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Gamma-glutamyltransferase and risk of hypertension: a systematic review and dose-response meta-analysis of prospective evidence

Running Head: GGT and hypertension risk

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Abstract

Objective: To obtain a reliable estimate of the magnitude of the prospective association between gamma-glutamyltransferase (GGT) and risk of hypertension, and to characterize the nature of the dose-response relationship.

Methods: We conducted a systematic review and dose-response meta-analysis of published prospective studies. Relevant studies were identified in a literature search of MEDLINE, EMBASE, and Web of Science databases up to May 2015. Study specific relative risks (RRs) were meta-analysed using random effects models. We examined a potential nonlinear relationship using restricted cubic splines.

Results: Of the 612 titles reviewed, we included 14 cohort studies with data on 44,582 participants and 5,270 hypertension cases. In a comparison of extreme thirds of baseline levels of GGT, RR for hypertension in pooled analysis of all 14 studies was 1.32 (95% confidence interval: 1.23-1.43). There was heterogeneity among the studies ($P < 0.001$), which was to a large part explained by average age of participants at baseline, average duration of follow-up, and the degree of confounder adjustment. In a pooled dose-response analysis of 10 studies with relevant data, there was evidence of a linear association between GGT and hypertension risk (P for nonlinearity = 0.37). The pooled RR of hypertension per 5 U/L increment in GGT levels was 1.08 (95% confidence interval: 1.04-1.13).

Conclusion: Baseline circulating GGT level is associated with an increased risk of hypertension in the general population, consistent with a linear dose-response relationship. Further investigation of any potential relevance of GGT in hypertension prevention is warranted.

Keywords: gamma-glutamyltransferase; hypertension; high blood pressure; prospective studies; dose-response; meta-analysis

Abbreviations: BP, blood pressure; CI, confidence interval; CVD, cardiovascular disease; GGT, gamma-glutamyltransferase; NOS, Newcastle–Ottawa Scale; RR, relative risk; SD, standard deviation

INTRODUCTION

Hypertension or high blood pressure (BP) has risen to pandemic proportions - affecting over 1 billion people worldwide and it has been estimated that this number will reach 1.56 billion by 2025.[1] In addition to being the leading global risk for mortality in the world,[2] hypertension is the most common modifiable and leading risk factor for cardiovascular disease (CVD),[3] which represents a worldwide epidemic and is the leading cause of mortality globally.[4] To date, established risk factors for hypertension include excess body weight, excess dietary sodium intake, reduced physical activity, and excess alcohol intake.[5, 6] In line with the 2013 guidelines developed by the European Society of Hypertension and the European Society of Cardiology (ESH/ESC),[7] lifestyle changes have been recommended as the cornerstone for the prevention of hypertension or high BP. These include a combination of population-based and intensive targeted approaches such as reduction of salt and alcohol consumption, maintaining a healthy body weight, regular exercise, and elimination of smoking.[7] Though established risk factors for hypertension explain a large proportion of its risk, its pathogenesis is still not fully established as multiple factors appear to be involved. There is therefore a need to further assess potential risk factors which may have causal or predictive relevance to hypertension and which will help further tailor preventive and therapeutic interventions

Gamma-glutamyltransferase (GGT), a sensitive but non-specific index of liver injury and a biological clue of excessive alcohol intake, has been strongly linked to the development of adverse cardiometabolic outcomes [8-10] including hypertension.[11] Elevated serum levels of GGT has been postulated to reflect the development and progression of hepatic steatosis; which may play an important role in the development of insulin resistance and hyperinsulinemia, resulting in high blood pressure or hypertension.[12-14] Until recently, there has been uncertainty regarding the magnitude and nature of the prospective association between GGT level and risk of hypertension. Liu and colleagues[15] synthesized available prospective epidemiological data on the association between GGT and hypertension and reported a pooled

multivariate adjusted relative risk (RR) (95% confidence interval) of 1.94 (1.55-2.43) for hypertension in a comparison of top versus bottom category of baseline GGT levels. However, in this review, the authors did not standardize the reported risk estimates (they reported comparisons comparing the highest versus lowest category of GGT levels irrespective of the risk estimates the eligible studies reported) to a consistent comparison before pooling. In addition, they separately pooled the results of three studies that provided risk estimates per 1 standard deviation (SD) increment in $\log_e$ GGT levels. Given these, the magnitude of the association could not be precisely determined. In addition, although the evidence suggests there is a strong association between elevated baseline circulating GGT and risk of incident hypertension; characterization of the nature and magnitude of the dose-response relationship is however still lacking, as this was not addressed by previous studies and the recent review. It is uncertain if there is a clear continuous dose-response relationship to the association or if this association is evident only beyond a particular threshold level of GGT. It is important to establish this, especially if there exists a threshold which would potentially optimize the detection of individuals at increased risk of hypertension. A dose-response analysis is more efficient than comparing the highest to lowest category approach, as it uses all of the exposure-disease information and provides a detailed description of the risk of the disease throughout the observed range of the exposure.[16] Against this background, our first objective using a meta-analytic approach, was to obtain a reliable estimate of the magnitude of the association between GGT and hypertension, by including all relevant studies and standardising reported risk estimates from all studies to a consistent comparison (top versus bottom thirds of baseline levels of GGT) before pooling. Our second objective was to quantify and characterize in detail the nature of the dose-response relationship between GGT level and risk of hypertension.

METHODS

Data sources and searches

This systematic review and meta-analysis of studies was conducted using a predefined protocol and reported in accordance with PRISMA and MOOSE guidelines [17, 18] (**Supplementary Materials 1-2**). We searched MEDLINE, EMBASE, and Web of Science for prospective (cohort, case-cohort or "nested case control") population-based studies that measured the level of enzymatic activity of GGT and evaluated associations between baseline circulating level of GGT with risk of hypertension or high BP up to May 2015. The computer-based searches combined free and MeSH search terms and combined key words related to GGT (e.g., "gamma glutamyltransferase") and hypertension (e.g., "hypertension", "blood pressure"). There were no restrictions on language or the publication date. We scanned the reference lists of retrieved articles for all relevant additional studies and review articles. We restricted the search to studies of humans. Further details on the search strategy are presented in **Supplementary Material 3**.

Study selection

Observational cohort studies were included if they had at least 1 year of follow-up, assessed associations of GGT with hypertension in adults (>18 years), measured samples at baseline, recruited participants representative of approximately general populations (i.e., did not select participants on the basis of confirmed pre-existing medical conditions such as hypertension or high blood pressure, cardiovascular disease, liver disease, or chronic kidney disease at baseline). Retrospective studies were not included.

Data extraction and quality assessment

Two authors independently abstracted data and performed quality assessments using a standardized predesigned data collection form. Data were abstracted, where available, on study, publication date, geographical location, population source, time of baseline survey, sample population, study design, sample source (plasma/serum), nature of sample (fresh or frozen and

storage temperature), assay type and source, sample size, number of hypertension cases, hypertension case definition, mean age range at start of study, duration of follow-up, and degree of adjustment for potential confounders (defined as '+' when RRs were adjusted for age and/or sex; '++' further adjustment for potential risk factors for hypertension such as body mass index, plasma or serum lipids, smoking status, exercise, or alcohol consumption; and '+++' additional adjustment for other liver enzymes and or inflammatory markers). We extracted RRs reported for the greatest degree of adjustment. In the case of multiple publications involving the same cohort, the most up-to-date study or study with the most comprehensive information was abstracted. We contacted authors of eligible studies where the published data were insufficient, to provide relevant missing information.

Study quality was assessed based on the nine-star Newcastle–Ottawa Scale (NOS)[19] using pre-defined criteria namely: selection (population representativeness), comparability (adjustment for confounders), and ascertainment of outcome. The NOS assigns a maximum of four points for selection, two points for comparability, and three points for outcome. Nine points on the NOS reflects the highest study quality. A score of ≥ 5 indicated adequate quality for inclusion in the review.

Data synthesis and analysis

The RR with 95% CIs was used as the common measure of association across studies. To enable a consistent approach to the meta-analysis and enhance interpretation of the findings, reported study-specific risk estimates (per standard deviation change, quintiles, quartiles, and user-defined cut-offs) were transformed to involve comparisons between the top third and bottom third of each study population's baseline distribution of GGT levels, using standard statistical methods [20, 21] which have been described in detail in **Supplementary Material 4**. Briefly, log risk estimates were transformed assuming a normal distribution (or that a transformation of the explanatory variable for which the risk ratio is based was normally

distributed), with the comparison between top and bottom thirds being equivalent to 2.18 times the log risk ratio for a 1 standard deviation increase (or equivalently, as 2.18/2.54 times the log risk ratio for a comparison of extreme quarters and as 2.18/2.80 times the log risk ratio for a comparison of extreme quintiles). Standard errors of the log risk estimates were calculated using published confidence limits and were standardised in the same way. When studies published more than one estimate of the association according to subgroups (e.g., by sex), we obtained a within-study summary estimate using a fixed effect meta-analysis. Summary RRs were pooled using a random effects model to minimize the effect of between-study heterogeneity.[22]

To avoid making an assumption of linearity for an exposure-response (e.g. GGT-hypertension) relation, exposure-response relations are usually reported through RRs corresponding to ranges of exposure levels. Therefore, in a meta-analysis, it is useful to model the relation in a flexible nonlinear manner and assess evidence for or lack of nonlinearity, using graphical and statistical testing procedures.[23] We therefore performed a 2-stage dose-response meta-analysis using the method proposed by Orsini,[24] to examine a potential nonlinear relationship between GGT levels and hypertension risk by modeling GGT levels using restricted cubic splines with 3 knots at percentiles 25%, 50%, and 75% of the distribution.[25] This method requires that the number of cases, person-years of follow-up or non-cases, and the RRs with the variance estimates for at least three quantitative categories of GGT levels are known. The median or mean level of GGT for each category was assigned to each corresponding RR. If data were not available, we estimated the median using the midpoint of each category. When the highest or lowest category was open, we assumed it to be the same amplitude as the adjacent category. In the first stage, as described by Orsini et al,[24] a restricted cubic spline model with 2 spline transformations (3 knots minus 1) was estimated using generalized least-squares regression taking into account the correlation within each set of published RRs. In the second stage, the 2 regression coefficients and the variance/covariance matrix that had been estimated within each study were combined using the restricted maximum likelihood method in a multivariate random-effects meta-

analysis.[26] A *P* value for nonlinearity was calculated by testing that the coefficient of the second spline was equal to zero.[27]

Statistical heterogeneity across studies was quantified using Cochran χ^2 and the I^2 statistics.[28, 29] Study-level characteristics including geographical location, sex, average age at baseline, average duration of follow-up, number of cases, case definition for hypertension, degree of adjustment, and study quality were pre-specified as characteristics for assessment of heterogeneity, which was conducted using stratified analysis and random effects meta-regression.[30] We assessed the potential for small study effects such as publication bias through formal tests, namely Begg's funnel plots[31] and Egger's regression symmetry test.[32] Finally, we adjusted for the effect of publication bias by the use of the Duval and Tweedie's nonparametric trim-and-fill method.[33] All analyses were conducted using Stata version 13 (Stata Corp, College Station, Texas).

RESULTS

Study identification and selection

Our initial search identified 612 potentially relevant citations (**Figure 1**). After screening the titles and abstracts, 23 articles remained for further evaluation. We reviewed and assessed these 23 articles, and excluded 9 articles because (i) they had no relevant outcome (n = 6) (ii) they were not prospective (*n* = 2) or duplicated a previous publication using the same cohort (*n* = 1). In sum, this meta-analysis included 14 articles (**Supplementary Material 5**) based on 14 unique prospective cohort studies comprising 44,582 participants and 5,270 hypertension cases.

Study characteristics and quality

Table 1 provides details of the eligible studies. The mean age of participants at baseline ranged from approximately 25 to 62 years. One study included participants aged 15 years and over,

however, participants who were less than 18 years comprised only 9.3% of the total sample.[34] Two studies included participants from Europe (France and Turkey), two from North America (United States), nine from Asia (South Korea, Hong Kong, Japan, and China), and one from Australia. Duration of follow-up to the development of hypertension ranged from 3 to 15 years. Studies ascertained the diagnosis of hypertension (or high blood pressure) using the following definitions: blood pressure ≥ 130/85 mmHg, 140/90 mmHg, 160/95 mmHg and/or taking antihypertensive medication. All studies evaluated the associations in approximately general healthy populations with the exception of one study which was conducted among prehypertensive adults.[35] The degree of covariate adjustment varied, but majority of studies adjusted for potential risk factors for hypertension such as age, body mass index, smoking status, exercise, and alcohol consumption, with three additionally adjusting for another liver enzyme or inflammatory markers. Two studies adjusted for only age. An unadjusted estimate was calculated for one study. Overall, we judged all of the included studies to be of adequate quality (quality score: 6-9). One study scored 9 points, four studies scored 8 points, seven studies scored 7 points, and two studies scored 6 points. **Supplementary Material 6** provides assay characteristics of measured levels of GGT from studies contributing to the analysis. Apart from 7 studies which did not provide specific details of type of assays used for GGT measurements, all other studies employed the enzymatic colorimetric method which has been shown to be precise for detecting GGT activity.[36] As reported in **Supplementary Material 6**, the majority of studies assessed the associations within normal reference ranges of GGT.

Association of GGT and hypertension

The pooled RR (95% CI) of hypertension in a comparison of individuals in the top thirds with those in the bottom thirds of baseline GGT level for all 14 studies was 1.32 (1.23-1.43) (**Figure 2**). The combined RR excluding the study which was conducted among participants with prehypertension was 1.31 (1.22-1.42), which was similar to the main finding. Similarly, the pooled RR was 1.26 (1.18-1.35) on excluding the study with an unadjusted estimate and 1.30

(1.21-1.40) on excluding the study that included participants aged 15 years and over. The pooled RR was minimally attenuated on simultaneously excluding all three studies 1.23 (1.15-1.31). On simultaneous exclusion of the study with an unadjusted estimate and studies that presented only age-adjusted estimates, the pooled RR was attenuated but not significantly altered 1.08 (1.02-1.13). There was substantial heterogeneity between studies (I^2>70%), which was partly explained by study level characteristics such as age at baseline (*P* for meta-regression = 0.007), average follow-up duration (*P* for meta-regression = 0.04), and degree of adjustment (*P* for meta-regression < 0.0001) (**Supplementary Material 7**). A stronger association was observed in studies that included older participants (≥ 45 years) compared to studies with younger participants (< 45 years) and studies with a longer duration of follow-up (≥ 5 years) compared to studies with shorter duration of follow-up (< 5 years). In further subgroup analysis (data not shown), a stronger association was observed in Asian studies 2.16 (1.47-3.19) compared to other populations 1.53 (1.12-2.10) (*P* for meta-regression = 0.293). Egger's test was significant (*P* = 0.001), consistent with observed funnel plot asymmetry (**Supplementary Material 8**), suggesting that studies with less striking results were less likely to have been reported. Despite the concern that small studies with null results often tend not to be published, we found no definitive evidence of such selective reporting when studies were grouped by size in meta-regression analysis (**Supplementary Material 7**). Duval and Tweedie's trim-and-fill method identified 7 missing studies and addition of these hypothetical missing studies did not alter the significant association between GGT and hypertension risk, although substantially weaker (pooled RR comparing top versus bottom third, 1.11: 1.02-1.20).

Dose-response analysis

In pooled analysis of 10 studies (total of 13 data points because results for males and females were reported separately for some of the studies) providing relevant data, we found no evidence of statistically significant departure from linearity (*P* for nonlinearity =0.37) between GGT levels and risk of hypertension, which was present across the spectrum of GGT values (4.5-54.5

U/L) in our study. Visual inspection of the plot was also consistent with a linear shape (**Figure 3**). The combined RR (95% CI) of hypertension for a 5 U/L increment in GGT level was 1.08 (1.04-1.13).

DISCUSSION

Unlike the previous elegant review by Liu and colleagues,[15] who presented a pooled estimate for hypertension comparing the highest versus lowest category of GGT levels irrespective of the risk comparisons reported by the included studies; the present meta-analysis provides a more precise estimate of the magnitude of the association between baseline circulating GGT and incident hypertension. Comparing individuals in the top versus bottom thirds of circulating GGT levels, our results show an approximately 30% increased risk of future hypertension in pooled analysis of 14 variably adjusted eligible studies. The risk was attenuated to 8% in pooled results of only studies that adjusted for established risk factors and/or other potential confounders. The observed heterogeneity among the studies seemed to be explained by average age of participants at baseline, average duration of follow-up, and the degree of confounder adjustment. There were more extreme results in studies conducted among older individuals, consistent with established evidence that increasing age is associated with a significant increase in the incidence of hypertension or high BP. As expected, a stronger association with longer follow-up duration was also demonstrated. A stronger association was observed in Asian populations compared to Western populations (though *P*-value for meta-regression > 0.05), consistent with findings from the previous review[15] and the fact that liver diseases and metabolic syndrome (strongly associated with hypertension or high BP) are very prevalent in Asians. A stronger association was also observed in males compared to females (though *P*-value for meta-regression > 0.05); which is consistent with the significant gender differences in GGT levels, with males having higher levels than females.[37] In addition, males are more likely to develop cardiometabolic diseases at lower average levels of risk markers such as body mass index,[38] which is also causally associated with GGT levels.[39] However, in the context of

the greater proportion of studies featuring more male than female participants in our review, these findings should be interpreted with caution. Our study also provides for the first time, a detailed assessment of the dose-response nature of the association between circulating GGT level and risk of hypertension. The findings were consistent with a linear dose-response relationship, which was characterised by an 8% increase in the risk of hypertension for every 5 U/L increment in circulating GGT level.

Possible explanations for findings

A large body of evidence has shown that GGT is positively and independently associated with cardiovascular disease (CVD) risk and in a linear fashion.[10, 40] Several mechanistic pathways postulated for this association include oxidative stress, increased inflammation, and underlying fatty liver. [41] These same pathways have also been implicated in the relationship between GGT and risk of hypertension. Elevations of serum hepatic enzymes including GGT, have been linked to the development and progression of fatty liver with increasing body mass index.[42] Elevated GGT levels are also suggested to signify oxidative stress and a state of chronic inflammation. [43] The states of oxidative stress, increased inflammation, and fatty liver may impair insulin signalling in the liver, leading to impaired insulin secretion and insulin resistance, which have been implicated in the development of hypertension or high BP. [12, 14]

Implications of findings

Our findings are relevant as they provide further insight concerning the relationship between baseline circulating GGT levels and risk of hypertension and may also have implications for the prevention of hypertension or high BP. Though the cut-off value and reference range for GGT has not been clearly defined, and is essentially arbitrary, being determined ideally by enzyme measuring activity in a healthy population and using the central 95% of values obtained from the population;[44] the recommended cut-off for the upper normal limit of GGT is set at an average of 51 U/L for men and 33 U/L for women.[45] Consistent with the large body of

evidence suggesting an increased risk of adverse cardiometabolic outcomes at GGT levels considered to reflect normal reference ranges,[8, 9, 40] our findings also underscore a potentially deleterious role of increasing GGT levels within the normal range on future risk of hypertension in general population settings. Lifestyle measures such as salt restriction, moderation of alcohol consumption, high consumption of vegetables and fruits and low-fat, maintaining a healthy body weight, regular physical exercise, and elimination of smoking been recommended as the cornerstone for the prevention of hypertension in non-hypertensive individuals.[7] Given that serum GGT levels can be considerably reduced by most of these lifestyle interventions,[46] which also affect levels of established risk factors for hypertension; there remains a possibility that lowering or modification of serum levels of GGT may help in hypertension prediction or prevention. Further evaluation is warranted.

Strengths and limitations

The strengths and limitations of this meta-analysis merit careful consideration. The notable strengths include our ability to transform reported risk estimates from all contributing studies to a consistent comparison (top versus bottom thirds) to allow a consistent combination of estimates across studies, therefore obtaining a reliable estimate of the magnitude of the association and enhancing interpretation of the overall findings. We have also provided a detailed assessment of the dose-response relationship between GGT and risk of hypertension, which has not been previously demonstrated. We systematically explored and identified the possible sources of heterogeneity using stratified analyses and meta-regression. Formal tests demonstrated evidence of publication bias, suggesting that studies with less striking results were less likely to have been reported. However, there was no clear evidence of such selective reporting when studies were grouped by size. A detailed quality assessment of eligible studies was performed, with all included studies attaining moderate to high quality scores. Our main weakness was the inability to fully examine the impact of adjustment for potential confounding factors, because the review was based on variably adjusted data reported in the published

literature. However, majority of included studies adjusted for major potential confounders (including alcohol consumption which is known to increase serum levels of GGT) of the GGT-hypertension association and grouping the studies by degree of adjustment did not appreciably alter the direction of the association. In addition, the dose-response analysis was based on data points from ten out of the 14 eligible studies, as the investigators concerned did not respond to our request for additional data or could not be contacted at all. Finally, it was not possible to correct the estimates for within-individual variation in levels of GGT, because the included studies lacked serial assessments of circulating levels of this exposure in the same individuals.

Conclusions

Circulating level of GGT is associated with an increased risk of hypertension in the general population, consistent with a linear dose-response relationship. Further investigation of any potential relevance of GGT in hypertension prevention is warranted.

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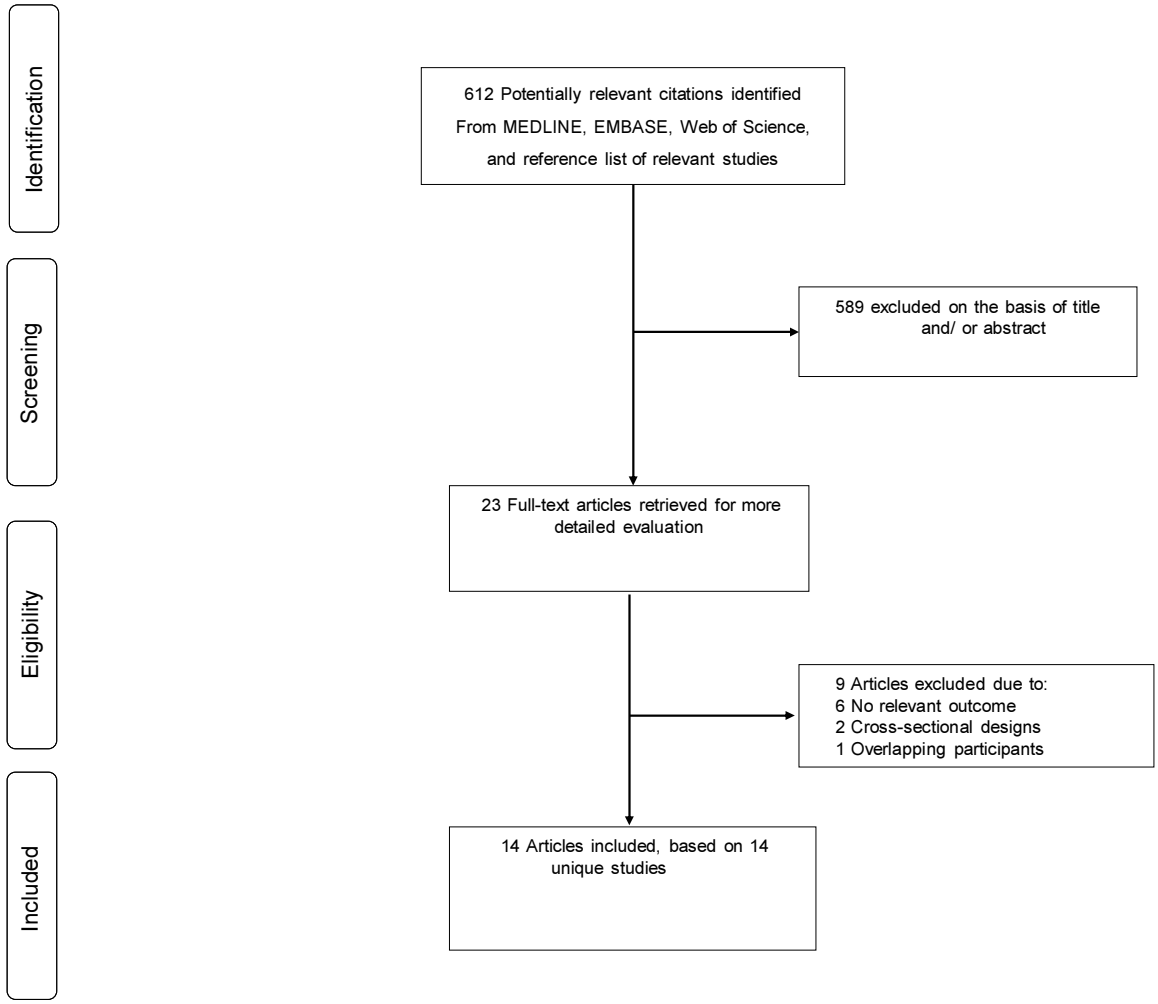
44. Shield KD, Gmel G, Kehoe-Chan T, Dawson DA, Grant BF, Rehm J. Mortality and potential years of life lost attributable to alcohol consumption by race and sex in the United States in 2005. PloS one. 2013; 8 (1):e51923.

45. Gunter EW, Lewis BG, Koncikowski SM. Laboratory procedures used for the Third National Health and Nutrition Examination Survey (NHANES III), 1988-1994. Hyattsville, MD: US Department of Health and Human Services, Centers for Disease Control and Prevention, National Center for Environmental Health, National Center for Health Statistics; 1996.

46. Thoma C, Day CP, Trenell MI. Lifestyle interventions for the treatment of non-alcoholic fatty liver disease in adults: a systematic review. J Hepatol. 2012; 56 (1):255-66.

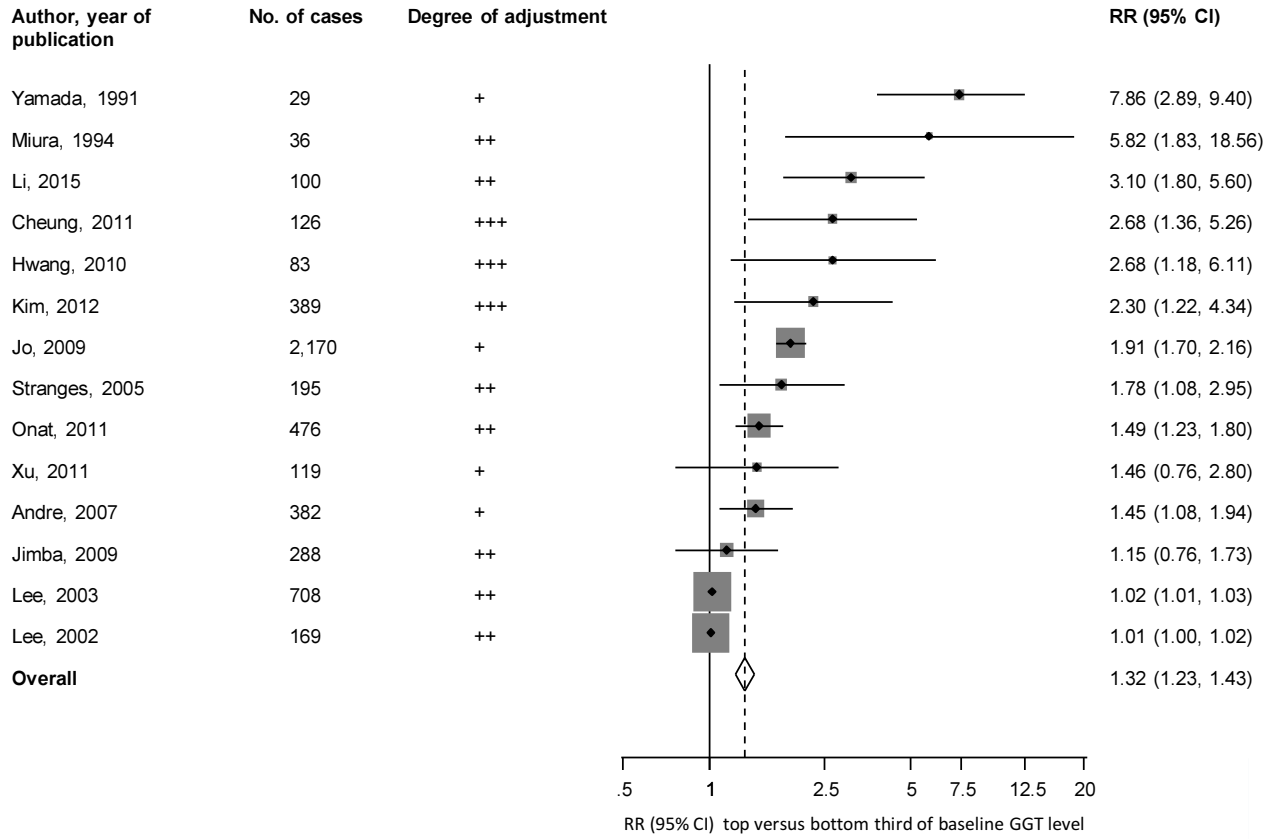
Figure legends

Figure 1. Selection of studies included in the meta-analysis



GGT, gamma-glutamyltransferase.

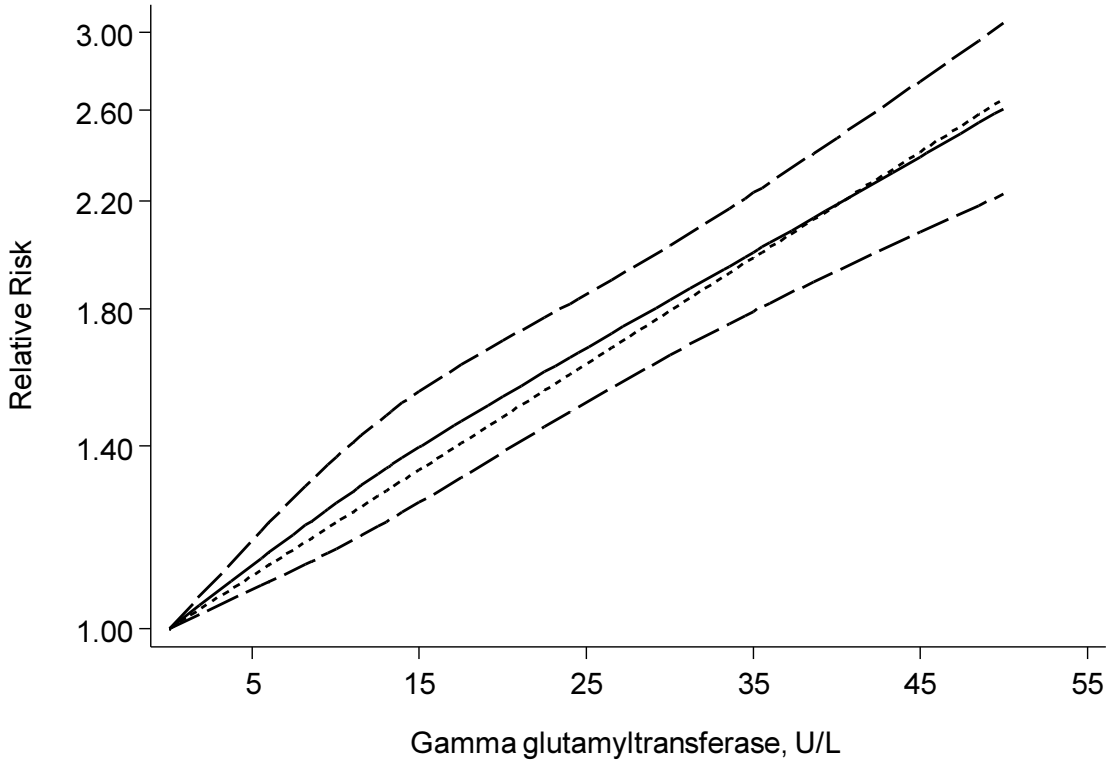
Figure 2. Relative risks for hypertension in individuals in the top compared to the bottom third of baseline levels of gamma-glutamyltransferase in eligible studies



The summary estimate presented was calculated using a random effects model; †, Degree of adjustment: +, unadjusted or adjusted for age and/ or sex; ++, further adjustment for potential hypertension risk factors; +++, additional adjustment for other liver markers or inflammatory markers; Size of data markers are proportional to the inverse of the variance of the relative ratio; CI, confidence interval (bars); GGT, gamma-glutamyltransferase; RR, relative risk

Risk comparisons originally reported by the eligible studies are as follows: Yamada 1991, reported number of hypertension cases by GGT categories (≥ 50 and < 50 U/L); Miura 1994, user-defined cut-offs; Li 2015, estimates provided by authors; Cheung 2011, tertiles; Hwang 2010, quartiles; Kim 2012, quartiles; Jo 2009, quartiles; Stranges 2005, quintiles; Onat 2011, per standard deviation change; Xu 2011, quartiles; Andre 2007, quartiles; Jimba 2009, tertiles; Lee 2003, user-defined cut-offs; and Lee 2002, user-defined cut-offs

Figure 3. Dose-response relation between gamma-glutamyltransferase levels and relative risk of hypertension for pooled results of studies providing relevant data



Adjusted relative risks and 95% confidence intervals (CIs; dashed lines) are reported. GGT levels were modeled with restricted cubic splines with 3 knots. Lines with long dashes represent the pointwise 95% confidence intervals for the fitted linear trend (solid line). Lines with short dashes represent the linear trend. The vertical axis is on a log scale; GGT, gamma-glutamyltransferase

Table 1. Characteristics of published prospective studies evaluating associations between gamma-glutamyltransferase and incident hypertension

Lead author, publication year	Name of study or source of participants	Location of study	Year(s) of baseline survey	Baseline mean age (age range), years	% male	Duration of follow-up	Total no. of participants	No. of cases	Hypertension case definition	Covariates adjusted for	Study quality
Yamada, 1991	Metal Products Factory	Japan	1983	43.0 (35-54)	100.0	5.0	1,393	29	SBP ≥ 160 mmHg, DBP ≥ 95 mmHg	Unadjusted	6
Miura, 1994	Rural community	Japan	1979-1980	47.8 (30-69)	100.0	10.0	77	36	SBP≥140 mmHg, DBP ≥ 90 mmHg, or taking antihypertensive medication	Age, SBP, DBP, alcohol consumption	8
Lee, 2002	Steel Manufacturing Company	South Korea	1994; 1998	NS (25-50)	100.0	4	8,170	169	SBP ≥ 160 mmHg, DBP ≥ 95 mmHg, and/or taking antihypertensive medication	Age, BMI, smoking (pack years), drinking, exercise, family history of hypertension, SBP or DBP, changes of BMI, drinking during four years	7
Lee, 2003	CARDIA	USA	1985-1986	25.0 (18-30)	NS	15.0	4,704	708	SBP ≥ 140 mmHg, DBP ≥ 90 mmHg, or taking antihypertensive medication	Study center, race, sex, age, alcohol consumption, BMI, smoking, PA, fasting serum glucose, insulin for diabetes, SBP, insulin for hypertension	8
Stranges, 2005	WNYS	USA	1986-2001	NS (39-79)	65.4	6.0	897	195	SBP ≥ 140 mmHg, DBP ≥ 90 mmHg, or taking antihypertensive medication	Age, gender, race, average amount of alcohol, smoking status, BMI, PA, SBP	7
Andre, 2007	DESIR	France	1994-1996	46.0 (30-65)	55.2	3.0	1,776	377	SBP ≥ 130 mmHg, DBP ≥ 85 mmHg or treatment of previously diagnosed hypertension	Age	7
Jo, 2009	HPC	South Korea	2002	38.7 (19-86)	70.8	4.0	17,281	2,170	SBP ≥ 130 mmHg, DBP ≥ 85 mmHg, or taking antihypertensive medication	Age	6
Jimba, 2009	SSK Hospital	Japan	2002-2003	49.0 (NS)	NS	3.0	1,027	288	SBP ≥ 130 mmHg, DBP ≥ 85 mmHg, or taking antihypertensive medication	Age, sex, alcohol habits, BMI at baseline	7

Lead author, publication year	Name of study or source of participants	Location of study	Year(s) of baseline survey	Baseline mean age (age range), years	% male	Duration of follow-up	Total no. of participants	No. of cases	Hypertension case definition	Covariates adjusted for	Study quality
Hwang, 2010	Community	South Korea	2003	54.1 (> 30)	39.2	5.0	293	83	SBP ≥ 140 mmHg, DBP ≥ 90 mmHg, or taking antihypertensive medication	Age, education, BMI, alcohol intake, smoking, exercise, salt intake, family history of hypertension, ALT	7
Cheung, 2011	CRISPS-2	Hong Kong	2005-2008	47.3 (25-75)	39.5	5.3	708	126	SBP ≥ 140 mmHg, DBP ≥ 90 mmHg, or taking antihypertensive medication	Age, sex, SBP at baseline and follow-up duration, baseline BMI, HDL-C, HOMA-IR, CRP, fibrinogen, current smoking, change in BMI	9
Onat, 2011	TARFS	Turkey	2003-2004	52.0 (33-84)	49.1	4.0	1,422	476	SBP ≥ 140 mmHg, DBP ≥ 90 mmHg, or taking antihypertensive medication	Age, sex, menopause, BMI, alcohol use	8
Xu, 2011	Shangai	China	2004-2008	NS (≥ 40)	60.2	3.5	285	119	SBP>=130 mmHg, DBP>=85 mmHg, or taking antihypertensive medication	Age and sex	7
Kim, 2012	Kangbuk Samsung Hospital	South Korea	2002-2005	44.0 (NS)	67.9	3.0	4,783	389	SBP ≥ 140 mmHg, DBP ≥ 90 mmHg, or taking antihypertensive medication	Age, sex, alcohol amount, smoking status, PA, baseline glucose, uric acid, HDL-C, LDL-C, TG, hsCRP, SBP	8
Li, 2015	Rural indigenous community	Australia	1997-2008	31.4 (15-78)	41.0	6.6	1,766	100	SBP ≥ 140 mmHg, DBP ≥ 90 mmHg, or taking antihypertensive medication	Age, sex, ethnicity, abdominal obese, PA, diabetes, dyslipidemia	7
Total							44,582	5,270			

CARDIA, Coronary Artery Risk Development in Young Adults; CRISPS-2, Cardiovascular Risk Factor Prevalence Study; DESIR, Data from Epidemiological Study on the Insulin Resistance Syndrome; HPC, Health Promotion Centre; SSK, Saitama-ken Saiseikai Kurihashi; TARFS, Turkish Adult Risk Factor Study; WNYS, Western New York Health Study;

ALT, alanine aminotransferase; BMI, body mass index; DBP, diastolic blood pressure; HDL-C, high density lipoprotein cholesterol; hsCRP, high sensitivity C-reactive protein; HOMA-IR, homeostasis model assessment of insulin resistance; LDL-C, low density lipoprotein cholesterol; NS, not stated; PA, physical activity; SBP, systolic blood pressure; TC, total cholesterol; TG, triglycerides

SUPPLEMENTARY MATERIAL

Supplementary Material 1	PRISMA checklist
Supplementary Material 2	MOOSE checklist
Supplementary Material 3	Literature search strategy
Supplementary Material 4	Risk conversion method
Supplementary Material 5	Reference list of included studies
Supplementary Material 6	Study and assay characteristics of studies contributing data to current analysis
Supplementary Material 7	Relative risks for hypertension in individuals in the top versus bottom thirds of baseline levels of gamma-glutamyltransferase, grouped according to several study characteristics
Supplementary Material 8	Assessment of small study effects by funnel plot and Egger's test

Supplementary Material 1: PRISMA 2009 check-list

Section/topic	Item No	Checklist item	Reported on page No
Title			
Title	1	Identify the report as a systematic review, meta-analysis, or both	1
Abstract			
Structured summary	2	Provide a structured summary including, as applicable, background, objectives, data sources, study eligibility criteria, participants, interventions, study appraisal and synthesis methods, results, limitations, conclusions and implications of key findings, systematic review registration number	2
Introduction			
Rationale	3	Describe the rationale for the review in the context of what is already known	4
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS)	5
Methods			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (such as web address), and, if available, provide registration information including registration number	None
Eligibility criteria	6	Specify study characteristics (such as PICOS, length of follow-up) and report characteristics (such as years considered, language, publication status) used as criteria for eligibility, giving rationale	5-6
Information sources	7	Describe all information sources (such as databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched	5-6
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated	Supplementary Material 3
Study selection	9	State the process for selecting studies (that is, screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis)	6-7
Data collection process	10	Describe method of data extraction from reports (such as piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators	6-7
Data items	11	List and define all variables for which data were sought (such as PICOS, funding sources) and any assumptions and simplifications made	7
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis	7-8
Summary measures	13	State the principal summary measures (such as risk ratio, difference in means).	7-8
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (such as I^2 statistic) for each meta-analysis	8-9
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (such as publication bias, selective reporting within studies)	8-9
Additional analyses	16	Describe methods of additional analyses (such as sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-	8-9

Section/topic	Item No	Checklist item	Reported on page No
		specified	
Results			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram	9 and Figure 1
Study characteristics	18	For each study, present characteristics for which data were extracted (such as study size, PICOS, follow-up period) and provide the citations	9-10, Table 1
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome-level assessment (see item 12).	10, Table 1
Results of individual studies	20	For all outcomes considered (benefits or harms), present for each study (a) simple summary data for each intervention group and (b) effect estimates and confidence intervals, ideally with a forest plot	10-11, Figure 2
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency	10-11, Figure 2
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see item 15)	10-11, Supplementary Material 7-8
Additional analysis	23	Give results of additional analyses, if done (such as sensitivity or subgroup analyses, meta-regression) (see item 16)	11, Supplementary Material 7
Discussion			
Summary of evidence	24	Summarise the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (such as health care providers, users, and policy makers)	11-12
Limitations	25	Discuss limitations at study and outcome level (such as risk of bias), and at review level (such as incomplete retrieval of identified research, reporting bias)	13
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research	13
Funding			
Funding	27	Describe sources of funding for the systematic review and other support (such as supply of data) and role of funders for the systematic review	None

Supplementary Material 2: MOOSE checklist

Gamma-glutamyltransferase and risk of hypertension: a systematic review and dose-response meta-analysis of prospective evidence

Criteria		Brief description of how the criteria were handled in the review
Reporting of background		
√	Problem definition	Elevated baseline circulating gamma-glutamyltransferase (GGT) has been demonstrated to be strongly associated with risk of hypertension or high blood pressure (BP), but the precise magnitude of the association and nature of the dose-response relationship is uncertain
√	Hypothesis statement	There is a linear dose-response relationship between GGT level and risk of hypertension
√	Description of study outcomes	Hypertension
√	Type of exposure	Blood levels of GGT
√	Type of study designs used	Prospective (cohort, case-cohort or "nested case control") population-based studies
√	Study population	Approximately general populations (i.e., did not select participants on the basis of confirmed pre-existing medical conditions such as hypertension, cardiovascular disease, liver disease, or chronic kidney disease at baseline).
Reporting of search strategy should include		
√	Qualifications of searchers	Setor Kunutsor, MD PhD; Tanefa A. Apekey, PhD
√	Search strategy, including time period included in the synthesis and keywords	Time period: from inception of MEDLINE, EMBASE, Web of Science to May 2015. **Search strategy:** 1 (Gamma glutamyltransferase"[MeSH] OR "gamma glutamyltransferase"[All Fields]) 2 ("Hypertension"[MeSH] OR "Blood pressure"[All Fields]) 3 ("humans"[MeSH Terms]) 4 (1 AND 2 AND 3)
√	Databases and registries searched	MEDLINE, EMBASE, and Web of Science
√	Search software used, name and version, including special features	Ovid was used to search EMBASE Reference Manager used to manage references
√	Use of hand searching	We searched bibliographies of retrieved papers
√	List of citations located and those excluded, including justifications	Details of the literature search process are outlined in the flow chart. The citation list for excluded studies is available upon request.
√	Method of addressing articles published in languages other than English	We placed no restrictions on language
√	Method of handling abstracts and unpublished studies	None found
√	Description of any contact with authors	We contacted authors who did not report relative risks with 95% confidence intervals for at least three quantitative categories of GGT or a linear dose-response trend
Reporting of methods should include		
√	Description of relevance or appropriateness of studies assembled for assessing the hypothesis to be tested	Detailed inclusion and exclusion criteria are described in the Methods section.
√	Rationale for the selection and coding of data	Data extracted from each of the studies were relevant to the population characteristics, study design, exposure, outcome, and possible effect modifiers of the association.

√	Assessment of confounding	We assessed confounding by ranking individual studies on the basis of different adjustment levels, and performed sub-group analyses to evaluate differences in the overall estimates according to levels of adjustment.
√	Assessment of study quality, including blinding of quality assessors; stratification or regression on possible predictors of study results	Study quality was assessed based on the nine-star Newcastle–Ottawa Scale using pre-defined criteria namely: population representativeness, comparability (adjustment of confounders), ascertainment of outcome. Sensitivity analyses by several quality indicators such as study size, duration of follow-up, and adjustment factors.
√	Assessment of heterogeneity	Heterogeneity of the studies was explored with I^2 statistic that provides the relative amount of variance of the summary effect due to the between-study heterogeneity.
√	Description of statistical methods in sufficient detail to be replicated	Description of methods of meta-analyses, sensitivity analyses, meta-regression and assessment of publication bias are detailed in the methods. We performed random effects meta-analysis with Stata 13.
√	Provision of appropriate tables and graphics	Table 1, Figures 1-3, Supplementary Materials 7-8
Reporting of results should include		
√	Graph summarizing individual study estimates and overall estimate	Figure 2
√	Table giving descriptive information for each study included	Table 1 and Supplementary Material 6
√	Results of sensitivity testing	Sensitivity analysis was conducted to assess the influence of each individual study by omitting one study at a time and calculating a pooled estimate for the remainder of the studies. Results section
√	Indication of statistical uncertainty of findings	95% confidence intervals were presented with all summary estimates, I^2 values and results of sensitivity analyses
Reporting of discussion should include		
√	Quantitative assessment of bias	Sensitivity analyses indicate heterogeneity in strengths of the association due to most common biases in observational studies. Limitations have been discussed.
√	Justification for exclusion	All studies were excluded based on the pre-defined inclusion criteria in methods section.
√	Assessment of quality of included studies	Brief discussion included in ‘Methods’ section
Reporting of conclusions should include		
√	Consideration of alternative explanations for observed results	Discussed in the context of the results.
√	Generalization of the conclusions	Discussed in the context of the results.
√	Guidelines for future research	Assessment of the potential utility of GGT in prediction of hypertension
√	Disclosure of funding source	No separate funding was necessary for the undertaking of this systematic review.

Supplementary Material 3: Literature search strategy

Relevant studies, published before May 20, 2015 (date last searched), were identified through electronic searches not limited to the English language using MEDLINE, EMBASE, and the Science Citation Index databases. Electronic searches were supplemented by scanning reference lists of articles identified for all relevant studies (including review articles), by hand searching of relevant journals and by correspondence with study investigators. The computer-based searches combined search terms related to gamma-glutamyltransferase and hypertension without language restriction.

(i) MEDLINE strategy to identify relevant exposures:
(“Gamma glutamyltransferase”[MeSH] OR "gamma glutamyltransferase"[All Fields] OR "Gamma glutamyltranspeptidase"[MeSH] OR "gamma glutamyltranspeptidase"[All Fields])

(ii) MEDLINE strategy to identify relevant outcomes:
("Hypertension"[MeSH] OR “hypertension”[All Fields] OR "Blood pressure"[MeSH] OR “blood pressure”[All Fields])

(iii) MEDLINE strategy to identify relevant population:
("humans"[MeSH Terms])

Parts i, ii and iii were combined using ‘AND’ to search MEDLINE. Each part was specifically translated for searching alternative databases.

Supplementary Material 4: Risk conversion method

To enable a consistent approach to the meta-analysis and enhance interpretation of findings, relative risk estimates for association of gamma-glutamyltransferase (GGT) and hypertension or high blood pressure (BP) that were often differently reported by each study [e.g. per unit or standard deviation (SD) change, quintiles, quartiles, or other groupings] were transformed to involve comparisons between the top third and bottom third of each study population's baseline distribution of GGT levels using standard statistical methods.[1,2] Briefly, assuming a normally distributed exposure (e.g. log GGT) with a log-linear association with hypertension risk (i.e. linear relationship between log relative risk estimates and levels of the exposure), conversion factors to convert log relative risks from reported scale comparisons to top versus bottom third comparisons are derived based on the ratio of expected differences in mean levels of the standardised exposure (i.e. SD scale), for the target comparison versus reported comparison. For example, the expected difference in means of the top versus bottom thirds of the standard normal distribution is 2.18 SDs, 2.54 SDs for the top versus bottom quartile, and 2.80 SDs for the top versus bottom quintile. Hence, relative risk estimates reported for comparisons of extreme quartiles can be converted to comparisons of extreme thirds by applying a multiplication conversion factor of 2.18/2.54 to the log relative risk and its standard error and estimates reported for comparisons of extreme quintiles can be converted to comparisons of extreme thirds by applying a multiplication conversion factor of 2.18/2.80 to the estimates. Similarly, estimates reported per 1 SD can be multiplied by 2.18 to obtain the top versus bottom third comparison, and those reported per unit change can be multiplied by 2.18*SD of exposure, to obtain similar comparison. Conversion factors for other possible reported comparisons are derived similarly. The method has been generally been implemented in Stata function --riskconv-- available from http://www.phpc.cam.ac.uk/ceu/research/erfc/stata/[3] and has been used in previous numerous published meta-analyses.[4-6]

1. Chêne, G and Thompson, SG. Methods for Summarizing the Risk Associations of Quantitative Variables in Epidemiologic Studies in a Consistent Form. American Journal of Epidemiology. 1996;144:610-621
2. Greenland, S and Longnecker, MP. Methods for trend estimation from summarized dose-response data, with applications to meta-analysis. American Journal of Epidemiology. 1992;135:1301-1309.
3. The Emerging Risk Factors Collaboration. ERFC Methods. Accessed at http://www.phpc.cam.ac.uk/ceu/research/erfc/methods/ on 26 February 2014.
4. Thompson A and Danesh J. Associations between apolipoprotein B, apolipoprotein AI, the apolipoprotein B/AI ratio and coronary heart disease: a literature-based meta-analysis of prospective studies. J Intern Med. 2006;259:481-492
5. Chowdhury R, Stevens S, Gorman D, Pan A, Warnakula S, Chowdhury S et al. Association between fish consumption, long chain omega 3 fatty acids, and risk of cerebrovascular disease: systematic review and meta-analysis. BMJ. 2012;345:e6698.
6. Kunutsor SK, Apekey TA, Walley J. Liver aminotransferases and risk of incident type 2 diabetes: a systematic review and meta-analysis. Am J Epidemiol. 2013; 178 (2): 159-17

Supplementary Material 5: Reference list of included studies

1. Yamada Y, Ishizaki M, Kido T, Honda R, Tsuritani I, et al. (1991) Alcohol, high blood pressure, and serum gamma-glutamyl transpeptidase level. Hypertension 18: 819-826.

2. Miura K, Nakagawa H, Nakamura H, Tabata M, Nagase H, et al. (1994) Serum gamma-glutamyl transferase level in predicting hypertension among male drinkers. J Hum Hypertens 8: 445-449.

3. Lee DH, Ha MH, Kim JR, Gross M, Jacobs DR, Jr. (2002) Gamma-glutamyltransferase, alcohol, and blood pressure. A four year follow-up study. Ann Epidemiol 12: 90-96.

4. Lee DH, Jacobs DR, Jr., Gross M, Kiefe CI, Roseman J, et al. (2003) Gamma-glutamyltransferase is a predictor of incident diabetes and hypertension: the Coronary Artery Risk Development in Young Adults (CARDIA) Study. Clin Chem 49: 1358-1366.

5. Stranges S, Trevisan M, Dorn JM, Dmochowski J, Donahue RP (2005) Body fat distribution, liver enzymes, and risk of hypertension: evidence from the Western New York Study. Hypertension 46: 1186-1193.

6. Andre P, Balkau B, Vol S, Charles MA, Eschwege E, et al. (2007) Gamma-glutamyltransferase activity and development of the metabolic syndrome (International Diabetes Federation Definition) in middle-aged men and women: Data from the Epidemiological Study on the Insulin Resistance Syndrome (DESIR) cohort. Diabetes Care 30: 2355-2361.

7. Jo SK, Lee WY, Rhee EJ, Won JC, Jung CH, et al. (2009) Serum gamma-glutamyl transferase activity predicts future development of metabolic syndrome defined by 2 different criteria. Clin Chim Acta 403: 234-240.

8. Jimba S, Nakagami T, Oya J, Wasada T, Endo Y, et al. (2009) Increase in gamma-glutamyltransferase level and development of established cardiovascular risk factors and diabetes in Japanese adults. Metab Syndr Relat Disord 7: 411-418.

9. Hwang JH, Shin JY, Chun B, Lee DH, Kim KY, et al. (2010) [Association between gamma-glutamyltransferase and hypertension incidence in rural prehypertensive adults]. J Prev Med Public Health 43: 18-25.

10. Cheung BM, Ong KL, Tso AW, Cherny SS, Sham PC, et al. (2011) Gamma-glutamyl transferase level predicts the development of hypertension in Hong Kong Chinese. Clin Chim Acta 412: 1326-1331.

11. Onat A, Can G, Ornek E, Cicek G, Ayhan E, et al. (2012) Serum gamma-glutamyltransferase: independent predictor of risk of diabetes, hypertension, metabolic syndrome, and coronary disease. Obesity (Silver Spring) 20: 842-848.

12. Xu Y, Bi YF, Xu M, Huang Y, Lu WY, et al. (2011) Cross-sectional and longitudinal association of serum alanine aminotransaminase and gamma-glutamyltransferase with metabolic syndrome in middle-aged and elderly Chinese people. J Diabetes 3: 38-47.

13. Kim NH, Huh JK, Kim BJ, Kim MW, Kim BS, et al. (2012) Serum gamma-glutamyl transferase level is an independent predictor of incident hypertension in Korean adults. Clin Exp Hypertens 34: 402-409.

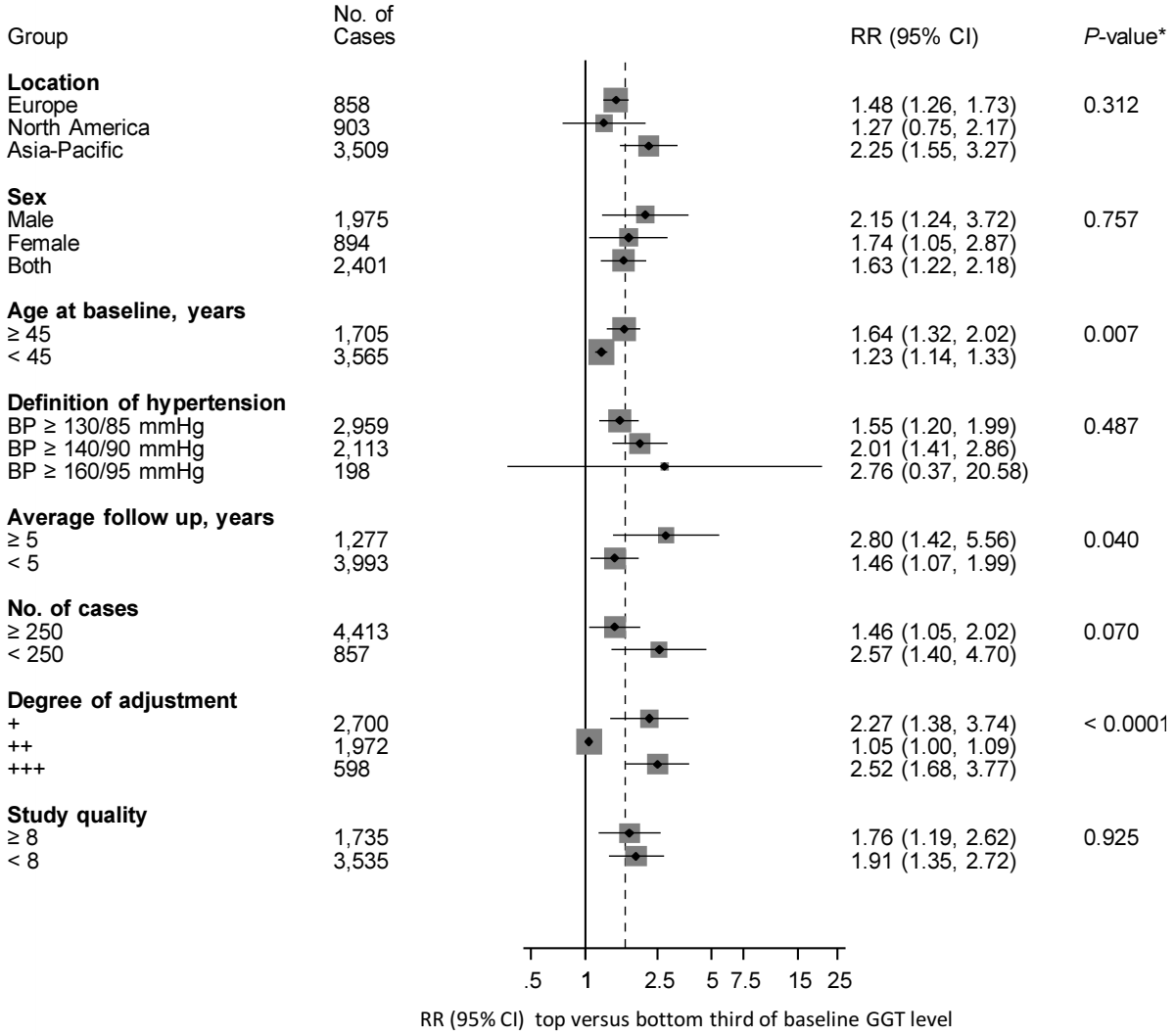
14. Li M, McDermott R (2015) Obesity, albuminuria, and gamma-glutamyl transferase predict incidence of hypertension in indigenous Australians in rural and remote communities in northern Australia. J Hypertens 33: 704-710.

Supplementary Material 6: Study and assay characteristics of studies contributing data to current analysis

Lead Author, publication year	Name of study or source of participants	Sampling method	Sample source	Fasting samples	Sample state before analysis, storage, temperature(°C) if frozen	Reference ranges (mean GGT levels) in study, U/L*	Assay method	Assay source (Manufacturer)
Yamada, 1991	Metal Products Factory	Complete	Serum	NS	Fresh	NS (24.7)	NS	Automatic analyzer (SMAC III, Technicon, Tarrytown, N.Y.)
Miura, 1994	Rural community	Complete	Serum	NS	NS	NS (17.5)	L-gamma-glutamyl-p-nitroanilide used as substrate	Automatic analyser (Hitachi-716, Hitachi, Tokyo)
Lee, 2002	Steel Manufacturing Company	Complete	Serum	Yes	Fresh	0-49 (NS)	NS	Automatic analyser (normal range 0–50 U/L; Hitachi 7170, Japan)
Lee, 2003	CARDIA	Complete	Serum	NS	Frozen, -70	NS (NS)	NS	SMA-CII continuous-flow analyzer (Technicon Instruments Corp.)
Stranges, 2005	WNYS	Complete	Serum	Yes	Fresh	NS (22.4)	Kinetic method	Paramax Automated Chemistry System
Andre, 2007	DESIR	Complete	Serum	Yes	Fresh	Men: < 30 (37.1) Women: < 24 (20.9)	NS	Technicon DAX
Jo, 2009	HPC	Complete	Serum	Yes	NS	Men: (36.4) Women: (13.5)	Modified Szasz method	ADVIA 1650 auto-analyzer (Siemens, Tarrytown NY)
Jimba, 2009	SSK Hospital	Complete	NS	Yes	NS	12-58 (47.0)	l-γ-glutamyl-p-nitroanilide method	NS
Hwang, 2010	Community	Complete	NS	NS	NS	NS (Median, 16.0)	NS	NS
Cheung, 2011	CRISPS-2	Random	Plasma	Yes	NS	NS (20.5)	NS	Hitachi 912 analyzer
Onat, 2011	TARFS	Complete	Serum	Yes	Frozen, -75	Men: < 50 (Median, 24.9) Women: < 30 (Median, 17.0)	Kinetic method	Hitachi 902 Autoanalyzer
Xu, 2011	Shangai	Complete	Serum	Yes	NS	NS (Range, 12-68)	NS	Autoanalyser (CX-7 Biochemical Autoanalyser; Beckman Coulter, BREA, CA, USA
Kim, 2012	Kangbuk Samsung Hospital	Complete	Serum	Yes	NS	Men: 0-51 (25.8) Women:0-51 (13.3)	Kinetic spectrophotometric method	Autoanalyzer (Adiva 1800, Siemens Healthcare Diagnostics, Tokyo, Japan)
Li, 2015	Rural indigenous community	Complete	Plasma	Yes	Fresh	Men: NS (56.0) Women: NS (27.5)	Kinetic spectrophotometric method	Cobas Integra 800 (Roche Diagnostics, New York, USA)

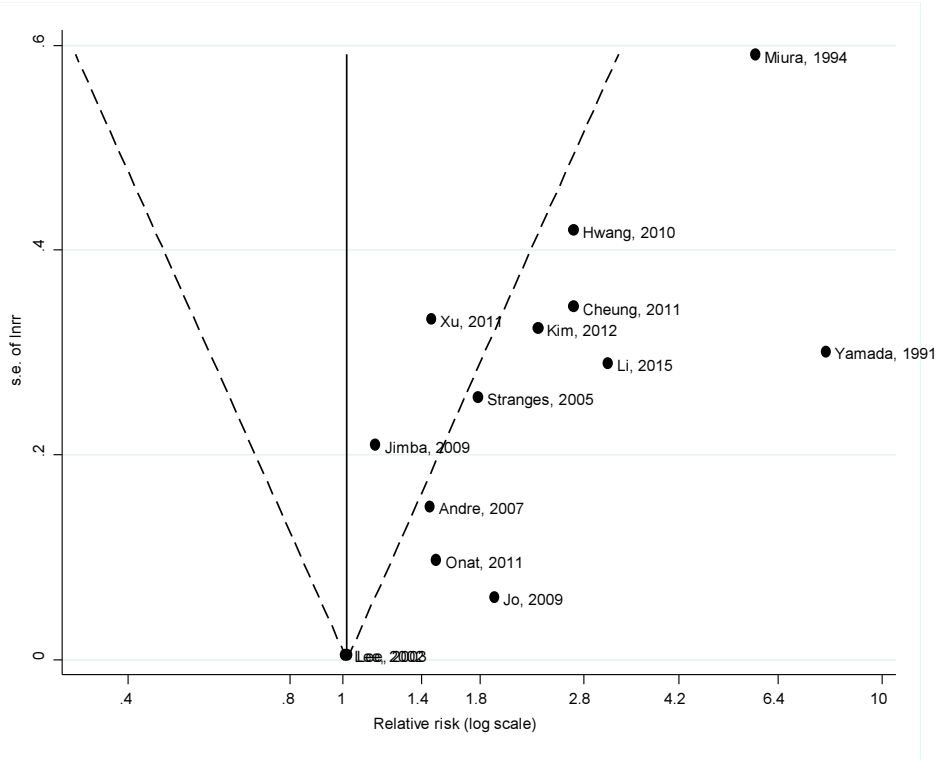
Study acronyms are provided in **Table 1**; Reference list of included studies in **Supplementary Material 5**; GGT, gamma-glutamyltransferase; NS, not stated; *, values in parenthesis are mean values unless otherwise stated.

Supplementary Material 7: Relative risks for hypertension in individuals in the top versus bottom thirds of baseline levels of gamma-glutamyltransferase, grouped according to several study characteristics



The summary estimates presented were calculated using random effects models; Size of data markers are proportional to the inverse of the variance of the relative ratio; BP, blood pressure; CI, confidence interval (bars); GGT, gamma-glutamyltransferase; RR, relative risk; *, *P*-value for meta-regression

Supplementary Material 8: Assessment of small study effects by funnel plot and Egger's test



Study references are provided in **Supplementary Material 5**. The dotted lines show 95% confidence intervals around the overall summary estimate calculated using a fixed effect model; GGT, gamma-glutamyltransferase; *P*-value for bias calculated using Egger's test was 0.001