Διατροφή, Τρόπος Ζωής, Γενετική Προδιάθεση & MASLD

ΠΡΟΓΡΑΜΜΑ ΜΕΤΑΠΤΥΧΙΑΚΩΝ ΣΠΟΥΔΩΝ

«*ΕΦΑΡΜΟΣΜΕΝΗ ΔΙΑΙΤΟΛΟΓΙΑ – ΔΙΑΤΡΟΦΗ*»

Νάνα Καλαφάτη
Επίκουρη Καθηγήτρια ΠΘ
Γενετική προδιάθεση, διατροφή & διαιτολογία

ΧΑΡΟΚΟΠΕΙΟ ΠΑΝΕΠΙΣΤΗΜΙΟ
HAROKOPIO UNIVERSITY

Special Article

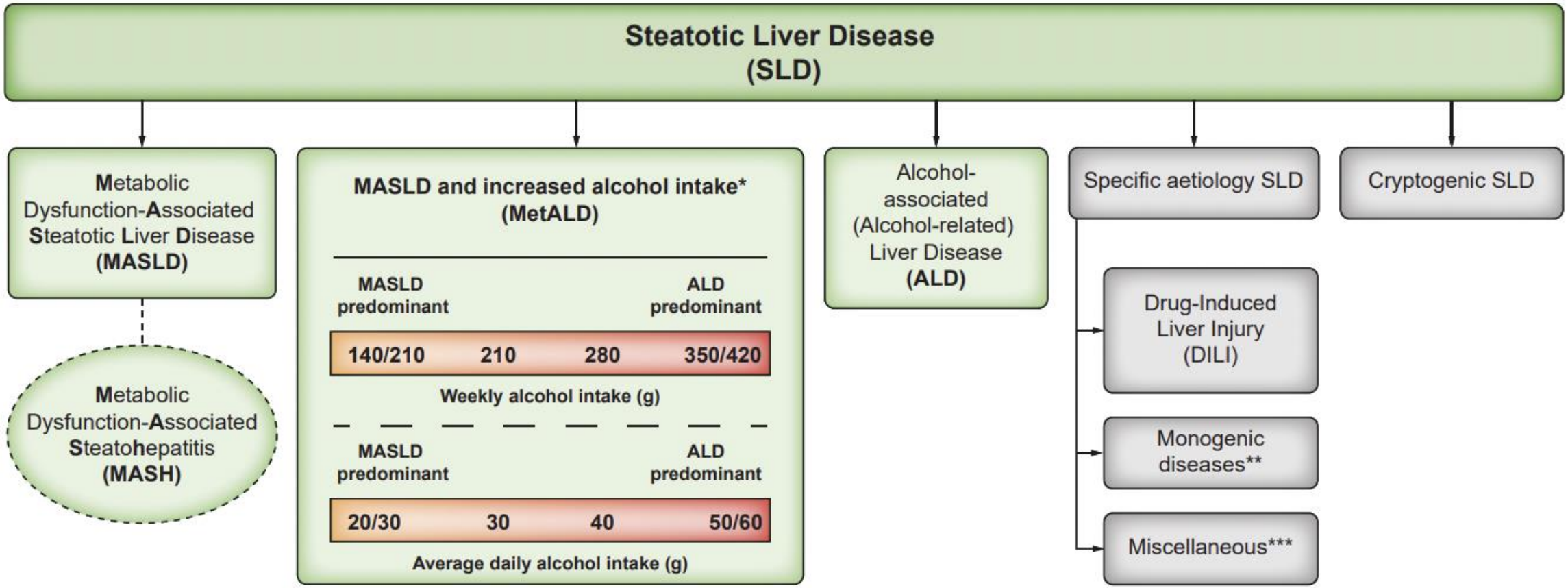
JOURNAL
OF HEPATOLOGY

A multisociety Delphi consensus statement on new fatty liver disease nomenclature

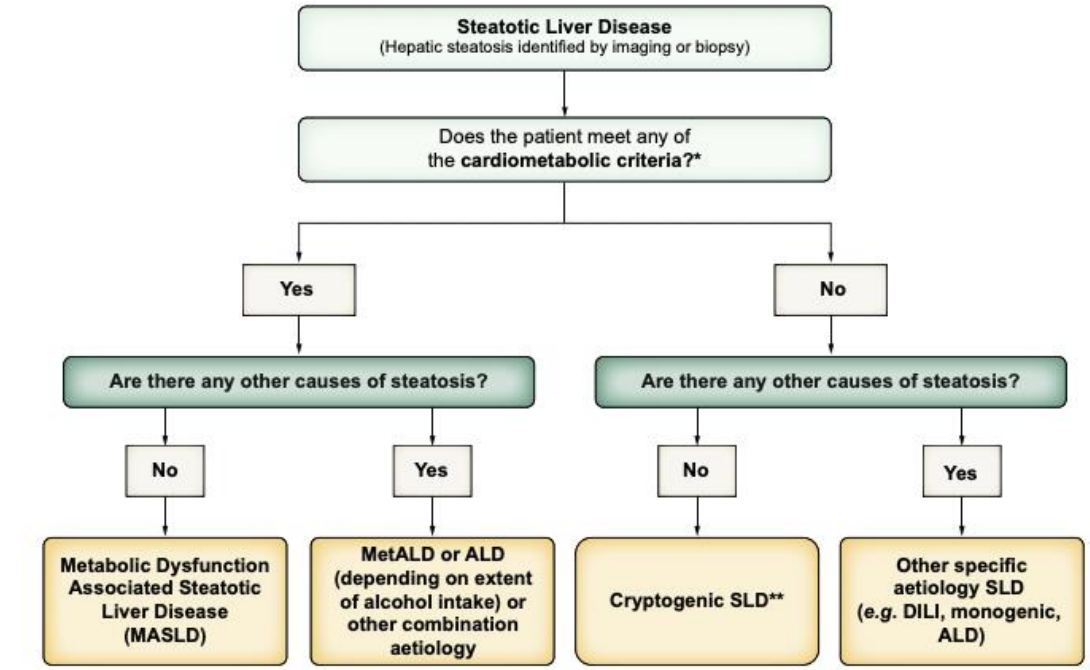
Mary E. Rinella[1,*], Jeffrey V. Lazarus[2,3], Vlad Ratziu[4], Sven M. Francque[5,6], Arun J. Sanyal[7], Fasiha Kanwal[8,9], Diana Romero[2], Manal F. Abdelmalek[10], Quentin M. Anstee[11,12], Juan Pablo Arab[13,14,15], Marco Arrese[15,16], Ramon Bataller[17], Ulrich Beuers[18], Jerome Boursier[19], Elisabetta Bugianesi[20], Christopher D. Byrne[21,22], Graciela E. Castro Narro[16,23,24], Abhijit Chowdhury[25,26], Helena Cortez-Pinto[27], Donna R. Cryer[28], Kenneth Cusi[29], Mohamed El-Kassas[30], Samuel Klein[31], Wayne Eskridge[32], Jiangao Fan[33], Samer Gawrieh[34], Cynthia D. Guy[35], Stephen A. Harrison[36], Seung Up Kim[37], Bart G. Koot[38], Marko Korenjak[39], Kris V. Kowdley[40], Florence Lacaille[41], Rohit Loomba[42], Robert Mitchell-Thain[43], Timothy R. Morgan[44,45], Elisabeth E. Powell[46,47,48], Michael Roden[49,50,51], Manuel Romero-Gómez[52], Marcelo Silva[53], Shivaram Prasad Singh[54], Silvia C. Sookoian[15,55,56], C. Wendy Spearman[57], Dina Tiniakos[11,58], Luca Valenti[59,60], Miriam B. Vos[61], Vincent Wai-Sun Wong[62], Stavra Xanthakos[63], Yusuf Yilmaz[64], Zobair Younossi[65,66,67], Ansley Hobbs[2], Marcela Villota-Rivas[68], Philip N. Newsome [69,70,*], on behalf of the NAFLD Nomenclature consensus group

Από τη NAFLD στη MASLD

Τύποι Ηπατική Στεάτωσης



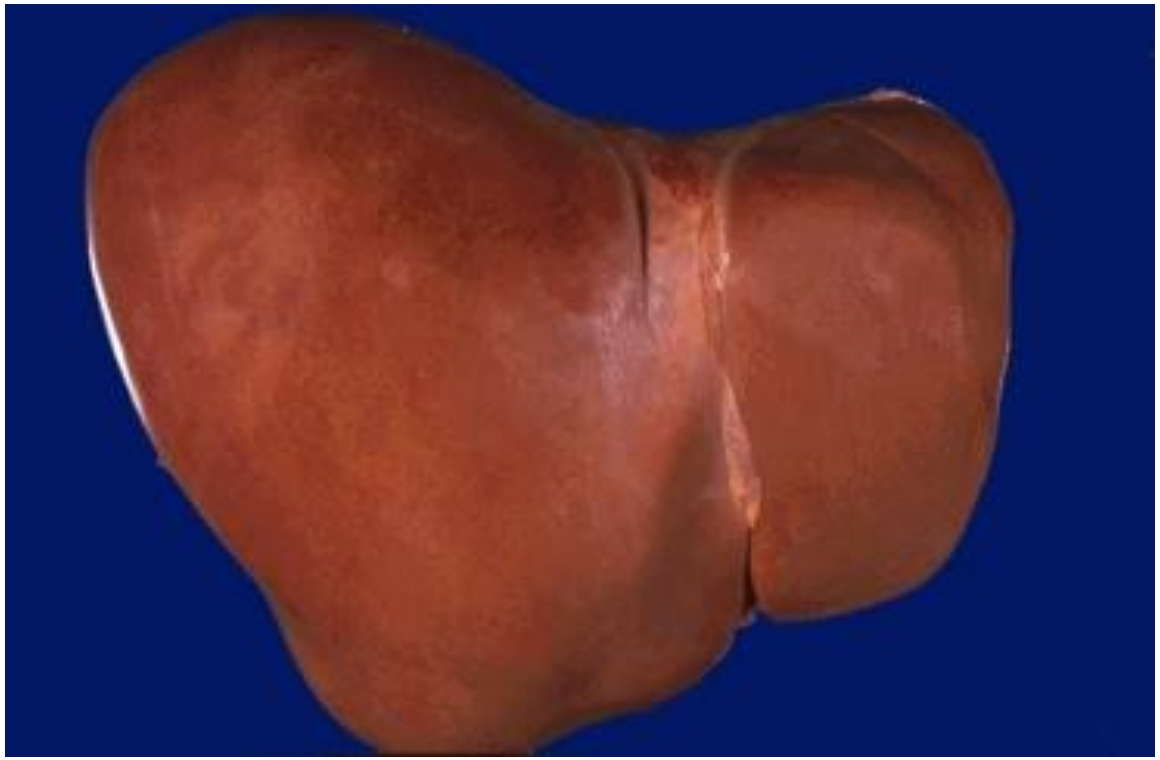
Κριτήρια Διάγνωσης



*Cardiometabolic criteria

Adult criteria	Paediatric criteria
At least 1 out of 5:	**At least 1 out of 5:**
☐ BMI ≥25 kg/m² [23 Asia] **OR** WC >94 cm (M) 80 cm (F) **OR** ethnicity adjusted equivalent	☐ BMI ≥85th percentile for age/sex [BMI z score ≥+1] **OR** WC >95th percentile **OR** ethnicity adjusted equivalent
☐ Fasting serum glucose ≥5.6 mmol/L [100 mg/dl] **OR** 2-hour post-load glucose levels ≥7.8 mmol/L [≥140 mg/dl] **OR** HbA1c ≥5.7% [39 mmol/L] **OR** type 2 diabetes **OR** treatment for type 2 diabetes	☐ Fasting serum glucose ≥5.6 mmol/L [≥100 mg/dl] **OR** serum glucose ≥11.1 mmol/L [≥200 mg/dl] **OR** 2-hour post-load glucose levels ≥7.8 mmol [140 mg/dl] **OR** HbA1c ≥5.7% [39 mmol/L] **OR** already diagnosed/treated type 2 diabetes **OR** treatment for type 2 diabetes
☐ Blood pressure ≥130/85 mmHg **OR** specific antihypertensive drug treatment	☐ Blood pressure age <13 yr, BP ≥95th percentile **OR** ≥130/80 mmHg (whichever is lower); age ≥13 yr, 130/85 mmHg **OR** specific antihypertensive drug treatment
☐ Plasma triglycerides ≥1.70 mmol/L [150 mg/dl] **OR** lipid lowering treatment	☐ Plasma triglycerides age <10 yr, ≥1.15 mmol/L [≥100 mg/dl]; age ≥10 yr, ≥1.70 mmol/L [≥150 mg/dl] **OR** lipid lowering treatment
☐ Plasma HDL-cholesterol ≤1.0 mmol/L [40 mg/dl] (M) and ≤1.3 mmol/L [50 mg/dl] (F) **OR** lipid lowering treatment	☐ Plasma HDL-cholesterol ≤1.0 mmol/L [≤40 mg/dl] **OR** lipid lowering treatment

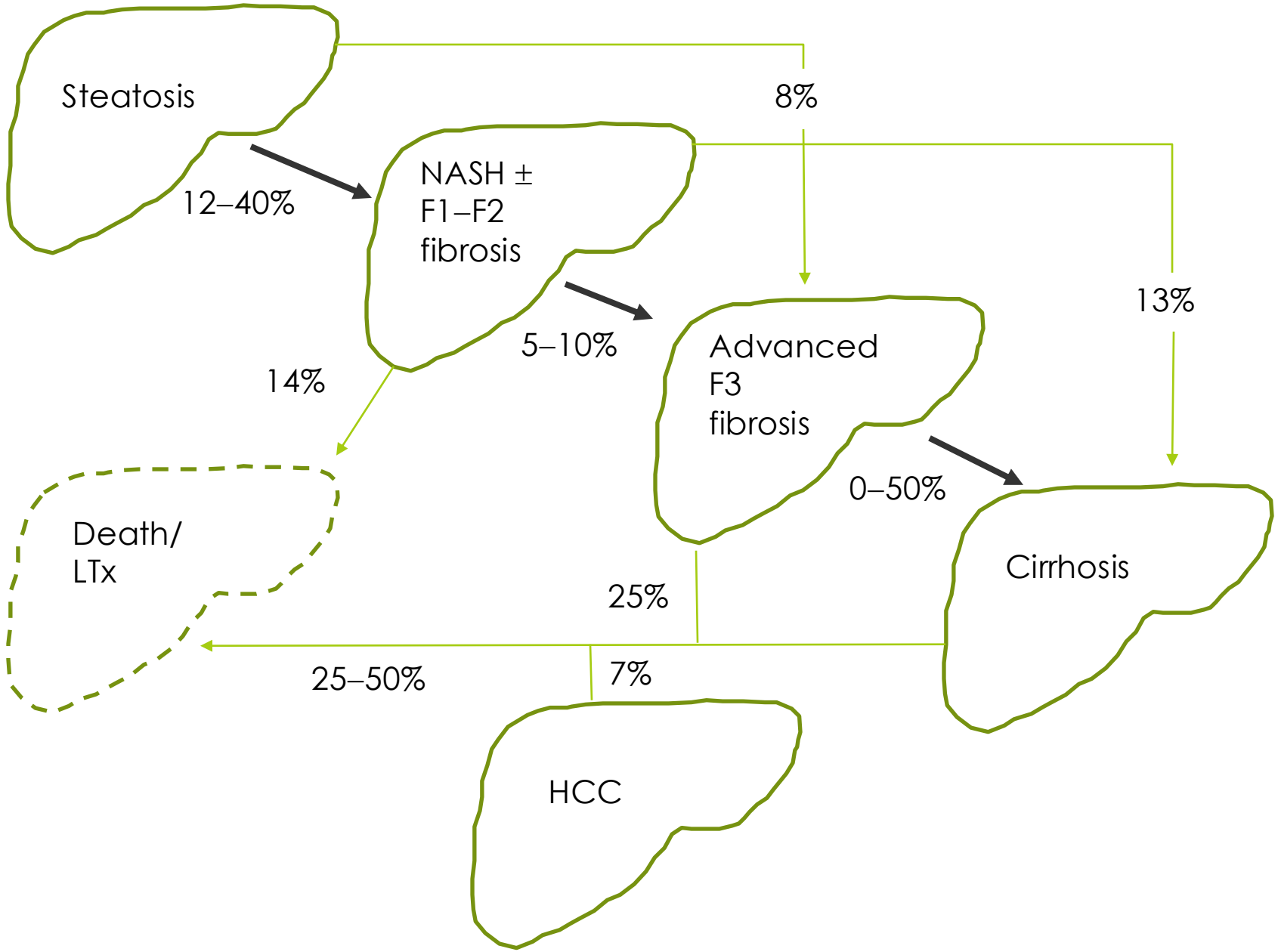
Υγιές ήπαρ



Κιρρωτικό ήπαρ

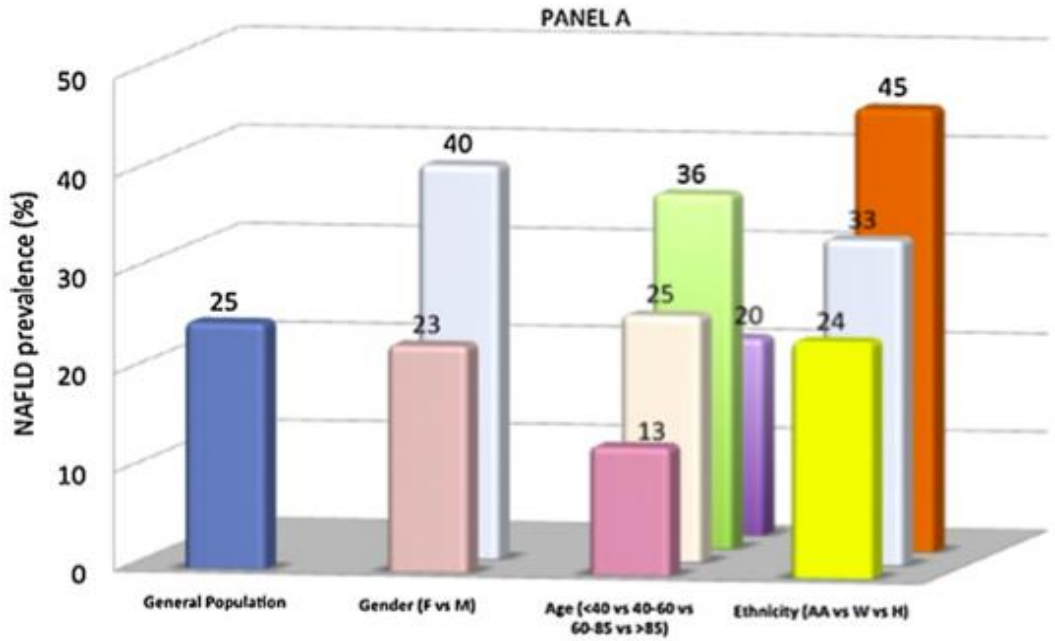
MASLD = Ηπατική εκδήλωση του μεταβολικού συνδρόμου

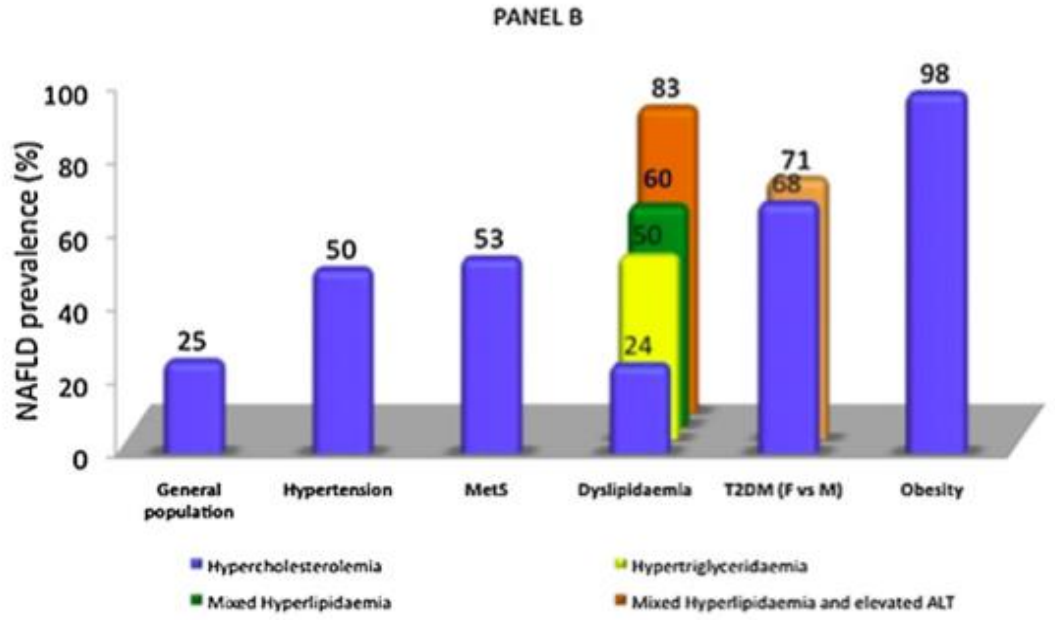
EASD guidelines 2016, Buzzetti et al, 2016



Epidemiology NAFLD

Επιπολασμός



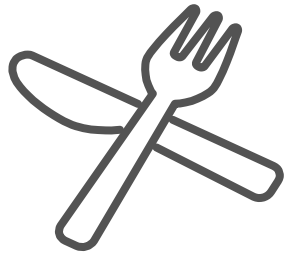


<u>Παγκόσμιος επιπολασμός: 25-30%</u>

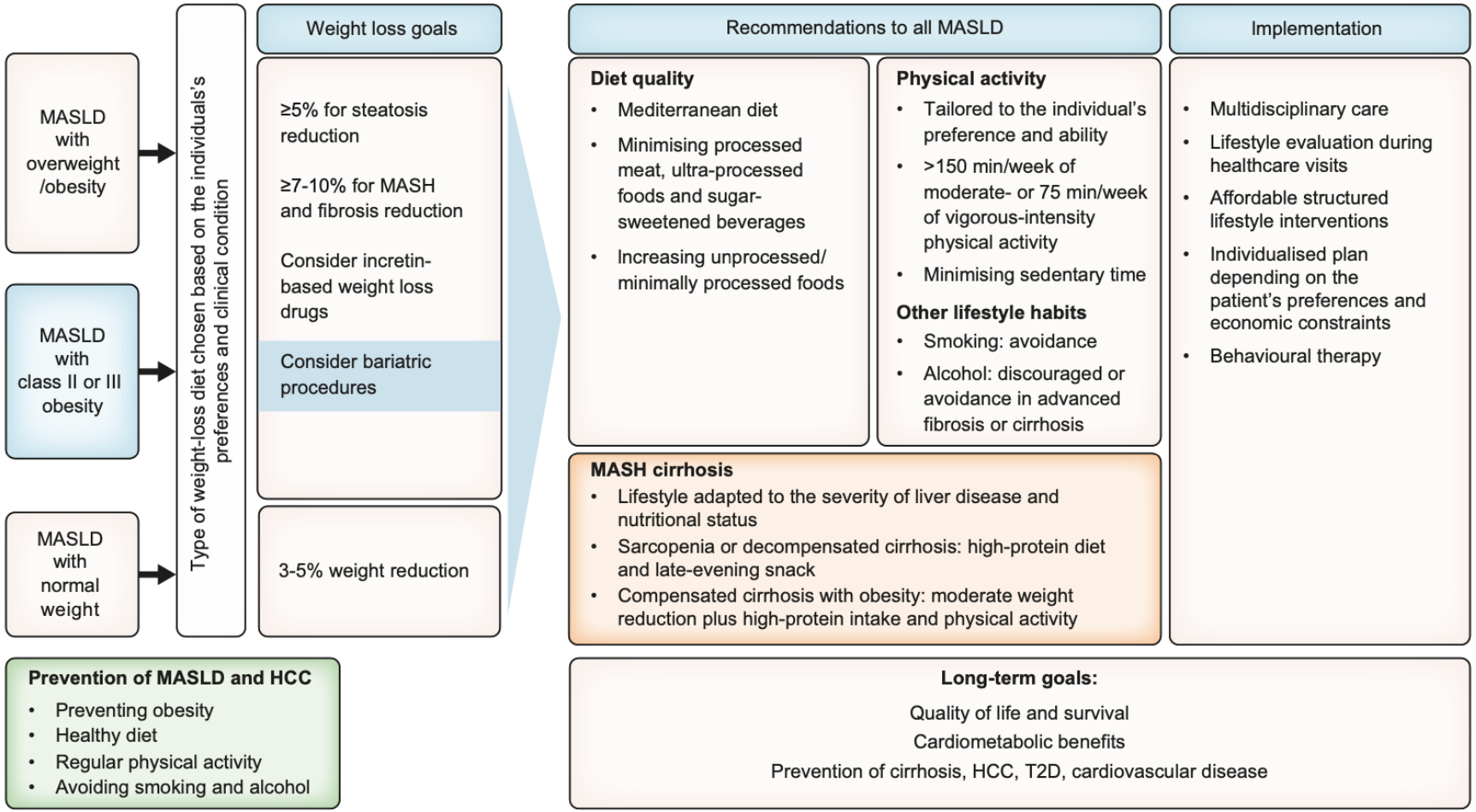
Ιδιαίτερες περιπτώσεις εμφάνισης NAFLD:

- Ασθενείς με φυσιολογικό ΔΜΣ - **Lean NAFLD**
- Αφροαμερικανοί: χαμηλά ποσοστά
- Αστικές ≠ Αγροτικές περιοχές

Lonardo et al, 2015,
Younossi et al., 2018



Ο ρόλος του τρόπου ζωής



Αλγόριθμος Διαχείρισης – Τρόπος Ζωής

EASL-EASD-EASO 2024

Φυσική δραστηριότητα

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BMC Gastroenterology

RESEARCH ARTICLE Open Access

Physical activity intervention for non-diabetic patients with non-alcoholic fatty liver disease: a meta-analysis of randomized controlled trials

Shu-ting Wang[1†], Jing Zheng[1†], He-wei Peng[1], Xiao-lin Cai[1], Xin-ting Pan[1], Hui-quan Li[1], Qi-zhu Hong[1] and Xian-E Peng[1,2*]

Μόνο 1 μελέτη
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μη αξιοπιστία

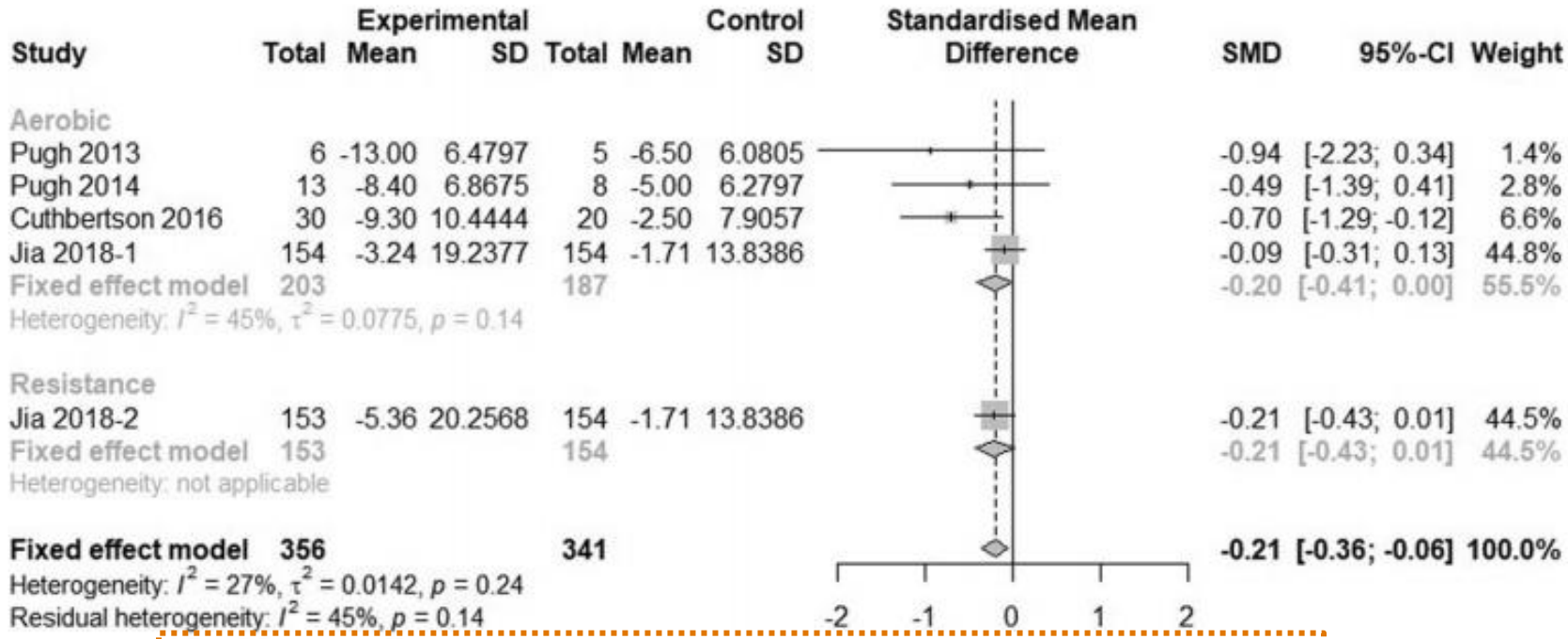

Fig. 9 Subgroup analysis of the effect of physical activity intervention types on intra-hepatic lipid content

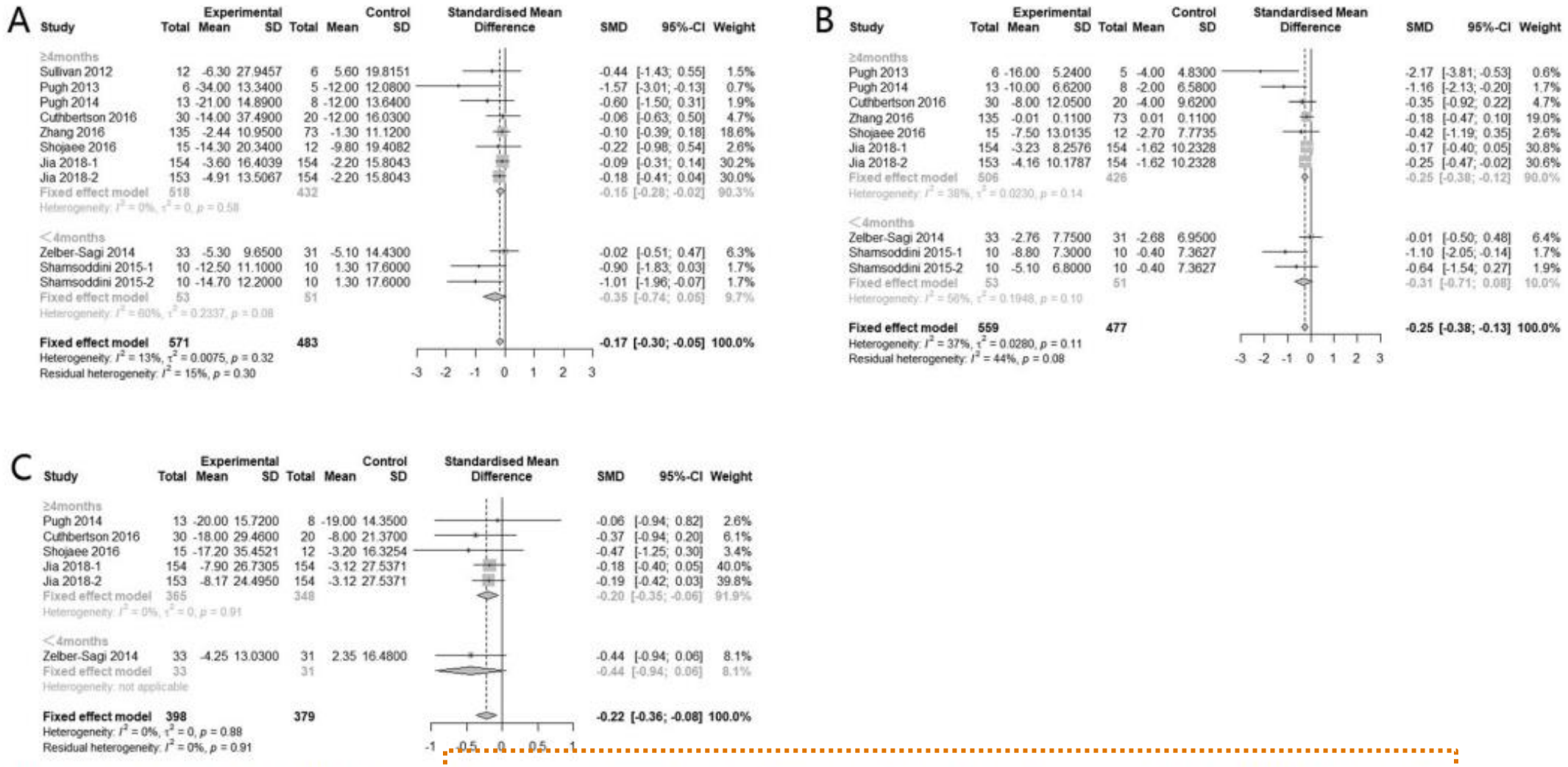

Fig. 4 Subgroup analysis of the effects of physical activity intervention duration on hepatic enzyme parameters (**a**: ALT, **b**: AST, **c**: GGT)

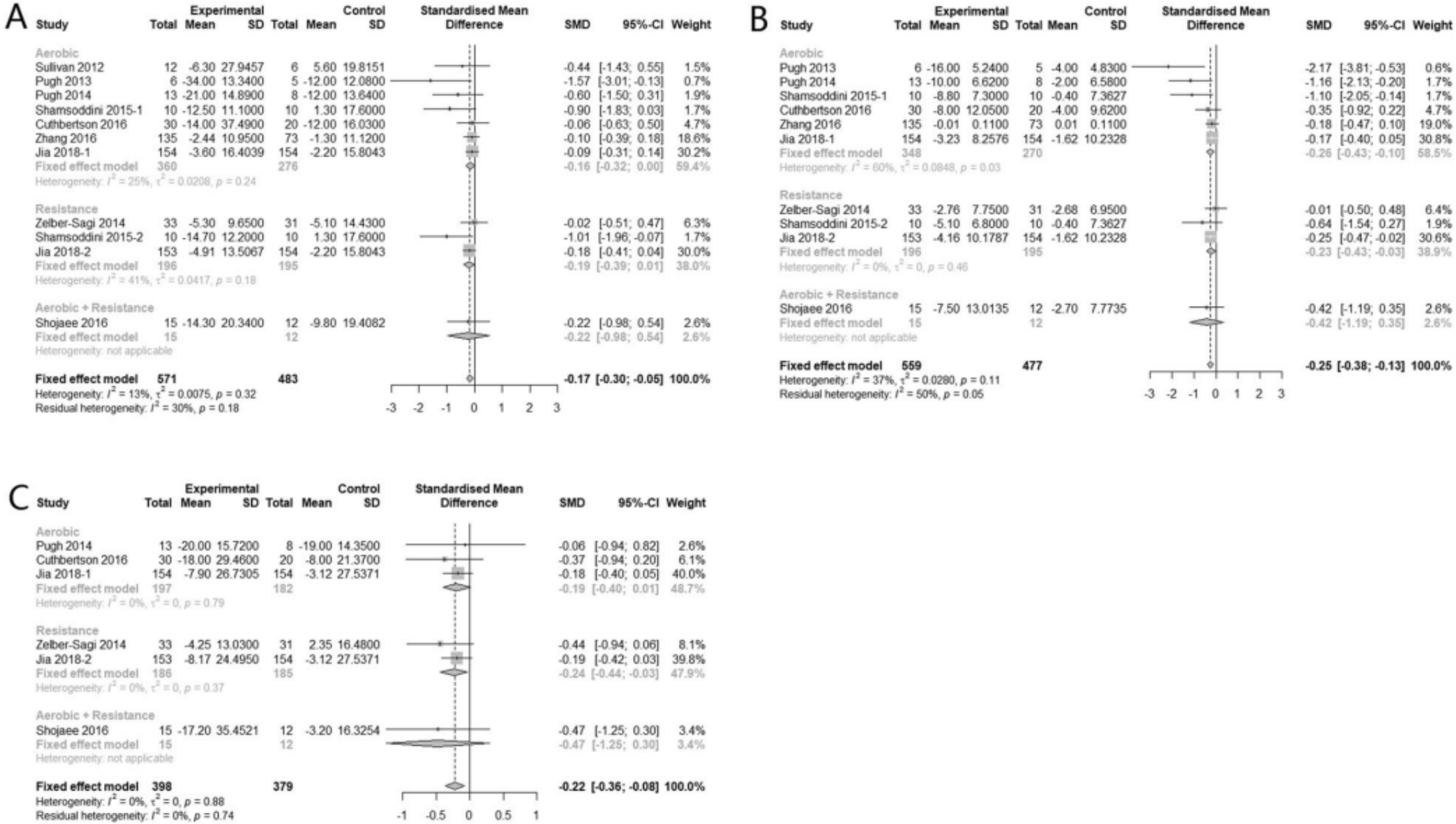

Fig. 3 Subgroup analysis of the effects of physical activity intervention type on hepatic enzyme parameters (**a**: ALT, **b**: AST, **c**: GGT)

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DOI: 10.3109/07853890.2015.1077989

ORIGINAL ARTICLE

Television viewing and fatty liver in early midlife. The Cardiovascular Risk in Young Finns Study

Harri Helajärvi[1], Katja Pahkala[1,2], Olli J. Heinonen[1], Markus Juonala[3,4], Mervi Oikonen[2], Tuija Tammelin[5], Nina Hutri-Kähönen[6], Mika Kähönen[7], Terho Lehtimäki[8], Vera Mikkilä[2,9], Jorma Viikari[3] & Olli T. Raitakari[2,10]

- Προοπτική μελέτη – 10 έτη
- 1367 συμμετέχοντες
- 34-49 ετών
- Αλλαγές στα επίπεδα γGT + FLI μέσα στα 10 έτη
- Συγχρονική ανάλυση για NAFLD

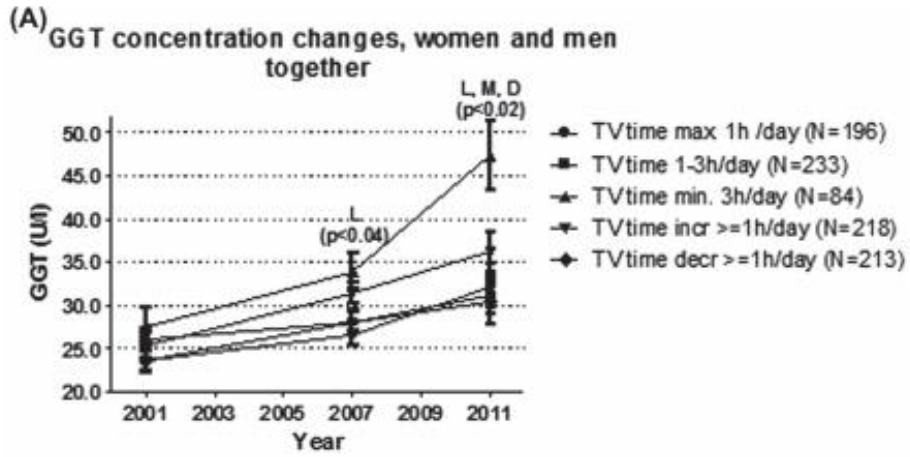
Table I. Mean increase in GGT and FLI during the 10-year follow-up in all TV time groups and by sex. Comparison of the magnitude of change between the constantly high and constantly low TV time groups is presented separately. Analyses adjusted for age and sex, baseline FLI, physical activity, occupational physical strain, energy intake, diet composition, alcohol use, sleep duration, socioeconomic status, and smoking. BMI is included in the FLI as per definition.

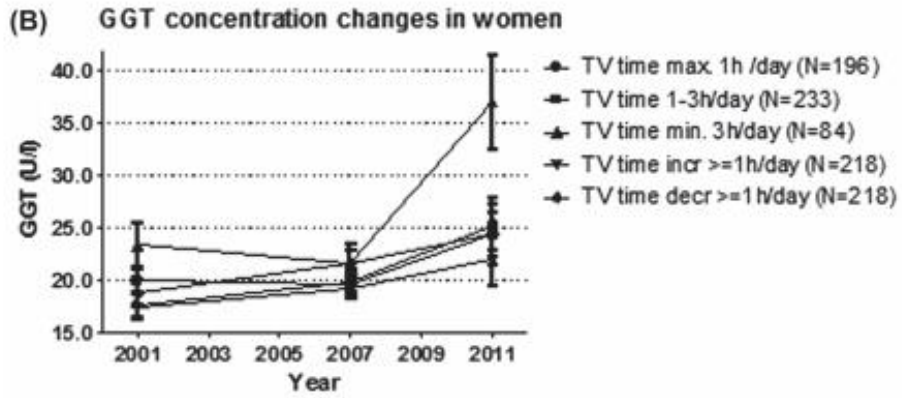
	Low (SD)	Moderate (SD)	High (SD)	Increased (SD)	Decreased (SD)	Difference (%), high versus low
GGT (U/L)						
All	6.2 (18.5)	5.7 (26.8)	23.2 (62.7)	12.6 (34.7)	8.6 (29.1)	+374[a]
Women	5.7 (16.7)	5.6 (33.3)	18.0 (50.0)	5.2 (14.1)	8.5 (32.7)	+316[a]
Men	6.8 (20.8)	5.9 (13.9)	27.0 (71.0)	19.9 (46.0)	8.7 (25.1)	+397[a]
FLI (range 0–7)						
All	1.3 (4.9)	1.3 (5.7)	5.0 (12.6)	3.3 (9.0)	2.2 (8.6)	+385[a]
Women	1.1 (4.7)	1.1 (6.0)	5.4 (13.9)	2.1 (7.6)	2.1 (8.4)	+491[a]
Men	1.7 (5.1)	1.6 (5.2)	4.6 (11.7)	4.5 (10.1)	2.3 (8.8)	+271[a]

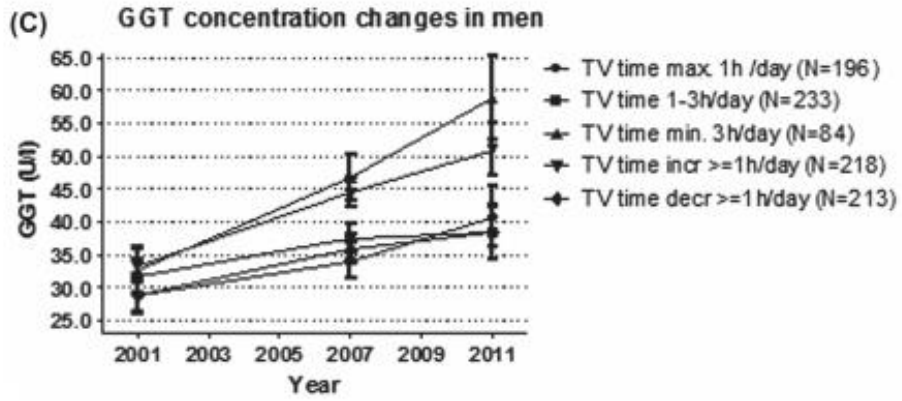
Low = TV viewing time constantly ≤ 1 h/day between 2001 and 2011. Moderate = TV viewing time constantly 1–3 h/day between 2001 and 2011. High = TV viewing time constantly ≥ 3 h/day between 2001 and 2011. Increased = TV time increased with ≥ 1 h between 2001 and 2011. Decreased = TV time decreased with ≥ 1 h between 2001 and 2011.

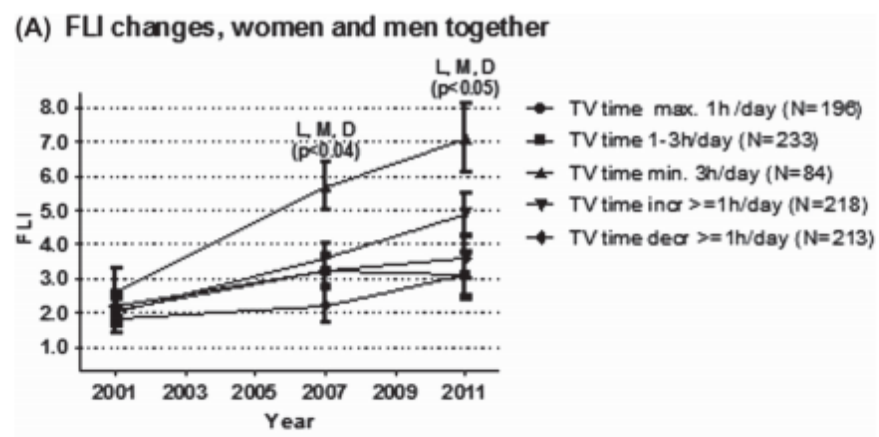
[a]Difference in increase between constantly high (≥ 3 h/day) and constantly low (≤ 1 h/day) TV time groups ($P < 0.0001$ in all).

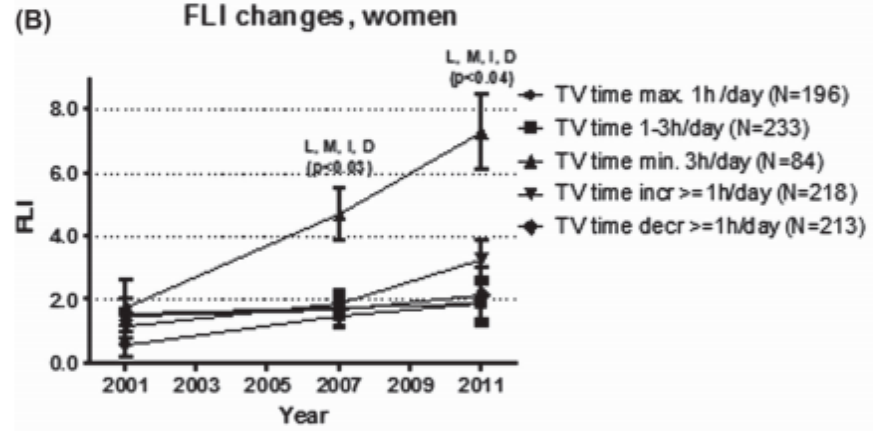
FLI = Fatty Liver Index; GGT = serum gamma-glutamyltransferase.


(A)
GGT concentration changes, women and men together
L, M, D
(p<0.02)
L
(p<0.04)
GGT (U/l)
Year
TV time max. 1h /day (N=196)
TV time 1-3h/day (N=233)
TV time min. 3h/day (N=84)
TV time incr >=1h/day (N=218)
TV time decr >=1h/day (N=213)


(B)
GGT concentration changes in women
GGT (U/l)
Year
TV time max. 1h /day (N=196)
TV time 1-3h/day (N=233)
TV time min. 3h/day (N=84)
TV time incr >=1h/day (N=218)
TV time decr >=1h/day (N=218)


(C)
GGT concentration changes in men
GGT (U/l)
Year
TV time max. 1h /day (N=196)
TV time 1-3h/day (N=233)
TV time min. 3h/day (N=84)
TV time incr >=1h/day (N=218)
TV time decr >=1h/day (N=213)


(A) FLI changes, women and men together
L, M, D
(p<0.05)
L, M, D
(p<0.04)
FLI
Year
TV time max. 1h /day (N=196)
TV time 1-3h/day (N=233)
TV time min. 3h/day (N=84)
TV time incr >=1h/day (N=218)
TV time decr >=1h/day (N=213)


(B)
FLI changes, women
L, M, I, D
(p<0.04)
L, M, I, D
(p<0.03)
FLI
Year
TV time max. 1h /day (N=196)
TV time 1-3h/day (N=233)
TV time min. 3h/day (N=84)
TV time incr >=1h/day (N=218)
TV time decr >=1h/day (N=213)

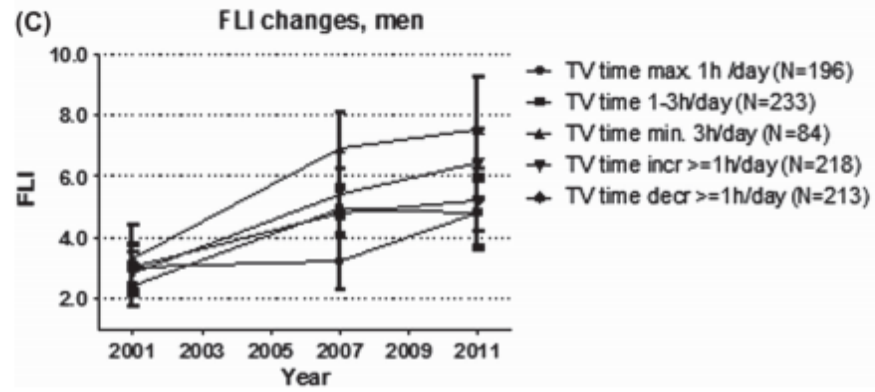

(C)
FLI changes, men
FLI
Year
TV time max. 1h /day (N=196)
TV time 1-3h/day (N=233)
TV time min. 3h/day (N=84)
TV time incr >=1h/day (N=218)
TV time decr >=1h/day (N=213)

Table II. Risk ratios (RRs) and 95% confidence intervals (95% CI) for ultrasonographical diagnosis of fatty liver in all TV time groups. Generalized linear modelling adjusted for age and sex, leisure-time and occupational physical activity, energy intake, diet composition, alcohol use, sleep duration, socioeconomic status, and smoking, with and without BMI.

	All ($n = 1084$)		Women ($n = 586$)		Men ($n = 498$)	
TV group	RR	95% CI	RR	95% CI	RR	95% CI
Without BMI						
Low TV time	1.00		1.00		1.00	
Moderate TV time	1.17	0.65–2.11	1.15	0.37–3.53	1.13	0.56–2.26
High TV time	2.34	1.22–4.48	2.15	0.56–8.23	2.44	1.16–5.16
Increased TV time	1.41	0.80–2.48	1.31	0.43–4.01	1.33	0.68–2.59
Decreased TV time	1.38	0.76–2.51	1.74	0.53–3.85	1.19	0.59–2.41
With BMI						
Low TV time	1.00		1.00		1.00	
Moderate TV time	1.03	0.57–1.87	0.75	0.24–2.35	1.07	0.53–2.15
High TV time	1.75	0.91–3.38	0.82	0.20–3.33	2.19	1.03–4.66
Increased TV time	1.11	0.62–1.96	0.80	0.24–2.61	1.12	0.57–2.18
Decreased TV time	1.12	0.61–2.04	1.40	0.44–4.44	1.01	0.50–2.05

Low TV time = TV viewing time constantly ≤ 1 h/day between 2001 and 2011. Moderate TV time = TV viewing time constantly 1–3 h/day between 2001 and 2011. High TV time = TV viewing time constantly ≥ 3 h/day between 2001 and 2011. Increased TV time = TV time increased with ≥ 1 h between 2001 and 2011. Decreased TV time = TV time decreased with ≥ 1 h between 2001 and 2011.

- Η συνεχώς αυξημένη διάρκεια τηλεθέασης σχετίστηκε με αυξημένη πιθανότητα παρουσίας της νόσου
- Η διόρθωση για το BMI εξασθένησε το αποτελέσμα.

Συνήθειες ύπνου

Open access Original research

BMJ Open

Effects of sleep quality on non-alcoholic fatty liver disease: a cross-sectional survey

Atsushi Takahashi ,[1] Yukio Anzai,[2] Masahito Kuroda,[3] Masae Kokubun,[4] Yuichiro Kondo,[5] Takashi Ogata,[6] Masashi Fujita,[1] Manabu Hayashi,[1] Hiromichi Imaizumi,[1] Kazumichi Abe,[1] Nobuo Tanji,[2] Hiromasa Ohira[1]

- 4828 συμμετέχοντες
- Ασθενών - μαρτύρων
- PSQI

Table 1 Characteristics of participants

	Men (n=1864)	Women (n=2964)	P value
Age (years)	55.5±12.7	56.6±12.4	0.002
Body mass index (kg/m^2)	23.4±3.3	22.9±3.5	<0.001
Sleep duration (min/day)	388.0±63.0	380.0±59.0	<0.001
Physical activity	41.5% (774)	47.1% (1395)	<0.001
Current smoker	25.1% (467)	5.6% (165)	<0.001
NAFLD	47.0% (876)	37.1% (1099)	<0.001
ALT (U/L)	24.5±15.5	20.7±15.2	<0.001
Global PSQI score	4.9±2.6	5.2±2.6	<0.001

ALT, alanine aminotransferase; NAFLD, non-alcoholic fatty liver disease; PSQI, Pittsburgh Sleep Quality Index.

Table 2 Comparison of each PSQI score between the groups with and without NAFLD

	With NAFLD	Without NAFLD	P value
Men			
Global PSQI score	5.02±2.65	4.85±2.47	0.216
Subjective sleep quality	1.14±0.61	1.07±0.59	0.077
Sleep latency	0.63±0.78	0.58±0.74	0.066
Sleep duration	1.31±0.81	1.27±0.82	0.863
Habitual sleep efficiency	0.40±0.66	0.40±0.65	0.808
Sleep disturbance	0.70±0.51	0.69±0.50	0.414
Use of sleep medication	0.13±0.59	0.21±0.74	0.044
Daytime dysfunction	0.71±0.80	0.62±0.72	0.074
Women			
Global PSQI score	5.19±2.59	5.29±2.64	0.409
Subjective sleep quality	1.11±0.60	1.11±0.59	0.935
Sleep latency	0.72±0.85	0.76±0.84	0.443
Sleep duration	1.40±0.77	1.41±0.78	0.314
Habitual sleep efficiency	0.40±0.63	0.40±0.70	0.672
Sleep disturbance	0.69±0.51	0.70±0.50	0.947
Use of sleep medication	0.20±0.70	0.28±0.82	0.030
Daytime dysfunction	0.66±0.73	0.63±0.69	0.390

NAFLD, non-alcoholic fatty liver disease; PSQI, Pittsburgh Sleep Quality Index.

Table 3 OR of NAFLD by the PSQI and its components in men (n=1864)

	Score	N	Model 1 OR (95% CI)	Model 1 P value	Model 2 OR (95% CI)	Model 2 P value
Global PSQI score	≤5	1202	1.00 (reference)		1.00 (reference)	
	≥6	662	1.08 (0.89–1.30)	0.458	1.17 (0.94–1.47)	0.161
Subjective sleep quality	0	223	1.00 (reference)		1.00 (reference)	
	1	1252	1.10 (0.83–1.47)	0.506	1.17 (0.83–1.64)	0.377
	2	363	1.24 (0.89–1.75)	0.207	1.28 (0.86–1.90)	0.224
	3	26	2.02 (0.87–4.67)	0.101	1.68 (0.64–4.45)	0.295
Sleep latency	0	1011	1.00 (reference)		1.00 (reference)	
	1	624	1.05 (0.86–1.29)	0.622	1.03 (0.82–1.31)	0.781
	2	186	1.37 (1.00–1.88)	0.050	1.66 (1.14–2.02)	0.008
	3	43	1.31 (0.70–2.43)	0.398	1.31 (0.63–2.74)	0.467
Sleep duration	0	368	1.00 (reference)		1.00 (reference)	
	1	656	0.99 (0.76–1.28)	0.923	0.91 (0.67–1.23)	0.537
	2	778	1.01 (0.78–1.31)	0.937	0.89 (0.66–1.21)	0.458
	3	62	1.04 (0.60–1.80)	0.894	1.00 (0.52–1.93)	0.999
Habitual sleep efficiency	0	1262	1.00 (reference)		1.00 (reference)	
	1	500	1.00 (0.81–1.23)	0.991	1.01 (0.79–1.29)	0.931
	2	64	0.94 (0.57–1.57)	0.820	0.79 (0.42–1.47)	0.456
	3	38	1.23 (0.64–2.37)	0.534	1.71 (0.82–3.55)	0.152
Sleep disturbance	0	607	1.00 (reference)		1.00 (reference)	
	1	1218	1.07 (0.88–1.30)	0.499	1.08 (0.86–1.37)	0.493
	2	38	1.13 (0.58–2.19)	0.726	0.93 (0.41–2.10)	0.852
	3	1	–	–	–	–
Use of sleep medication	0	1730	1.00 (reference)		1.00 (reference)	
	1	26	0.97 (0.44–2.12)	0.939	1.09 (0.46–2.62)	0.842
	2	19	1.06 (0.43–2.65)	0.894	1.40 (0.53–3.90)	0.522
	3	89	0.60 (0.38–0.95)	0.030	0.61 (0.36–1.04)	0.068
Daytime dysfunction	0	912	1.00 (reference)		1.00 (reference)	
	1	702	1.00 (0.82–1.22)	0.992	1.16 (0.92–1.47)	0.203
	2	210	1.11 (0.82–1.50)	0.520	1.16 (0.81–1.66)	0.414
	3	40	2.82 (1.39–5.75)	0.004	2.04 (0.92–4.54)	0.079

Model 1: adjustment for age, smoking habits and physical activity; model 2: model 1 plus adjustment for body mass index.
NAFLD, non-alcoholic fatty liver disease; PSQI, Pittsburgh Sleep Quality Index.

Table 4 OR of NAFLD by the PSQI and its components in women (n=2964)

	Score	N	Model 1 OR (95% CI)	Model 1 P value	Model 2 OR (95% CI)	Model 2 P value
Global PSQI score	≤5	1783	1.00 (reference)		1.00 (reference)	
	≥6	1181	0.99 (0.85–1.15)	0.847	1.17 (0.94–1.47)	0.161
Subjective sleep quality	0	332	1.00 (reference)		1.00 (reference)	
	1	2029	0.86 (0.68–1.10)	0.233	0.93 (0.70–1.23)	0.610
	2	554	1.02 (0.77–1.35)	0.902	1.11 (0.80–1.55)	0.538
	3	49	0.67 (0.35–1.30)	0.233	0.81 (0.39–1.68)	0.565
Sleep latency	0	1399	1.00 (reference)		1.00 (reference)	
	1	1038	0.82 (0.69–0.97)	0.022	0.83 (0.68–1.01)	0.068
	2	405	0.95 (0.75–1.20)	0.659	0.98 (0.74–1.29)	0.865
	3	122	1.02 (0.69–1.50)	0.920	0.82 (0.52–1.29)	0.392
Sleep duration	0	430	1.00 (reference)		1.00 (reference)	
	1	994	1.15 (0.90–1.45)	0.262	1.22 (0.92–1.60)	0.169
	2	1444	0.94 (0.75–1.18)	0.579	0.92 (0.70–1.20)	0.520
	3	96	1.17 (0.74–1.84)	0.510	1.07 (0.63–1.82)	0.810
Habitual sleep efficiency	0	2030	1.00 (reference)		1.00 (reference)	
	1	749	1.29 (1.09–1.53)	0.004	1.21 (0.99–1.48)	0.069
	2	118	0.80 (0.53–1.21)	0.296	0.96 (0.60–1.54)	0.859
	3	67	0.73 (0.42–1.26)	0.255	0.66 (0.37–1.25)	0.199
Sleep disturbance	0	956	1.00 (reference)		1.00 (reference)	
	1	1946	0.97 (0.83–1.14)	0.725	0.97 (0.80–1.17)	0.763
	2	62	1.17 (0.69–1.99)	0.551	1.30 (0.70–2.44)	0.410
	3	0	–			–
Use of sleep medication	0	2644	1.00 (reference)		1.00 (reference)	
	1	79	0.69 (0.42–1.13)	0.142	0.97 (0.55–1.72)	0.919
	2	54	0.68 (0.37–1.24)	0.202	0.62 (0.31–1.22)	0.166
	3	187	0.75 (0.54–1.04)	0.084	0.69 (0.46–1.02)	0.061
Daytime dysfunction	0	1417	1.00 (reference)		1.00 (reference)	
	1	1234	0.96 (0.82–1.13)	0.626	0.98 (0.81–1.19)	0.848
	2	273	1.04 (0.79–1.36)	0.805	0.94 (0.68–1.30)	0.718
	3	40	2.08 (1.10–3.92)	0.024	2.62 (1.20–5.72)	0.015

Model 1: adjustment for age, smoking habits and physical activity; model 2: model 1 plus adjustment for body mass index.
NAFLD, non-alcoholic fatty liver disease; PSQI, Pittsburgh Sleep Quality Index.

Association between Sleep Disturbances and Liver Status in Obese Subjects with Nonalcoholic Fatty Liver Disease: A Comparison with Healthy Controls

Bertha Araceli Marin-Alejandre [1,†], Itziar Abete [1,2,†], Irene Cantero [1], Jose I. Riezu-Boj [1,3], Fermín I. Milagro [1,2,3], J. Ignacio Monreal [3,4], Mariana Elorz [3,5], José Ignacio Herrero [3,6,7], Alberto Benito-Boillos [3,5], Jorge Quiroga [3,7,8], Ana Martinez-Echeverria [3,9], Juan Isidro Uriz-Otano [3,9], María Pilar Huarte-Muniesa [3,9], Josep A. Tur [2,10], J. Alfredo Martínez [1,2,3,11,*] and M. Angeles Zulet [1,2,3]

- 94 ασθενείς με NAFLD και υπέρβαρο/παχυσαρκία
- 40 μάρτυρες φυσιολογικού βάρους
- Υπέρηχος ήπατος: παρουσία νόσου
- Ελαστογραφία: ηπατική ακαμψία

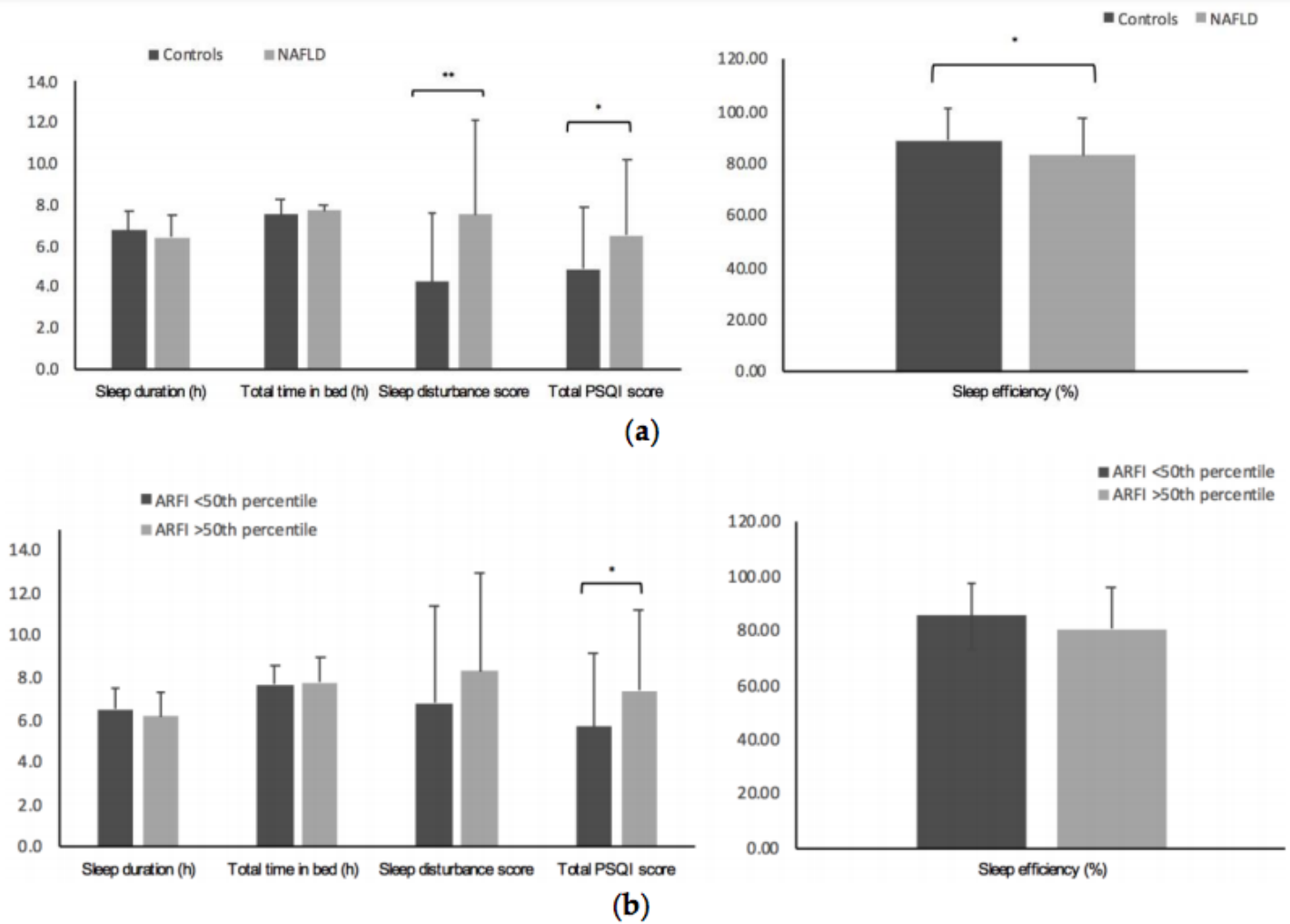


Figure 1. (**a**) Sleep characteristics of patients with NAFLD (n = 94) and normal weight controls (n = 40). (**b**) Sleep characteristics of patients with NAFLD and liver stiffness < 50th percentile (n = 46) vs. liver stiffness > 50th percentile (n = 46). Liver stiffness assessed by Acoustic Radiation Force Impulse (ARFI) elastography. Data expressed as mean ± SD CI95%, * $p < 0.05$, ** $p < 0.01$.

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➢ Παρατηρήθηκαν στατιστικά σημαντικές συσχετίσεις της παρουσίας νόσου με τη διάρκεια ύπνου, το σκορ διαταραχής ύπνου και το συνολικό σκορ ποιότητας ύπνου

Table 3. Association between sleep characteristics and risk for hepatic steatosis assessed by ultrasonography in NAFLD patients ($n = 94$) and controls ($n = 40$).

	Model 1	Model 2	Model 3	Model 4	Model 5
	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)
Sleep duration ≤6 h or >6 h	0.33 (0.13; 0.84) *	0.37 (0.14; 0.98) *	0.39 (0.09; 1.71)	0.34 (0.13; 0.85) *	0.15 (0.02; 1.04)
Sleep efficiency (%)	0.974 (0.94; 1.009)	0.981 (0.94; 1.01)	0.979 (0.93; 1.02)	0.975 (0.94; 1.01)	0.981 (0.93; 1.03)
Total time in bed (h)	1.19 (0.75; 1.88)	1.11 (0.67; 1.83)	1.79 (0.75; 4.29)	1.20 (0.76; 1.89)	1.29 (0.50; 3.32)
Sleep disturbance score	1.23 (1.08; 1.39) **	1.21 (1.06; 1.38) **	1.38 (1.08; 1.75) **	1.22 (1.08; 1.39) **	1.59 (1.11; 2.28) *
Sleep quality (Total PSQI score)	1.15 (1.01; 1.33) *	1.13 (0.98; 1.31)	1.14 (0.93; 1.39)	1.15 (0.99; 1.32)	1.10 (0.88; 1.38)

Odds Ratio (95% confidence interval) for hepatic steatosis were compared by logistic regression. *Model 1*: adjusted for age and sex. *Model 2*: adjusted for age, sex and physical activity (METs). *Model 3*: adjusted for age, sex and insulin. *Model 4*: adjusted for age, sex and smoking. *Model 5*: adjusted for age, sex, physical activity (METs), insulin and smoking. * $p < 0.05$, ** $p < 0.01$.

Association between Sleep Disturbances and Liver Status in Obese Subjects with Nonalcoholic Fatty Liver Disease: A Comparison with Healthy Controls

Bertha Araceli Marin-Alejandre [1,†], Itziar Abete [1,2,†], Irene Cantero [1], Jose I. Riezu-Boj [1,3], Fermín I. Milagro [1,2,3], J. Ignacio Monreal [3,4], Mariana Elorz [3,5], José Ignacio Herrero [3,6,7], Alberto Benito-Boillos [3,5], Jorge Quiroga [3,7,8], Ana Martinez-Echeverria [3,9], Juan Isidro Uriz-Otano [3,9], María Pilar Huarte-Muniesa [3,9], Josep A. Tur [2,10], J. Alfredo Martínez [1,2,3,11,*] and M. Angeles Zulet [1,2,3]

➢ Παρατηρήθηκαν στατιστικά σημαντικές συσχετίσεις μεταξύ της ηπατικής ακαμψίας, του σκορ διαταραχής ύπνου και του συνολικού σκορ ποιότητας ύπνου

Table 4. Regression analysis of sleep characteristics and liver stiffness assessed by ARFI in patients with NAFLD.

		β (95% IC)	*p*	Adjusted R^2	*p* Model
Sleep duration ≤6 h or >6 h	Model 1	−0.30 (−0.57; −0.02)	0.034		
	Model 2	−0.28 (−0.56; −0.002)	0.048	0.028	0.135
	Model 3	−0.25 (−0.54; 0.02)	0.078	0.099	0.022
	Model 4	−0.22 (−0.53; 0.08)	0.154	0.058	0.123
	Model 5	−0.27 (−0.55; 0.01)	0.059	0.188	0.002
	Model 6	−0.22 (−0.50; 0.06)	0.114	0.205	<0.001
Sleep Efficiency	Model 1	−0.01 (−0.02; −0.0002)	0.045		
	Model 2	−0.009 (−0.01; 0.0005)	0.063	0.023	0.165
	Model 3	−0.008 (−0.01; 0.001)	0.087	0.097	0.023
	Model 4	−0.008 (−0.02; 0.002)	0.131	0.061	0.114
	Model 5	0.008 (−0.01; 0.0008)	0.075	0.184	0.002
	Model 6	−0.005 (−0.01; 0.004)	0.248	0.195	0.001
Total time in bed	Model 1	0.02 (−0.11; 0.15)	0.750		
	Model 2	0.01 (−0.12; 0.15)	0.805	−0.014	0.646
	Model 3	0.002 (−0.13; 0.13)	0.974	0.064	0.072
	Model 4	−0.01 (−0.16; 0.13)	0.863	0.031	0.233
	Model 5	−0.01 (−0.14; 0.11)	0.868	0.150	0.007
	Model 6	−0.02 (−0.14; 0.10)	0.781	0.182	0.002
Sleep disturbance score	Model 1	0.03 (0.001; 0.06)	0.037		
	Model 2	0.02 (−0.001; 0.06)	0.064	0.023	0.166
	Model 3	0.02 (−0.002; 0.05)	0.069	0.102	0.020
	Model 4	0.04 (0.005; 0.07)	0.024	0.097	0.042
	Model 5	0.04 (0.005; 0.07)	0.024	0.203	0.001
	Model 6	0.03 (0.004; 0.07)	0.081	0.212	<0.001
Sleep quality (Total PSQI score)	Model 1	0.04 (0.004; 0.07)	0.029		
	Model 2	0.03 (−0.0002; 0.07)	0.051	0.027	0.142
	Model 3	0.04 (0.006; 0.08)	0.022	0.123	0.009
	Model 4	0.04 (0.002; 0.09)	0.039	0.086	0.057
	Model 5	0.04 (0.006; 0.08)	0.023	0.204	0.001
	Model 6	0.03 (−0.005; 0.07)	0.085	0.211	<0.001

Model 1: unadjusted variable. Model 2: adjusted for age and sex. Model 3: adjusted for age, sex, smoking, fat mass (%), physical activity (METs). Model 4: adjusted for age, sex, smoking, fat mass (%), physical activity (METs) and total energy intake (kcal/day). Model 5: adjusted for age, sex, smoking, fat mass (%), physical activity (METs) and coughing or snoring. Model 6: adjusted for age, sex, smoking, BMI, physical activity (METs) and coughing or snoring.

Κάπνισμα

Smoking and the Risk of Non-alcoholic Fatty Liver Disease: A Cohort Study

Hyun-Suk Jung, MD[1], Yoosoo Chang, MD, PhD[1,2,3], Min-Jung Kwon, MD, PhD[2,4], Eunju Sung, MD, PhD[1,4], Kyung Eun Yun, MD, PhD[1], Yong Kyun Cho, MD, PhD[5], Hocheol Shin, MD, PhD[1,6] and Seungho Ryu, MD, PhD[1,2,3]

- 199.468 εθελοντές από Κορέα
- Προοπτική μελέτη – 4.1 έτη
- U/S για διάγνωση NAFLD
- Αλγόριθμοι διάγνωσης για ηπ. ίνωση

Table 1 Baseline characteristics of study participants by self-reported smoking status among men

Characteristics		Smoking status			*P* value	Multiple comparison
	Overall	Never smoker (a)	Ex-smoker (b)	Current smoker (c)		
Number	87,677	32,538	22,327	32,812		
Age (years)[a]	36.5 (7.7)	35.3 (7.6)	38.4 (8.8)	36.2 (6.8)	<0.001	a≠b≠c
BMI (kg/m^2)	23.2 (2.4)	23.1 (2.4)	23.4 (2.3)	23.2 (2.5)	<0.001	a≠b≠c
Waist circumference (cm)[a,b]	81.7 (6.8)	81.4 (6.6)	82.3 (6.5)	81.8 (6.9)	<0.001	a≠b≠c
Obesity (%)	22.1	20.1	23.5	23.0	<0.001	a≠b,a≠c
Alcohol intake (%)[c]	44.6	33.0	46.6	54.6	<0.001	a≠b≠c
Regular exercise (%)[d]	15.4	15.6	19.4	12.5	<0.001	a≠b≠c
High education level (%)[e]	86.4	89.9	85.7	83.1	<0.001	a≠b≠c
Diabetes (%)	1.4	1.0	2.0	1.5	<0.001	a≠b≠c
Hypertension (%)	11.7	10.8	14.9	10.4	<0.001	a≠b, b≠c
Systolic BP (mmHg)[a]	114.4 (11.7)	114.4 (11.6)	115.3 (12.2)	113.9 (11.5)	<0.001	a≠b≠c
Diastolic BP (mmHg)[a]	73.7 (9.0)	73.3 (8.8)	74.6 (9.2)	73.6 (8.9)	<0.001	a≠b≠c
Glucose (mg/dL)[a]	93.1 (11.4)	92.8 (10.2)	93.9 (11.9)	92.8 (12.3)	<0.001	a≠b, b≠c
Total cholesterol (mg/dL)[a]	191.8 (32.4)	189.8 (31.6)	194.4 (32.7)	192.1 (32.7)	<0.001	a≠b≠c
LDL-C (mg/dL)[a]	116.2 (28.5)	115.5 (27.9)	117.6 (28.7)	115.9 (28.8)	<0.001	a≠b, b≠c
HDL-C (mg/dL)[a]	54.6 (11.8)	55.4 (11.9)	55.2 (11.9)	53.3 (11.5)	<0.001	a≠c, b≠c
Triglycerides (mg/dL)[f]	100 [74–138]	93.0 (92.6–93.5)	102.7 (102.1–103.3)	112.2 (111.6–112.8)	<0.001	a≠b≠c
AST (U/L)[f]	21.0 (18.0–25.0)	21.5 (21.4–21.6)	22.4 (22.3–22.4)	21.9 (21.8–22.0)	<0.001	a≠b≠c
ALT (U/L)[f]	21.0 (16.0–28.0)	20.7 (20.7–20.8)	21.9 (21.8–22.0)	22.1 (22.0–22.2)	<0.001	a≠b, a≠c
GGT (U/L)[f]	22.0 (16.0–32.0)	21.5 (21.4–21.7)	24.2 (24.0–24.4)	26.5 (26.3–26.6)	<0.001	a≠b≠c
HOMA-IR[f]	1.42 (0.99–1.92)	1.28 (1.28–1.29)	1.36 (1.35–1.37)	1.35 (1.34–1.35)	<0.001	a≠b,a≠c
hsCRP (mg/L)[f]	0.4 (0.2–0.8)	0.4 (0.4–0.4)	0.5 (0.4–0.5)	0.5 (0.4–0.5)	<0.001	a≠b,a≠c
Urinary cotinine > 100 ng/mL (%)[g]	881.5 (390.0–1480.5)	451.0 (386.4–526.3)	386.3 (347.6–429.3)	788.7 (769.6–808.4)	<0.001	a≠c, b≠c

Table 2 Baseline characteristics of study participants by self-reported smoking status among women

Characteristics		Smoking status			*P* value	Multiple comparison
	Overall	Never smoker (a)	Ex-smoker (b)	Current smoker (c)		
Number	111,791	105,668	3643	2480		
Age (years)[a]	36.0 (7.4)	36.1 (7.5)	34.6 (6.7)	35.8 (7.6)	<0.001	a≠b, b≠ca≠b≠c
BMI (kg/m^2)	21.2 (2.5)	21.2 (2.5)	21.2 (2.7)	21.1 (2.6)	<0.001	a≠ca≠b≠c
Waist circumference (cm)[b]	73.0 (7.0)	73.0 (7.0)	73.6 (7.6)	72.8 (7.2)	<0.001	a≠b, b≠c
Obesity (%)	7.9	7.9	8.7	7.5	0.178	—
Alcohol intake (%)[c]	7.3	6.6	15.5	23.0	<0.001	a≠b≠c
Regular exercise (%)[d]	12.2	12.0	12.1	18.4	<0.001	a≠c, b≠c
High education level (%)[e]	74.9	74.9	74.4	72.2	0.029	a≠c
Diabetes (%)	0.7	0.7	0.7	0.5	0.532	—
Hypertension (%)	3.9	4.0	2.5	3.3	<0.001	a≠b
Systolic BP (mmHg)[a]	104.3 (12.1)	104.4 (12.1)	103.1 (11.3)	103.4 (11.4)	<0.001	a≠b
Diastolic BP (mmHg)[a]	66.6 (8.6)	66.6 (8.6)	65.7 (8.3)	66.2 (8.4)	<0.001	a≠b
Glucose (mg/dL)[a]	89.8 (9.0)	89.8 (9.0)	89.3 (8.8)	89.2 (9.6)	<0.001	a≠b
Total cholesterol (mg/dL)[a]	183.4 (31.5)	183.5 (31.6)	182.4 (31.0)	182.7 (30.8)	0.059	—
LDL-C (mg/dL)[a]	103.6 (26.9)	103.8 (27.0)	101.7 (26.4)	101.8 (26.8)	<0.001	a≠b
HDL-C (mg/dL)[a]	63.8 (13.9)	63.8 (13.9)	64.5 (14.2)	64.0 (13.9)	0.004	a≠b
Triglycerides (mg/dL)[f]	70.0 (54.0–94.0)	73.0 (72.8—73.2)	72.8 (71.8–73.9)	77.0 (75.7–78.2)	<0.001	b≠c
AST (U/L)[f]	18.0 (16.0–21.0)	18.6 (18.5–18.6)	18.4 (18.2–18.5)	18.4 (18.2–18.6)	0.012	a≠b
ALT (U/L)[f]	14.0 (11.0–18.0)	14.0 (14.0–14.1)	13.9 (13.7–14.1)	14.0 (13.8–14.2)	0.412	–
GGT (U/L)[f]	12.0 (9.0–15.0)	12.1 (12.1–12.2)	12.4 (12.2–12.6)	13.5 (13.2–13.8)	<0.001	a≠b≠ca≠b, b≠c
HOMA-IR[f]	1.38 (0.91–1.90)	1.27 (1.27–1.28)	1.24 (1.22–1.26)	1.34 (1.31–1.37)	<0.001	a≠b, b≠c
hsCRP (mg/L)[f]	0.3 (0.1–0.6)	0.3 (0.3–0.3)	0.3 (0.3–0.3)	0.3 (0.3–0.3)	<0.001	b≠c
Urinary cotinine > 100 ng/mL (%)[g]	169.0 (0.0–640.0)	236.9 (212.4–264.3)	359.0 (300.1–429.6)	535.5 (487.9–587.8)	<0.001	a≠b, b≠c

- Παρατηρήθηκαν στατιστικά σημαντικές συσχετίσεις μεταξύ των καπνιστικών συνηθειών και της πιθανότητας ανάπτυξης NAFLD.

- Στατιστικά σημαντική αλληλεπίδραση φύλου-πακετοετών για τη νόσο (p_{int}=0,017)

Table 3 Development of NAFLD by self-reported smoking status and smoking pack-years

	Person-years	Incident cases	Incidence density (per 100 person-years)	Age adjusted HR (95% CI)	Multivariable-adjusted HR (95% CI)[a]		HR (95% CI) in the model using time-dependent variables[b]
					Model 1	Model 2	
Men (n=87,677)							
Smoking status							
Never smoker	164,883.5	10,405	6.3	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)
Ex-smoker	117,539.7	7578	6.4	1.01 (0.98–1.04)	1.00 (0.97–1.03)	0.98 (0.95–1.01)	1.01 (0.98–1.04)
Current smoker	176,686.8	13,260	7.5	1.18 (1.15–1.21)	1.23 (1.20–1.26)	1.15 (1.12–1.18)	1.10 (1.07–1.13)
Pack-years							
0	165,139.8	10,416	6.3	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)
<10	108,398.0	7646	7.1	1.13 (1.09—1.16)	1.10 (1.07–1.14)	1.06 (1.03–1.10)	1.05 (1.02–1.08)
10–19.9	75,421.6	5782	7.7	1.21 (1.17–1.25)	1.25 (1.21–1.29)	1.16 (1.13–1.20)	1.11 (1.08–1.15)
≥0.1	30,779.2	2625	8.5	1.34 (1.28–1.40)	1.36 (1.30–1.42)	1.24 (1.18–1.30)	1.33 (1.27–1.39)
P for trend				<0.001	<0.001	<0.001	<0.001
Women (111,791)							
Smoking status							
Never smoker	579,228.6	13,387	2.3	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)
Ex-smoker	19,836.4	431	2.2	1.03 (0.93–1.13)	0.95 (0.86–1.05)	0.95 (0.86–1.05)	0.92 (0.83–1.03)
Current smoker	12,815.8	348	2.7	1.24 (1.12–1.38)	1.17 (1.05–1.31)	1.14 (1.03–1.27)	1.14 (1.03–1.27)
Pack-years							
0	579,299.5	13,388	2.3	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)
<5	16,184.2	356	2.2	1.16 (1.04–1.29)	1.01 (0.91–1.12)	1.01 (0.91–1.13)	1.04 (0.93–1.15)
5–9.9	4044.6	118	2.9	1.28 (1.06–1.53)	1.25 (1.04–1.50)	1.16 (0.97–1.40)	1.26 (1.06–1.50)
≥0.2	1626.5	83	5.1	1.71 (1.38–2.13)	1.46 (1.17–1.81)	1.30 (1.05–1.62)	1.44 (1.16–1.77)
P for trend				<0.001	<0.001	0.010	<0.001

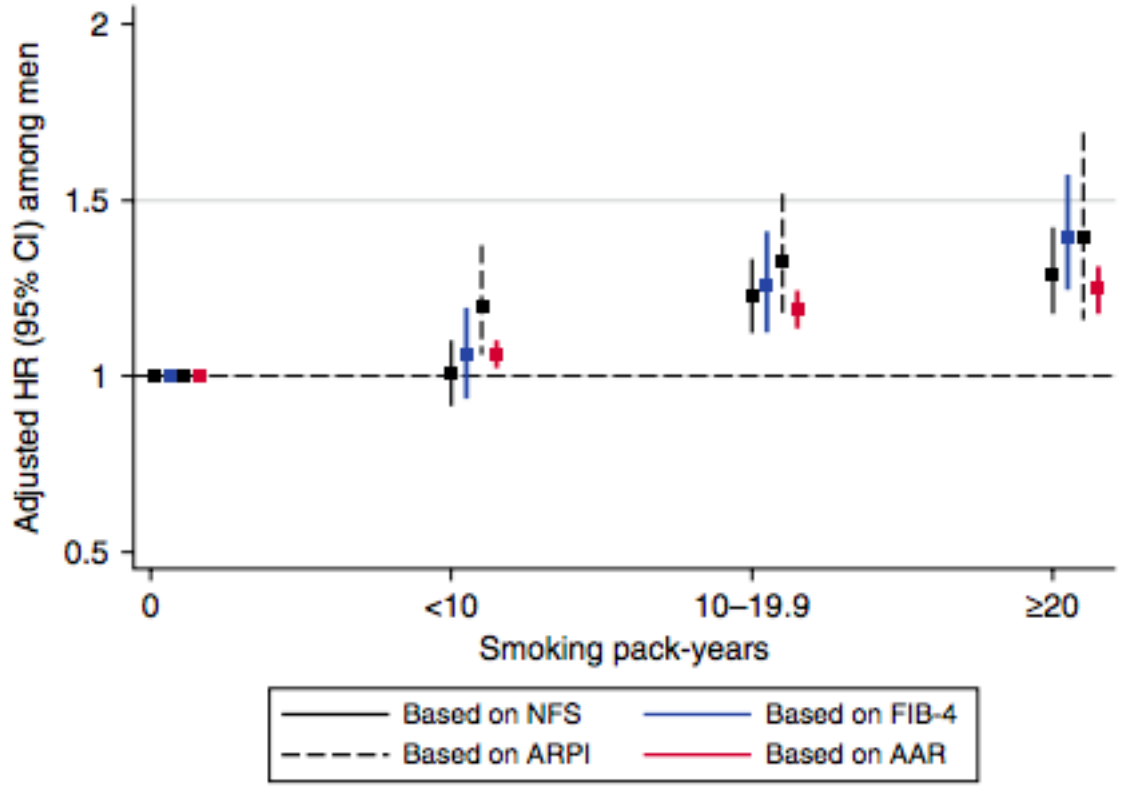


Fig. 2 Hazard ratios (95% CI) for development of NAFLD with intermediate/high probability of advanced fibrosis according to smoking pack-years among men

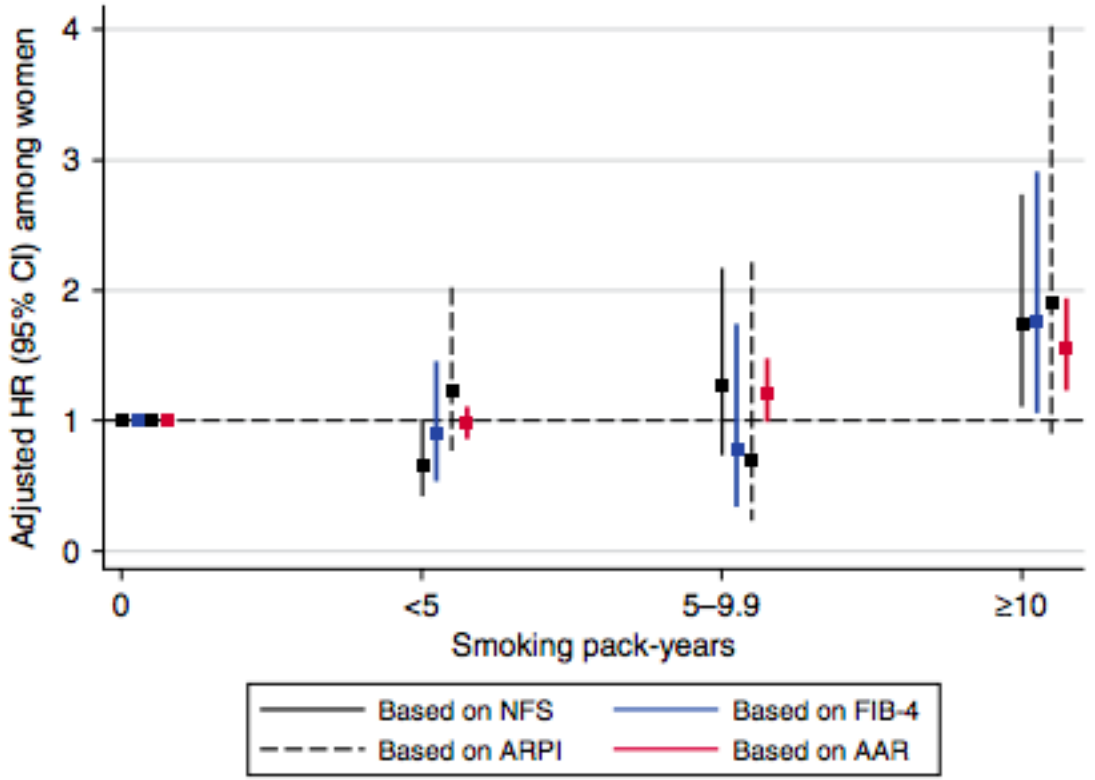
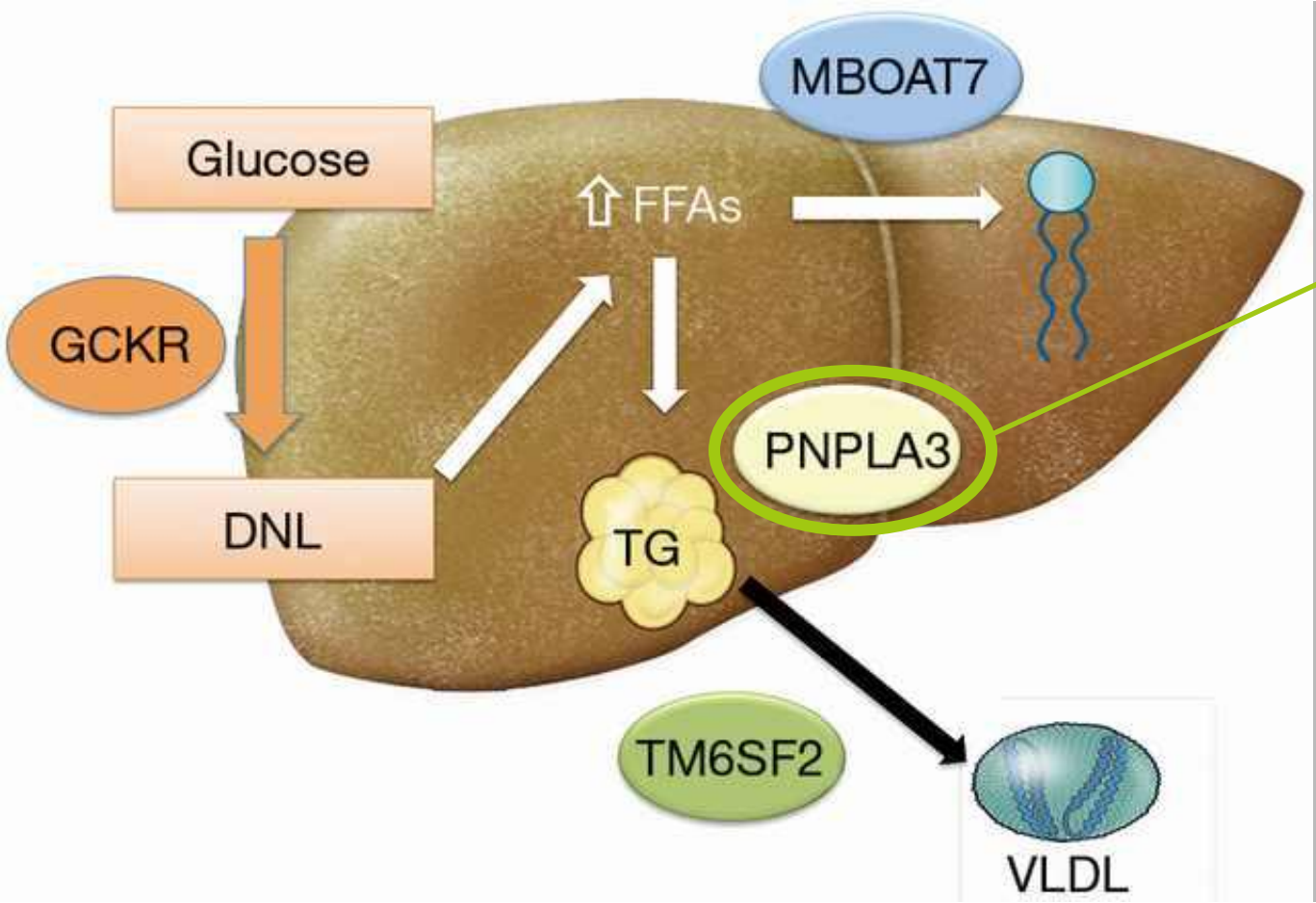


Fig. 3 Hazard ratios (95% CI) for development of NAFLD with intermediate/high probability of advanced fibrosis according to smoking pack-years among women. AAR aspartate transaminase to alanine

Ο ρόλος του γονιδιώματος

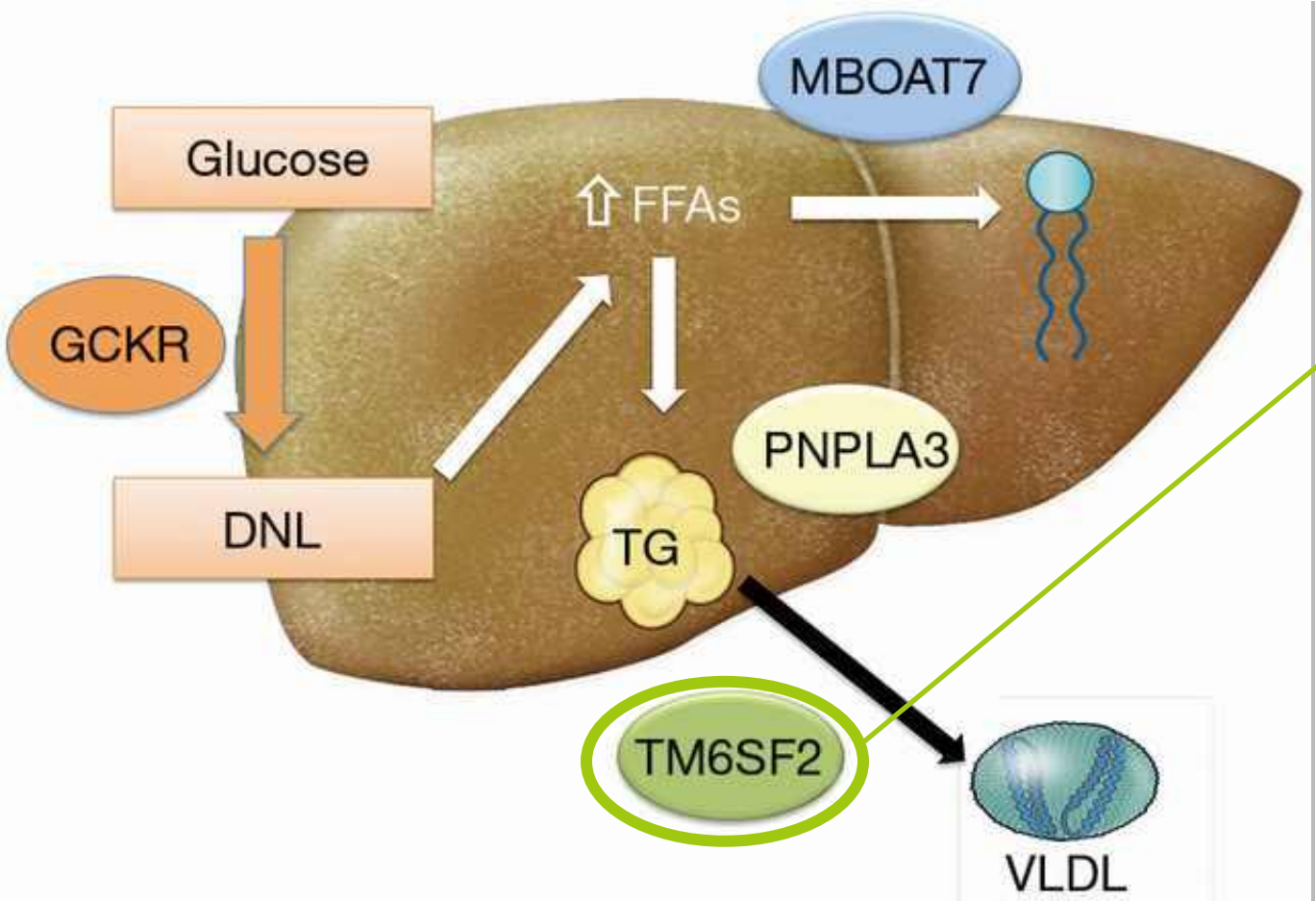


- <u>Διάσπαση τριγλυκεριδίων</u>
  - Δράση λιπάσης
    - rs738409
  - Μειωμένη ικανότητα διάσπασης TG →συσσώρευση
    - rs738409
    - *(2η θεωρία)*

<u>Παραγωγή τριγλυκεριδίων</u>

- "Gain of function"
- Επάγει τη δράση της ακετυλοτρανσφεράσης του

↑ηπατικό λίπος, ηπατικά ένζυμα

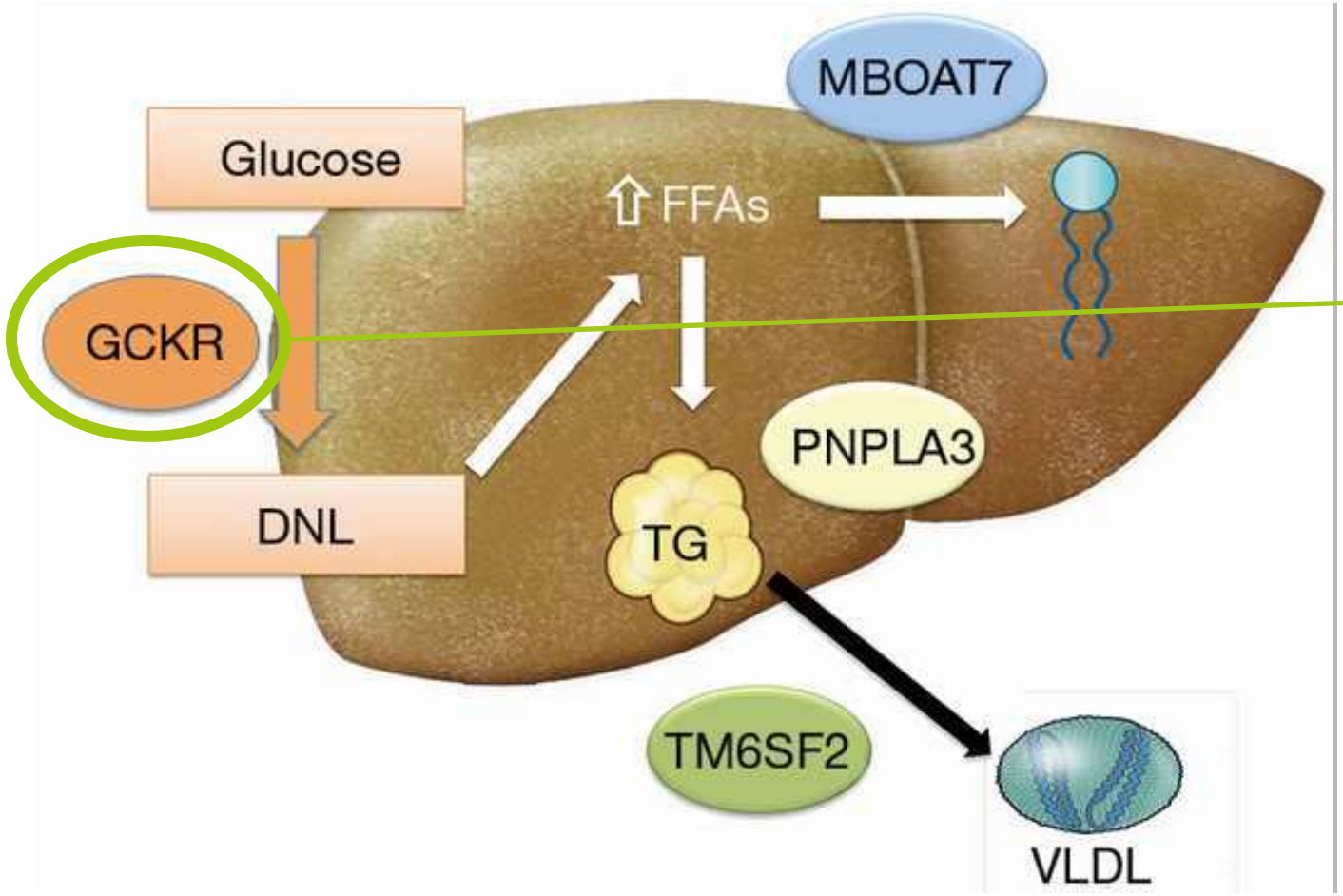


- <u>Ρύθμιση ενδοηπατικού λίπους</u>
  - Απέκκριση VLDL
    - Απέκκριση τριγλυκεριδίων
    - Περιεχόμενο σταγονιδίων λίπους

rs58542926

- Αυξημένα επίπεδα VLDL, TG ήπατος
- Διαταραγμένη σύνθεση λιπιδίων από PUFAs

↑ηπατικό λίπος, VLDL & TG ήπατος, αραχιδονικό οξύ, ηπατικά ένζυμα ορού
↓VLDL & TG ορού, κίνδυνος CVD

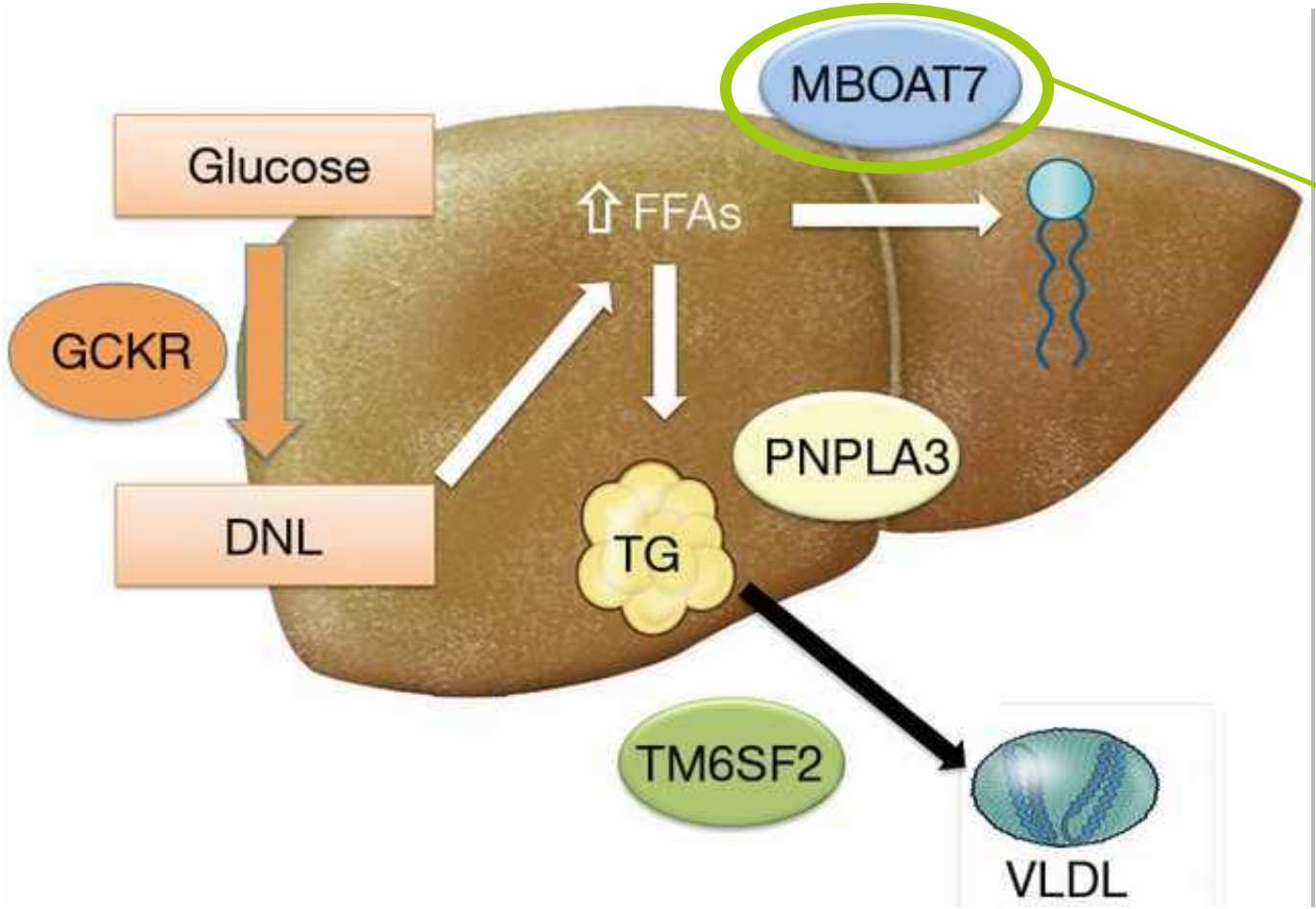


- Αναστολή της δράσης της γλυκοκινάσης
- <u>Ρύθμιση της εισόδου γλυκόζης στα ηπατοκύτταρα</u>

rs780094

- Ανεξέλεγκτη εισροή γλυκόζης
  - Αυξημένα επίπεδα τριγλυκεριδίων ορού
  - Μειωμένα επίπεδα γλυκόζης και ινσουλίνης ορού

↑Ηπατικό λίπος, TG, CRP ορού
↕ Glu, Ins ορού



- Ακυλοτρανσφεράση
- <u>Αναδιαμόρφωση φωσφατιδυλοινοσιτόλης με το αραχιδονικό οξύ</u>

rs641738

  - Αραχιδονικό οξύ λιγότερο πλούσιο σε φωσφατιδυλοινοσιτόλη
    - Διαταραγμένη μετακίνηση λιπιδίων στο ηπατοκύτταρο
    - Αυξημένα επίπεδα προφλεγμονωδών μεταβολιτών

⬆Ηπατικό λίπος, ηπατική ίνωση, ALT, CRP ορού, ινσουλίνη ορού (;)

Namjou et al. BMC Medicine (2019) 17:135
https://doi.org/10.1186/s12916-019-1364-z

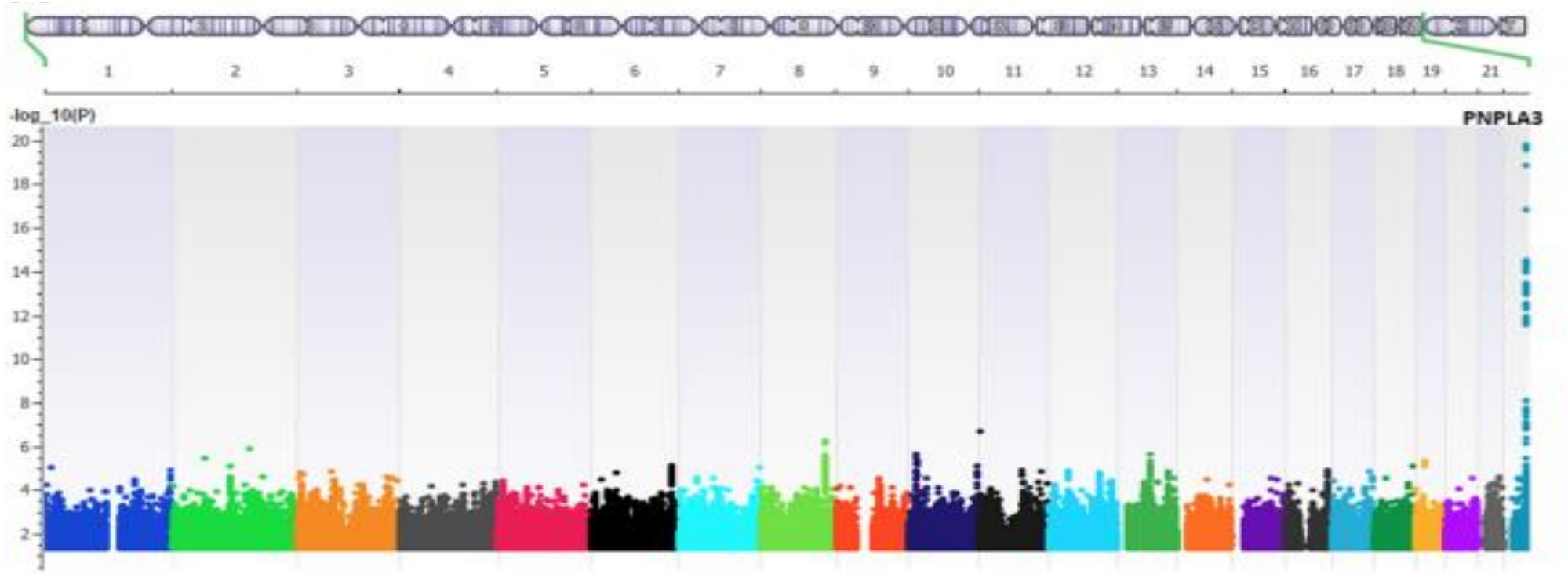
BMC Medicine

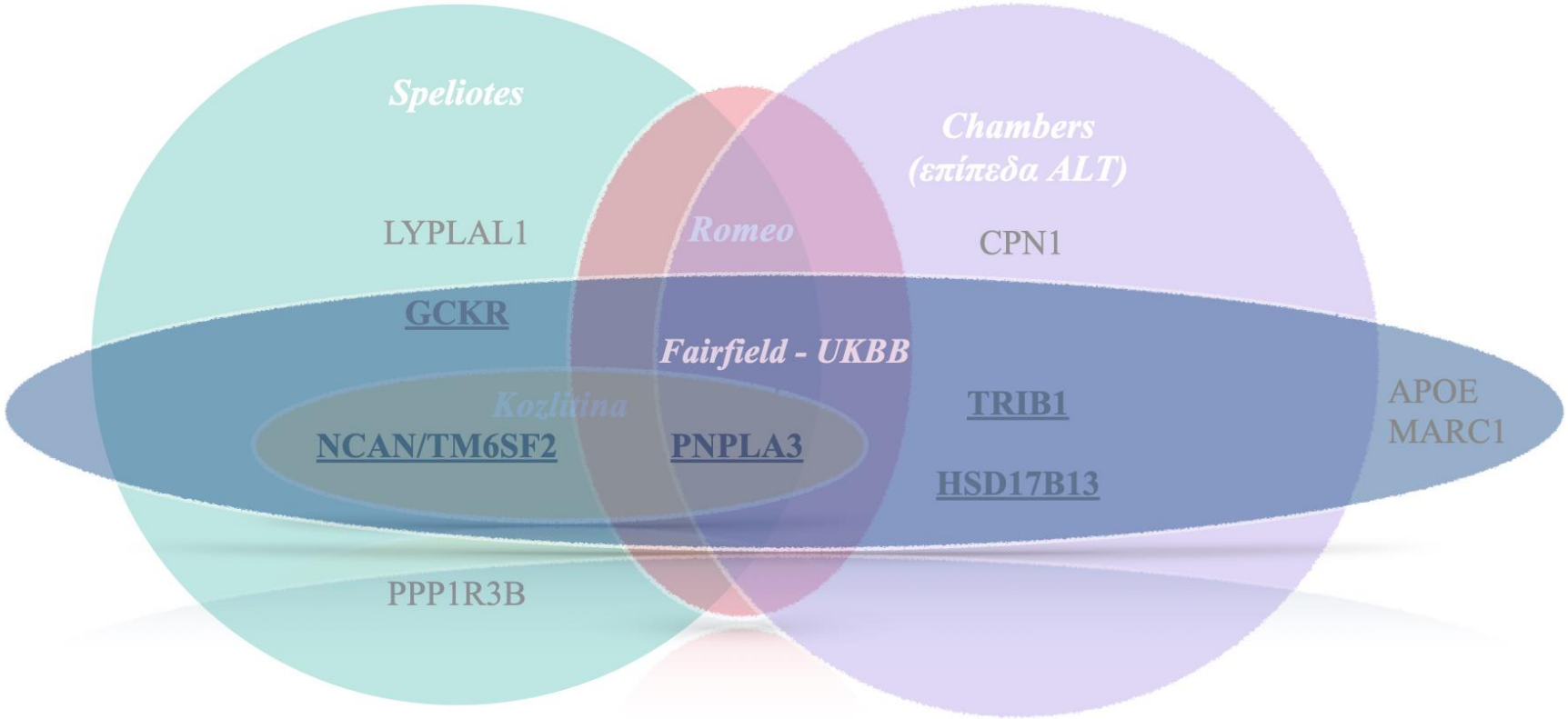
Beyond Big Data to new Biomedical and Health Data Science: moving to next century precision health

RESEARCH ARTICLE Open Access

GWAS and enrichment analyses of non-alcoholic fatty liver disease identify new trait-associated genes and pathways across eMERGE Network

Bahram Namjou[1,2*], Todd Lingren[2,3], Yongbo Huang[1], Sreeja Parameswaran[1], Beth L. Cobb[1], Ian B. Stanaway[4], John J. Connolly[5], Frank D. Mentch[5], Barbara Benoit[6], Xinnan Niu[7], Wei-Qi Wei[7], Robert J. Carroll[7], Jennifer A. Pacheco[8], Isaac T. W. Harley[9], Senad Divanovic[9], David S. Carrell[10], Eric B. Larson[10], David J. Carey[11], Shefali Verma[12], Marylyn D. Ritchie[12], Ali G. Gharavi[13], Shawn Murphy[14], Marc S. Williams[15], David R. Crosslin[4], Gail P. Jarvik[16], Iftikhar J. Kullo[17], Hakon Hakonarson[5,18], Rongling Li[19], The eMERGE Network[19], Stavra A. Xanthakos[20] and John B. Harley[1,2,21]

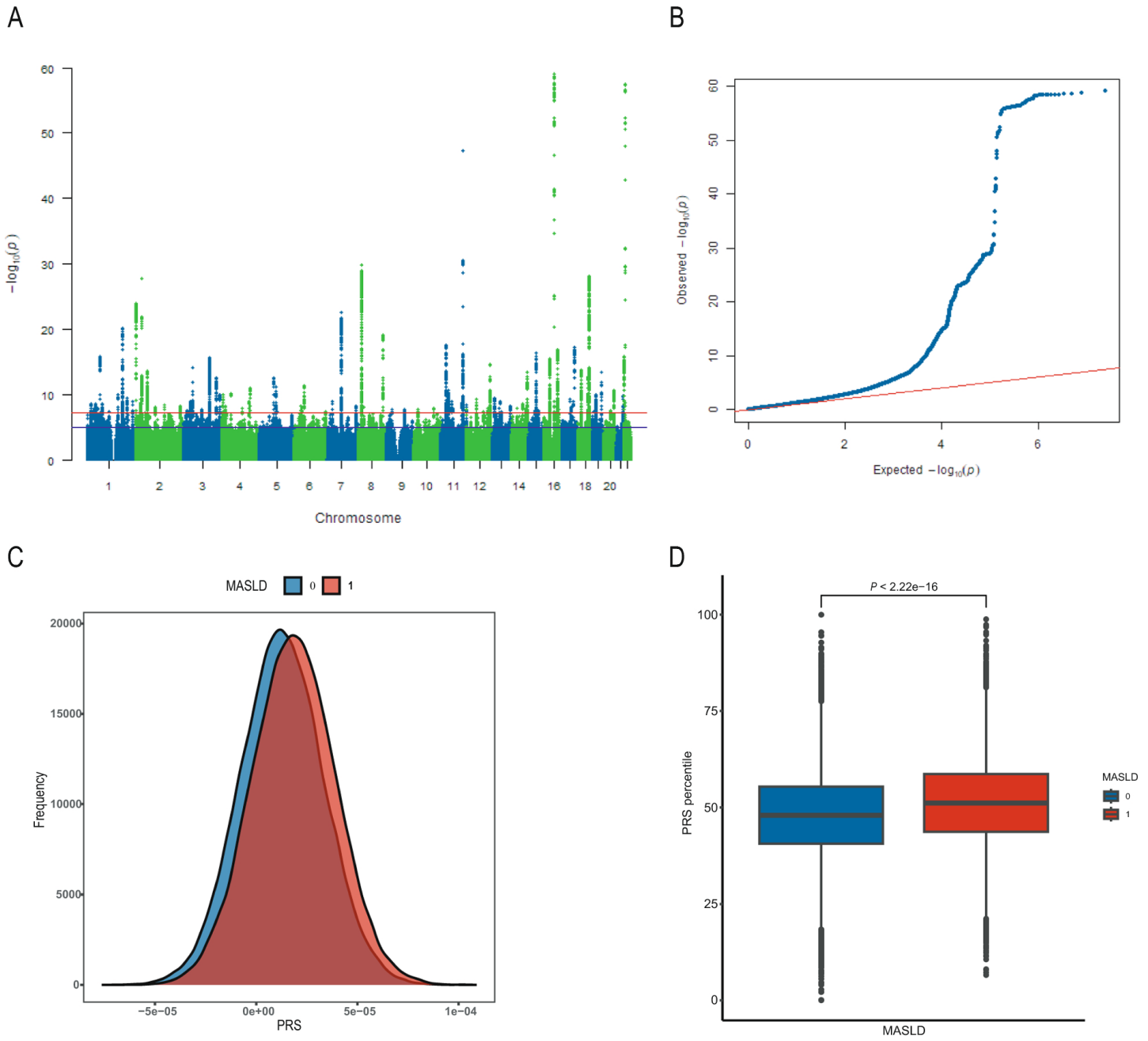




Αποτελέσματα από UKBB

MASLD-PRS από την UKBB

Ισχυρή συσχέτιση και με ΣΔ2

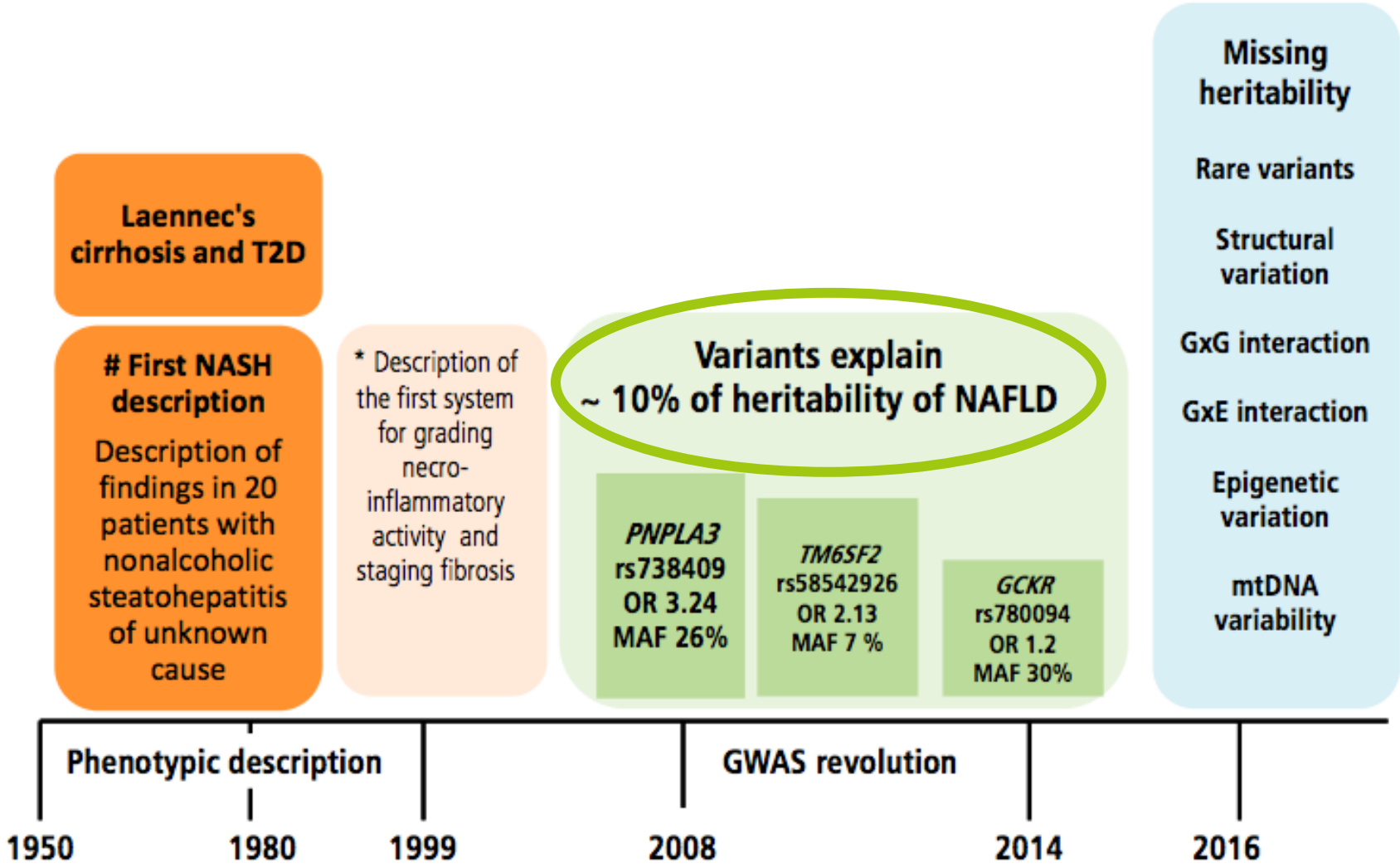


J Transl Med. 2024 Jul 12;22(1):650. doi: 10.1186/s12967-024-05478-z.

Polygenic risk score of metabolic dysfunction-associated steatotic liver disease amplifies the health impact on severe liver disease and metabolism-related outcomes

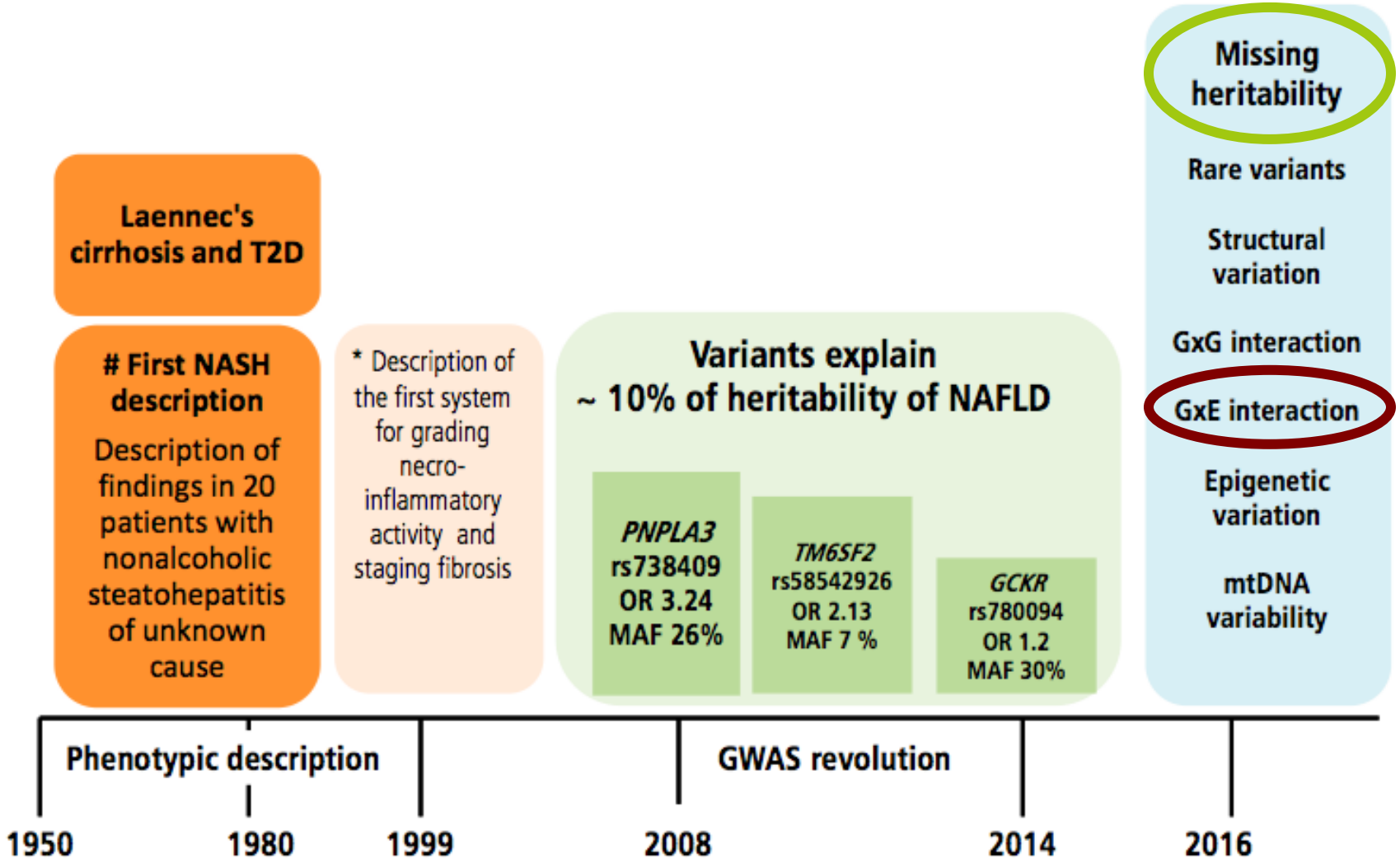
Lushan Xiao [# 1 2], Yan Li [# 2], Chang Hong [# 2], Pengcheng Ma [# 3], Hongbo Zhu [# 4], Hao Cui [2], Xuejing Zou [2], Jiaren Wang [2], Ruining Li [2], Jingzhe He [2], Shengxing Liang [5], Zeyang Li [6], Lin Zeng [7], Li Liu [8 9]

Τι γνωρίζαμε μέχρι χθες...



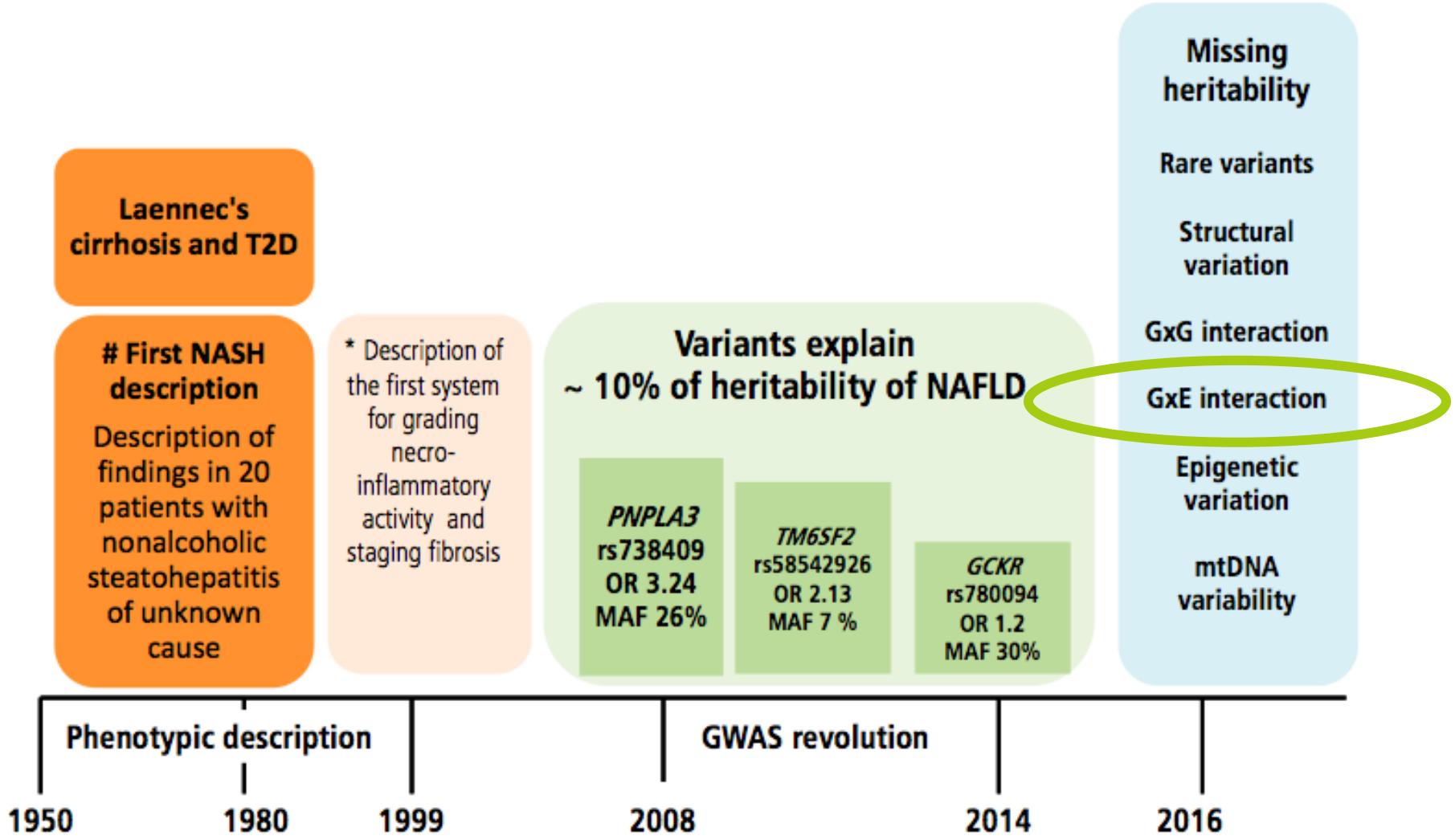
Sookoian et al, 2017

Τι γνωρίζουμε σήμερα...

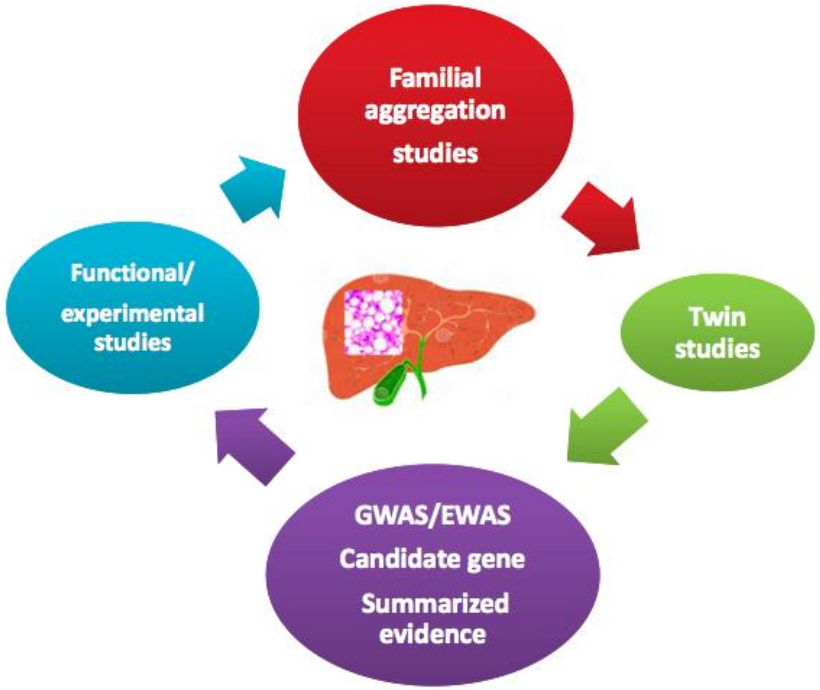


Sookoian et al, 2017

Τι γνωρίζαμε μέχρι χθες...



Sookoian et al, 2017



NAFLD assessed by abdominal CT-scan in population-based studies

GIANT, MAGIC, GOLD Consortiums Population-based study Sample size: 6629 European ancestry **Heritability: ~ 27 %**	IRAS Family Study Population-based study Sample size: 1142 Hispanics and African Americans **Heritability: ~ 31 %**	JHS, ARIC , GENOA, FamHS , IRASFS -Study Population-based study Sample size: 3973 Hispanics and African Americans **Heritability: ~ 22-34 %**
Speliotes et al. 2011	*Wagenknecht et al. 2009*	*Palmer et al. 2013*

NAFLD assessed by liver biopsy, MRS or liver US in family-based or twin-studies

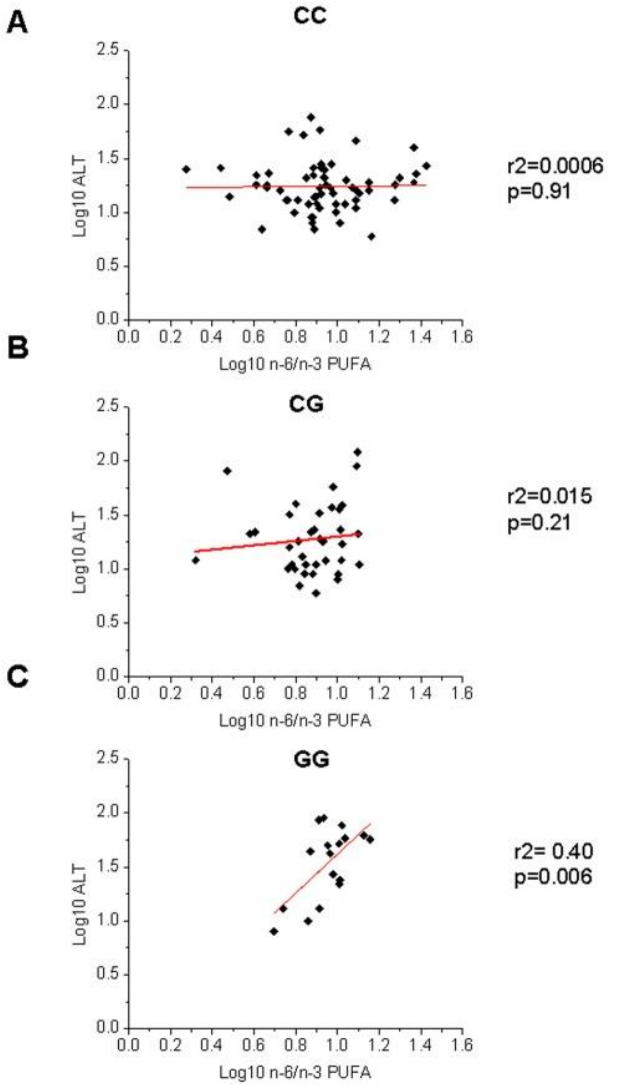
Familial aggregation study. Hospital-based Sample size: Probands: 11 controls/ 33 NAFLD. Siblings: 12 controls/29 NAFLD and parents: 19 controls/55 NAFLD. Probands: liver biopsy **Heritability: ~ 38 %**	The Genetics of NAFLD in Twins Consortium Hospital-based Sample size: 60 pairs of twins (42 monozygotic and 18 dizygotic). MRI-PDFF/ MRE Ethnicity: mixed **Heritability: ~ 50 %**	Twin-study Hospital-based Sample size: 208 adult Hungarian twins (63 monozygotic and 41 dizygotic pairs). NAFLD: liver US **Shared and unshared environmental effects 74.2% and 25.8%**
Schwimmer *et al. 2009*	*Loomba et al. 2015*	*Tarnoki et al. 2012*

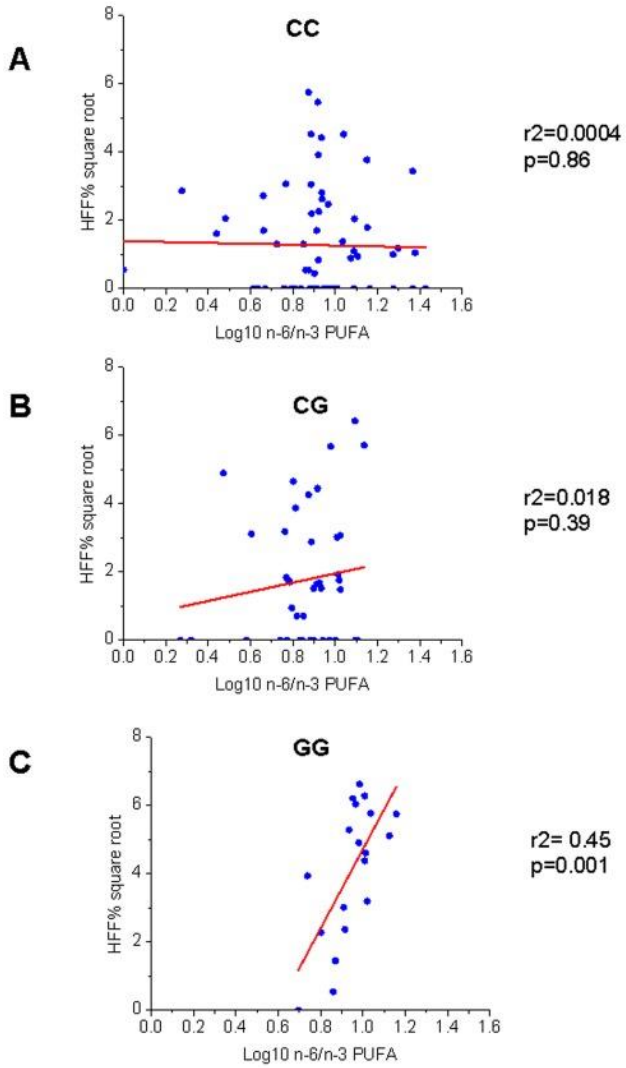
Σε τι ποσοστό συμμετέχει η γενετική αιτιολογία;

Sookoian et al, 2017

Αλληλεπιδράσεις γονιδίων - διατροφής

PNPLA3 * ω-6/ω-3 ~ ALT, ενδοηπατικό λίπος





- παιδιά & έφηβοι με παχυσαρκία
- Διαφόρων εθνικοτήτων

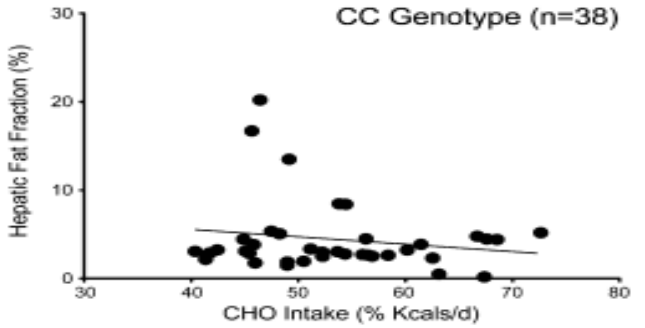
Παρατηρήθηκαν στατιστικά σημαντικές αλληλεπιδράσεις ΜΟΝΟ στους ομόζυγους για το αλληλομορφο κινδυνου

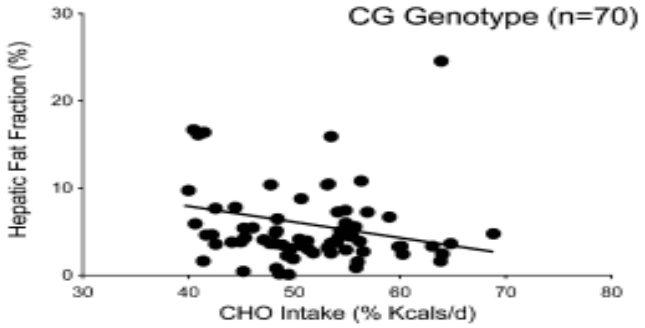
APA

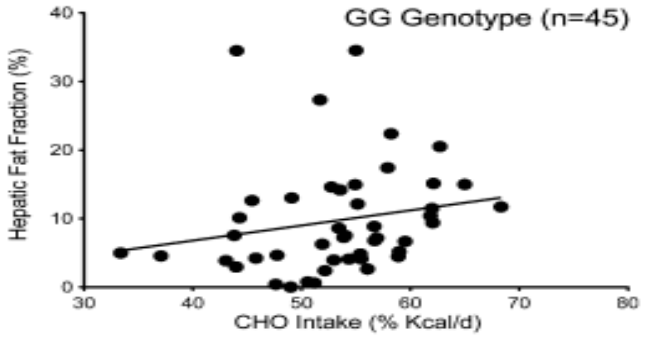
Η τροποποίηση του λόγου ω-6/ω-3 φαίνεται ότι είναι πιο ωφέλιμη για κάποιους!

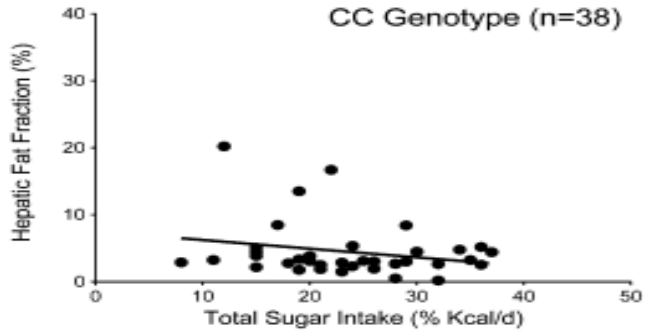
Santoro et al., 2012

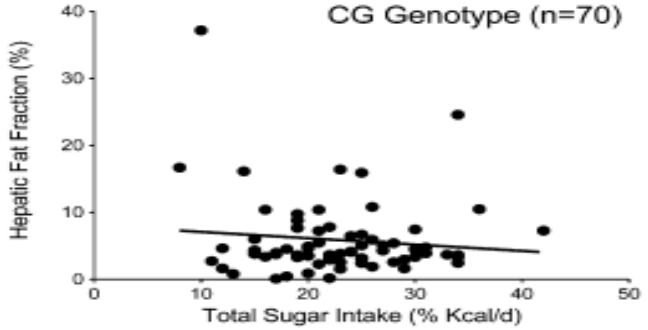
PNPLA3 * CHO ~ ενδοηπατικό λίπος

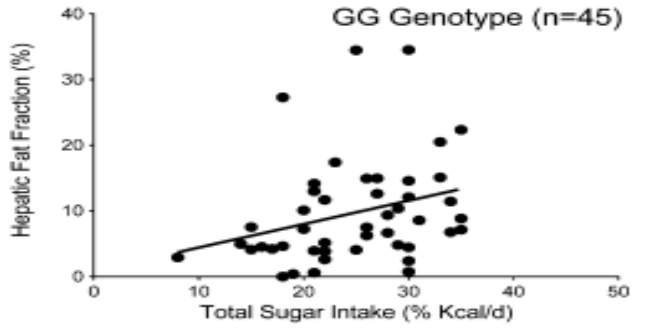












- παιδιά & έφηβοι με παχυσαρκία
- Ισπανοί

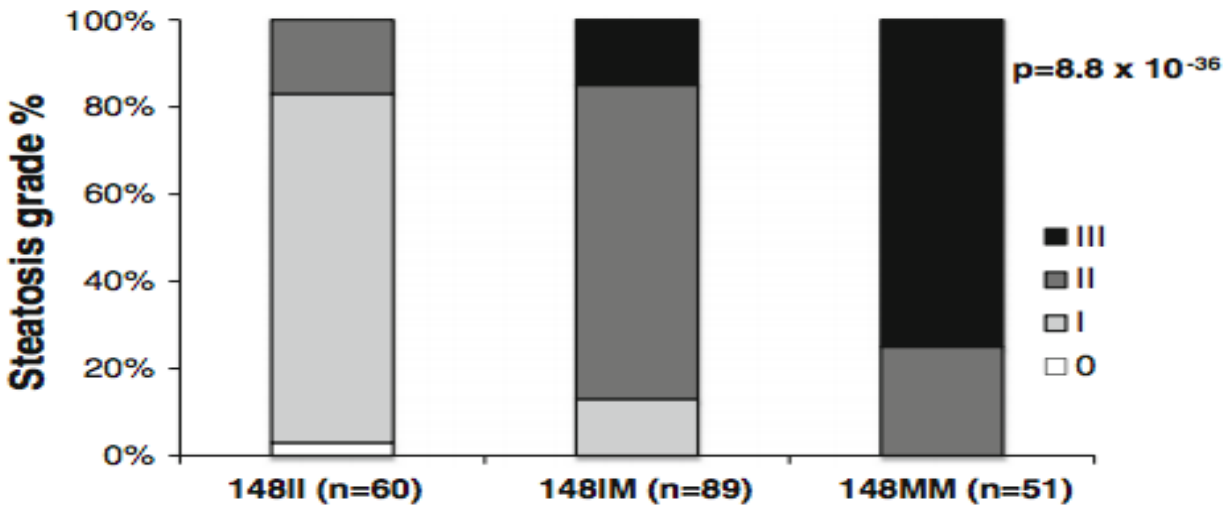
Παρατηρήθηκαν στατιστικά σημαντικές αλληλεπιδράσεις ΜΟΝΟ στους ομόζυγους για το αλληλομορφο κινδυνου

APA

Η τροποποίηση του % προσλαμβανόμενων CHO/απλών σακχάρων φαίνεται ότι είναι πιο ωφέλιμη για κάποιους!

Davis et al., 2010

PNPLA3 * ομάδες τροφίμων~ ηπατική στεάτωση



Η επίδραση του rs738409 στην παρουσία προχωρημένου σταδίου NAFLD φάνηκε να αυξάνεται στατιστικά σημαντικά όταν η κατανάλωση σακχαρούχων αναψυκτικών είναι τουλάχιστον 1 την εβδομάδα σε σύγκριση με τη μη κατανάλωση.

Η επίδραση του rs738409 στην παρουσία προχωρημένου σταδίου NAFLD φάνηκε να μειώνεται στατιστικά σημαντικά όταν η δίαιτα των εθελοντών ήταν φτωχή σε λαχανικά.

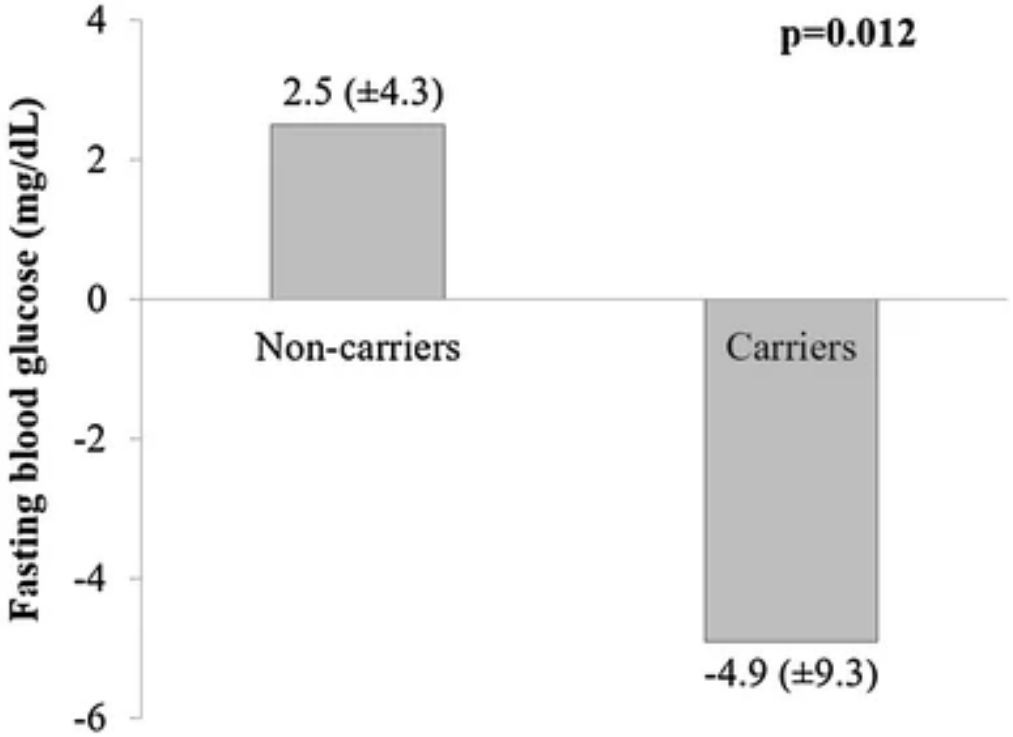
- 200 υπέρβαρα παιδιά & έφηβοι
- Η συντριπτική πλειοψηφία διεγνώσθη με ήπια έως σοβαρή NAFLD .
- Καλές διατροφικές συνήθειες στο σύνολο

	Estimate	SE	*p* value
Age (years)	+0.21	0.08	1.7×10^{-2}
WC centile	+0.15	0.06	1.6×10^{-2}
I148M alleles	+4.32	0.50	2.0×10^{-18}
Physical exercise hours	−1.78	0.61	3.4×10^{-3}
I148M × sodas	+0.76	0.35	2.3×10^{-2}
I148M × vegetables	−1.31	0.62	3.4×10^{-2}

WC waist circumference

Nobili et al., 2014

GCKR * απόκριση στη διατροφική συμβουλευτική ~ FGlu, oxLDL



- 44 υπέρβαροι/παχύσαρκοι ασθενείς με NAFLD
- Διατροφική καθοδήγηση
- 6 μήνες

- Βελτίωση ανθρωπομετρικών χαρακτηριστικών, ηπατικής απεικόνισης και ίνωσης σε όλους

Ωστόσο...

- Οι φορείς του αλληλομόρφου κινδύνου εμφάνισαν καλύτερη απόκριση στην παρέμβαση ως προς τη γλυκόζη νηστείας και λιγότερη καλή ως προς την oxLDL.

	beta	SE	p-value
FGlu (mg/dL)	-6.107	2.934	**0.044**
oxLDL (U/L)	30.048	11.335	**0.012**

Kaliora et al., 2017

GCKR * Μεσογειακή Διατροφή ~ TGs

	Combined effect (*GCKR* dominant + *GCK* recessive)								
	PP + AA (*n* 12)		PP + (GA + AA) (*n* 253)		(PL + LL) + AA (*n* 608)		(PP + LL) + (GG + GA) (*n* 14)		
	Mean	SE	Mean	SE	Mean	SE	Mean	SE	*P* for joint effect
TAG (mmol/l)									
Crude									0·012
Mean	1·12		1·33		1·35		1·53		
SD	0·49		0·58		0·72		0·90		
Model 1†	1·06	0·24	1·35	0·05	1·27	0·22	1·53	0·03	0·010
Model 2‡	1·11	0·27	1·36	0·06	1·21	0·24	1·52	0·04	0·033
Glucose (mmol/l)									
Crude									0·799
Mean	7·19		6·75		7·20		6·78		
SD	1·69		2·05		2·13		2·16		
Model 1†	7·32	0·64	6·73	0·14	7·05	0·59	6·78	0·09	0·784
Model 2‡	6·49	0·58	6·73	0·12	5·74	0·56	6·77	0·08	0·311

* *P* value for comparisons between genotypes and TAG concentrations. *P* value for log TAG.
† Adjusted for age, sex and BMI.
‡ Model 1+smoking + diabetes + lipid medication.

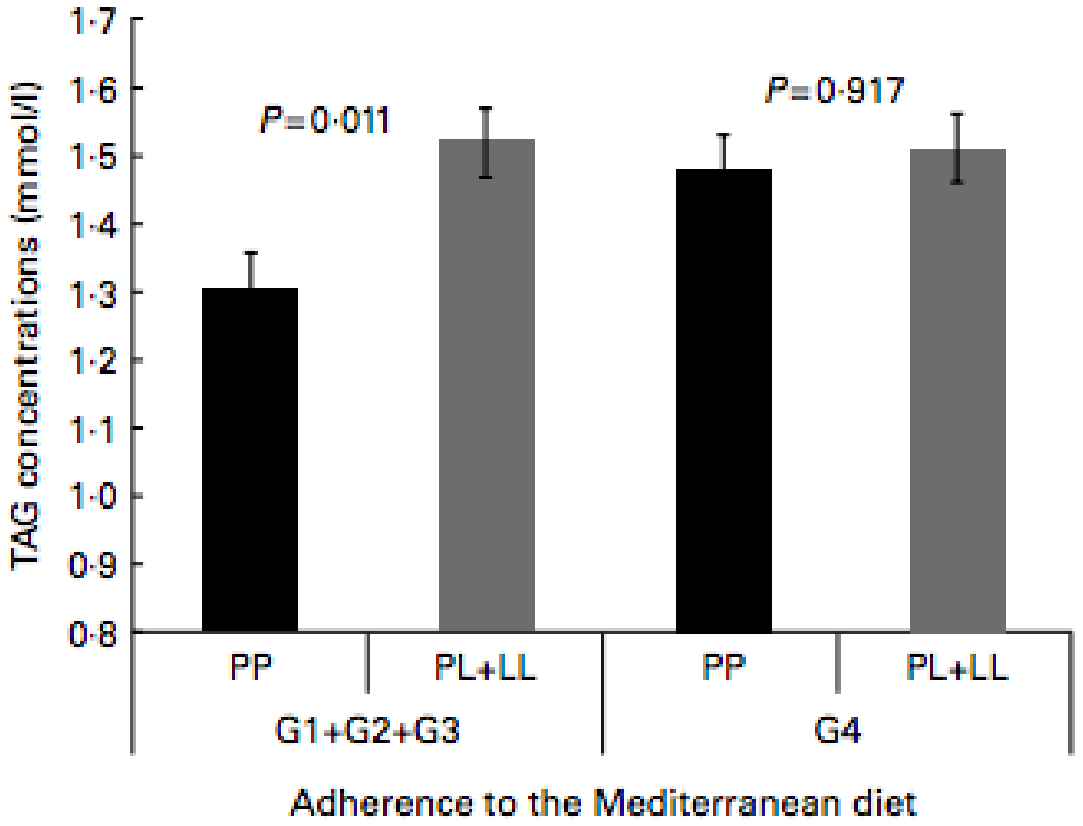
- 945 εθελοντές
- Υψηλού κινδύνου για CVD
- Μο ηλικίας 67 έτη

- Τα επίπεδα TGs ορού φάνηκε ότι συσχετίζονται θετικά (στατιστικά σημαντικά) τόσο ξεχωριστά όσο και συνδυαστικά με την παρουσία rs1799884 & rs1260326.
- Καμία συσχέτιση δε βρέθηκε με τα επίπεδα Glu.

Sotos – Prieto et al., 2013

GCKR * Μεσογειακή Διατροφή ~ TGs

- Μελετήθηκε η προσκόλληση στη Μεσογειακή διατροφή ανά γονότυπο, ανεξάρτητα από ηλικία, φύλο, ΔΜΣ, κάπνισμα, παρουσία ΣΔ και αγωγή για υπερλιπιδαιμία.
- Βρέθηκαν στατιστικά σημαντικά υψηλότερα επίπεδα TGs στους φορείς του GCKR πολυμορφισμού σε σχέση με τους μη φορείς, όταν η προσκόλληση στη ΜΔ ήταν χαμηλή έως μέτρια.
- Στην υψηλότερη προσκόλληση, η επίδραση του γονοτύπου «εξαφανίστηκε»!
- Η μελέτη της αλληλεπίδρασης δε βρέθηκε στατιστικά σημαντική.



Sotos – Prieto et al., 2013

GCKR * Μεσογειακή Διατροφή ~ TGs

	PP		PL + LL			
	Mean	SE	Mean	SE	*P* for joint effects*	*P* food item*
Olive oil (tbs/d)						
< 4	1·44	0·08	1·63	0·07	0·035	0·116
≥ 4	1·30	0·06	1·49	0·04		
Vegetables (servings/d)†						
< 2	1·40	0·07	1·59	0·05	0·012	0·022
≥ 2	1·29	0·06	1·47	0·04		
Fruit (including natural fruit juice, servings/d)‡						
< 3	1·33	0·06	1·51	0·05	0·084	0·931
≥ 3	1·34	0·06	1·52	0·05		
Red meat (hamburgers or meat products, servings/d)§						
≥ 1	1·24	0·09	1·41	0·08	0·017	0·035
< 1	1·36	0·06	1·54	0·04		
Butter, margarine or cream (servings/d)‖						
≥ 1	1·20	0·11	1·38	0·10	0·039	0·145
< 1	1·35	0·06	1·53	0·04		
Sweetened carbonated beverages (servings/d)¶						
≥ 1	1·28	0·10	1·47	0·09	0·036	0·896
< 1	1·34	0·06	1·53	0·04		
Wine (servings/week)**						
< 7	1·32	0·06	1·42	0·01	0·051	0·230
≥ 7	1·42	0·09	1·60	0·08		
Legumes (servings/week)††						
< 3	1·33	0·06	1·52	0·04	0·116	0·703
≥ 3	1·34	0·06	1·53	0·06		
Fish/shellfish (servings/week)‡‡						
< 3	1·32	0·06	1·50	0·05	0·104	0·541
≥ 3	1·35	0·06	1·53	0·05		
Sweets or pastries (servings/week)§§						
< 2	1·34	0·07	1·52	0·06	0·101	0·476
≥ 2	1·33	0·06	1·52	0·04		
Nuts (servings/week)‖‖						
< 3	1·31	0·06	1·50	0·04	0·038	0·314
≥ 3	1·38	0·07	1·57	0·06		
Consumption preferentially of chicken, rabbit or turkey instead of veal, pork, hamburger, sausage¶¶						
No	1·27	0·08	1·45	0·06	0·099	0·480
Yes	1·35	0·06	1·54	0·04		
Vegetables, pasta, rice with sofritos (servings/week)***						
< 2	1·32	0·06	1·51	0·05	0·088	0·693
≥ 2	1·34	0·06	1·52	0·04		

- Μελετήθηκε επιπλέον η επίδραση των επιμέρους τροφίμων της ΜΔ & η αλληλεπίδρασή τους με τον πολυμορφισμό του GCKR ως προς τα επίπεδα TGs.

Sotos – Prieto et al., 2013

GCKR * Μεσογειακή Διατροφή ~ TGs

	PP		PL + LL			
	Mean	SE	Mean	SE	*P* for joint effects*	*P* food item*
Olive oil (tbs/d)						
<4	1·44	0·08	1·63	0·07	0·035	0·116
≥4	1·30	0·06	1·49	0·04		
Vegetables (servings/d)†						
<2	1·40	0·07	1·59	0·05	0·012	0·022
≥2	1·29	0·06	1·47	0·04		
Fruit (including natural fruit juice, servings/d)‡						
<3	1·33	0·06	1·51	0·05	0·084	0·931
≥3	1·34	0·06	1·52	0·05		
Red meat (hamburgers or meat products, servings/d)§						
≥1	1·24	0·09	1·41	0·08	0·017	0·035
<1	1·36	0·06	1·54	0·04		
Butter, margarine or cream (servings/d)‖						
≥1	1·20	0·11	1·38	0·10	0·039	0·145
<1	1·35	0·06	1·53	0·04		
Sweetened carbonated beverages (servings/d)¶						
≥1	1·28	0·10	1·47	0·09	0·036	0·896
<1	1·34	0·06	1·53	0·04		
Wine (servings/week)**						
<7	1·32	0·06	1·42	0·01	0·051	0·230
≥7	1·42	0·09	1·60	0·08		
Legumes (servings/week)††						
<3	1·33	0·06	1·52	0·04	0·116	0·703
≥3	1·34	0·06	1·53	0·06		
Fish/shellfish (servings/week)‡‡						
<3	1·32	0·06	1·50	0·05	0·104	0·541
≥3	1·35	0·06	1·53	0·05		
Sweets or pastries (servings/week)§§						
<2	1·34	0·07	1·52	0·06	0·101	0·476
≥2	1·33	0·06	1·52	0·04		
Nuts (servings/week)‖‖						
<3	1·31	0·06	1·50	0·04	0·038	0·314
≥3	1·38	0·07	1·57	0·06		
Consumption preferentially of chicken, rabbit or turkey instead of veal, pork, hamburger, sausage¶¶						
No	1·27	0·08	1·45	0·06	0·099	0·480
Yes	1·35	0·06	1·54	0·04		
Vegetables, pasta, rice with sofritos (servings/week)***						
<2	1·32	0·06	1·51	0·05	0·088	0·693
≥2	1·34	0·06	1·52	0·04		

- Μελετήθηκε επιπλέον η επίδραση των επιμέρους τροφίμων της ΜΔ & η αλληλεπίδρασή τους με τον πολυμορφισμό του GCKR ως προς τα επίπεδα TGs.

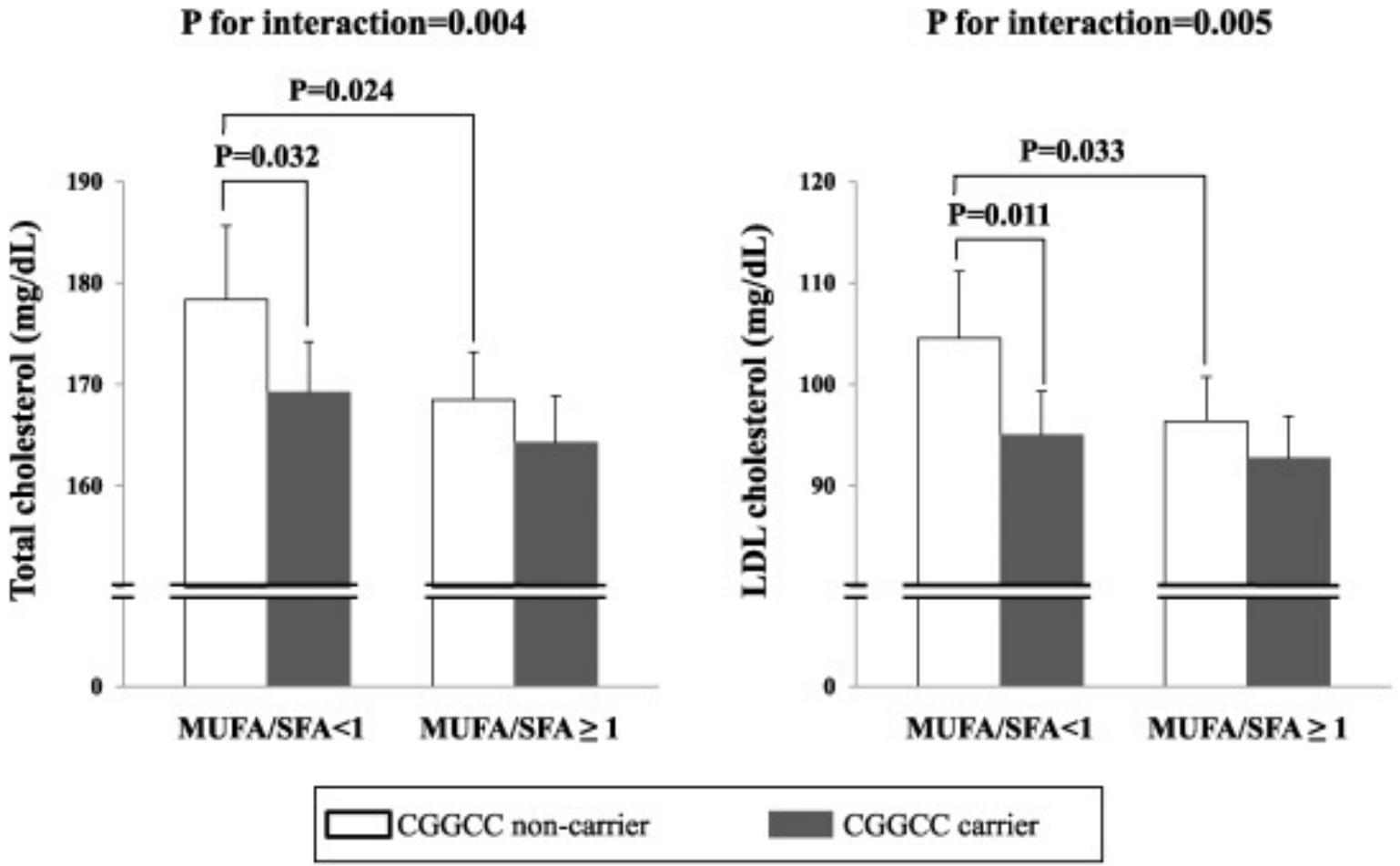
- Οι φορείς τουλάχιστον 1 αλληλομόρφου κινδύνου σε σύγκριση με τους μη φορείς εμφανίζουν χαμηλότερα επίπεδα TGs όταν η κατανάλωση ελαιολάδου είναι >=4κ.σ. ημερησίως, ανεξάρτητα από ηλικία, φύλο, ΔΜΣ, κάπνισμα, παρουσία ΣΔ και αγωγή για υπερλιπιδαιμία, με p-value=0.035.
- Ομοίως και για άλλες ομάδες τροφίμων.
- Η μελέτη των αλληλεπιδράσεων δε βρέθηκε στατιστικά σημαντική.

Sotos – Prieto et al., 2013

GCKR * MUFAs/SFAs ~ λιπίδια ορού

- Γονοτυπήθηκε DNA 711 παιδιών για GCKR πολυμορφισμούς.

- Βρέθηκε στατιστικά σημαντική αρνητική συσχέτιση του υπολειπόμενου αλληλομόρφου του GCKR με τα επίπεδα TC και LDL.
- Παρατηρήθηκε στατιστικά σημαντική αλληλεπίδραση μεταξύ της διχοτομημένης πρόσληψης του λόγου MUFAs/SFAs και των GCKR variant ως προς την TC & LDL & TGs.



Lee et al., 2015

PNPLA3 & TM6SF2 * υποθερμιδική δίαιτα

Feature	*PNPLA3* p.148II (n = 45)		*PNPLA3* p.148IM (n = 27)		*PNPLA3* p.148MM (n = 16)		p value [II] vs. [IM] vs. [MM]
	Δ	p value	Δ	p value	Δ	p value	
ALT, U/l	8.0	0.05	20.0	0.001	9.6	NS	NS
AST, U/l	0.4	NS	3.3	NS	2.7	NS	NS
GGT, U/l	−59	NS	3.2	NS	24.4	NS	NS
Hamaguchi score	1.0	<0.0001	1.0	<0.0001	0.7	0.0005	NS
BMI, kg/m^2	1.7	<0.0001	2.5	<0.0001	1.9	<0.0001	NS
Body mass, kg	4.9	<0.0001	6.8	0.003	6.0	<0.0001	NS
Hip circumference, cm	3.4	<0.0001	3.8	0.0016	1.6	NS	NS
Waist circumference, cm	5.5	<0.0001	5.3	0.0002	8.1	<0.0001	NS
WHR	0.02	0.009	0.02	NS	0.06	<0.0001	0.02
HOMA-IR	3.1	NS	1.3	NS	1.9	NS	NS
HDL cholesterol, mg/dl	−0.8	NS	−3.0	0.045	−3.2	NS	NS
LDL cholesterol, mg/dl	2.0	NS	1.6	NS	−8.7	NS	NS
Total cholesterol, mg/dl	1.5	NS	0.2	NS	1.1	NS	NS
Triglycerides, mg/dl	0.1	NS	5.0	NS	−23.8	NS	NS
Total lipids, mg/dl	3.1	NS	4.6	NS	−21.3	NS	NS

Δ – mean difference, calculated as: value at entry – value after diet.
M = Methionine; NS = not significant; p = protein (amino acid number).

- 143 ασθενείς με NAFLD vs 180 μάρτυρες.
- 4μηνη διατροφική παρέμβαση: υποθερμιδική δίαιτα, διατήρηση ΦΔ.
- 88 ασθενείς ολοκλήρωσαν την παρέμβαση.

- Παρατηρήθηκε βελτίωση ανθρωπομετρικών δεικτών και ηπατικής στεάτωσης, ανεξάρτητα από τους γονότυπους, εκτός από το WHR.

Krawczyk et al., 2016

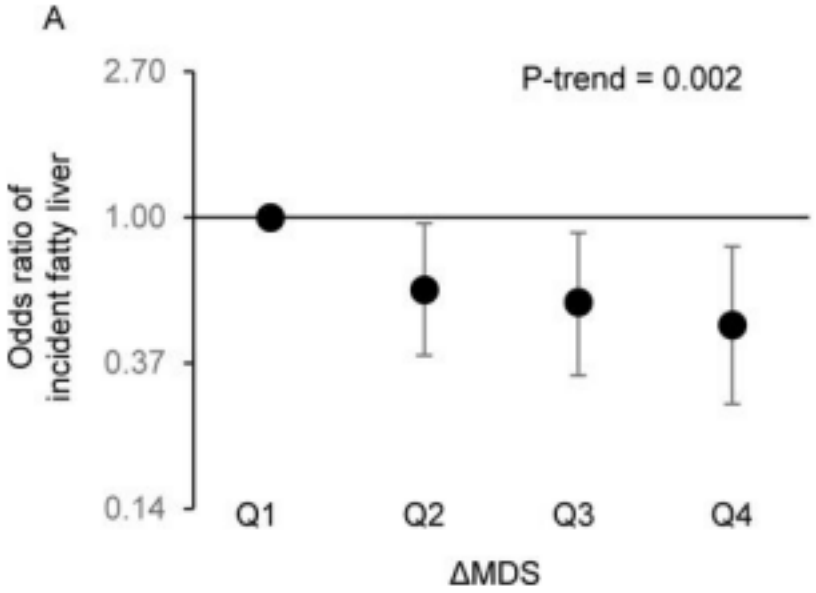
Αλληλεπιδράσεις άλλων γονιδίων

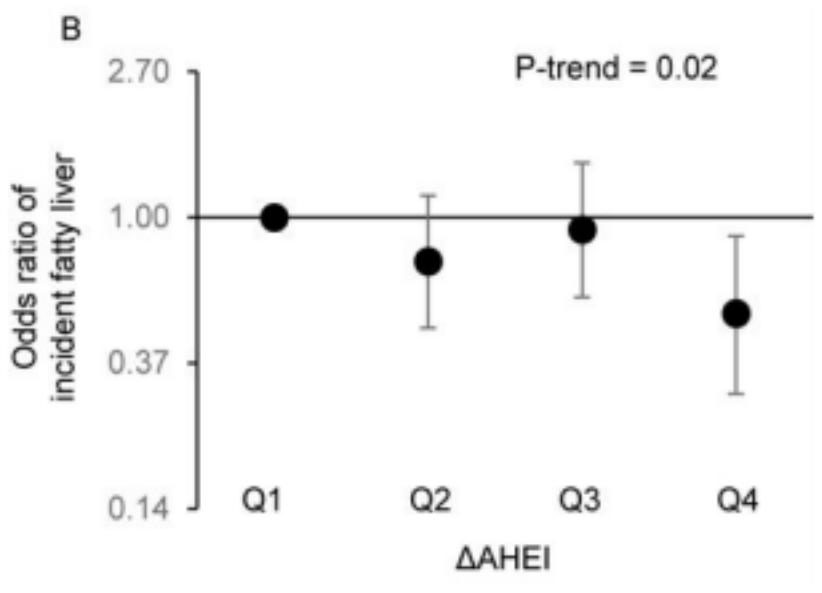
	Alcohol intake		Fruit intake		Grilled meat or fish intake	
	Never drinkers	Males: <30 g Females: <20 g	0–2/day	>2/day	0–1/week	>1/week
GSTM1						
Present	1.00	0.56 [0.29; 1.07]	1.00	3.06 [1.60; 5.84]	1.00	1.83 [0.96; 3.46]
Null	0.89 [0.48; 1.66]	0.56 [0.29; 1.07] $p^b = 0.081$	0.77 [0.41; 1.45]	3.55 [1.88; 6.68] $p < 0.001$	0.68 [0.34; 1.36]	2.18 [1.18; 4.03] $p = 0.013$
GSTT1						
Present	1.00	0.59 [0.35; 1.01]	1.00	4.23 [2.46; 7.29]	1.00	2.65 [1.54; 4.58]
Null	1.47 [0.71; 3.06]	0.85 [0.41; 1.76] $p = 0.655$	1.83 [0.89; 3.76] [−0.829; 0.732]	4.82 [2.26;10.32] $p < 0.001$	1.82 [0.82; 4.03] [−0.856;0.726]	3.26 [1.57; 6.79] $p = 0.002$
CYP1A1						
*CYP1A1*1/*1*	1.00	0.55 [0.32; 0.94]	1.00	3.06 [1.80; 5.20]	1.00	2.37 [1.39; 4.04]
*CYP1A1*2A carriers*	0.92 [0.43; 1.99]	0.70 [0.34; 1.43] $p = 0.326$	0.72 [0.34; 1.53]	5.17 [2.37;11.27] $p < 0.001$	1.10 [0.48; 2.51] [−0.686; 0.779]	2.59 [1.25; 5.36] $p = 0.011$
$CYP2E1_{PstI}$						
*CYP2E1*1A/1A*	1.00	0.62 [0.38; 1.00]	1.00	3.82 [2.34; 6.25]	1.00	2.23 [1.37; 3.62]
*CYP2E1*5B carriers*	0.92 [0.28; 3.08]	0.25 [0.06; 0.98] $p = 0.046$	0.68 [0.18; 2.58]	2.31 [0.71; 7.47] $p = 0.163$	0.41 [0.10; 1.71]	1.93 [0.59; 6.28] $p = 0.273$
$CYP2E1_{DraI}$						
*CYP2E1*1A/1A*	1.00	0.56 [0.34; 0.92]	1.00	3.53 [2.14; 5.82]	1.00	2.38 [1.45; 3.91]
*CYP2E1*6 carriers*	1.09 [0.36; 3.32]	0.92 [0.22; 3.80] $p = 0.911$	0.52 [0.13; 2.05]	11.34 [2.70;47.55] $p = 0.001$	2.32 [0.37; 14.67] [−2.547; 1.682]	2.58 [0.95; 7.04] $p = 0.063$
SULT1A1						
*SULT1A1*1/*1*	1.00	0.55 [0.30; 1.01]	1.00	4.05 [2.17; 7.53]	1.00	2.07 [1.12; 3.83]
*SULT1A1*2carriers*	1.04 [0.56; 1.94]	0.71 [0.36; 1.38] $p = 0.314$	1.28 [0.68; 2.42] [−0.697; 0.624]	4.18 [2.20; 7.94] $p < 0.001$	0.97 [0.48; 1.95]	2.69 [1.42; 5.10] $p = 0.002$

- 294 ασθενείς με NAFLD, 359 μάρτυρες
- Μελετήθηκαν και βρέθηκαν σημαντικές αλληλεπιδράσεις διατροφής με γονίδια που εμπλέκονται στα μονοπάτια οξειδωτικού στρες.

Miele et al, 2014

Αλληλεπιδράσεις με GRS

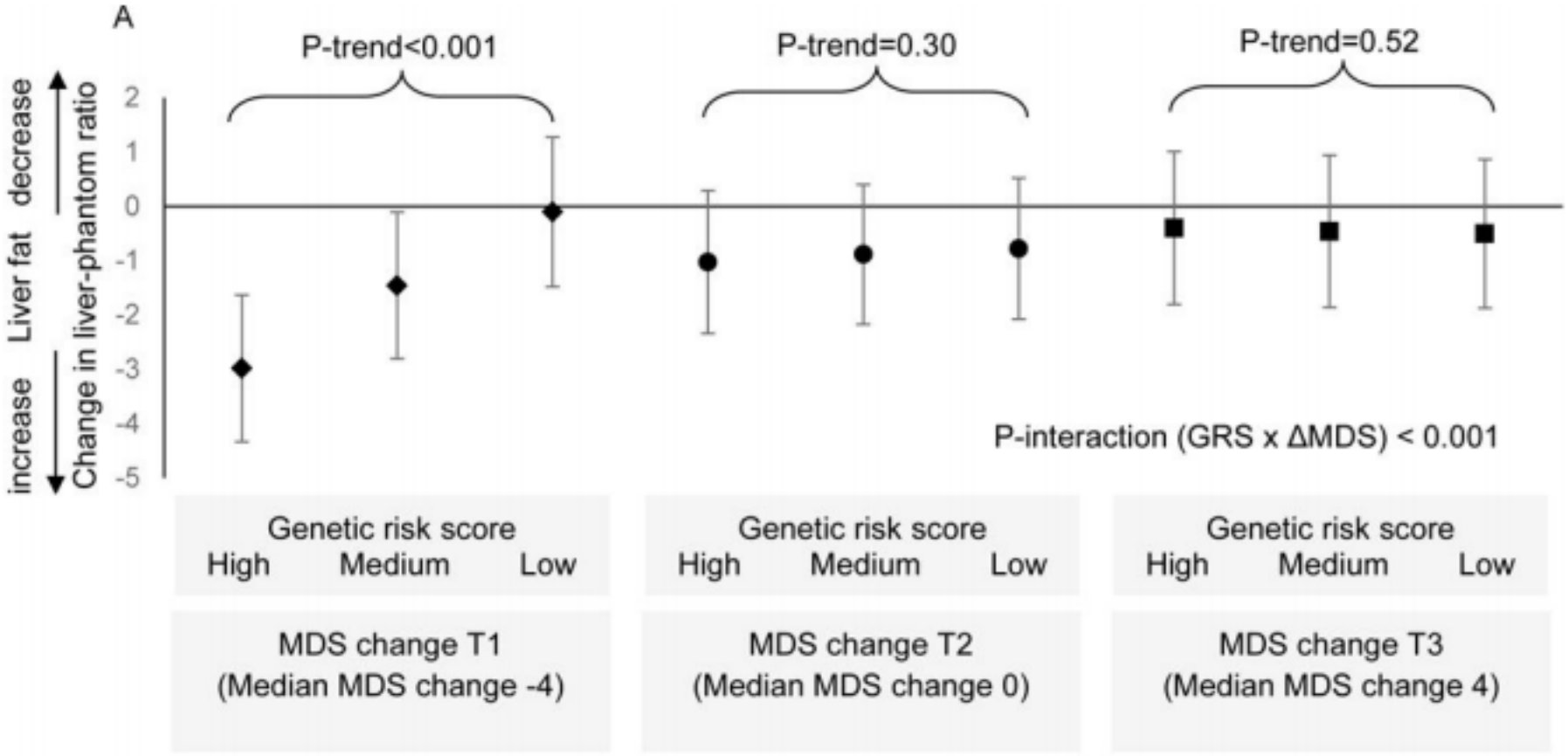




- Προοπτική μελέτη
- 1521 εθελοντες
- Μελετήθηκαν αλληλεπιδράσεις διατροφής με γενετικά και τη διαφορά σε διατροφικά σκορς

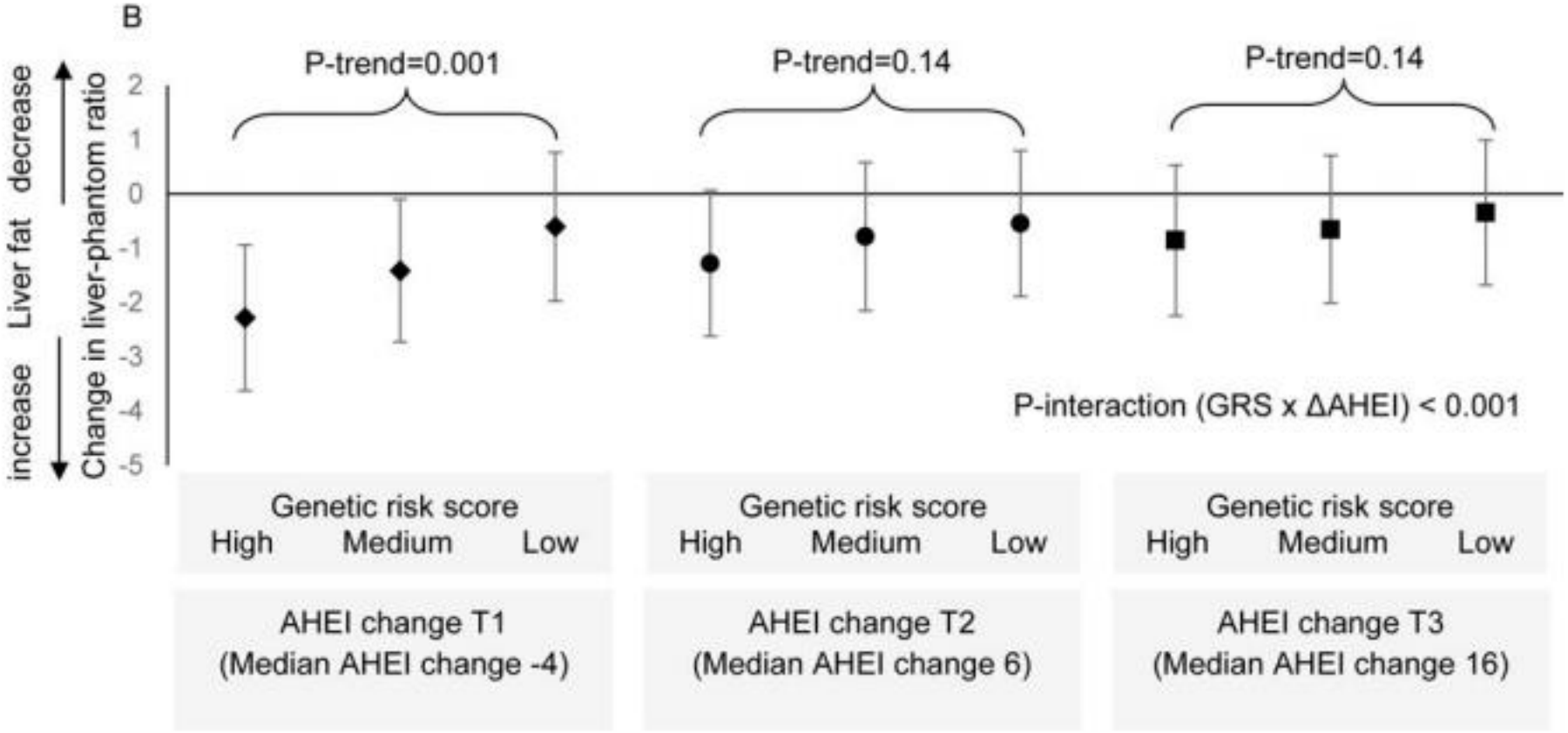
- Τα διατροφικά σκορς MDS & AHDI συσχετίστηκαν αρνητικά με την πιθανότητα εμφάνισης ηπατικής στεάτωσης.

Ma et al, 2018



- Παρατηρήθηκε στατιστικά σημαντική αλληλεπίδραση του GRS με την αλλαγή στο MDS
- MONO στην ομάδα με αρνητική ΔMDS παρατηρήθηκε η γενετική επίδραση στο ηπατικό λίπος.

Ma et al, 2018



- Παρατηρήθηκε στατιστικά σημαντική αλληλεπίδραση του GRS με την αλλαγή στο AHEI
- ΜΟΝΟ στην ομάδα με αρνητική ΔAHEI παρατηρήθηκε γενετική επίδραση στο ηπατικό λίπος.

Ma et al, 2018

Αλληλεπιδράσεις γονιδίων – άλλων παραγόντων τρόπου ζωής

Wang et al. BMC Medical Genetics (2016) 17:90
DOI 10.1186/s12881-016-0352-9

BMC Medical Genetics

RESEARCH ARTICLE Open Access

Physical activity and sedentary behavior can modulate the effect of the *PNPLA3* variant on childhood NAFLD: a case-control study in a Chinese population

Shuo Wang[1,2], Jieyun Song[1], Xiaorui Shang[1,3], Nitesh Chawla[2], Yide Yang[1], Xiangrui Meng[1,4], Haijun Wang[1*] and Jun Ma[1*]

- Ασθενών-μαρτύρων
- 1027 παιδιά & έφηβοι
- Μελετήθηκαν αλληλεπιδράσεις της φυσικής δραστηριότητας/καθιστικών δραστηριοτήτων με το PNPLA3

Table 1 Demographic and behavioral characteristics of NAFLD and non-NAFLD children

	Total (n = 1027)	NAFLD (n = 162)	Controls (n = 865)	P	P'	OR
Age (years)	11.5 ± 2.9	11.8 ± 2.2	11.4 ± 3.0	0.060	·	·
Male (%)	574 (55.9)	115 (71.0)	459 (53.1)	<0.001	·	·
Body-mass index (kg/m^2)	21.7 ± 4.3	26.8 ± 3.8	20.7 ± 3.6	<0.001	·	·
Physical Activity (PA)						
PA ≥ 1 h/d	531 (51.7)	76 (46.9)	415 (48.0)	0.798	0.900	1.02 (0.71–1.48)
PA < 1 h/d	459 (44.7)	70 (43.2)	365 (42.2)			
Sedentary Behavior (SB)						
SB < 2 h/d	628 (61.1)	75 (46.3)	509 (58.8)	0.001	0.008	1.64 (1.14–2.36)
SB ≥ 2 h/d	362 (35.2)	71 (43.8)	271 (31.3)			

Data are presented by mean (SD) or number(percentage). P values were calculated by t-tests or Chi-square tests
OR and P' values were for PA or SB calculated in logistic regression models adjusted by age and gender. The models were constructed for PA or SB separately
NAFLD Non-Alcoholic Fatty Liver Disease, *PA* Physical Activity, *SB* Sedentary Behavior

Table 2 Interaction analyses of the *PNPLA3* rs738409 polymorphism and behavioral factors on childhood NAFLD

	Percentage of NAFLD children (number of NAFLD cases/number of the subgroup)						
	CC	GC	GG	ORa (95% CI)	P_a	ORb (95% CI)	P_b
Total	15.1 (60/398)	15.0 (74/492)	20.4 (28/137)	1.57 (1.15–2.16)	0.005		
Physical Activity (PA)							
PA ≥ 1 h/d	16.2 (31/191)	16.0 (38/237)	11.1 (7/63)	1.02 (0.63–1.66)	0.923	3.13 (1.57–6.24)	0.001
PA < 1 h/d	11.9 (19/160)	14.7 (31/211)	31.3 (20/64)	3.05 (1.82–5.12)	<0.001		
Sedentary Behavior (SB)							
SB < 2 h/d	14.2 (32/226)	9.8 (27/276)	19.5 (16/82)	1.22 (0.80–1.87)	0.363	2.47 (1.25–4.91)	0.010
SB ≥ 2 h/d	14.4 (18/125)	24.4 (42/172)	24.4 (11/45)	3.41 (1.88–6.18)	<0.001		
PA and SB							
PA ≥ 1 h/d & SB < 2 h/d	17.2 (22/128)	9.5 (14/147)	7.3 (3/41)	0.50 (0.26–0.96)	0.039	6.11 (2.79–13.37)	<0.001
PA < 1 h/d or SB ≥ 2 h/d	12.6 (28/223)	18.3 (55/301)	27.9 (24/86)	3.17 (2.02–4.96)	<0.001		

NAFLD Non-Alcoholic Fatty Liver Disease, *PNPLA3* The patatin like phospholipase containing domain 3 gene, *PA* Physical Activity, *SB* Sedentary Behavior
a: the *P* value of rs738409 in logistic model conducted in each behavioral level, including age, gender, BMI and rs738409 as independent variables
b: the *P* value of rs738409 × behavior in logistic model conducted for each behavior, including age, gender, BMI, rs738409, behavior, rs738409 × behavior as independent variables

- Στατιστικά σημαντικές αλληλεπιδράσεις rs738409 * φυσική δραστηριότητα/καθιστικές δραστηριότητες

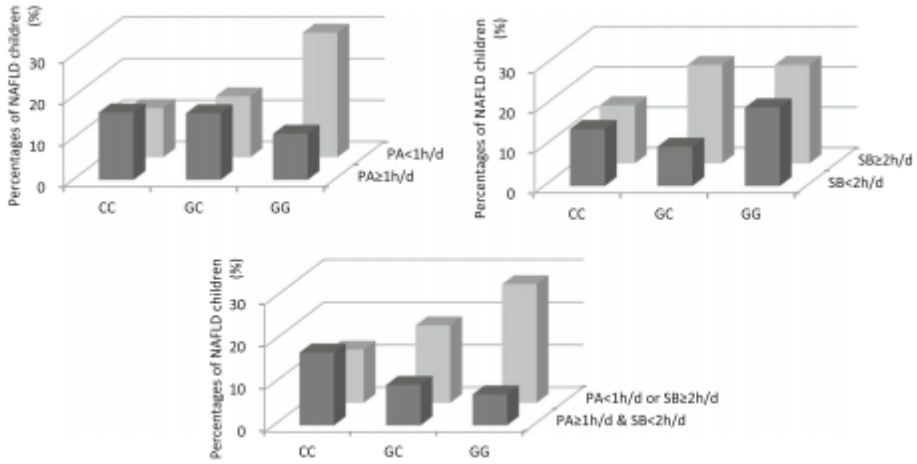


Fig. 1 Percentages of NAFLD children in different genotypes of the *PNPLA3* rs738409 polymorphism and behavioral groups. NAFLD: Non-Alcoholic Fatty Liver Disease; *PNPLA3*: The patatin like phospholipase containing domain 3 gene; PA: Physical Activity; SB: Sedentary Behavior

Interaction of Polymorphisms of Resistin Gene Promoter -420C/G, Glutathione Peroxidase -1 Gene Pro198Leu and Cigarette Smoking in Nonalcoholic Fatty Liver Disease

Chao-Xian Zhang[1], Li-Ke Guo[2], Yong-Mei Qin[1], Guang-Yan Li[1]

- 900 ασθενείς – 900 μάρτυρες
- Εκκινητής ρεζιστίνης & Υπεροξειδάση της γλουταθειόνης
- Μελετήθηκαν αλληλεπιδράσεις του καπνίσματος με 2 πολυμορφισμούς

- Στατιστικά σημαντικές συσχετίσεις μεταξύ καπνιστικών συνηθειών και της παρουσίας νόσου, καθώς και των γονιδίων και της νόσου.

Table 1: Background information of NAFLD and control groups, *n* (%)

Groups	Gender		Age		Smoking status		
	Male	Female	≤50 years	>50 years	Nonsmoking	SI ≤400	SI >400
Control (*n* = 900)	537 (59.67)	363 (40.33)	409 (45.44)	491 (54.56)	693 (77.00)	116 (12.89)	91 (10.11)
NAFLD (*n* = 900)	542 (60.22)	358 (39.78)	406 (45.11)	494 (54.89)	453 (50.33)	144 (16.00)	303 (33.67)
*OR**					1.0000	1.8990	5.0937†
95% *CI*						1.3728–2.5492	3.0195–8.3526
P	0.1037		0.0974			0.0083	0.0051

*Adjusted for other factors; †*P*<0.05, compared with SI ≤400. NAFLD: Nonalcoholic fatty liver disease; *CI*: Confidence interval; *OR*: Odds ratio; SI: Smoking index.

Table 2: Distribution of the resistin gene promoter −420C/G polymorphism genotypes, alleles, and analysis of the genetic model

Groups	Genotype, *n* (%)		Allele, *n* (%)		Dominant model	Recessive model
	CC+CG	GG	C	G	(CG+GG)/CC	GG/(CG+CC)
Control (*n* = 900)	687 (76.33)	213 (23.67)	966 (53.67)	834 (46.33)	621:279	213:687
NAFLD (*n* = 900)	454 (50.44)	446 (49.56)	701 (38.94)	1099 (61.05)	653:247	446:454
*OR**	1.0000	3.1685	1.0000	1.8159	1.1878	3.1685
95% *CI*	1.9366–5.2073		1.3047–2.8671		0.8387–1.7593	1.9366–5.2073
P	0.0069		0.0085		0.0857	0.0069

*Adjusted for sex, age, and smoking status. NAFLD: Nonalcoholic fatty liver disease; *CI*: Confidence interval; *OR*: Odds ratio.

Table 3: Distribution of the *GPx-1* Pro198Leu polymorphism genotypes, alleles, and analysis of the genetic model

Groups	Genotype, *n* (%)		Allele, *n* (%)		Dominant model	Recessive model
	PP+PL	LL	P	L	(PL+LL)/PP	LL/(PL+PP)
Control (*n* = 900)	682 (75.78)	218 (24.22)	959 (53.28)	841 (46.72)	623:277	218:682
NAFLD (*n* = 900)	449 (49.89)	451 (50.11)	700 (38.89)	1100 (61.11)	649:251	451:449
*OR**	1.0000	3.1424	1.0000	1.7919	1.1496	3.1424
95% *CI*	1.7951–5.2367		1.3583–4.0706		0.7095–1.9041	1.7951–5.2367
P	0.0072		0.0095		0.0894	0.0072

*Adjusted by sex, age, and smoking status. *GPx-1*: Glutathione peroxidase-1; NAFLD: Nonalcoholic fatty liver disease; *CI*: Confidence interval; *OR*: Odds ratio.

Table 6: Interaction of the −420C/G polymorphism and cigarette smoking in NAFLD, *n* (%)

Groups	−420C/G genotype and smoking status					
	CC+CG/nonsmoking	CC+CG/SI ≤400	CC+CG/SI >400	GG/nonsmoking	GG/SI ≤400	GG/SI >400
Control (n = 900)	582 (64.67)	54 (6.00)	51 (5.67)	111 (12.33)	62 (6.89)	40 (4.44)
NAFLD (n = 900)	361 (40.11)	40 (4.44)	53 (5.89)	92 (10.22)	104 (11.56)	250 (27.78)
*OR**	1.0000	1.1942† (OR_e)	1.6754† (OR_e)	1.3362‡ (OR_g)	2.7032§ (OR_{eg})	10.0762§ (OR_{eg})
95% *CI*		0.8721–1.6285	1.2470–2.1649	0.9325–2.6457	1.9727–3.5193	7.0958–13.6125
β		0.0771† (β_e)	0.2241† (β_e)	0.1259‡ (β_g)	0.4319§ (β_{eg})	1.0033§ (β_{eg})
P		0.0849	0.0253	0.0637	0.0076	0.0038

*Adjusted for sex and age; †*OR* (β) value by simple smoking exposure (OR_e [β_e]); ‡*OR* (β) value by simple homozygous mutant type exposure (OR_g [β_g]); §*OR* (β) value by the interaction of smoking and homozygous mutant (OR_{eg} [β_{eg}]). NAFLD: Nonalcoholic fatty liver disease; *CI*: Confidence interval; *OR*: Odds ratio; SI: Smoking index.

- Στατιστικά σημαντικές αλληλεπιδράσεις γενετικών πολυμορφισμών *κάπνισμα

Table 7: Interaction of the Pro198Leu polymorphism and cigarette smoking in NAFLD, *n* (%)

Groups	Pro198Leu genotype and smoking status					
	PP+PL/nonsmoking	PP+PL/SI ≤400	PP+PL/SI >400	LL/nonsmoking	LL/SI ≤400	LL/SI >400
Control (n = 900)	579 (64.33)	53 (5.89)	50 (5.56)	114 (12.67)	63 (7.00)	41 (4.56)
NAFLD (n = 900)	359 (39.89)	39 (4.33)	51 (5.67)	94 (10.44)	105 (11.67)	252 (28.00)
*OR**	1.0000	1.1868† (OR_e)	1.6451† (OR_e)	1.3299‡ (OR_g)	2.6880§ (OR_{eg})	9.9129§ (OR_{eg})
95% *CI*		0.7694–1.8923	1.2548–2.2760	0.9499–2.0978	1.9902–4.1749	6.5294–12.2581
β		0.0744† (β_e)	0.2162† (β_e)	0.1238‡ (β_g)	0.4294§ (β_{eg})	0.9962§ (β_{eg})
P		0.0861	0.0375	0.0708	0.0082	0.0043

*Adjusted for sex and age; †*OR* (β) value by simple smoking exposure (OR_e [β_e]); ‡*OR* (β) value by simple homozygous mutant type exposure (OR_g [β_g]); §*OR* (β) value by the interaction of smoking and homozygous mutant (OR_{eg} [β_{eg}]). NAFLD: Nonalcoholic fatty liver disease; *CI*: Confidence interval; *OR*: Odds ratio; SI: Smoking index.

The Hellenic NAFLD study

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ORIGINAL CONTRIBUTION

Fish intake interacts with TM6SF2 gene variant to affect NAFLD risk: results of a case–control study

I. P. Kalafati[1] · M. Dimitriou[1] · D. Borsa[1] · J. Vlachogiannakos[2] · K. Revenas[3] · A. Kokkinos[2] · S. D. Ladas[2] · G. V. Dedoussis[1]

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Applied nutritional investigation

Dietary patterns and non-alcoholic fatty liver disease in a Greek case–control study

Ioanna P. Kalafati MSc [a,*], Dimitra Borsa MSc [a], Maria Dimitriou Ph.D [a], Konstantinos Revenas M.D. [b], Alexander Kokkinos Ph.D [c], George V. Dedoussis Ph.D [a]

Μεθοδολογία

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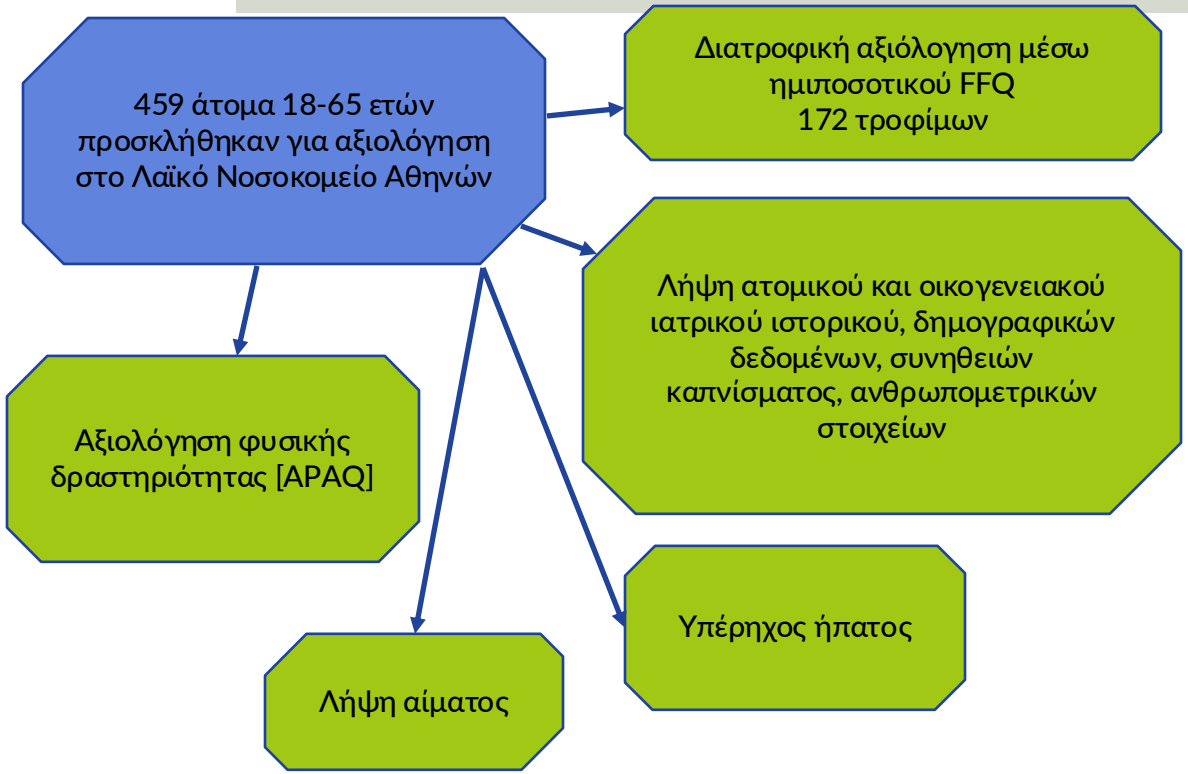
459 άτομα 18-65 ετών προσκλήθηκαν για αξιολόγηση στο Λαϊκό Νοσοκομείο Αθηνών
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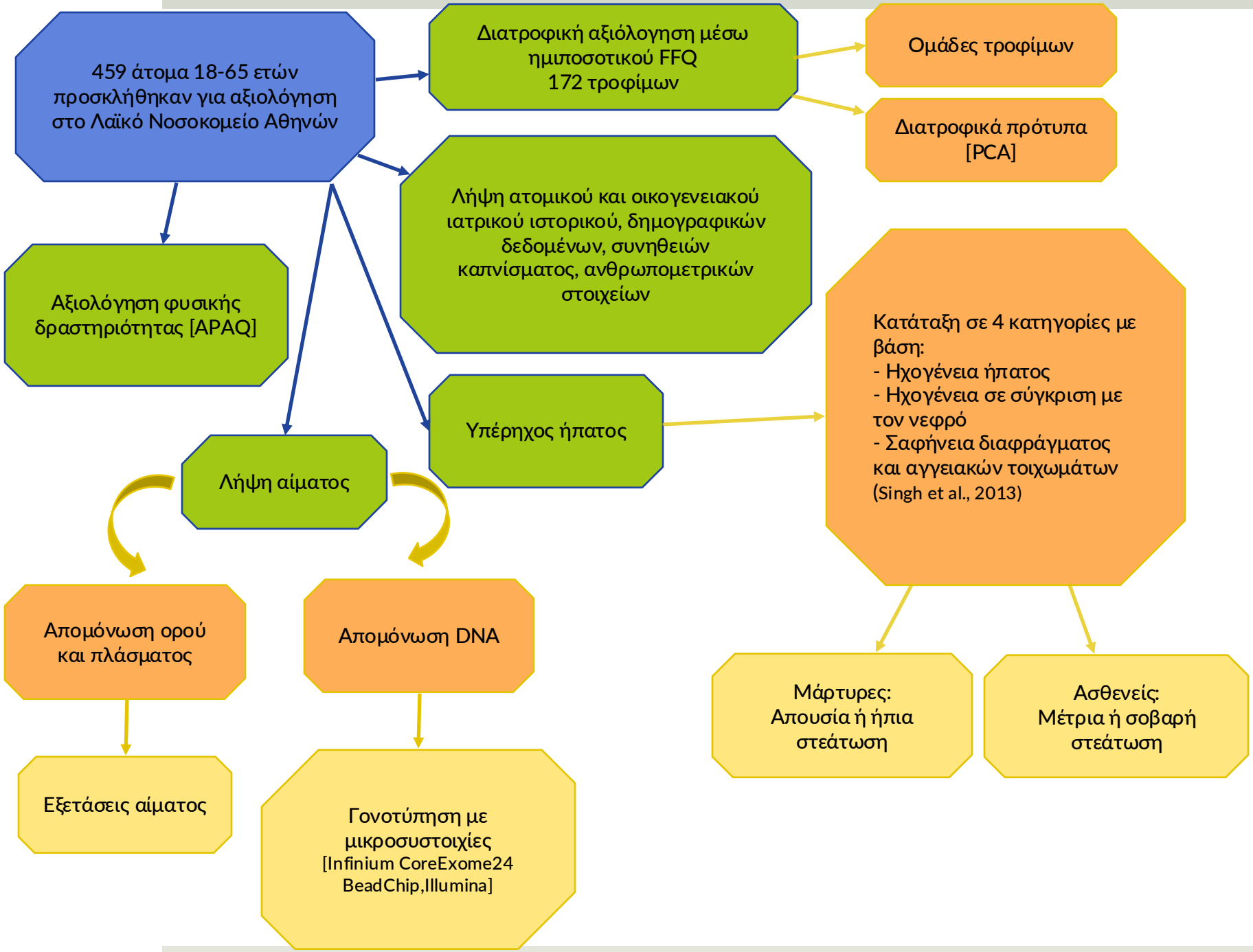
Αξιολόγηση φυσικής δραστηριότητας [APAQ]
Υπέρηχος ήπατος
Λήψη αίματος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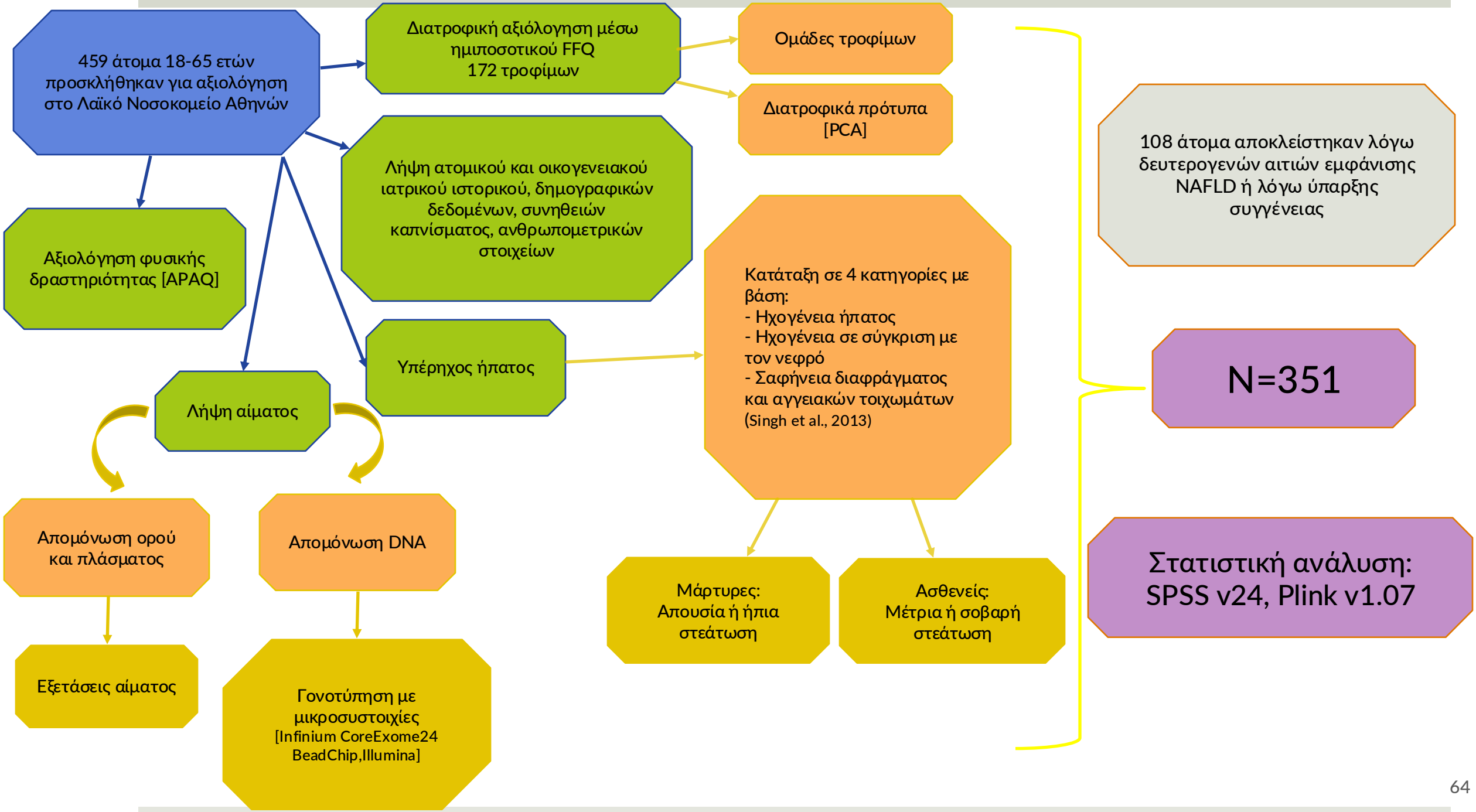
- Ηχογένεια ήπατος
- Ηχογένεια σε σύγκριση με τον νεφρό
- Σαφήνεια διαφράγματος και αγγειακών τοιχωμάτων
(Singh et al., 2013)
Λήψη αίματος
Απομόνωση ορού και πλάσματος
Απομόνωση DNA
Μάρτυρες: Απουσία ή ήπια στεάτωση
Ασθενείς: Μέτρια ή σοβαρή στεάτωση
Εξετάσεις αίματος
Γονοτύπηση με μικροσυστοιχίες [Infinium CoreExome24 BeadChip,Illumina]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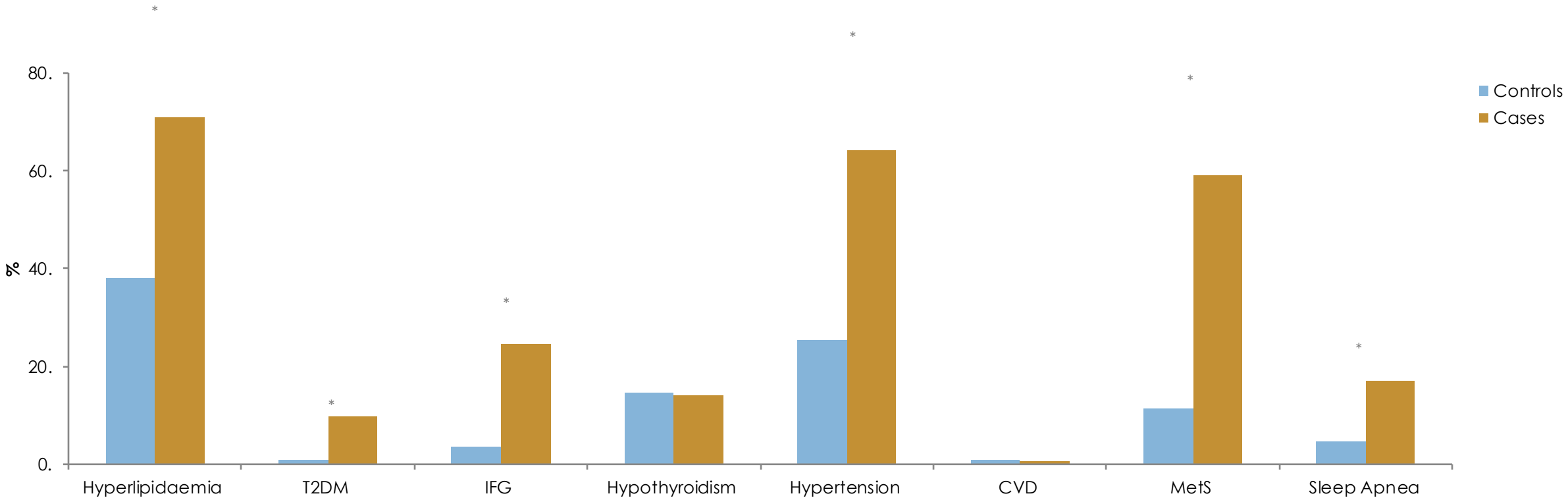
Μάρτυρες: Απουσία ή ήπια στεάτωση
Ασθενείς: Μέτρια ή σοβαρή στεάτωση
108 άτομα αποκλείστηκαν λόγω δευτερογενών αιτιών εμφάνισης NAFLD ή λόγω ύπαρξης συγγένειας
N=351
Στατιστική ανάλυση: SPSS v24, Plink v1.07

Αποτελέσματα

	Controls (N=217)	Cases (N=134)	P
Gender (% males)	39.2	45.5	0.144
Age (years)	43.75±11.23	50.36±10.51	**<0.001**
Education Years	15.25±3.60	14.02±3.99	**0.005**
Annual Family Income (€)			
<8,000	10.9	14.7	
8,000-15,000	25.1	26.4	0.507
15,000-25,000	29.9	23.3	
>25,000	34.1	35.7	
Marital Status (%)			
Single	30.0	17.2	
Married	58.1	70.1	0.061
Widowed	2.3	2.2	
Divorced	9.7	10.4	

	Controls (N=217)	Cases (N=134)	P
BMI (kg/m^2)	24.92±3.27	31.11±4.72	<0.001
WC (cm)	84.94±10.22	103.59±11.72	<0.001
WHR	0.83±0.09	0.92±0.08	<0.001
Fat Mass (%)	26.23±8.64	33.76±8.93	<0.001
Fat Free Mass (kg)	52.85±11.03	59.25±12.68	<0.001


80.
60.
40.
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Controls
Cases
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*
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Hyperlipidaemia
T2DM
IFG
Hypothyroidism
Hypertension
CVD
MetS
Sleep Apnea

Age-adjusted	Mean (95% CI)				Mean (95% CI)		
	Controls (N=217)	**Cases (N=134)**	**P**		**Controls (N=217)**	**Cases (N=134)**	**P**
SBP(mmHg)	119.4 (117.6 – 121.3)	128.8 (126.5 – 131.2)	<0.001	HDL(mg/dL)	58.6 (56.7 – 60.4)	49.9 (47.6 – 52.2)	<0.001
DBP(mmHg)	74.4 (73.1 – 75.7)	83.1 (81.4 – 84.7)	<0.001	TG(mg/dL)	79.5 (72.9 – 86.1)	125.8 (117.4 – 134.3)	<0.001
WBC(K/uL)	5.9 (5.8 – 6.2)	6.8 (6.5 – 7.1)	0.001	AST(U/L)	21 (20 – 22)	23.9 (22.6 – 25.2)	0.002
PLT(K/uL)	239.6 (232.1 – 247.1)	249.9 (240.4 – 259.4)	0.052	ALT(U/L)	21.2 (19.5 – 22.9)	30.7 (28.4 – 32.9)	<0.001
Fe(ug/dL)	97.7 (92.6 – 102.8)	107 (100.5 – 113.6)	0.011	AST/ALT	1.09 (1.05 – 1.12)	0.83 (0.78 – 0.88)	<0.001
Fer(ng/mL)	76.6 (65.8 – 87.4)	115 (101.1 – 128.9)	<0.001	γ-GT(U/L)	20.4 (17.7 – 23.1)	27.6 (24.1 – 31)	<0.001
CRP(mg/L)	2.6 (2.3 – 2.9)	3.8 (3.4 – 4.2)	<0.001	Uric Acid(mg/dL)	4.7 (4.5 – 4.8)	5.7 (5.5 – 6)	<0.001
FGlu(mg/dL)	84.9 (83.7 – 86.3)	92.4 (90.6 – 94.1)	<0.001	Direct Bilirubin(mg/dL)	0.23 (0.22 – 0.25)	0.22 (0.2 – 0.24)	0.013
FIns(uU/mL)	10.2 (9 – 11.4)	16.7 (15.1 – 18.2)	<0.001	Albumin(g/dL)	4.52 (4.49 – 4.55)	4.61 (4.56 – 4.65)	0.114
HOMA-IR	2.2 (1.9 – 2.5)	3.9 (3.5 – 4.3)	<0.001	ALP(U/L)	59.8 (56.9 – 62.7)	67.3 (63.9 – 70.6)	<0.001
HbA1c (%)	5.3 (5.2 – 5.3)	5.5 (5.4 – 5.6)	<0.001	Leptin (ng/mL)	16.4 (13.4 – 19.4)	30 (26.1 – 33.9)	<0.001
TC(mg/dL)	197.8 (192.9 – 202.6)	205.5 (199.2 – 211.7)	0.001	NASH Score	-1.83 (-1.91 – -1.75)	-1.42 (-1.52 – -1.32)	<0.001
LDL(mg/dL)	122.5 (118.2 – 126.8)	130.4 (124.9 – 135.9)	0.001	NFS	-2.63 (-2.76 – -2.5)	-2.24 (-2.41 – -2.07)	<0.001

NAFLD	Model 1			Model 2		
	OR	95% CI	p	OR	95% CI	p
Age (years)	1.059	1.029-1.090	<0.001	1.058	1.028-1.090	<0.001
Gender (Males)	2.160	1.161-4.017	0.015	2.127	1.136-3.985	0.018
BMI (kg/m²)	1.533	1.390-1.691	<0.001	1.520	1.378-1.677	<0.001
WC (cm)	1.121	1.066-1.178	<0.001	1.119	1.064-1.177	<0.001
WHR	1.079 *	1.038-1.122	<0.001	1.081	1.039-1.124	<0.001
Fat Mass (%)	1.280	1.209-1.355	<0.001	1.274	1.203-1.350 *	<0.001
Fat Free Mass (kg) *	1.213	1.151-1.279	<0.001	1.220	1.156-1.288	<0.001
Vertical Liver size (cm)	1.684	1.337-2.122	<0.001	1.749	1.377-2.221	<0.001
MetS (Yes)	3.945	2.035-7.651	<0.001	4.142	2.107-8.144	<0.001
Hypertension (Yes)	2.935	1.556-5.534	0.001	2.818	1.487-5.341	0.001
IFG (Yes)	3.670	1.332-10.110	0.012	3.494	1.276-9.567	0.015
Hyperlipidemia (Yes)	1.934	1.044-3.580	0.036	1.931	1.031-3.616	0.040

Model 1: Model adjusted for age, gender & BMI
Model 2: Model adjusted for age, gender, BMI, pack-years & PAL

NAFLD	Model 1			Model 2		
	OR	95% CI	p	OR	95% CI	p
DBP (mmHg)	1.064	1.026-1.103	0.001	1.062	1.025-1.102	<0.001
WBC (K/uL)	1.231	1.033-1.467	0.020	1.220	1.019-1.462	0.031
Fe (ug/dL)	1.014	1.005-1.024	0.003	1.014	1.005-1.024	0.004
Fer (ng/mL)	1.005	1.000-1.010	0.030	1.005	1.000-1.009	0.051
FGlu (mg/dL)	1.060	1.027-1.094	<0.001	1.058	1.025-1.093	0.001
FIns (uU/mL)	1.059	1.013-1.107	0.012	1.058	1.013-1.106	0.012
HOMAIR	1.340	1.097-1.636	0.004	1.328	1.091-1.616	0.005
HbA1c (%)	3.613	1.183-11.031	0.024	3.656	1.185-11.277	0.024
HDL (mg/dL)	0.976	0.953-0.999	0.041	0.976	0.953-1.000	0.053
TG (mg/dL)	1.018	1.011-1.026	<0.001	1.018	1.011-1.026	<0.001
AST (U/L)	1.041	1.000-1.084	0.050	1.043	1.001-1.086	0.045
ALT (U/L)	1.040	1.016-1.066	0.001	1.043	1.018-1.069	0.001
AST/ALT	0.967	0.953-0.982	<0.001	0.033	0.007-0.149	<0.001
Uric acid (mg/dL)	1.650	1.207-2.256	0.002	1.687	1.230-2.313	0.001

Model 1: Model adjusted for age, gender & BMI
Model 2: Model adjusted for age, gender, BMI, pack-years & PAL

SNP	Gene	Chr	Strand	Build	Position	Effect Allele	Non Effect Allele	HWE p-value	EAF
rs738409	PNPLA3	22	+	37	44324727	G	C	0.2922	0.2895
rs58542926	TM6SF2	19	-	37	19379549	A	G	1	0.0556
rs780094	GCKR	2	+	37	27741237	A	G	0.0964	0.5733
rs641738	MBOAT7	19	+	37	54173068	A	G	0.5101	0.4453

SNP: Single nucleotide polymorphism; Chr: Chromosome; HWE p-value: Hardy-Weinberg Equilibrium test p-value; EAF: Effect allele frequency

NAFLD	Model 1			Model 2		
	OR	95% CI	P*	OR	95% CI	P*
PNPLA3 rs738409 (G)	1.588	1.113-2.266	**0.011**	1.587	1.102-2.283	**0.013**
TM6SF2 rs58542926 (A)	1.343	0.6637-2.716	0.412	1.386	0.6797-2.827	0.369
GCKR rs780094 (A)	1.108	0.7751-1.584	0.574	1.062	0.7398-1.525	0.745
MBOAT7 rs641738 (A)	1.167	0.8419-1.618	0.354	1.155	1.613-0.849	0.396

*Bonferroni correction was applied and level of statistical significance was set to a=0.0125.
Model 1: Model adjusted for age, gender & BMI
Model 2: Model 1 included model 1, pack-years & PAL

	BETA	SE	p*
PNPLA3 rs738409 (G)			
ALT (U/L)	2.279	2.231	**0.02634**
AST/ALT	-0.07956	-3.453	**6.3E-4**
HbA1c (%)	0.08201	2.191	**0.02949**
TM6SF2 rs58542926 (A)			
gamma-GT (U/L)	7.89	2.282	**0.02319**
GCKR rs780094 (A)			
AST (U/L)	1.452	2.448	**0.01487**

*Bonferroni correction was applied and level of statistical significance was set to a=0.0125.
Linear regression models were adjusted for age, gender, BMI & NAFLD status. Additive models were assumed for PNPLA3 and GCKR, whereas a dominant model was assumed for TM6SF2.

Portions/day	Controls (N=217)	Cases (N=134)	P	*Portions/week*	Controls (N=217)	Cases (N=134)	P
Energy Intake (kcal/day)	2.557.30±1188.23	2.501.77±1011.46	0.773	**Red Meat**	5.49±3.74	5.52±4.05	0.790
Refined Starchy Foods	2.08±1.95	2.52±2.09	**0.046**	**Processed red meat**	3.03±3.76	2.92±3.44	0.855
Whole-grain starchy foods	1.59±1.53	1.46±1.71	0.073	**Eggs**	1.94±2.56	1.70±1.89	0.713
Full-fat dairy	0.21±0.37	0.15±0.33	0.077	**Oil-based cooked vegetables**	2.60±2.34	2.45±2.55	0.238
Low-fat dairy	0.49±0.61	0.51±0.57	0.265	**Savoury and puff pastry snacks**	1.58±1.61	1.72±1.88	0.497
Full-fat cheese	1.69±1.39	1.93±1.75	0.478	**Sweets**	8.71±7.08	8.46±7.00	0.674
Low-fat cheese	0.26±0.48	0.35±0.59	0.266	**Legumes**	2.06±1.84	2.04±1.69	0.721
Fruits	2.37±1.74	2.27±1.64	0.743	**Fast food**	1.36±1.67	1.51±1.77	0.402
Fresh fruit juice	0.22±0.29	0.15±0.26	**0.003**	**Fish**	2.77±2.38	2.37±2.17	0.117
Fruit drinks	0.07±0.15	0.06±0.12	0.990	**Fatty fish**	1.39±1.43	1.17±1.26	0.191
Vegetables	4.32±2.59	4.42±2.94	0.958	**Poultry**	2.64±2.74	2.31±2.25	0.860
Potatoes	2.33±2.09	2.43±2.41	0.869	**Fried food**	2.21±2.49	2.62±2.49	**0.044**
Nuts	5.90±7.61	4.35±6.46	0.079	**Sweetened soft drinks (portions/day)**	0.07±0.18	0.07±0.16	0.148
MUFAs rich foods	0.36±0.44	0.41±0.49	0.786	**Unsweetened soft drinks (portions/day)**	0.05±0.14	0.05±0.15	0.748
Sauces	0.93±1.47	1.48±2.30	0.072	**Tea (portions/day)**	0.22±0.42	0.16±0.31	0.257
Spreads	0.13±0.26	0.18±0.33	0.974	**Alcohol drinks (portions/day)**	0.39±0.47	0.39±0.47	0.723

NAFLD	Model 1			Model 2		
	OR	95% CI	p	OR	95% CI	p
Refined starchy foods (portions/day)	1.143	1.007-1.296	0.038	1.162	1.021-1.322	0.022
Cheese full fat (portions/day)	1.172	0.992-1.386	0.063	1.192	1.001-1.418	0.048
Fast food (portions/ week)	1.321	1.108-1.576	0.002	1.345	1.123-1.612	0.001
Sweet spreads and sugar (portions/day)	1.175	1.002-1.378	0.047	1.188	1.009-1.400	0.039
Sauces (portions/day)	1.215	1.059-1.393	0.006	1.203	1.045-1.385	0.010
Fried food (portions/ week)	1.130	1.017-1.256	0.023	1.128	1.012-1.258	0.030
Fish (portions/week)	0.859	0.766-0.962	0.009	0.845	0.751-0.950	0.005
Fatty fish (portions/ week)	0.790	0.658-0.948	0.011	0.769	0.636-0.931	0.007
Nuts (portions/day)	0.954	0.919-0.991	0.016	0.947	0.910-0.984	0.006

Model 1: Model adjusted for age, gender & energy intake
Model 2: Model adjusted for age, gender, energy intake, pack-years & PAL

NAFLD	Model 1			Model 2		
	OR	95% CI	p	OR	95% CI	p
Refined starchy foods (portions/day)	1.143	1.007-1.296	0.038	1.162	1.021-1.322	0.022
Cheese full fat (portions/day)	1.172	0.992-1.386	0.063	1.192	1.001-1.418	0.048
Fast food (portions/ week)	1.321	1.108-1.576	0.002	1.345	1.123-1.612	0.001
Sweet spreads and sugar (portions/day)	1.175	1.002-1.378	0.047	1.188	1.009-1.400	0.039
Sauces (portions/day)	1.215	1.059-1.393	0.006	1.203	1.045-1.385	0.010
Fried food (portions/ week)	1.130	1.017-1.256	0.023	1.128	1.012-1.258	0.030
Fish (portions/week)	0.859	0.766-0.962	0.009	0.845	0.751-0.950	0.005
Fatty fish (portions/ week)	0.790	0.658-0.948	0.011	0.769	0.636-0.931	0.007
Nuts (portions/day)	0.954	0.919-0.991	0.016	0.947	0.910-0.984	0.006

Model 1: Model adjusted for age, gender & energy intake
Model 2: Model adjusted for age, gender, energy intake, pack-years & PAL

Foods	Fast-food type	Prudent	High protein	Unsaturated FA
Fast-food main dishes	**0.703**	-	-	-
Sugar-sweetened soft drinks	**0.655**	-	-	-
Fried potatoes	**0.644**	-	-	-
Savory and puff pastry snacks	**0.471**	-	-	-
Olive oil-based cooked vegetables	-	0.745	-	-
Legumes	-	0.669	-	-
Potatoes	0.358	0.540	-	-
Fruits & Vegetables	-	0.528	-	-
Fatty fish	-	0.510	-	-
Poultry	-	-	0.740	-
Eggs	-	-	0.682	-
Red meat	0.460	-	0.575	-
Nuts	-	-	-	0.654
Chocolate	-	-	-	0.604
Foods rich in unsaturated FA	-	-	-	0.595

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Fast-food main dishes	0.703	-	-	-
Sugar-sweetened soft drinks	0.655	-	-	-
Fried potatoes	0.644	-	-	-
Savory and puff pastry snacks	0.471	-	-	-
Olive oil-based cooked vegetables	-	**0.745**	-	-
Legumes	-	**0.669**	-	-
Potatoes	0.358	**0.540**	-	-
Fruits & Vegetables	-	**0.528**	-	-
Fatty fish	-	**0.510**	-	-
Poultry	-	-	0.740	-
Eggs	-	-	0.682	-
Red meat	0.460	-	0.575	-
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Red meat	0.460	-	0.575	-
Nuts	-	-	-	**0.654**
Chocolate	-	-	-	**0.604**
Foods rich in unsaturated FA	-	-	-	**0.595**

NAFLD	Model 1[a]			Model 2[b]			Model 3[c]			Model 4[d]		
Fast-food type	**OR**	**95% CI**	**p**	**OR**	**95% CI**	**p**	**OR**	**95% CI**	**p**	**OR**	**95% CI**	**p**
Q1	Ref			Ref			Ref			Ref		
Q2	1.192	0.631-2.253	0.589	1.276	0.664-2.453	0.465	1.720	0.788-3.755	0.173	1.822	0.810-4.100	0.147
Q3	1.399	0.741-2.641	0.301	1.638	0.834-3.216	0.152	2.194	0.973-4.945	0.058	2.296	0.977-5.395	0.056
Q4	1.730	0.928-3.226	0.085	2.629	1.250-5.532	0.011	3.900	1.571-9.682	0.003	4.243	1.589-11.328	0.004

[a] Model 1: unadjusted
[b] Model 2: adjusted for age, sex, energy intake
[c] Model 3: adjusted for age, sex, energy intake, PAL, pack-years, education years, presence of MetS
[d] Model 4: adjusted for age, sex, energy intake, PAL, pack-years, education years, presence of MetS, the other 3 dietary patterns

NAFLD	Model 1[a]			Model 2[b]			Model 3[c]			Model 4[d]		
Prudent	**OR**	**95% CI**	**p**	**OR**	**95% CI**	**p**	**OR**	**95% CI**	**p**	**OR**	**95% CI**	**p**
Q1		Ref			Ref			Ref			Ref	
Q2	0.633	0.340-1.178	0.149	0.554	0.293-1.050	0.070	0.641	0.301-1.366	0.249	0.753	0.339-1.670	0.485
Q3	0.751	0.405-1.390	0.362	0.653	0.346-1.235	0.190	0.946	0.450-1.990	0.884	1.098	0.504-2.390	0.815
Q4	0.644	0.345-1.201	0.166	0.585	0.303-1.128	0.109	0.576	0.262-1.263	0.168	0.700	0.302-1.627	0.407

[a] Model 1: unadjusted
[b] Model 2: adjusted for age, sex, energy intake
[c] Model 3: adjusted for age, sex, energy intake, PAL, pack-years, education years, presence of MetS
[d] Model 4: adjusted for age, sex, energy intake, PAL, pack-years, education years, presence of MetS, the other 3 dietary patterns

NAFLD	Model 1[a]			Model 2[b]			Model 3[c]			Model 4[d]		
High protein	OR	95% CI	p	OR	95% CI	p	OR	95% CI	p	OR	95% CI	p
Q1	Ref			Ref			Ref			Ref		
Q2	1.188	0.647-2.181	0.579	1.239	0.664-2.314	0.501	1.528	0.724-3.227	0.266	1.856	0.837-4.120	0.128
Q3	0.581	0.306-1.102	0.096	0.630	0.326-1.218	0.169	0.662	0.301-1.457	0.305	0.685	0.302-1.553	0.365
Q4	0.912	0.489-1.699	0.771	1.094	0.555-2.157	0.795	1.450	0.645-3.262	0.368	1.677	0.716-3.931	0.234

[a] Model 1: unadjusted
[b] Model 2: adjusted for age, sex, energy intake
[c] Model 3: adjusted for age, sex, energy intake, PAL, pack-years, education years, presence of MetS
[d] Model 4: adjusted for age, sex, energy intake, PAL, pack-years, education years, presence of MetS, the other 3 dietary patterns

NAFLD	Model 1[a]			Model 2[b]			Model 3[c]			Model 4[d]		
Unsaturated FA	**OR**	**95% CI**	**p**	**OR**	**95% CI**	**p**	**OR**	**95% CI**	**p**	**OR**	**95% CI**	**p**
Q1	Ref			Ref			Ref					
Q2	0.662	0.354-1.239	0.197	0.565	0.296-1.078	0.083	0.443	0.205-0.961	0.039	0.497	0.224-1.102	0.085
Q3	0.987	0.536-1.819	0.968	0.862	1.622	0.646	0.949	0.451-1.996	0.889	1.135	0.524-2.457	0.749
Q4	0.686	0.366-1.286	0.240	0.618	1.187	0.148	0.647	0.299-1.400	0.269	0.824	0.367-1.850	0.640

[a] Model 1: unadjusted
[b] Model 2: adjusted for age, sex, energy intake
[c] Model 3: adjusted for age, sex, energy intake, PAL, pack-years, education years, presence of MetS
[d] Model 4: adjusted for age, sex, energy intake, PAL, pack-years, education years, presence of MetS, the other 3 dietary patterns

		Fast-food type			Prudent			High protein			Unsaturated FA		
		Beta	SE	p	Beta	SE	p	Beta	SE	p	Beta	SE	p
AST	Model 1[a]	-0.403	0.462	0.383	-0.167	0.426	0.696	0.358	0.445	0.421	-0.405	0.411	0.326
	Model 2[b]	-0.418	0.503	0.406	-0.263	0.449	0.559	0.151	0.483	0.755	-0.477	0.423	0.292
ALT	Model 1[a]	-0.165	0.803	0.838	0.335	0.740	0.651	-0.153	0.773	0.843	-1.038	0.713	0.147
	Model 2[b]	-0.567	0.875	0.517	0.057	0.780	0.942	-0.377	0.840	0.654	-1.099	0.736	0.136
AST/ALT	Model 1[a]	-0.014	0.019	0.445	$-2.269 *10^{-5}$	0.017	0.999	-0.005	0.018	0.778	0.018	0.017	0.271
	Model 2[b]	-0.002	0.020	0.920	0.004	0.018	0.814	-0.005	0.019	0.779	0.020	0.017	0.238
TG	Model 1[a]	-2.877	3.032	0.343	-3.535	2.791	0.206	-1.573	2.932	0.592	-4.035	2.696	0.135
	Model 2[b]	-4.888	3.203	0.128	-5.960	2.843	**0.037**	-1.777	3.096	0.566	-5.211	2.678	0.053
FPG	Model 1[a]	0.196	0.631	0.756	0.576	0.581	0.322	-0.819	0.604	0.176	-0.711	0.562	0.207
	Model 2[b]	-0.058	0.635	0.927	0.176	0.566	0.756	-0.808	0.609	0.186	-0.742	0.535	0.166
LnFins	Model 1[a]	0.005	0.027	0.850	-0.047	0.025	0.058	0.011	0.026	0.659	-0.068	0.024	**0.004**
	Model 2[b]	0.021	0.027	0.420	-0.044	0.024	0.071	0.012	0.026	0655	-0.061	0.023	**0.008**
LnHOMAIR	Model 1[a]	0.004	0.030	0.710	-0.040	0.027	0.147	0.001	0.028	0.963	-0.071	0.026	**0.007**
	Model 2[b]	0.025	0.029	0.379	-0.040	0.026	0.127	0.001	0.028	0.964	-0.064	0.025	**0.011**
LnCRP	Model 1[a]	0.048	0.025	0.063	0.002	0.023	0.927	-0.004	0.025	0.871	-0.001	0.023	0.970
	Model 2[b]	0.054	0.026	**0.041**	0.002	0.024	0.931	-0.002	0.026	0.937	-0.001	0.023	0.979
Uric acid	Model 1[a]	0.302	0.075	**<0.001**	-0.226	0.069	**0.001**	0.038	0.073	0.609	-0.133	0.068	0.053
	Model 2[b]	0.294	0.081	**<0.001**	-0.153	0.072	**0.035**	0.051	0.077	0.511	-0.090	0.069	0.193

[a]Model 1: adjusted for age, sex, energy intake, presence of NAFLD
[b] Model 2: adjusted for age, sex, energy intake, presence of NAFLD, PAL, pack-years, education years, presence of MetS, the other 3 dietary patterns

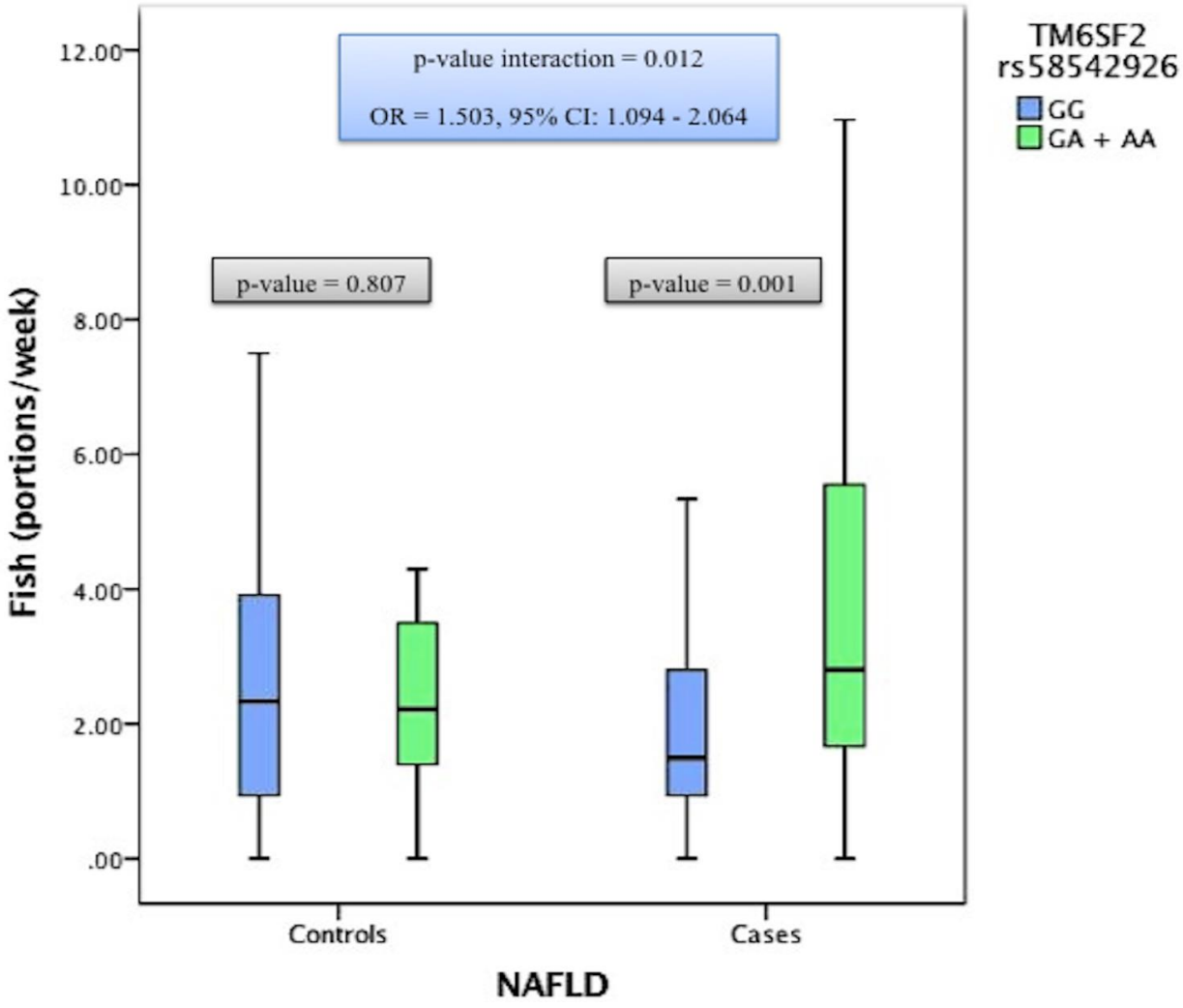
	Controls (N=217)	Cases (N=134)	P
Physical activity habits			
Exercise (%Yes)	49.5	32.1	**0.001**
PAL	1.43±0.22	1.38±0.23	**0.011**
Sleep duration/day (hours)	7.07±1.17	7.16±1.22	0.506
TV viewing (hours/day)	1.59±1.72	2.24±2.5	**0.004**
Smoking habits			
Smokers (%)			
Current	33.6	29.9	
Ex	13.8	26.1	**0.015**
Never	52.5	44	
Age at smoking start (years)	20.15±5.71	19.45±4.07	0.366
Number of cigarettes/day	15.61±12.01	20.12±15.85	**0.033**
Years of smoking	21.53±9.72	25.93±10.67	**0.005**
Pack-years	8.08±13.71	15.19±24.49	**0.024**

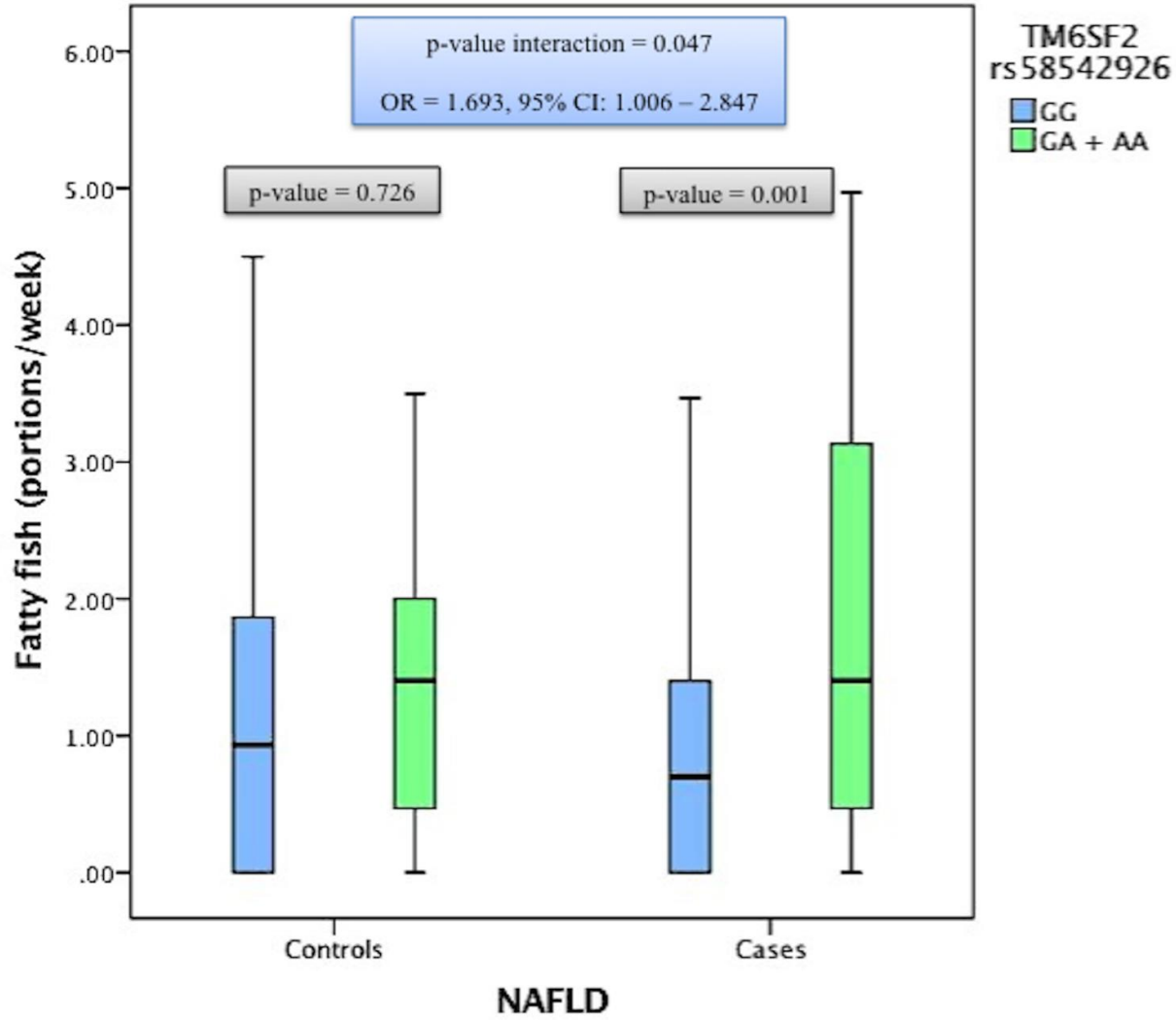
NAFLD	OR	95% CI	p
Physical activity habits			
Exercise (Yes)	1.535	0.843-2.796	0.161
PAL	0.349	0.092-1.328	0.123
Sleep duration/day (hours)	1.143	0.883-1.480	0.310
TV viewing hours/day	1.031	0.878-1.210	0.709
Smoking habits			
Age at starting smoking (years)	0.905	0.826-0.991	**0.032**
Number of Cigarettes/day	0.993	0.964-1.022	0.620
Years of smoking	1.058	1.004-1.115	**0.034**
Pack-years	1.004	0.987-1.022	0.617

Logistic regression models were adjusted for age, gender and BMI

	BETA	SE	p
Pack-years			
ALT (U/L)	-0.074	0.037	**0.042**
HDL (mg/dL)	-0.136	0.036	**<0.001**
TGs (mg/dL)	0.428	0.141	**0.003**
Uric acid (mg/dL)	-0.006	0.003	**0.045**
Sleep duration/day (hours)			
TGs (mg/dL)	4.422	2.140	**0.040**
TV viewing hours/day			
AST (U/L)	0.742	0.193	**<0.001**
FPG(mg/dL)	1.010	0.259	**<0.001**
LnCRP (mg/L)	0.026	0.012	**0.032**

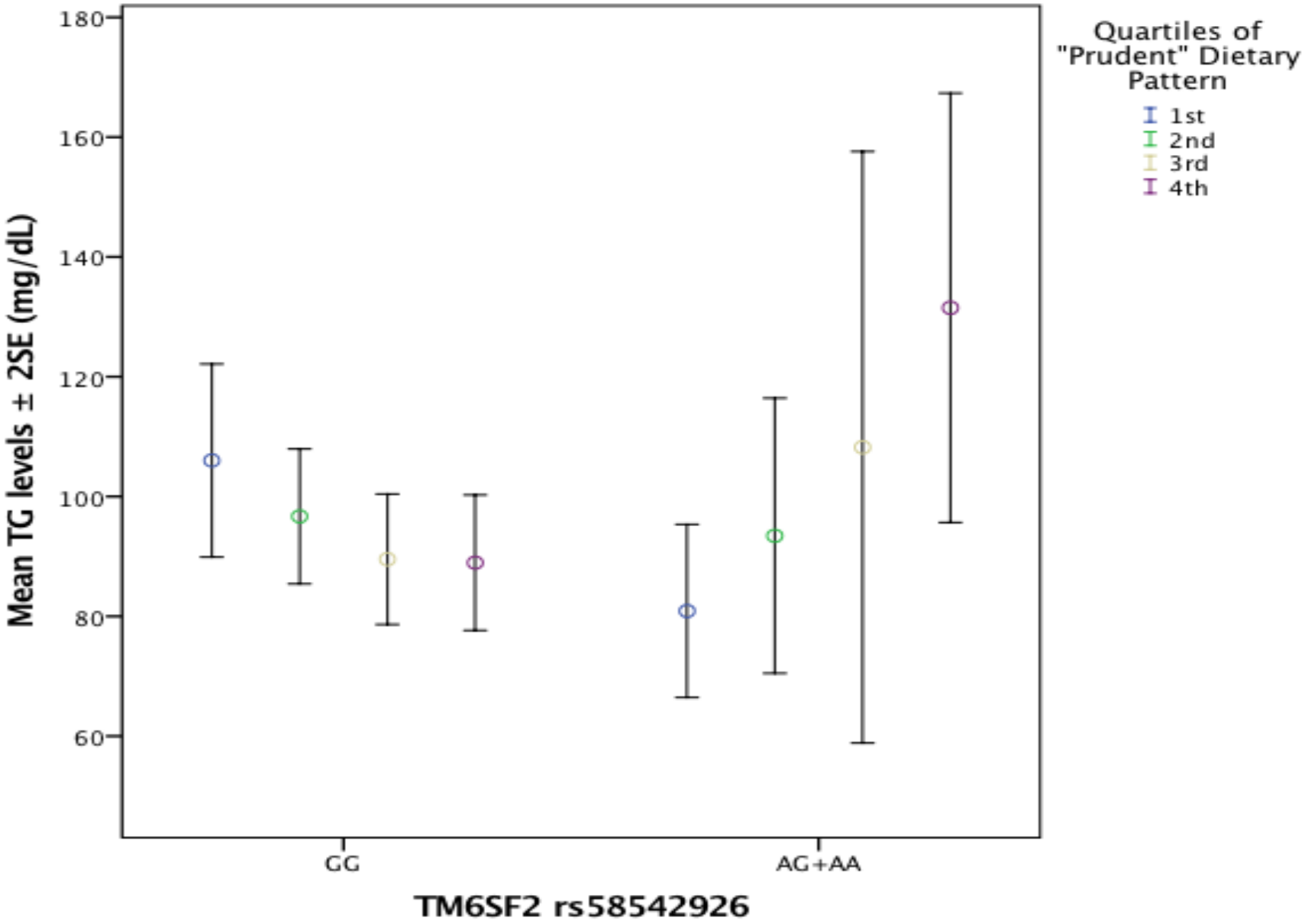
Linear regression models were adjusted for age, gender, BMI & NAFLD status


p-value interaction = 0.012
OR = 1.503, 95% CI: 1.094 - 2.064
p-value = 0.807
p-value = 0.001
TM6SF2
rs58542926
GG
GA + AA
Fish (portions/week)
12.00
10.00
8.00
6.00
4.00
2.00
.00
Controls
Cases
NAFLD


p-value interaction = 0.047
OR = 1.693, 95% CI: 1.006 – 2.847
p-value = 0.726
p-value = 0.001
TM6SF2
rs58542926
GG
GA + AA
Fatty fish (portions/week)
6.00
5.00
4.00
3.00
2.00
1.00
.00
Controls
Cases
NAFLD

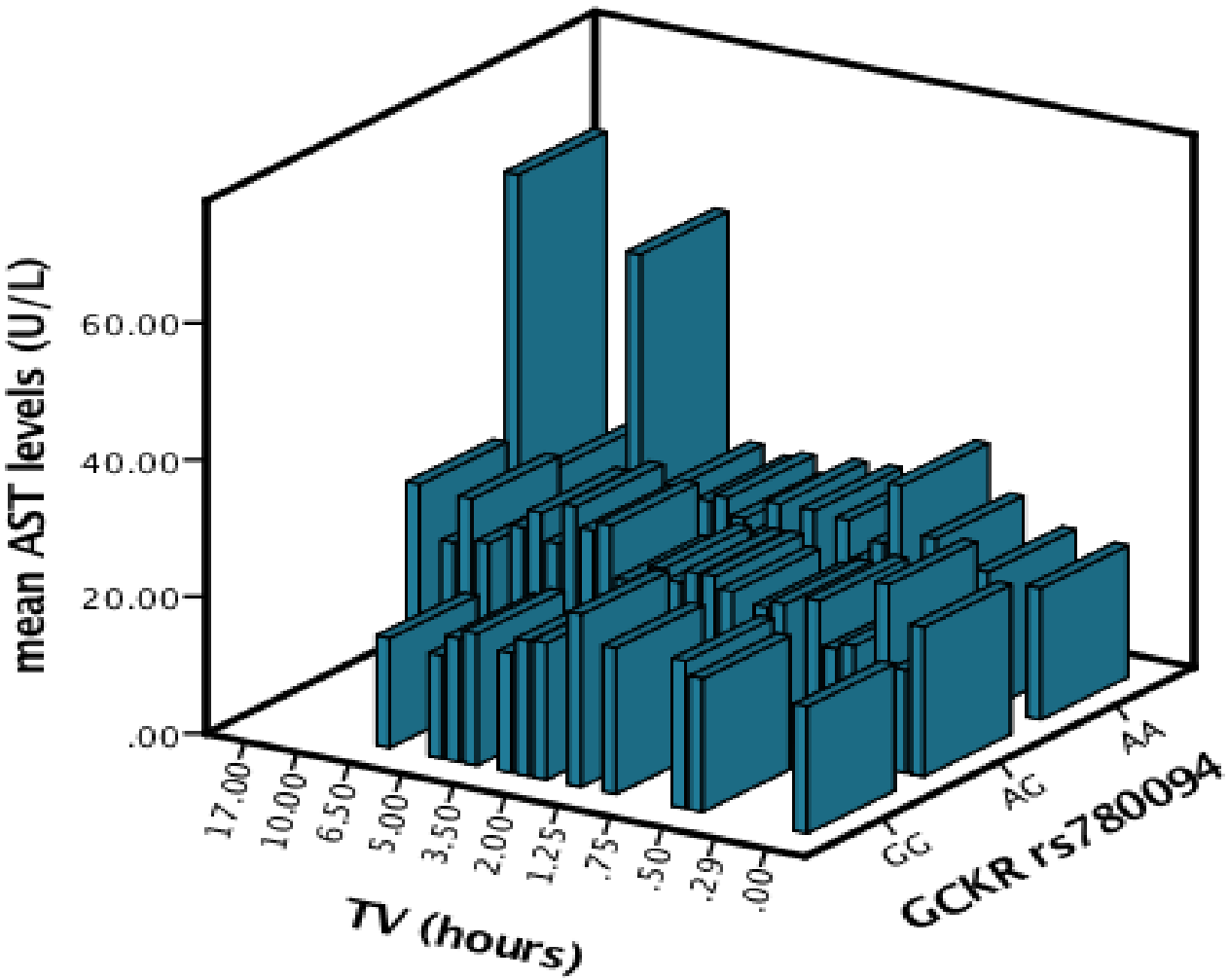
	Model 1			Model 2		
NAFLD	**OR**	**95% CI**	**p***	**OR**	**95% CI**	**p***
TM6SF2 rs58542926-A * Fish (portions/week)	1.442	1.061-1.96	0.019	1.503	1.094-2.064	**0.012**
TM6SF2 rs58542926-A * Fatty fish (portions/week)	1.604	0.9688-2.655	0.066	1.693	1.006-2.847	**0.047**

Dominant model of inheritance assumed.
*Bonferroni correction was applied and level of statistical significance was set to a=0.017
Model 1: linear regression model adjusted for age, gender, energy intake, rs58542926 genotype, fish intake
Model 2: model further adjusted for PAL, pack-years


Mean TG levels ± 2SE (mg/dL)
180
160
140
120
100
80
60
GG
AG+AA
TM6SF2 rs58542926
Quartiles of "Prudent" Dietary Pattern
1st
2nd
3rd
4th

	Model 1			Model 2		
TG (mg/dL)	**BETA**	**SE**	**p***	**BETA**	**SE**	**p***
TM6SF2 rs58542926-A * "Prudent" dietary pattern score	20.53	7.57	**7.1E-4**	28.32	2.139	0.033

Dominant model of inheritance assumed.
*Bonferroni correction was applied and level of statistical significance was set to a=0.0125
Model 1: linear regression model adjusted for age, gender, energy intake, NAFLD status, rs58542926 genotype, “Prudent” dietary pattern score
Model 2: linear regression model adjusted for age, gender, NAFLD status, rs58542926 genotype, “Prudent” dietary pattern score , education years, pack-years, PAL, MetS, energy intake


mean AST levels (U/L)
60.00
40.00
20.00
.00
17.00
10.00
6.50
5.00
3.50
2.00
1.25
.75
.50
.29
.00
TV (hours)
GG
AG
AA
GCKR rs780094

	Model 1			Model 2		
AST (U/L)	**BETA**	**SE**	**p***	**BETA**	**SE**	**p***
GCKR rs780094-A * TV viewing hours	1.088	3.476	**5.7E-4**	1.079	3.453	**6.3E-4**

Additive model of inheritance assumed.
*Bonferroni correction was applied and level of statistical significance was set to a=0.0125
Model 1: linear regression model adjusted for age, gender, BMI, NAFLD status, rs780094 genotype, TV viewing hours
Model 2: linear regression model further adjusted for exercise (Yes/No)