The association of exposure to hepatitis B and C viruses with lung function and respiratory disease: A population based study from the NHANES III database

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KEYWORDS
Hepatitis B and C virus;
FEV₁;
FVC;
Asthma;
COPD;
Lung function

Summary

Background: Globally, 500 million people are chronically infected with Hepatitis B virus (HBV) and Hepatitis C virus (HCV). While these viruses are notorious for their detrimental effect on the liver they are also known to affect multiple organs in the body including the lungs.

Aim: To investigate if exposure to HBV and HCV is associated with lung function and respiratory diseases.

Methods: Data from the Third National Health and Nutrition Examination Survey (NHANES III) was analysed using multiple linear regressions to investigate the association between exposure to HBV and HCV with the various measures of lung function, while multiple logistic regressions were used to evaluate the association with the respiratory diseases asthma and chronic obstructive pulmonary disease (COPD).

Results: Exposure to HCV was significantly associated with an increase in Forced Expiratory Volume in 1 s, FEV₁ (Coef: 97.94 ml, 95% CI: 38.87 to 157.01) and Full Vital Capacity, FVC (Coef: 90 ml, 95% CI: 14.50 to 166.24). Individuals who had been exposed to both HBV and HCV also had a significantly higher FEV₁ (Coef: 145.82, CI: 60.68 to 230.94) and FVC (Coef: 195.09, CI: 78.91 to 311.26). There was also a significant association between exposure to HBV and asthma (OR: 1.28, 95% CI: 1.05 to 1.58). These associations were no longer significant after additionally adjusting for cocaine and marijuana use as well as poverty income ratio.

Conclusion: Our research implies that hepatotropic viruses may affect the respiratory system, but more work at a population level is needed to further explore these associations.

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Background

Hepatitis B virus (HBV) and hepatitis C virus (HCV) account for the majority of chronic blood-borne infections affecting the liver. Both are major public health problems and are among the top ten causes of death by infectious diseases worldwide [1,2]. Currently, 500 million people around the world are chronically infected with HBV or HCV — this translates to about 1 in every 12 individuals [3]. Furthermore, co-infection with these viruses is possible due to similar modes of transfer (e.g., blood transfusion, intravenous drug use, sexual contact, percutaneous injuries in a hospital setting), resulting in a more potent disease [2,4–7].

While the hepatotrophic effects of HBV and HCV are well-known, these viruses also produce systemic effects [8,9]. Research has shown that these infections (HCV in particular) manifest in several extrapathic conditions such as lymphoproliferative, dermatological, nephrological, neurological, endocrinological, cardiocirculatory and pulmonary disorders [10–14]. So far, mixed cryoglobulinemia and non-hodgkin’s lymphoma are the two most common conditions associated with hepatitis virus infections [15].

There have been many biological mechanisms put forth as to how viral hepatitis affects the lungs. The effects on the lung could be direct or indirect. Directly, several studies and case reports have linked HCV to interstitial lung disease [16–28], asthma [29,30], COPD [31] and found these viruses to affect lung function [30,32,33]. Indirect effects are thought to arise through associated diseases such as cryoglobulinaemia [21,34–41], liver cirrhosis [42] or in relation to treatment used for HCV — interferon therapy, which has been known to cause the development of pulmonary sarcoidosis, interstitial lung disease and other pulmonary complications [28,43–61].

An association between systemic viral infections and lung disease had been suggested some years ago but despite the increasing numbers of HBV and HCV patients diagnosed, it has not become an obvious clinical issue either in the respiratory or gastrointestinial clinics [16–19,62]. Furthermore, research in this area has been very mixed and has largely been in the form of case reports. Much research on this topic has focused on the effect of HCV on the lung while HBV or HBV–HCV co-infection has not been considered. There is also very limited literature on whether HBV or HCV infection is associated with COPD or asthma. To examine whether earlier findings of an association imply a bias in reported studies or if this association just being missed in clinical practice, we have performed a population based study utilising objective spirometric measures of lung function and questionnaires to identify respiratory diseases.

Methods

Study population

This research was secondary analysis study conducted using data from the Third National Health and Nutrition Examination Survey (NHANES III). The NHANES III is a series of surveys conducted of the U.S. non-institutionalised population carried out between 1988 and 1994 [63]. Full details of the examination and survey procedures have been published by the National Centre for Health Statistics [63]. All participants aged over 17 years of age were included in the analysis, provided they had complete data for relevant exposures, outcomes, and confounding factors. Institutional Review Board (IRB) approval and documented consent was obtained from participants [64].

Data collection

Questionnaire data was collected by trained interviewers who gathered information on age, sex, race/ethnicity, medical history, socioeconomic status, smoking history and illicit drug use history. Participants attended a mobile examination unit where all anthropometric measurements were taken: height, weight, waist measurements and hip measurements. Blood samples were taken for biochemical assays [65]. Spirometric measurements were taken to provide data on FEV₁ and FVC [66].

Statistical analyses

Participants were classified into three groups based on their self-reported smoking history: never-smokers, current smokers and ex-smokers. Total cigarette smoking was quantified in terms of pack-years. The ratio of FEV₁ to FVC was calculated: FEV₁/FVC. Asthma was defined as self-reported physician-diagnosed asthma [65]. Chronic Obstructive Pulmonary Disease was defined using the Global Initiative for Chronic Obstructive Lung Disease (GOLD) spirometry criteria: FEV₁/FVC < 70% and FEV₁ < 80% percent-predicted (percentage of the average expected of someone of your height, age, sex and race) [66]. COPD was also defined through the self-reporting of participants on being diagnosed by a physician with emphysma and/or chronic bronchitis [9,66]. Hepatitis B core antibody (anti-HBC) positivity was used to determine exposure to HBV, while Hepatitis B surface antigen (HBsAg) positivity showed infection with HBV [67]. Hepatitis C antibody (anti-HCV) positivity was used to determine exposure to HCV [6,68]. The poverty income ratio (PIR) was calculated as a ratio of the midpoint of the observed family income category to the poverty threshold [65]. Body mass index (BMI) was calculated: weight (kg)/height (m²). Waist to Hip ratio was calculated: waist circumference/hip circumference. Total cocaine and marijuana usage in the participant’s lifetime was also taken into account — this was only measured in patients aged 18–60 years old.

The associations of HBV and HCV infection with COPD and asthma were analysed using a multiple logistic regression model and the baseline model included adjustments for the following a priori confounders: age, sex, race-ethnicity and smoking history (status and years of smoking). BMI, waist: hip ratio, cocaine and marijuana use as well as poverty income ratio were also checked and added to the baseline model if they changed the regression coefficient or odds ratio by 10% or more when added to the model. The associations of HBV and HCV infection with FEV₁, FVC and FEV₁/FVC were analysed using a multiple linear regression models and adjusted for the a priori confounders: age, sex,
height, race-ethnicity and smoking history (status and years of smoking) and similar additional confounders as before. The data analysis was carried out using STATA version 11.

Results

From the total study population of 20,050 subjects aged 17 to 90 over years who provided data for the NHANES III survey, 14,055 people met the inclusion criteria for the baseline model (including a priori confounders). After eliminating a further 4896 individuals for missing data on the additional confounders, marijuana use, cocaine use and poverty-income ratio, the restricted study population model was 9159 people (Table 1).

The demographics and other characteristics of the subjects in the study population and excluded group were very similar except that the excluded subjects were on average about 8 years older than the included subjects. Among the study population, the prevalence of COPD was 11.8%, anti-
HBc positive was 6.9%, HBsAg positive was 0.3%, anti-HCV was 2.3% and the prevalence both anti-HBc positive and anti-HCV positive was 0.9%. The excluded group had a higher percentage of subjects who had COPD (15%), were anti-HBc positive (15%), HBsAg positive (1.1%), anti-HCV (2.5%) and positive for both anti-HBc and anti-HCV (1.5%) compared to the study population (Table 1).

Individuals positive for anti-HCV showed a significant increase of nearly 100 ml (95% CI: 38.87 to 157.01) of FEV₁ and a significant rise of 90 ml (95% CI: 14.50 to 166.24) of FVC in the study population. Similarly in individuals positive for both anti-HCV and anti-HBc there was a significant increase of 145 ml (95% CI: 60.68 to 230.94) of FEV₁ and 195 ml of FVC (95%: 78.91 to 311.26) in the study population but not in the restricted study population in which there was additional adjustment for cocaine and marijuana use as well as poverty income ratio (Table 2).

Individuals positive for anti-HBc were 28% more likely to have asthma than an individual negative for anti-HBc (95% CI: 1.05 to 1.58) and this relationship was again

### Table 2 Association of hepatitis B and hepatitis C serum markers with lung function and respiratory diseases.

<table>
<thead>
<tr>
<th>FEV₁</th>
<th>Serum markers</th>
<th>Baseline population (n = 14,055)</th>
<th>Restricted population (n = 9159)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>FEV₁ Coef. (mL)</td>
<td>95% CI</td>
<td>FEV₁ Coef. (mL)</td>
</tr>
<tr>
<td>Anti-HBc</td>
<td>-5.96&lt;sup&gt;b&lt;/sup&gt;</td>
<td>-36.66 to 24.73</td>
<td>-12.76</td>
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<tr>
<td>HBsAg</td>
<td>-3.15</td>
<td>-174.86 to 168.56</td>
<td>27.98</td>
</tr>
<tr>
<td>Anti-HCV</td>
<td>97.94</td>
<td>38.87 to 157.01</td>
<td>46.87</td>
</tr>
<tr>
<td>Anti-HCV &amp; Anti-HBc</td>
<td>145.81&lt;sup&gt;b&lt;/sup&gt;</td>
<td>60.68 to 230.94</td>
<td>72.13</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>FVC</th>
<th>Serum markers</th>
<th>Baseline population (n = 14 055)</th>
<th>Restricted population (n = 9159)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>FVC Coef. (mL)</td>
<td>95% CI</td>
<td>FVC Coef. (mL)</td>
</tr>
<tr>
<td>Anti-HBc</td>
<td>-17.97</td>
<td>-53.21 to 17.49</td>
<td>-26.95</td>
</tr>
<tr>
<td>HBsAg</td>
<td>-18.91</td>
<td>-236.01 to 198.16</td>
<td>35.65</td>
</tr>
<tr>
<td>Anti-HCV</td>
<td>90.37</td>
<td>14.50 to 166.24</td>
<td>83.50</td>
</tr>
<tr>
<td>Anti-HCV &amp; Anti-HBc</td>
<td>195.09&lt;sup&gt;b&lt;/sup&gt;</td>
<td>78.91 to 311.26</td>
<td>-53.19</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>FEV₁:FVC</th>
<th>Serum markers</th>
<th>Baseline population (n = 14 055)</th>
<th>Restricted population (n = 9159)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>FEV₁:FVC Ratio Coef. (%)</td>
<td>95% CI</td>
<td>FEV₁:FVC Ratio Coef. (%)</td>
</tr>
<tr>
<td>Anti-HBc</td>
<td>0.02&lt;sup&gt;b&lt;/sup&gt;</td>
<td>-0.53 to 0.56</td>
<td>0.08</td>
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<tr>
<td>HBsAg</td>
<td>0.88</td>
<td>-0.11 to 1.88</td>
<td>0.50</td>
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<tr>
<td>Anti-HCV</td>
<td>0.02&lt;sup&gt;b&lt;/sup&gt;</td>
<td>-1.54 to 1.57</td>
<td>0.40</td>
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<tr>
<td>Anti-HCV &amp; Anti-HBc</td>
<td>-0.69</td>
<td>-3.42 to 2.41</td>
<td>1.30&lt;sup&gt;e&lt;/sup&gt;</td>
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<table>
<thead>
<tr>
<th>Asthma</th>
<th>Serum markers</th>
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<th>Restricted population (n = 9159)</th>
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<tr>
<td></td>
<td>Odds ratio</td>
<td>95% CI</td>
<td>Odds ratio</td>
</tr>
<tr>
<td>Anti-HBc</td>
<td>1.28</td>
<td>1.03 to 1.58</td>
<td>1.33&lt;sup&gt;e&lt;/sup&gt;</td>
</tr>
<tr>
<td>HBsAg</td>
<td>1.56</td>
<td>0.66 to 3.37</td>
<td>1.16&lt;sup&gt;e&lt;/sup&gt;</td>
</tr>
<tr>
<td>Anti-HCV</td>
<td>1.20</td>
<td>0.84 to 1.72</td>
<td>0.99&lt;sup&gt;f&lt;/sup&gt;</td>
</tr>
<tr>
<td>Anti-HCV &amp; Anti-HBc</td>
<td>1.68</td>
<td>0.97 to 2.94</td>
<td>1.20&lt;sup&gt;d&lt;/sup&gt;</td>
</tr>
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<tr>
<th>Chronic obstructive pulmonary disease (COPD)</th>
<th>Serum Markers</th>
<th>Baseline (n = 14 055)</th>
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<th>-</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Odds ratio</td>
<td>95% CI&lt;sup&gt;i&lt;/sup&gt;</td>
<td>Odds ratio</td>
<td>95% CI&lt;sup&gt;i&lt;/sup&gt;</td>
</tr>
<tr>
<td>Anti-HBc</td>
<td>1.00</td>
<td>0.81 to 1.24</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>HBsAg</td>
<td>1.35</td>
<td>0.49 to 3.69</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Anti-HCV</td>
<td>0.91</td>
<td>0.61 to 1.35</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Anti-HCV &amp; Anti-HBc</td>
<td>0.95</td>
<td>0.57 to 1.60</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

Study population: Results were adjusted for age, sex, height, smoking (status and pack-years), and race/ethnicity.

Restricted Study Population: Results were additionally adjusted for cocaine and marijuana use as well as poverty income ratio.

<sup>a</sup> CI, Confidence Interval.

<sup>b</sup> Adjusted for BMI and Waist: Hip ratio.

<sup>c</sup> Adjusted for marijuana use.

<sup>d</sup> Adjusted for cocaine and marijuana use.

<sup>e</sup> Not adjusted for additional confounders.
significant in the study population but not in the restricted study population (Table 2). There were no significant associations noted with any of the markers of exposure with FEV1:FVC ratio and COPD in either population (Table 2).

Discussion

Hitherto, there have been no large-scale population studies looking at the association between hepatitis viral infections with lung function and disease. The strengths of this study include a large representative sample, and a high response rate — 86% of the invited individuals chose to participate in the questionnaire survey and 78% of the invited individuals participated in the medical examination. A subset of the study population was created as a restricted study population because it was felt that the additional confounders of marijuana use, cocaine use and poverty income ratios needed to be considered. Marijuana and cocaine are often used concurrently with both smoking and intravenous drug use. We were unfortunately unable to adjust for intravenous drug use as a confounder as there was insufficient data on the NHANES III.

The main findings of the study were that individuals positive for anti-HCV as well as both anti-HBc and anti-HCV had a significant increase in FEV1 and FVC. Individuals who were anti-HBc positive also had a significantly increased risk of asthma. Our findings are in contradiction to each other as asthma is an obstructive respiratory disease and is characterised spirometrically by a decrease in lung function. The findings that exposure to HCV and HBV are associated with higher lung function is very surprising, however this was only in the model which adjusts for age, sex, height, smoking (status and pack-years), and race/ethnicity. When you further adjust for drug use and social class this effect disappears, therefore suggesting that the initial results possible arose due to confounding. We also found HBV to be associated with asthma. This is a new finding as no previous studies have focused on HBV infection and asthma. Nevertheless, this association was again not significant in the restricted study population.

A limitation of this study lies in the identification of asthma and COPD. Firstly, the NHANES III database contains a limited number of respiratory questions used to identify both asthma and COPD compared to later NHANES questionnaire iterations. Indeed several epidemiological studies such as the European Community Respiratory Health Survey and International study of Asthma and Allergy in Childhood commonly identify asthma on the basis of symptoms and/or treatment in an attempt to avoid exclusion. Having said that, we also note that the symptoms of asthma are not completely specific to the condition and it is difficult to identify asthma purely on the basis of symptoms. A more certain way of diagnosing asthma in the future would be to use a combination of spirometry, medical history, and a physical examination. Secondly, asthma and COPD are prone to considerable variability and it is possible that lung function testing may have occurred after successful treatment, during well or poorly controlled periods of the disease. Furthermore, a large population of asthmatics can be described as intermittent, with generally normal lung function. Just looking at the general population at large there is a considerable variability of lung function.

The anti-HBc, HBsAg and anti-HCV markers were objective measures for establishing either an exposure to HBV or HCV therefore eliminating misclassification bias. However, this is not ideal as we would have preferred a more detailed clinical picture of our subjects. Purely based on the serology results, we were unable to discern the HBV or HCV status of the individual (acute, chronic, resolved infection or vaccination against HBV) at the time the blood was taken. Furthermore we do not know if the subjects have undergone treatment for their disease specifically treatment with interferons — which has been known to cause the development of pulmonary sarcoidosis and interstitial lung disease [29,43--48]. In more recent NHANES surveys, polymerase chain reaction has been used for confirmation and blood results for alanine aminotransferase, aspartate aminotransferase and alkaline phosphatase which could potentially be used as a proxy for liver pathology. An even better marker would be liver biopsies to confirm liver cirrhosis.

Views on the subject matter have been very mixed but the results of this exploratory study serves to add to the growing body of research. Three previous studies have found that hepatitis C infection is associated with decreased lung function. A small prospective cohort study reported that the decline of FEV1 was greater in COPD patients who had HCV infection than in those who were HCV negative [30]. However, almost half of the HCV patients had received interferon treatment, which may have caused a confounding effect on the result of the study. Another prospective observational study by Erturk et al. demonstrated that HCV-infection was associated with decreased FEV1 and FVC readings [32]. However, these findings were possibly subject to much bias and confounding as the sample size (20 individuals) was very small and was not adjusted for any confounders. Furthermore, 12 of the participants had received therapy of interferon and ribavirin for HCV infection. A separate observational study which looked at 178 non-cirrhotic patients with chronic viral hepatitis found no significant impairment of FEV1 and FVC [33].

Three studies have been carried out with respect to COPD and viral hepatitis. The first, a large study carried out in Japan by Minakata et al. found no significant association between HCV infection and COPD [69]. A second by Silva et al. and third study by Kanazawa et al. showed otherwise, the former found a higher prevalence of COPD in HCV positive individuals compared to HCV-negative individuals and the latter found that HCV infections increased the rate of deterioration of lung function in patients with COPD compared to patients not infected with HCV [30,31]. In the study by Silva et al. selection was from hospital outpatients and only 68% of the participants had co-morbidities while the population in the Minakata et al. study were specifically selected individuals who had chronic diseases other than respiratory diseases. The difference in the criteria of selection will have made the two study populations not directly comparable and may explain the discrepancy in the results. The third study is not comparable to the other...
Conclusion

There has been much interest in viral hepatitis and its effects on the lung. However, the research has been inconclusive. Nevertheless, there has been an overall increased appreciation that viral hepatitis infection results in respiratory manifestations that lead to additional morbidity [16–19,31]. Studies of viral hepatitis may result in enhanced understanding of its pathophysiology and its effects on multiple organ systems including the lungs. This information can then be tailored to create targeted interventions to benefit the individual patient. This is the first large-scale population based study to look at the association of viral hepatitis infection with lung function and respiratory disease. We found associations between exposure to HBV and HCV with changes to lung function as well as a significant association between HBV and asthma in this large cross-sectional study. The latter is a novel finding as no studies have been carried out specifically with subjects exposed to HBV infection in relation to asthma. Previous studies have only discussed the impact of HCV infection on the way asthmatic patients respond to various bronchodilators [29,30]. Furthermore, our study has highlighted the importance of involving objective measures for both the hepatitis infections and pulmonary disease. Our research implies that hepatotropic viruses may affect the respiratory system, but more work at a population level is needed to further explore these associations.

Authors contributions

Conceived and designed the experiment: LYG AWF TMM. Analysed the data: LYG. Wrote the paper: LYG. Contributed to interpretation and editing of manuscript: LYG AWF TMM.

Competing interest

The authors declare they have no competing interests.

Acknowledgements

None.

Abbreviations

HBV hepatitis B virus
HCV hepatitis C virus
FEV₁ forced expiratory volume in 1 s
FVC full vital capacity
COPD chronic obstructive pulmonary disease
NHANES III third National Health and Nutrition Examination Survey
GOLD Global Initiative for Chronic Obstructive Lung Disease
Anti-HBc hepatitis B core antibody
HBsAg hepatitis B surface antigen
Anti-HCV hepatitis C antibody
PIR poverty income ratio
BMI body mass index

References

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