



Original article

Metabolic syndrome in first degree relatives of patients with type 2 diabetes: Incidence and risk factors

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ABSTRACT

Aims: First degree relatives (FDRs) of people with type 2 diabetes are at greater cardiovascular and diabetes risk. It is not known whether they are also at greater risk of metabolic syndrome (MetS). The objectives of present study were to assess the incidence of and risk factors for the development of MetS in FDRs of patients with type 2 diabetes.

Methods: A total of 3217 (842 men and 2375 women) FDRs of consecutive patients with type 2 diabetes aged 30–70 years in 2003–2005 were followed through 2010. At baseline participants underwent a standard 75 g 2-h standard OGTT and HbA_{1c} measurements. MetS was defined by the NCEP-ATP III. The study group consisted of 734 participants without MetS and history of known diabetes at baseline and had at least one subsequent review in mean (SD) follow-up period of 5.5 (1.2) years.

Results: The prevalence of MetS was 35.8% (95% CI: 34.2, 37.5). The incidence of MetS was 4.3% (95% CI: 3.7, 4.9) (4.6% men and 4.2% women) per year. Multivariate analysis revealed that impaired glucose tolerance (IGT) (RR 1.89 (95% CI: 1.28, 2.79)), impaired fasting glucose (IFG) (RR 1.39 (95% CI: 1.10, 1.73)) and lower HDL (RR 1.34 (95% CI: 1.12, 1.60)) were associated with MetS.

Conclusions: The findings of this study illustrate for the first time the incidence of MetS in FDRs of patients with type 2 diabetes in Iran. Risk of MetS may increase with IGT, IFG and lower HDL.

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1. Introduction

Metabolic syndrome (MetS) is an important public health problem worldwide, and its prevalence is increasing [1]. Patients with MetS are at greater risk of cardiovascular disease and type 2 diabetes [2]. This is particularly relevant in first degree relatives (FDRs) of people with type 2 diabetes, who are at even greater cardiovascular and diabetes risk [3,4].

Despite abundant epidemiological research that has been published on MetS, there are few prospective data on the incidence of MetS and none in Iran. At present, no data exist about the incidence and risk factors associated with MetS in FDRs of people with type 2 diabetes.

With the increasing prevalence of diabetes and obesity worldwide [1,2,5] and the number of first degree relatives (FDRs) of people with type 2 diabetes, and thus an increased risk of developing MetS, will also increase. Identifying risk factors associated with susceptibility to MetS becomes increasingly

important. Accurate information regarding the incidence of MetS and associated risk factors in FDRs of people with diabetes is important to get a better understanding of the etiology and possibly to prevent or delay its development and complications of disease in this population. However, based on the high prevalence and high incidence of obesity and type 2 diabetes in the FDRs of people with type 2 diabetes [3,4], one can expect that the inheritance pattern may play an essential role in the development of MetS.

The objective of this study was therefore to estimate the incidence of MetS in FDRs of patients with type 2 diabetes and to identify its risk factors.

2. Subjects and methods

2.1. Participants and data collection

The Isfahan Diabetes Prevention Study (IDPS) is being conducted in Isfahan, a very large urban area situated in central Iran, located on 1590 m height above sea level, between latitudes 30 and 34 degrees north of the equator and longitude 49–55° east, with a population of almost four and half million (4,559,256 in 2006 (men 2,335,399, women 2,223,857)). The IDPS is an ongoing cohort study to assess the efficacy of diet and intensive exercise to prevent or delay the onset of type 2 diabetes in FDRs of patients with

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type 2 diabetes. The study participants were recruited and their baseline data were collected between 2003 and 2005 when 3217 (842 men and 2375 women) FDRs of a consecutive sample of patients with type 2 diabetes attending clinics at Isfahan Endocrine and Metabolism Research Center were included in the study. The participants completed laboratory tests including standard 75 g 2-h oral glucose tolerance test (OGTT), glycosylated hemoglobin (HbA_{1c}) and a questionnaire on their health status and on various potential risk factors for diabetes and MetS. Participants received follow-up tests according to a medical care standard in diabetes [6] to update information on demographic, anthropometric, and lifestyle factors and on newly diagnosed diabetes and MetS. Accordingly, if OGTT was normal at baseline, repeated testing was carried out at least at 3-year intervals. Otherwise, repeat testing was carried out annually. The IDPS baseline methods have been described in detail elsewhere [3,4]. The participants included siblings and children. Institutional review board of the Isfahan University of Medical Sciences approved this study (approval no. 189135 dated 13 April 2010), and an informed consent form was signed by each participant.

2.2. Ascertainment of MetS

Cases of MetS were identified according to the Third report of the National Cholesterol Education Program Adult Treatment Panel III (NCEP-ATP III) [7]. It was considered present when at least three of the following characteristics were observed: waist circumference ≥ 102 cm in men and ≥ 88 cm in women; triglycerides ≥ 150 mg/dl; high density lipoprotein (HDL) cholesterol < 40 mg/dl in men and < 50 mg/dl in women; blood pressure (BP) $\geq 130/85$ mm Hg; and fasting glucose ≥ 100 mg/dl. Pregnant women were excluded. This study used data of 734 FDRs (195 men and 539 women) who were free of MetS at registration and without history of known diabetes mellitus and had at least one subsequent review in mean (standard deviation [SD]) follow-up period of 5.5 (1.2) years and who were aged 30 years and over (Fig. 1).

2.3. Variables measured

Subjects were asked to abstain from vigorous exercise in the evening before and in the morning of the investigations. Smokers were encouraged to abstain from smoking in the morning of the investigations. On arrival in the clinic the information given by the FDRs in the questionnaire on family history was first verified. Then height and weight were measured with subjects in light clothes and without shoes using standard apparatus. Weight was measured to the nearest 0.1 kg on a calibrated beam scale. Height, waist and hip circumference were measured to the nearest 0.5 cm with a measuring tape. Waist was measured midway between the lower rib margin and the iliac-crest at the end of a gentle expiration. Hip circumference was measured over the greater trochanters directly

over the underwear. Body mass index (BMI) (weight/height² [kg/m²]) is recognized as the measure of overall obesity. Normal BMI was defined as BMI < 25 , overweight as BMI 25–29.99, and obesity as BMI ≥ 30 . A waist-to-hip ratio (WHR) of < 0.80 in women and < 0.95 in men was considered normal. Resting blood pressure (BP) was measured after subjects had been seated for 10 min by using a mercury sphygmomanometer and appropriately sized cuffs, using standard techniques. Subjects with fasting plasma glucose (FPG) < 126 mg/dl underwent a standard OGTT (75 g glucose 2-h) according to the American Diabetes Association criteria [8]. Venous blood was sampled 30, 60, and 120 min after oral glucose administration. Plasma samples obtained after centrifugation were analyzed the same day.

HbA_{1c} (measured by ion-exchange chromatography), total cholesterol, triglyceride, HDL (measured using standardized procedures), and low-density lipoprotein (LDL) cholesterol (calculated by the Friedewald equation [9]) provided total triglycerides did not exceed 400 mg/dl) were assessed. Assay of blood samples were performed in the central laboratory of the Isfahan Endocrine and Metabolism Research Center using enzyme-linked method.

2.4. Definitions

Impaired glucose tolerance (IGT) was defined as FPG < 126 mg/dl, but the 2-h plasma glucose concentration ≥ 140 and < 200 mg/dl. If the FPG was in the range of 100–126 mg/dl and the 2-h plasma glucose was < 140 mg/dl, it was considered as impaired fasting glucose (IFG); whereas, if the FPG was below 100 mg/dl and the 2-h plasma glucose < 140 mg/dl, it was considered a sign of normal glucose tolerance (NGT) [8].

2.5. Determination of MetS incidence

Incidence of MetS was expressed as the number of cases of MetS per 100 person-years of follow-up. As the relevant period was considered the date of completion of the baseline examination between 2003 and 2005 until the either (i) occurrence of MetS, (ii) the date of the last completed follow-up, (iii) death, or (iv) end of follow-up on December 31, 2010, whichever came first. For ease of interpretability, we report the incidence rates in terms of percent per year.

2.6. Statistical analysis

Statistical methods used included Student's *t*-test; Chi squared test, analysis of variance or Kruskal–Wallis tests for normally or non-normally distributed continuous variables respectively and Cox's proportional hazards model. Univariate and multivariate Cox's proportional hazards models were fitted to identify predictors of new-onset MetS using SPSS version 18 for Windows (SPSS Inc., Chicago, IL, USA). All the significant baseline variables in the bivariate analysis were included as independent variables in the multivariate-adjusted analyses. Variables age, gender, BMI, waist circumference, triglyceride, LDL, HDL, total cholesterol, glucose intolerance and BP were entered in the multivariate-adjusted analyses as categorical variables. Age-adjusted means were calculated and compared using general linear models. All tests for statistical significance were two-tailed, confidence intervals (CI) were set at 95% and $P < 0.05$ was considered significant.

3. Results

3.1. Subject characteristics

The age-adjusted characteristics of the FDRs who completed the baseline study ($n = 3217$), non-attendees ($n = 2483$), and the

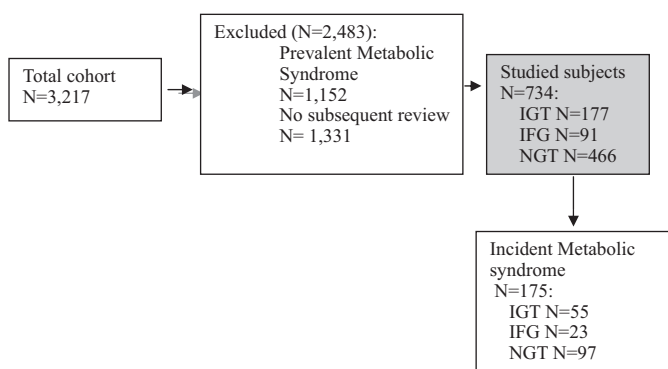


Fig. 1. Schematic diagram of the study population.

Table 1

Age and age-adjusted means (SE) and proportion of selected characteristics of the baseline, non-attendees and attendees at follow-up samples.

Characteristics	Baseline N = 3217	Excluded N = 2483	Attendees at follow-up N = 734
Age (year)	43.3 (0.12)	43.7 (0.14)	42.0 (0.25) [†]
Height (cm)	159.7 (0.15)	159.7 (0.17)	159.4 (0.31)
Weight (kg)	73.9 (0.22)	75.0 (0.25)	70.2 (0.46) [†]
Body mass index (kg/m ²)	29.0 (0.08)	29.4 (0.09)	27.7 (0.16) [†]
Waist circumference (cm)	89.3 (0.17)	90.2 (0.20)	86.1 (0.36) [†]
Hip circumference (cm)	107.7 (0.16)	108.4 (0.18)	105.4 (0.34) [†]
Waist-to-hip ratio	0.83 (0.001)	0.83 (0.001)	0.82 (0.003) [†]
Fasting glucose baseline (mg/dl)	101.1 (0.51)	103.6 (0.58)	92.7 (1.06) [†]
Plasma glucose 30 min (mg/dl)	149.4 (0.80)	152.0 (0.92)	141.2 (1.64) [†]
Plasma glucose 60 min (mg/dl)	156.4 (1.03)	160.2 (1.18)	144.0 (2.12) [†]
Plasma glucose 120 min (mg/dl)	126.8 (0.96)	129.8 (1.10)	117.0 (2.00) [†]
HbA _{1c} (%)	5.2 (0.02)	5.3 (0.02)	5.0 (0.05) [†]
Cholesterol (mg/dl)	198.7 (0.71)	201.7 (0.81)	188.6 (1.50) [†]
LDL-cholesterol (mg/dl)	120.4 (0.63)	122.2 (0.72)	114.4 (1.35) [†]
HDL-cholesterol (mg/dl)	45.8 (0.22)	45.3 (0.25)	47.5 (0.47) [†]
Triglyceride (mg/dl)	168.5 (1.86)	177.0 (2.11)	139.4 (3.91) [†]
Systolic BP (mm Hg)	115.5 (0.29)	116.9 (0.33)	110.5 (0.61) [†]
Diastolic BP (mm Hg)	75.0 (0.22)	76.2 (0.25)	71.0 (0.46) [†]
Characteristics	Baseline N = 3217 %	Excluded N = 2483 %	Attendees at follow-up N = 734 %
Men	26.2	26.2	26.5
Obesity	36.4	40.3	22.9 [†]
Normal glucose tolerance	51.9	48.6	63.1 [†]
Impaired fasting glucose	18.3	20.0	12.5 [†]
Impaired glucose tolerance	20.6	19.5	24.3 [†]
Diabetes mellitus	9.2	11.9	–

Age-adjusted means were calculated using general linear models. The difference in the mean or percentage of the variables between excluded and attendees at follow-up. [†] $P < 0.001$.

attendees at follow-up ($n = 734$) are shown in Table 1. As expected, attendees at the follow-up visit differ significantly from non-attendees regarding most baseline characteristics: age, weight, BMI, WC, hip circumference, waist-to-hip ratio (WHR) and levels of plasma glucose, HbA_{1c}, cholesterol, LDL, HDL, triglyceride, BP and obesity.

3.2. Prevalence

Of the 3217 FDRs of people with type 2 diabetes (842 men and 2375 women), 1152 had MetS. Overall prevalence of MetS was 35.8% (95% CI: 34.2, 37.5). Prevalence of MetS was higher in women (37.5%; 95% CI: 35.5, 39.4) than men (31.3%; 95% CI: 28.1, 34.4). As expected, there was a statistically increasing prevalence of MetS with increasing age.

3.3. Incidence

Of the 734 non-diabetic FDRs of patients with type 2 diabetes without MetS, 175 (23.8%) (49 men and 126 women) developed MetS in 4065 (1064 men and 3001 women) person-years of follow-up. The overall incidence of subsequent MetS was 4.3% (95% CI: 3.7, 4.9) per year. Incidence rates were slightly higher in men (4.6% (95% CI: 3.4, 6.1) per year) than women (4.2% (95% CI: 3.5, 5.0)). This difference was not statistically significant. Of the 177 FDRs of patients with type 2 diabetes who had IGT at initial registration, 55 subsequently developed MetS, giving an incidence of 5.9% (95% CI: 4.5, 7.6) per year. This was higher than the incidence rates seen for NGT, 3.6% per year (95% CI: 2.9, 4.4) ($P < 0.05$). Of the 91 FDRs who had IFG at initial registration, 23 subsequently developed MetS, giving an incidence of 5.1% (95% CI: 3.3, 7.5) per year.

3.4. Risk factors

Table 2 shows the group means (SE) and proportions for those FDRs who did and did not develop MetS. As expected, those who developed MetS were older and had higher systolic BP, weight, BMI, WC, WHR, FPG, plasma glucose at 30, 60 and 120 min, HbA_{1c}, triglyceride and number of follow-up visit and have lower HDL, but have higher proportion of IGT and obesity at baseline.

A univariate analysis (Table 3) showed that FPG, HbA_{1c}, triglyceride, BMI, abdominal obesity (WHR or WC criteria), and IGT were significantly associated with the risk of developing MetS. Although, there was a crude association of MetS with general and abdominal obesity, this effect did not remain significant after adjustment.

The incidence of MetS was also analyzed with multivariate model. Cox's proportional hazards model showed that IGT, IFG and lower HDL at baseline significantly predicted the onset of MetS after mean 5.5 years. No other variables were significant (Table 3).

4. Discussion

This is the first follow-up study among the FDRs of patients with type 2 diabetes that reports the incidence of MetS and relative risk for progression to MetS according to the NCEP-ATP III proposed criteria in Iran. In this follow-up study of 734 FDRs of patients with type 2 diabetes, the incidence of MetS was 4.3% per year (175 patients) over an average follow-up of 5.5 years. The incidence rates were 3.6% per year in FDRs with NGT, 5.9% in IGT, and 5.1% in IFG. It seems that the NGT and higher HDL level at baseline lower the risk of progression to MetS. Incidence and prevalence rates of MetS in general populations in various studies from around the world show considerable variation [10,11]. Estimates of incidence

Table 2
Age and age-adjusted means (SE) and proportions of selected baseline characteristics between 175 first-degree relatives of patients with type 2 diabetes who did and 559 who did not developed metabolic syndrome (MetS).

Variables	Developed MetS Mean (SE)	Not developed MetS Mean (SE)	Difference (95% CI)
Age (year)	43.1 (0.48)	41.6 (0.27)	1.5 (0.42, 2.58)**
Follow-up (year)	5.6 (0.09)	5.5 (0.05)	0.1 (−0.11, 0.31)
Number of follow-up visit	2.9 (0.08)	2.7 (0.05)	0.2 (0.01, 0.39)*
Height (cm)	159.8 (0.62)	159.5 (0.34)	0.3 (−1.20, 1.60)
Weight (kg)	73.9 (0.79)	69.2 (0.43)	4.7 (2.84, 6.36)***
BMI (kg/m ²)	29.0 (0.27)	27.2 (0.15)	1.8 (1.19, 2.41)***
Waist circumference (cm)	89.7 (0.61)	84.7 (0.34)	5.0 (3.91, 6.69)***
Waist-to-hip ratio	0.83 (0.005)	0.81 (0.003)	0.02 (0.02, 0.04)***
Systolic BP (mm Hg)	111.3 (1.01)	109.3 (0.56)	2.0 (0.29, 4.91)*
Diastolic BP (mm Hg)	72.8 (0.80)	70.5 (0.45)	2.3 (−0.21, 3.41)
Baseline fasting glucose (mg/dl)	94.3 (0.84)	91.5 (0.47)	2.8 (1.31, 5.09)**
Plasma glucose 30 min (mg/dl)	149.5 (2.34)	137.5 (1.31)	12.0 (7.50, 18.10)***
Plasma glucose 60 min (mg/dl)	155.2 (3.06)	138.1 (1.72)	17.1 (11.6, 25.4)***
Plasma glucose 120 min (mg/dl)	123.8 (2.46)	113.5 (1.38)	10.3 (5.17, 16.20)***
HbA _{1c} (%)	5.2 (0.07)	4.9 (0.04)	0.3 (0.15, 0.44)**
Triglyceride (mg/dl)	163.2 (6.47)	130.8 (3.51)	32.4 (18.7, 47.5)***
Cholesterol (mg/dl)	189.8 (2.94)	186.8 (1.60)	3.0 (−2.16, 11.5)
HDL cholesterol (mg/dl)	45.1 (0.97)	48.0 (0.52)	−2.9 (−4.95, −0.65)**
LDL cholesterol (mg/dl)	112.6 (2.74)	113.7 (1.47)	−1.1 (−5.89, 6.49)

Variables	Developed MetS %	Not developed MetS %	Difference (95% CI)
Men	28.0	26.1	1.9 (−5.7, 9.5)
Obesity (BMI ≥30)	34.1	19.4	14.7 (6.8, 22.6)***
Normal glucose tolerance	54.6	65.5	−10.9 (−19.3, 2.5)*
Impaired fasting glucose	13.2	12.2	1.0 (−4.7, 6.7)
Impaired glucose tolerance	31.6	21.9	9.7 (1.9, 17.4)*
Smoking			
Never-smoker	94.4	87.5	6.9 (−19.8, 5.9)
Current-smoker	5.6	12.5	−
Education			
Primary or below	56.7	48.3	8.4 (−0.07, 17.0)
Secondary	28.7	34.3	−5.6 (−13.5, 2.2)
Matriculation or above	14.6	17.4	−2.8 (−9.0, 3.4)

CI = confidence interval. The difference in the mean or percentage of the variables between diabetes and no diabetes.

* $P < 0.05$.

** $P < 0.01$.

*** $P < 0.001$.

and prevalence of MetS will depend upon the methodological factors, the definition of the MetS used, and the composition of the community examined by age and gender, making comparisons between studies limited. Several cross-sectional studies conducted at different moments and in different populations and suggested varied prevalence. The prevalence of MetS in FDRs of patients with type 2 diabetes is higher than the general population in Iran ranging from 10.7% to 35.1% for men and women over 20 years [12–14]. In the National Health and Nutritional Examination Survey III, the MetS prevalence was 23.7% which varied from 19.9% to 35.6% according to race and gender [15]. In European societies, the prevalence of MetS in people 40–55 years is 7–36.3% in men and 5–22% in women, using the WHO definition [16]. The prevalence of MetS in Turkey is approximately 32.2% in men and 45% in women [17]. The prevalence of MetS in FDRs of people with type 2 diabetes of 35.8% as reported in this study is higher than the general population and requires serious consideration since patients with MetS are at greater risk of cardiovascular disease and type 2 diabetes.

Consistent with prior studies [3,4,6–9,15], the present study found similarly higher prevalence of MetS in women. The reason(s) for this gender difference in MetS has not been explored, but some studies suggest that female sex hormones may contribute [10–13,18] while others failed to see an effect on glucose metabolism [9,13,15].

The incidence of MetS that we report in this study is lower than that reported in Korean male workers [19]. Longitudinal study of

Korean male workers ages 30–39 reported that incidence of MetS was 7.7% per year. But this was higher than that reported in Japanese men ages 35–59 which was 3.6% per year [20]. Almost similar to our findings, another study from an urban area of Portugal reported an incidence of 4.7% per year, similar in men and women [21]. Baltimore Longitudinal Study of Aging reported an incidence of 25.5% (5.5% per year) in men and 14.8% (2.7% per year) in women after an average follow-up of 6-years [22]. The Insulin Resistance Atherosclerosis Study reported an incidence of 17.1% (4.7% per year) in men and 20.9% (4.8% per year) in women after a follow-up period of 5-years [23]. The San Antonio Heart Study showed a 15% incidence of MetS in men (2.0% per year) and a 17% (2.3% per year) in women after 8 years of follow-up [24].

The role of gender as a risk factor for MetS remains unsettled. There have been conflicting reports about the relationship between gender and MetS incidence; in some studies MetS incidence was higher in women [23–25]; whereas in other studies MetS incidence was higher in men [22,26–28]. Similar to our results, some other cohorts from different ethnic background reported no significant differences regarding gender [21,29].

The excess risk of MetS associated with FDRs of patients with type 2 diabetes was amplified in the presence of IFG, IGT and low HDL. The FDRs of people with type 2 diabetes who were IFG or IGT at baseline were at higher risk of MetS than NGT relatives. This suggests that genetic factors beside lifestyle, obesity, and dyslipidemia may be a part of the risk factors for MetS. Diet with high trans unsaturated fat could lower HDL cholesterol levels,

Table 3
Incidence rates and relative risks (RR) for metabolic syndrome by baseline variables.

Variables	At risk (no.)	Cases (no.)	Person-year	Incidence/100 person-year	Crude RR (95% CI)	Multiple-adjusted RR (95% CI) ^a
All	734	175	4065	4.3	–	–
Gender						
Men	195	49	1064	4.6	1.00	1.00
Women	539	126	3001	4.2	0.91 (0.66, 1.26)	0.97 (0.78, 1.19)
Age (year)						
<40	288	62	1629	3.8	1.00	1.00
40–49	335	81	1852	4.4	1.15 (0.83, 1.59)	1.14 (0.96, 1.36)
≥50	108	32	568	5.6	1.47 (0.98, 2.24)	1.14 (0.88, 1.46)
Fasting glucose (mg/dl)						
<100	570	129	3239	4.0	1.00	1.00
≥100	160	45	800	5.6	1.40 (1.01, 1.97)*	1.05 (0.77, 1.42)
HbA _{1c} (%)						
<6.5	534	115	2821	4.1	1.00	1.00
≥6.5	16	8	92	8.7	2.12 (1.07, 4.24)*	0.90 (0.62, 1.29)
Systolic BP (mm Hg)						
<130	654	150	3592	4.2	1.00	1.00
≥130	50	16	282	5.7	1.36 (0.82, 2.24)	1.05 (0.71, 1.555)
Diastolic BP (mm Hg)						
<85	651	146	3562	4.1	1.00	1.00
≥85	53	20	312	6.4	1.56 (0.99, 2.46)	0.86 (0.59, 1.28)
Cholesterol (mg/dl)						
<200	453	99	2524	3.9	1.00	1.00
200–219	132	33	714	4.6	1.18 (0.80, 1.72)	0.88 (0.69, 1.12)
>220	114	27	611	4.4	1.13 (0.74, 1.71)	0.99 (0.77, 1.28)
HDL (mg/dl)						
Men ≥40 and women ≥50	323	63	1677	3.8	1.00	1.00
Men <40 and women <50	343	85	1949	4.4	1.16 (0.84, 1.60)	1.34 (1.12, 1.60)***
LDL (mg/dl)						
<100	221	49	1225	4.0	1.00	1.00
≥100	426	96	2287	4.2	1.05 (0.75, 1.47)	1.04 (0.85, 1.26)
Triglyceride (mg/dl)						
<150	509	102	2789	3.7	1.00	1.00
≥150	185	56	1023	5.5	1.49 (1.09, 2.06)**	1.00 (0.81, 1.23)
BMI (kg/m ²)						
<25	158	14	861	1.6	1.00	1.00
25–29.9	400	96	2216	4.3	2.69 (1.53, 4.64)***	1.00 (0.82, 1.23)
≥30	165	57	919	6.2	3.88 (2.14, 6.79)***	1.01 (0.75, 1.35)
Abdominal obesity (WC)						
No	584	112	3217	3.5	1.00	1.00
Yes	140	57	785	7.3	2.09 (1.53, 2.84)***	0.81 (0.60, 1.09)
Abdominal obesity (WHR)						
No	455	80	2552	3.1	1.00	1.00
Yes	222	76	1195	6.4	2.06 (1.49, 2.76)***	1.22 (0.99, 1.51)
OGTT						
Normal glucose tolerance	459	95	2642	3.6	1.00	1.00
IGT	177	55	931	5.9	1.64 (1.19, 2.27)*	1.89 (1.28, 2.79)**
IFG	91	23	452	5.1	1.42 (0.91, 2.21)	1.39 (1.10, 1.73)**

Total number of person-years and at risk is not the same for each variable because of missing values. Abdominal obesity was defined as waist circumference ≥102 cm in men and ≥88 cm in women or waist-to-hip ratio ≥0.95 in men and ≥0.8 in women. CI, confidence interval; RR, relative risk; WC, waist circumference; WHR, waist-to-hip ratio; BP, blood pressure; HDL, high density lipoprotein cholesterol; LDL low density lipoprotein cholesterol; OGTT, oral glucose tolerance test; IGT, impaired glucose tolerance; IFG, impaired fasting glucose.

* $P < 0.05$.

** $P < 0.01$.

*** $P < 0.001$.

^a Relative risks (with 95% CI) calculated by Cox's proportional hazards model.

increase triglyceride levels, and impede metabolism of fatty acids. These results stress the importance of both low HDL and impaired glucose levels in the occurrence of this clinical entity [30].

The strengths of the present study include the prospective cohort design, the sample consisting of both men and women of a wide age range from an Iranian population, diagnosis of MetS based on repeat measurement. The multiple examinations make the progression rates very accurate. Anthropometric variables collected by using direct measurement rather than self-report. Selection and information bias is considered unlikely by virtue of the prospective design. Losses to follow-up are the major source of bias in longitudinal studies. This is an ongoing cohort, and during this average 5.5 year follow-up period 41.0% of the participants that attended the baseline survey had not been yet contacted for

this re-evaluation. This may have some impact on our findings. However, when assessing baseline status of the component features of MetS, gender, age, and education, no significant differences observed between those included in the study and those who were not yet contacted for this longitudinal analysis. Despite the above limitations, the findings here add to our understanding of the prevalence, incidence and risk factors of MetS in FDRs of people with type 2 diabetes in Iran. Furthermore, this study provides new data from Iran, a developing country that has been underrepresented in past studies.

In summary, the findings of this study illustrate for the first time the incidence of MetS in FDRs of patients with type 2 diabetes in Iran. These findings may prove useful in identifying a specific subset of the population at particular risk of developing MetS

known to predispose to cardiovascular disease and diabetes and strongly support the regular screening of FDRs of patients with type 2 diabetes.

Contributions

Janghorbani M conceived and designed the study, analyzed the data and wrote the manuscript, Amini M, recruited samples and contributed to discussion and revision of the manuscript and obtained funding for the IDPS. All authors discussed the results and reviewed and edited the manuscript.

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Conflict of interest statement

None to declare.

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