

# Cocktails and Covid 19 Pounds: The Essential Ingredients for Early Cirrhosis in Women

Elyssa Del Valle, M.D. DBIM 2022



# Women Increasingly at Risk for Alcohol –Related Liver Disease. Let's explore why

# Seems a whole new culture began since that HBO series aired



## HAPPENING NOW

Russia launches a large-scale attack on Ukraine. Watch CNN's live coverage and analysis of the invasion

## We really did buy more alcohol during the early pandemic, study finds

By Sandee LaMotte, CNN

🕒 Updated 3:15 PM ET, Wed December 15, 2021

## Economist: Liquor store sales up 28% during pandemic; bars down 33%

by Roby Brock (robby@talkbusiness.net) 🕒 January 31, 2021 1:13 pm 👁 1,106 views

INFECTIOUS DISEASE, SUBSTANCE USE **Aug. 20 2021**

## Study Shows Uptick in U.S. Alcohol Beverage Sales During COVID-19 Pandemic

HIGHEST VARIATION WAS A 7.5-BILLION-DOLLAR INCREASE IN LIQUOR STORE SALES BETWEEN THE FIRST THREE QUARTERS OF 2019 AND 2020

# Objectives

- Set the STAGE....Alarming DATA
- Susceptibility factors that increase the prevalence of alcohol related liver disease in young women
- Covid 19 pounds – review data on BMI mortality especially in younger ages
- All you want to know about Cirrhosis but were afraid to ask
- The Antidote
- Discuss the projected prevalence and mortality associated with alcohol-related liver disease in women
- Review underwriting implications as a result of the rise of alcohol related liver disease in women

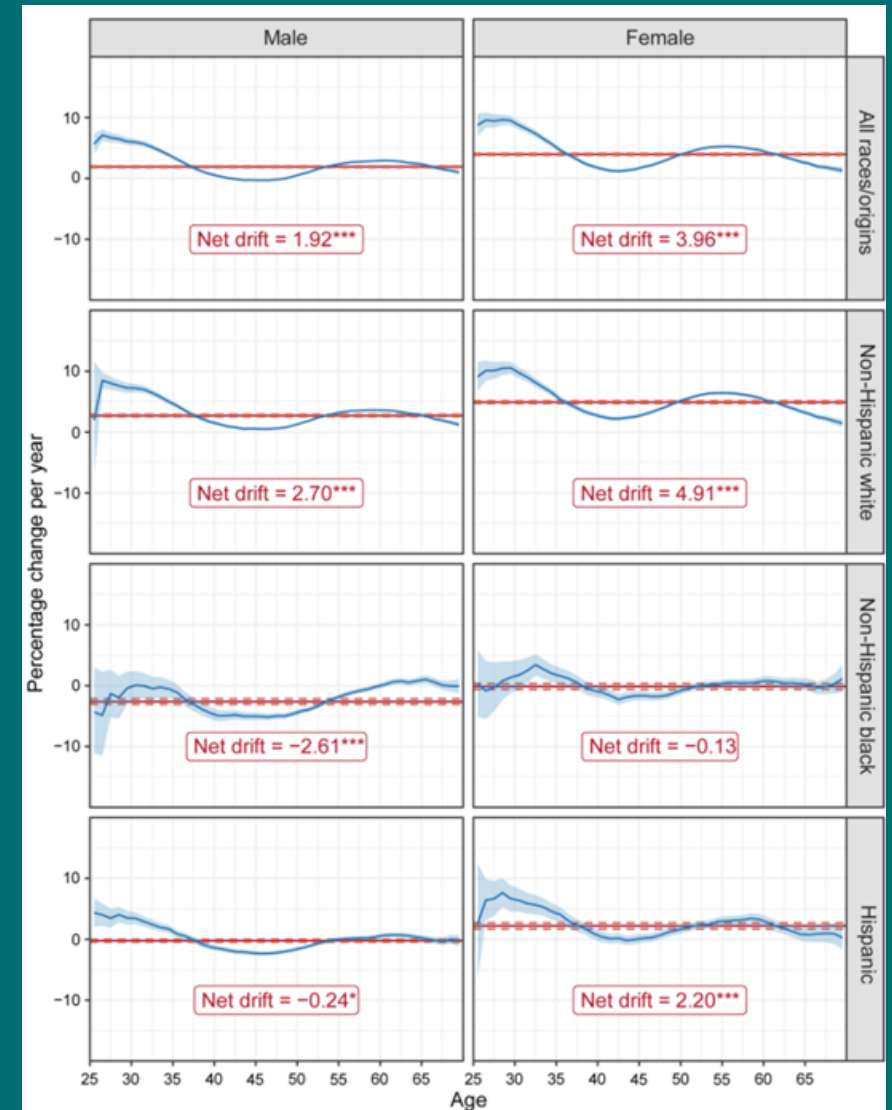
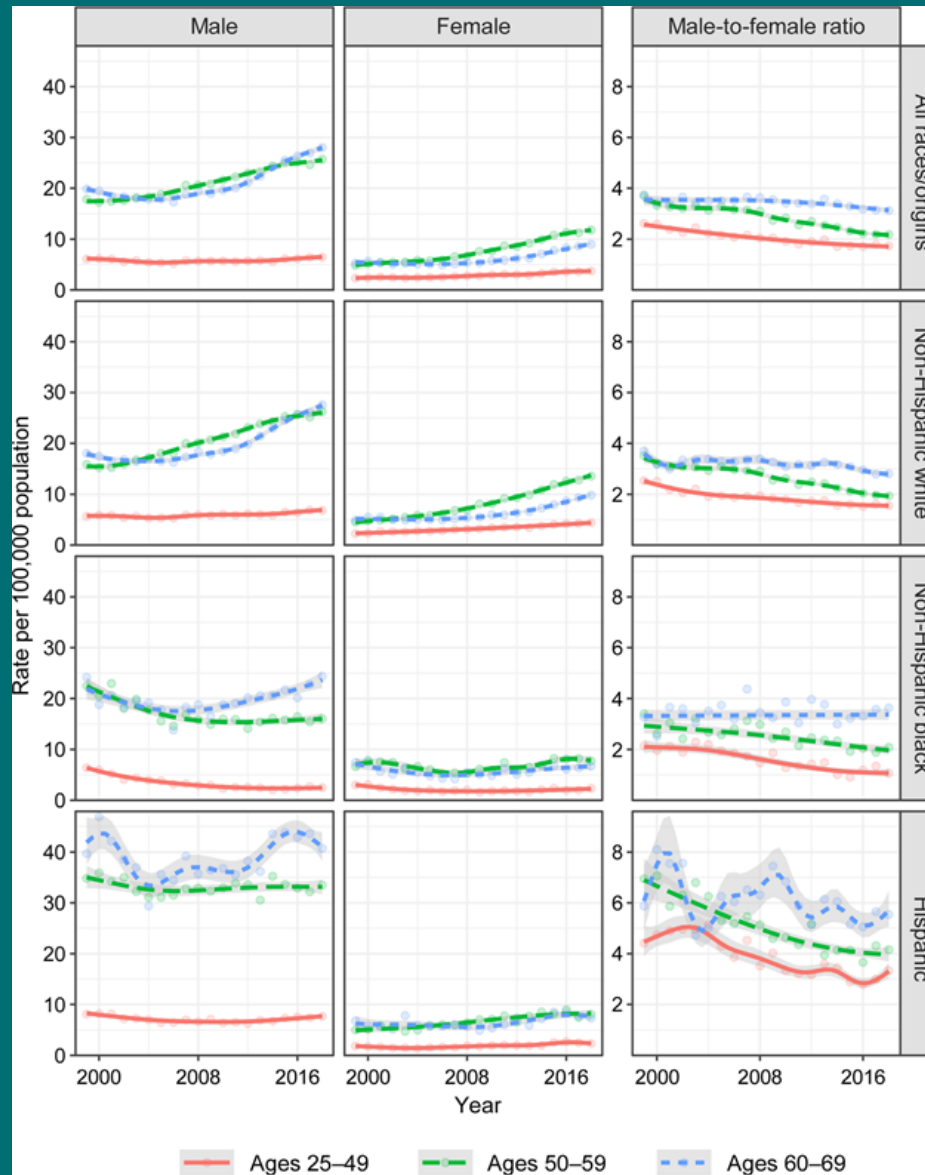
# Setting the Stage on Alcohol Use Among Women

Per CDC:

- Half of adult women report drinking alcohol
- 13% adult women report binge drinking and on average 4/month consuming 5 drinks per binge
- 18% of women 18-44 binge drink
- in 2019, 32% of female HS students consumed alcohol compared to 26% of male HS counterparts and binge drinking 15% as compared to 13% of HS students
- In 2019, 4% of women overall and 8% of those age 18-25 had an alcohol use disorder



# Data that sounds the Alarm

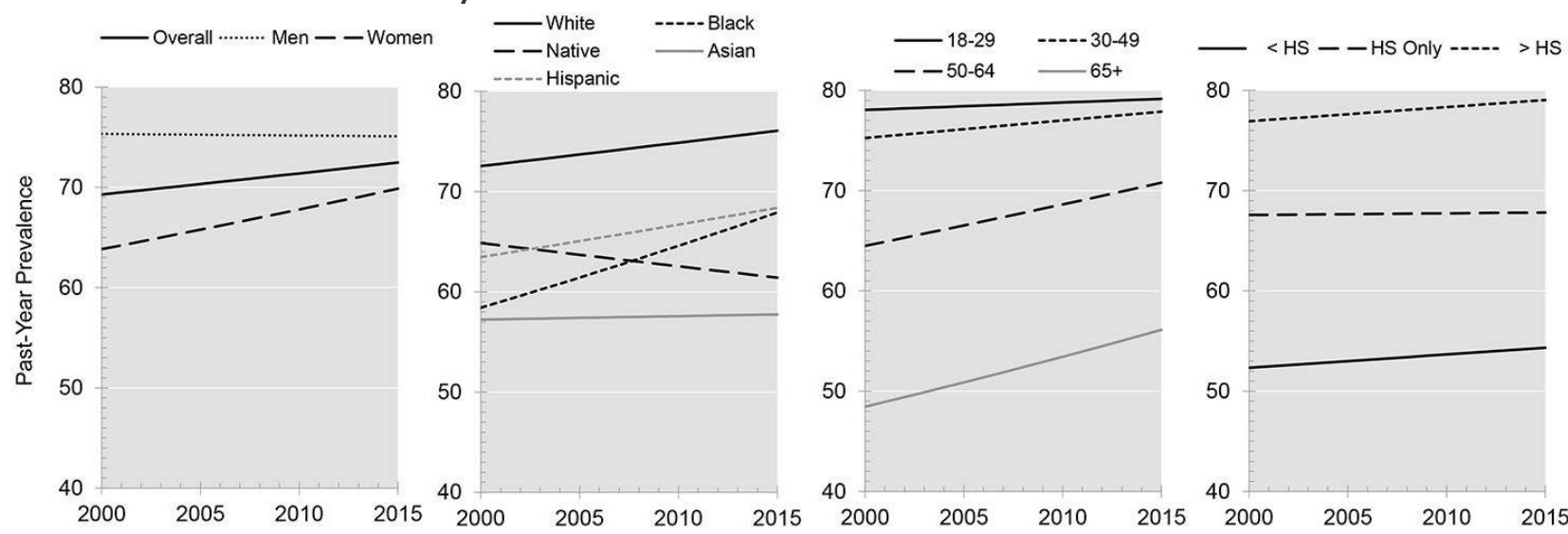


Age-adjusted (net drift) and age-specific annual percentage changes (APC) for alcoholic liver disease mortality, by sex and race/Hispanic origin, in the U.S., 1999–2018.

Note: Dashed lines and gray areas indicate 95% CIs for age-adjusted and age-specific APC, respectively (\* $p < 0.05$ ; \*\*\* $p < 0.001$ ).

# More Data to Sound an **Alarm**

## Trends in Adult Alcohol Use and Binge Drinking in the Early 21st Century United States: A Meta-Analysis of Six National Survey Series



Conclusion: Number of women 18 and older who drink each year rose by 0.6% each year as well as number of women who binge drink. Gaps in alcohol related harm between men and women is narrowing – A Cause for **ALARM**



# Few Stark Conclusions

- Largest increase in Alcoholic liver disease is in women ages 25-34
- Typically takes 10 or more years of drinking to develop liver disease, thus a concern if seeing premature mortality from liver disease in ages under 35
- Women dying from ALD 2-3 yrs earlier than men
- Alcoholic liver disease is a leading indication for liver transplantation in USA which was stable for over 3 decades until now

**WHY ARE WOMEN MORE SUSCEPTIBLE ?**

# Susceptibility factors in women

## What makes women more susceptible to adverse effects of Alcohol?

- Higher levels of **endotoxins** from gut bacteria found in women compared to men after one single episode of binge drinking
- Alcohol boosts the **permeability of gut endotoxins** and bacteria to enter bloodstream, triggering inflammation in liver and elsewhere
- Rise in alcohol misuse – higher occurrence of alcoholic hepatitis
- Theory that women have less water in their bodies than men (leads to smaller **volume of distribution**) which causes higher concentration of alcohol in blood, with greater harmful levels of exposure to organs
- Women absorb more alcohol and take **longer to metabolize** it and thus, the immediate effects occur more quickly and last longer than in men.
- Increase Kupffer cell activation with **estrogens** which leads to cytokine release and inflammation
- Women have lower levels of **cytochrome P4502E1**, important for EtOH metabolism
- **PNPLA3** (*Patatin-like phospholipase domain protein 3*) – *genetic predisposition for NAFLD*

# *PNPLA3 Gene polymorphism is associated with predisposition to and severity of alcoholic liver disease*

## ***PNPLA3 Gene polymorphism is associated with predisposition to and severity of alcoholic liver disease***

Meta-analysis review of 10 studies

Increased risk for entire spectrum of **ALD** among drinkers

OR 1.45 (CI 1.24-1.69) and 2.22 (CI 1.50-3.28) for Acute Liver Injury

OR 2.09 (CI 1.79-2.44) and 3.37 (CI 2.49-4.58) for Alcoholic Cirrhosis

OR 2.87 (CI 1.61-5.10) and 12.41 (CI 6.99-22.03) for Cirrhotics with Hepatocellular Carcinoma

OR 2.62 (CI 1.73-3.97) and 8.45 (CI 2.52-28.37) for Alcoholic Liver disease

Am Gastroenterology. 2015 Jun; 110 (6):846-56 Habeeb Salameh et al

## **PNPLA3 gene in liver disease**

2008, a GWAS performed in a population-based sample study, where hepatic liver fat content was measured by magnetic spectroscopy, showed a strong association between a variant (rs738409 C>G p.I148M) in PNPLA3 gene and **NALFD**

Robust associations between PNPLA3 and steatosis, fibrosis/cirrhosis, and hepatocellular carcinoma on a background of metabolic, alcoholic, and viral insults.

The PNPLA3 protein has lipase activity towards triglycerides in hepatocytes and retinyl esters in hepatic stellate cells. The I148M substitution leads to a loss of function promoting triglyceride accumulation in hepatocytes.

J Hepatology. 2016 Aug;65(2):399-412 Eric Trepo et al

# Cocktails and now the COVID 19 POUNDS

Insulin Resistance

**Covid 19 Pounds**

# The Condition 42% of Adults Have That Can Cause Early Death

Being grossly overweight was a problem in America before the pandemic, and it appears to have gotten worse.

By **Aaron Smith** | August 26, 2022

Americans are getting bigger, and not in a good way, as the Covid-19 pandemic drags on.

A survey from **New Mexico State University** said 48% of respondents **gained weight** during the pandemic. That could be bad news for life insurers.

**life annuity**  
specialist

# Conditions Associated with Insulin Resistance

Diabetes

Obesity

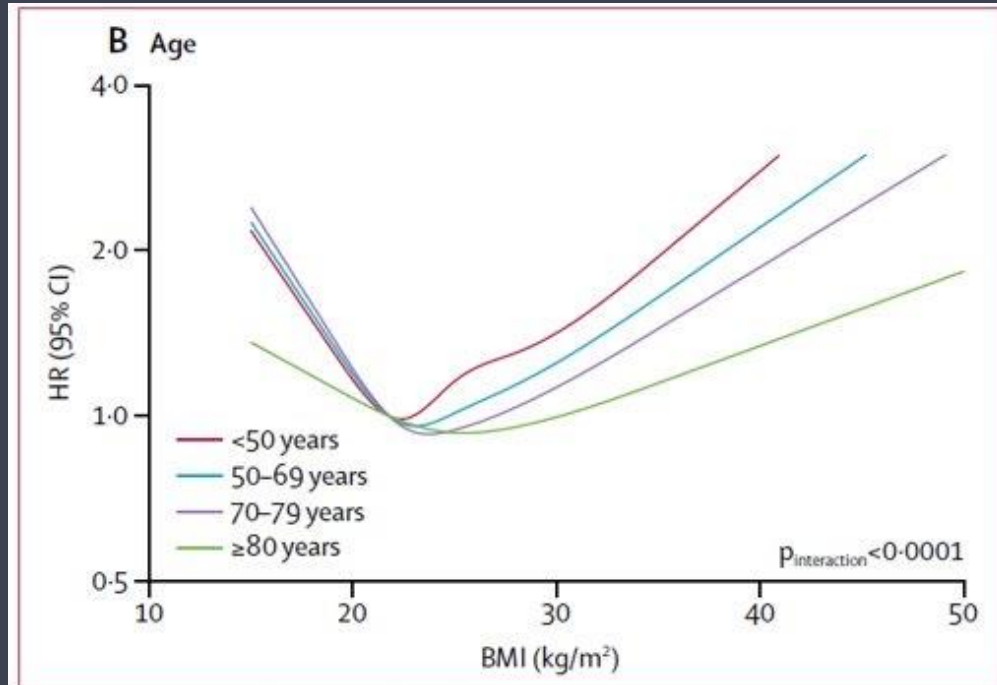
Glucose  
Intolerance

HTN  
^ Trigs  
^ LDL  
^ Fasting  
Insulin

PCOS  
Central  
Obesity  
Type A  
(inherited)  
Type B  
(autoantibodies to  
insulin receptors,  
severe form)  
Syndromes  
Acanthosis  
Nigricans

## Strong Evidence Risk of BMI Varies by AGE

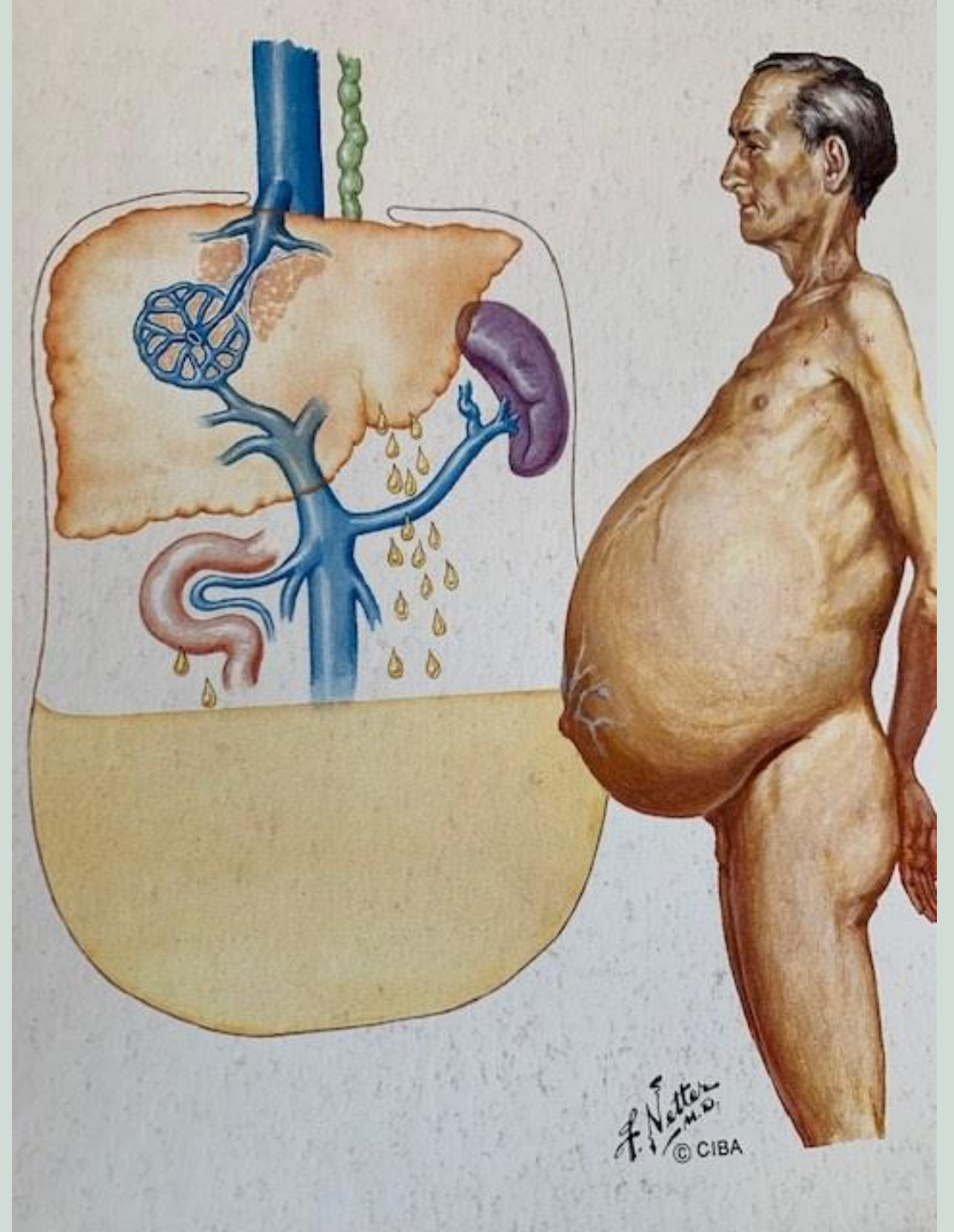
YOUNGER Women at greater risk than older women



**Figure 3: Association between BMI and all-cause mortality among never-smokers, by age (B)**  
5-year exclusion period applied for person-time and events after a BMI record; estimates adjusted for age, deprivation, calendar year, diabetes, and alcohol status (all as defined at date of BMI measure) and stratified by sex. HR=hazard ratio.

Bhaskaran et al  
Lancet Diabetes Endocrinol 2018; 6: 944–53

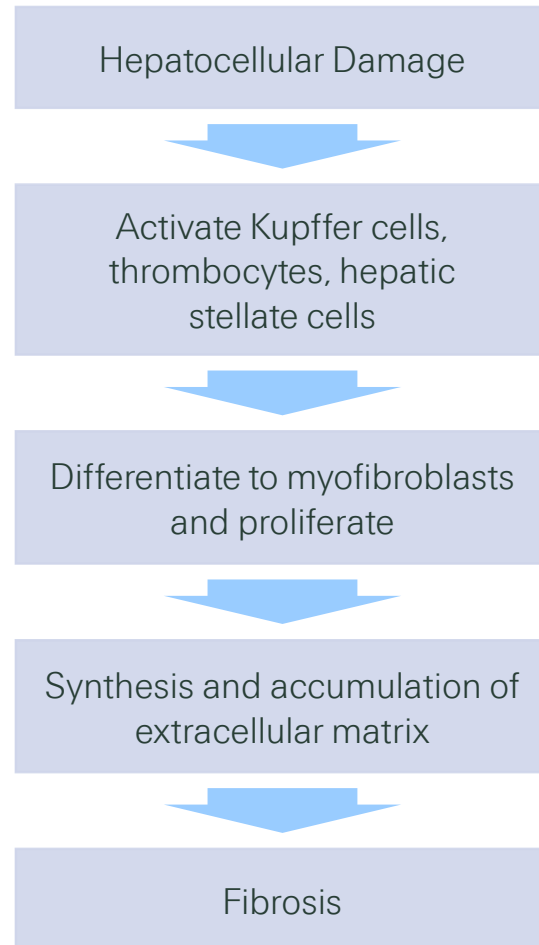
Everything you want to know  
about Cirrhosis but were  
afraid to ask!



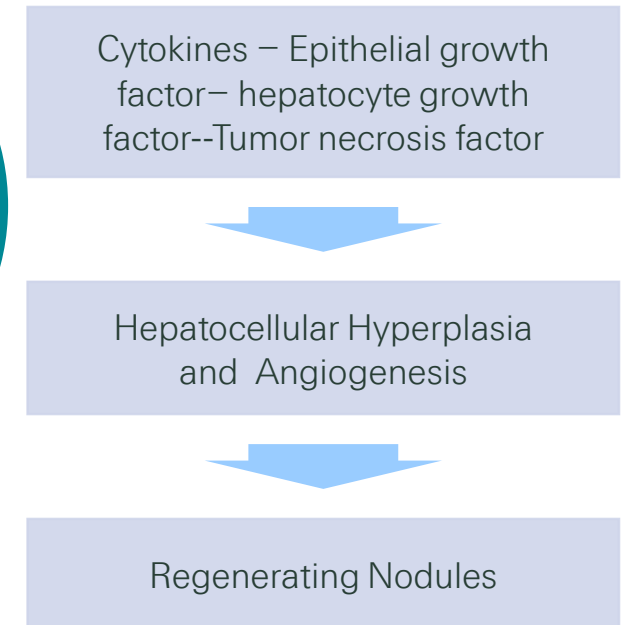


# How does fat & alcohol turn a healthy liver into a cirrhotic liver?

## Hepatic Fibrosis

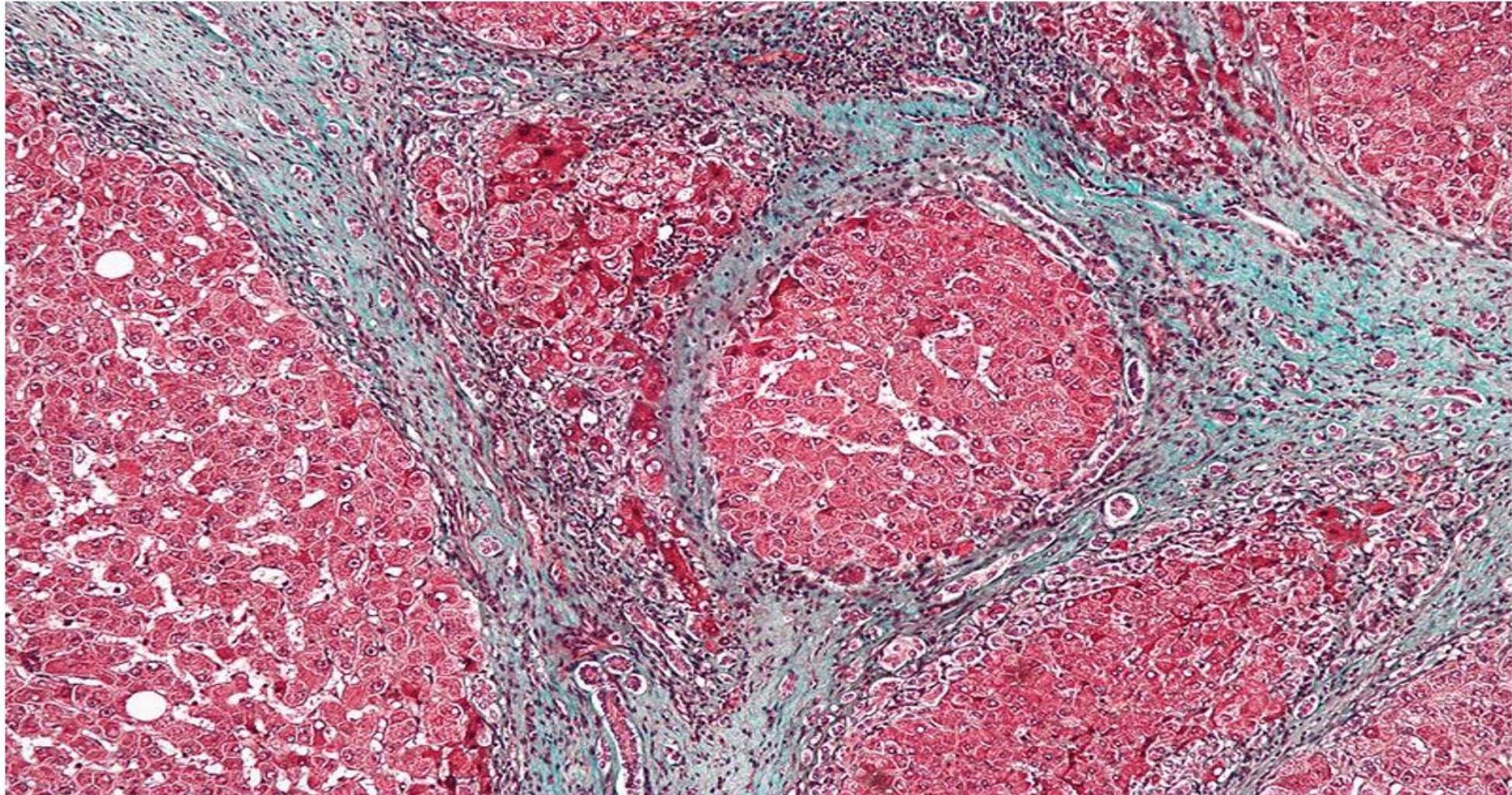


## Regenerating Liver Cells



Venous drainage cannot accommodate the additional blood volume and the regenerating nodules compress hepatic venules all causing portal vein pressure to increase

# Histology of Liver Cirrhosis



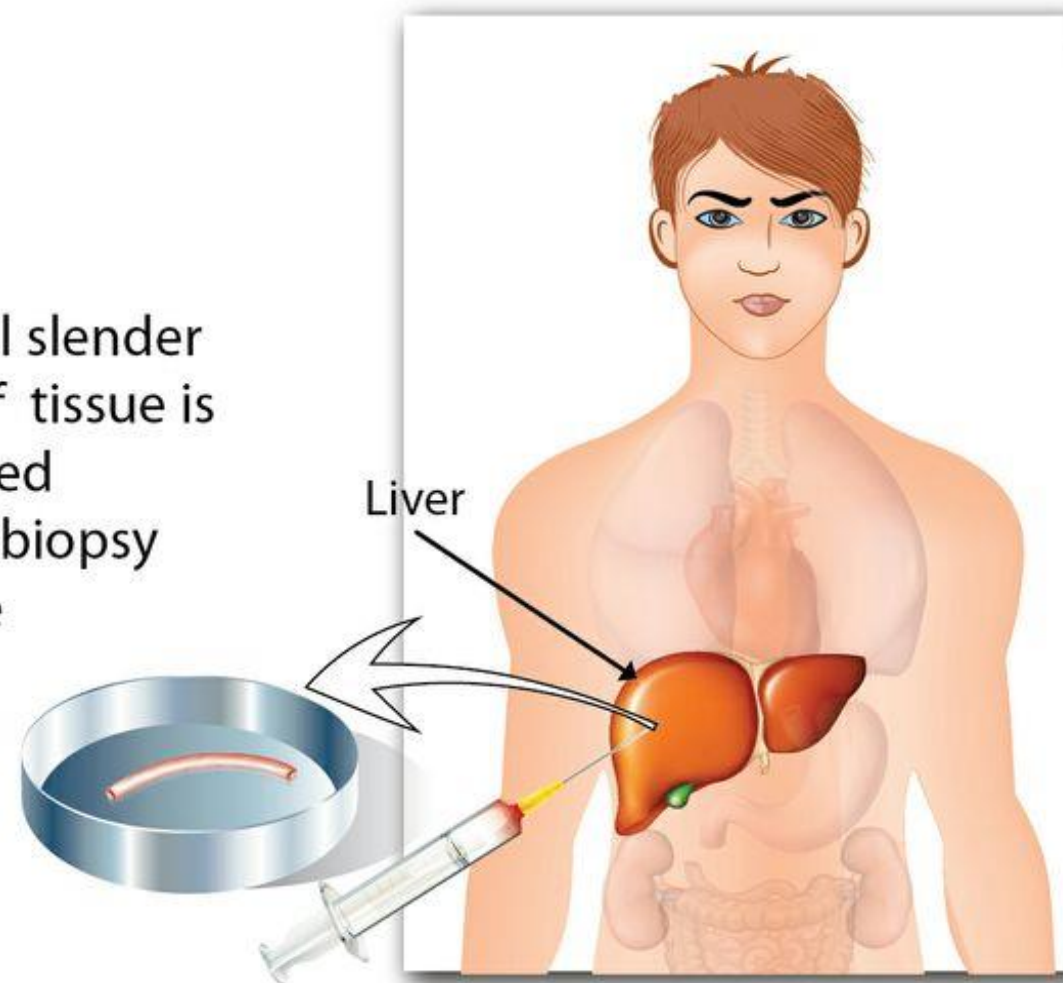
# Gold Standard

First liver aspirate performed by  
German physician: Paul Ehrlich  
in 1883

Reportedly, first liver biopsy  
performed percutaneously in  
1920s

## Liver biopsy

A small slender  
core of tissue is  
removed  
with a biopsy  
needle



**HELP**

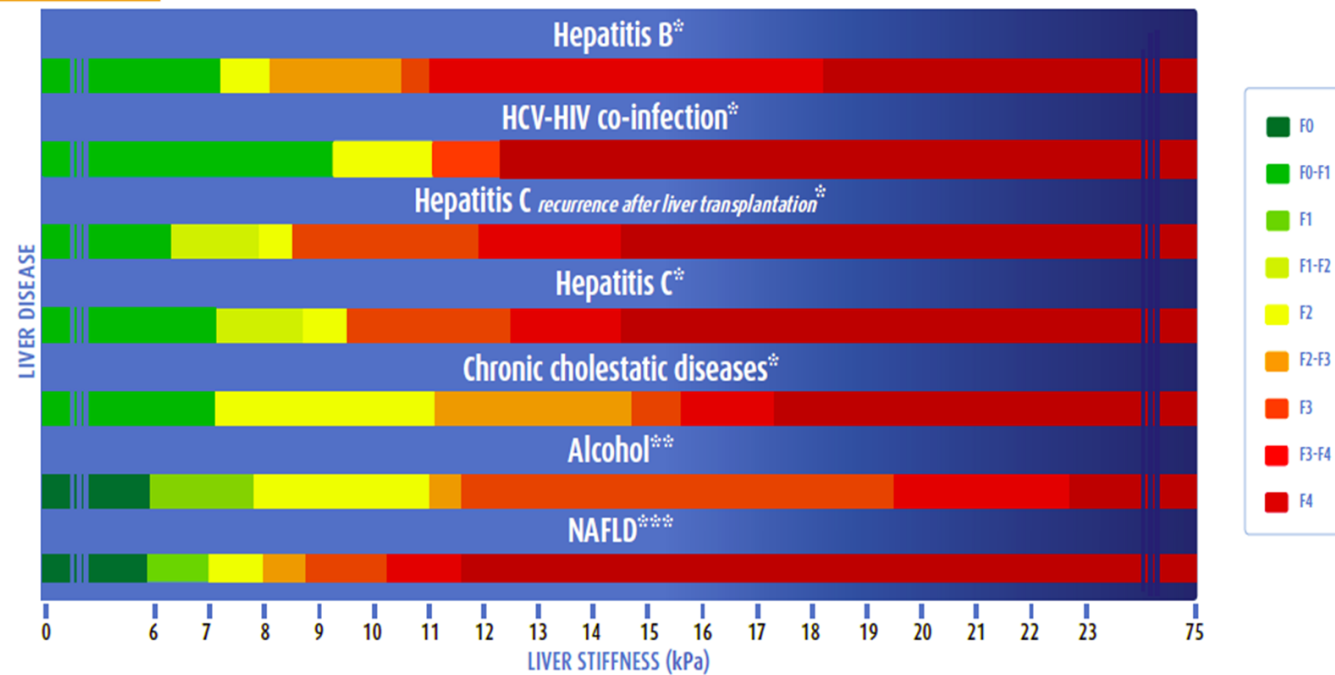
Health Education Library for People

© 2013 www.healthlibrary.com

# FibroScan

## SCORING CARD

CORRELATION BETWEEN LIVER STIFFNESS (kPa) & FIBROSIS STAGE



# FibroTest

marketed in Europe

# FibroSure

marketed in USA

- Non invasive method developed by Australian investigators
- Validated Predictor of Liver Fibrosis using 3 ccs of fasting blood
- Score from 0-1
- Based on age, gender and these 6 serum analytes:
  - 1) Serum bilirubin
  - 2) ALT
  - 3) GGT
  - 4) Alpha 2 macroglobulin
  - 5) Alpha 2 globulin (haptoglobin)
  - 6) Apolipoprotein A1
- FibroTest has been recommended the first line assessment for fibrosis with untreated Chronic Hepatitis C in 2006 by the French National Authority for Health



# Bonacini Cirrhosis Discriminant Score



## Platelets (x1000/mm<sup>3</sup>):

- >340 – zero points
- 280 to 339 – one point
- 220 to 279 – two points
- 160 to 219 – three points
- 100 to 159 – four points
- 40 to 99 – five points
- <40 – six points

## ALT/AST ratio

- >1.7 – zero points
- 1.2 to 1.7 – one point
- 0.6 to 1.19 – two points
- <0.6 – three points

## INR

- <1.1 – zero points
- 1.1 to 1.4 – one point
- >1.4 – two points

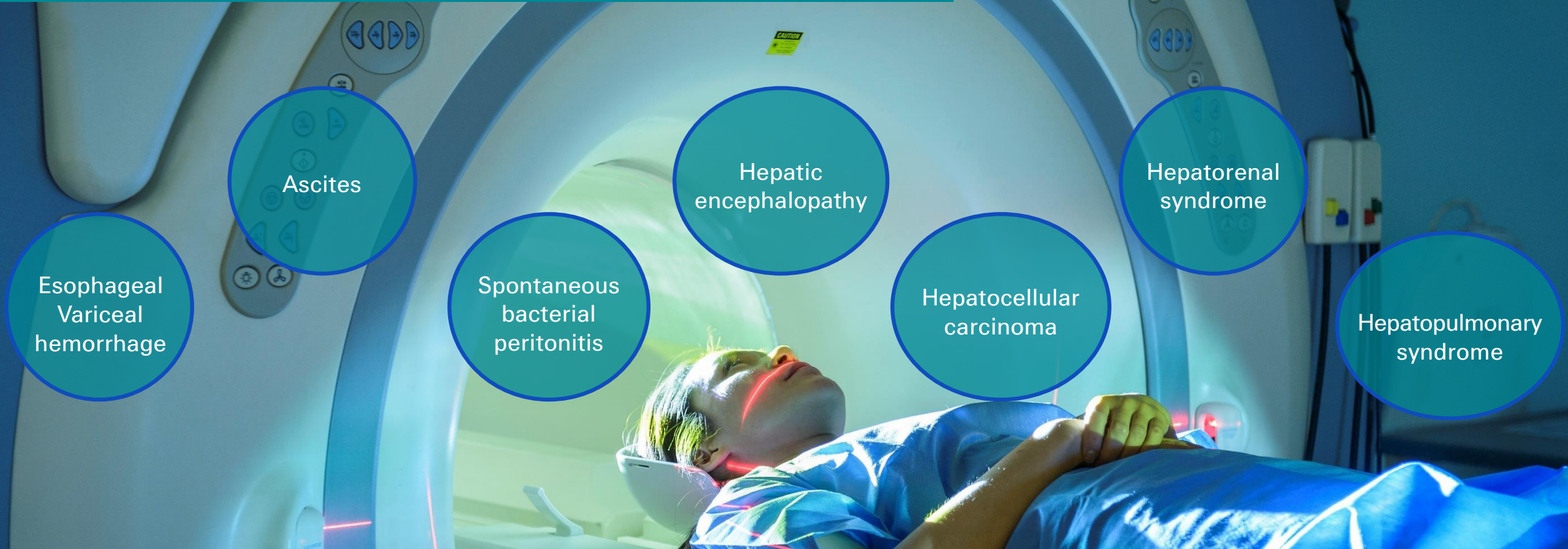
modified three parameter CDS by Dr. Maurizio Bonacini in 1997

# How to Suspect Liver Cirrhosis w/o Biopsy or Fibroscan or Fibrosure

Evidence of decompensated cirrhosis:

Stigmata of chronic liver disease: physical exam findings

# Liver Cirrhosis: Decompensated



No way to reverse these late stages of Cirrhosis Decompensation  
Only treatment at late stage is Liver Transplantation



# Stigmata of Liver Disease

Join me on hospital rounds

# Terry's Nails



**Pop Question:**  
What sequela of  
cirrhosis does  
this depict?



# Caput medusa

Distended abdominal veins

[CAPUT MEDUSAE: Causes- Risk factors- Meaning- Symptoms- Treatment- Palm Tree Sign - YouTube](#)

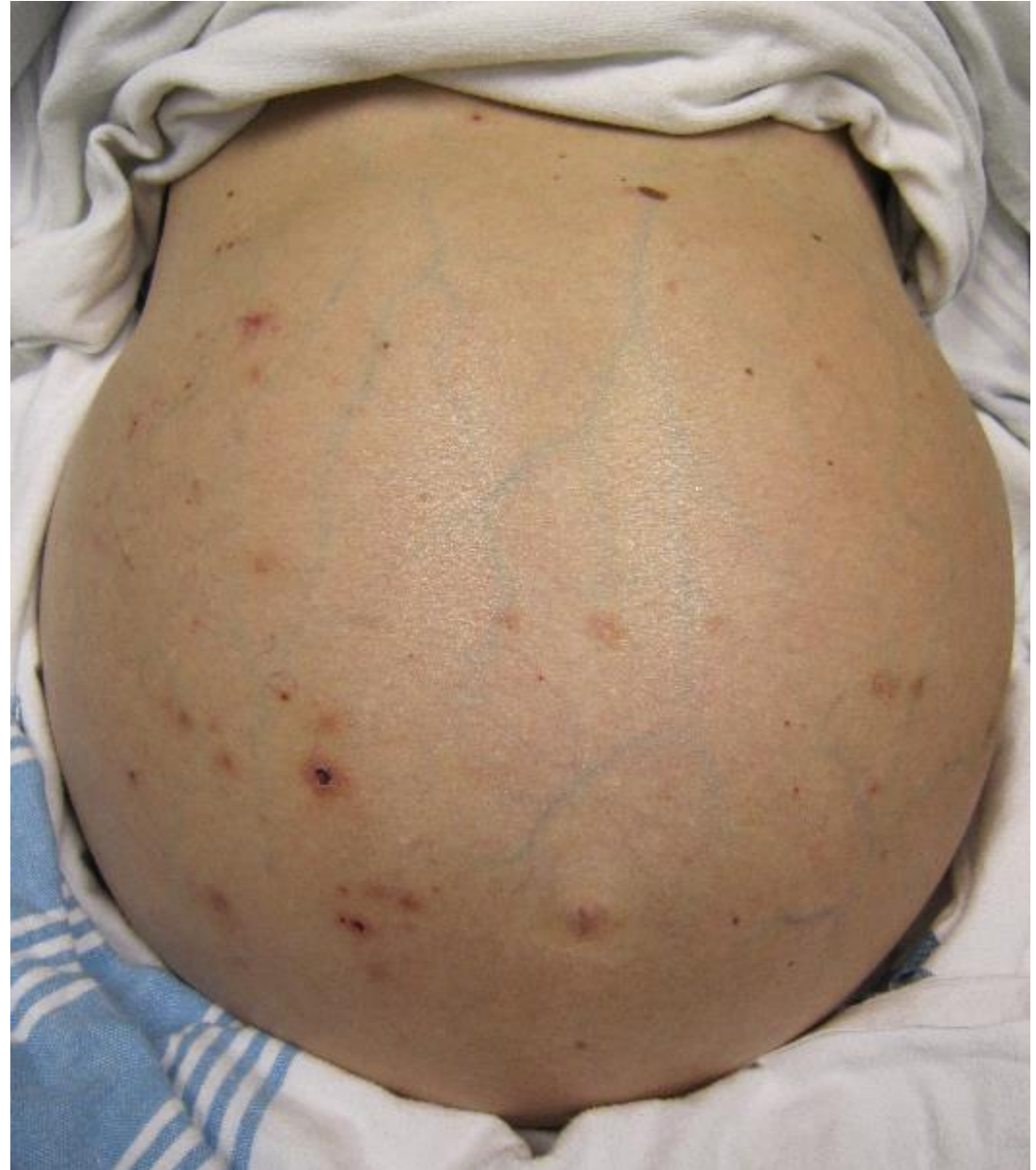


Can you guess  
which depicts  
gynecomastia due  
to liver cirrhosis



Wikipedia images

# Ascites



Wikipedia image

# Spider Nevi or Facial Telangectasia



Wikipedia image

# Palmar Erythema



**D**



# Jaundice



Wikipedia image

# William Bean's poem on Spider nevi

"An older Miss Muffett...

...Decided to rough it...

...And lived upon whisky and gin."

"Red hands and a spider...

...Developed outside her –

...Such are the wages of sin."

Bean studied spider nevi extensively and noted its association with alcoholic cirrhosis. He was a British physician of the 19<sup>th</sup> century

# The Antidote



# Projections/Modeling on Premature Liver Cirrhosis

2 Studies

# More Data to Sound an **Alarm**

Here is one modeling study

Ana Best PhD et. Premature mortality projections in the USA through 2030: a modelling study  
The Lancet Public Health Volume 3, issue 8 Aug 1, 2018

Focus on Purple

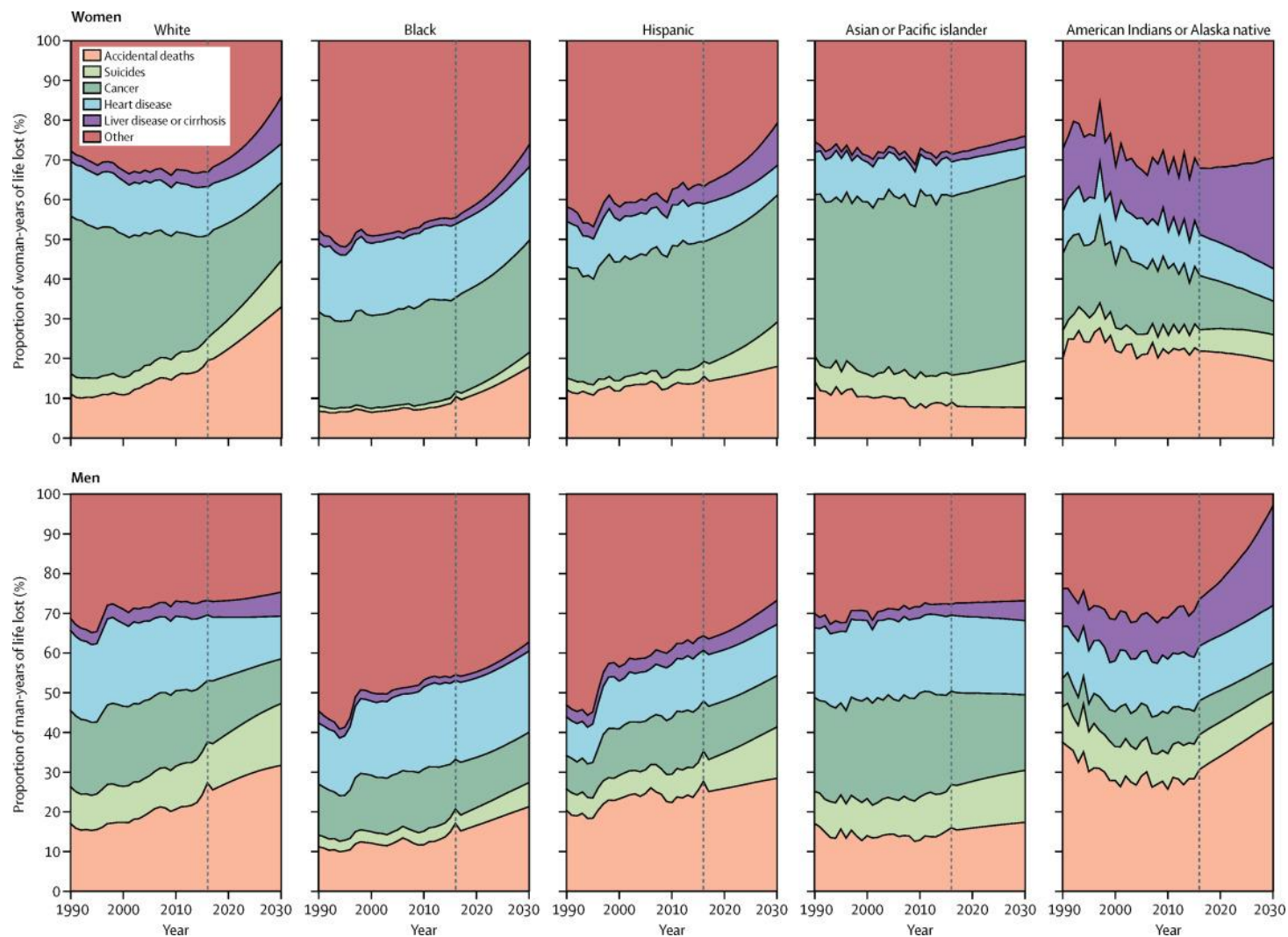
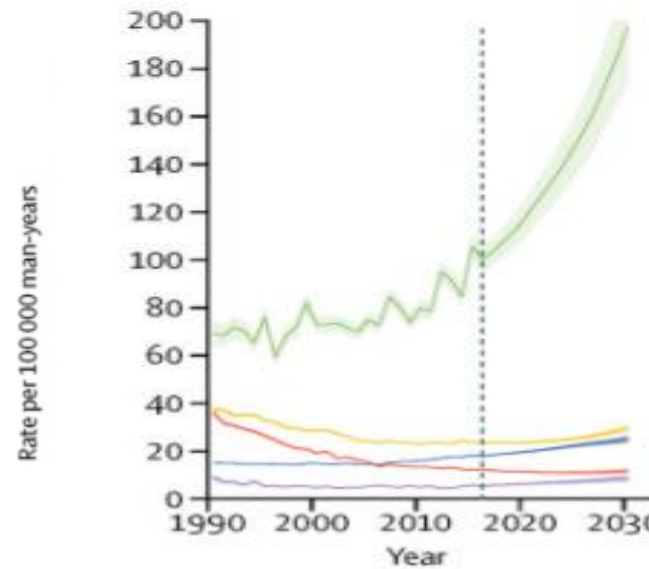
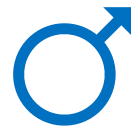
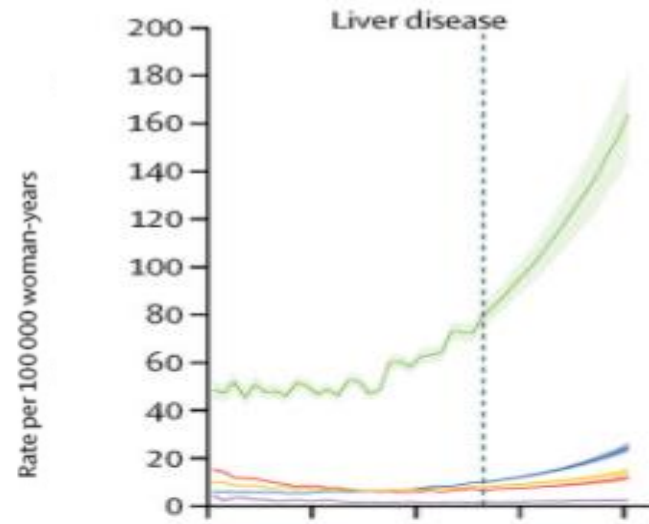


Figure 3: Observed and projected proportion of total annual person-years of life lost up to age 65 years

# Projected prevalence and mortality Pre Covid

Prior to Covid, premature deaths from cirrhosis were expected to rise for all racial and ethnic groups except Black men until 2030 per Lancet



— White — Black — Hispanic — Asian or Pacific islanders — American Indians or Alaska natives

Figure 2: Observed and projected age-standardized cause-specific mortality rates for those aged 25–64 years

y-axis limits vary by column. The vertical dashed line indicates the end of the observation period. Shaded areas denote pointwise 95% CIs for the mean age-standardized rate.

# Pre Covid-Projections

## Deaths averted or in excess 2017–30 (percentage difference from observed rate projection)

	Women						Men					
	White	Black	Hispanic	Asian or Pacific islander	American Indian or Alaska native	Total	White	Black	Hispanic	Asian or Pacific islander	American Indian or Alaska native	Total
Accidents	74 900 (+29%)	-8 600 (-18%)	-1 900 (-5%)	-1 500 (-25%)	1 200 (+17%)	64 100 (+18%)	35 900 (+6%)	-43 200 (-35%)	-35 000 (-26%)	-3 600 (-24%)	-1 600 (-10%)	-47 500 (-5%)
Suicides	5 900 (+7%)	-700 (-14%)	-200 (-2%)	300 (+8%)	700 (+50%)	6 000 (+6%)	12 300 (+5%)	-4 100 (-20%)	-5 200 (-15%)	-500 (-5%)	200 (+5%)	2 700 (+1%)
Cancer	-75 900 (-10%)	-32 100 (-16%)	-16 000 (-12%)	-10 800 (-21%)	800 (+9%)	-134 000 (-12%)	-86 000 (-10%)	-55 400 (-28%)	-14 100 (-10%)	-8 100 (-17%)	1 900 (+19%)	-161 700 (-13%)
Heart disease	23 600 (+7%)	-18 800 (-13%)	-5 600 (-12%)	-1 900 (-17%)	2 400 (+40%)	-300 (-0%)	-58 900 (-8%)	-43 900 (-18%)	-17 800 (-13%)	-2 900 (-8%)	1 300 (+9%)	-122 200 (-10%)
Chronic liver disease or cirrhosis	9 800 (+12%)	-5 300 (-45%)	-2 900 (-16%)	0	1 300 (+21%)	2 900 (+2%)	-10 200 (-7%)	-11 600 (-58%)	-17 200 (-31%)	-500 (-13%)	1 100 (+13%)	-38 400 (-16%)
All	221 100 (+10%)	-130 500 (-19%)	-60 300 (-16%)	-20 400 (-19%)	16 800 (+36%)	26 700 (+1%)	-156 100 (-4%)	-314 600 (-30%)	-236 000 (-31%)	-28 000 (-18%)	1 800 (+2%)	-732 900 (-13%)

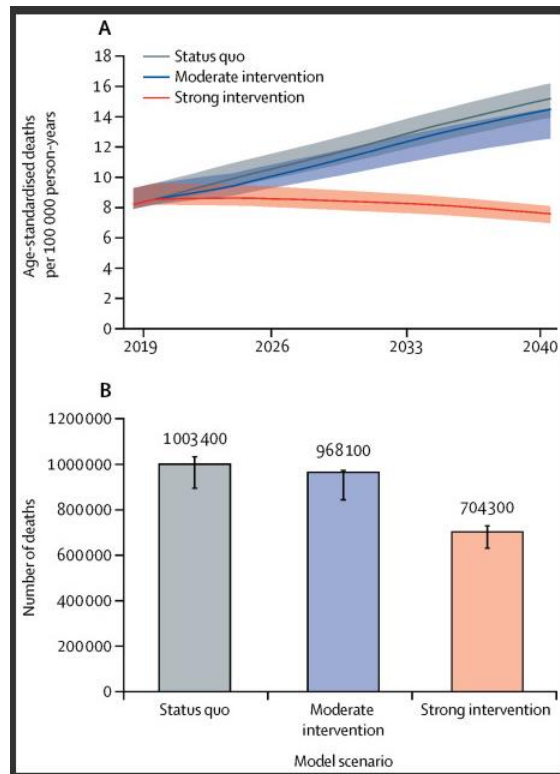
Counts are given by sex, race or ethnic origin, and cause of death, and estimates are rounded to the nearest 100 deaths and 1%.

Table: Total number of projected deaths for 2017–30 among individuals aged 25–64 years at the most recently observed mortality rate (2015 for American Indians and Alaska natives, 2016 for all other groups) and at the model-projected rate, with excess or reduction in deaths in the projection relative to the observed rate

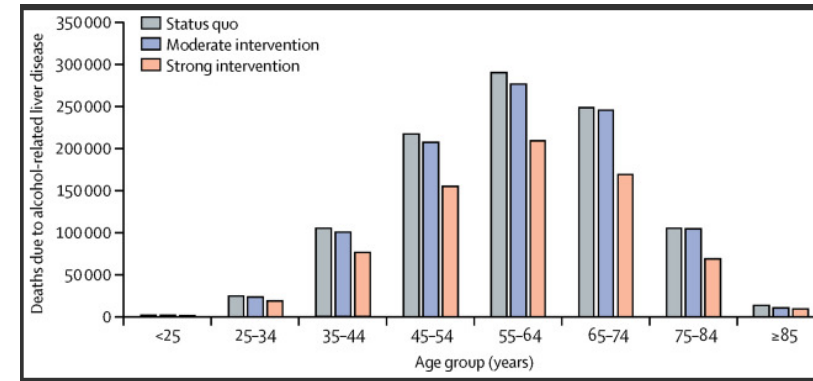
# Projected Prevalence and Mortality associated with Alcohol related liver disease in the USA, 2019-2040: a modeling study

**Figure 2: Model-predicted mortality due to alcohol-related liver disease in the USA, 2019–40**

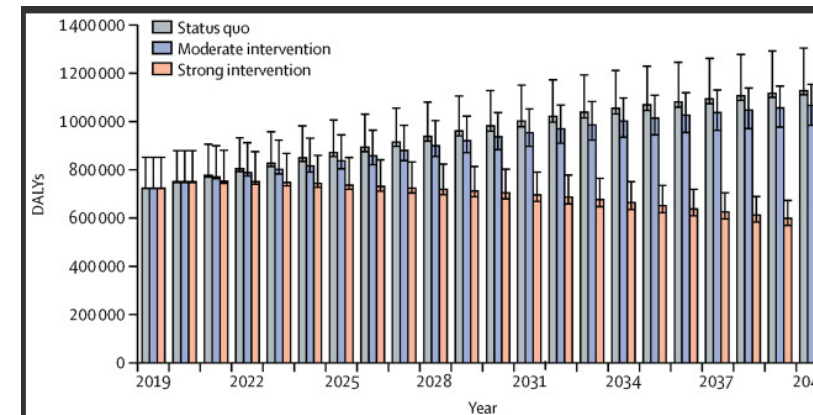
(A) Annual mortality, by scenario, with solid lines showing estimated mortality and shaded areas showing 95% uncertainty intervals. (B) Cumulative mortality by scenario, with error bars showing 95% uncertainty intervals.



**Figure 3: Deaths due to alcohol-related liver disease by intervention scenario among high-risk drinkers in the USA by age group, 2019–40**



**Figure 4: Model-predicted annual DALYs for alcohol-related liver disease by intervention scenario among high-risk drinkers in the USA, 2019–40**



DALY (Disability-adjusted live years)



## Case Study #1

29 F marketing advisor applying for 500K WL. Part 2 indicates she was seen by PCP last year for GI complaints, condition resolved

APS: 2021 Hx: F/U discharge from 48 hour hospital stay. Went to ED 2 weeks ago for hx of nausea, vomiting and RUQ abdominal pain. Was given 2 liters of IV fluids. DX acute pancreatitis/gastritis. Improved within a week. ETOH hx 1-2 glasses of wine 5 days week. Weight up 11 pounds since last year's physical attributes to less exercise and poor diet

ED records: Fever 101.2 slight scleral icterus

CBC: Hgb/HCT 12/36 MCV 95 WBC 22,500 Plts 265,000

amylase 110, Lipase 60, AST 255, ALT 155, T.Bili 3.9, alk phos 210 Albumin 3.6

Abd US: Gall stone present, slight thickening of gall bladder wall, no dilatation of ducts, hyperechoic liver

CT abdomen revealed significant hypoattenuation of liver at 38 HU suggestive of moderately severe steatosis; focal pancreatic edema

PCP records: afebrile, NAD, Weight 171

PE abd soft, nontender

Repeat Labs:

AST 55 ALT 72 Bili 1.5 Albumin 3.8 Alk phos 115

CBC Hgb/HCT 13/38 Plts 290K WBC 6.3

RX: Prilosec 20 mg daily, referral to dietician

Paramed:

5'2" 175 lbs

BP 110/68

Chemistries: ALT 75 AST 52 GGT 75 Albumin 3.9

A1C 5.9 BUN 18 Creat 1.0

Total Cholesterol 255

HDL 72

Trigs 199

What are your underwriting concerns?

## Case Study #1

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Albumin 3.6**

Abd US: **Gall stone present, slight thickening of gall bladder wall, no dilatation of ducts, hyperechoic liver**

CT abdomen revealed significant **hypoattenuation of liver at 38 HU suggestive of moderately severe steatosis; focal pancreatic edema**

Liver attenuation on CT should be greater than the spleen as usually around 60 HU on nonenhanced imaging

PCP records: afebrile, NAD, Weight **171**

PE abd soft, nontender

Repeat Labs:

AST 55 ALT 72 Bili 1.5 Albumin 3.8 Alk phos 115

CBC Hgb/HCT 13/38 Plts 290K WBC 6.3

RX: Prilosec 20 mg daily, referral to dietician

Paramed:

5'2" **175 lbs**

BP 110/68

Chemistries: **ALT 75 AST 52 GGT 75 Albumin 3.9**

A1C **5.9** BUN 18 Creat 1.0

Total Cholesterol 255

HDL 72

Trigs 199

What are your underwriting concerns?

# Underwriting Decision

## FAVORABLE

Clinically improved  
LFTs improved  
ALT > AST  
Plts 290K  
albumin 4.2  
Bonacini w/o INR would be a  
score of 2 so highest score  
would not be more than 4



## UNFAVORABLE

ED visit with elevated lipase,  
amylase and markedly high LFTs  
CT noting liver hypoattenuated to 38  
HU(nml >60) suggestive significant  
steatosis  
Current LFTs still high  
Gained 11 + 4 pounds  
A1C 5.9 and trigs elevated  
ETOH wine possibly more than she's  
admitting

Alcoholic hepatitis vs Acute Pancreatitis vs Gall stone pancreatitis  
Fatty Liver, cirrhosis unlikely  
ETOH possibly more than disclosed  
A1C and trigs = Metabolic syndrome

# Case #2

## The Claim

Female insured died at age 40 of liver cirrhosis 1.5 years after the policy was issued

# Claim Investigation

- Health records obtained
- No alcohol criticisms until post-issue

# Post Issue Investigation

## 38 F small business owner applying for 1.5 million WL PCP is GYN

6 months prior to application: GYN routine PAP

Reported anxiety, overwhelmed by work and her 2 young children ages 7 and 9 home due to pandemic. Marriage under stress. Requested something for nerves.

SH: nonsmoker, drinks 1 glass wine or 1 Bourbon/night. Occasionally gets an evening to have girl's night out and may have 2-3 cocktails

P.E. BP 150/85, weight 152 (wt down 5 pounds from last year)  
Pelvic exam nml

Labs drawn. Referred to counselor.

RX: Buspar 10 mg tid prn anxiety

Lab Results:

CBC with Hgb/HCT 12/35 MCV 108, WBC 5.5, RDW 18  
Platelets 145K

Glucose 72, ALT 19, AST 40, TSH 1.5,

Paramed and Insurance Labs:

BP 155/94, Height 5'6" 145 lbs

Labs:

Glucose 95, A1C 5.5

T.Bili 2.5, ALT 23, AST 42, GGT 65 Albumin 3.5

Cholesterol 185 HDL 82

Medical: clean sheeted

Family Hx: Father, brother, sister healthy

Mother died of a liver disorder

ETOH: 1 drink (cocktail, wine)/day

MVR Clear

MIB: Nothing

# What are your concerns?

38 F small business owner applying for 1.5 million WL and 250K CI  
PCP is GYN

6 months prior to application: GYN routine PAP

Reported **anxiety, overwhelmed** by work and her 2 young children ages 7 and 9 home due to pandemic. Marriage under stress. **Requested something for nerves.**

SH: nonsmoker, drinks **1 glass wine or 1 Bourbon/night.**  
Occasionally gets an evening to have girl's night out and may have **2-3 cocktails**

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Paramed and Insurance Labs:

BP **155/94**, Height 5'6" **145 lbs**

Labs:

Glucose 95, A1C 5.5

**T.Bili 2.5, ALT 23, AST 42, GGT 65 Albumin 3.5**

Cholesterol 185 **HDL 82**

Medical: clean sheeted

Family Hx: Father, brother, sister healthy

Mother died of a **liver disorder**

ETOH: Disclosed 1 drink (cocktail, wine)/day

MVR Clear

MIB: Nothing

# How **would** you have underwritten this case if you could have seen the labs/APS?

Alcohol concerns??? Fam Hx???

Try a Bonacini:

ALT/AST = 23/42 = 0.54 = 3 points

Platelets 145K = 4 points

7 points without INR

Underwriting Risk Assessment

Choices:

A. substandard rate for alcohol

B. Decline

C. Postpone and reconsider with WHAT???



## What ensued after Applicant's policy in force?

Answer: Followed by hepatologist after hospitalization for vomiting blood 6 months after policy in force.

Fibroscan Median kPa is 16.8

Fibrotest is 0.72

Ultrasound reveals no liver masses

Scheduled for EGD

In closing:

Quote out of Pedro Valenzuela's paper from Brain Behavioral Immunology

[Brain Behav Immun.](#) 2021 May; 94: 1–3.

PMCID: PMC7937336

Published online 2021 Mar 7. doi: [10.1016/j.bbi.2021.03.003](https://doi.org/10.1016/j.bbi.2021.03.003)

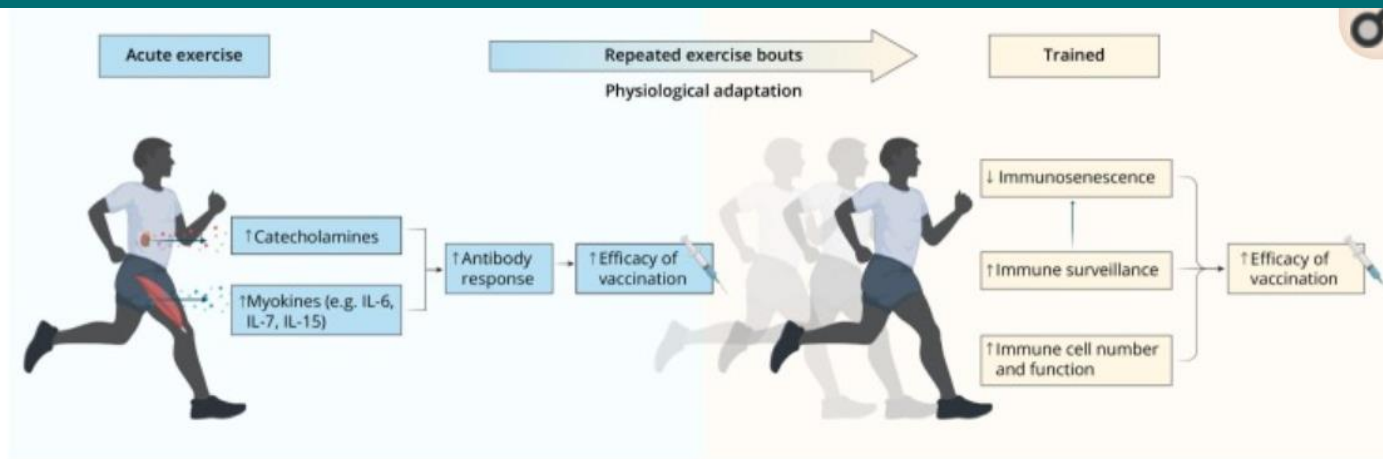
PMID: [33691149](https://pubmed.ncbi.nlm.nih.gov/33691149/)

### Physical activity: A coadjuvant treatment to COVID-19 vaccination?

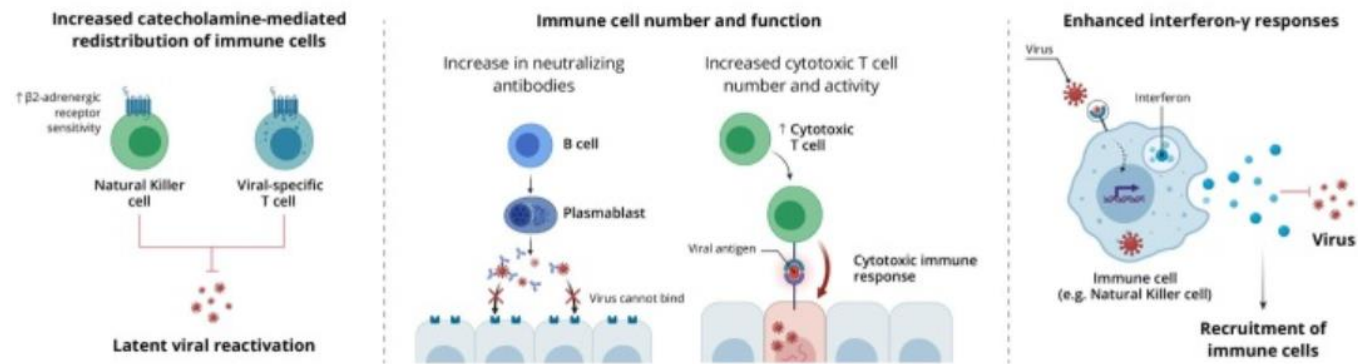
[Pedro L. Valenzuela](#),<sup>a,\*</sup> [Richard J. Simpson](#),<sup>b,c,d</sup> [Adrián Castillo-García](#),<sup>e</sup> and [Alejandro Lucia](#)<sup>a,f</sup>

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Beyond vaccination, the current pandemic has taught us the importance of preventive lifestyle measures. Social distancing, good hygiene and forced lockdowns are indeed necessary, but so too is physical exercise, which is not just safe but has also a potential preventive role, especially for the most vulnerable groups.



**Potential mechanisms of physical activity as an immune adjuvant to enhance responses to vaccines**



Potential mechanisms explaining the benefits of regular — and potentially acute — exercise performed before vaccination to enhance immune response. Abbreviation: IL, interleukin.

Any  
questions?

# Thank you!

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