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Original Article

Association between urinary trans,trans-muconic acid and diabetes: a cross-sectional analysis of data from Korean National Environmental Health Survey (KoNEHS) cycle 3 (2015–2017)

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Abbreviations
BMI: body mass index; CI: confidential interval; IRB: Institutional Review Board; KoNEHS: Korean National Environmental Health Survey; NIER: National Institute of Environmental Research; OR: odds ratio;

ABSTRACT

Background: Benzene is a ubiquitous air pollutant that is well known to cause hematopoietic effects in humans including leukemia. Recently, several studies have discussed its non-carcinogenic effects such as diabetes. This study aimed to investigate the association between diabetes and urinary trans,trans-muconic acid (t,t-MA), one of benzene metabolite, using adult data from Korean National Environmental Health Survey (KoNEHS) cycle 3 (2015–2017).
Methods: This study analyzed 3,777 adults (1,645 men and 2,132 women) from the KoNEHS cycle 3 (2015–2017). The distribution and fraction of each independent variable were presented separately according to the urinary benzene metabolite levels (t,t-MA quartiles) and diabetes to determine the general characteristics of the subjects. Odds ratios (ORs) were calculated using logistic regression after stratification by gender and smoking status to identify the association between urinary t,t-MA and diabetes.
Results: Compared with the first quartile (reference), the risk of diabetes significantly increased above the 4th (1.834 [1.107–3.039]) quartile in men and above the 3rd (1.826 [1.095–3.044]) and 4th (2.243 [1.332–3.776]) quartiles in women after adjustment. Stratified analysis based on smoking revealed that the ORs for the 3rd (1.847 [1.146–2.976]) and 4th (1.862 [1.136–3.052]) quartiles in non-smokers and those for the 2nd (1.721 [1.046–2.832]), 3rd (1.797 [1.059–3.050]), and 4th (2.546 [1.509–4.293]) quartiles in smokers were significantly higher.
Conclusions: We confirmed that urinary t,t-MA is significantly associated with diabetes regardless of gender and smoking status. And further studies are necessary to access the clinical impacts of this findings.

Keywords: Benzene; Trans,trans-muconic acid; Diabetes; Korean National Environmental Health

S-PMA: S-phenylmercapturic acid; t,t-MA: trans,trans-muconic acid; VOC: volatile organic compound; U-benzene: urinary benzene.

Competing interests
The authors declare that they have no competing interests.

Author contributions
Conceptualization: Yang EH, Ryoo JH; Data curation: Ryoo JH; Formal analysis: Yang EH, Nam DJ, Lee HC, Shin SS; Metholdology: Yang EH, Ryoo JH; Writing - original draft: Yang EH, Nam DJ, Lee HC, Shin SS; Writing - review&editing: Yang EH, Ryoo JH.

BACKGROUND

Benzene is a ubiquitous volatile organic compound (VOC) with a highly stable ring-shaped chemical structure that forms the base of the aromatic hydrocarbon family and is known as one of the main air pollutants in the environment.[1] The exposure can be divided into occupational and environmental exposures. As benzene is an intermediate product of styrene, phenol, cyclohexane, and other organic chemicals, occupational exposure to high concentrations of benzene can occur in the paint, rubber, printing, and petroleum industries, especially during the cleaning, sampling, and mass transportation processes.[2] In addition to this occupational exposure, benzene is also present in the atmosphere in low concentrations. The major sources of exposure to the general population include automobile exhaust gases and smoking. In addition, exposure may also occur via unpurified wastewater from industries that use benzene or via smoke from oil refineries. At home, benzene is present in indoor floor adhesives, cleaning products, mats, carpets, and furniture wax, which may be exposed to air over time. Exposure may also occur via ingestion of foods containing benzene. For the vast majority of people, this environmental exposure to benzene has become more important problem.[3,4]

Benzene is well-known to cause hematopoietic disorder in occupational environments. It is classified as International Agency for Research on Cancer group I carcinogen and there is sufficient evidence to suggest that it causes acute myeloid cell leukemia in humans. It was also associated with hematopoietic diseases such as myelodysplastic syndrome, chronic lymphocytic leukemia, acute lymphocytic leukemia, multiple myeloma and non-Hodgkin's lymphoma.[5-7] Hence, to prevent the risk of hematopoietic disorders, the Ministry of Employment and Labor has limited occupational benzene exposure to less than 0.5 ppm.[8]

Most of the previous studies on benzene have determined the health effects of occupational exposure at high concentrations. Recently, however, the focus has shifted to health effects of long-term exposure to low concentration of benzene. According to the emission information from National Air Pollutants Emission Service of South Korea implemented by the National Institute of Environmental Sciences,[9] VOC emissions tended to increase steadily from 665,043 tons in 1999 when the survey was started to 1,047,585 tons in 2017. Therefore, urban population is constantly exposed to VOCs such as benzene. In addition, in the KoNEHS,[10] which is conducted every 3 years, the concentration of urinary trans,trans-muconic acid (t,t-MA), which is a metabolite of benzene, tended to increase continuously in each phase (first phase: 40 μg/L, second phase: 58.8 μg/L, third phase: 86.2 μg/L). This suggests that exposure to benzene continues to increase in the general population and even at low concentrations, long-term lifetime exposure to a significant proportion of population can cause public health problems.

After benzene is absorbed, it is metabolized by cytochrome P450 2E1 enzyme (phase I biotransformation) to benzene oxide, which is in equilibrium with its tautomer, oxepin. A second CYP oxidation of oxepin, followed by ring opening, produces the muconaldeyhdes, and then ultimately converted to muconic acid. Urinary t,t-MA, along with S-phenylmercapturic acid (S-PMA), is one of the most sensitive and reliable benzene biomarkers and is known to be useful in evaluating benzene exposure at low concentrations.[11,12]

Although the mechanism of benzene toxicity in humans has not been fully identified, one possible mechanism is oxidative damage caused by reactive oxygen species produced by benzene metabolites such as phenol, hydroquinone and catechol.[13,14] Since these mechanisms associated with oxidative damage are often observed in the pathogenesis of several diseases,

they are likely to cause other diseases in addition to the previously well-known effects such as hematopoietic disorder. Several studies have been conducted to identify non-cancerous effects such as diabetes in addition to the hematopoietic disease caused by environmental exposure of benzene.[15-17] To the best of our knowledge, no study has analyzed the association between environmental benzene exposure and diabetes in a large general population. This study aimed to identify whether there is a significant association between urinary t,t-MA, one of benzene metabolite, and diabetes using data representing the general Korean population.

METHODS

Survey characteristics and study participants

This study based on adult participants aged 19 years or older who participated in the KoNEHS cycle 3 (2015–2017). Details about the survey design have been described previously.[18,19] This study included 3,777 (1,645 men and 2,132 women) of the 3,787 adults who participated in the KoNEHS cycle 3. Ten participants were excluded due to missing data regarding urinary t,t-MA levels.

The KoNEHS cycle 3 was approved by the Institutional Review Board (IRB) at the National Institute of Environmental Research (NIER), Korea (IRB No. NIER-2016-BR-003-01, NIER-2016-BR-003-03). Ethics approvals for the study protocol and analysis of the data were obtained from the IRB of Kyung Hee University Hospital (IRB file No. KHUH 2021-08-002). The informed consent requirement was exempted by IRB because researchers only accessed retrospectively a de-identified database for analysis purposes.

Variables of interest

In this study, diabetes was defined as self-reported questionnaire of antidiabetic medication. The social demographic variables and health behavior variables of the study participants were classified as follows. Among the socio-demographic variables, gender was analyzed by stratification by men and women. Age, body mass index (BMI) were presented as the average value. The education level was divided into no education, below high school graduation, and college graduation or higher. Marriage status was categorized into single, married and cohabited, or others (divorce, separation) and the economic level was classified into household monthly income of less than 1 million won, 1 million won to less than 3 million won, 3 million won to less than 5 million won, more than 5 million won, or unknown. Alcohol was classified as none or ex drinking and current drinking, and physical activity was classified as yes or no. Smoking was classified as none or ex-smoking and current smoking.

Urinary benzene metabolites

The urine sample is collected in a sterilized container and transferred to a storage container that is not transparent for light blocking. After that, lower the temperature of the sample in ice water for 20 minutes in a light-shielding state. Use an icebox to move it to the laboratory in a refrigerated state. The collected samples are frozen at −20°C until analyzed. Details of analytical procedures for benzene metabolites in urine were described previously.[20] Briefly, Urinary t,t-MA concentration was measured using Ultra Performance Liquid chromatograph-mass spectrometry with electrospray ionization. Quality control procedures followed NIER of Korea protocol. Method detection limit for urinary t,t-MA was 2.3 μg/L. In this study, urinary t,t-MA presented after creatinine adjustment.

Statistical analysis

Analysis of variance, t-test and χ^2-test were used to analyze the differences among the characteristics of the study participants with respect to the quartile levels of urinary t,t-MA and diabetes. Data were expressed as means ± standard deviation for continuous variables and as number (percentages) for categorical variables.

After stratification by sex, a logistic regression model was used to calculate odds ratio (OR) and 95% confidence interval (CI) for diabetes according to the quartile levels of urinary t,t-MA. The logistic regression model was adjusted for multiple confounding factors. The adjusted covariates that might confound the association between urinary t,t-MA and diabetes included age, BMI, education level, marital status, household income, alcohol, physical activity, smoking. In addition, another stratification analysis was conducted based on smoking, which can significantly affect the association between diabetes and environmental benzene exposure levels. A likelihood ratio test was used to test whether there were positive linear dose-response relationships of OR for diabetes with increasing urinary t,t-MA concentration. And each logistic regression model was analyzed by applying the weights presented in the original dataset according to the KoNEHS analysis guideline. IBM SPSS (version 19 for window; IBM Corp., Armonk, NY, USA) was used for all statistical analyses and a *p*-value of < 0.05 was considered statistically significant.

RESULTS

The distribution and fraction of independent variables according to the urinary t,t-MA quartiles are shown in **Table 1**. This study included 2,132 (56.45%) women and 1,645 (43.55%) men. The overall prevalence of diabetes was 8.95%. All variables showed statistical significance except BMI, marital status, physical activity. In this analysis, percentage of female, smoking showed a graded increasing trend in relation to quartile groups of urinary t,t-MA.

The baseline characteristics of those with and without diabetes are shown in **Table 2**. All variables except physical activity showed statistically significant differences according to diabetes. Those in diabetes group had significantly higher concentrations of urinary t,t-MA than those in non-diabetes group.

Logistic regression analysis was performed after stratified by sex to determine the relevance of diabetes according to urinary t,t-MA levels (**Table 3**). Compared with the first quartile(reference), the risk of diabetes significantly increased above the 4th (1.834 [1.107–3.039]) quartile in men and above the 3rd (1.826 [1.095–3.044]), the 4th (2.243 [1.332–3.776]) quartile in women after adjustment. The multivariate adjusted model showed a significantly graded association between diabetes and the quartile groups of urinary t,t-MA.

We also considered smoking as a factors that could greatly affect the association between environmental benzene exposure and diabetes. After dividing smoking into non-smokers and smokers (past and current-smokers), logistic regression was performed again and the results are presented in **Table 4**. Compared with first quartile (reference), The ORs for the 3rd (1.847 [1.146–2.976]), the 4th (1.862 [1.136–3.052]) quartile in non-smokers, and those for the 2nd (1.721 [1.046–2.832]), the 3rd (1.797 [1.059–3.050]), the 4th (2.546 [1.509–4.293]) quartile in smokers were significantly higher after adjustment. In multivariate adjusted model, the risk of diabetes showed a graded increasing trend in relation to quartile groups of urinary

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Table 1. Comparison of baseline characteristics among quartile groups of urinary trans,trans-muconic acid (n = 3,777)

Characteristics		Total	Urinary t,t-muconic acid (μg/g creatinine)				*p* for trend[a]
			Q1 (< 58.285) (n = 944)	Q2 (≥ 58.285, < 100.668) (n = 944)	Q3 (≥ 100.668, < 178.013) (n = 945)	Q4 (≥ 178.013) (n = 944)	
Sex	Male	1,645 (43.55)	429 (45.44)	426 (45.13)	403 (42.65)	387 (41.00)	0.028
	Female	2,132 (56.45)	515 (54.56)	518 (54.87)	542 (57.35)	557 (59.00)	
Age (years)		52.97 ± 14.84	53.65 ± 15.53	54.90 ± 14.44	52.67 ± 14.91	50.66 ± 14.12	< 0.001
BMI (kg/m^2)		24.61 ± 3.52	24.60 ± 3.45	24.57 ± 3.33	24.71 ± 3.43	24.54 ± 3.84	0.949
Education	None	122 (3.23)	41 (4.34)	33 (3.50)	24 (2.54)	24 (2.54)	0.022
	≤ High school	2,327 (61.61)	581 (61.55)	595 (63.03)	581 (61.48)	570 (60.38)	
	≥ College	1,328 (35.16)	322 (34.11)	316 (33.47)	340 (35.98)	350 (37.08)	
Marital status	Single	418 (11.07)	112 (11.86)	79 (8.37)	110 (11.64)	117 (12.39)	0.794
	Married, cohabited	2,928 (77.52)	739 (78.28)	756 (80.08)	717 (75.87)	716 (75.85)	
	Others (divorce, separation)	431 (11.41)	93 (9.85)	109 (11.55)	118 (12.49)	111 (11.76)	
Household income (million won)[b]	< 100	709 (18.77)	182 (19.28)	185 (19.60)	202 (21.38)	140 (14.83)	0.033
	100–300	1,522 (40.30)	378 (40.04)	398 (42.16)	361 (38.20)	385 (40.78)	
	300–500	934 (24.73)	231 (24.47)	226 (23.94)	219 (23.17)	258 (27.33)	
	≥ 500	595 (15.75)	149 (15.78)	129 (13.67)	161 (17.04)	156 (16.53)	
	Not known	17 (0.45)	4 (0.42)	6 (0.64)	2 (0.21)	5 (0.53)	
Alcohol		3,017 (79.88)	737 (78.07)	744 (78.81)	758 (80.21)	778 (82.42)	0.013
Physical activity		1,401 (37.09)	357 (37.82)	368 (38.98)	343 (36.30)	333 (35.28)	0.142
Smoking		1,361 (36.03)	299 (31.67)	338 (35.81)	351 (37.14)	373 (39.51)	< 0.001
Diabetes		338 (8.95)	64 (6.78)	92 (9.75)	92 (9.75)	90 (9.53)	0.047

Categorical data presented as number (%); continuous data presented as mean ± standard deviation.
Urinary t,t-muconic acid presented after creatinine adjustment.
BMI: body mass index.
[a]The *p* for trend by likelihood ratio test for linear dose-response relationships of the odds ratio for diabetes with increasing urinary t,t-MA concentration; [b]100 million won = 871 US dollar, 300 million won = 2,614 US dollar, 500 million won = 4,357 US dollar.

Table 2. Comparison of baseline characteristics between non-diabetes and diabetes (n = 3,777)

Characteristics		Non-diabetes (n = 3,439)	Diabetes (n = 338)	*p*-value[a]
Sex	Male	1,472 (42.80)	173 (51.18)	0.003
	Female	1,967 (57.20)	165 (48.82)	
Age (years)		51.84 ± 14.83	64.44 ± 8.81	< 0.001
BMI (kg/m^2)		24.50 ± 3.51	25.71 ± 3.46	< 0.001
Education	None	101 (2.94)	21 (6.21)	< 0.001
	≤ High school	2,066 (60.08)	261 (77.22)	
	≥ College	1,272 (36.99)	56 (16.57)	
Marital status	Single	411 (11.95)	7 (2.07)	< 0.001
	Married, cohabited	2,663 (77.44)	265 (78.40)	
	Others (divorce, separation)	365 (10.61)	66 (19.53)	
Household income (million won)[b]	< 100	574 (16.69)	135 (39.94)	< 0.001
	100–300	1,398 (40.65)	124 (36.69)	
	300–500	879 (25.56)	55 (16.27)	
	≥ 500	572 (16.63)	23 (6.80)	
	Not known	16 (0.47)	1 (0.30)	
Alcohol		2,775 (80.69)	242 (71.60)	< 0.001
Physical activity		1,262 (36.70)	139 (41.12)	0.108
Smoking		1,203 (34.98)	158 (46.75)	< 0.001
Urinary t,t-muconic acid (μg/g creatinine)		103.54 ± 2.39	117.92 ± 2.25	0.004

Categorical data presented as number (%); continuous data presented as mean ± standard deviation. Urinary t,t-muconic acid presented after creatinine adjustment.
BMI: body mass index.
[a]The *p*-value by t-test for continuous variables and χ^2 test for categorical variables; [b]100 million won = 871 US dollar, 300 million won = 2,614 US dollar, 500 million won = 4,357 US dollar.

t,t-MA. Each logistic regression analysis (**Tables 3** and **4**) was analyzed again in consideration of weights, and similar significant results and tendencies were confirmed (**Supplementary Tables 1** and **2**).

Table 3. Odds ratios and 95% confidence intervals for diabetes according to quartile groups of urinary trans,trans-muconic acid after stratification of sex

Category	Overall (n = 3,777)		Male (n = 1,645)		Female (n = 2,132)	
	Unadjusted	Multivariate adjusted[a]	Unadjusted	Multivariate adjusted[a]	Unadjusted	Multivariate adjusted[a]
Urinary trans,trans-muconic acid						
Q1	1 (Referrence)	1 (Referrence)	1 (Referrence)	1 (Referrence)	1 (Referrence)	1 (Referrence)
Q2	1.485 (1.065–2.071)	1.440 (1.018–2.037)	1.377 (0.878–2.188)	1.359 (0.850–2.174)	1.636 (0.995–2.691)	1.618 (0.960–2.725)
Q3	1.483 (1.063–2.068)	1.609 (1.135–2.283)	1.265 (0.797–2.009)	1.538 (0.938–2.525)	1.796 (1.105–2.921)	1.826 (1.095–3.044)
Q4	1.449 (1.038–2.024)	1.917 (1.344–2.735)	1.359 (0.857–2.154)	1.834 (1.107–3.039)	1.627 (0.996–2.659)	2.243 (1.332–3.776)
p for linear trend	0.047	< 0.001	0.276	0.014	0.058	0.007

[a]Multivariate adjusted model: adjusted for age, body mass index, education level, marital status, household income, alcohol, physical activity, smoking.

Table 4. Odds ratios and 95% confidence intervals for diabetes according to quartile groups of urinary trans,trans-muconic acid after stratification of smoking status

Category	Overall (n = 3,777)		Non-smokers (n = 2,416)		Smokers (n = 1,361)	
	Unadjusted	Multivariate adjusted[a]	Unadjusted	Multivariate adjusted[a]	Unadjusted	Multivariate adjusted[a]
Urinary trans,trans-muconic acid						
Q1	1 (Reference)	1 (Reference)	1 (Reference)	1 (Reference)	1 (Reference)	1 (Reference)
Q2	1.485 (1.065–2.071)	1.492 (1.055–2.111)	1.560 (0.977–2.491)	1.484 (0.910–2.420)	1.506 (0.933–2.430)	1.721 (1.046–2.832)
Q3	1.483 (1.063–2.068)	1.724 (1.216–2.445)	1.889 (1.199–2.975)	1.847 (1.146–2.976)	1.171 (0.711–1.929)	1.797 (1.059–3.050)
Q4	1.449 (1.038–2.024)	2.090 (1.468–2.975)	1.524 (0.952–2.438)	1.862 (1.136–3.052)	1.393 (0.858–2.262)	2.546 (1.509–4.293)
p for linear trend	0.047	< 0.001	0.061	0.015	0.366	0.003

Smoking includes ex-smokers and current-smokers.
[a]Multivariate adjusted model: adjusted for gender, age, body mass index, education level, marital status, household income, alcohol, physical activity.

DISCUSSION

Benzene is metabolized by multiple enzymes in the liver, about 70 to 85% of which are phenol, about 5–10% are catechol and t,t-MA, and less than 1% are S-PMA.[21] Among the benzene metabolites, urinary t,t-MA is a biomarker used to assess low benzene exposure along with S-PMA and urinary benzene (U-benzene).[22,23] In the present study, the following issues were considered using urinary t,t-MA to evaluate environmental low benzene exposure. 1) According to the 2019 report of air quality in Korea,[24] the actual concentration of benzene in the atmosphere were 0.41 ppb (2015′), 0.31 ppb (2016′), and 0.29 ppb (2017′), when the KoNEHS cycle 3 (2015–2017) was implemented. Therefore, it is controversial whether urinary t,t-MA can reflect this extremely low environmental benzene exposure, as the actual exposure concentration in the general population was below 1ppb.[25,26] However, there are several studies have used urinary t,t-MA to evaluate environmental benzene exposure and it is considered exploitable due to significant correlation coefficients with environmental benzene exposure.[23,25,27,28] 2) Urinary benzene metabolite level including those of urinary t,t-MA are strongly influenced by cigarette smoking.[22,26] Therefore, smoking should be considered an important factor to determining the association between urinary benzene metabolites and diabetes. Hence, we conducted stratification analysis based on smokers (past and current smokers) and non-smokers, which showed that the risk of diabetes increased with an increase in the concentration of urinary t,t-MA with or without smoking. 3) It has been reported that foods preserved using sorbic acid cause substantial interference with urinary t,t-MA as a biomarker for both occupational and environmental benzene exposure.[29] Therefore, the effects of sorbic acid intake on urinary t,t-MA level should be considered. However, the data used in this study did not confirm the levels of sorbic acid intake. Thus, further studies should consider the intake of foods preserved using sorbic acid.

Several recent studies have been conducted on benzene-induced oxidative damage and insulin resistance. Previous two epidemiological studies[30,31] involving older populations aged 60 years and older showed urinary t,t-MA was associated with insulin resistance indicator.

And suggest that environmental benzene exposure is likely to affect insulin resistance, and oxidative damage is involved in the mechanism. Another study[32] was conducted to determine whether environmental benzene exposure caused oxidative damage and affected insulin resistance in children and adolescents aged 5–18 years who had a low incidence of diabetes. The study also suggests that environmental benzene exposure even in low concentrations may be linked to insulin resistance and oxidative damage in children and adolescents. However, these epidemiological studies involved special age groups and small sample size.

The results of the present study were consistent with those of previous studies. Higher urinary t,t-MA concentrations were linearly associated with diabetes in the multivariate adjusted model. Although similar results have been reported in previous studies, the present study had a large sample consisting of adults aged 18 years and above. Moreover, the study differs from previous studies, as it identified the association between urinary t,t-MA and diabetes prevalence rather than insulin resistance.

The results of this study (**Table 1**) showed that the higher the urinary t,t-MA concentration, the higher the proportion of women and smokers, respectively, in a similar context to previous studies.[33,34] It was reported that women have higher urinary t,t-MA concentration than men because of the higher t,t-MA extraction rate in the same benzene exposure.[34] In this study, gender was stratified (**Table 3**), and it was confirmed that the OR increased significantly regardless of gender. In addition, smoking, along with sorbic acid intake, is known as a representative variable that can affect urinary t,t-MA concentration in environmental benzene exposure. It is known that smoking accounts for about 90% of benzene exposure in smokers, while environmental smoking accounts for only about 10% of benzene exposure in non-smokers.[4] And it was reported that all biomarkers (t,t-MA, S-PMA, U-benzene) for benzene are measured higher in smokers than in non-smokers (up to 8 times), and smoking is a variable that must be considered as a major benzene exposure source in low environmental benzene exposure below 15 ppm.[35] In this study, it was stratified with or without smoking, and it was confirmed that the OR was significant in both smokers and non-smokers. In other words, in this study, regardless of gender and smoking status, diabetes tended to increase significantly as the concentration of urinary t,t-MA increased.

The strength of the present study is that it utilized data representing a large population. To the best of our knowledge, this is the first study involving a large general population to study benzene exposure and its association with diabetes in Korea. In addition, stratification analysis was carried out based on smoking, an important confounding variable, for identifying the association between environmental exposure levels of benzene and diabetes. At low environmental exposure levels of benzene, smoking can cause significant changes in the concentration of urinary t,t-MA, which can greatly affect the evaluation of its association with diabetes. Hence, stratification by smoking can be considered a strength of the present study.

The present study has some limitations. First, it was difficult to identify the causality and temporality of the association between benzene and diabetes outbreaks due to the cross-sectional nature of the study. Second, diabetes were defined as those taking diabetic medication. Thus, it was not possible to distinguish the types of diabetes (type I or type II). Third, the possibility of missing the diagnosis of diabetes could not be excluded, as the study involved a self-questionnaire survey. Fourth, it is difficult to suggest that urinary t,t-MA originated entirely from benzene in this study, which did not adjust individual sorbic acid

intake. Therefore, the results of the study show the association between urinary t,t-MA and diabetes, but it may be currently difficult to directly link it with benzene.

Despite the aforementioned limitations, we confirmed an association between urinary t,t-MA levels and diabetes. Future studies need to address these limitations by evaluating individual exposure more accurately.

CONCLUSIONS

The present study confirmed that urinary t,t-MA, a benzene metabolite, was associated with diabetes regardless of gender and smoking status. And further studies are necessary to assess the clinical impacts of this findings.

SUPPLEMENTARY MATERIALS

Supplementary Table 1

Odds ratios and 95% confidence intervals for diabetes according to quartile groups of urinary trans,trans-muconic acid analyzed in consideration of weights after stratification of sex

Click here to view

Supplementary Table 2

Odds ratios and 95% confidence intervals for diabetes according to quartile groups of urinary trans,trans-muconic acid analyzed in consideration of weights after stratification of smoking status

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