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ORIGINAL RESEARCH

A socioeconomic and behavioral survey of patients with difficult-to-control type 2 diabetes mellitus reveals an association between diabetic retinopathy and educational attainment

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Background: We have recently reported that the attitude of patients toward risk could be a factor in the progression of diabetic complications. In general, risk preference is closely related to socioeconomic status (SES), which includes factors such as age, sex, income, and educational attainment.

Objective: We aimed to determine the effect of SES and behavioral propensity on the progress of diabetic complications in patients with type 2 diabetes mellitus (T2DM).

Methods: We conducted a survey of 238 patients with difficult-to-control T2DM treated at a hospital in Japan using a modified behavioral economics questionnaire that included questions related to SES. The patients had been referred by general practitioners or other departments in the hospital because of poor metabolic control or unstable complications.

Results: Educational attainment was significantly associated with progression of retinopathy in patients <65 years of age. Educational attainment of a high school diploma (12 years of education) or lower was a significant risk factor, but there were no differences among levels of attainment beyond high school (13–16 years or more of education). Behavioral propensities were also weakly associated with complications, but not as much as educational attainment. Personal income level and economic status did not show an association with the retinopathy levels.

Conclusion: Lower educational attainment is a strong risk factor for diabetic retinopathy, and it is independent of the economic status. The result suggests that cognitive function may play an important role in the progression of diabetic retinopathy in patients with T2DM.

Keywords: behavioral economics, cognitive function, diabetic nephropathy, economic status, income

Introduction

The standard treatment for type 2 diabetes mellitus (T2DM) is dietary therapy and appropriate exercise, followed by the sequential addition of oral antihyperglycemic agents, glucagon-like peptide-1 receptor agonists, or insulin injection (basal and/or mealtime).[1] Large prospective clinical studies have shown a strong relationship between hyperglycemia and diabetic microvascular complications in both type 1 diabetes mellitus (T1DM) and T2DM.[2,3] However, modification of lifestyle habits, as well as adherence to pharmacological treatment, proves to be challenging in many patients.[4,5] It remains unclear why many patients with diabetes cannot make the necessary lifestyle changes and cannot adhere to pharmacological treatment, both of which are clearly beneficial for their future health.

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The theory of neuroeconomics, an emerging field of study focusing on anomalies in the classical economics rationale, can provide important clues for understanding unreasonable human behavior regarding decisions over outcomes that occur at different time points.[6,7] Neuroeconomic studies have demonstrated that humans and animals prefer rewards available to them in the short term over rewards only available in the long term. Recently, we reported a behavioral economics survey of patients with difficult-to-control T1DM or T2DM.[8] The patients' attitude to risk was estimated by the pricing of hypothetical lotteries; such questions are closely related to socioeconomic status (SES), a combined measure that includes factors such as age, sex, income, and educational levels.[9] The results suggested that the attitude of patients toward risk could be a factor in the progression of diabetic complications. However, in that study, we could not differentiate between patients who were risk-seeking and those with low literacy proficiency.

SES has been reported to have a serious impact on the prevalence of T1DM and T2DM as well as associated complications and mortality in every major ethnic group worldwide.[10–16] In order to determine the effect of SES and behavioral economics propensity on the progress of diabetic complications, in the present study, we conducted a survey among patients with diabetes using modified behavioral economics questionnaires, including those related to SES.

Methods

Participants

This study initially included every patient (497 in total) with diabetes treated by two endocrinologists at the outpatient clinic of endocrinology at the Nippon Medical School Chiba-Hokusoh Hospital from July to September 2015 (Figure S1). The hospital is one of the three base hospitals in a locality with a population of 700,000 that consists of several cities, towns, and villages near to metropolitan Tokyo, Japan. The clinic provides care to patients with diabetes referred by general practitioners or other departments in the hospital because the diabetes was difficult to control due to poor metabolic control or unstable complications. Of the 497 patients, 112 were excluded because of active psychiatric disease, mental retardation, dementia, active malignant disease, unstable endocrine disease, or inability to understand the Japanese language, or because they needed assistance for daily life or refused to participate in the survey. This left 385 patients eligible to participate. The patients defined as having T1DM (89 patients) were those with acute onset of insulin-dependent diabetes or who had positive anti-glutamic acid decarboxylase or anti-islet antigen-2 antibodies. All other patients, except those with pancreatitis or total pancreatectomy (5 patients), were defined as having T2DM (291 patients). The present study analyzed survey questionnaire data from the patients with T2DM.

The study protocol, including a consent form with a confidentiality clause, was approved by the Internal Review Board of the Nippon Medical School Ethics Committee. The survey and an explanation sheet that included the consent form were handed out at the outpatient clinic. The completed survey forms and consent forms were returned by mail. Participants received a book coupon worth 500 yen (equivalent to USD 5) as token remuneration. The survey questionnaire used in this study is shown in Figure S2. The questions were modified versions of those from our previous report[8] and from the Japan Household Survey on Consumer Preferences and Satisfaction.[17,18] In the present study, we analyzed only the responses of the participants with T2DM. The survey response rate for these participants was 81.8% (238 out of 291 patients responded). Hemoglobin A1c (HbA1c) levels were determined by high-performance liquid chromatography using an HLC723G8 analyzer (Tosoh, Co., Tokyo, Japan) and presented as the equivalent National Glycohemoglobin Standardization Program values. To evaluate retinopathy, ophthalmologists performed fundoscopy after pupillary dilatation, following the Davis classification: no diabetic retinopathy, simple diabetic retinopathy, preproliferative diabetic retinopathy, and proliferative diabetic retinopathy including panretinal photocoagulation. Nephropathy was classified according to the Classification of Diabetic Nephropathy 2014: Stage 1, urinary albumin excretion (UAE) <30 mg/g creatinine; Stage 2, UAE 30–299 mg/g creatinine; Stage 3, UAE ≥ 300 mg/g creatinine; Stage 4, estimated glomerular filtration rate <30 mL/min/1.73 m^2; and Stage 5, dialysis therapy.[19]

Statistical analyses

In the analysis, retinopathy level was represented as an ordinal variable with three possible values: 0, no diabetic retinopathy; 1, simple diabetic retinopathy; or 2, preproliferative diabetic retinopathy and proliferative diabetic retinopathy including panretinal photocoagulation. Nephropathy was represented by an ordinal variable with four possible values based on the nephropathy stage: 1, Stage 1; 2, Stage 2; 3, Stage 3; or 4, Stages 4 and 5. Personal income and household income were obtained by self-report (from Q17 and Q18 in Figure S2) as categorical data, and the median values for each category were treated as continuous variables with a

maximum of 11 million yen. Statistical analyses were performed using JMP® 11 (SAS Institute Inc., Cary, NC, USA). Frequency analysis was performed using Fisher's exact test. The Kruskal–Wallis rank sum test was used to compare income levels. Pearson's χ^2 test was performed to analyze differences between categorical data. $P<0.01$ was considered to be significant. Multiple logistic regression analysis was used to select parameters significantly associated with diabetic complications as follows.

Parameter selection

Stepwise logistic regression methods were used to identify the survey items associated with the progress of retinopathy or nephropathy. All 20 questionnaire questions, age, sex, duration of diabetes, body mass index (BMI), and HbA1c at the time of the survey were entered as independent variables in the stepwise regression model. Items were eliminated by the model in a backward stepwise fashion using minimum Akaike's information criterion with a correction (for finite sample sizes) to choose the best model. In the Wald test and the effect likelihood ratio test, $P<0.01$ was considered to show a significant association and $P<0.05$ a weak association.

Results

The characteristics of the participants who responded and whose data were analyzed in this study are shown in Table 1. It has been reported that SES differences in health are age-dependent, are greatest during the young- to middle-age adult years, and are not so pronounced among older people.[20–24] We therefore divided the participants into two groups according to their age (<65 and ≥65 years) for further analysis. BMI were significantly higher in patients <65 years of age, and diabetes durations were longer in patients ≥65 years of age. Gender ratio, HbA1c, prevalence of retinopathy and nephropathy were not significantly different between age groups. Tables 2 and 3 show the results of the ordinal logistic regression analysis of factors associated with retinopathy and nephropathy for the participants with T2DM at all ages. Diabetes duration, procrastination, educational attainment, and savings status (not increased) were factors significantly associated with the retinopathy level. Sex (male), BMI, and shortage of sleep were factors associated with nephropathy level. Tables 4 and 5 show the results of the ordinal regression analysis of factors associated with the retinopathy level and nephropathy levels for the participants <65 years of age. Educational attainment was the only factor significantly associated with the retinopathy level in these participants. Sex (male), diabetes duration, procrastination, medical spending, risk preference, and job status were weakly associated with retinopathy ($P<0.05$). Factors significantly associated with nephropathy for those <65 years of age were age and BMI. Tables 6 and 7 show the results of the ordinal regression analysis of factors associated with retinopathy and nephropathy for participants ≥65 years of age. Diabetes duration, unwillingness to accept medical uncertainty, and job status were significantly associated with retinopathy level. Only diabetes duration was significantly associated with nephropathy in the older participants. Figure 1 shows the association between retinopathy level and educational attainment for the participants <65 years of age. Educational attainment of high school or lower (ie, 12 years of education) was a significant risk factor for the progression of retinopathy in the participants <65 years of age (Pearson's χ^2 test, $P=0.0058$); the risk exhibited a threshold at the high school level, and there were no marginal differences between educational attainment levels above high school (ie, 13–16 years or more of education). There was no association between retinopathy level and educational attainment in the older participants (Pearson's χ^2 test, $P=0.89$). Educational attainment and income are closely associated;

Table 1 Patient characteristics

Characteristic	Total	Age <65 years	Age ≥65 years	*P*-value[1]
Number of patients	238	128	110	
Age (years)	61.4±12.4	52.9±10.0	71.3±5.7	
Male/female	129/109	71/57	58/52	0.672
BMI (kg/m^2)	25.6±4.6	26.5±4.8	24.3±4.0	<0.001
Diabetes duration (years)	13.2±9.7	10.3±7.6	16.6±10.9	<0.001
HbA1c (%)	7.70±4.5	7.52±1.0	7.89±6.5	0.525
Retinopathy ±[2] (retinopathy rate)	111/121 (47.8%)	61/66[3] (48.0%)	50/55[4] (47.6%)	0.950
Nephropathy ±[5] (nephropathy rate)	95/143 (39.9%)	45/83 (35.2%)	50/60 (45.5%)	0.106

Notes: Values are presented as mean ± standard deviation. [1]Age <65 versus ≥65 years, frequency analysis was performed with Fisher's exact test. [2]Retinopathy includes simple, preproliferative, proliferative retinopathy, and panretinal photocoagulation. [3]One patient did not have eye examination by ophthalmologists. [4]Five patients did not have eye examination by ophthalmologists. [5]Nephropathy includes stages 2–5 nephropathy.
Abbreviations: BMI, body mass index; HbA1c, hemoglobin A1c.

Table 2 Ordinal logistic regression analysis[1] of factors associated with retinopathy level[2] in patients with T2DM all ages

Parameter	Estimate	Standard error	Chi-square test	*P*-value[4]
Age	–0.02764	0.01583	3.05	0.0807
Sex (female)	–0.38540	0.16622	5.38	0.0204
Diabetes duration	0.06717	0.01753	14.68	0.0001[5]
Q1[3] General risk preference, weather	–0.00717	0.00740	0.94	0.3326
Q2 General risk averse, travel	0.01384	0.01285	1.16	0.2815
Q3 Dissatisfaction to life	0.09261	0.15301	0.37	0.5450
Q8 Procrastination, if now (2&3 vs 1)	0.39389	0.15333	6.60	0.0102[5]
Q10 Medical spending	0.00002	0.00001	2.76	0.0967
Q13 Risk loving, lottery	0.00005	0.00005	1.29	0.2558
Q15 Educational level (high)	–0.32113	0.11304	8.07	0.0045[5]
Q16 Job (worked)	–0.40064	0.17874	5.02	0.0250
Q18 Household income	0.00079	0.00069	1.31	0.2532
Q18 Household income/person	–0.00170	0.00161	1.12	0.2892
Q19 Savings (1&3&4 vs 2)	0.79641	0.30449	6.84	0.0089[5]
Q19 Savings (1&3 vs 4)	0.10406	0.15369	0.46	0.4984
Q20 Economic status (affluent)	0.21864	0.22167	0.97	0.3240

Notes: [1]Whole model test: degrees of freedom 16, likelihood ratio chi-square test 52.54, *P*-value <0.0001. [2]Levels of diabetic retinopathy; 0, NDR; 1, SDR; 2, PPDR + PDR + PRP. [3]Survey questionnaires are shown in Figure S2. [4]Wald test for effects. [5]$P<0.01$, significant by effect likelihood ratio test.
Abbreviations: NDR, no diabetic retinopathy; PDR, proliferative diabetic retinopathy; PPDR, preproliferative diabetic retinopathy; PRP, panretinal photocoagulation; SDR, simple diabetic retinopathy; T2DM, type 2 diabetes mellitus.

we therefore analyzed the relationship between retinopathy, educational attainment, and income. Figure 2 shows a comparison of personal and household income by retinopathy level for the participants <65 years of age. Personal income level did not differ between retinopathy levels (Kruskal–Wallis test, $P=0.51$), and household income tended to be higher in participants <65 years of age with no diabetic retinopathy (Kruskal–Wallis tests, $P=0.032$). Figure 3 shows a comparison of personal income and household income by educational attainment in the participants <65 years of age. Although participants with a university or graduate school qualification showed significantly higher personal income (Kruskal–Wallis test, $P=0.0073$) and household income (Kruskal–Wallis test, $P=0.028$), the difference between personal and household income was not significant for other levels of educational attainment.

Table 3 Ordinal logistic regression analysis[1] of factors associated with nephropathy levels[2] in patients with T2DM all ages

Parameter	Estimate	Standard error	Chi-square test	*P*-value[4]
Age	0.03890	0.01613	5.82	0.0158
Sex (female)	–0.57584	0.17368	10.99	0.0009[5]
BMI	0.12557	0.03464	13.14	0.0003[5]
Q1[3] General risk preference, weather	0.01035	0.00776	1.78	0.1819
Q3 Dissatisfaction to life	0.08581	0.15771	0.30	0.5864
Q6 Sleep enough	–0.44858	0.14285	9.86	0.0017[5]
Q8 Procrastination, if now (2 vs 3&1)	0.32860	0.17183	3.66	0.0558
Q9 Medical uncertainty (unacceptable)	–0.39584	0.18867	4.40	0.0359
Q12 Pay for reducing CVD risk	–0.00002	0.00002	1.92	0.1656
Q13 Risk loving, lottery	0.00008	0.00004	3.54	0.0598
Q13 Risk averse, insurance	–0.00004	0.00002	3.15	0.0758
Q15 Educational level (high)	–0.19004	0.11540	2.71	0.0996
Q16 Job (worked)	–0.38579	0.18095	4.55	0.0330
Q18 Household income/person	–0.00261	0.00140	3.45	0.0631
Q19 Savings (3&4&1 vs 2)	0.42929	0.31374	1.87	0.1712
Q20 Economic status (affluent)	0.37107	0.23395	2.52	0.1127

Notes: [1]Whole model test: degrees of freedom 16, likelihood ratio chi-square test 57.05, *P*-value <0.0001. [2]Levels of nephropathy; stages 1–5. [3]Survey questionnaires are shown in Figure S2. [4]Wald test for effects. [5]$P<0.01$, significant by effect likelihood ratio test.
Abbreviations: BMI, body mass index; T2DM, type 2 diabetes mellitus; CVD, cardiovascular disease.

Table 4 Ordinal logistic regression analysis[1] of factors associated with retinopathy level[2] in patients with T2DM <65 years of age

Parameter	Estimate	Standard error	Chi-square test	*P*-value[4]
Sex (female)	–0.59851	0.24340	6.05	0.0139
Diabetes duration	0.05826	0.02885	4.08	0.0434
Q3[3] Dissatisfaction to life	0.39370	0.21583	3.33	0.0681
Q7 Procrastination, childhood (2 vs 3&1)	0.71680	0.31475	5.19	0.0228
Q8 Procrastination, if now (2 vs 3&1)	0.32618	0.25436	1.64	0.1997
Q10 Medical spending	0.00005	0.00002	6.45	0.0111
Q13 Risk loving, lottery	0.00010	0.00005	3.86	0.0495
Q14 Risk averse, insurance	–0.00006	0.00003	4.16	0.0415
Q15 Educational level (high)	–0.58845	0.16983	12.01	0.0005[5]
Q16 Job (worked)	–0.59446	0.25188	5.57	0.0183
Q19 Savings (3&1–4&2)	0.34967	0.21029	2.76	0.0963
Q20 Economic status (affluent)	0.48419	0.29603	2.68	0.1019

Notes: [1]Whole model test: degrees of freedom 12, likelihood ratio chi-square 48.55, *P*-value <0.0001. [2]Levels of diabetic retinopathy; 0, NDR; 1, SDR; 2, PPDR + PDR + PRP. [3]Survey questionnaires are shown in Figure S2. [4]Wald test for effects. [5]*P*<0.01, significant by effect likelihood ratio test.
Abbreviations: NDR, no diabetic retinopathy; PDR, proliferative diabetic retinopathy; PPDR, preproliferative diabetic retinopathy; PRP, panretinal photocoagulation; SDR, simple diabetic retinopathy; T2DM, type 2 diabetes mellitus.

Table 5 Ordinal logistic regression analysis[1] of factors associated with nephropathy levels[2] in patients with T2DM <65 years of age

Parameter	Estimate	Standard error	Chi-square test	*P*-value[4]
Age	0.08739	0.03009	8.44	0.0037[5]
Sex (female)	–0.76274	0.30759	6.15	0.0131
BMI	0.13791	0.05130	7.23	0.0072[5]
Q1[3] General risk preference, weather	0.01964	0.01290	2.32	0.1278
Q5 Sleeping hours	–0.13897	0.24355	0.33	0.5683
Q6 Sleep enough	–0.56260	0.27186	4.28	0.0385
Q7 Procrastination, childhood (2 vs 3&1)	0.38849	0.27289	2.03	0.1546
Q9 Medical uncertainty (unacceptable)	–0.68812	0.28418	5.86	0.0155
Q13 Risk loving, lottery	0.00011	0.00007	2.40	0.1214
Q14 Risk averse, insurance	–0.00009	0.00007	1.97	0.1608
Q15 Educational level (high)	–0.42920	0.19364	4.91	0.0267
Q17 Income	–0.00113	0.00127	0.80	0.3701
Q18 Household income/person	–0.00556	0.00231	5.81	0.0159

Notes: [1]Whole model test: degrees of freedom 13, likelihood ratio chi-square test 44.33, *P*-value <0.0001. [2]Levels of nephropathy; stages 1–5. [3]Survey questionnaires are shown in Figure S2. [4]Wald test for effects. [5]*P*<0.01, significant by effect likelihood ratio test.
Abbreviations: BMI, body mass index; T2DM, type 2 diabetes mellitus.

Table 6 Ordinal logistic regression analysis[1] of factors associated with retinopathy levels[2] in patients with T2DM ≥65 years

Parameter	Estimate	Standard error	Chi-square test	*P*-value[4]
Age	–0.10114	0.04474	5.11	0.0238
Diabetes duration	0.10235	0.02830	13.08	0.0003[5]
Q1[3] General risk preference, weather	–0.01902	0.01142	2.77	0.0959
Q7 Proclatination, childhood (2&1 vs 3)	0.49517	0.25583	3.75	0.0529
Q8 Procrastination, if now (3&2 vs 1)	0.52443	0.25508	4.23	0.0398
Q9 Medical uncertainty (unacceptable)	0.86806	0.30157	8.29	0.0040[5]
Q12 Pay for reducing CVD risk	0.00001	0.00002	0.20	0.6561
Q13 Risk loving, lottery	0.00027	0.00014	3.51	0.0609
Q16 Job (worked)	–0.78320	0.28168	7.73	0.0054[5]

Notes: [1]Whole model test: degrees of freedom 9, likelihood ratio chi-square 33.4, *P*-value <0.0001. [2]Levels of diabetic retinopathy; 0, NDR; 1, SDR; 2, PPDR + PDR + PRP. [3]Survey questionnaires are shown in Figure S2. [4]Wald test for effects. [5]*P*<0.01, significant by effect likelihood ratio test.
Abbreviations: CVD, cardiovascular disease; NDR, no diabetic retinopathy; PDR, proliferative diabetic retinopathy; PPDR, preproliferative diabetic retinopathy; PRP, panretinal photocoagulation; SDR, simple diabetic retinopathy; T2DM, type 2 diabetes mellitus.

Table 7 Ordinal logistic regression analysis[1] of factors associated with nephropathy levels[2] in patients with T2DM

Parameter	Estimate	Standard error	Chi-square test	*P*-value[4]
Diabetes duration	0.05668	0.01885	9.04	0.0026[5]
Q6[3] Sleep enough	–0.15117	0.16279	0.86	0.3531
Q8 Procrastination, if now (2 vs 1&3)	0.36467	0.22726	2.57	0.1086
Q13 Risk loving, lottery	0.00030	0.00011	6.60	0.0102
Q20 Economic status (affluent)	0.16770	0.22285	0.57	0.4517

Notes: [1]Whole model test: degrees of freedom 5, likelihood ratio chi-square 16.77, *P*-value <0.0050. [2]Levels of nephropathy; stages 1–5. [3]Survey questionnaires are shown in Figure S2. [4]Wald test for effects. [5]*P*<0.01, significant by effect likelihood ratio test.
Abbreviation: T2DM, type 2 diabetes mellitus.

Discussion

In this study, we demonstrated the impact of educational attainment of the progress of retinopathy in patients with difficult-to-control T2DM. In the participants <65 years of age, educational attainment was the only factor significantly associated with the progression of retinopathy. An educational attainment of high school or lower appeared to be a strong risk factor for this complication. Above high school level, there was no difference between vocational college, junior/technical college, and university/graduate school in the association with retinopathy level. This result suggests that the association between educational attainment and diabetic complications may have a threshold point between gaining a high school diploma and education above high school level.

The reason why highly educated persons are healthier can be attributed to higher income and higher cognitive ability, as well as other factors including time and risk preferences, and self-control.[25] In general, educational and income levels are closely related. Individuals of lower SES have limited income, poorer occupational opportunity, and reduced access to health care services and information. The patients with the lowest household income have been shown to have the highest prevalence of retinopathy and neuropathy.[15] However, in the present study, we did not find a significant association between income level and retinopathy level. In Japan, it has been suggested that low income may not necessarily be associated with worse health outcome given the universally available and egalitarian Japanese health care system.[16] These results suggest that the impact of educational attainment on

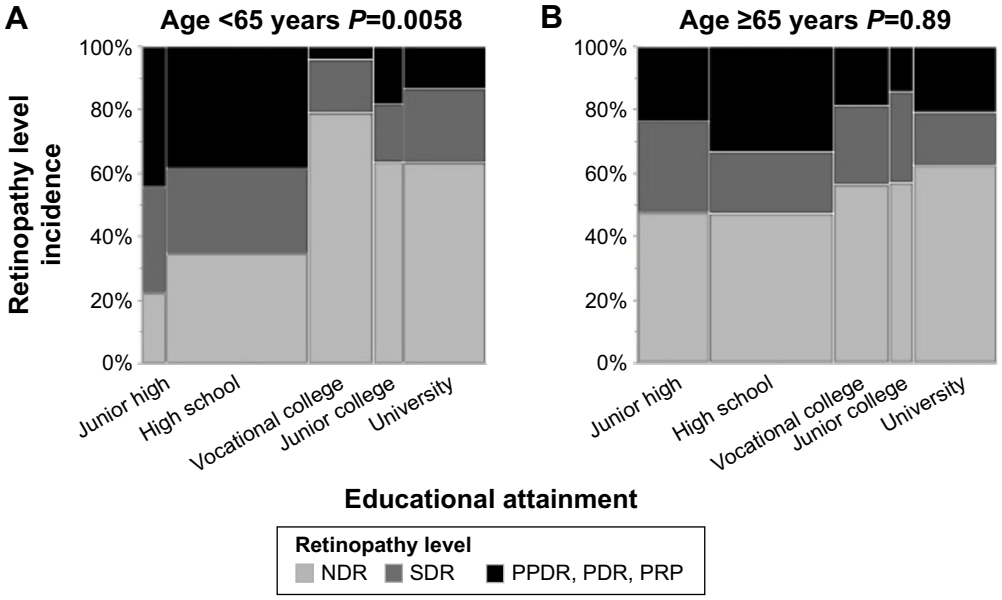

Figure 1 Association between retinopathy level and educational level attainment in participants with T2DM.
Notes: (**A**) <65 years of age; (**B**) ≥65 years of age, educational attainment (total educational years): junior high school (9 years); high school (12 years); vocational college (13–15 years); junior college including technical college (14–15 years); university including graduate school (≥16 years). Retinopathy levels; NDR, SDR, PPDR, PDR, and PRP. Pearson's χ^2 test: <65 years of age: *n*=126, χ^2 21.58, *P*=0.0058; ≥65 years of age: *n*=104, χ^2 3.58, *P*=0.89.
Abbreviations: NDR, no diabetic retinopathy; PPDR, preproliferative diabetic retinopathy; PDR, proliferative diabetic retinopathy; PRP, panretinal photocoagulation; SDR, simple diabetic retinopathy; T2DM, type 2 diabetes mellitus.

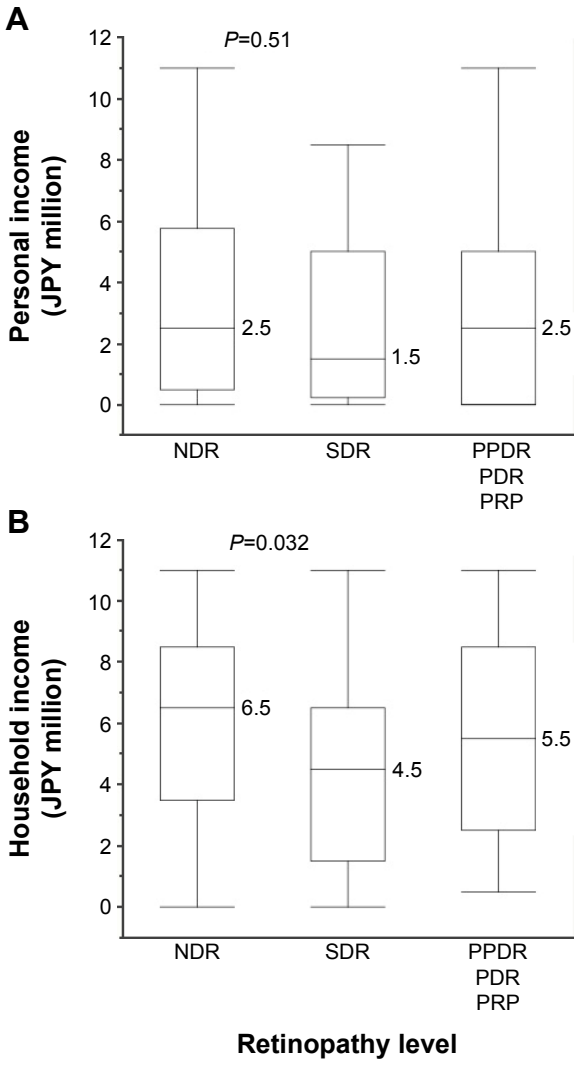

Figure 2 Comparison of (**A**) personal and (**B**) household income by retinopathy level for participants with T2DM <65 years of age.
Notes: Retinopathy levels: NDR, SDR, PPDR, PDR, and PRP. Kruskal–Wallis rank sum test: personal income: χ^2 1.33, *P*=0.51; household income: χ^2 6.87, *P*=0.032.
Abbreviations: JPY, Japanese Yen (JPY 1 million = USD 10,000); NDR, no diabetic retinopathy; PDR, proliferative diabetic retinopathy; PPDR, preproliferative diabetic retinopathy; PRP, panretinal photocoagulation; SDR, simple diabetic retinopathy; T2DM, type 2 diabetes mellitus.

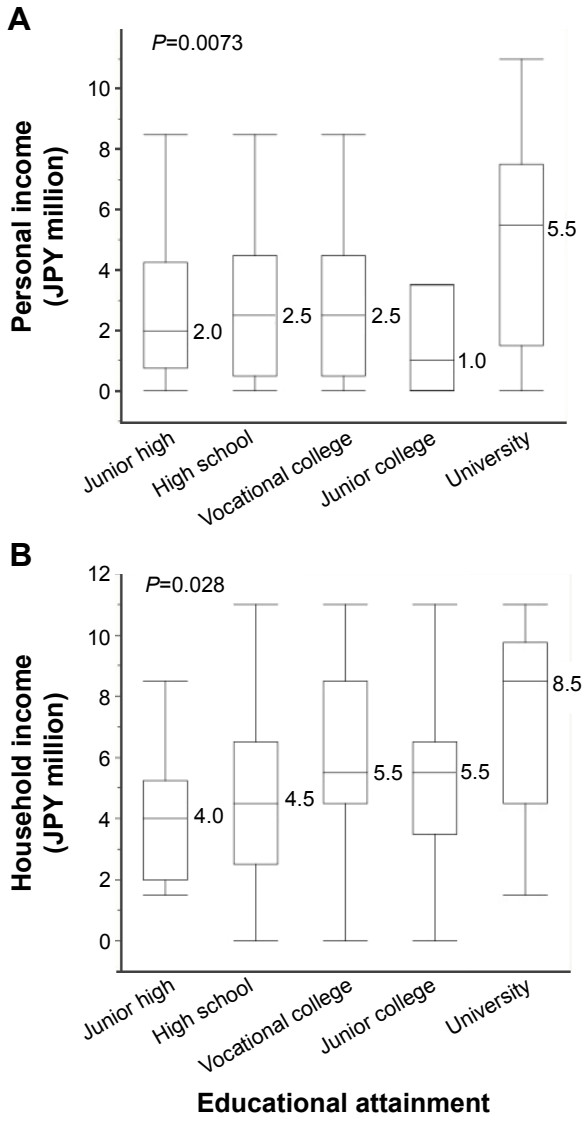

Figure 3 Comparison of (**A**) personal and (**B**) household income by educational attainment for participants with T2DM <65 years of age.
Notes: Educational attainment (total educational years): junior high school (9 years); high school (12 years); vocational college (13–15 years); Junior college including technical college (14–15 years); university including graduate school (≥16 years), Kruskal–Wallis rank sum test: personal income: χ^2 14.01, *P*=0.0073; household income: χ^2 10.87, *P*=0.028.
Abbreviations: JPY, Japanese Yen (JPY 1 million = USD 10,000); T2DM, type 2 diabetes mellitus.

the progression of retinopathy is independent of personal income level.

It has been reported that lower cognitive function during late adolescence is independently associated with an elevated risk for impaired fasting glucose and diabetes.[26,27] We demonstrated in our previous report that patients with T2DM tended to have a preference for risk-seeking compared to those with T1DM. Risk-seeking is weakly associated with nephropathy in older patients (Table 7, Q13 lottery *P*=0.0102) in the present study, but this result may be due to lower quantitative literacy proficiency, as discussed in the previous report. We also suggested that lower quantitative literacy proficiency among patients with T2DM may not be a result of high glucose levels, but could be a reflection of the essential pathophysiology of T2DM, such as insulin resistance.[8] In this context, brain insulin resistance seems the most plausible explanation of the association between cognitive function and T2DM.[28–30] Further studies will be necessary to test this hypothesis.

Nephropathy stage was significantly associated with only age and BMI in the participants <65 years of age. Although sex, sleep, unwillingness to accept medical uncertainty,

educational attainment, and household income were weakly associated with nephropathy level ($P<0.05$), SES and behavioral propensity may not be essential factors for the progression of nephropathy. The reason why the effects of educational attainment on the progress of retinopathy and nephropathy were not the same is unknown. Factors other than hyperglycemia, including blood pressure, lipid level, atherosclerosis, and especially the use of renin angiotensin system inhibitors and HMG-CoA reductase inhibitors, may have affected the progress of nephropathy strongly enough to reduce the impact of educational level.[31]

In older participants, there was no prominent effect of SES on the progress of retinopathy and nephropathy. These results are compatible with general morbidity and mortality in older people.[20–24] This is probably because there are social security and health care systems focused on older patients in many developed countries. As a result, the duration of diabetes has the strongest effect on the progress of retinopathy and nephropathy in older patients. Even in this situation, acceptance of medical uncertainty (Q9 in Figure S2) and job status were significantly associated with retinopathy in the older participants in the present study. Older participants who worked during the previous month were less likely to have higher levels of retinopathy, probably because they were independent and active and may have had higher cognitive function. Conversely, the older participants who were less accepting of medical uncertainty (Q9 in Figure S2) were more likely to have higher levels of retinopathy. This result was reversed in participants <65 years of age, although the significance was weak ($P<0.05$). The reason for these contradictory results is not clear. One possible explanation is that being less willing to accept medical uncertainty may be a result of self-confidence in middle-aged and young participants, whereas in older participants it may simply result in reduced access to health care services.

Limitations of this study include self-reporting and a limited number of cases, especially of patients with difficult-to-control T2DM, in one locality in Japan. The median of self-reported household income in this study was 4.5 million yen, which was compatible with 4.32 million yen reported by Japanese Ministry of Health, Labor and Welfare in 2013. The proportions of participants with a high school diploma or lower (51.7%) and with qualifications above high school (48.3%) did not differ significantly from those in the report of the national census in 2010 (65.3% and 34.7%, respectively). These data support the reliability of the self-reported data in the present study. The survey was performed in a locality of Japan with a limited number of patients. This study is not strictly random sampling. However, characteristics of patients were consistent with the report of Japan Diabetes Complication Study which is a multicenter prospective study by universities and general hospitals in Japan.[32] Therefore, the patients in the present study could be considered as representative of the patients with difficult-to-control T2DM in a local area in Japan. In many countries, educational level and economic status are closely related, and it is impossible to examine their effect on diabetic complications independently. The present study demonstrated that the impact of educational attainment on diabetic retinopathy was independent of personal economic status. Two important factors may partially explain this finding: the egalitarian health care system in Japan and the diabetes specialist referral system for patients with difficult-to-control T2DM established in a locality with a relatively large population (of 700,000 people). The essence of the findings of this study could be applied to patients with T2DM worldwide.

In conclusion, this study demonstrated that lower educational attainment, especially attaining only a high school diploma or lower, is a strong risk factor for diabetic retinopathy in patients with T2DM <65 years of age. Some other behavioral propensities were also found to be associated with the progress of diabetic complications, but not to as great an extent as educational attainment. We also demonstrated that the association between diabetic retinopathy and educational attainment level was independent of personal economic status. These results suggest that cognitive function may play an important role in the progression of diabetic retinopathy in patients with T2DM.

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Disclosure

The authors report no conflicts of interest in this work.

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Supplementary materials

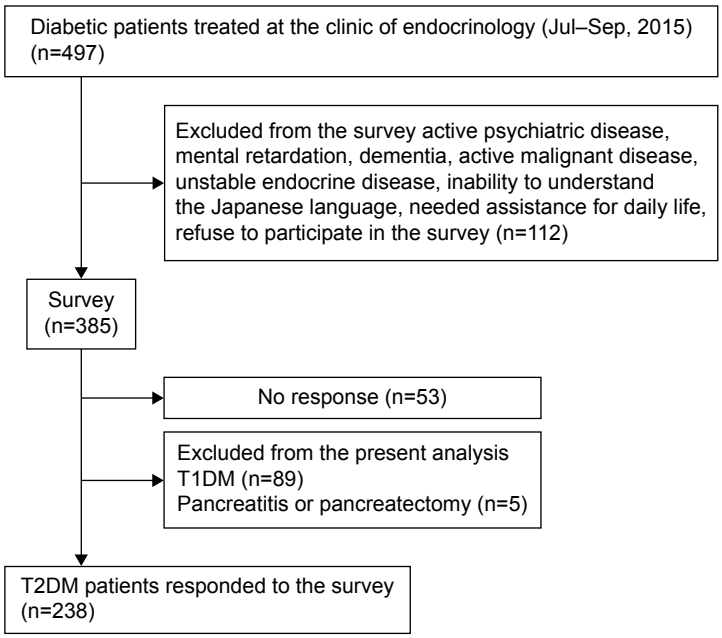

Figure S1 Study flow diagram.
Abbreviations: T1DM, type 1 diabetes mellitus; T2DM, type 2 diabetes mellitus.

	Construct	Text
Q1	General risk preference, weather	Suppose it is not raining when you go out. At what percentage of probability of rain would you take your umbrella or some other measure for rain? Please circle the closest to your answer from the following choices. 0%, 10%, 20%, 30%, 40%, 50%, 60%, 70%, 80%, 90%, 100%
Q2	General risk averse, travel	When you have a seat reservation for a train, how many minutes early do you usually arrive at the station? Please circle the closest to your answer from the following choices. 3 min, 5 min, 7 min, 10 min, 15 min, 20 min, 25 min, 30 min, 35 min, 40 min, 45 min, 50 min, 60 min or more
Q3	Dissatisfaction to current life	Are you satisfied with your current life? Please circle the closest to your answer from the following choices. 1. Satisfied 2. Somewhat satisfied 3. Cannot say either way 4. Somewhat dissatisfied 5. Not satisfied at all
Q4	Time to spare	Are you so busy as to feel rushed? Please circle the closest to your answer from the following choices. 1. Feel very rushed 2. Feel somewhat rushed 3. Cannot say either way 4. Somewhat have time to spare 5. Have plenty of time to spare
Q5	Sleeping hours	How many hours do you sleep per day on average? About_____ hours
Q6	Sleep enough	Do you get enough sleep? Please circle the closest to your answer from the following choices. 1. Never enough 2. Not quite enough 3. Cannot say either way 4. Nearly enough 5. More than enough
Q7	Procrastination, childhood	Thinking about when you were a child and you were given an assignment during school vacation, how early did you usually finish up the assignment? 1. I tended to get it done early, before the due date. 2. I worked on it daily, up until the due date. 3. I tended to get it done toward the end.
Q8	Procrastination, if now	Thinking about yourself now, if you were given an assignment during school vacation, how early would you finish up the assignment? 1. I would get it done rather early, before the due date. 2. I would work on it daily, up until the due date. 3. I would get it done rather toward the end.

Figure S2 (*Continued*)

	Construct	Text
Q9	Acceptance to medical uncertainty	A doctor tells you that the effectiveness of the medicine they are prescribing can vary among individuals, and that it may or may not end up working for your ailment. Would this explanation be sufficient for you? 1. Yes 2. Probably 3. Not sure 4. Probably not 5. No
Q10	Average spending on medical care	On average, how much do you spend on medical treatments every month? Monthly average: Yen
Q11	Subjective risk estimation for cardiovascular disease	Out of 100 people including yourself, how many of them do you think will have a heart attack or stroke within 10 years that makes you think you will also have a heart attack or stroke? people out of 100
Q12	Willingness to pay for a medicine reducing disease risk	Out of 100 people including yourself, say that 50 of them will have a heart attack or stroke within 10 years. A certain kind of medicine can reduce that number to 25. How much would you pay every month to continue taking that medicine? I would pay up to yen every month just for that medicine
Q13	Risk loving, lottery	Suppose that there is a speed lottery with a 1% chance of winning JPY 100,000. If you win, you get the prize right away. If you lose get nothing. How much would you spend to buy a ticket for this lottery. Choose "Buy" or "Do not buy" for each price of the ticket. Lottery price JPY 10 1. Buy 2. Do not buy JPY 100 1. Buy 2. Do not buy JPY 300 1. Buy 2. Do not buy JPY 500 1. Buy 2. Do not buy JPY 1,000 1. Buy 2. Do not buy JPY 2,000 1. Buy 2. Do not buy JPY 3,000 1. Buy 2. Do not buy JPY 5,000 1. Buy 2. Do not buy JPY 10,000 1. Buy 2. Do not buy JPY 50,000 1. Buy 2. Do not buy
Q14	Risk averse, insurance	Assume that you know there is a 1% chance of losing JPY 100,000 on a given day. You can take out insurance to cover this amount in case of loss. If an insurance policy is sold as listed below, would you purchase it? Choose "purchase" or "do not purchase" for each of the insurance price. Insurance price JPY 10 1. Purchase 2. Do not purchase JPY 100 1. Purchase 2. Do not purchase JPY 300 1. Purchase 2. Do not purchase JPY 500 1. Purchase 2. Do not purchase JPY 1,000 1. Purchase 2. Do not purchase JPY 2,000 1. Purchase 2. Do not purchase JPY 3,000 1. Purchase 2. Do not purchase JPY 5,000 1. Purchase 2. Do not purchase JPY 10,000 1. Purchase 2. Do not purchase JPY 50,000 1. Purchase 2. Do not purchase
Q15	Educational attainment (total educational years)	Please circle your highest academic qualification from the following choices. 1. Junior high school (9 years) 2. high school (12 years) 3. Vocational college (13–15 years) 4. Junior college/technical college (14–15 years) 5. University (16 years) 6. Graduate school (18 years or more)
Q16	Job status	Please tell us about your work. Please choose A if you have worked to earn an income during the last 1 month, or B if you did not work at all, then circle the choice that applies to you. 1. Worked 2. Did not work
Q17	Personal income	How much is your total annual income? Please circle the closest to your answer from the following choices. * Income includes your earnings from work; rental income from your properties, such as houses or land; stock dividends, etc. * You don't need to consider tax you have paid or pension you have received. a. None b. Less than JPY one million c. JPY 1 million to 1.99 million d. JPY 2 million to 2.99 million e. JPY 3 million to 3.99 million f. JPY 4 million to 4.99 million g. JPY 5 million to 5.99 million h. JPY 6 million to 7.99 million i. JPY 8 million to 9.99 million j. JPY More than 10 million

Figure S2 (*Continued*)

	Construct	Text
Q18	Household income	How much is the total annual income of your household? Please circle the closest to your answer from the following choices. a. None b. Less than JPY one million yen c. JPY 1 million to 1.99 million d. JPY 2 million to 2.99 million e. JPY 3 million to 3.99 million f. JPY 4 million to 4.99 million g. JPY 5 million to 5.99 million h. JPY 6 million to 7.99 million i. JPY 8 million to 9.99 million j. JPY More than 10 million
Q19	Savings	Do you currently have savings? If you do, have they increased or decreased during the last one year? Please circle the closest to your answer from the following choices. 1. I do not have any savings. 2. My savings have increased. 3. My savings have not changed. 4. My savings have decreased.
Q20	Economic status	How do you feel about your current economic situation in your life as a whole? Please circle the closest to your answer from the following choices. 1. Very hard 2. Somewhat hard 3. Normal 4. Somewhat affluent 5. Very affluent

Figure S2 Survey questionnaires.

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