Concise review: Breastfeeding, lactation, and NAFLD. An updated view of cross-generational disease transmission and prevention

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Abstract

Evidence suggests that breastfeeding protects the mother-infant dyad against the development and progression of nonalcoholic fatty liver disease (NAFLD). In this context, we aim to provide insight into the most notable and representative epidemiological studies published in the literature. Furthermore, we will delve into the potential underlying pathomechanisms that might be involved in this relationship. The current definitions of breastfeeding, lactation, mother-infant dyad, and nonalcoholic fatty liver disease (NAFLD) are provided. Next, the epidemiological evidence supporting potential benefits for the (long-term) lactating mother in terms of protection from the development and progression of NAFLD is reviewed. The putative mechanisms underlying this protection are also analyzed. Similarly, clinical and epidemiological studies evaluating the benefits of breastfeeding for the offspring are examined, together with a discussion of the putative underlying mechanisms. In conclusion, our understanding of breastfeeding (for the offspring) and lactation (for the mother) as protective factors from NAFLD development and fibrotic progression will provide further insight into unprecedented disease mechanisms shared by the mother-infant dyad promising to interrupt the vicious cycle of NAFLD transmission across generations.

Keywords: Breastfeeding, lactation, liver fibrosis, NAFLD, NASH
INTRODUCTION
Definitions and history
Breastfeeding and lactation
Breastfeeding is an overarching term lacking distinction between the provider and recipient of human milk; both a mother and her infant can be termed as "breastfeeding"\[1\]. On the other hand, "lactation" precisely describes the physiological process of milk production and secretion from mammary glands, focusing on the mother's perspective\[1\].

To achieve the optimal growth of offspring, the World Health Organization (WHO) recommends exclusive breastfeeding (EBF) for infants till six months of age\[2\]. However, EBF remains under-practiced in many countries, and breastfeeding campaigns effectively increase EBF rates\[3\].

The mother-child dyad
The mother-and-offspring unit shares such a powerful bio-psycho-social relationship\[4\] as to suggest defining the "mother-child dyad", to specifically focus on those maternal and infant characteristics that are associated with an excess infant mortality rate\[5\]. However, since 1967, when it was coined, the notion of mother-child dyad has been used extensively in a variety of settings to clearly distinguish the mother’s from the infant’s perspective in various clinical outcomes.

Nonalcoholic fatty liver disease
In the 1980s, two groups of clinical liver pathologists independently from each other described "nonalcoholic steatohepatitis" (NASH) and "nonalcoholic fatty liver disease" (NAFLD) as a spectrum of disorders indistinguishable from alcohol-associated liver disease though occurring in the nonalcoholic\[6,7\]. Individuals with NAFLD and NASH often have diabesity at the baseline or are prone to developing features of metabolic syndrome (MetS) over a short-term follow-up\[8\], indicating that NAFLD-related insulin resistance, oxidative stress, subclinical inflammation and perturbed metabolism of glucose and lipids strongly affect systemic milieu.

History
In the same years when NAFLD began to be described, other investigators reported that breastfeeding could protect from severe liver disease and early mortality among infants with alpha 1-antitrypsin deficiency\[9\]. This was the first published evidence that breastfeeding could affect liver disease.

Aims
Evidence suggests that breastfeeding protects the mother-infant dyad against the development and progression of NAFLD. In this context, we aim to provide insight into the most notable and representative epidemiological studies published in the literature. Furthermore, we will delve into the potential underlying pathomechanisms that might be involved in this relationship. Given that excellent reviews have already been published on this topic\[10\], the most recent publications are specifically focused here.

THE MOTHER’S SIDE OF THE DYAD
Epidemiological evidence
Compared to the benefits for the infant, the notion that breastfeeding may benefit the mother’s health (and particularly liver health) is less immediately intuitive. However, a consistent body of research showing the cardiometabolic benefits for the lactating mother conducting protracted breastfeeding\[11-14\] has prompted the evaluation of potentially favorable hepatic outcomes in NAFLD arena.
The first study disclosing an association between duration of lactation and reduced risk of NAFLD was conducted by Ajmera et al. in 2019[15]. These authors reported that among 844 participants from the multi-ethnic Coronary Artery Risk Development in Young Adults cohort study (48% black and 52% white, with a median age of 25 years) who delivered at least one child after enrollment, 25 years after entry in the study, longer duration of lactation protected from NAFLD (adjusted odds ratio (OR) 0.46; 95% CI: 0.22-0.97; \( P = 0.04 \)) comparing women who reported > 6 months lactation to those reporting 0-1 month. NAFLD was defined as liver attenuation ≤ 40 Hounsfield Units at computed tomography (CT) scanning in the absence of any competing etiologies of steatogenic liver disease. This study found that a longer duration of lactation (especially > 6 months) was associated with a reduced risk of NAFLD in mid-life and is, therefore, a modifiable risk factor for NAFLD.

Two years later, Park et al. assessed 6,893 Korean parous women (30-50 years) enrolled in the Korean National Health and Nutrition Examination Survey for the nexus linking lactation and NAFLD, which was assessed with the hepatic steatosis index, and found that 15.2% of women had NAFLD[16]. In a statistical model fully adjusted for confounding (metabolic, socioeconomic, and maternal) factors, breastfeeding ≥ 1 month was associated with reduced NAFLD prevalence (OR, 0.67; 95% CI: 0.51-0.89). Interestingly, a clear dose-response curve was also found, implying that the longer the duration of lactation (≥ 1- < 3, ≥ 3- < 6, ≥ 6- < 12, and ≥ 12 months), the greater the protection from NAFLD [adjusted ORs (95% CI): 0.74 (0.49-1.11), 0.70 (0.47-1.05), 0.67 (0.48-0.94), and 0.64 (0.46-0.89)].

Mantovani et al. performed a meta-analysis incorporating the two aforementioned studies and found that breastfeeding conducted > 6 months was strongly associated with a 37% lower risk of NAFLD in later life among parous women (random-effects OR 0.63, 95% CI: 0.51-0.79, I2 = 0%), having breastfeeding lasting < 1 month as a reference[17].

Finally, bringing this line of research further, Karachaliou et al. performed a cross-sectional analysis involving 422 women (median age 52) with biopsy-proven NAFLD from the Duke NAFLD Database and whose reproductive information was available[18]. These authors investigated the association of live birth and cumulative lifetime breastfeeding with metabolic and histologic features of NAFLD. Most women were white and had traits of the MetS, while 23% had advanced liver fibrosis. Interestingly, this study found that parous women had a significantly lower BMI than nulliparous, while no associations with other metabolic features were noted. Moreover, an intriguing discovery emerged, a longer history of lactation was linked to a reduced risk of portal inflammation and hepatic fibrosis, although it did not show any such associations with other fundamental characteristics of NASH histology. Notably, these associations were primarily observed among women aged 50 or younger at the time of their liver biopsy. It is important to note that this study has limitations, mainly stemming from its cross-sectional design and the lack of detailed data regarding exclusive versus combined formula breastfeeding. Nevertheless, these findings highlight the need for further experimental and epidemiological research to enhance our understanding of the roles of lactation as a contributing factor to NAFLD progression and parity’s potential protective impact against obesity.

**Putative mechanisms**

Epidemiological evidence suggests that lactation positively affects a mother’s cardiometabolic health, similar to the benefits of aerobic training. In a study by Butte et al., 40 lactating women were compared to 36 non-lactating women[19]. The findings showed that breastfeeding mothers had lower glucose, lipids, and insulin levels in their blood. These changes were primarily attributed to the mammary gland’s uptake of circulating glucose for milk production, independently of insulin. Another study by Farahmand et al. involved a
community-based cohort of 1,176 women, including 175 who had gestational diabetes mellitus (GDM). Over a median follow-up period of 16.3 years, it was found that longer breastfeeding duration was associated with a reduced risk of developing MetS. Specifically, for every additional month of lactation, there was a 2% decrease in the risk of MetS. Notably, women with GDM experienced an even greater reduction in the risk of MetS (a hazard ratio of 0.93, 95% CI: 0.88-0.98) compared to those without GDM. Taken together, these findings suggest that extended lactation provides protection against the risk of NAFLD via the mammary "sequestration" of circulating nutrients for milk production, as well as the risk reduction of developing insulin resistance (i.e., MetS). Moreover, breastfeeding mothers exhibit a reduced risk of diabetes. Aune et al. reported in their meta-analytic review that lactating mothers have a reduced risk of developing type 2 diabetes. The summary relative risk (calculated after estimating the average of the natural logarithm of the RRs from each study weighted by the inverse of the variance, and then un-weighted by applying a random effects variance component which is derived from the extent of variability) for those with the highest duration of breastfeeding compared to the lowest was 0.68 (95% CI: 0.57-0.82). This beneficial metabolic effect can be attributed, in part, to lactation increasing a mother's energy requirements. Lactating mothers have a net increase in energy needs of 1.9 MJ per day compared to the energy requirements of individuals who are neither pregnant nor lactating. This increment, based on calculation for a subject weighing 65 Kg, is roughly equivalent to engaging in 30-40 min of high-intensity biking exercise or 30-40 min of running. Consequently, lactation serves as a mechanism for consuming the energy reserves accumulated during pregnancy, estimated at an average of 321 to 325 MJ based on a weight gain of 12 kg throughout pregnancy. Additionally, this process assists in resetting the metabolic alterations that occur during pregnancy.

In the 1940s, it was initially believed that prolactin, like other hormones produced by the anterior pituitary gland, could potentially promote diabetes. However, our understanding has since evolved. We now know that normal prolactin levels in the bloodstream have a relatively narrow range, and both levels below this range and levels above it are associated with an increased risk of metabolic disorders. In contrast to pathological hyperprolactinemia, which represents a significant risk factor for cardiometabolic issues, the natural increase in prolactin during pregnancy serves the essential purpose of meeting the heightened metabolic demands that come with being pregnant. Therefore, rather than being beneficial, the fall in prolactin levels potentially accounts for the observed increased risk of NAFLD occurring in postpartum women without lactation. Mechanistically, this is plausible as prolactin exerts multiple metabolic effects by acting on beta cells, hepatocytes, adipose tissue, and hypothalamus in addition to its role in lactation. In support of this, genetically engineered mice lacking prolactin receptors display metabolic imbalances, including diabetes, obesity, and NAFLD. Moreover, lower levels of prolactin are associated with an increased risk of NAFLD in both children and adults, while the administration of prolactin or overexpression of prolactin receptors in cell cultures (HepG2 cells) treated with free fatty acids improves hepatic steatosis via the CD36 pathway. Taken together, the aforementioned data may indicate that a reduction in prolactin levels after weaning could potentially play a role in influencing the risk of NAFLD. However, additional investigation is needed to fully understand this relationship.

Further to disease development, lactation may also specifically protect from the fibrosing progression of NAFLD and NASH via hormonal route. In this connection, it has been postulated that high prolactin levels could eventually lead to suppression of YAP (a target of the Hippo kinase pathway) and inhibition of ductular reaction, portal inflammation, and hepatic fibrosis.

According to the “reset hypothesis” proposed by Stuebe and Rich-Edwards, weaning, not delivery, terminates the maternal metabolic effects of pregnancy. In this regard, the finding that obese women are at
increased risk of either not lactating or interrupting lactation prematurely\textsuperscript{[31]} is of concern as much as it may lay the foundations of a dysmetabolic vicious circle.

Numerous pathways contribute to NAFLD pathogenesis. Enhanced hepatic influx of non-esterified fatty acids, driven by heightened visceral adiposity and peripheral insulin resistance, along with increased de novo lipogenesis and reduced VLDL export and fatty acid oxidation, collectively elevate NAFLD risk. Genetic variants associated with NAFLD risk\textsuperscript{[32]} point to additional lipid metabolism pathways contributing to NAFLD development and progression. An experimental study involving postpartum women indicated the potential of serum prolactin to provide protection by lowering intrahepatic triglycerides, potentially through enhanced VLDL-triglyceride export, thus supporting liver health during lactation\textsuperscript{[33]}.

In conclusion, given that the apparent multiplicity of involved mechanisms remains incompletely characterized, additional studies will have to determine the array of anthropometric, hormonal, and metabolic determinants involved in reducing the risk of development and progression of NAFLD/NASH to enable more personalized approaches to disease prevention, diagnosis, and management among women of fertile age.

**THE OFFSPRING’S SIDE**

**Epidemiological evidence**

In 2009, Nobili \textit{et al.}, in their series of 191 consecutive NAFLD Caucasian children aged 3 to 18 years, 48% of whom had been breastfed for a median time of 8 months, were first in reporting that, compared to non-breastfeeding, breastfeeding was associated with a reduced risk of NASH (OR 0.04, 95% CI: 0.01 to 0.10) and fibrosis (OR 0.32, 95% CI: 0.16 to 0.65)\textsuperscript{[34]}. Interestingly, the risk of NASH (OR 0.70, exact 95% CI: 0.001 to 0.87) and fibrosis (OR 0.86, exact 95% CI: 0.75 to 0.98) decreased in parallel with the length of breastfeeding, implying that breastfeeding dose-dependently prevents NASH and NASH fibrosis 3 to 18 years later.

The protective effects of breastfeeding on offspring NAFLD were also demonstrated in a population-based study by Ayonrinde \textit{et al.} in 2017\textsuperscript{[35]}. These authors utilized the Western Australian Pregnancy (Raine) Cohort study to identify a cohort of 1,170 adolescents, 15.2% of whom had NAFLD. Analysis of data showed that breastfeeding without supplementary milk 6 months was associated with a reduced risk of NAFLD (adjusted odds ratio [OR]: 0.64; 95% CI: 0.43-0.94, \(P = 0.02\)). Conversely, both maternal pre-pregnancy obesity (adjusted OR: 2.29; 95% CI: 1.21-4.32, \(P = 0.01\)) and adolescent obesity (adjusted OR: 9.08; 95% CI: 6.26-13.17, \(P < 0.001\)) were both associated with NAFLD independent of the dietary pattern followed at age 17. Collectively, data suggest that while NAFLD was usually facilitated by adiposity gains, breastfeeding for at least 6 months, together with other risk modifiers (such as avoidance of early supplementary formula milk feeding, and normal maternal pre-pregnancy BMI) protected from NAFLD during adolescence.

However, in 2021, a large community-based birth cohort study by Abeysekera \textit{et al.} did not demonstrate significant protection from NAFLD conferred by breastfeeding among offspring at the age of 24 years\textsuperscript{[36]}. Out of 4,021 initial participants, 2,961 individuals with valid CAP measurements for NAFLD, after excluding those with alcohol consumption, served as a final cohort for the analysis. Data have shown only non-significant protection on NAFLD in offspring exerted by exclusive (OR 0.92 [95% CI: 0.66-1.27]) and non-EBF ≥ 6 months [OR 0.90 (95% CI: 0.67-1.21)]. Conversely, there was an increased risk of offspring NAFLD in overweight pre-pregnancy maternal BMI OR 2.09 (95% CI: 1.62-2.68) and paternal BMI OR 1.33 (95% CI: 1.07-1.65). Similarly, odds of offspring NAFLD with obese pre-pregnancy maternal BMI and paternal BMI was OR 2.66 (95% CI: 1.71-4.14) and OR 1.35 (95% CI: 0.91-2.00), respectively, with the ratio
of effect sizes OR 1.98 (95% CI: 1.05-3.74). Their data suggest that maternal and paternal pre-pregnancy BMI (confering an increased risk) rather than breastfeeding (showing no protection) was associated with NAFLD in offspring.

Rajindrajith et al., in their study population comprising 499 adolescents (51.8% girls) born in 2000 and residents in Sri Lanka, in the area of Ragama Medical Officer of Health, found that having been breastfed for < 4 months was one of the significant risk factors for NAFLD (33.3% vs. 17.1 in controls, \( P = 0.02 \)) identified with ultrasonography in the absence of alcohol consumption\(^{37}\).

At variance with all the above studies, which utilized ultrasonography to diagnose steatosis, Cantoral et al. used hepatic fat fraction at magnetic resonance imaging (MRI) to gauge the amount of intrahepatic fat content in 97 young adults (mean age of 21 years) from the ELEMENT birth cohort in Mexico City. This study found no association between breastfeeding vs. non-breastfeeding and duration of breastfeeding with NAFLD and identified NAFLD in as few as 17 individuals among the 97 participants (17.5%)\(^{38}\).

Two additional studies, one conducted among 70 infants (36 breastfed, 9 mixed-fed, and 25 formula-fed)\(^{39}\) and the other a population-based prospective cohort study of 4,444 primary school children\(^{40}\), found no significant differences in the median intrahepatic fat content between patients who were and were not breastfed.

Following their pioneering 2009 study\(^{34}\), the group of investigators led by Mosca et al. published a second contribution based on an analysis of 182 children with overweight/obesity and biopsy-proven NAFLD\(^{41}\). This novel study found that not being breastfed was associated with a three-fold increased risk of hepatic fibrosis, suggesting that further to preventing disease development, breastfeeding could also mitigate its progression to fibrosing NASH in infants.

Finally, to provide a global perspective of published studies, Querter et al. included in their systematic review 33 published articles (six of which evaluated breastfeeding), which exhibited considerable heterogeneity regarding patient populations, diagnostic tools, and overall quality\(^{42}\). The authors found that breastfeeding conferred protection from NAFLD, NASH, and fibrosis, especially in studies evaluating breastfeeding conducted for at least 6 months or longer.

**Putative pathomechanisms**

In mammals, the mother transmits information regarding nutrient availability to the embryo, fetus, and infant, establishing a process by which early insults at critical stages of development may lead to permanent structural and functional tissue changes\(^{43,44}\). This process, named programming, collectively defines those adaptive responses implemented by the fetus or infant to environmental stimuli transmitted by the mother via placental and breastfeeding routes\(^{44}\). Programming accounts for the finding that the offspring of obese and/or diabetic women are exposed to greater risks of developing metabolic disorders, even during childhood, because maternal hyperglycemia leads to fetal hyperinsulinemia and fat deposition\(^{45}\). As shown by experimental studies conducted in rodents, the intake of fat by the mother, via impairment of metabolism of hepatocyte mitochondria and up-regulation of lipogenesis in the liver, may eventually enhance the risk of NASH occurring in adult offspring\(^{46}\). Coronary heart disease in adult offspring has longitudinally been associated with maternal obesity\(^{47}\). In this intriguing scenario, metabolic plasticity is not limited to the intrauterine phase of growth but also extends post-natally via breastfeeding, which may either exert a favorable “metabolic imprinting” or post-transcriptionally modulate the expression of genes involved in the development of the MetS, its individual traits, and NAFLD\(^{48}\). In this connection, the finding
that nutritional components of maternal milk, such as docosahexaenoic acid, could potentially exert anti-fibrogenic activities by acting as PPAR-agonists\(^{49}\) offers an additional, biologically credible, putative mechanism that could explain the “hepatoprotective” effects of breastfeeding.

Prolonged breastfeeding carries innumerable benefits for the infant, particularly in the course of the first semester after birth, including a positive impact on the development of healthy intestinal microbiota\(^{50}\). However, breastfeeding shapes the infant intestinal microbiota based on the maternal intestinal microbiota\(^{51}\). Moreover, NAFLD and related metabolic disorders are typically associated with gut dysbiosis\(^{52}\). Therefore, it seems logical to postulate that mothers with metabolic disorders, particularly NAFLD, may transmit their dysmetabolism and NAFLD to the offspring via breastfeeding and inherent changes in the gut microbiota. Mechanistically, this occurs owing to the gut microbiota taking part in harvesting energy from nutrients, allowing the digestion of fibers and otherwise indigestible nutrients, and producing short-chain fatty acids, vitamins and chemical compounds involved in the regulation of whole-body metabolism while triggering subclinical systemic proinflammatory responses which are major correlates of the MetS and NAFLD\(^{52}\).

Recently identified variations in bacterial diversity, microbiota age, Bacteroidetes and Firmicutes ratio, and microbial pathways related to carbohydrate metabolism in infant gut microbiota associated with EBF (compared to non-EBF infants)\(^{53}\) all contribute to substantiating additional mechanisms of intestinal origin involved in the beneficial metabolic effects of breastfeeding as seen from the infant side of the mother-offspring unit.

Moreover, breastfeeding correlates with diminished offspring visceral adiposity at age 30, potentially curbing hepatic free fatty acid inflow\(^{54}\). The interaction with the FTO gene, a fat mass, and obesity-associated gene, likely contributes to this effect, influencing appetite and energy expenditure regulation\(^{54}\).

In principle, breastfeeding might exert beneficial effects on NAFLD-associated liver fibrosis via a variety of indirect mechanisms, including modulation of gut barrier function in early life through the processes of colonization and development of the gut microbiota, of the intestinal epithelium and immune system in infants\(^{55,56}\). Moreover, docosahexaenoic acid contained in human milk had initially attracted Researchers’ attention given that it can directly or indirectly act as PPAR agonist suppressing liver fibrosis by activating antioxidant defenses in experimental rodent models\(^{49}\). However, a more recent line of research has focused on human milk-derived extracellular vesicles (HMEVs). HMEVs comprise an external coat of phospholipid bilayer membrane containing a complex cargo of metabolically active molecules such as proteins and miRNAs, which are deemed to be critical for multiple physiological and pathological biological processes\(^{57}\). By inhibiting lipogenesis and increasing lipolysis, HMEVs alleviate steatosis and insulin resistance in a mouse model of high-fat diet-induced NAFLD and inhibit the FFA-induced accumulation of lipids in hepatocyte cultures\(^{58}\). Interestingly, HMEVs also inhibit the proliferation and the expression of fibrogenic mediators, including collagen, α-SMA and TIMP1, and upregulate PPAR- expression in hepatic stellate cells by altering the miRNA profile within such cells\(^{59}\). How long HMEVs, through breastfeeding, can affect offspring’s metabolism and biology remains elusive. However, the above findings may explain how mechanistically breastfeeding protects the offspring from NAFLD and NAFLD-related hepatic fibrosis and may pave the way for innovative treatment approaches in the NAFLD arena.

**CONCLUSIONS**

To sum up, several studies have evaluated the association between breastfeeding and NAFLD [Table 1]. Somewhat external, if not even frankly extraneous to the traditional risk modifiers of liver disease,
understanding breastfeeding as a potentially protective factor for NAFLD in the offspring was initiated by expert liver pediatricians in 2009\textsuperscript{34}. Even more unexpectedly, this line of research has later come to investigate the notion that the mother also receives potential metabolic and hepatological benefits, leading to envisage breastfeeding as a novel NAFLD cofactor, adding to those recently described elsewhere in this journal\textsuperscript{66}.

Protection from NAFLD development and progression has not been universally found in all studies, particularly in as much as the infant side of the dyad is concerned. Importantly, the benefits of breastfeeding against the risk of NAFLD seem to diminish in adolescence and young adulthood\textsuperscript{36,37}. The underlying reasons for this shift, whether it signifies a gradual decline in protection during this life stage or is attributed to disparities among birth cohorts, remain enigmatic. To gain clarity, a sequential assessment of a cohort spanning from childhood to adulthood is warranted.

### Table 1. Principal studies on the association of breastfeeding with NAFLD

<table>
<thead>
<tr>
<th>Author, year [Ref.]</th>
<th>Population description</th>
<th>Findings</th>
<th>Conclusion</th>
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<tr>
<td>Nobili et al. 2009\textsuperscript{34}</td>
<td>Three- to 18-year-old consecutive patients with biopsy-proven NAFLD (n = 191) at a Liver clinic</td>
<td>After adjusting for confounding factors (age, WC, gestational age, and neonatal weight), patients who were breastfed exhibited reduced odds of NASH and fibrosis compared to those who were not breastfed (OR 0.04, 95% CI: 0.01 to 0.10; OR 0.32, 95% CI: 0.16 to 0.65, respectively). Furthermore, the risks of NASH and fibrosis decreased with each additional month of breastfeeding. (OR 0.70, exact 95% CI: 0.001 to 0.87; OR 0.86, exact 95% CI: 0.75 to 0.98, respectively)</td>
<td>Irrespective of the present or neonatal body size of children, breastfeeding protects offspring from NASH and hepatic fibrosis</td>
</tr>
<tr>
<td>Ayonrinde et al. 2017\textsuperscript{35}</td>
<td>A population-based cohort including Australian adolescents (n = 1,170) at the age of 17 years old: 94% exclusive breastfeeding more than 4 M: 15.2% NAFLD by ultrasonography</td>
<td>Irrespective of dietary patterns of the participants, exclusive breastfeeding for ≥ 6, maternal pre-conceptional obesity, and adolescent obesity affected the risk of NAFLD (aOR: 0.64; 95% CI: 0.43-0.94, P = 0.02; aOR: 2.29; 95% CI: 1.21-4.32, P = 0.01; aOR: 9.08; 95% CI: 6.26-13.17, P &lt; 0.001, respectively)</td>
<td>Engaging in exclusive breastfeeding for ≥ 6 months and having a normal maternal pre-pregnancy BMI can help reduce the risk of NAFLD in offspring at age 17 years</td>
</tr>
<tr>
<td>Ajmera et al. 2019\textsuperscript{35}</td>
<td>Within a community-based longitudinal cohort (CARDIA), 844 women who gave birth to ≥ 1 child during the 25-year follow-up were characterized for cumulative breastfeeding duration and hepatic steatosis by CT at Year 25: 43% breastfeeding &gt; 6M: 6% NAFLD by CT.</td>
<td>Compared to those reporting 0-1 month, Women with &gt; 6 months lactation exhibited a reduced risk of NAFLD without and with adjusting for clinical confounders (OR = 0.48, 95% CI: 0.25-0.94; P = 0.03 and aOR 0.46; 95% CI: 0.22-0.97; P = 0.04, respectively).</td>
<td>A longer duration of lactation, particularly exceeding 6 months, is linked to a decreased risk of NAFLD among mothers in midlife</td>
</tr>
<tr>
<td>Abeyeskara et al. 2021\textsuperscript{36}</td>
<td>In a community-based birth cohort (ALSPAC), 2,961 out of 10,018 remaining active offspring participants who met the study criteria were characterized for CAP, breastfeeding history, and maternal and paternal pre-conceptual BMI at 24 years</td>
<td>Any breastfeeding ≥ 6 months had a statistically non-significant protective effect on NAFLD in offspring (OR 0.92 [95% CI: 0.66-1.27] and OR 0.90 [0.67-1.21] respectively), while maternal as well as paternal preconceptual overweight and obesity significantly heightened the risk of NAFLD in offspring.</td>
<td>This 24-year birth cohort study did not find a significant protective effect of breastfeeding against NAFLD in offspring</td>
</tr>
<tr>
<td>Park et al. 2021\textsuperscript{34}</td>
<td>A total of 6,893 Korean parous women aged 30-50 years who participated in the KNHANES were assessed for averaged breastfeeding duration per breastfed child and hepatic steatosis index: 80.3% breastfeeding ≥ 1M per breastfed child: 15.2% NAFLD by HSI</td>
<td>After adjusting for confounding factors, women with lactation ≥ 1 month vs. &lt; 1 month per breastfed child showed a reduced risk of NAFLD (aOR, 0.67; 95% CI: 0.51-0.89). The risk reduction followed a trend with increasing lactation duration, with an aOR of 0.74 for 1-3 months and 0.64 for ≥ 12 months of lactation per breastfed child</td>
<td>Parous women at the age of 30-50 years who breastfed their children for a longer duration exhibited a dose-dependent protective effect against NAFLD in later life</td>
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</table>

ALSPAC: The Avon Longitudinal Study of Parents and Children; aOR: adjusted odds ratio; BMI: body mass index; CAP: controlled attenuation parameter; CARDIA: Coronary Artery Risk Development in Young Adults; CI: confidence interval; CT: computed tomography; HSI: hepatic steatosis index; KNHANES: Korean National Health and Nutrition Examination Survey; NAFLD: nonalcoholic fatty liver disease; NASH: nonalcoholic steatohepatitis; OR: odds ratio; TE: transient elastography; WC: waist circumference.
Figure 1. Lactation and breastfeeding may potentially prevent NAFLD development and progression on both sides of the mother-infant dyad. This cartoon schematically summarizes the potential benefits for both the lactating mother and the breastfed infant. While underlying mechanisms require further clarity, current evidence suggests breastfeeding engages diverse protective pathways, mitigating obesity, metabolic dysfunction, and NAFLD risk in both mothers and offspring. Collectively, as discussed in the text, these benefits may contribute to transforming the vicious circle of cross-generational transmission of NAFLD into a virtuous one\(^{44,61}\). NAFLD: nonalcoholic fatty liver disease.

Differences in the study populations and disease assessment methods probably account for such discrepancies. Therefore, to fill the gap in current knowledge, additional studies must be conducted accounting for confounding factors such as pre-pregnancy BMI of the mother and father, smoking habits, alcohol intake, a history of gestational diabetes, and obesity/diabetes at the time of NAFLD diagnosis. However, this innovative line of research undoubtedly has had the merit of putting together investigators of different cultural extractions, such as pediatricians, gynecologists, hepatologists, and endocrinologists. Their concerted research effort promises to interrupt the vicious cycle of NAFLD transmission across generations\(^{61}\) while gaining further insight into unprecedented disease mechanisms shared by the mother-infant dyad [Figure 1].

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Authors’ contributions
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Editing and final revision of the manuscript: Lonardo A, Suzuki A

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Ethical approval and consent to participate
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REFERENCES
2. WTO. The optimal duration of exclusive breastfeeding: report of an expert consultation.
32. Stefan N, Cusi K. A global view of the interplay between non-alcoholic fatty liver disease and diabetes. Lancet Diabetes Endocrinol 2022;10:284-96. DOI


Reif S, Atias A, Musseri M, Koroukhov N, Gerstl RG. Beneficial effects of milk-derived extracellular vesicles on liver fibrosis progression by inhibiting hepatic stellate cell activation. *Nutrients* 2022;14:4049. DOI PubMed PMC

Lonardo A, Singal AK, Osna N, Kharbanda KK. Effect of cofactors on NAFLD/NASH and MAFLD. a paradigm illustrating the pathomechanics of organ dysfunction. *Metab Target Organ Damage* 2022;2:12. DOI PubMed PMC