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ORIGINAL ARTICLE

FTO-rs9939609 Polymorphism is a Predictor of Future Type 2 Diabetes: A Population-Based Prospective Study

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Abstract

The study aimed to evaluate the contribution of the *FTO* A/T polymorphism (*rs9939609*) to the prediction of the future type 2 diabetes (T2D). A population-based prospective study included 1443 nondiabetic subjects at baseline, and they were examined for developing T2D after 5-year follow-up. Cox proportional hazards model was used to evaluate the hazard ratio (HR) of *rs9939609* to the future T2D in the models adjusted for the confounding factors including socio-economic status, lifestyle factors (smoking and drinking history, sporting habits, and leisure time), and clinical patterns (obese status, blood pressures, and dyslipidemia) at baseline. The area under receiver operating characteristic curve (AUC) was used to measure the power to predict individuals with T2D. The *FTO-rs9939609* polymorphism was a significant predictor of future T2D in the model unadjusted, and it remained significant in the final model after adjustment for the confounding factors, showing an additive effect of the A-allele (HR = 1.35, 95% CI = 1.02–1.78, $P = 0.036$, AUC = 0.676). For normoglycemic subjects at baseline, the similar final adjusted model reported the increased HR per A-allele (HR = 1.50, 95% CI = 1.09–2.07, $P = 0.012$, AUC = 0.697). Five-year changes in BMI, waist circumference, and systolic blood pressure did not remove the contribution of *rs9939609* to increased HR of T2D. The population attributable risk for risk genotype was 13.6%. In conclusion, the study indicates that the *FTO*-rs9939609 polymorphism is an important genetic predictor for future T2D in Vietnamese population.

Keywords Prediction · Hazard ratio · Population attributable risk · Type 2 diabetes · *FTO* gene · Vietnamese population

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Abbreviations

T2D	Type 2 diabetes
FTO	Fat mass and obesity associated
BMI	Body mass index
OR	Odd ratio
RR	Relative ratio
HR	Hazard ratio
FPG	Fasting plasma glucose test
OGTT	Oral glucose tolerance test
WC	Waist circumference
HC	Hip circumference
WHR	Waist–hip ratio
BF	Body fat
SBP	Systolic blood pressure
DBP	Diastolic blood pressure
HDL–C	High-density lipoprotein–cholesterol
TC	Total cholesterol
LDL-C	Low-density lipoprotein
TG	Triglyceride
DNA	Deoxyribonucleic acid
bp	Base pair
SNP	Single-nucleotide polymorphism
ASP	Allele-specific primer
RFLP	Restriction fragment length polymorphism
PCR	Polymerase chain reaction
HWE	Hardy–Weinberg equilibrium
ROC	Receiver operating characteristic
AUC	The area under ROC curve
PAR	Population attributable risk
IQR	Interquartile range
TV	Television

Introduction

Type 2 diabetes (T2D) is a global pandemic and became one of the major threatens to human health in the twenty-first century (Unnikrishnan et al. 2017). The global diabetes prevalence among adults aged 20–79 years is estimated to be 9.3% in 2019, rising to 10.2% by 2030. One in two people living with diabetes do not know that they have diabetes (Saeedi et al. 2019). Of note, the onset of the disease can be postponed or is partially preventable by changes in the lifestyles of high-risk subjects (Tuomilehto et al. 2001). Detection of individuals with high T2D risk and personalized prediction of future T2D are important for early intervention and to avoid chronic complications associated with the disease.

Genetic factors play a crucial role in the pathogenesis of T2D, together with lifestyle factors. Genome-wide association studies on T2D carried out in

large-scale case–control cohorts have found novel genes with modest effect for T2D (Saxena et al. 2012; Palmer et al. 2012; Li et al. 2013). The common T > A polymorphism (*rs9939609*) in the fat mass and obesity-associated (*FTO*) gene was firstly reported to be significantly associated with T2D through body mass index (BMI) mediation in European populations (Dina et al. 2007; Frayling et al. 2007). To date, there has been an inconsistent association between the *FTO*-rs9939609 polymorphism and T2D in meta-analyses performed in Asian populations (Xi et al. 2009; Liu et al. 2010; Li et al. 2012; Phani et al. 2016). These results may be explained partly by the study design and the differences in socio-economic status, lifestyle factor, clinical pattern, and genetic background (Adeyemo et al. 2010). These factors need to be considered when investigating the contribution of the polymorphism with T2D (Weber et al. 2012).

The *FTO*-rs9939609 polymorphism has been paid a great attention to investigate the genetic marker for developing T2D. Recent meta-analysis of 62 case–control studies in multiple populations showed the OR = 1.11 (95% CI = 1.05–1.17) per A-allele after adjustment of BMI (Yang et al. 2017). It has been accepted widely that the polymorphism has moderate effect on T2D. However, most of findings express as ORs of T2D, which result from the cross-sectional and case–control studies (Frayling et al. 2007; Liu et al. 2010; Li et al. 2012; Li et al. 2013; Phani et al. 2016; Yang et al. 2017). So far, there have been rare reports with relative risk (RR) or HR of T2D from population-based prospective studies. Our previous study reported that the *FTO*-rs9939609 polymorphism was significantly associated with type 2 diabetes, independent of obesity-related traits in Vietnamese population (Binh et al. 2013). However, this study was limited by its cross-sectional nature, and this does not allow for the prediction for future T2D. Therefore, we have designed a population-based prospective study involving subjects without T2D at baseline and checking for incident T2D after 5-year follow-up to investigate whether the common *FTO*-rs9939609 polymorphism is a predictor of future T2D, considering the confounding factors including socio-economic status, lifestyle factors, and clinical patterns.

Materials and Methods

Study Design

This study was the main part of the DiaMetS-VN population-based prospective study that has been conducted since 2011, in Ha Nam province located in the Red River Delta, Vietnam. The study was composed of 1443 subjects without T2D at baseline (1221 normoglycemic subjects and 222 subjects with prediabetes), and they then were examined for having T2D after 5-year follow-up, using fasting plasma glucose (FPG) and 2-h plasma glucose by oral glucose tolerance test (OGTT). The baseline characteristics of the population were reported previously (Binh et al. 2012). The Ethics Committee of the National Institute of Hygiene and

Epidemiology, Vietnam, approved the study protocol (IRB-VN01057-34/2016). All participants provided written informed consent before entering the study.

Data Collection

All participants were directly interviewed to collect data on socio-economic status and lifestyle factors using a structured questionnaire (Binh et al. 2012). Socio-economic status included age, gender, residence, educational level, occupation, marital status, and income level. Lifestyle factors were comprised of smoking and drinking history, sporting habits, leisure time spent sitting, watching TV, and sleeping. Clinical patterns were characterized by obesity-related traits [BMI, waist circumference (WC), hip circumference (HC), waist-to-hip ratio (WHR), and body fat (BF)], systolic blood pressure (SBP), diastolic blood pressure (DBP), and dyslipidemia.

Serum glucose and lipid profile were measured using laboratory methods as reported previously (Binh et al. 2012). The glycemic status of subjects was determined using FPG and OGTT tests. A subject is classified as having T2D if FPG $\geq$ 7.0 mmol/L or 2 h OGTT $\geq$ 11.1 mmol/L or with previous diagnosis of T2D and current use of drug for its treatment (WHO 2006). Normoglycemic level is classified when FPG level $<$ 5.6 mmol/L and OGTT $<$ 7.8 mmol/L. Dyslipidemia is defined as high-density lipoprotein (HDL-C) $<$ 40 mg/dL for men and $<$ 50 mg/dL for women, and total cholesterol (TC), low-density lipoprotein (LDL-C) and triglyceride (TG) levels $\geq$ 200, $\geq$ 130 , and $\geq$ 150 mg/dL, respectively (NCEP ATPIII 2001).

Genetic Analysis

Genomic DNA was extracted from peripheral blood leukocytes, using Wizard® Genomic DNA Purification Kit (Promega Corporation, USA). All samples were typing for *FTO*-rs9939609 polymorphism using the previous method (Binh et al. 2012). In summary, the typing strategy was to use the allele-specific primer (ASP) typing method, and then 10% of all samples were typed using restriction fragment length polymorphism (RFLP) analysis to validate observed results. There was full concordance of the result between ASP typing method and RFLP analysis among the samples checked.

Statistical Analysis

Quantitative variables were checked for normal distribution and compared using One-Way ANOVA or Kruskal–Wallis test when appropriate. An additive model of inheritance was used with coded genotypes as 0, 1, and 2, depending on the number of copies of the A risk allele. Genotype distribution was tested for Hardy–Weinberg equilibrium (HWE) by Chi-square test. Exposure time was calculated as the duration between the baseline and follow-up surveys for subjects without developing diabetes and the mid-interval was used for subjects with newly diagnosed diabetes. Cox proportional hazards model was used to estimate the hazard ratio (HR) of developing T2D according to the *FTO*-rs9939609 polymorphism, taking into account

socio-economic status (age, gender, residence, marital status, education level, occupation, and income level), lifestyle factors (alcohol consumption, sweet drinks, smoking, sporting habit, time spending for night's sleep, siesta, leisure sitting, and watching TV), and clinical patterns (obesity-related traits (BMI, WC, HC, WHR, and BF), blood pressures, and dyslipidemia) at baseline. In second step, the changes over time in BMI (ΔBMI), WC (ΔWC), and SBP (ΔSBP) were included as additional cofactors. A receiver operating characteristic (ROC) curve was used to calculate probabilities resulting from the models, and the area under ROC curve (AUC) was used to measure the power to predict individuals with T2D (Kamarudin et al. 2017). The population attributable risk (PAR) was calculated based on prospective studies:

$$PAR = \frac{p_e(HR-1)}{p_e(HR-1)+1},$$

where p_e is the rate of the risk genotypes (AA and AT) in general population, and the HR (hazard ratio from adjusted model) is the estimated relative risk of T2D in individuals with the risk genotypes (AA and AT) relative to the referent group (TT). Statistical significance was considered when P value under 0.05 for all analyses. Data were analyzed with SPSS version 16.0 (SPSS, Chicago, USA) and R version 3.5.3 with packages survival and clinfun.

Results

Characteristics of the Subjects

Table 1 shows the characteristics of subjects according to the *FTO* genotypes at baseline. The AA genotype carriers had higher values of obesity-related traits

Table 1 Characteristics of the studied subjects according to the *FTO* genotypes at baseline

Variables	Total ($n=1443$)	TT ($n=953$)	AT ($n=431$)	AA ($n=59$)	P value
Age (year)	51 (46–57)	51 (46–57)	51.0 (46–56)	51.3 (46–57)	0.968
Follow-up year	5.17 (5.13–5.21)	5.17 (5.14–5.21)	5.17 (5.13–5.20)	5.17 (5.13–5.20)	0.328
Height (cm)	155.7 ± 6.9	155.8 ± 6.9	155.5 ± 6.8	156.3 ± 7.2	0.618
Weight (kg)	52.7 ± 7.8	51.7 ± 7.7	52.3 ± 7.9	54.6 ± 6.8	0.012
BMI (kg/m^2)	21.4 ± 2.5	21.3 ± 2.5	21.6 ± 2.6	22.4 ± 2.5	0.001
WC (cm)	74 (69–80)	73.5 (69–79.4)	74 (69–80)	76.5 (73–80.5)	0.006
HC (cm)	88 (84.5–92)	88.0 (91.1–84)	88 (84.5–92)	90 (86.5–93)	0.025
WHR	0.84 (0.80–0.88)	0.84 (0.80–0.88)	0.84 (0.80–0.89)	0.85 (0.82–0.90)	0.037
Body fat (%)	27.6 (23.6–31.6)	27.4 (23.4–31.4)	28.2 (24.–32.0)	29.1 (22.7–32.1)	0.174
SBP (mmHg)	115 (100–130)	115 (100–130)	115 (102.5–130)	110 (107.5–130)	0.940
DBP (mmHg)	70 (65–80)	70 (65–80)	70 (65–80)	70 (69–80)	0.917

Data expressed as median (interquartile range) except for height, weight, and BMI (mean ± standard deviation). P values from ANOVA or Kruskal–Wallis Test

BMI body mass index; *WC* waist circumference; *HC* hip circumference; *WHR* waist-to-hip ratio, *SBP* systolic blood pressure; *DBP* diatolic blood pressure

(weight, BMI, WC, HC, and WHR) than the others with TT or AT genotypes. There were no significant differences among the three genotypes in age, follow-up duration, height, BF, SBP, and DBP.

Table 2 presents the distribution of the *FTO*-rs9939609 genotypes in subjects with or without T2D at follow-up. The frequencies of AT and AA genotypes were significantly higher in diabetic group compared with nondiabetic group ($P=0.032$). Based on this table, the minor A-allele frequency was 18.8% in the total subjects, 24.8% in diabetic group, and 18.1% in nondiabetic group. The observed genotype frequencies in total samples, diabetic, and nondiabetic groups were in Hardy–Weinberg equilibrium ($P=0.129$, $P=0.392$, and $P=0.119$, respectively).

FTO-rs9939609 Polymorphism as Predictor of Future Type 2 Diabetes

Table 3 shows the contribution of the *FTO*-rs9939609 polymorphism in predicting T2D after 5-year follow-up. For subjects without T2D at baseline, the *FTO*-rs9939609 polymorphism was found to be a significant predictor of future T2D in the model unadjusted (HR per A-allele = 1.42, 95% CI = 1.08–1.84, $P=0.011$), and it remained consistently replicated in the final model (Model 4) after adjustments for socio-economic status, lifestyle factors, and clinical patterns, indicating an increased T2D risk with an additive effect of the A-allele (HR = 1.35, 95% CI = 1.02–1.78, $P=0.036$, AUC = 0.676). Adding the *FTO* polymorphism variable in the final model improved the AUC slightly (from 0.673 to 0.676). For normoglycemic subjects, the final similar model adjusted reported the increased risk for A-allele copy number (HR = 1.50, 95% CI = 1.09–2.07, $P=0.012$, AUC = 0.697). Replacing BMI by one of the obesity-related traits (WC, HC, WHR, and BF) in Model 4 gave similar results (data not shown). As shown in Model 5, the changes over time in BMI (median = 0.21, IQR = − 0.37–1.34 kg/m^2), WC (median = 4.5, IQR = 0–8.5 cm), and SBP (median = 10, IQR = 0–21.5 mmHg) did not remove the contribution of the *FTO* polymorphism to future T2D.

To investigate the incident T2D events occurring over time, we analyzed time-to-event curves using Cox proportional hazards regression in Model 4. Figure 1 shows the cumulative hazard curve of three genotypes for new-onset T2D during

Table 2 Genotype distribution in the studied subjects with or without diabetes at follow-up

Genotype	Total sample ($n=1443$)	Diabetic group ($n=139$)	Nondiabetic group ($n=1304$)	*P* value*
TT	953 (66.0)	78 (56.1)	875 (67.1)	
AT	431 (29.9)	53 (38.1)	378 (29.0)	0.032
AA	59 (4.1)	8 (5.8)	51 (3.9)	
P value for Hardy–Weinberg equilibrium	0.129	0.392	0.119	

Data expressed as number (%). *P* values by Chi-square test

**P*-value for comparing the distribution of three genotypes (TT, AT, and AA) between diabetic and nondiabetic groups

Table 3 Analysis of the contribution of the *FTO*-rs9939609 polymorphism as a predictor of future type 2 diabetes

Prediction model	Nondiabetic subjects ($n=1443$)			AUC (se)	Normoglycemic subjects ($n=1221$)[a]			AUC (se)
	Beta (se)	HR (95% CI)	*P* value		Beta (se)	HR (95% CI)	*P* value	
Model 1	0.347 (0.136)	1.42 (1.08–1.85)	0.011	0.545 (0.017)	0.422 (0.155)	1.53 (1.13–2.07)	0.006	0.555 (0.019)
Model 2	0.345 (0.138)	1.41 (1.08–1.85)	0.012	0.616 (0.020)	0.415 (0.157)	1.51 (1.11–2.06)	0.008	0.626 (0.023)
Model 3	0.333 (0.141)	1.39 (1.06–1.84)	0.018	0.651 (0.018)	0.408 (0.161)	1.50 (1.10–2.06)	0.011	0.670 (0.021)
Model 4	0.297 (0.142)	1.35 (1.02–1.78)	0.036	0.676 (0.016)	0.408 (0.162)	1.50 (1.09–2.07)	0.012	0.697 (0.019)
Model 5	0.289 (0.142)	1.33 (1.01–1.76)	0.042	0.677 (0.016)	0.397 (0.163)	1.49 (1.08–2.05)	0.015	0.670 (0.019)

HR hazard ratio; *CI* confidence interval; AUC the area under receiver operating characteristic curve

[a]Normoglycemic subjects were selected from 1443 nondiabetic subjects

Model 1: unadjusted

Model 2: Model 1 adjusted for socioeconomic status at baseline (age, gender, residence, marital status, education level, occupation, and income level)

Model 3: Model 2 adjusted for lifestyle at baseline (alcohol consumption, sweet drinks, smoking, sporting habit, time spending for night's sleep, siesta, leisure sitting, and watching TV)

Model 4: Model 3 adjusted for clinical patterns at baseline (body mass index, systolic blood pressure, diastolic blood pressure, and dyslipidemia)

Model 5: Model 4 adjusted for the changes over time of body mass index and systolic blood pressure

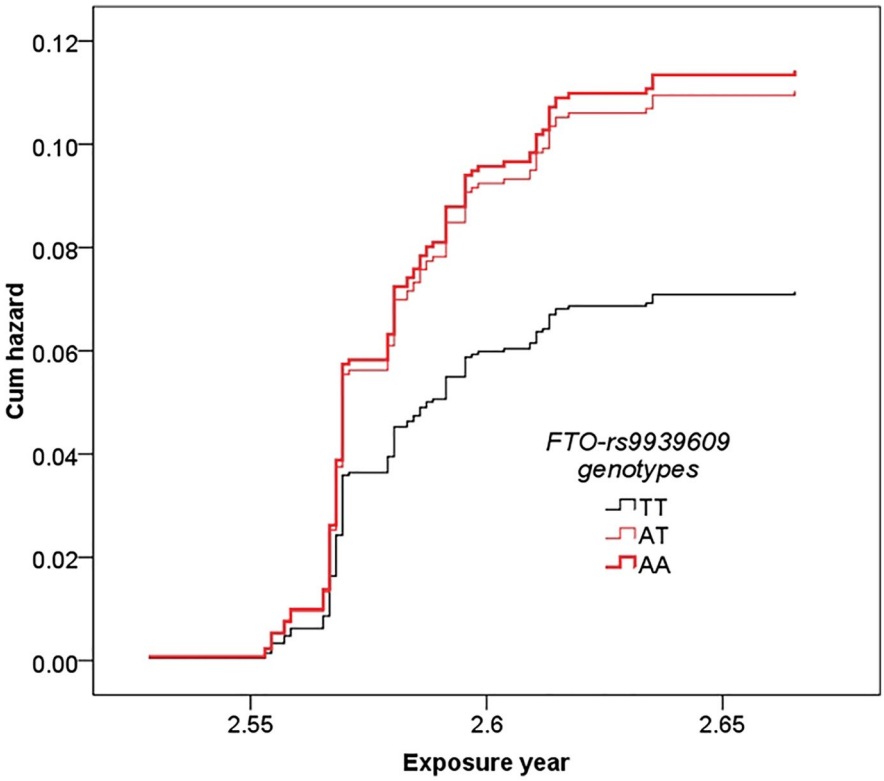

Fig. 1 Cumulative hazard curve of 3 *FTO*-rs9939609 genotypes for new-onset T2D events during the exposure times

the exposure times. The cumulative hazard was significantly lower in TT genotype group compared with AA or AT groups ($P = 0.036$).

Based on a fully adjusted hazard ratio (AA + AT *vs.* TT) of 1.49 and a risk genotype (AA + AT) frequency of 0.32 in general population (1000 Genome Project), the PAR percentage associated with the risk genotypes was 13.6% (95% CI = 1.6–25.9%).

Discussion

It is well known that the predictive ability of risk models is preferably investigated in prospective cohort studies. To the best of our knowledge, this is the first population-based prospective study in Asia reporting the HR and PAR of the *FTO*-rs9939609 polymorphism to the development of T2D after 5-year follow-up, taken into account the socio-economic status, lifestyle factors, and clinical patterns including obesity-related traits, blood pressures, and dyslipidemia. The carriers with additional A-allele increased 1.35-fold risk (95% CI = 1.02–1.78) of T2D in comparison

with the A-allele noncarriers. Moreover, 13.6% of all T2D cases in the study population were attributable to the risk genotypes. The present finding also confirms the significant association between the *FTO*-rs9939609 polymorphism and T2D in the previous case–control study (OR = 1.85, 95% CI = 1.11–3.08, $P = 0.018$) (Binh et al. 2012).

To date, there have been few population-based prospective studies reporting RR or HR of T2D. An hospital-based prospective study ($n = 738$) in Western Saudi population showed no significant association of the *FTO*-rs9939609 polymorphism with T2D (RR = 1.07, $P = 0.190$) as an independent variable, whereas the combined genotypes of A/A for *FTO* rs9939609, C/C for *PPAR* rs1801282, and C/C for *MC4R* rs2229616 significantly increased the risk of T2D by 1.82, $p = 0.045$ (Bakhashab et al. 2020). Another longitudinal study (median follow-up of 5.9 years) reported no involvement of the *FTO*-rs9939609 polymorphism in T2D risk in postmenopausal women including White ($n = 1972$), Black ($n = 1098$), Hispanic ($n = 456$), and Asian/Pacific Islanders ($n = 294$) in the USA (Song et al. 2008). A meta-analysis of 41,504 Scandinavians (Hertel et al. 2011) from population-based prospective studies across adult life span indicated that the *FTO*-rs9939609 polymorphism alters type 2 diabetes risk partly independent of its observed effect on BMI (OR = 1.09, 95% CI = 1.04–1.15). Reviewing SNPs in linkage disequilibrium (LD) block of the *FTO* gene in relation to future T2D shows different findings. *Rs9939609* and *rs8050136* are 4,251 bp apart within intron 1 of *FTO* gene; and they locate in the region of high LD. The *FTO*-rs8050136 polymorphism was found to be the significant predictor of postpartum diabetes (HR = 1.36, 95% CI = 1.06–1.74, $P = 0.015$) after adjustment for age and ethnicity in 793 multiethnic women with gestational diabetes mellitus after a median follow-up of 2.4 year (Ekelund et al. 2012). However, adjusting for BMI attenuated the effect of the *FTO*-rs8050136 variant (HR = 1.30, 95% CI = 0.98–1.73, $P = 0.069$), suggesting that the effect was mediated through its effect on BMI.

BMI, WC, and SBP are very important clinical determinants of T2D. They have been used in prediction models of incident and prevalent T2D (Collins et al. 2011). The present study showed that the changes over time in BMI (median = 0.21 kg/m^2), WC (median = 4.5 cm), and SBP (median = 10 mmHg) did not modify the contribution of the *FTO* polymorphism to future T2D. It is important to note that most subjects of this population had values of BMI and WC in normal ranges at baseline: BMI (21.4 ± 2.5 kg/m^2), WC (males: median (IQR) = 77 (70.5–82 cm); females: median (IQR) = 73 (68–78 cm). Moreover, diabetic subjects had also values of BMI (22.7 ± 2.6 kg/m^2) and WC (males: 82.9 ± 7.3 cm; females: 80.1 ± 8.0 cm) in nearly normal ranges; and rates of overweight ($25 \leq$ BMI < 30 kg/m^2) and obesity (BMI ≥ 30 kg/m^2) were 18 and 0.7%, respectively, in diabetic subjects. This finding had confirmed that Vietnamese develop T2D with small increases in BMI and WC as suggested in previous cross-sectional studies (Le et al. 2003; Yamamoto et al. 2013).

The *FTO* polymorphism predicted the progression from normal glucose tolerance to T2D (HR = 1.50, $P = 0.013$, $n = 1304$) in this study. It is consistent with a prospective study in Scandinavians (OR adjusted for age and sex = 1.16; $P = 0.007$, $n = 12{,}117$) (Lyssenko et al. 2008). The *FTO* polymorphism did not predict the transition from prediabetes (impaired fasting glucose and/or impaired glucose tolerance)

to manifest diabetes in the present study ($n = 222$, data not shown), whereas the association was found in a large prospective study (OR adjusted for age and sex = 1.13; $P = 0.028$, $n = 3814$) (Lyssenko et al. 2008), suggesting that sample size may be explained for this difference. Larger prospective study is needed to investigate the contribution of the *FTO* polymorphism to the transition from prediabetes to T2D in Vietnamese population.

Major strengths of our study are the population-based prospective study and the nature of the cohort, which was based on the general homogeneous population of without other ethnic admixtures. Moreover, the T2D cases were diagnosed based on both FPG test and OGTT test. The HR has been evaluated, considering the possible confounders including obesity-related traits, clinical patterns, as well as socio-economic status and lifestyle factors.

This study had several limitations: First, as the study was conducted in Viet population in the rural area of Northern Vietnam, the finding should not be applied for other ethnic populations. Next, T2D diagnosis was only conducted after 5-year follow-up and this leads to overestimated exposure time of newly diagnosed diabetes. Lastly, since the prediction model was developed based on a single gene and the effect of this *FTO* polymorphism was small to get powerful prediction of future diabetes, it is necessary to build genetic prediction models involving a large genetic variance detected from genome-wide association studies in Vietnamese population.

Conclusion

The present study indicates that the *FTO*-rs9939609 polymorphism is a predictor for future type 2 diabetes, independent of socio-economic status, lifestyle factor, and clinical pattern. This polymorphism should be used to develop predictive models for future diabetes in Vietnamese populations.

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Author Contributions TQB: Conceptualization of the study, study design, proposal writing, data collection, data analysis, discussion, and editing of the final draft for publication. DTL, LTKC, PTP, BTTN, NAN. TQT, DDT, BTN: Conceptualization of the study, study design, data collection, data analysis, discussion, and editing of the final draft for publication. All authors read and approved the final manuscript.

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Declarations

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval The Ethics Committee of the National Institute of Hygiene and Epidemiology, Vietnam, approved the study protocol (IRB-VN01057-34/2016).

Consent to participate All participants provided written informed consent before entering the study.

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