


# Maternal hepatitis B or C carrier status and long-term risk for offspring neurological morbidity: a population-based cohort study

Israel Yoles<sup>1,2</sup> , Eyal Sheiner<sup>1</sup>, Naim Abu-Freha<sup>3</sup> and Tamar Wainstock<sup>4</sup>

## Original Article

**Cite this article:** Yoles I, Sheiner E, Abu-Freha N, and Wainstock T. (2022) Maternal hepatitis B or C carrier status and long-term risk for offspring neurological morbidity: a population-based cohort study. *Journal of Developmental Origins of Health and Disease* 13: 115–119. doi: [10.1017/S2040174420001397](https://doi.org/10.1017/S2040174420001397)

Received: 4 August 2020  
Revised: 15 December 2020  
Accepted: 15 December 2020  
First published online: 21 January 2021

### Keywords:

Pregnancy; follow-up studies; hepatitis B; hepatitis C; nervous system diseases

### Address for correspondence:

Israel Yoles MD, Clalit Health Services, the Central District, 30 Hertzl St., Rishon LeZion, Israel. Email: [yoles@netvision.net.il](mailto:yoles@netvision.net.il)

<sup>1</sup>Department of Obstetrics and Gynecology, Soroka University Medical Center, Ben-Gurion University of the Negev, Beer-Sheva, Israel; <sup>2</sup>Clalit Health Services, The Central District, Rishon LeZion, Israel; <sup>3</sup>Gastroenterology and Hepatology Department, Soroka University Medical Center, Ben-Gurion University of the Negev, Beer-Sheva, Israel and <sup>4</sup>Department of Public Health, Faculty of Health Sciences, Ben-Gurion University of the Negev, Beer-Sheva, Israel

### Abstract

Hepatitis B and hepatitis C (HBV/HCV) are important global public health concerns. We aimed to evaluate the association between maternal HBV/HCV carrier status and long-term offspring neurological hospitalisations. A population-based cohort analysis compared the risk for long-term childhood neurological hospitalisations in offspring born to HBV/HCV carrier vs. non-carrier mothers in a large tertiary medical centre between 1991 and 2014. Childhood neurological diseases, such as cerebral palsy, movement disorders or developmental disorders, were pre-defined based on ICD-9 codes as recorded in hospital medical files. Offspring with congenital malformations and multiple gestations were excluded from the study. A Kaplan–Meier survival curve was constructed to compare cumulative neurological hospitalisations over time, and a Cox proportional hazards model was used to control for confounders. During the study period (1991–2014), 243,682 newborns met the inclusion criteria, and 777 (0.3%) newborns were born to HBV/HCV mothers. The median follow-up was 10.51 years (0–18 years). The offspring from HBV/HCV mothers had higher incidence of neurological hospitalisations (4.5 vs. 3.1%, hazard ratio (HR) = 1.91, 95% CI 1.37–2.67). Similarly, the cumulative incidence of neurological hospitalisations was higher in children born to HBV/HCV carrier mothers (Kaplan–Meier survival curve log-rank test  $p < 0.001$ ). The increased risk remained significant in a Cox proportional hazards model, which adjusted for gestational age, mode of delivery and pregnancy complications (adjusted HR = 1.40, 1.01–1.95,  $p = 0.049$ ). We conclude that maternal HBV or HCV carrier status is an independent risk factor for the long-term neurological hospitalisation of offspring regardless of gestational age and other adverse perinatal outcomes.

## Introduction

Infection with hepatitis B and hepatitis C (HBV/HCV) is a major public health problem.<sup>1</sup> Approximately two billion people worldwide have been infected with HBV. Overall, 360 million have chronic infection, and 600,000 die each year from HBV-related liver disease.<sup>1,2</sup> Most chronic HBV infections are acquired in infancy or early childhood, primarily through mother-to-child transmission.<sup>1,3</sup> Exposure later in life can also lead to chronic infection but more frequently results in viral clearance and immunity.<sup>2</sup>

The estimated global prevalence of hepatitis C (HCV) is 1.5–2%, affecting up to 71 million people.<sup>4</sup> The prevalence of HCV acquired by vertical transmission is 0.2–0.4% in the USA and Europe.<sup>5</sup> Perinatal transmission of HBV/HCV from an infected mother to her infant may occur via the following three possible routes: (1) transplacental transmission of virus in utero<sup>4–7</sup>; (2) perinatal transmission during delivery and (3) postnatal transmission.<sup>8,9</sup>

Maternal HBV/HCV has been found to be associated with adverse pregnancy and delivery outcomes, including premature deliveries, premature rupture of membranes, placental abruption, caesarean deliveries, perinatal mortality, congenital malformations and low birthweight,<sup>10,11</sup> as well as later effects on offsprings' health during childhood and adulthood, including long-term gastrointestinal morbidity,<sup>12</sup> higher prevalence of respiratory\*,<sup>13</sup> endocrine<sup>14</sup> and infectious hospitalisations.<sup>15</sup> However, to the best of our knowledge, the effect on neurological morbidity has not yet been investigated.

Therefore, we sought to examine the association between maternal HBV/HCV status during pregnancy and offspring neurological hospitalisations during childhood.

© The Author(s), 2021. Published by Cambridge University Press in association with International Society for Developmental Origins of Health and Disease. This is an Open Access article, distributed under the terms of the Creative Commons Attribution-NonCommercial-ShareAlike licence (<http://creativecommons.org/licenses/by-nc-sa/4.0/>), which permits non-commercial re-use, distribution, and reproduction in any medium, provided the same Creative Commons licence is included and the original work is properly cited. The written permission of Cambridge University Press must be obtained for commercial re-use.

## Method

### Study design

A population-based cohort analysis was performed, which included all singleton infants born between the years 1991 and 2014 and discharged alive from Soroka University Medical Centre (SUMC). SUMC is the only tertiary hospital in Israel's southern region and includes the largest birth centre in Israel. In Israel, all prenatal care and tests are fully covered by a national health law, allowing free access to prenatal care; therefore, this is a non-selective population-based study. The study protocol was approved by the SUMC institutional review board, and informed consent was exempt.

The independent variable was defined as maternal HBV/HCV status verified through medical records, which were summarised in an electronic chart. The perinatal data set consisted of information recorded directly following delivery by the midwife and obstetrician. This perinatal data set was cross-linked and matched with the paediatric hospitalisation data set based on personal identifying numbers of both the mother and offspring.

The outcome variable was defined as the first paediatric hospitalisation of the offspring with any neurological diagnosis. The paediatric hospitalisation data set included ICD-9 codes for the diagnoses as well as demographic information. All neurological diagnoses mentioned in the paediatric admission/discharge database were identified and grouped. A list of the grouped diagnoses and ICD-9 codes is presented in Supplementary Table 1. The follow-up time in the study was calculated from birth to an event, death (if occurred in the hospital), end of the study period or age 18 (censored). If more than one neurological diagnosis existed in the record of first hospitalisation, all diagnoses were counted and compared between the study groups. Since neurodevelopmental impairment maybe higher in newborns with congenital malformations or multiple gestations, these newborns were excluded from the study. The study protocol was approved by the SUMC institutional review board, and informed consent was exempt.

### Statistical analysis

The initial analysis compared the background, pregnancy and perinatal characteristics of the two study groups using chi-square (or Fisher's exact test in case less than 5 cases per cell) and *t*-tests based on variable characteristics and normal distribution. All analyses were two-sided with  $p < 0.05$  considered statistically significant.

The background and perinatal characteristics included maternal age, parity, pregnancy complications (such as pregestational or gestational diabetes [GDM]), hypertensive disorders of pregnancy (including chronic hypertension, gestational hypertension and preeclampsia) and gestational age at delivery.

Individual diagnoses were grouped, that is, movement disorders or developmental disorders (Supplementary Table 1) and the analysis was conducted on the group level.

Incidence rates of neurological-related hospitalisations were calculated and compared between study groups. Kaplan–Meier survival curves were constructed, and the cumulative neurological-related hospitalisation incidence was compared between the groups using the Cox–Mantel log-rank test.

A Cox multivariable survival analysis was conducted, after verifying its assumptions were met, to study the association between either HCV or HBV and neurological-related hospitalisations while adjusting for confounding variables. In addition to variables with clinical importance, variables significantly different between

the study groups, which were also associated with morbidity risk (but were not an intermediate variable between exposure and outcome) and suspected as confounders, were considered in the multivariable models. These variables included maternal and gestational age (continuous), and pregnancy complications (dichotomised), year of birth (to address possible cohort effect) and ethnicity (as a measure of socio-economic status). The final model was selected based on best fit and minimum log-likelihood.

## Results

During the study period, 242,342 newborns met the inclusion criteria. In total, 777 (0.3%) newborns were born to mothers with either HCV or HBV (HBV/HCV+), and 241,571 (99.7%) newborns were born to non-HBV/non-HCV mothers. Table 1 presents background characteristics of the study groups. HBV/HCV mothers were older than non-HBV/non-HCV mothers, and they were more likely to have hypertensive disorders, premature deliveries, low birthweight and caesarean delivery.

During the follow-up period (median = 10.51 years; range = 0–18 years), 7543 neurological-related hospitalisations were documented (3.1%). The incidence rates by study group of selected neurological morbidities at hospitalisations are presented in Table 2. Compared to the offspring of non-HBV/non-HCV mothers, a higher incidence of neurological-related hospitalisations was documented among offspring in the HBV/HCV group (4.5 vs. 3.1%, HR = 1.92, 1.37–2.67). Specifically, hospitalisations for movement and developmental disorders were more likely to occur in the offspring of HBV/HCV mothers (3.6 vs. 1.8%, HR = 2.35, 1.62–3.40 and 0.4 vs. 0.1%, HR = 4.91, 1.57–15.33), respectively.

Fig. 1 presents the Kaplan–Meier log of survival for total neurological hospitalisations by study group. Cumulative survival among non-HBV/non-HCV offspring was significantly higher than that of HBV/HCV offspring (log-rank  $p < 0.001$ ).

Table 3 shows the results of the Cox multivariable model comparing the risk for hospitalisation with neurological morbidities between study groups. The model adjusted for maternal age, gestational age, diabetes (gestational or pregestational), hypertension (gestational or chronic), delivery mode (caesarean vs. vaginal delivery), ethnicity and year of birth. Compared to non-HBV/non-HCV offspring, HBV/HCV offspring were at increased risk for neurological-related hospitalisations (adjusted HR = 1.40, 1.01–1.95).

## Discussion

In the current study, maternal HBV/HCV was associated with a significantly increased risk for offspring neurological-related hospitalisations, mainly for movement disorders (tremor, chorea and other extrapyramidal movement disorders) and developmental disorders (mild cognitive impairment, unspecified mental retardation and unspecified delay in development; Supplement A). To the best of our knowledge, this association has not yet been described. Maternal HBV/HCV was previously found to be associated also with offspring endocrine, respiratory and infectious morbidity.<sup>13–15</sup> Thus, offspring of mothers having a chronic infectious disease (HBV/HCV) are prone to higher risk of non-communicable diseases, confirming again the concept of fetal origin of lifespan diseases. Because HBV/HCV mothers had higher premature birth rates, one may speculate that this may explain higher rates of neurological hospitalisations in offspring. However, this association remained significant even

**Table 1.** Obstetrical and perinatal characteristics by maternal HBC/HCV status

	HBV or HCV <i>n</i> (%) 777 (0.3)	Non-HBC and non-HCV <i>n</i> (%) 242,905 (99.7)	OR, 95% CI, <i>p</i>
Maternal age (mean ± SD)	29.25 ± 5.8	28.16 ± 5.8	<i>p</i> < 0.001
Ethnicity			2.02, 1.75–2.34, <i>p</i> < 0.001
Jewish	501 (64.5)	114,853 (47.3)	
Bedouin	276 (35.5)	128,052 (52.7)	
Parity			<i>p</i> = 0.013
1	209 (26.9)	57,296 (23.6)	
2–4	403 (51.9)	124,111 (51.1)	
≥5	165 (21.2)	61,445 (25.3)	
Diabetes mellitus (gestational and pregestational)	39 (5.0)	12,120 (5.0)	1.00, 0.73–1.39, <i>p</i> = 0.94
Hypertensive disorders (gestational and chronic)	56 (7.2)	12,191 (5.0)	1.47, 1.12–1.93, <i>p</i> = 0.007
Caesarean delivery	180 (23.2)	32,846 (13.5)	1.93, 1.63–2.28, <i>p</i> < 0.001
Gestational age (weeks) (mean ± SD)	38.7 ± 2.1	39.1 ± 1.9	<i>p</i> < 0.001
Premature delivery (<37 gestational weeks)	73 (9.4)	16,647 (6.9)	1.41, 1.11–1.79, <i>p</i> = 0.006
Birthweight (g) (mean ± SD)	3,195 ± 590	3,205 ± 510	<i>p</i> = 0.57
Low birthweight (<2,500 g)	74 (9.5)	16,330 (6.7)	1.46, 1.15–1.86, <i>p</i> = 0.002
Apgar 5 score <7	12 (1.5)	5,497 (2.3)	0.68, 0.38–1.19, <i>p</i> = 0.23
Newborn gender			1.07, 0.93–1.24, <i>p</i> = 0.31
Male	409 (52.6)	123,468 (50.8)	
Female	368 (47.4)	119,437 (49.2)	
Perinatal mortality	6 (0.8)	1,334 (0.5)	1.41, 0.63–3.15, <i>p</i> = 0.33

**Table 2.** Main neurological hospitalisations

	HBV or HCV carrier <i>n</i> = 771 (0.3%)	Non-HBV or non-HCV carrier <i>n</i> = 241,571 (99.7%)	Hazard ratio, 95% CI
Movement disorders	28 (3.6)	4444 (1.8)	2.35, 1.62–3.40
Developmental disorders	3 (0.4)	236 (0.1)	4.91, 1.57–15.33
Eating disorders	1 (0.1)	434 (0.2)	0.91, 0.13–6.49
CP, plegia, palsy	1 (0.1)	200 (0.1)	2.36, 0.33–16.88
Psychiatric, emotional	3 (0.4)	1,192 (0.5)	1.03, 0.33–3.20
Other	2 (0.3)	915 (0.4)	1.72, 0.43–6.89
Total neurological	35 (4.5)	7508 (3.1)	1.92, 1.37–2.67

after adjusting for mode and week and of delivery as well as maternal complications (Table 3).

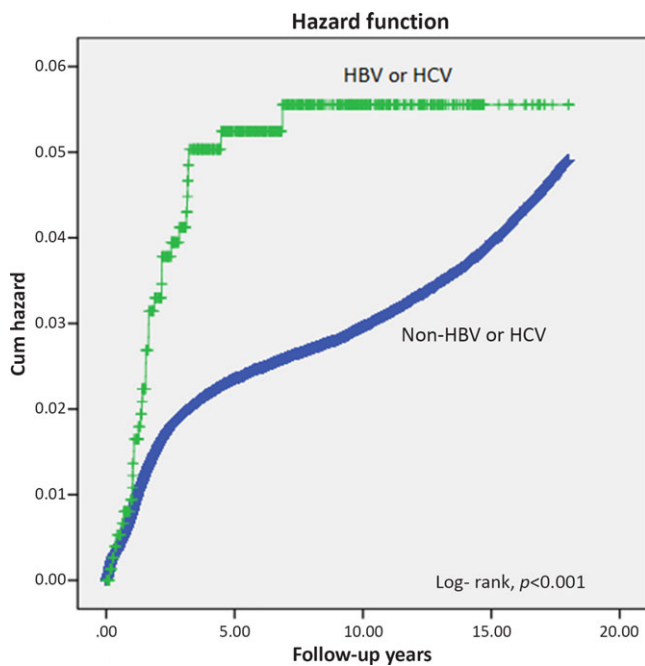
Several theories may explain these findings, including the microbiome theory, which suggest that HBV alters the normal gut microbiota.<sup>16,17</sup> Immune alterations, such as viral infections during pregnancy, have been shown to alter maternal intestinal microbiome, resulting in potentially long-lasting consequences for offspring.<sup>17</sup> Moreover, among patients with chronic HBV infection, the composition of gastrointestinal fungi has been found to be positively correlated with disease progression.<sup>18</sup> Alterations in maternal microbiota have been found to affect various offspring health conditions, such as fetal microbiome,<sup>19</sup> glucose and lipid metabolism.<sup>20</sup> In animal models, an aberrant maternal microbiome

has been shown to affect fetal brain development, and neurodevelopmental disorders have been suggested to determine life-long neurological outcomes.<sup>21,22</sup> Moreover, HBV/HCV women had a higher rate of caesarean delivery, which was shown to alter fetal microbiome as compared to vaginal deliveries.<sup>23,24</sup> Thus, maternal microbiome changes in chronic HBV/HCV carriers contribute, at least in part, to the higher incidence of neurological diseases in offspring.

The association between maternal HBV/HCV and neurological disorders in offspring may also be explained by the immune theory. Several animal studies have shown that alteration in maternal immune response following viral infections results in increased incidence of various developmental, neurological and

**Table 3.** Cox multivariable model for the association between HBV/HCV mothers and offspring neurological hospitalizations

	Hazard ratio, 95% CI	<i>p</i>
HBV/HCV offspring vs. non-HBV/non-HCV offspring	1.40, 1.01-1.95	0.049
Maternal age	0.99, 0.99-1.00	0.01
Gestational age	0.95, 0.94-0.96	<0.0001
Diabetes (pregestational or gestational)	1.14, 1.03-1.26	0.009
Hypertension (chronic or gestational-related)	1.20, 1.10-1.32	<0.001
Caesarean vs. vaginal delivery	1.15, 1.08-1.23	<0.001
Ethnicity	1.02, 0.97-1.07	0.41
Year of birth	1.10, 1.09-1.10	<0.001

**Fig. 1.** Kaplan–Meier log of survival for total neurological hospitalisations by study group (*n* at risk = 242,342).

psychiatric disorders.<sup>25–28</sup> Injecting pregnant rodents with bacterial lipopolysaccharide, which induces strong innate immune responses in the absence of infection, results in behavioural and histological abnormalities in adult offspring similar to those observed in offspring of infected mothers.<sup>25</sup> Other studies in animal models have shown that alterations in maternal immune response result in increased incidence of various developmental, neurological and psychiatric disorders.<sup>26,27</sup>

HBV and HCV have been found to trigger epigenetic changes in hepatitis carriers,<sup>29–31</sup> which may also explain the present findings. Cheng *et al.* found altered DNA methylation status in offspring of mothers with HBV compared to offspring of non-infected mothers, and these authors concluded that prenatal HBV exposure, even without malformations or premature birth, may alter the epigenome profile in newborns.<sup>32</sup>

Our study has several strengths. This is a long follow-up study on a large cohort of a single tertiary hospital in this region. Thus, offspring born in this centre are admitted to the same hospital, which enables accessibility to data regarding offspring hospitalisation events.

Our study has several limitations. The study data were obtained from hospital admission charts; therefore, we expect an underestimation of the outcome because only the more severe cases of neurological morbidities are hospitalised. This misclassification, however, would most likely be non-differential and occur independently of maternal HBV/HCV status, and it would shift our findings towards the null hypothesis. In addition, data on antiviral treatment of HBV/HCV mothers were unavailable, but most parturients do not require therapy. Antiviral therapies are listed as category B or C under the FDA pregnancy categories.<sup>33,34</sup> Therefore, it is unlikely that maternal antiviral treatment accounted for our findings.

Studies should further investigate whether changes in the microbiome of HBV/HCV mothers, immune system modulation or epigenetic changes lead to increased susceptibility to neurological hospitalisations as found in the current study. Future studies should also include data on antiviral treatments and consider their effect on offspring health.

## Conclusions

Maternal HBV/HCV during pregnancy is associated with a significantly increased risk for offspring neurological hospitalisations. These findings may be explained, at least in part, by microbiome, immune or epigenetic changes in the offspring of mothers with HBV/HCV, but the exact mechanism merits further investigation.

**Supplementary material.** To view supplementary material for this article, please visit <https://doi.org/10.1017/S2040174420001397>

**Financial support.** No financial support was received for the study.

**Conflicts of interest.** None of the authors have any commercial association or other conflicts of interest to declare.

**Ethical standards.** The study protocol was approved by the SUMC institutional review board, and informed consent was exempt.

## References

1. Cooke GS, Andrieux-Meyer I, Applegate TL, *et al.* Accelerating the elimination of viral hepatitis: a lancet gastroenterology & hepatology commission. *Lancet Gastroenter Hepatol.* 2019; 4, 135–184.
2. Shepard CW, Simard EP, Finelli L, Fiore AE, Bell BP. Hepatitis B virus infection: epidemiology and vaccination. *Epidemiol Rev.* 2006; 28, 112–125.
3. Tang LSY, Covert E, Wilson E, Kottlilil S. Chronic hepatitis B infection a review. *J Am Med Assoc.* 2018; 319, 1802–1813.
4. Thomas DL. Global elimination of chronic hepatitis. *N Engl J Med.* 2019; 380, 2041–2050.
5. Dibba P, Cholankeril R, Li AA, *et al.* Hepatitis C in pregnancy. *Diseases* 2018; 6, 31.
6. Towers CV, Asrat T, Rumney P. The presence of hepatitis B surface antigen and deoxyribonucleic acid in amniotic fluid and cord blood. *Am J Obstet Gynecol* 2001; 184, 1514–1520.
7. Wiseman E, Fraser MA, Holden S, *et al.* Perinatal transmission of hepatitis B virus: an Australian experience. *Med J Austr* 2009; 190, 489–492.
8. Chaudhary RK. Perinatal transmission of hepatitis B virus. *Can Med Assoc J.* 1983; 128, 664–666.

9. Le Campion A, Larouche A, Fauteux-Daniel S, Soudeyns H. Pathogenesis of hepatitis C during pregnancy and childhood. *Viruses* 2012; 4, 3531–3550.
10. Money D, Boucoiran I, Wagner E, et al. Obstetrical and neonatal outcomes among women infected with hepatitis C and their infants. *J Obstetr Gynaecol Canada* 2014; 36, 785–794.
11. Safir A, Levy A, Sikuler E, Sheiner E. Maternal hepatitis B virus or hepatitis C virus carrier status as an independent risk factor for adverse perinatal outcome. *Liver Int.* 2010; 30, 765–770.
12. Yoles I, Sheiner E, Abu-Freha N, Wainstock T. Maternal hepatitis B or C status and the long-term risk of gastrointestinal morbidity for offspring: a population-based cohort study. *Liver Int.* 2019. doi: [10.1111/liv.14193](https://doi.org/10.1111/liv.14193).
13. Govrin-Yehudain Y, Wainstock T, Abu-Freha N, Sheiner E. Maternal hepatitis B virus and hepatitis C virus carrier status during pregnancy and long-term respiratory complications in the offspring. *Early Hum Dev.* 2019; 140, 104904.
14. Abu Freha N, Wainstock T, Menachem TN, Sheiner E. Maternal hepatitis B virus or hepatitis C virus carrier status and long-term endocrine morbidity of the offspring - a population-based cohort study. *J Clin Med.* 2020; 9, 796.
15. Abu Freha N, Wainstock T, Poupko L, Yonat Shemer A, Sergienko R, Sheiner E. Maternal hepatitis B or hepatitis C virus carrier status and long-term infectious morbidity of the offspring: a population-based cohort study. *J Viral Hepat.* 2020; 27, 794–799.
16. Wei X, Yan X, Zou D, et al. Abnormal fecal microbiota community and functions in patients with hepatitis B liver cirrhosis as revealed by a metagenomic approach. *Bio-Med Centr Gastroenterol.* 2013; 13, 175.
17. Zhang Y, Lun CY, Tsui S. Metagenomics: a new way to illustrate the cross-talk between infectious diseases and host microbiome. *Int J Mol Sci* 2015; 16, 26263–26279.
18. Chen Y, Chen Z, Guo R, et al. Correlation between gastrointestinal fungi and varying degrees of chronic hepatitis B virus infection. *Diagn Microbiol Infect Disease* 2011; 70, 492–498.
19. Bhagavata Srinivasan SP, Raipuria M, Bahari H, Kaakoush NO, Morris MJ. Impacts of diet and exercise on maternal gut microbiota are transferred to offspring. *Front Endocrinol* 2018; 29, 716
20. Zhou L, Xiao X, Zhang Q, et al. Improved glucose and lipid metabolism in the early life of female offspring by maternal dietary genistein is associated with alterations in the gut microbiota. *Front Endocrinol* 2018; 9, 516.
21. Degroote S, Hunting DJ, Baccarelli AA, Takser L. Maternal gut and fetal brain connection: Increased anxiety and reduced social interactions in Wistar rat offspring following peri-conceptional antibiotic exposure. *Progr Neuro-Psychopharmacol Biol Psychiatry* 2016; 71, 76–82.
22. Hsiao EY, McBride SW, Hsien S, et al. Microbiota modulate behavioral and physiological abnormalities associated with neurodevelopmental disorders. *Cell.* 2013; 155, 1451–1463.
23. Salas Garcia MC, Yee AL, Gilbert JA, Dsouza M. Dysbiosis in children born by caesarean section. *Ann Nutr Metab.* 2018; 73 (Suppl. 3), 24–32.
24. Shao Y, Forster SC, Tsaliki E, et al. Stunted microbiota and opportunistic pathogen colonization in caesarean-section birth. *Nature* 2019; 574, 117–121.
25. Shi L, Tu N, Patterson PH. Maternal influenza infection is likely to alter fetal brain development indirectly: the virus is not detected in the fetus. *Int J Dev Neurosci.* 2005; 23, 299–305.
26. Patterson PH. Maternal infection: window on neuroimmune interactions in fetal brain development and mental illness. *Curr Opin Neurobiol.* 2002; 12, 115–118.
27. Patterson PH. Maternal influenza infection leads to neuropathology and behavioral abnormalities in adult offspring. *Neuropsychopharmacology* 2005; 30, S9–S9.
28. Armario A, Hernandez J, Bluethmann H, Hidalgo J. IL-6 deficiency leads to increased emotionality in mice: evidence in transgenic mice carrying a null mutation for IL-6. *J Neuroimmunol.* 1998; 92, 160–169.
29. Vivekanandan P, Daniel HDJ, Kannangai R, Martinez-Murillo F, Torbenson M. Hepatitis B virus replication induces methylation of both host and viral DNA. *J Virol.* 2010; 84, 4321–4329.
30. Khan FS, Ali I, Afridi UK, Ishtiaq M, Mehmood R. Epigenetic mechanisms regulating the development of hepatocellular carcinoma and their promise for therapeutics. *Hepatol Int.* 2017; 11, 45–53.
31. Hong X, Kim ES, Guo H. Epigenetic regulation of hepatitis B virus covalently closed circular DNA: implications for epigenetic therapy against chronic hepatitis B. *Hepatology* 2017; 66, 2066–2077.
32. Cheng Q, Zhao B, Huang Z, et al. Epigenome-wide study for the offspring exposed to maternal HBV infection during pregnancy, a pilot study. *Gene* 2018; 658, 76–85.
33. Wong GLH, Seto WK, Wong VW-S, Yuen MF, Chan HL-Y. Review article: long-term safety of oral anti-viral treatment for chronic hepatitis B. *Aliment Pharmacol Therapeut.* 2018; 47, 730–737.
34. Bzowej NH. Hepatitis B therapy in pregnancy. *Curr Hepatitis Rep.* 2010; 9, 197–204.