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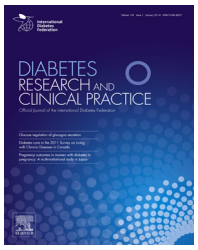

Metabolic syndrome, glucose tolerance categories and the cardiovascular risk in Spanish population

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ABSTRACT

We examined the prevalence of metabolic syndrome (MetS), glucose tolerance categories and risk factors of cardiovascular-disease (CVD) in the general Spanish population.

We studied 3844 randomly sampled subjects (46% males) aged 35–74 years. Glucose tolerance categories were defined according to the 2003 ADA and MetS according to the Harmonized Consensus Criteria with waist circumference (WC) cut-off-points previously reported in Spanish population (≥94.5/≥89.5 cm for males/females).

The prevalences of normoglycemia (NG), impaired fasting glucose (IFG), impaired glucose tolerance (IGT), IFG and IGT considered together (IFG/IGT), and diabetes mellitus (DM) were 67.6/16.6/5.0/3.3, and 7.5%, respectively. The overall prevalence of MetS was 31.2%. In subjects with NG, IFG, IGT, IFG/IGT, and DM the MetS prevalence's were 16.3/57.1/31.5/66.1, and 74.4% ($p < 0.001$), respectively. MetS was more common in males, older subjects, smokers, and/or individuals with obesity, IFG, IFG/IGT, DM, or insulin resistance (HOMA-IR ≥3.8). MetS was less prevalent in individuals with low alcohol intake and/or high education level. Regarding the risk level of CVD estimated by Framingham and SCORE risk charts, IGT had higher estimated CVD-risk than IFG and IFG/IGT. The presence of MetS increases the risk 4.85 times by Framingham and 2.43 times by SCORE.

Prevalence of prediabetes (IFG/IGT) and MetS were 25% and 31.2% respectively. Prevalence of MetS has not changed in the past decade in Spanish females, but has slightly increased in males. We found that subjects with IGT showed a higher risk of CVD than IFG and IFG/IGT according to the Framingham and SCORE. MetS increased the CVD-risk previously estimated by Framingham and SCORE.

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1. Introduction

The prevention of diabetes mellitus (DM) and its associated burden has become a major priority worldwide as it is one of the most expensive and rapidly increasing serious chronic diseases [1].

The global prevalence of type 2 DM has increased exponentially in the last decades all over the world and by the year 2035 it is expected to affect more than 592 million persons [2]. Patients with type 2 DM are at increased risk of coronary heart disease [3].

Prediabetes, typically defined as blood glucose concentrations higher than normal, but lower than Diabetes thresholds, is a high-risk state for diabetes development [4,5] as well as it is for cardiovascular disease (CVD) [6,7]. In this report, impaired fasting glucose (IFG) and impaired glucose tolerance (IGT) are considered intermediate metabolic states between normal and diabetic glucose status [8]. IFG and IGT are characterized by different physiopathological mechanisms [4]. Both IGT and IFG are insulin resistant states. Subjects with IFG predominantly have hepatic insulin resistance and normal muscle insulin sensitivity, whereas individuals with IGT have normal to slightly reduced hepatic sensitivity and moderate to severe muscle insulin resistance (IR) [9]. An important percentage of the population has reached a prediabetes state. In Spain, the prevalence estimated is above 12%, but there are very few studies that support this issue [10].

The metabolic Syndrome (MetS) is a multifactorial condition that includes interrelated risk factors of metabolic and non-metabolic origin. MetS increases the risk of CVD although its ability in the prediction of CVD events is lower then CV-risk charts [11]. The accepted metabolic components of the MetS are abdominal obesity, altered glucose tolerance, high blood pressure, and dyslipidemia, but there are other components such as abnormalities in fibrinolysis and coagulation, chronic inflammation, and endothelial dysfunction which are also considered important. It has been discussed when, how and use the concept of MetS in clinical practice or if it even exists as such syndrome [12,13]. The International Diabetes Federation (IDF) elaborated a definition of the MetS for epidemiological studies worldwide [14]. Recently the Harmonized definition was proposed in an attempt to unify previous criteria [15]. There was therefore, a lack of data on the Harmonized MetS prevalence and the associated risk of CVD in Spanish population.

The purpose of our study was to examine the prevalence of glucose tolerance categories, MetS and the associated cardiovascular risk in individuals of the general Spanish population. The prevalence of MetS according to the Harmonized criteria [15] includes cut-off points for waist circumference equal or greater than 94.5 cm in males and equal or greater than 89.5 cm in females [16] for Spanish population. Another parameter which is too assessed is the relationship between the different groups of glucose tolerance categories and individual CVD risk factors.

2. Design and study population

We studied 4097 randomly sampled subjects of the general Spanish population from two cohorts focused on cardiovascular risk factors: (1) Spanish Insulin Resistance Study (SIRS) is a population-based study conducted in 7 small and middle-size towns across Spain. From a targeted population of 348,980 inhabitants, age 35–69 years, a total of 2949 men and non-pregnant women completed the survey (overall response rate, 66.9%). (2) Segovia Insulin Resistance Study is a cross-sectional population-based study in the Spanish province of Segovia (Autonomous Community of Castilla-León) including subjects from the Segovia Public Health census tract, of 14 small and middle size towns. A random sample of 2992 subjects aged 35–74 years was selected from a target population of 63.417 inhabitants (rural: 62%, urban: 38%), a total of 1166 individuals agreed to participate (response rate, 39%), 900 completed the survey. In brief, 5941 males and non-pregnant females (54%) aged 35–74 years, from a targeted population of 496,674 subjects from 21 small and middle-sized towns across Spain were invited to participate and finally 3844 were included in the survey (1754 males and 2090 females) and 253 excluded because they met one or more of the exclusion criteria: type 1 diabetes [defined by the presence of one or more of the following autoimmune markers – islet cell autoantibodies, autoantibodies to insulin, autoantibodies to GAD (GAD65), autoantibodies to the tyrosine phosphatases IA-2 and IA-2b, and autoantibodies to zinc transporter 8 (ZnT8) – and insulin deficiency], some type of heart or hepatic failure, surgery during the previous year, weight changes >5 kg within the previous 6 months, and hospitalization, as well as five who did not meet a glucose value.

We have compared our cohorts to the Census of the National Institute of Statistics of Spain (www.ine.es) for the same years and found that they were nearly identical in age and sex. More details of recruitment and study protocols of these population-based surveys were previously described [17,18].

All subjects were sent a personalized letter signed by the principal investigator and the authorities of the Regional Public Health Service, explaining the purpose of the study and requesting volunteering for participation. In case of no response, people were again contacted by telephone up to three times.

The standard procedures were adapted from the WHO MONICA protocol (WHO, 1990) [19] approved by our Ethics Committee of San Carlos Clinic Hospital. All participants were given written information about their consent to be included in our study.

A medical questionnaire was obtained by trained interviewers, requesting from each participant data related to demographic characteristics, including age, sex, education status, socioeconomic status, physical activity, cigarette smoking, alcohol consumption, family history of diabetes and its treatment, hypertension, and other selected chronic diseases.

Weight, height and waist circumference (WC) were measured using a standardized protocol. In all participants, measurements were validated by comparing the values taken by three interviewers. Body mass index (BMI) was defined as weight (kg) divided by the square of height (m). Physical activity was reported by asking participants, and quantified by estimating the number of metabolic equivalents (MET) as previously described by the Centers for Disease Control [20]. MET is the same as the number of hours spent on a particular activity multiplied by a score that was specific for that activity. Educational status was estimated by the number of completed

school years [21]. Subjects were classified in three groups according to their physical activity: low <3 METs; moderate 3.0–6.0 METs; high >6.0 METs. Alcohol intake was categorized in the following intervals: no alcohol intake 0 g alcohol/day, 1–14.99 g/day, ≥15–29.99 g/day, and ≥30 g/day [22,23]. Smoking was grouped in three categories: current, (at least one cigarette per day); never, (those who had never smoked); and former, (people who quit smoking >1 year ago at the time of the study) [24].

Ten-years CVD risk estimates were calculated according to formulas published by Framingham [25] and SCORE [26] charts and programmed by a mathematician as follows: Framingham's general formula – $p = 1 - S_0(t)\exp\left(\sum_{i=1}^{p}\beta_i X_i - \sum_{i=1}^{p}\beta_i X_i\right)$ – where $S_0(t)$ is baseline survival at follow-up time t (here t = 10 years), βi is the estimated regression coefficient (log hazard ratio), Xi is the log-transformed value of the ith risk factor, (if continuous), X_i is the corresponding mean, and p denotes the number of risk factors; and the SCORE which is a six steps formula that estimates the fatal CVD risk where the last step combines the risks for coronary heart disease and non-coronary cardiovascular risk.

High CV-risk was estimated as ≥20% with the Framingham Risk score and ≥5% of the SCORE Project for populations at low CV-risk. When calculated the risk, diabetic subjects are excluded.

2.1. *Procedures and laboratory studies*

After an overnight period, 20 ml of blood were obtained from an antecubital vein without compression. Plasma glucose concentration was determined twice by a glucose-oxidase method adapted to an Autoanalyzer (Hitachi 704, Boehringer Mannheim, Germany). Total cholesterol, triglycerides and high-density lipoprotein (HDL-C) cholesterol were determined by enzymatic methods using commercial kits (Boehringer Mannheim, Germany). Low-density lipoprotein (LDL-C) cholesterol was calculated by the Friedewald formula.

A 75 g oral glucose tolerance test (OGTT) was performed and interpreted according to the 2003 criteria of the American Diabetes Association [4] after excluding clinically diagnosed diabetic patients. DM was analytically diagnosed when fasting plasma glucose (FPG) was ≥7.0 mmol/l (≥126 mg/dl) or 2-h glucose ≥11.1 mmol/l (≥200 mg/dl). Subjects on antidiabetic medications were also considered to have diabetes. In nondiabetic subjects, IFG was defined as FPG 5.6–6.9 mmol/l (100–125 mg/dl), IGT as 2-h glucose 7.8–11.0 mmol/l (140–199 mg/dl), and IFG/IGT as FPG 5.6–6.9 mmol/l (100–125 mg/dl) and 2-h glucose 7.8–11.0 mmol/l. (140–199 mg/dl). Serum insulin concentrations were determined by RIA (Human Insulin Specific RIA kit, Linco Research Inc., St Louis MO, USA) with a lower detection limit of 2 μU/ml. Intra and inter-assays coefficients of variation were <1% and <7.4%, respectively. Cross reactivity with proinsulin was less than 2%.

Insulin resistance (IR) was estimated by a homeostasis model assessment of insulin resistance (HOMA-IR) using the following formula [27]: Fasting Insulin (uU/ml) × fasting glucose (mmol/l)/22.5. In subjects with IR, the 90th percentile for the HOMA-IR was equal to or greater than 3.8. This value was considered diagnostic of IR as indicated by Ascaso et al. for the Spanish population [28].

MetS was diagnosed when the new Harmonized definition was applied using European [29] cut-off points (≥102 cm in males and ≥88 cm in females) and specific cut-off points for WC previously reported for the Spanish population (≥94.5 cm in males ≥89.5 cm in females) [16]. Diagnosis of MetS requires fulfilment of at least 3 of the following criteria. WC: ≥94.5 and ≥89.5 cm for males and females, respectively, high blood pressure: systolic blood pressure (SBP) ≥130 mmHg, diastolic blood pressure (DBP) ≥85 mmHg and/or treatment of previously diagnosed hypertension, hypertriglyceridemia ≥150 mg/dl [1.7 mmol/l], low HDL-C: <40 mg/dl (0.9 mmol/l) in males and <50 mg/dl (1.1 mmol/l) in females, or specific treatment for this lipid abnormality, elevated FPG, (FPG) ≥100 mg/dl (5.6 mmol/l) or previously diagnosed of DM.

Hypertension was diagnosed in those subjects treated with blood pressure medication and/or have a mean three times blood pressure measurement in a seated position as follows: equal or higher of 130 mmHg of systolic blood pressure (SBP) or alternatively equal or higher of 85 mmHg of diastolic blood pressure (DBP), as previously reported [18]. Information on pharmacological treatment of hypertension and elevated glucose was based on the participant's reported use of any medication and the transcription and coding of all medication names.

Subjects with a history of hyperlipidemia, hypertension or diabetes were deemed to have the respective risk factors, regardless the biochemical values. Subjects were considered obese if their BMI was ≥30 kg/m^2.

2.2. *Statistical methods*

The student's T test or ANOVA were used to compare continuous variables expressed as means ± standard deviation (SD). Natural logarithmic transformation was applied to variables with no normal distribution. The Bonferroni significance correction test was used when comparing more than two means. Categorical variables were compared using the Chi-square test. The relation of relevant factor to MetS prevalence and scores was assessed by logistic regression analysis. Odds ratios were estimated and their confidence interval (CI) was considered to be 95%. Variables with significant association by univariate analysis were included in multivariate analysis. The selection of the methods used was chosen according to what was found in literature [30]. The null hypothesis was rejected in each statistical test when $p < 0.05$. Analyses were performed using Windows SPSS version 15.0 software.

3. Results

The anthropometric parameters of the study subjects stratified by glucose tolerance categories are listed in Table 1. The overall prevalence of NG, IFG, IGT, IFG/IGT, and DM was 67.6, 16.6, 5.0, 3.3, and 7.5%, respectively. The prevalence of IFG was higher in males than in females ($p < 0.001$). Subjects with DM were older than those with NG, IFG, IFG/IGT ($p < 0.001$). Subjects with higher level of education had lower prevalence of IFG, IGT, IFG/IGT or DM. When the age range was considered in the analysis, we found a higher proportion of males less

Table 1 – Basic characteristics and anthropometric parameters in males and females adjusted by age.

Group Males	NG N = 1121/63.9% M (SD)	IFG N = 342/19.5% M (SD)	IGT N = 82/4.7% M (SD)	IFG/IGT N = 63/3.6% M (SD)	DM N = 146/8.3% M (SD)	Overall *p*
Age (years)	49 (10)	49 (9)	55 (11)	54 (9)	56 (10)	<0.001[a]
≤44 years	36.9%	37.9%	26%	22%	15.2%	
>44–54 years	32.8%	32.3%	20.8%	28.8%	26.8%	
>54–64 years	22.9%	25.5%	35.1%	37.3%	37.7%	
>64 years	7.3%	4.3%	18.2%	11.9%	20.3%	
	M (95% CI)	M (95% CI)	M (95% CI)	M (95% CI)	M (95% CI)	
BMI (kg/m^2)	27.18 (26.97–27.4)	27.81 (27.43–28.20)	28.17 (27.37–28.96)	28.44 (27.53–29.34)	28.76 (28.16–29.36)	<0.001[b]
WC (cm)	93.63 (93.04–94.22)	95.5 (94.44–96.57)	96.74 (94.54–98.93)	97.20 (94.71–99.68)	98.97 (97.31–100.62)	<0.001[c]
SBP (mmHg)	125 (124–126)	129 (127–131)	128 (124–131)	136 (131–140)	131 (128–134)	<0.00[d]
DBP (mmHg)	79 (78–79)	80 (79–82)	81 (78–83)	84 (81–87)	81 (79–83)	0.001[e]
Group Females	NG N = 1473/70.5% M (SD)	IFG N = 299/14.3% M (SD)	IGT N = 111/5.3% M (SD)	IFG/IGT N = 65/3.1% M (SD)	DM N = 142/6.8% M (SD)	Overall *p*
Age (years)	49 (9)	52 (9)	57 (11)	54 (9)	57 (10)	<0.001[a]
≤44 years	38.2%	23.1%	17.1%	19.4%	11.9%	
>44–54 years	32.2%	36.7%	19%	29%	20.9%	
>54–64 years	23.6%	34.2%	39%	41.9%	45.5%	
>64 years	6.0%	6.0%	24.8%	9.7%	21.6%	<0.001
	M (95% CI)	M (95% CI)	M (95% CI)	M (95% CI)	M (95% CI)	
BMI (kg/m^2)	27.39 (27.14–27.63)	29.32 (28.79–29.86)	28.51 (27.63–29.39)	29.51 (28.36–30.66)	30.51 (29.72–31.30)	<0.001[b]
WC (cm)	84.09 (83.57–84.62)	89.25 (88.08–90.42)	87.38 (85.46–89.31)	91.69 (89.21–94.18)	92.63 (90.92–94.35)	<0.001[c]
SBP (mmHg)	125 (124–126)	132 (129–134)	128 (124–131)	137 (133–142)	136 (133–139)	<0.001[d]
DBP (mmHg)	78 (77–79)	80 (79–81)	80 (77–81)	83 (81–86)	82 (80–84)	<0.001[e]

M (SD): data are means (standard deviation), M (95% CI): means (95% confidence interval). BMI: body mass index, WC: waist circumference; SBP: systolic blood pressure; DBP: diastolic blood pressure.

Males:

[a] NG vs. IGT; NG vs. IFG/IGT; NG vs. DM; IFG vs. IFG/IGT;IFG vs. DM ($p < 0.05$)*.

[b] NG vs. IFG; NG vs. DM ($p < 0.05$)*.

[c]NG vs. IFG; NG vs. DM; IFG vs. DM ($p < 0.05$)*.

[d]NG vs. IFG; NG vs. IFG/IGT; NG vs. DM; IFG vs. IFG/IGT; ($p < 0.05$)*.

[e]NG vs. IFG/IGT ($p < 0.05$)*.

*All comparisons.

Females:

[a] NG vs. IFG; NG vs. IGT, NG vs. IFG/IGT; NG vs. DM; IFG vs. IGT; IFG vs. DM ($p < 0.05$)*.

[b] NG vs. IFG; NG vs. IFG/IGT; NG vs. DM ($p < 0.05$)*.

[c] NG vs. IFG; NG vs. IGT, NG vs. IFG/IGT; NG vs. DM; IFG vs. DM ($p < 0.05$)*.

[d] NG vs. IFG; NG vs. IFG/IGT; NG vs. DM; IFG vs. IFG/IGT; IGT vs. IFG/IGT, IGT vs. DM ($p < 0.05$)*.

[e] NG vs. IFG; NG vs. IFG/IGT; NG vs. DM ($p < 0.05$)*.

*All comparisons.

than 50 years old with IGT as compared with females. A DM diagnosis was more frequently established in males than females aged 40–50 years old, Table 1.

SBP and DBP were higher in the IFG/IGT category than in the IFG and IGT categories. BMI and WC increased with decreasing glucose tolerance ($p < 0.001$). Overall prevalence of obesity was in NG, IFG, IGT, IFG/IGT and DM were 22.8%, 33.3%, 38.1%, 32.5% and 46.5% respectively. Obesity was more prevalent in individuals with IGT than in those with IFG or IFG/IGT. FPG was higher in the IFG category than in the IGT category ($p < 0.001$), but 2-hour glucose was higher in the IFG/IGT category than in the IFG category ($p < 0.001$). Total cholesterol and LDL-C values were greater in the IFG group than in the NG group. Triglycerides were higher in the IFG, IFG/IGT and DM categories than in the NG category. HDL-C was lower in the IFG, IGT and DM groups than in the NG group, Table 2.

HOMA-IR was higher in the IFG/IGT group than in the IGT and IFG groups. The prevalence of IR was similar in both sexes except for individuals with IFG (men, 35.4% vs. women, 43.5%; $p = 0.026$).

Obese individuals were more insulin resistant than non-obese counterparts (23.7% vs. 8.5%, $p < 0.001$) across all categories of glucose tolerance: IFG (56.6% vs. 30.7%; $p < 0.001$), IGT (37.5% vs. 19.8%, $p = 0.010$), IFG/IGT (67.6% vs. 45.6%, $p = 0.022$), and DM (72.1% vs. 60.9%, $p = 0.037$). Abdominal obesity was more prevalent in males than in females (50.9% vs. 35.1%, $p < 0.001$). The overall prevalence of MetS when the new Harmonized definition was applied using specific cut-off points for WC previously reported for the Spanish population (≥94.5 cm in males ≥89.5 cm in females) was 31.2%, higher in males than in females (34.2% vs. 28.5%, $p = 0.001$). The prevalence of the MetS in participants with NG, IFG, IGT, IFG/IGT, and DM were 16.3, 57.1, 31.5, 66.1, and 74.4%,

Table 2 – Biochemical characteristics of the survey population in males and females adjusted by age.

Group Males	NG	IFG	IGT	IFG/IGT	DM	Overall *p*
	M (95% CI)	*M* (95% CI)	*M* (95% CI)	*M* (95% CI)	*M* (95% CI)	
FPG (mmol/l)	4.79 (4.74–4.85)	5.95 (5.85–6.05)	4.96 (4.74–5.17)	6.04 (5.79–6.28)	8.71 (8.55–8.87)	<0.001[a]
2-h glucose (mmol/l)	4.99 (4.88–5.09)	5.48 (5.28–5.67)	8.85 (8.51–9.19)	9.00(8.62–9.39)	10.87 (10.51–11.23)	<0.001[b]
TC (mmol/l)	5.65 (5.58–5.72)	5.91 (5.79–6.03)	5.90 (5.66–6.15)	5.89 (5.61–6.17)	5.93 (5.75–6.12)	<0.001[c]
TG (mmol/l)	1.35 (1.28–1.41)	1.69 (1.57–1.81)	1.52 (1.28–1.76)	1.60 (1.33–1.88)	1.29 (2.11–2.48)	<0.001[d]
HDL-C (mmol/l)	1.27 (1.25–1.29)	1.20 (1.16–1.24)	1.25 (1.17–1.33)	1.22 (1.12–1.31)	1.13 (1.06–1.19)	<0.001[e]
LDL-C (mmol/l)	3.76 (3.70–3.82)	3.93 (3.82–4.03)	3.94 (3.72–4.16)	3.92 (3.67–4.18)	3.67 (3.50–3.84)	0.02[f]
FI (uU/ml)	11.7 (11.2–12.3)	13.7 (12.7–14.6)	14.4 (12.3–16.5)	16.7 (14.4–19.0)	15.6 (14.0–17.1)	<0.00[g]
HOMA-IR	2.49 (2.33–2.65)	3.59 (3.31–3.87)	3.19 (2.60–3.78)	4.47 (3.80–5.14)	5.93 (5.49–6.37)	<0.00[h]
Group Females	NG	IFG	IGT	IFG/IGT	DM	Overall *p*
	M (95% CI)	*M* (95% CI)	*M* (95% CI)	*M* (95% CI)	*M* (95% CI)	
FPG (mmol/l)	4.65 (4.60–4.69)	5.97 (5.87–6.06)	4.77 (4.61–4.94)	6.06 (5.85–6.27)	8.01 (7.86–8.16)	<0.001[a]
2-h glucose (mmol/l)	5.24 (5.17–5.32)	5.72 (5.53–5.91)	8.65 (8.40–8.90)	8.97(8.65–9.29)	12.18 (11.87–12.49)	<0.001[b]
TC (mmol/l)	5.58 (5.53–5.64)	5.89 (5.77–6.00)	5.53 (5.33–5.72)	5.61 (5.36–5.86)	5.80 (5.62–5.97)	<0.001[c]
TG (mmol/l)	1.00 (0.90–1.04)	1.28 (1.22–1.36)	1.18 (1.06–1.29)	1.23 (1.08–1.37)	1.64 (1.54–1.74)	<0.001[d]
HDL-C (mmol/l)	1.51 (1.49–1.53)	1.41 (1.36–1.46)	1.36 (1.29–1.44)	1.41 (1.32–1.51)	1.29 (1.22–1.36)	<0.001[e]
LDL-C (mmol/l)	3.61 (3.56–3.66)	3.89 (3.78–4.00)	3.62 (3.44–3.80)	3.63 (3.40–3.86)	3.75 (3.59–3.91)	<0.001[f]
FI (uU/ml)	12.0 (11.4–12.7)	15.1 (13.7–16.5)	13.2 (10.9–15.5)	15.4 (12.4–18.3)	17.0 (14.9–19.0)	<0.00[g]
HOMA-IR	2.49 (2.35–2.64)	4.00 (3.68–4.32)	2.81 (2.27–3.35)	4.14 (3.45–4.82)	5.89 (5.42–6.37)	<0.00[h]

M (95% CI): mean (95% confidence interval). FPG: fasting plasma glucose; TC: total cholesterol; TG: triglycerides; HDL-C: high density lipoprotein cholesterol; LDL-C: low density lipoprotein cholesterol; FI: fasting insulin; HOMA-IR: homeostasis model assessment insulin resistance.

Males:

[a] NG vs. IFG; NG vs. IFG/IGT; NG vs. DM; IFG vs. IGT; IFG vs. DM; IGT vs. IFG/IGT; IGT vs. DM; IFG/IGT vs. DM ($p < 0.05$)*.

[b] NG vs. IFG; NG vs. IGT; NG vs. IFG/IGT; NG vs. DM; IFG vs. IGT; IFG vs. IFG/IGT; IFG vs. DM, IGT vs. DM; IFG/IGT vs. DM ($p < 0.05$)*.

[c] NG vs. IFG; ($p < 0.05$).

[d] NG vs. IFG; NG vs. DM; IFG vs. DM; IGT vs. DM; IFG/IGT vs. DM ($p < 0.05$)*.

[e] NG vs. IFG; NG vs. DM ($p < 0.05$)*.

[f] No significant differences.

[g] NG vs. IFG; NG vs. IFG/IGT; NG vs. DM ($p < 0.05$)*.

[h] NG vs. IFG; NG vs. IFG/IGT; NG vs. DM; IFG vs. DM; IGT vs. IFG/IGT; IGT vs. DM; IFG/IGT vs. DM ($p < 0.05$)*.

* All comparisons.

Females:

[a] NG vs. IFG; NG vs. IFG/IGT; NG vs. DM; IFG vs. IGT; IFG vs. DM; IGT vs. IFG/IGT; IGT vs. DM;. IFG/IGT vs. DM ($p < 0.05$)*.

[b] NG vs. IFG; NG vs. IGT; NG vs. IFG/IGT; NG vs. DM; IFG vs. IGT; IFG vs. IFG/IGT; IFG vs. DM, IGT vs. DM; IFG/IGT vs. DM ($p < 0.05$)*.

[c] NG vs. IFG; IFG vs. IGT ($p < 0.05$)*.

[d] NG vs. IFG; NG vs. IFG/IGT; NG vs. DM; IFG vs. DM; IGT vs. DM; IFG/IGT vs. DM ($p < 0.05$)*.

[e] NG vs. IFG, NG vs. IGT; NG vs. DM; IFG vs. DM; ($p < 0.05$)*.

[f] NG vs. IFG ($p < 0.05$).

[g] NG vs. IFG; NG vs. IFG/IGT; NG vs. DM ($p < 0.05$)*.

[h] NG vs. IFG; NG vs. IFG/IGT; NG vs. DM; IFG vs. DM; IFG vs. IGT; IGT vs. IFG/IGT; IGT vs. DM; IFG/IGT vs. DM ($p < 0.05$)*.

*All comparisons.

respectively ($p < 0.001$). The prevalence of specific abnormalities of the MetS was directly associated with worsening glucose tolerance (Fig. 1). The most frequent combination in factors of MetS in all categories of glucose tolerance were abdominal obesity and hypertension.

The prevalence of MetS without DM was 27% when we used specific cut-off point of WC for our Spanish population, and lowered to 24.2% when we used European cut off point of WC (≥102 cm in males and ≥88 cm in females).

Independent associations of MetS with age, sex, smoking (in males), glucose tolerance, IR, obesity, alcohol intake, and education were also examined in a different logistic regression model (Table 3). MetS was directly associated with age, female gender, IFG, IFG/IGT and DM, and inversely associated with low alcohol consumption, and high education level, Table 3. IGT and physical activity were not independently associated with MetS (data not shown for Physical activity), although IGT remained closely related (IGT OR: 1.51; 95%CI 0.99–2.31, $p = 0.04$). Smoking habit was related to MetS in males (smoker and former smoker), but in females this relationship was inverse for former smokers as compared to non smokers.

The risk estimation by Framingham and SCORE (Table 4) showed that IGT had a higher estimated CVD risk than IFG/IGT. The presence of MetS increases the risk by Framingham 4.85 times and 2.43 times by SCORE. The estimated CVD risk associated to IFG was similar to NG subjects by both charts, and oppositely significantly higher, more than double according to SCORE, for IGT category.

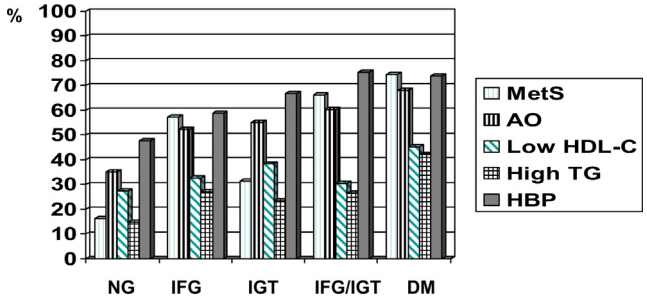

Fig. 1 – Prevalence of the metabolic syndrome and its abnormalities according to glucose tolerance categories. MetS: metabolic syndrome; AO: abdominal obesity, Low HDL-C: low high-density lipoprotein; High TG: high triglycerides; HBP: high blood pressure.

4. Discussion

In the present study we found a prevalence of 16.6% of IFG, 5.0% of IGT, 3.3% of IFG/IGT, and 7.5% of DM. The prevalence of MetS was 31.2%, higher in males than in females. The prevalence of the MetS in participants with NG, IFG, IGT, IFG/IGT, and DM was 16.3, 57.1, 31.5, 66.1, and 74.4%, respectively. CVD risk estimated by Framingham and SCORE showed that IGT was associated to a higher estimated CVD risk than NG, IFG and IFG/IGT subjects. There was no higher CVD risk associated to IFG as compared to NG subjects by both charts. CVD risk was significantly higher for MetS subjects by Framingham and more than double by SCORE, as compared to NG subjects.

As for the relationships between prediabetes and CVD risk, Ford et al. published a thorough systematic review [31] based on a critical in-depth literature search on this issue, in which the most important finding can be summarized as follows: 18 reports examined IFG, and fixed effects concluded that relative risk [RR] estimates for CVD was 1.20. Another 8 reports looked at IFG, fixed effects remarks that the RR estimated was 1.18. In 8 reports on IGT, the estimated RR was 1.20. Five studies combined IFG and IGT, where the summary RR was 1.10 [32]. Well then, our calculated OR seems to be partially in accordance with these results. Additionally, two large meta-analysis [33,34] have shown that a diagnosis of MetS raises the risk for CVD by approximately two fold. These authors suggest that as a high proportion of patients with MetS had prediabetes, it could in fact influence the higher associated MetS CVD risk.

Table 3 – Logistic regression model with metabolic syndrome as dependent variable.

Independent variables	OR	95% CI	p^a
Age (years)			
≥35–40	1.00		
>40–50	1.19	0.85–1.69	0.30
>50–60	1.64	1.37–2.35	0.01
>60	1.62	1.10–2.38	0.01
Glucose tolerance			
NG	1.00		
IFG	6.71	5.22–8.64	<0.001
IGT	1.51	0.99–2.31	0.04
IFG/IGT	9.67	6.05–15.46	<0.001
DM	10.74	7.45–15.48	<0.001
HOMA-IR (≥3.8)	1.73	1.37–2.18	<0.001
Alcohol intake			
0 g/day	1.00		
1–14.99 g/day	0.61	0.46–0.80	<0.001
≥15–29.99 g/day	0.73	0.54–0.98	0.07
≥30 g/day	1.15	0.81–1.65	0.48
Education level			
No formal	1.00		
Primary	0.65	0.49–0.84	0.003
Secondary	0.73	0.53–1.00	0.132
University	0.47	0.29–0.77	0.01

	Males			Females		
	OR	95% CI	p	OR	95%CI	p^a
Cigarette smoking						
Non smokers	1.00			1.00		
Smokers	2.12	1.43–3.14	<0.001	1.25	0.80–1.94	0.33
Former smokers	1.74	1.17–2.61	0.01	0.53	0.30–0.93	0.03
Obesity						
(BMI ≥30 kg/m^2)	5.29	3.83–7.85	<0.001	9.01	6.67–12.17	<0.001

OR: Odds ratio; CI: confidence interval; NG: normal glucose tolerance; IFG: impaired fasting glucose; IGT: impaired glucose tolerance; DM: diabetes mellitus.
[a] Likelihood ratio to model.

Table 4 – Logistic regression model with Framingham risk (≥20%) and CV Risk SCORE (≥5%) as dependent variables.

	OR	95% CI	p
Framingham risk (≥20%)			
NG	1.00		0.001
IFG	0.97	0.73–1.29	0.86
IGT	1.68	1.10–2.55	0.02
IFG/IGT	1.32	0.82–2.12	<0.001
MetS	4.85	3.80–6.20	<0.001
CV risk score (≥5%)			
NG	1.00		0.001
IFG	1.03	0.67–1.57	0.88
IGT	2.53	1.51–4.22	<0.001
IFG/IGT	2.06	1.13–3.75	0.02
MetS	2.43	1.72–3.45	<0.001

OR: Odds ratio; CI: confidence interval; NG: normal glucose tolerance; IFG: impaired fasting glucose; IGT: impaired glucose tolerance; MetS: metabolic syndrome.

The higher CVD risk related to MetS is probably the consequence of additive risks of a proinflammatory state or disorders different from glucose disturbances, since IFG did not confer a higher CVD risk by any of the charts and IGT showed lower than double risk by Framingham. These results are in accordance with previous reports, as IFG an IGT have been associated with modest progressive increases in the CVD risk [31,35].

Furthermore, in a report by Onat et al., when MetS is considered analyzing the CVD risk of IFG subjects, the CVD risk is not higher for IFG subjects without MetS, compared to NG subjects [36]. Low serum Lp(a), mediated by immune activation, could be a determinant of CVD risk in subjects with IFG and MetS [37].

Using the 1999 World Health Organization (WHO) Criteria, the DECODE [38] study group reported the age and sex-specific prevalence of DM and impaired glucose regulation (IGR) in 15,606 subjects from 13 European cohorts. Most of these populations had a moderate to low prevalence of DM. Nevertheless, Impaired Glucose Regulation (IGR) could be underestimated in Europe in this study, particularly in women and elderly men, because the diagnosis was based on fasting glucose determination alone and because the WHO criteria included cut off levels of glucose ≥6.1 mmol/l (110 mg/dl). This study partially included our experience in the Spanish population [38]. In a subsequent report of the DECODE group, IGT was more strongly associated with age than HOMA-IR and IFG [39].

Recently in Spain, the nationwide Di@bet.es study [10], revealed that 30% of the population had some carbohydrate disturbance, representing a slightly higher prevalence than in our current study, perhaps as a consequence of the rising glucose disturbances prevalences in Spain in the past decade. In fact, the overall prevalence of DM in this more recently enrolled cohort was significantly higher (13.8%). Of this 13.8% about half had unknown diabetes, in contrast to all previous Spanish cohorts, including ours. The prevalence rate of isolated IFG was 3.4%; surprisingly low as compared to the 16.6% found in our population, and finally, IGT and combined IFG/IGT were 9.2% and 2.2%, respectively. In the Canary Islands, Novoa et al. [40] found in 902 nondiabetic subjects between 30 and 80 years of age that 14.6% participants had isolated IFG, 6.5% isolated IGT, and 5.3% combined IFG/IGT, more in accordance with our results.

In a large tri-ethnic population including nondiabetic individuals, Festa et al. reported that individuals with isolated IGT are more IR than individuals with isolated IFG, which may explain the increased CVD risk associated with IGT [41].

Other studies that used HOMA as a marker of IR have shown that individuals with IFG have increased IR [42,43]. Our results also indicate that IR is increased in subjects with isolated IFG or IFG/IGT.

As for the prevalence of the MetS in Spain, there are very few nation-wide or population based recent studies. The dia@betes study, carried out in 2009 [28], applied the Harmonized definition using regional cut-off points, and found moderately higher prevalence in men but similar in females. Another Spanish study called ENRICA [44], based on a representative cross-sectional cohort carried out from 2008 to 2010, reported a lower prevalence of 22.7%, probably because Harmonized definition was considered with the European cut-off points of WC [≥102 in males ≥88 in females]. Nevertheless, Berges et al. [45], studying 11 cohorts recruited in the first decade of 21st century from different Spanish communities and applying the Harmonized criteria with the European WC criterion, found a prevalence of 31% [32% in males, 29% in females]. It seems that differences in prevalence are partially explained by the different WC criterion used and do not reflect a really significant increase in the MetS prevalence in the past decade in Spain.

Several studies have demonstrated a positive association between smoking and metabolic abnormalities [46,47]. Other authors support the idea that MetS is an underlying mechanism which links smoking with atherosclerosis [48]. Here, we also confirmed an association between MetS and smoking habit in males (smoker and former smoker). Smoker females have not a higher prevalence of MetS compared to non smokers. As described by others, it may be a relationship between MetS and education [41,49]. On the other hand, our results indicate that moderate alcohol consumption was associated with a lower prevalence of MetS. This finding is consistent with the results reported by others [50,51] and also by a previous report by our group [52]. However, other studies have been discordant and did not find a significant relationship between the prevalence of MetS and alcohol intake [53,54].

In Spain we are aware of just one prospective population based study aimed to examine CVD in people with prediabetes which is currently taking place.

Finally, we acknowledge some limitations of our study, such as the cross-sectional design, which does not allow establishing causality. Longitudinal studies are needed to confirm our results. Our study was not designed with a target population of the entire country, although it was population-based in 21 small and middle-sized towns across the north to south of Spain. Nevertheless, we believe that this population is representative of the Spanish general population as we have compared our cohort with the Census of the National Institute of Statistics of Spain (www.ine.es) for the same years and found that they were nearly identical in age and sex.

5. Conclusions

According to our results: (1) The prevalences of prediabetes and MetS in Spain were 25% and 31.2%, respectively. (2) On the other hand, the prevalence of MetS has remained stable in the last decade in Spanish females (28.5%) but has slightly increased in males (34.2%). (3) Subjects with IGT showed a higher estimated cardiovascular disease risk than IFG and IFG/IGT by Framingham (≥20%) and SCORE (≥5%) risks charts. (4) MetS also increased the cardiovascular disease risk estimated by Framingham and SCORE. (5) As diabetes prevalence is rising in Spain and somehow becoming an epidemic burden disease (as in other developed countries), strategies for early diagnosis and treatment should be implemented.

Conflict of interest

No conflicts of interest related to this work are declared.

Author's contributions

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