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Metabolic syndrome is associated with similar long-term prognosis in non-obese and obese patients. An analysis of 45 615 patients from the nationwide LIPIDOGRAM 2004-2015 cohort studies.

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Running Title: *Lean metabolic syndrome and long-term prognosis*

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ABSTRACT:

Aims: We aimed to evaluate the association between metabolic syndrome (MetS) and long-term all-cause mortality.

Methods: The LIPIDOGRAM studies were carried out in the primary care in Poland in 2004, 2006 and 2015. MetS was diagnosed based on the National Cholesterol Education Program, Adult Treatment Panel III (NCEP/ATP III) and Joint Interim Statement (JIS) criteria. The cohort was divided into four groups: non-obese patients without MetS, obese patients without MetS, non-obese patients with MetS and obese patients with MetS. Differences in all-cause mortality was analyzed using Kaplan-Meier and Cox regression analyses.

Results: 45,615 participants were enrolled (mean age 56.3, standard deviation: 11.8 years; 61.7% female). MetS was diagnosed in 14,202 (31%) by NCEP/ATP III criteria, and 17,216 (37.7%) by JIS criteria. Follow-up was available for 44,620 (97.8%, median duration 15.3 years) patients. MetS was associated with increased mortality risk among the obese (hazard ratio, HR: 1.88 [95% CI, 1.79-1.99] and HR: 1.93 [95% CI 1.82-2.04], according to NCEP/ATP III and JIS criteria, respectively) and non-obese individuals (HR: 2.11 [95% CI 1.85-2.40] and 1.7 [95% CI, 1.56-1.85] according to NCEP/ATP III and JIS criteria respectively). Obese patients without MetS had a higher mortality risk than non-obese patients without MetS (HR: 1.16 [95% CI 1.10-1.23] and HR: 1.22 [95%CI 1.15-1.30], respectively in subgroups with NCEP/ATP III and JIS criteria applied).

Conclusions. MetS is associated with increased all-cause mortality risk in non-obese and obese patients. In patients without MetS obesity remains significantly associated with mortality. The concept of metabolically healthy obesity should be revised.

Keywords: Metabolic syndrome, Lean metabolic syndrome, obesity

Lay summary.

Metabolic syndrome (MetS) is used to describe a constellation of metabolic disturbances such as elevated blood glucose, increased levels of triglycerides (TG) and decreased level of high-density lipoprotein cholesterol (HDL-C). They are often accompanied by elevated blood pressure and central obesity, defined as increased waist circumference. Usually, those metabolic disturbances occur in obese individuals, but sometimes they can also occur in lean subjects. This relatively recent concept is often referred to as lean MetS.

A key conclusion from our paper is that MetS, when it occurs in lean patients, is associated with similarly unfavorable long-term prognosis as in obese patients. Additionally, our analysis shows that, lean patients with MetS are less often treated with lipid lowering drugs despite having higher low-density lipoprotein cholesterol levels (LDL-C).

An additional finding, that is important from a public health perspective, is that obese patients who do not fulfill MetS criteria have higher long-term all-cause mortality than their lean counterparts without MetS. This finding should be an argument to encourage maintenance of normal body weight.

INTRODUCTION

Obesity is a growing epidemic worldwide.[1] Overweight and obesity affects almost 60% of adults in the European Union (EU).[2] Obesity does not simply represent a state of excess weight, it is also associated with higher rates of insulin resistance, type 2 diabetes mellitus (T2DM), hypertension (HTN), dyslipidemia, coronary heart disease (CHD), obstructive sleep apnea, non-alcoholic fatty liver diseases and some malignancies, including endometrial, breast, and colon cancer. It is also the leading risk factor for disability.[3,4] Abnormal body mass index (BMI) and waist circumference (WC) have consistently been associated with adverse health outcomes over long term follow-up[5–7] including those secondary to the development of the metabolic syndrome (MetS). [3,4]

Definitions of MetS have been proposed by World Health Organization (WHO), European Group for the Study of Insulin Resistance (EGIR)[8], National Cholesterol Education Program Adult Treatment Panel III (NCEP/ATP III)[9,10], American Association of Clinical Endocrinology (AACE)[8], International Diabetes Federation (IDF)[11] and the American Heart Association/National Heart, Lung and Blood Institute (AHA/NHLBI)[12] . The first definition was created by WHO in 1998 with insulin resistance as an obligatory criterion of MetS as for the EGIR definition.[13] In 2005, IDF proposed a definition with central obesity or BMI ≥30 kg/m^2 as an obligatory criterion for the diagnosis of MetS.[14] In the remaining definitions (NCEP/ATP III, AACE and AHA/NHLBI), and Joint Interim Statement Consensus (JIS) 2009 definition[15] central obesity, along with impaired glucose tolerance, elevated blood pressure, and dyslipidemia, were no longer obligatory criteria for diagnosing MetS.[8,9,12,15]

Obesity is not synonymous with MetS, because some obese patients do not have metabolic disorders that meet the criteria of the syndrome. On the other hand, some lean patients

suffer from disorders of carbohydrate and lipid metabolism; have elevated blood pressure, and fulfill the criteria for the diagnosis of MetS. Recent studies suggest that metabolic disorders are also highly prevalent in lean individuals. In an Italian cohort, Buscemi et al.[16] using a definition of MetS not based on anthropometric parameters, observed that 27.4% of the overweight-obese participants were metabolically healthy while 36.7% of the normal-weight participants were metabolically unhealthy. As a result, the concepts of metabolically healthy obesity and lean MetS have emerged.[17–19] Moreover, recent research has also revealed that an abnormal metabolic profile, rather than elevated BMI, is linked with higher risk of T2DM, coronary heart disease[20–22] and stroke. [23–26]

The present analysis aimed to assess the association between metabolic health and obesity with mortality in an adult cohort representative of Polish patients in a primary care setting over a 15-year follow-up period.

METHODS

Study design

A nationwide cohort study was conducted in 2004, 2006 and 2015 in primary health care practices in Poland with follow-up to assess all-cause mortality. Information about the deaths of the recruited patients, based on a unique identification number for each participant, was extracted from the database of the Central Statistical Office. Death registration is mandatory in Poland. The study protocol complied with the Declaration of Helsinki and was approved by the Bioethical Committee of the Polish Chamber of Physicians (no. 51/2004/U) for years 2004/ 2006 and by the Bioethical Commission of the District Medical Chamber in Częstochowa (no K.B.Cz.–0018/2015) for years 2015.

Study Population

LIPIDOGRAM is a nationwide survey of cardiovascular risk factors carried out through primary care outpatient centers in Poland in 2004, 2006 and 2015. The methodology of each of the LIPIDOGRAM surveys has been described in detail. [27,28] Briefly, physicians were selected randomly, using Medical Data Management Software. The number of physicians in each of the administrative regions in Poland was selected in a manner proportional to the number of inhabitants. Patients aged ≥18 years were eligible for recruitment. Exclusion criteria included an inability to provide informed consent and incomplete clinical or biochemical data (e.g., due to blood sample loss). In 2004, a total of 675 primary care physicians actively enrolled 17,522 individuals in 444 towns/cities. In 2006, 556 primary care practitioners from 402 Polish cities recruited a total of 15,465 patients, while in 2015 a group of 438 physicians also in primary care practices recruited an additional 13,724 patients. We excluded patients that were recruited more than once in the subsequent LIPIDOGRAM surveys, including 1627 from the LIPIDOGRAM PLUS substudy and 113 patients that were recruited in 2004 or 2006 and 2015. Additionally, we excluded 43 patients that were mistakenly recruited twice during the same LIPIDOGRAM edition. Follow-up data was collected up to December 2021. A study flow chart is presented in **Figure 1.**

Anthropometric measurements and physical examination.

Height and weight measurements were carried out by nurses or physicians on patients in their underwear and barefoot. The BMI was calculated by dividing body weight in kilograms (kg) by squared height in meters (m) [kg/m^2]. WC was measured at the midpoint between the lower margin of the ribs and the anterior superior iliac crest spine in centimeters (cm). In 2015 physicians also measured heart rate and office BP.[28] They used standard

sphygmomanometers and implemented a procedure compliant with the European guidelines for the management of arterial hypertension. [29]

Biochemical analyses

Blood samples were collected after fasting (>12h following last meal). After centrifugation, blood samples were transferred to a core facility for processing. Biochemical analyses were performed within 12h after blood sample collection. Serum concentrations of total cholesterol were measured using a photometric method. High density lipoprotein (HDL) cholesterol (HDL-C) and triglycerides were measured by immunoseparation-based homogenous assay and colorimetric enzymatic test with glycerol-3-phosphateoxidase, respectively (DiaSys – Diagnostic Systems, Holzheim, Germany). Low density lipoprotein cholesterol (LDL-C) was calculated using the Friedewald formula (2004 and 2006 LIPIDOGRAM surveys) or was measured directly (2015 LIPIDOGRAM surveys). Fasting blood glucose levels, for patients recruited in LIPIDOGRAM 2015 edition, was measured using a glucometer (Bionime, Taichung City, Taiwan) and Rightest strip tests (Bionime Taichung City, Taiwan).

Definitions

MetS was diagnosed according to the NCEP/ATP III definition[10] and for the purpose of comparison according to JIS 2009 definition[15]. To fulfill definition of MetS according to the NCEP/ATP III and JIS definition of MetS ≥3 out of 5 criteria had to be met (**Table 1**). Patients within BMI categories of <25, 25-29.9 or ≥30 kg/m^2 were considered as lean, overweight, and obese, respectively. Central obesity was defined as waist circumference (WC) ≥ 102 cm in men and ≥ 88cm in women. Based on the presence of MetS and obesity (defined as BMI ≥ 30 kg/m^2 or central obesity), the study cohort was divided into four groups: 1) non-obese patients without MetS, 2) non-obese patients with MetS, 3) obese patients, without MetS and, 4) obese subjects with MetS.

Patients were also grouped into five age categories. Young adults were defined as participants between 18-35 years old, early middle-aged adults were defined as 36-49 years, old late middle-aged adults were defined as 50-64 years old.[30] Patients between 65-74 years were defined as early elderly, and those aged 75 years or older were described as late elderly.[31]

Statistical analyses

Continuous variables are presented by means and standard deviations (SD). The comparison of continuous variables was performed using Student's t-tests. The comparison of dichotomous variables was performed using the chi-square test. Associations between obesity (BMI ≥ 30 kg/m^2 or central obesity) and presence of MetS defined according to NCEP/ATP III[9] and JIS[15] criteria and long-term outcome in the whole cohort and predefined age groups were analyzed using Kaplan-Meier estimates. Kaplan-Meier analysis was also carried out in patients with MetS to explore associations between BMI categories and mortality in patients with MetS. To assess the magnitude of influence of different clinical variables on long-term outcome, after checking the proportional hazards assumption, a univariate Cox regression model was used. Associations between clinical variables and age groups were tested using the Jonckheere-Terpstra test for trend in continuous data and the Cochrane-Armitage test for trend in categorical data. As data on glucose level and blood pressure were only available for patients recruited in the 2015 LIPIDOGRAM survey (Figure 1), to verify results from the whole cohort a separate survival analysis was performed only in patients recruited in 2015. A Two-sided p <0.05 was considered statistically significant.

RESULTS

Clinical characteristics

Whole cohort

45,615 participants were enrolled in the study (mean age 56.3 (SD -11.8) years and 61.7% were female). MetS was diagnosed in 14,202 (31%) by NCEP/ATP III criteria and 17,216 (37.7%) by JIS 2009 JIS criteria (**Table 2**). Patients with MetS were older, more likely to be female and less likely to have secondary or higher education (Table 2, Table S1, Table S2). Individuals in late middle age were about twice as likely as young adults to meet the criteria for MetS. Elderly patients were about three times as likely as young adults and early middle-aged individuals to meet the criteria for MetS (**Table S4**). The prevalence of obesity (BMI ≥ 30 kg/m^2 or central obesity), hypertension and dyslipidemia were higher in the MetS group regardless of definition Table 2. Patients with MetS were less likely to report physical activity, were more likely to receive lipid-lowering therapy, and had a higher blood pressure and glucose levels. HDL-C levels were lower and triglycerides levels were higher in patients with MetS. No significant differences (JIS definition), or very small differences (NCEP/ATP III definition) in LDL-C were observed. TC levels were slightly higher among patients without MetS (**Table 2, Table S1, S2).**

Clinical characteristics of patients with MetS according to BMI categories.

Out of the entire cohort 11,307 (24.8%) patients had BMI below 25 kg/m2, 19,134 (41.9%) were overweight and 15,174 (33.3%) had BMI ≥ 30 kg/m^2. Application of NCEP/ATP III definition as compared to JIS definition led to less frequent diagnosis of MetS especially in lean (7.1% vs. 12.5%) and overweight (25.9% vs. 35.6%) patients. Table 4.

In the group of lean patients with MetS, there were more females, while diabetes and hypertension were less prevalent in this subgroup of patients with MetS. Triglycerides were higher in lean patients with MetS diagnosed according to NCEP/ATP III criteria. Lean patients with MetS were also less likely to be treated with statins and fibrates despite significantly higher triglyceride and LDL-C levels compared participants with overweight and obese MetS.

Smoking was most prevalent in lean subjects compared with obese and overweight individuals (**Table 4**).

Long term prognosis

Whole cohort

Follow-up data were available for 44,620 (97.8%) of patients. Median follow-up was 15.3 years [interquartile range IQR 5.7-17.2]. There were 7559 (16.9%) deaths during follow-up. Mortality risks for each of the metabolic health categories are given in **Table 3**. The most important predictors of all-cause mortality were history of myocardial infarction (HR: 3.08, 95%CI 2.89-3.28, p<0.0001) and diabetes (HR: 2.71, 95% CI 2.66-2.86, p <0.0001). Table S3. Irrespective of diagnostic criteria, MetS was associated with worse long-term outcomes in obese (BMI ≥ 30 or central obesity) and non-obese individuals as compared to obese and non-obese patients without MetS (Figure 2 A, B, Table 3 and Table S4). MetS was associated with higher risk of death in obese and non-obese patients after the first five years of follow-up according to NCEP/ATP III criteria (HR: 1.7, 95% CI, 1.53 – 1.89, p <0.0001 and HR: 1.93, 95% CI 1.55 – 2.4, respectively), and JIS definition (HR: 1.74, 95% CI, 1.56 – 1.93, p <0.0001 and HR: 1.57, 95% CI, 1.34 – 1.84, p <0.0001, respectively). Throughout the whole observation period, obese and non-obese patients with MetS had a similarly increased risk of death when MetS diagnosed based on both the NCEP/ATP III definition (HR: 1.88, 95% CI 1.78-1.98, p<0.0001 and HR: 2.11, 95% CI 1.85-2.39, p<0.0001 respectively) and JIS criteria (HR: 1.93 , 95% CI 1.82 – 2.04 , p <0.0001 and HR: 1.7, 95%CI 1.56 – 1.85, p <0.0001).

In the first five years of observation obese (BMI ≥ 30 kg/m^2 or central obesity) patients without MetS had similar prognosis as their non-obese counterparts regardless of MetS definition applied (HR: 0.96, 95% CI, 0.85 – 1.09, p=0.51, NCEP/ATP III criteria and HR: 1.0, 95% CI 0.88 – 1.14, p=0.98, JIS criteria). In contrast to the initial five years of observation,

obese patients without MetS diagnosed according to NCEP/ATP III or JIS criteria had a higher risk of dying throughout the whole observation period, than non-obese patients without MetS (HR: 1.16, 95% CI, 1.10 – 1.23, p<0.0001 and HR: 1.22, 95% CI 1.15-1.30 p<0.0001) (**Figure 2, Table S3**). The results of the landmark analysis performed at a 5 year cut-off point for patients without MetS according to obesity status is presented in **Figure S1.**

Similar results were obtained for men and women (Figure 3 and 4) and for all age groups except for young adults and late elderly were there were no significant differences in mortality in long-term follow-up (**Figures S2-S7**).

Long term outcome in patients with MetS across BMI categories

Among patients with MetS (NCEP/ATPIII criteria), lean patients (BMI <25 kg/m^2) had worse long-term outcome as compared to overweight (BMI 25-30 kg/m^2) and obese (>30 kg/m^2). individuals (HR – 1.36, 95% CI – 1.16 – 1.61, p =0.0001 and HR – 1.31, 95%CI – 1.12-1.53, p = 0.0008 respectively) (**Figure 2C**). Lean patients with MetS diagnosed according to JIS had less favorable prognosis as compared to overweight (HR – 1.13, 95%CI – 0.99-1.3, p=0.05), but not to obese individuals (HR – 1.05, 95% CI 0.92-1.19, p=0.49) (Figure 2D).

DISCUSSION

The results of this cohort study show that MetS is present in a third of primary care patients in Poland and is more common in women, older and less educated patients. Second, MetS is associated with higher risk of all-cause death in both obese and non-obese people and the magnitude of long-term risk is similar in these both groups. Third, obese subjects without MetS also have a greater risk of death than their non-obese counterparts.

The prevalence of MetS ranges from 13-43% in European countries [32,33], with an average of 24.3% (NCEP/ATP III criteria), which is lower than in our population.[32] Those differences can be partly explained by difference in age between study participants as well as the fact that

the prevalence of MetS is constantly increasing.[34] The incidence of MetS, depends not only on the region, but also on the definition of MetS used in the study. [35–37] Heverinen et al. showed that using different MetS definitions led to different estimates of prevalence, ranging from 18-43%.[38] Regardless of the definition used, the prevalence of MetS in our population, although high, is consistent with data from other epidemiological studies conducted in our country.[39] As in other studies[40] we also observed an increase in the prevalence of MetS and a greater proportion of people with MetS in rural residents and those with primary and vocational education. However, the differences related to the place of residence were smaller than in other countries.[41–43]

Non-obese patients with MetS had similarly unfavorable long-term prognosis as patients with BMI ≥30 kg/m^2 and/or with central obesity. This was true regardless of MetS definition used, and was the same for women and men and for all age groups. Obese patients without MetS had a similar 5-year prognosis as their non-obese counterparts. This is in line with possible early follow-up bias reported in some epidemiologic studies examining the association between obesity and mortality.[6] However, importantly, our analysis similarly to other analyses with long term follow-up[5–7], demonstrated that during a median follow-up of 15 years, mortality rate in this group of patients was significantly higher and got closer to that observed in patients with MetS. This might be due to the fact that obesity without MetS is not a stable phenotype and progresses to MetS over time[44], which was also pointed out in the recent ESC guidelines on cardiovascular disease prevention.[45] In the previous analysis, we demonstrated that metabolome of so called metabolically healthy obese patients resembles that of obese patients with MetS.[46] Therefore, we are the opinion that the term metabolically healthy obesity is not appropriate and may undermine the importance of body weight

reduction in subject not fulfilling MetS criteria. We believe that it is worth considering replacing it with other term in official documents regarding cardiovascular prevention[45].

When stratified according to BMI categories, worst prognosis was observed for lean patients (MetS/NCEP ATP III criteria) or as unfavorable as in patients with BMI $\geq$ 30 (JIS criteria). Every 12th patient with MetS (defined by the NCEP/ATP III and JIS criteria) in our population, had a BMI <25 kg/m^2. At the same time, in publications that define MetS regardless of WC or BMI, the combined presence of at least two of the abnormalities characteristics of MetS (carbohydrate and lipid metabolism disorders or increased blood pressure values) was found in nearly 25% to over 37% of normal weight individuals[16,47–49]. Recent ESC guidelines on cardiovascular disease prevention recommend screening for MetS in all individuals, regardless of their BMI.[45] The diagnosis of MetS in a lean person, requires however the coexistence of increased blood pressure, abnormalities in lipid and carbohydrate metabolism, and in an obese person diagnosis of MetS requires only two of these factors. Therefore it remains an open question whether the currently used criteria are sensitive enough for the diagnosis of MetS in lean individuals. Our analysis showed that applying JIS definition instead of NCEP/ATP III criteria led to 75% increase in percentage of patients diagnosed with MetS among lean individuals, as more lean patients fulfilled WC criterion. Despite this in the group of patients with WC values smaller than cut-off values according to JIS criteria, 1399 (25.5%) men and 815 (14.1%) women still fulfilled at least two criteria for MetS. Nonetheless in this in this subgroup of patients only 496 (4.4%) could be diagnosed with MetS. Differences in clinical characteristics may at least partially account for such high mortality in the lean MetS group. In particular, in this group of patients, there was a higher percentage of smokers and higher levels of LDL-C and TG, with significantly less frequent use of statins and fibrates. Less frequent use of lipid-lowering drugs may be due to the fact that a lean person appears

healthier and consequently, physicians may be less likely to prescribe pharmacological treatment for hypercholesterolaemia.[50] The poor prognosis of patients with MetS, whether they are lean, overweight or obese, is primarily due to the pathophysiology of MetS, which includes insulin resistance, chronic systemic inflammation[51] oxidative stress, an increased thrombotic tendency that aggravates metabolic disorders and accelerated progression of atherosclerotic disease. [52,53] The quality and caloric value of the diet is also important. In a recent analysis of a different patient population, we showed that the Western diet contributes to the development of MetS regardless of BMI.[54]

Study strengths and limitations. The main strength of this study is the inclusion of a large number of patients and very long-term follow-up. To our knowledge few studies have explored the area of MetS in such a large population. Importantly, patients involved in the study were recruited from all 16 regions of Poland and were representative of the population of primary health care. At this level of care, MetS should be diagnosed and treated. Another strength of the study is the fact that all the biochemical analyses were conducted in a central laboratory, which conforms with all the required quality control standards and ensures reliability of the test results. Data on the medical history and office measurements were collected by doctors who knew the patients and looked after them on a daily basis. In 2004 and 2006, the data gathered was the same, but in 2015 was extended to include blood pressure, heart rate and blood glucose.

A limitation of the study is that it was conducted in only one country. We also do not have data on other factors that might influence long term prognosis such as lipoprotein a. Primary healthcare practices were selected at random, but physicians enrolled patients consecutively. Moreover, we did not gain access to data on the causes of deaths of patients and, therefore, conducted our analysis based on all-cause deaths. Data on glucose levels and blood pressure

were available only for patients recruited in 2015. For patients recruited in 2004 and 2006 the diagnosis of MetS was based on lipid measurements, waist circumference, and the presence of hypertension and or diabetes. However, the results of the analysis carried out on in the group of patients recruited in LIPDIOGRAM 2015 edition were similar to those from earlier years (**Figure 8A and S8B**).

In conclusions, MetS is associated with elevated long term mortality risk in both non-obese and obese patients. Lean patients with MetS, despite having more severe metabolic disorders, are less often treated with lipid-lowering drugs. Both physicians and patients should be aware of MetS in lean subjects and should initiate appropriate therapy including behavioral changes and drug treatment. Obesity remains significantly associated with increased mortality risk in patients not fulfilling MetS criteria, therefore the concept of metabolically healthy obesity should be revised.

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Data Availability: The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

Ethical Approval: Research involving human subjects complied with all relevant national regulations, institutional policies and is in accordance with the tenets of the Helsinki Declaration (as revised in 2013), and has been approved by the Bioethical Committee of the Chamber of Physicians (No.K.B.Cz.-0018/2015).

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Table 1. Definition of metabolic syndrome.

Parameter	Cut-offs
Central obesity (NCEP/ATP III)	WC ≥102 cm in men and ≥88 cm in women
Central obesity (2009 JIS)	WC ≥94 cm in men and ≥80 cm in women*
Blood Pressure	SBP ≥130 mmHg or DBP ≥85 mmHg Or use of antihypertensive medication
Triglycerides	≥150 mg/dl (1.7 mmol/l) Or use of triglyceride lowering medication (e.g., fibrate or nicotinic acid or high dose omega-3 fatty acids**)
HDL cholesterol	Men <40 mg/dl (1.0 mmol/l), Women <50 mg/dl (1.3 mmol/l) or use fibrate or nicotinic acid
Glucose	≥ 100 mg/dl (5.6 mmol/l) or diabetes mellitus type 2
Metabolic Syndrome diagnosis	0-1 of the above criteria ≥3 of the above criteria

*WC – waist circumference, SBP – systolic blood pressure, DBP – diastolic blood pressure, MetS – metabolic syndrome, NCEP/ATP III – National Cholesterol Education Program/Adult Treatment Panel III, JIS – Joint Interim Statement. * For triglyceride lowering drugs we had information only on fibrates. Nicotinic acid was never available in Poland. ** WC cut-offs for Caucasians.*

Table 2. Clinical characteristics of the study population and patients with MetS* according to NCEP/ATP III criteria and JIS criteria.

Values in tables are given as means (standard deviation) or numbers (%).

Comparison of clinical characteristics between patients with MetS *vs* without Mets is shown in Table S1.

	Whole population (n=45 615)	MetS NCEP/ATP III (n=14 202)	MetS JIS (n=17 216)
Age (years)	56.3 (11.8)	59.9 (10.8)	59.4 (10.9)
Females	28150 (61.7)	9173 (64.6)	10645 (61.8)
Secondary/higher education	26031 (57.1)	6689 (47.1)	8421 (48.9)
Urban place of residence	25266 (55.4)	7536 (53.1)	9625 (54.1)
Obesity	24203 (53.1)	12 812 (90.2)	13 365 (77.6)
Central obesity	22093 (48.4)	12 477 (87.9)	12 477 (72.5)
BMI [kg/m^2]	28.3 (4.8)	31.4 (4.6)	30.7 (4.6)
WC [cm] women	89.8 (13.4)	99.6 (11.2)	97.3 (11.9)
men	98.6 (11.5)	107.6 (10.7)	105.3 (10.3)
Diabetes mellitus	5692 (12.5)	4500 (31.7)	4947 (28.7)
Hypertension	23509 (51.5)	11 543 (81.3)	13 751 (79.9)
Previous MI	2707 (5.9)	1086 (7.6)	1328 (7.7)
Dyslipidemia	22490 (49.3)	8541 (60.1)	10 219(59.4)
Current smoker	8622(18.9)	2273 (16.0)	2878 (16.7)
Physical activity	9175 (30.8)	3304 (29.2)	3992 (29.6)
Statin	13037 (28.6)	5474 (38.5)	6471 (37.6)
Fibrate	1595 (3.5)	771 (5.4)	908 (5.3)
SBP [mmHg]*	132 (18.5)	139 (18.1)	138 (17.9)
DBP [mmHg]*	78 (10.2)	82 (10.5)	83 (10.5)
TC [mg/dl]	215 (45)	212(48)	213 (48)
LDL-C [mg/dl]	129 (38)	128 (40)	129 (40)
HDL-C [mg/dl] Women	63 (15)	53 (12)	54 (13)
Men	54 (14)	45 (11)	47 (12)
TG [mg/dl]	147 (86)	196 (111)	192 (107)
Glucose* [mg/dl]	103 (25)	114 (29)	112 (28)

**Data available for patients recruited in 2015. BMI – body mass index, WC – waist circumference, MI – myocardial infarction, SBP – systolic blood pressure, DBP – diastolic blood pressure. TC – total cholesterol, LDL-C – low density lipoprotein cholesterol NCEP/ATP III - National Cholesterol Education Program, Adult Treatment Panel III. JIS – Joint Interim Statement.*

Table 3. Mortality risks according to diagnosis of MetS and presence of obesity during follow-up period.

	Obese* patients with MetS	Non-Obese patients with MetS	Obese* patients without MetS	Non-obese patients without MetS
NCEP/ATP IIII definition				
Mortality risk – 5 years	747/12 560 (5.9%)	92/1367 (6.7%)	379/11 164 (3.4%)	691/19 529 (3.5%)
Mortality risk – 15 years*	2553/12 560 (20.3%)	258/1367 (18.9%)	1929/11 164 (17.3%)	2819/19 529 (14.4%)
JIS definition				
Mortality risk – 5 years	765/13 106 (5.8%)	200/3778 (5.3%)	361/10 618 (3.4%)	583/17 118 (3.4%)
Mortality risk – 15 years*	2642/13 106 (20.2%)	675/3778 (17.9%)	1840/10 618 (17.3)	2402/17 118 (14.0%)

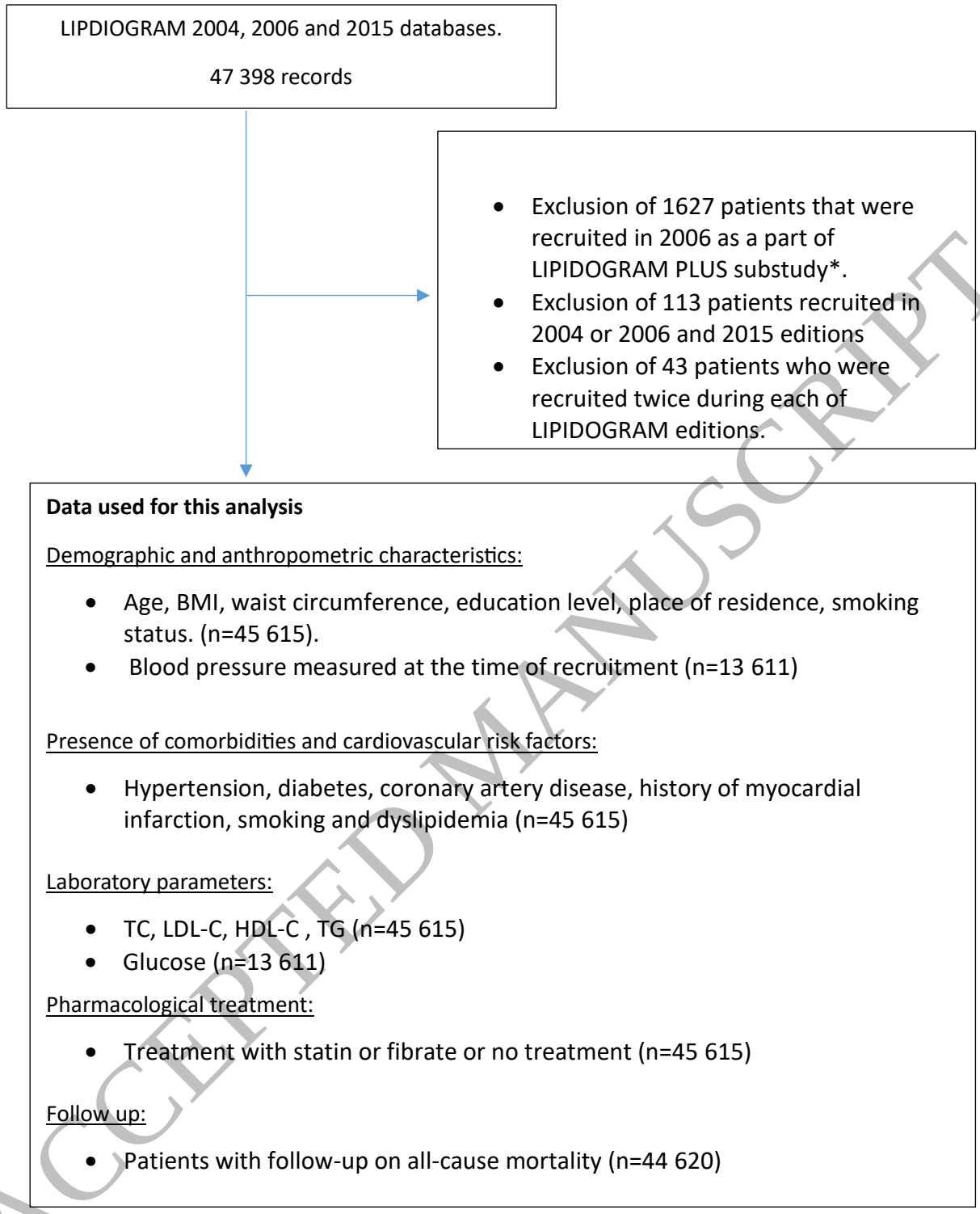
*MetS – Metabolic Syndrome, NCEP/ATP III - National Cholesterol Education Program, Adult Treatment Panel III, JIS – Joint Interim Statement. Results are given as death count/number of patients in the given group. *Refers to median follow-up.* Patients with BMI* $\geq$ 30 kg/m^2, or central obesity.

Table 4. Clinical characteristics of patients with MetS according to BMI categories.

	MetS (NCEP/ATP III) n = 14 202			MetS (JIS) n = 17 216		
	Lean n=804	**Overweight n =4947**	**Obese n=8451**	**Lean n=1409**	**Overweight n=6803**	**Obese n=9004**
Age	61.3 (12.1)	60.8 (11.1)	59.2 (10.5)	60.4 (11.9)	59.9 (10.6)	58.9 (11.1)
Females	620 (77.1)	3319 (67.1)	5234 (61.9)	1102 (78.2)	4176 (59.6)	5367 (61.4)
BMI [kg/m^2]	23.3 (1.6)	27.9 (1.4)	34.2 (3.6)	23.34 (1.5)	27.73 (1.4)	34.06 (3.6)
Diabetes	211 (26.2)	1355 (27.4)	2934 (34.7)	288 (20.4)	1628 (23.9)	3031 (33.7)
Hypertension	575 (71.5)	3873 (78.3)	7095 (84.0)	975 (69.2)	5230 (76.8)	7546 (83.8)
Previous MI	55 (6.8)	396 (8.0)	635 (7.5)	89 (6.3)	564 (8.3)	675 (7.5)
Dyslipidemia	456 (56.7)	2964 (60.0)	5121 (60.6)	786 (55.8)	3999 (58.8)	5434 (60.4)
Current smoker	204 (25.4)	836 (16.9)	1233 (14.6)	355 (25.2)	1196 (17.6)	1327 (14.7)
Physical activity	204 (29.7)	1245 (31.2)	1855 (28.1)	344 (29.8)	1677 (31.4)	1971 (28.2)
Statin	277 (34.5)	1895 (38.3)	3302 (39.1)	462 (32.8)	2510 (36.9)	3499 (38.8)
Fibrate	39 (4.7)	259 (5.2)	473 (5.6)	54 (3.8)	352 (5.2)	502 (5.6)
TC [mg/dl]	219219 (52)	213 (47)	210 (47)	220 (51)	215 (48)	210.6 (47.1)
LDL-C [mg/dl]	134 (45)	130 (41)	127 (40)	135 (44)	131 (41)	127.0 (39.5)
HDL-C Women	54 (14)	53 (13)	53 (12)	56 (142)	55 (13)	53 (12)
[mg/dl] Men	43 (12)	45 (12)	45 (11)	48 (14)	48 (12)	46 (11)
TG [mg/dl]	208208 (176)	192 (92)	197 (114)	188 (142)	187 (89)	197 (112)
Glucose [mg/dl]	110 (24)	110 (24)	116 (32)	107 (23)	109 (24)	116 (32)

BMI – body mass index, MI – myocardial infarction, TC – total cholesterol, LDL-C – low density lipoprotein cholesterol. NCEP/ATP III - National Cholesterol Education Program/Adult Treatment Panel III. JIS – Joint Interim Statement. Values in tables are given as means (standard deviation) or numbers (%).

Figure 1. Study flow-chart



*BMI – body mass index, TC – total cholesterol, LDL-C – low density lipoprotein cholesterol, HDL-C – high density lipoprotein cholesterol, TG – triglycerides. *LIPIODOGRAM PLUS was a planned follow-up of a subset of patients (n=1627) recruited in 2004 and then again in 2006.*

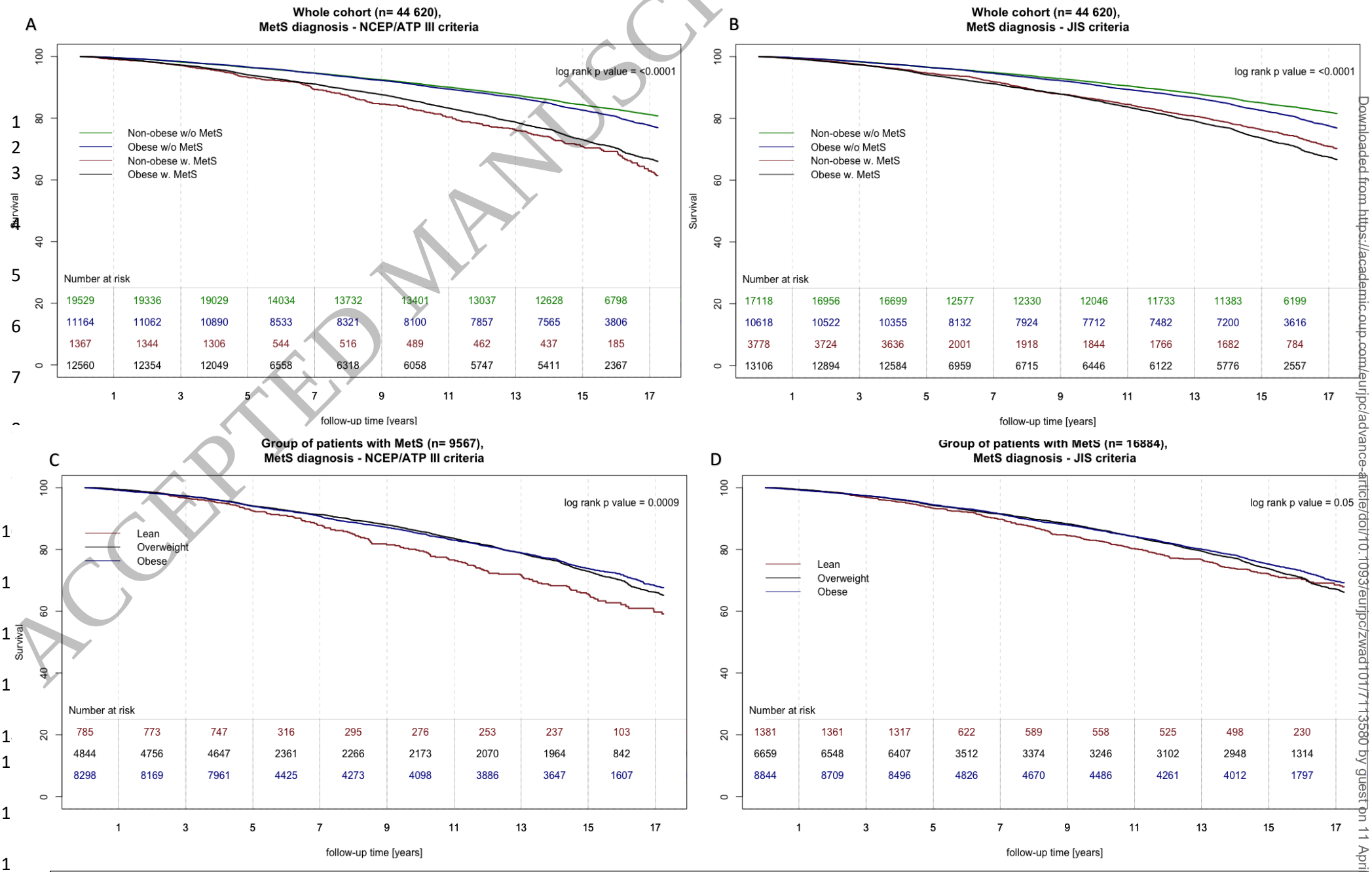
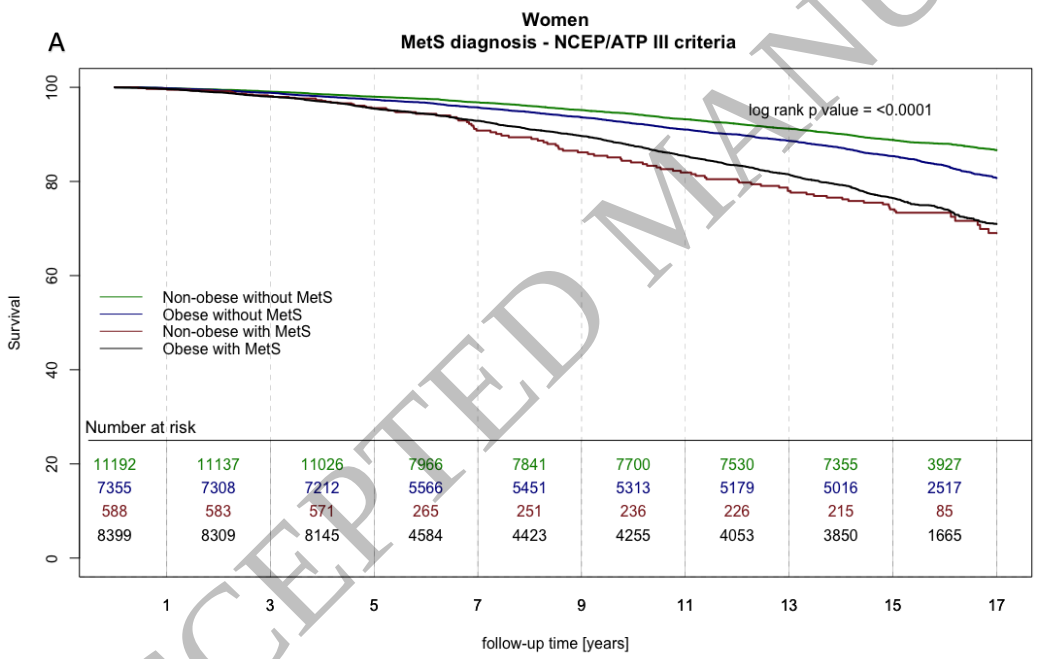


Figure 2. A) Long term outcome in patients with or without MetS (NCEP/ATP III criteria), with respect to obesity. B) Long term outcome in patients with or without MetS (JIS criteria) with respect to obesity. C) Long term outcome in patients with MetS (NCEP/ATPIII) criteria stratified by BMI categories. D) Long term outcome in patients with MetS (JIS criteria) stratified by BMI categories. NCEP/ATP III - National Cholesterol Education Program, Adult Treatment Panel III, JIS – Joint interim statemen



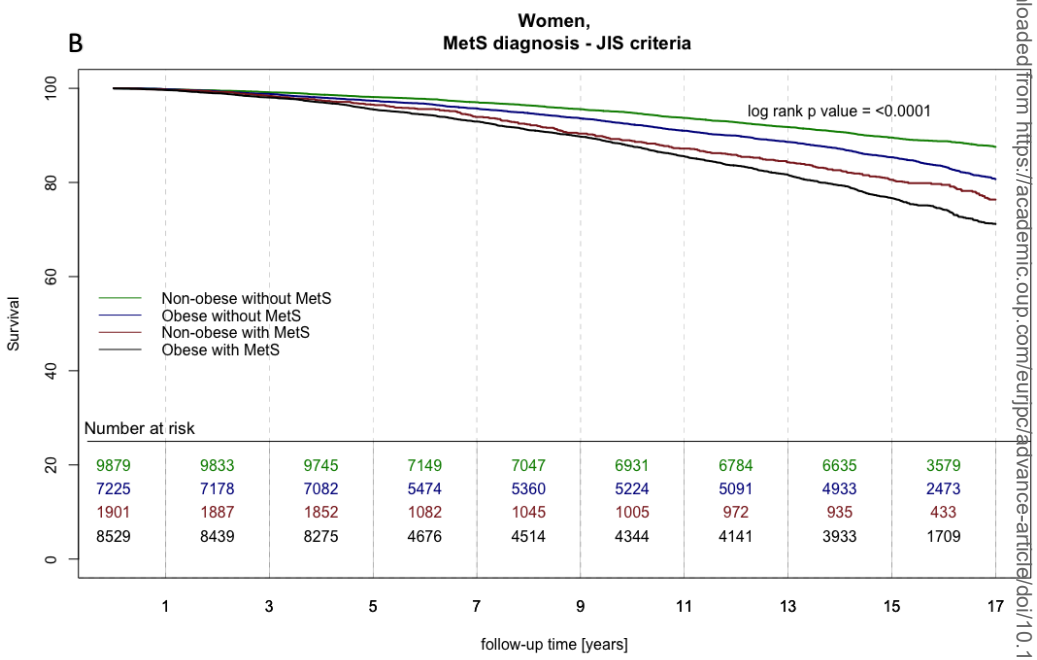


Figure 3. A) Long term outcome in women with or without MetS (NCEP/ATP III criteria), with respect to obesity. B) Long term outcome in women with or without MetS (JIS criteria) with respect to obesity.

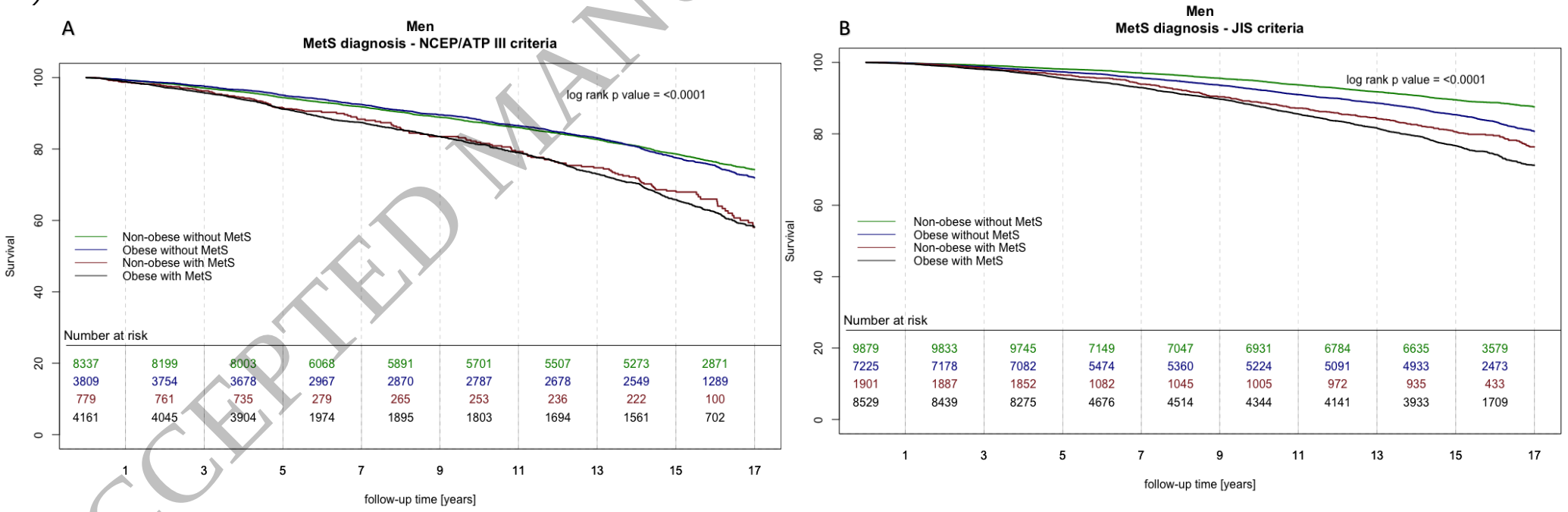


Figure 4. Long term outcome in men with or without MetS (NCEP/ATP III criteria), with respect to obesity. B) Long term outcome in men with or without MetS (JIS criteria) with respect to obesity.