Eur Arch Psychiatry Clin Neurosci (2011) 261:69–78
DOI 10.1007/s00406-010-0118-x

ORIGINAL PAPER

The prevalence and clinical correlates of metabolic syndrome in patients with schizophrenia: findings from a cohort in Turkey

M. K. Yazıcı · A. E. Anıl Yağcıoğlu · A. Ertuğrul · N. Eni · S. Karahan · E. Karaağaoğlu · S. L. Tokgözoğlu

Received: 27 January 2010 / Accepted: 12 May 2010 / Published online: 3 June 2010

Abstract Most studies point to an increased prevalence of metabolic syndrome (MS) and an increased risk of coronary heart disease (CHD) in schizophrenia patients with MS. The aims of this study were to compare the prevalence of MS in schizophrenia patients with the general population, to explore the clinical correlates and predictors of MS and to evaluate the risk for CHD within 10 years. Consecutive 319 patients, aged 18–75 years, with a diagnosis of schizophrenia according to the DSM-IV were enrolled. The ATP-III, the ATP-IIIA and the IDF criteria were used to define MS. 10-year risk of CHD events was calculated with the Framingham score. One hundred nine (34.2%) patients met the ATP-III criteria, 118 (37%) the ATP-IIIA and 133 (41.7%) the IDF criteria for MS. Patients with MS were older, had a later onset of illness and an older age at first hospitalization. The prevalence of MS in schizophrenia patients was higher from the general population only within the 20–29 age group. Patients with MS had a higher age and sex-corrected 10-year risk of CHD events. The only predictor of MS was the age of illness onset. In conclusion, countries where the general population prevalence of MS is already too high, schizophrenia patients younger than 30 years of age might be under higher risk of morbidity and mortality related with MS. This study points to the necessity for aggressive interventions to correct MS in schizophrenia as early as possible, within the first 10 years of post detection.

Keywords Metabolic syndrome · Schizophrenia · Prevalence · Correlates · Cardiovascular risk

Introduction

The metabolic syndrome (MS), comprising a cluster of factors including visceral obesity, dyslipidemia, hyperglycemia and hypertension, has become one of the major public health challenges worldwide. Currently, the most widely used definitions for the MS are the Adult Treatment Protocol (ATP-III) of the National Cholesterol Education Program (NCEP) [1], the adapted ATP-III A [2, 3] and the more recent definition by the International Diabetes Federation [4].

Patients with schizophrenia show increased rates of morbidity and mortality and have nearly 20% shorter life expectancy as compared to the general population which is largely due to the increased incidence of diabetes and cardiovascular disease [5–7]. The prevalence of MS in patients with schizophrenia and schizoaffective disorder defined according to the ATP-III criteria range between 19 and 63% in studies carried out in North and South America, Europe, Asia and Australia on varying ethnic groups (Table 1) [8–36]. Although most of the studies have utilized the ATP-III criteria to define MS in patients with schizophrenia, some have also utilized the more recent

Part of the data was presented at the 18th Congress of the European College of Neuropsychopharmacology (ECNP), Amsterdam, The Netherlands, 2005.

M. K. Yazıcı (✉) · A. E. Anıl Yağcıoğlu · A. Ertuğrul · N. Eni
Department of Psychiatry, Hacettepe University Faculty of Medicine, 06100 Ankara, Turkey
e-mail: kyazici@hacettepe.edu.tr

S. Karahan · E. Karaağaoğlu
Department of Biostatistics, Hacettepe University Faculty of Medicine, 06100 Ankara, Turkey

S. L. Tokgözoğlu
Department of Cardiology, Hacettepe University Faculty of Medicine, 06100 Ankara, Turkey

Table 1 Prevalence estimates of the metabolic syndrome in patients with schizophrenia and schizoaffective disorder in different countries [8–36]

Study	Country	Sample	*N* (female/male)	Mean age (years)	Criteria	Prevalence
Heiskanen et al. [8]	Finland	Outpatients	35 (16/19)	44.5	ATP-III	37.1%
Littrell et al. [9]	USA and Taiwan	In–outpatients	USA 98 (37/61)	USA 41.8	ATP-III	USA 51%
			Taiwan 27 (13/14)	Taiwan 42		Taiwan 22.2%
Kato et al. [10]	USA	Outpatients	48 (24/24)	40.3	ATP-III	63.0%
Basu et al. [11]	USA	Outpatients	33 (19/14)	44.5	ATP-III	42.4%
Cohn et al. [12]	Canada	In–outpatients	240 (84/156)	43.3	ATP-III	44.7%
Meyer et al. [13]	USA	Outpatients	121 (60/61)	41.1	ATP-III	52.1%
Saari et al. [14]	Finland	1966 Finland birth cohort	31 (13/18)	–[a]	ATP-III	19.4%
Koponen et al. [15]					ATP-IIIA	29%
					IDF	29%
McEvoy et al. [18]	USA	In–outpatients	689 (180/509)	40.4	ATP-III	40.9%
					ATP-IIIA	42.7%
Hagg et al. [17]	Sweden	In–outpatients	269 (92/177)	46[b]	ATP-III	34.6%
Meyer et al. [18]	USA	In–outpatients	84 (6/78)	49.0	ATP-III	48.8%
					ATP-IIIA	56.3%
Correll et al. [19]	USA	Inpatients	176[c]	–[d]	ATP-III	37.3%
Lamberti et al. [20]	USA	Outpatients	93 (31/62)	34.4	ATP-IIIA	53.8%
De Hert et al. [21]	Belgium	In–outpatients	430 (151/279)	36.5	ATP-III	28.4%
					ATP-IIIA	32.3%
					IDF	36%
Teixeira and Rocha [22]	Brazil	Inpatients	44 (10/34)	42.2	ATP-III	31.8%
Sanchez-Arana Moreno et al. [23]	Canary Islands	Inpatients	136 (47/89)	39.1	ATP-III	36%
Tirupati and Chua [24]	Australia	Outpatients	202 (45/157)	38.1	IDF	69.3%
Srisurapanont et al. [25]	Thailand	Outpatients	57 (33/24)	37.5	IDF	22.8%
Kurt et al. [26]	Turkey	Inpatients	296 (138/158)	55.2	IDF	18.9%
Bobes et al. [27]	Spain	Outpatients	1452 (555/863)	40.7	ATP-III	24.6%
Rejas et al. [28]					ATP-IIIA	25.5%
Saddichha et al. [29]	India	Inpatients	99 (47/52)	26.0	ATP-IIIA	10.1%
					IDF	18.2%
Correll et al. [30]	USA	Inpatients	111 (57/54)	44.3	ATP-III	45.9%
					ATP-IIIA	54%
Cerit et al. [31]	Turkey	Outpatients	100 (41/59)	34.7	ATP-III	21%
					ATP-IIIA	34%
					IDF	41%
Boke et al. [32]	Turkey	Inpatients	231 (57/174)	38.5	IDF	32%
Oyekcin [33]	Turkey	Outpatients	34 (24/10)	33.7	ATP-III	35.3%
Kaya et al. [34]	Turkey	Outpatients	87 (36/51)	34.4	ATP-III	29.9%
					ATP-IIIA	35.6%
					IDF	42.5%
Brunero et al. [35]	Australia	Outpatients	73 (28/45)	39.3	IDF	61.6%
Huang et al. [36]	Taiwan	Outpatients	650 (298/352)	45.9	ATP-III	34.9%

ATP-III Adult Treatment Protocol of the National Cholesterol Education Program (NCEP) [1], *ATP-III A* Adapted Adult Treatment Protocol [2, 3], *IDF* International Diabetes Federation [4]

[a] Mean age 39 years for the whole sample

[b] Median value

[c] Female/male ratio (169/198) for the whole sample of 367 patients with mixed diagnosis

[d] Mean age 42.9 years for the whole sample of 367 patients with mixed diagnosis

ATP-IIIA and IDF criteria, finding prevalence rates ranging between 10 and 56% and 18 and 69%, respectively (Table 1). Studies that use more stringent MS criteria (i.e. ATP-IIIA and IDF) point to higher prevalence rates. Despite the variance, most of the studies point to an increased prevalence of MS in schizophrenia patients as compared to the general population, although some studies have not provided comparison with the general population as in the study by Littrell et al. [9] where general population rates were not available for Taiwanese patients.

Variations seen in the prevalence rates of MS in schizophrenia patients in different studies conducted in various parts of the world might also be related with sample characteristics, such as age, sample size, gender ratio, illness duration and geographical background which is probably influenced by life style and dietary characteristics and/or various genetic factors. In general, the European MS prevalence rates both in the schizophrenia patients and the general population have been found to be lower as compared to the USA rates, even when the same ethnic groups are investigated [21].

Comparison of the prevalence rate of MS in schizophrenia patients to that observed in the general population reveal some interesting findings, such as a differential loading of the lowest and highest rates in different age groups. In the general population, an age related increase of MS is expected. Although there are studies which support the same finding in schizophrenia patients [31], some findings from large studies conducted on schizophrenia are unexpected [18]. For example, an equal prevalence among those under and over 45 years of age [12], a lower prevalence among patients who are 50–59 years of age than in the cohort 40–49 years of age [16, 17] or even 20–29 years of age [17] have been reported.

Given the fact that cardiovascular disease accounts as much as 50% of the excess mortality in patients with schizophrenia in large epidemiological studies and patients with schizophrenia have twice the standardized mortality from cardiovascular disease [18], investigation of coronary heart disease (CHD) and cardiovascular mortality risks in schizophrenia patients with MS has gained increasing importance. An increased mean risk of serious fatal and nonfatal CHD in schizophrenia patients within 10 years as compared to the normal population has been found in studies such as CATIE [37] and CLAMORS [27]. The existence of MS in schizophrenia patients has been shown to further increase the CHD risk [19, 38].

The aim of this study was to investigate the prevalence of MS utilizing the three aforementioned criteria in patients with schizophrenia and to compare it with the prevalence observed in the general population in Turkey. For this comparison, we utilized a recent MS prevalence data including random samples from both urban and rural populations ($N = 4{,}264$) in the seven geographical regions in Turkey [39]. We also aimed to explore the clinical correlates and predictors of MS along with the risk for CHD within 10 years according to the Framingham function.

Methods

Study site and patients

This study was conducted at the Department of Psychiatry, Hacettepe University Faculty of Medicine, Ankara, Turkey. The study was carried out between December 2004 and January 2007 and included patients from both in- and outpatient clinics. Consecutive 319 patients aged 18–75 years who accepted participation were enrolled, with a diagnosis of schizophrenia according to the DSM-IV. Eighteen patients refused participation due either to the lack of time or unwillingness to give a blood sample. The Local Research Ethics Committee at the Hacettepe University Faculty of Medicine approved the study protocol. A written informed consent was obtained from all the participating patients prior to the entry of the study.

Study design

A physical examination, laboratory analyses and clinical assessment were all made on the same visit. The subjects' blood pressure, weight, height and waist circumference measurements were recorded. Waist circumference was measured midway between the lowest rib and the iliac crest with the subjects standing. Medical records were reviewed to obtain demographic, clinical, and drug treatment data. A questionnaire was filled for each patient by a psychiatric nurse (N.E.) to provide additional clinical and demographical information including smoking status and their family medical health history. The laboratory analyses included fasting blood glucose and lipid profile, including triglyceride, total cholesterol, and high-density lipoprotein (HDL) measurements for each subject. The patients were instructed strictly to fast overnight for at least 8 h. Their relatives confirmed the fasting status. The blood samples were collected in the morning at 8:30 a.m. Any patient who could not comply to the fasting instructions was called in the next morning.

Metabolic syndrome was defined according to the ATP-III, the ATP-IIIA and the IDF criteria (1–4).

The 10-year risk of CHD events, expressed as a percentage, for non-diabetic patients was calculated with the NCEP's version of the Framingham score which is a gender-specific instrument that assigns points for age, blood pressure, cigarette smoking, total cholesterol and HDL cholesterol [1]. The 10-year risk of CHD events in

Table 2 Sociodemographic and clinical characteristics of the patients in the total sample and comparison within groups

	Total sample	IDF criteria		
		Patients with MS	Patients without MS	*p*
Age (mean ± SD)	38.4 ± 12.4	41.1 ± 12	36.5 ± 12.3	0.001
Gender, *n* (%)				
Male	141 (44.2%)	60 (45.1%)	81 (43.5%)	0.781
Female	178 (55.8%)	73 (54.9%)	105 (56.5%)	
Age of illness onset, mean ± SD	25.4 ± 10	27.4 ± 11.1	24.0 ± 9.0	0.003
Duration of illness (years), mean ± SD	12.9 ± 10.3	13.6 ± 10.9	12.5 ± 10.0	0.356
Age of first hospitalization (years), mean ± SD	28.4 ± 10.4	29.9 ± 10.5	27.2 ± 10.1	0.047
Antipsychotic treatment, *n* (%)				
Risperidone	59 (18.5%)	25 (19.1%)	34 (18.4%)	0.889
Olanzapine	64 (20.1%)	28 (21.4%)	36 (19.5%)	
Clozapine	104 (32.6%)	43 (32.8%)	61 (33%)	
Quetiapine	26 (8.2%)	11 (8.4%)	15 (8.1%)	
Ziprasidone	2 (0.6%)	–	2 (1.1%)	
Typical antipsychotics	61 (19.1%)	24 (18.3%)	37 (20%)	
Duration of current antipsychotic treatment (months), mean ± SD	43.2 ± 54.5	44.9 ± 57.8	42 ± 52.2	0.808
Body mass index (kg/m^2), mean ± SD	28.9 ± 19.9	30.2 ± 5.8	27.9 ± 25.6	0.344
Risk of coronary heart disease in 10 years (Framingham score), mean ± SD[a]	5.9 ± 6.6	7.8 ± 8.1	4.2 ± 4.2	<0.0001
Smoking, *n* (%)	144 (45.1%)	62 (46.6%)	82 (44.3%)	0.685
Family history of schizophrenia	145 (45.5%)	61 (45.9%)	84 (45.2%)	0.853
Family history of multiple cases of schizophrenia	60 (18.9%)	28 (21.1%)	32 (17.2%)	0.368
Family history of diabetes, *n* (%)	135 (42.5%)	52 (39.4%)	83 (44.6%)	0.353
Family history of hypertension, *n* (%)	204 (63.9%)	80 (60.6%)	124 (66.7%)	0.267
Family history dyslipidemia, *n* (%)	135 (42.3%)	47 (35.6%)	88 (47.3%)	0.037
Family history of coronary heart disease, *n* (%)	56 (17.6%)	20 (15.2%)	36 (19.4%)	0.332
Family history of obesity, *n* (%)	13 (4.1%)	3 (2.3%)	10 (5.4%)	0.168

According to the presence of metabolic syndrome (MS) defined by the IDF criteria

[a] Framingham scores calculated for a total of 218 patients ($N = 103$ with MS, $N = 115$ without MS)

diabetics was calculated with a version of the Framingham algorithm that assigns points for the presence of diabetes mellitus [40].

Data analysis

The mean and standard deviations were calculated for quantitative variables. The frequency and percentage were used to determine demographic and clinical characteristics of the patients and the prevalence of MS, its components and various risk factors. Continuous variables were compared using the Student's *t* test, and categorical variables were compared using a χ^2 test. The 10-year risk of CHD events expressed as a percentage (Framingham score) was compared between males and females using multiple linear regression, adjusting for age. The gender-specific cardiovascular risk in patients with and without MS was compared using multiple linear regression, adjusting only for age. Stepwise forward logistic regression analysis was used to determine the effect of more than one independent variable on MS. A $p < 0.05$ was considered statistically significant. The SPSS version 15.0 statistical package was used for the analyses.

Results

Sample characteristics

The sociodemographic and clinical characteristics of the patients are presented in Table 2. The majority of the patients was on atypical anti-psychotics with clozapine being the most frequently prescribed ($N = 104$, 32.6%, mean dose = 417.4 ± 166.0 mg/day), followed by olanzapine ($N = 64$, 20.1%, mean dose = 13.82 ± 7.0 mg/day). Three patients (0.9%) were not using any antipsychotics at the time of the assessment. Although antipsychotic polypharmacy

Table 3 Prevalence of metabolic syndrome (MS) and components of the criteria met in schizophrenia patients according to ATP, ATP-IIIA and IDF criteria

Characteristic	Metabolic syndrome *N* (%)			
	Total sample ($N = 319$)	Men ($N = 141$)	Women ($N = 178$)	p
ATP-III criteria	109 (34.2%)	39 (27.7%)	70 (39.3%)	0.029
ATP-IIIA criteria	118 (37%)	46 (32.6%)	72 (40.4%)	0.151
IDF criteria	133 (41.7%)	60 (42.6%)	73 (41.0%)	0.781

	ATP criteria		ATP-A criteria		IDF criteria	
	Patients with MS	Patients without MS	Patients with MS	Patients without MS	Patients with MS	Patients without MS
Criteria met, *N* (%)						
Waist	100 (91.7%)	111 (52.9%)	104 (88.1%)	107 (53.2%)	133 (100%)	159 (85.5%)
Blood pressure	73 (64.6%)	40 (19%)	77 (68.1%)	36 (31.9%)	86 (64.7%)	27 (14.5%)
Triglycerides	85 (78%)	49 (23.3%)	91 (77.1%)	43 (21.4%)	100 (75.2%)	34 (18.3%)
HDL cholesterol	72 (66.1%)	37 (17.6%)	76 (64.4%)	33 (16.4%)	80 (60.2%)	29 (15.6%)
Glucose	40 (36.7%)	13 (6.2%)	65 (55.1%)	35 (17.4%)	73 (54.9%)	27 (14.5%)

ATP-III Adult Treatment Protocol of the National Cholesterol Education Program (NCEP) [1], *ATP-III A* Adapted Adult Treatment Protocol [2, 3], *IDF* International Diabetes Federation [4]

was not the case for the majority of patients, 32 patients (10%) were receiving a low-dose second antipsychotic in combination. The antipsychotics used for combination consisted of typical antipsychotics ($N = 15$, 4.7%), risperidone ($N = 6$, 1.9%), clozapine ($N = 5$, 1.6%), olanzapine ($N = 1$, 0.3%), amisulpride ($N = 2$, 0.6%), sulpride ($N = 1$, 0.3%) and ziprasidone ($N = 8$, 0.6%). Among the whole sample, 13 patients (4.1%) were on lipid lowering, 20 (6.3%) were on antihypertensive and 12 patients (%3.8) were on anti-diabetic drugs.

Comparison of sociodemographic and clinical characteristics in patients with and without metabolic syndrome

Patients with MS defined by the IDF criteria were not significantly different than patients without MS regarding gender, duration of illness, antipsychotic type and duration, BMI, smoking status, family history of schizophrenia, family history of multiple cases of schizophrenia and family history of diabetes, hypertension, CHD and obesity. However, patients with MS were significantly older ($p = 0.001$), had a later onset of illness ($p = 0.003$), an older age at first hospitalization ($p = 0.047$) and a lower rate of family history of dyslipidemia ($p = 0.037$) (Table 2).

The comparison between patients with and without MS defined by the ATP and ATP-A criteria were similar (data not presented), except the rate of family history of dyslipidemia did not differ between the two groups. In addition, there were more female patients with MS than male patients ($N = 70$, 39.3% vs $N = 39$, 27.7%, $p = 0.029$) with the ATP criteria.

Prevalence of metabolic syndrome, frequency of the metabolic syndrome criteria met in schizophrenia patients

One hundred nine (34.2%) of the 319 patients met the ATP-III criteria, 118 (37%) met the ATP-IIIA and 133 (41.7%) met the IDF criteria for MS. According to the ATP criteria, MS was more prevalent among women, but there was no gender difference according to the ATP-IIIA and IDF criteria. Among the criteria met in this study sample, abdominal obesity criterion was the most prevalent, followed by triglycerides, blood pressure and HDL cholesterol, whereas the serum glucose was the least prevalent according to both the ATP-A and the IDF criteria. The same order for the criteria met was also observed for MS patients defined by the ATP criteria, except a switch of placement between blood pressure and HDL cholesterol (Table 3).

Comparison of the MS criteria met between male and female patients with MS revealed that abdominal obesity was more prevalent in females both with the ATP ($N = 151$, 84.8% vs. $N = 60$, 42.6%, $p < 0.0001$) and ATP-A/IDF ($N = 177$, 99.4% vs. $N = 115$, 81.6%, $p < 0.0001$) definitions. Triglyceride levels were higher in male patients with metabolic syndrome ($N = 72$, 51.1% vs. $N = 62$, 34.8%, $p = 0.004$). All other MS parameters did not differ significantly between male and female patients.

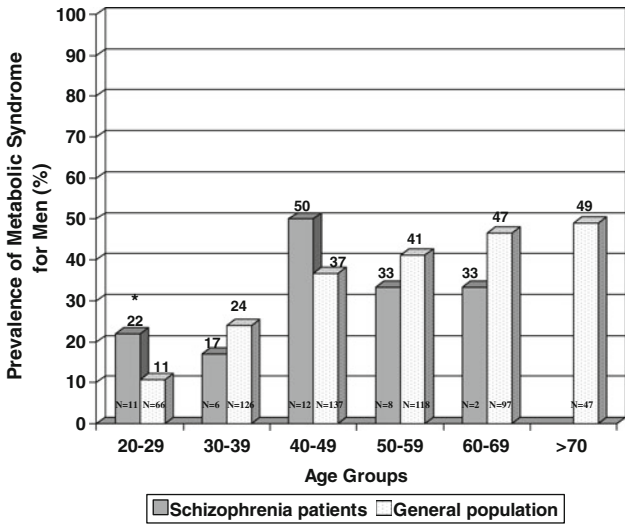

Fig. 1 Prevalence of metabolic syndrome for men in schizophrenia patients and general population (METSAR Study) [39] according to the ATP criteria

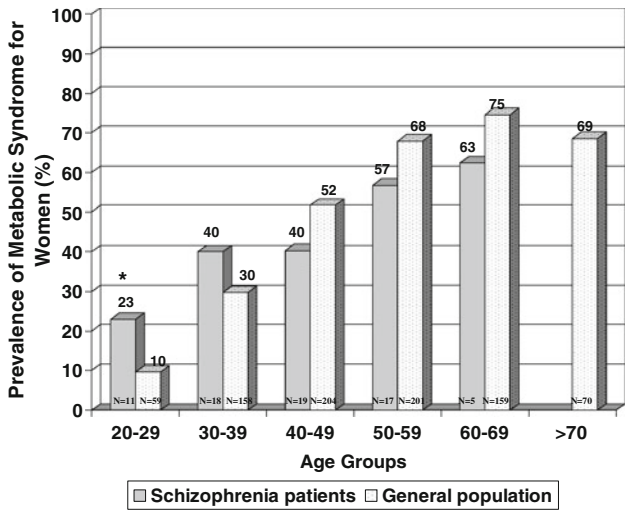

Fig. 2 Prevalence of metabolic syndrome for women in schizophrenia patients and general population (METSAR Study) [39] according to the ATP criteria

Comparison of the prevalence of metabolic syndrome in schizophrenia patients and general population in Turkey (METSAR study) in different age groups

Comparisons of the MS prevalence between the schizophrenia patients in this study and general population in Turkey (the METSTAR study) [39] could only be made in five age groups (20–29, 30–39, 40–49, 50–59 and 60–69), as our study had only two male patients without MS in the >70 age group (Figs. 1, 2). The prevalence of MS in schizophrenia patients according to the ATP criteria was significantly higher from the general population in the whole sample (22.4 vs. 10.2%, $p = 0.0002$), and in both male (22 vs. 10.7%, $p = 0.0162$) and female patients (22.9 vs. 9.6%, $p = 0.0039$) only within the 20–29 age group.

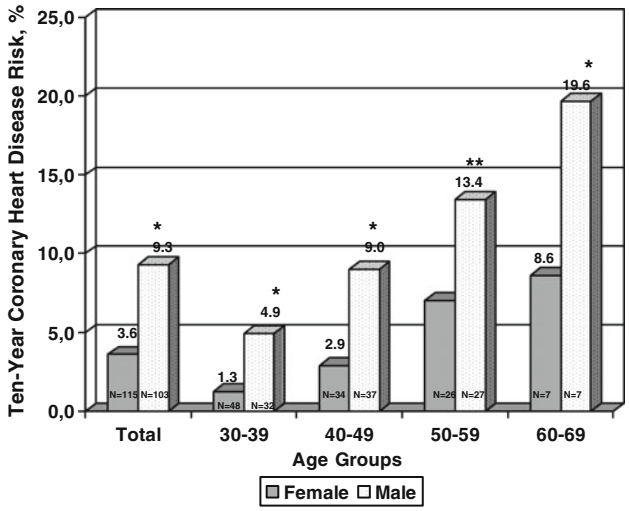

Fig. 3 Effect of sex on 10-year coronary heart disease risk in schizophrenia patients

Ten-year risk of CHD events

The 10-year risk of CHD events was calculated for a total of 218 patients within the age range of 30–74, as the Framingham score could only be calculated within this age range. The overall 10-year risk of CHD events was 5.9% (SD = 6.6) and significantly higher in MS patients when compared with patients without MS diagnosed according to the IDF criteria: 7.8 versus 4.2% ($p < 0.0001$) (Table 2).

The overall age-corrected 10-year risk of CHD events measured by the Framingham score was 9.31% (SD = 8.17) in men and 3.61% (SD = 3.79) in women. The risk was significantly greater in men as compared to women in all age groups, except in the 60–69 age group (Fig. 3).

Patients with MS had a significantly higher ($p < 0.0001$) age- and sex-corrected 10-year risk of CHD events (7.87%, SD = 8.07) as compared to patients without MS (4.21%, SD = 4.24). Adjusted for age, the 10-year risk of CHD events in patients with MS was significantly higher as compared to patients without MS in both males (12.14%, SD = 9.97 vs. 6.79%, SD = 5.02, $p = 0.002$) and females (4.93%, SD = 4.60 vs. 2.43%, SD = 2.33, $p < 0.0001$) (Fig. 4).

Predictors of metabolic syndrome in schizophrenia patients

In addition to the age of illness onset, which was significantly different between patients with and without MS,

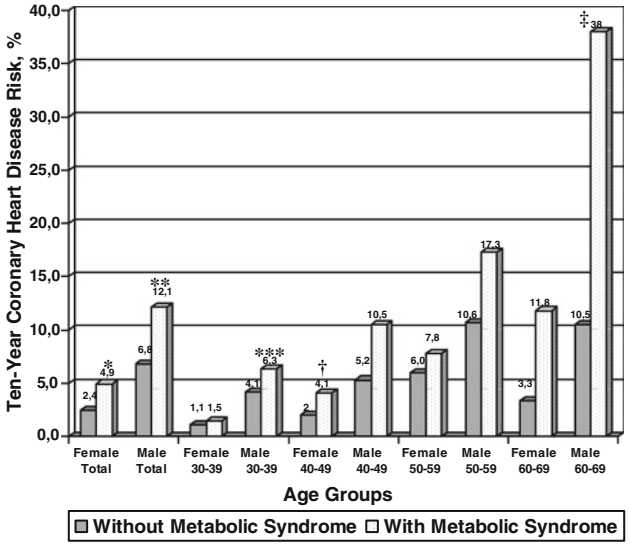

Fig. 4 Effect of metabolic syndrome by sex and age on 10-year coronary heart disease

antipsychotic type, antipsychotic duration, sex, age groups (20–29, 30–39, 40–49, 50–59 and 60–69), body mass index and family history of schizophrenia were included in the stepwise forward logistic regression analysis to determine the predictors of metabolic syndrome. Although the Framingham score was also significantly different between the patient groups with and without MS, this variable was excluded from the logistic regression analysis due to the overlap of most of its defining criteria with that of MS. Age and age of first hospitalization, which were also significantly different between the patient groups with and without MS, were excluded from the logistic regression analysis as they were variables correlated with the variables defined as age groups and age of illness onset. The only significant predictor was found to be the age of illness onset (B = 0.034, OR = 1.04, 95% CI = 1.01–1.06, $p = 0.004$).

Discussion

In this cross-sectional study investigating schizophrenia patients, MS defined by the ATP, ATP-IIIA and IDF criteria was present in more than one-third of the cohort. The observed prevalence rates are in line with four previous studies reporting the prevalence of MS within the range 21–35% according to the ATP, 34–36% according to the ATP-A, 32–43% according to the IDF criteria in schizophrenia patients in Turkey [31–34]. One other study from Turkey which reported a rate of 18.9% with the stringent IDF criteria has been conducted on chronic schizophrenia patients with a long duration of inpatient hospitalization (mean 16 years), and the comparably low prevalence has been discussed by the authors as an outcome of balanced hospital diets and optimum medical care provided in the hospital setting [26].

The prevalence rates of MS in schizophrenia patients appear to be lowest among studies utilizing comparable criteria in some Asian countries, such as India and Thailand, and to be highest in USA, Canada and Australia, followed by comparably lower prevalence rates in some other Asian (Taiwan), European (Spain, Belgium), Euro-Asian (Turkey), South American (Brazil) and Scandinavian countries (Finland, Sweden) in studies conducted in the past decade (Table 1) [8–36]. The prevalence of MS according to the ATP criteria in this Turkish cohort with schizophrenia 34.2% (27.7% for men, 39.3% for women) appears to fall near mid-high rates.

The prevalence of MS estimated using the ATP criteria in Turkey has been found as 28% in men ($N = 2,108$) and 39.6% in women ($N = 2,151$) in the METSTAR study [39], and 27% in men ($N = 1,202$) and 45.2% in women ($N = 1,253$) in the Turkish Adult Risk Factor Study [41]. We have compared our MS prevalence results with that of the METSTAR study as it is more recent and includes a larger sample size. An interesting finding of our study is that the MS prevalence rate defined by the ATP criteria in schizophrenia patients is higher than MS rates in the general population represented by the METSTAR study only in the 20–29 age group. A higher prevalence of MS in this group of young schizophrenia patients could be the reflection of patients with less metabolic problems surviving to live to an older age. Comparable findings suggesting that schizophrenia patients with MS at a younger age may expire at a young age have earlier been reported [12, 17, 36]. An almost double rate of MS in patients aged 20–29 years compared to the general population points to a serious public health problem, considering the increased risk of cardiovascular events and premature mortality associated with the presence of MS.

A similar rate of MS in schizophrenia patients in age groups over 29 years and the general population in our study is an unexpected finding regarding the general literature of MS prevalence in schizophrenia patients. However, this result seems to appear consistently in MS prevalence studies in schizophrenia patients in Turkey either as a similar [33] or lower prevalence rate [31, 34] as compared to the general Turkish population. An already too high MS prevalence in the general Turkish population could partially explain this finding. Turkish population has earlier been reported to have one of the highest prevalences of MS in the world [39]. Parallel to the findings of gender-specific MS prevalences defined by the ATP criteria in the general Turkish population [39, 41], MS prevalence defined by the ATP criteria in this study has been found

more prevalent among female schizophrenia patients (39.3 vs. 27.7%). Higher prevalence of MS in women in Turkey has been thought to be related with higher prevalence of abdominal obesity in women compared with men [39, 41], which is also the case in our sample of schizophrenia patients. Triglyceride level has also been found to be higher in males both in schizophrenia patients in this study and the general Turkish population [39, 41]. The same gender-specific clustering of these two particular MS criteria has also been observed in other samples of schizophrenia patients in Turkey [31, 33, 34]. In our cohort of schizophrenia patients, the most frequent components of MS appeared as abdominal obesity, followed by triglycerides, blood pressure and HDL cholesterol and serum glucose, more in line with the other MS studies in schizophrenia patients conducted in Turkey [31, 34]. Abdominal obesity appears to be one of the most important determinants of the development of MS in schizophrenia patients [42].

The family history of diabetes and cardiovascular disease has been questioned in limited studies investigating MS in schizophrenia. In several studies including some conducted in Turkey [10, 31, 32] and our study, no significant difference between family history of diabetes, hypertension, and cardiovascular disease in schizophrenia patients with and without MS was found. Unexpectedly, in our study, family history of dyslipidemia was higher in schizophrenia patients without MS. Family history of cardiovascular disease, diabetes, and other related disease should be questioned for the cardiovascular and MS risk assessment in schizophrenia patients both in clinical practice and research [43, 44]. Our finding that a quite low proportion of schizophrenia patients are on anti-lipidemic, antihypertensive and anti-diabetic medications points to the fact that these metabolic and cardiovascular disorders remain unnoticed and untreated. Implementation of cardiovascular risk management strategies in patients with severe mental illness, such as the position statement of the European Psychiatric Association [44] is of great importance.

The mechanisms underlying the increased rates of MS in schizophrenia patients are not clear. It has been proposed that factors inherent in the disease process itself such as heredity, lifestyle and poor health care and second generation antipsychotics (SGA) may contribute to its development by causing weight gain, insulin resistance and dyslipidemia [19]. There are also indications that the level of metabolic abnormality risks are increased with SGA as compared to first generation antipsychotics (FGA) and that this risk varies among the SGA commonly used in the treatment of schizophrenia today, with a higher risk for olanzapine and clozapine [19, 29, 45–47]. Regarding the antipsychotic treatment, histamine H1 and serotonin 5HT2C antagonism have been linked to the risk of weight gain. Receptors for dyslipidemia and insulin resistance are not yet identified and some findings suggest that both hypertriglyceridemia and insulin resistance can occur in the absence of weight gain with certain SGA [48]. In this study, antipsychotic type and treatment duration have not been found to be an important determinant regarding the development of MS despite the fact that majority of patients were using clozapine and olanzapine. Lack of an association between MS and antipsychotic type and duration is an unexpected finding which has nevertheless been reported in other studies, including some MS studies in schizophrenia conducted in Turkey [8, 10, 21, 31, 33, 34, 42]. The mean dose of clozapine and olanzapine used in this study can be regarded within the dosing range reflecting standard practice. A dose–response relationship between clozapine and olanzapine serum concentrations and metabolic outcomes has recently been reported [49] and therefore in a population receiving higher doses of both compounds the results might have differed. The cross-sectional design and relatively small number of subjects may have masked potential differences among antipsychotic agents.

In this study, we have confirmed the previous findings from the CATIE and CLAMORS studies [27, 37] that patients with MS have a significantly higher 10-year risk of CHD events compared to patients without MS with the risk greater in men compared with women. We have estimated that the overall age-corrected 10-year risk of CHD events measured by the Framingham score was 9.31% in men and 3.61% in women.

Age of illness onset was found to be the only predictor for the development of MS in this sample of schizophrenia patients. A significantly later age of illness onset [50] and tendency for a similar difference [8] in schizophrenia patients with MS have earlier been reported in a few studies. Age of illness onset appears to be a variable which is not adequately investigated in studies exploring MS and its correlates in schizophrenia and should further be examined.

The cross-sectional design and restriction to one site is the major limitation of this study. The fact that patients were not equally spread over different age groups, with especially a low number of older patients can also be considered as a limitation.

In conclusion, this study points to the necessity for aggressive interventions to correct or improve the metabolic parameters associated with MS in schizophrenia as early as possible, within the first 10 years of post detection. It appears that in some geographical settings, such as Turkey, where MS prevalence is already too high in the general population, young schizophrenia patients may be under higher risk of morbidity and mortality associated with MS.

Acknowledgments We thank Professor Sanjay Gupta MD for his contribution to the study design.

References

1. Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (2001) Executive summary of the third report of the National Cholesterol education Program (NCEP) expert panel on detection, evaluation, and treatment of high blood cholesterol in adults (Adult Treatment Panel III). JAMA 285:2486–2497
2. Expert Committee on the Diagnosis and Classification of Diabetes Mellitus (2003) Follow-up report on the diagnosis of diabetes mellitus. Diabetes Care 26:3160–3166
3. Grundy SM, Brewer B, Cleeman JL, Smith SC, Lenfant C (2004) Definition of metabolic syndrome: report of the National Heart, Lung, And Blood Institute/American Heart Association Conference on scientific issues related to definition. Circulation 109:433–438
4. IDF (2005) The IDF Consensus Worldwide Definition of the Metabolic Syndrome. International Diabetes Federation, Brussels
5. Suvisaari J, Perälä J, Saarni SI, Härkänen T, Pirkola S, Joukamaa M, Koskinen S, Lönnqvist J, Reunanen A (2008) Type 2 diabetes among persons with schizophrenia and other psychotic disorders in a general population survey. Eur Arch Psychiatry Clin Neurosci 258:129–136
6. Barnett AH, Millar HL, Loze JY, L'Italien GJ, van Baardewijk M, Knapp M (2009) UK cost-consequence analysis of aripiprazole in schizophrenia: diabetes and coronary heart disease risk projections (STAR study). Eur Arch Psychiatry Clin Neurosci 259:239–247
7. Leucht S (2009) Physical illness and schizophrenia. Eur Arch Psychiatry Clin Neurosci 259(Suppl 1):S34
8. Heiskanen T, Niskanen L, Lyytikainen R, Saarinen PI, Hintikka J (2003) Metabolic syndrome in patients with schizophrenia. J Clin Psychiatry 64:575–579
9. Littrell KH, Petty R, Ortega TR, Moore D, Ballard A, Clough R, Lan TS, Selby C (2003) Insulin resistance and Syndrome X among patients with schizophrenia. Abstract presented at the American Psychiatric Association Annual Meeting, San Francisco
10. Kato MM, Currier MB, Gomez CM, Hall L, Gonzalez-Blanco M (2004) Prevalence of metabolic syndrome in Hispanic and non-Hispanic patients with schizophrenia. Prim Care Companion J Clin Psychiatry 6:74–77
11. Basu R, Brar JS, Chengappa KNR, John V, Parapally H, Gershon S, Schlicht P, Kupfer D (2004) The prevalence of the metabolic syndrome in patients with schizoaffective disorder-bipolar subtype. Bipolar Disord 6:314–318
12. Cohn T, Prud'homme D, Streiner D, Kameh H, Remington G (2004) Characterizing coronary heart disease risk in schizophrenia: high prevalence of the metabolic syndrome. Can J Psychiatry 49:753–760
13. Meyer JM, Pandina G, Bossie CA, Turkoz I, Greenspan A (2005) Effects of switching from olanzapine to risperidone on the prevalence of the metabolic syndrome in overweight or obese patients with schizophrenia or schizoaffective disorder: analysis of a multicenter, rater-blinded, open-label study. Clin Ther 27:1930–1941
14. Saari KM, Lindeman SM, Viilo KM, Isohanni MK, Jarvelin M-R, Lauren LH, Savolainen MJ, Koponen HJ (2005) A 4-fold risk of metabolic syndrome in patients with schizophrenia: the northern Finland 1966 birth cohort study. J Clin Psychiatry 66:559–563
15. Koponen HJ, Hakko HH, Saari KM, Lindeman SM, Karvonen KM, Isohanni MK, Lauren LH, Savolainen MJ, Jarvelin MR (2008) The prevalence and predictive value of individual criteria for metabolic syndrome in schizophrenia: a Northern Finland 1966 Birth Cohort Study. World J Biol Psychiatry 1–6
16. McEvoy JP, Meyer JM, Goff DC, Nasrallah HA, Davis SM, Sullivan L, Meltzer HY, Hsiao J, Stroup TS, Lieberman JA (2005) Prevalence of the metabolic syndrome in patients with schizophrenia: baseline results from the clinical antipsychotic trial and comparison with national estimates from NHANES III. Schizophr Res 80:19–32
17. Hagg S, Lindblom Y, Mjorndal T, Adolfsson R (2006) High prevalence of the metabolic syndrome among a Swedish cohort of patients with schizophrenia. Int Clin Psychopharmacol 21:93–98
18. Meyer JM, Loh C, Leckband SG, Boyd JA, Wirshing WC, Pierre JM, Wirshing D (2006) Prevalence of the metabolic syndrome in veterans with schizophrenia. J Psychiatr Pract 12:5–10
19. Correll CU, Frederickson AM, Kane JM, Manu P (2006) Metabolic syndrome and the risk of coronary heart disease in 367 patients treated with second-generation antipsychotic drugs. J Clin Psychiatry 67:575–583
20. Lamberti JS, Olson D, Crilly JF, Olivares T, Williams GC, Tu X, Tang W, Wiener K, Dvorin S, Dietz MB (2006) Prevalence of the metabolic syndrome among patients receiving clozapine. Am J Psychiatry 163:1273–1276
21. De Hert M, van Winkel R, Van Eyck D, Hanssens L, Wampers M, Scheen A, Peuskens J (2006) Prevalence of the metabolic syndrome in patients with schizophrenia treated with antipsychotic medication. Schizophr Res 83:87–93
22. Teixeira PJ, Rocha FL (2007) The prevalence of metabolic syndrome among psychiatric inpatients in Brazil. Rev Bras Psiquiatr 29:330–336
23. Sanchez-Arana Moreno T, Tourino Gonzalez R, Hernandez Fleta JL, Leon Perez P (2007) Prevalence of the metabolic syndrome among schizophrenic patients hospitalized in the Canary Islands. Actas Esp Psiquiatr 35:359–367
24. Tirupati S, Chua LE (2007) Body mass index as a screening test for metabolic syndrome in schizophrenia and schizoaffective disorders. Australas Psychiatry 15:470–473
25. Srisurapanont M, Likhitsathian S, Boonyanaruthee V, Charnsilp C, Jarusuraisin N (2007) Metabolic syndrome in Thai schizophrenic patients: a naturalistic one-year follow-up study. BMC Psychiatry 7:14
26. Kurt E, Altinbas K, Alatas G, Ozver İ (2007) Metabolic syndrome prevalence among schizophrenic patients treated in chronic inpatient clinics. Psychiatry in Türkiye 3:141–145
27. Bobes J, Arango C, Aranda P, Carmena R, Garcia-Garcia M, Rejas J, Study Collaborative Group CLAMORS (2007) Cardiovascular and metabolic risk in outpatients with schizophrenia treated with antipsychotics: results of the CLAMORS study. Schizophr Res 90:162–173
28. Rejas J, Bobes J, Arango C, Aranda P, Carmena R, Garcia-Garcia M (2008) Concordance of standard and modified NCEP ATP III criteria for identification of metabolic syndrome in outpatients with schizophrenia treated with antipsychotics: a corollary from the CLAMORS study. Schizophr Res 99:23–28, 26
29. Saddichha S, Manjunatha N, Ameen S, Akhtar S (2008) Metabolic syndrome in first episode schizophrenia—a randomized double-blind controlled, short-term prospective study. Schizophr Res 101:266–272
30. Correll CU, Frederickson AM, Kane JM, Manu P (2008) Equally increased risk for metabolic syndrome in patients with bipolar disorder and schizophrenia treated with second-generation antipsychotics. Bipolar Disord 10:788–797

31. Cerit C, Ozten E, Yildiz M (2008) The prevalence of metabolic syndrome and related factors in patients with schizophrenia. Turk Psikiyatri Derg 19:124–132
32. Boke O, Aker S, Sarisoy G, Saricicek EB, Sahin AR (2008) Prevalence of metabolic syndrome among inpatients with schizophrenia. Int J Psychiatry Med 38:103–112
33. Oyekcin DG (2009) The frequency of metabolic syndrome in patients with schizophrenia and schizoaffective disorder. Anatolian J Psychiatry 10:26–33
34. Kaya MC, Virit O, Altındağ A, Selek S, Bülbül F, Bulut M, Savaş HA (2009) Prevalence of metabolic syndrome, characteristics of metabolic syndrome and relationship with the antipsychotics used in schizophrenia. Arch Neuropsychiatry 46:13–18
35. Brunero S, Lamont S, Fairbrother G (2009) Prevalence and predictors of metabolic syndrome among patients attending an outpatient clozapine clinic in Australia. Arch Psychiatr Nurs 23:261–268
36. Huang MC, Lu ML, Tsai CJ, Chen PY, Chiu CC, Jian DL, Lin KM, Chen CH (2009) Prevalence of metabolic syndrome among patients with schizophrenia or schizoaffective disorder in Taiwan. Acta Psychiatr Scand 120:274–280
37. Goff DC, Sullivan LM, McEvoy JP, Meyer JM, Nasrallah HA, Daumit GL, Lamberti S, D'Agastino RB, Stroup TS, Davis S, Lieberman JA (2005) A comparison of ten-year cardiac risk estimates in schizophrenia patients from the CATIE study and matched controls. Schizophr Res 80:45–53
38. Arango C, Bobes J, Aranda P, Carmena R, Garcia-Garcia M, Rejas J; on behalf of the CLAMORS study collaborative group (2008) A comparison of schizophrenia outpatients treated with antipsychotics with and without metabolic syndrome: findings from the CLAMORS study. Schizophr Res 104:1–12
39. Kozan O, Oguz A, Abaci A, Erol C, Ongen Z, Temizhan A, Celik S (2007) Prevalence of the metabolic syndrome among Turkish adults. Eur J Clin Nutr 61:548–553
40. Wilson PW, D'Agostino RB, Levy D, Belanger AM, Silbershatz H, Kannel WB (1998) Prediction of coronary heart disease using risk factor categories. Circulation 97:1837–1847
41. Onat A, Sansoy V (2002) Metabolic syndrome, major culprit of coronary disease among Turks: its prevalence and impact on coronary risk. Türk Kardiyol Dern Arş 30:8–15
42. Straker D, Correll CU, Kramer-Ginsberg E, Abdulhamid N, Koshy F, Rubens E, Saint-Vil R, Kane JM, Manu P (2005) Cost-effective screening for the metabolic syndrome in patients treated with second-generation antipsychotic medications. Am J Psychiatry 162:1217–1221
43. De Hert M, Schreurs V, Vancampfort D, Van Winkel RD (2009) Metabolic syndrome in people with schizophrenia: a review. World Psychiatry 8:15–22
44. De Hert M, Dekker JM, Wood D, Kahl KG, Holt RIG, Möller HJ (2009) Cardiovascular disease and diabetes in people with severe mental illness position statement from the European Psychiatric Association (EPA), supported by the European Association for the Study of Diabetes (EASD) and the European Society of Cardiology (ESC). Eur Psychiatry 24:412–424
45. Haupt DW (2006) Differential metabolic effects of antipsychotic treatments. Eur Neuropsychopharmacol 16:S149–S155
46. De Hert M, Schreurs V, Sweers K, Van Eyck D, Hanssens L, Sinko S, Wampers M, Scheen A, Peuskens J, van Winkel R (2008) Typical and atypical antipsychotics differentially affect long-term incidence rates of the metabolic syndrome in first-episode patients with schizophrenia: a retrospective chart review. Schizophr Res 101:295–303
47. Meyer JM, Davis VG, Goff DC, McEvoy JP, Nasrallah HA, Davis SM, Rosenheck RA, Daumit GL, Hsiao J, Swartz MS, Stroup TS, Lieberman JA (2008) Change in metabolic syndrome parameters with antipsychotic treatment in the CATIE Schizophrenia Trial: prospective data from phase 1. Schizophr Res 101:273–286
48. Stahl SM, Mignon L, Meyer JM (2009) Which comes first: atypical antipsychotics treatment or cardiometabolic risk? Acta Psychiatr Scand 119:171–179
49. Simon V, van Winkel R, De Hert M (2009) Are weight gain and metabolic side effects of atypical antipsychotics dose dependent? A literature review. J Clin Psychiatry 70:1041–1050
50. Bermudes RA, Keck PE Jr, Welge JA (2006) The prevalence of the metabolic syndrome in psychiatric inpatients with primary psychotic and mood disorders. Psychosomatics 47:491–497