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ORIGINAL RESEARCH ARTICLE

Maternal gestational hypertension, smoking and pre-eclampsia are associated with metabolic dysfunction-associated fatty liver disease in overweight offspring

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Abstract

Introduction: Due to a steep increase in obesity, metabolic dysfunction-associated fatty liver disease (MAFLD) has also become the most common chronic hepatic condition among children and adolescents. Various maternal and pregnancy-related factors have also been implicated in the development of MAFLD, but human studies remain scarce.

Material and methods: Comprehensive data of 460 overweight or obese children aged 2–16 years were collected and combined with data on selected maternal and pregnancy-related factors for a case–control study. MALFD was defined as alanine aminotransferase >2× upper limit of normal. Children with and without MAFLD were compared regarding to the study variables and multivariable regression analysis was utilized.

Results: Median age of the study children was 11.8 (quartiles 9.1–14.2) years; 44% were girls and 17.8% had MAFLD. Children with MAFLD were older (12.7 vs. 11.6 years, $p = 0.002$), while the groups did not differ age-standardized body mass index (BMI-SDS) or gender. Factors associated with MAFLD in a multivariable model considering also the offspring's present BMI-SDS, sex, and maternal prepregnancy

Abbreviations: ALT, alanine aminotransferase; BMI-SDS, body-mass index standard deviation score; DOHaD, developmental origin of health and disease; GDM, gestational diabetes mellitus; ICD, international classification of diseases; MAFLD, metabolic dysfuction-associated fatty liver disease; MASLD, metabolic dysfunction-associated steatotic liver disease; NAFLD, nonalcoholic fatty liver disease; OGTT, oral glucose tolerance test.

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overweight, were child's older age (odds ratio [OR] 1.16, 95% confidence interval [CI]: 1.06–1.28), maternal gestational smoking (OR 2.01, 95% CI: 1.16–3.47), gestational hypertension (OR 3.44, 95% CI: 1.08–11.0) and pre-eclampsia (OR 2.93, 95% CI: 1.15–7.45). There was no significant association between MAFLD and maternal BMI, birth anthropometrics or perinatal complications.

Conclusions: Maternal smoking, gestational hypertension and pre-eclampsia were associated with MAFLD among overweight or obese children. Further prospective studies are needed to verify causal relationships.

KEYWORDS
children, fatty liver, MAFLD, obesity, overweight, pregnancy, prenatal

1 | INTRODUCTION

The prevalence of overweight, obesity and their comorbidities is increasing in all ages.[1] One well-known complication of excess body adiposity is nonalcoholic fatty liver disease (NAFLD), nowadays preferably called metabolic dysfunction-associated fatty liver disease (MAFLD) or steatotic liver disease (MASLD), which has gradually become the most common chronic hepatic condition among children and adolescents.[2] The exact pathogenesis of the condition remains incompletely understood, but likely involves complex interaction between genetic predisposition and various environmental factors. However, the steep increase and highly variable phenotype and natural history of the disease cannot be attributed solely to genetic risk and changes in the prevalence of overweight, indicating the role of additional contributing factors, many of which could affect particularly during fetal life and early childhood.[3–5]

The Developmental Origins of Health and Disease (DOHaD) theory suggests that intrauterine environment modifies later health of offspring. For example, maternal obesity and hypertension may increase the child's risk of cardiovascular disease.[6–8] Maternal overweight could predispose also to fatty liver disease in offspring, whereas the effects of, for example, gestational diabetes (GDM) and birth size are more controversial.[9–12] Interpretation of the results is hampered by the challenging diagnostics, as imaging methods have suboptimal sensitivity or limited availability, and liver biopsy is rarely performed in children.[13] Moreover, previous studies often have not adjusted for childhood obesity,[9,14] have had low prevalence of affected children[10,15,16] or have investigated only a few possible risk factors.[11,12,16] Altogether, there is a need for additional research on the association between maternal and intrauterine factors and later MAFLD in the offspring.

MAFLD is a modified definition of NAFLD which can be diagnosed in children with overweight based on laboratory evidence of liver steatosis.[17] By utilizing this simplified and less biased definition, we aimed to further scrutinize the role of pre- and perinatal factors in the risk of MAFLD among overweight or obese offspring.

Key message

Exposure to gestational hypertension, pre-eclampsia and maternal smoking during pregnancy were associated with increased risk of developing metabolic dysfunction-associated fatty liver disease in children aged 2–16 years. There was no association with maternal BMI or with child's sex and BMI- standard deviation score.

2 | MATERIAL AND METHODS

2.1 | Patients and study design

This case–control study was carried out in the Tampere Center for Child, Adolescent and Maternal Health Research. The study comprised 553 consecutive children aged 2–16 years who underwent at least one healthcare visit due to overweight or obesity (ICD-10 codes E65, E66.0-9 or R63.5) in years 2002–2020 in pediatric endocrinology or teaching outpatient clinics and had been born in the same hospital as these clinics, as well as their biological mothers. Comprehensive data of these child–mother pairs were collected from systematically maintained medical records. The maternal and child data were collected independently by the study authors (LA, HR, SL, HdeR). Maternal data were further supplemented from the National Birth Registry that contains information on all live births in Finland.[18] Child–mother pairs with insufficient data, and those including a child with a confounding condition and/or medication possibly affecting liver transaminases, were excluded. After the data collection, the children were divided for further analyses to those who did (cases) or who did not (controls) fulfill the criteria of MAFLD.

2.2 | Data collection and definitions

The collected maternal data included age at delivery, socioeconomic status, parity, prepregnancy hypertension or diabetes, prepregnancy

weight as recorded at the first maternity clinic visit, gestational weight gain, smoking and use of alcohol or illicit drugs during pregnancy, and the possible presence of gestational hypertension, pre-eclampsia, GDM and intrahepatic cholestasis of pregnancy.

Prepregnancy overweight was defined as body mass index (BMI, kg/m^2) >25.0 and obesity as BMI >30.0. If BMI was unavailable, overweight and obesity recorded by the physician were also noted. Gestational diabetes was defined as at least one abnormal blood glucose value (fasting ≥5.3 mmol/L, 1 h ≥10.0 mmol/L, 2 ≥8.6 mmol/L) in 75-g oral glucose tolerance test (OGTT) according to the Finnish national guidelines.[19] Chronic hypertension, gestational hypertension and pre-eclampsia were diagnosed by the treating clinician following widely used international criteria.[20] The diagnosis of intrahepatic cholestasis of pregnancy was established on basis of pruritus with elevated serum bile acids and/or aminotransferase levels. Maternal employment status was further subclassified as lower- or higher-level employee, manual worker, self-employed, or other (students, unemployed, on parental leave).

The collected perinatal data included pregnancy duration, mode of delivery (vaginal birth vs. cesarean section), antibiotic use during labor, birthweight, length and head circumference, 1- and 5-min Apgar scores, umbilical cord arterial pH, and placental/birthweight ratio to elucidate possible differences in anthropometrics and birth outcomes which could be related to hypoplastic placentation, as well as use of antenatal corticosteroid treatment, presence of neonatal infection, hypoglycemia and need for respiratory support, and admission to neonatal ward or intensive care unit.

Birthweight was standardized for sex and gestational weeks and reported as standard deviations (SDs), and was further classified as small for gestational age (birthweight below −2 SD) and large for gestational age (birthweight >2 SD) according to the national reference values.[21] Macrosomia was defined as birthweight >4.5 kg, and neonatal hypoglycemia was recorded if diagnosed by the physician in charge.

The collected offspring data at the time of the first overweight- or obesity-related healthcare visit included demographic and anthropometric characteristics, blood pressure and plasma alanine aminotransferase (ALT) values, as well as the presence of possibly liver-affecting chronic diseases and their medications, use of supplements, herbal products, alcohol and illicit drugs. The need for ALT measurement had been based on clinical judgment by the physician in charge.

Overweight in children was further classified using either age-standardized BMI (BMI-SDS) scores or weight-to-height percentages as described elsewhere.[22,23] Hypertension was diagnosed according to Clinical Practice Guideline by the American Academy of Pediatrics.[24] MAFLD was defined as serum ALT value >2× the upper limit of normal (>44 U/L for girls and >50 U/L for boys) together with confirmed overweight or obesity.[17,25]

2.3 | Statistical analyses

The association between the child's MAFLD and selected characteristics of the mother and offspring were analyzed using stepwise logistic regression. Most of the continuous variables were found to be markedly skewed in the Shapiro–Wilk and Kolmogorov–Smirnov tests as well as visual assessment, and therefore, for simplicity, only nonparametric tests were used. For the regression analysis, all included variables were first tested in univariate analysis for independent associations applying the Mann–Whitney or Kruskal–Wallis test for continuous variables and the Chi-square or Fisher's exact test for categorical variables. Next, variables with a p-value <0.1 in the univariate analysis,[26] as well as selected variables that had been reported to be associated with NAFLD in the previous literature, that is child's sex, BMI-SDS and maternal prepregnancy overweight,[9,27] were tested in a multivariable logistic regression model. Results of the univariate analysis are reported either as numbers of cases and percentages or as medians with lower and upper quartiles, and those of multivariable analysis as odds ratios (OR) with 95% confidence intervals (CIs). Statistical significance was defined as p-value <0.05 or as OR 95% CI below or above 1.00 in the logistic regression. All analyses were performed using SPSS version 25.0 (IBM Corp.).

3 | RESULTS

3.1 | Child-related and perinatal factors

After exclusions, the final study cohort comprised 460 children (Figure S1). Their median age was 11.8 (interquartile range 9.1 and 14.2) years, and 43.5% were girls, 88.0% were obese, 47.0% were severely obese, and 49.6% had hypertension. Of the children, >90% were white Caucasians, and 98.0% were born from a singleton pregnancy. Children who were excluded due to lacking ALT measurement were comparable with included patients in age (median 11.5 years, $p=0.116$) and sex (35.1% girls, $p=0.178$), and prevalence of obesity (81.1%, $p=0.133$), severe obesity (47.3%, $p=0.957$), and hypertension (46.2%, $p=0.641$).

In total, 82 (17.8%) children fulfilled the criteria of MAFLD (Figure S1). The median ALT value in children with MAFLD was 66 (interquartile range 55 and 105) U/L and those without MAFLD 23[18,30] U/L. Children with MAFLD were older at first overweight-related healthcare visit than those without MAFLD. Children with and without MAFLD did not differ in gender, BMI-SDS, prevalence of hypertension, birth anthropometrics, Apgar scores or complications after birth (Table 1). In addition, the groups were comparable in ethnicity, being born small for gestational age, being from a singleton pregnancy or having received treatment for neonatal infection (data not shown).

3.2 | Maternal and pregnancy-related factors

The median prepregnancy BMI of the mothers (available from 250 individuals) was 27.7 (interquartile range 23.7 and 32.8). BMI was >25.0 in 65.4% and >30.0 in 40.5% of the mothers. Altogether 40.4% of the mothers were classified as lower level-employees,

TABLE 1 Comparison of child-related factors between 460 overweight/obese children with or without metabolic associated fatty liver disease (MAFLD).

	MAFLD, $n=82$			No MAFLD, $n=378$			
	Data available	Median	Q_1, Q_3	Available	Median	Q_1, Q_3	*p*-value
At the obesity visit							
Age, years	82	12.7	10.7, 14.5	378	11.6	8.7, 14.0	**0.002**
BMI-SDS	82	2.4	2.1, 2.7	378	2.5	2.2, 2.8	0.233
Boys (*n*, %)	82	51	62.2	378	209	55.3	0.253
Hypertension[a] (*n*, %)	68	33	48.5	309	154	49.8	0.845
After birth							
Birthweight, SD	81	0.1	−0.7, 1.0	375	0.3	−0.4, 1.0	0.821
Birth length, SD	81	0.2	−0.7, 0.8	374	0.2	−0.6, 0.9	0.695
Head circumference, SD	66	0.5	−0.6, 1.2	301	0.3	−0.4, 1.0	0.166
Ponderal index[b] at birth	82	27.8	26.4, 29.7	375	28.1	26.5, 30.0	0.409
1-min Apgar score	81	9	8, 9	374	9	8, 9	0.317
5-min Apgar score	69	9	9, 9	309	9	9, 9	0.158
Arterial umbilical cord pH	27	7.29	7.21, 7.37	162	7.29	7.22, 7.34	0.335
	MAFLD, $n=82$			No MAFLD, $n=378$			
	Data available	*n*	%	Available	*n*	%	*p*-value
Birthweight >2 SD	81	7	8.6	375	34	9.1	0.904
Macrosomia[c]	81	5	6.2	375	22	5.9	1.000
Birth length >2 SD	81	7	8.6	375	17	4.5	0.166
Head circumference >2 SD	66	5	7.6	301	24	8.0	0.914
Need for respiratory support	82	5	6.1	378	10	2.7	0.159
Need for neonatal ward or ICU	82	16	19.5	378	78	20.6	0.819
Neonatal hypoglycemia	82	8	10.0	378	30	8.0	0.587

Note: Bold numbers denote statistical significance.

Abbreviations: BMI-SDS, body mass index standard deviation score; ICU, intensive care unit, Q_1, Q_3, lower and upper quartiles; SD, standard deviation.

[a]Systolic or diastolic blood pressure >95th percentile.

[b]Weight/height^3.

[c]Birthweight >4.5 kg.

35.8% as manual workers, 6.6% as upper-level employees and 2.7% as self-employed, and 14.5% were either students, unemployed or on parental leave. Altogether, 1.5% of the mothers had prepregnancy diabetes and 1.4% chronic hypertension.

The majority of data was collected before universal screening for GDM in Finland, so OGTT results were available only for 21% of the mothers. The maternal median 2-h glucose value in OGTT was significantly higher and there was a trend for increased need for insulin treatment for GDM in mothers of children with MAFLD. Gestational hypertension was more common among mothers of children with MAFLD than in those without it, whereas the groups did not differ in maternal age, prepregnancy BMI, presence of overweight or obesity, weight gain or smoking during pregnancy, pregnancy duration, other OGTT measurements, placenta/birthweight ratio, parity, need for insulin-treatment for GDM or type of delivery (Table 2). The groups were also comparable in maternal employment status, presence of prepregnancy hypertension and diabetes, alcohol and illicit drug use, intrahepatic cholestasis of pregnancy, antenatal corticosteroid treatment and antibiotic use during labor (data not shown).

3.3 | Risk factors for MAFLD

Factors associated with MAFLD in offspring were age of the child at first overweight- or obesity-related healthcare visit, maternal smoking during pregnancy, gestational hypertension and pre-eclampsia (Figure 1). Smoking during pregnancy, gestational hypertension and pre-eclampsia were independent risk factors for MAFLD. Altogether, 7.4% of mothers who were smokers during pregnancy and 11.6% of nonsmokers had gestational hypertension or pre-eclampsia during pregnancy ($p=0.251$).

TABLE 2 Comparison of maternal and pregnancy-related factors between 460 overweight/obese children with and without metabolic-associated fatty liver disease (MAFLD).

	MAFLD, $n=82$			No MAFLD, $n=378$			
	Data available	Median	Q_1, Q_3	Data available	Median	Q_1, Q_3	*p*-value
Age at delivery, years	78	29.7	25.2, 33.5	353	29.2	25.6, 33.1	0.885
Pregestational BMI, kg/m^2	46	27.2	23.7, 33.6	223	28.3	23.6, 33.6	0.261
Weight gain in pregnancy, kg	35	11.0	6.0, 17.0	186	13.0	9.0, 18.1	0.133
Pregnancy duration, weeks	81	39.4	38.6, 40.7	376	39.9	38.8, 40.9	0.632
Gestational measurements							
Fasting glucose, mmol/L	18	4.9	4.4, 5.3	103	4.9	4.6, 5.3	0.564
1-h OGTT, mmol/L	18	9.8	6.4, 10.5	101	8.4	6.8, 10.0	0.304
2-h OGTT, mmol/L	16	6.9	6.6, 8.4	100	6.5	5.5, 7.5	**0.024**
Placenta/birthweight ratio, %	57	18.2	16.0, 19.6	266	17.5	15.6, 19.5	0.341
	MAFLD, $n=82$			No MAFLD, $n=378$			
	Data available	*n*	%	Data available	*n*	%	*p* value
Primiparous	81	24	29.6	376	125	33.2	0.529
Pregestational overweight	80	36	45.0	368	157	42.7	0.702
Smoked during pregnancy[a]	80	30	37.5	368	101	27.5	0.073
Gestational diabetes	23	18	78.3	138	95	68.8	0.361
Dietary treatment only	17	8	47.1	88	42	47.7	0.960
Oral medication	17	0	0	88	7	8.0	0.595
Insulin	17	6	35.3	88	12	13.6	0.071
Gestational hypertension	82	7	8.5	376	11	2.9	**0.018**
Pre-eclampsia	81	9	11.1	376	20	5.3	0.052
Cesarean section	82	14	17.1	378	59	15.6	0.816

Note: Bold numbers denote statistical significance.

Abbreviations: BMI, body mass index; OGTT, oral glucose tolerance test; Q_1, Q_3, lower and upper quartiles.

[a]Recorded if any.

4 | DISCUSSION

The main finding of the present case–control study was that maternal smoking during pregnancy and gestational hypertension and pre-eclampsia were associated with the development of MAFLD in overweight or obese children.

Previous research on the possible impact of maternal factors on the development of N/MAFLD is sparse. However, a recent Swedish study using national health register data[14] reported an association between pre-eclampsia and NAFLD, as diagnosed by liver biopsy, in offspring aged ≤25 years, although maternal obesity was the strongest independent risk factor for NAFLD. The main limitations of that study were the use of selectively performed biopsy to diagnose NAFLD, lacking data on gestational hypertension and no adjustment for child's BMI. As an indirect comparison, a recent meta-analysis reported an association between pre-eclampsia and an increased risk of childhood obesity,[28] whereas another meta-analysis found an association between gestational hypertension and childhood obesity.[29] In a Danish study using national health register data, maternal hypertensive disorders during pregnancy were associated with an increased risk of cardiovascular disease in the offspring in adulthood.[8] In addition to differences in study designs and outcomes used, the somewhat inconsistent results could be influenced by confounders. For instance, the associations of pre-eclampsia and gestational hypertension with obesity in childhood were attenuated after controlling for child's sex[28] and maternal BMI.[28,29]

A plausible mechanism for the associations of pre-eclampsia and gestational hypertension with MAFLD may be that they result in adverse vascular changes and placental hypoperfusion and thereby lead to fetal hypoxia and growth restriction.[30–33] Suboptimal oxygenation and growth of the fetus have been found to increase the offspring's risk of NAFLD in animal models[34,35] and in epidemiological studies.[11,12] Hence, albeit we found no difference in birth anthropometric measures between children with and without MAFLD, subclinical placental dysfunction may contribute to the observed associations of gestational hypertension and pre-eclampsia with MAFLD, and is an important area for future research. Other pathophysiological mechanism of MAFLD

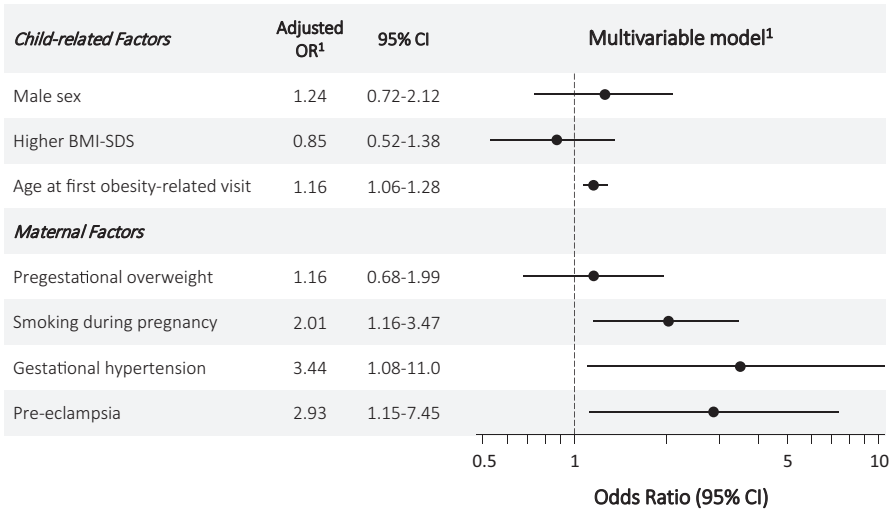

FIGURE 1 Multivariable logistic regression model including child-related and maternal factors for pediatric metabolic dysfunction-associated fatty liver disease (MAFLD) in 77 overweight or obese children with MAFLD and 350 overweight or obese children without it. [1]The model includes factors with a *p*-value of <0.1 in the univariate analysis (Tables 1 and 2) and suggested risk factors for MAFLD in the literature, including child's sex and BMI-SDS and maternal overweight. BMI-SDS, body mass index standard deviation score; CI, confidence interval; OR, odds ratio. Black dots denote odds ratios (ORs) and lines 95% confidence intervals (CIs) on a logarithmic scale.

in children could be, for example, metabolic and epigenetic priming.[36] Of note, the often undiagnosed maternal NAFLD may also predispose to hypertensive disorders in pregnancy,[37] and thus the observed associations could partially reflect inherited susceptibility to these conditions.[38]

Our findings are in line with the proven harmful impact of smoking on maternal and fetal health outcomes.[39,40] The above-mentioned Swedish study found an association between mother's smoking at least 10 cigarettes per day and an increased risk of NAFLD in their children.[14] Mice exposed to smoking during the fetal period also showed more advanced forms of fatty liver disease than those with no such exposure.[34] Moreover, maternal smoking during pregnancy may predispose children to pediatric obesity and metabolic syndrome.[41–44] It is challenging to distinguish causal effects of the observed association from other potentially harmful lifestyle factors. However, we found no difference in maternal socioeconomic status or substance use between children with MAFLD and those without it in our study, which supports an independent effect of smoking. Smoking could also interact with hypertensive disorders in several ways, but this is controversial as both predisposing and even protective effects of smoking have been reported.[45–47]

As regards to other pregnancy-related factors, our findings were in accordance with a recent systematic review which reported no associations of GDM, birth anthropometrics and prematurity with NAFLD in offspring.[9] There was also no association between GDM and NAFLD of offspring in the Swedish study.[13] However, we observed significantly higher maternal 2-h blood glucose values in OGTT and a trend for higher likelihood of insulin-treatment for GDM among children with MAFLD than among those without it. This implies that the mothers of affected offspring had a worse metabolic profile. Consistent with this finding, increased hepatic fat content has been reported in newborns exposed to maternal GDM.[48] Unfortunately, GDM screening was unsystematic during the early study period, and thus the number of mothers with GDM was too small for reliable analyses and conclusions. Contrary to our findings, increased maternal prepregnancy BMI has also been found to be an independent risk factor for childhood MAFLD in some studies.[8,13]

Altogether, assessing the associations of obesity, metabolic disturbances and smoking with pediatric MAFLD is challenging due to the complex interactions of these possible risk factors. For example, maternal overweight by itself has been found to be associated with an increased risk of hypertensive complications during pregnancy[49] and obesity in offspring.[50] Obesity, GDM and related dyslipidemia could increase the risk of fetal macrosomia,[51] whereas hypertensive complications and smoking may have an opposite effect on intrauterine growth. Interpretation of the results across studies is further complicated by varying methods used to assess the outcomes, examination of children in different age groups from infants to adolescents and varying prevalence of MAFLD among the children included.[10–12,14–16] Well-designed prospective studies are thus called for, although it must be realized that the hepatic abnormalities may develop only at a later age, and that studies requiring randomization for treatment of known risk factors during pregnancy are unethical.

The main strengths of our study were the well-defined cohort of children and their mothers and the availability of diverse gestational and perinatal factors. The risk of selection bias was reduced by including consecutive children referred to the hospital and excluding those with a hepatic comorbidity. Systematically measured ALT and BMI can also be considered less biased measures for MAFLD than

selectively performed imaging studies and biopsy.[13,17,52] The design used with clinical patient selection prevented quantitative evaluation of exposures and might have led to variable criteria for maternal conditions, although this was counterbalanced by systematically maintained patient records and nationwide guidelines.[53] Screening of GDM in particular has changed over time during the study period, as before 2008 it was assessed individually based on maternal risk factors and became systematic only after introduction of new national guidelines. Additional limitations are the lack of data on dietary factors, physical activity and the timing and intensity of smoking.[41] The ethnic and socioeconomic homogeneity of the Finnish population likely improves internal validity of the study but it also reduces generalizability of the results to more diverse populations and healthcare settings. Additionally, the study was conducted in a selected high-risk population obtained from clinical practice, which further limits the generalizability. In must also be emphasized that the criteria of MAFLD remain debated, and that optimal ALT values may differ depending, for example, on ethnicity, age and stage of puberty.

5 | CONCLUSION

We found that maternal gestational hypertension, pre-eclampsia and smoking were associated with the risk of MAFLD in overweight and obese children. We believe that our findings will help to design future studies to verify the observed associations between maternal factors and risk of pediatric MAFLD, as well as decipher possible biological mechanisms underlying these effects.

AUTHOR CONTRIBUTIONS

Hanna de Ruyter and Linnea Aitokari: Study design, data collection and analysis and drafting of the manuscript. Siiri Lahti and Hanna Riekki: Data collection and critical revision of the manuscript. Heini Huhtala: Study design, statistical analysis and critical revision of the manuscript. Hannele Laivuori and Timo Lakka: Study design and critical revision of the manuscript. Kalle Kurppa: Study design, study supervision and critical revision of the manuscript. No writing assistance was received. All authors approved the final version of the manuscript.

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CONFLICT OF INTEREST STATEMENT

All authors declare they have no conflicts of interest.

ETHICS STATEMENT

The study design and collection of health data were approved by the Tampere University Hospital and the Finnish Social and Health Data Permit Authority Findata (permission THL/246/14.02.00/2021, accepted February 4, 2022). Declaration of Helsinki was strictly followed in all stages. Informed consent from the study participants was not required based on national ethical and data processing regulations, since none of them were contacted during the study.[54]

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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