



## T-wave axis deviation, metabolic syndrome and estimated cardiovascular risk – In men and women of the MOLI-SANI study



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### ABSTRACT

**Aim:** We aimed at investigating the association between T-wave axis deviation, metabolic syndrome (MetS), its components and estimated risk of cardiovascular disease (CVD) at 10 years in an adult Italian population.

**Methods:** 11,143 women (54 ± 11 years) and 9742 men (55 ± 11 years) were analyzed from the Moli-sani cohort, randomly recruited from the general population. MetS was defined using the ATPIII criteria. T-wave axis deviation was measured from the standard 12-lead resting electrocardiogram. CVD risk in ten years was estimated by the CUORE score.

**Results:** 29% of men and 27% of women with MetS showed borderline or abnormal T-wave as compared to 24% and 17% without MetS ( $p < 0.0001$  for both genders).

Among components of MetS, elevated waist and blood pressure were strongly associated with T-wave axis deviation, whereas glucose, HDL and triglycerides were only marginally. The odds of having borderline or abnormal T-wave axis deviation in multivariable regression analysis, was 1.38 (95% CI: 1.25–1.53) in MetS men and 1.68 (95% CI: 1.51–1.87) in MetS women compared to those without. Further adjustment for MetS components completely abolished the associations. Abnormal T-wave axis deviation was associated with an increased risk of CVD in 10 years in men (OR = 4.4; 95% CI: 1.10–17.9).

**Conclusion:** T-wave axis deviation is strongly associated with components of the MetS, in particular high waist circumference and blood pressure and with an increased CVD risk, particularly in men. ECG monitoring to identify T-wave axis deviation in obese, hypertensive or MetS subjects can be an early indicator of vascular disease and help in reducing cardiac events.

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### 1. Introduction

T-wave axis deviation reflects abnormal ventricular repolarization which is associated with higher risk of arrhythmias and it is indicative of subclinical myocardial damage. T-wave axis deviation has been associated with increased risk of coronary heart disease (CHD) and total mortality, independently of other cardiovascular risk factors and particularly in the elderly population [1,2]. Results

from Rautahariu et al. [1] suggest that T-axis deviation is an easily quantified marker for subclinical disease and an independent indicator for the risk of incident CHD events in older men and women free of CHD. In respect to other measurements of ventricular repolarization as QT dispersion and QTC duration, frontal plane T-wave axis deviation can be easily and repeatedly evaluated from a standard ECG [2] in epidemiological settings.

A recent epidemiological report from the US showed that abnormal T-wave axis shift is also independently associated with metabolic syndrome (MetS) [3], suggesting to perform a careful electrocardiographic recording among persons with MetS for early detection of abnormal T-wave axis in clinical practice to prevent severe and often fatal arrhythmias.

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MetS is a cluster of cardiovascular risk factors which has been rapidly interesting millions of people worldwide. In the United States approximately one-quarter of people is affected by MetS and this number is likely to rise in future years according to the latest data on the obesity pandemic [4]. Similar figures have been reported in Europe and in particular in Southern European countries where the prevalence of MetS is reaching worrying levels. MetS has been associated with a 2-fold increase in cardiovascular disease (CVD) and a 1.5-fold increase in all-cause mortality [5].

We further investigated T-wave axis deviation, by assessing its relationship with MetS, its components and with estimated risk of CVD, separately in men and women in a large community sample of the Italian adult population in the framework of the Moli-sani Study.

## 2. Material and methods

The cohort of the Moli-sani Study was randomly recruited in the Molise region from city hall registries by a multistage sampling [6,7]. First, townships were sampled in major areas by cluster sampling; then, within each township, participants aged  $\geq 35$  years were selected by simple random sampling. Exclusion criteria were pregnancy at the time of recruitment, disturbances in understanding or willingness, current poly-traumas or coma, or refusal to sign the informed consent. Thirty percent of subjects refused to participate; these were generally older and had a higher prevalence of CVD and cancer.

Between March 2005 and April 2010, 24,325 subjects were recruited in two centers: the Catholic University of Campobasso ( $n = 19,217$ ; 79%) and San Timoteo Hospital of Termoli ( $n = 5108$ ; 21%), by research personnel, accurately trained. The recruitment strategies were carefully defined and standardized across the two recruiting centers. Structured digitalized questionnaires were administered to collect personal and clinical information.

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The Moli-sani study complies with the Declaration of Helsinki and was approved by the Catholic University ethical committee. All participants enrolled provided written informed consent.

### 2.1. Anthropometric and blood pressure (BP) measurements

Body weight and height were measured on a standard beam balance scale with an attached ruler with subjects wearing no shoes and only light indoor clothing. BMI was calculated as  $\text{kg/m}^2$ . Waist circumferences were measured according to the NIH, Heart, Lung, and Blood guidelines [8].

Blood pressure was measured by an automatic device (OMRON-HEM-705CP) three times on the non-dominant arm and the average of the last two values was taken as the BP [9].

### 2.2. Frontal T-wave axis measurement

T-wave axis deviation was measured from the standard 12-lead resting electrocardiogram (ECG). ECG was measured using a Cardiette<sup>®</sup>ar2100-view electrocardiograph storing ECG in SCP format. The ECG was then processed by the “University of Glasgow 12-Lead ECG Analysis Algorithm” [10] that produces the value of rotation of the T-wave in the frontal axis.

T-wave was categorized in normal ( $\geq 15^\circ$  to  $\leq 75^\circ$ ), borderline ( $> 75^\circ$  to  $\leq 105^\circ$  or  $< 15^\circ$  to  $\geq -15^\circ$ ), and abnormal ( $< -15^\circ$  to  $\geq -180^\circ$  or  $> 105^\circ$  to  $\leq 180^\circ$ ) [2].

### 2.3. Definition of risk factors

Hypertension was defined as systolic BP  $\geq 160$  mm Hg and/or diastolic BP  $\geq 95$  mm Hg, or using pharmacological treatment. Hypercholesterolemia was considered as cholesterol  $\geq 240$  mg/dl or using pharmacological treatment. Diabetes was defined as fasting glucose level  $\geq 126$  mg/dl or current treatment with antidiabetic drugs.

Subjects were classified as non-smokers if they had smoked less than 100 cigarettes longlife or they had never smoked cigarettes, ex-smokers if they had smoked cigarettes in the past and had stopped smoking for at least 1 year, and current smokers those who reported having smoked at least 100 cigarettes in their lifetime and still smoked or had quit smoking within the preceding year.

Socio-economic status was defined as a score based on 6 variables (incoming, education, housing, ratio between the number of live-in partners and the number of rooms - both current and in the childhood - and availability of hot water at home in the childhood); the highest the score, the highest the level of socio-economic status [11]. Physical activity was assessed by a structured questionnaire and expressed as daily energy expenditure in metabolic equivalent task-hours (MET-h).

Metabolic syndrome (MetS) was defined according to Adult Treatment Panel III criteria [12]: at least three of these criteria: elevated waist circumference ( $\geq 102$  cm in men  $\geq 88$  cm in women); elevated triglycerides ( $\geq 150$  mg/dl) or drug treatment for elevated triglycerides; reduced HDL-C  $< 40$  mg/dl (1.03 mmol/L) in men  $< 50$  mg/dl (1.3 mmol/L) in women or drug treatment for reduced HDL-C, elevated blood pressure ( $\geq 130$  mm Hg systolic blood pressure or  $\geq 85$  mm Hg diastolic blood pressure) or anti-hypertensive drug treatment in a patient with a history of hypertension; elevated fasting glucose ( $\geq 100$  mg/dl) or drug treatment for elevated glucose.

Global individual CVD risk was calculated applying the risk equations of the CUORE project [13,14]. Subjects older than 69 years or with previous cardiovascular events were excluded from this analysis.

Subjects ( $n = 1250$ ) with altered QRS duration according to the Glasgow algorithm [10] were excluded since this condition might provoke T-wave changes to altered ventricular depolarization sequence. After excluding subjects with incomplete questionnaire ( $n = 235$ ), or history of CVD ( $n = 1140$ ), or left ventricular hypertrophy ( $n = 1141$ ), or T-axis value missing ( $n = 195$ ), or at least one component of the metabolic syndrome missing ( $n = 184$ ), 20,885 (86%), 11,143 women (mean age  $55 \pm 11$ ) and 9742 men (mean age  $55 \pm 11$ ) were analyzed.

### 2.4. Biochemical measurements

Serum lipids and glucose were assayed by enzymatic reaction methods using an automatic analyzer (ILab 350, Instrumentation laboratory (IL), Milan, Italy). LDL-cholesterol was calculated according to Friedewald.

### 2.5. Statistical analysis

Serum triglyceride, blood glucose and global individual CVD risk score were transformed into natural logarithms to reduce their positive skewness, but data were reported untransformed for clarity. Values for continuous variables are means  $\pm$  Standard Deviation.

All the analyses were conducted separately by sexes. The potential predictors tested for association with abnormalities of T-axis (three levels, coded 0, 1, 2, from normal to abnormal) included socio-demographic variables (age, sex, smoking habit, social status

and physical activity), serum lipid concentrations (total-, HDL-, and LDL-cholesterol, and triglycerides), systolic and diastolic blood pressure, blood glucose, BMI, waist to hip ratio, menopause status, heart rate, QRS complex duration, hypertension, dyslipidemia, diabetes, hyperthyroidism or hypothyroidism. Generalized linear models (PROC GENMOD in SAS) were used for testing the association of the T wave axis classification (considered as the dependent variable) with potential predictors, or the association of general characteristics with MetS. Using multivariable logistic regression analysis, odds ratio (ORs) with corresponding 95% confidence intervals (95%CI) were calculated to quantify the association of MetS or components of MetS with status of borderline or abnormal T wave axis in comparison with normal condition. Variables associated with T wave axis in analysis adjusted for age with  $P < 0.05$  were included in the multivariable analysis.

The data analysis was generated using SAS/STAT software, Version 9.1.3 of the SAS System for Windows©2009. SAS Institute Inc. and SAS are registered trademarks of SAS Institute Inc., Cary, NC, USA.

### 3. Results

General characteristics of men and women included in the study are illustrated in Table 1a and b

MetS was prevalent in 27% ( $n = 2643$ ) of men and 24% ( $n = 2663$ ) of women. MetS was associated, both in men and women, with older age, smoking habits, lower socio economic status and higher prevalence of menopause (in women). High systolic blood pressure, triglycerides and waist circumference were the most represented features of the MetS in both genders.

T-wave axis deviation was categorized in normal (15–75°; prevalence: 74.5% in men and 80.9% in women), borderline (–15 to 15; 23.6% and 17.3%) and abnormal (–180 to –15 or 75–180; 1.9% and 1.8%).

#### 3.1. MetS and T-wave axis deviation abnormalities in men

In men with MetS the prevalence of borderline or abnormal T-wave axis deviation was higher than in subjects without MetS

**Table 1a**  
Male subjects characteristics by MetS status.

Men Characteristics	Metabolic syndrome			P-value age adjusted
	All 9742	Absent 7099 (73%)	Present 2643 (27%)	
Age, yrs, (sd)	55 (11)	54 (12)	57 (11)	<0.0001 <sup>a</sup>
Smokers n, (%)				<0.0001
Never	3214 (33)	2542 (36)	672 (25)	
Current	2623 (27)	1862 (26)	761 (29)	
Former	3897 (40)	2689 (38)	1208 (46)	
Socio-economic status score	3.5 (1.4)	3.6 (1.3)	3.4 (1.3)	<0.0001
Physical activity, MET-h/day (sd)	44.0 (10)	44.1 (9.8)	43.4 (10.1)	0.25
BMI, kg/m <sup>2</sup> (sd)	28.2 (4.1)	27.1 (3.4)	31.1 (4.3)	<0.0001
Malignancies n, (%)	197 (2.0)	142 (2.0)	55 (2.1)	0.33
MetS Features n, (%)	2643 (27.1)			
Waist circumference $\geq 88$ cm	2690 (27.6)	956 (13)	1734 (66)	<0.0001
Triglycerides $\geq 150$ mg/dl	3497 (35.9)	1487 (21)	2010 (76)	<0.0001
HDL $< 50$ mg/dl	1466 (15.1)	455 (6)	1011 (38)	<0.0001
SBP $\geq 130$ or DBP $\geq 85$ mm Hg	7604 (78.1)	5042 (72)	2562 (97)	<0.0001
Fasting glucose $\geq 110$ mg/dl	2674 (27.5)	1006 (14)	1668 (64)	<0.0001
Heart rate b/m	66 (10)	65 (10)	68 (11)	<0.0001
QRS complex duration, ms	91.1 (8)	91.0 (8)	91.2 (8)	0.21
T-wave axis deviation n, (%)				<0.0001
Normal	7256 (74.5)	5408 (76.2)	1848 (69.9)	
Borderline	2301 (23.6)	1572 (22.1)	729 (27.6)	
Abnormal	185 (1.9)	119 (1.7)	66 (2.5)	

<sup>a</sup> Univariable.

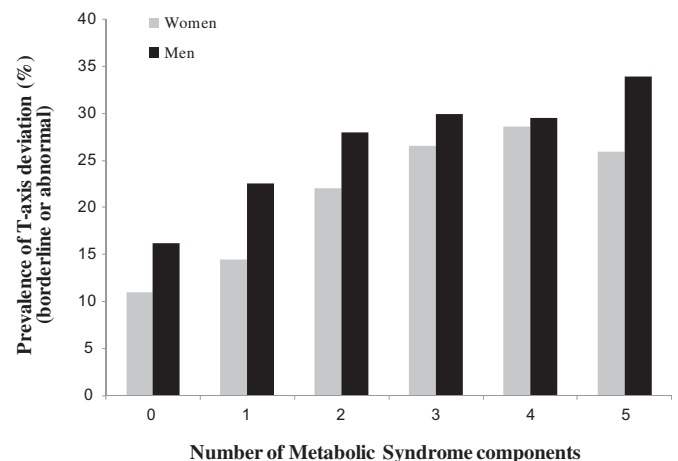
**Table 1b**  
Female subjects characteristics by MetS status.

Women Characteristics	Metabolic syndrome			P-value age adjusted
	All 11,143 (100%)	Absent 8480 (76%)	Present 2663 (24%)	
Age, yrs, (sd)	54 (11)	53 (11)	60 (11)	<0.0001 <sup>a</sup>
Smokers n, (%)				0.0060
Never	7213 (64.8)	5326 (63)	1887 (71)	
Current	2358 (21.2)	1906 (23)	452 (17)	
Former	1557 (14.0)	1238 (15)	319 (12)	
Socio-economic status score	3.5 (1.4)	3.6 (1.4)	3.1 (1.3)	<0.0001
Physical activity, MET-h/day (sd)	42.6 (7.5)	42.7 (7.6)	42.3 (6.9)	0.54
BMI, kg/m <sup>2</sup> (sd)	27.7 (5.3)	26.5 (4.7)	31.7 (5.1)	<0.0001
Menopause n, (%)	6146 (55.2)	4115 (48.6)	2031 (76.3)	<0.0001
Malignancies n, (%)	400 (3.6)	278 (3.3)	122 (4.6)	0.44
MetS Features n, (%)	2663 (23.9)			
Waist circumference $\geq 88$ cm	6432 (57.7)	3,96 (46)	2526 (95)	<0.0001
Triglycerides $\geq 150$ mg/dl	2042 (18.3)	449 (5)	1593 (60)	<0.0001
HDL $< 50$ mg/dl	1977 (17.7)	631 (7)	1346 (51)	<0.0001
SBP $\geq 130$ or DBP $\geq 85$ mm Hg	7015 (63.0)	4495 (53)	2520 (95)	<0.0001
Fasting glucose $\geq 110$ mg/dl	1471 (13.2)	292 (3)	1179 (44)	<0.0001
Heart rate b/m	69 (10)	68 (10)	70 (11)	<0.0001
QRS complex duration, ms	86.1 (8)	86.0 (8)	86.4 (7)	0.014
T-wave axis deviation n, (%)				<0.0001
Normal	9012 (80.9)	7078 (83.5)	1934 (72.6)	
Borderline	1929 (17.3)	1264 (14.9)	665 (25.0)	
Abnormal	202 (1.8)	138 (1.6)	64 (2.4)	

<sup>a</sup> Univariable.

(26.6% vs. 22.1% and 2.5% vs. 1.7% for borderline and abnormal levels, respectively;  $P < 0.0001$ , Table 1a). Prevalence of T-axis deviation (borderline or abnormal) increased from 16% to 44% when the number of MetS components increased from zero to five ( $p < 0.0001$ , Fig. 1). Among components of MetS, elevated waist circumference, blood pressure and glucose levels were strongly associated with T-wave axis deviation, whereas HDL cholesterol and triglycerides only marginally or not (Table 1Sa).

Men with MetS had increased risk of having either borderline or abnormal T-wave axis deviation (Table 2a). The odds of having borderline or abnormal T-wave axis deviation was 1.38 (95% CI: 1.25–1.53) times greater in men with MetS compared to those without, after adjustment for age, cigarette smoking, social status, physical activity and QRS duration (Table 2a). After further adjustment for all the components of MetS, the OR for MetS



**Fig. 1.** Prevalence of T-axis deviation (borderline or abnormal) in men and women, according to number of metabolic syndrome components.

**Table 2a**  
Relationship of MetS and MetS components with T-wave axis deviation in men.

	OR (95%CI)	
	Model 1	Model 2
<i>Normal vs. borderline or abnormal</i>		
MetS absent	-1-	-1-
MetS present	1.38 (1.25–1.53)	0.79 (0.66–0.95)
Zero components of MetS	-1-	-1-
OR for 1 additional component	1.21 (1.16–1.26)	1.15 (1.03–1.27)
Waist circumference $\geq$ 88 cm	1.72 (1.56–1.90)	1.62 (1.47–1.80)
Triglycerides $\geq$ 150 mg/dl	1.09 (0.99–1.29)	0.97 (0.87–1.07)
HDL $<$ 50 mg/dl	1.14 (1.00–1.25)	1.07 (0.94–1.23)
SBP $\geq$ 130 or DBP $\geq$ 85 mm Hg	1.53 (1.35–1.73)	1.40 (1.24–1.59)
Fasting glucose $\geq$ 110 mg/dl	1.27 (1.15–1.41)	1.15 (1.03–1.27)
<i>Normal vs. borderline</i>		
MetS absent	-1-	-1-
MetS present	1.37 (1.24–1.53)	0.79 (0.65–0.95)
Zero components of MetS	-1-	-1-
OR for 1 additional component	1.21 (1.16–1.26)	1.13 (1.01–1.26)
Waist circumference $\geq$ 88 cm	1.73 (1.56–1.91)	1.64 (1.47–1.82)
Triglycerides $\geq$ 150 mg/dl	1.10 (0.99–1.21)	0.98 (0.88–1.08)
HDL $<$ 50 mg/dl	1.14 (0.99–1.29)	1.07 (0.94–1.23)
SBP $\geq$ 130 or DBP $\geq$ 85 mm Hg	1.51 (1.33–1.71)	1.39 (1.22–1.58)
Fasting glucose $\geq$ 110 mg/dl	1.25 (1.13–1.39)	1.13 (1.01–1.26)
<i>Normal vs. abnormal</i>		
MetS absent	-1-	-1-
MetS present	1.46 (1.07–1.99)	0.90 (0.50–1.61)
Zero components of MetS	-1-	-1-
OR for 1 additional component	1.23 (1.09–1.39)	1.40 (1.02–1.91)
Waist circumference $\geq$ 88 cm	1.56 (1.15–2.12)	1.42 (1.03–1.95)
Triglycerides $\geq$ 150 mg/dl	1.02 (0.75–1.40)	0.89 (0.64–1.23)
HDL $<$ 50 mg/dl	1.14 (0.76–1.70)	1.09 (0.72–1.66)
SBP $\geq$ 130 or DBP $\geq$ 85 mm Hg	1.92 (1.17–3.14)	1.75 (1.06–2.89)
Fasting glucose $\geq$ 110 mg/dl	1.52 (1.12–2.07)	1.40 (1.02–1.91)

decreased to 0.79 and it was no longer statistically significant (Table 2a).

Each additional component of MetS increased the odds of having borderline or abnormal T-wave axis deviation by 21%, compared to those with zero MetS components (Table 2a).

The odds for borderline or abnormal T-wave axis deviation were 1.62, 1.40 and 1.15 for elevated waist, blood pressure and glucose levels, whereas they were no statistically significant for lipids abnormalities (Table 2a) after adjustment.

### 3.2. MetS and T-wave axis deviation abnormalities in women

In women with MetS the prevalence of borderline or abnormal T-wave axis deviation was higher than in subjects without MetS (25% vs. 15% and 2.4% vs. 1.6% for borderline and abnormal levels, respectively;  $P < 0.0001$ , Table 1b). Prevalence of T-axis deviation (borderline or abnormal) increased from 11% to 26% when the number of MetS components increased from zero to five (Fig. 1). At difference with findings in men, all the components of MetS were strongly associated with T-wave axis deviation (Table 1Sb).

The model 1 odds of having T-wave axis deviation abnormalities was 1.68 (95% CI: 1.51–1.87) times greater in women with MetS compared to those without (Table 2b). After further adjustment for all the components of MetS, the OR for MetS decreased to 1.10 and it was no longer statistically significant (Table 2b). Women with MetS had an increased risk of having borderline T-wave axis deviation, while (Table 2b) there association with abnormal T-wave axis deviation did not reached a statistical significance.

All the MetS components, but glucose levels were significantly and independently associated with an increased risk of T-wave axis deviation (Table 2b).

**Table 2b**  
Relationship of MetS and MetS components with T-wave axis deviation in women.

	OR (95%CI)	
	Model 1	Model 2
<i>Normal vs. borderline or abnormal</i>		
MetS absent	-1-	-1-
MetS present	1.68 (1.51–1.87)	1.10 (0.91–1.34)
Zero components of MetS	-1-	-1-
OR for 1 additional component	1.31 (1.26–1.36)	1.05 (0.92–1.21)
Waist circumference $\geq$ 88 cm	1.95 (1.75–2.17)	1.77 (1.59–1.98)
Triglycerides $\geq$ 150 mg/dl	1.43 (1.27–1.60)	1.19 (1.06–1.35)
HDL $<$ 50 mg/dl	1.37 (1.21–1.54)	1.17 (1.03–1.32)
SBP $\geq$ 130 or DBP $\geq$ 85 mm Hg	1.57 (1.40–1.77)	1.36 (1.21–1.54)
Fasting glucose $\geq$ 110 mg/dl	1.26 (1.10–1.44)	1.05 (0.92–1.21)
<i>Normal vs. borderline</i>		
MetS absent	-1-	-1-
MetS present	1.74 (1.56–1.94)	1.12 (0.92–1.37)
Zero components of MetS	-1-	-1-
OR for 1 additional component	1.32 (1.27–1.38)	1.04 (0.90–1.20)
Waist circumference $\geq$ 88 cm	1.98 (1.77–2.22)	1.79 (1.60–2.01)
Triglycerides $\geq$ 150 mg/dl	1.48 (1.31–1.67)	1.23 (1.08–1.40)
HDL $<$ 50 mg/dl	1.41 (1.25–1.59)	1.19 (1.05–1.35)
SBP $\geq$ 130 or DBP $\geq$ 85 mm Hg	1.59 (1.40–1.79)	1.36 (1.20–1.55)
Fasting glucose $\geq$ 110 mg/dl	1.26 (1.10–1.45)	1.04 (0.90–1.20)
<i>Normal vs. abnormal</i>		
MetS absent	-1-	-1-
MetS present	1.20 (0.88–1.65)	0.96 (0.54–1.69)
Zero components of MetS	-1-	-1-
OR for 1 additional component	1.15 (1.02–1.30)	1.18 (0.82–1.71)
Waist circumference $\geq$ 88 cm	1.63 (1.18–2.25)	1.57 (1.12–2.19)
Triglycerides $\geq$ 150 mg/dl	0.96 (0.67–1.37)	0.88 (0.60–1.28)
HDL $<$ 50 mg/dl	0.99 (0.68–1.43)	0.94 (0.64–1.38)
SBP $\geq$ 130 or DBP $\geq$ 85 mm Hg	1.46 (0.99–2.14)	1.34 (0.90–1.97)
Fasting glucose $\geq$ 110 mg/dl	1.26 (0.88–1.82)	1.18 (0.82–1.71)

Model 1: adjusted for age, cigarette smoking, social status, physical activity and QRS duration.

Model 2: model 1, further adjusted for all the components of MetS.

### 3.3. T-wave axis deviation abnormalities and estimated cardiovascular risk score

T-wave anomalies were associated with increased age, higher prevalence of former smokers (in men) or non smokers (in women), lower socio economic status or physical activity, higher prevalence of hypertension and diabetes and of hypothyroidism or menopause (in women) (Table 2Sa and 2Sb).

After adjustment for age, there was a significant association between T-wave axis deviation and cardiovascular risk score at 10 years, in both genders (Table 2Sa and 2Sb). In men, borderline and abnormal T-wave axis deviation were associated with an increase in the risk to develop a cardiovascular event in 10 years of 1.38 and 4.44 after adjustment for age, cigarette smoking, social status, physical activity and QRS duration (Table 3). In women, the association reached significant levels only in univariable analysis (Table 3). In a model adjusted for the MetS components, the OR were 0.73 (0.62–0.87) and 1.83 (1.04–3.21) in men and 0.88 (0.76–1.01) and 1.43 (0.95–2.17) in women, respectively for borderline and abnormal t-wave axis deviation.

## 4. Discussion

We have used T wave axis deviation as an indicator of ventricular repolarization to better stratify cardiovascular risk in patients with MetS a cluster of cardiovascular risk factors, driven by abdominal adiposity, that has been related to the risk of diabetes, CVD and total mortality [5].

Faramawi S et al. [3] have already shown an independent association between MetS and an abnormal T-wave axis shift in the

**Table 3**  
Odds ratio for high vs. low estimate CVD risk scores according to T-wave axis deviation.

Men		
CUORE risk $\leq 3\%$ vs $\geq 10\%$	Univariable	Multivariable <sup>a</sup>
Normal	-1-	-1-
Borderline	1.00 (0.86–1.14)	1.38 (0.84–2.26)
Abnormal	2.59 (1.06–4.18)	4.44 (1.10–17.9)
WOMEN		
CUORE risk $\leq 3\%$ vs. $\geq 3\%$	Univariable	Multivariable <sup>a</sup>
Normal	-1-	-1-
Borderline	1.37 (1.22–1.55)	1.17 (0.98–1.38)
Abnormal	1.78 (1.24–2.55)	1.16 (0.70–1.93)

<sup>a</sup> Adjusted for age, cigarette smoking, social status, physical activity and QRS duration.

population of the NANHES III study in US. We extended these results to a large European population, allowing separated analysis for men and women.

Our findings add the following to current knowledge: 1) The association between MetS or its components and borderline or abnormal T wave axis deviation is stronger in men than in women; 2) the association mainly depends on individual components of the MetS, since adjustment for such components completely abolish the association; 3) Among MetS components, elevated waist and blood pressure levels are the main responsible for the association with T-wave axis deviation, whereas glucose, HDL cholesterol and triglycerides only marginally; 4) In men, each additional component of MetS, independently from the others, increases the odds of having borderline or abnormal T-wave axis deviation by 15%; 5) In men, alterations of T-wave axes deviation are associated with an increased risk of cardiovascular events in 10 years.

Differences between gender suggest a sexual dimorphism in the association between t-wave axis deviation and metabolic risk factors and it is in agreement with the notion that CAD risk is lower in women than in men [16].

The finding that T-wave axis deviation depends from single components of MetS is in line with other observations showing that MetS does not correlate with a measure of subclinical atherosclerosis to a greater extent than what expected from its individual components or from their total number [17] or with other studies performed in American or in European general populations using “hard” cardiovascular endpoints [18,19]. These findings, however, are not unexpected in syndromes whose signs and symptoms have a single underlying cause. Probably, the link between MetS and possible cardiac damage detectable by T axis deviation has to be searched in insulin resistance as showed for several other abnormalities [20]. Insulin resistance causes oxidative stress responsible for endothelial dysfunction and chronic inflammation which represents potential risk factors for both obesity and hypertension and subclinical conditions for CVD [21].

Abnormal T-wave deviation is an indicator of alteration of ventricular repolarization. The latter, may reflect subclinical damage often predisposing to fatal arrhythmias. Population-based reports in older populations [1,2] suggested that T-wave deviation could be an indicator of increased risk of coronary heart disease and total mortality, independently from other cardiovascular risk factors; however such data were not confirmed in middle age subjects [22,23]. We used the predicted risk of CVD in the Italian population, as a markers of ischemic cardiovascular risk, by applying the individual CUORE risk score [14,15], which provides an estimate of the probability of the first coronary or cerebrovascular event in the next ten years, based on a risk function derived from

several Italian cohorts [24]. Estimated risk for CVD has been already used as a surrogate for CVD to evaluate the association with novel risk factors [25,26]. We found a strong association between T-wave axis deviation and the risk of CVD at 10 years, both in men and women. However, multivariate analysis adjusting for age, cigarette smoking, social status, physical activity and QRS duration indicated an increased risk of having a CVD event in the next 10 years only in men, but not in women with borderline and abnormal T-wave axis deviation. Such difference between genders could be attributed to the low number of women in the higher risk CVD and abnormal t-wave axis deviation categories. In alternative it reflects the weaker association of CVD risk components with T-wave axis deviation in women. We also adjusted the association between t-wave axis deviation and CVD risk for the MetS components; the OR in men was decreased, but still significant, suggesting that the presence of abnormal T-wave axis deviation portends an independently elevated CVD risk over and above that associated with MetS.

Although estimated CVD risk is only a surrogate of the real risk of CVD our results suggest that T-wave axis deviation is a good parameter to stratify the future risk of CVD of both general population and subjects with metabolic risk factors for CVD.

The use of T wave axis deviation is easier compared to traditional markers as QT, QT dispersion and T wave alternans, since it is independent from heart rate and it is less susceptible to noise and to definition problems. Its value is already incorporated in the electrocardiograph and it is easy to understand by clinicians. Electrocardiography still represents the most widely used cardiovascular test in clinical practice. Despite this, physician rarely takes full advantage of the amount of information provided by this simple and inexpensive tool. The introduction of digital electrocardiography, currently standard in most countries, has further widened the diagnostic capabilities of this technique for pharmacological, epidemiological studies and for a preclinical diagnosis of cardiac diseases [15]. T wave axis seems a peculiar abnormality useful to better stratify individual risk, as compared with a traditional use of cardiovascular risk factors [1–3].

Large sample size and random allocation into the cohort minimizing selection bias are some strengths of the study; however, there are some limitations: its cross-sectional nature does not allow for inference of causality or for establishment of temporality between MetS and T-wave axis abnormalities and the latter and estimated cardiovascular risk. The presence of unknown or residual confounders could not be completely ruled out, although adjustment for potential key confounders was performed. Prospective evaluations will be necessary to confirm the findings reported in this study.

In conclusion, in a large adult Italian population components of the MetS are strongly associated with abnormal T-wave axis deviation, that is in turn associated with an increased risk of CVD estimated at 10 years. We suggest that an easy-to-use and relatively low-cost tool such as ECG monitoring to identify T-wave axis deviation in obese, hypertensive or MetS subjects can be used as an early indicator of vascular disease and help in reducing cardiac events.

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## Appendix B. Supplementary data

Supplementary data related to this article can be found at <http://dx.doi.org/10.1016/j.atherosclerosis.2012.11.010>.

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