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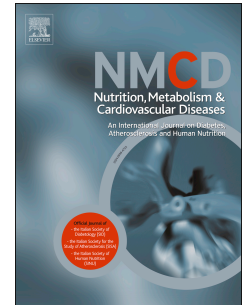
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Sex differences in food choices, adherence to dietary recommendations and plasma lipid profile in type 2 diabetes – The TOSCA.IT Study

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72 **Abbreviations used:** CVD, cardiovascular disease; CV, cardiovascular; CHD, coronary heart
73 disease; BMI, body mass index; HbA1c, glycated hemoglobin; DNSG, Diabetes and Nutrition
74 Study Group; SID, Italian Diabetes Society; SAFA, saturated fatty acid.

75

76 **Abstract**

77 **Background and aims:** Diabetic women have a more adverse plasma lipid profile than men. Sex
78 differences in dietary habits may play a role, but are little investigated. The study evaluates the
79 quality of diet, adherence to the nutritional recommendations of the Diabetes and Nutrition Study
80 Group and their relation with plasma lipid in men and women with diabetes.

81 **Methods and results:** We studied 2573 people, aged 50-75, enrolled in the TOSCA.IT study
82 (clinicaltrials.gov; NCT00700856). Plasma lipids **were** measured centrally. Diet **was** assessed with
83 a semi-quantitative food frequency questionnaire. Women **had** a more adverse plasma lipid profile
84 than men. Women **consumed** significantly more legumes, vegetables, fruits, eggs, milk, vegetable
85 oils, and added sugar, whereas men **consumed** more starchy foods, soft drinks and alcoholic
86 beverages. This stands for a higher proportion (%) of energy intake from saturated fat and added
87 sugar (12.0 ± 2.4 vs 11.5 ± 2.5 and 3.4 ± 3.2 vs 2.3 ± 3.2 , $p < 0.04$), and a higher intake of fiber (11.2 ± 2.8
88 vs 10.4 ± 2.6 g/1000Kcal/day) in women. Adherence to the recommendations for saturated fat and
89 fiber consumption **was** associated with significantly lower LDL-cholesterol regardless of sex.
90 Adherence to the recommendations for added sugars **was** associated with significantly lower
91 triglycerides and higher HDL-cholesterol in men and women.

92 **Conclusions:** Men and women with diabetes show significant differences in adherence to
93 nutritional recommendations, but sex differences in plasma lipid profile are unlikely to be explained
94 by nutritional factors. Adherence to the nutritional recommendations is associated with a better
95 plasma lipid profile regardless of sex, thus reinforcing the importance of substituting saturated for
96 unsaturated fat sources, increasing fiber and reducing added sugar intake.

97

98 **Keywords:** Diabetes; Dietary habits, Nutritional recommendations; Sex differences; Men; Women;
99 Cardiovascular risk factors

100 **Introduction**

101 There is convincing evidence that diabetes increases the risk of cardiovascular disease (CVD) to a
102 greater extent in women as compared with men (1). Although the absolute cardiovascular risk
103 remains lower in diabetic women as compared to diabetic men, relative risk for CVD morbidity and
104 mortality in diabetic versus non-diabetic people is generally higher in women, ranging from 1 to 3
105 in men and from 2 to 5 in women.

106 The causes of this sex difference are not completely understood. Several **hypotheses** have been **put**
107 **forward**. A greater burden and poorer control of CV risk factors in women with diabetes compared
108 to men **has been reported** (2-4); **furthermore**, a lower risk perception **by the patients and/or** by
109 health care providers **may lead to** a less intensive treatment in women. **Finally, response to**
110 **treatments may differ in men and women** (5, 6). Among others sex differences in dietary habits,
111 due to biological, cultural, behavioral, psychological or socio-economic factors may play a role, but
112 are little investigated.

113 The medical nutrition therapy is a cornerstone in the treatment of diabetes; the main goal is to
114 improve glucose control and the cardiovascular risk factors profile. However, adherence to the
115 nutritional guidelines is generally poor (7-9). The most unattended recommendations are those on
116 fat and fiber, whose consumption is respectively higher and lower than recommended, and reflects
117 the wider problem of **the overabundance of** saturated fat and refined cereals in the western diet. In
118 addition, the amount of added sugar that can be safely tolerated in people with diabetes is still
119 debated. Recent prospective studies in non-diabetic people **have shown** a dose-dependent effect of
120 the consumption of sweetened beverages on plasma lipid and CVD mortality (10, 11).

121 **No previous studies have evaluated sex differences in food choices and nutrients intake and**
122 **their relation with the plasma lipid profile in people with type 2 diabetes. This is relevant to**
123 **investigate in view of the more adverse lipid profile and the greater increase in CV risk**
124 **conferred by diabetes in women.**

125 Whether men and women with diabetes have different adherence to dietary recommendations for
126 the management of diabetes, and to what extent this may contribute to the more adverse lipid profile
127 reported in women, it is not known. A better knowledge of this issue would be in line with recent
128 views of gender medicine and **may potentially** address therapeutic strategies.

129 The aim of the study is **to** investigate, in a large, nationally representative, cohort of men and
130 women with type 2 diabetes, the quality of diet, the adherence to the nutritional recommendations
131 with regard to fat, fiber and added sugars and their relation with the plasma lipid profile.

132

133 **Methods**

134 We studied 2573 people with type 2 diabetes, 1535 men and 1038 women, aged 50 to 75, enrolled
135 in the TOSCA.IT study, a randomized clinical trial designed to compare the impact of glucose
136 lowering drugs on cardiovascular events (clinicaltrials.gov NCT00700856). The study protocol has
137 been published (12). The study participants were recruited in 60 centers distributed all over Italy.
138 The Ethics Review Committee of the Coordinating Centre and of each participating centre have
139 approved the study protocol, and written informed consent was obtained from all participants.

140 In this study baseline data, collected prior to randomization to study treatments, were used. Patients
141 with co-morbidities requiring a special dietary treatment were excluded from the analysis. Among
142 others body weight, height, waist and hip circumference were measured according to a standard
143 protocol. Body Mass Index (BMI) was calculated as weight (kg)/height (m²). Fasting blood samples
144 were obtained, biochemical analyses were performed in a central laboratory. Total cholesterol,
145 HDL-cholesterol and triglycerides were measured by standard methods. LDL-cholesterol was
146 calculated according to the Friedewald equation only for triglycerides values <400 mg/dl. Glycated
147 hemoglobin (HbA1c) was measured with High Liquid Performance Chromatography. Use of
148 medications was assessed. All patients were treated with metformin, as per study inclusions criteria.
149 A high proportion (65%) was on lipid lowering medications.

150 The dietary habits were assessed with the Italian version of the European Prospective Investigation
151 into Cancer and Nutrition (EPIC) questionnaire (13, 14). The questionnaire contains 248 items
152 including the type of fat used as condiment, or added after cooking. The respondent indicates the
153 absolute frequency of consumption of each item (per day, week, month or year). The quantity of the
154 food consumed was assessed with the use of pictures of portions showing a small, medium and
155 large portion, with additional quantifiers (e.g. “smaller than the small portion” or “between the
156 small and medium portion” etc...). The nutrient’s composition of the diet was calculated with the
157 use of a software containing the Italian Food Tables (15, 16). Incomplete and/or implausible
158 questionnaire (i.e. reporting energy intake less than 800 or greater than 5000 Kcal/day) were
159 excluded from the analyses.

160

161 **Statistical Analysis**

162 Data **are** given as mean and standard deviation ($M \pm SD$), or number and proportion, as appropriate.
163 Not normally distributed variables were logarithmically transformed for statistical analyses and
164 back transformed to natural units for presentation in the text and tables. Means were compared by
165 unpaired t-test. Differences between proportions were tested by χ^2 test. For analytical purposes, the
166 adherence to the dietary recommendations was based on recommendations from the Diabetes and
167 Nutrition Study Group (DNSG) of the European Association for the Study of Diabetes endorsed by
168 the Italian Diabetes Society (SID) (17, 18). The separate and combined effect of sex and adherence
169 to dietary guidelines on plasma lipid was assessed **with the two way analysis of variance with**
170 **adjustment for BMI**. All statistical analyses were performed with the SPSS software for Windows,
171 version 19.0.

172

173 **Results**

174 The general characteristics of the study participants are given in Table 1 for the total population and
175 by sex. Age and diabetes duration **were** comparable in men and women, BMI **was** significantly

176 higher in women and glucose control, evaluated as HbA1c, **was** marginally better in women. **No**
177 **significant differences were observed for systolic blood pressure; whereas diastolic blood**
178 **pressure was slightly lower in women.** Plasma LDL-cholesterol and the proportion of the cohort
179 not meeting the treatment target of <100 mg/dl **were** significantly higher in women. HDL-
180 cholesterol **was** significantly higher in women, however a significantly higher proportion of females
181 as compared with males failed achieving the desirable value (i.e. >40 mg/dl for men; >50 mg/dl for
182 women). No significant difference **was** observed for plasma triglycerides. **Sex differences in**
183 **plasma lipids hold true after correction for BMI.** The proportion of people on lipid lowering
184 medications **was** similarly high in men and in women, **the most widely used class of drugs were**
185 **statins.** The findings were confirmed in a sensitivity analysis performed in the subsample of the
186 cohort not on lipid lowering medications (**Supplementary Table 1**). **Finally, the proportion of the**
187 **cohort with metabolic syndrome was significantly higher in women.**

188 The nutrients composition of the diet and the proportion of the cohort achieving the recommended
189 intake is given in Table 2, along with the DNSG nutritional recommendations (17). The least
190 attended recommendations **were** those on saturated fat intake, **cholesterol** and fiber with 81.9%,
191 **82.6%** and 93.1% of the cohort not meeting the recommended intake. Adherence **was** fair for
192 carbohydrates and good for added sugars, monounsaturated and polyunsaturated fat, **and alcohol.**
193 **However,** there **were** sex differences. The proportion of energy from total fat and saturated fat **was**
194 significantly higher in women, as well as the proportion of the cohort exceeding the recommended
195 intake for saturated fat (Table 2). **The intake of cholesterol and alcohol was significantly lower**
196 **in women.** The intake of fiber and the proportion of cohort achieving the recommend intake **were**
197 **generally low, and** significantly higher in women; **accordingly, the glycemic load of the diet was**
198 **lower in women** (Table 2).

199 The sex differences in the composition of the diet reflected different food choices: women
200 consumed significantly more legumes, vegetables, fruits, eggs, milk, vegetable oils (**mainly olive**

201 **oil**), and sugars added by the consumer, whereas men had a higher consumption of starchy foods
202 (pasta and bread), soft drinks and alcoholic beverages (Table 3).

203 Table 4 gives plasma lipid and BMI according to sex and adherence to the recommendation for the
204 intake of SAFA, fiber and added sugars. Adherence to the recommendations **for SAFA intake was**
205 associated with significantly **lower LDL-cholesterol** and BMI in men and women. No significant
206 association with HDL-cholesterol, or triglycerides was observed. The findings were confirmed in a
207 sensitivity analysis conducted after the exclusion of people on lipid lowering drugs (**Table 5**).

208 Adherence to the recommendations **for fiber intake (Table 4) was** associated with lower BMI in
209 men and women. No differences were observed for plasma lipid; however, in the subsample of
210 cohort not on lipid lowering medications, the adherence to the recommendations for fiber intake
211 was associated with significantly lower LDL-cholesterol and triglycerides in both men and women
212 (**Table 5**).

213 The adherence to the recommendations for added sugar **was** generally good with only a small
214 proportion of the cohort (2.7% in men and 2.8% in women) not meeting the recommended intake.
215 Notwithstanding the small numbers and the limited statistical power, adherence to the
216 recommendation for sugar intake **was** associated with significantly lower triglycerides and higher
217 HDL-cholesterol, both in men and women independent of BMI (**Table 4**). The finding on
218 triglycerides were confirmed in the subsample not taking lipid lowering medications (**Table 5**).

219

220 **Discussion**

221 The study evaluated sex differences in food choices, nutrients intake and adherence to the
222 nutritional recommendations and their relation with the plasma lipid profile in men and women with
223 type 2 diabetes in real life clinical practice. Data on the quality of diet in people with type 2 diabetes
224 are scant (8, 9). **To the best of our knowledge no prior data on sex differences were reported.**

225 **Women consumed more legumes, vegetables, fruits, eggs, milk, vegetable oils, and sugars**
226 **added by the consumer, but less starchy foods (pasta and bread), soft drinks and alcoholic**

227 **beverages.** This translated into slightly, but significantly lower adherence to the recommendations
228 for SAFA intake and higher adherence to the recommendations for fiber intake in women as
229 compared to men. **Sugar intake was higher in women and was counterbalanced by a lower**
230 **consumption of soft drinks. The consumption of whole grains was negligible in both men and**
231 **women and their effect could not be evaluated.** The DNSG recommendations for people with
232 diabetes are close to the Mediterranean style diet, **which has been shown effective in the**
233 **prevention of diabetes and its complications (23-24).** In theory in Italy, due to their gastronomic
234 background, people with diabetes should be facilitated in following the nutritional
235 recommendations, yet this was not the case as far as SAFA and fiber intake is concerned. **A low**
236 **adherence to SAFA and fiber intake in people with type 2 diabetes was also reported in a**
237 **prior Italian study and** was also described in other cohorts (7-9). A recent study conducted in
238 Ireland in **people with type 2 diabetes (8)** reports average fat intake of 38.8% that is close to what
239 we found in our cohort, and is a reflection of the more general problem of saturated fat and refined
240 carbohydrates overabundance in the western diet.

241 Notwithstanding some debates as to which diet is best for people with type 2 diabetes, there is a
242 general consensus on the need to reduce the intake of saturated fat while increasing the intake of
243 dietary fiber, particularly from whole grain cereals (19). One general criticism is that the nutritional
244 recommendations are insufficiently evidence based. Our study provided strong observational data in
245 support of the DNSG recommendations. As a matter of fact adherence to SAFA and fiber intake
246 was associated with better plasma lipid profile in both men and women, independent of BMI and, to
247 some extent, independent of lipid lowering treatment. The amount of added sugars that can be
248 safely tolerated is debated (20, 21). In the present study adherence to the DNSG nutritional
249 guidelines (i.e., added sugars below 10% of energy intake) was associated with significantly higher
250 HDL-cholesterol and lower triglycerides in both men and women, so reinforcing the importance of
251 this recommendation. The indication of maintaining the added sugars intake well below 10% of

252 total energy is further sustained by recent studies showing a dose-related response of plasma lipid
253 and CVD mortality with progressively increasing consumption of sweetened beverages (10, 11).

254 **Our observations were in line with recent studies showing that a Mediterranean style diet has**
255 **beneficial effects on diabetes control and cardiovascular risk factors modification (reviewed in**
256 **23).** The more adverse plasma lipid profile observed in women in the present study was coherent
257 with findings of other studies (2, 3, 22) and it was unlikely to be explained by differences in
258 adherence to the nutritional guidelines, as it persisted when limiting the analyses to people with
259 good adherence to the dietary recommendations.

260 The major study strengths relayed on the large sample size, the selection of a cohort representative
261 of real life clinical practice, the standardized collection of nutritional data and the centralized
262 measurement of plasma lipids. Among the study limitations we acknowledge the **cross-sectional**
263 **design that did not allow to explore “cause-consequence” relationships.** In addition, the dietary
264 data were collected only once and could be prone to recall bias and seasonal variation. **Finally,** the
265 extensive use of hypolipidemic drugs could have partly offset the quantitative effect of nutritional
266 factors. In this regard the appreciation of the impact of diet adherence in the face of
267 pharmacological treatment was relevant.

268 In conclusion, this study showed that men and women with diabetes make different food choices,
269 but sex differences in plasma lipids are unlikely to be explained by nutritional factors. Adherence to
270 the nutritional recommendations for SAFA, fiber and added sugar intake was associated with a
271 better plasma lipid profile **within men and women** over and above the effect of medications. These
272 findings reinforced the importance of substituting saturated for unsaturated fat sources, increasing
273 fiber intake and reducing the consumption of added sugars, and provided strong observational data
274 in support of the DNSG nutritional recommendations. Although small in magnitude, the observed
275 differences in plasma lipids were coherent with the results of lifestyle interventions studies (25)
276 and, at the population level, may significantly impact on the population’s absolute cardiovascular
277 risk.

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284

285 Conflict of Interest

286 No conflicts of interest to report.

287

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291

292 Authors' contributions to manuscript

293 O. V., G. R., M. M., E. B., F. C., and S. S. designed research; S. C., R. A., A. C. B., M. B., R. B., R.
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297 C., and S. S. analyzed data and performed statistical analysis; O. V., G. R., and M. V. wrote paper;
298 O. V., M. V., and G. R. had primary responsibility for final content.

299 All authors have read and approved the final manuscript.

References

1. Peters SA, Huxley RR, Woodward M. Diabetes as risk factor for incident coronary heart disease in women compared with men: a systematic review and meta-analysis of 64 cohorts including 858,507 individuals and 28,203 coronary events. *Diabetologia* 2014; 57 (8): 1542-51. doi: 10.1007/s00125-014-3260-6.
2. Rivellese AA, Riccardi G, Vaccaro O. Cardiovascular risk in women with diabetes. *Nutr Metab Cardiovasc Dis* 2010; 20 (6): 474-80. doi: 10.1016/j.numecd.2010.01.008.
3. Penno G, Solini A, Bonora E, Fondelli C, Orsi E, Zerbini G, Trevisan R, Vedovato M, Gruden G, Laviola L, et al. Gender differences in cardiovascular disease risk factors, treatments and complications in patients with type 2 diabetes: the RIACE Italian multicentre study. *J Intern Med* 2013; 274 (2): 176-91. doi: 10.1111/joim.12073.
4. Franzini L, Ardigò D, Cavalot F, Miccoli R, Rivellese AA, Trovati M, Zavaroni I, Vaccaro O. 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. *Nutr Metab Cardiovasc Dis* 2013; 23 (3): 235-41. doi: 10.1016/j.numecd.2011.12.003.
5. De Berardis G, Sacco M, Strippoli GF, Pellegrini F, Graziano G, Tognoni G, Nicolucci A. Aspirin for primary prevention of cardiovascular events in people with diabetes: meta-analysis of randomised controlled trials. *BMJ* 2009; 339: b4531. doi: 10.1136/bmj.b4531.
6. Hsue PY, Bittner VA, Betteridge J, Fayyad R, Laskey R, Wenger NK, Waters DD. Impact of Female Sex on Lipid Lowering, Clinical Outcomes and Adverse Effects in Atorvastatin Trials. *Am J Cardiol* 2015; 115 (4): 447-53. doi: 10.1016/j.amjcard.2014.11.026.
7. Rivellese AA, Boemi M, Cavalot F, Costagliola L, De Feo P, Miccoli R, Patti L, Trovati M, Vaccaro O, Zavaroni I; Mind.it Study Group. Dietary habits in type II diabetes mellitus: how is adherence to dietary recommendations?. *Eur J Clin Nutr* 2008; 62 (5): 660-4.

8. Breen C, Ryan M, McNulty B, Gibney MJ, Canavan R, O'Shea D. High saturated fat and low fibre intake: a comparative analysis of nutrient intake in individuals with and without type 2 diabetes. *Nutr Diabetes* 2014; 4: e104. doi: 10.1038/nutd.2014.2.
9. Soedamah-Muthu SS, Chaturvedi N, Fuller J, Toeller M. EURODIAB Prospective Complications study Group. Do European people with type 1 diabetes consume a high atherogenic diet? 7-year follow-up of the EURODIAB Prospective Complications Study. *Eur J Nutr* 2013; 52 (7): 1701-10. doi: 10.1007/s00394-012-0473-7.
10. Stanhope KL, Medici V, Bremer AA, Lee V, Lam HD, Nunez MV, Chen GX, Keim NL, Havel PJ. A dose- response study of consuming high-fructose corn syrup-sweetened beverages on lipid /lipoprotein risk factors for cardiovascular disease in young adults. *Am J Clin Nutr* 2015; 101 (6): 1144-54. doi: 10.3945/ajcn.114.100461.
11. Yang Q, Zhang Z, Gregg EW, Flanders D, Merritt R, Hu FB. Added sugar intake and cardiovascular diseases mortality among US adults. *JAMA Intern Med* 2014; 174 (4): 516-24. doi: 10.1001/jamainternmed.2013.13563.
12. Vaccaro O, Masulli M, Bonora E, Del Prato S, Giorda CB, Maggioni AP, Mocarelli P, Nicolucci A, Rivellese AA, Squatrito S, Riccardi G; TOSCA.IT study group (Thiazolidinediones Or Sulphonylureas and Cardiovascular Accidents. Intervention Trial). Addition of either pioglitazone or a sulfonylurea in type 2 diabetic patients inadequately controlled with metformin alone: Impact on cardiovascular events. A randomized controlled trial. *Nutr Metab Cardiovasc Dis* 2012; 22 (11): 997-1006. doi: 10.1016/j.numecd.2012.09.003.
13. Pala V, Sieri S, Palli D, Salvini S, Berrino F, Bellegotti M, Frasca G, Tumino R, Sacerdote C, Fiorini L, et al. Diet in the Italian EPIC cohorts: presentation of data and methodological issues. *Tumori*; 89 (6): 594-607.

14. Pisani P, Faggiano F, Krogh V, Palli D, Vineis P, Berrino F. Relative validity and reproducibility of a food frequency dietary questionnaire for use in the Italian EPIC centres. *Int J Epidemiol* 1997; 26 (Suppl 1): S152-60.
15. Salvini S, Parpinel M, Gnagnarella P, Maisonneuve P, Turrini A (eds). Banca dati di composizione degli alimenti per studi epidemiologici in Italia. Istituto Europeo di Oncologia 1998.
16. Carnovale E, Marletta L (eds). Tabella di composizione degli alimenti. INRAN 2000.
17. Mann JI, De Leeuw I, Hermansen K, Karamanos B, Karlström B, Katsilambros N, Riccardi G, Rivellese AA, Rizkalla S, Slama G, et al. on behalf of the Diabetes and Nutrition Study Group (DNSG) of the European Association for the Study of Diabetes (EASD). Evidence based nutritional approaches to the treatment and prevention of diabetes mellitus. *Nutr Metab Cardiovasc Dis* 2004; 14 (6): 373–94.
18. Gruppo di studio ADI-AMD-SID “Nutrizione e diabete”. La terapia medico-nutrizionale nel diabete mellito. Le raccomandazioni nutrizionali 2013-2014. http://www.aemmedi.it/files/Linee-guida_Raccomandazioni/2013/RAC_NUTRIZIONE_DEF_2013-2014.pdf
19. Ajala O, English P, Pinkney J. Systematic review and meta-analysis of different dietary approaches to the management of type 2 diabetes. *Am J Clin Nutr* 2013; 97 (3): 505-16. doi: 10.3945/ajcn.112.042457.
20. Dhurandhar N, Thomas D. The link between dietary sugar intake and cardiovascular disease mortality: an unresolved question. *JAMA* 2015; 313 (9): 959-60. doi: 10.1001/jama.2014.18267.
21. Singh GM, Micha R, Khatibzadeh S, Lim S, Ezzati M, Mozzafarian D. Global Burden of Diseases Nutrition and Chronic Diseases Expert Group (NutriCoDE). Estimated global, regional and national disease burdens related to sugar-sweetened beverage consumption in 2010. *Circulation* 2015. pii: CIRCULATIONAHA.114.010636. [Epub ahead of print].

22. Peters SA, Huxley RR, Sattar N, Woodward M. Sex Differences in the Excess Risk of Cardiovascular Diseases Associated with Type 2 Diabetes: Potential Explanations and Clinical Implications. *Curr Cardiovasc Risk Rep* 2015; 9 (7): 36.
23. Salas-Salvadó J, Bulló M, Estruch R, Ros E, Covas MI, Ibarrola-Jurado N, Corella D, Arós F, Gómez-Gracia E, Ruiz-Gutiérrez V, et al. Prevention of diabetes with Mediterranean diets: a subgroup analysis of a randomized trial. *Ann Intern Med* 2014; 160 (1): 1-10.
24. **Sleiman D, Al-Badri MR and Azar ST. Effect of Mediterranean diet in diabetes control and cardiovascular risk modification: a systematic review. *Front Public Health* 2015; 3: (69).**
25. Chen L, Pei JH, Kuang J, Chen HM, Chen Z, Li ZW, Yang HZ. Effect of lifestyle intervention in patients with type 2 diabetes: A meta-analysis. *Metabolism* 2015; 64 (2): 338-47. doi: 10.1016/j.metabol.2014.10.018.

Table 1. Clinical characteristics of the study participants

	Total Population	Men (1535)	Women (1038)
Age (years)	62.1±6.5	62.0±6.5	62.3±6.4
Diabetes duration (years)	8.5±5.7	8.4±5.6	8.6±5.8
BMI (Kg/m ²)	30.3±4.5	29.7±4.0	31.2±4.9*
HbA1c (%)	7.68±0.51	7.71±0.51	7.65±0.50*
% on target (<7.5%)	41.0	38.6	44.6*
Systolic Blood Pressure (mm/Hg)	134.8±15.4	135.0±15.2	134.4±15.8
Diastolic Blood Pressure (mm/Hg)	80.1±9.1	80.7±9.2	79.1±8.7*
% on pressure lowering medications	92.5	91.0	94.5
HDL-Cholesterol (mg/dl)	46.1±12.0	43.5±11.0	59.6±10.1*
% on target (Men>40; Women>50 mg/dl)	53.5	59.4	44.7*
LDL-Cholesterol (mg/dl)	102.8±31.4	100.8±31.2	103.5±73.1*
% on target (< 100 mg/dl)	49.1	51.0	46.4*
Triglycerides (mg/dl)	150.6±75.0	151.5±78.9	148.8±31.5
% on target (< 150 mg/dl)	60.4	60.2	60.6
% on lipid lowering medications	62.0	60.9	63.7
% on statins	51.7	51.2	52.8
% on other lipid lowering medications	10.3	9.7	10.9
% with metabolic syndrome	52.8	48.2	59.5*

M±SD

* P<0.05, vs Men

Table 2. Nutrient composition of the diet and adherence to the nutritional recommendations in men and women with type 2 diabetes

	Men	Women	Recommendations (DNSG ¹⁷ / SID ¹⁸)	Non Adherence % (Men N 1535)	Non Adherence % (Women N 1038)
Energy (Kcal/day)	1934±674	1680±593*			
Proteins (% of total energy)	18.3±2.5	18.2±2.5	10-20%	22.3 (343)	21.8 (226)
Fat (% of total energy)	36.4±5.9	37.0±6.1*	<35%	59.9 (920)	63.7 (661)*
SFA (% of total energy)	11.5±2.5	12.0±2.4*	<10%	81.8 (1256)	82.4 (855)*
MUFA (% of total energy)	17.7±3.6	18.1±3.9	10-20%	24.3 (373)	28.4 (295)*
PUFA (% of total energy)	4.4±1.0	4.5±1.1	<10%	0.4 (6)	0.8 (8)
Cholesterol (mg/day)	344±148	304±135*	<200 mg	85.6 (1314)	79.6 (826)*
Carbohydrates (% of total energy)	45.3±7.1	44.8±7.3*	45-60%	51.2 (786)	53.8 (558)
Added Sugars [§] (% of total energy)	2.3±3.2	3.4±3.2*	<10%	2.7 (41)	2.8 (29)
Fiber (g/1000 Kcal/day)	10.4±2.6	11.2±2.8*	>15g/1000 Kcal	94.8 (1455)	90.6 (940)*
Glycemic Index (%)	51.8±3.4	51.6±3.2			
Glycemic Load	123.0±53.3	103.4±42.6*			
Alcohol (g/day)	15.9±17.9	4.0±8.2*	<20 g for men and <10g for women	0.8 (12)	0.2 (3)

M±SD

* P<0.05 vs Men

[§] Soft drinks + sugar added by consumer

DNSG (Diabetes and Nutrition Study Group); SID (Italian Diabetes Society).

Table 3. Food groups (g/1000Kcal/day) in men and women with type 2 diabetes

	Men	Women
Starch (Pasta, Rice, Bread)	102.9±37.0	95.2±38.1*
Legumes	43.1±38.8	48.7±36.7*
Vegetables	87.6±44.9	102.6±50.3*
Fresh Fruit	160.9±88.8	190.6±99.6*
Meat and Salami	56.8±26.1	56.2±26.4
Fish	21.7±16.5	23.8±16.0
Eggs	10.6±7.6	12.4±9.1*
Dairy Products	18.9±12.6	19.4±12.9
Milk and Yogurt (Whole)	27.8±38.2	36.8±44.1*
Milk and Yogurt (Low Fat)	56.1±77.3	76.7±84.3*
Vegetable Oils (Condiment)	12.8±5.5	14.6±6.2*
Olive oil	11.4±4.6	13.5±5.7*
Other vegetable oils	1.3±1.7	1.2±1.9
Animal Fats (Condiment)	1.4±1.5	1.2±1.3
Cake and Pastries	18.7±18.7	20.2±20.1
Soft Drinks	17.9±43.6	15.6±37.5*
Sugar added by consumer	2.6±5.3	4.3±7.1*
Wine and Beer	89.1±92.3	24.6±48.2*

M±SD

* P<0.05, vs Men

Table 4. Plasma lipid profile by sex and adherence to the recommendations for intake of saturated fat (panel a), fiber (panel b) and added sugars (panel c)**Panel a**

	Adherence		Non Adherence		P for two-factors ANOVA		
	Men (n=279)	Women (n=183)	Men (n=1252)	Women (n=850)	Sex	Adherence	Sex x Adherence
HDL-Cholesterol (mg/dl)	43.0±10.4	49.8±12.1	43.6±11.1	49.9±12.3	.001	.142	.912
LDL-Cholesterol (mg/dl)	98.3±32.1	102.7±31.2	101.6±30.8	106.0±31.8	.010	.051	.971
Triglycerides (mg/dl)	155.5±77.4	150.6±75.1	150.7±79.2	149.0±67.5	.070	.110	.945
BMI (Kg/m²)	29.3±4.0	30.0±4.9	29.8±4.0	31.4±4.9	.001	.001	.060

Panel b

	Adherence		Non Adherence		P for two-factors ANOVA		
	Men (n=80)	Women (n=98)	Men (n=1455)	Women (n=940)	Sex	Adherence	Sex x Adherence
HDL-Cholesterol (mg/dl)	43.5±9.7	52.2±11.9	43.5±11.1	49.7±12.3	.001	.343	.260
LDL-Cholesterol (mg/dl)	99.4±32.0	103.8±27.7	101.1±31.0	105.6±32.1	.081	.497	.993
Triglycerides (mg/dl)	146.8±60.8	143.1±69.5	151.8±79.7	149.9±68.8	.282	.558	.915
BMI (Kg/m²)	29.4±4.0	30.0±4.4	29.7±4.0	31.3±4.9	.001	.022	.166

Panel c

	Adherence		Non Adherence		P for two-factors ANOVA		
	Men (n=1488)	Women (n=1002)	Men (n=41)	Women (n=28)	Sex	Adherence	Sex x Adherence
HDL-Cholesterol (mg/dl)	43.6±11.0	50.0±12.4	39.6±9.7	46.1±9.4	.001	.009	.901
LDL-Cholesterol (mg/dl)	96.3±34.7	105.3±31.6	101.1±31.0	110.2±34.9	.024	.992	.222
Triglycerides (mg/dl)	150.3±78.1	148.7±68.9	196.3±94.0	170.3±66.0	.039	.001	.178
BMI (Kg/m²)	29.7±4.0	31.2±4.9	30.2±3.5	31.7±4.9	.005	.325	.944

Table 5. Plasma lipid profile by sex and adherence to the recommendations for intake of saturated fat (panel a), fiber (panel b) and added sugars (panel c) in population not on lipid lowering medications

Panel a

	Adherence		Non Adherence		Sex	P for two-factors ANOVA	
	Men (n=90)	Women (n=62)	Men (n=448)	Women (n=289)		Adherence	Sex x Adherence
HDL-Cholesterol (mg/dl)	43.8±10.8	48.0±12.5	43.6±10.5	49.6±12.0	.001	.252	.457
LDL-Cholesterol (mg/dl)	109.4±28.6	116.7±32.0	115.9±28.3	121.0±29.3	.021	.049	.656
Triglycerides (mg/dl)	157.1±80.8	159.4±80.8	153.3±76.9	145.5±66.4	.464	.124	.544
BMI (Kg/m ²)	29.7±4.2	30.9±5.4	29.9±4.0	32.0±5.2	.001	.141	.309

Panel b

	Adherence		Non Adherence		Sex	P for two-factors ANOVA	
	Men (n=31)	Women (n=62)	Men (n=509)	Women (n=319)		Adherence	Sex x Adherence
HDL-Cholesterol (mg/dl)	46.5±11.3	53.7±12.1	43.4±10.5	48.9±12.0	.001	.142	.254
LDL-Cholesterol (mg/dl)	107.5±20.3	118.4±24.8	115.2±28.8	120.5±30.3	.154	.032	.523
Triglycerides (mg/dl)	124.6±55.4	134.1±53.9	155.5±78.2	149.3±70.5	.987	.036	.588
BMI (Kg/m ²)	28.5±3.9	30.1±4.4	29.9±4.0	32.0±5.3	.003	.008	.755

Panel c

	Adherence		Non Adherence		Sex	P for two-factors ANOVA	
	Men (n=525)	Women (n=341)	Men (n=9)	Women (n=8)		Adherence	Sex x Adherence
HDL-Cholesterol (mg/dl)	43.6±10.6	49.4±12.2	42.4±12.2	45.3±6.5	.154	.294	.597
LDL-Cholesterol (mg/dl)	114.7±28.4	120.3±29.9	118.6±34.4	119.5±25.6	.547	.252	.780
Triglycerides (mg/dl)	152.3±76.1	146.7±68.7	252.2±96.6	198.5±80.1	.056	.001	.216
BMI (Kg/m ²)	29.9±4.0	31.8±5.2	29.8±2.8	33.4±6.3	.013	.481	.440

Supplemental Table 1. Clinical characteristics of the study participants not on lipid lowering medications

	Total Population	Men (538)	Women (350)
Age (years)	61.3±6.5	61.6±6.6	61.0±6.4
Diabetes duration (years)	8.3±5.7	8.2±5.5	8.4±6.0
BMI (Kg/m²)	30.6±4.6	29.9±4.0	31.8±5.2*
HbA1c (%)	7.73±0.53	7.76±0.53	7.70±0.51*
<i>% on target (<7.5%)</i>	37.3	33.6	42.1*
Systolic Blood Pressure (mm/Hg)	134.4±15.0	134.8±14.6	133.9±15.5
Diastolic Blood Pressure (mm/Hg)	80.7±9.0	81.5±9.1	79.4±8.6*
<i>% on pressure lowering medications</i>	88.2	84.0	89.3
HDL-Cholesterol (mg/dl)	45.9±11.5	43.6±10.6	49.3±12.1*
<i>% on target (Men>40; Women>50 mg/dl)</i>	55.4	61.2	43.2*
LDL-Cholesterol (mg/dl)	116.9±29.1	114.8±28.5	120.3±29.8*
<i>% on target (< 100 mg/dl)</i>	47.2	53.1	42.8*
Triglycerides (mg/dl)	151.7±74.4	154.0±77.5	148.2±69.2
<i>% on target (< 150 mg/dl)</i>	61.2	60.8	61.6
<i>% with metabolic syndrome</i>	51.9	44.9	59.1*

M±SD

* P<0.05, vs Men

Highlights

- Diabetic women have a more adverse plasma lipid profile than men.
- Sex differences in dietary habits may impact on plasma lipid profile.
- Men and women make different food choices.
- Adherence to the nutritional recommendations is significantly different between men and women.
- Adherence to the nutritional recommendations is associated with a better plasma lipid profile in both men and women.