

Title: Diabetes and Suicide: A Nationwide Longitudinal Cohort Study among the Japanese Working-age Population

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ABSTRACT

Background

Although the mental health burden of diabetes has received substantial attention, there is limited evidence on whether the risk of suicide—a severe consequence of mental health problems—increases among individuals with diabetes. Therefore, this study investigated the association between diabetes and suicide in Japan.

Methods

This nationwide longitudinal cohort study included adults aged 18–74 years, who were enrolled in the Japan Health Insurance Association's health insurance program between 2015 and 2022. Individuals newly diagnosed with diabetes were matched in a 1:1 ratio with those without diabetes, based on age and sex. We employed multivariable Cox proportional hazard models to estimate the hazard ratios for suicide in relation to the diagnosis of diabetes, adjusting for potential confounders, such as sociodemographic characteristics, history of psychiatric disorders, physical measurements, health behaviors, and laboratory data.

Results

Among 4,210,272 individuals in the matched-pair cohort, we observed 337 deaths by suicide among those with diabetes and 250 deaths by suicide among those without diabetes. After conditioning on potential confounders, diabetes diagnosis was linked to an increased risk of suicide (HR [95% CI] = 1.25 [1.06 to 1.47]). The association tended to be larger among those aged younger than 40 years and among women (among those aged 18–39 years, HR = 1.69 [95%CI, 1.05–2.73]; among women, HR = 1.56 [95%CI, 0.92–2.64]).

Conclusion

Diabetes diagnosis may increase suicide risk among the working-age population, even after conditioning on potential confounders. Our findings underscore the importance of psychosocial support following a diagnosis.

SUMMARY

What is already known on this topic

- Although the mental health burden of diabetes has received substantial attention in the last three decades, there is limited evidence on whether and to what extent the risk of suicide—a severe consequence of mental health problems—increases among individuals with diabetes, especially after diagnosis.
- Moreover, there is limited evidence regarding whether the association between diabetes and death by suicide differs by demographic characteristics, which may help decision-makers develop effective suicide prevention strategies in diabetes management.

What this study adds

- Among a total of 4,210,272 matched individuals, we found an association between diabetes and an increased risk of death by suicide (adjusted hazard ratio [95% CI] = 1.47 [1.08 to 1.99]) after adjusting for sociodemographic characteristics, history of psychiatric disorders, health behaviors, and laboratory data.
- The association tended to be stronger among those aged < 40 years and among women, although the difference was not statistically significant.

How this study might affect research, practice or policy

- These results highlight the necessity of regular psychosocial assessment and treatment for individuals with diabetes, which boosts the current guideline recommendations.

INTRODUCTION

Diabetes affected 537 million adults worldwide in 2021 and was responsible for 6.7 million deaths; it is projected to affect 643 million by 2023 [1]. In addition to the traditional complications of diabetes (e.g., coronary heart disease, stroke, peripheral arterial disease, diabetic kidney disease, retinopathy, and peripheral neuropathy) [2], the mental health burden of diabetes has received substantial attention over the last three decades [3], potentially through multiple pathways including biological mechanisms (e.g., impaired glucose metabolism [4]) and psychosocial mechanisms (e.g., stigma after the diagnosis of diabetes [5]). Among diabetes-related mental health issues, suicide is an emerging concern. A meta-analysis showed that diabetes is associated with an increased risk of suicide, with a pooled risk ratio of 1.56 [6]. Furthermore, a recent cohort study using a Swedish nationwide cohort showed that diabetes is associated with suicide, and this association was not explained by pre-existing psychiatric disorders [7].

Despite the critical role of suicidality in diabetes management, it has been less investigated than other mental health issues such as depression [8]. Recent studies have not completely addressed residual confounding and have overlooked a broad spectrum of potential confounders, including sociodemographic, psychiatric, behavioral factors, and objective metrics like blood glucose, blood pressure, and body mass index. Given the substantial influence of these factors on diabetes and mental health outcomes [9], it is imperative to incorporate a thorough set of potential confounders to assess the extent to which diabetes affects suicide risk among the population.

Moreover, there is limited evidence regarding whether the association between diabetes and death by suicide differs by demographic characteristics, which may help decision-makers develop effective suicide prevention strategies in diabetes management. Younger generations

with diabetes, such as those aged 40 years or younger, are potentially vulnerable populations against psychosocial issues in part because of conflict with education, employment, and family life, compared with those with later-onset type 2 diabetes [10–15], indicating the urgent need to promote the research revealing the age-specific risks. In Japan, for example, psychiatric disorders are a leading cause of the allowance for injuries and diseases today, with a steady increase over the past decade [16]. Women with diabetes are more likely than men to experience diabetes-related distress and depression [12,17,18]. Given that these psychological challenges may be associated with an elevated risk of suicide [19,20], it is not surprising that the association between diabetes diagnosis and death by suicide varies with age and sex. However, limited research has explicitly assessed the heterogeneous associations by age and sex.

Therefore, we investigated the relationship between newly diagnosed diabetes and subsequent death by suicide in a working-age population, using a large nationwide database from the Japan Health Insurance Association (JHIA). In addition, we explored potential heterogeneous associations according to age and sex. We hypothesized that newly diagnosed diabetes is associated with increased suicide risk, even after adjusting on covariates, and that this suicide risk is prominent, particularly among younger adults and women.

METHODS

Study Design, Setting, and Population

We conducted a population-based matched-pair cohort study using data from JHIA, which is the largest health insurance organization in Japan that provides insurance for employees of small- and medium-sized companies, covering over 30 million working-age individuals and their families. We used data from April 1, 2015, to March 31, 2022, linked with monthly medical claims data from all medical institutions and pharmacies. Additionally, we linked the

data with annual health check-up information conducted by the health insurance organization for insured individuals between the ages of 35 and 74 years. The annual health check-up included health behavior questionnaires, physical examinations, and laboratory data. The participation rate in health check-ups among JHIA-insured individuals was 45.6–55.9% during the study period [21].

The eligibility criteria included individuals 1) aged 18 years or older, 2) having membership of the insurance for at least one year, 3) insured by themselves, i.e., workers who pay for health insurance independently, and 4) without a history of diabetes. Individuals without a history of diabetes were defined as those without a diabetes-related diagnosis for at least one year. We excluded individuals 1) aged <18 years, 2) insured by others, and 3) with preexisting diabetes. Furthermore, we excluded individuals from our analyzed samples if they had missing values for any of the variables used in each analysis.

This study focused on suicide risk related to newly diagnosed diabetes. To differentiate individuals with pre-existing diabetes and those with newly diagnosed diabetes, we implemented a run-in period (or wash-out period) of one year. Consequently, we restricted the analyzed participants to individuals who had insurance membership for at least one year.

During the study period, all newly diagnosed individuals with diabetes were matched by sex and age in a 1:1 ratio with individuals without diabetes. We followed each individual until the earliest of the following events: death, withdrawal from insurance, or the end of the study period (March 31, 2022). Newly diagnosed individuals with diabetes were eligible for inclusion in the exposed population even if they were selected as controls (details are described in **Supplementary Fig. 1**). This study was approved by the Institutional Review Board of Kyoto University (approval number: 022-00100).

Measurement of Variables

The study exposure was newly diagnosed diabetes, based on the International Statistical Classification of Diseases and Related Health Problems, 10th Revision (ICD-10; E10–E14). We identified exposed individuals as those who had a diabetes diagnosis but had not been diagnosed for at least one year. In the sensitivity analysis, we redefined exposed individuals as those with a diagnosis of diabetes based on ICD-10 codes and prescriptions for antihyperglycemic medications (**Supplementary Table 1**) in the same month [22].

The primary outcome was death by suicide. We determined the cause of death based on death records stored in the JHIA database. When a JHIA member died, their family or relatives reported the cause of death based on the death certificate. We classified the causes of death according to the ICD-10, and classified X60-X84 as death by suicide. We excluded deaths due to events of undetermined intent (ICD-10: Y10-Y34) as outcomes. We also used the diagnostic codes assigned by the hospital to minimize misclassifications.

We included demographic characteristics (sex and age), socioeconomic status (annual income and area-level deprivation index [23]), health behaviors (frequency of smoking and alcohol consumption, exercise habits, and sleep-related problems), and history of psychiatric disorders (depressive disorders, schizophrenia spectrum disorders, substance use disorders, and any other type of psychiatric disorder) based on ICD-10 codes. In this study, we focused on the entire relationship between newly diagnosed diabetes and suicide. Therefore, we adjusted for pre-existing psychiatric disorders to avoid overadjustment from controlling for potential mediators, including psychiatric disorders that develop after a diabetes diagnosis.. Detailed definitions and coding are provided in **Supplementary Table 2**, and the covariate collection windows are shown in **Supplementary Fig. 2**.

Statistical Analysis

Descriptive information regarding baseline characteristics was summarized as percentages (dichotomous variables) or means and standard deviations (SD; continuous variables). Incidence rates (IRs) and 95% confidence intervals (CIs) were calculated per 1,000,000 person-years. We applied the Kaplan–Meier estimator to estimate the cumulative incidence and 95% CI of death by suicide for individuals diagnosed with diabetes and those without diabetes. We also applied the log-rank test to assess the difference in the cumulative incidence between individuals with diabetes and individuals without diabetes.

We then estimated the hazard ratios (HRs) and 95% CIs using the Cox proportional hazards model. We fitted three models: a crude model, a model including major potential confounders (age, sex, history of psychiatric disorders, and socioeconomic status), and a full model (including lifestyle factors and laboratory data). Proportional hazard assumptions were checked using Schoenfeld residuals, which are the difference between the observed covariate values for an individual who experiences an event (i.e., suicide in our study) and the expected values of the covariate based on the model [24] (**Supplementary Fig. 3**). We also estimated the potential impacts in number in the society, calculating the population-attributable fraction (PAF) using the estimated HR and the prevalence of diabetes in this population. We conducted all analyses on those with no missing values, i.e., we conducted complete-case analysis. We applied an inverse probability weighting (IPW) approach to adjust for potential selection bias resulting from our listwise deletion in model 3.

Finally, using the same samples in Model 2, we assessed potential effect modifications by sex (men and women) and age (young: aged 18–39; middle-young: aged 40–49; middle-old: aged 50–59; and old: aged 60 or older). After estimating the HRs within each subgroup using

the Cox proportional hazard model, effect modifications of HRs were assessed on both additive (relative excess risk due to interaction; RERI) and multiplicative scales (HRs) with a 95% CI, using the Cox proportional hazard model with a product term.

To assess the robustness of our findings, we reanalyzed the data, defining exposed individuals as those with diabetes based on both ICD-10 codes and prescriptions of antihyperglycemic medications in the same month. All statistical analyses and data management were conducted using R Statistical Software (v4.3.0; R Core Team [25]).

RESULTS

Of 5,082,623 JHIA members diagnosed with diabetes, 2,105,136 were eligible for the exposed group (mean age 52.0 [SD, 11.9]; 67% men), and all of them were matched with controls in a 1:1 ratio (**Fig. 1**). Individuals with diabetes were more likely to have a history of psychiatric disorders, higher body mass index (BMI) and blood pressure, and less physical activity (**Table 1**). Among individuals with diabetes, less than 1% were diagnosed with type 1 diabetes (initial diagnosis: 0.33%, diagnosis throughout the study period: 0.56; **Supplementary Table 3**).

Risk of suicide after the diagnosis of diabetes

During the 9.49 million person-years (mean [SD]: 2.3 [1.7] years), there were 337 deaths by suicide among those with diabetes (IR=7.13/100,000 person-years [95%CI, 6.37-7.89]), and 250 deaths by suicide among those without diabetes (IR=5.24/100,000 person-years [95% CI, 4.59 to 5.89]). Among individuals with diabetes, those who died by suicide were more likely to be male, smokers, and have a history of psychiatric disorders (**Supplementary Table 4**). A similar pattern was observed in the individuals without diabetes.

The cumulative incidence curves for death by suicide demonstrated a higher cumulative incidence among individuals with diabetes than those without diabetes (log-rank test: $p < 0.01$; **Fig. 2**). Schoenfeld's residuals did not demonstrate any violation of the proportional hazard models (**Supplementary Fig. 3**).

The Cox proportional hazard regression models showed that newly diagnosed diabetes was associated with the increased risk of death by suicide after adjusting for history of psychiatric disorders and SES (HR=1.25 [95%CI, 1.06-1.47]; **Fig 3**). The association was also observed after additionally adjusting for lifestyles and laboratory data (HR=1.47 [95% CI, 1.08-1.99]; Model 3) and after applying the IPW approach (HR=1.49 [95% CI, 1.09-2.05]; Model 4) (**Supplementary Fig 4**). We estimated the PAF in this population to be 2.28%, with a diabetes prevalence of 9.32%, as of April 1, 2016.

In the subgroup analyses, we found the larger HRs among individuals aged less than 40 years than older individuals, and among men than women (**Fig 4**). However, we found no evidence of effect modification on both multiplicative and additive scale (**Supplementary Table 5**).

Sensitivity Analysis

On redefining newly diagnosed diabetes based on both diagnosis of diabetes and prescription of antihyperglycemic medications in the same month, 696,844 individuals were eligible for the exposed group. In this sensitivity analysis, we found that newly diagnosed diabetes was associated with death by suicide after adjusting for age, history of psychiatric disorders, and SES (HR=1.45 [95%CI, 1.10-1.93]: **Supplementary Table 6**; PAF = 1.79%).

DISCUSSION

In this nationwide cohort study in Japan, we found an association between newly diagnosed diabetes and death by suicide soon after the initial diagnosis and throughout the subsequent years. The association remained after adjusting for individual-level and area-level characteristics.

The results of our study are consistent with those of other reports on the association between diabetes and suicide risk, including nationwide population-based cohort studies [6,7]. Studies from Sweden and Denmark, utilizing nationwide registries, found an elevated suicide risk among people with diabetes [7,26–28]. The risk of suicide was particularly pronounced in patients with coexisting psychiatric disorders or severe mental illnesses [7,28]. However, these studies suffered from limited sample sizes; residual confounding factors including history of psychiatric disorders, health behaviors, and laboratory data; and concerns regarding statistical modeling, including controlling for mediator variables rather than confounders. In this context, our study included over 4 million individuals and established a clear temporality between diabetes and psychiatric disorders, along with a comprehensive set of covariates (i.e., sociodemographic characteristics, history of psychiatric disorders, physical measurements, health behaviors, and laboratory data), thus advancing the current state of knowledge regarding suicide risk in individuals with diabetes.

Our subgroup analysis showed that suicide risk tended to be higher among those aged less than 40 years, although heterogeneity was not statistically significant. This finding aligns with that of a Swedish cohort study that showed a high suicide risk among those aged < 40 years [26]. Moreover, a study focusing on patients aged > 65 years found no such associations [29]. Additionally, early onset adult type 2 diabetes is linked to increased psychological and psychiatric burdens [10–14], which might explain the observed association between diabetes diagnosis and death by suicide among those aged < 40 years, as supported by the ideation-to-

action theory [19,20]. The higher suicide risk among women is also consistent with studies that demonstrated a higher prevalence of diabetes distress and depression among women with diabetes than among men [12,17,18]. However, the evidence for heterogeneous suicide risk by sex is mixed. One study reported a higher hazard risk among women compared with men [7], whereas, other studies did not [26–28].

Although the underlying mechanisms have not been formally investigated, certain psychological and social factors have been linked to diabetes diagnosis and death by suicide. Diabetes is associated with an increased risk of subsequent depressive disorders [4], which can increase suicide risk, as depression itself increases suicidal tendencies [30]. Individuals with diabetes face emotional distress due to daily diabetes management (diabetes distress) [31]. Additionally, they encounter diabetes stigma, which includes experienced, perceived, or anticipated negative social judgment, stereotypes, prejudice, and discrimination as well as self-blame or shame [32]. These psychosocial burdens can increase the likelihood of suicidal ideation [19,20,31,33]. In Japan, along with other countries [32], diabetes stigma is an emerging issue [34]. The DAWN2 study, a multinational study that included Japan, found that 19.2% of individuals with diabetes experienced discrimination due to their condition [35]. An Internet-based survey in Japan also showed that 32.9% experienced diabetes-related shame and 17.5% concealed their disease from colleagues or friends [36]. Both direct and indirect financial burdens related to diabetes management, such as medication, hospitalization, absenteeism from work, and reduced productivity [37], can elevate suicide risk, as financial difficulties (e.g., low income and unemployment) increase suicide risk [38]. Although Japan has a healthcare system that can minimize direct medical costs, certain antihyperglycemic, such as glucagon-like peptide-1 (GLP-1) receptor agonists, remain expensive today. The annual medical cost of GLP-1 receptor agonists was estimated at 968,000 yen, which was more than twice as high as that of biguanide, leading to a significant direct financial burden [39].

Additionally, health-related issues are a leading cause of job loss in Japan [40], suggesting the social security system in Japan may offer limited job security for individuals with diseases and injuries, including diabetes. It leads to increased indirect financial burdens, such as conflict with employment and self-imposed work restrictions, among individuals with diabetes. Easy access to antihyperglycemic medications like insulin might heighten the risk, as these can be used in suicide attempts [26,41,42]; easy access to potentially lethal means may increase the risk of death by suicide, as suggested by studies that demonstrated the association between limited access to lethal means (e.g., firearms and pesticides) and decreased suicide risks [43,44].

This study had some limitations. First, our findings suffer from exposure and outcome misclassification, given that the sensitivity and specificity of the ICD-10 codes for diabetes were 88–90% and 92–96% in Japan, respectively [22,45]. However, we found consistent results even after redefining the diabetes diagnosis using not only ICD-10 codes but also prescriptions of antihyperglycemic medications. Moreover, our definition of death by suicide based on self-reports may have been misclassified or underreported, as in other studies. Future studies using more accurate information on the causes of death, such as death certificates, are warranted. Second, there was a potential for residual confounding affecting our findings to some degree. Third, the limited sample size for subgroup analyses made it difficult to assess the heterogeneity among the populations. Specifically, we were not able to explore the suicide risk among individuals with type 1 diabetes, a potentially vulnerable population at risk for suicide. Fourth, the generalizability and transportability of this study are limited because we used a database of the working-age population in Japan. Fifth, this study did not investigate a path-specific association, particularly the pathway mediated by psychiatric disorders, such as depressive disorders and anxiety disorders, after the diagnosis of diabetes. Future studies should consider the bidirectional relationship between diabetes and psychiatric disorders [46] and explore the role of psychiatric disorders after a diabetes diagnosis in the context of suicide.

Lastly, the follow-up period in this study was limited because the JHIA data has been available only since 2015. As a result, this study did not provide insight into the long-term association between diabetes diagnosis and suicide.

CONCLUSION

Over 6 years, this study found an association between newly diagnosed diabetes and increased risk of death by suicide after adjusting for sociodemographic characteristics, history of psychiatric disorders, health behaviors, and laboratory data. Our results highlight the necessity of regular psychosocial assessment and treatment for individuals with diabetes beginning in the early days following the diagnosis, which boosts the current guideline recommendations. The integration of suicidality assessments and subsequent treatments into the psychosocial care of newly diagnosed diabetes patients has the potential to prevent avoidable death by suicide.

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COMPETING INTERESTS

All authors have completed the ICMJE uniform disclosure format (available on request from the corresponding author) and declarations.

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DATA SHARING STATEMENTS

The data that support the findings of this study are available from the Japan Health Insurance Association; however, we used these under license for the current study, and so the data are not

publicly available.

AUTHORS' CONTRIBUTIONS

Dr. Komura and Dr. Inoue had full access to all of the data in the study and took responsibility for the integrity of the data and the accuracy of the data analysis.

Concept and design: Komura, Inoue, Kondo.

Acquisition, analysis, or interpretation of data: Komura, Inoue, Ishimura, Kondo.

Drafting of the manuscript: Komura, Inoue, Kondo.

Critical revision of the manuscript for important intellectual content: Komura, Inoue, Ishimura, Taura, Harada, Inagaki, Kondo.

Statistical analysis: Komura, Inoue, Ishimura.

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Table 1 Baseline characteristics of the matched-pair cohort.

Characteristic	no. missing	Overall population N = 4,210,272	With diabetes N = 2,105,136	Without diabetes N = 2,105,136
Age, mean (SD)	0	52.0 (11.9)	52.0 (11.9)	52.0 (11.9)
Sex, n (%)	0			
Women		1,394,596 (33.1)	697,298 (33.1)	697,298 (33.1)
Men		2,815,676 (66.9)	1,407,838 (66.9)	1,407,838 (66.9)
Annual income, 1000,000 Japanese yen, mean (SD)	2,770	3.88 (3.61)	3.92 (3.80)	3.83 (3.41)
Standardized area-level deprivation index, mean (SD)	4,916	0.54 (0.28)	0.54 (0.28)	0.53 (0.28)
Histories of psychiatric disorders	0			
Depressive disorders, n (%)		138,079 (3.3)	85,634 (4.1)	52,445 (2.5)
Schizophrenia spectrum disorders, n (%)		33,044 (0.8)	21,774 (1.0)	11,270 (0.5)
Substance use disorders, n (%)		24,122 (0.6)	15,375 (0.7)	8,747 (0.4)
Any other psychiatric disorders, n (%)		278,152 (6.6)	168,147 (8.0)	110,005 (5.2)
Follow up period, years, mean (SD)	0	2.3 (1.7)	2.2 (1.7)	2.3 (1.7)
BMI, kg/m ² , mean (SD)	2,284,451	24.3 (4.3)	25.3 (4.6)	23.4 (3.6)
Systolic blood pressure, mmHg, mean (SD)	2,284,193	127.8 (18.9)	130.6 (19.6)	125.1 (17.7)
Diastolic blood pressure, mmHg, mean (SD)	2,284,201	79.3 (12.9)	81.1 (13.3)	77.6 (12.2)
Total cholesterol, mg/dL, mean (SD)	2,285,035	213.2 (37.4)	216.0 (39.9)	210.4 (34.9)
Triglyceride, mg/dL, mean (SD)	2,284,822	133.3 (128.0)	150.4 (149.8)	116.4 (98.8)
HDL-C, mg/dL, mean (SD)	2,284,718	61.1 (17.2)	58.9 (16.9)	63.3 (17.3)
LDL-C, mg/dL, mean (SD)	2,290,408	128.7 (33.9)	131.5 (35.5)	126.0 (31.9)
Fasting blood glucose, mg/dL, mean (SD)	2,435,826	106.9 (32.4)	117.1 (41.0)	96.6 (14.6)
HbA1c, %, mean (SD)	3,520,121	5.9 (1.1)	6.3 (1.4)	5.6 (0.5)
eGFR, ml/min/1.73m ² , mean (SD)	2,286,076	77.1 (15.4)	77.5 (16.5)	76.6 (14.1)
Smoking status (currently smoking), n (%)	2,284,087	643,021 (33.4)	321,106 (33.4)	321,915 (33.4)

Daily exercise habit (yes), n (%)	2,471,717	625,513 (36.0)	298,720 (34.4)	326,793 (37.6)
Alcohol consumption	2,461,907			
seldom, n (%)		680,839 (38.9)	350,581 (40.1)	330,258 (37.8)
sometime, n (%)		498,951 (28.5)	249,626 (28.6)	249,325 (28.5)
every day, n (%)		568,575 (32.5)	273,421 (31.3)	295,154 (33.7)
Sleeping condition (well), n (%)	2,483,318	1,036,916 (60.0)	505,481 (58.6)	531,435 (61.5)

BMI, body mass index; HDL-C, high density lipoprotein cholesterol; LDL-C, low density lipoprotein cholesterol; HbA1c, hemoglobin A1c; eGFR, estimated glomerular filtration rate.

Fig. 1: Flowchart of participants selection and matching.

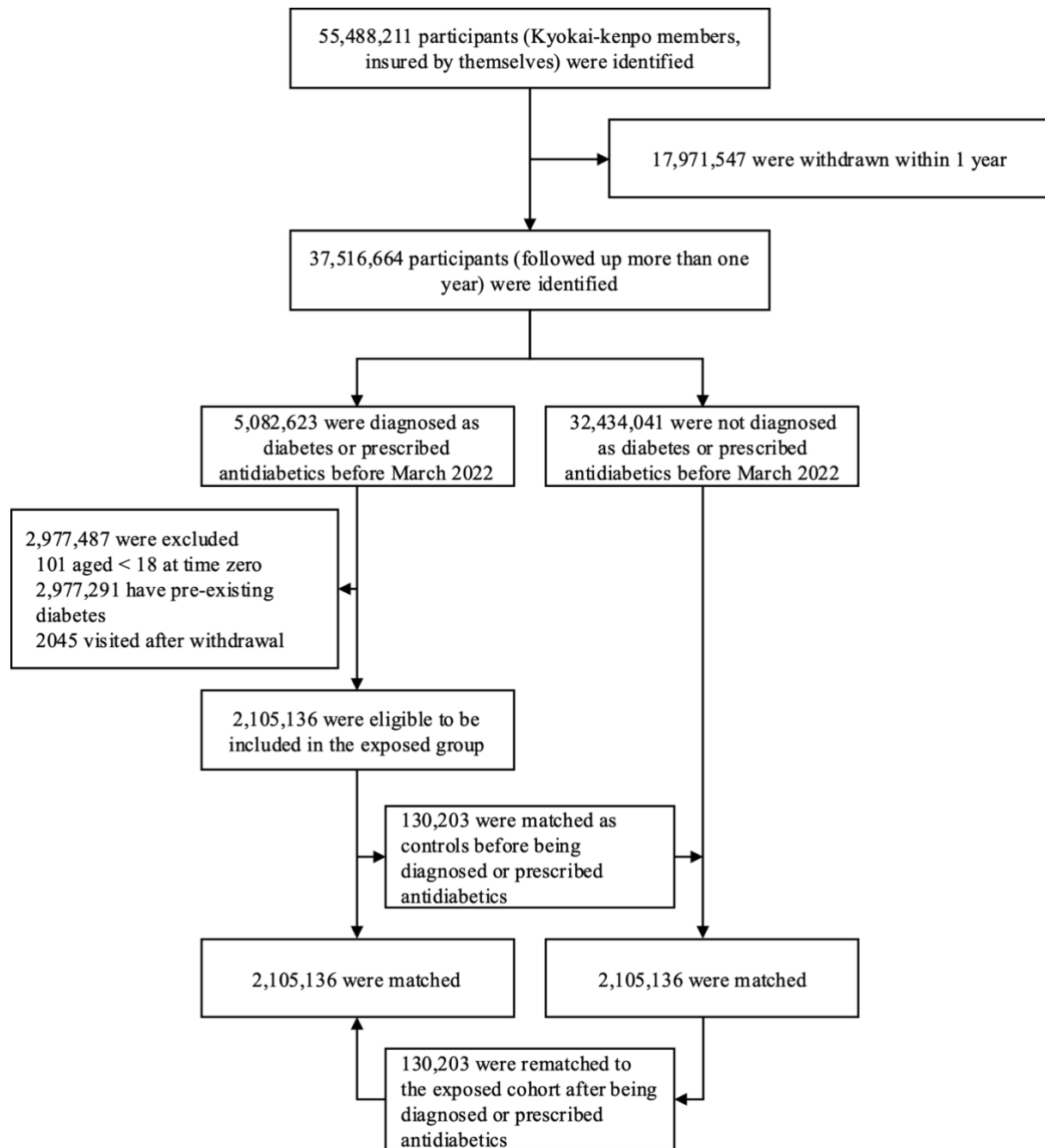


Fig 2. Cumulative incidences of death by suicide according to diabetes status.

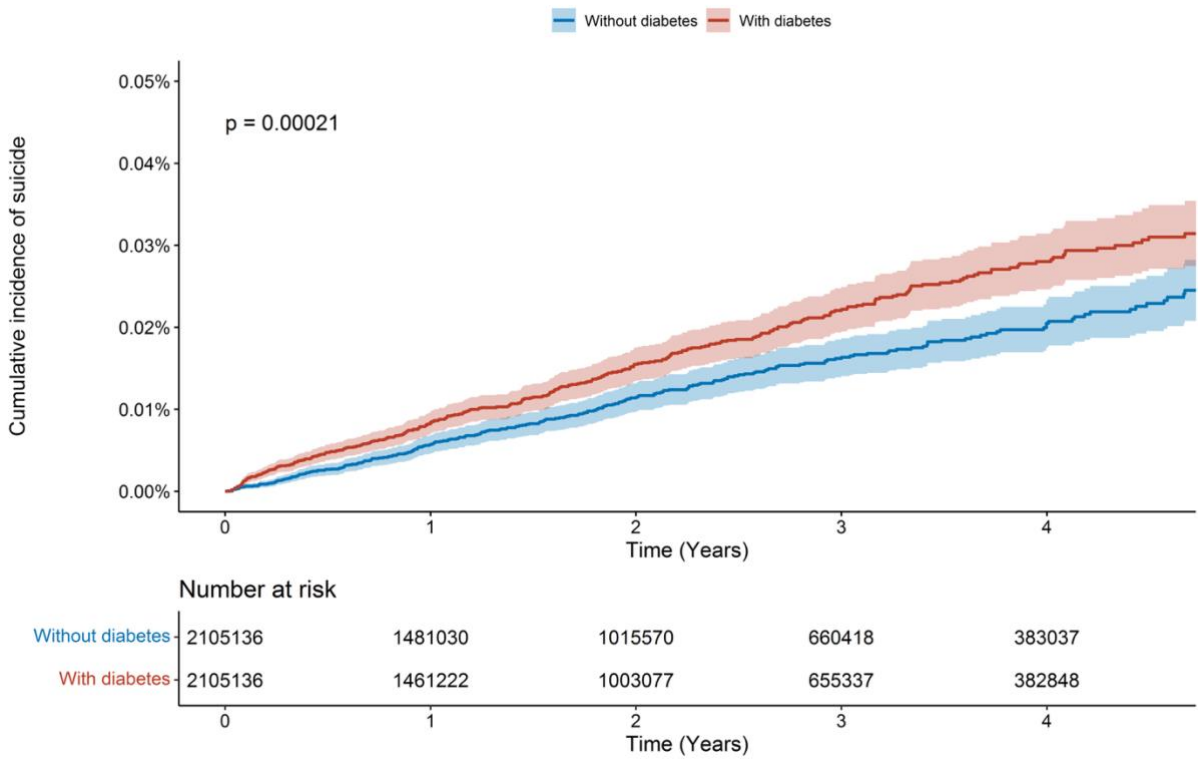


Fig 3. Association between diabetes and death by suicide.

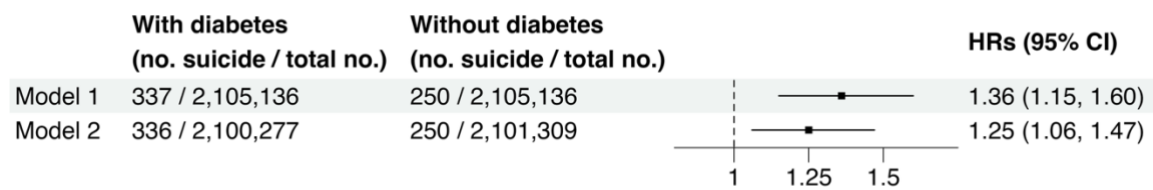
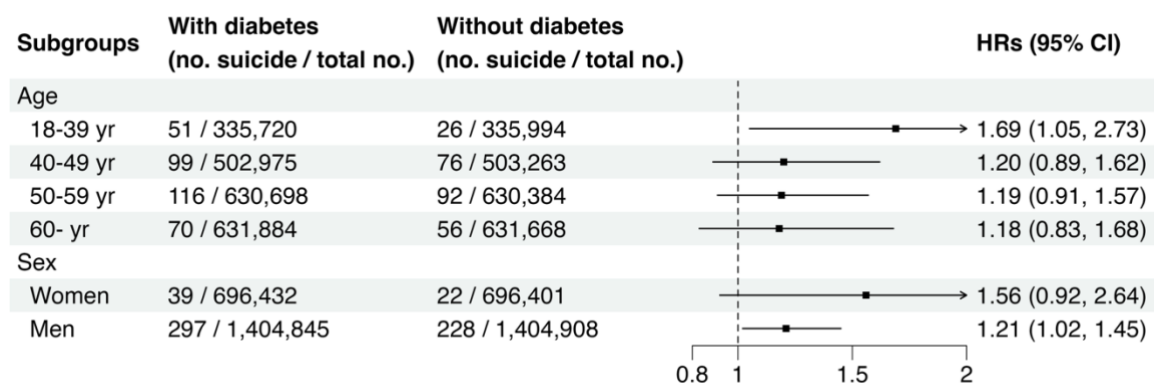


Fig 4. Subgroup analyses for the association between diabetes and death by suicide by age and sex.



Supplementary Information

Supplementary Fig. 1: Graphical representation of the Matching procedures.

Supplementary Fig. 2: Covariates collection windows.

Supplementary Fig. 3: Schoenfeld's residuals

Supplementary Fig 4: Association between diabetes and death by suicide, after adjusting for physical examination, lifestyle factors, and laboratory data, as well as sociodemographic factors and history of psychiatric disorders.

Supplementary Table 1. Antihyperglycemic medications.

Supplementary Table 2. Covariates table.

Supplementary Table 3. Initial diagnosis and diagnosis throughout the study period.

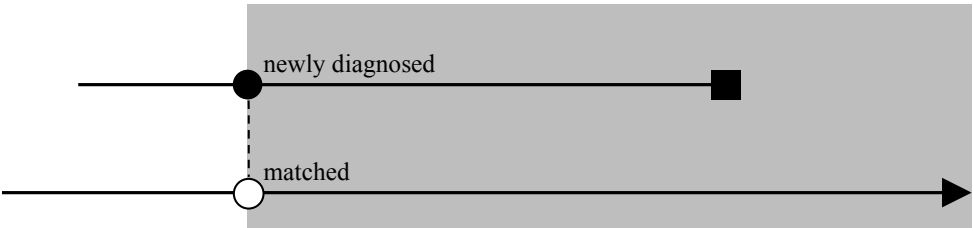
Supplementary Table 4. Baseline characteristics by death by suicide among individuals with and without diabetes.

Supplementary Table 5. Measures of effect modification on multiplicative and additive scale.

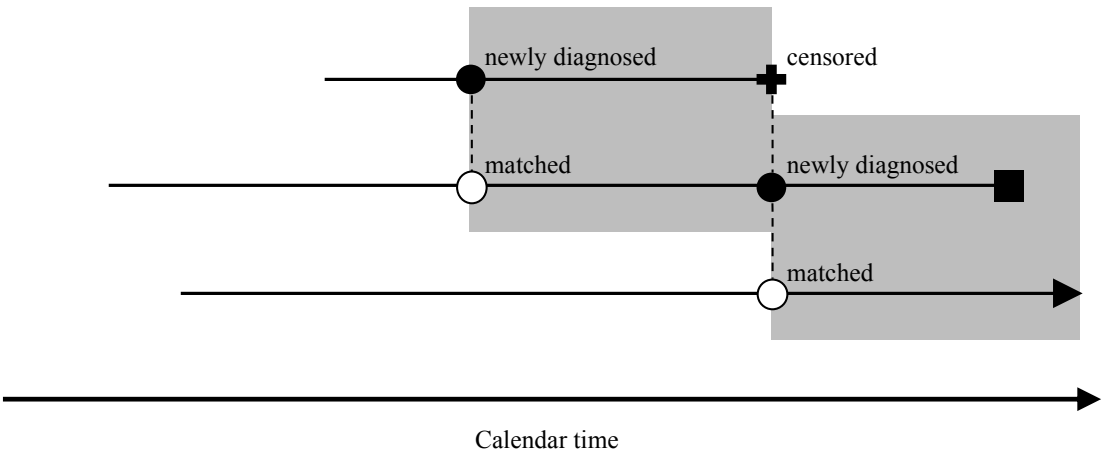
Supplementary Table 6. Sensitivity analysis by redefining the new onset of diabetes based on the diagnosis of diabetes and prescription of antihyperglycemic medications in the same month.

Supplementary Fig. 1: Graphical representation of the Matching procedures.

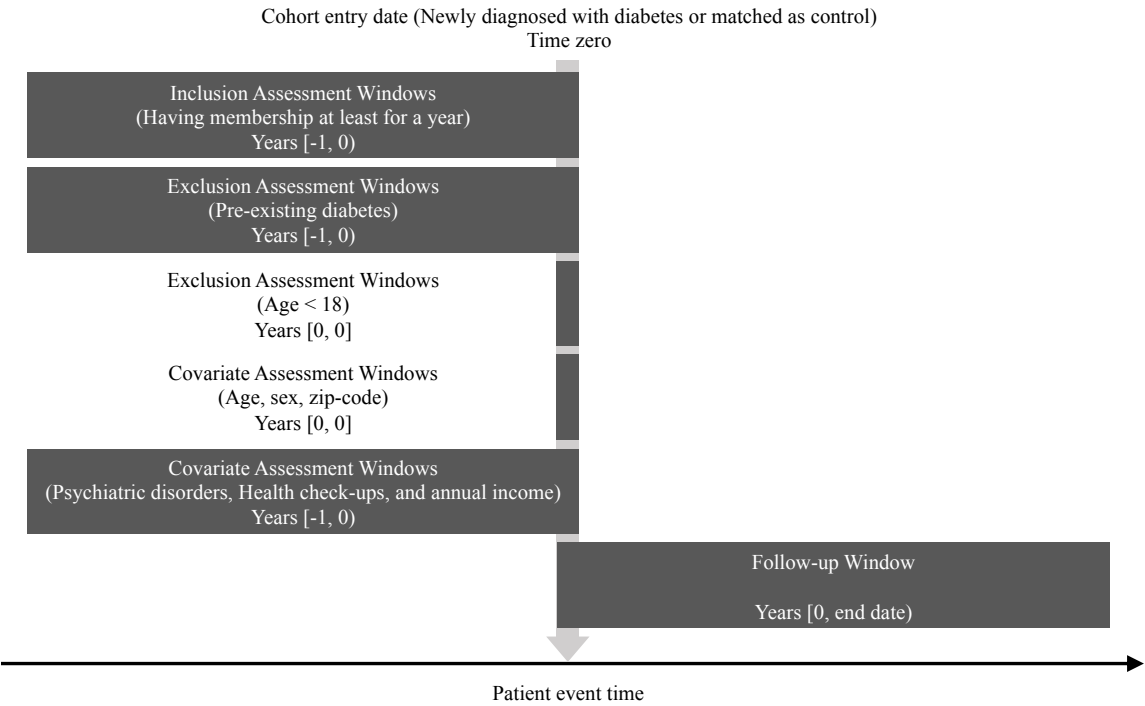
(A) A control individual was never diagnosed with diabetes during the study period.



(B) A control individual was diagnosed with diabetes after their matching.

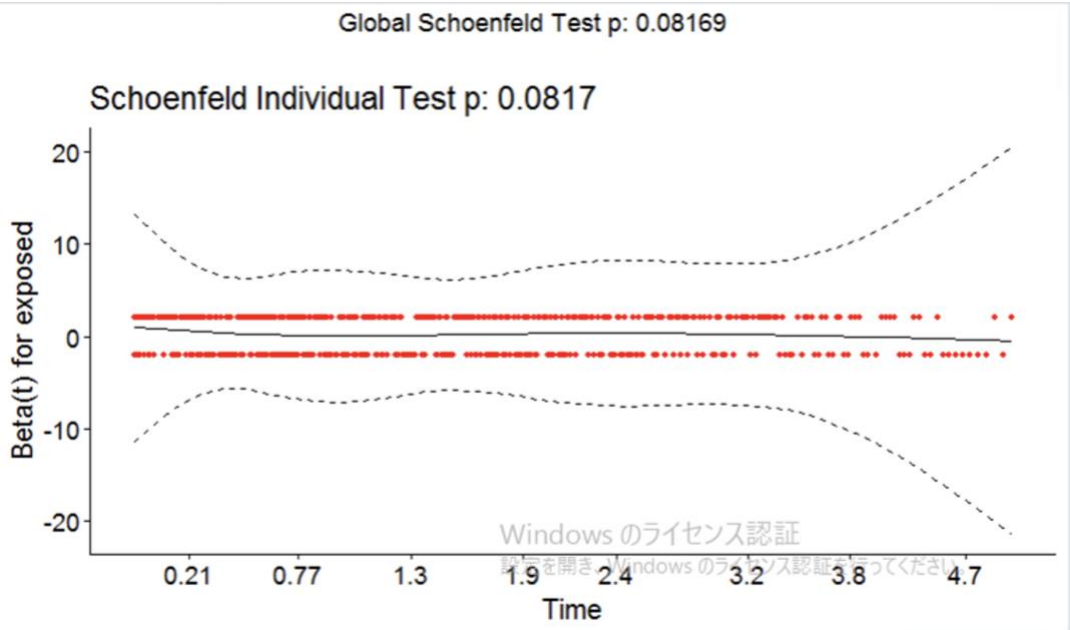


Supplementary Fig. 2: Covariates collection windows.

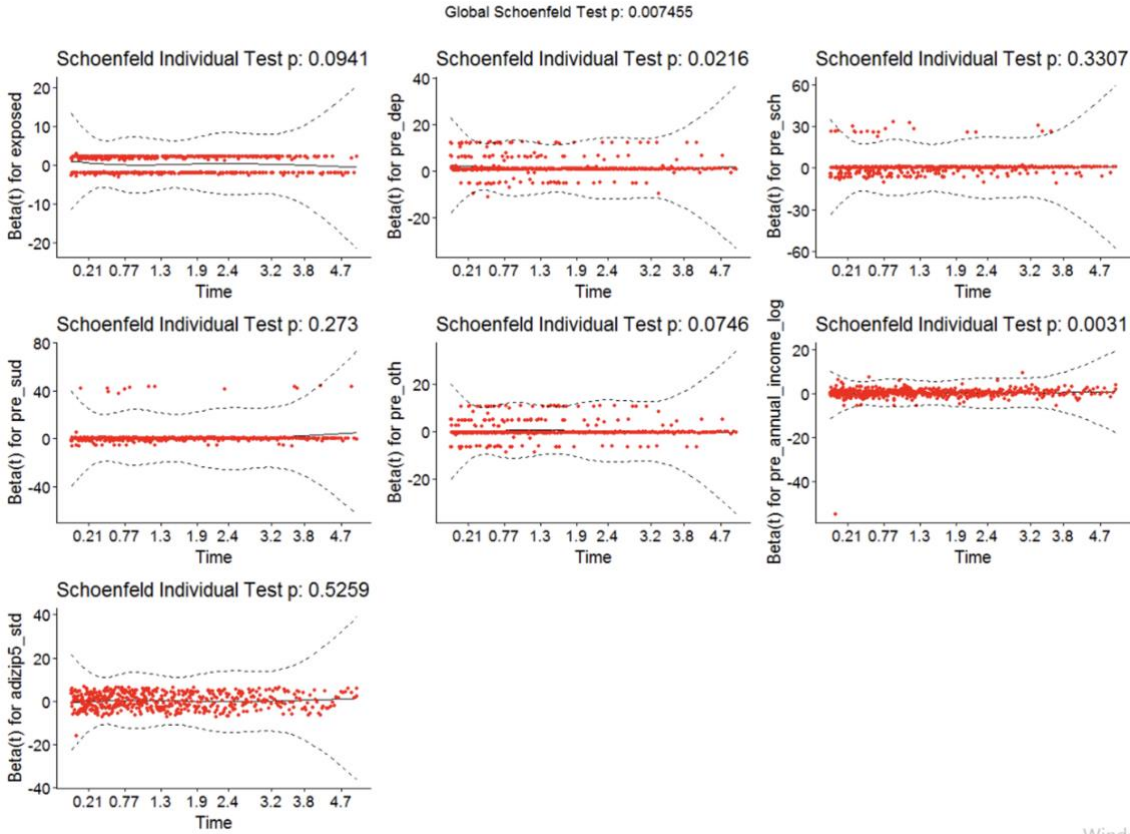


Supplementary Fig. 3: Schoenfeld's residuals

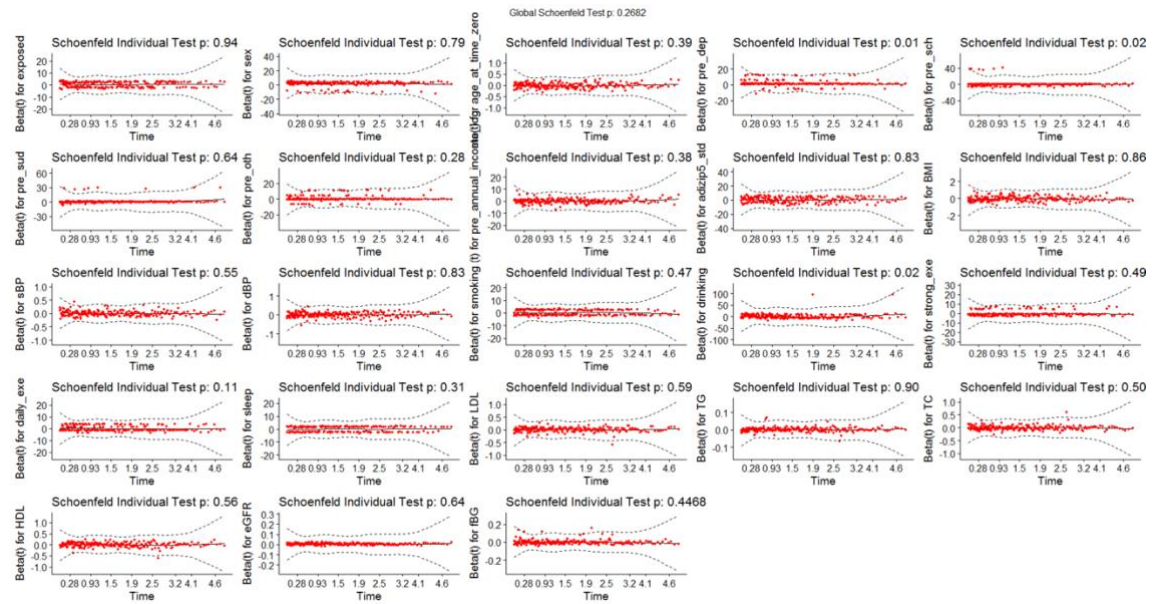
Model 1



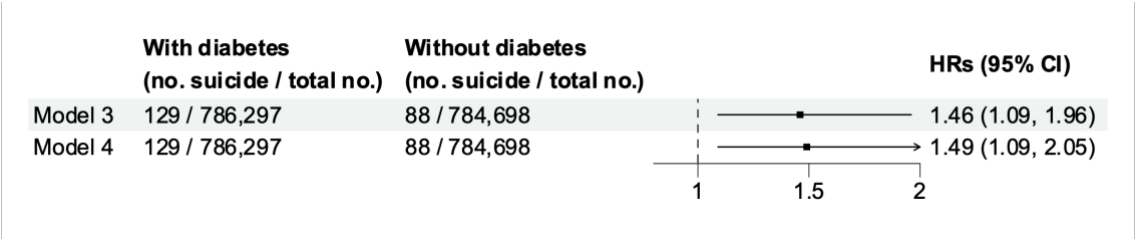
Model 2



Model 3



Supplementary Fig 4. Association between diabetes and death by suicide, after adjusting for physical examination, lifestyle factors, and laboratory data, as well as sociodemographic factors and history of psychiatric disorders.



Model 3 and Model 4 included the variable in Model 2 (diabetes diagnoses, sex, age, histories of psychiatric disorders [depressive disorders, schizophrenia spectrum disorders, substance use disorders, and any other psychiatric disorders], and SES [area-level deprivation index and log-transformed annual income]) and physical examination (BMI, and systolic and diastolic blood pressure), lifestyle factors (smoking status, alcohol consumption, daily sleeping condition, and daily exercise habit.), and laboratory data (TC, TG, LDL-C, HDL-C, eGFR, and fasting blood glucose). Model 4 used inverse probability of listwise deletion as weights to adjust selection bias due to listwise deletion related to missing values.

Supplementary Table 1. Antihyperglycemic medications.

Generic name	Class
Acarbose	α -glucosidase inhibitor
Acetohexamide	Sulfonylurea
Alogliptin	Dipeptidyl peptidase-4 inhibitor
Anagliptin	Dipeptidyl peptidase-4 inhibitor
Buformin	Biganide
Canaglyflozin	Sodium-dependent glucose transporter-2 inhibitor
Chlorpropamide	Sulfonylurea
Dapagliflozin	Sodium-dependent glucose transporter-2 inhibitor
Dulaglutide (genetical recombination)	Glucagon-like peptide-1 receptor agonist
Empagliflozin	Sodium-dependent glucose transporter-2 inhibitor
Empagliflozin/linagliptin	Sodium-dependent glucose transporter-2 inhibitor/dipeptidyl peptidase-4 inhibitor
Epalrestat	Aldose reductase inhibitor
Exenatide (genetical recombination)	Glucagon-like peptide-1 receptor agonist
Glibenclamide	Sulfonylurea
Gliclazide	Sulfonylurea
Glimepiride	Sulfonylurea
Glybuzole	Sulfonylurea
Glyclopamide	Sulfonylurea
Insulin aspart (genetical recombination)	ultra-rapid-acting insulin
Insulin aspart (genetical recombination)	ultra-rapid-acting insulin/immediate-acting insulin

Insulin aspart/degludec (genetical recombination)	ultra-rapid-acting insulin/long-acting insulin
Insulin degludec (genetical recombination)	long-acting insulin
Insulin degludec/liraglutide (genetical recombination)	long-acting insulin/glucagon-like peptide-1 receptor agonist
Insulin detemir (genetical recombination)	long-acting insulin
Insulin glargine (genetical recombination)	long-acting insulin
Insulin glargine /lixisenatide (genetical recombination)	long-acting insulin/glucagon-like peptide-1 receptor agonist
Insulin glulisine (genetical recombination)	ultra-rapid-acting insulin
Insulin human (genetical recombination)	immediate-acting insulin
Insulin human (genetical recombination)	rapid-acting insulin
Insulin human (genetical recombination)	rapid-acting insulin/immediate-acting insulin
Insulin lispro (genetical recombination)	ultra-rapid-acting insulin
Insulin lispro (genetical recombination)	ultra-rapid-acting insulin/immediate-acting insulin
Insulin lispro (genetical recombination)	immediate-acting insulin
Ipragliflozin L-proline	Sodium-dependent glucose transporter-2 inhibitor
Linagliptin	Dipeptidyl peptidase-4 inhibitor
Liraglutide (genetical recombination)	Glucagon-like peptide-1 receptor agonist
Lixisenatide (genetical recombination)	Glucagon-like peptide-1 receptor agonist

Luceogliflozin	Sodium-dependent glucose transporter-2 inhibitor
Metformin	Biganide
Metformin/alogliptin	Biganide/dipeptidyl peptidase-4 inhibitor
Metformin/anagliptin	Biganide/dipeptidyl peptidase-4 inhibitor
Metformin/vildagliptin	Biganide/dipeptidyl peptidase-4 inhibitor
Miglitol	α -glucosidase inhibitor
Mitiglinide	Meglitinide
Mitiglinide/voglibose	Meglitinide/ α -glucosidase inhibitor
Nateglinide	Meglitinide
Omarigliptin	Dipeptidyl peptidase-4 inhibitor
Pioglitazone	Thiazolidine
Pioglitazone/alogliptin	Thiazolidine/dipeptidyl peptidase-4 inhibitor
Pioglitazone/glimepiride	Thiazolidine/sulfonylurea
Pioglitazone/metformin	Thiazolidine/biganide
Repaglinide	Meglitinide
Saxagliptin	Dipeptidyl peptidase-4 inhibitor
Semaglutide	Glucagon-like peptide-1 receptor agonist
Sitagliptin	Dipeptidyl peptidase-4 inhibitor
Sitagliptin/ipragliflozin L-proline	Sodium-dependent glucose transporter-2 inhibitor/dipeptidyl peptidase-4 inhibitor
Teneligliptin	Dipeptidyl peptidase-4 inhibitor
Teneligliptin/canaglyflozin	Sodium-dependent glucose transporter-2 inhibitor/dipeptidyl peptidase-4 inhibitor
Tofogliflozin	Sodium-dependent glucose transporter-2 inhibitor

Tolbutamide

Sulfonylurea

Torbutamide

Sulfonylurea

Trelagliptin

Dipeptidyl peptidase-4 inhibitor

Troglitazone

Thiazolidine

Vildagliptin

Dipeptidyl peptidase-4 inhibitor

Voglibose

α -glucosidase inhibitor

Supplementary Table 2. Covariates table.

Covariates	Data source	Definition	Assessment window	The way to be handle in statistical analysis (coding)	Other details
Demographic factors					
Age	The registration profiles	Age at time when individuals were diagnosed as diabetes or matched as controls.	Time zero Year [0,0]	Continuous integer	
Sex	The registration profiles	Self-reported sex	Time zero Year [0,0]	Dichotomous (male or female)	
Socioeconomic status					
Annual income	The registration profiles	Annual income for a year prior to the time zero .	A year prior to the time zero	Continuous (log transformed)	Minimum unit is 1,000

			Year. [-1, 0)		Japanese yen
Area-level deprivation index	5-digit zip codes were collected from the registration profiles. Area-level deprivation index was calculated using 2015 census data.	5-digit zip code area-level deprivation index for individuals lived.	Time zero Year [0,0]	Continuous	ADI was standardized based on the number of households.
Medical histories					
Depressive disorders	Monthly medical claims data from all medical institutes.	ICD-10 codes: F32, F33.0–33.3, F33.8, and F33.9	A year prior to the time zero Year. [-1, 0)	Dichotomous (yes or no)	
Schizophrenia spectrum disorders	Monthly medical claims data from all medical institutes.	ICD-10 codes: F20–F29	A year prior to the time zero Year. [-1, 0)	Dichotomous (yes or no)	

Substance use disorders	Monthly medical claims data from all medical institutes.	ICD-10 codes: F10–F14, F16–F19	A year prior to the time zero Year. [-1, 0)	Dichotomous (yes or no)	
Any other psychiatric disorders	Monthly medical claims data from all medical institutes.	ICD-10 codes: any F codes, but other than the listed above.	A year prior to the time zero Year. [-1, 0)	Dichotomous (yes or no)	
Physical examinations					
Body mass index, BMI	Annual health check-ups.	Weight / Height ² . Height and weight were measured in physical examination of annual health check-ups.	A year prior to the time zero Year. [-1, 0)	Continuous	
Vital signs					
Systolic blood	Annual health check-ups.	The average of the twice	A year prior to the	Continuous	

pressure		blood pressure recordings.	time zero Year. [-1, 0)		
Diastolic blood pressure	Annual health check-ups.	The average of the twice blood pressure recordings.	A year prior to the time zero Year. [-1, 0)	Continuous	
Hematology and clinical chemistry					
HbA1c	Annual health check-ups.	Laboratory test conducted in annual health check-ups.	A year prior to the time zero Year. [-1, 0)	Continuous	
Fasting blood glucose	Annual health check-ups.	Laboratory test conducted in annual health check-ups.	A year prior to the time zero Year. [-1, 0)	Continuous	
Total cholesterol,	Annual health check-ups.	Laboratory test conducted	A year prior to the	Continuous	

TC		in annual health check-ups.	time zero Year. [-1, 0)		
Triglyceride, TG	Annual health check-ups.	Laboratory test conducted in annual health check-ups.	A year prior to the time zero Year. [-1, 0)	Continuous	
High-density lipoprotein cholesterol, HDL- C	Annual health check-ups.	Laboratory test conducted in annual health check-ups.	A year prior to the time zero Year. [-1, 0)	Continuous	
Low-density lipoprotein cholesterol, LDL- C	Annual health check-ups.	Laboratory test conducted in annual health check-ups.	A year prior to the time zero Year. [-1, 0)	Continuous	
Estimated glomerular	Annual health check-ups.	Calculated using serum Creatinine.	A year prior to the time zero	Continuous	

filtration rate, eGFR		Male: $194 \times \text{serum Cre}^{-1.094} \times \text{age}^{-0.287}$ Female: $194 \times \text{serum Cre}^{-1.094} \times \text{age}^{-0.287} \times 0.739$	Year. [-1, 0)		
Lifestyle factors					
Smoking status	Annual health check-ups.	Self-reported smoking status, which categorized into two levels: currently smoking, or not.	A year prior to the time zero Year. [-1, 0)	Dichotomous (yes or no)	
Alcohol consumption	Annual health check-ups.	Self-reported drinking habits, which categorized into three levels: daily drinking, sometimes drinking, and seldom or	A year prior to the time zero Year. [-1, 0)	Categorical (daily, sometimes, or seldom)	

		never drinking.			
Daily sleeping condition	Annual health check-ups.	Self-reported sleeping habits, which categorized into two levels: sleep well and enough, or not.	A year prior to the time zero Year. [-1, 0)	Dichotomous (yes or no)	
Daily exercise habit	Annual health check-ups.	Self-reported exercise habits, which categorized into two levels: doing walk or do any equivalent amount of physical activity more than one hour a day, or not.	A year prior to the time zero Year. [-1, 0)	Dichotomous (yes or no)	

Supplementary Table 3. Initial diagnosis and diagnosis throughout the study period.

	E10	E11	E12	E13	E14
Initial diagnosis, n (%)	7018	657753	345	11547	1552807
	(0.33)	(31.25)	(0.02)	(0.55)	(73.76)
Diagnosis throughout the study	11735	788966	372	14977	1601025
period, n (%)	(0.56)	(37.48)	(0.02)	(0.71)	(76.05)

Supplementary Table 4. Baseline characteristics by death by suicide among individuals with and without diabetes.

Characteristic	With diabetes		Without diabetes	
	not died by suicide	died by suicide	not died by suicide	died by suicide
	N = 2,104,799	N = 337	N = 2,104,886	N = 250
Age at time zero, years, mean (SD)	52.0 (11.9)	50.8 (10.6)	52.0 (11.9)	51.9 (9.9)
Sex				
Women, n (%)	697,258 (33.1)	40 (11.9)	697,276 (33.1)	22 (8.8)
Men, n (%)	1,407,541 (66.9)	297 (88.1)	1,407,610 (66.9)	228 (91.2)
Annual income, 1,000,000 Japanese yen, mean (SD)	3.92 (3.80)	4.10 (3.01)	3.83 (3.41)	4.12 (4.44)
Standardized area-level deprivation index, mean (SD)	0.54 (0.28)	0.54 (0.28)	0.53 (0.28)	0.57 (0.27)
Histories of psychiatric disorders				
Depressive disorders, n (%)	85,570 (4.1)	64 (19.0)	52,414 (2.5)	31 (12.4)
Schizophrenia spectrum disorders, n (%)	21,756 (1.0)	18 (5.3)	11,263 (0.5)	7 (2.8)
Substance use disorders, n (%)	15,365 (0.7)	10 (3.0)	8,744 (0.4)	3 (1.2)
Any other psychiatric disorders, n (%)	168,079 (8.0)	68 (20.2)	109,973 (5.2)	32 (12.8)

Follow up period, years, mean (SD)	2.2 (1.7)	1.5 (1.2)	2.3 (1.6)	1.6 (1.2)
Body mass index, kg/m ² , mean (SD)	25.3 (4.6)	24.2 (3.9)	23.7 (3.1)	23.4 (3.6)
Systolic blood pressure, mmHg, mean (SD)	130.6 (19.6)	129.3 (18.6)	125.1 (17.7)	127.8 (19.9)
Diastolic blood pressure, mmHg, mean (SD)	81.1 (13.3)	81.0 (11.7)	77.6 (12.2)	79.8 (13.5)
Total cholesterol, mg/dL, mean (SD)	216.0 (39.6)	215.8 (41.1)	210.4 (34.9)	205.0 (32.4)
Triglyceride, mg/dL, mean (SD)	150.4 (149.8)	148.5 (152.6)	116.4 (98.7)	139.6 (127.0)
High-density lipoprotein cholesterol, mg/dL, mean (SD)	58.9 (16.9)	58.7 (16.4)	63.3 (17.3)	60.6 (16.2)
Low-density lipoprotein cholesterol, mg/dL, mean (SD)	131.5 (35.5)	131.3 (40.9)	126.0 (31.9)	122.2 (29.1)
Fasting blood glucose, mg/dL, mean (SD)	117.1 (41.0)	116.4 (40.2)	96.6 (14.6)	97.6 (14.2)
HbA1c, %, mean (SD)	6.28 (1.40)	6.10 (0.75)	5.55 (0.47)	5.53 (0.31)
eGFR, ml/min/1.73m ² , mean (SD)	77.5 (16.5)	81.2 (14.6)	76.6 (14.1)	78.7 (14.4)
Smoking (yes), n (%)	321,037 (33.4)	69 (42.1)	321,866 (33.4)	49 (41.9)
Daily exercise habit (yes), n (%)	298,672 (34.4)	48 (34.5)	326,758 (37.6)	35 (36.5)

Alcohol consumption				
seldom, n (%)	350,527 (40.1)	54 (38.6)	330,226 (37.8)	32 (33.3)
sometime, n (%)	249,589 (28.6)	37 (26.4)	249,299 (28.5)	26 (27.1)
every day, n (%)	273,372 (31.3)	49 (35.0)	295,116 (33.7)	38 (39.6)
Sleeping condition (well), n (%)	505,410 (58.6)	71 (50.7)	531,374 (61.5)	61 (64.2)

Supplementary Table 5. Measures of effect modification on multiplicative and additive scale.

Variables	HR with single references		HR (95%CI) within stratum	measures of effect modification	
	Without diabetes	With diabetes		On multiplicative scale	On additive scale
Age					
18–39yr	reference	1.77 (1.10, 2.59)	1.69 (1.05, 2.73)	reference	reference
40–49yr	1.66 (1.06, 2.59)	1.97 (1.28, 3.04)	1.20 (0.89, 1.62)	0.67 (0.38, 1.17)	-0.45 (-1.37, 0.46)
50– 59yr	1.79 (1.15, 2.76)	2.11 (1.38, 3.24)	1.19 (0.91, 1.57)	0.67 (0.39, 1.15)	-0.44 (-1.35, 0.47)
60yr–	1.15 (0.72, 1.84)	1.37 (0.87, 2.15)	1.18 (0.83, 1.68)	0.67 (0.37, 1.21)	-0.55 (-1.44, 0.33)
Gender					
Women	reference	1.59 (0.94, 2.69)	1.56 (0.92, 2.64)	reference	reference
Men	5.51 (3.55, 8.56)	6.68 (4.32, 10.34)	1.21 (1.02, 1.45)	0.76 (0.44, 1.32)	+0.58 (-0.59, 1.75)

Model included diabetes diagnoses, age, sex, histories of psychiatric disorders (depressive disorders, schizophrenia spectrum disorders, substance use disorders, and any other psychiatric disorders), and SES (area-level deprivation index and log-transformed annual income) as covariates.

Supplementary Table 6. Sensitivity analysis by redefining the new onset of diabetes based on the diagnosis of diabetes and prescription of antihyperglycemic medications in the same month.

	no. suicide / total no.		HRs (95% CI)
	With diabetes	Without diabetes	
Model 1	119 / 696,844	81 / 696,844	1.50 (1.13, 1.99)
Model 2	119 / 695,458	81 / 695,442	1.45 (1.10, 1.93)
Model 3	18 / 170,650	7 / 175,015	-

-: Model 3 did not achieve convergence.

Model 1 included diabetes diagnoses only. Model 2 included diabetes diagnoses, age, sex, histories of psychiatric disorders (depressive disorders, schizophrenia spectrum disorders, substance use disorders, and any other psychiatric disorders), and SES (area-level deprivation index and log-transformed annual income) as covariates. Model 3 included the variable in Model 2 and physical examination (BMI, and systolic and diastolic blood pressure), lifestyle factors (smoking status, alcohol consumption, daily sleeping condition, and daily exercise habit.), and laboratory data (TC, TG, LDL-C, HDL-C, eGFR, and fasting blood glucose).