The impact of an additional year of education on myopia: an interrupted time series in the UK Biobank.

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Abstract

Introduction: In the past decade, the minimal school leaving age has been raised twice. Previous studies have found evidence for a link between this type of policy and myopia. We aim to use the 1972 raising of school leaving age to estimate the effect of the raising of school leaving age in 2013 and 2015.

Methods: We use a segmented regression model to conduct an instrumental time series analyses of the effect of years of education on myopia using the 1972 raising of school leaving age. To recover the effect of a one-year change, we use the effect of the change on years of education and reflective error in an instrumental variables analysis.

Results: We found evidence for a 0.60 (SE = 0.10) increase in years of education and, after adjusting for probability of having missing data and sex, a -0.14d (SE = 0.03) for refractive error. Instrumental variables analyse implies a -0.24 d/year (SE = 0.05) change in refractive error for each additional year in education.

Conclusion: Our results triangulate the findings of pervious quasi-experimental methods on the effect of years of education on myopia and imply that each raising of school leaving age in the 2010s should be expected to a lead to -0.07 d/yr change in refractive error in the UK population.

Introduction

There has been mounting evidence to suggest that there is a causal relationship between the years of education and Myopia. Although most of the evidence is observational, [1–5] it has been replicated using quasi-experimental designs. For example, Mountjoy et al found using a Mendelian randomisation design that was positively associated with years of education.[6]. Likewise, Zylbermann found a similar result by matching orthodox Jews in Israel with a discordant number of years in education.[7] Increasing years of education, and its intensity, in east Asian countries like China is therefore thought to explain the rise of myopia in these countries.[8] In 2013 the British Government raised the school leaving age from 16 to 17, and then to 18 in 2015.[9] This raises a question about the long term impact these policies may have on the prevalence of myopia in the UK.

Interrupted Time Series (ITS) is a powerful method of policy evaluating in which time trends created separately before and after the introduction of a policy. The difference in the trends around the time of the intervention is then used to estimate the casual effect of the intervention. ITS is robust to standard threats to validity like differential measurement error, confounding, and selection bias as long as these do not themselves change at the same time as the intervention.[10–13] This is generally plausible if the intervention is targeted at a specific outcome and has an exogenous cause.

This study aims to conduct an ITS analysis to explore the impact of raising the compulsory level of schooling by one year. Because an insufficient amount of time has elapsed since these policies to evaluate their long-term effect using an ITS analysis,[14] we used the 1972 increase in compulsory leaving age from 15 to 16 as a policy intervention, using the UK Biobank. Additionally, because ITS is

subject to different biases from the previous quasi-experimental designs, this study will also help to triangulate the previously collected evidence.[15]

Methods

Study Design

This study is an interrupted time series analysis (ITS) analysing the impact of the 1972 change in minimal school leaving age from 15 to 16 on myopia using the UK Biobank. It compares the time trends in the average level of mean spherical equivalent refractive error before and after the introduction of this policy on the 1st of September 1972. This report has been written using the STROBE Checklist.[16]

Settings

The UKB is a large cohort study of around half a million British citizens. Recruitment occurred around the UK between 2006 and 2010 [17, 18]. A full description of the study design, participants and quality control (QC) methods have been described in detail previously.[19] UK Biobank received ethical approval from the Research Ethics Committee (REC reference for UK Biobank is 11/NW/0382), and all participants provided written informed consent.

Participants

To be enrolled into the UK Biobank, participants had to be aged between 40 and 69. All participants attended a baseline assessment at one of 22 assessment centres. While at the centre participants provided information via questionnaires and interviews on demographics, lifestyle, cognitive and psychological measures, health status, as well as anthropometric and biomarker measures.[20] Other measures have subsequently been made at follow-ups, which are generally online (data available at www.ukbiobank.ac.uk).

Eligibility

We included all UKB participants who provided information on the outcome(s) of interest. To avoid any contamination or misclassification effects, we additionally excluded participants born in 1957 from the regression models.

Variables

The primary outcome of this study is mean spherical equivalent refractive error. Other variables were used as negative controls and included: the log odds of reporting the primary outcome, and confounding noted in the prior literature (sex, polygenic risk score of myopia, deprivation) [1, 5, 6]. All variables were created by aggregating the data stratified by birth year.

Data sources

Year of birth (UKB ID: 34) and sex (UKB ID: 31) were recorded at baseline using a mixture of self-report and NHS central registry data.

Age of completing full time education (UKB ID: 845) was asked through a touchscreen question "At what age did you complete your continuous full-time education" at the UK Biobank assessment centre. Answers which were greater than the participants age, or less than five were removed, and participants who put greater than 40 were asked to double check they had put the right number of years down.

Myopia (UKB ID: 20261) was measured using the mean spherical equivalent refractive error, averaged between the eyes. This information was collected at a UKB assessment centre, and calculated using a standardised and publicly available protocol (https://biobank.ndph.ox.ac.uk/showcase/showcase/docs/Visualacuity.pdf). The odds of reporting the primary outcome were then calculated as the ratio of the number of participants in the UKB who had provided information for this item over the number who had not.

The polygenic risk score (PGRS) of myopia was created using summary data from the Pickrell et al. [21] GWAS of myopia, extracted from the EBI GWAS catalogue (https://www.ebi.ac.uk/gwas/efotraits/HP_0000545). This study was conducted using 106086 self-reported cases and 85757 controls who had answered the question "Have you ever been diagnosed by a doctor with near-sightedness (near objects are clear, far objects are blurry)?" for the company 23andMe. The PGRS was then created using the MR-Base GRS extension.[22]

Study size,

The number of participants included in this study was determined by the number of participants in the UKB who met the inclusion criteria.

Quantitative variables

Quantitative variables were by default assumed to be linear, with non-linear terms being added if they improved model fit. Binary variables were converted to log odds and then treated as quantitative variables.

Statistical methods

The time trends were modelled used a segmented ARMA regression model. Each model included a variable for time, a dummy variable for observations occurring after the intervention, and an interaction term between these two variables. Autocorrelation was explored by examining the residuals of an OLS regression, and the ACF, PACF plots, as well as using the Durbin-Watson test.

To check that the intervention did impact on years of education, we ran a sensitivity analysis using years of fulltime education as the outcome. ITS assumes that there is no change in confounding or selection effects at the time of the intervention's introduction. To examine this assumption, we conducted

falsification tests by re-running the analyses using the confounders (Myopia PGRS, sex, and deprivation) previously identified in the literature and the odds of reporting the primary outcome as negative control outcomes. All GLS analyses were conducted using the NLME package in R 4.0.2.[23, 24]. The standard error of predicted points as calculated using the AICcmodavg package.[25]

Because the actual effect of the intervention will not be a one year change in the number of years in school, due to some participants, we used an instrumental variable Wald Ratio to recover the causal effect of a one year increase in education on myopia, using the TwoSampleMR R package.[26] As a sensitivity analyses we calculated the E-value of the point estimate and lower 95% Confidence interval using the E-Value package.[27]

Results

After excluding participants who had withdrawn consent, the sample included 462731 UKB participants with genetic data. Of these, 362974 were excluded because they did not provide data on refractive error (Fig. 1). The data stratified by year of birth is provided in Supplementary Table 1.

Descriptive data

Table 1 provides information on descriptive data included in the study. Refractive error had a mean of -0.34 (SD = 2.39) and years of education had a mean of 16.51 (SD = 3.08). The only variable with missing data within the included dataset was years of education, with 34858 missing values. Of the covariates, all were associated with refractive error, but only year of birth was associated with years in education.

Outcome Data

The primary outcome, refractive error, had a mean of -0.24 (SD = 2.39). Years of education had a mean of 16.51 (SD = 3.08), and the crude mean difference between them was − 0.06 d/year (SE = 0.00, p < 0.001, Table 1).

Main results

After accounting for auto correlation (Supplementary Fig. 1), we found a significant difference in the years of education before and after the introduction of the intervention (Table 2), equivalent to a 0.600 (SE = 0.098) increase in years of education for the 1958 birth cohort. After accounting for autocorrelation (Supplementary Fig. 2) we also found a significant difference in the years of education before and after the introduction of the intervention (Supplementary Table 2), equivalent to a -0.122 d change in refractive error for the 1958 birth cohort. However, we found evidence of a discontinuity in the trends of the log odds of being male and the log odds of having missing data (Supplementary Tables 5 and 6), and so these variables were included as covariates in the final model. This model found evidence of a -0.141 d (SE = 0.032) change in refractive error for those born in 1958.

The instrumental variables Wald estimate for the causal effect of a one-year increase in education on refractive error was − 0.235 d/year (SE = 0.053, 95%CI -0.130 to -0.339). Instrumental variables analysis makes three assumptions: that the intervention does impact the exposure, that the intervention does not impact the outcome other than via the exposure, and that the intervention-outcome association is not confounded. The first assumption can be guaranteed by the strong association we found in the ITS using years of education as an outcome. Although the second assumption cannot be proved statistically, it is unclear how raising the school leaving could impact on myopia other than via the years in education. The final assumption also cannot be proven. However, E-value for the impact of the association between the intervention and refractive error was 1.296 (point estimate) or 1.206 (lower 95% CI). This means that the any variable would need to have a relative risk of around 1.3 with both the intervention and myopia to completely confound the association. This seems implausible given that the risk ratios for the two known confounders, sex and missingness, with the intervention were around 1.07 and 1.06 respectively.

Other analyses

The secondary ITS analyses with potential confounders are reported in the supplementary results (Supplementary Tables 3−6, and Supplementary Figs. 3−10).

Table 1
Descriptive information on sample.

Variable	N	Mean (SD)	Linear association with refractive error (SE, p-value)	Linear association with years of education (SE, p-value)
refractive error	99757	-0.34 (2.39)	NA	-0.11 (0.01, <2e-16)
Years in education	64899	16.51 (3.08)	-0.06 (0.00, <2e-16)	NA
Year of birth	99757	1952 (7.99)	-0.04 (0.00, <2e-16)	0.035 (0.002, <2e-16)
Myopia GRS	99757	0.40 (0.41)	-0.69 (0.02, <2e-16)	-0.00 (0.03, 0.892)
Sex		NA	0.04 (0.02, 0.0188)	-0.04 (0.02, 0.138)
male	46042			
female	53715			

Table 2

Final segmented regression model for the discontinuity in mean years of education.

Coefficient*	Beta (95% CI)	Standard error	p-value
Intercept	-73856.52 (-1.266609e + 05 to-2.105219e + 04)	23698.852	0.0109
Year of birth	75.65 (2.155647e + 01 to 1.297345e + 02)	24.275	0.0109
Year of birth squared**	-0.02 (-3.321625e-02 to -5.513824e-03)	0.006	0.0110
Pre/post intervention	0.50 (1.434375e-01 to 8.534892e-01)	0.159	0.0107
YoB Trend post intervention	-29.38 (-4.847863e + 01 -to -1.027435e + 01)	8.573	0.0065
YoB^2 Trend post intervention**	7.689155e-06 (2.701612e-06 to 1.267670e-05)	0.000	0.0064

*P-value for having a moving-average lag of 2: 0.1197, P-value autorepression lag of 1: 0.8251.

**P value for departure from linearity in time tend: 0.0016

Table 3

Final segmented regression model for the discontinuity in mean refractive error.

Coefficient	Beta (95% CI)	Standard error	p-value
Intercept	31169.507 (9.866819e + 03 to 5.247220e + 04)	9237.923	0.0097
Year of birth	-31.879 (-5.369036e + 01 -to -1.006758e + 01)	9.459	0.0098
Year of birth squared	0.008 (2.567983e-03 to 1.373375e-02)	0.002	0.0098
Pre/post intervention	-0.111 (-2.269750e-01 − to 5.026303e-03)	0.050	0.0584
YoB Trend post intervention	9.024 (1.758912e + 00 to 1.628923e + 01)	3.151	0.0210
YoB^2 Trend post intervention	-2.361655e-06 (-4.260877e-06 to -4.624335e-07)	0.000	0.0209
Log odds of being male	0.143 (-8.098340e-01 to 1.096214)	0.413	0.7379
Log odds of missing data	-0.350 (-1.160521 to 4.609127e-01)	0.352	0.3489

Discussion

Key Results

This study aimed to use the 1972 raising of the school leaving age as a discontinuity in an ITS analysis to explore the causal effect of increasing years of education on myopia/refractive error. It found that the change of policy lead to a 0.600 a year increase in the average years in education in the UKB and a -0.122 d change in refractive error. This translated into a -0.235 (95%CI -0.130 to -0.339) d/year change in refractive error from increasing years of education.

Limitations

A strength of using an ITS design is that it is robust to most form of bias in an observational study. However, confounders, selection effects, and measurements which change at the point of intervention will bias an ITS analyses. One worry may be that because a reasonably high proportion of potential confounders did appear to change with the intervention, that there may be some residual confounding. However, even if there were residual confounding, the E-value implies that the confounder would need to have a much larger effect than any of the candidates explored in this study. Likewise, although we found that the total number of participants recruited into the UKB did not change, we cannot guarantee that there was a change in the type of person that was recruited after the 1957 birth cohort. However, the absence of a corresponding change in the mean myopia GRS scores implies any bias may not be large. Finally, because all measures were taken at roughly the same time using a standardised protocol, there is unlikely to be any differential measurement error.

A final potential limitation is that the exclusion restriction assumption for the instrumental variables analysis would be violated if there was another change in policy which impacted myopia which effected birth cohorts after 1957 but before.

Interpretation

This study found evidence of a causal effect of a year of education on refractive error between − 0.130 to -0.339 d/year.[6] This is comparable with the estimate found by Mountjoy et al, who found a -0.27 d/y (95%CI -0.37 to -0.17) in a Mendelian randomisation design, and an observational change of -0.18 d/y (95% CI -0.19 to -0.17). As with Mountjoy, we found that adjusting for more confounders increased the effect size. Although the biological mechanism relating years of education to myopia is unclear, the similarity of these results using different quasi-experimental designs is indicative of a true effect being around − 0.25 d/y.

Generalizability

The results of the effect of the raising of school leaving age on myopia are unlikely to generalise to other populations. Firstly, the UKB is a highly selective population, who are more likely to leave school after the minimal school leaving age than the general population.[28]

Given the evidence that the true effect is around − 0.23 d/y an approximation of the population attributable risk from the policies is recoverable with information on the prevalence of the youths leaving school at the minimal age. In Hansard proportions cited at the time of the policy's debate in parliament

range from 55% in the Northeast leaving at the minimal age, to around 40% in the Southeast.[29] These would imply a PAR of − .09 to -0.13 d.

Likewise, it is estimated that only around 30% of youths in the early 2010s were leaving school at the minimal age, which would imply a -0.07 d change per school year added.[30] Therefore, although years of education appears to have a relatively large effect on refractive error, it is likely that the two year increase in minimal school leaving age in the 2010s will have a similar effect on the UK population's eye sight as the one year change in the 1970s.

Other Information

UK Biobank statement

This project was conducted using UKB application no. 21829. UK Biobank was established by the Wellcome Trust medical charity, Medical Research Council, Department of Health, Scottish Government and the Northwest Regional Development Agency. It has also had funding from the Welsh Government, British Heart Foundation, Cancer Research UK and Diabetes UK. UK Biobank is supported by the National Health Service (NHS). UK Biobank is open to bona fide researchers anywhere in the world.

Protocol registration

The protocol was pre-registered at: https://osf.io/mkwfj/ on 04/06/2021.

R Code

The R code used in this study is available in the supplementary methods.

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Disclosures

Both authors are dyslexic and apologises for any unnoticed typos or spelling mistakes.

Declarations

Competing interests: The authors declare no competing interests.

References

1. Rosner M, Belkin M. Intelligence, education, and myopia in males. Archives of ophthalmology. 1987 Nov 1;105(11):1508–11.

2. Al-Bdour MD, Odat TA, Tahat AA. Myopia and level of education. European journal of ophthalmology. 2001 Jan;11(1):1–5.

3. Eong KA, Tay TH, Lim MK. Education and myopia in 110,236 young Singaporean males. Singapore Med J. 1993 Dec 1;34(6):489 – 92.

4. Williams KM, Bertelsen G, Cumberland P, Wolfram C, Verhoeven VJ, Anastasopoulos E, Buitendijk GH, Cougnard-Grégoire A, Creuzot-Garcher C, Erke MG, Hogg R. Increasing prevalence of myopia in Europe and the impact of education. Ophthalmology. 2015 Jul 1;122(7):1489-97.

5. Mirshahi A, Ponto KA, Hoehn R, Zwiener I, Zeller T, Lackner K, Beutel ME, Pfeiffer N. Myopia and level of education: results from the Gutenberg Health Study. Ophthalmology. 2014 Oct 1;121(10):2047-52.

6. Mountjoy E, Davies NM, Plotnikov D, et al. Education and myopia: assessing the direction of causality by mendelian randomisation. BMJ 2018;361:k2022

7. Zylbermann R, Landau D, Berson D. The influence of study habits on myopia in Jewish teenagers. J Pediatr Ophthalmol Strabismus 1993;30:319-22.8254449

8. Morgan IG, French AN, Rose KA. Intense schooling linked to myopia.

9. https://en.wikipedia.org/wiki/Raising_of_school_leaving_age_in_England_and_Wales Accessed on 04/06/2021

10. Jandoc R, Burden AM, Mamdani M, Lévesque LE, Cadarette SM. Interrupted time series analysis in drug utilization research is increasing: systematic review and recommendations. Journal of clinical epidemiology. 2015 Aug 1;68(8):950-6.

11. Wagner AK, Soumerai SB, Zhang F, Ross-Degnan D. Segmented regression analysis of interrupted time series studies in medication use research. Journal of clinical pharmacy and therapeutics. 2002 Aug;27(4):299–309.

12. Lagarde M. How to do (or not to do)… Assessing the impact of a policy change with routine longitudinal data. Health policy and planning. 2012 Jan 1;27(1):76–83.

13. Bernal JL, Cummins S, Gasparrini A. Interrupted time series regression for the evaluation of public health interventions: a tutorial. International journal of epidemiology. 2017 Feb 1;46(1):348 – 55.

14. Penfold RB, Zhang F. Use of interrupted time series analysis in evaluating health care quality improvements. Academic pediatrics. 2013 Nov 1;13(6):S38-44.

15. Munafò MR, Smith GD. Robust research needs many lines of evidence.

16. Von Elm E, Altman DG, Egger M, Pocock SJ, Gøtzsche PC, Vandenbroucke JP. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement: guidelines for reporting observational studies. Annals of internal medicine. 2007 Oct 16;147(8):573–7.

17. Allen N, Sudlow C, Downey P, et al. UK Biobank: current status and what it means for epidemiology. Health Policy Technol. 2012;1(3):123–126.

18. Allen, N. E., Sudlow, C., Peakman, T., Collins, R. & UK Biobank. UK Biobank Data: Come and Get It. Sci. Transl. Med. 6, 224ed4-224ed4 (2014).

19. Collins, R., Peakman, T., Alegre-Diaz, J., al., et & al., et. What makes UK Biobank special? Lancet (London, England) 379, 1173–4 (2012).

20. Ruth Mitchell, Elsworth, BL, Mitchell, R, Raistrick, CA, Paternoster, L, Hemani, G, Gaunt, TR (2019): MRC IEU UK Biobank GWAS pipeline version 2. https://doi.org/10.5523/bris.pnoat8cxo0u52p6ynfaekeigi

21. Pickrell JK, Berisa T, Liu JZ, Ségurel L, Tung JY, Hinds DA. Detection and interpretation of shared genetic influences on 42 human traits. Nat Genet 2016;48:709–17. doi:10.1038/ng.3570

22. https://github.com/sean-harrison-bristol/UK_Biobank_PRS

23. R Core Team (2020). R: A language and environment for statistical computing. R Foundation for Statistical computing, Vienna, Austria. URL https://www.R-project.org/

24. Jose Pinheiro and Douglas Bates and Saikat DebRoy and Deepayan Sarkar and R Core Team: Linear and Nonlinear Mixed Effects Models. https://CRAN.R-project.org/package=nlme

25. Marc J. Mazerolle (2020) AICcmodavg: Model selection and multimodel inference based on (Q)AIC(c)}, https://cran.r-project.org/package=AICcmodavg}.

26. Hemani G, Zheng J, Elsworth B, Wade KH, Baird D, Haberland V, Laurin C, Burgess S, Bowden J, Langdon R, Tan VY, Yarmolinsky J, Shihab HA, Timpson NJ, Evans DM, Relton C, Martin RM, Davey Smith G, Gaunt TR, Haycock PC, The MR-Base Collaboration. The MR-Base platform supports systematic causal inference across the human phenome. eLife 2018;7:e34408. doi: 10.7554/eLife.34408

27. VanderWeele TJ, Ding P (2011). "Sensitivity analysis in observational research: introducing the E-value." Annals of Internal Medicine, **167**(4), 268–274.

28. Clark D, Royer H. The Effect of Education on Adult Mortality and Health: Evidence from Britain. Am Econ Rev. 2013;103:2087–2120.

29. https://api.parliament.uk/historic-hansard/commons/1972/mar/23/school-leaving-age
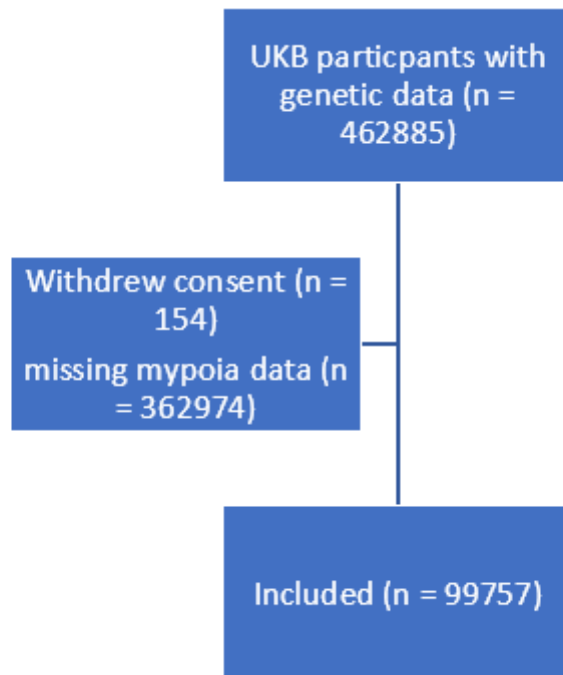
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Figures

Figure 1

Participant Flow Diagram

Figure 2

Discontinuity in mean years of education. Black vertical lines indicate the year of intervention, blue vertical lines indicate the data analysed. The black trend lines represent the observed data, while the blue trend line represents the counterfactual trend.
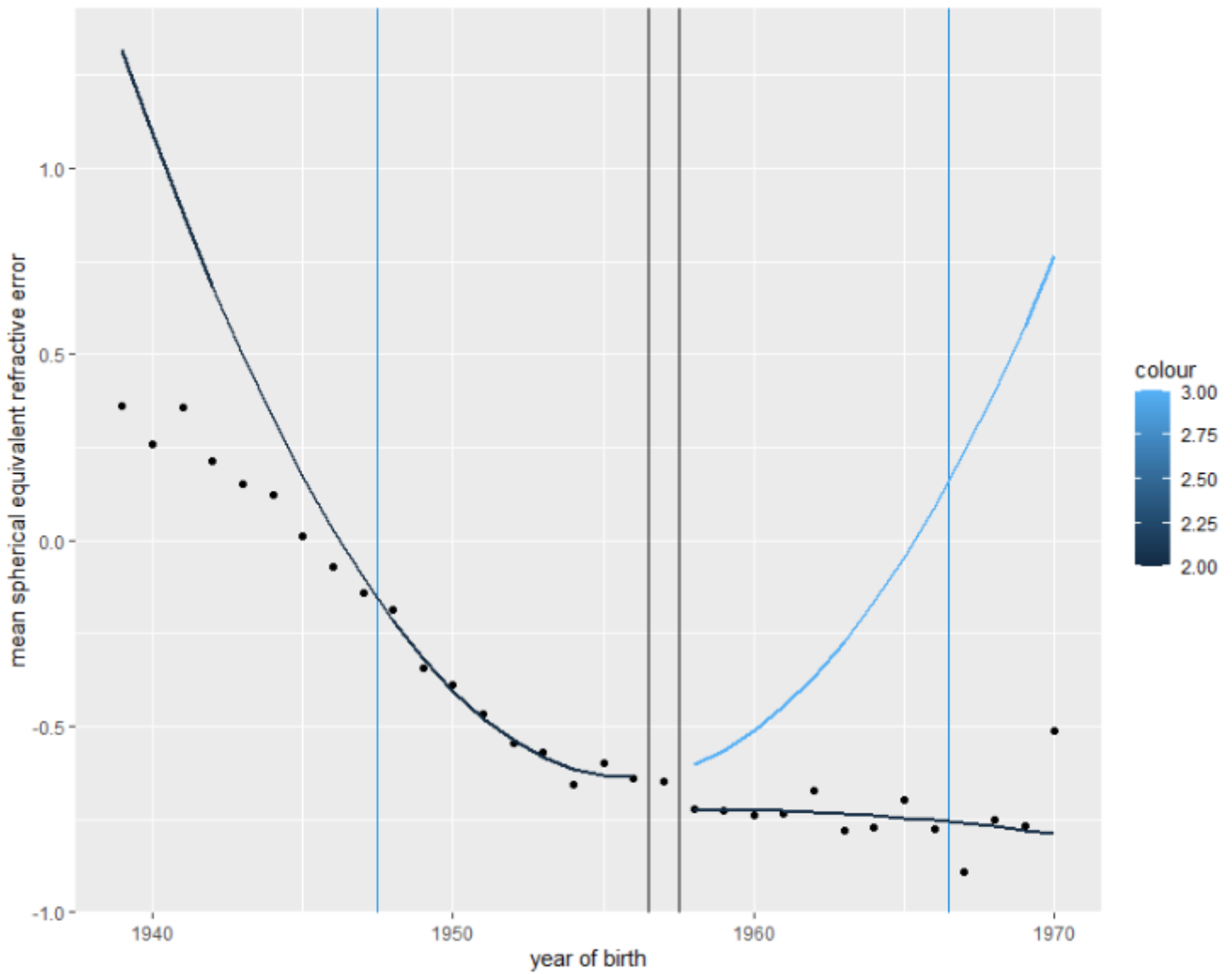
Figure 3

iscontinuity in mean refractive error. Black vertical lines indicate the year of intervention, blue vertical lines indicate the data analysed. The black trend lines represent the observed data, while the blue trend line represents the counterfactual trend.

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- myopiaitssupresults.docx
- Stab1.csv
- Rcode.docx