

Atherosclerosis  
Elsevier Editorial System(tm) for  
Manuscript Draft

Manuscript Number: ATH-D-12-00356R1

Title: T-wave axis deviation, metabolic syndrome and estimated cardiovascular risk in men and women of the MOLI-SANI Study

Article Type: Clinical Investigation

Keywords: T-wave axis deviation, metabolic syndrome, estimated cardiovascular risk

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## T-wave axis deviation, metabolic syndrome and estimated cardiovascular risk

### In men and women of the MOLI-SANI Study

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**Grant Support:** The *MOLI-SANI* Project enrolment was supported by research grants from Pfizer Foundation (Rome, Italy) and the Italian Ministry of University and Research (MIUR, Rome, Italy)–Programma Triennale di Ricerca, Decreto no.1588.

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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 a adult Italian population.

**Methods:** 11,143 women (54±11 years) and 9,742 men (55±11 years) were analysed 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.

**Word count: 250**

**Key words:** T-wave axes deviation, metabolic syndrome, estimated cardiovascular risk

## Introduction

1  
2 T-wave axis deviation reflects abnormal ventricular repolarization which is associated with higher  
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4 risk of arrhythmias and it is indicative of subclinical myocardial damage. T-wave axis deviation has  
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6 been associated with increased risk of coronary heart disease (CHD) and total mortality,  
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8 independently of other cardiovascular risk factors and particularly in the elderly population (1, 2).  
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10 Results from Rautahariu et al (1) suggest that T-axis deviation is an easily quantified marker for  
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12 subclinical disease and an independent indicator for the risk of incident CHD events in older men  
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14 and women free of CHD. In respect to other measurements of ventricular repolarization as QT  
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16 dispersion and QTC duration, frontal plane T-wave axis deviation can be easily and repeatedly  
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18 evaluated from a standard ECG (2) in epidemiological settings.  
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24 A recent epidemiological report from the US showed that abnormal T-wave axis shift is also  
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26 independently associated with metabolic syndrome (MetS) (3), suggesting to perform a careful  
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28 electrocardiographic recording among persons with MetS for early detection of abnormal T-wave  
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30 axis in clinical practice to prevent severe and often fatal arrhythmias.  
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34 MetS is a cluster of cardiovascular risk factors which has been rapidly interesting millions of people  
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36 worldwide. In the United States approximately one-quarter of people is affected by MetS and this  
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38 number is likely to rise in future years according to the latest data on the obesity pandemic (4).  
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40 Similar figures have been reported in Europe and in particular in Southern European countries where  
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42 the prevalence of MetS is reaching worrying levels. MetS has been associated with a 2-fold  
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44 increase in cardiovascular disease (CVD) and a 1.5-fold increase in all-cause mortality (5).  
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48 We further investigated T-wave axis deviation, by assessing its relationship with MetS, its  
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50 components and with estimated risk of CVD, separately in men and women in a large community  
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52 sample of the Italian adult population. in the framework of the Moli-sani Study.  
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## 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=5,108; 21%), by research personnel, accurately trained. The recruitment strategies were carefully defined and standardised across the two recruiting centres. Structured digitalized questionnaires were administered to collect personal and clinical information.

The authors of this manuscript have certified that they comply with the Principles of Ethical Publishing in the International Journal of Cardiology: Shewan LG and Coats AJ. Ethics in the authorship and publishing of scientific articles. Int J Cardiol 2010;144:1-2.

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.

### *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).

### ***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®ar2100-view electrocardiograph storing ECG in SCP format.

The ECG were 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).

### ***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 antihypertensive 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=1,140), or left ventricular hypertrophy (n=1,141), 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 9,742 men (mean age  $55\pm 11$ ) were analyzed.

### ***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.

### ***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

1 concentrations (total-, HDL-, and LDL-cholesterol, and triglycerides), systolic and diastolic blood  
2 pressure, blood glucose, BMI, waist to hip ratio, menopause status, heart rate, QRS complex  
3 duration, hypertension, dyslipidemia, diabetes, hyperthyroidism or hypothyroidism. Generalized  
4 linear models (PROC GENMOD in SAS) was used for testing the association of the T wave axis  
5 classification (considered as the dependent variable) with potential predictors, or the association of  
6 general characteristics with MetS. Using multivariable logistic regression analysis, odds ratio (ORs)  
7 with corresponding 95% confidence intervals (95%CI) were calculated to quantify the association of  
8 MetS or components of MetS with status of borderline or abnormal T wave axis in comparison with  
9 normal condition. Variables associated with T wave axis in analysis adjusted for age with  $P < 0.05$   
10 were included in the multivariable analysis.  
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24 The data analysis was generated using SAS/STAT software, Version 9.1.3 of the SAS System for  
25 Windows©2009. SAS Institute Inc. and SAS are registered trademarks of SAS Institute Inc., Cary,  
26 NC, USA.  
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## 34 **Results.**

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36 General characteristics of men and women included in the study are illustrated in Tables 1a and 1b.  
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38 MetS was prevalent in 27% (n=2,643) of men and 24% (n=2,663) of women. MetS was associated,  
39 both in men and women, with older age, smoking habits, lower socio economic status and higher  
40 prevalence of menopause (in women). High systolic blood pressure, triglycerides and waist  
41 circumference were the most represented features of the MetS in both genders.  
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48 T-wave axis deviation was categorized in normal (15 to 75 degree; prevalence: 74.5% in men and  
49 80.9% in women), borderline (-15 to 15; 23.6% and 17.3%) and abnormal (-180 to -15 or 75 to 180;  
50 1.9% and 1.8%).  
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### 58 ***MetS and T-wave axis deviation abnormalities in Men***

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1 In men with MetS the prevalence of borderline or abnormal T-wave axis deviation was higher than  
2 in subjects without MetS (26.6% vs 22.1% and 2.5% vs 1.7% for borderline and abnormal levels,  
3 respectively; P<0.0001, Table 1a). Prevalence of T-axis deviation (borderline or abnormal)  
4 increased from 16% to 44% when the number of MetS components increased from zero to five  
5 (p<0.0001, Fig. 1). Among components of MetS, elevated waist circumference, blood pressure and  
6 glucose levels were strongly associated with T-wave axis deviation, whereas HDL cholesterol and  
7 triglycerides only marginally or not (Table 1Sa).

8 Men with MetS had increased risk of having either borderline or abnormal T-wave axis deviation  
9 (table 2a). The odds of having borderline or abnormal T-wave axis deviation was 1.38 (95% CI:  
10 1.25-1.53) times greater in men with MetS compared to those without, after adjustment for age,  
11 cigarette smoking, social status, physical activity and QRS duration (Table 2a). After further  
12 adjustment for all the components of MetS, the OR for MetS decreased to 0.79 and it was no longer  
13 statistically significant (Table 2a).

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

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

### 19 ***MetS and T-wave axis deviation abnormalities in women***

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

1 The model 1 odds of having T-wave axis deviation abnormalities was 1.68 (95% CI: 1.51-1.87)  
2 times greater in women with MetS compared to those without (Table 2b). After further adjustment  
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4 for all the components of MetS, the OR for MetS decreased to 1.10 and it was no longer statistically  
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6 significant (Table 2b). Women with MetS had an increased risk of having borderline T-wave axis  
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8 deviation, while (Table 2b) there association with abnormal T-wave axis deviation did not reached a  
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10 statistical significance.  
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13 All the MetS components, but glucose levels were significantly and independently associated with  
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15 an increased risk of T-wave axis deviation (Table 2b).  
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### 21 *T-wave axis deviation abnormalities and estimated cardiovascular risk score*

22 T-wave anomalies were associated with increased age, higher prevalence of former smokers (in  
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24 men) or non smokers (in women), lower socio economic status or physical activity, higher  
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26 prevalence of hypertension and diabetes and of hypothyroidism or menopause (in women) (Table  
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31 2Sa and 2Sb).  
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33 After adjustment for age, there was a significant association between T-wave axis deviation and  
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35 cardiovascular risk score at 10 years, in both gender (Table 2Sa and 2Sb). In men, borderline and  
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37 abnormal T-wave axis deviation were associated with an increase in the risk to develop a  
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39 cardiovascular event in 10 years of 1.38 and 4.44 after adjustment for age, cigarette smoking, social  
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41 status, physical activity and QRS duration (Table 3). In women, the association reached significant  
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43 levels only in univariable analysis (Table 3). In a model adjusted for the MetS components, the OR  
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45 were 0.73 (0.62 to 0.87) and 1.83 (1.04 to 3.21) in men and 0.88 (0.76 to 1.01) and 1.43 (0.95 to  
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47 2.17) in women, respectively for borderline and abnormal t-wave axis deviation.  
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## 54 **Discussion**

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1 We have used T wave axis deviation as an indicator of ventricular repolarization to better stratify  
2 cardiovascular risk in patients with MetS a cluster of cardiovascular risk factors, driven by  
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4 abdominal adiposity, that has been related to the risk of diabetes, CVD and total mortality (5).  
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7 Faramawi S et al (3) have already shown an independent association between MetS and an abnormal  
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9 T-wave axis shift in the population of the NANHES III study in US. We extended these results to a  
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11 large European population, allowing separated analysis for men and women.  
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14 Our findings add the following to current knowledge: 1) The association between MetS or its  
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16 components and borderline or abnormal T wave axis deviation is stronger in men than in women;  
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18 2) the association mainly depends on individual components of the MetS, since adjustment for such  
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20 components completely abolish the association; 3) Among MetS components, elevated waist and  
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22 blood pressure levels are the main responsible for the association with T-wave axis deviation,  
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24 whereas glucose, HDL cholesterol and triglycerides only marginally; 4) In men, each additional  
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26 component of MetS, independently from the others, increases the odds of having borderline or  
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28 abnormal T-wave axis deviation by 15%; 5) In men, alterations of T-wave axes deviation are  
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30 associated with an increased risk of cardiovascular events in 10 years.  
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35 Differences between gender suggest a sexual dimorphism in the association between t-wave axis  
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37 deviation and metabolic risk factors and it is in agreement with the notion that CAD risk is lower in  
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39 women than in men (16).  
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43 The finding that T-wave axis deviation depends from single components of MetS is in line with  
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45 other observations showing that MetS does not correlate with a measures of subclinical  
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47 atherosclerosis to a greater extent than what expected from its individual components or from the  
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49 their total number (17) or with other studies performed in American or in European general  
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51 populations using “hard” cardiovascular endpoints (18, 19). These findings, however, are not  
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53 unexpected in syndromes whose signs and symptoms have a single underlying cause. Probably, the  
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55 link between MetS and possible cardiac damage detectable by T axis deviation has to be searched in  
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57 insulin resistance as showed for several other abnormalities (20). Insulin resistance causes oxidative  
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1 stress responsible for endothelial dysfunction and chronic inflammation which represent a potential  
2 risk factors for both obesity and hypertension and subclinical condition for CVD (21).  
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4 Abnormal T-wave deviation is an indicator of alteration of ventricular repolarization. The latter,  
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6 may reflect subclinical damage often predisposing to fatal arrhythmias. Population-based reports in  
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8 older populations (1, 2) suggested that T-wave deviation could be an indicator of increased risk of  
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10 coronary heart disease and total mortality, independently on other cardiovascular risk factors;  
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12 however such data were not confirmed in middle age subjects (22, 23). We used the predicted risk  
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14 of CVD in the Italian population, as a markers of ischemic cardiovascular risk, by applying the  
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16 individual CUORE risk score (14, 15), which provides an estimate of the probability of the first  
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18 coronary or cerebrovascular event in the next ten years, based on a risk function derived from  
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20 several Italian cohorts (24). Estimated risk for CVD has been already used as a surrogate for CVD  
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22 to evaluate the association with novel risk factors (25,26). We found a strong association between  
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24 T-wave axis deviation and the risk of CVD at 10 years, both in men and women. However,  
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26 multivariate analysis adjusting for age, cigarette smoking, social status, physical activity and QRS  
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28 duration indicated an increased risk of having a CVD event in the next 10 years only in men, but not  
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30 in women with borderline and abnormal T-wave axis deviation. Such difference between genders  
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32 could be attributed to the low number of women in the higher risk CVD and abnormal t-wave axis  
33  
34 deviation categories. In alternative it reflects the weaker association of CVD risk components  
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36 with T-wave axis deviation in women. We also adjusted the association between t-wave axisi  
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38 deviation and CVD risk for the MetS components; the OR in men was decreased, but still  
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40 significant, suggesting that the presence of abnormal T-wave axis deviation portends an  
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42 independently elevated CVD risk over and above that associated with MetS.  
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53 Although, estimated CVD risk is only a surrogate of the real risk of CVD our result suggest that T-  
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55 wave axis deviation is a good parameter to stratify the future risk of CVD of both general  
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57 population and subjects with metabolic risk factors for CVD.  
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1 The use of T wave axis deviation is easier compared to traditional markers as QT, QT dispersion and  
2 T wave alternans, since it is independent from heart rate and it is less susceptible to noise and to  
3 definition problems. Its value is already incorporated in the electrocardiograph and it is easy to  
4 understand by clinicians. Electrocardiography still represents the most widely used cardiovascular  
5 test in clinical practice. Despite this, physician rarely take full advantage of the amount of  
6 information provided by this simple and inexpensive tool. The introduction of digital  
7 electrocardiography, currently standard in most countries, has further widened the diagnostic  
8 capabilities of this technique for pharmacological, epidemiological studies and for a preclinical  
9 diagnosis of cardiac diseases (15). T wave axis seems a peculiar abnormality useful to better stratify  
10 individual risk, as compared with a traditional use of cardiovascular risk factors (1-3).

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

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

## 23 **Acknowledgments**

24 The Authors thank Associazione Cuore-Sano (Campobasso, Italy), IL Instrumentation-Laboratory  
25 (Milano, Italy), Derby-Blue (San Lazzaro di Savena, Bologna, Italy), Caffè Monforte (Campobasso,

Italy) and Sepinia SpaA (Sepino, Italy) for their support to the *MOLI-SANI* project.

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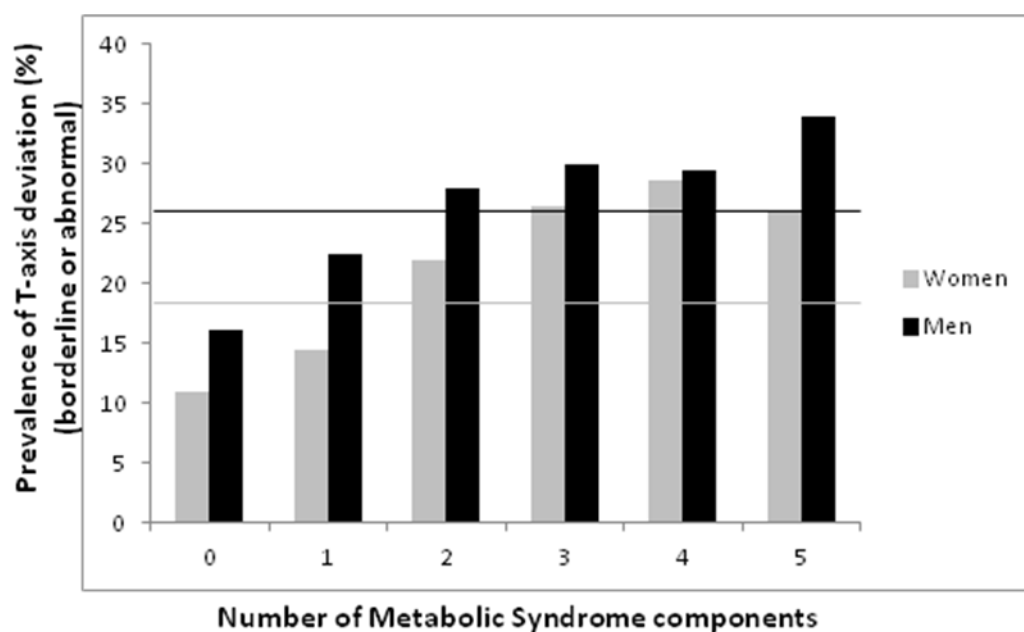
**Figure legend**

Prevalence of T-axis deviation (borderline or abnormal) in men and women, according to number of Metabolic Syndrome components.

### Answers to the reviewers.

**Reviewer #1:** This is a useful study with valuable results since it adds meaning to a readily- and non-invasively available parameter. The study is based on a large cohort and significantly supports interpretation of T-wave axis deviation by backing association with CVD risk. Experimental data support the comprehensible conclusions which are sufficiently treated in the discussion. The paper would further benefit if the main message would be visualized in at least one figure.

**We have added figure 1 in the text showing the prevalence of T axis deviation in men and women according to the number of metabolic syndrome components, and modified table 1Sa and b).**



Lines are population percentage of T-axis deviation in men and women

**Reviewer #2:** Large sample size and random allocation into the cohort minimizing selection bias are some strengths of the study. However, there are several fundamental limitations:

1. Cross-sectional study design which precludes establishment of causality or time dependent effects as stated by the authors. Residual confounding also cannot be excluded.

**We have clearly indicated these two limitations in the discussion and added the study strengths as indicated by the reviewer.**

2. The study did not record CV events but used calculated CVD risk as a surrogate.

**This is clearly stated into the manuscript. The use of calculated CVD risk as surrogate of recorded risk has been already used in other published studies (see ref 25). We now added reference 26 on the use of calculated CVD risk in the Moli-sani population.**

3. The authors demonstrated that the association between T-wave axis abnormality and metabolic syndrome got attenuated after adjustment for individual factors constituting metabolic syndrome. T-wave abnormalities were associated with high risk of CV death but the authors did not adjust for metabolic syndrome components this time. Hence, it is hard to prove that T-wave axis abnormality is in itself associated with CV death. In other words, presence of T-wave axis deviation does not seem to portend an independently elevated CVD risk over and above that associated with just metabolic syndrome. This does not necessarily offer any further means of risk stratifying patients with known traditional cardiovascular risk factors.

**As suggested by the reviewer, we adjusted the association between T-wave abnormalities and the estimated risk of CVD for the components of the metabolic syndrome. The OR were 0.73 (0.62 to 0.87) and 1.83 (1.04 to 3.21) in men and 0.88 (0.76 to 1.01) and 1.43 (0.95 to 2.17) in women. The OR in men was decreased, but still significant, suggesting that the presence of abnormal T-wave axis deviation seem to portend an independently elevated CVD risk over and above that associated with just metabolic syndrome.**

**Reviewer #4:** This study demonstrated that T-wave axis deviation is associated with component of MetS and T-wave could be an early indicator of vascular disease.

Comments

1. There is no mention about the drug therapy of these subjects. Could drug therapy influence the values of T-wave axis? Were diabetic or hypertensive patients included in this study?

**As indicated in the methods therapies are included in the definition of hypertension, dislipidemia and diabetes (see Methods, Definition of risk factors, parag. 1).**

**We have now added in tables 2Sa and b and commented in the results, the association of hypertension, diabetes and dislipidemia (including their therapies) with T-wave axis deviation. Hypertension and diabetes were associated with T-wave axis deviation both in men and women, while dislipidemia not.**

**The exclusion criteria are clearly stated in the methods (see Methods, Definition of risk factors, last paragraph). Diabetic or hypertensive patients have been included and they fall in the definition of MetS if hypertension or diabetes are also associated to at least other two components of the MEtS.**

**We have now reported the correct reference (12) and described the criteria for MetS in the Method section.**

2. The tables are not clear. The values of clinical parameters means and ES should be reported and not the percentage.

**The definition of MetS and T axis deviation requires the categorization of continuous variables. Therefore we had to report percentage and not means.**

*Università cattolica del Sacro Cuore*  
*Fondazione di Ricerca e Cura 'Giovanni Paolo II'*  
*Largo A. Gemelli, 1 – 86100 Campobasso*

Campobasso, September 23, 2012

RE: No. ATH-D-12-00356

To the Editor of  
**Atherosclerosis**

Dear Editor,

Thank you for your letter of July 29, and the comments to our manuscript “T-wave axis deviation, metabolic syndrome and estimated cardiovascular risk in men and women of the MOLI-SANI Study” by Rago L. et al.

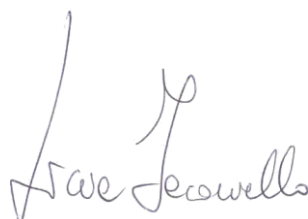
We are now submitting a revised version our manuscript. The reviewers’ suggestions have been carefully considered and revised parts have been underlined.

A point-by-point answer to the reviewers has been included.

We hope that, in its present form, the manuscript can now meet the requirements for publication in your journal.

Thank you in advance for your attention.

Best regards



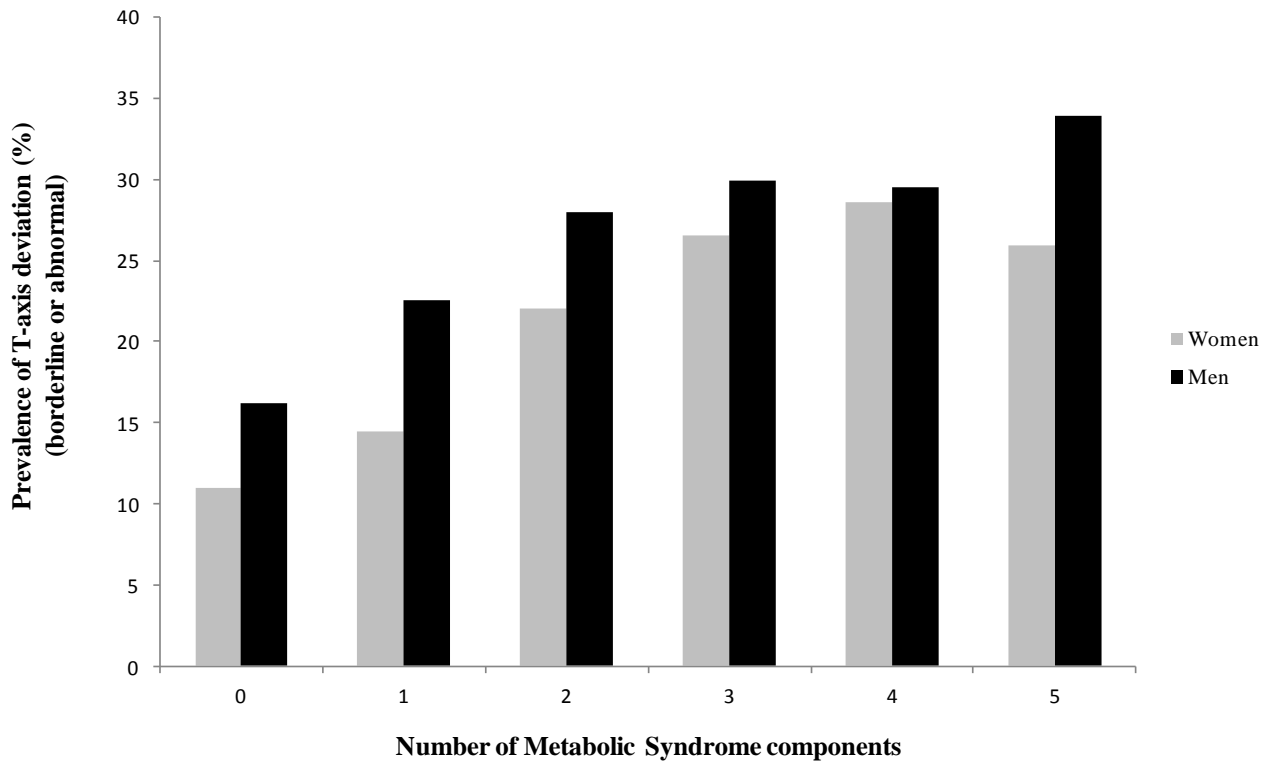
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Figure(s)



**Supplementary Material for online publication only**

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

MEN	Metabolic Syndrome			P-value
	All	Absent	Present	
<b>Characteristics</b>	<b>9,742</b>	<b>7,099</b> (73%)	<b>2,643</b> (27%)	<b>Age adjusted</b>
<b>Age, yrs, (sd)</b>	55(11)	54(12)	57 (11)	<.0001#
<b>Smokers n, (%)</b>				<.0001
<i>Never</i>	3,214 (33)	2,542 (36)	672 (25)	
<i>Current</i>	2,623 (27)	1,862 (26)	761 (29)	
<i>Former</i>	3,897 (40)	2,689 (38)	1,208 (46)	
<b>Socio-economic status score</b>	3.5 (1.4)	3.6 (1.3)	3.4 (1.3)	<.0001
<b>Physical activity, MET-h/day (sd)</b>	44.0 (10)	44.1 (9.8)	43.4 (10.1)	0.25
<b>BMI, kg/m<sup>2</sup> (sd)</b>	28.2 (4.1)	27.1 (3.4)	31.1 (4.3)	<.0001
<b>Malignancies n, (%)</b>	197 (2.0)	142 (2.0)	55 (2.1)	0.33
<b>MetS Features n, (%)</b>	2,643 (27.1)			
<i>Waist circumference ≥88 cm</i>	2,690 (27.6)	956 (13)	1,734 (66)	<.0001
<i>Triglycerides ≥150 mg/dl</i>	3,497 (35.9)	1,487 (21)	2,010 (76)	<.0001
<i>HDL &lt;50 mg/dl</i>	1,466 (15.1)	455 (6)	1,011 (38)	<.0001
<i>SBP ≥130 or DBP ≥85 mm Hg</i>	7,604 (78.1)	5,042 (72)	2,562 (97)	<.0001
<i>Fasting glucose ≥110 mg/dl</i>	2,674 (27.5)	1,006 (14)	1,668 (64)	<.0001
<b>Heart rate b/m</b>	66 (10)	65 (10)	68 (11)	<.0001
<b>QRS complex duration, ms</b>	91.1 (8)	91.0 (8)	91.2 (8)	0.21
<b>T-wave axis deviation n, (%)</b>				<.0001
<i>Normal</i>	7,256 (74.5)	5,408 (76.2)	1,848 (69.9)	
<i>Borderline</i>	2,301 (23.6)	1,572 (22.1)	729 (27.6)	
<i>Abnormal</i>	185 (1.9)	119 (1.7)	66 (2.5)	

# Univariable

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

WOMEN	Metabolic syndrome			
	All	Absent	Present	P-value
<b>Characteristics</b>	<b>11,143</b>	<b>8,480</b>	<b>2,663</b>	<b>Age adjusted</b>
	<b>(100%)</b>	<b>(76%)</b>	<b>(24%)</b>	
<b>Age, yrs, (sd)</b>	54 (11)	53 (11)	60 (11)	<.0001#
<b>Smokers n, (%)</b>				0.0060
<i>Never</i>	7,213 (64.8)	5,326 (63)	1,887 (71)	
<i>Current</i>	2,358 (21.2)	1,906 (23)	452 (17)	
<i>Former</i>	1,557 (14.0)	1,238 (15)	319 (12)	
<b>Socio-economic status score</b>	3.5 (1.4)	3.6 (1.4)	3.1 (1.3)	<.0001
<b>Physical activity, MET-h/day (sd)</b>	42.6 (7.5)	42.7 (7.6)	42.3 (6.9)	0.54
<b>BMI, kg/m<sup>2</sup> (sd)</b>	27.7 (5.3)	26.5 (4.7)	31.7 (5.1)	<.0001
<b>Menopause n, (%)</b>	6,146 (55.2)	4,115 (48.6)	2,031 (76.3)	<.0001
<b>Malignancies n, (%)</b>	400 (3.6)	278 (3.3)	122 (4.6)	0.44
<b>MetS Features n, (%)</b>	2,663 (23.9)			
<i>Waist circumference ≥ 88 cm</i>	6,432 (57.7)	3,96 (46)	2,526 (95)	<.0001
<i>Triglycerides ≥ 150 mg/dl</i>	2,042 (18.3)	449 (5)	1,593 (60)	<.0001
<i>HDL &lt; 50 mg/dl</i>	1,977 (17.7)	631 (7)	1,346 (51)	<.0001
<i>SBP ≥ 130 or DBP ≥ 85 mm Hg</i>	7,015 (63.0)	4,495 (53)	2,520 (95)	<.0001
<i>Fasting glucose ≥ 110 mg/dl</i>	1,471 (13.2)	292 (3)	1,179 (44)	<.0001
<b>Heart rate b/m</b>	69 (10)	68 (10)	70 (11)	<.0001
<b>QRS complex duration, ms</b>	86.1 (8)	86.0 (8)	86.4 (7)	0.014
<b>T-wave axis deviation n, %</b>				<.0001
<i>Normal</i>	9,012 (80.9)	7,078 (83.5)	1,934 (72.6)	
<i>Borderline</i>	1,929 (17.3)	1,264 (14.9)	665 (25.0)	
<i>Abnormal</i>	202 (1.8)	138 (1.6)	64 (2.4)	

# Univariable



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

Normal vs borderline or abnormal	OR (95%CI)			
		Model 1	Model 2	
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)
<b>Normal vs borderline</b>				
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)
<b>Normal vs abnormal</b>				
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

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

<b>MEN</b>				
<b>CUORE risk&lt;3% vs &gt;=10%</b>				
	<b>Univariable</b>		<b>Multivariable*</b>	
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)
<b>WOMEN</b>				
<b>CUORE risk&lt;3% vs &gt;=3%</b>				
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)

\* Adjusted for age, cigarette smoking, social status, physical activity and QRS duration

Highlights:

- 1) There is an association between MetS or its components and borderline or abnormal T wave axis deviation that 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;
- 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.

**Statement of originality**

The manuscript is original work not previously published in any substantial part, is not under consideration of publication elsewhere. The manuscript has been read and approved for submission by all qualified authors.