Educational inequalities in statin treatment for preventing cardiovascular disease: cross-sectional analysis of UK Biobank

Alice R Carter, Epidemiologist 1,2*, Dipender Gill, Clinician Scientist 3, Richard Morris, Professor of Medical Statistics 2,4, George Davey Smith, Professor of Clinical epidemiology 1,2,5, Amy E Taylor, Research fellow 2,5, Neil M Davies†, Senior research fellow 1,2,6, Laura D Howe†, Reader in Epidemiology and Biostatistics 1,2

1) MRC Integrative Epidemiology Unit, University of Bristol
2) Population Health Sciences, Bristol Medical School, University of Bristol
3) Department of Epidemiology and Biostatistics, School of Public Health, Imperial College London, London, UK
4) Centre for Academic Primary Care, University of Bristol
5) NIHR Bristol Biomedical Research Centre, University of Bristol
6) K.G. Jebsen Center for Genetic Epidemiology, Department of Public Health and Nursing, NTNU, Norwegian University of Science and Technology, Norway.

†NMD and LDH contributed equally

Corresponding author:
Ms Alice R Carter
Oakfield House,
Oakfield Grove,
Bristol,
BS8 2BN
alice.carter@bristol.ac.uk

@alicerosecarter

Funding

No funding body has influenced data collection, analysis or its interpretations. This research was conducted using the UK Biobank Resource using application 10953. ARC is funded by the UK Medical Research Council Integrative Epidemiology Unit, University of Bristol (MC_UU_00011/1). ARC, GDS, AET, NMD and LDH work in a unit that receives core funding from the UK Medical Research Council and University of Bristol (MC_UU_00011/1). DG is supported by the Wellcome Trust 4i Programme (203928/Z/16/Z) and British Heart Foundation Centre of Research Excellence (RE/18/4/34215) at Imperial College London. AET and GDS are supported by the National Institute for Health Research (NIHR) Biomedical Research Centre based at University Hospitals Bristol NHS Foundation and the

NOTE: This preprint reports new research that has not been certified by peer review and should not be used to guide clinical practice.
University of Bristol. The views expressed are those of the authors and not necessarily those of the NHS, the NIHR, or the Department of Health. The Economics and Social Research Council support NMD via a Future Research Leaders grant (ES/N000757/1) and a Norwegian Research Council Grant number 295989. LDH is funded by a Career Development Award from the UK Medical Research Council (MR/M020894/1).

Disclosures

DG is employed part-time by Novo Nordisk. The remaining authors have no conflicts of interest to declare.

Contributions:

ARC designed the study, cleaned and analysed the data, interpreted the results, wrote and revised the manuscript. DG advised on defining medications, interpreted the results and critically reviewed and revised the manuscript. RM advised on analyses, interpreted the results and critically reviewed and revised the manuscript. GDS, AET, NMD and LDH all designed the study, interpreted the results, critically reviewed and revised the manuscript and provided supervision for the project. NMD and LDH contributed equally and are joint senior authors on this manuscript. ARC and LDH serve as guarantors of the paper. The corresponding author attests that all listed authors meet authorship criteria and that no others meeting the criteria have been omitted.

Transparency statement:

ARC affirms that the manuscript is an honest, accurate and transparent account of the study being reported and no important aspects of the study have been omitted.

Acknowledgements:

This work was carried out using the computational facilities of the Advanced Computing Research Centre - http://www.bris.ac.uk/acrc/ and the Research Data Storage Facility of the University of Bristol - http://www.bris.ac.uk/acrc/storage/.

Word count: 4658
Abstract

Importance: The most socioeconomically deprived individuals remain at the greatest risk of cardiovascular disease. Differences in risk adjusted use of statins between educational groups may contribute to these inequalities.

Objective: To identify whether people with lower levels of educational attainment are less likely to take statins for a given level of cardiovascular risk.

Design: Cross-sectional analysis of a population-based cohort study and linked longitudinal primary care records.

Setting: UK Biobank data from baseline assessment centres, linked primary care data and hospital episode statistics

Participants: UK Biobank participants (N = 489 679, mean age = 56, 54% female) with complete data on educational attainment and self-reported medication use. Secondary analyses were carried out on a subsample of participants with linked primary care data (N = 217 675).

Main outcome measures: Statin use self-reported to clinic nurses at baseline assessment centres, validated with linked prescription data in a subsample of participants in secondary analyses.

Results: Greater education was associated with lower statin use, whilst higher cardiovascular risk (assessed by QRISK3 score) was associated with higher statin use in both females and males. There was evidence of an interaction between QRISK3 and education, such that for the same QRISK3 score, people with more education were more likely to report taking statins. For example, in women with 7 years of schooling, equivalent to leaving school with no formal qualifications, a one unit increase in QRISK3 score was associated with a 6% higher odds of statin use (odds ratio (OR) 1.06, 95% CI 1.05, 1.06). In contrast, in women with 20 years of schooling, equivalent to obtaining a degree, a one unit increase in QRISK3 score was associated with an 11% higher odds of statin use (OR 1.11, 95% CI 1.10, 1.11). Comparable ORs in men were 1.04 (95% CI 1.04, 1.05) for men with 7 years of schooling and 1.07 (95% CI 1.07, 1.07) for men with 20 years of schooling.

Conclusions: For the same level of cardiovascular risk, individuals with lower educational attainment are less likely to receive statins, likely contributing to health inequalities.

Keywords: Inequalities, cardiovascular disease, statins, education, QRISK
Summary

What is already known on this topic?

- Despite reductions in the rates of cardiovascular disease in high income countries, individuals who are the most socioeconomically deprived remain at the highest risk.
- Although intermediate lifestyle and behavioural risk factors explain some of this, much of the effect remains unexplained.

What does this study add?

- For the same increase in QRISK3 score, the likelihood of statin use increased more in individuals with high educational attainment compared with individuals with lower educational attainment.
- These results were similar when using UK Biobank to derive QRISK3 scores and when using QRISK scores recorded in primary care records, and when using self-reported statin prescription data or prescription data from linked primary care records.
- The mechanisms leading to these differences are unknown, but both health seeking behaviours and clinical factors may contribute.
Introduction

Despite reductions in cardiovascular morbidity and mortality in high income countries, the most socioeconomically deprived groups remain at the highest risk of cardiovascular disease (CVD) (1, 2). There is evidence that education is a causal risk factor for CVD (3-5). We have previously demonstrated that part of this association acts through three modifiable risk factors; body mass index (BMI), systolic blood pressure and lifetime smoking behaviour (5). However, as much as 60% of the effect of education on CVD remains unexplained.

Previous studies have assessed the association of socioeconomic position (SEP) with primary (prescribed prior to a cardiovascular event) and secondary (prescribed as a result of a cardiovascular event) CVD preventative treatment rates; however, the direction of effect has been mixed (6-10). In an analysis of the Whitehall II cohort study (11), and in the British Regional Heart Study (12) there was no evidence of socioeconomic differences in statin prescribing. In other studies it has been reported that those with lower socioeconomic position are more likely to be prescribed statins (6, 8, 13, 14). Conversely, some studies have found that individuals of lower socioeconomic position are less likely to be prescribed statins (9, 10, 15, 16).

One key challenge in trying to unpick the role of education in statin prescribing (or other primary or secondary prevention mechanisms) is that lower education is associated with higher levels of cardiovascular risk factors. For example, lower education is associated with higher BMI, smoking, higher blood pressure, and lower levels of physical activity (5, 17, 18). Therefore, individuals with low education likely have a greater underlying risk of CVD and therefore potentially have a greater need for statins. However, it is possible that educational differences in health-seeking behaviour or interactions between patients and healthcare professionals may result in those with higher educational levels being prescribed preventative medication at a lower level of clinical ‘need’ (19, 20). Consequently, it is more informative to test whether there are educational differences in statin use dependent upon cardiovascular risk, rather than to look at the crude association of education and statin use.

Using the UK Biobank cohort, we investigated whether for a given level of cardiovascular risk, measured using the QRISK3 cardiovascular risk score, people with lower education were less likely to report taking statins as primary prevention than those with higher education (21-23). In secondary analyses we identify whether there are inequalities in the type of statin (Atorvastatin compared with Simvastatin) prescribed, given that Atorvastatin has greater efficacy than Simvastatin but is more costly (24-27).
Methods

UK Biobank

The UK Biobank study recruited 503,317 UK adults between 2006 and 2010. Participants attended baseline assessment centres involving questionnaires, interviews, anthropometric, physical and genetic measurements (15, 16). All UK Biobank participants are linked to hospital episode statistic (HES) data, with data available from 1997 in England, 1998 in Wales and 1981 in Scotland (28), with the most recent entry recorded in this analysis in May 2017. Additionally, a subset of participants (approximately 230,000 participants) are linked with primary care data and prescribing data (29). In this analysis, we use data from baseline assessment centres, HES data, and linked primary care data where available.

QRISK risk score

We created a risk score for cardiovascular disease using the QRISK3 algorithm (23). The QRISK3 score is currently used in primary care systems in England and Wales to define the treatment threshold for statin prescriptions. Current guidelines recommend prescribing statins to individuals with a 10% or greater risk of having a cardiovascular event within 10 years (30, 31). QRISK3 scores were derived for all participants with complete data for educational attainment and reported statin use (N= 489,679) (Supplementary Figure 1). For individuals with missing data in any of the QRISK3 variables multiple imputation was used (see statistical analysis section). Scores were derived according to the publicly available QRISK3 algorithm https://qrisk.org/three/index.php.

Where measures were recorded in baseline assessment centres, such as BMI, Townsend deprivation score or systolic blood pressure, these values were used. With the exception of systolic blood pressure variability (standard deviation of repeated values) and coronary heart disease in a first-degree relative under 60 years of age, all QRISK3 variables were available in UK Biobank. In the absence of repeated measures of systolic blood pressure on UK biobank a measure of systolic blood pressure variability was derived from the standard deviation of the two recorded measurements of systolic blood pressure at the baseline assessment centre. A measure of family history of CVD was ascertained from reported heart disease in mothers, fathers and siblings of UK Biobank participants, however age of diagnosis and subtype of CVD, could not be determined.

Full details of all variable measurements are available in the supplementary materials. All variables used and assumptions made when deriving QRISK3 scores are available in Supplementary Table 1. UK Biobank treatment codes used to identify cases and ICD9, ICD10 codes and are presented in Supplementary Tables 2 and 3.
In a subset of individuals with linked primary care data, QRISK (read 2 code: 38DF.) (N=1 069) (21), or QRISK2 scores (read 2 code: 39DP.) (N = 7 133) (22) were recorded from 2007 onwards.

**Measuring educational attainment**

UK Biobank participants reported their highest qualification achieved at baseline assessment centres, which was converted to the International Standard Classification for Education (ISCED) coding of years of education (Supplementary Table 4) (32).

**Measuring statin use**

Participants were asked about regular medication they were taking, details of which were recorded by UK Biobank study nurses. From this, a primary variable for any reported statin use was generated. The type of statin used (Atorvastatin, Simvastatin, Fluvastatin, Pravastatin and Rosuvastatin) was recorded by study nurses and was used to derive a variable for type of statin.

In individuals with linked primary care data, statin prescriptions were recorded in prescription data. In these individuals, a measure of validated statin use was created, defined by a prescription in both the 3 months before and 3 months after baseline. For sensitivity analyses in individuals with a QRISK or QRISK2 score recorded in primary care data, statin use was defined as any statin prescription after a QRISK score was recorded.

**Exclusion criteria**

Prevalent CVD cases at baseline, who would receive a statin prescription according to NICE guidelines (30, 31, 33, 34), were excluded from analyses. These cardiovascular diagnoses and events were ascertained through linkage to HES data, with cases defined according to ICD-9 and ICD-10 codes (Supplementary Table 3). Individuals were excluded if they had experienced at least one diagnosis of myocardial infarction, angina, stroke, transient ischaemic attack, peripheral arterial disease, type 1 diabetes, chronic kidney disease or familial hypercholesterolaemia (30, 34). The date for each diagnosis is provided in the HES data, which was linked with the date of assessment centre visit provided by UK Biobank.

Complete case analyses were carried out on 381 784 individuals, with complete data on age, sex, educational attainment, self-reported statin (medication) use and all variables required for the QRISK3 score (Supplementary Table 1 and Supplementary Figure 1).

**Code and data availability**

The derived variables have been returned to UK Biobank for archiving. The code used to derive QRISK3 scores and carry out analyses is available at github.com/alicerosecarter/statin_inequalities.
Patient and public involvement

Ethical approval for this study was sought from the UK Biobank (project 10953). No patients or participants were involved in setting the research question or the outcome measures, nor were they involved in developing plans for design or implementation of the study. No patients were asked to advise on the interpretation or writing up of results.

Statistical analyses

To maximise power and potentially reduce bias, multivariable multiple imputation by chained equations (35) was used to impute variables included in the QRISK3 score with missing data, under the missing at random assumption. The sample for imputation was defined as all individuals with complete data on educational attainment and reported statin use. The proportion of missing data ranged from 0% to 15% (see Supplementary Table 5 for full details). In total, 78% of participants had no missing data, 13% of participants were missing data for one QRISK3 variable, 8% of participants were missing data for two QRISK3 variables and 1% of participants were missing data for three, four or five variables. A total of 25 imputed datasets were generated (36). Imputation was carried out separately within strata of years of education and sex to preserve interactions tested in the statistical analyses (37). The mean and standard deviation of continuous variables or proportion and standard error of categorical variables in the imputed data were compared with those from the complete data. All analyses were then carried out in each imputed dataset, with results combined according to Rubin’s rules.

It was determined a priori to carry out all analyses stratified by sex given the known differences in cardiovascular risk profiles for males and females (38, 39), as well as the QRISK3 score being derived separately by sex (23).

To confirm the validity of the derived QRISK3 score, a univariable logistic regression model was used to assess the association of the risk score with i) self-reported statin use and ii) incident CVD.

We estimated the associations of years of education with i) QRISK3 score (using linear regression) and ii) statin use (using logistic regression).

Testing for interaction between QRISK3 score and educational attainment on statin use

Logistic regression was used to estimate the association of QRISK3 score with self-reported statin use, stratified by years of education, providing an estimate of interaction on the multiplicative scale (sFigure 2, Route 1). These analyses were not adjusted for any other covariates, assuming all relevant variables are incorporated into the QRISK3 score. Evidence of an interaction between
QRISK3 score and years of education was evaluated in a linear model where the interaction term QRISK3×educational attainment was included in the regression model.

Secondary analyses

To test the hypothesis that there may be educational inequalities in the type of statin prescribed, in individuals who reported using statins to baseline study nurses, we assessed i) whether there was an association of QRISK3 score and years of education independently with self-reported Atorvastatin, which has been suggested to have a greater efficacy, compared with self-reported Simvastatin (baseline) (24-26) and ii) whether there was any evidence of an interaction between QRISK3 score and years of education on type of statin prescribed (sFigure 2, Route 2).

Analyses testing the association between QRISK3 and years of education on statin use and statin type independently, as well as for any interaction between QRISK3 score and educational attainment, on statin use and type of statin prescribed were replicated using complete case data (sFigure 2, Route 3 and 4).

To test whether the self-reported statin use data affected the results, we repeated our analysis with statin use defined as a prescription both 3 months before and after baseline from linked primary care prescription data (sFigure 2, Route 5), and also repeated our main analysis with self-reported statin use in the subset of participants with the linked prescription data (sFigure 2, Route 6).

In the subsample of primary care individuals with a QRISK or QRISK2 score recorded, analyses were replicated to test for evidence of an interaction between QRISK score and incident statin prescribing. This was defined as any prescription for a statin recorded in primary care data, excluding individuals who reported using statins to study nurses at the baseline assessment centre (sFigure 2, Route 7). QRISK scores were included if they were recorded on or prior to the date of first statin prescription, but consideration was not given to the time between both events.

Two further estimates of QRISK3 were derived excluding i) variability of systolic blood pressure and ii) family history of cardiovascular disease from QRISK3 scores. The pairwise correlation between scores with and without these variables was tested.

Results

UK Biobank sample

In the main analyses (N = 489 679) 54% of participants were female with a mean age of 56. In females, the QRISK3 score implied a mean 10-year risk of a cardiovascular event of 7.9% (standard
deviation (SD) = 7.9). In males, the QRISK3 score implied mean a 10-year risk of a cardiovascular event of 14.8% (SD = 11.2). Participants were more likely to have completed 20 years of education (female = 32%, male = 35%) than 7 years of education (female = 17%, male = 17%). 11% of females and 20% of males reported using statins.

The distribution of variables was similar between the multiply imputed dataset, complete case data, and in the subset of participants with linked primary care data (Supplementary Table 6).

**Association of QRISK3 score with statins and cardiovascular disease**

For a one unit increase in QRISK3 score (i.e. a 1% increase in the 10-year risk of experiencing a cardiovascular event) in females, the odds ratio (OR) for reporting statin use to study nurses was 1.09 (95% confidence interval (CI): 1.09 to 1.09) and the OR for an incident cardiovascular event was 1.09 (95% CI: 1.09 to 1.09) (Figure 1 and Supplementary Table 7). Females with a QRISK3 score of 10 or greater were 1.57 (95% CI: 1.55 to 1.60) times as likely to report using statins than those with a QRISK score of less than 10. In males, the OR for statin use was 1.06 (95% CI: 1.06 to 1.07) and for an incident cardiovascular event the OR was 1.07 (95% CI: 1.07 to 1.07) per unit higher QRISK3 score (Figure 1 and Supplementary Table 7). Males with a QRISK3 score of 10 or greater were 1.70 (95% CI: 1.67 to 1.73) times as likely to report using statins than those with a QRISK score of less than 10.

**Association of education with QRISK3 score and statin prescribing**

Per year increase in educational attainment was associated with a -0.37 (95% CI: -0.38 to -0.37) reduction in mean QRISK3 score in females and a -0.47 (95% CI: -0.48 to -0.46) reduction in mean QRISK3 score in males (Supplementary Table 8 and Supplementary Figure 3).

The prevalence of statin use was highest in those in the lowest strata of educational attainment (equivalent to leaving school after 7 years, with no formal qualifications) (Supplementary Figure 4). Not accounting for cardiovascular risk, each additional year of education was associated with a lower odds of being prescribed statins (all types), (OR in females: 0.92 95% CI: 0.92 to 0.93, OR in males: 0.95 95% CI: 0.95 to 0.95) (Supplementary Table 7 and Supplementary Figure 5).

**Interaction between education and QRISK3 score in relation to statin prescribing**

In both females and males, there was evidence of an interaction between QRISK3 score and years of education on statin use, such that for the same increase in QRISK3 score, the likelihood of statin use increased more for those of high educational attainment. In females, per unit increase in QRISK3, the OR for reporting statin use in those with the greatest years of education (20 years, equivalent to obtaining a degree) was 1.11 (95% CI: 1.10 to 1.11) compared with an OR of 1.06 (95% CI: 1.05 to
1.06) for those with the least years of education (7 years, equivalent to leaving school with no formal qualifications) (Figure 1). In males, the OR for statin use per unit increase in QRISK3 score in those with 20 years of education was 1.07 (95% CI: 1.07 to 1.07) compared with an OR of 1.04 (95% CI: 1.04 to 1.05) for those with 7 years of education (Figure 1). For both females and males the P value for interaction was <0.001.

**Secondary analyses**

Among individuals prescribed with either atorvastatin or simvastatin, those with higher QRISK3 scores were more likely to have been prescribed the more effective Atorvastatin. A one unit higher QRISK3 score in females was associated with an increase in reporting Atorvastatin use, OR: 1.02 (95% CI: 1.02 to 1.02) (Supplementary Table 9). This was similar in males, OR: 1.02 (95% CI: 1.01 to 1.02). Both females and males were less likely to have been prescribed Atorvastatin if they had more years of education; e.g. the OR for Atorvastatin prescription for 20 years of education versus 7 years of education was 0.85 in females (95% CI 0.78 to 0.93) and 0.94 in males (95% CI 0.88 to 1.00). There was little evidence of an interaction between QRISK3 score and educational attainment on statin type in females (P value for interaction in females = 0.5) (Supplementary Figure 6). However, there was evidence of an interaction in males (P value for interaction = 0.001) such that higher educated males were more likely to receive Atorvastatin, compared with lower educated males (Supplementary Figure 6).

When analyses were replicated using eligible participants with linked primary care data using i) baseline measures of QRISK3 and self-report statin use, ii) baseline measures of QRISK3 with statin use validated by a prescription and iii) QRISK or QRISK2 score recorded in primary care data with a statin prescription, the evidence for interaction between QRISK3 and educational attainment on statin use remained (Figure 2 and Supplementary Figure 7).

In the complete case sample, there was evidence of an interaction between QRISK3 and education in both males and females considering reported statin use as the outcome, where the P value for interaction was <0.001 for both females and males. However, there was little evidence of an interaction between QRISK3 and education on statin type (Supplementary Table 10).

Pairwise correlation between the baseline derived QRISK3 score and QRISK3 scores derived excluding i) systolic blood pressure variability estimated from the difference between two baseline measures and ii) self-report of any CVD in a mother, father or sibling, were high (all >0.97) (Supplementary Table 11).
Discussion

Despite there being a higher prevalence of statin prescribing overall in those with lower levels of education, at a given level of QRISK3 score as a measure of clinical assessment of cardiovascular risk, less educated individuals were less likely to receive statin treatment compared to more highly educated individuals.

Results in context

Lifestyle and behavioural factors, such as BMI, diet, smoking, risky drinking and exercise have previously been implicated as mediators of the association between education and CVD (17, 18, 40-46). Indeed, the higher overall prevalence of statins in lower educated individuals is likely due to the greater prevalence of these intermediate risk factors, compared with those of greater education (5, 17, 44). However, much of the association between education and CVD remains unexplained. The results presented in this analysis suggest that access to preventative medication for CVD may be contributing to persisting socioeconomic inequalities.

It has previously been reported that inequalities exist in favour of those with higher SEP when accessing preventative healthcare (47). In the UK, National Health Service (NHS) health checks are offered to all residents aged between 40 and 74 without pre-existing conditions every 5 years, with the aim of preventing a number of diseases including CVD (such as by calculating QRISK scores), kidney disease and dementia (48). In a recent systematic review by Bunten and colleagues, seven studies were identified that indicated uptake of these health checks is lower in more socioeconomically deprived groups (49). Additionally one study included in this systematic review identified a trend towards lower uptake in smokers; an important risk factor for CVD that is also socially patterned (49, 50). Similar findings were also reported by Wilson and colleagues (51). These reasons for non-uptake of health checks, in combination with the inequalities identified in this study, indicate that methods to improve engagement with NHS health checks and preventative screening methods may reduce inequalities in cardiovascular outcomes.

Indeed, differences in health seeking behaviours may be driving some of the inequalities in statin use identified in our study. However, when interaction analyses were repeated using QRISK or QRISK2 scores recorded in primary care data and primary care records of statin prescriptions, these inequalities remained. Therefore, attendance to primary care clinics cannot be the sole driver of these inequalities.

The literature is mixed in the direction to which inequalities in access to statins exist, where some studies suggest that individuals with lower socioeconomic position are less likely to be prescribed
statins (9, 10, 15, 16) and other studies finding the opposite or no differences (6, 8, 11, 13, 14). Of these previous studies, there was limited consideration for underlying cardiovascular risk in the analyses. Some studies adjusted for cardiovascular comorbidities (8, 13, 15, 16) such as cholesterol level, diabetes status or prevalent cardiovascular events. However, we only identified one other study that comprehensively adjusted for cardiovascular risk (11). Forde and colleagues established risk status via 10-year absolute risk of coronary heart disease determined using the Framingham study (11, 52) and assessed SEP by British civil service grade of employment. In contrast to our results using educational attainment as a measure of SEP, they did not find evidence of inequalities in statin use. The differences in our results compared with Forde and colleagues could be the different measure of SEP used (income vs education) or due to cohort differences, where Forde and colleagues used an occupational cohort study and here, we have used a population based cohort. Additionally, it has been demonstrated that the QRISK score has a greater predictive power compared with the Framingham score (53). Therefore, our analyses may better account for underlying differences in cardiovascular risk.

Currently, the QRISK3 scores capture the prevalence of key risk factors in individuals, such as BMI, blood pressure and smoking, but our results show that accounting for these factors alone is not enough to address cardiovascular inequalities. Cardiovascular risk scores may need to be adapted to pay greater attention to SEP; something that has been described previously in the literature (54-56) These risk scores should be in principle, easy to use and clear for clinicians, where it has previously been reported that the use of risk scores in general practice is a source of confusion (57).

Despite there being around 15,000 recorded statin prescriptions after 2007 (when QRISK scores were first introduced), in the primary care data linked with UK Biobank, there were only around 8000 recorded QRISK or QRISK2 scores in the same data. This is slightly higher than in previous research by Finnikin and colleagues, where they identified using primary care records, that only 27% of patients prescribed statins had a recorded QRISK2 score (58). However, the lack of recorded QRISK scores, suggests the decision to prescribe statin treatment may be independent of an objective measure of cardiovascular risk, and potentially prescribed based on more subjective measures by the clinician or the patient.

In individuals with linked primary care data, 12% of individuals who reported statin use to study nurses had no linked prescription in the three months before and after baseline. These individuals are likely a combination of individuals who are purchasing statins over the counter, have received a prescription from a private clinician, or are no longer prescribed statins. The majority (80%) of those without a linked prescription reported taking Simvastatin (currently the only statin available as an
over the counter medicine). Although we cannot definitively discern the reason these individuals did not have a prescription, it is possible that accessing statins through non-NHS GPs (i.e. through private practices) or over the counter is further contributing to inequalities in cardiovascular outcomes. There is, to date, little freely available data on the prevalence of purchasing statins over the counter, rather than via attending a primary care clinic. However, our data suggests it could indeed be highly prevalent in the population.

**Strengths and limitations**

The major strength of our work is the large sample size and array of data available. Given the age range of our participants (45-76 years) reported statin use is highly prevalent (10% in females and 18% in males). Additionally, the linked primary care data for 44% of the analysis sample allowed us to i) validate self-reported statin use and ii) compare different mechanisms inequalities may be arising. Where inequalities are present in primary care recorded QRISK scores, inequalities are unlikely to be due to health seeking behaviour and more likely due to factors arising within clinic settings. Conversely, where data is used from UK Biobank baselines assessment, inequalities may be due to either differences in health seeking behaviour (i.e. attending NHS health checks) or factors that arise within the healthcare setting.

Lifestyle and behavioural characteristics, which are incorporated in to the QRISK3 score, are likely to be captured much more accurately and completely in UK Biobank compared with a primary care setting. However, there may be some settings where UK Biobank variables may have been measured differently than they would in primary care (59), such as non-fasting blood biomarker measurements. However, the magnitude to which these measurements differ is unlikely to introduce much bias to estimates of the QRISK3 score. Additionally, selection bias is present in UK biobank, where participants are generally of a higher socioeconomic position and healthier than the general population (60). Those who are of a lower socioeconomic position in the UK Biobank potentially differ to those of an equivalent socioeconomic position (or level of educational attainment) in the general population, where UK Biobank participants may be more health conscious and health aware. Therefore, it is possible that the inequalities in the wider population are greater than the inequalities reported here.

Despite our large sample size and wealth of data, a number of assumptions were made when generating the QRISK3 scores. For example, in the QRISK3 algorithm (23), the study authors specify medications should be considered if the individual has two or more prescriptions for each class of medication (e.g. corticosteroid or atypical antipsychotic). We were not able to determine the number of prescriptions at baseline and relied on a single self-report measure of medication use.
Therefore, medication use may be overestimated in our sample, which would result in an overestimate of the QRISK3 score. Additionally, some measures, such as systolic blood pressure variability and coronary heart disease in a first degree relative under the age of 60, are not available in the UK Biobank data. Although we have included measures likely to capture some of these variables, this may introduce bias to the QRISK3 estimate in UK Biobank compared with a primary care setting.

The ISCED definitions of educational attainment (years in schooling) can differ with respect to other measures of socioeconomic position. For example, using ISCED definitions, individuals who left school with a vocational qualification are given a high number of years of schooling (19 years) but will typically go into manual labour jobs. This is likely to explain some of the non-linearities in effects stratified by educational attainment.

Clinical implications

The results presented here highlight inequalities in statin use by educational attainment. Given the persisting inequalities in CVD, addressing the contribution of differences in statin prescription provides a clear policy target. The two complimentary data sources used in this analysis, UK Biobank baseline data and linked primary care data, indicate two potential mechanisms for these inequalities. Firstly, there are likely to be differences in health seeking behaviour such as in attending NHS health checks as previously evidenced in the literature. Secondly, the inequalities present in the primary care data suggest there are important interactions between the healthcare practitioner and patient that result in unequal prescribing of statins.

Healthcare professionals should consider potential biases in prescribing preventative treatments, or in carrying out risk assessments, such as calculating a QRISK score. Additionally, patient preference for treatment may be socially patterned (61). However, addressing these inequalities requires systemic change and different interventions may be required to address the different mechanisms of inequalities. For example, policy makers and healthcare professionals should consider how they can improve the uptake of NHS health checks, where these risk assessments are carried out, in those who are socioeconomically deprived.

Conclusions

Our analyses demonstrate that at a given level of cardiovascular risk, people with lower levels of educational attainment are less likely to be prescribed statins than people with higher educational attainment, meaning differences in statin prescribing likely contribute to inequalities in cardiovascular disease. Policies should consider how these inequalities can be minimised.
References

1. Marmot MG, McDowall ME. Mortality decline and widening social inequalities. Lancet. 1986;2(8501):274-6.
2. Bajekal M, Scholes S, O’Flaherty M, Raine R, Norman P, Capewell S. Unequal trends in coronary heart disease mortality by socioeconomic circumstances, England 1982-2006: an analytical study. PLoS One. 2013;8(3):e59608.
3. Tillmann T, Vaucher J, Okbay A, Pikhart H, Peasey A, Kubinova R, et al. Education and coronary heart disease: mendelian randomisation study. BMJ. 2017;358:j3542.
4. Davies NM, Dickson M, Davey Smith G, van de n Berg GJ, Windmeijer F. The causal effects of education on health outcomes in the UK Biobank. Nature Human Behaviour. 2018;2(2):117-25.
5. Carter AR, Gill D, Davies NM, Taylor AE, Tillmann T, Vaucher J, et al. Understanding the consequences of education inequality on cardiovascular disease: mendelian randomisation study. BMJ. 2019;365:l1855.
6. Fleetcroft R, Schofield P, Ashworth M. Variations in statin prescribing for primary cardiovascular disease prevention: cross-sectional analysis. BMC Health Serv Res. 2014;14:414.
7. O’Keeffe AG, Petersen I, Nazareth I. Initiation rates of statin therapy for the primary prevention of cardiovascular disease: an assessment of differences between countries of the UK and between regions within England. BMJ Open. 2015;5(3):e007207.
8. Simpson CR, Hannaford PC, Williams D. Evidence for inequalities in the management of coronary heart disease in Scotland. Heart. 2005;91(5):630-4.
9. Thomsen RW, Johnsen SP, Olesen AV, Mortensen JT, Boggild H, Olsen J, et al. Socioeconomic gradient in use of statins among Danish patients: population-based cross-sectional study. Br J Clin Pharmacol. 2005;60(5):534-42.
10. Packham C, Robinson J, Morris J, Richards C, Marks P, Gray D. Statin prescribing in Nottingham general practices: a cross-sectional study. J Public Health Med. 1999;21(1):60-4.
11. Forde I, Chandola T, Raine R, Marmot MG, Kiwimaki M. Socioeconomic and ethnic differences in use of lipid-lowering drugs after deregulation of simvastatin in the UK: the Whitehall II prospective cohort study. Atherosclerosis. 2011;215(1):223-8.
12. Ramsay SE, Morris RW, Papacosta O, Lennon LT, Thomas MC, Whincup PH. Secondary prevention of coronary heart disease in older British men: extent of inequalities before and after implementation of the National Service Framework. J Public Health (Oxf). 2005;27(4):338-43.
13. Ashworth M, Lloyd D, Smith RS, Wagner A, Rowlalls G. Social deprivation and statin prescribing: a cross-sectional analysis using data from the new UK general practitioner 'Quality and Outcomes Framework'. J Public Health (Oxf). 2007;29(1):40-7.
14. O'Keeffe AG, Nazareth I, Petersen I. Time trends in the prescription of statins for the primary prevention of cardiovascular disease in the United Kingdom: a cohort study using The Health Improvement Network primary care data. Clin Epidemiol. 2016;8:123-32.
15. Forsberg PO, Li X, Sundquist K. Neighborhood socioeconomic characteristics and statin medication in patients with myocardial infarction: a Swedish nationwide follow-up study. BMC Cardiovasc Disord. 2016;16(1):146.
16. Rasmussen JN, Gislason GH, Rasmussen S, Abildstrom SZ, Schramm TK, Kober L, et al. Use of statins and beta-blockers after acute myocardial infarction according to income and education. J Epidemiol Community Health. 2007;61(12):1091-7.
17. Mejean C, Droomers M, van der Schouw YT, Sluijs I, Czernichow S, Grobbee DE, et al. The contribution of diet and lifestyle to socioeconomic inequalities in cardiovascular morbidity and mortality. International Journal of Cardiology. 2013;168(6):5190-5.
18. Veronesi G, Ferrario MM, Kuulasmaa K, Bobak M, Chambless LE, Salomaa V, et al. Educational class inequalities in the incidence of coronary heart disease in Europe. Heart. 2016;102(12):958-65.
19. Mitchell AJ, Selmes T. Why don't patients attend their appointments? Maintaining engagement with psychiatric services. Advances in Psychiatric Treatment. 2018;13(6):423-34.
20. Campbell K MA, McCartney G, McCullough S (NHS Health Scotland). Who is least likely to attend? An analysis of outpatient appointment 'Did Not Attend' (DNA) data in Scotland. NHS Health Scotland; 2015.
21. Hippisley-Cox J, Coupland C, Vinogradova Y, Robson J, May M, Brindle P. Derivation and validation of QRISK, a new cardiovascular disease risk score for the United Kingdom: prospective open cohort study. BMJ. 2007;335(7611):136.
22. Hippisley-Cox J, Coupland C, Vinogradova Y, Robson J, Minhas R, Sheikh A, et al. Predicting cardiovascular risk in England and Wales: prospective derivation and validation of QRISK2. BMJ. 2008;336(7659):1475-82.
23. Hippisley-Cox J, Coupland C, Brindle P. Development and validation of QRISK3 risk prediction algorithms to estimate future risk of cardiovascular disease: prospective cohort study. BMJ. 2017;357:j2099.
24. Farnier M, Portal JJ, Maigret P. Efficacy of atorvastatin compared with simvastatin in patients with hypercholesterolemia. J Cardiovasc Pharmacol Ther. 2000;5(1):27-32.
25. Insull W, Kafonek S, Goldner D, Zieve F. Comparison of efficacy and safety of atorvastatin (10mg) with simvastatin at six weeks. ASSET Investigators. Am J Cardiol. 2001;87(5):554-9.
26. Karalis DG, Ross AM, Vacari RM, Zarren H, Scott R. Comparison of efficacy and safety of atorvastatin and simvastatin in patients with dyslipidemia with and without coronary heart disease. Am J Cardiol. 2002;89(6):667-71.
27. Moon JC, Bogle RG. Switching statins. BMJ. 2006;332(7554):1344-5.
28. Biobank U. Hospital inpatient data. https://biobank.ctsu.ox.ac.uk/crystal/crystal/docs/HospitalEpisodeStatistics.pdf; 2019 September 2019.
29. Biobank U. Primary Care Linked Data. http://biobank.ctsu.ox.ac.uk/crystal/crystal/docs/primary_care_data.pdf; 2019 September 2019.
30. NICE. Cardiovascular disease: risk assessment and reduction, including lipid modification. www.nice.org.uk/guidance/cg1812014.
31. NICE. Cardiovascular risk assessment and lipid modification. www.nice.org.uk/guidance/qs1002015.
32. Okbay A, Beauchamp JP, Fontana MA, Lee JJ, Pers TH, Rietveld CA, et al. Genome-wide association study identifies 74 loci associated with educational attainment. Nature. 2016;533(7604):539-42.
33. NICE. Familial hypercholesterolaemia. https://www.nice.org.uk/guidance/qs412013.
34. NICE. Lipid modification - CVD prevention. https://cks.nice.org.uk/lipid-modification-cvd-prevention2019.
35. Royston P. Multiple Imputation of Missing Values. The Stata Journla. 2004;4(3):227-41.
36. Spratt M, Carpenter J, Sterne JA, Carlin JB, Heron J, Henderson J, et al. Strategies for multiple imputation in longitudinal studies. Am J Epidemiol. 2010;172(4):478-87.
37. Tilling K, Williamson EJ, Spratt M, Sterne JA, Carpenter JR. Appropriate inclusion of interactions was needed to avoid bias in multiple imputation. J Clin Epidemiol. 2016;80:107-15.
38. Zhao M, Vaartjes I, Graham I, Grobbee D, Spiering W, Klipstein-Grobusch K, et al. Sex differences in risk factor management of coronary heart disease across three regions. Heart. 2017;103(20):1587-94.
39. Millett ERC, Peters SAE, Woodward M. Sex differences in risk factors for myocardial infarction: cohort study of UK Biobank participants. BMJ. 2018;363:k4247.
40. Hossin MZ, Koupil I, Falkstedt D. Early life socioeconomic position and mortality from cardiovascular diseases: an application of causal mediation analysis in the Stockholm Public Health Cohort. BMJ Open. 2019;9(6):e026258.
41. Havranek EP, Mujahid MS, Barr DA, Blair IV, Cohen MS, Cruz-Flores S, et al. Social Determinants of Risk and Outcomes for Cardiovascular Disease A Scientific Statement From the American Heart Association. Circulation. 2015;132(9):873-98.
42. Nordahl H, Rod NH, Frederiksen BL, Andersen I, Lange T, Diderichsen F, et al. Education and risk of coronary heart disease: assessment of mediation by behavioral risk factors using the additive hazards model. Eur J Epidemiol. 2013;28(2):149-57.
43. Degano IR, Marrugat J, Grau M, Salvador-Gonzalez B, Ramos R, Zamora A, et al. The association between education and cardiovascular disease incidence is mediated by hypertension, diabetes, and body mass index. Sci Rep. 2017;7(1):12370.
44. Kershaw KN, Droomers M, Robinson WR, Carnethon MR, Daviglus ML, Monique Verschuren WM. Quantifying the contributions of behavioral and biological risk factors to socioeconomic disparities in coronary heart disease incidence: the MORGEN study. Eur J Epidemiol. 2013;28(10):807-14.
45. van Oort FVA, van Lenthe FJ, Mackenbach JP. Material, psychosocial, and behavioural factors in the explanation of educational inequalities in mortality in the Netherlands. J Epidemiol Commun H. 2005;59(3):214-20.
46. Lynch JW, Kaplan GA, Cohen RD, Tuomilehto J, Salonen JT. Do cardiovascular risk factors explain the relation between socioeconomic status, risk of all-cause mortality, cardiovascular mortality, and acute myocardial infarction? American Journal of Epidemiology. 1996;144(10):934-42.
47. Cookson R, Propper C, Asaria M, Raine R. Socio-Economic Inequalities in Health Care in England. Fisc Stud. 2016;37(3):371-403.
48. England PH. Using the world leading NHS Health Check programme to prevent CVD [updated 24/01/2018. Available from: https://www.gov.uk/government/publications/using-the-world-leading-nhs-health-check-programme-to-prevent-cvd]https://www.gov.uk/government/publications/using-the-world-leading-nhs-health-check-programme-to-prevent-cvd.2018]
49. Bunten A, Porter L, Gold N, Bogle V. A systematic review of factors influencing NHS health check uptake: invitation methods, patient characteristics, and the impact of interventions. BMC Public Health. 2020;20(1):93.
50. Dalton AR, Bottle A, Okoro C, Majeed A, Millett C. Uptake of the NHS Health Checks programme in a deprived, culturally diverse setting: cross-sectional study. J Public Health (Oxf). 2011;33(3):422-9.
51. Wilson R, Kuh D, Stafford M. Variations of health check attendance in later life: results from a British birth cohort study. BMC Public Health. 2019;19(1):1518.
52. D’Agostino RB, Sr., Vasan RS, Pencina MJ, Wolf PA, Cobain M, Massaro JM, et al. General cardiovascular risk profile for use in primary care: the Framingham Heart Study. Circulation. 2008;117(6):743-53.
53. Collins GS, Altman DG. An independent external validation and evaluation of QRISK cardiovascular risk prediction: a prospective open cohort study. BMJ. 2009;339:b2584.
54. Brindle PM, McConnachie A, Upton MN, Hart Cl, Davey Smith G, Watt GC. The accuracy of the Framingham risk-score in different socioeconomic groups: a prospective study. Br J Gen Pract. 2005;55(520):838-45.
55. Tunstall-Pedoe H, Woodward M, estimation Sgor. By neglecting deprivation, cardiovascular risk scoring will exacerbate social gradients in disease. Heart. 2006;92(3):307-10.
56. Woodward M, Brindle P, Tunstall-Pedoe H, estimation Sgor. Adding social deprivation and family history to cardiovascular risk assessment: the ASSIGN score from the Scottish Heart Health Extended Cohort (SHHEC). Heart. 2007;93(2):172-6.
57. Liew SM, Blacklock C, Hislop J, Glasziou P, Mant D. Cardiovascular risk scores: qualitative study of how primary care practitioners understand and use them. Br J Gen Pract. 2013;63(611):e401-7.
58. Finnikin S, Ryan R, Marshall T. Statin initiations and QRISK2 scoring in UK general practice: a THIN database study. Br J Gen Pract. 2017;67(665):e881-e7.
59. Elliott P, Peakman TC, Biobank UK. The UK Biobank sample handling and storage protocol for the collection, processing and archiving of human blood and urine. Int J Epidemiol. 2008;37(2):234-44.

60. Fry A, Littlejohns TJ, Sudlow C, Doherty N, Adamska L, Sprosen T, et al. Comparison of Sociodemographic and Health-Related Characteristics of UK Biobank Participants With Those of the General Population. Am J Epidemiol. 2017;186(9):1026-34.

61. Schroder SL, Fink A, Richter M. Socioeconomic differences in experiences with treatment of coronary heart disease: a qualitative study from the perspective of elderly patients. BMJ Open. 2018;8(11):e024151.
Figures

Figure 1: Odds of self-report statin use per unit increase in baseline QRISK3 score with no education interaction and stratified by years of education in females and males

| Exposure     | Sex          | Years of Education | Odds Ratio (95% CI) | N  | (%) |
|--------------|--------------|--------------------|---------------------|----|-----|
| QRISK (per unit) | Female | No education interaction | 1.09 (1.05, 1.09) | 267,189 | 29 112 (11) |
|               |            | 7 years            | 1.06 (1.05, 1.06)   | 45,411 | 5 880 (20) |
|               |            | 10 years           | 1.09 (1.05, 1.10)   | 51,760 | 5 524 (11) |
|               |            | 13 years           | 1.10 (1.10, 1.11)   | 18,303 | 1 341 (9)  |
|               |            | 15 years           | 1.09 (1.05, 1.09)   | 35,112 | 4 060 (13) |
|               |            | 19 years           | 1.10 (1.06, 1.10)   | 33,977 | 3 012 (9)  |
|               |            | 20 years           | 1.11 (1.10, 1.11)   | 85,432 | 5 880 (7)  |

| Exposure     | Sex          | Years of Education | Odds Ratio (95% CI) | N  | (%) |
|--------------|--------------|--------------------|---------------------|----|-----|
| QRISK (per unit) | Male | No education interaction | 1.08 (1.06, 1.07) | 222,450 | 44 845 (20) |
|               |            | 7 years            | 1.04 (1.04, 1.06)   | 38,370 | 16 649 (30) |
|               |            | 10 years           | 1.07 (1.07, 1.07)   | 30,053 | 5 796 (19) |
|               |            | 13 years           | 1.06 (1.06, 1.07)   | 11,152 | 2 025 (18) |
|               |            | 15 years           | 1.06 (1.06, 1.06)   | 22,775 | 5 096 (22) |
|               |            | 19 years           | 1.07 (1.07, 1.07)   | 43,158 | 8 165 (19) |
|               |            | 20 years           | 1.07 (1.07, 1.07)   | 76,842 | 12 252 (16) |

Analyses stratified by years of education provide an estimate of interaction on the multiplicative scale

P value for interaction in females = <0.001 and males = <0.001
Figure 2: Odds of statin use recorded in primary care prescription data per unit increase in A) baseline QRISK3 score and B) QRISK or QRISK2 score recorded in primary care, in females and males

Analyses stratified by years of education provide an estimate of interaction on the multiplicative scale

Baseline QRISK3: P value for interaction in females = <0.001 and males = <0.001

QRISK score recorded in primary care: P value for interaction in females = 0.013 and males = 0.021
