2ᵈ Paris NASH Symposium, June 30th- July 1st 2016, Institut Pasteur

Variability of disease state transitions based on clinical phenotype and country of origin

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NAFLD: natural history

Age
Obesity
Type 2 diabetes
Insulin resistance
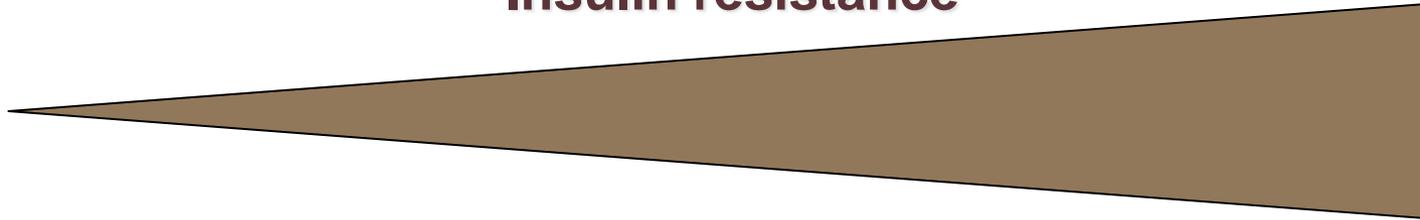
Pure steatosis

Steatosis + inflammation

NASH
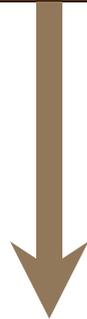
Disease progression

High prevalence of lean patients with NAFLD in developping countries

inhabitants of a rural administrative unit of West Bengal

HBV, HCV, alcohol

n=1911 age>18 yrs

US or CT scan

n=167 steatosis (8.7%)

54% with normal BMI

LB if ALT>N

NASH 2.3%

Cirrhosis 0.2%
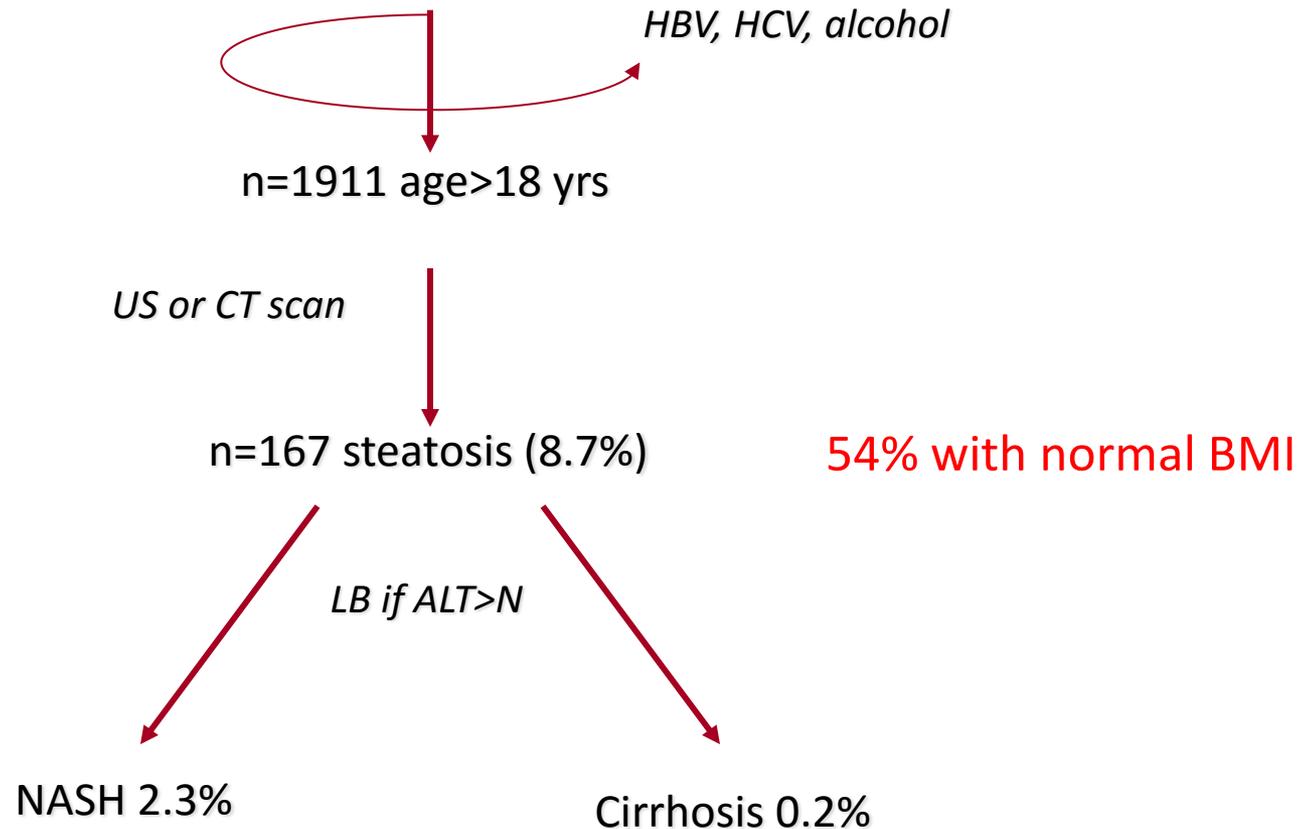
NAFLD in lean vs obese patients

Author	Country	Metabolic risk factors	Liver injury
Leung JC et al	Hong Kong	Less frequent	Less severe
Feng RN et al	China	More frequent	*NA*
Akyuz U et al	Turkey	Less frequent	Less severe
Maragariti E et al	Greece	Less frequent	More severe
Younossi ZM et al	US	Less frequent	*NA*

Leung JC et al. Hepatology 2016; in press
Feng RN, et al. World J Gastroenterol 2014;20:17932-40.
Akyuz U, et al. Scand J Gastroenterol 2015;50:341-6.
Younossi ZM, et al. Medicine (Baltimore) 2012;91:319-27.
Margariti E, et al. Ann Gastroenterol 2012;25:45-51.

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The Global NAFLD Consortium

- To assess the regional similarities and differences in the pathophysiological, epidemiological, clinical, histological and therapeutic-response profiles of NAFLD around the world.

- Academic investigators : North America (USA), South America (Brazil), Europe (France) and Asia (India)

- Primary aim: to define: (1) the similarities and differences between lean versus obese subjects with NAFLD in different countries, (2) whether subjects within specific weight strata from one country are comparable to similar subjects in another country from a different continent.

Demographic of patients

430 biopsy-proven NAFLD

Parameter	USA n=139	France n=96	Brazil n=125	India n=63
Age (yrs)	53.3±0.92	49.7±1.2*	55.08±0.2	38.06±1.6*
Females (%)	71.2 *	30.9	46.5	66.2*
T2 DM (%)	21.1	21.6	53.3*	31.0
Hypertension (%)	43.7	25.3	67.4*	11.6
Triglycerides (mg/dL)	204.9±10.3	112.5±11.4*	218.0±7.9	198.3±12.4
Total Cholesterol	197.8±4.2	206.5±5.5	193.5±4.2	165.8±7.7
LDL-XOL (mg/dL)	125.8±4.5	135.6±7.1	115.5±3.2	93.3±6.6
HDL-XOL (mg/dL)	44.0±5.4	43.0±5.2	46.0±5.5	40.0±4.7

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Distribution of BMI

430 patients with biopsy proven NAFLD

n

Legend: Lean, Overweight, Obesity

US: 13, 23, 103
France: 22, 52, 22 *
Brazil: 16, 28, 81
India: 19, 33, 11

Oliveira C et al. submitted
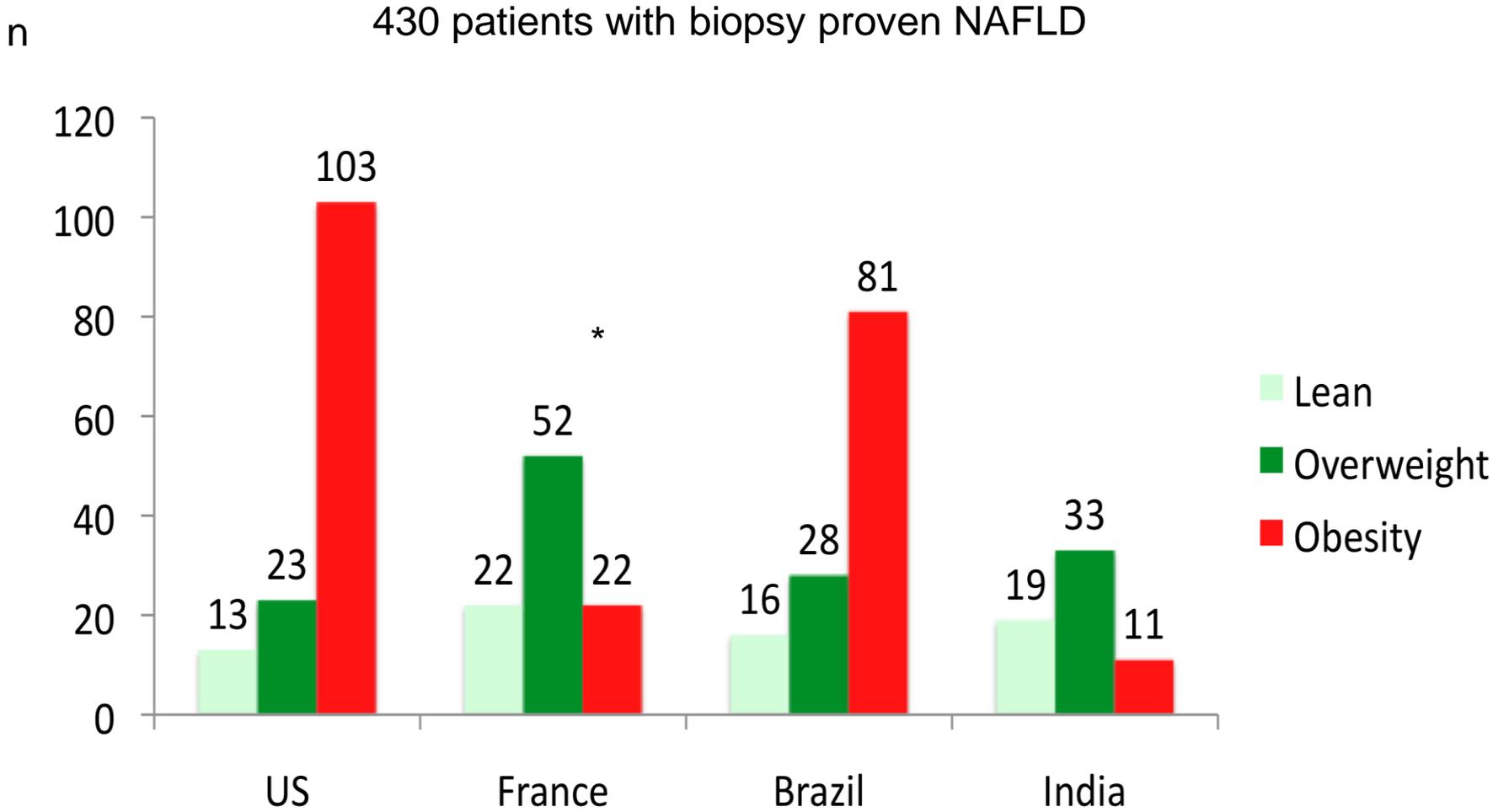
High blood pressure
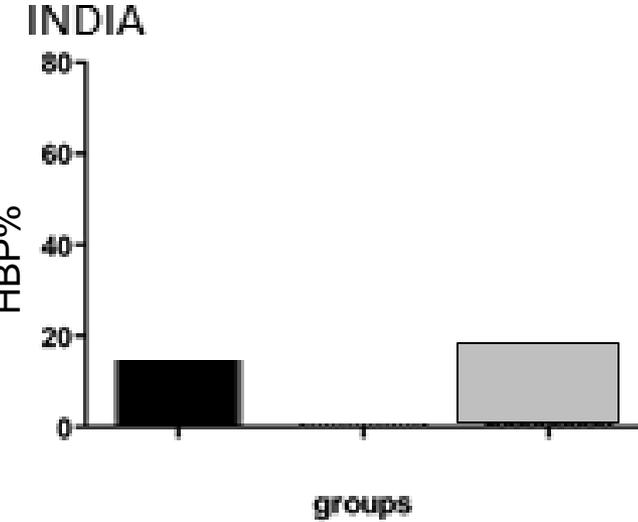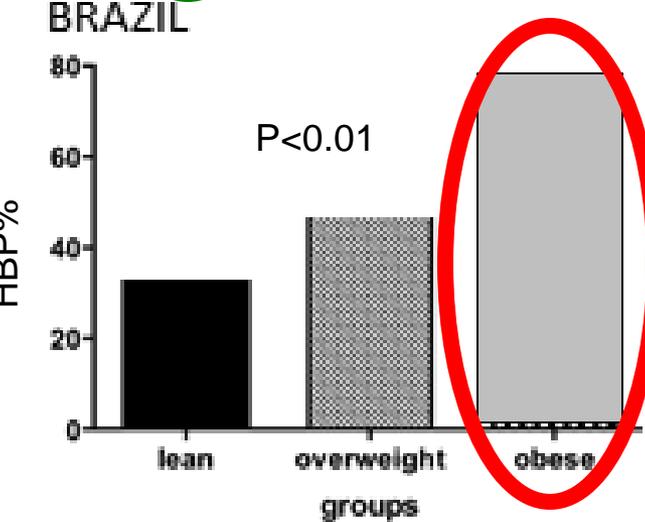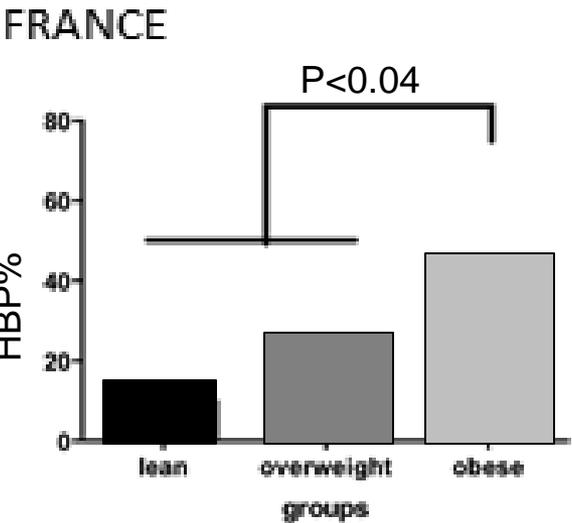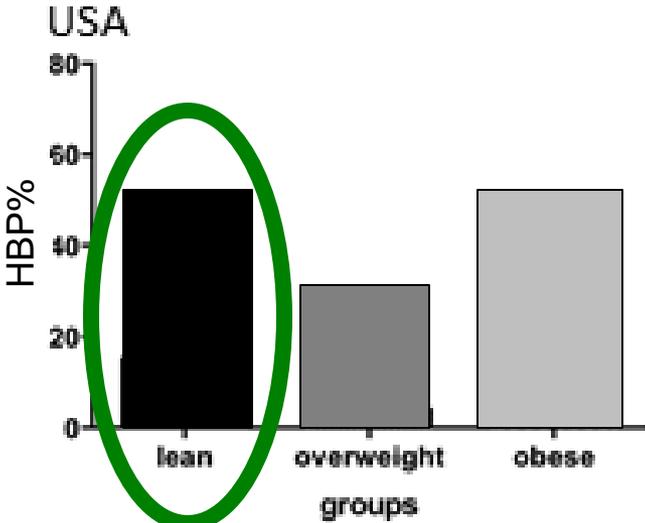
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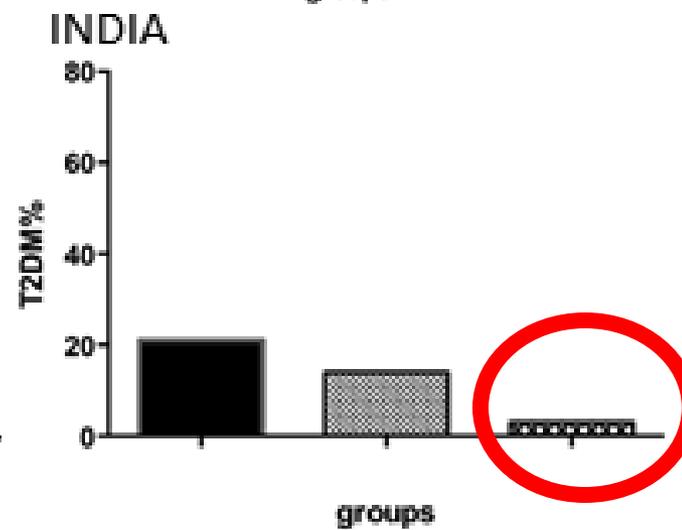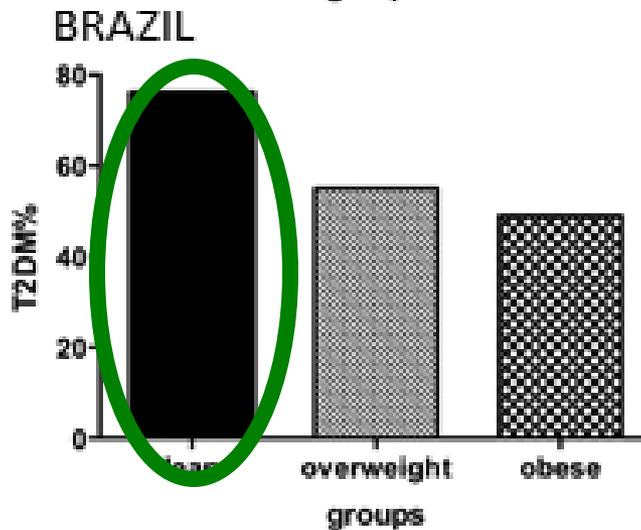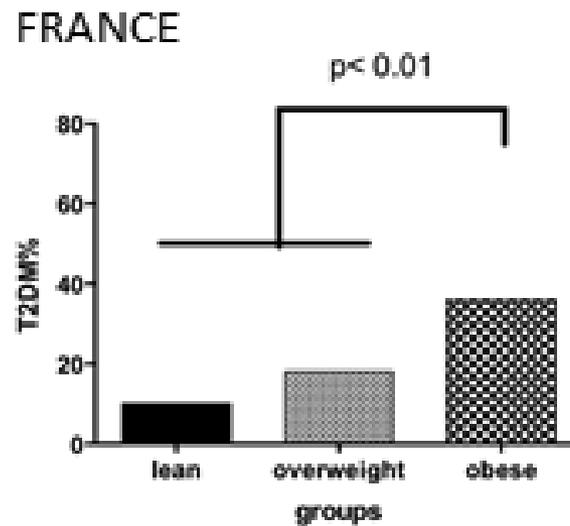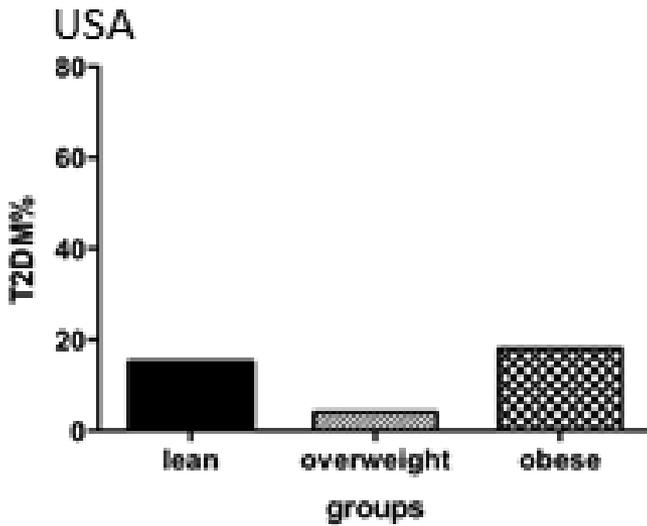
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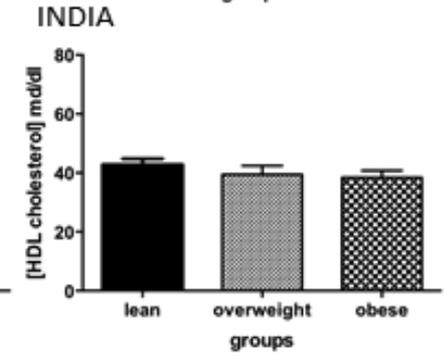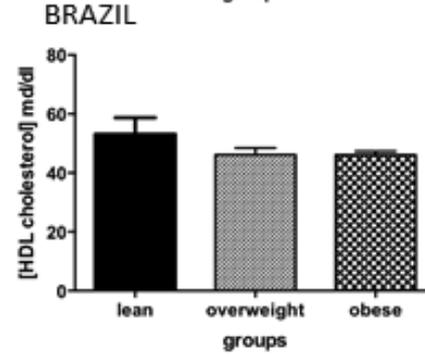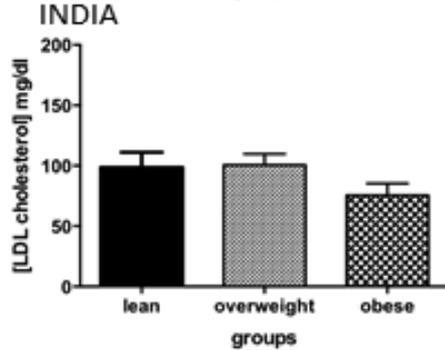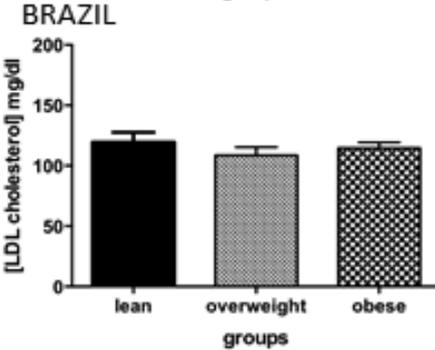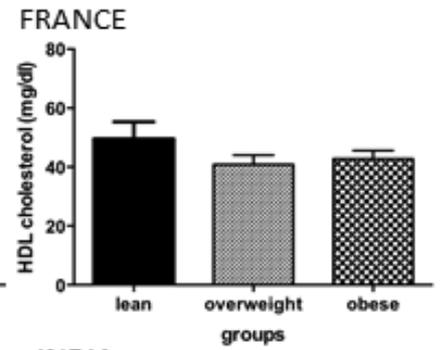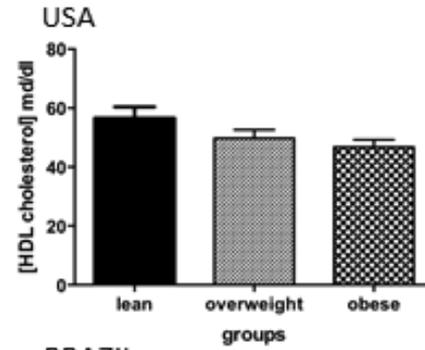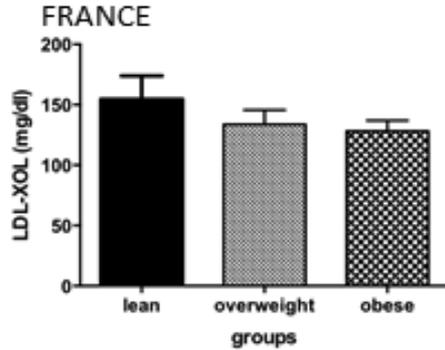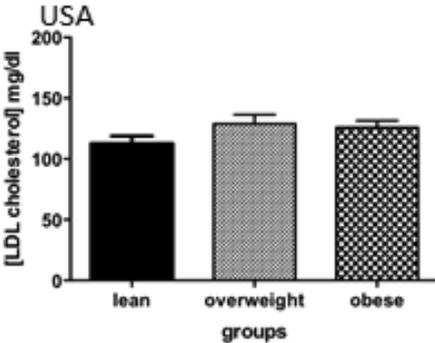
Triglycerides
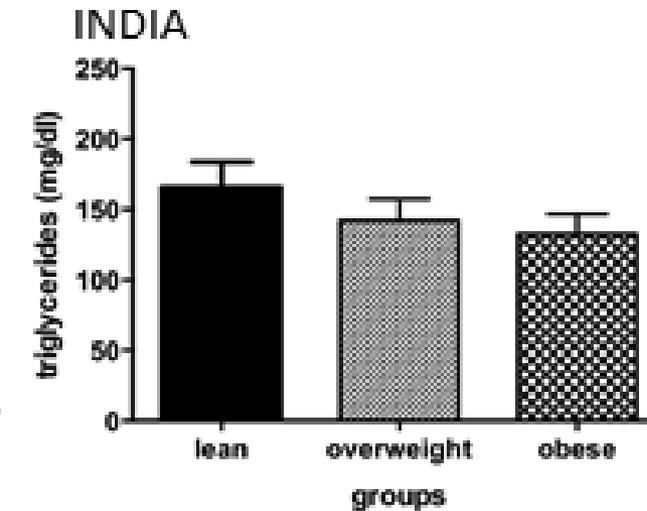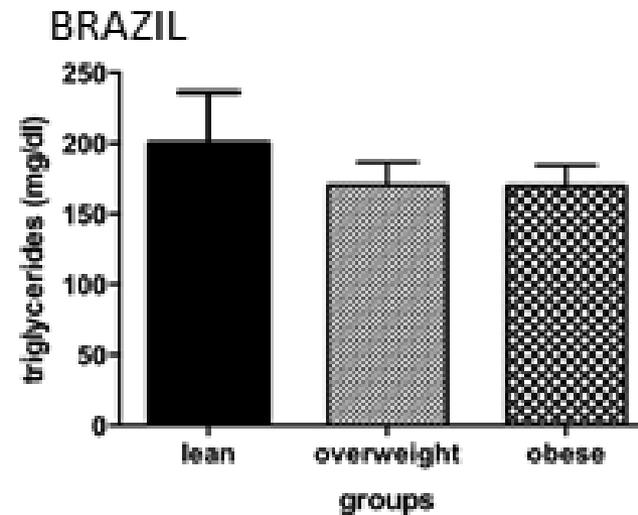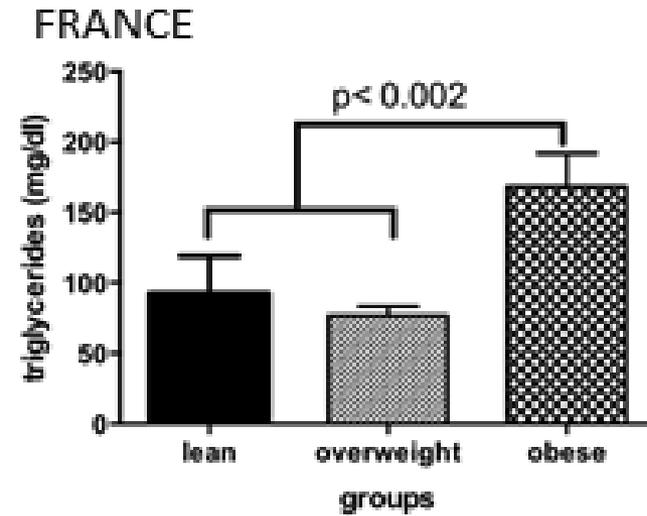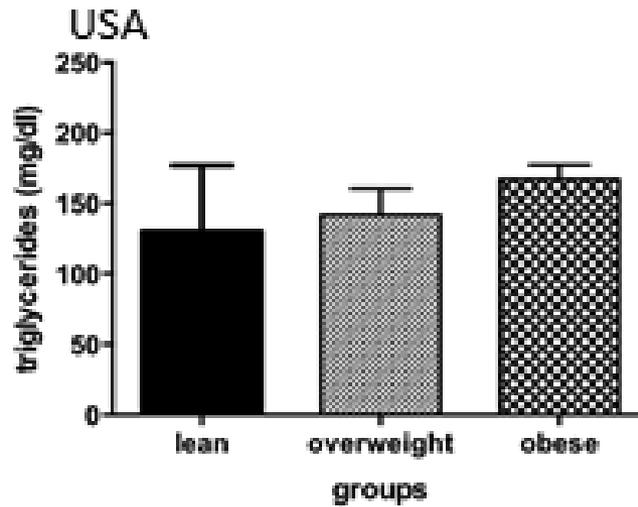
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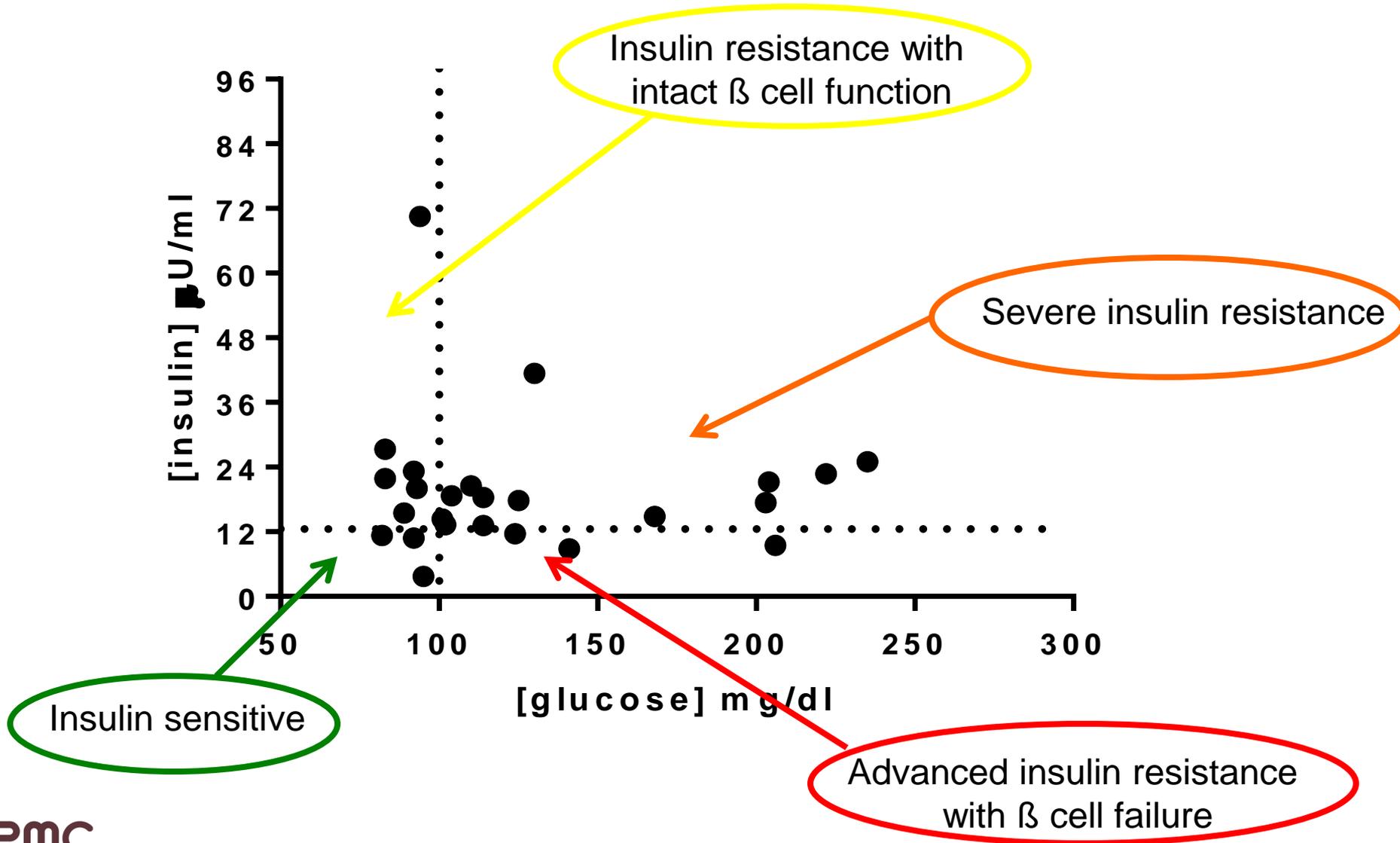
Insuline resistance
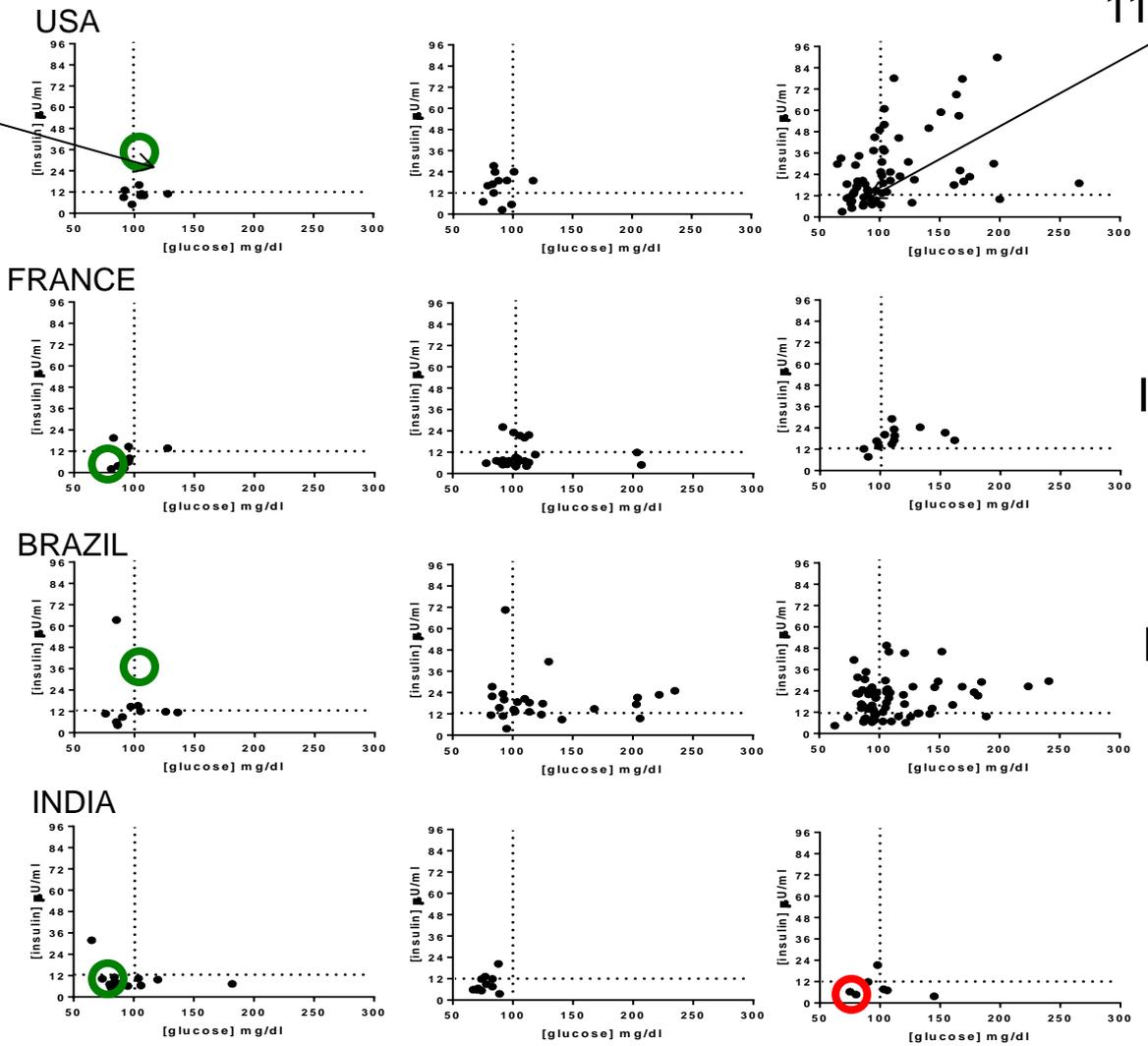
Lean   Overweight   Obese

Steatosis
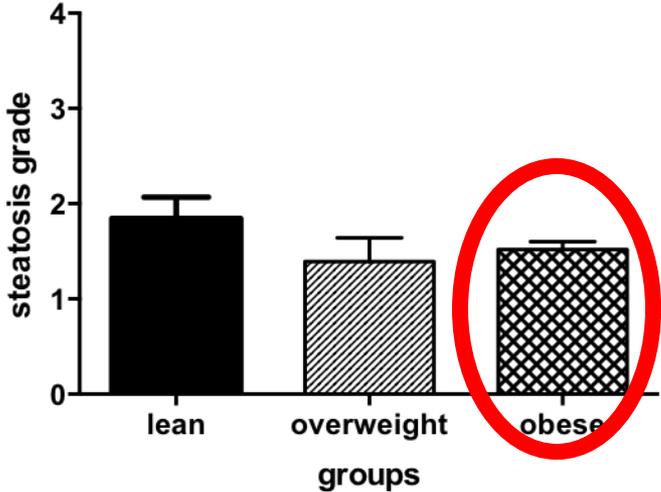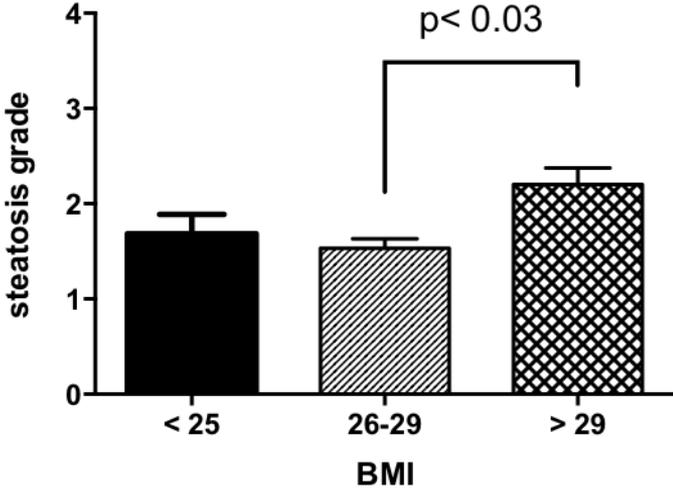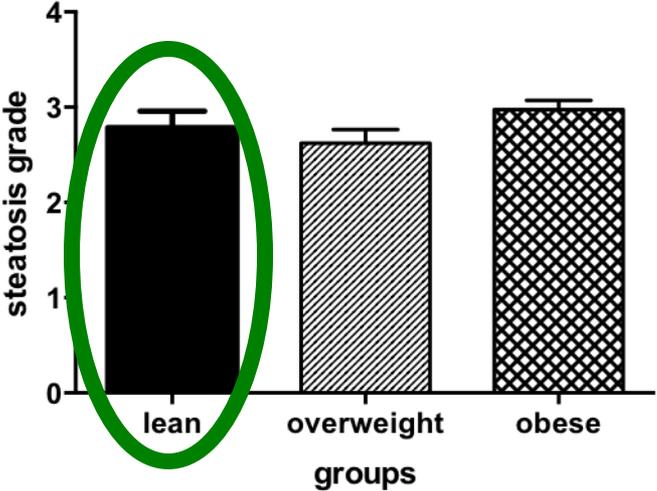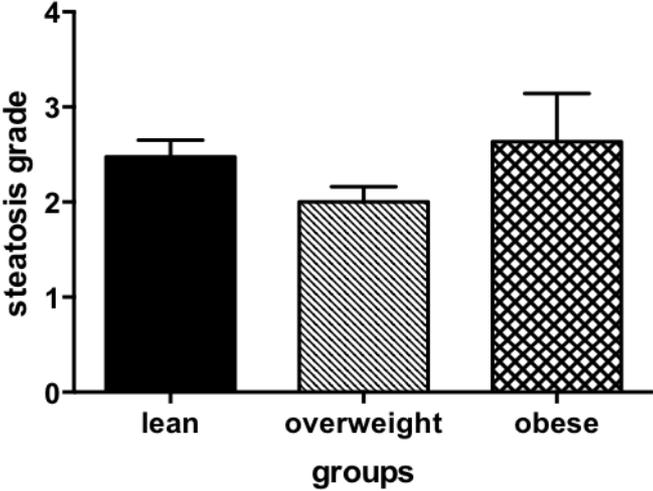
Hepatocellular ballooning
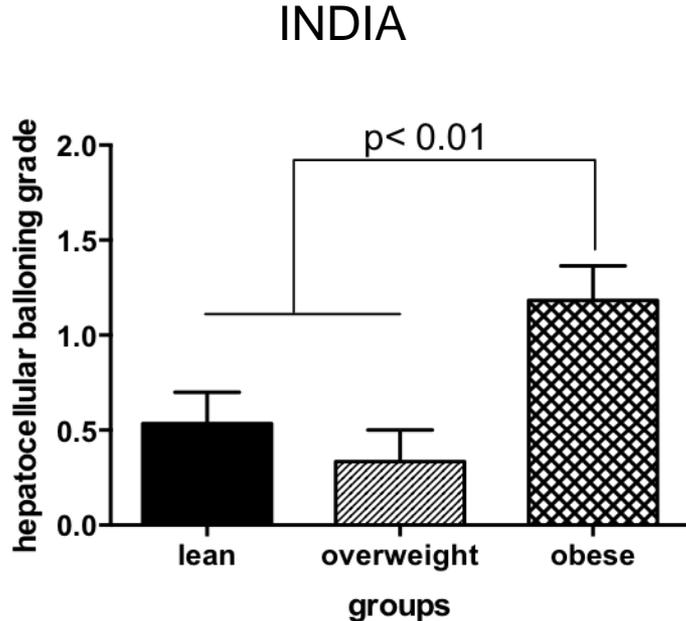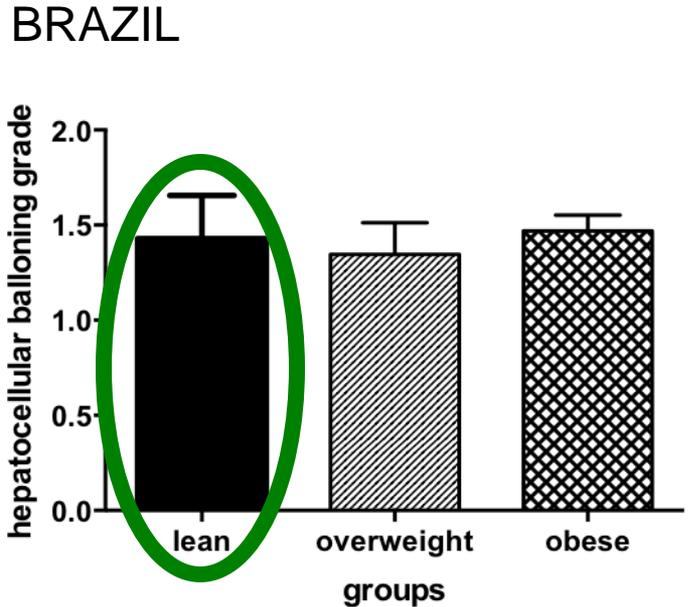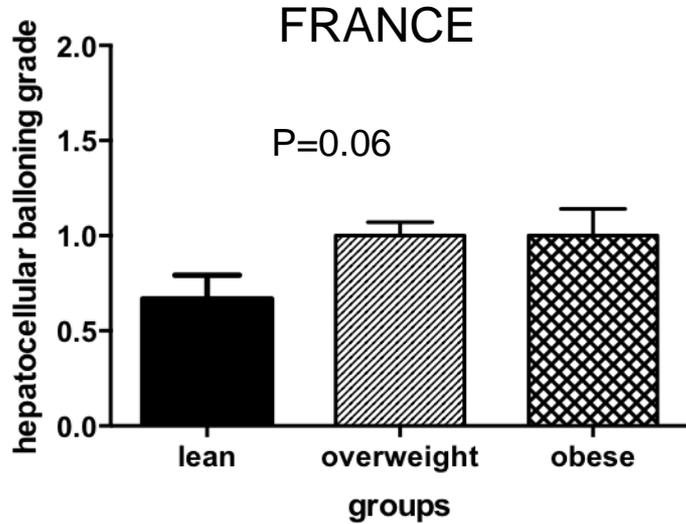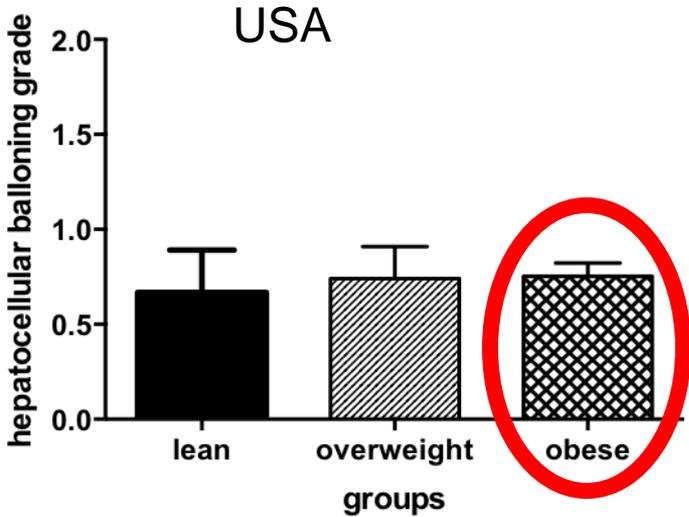
# Fibrosis stage
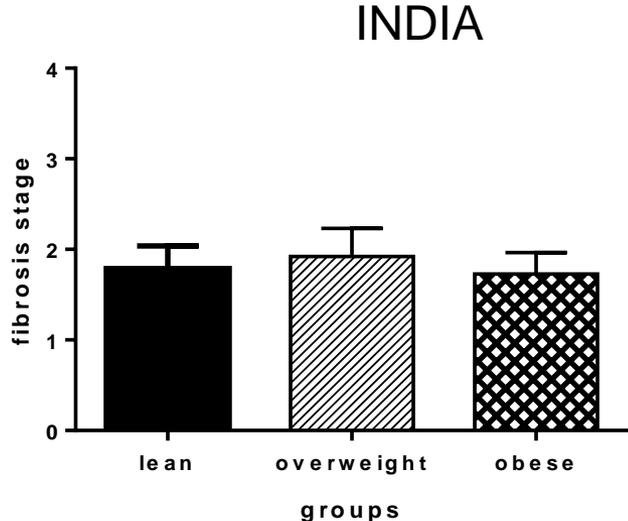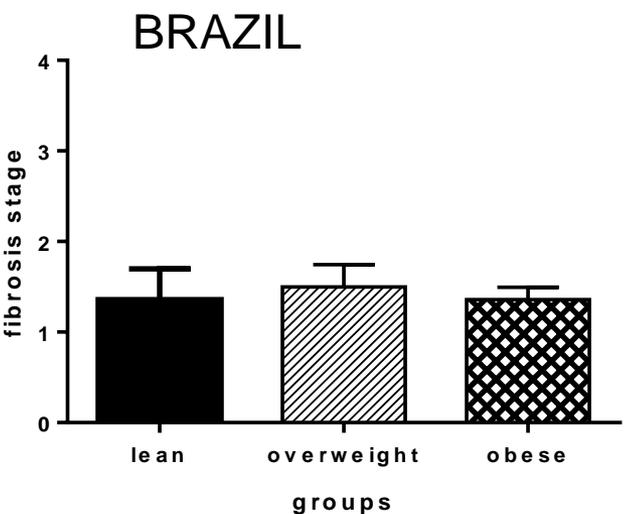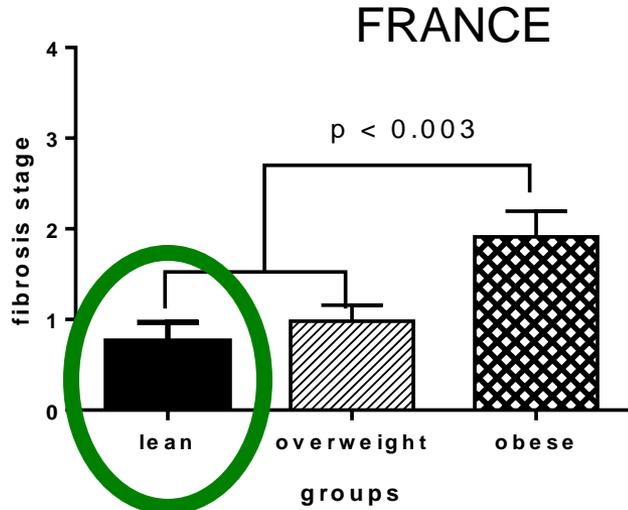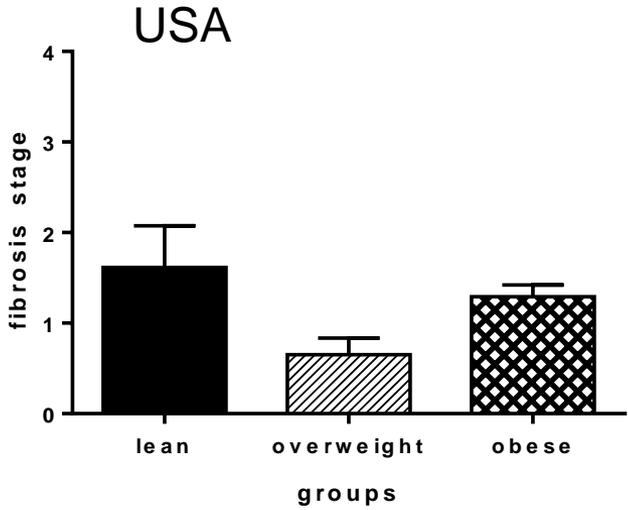
In summary

- This study suggests variability in disease phenotype in lean as well as overweight and obese subjects in different parts of the world.

- It challenges the paradigm that all lean subjects with NAFLD have mild insulin resistance and have mild forms of liver disease.

- Conversely, it also demonstrates that a fraction of obese subjects with the full spectrum of NAFLD may be relatively insulin sensitive.

Perspectives

- Development of "region-specific" risk stratification approaches.

- Whether drugs developed for NASH in subjects with a specific clinical-physiological phenotype will work in those with alternate phenotypes both in the West and around the world.

- Future studies to define the mechanistic basis for different disease phenotype may inform therapeutic choices in subjects in different regions.

# Lobular inflammation

USA
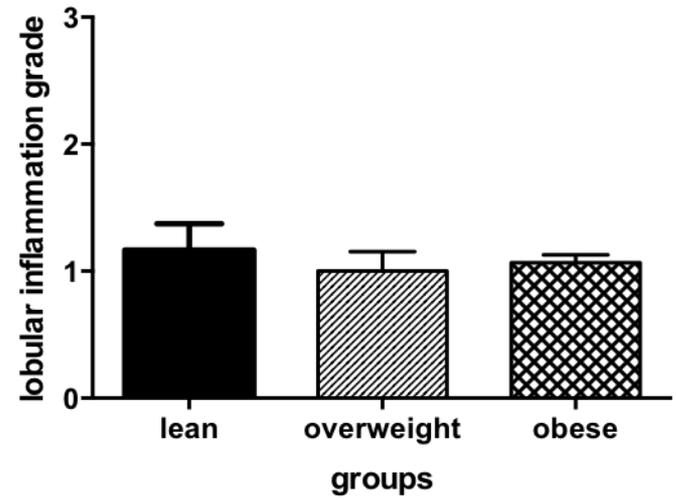
FRANCE
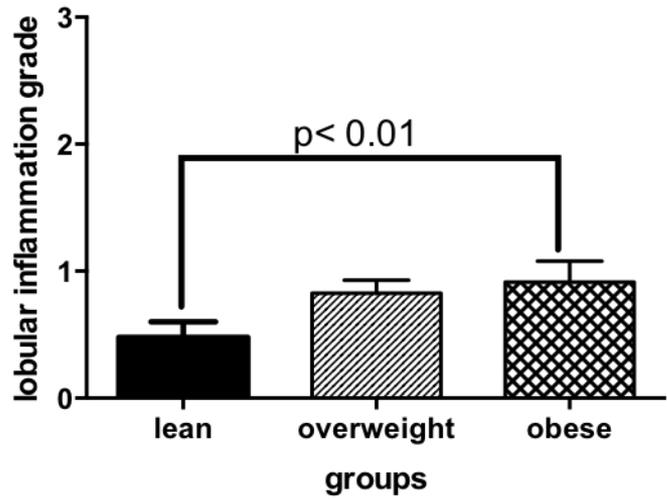
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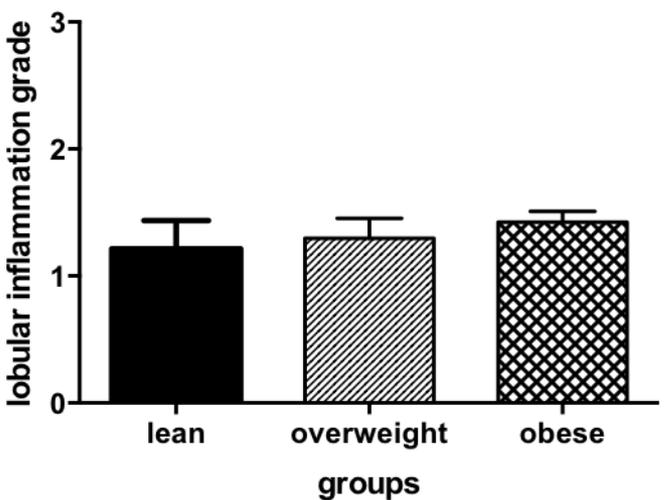
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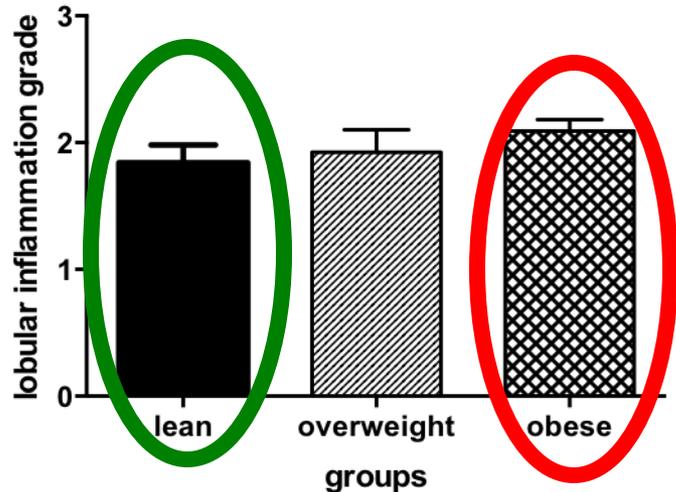
Type 2 diabetes

Distribution of BMI

430 patients with biopsy proven NAFLD

Legend: Lean (light green), Overweight (dark green), Obesity (red)
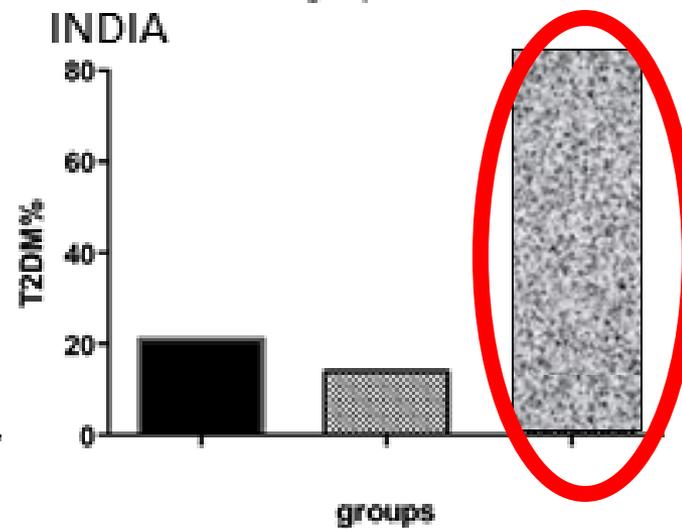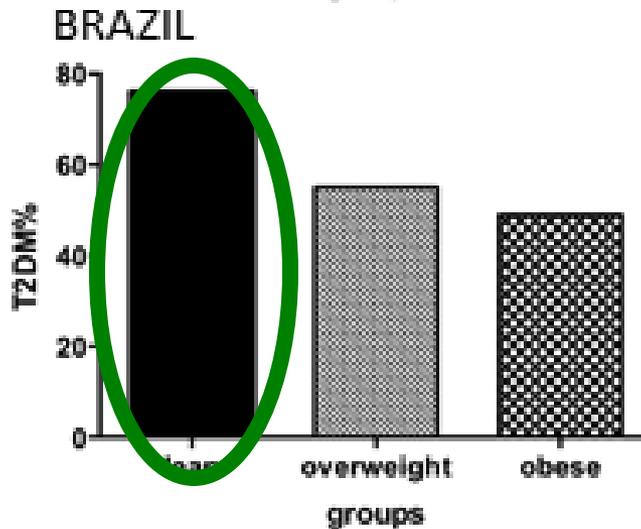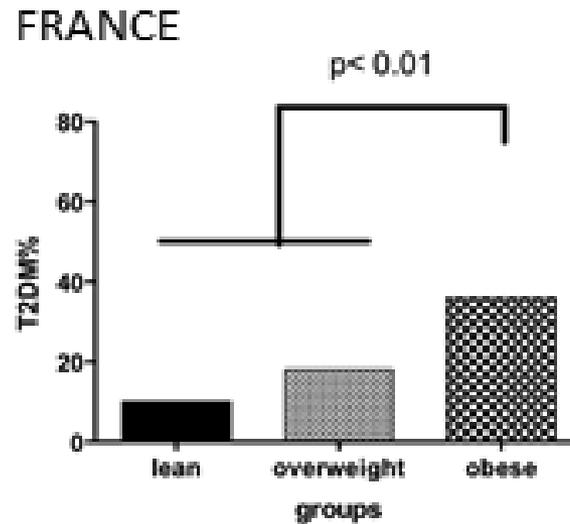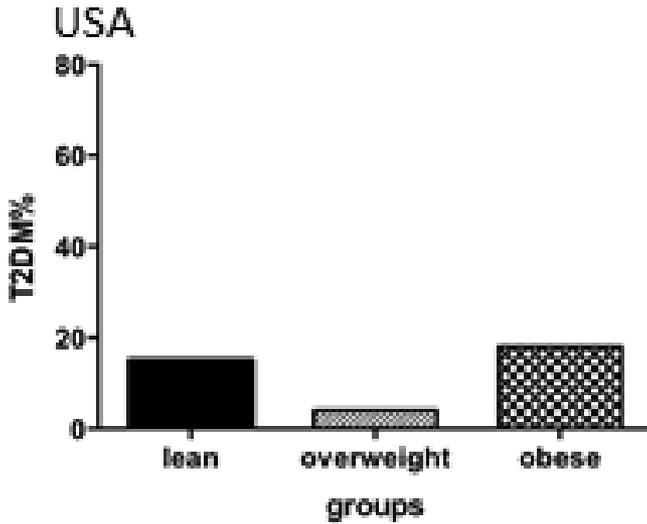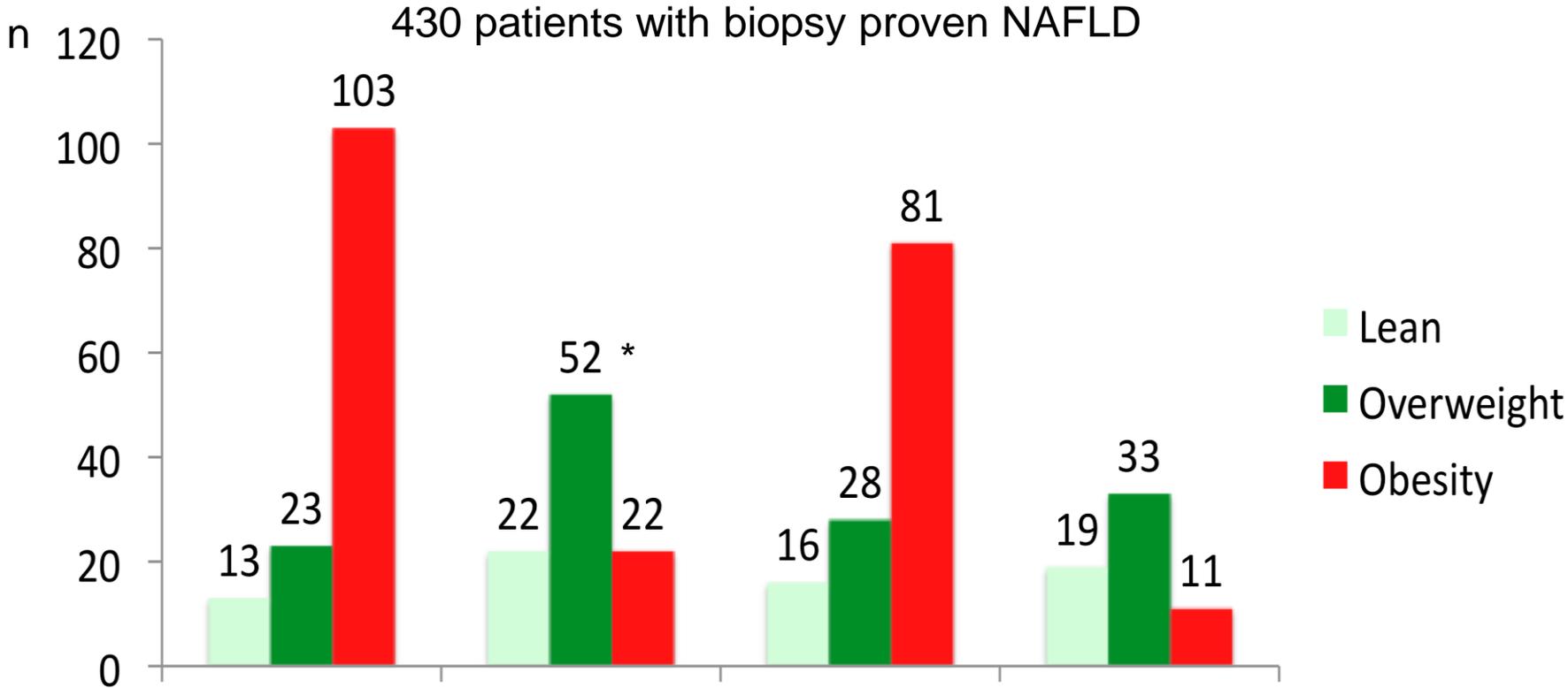
	US	France	Brazil	India
Lean	13	22	16	19
Overweight	23	52 *	28	33
Obesity	103	22	81	11
Age (yrs)	62/53/52 *	46/51/49	54/56/52	40/34/30

Oliveira C et al. submitted