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REVIEW

- 1053 Impact of direct-acting antiviral regimens on hepatic and extrahepatic manifestations of hepatitis C virus infection
Salama II, Raslan HM, Abdel-Latif GA, Salama SI, Sami SM, Shaaban FA, Abdelmohsen AM, Fouad WA

MINIREVIEWS

- 1074 Second-line treatment of advanced hepatocellular carcinoma: Time for more individualized treatment options?
Rajappa S, Rau KM, Dattatreya PS, Ramaswamy A, Fernandes P, Pruthi A, Cheng R, Lukanowski M, Huang YH
- 1087 Metabolic-associated fatty liver disease from childhood to adulthood: State of art and future directions
Lanzaro F, Guarino S, D'Addio E, Salvatori A, D'Anna JA, Marzuillo P, Miraglia del Giudice E, Di Sessa A
- 1099 Liver dysfunction during COVID-19 pandemic: Contributing role of associated factors in disease progression and severity
Sahu T, Pande B, PL M, Verma HK
- 1111 Understanding fatigue in primary biliary cholangitis: From pathophysiology to treatment perspectives
Lynch EN, Campani C, Innocenti T, Dragoni G, Biagini MR, Forte P, Galli A
- 1120 Fibrosis regression following hepatitis C antiviral therapy
Elsharkawy A, Samir R, El-Kassas M

ORIGINAL ARTICLE**Basic Study**

- 1131 COVID-19 liver and gastroenterology findings: An *in silico* analysis of SARS-CoV-2 interactions with liver molecules
Peiter GC, de Souza CBT, de Oliveira LM, Pagliarin LG, dos Anjos VNF, da Silva FAF, de Melo FF, Teixeira KN

Case Control Study

- 1142 Clinical outcomes of coronavirus disease 2019 in liver transplant recipients
Shafiq M, Gibson C

Retrospective Cohort Study

- 1150 Intensive care unit readmission in adult Egyptian patients undergoing living donor liver transplant: A single-centre retrospective cohort study
Salah M, Montasser IF, El Gendy HA, Korraa AA, Elewa GM, Dabbous H, Mahfouz HR, Abdelrahman M, Goda MH, Bahaa El-Din MM, El-Meteini M, Labib HA

- 1162 Impact of alcohol consumption on treatment outcome of hepatocellular carcinoma patients with viral hepatitis who underwent transarterial chemoembolization

Rattanasupar A, Chang A, Prateepchaiboon T, Pungpipattrakul N, Akarapatima K, Songjamrat A, Pakdeejit S, Prachayakul V, Piratvisuth T

Retrospective Study

- 1173 Relationship between phase angle, steatosis, and liver fibrosis in patients coinfecting with human immunodeficiency virus/hepatitis C virus

Fernandes SA, Tovo CV, da Silva ALM, Pinto LP, Carteri RB, Mattos AA

- 1182 DNA and RNA oxidative damage in hepatocellular carcinoma patients and mortality during the first year of liver transplantation

Lorente L, Rodriguez ST, Sanz P, González-Rivero AF, Pérez-Cejas A, Padilla J, Díaz D, González A, Martín MM, Jiménez A, Cerro P, Portero J, Barrera MA

- 1190 Direct-acting antivirals for hepatitis C virus-infected patients with hepatocellular carcinoma

Tajiri K, Ito H, Kawai K, Kashii Y, Hayashi Y, Murayama A, Minemura M, Takahara T, Shimizu Y, Yasuda I

- 1200 Use of doppler ultrasound to predict need for transjugular intrahepatic portosystemic shunt revision

Duong N, Healey M, Patel K, Strife BJ, Sterling RK

Observational Study

- 1210 Gut dysbiosis and body composition in cirrhosis

Maslennikov R, Ivashkin V, Alieva A, Poluektova E, Kudryavtseva A, Krasnov G, Zharkova M, Zharikov Y

- 1226 Prevalence of nonalcoholic fatty liver disease and its association with age in patients with type 2 diabetes mellitus

Yamane R, Yoshioka K, Hayashi K, Shimizu Y, Ito Y, Matsushita K, Yoshizaki M, Kajikawa G, Mizutani T, Watarai A, Tachi K, Goto H

SYSTEMATIC REVIEWS

- 1235 Factors early in life associated with hepatic steatosis

Quek SXZ, Tan EXX, Ren YP, Muthiah M, Loo EXL, Tham EH, Siah KTH

META-ANALYSIS

- 1248 Efficacy and safety of sofosbuvir/velpatasvir with or without ribavirin in hepatitis C genotype 3 compensated cirrhosis: A meta-analysis

Loo JH, Xu WXF, Low JT, Tay WX, Ang LS, Tam YC, Thuraiajah PH, Kumar R, Wong YJ

- 1258 Spontaneous bacterial empyema in cirrhosis: A systematic review and meta-analysis

Reiche W, Deliwala S, Chandan S, Mohan BP, Dhindsa B, Ramai D, Perisetti A, Rangray R, Mukherjee S

ABOUT COVER

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WJH mainly publishes articles reporting research results and findings obtained in the field of hepatology and covering a wide range of topics including chronic cholestatic liver diseases, cirrhosis and its complications, clinical alcoholic liver disease, drug induced liver disease autoimmune, fatty liver disease, genetic and pediatric liver diseases, hepatocellular carcinoma, hepatic stellate cells and fibrosis, liver immunology, liver regeneration, hepatic surgery, liver transplantation, biliary tract pathophysiology, non-invasive markers of liver fibrosis, viral hepatitis.

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Factors early in life associated with hepatic steatosis

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Abstract

BACKGROUND

The rise in prevalence of non-alcoholic fatty liver disease (NAFLD) mirrors the obesity epidemic. NAFLD is insidious but may gradually progress from simple steatosis to steatohepatitis, fibrosis and cirrhosis and/or hepatocellular carcinoma. Intervention strategies to ameliorate developmental programming of NAFLD may be more efficacious during critical windows of developmental plasticity.

AIM

To review the early developmental factors associated with NAFLD.

METHODS

Databases MEDLINE *via* PubMed, and EMBASE and Reference Citation Analysis were searched and relevant publications up to April 30, 2021 were assessed. Original research studies that included risk factors associated with early development of NAFLD in human subjects were included. These factors include:

Maternal factors, intrauterine and prenatal factors, post-natal factors, genetic and ethnic predisposition, childhood and adolescence environmental factors. Studies were excluded if they were review articles or animal studies, case reports or conference abstracts, or if NAFLD was not clearly defined and assessed radiologically.

RESULTS

Of 1530 citations identified by electronic search, 420 duplicates were removed. Of the 1110 citations screened from title and abstract, 80 articles were included in the final analysis. Genetic polymorphisms such as patatin-like phospholipase domain-containing protein 3 (PNPLA3) and membrane-bound O-acyltransferase domain-containing protein 7 (MBOAT7) were associated with increased risk of NAFLD. Familial factors such as maternal obesogenic environment and parental history of hepatic steatosis was associated with offspring NAFLD. Longer duration of exclusive breastfeeding in infancy was associated with a lower risk of developing NAFLD later in life while metabolic dysfunction and/or obesity in adolescence was associated with increased risk of NAFLD. Studies relating to socioeconomic factors and its association with NAFLD reported confounding results.

CONCLUSION

Maternal metabolic dysfunction during pregnancy, being exclusively breastfed for a longer time postnatally, diet and physical activity in childhood and adolescence are potential areas of intervention to decrease risk of NAFLD.

Key Words: Epidemiology; Natural history; Obesity; Fatty liver; Developmental

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Core Tip: Prevalence of non-alcoholic fatty liver disease (NAFLD) in adolescents has more than doubled in the last two decades, with its downstream complications placing an increasing burden on healthcare systems globally. The aim of this study is to review the early developmental factors associated with NAFLD and potentially identify areas where intervention can be made to halt the progress to steatohepatitis, fibrosis and cirrhosis and/or hepatocellular carcinoma which may develop later in life.

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INTRODUCTION

The global prevalence of non-alcoholic fatty liver disease (NAFLD) is approaching 30%, in keeping with the growing obesity epidemic[1]. With rising obesity rates worldwide, the prevalence of NAFLD is set to increase markedly in the near future. The pathogenesis of NAFLD has been considered to be a “multi-hit” disease, where epigenetic, genetic, and environmental factors may interplay to cause progressive disease. The initial hit in this multifactorial process may be early in life – during pre-conception, in-utero, infancy and early childhood[2]. For example, the predictive adaptive response hypothesis has been proposed to explain the phenomenon where poor conditions during childhood increase the risk of metabolic diseases later in life[3,4]. Being aware of factors associated with early development of NAFLD allows physicians to alter the natural course of disease progression, be it through lifestyle or pharmacological interventions. This is made even more important as the mainstay of treatment of NAFLD at present is weight loss, which is often difficult to achieve and sustain[5]. Interventional strategies to ameliorate the developmental programming of NAFLD may thus potentially be more efficacious during the critical windows of developmental plasticity, negating the need for strategies to reverse NAFLD later in life. This systematic review aims to review the early developmental factors associated with NAFLD. These factors include maternal and paternal factors, intrauterine factors, postnatal factors such as breastfeeding, lifestyle factors in adolescence including sleep, physical activity, nutrition and presently still non-modifiable factors such as genetic polymorphisms.

MATERIALS AND METHODS

Search strategy and data extraction

The study was carried out using the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) standards (Supplementary Table 1). A comprehensive search of databases and conference proceedings to identify all relevant studies up to April 30, 2021, was performed. The following electronic databases were searched: Medline *via* PubMed, Embase, and Reference Citation Analysis. We use both text words and medical subject heading terms. The literature search strategy was adapted to suit each database. Our study was only restricted to full text articles in English language. For example, on PubMed, we used the combination of the following medical subject heading terms: "non-alcoholic fatty liver disease" and "Risk" and "maternal-fetal relations" or "maternal nutritional physiological phenomena" or "maternal exposure" or "maternal-fetal exchange" or "maternal behavior" or "obesity, maternal" or "maternal age" or "maternal inheritance" or "maternal health" or "educational status" or "pregnancy complications, infectious" or "gestational weight gain" or "perinatal care" or "prenatal nutritional physiological phenomena" or "prenatal care" or "prenatal education" or "prenatal exposure delayed effects" or "prenatal diagnosis" or "embryonic and fetal development" or "growth and development" or "fetal weight" or "pregnancy" or "fetal therapies" or "parents" or "parent-child relations" or "paternal exposure" or "paternal behavior" or "paternal age" or "nutrition assessment" or "child nutrition disorders" or "nutrition disorders" or "infant nutrition disorders" or "diet, food, and nutrition" or "nutritional physiological phenomena" or "fetal nutrition disorders" or "child nutrition sciences" or "nutritional status" or "nutritional sciences" or "adolescent nutritional physiological phenomena" or "exercise".

The methods for data collection and analysis were based on the Cochrane Handbook of Systematic Reviews for Interventions. Corresponding authors were contacted through electronic mail for clarification when required. Literature search and data review was performed using a case report form independently by pairs of investigators (SQ, ET, RYP) and each article was independently inspected to verify that they met the pre-specified inclusion criteria. Duplicates were excluded. Discordance during the data extraction process was resolved by consensus between the two reviewers and or consultation with a third and senior investigator (ET, KS). The study selection process is summarized in Figure 1.

Inclusion and exclusion criteria

Original research studies that included risk factors associated with early development of NAFLD in human subjects were included in this study. The risk factors of particular interest included: maternal factors, intrauterine and prenatal factors, post-natal factors, genetic and ethnic predisposition, childhood and adolescence environmental factors – such as (but not limited to) nutrition and physical activity. Studies were excluded if they were review articles or animal studies, case reports or conference abstracts, or if NAFLD was not clearly defined in the study. Definition of hepatic steatosis in this review was based on hepatic ultrasound, computed tomography or magnetic resonance imaging.

RESULTS

Search results

Of 1530 citations identified by electronic search, 420 duplicates were removed. Of the 1110 citations screened from title and abstract, 957 articles were excluded. Full text review of the 150 potentially relevant citations was performed to assess eligibility for inclusion into study and 70 reports were excluded. 80 articles were included in the final analysis (Figure 1).

Maternal, paternal factors and intrauterine factors

Seven articles included assessment of maternal, paternal and intrauterine factors on the risk of development of NAFLD. Maternal diabetes and pre-natal obesity was associated with increased odds of offspring NAFLD[6] (Supplementary Table 1). This was also reported in Patel *et al*[7]'s study of 1215 patients, where maternal diabetes was found to be associated with offspring NAFLD, with an adjusted odds ratio (OR) of 6.74 (95%CI 2.47-18.40). Moreover, a higher pre-pregnancy body mass index (BMI) was associated with greater odds of fatty liver in offspring, even when adjusted for confounding factors, with adjusted OR 2.72 (95%CI 1.20-6.15, $P < 0.001$). Similarly, in a study from Australia[6], which studied NAFLD in adolescents at the age of 17 years, prevalence of NAFLD was associated with maternal obesity and maternal weight gain ≥ 6.0 kg by 18th week of gestation. These studies suggest that the in-utero environment can be associated with development of NAFLD later in life. On the contrary, a smaller study by Rajindrajith *et al*[8] reported in 499 adolescents that maternal or paternal history of metabolic syndrome was not associated with NAFLD.

Parental diagnosis of fatty liver was also associated with NAFLD in offspring. Long *et al*[9] reported that a larger proportion of patients with parental history of hepatic steatosis was diagnosed with hepatic steatosis (21.3% *vs* 12.6%, $P = 0.004$). After adjustment for confounding factors such as insulin resistance,

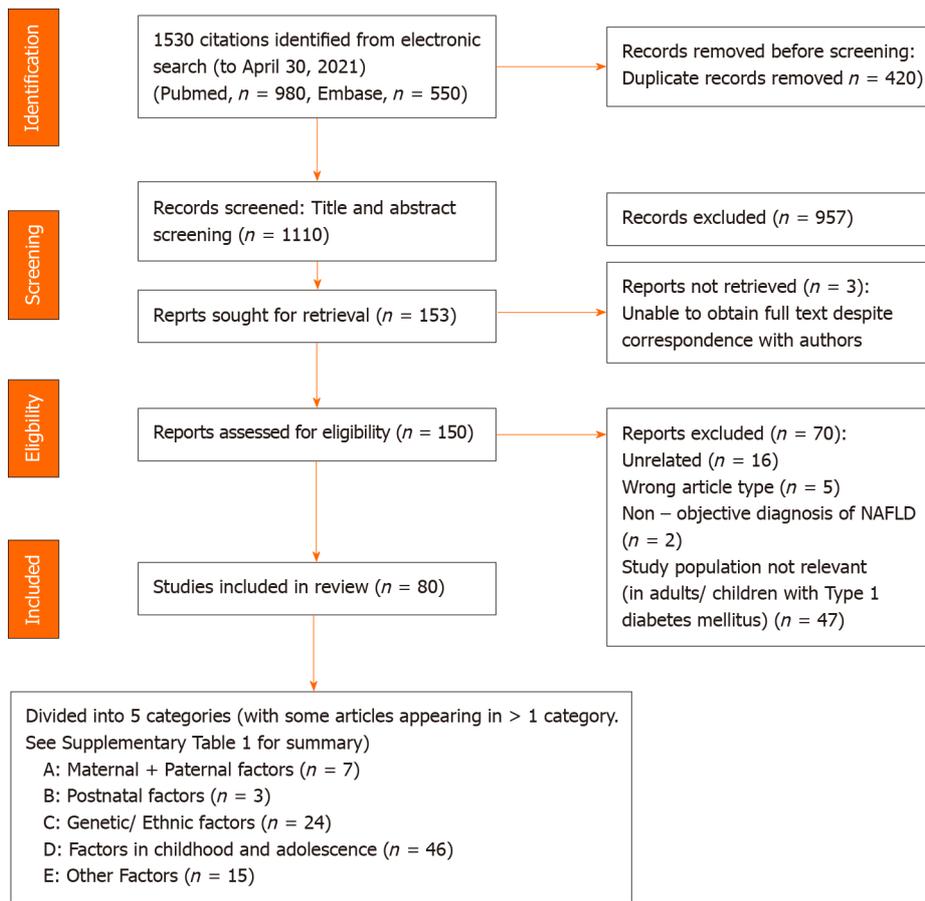


Figure 1 PRISMA flow diagram.

BMI, age and gender, the odds of hepatic steatosis in an individual remained increased in individuals with at least one parent diagnosed with hepatic steatosis. Similar findings were reported in a study from India[10], which included 99 subjects. The authors reported that presence of NAFLD in one and two parents increased the odds of an offspring being diagnosed with NAFLD by 3.9 and 6.7 times respectively. Long and colleagues found that parental history of hepatic steatosis was only a significant risk factor for NAFLD among subjects without cardiometabolic risk factors: (16.1% vs 5.2%, $P < 0.001$) in those with no cardiometabolic coexisting disease compared to (30.3% vs 28.5%, $P = 0.78$) in patients with cardiometabolic risks[9].

Malnutrition pre- and postnatally was reported in two studies to be associated with prevalence of NAFLD in offsprings[6,11,12]. A study from China studied 8752 patients and classified them into various categories in relation to the Great Chinese famine in 1959-1961. They analysed the prevalence of various metabolic diseases in relation to famine exposure. In that study, authors found that the prevalence of NAFLD was higher in participants born around the time of the Great Chinese famine; prenatally (born 1960-1961) and postnatally (born 1957-1958) exposed subjects, compared to those who were non-exposed (born 1963-1964): Prevalence 23.0%, 22.9%, 17.3% respectively ($P = 0.02$). Consequently, the adjusted OR of offspring NAFLD in prenatally and postnatally exposed compared to non-exposed women for NAFLD were 2.42 (95%CI 1.14-5.16) and 1.61 (95%CI 1.29-2.01) respectively ($P < 0.05$).

Other socioeconomic factors at time of birth may be associated with NAFLD development however there is heterogeneity in available literature. For example, Ayonrinde *et al*[11] reported that lower socioeconomic status at birth was significantly associated with increased risk of NAFLD in male adolescents residing in Australia. On the other hand, a study from Sri Lanka by Rajindrajith *et al*[8] that studied 499 adolescents found that parental highest education and family income were not associated with NAFLD in adolescents.

Postnatal factors

Five studies examined postnatal factors associated with NAFLD (Supplementary Table 2). Duration of breastfeeding was negatively associated with NAFLD. Rajindrajith *et al*[8] reported more subjects who had NAFLD were breastfed less than four months, compared to non-NAFLD subjects (33.3% vs 17.1%, $P = 0.02$). A similar finding was reported from an Australian cohort, where exclusive breastfeeding in

excess of six months was associated with decreased odds of NAFLD development at adolescence (OR 0.64, 95%CI 0.43-0.94, $P = 0.02$)[11] which persisted after adjustment for adolescent dietary patterns. Moreover, breastfeeding without supplementary milk for ≥ 6 mo compared with < 6 mo was associated with decreased prevalence of severe steatosis (3.5% vs 7.7%, $P = 0.005$). Additionally, some studies[13, 14] have also reported that a more rapid increase in weight in early life is associated with NAFLD. However, these studies have not been included in this systematic review, as the diagnosis of hepatic steatosis was not determined by imaging a priori.

Factors in childhood and adolescence

45 studies reported factors in childhood and adolescence that are associated with NAFLD (Supplementary Table 3). We have further divided this section into obesity as defined by BMI, other anthropometric factors, metabolic dysfunction, dietary, physical activity and sleep, and menarche in females.

Obesity (BMI) and changes in weight: A BMI > 25 kg/m² in Sri Lankan adolescents was shown by Rajindrajith *et al*[8] in a study to be significantly associated with NAFLD. Adolescents with NAFLD also had a higher amount of total body fat ($P < 0.001$) and subcutaneous fat ($P < 0.001$) than those without NAFLD. Studies from China also supported these findings[15,16]. For example, Yan *et al*[16], in a cohort study of 1350 subjects, reported that overweight or obese children were more likely to develop NAFLD in adulthood: males and females OR 2.49 (95%CI 1.51-4.11) and OR 3.34 (95%CI 1.77-6.29) respectively, $P < 0.001$. However, in a cohort of 242 adolescents undergoing bariatric surgery of which 59% had NAFLD, Shulman *et al*[17] showed that the presence of more severe stages of NAFLD on liver biopsy was not associated with BMI in this obese cohort.

It has been widely reported in adult NAFLD literature that weight gain was strongly associated with NAFLD. Interestingly, Virtue *et al*[18] found that a gain in BMI from 7 to 13 years of age conferred an increased risk of NAFLD and suggested that this increased risk may be irrespective of initial or attained BMI. In this large study population of 244464 children, adjusting for BMI z-score at age 7 years, the hazard ratio of adult NAFLD was 1.15 (95%CI 1.05-1.26) and 1.12 (95%CI 1.02-1.23) per 1-unit gain in BMI z-score in males and females, respectively. Importantly, the increased odds of development of NAFLD seen in obese children may potentially be ameliorated by obtaining a normal BMI by adulthood [16].

Other anthropometric/body fat measurements: Obese adolescents with NAFLD may have a different composition compared to those without NAFLD – with greater fat body mass and visceral fat compared to those without NAFLD[19]. Besides waist circumference, other measurements such as subcutaneous adipose tissue (SCAT), intra-abdominal adipose tissue (IAAT), and anthropometric measurements including suprailiac skinfold thickness and neck circumference were shown to be associated with NAFLD. Silveira *et al*[20] studied 182 obese sedentary children and adolescents and showed that a higher IAAT but not SCAT was positively associated with NAFLD. In another study of adolescent girls, suprailiac skinfold thickness was found to be independently associated with NAFLD (OR 1.14, 95%CI 1.08-1.20, $P < 0.001$)[21]. Peña-Vélez *et al*[22] reported neck circumference was larger in NAFLD pediatric patients compared to those without NAFLD ($P < 0.001$) and this was found to be an independent risk factor in multivariate analysis (OR 1.172, 95%CI 1.008-1.362, $P = 0.038$).

Metabolic dysfunction: Metabolic syndrome was shown to be associated with NAFLD, highlighted in four studies. In a study by Rajindrajith *et al*[8] consisting of 499 adolescents, 8.2% with NAFLD living in an urban Sri Lankan community, more children with NAFLD were found to have metabolic derangements as compared to those without (85.8% vs 26.3% in controls, $P < 0.0001$). In this study, children with NAFLD had a significantly higher waist circumference, homeostatic model assessment for insulin resistance (HOMA-IR) result and hypertriglyceridemia. These results were mirrored by other studies from Poland, Egypt and Italy[23-25]. In the study by Prokopowicz *et al*[23], which studied 108 obese hospitalized children in Poland, fasting insulin concentration was the strongest independent factor associated with NAFLD. Alkassabany *et al*[24] reported that the odds for NAFLD increased in school children aged 6 to 18 years with an increased number of components of metabolic syndrome. When there were three or more components of metabolic syndrome, the OR of NAFLD was 158.3 (95%CI 87.4-202.9, $P < 0.05$)[24] as compared to school children without any components of the metabolic syndrome.

Most studies that investigated associations of insulin resistance and NAFLD reported a positive association with a few exceptions[19,21,26-28]. Pre-diabetes and diabetes was associated with a two-fold increased risk in non-alcoholic steatoph hepatitis (NASH)[25]. In a group of 520 obese children in China, it was also reported that high levels of fasting c-peptide was independently associated with NAFLD[29]. In another study, insulin like growth factor 1 (IGF-1) standard deviation scores (IGF-1 SDS) was significantly lower in adolescents with NAFLD as compared to the control group (OR 0.727, 95%CI 0.559-0.946, $P = 0.017$)[27]. In contrast, Jimenez-Rivera *et al*[28] reported in their study of 97 obese children that while median triglyceride (TG) level was higher in those with NAFLD (1.5 ± 0.9 vs 1.1 ± 0.5 mmol/L, $P = 0.01$), other factors such as HOMA-IR, hyperlipidemia and BMI were not associated with NAFLD. NAFLD was more prevalent in girls with polycystic ovarian syndrome (PCOS) compared to

girls without (37.5% *vs* 15.1%, $P = 0.003$), and PCOS was found to be independently predictive of NAFLD (OR 2.99, 95%CI 1.01-8.82, $P = 0.048$)[22].

Dietary: NAFLD is predominantly a condition associated with net caloric excess. Thus it is unsurprising that total calorie intake was found to be significantly higher in overweight children with NAFLD compared to similarly overweight children without NAFLD by (approximately 250 kcal per day)[30]. Dissecting down to the type of macronutrient composition and its association with NAFLD, the total intake of carbohydrates trended higher in overweight children with NAFLD than those without (approximately 120 kcal per day). In particular, intakes of fructose[31] and glucose were higher in overweight children with NAFLD than those without, whereas intake of fat protein and fiber was similar. Similarly, Félix *et al*[32] also showed that high amounts of refined carbohydrates in diet was independently associated with the presence of NAFLD (OR 2.17, 95%CI 1.05-6.82, $P = 0.038$). Mosca *et al* [31] studied 271 biopsy-proven NAFLD obese children and found that fructose consumption in this group of patients was independently associated with NASH (OR 1.612, 95%CI 1.25-1.86, $P = 0.001$) after adjustment for confounders[31]. In a study from India performed on 242 undergraduate students, soft drink consumption was associated with NAFLD. The prevalence of NAFLD was 75% in the group who consumed ≥ 2 soft drinks per day, 16% in the group that consumed 1 soft drink per day and 4% in the group that consumed < 1 soft drink per day ($P = 0.001$). Importantly, Siddiqi and colleagues found no differences in baseline metabolic risks in those who consumed diet soft drinks which are often marketed as a healthier alternative, *vs* regular soft drinks in that study[33].

A Western diet, which is generally characterized by high intakes of take-away foods, red and processed meats, full-fat dairy products, fried potatoes, refined sugars and soft drinks, has been shown to be associated with a higher risk of NAFLD[34]. Liu *et al*[35] compared different types of diets (Chinese *vs* Western *vs* High Energy) of 1639 participants in Shandong Province, China. After adjustment for confounders, those with traditional Chinese dietary pattern had the lowest risk (OR 0.726, 95%CI 0.383-0.960, $P < 0.05$), while the Western dietary pattern was associated with an increased risk of NAFLD (OR 1.197, 95%CI 1.013-1.736, $P < 0.01$). On the contrary, in a study of 1170 adolescents in Australia, neither a Western dietary nor healthy dietary pattern at age 14 was associated with NAFLD at 17 years of age. Only in a subgroup of obese adolescents was a Western dietary pattern at 14 years significantly associated with NAFLD at age 17 years (OR 1.45, 95%CI 1.05-2.00, $P = 0.03$). Nevertheless, this became insignificant when it was further adjusted for duration of breastfeeding and maternal obesity[11].

The Mediterranean diet is beneficial in the treatment of NAFLD and has been included in guidance for adult NAFLD[36]. However, this has not been widely studied in pediatric literature. Della Corte *et al* [37] studied 243 obese children and performed liver biopsy on 100 out of 166 children who had hepatic steatosis on ultrasound. In that study, it was found that low adherence to Mediterranean diet was significantly higher in patients with NASH compared with patients without NASH or hepatic steatosis. Similar findings were reported in two other studies[38,39]. Moreover, poor adherence to Mediterranean diet was also correlated with liver damage, liver inflammation and fibrosis[37].

Docosahexaenoic (DHA) supplementation was studied in a double blind, parallel group placebo-controlled randomized trial by Pacifico *et al*[40]. The final analysis at 6 mo showed that liver fat was reduced by 53.4% (95%CI 33.4-73.4) in the group that received DHA supplementation, as compared with 22.6% (95%CI 6.2-39.0) in the placebo group ($P = 0.04$). Other metabolic factors such as fasting insulin and TG were also significantly reduced in the group treated with DHA supplementation.

Physical activity and sleep: A sedentary lifestyle was shown to be associated with an increased risk of NAFLD. Nier *et al*[30] compared normal weight healthy children with overweight children with NAFLD in Southern Germany aged 5 to 9 years. Normal weight children on average spent 140 min per day compared to overweight children with NAFLD who spent approximately 215 min per day on sedentary activities (*i.e.* handcrafting, drawing, reading, watching television or playing video games). While the previous study may be confounded by participants' BMI, Félix *et al*[32] also reported that a sedentary lifestyle was a significant independent predictive factor of NAFLD in a study population that only included obese children (OR 3.35, 95%CI 1.97-11.76, $P = 0.006$). In another study by Trovato and colleagues, on multiple regression sleep shortage and wearing over-sized clothing was shown to be associated with NAFLD[39].

Menarche: Ryu *et al*[41] conducted a cross sectional study involving 76415 women, 9601 of whom were diagnosed with NAFLD and an inverse association between age of menarche and development of NAFLD was seen. The prevalence ratios for NAFLD for early menarche and menarche at 12, compared with menarche at 13 years were: 1.26 (95%CI 1.14-1.39) and 1.04 (95%CI 0.97-1.12) respectively, whereas prevalence ratio of menarche at 14, 15, and 16 to 18 years compared with menarche at 13 years were 0.94 (95%CI 0.89-1.00), 0.91 (95%CI 0.86-0.97), and 0.83 (95%CI 0.78-0.89), respectively ($P < 0.001$). Even adjusting for other variables, the association between time of menarche and NAFLD persisted. Similarly, Mueller *et al*[42] reported in their study of 1214 women that one-year earlier menarche was associated with higher prevalence of NAFLD at young adulthood even after adjustment for body weight (RR 1.15, 95%CI 1.07-1.24, $P < 0.05$).

Genetic and ethnic factors associated with NAFLD

Gene polymorphisms: Several gene polymorphisms were found to be associated with NAFLD and have been extensively reported in adult NAFLD (Supplementary Table 4). Patatin-like phospholipase domain-containing protein 3 (PNPLA3) is the most widely reported. Other polymorphisms reported in the included studies in this review include: Transmembrane 6 Superfamily Member 2 (TM6SF2), heme-oxygenase-1 (HO-1), and membrane-bound O-acyltransferase domain-containing protein 7 (MBOAT7).

PNPLA3 polymorphisms and its association with NAFLD in children and adolescents were reported in several studies[25,43]. A study of 230 Italian children with obesity reported that homozygous PNPLA3 carriers (GG genotype) showed the highest risk of NAFLD (OR 14.9, 95%CI: 4.3-51.5, $P < 0.001$). In a study comprising 1010 adolescents, Grandone *et al*[43] found that the E167K allele of TM6SF2 gene was associated with hepatic steatosis ($P < 0.0001$). Interestingly in subjects homozygous for the PNPLA3 148M allele, carrying this rare variant of TM6SF2 showed increased odds of 12.2 (CI 3.8-39.6, $P \leq 0.001$) to have raised alanine transaminase (ALT) as compared to the remaining patients[43]. This is further substantiated by Zusi and colleagues[44], who found in their cohort of 514 obese children and adolescents that genetic variants in TM6SF2 rs58542926, Glucokinase regulatory protein (GCKR) rs1260326, PNPLA3 rs738409, and Elongation of Very Long chain fatty acids-2 (ELOVL2) rs2236212 were significantly associated with a higher risk of NAFLD. These genetic variants in TM6SF2, GCKR and PNPLA3 were also found to be independently associated with NAFLD.

Multiple studies also reported associations with the MBOAT7 gene. A study by Di Sessa *et al*[45] found that carriers of the MBOAT7 T allele showed both significantly higher ALT and Pediatric NAFLD Fibrosis Index (PNFI) values compared to non-carriers. The MBOAT7 rs641738 variant was also found to exert an additive effect with PNPLA3 and TM6SF2 variants on NAFLD risk in obese children. Other variants in the MBOAT7 gene were found not to be associated NAFLD, such as with the rs641738 single nucleotide polymorphism (SNP) as reported by Lin *et al*[46]. Additionally, Di Costanzo *et al*[25] reported no association identified between hepatic fat content and MBOAT7 genotypes. In addition, the HO-1 gene promoter polymorphism was found to play an important role in the development of NAFLD. Chang *et al*[47] reported that patients 6 to 17 years with L alleles to the HO-1 gene were at higher risk of developing pediatric NAFLD (OR 18.84, 95%CI 1.45-245.22, $P = 0.025$). SNPs analysed and found not to be associated with risk of NAFLD include rs62064119, rs2297508, rs11868035 and rs13306741 in the sterol regulatory element binding protein 1c (SREBP1c) gene as reported by Peng *et al*[48].

Ethnic factors associated with NAFLD in adolescence and adulthood: Few ethnic factors were also found to be associated with NAFLD. In a study conducted by Younossi *et al*[49] in the US, 11613 participants aged 20 or older were enrolled and assessed according to four major racial or ethnic groups: non-Hispanic whites, non-Hispanic blacks, Hispanics, and "Other," (Aleut, Eskimo, American Indian, Asian, or Pacific Islander). Multivariate analysis showed that NASH was independently associated with being Hispanic, having a younger age, and having components of metabolic syndrome such as hypertension ($P < 0.05$). On the other hand, smaller studies such as Lee *et al*[50] from Canada found in a study of 57 children analysing age, ethnicity, total body fat, fat-free mass, visceral fat, abdominal subcutaneous fat, and cardiorespiratory fitness, 'visceral fat' was the only factor to be independently associated with increased odds of having hepatic steatosis (OR 1.12, 95%CI 1.04-1.21, $P = 0.003$).

Gut microbiota

NAFLD is associated with gut microbiota dysbiosis, which has been associated with increased intestinal permeability (Supplementary Table 5). Circulating zonulin levels, a known mediator of intestinal permeability and modulating intracellular tight junctions is increased in children with NAFLD. Circulating zonulin is also significantly correlated with histological severity of hepatic steatosis[51]. Lipopolysaccharide-binding protein (LBP), possible surrogates of intestinal barrier function, were found to be significantly higher in overweight children with NAFLD than in those without[30]. In another study from Romania, Belei and colleagues investigated small intestinal bacterial overgrowth (SIBO) by glucose hydrogen breath test in 445 children[52]. NAFLD was detected in 28 of 47 (59.5%) of the SIBO positive obese group, compared to only 8 of 78 (10.2%) of the SIBO negative obese group ($P < 0.001$) and 0/120 (0%) non-obese group ($P < 0.001$).

Miscellaneous factors

Other markers that have been studied in relation to NAFLD include serum 25-Hydroxyvitamin D levels uric acid levels. Two studies reported the association of serum 25-hydroxyvitamin D and NAFLD (Supplementary Table 5). The first study conducted in West Australia involved 994 adolescents, where vitamin D concentrations were measured at ages 14 and 17 years and liver ultrasonography was done at 17 years to diagnose NAFLD. In the cohort, 16% ($n = 156$) had NAFLD, of which 51% and 17% had insufficient or deficient vitamin D status respectively[53]. Lower serum vitamin D concentrations at 17 years were significantly associated with NAFLD (independent of BMI and insulin resistance OR 0.74, 95%CI 0.56-0.97, $P = 0.029$). The second study conducted in Turkey[54] reported 87 obese adolescents ($n = 42$ with NAFLD) also showed an association of serum vitamin D and NAFLD. The group of adolescents with NAFLD had significantly lower measurements of serum vitamin D than the non-NAFLD group (29.5 ± 18.4 vs 41.0 ± 17.9 ng/mL, $P < 0.001$).

Four studies described the association of serum uric acid levels and NAFLD. Two studies reported uric acid to be independently associated with histologically more advanced NAFLD after adjustment for measured confounders[27,31]. On the contrary, in a cross-sectional study including 129 obese children and adolescents, authors found no significant association between high levels of uric acid and NAFLD. Instead, in that study, uric acid levels was only associated with the presence of metabolic syndrome and age range. However, the severity of NAFLD was not further characterised in this study[55].

DISCUSSION

Prevalence of NAFLD in adolescents has more than doubled in the last two decades[56]. Without early intervention, young patients with NAFLD can also develop steatohepatitis and finally decompensated cirrhosis and/or hepatocellular carcinoma later in life. Here, we have reported several studies which suggest that a maternal obesogenic environment has been associated with NAFLD in offspring. Lifestyle factors in early childhood and adolescence such as a sedentary lifestyle, sleep deficit and/or a high calorie, high carbohydrate diet are also factors associated with hepatic steatosis; while a longer period of exclusive breastfeeding, a Mediterranean diet and DHA supplementation appears to be protective. In the studies looking at gene polymorphisms, we also see that even among those who are obese and have metabolic risk factors, there are gene polymorphisms (PNPLA3, TM6SF2, HO-1 and MBOAT7) that increase the risk of NAFLD.

NAFLD may be the first silent manifestation of metabolic syndrome and predictive of other metabolic diseases, which contribute to adverse health outcomes. Metabolic syndrome and NAFLD is often linked to nutrient excess and obesity, though not all that are obese are metabolically unhealthy and vice versa. The adipose tissue expandability hypothesis by Virtue and Puig suggests that capacity to store lipids by expanding adipose tissue is variable in different individuals. When capacity is reached, adipose tissue then gets stored in ectopic tissues like the muscle and liver. Increase in visceral adipose tissue appears to be associated with metabolic disorders[17]. This concept suggests that instead of obesity in general, fat distribution, adipose tissue functionality and presence of insulin resistance are the likely key drivers of metabolic syndrome and NAFLD[18], which often exist as a continuum.

At present, there are no current FDA approved pharmacological agents to treat NAFLD. A 7%-10% weight loss is the first line treatment for adult NAFLD, which is often challenging, and difficult to maintain. Developmental plasticity is the ability where a given genotype may produce different phenotypes in response to different environments[57,58]. An exposure to a suboptimal condition during critical period of developmental programming can result in a diseased state. It is thought that the programmable windows of human obesity, which is tightly associated with NAFLD, may exist during periods of greatest weight velocity[59]. Thus, it is imperative to also target these modifiable factors associated with NAFLD early in life.

A maternal obesogenic environment has been associated with NAFLD in offspring *via* various potential mechanisms, associated with maternal insulin resistance, including inflammation, hormones and fetal hypoxia[2,60,61]. In animal model studies, it was shown that a maternal obesogenic diet was associated with fetal fatty liver in absence of fetal or maternal adiposity[62]. This is suggestive that maternal circulating hormones, lipids or cytokines could result in hepatic steatosis in-utero[63-65]. Other studies show that exposure to maternal obesogenic diet in early life was associated with an increased expression of hepatic transcription factor SREBP1c and its co-activators in offspring[66,67]. Furthermore, animal studies support that exposure to an obesogenic diet in early life may have long lasting consequences during these periods of developmental plasticity. Studies in mice and macaques have shown that in offsprings exposed to these diets, weaning to standard control diet does not completely reverse NAFLD, even in the absence of obesity in offspring[68,69].

While maternal obesity has been widely reported to be associated with NAFLD, poor nutrition in the form of undernourishment in-utero has also been associated with NAFLD in offspring[70-73]. This hypothesis was explored by Zheng *et al*[12] as summarized in the results section earlier. However, the mechanisms which potentiate metabolic dysfunction and/or NAFLD in the offspring, remains unclear. In murine studies, exposure to undernourishment in the in-utero environment increased activation of *de novo* lipogenesis is observed in parallel with the occurrence of NAFLD[74]. This was also associated with increased carbohydrate responsive element binding protein and SREBP1c expression at both transcriptional and protein levels.

Ex-utero, breastfeeding may confer some protective effects against NAFLD later in life. Breast milk contains high levels of oligosaccharides, which are complex sugars with substantial prebiotic effects for desired gut microbial growth. Additionally, it is also a rich source of long chain polyunsaturated fatty acids that has been reported to suppress *de novo* lipogenesis *via* inhibition of SREBP-1c[75,76]. However, these hypothesized mechanisms have yet to be clearly proven in the setting of NAFLD as protection against NAFLD.

While we present a comprehensive review of early developmental factors of NAFLD, which is not widely reported, our study is not without limitations. Firstly, there are only seven studies looking at maternal, paternal and postnatal factors associated with NAFLD. Secondly, most of the studies included

in this systematic review are cross-sectional or cohort studies, and thus an inherent limitation of such studies is its inability to prove causation. For example, in most studies that reported in-utero factors, genetic polymorphisms, a major confounding factor, was not concurrently studied. Furthermore, post-natal factors such as lifestyle factors in childhood and adolescence have been associated with NAFLD. In particular, a high calorie, high refined carbohydrate and/or Western diet have been associated with NAFLD and adherence to Mediterranean diet was protective. Hepatic steatosis develops when the rate of fatty acid uptake and synthesis is greater than the rate that the liver can oxidise and export fatty acid [77]. It is difficult to establish if such dietary choices directly affect hepatic lipid metabolism independent of obesity, as obese individuals have more free fatty acid being released from adipose tissues with increase delivery and uptake into the liver. Nevertheless, this is an inherent limitation in any observational cross sectional study. Fourthly, only patients with imaging findings of hepatic steatosis were included, and we were unable to choose studies that only included patients who had secondary causes for hepatic steatosis and other liver diseases excluded. However, we expect that the proportion of patients who have viral hepatitis would be low [78]. Lastly, NAFLD is an umbrella term consisting of simple steatosis, steatohepatitis and/or fibrosis. Those with NASH and/or fibrosis are at highest risk of cardiovascular mortality and liver related morbidity. In this review, only 5 studies further graded severity of NAFLD by histology and reported factors associated with NAFLD severity grade, thus limiting the reporting of factors associated with severe NAFLD.

In spite of these limitations, our review serves as a useful overview and identifies areas in which further interventional studies can be considered. Measures to ameliorate the developmental programming of NAFLD should be introduced in early life, during times of developmental plasticity to elicit the most effective benefits. Some potential areas for further studies would be maternal control of metabolic dysregulation, maternal dietary intake during gestation and breastfeeding for example. Furthermore, studies in lean individuals with NAFLD are needed and would help to identify risk factors without the confounder of BMI.

CONCLUSION

In summary, our systematic review summarizes the current available literature on early developmental factors associated with hepatic steatosis. Maternal in utero environment, breastfeeding and nutritional, physical and genetic factors are associated with NAFLD. This time period in early life is potentially a time of developmental plasticity and may be a window of opportunity for early intervention to alter the natural course of this increasingly common and potentially debilitating disease.

ARTICLE HIGHLIGHTS

Research background

Prevalence of non-alcoholic fatty liver disease (NAFLD) in adolescents has more than doubled in the last two decades, with its downstream complications placing an increasing burden on healthcare systems globally.

Research motivation

At present, there is a paucity of treatment options NAFLD. In line with the developmental origins of health and disease (DOHaD) concept, we hope to identify factors in early life where possible intervention can be instituted to prevent the development of NAFLD later in life.

Research objectives

To review the early developmental factors associated with NAFLD and potentially identify areas where intervention can be made to halt the progress to steatohepatitis, fibrosis and cirrhosis and/or hepatocellular carcinoma which may develop later in life.

Research methods

Original research studies that included risk factors associated with early development of NAFLD in human subjects were identified from databases MEDLINE *via* PubMed, and EMBASE and relevant publications up to April 30, 2021 were assessed.

Research results

Genetic polymorphisms, familial factors such as maternal obesogenic environment and parental history of hepatic steatosis was associated with offspring NAFLD. Longer duration of exclusive breastfeeding in infancy was associated with a lower risk of developing NAFLD later in life while metabolic dysfunction and/or obesity in adolescence was associated with increased risk of NAFLD.

Research conclusions

Our systematic review summarizes the current available literature on early developmental factors associated with hepatic steatosis. Maternal in utero environment, breastfeeding and nutritional, physical and genetic factors are associated with NAFLD.

Research perspectives

Maternal metabolic dysfunction during pregnancy, being exclusively breastfed for a longer time postnatally, diet and physical activity in childhood and adolescence are potential areas where research and interventions can be explored to prevent the development of NAFLD. Studied in lean individuals with NAFLD are needed and would help to identify risk factors without the confounder of BMI.

FOOTNOTES

Author contributions: Tan EXX, Quek SXZ, Kewin STH contributed to study design; Tan EXX, Quek SXZ, Ren YP contributed to data acquisition and data analysis; Kewin STH contributed to study concept and study supervision; All authors contributed to manuscript drafting; Tan EXX, Quek SXZ contributed equally to this manuscript.

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