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Glutathione S-transferase polymorphisms, asthma susceptibility and confounding variables: a meta-analysis

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Abstract Oxidative stress is one of the main risk factors for asthma development. Glutathione S-transferases play an important role in antioxidant defences and may influence asthma susceptibility. In particular, GSTM1 and GSTT1 positive/null genotypes and the GSTP1*Ile105 Val polymorphism have been analyzed in a number of genetic association studies, with conflicting outcomes. Two previous meta-analyses have attempted to clarify the associations between GST genes and asthma, but these studies have also showed contrasting results. Our aim was to perform a meta-analysis that included independent genetic association studies on GSTM1, GSTP1, and GSTT1, evaluating also the effect of potential confounding variables (i.e. ethnicity, population age, and urbanization). Systematic review and meta-analysis of the effects of GST genes on asthma were conducted. The meta-analyses were performed using a fixed or, where appropriate, random effects model. The meta-analysis of the GSTM1 ($n = 35$), GSTT1 ($n = 31$) and GSTP1 ($n = 28$) studies suggests that no significant associations with asthma susceptibility were observed for GSTM1 and GSTP1 gene polymorphisms, whereas a significant outcome was detected for the GSTT1 positive/null genotype (pooled OR = 1.33, 95 %CI = 1.10–1.60). However, high between-study heterogeneity was identified in all the general analyses ($p_{\text{heterogenetity}} < 0.05$). The stratification analysis seems to explain the heterogeneity only in few cases. This picture is probably due to the interactive process of genetics and environment that characterizes disease pathogenesis. Further studies on interactions of GST genes with the potential oxidative stress sources and with other antioxidant genes are needed to explain the role of GST enzymes in asthma.

Keywords Asthmatic disease · Genetic predisposition to disease · GSTM1 · GSTP1 · GSTT1 · Oxidative stress

Introduction

Asthma is an inflammatory disorder of the airways characterized by reversible airway obstruction and bronchial hyper-responsiveness [1]. To date, several studies have revealed that the complex interaction of cell and pro-inflammatory mediators are responsible for the pathogenesis of asthma. Among the inflammatory mediators, sources of oxidant injury are endogenous reactive oxygen species generated by cellular metabolism and by the inhalation of atmospheric pollutants [2]. These factors, which contribute to the severity and symptom exacerbation of asthma, are countered by both enzymatic and non enzymatic antioxidants, including vitamins C and E and glutathione (GSH), a major protective antioxidant in the lungs that also plays a fundamental role in the regulation of inflammatory responses [3]. Glutathione S-transferases (GSTs) catalyze

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the conjugation of electrophilic compounds to GSH. Their catalytic activities make these enzymes crucial to the detoxification of a wide range of endogenous and exogenous compounds [4]. Polymorphisms of genes encoding GST enzymes influence their functionality in the lungs and other organs, and this can confer genetic susceptibility to oxidative stress and, consequently, to asthma [5, 6].

For this reason, the potential role for GST polymorphisms to modulate disease and adverse responses has been the subject of numerous molecular epidemiologic studies [7–9]. The most extensively studied GST polymorphisms occurs in three isozymes: GSTM1, GSTP1, and GSTT1. Gene polymorphisms affect the activity of these enzymes: gene deletion polymorphisms occurs in the *GSTM1* and *GSTT1* gene, whereas a missense substitution (I105V, rs1695) characterizes GSTP1 [10].

Considering their biochemical function, the association between GST genes and asthma development risk has been thoroughly examined; published data have reported contrasting results [11, 12]. Specifically, studies have assessed the effects of GSTM1 and GSTT1 null genotypes and GSTP1 Val105 allele. Studies on GSTM1, GSTT1 and asthma have confirmed or rejected that these genes have been associated with an increased susceptibility to asthma development in children and adults. Also, for the *GSTP1* gene, the Val allele reportedly protects against asthma in adults [13–15]. Conversely, in other studies, the Val105 allele seems to increase the risk of asthma in children [16, 17]. Others authors have not noted evidence of associations between GSTP1*Ile105Val polymorphism and asthma [18, 19]. All the mentioned studies have reflected upon the meta-analytical level, albeit with significant potential for improvement. Concerning the association between GST polymorphisms and asthma, only two meta-analyses have been published, with conflicting outcomes [2, 20]. Careful examination of the studies included therein reveals, however, that other eligible case–control studies have not been taken into account; additional studies have appeared, thereby increasing the amount of the available data. Furthermore, the previous meta-analyses did not analyze the effects of important confounding variables, such as ethnicity and urbanization.

The aim of our study is to perform a meta-analysis that includes genetic association studies on GST and asthma risk, analyzing the effect of ethnicity, population age, and urbanization in order to explain the heterogeneity of the results.

Materials and methods

Literature search

Eligible articles were identified through a search of the Medline and Hugenet databases through February of 2012 using combination of the following keywords: "glutathione S-transferase", "GST", "glutathione S-transferase M1", "GSTM1", "glutathione S-transferase P1", "GSTP1", "glutathione S-transferase T1", "GSTT1", "asthma", and "asthma development". In addition, we checked all the references of relevant reviews and eligible articles that our search retrieved. No restrictions were placed on language or type of report, and conference abstracts were also included. When multiple reports were available for a single study, only the most recent article, or the article with the largest sample size, was included. Authors of studies were contacted for further information whenever the data required by the meta-analysis were not fully reported in the article.

Meta-analysis

Case–control, cohort, and cross sectional studies with any sample size examining the association between asthma and GSTM1 null genotype, GSTT1 null genotype and GSTP1 Ile105Val polymorphism were considered eligible for this meta-analysis. For each study we collected the following data: journal name, year of publication, characteristics of the included studies (in relation to the source of cases and controls), method of ascertainment of the diagnosis (inclusion and exclusion criteria), asthma characteristics (atopic or non- atopic), demographic characteristics of the population being studied, prevalence of meaningful risk factors (smoking habits, and family history of asthma). This was done both in cases and controls. We also collected data on geographical location and ethnicity. On the basis of the information reported by the authors, we divided geographical location in urban areas or non urban areas by population estimate in accordance with demographia world urban areas: seventh annual edition [http://www.demographia.com/db-worldua.pdf].

We excluded from our analysis familiar, only-case, and occupational asthma studies. For each study frequencies of GSTP1*I105V genotypes and frequencies of GSTM1 and GSTT1 positive/null genotypes in cases and controls and crude odds ratios (ORs) were collected. A wide range of studies evaluated *GSTM1* and *GSTT1* as presence/absence of gene deletion, so meta-analyses of these polymorphisms were performed using a single OR (null vs. present). Results for GSTP1 Ile105Val were reported as two ORs: a dominant OR (Ile/Val + Val/Val vs. Ile/Ile) and a recessive OR (Val/Val vs. Ile/Ile + Ile/Val). Regarding GSTP1 Ile105Val polymorphisms, a sensitivity analysis was performed excluding studies where allele frequencies exhibited a significant deviation from the Hardy–Weinberg equilibrium (HWE). Statistical significance was defined as $p < 0.05$. The Q test and the I^2 statistic were used to investigate respectively the presence of between-study

heterogeneity and the proportion of variation across studies due to heterogeneity rather than random error [21]. Possible causes of heterogeneity were investigated by subgroup analyses based on ethnicity, urbanization, and population age. For ethnicity, we considered four ethnic classes: Asian, European, Mediterranean African, and Turkish. For urbanization, the variables were defined as metropolis (>1 million inhabitants), city (500 thousand to 1 million inhabitants), and country-side (<500 thousand inhabitants). In the analyses, we used as a subgroup variable the combination of these categories, or, rather, we used a variable with four categories: 1= "Cases: Adults and Controls: Adults", 2= "Cases: Children and Controls: Children–Adults", 3= "Cases: Children and Controls: Adults", 4= "Cases: Children and Controls: Children". All statistical analyses were performed using STATA 10.1 (Stata Corp, College Station, TX, USA); the meta-analyses were performed using a fixed or, where appropriate, random effects model to estimate pooled OR. Publication bias was evaluated with the funnel plot and the Begg and Mazumdar Rank correlation test and Egger's regression method. Then with Duvall and Tweedie's trim and fill procedure, we tested how the effect size would shift, when the apparent bias was removed. Temporal effect was also estimated with a cumulative meta-analysis.

Results

Systemic review and meta-analysis

In Fig. 1, we reported the flow-chart that represents the inclusion and exclusion criteria of studies. From our initial research we identified 2,483 articles. Among those, after screening for titles and abstracts, we identified 95 studies; after cross-checking references we identified 20 additional papers so we examined and retrieved 115 papers for more detailed evaluation. 43 eligible articles were considered; we excluded occupational asthma reports, multiple reports of the same studies, family-based studies, other outcomes reports, editorials and reviews. We contacted the authors of 14 papers with no genotype data available and seven of those authors gave us the genotype data.

We included in the meta-analysis data collected from cohorts ($n = 3$), cross-sectional studies ($n = 3$), and case–control studies ($n = 37$). For the cohorts and cross-sectional studies we contacted authors to better define a control group (defined as group of individual without any respiratory disease), in order to equate to a case–control study and to collect data on GST gene polymorphism distribution. Association with asthma was evaluated in 35 studies on GSTM1, 31 on GSTT1, and 28 on GSTP1. In Table 1, other characteristics of the population based

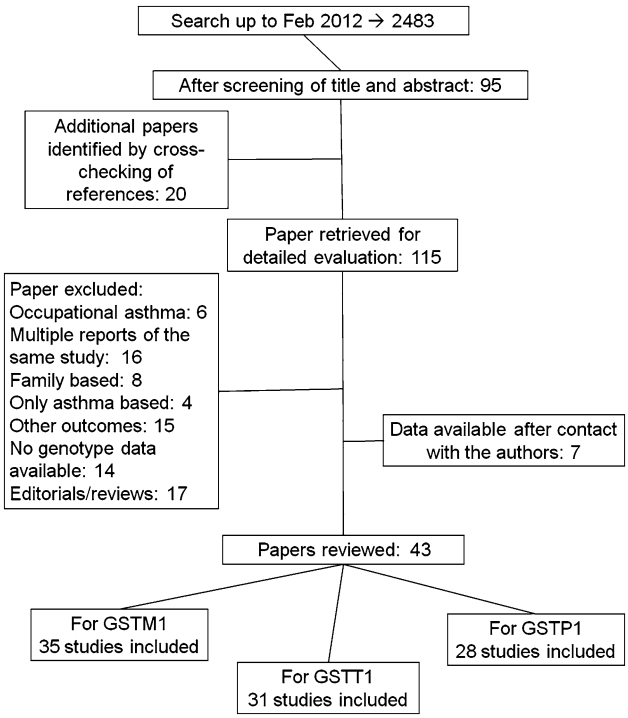

Fig. 1 The flow chart of the studies included in the meta-analysis

studies included in the meta-analyses are summarized, while genotype counts by disease outcome are reported in Supplemental Table 1 (Online Resource 1).

Meta-analyses on GSTM1 positive/null genotype

For the evaluation of the association of GSTM1 and asthma, 35 published studies were considered, a total of 6,661 affected and 17,220 non-affected individuals were included. The meta-analysis showed an increased risk of asthma associated with the GSTM1 null genotype (pooled OR = 1.12, 95 %CI = 0.99–1.26, $p = 0.072$; Fig. 2). This outcome, however, appears to be insignificant and large between-study heterogeneity was observed ($Q = 109.17$, $p < 0.001$; $I^2 = 68.9$ %). A funnel plot was performed to evaluate the publication bias of literature on GSTM1 and asthma. The shape of the funnel plot seemed asymmetrical (Supplemental Fig. 1; Online Resource 2), but the Begg and Mazumdar Rank correlation test ($p = 0.551$) and Egger's regression method (bias = 1.95, $t = 1.06$, $p = 0.299$) highlighted no publication bias. Moreover, a temporal effect has been recognized in the study outcomes (Supplemental Fig. 2; Online Resource 3).

To explain the large heterogeneity in the general meta-analysis, stratification analyses were conducted. Firstly we considered ethnicity as a stratification variable. 16 studies were carried out on European populations, ten studies on Asian populations, four studies on Turkish population, and

Table 1 Characteristics of the studies evaluating the effects of GST genes on asthma risk

Study/year	Study population	Location/ethnicity	Adults children	Sample size	Definition of disease outcome
Fryer et al. [13]	Cases: patient database of the department of respiratory medicine of the North Staffordshire Hospital Controls: volunteers recruited at the department of respiratory medicine of the North Staffordshire Hospital	UK, North Staffordshire	Adults	202	Diagnosed by a physician. Atopic asthma: (1) a history of wheezing, cough, dyspnea, and/or chest tightness; (2) spirometric demonstration of airflow obstruction reversible with ab-agonist bronchodilator (15 % change in FEV1); and (3) positive atopic status. Non atopic asthma: asthma diagnosis (point 1–3) and a negative atopic status.
Chung et al. [31]	Cases and controls: volunteers from the employers of local government	Korea, Seoul	Adults	99	Diagnosed by a physician. Asthma diagnosis based on spirometry and methacholine test
Freidin et al. [24]	Cases: patients treated at Tomsk hospital Controls: N/A	Russia, Tomsk	N/A	126	N/A
Ivaschenko et al. [32]	Cases: patients attending the Institute of Pulmonology and St. Olga's Children's Hospital in St. Petersburg Controls: volunteers from St. Petersburg and North western Russia	Russia, St. Petersburg	Both	199	Diagnosed by a physician. Asthma diagnosis: standard spirometry and methacholine challenge test; to asses atopic status skin prick test was performed
Vavilin et al. [33]	N/A	Russia, Novosibirsk region	Children	204	N/A
Safranova et al. [18]	Cases: patients were recruited from the Municipal Children's Emergency Hospital No. 1 Controls: volunteers were recruited from the department of traumatology of the Municipal Children's Emergency Hospital No. 1 and from the Municipal Children's Hospital No. 1	Russia, Novosibirsk region	Children	298	N/A
Aynacioglu et al. [34]	Cases: outpatients of the Department of Pulmonology, Sahinbey Hastanesi, Gaziantep, Turkey Controls: staff of the Medical Faculty of Gaziantep and outpatients of other Departments of the same Hospital	Turkey, South-Est Anatolia, Gaziantep and around	Adults	475	Diagnosed by a physician. Asthma diagnosis on the basis of the protocol of The European Community Respiratory Health Survey (ECRHS)
Kabesh et al. [35]	Cases and controls were recruited in a cross-sectional study conducted in Munich and Dresden in 1995 and 1996. Asthmatics were defined on the basis of diagnosis criteria. For controls, we asked more information to the authors: only healthy individuals without any respiratory disease diagnosis or symptoms were chosen	Germany, Munich and Dresden	Children	1005	Diagnosed by a physician. Asthma diagnosis based on ISAAC questionnaire, pulmonary function testing, and bronchial challenge with hyperosmolar saline. Atopy was assessed by skin prick test.
Saadat et al. [22]	N/A	Iran	Adults	170	Diagnosed on the basis of at least two of three criteria: typical history of attacks of breathlessness and/or wheezing, nocturnal cough, chest tightness either spontaneously or triggered; (2) reversibility of FEV1, greater than 15 % after a standard dose of inhaled b2-agonist; (3) diurnal variability in peak expiratory flow (PEF) rate of greater than 20 %.

Table 1 continued

Study/year	Study population	Location/ethnicity	Adults children	Sample size	Definition of disease outcome
Tamer et al. [16]	Cases: patients who visited Mersin University Hospital Controls: healthy individuals who visited Mersin University Hospital for an annual check-up and hospital staff	Turkey, Mersin	Adults	204	Diagnosis based according to the American Thoracic Society statement. Atopy was defined by the presence of a personal history of allergies, seasonal rhinitis, eczema, or allergic conjunctivitis and a positive skin prick test response
Ebrahimi et al. [36]	Cases: patients of the Pulmonolgy Institute in Kiev, Ukraine Controls: N/A	Ukraine, Kiev city	Adults	348	Diagnosed by a physician. Asthma diagnosis: (1) recurrent breathlessness and chest tightness; (2) physician documented wheeze; (3) documented labile airflow obstruction with variability in serial peak expiratory flow rates greater than 15 %.
Zhang et al. [37]	N/A	China, Tangshan	Adults	120	N/A
Lee et al. [38]	Cross-sectional school based survey between February and June 2001	Taiwan, Tainan city	Children	266	Asthma diagnosis were based on a questionnaire; pulmonary function test based on the American Thoracic Society statement and methacoline challenge test.
Nickel et al. [39]	(a) Freiburg asthmatic population. Cases: patients were recruited at the Children's University Hospital in Freiburg, (b) Multicenter Allergy Study (MAS) population.	Germany, (a) Freiburg; (b) Berlino, Dusseldorf, Freiburg, Mainz, Monaco	Children	(a) $N = 300$, (b) $N = 205$	(a) Diagnosis included questionnaires on asthma symptoms and medication, determination of total and specific IgE antibodies, pulmonary function tests, determination of exercise-induced fall in FEV1, and bronchial histamine provocations. (b) Clinical diagnosis with pulmonary function tests and histamine provocations were performed at 7 years old
Oh et al. [40]	Cases: patients were recruited at the Allergy Clinic at Ajou University Hospital, Soonchunhyang University Seoul Hospital and Buchon Hospital, in Korea Controls: volunteers were recruited at the Allergy Clinic at Ajou University Hospital, Soonchunhyang University Seoul Hospital and Buchon Hospital, in Korea	Korea, Ajou, Seoul and Buchon	Adults	361	Diagnosis of asthma was based Bronchial hyperresponsiveness was assessed by themethacholine bronchial challenge test. Aspirin intolerant asthma was diagnosed on positive responses to a lysine aspirin (L-ASA) bronchoprovocation test for. Skin prick tests were performed to asses atopic status.
Arbag et al. [41]	Cases: patients with asthma diagnoses recruited at the Department of chest disease, Meram Medical School, University of Selcuk Controls: healthy people with no history of diseases were recruited at the Meram Medical School, University of Selcuk	Turkey, Konya	Adult	133	Diagnosed by a physician
Ercan et al. [42]	Cases: children who were diagnosed at the Pediatric Allergy and Asthma Unit of Hacettepe University, School of Medicine, Ankara, Turkey Controls: school children who responded negatively to an established and validated asthma questionnaire	Turkey	Children	567	Diagnosed by a physician; asthma diagnosis was based on GINA criteria

Table 1 continued

Study/year	Study population	Location/ethnicity	Adults children	Sample size	Definition of disease outcome
Holla et al. [43]	Cases: N/A Controls:N/A	Czech Republic, South Moravia region	Adults	1006	Diagnosed by a physician; asthma diagnosis was based on GINA criteria
Plutecka et al. [25]	Cases: N/A Controls: N/A	Poland	Adults	609	N/A
Xi et al. [63]	Cases: N/A Controls: N/A	China	N/A	107	N/A
Abdel-Alim et al. [14]	Cases and controls: attendants of the outpatient clinic of allergy and immunology, Cairo University Paediatric Hospital	Egypt, Cairo	Children	90	Diagnosed by a physician; asthma diagnosis was based on GINA criteria
Hanene et al. [15]	N/A	Tunisia, Ariana	Children	217	Asthma diagnosis was based on a questionnaire
Imboden et al. [44]	Cases and controls: participants of the SAPALDIA cohorts	Switzerland	Adults	4053	Asthma diagnosis was based on a self-report of physician-diagnosed asthma; valid spirometry and bronchial challenge data
Kamada et al. [45]	(a) Cases: patients of the Osaka Prefectural Medical Center for Respiratory and Allergic Diseases and the Miyatake Asthma Clinic Controls: volunteers recruited in the Tokyo and Osaka areas (b) Cases: patients at Hospitals in the Sendai area Controls: volunteers recruited in the Sendai area	Japan	Both	Group (a) 1101, group (b) 299	Diagnosed by a physician; asthma diagnosis was based on the American Thoracic Society criteria
Mak et al. [46]	Cases: patients at asthma clinic at the Queen Mary Hospital in Hong Kong Controls: volunteers recruited from a random population sample in Hong Kong	China, Hong Kong and Guandong Province	Adults	630	Diagnosed by a physician; asthma diagnosis was based on the American Thoracic Society criteria
Salam et al. [47]	Cases and controls were drawn from the larger Children's Health Study population	California, U.S.A	Children	3673	Asthma diagnosis was based on parental report of physician-diagnosed asthma
Babusikova et al. [48]	Cases: patients of Jessenius Faculty of Medicine in Martin, Slovakia Controls: children recruited in the Department of Pediatrics of Jessenius Faculty of Medicine in Martin, Slovakia	Slovakia,	Children	225	Diagnosed by a physician; asthma diagnosis was based on a questionnaire and GINA criteria
Castro-Giner et al. [49]	Cases and controls: participants of the European Community Respiratory Health Survey II (ECRHS II) study	Sweden, United Kingdom, Spain, Germany, France and Belgium	Adults	2577	Asthma diagnosis was based on a questionnaire, a bronchial challenge with methacholine; atopy was defined as sensitization to any allergen
Federova et al. [50]	N/A	Russia, Bashkortostan	Both	184	Asthma diagnosis was based on clinical and laboratory data, including the results of skin tests and spirography
Gravina et al. [51]	N/A	Italy, Rome	Children	167	Diagnosed by a physician; asthma diagnosis was based on the Global Initiative on Asthma (GINA) criteria, symptoms and use of anti-asthma medication

Table 1 continued

Study/year	Study population	Location/ethnicity	Adults children	Sample size	Definition of disease outcome
Li et al. [52]	Cases and controls: participants of the Taiwanese Children's Health Study (TCHS).	Taiwan regions	Children	1092	Asthma diagnosis was based on a preliminary questionnaire and a stage II questionnaire, which was modified from the Chinese translated version of International Study of Asthma and Allergies in Childhood (ISAAC) core questionnaire
Polonikov et al. [53]	Cases: patients recruited at the Division of Pulmonology, Kursk Regional Clinical Hospital Controls: healthy individuals recruited at Division of Pulmonology, Kursk Regional Clinical Hospital	Russia, Central Russia	Adults	429	Diagnosed by a physician on the basis of characteristic symptoms (i.e. reversibility of airway obstruction, airway hyperresponsiveness to methacholine)
Ozcan et al. [54]	Cases: patients of the Department of Otorhinolaryngology, School of Medicine, Mersin University Controls: healthy individuals who visited the same hospital for an annual check-up and hospital staff	Turkey, South region	Adults	189	N/A
Passos-Lima et al. [23]	Cases: patients of the University Hospital of the State University of Campinas Controls: healthy blood donors from the same University Hospital	Brazil, Southeastern Brazil	Both	344	asthma diagnosis was based on the Global Initiative on Asthma (GINA) criteria
Undarmaa et al. [55]	N/A	Japan, Osaka and Chiba cities	Both	Group (a) 983, group (b) 656	Group (a) Asthma was diagnosed according to the American Thoracic Society criteria Group (b) Asthma diagnosis was based on the International Study of Asthma and Allergies in Childhood (ISAAC) questionnaire
Abd El-Aal et al. [56]	Cases and controls enrolled during their regular follow-up at Al Mounira hospital.	Egypt	Children	70	Diagnosed by a physician. Asthma patients were diagnosed and classified according to GINA criteria
Hersoug et al. [57]	Cases and controls: participants of the Health 2006 study	Denmark, South-Western part of Copenhagen	Adults	2083	Asthma diagnosis was based on a self-administrated questionnaire, Assessment of lung function and assessment of atopic status.
Mahmoud et al. [58]	N/A	Egypt, Alexandria	Adults	100	Asthma diagnosis was based on GINA criteria, assessment of atopic status and assessment of lung function by a spirometric measurament
Tatarskyy et al. [59]	Cases: N/A Controls: unrelated healthy adults from different regions of Ukraine	Ukraine, Kyiv and Dniprodzerzhynsk regions	Both	Group (a) 138, group (b) 148	Diagnosed by a physician. Asthma diagnosis was based on the basis of the recommendations of the Ministry of Health of Ukraine and GINA criteria
Karam et al. [60]	Cases: patients admitted and followed in Pediatrics and Chest Departments, Faculty of Medicine, Zagazig University Controls: randomly selected from the same geographical region	Egypt, Sharkia governorate	Children	294	Asthma diagnosis was based on the American Thoracic Society Statement, Pulmonary function tests and Skin prick test assays
Munoz et al. [19]	Cases and controls were recruited from the Instituto Mexicano del Seguro Social (IMSS) of Torreón City, Coahuila	Mexico, Torreón City	Children	201	Asthma diagnosis was based on the ISAAC questionnaire on respiratory and allergic symptoms

Table 1 continued

Study/year	Study population	Location/ethnicity	Adults children	Sample size	Definition of disease outcome
Piacentini et al. [61]	Cases and controls were recruited from the Department of Pediatrics, University of Chieti (Italy).	Italy, Chieti	Children	253	Asthma was diagnosed by a physician. Asthma diagnosis was based on GINA criteria. Lung function and atopic status were assessed
Piacentini et al. [62]	Cases and controls were recruited from the clinical pathophysiology center of "San Giovanni Calibita" Fatebenefratelli Hospital of Rome	Italy, Rome	Adults	399	Asthma was diagnosed by a physician. Asthma diagnosis was based on GINA criteria

three studies evaluated the Mediterranean African population. Two studies with particular ethnic origins (a study on Iranian population [22] and a study on a mixed European/African-American population [23]) were not reported. No statistical association was observed in each ethnic group (Europe: pooled OR = 1.08, 95 %CI = 0.98–1.19; Asia: pooled OR = 1.07, 95 %CI = 0.84–1.36; Turkey: pooled OR = 1.10, 95 %CI = 0.61–1.99; Mediterranean Africa: pooled OR = 0.84, 95 %CI = 0.28-–2.52) and a high heterogeneity within each group was observed, with the exception of the European subgroup in which there was a consistency (Europe: $I^2 = 24.6$ %, $p = 0.176$; Asia: $I^2 = 76.2$ %, $p < 0.001$; Turkey: $I^2 = 72.4$ %, $p < 0.013$; Mediterranean Africa: $I^2 = 88.9$, $p < 0.001$). In the stratification analysis by urbanization, we considered 18 studies on metropolis locations, and 15 studies on country-side locations. Two studies were not reported: a study conducted in a city [24], and a study without information about the sampling location [22]. The stratification analysis by urbanization did not reveal any significant associations (metropolis: pooled OR = 1.12, 95 %CI = 0.93–1.35; country-side: pooled OR = 1.07, 95 %CI = 0.91–1.25) and highlighted the presence of a high heterogeneity within each group (metropolis: $I^2 = 70.2$, $p < 0.001$; country-side: $I^2 = 66.3$, $p < 0.001$). In the age-stratification analysis we considered 14 "Cases: Adults and Controls: Adults" studies, 11 "Cases: Children and Controls: Children" studies, four "Cases: Children and Controls: Adults" studies, and two "Cases: Children and Controls: Children–Adults" studies; we did not report four studies without age information. The OR estimated for each subgroup was not statistically significant ("Cases: Adults and Controls: Adults": pooled OR = 1.08, 95 %CI = 0.91–1.27; "Cases: Children and Controls: Children": pooled OR = 1.07, 95 %CI = 0.86–1.32; "Cases: Children and Controls: Adults": pooled OR = 1.10, 95 %CI = 0.71–1.71; "Cases: Children and Controls: Children–Adults": pooled OR = 1.45, 95 %CI = 0.89–2.37) and high heterogeneity was observed in each subgroup, with the exception of "Cases: Children and Controls: Children–Adults" ("Cases: Adults and Controls: Adults": $I^2 = 62.4$ %, $p = 0.001$; "Cases: Children and Controls: Children": $I^2 = 66.9$ %, $p = 0.001$; "Cases: Children and Controls: Adults": $I^2 = 73.6$ %, $p = 0.010$; "Cases: Children and Controls: Children–Adults": $I^2 = 0.0$ %, $p = 0.368$).

Meta-analyses on GSTT1 positive/null genotype

A total of 31 published studies on the association of GSTT1 and asthma was taken into consideration, including a total of 5,454 cases and 14,513 controls. The meta-analysis for GSTT1 shows an OR of 1.33 (95 % CI 1.10–1.60; $p = 0.003$) with an increased risk of asthma

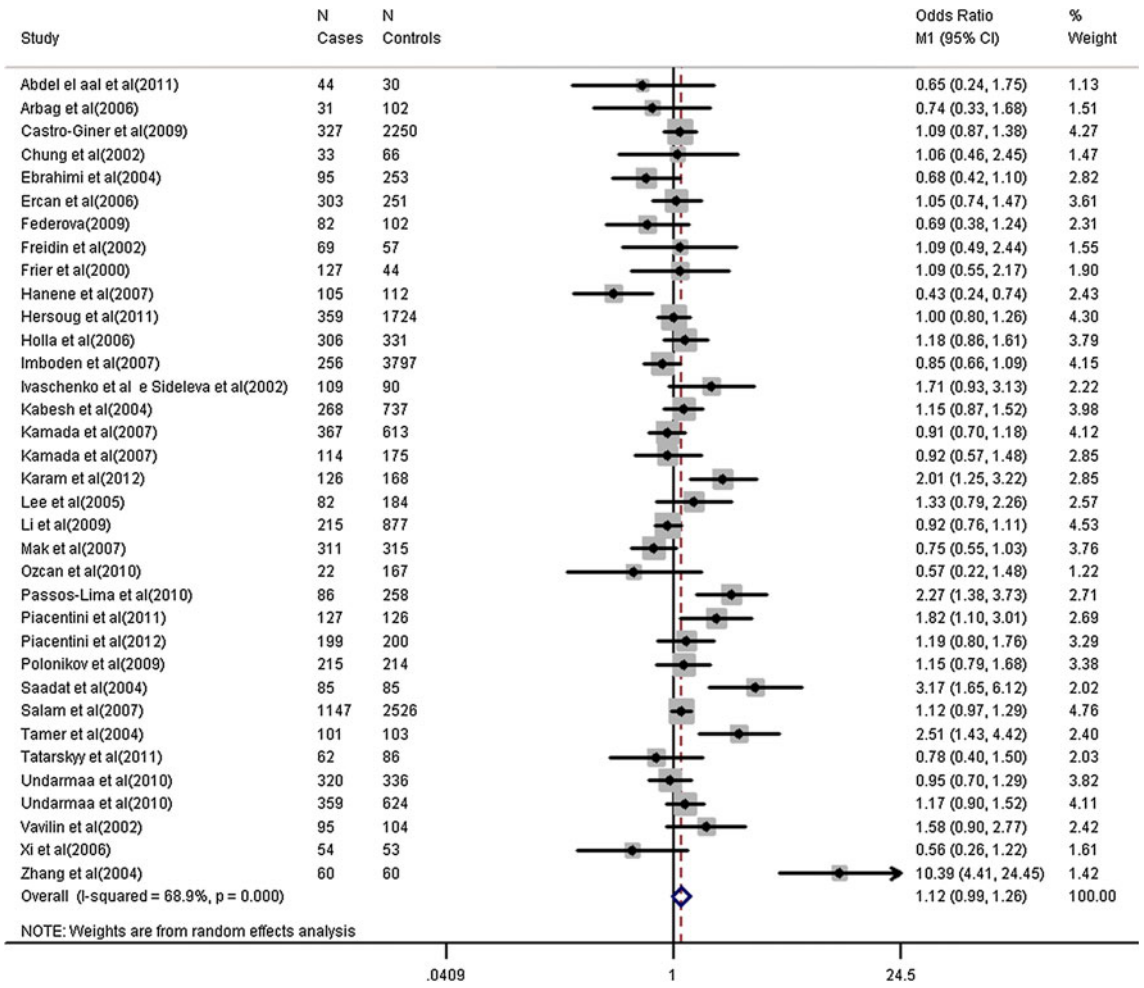

Fig. 2 Forest plot (random-effects model) of the association between GSTM1 null genotype and asthma

associated with the GSTT1 null genotype (Fig. 3). This estimate appears to be significant, but a large between-study heterogeneity was observed ($Q = 118.58$, $p < 0.001$; $I^2 = 74.7$ %). The funnel plot analysis revealed publication bias of literature on GSTT1 and asthma (Supplemental Fig. 3; Online Resource 4). The Begg and Mazumdar Rank correlation test ($p = 0.003$) and Egger's regression method (bias = 8.76, $t = 3.27$ $p = 0.003$) consistently confirmed the visual inspection of the funnel plot. After the trim and fill procedure, there was a relevant change in overall summary estimate (OR); the procedure suggested that almost 8 studies had to be included to convert the combined p value to a non-significant value ($p = 0.946$) and this brought the pooled OR of 1.33–1.01. Conversely, no temporal effect seemed to be present in the study outcomes (Supplemental Fig. 4; Online Resource 5).

In the stratification analysis by ethnicity, 18 studies were carried out on European populations, four studies on Asian populations, four studies on Turkish populations, and three studies on Mediterranean African populations. The studies conducted by Saadat et al. [22] on the Iranian population and by Passos-Lima et al. [23] on European/African-American population were not reported. No significant association was observed in the ethnic groups (Europe: pooled OR = 1.18, 95 %CI = 0.98–1.43; Asia: pooled OR = 2.12, 95 %CI = 0.62–7.26; Turkey: pooled OR = 1.41, 95 %CI = 0.93–2.16; Mediterranean Africa: pooled OR = 1.73, 95 %CI = 0.60–4.96) and the studies were characterized by high heterogeneity within the subgroups, with the exception of the Turkish group (Europe: $I^2 = 66.0$ %, $p < 0.001$; Asia: $I^2 = 92.5$ %, $p < 0.001$; Turkey: $I^2 = 37.2$ %, $p = 0.189$; Mediterranean Africa: $I^2 = 86.3$ %, $p = 0.001$).

For the stratification analysis by urbanization, we considered the same studies of GSTM1. The analysis revealed significant association with high heterogeneity for "metropolis" (pooled OR = 1.65, 95 %CI = 1.12–2.42; $I^2 = 85.0$ %, $p < 0.001$) and no association with low heterogeneity for "country-side" (pooled OR = 1.05, 95 %CI = 0.91–1.21; $I^2 = 27.2$ %, $p = 0.156$).

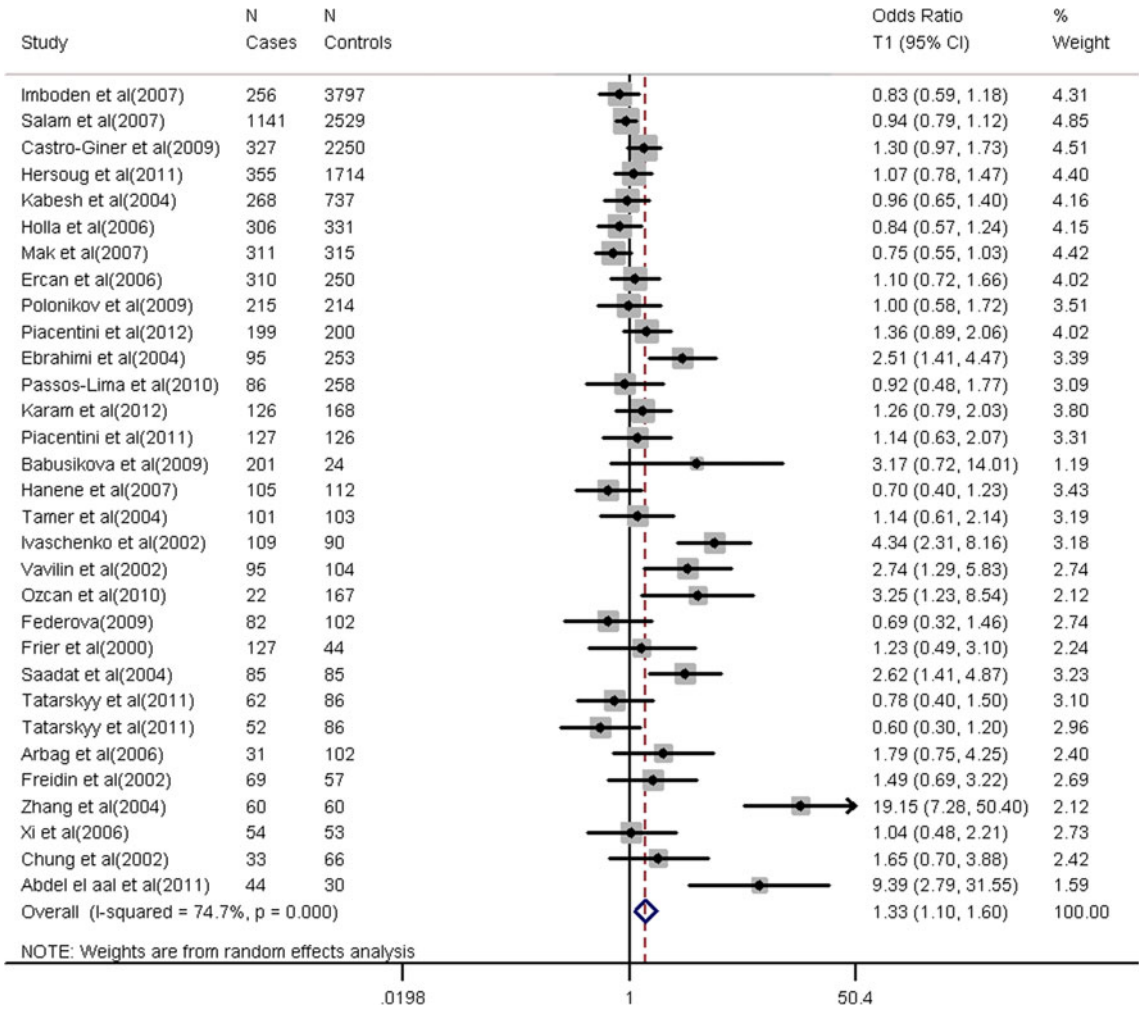

Fig. 3 Forest plot (random-effects model) of the association between GSTT1 null genotype and asthma

Regarding the population age-stratification analysis, we considered 13 "Cases: Adults and Controls: Adults" studies, nine "Cases: Children and Controls: Children" studies, three "Cases: Children and Controls: Adults" studies, and two "Cases: Children and Controls: Children–Adults" studies; we did not report four studies without age information. Significant associations were observed for "Cases: Children and Controls: Children–Adults" and "Cases: Children and Controls: Adults" subgroups ("Cases: Adults and Controls: Adults": pooled OR = 1.24, 95 %CI = 0.99–1.54; "Cases: Children and Controls: Children": pooled OR = 1.30, 95 %CI = 0.90–1.86; "Cases: Children and Controls: Adults": pooled OR = 0.76, 95 %CI = 0.52–1.12; "Cases: Children and Controls: Children–Adults": pooled OR = 2.80, 95 %CI = 1.09–7.21), but only in the "Cases: Children and Controls: Adults" subgroup was no significant heterogeneity observed ("Cases: Adults and Controls: Adults": $I^2 = 64.2$ %, $p = 0.001$; "Cases: Children and Controls: Children": $I^2 = 67.0$ %, $p = 0.683$; "Cases: Children and Controls: Adults": $I^2 = 74.7$ %, $p < 0.001$; "Cases: Children and Controls: Children–Adults": $I^2 = 68.6$ %, $p = 0.074$).

Meta-analyses on GSTP1 Ile105Val polymorphism

A total of 28 published studies with 5,559 affected and 9,199 non-affected individuals was available for the meta-analysis of GSTP1*Ile105Val polymorphism. For this variant, two genetic models were considered: dominant and recessive. Regarding the general meta-analysis, no significant association and high heterogeneity were found both for the dominant (pooled OR: 0.93, 95 %CI: 0.82–1.06; $Q = 59.44$, $p < 0.001$, $I^2 = 54.6$ %) and for the recessive (pooled OR = 0.92, 95 %CI = 0.73–1.15, $Q = 60.90$, $p < 0.001$, $I^2 = 57.3$ %) genetic models (Figs. 4, 5). The funnel plots did not reveal publication bias in literature on GSTP1 and asthma in both considered genetic models

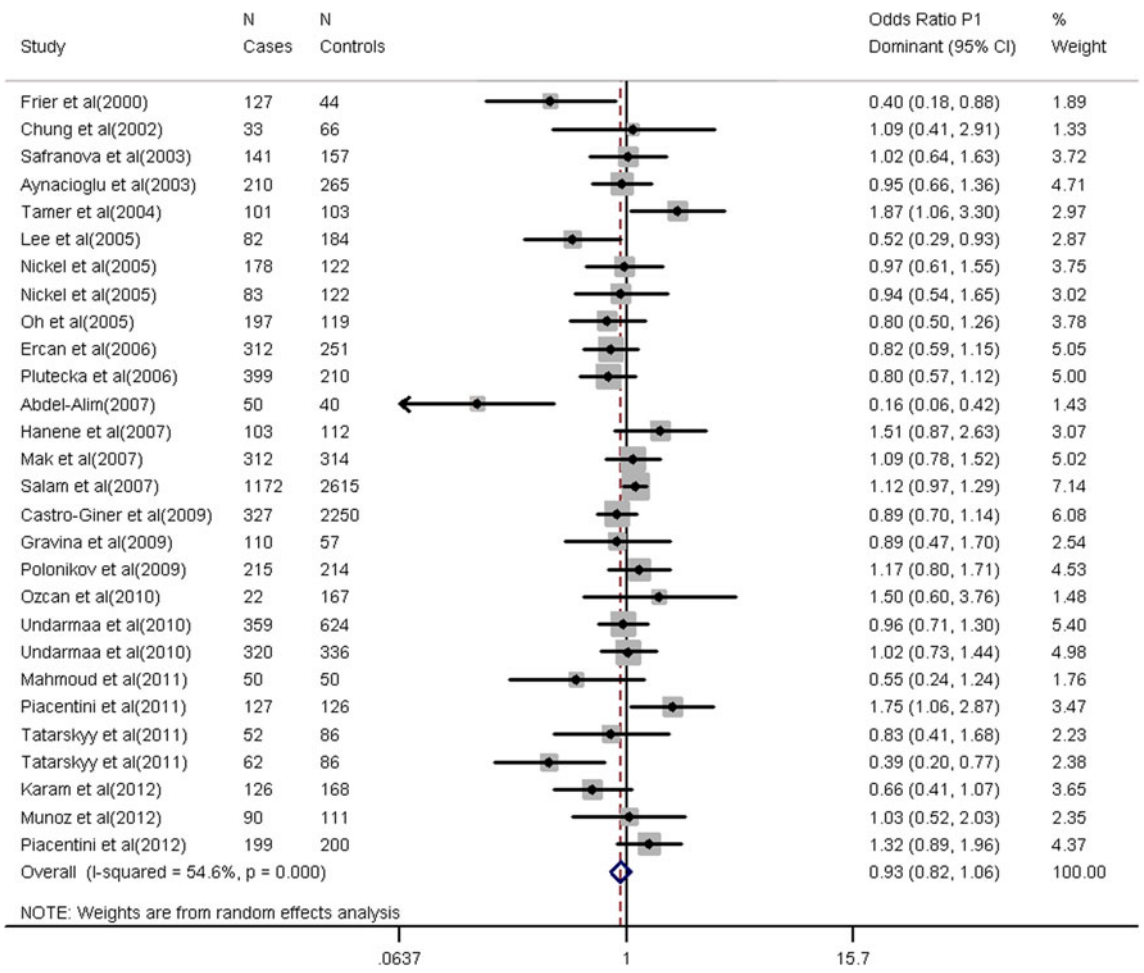

Fig. 4 Forest plot (random-effects model) of the association between GSTP1*I105V polymorphism (dominant genetic model) and asthma

(Supplemental Figs. 5 and 6; Online Resources 6, 7), and no temporal effects were observed (Supplemental Fig. 7 and 8; Online Resources 8, 9). The Begg and Mazumdar Rank correlation test ($p_{\text{dominant}} = 0.213$, $p_{\text{recessive}} = 0.868$) and Egger's regression model (dominant: bias = 0.34, $t = -1.90$, $p = 0.07$; recessive: bias = 0.04, $t = -0.29$, $p = 0.777$) also confirmed this assessment.

In the stratification analysis by ethnicity, 13 studies were carried out on European populations, five studies on Asian populations, four studies on Turkish population, and four studies on the Mediterranean African populations. The single study conducted by Munoz et al. [19] on Mexican population was not reported. For the dominant model, the subgroup analysis by ethnicity highlighted no significant association and high heterogeneity for each subgroup, with the exception of the Asian and Turkish subgroups where the non-significant association were linked to low heterogeneity across studies pooled (Europe: pooled OR = 0.96, 95 %CI = 0.82–1.14, $I^2 = 52.3$ %, $p = 0.014$; Asia: pooled OR = 0.93, 95 %CI = 0.78–1.11, $I^2 = 10.4$ %, $p = 0.349$; Turkey: pooled OR = 1.11, 95 %CI = 0.77–1.59, $I^2 = 55.7$ %, $p = 0.079$; Mediterranean Africa: pooled OR = 0.59, 95 %CI = 0.27–1.29, $I^2 = 82.4$ %, $p = 0.001$). For the recessive model, a similar outcome was observed (Europe: pooled OR = 1.28, 95 %CI = 0.88–1.20, $I^2 = 0.0$ %, $p = 0.457$; Asia: pooled OR = 1.12, 95 %CI = 0.69–1.82, $I^2 = 0.0$ %, $p = 0.578$; Turkey: pooled OR = 0.89, 95 %CI = 0.32–2.44, $I^2 = 83.4$ %, $p < 0.001$; Mediterranean Africa: pooled OR = 0.52, 95 %CI = 0.17–1.61, $I^2 = 83.8$ %, $p < 0.001$). For the urbanization stratification, only one study was conducted in a city [25] and, thereby, it was not reported. 20 studies were carried out on metropolis locations and 15 studies were carried out on country-side locations. For the dominant model, the subgroup analysis by urbanization highlighted no associations and high heterogeneity within each group (metropolis: pooled OR = 0.84, 95 %CI = 0.69–1.02, $I^2 = 52.7$, $p = 0.009$; country-side: pooled OR = 1.05,

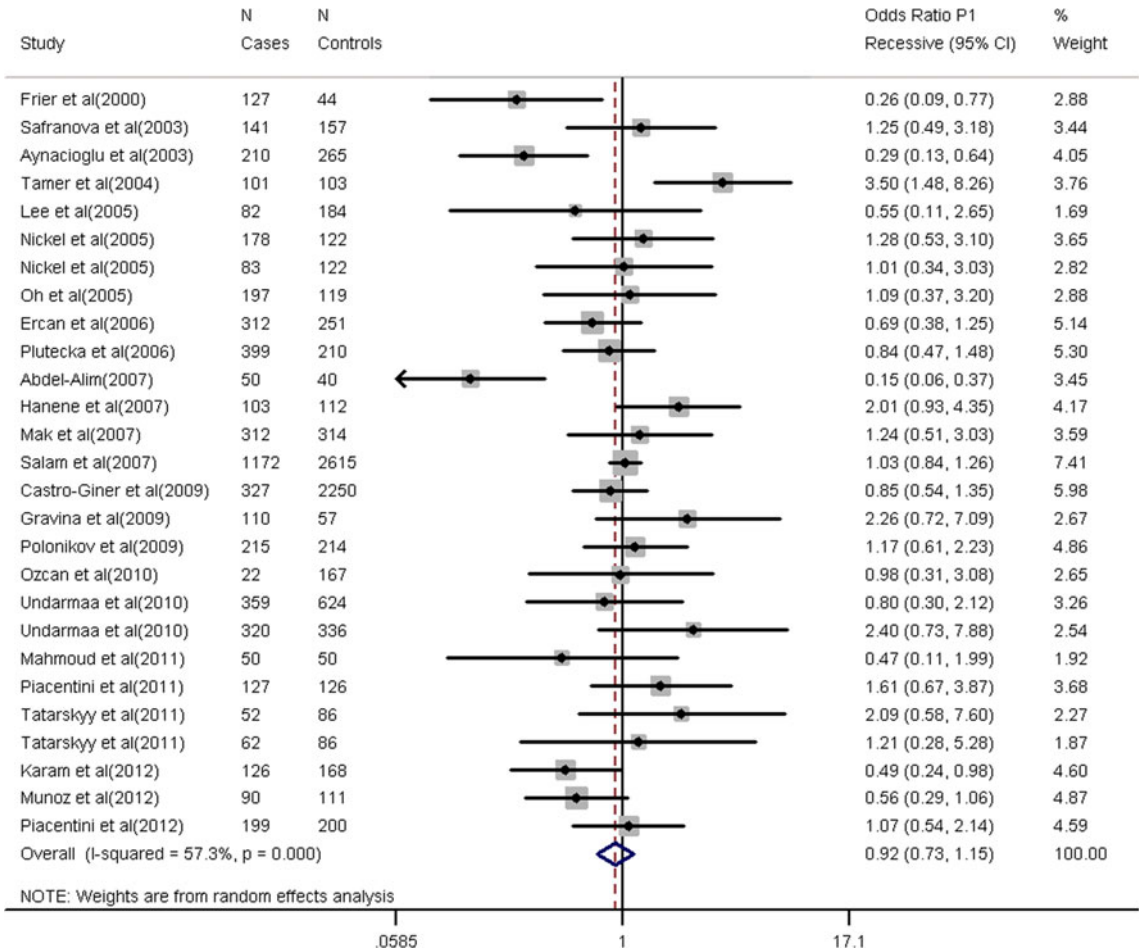

Fig. 5 Forest plot (random-effects model) of the association between GSTP1*I105V polymorphism (recessive genetic model) and asthma

95 %CI = 0.88–1.25, $I^2 = 55.2$, $p = 0.011$). The same results were observed in urbanization stratification for the recessive genetic model (metropolis: pooled OR = 0.81, 95 %CI = 0.52–1.24, $I^2 = 59.0$, $p = 0.003$; country-side: pooled OR = 1.03, 95 %CI = 0.77–1.38, $I^2 = 56.4$, $p = 0.003$). In the stratification analysis by population age, we considered 12 "Cases: Adults and Controls: Adults" studies and 13 "Cases: Children and Cases: Children" studies. three studies were not reported because no age information was available. This stratification analysis showed no association and high heterogeneity within each group for both dominant ("Cases: Adults and Controls: Adults": pooled OR = 0.98, 95 %CI = 0.84–1.14, $I^2 = 63.3$ %;$p = 0.001$; "Cases: Children and Controls: Children": pooled OR = 0.92, 95 %CI = 0.76–1.13, $I^2 = 41.9$ %; $p = 0.062$) and recessive ("Cases: Adults and Controls: Adults": pooled OR = 0.87, 95 %CI = 0.61–1.24, $I^2 = 55.8$ %; $p = 0.009$; "Cases: Children and Controls: Children": pooled OR = 0.92, 95 %CI = 0.65–1.30, $I^2 = 41.9$ %; $p = 0.001$) models.

Discussion

GSTs are involved in many detoxification processes, and it has been hypothesized that genetic alterations of GST enzymes may affect the ability of the airways to handle toxic substances and may influence airway inflammation [12].

A number of studies has investigated the role of functional GST polymorphisms in asthma susceptibility both in children and adults, with contrasting results. To the best of our knowledge, two previous meta-analyses have attempted to clarify the association between GST genes and asthma, but these studies showed conflicting outcomes [2, 20]. Saadat and Ansari-Lari [20] stated that GSTM1 and GSTT1 null genotypes are significantly associated with asthma phenotypes, especially for non-smokers and adults. Conversely, Minelli et al. [2] reported no significant association between GSTM1, GSTP1, and GSTT1 and asthma, with high heterogeneity among the studies, even though they were stratified by asthma diagnosis.

The aim of our study was to perform a meta-analysis that included independent genetic association studies on GSTM1, GSTP1, and GSTT1, evaluating also the effect of potential confounding variables (i.e. ethnicity, population age, and urbanization).

Our results highlighted that no significant associations with asthma susceptibility were observed for *GSTM1* and *GSTP1* gene polymorphisms whereas significant outcomes were detected for GSTT1 positive/null genotype. However, high between-study heterogeneity was identified in all the general analyses. This heterogeneity among the genetic association studies does not ensure that these results are reliable, though [26]. Moreover, the asymmetrical distribution of the studies on *GSTT1* genes in the funnel plot suggests the presence of a publication bias. In order to verify whether the heterogeneity among the studies was caused by the confounding effects of ethnicity, population age, and urbanization, we performed different stratification analyses. For GSTM1 and GSTP1 in which no associations with high heterogeneity were observed in the general analysis, the stratification revealed, in some cases, no associations with low heterogeneity, leaving most of the stratification analyses with high heterogeneity within the subgroups. Regarding GSTT1, in which a positive association was observed, a significant association with low heterogeneity was observed only in the "children versus adults" studies, whereas, in most of the other subgroups the non-significant associations were related to high heterogeneity. Therefore, the uncertainty about both the significant and non-significant results of our meta-analysis was confirmed, even after stratification analyses. Furthermore, for GSTT1 we obtained a non-significant association correcting the effect of publication bias through the trim and fill procedure. This situation is probably due to disease pathogenesis. Indeed, asthma expression is a complex process within genetics, and environment strongly impact it [27].

Our stratification analysis has tried to address confounding effects of environmental (urbanization), demographic (population age) and genetic (ethnicity) factors. Indeed, as previously reported by other authors, the inhalation of hazardous environmental factors may increase the risk for disease development or worsening of symptoms [28]. Given the multiplicity of exposures, there are many possible effects from a single pollutant, as well as from its interactions [29]. Furthermore, genetic predisposition may alter the ability of the airways to protect itself against these inhaled toxic substances from the environment [27] and genetic differences in the population structure of antioxidant enzymes may influence the genetic association between GSTs and asthma susceptibility [30]. Although our approach seems to explain a portion of this complex picture in a few cases, further studies on interactions of GST genes with environmental oxidative exposures and with other antioxidant genes are required to explain the role of GST enzymes in asthma pathogenesis.

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Conflict of interest The authors stated that there are no conflicts of interest regarding the publication of this article.

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