Serum HBV surface antigen positivity is associated with low prevalence of metabolic syndrome: A meta-analysis

Yuanyuan Li, Ying Zhao, Jianping Wu*
Department of Laboratory Medicine, The First Affiliated Hospital, College of Medicine, Zhejiang University, Hangzhou, China

* jpwuzyy@126.com

Abstract

Background and aim
As there is conflicting evidence for the relationship between hepatitis B virus surface antigen (HBsAg) positivity and the prevalence of metabolic syndrome (MetS), we performed a meta-analysis to investigate whether HBsAg positivity affects the incidence of MetS.

Methods
Observational studies on the relationship between HBsAg positivity and MetS were obtained from PubMed, Web of Science, and the Cochrane Library in April 2016. The pooled odds ratios (ORs) of MetS and its components (central obesity, increased fasting glucose, increased blood pressure, dyslipidemia) for subjects with or without HBsAg positivity were synthesized. The standardized mean difference of MetS components between HBsAg-positive participants and healthy controls was calculated. Heterogeneity was explored with subgroup analysis and sensitivity analysis. Publication bias was detected using Egger’s test and Begg’s test.

Results
Thirty studies were eligible for meta-analysis. The MetS OR for HBsAg-positive participants was significantly decreased compared with the controls [OR = 0.80, 95% confidence interval (CI), 0.70–0.90]. The negative effect of HBsAg positivity on elevated triglycerides (OR = 0.62, 95% CI, 0.59–0.64) was strong, while that for increased fasting blood glucose was weak (OR = 0.94, 95% CI, 0.90–0.98). The pooled ORs of central obesity (OR = 0.97, 95% CI, 0.91–1.04), reduced high-density lipoprotein cholesterol (OR = 0.98, 95% CI, 0.83–1.14), and elevated blood pressure (OR = 1.00, 95% CI, 0.80–1.25) for HBsAg-positive participants were all not significantly different compared with the controls. No publication bias was detected.
Conclusions
Serum HBsAg positivity is inversely associated with the prevalence of MetS. Among the five components of MetS, elevated triglycerides had the strongest inverse relationship with HBsAg positivity.

Introduction
Chronic hepatitis B virus (HBV) infection remains a globally challenging problem, as it can lead to chronic active hepatitis, liver cirrhosis, and hepatocellular carcinoma [1, 2]. Metabolic syndrome (MetS), characterized by a cluster of metabolic abnormalities including central obesity, increased fasting blood glucose (FBG), increased blood pressure (BP), and dyslipidemia, is another issue of global concern. MetS is a confirmed risk factor for type 2 diabetes mellitus and atherosclerotic cardiovascular disease [3], and its prevalence has grown rapidly over the past two decades [4].

The liver plays an undeniably important role in lipid and glucose metabolism. MetS involves dyslipidemia and glucose abnormalities. Dyslipidemia is associated with the development of obesity and hypertension, which are also components of MetS. Additionally, nonalcoholic steatohepatitis is considered the hepatic manifestation of MetS [5, 6], and MetS and nonalcoholic steatohepatitis are mutual promoters [7, 8]. Overall, MetS is related to the liver in some way. The hepatitis virus damages liver function; does it also disrupt the metabolism of lipids and glucose in the liver? Subsequently, does it affect the incidence of MetS?

HBV and hepatitis C virus (HCV) are two common types of hepatitis virus that share some similarities. Chronic HCV infection contributes to MetS, as it induced insulin resistance in a genotype-dependent model [9]. However, the relationship between HBV and MetS in the literature, including large population-based surveys, remains inconclusive. HBV surface antigen (HBsAg) positivity and HBV infection are not synonymous, e.g., there can be occult HBV infection with HBsAg-negative status. Even so, HBsAg positivity is closely related to various HBV infection statuses (HBV carrier, chronic active hepatitis, liver cirrhosis). Consequently, HBsAg is usually an indicator of HBV infection. Some studies [10–14] concluded that HBsAg seropositivity is a protective factor against MetS, while others [15–17] have found no association between HBsAg positivity and MetS. These conflicting evidences render a systematic assessment necessary. Unfortunately, the relevant systematic analysis has not been performed. Therefore, we performed this meta-analysis to investigate whether HBsAg seropositivity affects the incidence of MetS and whether HBsAg positivity is related to the components of MetS (central obesity, increased FBG, increased BP, dyslipidemia).

Materials and methods
Search strategy
This meta-analysis was performed according to a proposal for reporting meta-analysis of observational studies [18]. We searched the following databases without time limitations: PubMed, Web of Science, the Cochrane Library. The search strategy for identifying all relevant literature used the following keywords: hepatitis B, metabolic syndrome, hypertension, hyperglycemia, hypertriglyceridemia, dyslipidemia (see S1 Text). The literature search was updated in April 2016.
Study selection

Studies were deemed eligible if they met the following criteria: (1) investigated the association between HBsAg positivity and MetS (including components of MetS: central obesity; increased triglyceride [TG]; reduced high-density lipoprotein cholesterol [HDL-C]; increased BP; increased FBG). HBV infection was defined as HBsAg seropositivity; (2) used healthy subjects as the control group; (3) included >30 subjects with HBsAg positivity; otherwise, a study was excluded for low statistical power and poor reliability. Exclusion criteria were studies on co-infection, such as human immunodeficiency virus and HBV co-infection, liver cirrhosis, hepatocarcinoma, following antiviral therapy, pregnant or pediatric populations.

Methodological quality assessment and data extraction

Two authors (L.Y.Y. and Z.Y.) independently assessed the quality of eligible studies. The Newcastle-Ottawa Scale criteria [19] were recommended by the Cochrane Collaboration for assessing the quality of nonrandomized studies in a meta-analysis. As it was suitable for case-control and cohort studies, we modified it for cross-sectional studies (Table 1). An additional explanation was needed for Q4, which involved the definition of MetS and its components. MetS was defined as the presence of three or more of the following items [4, 20, 21]: (1) elevated waist circumference (WC) (population- and country-specific definitions); (2) elevated TG (≥150 mg/dL) or therapy; (3) reduced HDL-C (men, <40 mg/dL; women, <50 mg/dL) or therapy; (4) elevated BP (systolic ≥130 mmHg and/or diastolic ≥85 mmHg) or therapy; (5) elevated FBG or therapy. Elevated FBG was defined slightly differently (≥100 mg/dL [20] and ≥110 mg/dL [21]). The accurate definition of MetS must meet the above criteria. The accurate definition of a MetS component must match the corresponding item of the MetS component. For example, one study focused only on the relationship between HBsAg positivity and TG (one component of MetS), and the cutoff value for calculating the OR for elevated TG was identical with the item of MetS (TG ≥150 mg/dL). This study was also awarded one star for Q4.

Table 1. Checklist of methodological quality assessment.

| Code | Checklist |
|------|-----------|
| Q1   | The participants were recruited from general population, and were not from hospital; |
| Q2   | The subjects with HBsAg positivity and controls were from the same community; |
| Q3   | The experimental group was composed of subjects with HBsAg positivity; |
| Q4†  | The MetS and its components were defined accurately; |
| Q5   | The same detection method was applied to subjects with HBsAg positivity and controls; |
| Q6   | The same diagnostic criteria were applied to define MetS and its components for subjects with HBsAg positivity and controls; |
| Q7   | The studies list inclusion and exclusion criteria, and patients with hepatitis C virus infection should be excluded at least; |
| Q8   | The studies which were included to calculate combined standardized mean difference were matched for age and sex at least. The studies which were included to calculate combined odds ratio were adjusted for age and sex at least; |
| Q9   | The lifestyle (alcohol and smoking at least) should be considered. The confounding factors from lifestyle were not significantly different between subjects with HBsAg positivity and controls; or they were adjusted in calculating odds ratio. |

MetS, metabolic syndrome; HBsAg, hepatitis B surface antigen;
†, MetS was defined as the presence of three or more of the following items: (1) elevated waist circumference (population- and country-specific definitions); (2) elevated triglycerides (≥150 mg/dL) or therapy; (3) reduced high-density lipoprotein cholesterol (<40 mg/dL in men; <50 mg/dL in women) or therapy; (4) elevated blood pressure (systolic ≥130 mmHg and/or diastolic ≥85 mmHg) or therapy; (5) elevated fasting blood glucose (≥100 mg/dL or ≥110 mg/dL) or therapy. The accurate definition of MetS must meet the above criteria. The accurate definition of a MetS component must match the corresponding item of the MetS component. For example, one study focused only on the relationship between HBsAg positivity and TG (one component of MetS), and the cutoff value for calculating the OR for elevated TG was identical with the item of MetS (TG ≥150 mg/dL). This study was also awarded one star for Q4.

https://doi.org/10.1371/journal.pone.0177713.t001
mg/dL [21]). Both were allowable in this meta-analysis, and further subgroup analysis was performed. The checklist of Q4 was that “The MetS and its components were defined accurately”. Here, the accurate definition of MetS must meet the above criteria. The accurate definition of a MetS component must match the corresponding item of the MetS component. For example, one study focused only on the relationship between HBsAg positivity and TG (one component of MetS), and the cutoff value for calculating the odds ratio (OR) for elevated TG was identical with the item of MetS (TG ≥ 150 mg/dL). This study was also awarded one star for Q4. Discrepancies during methodological quality assessment were resolved by consensus agreement.

For continuous variables, the mean and standard deviation (SD) of WC, body mass index (BMI), TG, HDL-C, FBG, systolic BP, and diastolic BP for HBsAg positive subjects and the controls were extracted. For categorical variables, the adjusted OR was extracted; otherwise, the crude data were extracted to calculate the OR. In addition, the datasheet included the publication year, region, study design, source of subjects, sample size, mean age, gender distribution, and diagnostic criteria of MetS.

### Statistical analysis

The standardized mean difference (SMD) of WC, BMI, TG, HDL-C, FBG, systolic BP, and diastolic BP between the HBsAg-positive group and controls was calculated. Then, the pooled SMD and associated 95% confidence intervals (CI) were obtained from a DerSimonian and Laird random effects model [22]. More importantly, pooled OR was selected to assess the relationship between HBsAg positivity and MetS. Heterogeneity between eligible studies was evaluated by the $I^2$ test. The degree of heterogeneity was classified to three levels (minimal, $I^2 < 25%$; moderate, $25% \leq I^2 < 50%$; substantial, $I^2 \geq 50%$) [23]. If no significant heterogeneity was detected ($P > 0.05$ and $I^2 < 50%$), the fixed effect model was used to calculate the pooled OR and 95% CI. Otherwise, the random effect model was used. To investigate the source of heterogeneity, subgroup analysis and sensitivity analysis was performed according to the factors related to quality assessment. Publication bias was assessed with Egger’s test [24] and Begg’s test [25] (significance at $P < 0.05$). Statistical analyses were conducted with Review Manager 5.3 (The Cochrane Collaboration) and STATA 11.0 (Stata Corp., College Station, TX, USA).

### Results

#### Study characteristics

We retrieved 2687 studies using the described search strategies. We excluded 2657 studies in accordance with our inclusion and exclusion criteria (Fig 1). Ultimately, 30 studies [10–17, 26–47] were eligible for this meta-analysis. Table 2 lists their general characteristics. There were 139,167,581 subjects in total, and most of the studies were from the Asia-Pacific region. The sample sizes of the 30 studies varied from 73 [39] to 138,877,499 participants [12], but the majority of studies (n = 25) enrolled >500 subjects. The participants’ average age ranged 33–61 years. Ten studies [36–41, 44–47] only reported MetS components in the form of continuous variables, and they mainly affected the pooled SMD of MetS components. Consequently, we did not consider in our analysis the MetS criteria they used. In other words, whether these studies [36–41, 44–47] meet the MetS criteria (Q4: The MetS and its components were defined accurately) did not affect the statistical results (SMD), so they were labeled with “UR” (unrelated) for Q4 in Table 3. The remaining 20 studies [10–17, 26–35, 42, 43] reported ORs or crude data for calculating the ORs. The MetS criteria used in these 20 studies was similar, but not identical. S1 Table lists the detailed criteria applied in these 20 studies.
Fig 1. Flow diagram of screened, excluded, and analyzed literature.

https://doi.org/10.1371/journal.pone.0177713.g001
Table 2. Characteristics of the studies included in the meta-analysis.

| Author, year | Region          | Study design | General population | Age‡ | HBsAg (+) (male%)§ | HBsAg (-) (male%)§ |
|--------------|-----------------|--------------|--------------------|------|-------------------|-------------------|
| Huang CY, 2016 [10] | Taiwan | cross section | Yes | 36.2±3.8 vs. 36.1±3.9 | 2982 (54.4) | 14048 (41.4) |
| Katoonizadeh A, 2016 [15] | Iran | Unclear | Yes | 56.1±8.3 vs. 56.0±8.0 | 2249 (52.4) | 10532 (47.0) |
| Fan JY, 2015 [27] | Taiwan | cross section | Yes | 49.8±16.4 | 1265 (50.1) | 5540 (42.1) |
| Ha M, 2015 [11] | China | cross section | Patients | 40±13 vs. 44±15 | 121 (54.5) | 263 (56.3) |
| Hsu CS, 2015 [26] | Taiwan | cross section | Yes | 51.8±9.6 vs. 51±12.9 | 187 (56.7) | 184 (54.4) |
| Choi JS, 2015 [28] | Korea | cross section | Yes | 47.1±15.1 | 209 (51.2) | 4899 (41.6) |
| Park B, 2014 [29] | Korea | cross section | Yes | >30 | 916 (48.3) | 23355 |
| Jinjuvadia R, 2014 [12] | US | cross section | Yes | >18 | 593594 (68.1) | 138283905 (47.5) |
| Jarčuška P, 2014 [16] | Slovakia | cross section | Yes | 33.8±6.9 vs. 34.1±8.4 | 66 | 771 |
| Chung TH, 2014 [30] | Korea | cross section | Yes | 45.7±5.7 vs. 50.0±6.0(m)§ | 521 (83.9) | 8953 (80.0) |
| Liu PT, 2013 [31] | Taiwan | cross section | Yes | 47±11 | 1036 (64.1) | 6659 (56.6) |
| Li WC, 2013 [32] | Taiwan | cross section | Yes | 40.7±13.2 | 3408 (62.4) | 22897 (54.2) |
| Wong VWS, 2012 [33] | Hong Kong | cross section | Yes | 49±10 vs. 48±11 | 91 | 922 |
| Hsu CS 2012 [34] | Taiwan | cross section | Patients | unclear | 322 (53.1) | 870 (53.7) |
| Chen JY, 2010 [35] | Taiwan | cross section | Yes | 60.9±11.8 | 6133 | 50203 |
| Ishizaka N, 2008 [17] | Japan | cross section | Yes | 55.3±10.6 vs. 53.1±10.6 | 130 (71.5) | 12333 (64.2) |
| Yang KC, 2007 [42] | Taiwan | cross section | Yes | 48.0±9.6 vs. 48.4±10.7 | 87 (72.4) | 421 (76.48) |
| Luo B, 2007 [13] | China | cross section | Yes | 43.5 (32–87) | 858 (75.8) | 6579 (64.6) |
| Lin YC, 2007 [43] | Taiwan | cross section | Yes | 45.9±8.8 vs. 46.3±9.5 | 817 (59.9) | 4589 (49.5) |
| Jan CF, 2006 [14] | Taiwan | cross section | Yes | 30–79 | 5994 | 41699 |
| Chiang CH, 2013 [36] † | Taiwan | cross section | Yes | 33.0±8.6 vs. 23.5±2.4 | 147 (76.9) | 359 (63.0) |
| Cheng YL, 2013 [37] † | Taiwan | cross section | Yes | 49.5±11.5 vs. 52.2±13.3 | 3642 (59.3) | 29797 (54.4) |
| Lee JG, 2012 [38] † | South Korea | cross section | Yes | 48.9±10(m); 48.6±10(f) § | 7880 (48.9) |
| Karsen H, 2012 [39] † | Turkey | cross section | Unclear | 36.2±14.2 vs. 35.2±14.1 | 34 (47.1) | 39 (43.6) |
| Dai F, 2012 [40] † | China | cross section | Patients | 38.7±9.5 vs. 37.2±10.6 | 68 (69.1) | 67 (59.7) |
| Huang ZS, 2010 [41] † | Taiwan | cross section | Yes | 52.7±0.7 vs. 55.1±0.3 | 143 (79.0) | 1090 (72.5) |
| Wang CC, 2008 [47] † | Taiwan | cross section | Yes | 44.6±1.4 vs. 46.8±0.4 | 50 (60) | 457 (46.6) |
| Targher G, 2007 [45] † | Italy | cross section | Patients | 47±3 vs. 46±3 | 35 (65.7) | 60 (68.0) |
| Moritani M, 2005 [44] † | Japan | cross section | Yes | 48.3±1.3 vs. 49.3±0.2 | 39 (89.7) | 1736 (65.3) |
| Su TC, 2004 [46] † | Taiwan | cross section | Yes | 40.4±7.5 vs. 41.1±8.3 | 195 (36.9) | 1135 (29.3) |

HBsAg, hepatitis B surface antigen.
† These studies only reported components of MetS in the form of continuous variables.
‡ Age was usually expressed as “HBsAg-positive group” vs. “control group” or the overall age distribution including HBsAg-positive and control group.
§ age of HBsAg-positive group” vs. “age of control group” in male subgroup (m) and female subgroup (f), respectively.
○ Overall age distribution in male subgroup (m) and female subgroup (f), respectively.
¶ Data in parentheses are the percentage of males.

Methodological quality assessment

Table 3 lists the methodological quality of the studies; the average score of all 30 studies was 7.23. Five studies [11, 34, 39, 40, 45] did not collect information on HBsAg-positive subjects from the general population, but from patients in the infection department. One study [36] enrolled university graduates as the healthy controls, who were much younger than the HBsAg-positive group. One study [43] did not define the HBsAg-positive group explicitly. The definition criteria of MetS differed slightly in these studies even though most of them were
based on National Cholesterol Education Program Adult Treatment Expert Panel III (ATP III) [21] (S1 Table). Five studies involved the distinctive definition of MetS or its components. Jarčuška et al. [16] considered that MetS must present with central obesity. Increased BP was defined as systolic BP ≥ 140 mmHg or diastolic BP ≥ 90 mmHg in three studies [13, 27, 42] and as systolic BP ≥ 135 mmHg or diastolic BP ≥ 90 mmHg in one study [14]. The Q7, Q8, and Q9 checklists were mainly used to control confounders. Ten studies involved the confounding of HCV. Eleven studies did not control for confounding of age and sex well, while 20 studies did not control for confounding of lifestyle well.

Table 3. Methodological quality of eligible studies.

| Author, year | Q1 | Q2 | Q3 | Q4 | Q5 | Q6 | Q7 | Q8 | Q9 | Score |
|--------------|----|----|----|----|----|----|----|----|----|-------|
| Huang CY, 2016 [10] | yes | yes | yes | yes | yes | yes | yes | yes | yes | 9 |
| Katoonizadeh A, 2016 [15] | yes | yes | yes | yes | yes | yes | yes | yes | yes | 9 |
| Fan JY, 2015 [27] | yes | yes | yes | no | yes | yes | no | no | no | 5 |
| Ha M, 2015 [11] | no | yes | yes | yes | yes | yes | yes | yes | yes | 8 |
| Hsu CS, 2015 [26] | yes | yes | yes | yes | yes | yes | yes | yes | no | 8 |
| Choi JS, 2015 [28] | yes | yes | yes | yes | yes | yes | UC | yes | yes | 8 |
| Park B, 2014 [29] | yes | yes | yes | yes | yes | yes | no | no | no | 6 |
| Jinjuvadia R, 2014 [12] | yes | yes | yes | yes | yes | yes | yes | yes | yes | 9 |
| Jarčuška P, 2014 [16] | yes | yes | yes | no | yes | yes | yes | yes | no | 7 |
| Chung TH, 2014 [30] | yes | yes | yes | yes | yes | yes | UC | yes | yes | 8 |
| Liu PT, 2013 [31] | yes | yes | yes | yes | yes | yes | yes | yes | yes | 9 |
| Li WC, 2013 [32] | yes | yes | yes | yes | yes | yes | no | no | no | 6 |
| Wong VWS, 2012 [33] | yes | yes | yes | yes | yes | yes | yes | yes | yes | 9 |
| Hsu CS, 2012 [34] | no | yes | yes | yes | yes | yes | yes | yes | no | 7 |
| Chen JY, 2010 [35] | yes | yes | yes | yes | yes | yes | no | no | no | 6 |
| Ishizaka N, 2008 [17] | yes | yes | yes | yes | yes | yes | yes | yes | yes | 8 |
| Yang KC, 2007 [42] | yes | yes | yes | no | yes | yes | yes | no | no | 6 |
| Luo B, 2007 [13] | yes | yes | yes | no | yes | yes | no | yes | no | 6 |
| Lin YC, 2007 [43] | yes | yes | UC | yes | yes | yes | yes | no | no | 5 |
| Jan CF, 2006 [14] | yes | yes | yes | yes | yes | yes | no | yes | no | 6 |
| Chiang CH, 2013 [36] | yes | no | yes | UR | yes | yes | yes | no | yes | 7 |
| Cheng YL, 2013 [37] | yes | yes | yes | UR | yes | yes | yes | no | no | 7 |
| Lee JG, 2012 [38] | yes | yes | yes | UR | yes | yes | yes | no | no | 7 |
| Karsen H, 2012 [39] | UC | yes | yes | UR | yes | yes | yes | yes | no | 7 |
| Dai F, 2012 [40] | no | yes | yes | UR | yes | yes | yes | yes | no | 7 |
| Huang ZS, 2010 [41] | yes | yes | yes | UR | yes | yes | yes | no | no | 7 |
| Wang CC, 2008 [47] | yes | yes | yes | UR | yes | yes | yes | yes | no | 8 |
| Targher G, 2007 [45] | no | yes | yes | UR | yes | yes | yes | yes | no | 7 |
| Moritani M, 2005 [44] | yes | yes | yes | UR | yes | yes | yes | yes | yes | 9 |
| Su TC, 2004 [46] | yes | yes | yes | UC | yes | yes | no | no | no | 6 |

UC: unclear;
UR: unrelated. The last 10 studies [36–41, 44–47] in the table reported only metabolic syndrome (MetS) components in the form of continuous variables, and they mainly affected the pooled standardized mean difference (SMD) of the MetS components. SMD was not related to the diagnostic criteria of MetS. Whether these studies [36–41, 44–47] meet Q4 (Q4: MetS and its components were defined accurately) did not affect the statistical results (SMD), so they were labeled “UR” for Q4. The first 20 studies in the table reported OR or crude data for calculating the OR, and the MetS criteria they used affected the statistical results (pooled ORs) directly. Therefore, these studies were carefully investigated to confirm whether they met Q4 (Q4: MetS and its components were defined accurately).
HBV surface antigen positivity and metabolic syndrome prevalence

Twelve studies [10–17, 28, 30, 32, 33] reported the OR for HBsAg positivity and prevalence of MetS. In all, 610,021 HBsAg-positive subjects and 138,407,811 healthy controls were enrolled in the meta-analysis. The pooled OR for HBsAg positivity and MetS prevalence was 0.80 (95% CI, 0.70–0.90, I² = 72%, P < 0.01) (Fig 2), indicating an inverse association between HBsAg positivity and MetS prevalence. Table 4 lists the subgroup analysis results. The inverse

Table 4. Results of subgroup analysis according to quality assessments.

| Groups† | MetS‡ | Elevated WC | Elevated TG | Reduced HDL-C | Elevated BP | Elevated FBG |
|---------|-------|-------------|-------------|--------------|-------------|--------------|
| All     | 0.80 (0.70–0.90); I² = 72%, P = 0.001; n = 12 | 0.97 (0.91–1.04); I² = 50%, P = 0.03; n = 11 | 0.62 (0.59–0.64); I² = 0%, P = 0.52; n = 14 | 0.98 (0.83–1.14); I² = 85%, P = 0.01; n = 13 | 1.00 (0.80–1.25); I² = 95%, P = 0.01; n = 11 | 0.94 (0.90–0.99); I² = 89%, P = 0.01; n = 13 |
| Male    | 0.85 (0.74–0.98); I² = 64%, P = 0.01; n = 6 | 0.91 (0.81–1.02); I² = 51%, P = 0.11; n = 4 | -- | 1.21 (1.05–1.40); I² = 50%, P = 0.01; n = 4 | 0.97 (0.80–1.17); I² = 5%, P = 0.35; n = 3 | 0.63 (0.39–1.00); I² = 89%, P = 0.01; n = 4 |
| Female  | 0.91 (0.74–1.11); I² = 66%, P = 0.008; n = 6 | 0.95 (0.84–1.09); I² = 51%, P = 0.41; n = 4 | -- | 0.82 (0.50–1.35); I² = 82%, P = 0.009; n = 4 | 0.95 (0.66–1.39); I² = 0%, P = 0.89; n = 3 | 1.00 (0.88–1.14); I² = 0%, P = 0.80; n = 4 |
| Q1 (general population) | 0.81 (0.72–0.92); I² = 72%, P = 0.01; n = 11 | 0.97 (0.91–1.04); I² = 55%, P = 0.12; n = 10 | -- | 0.95 (0.83–1.09); I² = 78%, P = 0.01; n = 11 | 0.91 (0.87–0.96); I² = 0%, P = 0.63; n = 9 | 0.94 (0.90–0.99); I² = 27%, P = 0.18; n = 11 |
| Q4 (accurate diagnosis) | 0.80 (0.68–0.94); I² = 77%, P = 0.01; n = 9 | 0.99 (0.94–1.05); I² = 50%, P = 0.93; n = 6 | -- | 0.98 (0.82–1.16); I² = 86%, P = 0.01; n = 12 | 0.95 (0.88–1.02); I² = 0%, P = 0.63; n = 7 | 0.93 (0.87–0.99); I² = 1%, P = 0.42; n = 7 |
| Q7 (included and excluded criterion) | 0.70 (0.53–0.91); I² = 80%, P = 0.01; n = 7 | 0.93 (0.83–1.04); I² = 61%, P = 0.03; n = 6 | -- | 0.94 (0.72–1.21); I² = 89%, P = 0.01; n = 9 | 0.92 (0.85–1.00); I² = 0%, P = 0.68; n = 6 | 0.96 (0.91–1.03); I² = 37%, P = 0.14; n = 7 |
| Q8 and Q9 (control confounding factors) | 0.73 (0.61–0.88); I² = 63%, P = 0.02; n = 6 | 0.99 (0.91–1.08); I² = 64%, P = 0.04; n = 4 | -- | 0.88 (0.83–0.94); I² = 0%, P = 0.47; n = 6 | 0.90 (0.85–0.94); I² = 0%, P = 0.69; n = 4 | 0.97 (0.90–1.03); I² = 57%, P = 0.08; n = 4 |

MetS, metabolic syndrome; WC, waist circumference; TG, triglycerides; HDL-C, high-density lipoprotein cholesterol; BP, blood pressure; FBG, fasting blood glucose.

† Grouped according to checklist of quality assessment (Tables 1 and 3).
‡ The data in each grid are the OR (95% CI of OR); the parameters of heterogeneity (I², P-value); the number of included studies.
§ The studies included for calculating the pooled OR here were not identical to those for calculating the pooled SMD.

For “Elevated TG”, the pooled OR was from 14 studies [10–16, 26, 28, 30, 31, 33–35], and the SMD was from 14 studies [10, 16, 17, 26, 31, 34, 36, 37, 39, 42, 44–47]. They are not identical.

Similarly, for “Reduced HDL-C”, the pooled OR was from 13 studies [10–16, 26, 28, 30, 31, 33, 34], and the SMD was from 19 studies [10, 15–17, 26, 28, 30–34, 37–39, 42, 44–47].

For “Elevated BP”, the pooled OR was from 11 studies [10–15, 28, 30, 31, 33, 42]; the SMD of systolic BP was from 10 studies [10, 11, 17, 31, 33, 36, 37, 42, 44, 45], and the SMD of diastolic BP was from nine studies [10, 11, 17, 31, 33, 36, 37, 42, 44, 45].

For “Elevated FBG”, the pooled OR was from 13 studies [10–15, 27–31, 33, 34], and the SMD was from 16 studies [10, 11, 16, 17, 26, 31, 33, 36, 37, 40–42, 44–47].
relationship was robust in all but the female subgroup. In the general population, the pooled OR from 11 studies [10, 12–17, 28, 30, 32, 33] was 0.81 (95% CI, 0.72–0.92, I² = 72%, P < 0.01). The pooled OR from nine studies [10–12, 15, 17, 28, 30, 32, 33] that rigorously defined MetS with ATP III was 0.80 (95% CI, 0.68–0.94, I² = 77%, P < 0.01). After excluding the confounder of HCV, the pooled OR was 0.70 (95% CI, 0.53–0.91, I² = 80%, P < 0.01). The pooled OR from data adjusted for confounders was 0.73 (95% CI, 0.61–0.88, I² = 63%, P = 0.02). This inverse association was also found in the male subgroup (OR = 0.85; 95% CI, 0.74–0.98; I² = 64%, P = 0.01), but not in the female subgroup (OR = 0.91; 95% CI, 0.74–1.11; I² = 66%, P = 0.008). Furthermore, the heterogeneity did not decrease through subgroup analysis, therefore the specific factor leading to heterogeneity was not found.

**HBsAg positivity and central obesity**

WC and BMI are two common indices for assessing central obesity. Eleven studies [10–12, 14–16, 26, 28, 30, 33, 43] involving 606,706 HBsAg-positive subjects and 138,369,865 healthy controls reported the OR for HBsAg positivity and increased WC. The pooled OR was 0.97 (95% CI, 0.91–1.04; I² = 50%, P = 0.03) (S1 Fig), indicating that HBsAg positivity was neither a risk factor nor a protective factor for increased WC, and further subgroup analysis grouped according to quality assessment confirmed this. The pooled OR from six studies [10, 11, 14, 26, 33, 43] that defined central obesity as WC > 90 cm in men or > 80 cm in women was 0.99 (95% CI, 0.94–1.05; I² = 0%, P = 0.93). The heterogeneity also decreased in subgroups stratified by sex; the conclusion was identical to the total pooled OR (Table 4). Additionally, six studies [13, 16, 26, 27, 34, 43] reported the OR of BMI, and the pooled OR was 0.99 (95% CI, 0.95–1.04; I² = 0%, P = 0.65), which was consistent with WC.

**HBsAg positivity and elevated TG**

Fourteen studies [10–16, 26, 28, 30, 31, 33–35] involving 614,363 HBsAg-positive subjects and 138,430,492 healthy controls reported the OR for HBsAg positivity and increased circulating TG levels. The total OR of these 14 studies was 0.62 (95% CI, 0.59–0.64; I² = 0%, P = 0.52) (Fig 3), indicating that HBsAg positivity is inversely associated with elevated TG. The heterogeneity among the included studies was so low that the subsequent subgroup analysis was omitted.

![Fig 3. Forest plot of the prevalence of elevated TG in HBsAg-positive subjects versus healthy controls.](https://doi.org/10.1371/journal.pone.0177713.g003)
The SMD of the 14 studies \[10, 16, 17, 26, 31, 34, 36, 37, 39, 42, 44–47\] was -0.39 (95% CI, -0.59 to -0.18; \(I^2 = 98\%), P < 0.001), indicating that the HBsAg-positive subjects had lower TG than the healthy controls. Although the OR and SMD were calculated from different studies, they revealed a consistent trend.

**HBsAg positivity and reduced HDL-C**

Thirteen studies \[10–16, 26, 28, 30, 31, 33, 34\] involving 605,924 HBsAg-positive subjects and 138,363,354 healthy controls reported the OR for HBsAg positivity and reduced HDL-C. The total OR of the 13 controls was 0.98 (95% CI, 0.83–1.14, \(I^2 = 85\%), P < 0.01) (see S2 Fig), indicating that HBsAg positivity was not associated with reduced HDL-C. However, the pooled OR of six studies \[10, 12–14, 16, 31\] that controlled the confounding factors revealed an inverse relationship between HBsAg positivity and reduced HDL-C (OR = 0.88; 95% CI, 0.83–0.94; \(I^2 = 0\%), P = 0.47). The dramatic decrease in heterogeneity was due to adjusting for confounding factors (age, sex at least). However, the dramatic decrease in heterogeneity rendered the results more reliable, the inverse relationship was still weak.

**HBsAg positivity and elevated BP**

Eleven studies \[10–15, 28, 30, 31, 33, 42\] reported the OR for HBsAg positivity and elevated BP, and only two \[14, 15\] reported that HBsAg positivity was associated with increased BP. The pooled OR of all 11 studies was 1.00 (95% CI, 0.80–1.25; \(I^2 = 95\%), P < 0.001) (see S3 Fig). After excluding the two studies \[14, 15\], the heterogeneity decreased significantly, and the combined OR from the remaining nine studies \[10–13, 28, 30, 31, 33, 42\] was 0.94 (95% CI, 0.88–1.01, \(I^2 = 0\%), P = 0.76). The subgroup that included seven studies \[10–12, 28, 30, 31, 33\] based on ATP III (systolic BP \(\geq 130\) mmHg or diastolic BP \(\geq 85\) mmHg) also showed no relationship between HBsAg positivity and increased BP (OR = 0.95; 95% CI, 0.88–1.02; \(I^2 = 0\%), P = 0.63). Additionally, similar trends were found in the SMD of systolic BP and diastolic BP. In conclusion, HBsAg positivity was neither a risk factor nor a protective factor for increased BP, and the difference in BP between HBsAg-positive subjects and healthy controls was not significant.

**HBsAg positivity and elevated FBG**

Thirteen studies \[10–15, 27–31, 33, 34\] reported the OR for HBsAg positivity and elevated FBG. The total OR of these 13 studies, which involved 610,127 HBsAg-positive subjects and 138,408,194 controls, was 0.94 (95% CI, 0.90–0.98; \(I^2 = 21\%), P = 0.23) (see S4 Fig), indicating that HBsAg positivity is inversely associated with increased FBG, but this inverse relationship was not robust in the subsequent subgroup analysis (Table 4). Seven studies \[11, 15, 29–31, 33, 34\] defined elevated FBG as \(\geq 100\) mg/dL, and the pooled OR was 0.93 (95% CI, 0.87–0.99; \(I^2 = 1\%), P = 0.42). Six studies \[10, 12–14, 27, 28\] defined elevated FBG as \(\geq 110\) mg/dL, and the pooled OR was 0.95 (95% CI, 0.89–1.01; \(I^2 = 45\%), P = 0.11). The SMD derived from 16 studies \[10, 11, 16, 17, 26, 31, 33, 36, 37, 40–42, 44–47\] was 0.03 (95% CI, -0.21 to 0.27; \(I^2 = 99\%), P < 0.0001). Overall, the effect of HBsAg positivity on glucose homeostasis appeared slight. However, further research is required to confirm this.

**Publication bias**

Publication bias was not detected by Egger's test or Begg's test (Table 5). For Egger's test, the publication bias 95% CI of each group included zero and \(P > 0.05\), so there was no statistical difference between publication bias and zero, meaning no publication bias was present; Begg's
test derived the same conclusion. Taken together, this indicates that there was no publication bias in our meta-analysis.

Discussion

In this meta-analysis, HBsAg-positive individuals had lower prevalence of MetS. This negative association remained robust after adjustment for confounding factors (e.g., age, sex). Meanwhile, a strong inverse relationship was demonstrated between HBsAg positivity and elevated TG (one component of MetS). There was a slight effect of HBsAg positivity on glucose homeostasis. The total OR of all eligible studies indicated no association between HBsAg positivity and reduced HDL-C, but OR controlled for the confounding factors revealed a slight inverse relationship. Additionally, it was confirmed that HBsAg positivity is not associated with central obesity and increased BP. Overall, we speculate that HBsAg positivity protects against the incidence of MetS mainly due to its negative effect on elevated TG. Naturally, further research is required to confirm this.

There was a negative association between HBsAg positivity and the prevalence of MetS, and HBsAg positivity is closely related to HBV. HBV may prevent the occurrence of MetS instead of promoting it. That is, HBV may protect humans against MetS. HBV is considered a “metabolovirus”, as it adopts a regulatory system that is unique to the major hepatic metabolic genes that control hepatic glucose and lipid metabolism [48]. HBV infection alters bile acid and cholesterol metabolism as a consequence of impaired bile acid uptake [48]. Besides, HBV X protein induces the transcriptional activation of peroxisome proliferator–activated receptor γ (PPARγ) [49]. The activation of PPARγ gene expression during HBV replication boosts the increase in circulating adiponectin levels [50, 51]. Adiponectin has anti-inflammatory effects and protects against insulin resistance. It is inversely associated with BMI, type 2 diabetes mellitus, and several metabolic disorders [51, 52]. Additionally, nonalcoholic steatohepatitis is considered the hepatic manifestation of MetS. A meta-analysis and several large-cohort studies have proven that HBV has a protective effect against the development of hepatic steatosis [6, 53]. The evidence described above all support the inverse relationship between HBsAg positivity and the prevalence of MetS; however, prospective studies are warranted to elucidate the exact mechanism and to validate the inverse relationship.

A recent review [6] has also shown an inverse relationship between HBV and increased TG. The liver is the main organ for lipid metabolism, and hepatic dysfunction such as inflammation, liver fibrosis, cirrhosis, and hepatocellular carcinoma may occur during HBV infection. These processes all influence lipid biosynthesis and metabolism and relate to the change in TG

### Table 5. Analysis of publication bias of the included studies.

| Group       | Studies | Begg’s test (P-value) | Egger’s test (P-value) | 95% CI of bias |
|-------------|---------|-----------------------|------------------------|----------------|
| MetS        | 12      | 0.086                 | 0.089                  | -3.34 to 0.28  |
| Elevated BMI| 6       | 0.707                 | 0.300                  | -0.88 to 2.21  |
| Elevated WC | 11      | 0.119                 | 0.506                  | -2.03 to 1.08  |
| Elevated TG | 14      | 0.274                 | 0.228                  | -1.37 to 0.36  |
| Reduced HDL-C | 13    | 0.583                 | 0.866                  | -3.01 to 2.57  |
| Elevated BP | 11      | 1.000                 | 0.902                  | -5.66 to 5.06  |
| Elevated FBG| 13      | 0.161                 | 0.123                  | -2.09 to 0.29  |

MetS, metabolic syndrome; BMI, body mass index; WC, waist circumference; TG, triglycerides; HDL-C, high-density lipoprotein cholesterol; BP, blood pressure; FBG, fasting blood glucose.

https://doi.org/10.1371/journal.pone.0177713.t005
levels [35]. Kim et al. [49] reported that HBV X protein inhibits the secretion of apolipoprotein B. Apolipoprotein B in the liver is an important glycoprotein for the transport of TG-rich very low-density lipoprotein cholesterol and low-density lipoprotein cholesterol. Therefore, HBV X protein increases rapidly upon the active replication of HBV. Then, it inhibits very low-density lipoprotein cholesterol and low-density lipoprotein cholesterol production and promotes TG accumulation in hepatocytes, decreasing TG in the blood. Additionally, increased levels of adiponectin caused by HBV replication reduce serum TG levels and increase HDL-C levels [54]. Besides TG, accumulating evidence has revealed that chronic HBV infection is also inversely associated with other lipid profiles, including cholesterol and low-density lipoprotein cholesterol [6], and we found a similar trend. In our study, the OR for increased cholesterol from four studies [16, 31, 34, 35] was 0.76 (95%CI, 0.65–0.89), and the SMD from 13 studies [10, 11, 16, 17, 31, 33, 36, 37, 40, 42, 44, 46, 47] was -1.24 (95%CI, -1.64 to -0.84). The SMD of low-density lipoprotein cholesterol from 10 studies [16, 31, 33, 37–39, 42, 45–47] was -0.43 (95%CI, -0.69 to -0.16). The pooled OR of six studies that controlled the confounding factors revealed a slight inverse relationship between HBsAg positivity and reduced HDL-C. In fact, there was interaction between HBV infection and lipid metabolism. Moderate-severe hepatic steatosis may contribute to HBsAg seroclearance due to steatosis-induced apoptosis and inflammation [55]. In short, the possible mechanism for HBsAg positivity with lower TG levels could be related to viral factors and host factors. Furthermore, the weak inverse relationship between HBsAg positivity and reduced HDL-C should be confirmed via further investigation.

The inverse relationship between HBsAg positivity and increased FBG was statistically significant, but was weak in the clinic. The relationship between HBV and insulin resistance remains inconclusive and awaits further studies for clarification [6]. However, it is worth pointing out that cirrhosis and poor glycemic control are closely associated [56, 57]. It has been speculated that peripheral insulin clearance is reduced because of cirrhosis, and then insulin resistance and glucose abnormalities occur secondary to hyperinsulinemia [58].

To the best of our knowledge, this is the first meta-analysis to investigate the relationship between HBsAg positivity and MetS (including its components). Additionally, this meta-analysis was performed rigorously according to a proposal for reporting meta-analysis of observational studies [18]. Although Wang et al. [6] also focused on the association between HBV infection and MetS, theirs was more of an excellent review than a meta-analysis. Second, most of the included studies enrolled >500 subjects, and the large sample size made the conclusion more credible.

There are several limitations to the present meta-analysis. First, the majority of eligible studies were cross-sectional studies, which always demonstrate the least evidence among the three types of observational studies (case-control, cohort, cross-sectional). Additionally, time is an important factor that should be considered, as HBsAg-positive individuals may have different outcomes. Unfortunately, it was difficult to assess the impact of time in this meta-analysis, which we attribute to the cross-sectional nature of the included studies. Second, because only HBsAg was tested and/or it was tested for only once in most of the eligible studies, various conditions related to HBsAg were not taken into account. An HBsAg-positive individual may be a healthy carrier, a patient with chronic active hepatitis, or a patient with liver cirrhosis. Although most studies focused on the general population and most HBsAg-positive subjects may be HBV carriers in this meta-analysis, further stratification of HBsAg status is still needed to assess the exact role of HBsAg in the development of MetS in the future. Third, both age and gender play an important role in the natural history of chronic HBV infection. Unfortunately, the studies included in the subgroup analysis based on these two factors were very limited; however, the negative association between HBsAg passivity and MetS remained robust after adjustment for confounding factors (e.g., age, sex). Fourth, with respect to the definition...
of MetS, we were not concerned whether drug treatment was an alternate indicator. Finally, we were unsuccessful in obtaining supplemental information from several authors; however, no publication bias was detected.

Our meta-analysis has several implications for future research. First, a prospective large-cohort study is needed to validate our conclusion. In this regard, the Newcastle–Ottawa Scale [19] describes the requirements for a rigorous study design and methodology and is a good tool for guiding study design. The unified definition of MetS [4] should be used. As described above, some important factors, such as time, age, gender, and various conditions related to HBsAg, should be taken into account thoroughly in future research. On the other hand, the physiopathological mechanism of the inverse association between HBsAg positivity and MetS requires further research.

In conclusion, serum HBsAg positivity is inversely associated with MetS. Among the five components of MetS, elevated triglycerides had the strongest inverse relationship with HBsAg positivity.

Supporting information
S1 Checklist. PRISMA 2009 checklist.
(DOC)

S1 Fig. Meta-analysis of the prevalence of elevated WC in HBsAg positivity versus healthy control (forest plot).
(TIF)

S2 Fig. Meta-analysis of the prevalence of reduced HDL-C in HBsAg positivity versus healthy control (forest plot).
(TIF)

S3 Fig. Meta-analysis of the prevalence of elevated BP in HBsAg positivity versus healthy control (forest plot).
(TIF)

S4 Fig. Meta-analysis of the prevalence of elevated FBG in HBsAg positivity versus healthy control (forest plot).
(TIF)

S1 Table. Diagnostic criteria of MetS and its components in the included studies.
(DOC)

S1 Text. The electronic search strategy for PubMed database.
(DOCX)

Acknowledgments
We thank Elixigen Corporation (Huntington Beach, California, USA) for helping in proof-reading and editing the English of final manuscript.

Author Contributions

Conceptualization: YL.

Data curation: YL YZ.

Formal analysis: YL YZ.
Funding acquisition: JW.
Investigation: YL YZ JW.
Methodology: YZ.
Project administration: JW.
Resources: JW.
Supervision: JW.
Validation: YL.
Visualization: YL.
Writing – original draft: YL.
Writing – review & editing: YL YZ JW.

References
1. Locarnini S, Hatzakis A, Chen DS, Lok A. Strategies to control hepatitis B: Public policy, epidemiology, vaccine and drugs. J Hepatol. 2015; 62(1S):S76–S86.
2. Ganem D, Prince AM. Hepatitis B virus infection--natural history and clinical consequences. N Engl J Med. 2004; 350(11):1118–29. https://doi.org/10.1056/NEJMra031067 PMID: 15014185
3. Grundy SM, Hansen B, Smith SC Jr., Cleeman JI, Kahn RA. Clinical management of metabolic syndrome: report of the American Heart Association/National Heart, Lung, and Blood Institute/American Diabetes Association conference on scientific issues related to management. Circulation. 2004; 109(4):S51–6. https://doi.org/10.1161/01.CIR.0000112379.88385.67 PMID: 14757684
4. Eckel RH, Alberti KG, Grundy SM, Zimmet PZ. The metabolic syndrome. Lancet. 2010; 375(9710):161–3. https://doi.org/10.1016/S0140-6736(09)61794-3 PMID: 20109902
5. Patton HM, Yates K, Unalp-Arida A, Behling CA, Huang TT, Rosenthal P, et al. Association between metabolic syndrome and liver histology among children with nonalcoholic fatty liver disease. Am J Gastroenterol. 2010; 105(9):2093–102. https://doi.org/10.1038/ajg.2010.152 PMID: 20372110
6. Wang CC, Tseng TC, Kao JH. Hepatitis B virus infection and metabolic syndrome: fact or fiction? J Gastroenterol Hepatol. 2015; 30(1):14–20. https://doi.org/10.1111/jgh.12700 PMID: 25092429
7. Marchesini G, Bugianesi E, Forlani G, Cerrelli F, Lenzi M, Manini R, et al. Nonalcoholic fatty liver, steatohepatitis, and the metabolic syndrome. Hepatology. 2003; 37(4):917–23. https://doi.org/10.1053/jhep.2003.50161 PMID: 12668987
8. Yang KC, Hung HF, Lu CW, Chang HH, Lee LT, Huang KC. Association of Non-alcoholic Fatty Liver Disease with Metabolic Syndrome Independently of Central Obesity and Insulin Resistance. Sci Rep. 2016; 6:27034. https://doi.org/10.1038/srep27034 PMID: 27246655
9. Sheikh MY, Choi J, Qadri I, Friedman JE, Sanyal AJ. Hepatitis C virus infection: molecular pathways to metabolic syndrome. Hepatology. 2008; 47(6):2127–33. https://doi.org/10.1002/hep.22269 PMID: 18446789
10. Huang CY, Lu CW, Liu YL, Chiang CH, Lee LT, Huang KC. Relationship between chronic hepatitis B and metabolic syndrome: A structural equation modeling approach. Obesity (Silver Spring). 2016; 24(2):483–9.
11. Ha M, Xia W, Tang D, Wu J, Sun L, Shen W, et al. Hepatitis B e antigen-positive and high levels of alanine aminotransferase are associated with prevalence of metabolic syndrome in chronic HBV patients. Obes Res Clin Pract. 2015.
12. Jinjuvadia R, Liangpunsakul S. Association between metabolic syndrome and its individual components with viral hepatitis B. Am J Med Sci. 2014; 347(1):23–7. https://doi.org/10.1097/MAJ.0b013e31828b25a5 PMID: 23514672
13. Luo B, Wang Y, Wang K. Association of metabolic syndrome and hepatitis B infection in a Chinese population. Clin Chim Acta. 2007; 380(1–2):238–40. https://doi.org/10.1016/j.cca.2007.01.012 PMID: 17316990
14. Jan CF, Chen CJ, Chiu YH, Chen LS, Wu HM, Huang CC, et al. A population-based study investigating the association between metabolic syndrome and hepatitis B/C infection (Keelung Community-based Integrated Screening study No. 10). Int J Obes (Lond). 2006; 30(5):794–9.
15. Katoonizadeh A, Ghoroghi S, Sharafkhah M, Khoshnia M, Mirzaei S, Shayanrad A, et al. Chronic hepatitis B infection is not associated with increased risk of vascular mortality while having an association with metabolic syndrome. J Med Virol. 2016; 88(7):1230–7. https://doi.org/10.1002/jmv.24466 PMID: 26742819

16. Jarcuska P, Janicko M, Kruzliak P, Novak M, Veseliny E, Fedacko J, et al. Hepatitis B virus infection in patients with metabolic syndrome: A complicated relationship. Results of a population based study. Eur J Intern Med. 2014; 25(3):286–91. https://doi.org/10.1016/j.ejim.2014.01.006 PMID: 24445023

17. Ishizaka N, Ishizaka Y, Seki G, Nagai R, Yamakado M, Koike K. Association between hepatitis B/C viral infection, chronic kidney disease and insulin resistance in individuals undergoing general health screening. Hepatol Res. 2008; 38(8):775–83. https://doi.org/10.1111/j.1872-034X.2008.00334.x PMID: 18371161

18. Stroup DF, Berlin JA, Morton SC, Olkin I, Williamson GD, Rennie D, et al. Meta-analysis of observational studies in epidemiology: a proposal for reporting. Meta-analysis Of Observational Studies in Epidemiology (MOOSE) group. JAMA. 2000; 283(15):2008–12. PMID: 10789670

19. Wells G, Shea B, O’Connell D, Peterson J, Welch V, Losos M, et al. The Newcastle-Ottawa Scale (NOS) for assessing the quality of nonrandomised studies in meta-analyses. [WWW document] URL http://www.ohri.ca/programs/clinical_epidemiology/oxford.htm. (accessed May 12, 2014).

20. Alberti KG, Eckel RH, Grundy SM, Zimmet PZ, Cleeman JI, Donato KA, et al. Harmonizing the metabolic syndrome: a joint interim statement of the International Diabetes Federation Task Force on Epidemiology and Prevention; National Heart, Lung, and Blood Institute; American Heart Association; World Heart Federation; International Atherosclerosis Society; and International Association for the Study of Obesity. Circulation. 2009; 120(16):1640–5. https://doi.org/10.1161/CIRCULATIONAHA.109.192644 PMID: 19805654

21. Third Report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III) final report. Circulation. 2002; 106(25):3143–421. PMID: 12485966

22. DerSimonian R, Laird N. Meta-analysis in clinical trials. Control Clin Trials. 1986; 7(3):177–88. PMID: 3802833

23. Higgins JP, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. BMJ. 2003; 327(7414):557–60. https://doi.org/10.1136/bmj.327.7414.557 PMID: 12958120

24. Egger M, Davey Smith G, Schneider M, Minder C. Bias in meta-analysis detected by a simple, graphical test. BMJ. 1997; 315(7109):629–34. Epub 1997/10/06. PMID: 9310563

25. Begg CB, Mazumdar M. Operating characteristics of a rank correlation test for publication bias. Biometrics. 1994; 50(4):1088–101. PMID: 7786990

26. Hsu CS, Liu WL, Chao YC, Lin HH, Tseng TC, Wang CC, et al. Adipocytokines and liver fibrosis stages in patients with chronic hepatitis B virus infection. Hepatol Int. 2015; 9(2):231–42. https://doi.org/10.1007/s12072-015-9616-2 PMID: 25788201

27. Fan JY, Huang TJ, Jane SW, Chen MY. Prevention of Liver Cancer Through the Early Detection of Risk-related Behavior Among Hepatitis B or C Carriers. Cancer Nurs. 2015; 38(3):169–76. https://doi.org/10.1097/NCC.0000000000000153 PMID: 24836958

28. Choi JS, Han KJ, Lee S, Chun SW, Kim DJ, Kim HC, et al. Serum HBV Surface Antigen Positivity is Associated With Low Prevalence of Metabolic Syndrome in Korean Adult Men. J Epidemiol. 2015; 25 (1):74–9. https://doi.org/10.2188/jea.JE20140053 PMID: 25283312

29. Park B, Jung KW, Oh CM, Choi KS, Suh M, Jun JK. Prevalence of and factors influencing impaired glucose tolerance among hepatitis B carriers: a nationwide cross-sectional study in the Republic of Korea. Medicine (Baltimore). 2014; 93(20):e81.

30. Chung TH, Kim MC, Kim CS. Association between Hepatitis B Surface Antigen Seropositivity and Metabolic Syndrome. Korean J Fam Med. 2014; 35(2):81–8. https://doi.org/10.4082/kjfm.2014.35.2.81 PMID: 24724003

31. Liu PT, Hwang AC, Chen JD. Combined effects of hepatitis B virus infection and elevated alanine aminotransferase levels on dyslipidemia. Metabolism. 2013; 62(2):220–5. https://doi.org/10.1016/j.metabol.2012.07.022 PMID: 22938729

32. Li WC, Lee YY, Chen IC, Sun C, Chiu FH, Chuang CH. Association between the hepatitis B and C viruses and metabolic diseases in patients stratified by age. Liver Int. 2013; 33(8):1194–202. https://doi.org/10.1111/liv.12224 PMID: 23782533

33. Wong VW, Wong GL, Chu WC, Chim AM, Ong A, Yeung DK, et al. Hepatitis B virus infection and fatty liver in the general population. J Hepatol. 2012; 56(3):533–40. https://doi.org/10.1016/j.jhep.2011.09.013 PMID: 22027575
34. Hsu CS, Liu CH, Wang CC, Tseng TC, Liu CJ, Chen CL, et al. Impact of hepatitis B virus infection on metabolic profiles and modifying factors. J Viral Hepat. 2012; 19(2):e48–57. https://doi.org/10.1111/j.1365-2893.2011.01535.x PMID: 22239526

35. Chen JY, Wang JH, Lin CY, Chen PF, Tseng PL, Chen CH, et al. Lower prevalence of hypercholesterolemia and hyperglycemia found in subjects with seropositivity for both hepatitis B and C strains independently. J Gastroenterol Hepatol. 2010; 25(11):1763–8. https://doi.org/10.1111/j.1440-1746.2010.06300.x PMID: 21039839

36. Chiang CH, Lai JS, Hung SH, Lee LT, Sheu JC, Huang KC. Serum adiponectin levels are associated with hepatitis B viral load in overweight to obese hepatitis B virus carriers. Obesity (Silver Spring). 2013; 21(2):291–6.

37. Cheng YL, Wang YJ, Kao WY, Chen PH, Huo TL, Huang YH, et al. Inverse Association between Hepatitis B Virus Infection and Fatty Liver Disease: A Large-Scale Study in Populations Seeking for Check-Up. Plos One. 2013; 8(8).

38. Lee JG, Lee S, Kim YJ, Cho BM, Park JS, Kim HH, et al. Association of chronic viral hepatitis B with insulin resistance. World J Gastroenterol. 2012; 18(42):6120–6. https://doi.org/10.3748/wjg.v18.i42.6120 PMID: 23155341

39. Karsen H, Binici I, Sunnetcioglu M, Baran AI, Ceylan MR, Selek S, et al. Association of paraoxonase activity and atherosclerosis in patients with chronic hepatitis B. Afr Health Sci. 2012; 12(2):114–8. https://doi.org/10.4314/ahs.v12i2.6 PMID: 23056015

40. Dai FH, Zeng WQ, Jiang CY. Assessment of the factors associated with insulin resistance in patients with chronic hepatitis B infection. Zhonghua Gan Zang Bing Za Zhi. 2012; 20(7):517–21. https://doi.org/10.3760/cma.j.issn.1007-3418.2012.07.008 PMID: 23044237

41. Huang ZS, Huang TS, Wu TH, Chen MF, Hsu CS, Kao JH. Asymptomatic chronic hepatitis B virus infection does not increase the risk of diabetes mellitus: a ten-year observation. J Gastroenterol Hepatol. 2010; 25(8):1420–5. https://doi.org/10.1111/j.1440-1746.2010.06268.x PMID: 20659233

42. Yang KC, Chen MF, Su TC, Jeng JS, Hwang BS, Lin LY, et al. Hepatitis B virus seropositivity is not associated with increased risk of carotid atherosclerosis in Taiwanese. Atherosclerosis. 2007; 195(2):392–7. https://doi.org/10.1016/j.atherosclerosis.2006.10.018 PMID: 17134707

43. Lin YC, Hsiao ST, Chen JD. Sonographic fatty liver and hepatitis B virus carrier status: synergistic effect on liver damage in Taiwanese adults. World J Gastroenterol. 2007; 13(12):1805–10. https://doi.org/10.3748/wjg.v13.i12.1805 PMID: 17456470

44. Montani M, Adachi K, Arima N, Takashima T, Miyaoka Y, Niigaki M, et al. A study of arteriosclerosis in healthy subjects with HBV and HCV infection. J Gastroenterol. 2005; 40(11):1049–53. https://doi.org/10.1007/s00535-005-1655-3 PMID: 16322949

45. Targher G, Bertolini L, Padovani R, Rodella S, Arcaro G, Day C. Differences and similarities in early atherosclerosis between patients with non-alcoholic steatohepatitis and chronic hepatitis B and C. J Hepatol. 2007; 46(6):1126–32. https://doi.org/10.1016/j.jhep.2007.01.021 PMID: 17335930

46. Su TC, Lee YT, Cheng TJ, Chien HP, Wang JD. Chronic hepatitis B virus infection and dyslipidemia. J Formos Med Assoc. 2004; 103(4):286–91. PMID: 15175824

47. Wang CC, Hsu CS, Liu CJ, Kao JH, Chen DS. Association of chronic hepatitis B virus infection with insulin resistance and hepatic steatosis. J Gastroenterol Hepatol. 2008; 23(5):779–82. https://doi.org/10.1111/j.1440-1746.2007.05216.x PMID: 18028349

48. Shlomai A, Shaub Y. The "metabolovirus" model of hepatitis B virus suggests nutritional therapy as an effective anti-viral weapon. Med Hypotheses. 2008; 71(1):53–7. https://doi.org/10.1016/j.mehy.2007.08.032 PMID: 18334285

49. Kim KH, Shin HJ, Kim K, Choi HM, Rhee SH, Moon HB, et al. Hepatitis B virus X protein induces hepatic steatosis via transcriptional activation of SREBP1 and PPARgamma. Gastroenterology. 2007; 132(5):1955–67. https://doi.org/10.1053/j.gastro.2007.03.039 PMID: 17484888

50. Chiang CH, Huang KC. Association between metabolic factors and chronic hepatitis B virus infection. World J Gastroenterol. 2014; 20(23):7213–6. https://doi.org/10.3748/wjg.v20.i23.7213 PMID: 24966591

51. Wong VW, Wong GL, Yu J, Choi PC, Chan AW, Chan HY, et al. Interaction of adipokines and hepatitis B virus on histological liver injury in the Chinese. Am J Gastroenterol. 2010; 105(1):132–8. https://doi.org/10.1038/ajg.2009.560 PMID: 19809411

52. McManus DD, Lyass A, Ingelsson E, Massaro JM, Meigs JB, Aragam J, et al. Relations of circulating resistin and adiponectin and cardiac structure and function: the Framingham Offspring Study. Obesity (Silver Spring). 2012; 20(9):1882–6.
53. Machado MV, Oliveira AG, Cortez-Pinto H. Hepatic steatosis in hepatitis B virus infected patients: meta-analysis of risk factors and comparison with hepatitis C infected patients. J Gastroenterol Hepatol. 2011; 26(9):1361–7. https://doi.org/10.1111/j.1440-1746.2011.06801.x PMID: 21649726

54. Qiao L, Zou C, van der Westhuyzen DR, Shao J. Adiponectin reduces plasma triglyceride by increasing VLDL triglyceride catabolism. Diabetes. 2008; 57(7):1824–33. https://doi.org/10.2337/db07-0435 PMID: 18375436

55. Chu CM, Lin DY, Liaw YF. Does increased body mass index with hepatic steatosis contribute to sero clearance of hepatitis B virus (HBV) surface antigen in chronic HBV infection? Int J Obes (Lond). 2007; 31(5):871–5.

56. Hsieh PS, Hsieh YJ. Impact of liver diseases on the development of type 2 diabetes mellitus. World J Gastroenterol. 2011; 17(48):5240–5. https://doi.org/10.3748/wjg.v17.i48.5240 PMID: 22219592

57. Holstein A, Hinze S, Thiessen E, Plaschke A, Egberts EH. Clinical implications of hepatogenous diabetes in liver cirrhosis. J Gastroenterol Hepatol. 2002; 17(6):677–81. PMID: 12100613

58. Ahmadieh H, Azar ST. Liver disease and diabetes: association, pathophysiology, and management. Diabetes Res Clin Pract. 2014; 104(1):53–62. https://doi.org/10.1016/j.diabres.2014.01.003 PMID: 24485856