Best of ILC 2019

NAFLD

Shira Zelber-Sagi R.D. Ph.D
Dept. of Gastroenterology
Tel Aviv Medical Center
School of Public Health,
Haifa University
Israel
The prevalence of non-alcoholic fatty liver disease in young adults in the UK: An impending public health crisis?

**BACKGROUND & AIMS**
- A previous cross-sectional analysis in late teens (mean age 18 years) - NAFLD prevalence of 2.5% by ultrasound
- This study aimed to identify the prevalence of NAFLD in this cohort, now young adults, using TE to measure fibrosis and steatosis with CAP

**RESULTS**
- Mean age was 24 years (±0.8)
- 3,128 TE scans were eligible for fibrosis analysis
  - 76 (2.4%) had fibrosis; 8 (0.3%) had F4 fibrosis
  - ALT, AST, and GGT all associated with rising F score*
  - 780 (20.7%) had steatosis

CAP score positively associated with F score

**CONCLUSIONS**
This is the largest study to analyze fibrosis and steatosis in young adults

1 in 5 had steatosis and 1 in 40 had fibrosis at 24 years, an increase on the previous estimate within the same cohort 6 years prior.

*ALT p=0.0013; AST p<0.001; GGT p<0.001.
Abeysekera K, et al. ILC 2019; GS-08
Dietary Risk Factors for Non-alcoholic Fatty Liver Disease (NAFLD) by Cirrhosis Status: The US Multiethnic Cohort (MEC)

Mazen Noureddin¹,², Shira Zelber-Sagi³, Lynne R. Wilkens⁴, Jacqueline Porcel⁵, Carol J. Boushey⁴, Loïc Le Marchand⁴, Hugo R. Rosen⁶, Veronica Wendy Setiawan⁵,⁷

¹Division of Gastroenterology and Hepatology, Department of Medicine,  
²Comprehensive Transplant Center, Cedars-Sinai Medical Center, Los Angeles, CA  
³School of Public Health, University of Haifa, Haifa, Israel.  
⁴Epidemiology Program, University of Hawaii Cancer Center, Honolulu, HI  
⁵Department of Preventive Medicine, Keck School of Medicine of University of Southern California, Los Angeles, CA  
⁶Department of Medicine at the Keck School of Medicine of University of Southern California, Los Angeles, CA  
⁷Norris Comprehensive Cancer Center, University of Southern California, Los Angeles, CA
Aims

1. To perform a comprehensive analysis of dietary risk factors for NAFLD in large epidemiological cohort in the United States
   - This was done in African Americans, Native Hawaiians, Japanese Americans, Latinos, and whites in the U.S Multiethnic Cohort Study (MEC)

2. To do the analysis in NAFLD overall and by cirrhosis status
Methods

- Nested case-control analysis within the MEC
- NAFLD was determined using ICD codes

<table>
<thead>
<tr>
<th></th>
<th>All NAFLD Cases (N = 2,974)</th>
<th>NAFLD No Cirrhosis (N=2,456)</th>
<th>NAFLD with Cirrhosis (N=518)</th>
<th>Controls (N = 29,474)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age at cohort entry</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean (SD)</td>
<td>57.7 (7.8)</td>
<td>57.2 (7.8)</td>
<td>59.9 (7.5)</td>
<td>57.8 (7.8)</td>
</tr>
<tr>
<td>Sex, n (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Men</td>
<td>1,113 (37.4)</td>
<td>898 (36.6)</td>
<td>215 (41.5)</td>
<td>11,112 (37.7)</td>
</tr>
<tr>
<td>Women</td>
<td>1,861 (62.6)</td>
<td>1,558 (63.4)</td>
<td>303 (58.5)</td>
<td>18,362 (62.3)</td>
</tr>
<tr>
<td>Race/ethnicity, n (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>474 (15.9)</td>
<td>386 (15.7)</td>
<td>88 (17.0)</td>
<td>4,740 (16.1)</td>
</tr>
<tr>
<td>African American</td>
<td>206 (6.9)</td>
<td>156 (6.4)</td>
<td>50 (9.7)</td>
<td>2,060 (7.0)</td>
</tr>
<tr>
<td>Native Hawaiian</td>
<td>186 (6.3)</td>
<td>150 (6.1)</td>
<td>36 (6.9)</td>
<td>1,856 (6.3)</td>
</tr>
<tr>
<td>Japanese American</td>
<td>1,490 (50.1)</td>
<td>1,337 (54.4)</td>
<td>153 (29.5)</td>
<td>14,692 (49.8)</td>
</tr>
<tr>
<td>Latino</td>
<td>618 (20.8)</td>
<td>427 (17.4)</td>
<td>191 (36.9)</td>
<td>6,126 (20.8)</td>
</tr>
<tr>
<td></td>
<td>All NAFLD</td>
<td>NAFLD With Cirrhosis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>----------------------</td>
<td>-----------</td>
<td>----------------------</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>OR (95% CI)</td>
<td>OR (95% CI)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Total red meat</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤ 13.7</td>
<td>1.00 (ref.)</td>
<td>1.00 (ref.)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt; 13.7 to ≤ 23.3</td>
<td>1.08 (0.96-1.21)</td>
<td>1.22 (0.91-1.64)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt; 23.3 to ≤ 34.0</td>
<td>1.12 (1.00-1.26)</td>
<td>1.36 (1.02-1.82)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt; 34.0</td>
<td>1.15 (1.02-1.29)</td>
<td>1.43 (1.08-1.90)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>P-value for trend</strong></td>
<td>0.016</td>
<td>0.012</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Red meat excluding processed meat</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤ 9.3</td>
<td>1.00 (ref.)</td>
<td>1.00 (ref.)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt; 9.3 to ≤ 16.2</td>
<td>1.08 (0.97-1.21)</td>
<td>1.22 (0.91-1.64)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt; 16.2 to ≤ 24.1</td>
<td>1.11 (0.99-1.24)</td>
<td>1.28 (0.96-1.71)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt; 24.1</td>
<td>1.16 (1.04-1.30)</td>
<td>1.52 (1.15-2.01)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>P-value for trend</strong></td>
<td>0.011</td>
<td>0.003</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Processed red meat</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤ 3.0</td>
<td>1.00 (ref.)</td>
<td>1.00 (ref.)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt; 3.0 to ≤ 6.1</td>
<td>1.03 (0.92-1.16)</td>
<td>1.12 (0.85-1.48)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt; 6.1 to ≤ 10.0</td>
<td>1.05 (0.94-1.18)</td>
<td>0.97 (0.72-1.29)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt; 10.0</td>
<td>1.18 (1.05-1.32)</td>
<td>1.31 (0.99-1.71)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>P-value for trend</strong></td>
<td>0.004</td>
<td>0.112</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>All NAFLD</td>
<td>NAFLD With Cirrhosis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>--------------------------</td>
<td>-----------</td>
<td>----------------------</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>OR (95% CI)</td>
<td>OR (95% CI)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Total poultry</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤ 11.4</td>
<td>1.00 (ref.)</td>
<td>1.00 (ref.)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt; 11.4 to ≤ 18.0</td>
<td>1.07 (0.96-1.20)</td>
<td>1.06 (0.81-1.40)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt; 18.0 to ≤ 27.6</td>
<td>1.15 (1.02-1.28)</td>
<td>1.11 (0.85-1.46)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt; 27.6</td>
<td>1.16 (1.04-1.30)</td>
<td>1.03 (0.79-1.35)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>P-value for trend</strong></td>
<td>0.005</td>
<td>0.771</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Poultry excluding processed poultry</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤ 10.7</td>
<td>1.00 (ref.)</td>
<td>1.00 (ref.)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt; 10.7 to ≤ 17.0</td>
<td>1.11 (0.99-1.24)</td>
<td>0.96 (0.73-1.26)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt; 17.0 to ≤ 26.2</td>
<td>1.16 (1.04-1.30)</td>
<td>0.99 (0.76-1.30)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt; 26.2</td>
<td>1.17 (1.05-1.31)</td>
<td>1.02 (0.78-1.33)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>P-value for trend</strong></td>
<td>0.005</td>
<td>0.807</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dietary fiber (g/1,000 kcal/day)</td>
<td>All NAFLD</td>
<td>NAFLD With Cirrhosis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>---------------------------------</td>
<td>-------------------</td>
<td>---------------------</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>OR (95% CI)</td>
<td>OR (95% CI)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤ 8.5</td>
<td>1.00 (ref.)</td>
<td>1.00 (ref.)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt; 8.5 to ≤ 11.0</td>
<td>0.95 (0.85-1.05)</td>
<td>0.88 (0.66-1.16)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt; 11.0 to ≤ 14.0</td>
<td>0.89 (0.80-1.00)</td>
<td>0.94 (0.70-1.25)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt; 14.0</td>
<td>0.84 (0.74-0.95)</td>
<td>0.75 (0.55-1.02)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>P-value for trend</strong></td>
<td><strong>0.003</strong></td>
<td><strong>0.102</strong></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Cholesterol (mg/1,000 kcal/day)</th>
<th>All NAFLD</th>
<th>NAFLD With Cirrhosis</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>OR (95% CI)</td>
<td>OR (95% CI)</td>
</tr>
<tr>
<td>≤ 75.4</td>
<td>1.00 (ref.)</td>
<td>1.00 (ref.)</td>
</tr>
<tr>
<td>&gt; 75.4 to ≤ 97.3</td>
<td>0.99 (0.89-1.11)</td>
<td>1.05 (0.78-1.42)</td>
</tr>
<tr>
<td>&gt; 97.3 to ≤ 121.4</td>
<td>1.07 (0.95-1.19)</td>
<td>1.09 (0.81-1.46)</td>
</tr>
<tr>
<td>&gt; 121.4</td>
<td>1.16 (1.03-1.29)</td>
<td>1.52 (1.15-2.01)</td>
</tr>
<tr>
<td><strong>P-value for trend</strong></td>
<td><strong>0.005</strong></td>
<td><strong>0.002</strong></td>
</tr>
</tbody>
</table>
Conclusions

• Higher intakes of red meat, processed red meat, poultry, and cholesterol are risk factors for NAFLD, while dietary fiber is a protective factor.

• Red meat and cholesterol were associated with NAFLD-related cirrhosis.
BACKGROUND & AIMS

- Current NAFLD criteria allow alcohol intake ≤30 g/day for men and ≤20 g/day for women
  - Unknown if these levels may be harmful in the context of pre-existing NAFLD

- **Aim:** Analyze risk factors for the development of advanced liver disease in the general population with NAFLD

METHODS

- Data from Finnish national health surveys: 1992–2012 and Health 2000
- Linkage with national registers for hospitalization, death, and cancer using ICD codes reflecting liver cirrhosis, liver dysfunction, or liver cancer until 2013
- Alcohol use, binge drinking, *PNPLA3, TM6SF2*, exercise, and smoking
In NAFLD, alcohol drinking habits and genetics predict progression to advanced liver disease: Follow-up of population surveys

**RESULTS**

- 6,462 NAFLD subjects
  - 58 liver events
- **43% rise in risk of liver events per each additional alcohol drink/day**
- Validation against CDT measurements in a subgroup of subjects

**Independent predictors of incident advanced liver disease**

<table>
<thead>
<tr>
<th></th>
<th>HR</th>
<th>95% CI</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>1.05</td>
<td>1.02–1.07</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Waist–hip ratio (/1 SD)</td>
<td>1.80</td>
<td>1.32–2.44</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>HDL cholesterol</td>
<td>2.09</td>
<td>1.08–4.04</td>
<td>0.03</td>
</tr>
<tr>
<td>Alcohol use (10 g/day)</td>
<td>1.43</td>
<td>1.12–1.82</td>
<td>0.004</td>
</tr>
<tr>
<td>Binge drinking</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Less often</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Monthly</td>
<td>2.69</td>
<td>1.27–5.69</td>
<td>0.01</td>
</tr>
<tr>
<td>Weekly</td>
<td>1.48</td>
<td>0.61–3.58</td>
<td>0.39</td>
</tr>
<tr>
<td>TM6SF2 carrier</td>
<td>2.18</td>
<td>1.12–4.24</td>
<td>0.02</td>
</tr>
<tr>
<td>PNPLA3 carrier</td>
<td>1.88</td>
<td>1.09–3.26</td>
<td>0.02</td>
</tr>
</tbody>
</table>

**CONCLUSIONS** Alcohol drinking habits and genetics are important co-factors in the progression of NAFLD, and abstinence should be recommended to persons with NAFLD.
BACKGROUND & AIMS
• The effects of exercise therapy on NAFLD using histological assessment remain unknown

• **Aim**: Investigate the effects of a 12-week exercise intervention (EI) on hepatic fibrosis in individuals with biopsy-proven NAFLD

METHODS
• n = 16 exercise, 9 controls
  – Liver biopsy, transient elastography
  – EI group: 2 supervised and ≤3 unsupervised sessions per week, for 12 weeks
• Control group: 3 physical assessments

RESULTS
Significant regression in hepatic fibrosis stage in the EI group (n=12) at T1 in the absence of clinically significant weight loss (p<0.05)

*pExcept liver biopsy at T2.
O’Gorman P, et al. ILC 2019; PS-105*
Significant regression in fibrosis in paired liver biopsies following a 12-week aerobic exercise intervention in individuals with NAFLD

RESULTS (Cont.)

**Figure 2.** Significant improvement in VO$_{2\text{max}}$ in individuals in EI group who demonstrated fibrosis improvement at T1 (p<0.05)

**Figure 3.** Significant improvement in waist circumference in individuals in EI group who demonstrated fibrosis improvement at T1 (p<0.05)

CONCLUSIONS 58% of individuals demonstrated fibrosis regression at T1, despite only 3/12 achieving ≥5% weight loss

O’Gorman P, et al. ILC 2019; PS-105
• 918 non-cirrhotic underwent a liver biopsy for clinical suspicion of NAFLD in main referral tertiary centres in Italy and the United Kingdom

• Non-invasive fibrosis scores were calculated: NAFLD Fibrosis Score (NFS), APRI, FIB-4, BAAT and BARD

• Liver-related events (ascites, oesophageal varices or hepatic encephalopathy), n=75

• Cardiovascular events, n=91

• Median follow-up of 85 months

Ramy Younes
Longitudinal prognostic value of the most common algorithms for fibrosis in non-alcoholic fatty liver disease

- NFS and FIB4 predict both liver events and HCC
  - AUROC Liver Events 0.76 for both NFS and FIB4
  - AUROC HCC 0.82 and 0.80 for NFS and FIB4 respectively

- NFS > 0.675, a FIB4 > 2.67, an APRI > 1 or a BARD score ≥ 2 reported - worse survival

- All the scores did not show a high impact on the prediction of the cardiologic outcome

- No additional value was obtained when the different scores were combined together
Assessment and relevance of sarcopenia and frailty & Improvement by nutrition and exercise
Malnutrition is a frequent burden in cirrhosis

20% of patients
Compensated cirrhosis

>50% of patients
Decompensated cirrhosis

Muscle tissue depleted (sarcopenia) - equivalent of severe malnutrition

Adipose tissue depleted

ESPEN 2019 & EASL 2018 guideline

- Liver disease patients should be screened for malnutrition
- The presence of sarcopenia should be assessed

Merli M., EASL CPG. J Hepatol 2018
Plauth M., ESPEN guideline. Clinical Nutrition 2019
Sarcopenia- diagnosed when there is loss of muscle mass or muscle function

- Progressive skeletal muscle disorder
  - Muscle quantity
  - Muscle quality (changes in muscle architecture and composition)
  - Muscle strength
  - Low physical performance

Cruz-Jentoft AJ., Age and Ageing 2019
Sarcopenia: revised European consensus on definition and diagnosis

Short Physical Performance Battery (SPPB)

(1) Stance
   (a) feet side-by-side
   (b) semitandem stance
   (c) tandem stance

(2) Gait velocity

(3) Sit-to-stand time
CT- assessed sarcopenia in patients with cirrhosis

- CT image at L3 vertebra is an accurate technique to quantify muscle loss
- Abdominal skeletal muscles area normalized to height = **Skeletal Muscle Index (SMI)** (cm^2/m^2)
- The routine use of CT imaging, especially repeated assessments, is limited in clinical practice, but can be available in cirrhotic patients for other reasons

EASL CPG nutrition in chronic liver disease. J Hepatol 2018
Multicenter study to define sarcopenia in patients with end-stage liver disease

- 396 patients at 5 American transplant centers
- Skeletal muscle index (SMI cm\(^2\)/m\(^2\))

Survival in sarcopenic and nonsarcopenic using optimal SMI cutoffs:
- <50 cm\(^2\)/m\(^2\) for men
- <39 cm\(^2\)/m\(^2\) for women

Carey EJ., Liver Transpl 2017
‘Sarcopenic obesity’ - obesity with low skeletal muscle function and mass

Obesity exacerbates sarcopenia
• Increases infiltration of fat into muscle = myosteatosis
• Muscle oxidative stress, inflammation and insulin resistance

Muscle-catabolism & ‘anabolic resistance’
• Lowers physical function/ sedentary lifestyle

Recognizing it is especially important in the face of increasing prevalence of obesity and NAFLD

Prado CM., Annals of Medicine 2018
Barazzoni R., Obes Facts 2018, ESPEN & EASO statement
Should the MELD-sarcopenia score be incorporated into clinical practice?

• Further external validation is needed
  – The added value of incorporating sarcopenia into the MELD score was not demonstrated in an external validation study
  – c-statistics of 3-month mortality 0.82 vs. 0.84 for MELD score alone

  van Vugt JLA., J Hepatol 2017

• Lack of consensus on the methods for assessment of sarcopenia & cut-off values

• Unfeasibility of repeated monitoring, in contrast to the MELD
Interdependence between physical fitness and nutritional status

Cirrhosis

Physical fitness
- Decreasing exercise & daily living activities & Hypomobility
- Sarcopenia,
  - Sarcopenic obesity
  - Low cardiopulmonary endurance

Nutritional status
- Poor diet, Malabsorption, Catabolic status
- Sarcopenia (quantity/ quality)

Functional deterioration
- Frailty
- Death

Progressive malnutrition

Duarte-Rojo A., Liver Transplantation 2018
Exercise model for patients with cirrhosis

**Exercise intervention**

- **Aerobic training**
  - Cycling
  - Jogging
  - Walking
  - Light swim

- **Strenuous activities forbidden**

- **Resistance training**
  - Weights (1-2lb) 1 kg
  - Chair dips
  - Resistance band
  - Squats

- **Weight-bearing exercise**
  - Side/back leg raise
  - Sit-to-stand reps
  - Go around chair
  - Toe stand

- **Balance & strength**

**Dietary intervention**

- Nutritional therapy

**Mechanism**

- Improve physical fitness
- Increase cardiopulmonary endurance
- Increase muscle mass and strength
- Improve balance, ADL, & independence

**Target**

- Metabolic complications
- Complications from portal hypertension
- Halt/reverse sarcopenia
- Reverse frailty

**Outcome**

- Improve malnutrition
- Health-related quality of life
- Wait-list survival
- Posttransplant complications

---

Duarte-Rojo A., Liver Transplantation 2018
• The aim is to inform politicians, policy-makers and the general population across Europe about NAFLD and the measures required for prevention and treatment

• Addressing obesity in Europe which will then impact on the levels of NAFLD
EASL Recommends:

1. Public health policies to restrict advertising and marketing to children of SSBs and industrially processed foods high in saturated fat, sugar and salt.
2. Fiscal measures to discourage the consumption of SSBs and legislation to ensure that the food industry improves labelling and the composition of processed foods.
3. Health education programmes which emphasise the benefits of a Mediterranean diet and initiatives which promote water consumption, instead of SSBs.
4. Policies and changes to local infrastructure which promote and encourage regular physical activity, improve opportunities for exercise and reverse sedentary lifestyles.
5. Expansion of HCP (and public) knowledge of NAFLD and skills to conduct nutrition screening, counselling and engagement of patients in appropriate behaviour change initiatives.
6. Funding of new diagnostic research programmes.

Obesity Is Feeding The Rise in Non-Alcoholic Fatty Liver Disease (NAFLD) Across Europe

NAFLD affects 1 in 4 people across the EU.