Meta-analysis for the Relationship Between Hyperuricemia and CVD Incidence

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Abstract

BACKGROUND: Uric acid was once considered an effective endogenous antioxidant, but now more and more evidence shows that it may play a significant role in the pathophysiology of cardiovascular diseases.

OBJECTIVES: It has not been clear that UA is a sign of poor prognosis or a risk factor for CVD. Our aim is to figure out the exact relationship between CVD and uric acid.

METHODS: We studied 3356 publications in the past 44 years through MEDLINE, EMBASE, and Cochrane library searches, and selected 22 studies that met our inclusion criteria.

RESULTS: The meta-analysis showed that hyperuricemia was associated with an increased risk of death from CVD (RR=1.37; 95% CI:1.29-1.45; I2=31.4%, P=0.157). Sensitivity analysis reviewed several potential sources of heterogeneity between studies, such as average SUA level, study location, and outcome indicators.

Introduction

Cardiovascular Diseases (CVD) is one of the most challenging public health problems, which is the pathological condition of the heart, the blood vessel, or the pericardium. Cardiovascular diseases account for the majority of non-communicable disease deaths, 17.9 million per year, followed by cancer (8.8 million), respiratory diseases (3.8 million) and diabetes (1.5 million)[1] .Coronary artery disease (CAD), myocardial infarction (MI), heart failure (HF), and hypertension are the most important causes of mortality and morbidity in modern society[2]. Many risk factors affect CVD incidence. Traditional risk factor include behaviour-related risk factors such as smoking, obesity, alcoholism, unhealthy diet, lack of physical activity, depression, and physiological risk factors such as age, high blood pressure, dyslipidemia, and insulin resistance. Non-traditional risk factors include ankle-brachial index (ABI), high-sensitivity C-reactive protein (hsCRP) level, and coronary artery calcium (CAC) score. In the past, uric acid was regarded as an effective endogenous antioxidant produced by purine metabolism. It can chelate metal ions and react with effective bio-oxidants to produce relatively stable products. Its level is very important in humans due to the silencing of the uricase gene[3]. however, in recent decades, hyperuricemia has been considered as an independent risk factor of cardiovascular disease. The causes of this relationship is not yet clear, but possible mechanisms include NO reduction, oxidative stress, inflammatory processes, arterial stiffness, and endothelial damage. In addition, UA has been associated with smooth muscle cell proliferation, arterial calcification, platelet aggregation and thrombotic enhancement[4]. More importantly, the metabolism of purine from hypoxanthine to uric acid will produce a large amount of superoxides. And oxidative stress plays an important role in the pathophysiology of cardiovascular diseases [5].Since UA retains dual antioxidant and pro-oxidant capacity, the relationship between serum uric acid level and CVD is still contradictory. Several previous meta-analysis showed that hyperuricemia was significantly associated with the occurrence and mortality of stroke[6, 7], coronary

heart disease[8–13], hypertension[14–16], atrial fibrillation[17] and acute coronary syndrome[18]. But none of these meta-analysis provided an overview of all major cardiovascular diseases. It would be interesting to determine whether the hyperuricemia-cardiovascular diseases association differed by CVD subtype. Besides, some of limiations may existed in the former studies, such as the possibility of publication bias, high heterogeneity, lack of individual participant data, and limited sample size in subgroup analysis. As a result, a meta analysis that contains more high-quality clinical trials requires longer follow up periods. Therefore, we performed an updated meta-analysis to obtain a more accurate estimate of the association between hyperuricemia and CVD.

Methods

We studied literature from the past 44 years through MEDLINE, EMBASE, and Cochrane library searches. We searched all these databases from creation to June 19, 2020. We studied all articles issued since January 1975 to evaluate the objective association between serum uric acid (SUA) and cardiovascular disease. Keywords including ["uric acid", OR "urate", OR "gout", OR "purine metabolism", OR "hyperuricemia"] AND ["cardiovascular disease", OR "myocardial infarction", OR "coronary artery disease", OR "heart failure", OR "fibrillation atrial", OR "hypertension"] And ["mortality", OR "risk factor", OR "hazard ratio", OR "odd ratio"] in various combinations. The following search strategy was used for MEDLINE: ((((((uric acid) OR (urate)) OR (gout)) OR (purine metabolism)) OR (hyperuricemia)) AND ((((((cardiovascular disease) OR (myocardial infarction)) OR (coronary artery disease)) OR (heart failure)) OR (fibrillation atrial)) OR (hypertension))) AND (((((mortality) OR (risk factor)) OR (hazard ratio)) OR (odd ratio)). Then we limited the article types to clinical trails and randomized controlled trails. We used similar search strategies for the Cochrane library and EMBASE. Studies in the researches were identified thoroughly to ensure that relevant studies were not cross-referenced. We adopted the meta-analysis of observational studies in epidemiology (MOOSE) study guidelines[19]. We also searched the American College of Rheumatology Annual (ACR) and the European Association of Anti-Rheumatology Annual (EULAR) meeting reports and review articles for additional references.

We only considered studies that meet our inclusion criteria:1) prospective cohort and cross-sectional studies involving adult patients; 2) the follow-up period is longer than 3 months; 3) describe the relationship between hyperuricemia and the incidence of CVD; 4)the sample size exceeds 100 subjects; 5) reported adjusted risk estimates for the incidence of CVD, such as relative risk (RR), odds ratio (OR) or hazard ratio (HR) with a 95% confidence interval (95% CI); and, 6) researches on intervention and secondary prevention trials were excluded. No geographic restriction are implemented. Only English articles were selected.

Data extraction and quality assessment were conducted by two confirmed reviewers. Duplicate reports and review articles were checked to identify other sources of data. Full texts can be obtained if a study meets all the inclusion criteria or there is uncertainty about inclusion. The studies we selected are mainly randomized controlled clinical trials and a prospective cohort study concentrated on the relationship between SUA and various cardiovascular prognosis, including myocardial infarction (MI), coronary heart

disease, all adverse cardiovascular events, cardiovascular mortality, and all-cause mortality. The definition of CVD was based on ICD-10 and included all CVDs that could be verified in the Life Lines database; MI, heart failure, atrial fibrillation, heart valve disorders, arrhythmia, aneurysm, stroke, thrombosis, atherosclerosis, narrowing carotid arteries and a history of coronary artery bypass grafting (CABG)[20] .Hyperuricemia was defined as serum uric acid levels of 7.0 mg/dl for men and 6.0 mg/dl for women[21].

The methodological quality assessment criteria was inspired by the Newcastle–Ottawa scale[22]. The quality score was calculated based on three main components of the cohort study: study groups selection (0–4 points), study groups comparability (0–2 points), and ascertaining of the results of interest (0–3 points). The higher the score, the better the methodological quality. We chose a random-effects model to calculate the combined hazard ratios (HR) or odds ratio (OR) of mortality from any CVD or CHD event. The data are expressed as relative risk (RR) with 95% CI[23]. I^2 was utilized to calculate the heterogeneity between studies (mild, 0-30%; moderate, 31-50%; high, >50%)[24].

- Statistical analysis was performed using STATA SE 15. The metan, metabias, and metatrim commands[25] were used for all statistical analyses. A two-sided P-value below 0.05 is considered statistically significant. A subgroup analysis was performed to explore the heterogeneity of the study[26]. Statistical testing of the meta-regression analysis[27], Tau-squared and P-value can explore the potential sources of heterogeneity between studies. Forest plots and pooled estimates were registered[28]. Publication bias was assessed by using funnel plots[29]. Begg's rank correlation test and Egger's linear regression test were utilized to detect any asymmetry in the funnel chart that may be caused by publication bias[30]. We also performed a "trim and fill" method [31] to correct funnel plot asymmetry by simulating the hypothetical "missing" studies possibly caused by publication bias. Agreement between the before and after "trim and fill" RR provides confidence that the results are robust to possible publication bias. Finally, we calculated the fail-safe number[32], the number of non-significant studies that would find the P-value to non-significant, using 0.05 as the setting criterion.

Results

Selection and characteristics of studies

The pertinent articles obtained from the literature search and the reference lists were introduced into software EndnoteX9 for management. A total of 3356 publications were identified (Figure 1). After removing duplicates we excluded 1710 citations, based on the screening of titles and abstracts we excluded 1479 citations, and after a thorough assessment of the full-text, we excluded 58 citations. Among 109 eligible full text articles, 87 papers were excluded because of: – duplicate results from the same group of authors were reported (n =4); a retrospective study was carried out (n =7); – with less than 3 months of follow-up (n=8);– an outcome different from the one of interest was considered (n = 33); – with a sample size of fewer than 100 subjects (n=14); – definition of urate cut-offs or range limits were

lacking (n =16); and – did not report adjusted risk estimates for CVD incidence(n =5). Finally, we identified 22 studies [33–54] that met our inclusion criteria. The methodological quality of all the included studies was moderate to high, with NOS score varying from 7 to 8 and a median of 8. Table 1 display the characteristics and effect sizes of the 22 studies of uric acid level and risk of CVD incidence. 22 prospective studies with a total number of 421802 participants were entered in the meta-analysis. Six studied health check-ups and outpatients[34, 35, 42, 43, 50], and the other sixteen studies were restricted to patients with cardiac vascular disease (CVD) [33, 36–41, 44, 45, 47–49, 51–54]. The datum was removed from 18 cohort studies and 4 cross-section studies[39, 48–50]. And no disagreements between the two reviewers regarding study inclusion. Of the twenty-two trials, three were conducted primarily in the United States[33, 41, 44]. Twelve studies were made in Asian countries [34, 38, 39, 42, 43, 46–52] and seven studies were from European countries [35–37, 40, 45, 53, 54]. The number of participants ranged from 324 in a study by Palazzuoli et al[51] to 197144 in the cohort study by Shin Kawasoe et al [40]. Twenty-one studies included both men and women. One study included only men[33], and none of the studies included only women. Nine studies utilized a lower cut-off value to define hyperuricemia for women opposed to men [34, 36, 38, 40, 42, 43, 51, 52, 54]. Five studies reported gender-specific outcome for CHD mortality[33, 34, 36, 43, 51]. Thirteen studies provided hazard ratio estimates[24, 35, 37, 38, 40–42, 44, 45, 47, 52–54], eight studies provided odds ratio[36, 39, 43, 46, 48–51] and one provided relative risk ratio[33].

Hyperuricemia and cardiac event incidence

- The relationship between uric acid and cardiac event incidence could be presented in three ways: all-cause mortality (four studies, 11288 patients), mortality from CVDs (ten studies, 34897 patients), and other CVD incidences (eight studies, 375617 patients). All studies provided categorical data and none provided continuous data. Meta-analysis with a random-effects model suggested that there was problems with heterogeneity between hyperuricemia and cardiac event incidence (RR=1.30; 95% CI:1.24-1.37; I2=69.5%, P=0.00,Tau^2=0.0062) (Figure 2-1). In mortality from CVDs, the pooled result suggested a consistent relationship between hyperuricemia and CVD mortality (RR=1.37; 95% CI:1.29-1.45; I2=31.4%, P=0.157) (Figure 2-2).

Sensitivity Analysis

Subgroup analysis

A subgroup analysis of cardiac event incidence needed to be done to investigate the heterogeneity of the studies. The selected subsets including the year of publication (Year before 2010, Year after 2010), sample size (<1000, 1000-10000, 10001-100000, >100000), epidemiological research methods (cohort study, cross-sectional study), risk indicator (HR, OR, RR), study location (USA, Asian, Europe), sample source (patient had CVD versus Healthy population), CVD categories(coronary artery disease,hypertension,heart failure,atrial fibrillation,stroke) ,and outcome indicators (all-cause mortality, cardiovascular disease mortality, other cardiovascular morbidities). As the odds ratios could be deemed

to be accurate estimates of risk ratios, we, therefore, utilized RR as the common measure of association across studies. Published year before 2010(RR=1.32, 95% CI: 1.23-1.41; I2=24.8%, P=0.22), sample size less than one thousand(RR=1.24,95%CI: 1.12-1.37; I2=0.0%, P=0.56), lived in Europe (RR=1.39, 95% CI: 1.31-1.48, I2=41.7%, P=0.11), coronary artery disease(RR=1.27, 95% CI: 1.19-1.37, I2=42.2%, P=0.11), hypertension (RR=1.26, 95% CI: 1.19-1.33, I2=30.7%, P=0.22) and cardiovascular disease mortality (RR=1.37, 95% CI: 1.29-1.45, I2=31.4%, P=0.16) subgroups showed that hyperuricemia was associated with an increased risk of cardiac event incidence (table 2).

Meta-regression

Meta-regression analysis showed that mean SUA level (OR=1.04, p=0.047, Adj R^2=23.95%,tau^2 = 0.0053, in the univariate models) and CVD prevalence at baseline (OR=1.005, p=0.09, Adj R^2=24.2%,tau^2 = 0.005, in the univariate models)

- may effect the heterogeneity in this study for analyses of cardiac event incidence. Similarly, meta-regression analysis also showed that Study location and outcome indicators (p=0.002, I^2=27.3%,Adj R^2=83.72%,tau^2 = 0.0011, in the multivariate models)may contribute to the heterogeneity in this study(table 3).

Publication Bias Assessment

Funnel plots for CVD incidence were visually examined (Figure 3-1). No evidence of publication bias for studies was noted in the funnel plot, Egger regression asymmetry test (p=0.15), or Begg's test (p=0.26). Then we undertook a sensitivity analysis using public trim and fill method (Figure 3-2), which conservatively imputes hypothetical negative unpublished studies to mirror the progressive studies that cause funnel plot asymmetry. Four imputed studies for categorical data were needed to produce produce symmetrical funnel plots. The fail-safe number was 3384, indicating that 3384 "negative" studies would be necessary to increase the P-value for the meta-analysis of above 0.05.

Discussion

Although there are several reports[55, 56–59] of an association between high SUA and poor clinical outcomes in cardiovascular disease such as coronary heart disease, hypertension, acute myocardial infarction, heart failure, and atrial fibrillation, it has been unclear whether UA is a marker of adverse prognosis or a risk factor for CVD[60]. Some researches showed that uric acid appeared to be an antioxidant [61, 62]. It may function as one of the major antioxidants in plasma. Those research[63] led quite a few of the authorities to consider uric acid not to be a true cardiovascular risk factor. However, there is necessary some studies[64] found that elevated uric acid often preceded by hypertension. Those studies were also consistent with the possibility that uric acid might have a causal role in cardiac vascular disease development[55, 65]. As a consequence, the central paradox[66] is to determine whether uric acid acts as an antioxidant or pro-oxidant. Sautin YY et al [67] hypotheses that when uric acid is inside a cell, it activates NADPH oxidase and generates oxidants, whereas, in the extracellular

environment, it functions as an antioxidant. Although uric acid is only an antioxidant in the extracellular environment, they demonstrated that it is pro-oxidative inside the cell.

Our meta-analysis suggested that hyperuricemia was associated with an increased risk of cardiac mortality, which has a moderate elevation of relative risk factor (RR=1.37, 95% CI 1.29-1.45; I2=31.4%, P=0.157). This outcome is not dependent on traditional CVD risk factors, such as age, gender, older age, ethnicity, and location. In subgroup analyses and meta-regression, hyperuricemia appeared to greatly increase the risk of CHD incidence in people lived in Europe, patients who had higher serum uric acid level.

Our study has some limitations. Several potential limitations of this study are specific meta-analyses. First of all, there were different definitions of hyperuricemia across the studies which influence the subgroup[68]. However, different cut-off levels for hyperuricemia did not modify the study estimates of CHD risk derived from our meta-regression analysis. Secondly, in the sensitivity analysis such as subgroup analysis and meta regression, some groups has limited number of included studies which make us could not get a precise conclusions. Thirdly, this observational study may have some unmeasured confounding risk factors, such as medications intake and some other complications. Our study also presents several notable strengths. We selected large prospective studies which at least 100 subjects with follow-up periods of more than 6 months, which helped increase the precision of estimates while minimizing heterogeneity. Unmeasured confounding is likewise a widespread problem in observational studies, including prospective cohorts. So we performed outcome-specific subgroup analyses of the studies fully adjusting for traditional CVD risk factors. Multivariate meta-regression analysis further examined numerous potential sources of heterogeneity between the studies such as sample size, ethnicity, location, patients who had a history of CVD, higher serum uric acid level. It also indicates that as a risk factor, hyperuricemia is closer related to CVD death than other CVD incidence. Prospective clinical studies are needed to investigate whether a reduction in uric acid levels could prevent CVD or metabolic syndrome.

In conclusion, there is a modestly increased risk for CVD mortality associated with hyperuricemia in our meta-analysis. More pronounced increased risk factors for CVD mortality should be subject to future research. It would mean a lot to design further large, long-term studies that determine the effect of urate-lowering therapy on cardiovascular disease. Further studies are required to better establish uric acid's potential causative role in CVD.

Declarations

Competing interest:

The authors declare that they have no competing interests

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Tables

Due to technical limitations, table 1 to 3 is only available as a download in the Supplemental Files section.

Figures

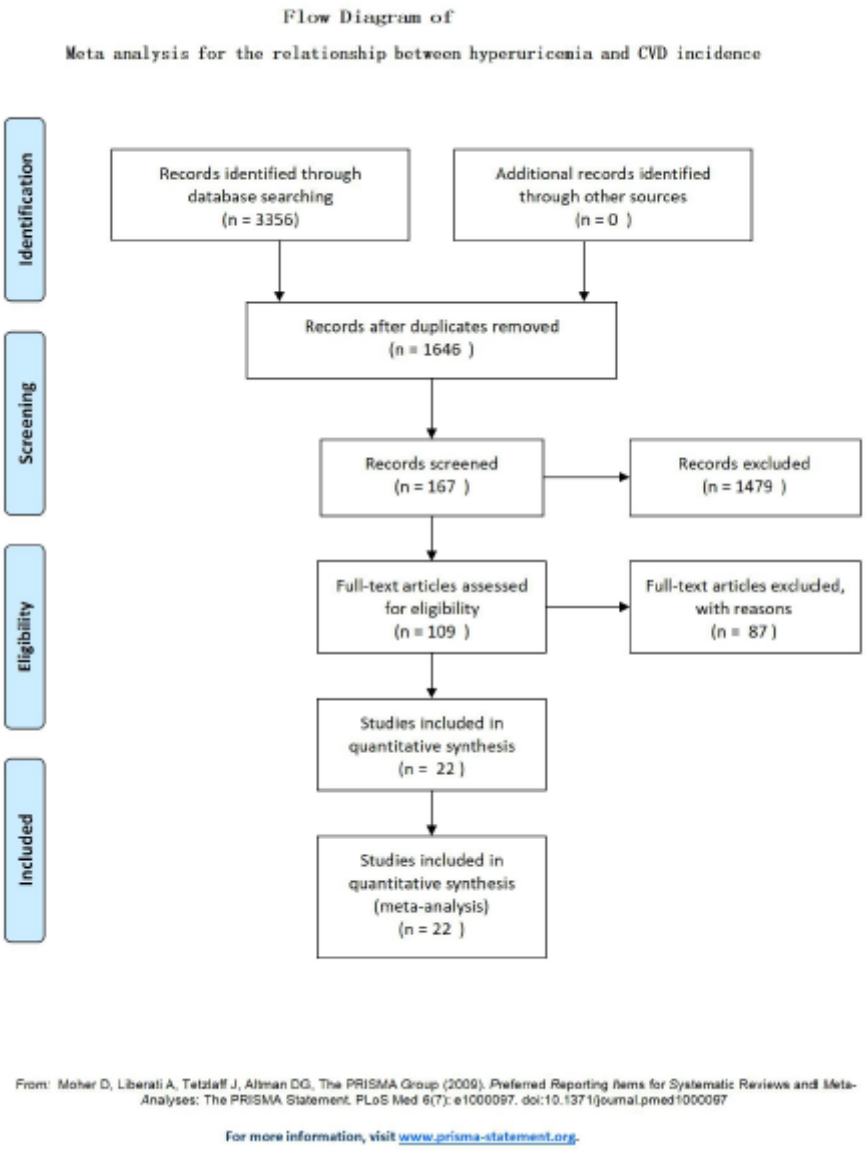
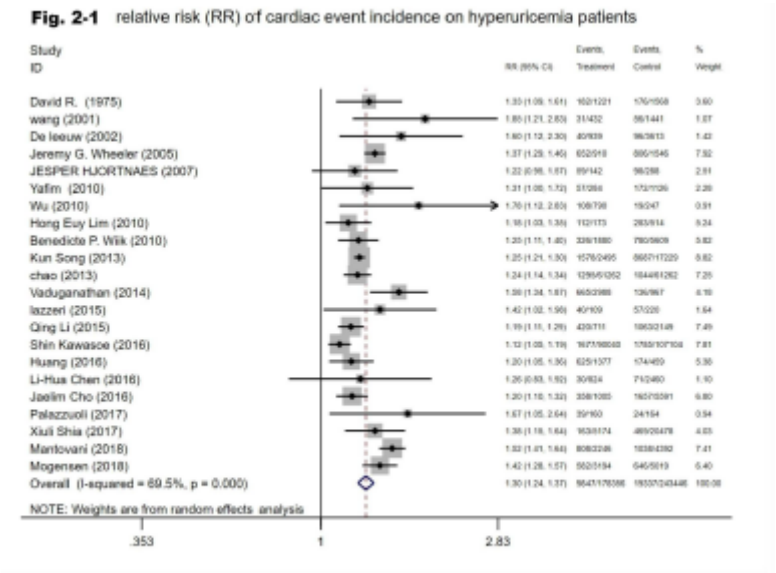


Figure 1

See image above for figure legend



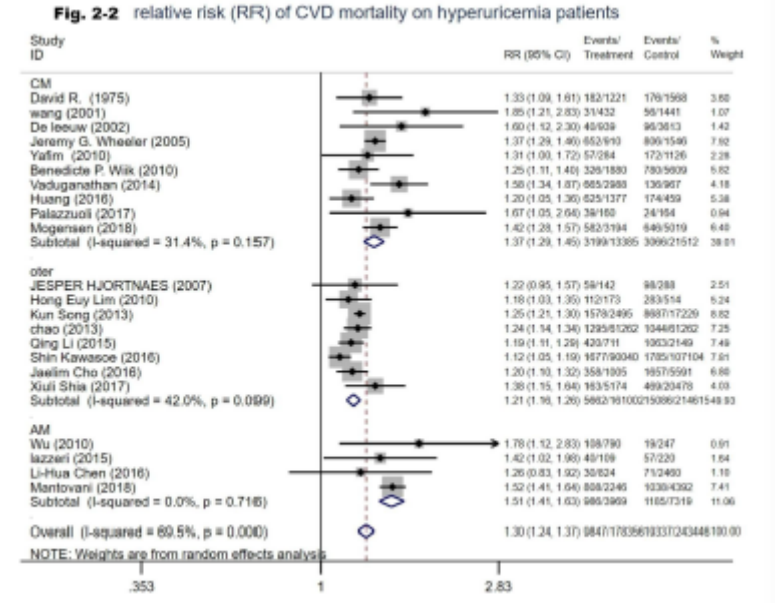


Figure 2

See image above for figure legend

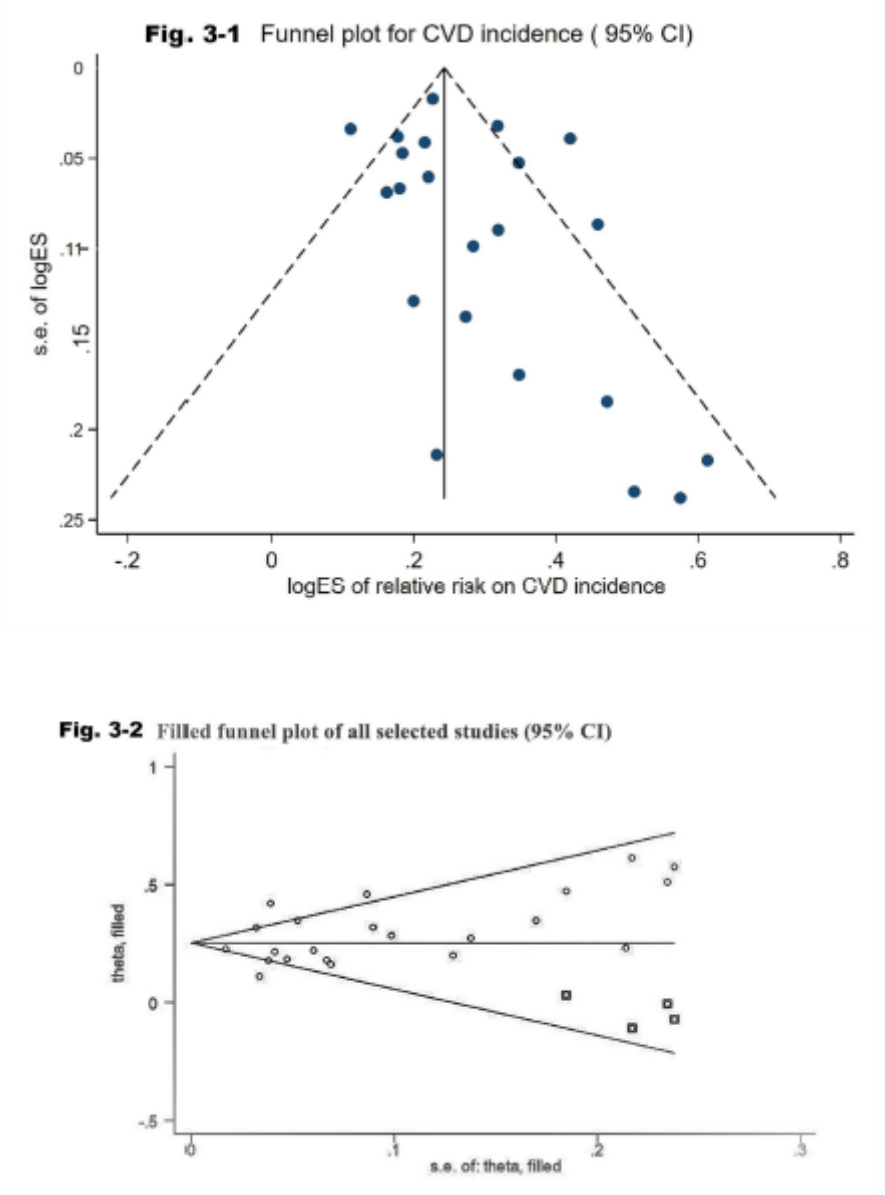


Figure 3

See image above for figure legend

Supplementary Files

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