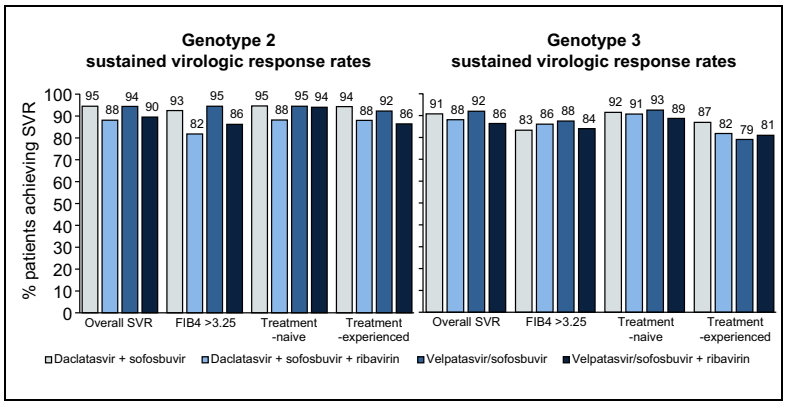
January 2019

Research Article
Viral Hepatitis

JOURNAL
OF HEPATOLOGY

Real-world effectiveness of daclatasvir plus sofosbuvir and velpatasvir/sofosbuvir in hepatitis C genotype 2 and 3

Graphical abstract



Highlights

- In HCV genotype 2 or 3 patients, SVR rates with DCV + SOF were comparable to VEL/SOF.
- SVR with DCV + SOF + RBV was comparable to SVR with VEL/SOF + RBV.
- Regimen did not impact the odds of SVR for either HCV genotype 2 or genotype 3.
- Results support using either DCV + SOF or VEL/SOF for HCV genotypes 2 and 3.
- As guidelines have changed, some of the patients in this cohort were treated outside the current guidelines.

Authors

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Lay summary

In clinical practice, cure rates for hepatitis C virus (HCV) genotype 2 were 94% and cure rates for HCV genotype 3 were 90%. The chance of achieving cure was the same whether a person received daclatasvir plus sofosbuvir or velpatasvir/sofosbuvir. Ribavirin did not affect cure rates. The chance of a cure was lowest in people who had received HCV medication in the past.

https://doi.org/10.1016/j.jhep.2018.09.018

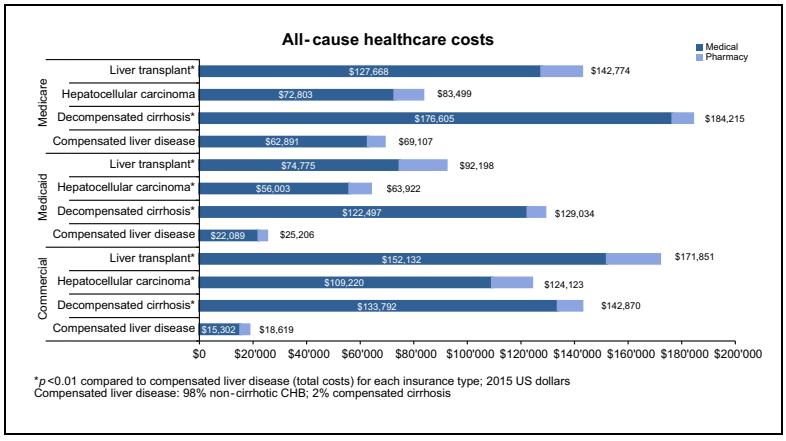
Published by Elsevier B.V. on behalf of European Association for the Study of the Liver. J. Hepatol. 2019, 70, 15–23

Research Article
Viral Hepatitis

JOURNAL
OF HEPATOLOGY

Healthcare resource utilization and costs by disease severity in an insured national sample of US patients with chronic hepatitis B

Graphical abstract



Highlights

- All-cause inpatient admissions (average stay 6–10 days) were more frequent in advanced liver disease states.
- Across all payers, patients with decompensated cirrhosis used the emergency department most (1.6–2.8 annual visits).
- HCC and liver transplant patients had highest proportion of outpatient hospital-based visits and annual visits.
- Advanced liver disease cohorts experienced 6–10× higher costs than patients with compensated liver disease.
- Compensated liver disease patients with CHB incurred 3× the cost of non-CHB controls.

Authors

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Lay summary

Hepatitis B virus can be a progressive disease leading to cirrhosis, hepatocellular carcinoma, liver transplant, and death. These progressive disease states are associated with a higher rate of hospitalizations, emergency room visits, outpatient visits, and costs compared to similar patients without hepatitis B. The most ill patients have the highest costs, but even patients who are less sick experience higher costs than patients without hepatitis B.

https://doi.org/10.1016/j.jhep.2018.09.021

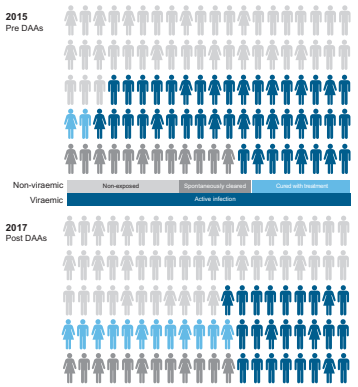
 J. Hepatol. 2019, 70, 24–32

Research Article
Viral Hepatitis

JOURNAL
OF HEPATOLOGY

Association between rapid utilisation of direct hepatitis C antivirals and decline in the prevalence of viremia among people who inject drugs in Australia

Graphical abstract



Highlights

- Evidence to support feasibility of elimination of hepatitis C as a public health threat.
- High uptake of hepatitis C treatment reflected in reduction in viraemic prevalence.
- Surveillance and monitoring are required to track progress toward elimination goals.

Authors

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Lay summary

The World Health Organization's goal to reduce hepatitis C virus incidence by 80% will be difficult to achieve without widespread scale up and a corresponding reduction in viraemic prevalence among those most at risk of onward transmission. Our results indicate that a population-level reduction in viraemic prevalence is achievable through high levels of treatment and cure among people who inject drugs.

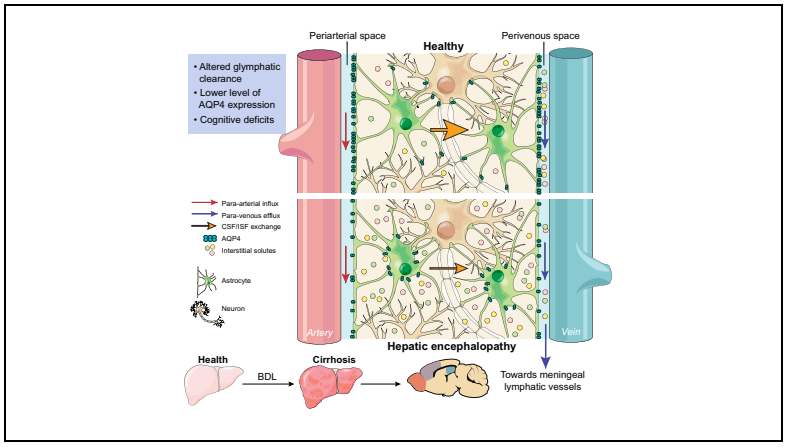
https://doi.org/10.1016/j.jhep.2018.09.030

 J. Hepatol. 2019, 70, 33–39

JOURNAL
OF HEPATOLOGY

Impaired brain glymphatic flow in experimental hepatic encephalopathy

Graphical abstract



Highlights

- Accumulation of noxious metabolites in the interstitial fluid of brain may contribute to hepatic encephalopathy.
- Accumulation of such products may be due to reduced glymphatic clearance mechanisms in the brain.
- We identified regions of impaired glymphatic clearance function, which aligned closely with cognitive/behavioural deficits.
- Reduced AQP4 expression was observed in the same regions.
- Altered AQP4 mediated glymphatic dysfunction may contribute to pathogenesis of hepatic encephalopathy.

Authors

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Lay summary

The 'glymphatic system' is a newly discovered brain-wide pathway that facilitates clearance of various substances that accumulate in the brain due to its activity. This study evaluated whether the function of this system is altered in a model of brain dysfunction that occurs in cirrhosis. For the first time, we identified that the clearance of substances from the brain in cirrhosis is reduced because this clearance system is defective. This study proposes a new mechanism of brain dysfunction in patients with cirrhosis and provides new targets for therapy.

https://doi.org/10.1016/j.jhep.2018.08.021

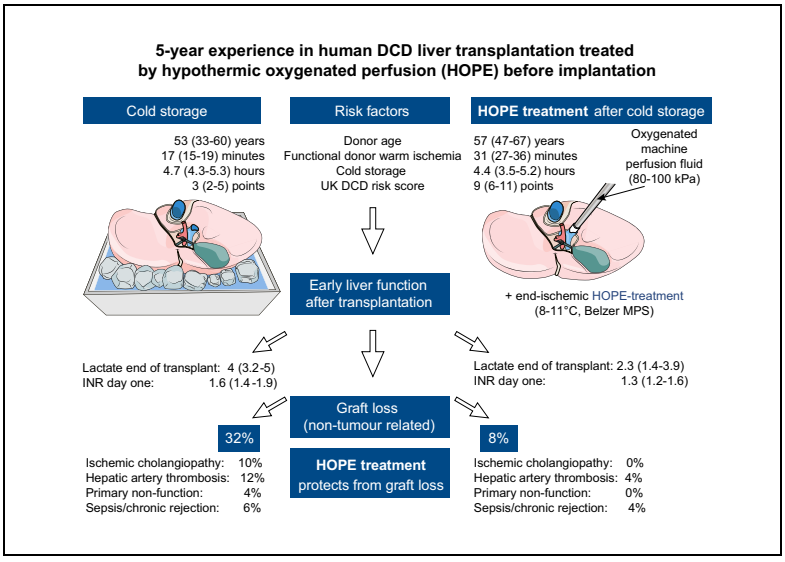
 J. Hepatol. 2019, 70, 40–49

Research Article
Transplantation

JOURNAL
OF HEPATOLOGY

Outcomes of DCD liver transplantation using organs treated by hypothermic oxygenated perfusion before implantation

Graphical abstract



Highlights

- End-ischemic HOPE protected against arterial and biliary complications, resulting in significantly less graft loss.
- Equivalent outcomes were achieved with HOPE as with primary DBD liver transplants.
- HOPE after cold storage is a simple and effective method to treat high-risk DCD livers prior to implantation.

Authors

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Lay summary

Machine perfusion techniques are currently being introduced into the clinic, with the aim of optimising injured grafts prior to implantation. While short-term effects of machine liver perfusion have been frequently reported in terms of hepatocellular enzyme release and early graft function, the long-term benefit on irreversible graft loss has been unclear. Herein, we report on 5-year graft survival in donation after cardiac death livers, treated either by conventional cold storage, or by 1–2 h of hypothermic oxygenated perfusion (HOPE) after cold storage. Graft loss was significantly less in HOPE-treated livers, despite longer donor warm ischaemia times. Therefore, HOPE after cold storage appears to be a simple and effective method to treat high-risk livers before implantation.

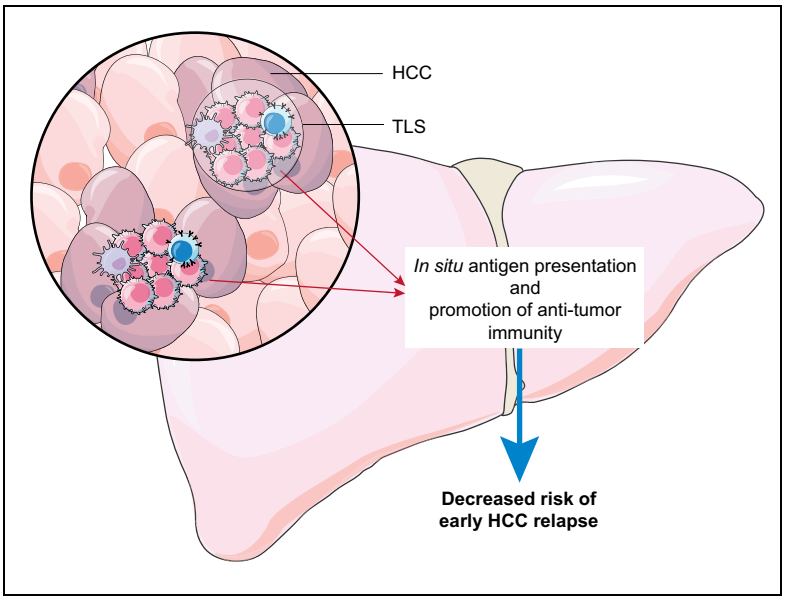
https://doi.org/10.1016/j.jhep.2018.10.005

Research Article
Cancer

JOURNAL
OF HEPATOLOGY

Intra-tumoral tertiary lymphoid structures are associated with a low risk of early recurrence of hepatocellular carcinoma

Graphical abstract



Highlights

- Intra-tumoral tertiary lymphoid structures are associated with decreased risk of early HCC relapse after surgery.
- Presence of intra-tumoral tertiary lymphoid structures is not linked to the etiology of the underlying liver disease.
- Our study suggests that tertiary lymphoid structures reflect ongoing, effective anti-tumor immunity.

Authors

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Lay summary

Tertiary lymphoid structures provide a critical microenvironment for generating anti-tumor immune responses, and are associated with improved clinical outcome in most cancers investigated. Their role in hepatocellular carcinoma is however debated. We show in the present study that intra-tumoral tertiary lymphoid structures are associated with a low risk of early relapse after surgical resection, suggesting that they reflect the existence of *in situ*, effective anti-tumor immunity.

https://doi.org/10.1016/j.jhep.2018.09.003

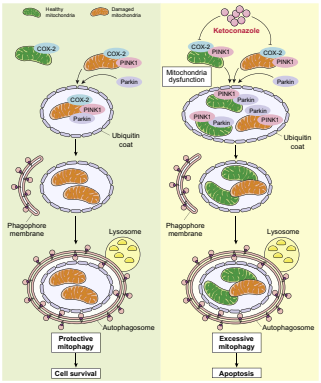
 J. Hepatol. 2019, 70, 58–65

Research Article
Cancer

JOURNAL
OF HEPATOLOGY

Ketoconazole exacerbates mitophagy to induce apoptosis by downregulating cyclooxygenase-2 in hepatocellular carcinoma

Graphical abstract



Highlights

- Ketoconazole induces apoptosis in HCC cells by triggering excessive mitophagy.
- Downregulation of cyclooxygenase 2 (COX-2) is key in the induction of excessive mitophagy via the PINK1/Parkin axis.
- HCC characterized by high COX-2 expression may benefit more from ketoconazole treatment than other subtypes.
- Ketoconazole acts synergistically with sorafenib in the suppression of HCC growth *in vitro* and *in vivo*.

Authors

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Lay summary

Hepatocellular carcinoma (HCC) is a common malignancy worldwide and remains a major clinical challenge. Our study reveals that ketoconazole, a broad-spectrum antifungal agent, activates PINK1/Parkin-mediated mitophagy by downregulating COX-2, consequently resulting in the acceleration of apoptosis and thereby inhibiting the growth of HCC. Furthermore, ketoconazole acts synergistically with sorafenib in the suppression of HCC growth *in vitro* and *in vivo*.

https://doi.org/10.1016/j.jhep.2018.09.022

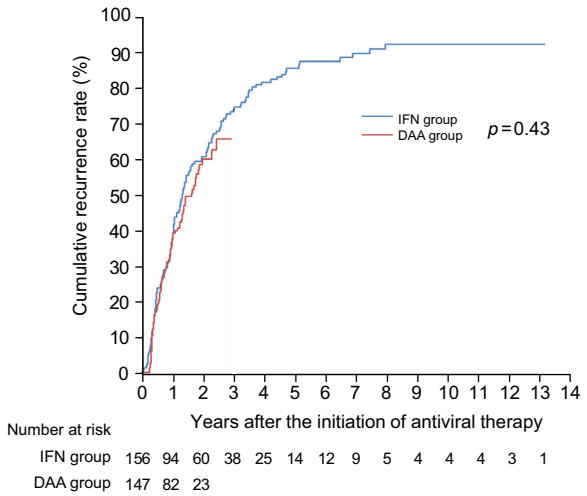
 J. Hepatol. 2019, 70, 66–77

Research Article
Cancer

JOURNAL
OF HEPATOLOGY

Impact of direct-acting antivirals on early recurrence of HCV-related HCC: Comparison with interferon-based therapy

Graphical abstract



Highlights

- There was no significant difference in the early HCC recurrence rate and pattern between IFN-based and DAA therapy.
- High AFP-L3, short recurrence-free period, and history of multiple HCC treatments were risk factors for early recurrence.
- Eradication of HCV after curative HCC treatments could preserve liver function, regardless of antiviral therapy regimen.

Authors

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Lay summary

We detected no significant difference in early hepatocellular carcinoma (HCC) recurrence rates and patterns between patients who received interferon-based and direct-acting antiviral therapy after HCC treatment. High *lens culinaris* agglutinin-reactive fraction of alpha-fetoprotein level, short recurrence-free period, and a history of multiple HCC treatments were independent risk factors for early HCC recurrence after the initiation of antiviral therapy.

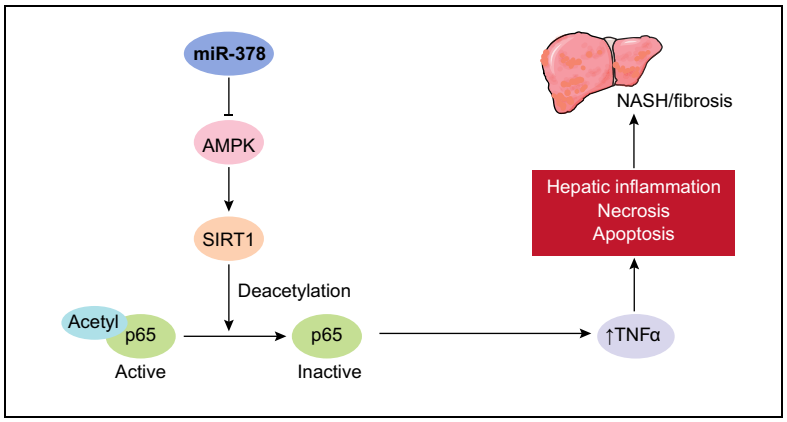
https://doi.org/10.1016/j.jhep.2018.09.029

Research Article
Molecular and Cell Biology

JOURNAL
OF HEPATOLOGY

MicroRNA-378 promotes hepatic inflammation and fibrosis via modulation of the NF-κB-TNFα pathway

Graphical abstract



Highlights

- Hepatic expression of miR-378 is significantly upregulated in fatty livers of mice and patients with NASH.
- miR-378 is a potent inhibitor of AMPK signaling.
- miR-378 facilitates an inflammatory pathway of NFκB-TNFα by targeting *Prkag2*.
- miR-378 robustly promotes hepatic inflammation and fibrosis in dietary obese mice.
- TNFα signaling is required for miR-378 to induce NASH progression.

Authors

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Lay summary

The recent epidemic of obesity has been associated with a sharp rise in the incidence of non-alcoholic fatty liver disease (NAFLD). However, the underlying mechanism(s) remains poorly described and effective therapeutic approaches against NAFLD are lacking. The results establish that microRNA-378 facilitates the development of hepatic inflammation and fibrosis and suggests the therapeutic potential of microRNA-378 inhibitor for the treatment of NAFLD.

https://doi.org/10.1016/j.jhep.2018.08.026

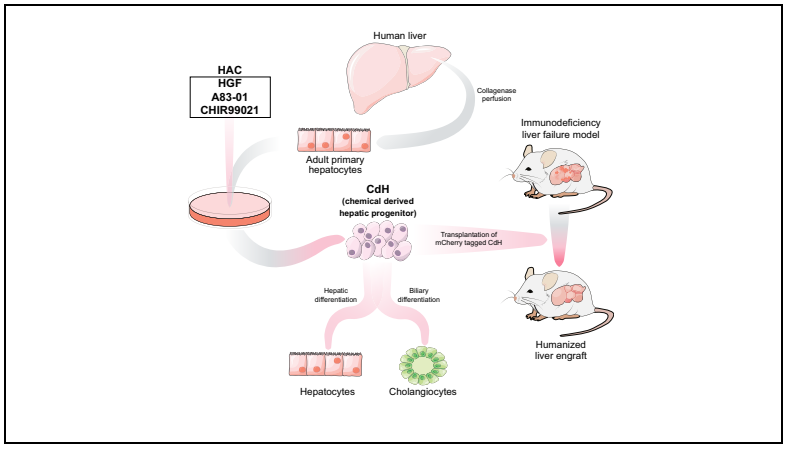
 J. Hepatol. 2019, 70, 87–96

Research Article
Molecular and Cell Biology

JOURNAL
OF HEPATOLOGY

Small molecule-mediated reprogramming of human hepatocytes into bipotent progenitor cells

Graphical abstract



Highlights

- Human hepatic progenitors (hCdHs) are generated from adult hepatocytes.
- HGF is required for chemical reprogramming induced by A83-01 and CHIR99021.
- hCdHs proliferate for at least 10 passages without losing differentiation potential *in vitro*.
- Bipotent hCdHs can repopulate injured liver and acquire functional properties.

Authors

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Lay summary

Human primary hepatocytes were reprogrammed towards hepatic progenitor cells by a combined treatment with 2 small molecules, A83-01 and CHIR99021, and HGF. Chemically derived hepatic progenitors exhibited a high proliferation potential and the ability to differentiate into hepatocytes and biliary epithelial cells both *in vitro* and *in vivo*. This approach enables the generation of patient-specific hepatic progenitors and provides a platform for personal and stem cell-based regenerative medicine.

https://doi.org/10.1016/j.jhep.2018.09.007

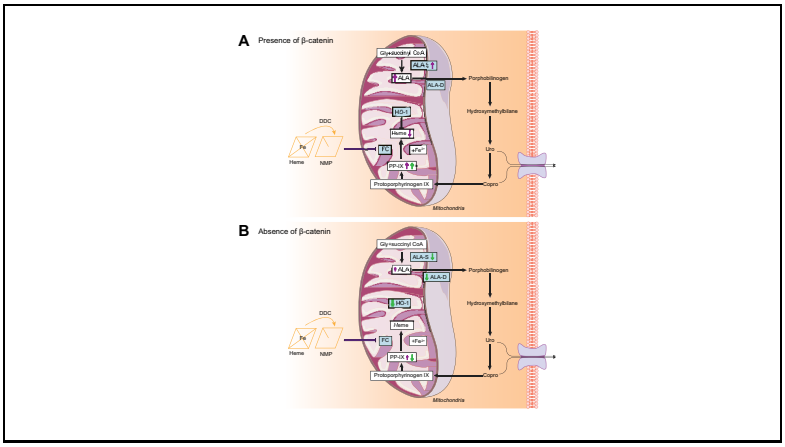
 J. Hepatol. 2019, 70, 97–107

Research Article
Molecular and Cell Biology

JOURNAL
OF HEPATOLOGY

Loss of hepatocyte β-catenin protects mice from experimental porphyria-associated liver injury

Graphical abstract



Highlights

- Porphyrias are caused by defects in heme biosynthesis, which can lead to cholestasis, inflammation, and fibrosis.
- The Wnt/β-catenin pathway plays a role in pathological processes in the liver, including cholestasis and biliary injury.
- Inhibiting β-catenin in a mouse model of porphyria resulted in decreased liver injury.
- Several key heme biosynthesis enzymes were downregulated in livers lacking β-catenin signaling.
- Mice lacking β-catenin had fewer protein aggregates, resulting in improved proteasomal activity and less autophagy.

Authors

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Lay summary

Porphyrias are disorders resulting from abnormalities in the steps that lead to heme production, which cause build-up of toxic by-products called porphyrins. Liver is commonly either a source or a target of excess porphyrins, and complications can range from minor abnormalities to liver failure. In this report, we inhibited Wnt/β-catenin signaling in an experimental model of porphyria, which resulted in decreased liver injury. Targeting β-catenin affected multiple components of the heme biosynthesis pathway, thus preventing build-up of porphyrin intermediates. Our study suggests that drugs inhibiting β-catenin activity could reduce the amount of porphyrin accumulation and help alleviate symptoms in patients with porphyria.

https://doi.org/10.1016/j.jhep.2018.09.023

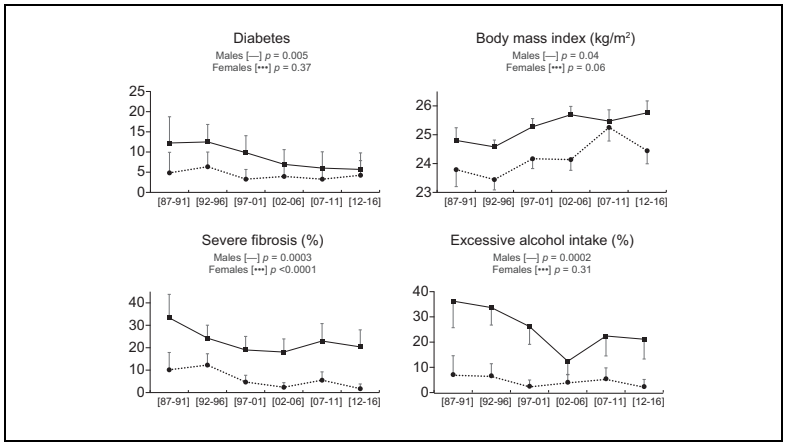
 J. Hepatol. 2019, 70, 108–117

Research Article
Genetic and Metabolic Diseases

JOURNAL
OF HEPATOLOGY

Reduced phenotypic expression in genetic hemochromatosis with time: Role of exposure to non-genetic modifiers

Graphical abstract



Highlights

- HFE hemochromatosis has become less and less severe over the last 30 years despite older age at diagnosis.
- Chronic fatigue and distal arthralgias remain the most frequent opening symptoms.
- Reduced alcohol intake and more overweight patients may explain decreased long-term iron load in hemochromatosis.
- Tobacco smoking may aggravate iron loading.

Authors

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Lay summary

Genetic hemochromatosis is an inherited disorder that leads to progressive iron overload in the body. It results in chronic fatigue and in potential liver (cirrhosis), pancreas (diabetes) and joint (arthritis) damage in adulthood. The present study showed that tobacco smoking may aggravate iron loading, but that hemochromatosis has become less and less severe over the last 30 years despite patients being older at diagnosis, likely because of the protective effects of lower alcohol consumption and of increased weight in the French population.

https://doi.org/10.1016/j.jhep.2018.09.009

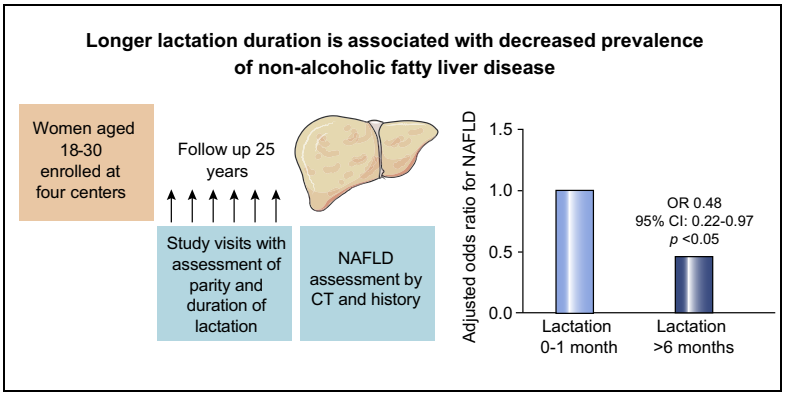
 J. Hepatol. 2019, 70, 118–125

Research Article
Genetic and Metabolic Diseases

JOURNAL
OF HEPATOLOGY

Longer lactation duration is associated with decreased prevalence of non-alcoholic fatty liver disease in women

Graphical abstract



Highlights

- Lactation duration >6 months was protective against NAFLD in mid-life after adjustment for confounders.
- The benefits of increased lactation duration on weight and waist circumference mediated <1/4 of this benefit.
- Longer lactation duration may be an important lifestyle intervention to prevent the NAFLD during mid-life.

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Lay summary

A longer duration of breastfeeding has been associated with multiple potential health benefits for the mother including reduction in heart disease, diabetes and certain cancers. In this study we found that breastfeeding for longer than 6 months was associated with a lower risk of non-alcoholic fatty liver disease in mid-life.

https://doi.org/10.1016/j.jhep.2018.09.013

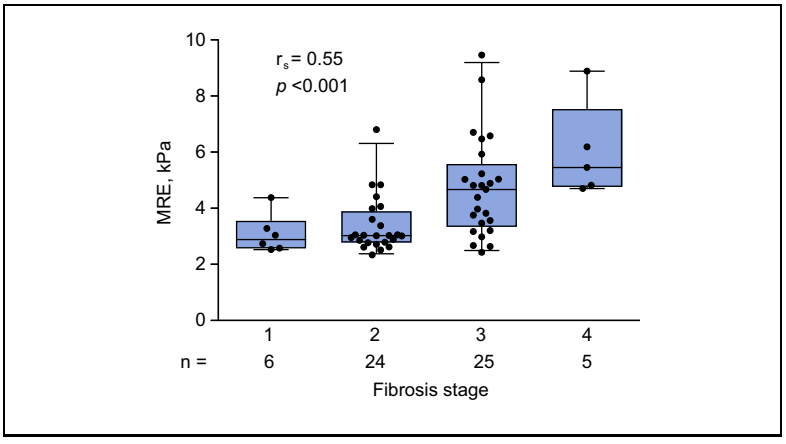
 J. Hepatol. 2019, 70, 126–132

Research Article
Genetic and Metabolic Diseases

JOURNAL
OF HEPATOLOGY

Longitudinal correlations between MRE, MRI-PDFF, and liver histology in patients with non-alcoholic steatohepatitis: Analysis of data from a phase II trial of selonsertib

Graphical abstract



Highlights

- Liver stiffness by magnetic resonance elastography (MRE) correlated with fibrosis.
- Reductions in liver stiffness by MRE were associated with improvement of fibrosis.
- Assessment of liver fat by magnetic resonance imaging (MRI) correlated with severity of liver steatosis.
- Reductions in MRI estimates of liver fat were correlated with reductions in liver fat on biopsy.

Authors

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Lay summary

Liver biopsy is a potentially painful and risky method to assess damage to the liver due to non-alcoholic steatohepatitis (NASH). We analyzed data from a clinical trial to determine if 2 methods of magnetic resonance imaging – 1 to measure liver fat and 1 to measure liver fibrosis (scarring) – could potentially replace liver biopsy in evaluating NASH-related liver injury. Both imaging methods were correlated with biopsy in showing the effects of NASH on the liver.

https://doi.org/10.1016/j.jhep.2018.09.024

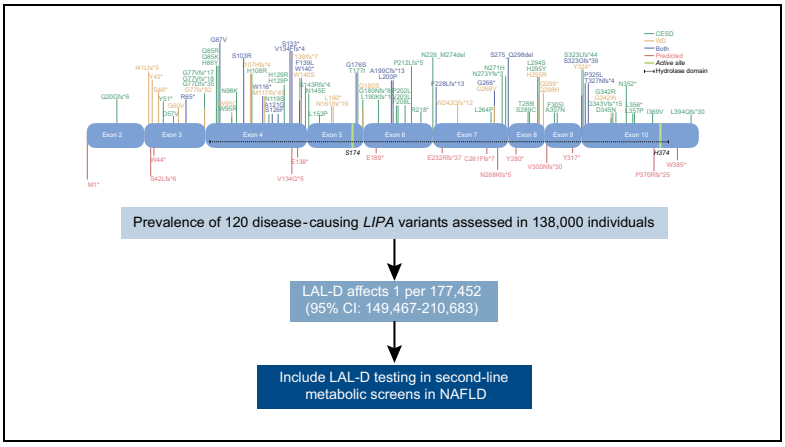
 J. Hepatol. 2019, 70, 133–141

Research Article
Genetic and Metabolic Diseases

JOURNAL
OF HEPATOLOGY

The global prevalence and genetic spectrum of lysosomal acid lipase deficiency: A rare condition that mimics NAFLD

Graphical abstract



Highlights

- There are 98 disease-causing *LIPA* variants associated with LAL-D.
- An additional 22 predicted pathogenic *LIPA* variants have been identified in humans.
- LAL-D has an estimated prevalence of 1 per 177,000.
- Clinicians can be reassured that LAL-D is an ultra-rare mimic of NAFLD.
- Consider LAL-D testing in a second-line metabolic screen in patients with atypical NAFLD.

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Lay summary

Lysosomal Acid Lipase Deficiency (LAL-D) is a rare genetic condition that can cause severe liver disease, but it is difficult to diagnose and sometimes can look like simple fatty liver. It was not clear how common LAL-D was and whether many cases were being missed. To study this, we searched for all genetic mutations that could cause LAL-D, calculated how common those mutations were, and added them up. This let us estimate that LAL-D affects roughly 1 in 175,000 people. We conclude that LAL-D is a very rare condition, but it is treatable so may be included in a 'second-line' of tests for causes of fatty liver.

https://doi.org/10.1016/j.jhep.2018.09.028

 J. Hepatol. 2019, 70, 142–150