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Original Article

Risk of diabetes according to the metabolic health status and degree of obesity

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ABSTRACT

Aim: To determine the progression rates from metabolically healthy or unhealthy normal weight, overweight and obese phenotype to type 2 diabetes (T2D) in a non-diabetic high risk population in Isfahan, Iran.

Methods: T2D incidence during a mean (SD) follow-up of 10.1 (2.3) years was examined among 1,982 non-diabetic first-degree relatives (FDR) of patients with T2D 30–70 years old. Participants were divided into 6 groups based on body mass index and metabolic syndrome component, except waist circumference, at baseline: metabolically healthy normal weight (MHNW), metabolically healthy overweight (MHOW), metabolically healthy obese (MHO), metabolically unhealthy normal weight (MUNW), metabolically unhealthy overweight (MUOW) and metabolically unhealthy obese (MUO).

Results: The MHO, MUOW, and MUO individuals at baseline were associated with incidence of T2D, independently of age and gender. MHO were 3 times (OR 2.96; 95% CI 1.07, 8.24) and MUOW were 2.75 times (95% CI 1.17, 6.45) more likely to develop T2D than those with MHNW. There was excess risk in MUO than MHO (OR 3.86; 95% CI 1.64, 9.11).

Conclusions: Obesity was a risk factor for T2D, even in the absence of any metabolic abnormalities. Metabolic abnormalities were a stronger predictor of incident T2D than obesity.

1. Introduction

Type 2 diabetes (T2D), obesity, and metabolic syndrome are escalating public health issue worldwide and are also a rapidly growing health problem in Iran [1]. Although obesity is a well-known risk factor for T2D [2], much of the increased risk for T2D among the obese is thought to stem from the underlying cardiometabolic abnormalities associated with excess fat [2]. Thus, obesity has different phenotypes, referred to metabolically healthy obese (MHO) and metabolically unhealthy obese (MUO). Although several studies have examined the relationship between T2D and MHO and MUO phenotype, the relationship remained controversial. Depend on the definition used for metabolic status, 10–40% of obese adults are metabolically healthy [3–5] with a good metabolic profile characterized by normal insulin sensitivity, no sign of hypertension, normal lipid levels, and a favourable fasting glucose, and inflammation profile [6–8], and do not show increased risk for T2D and cardiovascular disease or mortality [9–13] and a substantial number of individuals with metabolic disturbance do not conform to general obesity [3]. In contrast, other recent studies have reported that MHO was at increased risk for T2D or cardiovascular disease [4,5,12,14–19]. However, the nature of this association is not well understood.

Therefore, the objective of this cohort study was to investigate the relationship between BMI categories and the incidence of T2D in non-diabetic metabolically healthy and unhealthy FDRs of people with T2D.

2. Subjects and methods

2.1. Data collection

Data were drawn from the Isfahan Diabetes Prevention Study (IDPS), an ongoing prospective single-center observational study in central Iran which was conducted between 2003 and 2005. Recruitment methods and examination procedures have been described previously [20]. Briefly, our sample at baseline consisted of 3483 FDRs of consecutive patients with T2D (919 men and 2564 women). All patients were attendees at Isfahan Endocrine and Metabolism Research Center, which is part of Isfahan University of Medical Sciences, Iran.

At the time of each examination, they had anthropometric measurements and laboratory tests, including a standard 75 g 2-h oral glucose tolerance test (OGTT), and also completed a

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questionnaire on their health status and on various potential risk factors of diabetes. The participants were followed-up according to standard medical care in diabetes [21] to update information on demographic, anthropometric, and lifestyle factors and on newly diagnosed pre-diabetes and diabetes. If OGTT was normal at baseline, then repeat testing was carried out at least at 3-year intervals. Otherwise, repeat testing was usually carried out annually.

2.2. Ethics statement

The study protocol followed the Iranian government's ethical guidelines for epidemiological studies in accordance with the current version of the Declaration of Helsinki. Isfahan University of Medical Sciences ethical committee approval was granted, and all individuals participated in the study voluntarily, and informed consent was obtained from each participant.

2.3. Follow-up and diagnosis of T2D

Of the 3483 persons who participated at baseline, 1501 were excluded: 319 had type 1 diabetes (T1D) or T2D at baseline and 1182 did not attend follow-up examinations, resulting in 1982 participants who completed the study. The participants had a mean age of 43.0 (6.5) (range 30–70) years and all of them had at least one subsequent review during a mean (standard deviation (SD)) follow-up period of 10.1 (2.3) (range 4–13) years. The most of the baseline characteristics of individuals who did not return for the follow-up visit (non-respondents), such as age, height, weight, body mass index (BMI), waist circumference (WC), hip circumference (HC), waist-to-hip ratio (WHR), fasting plasma glucose (FPG), and low-density lipoprotein cholesterol (LDLC), total cholesterol, triglyceride, systolic and diastolic BP and obesity were similar to those who attended the follow-up visits. However, non-respondents had slightly lower plasma glucose (PG) at 30 min (140.0 mg/dl vs. 143.6 mg/dl, $P < 0.01$), 60 min (141.2 mg/dl vs. 149.1 mg/dl, $P < 0.001$), and 120 min. (111.2 mg/dl vs. 118.7 mg/dl, $P < 0.001$), levels of hemoglobin A1c (HbA1c) (5.0% vs. 5.1, $P < 0.05$) and had higher high-density lipoprotein cholesterol (HDLC) (46.9 mg/dl vs. 45.0 mg/dl, $P < 0.001$) than respondents.

2.4. Measurements

Information on age, gender, body size, HbA1c, cholesterol, LDLC, HDLC, triglycerides, BP, and family and personal medical history was collected at baseline and at follow-ups. The same methodology was used for baseline and follow-up studies. The participants were siblings and children of patients with T2D. They were asked to abstain from vigorous exercise in the evening before and in the morning of their visit when they reported to the clinics in the morning after an overnight fast. Smokers were encouraged to abstain from smoking in the morning of the investigations.

Firstly, on arrival at the clinic, the information provided by the participants in the questionnaire on family history was verified. Then, height, weight, WC and HC were measured using standard apparatus without shoes or heavy clothing. Resting systolic (phase I) and diastolic (Phase V) BP were recorded at each examination by a physician with the participants in a sitting position with their legs uncrossed, upon resting in this position for at least 10 min using a mercury column sphygmomanometer and appropriately sized cuffs. Average BP was calculated from the two consecutive measurements.

FPG was measured using the glucose oxidase method. T2D was defined as FPG $\geq$ 200 mg/dl, pharmacological treatment, or two FPG was $\geq$ 126 mg/dl. Those with FPG $<$ 126 mg/dl underwent a standard oral glucose tolerance test (OGTT) (75 g glucose 2-h) at baseline and follow-up visits. Venous blood was sampled 0, 30, 60, and 120 min after oral glucose administration. Plasma samples were centrifuged and analyzed the same day.

HbA1c, total cholesterol, triglycerides, HDLC, and LDLC were recorded. Lipids were measured directly, with the exception of LDLC, which was calculated [22]. All blood sampling procedures were performed in the central laboratory of the Isfahan Endocrine and Metabolism Research Center.

2.5. Definitions

BMI (weight (kg)/height^2 (m^2)) was used to define normal weight ($<$25 kg/m^2), overweight (25–29.9 kg/m^2), and obesity ($\geq$30 kg/m^2) and metabolic health status determined by the presence/absence of $\geq$1 components of metabolic syndrome according to the 2009 consensus criteria [23], which was the same as the third report of the National Cholesterol Education Program Adult Treatment Panel III (NCEP-ATP III) [24] as triglycerides $\geq$ 150 mg/dl; HDL $<$ 40 mg/dl in men and $<$50 mg/dl in women; BP $\geq$ 130/85 mmHg or on antihypertensive medication, or raised fasting plasma glucose (FPG) $\geq$ 100 mg/dl. WC was not included in this definition because of co-linearity with BMI. Participants who met none of the above four criteria were considered metabolically healthy. Metabolically unhealthy defined as at least one abnormality from the above criteria. In order to investigate the separate and combined effect of normal weight, overweight, obesity and an adverse metabolic profile on the incidence T2D, study participants were categorized into one of 6 groups: (1) MHNW (n = 79); (2) MHOW (n = 126); (3) MHO (n = 75) (4) metabolically unhealthy normal weight (MUNW) (n = 231); (5) metabolically unhealthy overweight (MUOW) (n = 808); and (6) MUO (n = 620). Participants with MHNW served as the reference group.

To study if there was a transition in metabolic phenotype between baseline and the last follow-up examination, we compared the prevalence of the 6 metabolic phenotypes and changes in these phenotypes between first and last visits, regardless of the interim examination results.

2.6. Analysis

Participants were followed until the occurrence of T2D, the date of the last completed follow-up, death, or end of follow-up on October 1, 2016, whichever event occurred first.

Statistical methods included the Student's *t*-test or Mann-Whitney *U* test, one-way analysis of variance (ANOVA) with Scheffe's method as the post hoc analysis or the Kruskal-Wallis test with the Dunn procedure for continuous variables; the chi squared test for categorical variables, and multiple logistic regression. Crude and multivariable logistic regression were used to calculate odds ratios (OR) with 95% confidence intervals (CI) and P values for incident T2D according to the 6 metabolic phenotype groups using the IBM SPSS version 21 for Windows. These multivariable models were adjusted for age at baseline (continuous) and gender. When a new case of T2D was identified we used the examination visit date as a new case of diabetes. Age-adjusted means were calculated and compared using general linear models. The interaction term between gender and BMI-metabolic status phenotypes revealed no difference, allowing us to combine them in the analysis. Reported P-values were two-tailed and P-values $<$0.05 were considered to be statistically significant.

3. Results

3.1. Characteristics

The baseline characteristics of the 79 (4.1%) normal weight, 128 (6.6%) overweight, and 75 (3.9%) obese metabolically healthy,

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and 231 (11.9%) normal weight, 808 (41.6%) overweight, and 620 (31.9%) obese metabolically unhealthy participants are shown in Table 1. In comparisons of variables at baseline, all variables were more likely to increase and HDLC were more likely to decrease with increasing BMI in both metabolically healthy and unhealthy groups. At baseline, 14.5% (282) of the participants were metabolically healthy and 28.0% of them were normal weight, 45.3% overweight and 26.7% obese. Of 1659 (85.5%) metabolically unhealthy individuals, 13.9% were normal weight, 48.6% overweight and 37.6% obese. All variables were higher and HDLC were lower in metabolically unhealthy individuals at any BMI status.

Table 2 shows the stability of metabolic phenotypes between baseline and last follow-up visit. In metabolically unhealthy group, about 62% of normal weight, 72% of overweight, and 70% obese were in the same group at baseline and last visit. However in metabolically healthy group, 39% of normal weight, 22% of overweight and 22% of obese individuals maintained their phenotype status at last follow-up visit. The status of most of the metabolically healthy group member changed to metabolically unhealthy, and none of the MHO or MUO individuals achieved the MHNW phenotype.

3.2. Incident of T2D

During 19,735 (5119 men and 14,616 women) person-years of follow-up, 370 (104 men and 266 women) incident cases of T2D occurred. Within this cohort without T2D at baseline, the overall incidence of subsequent T2D was 18.7 (95% CI: 16.9, 20.6) events per 1000 person-years. Incidence rates were almost similar in women (18.2, 95% CI: 16.0, 20.4 per 1000 person-years) and men (20.3, 95% CI: 16.5, 24.2).

3.3. Association with T2D

T2D incidence was 7.3 per 1000 person-years (95% CI: 2.8, 15.9) for MHNW, 5.3 (95% CI: 2.1, 10.8) for MHOW, 17.6 (95% CI: 9.6, 29.4) for MHO, 13.2 (95% CI: 8.9, 18.7) for MUNW, 18.9 (95% CI: 15.9, 21.8) for MUOW and 23.9 (95% CI: 20.2, 27.7) for MUO participants. Compared with MHNW participants, the highest risk of T2D incidence was observed in the MUO (OR 3.86; 95% CI: 1.64, 9.11), followed by the MHO (OR 2.96; 95% CI: 1.07, 8.24), MUOW (OR 2.75; 95% CI: 1.17, 6.45), and MUNW (OR 1.79; 95% CI: 0.71, 4.49) after adjustment for age and gender. Controlling for age and gender did not appreciably alter the OR compared to the un-adjusted model (Table 3). In another model, appropriate interaction term to test the impact of gender on relation of BMI-metabolic status to T2D incidence was included. The interaction term was not statistically significant for developing T2D ($P > 0.05$).

The risk of developing T2D rose in a stepwise fashion with increasing BMI. T2D incidence was 11.6 per 1000 person-years (95% CI: 8.1, 16.1) for participants with normal weight, 17.0 (95% CI: 14.4, 19.6) for overweight, and 23.2 (95% CI: 19.7, 26.7) for obese. Compared with participants with normal weight, the risk of T2D was 55% higher in those with overweight (OR 1.55; 95% CI: 1.05, 2.29), and 2.4 times higher in obese (OR 2.40; 95% CI: 1.62, 3.56), in age-, gender adjusted model. The metabolically unhealthy participants had a substantially higher risk of T2D than metabolically healthy participants. Compared with metabolically healthy participants, the risk of T2D was 9 times higher in metabolically unhealthy individuals (OR 9.00; 95% CI: 3.96, 20.46). When we re-analysed the data, compared participants with MHNW vs. MUNW, MHOW vs. MUOW, or MHO vs. MUO, MUNW had 8.6 times (OR 8.64; 95% CI: 1.15, 65.00), MUOW had 7 times (OR 7.10; 95% CI: 2.22, 22.76) and MUO individuals had 10 times higher risk of developing

Table 1
Age, age-adjusted means (SE) and proportion of selected baseline characteristics[a] of first-degree relatives of patients with type 2 diabetes by baseline metabolic health status and body mass index.

	Metabolically Healthy (n = 282)			Metabolically unhealthy (n = 1659)		
Characteristic	Normal weight	Overweight	Obese	Normal weight	Overweight	Obese
Number (%)	79 (4.1)	128 (6.6)	75 (3.9)	231 (11.9)	808 (41.6)	620 (31.9)
Age (year)	41.8 (0.73)	42.1 (0.58)	41.8 (0.75)	42.8 (0.43)	43.2 (0.23)	43.4 (0.26)*
Height (cm)	161.2 (0.91)	159.9 (0.72)	155.9 (0.95)***	160.5 (0.54)	161.0 (0.29)	158.3 (0.33)***
Weight (kg)	58.7 (0.98)	70.5 (0.77)	79.5 (1.01)***	60.2 (0.57)	71.7 90.31)	83.7 (0.35)***
Waist circumference (cm)	76.9 (0.83)	85.4 (0.64)	93.7 (0.84)***	79.6 (0.48)	87.7 (0.26)	96.5 (0.29)***
Hip circumference (cm)	96.6 (0.66)	105.1 (0.51)	114.7 (0.67)***	97.4 (0.38)	104.5 (0.20)	115.6 (0.23)***
Waist-to-hip ratio	0.80 (0.008)	0.81 (0.006)	0.82 (0.008)***	0.82 (0.004)	0.84 (0.002)	0.84 (0.003)***
Body mass index (kg/m^2)	22.6 (0.24)	27.6 (0.19)	32.6 (0.24)***	23.3 (0.14)	27.6 (0.07)	33.4 (0.08)***
Follow-up duration (yr.)	10.1 (0.26)	10.3 (0.20)	10.5 (0.26)	9.8 (0.15)	10.1 (0.08)	10.1 (0.09)
Fasting glucose baseline (mg/dl)	88.2 (1.28)	88.7 (1.01)	90.6 (1.32)***	95.0 (0.75)	96.1 (0.40)	97.8 (0.46)***
Plasma glucose 30 min (mg/dl)	132.1 (3.48)	130.1 (2.76)	138.8 (3.63)***	141.9 (2.06)	143.5 (1.11)	149.1 (1.27)***
Plasma glucose 60 min (mg/dl)	127.7 (4.65)	128.0 (3.67)	140.6 (4.78)***	141.7 (2.74)	149.7 (1.47)	159.1 (1.67)***
Plasma glucose 120 min (mg/dl)	103.9 (3.68)	108.0 (2.93)	114.9 (3.78)***	115.8 (2.16)	118.9 (1.15)	124.0 (1.32)***
HbA_{1c} (%)	5.0 (0.09)	4.8 (0.07)	5.0 (0.10)	5.0 (0.06)	5.1 (0.03)	5.1 (0.03)**
Cholesterol (mg/dl)	189.6 (4.67)	191.3 (3.59)	196.9 (4.74)***	188.4 (2.63)	196.9 (1.40)	201.5 (1.61)***
LDL- cholesterol (mg/dl)	112.2 (4.13)	116.2 (3.20)	118.4 (4.19)**	116.0 (2.32)	119.1 (1.26)	124.3 (1.43)**
HDL-cholesterol (mg/dl)	58.1 (1.29)	56.0 (0.99)	58.0 (1.30)***	43.1 (0.72)	42.9 (0.38)	43.3 (0.44)***
Triglyceride (mg/dl)	95.6 (11.48)	103.5 (8.71)	102.4 (11.48)***	148.6 (6.29)	182.7 (3.39)	176.1 (3.88)***
Systolic BP (mm Hg)	103.9 (1.69)	107.6 (1.33)	109.5 (1.76)***	112.4 (0.98)	116.0 (0.53)	120.6 (0.61)***
Diastolic BP (mm Hg)	66.4 (1.28)	70.1 (1.01)	72.1 (1.33)***	73.9 (0.74)	76.0 (0.40)	79.0 (0.46)***
Women, no. (%)	48 (60.0)	100 (78.1)	67 (88.2)***	158 (68.1)	588 (66.9)	521 (82.8)***
Developed type 2 diabetes, no. (%)	6 (7.5)	7 (5.4)	14 (18.4)***	30 (12.9)	154 (18.9)	152 (24.2)***
Abdominal obesity, no. (%)	0 (0.0)	19 (15.0)	55 (72.4)***	3 (0.4)	160 (20.0)	510 (83.2)***

[a] Age-adjusted means were calculated using general linear models. Data are express as mean (SE) or number (%). The difference in the mean or percentage of the variables between normal weigh overweight and obese.

* $P < 0.05$.
** $P < 0.01$.
*** $P < 0.001$.

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Table 2
Prevalence of metabolic phenotype at baseline and last follow-up study.

Baseline	Last follow-up					
	Metabolically Healthy			Metabolically unhealthy		
	Normal weight	Overweight	Obese	Normal weight	Overweight	Obese
Metabolically Healthy						
Normal weight	25 (38.5)	5 (4.7)	0 (0.0)	30 (16.2)	17 (2.4)	1 (0.2)
Overweight	5 (7.7)	31 (22.0)	9 (11.5)	5 (2.7)	54 (7.6)	23 (3.2)
Obese	0 (0.0)	4 (3.7)	17 (21.8)	0 (0.0)	3 (0.4)	49 (7.4)
Metabolically unhealthy						
Normal weight	23 (35.4)	9 (8.40	0 (0.0)	115 (62.2)	68 (9.6)	3 (0.5)
Overweight	12 (18.5)	49 (45.8)	11 (14.1)	33 (17.8)	509 (72.1)	127 (19.3)
Obese	0 (0.0)	9 (8.40	41 (52.6)	2 (1.1)	55 (7.8)	455 (69.1)

Table 3
Incidence type 2 diabetes and Odds ratios (OR) (95% CI) by baseline metabolic phenotype, The Isfahan Diabetes Prevention Study, 2003–2011.

	Metabolically Healthy			Metabolically unhealthy		
	Normal weight	Overweight	Obese	Normal weight	Overweight	Obese
Cases No. (%)	6 (7.5)	7 (5.4)	14 (18.4)	30 (12.9)	154 (18.9)	152 (24.2)
At risk No. (%)	80 (4.1)	129 (6.6)	76 (3.9)	232 (11.8)	813 (41.5)	629 (32.1)
Person-year	817	1326	797	2279	8165	6351
Incidence/1000 person-year (95% CI)	7.3 (2.8, 15.9)	5.3 (2.1, 10.8)	17.6 (9.6, 29.4)	13.2 (8.9, 18.7)	18.9 (15.9, 21.8)	23.9 (20.2, 27.7)
Crude OR (95% CI)	1.00	0.71 (0.23, 2.19)	2.79 (1.01, 7.68)*	1.83 (0.73, 4.58)	2.88 (1.23, 6.75)*	3.93 (1.68, 9.21)**
Gender-adjusted OR (95% CI)	1.00	0.74 (0.24, 2.27)	2.92 (1.06, 8.08)*	1.86 (0.74, 4.64)	2.92 (1.25, 6.83)*	4.09 (1.74, 9.60)**
Age-, gender-adjusted OR (95% CI)	1.00	0.73 (0.24, 2.27)	2.96 (1.07, 8.24)*	1.79 (0.71, 4.49)	2.75 (1.17, 6.45)*	3.86 (1.64, 9.11)**

Odds ratio (with 95% CI) calculated by multiple logistic regression. CI = confidence interval.
* $P < 0.05$.
** $P < 0.01$.

T2D (OR 10.45; 95% CI: 2.52, 43.37). Controlling for age and gender did not appreciably alter the OR compared to the un-adjusted model (Table 4).

It can be seen that in normal weight, overweight, and obese, participants with metabolically unhealthy had increased probability of developing T2D, which was significantly different compared with participants with normal weight, overweight and obese but without metabolic abnormality.

4. Discussion

This study demonstrated that among FDRs of patients with T2D, the highest risk estimate was seen in metabolically unhealthy BMI groups. Participants, who had metabolic abnormality, even in normal weight, were at higher risk of future T2D. Although the MHO group had 3 times higher risk of T2D compared with the MHNW phenotype, as reported previously

Table 4
The association of baseline body mass index and metabolic status with type 2 diabetes.

	Crude OR (95% CI)	Gender-adjusted OR (95% CI)	Age-, gender-adjusted OR (95% CI)
Body mass index			
Normal weight	1.00	1.00	1.00
Overweight	1.58 (1.07, 2.33)*	1.59 (1.08, 2.34)*	1.55 (1.05, 2.29)*
Obese	2.36 (1.60, 3.48)***	2.44 (1.65, 3.62)***	2.40 (1.62, 3.56)***
Metabolic status			
Metabolically healthy	1.00	1.00	1.00
Metabolically unhealthy	9.32 (4.11, 21.16)***	9.28 (4.09, 21.07)***	9.00 (3.96, 20.46)***
Normal weight			
Metabolically healthy	1.00	1.00	1.00
Metabolically unhealthy	8.63 (1.15, 64.65)*	8.85 (1.18,66.44)*	8.64 (1.15, 65.00)*
Overweight			
Metabolically healthy	1.00	1.00	1.00
Metabolically unhealthy	7.52 (2.35, 24.03)**	7.33 (2.29, 23.45)**	7.10 (2.22, 22.76)**
Obese			
Metabolically healthy	1.00	1.00	1.00
Metabolically unhealthy	10.65 (2.57, 44.01)**	10.83 (2.62, 44.84)**	10.45 (2.52, 43.37)**

Odds ratio (with 95% CI) calculated by multiple logistic regression. CI = confidence interval.
* $P < 0.05$.
** $P < 0.01$.
*** $P < 0.001$.

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[4,5,12,14–19], their risk was significantly lower than in the MUO. These associations suggest that in participants without T2D, metabolic abnormalities may be more contribute to the development of T2D than BMI status. The finding that MHO individuals were at an increased risk of incident T2D compared with MHNW is consistent with some, [4,5,14–19,25,26] but not all previous studies [9–13]. This study suggest that BMI is a risk factor for T2D regardless of the metabolic status of the participants. In the San Antonio Heart Study, MHO individuals had >2-fold increased risk of incidence T2D compared to MHNW controls [27]. A Korean studies reported a higher incidence of T2D in MHO men than normal controls [26]. In a meta-analysis of seven epidemiological studies and original data on elderly English adults, Bell et al. [25] reported that MHO individuals had an increased risk of develop diabetes compared with MHNW individuals. Other studies also suggested that MHO individuals had an increased risk of T2D [4,5,14–19]. In contrast, both the Framingham [10] and an Australian cohort study [9] reported that MHO and MHNW individuals had similar risk of developing diabetes during 11-year period. Appleton et al. found that MHO individuals are at increased risk of developing T2D only if they progress to an unhealthy phenotype [9]. In contrast, Kim et al. [28] and Lee et al. [29] found a higher incidence of T2D in persistent MHO individuals than individuals who did not maintained the MHO status during the study period.

Limitations to our study include that we limited our study to a cohort of individuals who are at increased risk of developing T2D, because they had a FDR with the patients with T2D, thus, the selection bias may lead to an overestimation of associations. We did not consider the residual confounding that are known T2D risk factors, such as visceral fat, plasma insulin, homeostasis model assessment index, inflammatory markers, physical activity and socioeconomic status. These variables could be relevant for explaining the relationship between overweight, obesity, metabolic abnormalities and incidence of T2D. In addition, the number of incident cases of diabetes in some of the BMI/metabolic abnormality categories was small as reflected by the wide CIs around the OR. Finally, our data cannot be readily generalized to other FDRs populations because the distribution of obesity, metabolic abnormalities is known to vary substantially across different race/ethnic groups.

In conclusion, these data provide evidence that metabolic abnormalities increased risk for incident T2D at any BMI status. In addition, the obesity is a risk factor for incidence T2D, even in the absence of any metabolic abnormalities. This finding emphasizes the importance of management of excess weight and any metabolic abnormality for FDRs of patients with T2D.

Conflicts of interest

The authors declared no conflict of interest.

Author's contributions

MJ designed the study, performed statistical analyses and interpreted the data and drafted the manuscript; AA, MRS and MA, recruited samples, contributed to interpretation of results and revised the manuscript. All authors approved the final version submitted for publication.

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