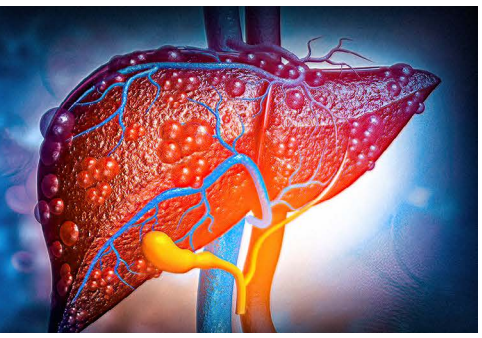
Liver Disease Research Review™



Making Education Easy

Issue 3 - 2022

In this issue:

Abbreviations used in this issue:

BMI = body mass index; **CI** = confidence interval; **CV** = cardiovascular; **HCC** = hepatocellular carcinoma; **HR** = hazard ratio; **IBD** = inflammatory bowel disease; **NAFLD** = non-alcoholic fatty liver disease; **NASH** = non-alcoholic steatohepatitis; **OR** = odds ratio; **PPAR** = peroxisome proliferator-activated receptor; **PSC** = primary sclerosing cholangitis; **RCT** = randomised controlled trial; **RR** = risk ratio; **SARS-CoV-2** = severe acute respiratory syndrome coronavirus type 2.

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Welcome to Issue 3 of Liver Disease Research Review.

A phase IIb RCT demonstrates that lanifibranor is effective in improving histological features of active NASH in non-cirrhotic patients when used over 24 weeks. A US study published in JAMA confirms the benefit of bariatric surgery in patients with NASH who are non-cirrhotic. Other topics covered in this issue include cancer risk in autoimmune hepatitis, granulocyte-colony stimulating factor for acute-on-chronic liver failure, early transplantation for alcohol-related cirrhosis, depression and anxiety in patients with cirrhosis, maternal pre-pregnancy BMI and NAFLD in young adults, and breastfeeding and NAFLD.

We hope you find these and the other selected studies interesting, and look forward to receiving any feedback you may have.

Kind Regards,

Dr David Prince
david.prince@researchreview.com.au

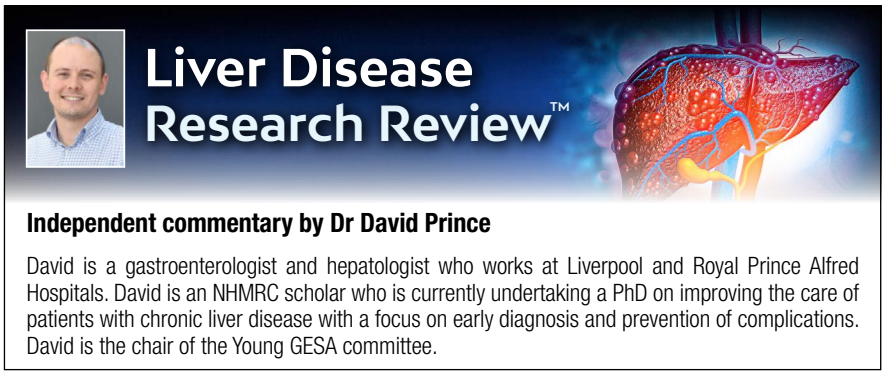
A randomized, controlled trial of the pan-PPAR agonist lanifibranor in NASH

Authors: Francque SM et al.

Summary: This double-blind, randomised, placebo-controlled, phase IIb trial compared lanifibranor 800 mg or 1200 mg versus placebo in 247 patients (42% with type 2 diabetes mellitus; 76% moderate or advanced fibrosis) with non-cirrhotic, highly active NASH. More lanifibranor 1200 mg, but not lanifibranor 800 mg, recipients had a decrease of ≥2 points in Steatosis, Activity, Fibrosis (SAF) activity score without worsening of fibrosis than those who received placebo (55% and 48% vs 33%; p = 0.007 and p = 0.07). The results favoured both lanifibranor 1200 mg and 800 mg over placebo for resolution of NASH without worsening of fibrosis (49% and 39% vs 22%), improvement in fibrosis stage of ≥1 without worsening of NASH (48% and 34% vs 29%), and resolution of NASH plus improvement in fibrosis stage ≥1 (35% and 25% vs 9%). Liver enzyme levels and most lipid, inflammatory, and fibrosis biomarkers improved with lanifibranor. Discontinuation for adverse events was <5% and did not differ between groups. Diarrhoea, nausea, peripheral oedema, anaemia, and weight gain occurred more frequently with lanifibranor.

Comment: This phase IIb RCT demonstrates that lanifibranor is effective in improving histological features of active NASH in non-cirrhotic patients when used over 24 weeks. The higher dose (1200 mg oral daily) has the most benefit with the lower dose (800 mg daily) not demonstrating benefit over placebo for some end points. The medication was safe and well tolerated; however, approximately 10% of patients experienced weight gain while on therapy. This may be a potential limitation of this medication. A phase III trial is needed to determine if longer-term treatment with lanifibranor will result in clinically significant benefits.

Reference: N Engl J Med 2021;385:1547-58
Abstract



Independent commentary by Dr David Prince

David is a gastroenterologist and hepatologist who works at Liverpool and Royal Prince Alfred Hospitals. David is an NHMRC scholar who is currently undertaking a PhD on improving the care of patients with chronic liver disease with a focus on early diagnosis and prevention of complications. David is the chair of the Young GESA committee.

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For the prevention of recurrence of hepatic encephalopathy[3]

MINIMUM PRODUCT INFORMATION : XIFAXAN® 550 mg (rifaximin) film coated tablets. INDICATIONS: For the prevention of the recurrence of hepatic encephalopathy where other treatments have failed or are contraindicated. **CONTRAINDICATIONS:** XIFAXAN is contraindicated in intestinal obstruction, patients with a hypersensitivity to rifaximin, any of the rifamycin antimicrobial agents, or any of the components in XIFAXAN. Hypersensitivity reactions have included exfoliative dermatitis, angioneurotic oedema, and anaphylaxis. **PRECAUTIONS: Use in pregnancy:** Pregnancy Category B1. **Use in lactation:** It is unknown whether rifaximin/metabolites are excreted in human milk. A risk to the child cannot be excluded. A decision must be made whether to discontinue breast–feeding or to discontinue/abstain from rifaximin therapy taking into account the benefit of breast–feeding for the child and the benefit of therapy for the woman. **Paediatric use:** Safety and effectiveness not established in patients under 18 years of age. **Clostridium difficile-Associated Diarrhoea:** *Clostridium difficile*–associated diarrhoea (CDAD) has been reported with use of nearly all antibacterial agents, including XIFAXAN, and may range in severity from mild diarrhoea to fatal colitis. **Severe (Child-Pugh C) Hepatic Impairment:** There is increased systemic exposure in patients with hepatic impairment. Use with caution in patients with severe hepatic impairment (Child–Pugh C). **INTERACTIONS WITH OTHER MEDICINES:** In healthy subjects co–administration of a single dose of ciclosporin (600 mg) with a single dose of rifaximin (550 mg) resulted in increases in rifaximin Cmax and AUC. The clinical significance of this is unknown. For patients on warfarin, monitor INR when starting or stopping XIFAXAN. **ADVERSE EFFECTS:** Adverse events that occurred at an incidence ≥ 5% and at a higher incidence in XIFAXAN 550 mg treated subjects than in the placebo group in the 6–month trial include anaemia, ascites, abdominal pain, abdominal distension, constipation, rash, pruritus, fatigue, peripheral oedema, arthralgia. Additional post–marketing adverse events reported include *C. difficile* infections, thrombocytopaenia. **DOSAGE AND ADMINISTRATION:** The recommended dose of XIFAXAN is one 550 mg tablet taken orally twice a day, with or without food. In the pivotal clinical trial of XIFAXAN for HE, 91% of the patients were using lactulose concomitantly. **PRESENTATION AND STORAGE CONDITIONS:** XIFAXAN 550 mg is a pink oval biconvex film–coated tablet marked RX on one side. Packs of 56. Store Below 25°C. **NAME AND ADDRESS OF THE SPONSOR: Australia:** Norgine Pty Limited, Suite 3.01, Building A, 20 Rodborough Road, Frenchs Forest NSW 2086. Telephone: (02) 8422 0800. **DISTRIBUTOR: AUS:** Healthcare Logistics, 7 Dolerite Way, Pemulwuy, NSW, 2145. Telephone: 1300 364 586. **POISON SCHEDULE OF THE MEDICINE:** Schedule S4 – Prescription Only Medicine.

PBS Information: Authority required. Prevention of hepatic encephalopathy. Refer to PBS Schedule for full authority information.

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References: 1. Vilstrup H, *et al. J Hepatol* 2014; 61(3): 642-659. **2.** Kang SH, *et al. Aliment Pharmacol Ther* 2017; 46(9): 845-855. **3.** XIFAXAN® 550 Product Information.

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NORGINE

Association of bariatric surgery with major adverse liver and cardiovascular outcomes in patients with biopsy-proven nonalcoholic steatohepatitis

Authors: Aminian A et al.

Summary: The SPLENDOR study examined long-term relationships between Roux-en-Y gastric bypass or sleeve gastrectomy (n = 650) versus nonsurgical care (n = 508) and incident major adverse liver outcomes and major adverse CV events in obese individuals with fibrotic non-cirrhotic NASH. Over a median 7 years of follow-up, five bariatric surgery patients and 40 nonsurgical patients experienced major adverse liver outcomes, while 39 and 60 patients experienced major adverse CV events. The 10-year cumulative incidence of major adverse liver outcomes was lower in the bariatric surgery versus nonsurgical group (2.3% vs 9.6%; adjusted HR 0.12; 95% CI 0.02-0.63), as was the 10-year cumulative incidence of major adverse CV events (8.5% vs 15.7%; HR 0.30; 95% CI 0.12, 0.72). In the first year after surgery, four patients died from surgical complications, including two from gastrointestinal leak and two from respiratory failure.

Comment: This study confirms the benefit of bariatric surgery in patients with NASH who are non-cirrhotic. It should be noted that patients were not randomly assigned to treatment groups, and it is likely that there may have been some bias in allocation. Patients who underwent surgery (either sleave gastrectomy 17%; Roux-en-Y gastric bypass 83%) had lower incidence of major adverse CV events (8.5% vs 15.7%) and liver outcomes (2.3% vs 9.6%) at 10 years compared to the control group. Of note, seven patients died during follow up for Roux-en-Y gastric bypass from causes potentially related to surgery and these deaths almost totally offset the reduced liver-related mortality. Additionally, up to 10% of patients undergoing surgery had cirrhosis and it is possible that surgical outcomes may have been different in this group (these patients were excluded from the study). This also highlights that bariatric NAFLD patients can be difficult to assess pre-operatively and that care is needed to detect cirrhosis. Quality of life outcomes between groups were not assessed and these would be useful to compare.

Reference: JAMA. 2021;326(20):2031-2042
Abstract

Increased cancer risk in autoimmune hepatitis: A Danish nationwide cohort study

Authors: Jensen MD et al.

Summary: This study used national Danish healthcare registries (1994-2018) to examine cancer risks in 1805 patients with autoimmune hepatitis (AIH) and 16,617 age- and sex-matched controls. Compared with controls, the 10-year risk of any cancer in patients with AIH was 13.6% (95% CI 11.7-15.6; RR 1.5; 95% CI 1.3-1.7); 10-year risk of hepatocellular carcinoma (HCC) was 0.5% (95% CI 0.2-1.1; RR 12.2; 95% CI 3.3-45.3). 10-year risk for colorectal cancer (CRC) was 1.6% (95% CI 1.0-2.5; RR 2.1; 95% CI 1.3-3.5) and for nonmelanoma skin cancer was 4.0% (95% CI 3.0-5.3; RR 1.8; 95% CI 1.3-2.5). Risk of cancer was higher among those with cirrhosis (HR 1.3; 95% CI 1.0-1.7) and increased 1.05-fold (95% CI 1.0-1.1) for every year of immunosuppressive treatment.

Comment: A large cohort study of 1805 patients with AIH confirmed they have increasing risk of malignancy compared to age- and sex-matched controls (HR 1.5 for all cancers). Rates of HCC (RR 12.2), CRC (RR 2.1) and non-melanomatous skin cancer (RR 1.8) were all increased over 10 years of follow up. There were also trends towards increased rates of haematological malignancy and lung cancer. Unsurprisingly, patients with cirrhosis and on immunosuppression had increased risk compared to patients without these factors. Azathioprine (used in 68% of patients) carried the highest risk of the immunosuppressive agents studied, with an annual HR of 1.41 for CRC and 1.23 for non-melanomatous skin cancer for each year of use. The association with CRC is not previously well described and was not explained by comorbid PSC/IBD. While this is unlikely to lead to changes in practice it reminds clinicians to consider skin and bowel cancer screening, where appropriate, particularly in AIH patients with cirrhosis or who have been on long-term azathioprine.

Reference: Am J Gastroenterol. 2022;117(1):129-137
Abstract

Granulocyte-colony stimulating factor (G-CSF) to treat acute-on-chronic liver failure: A multicenter randomized trial (GRAFT study)

Authors: Engelmann C et al.

Summary: This multicentre, prospective, controlled, open-label phase II study assessed the safety and efficacy of granulocyte-colony stimulating factor (G-CSF) plus standard medical therapy (SMT) or SMT alone in 176 patients with acute-on-chronic liver failure (ACLF). The study was prematurely terminated for futility. The 90-day transplant-free survival rate did not differ between G-CSF plus SMT recipients and SMT alone recipients (34.1% vs 37.5%; HR 1.05; 95% CI 0.711-1.551). At 360 days, transplant-free (HR 0.998; 95% CI 0.697-1.430) and overall survival (HR 1.058; 95% CI 0.727-1.548) also did not differ between groups. Serious adverse events (SAEs) occurred in 61 G-CSF plus SMT recipients and 57 SMT alone recipients. Overall, seven drug-related SAEs occurred in G-CSF recipients.

Comment: This important investigator-initiated multicentre RCT demonstrated no benefit in the use of G-CSF in ACLF. There have been several small studies previously published reporting therapeutic benefit from G-CSF in alcoholic hepatitis and ACLF. This is the first multicentre study which compared SMT to G-CSF plus SMT. There was no difference in any outcome between the two groups (90-day transplant-free survival, 360-day transplant-free survival or ACLF complication). There were no significant differences in any of predefined subgroups including patients with alcohol as a precipitant for ACLF. Seven (4%) patients developed significant side effects related to G-CSF and the study was terminated early due to futility. Based on this study, this therapy should be avoided unless compelling data emerges supporting its use.

Reference: J Hepatol. 2021;75(6):1346-1354
Abstract

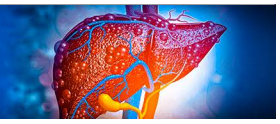
Results of early transplantation for alcohol-related cirrhosis: Integrated addiction treatment with low rate of relapse

Authors: Carrique L et al.

Summary: This single-centre prospective pilot study challenged the paradigm of the "6-month rule" of abstinence for 101 patients with alcohol-related liver disease requiring transplant using in-depth assessment of alcohol use, social support, psychiatric comorbidity, and provision of pre- and post-transplantation addiction treatment. In total, 44 (6.2%) patients received transplants and there were no differences in survival rates between pilot program participants and a control group with more than 6 months of abstinence. Three patients reinitiated alcohol use during post-transplantation follow-up (mean 339 days). Multivariate analysis indicated that younger age and lower Model for End-Stage Liver Disease (MELD) scores were associated greater likelihood of a return to alcohol use ($p < 0.05$), but length of abstinence did not predict return to alcohol use.

Comment: There is a growing body of evidence that a 6-month abstinence rule is a poor predictor of relapse post liver transplant. This pilot program trialled an alternative approach to assess suitability for transplant using multidisciplinary assessment and regular monitoring of biomarkers (urine ethyl glucuronide). Patients underwent baseline assessments by transplant medical, psychiatric, drug and alcohol and social work teams and those deemed unsuitable were excluded. Outcomes from patients transplanted through this scheme were compared to those of patients transplanted in the preceding 18 months for alcohol-related liver disease at the same institution based on the "6-month rule". It should be noted that the criteria used in this pilot were very strict, of 703 referrals only 164 (23.3%) met criteria for full evaluation and of this group only 101 were listed for transplant with 44 (6.3%) ultimately undergoing transplant. There was no difference in survival or relapse rates between this group and the control cohort. It is unclear the generalisability of these results given the very small number of patients actually transplanted under the scheme and the likelihood that if adopted more broadly, criteria may have a tendency to become less stringent over time in clinical practice. This study does, however, highlight the emerging role detailed psychology assessment of prospective recipients and the use of novel biomarkers have compared to relying solely on a time-based criterion.

Reference: Gastroenterology. 2021;161(6):1896-1906.e2
Abstract



SARS-CoV2-specific humoral and T-cell immune response after second vaccination in liver cirrhosis and transplant patients

Authors: Ruether DF et al.

Summary: This prospective cohort study compared vaccine-induced humoral and T-cell responses of 53 cirrhotic patients and 141 liver transplant recipients before and 10-84 days after a second SARS-CoV-2 vaccination. Seroconversion occurred in 63% of liver transplant recipients and 100% of cirrhotic patients and controls; median anti-SARS-CoV-2 titres were lower in transplant patients than in cirrhotic patients and controls ($p < 0.001$) while spike-specific T-cell response rates were 36.6%, 65.4%, and 100%. Overall, 28% of liver transplant recipients did not develop either a humoral or a T-cell response after second vaccination. Significant predictors of absent or low humoral response in transplant patients were age >65 years (OR 4.57; 95% CI 1.48-14.05) and arterial hypertension (OR 2.50; 95% CI 1.10-5.68), while vaccination failure was less likely with calcineurin inhibitors than other immunosuppressive regimens (OR 0.36; 95% CI 0.13-0.99).

Comment: This study compared both the humoral and T-cell immune response following two doses of the SARS-CoV2 vaccination between liver transplant recipients, patients with compensated and decompensated cirrhosis, and health controls. Humoral/antibody response (mediated by plasma B-cells) was assessed using two different assays and T-cell response was assessed using an interferon gamma release assay. Unsurprisingly healthy controls exhibited near perfect response on both tests. Reassuringly patients with cirrhosis (both compensated and decompensated) demonstrated good antibody response (100% seroconversion) and 65.4% demonstrated T-cell response. The significance of absent T-cell responses in the presence of a humoral response is as yet unknown. Concerning among transplant recipients only, approximately 50% developed an antibody response and median antibody titres were lower than both healthy controls and patients with cirrhosis. A T-cell response was seen in only 32%. There was significant discordance between humoral and T-cell response in transplant recipients with some patients exhibiting an isolated T-cell response (thought to confer some protection against severe disease). In a small subgroup analysis, liver transplant recipients who had received heterologous vaccination (AstraZeneca/mRNA; n = 11) had significantly higher seroconversion rates (81.8%) and demonstrated higher antibody titres. Predictors of poor vaccine response in transplant recipients were age >65 years, hypertension, or immunosuppression other than single-agent calcineurin inhibitor. Based on the relatively reassuring findings in decompensated cirrhosis patients, the study authors recommended routine vaccination of all patients prior to transplant.

Reference: Clin Gastroenterol Hepatol. 2022;20(1):162-172.e9
Abstract

Depression and anxiety are common among patients with cirrhosis

Authors: Hernaez R et al.

Summary: This US telephone-based survey of a multicentre cohort of 2874 patients with cirrhosis assessed the prevalence and risk factors for depression and anxiety. The survey response rate was 35.6%. The median Patient Health Questionnaire 9 (PHQ-9) score was 7 and the median State Trait Anxiety Inventory (STAI) score was 33. Overall, 15.6% of patients had moderately severe-to-severe depression and 42.6% had high anxiety. Multivariate analyses indicated moderately severe-to-severe depression was associated with self-reported poor health (OR 4.08; 95% CI 1.79-9.28), being widowed (OR 2.08; 95% CI 1.07-4.05), fear of hepatocellular carcinoma (OR 1.89; 95% CI 1.04-3.42), higher household income (OR 0.30; 95% CI 0.10-0.95), and Hispanic ethnicity (OR 0.57; 95% CI, 0.33-0.97). High anxiety was associated with male sex (OR 0.71; 95% CI 0.51-0.98), self-reported poor health (OR 2.73; 95% CI 1.73-4.32) and fear of hepatocellular carcinoma (OR 2.24; 95% CI 1.33-3.78).

Comment: This telephone-based survey assessed patients with clinically diagnosed cirrhosis across three US tertiary centres. Depression and anxiety were assessed using standardised questionaries. The study was targeted at patients with early cirrhosis with 74% of patients having Child Pugh A disease and those with Child Pugh C disease, a history of HCC or liver transplantation excluded. This was done to minimise cofounding from morbidity related to hepatic decompensation. Overall, 15.6% of patients had moderate-to-severe depression and 42.6% had high anxiety. Fear of developing HCC was associated with both anxiety and depression highlighting the potential importance of enquiring about and managing this in clinical practice. Further work is needed to determine if routine assessment of anxiety and depression and/or interventions designed to treat these will have an impact on clinical outcomes in this patient group. Limitations of the study were that only 35% of eligible patients participated in the study (a potential selection bias) and that those who did not speak either English or Spanish were excluded.

Reference: Clin Gastroenterol Hepatol. 2022;20(1):194-203.e1
Abstract

Trends and the course of liver cirrhosis and its complications in Germany: Nationwide population-based study (2005 to 2018)

Authors: Gu W et al.

Summary: This German population-based study assessed trends and the course of liver cirrhosis and complications based on all 248,085,936 hospital admissions within diagnosis-related groups (2005-18). In total 2,302,171 (0.94%) patients were admitted with cirrhosis, mainly as a comorbidity. Patients admitted with cirrhosis were younger, mainly male and had the highest in-hospital mortality rate compared with other chronic diseases. Cirrhosis was an independent risk factor for in-hospital mortality (OR 6.2; 95% CI 6.1-6.3) with the highest risk among all diagnoses. The prevalence of NAFLD increased four-fold from 2005 to 2018, while alcoholic cirrhosis is 20-fold more common that other aetiologies. Bleeding decreased over time, but ascites were the most common, and increasing, complication.

Comment: This German national cohort study confirms the significant rise in the cirrhosis-associated morbidity. Over the 14-year period that the study evaluated, cirrhosis was implicated in 0.94% of all hospitalisations. In 45.2% of cases, it was the primary reason for admission, whereas in 54.8% it was a comorbidity. As has been shown in other countries, patients admitted with cirrhosis were younger than those admitted for other comparable chronic conditions and also had significantly worse outcomes. Indeed, cirrhosis has the highest overall odds of mortality of any diagnosis, exceeding even admissions related to malignant disease. Throughout this period alcohol was the predominate aetiology of liver disease. Declines in admission related to hepatitis C were largely offset by increased admissions related to NAFLD. This study serves to highlight the high health system burden from decompensated liver disease and re-enforces the need for enhanced cirrhosis prevention and early detection programs.

Reference: Lancet Reg Health Eur. 2021;12:100240
Abstract

Association of maternal pre-pregnancy BMI and breastfeeding with NAFLD in young adults: A parental negative control study

Authors: Abeysekera KW et al.

Summary: This study examined the association between breastfeeding duration and maternal pre-pregnancy BMI on offspring NAFLD in 2961 young adults. A modest inverse association was identified between exclusive (OR 0.92; 95% CI 0.66-1.27) and non-exclusive (OR 0.90; 95% CI 0.67-1.21) breastfeeding of a duration ≥6 months and a protective effect on NAFLD in offspring. The odds of NAFLD were increased in offspring of mothers with overweight pre-pregnancy BMI (OR 2.09; 95% CI 1.62-2.68) and overweight paternal BMI (OR 1.33; 95% CI 1.07-1.65); the ratio of effect sizes OR was 1.57 (95% CI 1.11-2.22). The odds of offspring NAFLD for obese pre-pregnancy maternal (OR 2.66; 95% CI 1.71-4.14) and paternal BMI (OR 1.35; 95% CI 0.91-2.00) were also elevated; the ratio of effect sizes OR was 1.98 (95% CI 1.05-3.74).

Comment: This study confirms that parental pre-pregnancy weight has a strong association with risk of NAFLD in offspring. Unsurprisingly both paternal and maternal weight increased the odds of a baby subsequently developing NAFLD as an early adult (OR 2.09 and 1.33 respectively). Unlike previous studies breastfeeding was not shown to be protective for NAFLD development. Despite the 'negative parental control' using the paternal pre-pregnancy weight it is difficult to completely exclude common environmental factors as a major contributor to these results. These data could be helpful in educating young couples who are overweight or obese and are looking to conceive. More work is needed to determine if normalisation of parental weight prior to conception would change these outcomes.

Reference: Lancet Reg Health Eur. 2021;10:100206
Abstract

The association between breastfeeding and nonalcoholic fatty liver disease in parous women: A nation-wide cohort study

Authors: Park Y et al.

Summary: This analysis of data from the Korean National Health and Nutrition Examination Survey assessed the association between breastfeeding and NAFLD in 6893 Korean parous women aged 30-50 years. Overall, 1049 (15.2%) participants had NAFLD, with a prevalence of 18.3% in women breastfeeding for <1 month, 14.3% for 1-3 months, 12.3% for 3-6 months, 14.4% for 6-12 months, and 15.8% for ≥12 months. A model adjusting for metabolic, socioeconomic and maternal risk factors, suggested that breastfeeding for ≥1 month was associated with reduced NAFLD prevalence (OR 0.67; 95% CI 0.51-0.89). Fully adjusted ORs decreased with increasing breastfeeding duration.

Comment: This large Korean cohort study demonstrated a negative association between breastfeeding and subsequent development of NAFLD. When stratified by duration of breastfeeding there appeared to be a time-dependent relationship, with those who breastfed the longest having the lowest adjusted odds of developing NAFLD. This adds to the biological plausibly of the result and also supports the findings of a previous American study. There are however several limitations of this study, firstly this represents an association only, secondly, breastfeeding has been associated with several factors that are protective for NAFLD such as higher socioeconomic status, higher educational attainment and better health literacy. This study attempted to correct for several of these factors, but it is likely that there was still residual confounding. This study population was rather homogenous and further work is needed in more ethnically diverse populations to see if these results are replicated. Finally, the effect size is small so the number needed to treat would be large to prevent one case of NAFLD. There are other more compelling health reasons to promote breastfeeding.

Reference: Hepatology 2021;74(6):2988-2997
Abstract

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