

The Correlation of Glycemic Index, Glycemic Load, and Carbohydrates with the Risk of Hepatocellular Carcinoma: A Systematic Review and Meta-Analysis

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Research Article

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Abstract

Background Glycemic index (GI), glycemic load (GL), and carbohydrates have been shown to be associated with a variety of cancers, but their correlation with hepatocellular carcinoma (HCC) remains controversial. The purpose of our study was to investigate the correlation of GI, GL and carbohydrate with risk of HCC.

Methods Systematic searches were conducted in PubMed, Embase and Web of Science until November 2020. According to the size of heterogeneity, the random effect model or the fixed effect model was performed to calculate the pooled relative risks (RRs) and 95% confidence intervals (CIs) for the correlation of GI, GL, and carbohydrates with the risk of HCC.

Results Seven cohort studies involving 1,193,523 participants and 1,004 cases, and 3 case-control studies involving 827 cases and 5,502 controls were eventually included. The pooled results showed no significant correlation of GI (RR=1.11, 95%CI 0.80-1.53, $I^2=62.2\%$), GL (RR=1.09, 95%CI 0.76-1.55, $I^2=66\%$), and carbohydrate (RR=1.09, 95%CI 0.84-1.32, $I^2=0\%$) with the risk of HCC in general population. Subgroup analysis revealed that in hepatitis B virus (HBV) or/and hepatitis C virus (HCV)-positive group, GI was not correlated with the risk of HCC (RR=0.65, 95%CI 0.32-1.32, $p=0.475$, $I^2=0.0\%$), while GL was significantly correlated with the risk of HCC (RR=1.52, 95%CI 1.04-2.23, $p=0.016$, $I^2=70.9\%$). In contrast, in HBV and HCV-negative group, both GI (RR=1.23, 95%CI 0.88-1.70, $p=0.222$, $I^2=33.6\%$) and GL (RR=1.17, 95% CI 0.83-1.64, $p=0.648$, $I^2=0\%$) were not correlated with the risk of HCC.

Conclusion A high GL diet is correlated with a higher risk of HCC in people with hepatitis virus. A low GL diet may be recommended for patients with viral hepatitis to reduce the risk of HCC.

Introduction

Hepatocellular carcinoma (HCC) is the sixth most common tumor and the fourth most common cause of cancer-related death worldwide. [1, 2] More than 900,000 new cases were diagnosed in 2020, with an age-adjusted global incidence of 10.1 per 100,000 person years. [1, 3] About 80% of primary liver cancer is HCC, most of which occurs in developing countries in East Asia and Africa, and is often associated with cirrhosis caused by chronic hepatitis B virus (HBV) infection. [4–6] A recent study also revealed a higher HCC incidence in Asian populations with autoimmune hepatitis. [7] In western developed countries such as Europe and the United States, the more common reason is chronic hepatitis C virus (HCV) infection or alcoholic cirrhosis caused by heavy drinking. [4] HCC incidence has increased in developed countries in recent years, [8–11] partly due to lifestyle related obesity, insulin resistance, metabolic and hormonal changes which ultimately lead to type 2 diabetes (T2D) and/or non-alcoholic fatty liver disease (NAFLD). [12–14] Nonalcoholic steatohepatitis (NASH) can lead to the development of HCC in the absence of cirrhosis. [15, 16] Several studies have shown that diabetes increases the risk of HCC, and in recent years diabetes has been identified as a nonnegligible risk factor for HCC. [17–19]

The dietary glycemic index (GI) is the percentage of food containing 50g of valuable carbohydrates that elicits a glycemic response in the body over a given period of time (typically 2 hours after a meal), compared with an equivalent amount of glucose or white bread.[20] It is a quantitative assessment of a food based on post-ingestion glycemic levels. The higher the absorption rate of carbohydrates, the faster the increase of blood glucose and the higher the value of the GI. The dietary glycemic load (GL) is the product of the GI of a food and its sugar content.[20] It reflects the characteristics of food itself and the influence of glucose content on blood sugar, and is an indicator of the response of plasma glucose and insulin to different carbohydrates. The current study demonstrates that GI, GL and carbohydrates have been associated with diabetes and have been shown to be positively associated with several types of cancer.[21–24] Among the carcinogenic effects, they increase insulin concentrations, which contribute to glucose intolerance and insulin resistance and finally lead to hyperinsulinemia. Increased insulin down-regulates the IGF-binding protein, thereby increasing the bioactivity of free insulin-like growth factor-1 (IGF-1), which may stimulate hepatocyte proliferation and lead to HCC.

Multiple meta-analyses have now confirmed associations between dietary GI, GL, carbohydrates and several cancers, including colorectal cancer, breast cancer, and ovarian cancer.[22, 23, 30–32] Previous studies have investigated the relationship between a high diet of carbohydrate, GI or GL and the risk of HCC, however results have varied.[22, 23, 30–32] Therefore, we conducted this analysis to further clarify the correlation between them.

Materials And Methods

Search strategy

Literature searches were conducted using PubMed, Embase and web of science up to November 2020, about GI, GL or carbohydrate intake and HCC risk. Medical subject heading (MeSH) terms were used in this procedure. Searches were limited the studies to English language and conducted on humans.

Study selection

The identified articles were independently screened by two reviewers (Yang and Li) to determine whether they met the inclusion criteria. Duplicate research and unrelated research were first excluded, then the full text was browsed, and articles with the following content were included:(1) cohort study or case-control study; (2) studies evaluated the association between dietary carbohydrate intake, GI and GL, and the risk of HCC; (3) hazard ratio(HR) or risk ratio(RR) or odds ratio(OR) estimates and their 95 % confidence intervals(CI) were given or sufficient data were available for evaluation.

Data extraction

We extracted the following data from each study: the study name, the first author's last name, publication year, country, study design (case-control or cohort), follow-up period, sample size, gender, age, number of cases, dietary assessment method, exposure, quantity of intake, HRs or RRs or ORs and corresponding

95% CIs and variables adjusted for in the analysis. The data was independently extracted by the two authors (Yang and Li), then the results were combined and the accuracy was discussed.

Statistical analysis

According to the size of the heterogeneity, random effects models or fixed effects models were used to calculate summary RRs and 95% CIs for the highest vs. the lowest level of GI, GL and carbohydrate intake. [38] A random-effect model was used when the heterogeneity was significant ($p \leq 0.10$ and/or $I^2 > 50\%$). Otherwise, a fixed-effect model was applied. The RRs extracted referred to the top quartile or quintile of intake compared with the lowest category of intake. The average of the natural logarithm of the RRs was estimated, and the RR from each study was weighted by the inverse of its variance. A two-tailed $p < 0.05$ was considered statistically significant.

We also performed a dose response meta-analysis using the method of generalised least squares for trend estimation proposed by Greenland and Longnecker.[39] In this way more available data related to exposure can be used, which can improve the accuracy of the estimate. When the total number of participants in each layer was missing, it was obtained by dividing the total number of participants by the number of layers. When the number of cases in each layer was missing, it was calculated by the total number of cases, the total number of participants in each layer, RR or HR. The value assigned to each GI, GL and carbohydrate was the reported median, or the midpoint of the closed category and the assigned value of the open category based on the range of adjacent categories. The dose-response relationships for GI, GL and carbohydrate were expressed in increments of 10, 50 and 50 units, respectively.

Heterogeneity was assessed by Q test and I^2 , and the total variance was explained by inter-study variation.[39] Subgroup analyses by study type and sensitivity analyses by excluding each study one by one were used to investigate potential sources of heterogeneity. Publication bias is evaluated by Egger test[41] and Begg test[42], and the results were considered to indicate publication bias when $p < 0.10$.

Results

A flowchart of the identification of relevant studies is shown in Fig 1. After searching PubMed, Embase and Web of Science, 518 articles were identified. According to the inclusion criteria established in advance, we reviewed and finally included 7 studies,[11, 28, 33-37] including 4 cohort studies (7 cohorts) and 3 case-control studies. Three studies were from North-America, 3 from West-Europe, and 1 from Asia. All studies principally employed either self-reported or interviewer-administrated validated Food Frequency Questionnaires (FFQs). The characteristics of the studies are described in the Supplementary Table1.

Glycemic index

Four studies[11, 28, 33-37](5 cohorts, 1 case-control study) with approximately 1,062,000 participants were included to assess the association between GI and the risk of HCC. Comparing the highest with the lowest categories, GI was not significantly associated with HCC risk (pooled RR 1.11, 95%CI 0.80–1.53), and moderate heterogeneity among studies was observed ($I^2 = 62.2\%$, $p = 0.021$), as showed in Fig.2.

In cohorts study the pooled RR was 1.24 (95% CI 0.91-1.69), and heterogeneity decreased significantly ($I^2=43.0\%$, $p=0.135$). In the dose–response meta-analysis, the RR for per 10-unit increment of GI was 1.02 (95 % CI 1.00–1.05,Supplementary Table2), with indication of lower heterogeneity ($I^2=29.04$, $p=0.05$).In the sensitivity analysis, RR was strongest when we excluded the study of Hu, J et al (1.24, 95%CI 0.91-1.69) and weakest when we excluded the study of George(M) et al (1.00, 95%CI 0.73-1.39). Heterogeneity decreased slightly, and was still statistically significant. There was no evidence of publication bias using the Egger weighted regression method (p for bias 0.341) or the Begg rank correlation method (p for bias 0.707).

Glycemic load

Six studies[11, 28, 33-35, 37](5 cohorts, 3 case-control study) with approximately 1,058,000 participants were included to assess the association between GL and the risk of HCC. Comparing the highest with the lowest categories, GL was not significantly associated with HCC risk (pooled RR 1.09, 95 % CI 0.76–1.55), and moderate heterogeneity among studies was observed ($I^2 = 66.0\%$, $p = 0.004$), as showed in Fig.3.

The pooled RR was 0.84 (95% CI 0.53-1.27) in cohort studies, 1.64 (95%CI 1.00-2.68) in case–control studies, and heterogeneity was decreased in both. In the dose–response meta-analysis, the RR for per 50-unit increment of GL was 0.98 (95 % CI 0.93–1.03, Supplementary Table2), with indication of slight heterogeneity ($I^2=21.27$, $p=0.27$). In the sensitivity analysis, RR was strongest when we excluded the study of George(M) et al (1.22, 95%CI 0.88-1.70) and weakest when we excluded the study of Rossi, M et al (0.98, 95%CI 0.72-1.35). Heterogeneity decreased slightly, and was still statistically significant. There was no evidence of publication bias using the Egger weighted regression method (p for bias 0.28) or the Begg rank correlation method (p for bias 0.536).

Carbohydrates

Three studies[11, 33, 36](5 cohorts) with approximately 748,000 participants were included to assess the association between carbohydrates and the risk of HCC. Comparing the highest with the lowest categories, carbohydrates was not significantly associated with HCC risk (pooled RR 1.05, 95 % CI 0.84–1.32), and low heterogeneity among studies was observed ($I^2 = 0.0\%$, $p = 0.604$), as showed in Fig.4.

In the dose–response meta-analysis, the RR for per 50-unit increment of carbohydrates was 0.99 (95 % CI 0.96–1.03, Supplementary Table2), with indication of slight heterogeneity ($I^2=12.00$, $p=0.28$). No sensitivity analysis was performed due to small inter-study heterogeneity. There was no evidence of publication bias using the Egger weighted regression method (p for bias 0.436) or the Begg rank correlation method (p for bias 0.806).

Subgroup analysis

We divided the included population into HBV or/and HCV-positive and HBV and HCV-negative groups, then calculated the relationship between GI, GL and risk of HCC in each group.

In the HBV or/and HCV-positive group, GI was not correlated with the risk of HCC (RR=0.65, 95% CI: 0.32-1.32, $p = 0.475$, $I^2 = 0.0\%$, Fig 5), while GL was significantly correlated with the risk of HCC was 1.52 (RR=1.52, 95% CI: 1.04-2.23, $p = 0.016$, $I^2 = 70.9\%$, Fig 6). In contrast, in the HBV and HCV-negative group, both GI (RR=1.23, 95% CI: 0.88-1.70, $p = 0.222$, $I^2 = 33.6\%$; Fig 7) and GL (RR=1.17, 95% CI: 0.83-1.64, $p = 0.648$, $I^2 = 0.0\%$; Fig 8) were not correlated with the risk of HCC.

Discussion

In this systematic review, our results showed no statistically significant correlation of GI, GL, and carbohydrate with the risk of HCC in general population. However, among patients infected with viral hepatitis, the risk of HCC was significantly increased in those with a high GL diet. In the analysis of GI, GL and HCC risk, there was a moderate degree of heterogeneity, which may be caused by the difference between studies. In the meta-analysis, subgroup analysis based on study type demonstrated heterogeneity among different study types. In the analysis of GI cohort studies, most individual studies did not show a statistically significant association between GI and HCC risk, but vogtmann, E (SWHS) reported an evident and significantly increased risk. Differences in a few studies may be associated with the resulting heterogeneity. Due to the limitations of case-control studies, there may be selection and recall biases that make the results less credible, which is also a factor in heterogeneity.[43] More high-quality studies are warranted to assess the risk factors of HCC occurrence.

There are several mechanisms that may explain the association between GI, GL, carbohydrates, and cancer risk. It is widely recognized that increased insulin concentration causes glucose intolerance and insulin resistance leading to hyperinsulinemia.[25, 26] Increased insulin down-regulates IGF-binding proteins, thereby increasing the bioactivity of free IGF-1,[29, 44] which in turn inhibits cell apoptosis and stimulates cell proliferation to cause tumor development.[29, 44] On the other hand, in insulin resistance, production of pro-inflammatory mediators such as interleukin 6 (IL-6), tumor necrosis factor α (TNF- α), resistin and leptin is significantly increased, which creates an environment that leads to increased liver inflammation and steatosis, causing the occurrence of NAFLD and promoting the development of HCC. [45–47] Other nutrients in the diet, such as protein, fat and fiber, may influence this mechanism, but none of these dietary variables are actually associated with HCC risk, and are only potential confounding factors.[45–47] For the known diabetic population, they may change their original high sugar intake diet according to the doctor's advice or their own initiative diet change, while their insulin resistance still exists. This can also make the results less accurate.

Compared to other organs, the liver is special. The liver has its own metabolic functions by converting carbohydrates, fats and proteins into glycogen, which is stored in liver cells. A high GL diet will increase

the burden of liver glucose metabolism and increase the accumulation of liver glycogen. Recent studies have shown that in adjacent HCC tumors, smaller tumors have significantly more glycogen storage, indicating that glycogen accumulation promotes the early occurrence of HCC. Further mechanism investigation reveals that glycogen accumulation blocks Hippo signaling activity, thereby activating Yap, which promotes liver enlargement and HCC development.[48] Therefore, elimination of glycogen accumulation abrogates liver growth and HCC incidence, whereas increasing glycogen storage accelerates tumorigenesis.[48]

In both the general population and the population without viral hepatitis, an increase in HCC risk was observed with high GL, but without statistical significance. However, HCC risk increased significantly in people with high GL and viral hepatitis. This suggests that a possible synergistic effect between a high GL diet and viral hepatitis may enhance the impact of a high GL diet on HCC risk. This is of great significance to the dietary guidance of patients with viral hepatitis.

In this study, we expanded the search scope as much as possible to find possible studies to ensure that the inclusion of the article is more comprehensive. At the same time, we strictly included the principles to make the research quality higher. Our meta-analysis included cohort studies and case-control studies, and performed a dose-response relationship meta-analysis of cohort studies to further explore the association. According to the particularity of HCC, the analysis was further conducted based on whether there was viral hepatitis, and the correlation between GI, GL and risk of HCC was further discussed. The large number of participants and cases ensure the credibility of the systematic review.

There may be several limitations in our meta-analysis. Diets rich in carbohydrates and high in GI and GL may be associated with other characteristics of the population, including eating habits in different countries and regions, age, income, education, physical inactivity, overweight and obesity, history of diabetes, smoking, heavy drinking, and red meat. Due to the small number of studies included, the subgroup analysis did not effectively reduce the heterogeneity, and no publication bias was found. Though the studies we included all used sophisticated dietary intake assessment methods, which were able to effectively reduce errors that might affect the estimates of effects.[49] However, there is no denying that the FFQ list of foods is still limited, which may limit the corresponding range of detectability. Similarly, patients may have recently changed their diet due to symptoms or treatment, so FFQ results may not completely represent habitual intake.[50] At the same time, regional and population differences in diet also make an impact.

Conclusion

In summary, there is insufficient evidence to establish a relationship between GI, GL, carbohydrate, and the risk of HCC in the general population. However, in people with viral hepatitis, a high GL diet significantly increases the risk of HCC. A low GL diet may be recommended for patients with viral hepatitis to reduce the risk of HCC.

Abbreviations

GI, glycemic index

GL, glycemic load

HCC, hepatocellular carcinoma

RR, risk ratio

CI, confidence interval

HBV, hepatitis B virus

HCV, hepatitis C virus

HR, hazard ratio

OR, odds ratio

T2D, type 2 diabetes

NAFLD, non-alcoholic fatty liver disease

NASH, nonalcoholic steatohepatitis

IL-6, interleukin 6

TNF- α , tumor necrosis factor α

Declarations

Conflict of interest: There are no conflicts of interest to declare.

Data availability: All data and material analyzed during this study are included in this article.

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Author contributions:

YLS and LT designed the study. YLS, MGX and DZN performed the systematic search. YLS, YLJ, YSY, LHC, JGH, DZR, and CZQ selected eligible articles and conducted the quality assessment. YLS analyzed,

interpreted the data, and drafted the manuscript. LT revised the manuscript. All authors have read and approved the final version of the manuscript.

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Figures

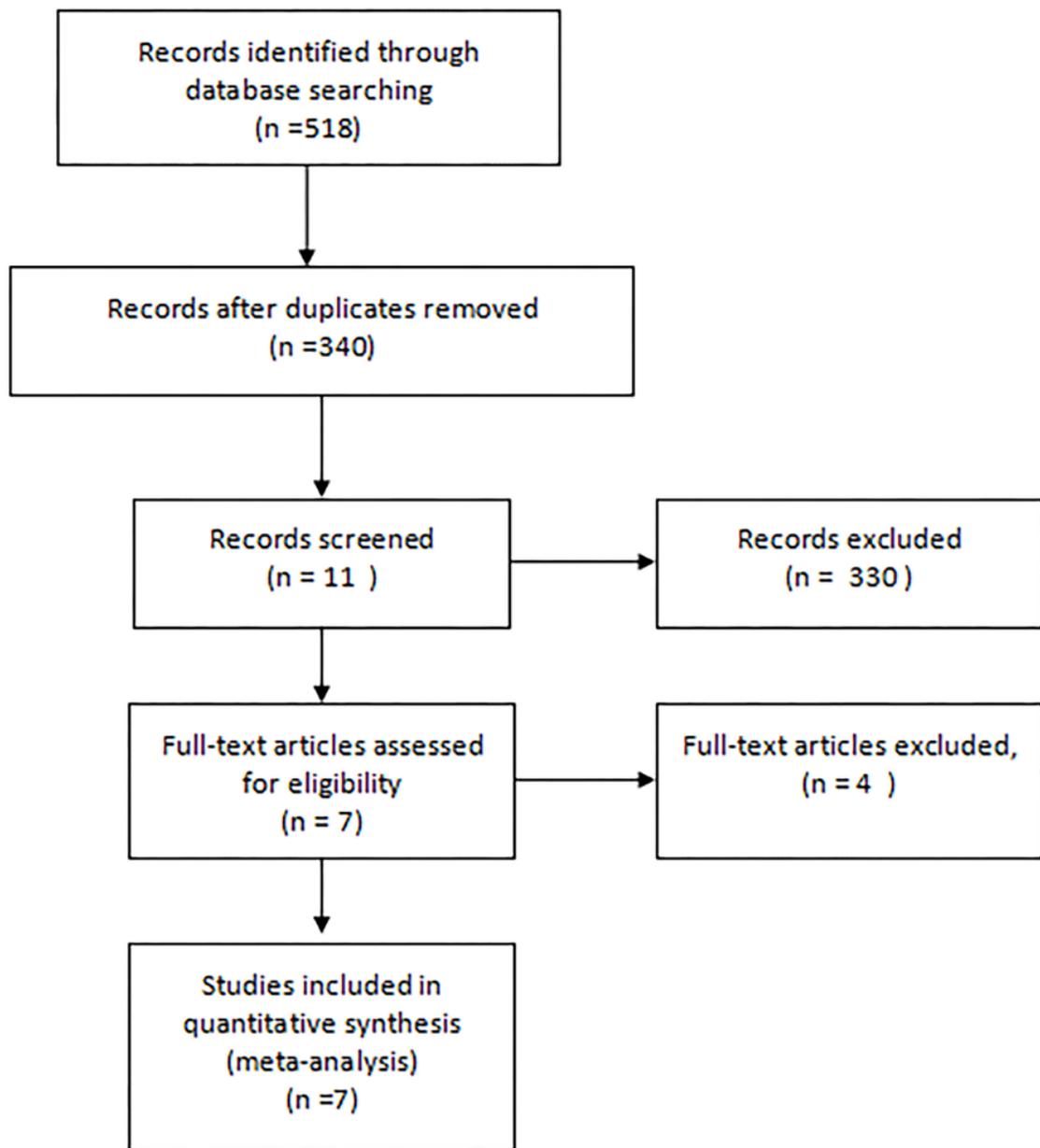


Figure 1

Study flow chart of the data extraction process and selection of studies for meta-analysis.

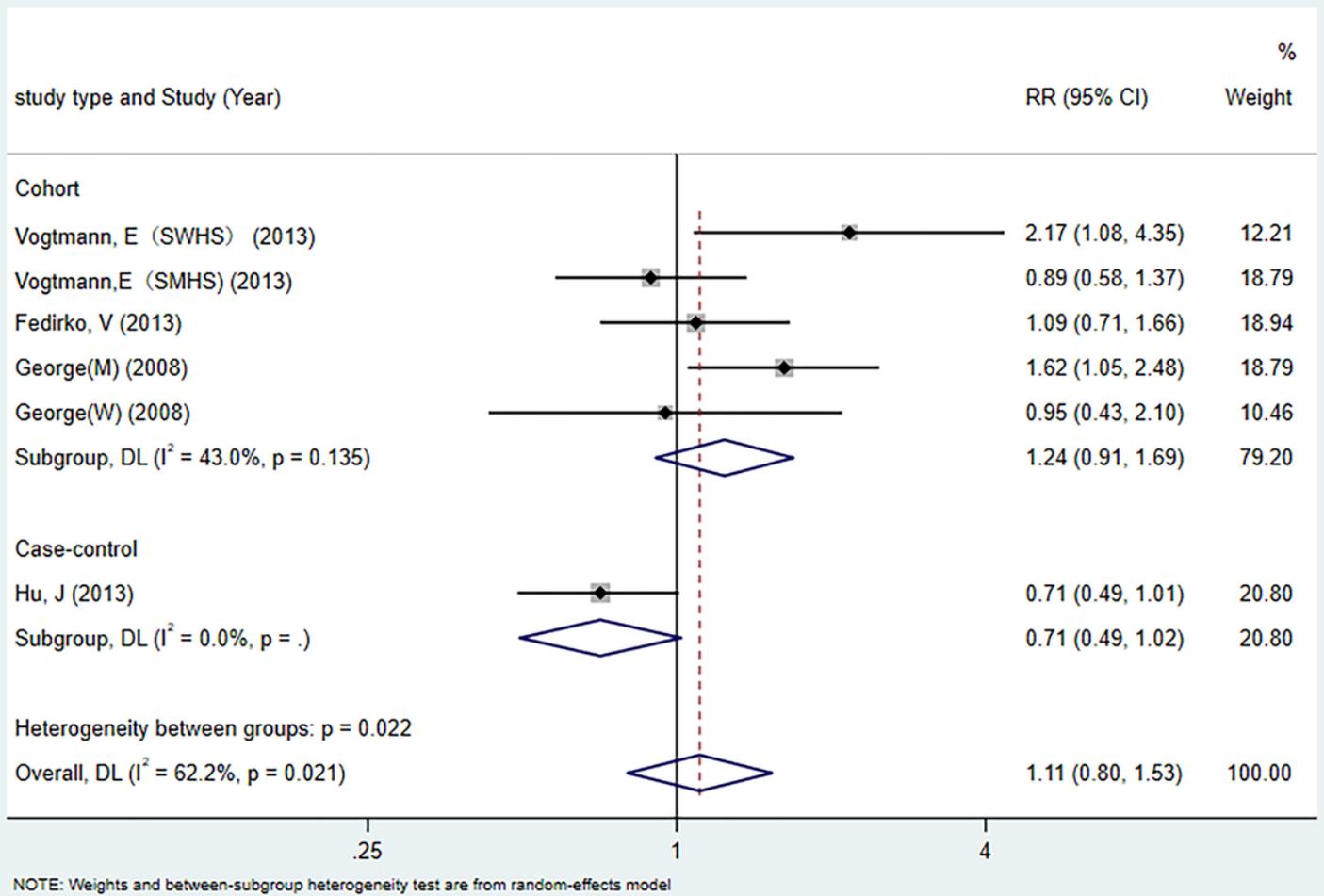


Figure 2

Forest plot of glycemic index and hepatocellular carcinoma in general population

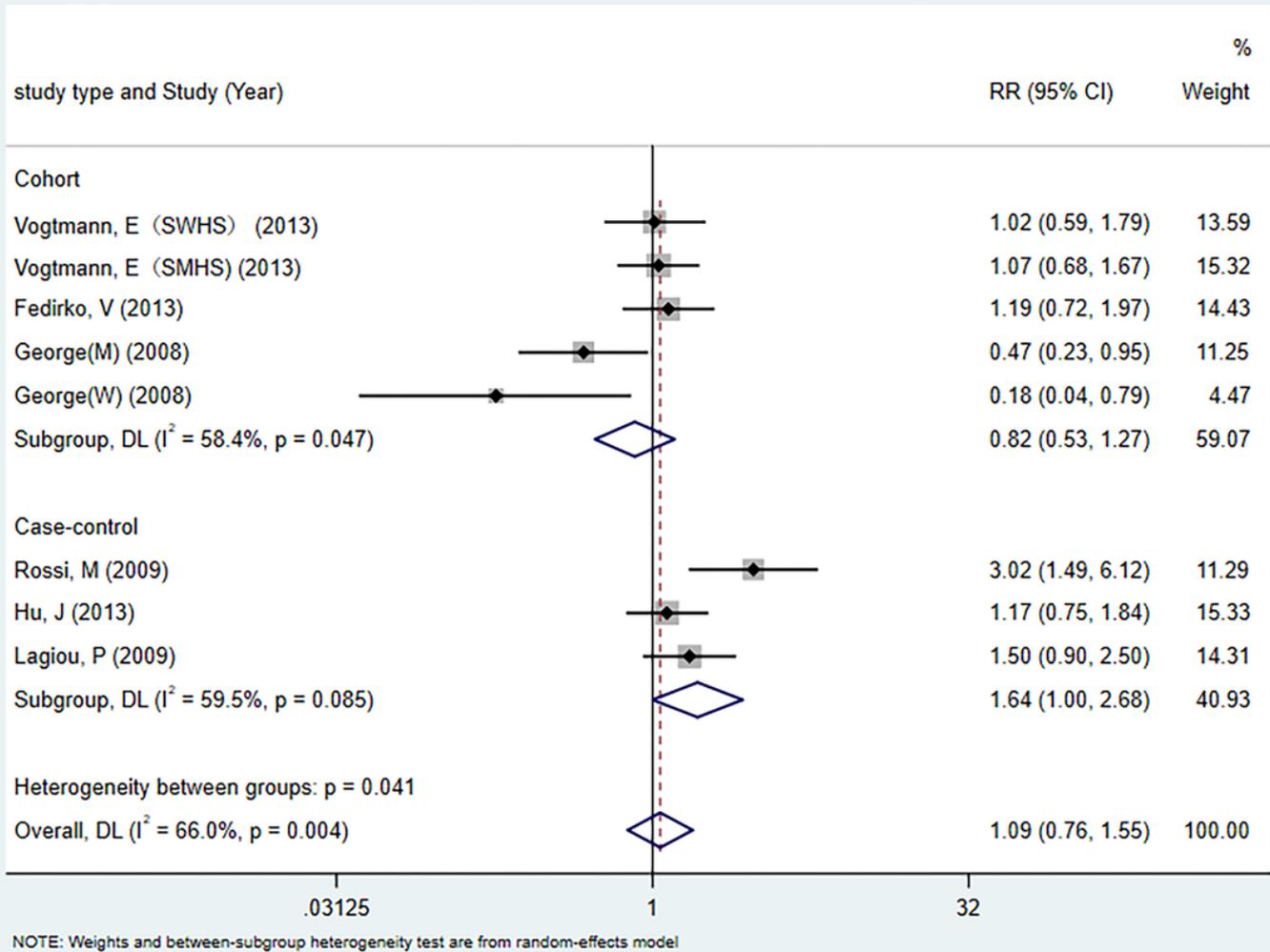


Figure 3

Forest plot of glycemic load and hepatocellular carcinoma in general population

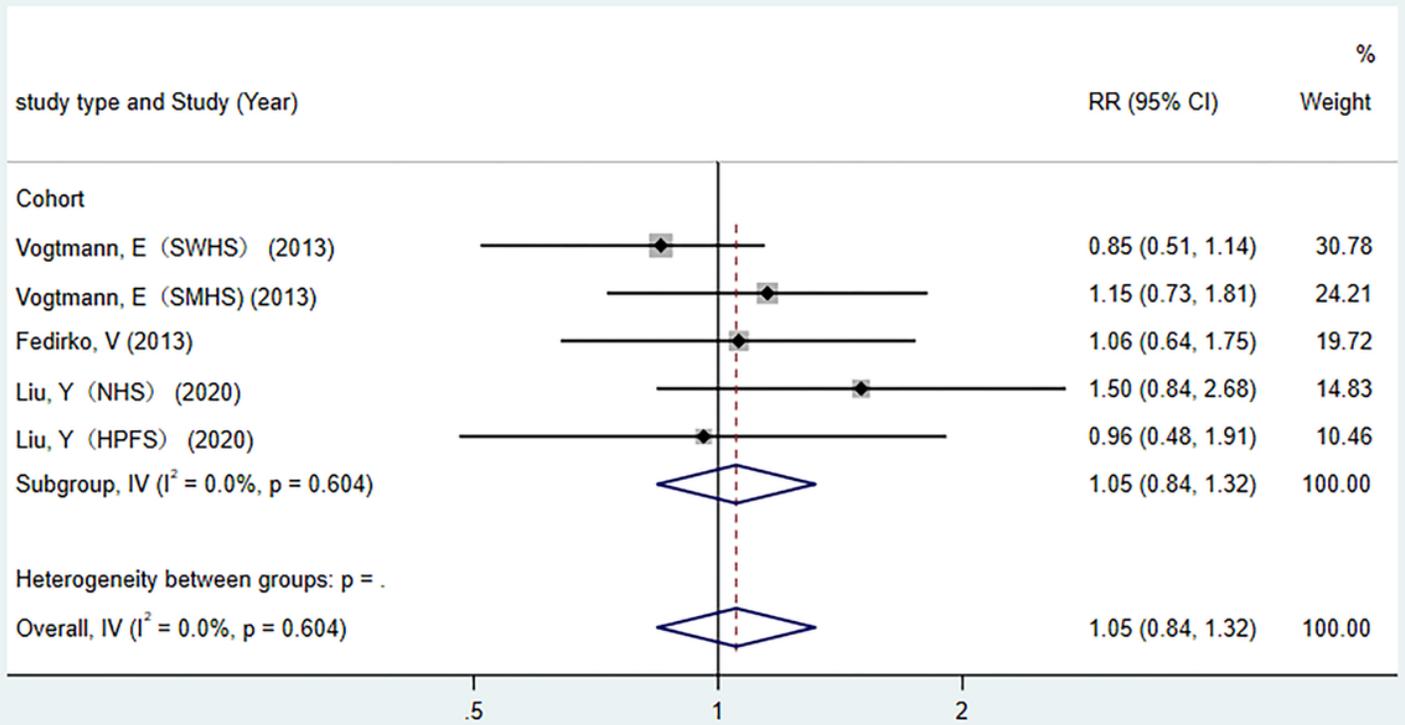


Figure 4

Forest plot of carbohydrates and hepatocellular carcinoma in general population

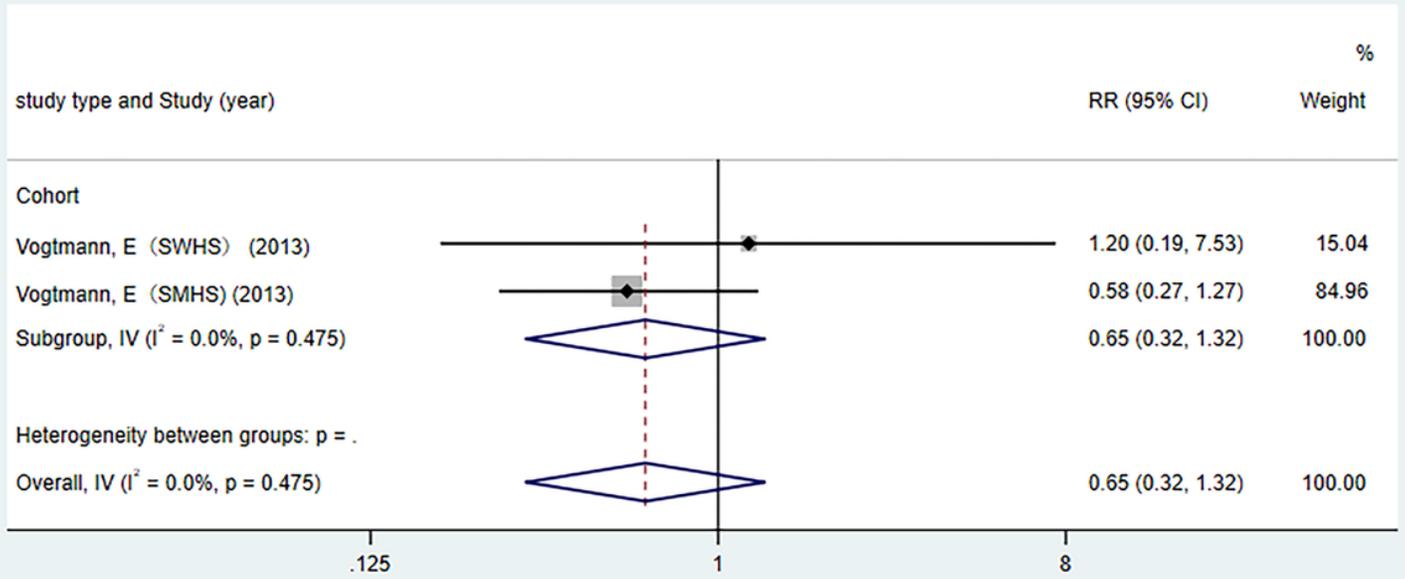


Figure 5

Forest plot of glycemic index and hepatocellular carcinoma in HBV or/and HCV-positive group

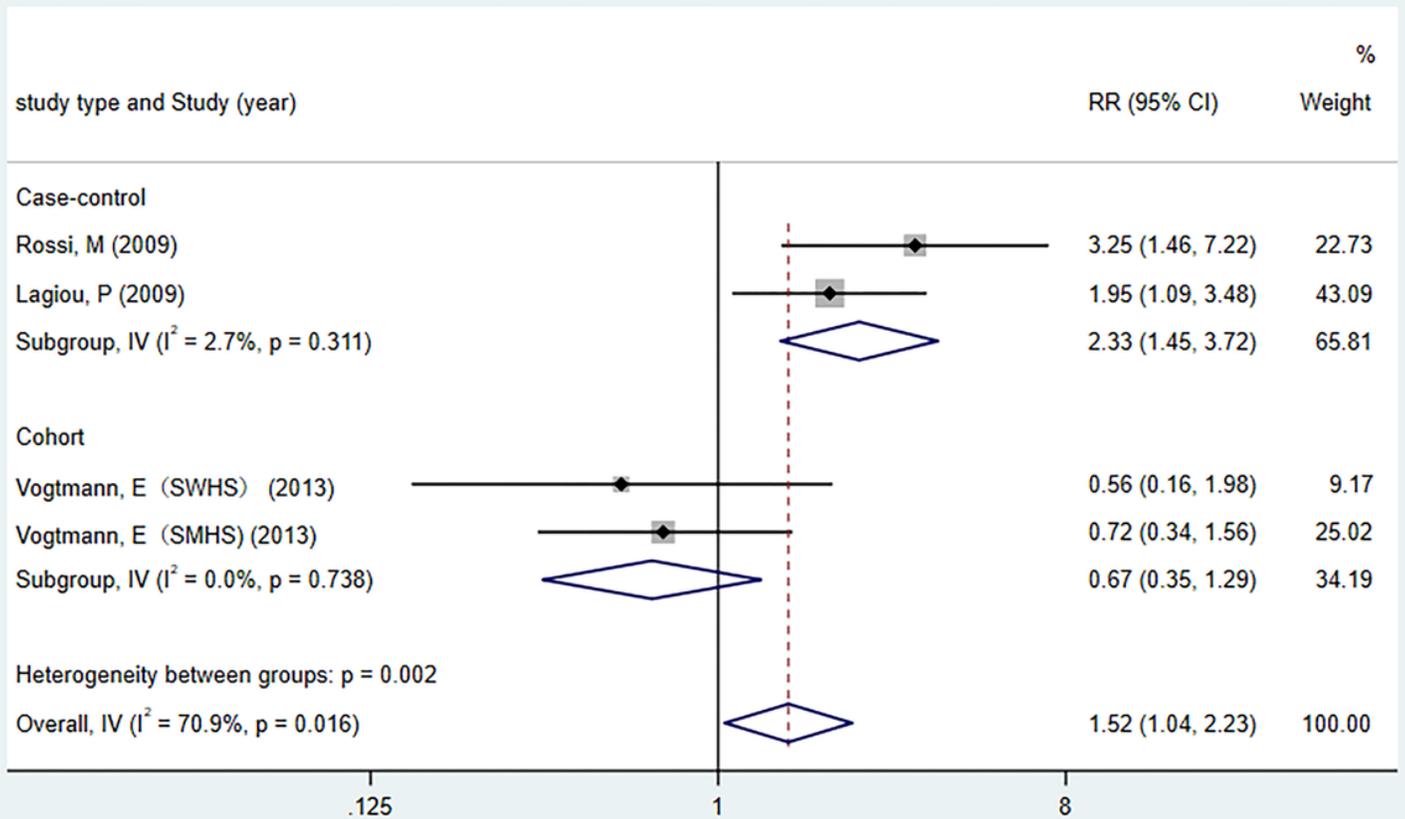


Figure 6

Forest plot of glycemic load and hepatocellular carcinoma in HBV or/and HCV-positive group

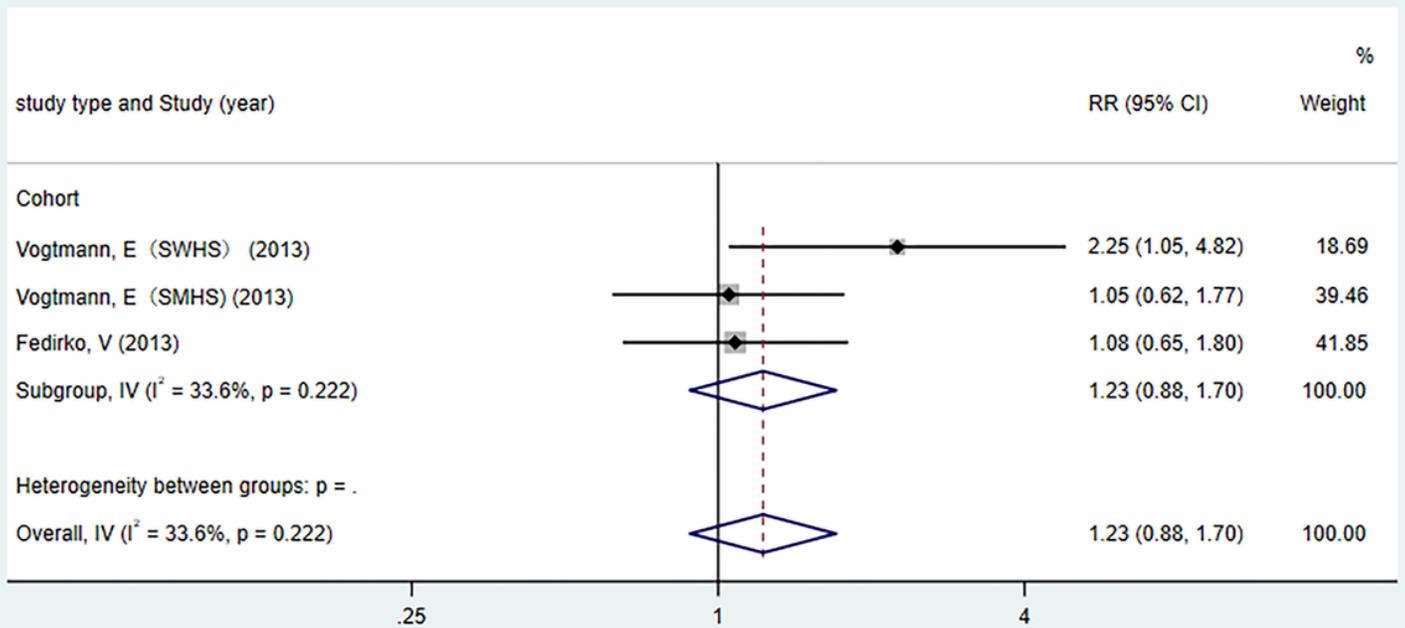


Figure 7

Forest plot of glycemic index and hepatocellular carcinoma in HBV and HCV-negative group

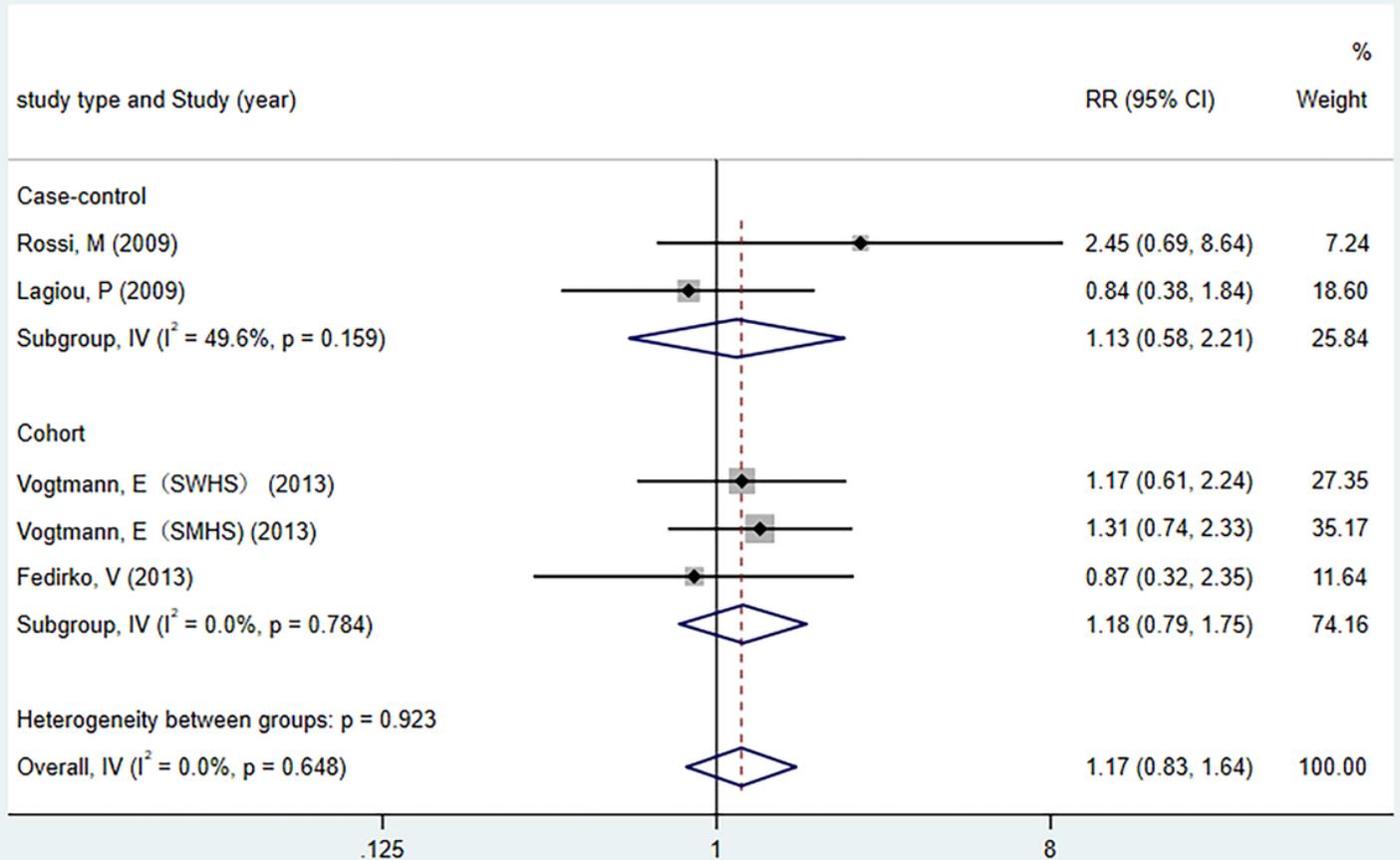


Figure 8

Forest plot of glycemic load and hepatocellular carcinoma in HBV and HCV-negative group

Supplementary Files

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- [SupplementaryTable1.docx](#)
- [SupplementaryTable2.docx](#)
- [SupplementaryFigure1.tif](#)
- [SupplementaryFigure2.tif](#)
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