Kim H, Ryu S, Jeon HJ, *et al*. Lifestyle factors and suicide risk: a nationwide population-based study. *J Affect Disord* 2023;328:215–21.
9 Smith GD, Ebrahim S. 'Mendelian randomization': can genetic epidemiology contribute to understanding environmental determinants of disease? *Int J Epidemiol* 2003;32:1–22.
10 Carter AR, Gill D, Davies NM, *et al*. Understanding the consequences of education inequality on cardiovascular disease: mendelian randomisation study. *BMJ* 2019;365:l1855.
11 Okbay A, Wu Y, Wang N, *et al*. Polygenic prediction of educational attainment within and between families from genome-wide

association analyses in 3 million individuals. *Nat Genet* 2022;54:437–49.
12 ErlangsenA, Appadurai V, Wang Y, *et al*. Data from: Genetics of suicide attempts in individuals with and without mental disorders: a population-based genome-wide association study. *Lundbeck Foundation Initiative for Integrative Psychiatric Research* 2023.
13 Kurki MI, Karjalainen J, Palta P, *et al*. Data from: Finngen provides genetic insights from a well-phenotyped isolated population. *FinnGen* 2023.
14 Zheng J, Baird D, Borges M-C, *et al*. Recent developments inMendelian Randomizationstudies. *Curr Epidemiol Rep* 2017;4:330–45.
15 Carter AR, Sanderson E, Hammerton G, *et al*. Mendelian randomisation for mediation analysis: current methods and challenges for implementation. *Eur J Epidemiol* 2021;36:465–78.
16 Savage JE, Jansen PR, Stringer S, *et al*. Genome-wide association meta-analysis in 269,867 individuals identifies new genetic and functional links to intelligence. *Nat Genet* 2018;50:912–9.
17 Lee JJ, Wedow R, Okbay A, *et al*. Gene discovery and polygenic prediction from a genome-wide association study of educational attainment in 1.1 million individuals. *Nat Genet* 2018;50:1112–21.
18 Okbay A, Beauchamp JP, Fontana MA, *et al*. Genome-wide association study identifies 74 loci associated with educational attainment. *Nature* 2016;533:539–42.
19 Skrivankova VW, Richmond RC, Woolf BAR, *et al*. Strengthening the reporting of observational studies in epidemiology using mendelian randomisation (STROBE-MR): explanation and elaboration. *BMJ* 2021;375:n2233.
20 Rosoff DB, Kaminsky ZA, McIntosh AM, *et al*. Educational attainment reduces the risk of suicide attempt among individuals with and without psychiatric disorders independent of cognition: a bidirectional and multivariable Mendelian randomization study with more than 815,000 participants. *Transl Psychiatry* 2020;10:388.
21 Yuan S, Xiong Y, Michaëlsson M, *et al*. Genetically predicted education attainment in relation to somatic and mental health. *Sci Rep* 2021;11:4296.
22 Cabello-Rangel H, Márquez-Caraveo ME, Díaz-Castro L. Suicide rate, depression and the human development index: an ecological study from Mexico. *Front Public Health* 2020;8:561966.
23 Rosengren A, Smyth A, Rangarajan S, *et al*. Socioeconomic status and risk of cardiovascular disease in 20 low-income, middle-income, and high-income countries: the prospective urban rural epidemiologic (PURE) study. *Lancet Glob Health* 2019;7:e748–60.
24 Taylor R, Page A, Morrell S, *et al*. Socio-economic differentials in mental disorders and suicide attempts in Australia. *Br J Psychiatry* 2004;185:486–93.
25 Ki M, Seong Sohn E, An B, *et al*. Differentiation of direct and indirect socioeconomic effects on suicide attempts in South Korea. *Medicine (Baltimore)* 2017;96:e9331.
26 Isaacs JY, Smith MM, Sherry SB, *et al*. Alcohol use and death by suicide: a meta-analysis of 33 studies. *Suicide Life Threat Behav* 2022;52:600–14.
27 Rosoff DB, Clarke T-K, Adams MJ, *et al*. Educational attainment impacts drinking behaviors and risk for alcohol dependence: results from a two-sample Mendelian randomization study with ~780,000 participants. *Mol Psychiatry* 2021;26:1119–32.
28 Katikireddi SV, Whitley E, Lewsey J, *et al*. Socioeconomic status as an effect modifier of alcohol consumption and harm: analysis of linked cohort data. *Lancet Public Health* 2017;2:e267–76.
29 Blasco-Fontecilla H, Rodrigo-Yanguas M, Giner L, *et al*. Patterns of comorbidity of suicide attempters: an update. *Curr Psychiatry Rep* 2016;18.
30 Assari S, Schatten HT, Arias SA, *et al*. Higher educational attainment is associated with lower risk of a future suicide attempt among non-Hispanic whites but not non-Hispanic. *J Racial Ethn Health Disparities* 2019;6:1001–10.

Jiahao Zhu is a research assistant at the School of Public Health at Hangzhou Medical College, China. He obtained a bachelor's degree from Hangzhou Medical College, China in 2022. His main research interests include genetic epidemiology and risk factors for major chronic noncommunicable diseases. He has authored more than 10 research papers on Mendelian randomisation.

Houpu Liu is a postgraduate student at the School of Public Health at Hangzhou Medical College, China. She obtained a bachelor's degree from the Communication University of China in 2021. Her main research interests include the assessment of risk factors for chronic noncommunicable diseases by integrating multi-omics data.