

14°

CONGRESSO NAZIONALE SINut

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Società Italiana di Nutraceutica

12-14 settembre 2024

Bologna



PERCHÉ OTTIMIZZARE UNA COLESTEROLEMIA SUBOTTIMALE? RAZIONALE PER IL TRATTAMENTO NUTRACEUTICO

Arrigo F.G. Cicero

Dip. di Scienze Mediche e Chirurgiche
Alma Mater Studiorum Università di
Bologna

Il sottoscritto Arrigo F.G. Cicero ai sensi dell'art. 3.3 sul Conflitto di Interessi, pag. 17 del Reg. Applicativo dell'Accordo Stato-Regione del 5 novembre 2009,

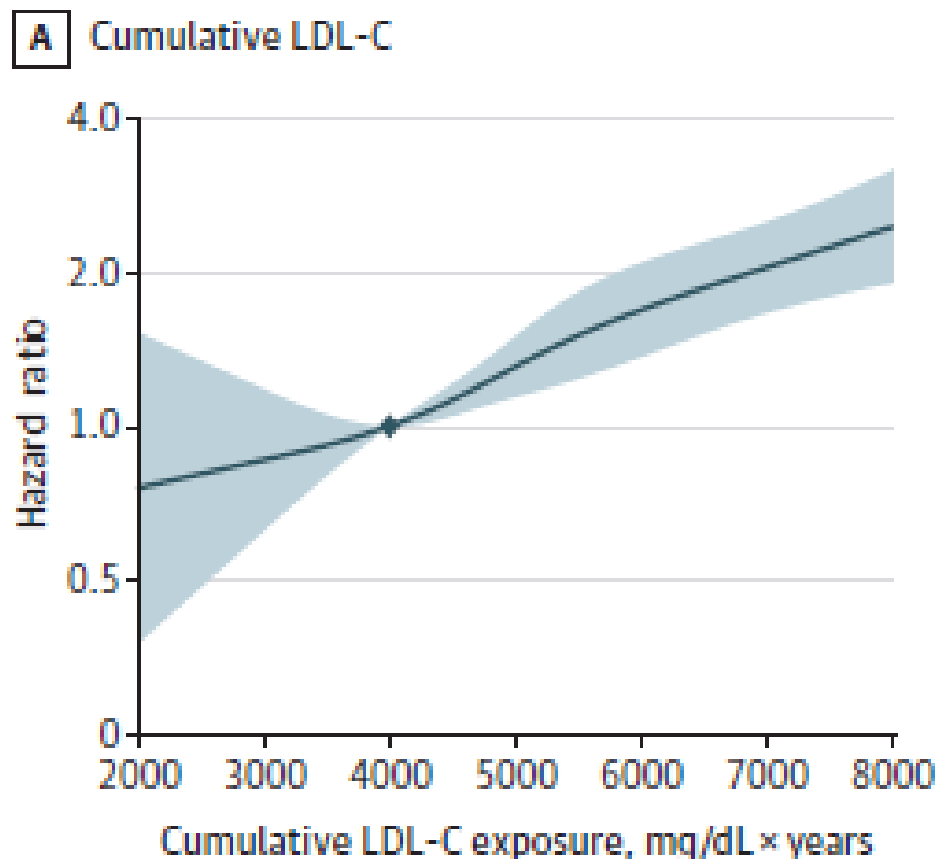
dichiara

che negli ultimi due anni ha avuto rapporti diretti di finanziamento con i seguenti soggetti portatori di interessi commerciali in campo sanitario:

- *Dr. Schaer*
- *Sharper*
- *Menarini*
- *Named*
- *Zentiva*

JAMA Cardiology | Original Investigation

Association Between Cumulative Low-Density Lipoprotein Cholesterol Exposure During Young Adulthood and Middle Age and Risk of Cardiovascular Events



CHD Risk

JAMA Cardiol. doi:10.1001/jamacardio.2021.3508
Published online September 22, 2021.

Journal of the American College of Cardiology
© 2012 by the American College of Cardiology Foundation
Published by Elsevier Inc.

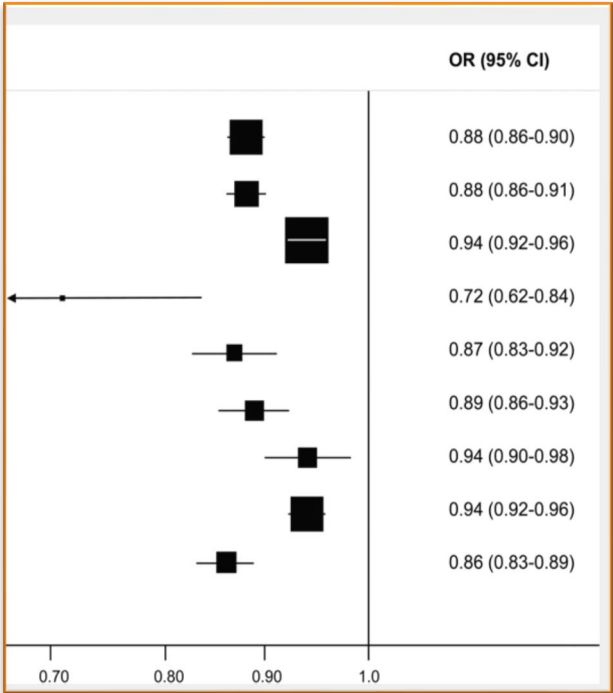
Vol. 60, No. 25, 2012
ISSN 0735-1097/\$36.00
<http://dx.doi.org/10.1016/j.jacc.2012.09.017>

Cardiometabolic Risk

Effect of Long-Term Exposure to Lower
Low-Density Lipoprotein Cholesterol Beginning
Early in Life on the Risk of Coronary Heart Disease
A Mendelian Randomization Analysis

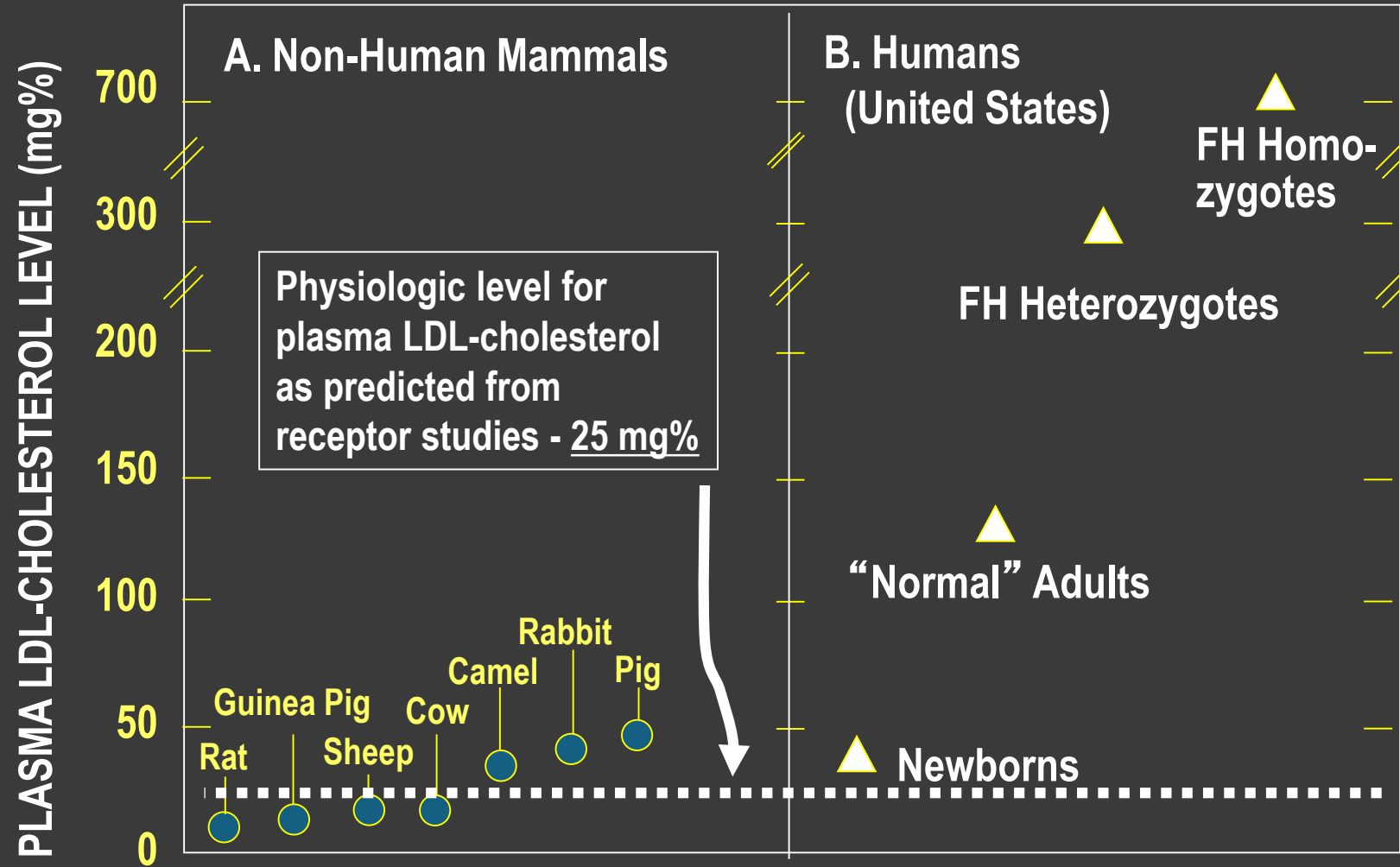
Nearby Gene	SNP	Sample Size (N)	Effect Size (95% CI) mmol/L	mg/dl
SORT1	rs599839 (13-19)	108,332	-0.16 (-0.17, -0.15)	-6.00 (-6.37, -5.64)
	rs646776 (5,13,15,18)	120,309	-0.15 (-0.16, -0.14)	-5.71 (-6.07, -5.34)
PCSK9	rs11206510 (14,16,18-20)	70,710	-0.08 (-0.09, -0.06)	-2.93 (-3.47, -2.39)
	rs11591147 (9,13,18,19,21-24)	149,372	-0.43 (-0.46, -0.41)	-16.68 (-17.66, -15.71)
LDLR	rs6511720 (5,13,18,19,22)	137,818	-0.19 (-0.21, -0.18)	-7.50 (-7.98, -7.03)
	rs2228671 (8,15,17,18,25,26)	61,865	-0.15 (-0.16, -0.13)	-5.70 (-6.30, -5.11)
HMGCR	rs12916 (5,13,18,22)	130,114	-0.07 (-0.08, -0.06)	-2.63 (-2.95, -2.32)
ABCG8	rs4299376 (5,16,18,22)	116,828	-0.07 (-0.08, -0.06)	-2.86 (-3.22, -2.51)
APOE	rs4420638 (5,13,14,18,27)	126,788	-0.18 (-0.20, -0.17)	-7.10 (-7.56, -6.65)
(I-squared = 99.7%, p < 0.001)				

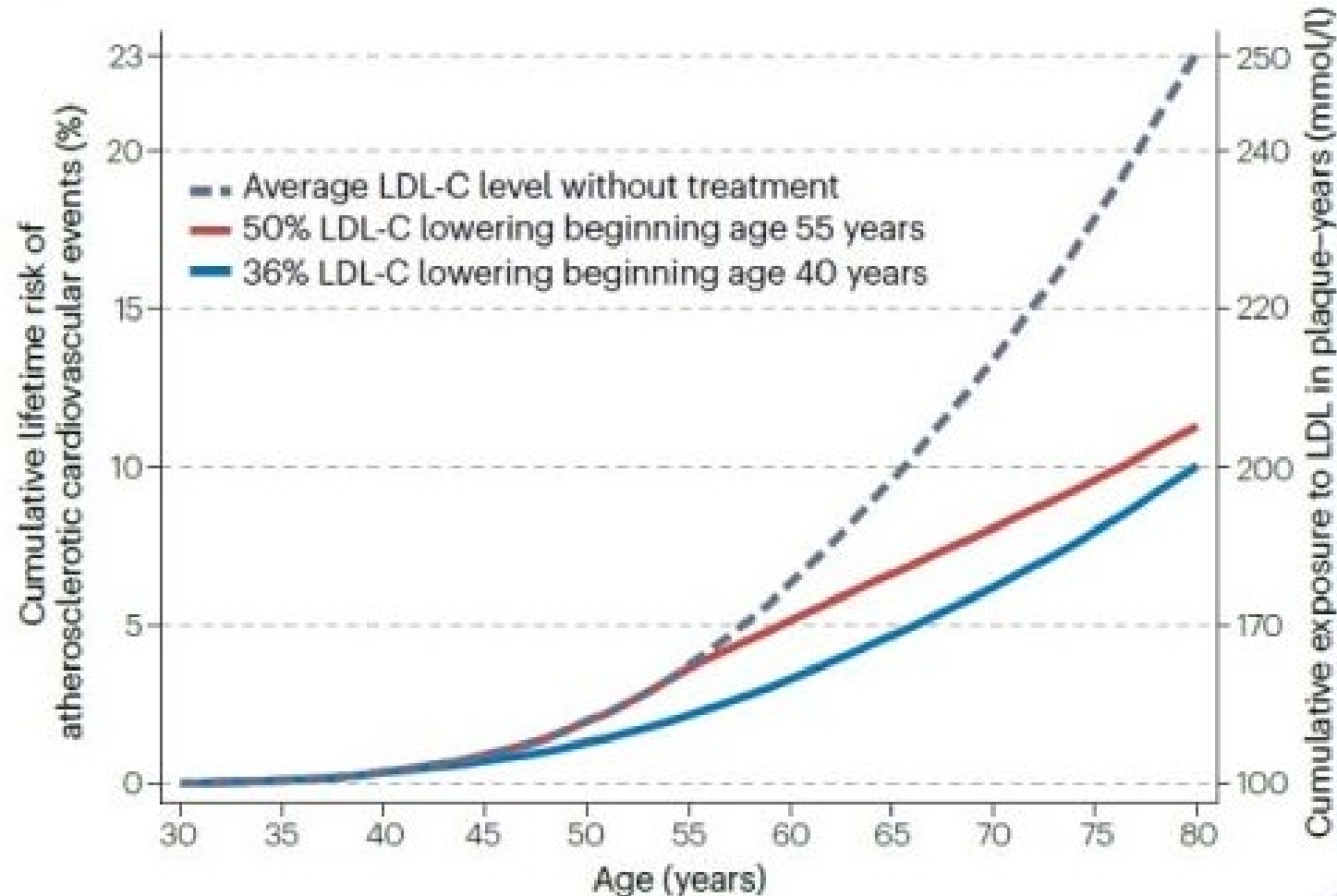
LDL-C level



CHD event risk

LDL-C LEVELS IN HUMANS AND NON-HUMAN MAMMALS

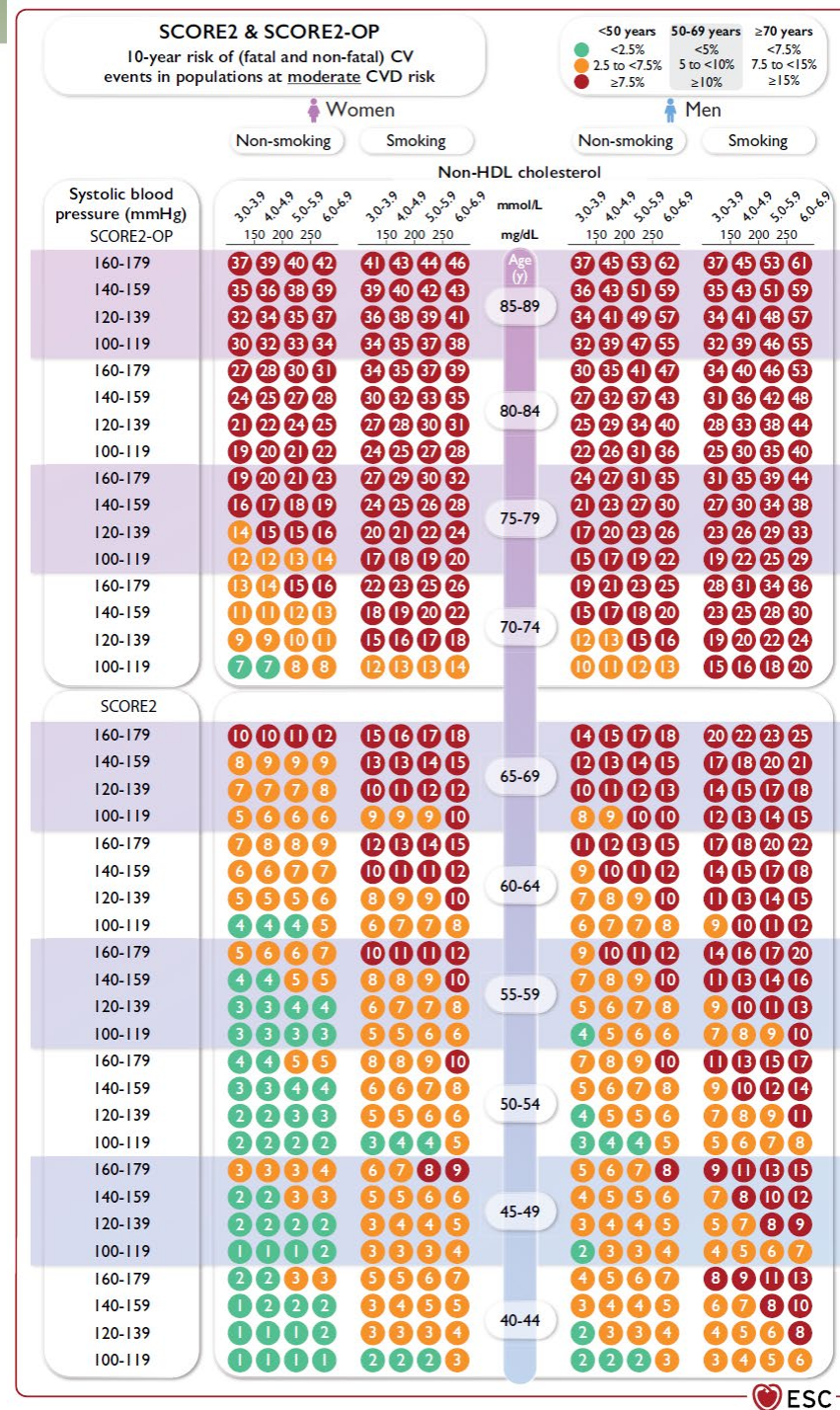
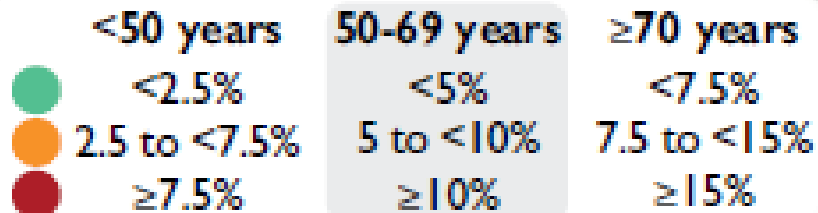




Ference, B.A., Braunwald, E. & Catapano, A.L. The LDL cumulative exposure hypothesis: evidence and practical applications. *Nat Rev Cardiol* (2024). <https://doi.org/10.1038/s41569-024-01039-5>

The new risk chart for moderate risk countries

Remember risk modifiers !



Total CV risk (SCORE)%	Untreated LDL-C levels					
	<1.4 mmol/L (55 mg/dL)	1.4 to <1.8 mmol/L (55 to <70 mg/dL)	1.8 to <2.6 mmol/L (70 to <100 mg/dL)	2.6 to <3.0 mmol/L (100 to <116 mg/dL)	3.0 to <4.9 mmol/L (116 to <190 mg/dL)	≥4.9 mmol/L (≥190 mg/dL)
Primary Prevention						
< 1 Low-risk	Lifestyle advice	Lifestyle advice	Lifestyle advice	Lifestyle advice	Lifestyle intervention, consider adding drug if uncontrolled	Lifestyle intervention and concomitant drug intervention
Class ^a /Level ^b	I/C	I/C	I/C	I/C	IIa/A	IIa/A
≥1 to <5, or moderate-risk	Lifestyle advice	Lifestyle advice	Lifestyle advice	Lifestyle intervention, consider adding drug if uncontrolled	Lifestyle intervention, consider adding drug if uncontrolled	Lifestyle intervention and concomitant drug intervention
Class ^a /Level ^b	I/C	I/C	IIa/A	IIa/A	IIa/A	IIa/A

**Intervention strategies
as a function of total
cardiovascular risk and
untreated low-density
lipoprotein cholesterol
levels (1)**

©ESC

Relative efficacy of life-style change in improving different CV risk factors

HDL-C

Lp(a)

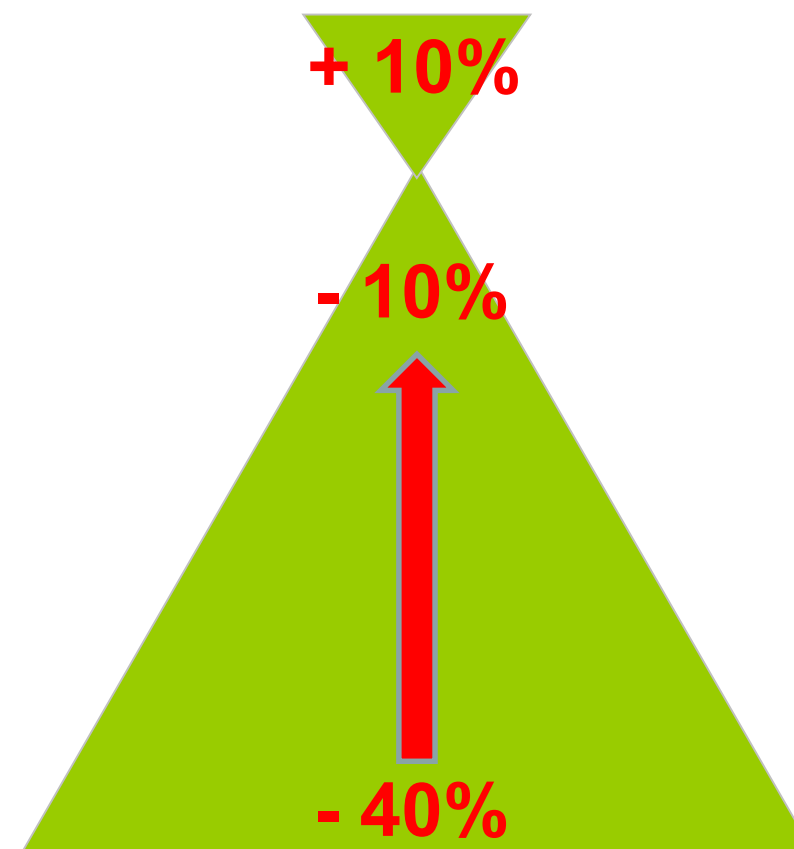
LDL-C

Microinflammation

Blood Pressure

Glycemia

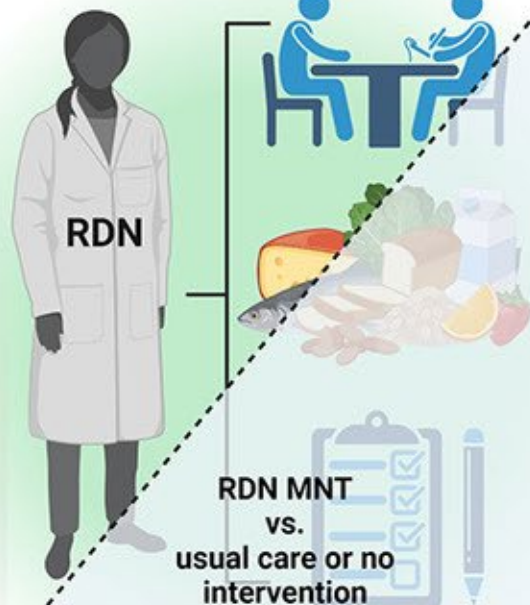
Triglyceridemia



Systematic Review: Effectiveness of Medical Nutrition Therapy (MNT) for Managing Dyslipidemia

Research Question
In adults with dyslipidemia, what is the effectiveness of MNT provided by a registered dietitian nutritionist (RDN), compared to usual care or no intervention, on lipid levels?

Intervention & Comparison



Primary CVD risk factor = Dyslipidemia

Search Results

Databases Searched:
MEDLINE
CINAHL
Cochrane CENTRAL
Cochrane Systematic Reviews

Full text articles screened = 89
Included RCTs = 7
Total $n = 838$

Intervention Characteristics

Provider	RDN alone ($n = 3$) Multidisciplinary team ($n = 4$)
Intervention Duration	8 to 12 months
# of contacts with RDN	2 to 12 in-person
Contact duration	30 to 120 minutes
Type of session	Individual session ($n = 2$) Group session ($n = 1$) Group + individual session ($n = 4$)

Meta-analysis Results

Reported as mean difference ($\pm 95\%$ CI)

		Certainty of Evidence
Total Cholesterol	-20.84 mg/dL (-40.60, -1.07), $P = 0.04$	⊕⊕⊕ MODERATE
Triglycerides	-32.55 mg/dL (-57.78, -7.32) $P = 0.01$	⊕⊕⊕ MODERATE
LDL Cholesterol	-11.56 mg/dL (-21.10, -2.03), $P = 0.02$	⊕⊕⊕ MODERATE
HDL Cholesterol	1.75 mg/dl (-1.43, 4.92), $P = 0.28$	⊕⊕ LOW

Conclusion

In adults with dyslipidemia, MNT provided by a RDN is effective for improving lipid levels, compared to usual care or no intervention.



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Contents lists available at ScienceDirect

Pharmacological Research

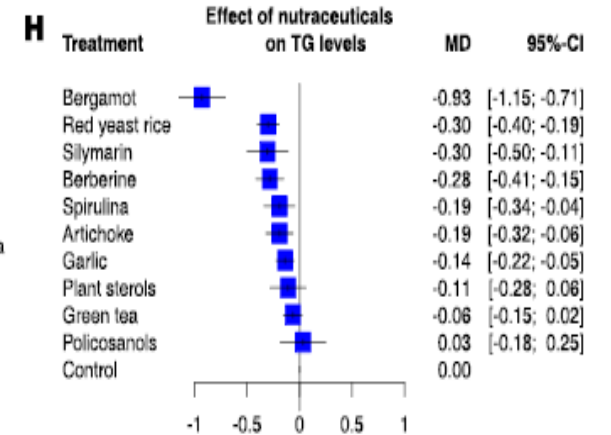
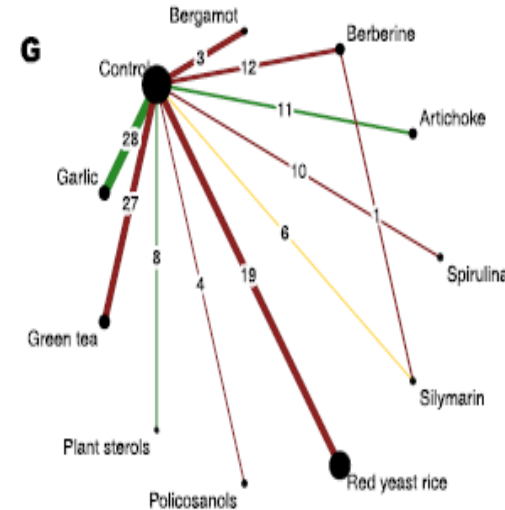
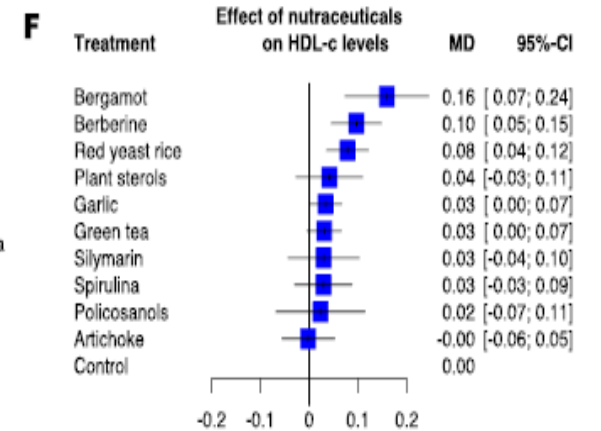
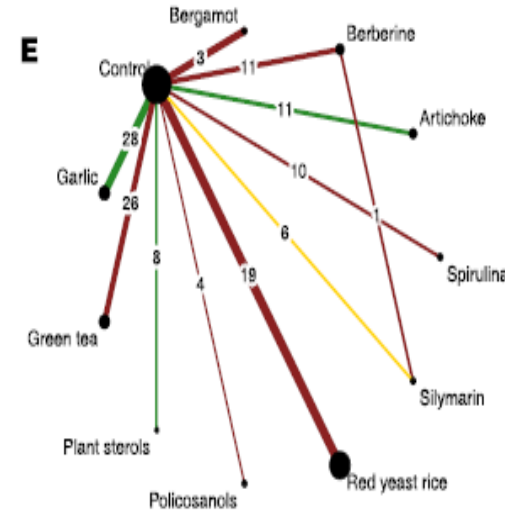
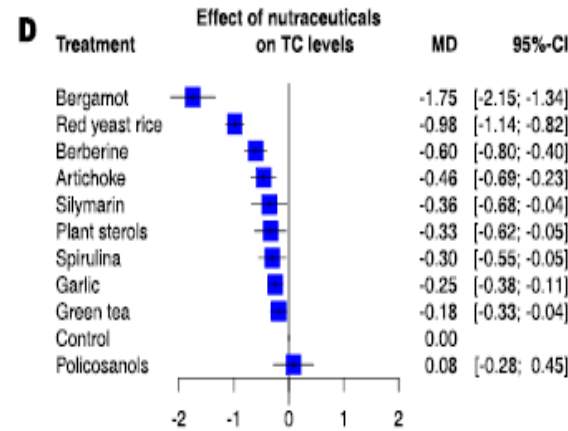
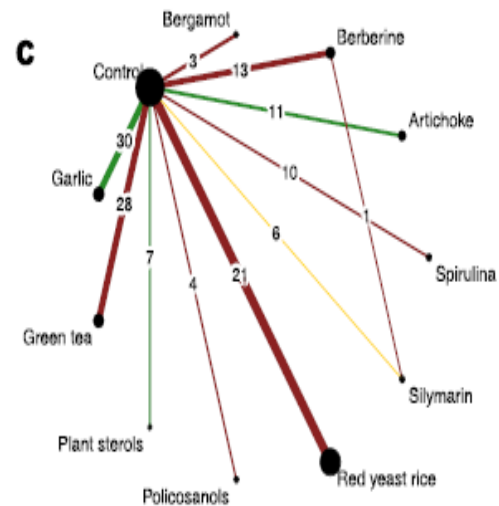
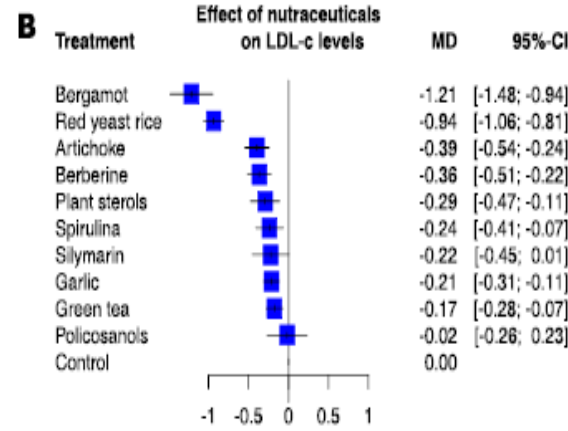
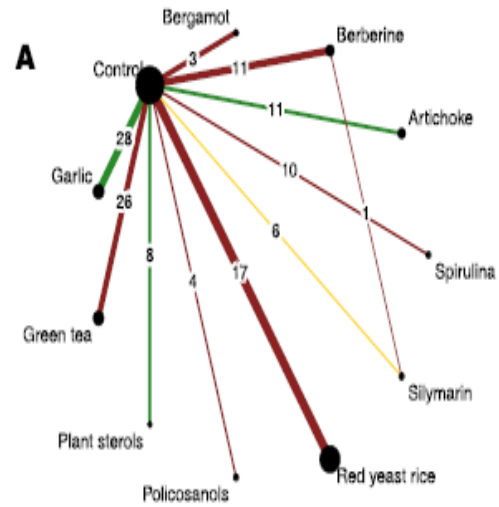
journal homepage: www.elsevier.com/locate/yphrs

Review

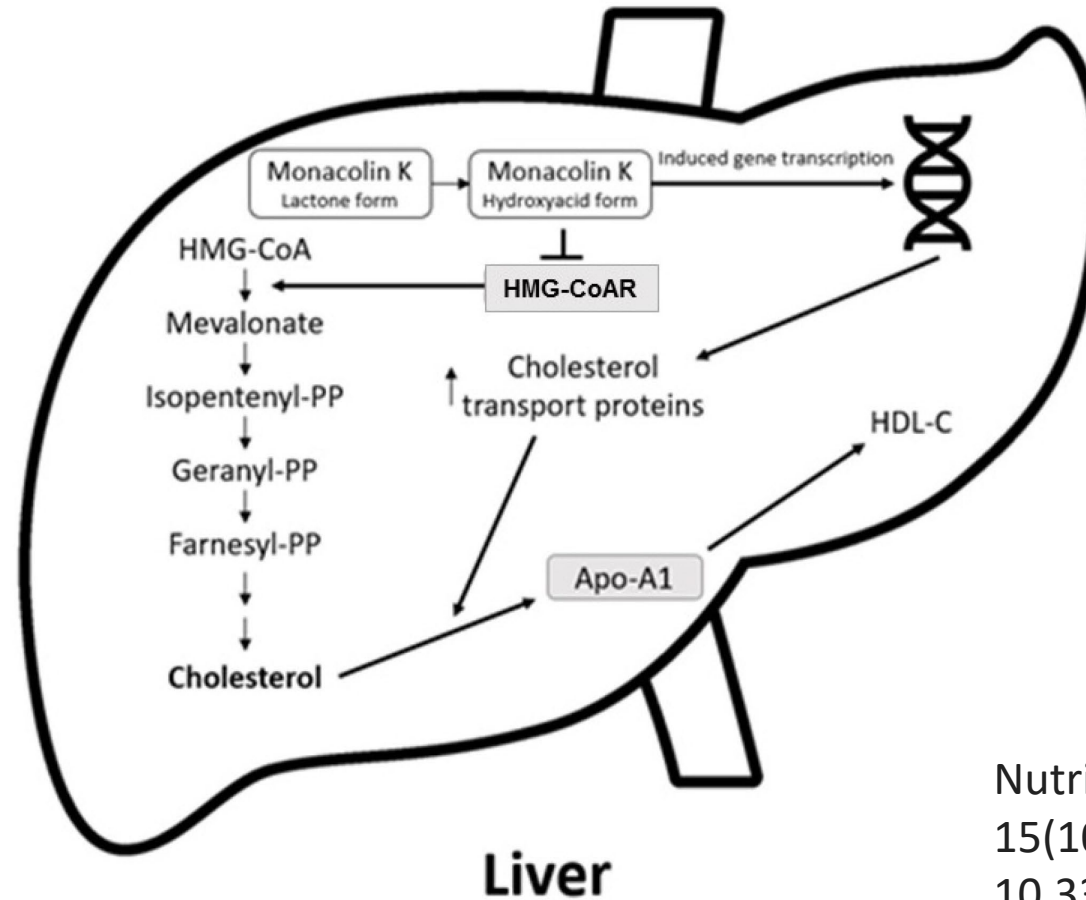
A network meta-analysis on the comparative effect of nutraceuticals on lipid profile in adults

Tadeusz Osadnik^a, Marcin Goławski^a, Piotr Lewandowski^a, Jakub Morze^b, Kamila Osadnik^a,
Natalia Pawlas^a, Mateusz Lejawa^a, Grzegorz K. Jakubiak^{a,c}, Agnieszka Mazur^a,
Lucas Schwingschackl^d, Mariusz Gąsior^e, Maciej Banach^{f,*}





Red yeast rice



(Similar processes occur in extra-hepatic tissues such as intestines, adipose tissue and skin)

Nutrients. 2023;
15(10):2288. doi:
10.3390/nu15102288.

JACC FOCUS SEMINAR: NUTRITIONAL SUPPLEMENTS AND THE HEART, PART 2

JACC FOCUS SEMINAR

Red Yeast Rice for Hypercholesterolemia



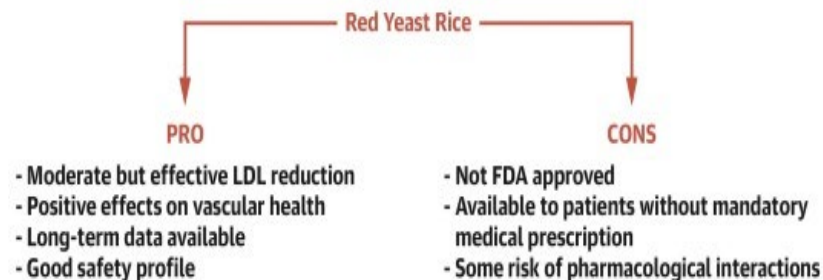
JACC Focus Seminar

Arrigo F.G. Cicero, MD, PhD,^a Federica Fogacci, MDc,^a Alberto Zambon, MD, PhD^b

TABLE 1 Positive Effects of RYR in Humans		
Parameter	Modification	Notes
Total, LDL and non-HDL-cholesterol	-15% to -25%	Confirmed in different ethnicities and meta-analyses of randomized clinical trials
Apolipoprotein B	Mild to moderate reduction: -10% to -15%	Confirmed in different trials
Triglycerides	Mild reduction -5% to -10%	Confirmed in meta-analyses of randomized clinical trials
HDL-C	Mild increase +5% to +10%	Confirmed in meta-analyses of randomized clinical trials
hsCRP, MMP-2, MMP-9	Mild decrease	Reported in some trials
Flow-mediated dilation	Mild increase	Reported in some trials
Pulse wave velocity	Mild decrease	Reported when RYR associated to other nutraceuticals only
Cardiovascular disease prevention	Moderate reduction	Limited to one large study carried out on Chinese people in secondary prevention for coronary artery disease

CENTRAL ILLUSTRATION: Effects of Long-Term Treatment With Red Yeast Rice on Hard Outcomes and in Older Secondary Prevention Trials Carried Out With First-Generation Statins: Implication for Use in Clinical Practice

	Treatment	Patients Involved	Mean Follow-Up Duration	Endpoint	Main Effect (RRR)
Chinese Coronary Secondary Prevention Study (CCSPS)	Red Yeast Rice vs. Placebo	4,870	4.5 years	Nonfatal myocardial infarction and death from coronary heart disease (Primary)	-45%
Cholesterol and Recurrent Events trial (CARE)	Pravastatin 40 mg vs. Placebo	4,159	5 years	Nonfatal myocardial infarction and death from coronary heart disease (Primary)	-24%
Long-Term Intervention with Pravastatin in Ischaemic Disease (LIPID)	Pravastatin 40 mg vs. Placebo	9,014	6.1 years	Nonfatal myocardial infarction and death from coronary heart disease (Secondary)	-24%
Scandinavian Simvastatin Survival Study (4S)	Simvastatin 20/40 mg vs. Placebo	4,444	5.4 years	Nonfatal myocardial infarction and death from coronary heart disease (Secondary)	-42%



Cicero, A.F.G. et al. J Am Coll Cardiol. 2021;77(5):620-8.



Pharmacological Research

Volume 143, May 2019, Pages 1-16



Review

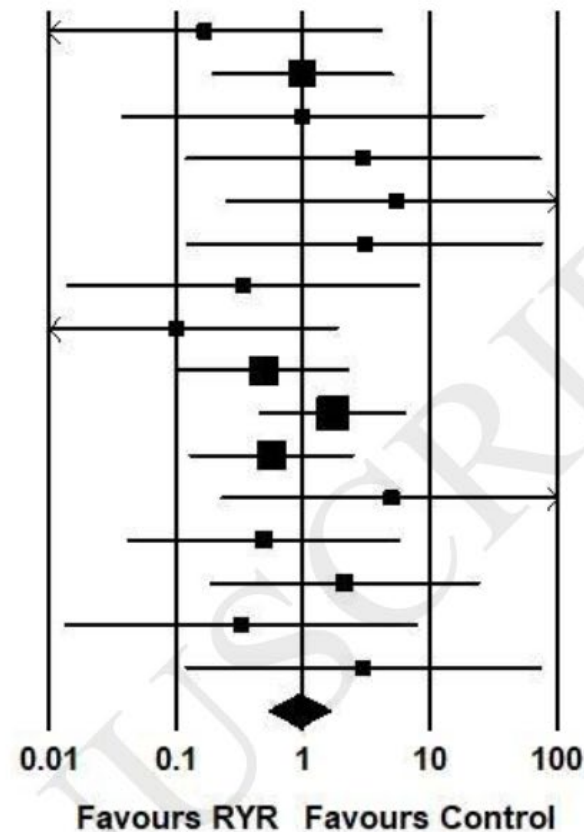
Safety of red yeast rice supplementation: A systematic review and meta-analysis of randomized controlled trials

Federica Fogacci ^{a, 1}, Maciej Banach ^{b, c, d, 1}, Dimitri P. Mikhailidis ^e, Eric Bruckert ^f, Peter P. Toth ^{g, h}, Gerald F. Watts ⁱ, Željko Reiner ^j, John Mancini ^k, Manfredi Rizzo ^l, Olena Mitchenko ^m, Daniel Pella ⁿ, Zlatko Fras ^o, Amirhossein Sahebkar ^{p, q}, Michal Vrablik ^r, Arrigo F.G. Cicero ^{s & 1}, on behalf of the Lipid and Blood Pressure Meta-analysis Collaboration (LBPMC) Group, the International Lipid Expert Panel (ILEP)

Data were pooled from 53 RCTs comprising 112 treatment arms, which included 8535 subjects, with 4437 in the RYR arm and 4303 in the control one. Monacolin K administration was not associated with increased risk of MuD (odds ratio [OR]=0.94, 95% confidence interval [CI] 0.53,1.65). Moreover, we showed reduced risk of Non-MuD (OR=0.59, 95%CI 0.50, 0.69) and SAE (OR=0.54, 95%CI 0.46, 0.64) vs. control.

Study nameStatistics for each studyOdds ratio and 95% CI

	Odds ratio	Lower limit	Upper limit	Z-Value	p-Value
D'Addato, S (2017 - I)	0.17	0.01	4.31	-1.08	0.28
Marazzi, G (2017)	1.00	0.19	5.21	0.00	1.00
Spigoni, V (2017)	1.00	0.04	26.68	0.00	1.00
Cicero, AF (2016 a)	3.00	0.12	75.90	0.67	0.51
Cicero, AF (2016 b)	5.43	0.25	118.96	1.07	0.28
Cicero, AF (2016 c)	3.08	0.12	77.80	0.68	0.50
Heinz, T (2016)	0.34	0.01	8.44	-0.66	0.51
Kasliwal, RR (2016)	0.10	0.01	1.91	-1.53	0.13
Verhoeven, V (2015)	0.50	0.10	2.35	-0.88	0.38
Verhoeven, V (2013)	1.74	0.46	6.62	0.81	0.42
Marazzi, G (2011)	0.57	0.13	2.55	-0.74	0.46
Bogsrud, MP (2010)	5.00	0.23	110.71	1.02	0.31
Halbert, SC (2010)	0.50	0.04	5.97	-0.55	0.58
Becker, DJ (2009)	2.14	0.18	24.96	0.61	0.54
Shang, XB (2007)	0.33	0.01	8.21	-0.68	0.50
Heber, D (1999)	3.00	0.12	75.79	0.67	0.50
	0.94	0.53	1.65	-0.22	0.82



N.B. Data reported for 16 RCTs only, because in the remaining 36 one, no muscular adverse event was reported

ADOPTED: 25 June 2018
doi: 10.2903/j.efsa.2018.5368



Scientific opinion on the safety of monacolins in red yeast rice

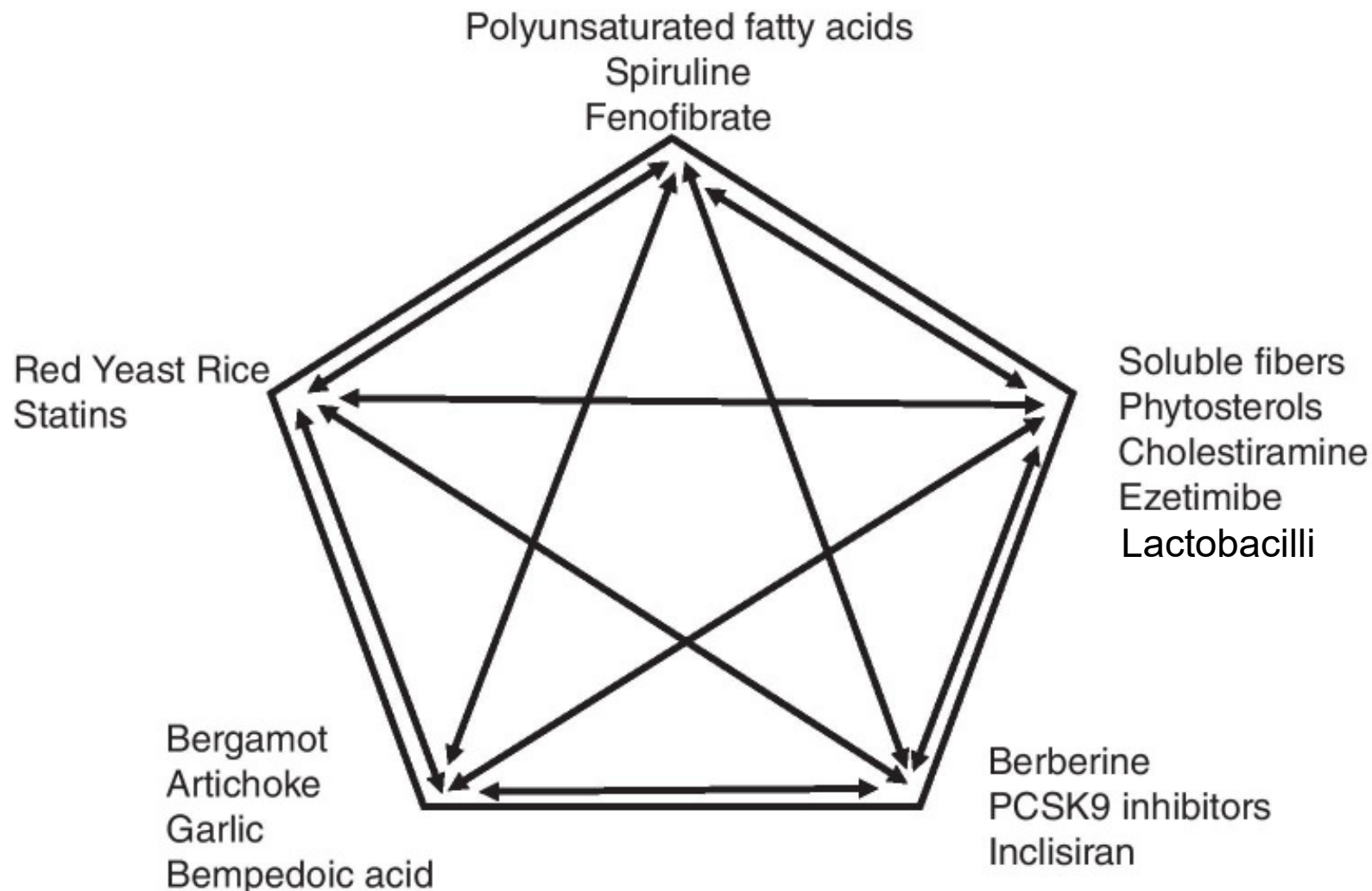
amending Annex III to Regulation (EC) No 1925/2006 of the European Parliament and of the Council as regards monacolins from red yeast rice

“... monacolins from RYR when used as food supplements were of significant safety concern at the use level of 10 mg/day. The Panel further considered that individual cases of severe adverse reactions have been reported for monacolins from RYR at intake levels as low as 3 mg/day. The Panel concluded that exposure to monacolin K from RYR could lead to severe adverse effects on musculo-skeletal system, including rhabdomyolysis, and on the liver...”

Restricted substance	Conditions of use	Additional requirements
Monacolins from red yeast rice added to foods or used in food supplements as defined by Directive 2002/46/EC.	Individual portion of food or food supplement for daily consumption shall provide less than 3mg of monacolins from red yeast rice.	The label shall provide the number of individual portions of the product for maximum daily consumption and a warning not to exceed daily amount of less than 3mg. The label shall indicate the content of monacolins per portion of the product. The label shall include the following warnings: “Should not be consumed by pregnant or lactating women, children below 18 years old and adults above 70 years old”. “Seek advice from a doctor on consumption of this product if you experience any health problems”; “Should not be consumed if you are taking cholesterol-lowering medication”; “Should not be consumed if you are already consuming other products containing red yeast rice”.

Nutra-Nutra and Nutra-Drug association ?

*Cicero AF et al. Curr
Atheroscler Rep.
2021;23(10):57.*



META-ANALYSIS

Potential Value of Probiotics on Lipid Profiles in Hyperlipidemia and Healthy Participants: Systematic Review and Meta-Analysis

Dongdong Su, MD; Yan Liu, MD; Li Zhang, PhD; Shanshan Zhao, PhD; Yifei Wang, MD; Rutao Bian, PhD;
Bianling Xu, PhD; Xiaoyang Chen, PhD; Xuegong Xu, PhD

Altern Ther Health Med. 2024 Feb;30(2):84-89.

The effect on LDL-C values in healthy and hypercholesterolemic subjects

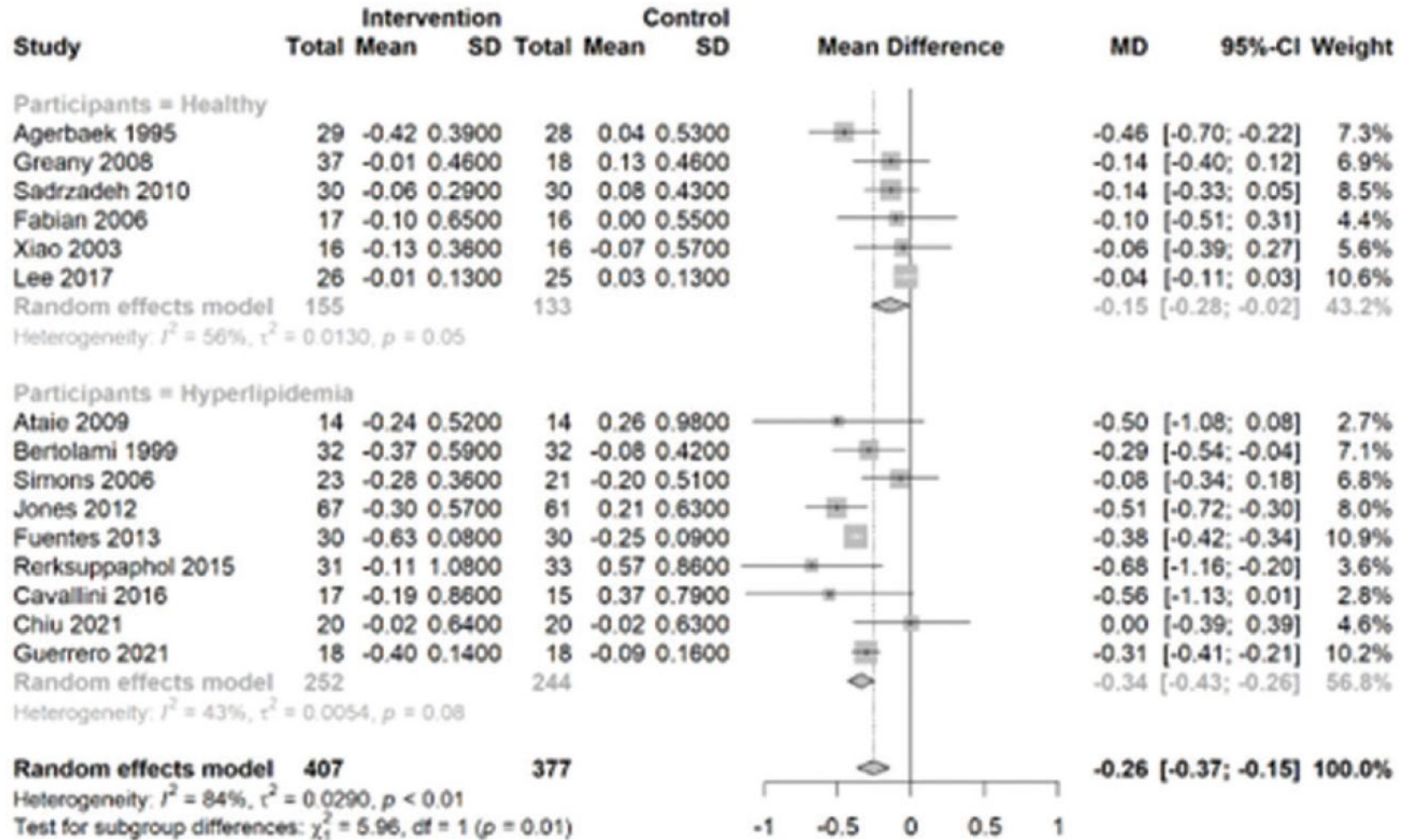
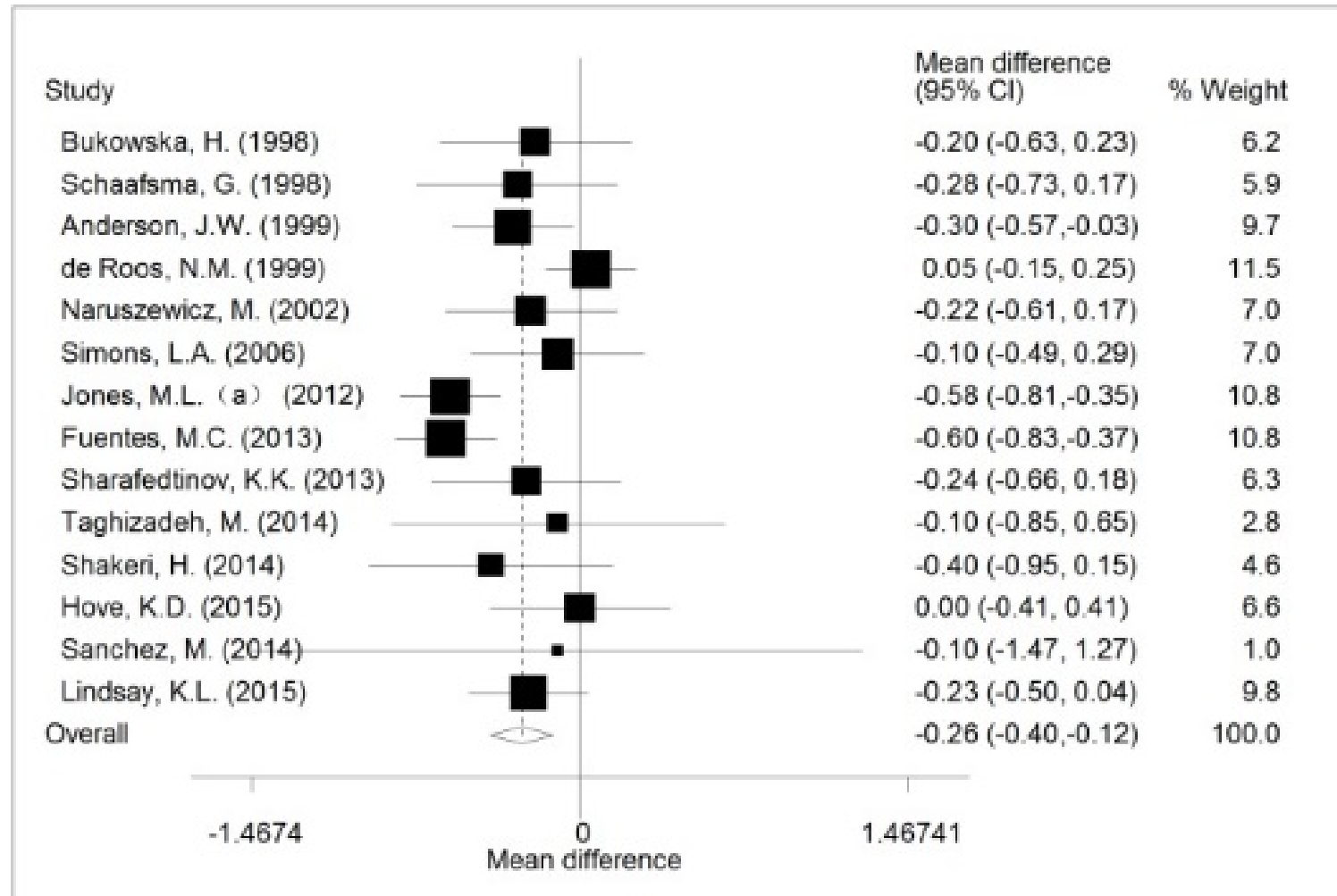


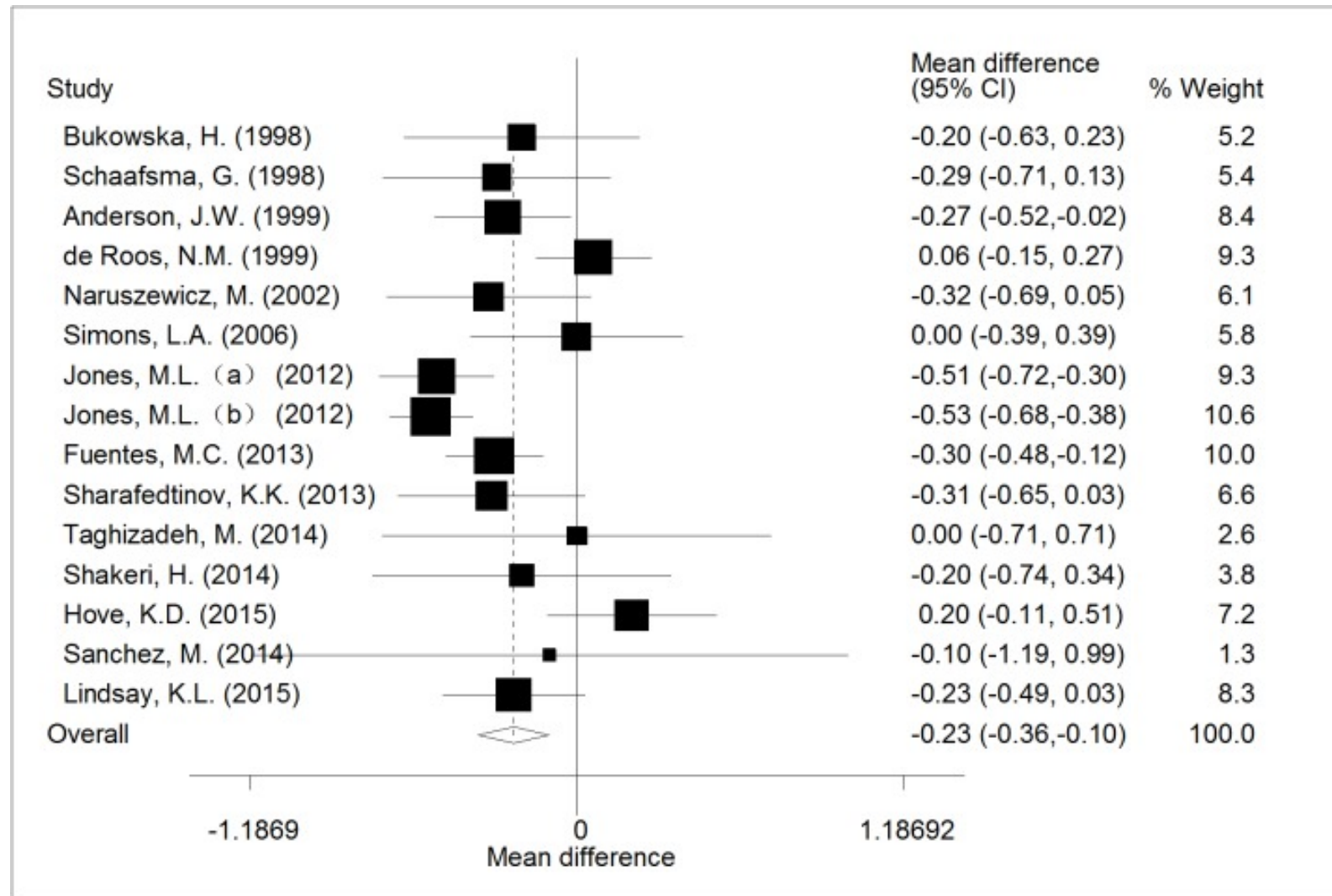
Table 2. Subanalysis of changes in TC.

		No. of trials(no. of references)	No. of participants(I/C)	MD (95% CI)(mmol/L)	P value
Pre TC	Normal (<5.7 mmol/L)	15 (3)	267/204	−0.06 (−0.15, 0.03)	0.18
	Hypercholesterolemic ($\geq$ 5.7 mmol/L)	11 (7)	335/315	−0.32 (−0.45, −0.18)	<0.00001
Pre LDL-C	Normal (<3.6 mmol/L)	15 (3)	267/204	−0.06 (−0.15, 0.03)	0.18
	Hypercholesterolemic ($\geq$ 3.6 mmol/L)	11 (7)	335/315	−0.32 (−0.45, −0.18)	<0.00001
BMI	Normal (<25 kg/m ²)	5 (4)	141/116	−0.23 (−0.35, −0.11)	0.0002
	Obese ($\geq$ 25 kg/m ²)	21 (7)	461/403	−0.16 (−0.28, −0.04)	0.01
Age	Young (<45 years of age)	16 (4)	308/247	−0.09 (−0.17, −0.01)	0.03
	Elderly ($\geq$ 45 years of age)	10 (7)	294/272	−0.37 (−0.47, −0.27)	<0.00001
Intake duration	Short-term ($\leq$ 4 weeks)	11 (4)	197/170	−0.05 (−0.15, 0.05)	0.36
	Long-term (>4 weeks)	15 (9)	405/349	−0.27 (−0.39, −0.15)	<0.00001

Lactobacilli and TC (15 RCTs, 976 pts.)



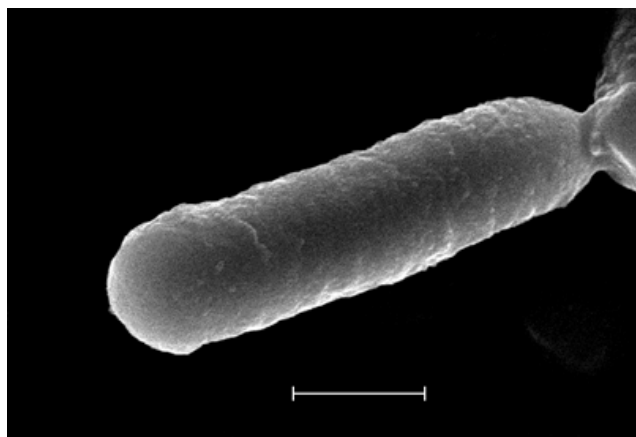
Lactobacilli and LDL-C (15 RCTs, 976 pts.)



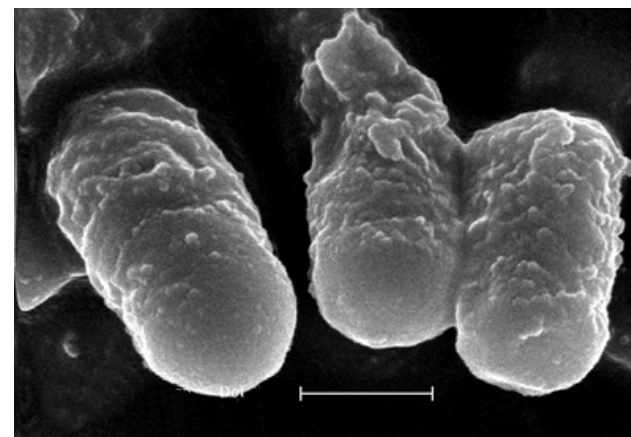
Come i probiotici possono ridurre la colesterolemia?

- **Prevenzione e trattamento del leaky gut**
- **Mantenimento omeostasi fra ceppi batterici residenti**
- **Inibizione dell'assorbimento intestinale del colesterolo**
- **Inibizione delle idrolasi dei Sali biliari**
- **...**

L. plantarum LP_{LDL}®



Microfotografia di *L. plantarum*
L. plantarum LP_{LDL}® coltivato
senza colesterolo nel terreno di
coltura

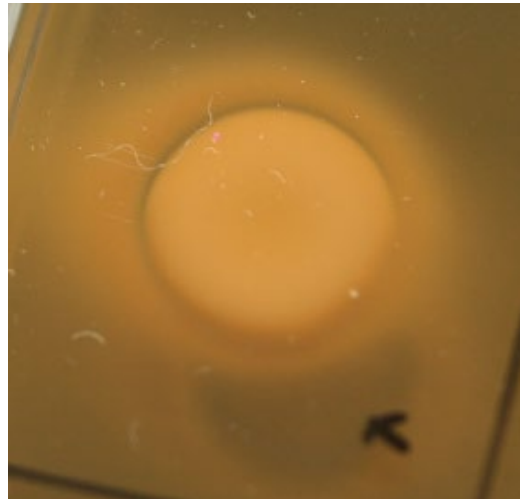


Microfotografia di *L. plantarum*
LP_{LDL}® coltivato con colesterolo
nel terreno di coltura.

Il colesterolo aderisce alla parete cellulare di *L. plantarum* LP_{LDL}®, il che può rappresentare uno dei meccanismi attraverso i quali il colesterolo viene eliminato dal terreno di coltura

L. plantarum LP_{LDL}®

L'attività dell'idrolasi dei sali biliari è stata identificata come noto meccanismo ipocolesterolemizzante. Alcuni ceppi probiotici (es.: LP_{LDL}®) mostrano in vitro elevata attività dell'idrolasi dei sali biliari.



14°

CONGRESSO NAZIONALE SINut

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Società Italiana di Nutraceutica

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Pharmanutrition and Functional Foods

TRIMESTRALE DI AGGIORNAMENTO SCIENTIFICO

ORGANO UFFICIALE

SINut
Società Italiana di Nutraceutica

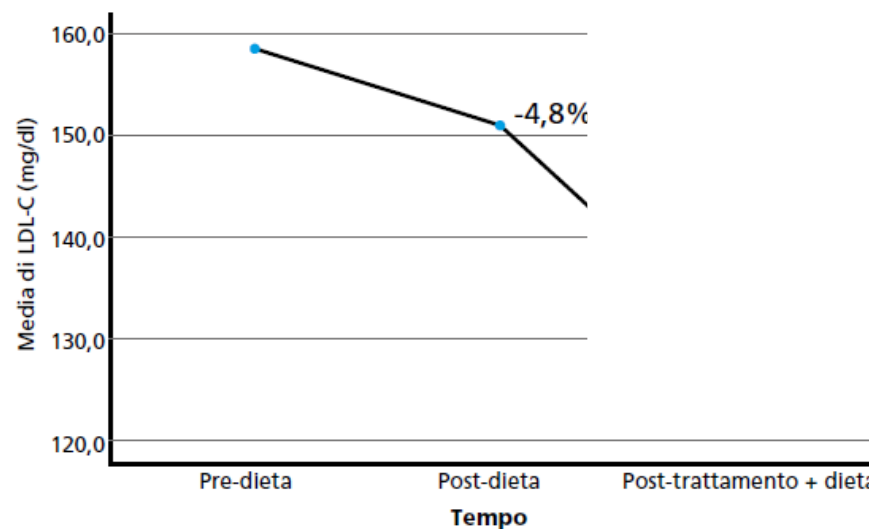
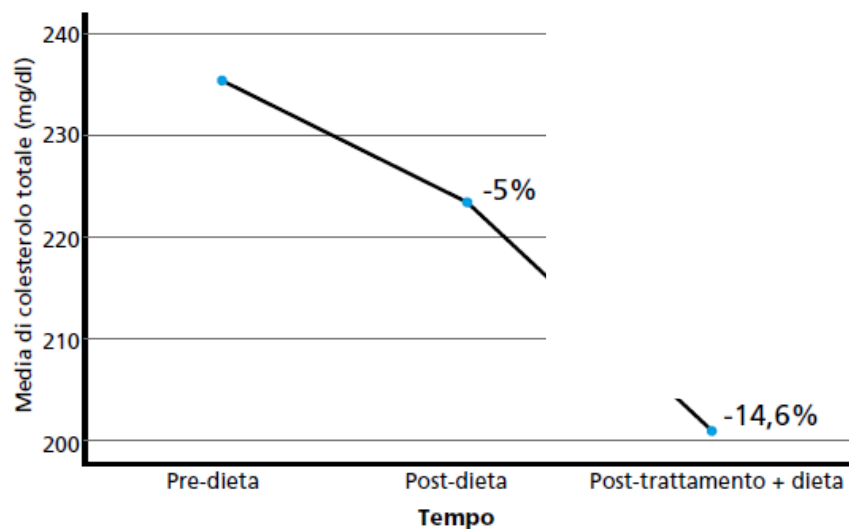
Plasma LDL cholesterol reduction after intake of red yeast rice and Lactobacillus plantarum LDL®: the results of a single-center, retrospective observational study

Federica Fogacci, Marilisa Bove, Maddalena Veronesi, Marina Giovannini, Enrico Strocchi, Arrigo F.G. Cicero

Centro di ricerca su Ipertensione e fattori di rischio cardiovascolari; Dip. di Scienze Mediche e Chirurgiche, Alma Mater Studiorum
Università di Bologna

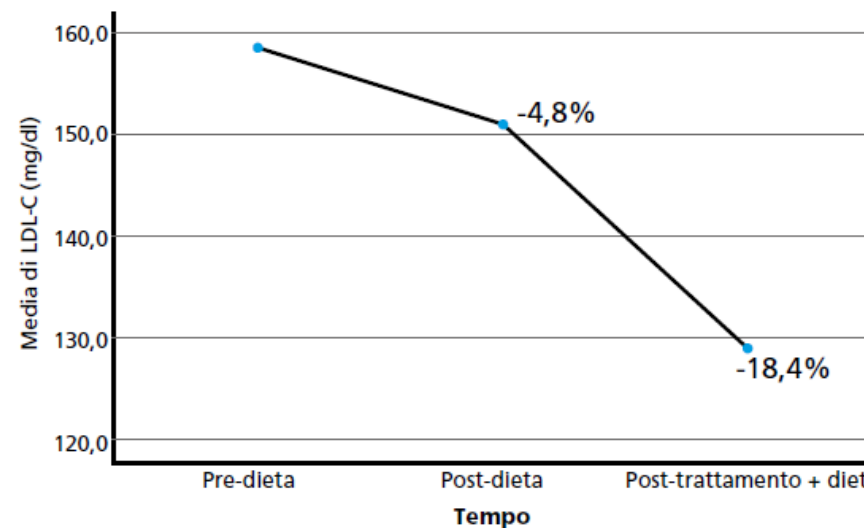
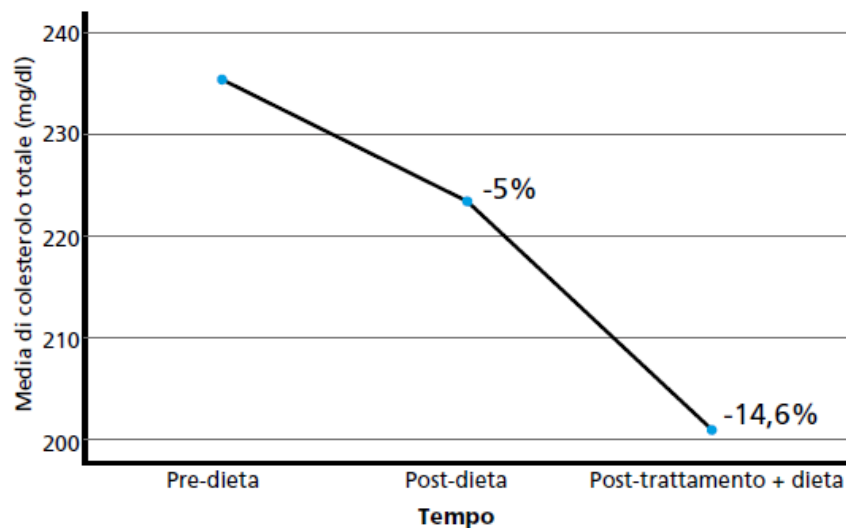
Variazione dei parametri lipidici nel corso dell'osservazione (*p<0.05 per trend)						
	Pre-dieta		Post-dieta		Post-Ezimega3®	
	Media	DS	Media	DS	Media	DS
Colesterolo totale (mg/dL)*	235,47	23,076	223,73	23,595	201,12	21,745
Trigliceridi (mg/dl)	120,70	53,207	111,55	53,663	111,88	54,397
Colesterolo HDL (mg/dL)	52,67	15,068	50,30	13,022	49,40	12,372
Colesterolo LDL (mg/dL)*	158,660	17,6327	151,123	21,8822	129,340	17,5664

Effetto dell'intensificazione della dieta su colesterolemia totale ed LDL



Variazione dei parametri lipidici nel corso dell'osservazione (*p<0.05 per trend)						
	Pre-dieta		Post-dieta		Post-Ezimega3®	
	Media	DS	Media	DS	Media	DS
Colesterolo totale (mg/dL)*	235,47	23,076	223,73	23,595	201,12	21,745
Trigliceridi (mg/dl)	120,70	53,207	111,55	53,663	111,88	54,397
Colesterolo HDL (mg/dL)	52,67	15,068	50,30	13,022	49,40	12,372
Colesterolo LDL (mg/dL)*	158,660	17,6327	151,123	21,8822	129,340	17,5664

Effetto del nutraceutico testato su colesterolemia totale ed LDL



Take home messages

- **La colesterolemia LDL è l'unico fattore di rischio metabolico per il quale non esista una soglia inferiore nota sotto la quale non vi sia un vantaggio protettivo per la salute delle arterie**
- **Le modificazioni dello stile di vita riducono la colesterolemia LDL-C di ca. il 10%**
- **L'impiego di nutraceutici può raddoppiare l'efficacia della dieta**
- **Le associazioni di più nutraceutici devono rispettare le regole della singola dose efficace e della farmacodinamica, nonché di aderenza e persistenza**
- **Gli esami di controllo vanno eseguiti in corso di assunzione**
- **La prescrizione può avere finalità educazionali**