# INDICATORI EPATICI negli Annali AMD

## Carlo B. Giorda

Direttore Diabetologia ASL TORINO 5
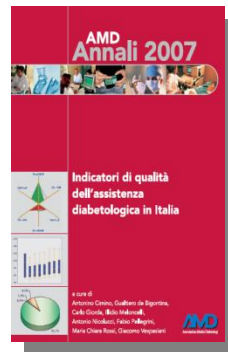
Past President Nazionale AMD

# Gli Annali AMD: un database in continua crescita
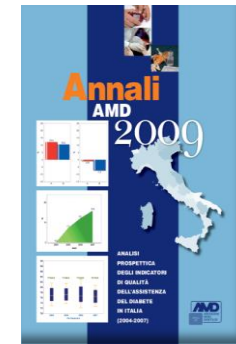
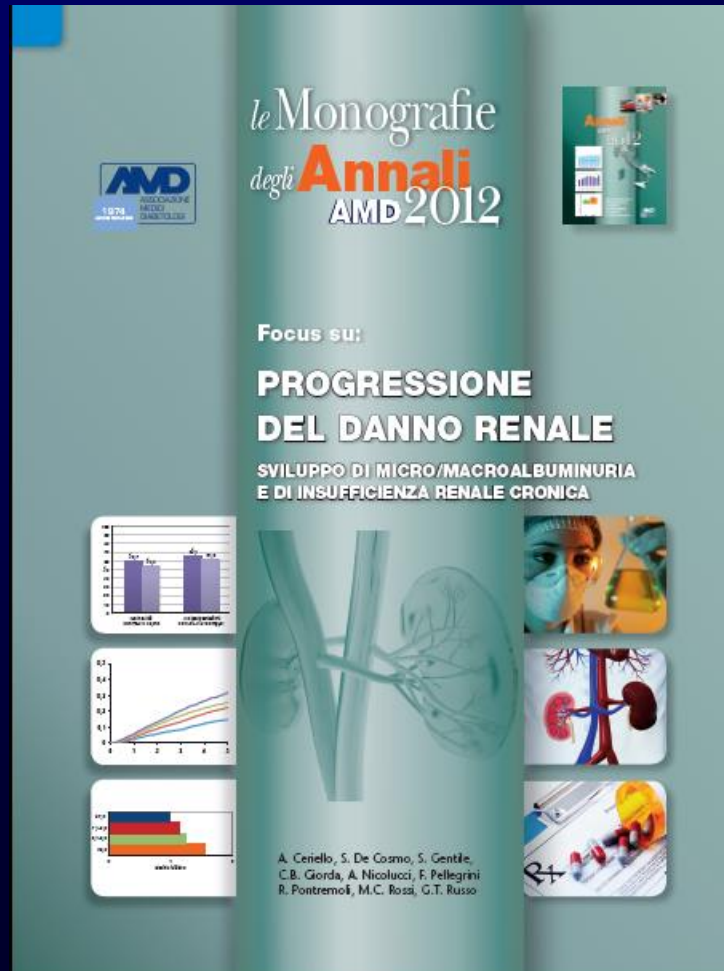|  | 2006 | 2007 | 2008 – 2009 | 2010 |
|---|---|---|---|---|
| N. Centri | 86 | 95 | 124 | 251 |
| N. Pazienti | 123863 | 139147 | 205244 | 451859 |

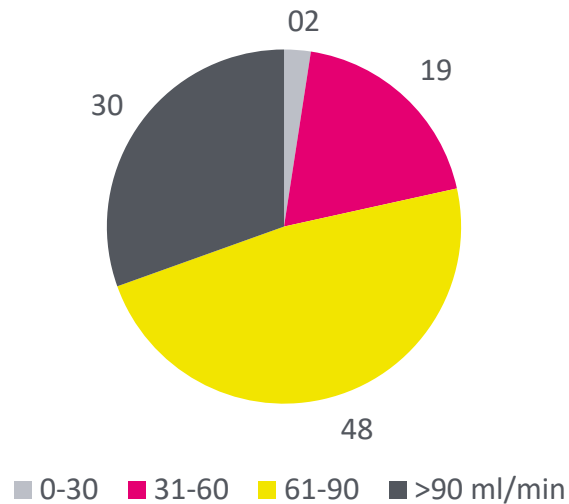Ultima edizione: estratti dati da circa 1/3 dei pazienti con diabete in Italia

# ANNALI DEL RENE AMD:
## Approfondimenti sull'evoluzione del danno nel tempo

# Annali AMD 2011

**Distribuzione della popolazione per classi di filtrato glomerulare (%)**

eGFR calcolato con formula CPK-EPI



Legend: 0-30 | 31-60 | 61-90 | >90 ml/min

Values: 02, 19, 48, 30

De Cosmo et al. KDT 2013

# STUDIARE IL FEGATO NEGLI ANNALI AMD?

# Fatty Liver Index

The **Fatty Liver Index (FLI)**

([**BMI**]), **waist circumference, triglycerides, gamma-glutamyltransferase** (GGT), and a natural logarithm (ln) as follows:

FLI=100×exp[0.953×ln(triglycerides)+0.139×BMI+0.718×ln(GGT)+0.053*[waistcircumference]−15.745]/(1+exp[0.953*ln(triglycerides)+0.139×BMI+0.718×ln(GGT)+0.053*[waist circumference]−15.745]).

## > 60 = elevata probabilità di NAFLD
## < 30 = elevata probabilità di assenza di NAFLD

*Research Article*

# The Burden of NAFLD and Its Characteristics in a Nationwide Population with Type 2 Diabetes

**Gabriele Forlani,[1] Carlo Giorda,[2] Roberta Manti,[2] Natalia Mazzella,[1] Salvatore De Cosmo,[3] Maria Chiara Rossi,[4] Antonio Nicolucci,[4] Paolo Di Bartolo,[5] Antonio Ceriello,[6] Pietro Guida,[7] and AMD-Annals Study Group[7]**

[1] Unit of Metabolic Diseases and Clinical Dietetics, "Alma Mater Studiorum" University of Bologna, 40138 Bologna, Italy
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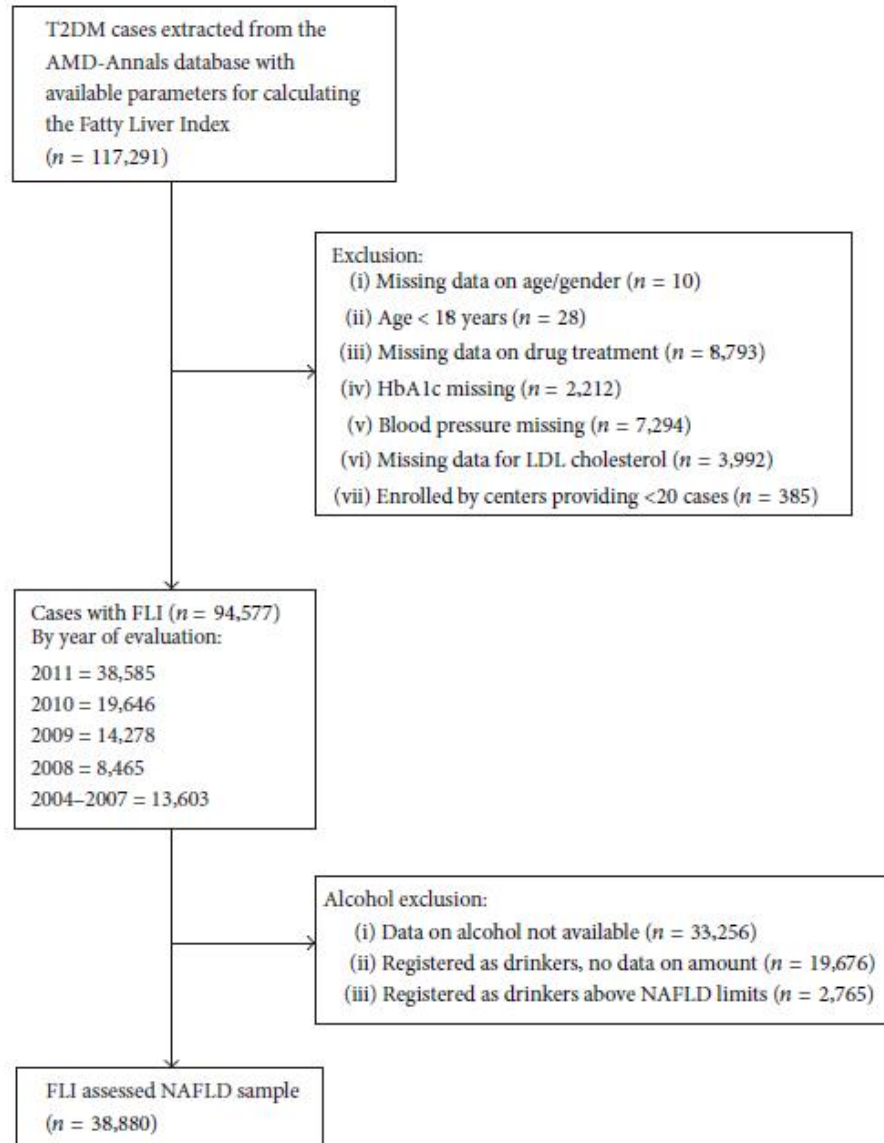[4] Center for Outcomes Research and Clinical Epidemiology (CORE), 65124 Pescara, Italy
[5] Diabetes Unit, AUSL Romagna, 48121 Ravenna, Italy
[6] Biomedical Research Institute August Pi Sunyer (IDIBAPS) and Center for Biomedical Research in Diabetes and Associated Metabolic Disorders (CIBERDEM), 08036 Barcelona, Spain
[7] AMD (Italian Association of Clinical Diabetologists), 00192 Rome, Italy

# Flow chart of sample selection



T2DM cases extracted from the AMD-Annals database with available parameters for calculating the Fatty Liver Index ($n = 117,291$)

Exclusion:
(i) Missing data on age/gender ($n = 10$)
(ii) Age < 18 years ($n = 28$)
(iii) Missing data on drug treatment ($n = 8,793$)
(iv) HbA1c missing ($n = 2,212$)
(v) Blood pressure missing ($n = 7,294$)
(vi) Missing data for LDL cholesterol ($n = 3,992$)
(vii) Enrolled by centers providing <20 cases ($n = 385$)

Cases with FLI ($n = 94,577$)
By year of evaluation:
2011 = 38,585
2010 = 19,646
2009 = 14,278
2008 = 8,465
2004–2007 = 13,603

Alcohol exclusion:
(i) Data on alcohol not available ($n = 33,256$)
(ii) Registered as drinkers, no data on amount ($n = 19,676$)
(iii) Registered as drinkers above NAFLD limits ($n = 2,765$)

FLI assessed NAFLD sample ($n = 38,880$)

# Clinical features of patients according to Fatty Liver Index

| | All | Fatty Liver Index | | | $p^1$ | $p^2$ | $p^3$ |
| | | <30 | 30-59 | ≥60 | | | |
| | n=38880 | n=5882 (15.1%) | n=9804 (25.2%) | n=23194 (59.6%) | | | |
| Male gender | 47.6% | 41.0% | 48.3% | 49.0% | δ | δ | - |
| Age (years) | 65±12 | 66±13 | 67±11 | 64±11 | α | δ | δ |
| Known duration of diabetes (years) | 9±9 | 10±10 | 9±9 | 8±9 | δ | δ | δ |
| BMI (body mass index) (Kg/m2) | 30±6 | 24±2 | 27±3 | 33±5 | δ | δ | δ |
| Waist circumference (cm) | 103±13 | 87±7 | 96±6 | 110±11 | δ | δ | δ |
| GGT (UI/L) | 39±45 | 19±14 | 28±26 | 48±52 | δ | δ | δ |
| Triglycerides (mg/dL) | 145±99 | 88±35 | 117±50 | 172±115 | δ | δ | δ |
| Fatty Liver Index | 64±27 | 18±8 | 46±9 | 84±12 | | | |
| Serum creatinine (mg/dL) | 0.95±0.51 | 0.89±0.50 | 0.94±0.51 | 0.97±0.50 | δ | δ | δ |
| eGFR (mL/min/1.73 m$^2$) | 79±22 | 81±20 | 78±21 | 78±22 | δ | δ | - |
| Albuminuria | 26.8% | 20.2% | 23.4% | 30.0% | β | δ | δ |
| HbA1c (% and mmol/mol) | 7.5(58)±1.6 | 7.3(56)±1.6 | 7.3(56)±1.5 | 7.6(60)±1.7 | - | δ | δ |
| Total cholesterol (mg/dL) | 184±42 | 178±38 | 180±40 | 188±43 | β | δ | δ |
| HDL- C<40 if male or<50 mg/dL if female | 40.4% | 21.4% | 32.6% | 48.5% | δ | δ | δ |
| LDL-C ≥100 mg/dL | 54.7% | 50.1% | 53.6% | 56.3% | δ | δ | δ |
| Systolic blood pressure (mmHg) | 138±19 | 134±20 | 137±19 | 139±19 | δ | δ | δ |
| Diastolic blood pressure (mmHg) | 79±10 | 76±9 | 78±10 | 80±10 | δ | δ | δ |
| Q Score | 27±9 | 29±8 | 28±9 | 26±9 | δ | δ | δ |
| Retinopathy | 12.0% | 12.5% | 12.1% | 11.8% | - | - | - |
| Smokers | 16.4% | 15.6% | 16.0% | 16.9% | - | α | β |
| FIB-4>3.25 (%) | | | | 4.4% | | | |
| Diabetes treatment: | | | | | | | |
| - Diet | | 8.2% | 7.0% | 5.9% | α | δ | δ |
| - Insulin and Metformin or Sulfonamides | 12.9% | 10.4% | 11.2% | 14.2% | - | δ | δ |
| - Metformin and Sulfonamides | 31.7% | 28.9% | 32.8% | 31.9% | δ | δ | - |
| - Metformin | 25.1% | 20.4% | 24.1% | 26.6% | δ | δ | δ |
| - Sulfonamides | 8.0% | 11.9% | 9.3% | 6.4% | δ | δ | δ |
| - Other drugs | 1.3% | 1.4% | 1.4% | 1.2% | - | - | - |
| - Thiazolidinediones | 3.5% | 3.0% | 3.4% | 3.6% | - | - | - |
| - Dipeptidyl peptidase 4 inhibitors | 2.2% | 2.2% | 2.3% | 2.2% | - | - | - |

*Forlani G et al. Journal of Diabetes Research. Volume 2016*

# Relative risk ratios adjusted for gender, age, and duration of diabetes

| | RRR for FLI $\geq 60\%$ | $p^2$ | $p^3$ |
|---|---|---|---|
| AST (by 10 UI/L) | 1.29 (1.20-1.38) | δ | δ |
| Serum creatinine (by 1 mg/dL) | 1.93 (1.59-2.34) | δ | δ |
| eGFR (by 10 mL/min/1.73 m²) | 0.82 (0.81-0.84) | δ | δ |
| Albuminuria | 1.72 (1.43-2.07) | δ | δ |
| HbA1c (by 1 %) | 1.18 (1.11-1.25) | δ | δ |
| Total cholesterol (by 20 mg/dL) | 1.13 (1.11-1.14) | δ | δ |
| HDL-C (by 10 mg/dL) | 0.57 (0.55-0.60) | δ | δ |
| LDL-C (by 20 mg/dL) | 1.08 (1.06-1.10) | δ | δ |
| Systolic/Diastolic blood pressure $\geq 140/85$ mmHg | 1.78 (1.66-1.91) | δ | δ |
| Q Score (by 10) | 0.67 (0.64-0.70) | δ | δ |
| Retinopathy | 1.15 (1.05-1.26) | β | α |
| Smokers | 0.92 (0.85-1.00) | - | β |

Permane forte associazione con fattori di IR

# Relative risk ratios adjusted for gender, age, and duration of diabetes for the overall population  ALCOHOL +

| | All | Fatty Liver Index | | | | | |
| --- | --- | --- | --- | --- | --- | --- | --- |
| | | <30 | 30-59 | ≥60 | | | |
| | n=94577 | n=13427 | n=24246 | n=56904 | RRR for FLI ≥60% | p² | p³ |
| AST (UI/L) | 24±16 | 21±12 | 22±14 | 26±18 | 1.35 (1.28-1.42) | δ | δ |
| Serum creatinine (mg/dL) | 0.97±0.51 | 0.90±0.45 | 0.96±0.49 | 0.99±0.53 | 2.16 (1.82-2.58) | δ | |
| eGFR (mL/min/1.73 m2) | 78±21 | 80±20 | 78±20 | 77±22 | 0.82 (0.80-0.83) | δ | |
| Albuminuria | 28.2% | 21.4% | 24.9% | 31.2% | 1.72 (1.46-2.04) | δ | |
| HbA1c (% and mmol/mol) | 7.5 (58) ±1.6 | 7.2 (55) ±1.5 | 7.3 (56) ±1.5 | 7.6 (60) ±1.7 | 1.21 (1.15-1.27) | δ | δ |
| Total cholesterol (mg/dL) | 185±41 | 178±38 | 180±39 | 188±43 | 1.13 (1.12-1.14) | δ | δ |
| HDL-C (mg/dL) | 50±14 | 58±16 | 52±14 | 47±13 | 0.60 (0.58-0.62) | δ | δ |
| LDL-C (mg/dL) | 107±36 | 104±33 | 106±34 | 109±37 | 1.07 (1.06-1.09) | δ | δ |
| Blood pressure ≥140/85 mmHg | 58.0% | 48.7% | 55.4% | 61.3% | 1.76 (1.67-1.87) | δ | δ |
| Q Score | 26±9 | 28±8 | 27±9 | 26±9 | 0.67 (0.64-0.69) | δ | δ |
| Retinopathy | 11.8% | 12.5% | 12.3% | 11.5% | 1.16 (1.07-1.26) | δ | α |
| Smokers | 18.1% | 17.6% | 17.6% | 18.3% | 0.87 (0.82-0.93) | δ | δ |
| Alcohol | 45.2% | 41.9% | 46.8% | 45.4% | 1.00 (0.93-0.07) | - | α |

Alcol o NO alcol nessuna differenza

# Conclusioni 1° lavoro NAFLD

- Non associata a età e durata diabete
- Associata ± compenso glicometabolico
- Forte associazione con fattori Insulino Resistenza (tipo s. metabolica)
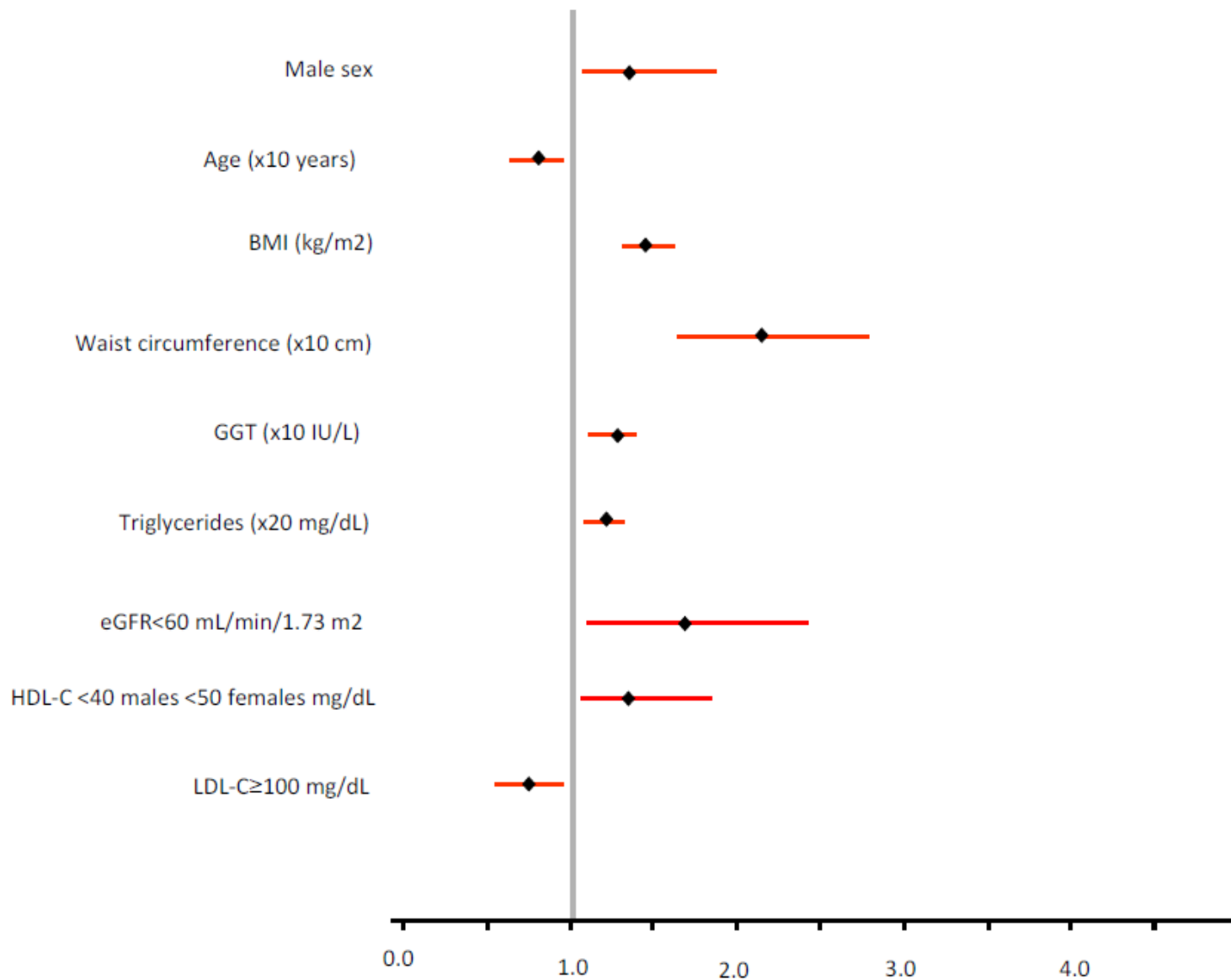- Alcol non rilevante per l'epidemiologia della NAFLD nel DM2

# OCCURRENCE OVER TIME AND REGRESSION OF NONALCHOLIC FATTY LIVER DISEASE IN TYPE 2 DIABETES

Carlo Giorda[1], Gabriele Forlani[2], Roberta Manti[1], Natalia Mazzella[2], Salvatore De Cosmo[3], Maria Chiara Rossi[4],

Antonio Nicolucci[4], Giuseppina Russo[5], Paolo Di Bartolo[6], Antonio Ceriello[7], Piero Guida[8], and the AMD-Annals
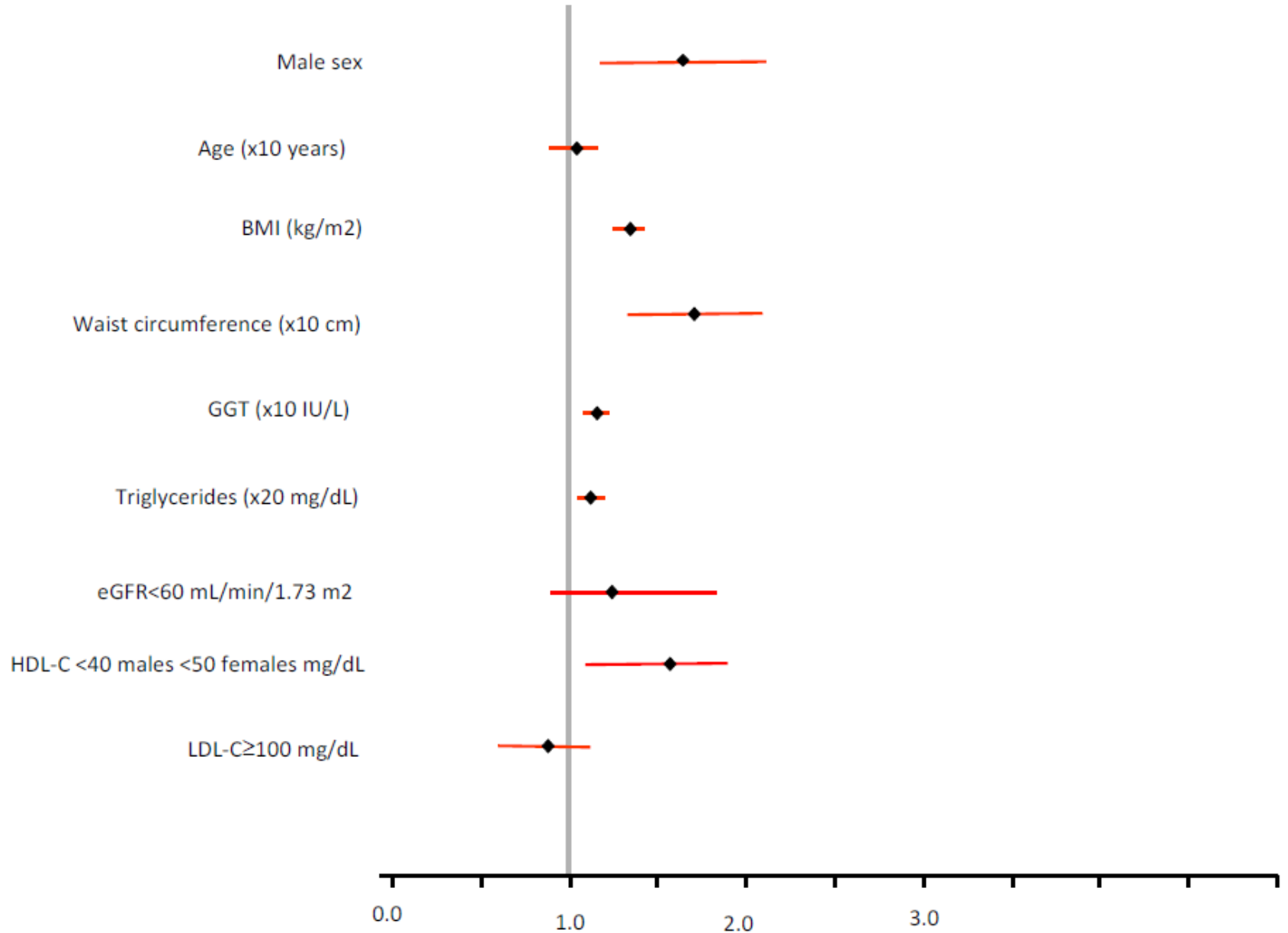
Study Group[9]

# Baseline clinical features of the study population according to 3-year FLI outcome.

| | NAFLD occurrence | | | NAFLD regression | | |
|---|---|---|---|---|---|---|
| | No | Yes | | No | Yes | |
| | n=1634 | n=313 | p | n=2673 | n=410 | p |
| Age (years) | 65±11 | 64±10 | 0.105 | 63±10 | 65±11 | 0.017 |
| BMI (kg/m$^2$) | 25.8±2.8 | 28.3±2.6 | <0.001 | 34±5 | 30±3 | <0.001 |
| Waist circumference (cm) | 91±8 | 97±6 | <0.001 | 110±11 | 102±7 | <0.001 |
| Fatty liver index (%) | 34±15 | 48±9 | <0.001 | 85±11 | 72±9 | <0.001 |
| eGFR<60 mL/min/1.73 m$^2$ | 219 (14.3%) | 57 (19.2%) | 0.032 | 471 (18.8%) | 63 (16.2%) | 0.243 |
| Albuminuria | 138 (13.0%) | 31 (15.2%) | 0.403 | 399 (23.4%) | 45 (17.1%) | 0.020 |
| Total cholesterol (mg/dL) | 185±38 | 179±36 | 0.010 | 190±42 | 195±39 | 0.021 |
| HDL-C (mg/dL) | 54±15 | 51±14 | <0.001 | 47±13 | 48±13 | 0.008 |
| HDL-C <40 males <50 females (mg/dL) | 454 (28.3%) | 116 (37.9%) | 0.001 | 1369 (52.5%) | 176 (44.6%) | 0.002 |
| LDL-C (mg/dL) | 110±33 | 106±31 | 0.038 | 109±36 | 112±34 | 0.040 |
| LDL-C≥100 mg/dL | 950 (59.2%) | 160 (51.8%) | 0.015 | 1470 (57.5%) | 244 (61.9%) | 0.096 |
| Systolic BP (mm Hg) | 138±19 | 139±20 | 0.330 | 141±19 | 139±19 | 0.044 |
| Diastolic BP (mm Hg) | 77±9 | 78±9 | 0.361 | 81±10 | 79±10 | <0.001 |
| Retinopathy | 197 (12.1%) | 49 (15.7%) | 0.080 | 373 (14.0%) | 39 (9.5%) | 0.023 |
| Treatment with statins | 665 (40.7%) | 127 (40.6%) | 0.970 | 1113 (41.6%) | 190 (46.3%) | 0.048 |
| Antihypertensive treatment | 996 (61.0%) | 200 (63.9%) | 0.325 | 1955 (73.1%) | 271 (66.1%) | 0.004 |
| Treatment with ACE-Is/ARBs | 832 (50.9%) | 173 (55.3%) | 0.156 | 1691 (63.3%) | 229 (55.9%) | 0.006 |
| *Antidiabetic therapy* | | | | | | |
| Insulin | 261 (16.0%) | 67 (21.4%) | 0.019 | 371 (13.9%) | 43 (10.5%) | 0.074 |
| Insulin and biguanides or sulfonylureas | 170 (10.4%) | 55 (17.6%) | <0.001 | 459 (17.2%) | 42 (10.2%) | 0.001 |
| Biguanides and sulfonylureas | 541 (33.1%) | 82 (26.2%) | 0.017 | 809 (30.3%) | 162 (39.5%) | <0.001 |
| Sulfonylureas | 209 (12.8%) | 18 (5.8%) | 0.001 | 157 (5.9%) | 33 (8.0%) | 0.100 |

*Giorda CB et al. DMRR*

# Multivariate analysis of 3-year NAFLD occurrence

# Multivariate analysis of 3-year Lack of NAFLD regression



*Giorda CB et al. DMRR*

# Analysis of 3-year clinical features of changes from baseline according to FLI outcome.

| | NAFLD occurrence | | | NAFLD regression | | |
|---|---|---|---|---|---|---|
| | No | Yes | | No | Yes | |
| | n=1634 | n=313 | p | n=2673 | n=410 | p |
| *Changes from baseline* | | | | | | |
| $\Delta$BMI (body-mass index) (kg/m$^2$) | -0.1±1.6 | 1.8±2.5 | <0.001 | 0.1±2.2 | -1.7±2.1 | <0.001 |
| $\Delta$Waist circumference (cm) | 1±6 | 7±7 | <0.001 | 1±7 | -4±6 | <0.001 |
| $\Delta$GGT (IU/L) | 0±18 | 11±26 | <0.001 | -2±41 | -15±30 | <0.001 |
| $\Delta$Triglycerides (mg/dL) | -4±43 | 42±61 | <0.001 | -17±119 | -61±85 | <0.001 |
| $\Delta$eGFR (mL/min/1.73 m$^2$) | -3±13 | -5±14 | 0.003 | -4±13 | -2±14 | 0.013 |
| $\Delta$HbA1c (%) | -0.1±1.3 | 0.1±1.5 | 0.003 | -0.2±1.6 | -0.6±1.5 | <0.001 |
| $\Delta$Total cholesterol (mg/dL) | -10±37 | 5±38 | <0.001 | -12±44 | -26±42 | <0.001 |
| $\Delta$HDL-C (mg/dL) | 1±11 | -1±11 | 0.007 | 0±10 | 3±11 | <0.001 |
| $\Delta$LDL-C (mg/dL) | -10±34 | -2±34 | <0.001 | -11±38 | -17±39 | 0.004 |
| $\Delta$ALT (IU/L) | -1±17 | 4±21 | <0.001 | -3±20 | -9±19 | <0.001 |
| $\Delta$Systolic BP(mm Hg) | -3±20 | 1±21 | 0.003 | -3±21 | -4±20 | 0.047 |
| $\Delta$ Diastolic BP (mm Hg) | -2±11 | 0±11 | 0.003 | -3±12 | -3±11 | 0.213 |
| $\Delta$Q Score | 2±10 | 0±9 | <0.001 | 2±10 | 4±10 | <0.001 |

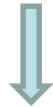*Giorda CB et al. DMRR*

# Conclusioni 2° lavoro NAFLD

- NAFLD is a dynamic condition.

- About 5% of diabetic patients entering or leaving the status every year. Younger male patients with insulin resistance or organ damage have a higher risk of presenting with *FLI*-NAFLD at baseline, developing *FLI*-NAFLD within 3 years, and a lower probability of regression.

- Alcol not relevant as regards epidemiology of NAFLD in T2DM

# Evoluzione verso la cirrosi

NAFLD

↓

NASH

↓

FIBROSI CIRROSI

**Trends over time of hepatic fibrosis scores and risk of cirrhosis in a cohort of type 2 diabetes**

Carlo Bruno Giorda [a], Gabriele Forlani[b], Roberta Manti [a], Natalia Mazzella[b], Salvatore De Cosmo[c],

Giuseppina Russo, Maria Chiara Rossi[d], Antonio Nicolucci[d], Paolo Di Bartolo[e], Antonio Ceriello[f],

Pietro Guida[g] on behalf of the AMD-Annals Study Group[h].

**The Fibrosis 4 score (FIB4)** algorithm is based on **age, serum alanine aminotransferase (ALT), aspartate aminotransferase (AST), and platelet count (PLT)** according to the formula: FIB-4=age[years]*AST[IU/L]/((PLT[109/L]*(ALT[IU/L])1/2)
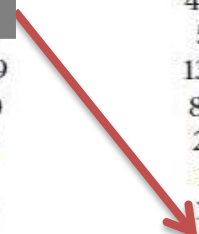
Baseline clinical features of the study population according to FIB-4 score.

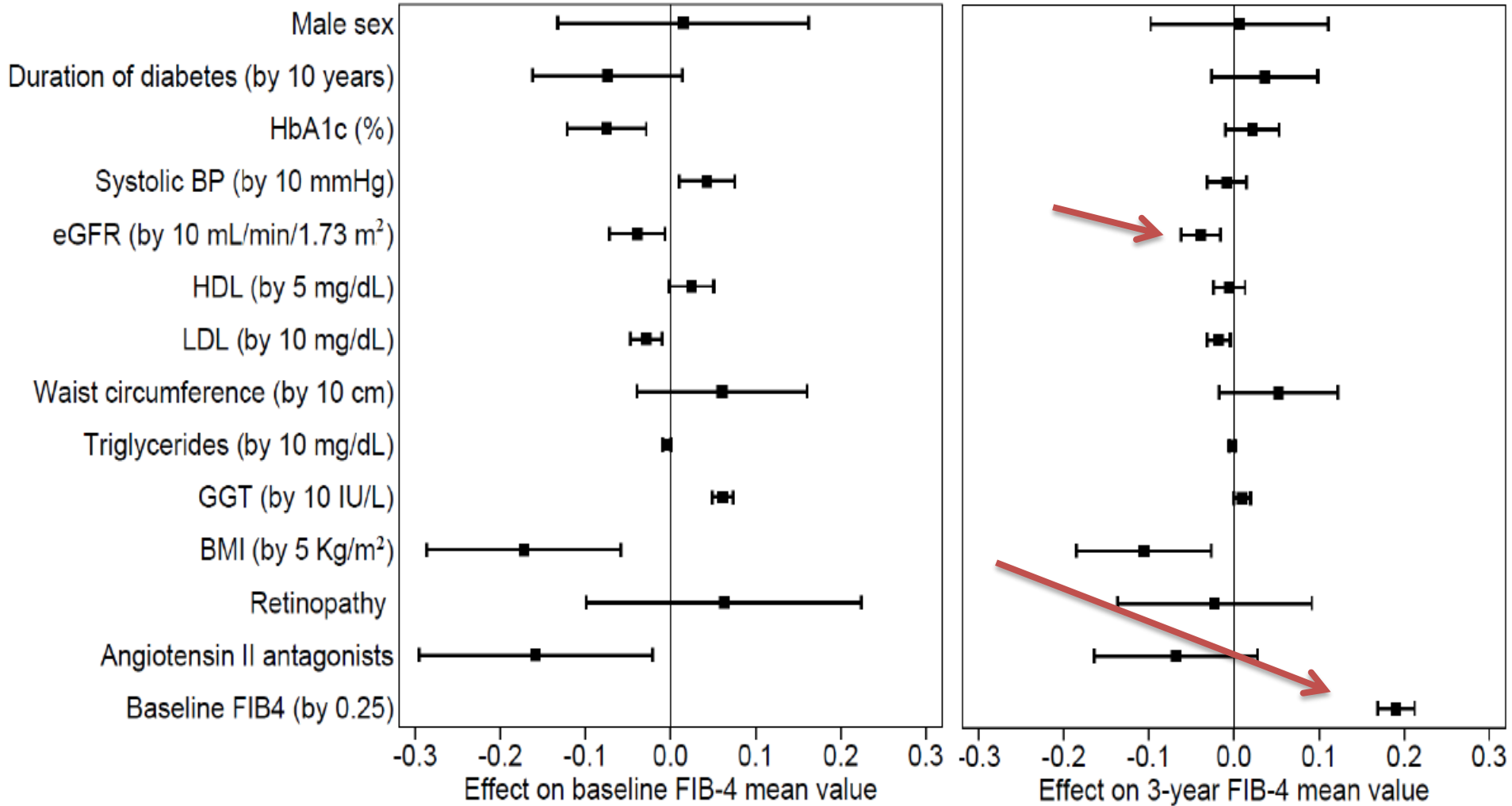| | All $n = 38880$ | Fatty Liver Index | | | $p^1$ | $p^2$ | $p^3$ |
|---|---|---|---|---|---|---|---|
| | | <30 $n = 5882$ (15.1%) | 30–59 $n = 9804$ (25.2%) | ≥60 $n = 23194$ (59.6%) | | | |
| Male gender | 47.6% | 41.0% | 48.3% | 49.0% | δ | δ | — |
| Age (years) | 65 ± 12 | 66 ± 13 | 67 ± 11 | 64 ± 11 | α | δ | δ |
| Known duration of diabetes (years) | 9 ± 9 | 10 ± 10 | 9 ± 9 | 8 ± 9 | δ | δ | δ |
| BMI (body mass index) (Kg/m$^2$) | | | | 33 ± 5 | δ | δ | δ |
| Waist circumference (cm) | | | | 110 ± 11 | δ | δ | δ |
| GGT (UI/L) | | | | 48 ± 52 | δ | δ | δ |
| Triglycerides (mg/dL) | | | | 172 ± 115 | δ | δ | δ |
| Fatty Liver Index | | | | 84 ± 12 | | | |
| Serum creatinine (mg/dL) | | | | 0.97 ± 0.50 | δ | δ | δ |
| eGFR (mL/min/1.73 m$^2$) | | | | 78 ± 22 | δ | δ | — |
| Albuminuria | | | | 30.0% | β | δ | δ |
| HbA1c (% and mmol/mol) | | | .5 | 7.6 (60) ± 1.7 | — | δ | δ |
| Total cholesterol (mg/dL) | | | | 188 ± 43 | β | δ | δ |
| HDL-C < 40 if male or <50 mg/dL if female | | | | 48.5% | δ | δ | δ |
| LDL-C ≥ 100 mg/dL | | | | 56.3% | δ | δ | δ |
| Systolic blood pressure (mmHg) | 138 ± 19 | 134 ± 20 | 137 ± 19 | 139 ± 19 | δ | δ | δ |
| Diastolic blood pressure (mmHg) | 79 ± 10 | 76 ± 9 | 78 ± 10 | 80 ± 10 | δ | δ | δ |
| Q score | 27 ± 9 | 29 ± 8 | 28 ± 9 | 26 ± 9 | δ | δ | δ |
| Retinopathy | 12.0% | 12.5% | 12.1% | 11.8% | — | — | — |
| Smokers | 16.4% | 15.6% | 16.0% | 16.9% | — | α | β |
| FIB-4 > 3.25 (%) | | | | 4.4% | | | |
| Diabetes treatment: | | | | | | | |
| (i) Diet | | 8.2% | 7.0% | 5.9% | α | δ | δ |
| (ii) Insulin and metformin or sulfonamides | 12.9% | 10.4% | 11.2% | 14.2% | — | δ | δ |
| (iii) Metformin and sulfonamides | 31.7% | 28.9% | 32.8% | 31.9% | δ | δ | — |
| (iv) Metformin | 25.1% | 20.4% | 24.1% | 26.6% | δ | δ | δ |
| (v) Sulfonamides | 8.0% | 11.9% | 9.3% | 6.4% | δ | δ | δ |
| (vi) Other drugs | 1.3% | 1.4% | 1.4% | 1.2% | — | — | — |
| (vii) Thiazolidinediones | 3.5% | 3.0% | 3.4% | 3.6% | — | — | — |
| (viii) Dipeptidyl peptidase 4 inhibitors | 2.2% | 2.2% | 2.3% | 2.2% | — | — | — |

**4% dei soggetti DM2 con FLI > 60 ha FIB4 sospetto per fibrosi**

Distribution of patients according to baseline and 3-year FIB4. The red and green cells refers to patient that, respectively, moved-up and -down the FIB-4 class

| FIB4 Baseline | 3-year <1.45 | 1.45-3.25 | >3.25 | Total |
|---|---|---|---|---|
| <1.45 | 780 | 212 | 11 | 1003 |
| 1.45-3.25 | 76 | 362 | 25 | 463 |
| >3.25 | 5 | 12 | 44 | 61 |
| Total | 861 | 586 | 80 | 1527 |

# Multivariate analysis of baseline and 3-years FIB-4 according to baseline clinical characteristics of patients

# Fegato negli ANNALI - Conclusioni dei 3 lavori

FASE steatosi

Prevalenza/Incidenza/Regressione non associate con età e durata. Associate in modo modesto con HbA1c

Associazione forte con fenotipo IR ed evidente con danno renale

Alcol non rilevante nella epidemiologia nel DM2

# Fegato negli ANNALI - Conclusioni dei 3 lavori

FASE fibrosi

Scompare l'associazione con fenotipo IR ma persiste con il danno renale

Alcol non rilevante nella epidemiologia

Ma il  fattore predittivo più forte è il FIB4 di base: la fibrosi «viaggia» indipendentemente da fattori metabolici?

Punto di debolezza: virus?

# Grazie per l'attenzione