Supplementary Table 1 Maternal and Paternal factors associated with Hepatic Steatosis

Maternal and Paternal Factors					
No.	Author name	N (study, NAFLD)	Country	Characteristics of study population	Dx of NAFLD	Summary of findings
1	*Rajindrajith et al*[1]	499	Sri Lanka	– Cross-sectional study – Adolescents aged 14 years – 51.8% females – 42 (8.4%) had NAFLD	US and no history of alcohol use	– Significant associations: – Being breast fed <4 months with NAFLD (33.3% *vs* 17.1% in controls, *P* = 0.02). – Higher WC, BMI, HOMA-IR, TG, increased subcutaneous and body fat with NAFLD. – More adolescents with metabolic derangements had NAFLD – No associations: Birth order, paternal education, maternal education, family income, period of gestation, BP and maternal or

						paternal history of metabolic syndrome with NAFLD.
2	Sood *et al*[2]	99	India	– Cross-sectional study – Obese / Overweight children aged <18 yr with / without NAFLD – 69 (69.7%) had NAFLD – Median age 11.1 yr, 59 (85.8%) boys	US and no history of viral hepatitis / alcohol	– For children with NAFLD, GG and CG statuses for PNPLA3 polymorphism were seen in 34.8% and 33.3% overweight / obese children compared with only 1 (3.33%) for homozygosity and 8/30 (26.7%) in the heterozygous group. – Presence of NAFLD in one parent and two parents increase the OR of offspring being diagnosed with NAFLD. – PNPLA3 was not an independently associated with NAFLD on multivariable regression. – There was high parental incidence with at least 1 parent with NAFLD or low HDL (84%), and > 2/3 of the families had insulin resistance, HTN and high TG for children with NAFLD

3	Long *et al*[3]	785	US	– Cross-sectional study – Cohort participants from second and third generations in the Framingham Heart study – Age ≥ 40 yr for females and age ≥ 35 yr for males – 23% had one parent who had hepatic steatosis, while 1.1% had both affected parents	CT, LPR ≤ 0.33 and no history of alcohol use	– OR of hepatic steatosis was 1.92 when adjusted for sex, age, alcohol use, lipid lowering treatment, HOMA-IR and BMI in those with one parent who had hepatic steatosis versus those without. The OR increased to 3.66 when both parents had hepatic steatosis.
4	Ayonrinde *et al*[4]	1710	Australia	– Cohort study – Adolescents aged 17 yr	US and no history of alcohol use	– Significant associations – Factors associated with NAFLD in female offspring after adjustment for obesity in adolescence were maternal obesity (OR 3.46 95%CI 1.49-8.05) and maternal weight gain ≥ 6.0kg by gestation week 18 on multivariate analysis

						– For males, the SES at time of birth with NAFLD after adjustment for adolescent obesity (OR 9.07 95%CI 1.54-53.29).
5	Ayonrinde *et al*[5]	1170	Australia	– Cohort study – Prospective data on infant feeding and maternal pregnancy were examined against NAFLD outcome at 17 yr old	US and no history of alcohol use	– Significant associations – Breastfeeding without milk supplement ≥ 6 months with decreased NAFLD (OR 0.64 95%CI 0.43-0.94). – Maternal pre-pregnancy obesity and adolescent obesity with NAFLD (OR 2.29 95%CI 1.21-4.32) and (OR 9.08 95%CI 6.26-13.17) respectively independent of a western dietary pattern at 17 yr old. – Intake of milk supplement before 6 months with greater prevalence of US severity of NAFLD compared to intake

						after 6 months (17.7% vs 11.2% and 7.8% vs 3.4%).
6	Patel *et al*[6]	1215	UK	– Cohort study – Participants underwent US of the liver at mean 17.8 yr old	US and no history of viral hepatitis / alcohol	– Significant associations – Maternal diabetes with higher odds of offspring US fatty liver. – Higher maternal pre-pregnancy BMI with higher odds of developing fatty liver in the offspring [aOR 2.72 (95% CI: 1.20-6.15)].
7	Zheng *et al*[7]	8752	China	– Cross sectional study – All participants were female patients who undertook routine physical examinations in public health center – Control group: born 1963-1964 – Fetal exposure group: born 1960-1961	US and no history of alcohol use	– Compared to non-exposed women (to the Chinese famine), women exposed during prenatal and postnatal periods had higher waist, BMI, DBP and SBP measurements (P < 0.01) and higher risks of NAFLD, OR 1.33 (1.04-1.70) and 1.26 (1.03-1.55), respectively.

	– Postnatal exposure group: born 1957-1958 – The Chinese famine was 1959-1961	– Women exposed only during prenatal period had higher risks of having abnormal ALT, OR 1.30 (1.05-1.61).

US: Ultrasound; NAFLD: Non alcoholic fatty liver disease; WC: Waist circumference; BMI: Body mass index; HOMA-IR: Homeostatic model assessment for insulin resistance; TG: Triglyceride; BP: Blood pressure; ALT: Alanine aminotransferase; PNPLA3: Patatin-like phospholipase domain-containing protein 3; OR: Odds ratio; aOR: Adjusted odds ratio; NASH: Non-alcoholic steatohepatitis; NAS CRN: NASH clinical research network; CT: Computed tomography; LPR: Liver phantom ratio, SES: Socioeconomic status; HFF: Hepatic fat fraction; HTN: Hypertension.

Supplementary Table 2 Postnatal factors associated with Hepatic Steatosis

Postnatal Factors						
No.	Author name	N (study, NAFLD)	Country	Characteristics of study population	Dx of NAFLD	Summary of findings
1	Rajindrajith *et al*[1]	499	Sri Lanka	– Cross-sectional study – Adolescents aged 14 years – 51.8% females – 42 (8.4%) had NAFLD	US and no history of alcohol use	– Significant associations: – Being breast fed <4 months with NAFLD (33.3% *vs* 17.1% in controls, p=0.02). – Higher WC, BMI, HOMA-IR, TG, increased subcutaneous and body fat with NAFLD. – More adolescents with metabolic derangements had NAFLD – No associations: Birth order, paternal education, maternal education, family income, period of gestation, BP and maternal

						or paternal history of metabolic syndrome with NAFLD.
2	Ayonrinde *et al*[5]	1170	Australia	– Cohort study – Prospective data on infant feeding and maternal pregnancy were examined against NAFLD outcome at 17 years old	US and no history of alcohol use	– Significant associations – Breastfeeding without milk supplement ≥ 6 months with decreased NAFLD (OR 0.64 95%CI 0.43-0.94). – Maternal pre-pregnancy obesity and adolescent obesity with NAFLD (OR 2.29 95%CI 1.21-4.32) and (OR 9.08 95%CI 6.26-13.17) respectively independent of a western dietary pattern at 17 years old. – Intake of milk supplement before 6 months with greater prevalence of US severity of NAFLD compared to intake after 6 months (17.7% vs 11.2% and 7.8% vs 3.4%).

3	Zheng *et al*[7]	8752	China	– Cross sectional study – All participants were female patients who undertook routine physical examinations in public health center – Control group: born 1963-1964 – Fetal exposure group: born 1960-1961 – Postnatal exposure group: born 1957-1958 – The Chinese famine was 1959-1961	US and no history of alcohol use	– Compared to non-exposed women (to the Chinese famine), women exposed during prenatal and postnatal periods had higher waist, BMI, DBP and SBP measurements ($p < 0.01$) and higher risks of NAFLD, OR 1.33 (1.04-1.70) and 1.26 (1.03-1.55), respectively. – Women exposed only during prenatal period had higher risks of having abnormal ALT, OR 1.30 (1.05-1.61).

NAFLD: Non alcoholic fatty liver disease; WC: Waist circumference; BMI: Body mass index; HOMA-IR: Homeostatic model assessment for insulin resistance; TG: Triglyceride; BP: blood pressure; SBP: Systolic blood pressure; DBP: Diastolic blood pressure; ALT: Alanine aminotransferase; OR: Odds ratio

Supplementary Table 3 Factors in Childhood and Adolescence associated with Hepatic Steatosis

Factors in Childhood and Adolescence						
No.	Author name	N (study, NAFLD)	Country	Characteristics of study population	Dx of NAFLD	Summary of findings
1	Rajindrajith *et al*[1]	499	Sri Lanka	– Cross-sectional study – Adolescents aged 14 years – 51.8% females – 42 (8.4%) had NAFLD	US and no history of alcohol use	– Significant associations: – Being breast fed <4 months with NAFLD (33.3% *vs* 17.1% in controls, $P = 0.02$). – Higher WC, BMI, HOMA-IR, TG, increased subcutaneous and body fat with NAFLD. – More adolescents with metabolic derangements had NAFLD – No associations: Birth order, paternal education, maternal education, family income, period of gestation, BP and

							maternal or paternal history of metabolic syndrome with NAFLD.
2	Nier *et al*[8]	125	Germany	– Case-control study – 89 overweight and 36 normal weight healthy children – Age 5-9 years	US	– Children with NAFLD were heavier and had higher WC – In overweight children, total consumption of carbohydrate was higher in those with NAFLD than without by 120kcal/day, specifically the increase in intake of fructose and glucose. – Overweight children with NAFLD had higher intake of sweetened beverages such as fruit juices.
3	Liu *et al*[9]	1639	China	– Cross-sectional study – Age 16-23 years – A semiquantitative food frequency questionnaire	US and no history of alcohol use	– Adolescents who consumed the highest quartile of whole grains had lower risk of NAFLD (0.72, 95% CI 0.61-0.98)

					(FFQ) of 85 items was used to assess diet		– Red meat and soft drink consumption were associated with NAFLD (1.34, 95% CI 1.06-1.72) – Those with NAFLD had less physical activity / week, higher BMI and WC, and higher proportion were obese – Traditional Chinese dietary pattern had the lowest risk while Western dietary pattern had higher risk of NAFLD after adjustment for confounders
4	Rong *et al*[10]	4141	China	– Cross-sectional study – Age 15-22 years – 2061 girls and 2080 boys		US, hepatitis B and C ruled out by serology and no history of alcohol use	– Body weight, BMI, AST and ALT were higher in those with NAFLD.

5	Ryu *et al*[11]	76415	Korea	– Cross-sectional study – Aged 30 and above who undertook regular health screening	US, hepatitis B and C ruled out by serology and no history of hepatitis/ alcohol use	– Age of menarche was negatively associated with prevalence of NAFLD independent of adult BMI and percent fat mass	
6	Prokopowicz *et al*[12]	108	Poland	– Cross-sectional study – Age 6-18years – Hospitalised in the department between 2012 and 2014	US and no history of hepatitis/ alcohol use	– NAFLD was associated with a significantly greater waist-hip ratio, WC and waist-height ratio. – NAFLD was significantly more often in children / adolescents with HOMA-IR exceeding reference values	
7	Ayonrinde *et al*[5]	1170	Australia	– Cohort study – Prospective data on infant feeding and maternal pregnancy were examined	US and no history of alcohol use	– Significant associations – Breastfeeding without milk supplement ≥ 6 months with	

				against NAFLD outcome at 17 years old		decreased NAFLD (OR 0.64 95%CI 0.43-0.94). – Maternal pre-pregnancy obesity and adolescent obesity with NAFLD (OR 2.29 95%CI 1.21-4.32) and (OR 9.08 95%CI 6.26-13.17) respectively independent of a western dietary pattern at 17 years old. – Intake of milk supplement before 6 months with greater prevalence of US severity of NAFLD compared to intake after 6 months (17.7% vs 11.2% and 7.8% vs 3.4%).
8	Siddiqi *et al*[13]	242	India	– Cross-sectional study – Participants who drank soft drinks were divided into three groups dependent on	US, hepatitis B and C ruled out by serology and no history of	– 75% of participants who drank ≥2 soft drinks/day (Group 1) had NAFLD, compared to 8% for 1 soft drink/day (Group 2) and 4% for <1 soft drink/day (Group 3)

				quantity of soft drinks consumed – Students age 18-26	alcohol use	– Participants in group 1 had higher WC / BMI / TG / DBP / HOMA-IR / Fasting insulin and lower HDL cholesterol compared to group 3
9	Jimenez-Rivera *et al*[14]	97	Canada	– Cross-sectional study – Obese children – Age range 8-17 years – Mean age: 12.9 +/- 3.2 years	US, hepatitis B and C ruled out by serology and no history of hepatitis/ alcohol use	– Mean TG was higher in patients with NAFLD. – HOMA-IR was ≥3.16 in 55% of NAFLD patients vs 40% in those without NAFLD
10	Felix *et al*[15]	39	Brazil	– Cross-sectional study – Prospective – Obese children – Age 3-14 years (Median: 9; Average age: 8.8 ± 2.5 years)	US, hepatitis B and C ruled out by serology	– Male gender (OR 1.62, 95%CI 1.08– 2.44; p = 0.038); high intake of refined carbohydrates (OR 2.17, 95%CI 1.05 – 6.82; p = 0.038) and lack of routine physical activity (OR 3.35, 95%CI 1.97 – 0.006; p = 0.006) were independently associated with NAFLD

11	Trovato *et al*[16]	708	Italy	– Cross-sectional study – Adolescent / young adults – Ages 15-35, mean 21.72	US and no history of hepatitis/ alcohol use	–	Patients with NAFLD take less Mediterranean diet – BMI, plus sized clothing for their actual size, sedentary life, lower frequency of daily food intake and sleep shortage were independently associated with NAFLD
12	Cakir *et al*[17]	181	Turkey	– Case-control study – Group 1: obese/overweight children recently diagnosis with NAFLD (n = 106, 12.4 – 2.6 years) – Group 2: obese children not diagnosed with NAFLD (n = 21, 11.3 – 2.6 years). – Group 3: healthy children not diagnosed with chronic	US and no history of hepatitis	–	Low adherence to Mediterrenean diet was associated with obesity and high BMI, and is a key predictor of NAFLD in obese children

					disease and of normal BMI (n = 54, 11.8 – 2.9 years)		
13	Della Corte C *et al*[18]	243	Italy	–	Cross-sectional study – Obese – Age 10-17 years	US and liver biopsy, hepatitis B and C ruled out by serology and no history of alcohol use	– Low adherence to mediterrenean diet correlated with increasing liver damage, NAFLD activity score and grade 2 fibrosis.
14	Anderson *et al*[19]	3188	UK	–	Cohort study – Prospective study from birth cohort and followed up at mean of 17.8 years of age	US and no history of hepatitis	– Energy intake at all ages was positively linked to liver outcomes. – After adjusting for total energy intake, absolute macronutrient intake and liver health outcomes had inconsistent associations.
15	Lee *et al*[20]	57	USA	–	Cross-sectional study – 31 Black /26 White children	Proton magnetic	– Liver fat was linked to ($P \leq 0.05$) total fat ($r = 0.31$), BMI percentile ($r = 0.28$), visceral fat

			– Age 12-18 years – Fatty liver/ without fatty liver: Black 5(16.1%)/26; White 8(30.8%)/18 – Fatty liver computed as follows: liver fat ([methylene lipid peak/methylene lipid peak +water peak] × 100) ≥5%	resonance spectros-copy (H-MRS) and no history of hepatitis	(r = 0.62), abdominal subcutaneous adipose tissue (r = 0.30), waist circumference (r = 0.38), and CRF (r = −0.27) after adjustment for ethnicity and age – Black boys had lower liver fat than white boys after adjustment for age and differences in BMI percentile or CRF, but not with waist circumference or visceral fat (P > 0.05). – Only visceral fat was independently associated with having fatty liver (OR 1.12, 95% CI 1.04-1.21; P = .003). – Visceral fat differences partially account for the racial disparities in liver fat in obese adolescents
16	Di Costanzo *et al*[21]	230	Italy	– Observational, cohort study	Liver MRI, hepatitis B and	– [T] allele in GCKR, [G] allele in PNPLA3 and [T] allele in TM6SF2 gene carriers had

				– Overweight [defined as body mass index (BMI) > 85th and < 95th percentile for gender and age] or obese (defined as BMI ≥ 95th percentile for gender and age) – 131 Boys/ 99 Girls – Aged 6–16 years, 10.2 SD 3.0 years	C ruled out by serology and no history of alcohol use	significantly higher levels of hepatic fat as compared to wild-type carriers. – Metabolic and genetic factors accounted for 8.7% and 16.1% of HFF% respectively.
17	Silveira *et al*[22]	182	Brazil	– Cohort study – Obese, sedentary – Age 6 to 16 years (Mean: 11 SD 2.7) – Male: 88/ Female:94	US	– Higher quartile of SCAT was linked to higher blood pressure (p = 0.015), but not to NAFLD (p = 0.665). – Higher IAAT was linked to increased dyslipidemia (p = 0.001), NAFLD (p = 0.005) and metabolic syndrome (p = 0.013).

18	Zimmermann *et al*[23]	244 464	Denmark	– Cohort study – 49.8% men – Age 7-13 years	Bloods, imaging, Biposy and no history of hepatitis/ alcohol use	–	Gaining BMI excessively during ages 7 to 13 years was associated with higher risk of routinely-diagnosed NAFLD in adulthood in both sexes – BMI z-score change between ages 7 to 13 years dependent on BMI z-score at age 7 years was associated with NAFLD during adulthood [HR 1.15 (95% CI 1.05 to 1.26) and HR 1.12 (95% CI 1.02 to 1.23) per 1-unit gain in BMI z-score] in males and females respectively – Childhood BMI increase predicted NAFLD during adulthood regardless of the initial or the final BMI.
19	Alkassabany *et al*[24]	800	Egypt	– Cross-sectional, nested case–control study	US and no history of hepatitis	–	History of chronic disease such as autoimmune disease and asthma resulted in

				– School children up to 18 years-old – 349 (43.6%) boys – 451 (56.4%) girls – 126 children with NAFLD (prevalence of 15.8%, 95% CI 13.2–18.3)		27 times higher risk of fatty liver development – Family history of DM, HTN, liver disease and especially obesity (OR=5.2) were significantly associated with fatty liver development.
20	Sanches *et al*[25]	79	Brazil	– Prospective interventional study – Post-pubescent obese – 33 and 46 patients with and without NAFLD – Interdisciplinary therapy targeting weight-loss comprising nutritional,	US and no history of alcohol use	– Insulin resistance conferred a 65% greater risk of NAFLD – Obese adolescents after weight loss, regardless of NAFLD diagnosis, had lowered deposition of body fat, including visceral fat, and improved inflammatory profile, represented by higher concentrations of adiponectin

				clinical and psychological interventions, combined exercise training and physiotherapy		concentrations and lower concentrations of leptin, plasminogen activator inhibitor-1 and mean leptin/adiponectin ratio
21	AyonrindeOT *et al*[26]	965	Australia	– Cohort study – 592 boys and 572 girls were tested for NAFLD – 244 girls were tested for PCOS – 199 girls attended both assessments – Girls: 12 had NAFLD with PCOS / 25 had NAFLD without PCOS / 20 had PCOS without NAFLD / 142 had neither NAFLD nor PCOS	US and no history of alcohol use	– Girls with PCOS had higher diagnosis of NAFLD versus those without PCOS (37.5% vs 15.1%, P = 0.003). – Increasing SST and pre-existing PCOS independently predicted for NAFLD

				– Boys: 59 had NAFLD / 527 had no NAFLD		
22	Xanthakos *et al*[27]	242	US	– Observational cohort study – ≤ 19 years, undergoing bariatric surgery – Mean age: 16.8±1.6 years – Median BMI: 52 kg/m2 – 72% Females – White (68%), non-Hispanic (91%)	Liver biopsy and no history of alcohol use	– Increasing NAFLD severity was linked to higher ALT, HTN, fasting glucose level (P<0.01) and WBC count (P= 0.04). – Diabetes was the only factor linked to fibrosis detection (OR 3.56; 95%CI 1.93−6.56). – Microarray analysis showed that NASH presence was associated with altered gene expression that control cholesterol absorption, macrophage chemotaxis, and fatty acid binding.
23	Oddy *et al*[28]	2868	Australia	– Cohort study – 2,900 pregnant women – 97% of 2,804 women gave birth to 2,868 babies	US and no history of hepatitis/ alcohol use	– Healthy dietary pattern was not associated with NAFLD

				– These children have been assessed at birth and ages 1, 2, 3, 5, 8, 10, 14, and 17 years		– Western dietary pattern score was positively linked to higher odds of NAFLD development at age 17 years
24	Yan *et al*[29]	1350	China	– Cohort study – Data collection started in 1987, of children 6 to 18 years, follow up of 1350 subjects of the original cohort from 2010 to 2014 (aged 28–45 years)	US and no history of hepatitis/ alcohol use	– Children who were overweight or obese had higher odds of NAFLD in adulthood as compared to those of normal weight. In males, subscapular skinfold thickness had OR of 2.78 and BMI had OR of 2.49; the ORs for females were OR 3.61 and 3.34 respectively (all Ps < 0.001). – They also had higher odds of ALT elevation. In males, subscapular skinfold thickness had OR 1.66 and BMI had OR of 1.64; the ORs for females were 3.01 and 2.12 respectively (all Ps < 0.05).

25	Liang *et al*[30]	168	China	– Cross-sectional study – Obese – Ages 6 to 19 years – 90 with NAFLD, 78 without NAFLD	US and no history of hepatitis/ alcohol use	–	Low IGF-1SDS and high HOMA-IR, BMI and uric acid were independently associated with NAFLD – An analysis of IGF-1 SDS, BMI, HOMA-IR and uric acid together could predict NAFLD accurately with high specificity (74.36%) and high sensitivity (78.89%).
26	Peña-Vélez *et al*[31]	112	Mexico	– Cross-sectional comparative study – 63 boys and 49 girls – Obese – Aged 6 - 18 years	US and no history of hepatitis/ alcohol use	–	Neck circumference was independently linked to NAFLD (OR = 1.172; 95% CI = 1.008–1.362; p = 0.038)
27	Nobili *et al*[32]	599	Italy	– Cross-sectional study – Children and adolescents of Caucasian ethnicity – 298 boys and 301 girls – Age range: 5–17 years	Liver biopsy, hepatitis B and C ruled out by serology and no history of	–	Participants with NAFLD proven using biopsy had nearly twice the prevalence of prediabetes/diabetes as compared to those without NAFLD (20.6% vs. 11%).

				– US diagnosis of severe hepatic steatosis or persistently elevated aminotransferase levels in the serum (≥6 months)	alcohol use	– Participants with NAFLD and abnormal glucose tolerance had 2.2 higher increased risk of NASH than those with normal glucose tolerance.
28	Cuthbertson *et al*[33]	2020	Finland	– Cohort study – Aged 3-18 years at recruitment with follow up after 31 years – Cardiovascular Risk in Young Finns Study multicenter study	US and no history of alcohol use	– Being overweight or obese in childhood, but not metabolic health, is linked to increased risk of NAFLD in adulthood. – Participant who were overweight or obese in childhood but not obese in adulthood did not have higher risk of adult NAFLD.
29	Lu *et al*[34]	4128	China	– Retrospective cohort study – Interviewers collected information about age of menarche using questionnaire from post-	US and no history of hepatitis/ alcohol use	– Women with lower age of menarche had higher risk of age-adjusted prevalence of insulin resistance, overweight / obesity and NAFLD. Increasing age of menarche was negatively linked to risk of NAFLD.

				menopausal Chinese women			
30	Mosca *et al*[35]	271	Italy	– Case-control study – Overweight/ Obese – 155 males – 102 patients had NASH and 169 without NASH – Mean age: 12.5 years	US and liver biopsy, hepatitis B and C ruled out by serology and no history of alcohol use	– The factors which were independently associated with NASH were concentration of uric acid (OR 2.488, 95% CI 1.87-2.83, p = 0.004) and consumption of fructose (OR 1.612, 95% CI 1.25-1.86, p = 0.001), after adjustment for confounders. – Consumption of fructose was also independently linked to hyperuricaemia (OR 2.021, 95% CI 1.66-2.78, P = 0.01)
31	Benitez *et al*[36]	513	Chile	– Longitudinal cohort study – 513 children born 2002-2003 – Annual anthropometric data	US and no history of hepatitis/ alcohol use	– Obesity after age 2 years increased the risk of adolescent NAFLD – Obesity at 5 years of age was linked to the highest risk of NAFLD (OR 8.91 95% CI 3.03-16.11)

				– Evaluated for presence of intrahepatic fat at 14-16 years old		
32	Nihal Hatipog˘lu *et al*[37]	248	Turkey	– Cohort study – 114 boys, 134 girls, all obese (BMI > 95th percentile)	US and no history of hepatitis/ alcohol use	– Most anthropometric indices and metabolic parameters were elevated in children diagnosed with NAFLD. – NC was the only risk factor in both boys and girls. The risk of NAFLD increased by 1.544-fold (p<0.001, 95% CI 1.357-2.214) in boys and 1.733-fold (p=0.001, 95% CI 1.185-2.012) in girls with every 1cm increase in NC.
33	Schlieske *et al*[38]	447	Germany	– Cross-sectional study – Overweight children – Mean BMI 32.4 +/- 5.2 kg/m2 – Mean age: 14.2 ± 1.9 years	US and hepatitis B and C ruled out by serology	– NAFLD was significantly associated with the amount of suprailiac, subscapular and abdominal subcutaneous adipose tissue (P < 0.001) and intra-abdominal depth (P < 0.001).

							– Analysis using stepwise logistic regression showed that NAFLD was independently associated with only intra-abdominal depth for both genders and subcutaneous suprailiac adipose tissue deposit in females.
34	Ozhan *et al*[39]	211	Turkey	– Cohort study – 99 male and 112 female children – Median age: 11.24 ± 2.65	US, hepatitis B and C ruled out by serology and no history of hepatitis/ alcohol use		– NAFLD was significantly less prevalent in prepubertal children than in obese adolescents (51.5% vs 65.8%). – The risk factors of NAFLD were WC, age and Quantitative insulin sensitivity check index (QUICKI).
35	Zhao *et al*[40]	186	China	– Case-control study – 93 obese children and 93 obese patients had fatty liver	US and no history of hepatitis/ alcohol use		– Multivariable logistic regression showed age, uric acid was positively associated with fatty liver in obese children. – Fatty liver incidence was significantly higher and the proportion of males as well

				– Simple obese group: BMI 25.5 ± 3.4Kg/m2, WC of 83.5±11.5 cm, 54 were male and age 1–16 years (median age: 9) – Obese with fatty liver group: BMI: 28.1 ± 3.7Kg/m2 and WC of 92.0 ± 9.9 cm, 73 were male and age 7–16 years (median age: 12)		as the level of WC, BMI and HOMA-IR ($p < 0.05$) were elevated with increasing uric acid level, while TG and TC were not significantly different among groups ($p > 0.05$). – Uric acid was positively correlated with WC, BMI and HOMA-IR ($r = 0.477$, 0.468 and 0.259, $p < 0.05$), but not correlated with TC ($r = -0.06$, $p = 0.42$).
36	Hamza *et al*[41]	85	Egypt	– Case-control study – 55 obese patients and 30 non-obese children and adolescents matched by sex, age and pubertal stage	US and no history of hepatitis	– Obese patients consumed more fructose from both natural and processed sources and had higher total intake of calories and fructose

				– A weekly semi-quantitative food frequency questionnaire (FFQ) was used to assess fructose consumption		– Higher intakes of calories and fructose in obese patients were associated with a progressive increase in NAFLD grade by US
37	Fintini *et al*[42]	111	Italy	– Cross-sectional study – 40 untreated (out of which 10 were females) with NAFLD proven using biopsy – 30 obese children (OB) (out of which 10 are females) without NAFLD as proven by ultrasonography children and 41 normal healthy lean children (NRM) (out of which 11 are	Liver biopsy, US and seconda-ry causes of steatosis excluded	– Reported sedentary activity (Physical activity questionnaire, PAQ) was similar in NRM and NAFLD but lower in OB – Children with NAFLD spent more time sedentary and less time engaging in physical activity than with NRM, but not with OB. – Active energy expenditure (EE, cal kg–1 d–1) in NAFLD was linked to insulin sensitivity index result, while total EE was inversely linked to homeostatic model assessment index result in OB.

				females), matched by age and pubertal stage served as controls		
38	Zhang *et al*[43]	189	China	– Cross-sectional study – BMI > 95th percentile in Chinese population – Age 5-16 years	Proton magnetic resonan-ce spectros-copy and no history of hepatitis/ alcohol use	– Subjects with metabolic syndrome had higher liver fat content (LFC) [median 9.7% (interquartile range 4.5–19.9%)] than those without metabolic syndrome [5.7% (2.0–12.8%)] ($p < 0.01$). – LFC was positively linked to the total number of components of the metabolic syndrome (p for trend < 0.01) – Higher levels of LFC were linked to a higher risk of hypertriglyceridemia and metabolic syndrome, and low HDL cholesterol ($p < 0.05$ for all associations). There were no associations with HTN or hyperglycemia development.

39	Patel *et al*[44]	1904	United Kingdom	– Prospective, population-based birth cohort – 791 male – From the Avon Longitudinal Study of Parents and Children (ALSPAC), participants had to have participated in the liver USS sub-study	US and Acoustic radiation force impulse-imaging (ARFI) and no history of alcohol use	– Fatty liver was associated with higher risk of central and peripheral DBP, SBP and MAP after adjusting for sex, age, puberty, social class and alcohol intake. – NAFLD is not linked to increased peripheral or central BP in adolescents after adjustment for adiposity
40	Pawar *et al*[45]	100	India	– Cross-sectional study – Overweight and obese children – Age 11- 15 years	US, ALT, Fibroscan and no history of hepatitis	– Systolic HTN, serum TG, APRI and AST were significantly higher in children who had NAFLD – Systolic hypertension was the only risk factor independently linked to NAFLD in binary logistic regression.

41	Mollard *et al*[46]	74	Canada	– Cross-sectional study – Overweight adolescents – Ages 13-19 years – Magnetic resonance imaging of visceral obesity (represented by visceral-to-subcutaneous adipose tissue ratio) – Harvard Youth Adolescent Food Frequency Questionnaire was used to measure food consumption and dietary habits.	MR spectroscopy	– Adolescents diagnosed with hepatic steatosis consumed more fried food than those without (41% vs 18%; P = 0.04). – Positive associations were observed between hepatic steatosis and total fat intake (β = 0.51, P = 0.03) and the consumption of .35% of daily energy intake from fat (OR 11.8; 95% CI 1.6, 86.6; P = 0.02).
42	Boyraz *et al*[47]	451	Turkey	– Cross-sectional study – Pubertal obese children – Ages 8—18 years	US	– 217 (48.1%) of children had NAFLD and 96 (21.3%) had metabolic syndrome.

				– Classified into three groups on the severity of steatosis.		– Patients with NAFLD had higher occurrence of metabolic syndrome components than those without – Number of metabolic syndrome components positively correlated with steatosis severity.
43	El-Karaksy *et al*[48]	76	Egypt	– Cross sectional study – Obese/ Overweight – Ages 2-15 years – Liver biopsy was performed in 33 patients.	US +/- liver biopsy and no history of hepatitis	– Combination of increased hepatic echogenicty by ultrasound, anthropometric measurements, lipid profile and insulin resistance predicted NAFLD well in obese children. – Only LDL cholesterol predicted NAFLD sensitively
44	Yang *et al*[49]	100	South Korea	– Cross–sectional study – 66 boys and 34 girls – 60 with NAFLD, 40 without NAFLD	US, AST/ ALT and no history of hepatitis/ alcohol use	– Significant differences between the two groups were observed for body fat and trunk fat percentage were ($p<0.001$ and

						p=0.003 respectively) and not for extremity fat percentage (p=0.683). – In obese children, insulin resistance was significantly correlated to age, body fat and trunk fat percentages, GGT, liver enzymes and uric acid. – Insulin resistance and trunk fat percentage were significantly linked to NAFLD development in obese children as assessed by multiple logistic regression.
45	El-Koofy *et al*[50]	33	Egypt	– Cross–sectional study – Overweight/ obese – Ages 2–13 years – Studied for IR, MS and NAFLD prevalence	US, ALT, Liver Biopsy and no history of hepatitis	– Patients with metabolic syndrome had a higher probability of being diagnosed with NAFLD using biopsy (P=0.001). – Children diagnosed with NAFLD had significantly higher WC, BMI, ALT, TC, LDL cholesterol, fasting insulin, TG and lower HDL cholesterol when compared to

							patients who had normal liver histology (P< 0.05) and fitted more with the criteria of metabolic syndrome (80% vs. 44%). – NAFLD patients had higher prevalence of insulin resistance (73% vs. 28%).
46	Mueller *et al*[51]	1214	United States	– Cohort study – Coronary Artery Risk Development in Young Adults (CARDIA) study – Menarche age was reliably reported at exam years 0 and 2 – Multiple-slice abdominal CT was conducted at exam year 25	Non Contrast CT and no history of hepatitis/ alcohol use	– Earlier menarche per year was linked to higher risk of NAFLD (RR 1.15; 95% CI 1.07–1.24), VAT (RR 6.7; 95% CI 4.3–9.0cc), IMAT (RR 1.0; 95% CI: 0.6–1.4cc), and SCAT (RR 19.3; 95% CI: 13.2–26.0cc) after adjustment. – VAT was the only significant factor (p=0.047) after adjusting for weight gain between exam year 0 and 25	

US: Ultrasound, NAFLD: non alcoholic fatty liver disease, WC: waist circumference, BMI: body mass index, HOMA-IR: homeostatic model assessment for insulin resistance, TG: triglyceride, BP: blood pressure, OR: odds ratio, CI: confidence interval, ALT: alanine aminotransferase, AST: asparate

aminotransferase, NASH: non-alcoholic steatohepatitis, DBP: diastolic blood pressure, HDL: high-density lipoprotein, CRP: C-reactive protein, CRF: cardiorespiratory fitness, MRI: magnetic resonance imaging, PNPLA3: Patatin-like phospholipase domain-containing protein 3, HFF%: percentage hepatic fat fraction, SCAT: subcutaneous adipose tissue, IAAT: intraabdominal adipose tissue, HR: hazard ratio, DM: diabetes mellitus, HTN: hypertension, PCOS: polycystic ovary syndrome, SST: suprailiac skinfold thickness, IGF-1: insulin like growth factor 1, SDS: standard deviation scores, NC: neck circumference, TC: total cholesterol, SBP: systolic blood pressure, MAP: mean arterial pressure, APRI: aspartate transaminases to platelet ratio index, LDL: low-density lipoprotein, GGT: gamma glutamyl transferase, VAT: visceral adipose tissue, IMAT: inter-muscular adipose tissue, CT: computed tomography, RR: relative risk

Supplementary Table 4 Genetic factors associated with Hepatic Steatosis

Genetic/ Ethnic factors						
No.	Author name	N (study, NAFLD)	Country	Characteristics of study population	Dx of NAFLD	Summary of findings
1	Chang *et al*[52]	101	Taiwan	– Cross-sectional study – Aged 6-17 years	US and no history of viral hepatitis / alcohol	– Patients with NAFLD were not different in BMI, although were older. More males than females had NAFLD and patients with NAFLD had higher HOMA-IR, 2h-OGTT – Having L allelles to the heme oxygenase-1 gene was significantly associated with developing pediatric NAFLD (OR 18.84, 95% CI 1.45-245.22). Other variables include HOMA-IR and age.
2	Lin *et al*[53]	831	Taiwan	– Cross sectional study – Age 7-15 years – 22.7% had hepatic steatosis.	US and no history of alcohol use	– GCKR rs780094, PNPLA3 rs738409 and TM6SF2 rs58542926 variants were linked to higher risk of hepatic steatosis and elevated ALT levels independently.

						– Both heterozygous and homozygous MBOAT7 rs641738 variants were not associated with insulin resistance, hepatic steatosis, liver enzymes and lipid levels. – Variants of GCKR rs780094 and PNPLA3 rs738409 were linked to serum levels of CK-18 fragment after confounder adjustment for gender, age and body mass index z-score, but no association was observed for MBOAT7 rs641738.
3	Lee *et al*[20]	57	USA	– Cross-sectional study – 31 Black /26 White children – Age 12-18 years – Fatty liver/ without fatty liver: Black 5 (16.1%)/26; White 8(30.8%)/18	Proton magnetic resonan-ce spectro-scopy and no history of viral	– Liver fat was linked to ($P \leq 0.05$) total fat ($r = 0.31$), BMI percentile ($r = 0.28$), visceral fat ($r = 0.62$), abdominal subcutaneous adipose tissue ($r = 0.30$), waist circumference ($r = 0.38$), and CRF ($r = -0.27$) after adjustment for ethnicity and age

					hepatitis / alcohol	– Black boys had lower liver fat than white boys after adjustment for age and differences in BMI percentile or CRF, but not with waist circumference or visceral fat ($P > 0.05$). – Visceral fat differences partially account for the racial disparities in liver fat in obese adolescents
4	Rausch *et al*[54]	234	USA	– Cohort study – Hispanic boys aged up to 18 years old (median 12 years) – Median BMI of 31.4 – Median HbA1c of 5.3% – Liver biopsy proven NAFLD	Liver biopsy, hepatitis B and C ruled out by serology and no history of alcohol use	– There were 10 SNPs identified using GWAS which were linked to BMI z-score (6 located within chromosome 2 and 1 within CAMK1D) and potentially influenced liver gluconeogenesis.

5	Grandone *et al*[55]	1010	Italy	– Cohort study – 522 female – Obesity defined as body mass index BMI > 95th percentile – Age 4-16 years	US, vaccinated against hepatitis B and hepatitis C ruled out by serology with no history of alcohol use	– 167K allele was associated with steatosis (P < 0.0001), higher ALT levels (P < 0.001) and lower LDL (P < 0.0001), total cholesterol (P < 0.00001), non-HDL levels (P < 0.000001) and TG (P = 0.02) – Subjects homozygous for the PNPLA3 148M allele carrying the rare variant of TM6SF2 had higher odds of (OR 12.2 CI 3.8–39.6, p=0.000001) hypertransaminasaemia compared with other patients.
6	Di Sessa *et al*[56]	1002	Italy	– Cohort study – Obese Children – Mean age 10.56 ± 2.97 years	US, hepatitis B and C ruled out by	– Subjects with the MBOAT7 T allele had higher PNFI values (p=0.04) and ALT (p=0.004) than those without. The same observations were reported for MBOAT7 T allele polymorphism with hepatic steatosis.

						serology and no history of alcohol use	
7	Nobili *et al*[57]	152	Italy	– Cohort study – Obese – 6-18YO (10 SD 3) – 92Boys/60Girls – 72 with NASH/ 81 no NASH		Liver biopsy, hepatitis B and C ruled out by serology and no history of alcohol use	– Taqman assays identified polymorphisms of SOD2 rs4880 C>T, PNPLA3 rs738409 C>G (I148 M), LPIN1 rs13412852 C>T and KLF6 rs3750861 G>A. – Genetic risk factors were significant predictors of NASH (AUC 0.75, 95% confidence interval [CI] 0.67– 0.82, P<0.0001) in multivariate logistic model.
8	Peng *et al*[58]	1186	China	– Case-control study – 593 with NAFLD, 72.41% male – 593 Controls, 72.41% male		US, hepatitis B and C	– Selection and genotyping of four common SNPs in the SREBP-1c gene (namely

						ruled out by serology and no history of alcohol use	rs2297508, rs62064119, rs13306741 and rs11868035) – In these SNPs, NAFLD patients and controls exhibited no significant differences in genotype and allele frequencies (all P > 0.05). – These polymorphisms in SREBF-1c gene were not linked to NAFLD development in Chinese Hans.
9	Younossi *et al*[59]	11,613	USA	– Cross-sectional study – Lean patients, BMI<25kg/m2 – 4 major racial groups: non-Hispanic blacks, non-Hispanic whites, Hispanics, and others (Aleut, American Indian, Asian, Eskimo or Pacific Islander).		US, hepatitis B and C ruled out by serology and no history of alcohol use	– NASH was independently associated with younger age, Hispanic race and components of metabolic syndrome including hypertension (p values < 0.05).

10	Di Costanzo *et al*[21]	230	Italy	– Observational, cohort study – Overweight [defined as body mass index (BMI) > 85th and < 95th percentile for gender and age] or obese (defined as BMI ≥ 95th percentile for gender and age) – 131 Boys/ 99 Girls – Aged 6–16 years, 10.2 SD 3.0 years	MRI, hepatitis B and C ruled out by serology and no history of alcohol use	– [T] allele in GCKR, [G] allele in PNPLA3 and [T] allele in TM6SF2 gene carriers had significantly higher levels of hepatic fat as compared to wild-type carriers. – Metabolic and genetic factors accounted for 8.7% and 16.1% of HFF% respectively.
11	Nishioji *et al*[60]	824	Japan	– Cross-sectional study – Mean age: 54.3 years – 548 cases in males (66.5%) and 276 cases in females (33.5%) – 198 cases (24.0%) were obese and 272 cases (33.0%) were diagnosed with NAFLD	US, hepatitis B and C ruled out by serology and no	– G allele of PNPLA3 rs738409 in subjects who had normal weight (OR 3.52; 95% CI: 1.42–8.71; P = 0.0063) and who were overweight (OR 2.60; 95% CI: 1.14–5.91; P = 0.0225) was linked to odds of NAFLD but not those who were obese.

						history of alcohol use	– Both G allele of PNPLA3 rs738409 and weight gain of at least 10kg after age 20 years were associated with NAFLD in subjects who had normal weight (OR 12.00; 95% CI: 3.71–38.79; p = 3.3×10−5) and those who were (OR 13.40; 95% CI: 2.92–61.36; P = 0.0008).
12	Lin *et al*[61]	520	Taiwan	– Cross-sectional study – Obese – Aged 6-18 years – Male: 346		US	– Patients with PNPLA3 rs738409 GG, CG and CC alleles were compared. – The risk of NAFLD was higher by 2.96 times (95% CI, 1.57 to 5.59, p = 0.0008) for CG alleles and by 5.84 times (95% CI, 2.59 to 13.16; p < 0.0001) for GG alleles when compared to CC alleles. – Patients with CG alleles and GG alleles were also associated with increased ALT compared to patients with CC alleles.

13	Guichelaar *et al*[62]	144	USA	– Cohort study, prospective – Severely obese, mean BMI of 46.6 ± 7.7 kg/m2 – 122 (84.7%) Females. – Mean age was 47.9 SD 10.7 years – 12 (8.3%) had normal liver histology – 72 (50%) had NASH, out of whom 15 (10.4% of total patients) had stage 2-3 fibrosis.	Liver Biopsy, hepatitis B and C ruled out by serology and no history of alcohol use	– PNPLA3 GG genotype was positively correlated ($p < 0.05$) with serum levels of AST, ALT, fibrinogen, glucose, HOMA-IR, insulin-dependent diabetes mellitus and NASH. – PNPLA3 rs738409 G (reference: C allele) was independently linked to NASH, as well as glucose >100mg/dl, CK-18 >145 IU/l and CRP >0.8 mg/ dl. Probability of developing NASH increased from 9% to 82% when presence of risk factors increased from 0 to 4.
14	Peng *et al*[63]	1106	China	– Frequency matched case–control study	US, no history of hepatitis/ alcohol	– rs139051 TT and rs738409 GG or GC genotypes were linked to increased risk of NAFLD with a dose-dependent relationship

				– 553 NAFLD patients consisting of 399 men and 154 women; mean age: 45.33 ± 12.48 years – 553 healthy individuals consisting of 399 men and 154 women; mean age: 43.87 ± 13.00 years) without steatosis by US		– PNPLA3 genetic polymorphisms might have an independent or joint influence on NAFLD development in Han Chinese
15	El-Koofy *et al*[64]	96	Egypt	– Cross-sectional study – 37 overweight (comprising of 17 males and 20 females) and 39 obese (comprising of 21 males and 18 females). – Aged 2-15 years (mean of 7.7 ± 3.5 years) – 20 healthy controls	US +/- Biopsy, hepatitis B and C ruled out by serology and no history of	– MTP G/G genotype was more common in patients with NASH (P = 0.002, CI: 2.9–392) than the controls. – All NASH patients also had the MnSOD T/T genotype.

					alcohol use	
16	Walker *et al*[65]	223	USA	– Cross-sectional study – Obese Hispanic children – Male:93/ Female:130 – Age 13.5 SD 2.9 – BMI: 30.5 SD 7.5	MRI and no history of hepatitis/ alcohol use	– Only PNPLA3 and APOC3 gene variants were linked to liver fat. – Subjects with a GRS54 had approximately three times higher liver fat content than subjects with GRS (genetic risk score) of 0
17	Bhatt *et al*[66]	335	India	– Case-Control study – 335 subjects who were overweight/obese, defined as body mass index BMI > 23 kg/m^2 – 162 (Age: 38.2 SD 7.0) cases and 173 (Age 37.1 SD 6.9) controls	US and no history of hepatitis/ alcohol use	– Cases had higher prevalence of G/G and C/G genotypes of the rs738409 gene than controls (P = 0.04). Hence, minor allele G frequency was also higher in cases (P = 0.003). – G allele was linked to higher HOMA-IR (P = 0.05), fasting insulin (P = 0.002), alanine transaminase (P = 0.003) and aspartate transaminase (P = 0.04) only in cases.

					– G/G genotype was associated with NAFLD [odds ratio (OR), 1.98, 95% CI 1.43–2.73, P = 0.04). – Asian Indians living in north India who had the allele rs738490 of PNPLA3 are more susceptible to NAFLD development.
18	Alkassabany *et al*[24]	800	Egypt	– Cross-sectional, nested case–control study – School children up to 18 years-old – 349 (43.6%) boys – 451 (56.4%) girls – 126 children with NAFLD (prevalence of 15.8%, 95% CI 13.2–18.3)	US and no history of hepatitis	– History of chronic disease such as autoimmune disease and asthma resulted in 27 times higher risk of fatty liver development – Family history of DM, HTN, liver disease and especially obesity (OR=5.2) were significantly associated with fatty liver development.

19	Xanthakos *et al*[27]	242	US	– Observational cohort study – ≤ 19 years, undergoing bariatric surgery – Mean age: 16.8±1.6 years – Median BMI: 52 kg/m2 – 72% Females – White (68%), non-Hispanic (91%)	Liver biopsy and no history of alcohol use	– Increasing NAFLD severity was linked to higher ALT, HTN, fasting glucose level (P<0.01) and WBC count (P= 0.04). – Diabetes was the only factor linked to fibrosis detection (OR 3.56; 95%CI 1.93−6.56). – Microarray analysis showed that NASH presence was associated with altered gene expression that control cholesterol absorption, macrophage chemotaxis, and fatty acid binding.
20	Zusi *et al*[67]	514	Italy	– Cohort study – Children and adolescents who were obese – Mean age [±SD]: 11.2 ± 2.8 years – z-BMI: 3.3 ± 0.8	US and no history of hepatitis/ alcohol use	– Genetic variants in GCKR rs1260326 (OR = 1.53, p = 0.003), TM6SF2 rs58542926 (OR = 4.13, p = 0.002), ELOVL2 rs2236212 (OR = 1.34, p = 0.047) and PNPLA3 rs738409 (OR = 1.58, p = 0.004) were linked to NAFLD development

				– NAFLD prevalence was 67.5% (347 patients)		– Including a 11-polymorphism GRS to clinically-established risk factors resulted in a modest but significant improvement to the ability of the regression model in predicting the susceptibility to NAFLD (with SNPs C-statistic 0.81 [95%CI 0.75–0.88] vs. 0.77 [0.70–0.84] without SNPs; p = 0.047)
21	Nobili *et al*[32]	599	Italy	– Cross-sectional study – Children and adolescents of Caucasian ethnicity – 298 boys and 301 girls – Age range: 5–17 years – US diagnosis of severe hepatic steatosis or persistently elevated aminotransferase levels in the serum (≥6 months)	Liver biopsy, hepatitis B and C ruled out by serology and no history of alcohol use	– Participants with NAFLD proven using biopsy had nearly twice the prevalence of prediabetes/diabetes as compared to those without NAFLD (20.6% vs. 11%). – Participants with NAFLD and abnormal glucose tolerance had 2.2 higher increased risk of NASH than those with normal glucose tolerance. – Association was attenuated after accounting for confounders sex, age, waist circumference

						(adjusted OR 1.69, 95% CI 1.06–2.69, p = 0.032), and polymorphism of PNPLA3 rs738409.
22	Monga *et al*[68]	73	United States	– Cross-sectional study – Obese children (defined BMI above 95th percentile) – 44 children with NAFLD (HFF ≥ 5.5%) – 29 children without NADLD (HFF < 5.5%) – Excluded patients with known hepatic diseases	MRI and no history of hepatitis/ alcohol use	– Children diagnosed with NAFLD had lower bacterial alpha-diversity than healthy children (p=0.013). – Children with NAFLD had higher Firmicutes to Bacteroidetes ratio and lower abundance of Bacteroidetes, Gemmiger, Prevotella and Oscillospira – Additive effect on HFF by PNPLA3 polymorphisms with Gemmiger and Oscillospira.
23	Perez-Diaz-Del-Campo *et al*[69]	110	Spain	– FLiO project (Fatty Liver in Obesity) which is a randomized controlled trial (NCT03183193)	US and no history of hepatitis/ alcohol use	– In patients with at risk genotype (SH2B1 rs7359397 (CT/TT) subjects), frequency of NASH was higher 69.1% vs 44.4%.

				– No significant difference in BMI between group with no risk genotype vs high risk genotype		– Carriers of risk allele had higher liver fat content and risk of NASH in multinomial logistic regression.
24	Abshagen *et al*[70]	63	Germany	– Cohort study – Liver biopsies from obese individuals who had NAFLD and fibrosis and underwent abdominal surgery for sleeve gastrectomy, Roux-en-Y gastric bypass or elective cholecystectomy – Male: n=21	Liver Biopsy	– Homozygous Del carriers (n=8) had lower NAFLD and fibrosis severity than wild-type allele carriers (n=55) – REPIN1 Del variant may be linked to a lower risk of NAFLD development

US: Ultrasound, MRI: magnetic resonance imaging, SD: standard deviation, NAFLD: non alcoholic fatty liver disease, BMI: body mass index, HOMA-IR: homeostatic model assessment for insulin resistance, OGTT: Oral glucose tolerance test, OR: odds ratio, CI: confidence interval, ALT: alanine aminotransferase, PNPLA3: Patatin-like phospholipase domain-containing protein 3, GCKR: Glucokinase Regulator, TM6SF2: transmembrane 6 superfamily member 2, MBOAT: membrane bound O-acyl transferase, CK: cytokeratin, CRF: cardiorespiratory fitness, WC: waist circumference, NASH:

non-alcoholic steatohepatitis, GWAS: genome-wide association study, SNP: single nucleotide polymorphisms, CAMK1D: Calcium/calmodulin-dependent protein kinase type 1D, LDL: low-density lipoprotein, TG: triglyceride, HDL: high-density lipoprotein, PNFI: pediatric NAFLD fibrosis index, SOD2: Superoxide dismutase 2, mitochondrial, KLF6: Kruppel Like Factor 6, LPIN-1: Lipin 1, AUC: Area under curve, AST: asparate aminotransferase, DBP: diastolic blood pressure, SREBP: sterol regulatory element binding proteins, HFF%: percentage hepatic fat fraction, CRP: C-reactive protein, MTP: Microsomal triglyceride transfer protein, MnSOD2: manganese-dependent superoxide dismutase, APOC3: Apolipoprotein C-III, DM: diabetes mellitus, HTN: hypertension, ELOVL2: ELOVL Fatty Acid Elongase 2, Del: deletion, REPIN1: Replication Initiator 1

Supplementary Table 5 Other factors associated with Hepatic Steatosis

Other Factors						
No.	Author name	N (study, NAFLD)	Country	Characteristics of study population	Dx of NAFLD	Summary of findings
1	Nier *et al*[8]	125	Germany	– Case-control study – 89 overweight and 36 normal weight healthy children – Age 5-9 years	US	– Children with NAFLD were heavier and had higher WC – In overweight children, total consumption of carbohydrate was higher in those with NAFLD than without by 120kcal/day, specifically the increase in intake of fructose and glucose. – Overweight children with NAFLD had higher intake of sweetened beverages such as fruit juices.
2	Antonella *et al*[35]	271	Italy	– Case-control study – Overweight/ Obese – 155 males	US and Liver biopsy, hepatitis B	– The factors which were independently associated with NASH were concentration of uric acid (OR 2.488, 95% CI 1.87-2.83, p = 0.004) and consumption of fructose (OR 1.612, 95% CI

				– 102 patients had NASH and 169 without NASH – Mean age: 12.5 years	and C ruled out by serology and no history of alcohol use	1.25-1.86, p = 0.001), after adjustment for confounders. – Consumption of fructose was also independently linked to hyperuricaemia (OR 2.021, 95% CI 1.66-2.78, P = 0.01)
3	Pacifico *et al*[71]	51	Italy	– Randomised controlled trial (double-blind and parallel-group) – Randomised treatment with Doxosahexaenoic acid (DHA) or placebo (n = 29 in each group) – 51 completed: 25 DHA, 26 placebo – 30 Male	Liver MRI + Liver biopsy, hepatitis B and C ruled out by serology and no	– After 6 months, the DHA group had lowered liver fat by 53.4% (95% CI, 33.4-73.4) while the placebo group decreased by 22.6% (6.2-39.0) (P=0.040 when comparing both groups). – In the DHA group, VAT and EAT were lowered by 7.8% (0-18.3) and 14.2% (0-28.2%), as compared to 2.2% (0-8.1) and 1.7% (0-6.8%) in the placebo group respectively (p=0.01 for both comparisons).

				– Age: Placebo 10.8 SD 2.8 years; DHA 11 SD 2.6 years	history of alcohol use	– The DHA group had significantly lower fasting insulin and TG (p=0.028 and p=0.041, respectively).
4	Cardoso *et al*[72]	129	Brazil	– Cross-sectional study – Females: 62.8% (81/129) – 65.9% (85/129) were non-white – Mean age 11.27 SD 3.72 years	US and no history of hepatitis/ alcohol use	– Uric acid levels were positively associated with metabolic syndrome, adolescence and SBP, but not with NAFLD.
5	Pirgon *et al*[73]	117	Turkey	– Cross-sectional study – 87 obese adolescents (consisting of 42 boys and 45 girls, mean age: 12.7±1.3 years, mean body mass index standard deviation score (BMI-SDS): 2.1 ± 0.3) – 30 lean adolescents (consisting of 15 boys and 15 girls, mean age: 12.3 ± 1.45 years, mean BMI-SDS: 0.5±0.7)	US, hepatitis B and C ruled out by serology	– Obese adolescents with and without NAFLD had lower 25(OH)D levels when compared with lean adolescents (29.5±18.4 vs. 41.0±17.9 vs. 48.1±22.2ng/mL). – Those with NAFLD had lower 25(OH)D levels than those without NAFLD ($p < 0.001$) and lean adolescents ($p < 0.001$) – For adolescents who were obese and NAFLD, 25(OH)D was negatively correlated with with

						ALT (r=−0.794, p=0.03) and HOMA-IR (r = −0.158, p = 0.01).
6	Pacifico *et al*[74]	80	Italy	– Case-control study – 40 Obese with NAFLD, 40 without – Both cases and controls consisted of 25 boys and 15 girls and five prepubertal children.	MRI, hepatitis B and C ruled out by serology and no history of alcohol use	– Subjects who were obese and diagnosed with NAFLD had higher Zonulin values as compared to those without NAFLD [median (interquartile range), 4.23 (3.18-5.89) vs 3.31 (2.05-4.63), P < 0.01]
7	Black *et al*[75]	2868	Australia	– Cohort study – Participants followed from birth – s25(OH)D levels were assessed at ages 14 and 17 years. – US done at 17 years	US and no history of alcohol use	– Higher s25(OH)D levels at 17 years lowered odds of NAFLD development (OR 0.74, 95% CI 0.56,0.97; p=0.029), after adjusting for race, sex, television/computer viewing, physical activity, insulin resistance and body mass index

8	Xu *et al*[76]	520	China	– Cohort study – Obese children – 376 boys, 144 girls – Age range: 3.4 –17.1 years	US and no history of hepatitis	–	Children who were obese and diagnosed with NAFLD had higher fasting insulin, fasting C-peptide and HOMA-IR ($p<0.001$) than those without NAFLD. – Fasting C-peptide (OR 2.367) was associated independently with NAFLD in obese children and WC (OR 1.047) in stepwise multiple logistic regression. – Fasting C-peptide tertiles were significantly associated with NAFLD 1.00 (as references), 1.896 (1.045–3.436), and 4.169 (1.822–9.537) after adjustment.
9	Olariu *et al*[77]	245	Romania	– Case-control study – 125 overweight and obese subjects aged 10–18 years and 120 controls of normal weight and matched by gender and age	US, MRI, CT and no history of hepatitis/ alcohol use	–	47 (37.6%) had intestinal dysbiosis and 78 (62.4%) were SIBO negative. – 4 (3.3%) controls were SIBO positive. – 28/47 (59.5%) of the subjects who were obese and SIBO positive had NAFLD.

					– 8/78 (10.2%) of the subjects who were obese and SIBO negative had NAFLD. – Out of 47 adolescents who were overweight or obese and diagnosed with intestinal dysbiosis, 28 (59.5%) had NAFLD as compared to 8 (10.2%) out of 78 overweight or obese subjects who were SIBO negative ($p < 0.001$). – Higher rate of NAFLD in SIBO positive obese children when compared to obese subjects without intestinal dysbiosis.
10	Liang *et al*[30]	168	China	– Cross-sectional study – Obese – Ages 6 to 19 years – 90 with NAFLD, 78 without NAFLD	US and no history of hepatitis/ alcohol use	– Low IGF-1SDS and high HOMA-IR, BMI and uric acid were independently associated with NAFLD – An analysis of IGF-1 SDS, BMI, HOMA-IR and uric acid together could predict NAFLD accurately with high specificity (74.36%) and high sensitivity (78.89%).

11	Monga *et al*[68]	73	United States	– Cross-sectional study – Obese children (defined BMI above 95th percentile) – 44 children with NAFLD (HFF ≥ 5.5%) – 29 children without NADLD (HFF < 5.5%) – Excluded patients with known hepatic diseases	MRI and no history of hepatitis/ alcohol use	– Children diagnosed with NAFLD had lower bacterial alpha-diversity than healthy children (p=0.013). – Children with NAFLD had higher Firmicutes to Bacteroidetes ratio and lower abundance of Bacteroidetes, Gemmiger, Prevotella and Oscillospira – Additive effect on HFF by PNPLA3 polymorphisms with Gemmiger and Oscillospira.
12	Zhao *et al*[40]	186	China	– Case-control study – 93 obese children and 93 obese patients had fatty liver – Simple obese group: BMI 25.5 ± 3.4Kg/m2, WC of 83.5±11.5 cm, 54 were male and age 1–16 years (median age: 9)	US and no history of hepatitis/ alcohol use	– Multivariable logistic regression showed age, uric acid was positively associated with fatty liver in obese children. – Fatty liver incidence was significantly higher and the proportion of males as well as the level of WC, BMI and HOMA-IR ($p < 0.05$) were elevated with increasing uric acid level, while

				– Obese with fatty liver group: BMI: 28.1 ± 3.7Kg/m2 and WC of 92.0 ± 9.9 cm, 73 were male and age 7–16 years (median age: 12)		TG and TC were not significantly different among groups (p >0.05). – Uric acid was positively correlated with WC, BMI and HOMA-IR (r = 0.477, 0.468 and 0.259, p < 0.05), but not correlated with TC (r = -0.06, p = 0.42).
13	Sezer *et al*[78]	111	Turkey	– Cohort study – Obese children included, divided into 2 subgroubs based on US (hepatosteatosis (52%) and non-hepatosteatosis) – Age 7-18 years	US, hepatitis B and C ruled out by serology and no history of alcohol use	– Those with and without hepatosteatosis did not differ in vitamin D levels.
14	Nichols *et al*[79]	4133	United States	– Cohort study	Liver biopsy and	– There were higher proportions of children who were boys (74.6 vs 39.4%, p < 0.001), had

				– 66 cases and 4067 controls (69.7 vs 59% who were of Hispanic/Latino ancestry, p = 0.1) – Age range: 5-18 years	no history of hepatitis/ alcohol use	elevated modified BMI-z scores (median 2.4 (IQR 1.7) vs 1.9 (IQR 1.7), p < 0.001), and abnormal metabolic parameters (TSH, TG, ALT, HDL cholesterol and non-HDL cholesterol) in those diagnosed with NAFLD. – The 4th quartile of TSH was significantly associated with NAFLD after adjusting for sex, age and obesity severity.
15	Kaltenbach *et al*[80]	332	Germany	– Cross-sectional study – Obese and overweight children – Either euthyroid or had subclinical hypothyroidism (TSH > 4 µU mL-1, normal thyroxine).	US, hepatitis B and C ruled out by serology and no history of alcohol use	– TSH concentrations were increased in children with NAFLD than those without (p=0.0007). – TSH values were divided into quartiles were associated with hepatic steatosis (p < 0.05).

US: Ultrasound, NAFLD: non alcoholic fatty liver disease, WC: waist circumference, NASH: non-alcoholic steatohepatitis, OR: odds ratio, CI: confidence interval, HFF: hepatic fat fraction, MRI: magnetic resonance imaging, VAT: visceral adipose tissue, EAT: epicardial adipose tissue, TG: triglyceride, SBP: systolic blood pressure, BMI: body mass index, HOMA-IR: homeostatic model assessment for insulin resistance, SD: standard deviation, SDS: standard deviation scores, s25(OH)D: serum 25- hydroxyvitamin D, ALT: alanine aminotransferase, SIBO: small intestine bacterial overgrowth, IGF-1: insulin like growth factor 1, PNPLA3: Patatin-like phospholipase domain-containing protein 3, TC: total cholesterol, HDL: high-density lipoprotein, IQR: interquartile range, TSH: thyroid stimulating hormone

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