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Disparities in the Burden of Pediatric NAFLD

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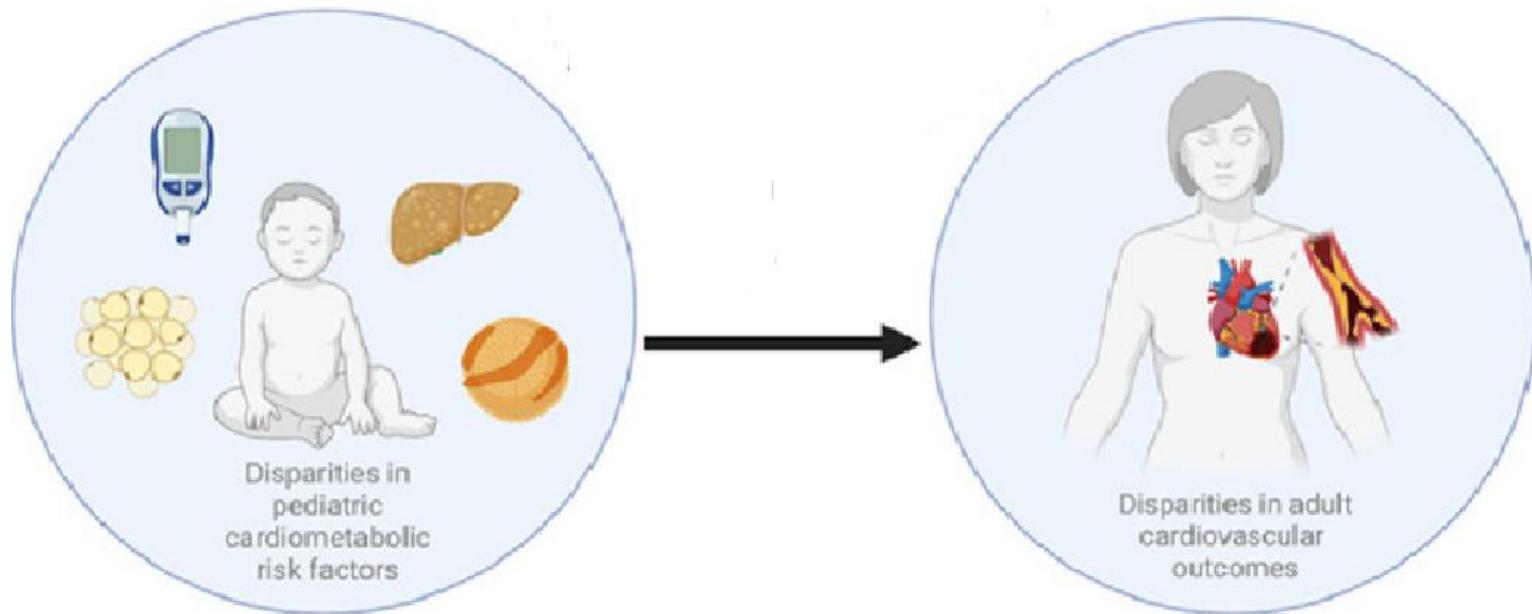
Emory University and Children's Healthcare of Atlanta



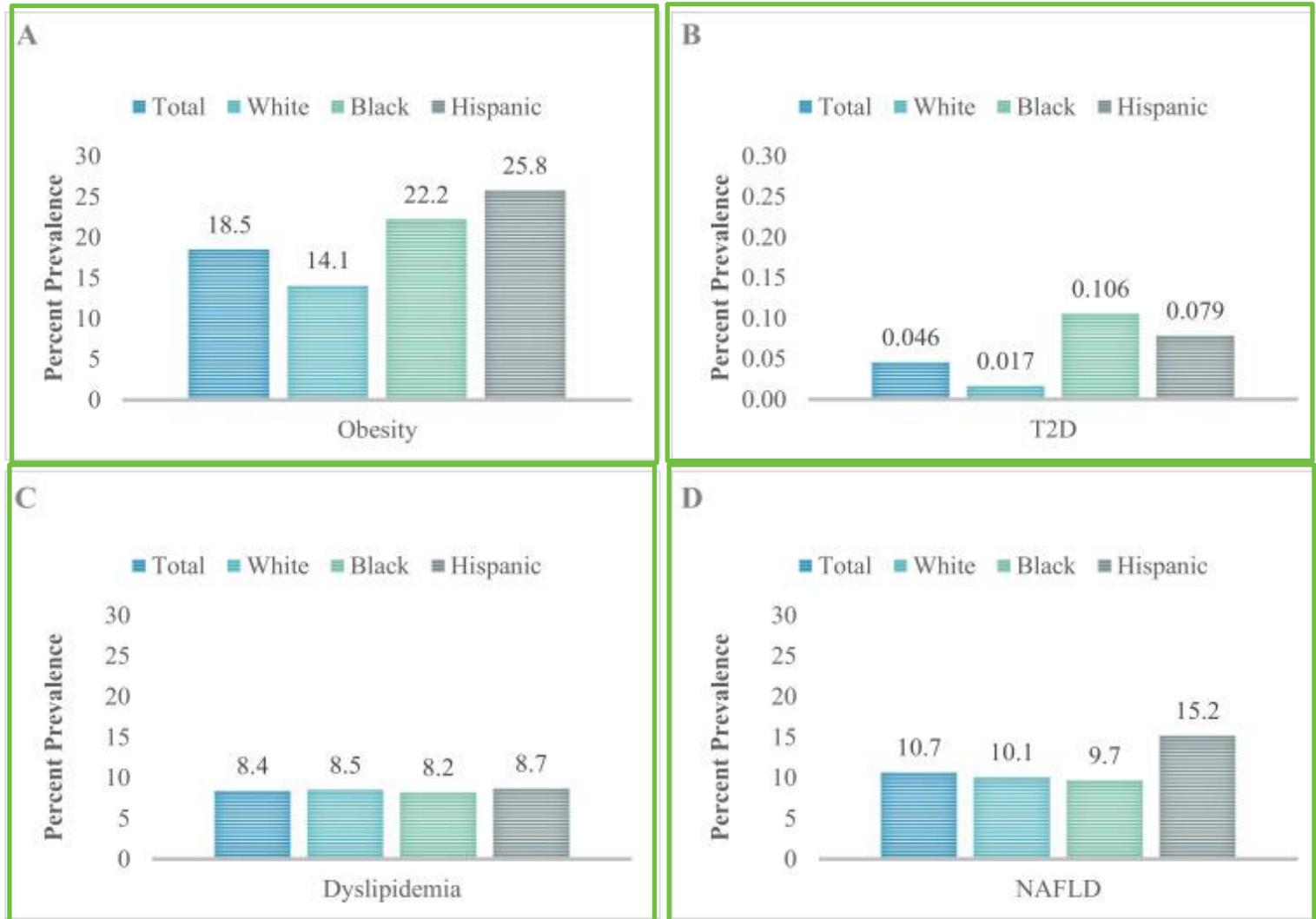
Disclosures

- Researcher: Bristol Myers Squibb
- Consultant: Boehringer Ingelheim, Eli Lilly, Novo Nordisk
- Speaker: Prosciento

Disparities in Child Health lead to Disparity in Adulthood



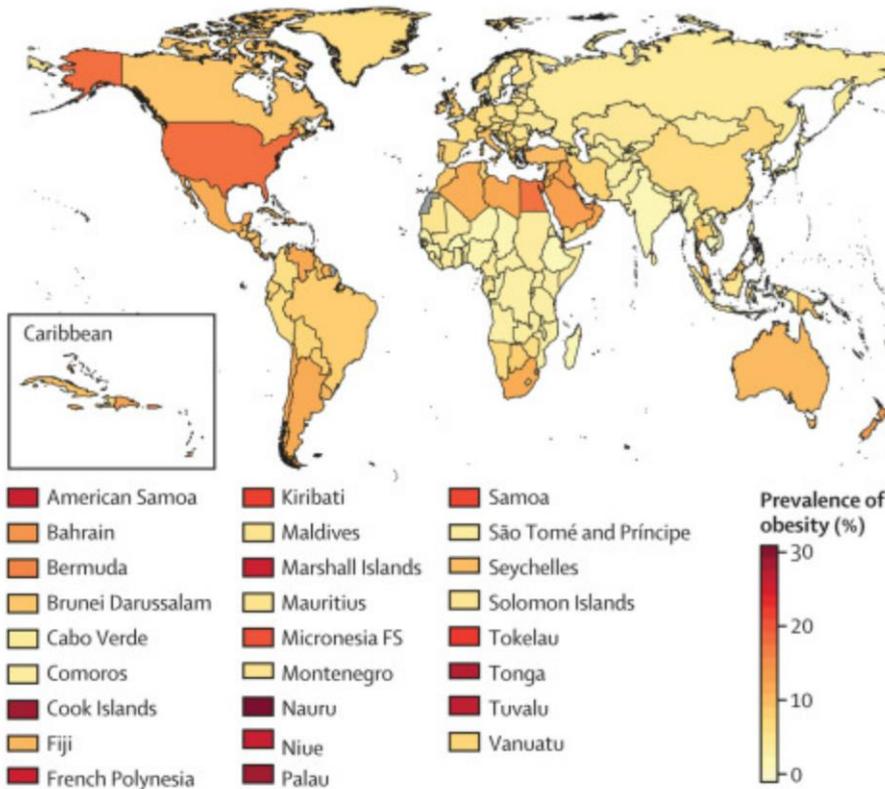
Cardiometabolic Disease Burden Varies by Race and Ethnicity in Children and Adolescents



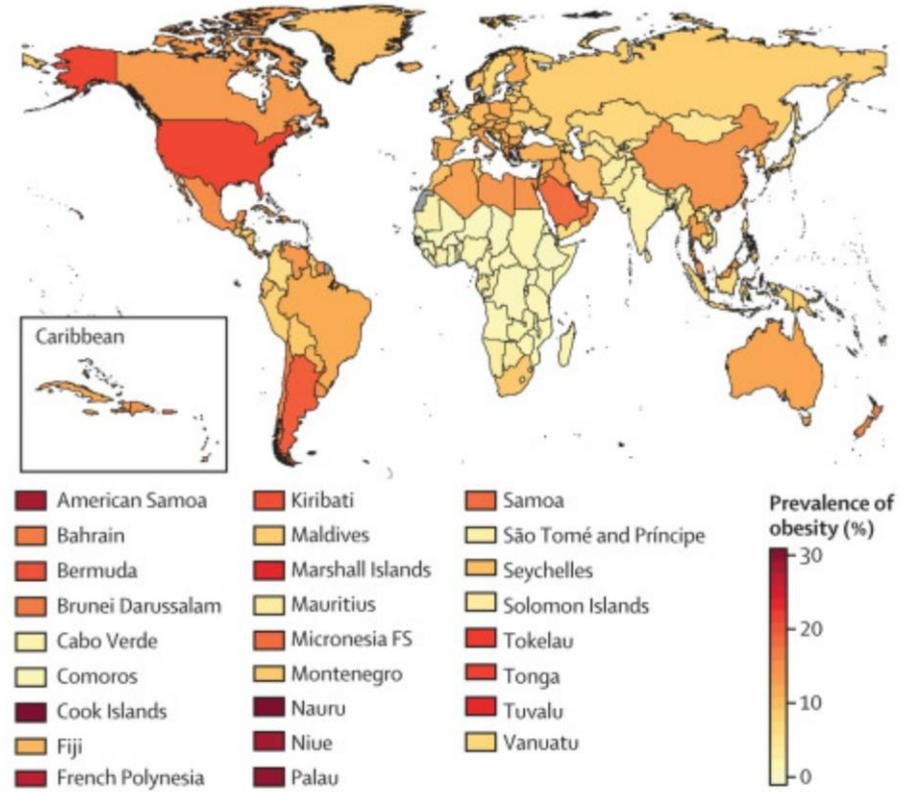
In children and adolescents (U.S. data)

Global Obesity Prevalence in Boys and Girls

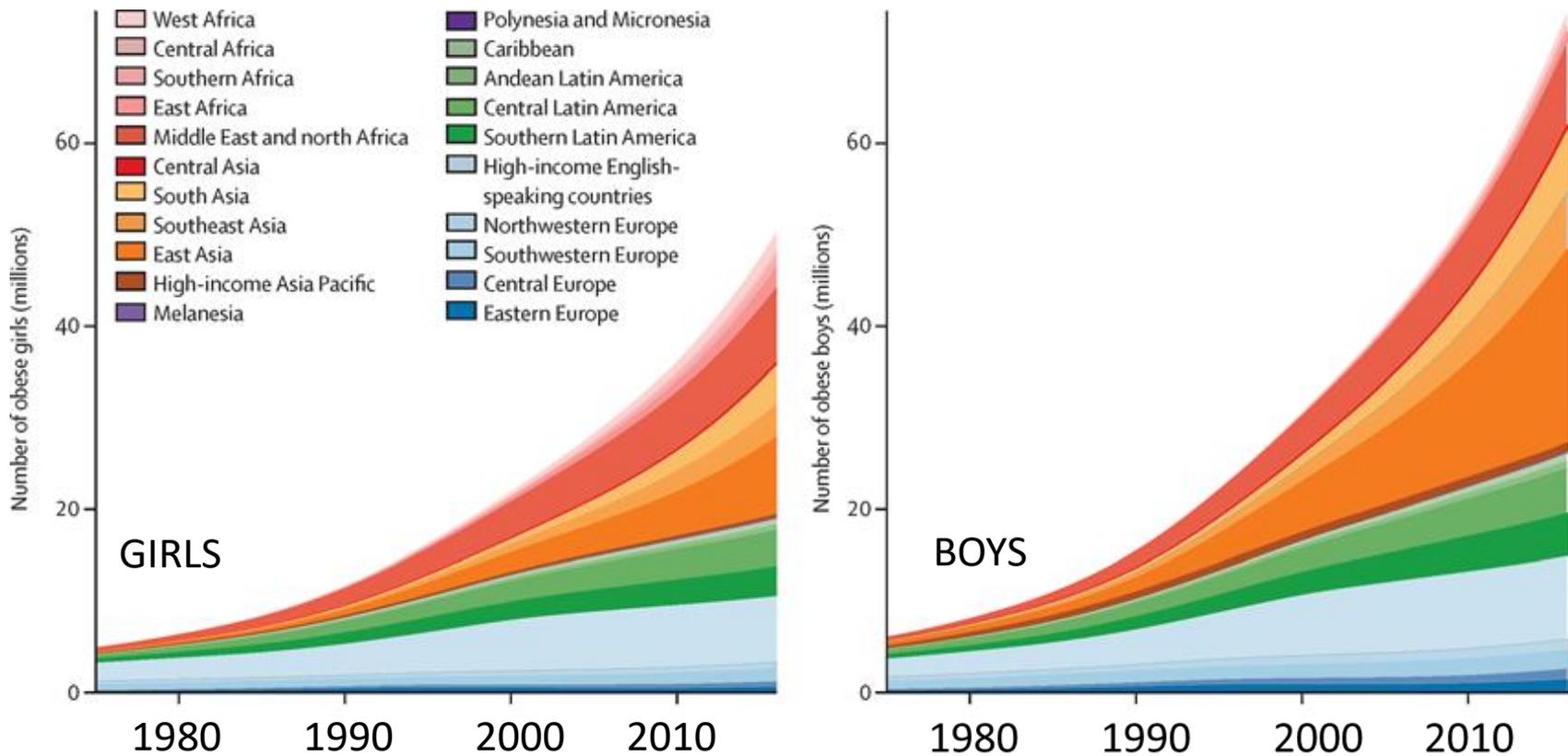
C Obesity prevalence in girls



D Obesity prevalence in boys



Global Trends in Childhood Obesity - Obesity Continues to Rise in Asia and Africa



Very early childhood – predictive of adult BMI

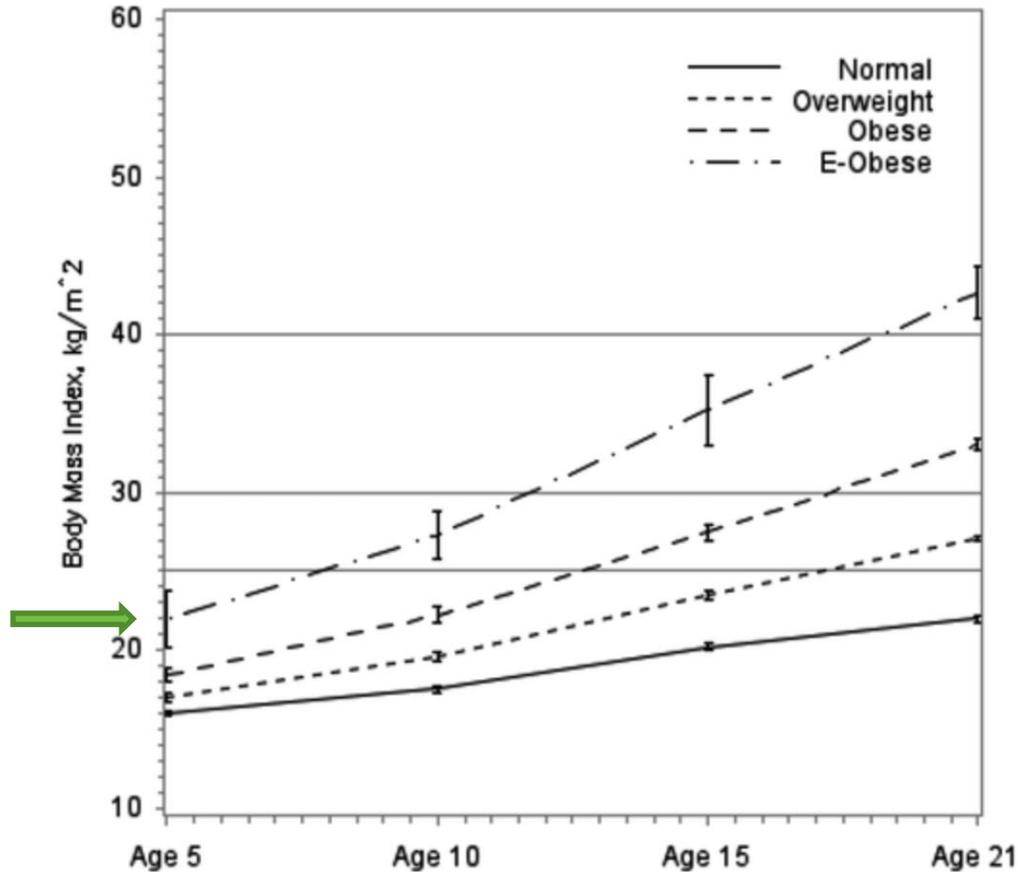
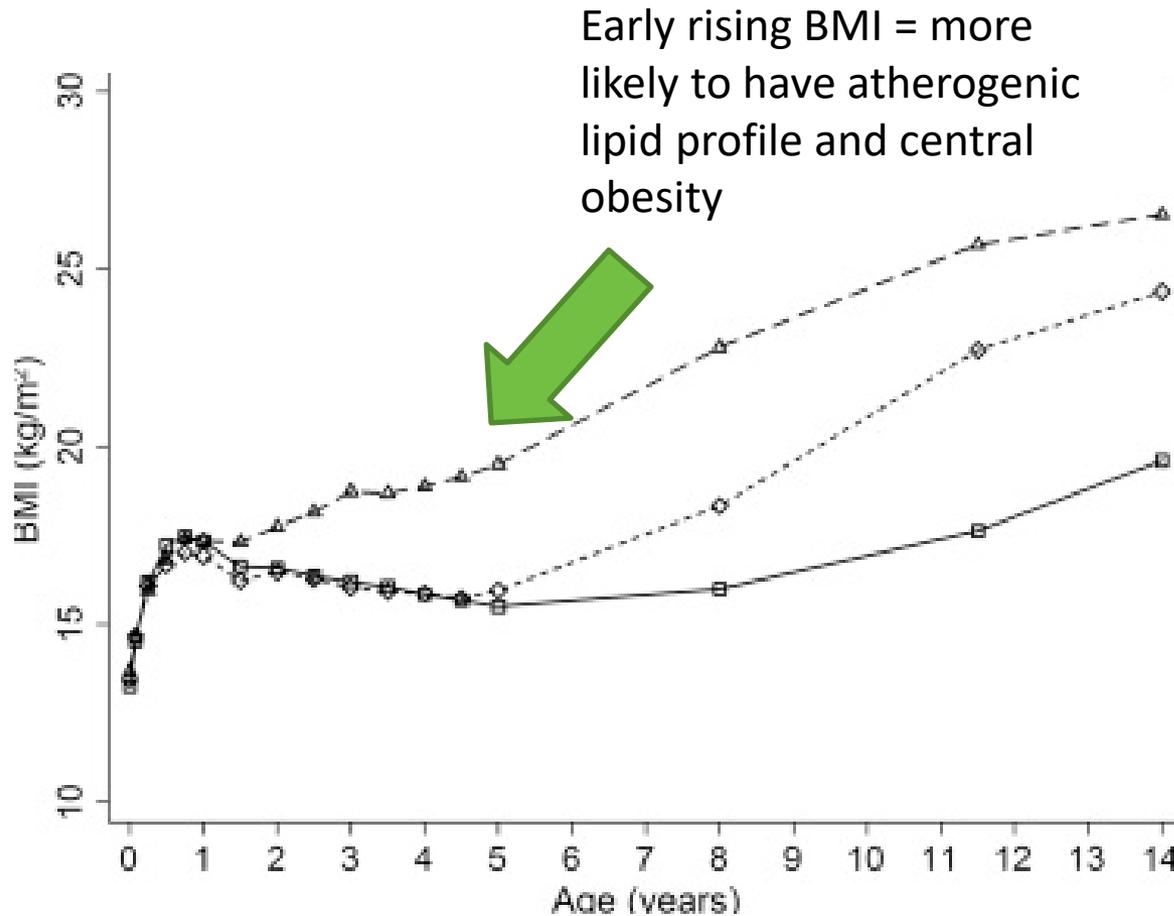
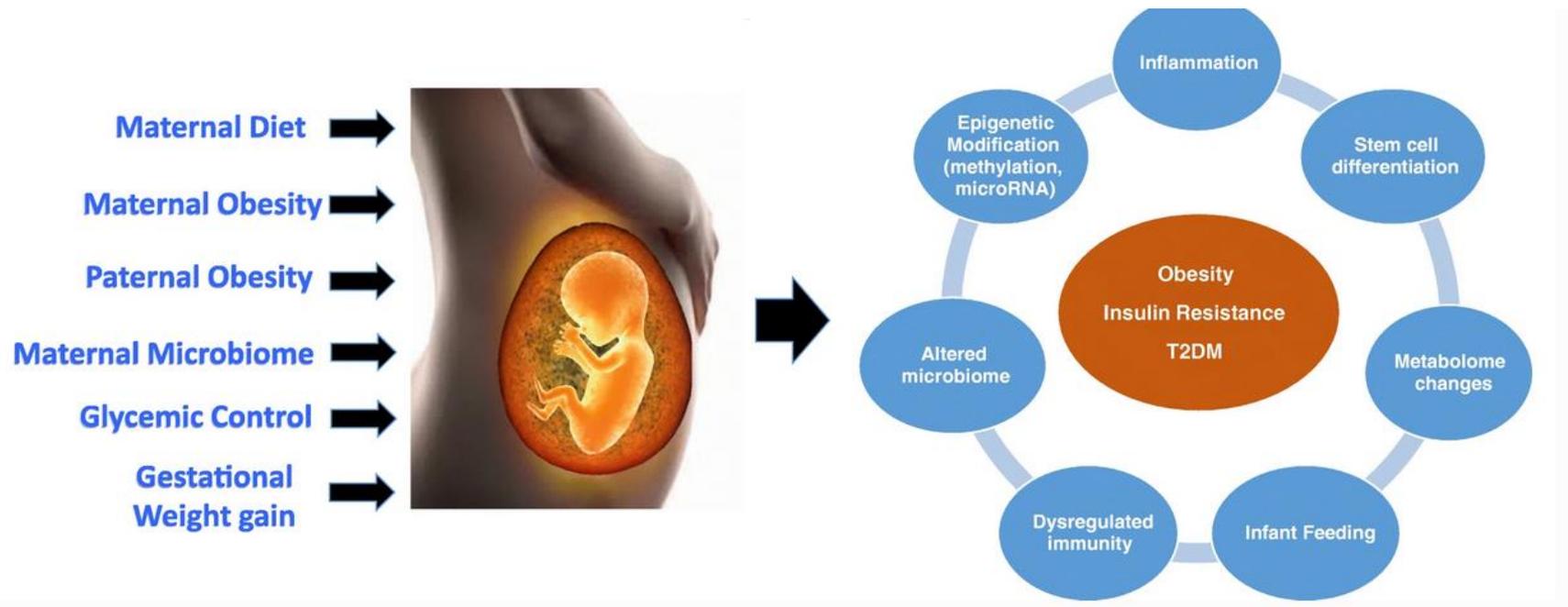


Figure 3. Growth trajectories of the four 21-year weight groups ($N = 1000$).

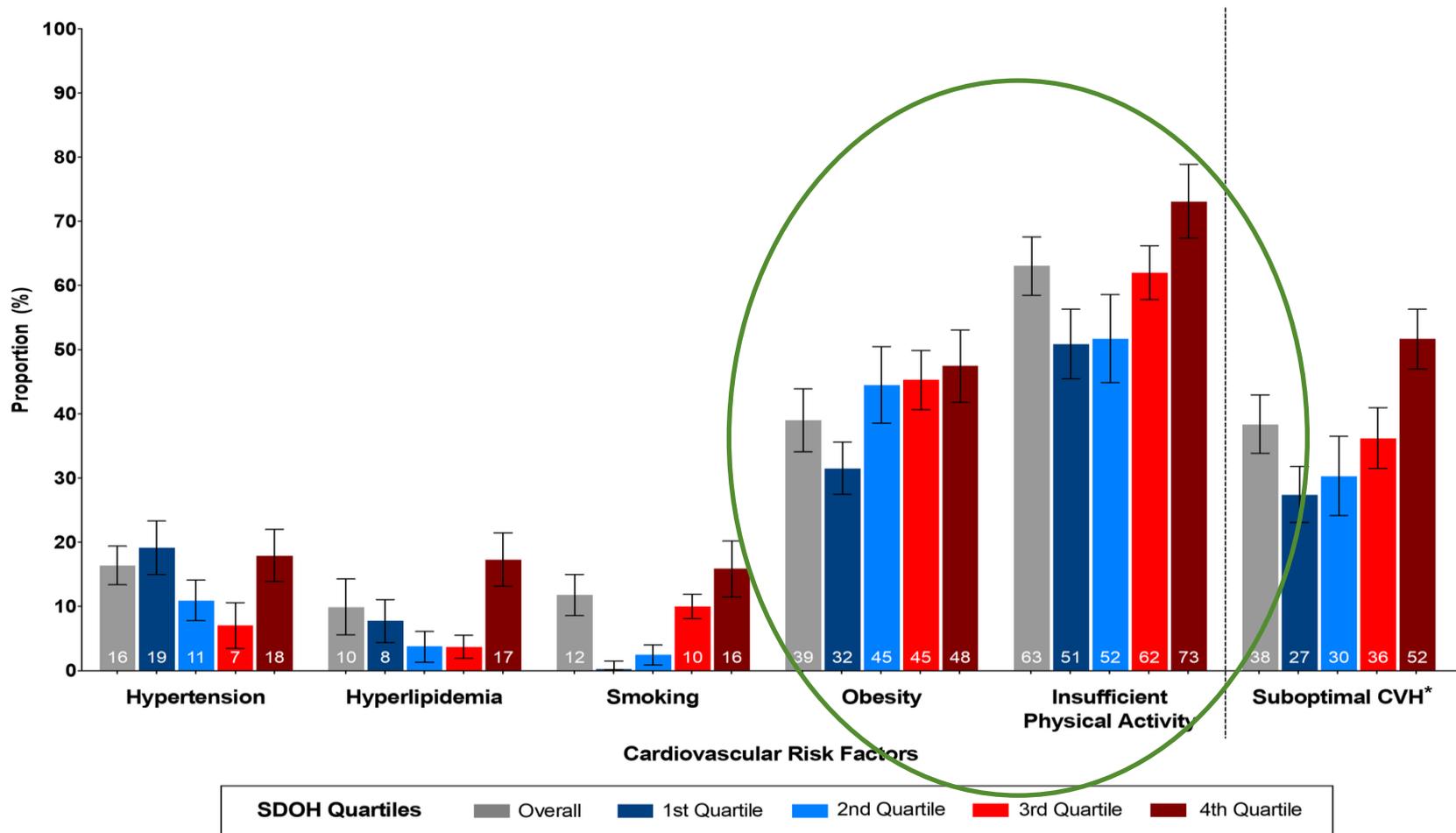
Early rising BMI has cardiovascular consequences



What causes obesity in children? Increasing Data for the Importance of Early Exposures



Obesity and Insufficient PA in Pregnant Women U.S. Data

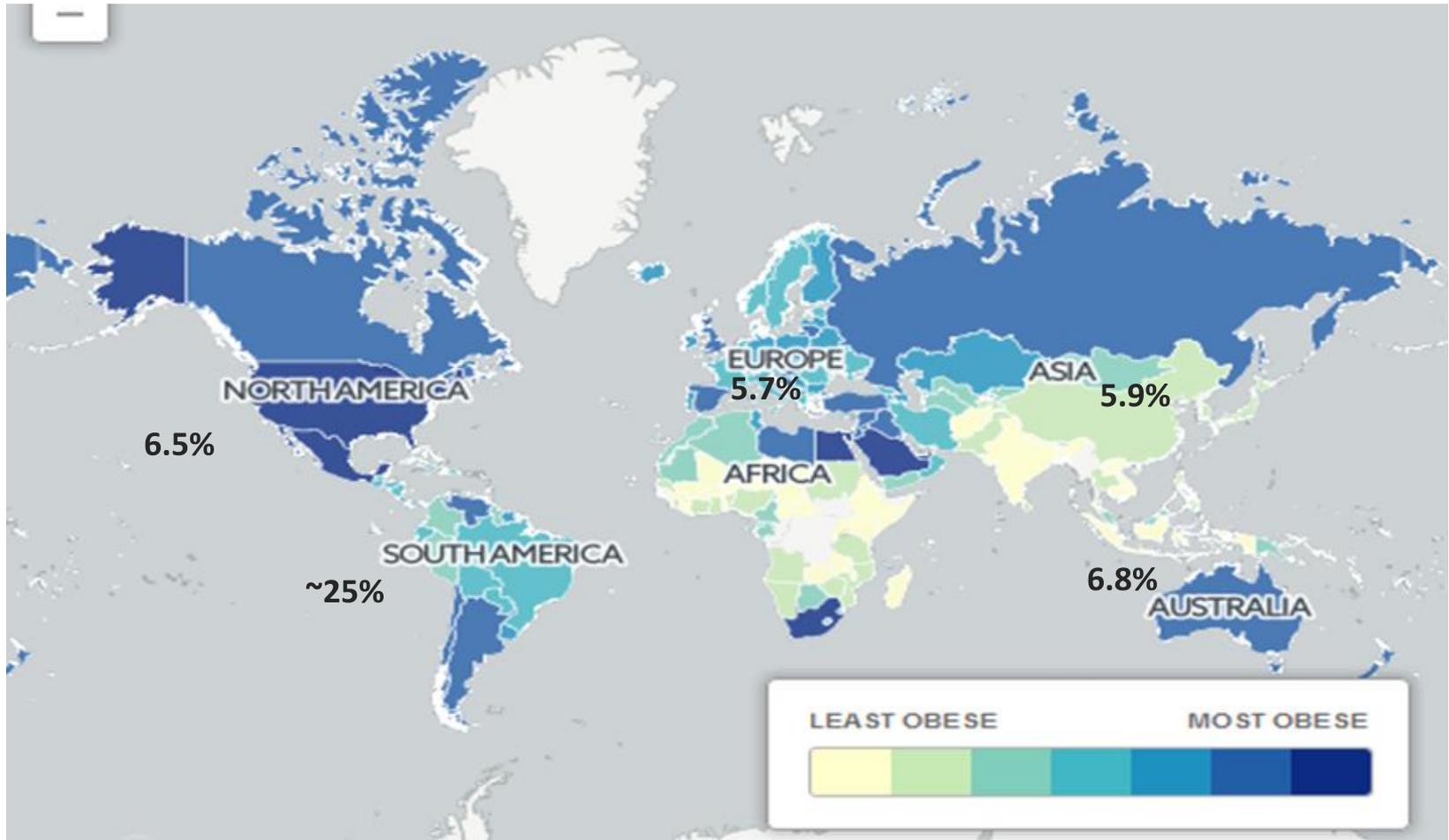


Garima Sharma. Journal of the American Heart Association. Social Determinants of Suboptimal Cardiovascular Health Among Pregnant Women in the United States, Volume: 11, Issue: 2, DOI: (10.1161/JAHA.121.022837)

Childhood Obesity Adverse Outcomes

- Hypertension
- Hyperlipidemia
- Type 2 diabetes
- Psychosocial consequences
- Adult Obesity
- Nonalcoholic fatty liver disease

Pediatric NAFLD Across the World



CIA World Fact book – Digital Traveler (Figure by Oliver Smith, March 2017)
Anderson et al, PLOS One, 2015. Welsh et al, J Ped 2013

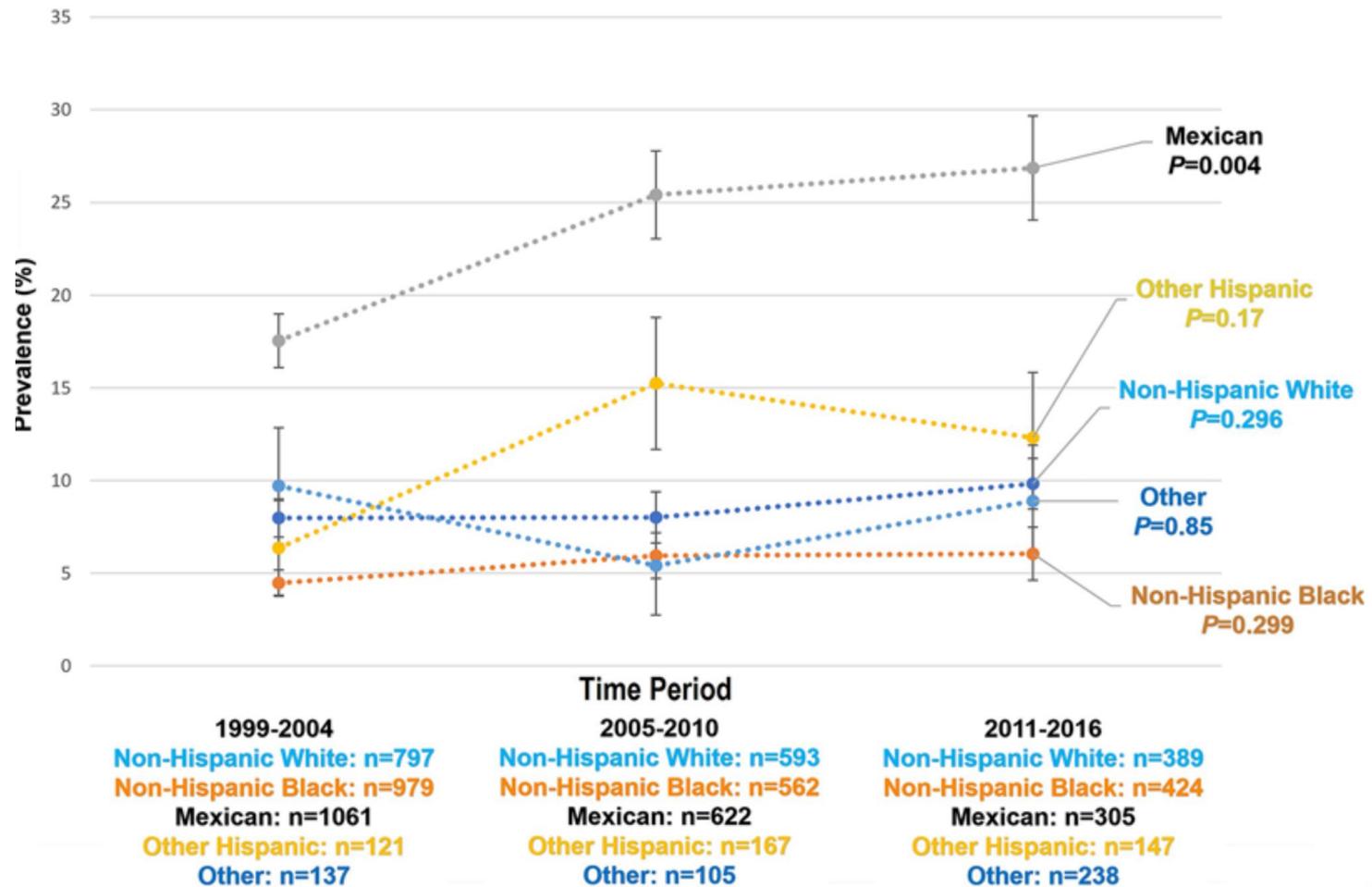
NAFLD in Obese Children

Data from Europe

- In multicenter study from Germany, Austria and Switzerland, 4932 overweight or obese children had liver enzymes measured.
- 49% had elevated ALT >24 U/L
- 12% had prediabetes
- 1.4% had T2DM

- Elevated ALT increased risk of prediabetes and T2D (1.5 fold)

Change in prevalence in Pediatric NAFLD – by ethnicity in the United States



Worldwide Distribution of PNPLA3

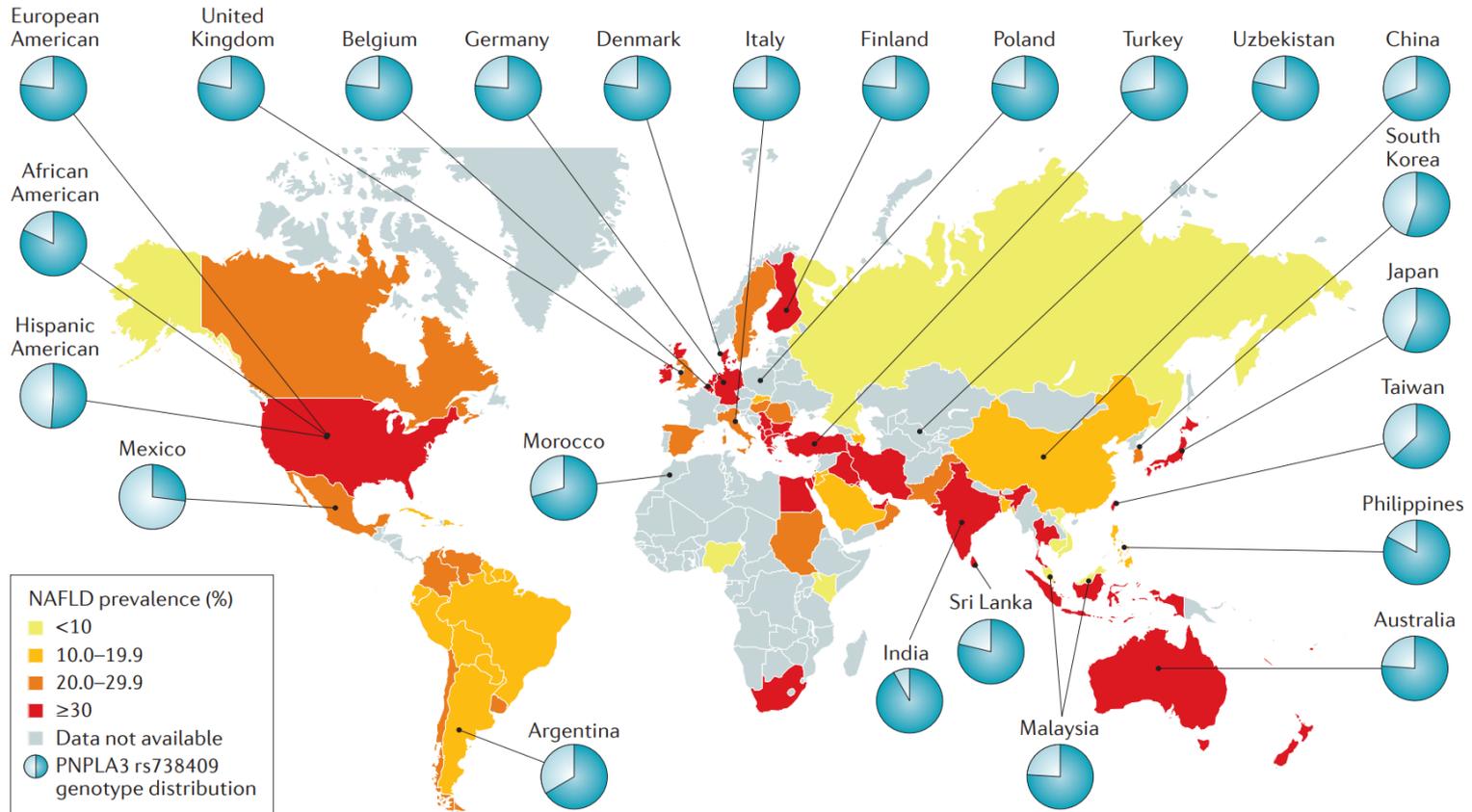
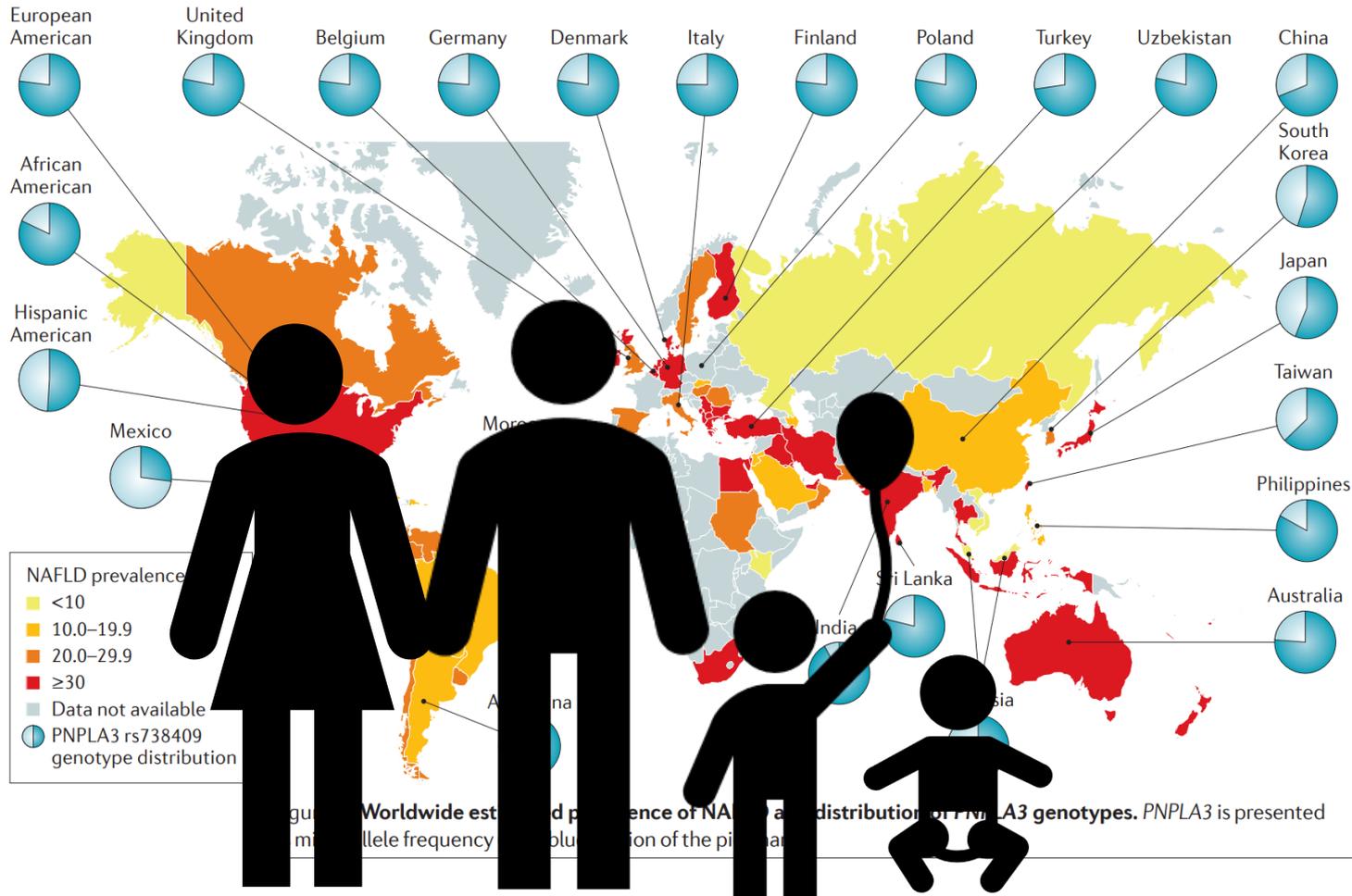


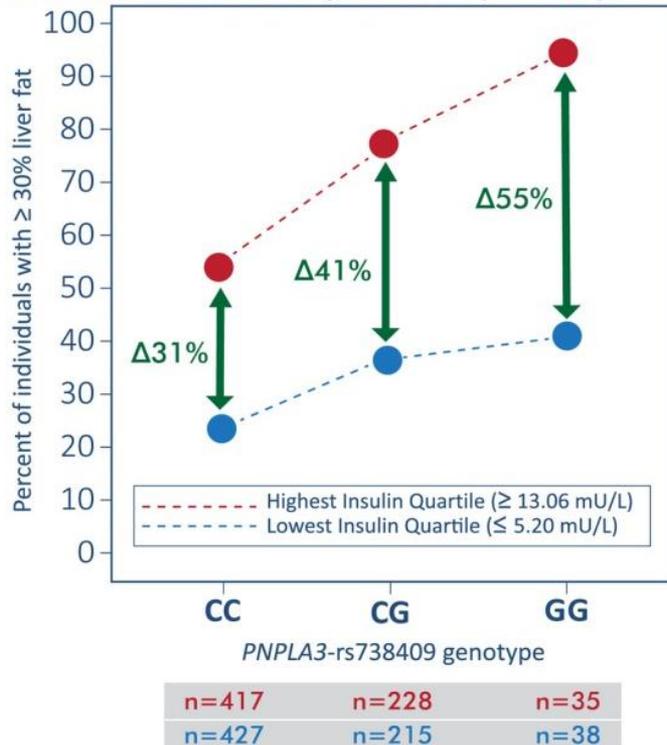
Figure 1 | **Worldwide estimated prevalence of NAFLD and distribution of PNPLA3 genotypes.** PNPLA3 is presented as minor allele frequency (light blue section of the pie chart).

Worldwide Distribution of PNPLA3 = Number of Children with Genetic Potential for NAFLD

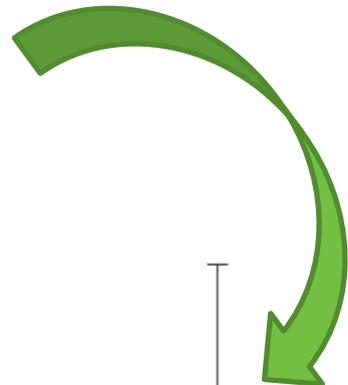
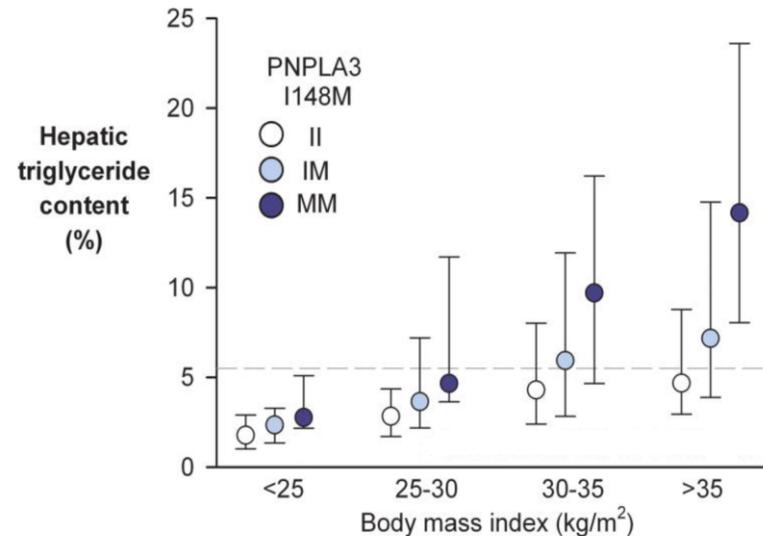


Fortunately, its not genetics alone – Interactions with Insulin & BMI

Hepatic steatosis in lowest and highest insulin quartiles by *PNPLA3* genotype



High BMI¹, High Insulin² plus homozygous (GG) increases risk of NAFLD.



¹Stender et al, Nat Genet 2017

²Barata et al, Hep Comm 2019

Consequences of NAFLD in Childhood

- Strongly associated with HTN, dyslipidemia, glycemia
- Likely leads to early CVD
- Evidence of increased risk of diabetes

- FEW studies track from childhood into adulthood
- Rising rate of liver transplant for NAFLD in young adults suggests negative outcome for some childhood onset
- However, identification of NAFLD early may bring opportunities for treatment

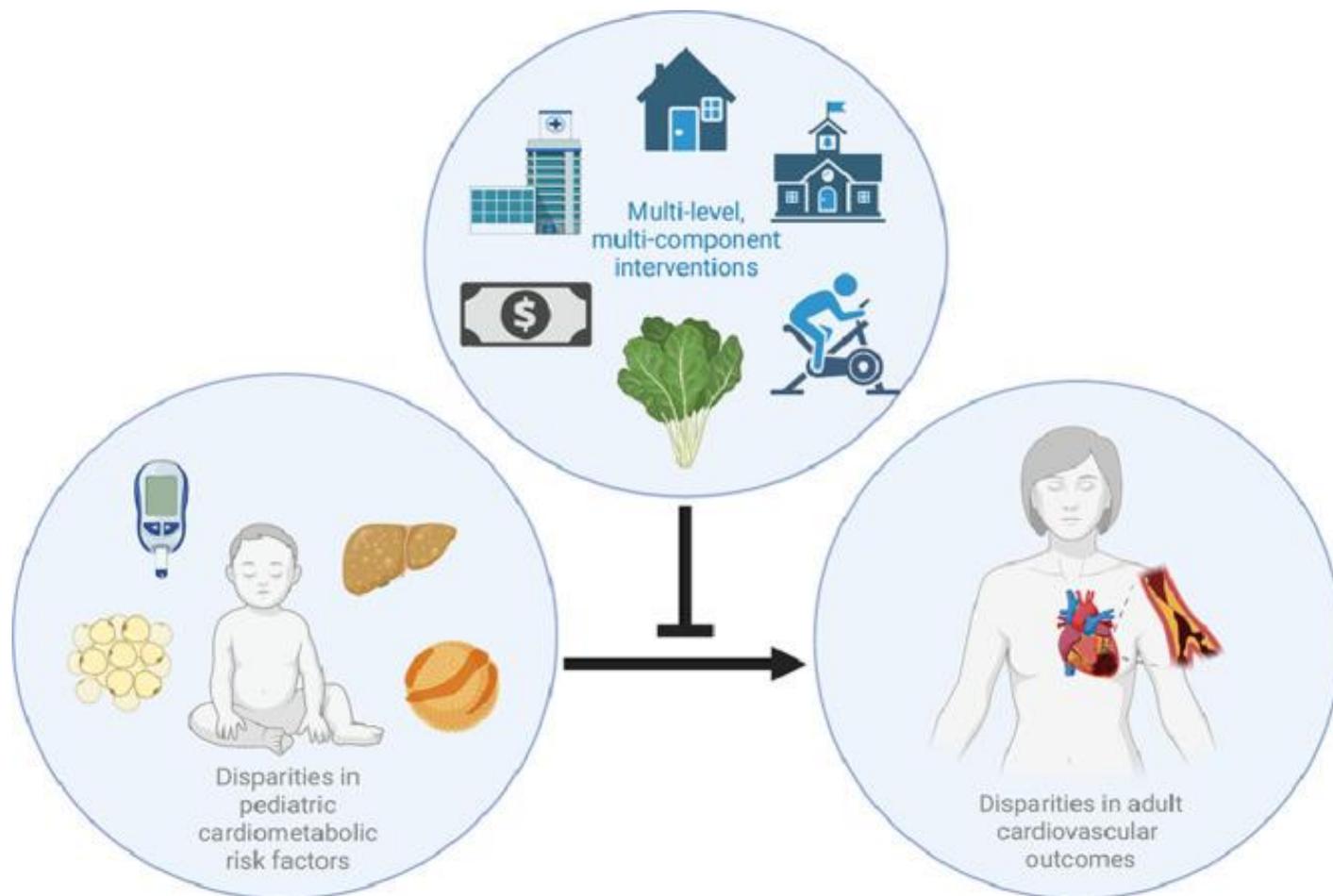
Pediatric NAFLD drives diabetes – a lifelong burden of chronic disease

Citation	Sample description	NAFLD	Pre/Diabetes
Schwimmer, 2003 ¹	n=43; <18y, primarily obese, Hispanic males	Biopsy-confirmed	T2DM: 14%
Manco, 2008 ²	n=120; 3-18y, primarily overweight and obese males	Biopsy-confirmed	Pre: 9.7% T2DM: 2.1%
Schwimmer, 2008 ³	n=150; mean=12.7y, primarily obese, Hispanic	Biopsy-confirmed	Pre: 19%
Newton, 2016 ⁴	n=675; <18y, primarily obese, Hispanic males	Biopsy-confirmed	Pre: 23.4 % T2DM: 6.5%
Koutny, 2020 ⁵	n=4932; mean=12.9y, obese, European	Elevated ALT: Mild 24-50U/L Advanced >50U/L	Pre+T2DM: 13.8% Pre+T2DM: 21.9%
Xanthakos, 2020 ⁶	n=122; 8-17y, primarily obese, Hispanic males	Biopsy-confirmed	T2DM Incidence: 5%
Bardugo, 2021 ⁸	N=633; 16-19y	Biopsy or imaging	T2DM Incidence: 1.9%. Hazard ratio 2.5

How do we decrease the burden of Pediatric NAFLD?

Type 2
PREVENTION
Cirrhosis

Interventions in Child Health Improve Adult Outcomes



Take Home Points

- Obesity and NAFLD are highly prevalent in children but vary by region, country and groups within countries
- Early childhood exposures and maternal obesity are some of the biggest modifiable drivers of cardiometabolic risk and NAFLD in children
- Childhood NAFLD is an opportunity for prevention – but studies are needed to develop the data to drive public health initiatives