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Association of socioeconomic status with diabetic microvascular complications: a UK Biobank prospective cohort study

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Abstract

Background Prior studies on the link between socioeconomic status (SES) and diabetic microvascular complications have been inconclusive. This study aimed to explore whether SES is associated with the risk of diabetic retinopathy (DR), nephropathy (DN) and diabetic peripheral neuropathy (DPN) using large prospective cohort.

Methods SES was evaluated using education attainment (individual level), household income (household level), and Townsend deprivation index (TDI, neighborhood level). This study included 28,339 participants without DR, 29,951 without DN and 29,762 without DPN at baseline from the UK Biobank. Weighted Cox proportional hazard models were used to investigate the relationship between SES and the risk of diabetic microvascular complications.

Results The median follow-ups of the DR, DN and DPN cohorts were 12.95, 12.89 and 13.02 years, respectively. In total, 3,177 (11.2%) participants developed DR, 4,418 (14.8%) developed DN and 1,604 (5.4%) developed DPN. After adjusting for confounders, higher education levels (DN: hazard ratios [HR] = 0.85; 95% CI, 0.82–0.89; $P < 0.001$; DPN: HR = 0.93; 95% CI, 0.87-1.00; $P = 0.040$), higher household income (DN: HR = 0.80; 95% CI, 0.75–0.85; $P < 0.001$; DPN: HR = 0.80; 95% CI, 0.73–0.89; $P < 0.001$), and lower TDI (DN: HR = 1.19; 95% CI, 1.14–1.23; $P < 0.001$; DPN: HR = 1.27; 95% CI, 1.19–1.36; $P < 0.001$) were associated with a lower risk of DN and DPN. In contrast, a lower risk of DR was only related to higher household income (HR = 0.92; 95% CI, 0.87–0.97; $P = 0.004$) and lower TDI (HR = 1.08; 95% CI, 1.02–1.13; $P = 0.004$).

Conclusions Low SES increases the risk of diabetic microvascular complications, emphasizing the need for equitable medical resource allocation to reduce diabetes-related inequity.

Keywords Socioeconomic status, Diabetic retinopathy, Diabetic nephropathy, Diabetic peripheral neuropathy, Diabetes inequity, UK Biobank

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Background

Diabetes is becoming a defining disease of the 21st century [1]. The global age-standardized prevalence of diabetes was estimated to have increased from 3.2% in 1990 to 6.1% in 2021 and is expected to reach 9.8% by 2050 [2]. More worryingly, 80% of diabetes cases occur in low-income and middle-income countries [3], and people with lower socioeconomic status (SES) exhibit a higher risk of diabetes [4]. SES refers to an individual's or group's position within the socioeconomic hierarchy, which is determined by a combination of factors such as wealth, prestige, and place of residence [5]. The increasing disparity in diabetes burden due to socioeconomic inequalities has been increasingly concerning [6]. However, the association between SES and the risk of diabetic microvascular complications remains controversial.

Diabetic microvascular complications mainly comprise diabetic retinopathy (DR), nephropathy (DN) and peripheral neuropathy (DPN), which are considered to be the main causes of blindness, end-stage renal disease and lower limb amputation in developed countries [7–9]. Epidemiological studies show that at least one out of every five to ten patients with diabetes will develop DR, DN or DPN, which poses an enormous burden on society and the family [10–12]. Thus, exploring the relationship between SES and diabetic microvascular complications can assist in the allocation of medical resources and reduce diabetes inequity. Despite several studies, the relationship between SES and diabetic microvascular complications is not fully understood and lacks consistency. While many studies suggest that low SES increases the risk of these complications [13–18], others report no correlation [19]. Very few studies adjusted their analyses according to glycated hemoglobin level (HbA1c) [20]. In addition, most previous studies assessed SES using a single indicator, such as education [18], which does not reflect the comprehensive SES. Moreover, most of the previous studies were limited by small sample sizes and cross-sectional designs, which may be biased by residual confounding and reverse causality [13, 15].

In this study, SES was evaluated at the individual, household, and neighborhood levels using education attainment, household income, and Townsend deprivation index (TDI) [21]. The present study aimed to investigate the association between SES and the risk of diabetic microvascular complications based on a prospective cohort study of 30,541 individuals with diabetes from the UK Biobank.

Methods

Study design

This large prospective cohort study investigated the link between SES, DR, DN and DPN using data from the UK Biobank (Fig. 1). SES was evaluated based on education attainment (individual level), household income (household level), and TDI (neighborhood level). The UK Biobank study (RRID: SCR_012815) was approved by the North West Multicenter Research Ethical Committee (REF: 11/NW/03820), and all participants provided informed consent.

Study populations

The UK Biobank is a population-based prospective cohort study that recruited over 500,000 participants aged 37 to 73 years from 22 medical centers throughout the United Kingdom from 2006 to 2010 [22]. The baseline information of all participants was obtained through self-reported touchscreen questionnaires, physical measurements, and biospecimen collection. The present study included 30,541 participants with confirmed baseline diabetes mellitus (DM) (including type 1 and type 2 diabetes). Subsequently, individuals without DR, DN or DPN at baseline were separated to yield three cohorts for the primary analysis. The inclusion and exclusion criteria for the study populations are shown in Fig. 1.

Exposure and outcome in the cohort study

The highest education qualifications of participants reported in the UK biobank were converted to the International Standard Classification for Education (ISCED) coding for years of education [23] (Supplementary Table 1). Household income was defined using a five-point scale corresponding to the total household income before tax, which was obtained through questionnaires. Each category was assigned a midpoint to allow for continuous analysis [24]. TDI was available as an area-level SES variable retrieved from national census data according to postcodes of residence, which considered factors including unemployment, family overcrowding, and not owning a house or car [25]. Higher TDIs indicate lower area-level SES.

The outcomes of the current study were incident DR, DN and DPN during follow-up. The follow-up period extended from the time participants enrolled in the UK Biobank until July 19, 2022, when the data were collected. Outcome events were defined using the following sources: hospital inpatient records of diagnosis (Field ID: 41270) and operation (Field ID: 41272), and self-reported information of diagnosis (Field ID: 20002) and operation (Field ID: 20004) [26–28]. Details of the disease-definition codes are provided in Supplementary Table 2. For patients with different sources of records, the earliest diagnosis was taken.

Covariates in the cohort study

The covariates included in the study were age, sex, race (Caucasian/other race), smoking status (yes or no), alcohol consumption status (heavy or not), mean arterial

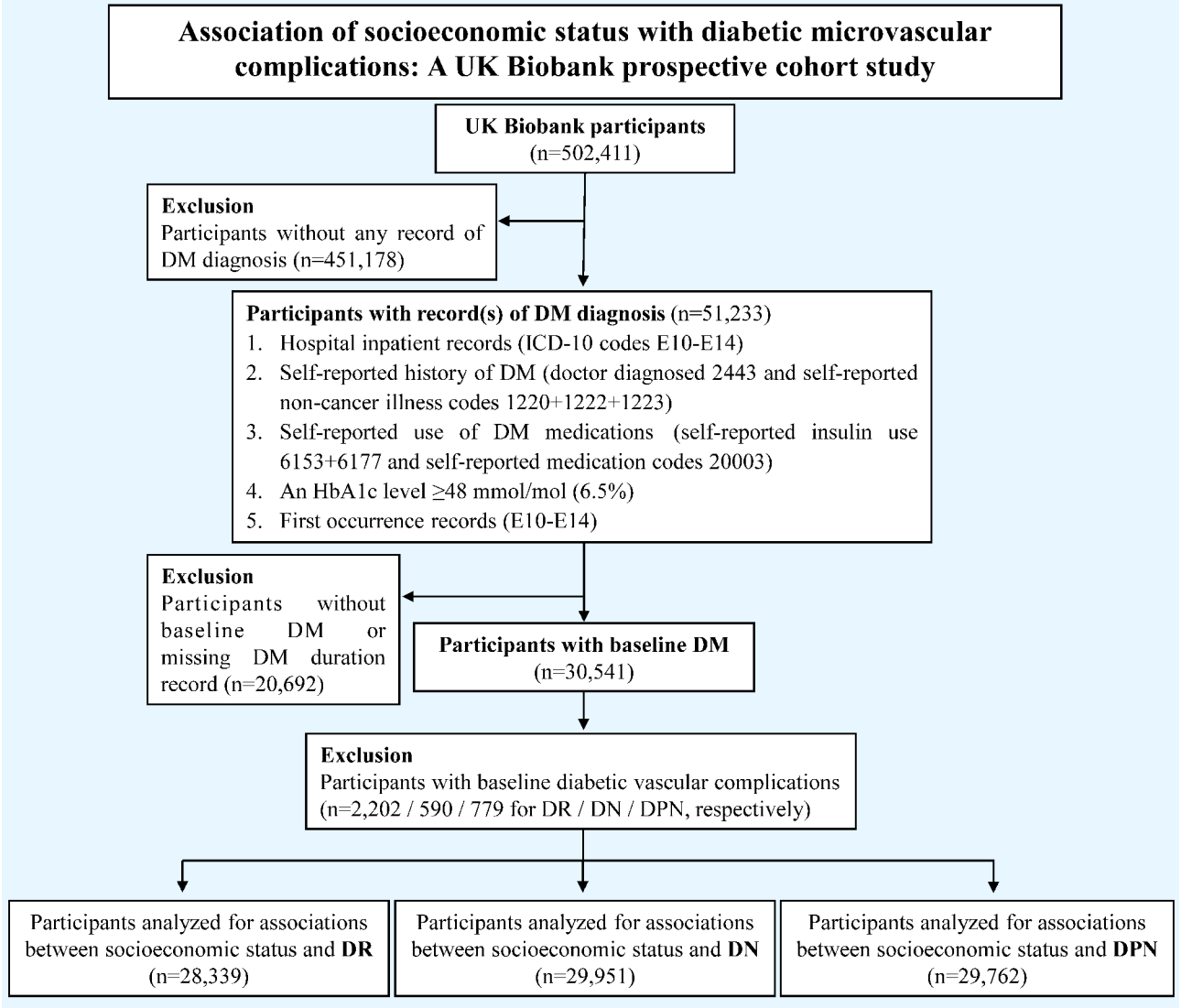

Fig. 1 Overview of the study design. This flow chart presents the inclusion and exclusion criteria for the UK Biobank cohort study. ICD: International Classification of Diseases, DM: diabetes mellitus, DR: diabetic retinopathy, DN: diabetic nephropathy, DPN: diabetic peripheral neuropathy, HbA1c: glycated hemoglobin

pressure (MAP, mmHg), HbA1c (%), triglyceride (TG, mmol/L), high-density lipoprotein cholesterol (HDL, mmol/L), low-density lipoprotein cholesterol (LDL, mmol/L), duration of DM (years), body mass index (BMI), oral hypoglycemic drug use (yes or no), and insulin treatment (yes or no). Blood pressure was measured with an Omron digital sphygmomanometer. Blood samples were obtained for measurement of HbA1c, TG, HDL, and LDL levels. Diabetes duration was calculated based on the disease onset to the recruitment time. In addition, BMI was calculated as body weight (kilogram) divided by the square of height (meters). All the remaining covariates were derived from participants' self-reported information at baseline.

Statistical analysis

Continuous and categorical variables were represented by the median (interquartile ranges, IQR) and frequency (percentages, %), respectively. Subsequently, medians and proportions were compared using the Mann−Whitney U test and chi-square test, respectively. Kaplan-Meier cumulative incidence plots were generated and statistically analyzed using the log-rank test. Weighted Cox proportional hazard models were used to estimate hazard ratios (HR) and their corresponding 95% confidence intervals (CI), both with and without adjustments for covariates. This model assigns relative importance to the HRs at different times based on the number of people at risk during those periods, creating a weighting function that accurately reflects each time point's contribution

to the partial likelihood. This approach ultimately provides an unbiased estimate of the average HR without depending on the proportional-hazard (PH) assumption [29]. Simulation studies have shown that when the PH assumption is violated, the weighted Cox model better summarizes the average effect of the exposure. Conversely, when the PH assumption holds true, the estimates produced by the weighted Cox model are similar to those generated by the standard Cox model [29, 30]. Model multicollinearity was measured using the variance inflation factor (VIF), with values greater than 10 indicating severe collinearity. Several sensitivity analyses were performed to test the robustness of our findings: (1) Excluding participants with less than 2 years of follow-up. (2) Using multiple imputations for missing data through chained Eq. 3) Converting continuous measures of exposure into categorical formats. 4) Adding further adjustments for covariates, which encompassed other medications (specifically lipid-lowering and antihypertensive drugs), key comorbidities (including hypertension, dyslipidemia, coronary heart disease, and stroke), diabetes type, family history of diabetes, physical activity, and heavy physical labor work. Subgroup analyses were conducted based on gender and diabetes type, with likelihood ratio tests employed to evaluate multiplicative scale interactions. Restricted cubic spline (RCS) curves were plotted to visualize the relationships between TDI and outcome (DR, DN and DPN). All statistical tests were two-sided, and $P<0.05$ was considered statistically significant. All the above analyses were performed using R software (version 4.2.1), and the weighted Cox models were fitted using the "coxphw" R package (version 4.0.3) and RCS curves were plotted using the "rcssci" R package (version 0.3.0).

Results

A total of 28,339, 29,951 and 29,762 eligible participants were included in the DR, DN and DPN cohorts, respectively. The baseline characteristics of the participants and missing data information are shown in Table 1. Among the DR cohort, the median follow-up was 12.95 years, and 3,177 (11.2%) participants suffered from DR (median age 62.00 years, 61.4% male). Among the DN cohort, the median follow-up was 12.89 years, and 4,418 (14.8%) participants suffered from DN (median age 64.00 years, 62.6% male). Among the DPN cohort, the median follow-up was 13.02 years, and 1,604 (5.4%) participants suffered from DPN (median age 61.00 years, 65.9% male). Compared with subjects without diabetic microvascular complications, those with DR, DN or DPN were more likely to have lower household income and higher TDI. They were also more prone to have higher HbA1c levels, longer duration of diabetes, and use of diabetes medication. According to the Kaplan-Meier analyses, higher educational attainment, higher household income and lower TDI were associated with a reduced risk of diabetic microvascular complications (log-rank test P-value <0.001, except for education and DR; Fig. 2).

The association between SES and incident diabetic microvascular complications is displayed in Table 2. After adjusting for confounders, every SD increment of education attainment was found to be associated with a 15% and 7% lower risk of DN (95% CI, 0.82–0.89; $P<0.001$) and DPN (95% CI, 0.87-1.00; $P=0.040$), but had no protective effect on DR (HR = 1.01; 95% CI, 0.97–1.06; $P=0.581$). Moreover, each SD increase in household income was associated with an 8% decreased risk of DR (95% CI, 0.87–0.97; $P=0.004$), a 20% reduced risk of DN (95% CI, 0.75–0.85; $P<0.001$) and DPN (95% CI, 0.73–0.89; $P<0.001$). Furthermore, each SD increase in TDI showed an 8% increased risk of DR (95% CI, 1.02–1.13; $P=0.004$), a 19% increased risk of DN (95% CI, 1.14–1.23; $P<0.001$) and a 27% increased risk of DPN (95% CI, 1.19–1.36; $P<0.001$). These results did not change significantly after excluding participants with less than 2 years of follow-up (Supplementary Table 3), multiple imputations for missing data (Supplementary Table 4), converting continuous measures of exposure to categorical forms (Supplementary Table 5), or further adjusting for covariates (Supplementary Table 6). Furthermore, the subgroup analyses indicated no interaction, highlighting that the effect of SES on diabetic microvascular complications was unaffected by either gender or diabetes type (Supplementary Tables 7–8). RCS curves were plotted to further evaluate the relationships between TDI and incident diabetic microvascular complications (Fig. 3).

Discussion

The present study revealed that higher education attainment, higher household income, and lower TDI were associated with a lower risk of DN and DPN in a population-based cohort, whereas the lower risk of DR was only related to higher household income and lower TDI (Fig. 4). With large cohort data from the UK Biobank, we present a clearer picture of the impact of SES on diabetic microvascular complications.

SES is broadly conceptualized as an individual's or group's position in the socioeconomic hierarchy, which has been significantly associated with multiple diseases. In a population-based cohort study, Zhang et al. reported that low SES was significantly related to higher risks of mortality and incidence of cardiovascular diseases [25]. A recent study by Conrad et al. revealed a socioeconomic gradient across several autoimmune diseases, including pernicious anemia, rheumatoid arthritis, Graves' disease, and systemic lupus erythematosus [31]. In addition, the association between socioeconomic inequality as a risk factor and diabetes is well established [6]. However, the

Table 1 Baseline characteristics of participants stratified by Incident Diabetic Microvascular complications

	DR-	DR+	Missing (%)	*P*	DN-	DN+	Missing (%)	*P*	DPN-	DPN+	Missing (%)	*P*
n	25,162	3177			25,533	4418			28,158	1604		
Male sex	15,494 (61.6)	1950 (61.4)	0	0.844	15,710 (61.5)	2767 (62.6)	0	0.169	17,318 (61.5)	1057 (65.9)	0	< 0.001
Age, years	61.00 (55.00, 65.00)	62.00 (56.00, 66.00)	0	< 0.001	61.00 (54.00, 65.00)	64.00 (60.00, 67.00)	0	< 0.001	61.00 (55.00, 65.00)	61.00 (56.00, 66.00)	0	0.029
Highest education qualifications			3.1	0.376			3	< 0.001			3	< 0.001
College or university degree	5819 (23.8)	730 (23.8)			6201 (25.0)	730 (17.1)			6591 (24.1)	305 (19.6)		
NVQ or HND or HNC or equivalent	3930 (16.1)	465 (15.2)			4030 (16.3)	615 (14.4)			4350 (15.9)	261 (16.8)		
Other professional qualifications, e.g.: nursing, teaching	2858 (11.7)	381 (12.4)			2952 (11.9)	454 (10.6)			3204 (11.7)	173 (11.1)		
A levels/AS levels or equivalent	1179 (4.8)	138 (4.5)			1241 (5.0)	159 (3.7)			1323 (4.8)	67 (4.3)		
O levels/GCSEs or equivalent	3079 (12.6)	364 (11.9)			3100 (12.5)	553 (12.9)			3443 (12.6)	197 (12.7)		
CSEs or equivalent	822 (3.4)	103 (3.4)			844 (3.4)	130 (3.0)			919 (3.4)	51 (3.3)		
None of the above	6718 (27.5)	887 (28.9)			6397 (25.8)	1632 (38.2)			7475 (27.4)	500 (32.2)		
Average total household income before tax			18.8	< 0.001			18.9	< 0.001			18.9	< 0.001
Less than £18,000	7430 (36.4)	1037 (40.2)			7291 (35.0)	1695 (49.1)			8278 (36.3)	625 (47.9)		
£18,000 to £30,999	5757 (28.2)	725 (28.1)			5888 (28.3)	970 (28.1)			6479 (28.4)	341 (26.1)		
£31,000 to £51,999	4188 (20.5)	496 (19.2)			4405 (21.1)	506 (14.6)			4678 (20.5)	214 (16.4)		
£52,000 to £100,000	2532 (12.4)	269 (10.4)			2686 (12.9)	253 (7.3)			2824 (12.4)	113 (8.7)		
Greater than £100,000	514 (2.5)	52 (2.0)			558 (2.7)	30 (0.9)			576 (2.5)	12 (0.9)		
Ethnicity			0.9	< 0.001			1	0.001			0.9	< 0.001
Caucasian	21,809 (87.5)	2666 (84.8)			21,942 (86.8)	3873 (88.6)			24,150 (86.6)	1441 (90.7)		
Other	3121 (12.5)	478 (15.2)			3350 (13.2)	498 (11.4)			3745 (13.4)	148 (9.3)		
Smoker	13,370 (54.4)	1654 (53.6)	2.4	0.408	13,245 (53.1)	2567 (59.7)	2.4	< 0.001	14,738 (53.6)	923 (58.8)	2.3	< 0.001
Heavy alcohol consumption	6736 (33.4)	791 (31.5)	19.9	0.067	6923 (33.4)	1014 (29.8)	19.5	< 0.001	7448 (32.8)	406 (31.8)	19.4	0.504
Systolic blood pressure, mmHg	143.00 (131.00, 155.00)	145.00 (133.00, 157.00)	0.5	< 0.001	143.00 (131.00, 155.00)	145.00 (132.00, 158.00)	0.5	< 0.001	143.00 (131.00, 156.00)	143.00 (131.00, 156.00)	0.5	0.577
Diastolic blood pressure, mmHg	82.00 (75.00, 89.00)	81.00 (74.00, 88.00)	0.5	< 0.001	82.00 (75.00, 89.00)	80.00 (72.00, 87.00)	0.5	< 0.001	82.00 (75.00, 89.00)	80.00 (73.00, 88.00)	0.5	< 0.001
Mean arterial pressure, mmHg	102.67 (95.00, 110.33)	102.33 (94.67, 110.00)	0.5	0.021	102.67 (95.33, 110.33)	101.33 (93.67, 109.67)	0.5	< 0.001	102.67 (95.00, 110.33)	101.33 (93.67, 108.67)	0.5	< 0.001
Plasma glucose, mmol/L	6.37 (5.27, 8.52)	7.40 (5.57, 10.69)	14.7	< 0.001	6.44 (5.29, 8.74)	6.77 (5.40, 9.28)	14.8	< 0.001	6.44 (5.29, 8.70)	7.43 (5.62, 10.71)	14.8	< 0.001
HbA1c, mmol/mol	49.80 (43.70, 57.50)	55.30 (47.60, 66.50)	6.9	< 0.001	50.20 (44.10, 58.60)	51.80 (45.50, 62.20)	7	< 0.001	50.20 (44.10, 58.60)	56.20 (47.27, 68.80)	7	< 0.001
HbA1c, %	6.71 (6.15, 7.41)	7.21 (6.51, 8.23)			6.74 (6.19, 7.51)	6.89 (6.31, 7.84)			6.74 (6.19, 7.51)	7.29 (6.48, 8.45)		
HbA1c category, %*			6.9	< 0.001			7	< 0.001			7	< 0.001
< 6.5	8811 (37.6)	716 (24.5)			8571 (36.0)	1288 (31.7)			9459 (36.1)	373 (25.6)		
6.5–7.4	9226 (39.3)	1015 (34.7)			9206 (38.7)	1464 (36.1)			10,164 (38.8)	453 (31.1)		

Table 1 (continued)

	DR-	DR+	Missing (%)	*P*	DN-	DN+	Missing (%)	*P*	DPN-	DPN+	Missing (%)	*P*
7.5–8.4	3168 (13.5)	590 (20.2)			3423 (14.4)	713 (17.6)			3827 (14.6)	282 (19.4)		
≥ 8.5	2241 (9.6)	604 (20.6)			2588 (10.9)	592 (14.6)			2778 (10.6)	348 (23.9)		
Triglycerides, mmol/L	1.91 (1.33, 2.73)	1.84 (1.28, 2.69)	7.2	0.007	1.86 (1.29, 2.68)	2.02 (1.43, 2.86)	7.2	< 0.001	1.88 (1.30, 2.69)	2.01 (1.43, 2.97)	7.1	< 0.001
High-density lipoprotein, mmol/L	1.14 (0.98, 1.36)	1.14 (0.97, 1.37)	14.8	0.769	1.16 (0.98, 1.37)	1.09 (0.93, 1.30)	14.8	< 0.001	1.15 (0.98, 1.36)	1.11 (0.94, 1.32)	14.8	< 0.001
Low-density lipoprotein, mmol/L	2.70 (2.23, 3.33)	2.59 (2.14, 3.13)	7.3	< 0.001	2.70 (2.23, 3.33)	2.55 (2.14, 3.08)	7.3	< 0.001	2.68 (2.22, 3.30)	2.59 (2.15, 3.11)	7.3	< 0.001
Duration of diabetes, year	4.00 (1.00, 8.57)	8.33 (3.51, 15.03)	0	< 0.001	4.32 (1.08, 9.33)	7.00 (3.00, 13.03)	0	< 0.001	4.44 (1.15, 9.46)	9.10 (4.00, 17.40)	0	< 0.001
BMI category, kg/m^2			1.2	0.824			1.2	< 0.001			1.2	< 0.001
< 18.5	30 (0.1)	5 (0.2)			32 (0.1)	2 (0.0)			29 (0.1)	4 (0.3)		
18.5–24.9	2677 (10.8)	347 (11.1)			2881 (11.4)	334 (7.7)			3069 (11.0)	161 (10.3)		
25.0-29.9	8524 (34.2)	1053 (33.7)			8942 (35.4)	1222 (28.2)			9673 (34.7)	439 (28.0)		
≥ 30.0	13,657 (54.9)	1717 (55.0)			13,407 (53.1)	2781 (64.1)			15,077 (54.1)	962 (61.4)		
Use of oral hypoglycemic agents	12,493 (49.8)	1958 (61.8)	0.3	< 0.001	12,734 (50.0)	2760 (62.7)	0.3	< 0.001	14,334 (51.0)	973 (61.0)	0.3	< 0.001
Use of insulin products	3365 (13.4)	1095 (34.5)	0.1	< 0.001	4142 (16.2)	1145 (26.0)	0.1	< 0.001	4524 (16.1)	649 (40.6)	0.1	< 0.001
TDI	-1.24 (-3.18, 2.05)	-0.92 (-3.11, 2.36)	0.2	0.006	-1.26 (-3.20, 2.00)	-0.67 (-2.86, 2.68)	0.2	< 0.001	-1.22 (-3.17, 2.05)	-0.13 (-2.83, 3.06)	0.2	< 0.001
TDI quintile			0.2	0.009			0.2	< 0.001			0.2	< 0.001
1	5042 (20.1)	616 (19.4)			5211 (20.4)	769 (17.4)			5679 (20.2)	264 (16.5)		
2	5045 (20.1)	612 (19.3)			5186 (20.3)	796 (18.0)			5667 (20.2)	276 (17.2)		
3	5069 (20.2)	593 (18.7)			5105 (20.0)	876 (19.8)			5660 (20.1)	283 (17.7)		
4	5010 (19.9)	649 (20.4)			5053 (19.8)	928 (21.0)			5591 (19.9)	352 (22.0)		
5	4956 (19.7)	704 (22.2)			4937 (19.4)	1045 (23.7)			5515 (19.6)	428 (26.7)		

Quantitative data were shown as median (IQR) and qualitative data as n (%), unless otherwise specified

* 6.5% = 47.5 mmol/mol, 7.5% = 58.5 mmol/mol, 8.5% = 69.4 mmol/mol

DR: diabetic retinopathy, DN: diabetic nephropathy, DPN: diabetic peripheral neuropathy, GCSEs: General Certificate of Secondary Education students, CSEs: Certificate of Secondary Education students, NVQ: National Vocational Qualification, HND: Higher National Diploma, HNC: Higher National Certificate, HbA1c: glycated hemoglobin, TDI: Townsend deprivation index

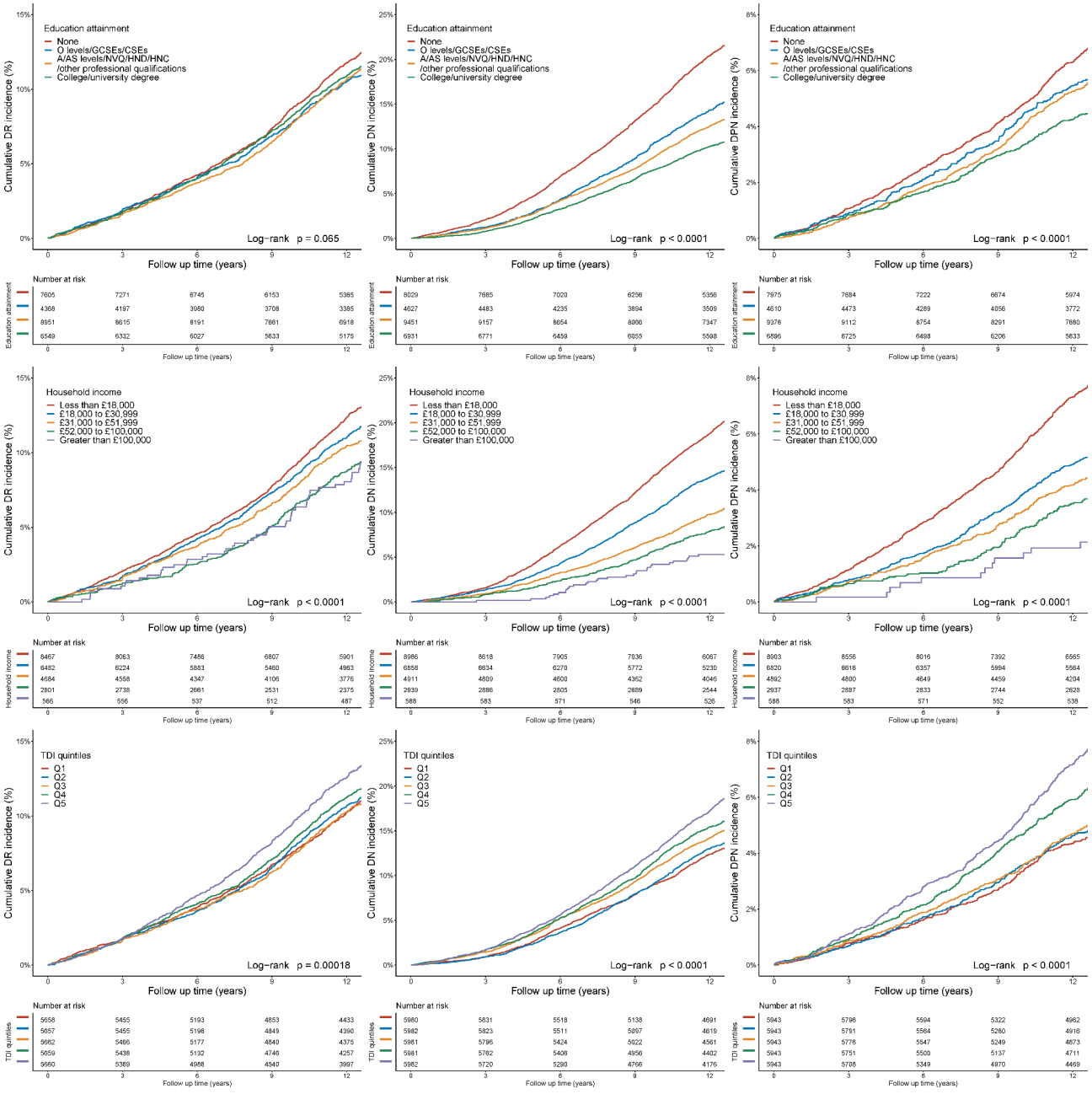

Fig. 2 Kaplan–Meier estimates of the cumulative incidence of diabetic microvascular complications according to SES. Kaplan-Meier cumulative incidence plots were generated according to education, income, and TDI levels to assess the associations between SES and the incidence of DR, DN, and DPN, and statistically analyzed using the log-rank test. SES: socioeconomic status, TDI: Townsend deprivation index, DR: diabetic retinopathy, DN: diabetic nephropathy, DPN: diabetic peripheral neuropathy

association between SES and diabetic microvascular complications remains controversial and high-quality evidence is lacking.

The results of the present study are in accordance with most previous observational studies and are well integrated with the role of SES on the three main diabetic microvascular complications, suggesting that patients with low SES are at increased risk of DR, DN and DPN. In a study with a mean follow-up of 6.2 years, Low et al. found that both person-level and area-level SES were associated with DR incidence, progression, and associated vision loss in Asians [16]. In addition, Emoto et al. revealed that lower educational attainment is a strong risk factor for DR in patients with difficult-to-control type 2 DM [32]. Partially consistent with these studies, the current study found that people with low household income and high TDI were associated with a higher risk of DR, but longer education attainment had no protective

Table 2 The association of SES with incident diabetic microvascular complications

Models	Exposure*	Outcome					
		Diabetic retinopathy		Diabetic nephropathy		Diabetic peripheral neuropathy	
		HR (95%CI)	*P*	HR (95%CI)	*P*	HR (95%CI)	*P*
Model 1†	Education attainment, year	0.96 (0.93-1.00)	0.038	0.77 (0.74–0.79)	< 0.001	0.89 (0.85–0.94)	< 0.001
	Average total household income before tax, £	0.90 (0.86–0.94)	< 0.001	0.67 (0.63–0.71)	< 0.001	0.75 (0.70–0.82)	< 0.001
	TDI	1.07 (1.01–1.13)	0.029	1.16 (1.08–1.25)	< 0.001	1.40 (1.13–1.75)	0.003
Model 2‡	Education attainment, year	0.99 (0.95–1.03)	0.538	0.83 (0.81–0.86)	< 0.001	0.89 (0.85–0.94)	< 0.001
	Average total household income before tax, £	0.93 (0.89–0.98)	0.002	0.76 (0.72–0.80)	< 0.001	0.75 (0.69–0.81)	< 0.001
	TDI	1.09 (1.04–1.15)	0.001	1.25 (1.16–1.34)	< 0.001	1.39 (1.17–1.66)	< 0.001
Model 3§	Education attainment, year	1.01 (0.97–1.06)	0.581	0.85 (0.82–0.89)	< 0.001	0.93 (0.87-1.00)	0.040
	Average total household income before tax, £	0.92 (0.87–0.97)	0.004	0.80 (0.75–0.85)	< 0.001	0.80 (0.73–0.89)	< 0.001
	TDI	1.08 (1.02–1.13)	0.004	1.19 (1.14–1.23)	< 0.001	1.27 (1.19–1.36)	< 0.001

* Per SD increase for each exposure

† Adjusted for none

‡ Adjusted for age and sex

§ Adjusted for age, sex, race, smoking status, alcohol consumption status, mean arterial pressure, glycated hemoglobin level, triglyceride, high-density lipoprotein cholesterol, low-density lipoprotein cholesterol, duration of diabetes, BMI level, oral hypoglycemic drug use and insulin treatment

SES: socioeconomic status, TDI: Townsend deprivation index, HR: hazard ratios

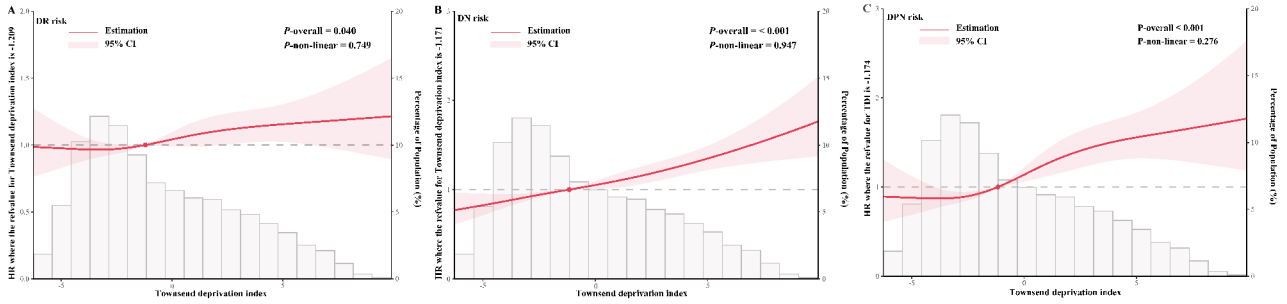

Fig. 3 Associations between TDI and incident DR (**A**), DN (**B**) and DPN (**C**) were evaluated by RCS curves. The HR (solid red line) and 95% CI (light red area) are from a multivariate adjusted Cox regression model using RCS curves with four knots (5th, 35th, 65th, and 95th percentiles). The reference value (red dot) of TDI was set to the median. The histogram shows the distribution of TDI. TDI: Townsend deprivation index, RCS: restricted cubic spline, DR: diabetic retinopathy, DN: diabetic nephropathy, DPN: diabetic peripheral neuropathy, CI: confidence interval, HR: hazard ratio

effect on DR. This may be due to residual confounding factors or mediators between SES and DR, such as lifestyle factors [25]. Further studies are needed to examine the possibility of other factors mediating the associations of SES with incident DR and the extent of the interactions. Winitzki et al. found that patients with low educational attainment had a higher risk for mortality, kidney failure, and DN in the German Chronic Kidney Disease Cohort study [17]. A cross-sectional study conducted by Wolf et al. revealed that lower SES was associated with DN [33]. Two other cross-sectional studies indicated that diabetic neuropathy is more prevalent in patients with type 1 and type 2 DM who have lower SES, emphasizing the necessity for longitudinal studies [13, 34]. Consistent with these studies, the current prospective study found that people with low SES (low education attainment, low household income, and high TDI) were exposed to a higher risk of DN and DPN.

The mechanism underlying the associations between low SES and diabetic microvascular complications is likely multifactorial. First, people with low SES may be more susceptible to malnutrition. In a prospective study, Du et al. found that higher fruit consumption was associated with lower risks of microvascular complications [35]. In addition, early screening and referral can effectively reduce the visual loss caused by DR [36], but patients with low SES may not have access to adequate healthcare services, such as screening. Further studies are needed to elucidate the underlying mechanism.

The main strengths of this study are the prospective design, large sample size, long-term follow-up, and adequate covariate adjustment to minimise the effect of confounding factors on the results. In addition, SES was comprehensively evaluated from the individual, household, and neighborhood levels using education attainment, household income, and TDI. Furthermore, a series of sensitivity analyses were conducted to demonstrate

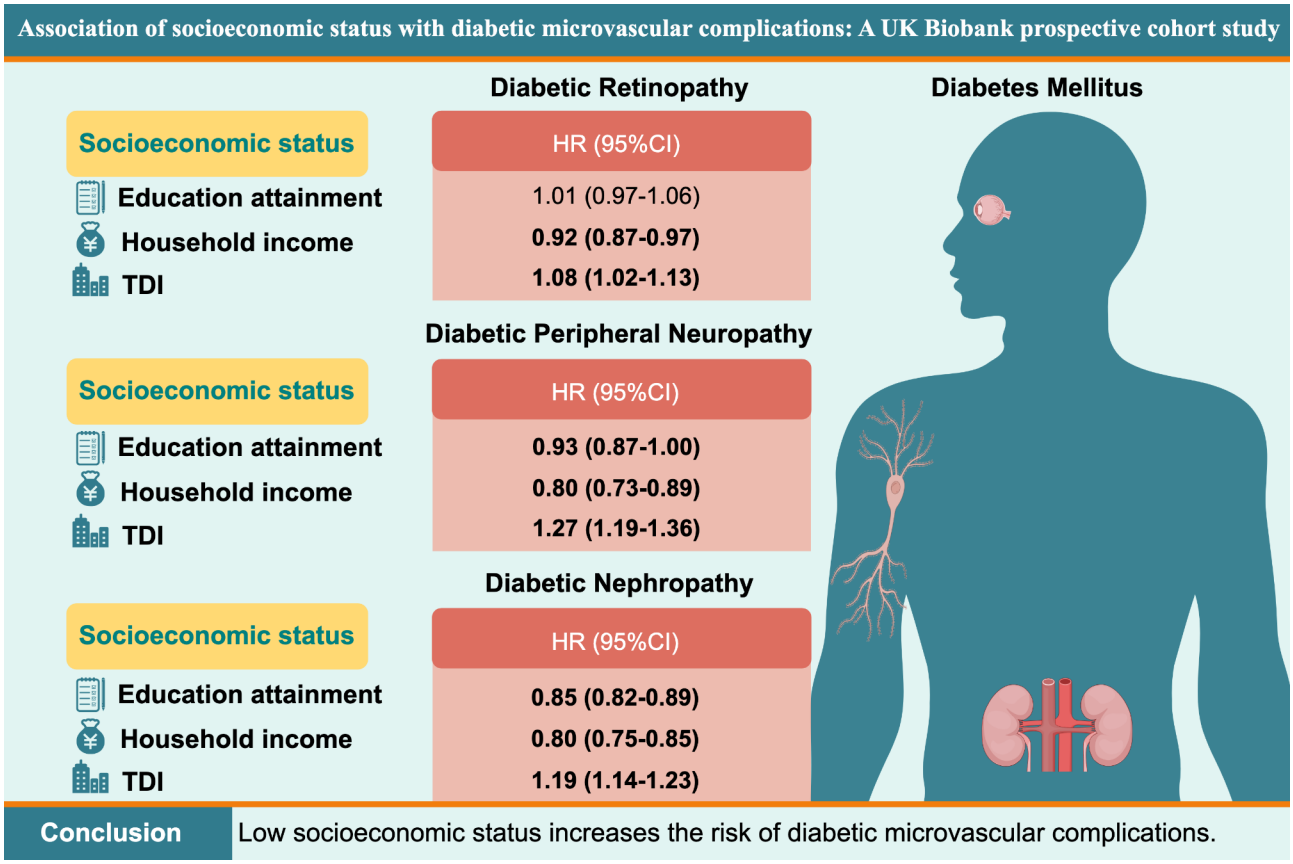

Fig. 4 Schematic illustration. Low socioeconomic status increases the risk of incident diabetic microvascular complications based on a large prospective cohort. TDI: Townsend deprivation index, HR: hazard ratio, CI: confidence intervals

the robustness of the findings. Nevertheless, the limitations of this study should be acknowledged. First, due to the observational nature, residual and unmeasured confounders or mediators cannot be completely excluded in the cohort study. Second, the present study lacks an overall SES variable comprising different aspects of SES. Third, the reduced sample size after grouping may have limited the statistical power of the subgroup analyses, leading to inconsistent results with the overall trend. Consequently, larger sample sizes will be warranted in the future to confirm the findings of the subgroup analyses. Finally, as the enrolled patients were mainly European, the relationship between SES and diabetic microvascular complications in other populations needs further investigations.

Conclusions

In summary, low SES was found to significantly increase the risk of incident DR, DN and DPN, which highlights the importance of allocating medical resources to reduce diabetes inequity. The mechanisms of the association between SES and diabetic microvascular complications should be studied further.

Abbreviations

BMI	Body mass index
CI	Confidence interval
DM	Diabetes mellitus
DN	Diabetic nephropathy
DR	Diabetic retinopathy
HbA1c	Glycated hemoglobin
HDL	High-density lipoprotein cholesterol
HR	Hazard ratio
ISCED	International Standard Classification for Education
LDL	Low-density lipoprotein cholesterol
MAP	Mean arterial pressure
PH	Proportional-hazard
RCS	Restricted cubic spline
SD	Standard deviation
SES	Socioeconomic status
TDI	Townsend deprivation index
TG	Triglyceride

Supplementary Information

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Supplementary Material 1

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Author contributions
Y.H.: Conceptualization, Data curation, Formal Analysis, Investigation, Methodology, Software, Validation, Visualization and Writing – original draft. Z.Z.: Funding acquisition, Supervision and Writing – review & editing. H.C.: Project administration, Resources, Supervision and Writing – review & editing. C.G.: Conceptualization, Data curation, Investigation, Writing – original draft and Writing – review & editing.

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Data availability
The datasets generated and/or analyzed during the current study are available in the UK Biobank (https://www.ukbiobank.ac.uk/enable-your-research/apply-for-access). This research was conducted using the UK Biobank Resource under Application Number 88982.

Declarations

Ethics approval and consent to participate
The UK Biobank study was approved by the North West Multicenter Research Ethical Committee (REF: 11/NW/03820), and all participants provided informed consent.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

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