Eco-Environment & Health 3 (2024) 452–457

Contents lists available at ScienceDirect

Eco-Environment & Health

journal homepage: www.journals.elsevier.com/eco-environment-and-health

Original Research Article

Styrene and ethylbenzene exposure and type 2 diabetes mellitus: A longitudinal gene–environment interaction study

Linling Yu [a,b,c], Wei Liu [a,c], Yongfang Zhang [a,c], Qiyou Tan [a,c], Jiahao Song [a,c], Lieyang Fan [a,c], Xiaojie You [a,c], Min Zhou [a,c], Bin Wang [a,c,*], Weihong Chen [a,c,*]

[a] Department of Occupational and Environmental Health, School of Public Health, Tongji Medical College, Huazhong University of Science and Technology, Wuhan 430030, China
[b] Department of Public Health, Tongji Hospital, Tongji Medical College, Huazhong University of Science and Technology, Wuhan 430030, China
[c] Key Laboratory of Environment and Health, Ministry of Education & Ministry of Environmental Protection, and State Key Laboratory of Environmental Health (Incubating), School of Public Health, Tongji Medical College, Huazhong University of Science and Technology, Wuhan 430030, China

ARTICLE INFO

Keywords:
Styrene
Ethylbenzene
Type 2 diabetes mellitus
Genetic risk score
Gene–environment interaction

ABSTRACT

Styrene and ethylbenzene (S/EB) are identified as hazardous air contaminants that raise significant concerns. The association between S/EB exposure and the incidence of type 2 diabetes mellitus (T2DM), and the interaction between genes and environment, remains poorly understood. Our study consisted of 2219 Chinese adults who were part of the Wuhan-Zhuhai cohort. A follow-up assessment was conducted after six years. Exposure to S/EB was quantified by determining the concentrations of urinary biomarkers of exposure to S/EB (UBE-S/EB; urinary phenylglyoxylic acid level plus urinary mandelic acid level). Logistic regression models were constructed to investigate the relations of UBE-S/EB and genetic risk score (GRS) with T2DM prevalence and incidence. The interaction effects of UBE-S/EB and GRS on T2DM were investigated on multiplicative and additive scales. UBE-S/EB was dose-dependently and positively related to T2DM prevalence and incidence. Participants with high levels of UBE-S/EB [relative risk (RR) = 1.930, 95% confidence interval (CI): 1.157–3.309] or GRS (1.943, 1.110–3.462) demonstrated the highest risk of incident T2DM, in comparison to those with low levels of UBE-S/EB or GRS. Significant additive interaction between UBE-S/EB and GRS on T2DM incidence was discovered with relative excess risk due to interaction (95% CI) of 0.178 (0.065–0.292). The RR (95% CI) of T2DM incidence was 2.602 (1.238–6.140) for individuals with high UBE-S/EB and high GRS, compared to those with low UBE-S/EB and low GRS. This study presented the initial evidence that S/EB exposure was significantly related to increased risk of T2DM incidence, and the relationship was interactively aggravated by genetic predisposition.

1. Introduction

Diabetes poses a significant global public health challenge, with a dramatically increasing prevalence projected in the coming years. In 2021, the global count of adults with diabetes reached 537 million, with estimates predicting an increase to 643 million by 2030 and 783 million by 2045 [1]. Over 90% of these diabetes instances are type 2 diabetes mellitus (T2DM), which has been recognized as a major global health threat [2]. Numerous epidemiological studies have linked environmental pollution to a higher incidence of T2DM, underscoring its significant impact [3–6].

Identified as hazardous contaminants in the air, styrene and ethylbenzene (S/EB) have drawn worldwide concern [7]. As fundamental building blocks of materials like polystyrene and polyethylene, S/EB emissions persist in the environment due to the widespread use of related products, including plastics, synthetic rubbers, and various resins [8]. Additionally, S/EB are present in food packed using polystyrene and polyethylene materials [9], and are also found in tobacco smoke, vehicle exhaust [10], and sanitizers [11]. The use of hand sanitizers containing S/EB has witnessed a significant increase during the global coronavirus pandemic that began in 2019 (COVID-19) as they aid in preventing viral spread [11]. Considering the ubiquity of S/EB in the environment and the heightened exposure of the general population to these substances, it is imperative to investigate the potential health implications associated with S/EB exposure. Of particular interest is the possible role of S/EB exposure in the development of abnormal glucose metabolism, a risk factor and precursor of T2DM, as prior animal studies have indicated [12, 13]. However, to our knowledge, no prior epidemiological research has explored the link between S/EB exposure and T2DM.

* Corresponding authors.
E-mail addresses: gentwong@163.com (B. Wang), wchen@mails.tjmu.edu.cn (W. Chen).

https://doi.org/10.1016/j.eehl.2024.07.001
Received 9 January 2024; Received in revised form 12 June 2024; Accepted 21 July 2024
Available online 12 August 2024

Genetics has been firmly established as a significant determinant in the development of T2DM [14]. However, single nucleotide polymorphisms (SNPs) provide limited genetic information. Over the past decade, genome-wide association studies (GWAS) have pinpointed numerous SNPs linked to T2DM [15–17]. These SNPs can be used to calculate a genetic risk score (GRS), providing a comprehensive assessment of cumulative genetic effects [18]. However, the contribution of genetic susceptibility to the relationship between S/EB exposure and the risk of T2DM remains poorly understood. Exploring the potential interaction between GRS and S/EB exposure to T2DM could facilitate targeted intervention for high-risk populations and inform public health strategies for T2DM prevention [19,20].

Therefore, we conducted this prospective cohort study aiming to evaluate the link between exposure to S/EB and the incidence of T2DM in an urban general population. Additionally, GRS for T2DM was introduced into our study to assess the impact of gene–environment interaction on T2DM.

2. Methods

2.1. Study population

All participants of this research were derived from the Wuhan-Zhuhai cohort, which has been thoroughly described in a previous publication [21]. Briefly, the cohort originally recruited 4812 individuals aged 18–80 years in China between 2011 and 2012, and physical examinations, questionnaires, and blood and urine samples were gathered. In the questionnaire, data concerning the occupational histories of the participants were collected. The subjects involved in this study had no occupational exposure to S/EB. After excluding individuals with missing data on urinary biomarkers of exposure to S/EB (UBE-S/EB) (n = 1089) or genotyping (n = 1405), as well as those with kidney disease (n = 99), a total of 2219 individuals were included for the cross-sectional analysis. At the follow-up after six years, 1236 participants completed the glycemic test and UBE-S/EB detection, after excluding those with T2DM at baseline or with kidney disease at follow-up. The fundamental characteristics and health-related factors, such as age, smoking status, drinking status, physical exercise, and family history of diabetes, showed no significant statistical differences between the included and excluded populations ($P > 0.05$). All participants provided informed consent. The study received approval from the Ethics and Human Subject Committee of Tongji Medical College Huazhong University of Science and Technology (No. 2011-17).

2.2. Measurement of S/EB exposure biomarker

According to previous studies, the sum of urinary mandelic acid (MA) and phenylglyoxylic acid (PGA) levels serves as credible UBE-S/EB [9,22]. The quantifications of PGA and MA were conducted through ultra-high performance liquid chromatography (Agilent 1290 Infinity II; Agilent Technologies Inc., Santa Clara, CA)-tandem mass spectrometry (Sciex API 6500 Triple Quad; Applied Biosystems, Foster City, CA). The measurement methodology and quality control procedures were detailed in our previously published study [22]. The limits of detection (LODs) were 4.0 ng/mL for PGA and 13.0 ng/mL for MA. For participants (less than 11%) with MA or PGA concentration below the LOD, an imputed value of $1/\sqrt{2}$ LOD was applied. To account for urinary dilution, the S/EB metabolite levels were adjusted for urinary creatinine (Cr) levels and reported in mg/g Cr.

2.3. T2DM ascertainment

Following the guidelines of the American Diabetes Association, the identification of T2DM was established through one or more of the following criteria: (1) utilization of antidiabetic medicine, (2) a diagnosis of T2DM confirmed by a physician and reported by the patient, or (3) a fasting plasma glucose level of 7.0 mmol/L or above [23]. The fasting plasma glucose measurement was performed using the RX Daytona fully-automatic biochemical analyzer (Randox Laboratories, Crumlin, U.K.).

2.4. Genotyping and genetic risk score calculation

DNA extraction was performed on whole blood samples preserved at −80 °C utilizing the Bioteke Whole Blood DNA Extraction Kit (Beijing, China). The genotyping process employed the Illumina Infinium OmniZhongHua-8 v1.3 BeadChip (CA, USA), which covers >890,000 autosomal SNPs. We performed genotype imputation in EAGLE2 and Minimac4, using the 1000 Genomes Phase 3 multiethnic reference panel. Quality control procedures in detail were documented in our previously published research [24].

GRS for T2DM was developed using summary statistics from GWAS available in the Biobank Japan (BBJ) dataset (http://jenger.riken.jp/en/result). For this study, we utilized 205 SNPs identified from previously published literature [25,26], as detailed in Supplementary Table S1. The number of risk alleles for every SNP was weighted according to the association strength with T2DM in the BBJ dataset, as follows:

$$\mathrm{GRS} = \sum_{i=1\ldots n} w_i X_i$$

The PRSice 2.0 program was employed to compute GRS. The GRS incorporates n SNPs, and each variant is assigned a weight w_i based on its association with the trait; X_i represents the count of effective alleles for each SNP, which can take on values of 0, 1, or 2. The GRS was normalized to a Z-score [mean = 0 and the standard deviation (SD) = 1]. The top ten principal components of ancestry were derived from PLINK's Principal Components Analysis.

2.5. Statistical analysis

The value of UBE-S/EB was naturally log-transformed, given the skewed distribution. The study population was classified into three categories based on the lower (P25) and upper (P75) quartiles of UBE-S/EB concentration at baseline (<P25, P25–P75, and ≥P75). Trend tests were performed using analysis of variance (ANOVA) for continuous data, while trend chi-square tests were employed for categorical data.

Logistic regression models were utilized to evaluate the cross-sectional and longitudinal associations of UBE-S/EB and GRS, both as continuous and categorical variables, with the risk of T2DM. In longitudinal analysis, the S/EB exposure level of each participant was determined by calculating the average concentration derived from baseline and follow-up measurements. The analysis accounted for a range of covariates identified through a review of the literature and preliminary analysis, including age (years), gender (male/female), body mass index (BMI, kg/m^2), smoking status (smoker/ex-smoker/non-smoker), passive smoking (yes/no), drinking status (drinker/ex-drinker/non-drinker), physical activity (active/inactive), educational attainment (up to primary school/junior or senior high school/college degree or beyond), annual household income (<forty thousand yuan/≥forty thousand yuan), family history of T2DM (yes/no), and city (Wuhan/Zhuhai). Furthermore, the association between GRS and T2DM was additionally adjusted for the first ten principal components of ancestry. Stratified analyses were performed based on several covariates such as age, gender, BMI, passive smoking, drinking status, smoking status, physical activity, educational attainment, annual household income, and family history of diabetes. To assess the potential modification effect of these covariates on the relationship between UBE-S/EB and T2DM, a product term of UBE-S/EB with each covariate was included in the regression model, with P for modification accordingly estimated.

For the gene–environment interaction assessment, participants were classified into four groups based on their S/EB exposure status

[low (<P75)/high (≥P75) level of UBE-S/EB] and GRS level [low (<P75)/high (≥P75)]. The relative risk (RR) of developing T2DM was estimated using logistic regression models, with the reference group being those with low UBE-S/EB and low GRS. To estimate the multiplicative interaction between genetic predisposition and S/EB exposure, we added an interaction term between UBE-S/EB and GRS into the regression models. In addition, the relative excess risk due to interaction (RERI) and attributable proportion (AP) was estimated to assess the additive interaction between genetic predisposition and S/EB exposure regarding T2DM. The additive interaction was considered insignificant if the 95% confidence interval (CI) of RERI or AP included 0 [27,28].

To examine the robustness of the relations between UBE-S/EB, GRS, and the risk of T2DM, further adjustment for diet frequency and ambient ozone was performed. Diet is one of the main factors affecting the risk of T2DM [29]. Diet frequency was evaluated by the number of times per month for consuming seven food categories, including fishery products, meats, cereals, coarse grains, fruits and vegetables, pickles and smoked items, as well as eggs and milk. Volatile organic compounds, including S/EB, are key precursors to ozone [30], which is also a risk factor for T2DM. Therefore, adjusting for ozone levels when assessing the health impacts of S/EB on T2DM provides a more precise understanding of the effects of S/EB. The ambient ozone level was estimated by a random forest model at 1 km spatial resolution [31].

Statistical evaluations were executed using R software, version 4.1.3. Logistic regression analysis was conducted using "lmerTest" package, additive interaction analysis was conducted using "epiR" package. A *P*-value of less than 0.05, determined via a two-tailed test, was considered to indicate statistical significance.

3. Results

3.1. Baseline characteristics of the study population

This study involved 2219 participants, with a proportion of males of 30.91%, the mean age was 53.62 years, and the average BMI was 24.25 kg/m^2. As the levels of UBE-S/EB increased, significant positive trends were observed in age and the percentages of drinkers, smokers, participants with lower educational achievements (up to primary education), and those with a family history of diabetes, as well as the prevalence of T2DM (Table 1).

3.2. Associations between UBE-S/EB, GRS, and T2DM

After adjusting for covariates, significant positive associations were observed between UBE-S/EB and the risks of T2DM prevalence and incidence. Each 1 unit increment in the ln-transformed level of UBE-S/EB was related to a 45.5% higher risk of prevalent T2DM [odds ratio (OR) = 1.455, 95% CI: 1.189–1.776] (Fig. 1). In the longitudinal analysis, subjects with upper quartile level of UBE-S/EB showed a 93% increased risk of developing T2DM (RR = 1.930, 95% CI: 1.157–3.309) when compared with those in the lowest quartile (Fig. 1). A significant increasing trend in incident T2DM risk was observed with an elevating level of UBE-S/EB (*P* for trend = 0.018). We observed similar results after further adjusting for diet frequency and ambient ozone (Tables S2 and S3). Stratified analyses indicated that age, gender, BMI, smoking status, drinking status, passive smoking, physical activity, educational attainment, annual household income, or city did not significantly alter the relationship between UBE-S/EB and T2DM risk (all *P* for modification > 0.05) (Tables S4 and S5).

In addition, an SD increase in GRS was related to a 50.5% increase in the risk of prevalent T2DM (OR = 1.505, 95% CI: 1.311–1.728) (Fig. 2). Compared to participants with lower quartile levels of GRS, those with upper quartile levels of GRS had a 94.3% elevated risk of incident T2DM (RR = 1.943, 95% CI: 1.110–3.462) (*P* and *P* for trend < 0.05) (Fig. 2). The results barely changed after further adjusting for diet frequency and ambient ozone (Tables S2 and S3).

3.3. Combined effect of UBE-S/EB and GRS on T2DM

In cross-sectional analysis, participants with high UBE-S/EB and high GRS showed a significantly elevated risk of prevalent T2DM compared with those with low UBE-S/EB and low GRS (OR = 3.182, 95% CI: 1.994–4.930) (Table 2). The RERI (95% CI) and AP (95% CI) for the

Table 1
Baseline characteristics of participants stratified by UBE-S/EB level (n = 2219).

Characteristics	All participants	UBE-S/EB level (mg/g Cr)			*P* for trend
		<P25 (0.12)	P25–P75 (0.12–0.28)	≥P75 (0.28)	
No. subjects	2219	555	1109	555	
Age, years	53.62 ± 11.58	53.17 ± 12.25	53.25 ± 11.36	54.81 ± 11.25	0.006
Male, %	686 (30.91)	167 (30.09)	303 (27.32)	216 (38.92)	<0.001
BMI, kg/m^2	24.25 ± 3.44	24.25 ± 3.28	24.35 ± 3.46	24.02 ± 3.54	0.206
Smoker, %					<0.001
Smoker	347 (15.64)	52 (9.37)	130 (11.72)	165 (29.73)	
Ex-smoker	119 (5.36)	29 (5.23)	61 (5.50)	29 (5.23)	
Non-smoker	1753 (79.00)	474 (85.41)	918 (82.78)	361 (65.05)	
Drinking status, %					<0.001
Drinker	314 (14.15)	67 (12.07)	134 (12.08)	113 (20.36)	
Ex-drinker	67 (3.02)	23 (4.14)	23 (2.07)	21 (3.78)	
Non-drinker	1838 (82.83)	465 (83.78)	952 (85.84)	421 (75.86)	
Passive smoking, %					0.695
Yes	942 (42.45)	244 (43.96)	467 (42.11)	231 (41.62)	
No	1277 (57.55)	311 (56.04)	642 (57.89)	324 (58.38)	
Physical activity, %					0.658
Active	1067 (48.08)	262 (47.21)	529 (47.70)	276 (49.73)	
Inactive	1152 (51.92)	293 (52.79)	580 (52.30)	279 (50.27)	
Educational attainment, %					0.026
Up to primary school	587 (26.45)	121 (21.80)	307 (27.68)	159 (28.65)	
Junior or senior high school	1389 (62.60)	362 (65.23)	694 (62.58)	333 (60.00)	
College degree or beyond	243 (10.95)	72 (12.97)	108 (9.74)	63 (11.35)	
Annual household income					0.145
<forty thousand yuan	1241 (55.93)	307 (55.32)	604 (54.46)	330 (59.46)	
≥forty thousand yuan	978 (44.07)	248 (44.68)	505 (45.54)	225 (40.54)	
Family history of diabetes, %	135 (6.08)	30 (5.41)	65 (5.86)	40 (7.21)	0.413
T2DM, %	202 (9.10)	38 (6.85)	87 (7.84)	77 (13.87)	<0.001

Data are mean ± SD or percentage (%). BMI, body mass index; SD, standard deviation; UBE-S/EB, urinary biomarker of exposure to styrene and ethylbenzene; T2DM, type 2 diabetes mellitus.

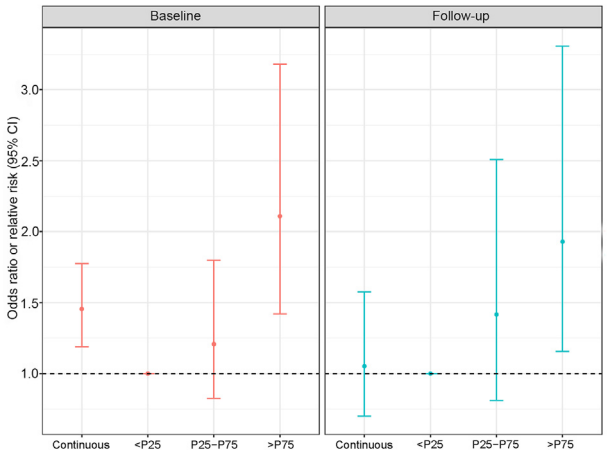

Fig. 1. Associations of UBE-S/EB with the prevalence and incidence risk of T2DM. Adjusted for age, gender, BMI, smoking status, passive smoking, drinking status, physical activity, educational attainment, annual household income, family history of diabetes, and city. CI, confidence interval.

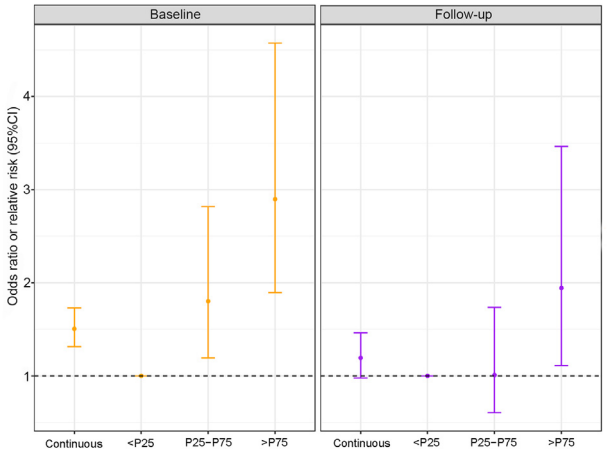

Fig. 2. Associations of GRS with the prevalence and incidence risk of T2DM. Adjusted for age, gender, BMI, smoking status, passive smoking, drinking status, physical activity, educational attainment, annual household income, family history of diabetes, city, and the first 10 principal components of ancestry. GRS, genetic risk score.

additive interaction between GRS and UBE-S/EB were 0.242 (0.051–0.433) and 0.118 (0.066–0.170), respectively (Table 2). Meanwhile, the multiplicative interaction was not observed with *P* for interaction = 0.706.

In longitudinal analysis, participants with high UBE-S/EB and low GRS had a significantly elevated risk of incident T2DM (RR = 2.186, 95% CI: 1.090–5.012), as did participants with high UBE-S/EB and high GRS (RR = 2.602, 95% CI: 1.238–6.140) when compared to those with low UBE-S/EB and low GRS (Table 2). However, no significant multiplicative interaction between UBE-S/EB and GRS was observed (*P* for interaction = 0.099) (Table 2). A positive additive interaction between UBE-S/EB and GRS on incident T2DM risk was observed. The RERI for the additive interaction between GRS and UBE-S/EB was 0.178 (95% CI: 0.065–0.292), suggesting the combined effect exceeds the additive individual effects by 0.178, contributing to 19.8% (AP = 0.198, 95% CI: 0.023–0.372) of the incidence of T2DM in subjects with both high UBE-S/EB level and high genetic risk (Table 2).

4. Discussion

This study presented the first attempt to examine the cross-sectional and longitudinal relationship of UBE-S/EB with the risk of T2DM, as well as the interaction role of genetic susceptibility and S/EB exposure in T2DM risk. Our findings indicated that both S/EB exposure and higher GRS for T2DM were independently associated with increased prevalence and incidence of T2DM. Individuals with higher GRS combined with higher S/EB exposure exhibited significantly elevated prevalence and incidence of T2DM. Additionally, our findings revealed a notable additive interaction between S/EB exposure and GRS concerning both the prevalence and incidence of T2DM. This suggests that genetic predisposition amplifies the impact of S/EB exposure on the development and prevalence of T2DM.

Despite the U.S. Environmental Protection Agency identifying S/EB as significant environmental contaminants [7], research into the risk of T2DM due to S/EB exposure remains limited. Two population-based studies have examined the association of exposure to S/EB with elevated levels of blood glucose, a physical state of evolution towards T2DM [13,32]. A cross-sectional analysis of 3950 individuals from Canada revealed a positive correlation between S/EB exposure and elevated blood glucose levels, specifically in female participants [12]. A possible explanation for the unobserved gender difference in the results of our current study may be the lack of gender difference regarding S/EB exposure level (median level of UBE-S/EB: 0.20 mg/g Cr for men vs. 0.19 mg/g Cr for women, $P = 0.471$), T2DM genetic susceptibility (mean level of Z-score normalized GRS: 0 for men vs. 0 for women, $P = 0.703$), and ethnicity (proportion of Han Chinese: 99.4% for men vs. 99.5% for women, $P = 0.948$). Similarly, a case-control study revealed that workers who were exposed to styrene, a type of S/EB, exhibited higher levels of fasting glucose, homeostasis model assessment of insulin resistance, and fasting insulin [13], which are typical characteristics and early indicators of T2DM [33]. According to previous literature [34–36], the UBE-S/EB (60.90–137.80 mg/g Cr) concentration in workers occupationally exposed to S/EB is generally 300 to 1000 times higher than that in the population of this study. In our prospective cohort study, encompassing a representative sample of the general adult population, we provided potent evidence demonstrating a substantial rise in the risks of both prevalent and incident T2DM associated with elevated levels of UBE-S/EB, even at relatively lower concentrations. This finding suggested that S/EB exposure was related to the risk increment of developing T2DM.

The mechanisms explaining how exposure to S/EB leads to a heightened risk of T2DM remain not fully understood. Animal studies have documented dose-dependent increments in reactive oxygen species (ROS) and lipid peroxidation (LPO) following S/EB exposure [37,38]. The accumulation of ROS and LPO plays significant roles in promoting the development of T2DM and its complications [39,40]. Furthermore, S/EB exposure may influence the activation of crucial enzymes involved in gluconeogenesis [37] and the regulation of genes associated with islet glycogenolysis, leading to impairments in fasting glucose and glucose tolerance [41], both of which serve as preliminary signs of T2DM. It is worth noting that common genetic variants associated with T2DM may also be involved in the regulation of oxidative stress [42]. Thus, there is a possibility of an interaction effect between exposure to S/EB and genetic risk, which collectively contribute to the risk of developing T2DM.

Genetic susceptibility significantly contributes to T2DM onset, with estimated heritability rates ranging between 30% and 70% [43]. Over the past few decades, GWAS, with large sample sizes, have successfully identified numerous genes associated with T2DM susceptibility, primarily in European populations. However, a limited number of these European-derived loci have been identified in East Asian populations, with less than 50% showing consistent associations [44]. Notable exceptions include variants near TCF7L2, CDKAL1, IGF2BP2, SLC30A8, HNF1B, and FTO, which have shown associations with T2DM in both European and East Asian populations [45,46]. The lack of replication in East Asian populations may be attributable to notable interethnic disparities in both the frequency and effect size of these risk alleles. In our study, which was conducted on a general Chinese population with the vast majority (>99%) being Han Chinese, we constructed a GRS for

Table 2
The joint effect of UBE-S/EB and GRS on T2DM risk.

Category	RR (95% CI)	*P* for interaction	RERI (95% CI)	AP (95% CI)
Baseline				
Low UBE-S/EB + low GRS	Ref	0.706	0.242 (0.051, 0.433)	0.118 (0.066, 0.170)
Low UBE-S/EB + high GRS	2.114 (1.468, 3.021)			
High UBE-S/EB + low GRS	2.070 (1.427, 2.977)			
High UBE-S/EB + high GRS	3.182 (1.994, 4.930)			
Follow-up				
Low UBE-S/EB + low GRS	Ref	0.099	0.178 (0.065, 0.292)	0.198 (0.023, 0.372)
Low UBE-S/EB + high GRS	1.842 (0.644, 5.152)			
High UBE-S/EB + low GRS	2.186 (1.090, 5.012)			
High UBE-S/EB + high GRS	2.602 (1.238, 6.140)			

Adjusted for age, gender, BMI, smoking status, passive smoking, drinking status, physical activity, educational attainment, annual household income, family history of diabetes, city, and the first 10 principal components of ancestry. RR, relative risk; RERI, relative excess risk due to interaction; AP, attributable proportion due to interaction.

T2DM using the SNPs reported in GWAS conducted on large East Asian populations. We observed a consistent positive association between the GRS and the risk of T2DM.

Most previous studies examining gene–environment interactions related to T2DM have focused on individual genetic risk variants [19,47]. Few studies have investigated the interaction effects between environmental factors and GRS, which represents cumulative genetic effects, on the risk of T2DM. Our study revealed that individuals with a high GRS (indicating higher T2DM genetic susceptibility) had a significantly increased risk of developing T2DM associated with S/EB exposure. We revealed that genetic susceptibility exacerbated the impact of S/EB exposure on T2DM risk through an additive interaction. This allowed us to identify the specific diabetic effects of S/EB exposure on individuals with varying levels of genetic susceptibility. These findings have the potential to inform the development of personalized and precise strategies for T2DM prevention.

Our study has several notable strengths. Firstly, it represents the first investigation to assess the multiplicative and additive interaction effects of S/EB exposure and genetic variants on the prevalence and incidence of T2DM. This novel approach expands our understanding of the interplay between environmental and genetic factors in T2DM development. Secondly, we employed UBE-S/EB, namely the sum of MA and PGA in urine, as a robust indicator of individual S/EB exposure levels from all latent sources. This comprehensive assessment of S/EB exposure enhances the accuracy and validity of our findings. Thirdly, our study benefits from a relatively large, representative sample of the general urban middle-aged and elderly population with daily-life S/EB exposure in China [21], ensuring a prospective design that enhances statistical power and strengthens the credibility of our findings.

Nevertheless, some limitations should be acknowledged in our study. Firstly, we were unable to obtain external S/EB exposure data, such as ambient S/EB levels, which could have provided additional insights. Future investigations could explore the association between exposure to external S/EB and T2DM risk to provide a more comprehensive understanding of the environmental factors at play. Secondly, environmental pollutants consist of various components besides S/EB, and we were unable to include other unmeasured chemicals, such as perfluoroalkyl compounds, which may be associated with T2DM. Addressing the challenge of multi-pollutant exposure is complex and a great challenge in environmental epidemiology research. Thirdly, the measurement of UBE-S/EB concentration was performed using a spot morning urine sample rather than a 24-h urine sample. This approach may incur measurement error and the possibility of inaccurately categorizing S/EB exposure levels. Nonetheless, it is worth noting that conducting 24-h urine collection in large-scale epidemiological studies poses significant logistical and financial challenges. In contrast, the use of spot morning urine samples is extensively accepted and recognized, and employed in a large number of relevant research [22,48–50]. Additionally, we employed mean UBE-S/EB concentrations to represent S/EB exposure levels over a six-year period. While this method streamlines the analysis, it may not precisely capture the fluctuations and potential peak exposures that could influence the risk of developing T2DM.

5. Conclusions

In conclusion, our study provided novel and potent evidence demonstrating significant associations between S/EB exposure and increased risks of both prevalent and incident T2DM. Moreover, we found that genetic predisposition factors exacerbated the adverse impact of S/EB on T2DM risk increment. These findings provide scientific evidence for formulating preventive strategies targeting T2DM and establishing regulations related to environmental pollution by S/EB.

CRediT authorship contribution statement

Linling Yu: Writing – review & editing, Writing – original draft, Visualization, Validation, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Wei Liu:** Writing – review & editing, Validation, Investigation. **Yongfang Zhang:** Writing – review & editing, Supervision, Methodology. **Qiyou Tan:** Writing – review & editing, Investigation. **Jiahao Song:** Writing – review & editing, Investigation. **Lieyang Fan:** Writing – review & editing, Investigation. **Xiaojie You:** Writing – review & editing, Investigation. **Min Zhou:** Writing – review & editing, Investigation. **Bin Wang:** Writing – review & editing, Validation, Supervision, Methodology, Investigation, Funding acquisition, Data curation, Conceptualization. **Weihong Chen:** Writing – review & editing, Supervision, Resources, Project administration, Investigation, Funding acquisition, Data curation, Conceptualization.

Declaration of competing interests

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgment

This study was supported by National Natural Science Foundation of China (82241088; 82203996).

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.eehl.2024.07.001.

References

[1] IDF, International Diabetes Federation Diabetes Atlas, tenth ed., 2021.
[2] WHO, Global Report on Diabetes, 2016. https://iris.who.int/bitstream/handle/10665/204871/9789241565257_eng.pdf?sequence=1.

[3] K. Cervantes-Martínez, D. Stern, J.S. Zamora-Muñoz, R. López-Ridaura, J.L. Texcalac-Sangrador, A. Cortés-Valencia, et al., Air pollution exposure and incidence of type 2 diabetes in women: a prospective analysis from the Mexican Teachers' Cohort, Sci. Total Environ. 818 (2022) 151833, https://doi.org/10.1016/j.scitotenv.2021.151833.
[4] GBD, Estimates, trends, and drivers of the global burden of type 2 diabetes attributable to PM(2·5) air pollution, 1990-2019: an analysis of data from the Global Burden of Disease Study 2019, Lancet Planet. Health 6 (2022) e586–e600, https://doi.org/10.1016/s2542-5196(22)00122-x.
[5] R. Li, M. Cai, Z.M. Qian, X. Wang, Z. Zhang, C. Wang, et al., Ambient air pollution, lifestyle, and genetic predisposition associated with type 2 diabetes: findings from a national prospective cohort study, Sci. Total Environ. 849 (2022) 157838, https://doi.org/10.1016/j.scitotenv.2022.157838.
[6] H. Xu, Y. Jia, Z. Sun, J. Su, Q.S. Liu, Q. Zhou, et al., Environmental pollution, a hidden culprit for health issues, Eco-Environ. Health 1 (2022) 31–45, https://doi.org/10.1016/j.eehl.2022.04.003.
[7] EPA, The Clean Air Act Amendments of 1990 List of Hazardous Air Pollutants, 2010.
[8] I. Ciucanu, M. Kaykhaii, L. Montero, J. Pawliszyn, J. Szubra, Continuous monitoring of thermooxidative degradation products of polystyrene by membrane extraction with sorbent interface and gas chromatography, J. Chromatogr. Sci. 40 (2002) 350–354, https://doi.org/10.1093/chromsci/40.6.350.
[9] K.M. Capella, K. Roland, N. Geldner, B. Rey de Castro, V.R. De Jesús, D. van Bemmel, et al., Ethylbenzene and styrene exposure in the United States based on urinary mandelic acid and phenylglyoxylic acid: NHANES 2005-2006 and 2011-2012, Environ. Res. 171 (2019) 101–110, https://doi.org/10.1016/j.envres.2019.01.018.
[10] W. Tang, I. Hemm, G. Eisenbrand, Estimation of human exposure to styrene and ethylbenzene, Toxicology 144 (2000) 39–50, https://doi.org/10.1016/s0300-483x(99)00188-2.
[11] V.K. Pal, S. Lee, M. Naidu, C. Lee, K. Kannan, Occurrence of and dermal exposure to benzene, toluene and styrene found in hand sanitizers from the United States, Environ. Int. 167 (2022) 107449, https://doi.org/10.1016/j.envint.2022.107449.
[12] S. Cakmak, C. Cole, C. Hebbern, J. Andrade, R. Dales, Associations between blood volatile organic compounds, and changes in hematologic and biochemical profiles, in a population-based study, Environ. Int. 145 (2020) 106121, https://doi.org/10.1016/j.envint.2020.106121.
[13] Y.L. Won, Y. Ko, K.H. Heo, K.S. Ko, M.Y. Lee, K.W. Kim, The effects of long-term, low-level exposure to monocyclic aromatic hydrocarbons on worker's insulin resistance, Saf. Health Work 2 (2011) 365–374, https://doi.org/10.5491/shaw.2011.2.4.365.
[14] J.B. Cole, J.C. Florez, Genetics of diabetes mellitus and diabetes complications, Nat. Rev. Nephrol. 16 (2020) 377–390, https://doi.org/10.1038/s41581-020-0278-5.
[15] A. Mahajan, C.N. Spracklen, W. Zhang, M.C.Y. Ng, L.E. Petty, H. Kitajima, et al., Multi-ancestry genetic study of type 2 diabetes highlights the power of diverse populations for discovery and translation, Nat. Genet. 54 (2022) 560–572, https://doi.org/10.1038/s41588-022-01058-3.
[16] C.N. Spracklen, M. Horikoshi, Y.J. Kim, K. Lin, F. Bragg, S. Moon, et al., Identification of type 2 diabetes loci in 433,540 East Asian individuals, Nature 582 (2020) 240–245, https://doi.org/10.1038/s41586-020-2263-3.
[17] A. Xue, Y. Wu, Z. Zhu, F. Zhang, K.E. Kemper, Z. Zheng, et al., Genome-wide association analyses identify 143 risk variants and putative regulatory mechanisms for type 2 diabetes, Nat. Commun. 9 (2018) 2941, https://doi.org/10.1038/s41467-018-04951-w.
[18] P. Zhuang, X. Liu, Y. Li, X. Wan, Y. Wu, F. Wu, et al., Effect of diet quality and genetic predisposition on hemoglobin A(1c) and Type 2 diabetes risk: gene-diet interaction analysis of 357,419 individuals, Diabetes Care 44 (2021) 2470–2479, https://doi.org/10.2337/dc21-1051.
[19] M.C. Cornelis, F.B. Hu, Gene-environment interactions in the development of type 2 diabetes: recent progress and continuing challenges, Annu. Rev. Nutr. 32 (2012) 245–259, https://doi.org/10.1146/annurev-nutr-071811-150648.
[20] V. Grishkevich, I. Yanai, The genomic determinants of genotype × environment interactions in gene expression, Trends Genet. 29 (2013) 479–487, https://doi.org/10.1016/j.tig.2013.05.006.
[21] Y. Song, J. Hou, X. Huang, X. Zhang, A. Tan, Y. Rong, et al., The Wuhan-Zhuhai (WHZH) cohort study of environmental air particulate matter and the pathogenesis of cardiopulmonary diseases: study design, methods and baseline characteristics of the cohort, BMC Public Health 14 (2014) 994, https://doi.org/10.1186/1471-2458-14-994.
[22] L. Yu, B. Wang, W. Liu, T. Xu, M. Yang, X. Wang, et al., Cross-sectional and longitudinal associations of styrene and ethylbenzene exposure with heart rate variability alternation among urban adult population in China, Sci. Total Environ. 845 (2022) 157231, https://doi.org/10.1016/j.scitotenv.2022.157231.
[23] American Diabetes Association Professional Practice Committee, 2. Classification and diagnosis of diabetes: standards of medical care in diabetes-2022, Diabetes Care 45 (Supplement_1) (2022) S17–S38, https://doi.org/10.2337/dc22-S002.
[24] J. Ma, X. Hao, X. Nie, S. Yang, M. Zhou, D. Wang, et al., Longitudinal relationships of polycyclic aromatic hydrocarbons exposure and genetic susceptibility with blood lipid profiles, Environ. Int. 164 (2022) 107259, https://doi.org/10.1016/j.envint.2022.107259.
[25] J. Chen, C.N. Spracklen, G. Marenne, A. Varshney, L.J. Corbin, J. Luan, et al., The trans-ancestral genomic architecture of glycemic traits, Nat. Genet. 53 (2021) 840–860, https://doi.org/10.1038/s41588-021-00852-9.
[26] K. Ishigaki, M. Akiyama, M. Kanai, A. Takahashi, E. Kawakami, H. Sugishita, et al., Large-scale genome-wide association study in a Japanese population identifies novel susceptibility loci across different diseases, Nat. Genet. 52 (2020) 669–679, https://doi.org/10.1038/s41588-020-0640-3.
[27] T. Andersson, L. Alfredsson, H. Källberg, S. Zdravkovic, A. Ahlbom, Calculating measures of biological interaction, Eur. J. Epidemiol. 20 (2005) 575–579, https://doi.org/10.1007/s10654-005-7835-x.
[28] Z. Fu, Q. Liu, J. Liang, Z. Weng, W. Li, J. Xu, et al., Air pollution, genetic factors and the risk of depression, Sci. Total Environ. 850 (2022) 158001, https://doi.org/10.1016/j.scitotenv.2022.158001.
[29] Y. Zheng, S.H. Ley, F.B. Hu, Global aetiology and epidemiology of type 2 diabetes mellitus and its complications, Nat. Rev. Endocrinol. 14 (2018) 88–98, https://doi.org/10.1038/nrendo.2017.151.
[30] D. Lv, S. Lu, X. Tan, M. Shao, S. Xie, L. Wang, Source profiles, emission factors and associated contributions to secondary pollution of volatile organic compounds (VOCs) emitted from a local petroleum refinery in Shandong, Environ. Pollut. 274 (2021) 116589, https://doi.org/10.1016/j.envpol.2021.116589.
[31] X. Meng, W. Wang, S. Shi, S. Zhu, P. Wang, R. Chen, et al., Evaluating the spatiotemporal ozone characteristics with high-resolution predictions in mainland China, 2013-2019, Environ. Pollut. 299 (2022) 118865, https://doi.org/10.1016/j.envpol.2022.118865.
[32] R. Liang, X. Feng, D. Shi, M. Yang, L. Yu, W. Liu, et al., The global burden of disease attributable to high fasting plasma glucose in 204 countries and territories, 1990-2019: an updated analysis for the Global Burden of Disease Study 2019, Diabetes Metab. Res. Rev. (2022) e3572, https://doi.org/10.1002/dmrr.3572.
[33] S. Lillioja, D.M. Mott, M. Spraul, R. Ferraro, J.E. Foley, E. Ravussin, et al., Insulin resistance and insulin secretory dysfunction as precursors of non-insulin-dependent diabetes mellitus. Prospective studies of Pima Indians, N. Engl. J. Med. 329 (1993) 1988–1992, https://doi.org/10.1056/nejm199312303292703.
[34] S. Fustinoni, P. Manini, L. Campo, G. De Palma, R. Andreoli, A. Mutti, et al., Assessing variability and comparing short-term biomarkers of styrene exposure using a repeated measurements approach, Toxicol. Lett. 192 (2010) 40–44, https://doi.org/10.1016/j.toxlet.2009.02.004.
[35] E. Strafella, M. Bracci, S. Staffolani, N. Manzella, D. Giantomasi, M. Valentino, et al., Occupational styrene exposure induces stress-responsive genes involved in cytoprotective and cytotoxic activities, PLoS One 8 (2013) e75401, https://doi.org/10.1371/journal.pone.0075401.
[36] G. Tranfo, M. Gherardi, E. Paci, M. Gatto, A. Gordiani, L. Caporossi, et al., Occupational exposure to styrene in the fibreglass reinforced plastic industry: comparison between two different manufacturing processes, Med. Lav. 103 (2012) 402–412. PMID: 23077800.
[37] K. Niaz, F. Mabqool, F. Khan, F. Ismail Hassan, M. Baeeri, M. Navaei-Nigjeh, et al., Molecular mechanisms of action of styrene toxicity in blood plasma and liver, Environ. Toxicol. 32 (2017) 2256–2266, https://doi.org/10.1002/tox.22441.
[38] H. Yaribeygi, T. Sathyapalan, S.L. Atkin, A. Sahebkar, Molecular mechanisms linking oxidative stress and diabetes mellitus, Oxid. Med. Cell. Longev. 2020 (2020) 8609213, https://doi.org/10.1155/2020/8609213.
[39] D.J. Betteridge, What is oxidative stress? Metabolism 49 (2000) 3–8, https://doi.org/10.1016/s0026-0495(00)80077-3.
[40] B. Wang, W. Qiu, S. Yang, L. Cao, C. Zhu, J. Ma, et al., Acrylamide exposure and oxidative DNA damage, lipid peroxidation, and fasting plasma glucose alteration: association and mediation analyses in Chinese urban adults, Diabetes Care 43 (2020) 1479–1486, https://doi.org/10.2337/dc19-2603.
[41] K. Niaz, F.I. Hassan, F. Mabqool, F. Khan, S. Momtaz, M. Baeeri, et al., Effect of styrene exposure on plasma parameters, molecular mechanisms and gene expression in rat model islet cells, Environ. Toxicol. Pharmacol. 54 (2017) 62–73, https://doi.org/10.1016/j.etap.2017.06.020.
[42] I. Azarova, E. Klyosova, V. Lazarenko, A. Konoplya, A. Polonikov, Genetic variants in glutamate cysteine ligase confer protection against type 2 diabetes, Mol. Biol. Rep. 47 (2020) 5793–5805, https://doi.org/10.1007/s11033-020-05647-5.
[43] P. Poulsen, K.O. Kyvik, A. Vaag, H. Beck-Nielsen, Heritability of type II (non-insulin-dependent) diabetes mellitus and abnormal glucose tolerance – a population-based twin study, Diabetologia 42 (1999) 139–145, https://doi.org/10.1007/s001250051131.
[44] C. Hu, W. Jia, Diabetes in China: epidemiology and genetic risk factors and their clinical utility in personalized medication, Diabetes 67 (2018) 3–11, https://doi.org/10.2337/dbi17-0013.
[45] R. Chen, E. Corona, M. Sikora, J.T. Dudley, A.A. Morgan, A. Moreno-Estrada, et al., Type 2 diabetes risk alleles demonstrate extreme directional differentiation among human populations, compared to other diseases, PLoS Genet. 8 (2012) e1002621, https://doi.org/10.1371/journal.pgen.1002621.
[46] Y.S. Cho, J.Y. Lee, K.S. Park, C.W. Nho, Genetics of type 2 diabetes in East Asian populations, Curr Diabetes Rep 12 (2012) 686–696, https://doi.org/10.1007/s11892-012-0326-z.
[47] J. Yin, X. Wang, S. Li, Y. Zhu, S. Chen, P. Li, et al., Interactions between plasma copper concentrations and SOD1 gene polymorphism for impaired glucose regulation and type 2 diabetes, Redox Biol. 24 (2019) 101172, https://doi.org/10.1016/j.redox.2019.101172.
[48] W. Liu, L. Yu, M. Zhou, Z. Ye, R. Liang, Q. Tan, et al., Cross-sectional and longitudinal associations between propylene oxide exposure and lung function among Chinese community residents: roles of oxidative DNA damage, lipid peroxidation, and protein carbonylation, Chest (2022), https://doi.org/10.1016/j.chest.2022.12.004.
[49] H.J. Tsai, C.F. Wu, C.A. Hsiung, C.H. Lee, S.L. Wang, M.L. Chen, et al., Longitudinal changes in oxidative stress and early renal injury in children exposed to DEHP and melamine in the 2011 Taiwan food scandal, Environ. Int. 158 (2022) 107018, https://doi.org/10.1016/j.envint.2021.107018.
[50] B. Wang, M. Cheng, S. Yang, W. Qiu, W. Li, Y. Zhou, et al., Exposure to acrylamide and reduced heart rate variability: the mediating role of transforming growth factor-β, J. Hazard. Mater. 395 (2020) 122677 https://doi.org/10.1016/j.jhazmat.2020.122677.