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Original Article

Risk of diabetes in combined metabolic abnormalities and body mass index categories

Mohsen Janghorbani [a,b,*], Norredin Soltanian [a], Mehri Sirous [c], Masoud Amini [a], Bijan Iraj [a]

[a] Isfahan Endocrine and Metabolism Research Center, Isfahan University of Medical Sciences, Isfahan, Iran
[b] Department of Epidemiology and Biostatistics, School of Public Health, Isfahan University of Medical Sciences, Isfahan, Iran
[c] Departement of Radiology, Isfahan University of Medical Sciences, Isfahan, Iran

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ABSTRACT

Aim: The present study was designed to estimate the progression rates from combination of normal weight, overweight, obesity, and number of metabolic abnormalities (MA) to type 2 diabetes (T2D) in a non-diabetic high risk population in Isfahan, Iran.
Methods: A total of 1869 non-diabetic first-degree relatives (FDR) of patients with T2D 30–70 years old were examined and followed for a mean (SD) of 7.3 (2.2) years for T2D incidence. At baseline and through follow-up, participants underwent a standard 75-g 2-h oral glucose tolerance test.
Results: The metabolically healthy overweight and obese at baseline were associated with incidence of T2D, independently of age and gender. Any one MA increased the risk of developing T2D among normal weight, overweight and obese individuals. Those with normal weight and ≥3 MA were over 20 times (odds ratios (OR) 20.21; 95% confidence intervals (CI) 2.4, 170.4) and those with overweight and ≥3 MA 22.5 times (OR 22.5; 95% CI 3.0, 167.0) and obese with ≥3 MA were 25.4 times (OR 25.4; 95% CI 3.4, 187) more likely to develop T2D than those with normal weight and without MA. Compared with participants without MA, obese individuals with concomitant MA were not significantly more likely to progress to T2D.
Conclusion: Our data provide further evidence that normal weight, overweight and obese individuals with MA had a higher risk of incident T2D than normal weight individuals without MA.

1. Introduction

Type 2 diabetes (T2D), obesity, and metabolic syndrome are rapidly growing health problems worldwide and are common causes of morbidity and often coexist, and are risk factors for cardiovascular disease and might share common genetic and environmental risk factors [1]. Overweight, obesity and metabolic syndrome are complex disorders and a well known risk factor for T2D [2–7]. Although adiposity plays a direct role [8], much of the increased risk for T2D among the obese is thought to stem from the underlying cardiometabolic abnormalities associated with excess fat [8]. Other contributing factors may include inflammation [9], higher level of visceral fat [10], an energy dense/nutrient-poor diet including excess sugar intake [11], and physical activity [12] along with genetic, ethnic and socioeconomic susceptibilities [13,14]. However, not all obese subjects seem to carry such risk. Some studies reported that metabolically healthy but overweight or obese (MHO) individuals have normal insulin sensitivity, no sign of hypertension, normal lipid levels, and a favorable inflammation profile [15,16], and do not show increased risk for T2D and cardiovascular disease or mortality [17–19]. In contrast, others have reported that MHO was at increased risk for T2D or cardiovascular disease [20,21]. However, the nature of this association is not well understood. Uncertainty also exists about the relationship between MHO and T2D incidence [19,20,22–28]. Most of these studies showed a positive association [20,25–28], whereas others reported no association [17–19].

To our knowledge, the association between combination of body mass index (BMI) categories and number of metabolic abnormalities (MA) and the risk of T2D has not been previously reported in first-degree relatives (FDR) of patients with T2D and whether increase BMI in the absence of overt MA infers risk for T2D is unknown. In addition, in almost all previous studies differences in number of MA were not considered in defining a metabolically healthy or unhealthy state and different definitions used for MHO and it is unclear whether the definitions of MHO phenotypes used

* Corresponding author at: Department of Epidemiology and Biostatistics, School of Public Health, Isfahan University of Medical Sciences, Isfahan, Iran.
Tel.: +98 31 32334893; fax: +98 31 36682509.
E-mail addresses: janghorbani@yahoo.com, janghorbani@hlth.mui.ac.ir (M. Janghorbani).

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in the previous studies [17,18,20,26,29–34] were adequate to predict development of T2D.

The objective of the present cohort study, therefore, was to investigate the relationship between BMI categories and number of MA, both separately and in combination, and the incidence of T2D in non-diabetic FDR of people with T2D. Our hypothesis was that in non-diabetic FDR of patients with T2D, overweight and obesity, regardless of number of MA, the number of MA regardless of BMI status and in combination would be associated with increased risk of diabetes.

2. Subjects and methods

2.1. Data collection

This study was conducted using the data from the Isfahan Diabetes Prevention Study (IDPS), an ongoing prospective single-center observational study in central Iran to assess the various potential risk factors for diabetes in subjects with family history of T2D (one of the main risk factors for T2D). The recruitment methods and examination procedures of the IDPS have been described previously [35]. The IDPS sample at baseline comprised 3483 (919 men and 2564 women) FDR of consecutive patients with T2D. All patients were attendees at clinics at Isfahan Endocrine and Metabolism Research Center, which is affiliated to Isfahan University of Medical Sciences, Iran. The study was conducted between the years 2003 and 2005. All participants were from Isfahan city and adjoining areas. They completed a standardized medical examination and laboratory tests including a standard 75 g 2-h oral glucose tolerance test (OGTT), standardized blood pressure (BP), a questionnaire on their health status and on various potential risk factors for diabetes. Participants received follow-up tests according to Standard of Medical Care in Diabetes [36] to update information on demographic, anthropometric, and lifestyle factors and on newly diagnosed pre-diabetes and diabetes. Accordingly, if OGTT was normal at baseline; repeat testing was carried out at least at 3-year intervals. Otherwise, repeat testing was usually carried out annually.

2.2. Ethics statement

The Iranian government's ethical guidelines regarding epidemiological studies in accordance with the current version of the Declaration of Helsinki were followed, and Isfahan University of Medical Sciences ethical committee approval was granted, and an informed consent form was signed by each participant.

2.3. Follow-up and ascertainment of T2D

Among 3483 persons who participated at baseline, 364 subjects were excluded because of diagnosis of type 1 diabetes (T1D) or T2D at baseline and 1250 did not attend any follow-up examination, leaving 1869 participants with a mean age 43.0 (6.5) (range 30–70) years for this analysis, all of whom had at least one subsequent review during a mean (standard deviation [SD]) follow-up period of 7.3 (2.2) (range 1–10) years. Attendees at the follow-up visit did not differ significantly from non-attendees regarding most baseline characteristics: e.g., age, height, weight, BMI, waist circumference (WC), hip circumference (HC), waist-to-hip ratio (WHR), and low-density lipoprotein cholesterol (LDLC), total cholesterol, triglyceride, systolic and diastolic BP and obesity. However, non-attendees had slightly lower fasting plasma glucose (FPG) (94.7 mg/dl vs. 95.7; $P < 0.05$), plasma glucose (PG) at 30 min (139.5 mg/dl vs. 144.2 mg/dl, $P < 0.001$), 60 min (140.8 mg/dl vs. 149.8 mg/dl, $P < 0.001$), and 120 min (110.6 mg/dl vs. 119.5 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) (46.7 mg/dl vs. 45.0 mg/dl, $P < 0.001$).

2.4. Procedures

Information on age, gender, body size, HbA1c, cholesterol, LDLC, HDLC, triglycerides and BP, family and personal medical history was collected at baseline and through follow-ups. The same methodology was used for baseline and follow-up studies. The participants included siblings and children of patients with T2D. Participants reported to clinics in the morning after an overnight fast. They were asked to abstain from vigorous exercise in the evening, and in the morning of their visit. Smokers were encouraged to abstain from smoking in the morning of the investigations. First, on arrival at the clinic, the information provided by the participants in the questionnaire on family history was verified. Then, with the subjects minimally clothed and without shoes, height, weight, and WC and HC were measured using standard apparatus. Weight was measured to the nearest 0.1 kg on a calibrated beam scale. Height, WC, and HC were measured to the nearest 0.5 cm with a measuring tape. The waist was measured midway between the lower rib margin and the iliac-crest at the end of gentle expiration in the standing position. HC was measured over the greater trochanters directly over the underwear. Resting BP was measured at each examination by physician with the participants in a sitting position after had been seated for 10 min with a mercury column sphygmomanometer and appropriately sized cuffs, using standard techniques. The systolic BP and diastolic BP were recorded at the first appearance (phase I) and the disappearance (phase V) of Korotkoff sounds. FPG was measured with the glucose oxidase method. Participants with FPG $\geq$200 mg/dl or pharmacological treatment were considered as persons with T2D. If FPG was $\geq$126 mg/dl and $<$200 mg/dl, a second FPG was measured on another day. If the second FPG was also $\geq$126 mg/dl, participants were considered as persons with T2D. Those with FPG $<$126 mg/dl underwent a standard OGTT (75 g glucose 2-h) at baseline and the 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 (measured by ion-exchange chromatography), total cholesterol, triglycerides, HDLC, LDLC were recorded. The LDLC levels were calculated with the Friedewald Equation [37]. All blood sampling procedures were performed in the central laboratory of the Isfahan Endocrine and Metabolism Research Center using enzyme-linked method.

To convert the values for triglycerides to millimoles per liter, multiply by 0.0113; HDLC, LDLC, and total cholesterol to millimoles per liter, multiply by 0.0259; and glucose to millimoles per liter, multiply by 0.0555.

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). Each BMI group was further divided according to the number of MA present at enrolment. *These were* identified according to the 2009 consensus criteria [38], which was the same as the third report of the National Cholesterol Education Program Adult Treatment Panel III (NCEP-ATP III) [39] as triglycerides $\geq$150 mg/dl; HDL $<$40 mg/dl in men and $<$50 mg/dl in women; BP $\geq$130/85 mm Hg or on antihypertensive medication, or raised PG, defined as 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 12 groups (Table 1): (1) normal weight (n = 76); (2) overweight (n = 114); (3) obese (n = 70) and without any MA; (4) normal weight (n = 115); (5) overweight (n = 291); (6) obese (n = 182) and one MA; (7) normal weight (n = 70); (8) overweight (n = 299); (9) obese (n = 216) and two MA; (10) normal weight (n = 33); (11) overweight (n = 175); or (12) obese (n = 205) and ≥3 MA. Participants with normal weight and without any MA served as the reference group when the combined effect of MA and BMI were to be evaluated. When MA was the predictor under evaluation, the reference group was individuals without MA. When BMI was the predictor under evaluation, the reference group was normal weight individuals.

2.6. Analysis

Incidence was expressed as the number of cases of T2D per 1000 person-years of follow-up in each category began at the date of completion of the baseline examination in 2003–2005 and ended at the time of diagnosis of T2D, the date of the last completed follow-up, death, or end of follow-up on March 21, 2014, whichever came 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, multiple logistic regression and survival analysis with product-limit (Kaplan–Meier) estimates. 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 number of MA and BMI

Table 1
Age, age-adjusted mean (SE) and proportion characteristics[†] of selected baseline characteristics in 282 first-degree relatives of patients with type 2 diabetes who did and 1587 who did not develop type 2 diabetes.

Variables	Progressed to T2D	Did not progress to T2D	Difference (95% CI)
	Mean (SE)	Mean (SE)	
Age (year)	44.4 (0.39)	42.7 (0.16)	1.7 (0.88, 2.52)***
Height (cm)	159.3 (0.50)	159.9 (0.21)	−0.6 (−1.86, 0.26)
Weight (kg)	76.8 (0.72)	73.3 (0.30)	3.5 (1.88, 4.92)***
Body mass index (kg/m^2)	30.3 (0.25)	28.7 (0.10)	1.6 (1.07, 2.13)***
Waist circumference (cm)	92.1 (0.57)	88.7 (0.24)	3.4 (2.58, 5.02)***
Waist-to-hip ratio	0.84 (0.004)	0.83 (0.002)	0.01 (0.001, 0.02)*
Hip circumferences (cm)	110.0 (0.53)	107.0 (0.22)	3.0 (1.77, 4.03)***
Follow-up duration (year)	7.8 (0.13)	7.2 (0.05)	0.6 (0.22, 0.78)***
Systolic BP (mm Hg)	117.4 (0.95)	115.5 (0.40)	1.9 (1.01, 5.19)*
Diastolic BP (mm Hg)	77.0 (0.72)	75.5 (0.30)	1.5 (0.56, 3.64)*
Fasting plasma glucose (mg/dl)	104.4 (0.68)	94.1 (0.28)	10.3 (9.36, 12.20)***
Plasma glucose 30 min (mg/dl)	163.9 (1.87)	140.7 (0.78)	23.2 (20.30, 28.30)***
Plasma glucose 60 min (mg/dl)	186.5 (2.41)	143.2 (1.01)	43.3 (39.80, 50.20)***
Plasma glucose 120 min (mg/dl)	146.7 (1.89)	114.6 (0.79)	32.1 (28.70, 36.70)***
HbA1c (%)	5.4 (0.05)	5.0 (0.02)	0.4 (0.29, 0.51)***
Triglyceride (mg/dl)	194.5 (6.04)	161.3 (2.52)	33.2 (22.50, 48.10)***
Cholesterol (mg/dl)	201.0 (2.43)	195.7 (1.01)	5.3 (2.34, 12.90)*
HDL cholesterol (mg/dl)	44.0 (0.73)	45.2 (0.30)	−1.2 (−2.55, 0.55)
LDL cholesterol (mg/dl)	120.3 (2.20)	119.3 (0.89)	1.0 (−1.85, 7.65)
	No. (%)	No. (%)	
Women	210 (74.5)	1170 (73.8)	0.7 (−4.83, 6.23)
Normal weight (BMI <25 kg/m^2)	26 (9.4)	268 (17.1)	−7.7 (−11.60, −3.84)***
Overweight (BMI 25–29.9 kg/m^2)	121 (43.5)	758 (48.3)	−4.8 (−11.10, 1.51)
Obese (BMI ≥30 kg/m^2)	131 (47.1)	542 (34.6)	12.5 (6.23, 18.90)***
No metabolic abnormality and normal weight	1 (0.4)	75 (4.8)	−4.4 (−5.69, −3.15)***
1 metabolic abnormality and normal weight	8 (2.9)	107 (6.8)	−3.9 (−6.27, −1.62)***
2 MA and normal weight	9 (3.2)	61 (3.9)	−0.7 (−2.94, 1.64)
≥3 MA and normal weight	8 (2.9)	25 (1.6)	1.3 (−0.78, 3.34)
No metabolic abnormality and overweight	4 (1.4)	110 (7.0)	−5.6 (−7.46, −3.69)***
1 metabolic abnormality and overweight	29 (10.4)	262 (16.7)	−6.3 (−13.39, −2.24)***
2 MA and overweight	45 (16.2)	254 (16.2)	0.0 (−4.71, 4.69)
≥3 MA and overweight	43 (15.4)	132 (8.4)	7.0 (2.58, 11.50)***
No metabolic abnormality and obese	12 (4.3)	58 (3.7)	0.6 (−1.95, 3.18)
1 metabolic abnormality and obese	28 (10.1)	154 (9.8)	0.3 (−3.58, 4.08)
2 MA and obese	36 (12.9)	180 (11.5)	1.4 (−2.78, 5.72)
≥3 MA and obese	55 (19.8)	150 (9.6)	10.2 (5.31, 15.1)***

Differences in the mean or percentage values of variables between T2D and no T2D. CI = confidence interval.
[†] Age-adjusted means were calculated using general linear models.
* $P < 0.05$.
** $P < 0.01$.
*** $P < 0.001$.

state using the IBM SPSS version 21 for Windows. These multivariable models were adjusted for age at baseline (continuous) and gender. The time to development of T2D was estimated according to number of MA and BMI state by the Kaplan–Meier method of survival analysis and statistical differences among groups were compared by the log-rank test. We used the exam visit date that a new case of diabetes was identified as the date of diagnosis. Age-adjusted means were calculated and compared using general linear models. We did not conduct gender-specific analyses because there were too few events in some subgroups to calculate stable risk estimates. All tests for statistical significance were two-tailed, and all were done assuming a type I error probability of <0.05.

3. Results

3.1. Characteristics

Baseline characteristics of the 282 (15.1%) participants who did and 1587 (84.9%) who did not progress to T2D are shown in Table 1. As expected, participants who progressed to T2D were older and had higher age-adjusted mean weight, BMI, WC, HC, follow-up duration, FPG, and PG at 30, 60 and 120 min, higher HbA1c, triglyceride, cholesterol, and BP at baseline and a higher proportion of obesity, combined overweight or obesity and $\geq$3 MA, and lower combined normal weight or overweight and without MA or one MA at baseline. Among participants who progressed to T2D, 19.8% had combined obesity and $\geq$3 MA, while 9.6% of participants who did not progress to T2D had combined obesity and $\geq$3 MA.

The baseline characteristics of the 262 (14.0%) participants without MA, 597 (31.9%) with one MA, 594 (31.8%) with two MA, and 416 (22.3%) with $\geq$3 MA are shown in Table 2. In comparisons of variables at baseline, all variables were more likely to increase and follow-up duration and HDLC were more likely to decrease across all four subject groups. The mean (SD) age was 41.8 (6.3) years for those without MA, 42.3 (6.4.) years for those with one MA, 43.1 (6.7) years for those with two MA and 44.6 (6.2) years for those with $\geq$3 MA. Among the participants, 15.9% were normal weight, 47.6% were overweight and 36.5% were obese. Of individuals without MA, 29.2% were normal weight, 43.8% were overweight and 26.9% were obese. Results were almost similar when normal weight, overweight and obese was assessed separately (data not shown).

3.2. Incident of T2D

During 13,571 (3460 men and 10,111 women) person-years of follow-up, 282 (15.1%) (72 men and 210 women) incident cases of T2D occurred. Within this cohort without T2D at baseline, the overall incidence of subsequent T2D was 20.8 (95% CI: 18.2, 23.2) events per 1000 person-years. Incidence rates were similar in women (20.8, 95% CI: 18.0, 23.5 per 1000 person-years) and men (20.8, 95% CI: 16.3, 26.2).

The incidence of T2D was 8.5 per 1000 person-years (95% CI 4.9, 13.6) for participants without MA, 14.7 (95% CI 11.1, 18.2) for participants with one MA, 21.3 (95% CI 16.9, 25.6) for those with

Table 2
Age, age-adjusted means (SE) and proportion of selected baseline characteristics of first-degree relatives of patients with type 2 diabetes by number of MA in the Isfahan Diabetes Prevention Study.

Characteristic	Number of MA			
	0	1	2	≥3
Total				
Number (%)	262 (14.0)	597 (31.9)	594 (31.8)	416 (22.3)
Age (year)	41.8 (0.40)	42.3 (0.26)	43.1 (0.27)	44.6 (0.32)***
Height (cm)	159.2 (0.52)	159.4 (0.34)	160.2 (0.34)	160.1 (0.41)
Weight (kg)	69.6 (0.72)	71.8 (0.48)	75.1 (0.48)	77.7 (0.57)***
Waist circumference (cm)	85.3 (0.57)	87.3 (0.38)	90.5 (0.38)	92.5 (0.46)***
Hip circumference (cm)	105.5 (0.55)	106.3 (0.36)	108.1 (0.36)	109.4 (0.44)***
Waist-to-hip ratio	0.81 (0.004)	0.82 (0.003)	0.84 (0.003)	0.85 (0.003)***
Body mass index (kg/m^2)	27.5 (0.25)	28.3 (0.17)	29.3 (0.17)	30.3 (0.20)***
Follow-up duration (year)	7.7 (0.13)	7.5 (0.09)	7.2 (0.9)	6.7 (0.11)***
Fasting glucose baseline (mg/dl)	88.8 (0.68)	93.2 (0.45)	96.1 (0.45)	102.7 (0.54)***
Plasma glucose 30 min (mg/dl)	133.3 (1.92)	140.0 (1.27)	144.5 (1.29)	156.3 (1.54)***
Plasma glucose 60 min (mg/dl)	132.5 (2.55)	142.7 (1.69)	150.3 (1.71)	169.9 (2.04)***
Plasma glucose 120 min (mg/dl)	109.6 (2.04)	115.3 (1.35)	120.7 (1.35)	130.7 (1.62)***
HbA_{1c} (%)	4.9 (0.05)	5.1 (0.04)	5.1 (0.04)	5.3 (0.04)***
Cholesterol (mg/dl)	192.1 (2.53)	193.4 (1.65)	194.8 (1.63)	205.6 (1.95)***
LDL-cholesterol (mg/dl)	115.0 (2.25)	121.1 (1.47)	117.9 (1.45)	121.9 (1.77)**
HDL-cholesterol (mg/dl)	57.5 (0.67)	47.2 (0.44)	42.5 (0.43)	38.4 (0.51)***
Triglyceride (mg/dl)	102.0 (5.72)	128.5 (3.69)	179.9 (3.65)	235.9 (4.35)***
Systolic BP (mm Hg)	106.7 (0.91)	111.8 (0.60)	119.9 (0.60)	125.1 (0.71)***
Diastolic BP (mm Hg)	69.3 (0.68)	72.5 (0.45)	76.8 (0.45)	82.7 (0.53)***
Women, no. (%)	199 (76.2)	456 (76.4)	420 (70.7)	305 (73.3)
Developed type 2 diabetes, no. (%)	17 (6.5)	68 (11.4)	91 (15.3)	106 (25.5)***
Normal weight (BMI <25 kg/m^2), no. (%)	76 (29.2)	115 (19.6)	70 (12.0)	33 (8.0)***
Overweight (BMI 25–29.9 kg/m^2), no. (%)	114 (43.8)	291 (49.5)	299 (51.1)	175 (42.4)***
Obese (BMI ≥30 kg/m^2), no. (%)	70 (26.9)	182 (31.0)	216 (36.9)	205 (49.6)***
Normal glucose tolerance, no. (%)	262 (100.00)	454 (76.0)	356 (60.0)	114 (27.4)***
Impaired fasting glucose, no. (%)	0 (0.00)	143 (24.0)	237 (40.0)	302 (72.6)***
Hyperteriglyceridemia, no. (%)	0 (0.00)	106 (18.5)	337 (57.5)	371 (89.4)***
Hypertension	0 (0.0)	61 (10.6)	185 (32.5)	276 (66.7)***
Low HDL, no. (%)	0 (0.00)	287 (51.8)	429 (74.4)	370 (89.8)***
Abdominal obesity, no. (%)	76 (29.6)	205 (35.3)	288 (49.4)	240 (59.6)***

Data are express as mean (SE) or number (%). The difference in the mean or percentage of the variables between no metabolic abnormality, 1, 2 and ≥3 MA.
* $P<0.05$.
** $P<0.01$.
*** $P<0.001$.

Table 3
Incidence rates and odds ratios (95% CI) of type 2 diabetes by number of MA and BMI status, the Isfahan Diabetes Prevention Study, 2003–2011.

Variables	At risk No. (%)	Cases No. (%)	Person-year	Incidence/1000 person-year (95% CI)	Crude OR (95% CI)	Age-adjusted OR (95% CI)	Age-, gender-adjusted OR (95% CI)
BMI <25 kg/m^2							
No MA	76 (4.1)	1 (1.3)	567	1.8 (0.06, 9.8)	1.00	1.00	1.00
1 MA	115 (6.2)	8 (7.0)	854	9.4 (4.1, 18.4)	5.61 (0.69, 45.78)	5.59 (0.68, 45.61)	5.59 (0.68, 45.61)
2 MA	70 (3.8)	9 (12.9)	472	19.1 (8.7, 35.8)	11.07 (1.36, 89.77)*	10.92 (1.35, 88.59)*	10.92 (1.35, 88.59)*
≥3 MA	33 (1.8)	8 (24.2)	199	40.2 (17.5, 77.5)	24.00 (2.86, 201.47)**	23.68 (2.82, 198.81)**	23.68 (2.82, 198.81)**
BMI 25–29.9 kg/m^2							
No MA	114 (6.2)	4 (3.5)	884	4.5 (1.3, 11.5)	2.73 (0.30, 24.88)	2.73 (0.30, 24.89)	2.76 (0.30, 25.19)
1 MA	291 (15.8)	29 (10.0)	2218	13.1 (8.7, 18.7)	8.30 (1.12, 61.95)*	8.14 (1.09, 60.81)*	8.14 (1.09, 60.81)*
2 MA	299 (16.2)	45 (15.1)	2142	21.0 (15.3, 28.0)	13.29 (1.80, 98.01)*	12.51 (1.69, 92.43)*	12.51 (1.69, 92.43)*
≥3 MA	175 (9.5)	43 (24.6)	1168	36.8 (26.8, 49.3)	24.43 (3.30, 181.03)**	22.51 (3.03, 167.01)**	22.51 (3.03, 167.00)**
BMI ≥30 kg/m^2							
No MA	70 (3.8)	12 (17.1)	547	21.9 (11.4, 38.0)	15.52 (1.96, 122.80)**	15.77 (1.99, 125.02)**	15.77 (1.99, 125.02)*
1 MA	182 (9.9)	28 (15.4)	1351	20.7 (13.9, 29.8)	13.64 (1.82, 102.15)*	13.09 (1.74, 98.30)*	13.09 (1.74, 98.30)*
2 MA	216 (11.7)	36 (16.7)	1620	22.2 (15.6, 30.6)	15.00 (2.02, 111.41)**	14.53 (1.95, 108.06)**	14.53 (1.95, 108.06)**
≥3 MA	205 (11.1)	55 (26.8)	1391	39.5 (30.0, 51.2)	27.50 (3.73, 202.60)**	25.35 (3.44, 187.00)**	25.34 (3.44, 186.99)**
Total							
No MA	260 (14.1)	17 (6.5)	1998	8.5 (4.9, 13.6)	1.00	1.00	1.00
1 MA	588 (31.8)	65 (11.4)	4423	14.7 (11.1, 18.2)	1.85 (1.07, 3.22)*	1.78 (1.02, 3.10)*	1.77 (1.01, 3.08)*
2 MA	585 (31.7)	90 (15.3)	4234	21.3 (16.9, 25.6)	2.61 (1.52, 4.47)**	2.49 (1.45, 4.28)**	2.48 (1.44, 4.26)**
≥3 MA	413 (22.4)	106 (25.5)	2758	38.4 (31.6, 46.3)	4.93 (2.88, 8.45)***	4.50 (2.62, 7.73)***	4.47 (2.60, 7.69)***
Total							
BMI <25 kg/m^2	294 (15.9)	26 (8.8)	2092	12.4 (8.1, 18.1)	1.00	1.00	1.00
BMI 25–29.9 kg/m^2	879 (47.6)	121 (13.8)	6412	18.9 (15.5, 22.2)	1.65 (1.05, 2.57)*	1.60 (1.02, 2.51)*	1.61 (1.03, 2.51)*
BMI ≥30 kg/m^2	673 (36.5)	131 (19.5)	4909	26.7 (22.2, 31.2)	2.49 (1.60, 3.89)***	2.43 (1.55, 3.80)***	2.43 (1.55, 3.80)***

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

two MA and 38.4 (95% CI 31.6, 46.3) for those with ≥3 MA. Compared with participants without MA, the risk of T2D was 78% higher in those with one (OR 1.78; 95% CI: 1.02, 3.10), 2.5 times higher in those with two (OR 2.49; 95% CI: 1.45, 4.28), 4.5 times higher in those with ≥3 MA (OR 4.50; 95% CI: 2.62, 7.73) in age-adjusted model. Controlling for age and gender did not appreciably alter the OR compared to the age-adjusted model (Table 3).

The incidence of T2D was 12.4 per 1000 person-years (95% CI 8.1, 18.1) for participants with normal weight, 18.9 (95% CI 15.5, 22.2) for participants with overweight, and 26.7 (95% CI 22.2, 31.2) for obese. Compared with participants with normal weight, the risk of T2D was 60% higher in those with overweight (OR 1.60; 95% CI: 1.02, 2.51), and 143% higher in obese (OR 2.43; 95% CI: 1.55, 3.80), in age-adjusted model. Controlling for age and gender did not appreciably alter the OR compared to the age-adjusted model (Table 3).

When we assessed the combined effect of MA and BMI status, as expected the normal weight individuals without MA had the lowest incidence rate of diabetes. The incidence rate of diabetes was markedly high in normal weight individuals with ≥3 MA (40.2 per 1000 person year) and obese individuals with ≥3 MA (39.5 per 1000 person year). The incidence rate of T2D increased with increasing MA in all BMI categories (Table 3). Of the 115 participant with normal weight and one MA at baseline 8 (7.0%) subsequently progressed to T2D at a rate of 9.4 (95% CI 4.1, 18.4) per 1000 person-year. Of the 70 participants with normal weight and two MA at baseline 9 (12.9%) subsequently progressed to T2D at a rate of 19.1 (95% CI 8.7, 35.8) per 1000 person-year. Of the 33 participants with normal weight and ≥3 MA at baseline 8 (24.2%) subsequently progressed to T2D at a rate of 40.2 (95% CI 17.5, 77.5) per 1000 person-year. These were higher than the progression rates seen for those without MA, 1.8 (95% CI 0.06, 9.8).

As shown in Table 3, the progression to diabetes increased across the 12 subject groups, from 1.8 per 1000 person-year in the normal weight and no MA group, to 40.2 per 1000 person-year in the combined normal weight and ≥3 MA group and 39.5 per

Table 4
Odds ratios (OR) (95% CI) of normal weight, overweight and obese individuals by MA, The Isfahan Diabetes Prevention Study, 2003–2011.

Variables	No MA	Crude OR (95% CI)	Age-adjusted OR (95% CI)	Age-, gender-adjusted OR (95% CI)
BMI <25 kg/m^2				
1 MA	1.00	5.61 (0.69, 45.78)	5.59 (0.68, 45.61)	5.59 (0.68, 45.61)
2 MA	1.00	11.07 (1.36, 89.77)*	10.92 (1.35, 88.59)*	10.92 (1.35, 88.59)*
≥3 MA	1.00	24.00 (2.86, 201.47)**	23.68 (2.82, 198.81)**	23.68 (2.82, 198.81)**
BMI 25–29.9 kg/m^2				
1 MA	1.00	3.0 4 (1.05, 8.86)*	3.07 (1.05, 8.93)*	3.04 (1.04, 8.85)*
2 MA	1.00	4.87 (1.71, 13.88)**	4.78 (1.68, 1.3.64)**	4.74 (1.66, 13.51)**
≥3 MA	1.00	8.96 (3.12, 25.74)***	8.96 (3.12, 25.74)***	8.88 (3.09, 25.51)***
BMI ≥30 kg/m^2				
1 MA	1.00	0.88 (0.42, 1.84)	0.83 (0.39, 1.75)	0.83 (0.39, 1.75)
2 MA	1.00	0.97 (0.47, 1.98)	0.90 (0.44, 1.87)	0.90 (0.44, 1.87)
≥3 MA	1.00	1.77 (0.89, 3.55)	1.58 (0.78, 3.18)	1.58 (0.78, 3.18)

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

1000 person-year in combined obese and ≥3 MA. Compared with participants with normal weight and without MA, the risk of T2D was 24.0 times higher in those with normal weight and ≥3 MA at baseline (OR 24.0; 95% CI: 2.86, 201.5), 24.4 times higher in those with overweight and ≥3 MA (OR 24.43; 95% CI: 3.30, 181.03) and 27.5 times higher in those with obesity and ≥3 MA (OR 27.5; 95% CI: 3.73, 202.60) in crude models. Controlling for age and gender did not appreciably alter the OR compared to the crude model (Table 3).

When we re-analyzed the data, compared participants with normal weight and without MA vs. normal weight with one, two, and ≥3 MA, overweight individuals and without MA vs. overweight with one, two, and ≥3 MA, or obese individuals without MA vs. obese with one, two, and ≥3 MA, the risk of T2D was statistically significant in normal weight and overweight. However, among obese individuals, when the MA was compared with obese individuals without MA, modest increases in ORs were not statistically significant. Controlling for age and gender, did not appreciably alter the ORs compared to the unadjusted model (Table 4).

3.3. Kaplan–Meier survival analysis

Fig. 1 shows the Kaplan–Meier estimates of the probability of remaining free of T2D in subjects with normal weight, overweight and obese combined with number of MA within a mean (SD) 7.3 (2.2) year (median, 8; range, 1–10). At 5 years, 80.3% of participants with normal weight but without MA, 75.7% of participants with one, 68.6% of participants with two, 54.5% of participants with ≥3 MA did not have T2D. At 7 years, 57.9% of participants with normal weight but without MA, 53.0% of participants with one, 41.4% with two, and 27.3% with ≥3 MA did not have T2D.

At 5 years, 85.1% of participants with overweight but without MA, 81.8% of participants with one, 77.3% with two, and 66.9% with ≥3 MA did not have T2D. At 7 years, 61.4% of participants with overweight but without MA, 58.8% of participants with one, 47.8% with two, and 40.0% with ≥3 MA did not have T2D.

At 5 years, 90.0% of participants with obesity but without MA, 80.8% of participants with one, 82.4% with two, 68.3% with ≥3 MA, did not have T2D. At 7 years, 62.9% of participants with obesity but without MA, 58.2% of participants with one, 57.4% with two, 43.4% with ≥3 MA, did not have T2D.

It can be seen that in normal weight, overweight, and obese, participants with higher number of MA had increased yearly probability of T2D, which was significantly different compared with participants with normal weight, overweight and obese but without MA ($P < 0.05$).

4. Discussion

The present study showed that the number of MA is a strong predictor of incident T2D independent of BMI status and overweight and obesity is a predictor of incident T2D independent of MA in a cohort of FDR of patients with T2D in Iran. The highest risk estimate was seen in obese and normal weight participants with ≥3 MA. Individuals, who had ≥3 MA, even in normal weight subjects, were substantially at higher risk of future T2D. This observation was also confirmed by the results from Kaplan–Meier method of survival analysis. These associations suggest that in participants without T2D, number of MA may be more contribute to the development of T2D than BMI status. Several cohort studies have investigated the combined effect of an elevated BMI and the presence of MA in the development of T2D [17,18,26,30–34]. Results suggest that a MHO phenotype might be associated with a non-significant or significant increased risk of the development of T2D in comparison with metabolically healthy

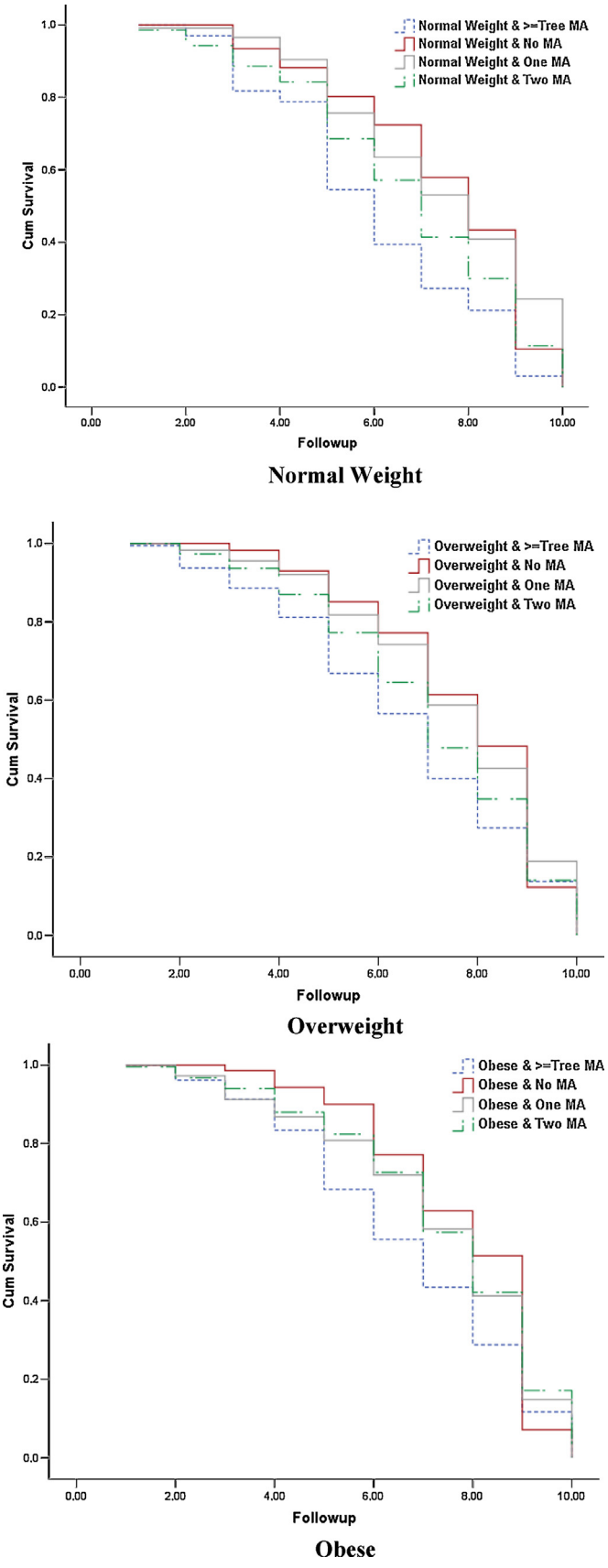

Fig. 1. Kaplan–Meier survival curve showing progression rate to type 2 diabetes in individuals with normal weight, overweight, and obesity, combined with number of MA.

normal weight individuals as defined in each study, which was in line with our results. The absence of a universal definition for the MHO phenotype and different definitions of obesity, T2D, and metabolic status, different ethnic group, incomplete control for confounders or limited number of study population has been raised as an important issue and may explain the inconclusive associations and might result in the misclassification of some individuals who actually have a high-risk phenotype as having low-risk phenotype. Meigs et al. [18] reported that all participants with metabolic syndrome were at higher risk for diabetes regardless of BMI status, whereas overweight/obese individuals without metabolic syndrome were at no increased risk. Sung et al. [32] in a study that investigate the individual role of insulin resistance, overweight or obesity, and fatty liver as risk factors for T2D reported that the overweight or obese status without insulin resistance and no liver fat was not associated with a significantly increased risk of T2D compared with the absence of any of the three factors. In contrast, our results showed that MHO individuals were not protected from the risk of T2D. In a meta-analysis of seven epidemiological studies and original data on elderly English adults, Bell et al. [40] reported that MHO individuals had an increased risk of develop diabetes compared with metabolically healthy and normal weight individuals. Other studies also suggested that MHO individuals had an increased risk of T2D [25,33,41,42]. We are agree with Vazquez et al. [3] that as few as one MA was not considered to be a metabolically benign state for the development of T2D, even among normal weight individuals; the presence of the minimum number of MA and the presence of overweight or obesity separately increased the risk of T2D. We also observed that among normal weight individuals the risk of T2D escalated with increases in the number of MA.

The present study had some limitations. Our study was limited 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 could not include several possible confounding variables 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, MA and incidence of T2D. In addition, the number of incident cases of diabetes in some of the BMI/MA categories was small as reflected by the very wide CIs around the OR and follow-up longer than 8 years might be required to be certain that overweight or obese individuals without MA are indeed high risk. Finally, our data cannot be readily generalized to other FDR populations because the distribution of obesity, MA is known to vary substantially across different race/ethnic groups [43].

In conclusion, these data provides further evidence that MA in normal weight, overweight and obese increased risk for incident T2D in high-risk individuals. In addition, the higher the number of MA, the greater the risk of T2D in normal weight, overweight and obese individuals. Assessments of MA, regardless of BMI, appear to identify subjects at increased risk of developing T2D and who may benefit from lifestyle modification.

Author's contributions

Janghorbani M. conceived and designed the study, analyzed the data and wrote the manuscript, Soltanian N., Sirous M. and Iraj B. provided the critical revision. Amini M., recruited samples and contributed to the discussion and revision of the manuscript and obtained funding for the IDPS. All authors have given final approval of the version to be published.

Conflict of interest

The authors have none to declare.

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