Childhood Asthma and Type 1 Diabetes Mellitus: A Meta-analysis and Bidirectional Mendelian Randomization Study

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Abstract

Objectives: World-wide incidence and prevalence of both asthma and type 1 diabetes mellitus (T1DM) has been increasing in past decades. Association between the two diseases has been found in some but not other studies. We conducted a meta-analysis to verify such an association, and bidirectional Mendelian randomization analysis to examine the potential cause-effect relationships. **Methods:** Three databases(PubMed, Embase and Web of Science) were searched from their inception to February 1, 2021. Pooled hazard ratios (HR) or odds ratios (OR), and 95% confidence intervals, were calculated. Associations between single-nucleotide polymorphisms with childhood asthma and T1DM were selected based on genome-wide association studies. The outcome datasets were obtained from FinnGen study. We used the inverse variance-weighted, weighted median and MR-Egger methods to estimate causal effects. To assess robustness and horizontal pleiotropy, MR-Egger regression and MR pleiotropy residual sum and outlier test was conducted. **Results:** In meta-analysis, childhood asthma was associated with an increased risk of T1DM (HR=1.30, 95% CI 1.05–1.61, P=0.014), whereas T1DM was not associated with the risk of asthma (HR=0.98, 95% CI 0.64–1.51, P=0.941; OR=0.84, 95% CI 0.65–1.08, P=0.168). MR analysis indicated increased genetic risk of T1DM in children with asthma (OR=1.308; 95% CI 1.030-1.661; P =0.028). Analysis using the IVW method indicated decreased genetic risk of asthma in children with T1DM (OR = 0.937, 95%CI 0.881-0.996, P = 0.037). **Conclusions:** Childhood asthma is a risk factor for T1DM; T1DM is a possible protective factor for childhood asthma.

INTRODUCTION

Asthma is one of the most frequent chronic disease in children.[1,2] Type 1 diabetes mellitus (T1DM) occurs at an incidence of 8-20 per 100,000 each year,[3] and is one of the most common immune-related diseases in children. The incidence and prevalence of both childhood asthma and T1DM have been increasing over the past decades,[1,3] suggesting common susceptibility factors.[4]

A meta-analysis published in 2003 suggested a weak inverse association between childhood asthma and T1DM.[5] However, majority of the studies included in the meta-analysis are case-control studies. In addition, cohort studies included in the meta-analysis are highly heterogeneous in disease definition and age spectrum. In addition, a positive association between the two diseases , which now attracts growing interest, has also been reported in several retrospective cohort studies with stronger quality of evidence.[6-8]

Since exaggerated immune response and inflammation underlie both asthma and T1DM, reciprocal cause-effect relationship between the two diseases is likely. Mendelian randomization (MR) analysis uses genetic variants as instrumental variables (IVs) for investigating potential cause-effect relationships between different human traits.[9] With increasing number of genome-wide association studies (GWAS), MR has been increasingly used. Bidirectional MR analysis is an extension to the basic MR approach that could evaluate whether an "exposure" causes the "outcome" or vice versa.[10] We conducted an updated meta-analysis of

original studies that examined the association between childhood asthma and T1DM. Data were analyzed using bidirectional MR analysis to examine the possible cause-effect relationship.

METHODS

Data Sources and Literature Search Strategy

The meta-analysis was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guidelines and registered in the Prospective Register of Systematic Reviews (PROSPERO ID CRD42021236232).[11] PubMed, Embase and Web of Science were searched from inception to February 1, 2021 using the following Medical Subject Heading (MeSH) terms, keywords and word variants: "insulin dependent" or "type 1 diabetes" and "asthma". Reference lists of the electronically identified articles were manually searched.

Eligibility Criteria

For inclusion in analysis, studies must meet the following criteria: (1) full-text published in English; (2) reported the odds ratio (OR), relative risk (RR), or hazard ratio (HR), with 95% confidence interval (95%CI), or adequate data to calculate these measures; (3) conducted primarily in children (<18 years of age); (4) sample size of at least 100. We excluded meta-analyses, review articles and case reports. Two reviewers (J.X. and W.L.) screened the titles and abstracts, and then assessed the full-text independently.

Data Extraction and Quality Assessment

Two investigators (J.X. and W.L.) extracted the following data from the identified studies: full title, first author, publication year, study design, follow-up period, sources of patient and participant, the number of asthma patients, T1DM patients, and OR/RR/HR with 95%CI. The quality of eligible literature was assessed using the Newcastle-Ottawa Scale (NOS), a tool recommended by the Cochrane Collaboration for the quality assessment of observational studies.[12] Eligible studies with scores of 0-3, 4-6, and 7-9 were considered as low, moderate, and high quality, respectively. Disagreements between the investigators in data extraction and quality assessment were resolved by consensus, and if consensus could not be reached, a third investigator (X.Z.) was consulted for a final decision.

Statistical Analysis

Meta-analysis was conducted using Stata14.0 (StataCorp, College Station, TX, USA). Heterogeneity was assessed by χ^2 analysis. Data synthesis was conducted using a random-effects model if $I^2 > 50\%$, and using a fixed-effects model otherwise. RR was converted to OR for data synthesis. Subgroup analysis was performed with stratification according to geographical location and quality grade. Meta-regression analysis was conducted using year of publication, region, incidence of asthma in the control group, sample size and quality score as explanatory covariates. Sensitivity analysis was conducted with the method of reducing one piece of literature at a time to evaluate the impact of a single study on this meta-analysis. Publication bias was examined using the funnel plot and Begg's bias test if 10 or more studies were included. $P<0.05$ (2-sided) was considered to be statistically significant.

Effect of Childhood Asthma on T1DM

A total of 56 single nucleotide polymorphisms (SNPs) associated with childhood asthma were selected for genome-wide significance (threshold: P $<5*10^{-8}$) from the hitherto largest asthma GWAS of UK Biobank (UKBB) (Table S1).[13] These SNPs explained 8.68% of the variation in childhood asthma risk. The F statistic is 2,881, indicating that the instruments could strongly predict childhood asthma.[14]We performed linkage disequilibrium (LD)-clumping restricted to r2 < 0.01, Clumping distance > 5000kb and retained SNPs at a GWAS threshold of statistical significance to eliminate LD. When a particular SNP was not available in the outcome dataset, proxy SNPs were used instead through LD tagging (Rsq > 0.8). Then 30 SNPs were selected as IVs for MR analysis by removing the SNPs for lack of required information, being palindromic or incompatible alleles. Effect estimates of these childhood asthma-associated SNPs on the risk of T1DM were assessed using the summary statistics from the FinnGen datasets (2,636 T1DM cases and 8,2655

controls of European ancestry). Detailed description is provided on the FinnGen research project website (https://www.finngen.fi/en).

Effect of T1DM on Childhood Asthma

A total of 28 T1DM-associated SNPs were selected based on GWAS analysis in the National Human Genome Research Institute (NHGRI) and the European Bioinformatics Institute (EBI) GWAS Catalog (https://www.ebi.ac.uk/gwas/) (Table S2).[15-21]The F-statistic ranges from 107 to 559 and could strongly predict T1DM (F>10). LD-clumping were applied to remove dependent SNPs and 20 of them were available in the outcome dataset. Effect estimates of T1DM-associated SNPs on the risk of childhood were assessed using the FinnGen study (992 childhood asthma cases and 65,481 controls of European ancestry).

Mendelian Randomization Analysis

The random-effects inverse-variance weighted (IVW) method was used to estimate the bidirectional causality between childhood asthma and T1DM by meta-analyzing the SNP specific Wald ratio estimates.[22] The causal effect estimates (beta coefficients) were transformed to odds ratios (OR). The weighted median, MR-Egger methods were also implemented to assess the causality.

Since many IVs are associated with multiple traits (pleiotropy), we used MR-Egger regression[23] and MR pleiotropy residual sum and outlier (MR-PRESSO)[24] method to examine the robustness of the main findings. When the MR-Egger intercept differs from zero (at $P < 0.05$), horizontal pleiotropy or violation of the MR assumption is indicated.[25]MR-PRESSO method was used to correct the IVW-estimate via outlier removal, when MR-PRESSO outlier test suggested the presence of outlying variants. All MR analysis were performed using R version (4.0.3) with the "TwoSampleMR" and "MRPRESSO" package.[26]

RESULTS

Study Selection

The initial search identified 30,775 studies. 30,749 studies were excluded after screening the titles or abstracts, and 11 studies were excluded after reading the full text (Figure 1). We finally included 15 studies in the meta-analysis.[6-8,27-38] Among them, 5 centers were included in the EURODIAB ACE(ED) study.

Study Characteristics and Quality Assessment

Table S3, S4 summarizes the detailed characteristics and quality assessment of all studies, respectively. Most articles were case-control studies. Geographical location included: Europe (12 studies), America (2 studies), and Asia (1 study). The total number in the 15 studies was 18,813 for cases (having T1DM) and 3,018,809 for controls (not having T1DM). The prevalence of asthma was 8.51% in the cases and 6.84%, in the controls. A moderate risk of bias was observed in the NOS assessment. The selection domain was mostly related to a case-control design; consecutive or representative sampling was not used. The exposure domain was assessed using questionnaire, and thus subjected to recall bias.

Meta-analysis

Two cohort studies reported HR as the measure for the risk of T1DM in asthmatic patients. There was significant heterogeneity ($I\ 2 = 90.2\%$, $P = 0.001$). In random-effects model analysis, pooled HR for the risk of T1DM was 1.30 (95% CI 1.05–1.61, P =0.014). Figure 2 shows the forest plot of the included studies.

Three studies reported HR as the measure for asthma risk in T1DM patients. There was significant heterogeneity ($I\ 2 = 92.7\%, P < 0.001$). In random-effects model analysis, pooled HR was 0.98 (95% CI 0.64–1.51,P =0.941). In the meta-analysis of the 12 studies that reported OR as the measure for asthma risk in T1DM patients, pooled OR was 0.84, 95% CI 0.65–1.08, P =0.168). Figure 3 shows the forest plot of the included studies. Subgroup analysis indicated that geographical location and quality grade could not explain the heterogeneity (Table S4). In meta-regression analysis, the observed heterogeneity could not be explained by the year of publication, region, incidence of asthma in the control group, sample size and quality score (Table

S5). Sensitivity analysis failed to show significant bias caused by any single study (Figure S1). Funnel plots indicated some degree of publication bias (Figure S2), but Begg's test did not confirm the bias (P of =0.82).

Mendelian Randomization Analysis

In the IVW analysis, children with asthma were at higher risk for T1DM (OR=1.308, 95% CI 1.030-1.661, P =0.028) (Table 1). Higher risk for T1DM in children with asthma was also apparent in MR-Egger analysis (OR=2.082, 95%CI 1.115-3.888, P=0.029). Analysis using the weighted median method failed to establish an association, but the direction of the general finding was consistent (OR=1.033, 95%CI 0.849-1.256, P=0.745) . Figure S3 illustrates method comparison plot(a) and forest plot(b). MR-Egger regression failed to identify evidence to support the existence of unbalanced pleiotropy in the genetic instruments (intercept β = -0.071, P = 0.126). The MR-PRESSO outlier test detected 2 specific horizontal pleiotropic outlier variants (rs4795399 and rs28407950). However, these 2 SNPs were not genome-wide significant associated with T1DM. The association of childhood asthma with T1DM was not statistically significant in MR-PRESSO outlier-corrected IVW analysis (OR = 1.175, 95%CI 0.960-1.438, P = 0.118).

IVW analysis suggested a protective effect of T1DM on the risk of childhood asthma (OR = 0.937, 95%CI 0.881-0.996, P = 0.037). Subsequent analysis using the MR-Egger (OR=0.918, 95%CI 0.850-0.991, P=0.041) and weighted median methods (OR=0.928, 95%CI 0.872-0.987, P=0.017) supported this finding. Figure S4 illustrates method comparison plot(a) and forest plot(b). No evidence of pleiotropy or outlier variants was found by either MR-Egger regression (intercept β = 0.016, p = 0.383) or MR-PRESSO outlier test.

DISCUSSION

In the current study, meta-analysis indicated an increased risk of T1DM in children with asthma, but not increased risk for asthma in children with T1DM. However, strong heterogeneity among the included studies was noted. Subgroup analysis, meta-regression, and sensitivity analysis failed to identify the sources of heterogeneity.

The results of MR analysis were not completely consistent with that of the meta-analysis. Specifically, children with asthma had higher risk of T1DM, whereas children with T1DM had lower risk of asthma. The importance in sequential appearance of the two diseases was apparently illustrates. However, in the majority of the included studies, it was not clear whether an asthma diagnosis or symptoms preceded the T1DM diagnosis, which could lead to reverse causality.[27-38]Only 3 cohort studies documented the sequence of disease occurrence, but the results were still conflicting.[6-8] The results of MR analysis are consistent with a previous cohort study by Metsala et al[7]. Similarly, Smew et al[6]indicated that childhood asthma was related to an increased risk of subsequent T1DM, whereas T1DM was not associated with a decreased risk of subsequent asthma. Hisiao et al[8], however, reported a markedly higher incidence of asthma in patients with T1DM in the Asian population. It is important to note that the MR analysis data came from European population. Whether the results of MR analysis in the current study could be extrapolated to other populations remained unknown.

Both nurture (i.e. the environment) and nature (i.e. genetics) contribute to the etiology of both asthma and T1DM. Asthma and T1DM tend to be comorbid and congregate within families.[6]Siblings of children with one disease have higher risk of the other disease.[6] For example, TLR2 rs3804100 T allele has been shown to be a susceptibility allele for both childhood asthma and T1DM.[39] In contrast, the T allele of rs9273349 and rs1063355 in HLA-DQB1 seems to be a protective factor to both diseases.[16] Adding to the complexity, susceptibility genes to one disease could be protective to the other disease. For example, GIMAP5 SNP (rs6965571) has been associated with increased risk for asthma but decreased risk for T1DM.[40] Future GWAS studies are required to better characterize the potential link between them.[41]

At a mechanistic level, lower risk of asthma in children with T1DM could be attributed to the anti-inflammatory properties of insulin. High levels of insulin promote Airway smooth muscle (ASM) contraction, enhance contractile responses to methacholine, which are likely to result in increased airway hyperresponsiveness, bronchoconstriction, and airway remodeling.[42] Insulin deficiency in T1DM could prevent airway

remodeling.[43] A recent study in a mouse model for asthma showed that insulin deficiency could prevent the development of allergic inflammation, eosinophilic pulmonary infiltration, and airway hyperresponsiveness in an asthma mouse model.[44] These findings mainly explain the reduced risk of asthma in patients with T1DM, but lacking mechanistic research on the increased risk of T1DM in children with asthma. The use of some anti-asthmatic drugs (inhaled corticosteroids and inhaled β-agonists) was potentially associated with the risk of T1DM in a case-cohort study. Therefore, future research is required to explore the underlying biological mechanisms of this relationships.

MR analysis makes sense only when it uses IVs that are: (1) associated with the exposure; (2) independent of factors confounding the association of the exposure and outcome; and (3) associated with the outcome only through exposure. With these premises, MR analysis can work as an analogue to RCT, which is more plausible to identify causality than observational analysis.[45] To satisfy the first assumption, we selected only SNPs with a genome-wide significant association ($P < 5*10^{-8}$) and the F statistic at > 10.[14] The second assumption is not verifiable. To satisfy the third assumption, MR-Egger regression was used to estimate horizontal pleiotropy.[23] Since these premises were fulfilled in our MR analysis, we believe that our findings were reached with least likelihood of confounding effects and maximal avoidance of reverse causality.

The meta-analysis in the current study has several limitations. First, majority of the studies included in the analysis are of case-control design; only three cohort studies were included. Second, due to the low prevalence of T1DM, most included studies were based on T1DM and considered asthma as potential risk factors. Third, there was significant heterogeneity among the included studies, but we were unable to identify the source of heterogeneity. The MR analysis also has several important limitations. First, the MR analysis used only one dataset, and lacks validation. Second, some of the SNPs (such as rs4795399 and rs28407950) utilized in this study are potentially correlated with confounding factors which may also influence the risk of T1DM or childhood asthma. We were unable to completely rule out the possible impact of pleiotropic effects on the findings. Third, the MR analysis data came from European population only, and whether the findings could be extrapolated to other populations remains unknown.

Conclusion

Childhood asthma is a risk factor for T1DM. In contrast, T1DM is a possible protective factor for childhood asthma. These findings encourage T1DM screening in children with asthma.

Contributors

Conception and design: Junyang Xie, Weixing Liu and Xiaowen Zhang; (II) Administrative support: Xiaowen Zhang; (III) Data analysis and interpretation: Chen Gui, Tianhao Liang, Ang Li, Yiyan Wang, Xiaofen Wang, Xiaoxuan Kuang, Wenjing Liao and Lijuan Song; (IV) Manuscript writing: All authors; (V) Final approval of manuscript: All authors.

Declaration of interests

All authors declare no competing interests.

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Data sharing

Our study is based on published data. The data supporting the findings of this study are available within this article and the appendix, and all data retrieved from original papers, together with tables and figures arising from these data, are available to share.

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Ethical Considerations

No ethical clearance was required for this research, since no human subjects were directly involved in the development of the research question or its outcome measures. Only secondary analysis was performed using published GWAS summary statistics available in the public domain.

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Table 1. MR estimates of the causality between childhood asthma and T1DM.

Exposure	Outcome	nSNP	method	OR	95% CI	P
Childhood asthma	T1DM	32	IVW	1.308	1.030, 1.661	0.028
			MR-Egger	2.082	1.115, 3.888	0.029
			Weighted median	1.033	0.849, 1.256	0.745
T1DM	Childhood asthma	20	IVW	0.937	0.881, 0.996	0.037
			MR-Egger	0.918	0.850, 0.991	0.041
			Weighted median	0.928	0.872, 0.987	0.017

Note: MR: Mendelian randomization; T1DM: type 1 diabetes mellitus; nSNP: number of single-nucleotide polymorphism; OR: odds ratios; CI: confidence interval; IVW: inverse variance weighted.

Figure legends

Figure 1 Flow diagram detailing the search strategy and identification of studies used in meta-analysis. *Reasons for exclusion of the 11 studies were: 2 studies used the replicated data from the same study population, 1 study not published in English, 7 studies with small sample sizes, and 1 study not related to the childhood period.

Figure 2 Meta-analysis of studies of asthma and the risk of type 1 diabetes using the random-effects model, ordered by date of publication.

Note: HR: hazard ratio; CI: confidence interval.

Figure 3 Meta-analysis of studies of type 1 diabetes and the risk of asthma using the random-effects model, ordered by date of publication.

Note: HR: hazard ratio; OR: odds ratio; CI: confidence interval.

Supplementary materials

Figure S1 Sensitivity analyses. The results indicated that none of the studies had a significant impact on the effects with regard to the outcomes mentioned above.

Figure S2 Funnel plots of observational studies of asthma exposures and diabetes.

Figure S3 Scatter plot and Forest plot. A: Scatter plot of SNP potential effects of childhood asthma and the risk of T1DM, with the slope of each line corresponding to estimated MR effect per method; B: Forest plot of the MR-based effect sizes of childhood asthma exposure instruments on FinnGen T1DM outcome.

Note: SNP: single-nucleotide polymorphism; IVW: inverse variance weighted method.

Figure S4 Scatter plot and Forest plot. A: Scatter plot of SNP potential effects of T1DM and the risk of childhood asthma, with the slope of each line corresponding to estimated MR effect per method; B: Forest plot of the MR-based effect sizes of T1DM exposure instruments on FinnGen childhood asthma outcome.

Note: SNP: single-nucleotide polymorphism; IVW: inverse variance weighted method.