Current Allergy and Asthma Reports (2018) 18: 20
https://doi.org/10.1007/s11882-018-0771-0

ALLERGIES AND THE ENVIRONMENT (M HERNANDEZ, SECTION EDITOR)

Do Glutathione S-Transferase Genes Modify the Link between Indoor Air Pollution and Asthma, Allergies, and Lung Function? A Systematic Review

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Published online: 20 March 2018

Abstract

Purpose of Review Glutathione S-transferase (GST) genes are involved in oxidative stress management and may modify the impact of indoor air pollution. We aimed to assess the influence of GST genes on the relationship between indoor air pollution and allergy/lung function.

Recent Findings Our systematic review identified 22 eligible studies, with 15 supporting a gene-environment interaction. Carriers of GSTM1/T1 null and GSTP1 val genotypes were more susceptible to indoor air pollution exposures, having a higher risk of asthma and lung function deficits. However, findings differed in terms of risk alleles and specific exposures. High-exposure heterogeneity precluded meta-analysis.

Summary We found evidence that respiratory effects of indoor air pollution depend on the individual's GST profile. This may help explain the inconsistent associations found when gene-environment interactions are not considered. Future studies should aim to improve the accuracy of pollution assessment and investigate this finding in different populations.

Keywords Epidemiology · Genetics · Rhinitis · Asthma · Atopic dermatitis · Reviews

Abbreviations

AD	Atopic dermatitis
CI	Confidence interval
ETS	Environmental tobacco smoke
FEV_1	Forced expiratory volume in 1 s
FVC	Forced vital capacity
GSTs	Glutathione s-transferases
$VFRC_{max}$	Maximal flow at functional residual capacity
NOS	Newcastle-Ottawa quality assessment scale
OR	Odds ratio
PEFR	Peak expiratory flow rate
NQO1	Quinone oxidoreductase-1
ROS	Reactive oxygen species
SES	Socio-economic status
SE	Standard error

Prior presentation This work was presented in Cleaner Air, Better Health: CAR Annual Symposium 2016 in Sydney, Australia, by Xin Dai in 05/05/2016.

This article is part of the Topical Collection on *Allergies and the Environment*

Electronic supplementary material The online version of this article (https://doi.org/10.1007/s11882-018-0771-0) contains supplementary material, which is available to authorized users.

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Introduction

The global prevalence of allergic diseases has increased steadily for more than 50 years [1], initially due to increasing prevalence in the developed countries and more recently in developing countries [2]. The etiology of these conditions is believed to be complex [3, 4]. Exposure to indoor air pollution has been hypothesized to be particularly relevant to allergic disease pathogenesis as people spend much of their time indoors [5]. Recognized indoor air pollutants include tobacco

smoke [6, 7], dust [8, 9], and pollutants generated from cooking and heating [10]. However, studies have failed to find consistent associations between indoor air pollutants and allergic disease [11, 12]. The reason for these inconsistent findings may be partly related to failure to account for potential gene-environment interactions.

One key group of genes proposed to modify the impact of air pollutants on asthma and allergies are the Glutathione S-transferases (GSTs) genes [13, 14]. The GSTs are major phase II detoxification enzymes found mainly in the cytosol and include the Mu (GSTM1), Theta (GSTT1), and Pi (GSTP1) classes [15]. These enzymes provide the first line of defense against oxidative stress through their ability to protect cells from reactive oxygen species (ROS) [16•, 17]. ROS are active participants in complex biological processes, including allergic sensitization and allergic asthma [18]. ROS can cause airway inflammation, which may result in airway dysfunction [19, 20]. The GSTM1 and GSTT1 genes have null alleles resulting in partial or complete loss of the enzyme activity [16•, 17, 21–23]. Despite the biological plausibility of a relationship between GST polymorphisms and allergies and poorer lung function, the supporting evidence is scarce and inconsistent. A 2010 systematic review investigated the role of GST genes in asthma, finding no direct association [24•]. The authors postulated that the null findings may be due to not including exposure data. Failure to take gene-environment interactions into account in this review may explain the absence of consistently reported observable effects of the GST genes. There have been no previous systematic syntheses of the literature focusing on the interaction between indoor environmental exposures and GST genes on outcomes of allergic disease and lung function.

Establishment of this potential gene-environment interaction may help to explain the inconsistencies found where these factors are investigated in isolation, and help identify an important subpopulation requiring intervention to prevent respiratory morbidity. We aimed to address this through a systematic review and meta-analysis of the existing literature investigating the influence of GST genes on the relationship between indoor air pollution and allergy/lung function.

Methods

We performed a systematic review of published studies that reported original data, according to PRISMA guidelines. The review protocol was registered with PROSPERO (CRD42017062275).

Literature Search and Study Selection

We searched PubMed and Embase databases from inception for journal articles written in English. The final search was performed on 25/03/2017. We used search terms in PubMed to identify articles having the following three categories in common: indoor air pollution (MeSH heading "smoke," "air pollution, indoor"), and, allergy (MeSH heading "asthma," "rhinitis," "allergic," "eczema," "dermatitis;" "food allergy") or lung function (MeSH heading "respiratory function test"), and GST (MeSH heading "glutathione s-transferase"). A similar search strategy was developed for Embase (see online supplement 1 and 2). The search was performed by two independent investigators (XD and GB).

Eligibility Criteria

To be included, a study had to meet the following criteria: (1) human population, (2) indoor air pollution exposure (smoke, cleaning products, heating, cooking, air quality and airborne exposure), (3) investigated interaction by GST genes, (4) assessed any allergic disease (asthma, rhinitis, eczema, dermatitis and food allergy) or lung function outcome, (5) cohort study, cross-sectional, or case-control study design. Non-English language papers, unpublished studies, and studies not reporting original data (reviews, editorials, and conference abstracts) were excluded. Two authors (XD and GB) independently evaluated all articles retrieved.

Data Extraction

Two researchers (XD and GB) independently reviewed titles and abstracts, and where necessary full texts, to determine if they met the inclusion criteria as described above. Any disagreements were settled by a third author (CL). For each included study, information regarding study design, target population, time of exposure measurement, outcome measures and age, interactions investigated, covariates included, comparison, and association/findings were extracted into a standard table and checked by two authors (XD and GB). Exposure and outcome definitions and effect estimates (odd ratios (OR), relative risks, prevalence ratios, lung function parameters) with 95% confidence interval (95% CI) were extracted where available for inclusion in meta-analyses.

Quality Assessment

Two authors (XD and GB) independently assessed the quality and bias of included studies using the Newcastle-Ottawa quality assessment scale (NOS). Each study was scored using a star (*) method to report the quality based on selection of sample, comparability and the ascertainment of the exposure or outcome measures. All papers were classified into high (8–9*), medium (6–7*), low (4–5*), and unsatisfactory quality (0–3*) based on the Newcastle-Ottawa quality score (supplemental table 1). We resolved any disagreement through

consensus with a third author (CL). We aimed to perform forest plots to address potential publication bias if applicable.

Results

Search Results

From a total of 576 citations identified initially, 71 were selected for full-text review and 22 met the inclusion criteria. Of these, 16 papers evaluated allergy-related outcomes, and 8 measured lung function outcomes (2 papers measured both asthma and lung function (Fig. 1). Supplemental table 2 outlines reasons for exclusion at the full-text review stage. We were unable to perform meta-analyses due to high heterogeneity, with specific gene-pollutant-outcome combinations lacking numbers.

Characteristics of the Included Studies

Of the 16 studies with allergic disease outcomes (Table 1), 14 investigated outcomes of asthma/wheeze [5, 25–34•, 35••, 36, 37••], and the remainder investigated outcomes of rhinitis [35••, 38] and dermatitis [35••, 39]. The 8 studies [5, 26, 40–45] investigating lung function outcomes (Table 2) used a variety of measurements including maximal flow at functional residual capacity ($VFRC_{max}$), forced expiratory volume in 1 s (FEV_1)%, forced vital capacity (FVC)%, peak expiratory flow rate (PEFR)%, FEV_1, FVC, FEV_1/FVC, FEV_1/height^2, 5-year change in FEV_1%, mean annual change in FEV_1, FVC, and high/low lung function categories. The ages at which outcomes

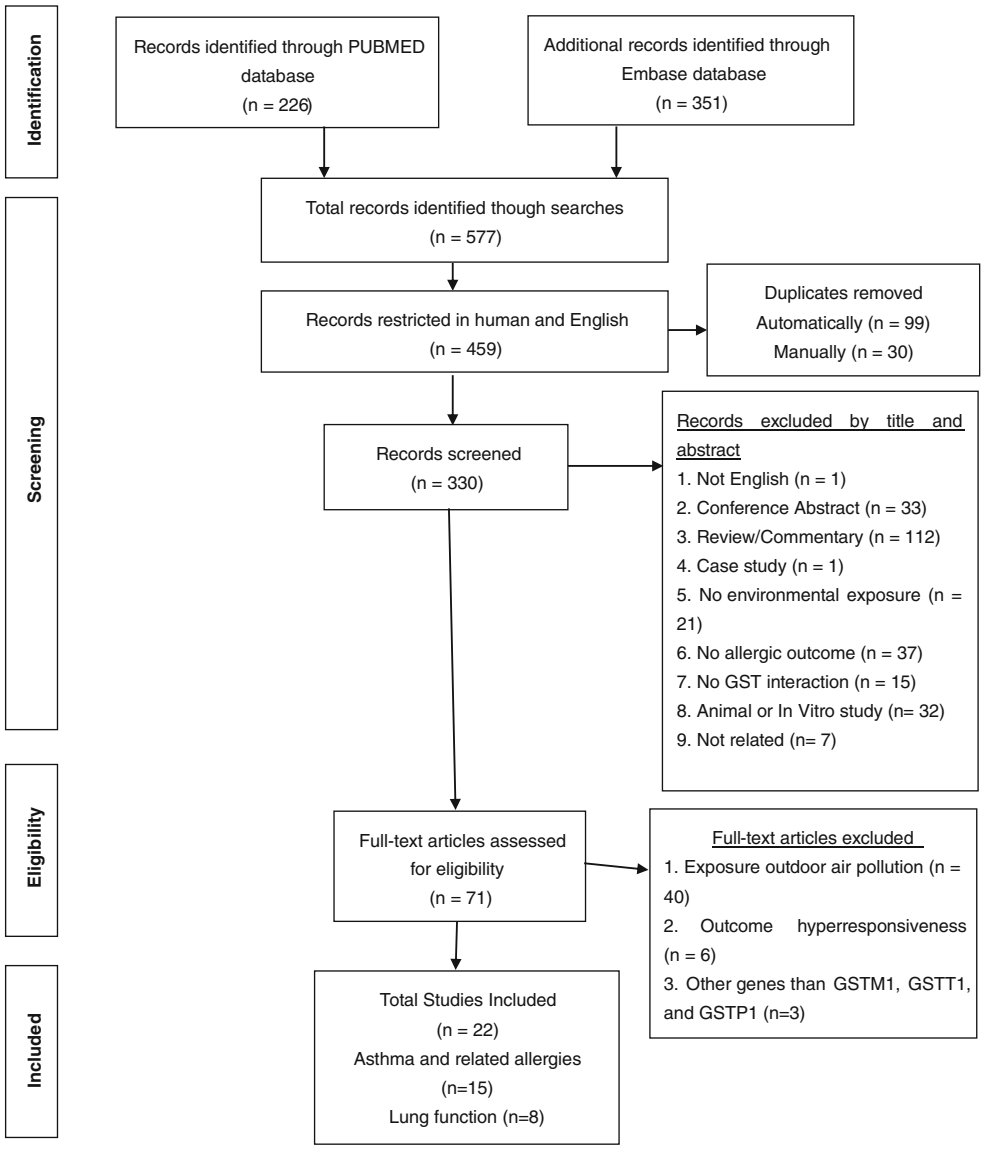

Fig. 1 PRISMA flow diagram

Table 1 Characteristics and methods of the 16 studies with allergic disease outcomes

Name of study (acronym)/ type of study/first author/date published/country	Number of participant and study dates	Exposure and age	Outcome age	Outcome measures	Interactions investigated	Association/findings	Conclusions
Birth Cohort study Wu et al. (2014) Taiwan Population based—Obstetric Clinic at Chang Gung Memorial Hospital	$N = 1848$ from 2001 to 2005, 6-year follow-up survey $N = 756$.	In-utero (3rd trimester) tobacco smoke (family member smoked at home indoors)	6 years	Ever asthma (EA) dermatitis, rhinitis	GSTM1: null and present	*EA* *OR_1 2.31 (1.33–4.00)* OR_2 1.22 (0.630–2.38) *Gender dependent* Females: *OR_1 4.107 (1.699–10.107)* OR_2 1.271 (0.469–3.448) Males: OR_1 1.510 (0.773–2.952) OR_2 1.134 (0.479–2.681) No associations found for dermatitis and rhinitis.	Evidence of interaction for GSTM1 in girls. ($p = 0.001$)
The Swiss Study on Air Pollution and Health in Adults (SAPALDIA) Population-based cohort study Gerbase et al. (2011)	$N = 9651$ in 1991, (age mean 40) $N = 8010$ in 2002. Final analysis $N = 2463$	Second-hand smoking (SHS) 3 categories exposure: 1. Never 2. Baseline 3. Baseline and Fup	Mean 50 years	Allergic rhinitis	GSTT1 and GSTM1: null and non-null; GSTP1 Ile105Val: Ile/Ile, Ile/val, val/val	No significant associations found between atopic rhinitis and GST genotypes in three categories of SHS exposure	No evidence of any GST interaction on SHS and rhinitis. (no p values given)
The Cincinnati Childhood Allergy and Air Pollution Study (CCAAPS) High Risk Birth cohort study (≥ 1 atopic parent) 7 counties Schroer et al. (2009)	$N = 570$ recruited between 2001 and 2003.	Household ETS (at least 1 smoker living in home), mold. (12 and 24 months)	12 and 24 months	Wheezing at 12 and 24 months, persistent wheezing	GSTP1, (Reference Ile/Ile) Ile105Val Ile/Ile, and Ile/val or val/val.	Carriers of Val105allele cf. Ile/Ile significantly more likely to wheeze at 12 and 24 months if ETS exposed. No significance for mold	No evidence for GSTP1 interaction ($p > 0.2$)
Childhood Asthma Management Program (CAMP) Asthma Cohort study (multi-center) Rogers et al. (2009) North American	$N = 1041$ enrolled $N = 511$ white subjects included in analysis.	In-utero smoking and ETS (postnatal until study enrolment) Both variables retrospectively recorded at study entry—mean age 8.8 years)	8.8 years ± 2.1	Current asthma (CA)	GSTM1 null or present	In smoke-exposed group, (in utero or ETS) interaction *p value = 0.03* for association between GSTM1 null and age of asthma onset (2.5 yrs. in nulls vs 4 in non-nulls) There was no evidence of a main association between GST genotype and asthma	Evidence of GSTM1 interaction ($p < 0.05$) Stronger for in-utero exposure ($p = 0.02$) compared with ETS $p = 0.08$
The Children's Health Study (CHS) Population-based cohort study—12 communities (public school children) Gilliland et al. (2002) Southern California	$N = 5925$ in 1993. Available buccal cell specimens $N = 950$	In-utero maternal smoking (retrospective at 4th, 7th, or 10th grade)	Over 8 years (range 8–> 14)	EA, CA, medication for asthma, early onset asthma, persistent asthma Ever wheezing (EW), wheeze with cold, wheeze without cold, persistent wheeze (CW).	GSTM1 null or present	Ref: GSTM1 present in non-exposed GSTM1 null in exposed: *OR_5 (EA) 1.4 (0.9–2.1);* *OR_5 (CA) 1.7 (1.1–2.8);* *OR_5 (EW) 1.8 (1.3–2.5);* *OR_5 (CW) 2.2 (1.3–4.0);* GSTM1 present in exposed: *OR_2 (EA) 0.9 (0.6–1.4);* *OR_2 (CA) 0.8 (0.5–1.3);*	Evidence for GSTM1 interaction ($p < 0.05$ for some outcomes)

Table 1 (continued)

Name of study (acronym)/ type of study/first author/date published/country	Number of participant and study dates	Exposure and age	Outcome age	Outcome measures	Interactions investigated	Association/findings	Conclusions
						OR_2 (EW) 1.3 (1.0–1.8); *OR_2 (CW) 1.6 (0.9–2.8);* GSTM1 null in non-exposed *OR_4 (EA) 1.0 (0.8–1.2);* *OR_4 (CA) 0.8 (0.6–1.1);* *OR_4 (EW) 1.0 (0.8–1.2);* *OR_4 (CW) 0.8 (0.6–1.2)*	
Cross-sectional study Lee et al. (2015) Seoul, Korea Population based—all children in single elementary school	*N* = 1111 (no year of study given)	ETS Exposure to tobacco > once/week	7–12 years	CA	GSTP1: Ile105Val AA; AA+AG AA = Ile/Ile Risk genotype Ile/Ile	No value provided for interaction between ETS, GSTP1 and CA. Increased asthma risk only seen among those with Ile/ile genotype for exposed children plus low vitamin A. (aOR, 4.44; 95% CI, 1.58–12.52)	No evidence of GSTP1 interaction. (No *p* values)
The Health 2006 Study Cross-sectional study Hersoug et al. (2012) Copenhagen Population based—drawn from civil registration system	Recruited between June 2006 to June 2008 *N* = 7931 Final analysis *N* = 3471	ETS (h/day in rooms with tobacco smoke) Use of woodstove/candles during wintertime Active smoking	18–69 years	CW	GSTM1 /T1 null copies, 1 or 2 copies	GSTM1: Interaction *p* value for: smoking status = 0.316; ETS = 0.821; woodstove = 0.245 candle use = 0.604 GSTT1: Interaction *p* value for: smoking status = 0.365; ETS = 0.321; woodstove = 0.475 candle use = 0.793	No evidence of GSTM1 and GSTT1 interaction. (*p* values ranged from 0.3 to 0.8)
Cross-sectional study Wang et al. (2011) Taiwan Population based (middle school children from public schools in 14 communities)	In 2007 Final analysis *N* = 3738.	Incense burning smoke in past 12 months 3 categories; 1) Never 2) Less than daily 3) Daily	7th grade, 12.26 ± 0.50 years	EA, CA, EW, CW, use of asthma medication exercise wheeze.	GSTT1 null, GSTM1 null, GSTP1 Ile105Val lle/lle	Ref: GSTT1 present in non-exposed. GSTT1 null in exposed, OR_5 (EA) 1.11 (0.79–1.58) OR_5 (CA) 1.56 (0.93–2.63) OR_5 (EW) 1.12 (0.84–1.49) OR_5 (CW) 1.03 (0.65–1.63) GSTT1 present in exposed, OR_2 (EA) 0.87 (0.61–1.25) OR_2 (CA) 1.09 (0.63–1.87) OR_2 (EW) 0.87 (0.65–1.17) OR_2 (CW) 0.79 (0.49–1.27) GSTM1 and GSTP1 had no interactive effect.	Evidence of GSTT1 interaction ($p < 0.05$)
The Perth Childhood Acute Asthma Study (PCAAS) Cross-sectional study in children with acute asthma presenting to ED	*N* = 221 Between July 2002 and November 2006.	ETS—any current indoor smoking in household	2–16 years	Asthma severity score (NIH) Atopy +ve SPT (3 mm) 11 allergens	GSTP1 Ile105Val (Reference Val/Val) genotypes:lle/lle, lle/val, val/val.	No significant difference in asthma severity found between genotypes and haplotypes or in combination	No evidence of GSTP1 interaction on asthma severity (no *p* values)

Table 1 (continued)

Name of study (acronym)/ type of study/first author/date published/country	Number of participant and study dates	Exposure and age	Outcome age	Outcome measures	Interactions investigated	Association/findings	Conclusions
at Princess Margaret Hospital Schultz et al. (2010)						with ETS exposure (no ORs or RRs given). Interactions between GSTP1, atopy and ETS. ($p = 0.08$)—higher risk in exposed Ile/Ile—OR 9.17 (1.42–59.12)	
Taiwanese Children's Health Study (TCHS) Cross-sectional study. Elementary school students, enriched 2 stage sampling for in-utero maternal smoking Li et al. (2009) Taiwan	$n = 1092$ in 2006 and 2008	ETS (1 or more smokers in household)	Grade 1–6	EA (ever doctor diagnosed)	GSTM1 Null or present	In exposed group: GSTM1 null vs present OR_3 0.8 (0.6–1.0). In non-exposed group GSTM1 null vs present OR_4 (EA) 1.0 (0.8–1.1) Interaction $p = 0.057$ GSTM1 genotype modified association between NQO1 polymorphism and asthma in children exposed to ETS ($p = 0.0002$).	Borderline evidence for GSTM1 interaction (no p value reported)
The Children's Health Study (CHS) Cross-sectional study. Population based—Children from public school classrooms (grades 4, 7, and 10) in 12 communities Li et al. (2008) Southern California	$N = 3082$ In 1993	In-utero smoking (maternal and household)	8–18 years	EA, CW, early/late onset Asthma (before/after 3 years age), current wheezing, medication for wheeze (MFW)	GSTP1 Ile105Val and 4 haplotype model	GSTP1 Ile105Val (baseline Ile/Ile) EA OR_2 1.1 (0.7–1.6); OR_1 1.2 (0.9–1.5); OR_5 1.4 (0.9–2.0). CW OR_2 1.2 (0.7–1.7); OR_1 1.0 (0.7–1.1); *$OR_5$1.9 (1.3–2.6)* MFW OR_2 0.9 (0.5–1.5); OR_1 1.1 (0.8–1.3); *$OR_5$1.9 (1.2–2.8)*	Evidence for GSTP1 interaction $p = 0.035$ CW $p = 0.043$ MFW
Cross-sectional study (part of ISAAC) Kabesch et al. (2004) Munich and Dresden	In 1995 and 1996, $N = 3054$	Current ETS In-utero ETS	9–11 years	CA, EW, CW	Presence or null of GSTM1 and GSTT1 gene.	GSTM1 null in exposed *OR_5 (CA) 5.48 (1.62–18.55)* *OR_5 (EW) 2.81 (1.31–6.04)* *OR_5 (CW) 4.74(1.79–12.57)* GSTM1 null in non-exposed OR_4 (CA) 1.40 (0.85–2.30) *OR_4 (EW) 2.81 (1.31–6.04)* *OR_4 (CW) 1.50 (1.01–2.22)* GSTM1 present in exposed OR_2 (CA) 2.94 (0.61–14.05)	Evidence for GSTM1 and GSTT1 interaction (p values ranged from 0.05–0.77)

Table 1 (continued)

Name of study (acronym)/ type of study/first author/date published/country	Number of participant and study dates	Exposure and age	Outcome age	Outcome measures	Interactions investigated	Association/findings	Conclusions
						OR_2 (EW) 1.81 (0.75–4.41) OR_2 (CW) 2.03 (0.55–7.54) GSTT1 null in exposed OR_5 (CA) 4.10 (0.43–39.04) OR_5 (EW) *4.37 (1.17–16.39)* OR_5 (CW) 3.30 (0.61–17.91) GSTT1 null in non-exposed OR_4 (CA) 0.73 (0.35–1.50) OR_4 (EW) *2.81 (1.31–6.04)* OR_4 (CW) 0.84 (0.60–1.19) GSTT1 present in exposed OR_2 (CA) *3.25 (1.14–9.27)* OR_2 (EW) 1.77 (0.92–3.42) OR_2 (CW) *2.61 (1.09–6.21)*	
Case control study Munoz et al. (2012) Coahiula Mexico	$N = 201$ Cases (asthma): $N = 90$ Controls: $N = 111$ No survey time was specified in paper.	ETS—3 cats 1. Not exposed 2. household exposure 3. In utero and household	6–9 years	Asthma (unable to define if it is current asthma or ever asthma)	GSTP1 Ile105Val A allele, G allele, AA genotype, AG genotype, GG genotype.	Among 5 genotyping groups in GSTP1, allelic and genotypic frequencies were similar and no significant differences were observed. No ORs or RRs were available in this study.	No evidence of GSTP1 interaction No interactions reported
Children, allergy, Milieu, Stockholm, Epidemiological Survey (BAMSE) Case control study nested in a birth cohort study Panasevich et al. (2010)	Cases (wheezers): $N = 542$ Controls: $N = 542$ Recruited in 1994–1996	Early maternal smoking (> = 1 cig/day in pregnancy or early childhood)	4 years	CA, early onset wheeze, late onset wheeze, transient wheeze.	GSTP1: Ile105val (rs1695)	Early onset wheeze GSTP1 ile, OR_2 1.5 (0.8–2.7); GSTP1 ile/val, OR_1 1.8 (1.1–3.2); GSTP1 val, OR_1 5.7 (1.4–22.2), interaction $p = 0.17$.	Evidence of GSTP1 interaction ($p = 0.17$)
Taiwan Birth Panel cohort study(TBPCS) Case control study nested in birth cohort Wang et al. (2010) Taiwan	Cases AD: $n = 34$; 4 matched (sex, age, enrolment time) Controls for each case: $n = 106$ TBPCS start 2004. This analysis in 2006	Prenatal ETS Cotinine level in cord blood Low vs high (0.1 ng/ml)	2 years	Atopic dermatitis (AD)- ISAAC	GSTM1 and GSTP null and present, GSTP1 (ref any val) Ile/val or val/val, Ile/Ile.	*GSTM1* *OR_3 5.21 (1.32–20.58)* OR_4 1.88 (0.46–7.69) GSTP1 OR_3 2.61 (0.75–9.12) *OR_4 6.63 (1.46–30.18)*	Evidence of GSTM1 and GSTP1 interaction (no p value provided)
Case control study drawn from a national cross-sectional study. Lee et al. (2007) Taiwan	In 2001. cases: $n = 216$; controls: $n = 185$	Household ETS (past 12 months) Participants with in-utero exposure or personal smoking excluded	Cases: 11.8 ± 1.7 years, controls: 12.1 ± 1.8 years	EW and CW	GSTP1-105 Ile. Ile/val, val/val GSTM1 null or present	GSTP1 *EW* *OR_5 0.85 (0.46–1.60)* *OR_1 2.22 (1.07–4.58);* *OR_4 0.43 (0.21–0.86)* *OR_2 0.67 (0.40–1.12))* *interaction p = 0.01* *CW* *OR_5 0.68 (0.31–1.46)* *OR_1 3.81 (1.34–10.84);*	Evidence of GSTP1 interaction ($p = 0.01$ for EW, $p = 0.004$ for CW)

Table 1 (continued)

Name of study (acronym)/ type of study/first author/date published/country	Number of participant and study dates	Exposure and age	Outcome age	Outcome measures	Interactions investigated	Association/findings	Conclusions
						OR_4 0.68 (0.37–1.25); OR_2 0.68 (0.37–1.25). Interaction p = 0.004	

Note: OR_1 odds of asthma/wheeze for participants with environmental exposure (EE) compared to participants without environmental exposure in carriers of the risk genotype (RG) (GSTM1null/GSTT1 null/GSTP1 ile/val or val/val), EE+/RG+ compared with EE−/RG+; OR_2 odds of asthma/wheeze for participants with environmental exposure compared to participants without exposure in carriers of the non-risk genotype (GSTM1present /GSTT1 present/GSTP1 ile/ile.) or 5 odds of asthma/wheeze in environmentally exposed without risk genotype compared to non-environmentally exposed without risk genotype, EE+/RG− compared with EE−/RG−; OR_3 odds of asthma/wheeze for participants with the risk genotype compared to those without the risk genotype in participants environmentally exposed, EE+/RG+ compared with EE+/RG−; OR_4 odds of asthma/wheeze for participants with the risk genotype compared to those without the risk genotype in participants not environmentally exposed, EE −/RG+ compared with EE−/RG−; OR_5 odds of asthma/wheeze in environmentally exposed with risk genotype compared to non-environmentally exposed without risk genotype, EE+/RG+ compared with EE−/RG−

were measured varied from 1 month [42] to 69 years [5]. No studies included an elderly population. Sample sizes ranged from 140 to 3738. The numbers of cohort, cross-sectional, and case-control studies were 9, 9, and 4, respectively.

Studies were conducted at a variety of locations across Europe, North American, Mexico, Australia, Taiwan, and South Korea. All papers reported the geographic location of their studies, 8 further provided information on ethnicity. Those 8 studies were mainly conducted on Non-Hispanic white/white/Caucasian.

Measurement of Exposures and Outcomes

Genetic Polymorphisms Genotyping methods were reported for all studies. Six of the 22 papers described confirmation of genotyping results by analyzing a duplicated random sample (5%–15%) and all were concordant with the initial results [27, 31, 33, 39, 42, 45].

Environmental Exposures Nineteen of the 22 studies evaluated indoor air pollutants by self-report questionnaires. The remaining 3 studies used more objective measures to quantitate exposure, including blood cotinine level [39], urinary cotinine level [30], and visible mold assessed by a home visit [33]. No studies measured indoor air pollution directly through air sampling (e.g., air quality monitors).

Outcome Assessment Asthma and allergic outcomes were evaluated by self-report questionnaires for most studies, apart from 1 that extracted asthma diagnosis from hospital records [31], and another that undertook independent clinical examination by doctors [26]. All lung function studies performed spirometry, except 1 study in infants that measured $Vmax_{FRC}$ using the rapid thoracoabdominal compression technique during tidal breathing [42].

Assessment of Quality of Included Studies

Based on NOS assessments, 6 studies were low, 11 studies medium, and 5 studies high quality. The main issue identified was failure to adjust for a minimum set of confounders, including age (not applicable for birth cohort studies), gender, socio-economic status (SES), and family history of allergic disease (Fig. 2). Only 5 studies fully adjusted for these variables [27, 28, 36, 38, 39], while 2 did not describe any confounders [30, 43].

Narrative Synthesis of All Identified Studies

Of the 22 included studies, 15 supported the presence of a gene-indoor air pollution interaction on the outcome of allergic disease, lung function, or both [25–29, 32, 34•, 35••, 36, 39–43, 45]. Interestingly, of those 7 papers failing to detect

Table 2 Characteristics and methods of the 8 studies with lung function outcomes

Name of study (acronym)/ type of study/first author/ date published/country	Study numbers and dates	Exposure and age	Outcome age	Outcome measures	Interactions investigated	Association/findings	Conclusions
The Perth Infant Asthma Follow-up (PIAF) Birth Cohort study—women attending local antenatal clinic Murdzoska et al. (2009) Australia	Between 1987 and 1990, DNA available for GSTM1/GSTT1, $n = 179$ GSTP1 $n = 180$	In-utero ever smoking	1, 6, and 12 months.	Maximal flow at functional residual capacity ($Vmax_{FRC}$)	Maternal and infant GSTT1 null/non-null, GSTM1 null/non-null, GSTP1 ile/ile, ile/val, and val/val	*Adjusting length, maternal smoking with GSTT1 non-null ß 37.05 (− 0.06, 74.17).* No association was found on GSTM1; GSTP1 data was not available on infant.	Evidence of GSTT1 interaction ($p = 0.008$)
The Childhood Asthma Management Program (CAMP) Asthma Cohort study (multi-center) Rogers et al. (2009) North American	$N = 511$	In-utero smoking and ETS (postnatal until study enrolment) Both variables retrospectively recorded at study entry—mean age 8.8 years)	8.8 years ± 2.1	FEV1% predicted, FVC % predicted, FEV1/FVC	GSTM1 null and non-null Copy number variants(CNV) Null hemizygotes and homozygotes	With in-utero smoke exposure, children with GSTM1 null have higher FVC% ($p = 0.04$) and lower FEV1/FVC ($p = 0.03$). Postnatal ETS are highly correlated in utero smoking. No number given.	Evidence of GSTM1 interaction ($p < 0.05$)
Swiss Cohort Study on Air Pollution and Lung Diseases in Adults (SAPALDIA) Cohort study Imboden et al. (2007)	Completed Spirometry in 2002. FEV1-4686 FVC-4591 FEF-4528	Ever(> 20 pk/years) and never smokers Ever further classified as persistent and others	Age at baseline 40.8 ± 11.5 years FUP for 11 years	Difference in mean annual change in FEV1, FVC and FEF2575 over 11 years (ml/year)	GSTT1 and GSTM1 (null and non-null), GSTP1 (105 Ile/Ile, Ile/val, val/val); GSTM1T1 (both non-null, either null, both null)	The GSTT1 effect in persistent smokers was modified by pack-years smoked to baseline and follow-up on FEV1 decline.	In male persistent smokers evidence of GSTT1 interaction on FEV1 decline with pack-years smoked at baseline ($p < 0.001$) and follow-up ($p = 0.029$)
Lung Health Study (LHS) Cohort study He et al. (2004) American	High lung function group, $n = 544$ Low lung function group, $n = 554$	Smoking history (pack-year)	35–60 years	High lung function (HL) and low lung (LL) function	GSTM1, GSTT1, null and present GSTP1: recessive, dominant, and Codominant.	GSTT1: *Mild smoker OR 4.28 (1.71, 10.96)* Moderate smoker OR 0.94(0.59, 1.49) Heavy smoker OR 0.91 (0.43. 2.02) No associations were found on GSTM1 and GSTP1.	Evidence of GSTT1 interaction (not with smoking, but pack-years) ($p = 0.038$)
Lung Health Study (LHS) Cohort study He et al. (2002) American	Fastest decline FEV1 $N = 299$ Slowest decline FEV1 $N = 322$	Active smoking during last 5 years	35–60 years	FEV1% predicted	GSTM1, GSTT1, null and wild-type present; GSTP1 AA, AG, GG.	Neither the combination of all GST polymorphisms nor a combination of GSTP1 AA showed a significant interaction with smoking history.	No evidence of interaction (no p value reported)
The Health 2006 Study Cross-sectional study Hersoug et al. (2012) Copenhagen	Final analysis $N = 3471$	ETS, Use of woodstove/candles during wintertime, Smoking status	18–69 years	FEV1% predicted	GSTM1 and GSTT1 with null copies GSTM1 and GSTT1 with 1 or 2 copies	Interaction p value for smoking status*GSTM1 0.281; for ETS*GSTM1 0.567; for wood stove *GSTM1 0.145; candles*GSTM1 0.362; smoking status*GSTT1 0.871; for ETS*GSTT1 0.740; for wood stove *GSTT1 0.761; candles*GSTT1 0.367;	No evidence of interaction (p values ranged from 0.3 to 0.9)
European Community Respiratory Health Survey (ECRHS) Cross-sectional study of Danish participants of ECRHS Malling et al. (2012) Denmark	$N = 1091$ Random sample (728) Symptomatic sample (460) (current asthma symptoms or adult onset asthma)	Current active smoker (I month) in those who have ever smoked for >1 year	22–44 years	FEV1% predicted; $FEV1/height^2$	GSTP1 (ref Ile/Ile) Ile/Ile, Ile/val, val/val, GSTT1, GSTM1 two copies, one copy and null,	Ref GSTM1 two copies. Adjusted FEV1%: With current active smoking, GSTM1 one copies ß − 9.3 (− 16, − 2.3), null ß − 11 (− 18, − 4.0). interaction $p = 0.03$ Interactions were not seen in GSTT1 and GSTP1.	Evidence of GSTM1 interaction ($p = 0.03$)

Table 2 (continued)

Name of study (acronym)/ type of study/first author/ date published/country	Study numbers and dates	Exposure and age	Outcome age	Outcome measures	Interactions investigated	Association/findings	Conclusions
BREATHE study Cross-sectional study of participants with physician diagnosed asthma Palmer et al. (2006) Primary/secondary clinics in 10 practices Scotland	In 2004–2005. $N = 504$	ETS (family smoking in the home environment)	Mean 10 (3–21 years) 2 groups; 3–12 and 13–21	% Predicted PEFR, FEV1, and FVC	GSTM1, GSTT1, null and present and GSTP val/val105 and Ile105/Ile105 or Ile105/val105	In the 13–21 years old, p value of association between GSTM1 genotype and peak expiratory follow rate (PEFR) in ETS exposed group is 0.010, but 0.235 in non-exposed group. (p int 0.003)	Evidence of GSTM1 interaction in older asthmatic children. ($p = 0.003$)

* Interaction

gene-air pollution interactions for allergies or lung function, 2 found interactions instead for outcomes of high total IgE [38]or atopy (positive skin prick test), which are recognized markers of allergy [31, 38]. Seventy-nine percent ($n = 11$) of childhood papers found at least one interaction [25–29, 32, 34•, 35••, 36, 39, 42] compared with only half ($n = 3$) of the papers in adulthood [40, 41, 45]. One paper that spanned both age groups (young children to young adults aged 3–21 years) also found an interaction [43]. All five Taiwanese studies identified genetic susceptibility for environmental factors, while 75% of the European studies and only half of the North American studies found an interaction.

Asthma and Wheeze

Fifteen papers reported results on asthma or wheeze, and nine identified an interaction with one or more of the GST polymorphisms. Four out of eight papers investigating the potentially modifying effect of GSTM1 on the association between indoor air pollution and allergies found that carriers of the null genotype had an increased risk of asthma/wheeze when school-aged children were exposed to markers of increased indoor air pollution [25, 26, 28, 35••]. However, one Taiwanese study found weak conflicting evidence: decreased risk of asthma in children carrying the null GSTM1 genotype and exposed to ETS ($p = 0.0573$) [29]. Another oxidative stress gene Quinone oxidoreductase 1 (NQO1) may be part of a three-way interaction with children carrying the GSTM1 null and NQO1 ser genotype at increased risk of asthma in the exposed group, but not in the unexposed group [29]. Of the three papers reporting on GSTT1, two cross-sectional studies investigating asthma in school-aged children found evidence of an interaction [25, 36]. They found that environmental pollutants including in-utero smoking and incense burning smoke were associated with increased risk of asthma/wheeze if children had GSTT1 null genotypes. The other GSTT1 paper failed to replicate this interaction in adulthood [5]. Of eight papers investigating GSTP1, three found that the GSTP1 val105 allele was associated with an increased risk of wheezing/asthma with in-utero smoking exposure and/or non-exposed children carrying GSTP1 ile105 alleles were at increased risk [27, 32, 34•]. One paper further investigated GSTP1 by using a haplotype-based analysis [34•]. GSTP1 genes were categorized by four haplotype variation tagging SNPs. Consistent with a risk effect of the GSTP1 val 105 variant, the effect of in-utero exposure to maternal smoking on wheezing was largest in children within the h1011 haplotype (105val with no other variants) compared with other haplotypes [34•]. In contrast, there was one study suggesting that GSTP1 ile105 increased the risk of atopy (but not asthma severity) when exposed to ETS [31]. Although a cross-sectional study in Korea did not observe an interaction between ETS, GSTP1, and asthma, when they further stratified by vitamin A intake (low vs high), they found that school children with GSTP1

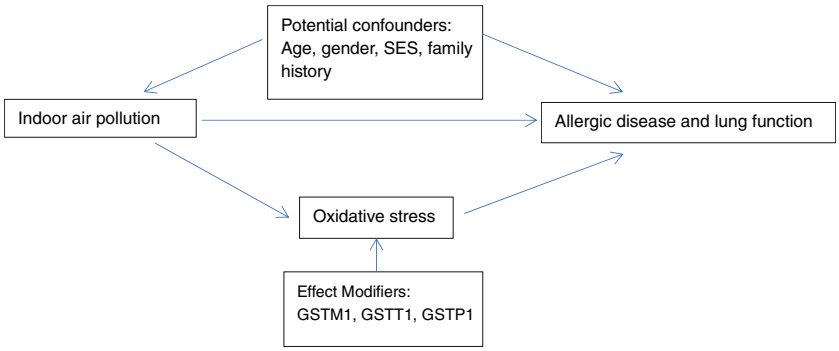

Fig. 2 Casual diagram for GST gene interaction on the association between indoor air pollution and allergic disease and lung function

homozygous ili genotypes exposed to ETS and low vitamin A had an increased risk of asthma [37••]. The remaining three studies showed no evidence of a GSTP1 interaction for all investigated current environmental exposures [30, 31, 33].

Other Allergic Disease

There were two studies investigating rhinitis [35••, 38], and two investigating atopic dermatitis (AD) [35••, 39]. No study investigated the outcome of food allergy. No significant associations were found between allergic rhinitis and GST genotypes in different smoking categories in adulthood [35••, 38]. However, children with GSTM1 null genotypes were found to be more susceptible to AD if they had been exposed to in-utero smoking, while GSTP1 ile105 homogeneity increased the risk of AD in the in-utero unexposed group, but no association was seen in the exposed group [39].

Lung Function

Six of the eight studies that investigated the potential interaction between smoking and GST genes found positive results. All three studies investigating GSTM1 found that carriers of null variants exposed to smoking, had an increased risk of impaired lung function in terms of FEV1% predicted [41, 43], PEFR % predicted [43], FVC% predicted, and FEV1/FVC ratio [26]. These associations were not seen in the non-smoke-exposed group. Two studies formally tested and found statistical evidence for an interaction term [41, 43]. For GSTT1, one study investigated infant lung function, finding that among infants exposed to in-utero smoking, those with null variants had reduced $Vmax_{FRC}$ in the first year compared with non-null infants. No significant associations were seen in the group not exposed to in-utero smoke [42]. Another two adult studies identified significant interactions between GSTT1 genotype and pack-years on lung function in smokers [40, 45]. Two studies which support the presence of interaction by GSTP1 provided evidence that in those exposed to tobacco smoke, having the GSTP1 val105 allele increased the risk of reduced lung function. One found that GSTP1 val105 homozygote individuals demonstrated a reduction in PEFR% predicted in the older ETS exposed group (13–21 years vs 3–12 years) [43]. The second study found that in persistent smokers, those homozygous for GSTP1 val105 had a faster rate of lung function decline in FVC during 11 years' follow-up compared to heterozygotes. However, irrespective of smoking status, no independent effect of GSTP1 was found [45].

Two adult studies did not identify any interaction. The Health 2006 study in Copenhagen found no evidence of GST interaction for a wide range of indoor exposures (active smoking, passive smoking, and use of woodstove or candles during wintertime) and the risk of FEV_1% predicted (interaction p varies from 0.1–0.6) [5]. Another study nested in the Lung Health Study in North America found no significant GST interactions between smoking history and rapid decline in lung function over 5 years, either using single genes or a combination [44].

Discussion

This is the first systematic review to investigate the interaction between indoor air pollution and GST genes on allergic disease and lung function. Our narrative synthesis of 22 studies found evidence that GST polymorphisms interact with indoor air pollution exposures to adversely affect lung health. Carriers of GSTM1 null, GSTT1 null, and GSTP 105val alleles were at greater risk of developing asthma and reduced lung function when exposed to tobacco smoke. Three of the seven papers that did not find an interaction between indoor air pollution, GST, and allergic disease reported interactions on other allergy-related outcomes, in term of IgE [38] or atopy status [31], or after consideration of antioxidant nutrient intake [37••]. Two previous systematic reviews on oxidative stress genes, outdoor air pollution, and lung function outcomes, both suggested the presence of an interaction [16•, 46]. We reviewed GST genes and indoor air pollution, providing further and more current evidence for the presence of an interaction.

Biologic Plausibility

Our findings are supported by a strong biologic plausibility. Oxidative stress is a key component of inflammatory

disorders, and host antioxidant systems are activated in response to an external "oxidant attack" caused by exposure to environmental pollution [47]. ETS has been shown to have detrimental effects on the lung, mostly related to increased oxidative stress [48], as well as suppression of the immune system through modulation of T cell function [49]. Several studies have demonstrated that environmental exposures can influence GST gene activity. A study in rats found that exposure to cigarette smoke five times/week led to an increase in GST activity in both the brain and lungs [50]. Similarly, a human study found that the degree of antioxidant gene expression is directly related to the amount of cigarette smoke exposure [51], suggesting upregulation in response to environmental stimuli. Individuals who lack the protection of certain antioxidant genes may have a lower capacity for antioxidant defense, and be more susceptible to environmental toxins. This may lead to increased risk of asthma or impaired lung function when faced with oxidative exposures. Fourteen studies supported that cigarette smoke-exposed carriers of the GSTM1/T1 null genotypes may have increased risk of allergic disease and impaired lung function.

Evidence for GSTP1 Risk Allele Is Inconsistent

We found that carrying the GSTP1 val105 allele increased the risk of asthma and lung function deficits in individuals exposed to indoor air pollution. One study on asthmatic children found that carriers of GSTP1 val/val genotypes had higher levels of oxidative stress (measured as plasma levels of malondiadehyde) and less antioxidant defense capacity (measured as glutathione levels), compared with other genotypes [47]. Therefore, if ile alleles are replaced by val alleles, the resultant-encoded enzyme can alter the level of antioxidative capacity in the individual and may further contribute to airway inflammation when exposed to oxidative threats [34•, 52]. Conversely, another study indicated that carriers of homozygous GSTP1 ile alleles may have increased risk of atopic dermatitis in those unexposed to in-utero smoking but not in the exposed group [39]. The reason for this contradictory outcome is unclear. There is evidence showing that enzymes with GSTP1 val105 have a greater catalytic effect for diol epoxides of polycyclic aromatic hydrocarbons but less effect with 1-chloro-2,4-dinitrobenzene compared to ile105 [53]. Therefore, we propose that the effect of GSTP1 gene polymorphisms on allergy risk and lung function is likely to vary for different pollutants or in different scenarios.

Reasons for Other Inconsistent Findings

Inconsistent findings from specific exposures may be caused by differing environmental conditions or study methodology. For instance, all 6 papers exploring in-utero smoking suggested that adverse effects were more likely to occur in individuals with a GST risk polymorphism. This suggests a potential critical time window, during which exposure may lead to long-term effects on fetal lung development [6]. Moreover, asthma and other allergic diseases are heterogeneous diseases with complex etiologies. A few studies in our review suggested the presence of complex interactions, including NQO1 [29], other GST genotypes [44, 45], bronchial hyperresponsiveness to methacholine chloride [45], antioxidative vitamins [37••], age [43, 45], and sex [35••, 45]. Asthma and reduced lung function may result from effects of multiple genes and their interactions with environmental and host factors. It is unlikely that a single gene polymorphism is the only mechanism responsible for management of oxidative stress within the lung. It is likely that multiple points of biological redundancy have been developed to protect the airways and prevent adverse respiratory outcomes. The influence of other factors may increase the magnitude of a proposed gene-environment interaction. The Cincinnati Childhood Allergy and Air Pollution Study suggested that GSTP1 genes could modify the negative effect of diesel exhaust particle (DEP) exposure. However, the protective effects of GSTP1 genotypes may be overridden when children are exposed to multiple environmental stresses in early life. In these infants, despite carrying genotypes considered protective for lesser levels and varieties of exposure, adverse outcomes were observed with multiple environmental loads [33]. Interactions were found more commonly in studies on children compared to adults, suggesting that the effect of gene-pollution interaction on respiratory health varies by age. Children's lungs are still developing and therefore may be more susceptible to noxious exposures. Furthermore, immune responses are relatively naïve in children when compared to adults. For both reasons, antioxidant defenses may play a crucial role in overcoming the adverse effects of environmental exposures on childhood respiratory health [54, 55].

Evidence from the Past 5 years

In terms of the most recent evidence, since 2013, there have only been two original research articles published on GST genes and indoor air pollutants [35••, 37••]. One provided evidence that low vitamin A intake in genetically susceptible children (GSTP1 1695 AA) exposed to ETS was associated with an increased risk of asthma [37••]. The authors suggested that low vitamin A diets may increase the level of oxidative stress making genetically susceptible children more likely to be affected by environmental exposures like ETS. This finding suggests that supplemental vitamin A may be a preventive measure for those at high risk. The other recent study provides new evidence on gender differences and risk alleles for the interactive effect of GSTM1 with in-utero smoking on childhood asthma [35••]. This study demonstrated that the GSTM1 null genotype could have a bipolar effect on childhood asthma

at 6 years depending on whether there is in-utero smoke exposure. The GSTM1 null genotype is a protective factor for asthma at age 6 years in girls without in-utero smoke exposure but becomes a risk factor for asthma with in-utero smoke exposure. The associations were not seen for boys. It has been suggested that the relative lack in antioxidant defenses resulting from the GSTM1 null genotype may be compensated for by increased antioxidant production by other members of the GST superfamily [56] or by other antioxidant enzymes. In support of this theory, two studies demonstrated that a protective polymorphism (Ser187) of a second antioxidant enzyme, quinone oxidoreductase 1 (NQO1), provided a protective effect among GSTM1 null subjects [57, 58]. These findings indicate the complexity of the body's buffering system for antioxidant stress and suggest a direction for future studies. Comprehensive studies in this area should consider both a series of antioxidant genes and dietary "antioxidant" intake, when investigating the relationship between environmental exposures such as ETS and lung health outcomes.

Limitations

We were unable to meta-analyze the data due to high heterogeneity. Specific gene-pollutant outcome combinations lacked numbers for meta-analysis. However, the reporting of significant interaction terms from 15 of the 22 studies provides evidence that it is likely this interaction exists. There is potential for negative studies not to be published, which may have led to a bias towards greater magnitude of interaction effects being identified. Some of the estimates were based on unadjusted measures or unexplained adjustment which may increase the differences between study estimates. Finally, most studies were conducted in Asians or Caucasians and thus, our results may only be applicable to these ethnic groups.

Future Directions

Further studies investigating these gene-environment interactions are needed. The ability of individual studies to measure true effects can be improved by larger sample sizes and more objective measures of exposures and outcomes at multiple time points. The majority of the current papers measured exposures and outcomes at one time by self-report. This is problematic as both exposures and outcomes change over time. Moreover, further studies should also consider recruiting participants in specific age ranges especially people over the age of 65 years, because antioxidant capacity is known to decrease with age [59] and the magnitude of gene-environment interaction may also change over time. More publications, with transparent methods, in varied populations in terms of age and ethnicity should be encouraged to obtain a clearer picture of the true magnitude of the relationship.

Conclusions

There is evidence that carriers of *GSTM1* null, *GSTT1* null, and *GSTP1* val genotypes are more susceptible to indoor air pollution exposure, having a higher risk of asthma and lung function deficits, although some findings are conflicting in terms of risk alleles and specific exposures. These interactions may help to explain the inconsistent effects seen when either indoor air pollution or GST genes are studied in isolation for their effects on respiratory health. The recognition of specific genetic risk alleles may allow for targeted preventive measures in susceptible subpopulations to improve respiratory health by avoiding indoor air pollutants or improving their antioxidant defenses through diet or supplemental vitamins.

Acknowledgements We thank Prof. Liyun Feng and Shuai Li who provided support on statistical methods.

Authors' Contributions Xin Dai, Prof. Shyamali Dharmage, and Dr. Caroline Lodge contributed to the study conception and design. Xin Dai, Gayan Bowatte, and Dr. Caroline Lodge contributed to the identification of the studies, data collection, study selection, and data extraction. Xin Dai, Prof Shyamali Dharmage, and Dr. Caroline Lodge led the analysis and interpretation of data, with support from Dr. Adrian Lowe, Dr. Melanie Matheson, Dr. John Burgess, A/Prof Lyle Gurrin, and Gayan Bowatte. Xin Dai wrote the initial draft of the manuscript which was critically revised for important content by all the authors. All authors approved the final version.

Declaration of All Sources of Funding Xin Dai, Prof. Shyamali Dharmage, Dr. Caroline Lodge, Dr. Melanie Matheson, and Dr. Adrian Lowe are funded by the National Health and Medical Research Council of Australia (NHMRC); Dr. John Burgess and Gayan Bowatte have no personal funding relationships to declare.

Compliance with Ethical Standards

Conflict of Interest All authors declare no support from any organization for the submitted work, no financial relationships with any organizations that might have an interest in the submitted work in the previous 3 years, and no other relationships or activities that could appear to have influenced the submitted work.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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- •• Of major importance

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