
12TH ANNUAL
NCSCG
POST-DDW
SYMPOSIUM

Impact of Obesity on Gastrointestinal and Liver Disease

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Impact of Obesity on Gastrointestinal and Liver Disease

- Obesity and…
  - Colon
    - Colorectal neoplasia (2 abstracts)
    - Inflammatory Bowel Disease (1 abstract)
  - Liver
    - Alcoholic hepatitis (1 abstract)
    - Hepatitis C (1 abstract)
    - NAFLD (2 abstracts)

Impact of Obesity on Gastrointestinal and Liver Disease

- Obesity and…
  - Colon
    - **Colorectal neoplasia**
    - Inflammatory Bowel Disease
  - Liver
    - Alcoholic hepatitis
    - Hepatitis C
    - NAFLD

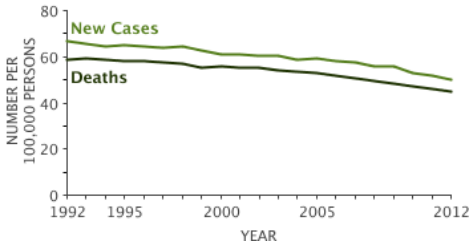
Obesity and Colorectal Neoplasia

- Each 5 kg/m^2 increase in BMI above 25 is associated with an increase in the RR for CRC of 1.24 for men and 1.09 for women.[1]
- Well-accepted association between insulin, IGF, IGF-IR and cancer risk[2]
- Current guidelines do not make specific recommendations about CRC screening based on obesity or diabetes.

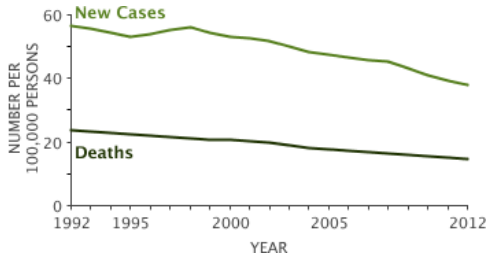
1. Renehan AG, Lancet 2008
2. Gallagher, Endocrinology 2011

Gastrointestinal Malignancy

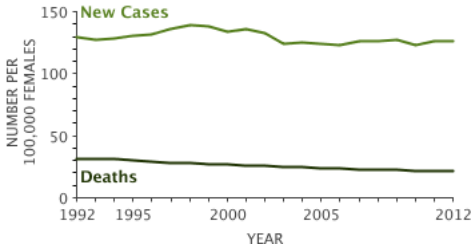
- **Lung & Bronchus**
  - 58.7/100,000 per year
  - 26.8% of cancer deaths
  - 17.4% 5-year survival



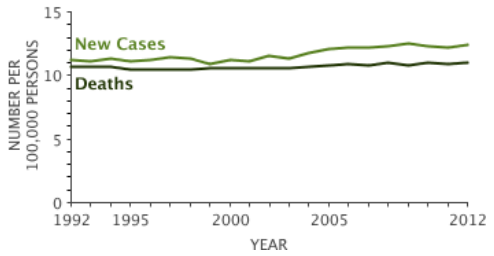
- **Colorectal**
  - 42.4/100,000 per year
  - 8.4% of cancer deaths
  - 64.9% 5-year survival



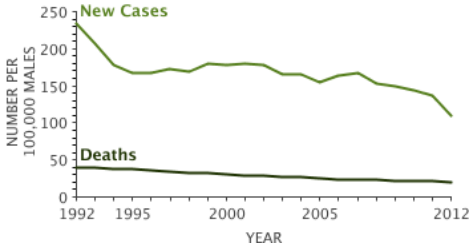
- **Breast**
  - 124.8/100,000 per year
  - 6.8% of cancer deaths
  - 89.4% 5-year survival



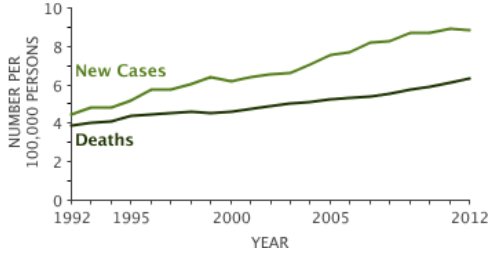
- **Pancreas**
  - 12.4/100,000 per year
  - 6.9% of cancer deaths
  - 7.2% 5-year survival



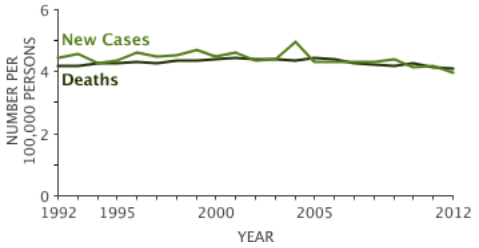
- **Prostate**
  - 137.9/100,000 per year
  - 4.7% of cancer deaths
  - 98.9% 5-year survival



- **Liver & I.H. Bile Duct**
  - 8.2/100,000 per year
  - 4.2% of cancer deaths
  - 17.2% 5-year survival



- **Esophagus**
  - 4.4/100,000 per year
  - 2.6% of cancer deaths
  - 17.9% 5-year survival



seer.cancer.gov/statfacts

Obesity, Waist-Hip-Ratio, Diet and Physical Activity and Risk of Serrated Polyps and Sessile Serrated Adenomas: A Cross-Sectional Study

- Pooled data from prior cross-sectional colonoscopy studies at UNC, 1998-2010
- Expert pathologist review to determine SSA
- Validated FFQ to determine dietary intake
- MV analysis adjusted for age, sex, study, date

Crockett SD, DDW 2015, Abstract #1319

Obesity, Waist-Hip-Ratio, Diet and Physical Activity and Risk of Serrated Polyps and Sessile Serrated Adenomas: A Cross-Sectional Study

- 2,308 patients undergoing colonoscopy
  - 57% with no polyps
  - 20% with conventional adenomas
  - 13.5% with serrated polyps
  - 1.7% with sessile serrated adenomas
- Only *trends* toward risk of all polyps with decreased physical activity, fiber intake; increased fat intake

Crockett SD, DDW 2015, Abstract #1319

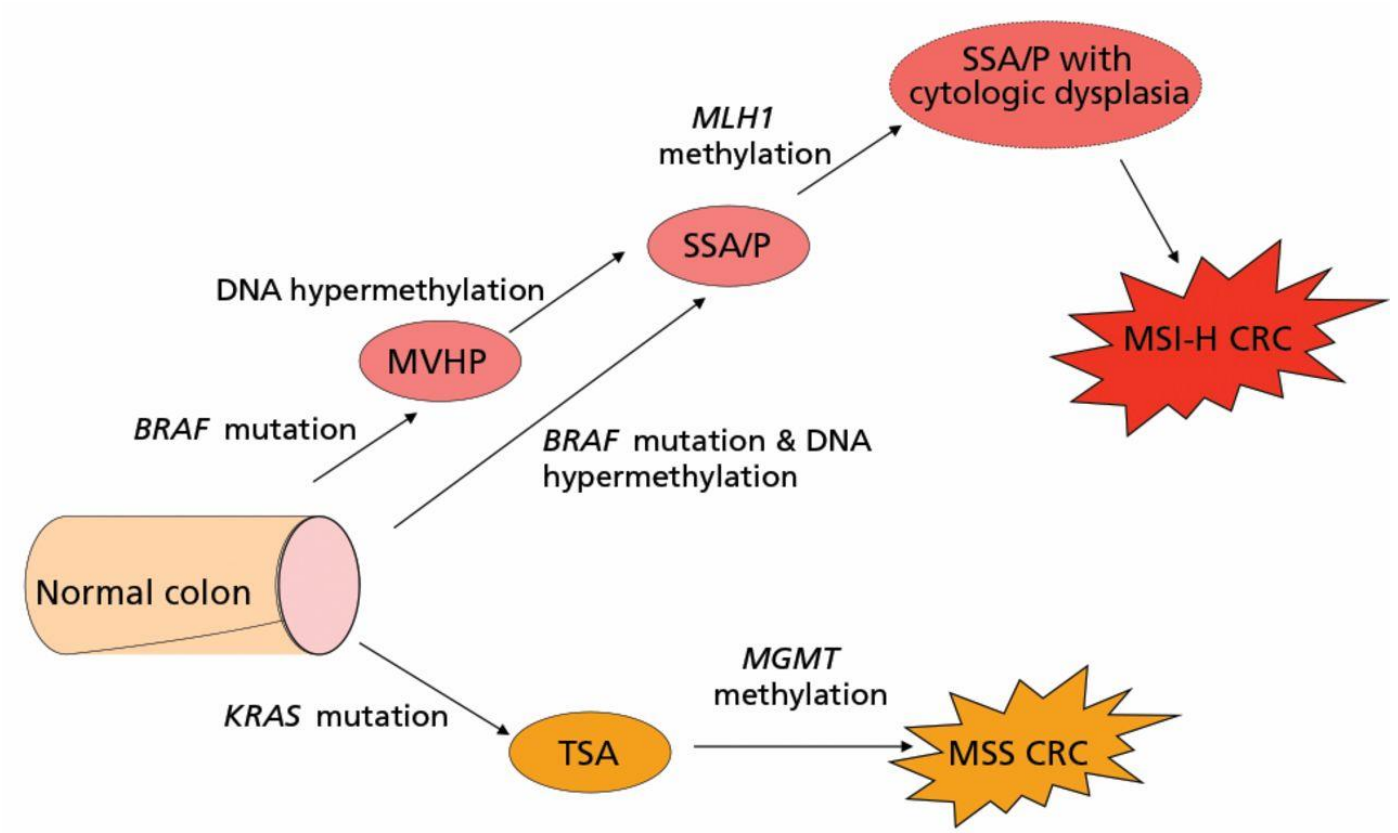
Obesity, Waist-Hip-Ratio, Diet and Physical Activity and Risk of Serrated Polyps and Sessile Serrated Adenomas: A Cross-Sectional Study

Variable	Conventional adenomas only n=460 OR (95% CI)	Serrated polyps only n=311 OR (95% CI)	SSA only n=39 OR (95% CI)
Body mass index (kg/m^2)	-	-	-
25-29.9	1.15 (0.88, 1.50)	1.21 (0.89, 1.63)	0.65 (0.29, 1.48)
≥30	1.66 (1.25, 2.19)	1.36 (0.99, 1.88)	1.11 (0.50, 2.45)
High waist-hip-ratio #	1.47 (1.12, 1.92)	1.21 (0.89, 1.64)	1.61 (0.74, 3.49)

- Obesity was associated with conventional adenomas but not serrated polyps or SSA's.
- Emphasizes epidemiologic, biologic differences between conventional adenomas and SSA's.

Crockett SD, DDW 2015, Abstract #1319

Tubular adenoma vs. sessile serrated polyp pathways



Kalady MF, J Natl Compr Canc Netw 2013

Associations of Anthropometric Factors with KRAS and BRAF Mutation Status of Primary Colorectal Cancer in Men and Women: A Cohort Study

		KRAS wild-type		KRAS mutated		BRAF wild-type		BRAF mutated	
Anthropometric Factor	tertile	n=148	HR	n=85	HR	n=208	HR	n=26	HR
Waist Hip Ratio (cm/cm)		44	1.00	23	1.00	59	1.00	8	1.00
		51	1.15 (0.77-1.72)	24	1.06 (0.60-1.89)	64	1.08 (0.76-1.54)	11	1.44 (0.78-3.59)
		53	1.45 (0.97-2.17)	38	2.13 (1.26-3.61)	85	1.76 (1.25-2.46)	7	1.20 (0.43-3.34)
	p trend		0.073		0.004		0.001		0.697
Body Mass Index (kg/m^2)		46	1.00	19	1.00	55	1.00	10	1.00
		43	0.81 (0.53-1.23)	24	1.18 (0.64-2.16)	60	0.96 (0.67-1.39)	7	0.66 (0.25-1.74)
		59	1.21 (0.82-1.80)	42	2.44 (1.41-4.23)	93	1.67 (1.19-2.35)	9	0.97 (0.39-2.44)
	p trend		0.287		0.001		0.001		0.939

Brandstedt J, PLoS One 2014

Association Between Nonalcoholic Fatty Liver Disease and Colorectal Adenoma: Updated Meta-Analysis

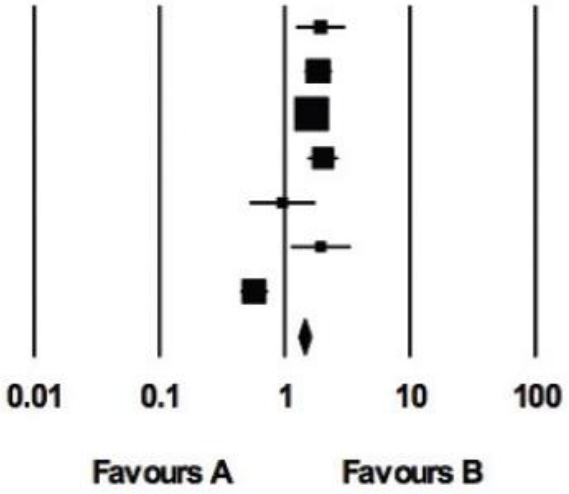
- Electronic database search for studies investigating association between NAFLD and colorectal adenoma
- 4 cross-sectional studies, 3 cohort studies: 4,095 subjects included
- 5 Asian studies, 2 European/North American studies

Abdelfatah M, DDW 2015, Abstract #1056

Association Between Nonalcoholic Fatty Liver Disease and Colorectal Adenoma: Updated Meta-Analysis

Meta Analysis

Model	Study name	Odds ratio	Lower limit	Upper limit	Z-Value	p-Value
	Wong 2011	1.930	1.219	3.057	2.803	0.005
	Stadlmayr, 2011	1.850	1.428	2.397	4.657	0.000
	Hwang, 2010	1.640	1.359	1.979	5.163	0.000
	Huang, 2013	2.020	1.513	2.696	4.773	0.000
	Touzin, 2011	0.960	0.520	1.771	-0.131	0.896
	Lee 2011	1.940	1.108	3.395	2.321	0.020
	Lin 2014	0.569	0.439	0.737	-4.268	0.000
Fixed		1.420	1.271	1.587	6.181	0.000



- NAFLD was associated with adenoma, OR 1.42.
- Association was more significant in Asian studies.

Abdelfatah M, DDW 2015, Abstract #1056

Relationship of Non-Alcoholic Fatty Liver Disease to Colorectal Adenomatous Polyps

- Retrospective review of 2,917 Korean patients undergoing routine colonoscopy
- NAFLD defined by abdominal ultrasound
- Multivariate analysis adjusting for age, sex, smoking, HTN, DM, metabolic syndrome and NAFLD

Hwang ST, J Gastroenterol Hepatol 2010

Relationship of Non-Alcoholic Fatty Liver Disease to Colorectal Adenomatous Polyps

- Colorectal adenomas (CRC-A) associated with age, sex smoking, NAFLD, MS, HTN and DM in unadjusted analysis
- Multivariate analysis for association with CRC-A:

	OR	95% CI	*P*
Age ≥50	2.23	1.80-2.85	<0.001
Male sex	1.89	1.44-2.46	<0.001
Current smoker	1.56	1.20-2.03	0.001
NAFLD	1.28	1.03-1.60	0.029

  - MS, HTN, DM no longer significant

Hwang ST, J Gastroenterol Hepatol 2010

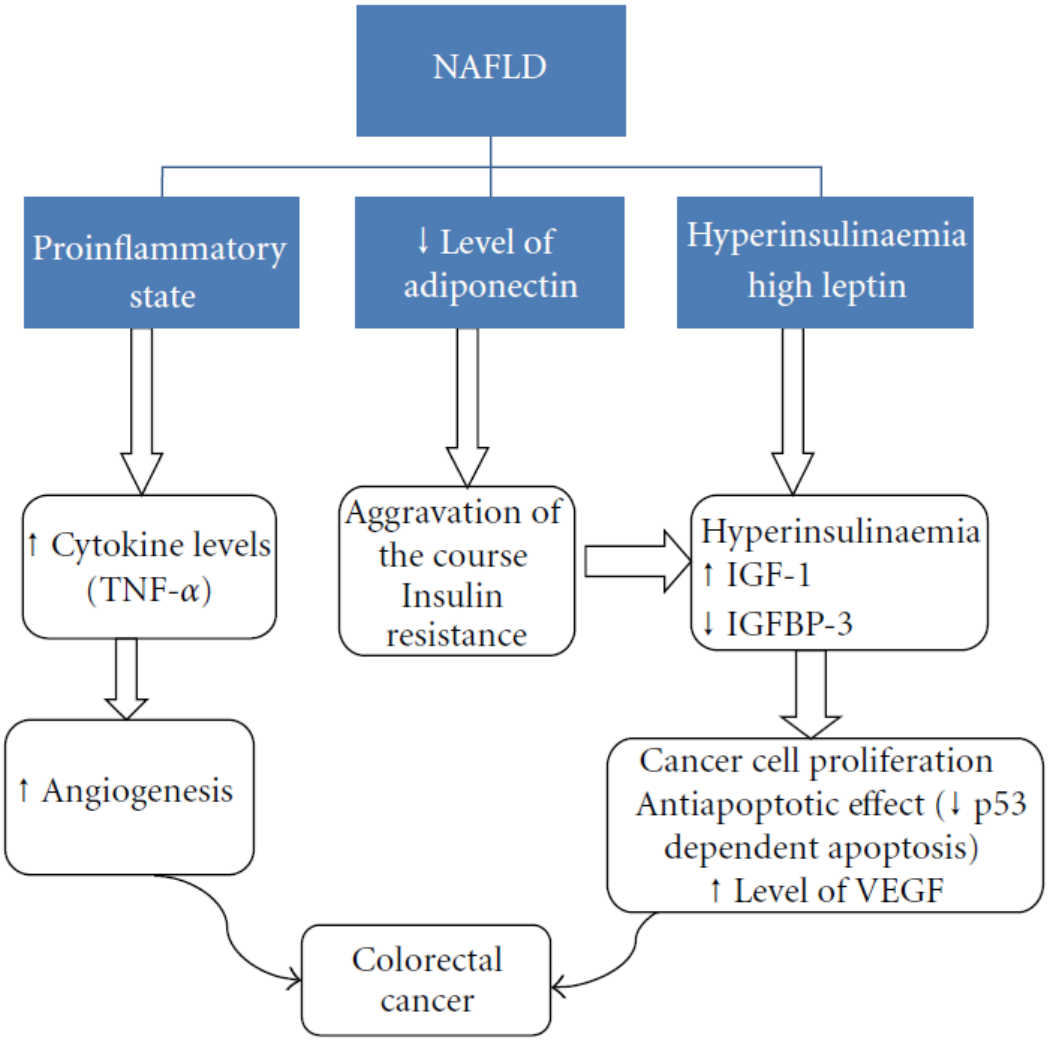
Relationship of Non-Alcoholic Fatty Liver Disease to Colorectal Adenomatous Polyps

- Risk for CRC-A by MS components and NAFLD (multivariate analysis):

	OR	95% CI	*P*
↑ Waist Circumference	1.40	1.12-1.75	0.004
Hypertension	1.08	0.87-1.33	0.510
Glucose Intolerance	1.24	1.00-1.54	0.047
Elevated Triglycerides	1.28	1.04-1.59	0.022
Low HDL	1.04	0.84-1.29	0.703
NAFLD	1.34	1.10-1.63	0.004

Hwang ST, J Gastroenterol Hepatol 2010

Proposed mechanism of influence of NAFLD on carcinogenesis in colorectal cancer



Muhidin SO, J Obes 2012

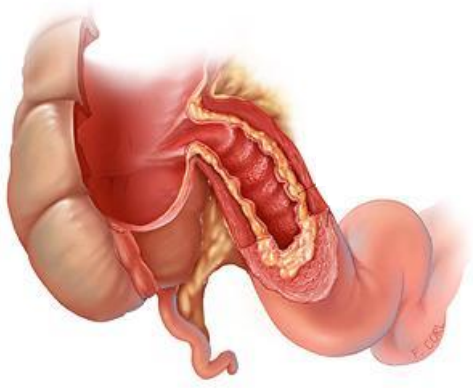
NAFLD is a proxy for a higher risk of diabetes and cardiovascular disease

- NAFLD + obesity confers higher risk of developing diabetes, OR 3.23 (1.78-5.89)[1]
  - Compare to obesity alone, OR 1.29 (0.62-2.71)
- Compared to NAFLD without fibrosis, NAFLD with fibrosis is associated with higher age- and sex-adjusted mortality, HR 1.69 (1.09-2.63)[2]
  - Largely driven by increased risk of cardiovascular mortality, HR 3.46 (1.91-6.25)

1. Sung K, Diabetes Care 2012
2. Kim D, Hepatology 2013

Impact of Obesity on Gastrointestinal and Liver Disease

- Obesity and…
  - Colon
    - Colorectal neoplasia
    - **Inflammatory Bowel Disease**
  - Liver
    - Alcoholic hepatitis
    - Hepatitis C
    - NAFLD



Obesity and Inflammatory Bowel Disease

- Obesity is associated with increased risk of IBD (CD>UC), disease progression and impaired response to therapy.[1,2]
- Secretion of adipokines may be involved in disease pathogenesis[3]
- Visceral fat in particular may play a role in IBD activity[4]

1. Versini M, Autoimmun Rev 2014
2. Khalili H, Inflamm Bowel Dis 2015
3. Fink C, Inflamm Bowel Eis 2012
4. Zulian A, Gut 2012

Adipose Tissue From Visceral Fat Has Much Higher Expression of IBD Susceptibility Genes Compared to Subcutaneous Fat

- ImmunoBase (database of genes associated with autoimmune disease) identifies IBD genes and associated loci.
- Publicly availabe gene expression profiles of normal tissue were compared to gene expression of IBD genes
  1. Compared IBD gene expression, ‘nearby’ genes and ‘other’ genes in SAT vs. other tissues
  2. Compared gene expression in VAT vs. SAT (prepubertal children)

Dave M, DDW 2015, Abstract #1747

Adipose Tissue From Visceral Fat Has Much Higher Expression of IBD Susceptibility Genes Compared to Subcutaneous Fat

- Compared to ‘nearby’ and ‘other’ genes, IBD genes were overexpressed in SAT
- Compared to SAT, VAT showed a greater increase in gene expression, IBD>nearby>other
- More IBD genes were overexpressed in VAT vs. SAT (n=63)
  - genes for immune signalling, NK cell cytotoxicity, CAM, IgA production

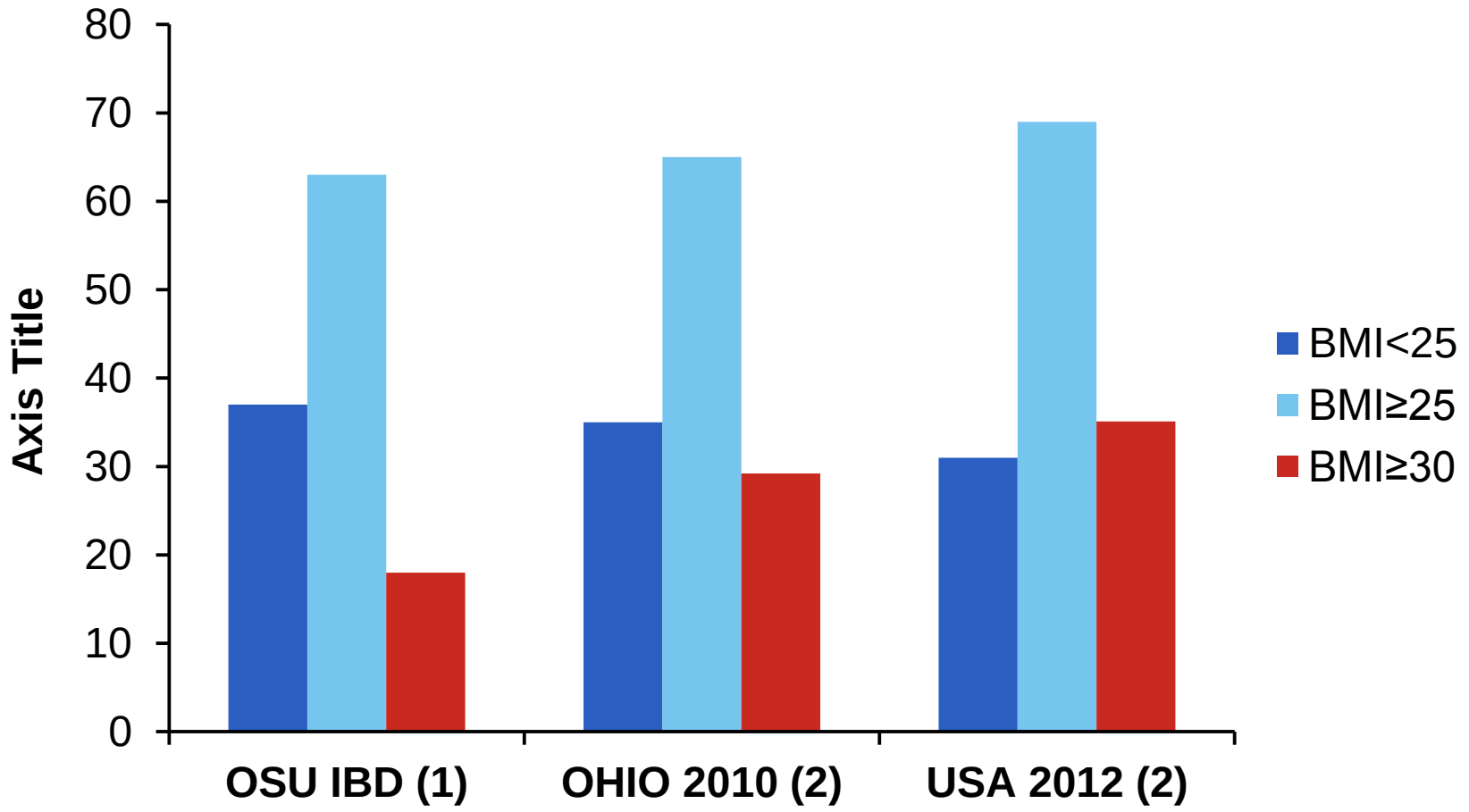
Dave M, DDW 2015, Abstract #1747

Adipose Tissue From Visceral Fat Has Much Higher Expression of IBD Susceptibility Genes Compared to Subcutaneous Fat

- Summary:
- Compared to other tissues, adipose tissue overexpressed genes associated with IBD
- Compared to SAT, VAT overexpressed these IBD susceptibility genes
- VAT may play a role in IBD pathogenesis

Dave M, DDW 2015, Abstract #1747

Is obesity disproportionately prevalent in Inflammatory Bowel Disease?



1. Ghigliotti G, Inflammation 2014
2. cdc.gov

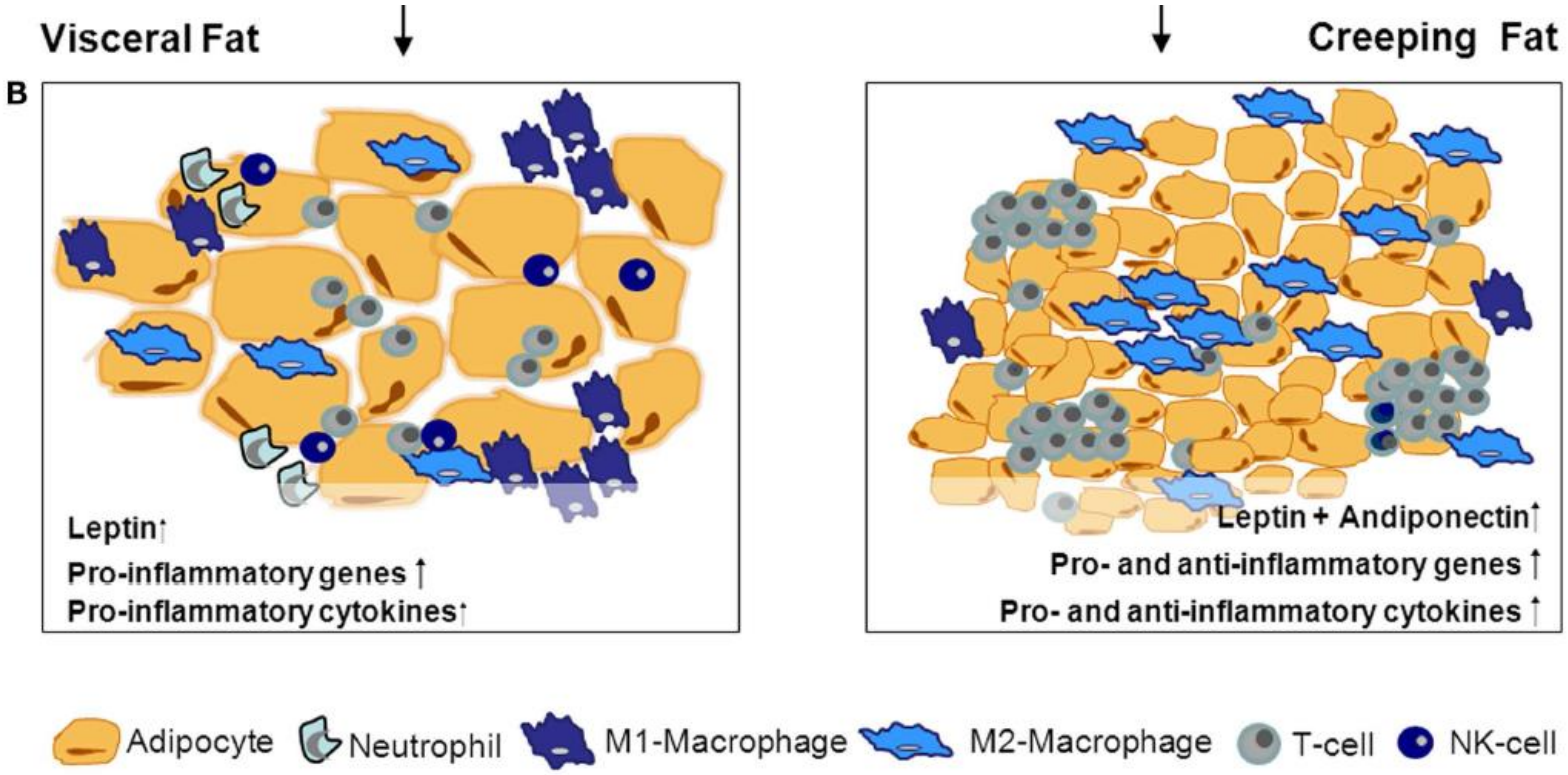
Does visceral obesity predispose to more aggressive inflammatory bowel disease?

- High mesenteric fat index is associated with more complicated Crohn's disease[1]

- However, visceral adiposity ≠ creeping fat

1. Erhayiem B, Clin Gastroenterol Hepatol 2011

Does visceral obesity predispose to more aggressive inflammatory bowel disease?



- CD: adipocyte proliferation & bidirectional immune modulation
- Obesity: adipocyte hypertrophy & unidirectional immune activation

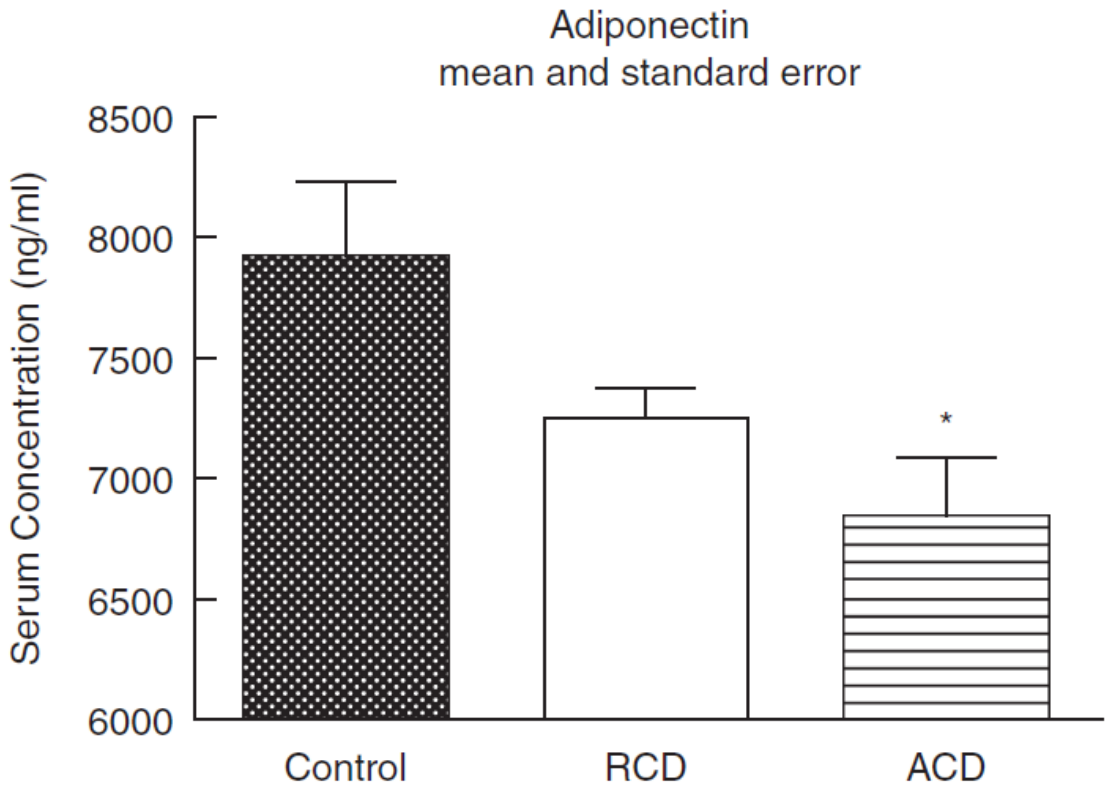
Kredel LI, Front Immunol, 2014

Serum Levels and Mesenteric Fat Tissue Expression of Adiponectin and Leptin in Patients with Crohn's Disease

- 8 patients with endoscopically-, histologically- and clinically-defined active CD (ACD) and 8 in remission (RCD) compared with 6 controls
- No difference in BMI among groups; VAT:SAT ratio not measured
- Serum adiponectin in ACD lower than controls but not lower than RCD

Rodrigues VS, Clin Exp Immunol 2012

Serum Levels and Mesenteric Fat Tissue Expression of Adiponectin and Leptin in Patients with Crohn's Disease



- VAT-associated adipokine secretion may be different in IBD vs. control, regardless of disease activity, supporting a role for VAT in IBD pathogenesis.

Rodrigues VS, Clin Exp Immunol 2012

Impact of Obesity on Gastrointestinal and Liver Disease

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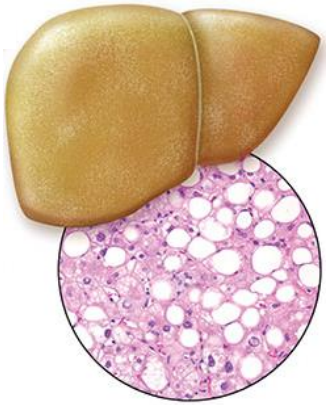
  - Colon
    - Colorectal neoplasia
    - Inflammatory Bowel Disease
  - Liver
    - **Alcoholic hepatitis**
    - Hepatitis C
    - NAFLD



Impact of Obesity on Mortality in Alcoholic Hepatitis

- What is the prevalence and association with in-hospital mortality in Alcoholic Hepatitis (AH)?
- 2011 Nationwide Inpatient Sample data including 33,097,667 adult admissions
- 0.3% had AH = 99,293 admissions

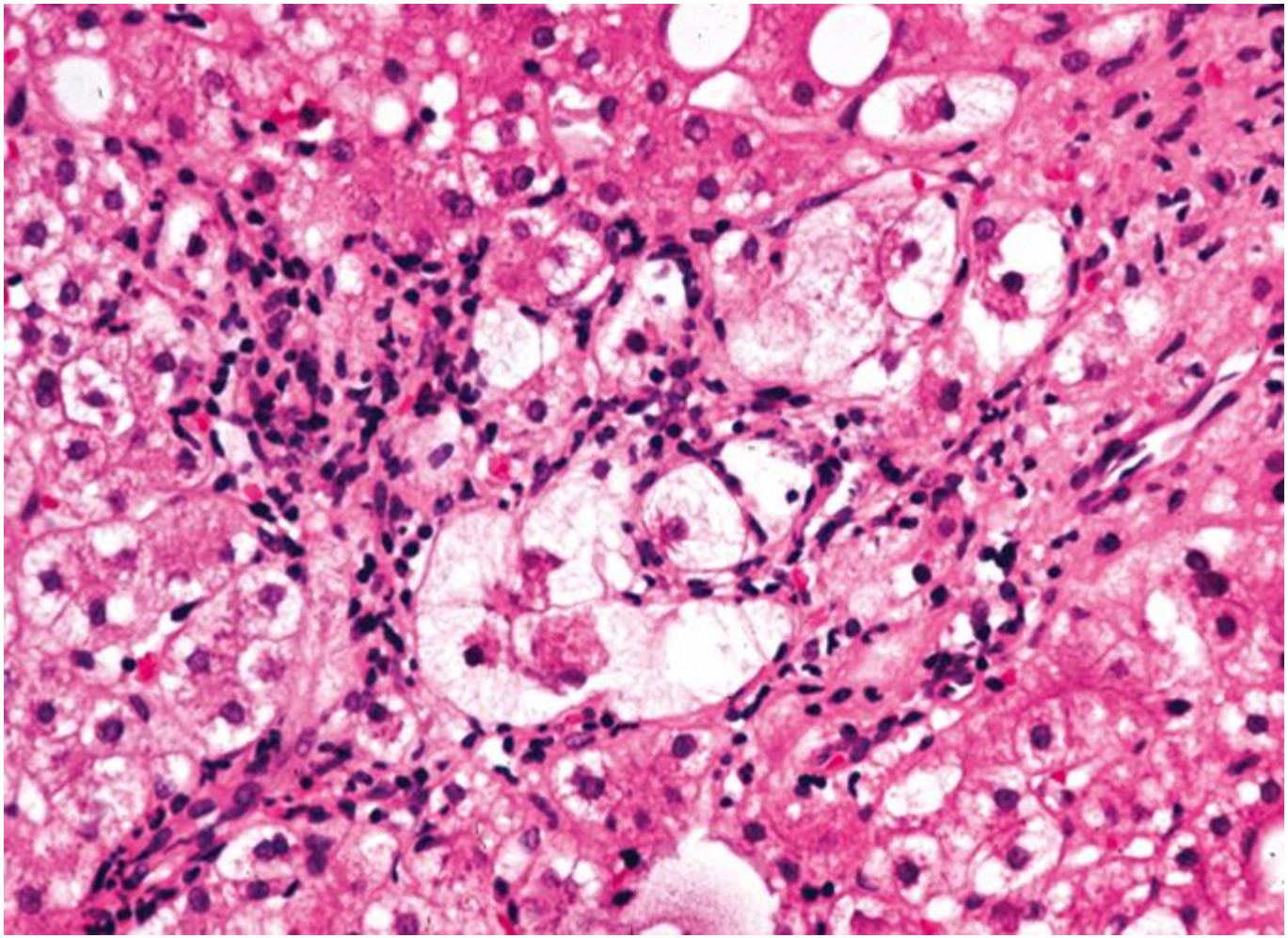
Mendu A, DDW 2015, Abstract #1815

Impact of Obesity on Mortality in Alcoholic Hepatitis

- 5.92% of AH had obesity = 5,888 admissions
  - vs. 10.9% obesity among non-AH admissions
- AH mortality:
  - 5.5% in obese patients vs.
  - 4.1% in non-obese patients ($p<0.0001$)
- Obesity independently associated with mortality, adjusted OR 3.7 (2.1-6.8, $p<0.0001$)
  - Infection was the only other predictor of mortality.

Mendu A, DDW 2015, Abstract #1815

Impact of Obesity on Alcoholic Hepatitis?



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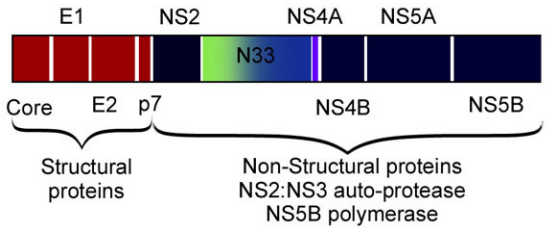
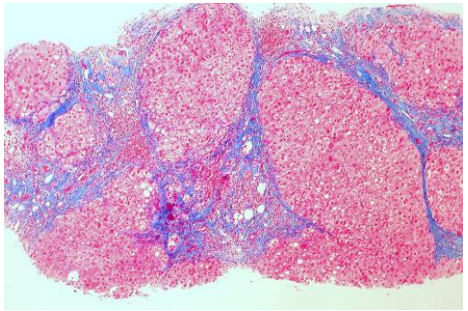




Concurrent Obesity, Diabetes, and Nonalcoholic Fatty Liver Disease Is Associated With an Increased Risk of Progression to Advanced Fibrosis Among Patients With Chronic Hepatitis C Virus Infection: A Systematic Review

- Review of studies evaluating obesity, DM, NAFLD and HCV from 2001 through 2014
- HIV, HBV, HCC, OLT excluded
- 20 studies (all cohort studies) included
  - 11 from Europe
  - 6 from United States
  - 3 from Asia-Pacific
- 13 good quality; 7 fair (Newcastle-Ottawa scale)

Dyal HK, DDW 2015, Abstract #1089

Concurrent Obesity, Diabetes, and Nonalcoholic Fatty Liver Disease Is Associated With an Increased Risk of Progression to Advanced Fibrosis Among Patients With Chronic Hepatitis C Virus Infection: A Systematic Review

- Obesity increased the risk of advanced fibrosis in 7 studies, OR range 1.081-7.69
  - 4 studies failed to show this association
- Diabetes increased the risk of advanced fibrosis in 6 studies, OR range 2.251-9.24
- NAFLD increased the risk of advanced fibrosis in 12 studies, OR range 1.80-14.3

Dyal HK, DDW 2015, Abstract #1089

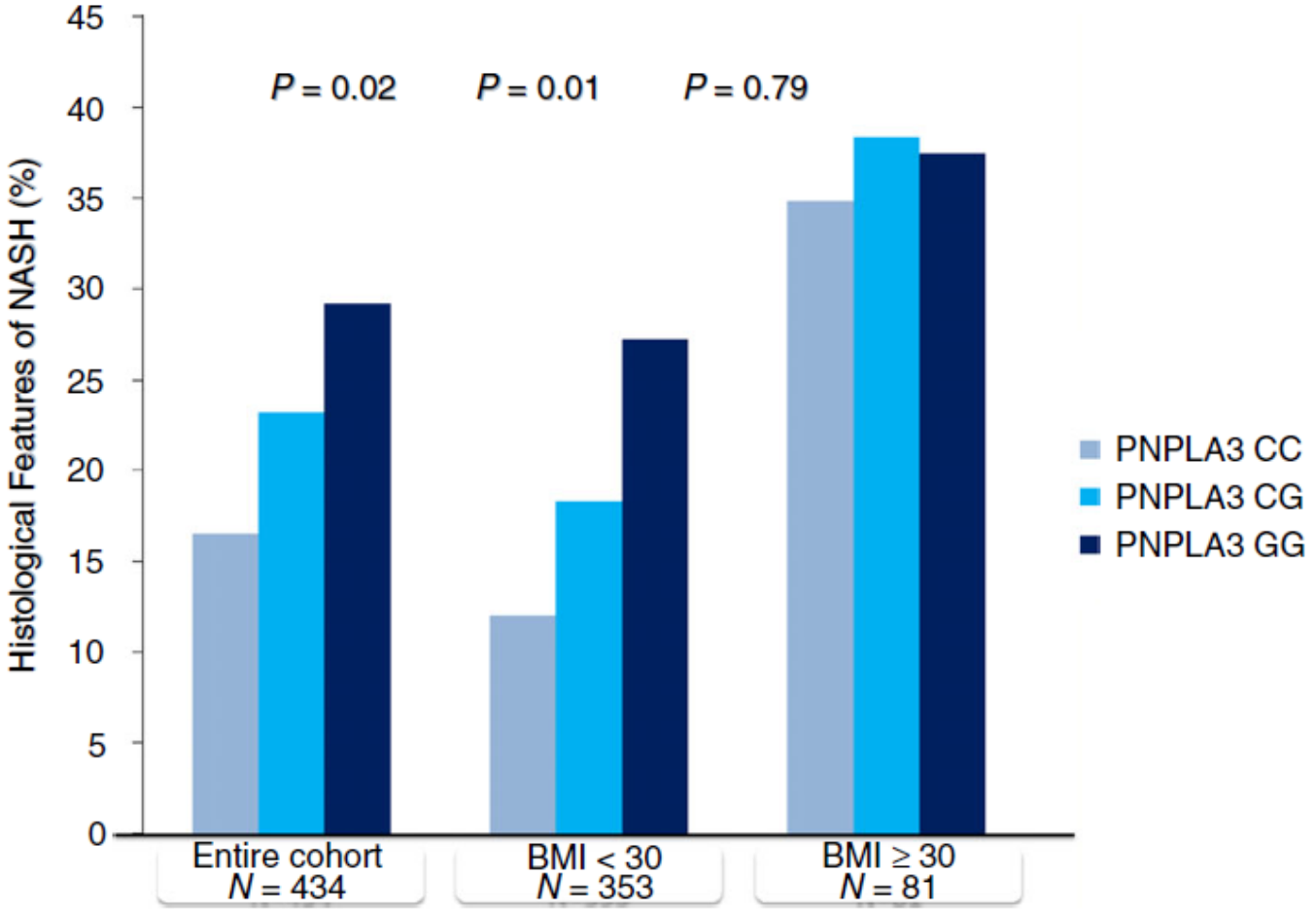
Factors Associated with Advanced Fibrosis in HCV

- 434 consecutively biopsied Caucasian (Italian) patients with genotype 1 chronic HCV
- PNPLA3 rs738409 phenotype described in all
  - I148M C→G mutation frequency 0.27
    - 9.4% GG homozygotes
    - 34.8% CG heterozygotes
- Multivariate analysis to identify factors associated with steatohepatitis and fibrosis

Petta S, Aliment Pharmacol Ther 2015

Factors Associated with Advanced Fibrosis in HCV

- Presence of NASH by PNPLA3 genotype and BMI



Petta S, Aliment Pharmacol Ther 2015

Factors Associated with Advanced Fibrosis in HCV

- NASH significantly associated with
  - Older age (OR 1.03)
  - BMI ≥30 kg/m^2, OR 2.06
  - Higher HOMA, OR 1.18
  - PNPLA3 G allele, OR 1.54
- Advanced Fibrosis significantly associated with
  - Older age (p=0.002)
  - Higher HOMA, OR 1.18
  - NASH, OR 2.05 → PNPLA G allele not predictive

Petta S, Aliment Pharmacol Ther 2015

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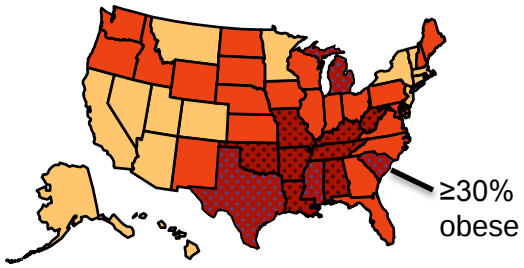
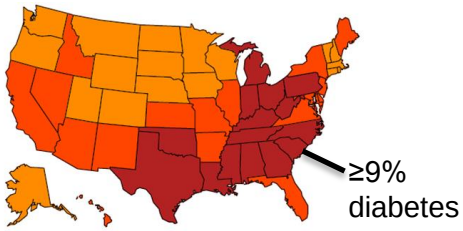




Diabetes Increases the Risk of Hepatocellular Carcinoma in Non Alcoholic Steatohepatitis and Alcoholic Cirrhosis

- UNOS database: adults with liver transplant from 1996 to June 2013
- 6,686 with LT for NAFLD; 27,581 for ALD
- Comparisons made between diabetes, BMI, HCC, MELD

Sourianarayanane A, DDW 2015, Abstract #465

Diabetes Increases the Risk of Hepatocellular Carcinoma in Non Alcoholic Steatohepatitis and Alcoholic Cirrhosis

	NASH	ALD	*p-value*
Age (years)	58.3	52.9	<0.001
Male (%)	49.9	75.9	<0.001
BMI >30 kg/m^2 (%)	32.6	14.3	<0.001
Diabetes (%)	52	9.8	<0.001
HCC (%)	6.2	3.7	<0.001

Sourianarayanane A, DDW 2015, Abstract #465

Diabetes Increases the Risk of Hepatocellular Carcinoma in Non Alcoholic Steatohepatitis and Alcoholic Cirrhosis

- Diabetes was independently associated with HCC in NASH patients, OR 1.52.
  - Among all patients, etiology of liver disease was not an independent risk factor for HCC.
  - Among diabetics, ALD was associated with higher risk of HCC than NASH, OR 1.56.

Sourianarayanane A, DDW 2015, Abstract #465

Impact of Obesity and Diabetes on HCC

- HCC is uncommon but increasing in U.S. and the U.K.[1,2]
  - HCC: 1.28% of U.S. cancers in 2005; 2.15% in 2015
- Traditionally associated with viral hepatitis
- Increasingly associated with obesity, diabetes and metabolic syndrome

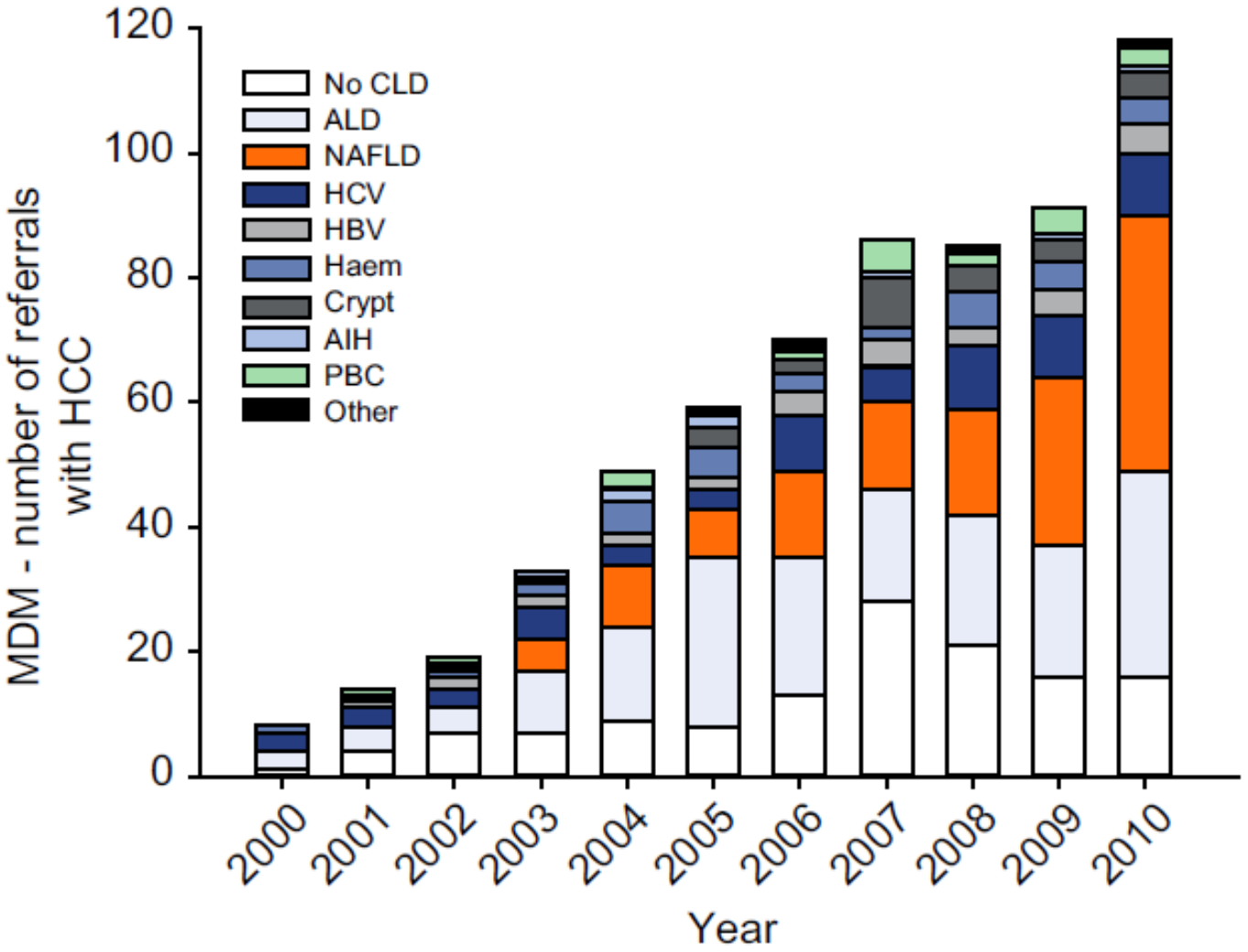
1. cancer.org
2. Dyson J, J Hepatol 2014

Impact of Obesity and Diabetes on HCC

- HCC referrals to regional hospital system in U.K. tracked 2000-2010
- Mortality data obtained from national public health record
- NAFLD diagnosis
  - Negative screen for other liver diseases
  - Steatosis on imaging or biopsy
  - ETOH <21/wk for men and <14/wk for women over the previous 5 years

Dyson J, J Hepatol 2014

Impact of Obesity and Diabetes on HCC



Dyson J, J Hepatol 2014

Impact of Obesity and Diabetes on HCC

- Characteristics of patients with HCC within etiologic groups

	ALD (n=178)	**NAFLD** (n=136)	***HCV*** *(n=65)*	***HBV*** *(=29)*	***Haem*** *(n=34)*	*p-value*
Age (years)	66.0	71.0	60.0	65.0	67.5	<0.001
Male (%)	92.7	77.9	78.5	89.7	91.2	<0.001
BMI (kg/m^2)	28.8±0.4	32.0±0.6	25.2±0.7	26.1±1.0	27.8±1.1	<0.001
Diabetes (%)	36.5	80.1	32.3	27.6	41.2	<0.001
Cirrhosis (%)	100	77.2	96.9	82.8	79.4	<0.001

Dyson J, J Hepatol 2014

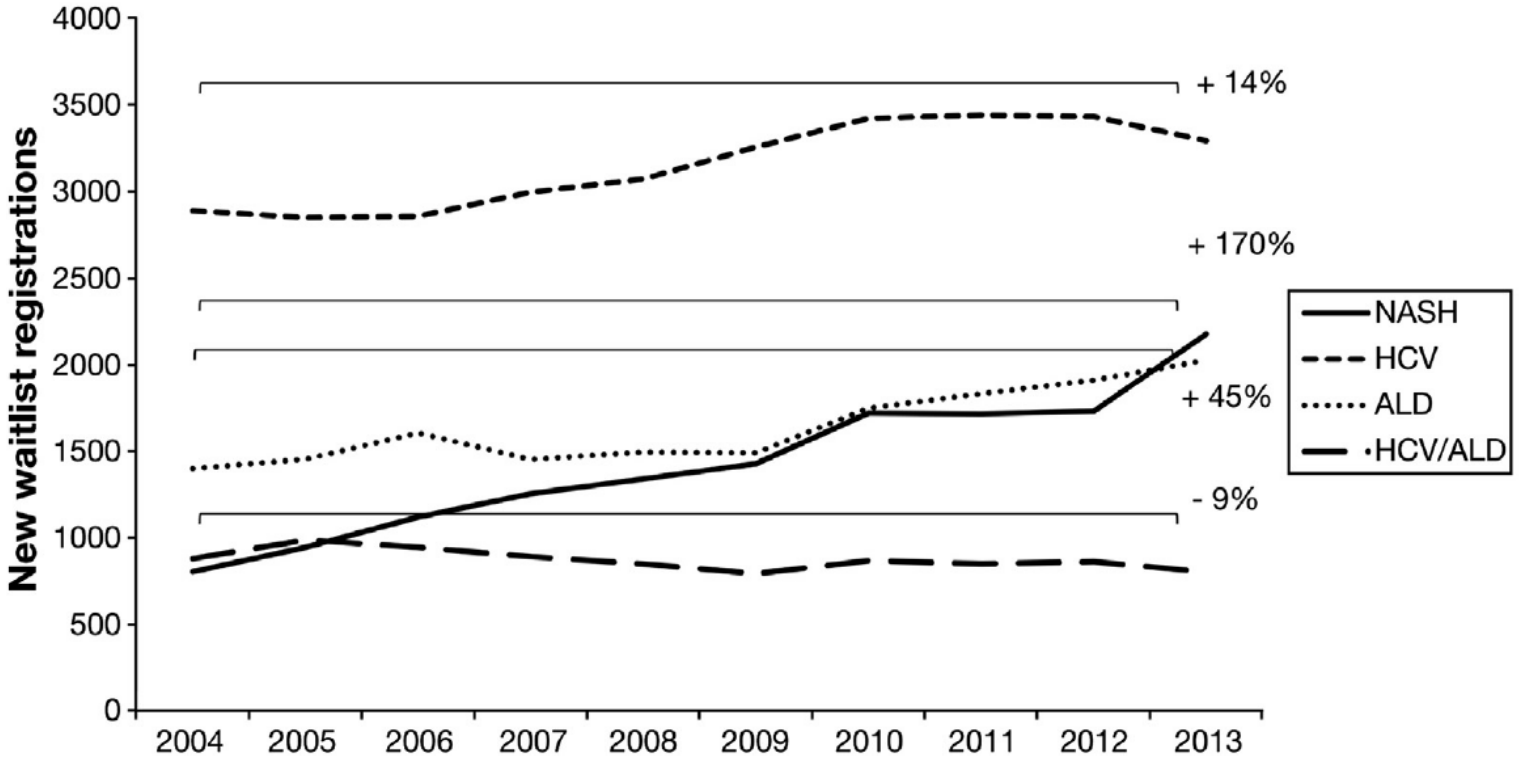
NAFLD and HCC in the United States

- SEER registry with Medicare claims 2004-2009
  - 7,255 with HCC and 21,765 controls identified
  - NAFLD by code and by obese diabetics with CC
- Etiology of liver disease for HCC cases:
  - HCV = 43%
  - NAFLD = 16%
  - ALD = 13%
  - HBV = 7%
- 4% annual increase in HCC (928 → 1,464)
  - 8% annual increase in HCV-HCC
  - 5% annual increase in NAFLD-HCC

Younossi Z, EASL 2015, Abstract #41

NAFLD and Liver Transplantation

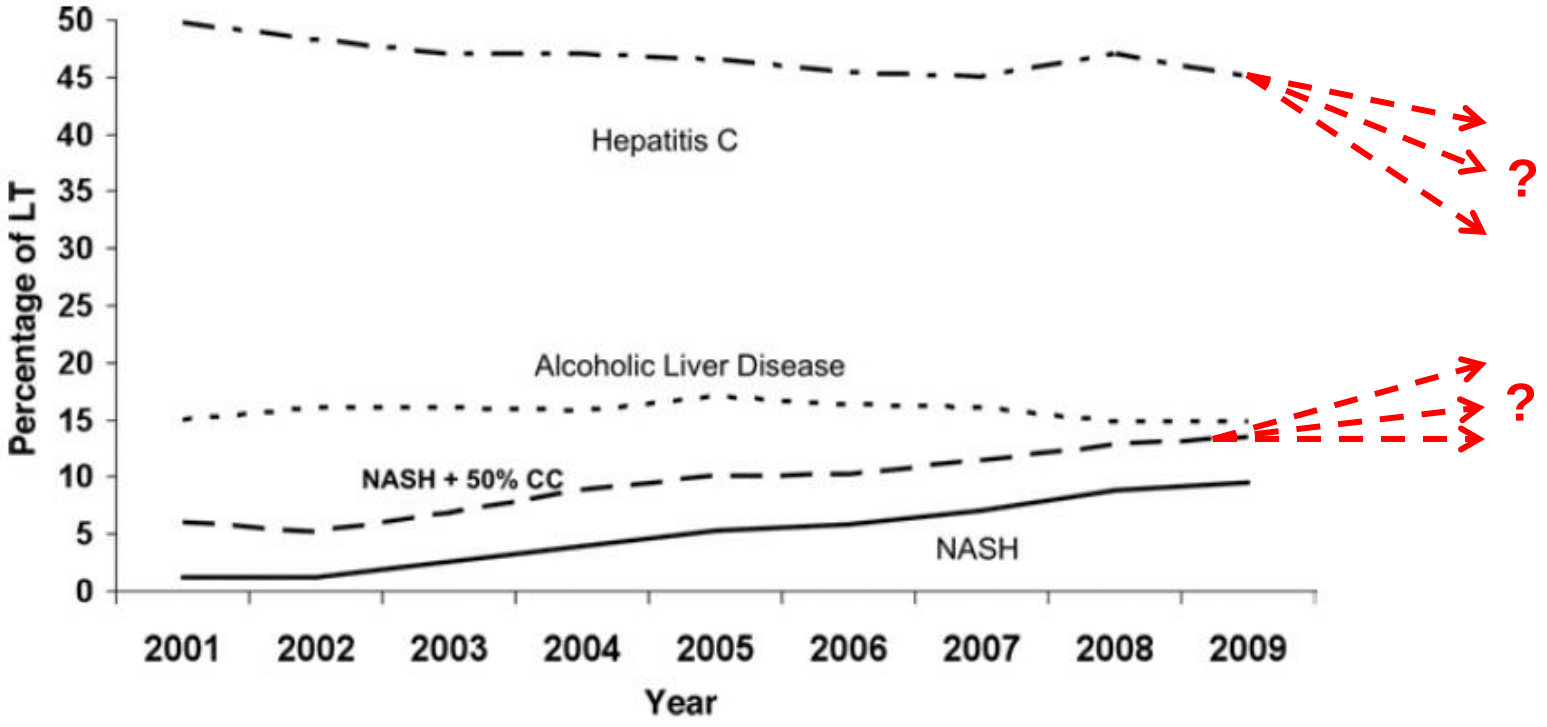
- NASH is now the second leading etiology of liver disease among adults awaiting liver transplantation in the US.



Wong RJ, Gastroenterology 2015

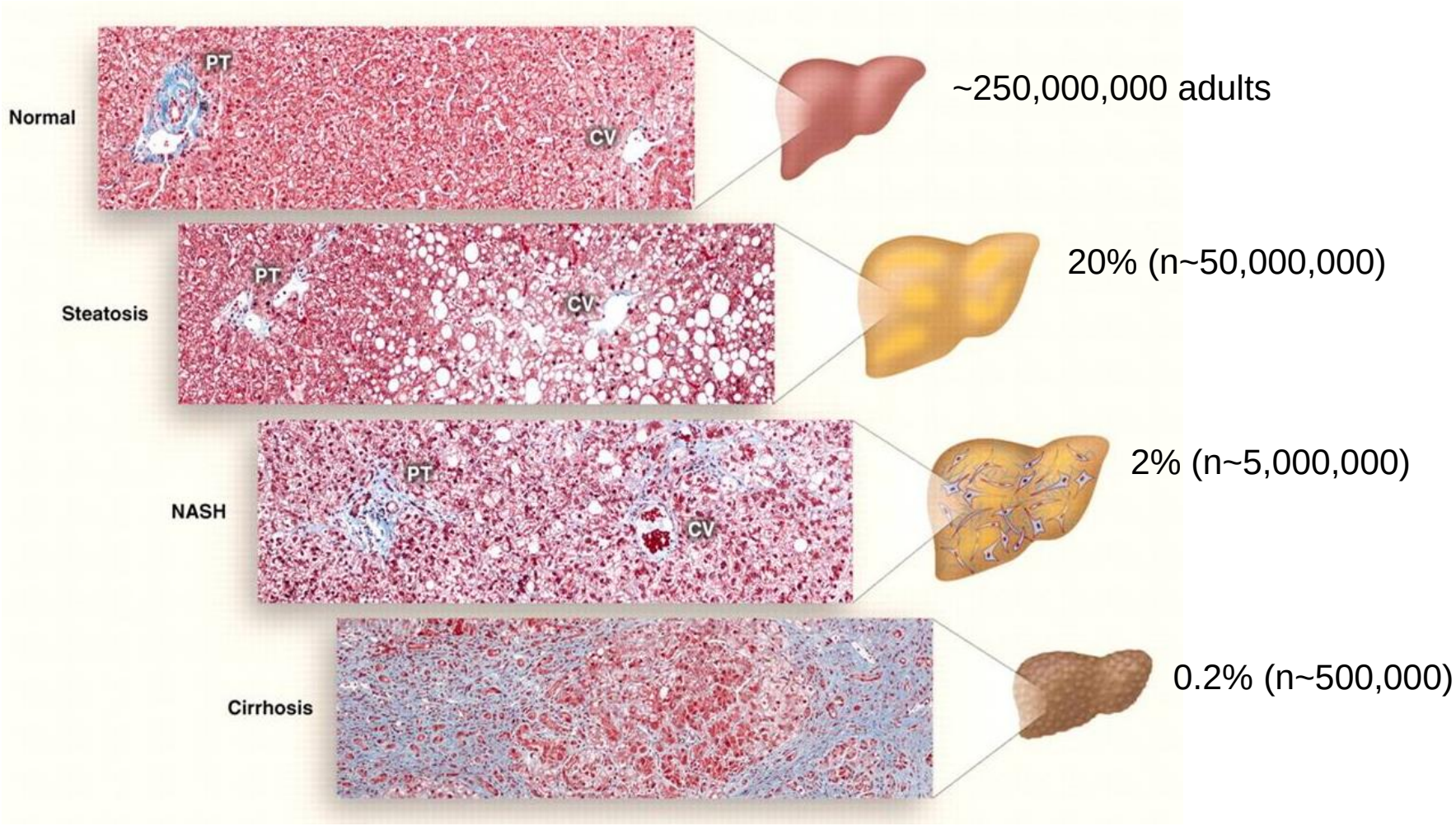
NAFLD and Liver Transplantation

- NASH is predicted to become the most common indication for liver transplantation between 2020 and 2025.



Charlton MR, Gastroenterology 2011

Prevalence of NAFLD in the United States



Cohen JC, Science 2011

Magnetic Resonance Elastography Is Superior to Clinical Prediction Models for Determination of Advanced Fibrosis in Patients With Non-Alcoholic Fatty Liver Disease: A Prospective Study

- Cross-sectional analysis of 102 patients with biopsy-proven NAFLD
- All patients had 2D-MRE within 1 year of biopsy

	AUROC	95% Confidence Interval	AUC Comparison of MRE vs. Clinical Prediction Models
2D-MRE	0.957	(0.918, 0.996)	N/A
Clinical Prediction Models			
AST to ALT ratio	0.825	(0.732, 0.918)	p = 0.013
APRI	0.807	(0.702, 0.911)	p = 0.006
BARD	0.816	(0.723, 0.910)	p = 0.001
FIB-4	0.861	(0.775, 0.946)	p = 0.039
NAFLD fibrosis score	0.818	(0.704, 0.932)	p = 0.013
Bonacini cirrhosis discriminant score	0.826	(0.725, 0.926)	p = 0.014
Lok index	0.838	(0.731, 0.944)	p = 0.046
NASH CRN model	0.796	(0.678, 0.915)	p = 0.009

Cui JY, DDW 2015, Abstract #1001

Summary

- Obesity and metabolic syndrome – particularly insulin resistance – are associated with increased risk of malignancy.
  - Association in CRC is stronger for traditional adenoma pathway
- Visceral adipose tissue is metabolically and immunologically active and may play a role in IBD pathogenesis.
- Metabolic syndrome, including NAFLD, is associated with progression of non-NAFLD liver diseases, particularly HCV.
- The consequences of NAFLD are not limited to liver disease, but there are already measurable increases in NAFLD-associated cirrhosis and HCC.