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Original Article

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Genetic Risk, Healthy Lifestyle Adherence, and Risk of Developing Diabetes in the Japanese Population

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Aim: This study examined the relationship between genetic risk, healthy lifestyle, and risk of developing diabetes.

Methods: This prospective cohort study included 11,014 diabetes-free individuals ≥ 20 years old from the Tohoku Medical Megabank Community-based cohort study. Lifestyle scores, including the body mass index, smoking, physical activity, and gamma-glutamyl transferase (marker of alcohol consumption), were assigned, and participants were categorized into ideal, intermediate, and poor lifestyles. A polygenic risk score (PRS) was constructed based on the type 2 diabetes loci from the BioBank Japan study. A multiple logistic regression model was used to estimate the association between genetic risk, healthy lifestyle, and diabetes incidence and to calculate the area under the receiver operating characteristic curve (AUROC).

Result: Of the 11,014 adults included (67.8% women; mean age [standard deviation], 59.1 [11.3] years old), 297 (2.7%) developed diabetes during a mean 4.3 (0.8) years of follow-up. Genetic and lifestyle score is independently associated with the development of diabetes. Compared with the low genetic risk and ideal lifestyle groups, the odds ratio was 3.31 for the low genetic risk and poor lifestyle group. When the PRS was integrated into a model including the lifestyle and family history, the AUROC significantly improved to 0.719 (95% confidence interval [95% CI]: 0.692-0.747) compared to a model including only the lifestyle and family history (0.703 [95% CI, 0.674-0.732]).

Conclusion: Our findings indicate that adherence to a healthy lifestyle is important for preventing diabetes, regardless of genetic risk. In addition, genetic risk might provide information beyond lifestyle and family history to stratify individuals at high risk of developing diabetes.

Key words: Genetic, Lifestyle, Diabetes mellitus, Epidemiology, Polygenic risk score

Introduction

Diabetes is a serious chronic disease, and its complications are a major cause of premature mortality[1]. According to the Global Burden of Disease, Injuries, and Risk Factors Study, as of 2021, there are 529 million people worldwide suffering from diabetes, which is expected to increase to more than 1.31 billion people by 2050 [2]. Therefore, diabetes prevention, a crucial public health issue, needs to be addressed urgently.

Both genetic and lifestyle factors play an important role in the development of diabetes[3]. Several intervention studies have demonstrated that lifestyle interventions, such as diet, exercise, and weight loss, prevent diabetes[4-6]. The American Diabetes Association and the European Society of Cardiology consequently emphasized that adherence to a healthy lifestyle, such as weight reduction, smoking cessation, physical activity, and reduced alcohol consumption, could help prevent diabetes[7, 8]. More than 270 independent diabetes susceptibility genetic loci have been identified from several large-scale genome-wide association studies (GWASs) to date[9-11].

Furthermore, the polygenic risk score (PRS), constructed based on the identified risk alleles from the GWAS, can predict the onset of type 2 diabetes in both European and non-European populations, providing a quantitative assessment of the genetic risk for diabetes[12-15]. Previous studies examined the joint associations of the PRS and lifestyle factors with diabetes incidence in general populations[16-20]. Both genetic and lifestyle risks were consistently and independently associated with diabetes incidence[16-20]. However, most previous studies were conducted among European and US populations[16-20]. Evidence from Asian populations has been limited, even though their genetics and lifestyles differ from other populations. Indeed, only one cross-sectional study has been conducted in Japan[21], and evidence from prospective studies is lacking.

If PRS can predict diabetes incidence, two questions arise: Is a family history of diabetes, used as an indirect measure of inherited susceptibility, along with lifestyle information sufficient for predicting diabetes incidence? Alternatively, would the addition of the PRS further improve the predictive ability for diabetes incidence? If the predictive ability remains unchanged when the PRS is added to conventional risk stratification methods that consider both the lifestyle and family history, subsequent genomic sequencing may be unnecessary due to the cost and ease of measurement. Thus, using a family history as a predictive factor may be sufficient for risk stratification.

A previous cross-sectional study revealed that the addition of the PRS to information on the lifestyle and family history achieved a greater area under the receiver operating characteristic curve (AUROC) than before this addition. However, the family history may be influenced by recall bias[21]. To clarify the role of the PRS and family history in diabetes incidence, prospective cohort studies are warranted.

The Tohoku Medical Megabank-Community-based Cohort (TMM CommCohort) study is a large-scale population-based prospective cohort study examining the influence of the long-term impact of earthquake-related disease and personalized medicine based on individuals' genetics and lifestyle[22, 23]. The TMM CommCohort completed a repeat assessment center-based survey during the second period (follow-up survey) in March 2021 [24], allowing the examination of the association between genetics, lifestyle, and one's family history with new-onset diabetes using a prospective cohort design.

Aim

In the present study, we examined the association between genetic and lifestyle factors and the incidence of diabetes. We also examined whether or not the addition of the PRS to the lifestyle and family history improved the predictive ability.

Methods

TMM CommCohort Study Participants

The TMM CommCohort Study included participants ≥ 20 years old from Miyagi Prefecture, Japan. Further details regarding the study have been described elsewhere[22, 23]. In brief, the study was started in May 2013 and continued until March 2016. More than 50,000 participants were recruited via the following approaches: a type 1 survey (n=40,433 participants), which was performed at specific municipal health checkup sites; a type 1 additional survey (n=664 participants), conducted on dates different from those of the specific health checkup

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sites; and a type 2 survey (n=13,855), performed at assessment centers. Participants completed a self-reported questionnaire regarding information on lifestyle and other potential health-related aspects and provided blood and urine samples. All participants provided their written informed consent before participation.

We invited respondents from the baseline survey to participate in a repeat assessment center-based survey during the second period (follow-up survey) from June 2016 to March 2021 [24]. This survey collected basic information similar to the baseline survey. This study was approved by the Institutional Review Board of the Tohoku Medical Megabank Organization (approval number: 2022-4-047; approval date: June 30, 2022).

This analysis initially included type 1 survey participants (n=40,433). We excluded participants who withdrew from the study by November 16, 2021 (n=770), had a history of cardiovascular disease (n=1,806), had type 1 or 2 diabetes at the baseline survey (n=3,146), lacked genetic information genotyped via the Affymetrix Axiom Japonica Array (v2) (n=6,438), or had missing information on lifestyle factors (n=6,431). We subsequently excluded participants who did not participate in the follow-up survey and thus had missing information on glucose and hemoglobin A1C (HbA1c) during the follow-up survey (n=10,808) as well as participants with data ≥ 6 standard deviations (SD) from the mean of each genetic principal component (n=20). Ultimately, data from 11,014 participants were analyzed **(Supplemental Fig. 1)**.

Healthy Lifestyle Factors

Based on a previous study [21], we constructed a healthy lifestyle score based on four diabetes risk factors: never smoker, non-obese, regular physical activity, and low gamma glutamyl-transferase (GGT) [7, 8, 25, 26]. Weight was measured to the nearest 0.1 kg via a body composition analyzer (InBody720; Biospace Co., Ltd., Seoul, Korea). Furthermore, 1.0 kg was subtracted to account for the weight of the participants' clothing. The body mass index (BMI) was calculated as the weight (kg) divided by the height squared (m^2). Information on smoking and drinking status, physical activity, and family history of diabetes was collected using a self-report questionnaire. Participants answered whether they drank alcohol at least once a month. Drinking status was classified into three categories: non-drinkers (consumed little or no alcohol or constitutionally incapable of alcohol consumption), ex-drinkers (stopped drinking alcohol), and current drinkers (drinking alcohol at least once a month). Participants disclosed the hours spent on each activity (sitting, standing, walking, strenuous work) on average in a day in a last year [27]. We assigned reports of 0, 30, 120, 240, 260, 480, 600, and 660 min spent on an activity to 0, <1, 1–3, 3–5, 5–7, 7–9, 9–11, and ≥ 11 h, respectively. The average frequency (times/week) and duration (min/time) of normal walking, brisk walking, and moderate- and hard-intensity exercise during leisure time were obtained [27-29]. Frequency was classified into the following categories: <1 time per month, 1–3 times per month, 1–2 times per week, 3–4 times per week, and almost daily. Duration was classified into the following categories: <30 min, 30–59 min, 1–2 h, 2–3 h, 3–4 h, and ≥ 4 h. This study defined "walking," "normal walking," "brisk walking," and "moderate-intensity exercise" as moderate physical activity and "strenuous work" and "hard-intensity exercise" as vigorous physical activity [27-30]. The average time of moderate and vigorous physical activity in leisure time was determined by multiplying the frequency and duration. Subsequently, we calculated the minutes of moderate-intensity activity per week by adding the duration of walking and the average duration of moderate physical activity during leisure time. Similarly, we calculated the minutes of vigorous physical activity per week by adding the duration of strenuous work and average duration of vigorous physical activity during leisure time. The participants disclosed whether or not they had a family history of diabetes through their biological parents or siblings. If participants answered that at least one of them had diabetes, they were considered to have a family history of diabetes. Non-fasting blood samples were collected. The serum GGT levels were measured using an enzymatic method.

Obesity was defined as a BMI of ≥ 25.0 kg/m^2 based on the Western Pacific Region of World Health Organization (WHO) criteria for Japanese individuals [31]. Non-smoking was defined as participants who had smoked <100 cigarettes during their lifetime [32]. Regular physical activity was defined as at least 150 or 75 minutes of moderate or vigorous intensity activity weekly, respectively [33]. High GGT was defined as GGT of ≥ 50 IU/L based on health examinations in Japan [24]. GGT was considered a marker of excessive alcohol consumption and visceral fat, especially related to hepatic steatosis [34, 35]. Elevated GGT levels are associated with diabetes, regardless of alcohol consumption and BMI [25, 26, 36]. Therefore, we used GGT levels as a surrogate marker for alcohol consumption due to the U-shaped relationship observed between alcohol consumption and diabetes incidence [26]. Overall lifestyle was subsequently

categorized into ideal (had at least three ideal lifestyle factors), intermediate (had two ideal lifestyle factors), or poor (had only one or no ideal lifestyle factor).

Diabetes

Non-fasting glucose and HbA1c levels were measured using the hexokinase and latex agglutination turbidimetry methods, respectively. Diabetes was defined as non-fasting glucose of ≥ 200 mg/dl, HbA1c ≥ 6.5%, and/or self-reported treatment for diabetes.

Genotyping, Imputation, and the PRS Derived from BioBank Japan

Participants were genotyped with an Affymetrix Axiom Japonica Array (v2) separately in 21 batches[21, 37, 38]. Direct genotype data were pre-phased using SHAPEIT2 [39], and the phased genotypes were subsequently imputed through IMPUTE 4 [40], with a cross-imputed haplotype reference panel of the 3.5KJPNv2 and the 1000 Genomes phase 3 panel[41, 42]. The cross-imputation of the two reference panels was executed using IMPUTE2 with the merge_ref_panels_output_ref option[43]. For quality control, we excluded plates with an average call rate <0.95, and samples with a Dish QC metric of <0.82 or step1 call rate of <0.97 before batch genotyping. Subsequently, we removed variants with a p-value of the Hardy-Weinberg equilibrium (HWE) test $<1.00\times10^{-6}$, a minor allele frequency (MAF) <0.01, or missing rate >0.01 from each batch. The imputed genotype dataset was obtained by merging the 21 batches using QCTOOL (v2.0.4) (https://www.well.ox.ac.uk~gavqctool). We also obtained a direct genotype dataset from the TMM CommCohort participants in PLINK BED format. Subsequently, we removed variants with MAF values of <0.01 and IMPUTE2 info score of <0.8 from the imputed dataset.

We calculated the PRS based on the summary statistics of a previous GWAS for diabetes in BioBank Japan (BBJ), publicly available at the National Bioscience Database Center[9]. Our participants were independent of the BBJ participants. All single nucleotide polymorphisms (SNPs) on the X and Y chromosomes were removed to eliminate the possibility of non-autosomal sex effects. The PRS was calculated via the clumping and thresholding (C+T) method using PLINK 1.9. Similar to a previous study[21], we performed clumping to capture the correct level of the causal signal using the following options: --clump-p1 1 --clump-r2 0.1 –clump-kb 250. After clumping, the PRS for each individual was calculated using the various variant sets. The PRS was calculated using the default formula in PLINK (https://choishingwan.github.io/PRS-Tutorial/plink/). We calculated the PRS using 9 different p value: 5.0×10^{-8}, 0.001, 0.01, 0.05, 0.1, 0.2, 0.3, 0.4, and 0.5 **(Supplemental Table 1)**. Since the settings of the best-fit PRS for HbA1c in a previous study used the PRS with $p<0.2$ [21], we also used the PRS constructed with $p<0.2$. Subsequently, the PRS was categorized into three groups: low (lowest), intermediate (second), and high (highest tertiles).

Statistical Analyses

Data are presented as the mean (SD) or median (interquartile range) and number (percentage) for continuous and categorical variables, respectively. Multivariate logistic regression analyses were performed to examine the association between lifestyle factors and incidence of diabetes. Adjusted odds ratios (ORs) and 95% confidence intervals (CIs) were calculated. Similarly, multivariate logistic regression analyses were performed to examine the association between the genetic risk scores and diabetes. Subsequently, we combined the PRS tertiles and lifestyles and categorized them into nine groups. The association between genetic and lifestyle factors and the incidence of diabetes was examined. The interaction between the PRS and generic risk was examined using a likelihood ratio test to compare the models with and without interaction terms between the lifestyle score and PRS. All models were adjusted for the age, sex, and first six principal components (adjusted for population structure). Furthermore, we combined the family history, PRS tertiles, and lifestyle risk to create 18 group categories and investigated the influence of the PRS on the association of lifestyle risk and family history with the incidence of diabetes. The same analysis was performed as described above. The AUROC and 95% CI were calculated to assess whether or not the addition of the PRS to the statistical model, which included lifestyle risk factors and family history, increased the predictive ability for diabetes incidence. The AUROC was compared using the DeLong test.

We conducted several sensitivity analyses. First, because the distribution and incidence of healthy lifestyles vary by sex, we conducted a stratified analysis by sex as a sensitivity analysis to confirm the robustness of our results. Second, the risk of developing diabetes differs according to the family history of maternal or paternal diabetes. Thus, we repeated the analysis according to this family history.

Statistical significance was set at $p<0.05$. Statistical analyses were performed using the R software program, version 4.1.2 (R Foundation for Statistical Computing, Vienna, Austria).

Results

Participants' Characteristics

This study included 11,014 participants (mean [SD] age, 59.1 [11.3] years old, 7,464 women [67.8%]), 297 (2.7%) of whom developed diabetes during a mean 4.3 (0.8) years of follow-up. The mean (SD) values for glucose and HbA1c in the baseline survey were 88.0 (11.9) mg/dl and 5.5 (0.3%), respectively. A total of 7,974 participants (72.4%) met at least 3 ideal lifestyle factors **(Table 1)**. Women were more likely than men to have an ideal lifestyle regardless of their genetic risk and family history. Participants who were obese or current drinkers were more likely to have high GGT levels than others **(Supplemental Table 2)**.

Compared to participants who did not meet the inclusion criteria, those who were older and had a lower BMI and GGT levels were more likely to have a family history of diabetes, be non-smokers, and be less likely to engage in regular physical activity than others **(Supplemental Table 3)**.

Association of Lifestyle with Risk of Developing Diabetes

We found that a poor lifestyle was associated with a significantly higher risk of developing diabetes than other lifestyles. The multivariate ORs were 1.00 (reference), 1.76 (1.33–2.30), and 3.63 (2.48–5.22) for ideal, intermediate, and poor lifestyles, respectively.

Associations of the PRS with Risk of Developing Diabetes

A higher PRS was associated with a higher OR for the incidence of diabetes. The multivariate ORs were 1.00, 1.65 (1.20–2.29), and 2.31 (1.71–3.15) for low, intermediate, and high genetic risk, respectively.

Associations of Combined Lifestyle and Genetic Risk with Risk of Developing Diabetes

A higher genetic risk and poor lifestyle were independently associated with a higher OR for the occurrence of diabetes. Compared with low genetic risk and an ideal lifestyle, those with a low genetic risk and a poor lifestyle had a significantly higher OR for diabetes incidence than others (3.31, 95% CI, 1.30–7.37). Those with a high genetic risk and an ideal lifestyle had a significantly higher OR than others (2.87 [95% CI, 1.89–4.47]) **(Table 2)**, although there was no interaction between the PRS and adherence to a healthy lifestyle for diabetes incidence (P=0.33).

Associations of Lifestyle, Genetic Risk, and Family History of Diabetes with Risk of Developing Diabetes

Initially, we examined the association between a family history of diabetes and the frequency of diabetes. Participants with a family history of diabetes had a significantly higher risk of developing diabetes than those without a family history (OR, 2.47 [95% CI, 1.84–3.26]) after adjusting for the age, sex, and top six principal components. No interaction was observed between family history and adherence to a healthy lifestyle for diabetes incidence (P=0.19). Subsequently, we examined the association between genetic and lifestyle risks and family history of diabetes. A higher genetic risk, poor lifestyle, and family history were independently associated with the risk of developing diabetes **(Table 3)**. Compared to the group with a low genetic risk, an ideal lifestyle, and no family history of diabetes, a family history was significantly associated with the risk of diabetes, even among participants with a low genetic risk and ideal lifestyle (OR, 2.97 [95% CI, 1.16–6.70]).

The AUROC values (95% CI) for the PRS, lifestyle, and family history were 0.662 (0.633–0.690), 0.684 (0.656–0.713), and 0.652 (0.621–0.683), respectively. In a clinical setting in which both the lifestyle and family history were considered, the AUROC was 0.703 (0.674–0.732). When the PRS was integrated into a model with lifestyle and family history, the AUROC significantly improved to 0.719 (0.692–0.747) compared to a model with only the lifestyle and family history included ($p<0.001$) **(Table 4)**.

We conducted several sensitivity analyses. First, we conducted a stratification analysis by sex, but similar trends were observed **(Supplemental Tables 4 and 5)**. Second, we repeated the analysis by a family history of maternal and paternal diabetes, and similar trends were confirmed **(Supplemental Tables 6 and 7)**.

Discussion

In this large community-based Japanese study, a high PRS was associated with diabetes incidence, independent of lifestyle. In addition, an ideal lifestyle was associated with a lower risk of developing diabetes, regardless of genetic risk. Even among participants with an ideal lifestyle, those with high genetic risk had a significantly higher risk of developing diabetes than participants with an ideal lifestyle and low genetic risk. The incorporation of the PRS into traditional risk factors, such as the lifestyle and family history, increases the predictive ability for diabetes incidence.

Several previous studies in European and US populations demonstrated that genetic risk and

Table 1. Participants' Characteristics According to Genetic and Lifestyle Risks

Genetic risk	Low			Intermediate		
Lifestyle	Ideal	Intermediate	Poor	Ideal	Intermediate	Poor
Number	2659	833	179	2670	805	196
Age, years	59.8 (11.0)	58.4 (11.7)	57.7 (11.5)	59.3 (11.0)	58.1 (12.3)	58.9 (11.0)
Women, %	2017 (75.9)	403 (48.4)	47 (26.3)	2042 (76.5)	416 (51.7)	53 (27.0)
BMI, kg/m^2	21.9 (2.6)	24.3 (3.6)	27.0 (2.6)	22.0 (2.7)	24.6 (3.6)	27.3 (2.8)
Follow-up duration, years	4.3 (0.8)	4.4 (0.8)	4.4 (0.8)	4.3 (0.8)	4.3 (0.8)	4.4 (0.8)
Glucose, mg/dl	87.9 (11.9)	88.9 (12.2)	89.6 (9.6)	87.3 (11.9)	89.4 (12.6)	92.6 (12.4)
HbA1c, %	5.5 (0.3)	5.5 (0.3)	5.6 (0.4)	5.5 (0.3)	5.5 (0.3)	5.7 (0.6)
Family history of diabetes, %	274 (10.3)	69 (8.3)	15 (8.4)	319 (11.9)	93 (11.6)	19 (9.7)
Physical activity						
Moderate-intensity physical activity, min/week	142.5 [55.5, 246.4]	75.0 [33.0, 129.6]	55.6 [33.0, 120.0]	150.0 [54.6, 252.5]	63.3 [33.0, 126.0]	45.3 [30.0, 104.2]
Vigorous intensity physical activity, min/week	30.0 [0.0, 120.0]	30.0 [0.0, 30.0]	30.0 [0.0, 30.0]	30.0 [0.0, 120.0]	30.0 [0.0, 30.0]	30.0 [0.0, 30.0]
GGT, IU/L	16.0 [13.0, 21.0]	19.0 [14.0, 25.0]	23.0 [17.0, 42.0]	17.0 [13.0, 21.0]	19.0 [14.0, 26.0]	25.5 [18.8, 48.5]
Smoking status, %						
Non-smoker	2173 (81.7)	222 (26.7)	10 (5.6)	2169 (81.2)	257 (31.9)	12 (6.1)
Ex-smoker	323 (12.1)	425 (51.0)	118 (65.9)	337 (12.6)	378 (47.0)	119 (60.7)
Current smoker	163 (6.1)	186 (22.3)	51 (28.5)	164 (6.1)	170 (21.1)	65 (33.2)
Drinking status, %						
Non-drinker	1308 (49.2)	273 (32.8)	43 (24.0)	1330 (49.8)	299 (37.1)	50 (25.5)
Ex-drinker	47 (1.8)	23 (2.8)	6 (3.4)	45 (1.7)	18 (2.2)	4 (2.0)
Current drinker	1300 (48.9)	536 (64.3)	130 (72.6)	1290 (48.3)	488 (60.6)	142 (72.4)
Unknown	4 (0.2)	1 (0.1)	0 (0.0)	5 (0.2)	0 (0.0)	0 (0.0)
Healthy lifestyle factors						
Non-obesity	2428 (91.3)	448 (53.8)	11 (6.1)	2419 (90.6)	413 (51.3)	11(5.6)
Non-smoker	2173 (81.7)	222 (26.7)	10 (5.6)	2169 (81.2)	257 (31.9)	12 (6.1)
Regular physical activity	1712 (64.4)	188 (22.6)	5 (2.8)	1781 (66.7)	169 (21.0)	11 (5.6)
GGT, $<$50.0	2655 (99.8)	808 (97.0)	138 (77.1)	2664 (99.8)	771 (95.8)	147 (75.)

Genetic risk	High			Overall
Lifestyle	Ideal	Intermediate	Poor	
Number	2645	841	186	11014
Age, years	59.4 (11.2)	57.9 (11.9)	57.1 (11.2)	59.1 (11.3)
Women, %	1990 (75.2)	434 (51.6)	62 (33.3)	7464 (67.8)
BMI, kg/m^2	22.2 (2.8)	24.6 (3.5)	27.6 (2.7)	22.9 (3.3)
Follow-up duration, years	4.3 (0.8)	4.3 (0.8)	4.3 (0.8)	4.3 (0.8)
Glucose, mg/dl	88.9 (13.7)	90.0 (13.2)	94.1 (14.6)	88.0 (11.9)
HbA1c, %	5.6 (0.4)	5.5 (0.3)	5.6 (0.3)	5.5 (0.3)
Family history of diabetes, %	355 (13.4)	109 (13.0)	29 (15.6)	1282 (11.6)
Physical activity				
Moderate-intensity physical activity, min/week	151.0 [55.5, 252.6]	62.1 [33.0, 129.6]	40.2 [30.0, 81.2]	123.2 [42.6, 229.3]
Vigorous intensity physical activity, min/week	30.0 [0.0, 120.0]	30.0 [0.0, 30.0]	30.0 [0.0, 30.0]	30.0 [0.0, 120.0]
GGT, IU/L	17.0 [14.0, 22.0]	20.0 [15.0, 27.0]	27.0 [18.0, 47.8]	17.0 [14.0, 23.0]
Smoking status, %				
Non-smoker	2140 (80.9)	271 (32.2)	12 (6.5)	7266 (66.0)
Ex-smoker	331 (12.5)	376 (44.7)	120 (64.5)	2527 (22.9)
Current smoker	174 (6.6)	194 (23.1)	54 (29.0)	1221 (11.1)
Drinking status, %				
Non-drinker	1283 (48.5)	291 (34.6)	40 (21.5)	4917 (44.6)
Ex-drinker	58 (2.2)	23 (2.7)	7 (3.8)	231 (2.1)
Current drinker	1300 (49.1)	526 (62.5)	139 (74.7)	5851 (53.1)
Unknown	4 (0.2)	0 (0.0)	0 (0.0)	15 (0.1)
Healthy lifestyle factors				
Non-obesity	2375 (89.8)	419 (49.8)	5 (2.7)	8529 (77.4)
Non-smoker	2140 (80.9)	271 (32.2)	12 (6.5)	7266 (66.0)
Regular physical activity	1794 (67.8)	190 (22.6)	9 (4.8)	5859 (53.2)
GGT, $<$50.0	2636 (99.7)	802 (95.4)	142 (76.3)	10763 (97.7)

BMI, body mass index; GGT, gamma-glutamyl transferase; METs, metabolic equivalents.
Non-obesity was defined as a BMI $<$25.0 kg/m^2 based on the Western Pacific Region of the WHO criteria for Japanese individuals; never-smokers, those who smoked $<$100 cigarettes during their lifetime; regular physical activity was defined as at least 150 or 75 min of moderate or vigorous activity per week, respectively; and "high GGT" was defined as GGT ≥50 IU/L based on a health examination. Overall lifestyle was categorized as ideal (having at least three ideal lifestyle factors), poor (having at least three poor lifestyle factors), or intermediate (all other combinations).

Table 2. Associations of Combined Lifestyle and Genetic Risks with Developing Diabetes

Genetic risk	Lifestyle	DM/number of participants	%	OR, 95% CI	
Low	Ideal (≤ 1 poor factors)	29/2659	(1.1)	Ref	
	Intermediate (2 poor factors)	26/833	(3.1)	2.73	(1.58–4.70)
	Poor (≥ 3 poor factors)	7/179	(3.9)	3.31	(1.30–7.37)
Intermediate	Ideal (≤ 1 poor factors)	53/2670	(2.0)	1.89	(1.20–3.01)
	Intermediate (2 poor factors)	30/805	(3.7)	3.35	(1.98–5.68)
	Poor (≥ 3 poor factors)	16/196	(8.2)	6.96	(3.58–13.12)
High	Ideal (≤ 1 poor factors)	79/2645	(3.0)	2.87	(1.89–4.47)
	Intermediate (2 poor factors)	36/841	(4.3)	3.94	(2.39–6.56)
	Poor (≥ 3 poor factors)	21/186	(11.3)	10.62	(5.77–19.28)

CI: confidence interval; DM: diabetes mellitus; OR: odds ratio.
Adjusted for the age, sex and first six principal components.
Diabetes: defined as non-fasting blood glucose ≥ 200 mg/dl and/or ≥ HbA1c 6.5% and/or self-reported treatment for diabetes.
Lifestyle was assessed using a healthy lifestyle score based on four diabetes risk factors: never smoking, non-obesity, regular physical activity, and low gamma glutamyl transferase (GGT). Obesity was defined as a body mass index (BMI) ≥ 25.0 kg/m^2. Non-smokers were defined as those who had smoked < 100 cigarettes in their lifetime. Regular physical activity was defined as at least 150 or 75 min of moderate or vigorous activity per week, respectively. A high GGT level was defined as a GGT ≥ 50 IU/L. Overall lifestyle was subsequently categorized as ideal (having at least three ideal lifestyle factors), poor (having at least three poor lifestyle factors), or intermediate (all other combinations). The PRS was categorized into the following cutoff points for tertiles: low, <-0.00005698764; intermediate, -0.00005698764 to -0.00002345474; and high, ≥ -0.00002345474.

Table 3. Associations of Family History and Genetic and Lifestyle Risks with Developing Diabetes

Family history	Genetic risk	Lifestyle	DM/number of participants	%	OR, 95% CI	
No	Low	Ideal (≤ 1 poor factors)	22/2385	(0.9)	Ref	
		Intermediate (2 poor factors)	24/764	(3.1)	3.19	(1.76–5.80)
		Poor (≥ 3 poor factors)	7/164	(4.3)	4.13	(1.59–9.50)
	Intermediate	Ideal (≤ 1 poor factors)	39/2351	(1.7)	1.85	(1.11–3.19)
		Intermediate (2 poor factors)	24/712	(3.4)	3.50	(1.94–6.37)
		Poor (≥ 3 poor factors)	13/177	(7.3)	7.06	(3.36–14.31)
	High	Ideal (≤ 1 poor factors)	56/2290	(2.4)	2.76	(1.70–4.63)
		Intermediate (2 poor factors)	29/732	(4.0)	4.24	(2.41–7.55)
		Poor (≥ 3 poor factors)	18/157	(11.5)	12.22	(6.24–23.65)
Yes	Low	Ideal (≤ 1 poor factors)	7/274	(2.6)	2.97	(1.16–6.70)
		Intermediate (2 poor factors)	2/69	(2.9)	3.37	(0.53–11.87)
		Poor (≥ 3 poor factors)	0/15	(0.0)	0.00	–
	Intermediate	Ideal (≤ 1 poor factors)	14/319	(4.4)	5.48	(2.70–10.75)
		Intermediate (2 poor factors)	6/93	(6.5)	7.94	(2.85–19.07)
		Poor (≥ 3 poor factors)	3/19	(15.8)	21.87	(4.76–73.89)
	High	Ideal (≤ 1 poor factors)	23/355	(6.5)	8.08	(4.43–14.77)
		Intermediate (2 poor factors)	7/109	(6.4)	7.65	(2.94–17.64)
		Poor (≥ 3 poor factors)	3/29	(10.3)	13.91	(3.11–44.65)

CI: confidence interval; DM: diabetes mellitus; OR: odds ratio.
Adjusted for the age, sex, and the first six principal components. The definitions are the same as those in Table 2.

lifestyle were independently associated with diabetes incidence[16-20]. However, Asians could have vulnerable beta cells, and a large-scale GWAS of the Japanese population detected genes related to pancreatic acinar cells and insulin secretion[9, 44]. Only three studies quantitatively evaluated the association between combined genetic and lifestyle risk in Asian populations[19-21], even though the frequency of genetic risk alleles and lifestyle risk factors differed between Asian and other populations[3, 45]. Our study revealed that genetic and lifestyle risks were independently associated with the risk of developing diabetes in the

Table 4. Area Under the Receiver Operating Characteristic Curve for Genetic and Lifestyle Risks to Predict Diabetes Incidence

	Area under the receiver operating characteristic curve (95% CI)
	Incidence of diabetes
Model 1[a]	0.632 (0.602–0.662)
Model 1 + PRS	0.662 (0.633–0.690)
Model 1 + lifestyle score	0.684 (0.656–0.713)
Model 1 + family history	0.652 (0.621–0.683)
Model 1 + PRS + lifestyle score	0.705 (0.678–0.732)
Model 1 + PRS + family history	0.677 (0.647–0.707)
Model 1 + lifestyle + family history	0.703 (0.674–0.732)
Model 1 + PRS + lifestyle + family history	0.719 (0.692–0.747)

CI: confidence interval; PRS: polygenic risk score.
[a]Model 1 included age, sex, and the first six principal components as predictive variables.
Diabetes: defined as non-fasting blood glucose ≥ 200 mg/dl and/or ≥ HbA1c 6.5% and/or self-reported treatment for diabetes.

Japanese population, which was consistent with previous observations in European, US, and Chinese populations[16-20]. These replication findings from a large, general Japanese population cohort confirmed that public health approaches that focused on lifestyle changes were effective in preventing diabetes, even without genetic information. Therefore, our findings provide strong evidence that adherence to a healthy lifestyle is beneficial for preventing diabetes, regardless of an individual's genetic risk profile. Conversely, even among participants with an ideal lifestyle, those with a high genetic risk had a significantly higher risk of developing diabetes than participants with an ideal lifestyle and low genetic risk. The mechanisms that link diabetes incidence to individuals with a high genetic risk, except for an ideal lifestyle, remain unclear. Future studies should clarify the mechanism of diabetes development and develop effective interventions for those who have a high genetic risk and an ideal lifestyle. These individuals may require more frequent screening to prevent diabetes and may benefit from early intervention.

A family history of diabetes is commonly used as a standard indirect measure of inherited susceptibility in clinical settings. If the predictive ability, considering the family history and lifestyle, is not different from that with the addition of the PRS, genetic information could be unnecessary for risk stratification from cost and usability perspectives. However, recent studies suggest that the family history and PRS are largely independent and provide complementary information[46, 47]. Furthermore, a previous cross-sectional TMM CommCohort study observed that the PRS, lifestyle risk, and family history were independently associated with the prevalence of diabetes. The incorporation of the PRS achieved a significantly higher AUROC for the prevalence of diabetes than models with only lifestyle factors and the family history according to a previous study[21]. However, that study was a cross-sectional one, so the lifestyle and family history may have been influenced by reverse causation. In the Framingham Offspring Study, genetic risk that included only 18 loci predicted diabetes onset better than traditional risk factors, which included the family history[48]. The Health Professionals Follow-up Study and Nurses' Health Study showed that genetic risk that included only 10 polymorphisms modestly improved the prediction of diabetes incidence when considered in addition to lifestyle factors and the family history[49].

However, recent studies have demonstrated that the combination of more SNPs improved risk prediction for common diseases, such as diabetes, over clinical risk scores, regardless of statistical significance[50, 51]. We used a PRS that included more than 60,000 SNPs, which provided a better understanding of its role in the lifestyle and family history with diabetes incidence. Our study showed that the PRS, lifestyle, and family history were independently associated with the risk of diabetes. Predictive ability improved when the PRS was incorporated into the models with lifestyle and family history, which is consistent with previous studies[21, 48, 49]. This finding suggests that the addition of the PRS to the lifestyle and family history could be useful for identifying high-risk patients. Even among individuals with an ideal lifestyle, a high PRS increases the risk of developing diabetes. Therefore, understanding one's genetic risk is essential for early intervention and treatment.

The strength of this study is its longitudinal population-based design. To our knowledge, this is the first study to provide a quantitative estimate of the association of a combined family history and genetic

and lifestyle risks with diabetes development in the general population.

However, this study also had several limitations. First, it included participants who voluntarily participated in the baseline and secondary surveys, which may have caused volunteer bias. In fact, the study population was relatively old, had a low BMI, and had a high rate of adherence to a healthy lifestyle. Therefore, the results may not be generalizable to other populations. Second, lifestyle scores were constructed based on lifestyle factors collected in the baseline survey. Therefore, it may not necessarily reflect long-term lifestyle exposure or behavioral changes before and after other diseases that affect risk estimates. Third, the study population included only Japanese participants. The frequency and effect of risk alleles and prevalence of diabetes risk factors may differ between the Japanese and other ethnicities[3, 45, 52]. Thus, future studies should examine other ethnic populations to confirm the generalizability of our findings. Finally, our study showed that the association between a family history of diabetes and the risk of diabetes is not completely explained by the PRS and lifestyle scores. Although more than 60,000 SNPs were included in our PRS, this only explained a small proportion of the heritability of diabetes. Additional variants associated with diabetes should be identified in future whole-exome and whole-genome sequencing studies. These variants may improve the genetic risk performance. Fourth, we only used casual blood glucose information. Thus, we may have overlooked participants with diabetes based on their fasting blood glucose levels. Fifth, we analyzed 18 groups combining the PRS, lifestyle, and family history, but the number of events for some groups was too small to estimate the risk. We conducted a repeat assessment center-based survey during the third period; thus, we plan to clarify this relationship through long-term repeated follow-up data.

In conclusion, adherence to a healthy lifestyle and the PRS were independently associated with the incidence of diabetes in a large Japanese cohort. Furthermore, the incorporation of the PRS achieved a significantly higher predictive ability than that of the model with only lifestyle factors and a family history. Therefore, our study supports the assumption that adherence to a healthy lifestyle is important for diabetes prevention, regardless of an individual's genetic profile. In addition, genetic risk can provide information beyond lifestyle factors and the family history to stratify high-risk individuals.

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Conflict of Interest

None.

Data Availability

M.T. had full access to all data in the study and was responsible for the integrity of the data and accuracy of the data analyses.

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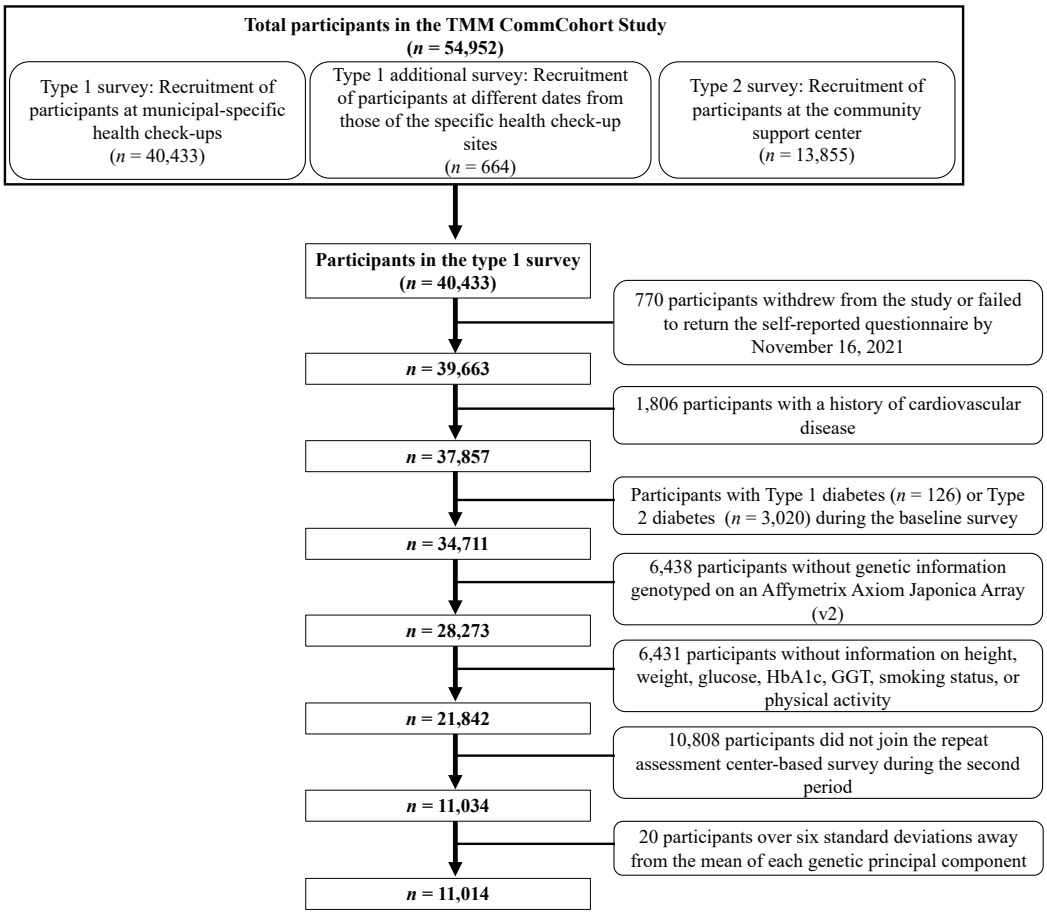

Supplemental Fig. 1.

Supplemental Table 1. *P*-value Threshold and Related Parameters on the PRS Construction

Traits	P-threshold	Number of SNPs	R^2
HbA1c	5.0×10^{-8}	124	0.019830
	0.001	2241	0.019986
	0.01	8853	0.017137
	0.05	25984	0.017594
	0.1	41717	0.016680
	0.2	66950	0.015078
	0.3	88095	0.014995
	0.4	106330	0.014434
	0.5	121934	0.014447

Note: R^2 shows that a variance of HbA1c is explained by the PRS.
In this population, the PRS constructed with $p < 0.001$ is the best-fit PRS for HbA1c levels. However, a previous study reported that PRS with $p < 0.2$ was the best fit for HbA1c; thus, we used PRS with $p < 0.2$ to avoid overfitting.

Supplemental Table 2. The number of participants and proportion of high GGT according to obesity and drinking status

Obesity status	Drinking status	High GGT levels/number of participants	(%)
Non-obesity	Never-drinker	33/3849	(0.9)
	Ex-drinker	0/188	(0.0)
	Current drinker	66/4482	(1.5)
	Unknown	0/10	(0.0)
Obesity	Never-drinker	67/1068	(6.3)
	Ex-drinker	4/43	(9.3)
	Current drinker	81/1369	(5.9)
	Unknown	0/5	(0.0)

Note: BMI: body mass index, GGT: Gamma-glutamyl transferase,Non-obesity: BMI <25.0 kg/m^2 based on the Western Pacific Region of WHO criteria for Japanese individuals.
High GGT was defined as GGT ≥ 50 IU/L based on health examination in Japan.

Supplemental Table 3. Comparison of Participants Included with Those not Included in the TMM Common Cohort Study

	Included	Not included
Number	11014	10828
Age, years	59.1 (11.3)	56.9 (12.7)
Women, %	7464 (67.8)	6878 (63.5)
BMI, kg/m^2	22.9 (3.3)	23.1 (3.5)
Glucose, mg/dl	88.0 (11.9)	88.7 (12.8)
HbA1c, %	5.5 (0.3)	5.5 (0.3)
Family history of diabetes, %	1282 (11.6)	974 (9.0)
Physical activity		
Moderate-intensity physical activity, min/week	30.0 [0.0, 120.0]	30.0 [6.0, 120.0]
Vigorous intensity physical activity, min/week	129.6 [51.3, 240.0]	126.4 [48.2, 241.0]
GGT, IU/L	17.0 [14.0, 23.0]	18.0 [14.0, 24.0]
Smoking status, %		
Non-smoker	7266 (66.0)	6570 (60.7)
Ex-smoker	2527 (22.9)	2319 (21.4)
Current smoker	1221 (11.1)	1939 (17.9)
Drinking status, %		
Non-drinker	4917 (44.6)	4913 (45.4)
Ex-drinker	231 (2.1)	291 (2.7)
Current drinker	5851 (53.1)	5595 (51.7)
Unknown	15 (0.1)	29 (0.3)
Healthy lifestyle factors		
Non-obesity	8529 (77.4)	2847 (73.7)
Non-smoker	7266 (66.0)	6570 (60.7)
Regular physical activity	5859 (53.2)	5981 (55.2)
GGT, <50.0	10763 (97.7)	10433 (96.4)

Note: BMI: body mass index, GGT: Gamma-glutamyl transferase, METs: metabolic equivalents, Diabetes: defined as non-fasting glucose ≥ 200 mg/dl, HbA1c ≥ 6.5 and/or self-reported treatment for diabetes.
Non-obesity: BMI <25.0 kg/m^2 based on the Western Pacific Region of WHO criteria for Japanese individuals.
Never-smokers: those who smoked <100 cigarettes during their lifetime.
Regular physical activity: defined as at least 150 and 75 minutes of moderate and vigorous activity per week, respectively.
High GGT was defined as GGT ≥ 50 IU/L based on health examination in Japan.
Overall lifestyle was subsequently categorized as ideal (having at least three ideal lifestyle factors), poor (having at least three poor lifestyle factors), or intermediate (all other combinations).

Supplemental Table 4. Associations of Family History and Genetic and Lifestyle Risks with Diabetes among Men

Family history	Genetic risk	Lifestyle	DM/number of participants	%	OR, 95%CI	
No	Low	Ideal (≤ 1 poor factors)	11/593	(1.9)	Ref	
		Intermediate (2 poor factors)	18/405	(4.4)	2.53	(1.20-5.60)
		Poor (≥ 3 poor factors)	5/126	(4.0)	2.28	(0.71-6.40)
	Intermediate	Ideal (≤ 1 poor factors)	11/573	(1.9)	1.05	(0.45-2.47)
		Intermediate (2 poor factors)	11/363	(3.0)	1.69	(0.72-4.00)
		Poor (≥ 3 poor factors)	6/132	(4.5)	2.58	(0.87-6.93)
	High	Ideal (≤ 1 poor factors)	29/585	(5.0)	2.85	(1.45-6.02)
		Intermediate (2 poor factors)	15/359	(4.2)	2.41	(1.10-5.45)
		Poor (≥ 3 poor factors)	13/106	(12.3)	7.57	(3.28-17.78)
Yes	Low	Ideal (≤ 1 poor factors)	2/49	(4.1)	2.25	(0.34-8.75)
		Intermediate (2 poor factors)	2/25	(8.0)	4.93	(0.73-19.96)
		Poor (≥ 3 poor factors)	0/6	(0.0)	-	-
	Intermediate	Ideal (≤ 1 poor factors)	4/55	(7.3)	4.36	(1.17-13.34)
		Intermediate (2 poor factors)	4/26	(15.4)	9.87	(2.57-31.69)
		Poor (≥ 3 poor factors)	3/11	(27.3)	21.73	(4.26-89.65)
	High	Ideal (≤ 1 poor factors)	9/70	(12.9)	8.26	(3.21-20.81)
		Intermediate (2 poor factors)	4/48	(8.3)	5.20	(1.39-16.04)
		Poor (≥ 3 poor factors)	1/18	(5.6)	3.51	(0.19-19.99)

Note: CI: confidence interval; DM: diabetes mellitus; OR: odds ratio.
Adjusted for age, sex and first six principal components. Definitions same as in Table 2.

Supplemental Table 5. Associations of Family History and Genetic and Lifestyle Risks with Diabetes among Women

Family history	Genetic risk	Lifestyle	DM/number of participants	%	OR, 95%CI	
No	Low	Ideal (≤ 1 poor factors)	11/1792	(0.6)	Ref	
		Intermediate (2 poor factors)	6/359	(1.7)	3.13	(1.76-5.57)
		Poor (≥ 3 poor factors)	2/38	(5.3)	3.90	(1.52-8.87)
	Intermediate	Ideal (≤ 1 poor factors)	28/1778	(1.6)	1.96	(1.20-3.27)
		Intermediate (2 poor factors)	13/349	(3.7)	3.68	(2.10-6.50)
		Poor (≥ 3 poor factors)	7/45	(15.6)	7.31	(3.58-14.43)
	High	Ideal (≤ 1 poor factors)	27/1705	(1.6)	3.20	(2.04-5.21)
		Intermediate (2 poor factors)	14/373	(3.8)	4.43	(2.59-7.66)
		Poor (≥ 3 poor factors)	5/51	(9.8)	11.89	(6.21-22.49)
Yes	Low	Ideal (≤ 1 poor factors)	5/225	(2.2)	5.30	(1.75-13.15)
		Intermediate (2 poor factors)	0/44	(0.0)	-	-
		Poor (≥ 3 poor factors)	0/9	(0.0)	-	-
	Intermediate	Ideal (≤ 1 poor factors)	10/264	(3.8)	6.83	(2.81-14.96)
		Intermediate (2 poor factors)	2/67	(3.0)	8.04	(1.85-24.47)
		Poor (≥ 3 poor factors)	0/8	(0.0)	-	-
	High	Ideal (≤ 1 poor factors)	14/285	(4.9)	5.62	(2.20-12.67)
		Intermediate (2 poor factors)	3/61	(4.9)	7.30	(1.67-22.32)
		Poor (≥ 3 poor factors)	2/11	(18.2)	19.06	(2.82-77.22)

Note: CI: confidence interval; DM: diabetes mellitus; OR: odds ratio.
Adjusted for age, sex and first six principal components. Definitions same as in Table 2.

Supplemental Table 6. Associations of Family History of the biological father and Genetic and Lifestyle Risks with Diabetes

Family history	Genetic risk	Lifestyle	DM/number of participants	%	OR, 95%CI	
No	Low	Ideal (≤ 1 poor factors)	28/2539	(1.1)	Ref	
		Intermediate (2 poor factors)	25/803	(3.1)	2.69	(1.54-4.67)
		Poor (≥ 3 poor factors)	7/170	(4.1)	3.44	(1.35-7.70)
	Intermediate	Ideal (≤ 1 poor factors)	49/2537	(1.9)	1.81	(1.14-2.93)
		Intermediate (2 poor factors)	28/768	(3.6)	3.23	(1.89-5.55)
		Poor (≥ 3 poor factors)	16/190	(8.4)	7.11	(3.64-13.47)
	High	Ideal (≤ 1 poor factors)	68/2507	(2.7)	2.56	(1.66-4.05)
		Intermediate (2 poor factors)	33/784	(4.2)	3.80	(2.27-6.41)
		Poor (≥ 3 poor factors)	20/173	(11.6)	10.63	(5.69-19.54)
Yes	Low	Ideal (≤ 1 poor factors)	1/120	(0.8)	0.86	(0.05-4.11)
		Intermediate (2 poor factors)	1/30	(3.3)	3.65	(0.20-18.33)
		Poor (≥ 3 poor factors)	0/9	(0.0)	-	-
	Intermediate	Ideal (≤ 1 poor factors)	4/133	(3.0)	3.43	(1.00-8.97)
		Intermediate (2 poor factors)	2/37	(5.4)	5.92	(0.93-21.14)
		Poor (≥ 3 poor factors)	0/6	(0.0)	-	-
	High	Ideal (≤ 1 poor factors)	11/138	(8.0)	9.47	(4.40-19.08)
		Intermediate (2 poor factors)	3/57	(5.3)	6.16	(1.43-18.36)
		Poor (≥ 3 poor factors)	1/13	(7.7)	9.97	(0.53-55.43)

Note: CI: confidence interval; DM: diabetes mellitus; OR: odds ratio.
Adjusted for age, sex and first six principal components. Definitions same as in Table 2.

Supplemental Table 7. Associations of Family History of the biological mother and Genetic and Lifestyle Risks with Diabetes

Family history	Genetic risk	Lifestyle	DM/number of participants	%	OR, 95%CI	
No	Low	Ideal (≤ 1 poor factors)	24/2551	(0.9)	Ref	
		Intermediate (2 poor factors)	25/808	(3.1)	3.13	(1.76-5.57)
		Poor (≥ 3 poor factors)	7/174	(4.0)	3.90	(1.52-8.87)
	Intermediate	Ideal (≤ 1 poor factors)	45/2530	(1.8)	1.96	(1.20-3.27)
		Intermediate (2 poor factors)	27/762	(3.5)	3.68	(2.10-6.50)
		Poor (≥ 3 poor factors)	14/185	(7.6)	7.31	(3.58-14.43)
	High	Ideal (≤ 1 poor factors)	72/2496	(2.9)	3.20	(2.04-5.21)
		Intermediate (2 poor factors)	33/798	(4.1)	4.43	(2.59-7.66)
		Poor (≥ 3 poor factors)	19/172	(11.0)	11.89	(6.21-22.49)
Yes	Low	Ideal (≤ 1 poor factors)	5/108	(4.6)	5.30	(1.75-13.15)
		Intermediate (2 poor factors)	1/25	(4.0)	4.56	(0.25-23.44)
		Poor (≥ 3 poor factors)	0/5	(0.0)	-	-
	Intermediate	Ideal (≤ 1 poor factors)	8/140	(5.7)	6.83	(2.81-14.96)
		Intermediate (2 poor factors)	3/43	(7.0)	8.04	(1.85-24.47)
		Poor (≥ 3 poor factors)	2/11	(18.2)	27.26	(3.93-117.63)
	High	Ideal (≤ 1 poor factors)	7/149	(4.7)	5.62	(2.20-12.67)
		Intermediate (2 poor factors)	3/43	(7.0)	7.30	(1.67-22.32)
		Poor (≥ 3 poor factors)	2/14	(14.3)	19.06	(2.82-77.22)

Note: CI: confidence interval; DM: diabetes mellitus; OR: odds ratio.
Adjusted for age, sex and first six principal components. Definitions same as in Table 2.