Rischio CV oltre il controllo glicemico: assetto lipidico e ruolo dell'infiammazione

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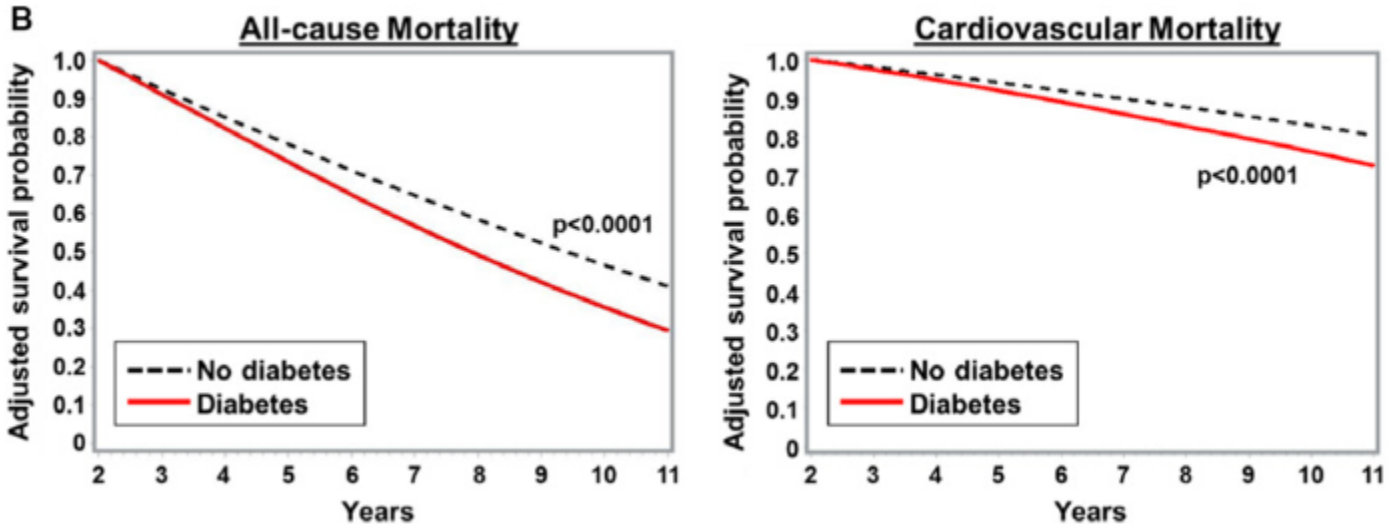
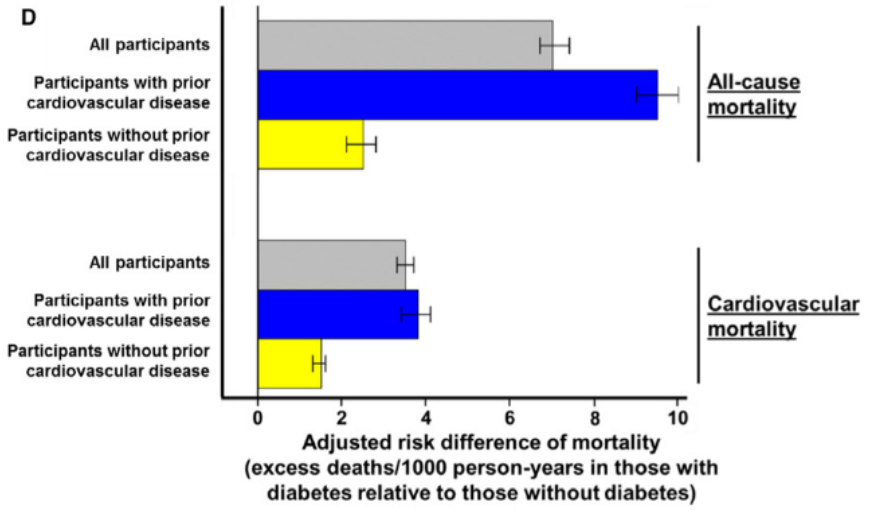
Diabetes and CV mortality





Raghavan S et al. J Am Heart Assoc. 2019 Feb 19;8(4):e011295.

Il rischio CV teorico del paziente diabetico

Il rischio CV teorico del paziente diabetico è sempre ALTO/MOLTO-ALTO !

…è una visione pragmatica assolutista che enfatizza la rilevanza del DM2, ma che espone a:

1. sovrastima del rischio ?
2. ipertrattamento ?
3. fatalismo gestionale del paziente (*ormai è tardi per invertire il processo di danno multi-organo…*) ?

Very high-risk	Subjects with any of the following: • Documented cardiovascular disease (CVD), clinical or unequivocal on imaging. Documented CVD includes previous myocardial infarction (MI), acute coronary syndrome (ACS), coronary revascularisation (percutaneous coronary intervention (PCI), coronary artery bypass graft surgery (CABG)) and other arterial revascularization procedures, stroke and transient ischaemic attack (TIA), and peripheral arterial disease (PAD). Unequivocally documented CVD on imaging is what has been shown to be strongly predisposed to clinical events, such as significant plaque on coronary angiography or carotid ultrasound. • DM with target organ damage such as proteinuria or with a major risk factor such as smoking, hypertension or dyslipidaemia. • Severe CKD (GFR <30 mL/min/1.73 m²). • A calculated SCORE ≥10% for 10-year risk of fatal CVD.
High-risk	Subjects with: • Markedly elevated single risk factors, in particular cholesterol >8 mmol/L (>310 mg/dL) (e.g. in familial hypercholesterolaemia) or BP ≥180/110 mmHg. • Most other people with DM (some young people with type 1 diabetes may be at low or moderate risk). • Moderate CKD (GFR 30–59 mL/min/1.73 m²). • A calculated SCORE ≥5% and <10% for 10-year risk of fatal CVD.
Moderate-risk	SCORE is ≥1% and <5% for 10-year risk of fatal CVD.
Low-risk	SCORE <1% for 10-year risk of fatal CVD.

2016 ESC/EAS Guidelines. European Heart Journal (2016) 37, 2999–3058

Il rischio CV teorico del paziente diabetico

Very high CV risk	Patients with T2DM with: • Clinically established ASCVD or • Severe TOD or • 10-year CVD risk ≥20% using SCORE2-Diabetes
High CV risk	Patients with T2DM not fulfilling the very high-risk criteria and a: • 10-year CVD risk 10 to <20% using SCORE2-Diabetes
Moderate CV risk	Patients with T2DM not fulfilling the very high-risk criteria and a: • 10-year CVD risk 5 to <10% using SCORE2-Diabetes
Low CV risk	Patients with T2DM not fulfilling the very high-risk criteria and a: • 10-year CVD risk <5% using SCORE2-Diabetes

2023 ESC Guidelines. European Heart Journal (2023) 44, 4043–4140

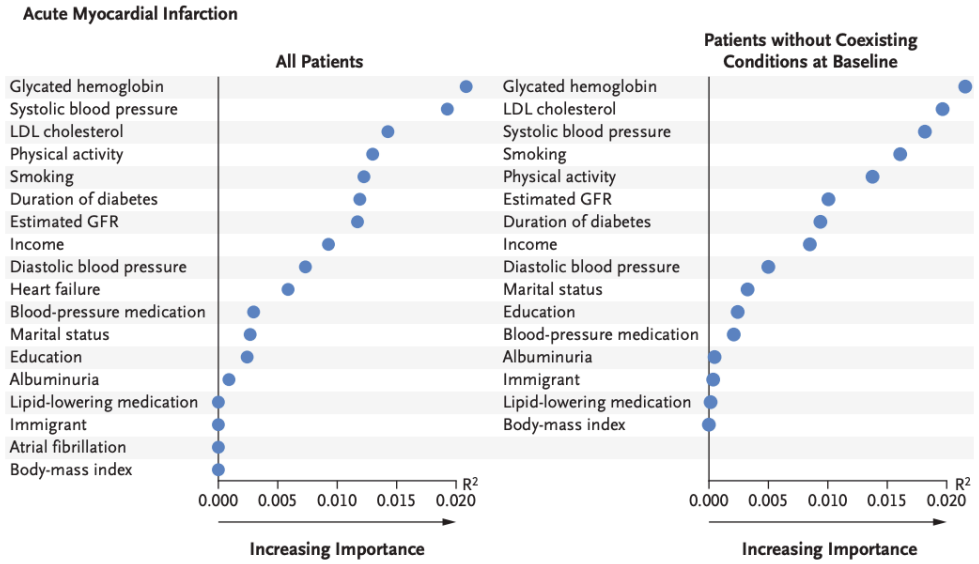
Il rischio CV teorico del paziente diabetico è sempre ALTO-MOLTO ALTO ?

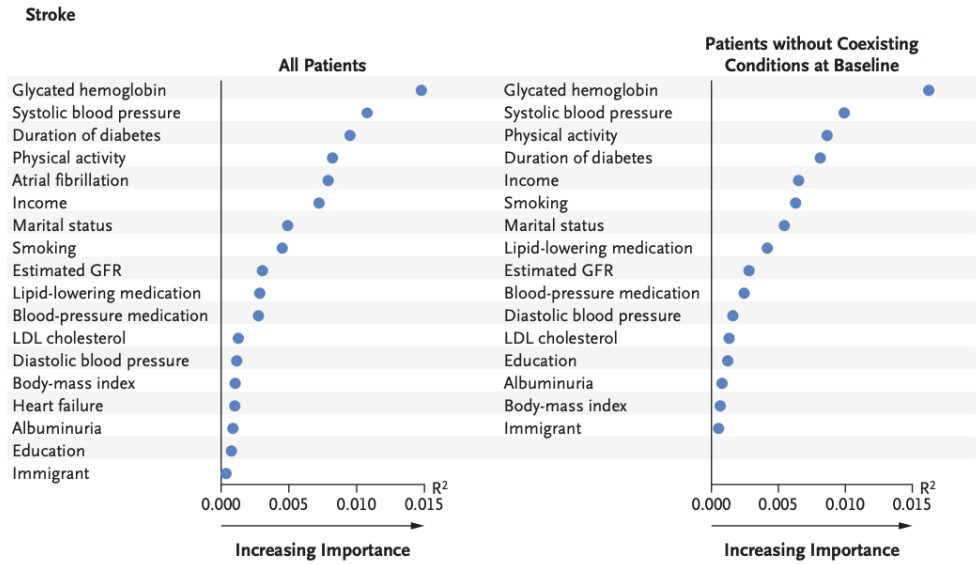
NO… quindi…

1. identifichiamo precocemente il paziente con DM2
2. ricerchiamo “olisticamente” tutti i determinanti del suo rischio e stratifichiamo il rischio
3. trattiamolo

Determinanti di ↑ rischio CV nel diabete mellito di tipo 2

271,174 patients with type 2 diabetes from the Swedish National Diabetes Register
and
1,355,870 matched controls





Rawshani A, et al. N Engl J Med. 2018 Aug 16;379(7):633-644.

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Diabete e rischio cardiovascolare

«Obesità»

Disglicemia
Disfunzione delle betacellule
Insulino-resistenza

Infiammazione
hsPCR
IL-1, IL-6, TNF-α

Stress ossidativo
oxLDL

Dislipidemia
LDL, FFAs, ApoB, ApoA-1

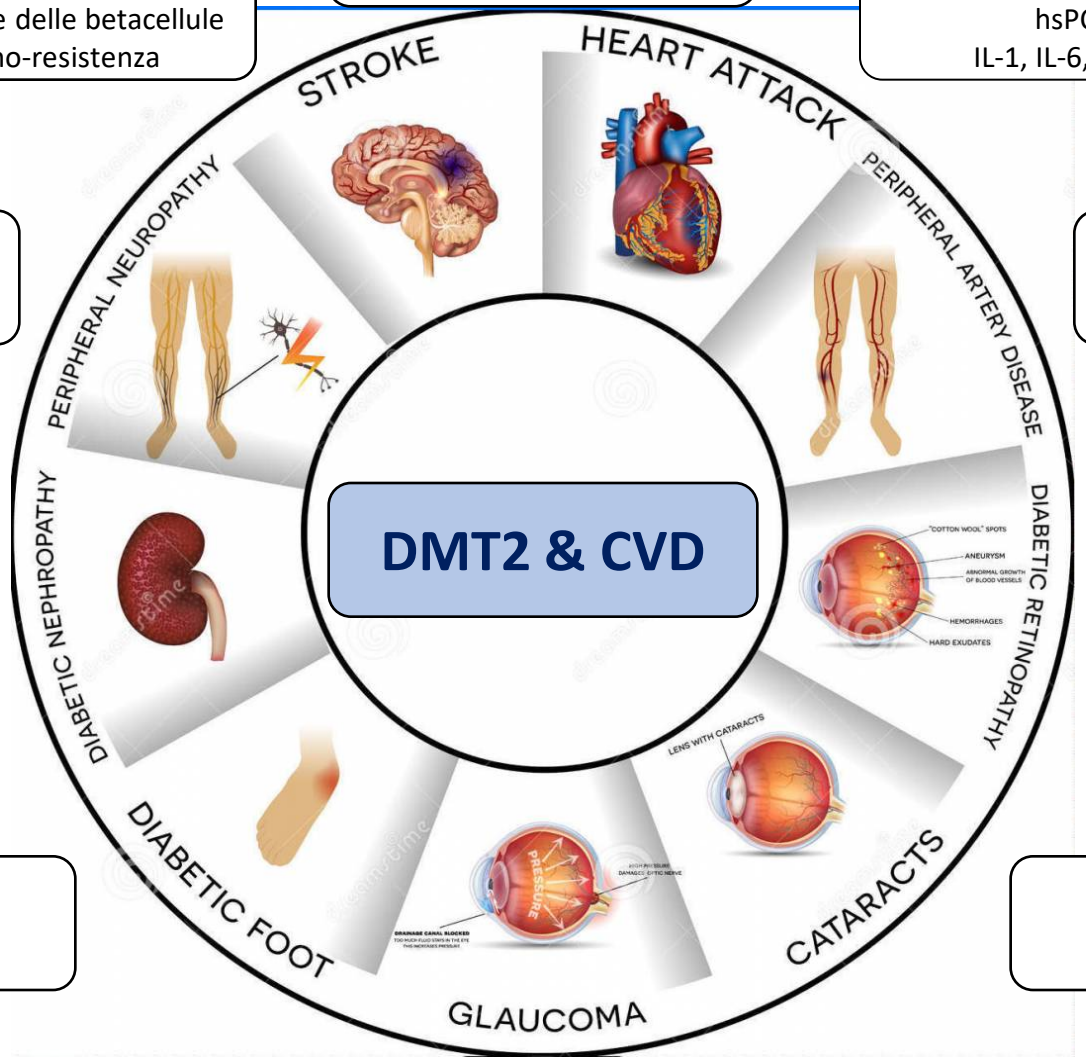
Disfunzione endoteliale

Ipercoagulabilità
Attività antitrombinica, fibrinogeno

Ipertensione

Iperuricemia

«……?……»



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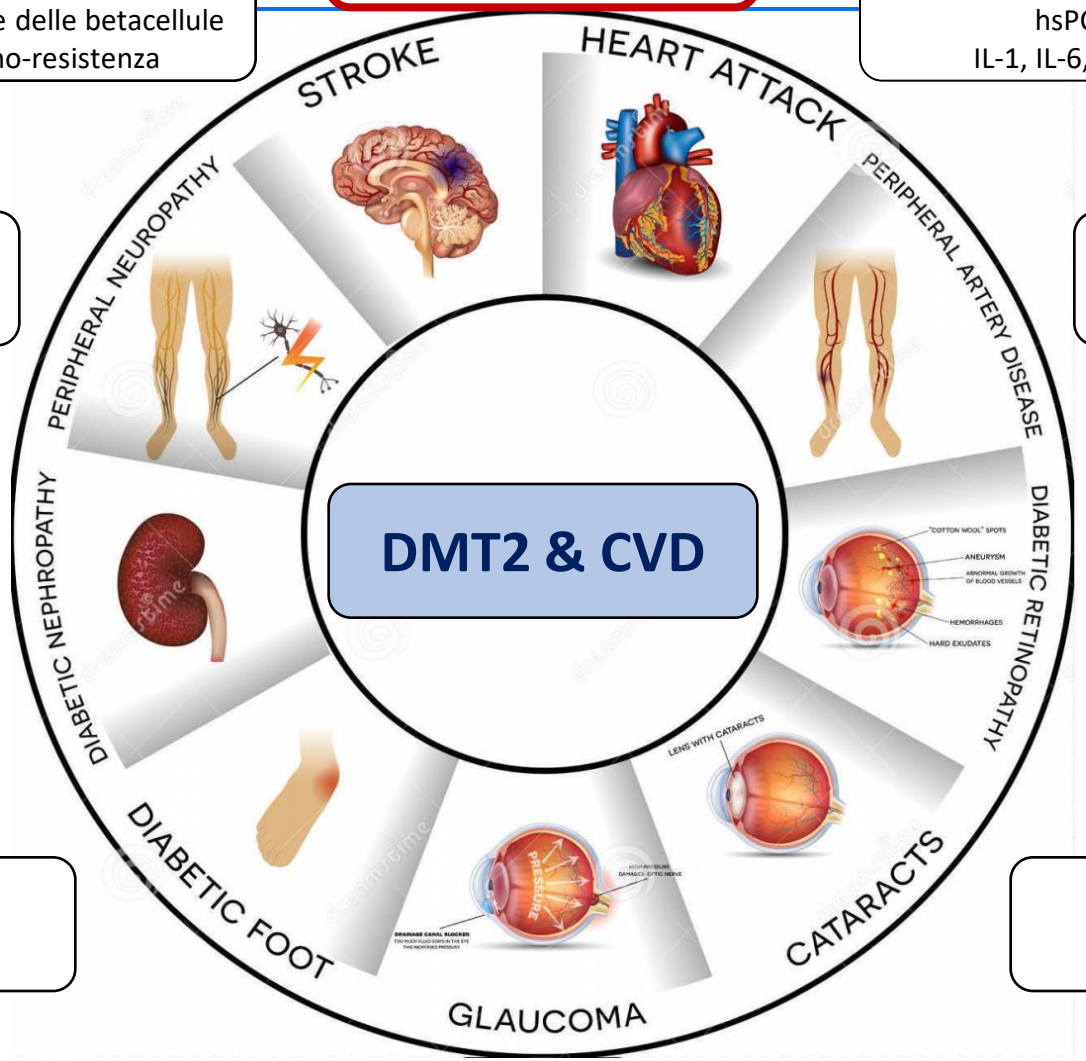
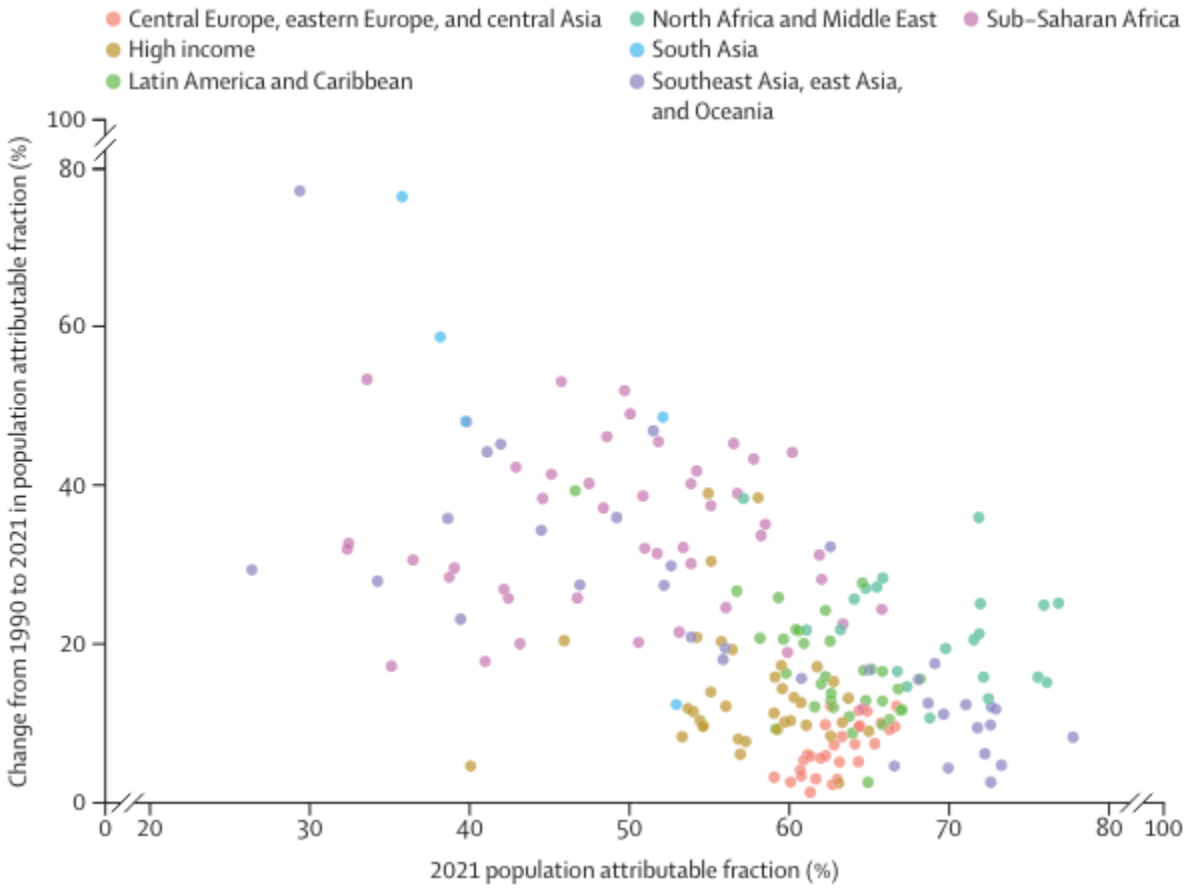


«……?……»

Diabetes attributable to high BMI

The proportion of global type 2 diabetes DALYs attributable to high BMI ***increased by 24·3%*** *(95% UI 18·5 to 30·4), from 42·2% (19·8 to 59·9) in 1990 to 52·2% (25·5 to 71·8) in 2021*



GBD Diabetes Collaborators. Lancet 2023; 402: 203–34

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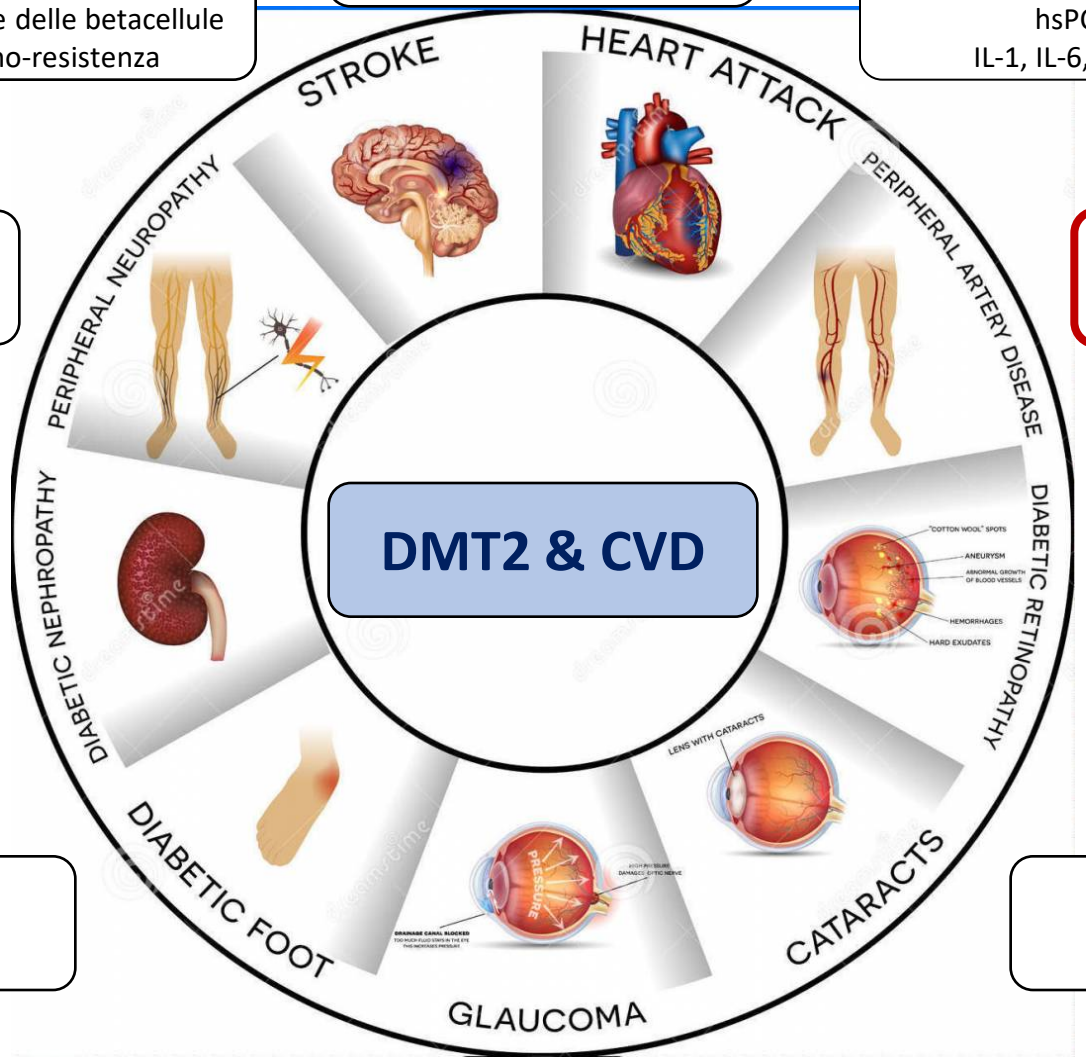

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«……?……»

La dislipidemia diabetica…

CETP

- ↑ triglycerides
- ↓ HDL-cholesterol
- ↑ sd-LDL
- = LDL-cholesterol (?)
- ↑ apoB
- ↑ non-HDL-cholesterol

Perché la dislipidemia diabetica è così determinante?

1) La dislipidemia diabetica è frequente

2) La dislipidemia diabetica causa ATS

3) La dislipidemia diabetica causa eventi cardio-vascolari

Studio della prevalenza dei fattori di rischio cardio-vascolare nella popolazione dislipidemica Umbra (n.1600)

Pazienti non trattati con statina

HDL colesterolo <40-50 mg/dl	25% della popolazione dislipidemica totale
Trigliceridi >150 mg/dl	62% della popolazione dislipidemica totale

Pazienti già in trattamento con statina

HDL colesterolo <40-50 mg/dl	24% della popolazione dislipidemica totale
Trigliceridi >150 mg/dl	45% della popolazione dislipidemica totale

Pazienti diabetici

HDL colesterolo <40-50 mg/dl	40% della popolazione diabetica
Trigliceridi >150 mg/dl	75% della popolazione diabetica
LDL colesterolo >100 mg/dl	84% della popolazione diabetica

Pirro M, Mannarino E et al. Eur J Intern Med. 2011 Aug;22(4):412-7.

La dislipidemia aterogena è altamente prevalente nel DM2...

4199 overweight/obese adults with type 2 diabetes; 40% (n=1659) had atherogenic dyslipidemia

	Whole Sample	Triglyceride and HDL-C Status				
		Normal Triglyceride, Normal HDL-C	High Triglyceride, Normal HDL-C	Normal Triglyceride, Low HDL-C	High Triglyceride, Low HDL-C	*P* Value
Sample size, n (%)	4199 (100)	1110 (26.4)	486 (11.6)	944 (22.5)	1659 (39.5)	...
Treatment assignment, n (%)						0.692
DM support and education	2111 (50.3)	557 (50.2)	233 (47.9)	484 (51.3)	837 (50.5)	
Intensive lifestyle intervention	2088 (49.7)	553 (49.8)	253 (52.1)	460 (48.7)	822 (49.6)	
Age, y	58.4 (6.6)	59.1 (6.4)	59.0 (6.4)	57.8 (7.0)	58.0 (6.6)	<0.001
Women, n (%)	2600 (61.9)	674 (60.7)	284 (58.4)	652 (69.1)	990 (59.7)	<0.001
Race/ethnicity, n (%)						<0.001
White	2726 (64.9)	630 (56.8)	346 (71.2)	527 (55.8)	1223 (73.7)	
Black (not Hispanic)	719 (17.1)	331 (29.8)	48 (9.9)	225 (23.8)	115 (6.9)	
Hispanic	610 (14.5)	101 (9.1)	73 (15.0)	157 (16.6)	279 (16.8)	
Other/mixed	144 (3.4)	48 (4.3)	19 (3.9)	35 (3.7)	42 (2.5)	
BMI, kg/m^2	36.0 (5.9)	35.7 (6.0)	35.8 (6.0)	36.4 (6.2)	36.1 (5.7)	0.026
Waist circumference, cm	113.6 (14.1)	111.8 (13.8)	113.3 (14.7)	113.9 (14.0)	114.8 (14.0)	<0.001
Current smoking, n (%)	170 (4.1)	38 (3.4)	13 (2.7)	36 (3.8)	83 (5.0)	0.058
Alcohol drinking, oz/wk	0.0 (0.0–5.0)	0.0 (0.0–7.5)	0.0 (0.0–6.5)	0.0 (0.0–5.0)	0.0 (0.0–5.0)	0.016
Systolic BP, mm Hg	129.1 (16.9)	129.3 (17.6)	129.8 (16.7)	128.2 (17.3)	129.3 (16.2)	0.269
Diastolic BP, mm Hg	70.5 (9.5)	70.4 (9.3)	70.5 (9.8)	70.0 (9.6)	70.7 (9.4)	0.279
Use of antihypertensive medication, n (%)	2987 (71.1)	789 (71.1)	353 (72.6)	666 (70.6)	1179 (71.1)	0.875
HbA_{1c}, %	7.2 (1.2)	7.1 (1.1)	7.2 (1.2)	7.1 (1.1)	7.4 (1.2)	<0.001
Duration of diabetes mellitus, years	5.0 (2.0–9.0)	5.0 (2.0–10.0)	5.0 (2.0–8.0	5.0 (2.0–10.0)	5.0 (2.0–8.0)	0.232
Use of insulin, n (%)	716 (17.1)	226 (20.4)	60 (12.4)	162 (17.2)	268 (16.2)	0.001
Triglyceride, mg/dL	152.0 (107.0–219.0)	96.0 (75.0–121.0)	190.0 (169.0–235.0)	114.0 (94.0–131.0)	226.0 (183.0–303.0)	<0.001
HDL-C, mg/dL	42.0 (36.0–50.0)	54.0 (49.0–61.0)	51.0 (44.0–57.0	39.0 (35.0–45.0)	36.0 (31.0–41.0)	<0.001
LDL-C, mg/dL	112.0 (92.0–134.0)	113.0 (93.0–134.0)	115.0 (94.0–138.0)	112.0 (93.0–134.0)	110.0 (89.0–132.0)	0.012

Kaze AD, et al. J Am Heart Assoc. 2021 Apr 6;10(7):e016947.

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Prevalence, awareness, treatment, and control of dyslipidemia among patients with DM in the Korean NHANES cohort (n. 4311)

Dyslipidemia: LDL-C ≥ 100 mg/dL, currently using lipid-lowering agents, or previously diagnosed with dyslipidemia

Variables	All % (SE)	By sex		
		Men % (SE)	Women % (SE)	*P* value
Prevalence[a]	83.3 (0.7)	78.1 (1.2)	88.3 (0.8)	0.000
Awareness[b]	36.5 (1.0)	34.3 (1.4)	38.3 (1.3)	0.038
Treatment[b]	26.9 (0.9)	25.8 (1.3)	27.9 (1.1)	0.232
Control[b]	18.8 (0.8)	18.9 (1.2)	18.7 (1.0)	0.873
Control among treated[c]	61.1 (1.8)	63.6 (2.8)	59.2 (2.2)	0.207

Kin SJ, et al. Lipids Health Dis . 2021 Mar 26;20(1):29.

Perché la dislipidemia diabetica è così determinante?

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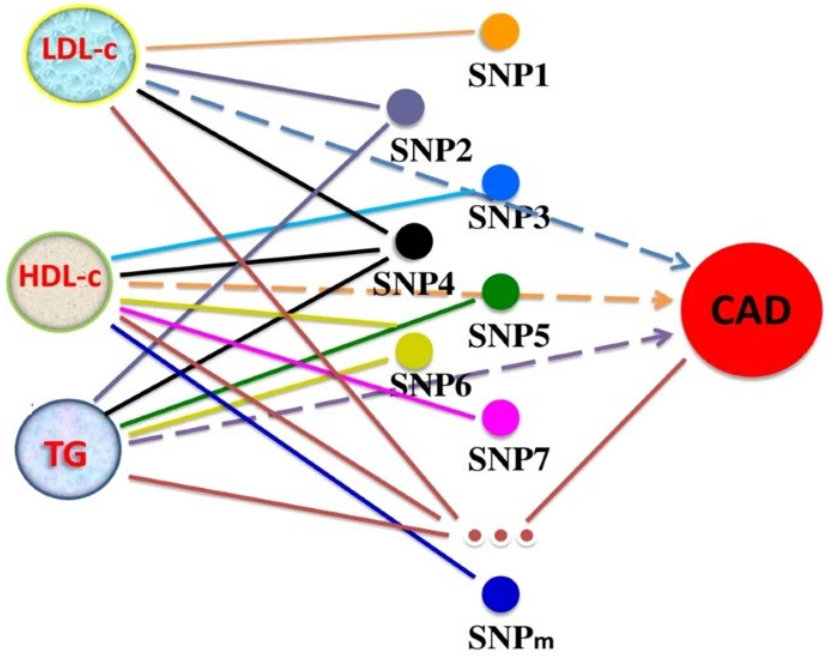
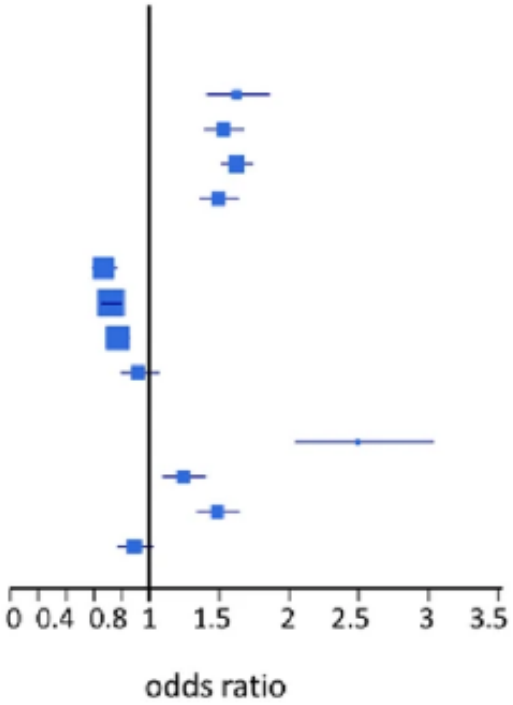
Polimorfismi associati ad LDL-C, HDL-C e TG e rischio CV
- Randomizzazione mendeliana -



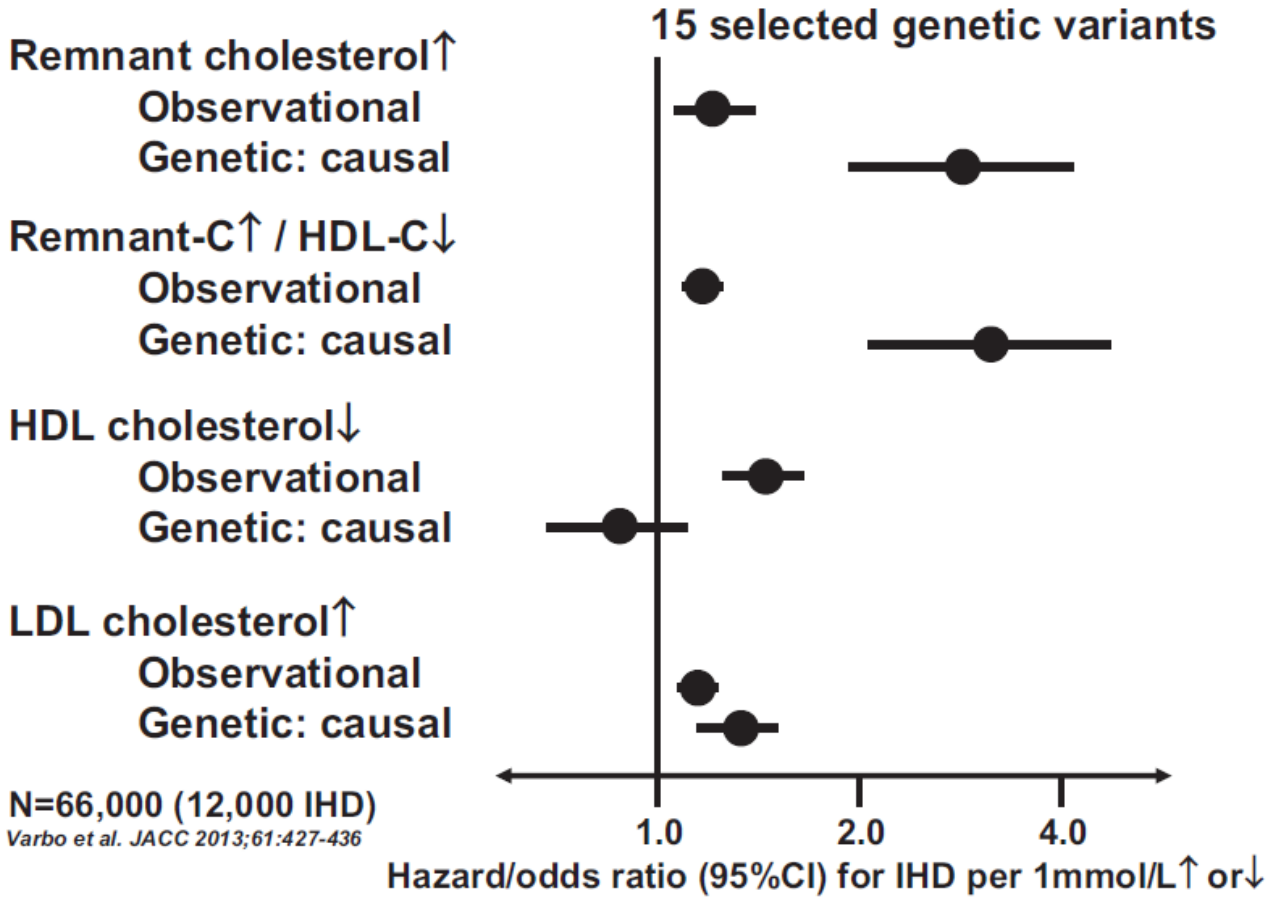
method	beta	beta	beta	se	p-value
Simple median	LDL-c	255	0.49	0.069	0
Weighted median	LDL-c	255	0.431	0.047	0
IVW	LDL-c	255	0.49	0.035	0
MR-Egger	LDL-c	255	0.406	0.047	0
Simple median	HDL-c	255	-0.386	0.065	0
Weighted median	HDL-c	255	-0.312	0.047	0
IVW	HDL-c	255	-0.251	0.051	0
MR-Egger	HDL-c	255	-0.074	0.074	0.315
Simple median	TG	255	0.918	0.1	0
Weighted median	TG	255	0.224	0.062	0
IVW	TG	255	0.401	0.052	0
MR-Egger	TG	255	-0.108	0.073	0.137

b



Tan YD, et al. Sci Rep 10, 9208 (2020). https://doi.org/10.1038/s41598-020-66027-4

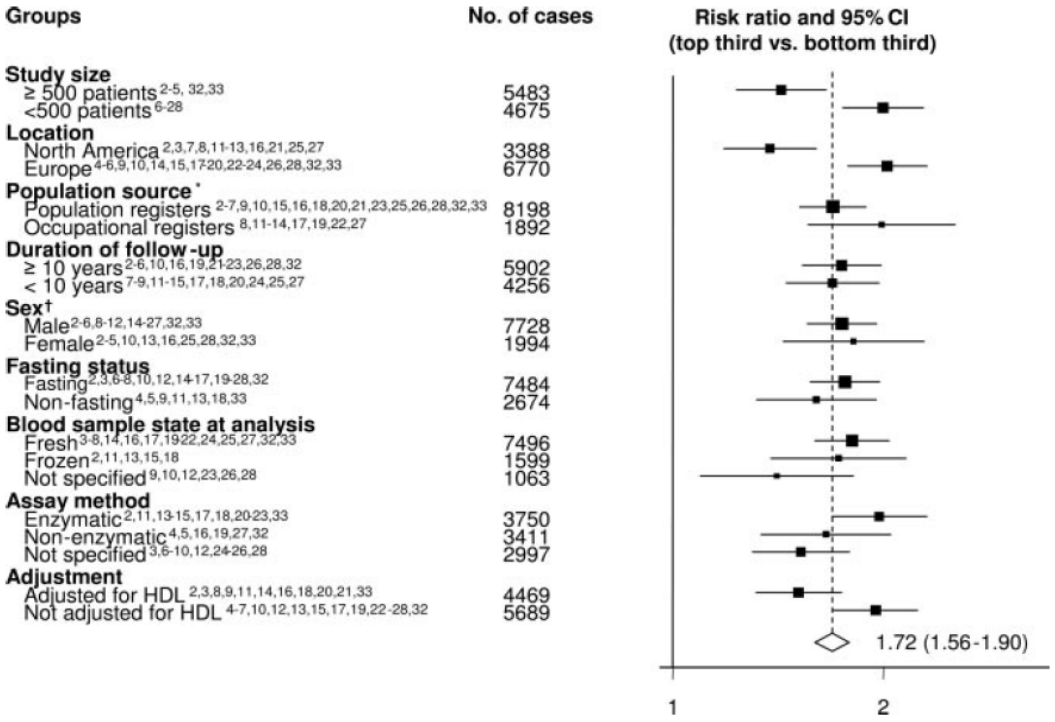
Polimorfismi associati a livelli di colesterolo delle TGRL e rischio CV
- Randomizzazione mendeliana -



Nordestgaard BG. Circ Res. 2016 Feb 19;118(4):547-63.

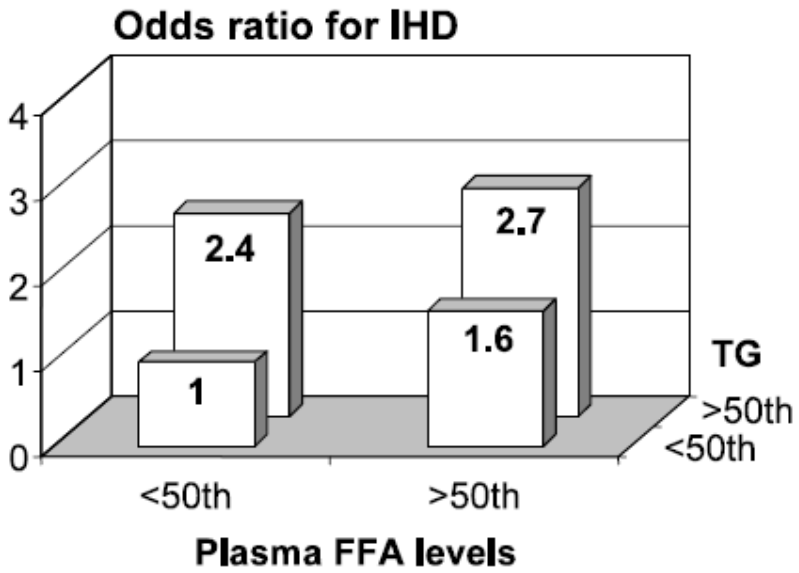
Trigliceridi e rischio cardio-vascolare

10158 Incident Cases Among 262525 Participants in 29 Western Prospective Studies



Sarwar N et al, Circulation. 2007 Jan 30;115(4):450-8.

2103 individuals without IHD at baseline among whom 114 developed IHD during a 5-year follow-up period



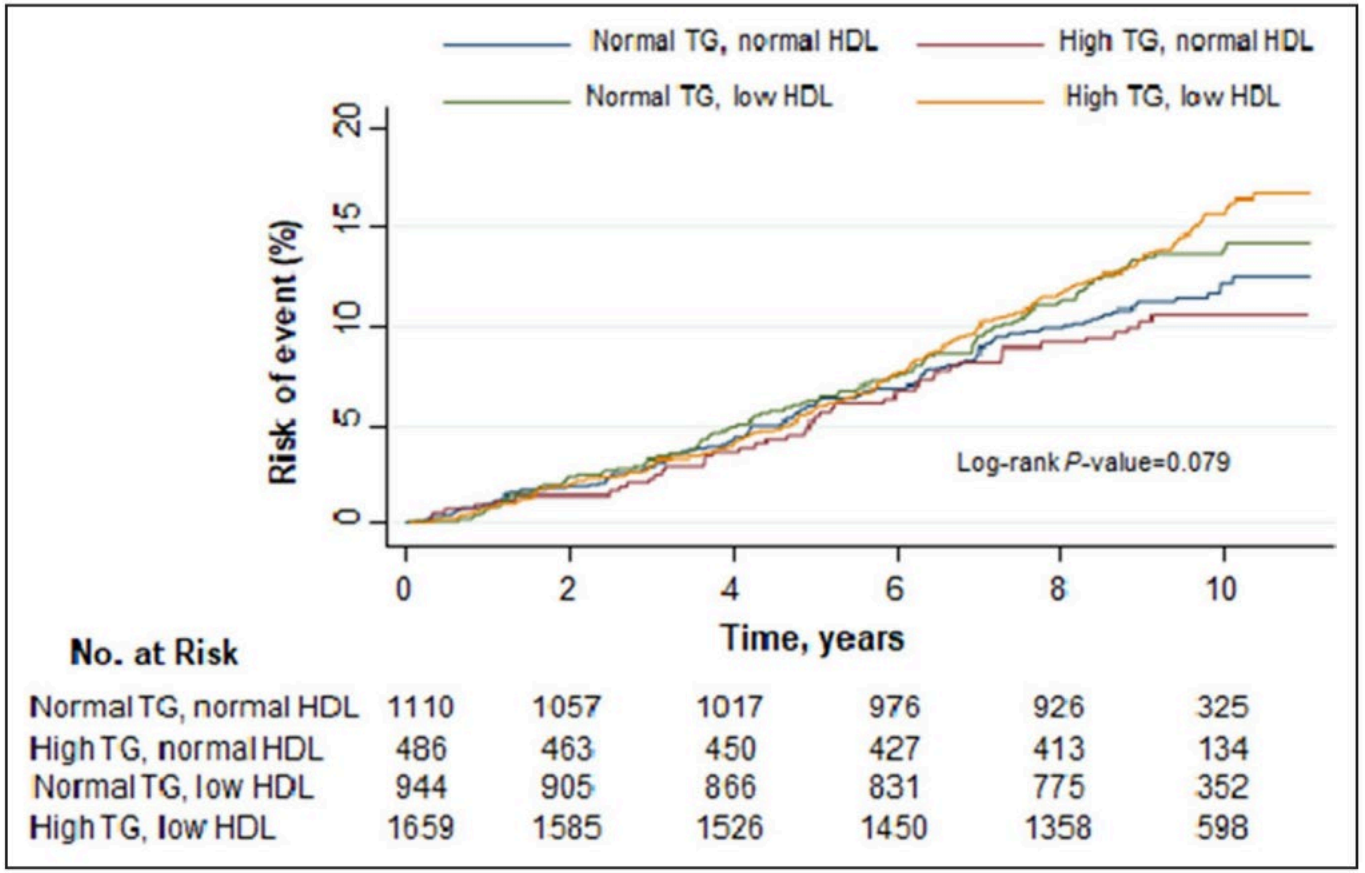
Pirro M et al. Atherosclerosis. 2002 Feb;160(2):377-84.

La dislipidemia aterogena è altamente prevalente nel DM2...
...e ne condiziona la prognosi

4199 overweight/obese adults with type 2 diabetes; 40% (n=1659) had atherogenic dyslipidemia

High TG + low HDL vs normal TG + normal HDL

HR, 1.30; 95% CI, 1.03-1.63 [*P*=0.025]

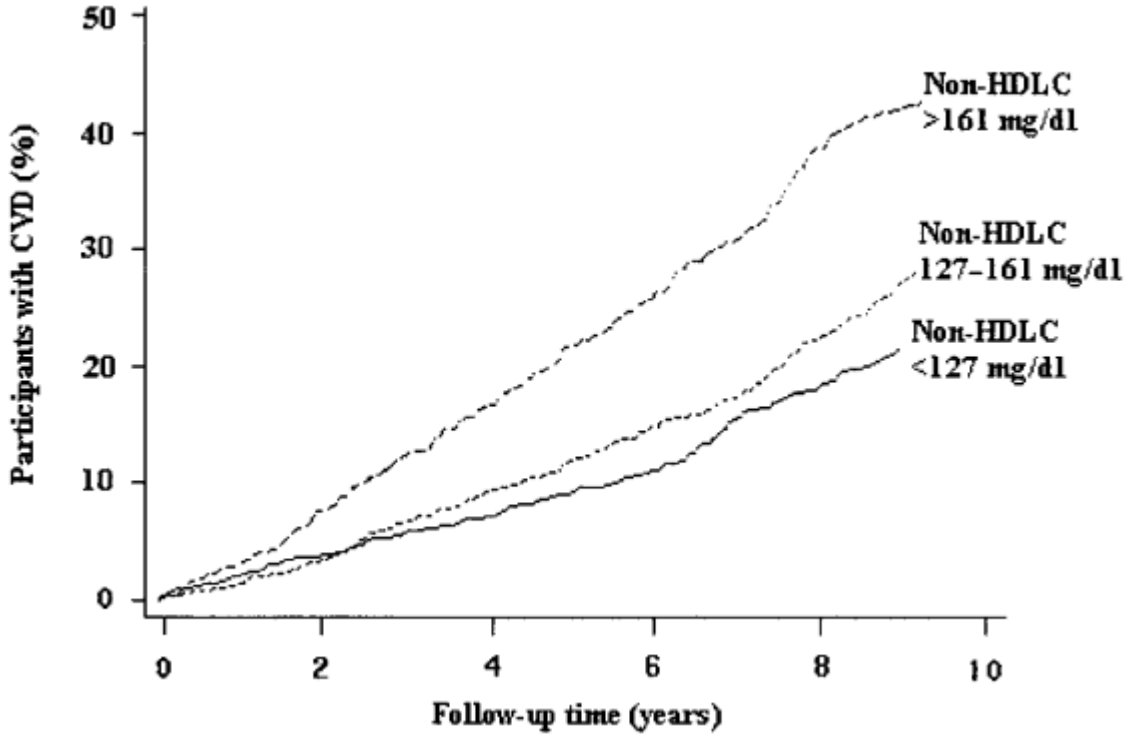


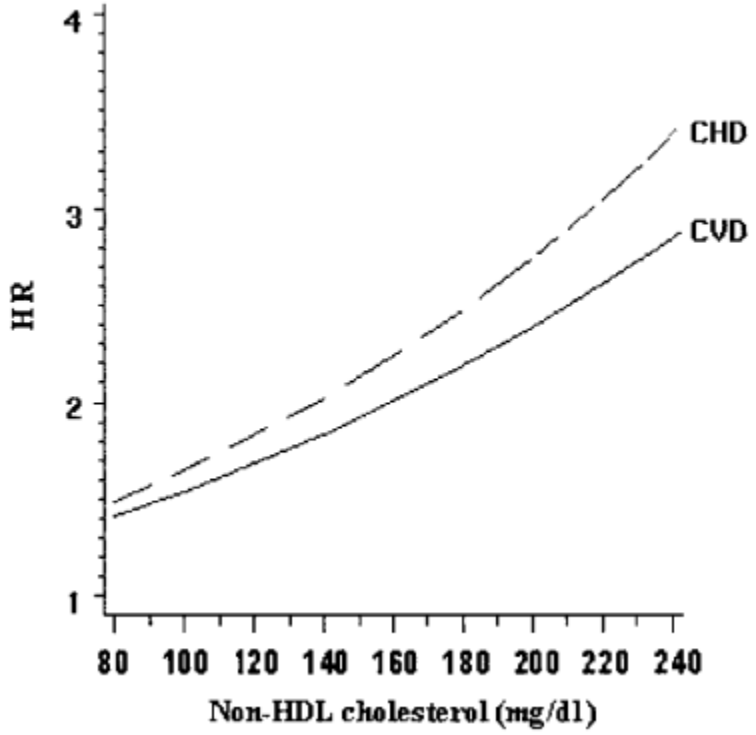
No. at Risk						
Normal TG, normal HDL	1110	1057	1017	976	926	325
High TG, normal HDL	486	463	450	427	413	134
Normal TG, low HDL	944	905	866	831	775	352
High TG, low HDL	1659	1585	1526	1450	1358	598

Kaze AD, et al. J Am Heart Assoc. 2021 Apr 6;10(7):e016947.

Non-HDL Cholesterol as a Predictor of CVD in Type 2 Diabetes
- Strong Heart Study -

Among 4,549 women and men aged 45-74 years participating in the study, **2,108** had diabetes but no CVD at baseline

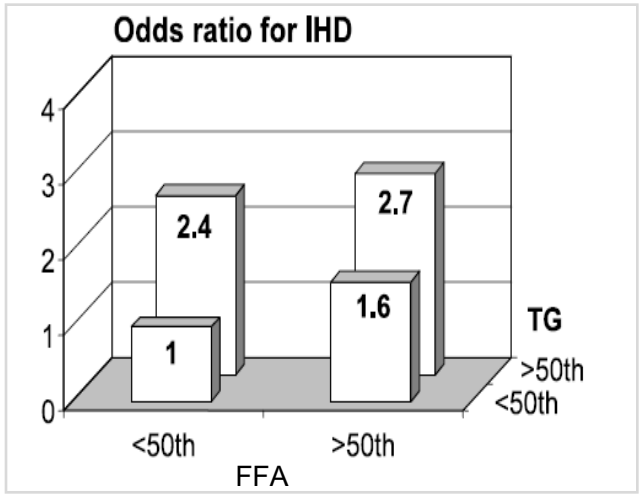




Lu W, et al. Diabetes Care 26:16–23, 2003

Acidi grassi liberi, LDL piccole e dense e…….. influenza congiunta sul rischio cardiovascolare

Quebec Cardiovascular Study



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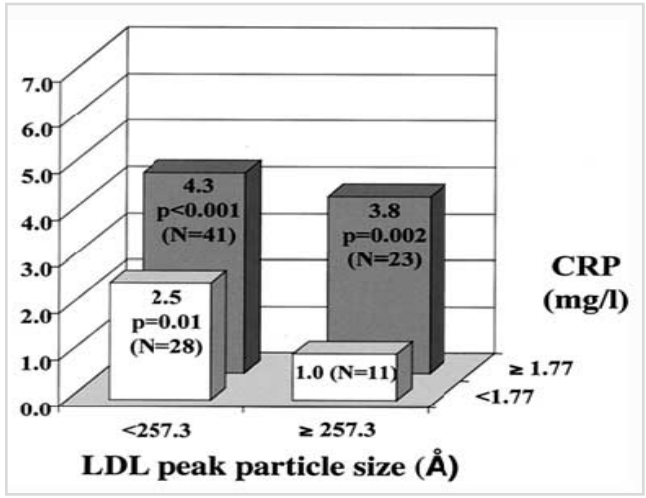
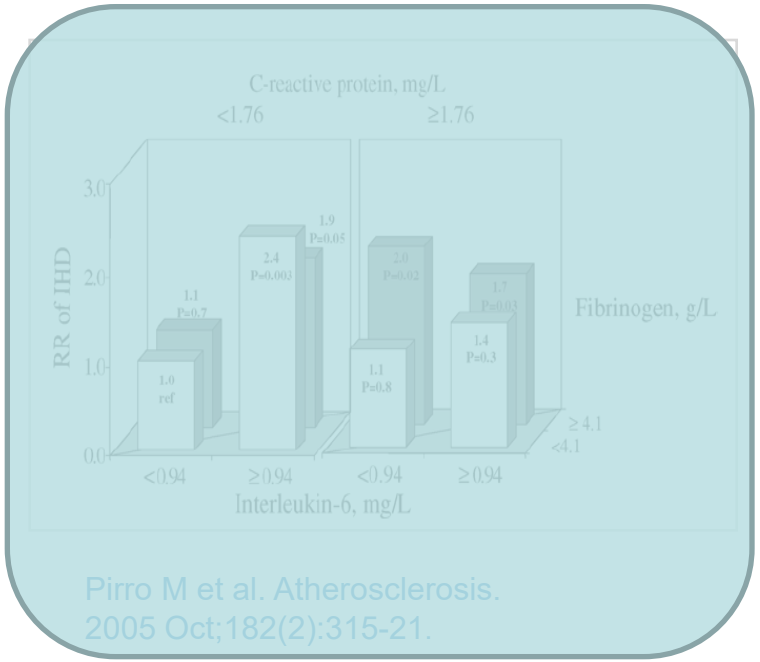


Pirro M et al. Am J Cardiol. 2003 Mar 1;91(5):555-8.



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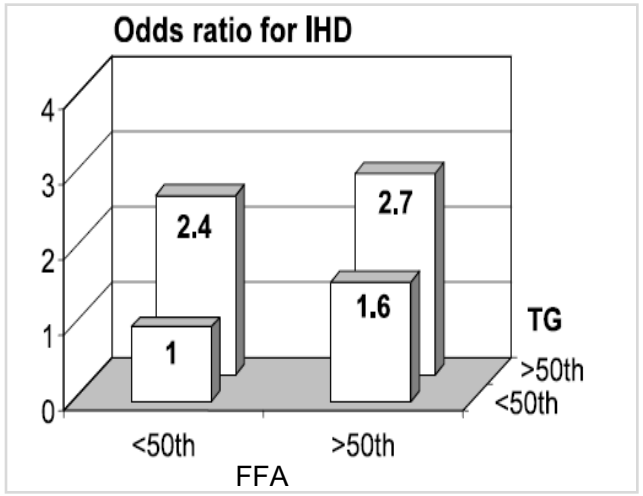

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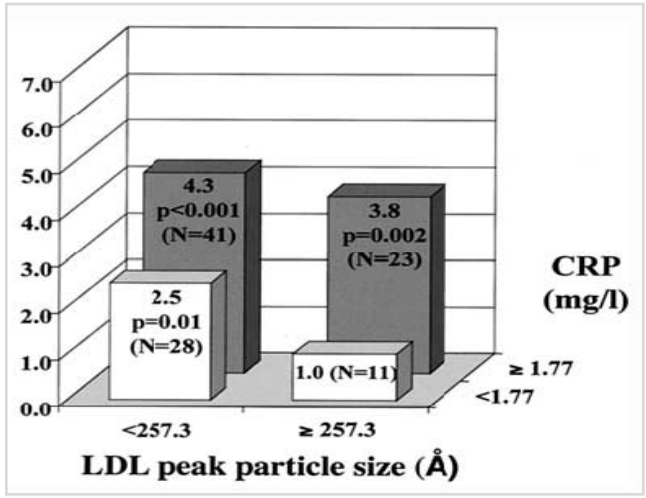

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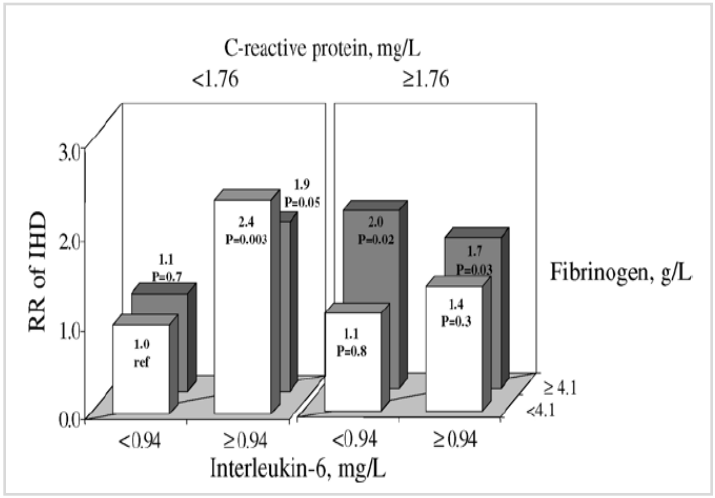

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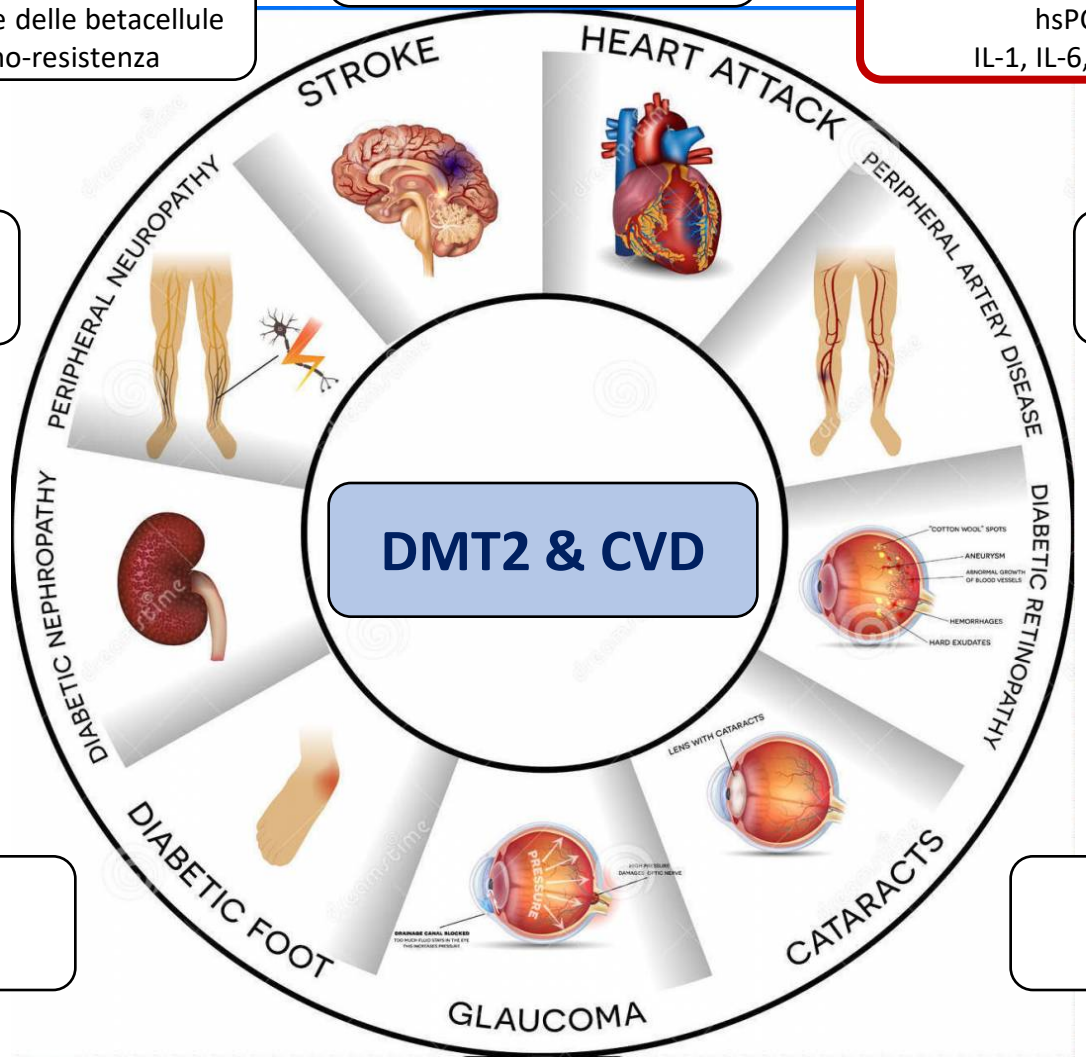

Disfunzione endoteliale

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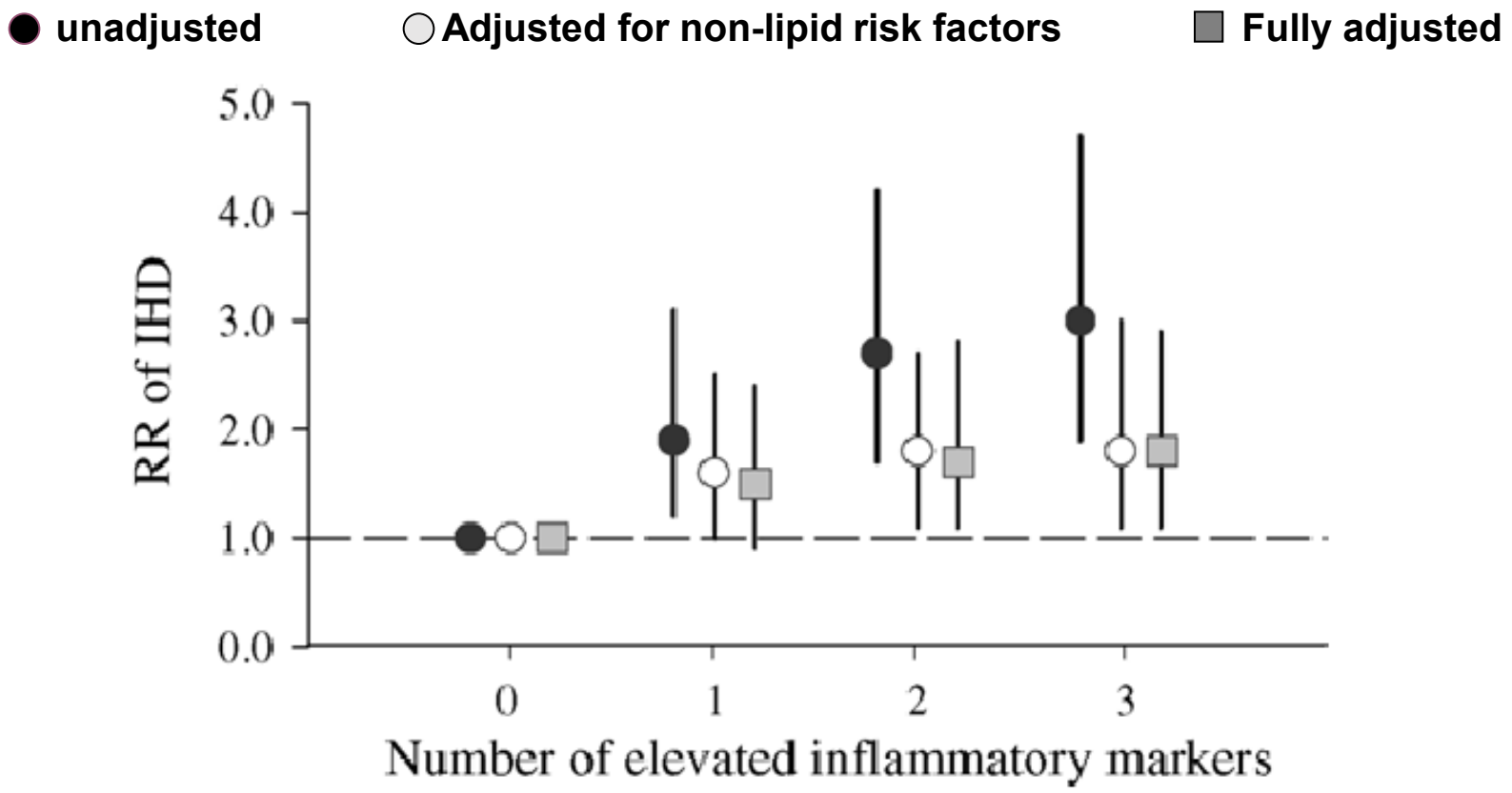
Ipertensione

Iperuricemia

«……?……»

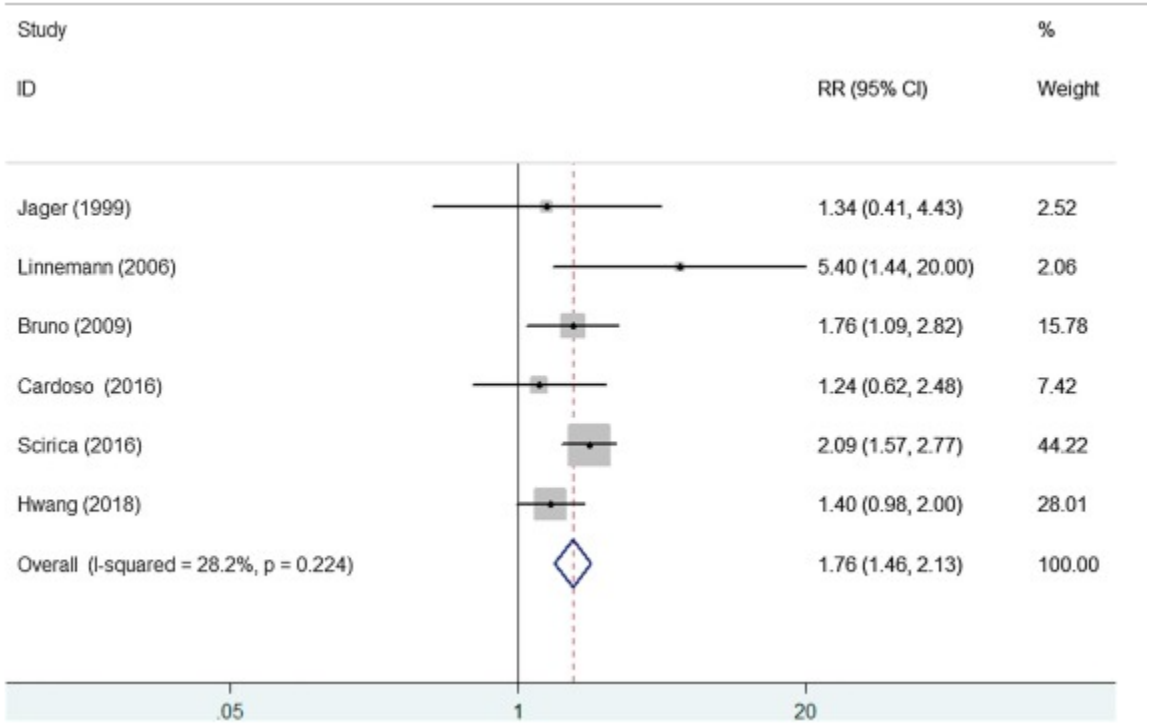
hsCRP, fibrinogen, interleukin-6 and ASCVD risk



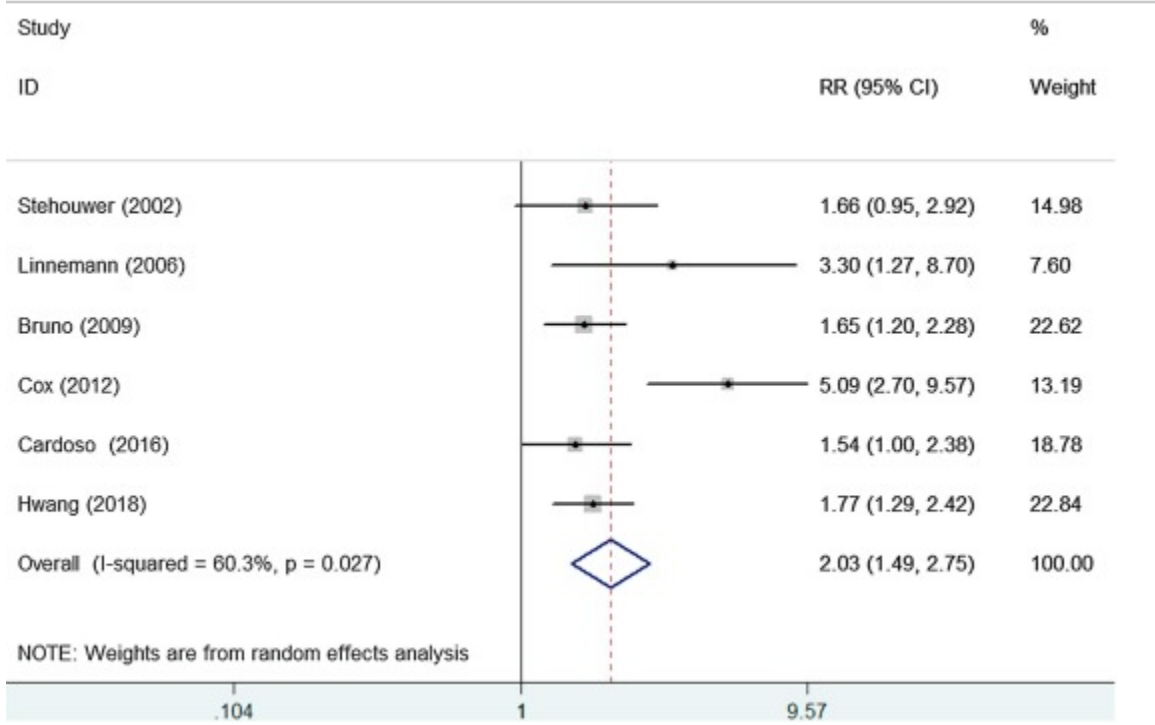
Pirro M, Despres JP, Lamarche B, et al. Atherosclerosis 2005;182:315-21

hsCRP and mortality risk in DM2: meta-analysis

CV mortality



All cause mortality



Tian R, et al. Cytokine, 2019; 117:59-64

Diabete e rischio cardiovascolare

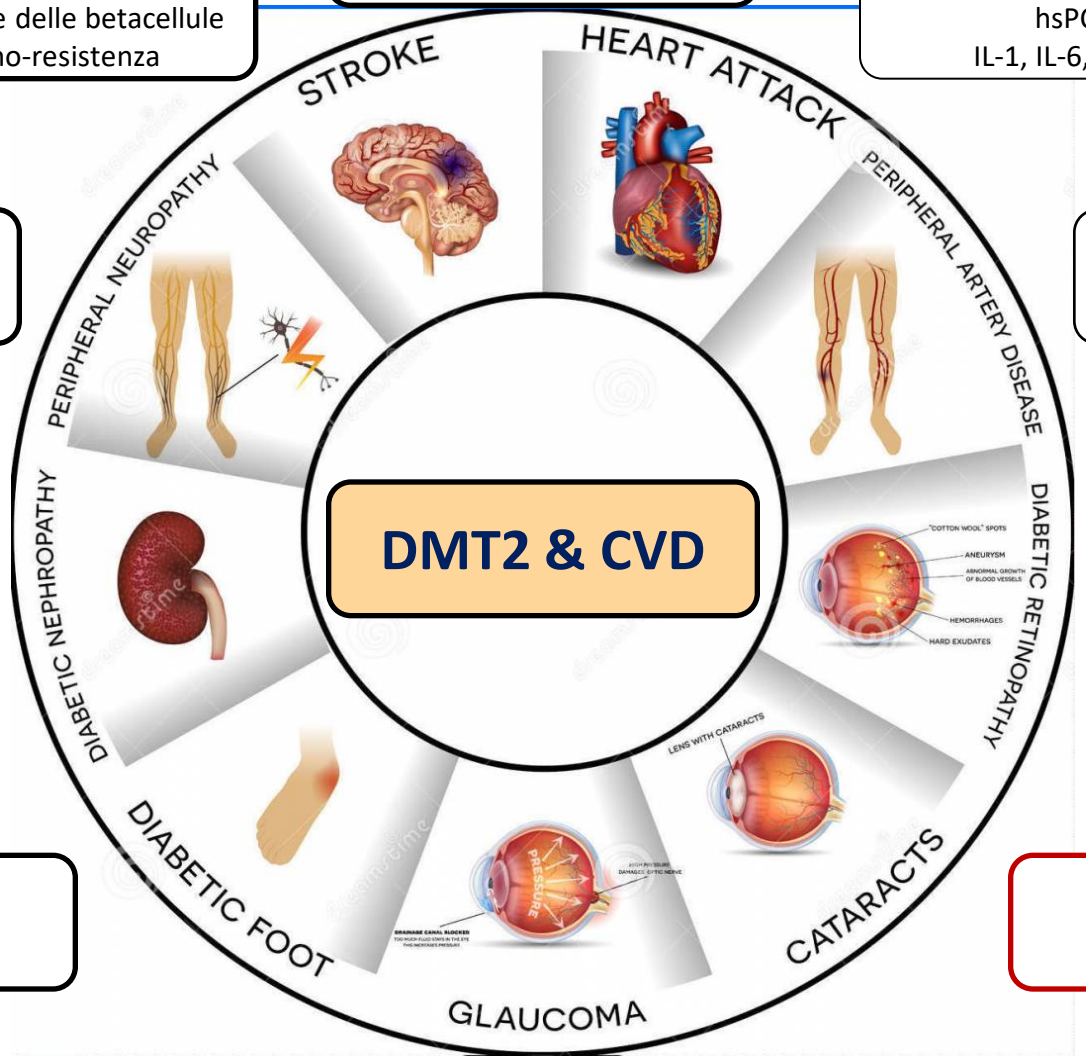
«Obesità»

Disglicemia
Disfunzione delle betacellule
Insulino-resistenza

Infiammazione
hsPCR
IL-1, IL-6, TNF-α

Stress ossidativo
oxLDL

Dislipidemia
LDL, FFAs, ApoB, ApoA-1



Disfunzione endoteliale

Ipercoagulabilità
Attività antitrombinica, fibrinogeno

Ipertensione

Iperuricemia

«.....?.....»

Sembra esistere un'associazione causale tra DM2 ed iperuricemia

Mendelian randomization analysis

(Genetic instruments for metabolic disorders and serum urate obtained from several GWAS studies on individuals of mainly European ancestry)

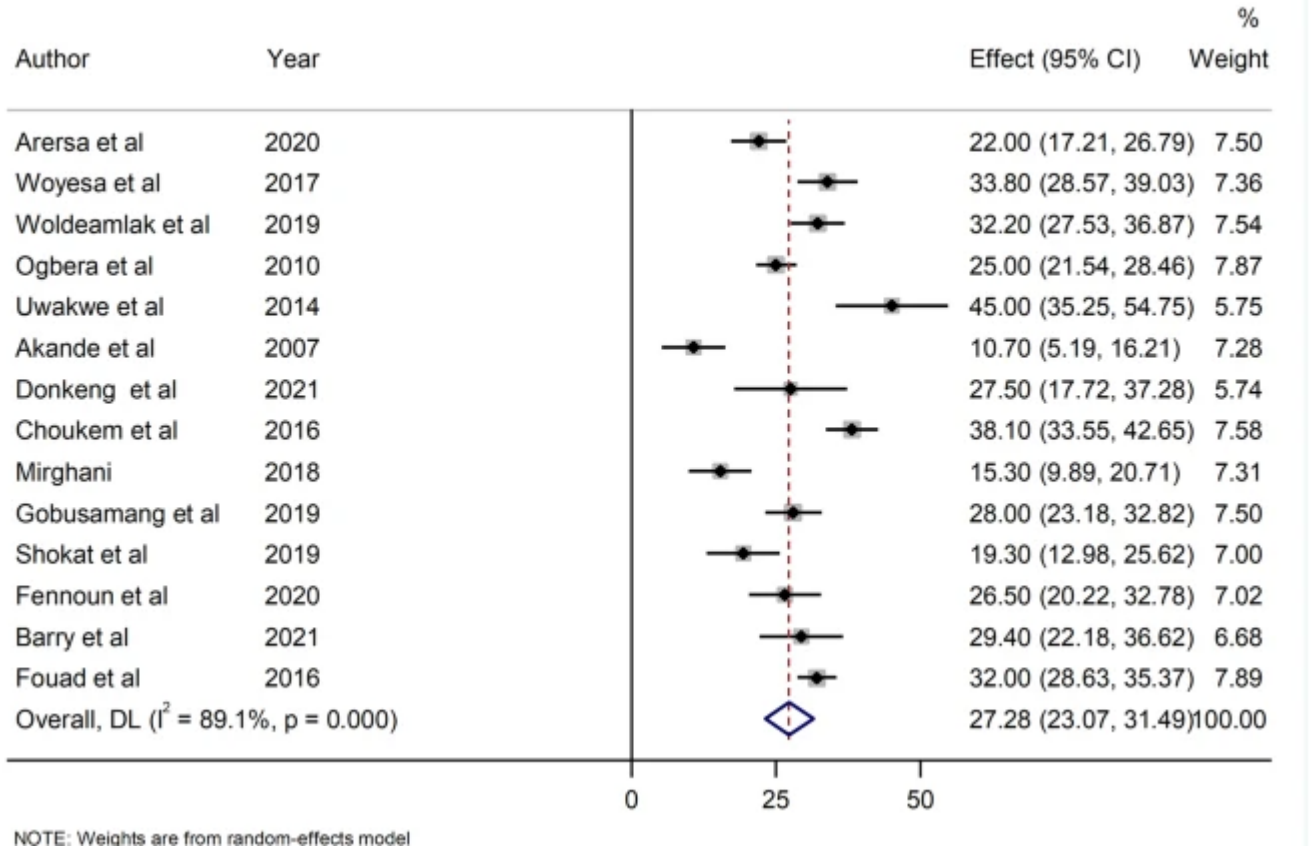
Outcome	Exposure	Method	Estimate	95% CI	P-value	MR-Egger intercept (P-value)
Serum urate	T2DM	IVW MR	0.027	-0.007-0.061	0.116	0.004 (0.112)
		Weighted median	0.029	-0.001-0.059	0.058	
		MR-Egger	-0.029	-0.104-0.046	0.456	
		MR-PRESSO	0.052	0.029-0.080	<0.001	
	FBG	IVW MR	-0.089	-0.382-0.204	0.551	0.005 (0.494)
		Weighted median	-0.028	-0.170-0.115	0.702	
		MR-Egger	-0.268	-0.854-0.318	0.377	
		MR-PRESSO	0.017	-0.116-0.15	0.802	
	FI	IVW MR	0.802	0.514-1.090	<0.001	0.005 (0.723)
		Weighted median	0.891	0.603-1.179	<0.001	
		MR-Egger	0.483	-1.272-2.237	0.597	
		MR-PRESSO	0.813	0.577-1.049	<0.001	

Yang Y, et al. Front Endocrinol (Lausanne). 2022 Aug 5;13:917056.

Prevalenza dell'iperuricemia nei pazienti con DM2

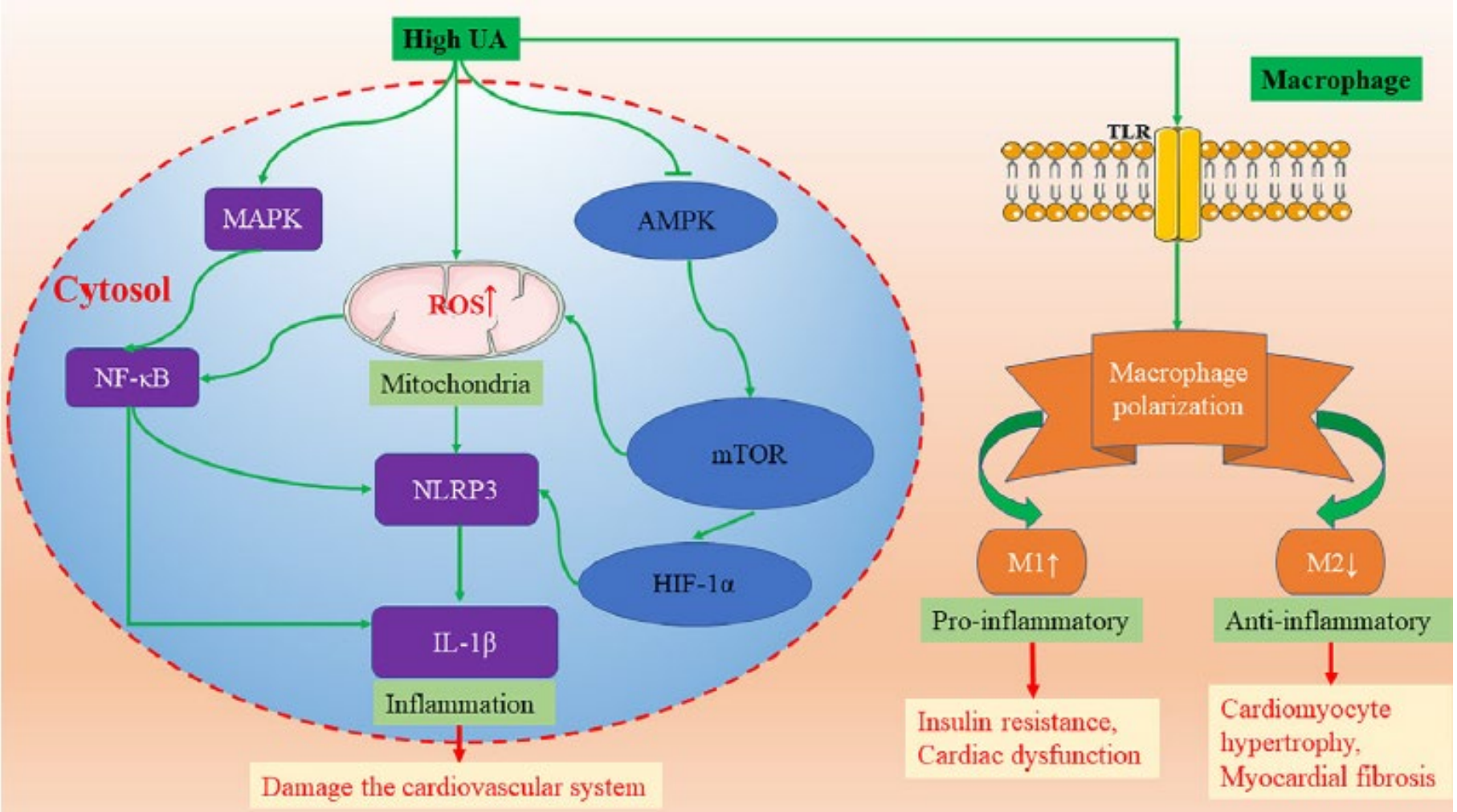
Meta-analysis

14 studies were included in this systematic review and meta-analysis



Jiang J, et al. Curr Diab Rep 23, 103–117 (2023).

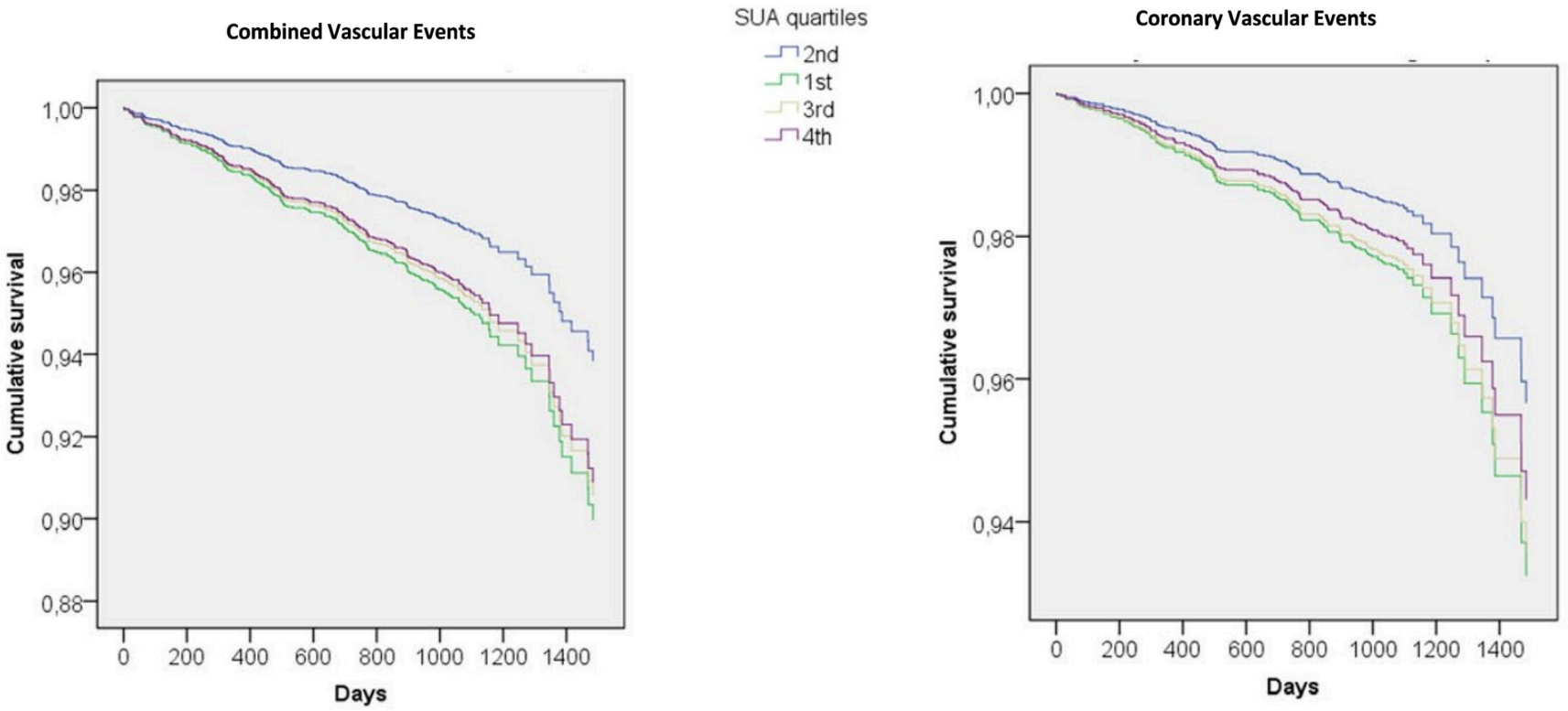
Sembra esistere un'associazione causale tra iperuricemia ed infiammazione sistemica



Yu W, et al. Front Pharmacol. 2020; 11: 582680

Aumentati livelli di acido urico si associano con ↑ rischio CV

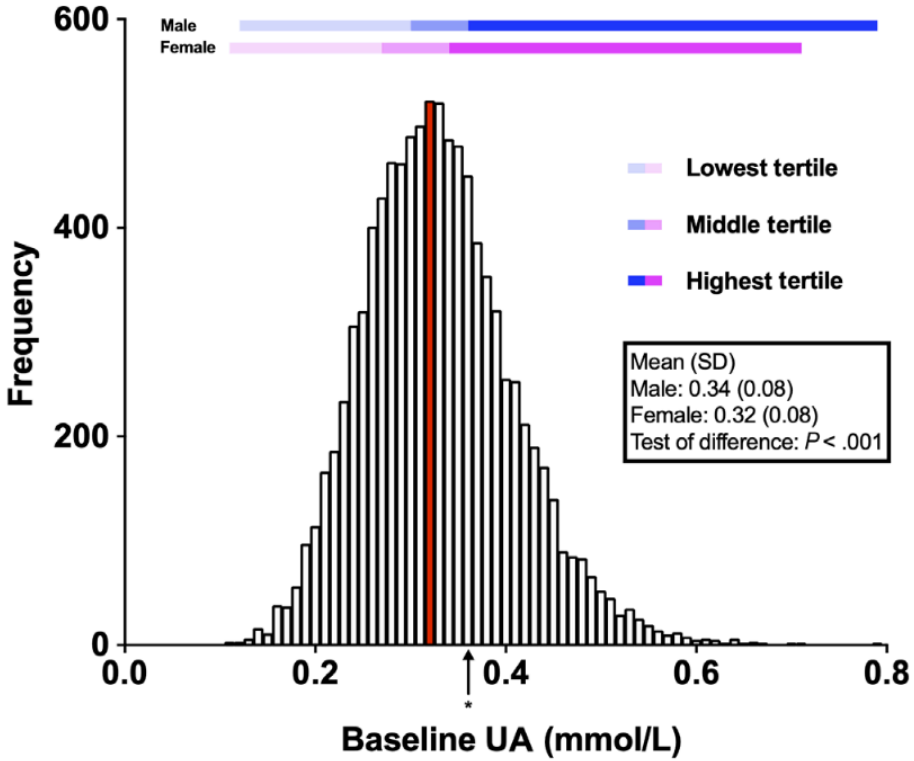
3,686 patients (median age 64 years; 48% men) with ≥ 3 CV risk factors and free from CV events at baseline (median 36.2-month follow-up)

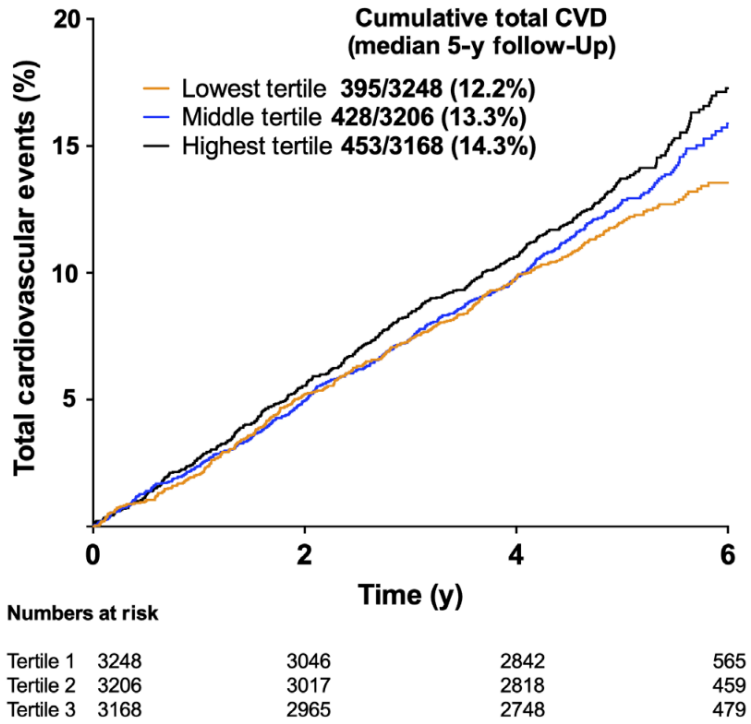


Mannarino MR, Pirro M, et al. J Am Heart Assoc. 2021 Jun;10(11):e020419.

L'iperuricemia è altamente prevalente nel DM2…
…e ne condiziona la prognosi

9795 adults with type 2 diabetes





Cao JY, et al. Diabetes Obes Metab. 2020 Aug;22(8):1388-1396.

ete e rischio cardiovascolare

«Obesità»

Disglicemia
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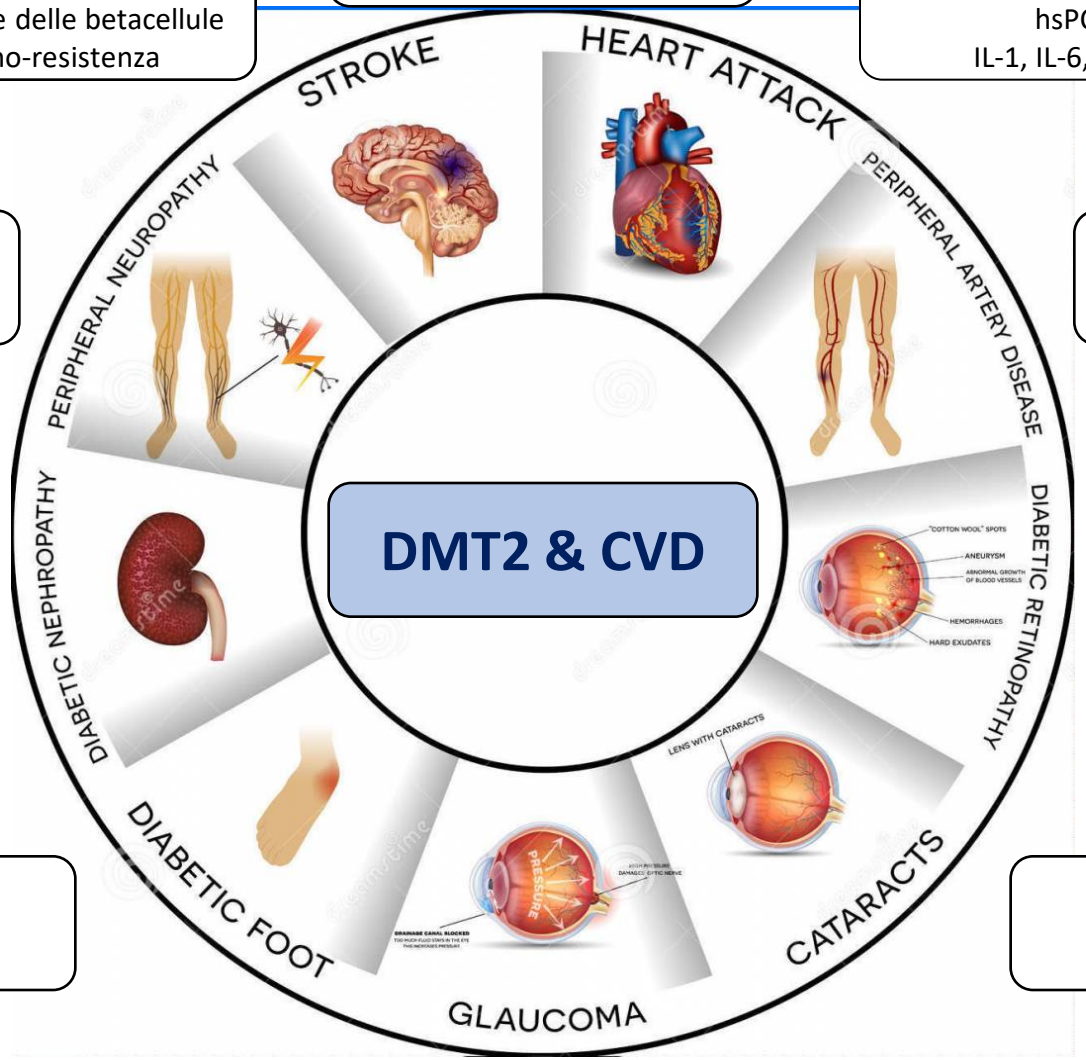


Disfunzione endoteliale

Ipercoagulabilità
Attività antitrombinica, fibrinogeno

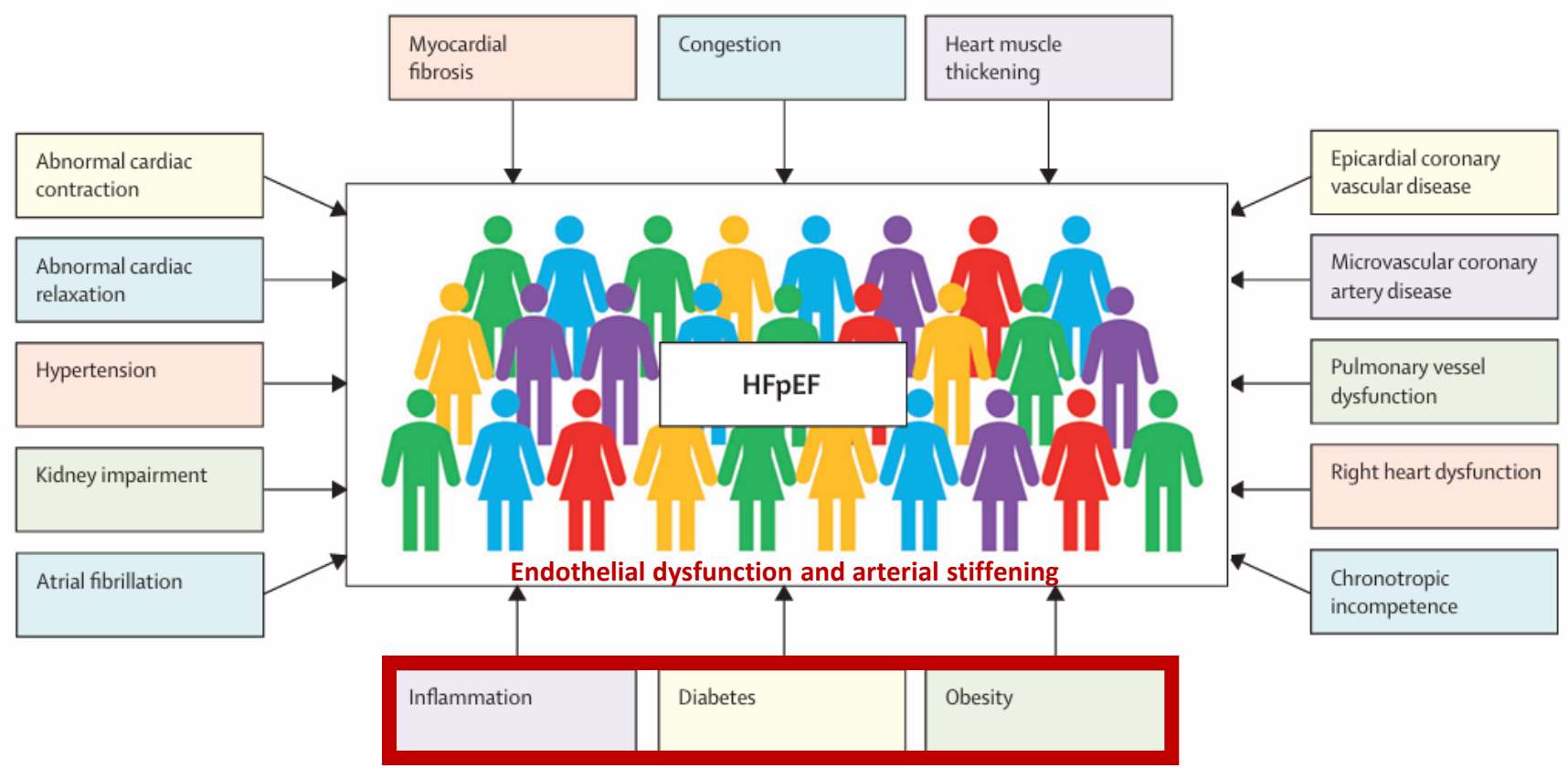
Ipertensione

Iperuricemia

«HFpEF»

Comorbidities predisposing to HFpEF

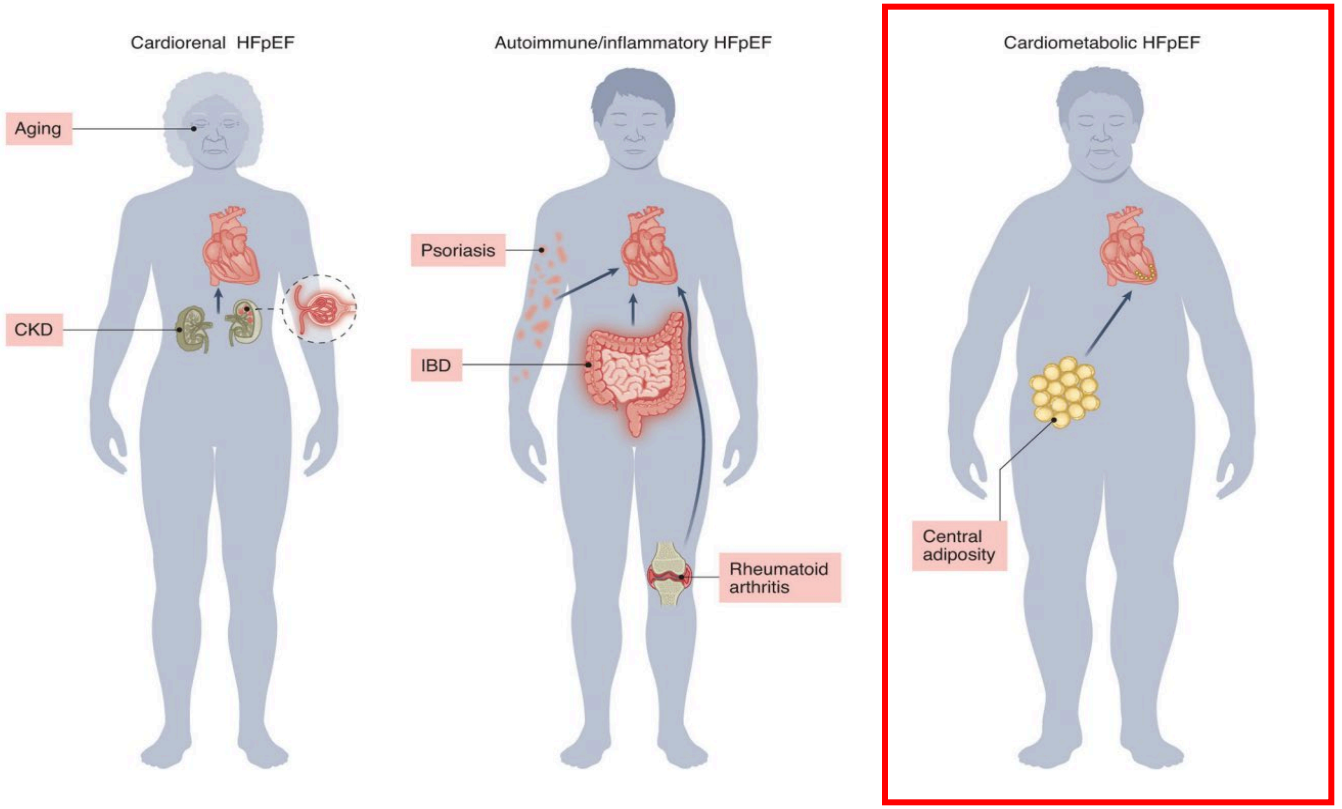
Risk factors for incident HFpEF



Modified from: Campbell P et al. Lancet. 2024 Feb 14:S0140-6736(23)02756-3.

HFpEF clustering in multiple phenotypes

The cardiometabolic HFpEF is the prevalent phenotype (>50% of cases)



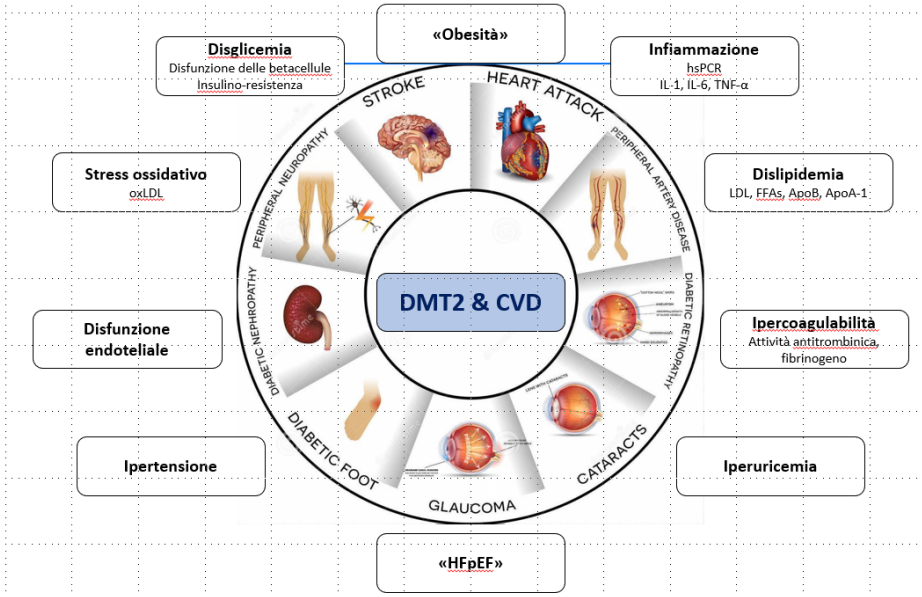
…other

Schiattarella GG et al. Nat Cardiovasc Res. 2022 Mar;1(3):211-222.

Controllo dell'infiammazione e rischio cardiovascolare

Gestione della glicemia e degli altri «triggers» infiammatori

Gestione diretta dell'infiammazione



Controllo dell'infiammazione e rischio cardiovascolare

Gestione della glicemia e degli altri «triggers» infiammatori

Gestione diretta dell'infiammazione