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Women show worse control of type 2 diabetes and cardiovascular disease risk factors than men: Results from the MIND.IT Study Group of the Italian Society of Diabetology

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Abstract *Background and aims:* The study explores the degree of control of hyperglycaemia and cardiovascular (CV) disease risk factors in men and women with type 2 diabetes and the impact thereon of obesity, central adiposity, age and use of medications.
Methods and results: A cross-sectional survey was conducted at 10 hospital-based outpatients diabetes clinics. 1297 men and 1168 women with no previous CV events were studied. Women were slightly (only one year) older and more obese than men: average BMI was respectively 30.7 ± 5.7 vs 28.6 ± 4.1 kg/m^2 ($p < 0.001$), and prevalence of abdominal obesity was 86% vs 44% ($p < 0.001$). Women smoked less, but had higher HbA1c, LDL cholesterol, non-HDL cholesterol, systolic blood pressure and serum fibrinogen than men. Accordingly optimal targets for HbA1c (<7%), LDL cholesterol (<100 mg/dL), HDL cholesterol (>40 for men, >50 for women, mg/dL), and systolic blood pressure (<130 mmHg) were less frequently achieved by women than men (respectively 33.8% vs 40.2%; 14.6% vs 19.2%; 34.1% vs 44.5%; 68.8% vs 72%; $p < 0.05$ for all). Findings were confirmed after stratification for waist circumference ($<$ or $\geq$ 88 cm for women; $<$ or $\geq$ 102 cm for men), BMI ($<$ or $\geq$ 25 kg/m^2) or age ($<$ or $\geq$ 65 years). As for treatment, women were more likely than men to take insulin, alone or in combination with oral hypoglycaemic drugs, to be under anti-hypertensive treatment, whereas the use of lipid lowering drugs was similar in men and women.

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Conclusions: Control of hyperglycaemia and major CVD risk factors is less satisfactory in women than men. The gender disparities are not fully explained by the higher prevalence of total and central obesity in women; or by a less intensive medical management in women.
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In women with type 2 diabetes cardiovascular disease (CVD) is the leading cause of morbidity and mortality [1]. In female diabetic patients the "hormonal protection" against CVD, usually seen in non diabetic pre-menopausal women, is less pronounced and several prospective cohort studies [1—3], have demonstrated that diabetes confers a greater increase of cardiovascular risk in women than in men. In a recent meta-analysis of 37 studies the relative risk for fatal coronary heart disease (CHD) conferred by diabetes was 50% higher in women than in men [4]. In addition, whereas CHD mortality has declined at a similar rate in men with or without diabetes in the last twenty-five years in the U.S. population, diabetic women have experienced an increase in CHD deaths over the same period of time [5,6], and the adverse effect of diabetes is particularly evident in younger women [7].

Among others, a greater burden of CVD risk factors in women has been postulated as a possible explanation [8]. Studies conducted in US and Northern Europe have found poorer control of blood pressure and LDL cholesterol in female compared to male patients [8—14]; disparities in the treatment that disadvantage women were also found in most studies [9—11]. No data are available so far from Southern Europe, in addition only a few studies put the sex disparities into perspective with age and BMI [9,11,15—17], and none has explored the role of abdominal obesity. Older age and obesity, particularly of the visceral type are more prevalent in women than in men with diabetes and are, *per se*, associated with insulin resistance, CVD risk factors and subclinical inflammation [1].

This study investigates, in a Southern European cohort of people with type 2 diabetes, the degree of control of hyperglycaemia and major CVD risk factors in men and women and the impact thereon of age, BMI, abdominal adiposity, and medical management. To this purpose we used the cross-sectional data of the Multi-factorial Intervention in type 2 Diabetes in Italy (MIND.IT) study, a large study of people with type 2 diabetes, representative of the diabetic population followed at hospital-based outpatients diabetes clinics.

Methods

MIND.IT is a two-phase study which includes an observational survey and a cardiovascular primary prevention trial in type 2 diabetic patients. The observational survey was performed in 2004—2006 in 10 large diabetes clinics nationwide. The participating centres were invited to consecutively enrol about 250 eligible individuals. The main eligibility criteria were: diagnosis of type 2 diabetes for at least two years; age 50—70 years; no prior CV events; serum creatinine <1.5 mg/dL; no liver disease.

At the screening visit a detailed explanation of the study aims and procedures was given and a written informed consent was obtained. A complete medical history, including current use of medications, was obtained by patients' interview. A full physical examination, with assessment of sitting blood pressure, heart rate, weight, height and waist circumference (WC), was performed

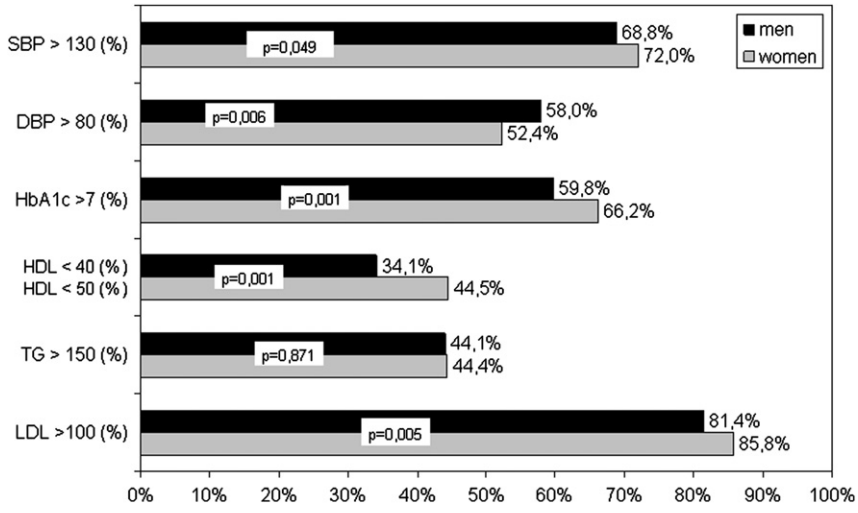


Figure 1 Proportion (%) of men and women out of target for glycated haemoglobin and the cardiovascular risk factors measured in the study. Abbreviations: SBP, systolic blood pressure; DBP, diastolic blood pressure; HbA1c, glycated haemoglobin; HDL, HDL cholesterol; TG, triglycerides; LDL, LDL cholesterol.

Table 1 Clinical characteristics and major cardiovascular disease risk factors in men and women by abdominal obesity status.

Variables	Without abdominal obesity		*p*	With abdominal obesity		*p*
	Women ($n = 159$)	Men ($n = 696$)		Women ($n = 963$)	Men ($n = 543$)	
Age (years)	62 ± 5	60 ± 6	**0.008**	61 ± 5	60 ± 5	0.087
Diabetes duration (years)	9 (8)	9 (7)	0.652	9 (7)	8 (7)	0.093
Waist circumference (cm)	80.8 ± 6.0	93.6 ± 6.1	**0.001**	103.5 ± 10.9	110.0 ± 7.1	**0.001**
BMI (Kg/m^2)	24.8 ± 3.9	26.5 ± 2.8	**0.001**	31.7 ± 5.5	31.4 ± 3.8	0.312
Systolic blood pressure (mmHg)	142 ± 18	140 ± 16	0.154	143 ± 17	142 ± 15	0.198
Diastolic blood pressure (mmHg)	84 ± 9	84 ± 9	0.762	84 ± 9	86 ± 9	**0.001**
Heart rate (beat/min)	73 ± 8	71 ± 10	**0.032**	75 ± 11	72 ± 10	**0.001**
Fasting plasma glucose (mg/dL)	159 ± 52	151 ± 43	**0.042**	161 ± 46	157 ± 40	0.141
Glycated haemoglobin (%)	7.6 ± 1.3	7.4 ± 1.3	**0.042**	7.7 ± 1.4	7.6 ± 1.4	**0.025**
HDL cholesterol (mg/dL)	56 ± 14	47 ± 12	**0.001**	52 ± 13	45 ± 10	**0.001**
Triglycerides (mg/dL)	120 (92)	135 (93)	0.152	142 (95)	153 (111)	**0.001**
LDL cholesterol (mg/dL)	140 ± 36	131 ± 34	**0.008**	135 ± 34	129 ± 34	**0.001**
Non-HDL cholesterol (mg/dL)	167 ± 39	161 ± 37	**0.050**	167 ± 37	163 ± 38	**0.039**
Fibrinogen (mg/dL)	330 ± 92	318 ± 73	0.124	345 ± 84	327 ± 80	**0.001**
Current smokers (%)	38 (24.2%)	210 (30.2%)	0.145	157 (16.4%)	133 (24.6%)	**0.001**

Abdominal obesity is defined as waist circumference ≥ 88 cm for women and ≥102 cm for men. Data is given as mean ± SD or median and (inter-quartile range) or as number and (%).
Significant values ($p < 0.05$) are highlighted in bold.

following a standardized protocol described in detail elsewhere [18]. Fasting plasma glucose, total and high density lipoprotein (HDL) cholesterol, triglycerides, glycated haemoglobin (HbA1c) and fibrinogen were measured. Low density lipoprotein (LDL) cholesterol was calculated according to Friedwald, non-HDL cholesterol was calculated as the difference between total and HDL cholesterol.

Biochemical analyses were performed at each centre. Prior to enrolment (start-up phase) an External Quality Assessment Service (EQAS) was performed in all the laboratories involved to verify the comparability and reliability of analytical methods, and to reach a standard of quality and traceability among the participating centres. All EQAS data were pooled together and normalized to target values; the bias % was calculated and a correction factor was applied for laboratories whose bias % exceeded (±) the accuracy criteria set by the Centre for Disease Control (CDC, Atlanta GA, USA). This service was provided by the Clinical Chemistry Standardization Laboratory of the San Raffaele Hospital (Milan, Italy).

The protocol was approved by the local ethics committees and is available at www.SIDitalia.it/research projects.

Table 2 Clinical characteristics and major cardiovascular disease risk factors in men and women by age.

Variables	Age < 65		*p*	Age ≥ 65		*p*
	Women ($n = 800$)	Men ($n = 944$)		Women ($n = 368$)	Men ($n = 353$)	
Age (years)	58 ± 4	58 ± 4	0.189	67 ± 2	67 ± 2	0.612
Diabetes duration (years)	7 (7)	7 (7)	0.703	10 (11)	9 (11)	0.788
Waist circumference (cm)	101 ± 13	101 ± 11	0.565	100 ± 13	101 ± 10	0.350
BMI (Kg/m^2)	31.1 ± 5.7	28.8 ± 4.0	**0.001**	29.8 ± 5.7	28.2 ± 4.1	**0.001**
Systolic blood pressure (mmHg)	141 ± 17	139 ± 15	**0.014**	146 ± 17	145 ± 16	0.310
Diastolic blood pressure (mmHg)	84 ± 9	85 ± 9	0.050	84 ± 8	84 ± 9	0.426
Heart rate (beat/min)	75 ± 10	72 ± 10	**0.001**	74 ± 12	72 ± 11	**0.007**
Fasting plasma glucose (mg/dL)	159 ± 47	153 ± 42	**0.002**	161 ± 48	157 ± 43	0.176
Glycated haemoglobin (%)	7.7 ± 1.5	7.5 ± 1.4	**0.001**	7.7 ± 1.3	7.5 ± 1.2	**0.038**
HDL cholesterol (mg/dL)	52 ± 13	45 ± 11	**0.001**	54 ± 13	48 ± 12	**0.001**
Triglycerides (mg/dL)	139 (91)	131 (33)	0.066	138 (98)	132 (90)	0.663
LDL cholesterol (mg/dL)	135 ± 34	131 ± 33	**0.014**	136 ± 33	128 ± 36	**0.001**
Non-HDL cholesterol (mg/dL)	166 ± 38	163 ± 37	0.092	167 ± 36	157 ± 37	**0.001**
Fibrinogen (mg/dL)	338 ± 83	319 ± 74	**0.001**	354 ± 87	331 ± 81	**0.001**
Current smokers (%)	142 (17.8%)	287 (30.4%)	**0.001**	55 (15.0%)	68 (19.3%)	0.138

Data are given as mean ± SD or median and (interquartile range) or as number and (%).
Significant values ($p < 0.05$) are highlighted in bold.

The study was registered at www.clinicaltrials.gov (NCT01240070).

Statistical analyses

The variables distribution was evaluated by the Kolmogorov–Smirnov test. Normally distributed variables are expressed as mean and standard deviation (SD), while not normally distributed variables as median and inter-quartile range.

Differences were tested by Chi-square for proportions, and by unpaired Students *t*-test or Wilcoxon test, as appropriate, for continuous variables. Analyses were conducted in the population as a whole and also after stratification for abdominal obesity, based on waist circumference (WC) cut off established by the ATP III ($<$ or $\geq$ 88 cm for women, $<$ or $\geq$ 102 cm for men); BMI ($<$ or $\geq$ 25 kg/m^2) or age ($<$ or $\geq$ 65 years), i.e. the WHO cut off for elderly populations (http://www.who.int/healthinfo/survey/ageingdefnolder/en/index.html).

Statistical analysis was performed using the SPSS software, version 17 (SPSS Inc., IL, US). Differences were considered significant at $p < 0.05$, two tails.

Results

All together 1297 men and 1168 women were studied. On average women were slightly, but significantly older than men (61 $\pm$ 5 vs 60 $\pm$ 5 years, $p = 0.007$), had a substantially higher BMI (30.7 $\pm$ 5.7 vs 28.6 $\pm$ 4.1 kg/m^2, $p < 0.001$), and a much higher prevalence of abdominal obesity (86% vs 44%, $p < 0.001$). Apart from smoking, which was less frequent in women (27.5% vs 16%, $p < 0.001$), the CVD risk factors profile was more unfavourable in women compared to men. Fig. 1 shows the proportion of women and men not at target for the CVD risk factors measured in the study: women were significantly less likely than men to achieve target values for systolic blood pressure, LDL and HDL cholesterol, and HbA1c; for diastolic blood pressure women were more frequently at target than men; and there was no difference in the proportion of women and men not reaching the triglycerides target value of 150 mg/dL.

To explore the confounding role of central adiposity glucose control and the CV risk factors profile were compared in men and women after stratification for WC (Table 1). In the group without abdominal obesity women had a BMI within the normal range (24.8 $\pm$ 3.9 kg/m^2) and significantly lower than men (26.5 $\pm$ 2.8 kg/m^2), $p < 0.001$; nonetheless, LDL cholesterol and HbA1c were significantly higher in women than in men. In the group with abdominal obesity, men and women had a similar BMI (31.4 $\pm$ 3.4 vs 31.7 $\pm$ 5.5 kg/m^2, $p = 0.312$), but significantly higher HbA1c, non-HDL cholesterol and fibrinogen. Similar results were obtained after stratification for BMI: in the normal weight group (BMI $<$ 25 kg/m^2); women maintained higher levels of LDL and non-HDL cholesterol. In the overweight/obese group (BMI $\geq$ 25 kg/m^2) women had a worse lipid profile, higher HbA1c, SBP and fibrinogen than men (data not shown).

In Table 2 the CVD risk factors profile for men and women was compared within age strata (below or above

Table 3 Treatment for diabetes and major cardiovascular disease risk factors in men and women stratified for abdominal obesity or age.

Variables	Without abdominal obesity		*p*	With abdominal obesity		*p*	Age $<$ 65			Age $\geq$ 65		*p*
	Women (n = 159)	Men (n = 696)		Women (n = 963)	Men (n = 543)		Women (n = 800)	Men (n = 944)		Women (n = 368)	Men (n = 353)	
Hypoglycaemic treatment												
Diet only (%)	36 (22.6)	122 (17.5)	0.145	123 (12.8)	75 (13.8)	0.141	123 (15.4)	162 (17.2)	0.330	49 (13.3)	50 (14.2)	0.747
Oral agents only (%)	102 (64.2)	498 (71.6)	0.069	677 (70.3)	409 (75.3)	**0.041**	558 (69.8)	677 (71.7)	0.370	244 (66.3)	256 (72.5)	0.076
Insulin alone or in combination with OA (%)	21 (13.2%)	76 (10.9)	0.407	163 (16.9)	59 (10.9)	**0.001**	119 (14.9)	105 (11.1)	**0.021**	75 (20.4)	47 (13.3)	**0.013**
Antihypertensive treatment (%)	77 (48.4%)	337 (48.4)	1.000	671 (69.7)	338 (62.2)	**0.004**	509 (63.6)	484 (51.3)	**0.001**	263 (71.5)	217 (61.5)	**0.005**
2 or more anti-hypertensives drugs (%)	22 (28.6%)	98 (29.0)	0.742	148 (32.1)	90 (26.1)	**0.040**	147 (36.6)	117 (24.0)	**0.001**	69 (33.2)	47 (25.7)	0.121
Lipid lowering treatment (%)	42 (26.4%)	189 (27.2)	0.921	268 (27.8)	149 (27.4)	0.905	211 (26.4)	257 (27.2)	0.704	105 (28.5)	88 (24.9)	0.313
Anti-platelet treatment (%)	32 (20.1%)	146 (21.0)	0.914	185 (19.2)	142 (26.2)	**0.002**	139 (17.4)	209 (22.1)	**0.014**	86 (23.4)	89 (25.3)	0.304

Abdominal obesity was defined as waist circumference $\geq$ 88 cm for women or $\geq$ 102 cm for men. Data are given as absolute number and (%).
Significant values ($p < 0.05$) are highlighted in bold.

65 years). In both groups women had significantly higher HbA1c, LDL cholesterol, and fibrinogen; in addition in the younger group women had also higher SBP.

To further confirm that differences between men and women were independent of age and adiposity, we performed a multivariate analysis by a general linear model, entering CV risk factors as dependent variables; age, duration of diabetes, and waist circumference (or alternatively BMI) as covariates; and gender as fixed factor. The results confirmed the observed differences between men and women independent of age, BMI or WC (data not shown).

Medication use for the treatment of diabetes and major CV risk factors is reported in Table 3 for women and men by WC and by age strata. In the group without abdominal obesity no significant differences were observed between men and women. In the group with abdominal obesity the use of insulin - alone or in combination with oral agents — was more frequent in women (16.6% vs 11.7% $p < 0.001$), as was the use of anti-hypertensive medication (66.1% vs 54%, $p < 0.001$) and also the combination of two or more anti-hypertensive agents (32.1% vs 26.1% $p = 0.040$). The proportion of men and women on lipid lowering drugs (26.6% vs 27.1%, $p = 0.569$) was similar, whereas anti-platelet treatment was less common in women (19.3% vs 23.0% $p = 0.014$). As for age (Table 3), women were more intensively treated than men at all ages. In both the younger and the older group women were more frequently treated with insulin than men (14.9% vs 11.1%, $p = 0.021$ and 20.4% vs 14.4%, $p = 0.013$) and with anti-hypertensive medications (63.6% vs 51.3%, $p = 0.001$ and 71.5% vs 61.5%, $p = 0.005$). In addition, in the younger group (below age 65) a higher proportion of women compared to men was treated with a combination of two or more anti-hypertensive drugs (36.6% vs 24%, $p = 0.001$).

Conclusions

The study shows, in a southern European cohort of people with type 2 diabetes and no previous CVD, that women are significantly less likely than men to achieve target values for systolic blood pressure, LDL and HDL cholesterol; fasting plasma glucose and HbA1c. Obesity and central adiposity are significantly more prevalent in women, but the observed gender differences are only partially accounted for by the greater prevalence of obesity or central obesity in women; they are, in fact, more pronounced in obese or centrally obese women and are attenuated, but not offset, after stratification for waist circumference or BMI. In addition the gender gap was confirmed at younger and older ages and it was not explained by a less intensive medical management of diabetes or CVD risk factors in women, as judged by the larger proportion of women on insulin, or on anti-hypertensive medications.

These findings are partially in keeping with previous reports and further expand current knowledge [19—23]. A gender difference in the CVD risk factors profile in people with diabetes has been, in fact, reported in other populations, but only few studies have put the gender gap into perspective with age and obesity. In the UK diabetic population described by Guthrie et al. [15], women are less likely to reach cholesterol targets than men, independent of BMI. Diabetic female patients with established CHD were less frequently on target for LDL cholesterol and HbA1c in the cohort of Wexler et al. [10] and for LDL cholesterol and systolic blood pressure in the Translating Research Into Action for Diabetes (TRIAD) study [11], independent of age. In a large population of about 44,000 type 2 diabetic people with prior CVD from Germany [14], LDL cholesterol, HbA1c and blood pressure were less likely to be on target in women than in men after adjustment for age and BMI. To our knowledge no prior study has investigated the impact of central adiposity, a condition particularly common in diabetic women and associated more closely than BMI, with insulin resistance [16,24], and an adverse CV risk factors profile.

As for medical management the more frequent treatment with insulin and anti-hypertensive drugs in women documented in our population is in contrast with most existing studies where the limited target achievement in CVD risk factors was accompanied by less prescriptions of drugs in women than in men [10,14]. However not all observations go in this direction. No gender difference in the prescriptions of anti-hypertensive and lipid lowering drugs was reported by Ferrara [11], and Mc Farlane [9], furthermore a study conducted in Northern Italy [25] showed higher HbA1c in women than in men, despite a more intensive hypoglycaemic treatment in women, thus lending support to our findings. As in the present study, the treatment was self reported by the study participants of that study. However we analysed the treatment(s) as reported by patients and we believe that this information reflects the actual medication compliance better than use of physician prescription data. Further speculation on treatment is limited by the lack of information on dosage and lack of information on hypoglycaemic events.

Among others lifestyle related factors, socio-economic status, and education, may explain the gender gap in the control of diabetes and modifiable CV risk factors [26]. None of these were investigated in our study, however in a subgroup of this same cohort habitual diet, assessed by the seven days food record, was similar in men and women; in particular the intake of carbohydrates, saturated fat, cholesterol, and salt, was not different for men and women [27], thus suggesting that major gender differences in dietary patterns are an unlikely explanation for our findings.

Based on current knowledge the reasons for the gender gap in the burden of CV risk factors remain largely unknown. Lately the hypothesis of a sexual dimorphism in the response to treatments is receiving increasing attention. A recent metanalysis of randomized controlled trials has shown that diabetic women are less responsive than diabetic men to the protective effect of aspirin treatment in the primary prevention of CVD [28]. A review of the trials reporting gender-specific effect sizes of anti-hypertensive medications indicates that drugs which target the RAS system — angiotensin converting enzyme inhibitors (ACEs) and angiotensin receptor blockers (ARBs) — may be less effective in women than in men in the prevention of cardiovascular events [29]. Due to paucity of trials that have included diabetic women it is not known to what extent this may apply to diabetic people.

The major limitation of the study is the "cross-sectional" design, that, by definition, does not permit to explore "cause-consequence" relationships and can only describe the clinical reality. Because of this, we can only speculate on the possible explanations for the observed gender differences and their impact on outcomes cannot be assessed. This is relevant also considering that women have greater longevity and tend to present CV events at later age [1,2]. Among the study limitation we must also acknowledge the lack of information on menstrual cycle, although considering the mean age of the population most women were presumably post-menopausal, nonetheless assessment of hormonal status would add relevant information.

In conclusion, findings of this study expand current knowledge by establishing in a Southern European population a poorer control of diabetes and modifiable CVD risk factors in diabetic women compared to men, independent of abdominal obesity, total obesity, older age and medical management. Based on the proven cost-effectiveness of optimal glucose, lipid and blood pressure control in reducing macro and microvascular events in patients with diabetes, more intensive treatment should be pursued in women.

Conflict of interest

None.

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