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The Association of plasma levels of liver enzymes and risk of gestational diabetes mellitus:

a systematic review and dose-response meta-analysis of observational studies

running head: liver enzymes and gestational diabetes mellitus

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Abstract

Aims: Relationship between liver enzymes such as gamma-glutamyl transferase (GGT), alanine aminotransferase (ALT), aspartate transaminase (AST), and alkaline phosphatase (ALP) and risk of gestational diabetes mellitus (GDM) is a controversial issue. The aim of this systematic review and dose-response meta-analysis was investigation the association between liver enzymes and risk of GDM in observational studies.

Methods: A Comprehensive systematic literature search was conducted in MEDLINE/PubMed, SCOPUS, and Web of Science databases up to September 2019. Combined odds ratios (ORs) with 95% confidence intervals (CIs) were evaluated by DerSimonian and Laird random-effects models. Dose-response analyses of these relationships were also carried out.

Results: Eight studies with 25,451 participants containing 2,549 cases were included in this study. Pooled results showed a significant association between GGT levels and risk of GDM (OR: 2.10, 95% CI: 1.14-3.86, I^2: 84%). In addition, random-effects model indicated a dramatic and direct significant association between GGT and risk of GDM in non-linear ($p<0.001$) and linear ($p<0.001$) dose-response analysis. Associations between ALT and AST with risk of GDM were found to be non-significant (OR: 1.32, 95% CI: 0.91-1.90, I^2: 65% and OR: 0.76, 95% CI: 0.52-1.10, I^2: 16%, respectively).

Conclusions: This systematic-review and dose-response meta-analysis highlights GGT as a significant and robust predictor of the incidence of GDM in pregnant women.

Keywords: gestational diabetes mellitus; gamma-glutamyl transferase; liver enzymes.

Introduction

Gestational diabetes mellitus (GDM) represents a significant health concern for both prospective mothers and their fetuses. Mothers are at risk of experiencing serious GDM-related gestational, perinatal and postnatal complications, including hypertension, obstetric complications and subsequent development of type-2 diabetes mellitus (T2DM). In turn, the GDM-exposed infant is at risk of developing macrosomia with subsequent birth trauma or hypoglycemia in the perinatal period [1]. In addition, long-term complications for the offspring include increased risk of metabolic syndrome and neonatal respiratory distress syndrome [2-4] and, potentially, impaired academic achievement [5]. A wide range in the incidence of GDM is often reported in the literature, which is generally attributed to disparities in diagnostic criteria between organizations; however, rates of between 6-7% of pregnancies are often cited previously, depending on the populations assessed [6, 7]. With obesity rates on a concerning upward trajectory globally and an increasing prevalence of geriatric mothers, the rates of GDM appear to be rising in concert in a diversity of cohorts [8, 9]. More recent estimates from the International Diabetes Federation suggest that there were 18.4 million cases of GDM-induced hyperglycemia in 2017 [10], which puts the current predicted rate at ~14%.

The early detection of GDM through screening programs is essential to the effective treatment of the disease and prevention of the aforementioned sequelae [11]. In many countries, prospective mothers will undergo clinical screening for risk factors of GDM at a first trimester antenatal booking visit, with subsequent testing by random blood glucose, fasting blood glucose or oral glucose tolerance test if pertinent risk factors are identified. However, such investigations are often costly and time-consuming, with inadequate sensitivity in the case of random blood glucose testing [12]. This is particularly pertinent in the context of low and middle-income countries, where GDM rates appear to be increasing most rapidly [13], but where appropriate

testing and treatment funds may not be available [14]. Therefore, an alternate cost-effective means of screening is currently of paramount importance in this context.

Non-alcoholic fatty liver disease (NAFLD) is a common complication of obesity and is associated with the metabolic dysfunction and insulin resistance observed in the phenotype [15]. In addition, abnormal liver enzyme profiles have demonstrated potential as initial biochemical markers of hepatic fatty deposition [16]. In line with this, several studies have investigated the utility of such markers as predictors of the development of diabetes and other disease[17, 18], with GGT appearing to provide the most robust association [19]. Therefore, it is perceivable that alterations in circulating liver enzyme levels may represent a reliable indicator of the metabolic dysfunction which predisposes mothers to the development of GDM. However, there remains a degree of discord amongst the literature examining this hypothesis. The present systematic review and meta-analysis aimed to synthesize the available observational data assessing the putative relationship between GDM and individual liver enzymes, GGT, ALT, ALP and AST. In addition, a dose response analysis was conducted to assess the nature and magnitude of the relationship between these markers and risk of GDM diagnosis.

Materials and Methods

MOOSE guidelines (Recommendations of the Meta-analysis Of Observational Studies in Epidemiology) were followed to conduct of this systematic-review and dose-response meta-analysis [20]. A comprehensive literature searches was conducted in PubMed/MEDLINE, Scopus, and Web of Science databases for observational studies that examine association between liver enzymes and GDM from inception to September 2019 without language or time limitations. The search strategy contained MESH and title/abstract format of “liver enzyme” AND “gestational diabetes mellitus” and their relative keywords (Supplementary Table 1). An email

alert service was activated to avoid any missing novel articles published after our comprehensive literature search. Furthermore, references of relevant papers were scrutinized to identify additional studies that may not have been identified through our systematic search.

Inclusion criteria, data extraction and quality assessment

The following inclusion criteria were applied: 1) observational design; 2) reported relation between liver enzyme and GDM in appropriate format (hazard ratio (HR), risk ratio (RR), or odd ratio (OR) and the corresponding 95% confidence intervals (CI)). We contacted corresponding authors for further information in papers with missing data. The studies with reviews and editorial design or non-human studies, case reports, and letters to editor were excluded from this study.

Studies were screened and data were extracted by two independent authors and discrepancies were resolved through the senior author. The following data were extracted: the first authors' name, year of publication, study location, design of study, total number of participants and cases, mean age of participants, time during pregnancy when liver enzymes were evaluated, confounding factors, summary estimates and 95% CIs of GDM incidence. We assessed the quality of the included studies using the Newcastle-Ottawa Quality Assessment Scale (NOS)[21].

Statistical analysis

The STATA 14.0 statistical software (Stata Corporation, College Station, Texas, USA) was used for statistical analysis of the dataset. Combined risk estimates of GDM incidence was evaluated using DerSimonian and Laird random-effects model [22]. Heterogeneity between studies was estimated using the Cochrane Q test and I^2 statistic with a significant cut point of 0.1 for Cochrane Q test and 50% for I^2 statistic. Restricted cubic splines (with three knots at percentiles 10%, 50%, and 90%) was used to evaluate curvilinear association between liver enzymes and risk of GDM [23]. Funnel plot, Begg's rank correlation test and Egger's regression test were conducted to

evaluate publication bias amongst the included studies. A p-value < 0.05 was considered as significant.

Results

Literature search

Figure 1 presents a flow diagram of literature database research. In our primary systematic search, 261 records were identified from PubMed/MEDLINE, Scopus, and Web of Science databases. From these, 122 were excluded as duplicates and 121 were excluded as irrelevant based on the title and/or abstract. Eighteen studies were evaluated in full text screening and 10 studies failed to meet inclusion criteria and were subsequently excluded. Finally, eight studies with a total of 25,451 participants were identified as eligible according to meta-analysis inclusion criteria [24-31].

Study characteristics and quality assessment

The selected characteristics of the eight included studies are presented in Table 1. No patients in the last two studies with similar first author name participated in both studies. All studies were published between 2008 to 2019. Three of the studies were performed in US [25, 27, 29], three in China [24, 26, 28], and two in Malaysia [30, 31]. Three studies had a prospective design and three were case-control studies. The mean age of participants was 29 years. Totally 2,549 cases and 25,451 participants were included in the analysis. The quality of included studies was evaluated by Newcastle-Ottawa Quality Assessment scale and most were found to be of good quality (Supplemental Table 2). Adjusted covariates presented in Supplemental Table 3.

Main results of the meta-analysis

Five studies provided data from 5,709 participants containing 965 cases for GGT [25, 26, 29-31]. The pooled OR (95% CI) in the highest category versus the lowest category of GGT was (OR: 2.10, 95% CI: 1.14-3.86, I^2: 84%) for risk of GDM (Figure 2). This OR means if we have 10 pregnancies with normal GT who developed gestational diabetes in total 1000 pregnancies with normal GT, there will exist 21 pregnancies with elevated GT who developed gestational diabetes in total 1000 pregnancies with elevated GT.

We pooled data from five studies containing six arms with 21,728 participants and 2,190 cases by random effect models [25, 27-30]. Combined results did not reveal a significant association with GDM in highest category of ALT compared to lowest category (OR: 1.32, 95% CI: 0.91-1.90, I^2: 65%).

Pooled results of included studies did not demonstrate a significant relationship between AST levels and OR for GDM (OR: 0.76, 95% CI: 0.52-1.10, I^2: 16%)[29, 30]. Furthermore, just one study was identified that evaluated the relationship between ALP and GDM [24] and we could therefore conduct an analysis; however, according to Xiong *et al*., there is a significant relation between ALP levels and OR for GDM 2.47 (95% CI 1.47, 4.15) in highest category of ALP compared to the lowest.

Dose-response analysis

The linear dose-response relationship between GGT, ALT, and AST and non-linear dose-response relationship between GGT and ALT with risk of GDM were evaluated. The pooled OR from the random-effects model indicated a dramatic direct significant association between GGT and risk of GDM in non-linear ($p<0.001$) and linear ($p<0.001$) dose-response analysis (Figure 3). This relationship was found to be direct and significant between ALT and GDM in the linear ($p<0.001$) dose-response analysis and was non-significant in the non-linear ($p=0.54$) dose-

response analysis. Finally, the relationship between AST and GDM was not significant in the linear (p=0.23) dose-response analysis.

Publication bias

No significant asymmetry was identified amongst included studies through Funnel Plotting (Figure 4). Additionally, Begg's and Egger's test did not identify publication bias (Begg's p=0.62 and Egger's p=0.73 for GGT; Begg's p=0.86 and Egger's p=0.86 for ALT; Begg's p=0.31 for AST).

Discussion

The relationship between liver enzymes, such as gamma-glutamyl transferase (GGT), alanine aminotransferase (ALT), aspartate transaminase (AST), and alkaline phosphatase (ALP) and risk of gestational diabetes mellitus (GDM) has yielded equivocal results in the literature. However, given that up to 70% of women with GDM go on to develop Type 2 diabetes, with a very large increase in incidence within the first five years, which is related with innumerable injurious health consequences [32-35]. Thus, it would be pragmatic to assimilate and analyze all contemporary evidence, in an effort to better inform clinicians, the public and other key stakeholders. Therefore, the aim of this systematic review and dose-response meta-analysis was investigation the association between liver enzymes and risk of GDM in observational studies. In accord with the aforementioned aim, pooled results showed a significant association between GGT levels and risk of GDM. Furthermore, a direct and significant association between GGT and risk of GDM was evident in non-linear ($p<0.001$) and linear ($p<0.001$) dose-response analyses. However, the association between ALT and AST, and risk of GDM, were non-significant, respectively.

Our findings with GGT are consistent with empirical research examining liver enzymes and diabetes onset. Numerous empirical studies have shown that higher GGT levels may predict the

development, and onset, of type 2 diabetes [36-38]. The relationship between GGT and, particularly, type 2 diabetes has been shown to manifest in a dose-response manner [37], whilst also being independent of other, recognized, diabetes risk factors [39]. For instance, Gao et al reported that GGT concentrations were related to risk of prediabetes and positively associated with insulin resistance, independently[40]. There is a paucity of literature that as examined liver enzyme levels during pregnancy, particularly with regards to GDM risk, and in instances it has been investigated, literature reported findings have been equivocal. Interestingly, in the absence of a hepatitis diagnosis, increased GGT levels is regarded to represent excess fat deposition in the liver [41], which is accepted to be characterized by insulin resistance [40]. Importantly, laboratory tests for GGT, ALT and AST are commonly utilised to assess the overall health of the liver, with results shown to correlate with features of insulin resistance independent of BMI and central obesity. While the *de facto* standard for measuring for a variety liver diseases is to perform a liver biopsy, testing of ALT, AST, and GGT demonstrably provides reasonable noninvasive surrogate measures [42]; and therein, given we highlighted the relationship between GGT and GDM, routine measurement of GGT may represent a viable and informative clinical practice.

Putative mechanism

The liver is essential in maintaining, during both fasted and postprandial states. glucose homeostasis, and thus represents a fundamental tent of type 2 diabetes development. Serum levels of GGT is also asserted to represent a marker of oxidative stress [43, 44], which is defined by increased free radicals' presence and lipid oxidation. Moreover, oxidative stress may play a role in type 2 diabetes etiology, primarily through inducing insulin resistance and impairing insulin secretion [45, 46]. GGT is shown to catabolize extracellular glutathione (GSH), which possesses an antioxidant role, thus, in response to oxidative stress, it is conceivable that GGT levels may rise

to produce more GSH [47]. Elevations in GGT levels may lead to increased permeation of the GSH tripeptide into cells, where it can act to protect against oxidative damage [48]. It has been speculated that GGT level may also represent a marker of exposure to environmental pollutants [49], which may be present in adipose tissue, perturb endocrine processes, and may further interact with obesity to negatively influence diabetes risk. In addition, it has been suggested that elevated liver enzymes may reflect underlying chronic inflammation, conceivably impairing insulin signaling [50, 51]. However, although we demonstrate the significant relationship between GGT and GDM, the mechanisms by which GGT influences, mediates, or contributes to the development of GDM must be investigated in greater detail.

With respect to AST and ALT, respectively; AST exists throughout the body and it elevation can manifest in a multitude of clinical pathologies [52]; furthermore, its' association with diabetes appears tenuous [53]. ALT is, primarily, found within the liver, and is believed to represent a biomarker of liver fat accumulation [54]. The non-significant association between ALT and GDM in the current study is somewhat surprising, particularly given that ALT is considered a risk marker for type 2 diabetes [53]; however, several, independant studies have reported no association between ALT and diabetes [55, 56].

Strength and limitations

The main strength of this study is the incorporation of a large sample size, consisting of over 25,000 participants. This provided findings that are generalizable and facilitated the opportunity for dose-response analysis. Visual inspection of the funnel plot and, indeed, formal statistical testing yielded no indication of publication bias, which is a clear improvement in the reliability of our results, compared to previous meta-analyses, where significant heterogeneity was reported [57]. We found that was no publication bias associated with any facet of our analyses,

and thus, we can conclude that the results of this meta-analysis are unlikely to be biased by a selective lack of unpublished, or grey literature, studies. Whilst the sample amalgamated in the present study is large; the results do not necessarily yield definitive findings of a causal inference; thus, it must be recommended that further studies be conducted in order to confirm our findings.

Conclusion

This systematic-review and dose-response meta-analysis highlights that GGT may represent a significant, clinically relevant, predictor related to the incidence of gestational diabetes mellitus. There was no evidence for an increased risk of GDM with AST or ALT level. Thus, we assert that further longitudinal studies long-term follow-up and repeat measurements are still warranted to avow the magnitude and direction of these associations, in addition to permitting greater clinical insight into management and treatment.

Conflict of interest

The authors declare no conflict of interest.

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Fig 1. Flow chart of included studies.

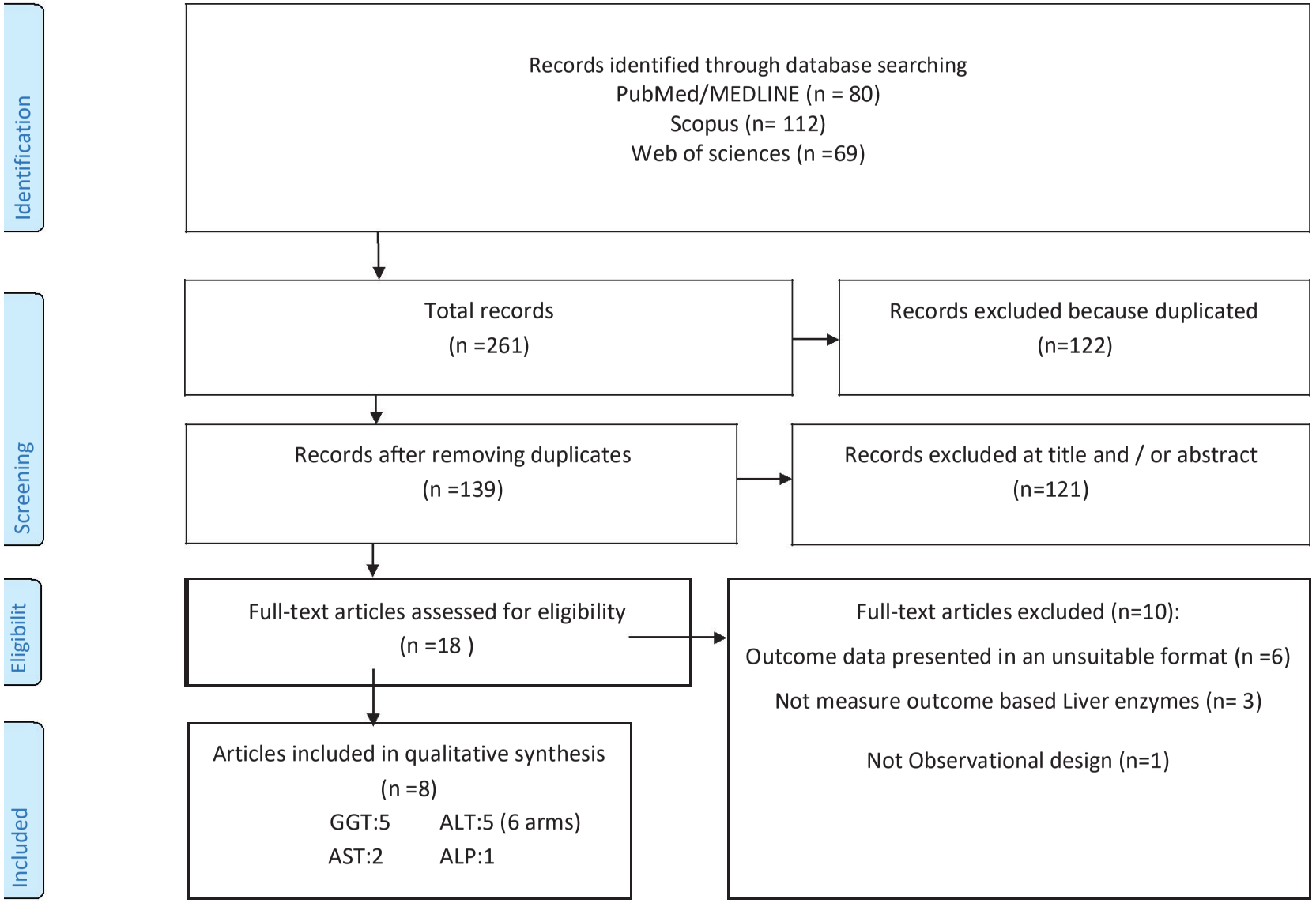
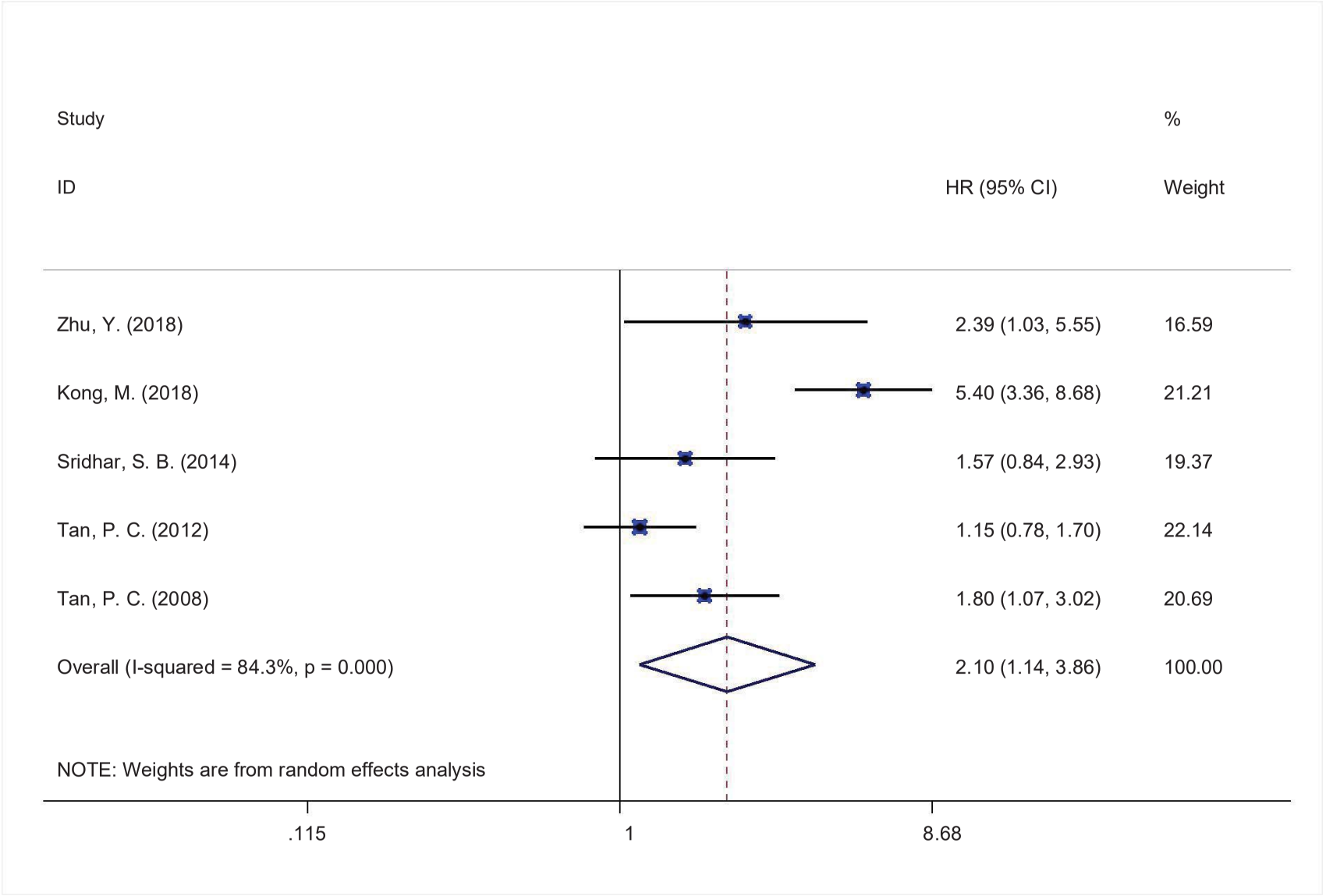
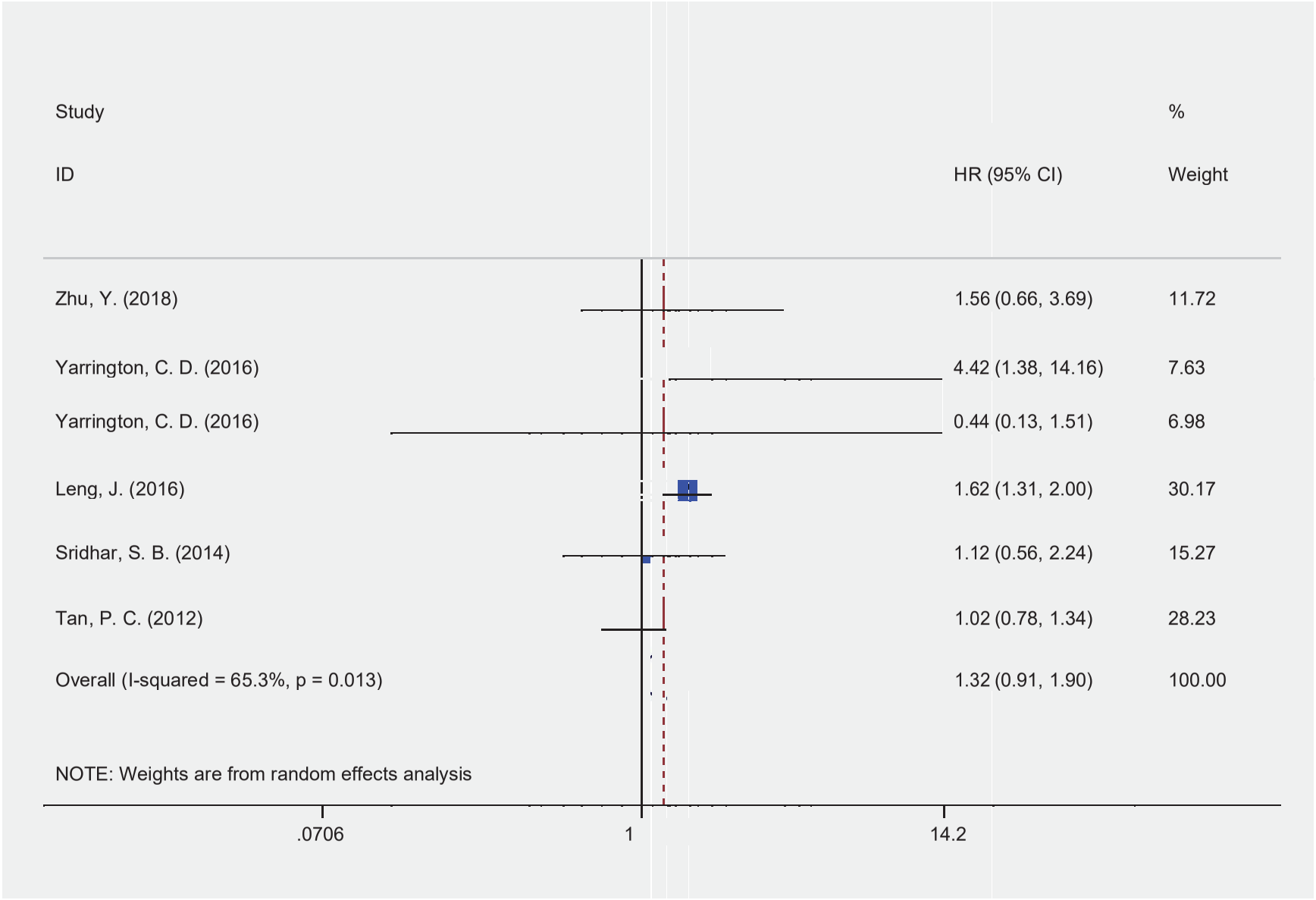


Figure 2. The forest plot of liver enzymes and risk of gestational diabetes mellitus.

a) GGT



b) ALT


Study
ID
HR (95% CI)
%
Weight
Zhu, Y. (2018)
1.56 (0.66, 3.69)
11.72
Yarrington, C. D. (2016)
4.42 (1.38, 14.16)
7.63
Yarrington, C. D. (2016)
0.44 (0.13, 1.51)
6.98
Leng, J. (2016)
1.62 (1.31, 2.00)
30.17
Sridhar, S. B. (2014)
1.12 (0.56, 2.24)
15.27
Tan, P. C. (2012)
1.02 (0.78, 1.34)
28.23
Overall (I-squared = 65.3%, p = 0.013)
1.32 (0.91, 1.90)
100.00
NOTE: Weights are from random effects analysis
.0706
1
14.2

c) AST

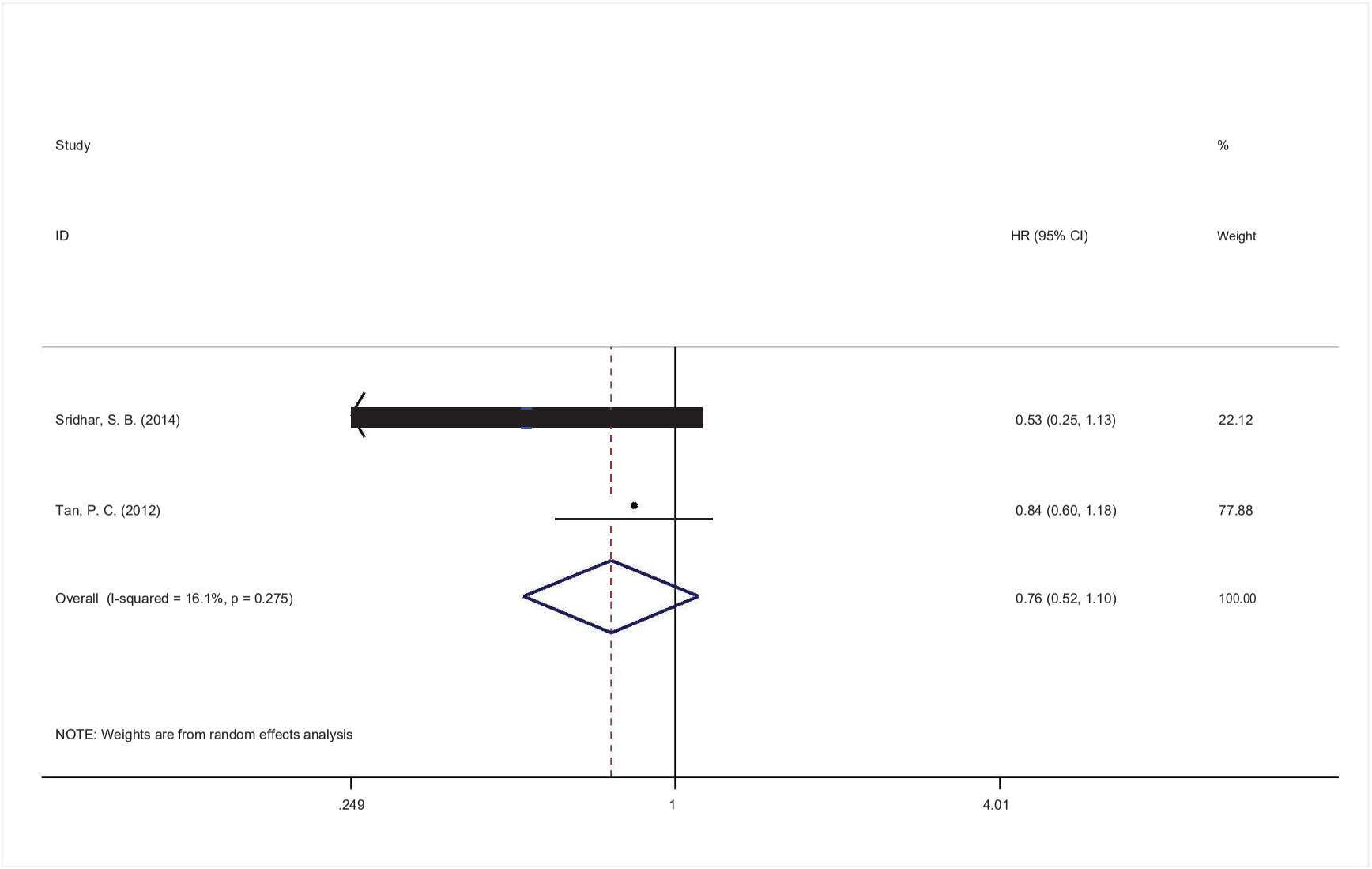
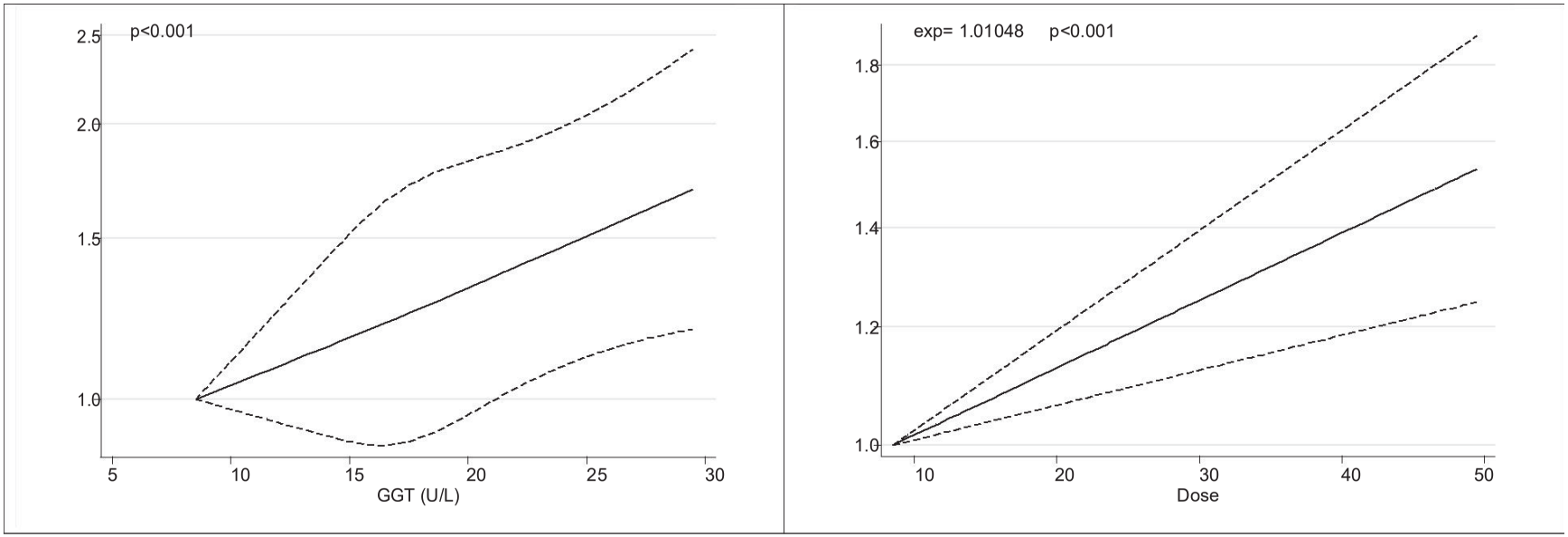
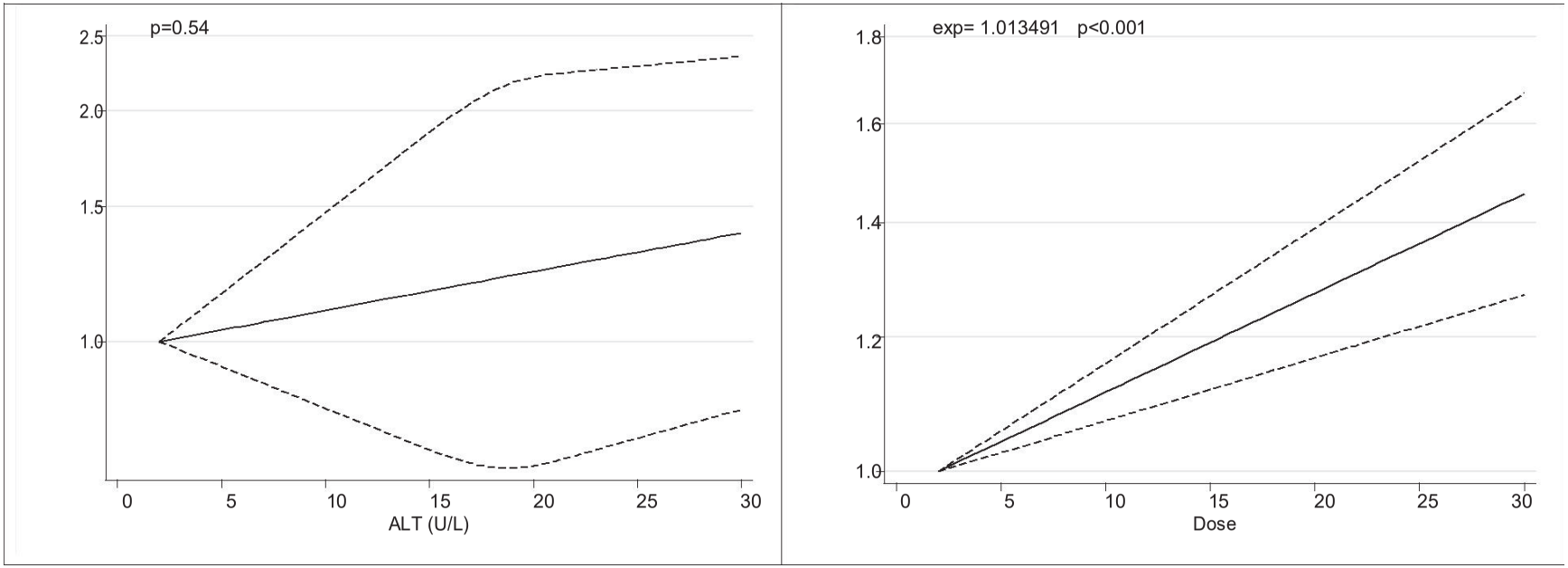

Study
ID
HR (95% CI)
%
Weight
Sridhar, S. B. (2014)
0.53 (0.25, 1.13)
22.12
Tan, P. C. (2012)
0.84 (0.60, 1.18)
77.88
Overall (I-squared = 16.1%, p = 0.275)
0.76 (0.52, 1.10)
100.00
NOTE: Weights are from random effects analysis
.249
1
4.01

Figure 3. The Dose-response analysis of liver enzymes and risk of gestational diabetes mellitus.

a) GGT



b) ALT


p=0.54
2.5
2.0
1.5
1.0
0
5
10
15
20
25
30
ALT (U/L)
exp= 1.013491 p<0.001
1.8
1.6
1.4
1.2
1.0
0
5
10
15
20
25
30
Dose

c) AST

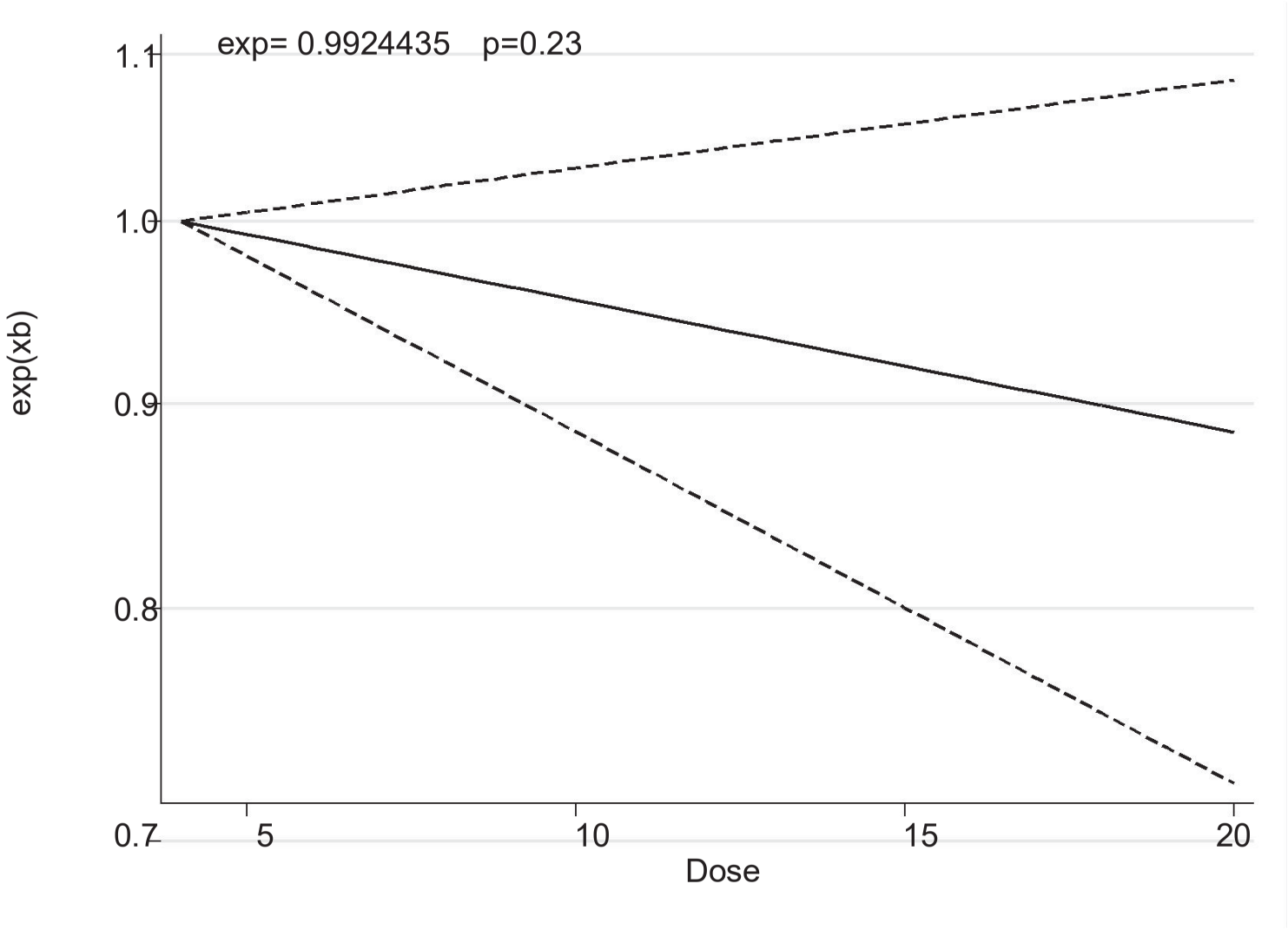
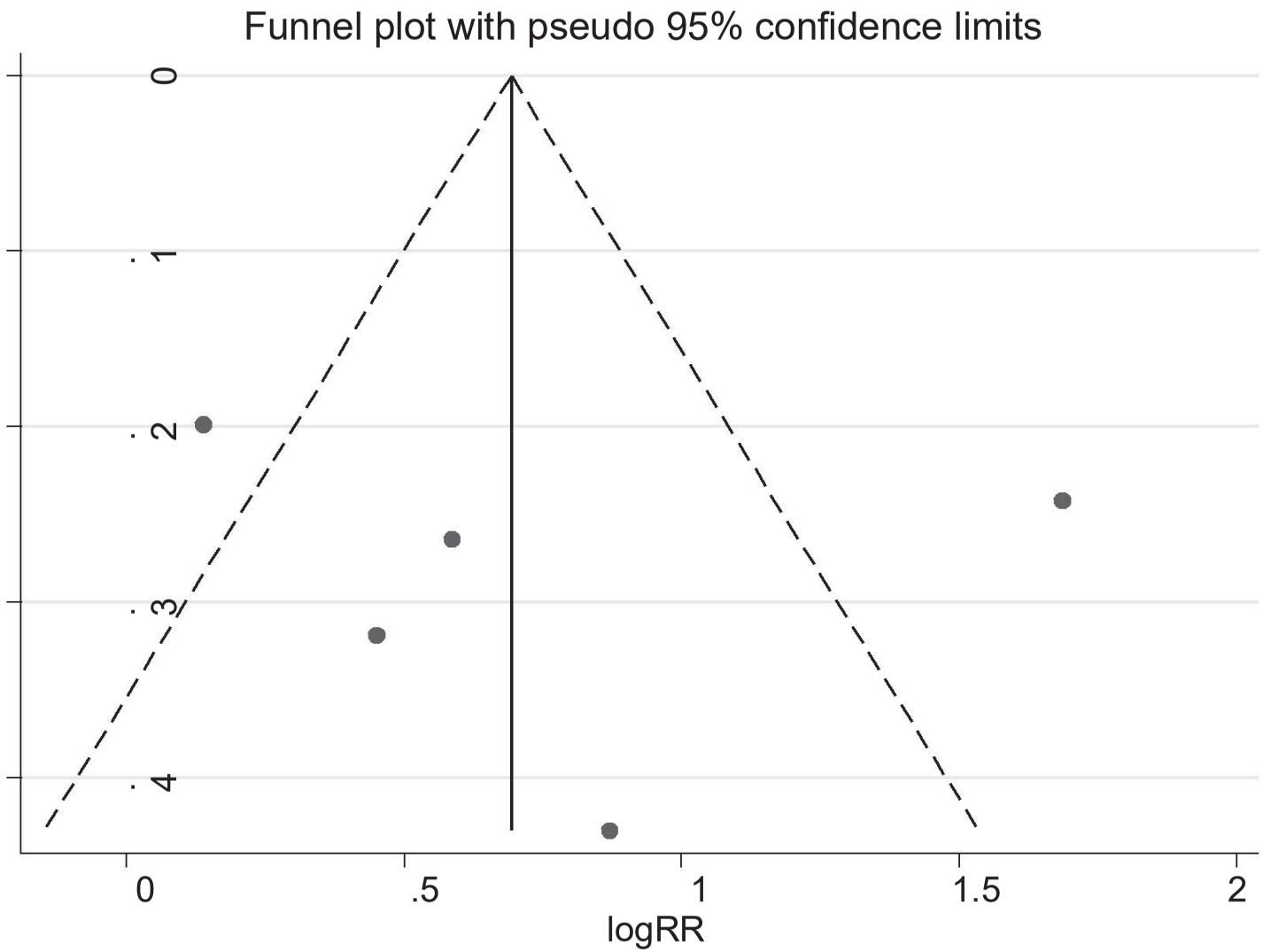
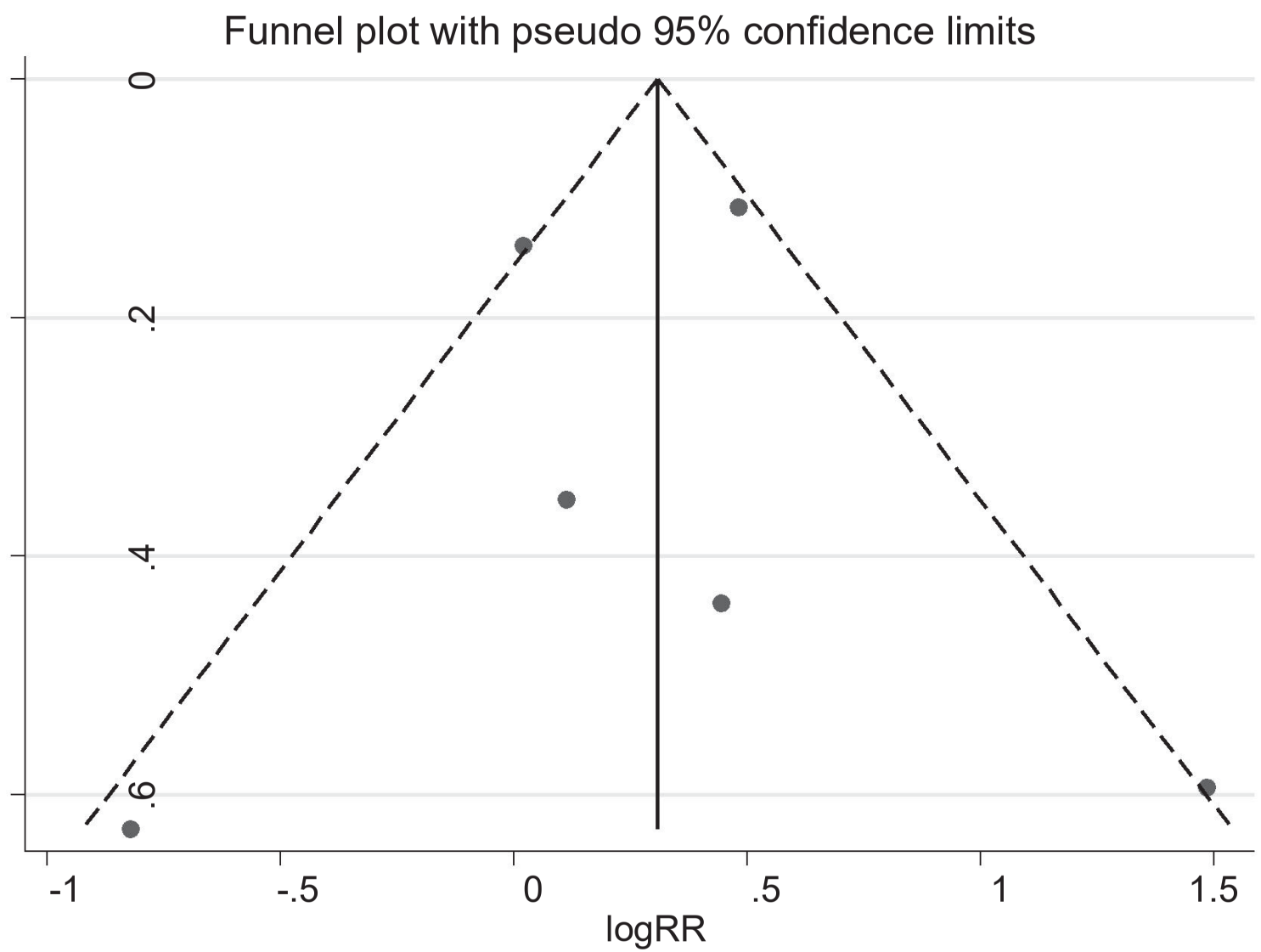


Fig. 4. Funnel plots of publication bias.
a) GGT



b) ALT


Funnel plot with pseudo 95% confidence limits
0
.2
.4
.6
-1
-.5
0
.5
1
1.5
logRR

c)AST

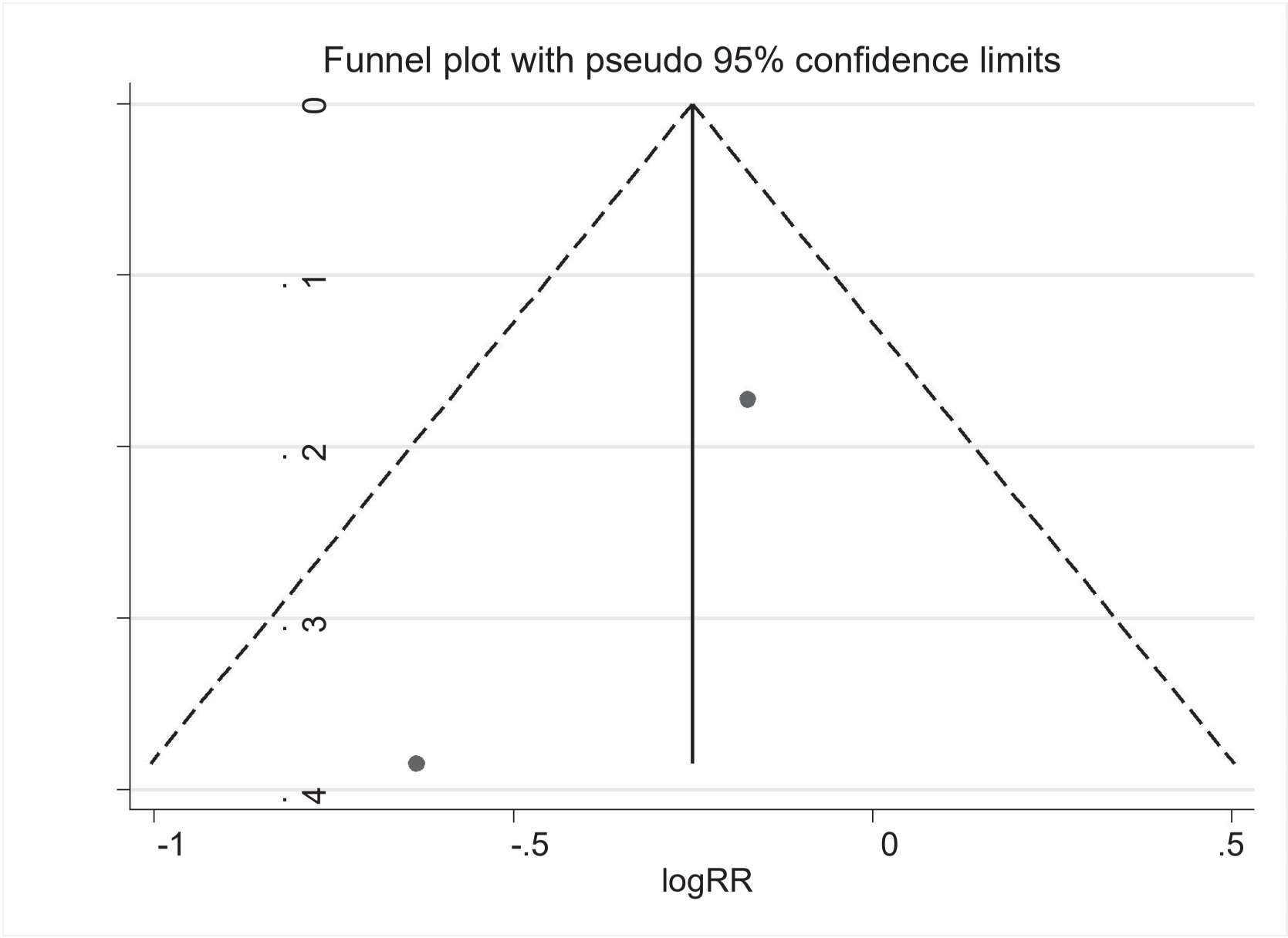

Funnel plot with pseudo 95% confidence limits
0
.1
.2
.3
.4
-1
-.5
0
.5
logRR

Table 1. Characteristics of included studies

Author	Year	Location	Time of liver enzyme assessment	Design of study	Age	Participants (n)	Case/ Control	Outcome
ng, T.	2019	China	before 20 weeks of gestation	prospective cohort	28	2073	169	ALP
ı, Y.	2018	US	10 to13 weeks of gestation	Case-control	18-45	349	117/232	GGT/ALT
ıg, M.	2018	Cina	14 to18 weeks of gestation	prospective cohort	28	1512	122	GGT
rington, C. D.	2016	US	10 weeks of gestation	Case-control	33	330	83/247	ALT
ıg, J.	2016	China	12 weeks of gestation	prospective cohort	28	17359	1332	ALT
dhar, S. B.	2014	US	Before gestation	nested case-control	28	750	256/497	ALT/AST/GGT
ı, P. C.	2012	Malaysia	Before gestation	prospective cohort	30	2610	319	ALT/AST/GGT
ı, P. C.	2008	Malaysia	Before gestation	prospective cohort	30	488	151	GGT