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Incidence and regression of metabolic syndrome in a representative sample of the Spanish population: results of the cohort di@bet.es study

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ABSTRACT

Introduction Metabolic syndrome (MetS) is an important predictor of cardiovascular mortality. Identification of occurrence and regression trends of MetS could permit elaboration of preventive strategies with new targets. The objective of this study was to analyze the occurrence and regression rates of MetS and its associated factors in the representative cohort of Spain of the di@bet.es study.

Research design and methods The di@bet.es study is a prospective cohort where 5072 people representative of the Spanish population over 18 years of age were randomly selected between 2009 and 2010. Follow-up was a median of 7.5 (IQR 7.2–7.9) years, with 2408 (47%) participating subjects. A total of 1881 (78%) subjects had all the pertinent data available and were included in this study.

Results Of the 1146 subjects without baseline criteria for MetS, 294 (25.7%) developed MetS during follow-up, while of the 735 patients with prior MetS, 148 (20.1%) presented regression. Adjusted MetS incidence per 1000 person-years was 38 (95% CI 32 to 44), while regression incidence was 36 (95% CI 31 to 41). Regression rate was independently higher than incidence rate in the following: women, subjects aged 18–45, university-degree holders, patients without central obesity, without hypertension, as well as those with body mass index of <25 kg/m^2. Lower progression and higher regression rates were observed with an adapted 14-point Mediterranean Diet adherence screener questionnaire score of >11 in both groups and with >500 and>2000 MET-min/week of physical activity, respectively.

Conclusions This study provides MetS incidence and regression rates, and identifies the target population for intervention strategies in Spain and possibly in other countries.

Significance of this study

What is already known about this subject?

- Metabolic syndrome (MetS) is one of the main predictors of cardiovascular mortality.
- Knowing the trends of occurrence and regression of the MetS and its associated factors can allow defining preventive strategies and new targets to intervene.

What are the new findings?

- Adjusted MetS incidence per 1000 person-years was 38 (95% CI 32 to 44), while regression incidence was 36 (95% CI 31 to 41).
- Regression rate was independently higher than incidence rate in the following: women, subjects aged 18–45, university-degree holders, patients without central obesity, without hypertension, as well as those with a body mass index of <25 kg/m^2.
- To reduce the occurrence of MetS it is necessary to achieve a higher degree of adherence to a Mediterranean diet.

How might these results change the focus of research or clinical practice?

- This study provides MetS incidence and regression rates and identifies the target population for intervention strategies in Spain and possibly in other countries. Lower progression and higher regression rates were observed with an adapted 14-point Mediterranean Diet adherence screener questionnaire score of >11 in both groups and with >500 and >2000 MET-min/week of physical activity, respectively.
- Researchers should further investigate how lifestyle can be optimized for health promotion and prevention of MetS.

INTRODUCTION

Metabolic syndrome (MetS) is the combination of a range of metabolic disorders that include central obesity, abnormal glucose

regulation, atherogenic dyslipidemia and arterial hypertension coexisting in the same individual, predisposing to cardiovascular disease (CVD) and type 2 diabetes mellitus (T2DM). The definition of MetS was agreed by different scientific societies during the last decade,[1] recommending the use of specific waist circumference measurements adapted to each population. Its fundamental component is represented by visceral obesity. The relevance of the MetS lies on doubling the risk of CVD between 5 and 10 years following the diagnosis, and the occurrence of T2DM by 5 years. The prevalence in Spain reached just over 42% of men and 32% of women in 2010.[2] Since then, national strategies for the prevention of T2DM and obesity have been reinforced.[3 4]

The Diabetes Prevention Program (DPP) study demonstrated the regression from pre-diabetes to normal glucose regulation achieved by the reduction of body weight[5 6] and was also associated with a reduction in a wide range of microvascular complications.[7] These findings explain why so much emphasis has been placed on obesity programs/interventions. Regression from pre-diabetes and T2DM has been consistently found after surgical treatment of obesity in several series[8–11] Considering that the clinical presentation of the MetS can evolve in two directions, occurrence and regression, both reducing its occurrence and facilitating its regression are equally important. In order to assess the efficacy of any intervention, the same population should be assessed simultaneously during the same period of time. So far, only the DPP has simultaneously analyzed the reduction in the risk for progression to type 2 diabetes (8%) and the regression to normal glucose regulation (35%) through an intensive lifestyle intervention or metformin treatment in overweight or obese subjects with impaired glucose regulation at low risk of developing T2DM.[6] Other components of the MetS have not been evaluated prospectively, and to our knowledge, the determinants associated with the regression or progression of the MetS are unknown.

The di@bet.es cohort was selected between 2009 and 2010 from the five basic healthcare units and was built from a representative sample of subjects of the non-institutionalized Spanish population. Its main objective was to evaluate the prevalence of T2DM based on the oral glucose tolerance test (OGTT), in order to define preventive strategies developed at the population level and plan improvements.[3 4] Our group has published previously the prevalence of T2DM[12] and MetS[2] from the data collected during the di@bet.es study. The cohort of subjects was followed up prospectively until 2016–2017, when a cross-sectional study was undertaken. The main aim of this study was to address the rate of progression of the subjects who were not diagnosed with MetS at baseline and the rate of regression of the subjects who did, and to analyze the determinants associated with both situations.

RESEARCH DESIGN AND METHODS

Population

A total of 5072 subjects over 18 years of age were randomly selected from the National Health System registry of users (covering over 99% of the Spanish population). This sample is representative of the non-institutionalized Spanish population. A broader description of the study design was previously published.[12] The cohort was re-evaluated during 2016–2017. A total of 2408 subjects participated in the follow-up analysis. The characteristics of non-responders and responders have been recently reported.[13]

A total of 1881 (78%) subjects had all the necessary information available for each of the MetS components at baseline and at follow-up. The subjects were divided into two groups: group A, without MetS at baseline (n=1146), and group B, with MetS at baseline (n=735). The characteristics of the patients are shown in table 1.

MetS definition

MetS was defined according to the Harmonized definition[1] using the specific waist circumference (WC) measurement of the Spanish population (94.5 cm in men and 89.5 cm for women) based on a Spanish population study[14] and confirmed in the baseline study[2] as the cut-off points with the highest sensitivity and specificity. The cut-off points for the rest of the components were –blood pressure (BP)>130/85 mm Hg, –triglyceride (TG)>150 mg/dL (1.7 mmol/L), –glucose>100 mg/dL (5.6 mmol/L) and –HDL-chol less than 40 mg/dL (1 mmol /L) for men and 50 mg/dL (1.3 mmol/L) for women. Subjects who received appropriate pharmacological treatment for hypertension, dyslipidemia or impaired glucose tolerance/diabetes were considered as having the respective risk factors. In order to establish the diagnosis of the MetS at least three abnormal components were required. Subjects who withdraw pharmacological treatment and were under the cut-off points were considered as having a regression for the respective component of the MetS.

Outcomes

In group A, the rate of the MetS occurrence was evaluated, in the subjects who fulfilled <3 criteria at baseline and who fulfilled ≥3 criteria during follow-up, and in group B, the regression rate of the MetS was evaluated in the subjects fulfilling ≥3 criteria at baseline and <3 at the follow-up visit, respectively.

Variables and procedures

The subjects were received in the laboratory of their healthcare unit between 08:00 and 09:00, after at least 10 hours of fasting. After signing the informed consent, a blood sample was obtained to analyze the levels of glucose (hexokinase enzymatic method), total cholesterol (cholesterol enzymatic method), HDL-chol (direct method), low-density lipoprotein cholesterol (Friedewald formula) and TGs (glycerol phosphate oxidase enzymatic method). Capillary blood glucose (One Touch

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Table 1 Characteristics of the study population stratified by absence (group A) or presence (group B) of metabolic syndrome at baseline

	All sample	Group A	Group B	P value
Number	1881	1146	735	
Men	802 (42.6)	419 (36.6)	383 (52.1)	<0.001
Women	1079 (57.4)	727 (63.4)	352 (47.9)	
Age (years)	50.22±14.47	46.06±13.90	56.69±12.89	<0.001
Body weight (kg)	75.02±14.91	70.03±12.75	82.83±14.71	<0.001
BMI (kg/m^2)	28.18±4.97	26.23±3.98	31.23±4.84	<0.001
WC (cm)				
Men	98.93±11.07	93.41±9.83	104.96±9.02	<0.001
Women	90.82±14.27	85.32±11.69	102.18±12.28	<0.001
SBP (mm Hg)	130.89±18.98	123.93±16.73	141.76±17.08	<0.001
DBP (mm Hg)	77.00±10.29	73.95±9.57	81.77±9.53	<0.001
FG (mmol/L)	5.52±1.52	5.05±0.81	6.26±2.01	<0.001
Total-chol (mmol/L)	5.12±1.01	5.06±0.97	5.22±1.07	0.005
TG (mmol/l)	1.37±1.05	1.06±0.47	1.87±1.44	<0.001
HDL-chol (mmol/L)	1.35±0.33	1.45±0.32	1.21±0.29	<0.001
LDL-chol (mmol/L)	2.75±0.76	2.69±0.73	2.85±0.79	<0.001
Obesity (≥30 kg/m^2)	571 (30.4)	182 (15.9)	389 (52.9)	<0.001
Uric acid (µmol/L)	307.09±88.66	283.52±80.60	343.82±88.21	<0.001
Educational level				<0.001
No studies	197 (10.5)	63 (5.5)	134 (18.3)	
Elementary	702 (37.3)	393 (34.3)	309 (42.0)	
Secondary education	671 (35.7)	450 (39.3)	221 (31.1)	
University degree	148 (7.9)	240 (20.9)	71 (9.6)	
Socioeconomic status				<0.001
Salaried worker	937 (49.8)	640 (55.8)	297 (40.4)	
Retired	333 (17.7)	141 (12.3)	192 (26.1)	
Unemployed	154 (8.2)	110 (9.6)	44 (6.0)	
Student	46 (2.4)	43 (3.8)	3 (0.4)	
Domestic work	366 (19.5)	190 (16.6)	176 (23.9)	
Others	45	22	23	

Data are mean±SD or n (%).
BMI, body mass index; DBP, diastolic blood pressure; FG, fasting serum glucose; HDL-chol, high-density lipoprotein cholesterol; LDL-chol, low-density lipoprotein cholesterol; SBP, systolic blood pressure; TG, triglyceride; Total-chol, total cholesterol; WC, waist circumference.

System, LifeScan, Johnson & Johnson, S.A., Madrid) was determined. If the capillary glucose was less than 126 mg/dL (7.8 mmol/L), a sample was obtained 2 hours after 75 g OGTT. A face-to-face interview was then conducted with a trained nurse, structured questionnaires on health status and lifestyle were applied, and a physical examination was performed.

Physical exam: weight without heavy clothing and height, in order to calculate the body mass index [BMI=weight (kg)/height^2 (m)], waist circumference (cm), BP with an appropriately sized cuff in a sitting position after 5 min of rest, taking three measurements 2 min apart with the last one being considered.

Sociodemographic variables: the following variables obtained in both phases were considered: age, educational level (categorized as no studies, elementary, secondary education and university degree), socioeconomic status (salaried worker, retired, unemployed, student, domestic work and others), family status (married or cohabiting, single, widowed or separated). Family history for first-degree relatives with T2DM was also collected.

Questionnaires: The questionnaires were applied in a face-to-face interview conducted by a trained nurse. The health questionnaire included the assessment of previous diseases, the family medical history and the pharmacological treatments that subjects were taking in order to determine the presence of clinical diabetes, hypertension or dyslipidemia. The level of physical activity was evaluated by applying the International Physical Activity Questionnaire (IPAQ)[15 16] to transform into metabolic equivalent of task (MET) the duration

and frequency of low, moderate and vigorous activities and all walking to the activities declared during the previous week. They were classified into one of these three categories: low, moderate or high expenditure, according to a previous study,[17] and the total energy expenditure of all physical activities was also calculated as MET-min/week of physical activity. The adapted 14-point MedDiet adherence screener (MEDAS) questionnaire[18] was applied to estimate adherence to the Mediterranean diet, after applying a qualitative food frequency questionnaire of 50 foods items. The cut-off point of 9 was considered to reflect high or low adherence to the Mediterranean diet.

Statistical study

Qualitative variables were summarized by their frequency distribution as well as quantitative variables by their mean±SD). The continuous non-normally distributed variables were summarized by the median and IQR: (P_{25}–P_{75}). Differences in variables according to the presence or absence of MetS were determined by the t-test for independent samples or the Mann-Whitney test when appropriate for quantitative variables and χ^2 test for qualitative variables. The sample incidence rates (IRs) for MetS or regression were calculated as number of events/person-time at risk, assuming a constant incidence over time. The IR was calculated adjusted for sex and age by direct method using as reference the Spanish population (https://www.ine.es/, accessed June 2009).

Univariate analysis for the incidence or regression of MetS was performed using logistical regression. For IRs and ORs obtained in logistic regression, 95% CIs were computed. A multivariate logistic regression model was fitted to identify the factors that were independently related to the incidence or regression of MetS. The variables for the adjustment were those which, in the univariate analyses, showed a level of statistical significance of p<0.05 and/or were considered clinically relevant. A first model (model 1) was adjusted by introducing the following variables: age (categorized as 18–45, 46–60, 61–75 and ≥76), gender, educational level (categorized as university degree or no university degree), marital status (categorized as married/cohabiting or others) and number of components of MetS. A second model was adjusted by adding the basic healthcare units to the variables of the first model (model 2). All analyses were performed using SPSS V.21.0 and STATA V.15.0 software. Statistical significance was assumed p<0.05.

RESULTS

Over a median follow-up of 7.5 (IQR 7.2–7.9) years, MetS developed in 294 (25.7%) subjects in group A. With 8646 person-years, the adjusted incidence (95% CI) per 1000 person-years was 38 (32-44), affecting more in men, increasing with age, in those with the lowest educational level and with the presence of 1 or 2 components of the MetS at baseline. The OR increases in overweight people 4.48 (95% CI 3.12 to 6.43), obesity 9.53 (95% CI 6.25 to 14.55) and with central fat distribution 4.16 (95% CI 3.12 to 5.44). The mean differences between the non-progressors compared with the progressors in the adapted MEDAS (9.2±1.4 vs 9.2±1.4, –0.0 (–0.2 to 0.2, p=0.519) and the median (IQR) MET-min/week of physical activity (1074 (396–3021) vs 1048 (394–3360), p=0.875) were not statistically significantly different. The probability of progression per 1000 person-years was observed by an adapted MEDAS score of >11 (31 (16–55) vs 34 (30–38)) in those with ≤11, but not by 9. Similarly, the probability decreases slightly as physical activity increases, and this trend is particularly observed in those who spent more than 500 MET-min/week (31 (25–39) vs 36 (29–43)) in those with ≤500 MET-min/week, respectively. These results are presented in table 2.

Regression occurred in 148 (20.1%) patients in group B, who fulfilled the criteria for MetS at baseline. With a follow-up of 5556 person-years, the adjusted regression rate per 1000 person-years was 36 (95% CI 31 to 41). The regression was more frequently observed in women, and especially in subjects fulfilling only three criteria of the MetS at baseline with an OR of 5.98 (2.36–15.15) compared with those with five criteria at baseline (reference group). The ORs in subjects without hypertension for MetS regression was 2.84 (1.75–4.61) and 1.77 (1.22–2.57) for those without hypertriglyceridemia, respectively. The likelihood of MetS regression decreases as body weight increases, with an ORs of 0.23 (0.11–0.49) in overweight subjects at baseline and 0.12 (0.06–0.26) in obese.

There were no differences in the adapted MEDAS score and in the physical activity obtained by the MET-min/week in the group of regressors compared with the non-repressors of MetS. The comparison of the mean score in the adapted MEDAS questionnaire in the regressors compared with the non-regressors was 8.9±1.3 vs 9.2±1.4, –0.3 (–0.6 to 0.1), p=0.543. Similarly, the comparison of the median between regressors and non-regressors in MET-min/week expenditure of physical activity was 876 (IQR 231–2772) vs 693 (IQR 231–2544), p=0.387. The regression rate per 1000 person-years of the MetS was greater in people who achieved an adapted MEDAS score of >11 (34 (11–78) vs (26 (22–31)) in those with ≤11 but not with 9. Similarly, a greater probability of MetS regression was observed when the subjects reached a MET-min/week expenditure of physical activity of ≥2000 MET-min/week (30 (23–40) vs 23 (17–33)) in those with <2000 MET-min/week, respectively. The data on the MetS regression (group B) are displayed in table 3.

Multivariate analysis adjusted by significant variables in univariate analysis (model 1) and adding basic healthcare units (model 2) showed no effect in the association factors with the progression/regression of MetS (online supplemental table 1).

The MetS regression rate was significantly higher than the MetS incidence in women, university-level subjects,

Table 2 Incidence of MetS in group A according to characteristics at baseline

	At risk (n)	Developing MetS (n)	P value	OR (95% CI)	Person-year	Incidence per 1000 person-years (95% CI)
All samples	1146	294 (25.7)			8646	38 (32 to 44)
Gender						
Men	419	153 (36.5)		2.39 (1.82 to 3.13)	3166	48 (41 to 57)
Women	727	141 (19.4)	0.000	1	5480	26 (22 to 30)
Age (years)						
18–45	592	85 (14.4)		1	4452	19 (15 to 24)
46–60	361	114 (31.6)		2.75 (2.00 to 3.79)	2730	42 (35 to 50)
61–75	172	83 (48.3)		5.56 (3.82 to 8.11)	1305	64 (51 to 79)
≥76	21	12 (57.1)	0.000	7.95 (3.25 to 19.45)	160	75 (39 to 131)
Marital status						
Single	218	39 (17.9)		1	1650	24 (17 to 32)
Married/cohabiting	836	235 (28.1)		1.80 (1.23 to 2.62)	6292	37 (33 to 42)
Widower	43	10 (23.3)		1.39 (0.63 to 3.06)	327	31 (15 to 56)
Divorced	49	10 (20.4)	0.016	1.18 (0.54 to 2.56)	378	27 (13 to 49)
Educational level						
No studies	62	34 (38.7)		3.70 (1.98 to 6.91)	471	51 (33 to 76)
Elementary	527	160 (30.4)		2.55 (1.71 to 3.82)	3973	40 (34 to 47)
Secondary education	316	75 (23.7)		1.82 (1.17 to 2.84)	2380	32 (25 to 40)
University degree	240	35 (14.8)	0.000	1	1814	19 (13 to 27)
Region of the country						
North	135	26 (19.3)		1	1040	25 (16 to 37)
South	447	122 (27.3)		1.57 (0.98 to 2.53)	3341	37 (30 to 44)
Centre	291	85 (29.2)		1.73 (1.05 to 2.84)	2221	38 (31 to 47)
Northeast	117	26 (22.2)		1.20 (0.65 to 2.21)	916	28 (19 to 42)
East coast	156	35 (22.4)	0.135	1.21 (0.69 to 2.14)	1127	31 (22 to 43)
Number of components of MetS						
0	294	16 (5.4)		1	2219	7 (4 to 11)
1	401	72 (18.0)		3.80 (2.16 to 6.69)	3023	24 (19 to 30)
2	451	206 (45.7)	0.000	14.61 (8.54 to 24.99)	3404	61 (53 to 69)
Glucose regulation						
Normal	885	214 (24.2)		1	6675	32 (28 to 37)
>99	261	80 (30.7)	0.023	1.39 (1.02 to 1.88)	1971	41 (32 to 51)
HDL-chol low						
No	968	245 (25.3)		1	7303	34 (30 to 38)
Yes	178	49 (27.5)	0.296	1.21 (0.78 to 1.61)	1343	37 (27 to 48)
Central obesity						
No	750	120 (16.0)		1	5684	21 (18 to 25)
Yes	396	174 (43.9)	0.000	4.16 (3.12 to 5.44)	2962	59 (50 to 68)
Hypertension						
No	736	141 (19.2)		1	5531	26 (22 to 30)
Yes	410	153 (37.3)	0.000	2.51 (1.92 to 3.30)	3115	49 (42 to 58)
Hyper-TG						
No	1088	266 (24.4)		1	8206	32 (29 to 37)
Yes	58	28 (48.3)	0.000	2.89 (1.69 to 4.92)	440	64 (42 to 92)
BMI (kg/m^2)						
18–<25	474	45 (9.5)	0.000	1	3582	13 (9 to 17)
25–<30	488	156 (32.0)		4.48 (3.12 to 6.43)	3683	42 (36 to 50)
>30	182	91 (50.0)		9.53 (6.25 to 14.55)	1366	67 (54 to 82)

Continued

Table 2 Continued

	At risk (n)	Developing MetS (n)	P value	OR (95% CI)	Person-year	Incidence per 1000 person-years (95% CI)
IPAQ						
High	278	69 (24.8)	0.933	1	2103	33 (26 to 42)
Moderate	387	99 (25.6)		1.04 (0.73 to 1.49)	2921	34 (28 to 41)
Low	480	125 (26.0)		1.07 (0.76 to 1.50)	3614	35 (29 to 41)
MET-min/week						
>500	777	194 (25.0)	0.241	1	3320	31 (25 to 39)
≤500	369	100 (27.1)		1.12 (0.84 to 1.48)	2773	36 (29 to 43)
MEDAS						
<9	345	85 (24.6)	0.330	1	2587	33 (26 to 41)
>9	801	209 (26.1)		1.08 (0.81 to 1.45)	6059	35 (30 to 40)
≤11	1095	282 (25.8)	0.434	1.28 (0.58 to 2.18)	8266	34 (30 to 38)
>11	51	12 (23.5)		1	379	31 (16 to 55)
Family history of T2DM						
No	528	134 (25.4)	0.425	1	3944	34 (28 to 40)
Yes	595	155 (26.1)		1.04 (0.79 to 1.35)	4476	35 (29 to 41)

Data are n (%).
BMI, body mass index; HDL-chol, high-density lipoprotein cholesterol; IPAQ, International Physical Activity Questionnaire; MEDAS, Mediterranean Diet adherence screener; MET, metabolic equivalent of task; MetS, metabolic syndrome; T2DM, type 2 diabetes mellitus; TG, triglyceride.

subjects with no central fat distribution, overweight or obesity, and without hypertension (all p<0.05).

DISCUSSION

According to the data obtained in our study, the incidence of MetS in a representative sample of the Spanish population is 38 cases per 1000 person-years but, on the contrary, regresses in 36 cases per 1000 person-years. This means that the MetS rate increases 2 cases per 1000 person-years in excess in relation to the regression rate, which for a population of 47 million people represents an increase in approximately of 94 000 cases per year, with about 257 more patients diagnosed with MetS daily.

This study has provided important information to identify the characteristics of progressors to MetS. The appearance of the MetS is significantly higher in men, in the age group over 45 years and in those who do not reach a university level, as reported in the baseline study. Those with at least one component of the MetS are four times more likely to develop it and if they have two components/criteria at baseline, about 15 times higher compared with those fulfilling no criteria at baseline. These results are in agreement to those reported in other populations,[19–22] probably indicating a slow progression in the occurrence of MetS. Although the presence of any component increases the probability of presenting MetS, the most determining factors are waist circumference, which multiplies the risk by 4, while being overweight or obese multiplies by more than nine times the probability of developing the MetS. The implications of these findings are that programs aimed to reduce body weight are essential to reduce the incidence of the MetS in Spain. Unexpectedly, a correct adherence to the Mediterranean diet evaluated by MEDAS is not associated with a reduction in the occurrence of MetS, if we define 9 as the cut-off point referred to identify adherents to Mediterranean diet (Med Diet), as identified in the PREDIMED study in the prevention of T2DM.[18 23] However, PREDIMED study also found no association with the occurrence or regression of the MetS.[24]

Using other questionnaires as tools to assess the adherence to the Med Diet and in a Spanish population with a high educational level, such as alumni from the University of Navarra in the SUN (Seguimiento Universidad de Navarra) study, a significant reduction in MetS occurrence was found associated with a higher level of adherence to Med Diet.[21] In our study, using other cut points, such as 11, we found that there is a trend to a decreased rate of occurrence, indicating that to reduce the occurrence of MetS, it is likely to be necessary to achieve a higher degree of adherence to Med Diet. On the other hand, we must consider that the MEDAS median in our cohort is nine and that the score greater than 7 is exceeded by 98% of the cohort included in the study. Thus, we can consider that in a population with a high degree of adherence to Med Diet, it may be necessary to achieve a higher adherence to Med Diet to observe benefits.[25 26] A larger sample size may also be necessary to observe a more favorable effect.

Regarding physical activity, there is a slight linear reduction in the appearance of MetS with moderate and high intensity; it begins to be favorable from being moderately active, that is, from 500 MET-min/week of physical activity. Physical activity has substantial beneficial effects on MetS.[27] There is agreement that being active, even at a low level, can be sufficient for the prevention

Table 3 Regression of MetS in group B according to characteristics at baseline

	At risk (n)	Regression to no MetS (n)	P value	OR (95% CI)	Person-year	Incidence per 1000 person-years (95% CI)
All samples	735	148 (20.1)			5556	36 (31 to 41)
Gender						
Men	383	59 (15.4)		1	2911	20 (15 to 26)
Women	352	89 (25.3)	0.001	1.86 (1.29 to 2.68)	2645	34 (27 to 41)
Age (years)						
18–45	146	42 (28.8)		1.77 (0.76 to 4.12)	1092	39 (28 to 52)
46–60	265	51 (19.2)		1.04 (0.46 to 2.38)	1998	26 (19 to 34)
61–75	281	47 (16.7)		0.88 (0.38 to 2.01)	2135	22 (16 to 29)
≥76	43	8 (18.6)	0.029	1	330	24 (11 to 48)
Marital status						
Single	61	17 (27.9)		1	465	37 (21 to 59)
Married/cohabiting	605	119 (19.7)		0.63 (0.35 to 1.15)	4579	26 (22 to 31)
Widower	46	7 (15.2)		0.47 (0.17 to 1.24)	342	21 (8 to 42)
Divorced	23	5 (21.7)	0.380	0.72 (0.23 to 2.24)	169	30 (10 to 69)
Educational level						
No studies	134	23 (17.2)		1	1013	23 (14 to 34)
Elementary	387	76 (19.6)		1.18 (0.71 to 1.97)	2931	26 (20 to 32)
Secondary education	143	33 (23.1)		1.45 (0.80 to 2.62)	1072	31 (21 to 43)
University degree	71	16 (22.5)	0.611	1.40 (0.69 to 2.87)	540	30 (17 to 48)
Region of the country						
North	68	19 (27.9)		1	531	36 (22 to 56)
South	285	57 (20.0)		0.65 (0.35 to 1.18)	2100	27 (21 to 35)
Center	205	32 (15.6)		0.48 (0.25 to 0.91)	1589	20 (14 to 28)
Northeast	83	19 (22.9)		0.77 (0.37 to 1.60)	653	29 (18 to 45)
East coast	94	21 (22.3)	0.209	0.74 (0.36 to 1.52)	684	31 (19 to 47)
Number of components of MetS						
3	408	111 (27.2)		5.98 (2.36 to 15.15)	3086	36 (30 to 43)
4	242	32 (13.2)		2.44 (0.92 to 6.48)	1835	17 (12 to 25)
5	85	5 (5.9)	0.000	1	635	8 (3 to 18)
Glucose regulation						
Normal	145	37 (25.5)		1.48 (0.97 to 2.27)	1095	34 (24 to 47)
>99	580	111 (18.8)	0.048	1	4461	25 (21 to 30)
HDL-chol, low						
No	386	74 (19.2)		0.88 (0.62 to 1.26)	2924	25 (20 to 32)
Yes	349	74 (21.2)	0.276	1	2632	28 (22 to 35)
Central obesity						
No	58	17 (29.3)		1.73 (0.95 to 3.14)	436	39 (23 to 62)
Yes	677	131 (19.4)	0.054	1	5120	26 (21 to 30)
Hypertension						
No	84	32 (38.1)		2.84 (1.75 to 4.61)	627	51 (35 to 72)
Yes	651	116 (17.8)	0.000	1	4929	24 (20 to 28)
Hyper-TG						
No	385	94 (24.4)		1.77 (1.22 to 2.57)	2926	32 (26 to 39)
Yes	350	54 (15.4)	0.002	1	2630	21 (15 to 27)
BMI (kg/m^2)						
18–<25	33	19 (57.6)	0.000	1	251	76 (46 to 118)
25–<30	309	74 (23.9)		0.23 (0.11 to 0.49)	2342	32 (25 to 40)
≥30	389	55 (14.1)		0.12 (0.06 to 0.26)	2934	19 (14 to 24)

Continued

Table 3 Continued

	At risk (n)	Regression to no MetS (n)	P value	OR (95% CI)	Person-year	Incidence per 1000 person-years (95% CI)
IPAQ						
High	118	28 (23.7)	0.534	1	893	31 (21 to 45)
Moderate	248	49 (19.8)		0.79 (0.47 to 1.34)	1887	26 (20 to 34)
Low	368	70 (19.0)		0.76 (0.46 to 1.24)	2768	25 (20 to 32)
MET-min/week						
≥2000	222	51 (23.0)	0.113	1.29 (0.88 to 1.89)	1680	30 (23 to 40)
<2000	512	96 (18.8)		1	3868	24 (20 to 30)
MEDAS						
<9	235	59 (25.1)	0.015	1	1777	33 (25 to 43)
≥9	500	89 (17.8)		0.65 (0.45 to 0.94)	3779	24 (19 to 29)
>11	20	5 (25)	0.376	1.33 (0.48 to 3.73)	149	34 (11 to 78)
≤11	715	143 (20)		1	5406	26 (22 to 31)
Family history of T2DM						
No	302	64 (21.2)	0.251	1	2303	28 (21 to 36)
Yes	408	77 (18.9)		0.87 (0.60 to 1.25)	3061	25 (20 to 31)

Data are n (%).
BMI, body mass index; HDL-chol, high-density lipoprotein cholesterol; IPAQ, International Physical Activity Questionnaire; MEDAS, MedDiet adherence screener; MET, metabolic equivalent of task; MetS, metabolic syndrome; T2DM, type 2 diabetes mellitus; TG, triglyceride.

of MetS, even if more benefits are obtained at a higher level of attained activity.[27–30] The population included in the di@bet.es study cohort at baseline was not very active, and the subgroup with lower activity was associated with an increase in the rate of some components of the MetS.[17] Our study is only observational, based on the two national strategies[3 4] and whose main recommendation is to be moderately active, such as walking daily and climbing stairs, which has been associated with an improvement in insulin sensitivity.

Our study identifies the characteristics that the population has at baseline with a greater probability of MetS regression. Those are being women, presenting fewer numbers of MetS criteria at baseline, higher educational level and young age, while the absence of hypertension, hypertriglyceridemia and overweight/obesity identifies the population that is most susceptible to population interventions and in whom MetS is more likely to regress.

An important finding of our study is that it is necessary to achieve a higher degree of adherence to Med Diet, estimated at 11 points, in the same way as to reduce the occurrence of MetS. In relation to physical activity, it is also necessary to reach a minimum level of ≥2000 MET-min/week of physical activity to observe a tendency to regression. This is in agreement with results obtained in other studies and are important treatment objectives in patients with MetS.[31–34]

Limitations

The participants in the di@bet.es study cohort were randomly selected from the population covered by National Health System, divided in five different basic healthcare units, which included 100 clusters (primary healthcare centers) throughout the national territory, and the interventions carried out in each center have not specifically been evaluated. However, the monitoring of this cohort represents in real time the modifications that have arisen with population strategies and the response of the public health system. Differences due to the area of origin of the surveyed subjects have been analyzed; the studied population is representative of the Spanish population, but it is not enough to achieve representativeness of each specific area, of the five in which Spain was divided. This means that the results by zones must be taken with caution. There could also be an underdiagnosis in the declared interpretation of the subjects in relation to the pharmacological treatment of some components of the MetS, and this cannot be ruled out. The assessment of diet and physical activity has been carried out by the IPAQ and MEDAS questionnaires, which may have some difficulty in their application. However, they were obtained both at baseline and during follow-up by the same nurses trained to carry out the surveys, so data collection is subject to less variability. The response rate during follow-up can also affect our results, but it has been more than 78% of those eligible, an important rate in this type of study, although the influence of some confounding factors cannot be ruled out.

CONCLUSIONS

Our data show that despite the designed population strategies, the rate of MetS occurrence in Spain exceeds that of regression, increasing the existence of MetS by 257 people each day. The high prevalence of MetS makes it mandatory to implement national policies for its prevention. Preventive strategies to reduce the occurrence of MetS should focus on the

population older than 45 years and with one or two components of MetS, especially in overweight/obese people and those with central body fat distribution. The strategies to achieve a MetS regression are more likely to be successful in the population that has fewer MetS components, and in particular those who do not have hypertension, hypertriglyceridemia or a normal weight with peripheral fat distribution. It is necessary to achieve a greater adherence to Med Diet (>11 points) and at least 2000 MET-min/week of physical activity to observe a trend to the MetS regression, while >500 MET-min/week of physical activity may be sufficient to observe a reduction on its occurrence. These data must be considered by the public health system in Spain and may be of interest to apply them in other countries. It will also be useful for comparing data obtained from patients with other chronic diseases and across countries. Researcher should further investigate how the lifestyle can be optimized for health promotion and prevention of cardiometabolic conditions like MetS.

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