Epidemiology of NAFLD

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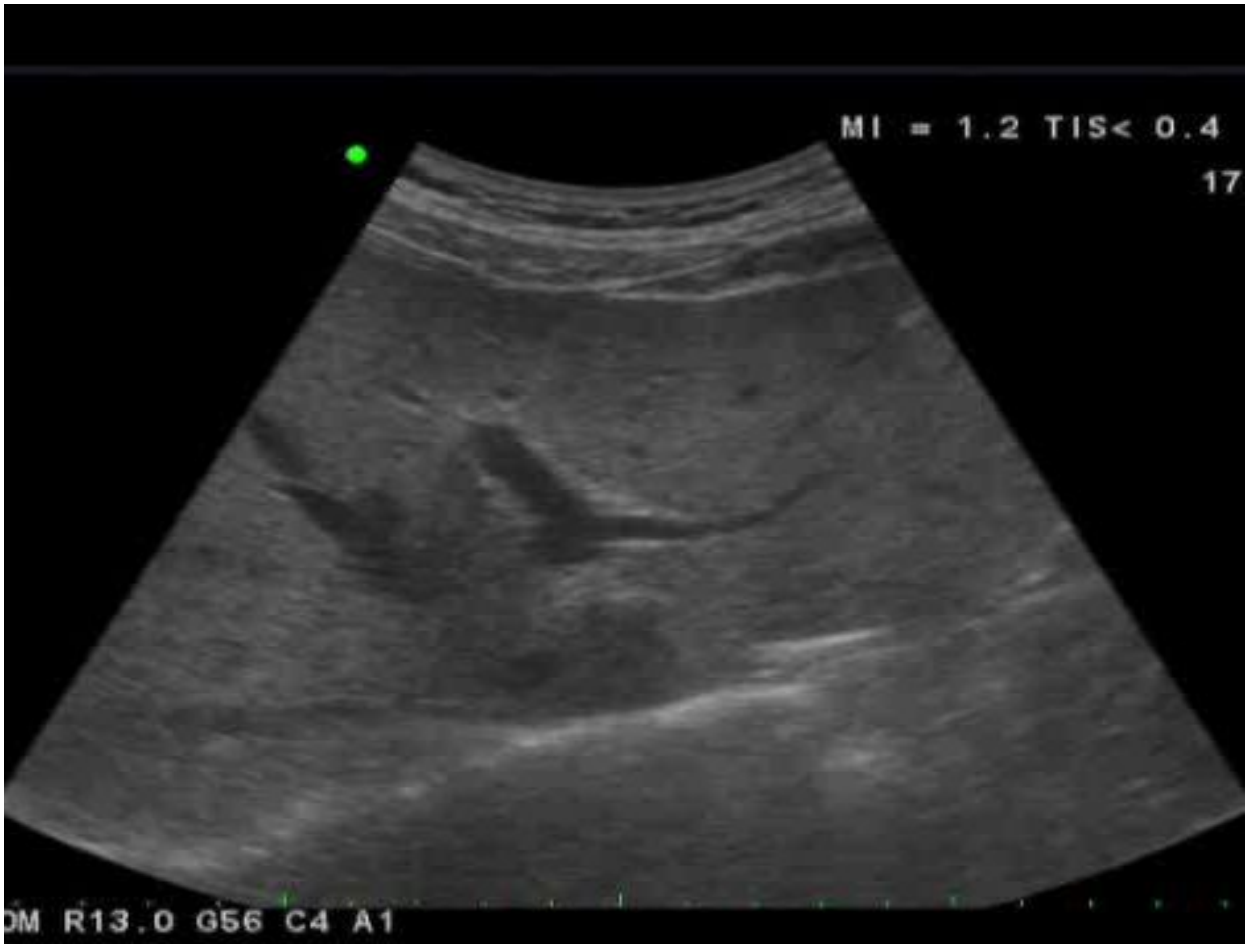
- 30/M, alcohol (-)
- C/C: easy fatigue, elevated liver enzyme



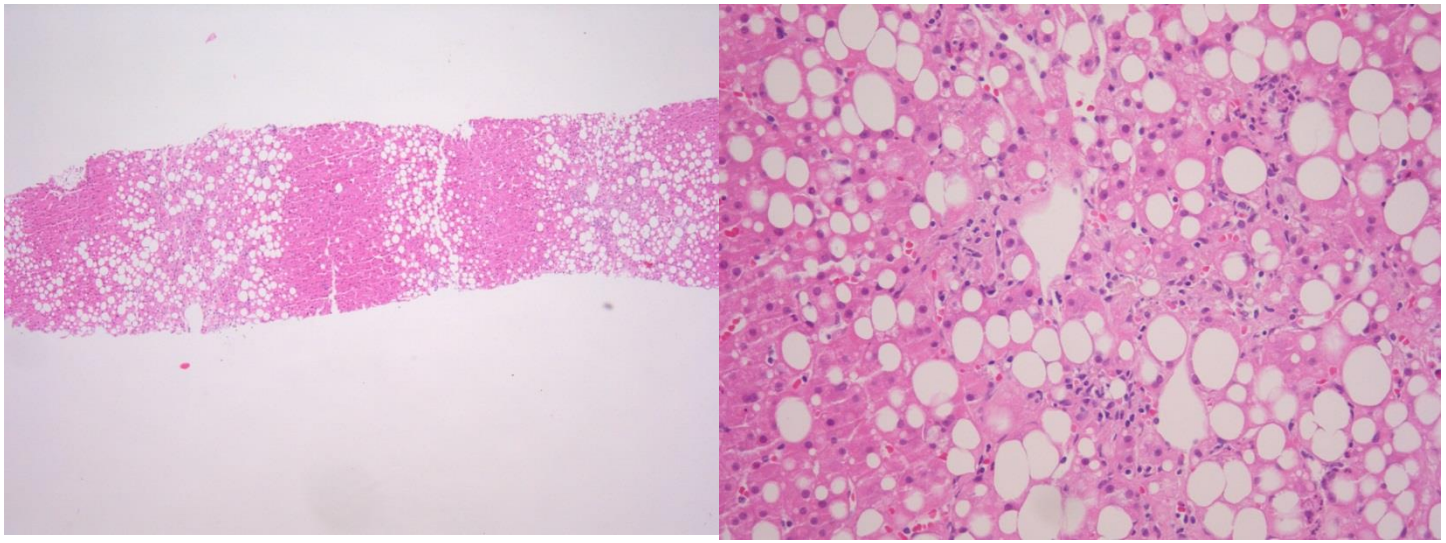
Lab findings

- BMI : 23.4 kg/m^2
- AST/ALT : 44/144 IU/L
- Albumin : 3.9 g/dl
- Glucose : 121 mg/dL
- Fasting insulin : 32.84 μIU/mL (2~25)
- Viral marker : all negative
- Fibroscan : stiffness – 3.9kPa, CAP score-295

What is the next step in the patient?

1) Calculate NAFLD firbosis score
2) Vit E or UDCA
3) Life style modification
4) Liver biopsy
5) Refer to hepatologist

Liver biopsy findings



Gr 2 steatosis, Hepatocyte ballooning, mild inflammation, perisinusoidal fibrosis 를 동반한 NASH

What are the challenges in NAFLD?

1) Where are the patients?
2) Which patients to treat?
3) Biomarkers to identify patients and guide treatment (static marker for dynamic disease)
4) How long to treat?
5) A symptomatic patients

Content

- Epidemiology

- Incidence and prevalence
- Population based study

- Non-obese NAFLD
- Natural course and clinical outcome

Epidemiology

"It is much more important to know what sort of a patient has a disease than what sort of disease a patient has."

- Sir William Osler-

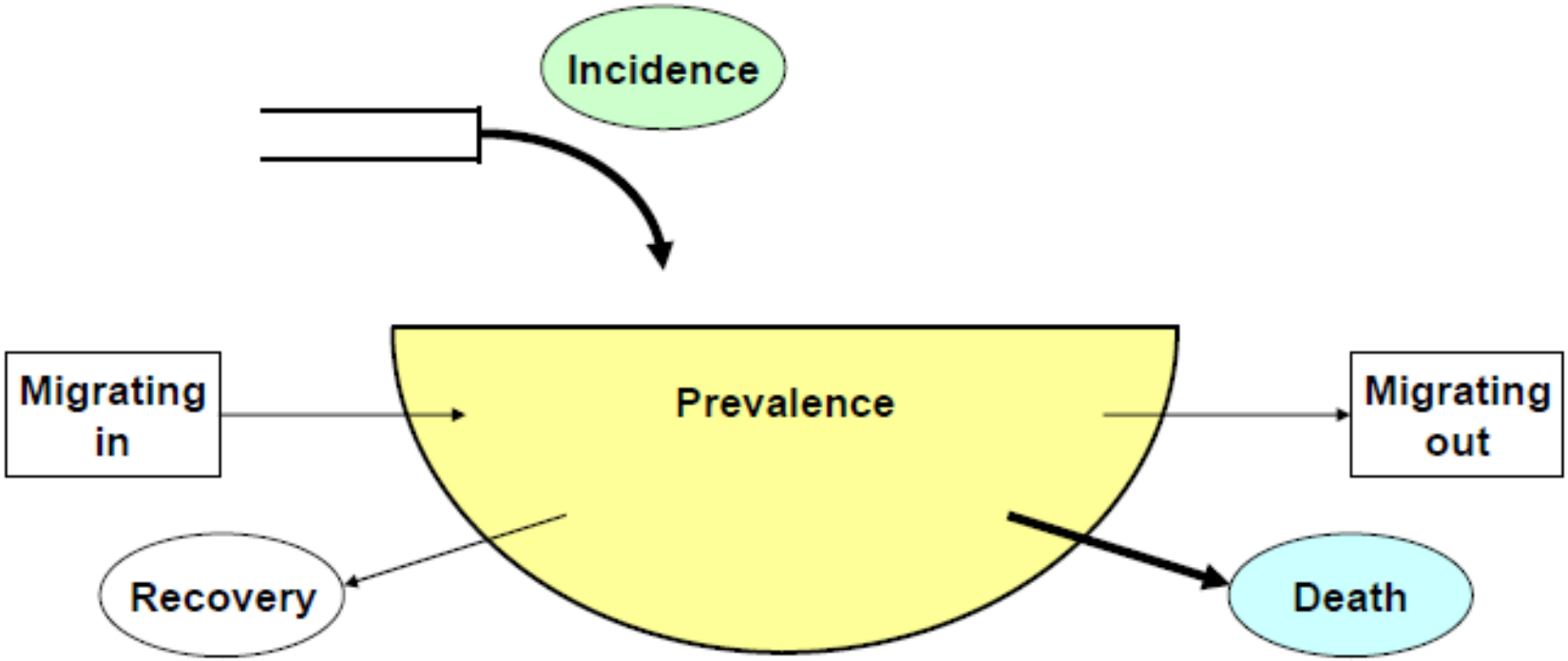
Prevalence vs. Incidence

Point Prevalence (ratio) = **Number of cases of disease present in the population on a given day** / **Number of persons in the population on that given day**

Incidence rate (density) = **Number of new cases of a disease occurring in the population during a specified period** / **Number of persons at risk of developing the disease during that period (person-years at risk)**

- Prevalence study = Cross-sectional design, Logistic regression, Chi-square analysis
- Incidence study = Cohort design, Time dependent analysis

Prevalence vs. incidence



Prevalence = Incidence x Average duration

Incidence of NAFLD

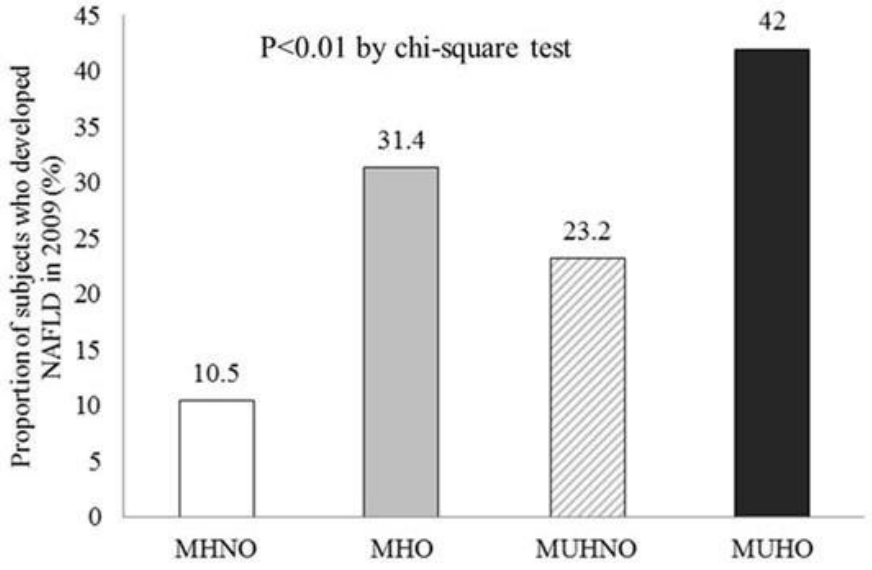
Author	Publication Year	Country	Age of Cohort at Baseline	Sex (% male)	Diagnosis Technique	Mean Follow-up Time (yrs.)	Number followed	Number of incident NAFLD cases	Unadjusted Incidence (/1000 person-years)
Hamaguchi [31]	2005	Japan	47.6	58.40%	Ultrasound	1.13	3147	308	87
Suzuki [42]	2005	Japan	35	73.20%	Blood Test (ALT >40 U/L and/or AST >35 U/L)	5	529	71	27
Wong [9]	2015	China	48	37.30%	MRS	3.9	565	76	34
Zelber-Sagi [64]	2014	Israel	51	47.60%	Ultrasound	6.8	147	28	28
Zhou [103]	2012	China	—	—	Ultrasound and Blood Test (ALT and/or AST and/or GGT elevated <5 times upper normal limit) and Risk Factors and Clinical Signs of Liver Disease	4	507	185	91

31. Hamaguchi M, Kojima T, Takeda N, et al. The metabolic syndrome as a predictor of nonalcoholic fatty liver disease. *Ann Intern Med*. 2005;143(10):722-728.
42. Suzuki A, Angulo P, Lymp J, et al. Chronological development of elevated aminotransferases in a nonalcoholic population. *Hepatol Baltim Md*. 2005;41(1):64-71. doi:10.1002/hep.20543.
64. Zelber-Sagi S, Salomone F, Yeshua H, et al. Non-high-density lipoprotein cholesterol independently predicts new onset of non-alcoholic fatty liver disease. *Liver Int Off J Int Assoc Study Liver*. 2014;34(6):e128-e135. doi:10.1111/liv.12318.
103. Zhou YJ, Li YY, Nie YQ, Huang CM, Cao CY. Natural course of nonalcoholic fatty liver disease in southern China: a prospective cohort study. *J Dig Dis*. 2012;13(3):153-160. doi:10.1111/j.1751-2980.2011.00571.x.

Younossi et al. Hepatology 2016

Metabolic health vs. Obesity for the development of NAFLD

A total of 3,045 subjects without NAFLD and diabetes at baseline were followed for four years.



metabolically healthy, non-obese (MHNO);
metabolically healthy, obese (MHO);
metabolically unhealthy, non-obese (MUHNO);
metabolically unhealthy, obese (MUHO).

The risk for NAFLD: MHNO (ref)
MHO 1.73, MUHNO 1.88

Metabolic health is more important than obesity in the development of non-alcoholic fatty liver disease

Lee MK et al. Endocrinol Metab 2015

Weight gain within the normal weight range associated with NAFLD development

Cohort of 4246 nondiabetic, men without NAFLD was followed for 5 years.
622 subjects developed NAFLD.

Quartiles of weight change (kg)	Age-adjusted HR (95% CI)		HR (95% CI) in time dependent model	
<-0.9	0.89	(0.69-1.14)	0.90	(0.71-1.15)
-0.9 to 0.5	1.00 (ref)		1.00 (ref)	
0.6 to 2.2	1.31	(1.05-1.64)	1.10	(0.88-1.36)
≥2.3	**1.52**	**(1.22-1.90)**	**1.26**	**(1.01-1.58)**

Weight gain per se increase the risk for developing NAFLD even among lean adult individuals.

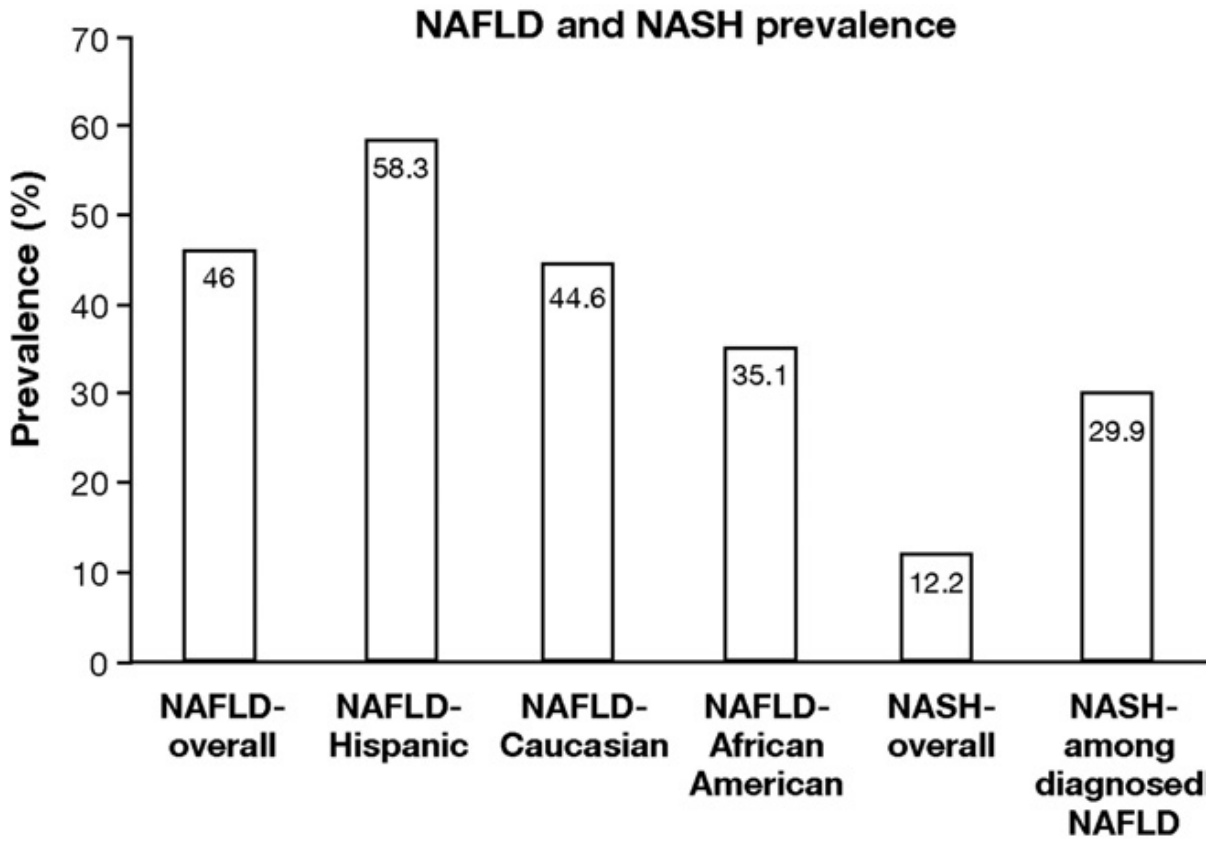
Chang Y et al. GUT 2009

Incidence or cohort study

- ADVANTAGES:
  - Temporal relationship clear
  - Can study course of disease development
  - Good for rare exposures
  - Decreases potential for many biases since disease has not occurred at time of classification

- DISADVANTAGES:
  - Time-consuming, expensive
  - Loss to follow-up and missing data
    for example) drop-outs, attrition, migration
  - Prohibitive for rare diseases
  - Does not eliminate confounding

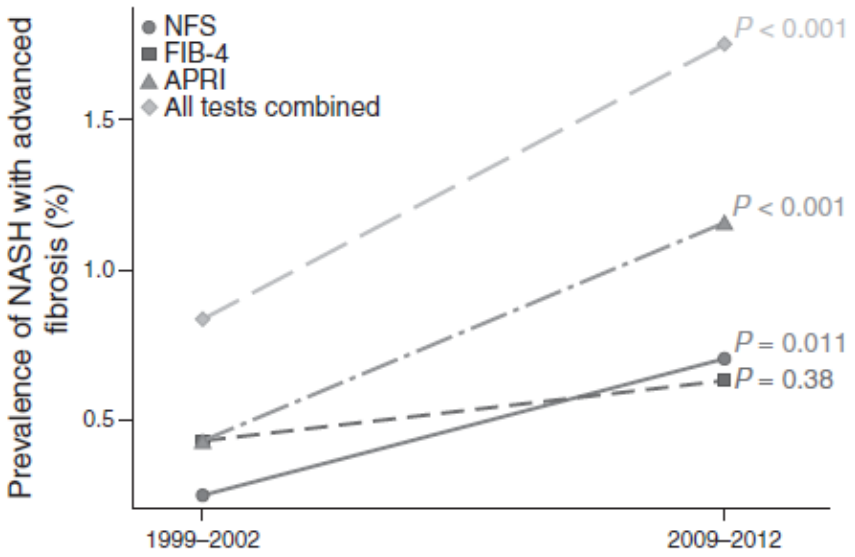
Prevalence of NAFLD and NASH

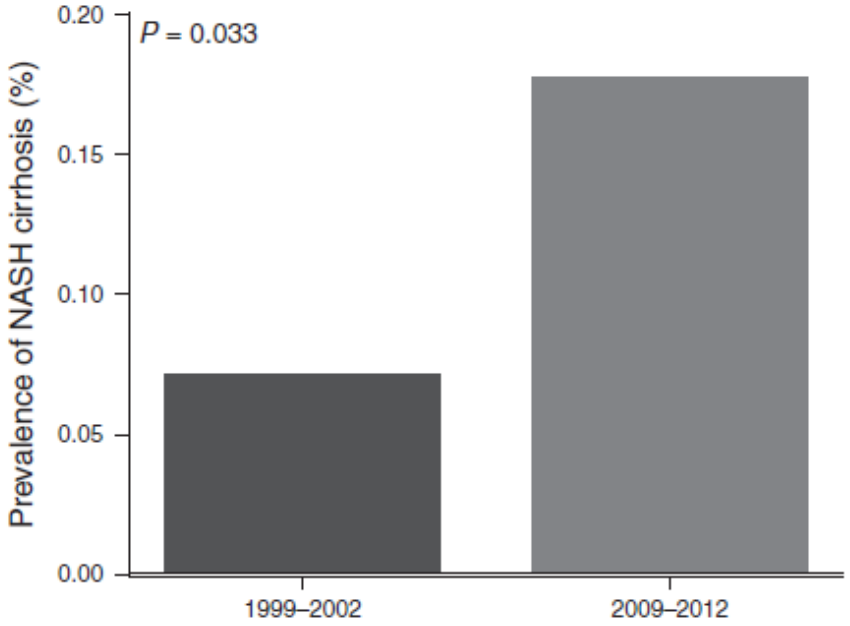


Williams et al. Gastroenterology 2011

Prevalence of NASH associated cirrhosis in the US (NHANES)

NHANES 1999-2002 vs. 2009-2012



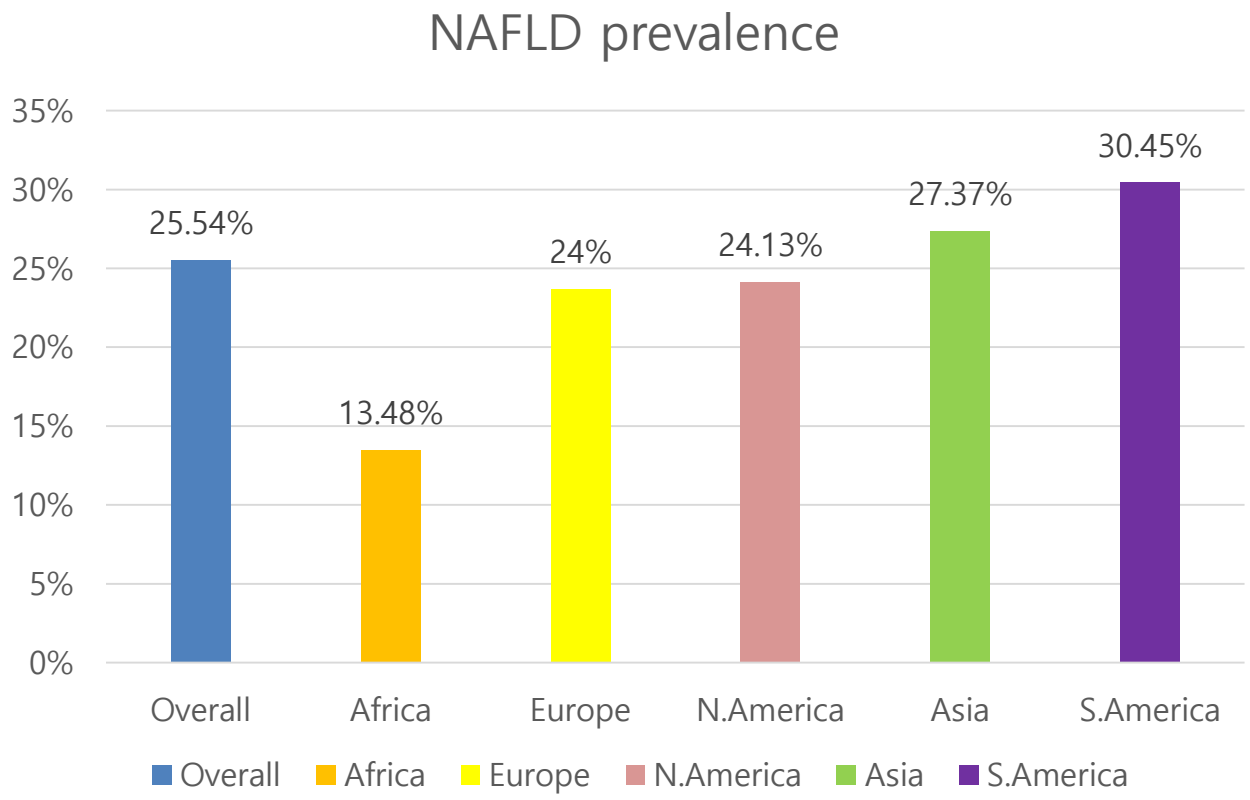


Increasing frequency of NASH and NASH-cirrhosis

Kabbany et al. AJG 2017

Prevalence of NAFLD : ethnic difference

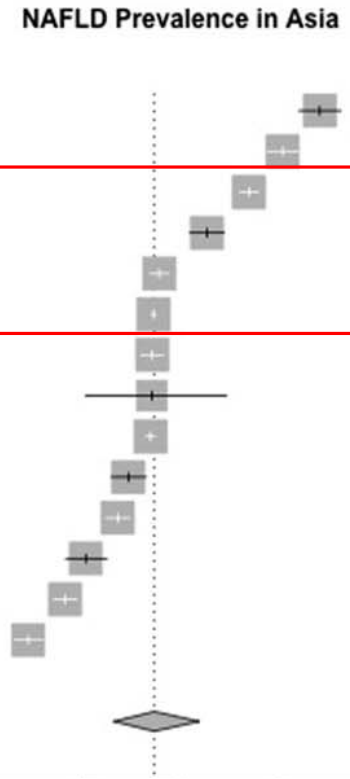
- Meta-analysis on 729 studies with 86 included



Younossi et al. Hepatology 2016

Prevalence of NAFLD

B



Study (Asia)	Events	Total	Prop (in %)	95%-CI	Reference
Cai, 2014 (China)	984	2241	43.91	[41.84; 45.99]	26
Kim, 2012 (Korea)	1617	4023	40.19	[38.67; 41.73]	36
Cai, 2013 (China)	3906	10605	36.83	[35.91; 37.76]	25
Dassanayake, 2009 (Sri Lanka)	974	2985	32.63	[30.95; 34.34]	30
Ju, 2013 (Korea)	2553	9159	27.87	[26.96; 28.80]	34
Jeong, 2013 (Korea)	44196	161891	27.30	[27.08; 27.52]	33
Shen, 2014 (Taiwan)	1769	6511	27.17	[26.09; 28.27]	41
Kim, 2014 (Korea)	45	166	27.11	[20.51; 34.54]	37
Chang, 2013 (Korea)	11652	43166	26.99	[26.58; 27.41]	27
Hong, 2012 (China)	625	2523	24.77	[23.10; 26.51]	32
Park, 2006 (Korea)	1240	5228	23.72	[22.57; 24.90]	40
Omagari, 2002 (Japan)	320	1559	20.53	[18.55; 22.62]	39
Hamaguchi, 2005 (Japan)	812	4401	18.45	[17.31; 19.63]	31
Chen, 2006 (Taiwan)	372	2520	14.76	[13.40; 16.21]	28
Random effects model		**256978**	**27.37**	**[23.29; 31.88]**	

Heterogeneity: I-squared=99.2%, tau-squared=0.1673, p<0.0001

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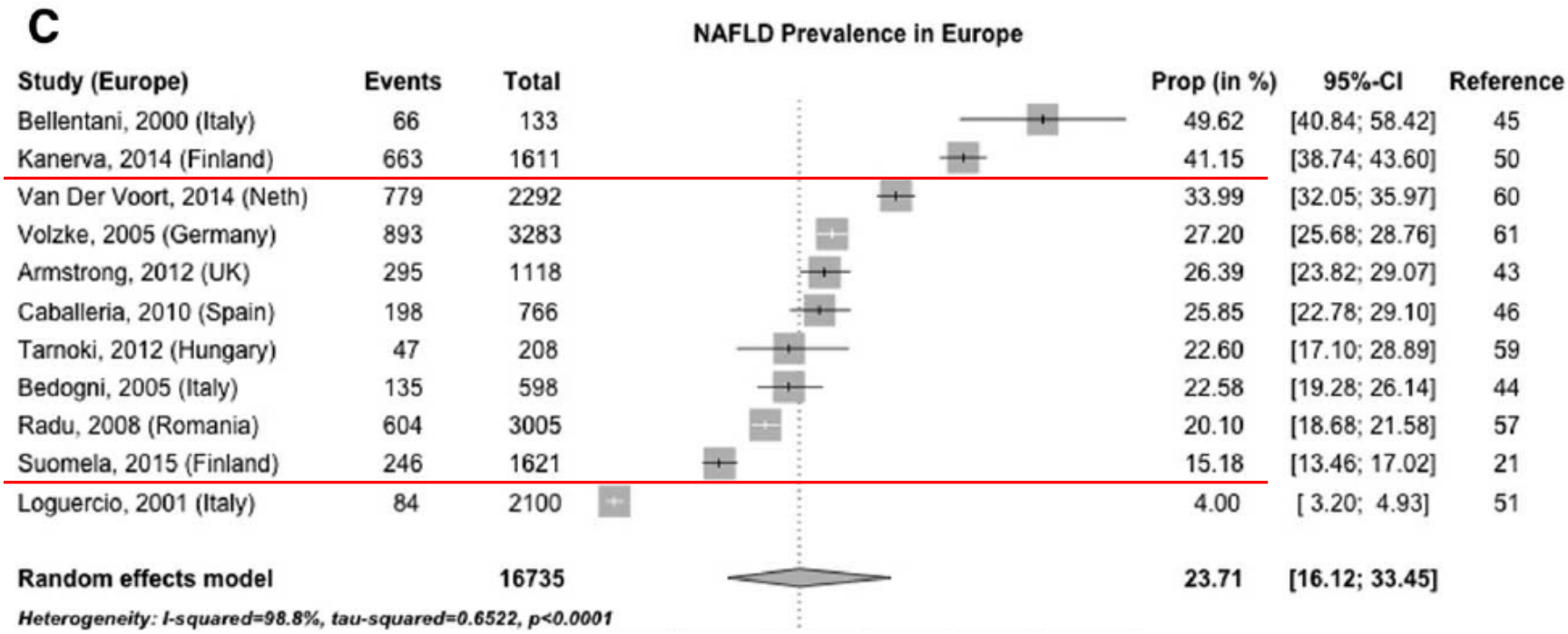
Prevalence of NAFLD



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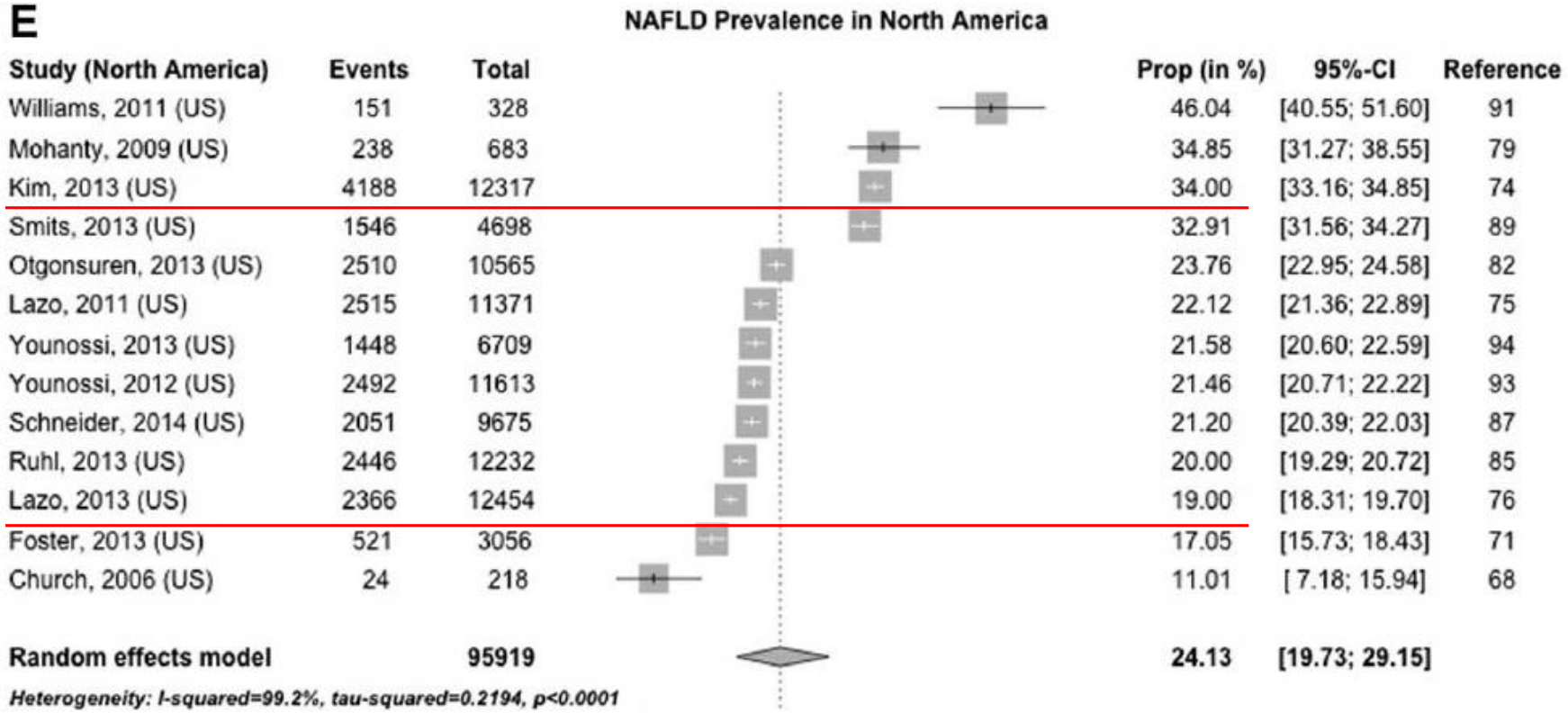
Prevalence of NAFLD

E

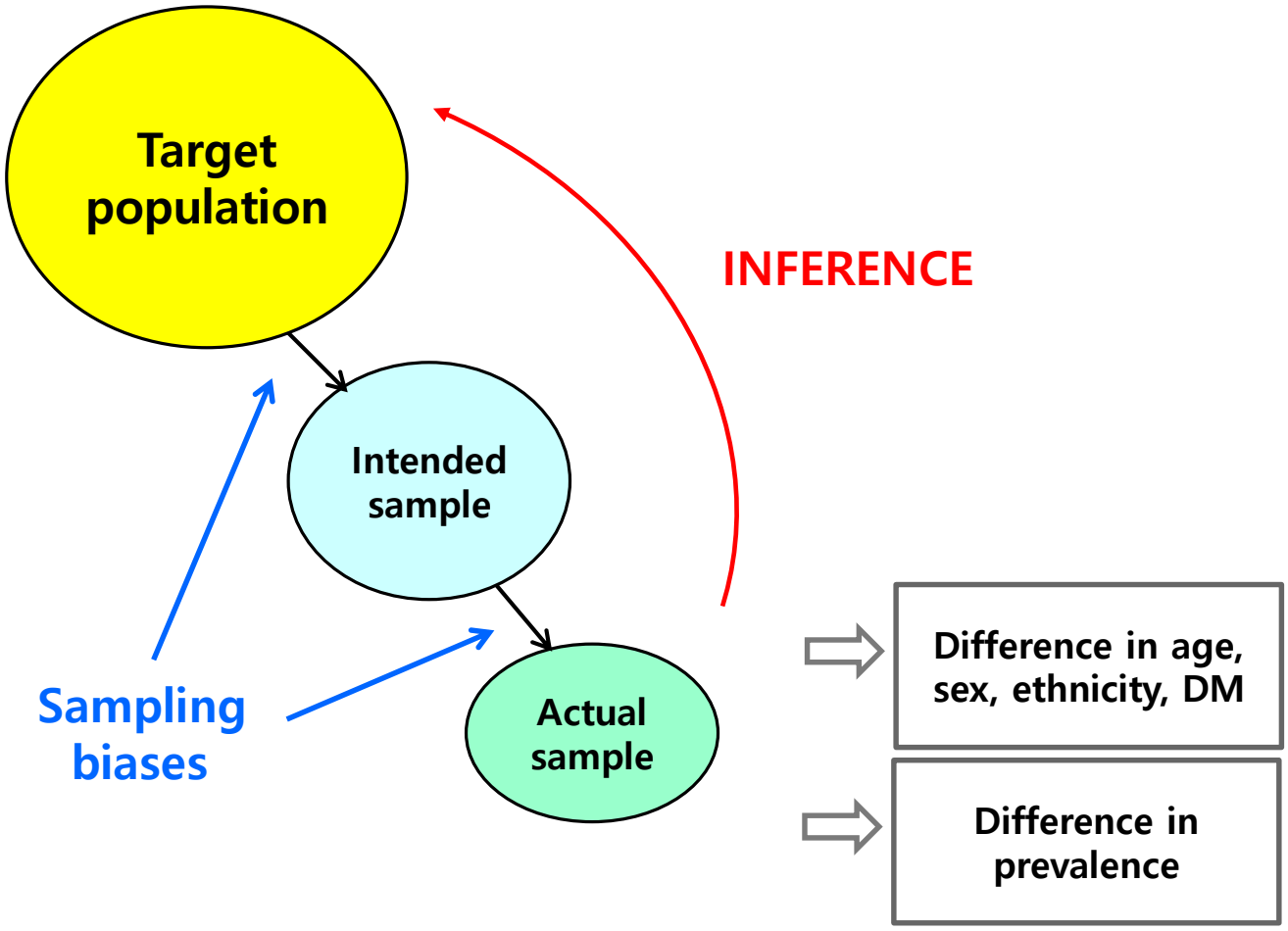


Study (North America)	Events	Total	Prop (in %)	95%-CI	Reference
Williams, 2011 (US)	151	328	46.04	[40.55; 51.60]	91
Mohanty, 2009 (US)	238	683	34.85	[31.27; 38.55]	79
Kim, 2013 (US)	4188	12317	34.00	[33.16; 34.85]	74
Smits, 2013 (US)	1546	4698	32.91	[31.56; 34.27]	89
Otgonsuren, 2013 (US)	2510	10565	23.76	[22.95; 24.58]	82
Lazo, 2011 (US)	2515	11371	22.12	[21.36; 22.89]	75
Younossi, 2013 (US)	1448	6709	21.58	[20.60; 22.59]	94
Younossi, 2012 (US)	2492	11613	21.46	[20.71; 22.22]	93
Schneider, 2014 (US)	2051	9675	21.20	[20.39; 22.03]	87
Ruhl, 2013 (US)	2446	12232	20.00	[19.29; 20.72]	85
Lazo, 2013 (US)	2366	12454	19.00	[18.31; 19.70]	76
Foster, 2013 (US)	521	3056	17.05	[15.73; 18.43]	71
Church, 2006 (US)	24	218	11.01	[7.18; 15.94]	68
Random effects model		**95919**	**24.13**	**[19.73; 29.15]**	

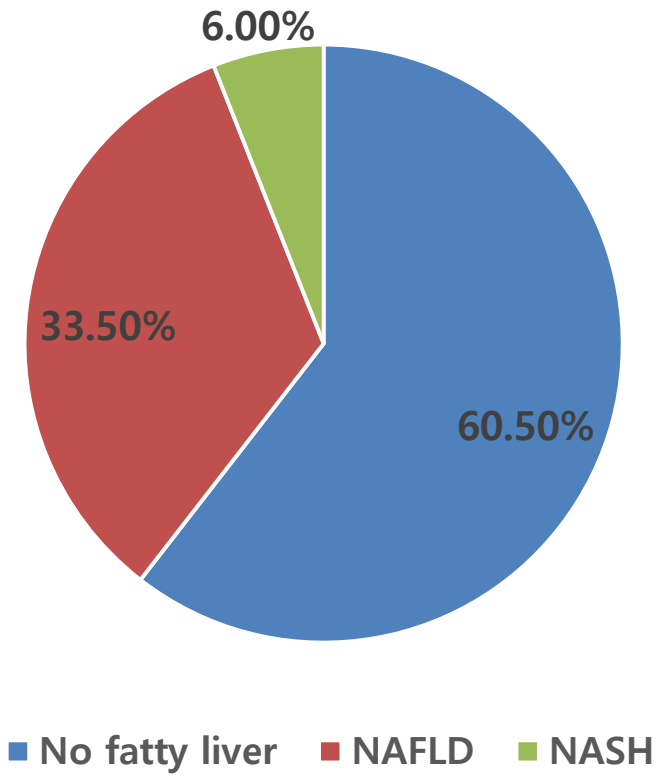
Heterogeneity: I-squared=99.2%, tau-squared=0.2194, p<0.0001

Younossi et al. Hepatology 2016

Population vs. Sample



Population-based estimate NAFLD



- Discovery in a Finish bariatric surgery group (n=296)
- Validation in a Italian non-bariatric NASH group (n=380)
- Estimation of prevalence in the general population in Finish Diabetes study (n=2,849)

Based on:
PNPLA3 genotype, insulin resistance, AST

Hyysalo et al. J Hepatol 2014

Non-obese NAFLD

How to define "Non-obese" ?

References	Country	Population (n)	Subject with BMI <25 kg/m^2 (n)	Non-obese Subjects with NAFLD	Definition of leanness/non-obese used	Prevalence of abdominal obesity in lean NAFLD	Prevalence of metabolic abnormalities in lean NAFLD
Chen et al. [4]	Taiwan	General population (n = 3,245)	1,444	61 (4.2 %)	BMI < 25 kg/m^2	NR	FPG ≥126 mg/dl in 9 TG ≥150 mg/dl in 34
Das et al. [12]	India	General population (n = 1,911)	1,777	90	BMI < 25 kg/m^2 WC <90 cm (male) and <80 cm (female)	–	Mean ± SD FBG 86 ± 25 mg/dl Mean ± SD TG 118.2 ± 66.3 mg/dl
Kim et al. [2]	Iceland	General population (n = 2,495)	941	NR	BMI < 25 kg/m^2	NR	NR
Margariti et al. [7]	Greece	NAFLD patients attending Liver clinic (n = 162)	19	–	BMI < 25 kg/m^2	33 %	MS 20 % diabetes 5 %
Younossi et al. [6]	US	National Health and Nutrition Examination Survey (NHANES III) (n = 11,613)	4,475	431 (7.39 %)	BMI < 25 kg/m^2	8.05 %	Diabetes 6.72 % hypercholesterolemia 62.65 %
Kim et al. [5]	Korea	Clinic based medical check-up (n = 786)	460	74 (16 %)	BMI < 25 kg/m^2	35 %	Hypertriglyceridemia 60.8 % IFG 8.1 %

Waist circumference in Asian: of ≥ 90 cm in men and ≥ 80 cm in women.
Abdominal obesity WHO : > 102 cm in men and ≥ 88 cm in women

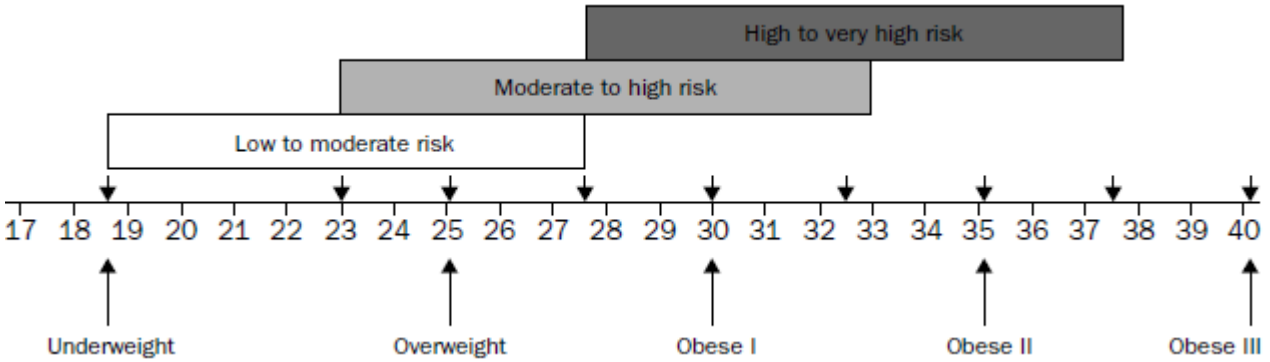
Das K et al. Hepatol Int 2013

"Non-obese"= not overweight

The current WHO BMI cut-off points	
<16 kg/m^2	severe underweight
16·0–16·9 kg/m^2	moderate underweight
17·0–18·49 kg/m^2	mild underweight
18·5–24·9 kg/m^2	normal range
≥25 kg/m^2	**overweight**
25–29·9 kg/m^2	preobese
≥30 kg/m^2	**obesity**

30–39·9 kg/m2 (obese class I), 35–39·9 kg/m2 (obese class II), 40 kg/m2 (obese class III)

The cut-off points of 23, 27·5, 32·5, and 37·5 kg/m2 (figure 2) are to be added as points for public health action.



WHO Expert consulation. Appropriate body-mass index for Asian populations and its implications for policy and intervention strategies . Lancet 2004 ; 363 : 157 – 63

Prevalence and severity of nonalcoholic fatty liver disease in non-obese patients

911 community subjects in Hong Kong. Intrahepatic triglycerides and liver fibrosis assessed by MR spectroscopy and fibroscan.

In non-obese (BMI <25kg/m^2), prevalence of NAFLD : 19.3%, prevalence of advanced fibrosis : 2.6%

Factors associated with NAFLD in non-obese		
Factors	OR (95% CI)	p-value
BMI	1.33 (1.11-1.59)	0.002
Waist circumference	1.11 (1.05-1.16)	<0.001
HOMA-IR	1.24 (1.09-1.41)	0.001
Ferritin	1.001 (1.00-1.001)	0.008
PNPLA3:CC(ref) vs CG/GG	4.37 (2.45-7.81)	<0.001

Wei JL et al. *Am J Gastroenterol* 2015

Prevalence of and risk factors for NAFLD in non-obese Japanese population

A cross-sectional study was performed with 5433 subjects who received health checkups from 2011 to 2012.

Prevalence of NAFLD in non-obese (BMI <25kg/m^2) : 15.2%,
in lean (BMI <22kg/m^2) : 6.3%

Factors associated with NAFLD in non-obese, male		
Factors	OR (95% CI)	p-value
Body fat percentage	1.13 (1.07-1.19)	<0.001
Waist circumference	1.11 (1.07-1.16)	<0.001
DPB	1.02 (1.00-1.04)	0.013
ALT	1.03 (1.01-1.04)	<0.001
Triglyceride	1.01 (1.00-1.01)	<0.001
Blood sugar	1.57 (1.10-2.23)	0.012

Nishioji K et al. *J Gastroenterol* 2015

Association of NAFLD with metabolic syndrome according to BMI in korean

29,994 adults who underwent routine comprehensive health evaluations including USG.

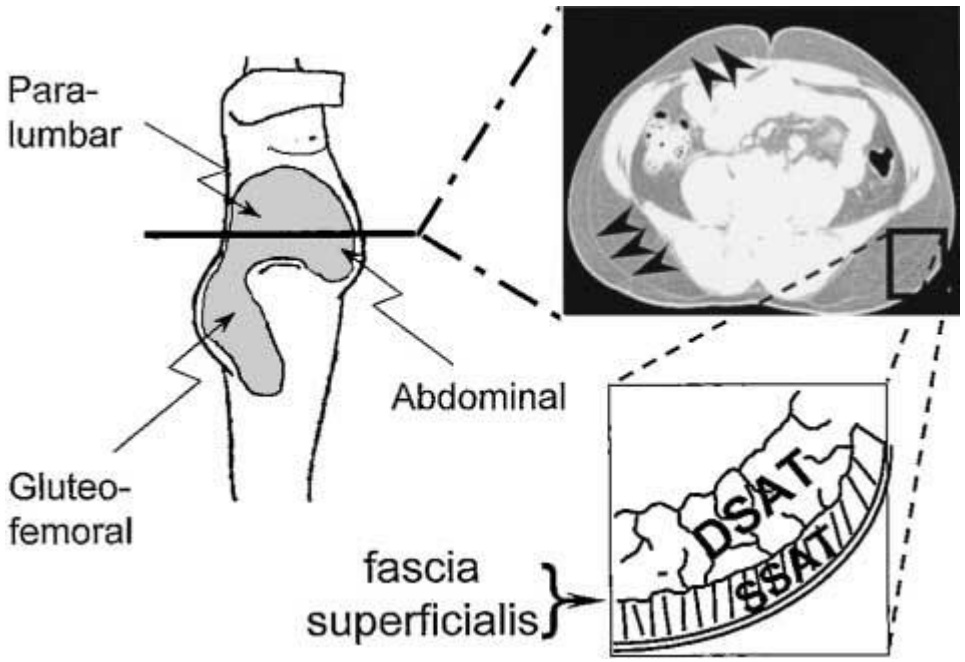
Prevalence of NAFLD in non-obese (BMI <25kg/m^2) : 12.6%,
in obese (BMI ≥25kg/m^2) : 50.1%

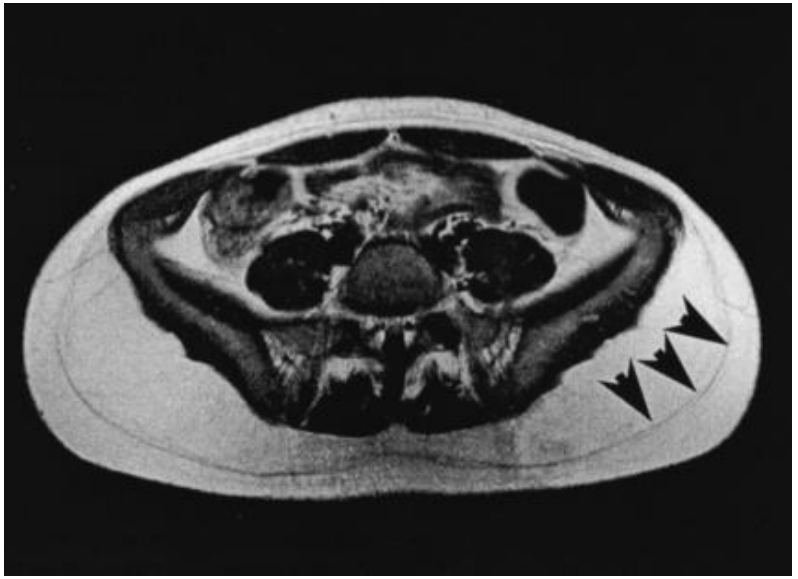
Metabolic syndrome	Non-obese		Obese		P for interaction
	OR (95% CI)		OR (95% CI)		
High BP	**1.41**	(1.31-1.51)	1.05	(0.89-1.22)	0.01
IFG	**2.04**	(1.95-2.13)	1.37	(1.21-1.53)	<0.01
Low HDL	**2.00**	(1.92-2.08)	1.40	(1.26-1.55)	<0.01
High TG	**3.36**	(3.24-3.47)	1.97	(1.76-2.17)	<0.01
Insulin resistance	**1.96**	(1.82-2.11)	1.66	(1.38-1.95)	0.40

The association between NAFLD and risk for components of MS was stronger in non-obese than in obese individuals.

Kwon YM et al. *Am J Gastroenterol* 2012

Contributions of total body fat, abdominal visceral and subcutaneous adipose tissue compartments to the metabolic complications of obesity



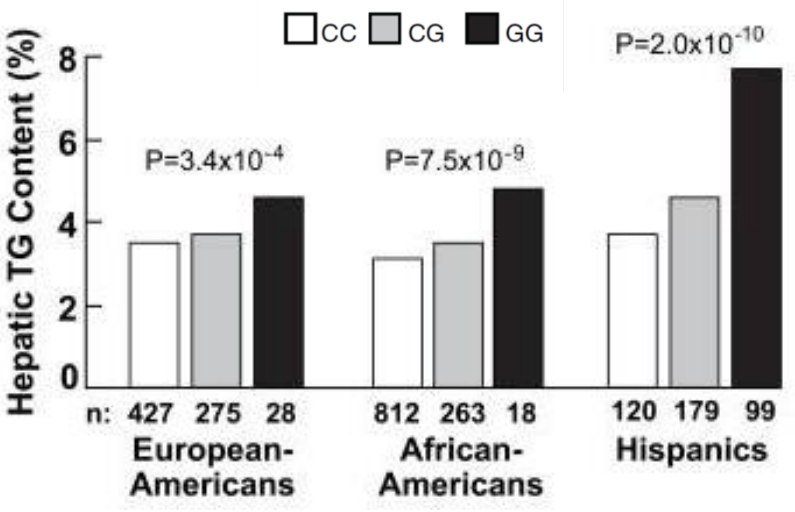


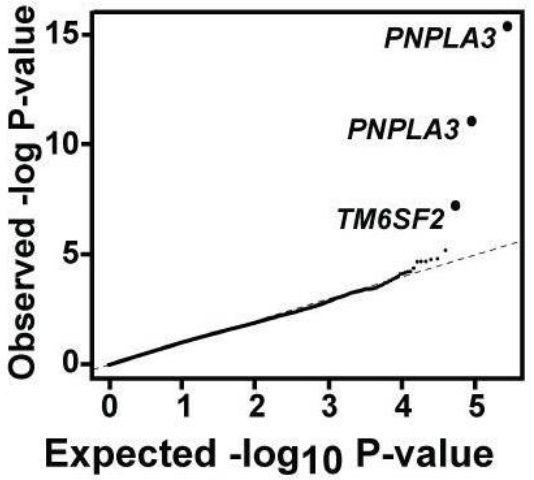
Total body fat is a major contributor to the metabolic sequelae of obesity, with specific fat depots, VAT, and DSAT also making significant contributions. It differs by sex and ethnicity.

Smith SR et al. Metabolism 2010, Staiano AE et al. Obesity 2013, Eastwood SV et al. PloS One 2013

Genetic variation in NAFLD

- genome-wide association scan of nonsynonymous sequence variations (n = 9,229) in a population comprising Hispanic, African American and European American individuals





- Variation in PNPLA3 contributes to inter-individual differences in hepatic fat content and susceptibility to NAFLD.
- TM6SF2 activity is required for normal VLDL secretion and that impaired TM6SF2 function causally contributes to NAFLD.

Romeo S et al. Nature Genetics 2008 Kozlitina et al. Nature Genetics 2014

NAFLD as a risk factor of DM

- a prospective cohort study on the 25,232 Korean men without type 2 DM for 5 years. Incidence rate of type 2 DM was compared according to the degree of NAFLD (normal, mild, and moderate to severe),

	Person-year	Incidence cases	Incidence density (per 1,000 person-year)	Hazard ratios (95% Confidence Interval)		
				Unadjusted	Model 1	Model 2
NAFLD						
Normal	61,936.4	1,146	18.5	1.00 (reference)	1.00 (reference)	1.00 (reference)
Mild	28,942.3	758	26.2	1.42 (1.30-1.56)	1.30 (1.04-1.62)	1.09 (0.81-1.48)
Moderate to severe	4,291.6	204	47.5	2.58 (2.22-2.99)	1.64 (1.06-2.53)	1.73 (1.00-3.01)
P for trend				<0.001	<0.001	<0.001

- Well-designed cohort study, time-dependent analysis

→ Strong temporal relation

- Dose-dependent association

Park SK et al. Hepatology 2013

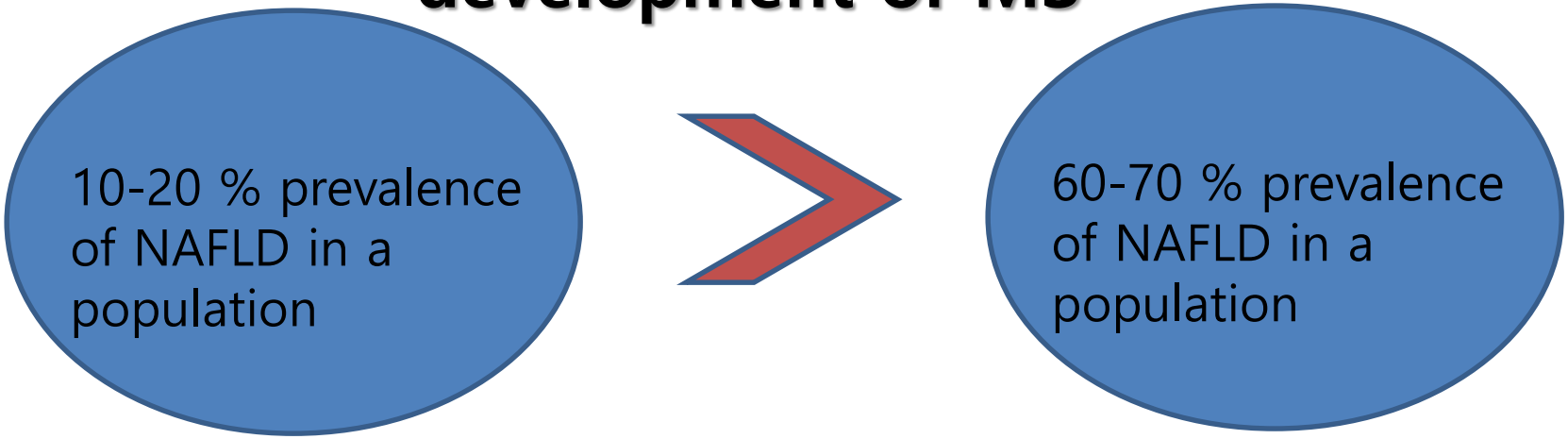
Type III error

- The causes of difference

Interindividual variation within a population

Rate difference between populations

Impact of NAFLD on development of MS



Where are NAFLD patients?

EASL-EASD-EASO Clinical Practice Guideline for the management of NAFLD

→ Recommended

Metabolic risk factors present (any component of MS) : USG/Liver enzyme

The diagnosis and management of NAFLD: Practice guideline by the AGA/AASLD/ACG

→ Not recommended

In practice Not done

- Lack of knowledge
- No treatment drug
- They just need to lose weight

Potential solutions

- ➢ New guidelines – AASLD/National
- → Closer working with primary care and diabetologists
- ➢ New diagnostic and treatment modality

Chalasani et al. Gastroenterology 2012

Natural history- Which patients to treat?

a retrospective analysis of 619 patients diagnosed with NAFLD from 1975 through 2005 at medical centers in the United States, Europe, and Thailand over a median follow-up period of 12.6 years

	Hazard ratio	95% CI of HR	*P* value
Model 1			
Fibrosis, stage 0	1 (reference)		
Fibrosis, stage 1	2.07	1.40–3.08	<.001
Fibrosis, stage 2	3.02	2.0–4.56	<.001
Fibrosis, stage 3	3.97	2.50–6.30	<.001
Fibrosis, stage 4	11.97	6.47–22.12	<.001

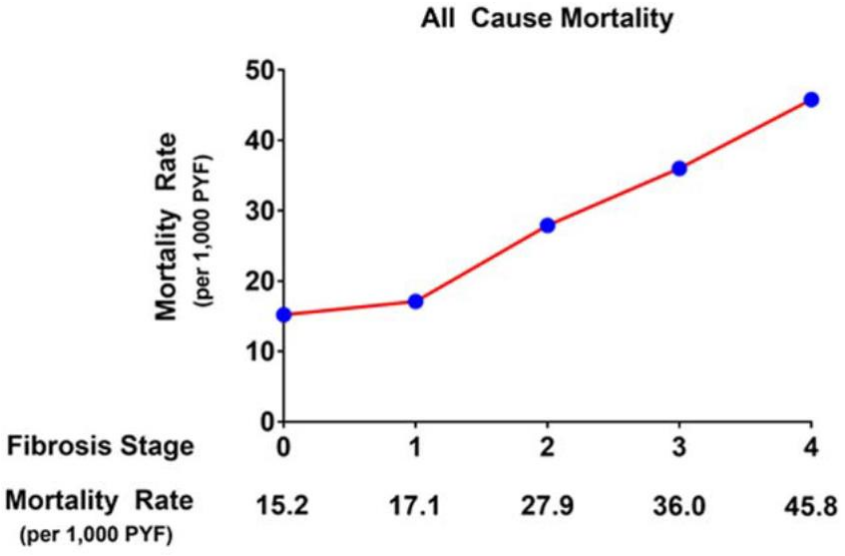
Outcome	Number
Death or OLT	(n = 193)
Cardiovascular disease	74 (38.3%)
Nonliver cancer	36 (18.7%)
Cirrhosis complications	15 (7.8%)

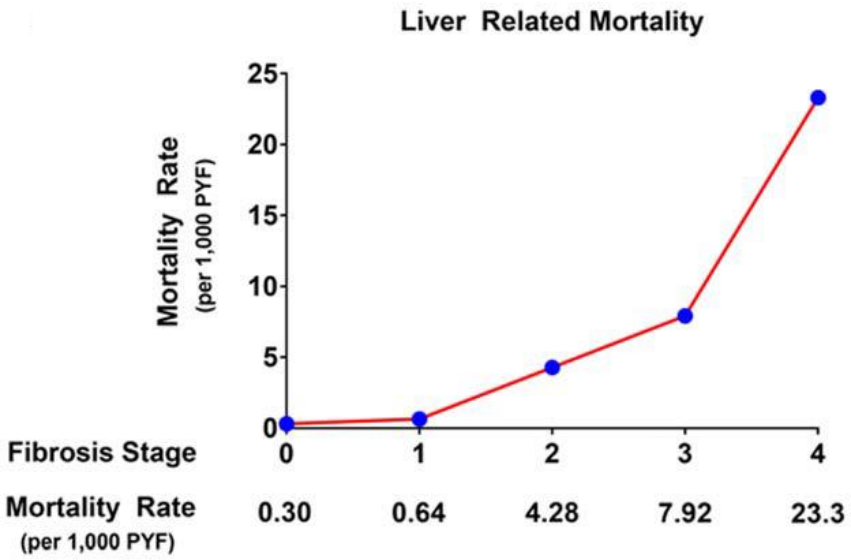
Fibrosis stage, but no other histologic features of steatohepatitis, were associated independently with long-term overall mortality.
Liver related complication or HCC was less than 20%.

Angulo P et al. Gastroenterology 2015

NAFLD and Mortality

Systematic literature review on NAFLD cohort on 17,000 patient years





Cause of Death
1. CVD, 2. Non-liver malignancy, 3. Liver-related causes

Dulai et al. Hepatology 2017

NAFLD and CV Mortality

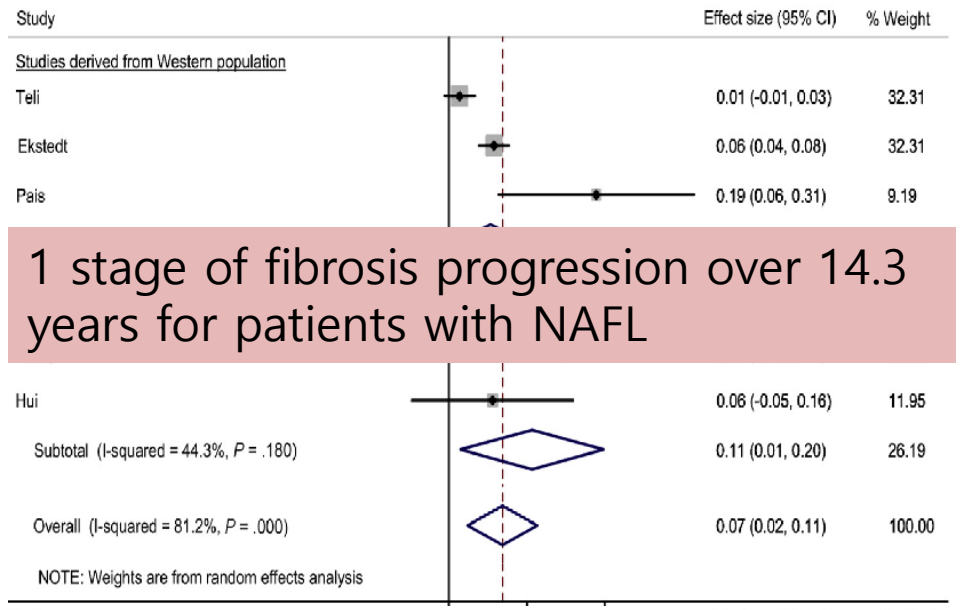
USA, NHANES III (n=11,154), Graded by NFS

NAFLD fibrosis score		Age, Sex-adjusted	Multivariable-adjusted
	n	Hazard ratio (95% CI)	Hazard ratio (95% CI)
Mortality from all cause	778		
No	290	1	1
Intermediate	389	1.30 (1.00-1.70)	1.26 (0.98-1.64)
Advanced	99	2.17 (1.40-3.36)	**1.69 (1.09-2.63)**
Cardiovascular disease	291		
No	88	1	1
Intermediate	162	2.01 (1.34-3.00)	2.16 (1.41-3.29)
Advanced	41	3.69 (2.06-6.61)	**3.46 (1.91-6.25)**

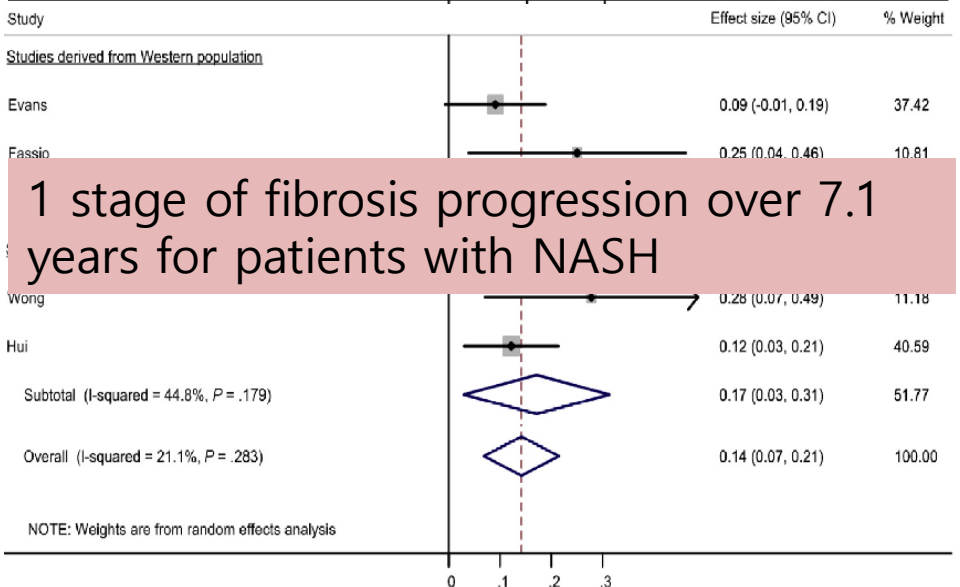
Multivariable models adjusted for age, sex, race-ethnicity, education, income, diabetes, hypertension, smoking status, waist circumference, alcohol consumption, caffeine consumption, total cholesterol, high-density lipoprotein-cholesterol, transferrin saturation, and C-reactive protein.

Kim D et al. Hepatology 2013;57:1357-65.

Potential solution: which patients to treat?



1 stage of fibrosis progression over 14.3 years for patients with NAFL



1 stage of fibrosis progression over 7.1 years for patients with NASH

Meta-analysis:

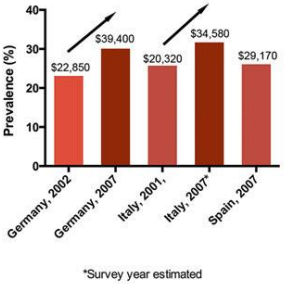
11 cohort studies including 411 patients with biopsy-proven NAFLD

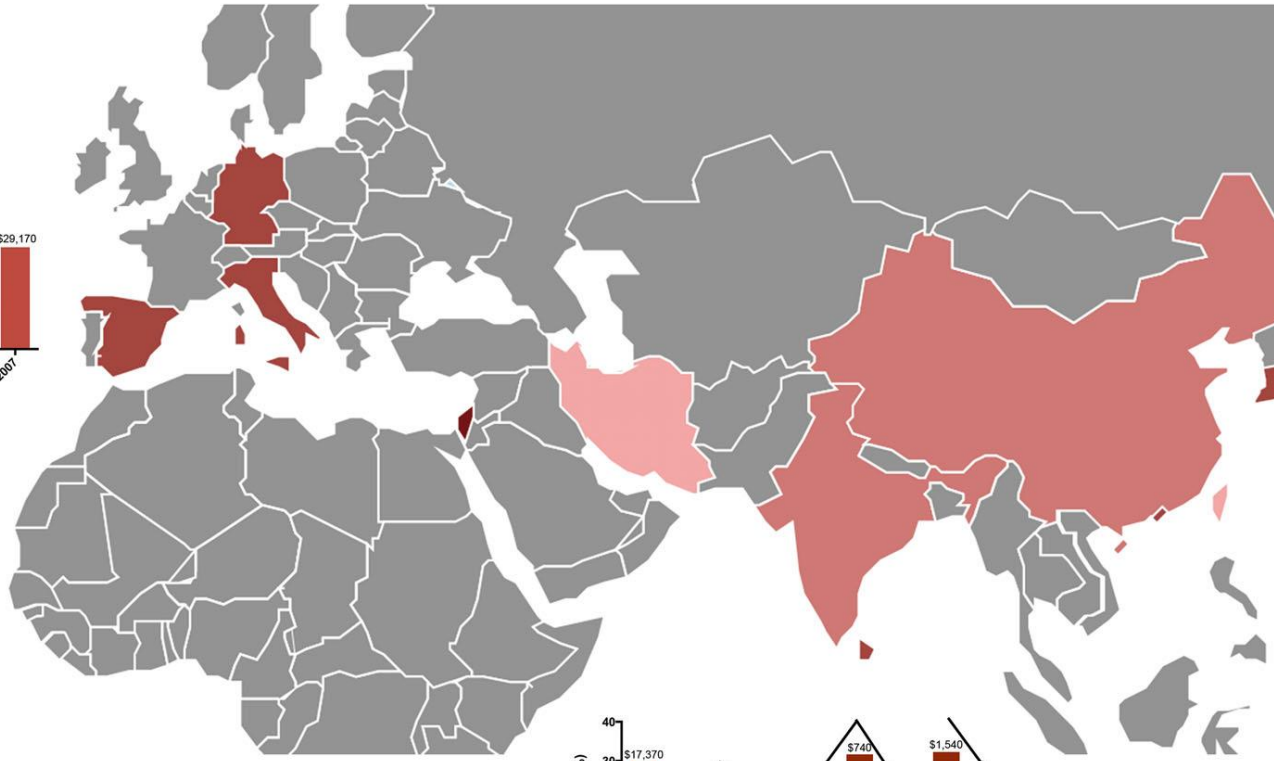
Singh S et al. CGH 2015

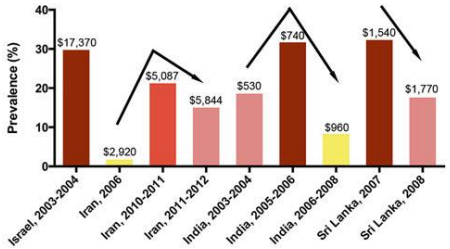
- **HCC incidence** (follow-up=3.2 yr)
  - NASH-LC: 12.8%
  - HCV-LC: 20.3%
- **HCC diagnosis age**
  - NASH-LC: 70-71 years
  - HCV-LC: 63-43 years

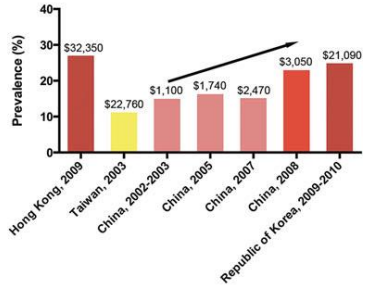
Yatsuji S et al. J Gastroenterol Hepatol. 2009

Prevalence of NAFLD : Role of the gross national income (GNI)









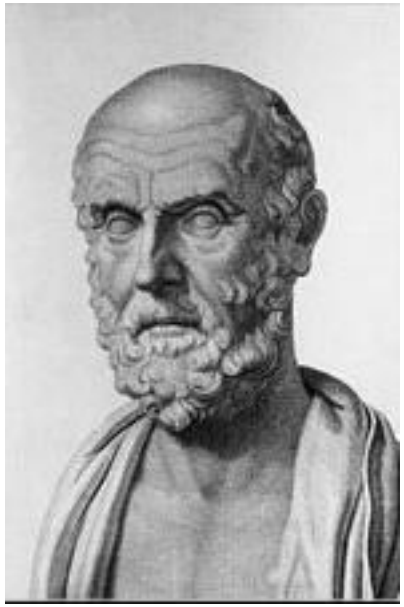
Zhu et al. Dig Dis Sci 2015

Food amount really matters..

Epidemology of NAFLD

- Are all calories the same?
  → Yes, with minor differences

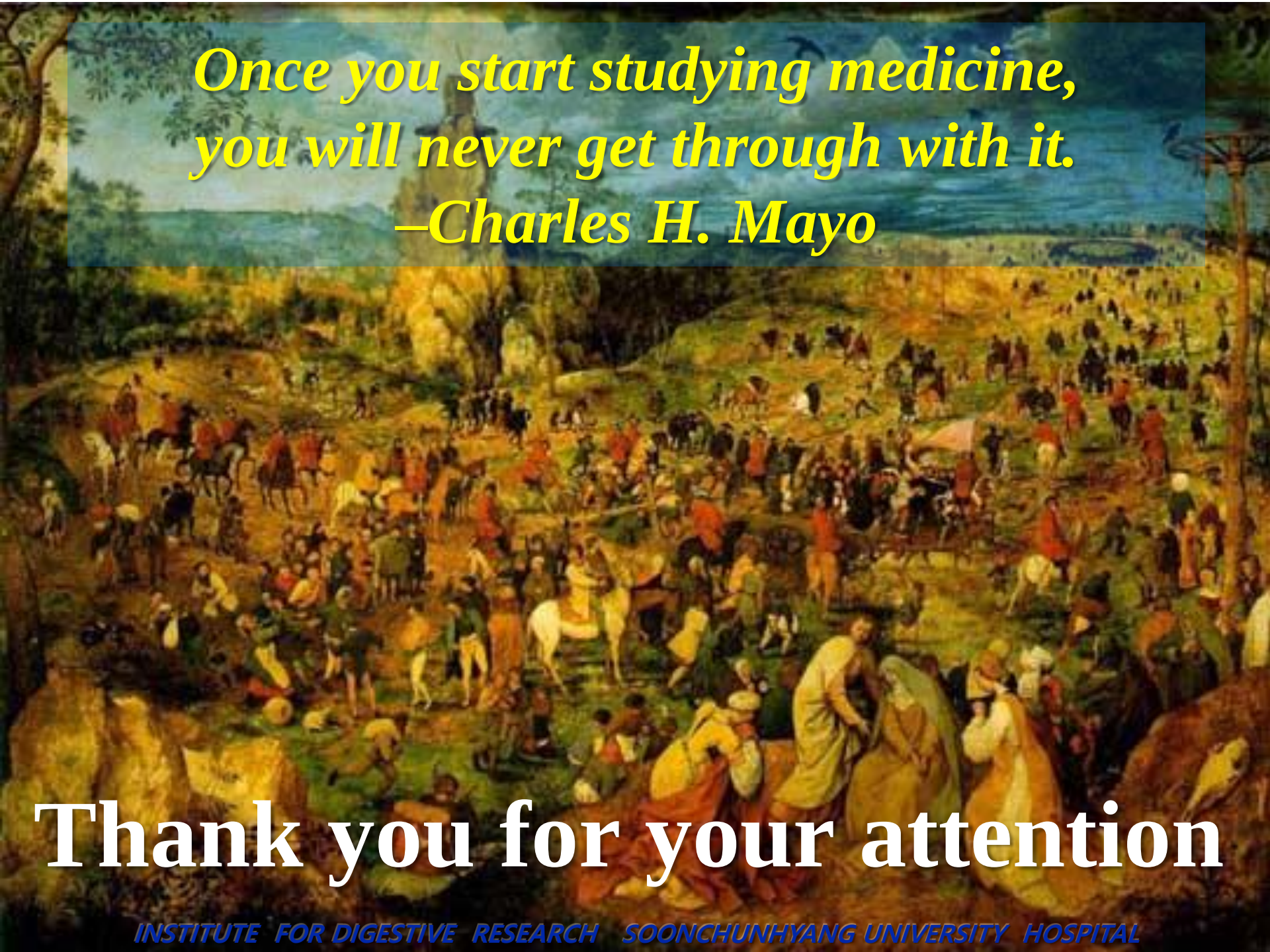
- Let food be your medicine!



Hippocrates BC 460-370

Conslusion

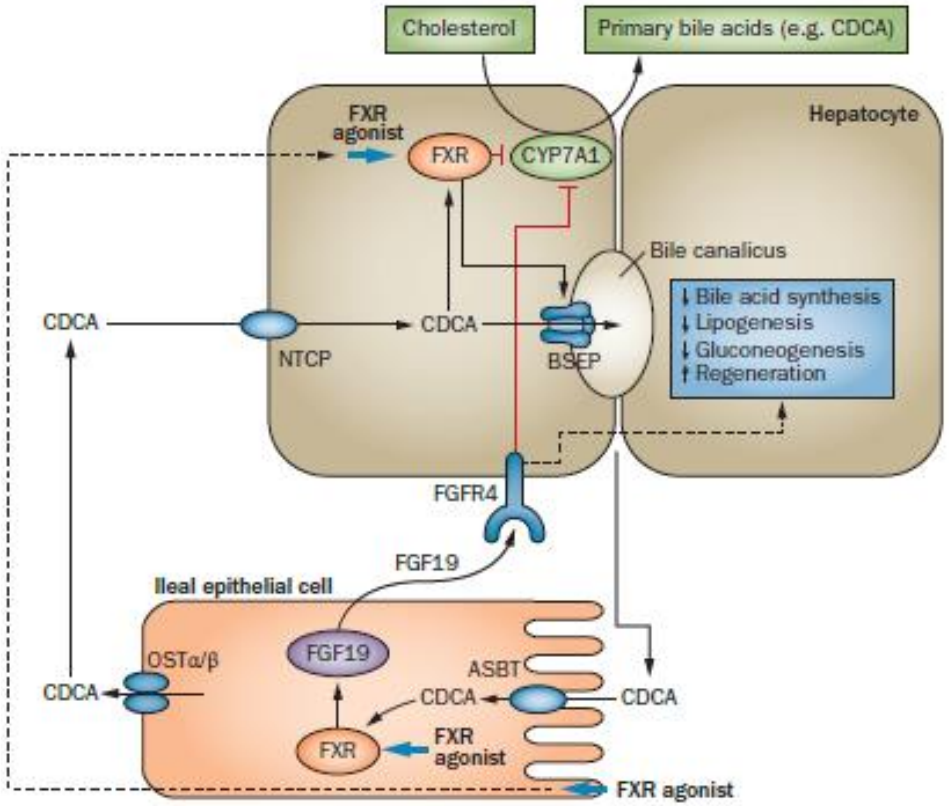
- The prevalence of NAFLD in Korean population is 23-40%. The incidence of NAFLD is 37/1000 person-years.
- NAFLD itself and NAFLD related other metabolic diseases are increasing.
- The patients who have metabolic syndrome should be monitored for NAFLD or NASH.
- Liver biopsy can be considered in patients with elevated liver enzyme or high NFS, Fib4 score.


Once you start studying medicine,
you will never get through with it.
–Charles H. Mayo
Thank you for your attention
INSTITUTE FOR DIGESTIVE RESEARCH SOONCHUNHYANG UNIVERSITY HOSPITAL

NASH therapeutic targets by mechanisms and sites of activity and type of outcomes

PPAR agonist Aramchol ASK-1 inhibitors DGAT inhibitors ACC inhibitors Anti-CB1 MetAP2 inhibitors others	DPP-4-i PPAR-agonist SGLT2-i FGF-19 FGF-21 ISIS-ANGPTL3 others	OCA FXR agonist ASBT-1 FGF-19 FGF-21 others	PPAR agonist CVC Anti-JNK Anti-Ask DHA Anti-CB1 others	OCA Anti-JNK-1 Anti-ASK PPAR agonist Nox inhibitors others	Simtuzamab Anti-gal 3 Anti-CTGF Angiotensin-R-blockers Pentraxin-2 Anti-IL-17 Anti-TGF-beta
Fatty acid synthesis	Insulin sensitivity	Bile acid synthesis	Anti-inflammatory	Anti-fibrotic Early stage	Anti-fibrotic Late stage
Steatosis, ballooning, and inflammation			Stage 1-3 fibrosis		Stage 3-4 fibrosis
Resolution of NASH		Reduce the rate of progression of fibrosis or Improvement in fibrosis			Reversal of advanced fibrosis or Improvement in fibrosis

Nuclear bile acid receptor; Farnesoid X receptor (FXR)



- Expressed predominantly in liver and intestine activated by endogenous bile acid (BA)
- Regulate BA synthesis, biotransformation and excretion.
- Key role in the control of glucose and fat homeostasis
- Protective roles against bacterial overgrowth and maintenance of barrier function in the gut

Intestinal FXR agonism promotes adipose tissue browning and reduces obesity and insulin resistance.

Schaap, F. G. et al. Nat. Rev. Gastroenterol. Hepatol. 2014

Anna LF et al. J of Hepatology 2011