NAPOLI, 17-20 maggio 2017

XXI CONGRESSO NAZIONALE AMD

ASSOCIAZIONE MEDICI DIABETOLOGI

1974 ANNO DI FONDAZIONE

La diabetologia di genere: un compito per il terzo millennio

PER UNA DIABETOLOGIA PREDITTIVA, PREVENTIVA, PERSONALIZZATA E PARTECIPATIVA

Giuseppina T. Russo

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DIPARTIMENTO DI MEDICINA CLINICA E SPERIMENTALE

DICHIARAZIONE
CONFLITTO D'INTERESSE DOCENTI

In ottemperanza alla normativa ECM ed al principio trasparenza delle fonti di finanziamento e dei rapporti con soggetti portatori di interessi commerciali in campo sanitario, il ***docente deve "rilasciare al provider o all'organizzatore la dichiarazione di conflitto d'interessi (ultimi 2 anni rapporti diretti con aziende) e che successivamente debba informare l'aula all'atto della sua presentazione o comunque prima della lezione/relazione dichiarandolo ai discenti"***.

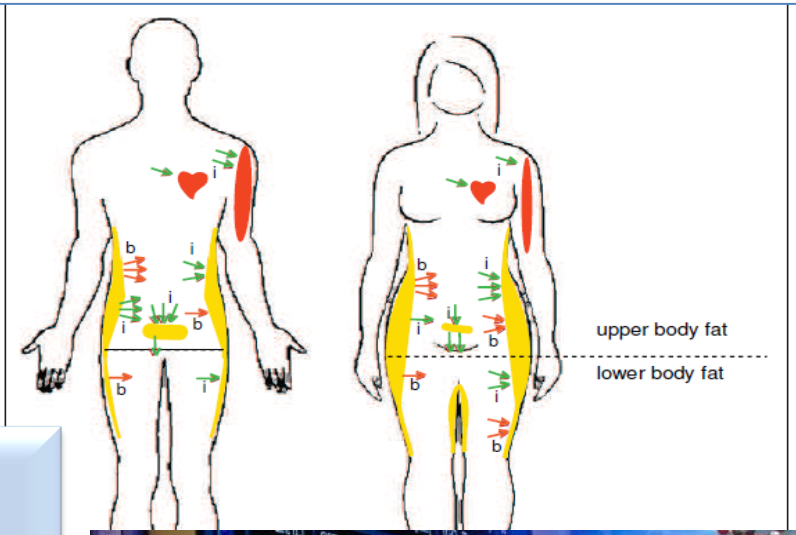
Lecturer , Scientific consultant for:

Boehringer Ingelheim - Eli-Lilly, Novo-Nordisk- Astra Zeneca -Merck

Medicina di precisione e genere

Uomini e donne non sono uguali …..

Le differenze di genere nel diabete sono state ancora poco esplorate

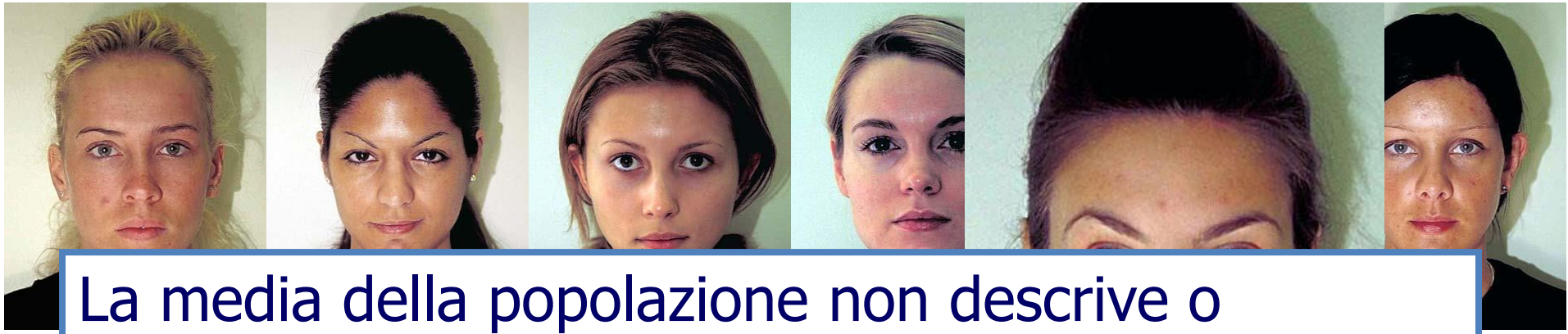


Differenze di Genere nell'epidemiologia, nei fattori di rischio, nella presentazione clinica e nella cura del Diabete e delle sue complicanze

- ✓MACROANGIOPATIA
- ✓MICROANGIOPATIA
  - Nefropatia diabetica
  - Neuropatia diabetica
  - Retinopatia diabetica

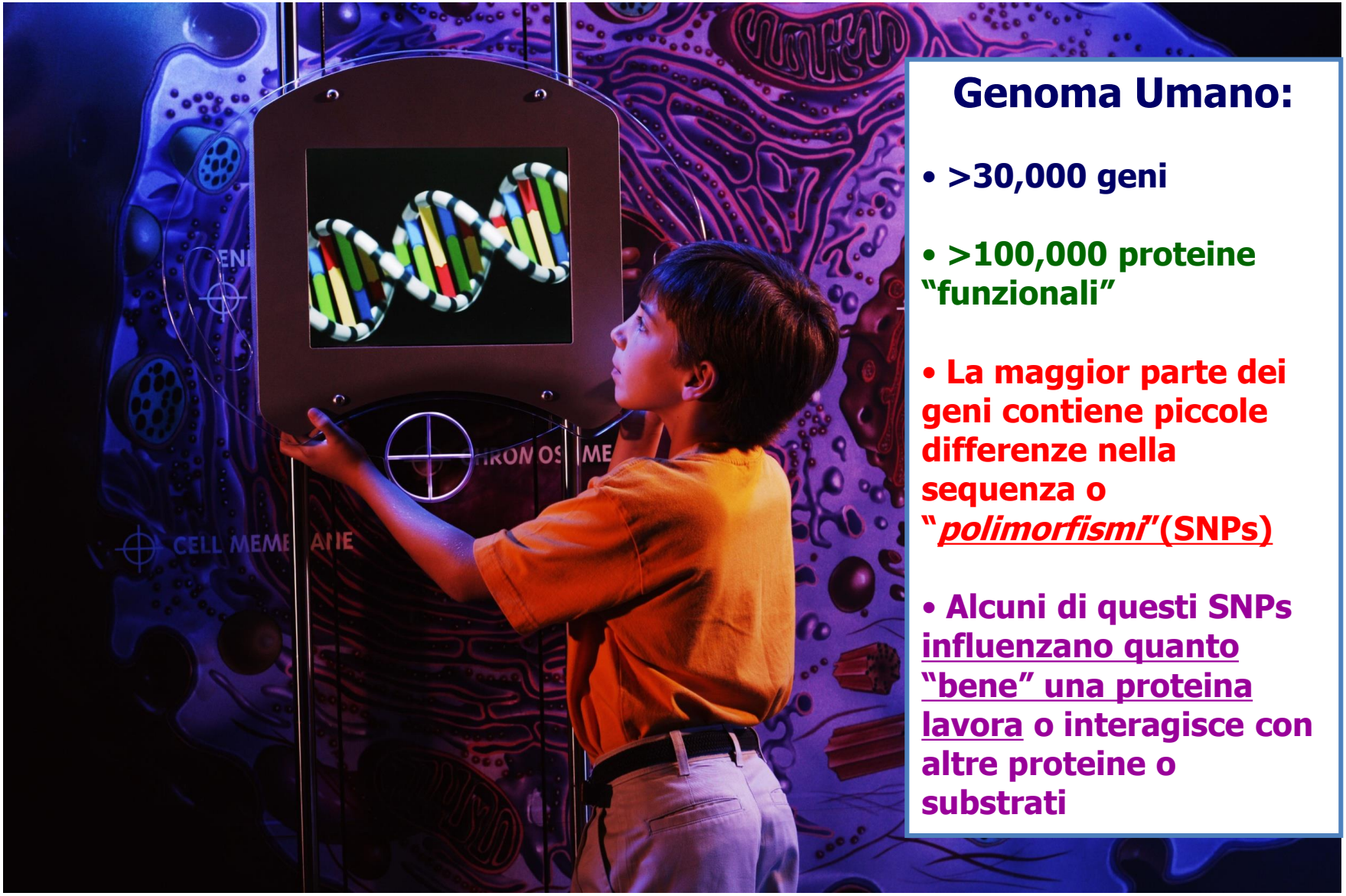
Identificare il difetto molecolare alla base della patologia per personalizzare il trattamento

Traditional Epidemiology



La media della popolazione non descrive o rappresenta in modo appropriato l'individuo all'interno della popolazione.

"One size does not fit all".



Genoma Umano:

- **>30,000 geni**
- **>100,000 proteine "funzionali"**
- **La maggior parte dei geni contiene piccole differenze nella sequenza o "*polimorfismi*" (SNPs)**
- **Alcuni di questi SNPs influenzano quanto "bene" una proteina lavora o interagisce con altre proteine o substrati**

Età, sesso, etnia

Stato di salute = ∫ Esposizione all'ambiente x Genetica

Livelli di determinati fattori di rischio cardiovascolare

Hindawi Publishing Corporation
International Journal of Endocrinology
Volume 2015, Article ID 832484, 2 pages
http://dx.doi.org/10.1155/2015/832484

Editorial

Type 2 Diabetes and Cardiovascular Risk in Women

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[3]*Laboratory of Clinical Epidemiology of Diabetes and Chronic Diseases, Fondazione Mario Negri Sud, Via Nazionale 8/A, 66030 Santa Maria Imbaro, Italy*
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Received 18 January 2015; Accepted 18 January 2015

Cardiovascular diseases (CVD) are the leading cause of death, also in diabetic women. Since 1998, when Haffner et al. [1] stated that subjects with type 2 diabetes mellitus (T2DM) had a CVD risk "equivalent" to previous myocardial infarction, a large number of studies have shown that this relative risk for CVD due to diabetes is greater in women than in men [2].

CVD in diabetic subjects is not entirely related to chronic hyperglycaemia and a number of other factors such as dyslipidemia, hypertension, hormonal, genetic, and environmental factors, as well as low-grade systemic inflammation and endothelial damage, lifestyle behaviours, adherence to therapies, and/or psychosocial factors may contribute to the worst outcomes observed in diabetic women. Notably, it is increasingly recognized that many of these factors show gender differences in their prevalence and/or association with CVD events, and this aspect should be specifically targeted when aiming at primary or secondary CVD prevention in diabetic subjects.

In this special issue, we looked at CVD in women with diabetes from different perspectives, giving a great contribution to this topic, in terms of mortality, management of risk factors, and therapies.

Two papers of this special issue looked at sex differences in CVD mortality associated with diabetes. One conducted on a large population-based sample from Italy demonstrated an excess of mortality in diabetic subjects as compared to nondiabetic ones and a greater impact of diabetes in females than in males for mortality for all causes, for CVD, and f
myocardial infarction and renal causes. In the other stu
G. Luo et al. showed in a retrospective analysis that fasti
plasma glucose was an independent predictor of in-hospi
mortality for nondiabetic female patients.

Gender-specific prevalence and management of maj
and emerging CVD risk factors in different populations we
also the main topic of several papers of this special issue.

The paper by S. Chen et al., with a very interesting expe
imental protocol, clarified the relationships of albuminur
a well-recognized CVD risk factor, with circulating lev
of angiopoietin-1 (Ang-1), Ang-2, and vascular endothel
growth factor (VEGF) in serum and urine.

Potential gender differences in the distribution and co
trol of major CVD risk factors were investigated in anoth
three very large high-risk populations. Thus, in the eCont
Study, a study on 286,791 patients with T2DM in Catalon
Spain, J. Franch-Nadal et al. found that cardiometabo
control was worse in subjects with prior CVD; but cont
of several risk factors showed gender differences, favouri
women with prior CVD only for smoking and BP, where
LDL-cholesterol (LDL-C) levels were remarkably unco
trolled in women both with and without CVD.

The results of an overall bad control of LDL-C in wom
were also demonstrated in a very large Italian diabe
outpatient population from the Annals Study Initiative. T
study, conducted on 415.294 patients (45.3% women) fro

- ✓ **La medicina di genere nasce dallo studio della patologia cardiovascolare**
- ✓ **Nelle donne le malattie cardiovascolari rappresentano la prima causa di morte**
- ✓ **Peculiarità ella presentazione clinica**
- ✓ **Latenza di circa 10 anni nelle manifestazioni cliniche rispetto all'uomo**

Published in final edited form as:
Circ Res. 2011 September 2; 109(6): 687–696. doi:10.1161/CIRCRESAHA.110.236687.

Estrogen Signaling and Cardiovascular Disease

Elizabeth Murphy
Cardiac Physiology Section, Systems Biology Center, NHLBI, NIH Bethesda, MD

I. How Does Estrogen Alter Cell Function?

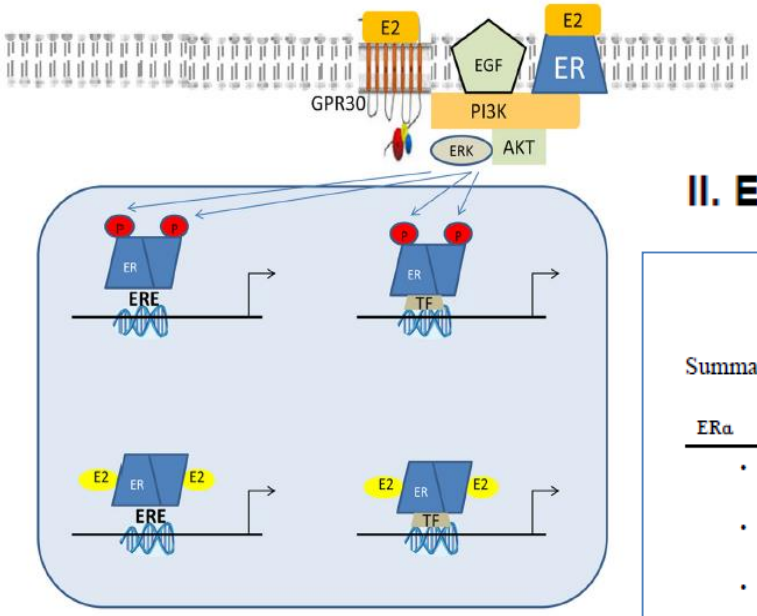


Figure 1.
Figure 1 shows the major mechanism by which ER can alter gene expression. Estrogen (E2) binds to ER resulting in dimerization and recruitment of co-regulators (not shown due to space limitations). The estrogen-ER complex binds to estrogen response elements (ERE) on the DNA resulting in altered gene transcriptions. Estrogen can also alter gene transcription by binding to transcription factors (TF) such as AP1. In addition, ER can be phosphorylated by growth factors and other plasma membrane estrogen receptors that are coupled to kinase signaling. Phosphorylated ER can activate gene transcription in a ligand-independent manner.

II. ERα and ERβ differentially regulate gene expression

Table 1

Summary of known genomic function associated with ERα and ERβ

ERα	ERβ
• Increases left ventricular mass and volume[159];	• Reduces pathologic cardiac hypertrophy[4];
• Reductions of infarct size after myocardial infarction[159];	• Prevents increases mortality in chronic heart failure[165, 166];
• Cardioprotection against ischemia-reperfusion injury[160–162];	• Cardioprotection against ischemia-reperfusion injury[41];
• Regulates GLUT4 expression[163];	• Regulation of vascular function and blood pressure[133];
• Regulates cardiac growth[164].	• modulates sex-specific response of the heart to exercise[50];
	• Decreases inflammatory response[41].

Published in final edited form as:
Circ Res. 2016 March 18; 118(6): 994–1007. doi:10.1161/CIRCRESAHA.115.305376.

The Expanding Complexity of Estrogen Receptor Signaling in the Cardiovascular System

Sara Menazza and **Elizabeth Murphy**
Systems Biology Center, National Heart Lung and Blood Institute, National Institutes of Health, Bethesda, MD 20892

Gli estrogeni svolgono moltelici effetti benefici sull'apparato cardiovascolare

Menazza and Murphy

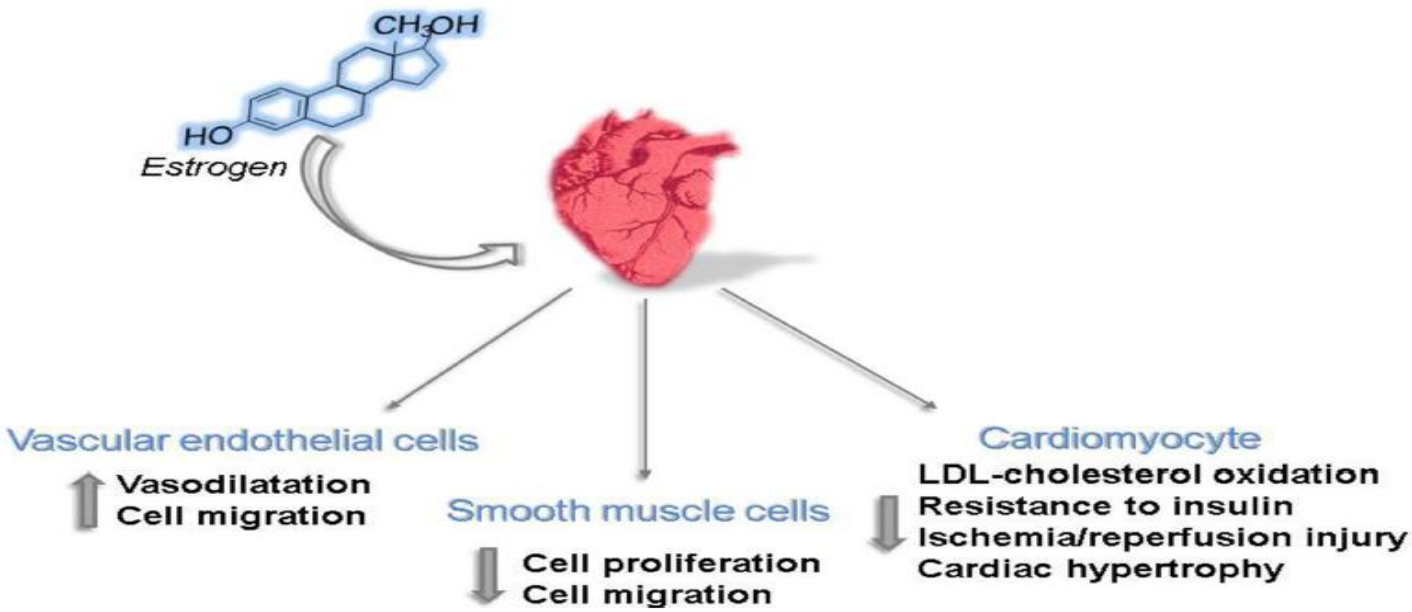
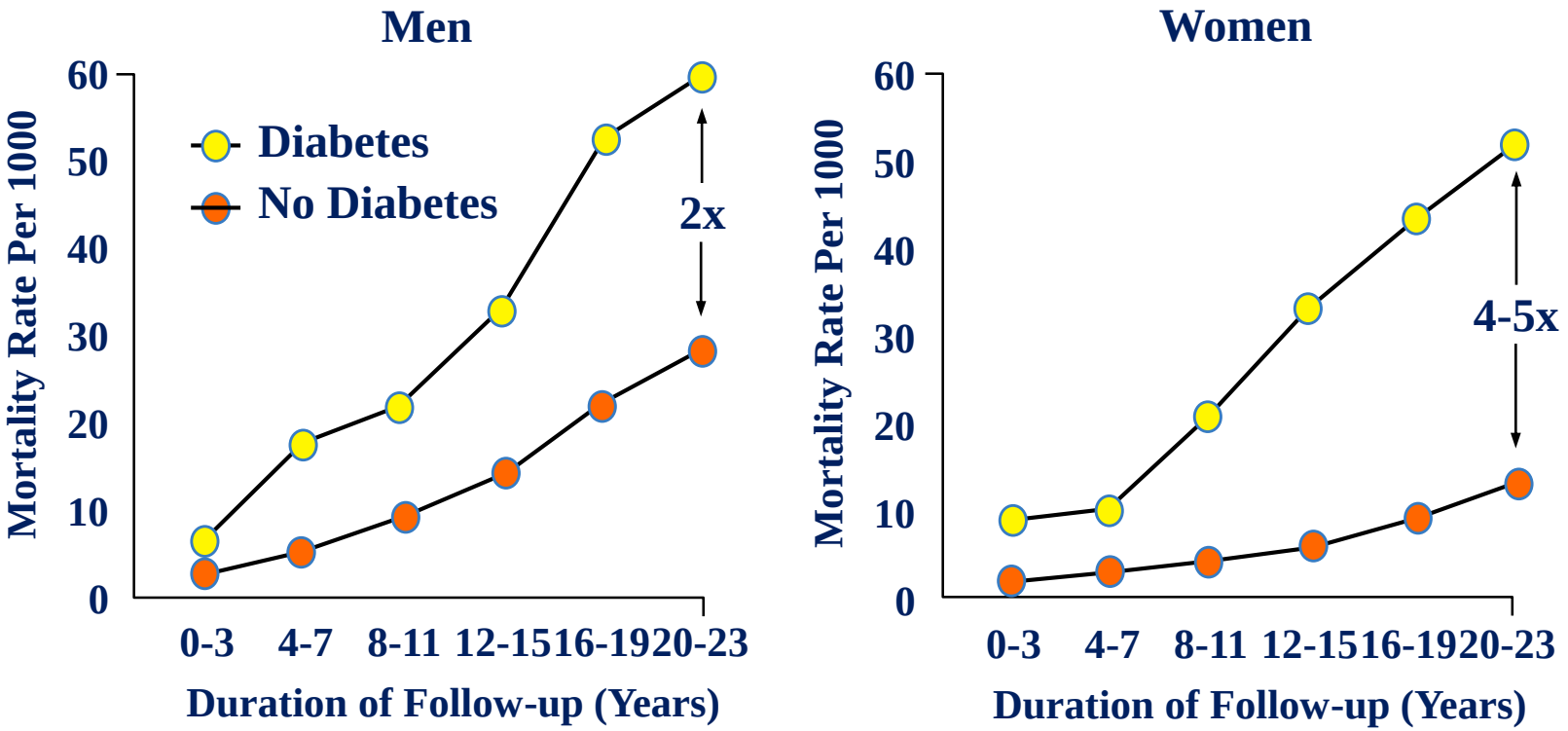


Figure 1. Effects of estrogen on the heart
Estrogen has many pleiotropic effects on the cardiovascular system. Estrogen can impact cardiovascular health and disease by direct effects: (i) on the vascular endothelial cells promoting vasorelaxation, cell proliferation and migration; (ii) on vascular smooth muscle cells decreasing cell proliferation and migration and (iii) on cardiomyocytes reducing LDL-cholesterol level and protecting against insulin resistance, infarct size and ischemia–reperfusion injury and cardiac hypertrophy.

Diabetes is a potent Cardiovascular (CVD) Risk Factor in men and women



Krolewski AS, et al. Evolving natural history of coronary disease in diabetes mellitus. *Am J Med* 1991;90(Supp 2A):56S-61S.

Diabetes as a risk factor for stroke in women compared with men: a systematic review and meta-analysis of 64 cohorts, including 775 385 individuals and 12 539 strokes

Sanne A E Peters, Rachel R Huxley, Mark Woodward

Summary

Background Diabetes mellitus is a major cause of death and disability worldwide and is a strong risk factor for stroke. Whether and to what extent the excess risk of stroke conferred by diabetes differs between the sexes is unknown. We did a systematic review and meta-analysis to estimate the relative effect of diabetes on stroke risk in women compared with men.

Lancet 2014; 383: 1973–80
Published Online
March 7, 2014
http://dx.doi.org/10.1016/S0140-6736(14)60040-4
See Editorial page 1945
See Comment page 1948
Julius Center for Health

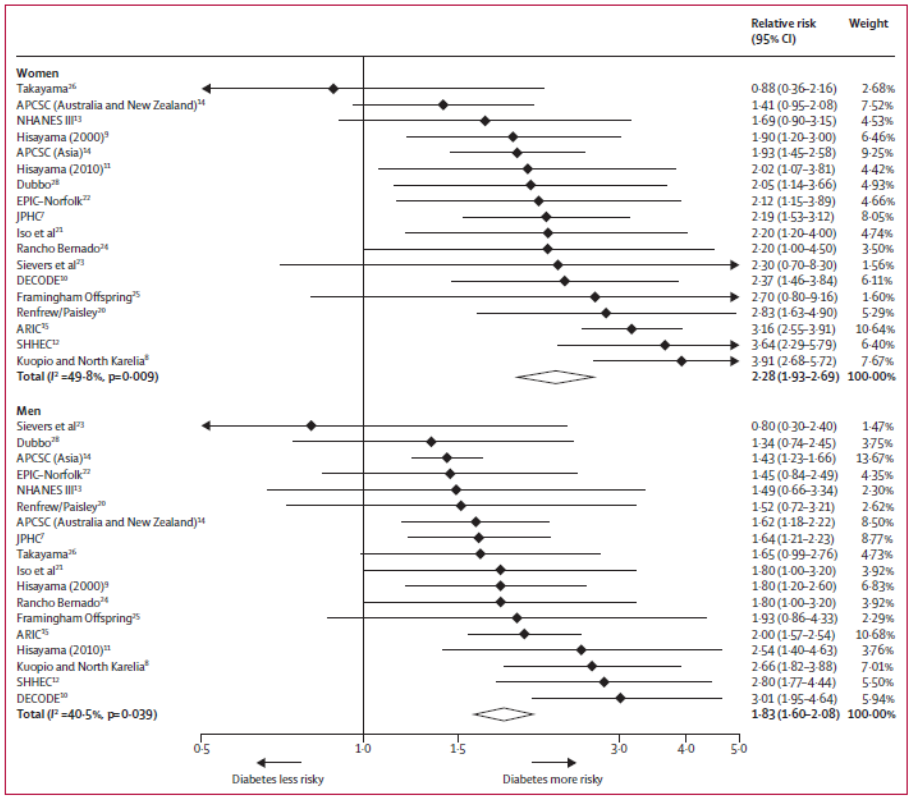


Figure 2: **Maximum-adjusted pooled relative risk for any stroke, comparing individuals with diabetes to those without diabetes**
Box sizes are in proportion to study weights. Asia Pacific Cohort Studies Collaboration (APCSC) provided separate estimates for cohorts from Asia and Australia and New Zealand. NHANES III=National Health And Nutrition Examination Survey III. EPIC-Norfolk=European Prospective Investigation into Cancer, Norfolk. JPHC=Japan Public Health Center study. DECODE=Diabetes Epidemiology: COllaborative analysis of Diagnostic criteria in Europe. ARIC=Atherosclerosis Risk in Communities study. SHHEC=Scottish Heart Health Extended Cohort study.

population-based cohort studies published
ted sex-specific estimates of the relative risk
a pooled the sex-specific RRs and their ratio

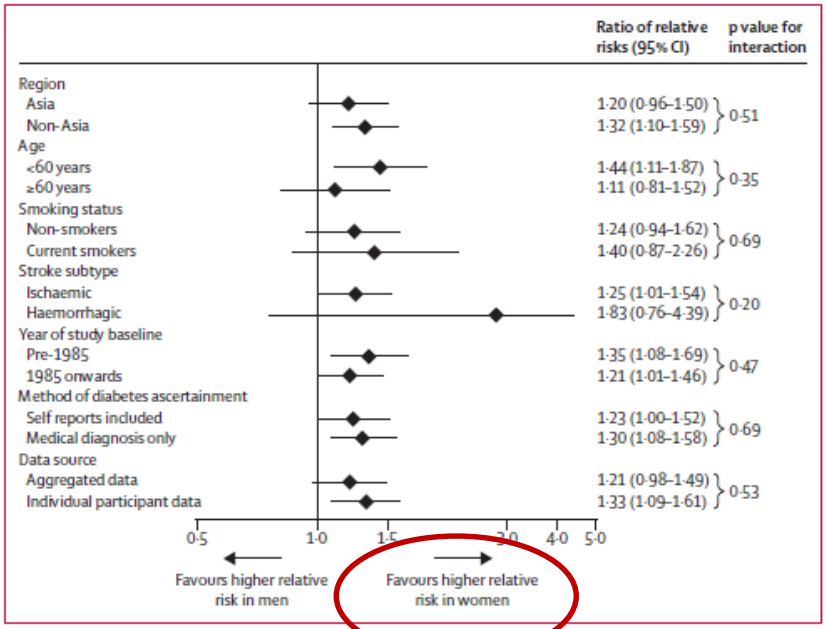


Figure 4: **Sensitivity analyses**

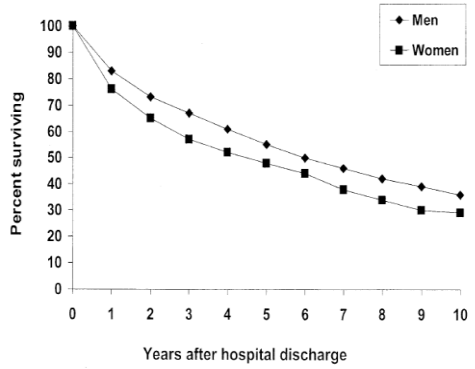
SH heading search strategy with the terms:
illitus", "diabetes", "prediabetes", "impaired
cose", "impaired glucose intolerance",
liabetes," "blood glucose", "hemoglobin A,
"cohort studies", "sex", "gender", "cardio-
ease", "stroke", "cerebrovascular disease",
ular attack", "cerebral ischemia", "brain
major cardiovascular risk factors have been taken into ischemia", and "intracranial hemorrhage". We also checked

Sex differences in survival after acute myocardial infarction in patients with diabetes mellitus (Worcester Heart Attack Study)

Amber Crowley, MD,[a] Vandana Menon, MD, MPH,[b] Darleen Lessard, MS,[c] Jorge Yarzebski, MD, MPH,[c] Elizabeth Jackson, MD, MPH,[c] Joel M. Gore, MD,[c] and Robert J. Goldberg, PhD[c] *New Haven, Conn, and Boston and Worcester, Mass*

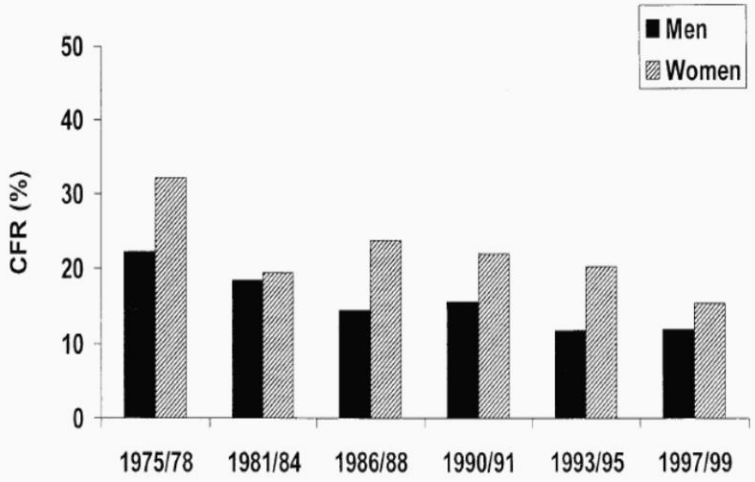
Le morti *intraospedaliere* dopo IMA si sono ridotte sia negli uomini che nelle donne con diabete; tuttavia le donne hanno ancora un rischio maggiore di morte intraospedaliera

Figure 2



Long-term survival after acute myocardial infarction in men and women with diabetes mellitus.

Figure 1



Trends in hospital CFRs for men and women with diabetes mellitus and AMI.

Diversi fattori possono contribuire all'eccesso di rischio CVD nelle donne con diabete

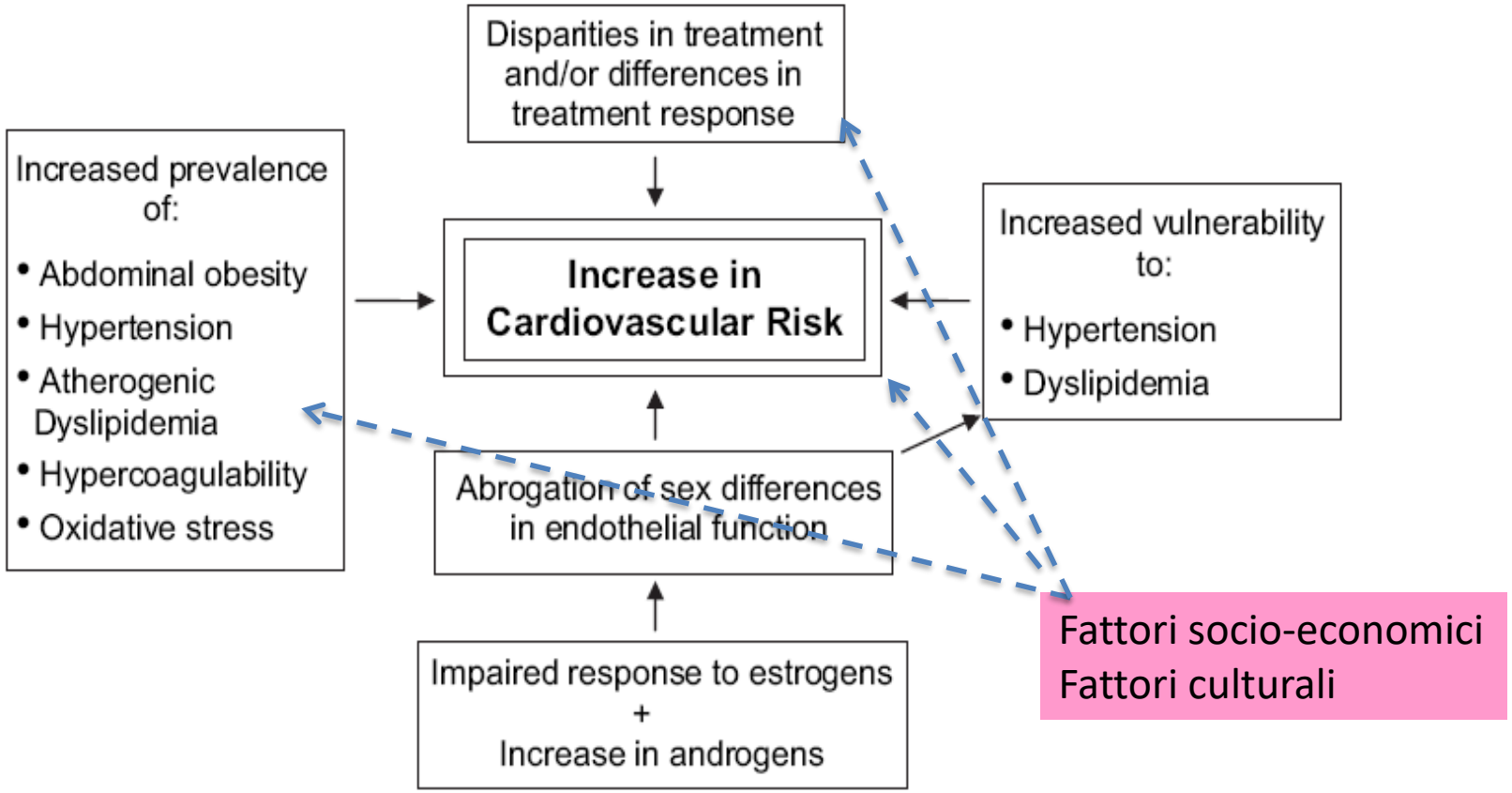


Figure 2 Possible causes of the high cardiovascular risk in women with diabetes.

Rivellese, Riccardi, Vaccaro. NMCD, 2010

Maggiore prevalenza dei fattori di rischio cardiovascolare nelle donne con DM2

Nutrition, Metabolism & Cardiovascular Diseases (2013) 23, 235–241

Available online at www.sciencedirect.com

SciVerse ScienceDirect

journal homepage: www.elsevier.com/locate/nmcd

Nutrition, Metabolism & Cardiovascular Diseases

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

L. Franzini [a,*,1], D. Ardigò [a,1], F. Cavalot [b,1], R. Miccoli [c,1], A.A. Rivellese [d,1], M. Trovati [b,1], I. Zavaroni [a,1], O. Vaccaro [d,1]

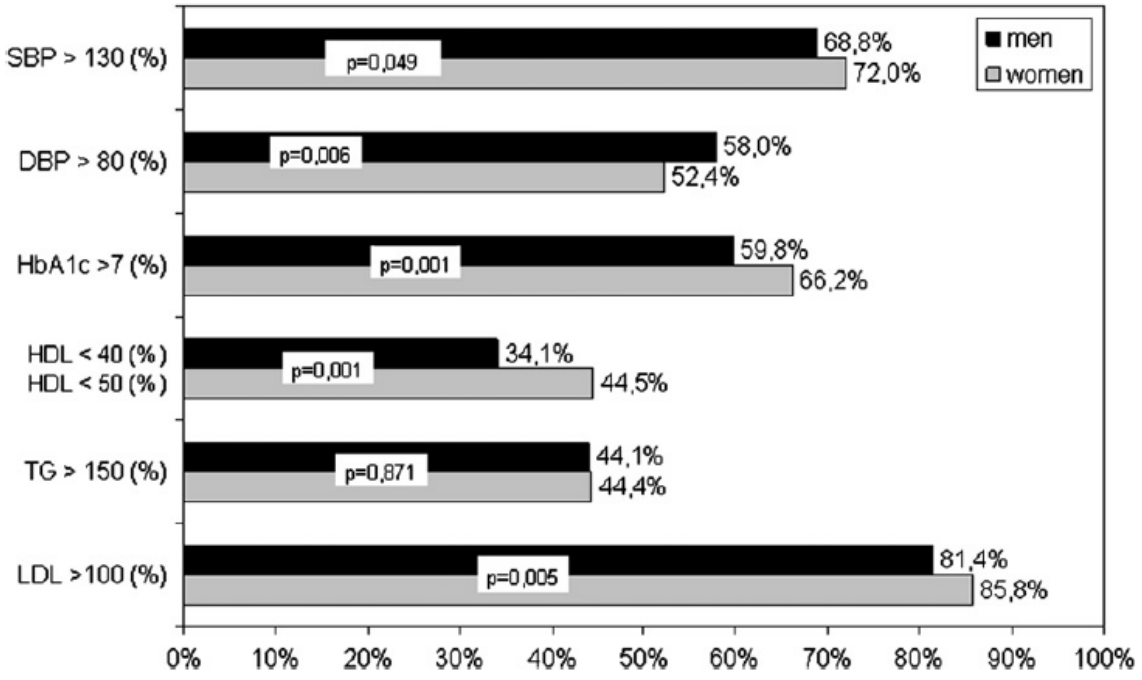


Figure 1 Proportion (%) of men and women out of target for glycated haemoglobin and the cardiovascular risk factors measured in the study. Abbreviations: SBP, systolic blood pressure; DBP, diastolic blood pressure; HbA1c, glycated haemoglobin; HDL, HDL cholesterol; TG, triglycerides; LDL, LDL cholesterol.

Epidemiology/Health Services Research
ORIGINAL ARTICLE

Sex Disparities in the Quality of Diabetes Care: Biological and Cultural Factors May Play a Different Role for Different Outcomes

A cross-sectional observational study from the AMD Annals initiative

MARIA CHIARA ROSSI, MSCPHARMCHEM[1]
MARIA ROSARIA CRISTOFARO, MD[2]
SANDRO GENTILE, MD[3]
GIUSEPPE LUCISANO, MSCSTAT[1]
VALERIA MANICARDI, MD[4]
MARIA FRANCA MULAS, MD[5]
ANGELA NAPOLI, MD[6]
ANTONIO NICOLUCCI, MD[1]
FABIO PELLEGRINI, MSCSTAT[1]
CONCETTA SURACI, MD[7]
CARLO GIORDA, MD[8]
ON BEHALF OF THE AMD ANNALS STUDY GROUP*

✓236 centri
✓188,125 donne
✓227,169 uomini

Donne con DM2 hanno:

+ 14% rischio di HbA1c>9%;
+ 42% rischio di LDL-C >130mg/dl

OBJECTIVE—To investigate the quality of type 2 diabetes care according to sex.

Sex disparities in the quality of diabetes care

Table 2—*Quality indicators of diabetes care according to sex*

	Quality indicators (%)		Crude OR (95% CI)	OR adjusted for case mix (age, diabetes duration, BMI) (95% CI)	OR adjusted for case mix and cluster (95% CI)	ICC
	M	F				
HbA_{1c} >9.0% (>75 mmol/mol) despite insulin treatment	24.8	26.5	1.09 (1.06–1.12)	1.13 (1.10–1.17)	1.14 (1.10–1.17)	0.06
LDL-C ≥130 mg/dL despite lipid-lowering treatment	21.1	25.9	1.28 (1.21–1.34)	1.42 (1.38–1.46)	1.42 (1.38–1.46)	0.03

Diabetologia (2005) 48: 2213–2220
DOI 10.1007/s00125-005-1930-0

REVIEW

Post-menopausal fall of estrogen levels may contribute to beta cell dysfunction in T2DM women

I. F. Godsland

Oestrogens and insulin secretion

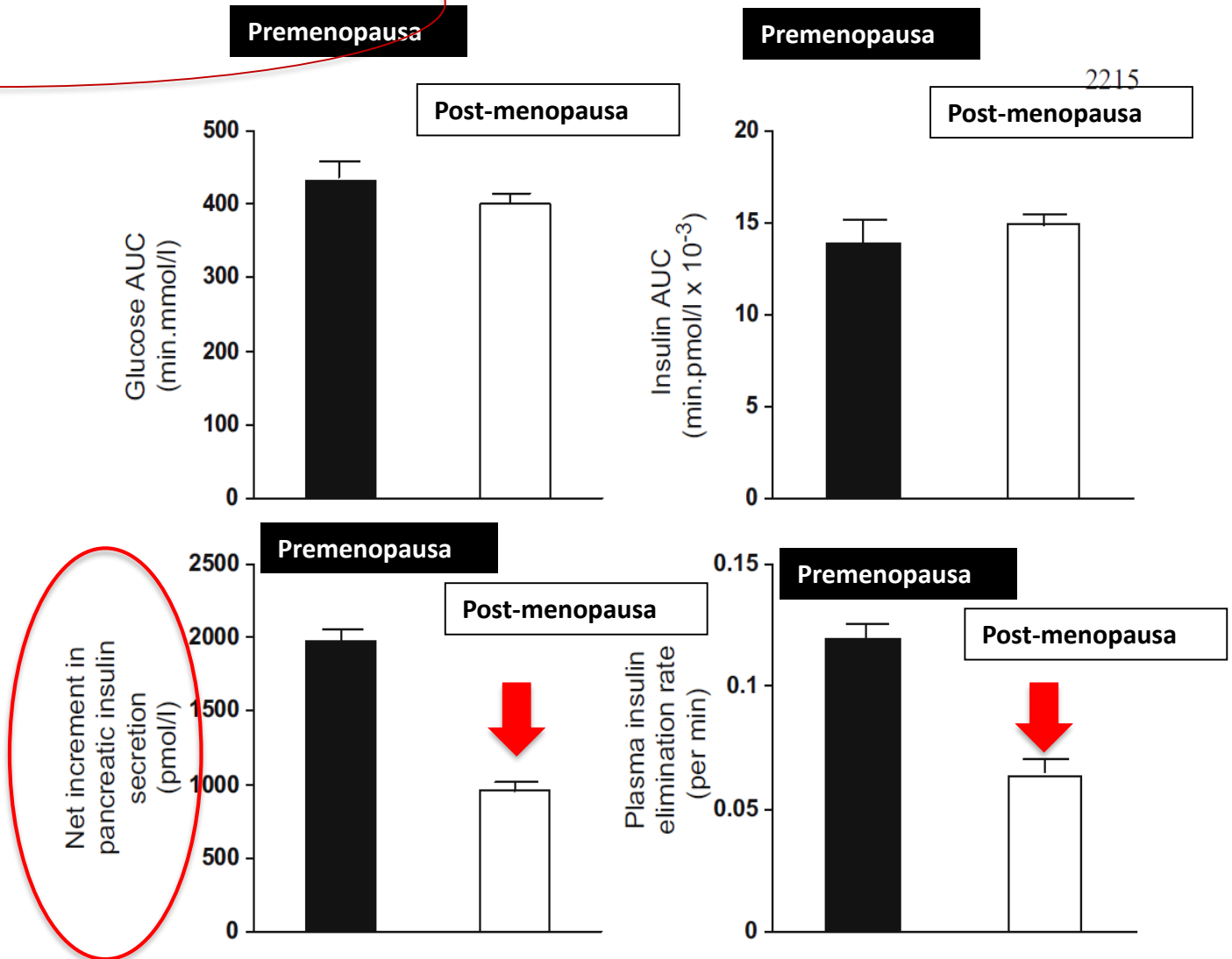


Fig. 2 IVGTT mean glucose AUC and insulin AUC, and mean net increment in insulin secretion and plasma insulin elimination rate derived by modelling analysis of IVGTT insulin and C-peptide concentrations (error bars show SEM). *Closed bars*: premenopausal women (n=66). *Open bars*: postmenopausal women (n=92). Data were standardised to the mean age and BMI for the group as a whole in each group separately to allow for differing effects of age in pre- and post-menopausal women. From data reported in reference [15]

Original Article

Association of the Estrogen Receptor-α Gene With the Metabolic Syndrome and Its Component Traits in African-American Families

The Insulin Resistance Atherosclerosis Family Study

Carla J. Gallagher,[1,2,3] Carl D. Langefeld,[4] Candace J. Gordon,[2] Joel K. Campbell,[4] Josyf C. Mychalecky,[2,4,5,6,7] Michael Bryer-Ash,[8] Stephen S. Rich,[6,7] Donald W. Bowden,[1,2,5] and Michèle M. Sale[2,5,6,9,10]

TABLE 6
Summary of pleiotropic effects of SNPs across ESR1 intron 1–intron 2 region

SNP	Metabolic syndrome	Type 2 diabetes	Fasting insulin	S_i	Triglycerides	LDL	Cholesterol	BMI	Waist circumference	SAT
rs6902771	X		X	X				X		
rs4870056				X						
rs9322331					X	X				
rs2234693				X						
rs9340799	X									
rs7774230			X	X						
rs1709181										
rs12664989						X	X			
rs712221						X				
rs1514348										
rs11155818										
rs827417										
rs2431260	X							X	X	X
rs1709183										
rs1033182	X	X								
rs2175898	X							X	X	
rs11155819										

X represents a positive association (reported in Tables 2 and 4).

original article

Diabetes, Obesity and Metabolism 17: 533–540, 2015.

Gender-based differences in glycaemic control and hypoglycaemia prevalence in patients with type 2 diabetes: results from patient-level pooled data of six randomized controlled trials

ORIGINAL ARTICLE

A. Kautzky-Willer[1], L. Kosi[1], J. Lin[2] & R. Mihaljevic[3]

[1] *Division of Endocrinology and Metabolism, Gender Medicine Unit, Medical University of Vienna, Vienna, Austria*
[2] *Novosys Health, Flemington, NJ, USA*
[3] *Scientific Affairs, Diabetes, Sanofi, Vienna, Austria*

Aims: To determine the impact of gender on glycaemic control and hypoglycaemia in insulin-naïve patients with type 2 diabetes (T2DM).

Methods: Data were pooled from six randomized clinical trials of insulin glargine or NPH insulin in insulin-naïve, inadequately controlled patients. Female [n = 1251; mean glycated haemoglobin (HbA1c) level 8.99%, age 56.91 years, diabetes duration 9.84 years] and male patients (n = 1349; mean HbA1c 8.9%, age 57.47 years, diabetes duration 10.13 years) were started on and treated with insulin glargine or NPH insulin for 24–36 weeks. HbA1c and fasting blood glucose levels, percent achieving HbA1c target of <7% and insulin dose change were recorded.

Results: For both men and women, HbA1c levels were significantly reduced over time ($p < 0.001$); a significantly greater HbA1c reduction was observed in men than in women (−1.36 vs. −1.22; $p = 0.002$). Significantly fewer women achieved target HbA1c of <7% ($p < 0.001$). At the study end, women had a significantly higher insulin dose/kg than men (0.47 vs. 0.42 U/kg; $p < 0.001$). The incidence rates of severe and severe nocturnal hypoglycaemia were significantly higher in women (3.28% vs. 1.85%; $p < 0.05$ and 2.24% vs. 0.59%; $p < 0.001$, respectively). Women were more likely to experience severe hypoglycaemia [odds ratio (OR) 1.80; 95% confidence interval (CI) 1.08, 3.00; $p = 0.02$] and severe nocturnal hypoglycaemia (OR: 3.80; 95% CI 1.72, 8.42; $p = 0.001$).

Conclusions: These observations confirm studies that found a smaller improvement in HbA1c and greater hypoglycaemia in women during insulin treatment. Physicians should be aware of the need to determine and closely monitor dosing, particularly in women, to optimize the balance between glycaemic control and hypoglycaemia risk.

Keywords: gender, hypoglycaemia, insulin glargine, NPH insulin, type 2 diabetes

Insulin dose is higher in T2DM women than men

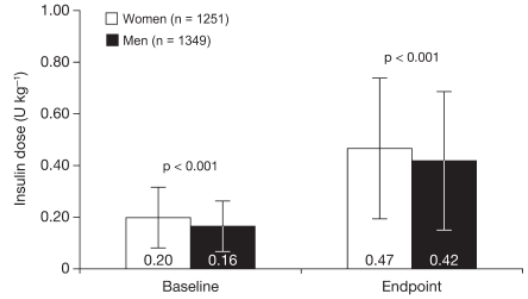


Figure 3. Baseline and study end insulin dose/kg by gender.

HbA1c reduction is lower in T2DM women than men

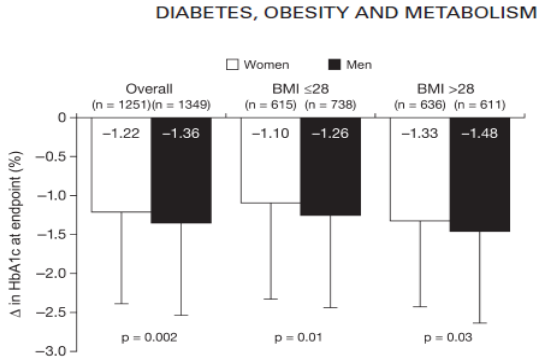


Figure 1. Change in glycated haemoglobin (HbA1c) by gender and body mass index (BMI) strata.

Hypoglyaemic risk is higher in T2DM women than men

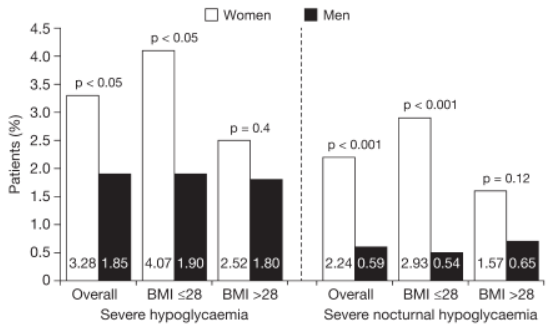


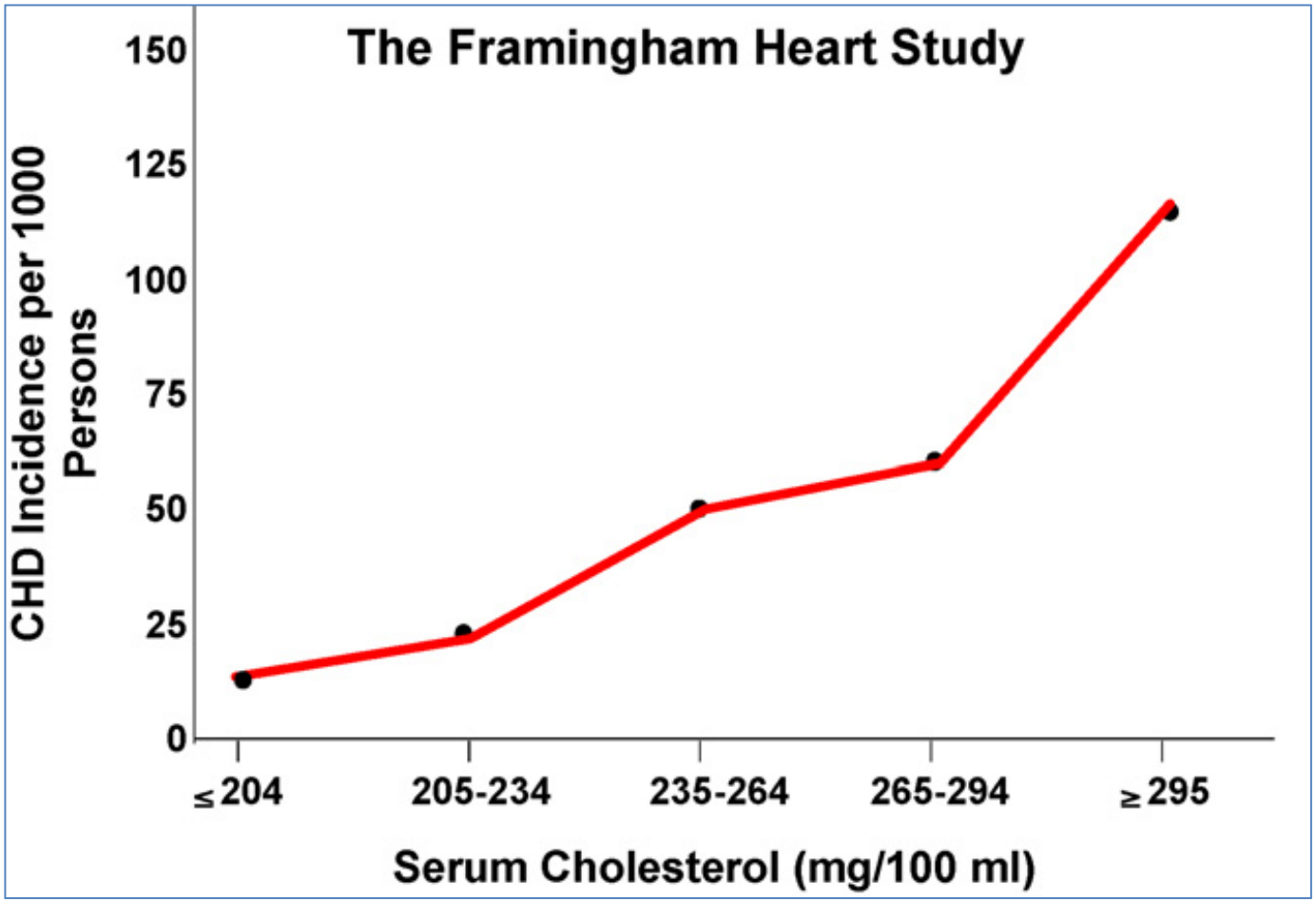
Figure 4. Incidence of severe hypoglycaemia and nocturnal hypoglycaemia by gender and body mass index (BMI).

women

men

A. Kautzy-Willer, et al. DOM 2015
"Gender-based differences in glycaemic control.."

Associazione lineare tra l'incidenza di cardiopatia ischemica e livelli di colesterolo totale nel Framingham Heart Study



Castelli WP, Am J Med 1984

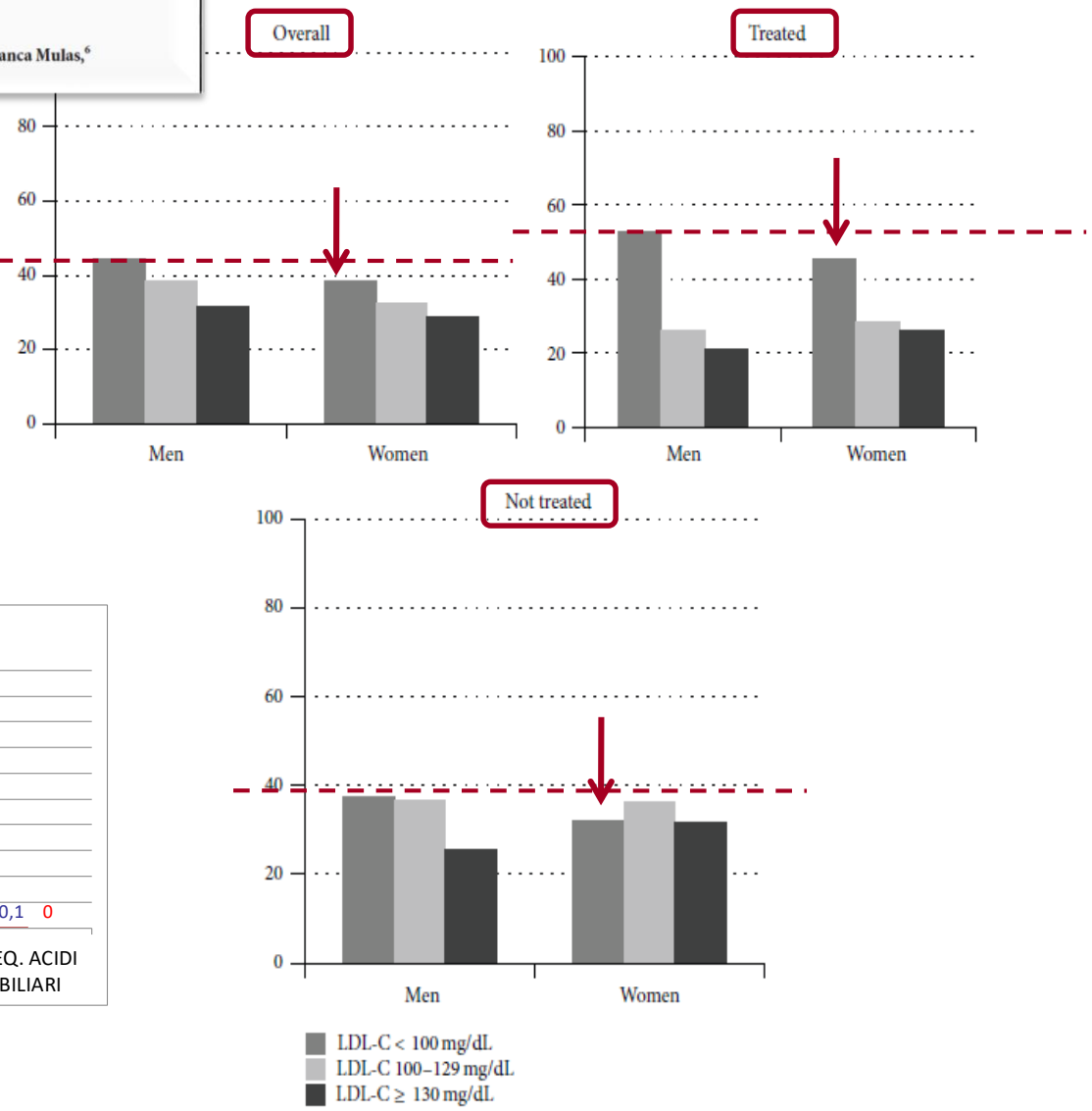
Research Article

Age- and Gender-Related Differences in LDL-Cholesterol Management in Outpatients with Type 2 Diabetes Mellitus

Giuseppina Russo,[1] Basilio Pintaudi,[2] Carlo Giorda,[3] Giuseppe Lucisano,[2] Antonio Nicolucci,[2] Maria Rosaria Cristofaro,[4] Concetta Suraci,[5] Maria Franca Mulas,[6] Angela Napoli,[7] Maria Chiara Rossi,[2] and Valeria Manicardi[8]

International Journal of Endocrinology

La percentuale di pazienti con DM2 che raggiungono i *target* di LDL-C è sempre più bassa nelle donne, sia trattate che non trattate



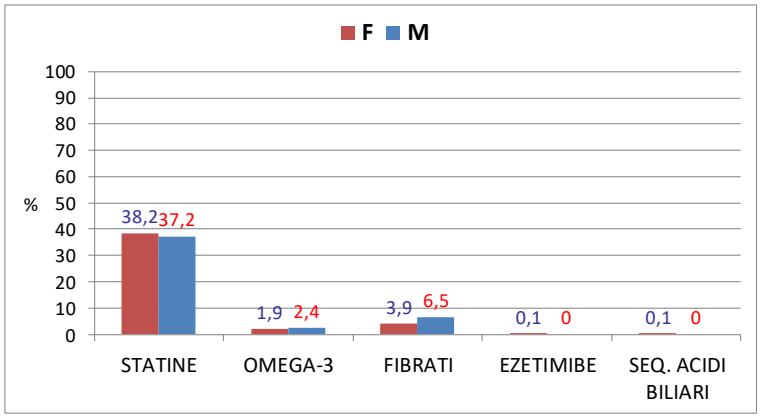
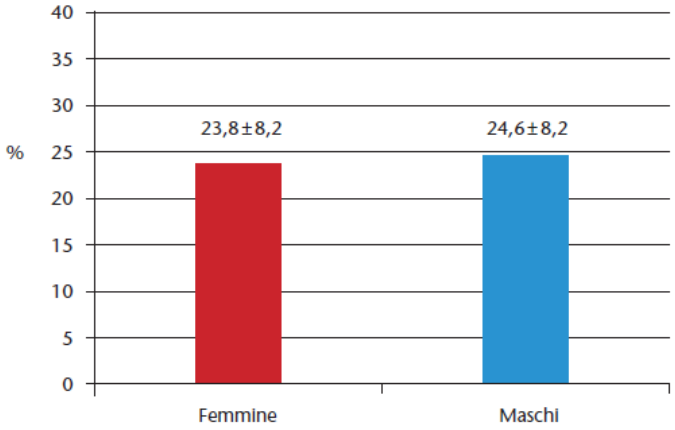


FIGURE 1: LDL-C classes according to gender and lipid-lowering treatment.

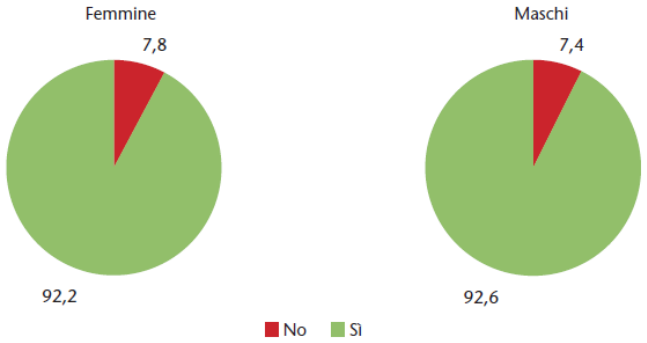
In Italy, quality of care is comparable in T2DM men and women

Score Q medio per sesso



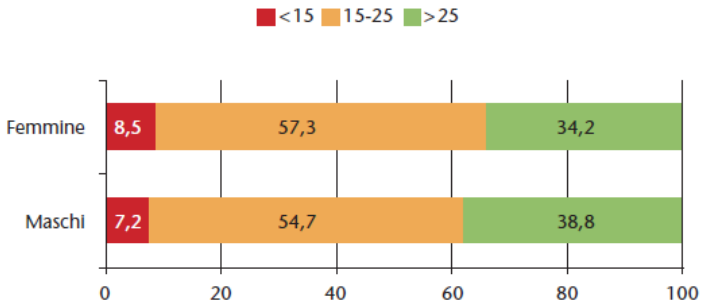
Il punteggio medio dello score di qualità complessiva (score Q) risulta leggermente più basso nelle donne.

Percentuale di soggetti ai quali è stata eseguita almeno una misurazione dell'HbA1c



I dati non mostrano una sostanziale differenza nella percentuale di soggetti che hanno ricevuto almeno una volta il monitoraggio dell'HbA1c negli ultimi 12 mesi; le percentuali sono estremamente elevate, superiori al 90%, in entrambi i sessi.

Score Q in classi per sesso



Uno score Q inferiore a 15 è stato rilevato solo in una bassa percentuale di casi, ma in una quota leggermente più elevata di donne. Analogamente, un punteggio superiore a 25 è presente in oltre un terzo dei casi, sebbene questa percentuale sia lievemente più bassa nelle donne.

Gene-Gender interactions on CVD risk factors

GENDER MEDICINE/VOL. 4, SUPPL. B, 2007

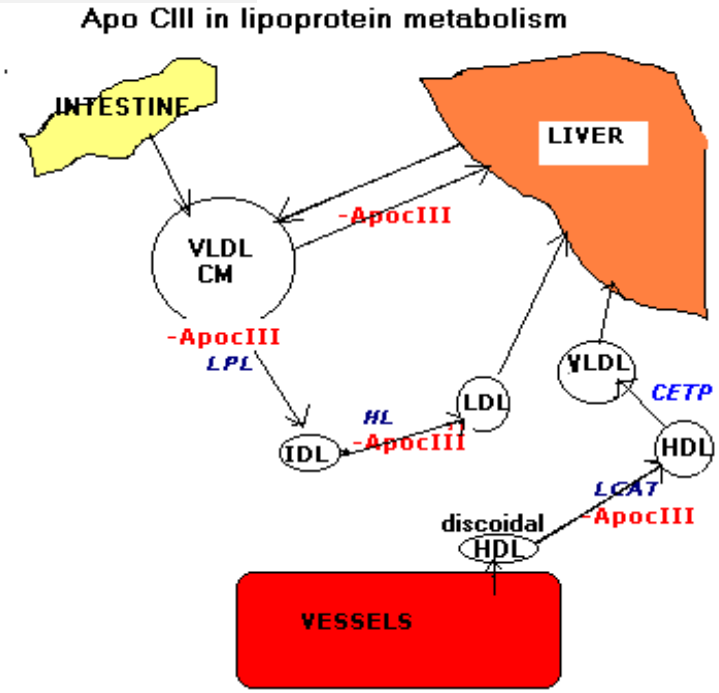
Gender, a Significant Factor in the Cross Talk Between Genes, Environment, and Health

Jose M. Ordovas, PhD

Nutrition and Genomics Laboratory, JM-USDA-Human Nutrition Research Center on Aging at Tufts University, Boston, Massachusetts

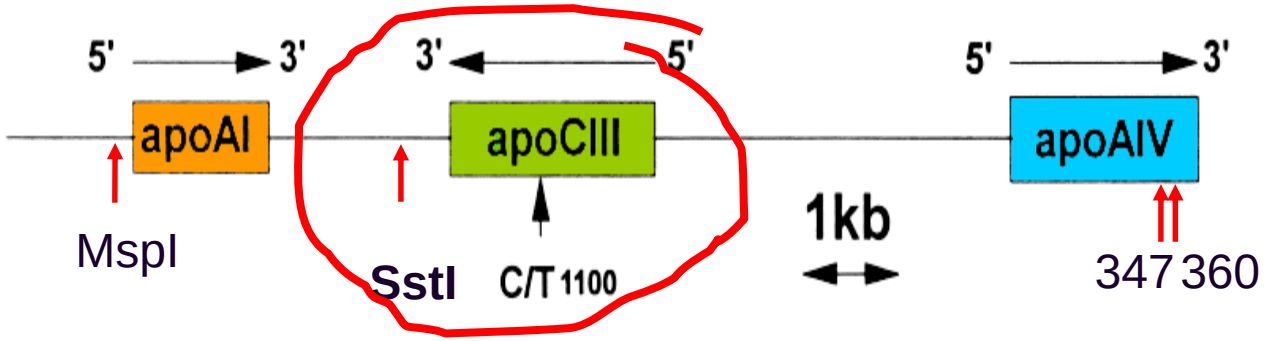
Results: Evidence from some key factors in lipid metabolism (apolipoprotein E [*APOE*]) and obesity (perilipin [*PLIN*]) indicates that the interplay between genes, gender, and environmental factors modulates disease susceptibility. In the Framingham Heart Study, complex interactions have been shown between a promoter polymorphism at the apolipoprotein A1 gene, gender, and dietary polyunsaturated fatty acid intake that modulate plasma concentrations of high-density lipoprotein cholesterol. Likewise, highly and clinically relevant interactions have been observed between the *APOE* gene common alleles *APOE2*, *APOE3*, and *APOE4*, gender, and smoking that determine cardiovascular disease risk. Most interesting is the gender-dependent association between common polymorphisms at the *PLIN* locus and obesity risk that has been replicated in several populations around the world.

APOC3



Glicoproteina di 79 aa sintetizzata dal fegato ed dall'intestino, costituente di CM e VLDL

- From *in vitro* studies: non competitive inhibitor for LpL
- From *animal studies*: overexpress of human APOC3 produce iperTG in transgenic mice
- From *human studies:* association of apo CIII levels with TG, TC and CHD.



ELSEVIER

Atherosclerosis 158 (2001) 173–181

ATHEROSCLEROSIS

www.elsevier.com/locate/atherosclerosis

Association of the Sst-I polymorphism at the *APOC3* gene locus with variations in lipid levels, lipoprotein subclass profiles and coronary heart disease risk: the Framingham offspring study

Giuseppina T. Russo [a], James B. Meigs [b], L. Adrienne Cupples [c], Serkalem Demissie [c], James D. Otvos [d], Peter W.F. Wilson [e], Carlos Lahoz [a], Domenico Cucinotta [f], Patrick Couture [a], Tonya Mallory [g], Ernst J. Schaefer [a], Jose M. Ordovas [a,*]

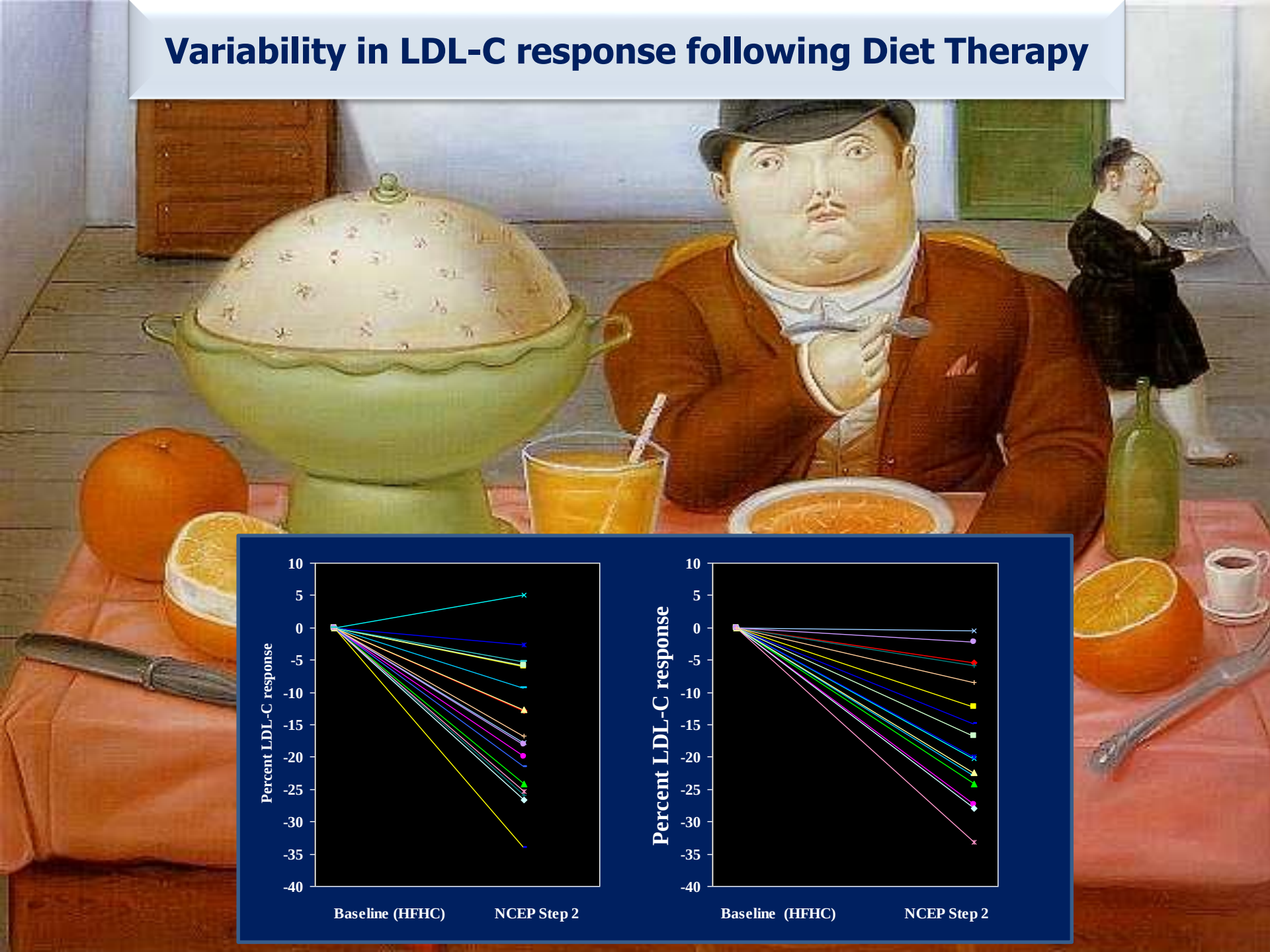
Nelle Donne, *S2* allele (mutato) associato con TC, LDL-C e ApoB;

Negli Uomini, *S2* allele (mutato) associato con sdLDL e insulinemia

Nessuna associazione con CHD in entrambi i sessi.

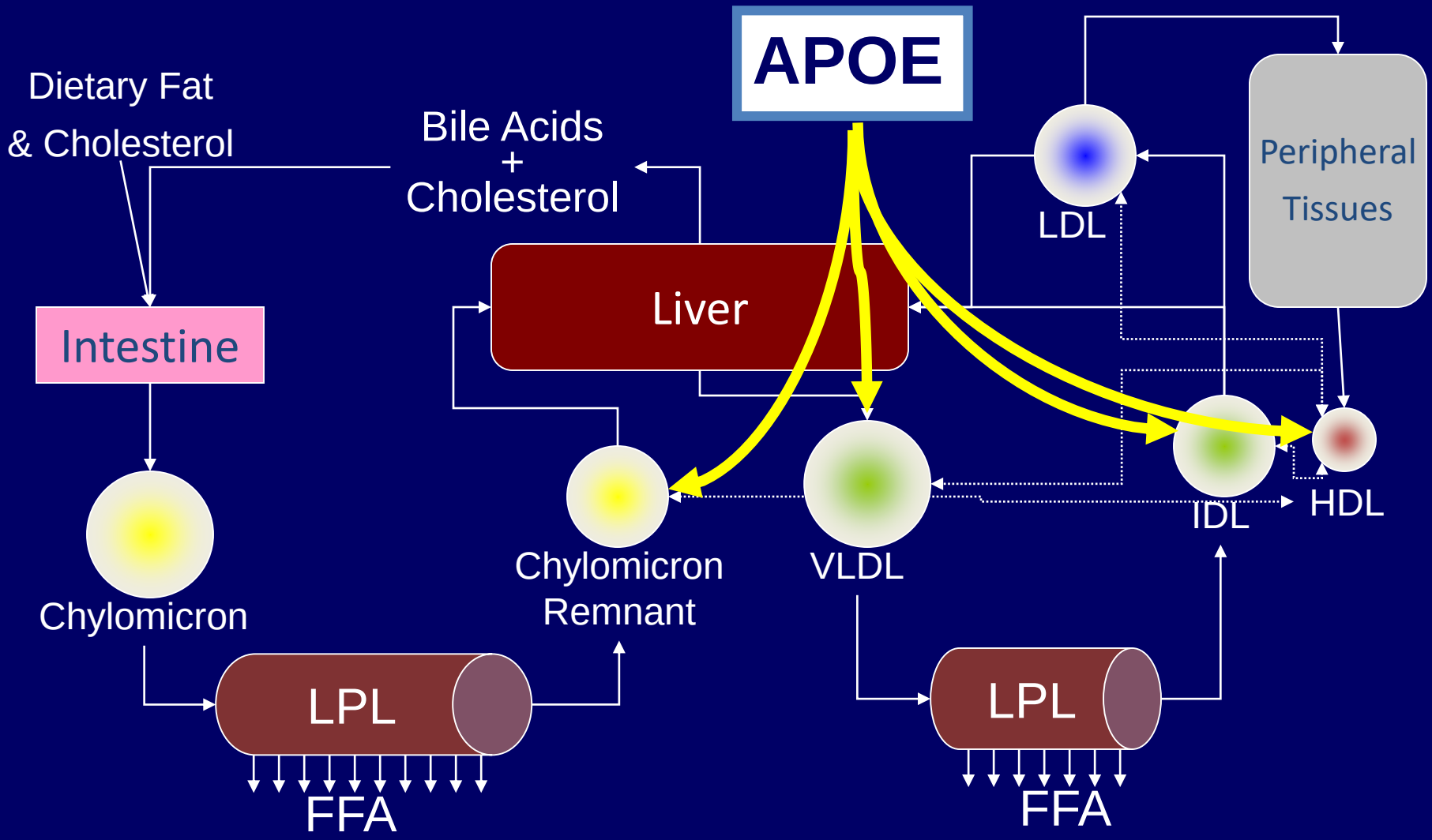
associations were observed in women. Despite the described associations with lipid and glucose metabolism related risk factors, we did not find any significant increase in CHD risk associated with the S2 allele in this population.

Variability in LDL-C response following Diet Therapy



Lipoprotein Metabolism

Exogenous - Pathway - Endogenous



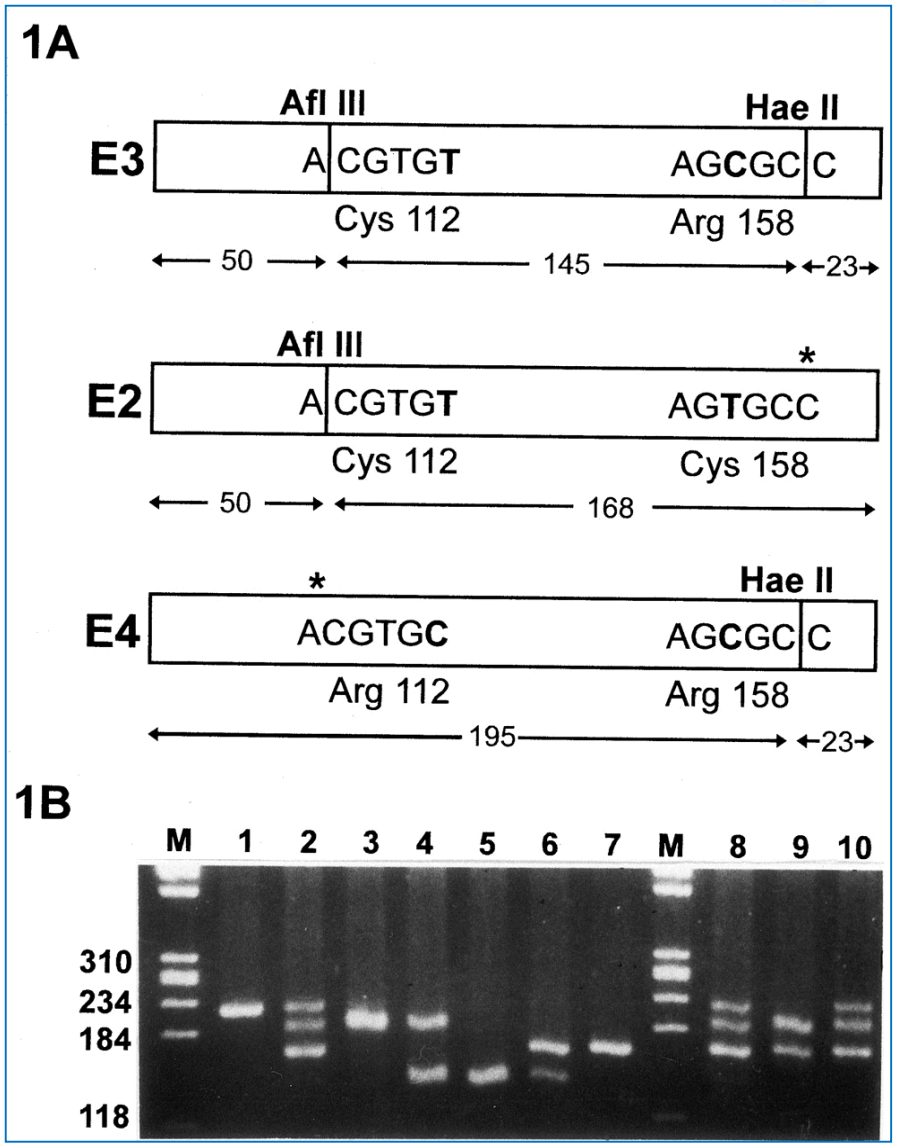
APOE gene

L'APO E è geneticamente controllata da 3 alleli (ε2,ε3, ε4) ad un singolo locus genico sul cromosoma 19 (insieme ad apo CI ed apo CII).

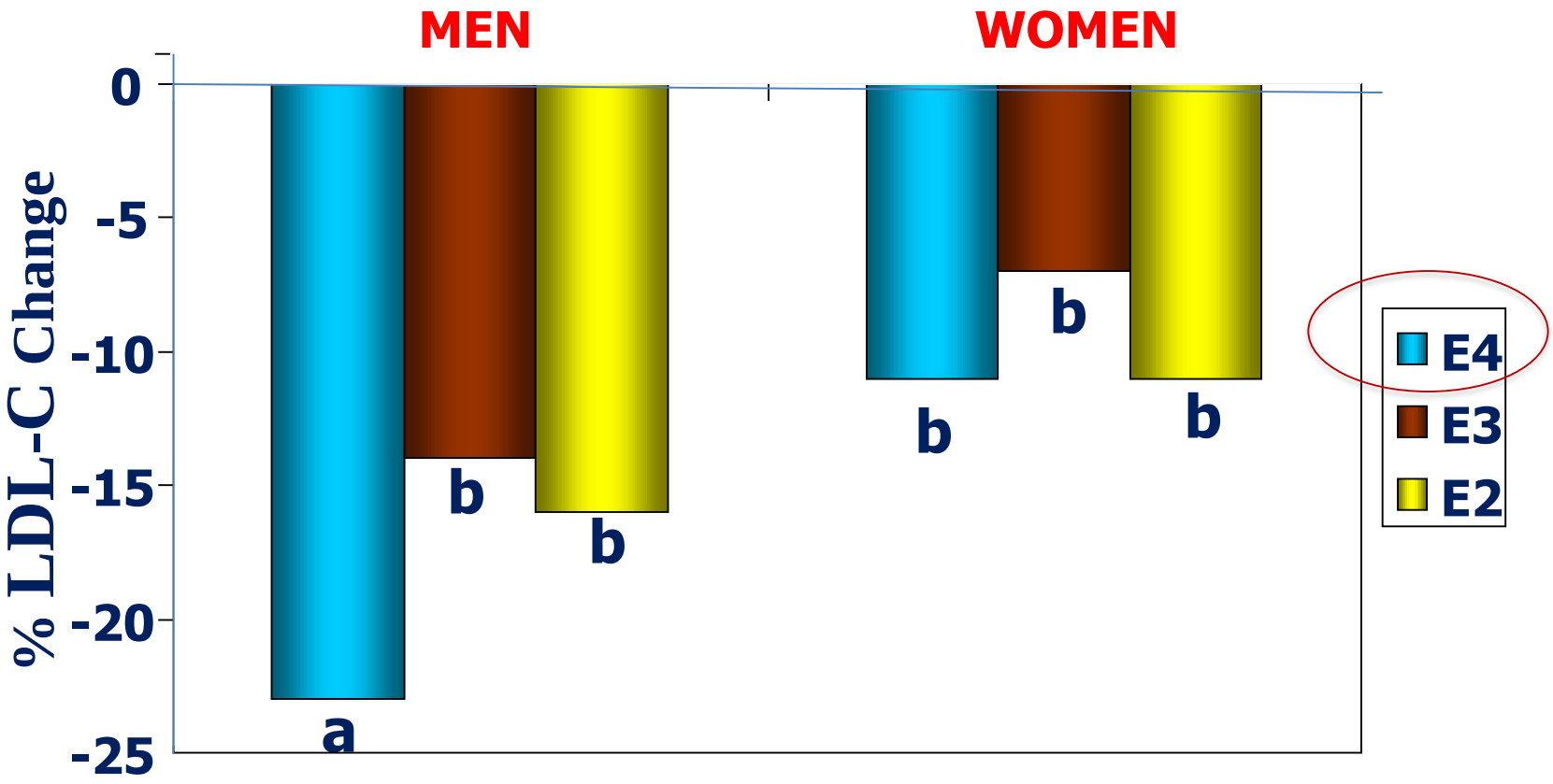
- ✓ **Le sostituzioni aminoacidiche nelle ApoE mature sono:**
  - ***Apo E3:*** **Cys 112, Arg 158**
  - ***Apo E2:*** **Cys 112, *Cys 158***
  - ***Apo E4: Arg 112*, Arg 158**

Nella popolazione Caucasica la distribuzione degli alleli dell'APOE è:

E3: 77%
E2: 8%
E4: 15%



LDL-C Response to a Therapeutic Diet by *APOE* allele



Lopez-Miranda et al. J Lipid Res. 1994;35:1965-75.

British Journal of Clinical Pharmacology DOI:10.1111/j.1365-2125.2003.02060.x

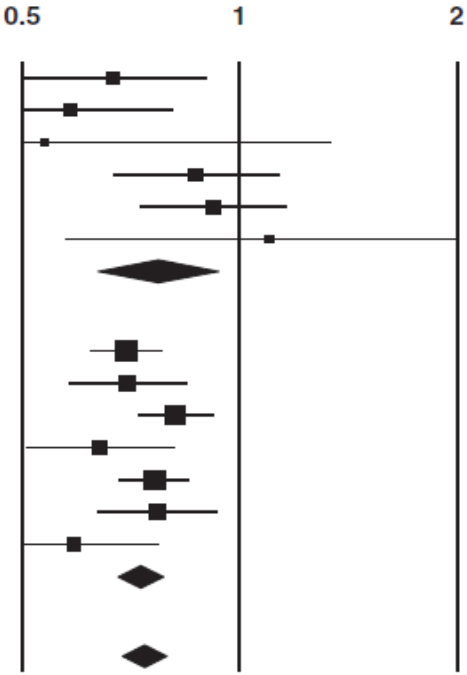
Efficacia terapia Ipolipemizzante nelle donne

Meta-analysis of large randomized controlled trials to evaluate the impact of statins on cardiovascular outcomes

Bernard M. Y. Cheung, Ian J. Lauder,[1] Chu-Pak Lau & Cyrus R. Kumana
Department of Medicine and [1]Statistics and Actuarial Science, University of Hong Kong, Queen Mary Hospital, Hong Kong

Major coronary events

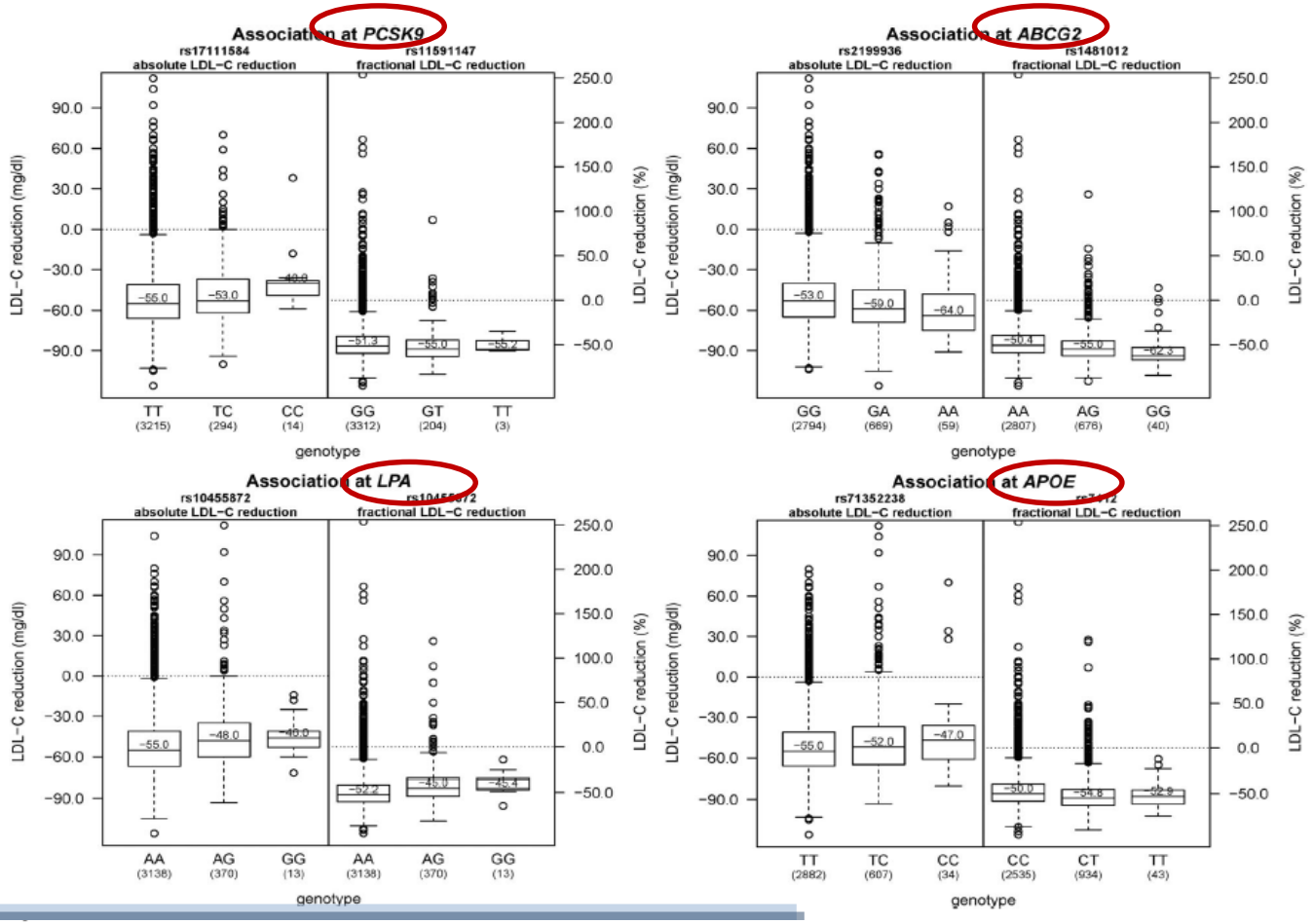
sex	Citation	Treated	Control	Effect	Lower	Upper
F	4S	59 / 407	91 / 420	.67	.50	.90
F	CARE	46 / 286	80 / 290	.58	.42	.81
F	AFCAPS/TexCAPS	7 / 499	13 / 498	.54	.22	1.34
F	LIPID	90 / 756	104 / 760	.87	.67	1.13
F	PROSPER	125 / 1495	137 / 1505	.92	.73	1.16
F	ASCOT-LLA	19 / 979	17 / 963	1.10	.57	2.10
F (6)		**346 / 4422**	**442 / 4436**	**.77**	**.64**	**.94**
M	4S	372 / 1814	531 / 1803	.70	.62	.78
M	WOSCOP	174 / 3302	248 / 3293	.70	.58	.84
M	CARE	384 / 1795	469 / 1788	.82	.72	.92
M	AFCAPS/TexCAPS	109 / 2805	170 / 2803	.64	.51	.81
M	LIPID	467 / 3756	611 / 3742	.76	.68	.85
M	PROSPER	167 / 1396	219 / 1408	.77	.64	.93
M	ASCOT-LLA	81 / 4189	137 / 4174	.59	.45	.77
M (7)		**1754 / 19057**	**2385 / 19011**	**.73**	**.68**	**.78**
Combined (13)		**2100 / 23479**	**2827 / 23447**	**.74**	**.69**	**.79**



Genetic Determinants of Statin-Induced Low-Density Lipoprotein Cholesterol Reduction

The Justification for the Use of Statins in Prevention: An Intervention Trial Evaluating Rosuvastatin (JUPITER) Trial

Daniel I. Chasman, PhD; Franco Giulianini, PhD; Jean MacFadyen, BA; Bryan J. Barratt, PhD; Fredrik Nyberg, MD, PhD, MPH; Paul M Ridker, MD, MPH



Conclusions—Inherited polymorphisms that predominantly relate to statin pharmacokinetics and endocytosis of LDL particles by the LDL receptor are common in the general population and influence individual patient response to statin therapy. **(*Circ Cardiovasc Genet*. 2012;5:257-264.)**

Circ Cardiovasc Genet. 2012;5:257-264

Published in final edited form as:
Atherosclerosis. 2008 September ; 200(1): 109–114. doi:10.1016/j.atherosclerosis.2007.12.004.

Genetic Variation at the LDL Receptor and HMG CoA Reductase Gene Loci, Lipid Levels, Statin Response, and Cardiovascular Disease Incidence in PROSPER

Eliana Polisecki[1], Hind Muallem[2], Nobuyo Maeda[2], Inga Peter[3], Michele Robertson[4], Alex D McMahon[4], Ian Ford[4], Christopher Packard[5], James Shepherd[5], J Wouter Jukema[6], Rudi G. J. Westendorp[6], Anton J. M. de Craen[6], Brendan M. Buckley[7], Jose M. Ordovas[8], and Ernst J. Schaefer[1] on behalf of the Prospective Study of Pravastatin in the Elderly at Risk (PROSPER) Investigators.

Percent LDL-C Response to Pravastatin by LDLR SNP Genotype

SNP	Adjusted Mean Percent LDL-Cholesterol Reduction [a]				P [b]
	N	Men	N	Women	
C44857T					
CC	530	−35.5 ± 1	534	−35.8 ± 1	
CT	343	−36.8 ± 1	358	−36.7 ± 1	0.08
TT	67	−34.7 ± 1	66	−37.5 ± 1	0.03 [c]
A44964G					
AA	523	−36.1 ± 1	543	−35.9 ± 1	
AG	363	−35.9 ± 1	361	−36.6 ± 1	0.75
GG	54	−34.8 ± 1	56	−36.4 ± 1	

Incidence of Coronary Heart Disease in Type 2 Diabetic Men and Women

Impact of microvascular complications, treatment, and geographic location

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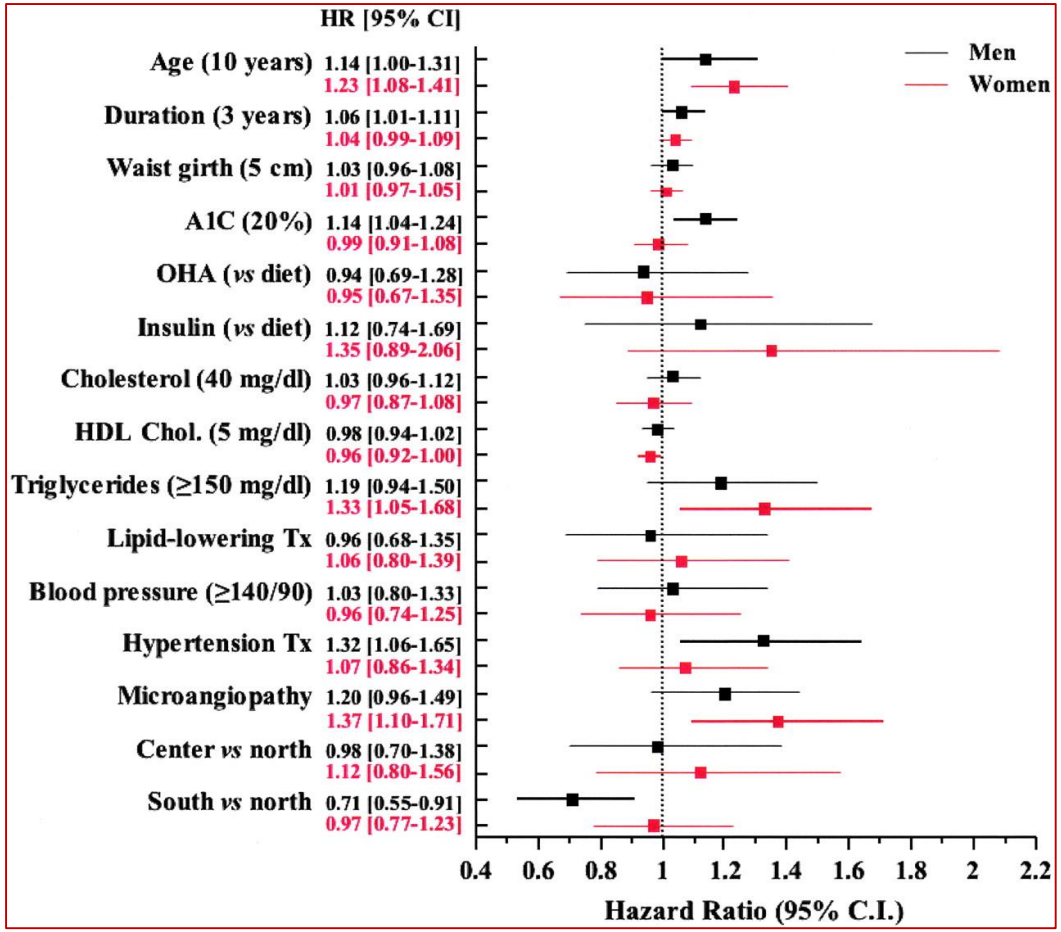
CARLO GIORDA, MD[2]
MARINA MAGGINI, PHD[3]
EDOARDO MANNUCCI, MD[4]
ROBERTO RASCHETTI, PHD[3]
FLAVIA LOMBARDO, PHD[3]
STEFANIA SPILA-ALEGIANI, PHD[3]
SALVATORE TURCO, MD[5]
MARIO VELUSSI, MD[6]
ELE FERRANNINI, MD[7]
FOR THE DIABETES AND INFORMATICS STUDY GROUP, ASSOCIATION OF CLINICAL DIABETOLOGISTS, ISTITUTO SUPERIORE DI SANITÀ

Diabetes is estimated to be responsible for 5.2% of all deaths (1). Since the Framingham Study (2), epidemiology has consistently shown that diabetes confers an increased risk for coronary heart disease (CHD) and cardiac mortality (3–6). Salient features of this association are the following: *1*) relative



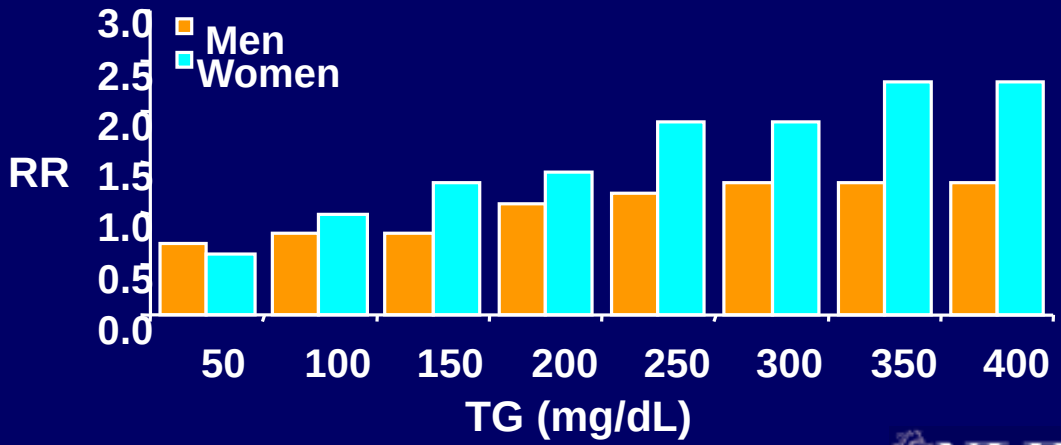
Independent predictors of incident CHD in diabetic men (black) and women (red).

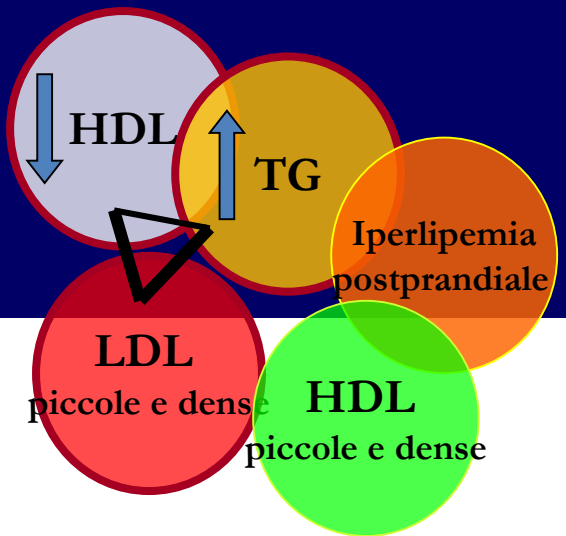
American Diabetes Association.

Diabetes Care 30:1241–1247, 2007

Impact of TG Levels on Relative Risk of CHD:
Framingham Heart Study

La dislipidemia aterogena è un importante fattore di rischio nelle donne





Castelli, Can J Cardiol 1988

HDL

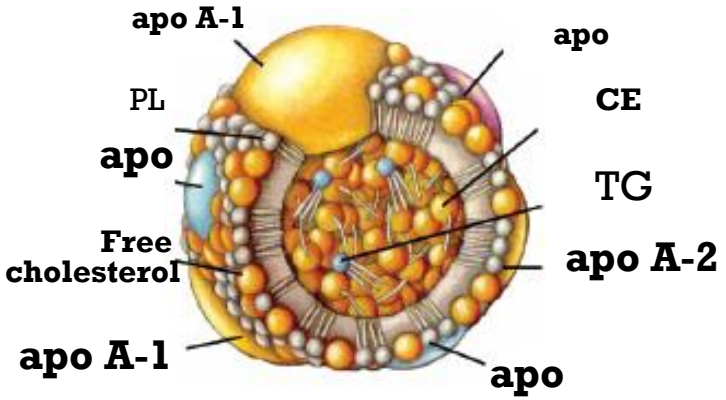
Bassi livelli di colesterolo HDL aumentano il rischio cardiovascolare

HDL
piccole e dense

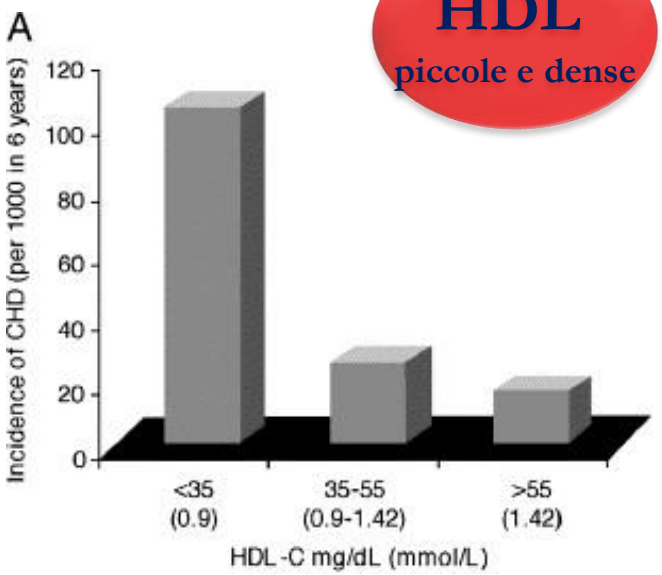
HDL-C as a predictor of CHD risk.
(A) Data from a 6-year follow up of the PROCAM study showing that the incidence of CHD decreases with higher levels of HDL-C (Assmann et al., 1996).

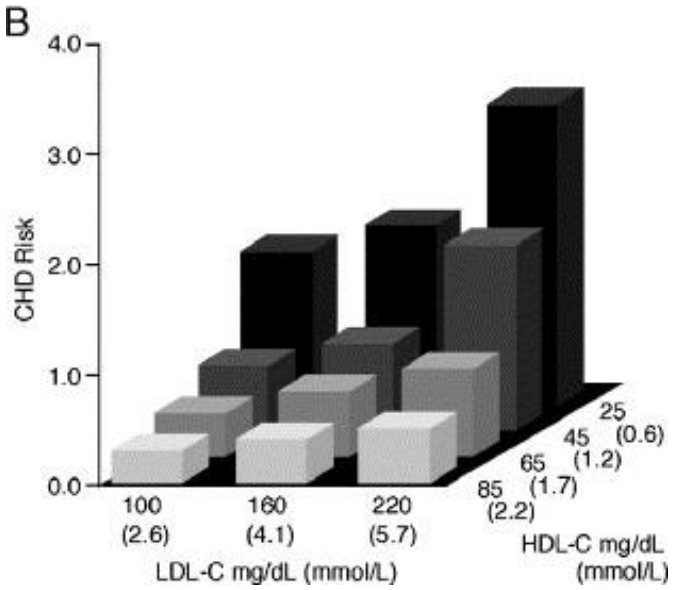
(B) Data from the Framingham study showing that high levels of HDL-C reduce the risk of CHD at all levels of LDL-C (Gordon et al., 1977).

HDL cholesterol ≥60 mg/dL counts as a "negative" risk factor; its presence removes one risk factor from the total count.
(Adult Treatment Panel III- ATP III Guidelines)



Sottopopolazioni HDL





Atherosclerosis 210 (2010) 294–301

Contents lists available at ScienceDirect

Atherosclerosis

journal homepage: www.elsevier.com/locate/atherosclerosis

Influence of menopause and cholesteryl ester transfer protein (CETP) *Taq*IB polymorphism on lipid profile and HDL subpopulations distribution in women with and without type 2 diabetes

Giuseppina T. Russo[a,*], Kathleen V. Horvath[b], Antonino Di Benedetto[a], Annalisa Giandalia[a], Domenico Cucinotta[a], Bela Asztalos[b]

[a] Department of Internal Medicine, University of Messina, Italy
[b] Lipid Metabolism Laboratory, JM-USDA-Human Nutrition Research Center on Aging at Tufts University, Boston, MA, USA

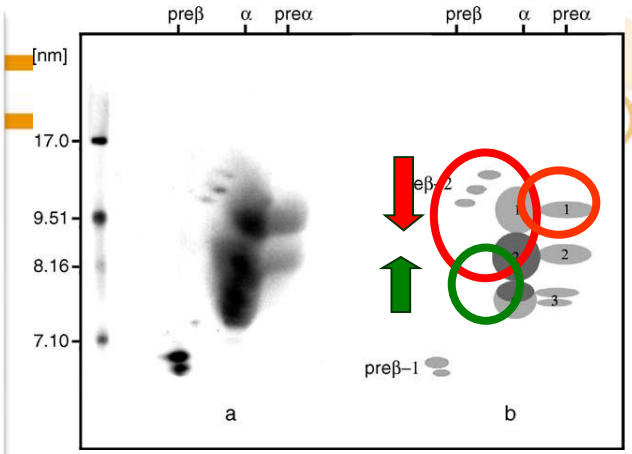


Table 2. Plasma lipids, lipoprotein and apo-A-I-containing HDL subpopulations in CHD-free pre- and postmenopausal women with and without type 2 diabetes.

	Type 2 Diabetic women		Control women			
	Pre-menopause	Post-menopause	Pre-menopause	Post-menopause	P1	P2
T-C (mg/dl)	189.0 ± 32.4	192.5 ± 26.9 ↑	179.8 ± 29.3	203.9 ± 24.7 ↑	NS	0.04
HDL-C (mg/dl)	45.9 ± 13.8	48.6 ± 13.4 ↑	56.9±11.8	55.6±11.7 ↑	0.0004	0.01
LDL-C (mg/dl)	127.1 ± 30.3 ↑	122.3 ± 24.6	116.3±27.4	134.2 ± 27.3 ↑	NS	0.04
VLDL-C (mg/dl)	28.0 ± 20.3 ↑	20.8 ± 9.1	15.6 ± 5.3	19.4 ± 8.7 ↑	<0.001	<0.001
Triglycerides (mg/dl)	140.1 ± 101.5 ↑	104.1 ± 45.5	78.2 ± 26.5	96.8 ± 43.7 ↑	<0.001	<0.001
Apo-A-I- containing HDL subpopulations						
α-1 HDL (mg/dl)	18.2 ± 8.2	20.2 ± 9.6	22.8 ± 8.1	23.8 ± 10.8	0.02	0.01
α-2 HDL (mg/dl)	42.5 ± 11.0	40.3 ± 8.2	45.9 ± 8.6	45.1 ± 9.4	NS	0.01
α-3 HDL (mg/dl)	17.8 ± 6.7	18.5 ± 4.3	16.4 ± 3.6	16.3 ± 3.9	NS	NS
Preα-1 HDL (mg/dl)	5.7 ± 3.4	5.3 ± 3.4	6.9 ± 2.5	6.6 ± 4.1	NS	NS

Modified from Russo GT et al.[48]. Values are n, mean ± SD. T-C, total cholesterol; -C, total cholesterol; LDL-C, low- density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol; VLDL, very low-density lipoprotein; NS, not significant. P1, pre-menopause diabetic vs controls; P2, post-menopause diabetic vs controls.

Hindawi Publishing Corporation
International Journal of Endocrinology
Volume 2014, Article ID 607924, 9 pages
http://dx.doi.org/10.1155/2014/607924

Research Article

Markers of Systemic Inflammation and Apo-AI Containing HDL Subpopulations in Women with and without Diabetes

Giuseppina T. Russo,[1] Annalisa Giandalia,[1] Elisabetta L. Romeo,[1] Angela Alibrandi,[2] Katalin V. Horvath,[3] Bela F. Asztalos,[3] and Domenico Cucinotta[1]

[1] *Department of Clinical and Experimental Medicine, University of Messina, Via C. Valeria, 98124 Messina, Italy*

Table 3: Univariate and multivariate regression analysis between hsCRP and IL-6 and metabolic, lipid, and Apo-AI containing HDL subpopulations profile in total population.

	hsPCR				IL-6			
	Univariate regression		Multivariate regression		Univariate regression		Multivariate regression	
	B	*P*	*B*	*P*	*B*	*P*	*B*	*P*
Anthropometric and metabolic parameters								
Di								
BM								
Wa								
Sy								
Fasting BG	0.03	0.005	—	—	0.01	0.009	0.011	0.02
Fasting insulin	0.09	0.004	—	—	0.04	0.009	—	—
Lipid and Apo-AI containing HDL subpopulations profile								
HDL-C	−0.10	0.005			−0.05	0.002	—	
Apo-AI	—	—	—	—	−0.03	0.003	—	—
Apo-AII	−0.21	0.04	—	—	−0.13	0.004	—	—
α-1 HDL	−0.11	0.04	—	—	—	—	—	—
α-2 HDL	—	—	—	—	−0.06	0.009	—	—
α-3 HDL	—	—	—	—	0.11	0.04	—	—
Pre-α-1 HDL	−0.39	0.007	−0.34	0.083	−0.13	0.03	—	—

Only significant *P* are presented. Waist C: waist circumference; BP: blood pressure; BG: blood glucose; Apo: apolipoprotein.

Nelle donne con DM2, le sottopopolazioni HDL più *ateroprotettive* si associano a ridotti livelli di hsPCR e IL-6

Patient Preference and Adherence

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ORIGINAL RESEARCH

Factors associated with adherence to oral antihyperglycemic monotherapy in patients with type 2 diabetes

Results: Of the 133,449 eligible patients, the mean age was 61 years and 51% were men.

PDC: proportion of days covered with therapy after first prescription

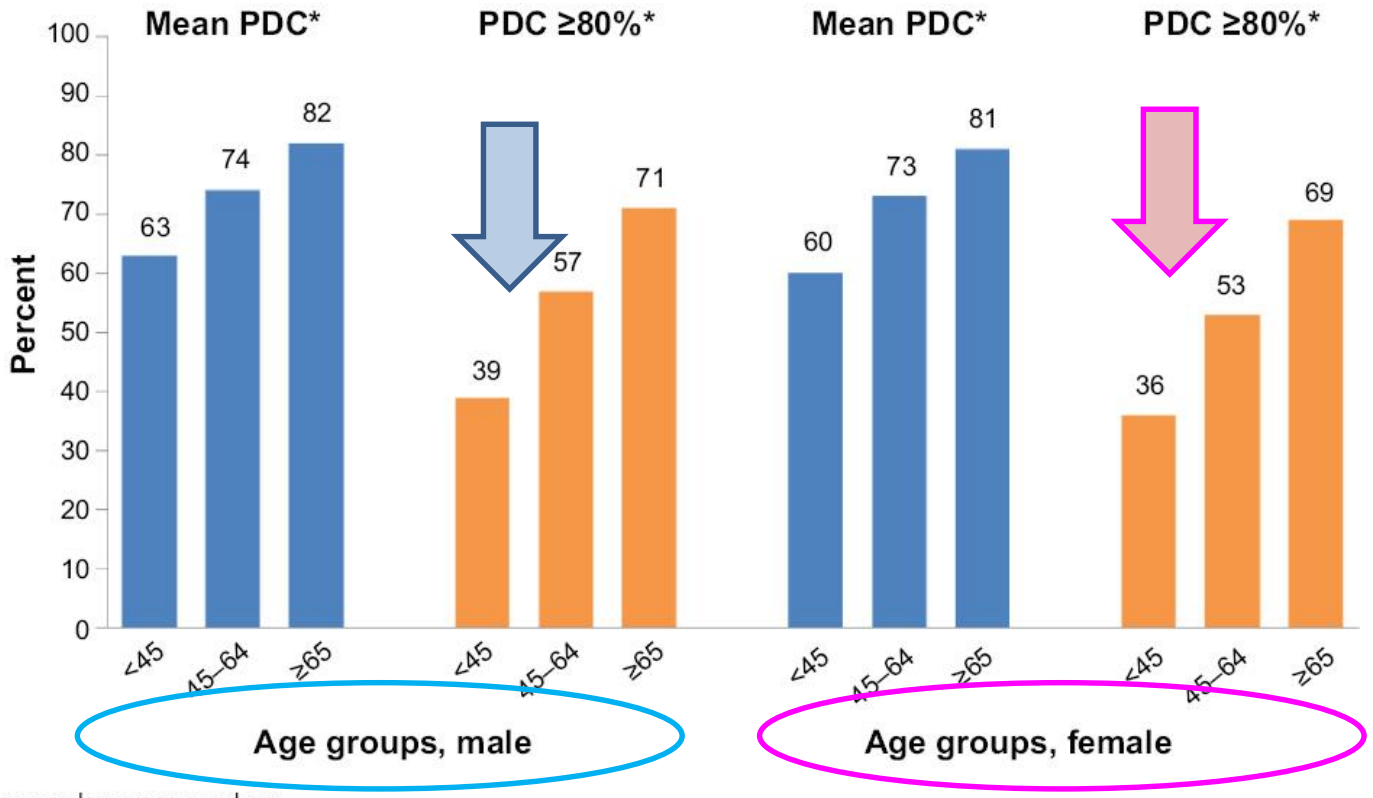


Figure 3 Adherence by age group and sex.
Note: *$P<0.0001$ versus reference group (≥65 years).
Abbreviation: PDC, proportion of days covered.

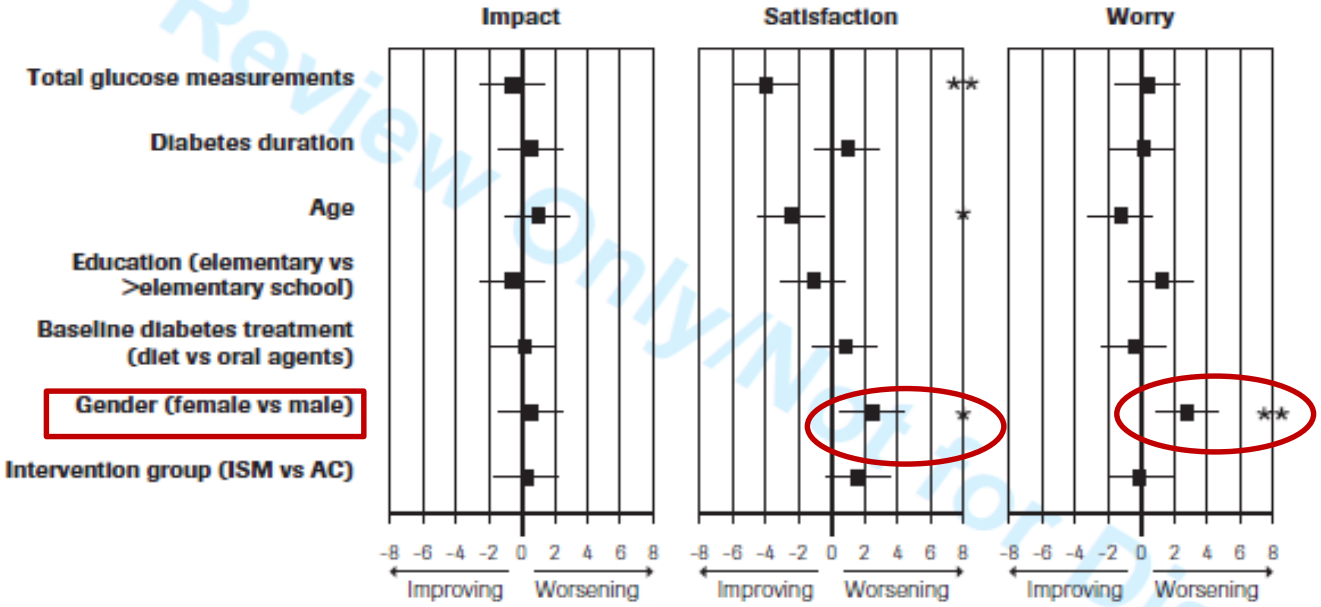
ORIGINAL ARTICLE

The Burden of Structured Self-Monitoring of Blood Glucose on Diabetes-Specific Quality of Life and Locus of Control in Patients with Noninsulin-Treated Type 2 Diabetes: The PRISMA Study

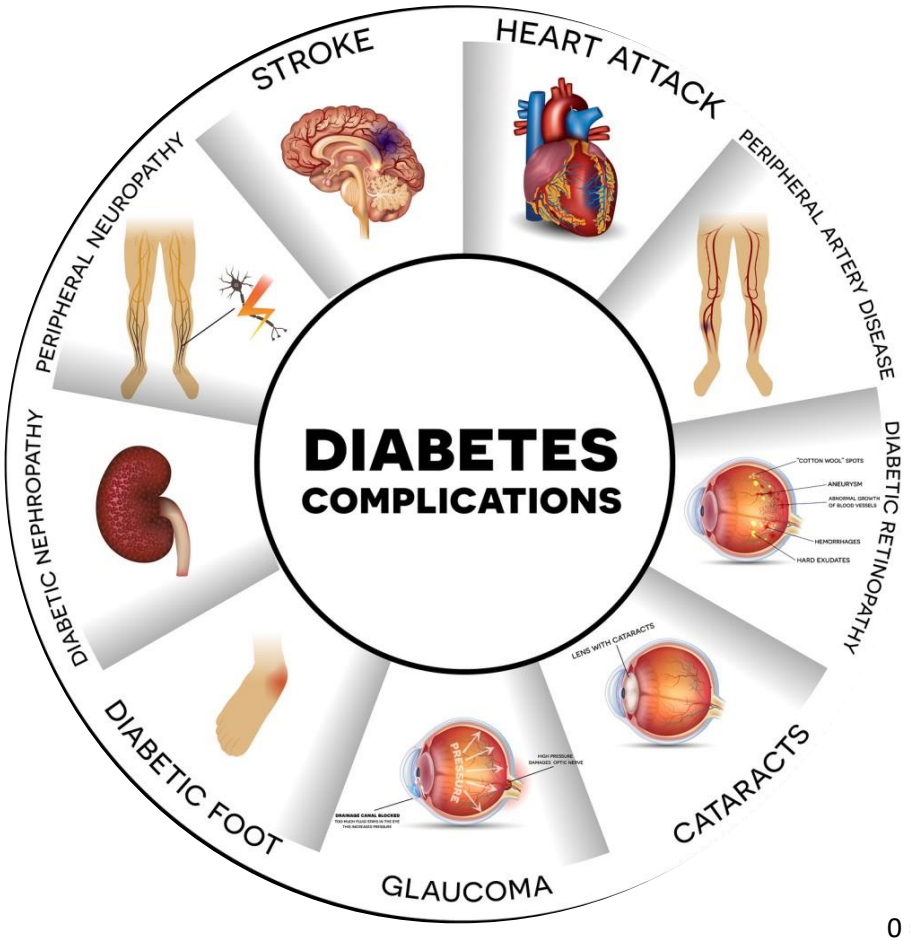
Giuseppina T. Russo, MD, PhD,[1] Marina Scavini, MD, PhD,[2] Elena Acmet, MD, MBA,[3] Erminio Bonizzoni, PhD,[4] Emanuele Bosi, MD,[2,5] Francesco Giorgino, MD, PhD,[6] Antonio Tiengo, MD,[7] and Domenico Cucinotta, MD[1]; on behalf of the PRISMA Study Group*

DIABETES TECHNOLOGY & THERAPEUTICS
Volume 18, Number 7, 2016
Mary Ann Liebert, Inc.
DOI: 10.1089/dia.2015.0358

Factors independently associated with QoL measures in T2DM subjects participating to the PRISMA study



Differenze di genere nelle complicanze microangiopatiche nel diabete di tipo 2



0 = death, 1 = life in perfect health

Huang S et al. Diabetes Care 2007

see original article on page 505

Gender differences in chronic kidney disease

Kunitoshi Iseki[1]

Women live longer than men. Can this phenomenon be explained by chronic kidney disease (CKD)? Gender differences in the prevalence and incidence of CKD are discussed.

Kidney International (2008) **74**, 415–417. doi:10.1038/ki.2008.261

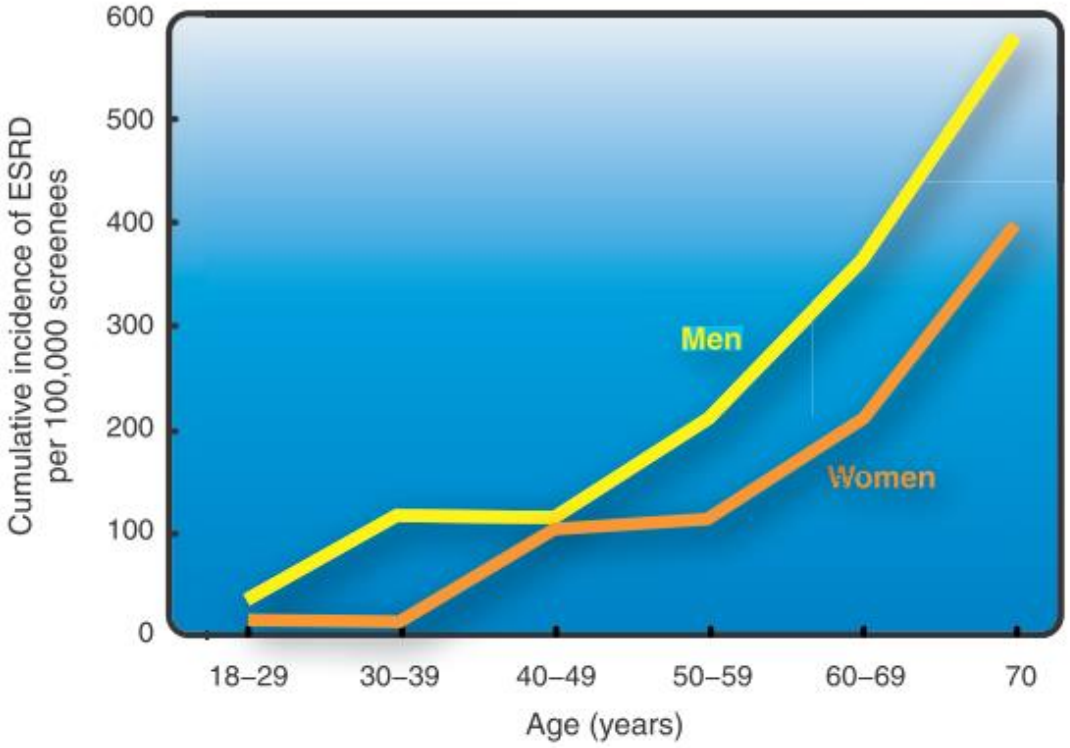
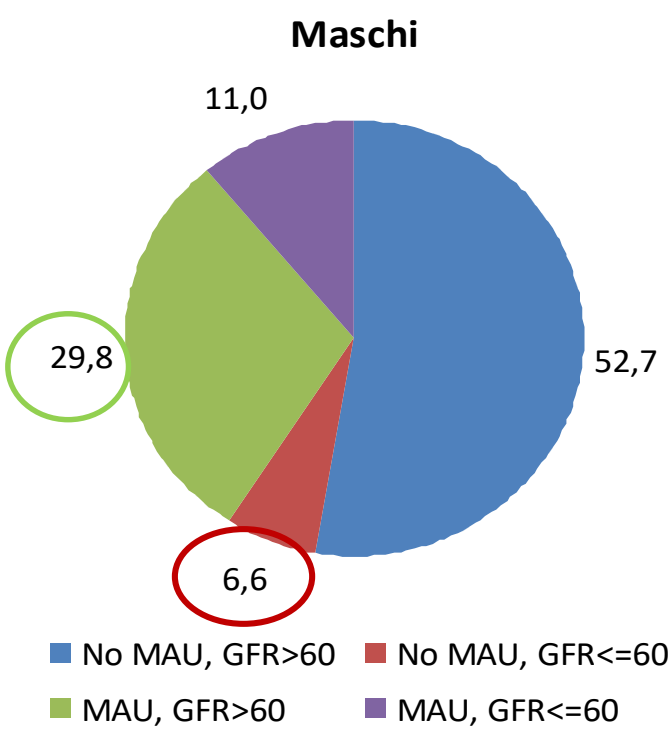
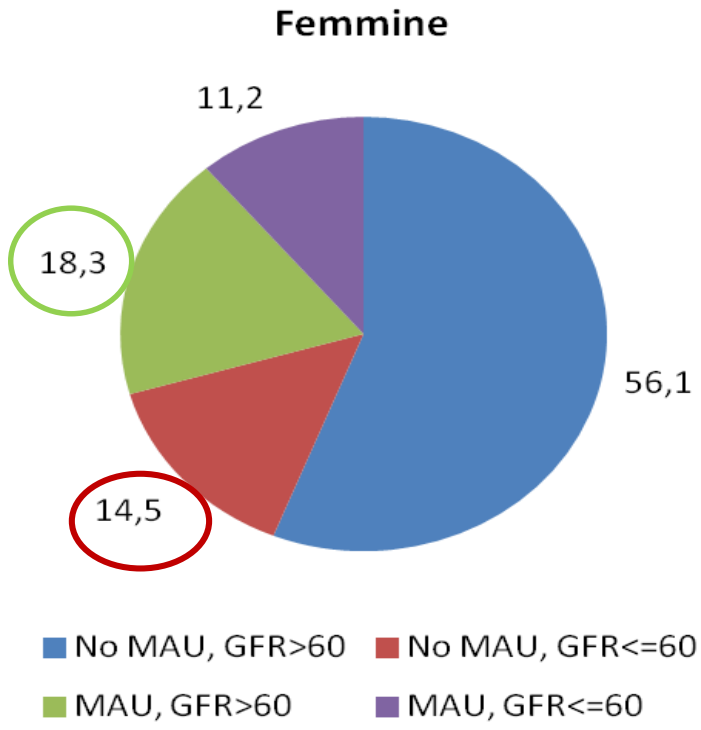


Figure 1 | The cumulative incidence of ESRD per 100,000 screenees, shown by age at screening in both men and women. Figure was created from database of ref. 2.

Distribuzione della popolazione divisa per SESSO in relazione alla presenza di MAU e di riduzione del GFR (%)





I dati raccolti nel corso della normale pratica clinica da 251 Servizi di Diabetologia diffusi sull'intero territorio nazionale

415.346 soggetti con diagnosi di diabete di tipo 2 (DM2) sono stati visti nel corso dell'anno 2009.

I dati raccolti mediante cartella clinica informatizzata e costituzione del File Dati AMD.


Nephrol Dial Transplant (2014) 29: 657–662
doi: 10.1093/ndt/gft506
Advance Access publication 6 January 2014

Kidney dysfunction and related cardiovascular risk factors among patients with type 2 diabetes

Salvatore De Cosmo[1], Maria Chiara Rossi[2], Fabio Pellegrini[2], Giuseppe Lucisano[3], Simonetta Bacci[1], Sandro Gentile[3], Antonio Ceriello[4], Giuseppina Russo[5], Antonio Nicolucci[2], Carlo Giorda[6], Francesca Viazzi[7], Roberto Pontremoli[7] and the AMD-Annals Study Group

Risk Factors for Renal Dysfunction in Type 2 Diabetes

U.K. Prospective Diabetes Study 74

Ravi Retnakaran, Carole A. Cull, Kerensa I. Thorne, Amanda I. Adler, and Rury R. Holman, for the UKPDS Study Group

TABLE 3
HRs derived from a stepwise proportional hazards regression models for albuminuria outcomes and renal insufficiency outcomes (n = 2,167)

	Albuminuria						Renal insufficiency					
	Microalbuminuria (N events = 756)			Macroalbuminuria (N events = 219)			Creatinine clearance ≤60 ml/min per 1.73 m^2 (N events = 584)			Doubling of plasma creatinine (N events = 58)		
Variable	Order entered	HR (95% CI)	P	Order entered	HR (95% CI)	P	Order entered	HR (95% CI)	P	Order entered	HR (95% CI)	P
Age at diagnosis (per 5 years)	—	1.01 (0.97–1.06)	0.58	—	1.02 (0.94–1.12)	0.59	—	2.15 (1.98–2.34)	<0.0001	—	0.91 (0.77–1.07)	0.25
Sex (male)	—	1.18 (1.01–1.39)	0.041	—	1.47 (1.06–2.02)	0.020	—	0.550 (0.424–0.715)	<0.0001	—	0.87 (0.51–1.48)	0.61
Ethnicity	—	—	—	—	—	—	—	—	—	—	—	—
White Caucasian	—	1	—	—	1	—	—	1	—	—	1	—
Afro-Caribbean	—	1.21 (0.89–1.65)	0.22	—	1.05 (0.59–1.86)	0.87	—	1.26 (0.91–1.76)	0.17	—	0.40 (0.10–1.68)	0.21
Indian Asian	—	2.02 (1.59–2.60)	<0.0001	—	2.07 (1.36–3.15)	0.00066	—	1.93 (1.38–2.72)	0.00015	—	1.51 (0.59–3.90)	0.39
Urinary albumin (per 20 mg/l)	3	1.004 (1.002–1.007)	0.00066	1	1.009 (1.005–1.012)	<0.0001	5	1.009 (1.002–1.015)	0.0075	—	—	—
Plasma creatinine (per 10 μmol/l)	—	—	—	8	1.087 (1.005–1.175)	0.038	2	1.34 (1.28–1.40)	<0.0001	—	—	—
Smoking status (ever)	9	1.20 (1.01–1.42)	0.036				7	1.25 (1.03–1.52)	0.022	—	—	—
Waist (cm)	7	1.010 (1.004–1.016)	0.00042	4	1.016 (1.006–1.026)	0.0019	1	0.95 (0.94–0.96)	<0.0001	—	—	—
Height (cm)	—	—					3	1.05 (1.036–1.072)	<0.0001	—	—	—
Systolic blood pressure (per 10 mmHg)	1	1.15 (1.11–1.20)	<0.0001	3	1.15 (1.07–1.24)	0.00019	4	1.107 (1.06–1.16)	0.000012	1	1.39 (1.23–1.57)	<0.0001
A1C (%)	6	1.08 (1.03–1.12)	0.00031	6	1.10 (1.02–1.18)	0.011	—	—	—	—	—	—
LDL cholesterol (mmol/l)	—	—	—	7	1.17 (1.02–1.33)	0.022	—	—	—	—	—	—
HDL cholesterol (mmol/l)	—	—	—	—	—	—	—	—	—	3	2.78 (1.01–7.68)	0.049
Plasma triglycerides (mmol/l)*	2	1.09 (1.04–1.14)	<0.0001	2	1.15 (1.09–1.21)	<0.0001	—	—	—	—	—	—
White cell count (10^9/l)	5	1.06 (1.02–1.10)	0.0012	—	—	—	—	—	—	—	—	—
Previous retinopathy	8	1.25 (1.05–1.49)	0.012	—	—	—	7	1.255 (1.020–1.544)	0.032	—	—	—
Previous sensory neuropathy	—	—	—	—	—	—	—	—	—	2	1.84 (1.03–3.30)	0.039
Previous CVD	4	1.46 (1.23–1.73)	<0.0001	5	1.58 (1.16–2.15)	0.0041	—	—	—	—	—	—

*Log_{10} transformed.

Observational Study

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Predictors of chronic kidney disease in type 2 diabetes

A longitudinal study from the AMD Annals initiative

Salvatore De Cosmo (MD)[a,*], Francesca Viazzi (MD)[b], Antonio Pacilli (MD)[a], Carlo Giorda (MD)[c], Antonio Ceriello (MD)[d], Sandro Gentile (MD)[e], Giuseppina Russo (MD)[f], Maria C. Rossi (MD)[g], Antonio Nicolucci (MD)[h], Pietro Guida (MSC)[h], Roberto Pontremoli (MD, PhD)[b], and the AMD-Annals Study Group

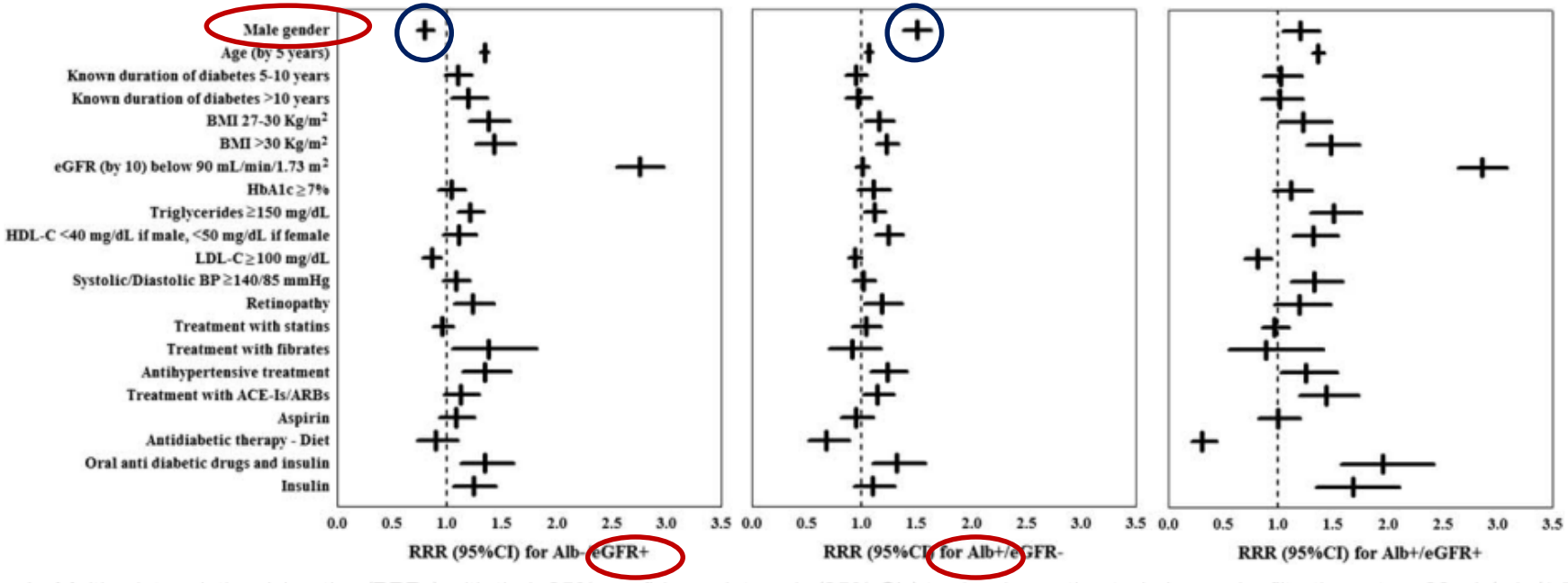


Figure 1. Multivariate relative risk ratios (RRRs) with their 95% confidence intervals (95% CIs) to develop estimated glomerular filtration rate <60 mL/min/1.73 m^2 (Alb−/eGFR+) = albuminuria (Alb+/eGFR−) = or both (Alb+/eGFR+). Antidiabetic therapy was analyzed by using oral antidiabetic drugs as reference category. Analysis performed by using a multinomial logistic regression model with the missing indicator method for each incomplete variable.

DIABETICMedicine
DOI: 10.1111/dme.12478

Research: Complications

The influence of sex on renal function decline in people with Type 2 diabetes

A. de Hauteclocque[1], S. Ragot[1], Y. Slaoui[2], E. Gand[3], A. Miot[4], P. Sosner[5,6], J.-M. Halimi[7], P. Zaoui[8], V. Rigalleau[9,10], R. Roussel[11,12,13,14], P.-J. Saulnier[1], S. Hadjadj Samy[1,4,15] for the SURDIAGENE Study group

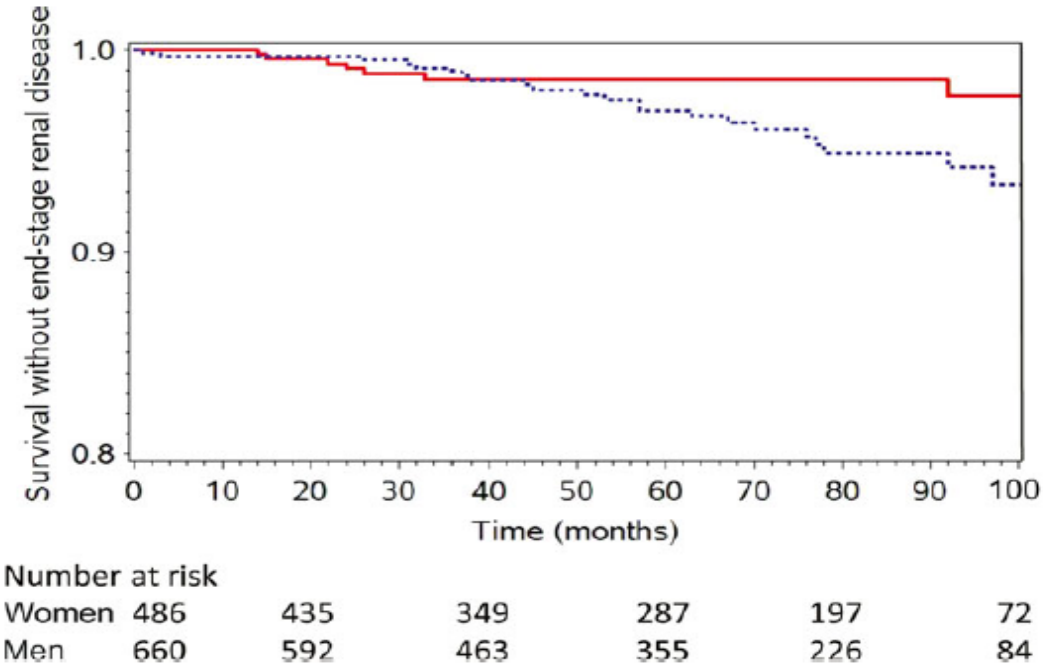


FIGURE 2 Survival without end-stage renal disease according to sex. The thick red line represents survival in women and the dotted blue line survival in men.

Men: OR 1.33 (1.01-1.04)
higher risk of steep decline

What's new?

- Male sex was an independent risk factor of steep eGFR decline.
- Estimated glomerular filtration rate trajectories were significantly different according to sex.
- Survival without end-stage renal disease was higher in women than in men.
- Male sex is suggested as an important independent factor associated with renal function decline in Type 2 diabetes.

Journal of Diabetes and Its Complications 29 (2015) 1042–1049

Contents lists available at ScienceDirect

Journal of Diabetes and Its Complications

journal homepage: WWW.JDCJOURNAL.COM

Gender differences in the association between hyperuricemia and diabetic kidney disease in community elderly patients

Mei Guo [a], Jian-Ying Niu [a], She-Ran Li [a], Xian-Wu Ye [a], Hong Fang [b], Yan-Ping Zhao [a], Yong Gu [a,c,*]

Table 4
Adjusted odds ratios (ORs) of hyperuricemia for reduced renal function and albuminuria stratified by gender.

Variables	Reduced renal function (GFR < 60 ml/min/1.73 m²)			More Severe Declined GFR (GFR < 45 ml/min/1.73 m²)			Albuminuria		
	OR	95% CI	P value	OR	95% CI	P value	OR	95% CI	P value
Unadjusted									
Gender (male vs female)	1.04	0.91–1.19	0.589	1.12	0.92–1.35	0.265	1.07	0.95–1.22	0.273
Hyperuricemia (yes vs. no)	4.97	4.45–5.55	<0.001	9.53	7.81–11.63	<0.001	1.34	1.23–1.47	<0.001
Gender* Hyperuricemia			0.334			0.047			<0.001
Model 1									
Gender (male vs female)	1.01	0.87–1.17	0.887	1.08	089–1.32	0.437	1.07	0.94–1.22	0.300
Hyperuricemia (yes vs. no)	4.79	4.26–5.37	<0.001	8.57	6.99–10.49	<0.001	1.30	1.19–1.42	<0.001
Gender* Hyperuricemia			0.305			0.053			<0.001
Model 2									
Gender (male vs female)	0.99	0.85–1.15	0.892	1.07	0.87–1.31	0.541	1.03	0.90–1.17	0.692
Hyperuricemia (yes vs. no)	4.73	4.20–5.32	<0.001	8.45	6.87–10.39	<0.001	1.22	1.12–1.34	<0.001
Gender* Hyperuricemia			0.189			0.075			<0.001

Model 1: adjusted for age.
Model 2: adjusted for age, duration of diabetes, BMI, triglyceride, LDL_C, HDL_C, hypertension (yes/no), HbA1c (≤7.0% yes/no).
GFR, glomerular filtration rate; BMI, body mass index; LDL_C, low density lipid cholesterol; HDL_C, high density lipid cholesterol; HbA1c, hemoglobin A1c.

Table 5
Logistic analysis of reduced renal function and albuminuria associated with hyperuricemia by gender.

Independent variables	Reduced renal function (GFR < 60 ml/min/1.73 m²)				More Severe Declined GFR (GFR < 45 ml/min/1.73 m²)				Albuminuria			
	Males		Females		Males		Females		Males		Females	
	Odds Ratio (95% CI)	P value	Odds Ratio (95% CI)	P value	Odds Ratio (95% CI)	P value	Odds Ratio (95% CI)	P value	Odds Ratio (95% CI)	P value	Odds Ratio (95% CI)	P value
Unadjusted	5.43 (4.71–6.25)	<0.001	4.97 (4.45–5.55)	<0.001	7.01 (5.56–8.82)	<0.001	9.53 (7.81–11.63)	<0.001	1.74 (1.55–1.96)	<0.001	1.34 (1.23–1.47)	<0.001
Model 1	5.29 (4.56–6.14)	<0.001	4.78 (4.26–5.36)	<0.001	6.31 (4.99–7.98)	<0.001	8.57 (6.99–10.49)	<0.001	1.69 (1.50–1.90)	<0.001	1.31 (1.20–1.43)	<0.001
Model 2	5.21 (4.47–6.07)	<0.001	4.83 (4.29–5.45)	<0.001	6.44 (5.04–8.21)	<0.001	8.44 (6.85–10.40)	<0.001	1.67 (1.48–1.88)	<0.001	1.23 (1.12–1.35)	<0.001

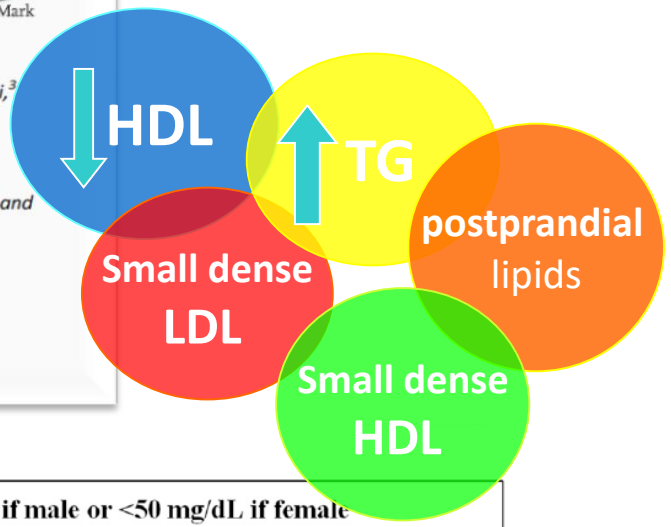
Model 1: adjusted for age.
Model 2: adjusted for age, duration of diabetes, BMI, triglyceride, LDL_C, HDL_C, hypertension (yes/no), HbA1c (≤7.0% yes/no).
GFR, glomerular filtration rate; BMI, body mass index; LDL_C, low density lipid cholesterol; HDL_C, high density lipid cholesterol; HbA1c, hemoglobin A1c.

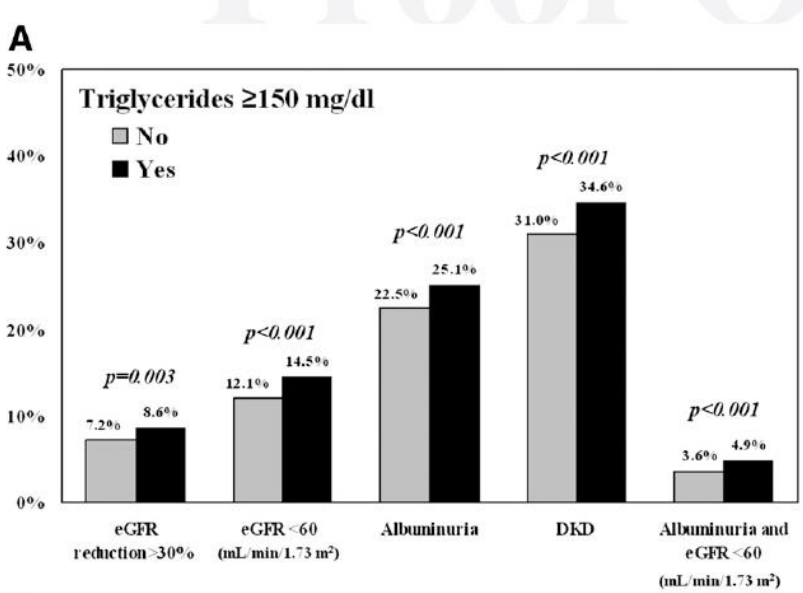
Diabetes Care Volume 39, December 2016 1

Plasma Triglycerides and HDL-C Levels Predict the Development of Diabetic Kidney Disease in Subjects With Type 2 Diabetes: The AMD Annals Initiative

Giuseppina T. Russo,[1] Salvatore De Cosmo,[2] Francesca Viazzi,[3] Antonio Pacilli,[2] Antonio Ceriello,[4,5] Stefano Genovese,[5] Pietro Guida,[6] Carlo Giorda,[7] Domenico Cucinotta,[1] Roberto Pontremoli,[3] Paola Fioretto,[8] and the AMD-Annals Study Group

Diabetes Care 2016;39:1–10 | DOI: 10.2337/dc16-1246





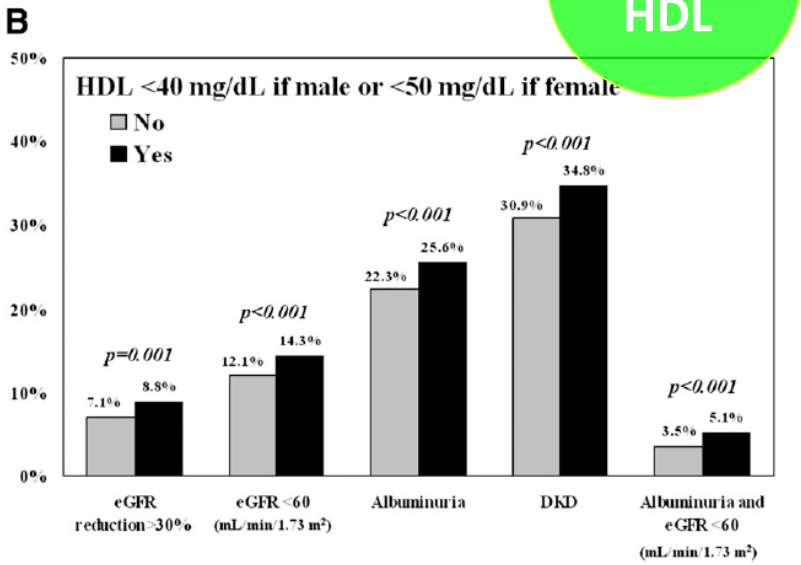


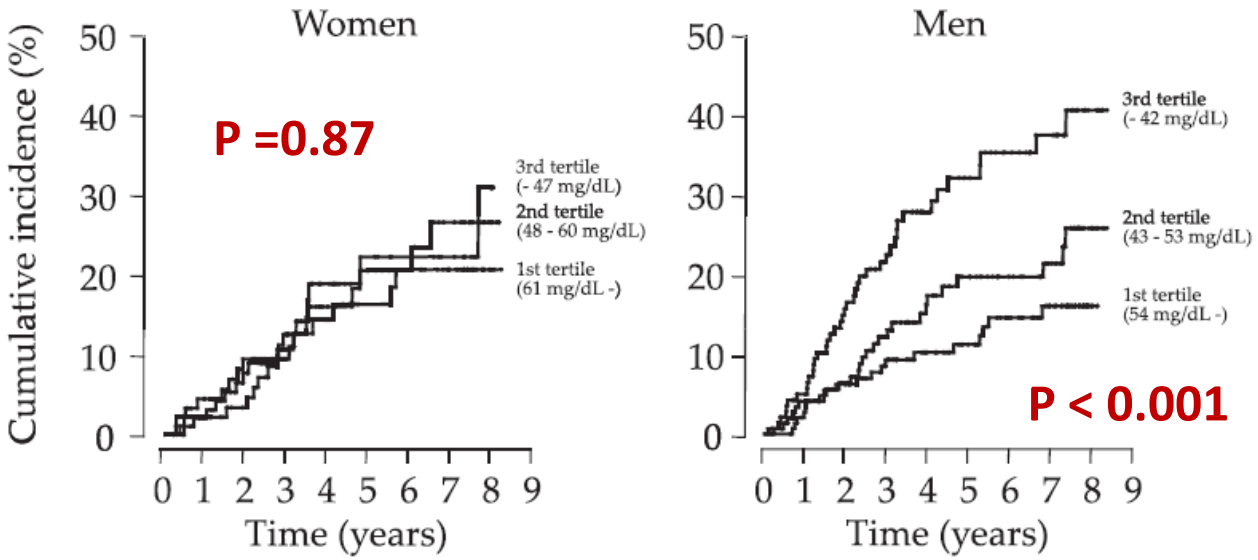
Figure 1—*A*: DKD incidence according to baseline TG ≥150 mg/dL. *B*: DKD incidence according to baseline HDL-C (<40 mg/dL in men; <50 mg/dL in women).

ROLE of GENDER

Gender differences in the association between HDL cholesterol and the progression of diabetic kidney disease in type 2 diabetic patients

Ko Hanai[1], Tetsuya Babazono[1], Naoshi Yoshida[1], Izumi Nyumura[1], Kiwako Toya[1], Toshihide Hayashi[1], Ryotaro Bouchi[1], Nobue Tanaka[1], Akiko Ishii[1] and Yasuhiko Iwamoto[2]

[1]Division of Nephrology and Hypertension, Diabetes Centre, Tokyo Women's Medical University School of Medicine, Tokyo, Japan and [2]Department of Medicine, Diabetes Centre, Tokyo Women's Medical University School of Medicine, Tokyo, Japan



Hanai K, Nephrol Dial Transplant 2012

HDL SUBCLASSES AND THE COMMON CETP TAQIB VARIANT PREDICT THE INCIDENCE OF MICROANGIOPATIC COMPLICATIONS IN TYPE 2 DIABETIC WOMEN: A 9 YEARS FOLLOW-UP STUDY

Factors associated to incidence of diabetic kidney disease (DKD) and diabetic retinopathy (DR)

FACTORS ASSOCIATED TO DKD INCIDENCE								
	Univariate regression analysis				*Stepwise regression analysis*			
	B	P	Exp(B)	95.0% CI	B	P	Exp(B)	95.0% CI
BMI	0.108	0.011	1.114	1.025-1.210	0.102	0.02	1.107	1.016-1.207
LDL/HDL	0.457	0.048	1.579	0.999-2.495				
HDL α-1	-0.099	0.042	0.906	0.824-0.996	-	-	-	-
FACTORS ASSOCIATED TO DR INCIDENCE								
	Univariate regression analysis				*Stepwise regression analysis*			
	B	P	Exp(B)	95.0% CI	B	P	Exp(B)	95.0% CI
HbA1c	0.688	0.004	1.989	1.250-3.165	0.695	0.02	2.004	1.117-3.595
TG	0.014	0.021	1.04	1.002-1.026	0.009	0.033	1.009	1.001-1.017
HDL-C	-0.079	0.011	0.924	0.869-0.982				
HDL α-1	-0.203	0.006	0.817	0.707-0.944	-	-	-	-
HDL α-3	0.267	0.003	1.306	1.093-1.562	0.294	0.009	1.345	1.076-1.683
HDL Pre $_{\alpha}$-3	0.770	0.021	2.160	1.122-4.160	-	-	-	-
HDL Pre-$_{\beta}$2	-1.060	0.053	0.346	0.118-1.016	-	-	-	-
CETP B1B1	1.199	0.028	0.301	0.103-0.878				

Only significant P values are shown. TG, triglycerides

Russo GT, Cucinotta D, submitted

Am J Nephrol. 2009;29(4):299-308.

Gender-dependent effect of ACE I/D and AGT M235T polymorphisms on the progression of urinary albumin excretion in Taiwanese with type 2 diabetes.

Tien KJ[1], Hsiao JY, Hsu SC, Liang HT, Lin SR, Chen HC, Hsieh MC.

BACKGROUND:

We investigated the gender differences in the effect of ACE I/D and AGT M235T polymorphisms on the prognosis of diabetic nephropathy (DN).

METHODS:

A total of 525 type 2 diabetics were enrolled to participate in this prospective observational study. ACE and AGT gene polymorphisms were analyzed by polymerase chain reaction. The progression of DN was defined as a shift to a higher stage of DN or a doubling of the baseline serum creatinine level by the end of the study.

RESULTS:

The baseline biophysical parameters show no gender differences in progression and non-progression of DN. The women who were ACE D allele carriers were found to be at an increased risk of DN progression compared to those with II genotypes (p = 0.024, OR 2.176). No such difference was seen in male patients (p = 0.619, OR 0.833). After adjusting for confounding factors (age, SBP, DBP, BMI, HbA1c, total cholesterol, TG, HDL-C, LDL-C, ACEI, and ARB) in our multiple regression analysis, these women were still found to be at increased risk of progressing to more severe DN (p = 0.008, OR 3.082) but not the men (p = 0.183, OR 0.586). Neither the AGT TT genotype nor the T allele were associated with the progression of DN in either sex after adjusting for confounding factors.

CONCLUSION:

Our follow-up study suggests that female diabetic carriers of the ACE D allele might be at an increased risk of DN progression.

Sex differences in the impact of diabetes on mortality in chronic dialysis patients

Juan J. Carrero[1,2,*], Renée de Mutsert[3,*], Jonas Axelsson[1], Olaf M. Dekkers[3,4], Kitty J. Jager[5], Elisabeth W. Boeschoten[6], Raymond T. Krediet[7], Friedo W. Dekker[3] and for the NECOSAD Study Group

Methods. This study was a prospective observational cohort study (NECOSAD) of incident dialysis patients with 5 years of follow-up where we calculated male:female odds ratios (OR) and relative risks of mortality (hazard ratio, HR) for the presence of CVD risk factors at the start of dialysis. We also examined the presence of interaction between sex and CVD risk factors in their association with mortality.

Results. In 1577 patients (61% men, 60±15 years), men presented more CVD co-morbidity [OR: 1.88 (95% CI: 1.51, 2.35)] but less diabetes mellitus (OR: 0.70 [0.55, 0.89]) than women. Both sexes presented equal survival [HR 0.98 (0.83, 1.16)]. Women with diabetes had a higher mortality risk [HR 2.93 (2.27, 3.79)] than their male counterparts [HR 1.99 (1.52, 2.59)], showing an interaction effect between sex and diabetes [relative excess risk due to interaction 1.18 (0.37, 2.00)].

Table 3. All-cause and CVD mortality rates for men and women with and without pre-existing diabetes in 5 years after the start of dialysis

	Women		Men	
Variable	Non-diabetes	Diabetes	Non-diabetes	Diabetes
N	457	162	765	193
Person-years (py)	1223.1	332.7	1926.5	433.3
Deaths from all causes	134	105	259	95
Deaths from CVD[a]	62	50	127	49
Deaths from all causes/1000 py	110	316	134	219
Deaths from CVD/1000 py	51	150	66	113

DM, diabetes mellitus; non-DM, without diabetes mellitus; CVD, cardiovascular diseases.
[a]Fourteen causes of death were missing, six in men and eight in women.

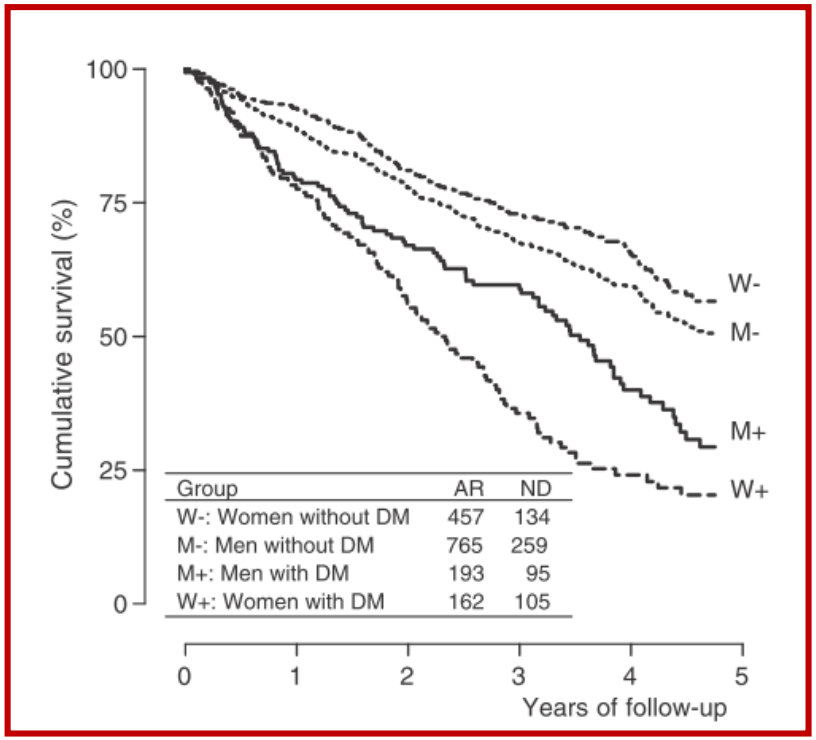


Fig. 1. Cumulative survival of women (W−) and men (M−) without diabetes and men (M+) and women (W+) with diabetes at baseline during 5 years after the start of dialysis (log rank $P < 0.001$); AR, number of patients at risk at the start of dialysis; ND, number of deaths during follow-up.

Nephrol Dial Transplant (2011) 26: 270–276
doi: 10.1093/ndt/gfq386
Advance Access publication 9 July 2010

J Endocrinol Invest
DOI 10.1007/s40618-013-0023-z

ORIGINAL ARTICLE

Lipid and non-lipid cardiovascular risk factors in postmenopausal type 2 diabetic women with and without coronary heart disease

G. T. Russo · A. Giandalia · E. L. Romeo · M. Marotta · A. Alibrandi · C. De Francesco · K. V. Horvath · B. Asztalos · D. Cucinotta

Table 3 Factors associated with coronary heart disease (CHD) in type 2 diabetic women

	Univariate associations			Multivariate associations		
	B	*P*	OR (95 % CI)	*B*	*P*	OR (95 % CI)
Age	0.126	0.001	1.134 (1.067–1.204)			
Menopause duration	0.131	0.001	1.140 (1.063–1.223)			
Creatinine clearance	−0.038	0.001	0.963 (0.941–0.985)	−0.70	0.017	0.932 (0.880–0.987)
Hypertension	2.24	0.004	9.395 (2.050–43.058)			
Triglycerides	0.014	0.004	1.014 (1.004–1.023)			
Creatinine	4.19	0.006	65.777 (3.420–1,264.983)			
Insulin therapy	2.81	0.01	16.571 (1.975–139.059)			
tHcy	0.09	0.02	1.098 (1.017–1.186)			
VCAM	0.002	0.02	1.002 (1.000–1.004)			
Diabetes duration	0.055	0.04	1.056 (1.002–1.113)			
CVD family history	1.306	0.04	3.692 (1.052–12.957)			
SdLDL	0.067	0.04	1.069 (1.003–1.139)	0.206	0.037	1.224 (1.012–1.492)
RLP-C	0.090	0.05	1.094 (0.998–1.199)			

Only significant associations are shown

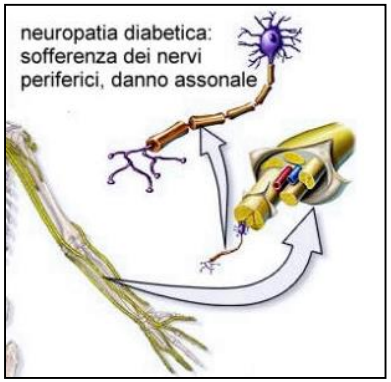
tHcy total homocysteine levels, *VCAM-1* soluble vascular cell adhesion molecule-1, *CVD* cardiovascular disease, *SdLDL* small dense LDL, *RLP-C* remnants-associated cholesterol

Gender Differences in Diabetic Neuropathy

Diabetic Neuropathy: A Position Statement by the American Diabetes Association

Rodica Pop-Busui,[1] Andrew J.M. Boulton,[2] Eva L. Feldman,[3] Vera Bril,[4] Roy Freeman,[5] Rayaz A. Malik,[6] Jay M. Sosenko,[7] and Dan Ziegler[8]

Diabetes Care 2017;40:136–154 | DOI: 10.2337/dc16-2042



Diabetic neuropathies are the most prevalent chronic complications of diabetes. This heterogeneous group of conditions affects different parts of the nervous system and presents with diverse clinical manifestations. The early recognition and appropriate management of neuropathy in the patient with diabetes is important for a number of reasons:

1. Diabetic neuropathy is a diagnosis of exclusion. Nondiabetic neuropathies may be present in patients with diabetes and may be treatable by specific measures.
2. A number of treatment options exist for symptomatic diabetic neuropathy.
3. Up to 50% of diabetic peripheral neuropathies may be asymptomatic. If not recognized and if preventive foot care is not implemented, patients are at risk for injuries to their insensate feet.
4. Recognition and treatment of autonomic neuropathy may improve symptoms, reduce sequelae, and improve quality of life.

Table 1—Classification for diabetic neuropathies

Diabetic neuropathies
- **A. Diffuse neuropathy**
  - DSPN
    - Primarily small-fiber neuropathy
    - Primarily large-fiber neuropathy
    - Mixed small- and large-fiber neuropathy (most common)
  - Autonomic
    - Cardiovascular
      - Reduced HRV
      - Resting tachycardia
      - Orthostatic hypotension
      - Sudden death (malignant arrhythmia)
    - Gastrointestinal
      - Diabetic gastroparesis (gastropathy)
      - Diabetic enteropathy (diarrhea)
      - Colonic hypomotility (constipation)
    - Urogenital
      - Diabetic cystopathy (neurogenic bladder)
      - Erectile dysfunction
      - Female sexual dysfunction
    - Sudomotor dysfunction
      - Distal hypohydrosis/anhidrosis,
      - Gustatory sweating
    - Hypoglycemia unawareness
    - Abnormal pupillary function
- **B. Mononeuropathy (mononeuritis multiplex) (atypical forms)**
  - Isolated cranial or peripheral nerve (e.g., CN III, ulnar, median, femoral, peroneal)
  - Mononeuritis multiplex (if confluent may resemble polyneuropathy)
- **C. Radiculopathy or polyradiculopathy (atypical forms)**
  - Radiculoplexus neuropathy (a.k.a. lumbosacral polyradiculopathy, proximal motor amyotrophy)
  - Thoracic radiculopathy

Nondiabetic neuropathies common in diabetes
- Pressure palsies
- Chronic inflammatory demyelinating polyneuropathy
- Radiculoplexus neuropathy
- Acute painful small-fiber neuropathies (treatment-induced)

Published in final edited form as:
J Peripher Nerv Syst. 2009 March ; 14(1): 1–13. doi:10.1111/j.1529-8027.2009.00200.x.

Il sesso maschile è un fattore di rischio per Neuropatia

Prevalence of diabetic peripheral neuropathy and relation to glycemic control therapies at baseline in the BARI 2D cohort

Rodica Pop-Busui[1], **Jiang Lu**[2], **Neuza Lopes**[3], **Teresa L. Z. Jones**[4], and **BARI 2D Investigators**[*]

N=1173 subjects (51%) with neuropathy (MNSI score>2)

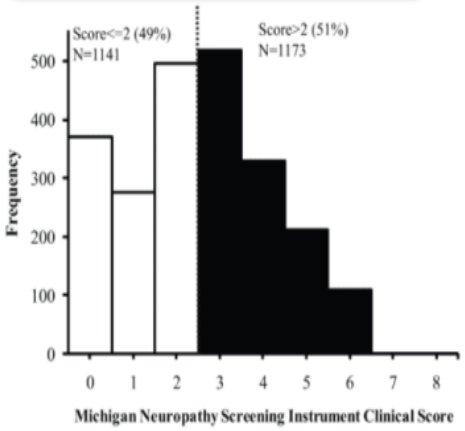


Table 1

Association of the presence of neuropathy and baseline characteristics.
HbA1c=hemoglobin A 1C, BMI=body mass index; HDLc=high density lipoprotein, LDLc=low density lipoprotein

Characteristic	Category	N	Neuropathy %	p-value
Age	< 50 years	195	35.4%	<0.001
	50-59 years	725	47.4%	
	60-69 years	892	52.6%	
	≥ 70 years	502	58.0%	
Sex	Women	682	46.2%	0.005
	Men	1632	52.6%	
Race/Ethnicity	White non Hispanic	1518	50.9%	0.026
	Black non Hispanic	392	55.4%	
	Hispanic	293	47.4%	
	Others	111	40.5%	

Figure 1.
Distribution of MNSI clinical score in the BARI 2D cohort at baseline. Scores with 0.5 increments were rounded up to the next integer.

Prevalence and Characteristics of Painful Diabetic Neuropathy in a Large Community-Based Diabetic Population in the U.K.

CAROLINE A. ABBOTT, PHD[1]
RAYAZ A. MALIK, PHD[1]
ERNEST R.E. VAN ROSS, FRCP[2]
JAI KULKARNI, FRCP[2]
ANDREW J.M. BOULTON, MD[1]

large, community-based survey of 9,710 predominantly type 2 diabetic patients derived from general practice in north-west England, the prevalence of at least neuropathic deficits as defined

Nello studio dei Medici di Medicina generale Inglesi: il *sesso femminile* è associato alla neuropatia

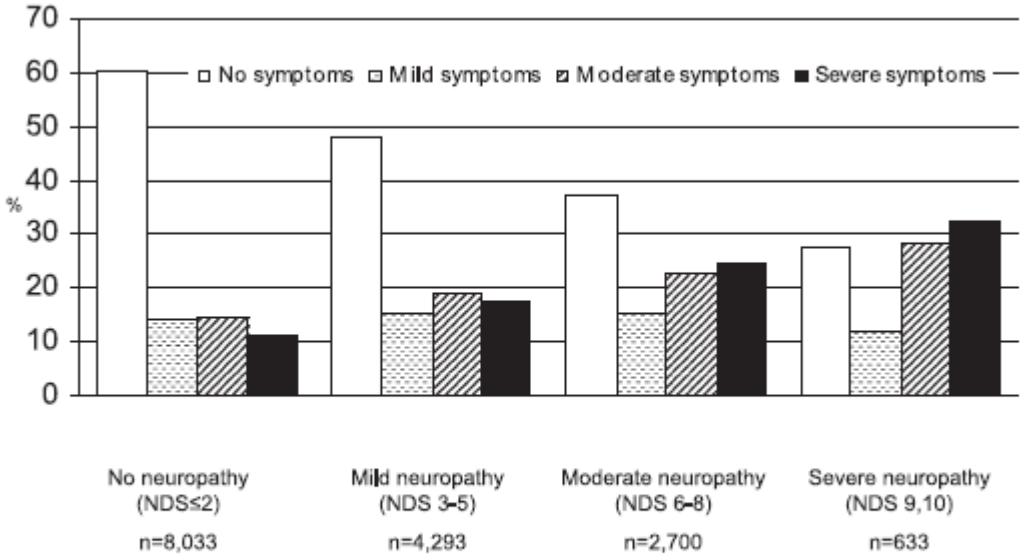


Figure 1—*Percentage prevalence of neuropathic symptoms in 15,659 diabetic patients characterized by their level of clinical neuropathy.*

Effect of sex

A significantly greater proportion of females (38% [2,732/7,212]) than males (31% [2,578/8,423]) reported painful neuropathy symptoms ($P < 0.0001$), despite fewer females than males having clinical neuropathy (NDS ≥6) (19 vs. 23%, $P < 0.0001$). PDN (NSS ≥5 and NDS ≥3) was, similarly, more prevalent in females than males (23 vs. 19%, respectively, $P < 0.0001$). After adjustments for age, diabetes duration, and differences in clinical neuropathy, women still had a 50% increased risk of painful symptoms compared with men (OR = 1.5 [95% CI 1.4–1.6], $P < 0.0001$).

ELSEVIER

Journal of Diabetes and Its Complications 22 (2008) 83–87

Journal of Diabetes and its Complications

Gender differences in the onset of diabetic neuropathy

Melanie L. Aaberg*, Draion M. Burch, Zarinah R. Hud, Michael P. Zacharias

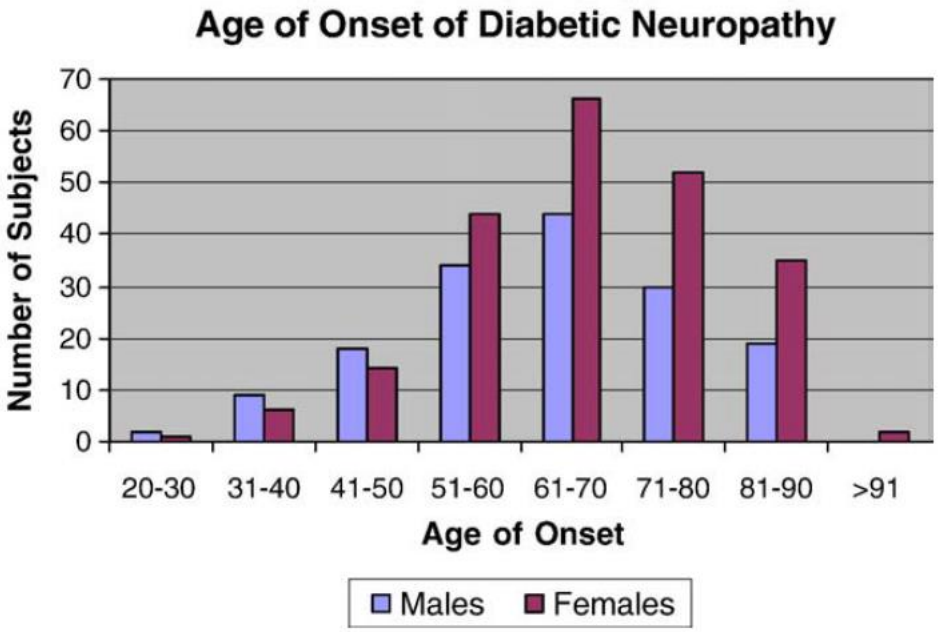


Fig. 1. Patients' age at onset of diabetic neuropathy.

Mean age at DPN onset :

- in men: ***63 years***
- in women: ***67 years***

(P=0.006)

Gender Differences of Lower Extremity Amputation Risk in Patients With Diabetic Foot: A Meta-Analysis

The International Journal of Lower Extremity Wounds
2014, Vol. 13(3) 197–204

DOI: 10.1177/1534734614545872
ijl.sagepub.com
SAGE

Zhu-Qi Tang, MD[1], Hong-Lin Chen, MD[2], and Fang-F

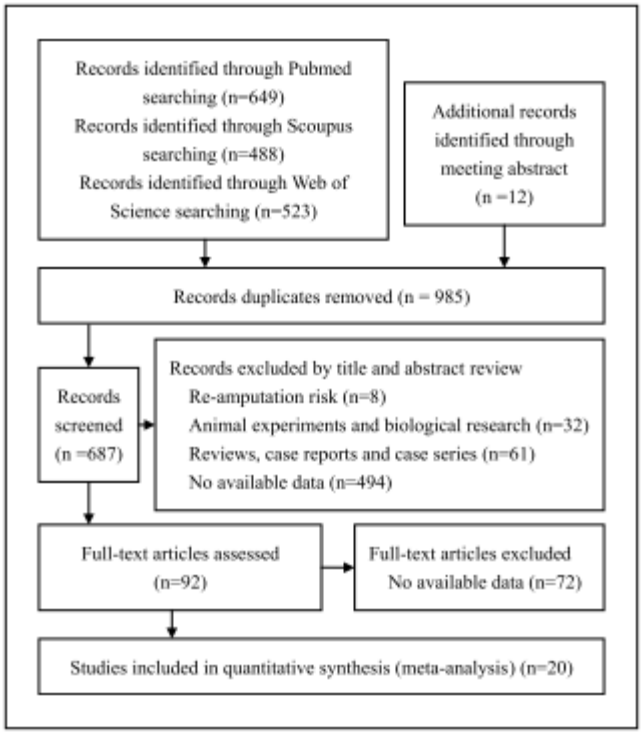
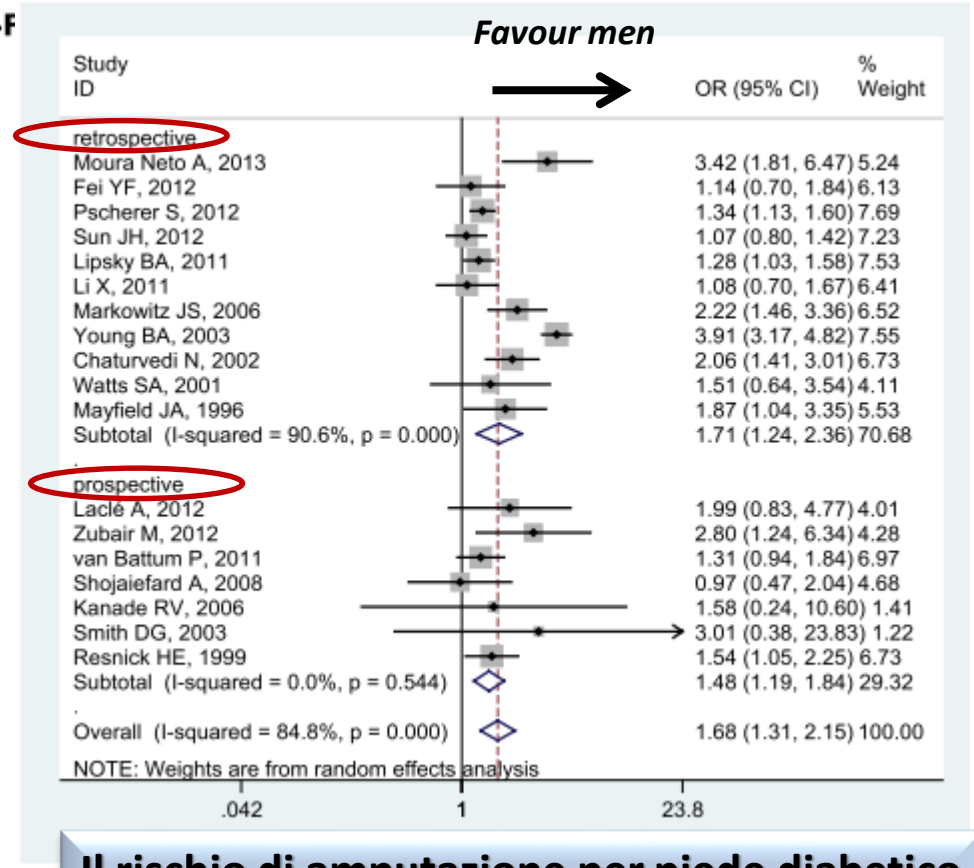


Figure 1. Flow diagram showing selection of studies.



Il rischio di amputazione per piede diabetico è aumentato negli uomini rispetto alle donne con diabete

Clin Orthop Relat Res (2011) 469:1951–1955
DOI 10.1007/s11999-010-1735-4

SYMPOSIUM: AAOS/ORS/ABJS MUSCULOSKELETAL HEALTHCARE DISPARITIES RESEARCH SYMPOSIUM

Gender Differences in Diabetes-related Lower Extremity Amputations

Monica E. Peek MD, MPH

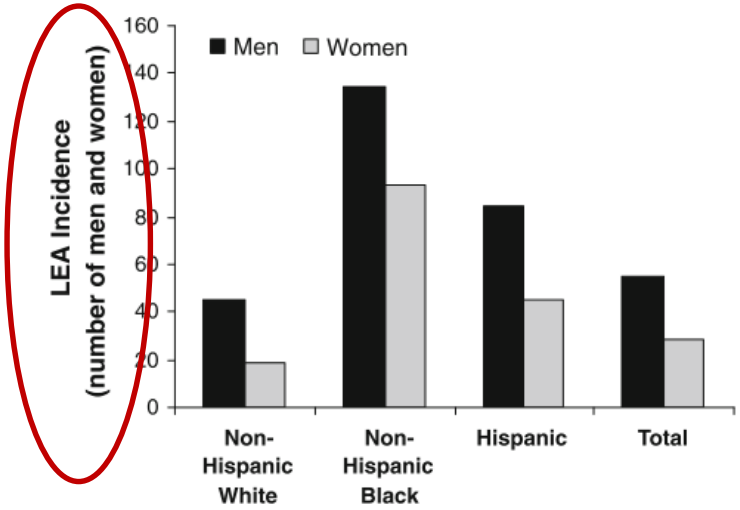


Fig. 1 A graph shows the differences in diabetes-related LEA incidence by race and gender. Men had a higher LEA incidence than women (55 versus 28 LEAs per 100,000 diabetes patients), and the gender differences persisted across racial/ethnic groups: 45 versus 19 LEAs among non-Hispanic white men and women, respectively; 134 versus 93 LEAs among African Americans; and 84 versus 45 LEAs among Hispanic Americans ($p < 0.05$ for all groups).

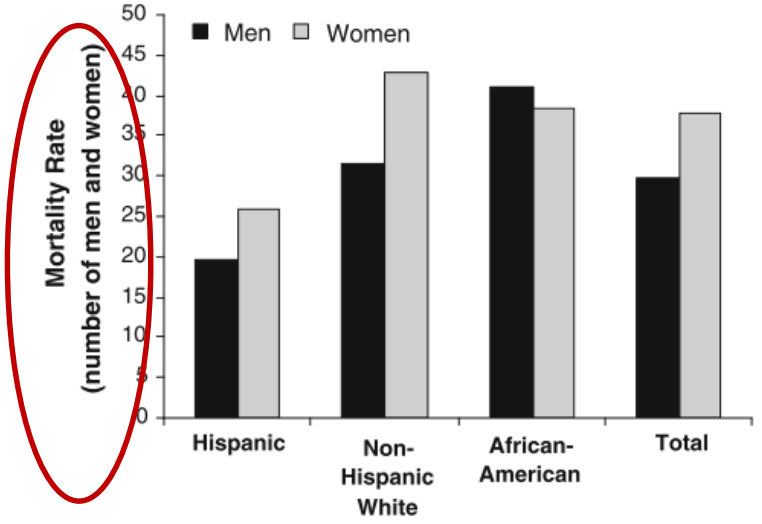
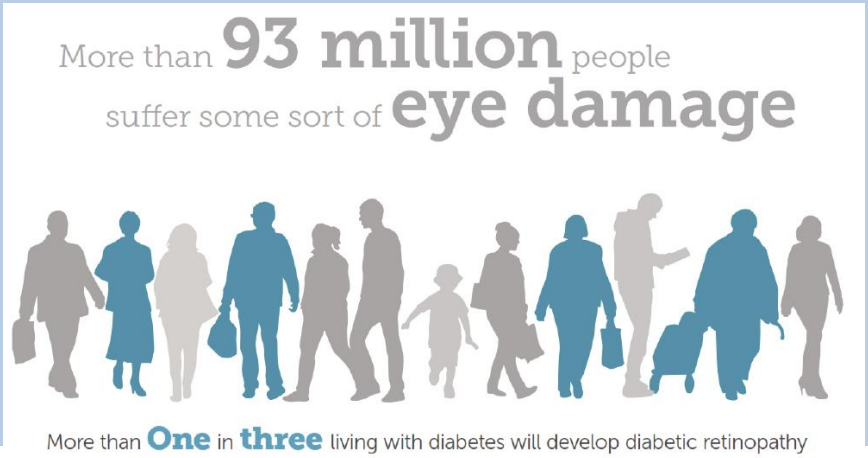


Fig. 2 A graph shows the differences in age-adjusted mortality associated with diabetes-related LEAs by race and gender. Women had a higher mortality rate than men (37.7 versus 29.7 deaths per 1000 amputations), and gender differences were found among whites (43.0 versus 31.5 deaths among women and men, respectively) and Hispanics (25.9 versus 19.7) but not African Americans (38.5 versus 41.5).

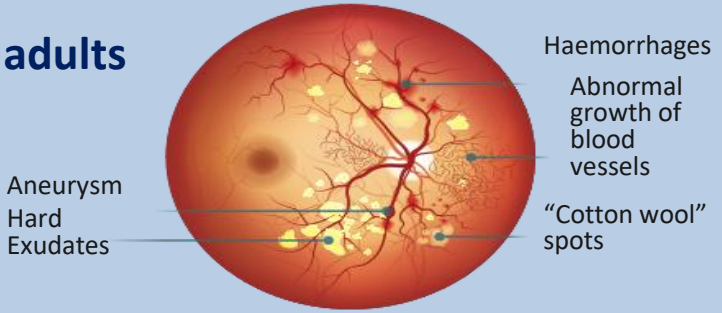
Gender differences in diabetic Retinopathy

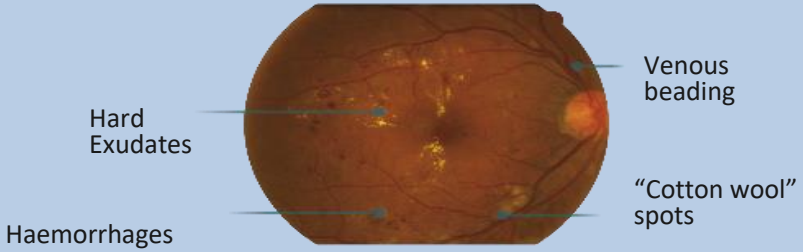
Of the 415 million people worldwide with diabetes in 2015, more than 93 million people currently suffer some sort of eye damage from diabetes

- **33% of subjects with diabetes will develop DR**
- **33% of subjects with DR will have impaired vision**
- **DR is the leading cause of vision loss in working-age adults**



Diabetic retinopathy





Severe non-proliferative diabetic retinopathy with severe diabetic macular edema

RESEARCH ARTICLE

Risk Factors for Retinopathy and DME in Type 2 Diabetes—Results from the German/ Austrian DPV Database

Hans-Peter Hammes[1]*, Reinhard Welp[2], Hans-Peter Kempe[3], Christian Wagner[4], Erhard Siegel[5], Reinhard W. Holl[6], DPV Initiative—German BMBF Competer Diabetes Mellitus[¶]

Design: Prospective study on >6000 T2DM patients from 2000 to 2013

Objective: to explore modifiable and not modifiable risk factors for RD

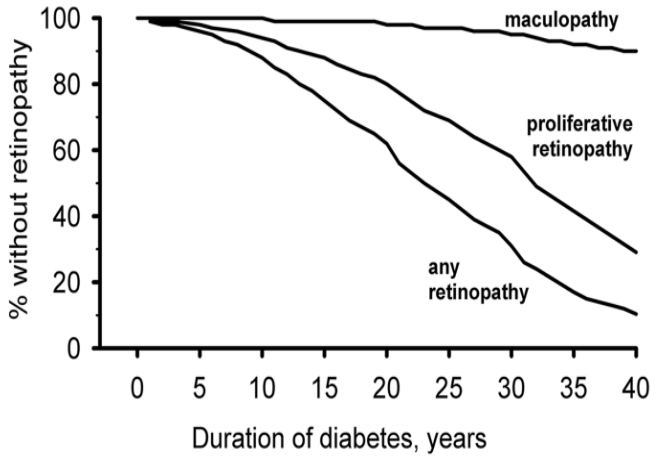


Fig 1. Kaplan-Meier analysis relating time to retinopathy (any versus severe versus DME) to duration of diabetes (individual survival curves are labeled).

Table 2. Multiple logistic regression analysis, any retinopathy.

Variable	OR	95% CI	P
Male gender	1,11	1,07–1,15	<0,0001
HbA_{1c}>8%	1,34	1,29–1,39	<0,0001
RR>140/80 mm Hg	1,15	1,11–1,20	<0,0001
BMI >35 kg/m^2	1,1	1,05–1,16	0,0005
Microalbuminuria	1,16	1,11–1,20	<0,0001

doi:10.1371/journal.pone.0132492.t002

Table 3. Multiple regression analysis, severe retinopathy.

Variable	OR	95% CI	P
HbA_{1c}>8%	1,21	1,137–1,279	<0,0001
RR>140/80 mm Hg	1,11	1,043–1,179	0,001
Microalbuminuria	1,2	1,14–1,271	<0,0001

doi:10.1371/journal.pone.0132492.t003

Table 4. Multiple regression analysis, macula edema.

Variable	OR	95% CI	P
HbA_{1c}>8%	1,57	1,288–1,903	<0,0001
RR>140/80 mm Hg	1,39	1,11–1,74	0,0041
Microalbuminuria	1,31	1,089–1,582	0,0042
Macroalbuminuria	2,77	2,105–3,655	<0,0001

doi:10.1371/journal.pone.0132492.t004

Diabetologia (2013) 56:109–111
DOI 10.1007/s00125-012-2742-7

SHORT COMMUNICATION

Diabetic retinopathy at diagnosis of type 2 diabetes in the UK: a database analysis

K. Kostev · W. Rathmann

Table 1 Characteristics of patients with type 2 diabetes in general practices in the UK (Disease Analyzer Database) stratified by retinopathy status

Characteristic	All	No diabetic retinopathy	Diabetic retinopathy	OR[a] (95% CI)	
				Univariate	Multivariate
n	12,524	10,139	2,385	–	–
Male sex (%)	56.4	56.1	58.0	1.08 (0.99, 1.18)	1.11 (1.01, 1.22)
Age (years)	65.3±13.1	65.1±13.2	66.3±12.8	1.01 (1.01, 1.01)	1.02 (1.01, 1.03)
BMI (kg/m^2)[b]	31.6±6.6	31.7±6.6	31.4±6.6	0.91 (0.83, 1.01)	1.00 (0.99, 1.01)
HbA_{1c} (%)[c]	7.9±1.9	7.8±1.9	8.1±2.0	1.07 (1.04, 1.10)	1.12 (1.02, 1.22)
HbA_{1c} (mmol/mol)[c]	63.0	62.0	65.0	-	-
Systolic BP (mmHg)[d]	141.6±20.4	141.3±20.2	142.6±20.7	1.03 (1.01, 1.06)	1.03 (1.01, 1.05)
Diastolic BP (mmHg)[d]	82.6±12.4	82.6±12.3	82.5±12.7	0.99 (0.96, 1.03)	1.02 (0.99, 1.06)
Antihypertensives (%)[e]	70.7	69.6	75.8	1.34 (1.21, 1.49)	1.37 (1.24, 1.52)

Data are mean±SD or proportion (%)

[a] ORs were computed using multiple logistic regression (dependent variable, retinopathy status) including all variables

[b] ORs for BMI are given for obese vs non-obese (BMI >30 kg/m^2)

[c] ORs for HbA_{1c} are given per 1% (11 mmol/mol)

[d] ORs for blood pressure are given per 10 units

[e] ATC: C03, C07, C08, C09

Methods The Disease Analyzer Database (UK) assembles longitudinal data on diagnoses, prescriptions and laboratory values reported from 674 office-based physicians (97 general practices). Patients with newly diagnosed type 2 diabetes (between 2005 and 2009) were identified and the presence of retinopathy was defined based on the International Classification of Diseases code (E11.3) or on the original diagnosis text. The time period between first diabetes diagnosis and first retinopathy diagnosis was calculated. Logistic regression was used to examine associations of potential risk factors with prevalent diabetic retinopathy.
Results There were 12,524 patients with newly diagnosed type 2 diabetes mellitus in the general practices. The mean

Diabetologia (2012) 55:2335–2342
DOI 10.1007/s00125-012-2596-z

ARTICLE

Diabetic retinopathy at diagnosis of type 2 diabetes in Scotland

H. C. Looker · S. O. Nyangoma · D. Cromie · J. A. Olson · G. P. Leese · M. Black · J. Doig · N. Lee · R. S. Lindsay · J. A. McKnight · A. D. Morris · S. Philip · N. Sattar · S. H. Wild · H. M. Colhoun · on behalf of the Scottish Diabetic Retinopathy Screening Collaborative and the Scottish Diabetes Research Network Epidemiology Group

Table 4 Characteristics near to diagnosis of diabetes mellitus by subsequent retinopathy status

	All (*n*=47,090)	No diabetic retinopathy (*n*=35,114)	Diabetic retinopathy (*n*=8,409)	OR for diabetic retinopathy vs no diabetic retinopathy (95% CI)	*p* value
Male sex	26,341 (55.9%)	19,654 (56%)	5,103 (60.7%)	1.19 (1.14, 1.25)	<0.001
Age (years)	61.3±12.4	60.4±12.0	60.6±12.1	1.02 (0.99, 1.04)	0.163
BMI (kg/m²)	32.0±6.4	32.2±6.4	31.7±6.4	0.87 (0.82, 0.93)	<0.001
HbA_{1c} (%)	8.1±2.1	8.0±2.1	8.4±2.2	1.07 (1.06, 1.08)	0.001
HbA_{1c} (mmol/mol)	65.0±23.1	63.9±23.1	68.3±24.2	1.06 (1.05, 1.08)	<0.001
Systolic BP (mmHg)	139.9±86.8	139.5±99.6	141.1±24.1		
Diastolic BP (mmHg)	80.9±12	80.9±12.2	81.8±11.4	1.01 (0.98, 1.03)	0.572
Higher socioeconomic status	21,308 (45.2%)	15,993 (45.5%)	3,704 (44.0%)	0.96 (0.91, 1.01)	0.122
Median time to screening (days)	315 (111–607)	305 (109–601)	353 (116–625)	1.12 (1.07–1.17)	<0.001

Data are mean ± SD, median with IQR or frequency with percentage

ORs and *p* values were computed by multiple logistic regression with a model that included all variables

ORs for continuous variables are per ten units except for: HbA_{1c}, which is given per 1% unit (11 mmol/mol); BMI, which is presented for obese vs non-obese; and time to screening, which is presented for screened after 1 year vs screened within 1 year

Methods We identified individuals diagnosed with type 2 diabetes mellitus in Scotland between January 2005 and May 2008 using data from the national diabetes database. We calculated the prevalence of retinopathy and ORs for risk factors associated with retinopathy at first screening.
Results Of the 51,526 people with newly diagnosed type 2 diabetes mellitus identified, 91.4% had been screened by 31 December 2010. The median time to first screening was 315 days (interquartile range [IQR] 111–607 days), but by 2008 the median was 83 days (IQR 51–135 days). The prevalence at first screening of any retinopathy was 19.3%,

www.impactjournals.com/oncotarget/ Oncotarget, 2016, Vol. 7, (No. 51), pp: 85464-85471

Research Paper

Impact of diabetes-related gene polymorphisms on the clinical characteristics of type 2 diabetes Chinese Han population

Jing Li[1,*], Jiachen Wei[2,*], Pengcheng Xu[3], Mengdan Yan[1,4], Jingjie Li[1,4], Zhengshuai Chen[1,4], Tianbo Jin[1,4]

Table 3: The associations between genetic polymorphisms and clinical characteristics of T2D

SNP	genotype	n	HbA1c		TG		Cr		Cys-c		BMI	
			mean ± SD	p^*	mean ± SD	p^*	mean ± SD	p^*	mean ± SD	p^*	mean ± SD	p^*
rs2811893(MYSM1)	TT	130	9.56±2.81	0.083	2.53±2.20	0.906	71.18±38.63	**0.006***	0.87±0.26	0.975	24.79±3.59	0.495
	CT	148	9.15±1.98		2.51±2.19		61.95±18.39		0.87±0.56		24.90±3.36	
	CC	40	8.68±1.66		2.68±2.37		11.93±1.89		0.86±0.17		25.52±3.24	
rs13064954(Unknown)	AA	4	10.95±2.03	0.343	7.59±5.17	**0.001***	66.47±21.70	0.584	0.85±0.20	0.615	25.27±3.94	0.555
	GG	257	9.22±2.40		2.53±2.20		64.67±27.78		0.85±0.23		24.82±3.52	
	AG	58	9.25±1.99		2.22±1.51		68.94±31.10		0.97±0.84		25.35±3.06	
rs17376456(KIAA0825)	AA	280	9.35±2.38	**0.039***	2.56±2.91	0.6	65.56±29.67	0.88	0.87±0.44	0.526	24.92±3.49	0.884
	GA	39	8.53±1.78		2.36±1.49		64.83±15.70		0.83±0.20		25.00±3.44	
rs7772697(Unknown)	TT	223	9.18±2.40	0.455	2.61±2.38	0.584	65.88±29.90	0.916	0.88±0.48	0.779	25.25±3.48	**0.028***
	CT	85	9.51±2.26		2.39±1.83		64.48±25.11		0.85±0.19		24.09±3.34	
	CC	11	8.85±1.23		2.08±0.90		63.29±18.46		0.83±0.30		24.69±2.28	
rs3918227(NOS3)	CA	49	8.96±1.74	0.338	2.00±1.07	0.117	63.85±18.03	0.664	1.02±0.91	**0.045***	25.09±3.53	0.075
	CC	270	9.31±2.42		2.63±2.35		65.76±29.82		0.84±0.23		24.89±3.43	
rs4838605(ARHGAP22)	TT	243	9.34±2.43	0.216	2.66±2.36	**0.041***	65.77±23.91	0.737	0.89±0.46	0.168	24.95±3.28	0.777
	TC	76	8.97±1.97		2.13±1.56		64.51±39.42		0.81±0.25		24.82±3.92	
rs6214(IGF1)	TT	72	10.10±3.34	**0.006***	2.51±2.36	0.155	61.03±15.20	0.319	0.85±0.27	0.571	25.10±3.43	0.803
	CC	105	8.98±1.86		2.22±1.60		66.57±26.55		0.90±0.63		24.76±3.51	
	TC	142	9.03±1.91		2.78±2.48		66.90±34.05		0.85±0.26		24.96±3.41	

HbA1C = glycosylated hemoglobin A1c; TG = triglyceride; Cr = creatinine; Cys-c = cystatin C; BMI = body mass index; OR = odds ratio; 95%CI = 95 % confidence interval;

*$p \leq 0.05$ indicates statistical significance.

Conclusioni

- ✓ **Un approccio personalizzato al diabete è raccomandato dalle linee guida sia in termini di efficacia che di sicurezza.**
- ✓ **Il genere condiziona la prevalenza, l'impatto e la risposta al trattamento dei principali fattori di rischio per le complicanze micro- e macroangiopatiche.**
- ✓ **Le crescenti evidenze sulle interazioni gene-gender e gene-drugs lasciano ipotizzare una loro futura applicazione nella pratica clinica.**
- ✓ **L'integrazione delle informazioni personali, fenotipiche e genetiche consentirà di fare le scelte più appropriate per il singolo individuo con diabete, consentendo di passare da una diabetologia "*personalizzata*" ad una diabetologia di "*precisione*".**

COMMENT

ILLUSTRATION BY GREG CLARKE

Time for one-person trials

Precision medicine requires a different type of clinical trial that focuses on individual, not average, responses to therapy, says **Nicholas J. Schork**.

Every day, millions of people are taking medications that will not help them.

US$215-million national Precision Medicine Initiative. This includes, among other things,

may prescribe one drug for hypertension and monitor its effect on a person's blood pres-

Recognition that physicians need to take individual variability into account is driving huge interest in 'precision' medicine. In January, US President Barack Obama announced a

Studies that focus on a single person — known as *N*-of-1 trials — will be a crucial part of the mix. Physicians have long done these in an ad hoc way. For instance, a doctor

results of many *N*-of-1 trials (all carried out in the same way) will offer information about how to better treat subsets of the population or even the population at large.

Grazie per l'attenzione