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Phthalates exposure as environmental risk factor for type 2 diabetes mellitus

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ABSTRACT

Phthalates exposure occurs in all areas, such as foods' plastic packaging, cosmetics, and others. Previous studies showed that phthalates are associated with the prevalence of T2DM. Type 2 Diabetes Mellitus (T2DM) is caused by a combination of defective insulin secretion by pancreatic β-cells and the insulin-resistance. This study aimed to investigate whether phthalate exposure is an environmental risk factor for T2DM. A case-control study was conducted among residents in the South Tangerang district from June 2020 to February 2021 using a purposive sampling technique. The cases were the patients diagnosed T2DM with HbA1c≥6.5% random blood sugar≥200 mg/dL, with history T2DM treatment. The respondents' urines were collected and evaluated using liquid chromatography/mass spectrometry (LC/MS). A total of 47 cases and 47 controls were recruited in the study. The lowest monomethyl phthalate (MEP) and mono (2-ethyl-5-hydroxyhexyl) phthalate (MEHHP) were 5.37 µg/L and 2.02 µg/L, respectively. On multivariable regression analysis, the high urinary MEP level (>131.91 µg/L) was independently associated with T2DM (OR: 3.754, 95% CI: 1.559–8.811, p-value: 0.002). MEP is an environmental risk factor for T2DM and likely has a significant impact on human health than MEHHP.

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1. INTRODUCTION

Diabetes mellitus (DM) is a chronic metabolic disease characterized by elevated blood glucose (or blood sugar) levels, which cause damage to the heart, eyes, kidneys, blood vessels, and nerves [1], [2]. Adults have a higher risk of type 2 diabetes mellitus (T2DM) due to the body's insulin resistance or inadequate production [3]. All types of T2DM has similar main characteristic, disfunction or pancreatic beta cells. The disease of diabetes mellitus (DM) has a high death rate in most developed countries and has become an epidemic in many developing countries [4]. International Diabetes Federation (IDF) in 2017 showed that there is 4 million death in age less than 60 years old in the world. As in the basic health research (RISKESDAS) data in 2018, based on the blood sugar level examination, the prevalence of DM in the population aged>15 years in Indonesia was 10.9% in urban areas and 11.2% in rural areas [5], and these numbers are likely to increase. One of the Indonesian provinces with the highest DM prevalence is Banten. It is shown that, in 2013, Cilegon had 2.2% of its population who had DM, Tangerang for 1.8%, and South Tangerang for 1.7%.

The disease is associated with obesity, genetic factors, diet, and physical activity [6], [7]. However, the possibility of the environment as a cause or risk factor also needs attention. Overweight and obesity are responsible for 70% of T2DM cases [8], while the other 30% is still uncertain [9]. Consequently, there is support for the "developmental obesity" hypothesis, which suggests that chemical exposure increases the risk of obesity by altering the adipocyte differentiation [10]. This finding is consistent with several studies that certain environmental chemicals act as “obesogens” or diabetic agents [11], [12]. Several cases also showed the mechanism of action of these chemicals in the disease condition using causal epidemiological relationship [12]–[14].

Toxic substances in the environment, such as phthalates, are associated with the prevalence of T2DM [12], [13]. Phthalates are a family of synthetic compounds that are extensively employed to make plastics more flexible in various consumer products [15]. The sources of these chemicals’ exposure are very diverse [16], and they are present in plastics widely used as wrappers/containers for food/beverages [17]. The role of these chemicals as plasticizers increases their transmission during human interactions with all types of materials, including plastic. They are also a chemical mixture of drugs and chemicals for personal care, cosmetics, and perfumes [18], [19]. Furthermore, environmental phthalate exposure varies with the exposure's duration, frequency, and continuity. The role of phthalates as plasticizers causes chemical exposure to be easily transmitted in human interactions. America and Europe have now banned the use of di-2-ethylhexyl phthalate (DEHP) in various forms and switched to DINP due to its lower toxicity. In Asia, di-2 DEHP is the dominant phthalate produced mainly by China [20]. Indonesia is a country that imports a lot of goods from China in various products containing DEHP or its derivative metabolites. Hence, the possibility of exposure to this toxic substance is more common. Phthalates have multiple effects on people’s health, such as obesity, thyroiditis, infertility, neurodevelopment, allergies, and osteoporosis [21]–[23]. The increasing prevalence of T2DM is a public health problem considering its impact on various diseases. Meanwhile, the risk factors are abnormalities within the human body, such as carbohydrates, fats, genetics, obesity, and others. Exposure to environmental toxicants as a risk factor for the disease has received less attention.

Moreover, it is found that bisphenol A (BPA) and phthalate exposure relate to the risk of T2DM. The higher the phthalate metabolites, the higher the diabetes prevalence [24], [25]. Another study also said there is an association between phthalate exposure and oxidative stress to T2DM diagnosis [26]. However, only a few studies in Indonesia talk about the phthalate and T2DM relationship, especially in South Tangerang, which has race, characteristics, and behavior that can indicate a different risk. Moreover, some Indonesian laboratories said there is no research examining the phthalate content in human urine. Thus, this research is essential to prove that phthalate is the risk factor for T2DM. The authors hope this study can be the reference and evaluation material for using phthalate material. It is expected to become a consideration in reducing phthalate exposure. Therefore, this study aimed to evaluate phthalates exposure as an environmental risk factor for T2DM in Indonesian adults.

2. RESEARCH METHOD

2.1. Study design and setting

This case-control study was conducted among urban adults in South Tangerang city, Indonesia. The sample size consisted of 47 cases and 47 controls subject. The sample size was calculated using the sample size formula for case control research. Subject selection was based on purposive sampling technique. Furthermore, the subjects were recruited through voluntary participation at the South Tangerang district between June 2020 and February 2021. Cases were subjects with HbA1c$\geq$6.5%, random blood sugar$\geq$200 mg/dL, with history of T2DM treatment. Controls were subjects with HbA1c<6.5%, random blood sugar<200 mg/dL, without history of T2DM treatment. Subjects with an infectious disease or a severe cardiovascular condition within the previous three years and an unstable weight (<5% weight change in the last three months) were excluded from the study. Also, the study subjects were individuals living in the South Tangerang district.

2.2. Variables and measures

The respondents were interviewed about age, gender, nutritional status, physical activity, dietary habit, and family history of T2DM using a questionnaire. The body mass index (BMI) was calculated as weight (kg) divided by the height square (m2), while the Baecke physical activity questionnaire (BQ) was used to measure physical activity. Subsequently, the writers collected 50 ml of spot first urine in the morning, or a spot excreted urine before 10.00 a.m. to measure the monomethyl phthalate (MEP) and mono-(2-ethyl-5-hydroxyphenyl) phthalate (MEHHP) levels. Containers and lids made of Pyrex-type glass were used for the urine collection. Monomethyl phthalate (MEP), a primary metabolite of diethyl phthalate (DEP), was used to measure phthalate from dermal exposure [27], while MEHHP, a secondary metabolite of di(2-Ethylhexyl) phthalate (DEHP) measured the phthalate from ingestion exposure [28]. Meanwhile, enzymatic deconjugation and solid-phase extraction of phthalate metabolites were performed to assess the amount of the metabolites [29]. The reagents

used include MEHHP Catalog No.M542510, MEHHP-d4 isotope Catalog No.M542512, MEP-d4 isotope Catalog No.M542582, and MEP Catalog No.M542580 from Toronto research chemicals. liquid chromatography/mass spectrometry (LC/MS) was also used to analyze the urine sample. The urinary MEP levels precision (%RSD) was 1.21-5.5%, accurate (% recovery) was 99.7-110.3%, the limit of detection (LOD) was 4.12 µg/L, and linearity (R2) was 0.999. Meanwhile, the urinary MEHHP levels precision (%RSD) was 2.34-6.45%, accurate (% recovery) was 95.27-107.57%, LOD was 1.49 µg/L and linearity (R2) was 0.999.

2.3. Data collection

Sample selection was made by purposive sampling, and the screening was carried out on 486 subjects through random blood sugar checks (RBS). Subject with high RBS (≥200 mg/dL), HbA1c results≥6.5% and history of T2DM treatment were confirmed as cases. The sampling flow is shown in Figure 1.

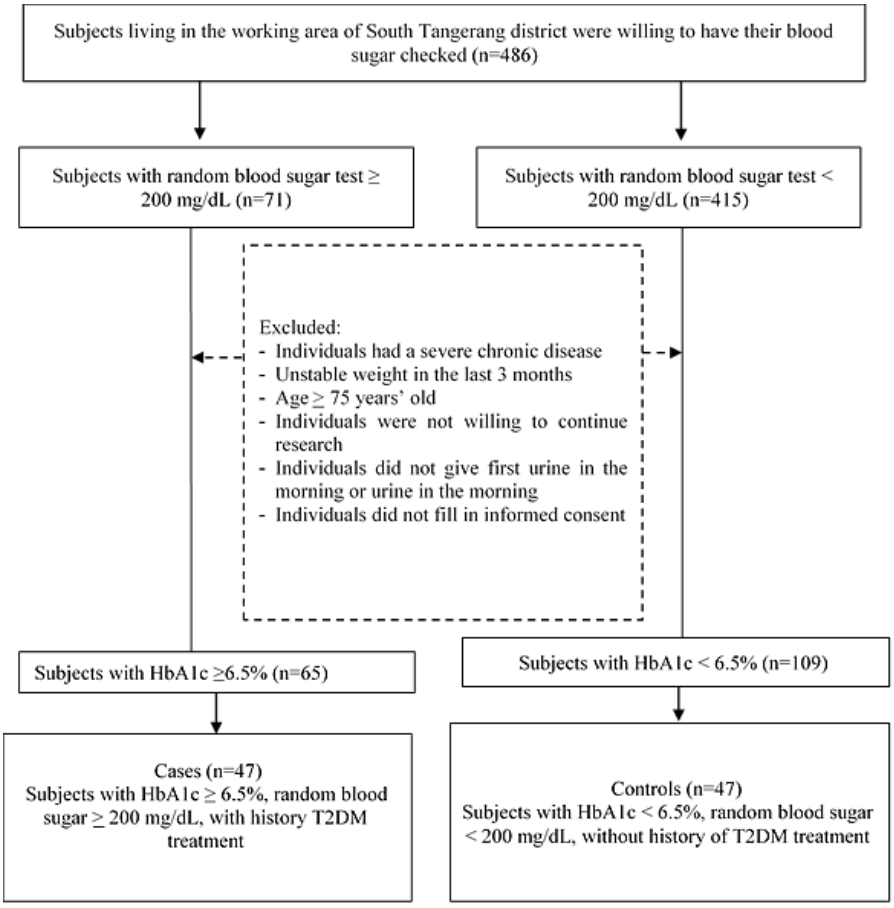

Figure 1. Sampling flow of the research

2.4. Statistical analysis

Independent t-test, Chi-square test, and Mann-Whitney test were used to analyze the association between risk factors and T2DM. They were also considered statistically significant with a p-value<0.05. Meanwhile, the median was used to determine phthalates levels' cut off point in the logistic regression analysis (likelihood ratio). The risk factors with p-value<0.25 in bivariate analysis were used for the logistic regression analysis and p-value <0.05 was considered as statistically significant.

2.5. Ethical consideration

This study has passed the ethical review by the ethical committee of the public health faculty, Diponegoro University and granted the ethical clearance letter of No. 177/EA/KEPK-FKM/2020. All the subjects have received informed consent and agree to participate in the study as shown by their signing in the informed consent forms.

3. RESULTS AND DISCUSSION

Table 1 shows that the case group had a mean value of 55 years, which was greater than the control group years. The group's overweight was also more than the control, while normal weight was dominant in the control group. Furthermore, the average physical activity using the baecke physical activity questionnaire (BQ) was not different in both groups [30], while the respondents in the control without a family history were 72.3%.

Table 1. Characteristics of cases and controls

Variables	Cases (n=47)	Controls (n=47)	p
Age (years), (mean±SD)	55.36±8.64	54.34±7.73	0.547[a]
Gender, *n* (%)			
Male	14 (29.8)	15 (31.9)	1.000[b]
Female	33 (70.2)	32 (68.1)	
Body Mass Index, (mean±SD)	25.37±3.192	24.59±3.848	0.286[a]
Physical activity, (mean±SD)	2.59±0.34	2.58±0.29	0.886[a]
Carbohydrate diet, *n* (%)			
Often (3-4 times/day)	23 (48.9)	24 (51.1)	1.000[b]
Not often (<3 times/day)	24 (51.1)	23 (48.9)	
Protein diet, n (%)			
Often (3-4 times/day)	22 (46.8)	28 (59.6)	0.301[b]
Not often (<3 times/day)	25 (53.2)	19 (40.4)	
Fat diet, n (%)			
Often (3-4 times/day)	22 (46.8)	23 (48.9)	1.000[b]
Not often (<3 times/day)	25 (53.2)	24 (51.1)	
Vegetables and fruits diet, n (%)			
Not often (<3 times/day)	26 (55.3)	18 (38.3)	0.148[b]
Often (3-4 times/day)	21 (44.7)	29 (61.7)	
Sweet drink diet, n (%)			
Often (≥1 time/day)	24 (51.1)	27 (57.4)	0.679[b]
Not often (<1 time/day)	23 (48.9)	20 (42.6)	
Family history of T2DM, n (%)			
Yes	17 (36.2)	13 (27.7)	0.507[b]
No	30 (63.8)	34 (72.3)	
Urinary MEP level (µg/L)			
Median	153.81	99.18	0.015[c]
Min-Max	13.06-4548.19	5.37-3101.58	
Urinary MEHHP level (µg/L)			
Median	123.28	159.30	0.511[c]
Min-Max	2.02-6026.76	2.41-8203.05	

The cases are: patients diagnosed as T2DM with HbA1c≥6.5%, random blood sugar≥200 mg/dL, with history of T2DM treatment. The control meets criteria: people with HbA1c<6.5%, random blood sugar<200 mg/dL, without history of T2DM treatment. The SD means standard deviation, [a]Independent t-test; [b]Chi-square test, [c]Mann-whitney test, Obese (BMI≥30), Overweight (BMI 25–29.9), Normal (BMI 18.5–24.9), Underweight (BMI<18.5) BMI: Body Mass Index, HbA1c: Glycated Hemoglobin; Physical activity was measured by the baecke physical activity questionnaire (or abbriviated as BQ).

The intake of carbohydrates, protein, fat, vegetables, fruits, and sweet drinks was insignificant in the incidence of the disease (p>0.05) among both groups. The regular intake of carbohydrate, protein and fat in the case group only had a little difference from the control. Meanwhile, the control's frequent vegetables and fruits diet were more than the case group, which was 55.3%, while the frequent intake of sweet drink diet in the control was higher than the case group, which was 57.4%. The overall dermal exposure and ingestion pattern in the case and control groups showed homogeneity. However, the proportion of subjects who experienced the dermal exposure route was higher than the ingestion route. Dietary carbohydrates, as much as 70% of the intake, affect the incidence of T2DM. Protein intake associated with the prevention of T2DM is found only in protein sources from legumes and seafood. A meta-analysis showed that fat intake (saturated fat and unsaturated fat) was not associated with T2DM, except that omega-3 fatty acids were associated with T2DM among Asians but not Europeans and Americans. Another study showed no significant difference between fruit and vegetable intake on the incidence of T2DM. One study showed that women who drank at least one or more sugar-sweetened beverages were at risk for T2DM compared to those who drank less frequently with mediated weight gain. Proboningsih *et al.* [31] found that bitter melon can be used as a medical treatment for reducing blood sugar levels. However, it will work when it is balanced with self-care regularly.

The lowest MEP and MEHHP levels were 13.06 µg/L and 2.02 µg/L, respectively. The median value of 131.91µg/L was used as the MEP cut-off point in the multivariate analysis, meanwhile the median of MEHHP was 151.82 µg/. Table 2 shows that variables, such as age, gender, nutritional status, physical activity, family history of T2DM, diet, and urinary MEHHP levels did not have a significant relationship

with T2DM (p>0.05). However, a strong correlation between the MEP levels and T2DM was revealed by the Chi-square test (p<0.05).

Table 2. Risk factors of type 2 diabetes mellitus

Risk factors	Cases		Controls		OR (95%CI)	p-value
	n=47	%	n=47	%		
Age						
≥45 years	43	91.5	42	89.4	1.280	1.000
<45 years	42	8.5	5	10.6	(0.321-5.096)	
Gender						
Male	14	29.8	15	31.9	0.905	1.000
Female	33	70.2	32	68.1	(0.377-2.173)	
Nutritional status, *n* (%)						
Overweight/obese	29	61.7	22	46.8	1.831	0.214
Undernutrition/normoweight	18	38.3	25	53.2	(0.805-4.161)	
Physical activity[b]						
Low (<2.59)	20	42.6	22	46.8	0.842	0.836
High (>2.59)	27	57.4	25	53.2	(0.373-1.900)	
Carbohydrate diet[c]						
Often (3-4 times/day)	23	48.9	24	51.1	0.918	1.000
Not often (<3 times/day)	24	51.1	23	48.9	(0.409-2.062)	
Protein diet[c]						
Often (3-4 times/day)	22	46.8	28	59.6	0.597	0.301
Not often (<3 times/day)	25	53.2	19	40.4	(0.264-1.352)	
Fat diet[c]						
Often (3-4 times/day)	22	46.8	23	48.9	0.918	1.000
Not often (<3 times/day)	25	53.2	24	51.1	(0.409-2.063)	
Vegetables and fruits diet[c]						
Not often (<3 times/day)	26	55.3	18	38.3	1.995	0.148
Often (3-4 times/day)	21	44.7	29	61.7	(0.876-4.540)	
Sweet drink diet[c]						
Often (>1 time/day)	24	51.1	27	57.4	0.773	0.679
Not often (<1 time/day)	23	48.9	20	42.6	(0.343-1.743)	
Family history of T2DM						
Yes	17	36.2	13	27.7	1.482	0.507
No	30	63.8	34	72.3	(0.619-3.549)	
Urinary MEP level (µg/L) [c]						
High (>131.91)	31	66.0	16	34.0	3.754	0.004
Not high (≤131.91)	16	34.0	31	66.0	(1.599-8.811)	
Urinary MEHHP level (µg/L) [c]						
High (>151.82)	21	44.7	26	55.3	0.652	0.409
Not high (≤151.82)	26	55.3	21	44.7	(0.289-1.471)	

Cases: patients diagnosed as T2DM with HbA1c≥6.5%, random blood sugar≥200 mg/dL, with history of T2DM treatment or family history of T2DM; Control: people with HbA1c<6.5%, random blood sugar<200 mg/dL, without history of T2DM treatment; HbA1c: Glycated Hemoglobin; [a]Reference Category; Obese (body mass index (BMI)≥30), Overweight (BMI 25-29.9), Normal (BMI 18.5-24.9), Underweight (BMI<18.5), BMI=body mass index; [b]Physical activity was measured by the Baecke Physical Activity Questionnaire (BQ), the results all showed light activity (<5.6) so that it was categorized according to a mean score of 2.59; [c]The median value was used as the cut-off point in the multivariate analysis.

Morevoer, the final model of logistic regression result in Table 3 shows that high urinary MEP levels were the independent risk factor for T2DM (OR: 3.754, 95% CI: 1.559-8.811, p-value: 0.002). The value of Nagelkerke R2 was 0.131.This is the first study in Indonesia showing phthalates exposure as an environmental risk factor for T2DM. Meanwhile, all the respondents' urine contained MEP and MEHHP metabolites, and high MEP levels were proven to be the disease's independent risk factor (OR: 3.754, 95% CI: 1.559-8.811, p-value: 0.002). These findings indicated that people with high MEP levels have a 3.754 times higher chance of developing T2DM than people with low MEP levels. Phthalates are phthalic acid dieters with a broad range of physical and chemical characteristics. Dermal and inhalation are the pathways for low molecular weight phthalate, while ingestion is the high molecular weight pathway [32]. Phthalate exposure with the low molecule is easier to absorb by the skin. MEP had molecule weight lower than MEHHP. It assumed that the body metabolism system absorbs the MEP higher than MEHHP. Moreover, the time exposure of MEP is more prolonged than MEHHP because the exposure path of MEP happens through the dermal. Phthalate exposure through the dermal route and inhalation significantly affect health because people spend most of their time in a room with relatively high plasticizer concentration [33]. In short, the plasticizer attaches to the skin (dermal) and is considered to assess phthalate exposure rather than ingestion.

Table 3. Multivariable analysis models (multivariable logistic regression)

Model	Variable	B	p-value	aOR	95% CI
Model 1	Vegetables and fruits diet	0.716	0.113	2.047	0.844-4.965
	Nutritional status	0.500	0.266	1.648	0.683-3.978
	Urinary MEP level	1.358	0.002	3.889	1.613-9.376
Model 2	Vegetables and fruits diet	0.774	0.084	2.168	0.902-5.207
	Urinary MEP level	1.371	0.002	3.938	1.643-9.441
Model 3[a]	Urinary MEP level	1.323	0.002	3.754	1.599-8.811

[a]Final model: Constanta=-0.921, Nagelkerke R^2=0.131; aOR=adjusted odds ratio, 95%CI=95% confident interval

A study foung that MEP levels significantly increased the prevalence of T2DM in elderly [34]. Moreover, the glucose triglyceride index (TyG) and its derivatives are prognostic markers of insulin resistance in none obese individuals, and they also have a positive relationship with MEP exposure [33]. Surprisingly, the MEHHP level did not appear as a risk factor for the disease (OR=0.652, 95% CI=0.289-1.471). It is speculated that because MEHHP was more excreted than MEP, the MEHHP level was lower at the time of analyses than the MEP level [27]. Previous studies also indicated that the toxic effects of these metabolites depend on endogenous hormones and race/ethnicity [19], [35]. The urinary MEP and MEHHP phthalate levels showed the lowest level of 13.06 µg/L and 2.02 µg/L, respectively. Meanwhile, the average LOD level was 0.4 µg/L, which is greater than the American community from a survey conducted by the NHANES in 2003-2004, showing a value of 0.32 µg/L [36].

The mean age in the case group was 55.36 years, which is greater than the control group (54.34) years. DM, specifically T2DM, is more common in the older age group, and generally, older people have other comorbidities [37]. The body's physiological function and ability to carry out activities begin to decline during the pre-elderly period, triggering the emergence of disease and reducing the health status [38]. Meanwhile, overweight and obese in the case group were 61.5%, while the control group were 49.2%. This result has a consistent relationship with the incidence of the disease [39].

The BQ score for light activity is<5.6, meanwhile in this research all respondent's activity was light activity. The average physical activity in the control group was slightly higher than in the case group. Similarly, Simbolon *et al.* and Linder *et al.* compared the physical activity patterns in the DM and non-DM groups and discovered that the pattern of physical activity in the non-DM group was higher [40], [41].

Control of blood glucose prevents or delays the development of T2DM [42]. The group of respondents with a family history of DM tends to experience insulin resistance (IR) and is associated with an increase in waist circumference, which is closely related to T2DM [43]. The intake of carbohydrates, protein, fat, vegetables and fruits, as well as sweet drinks was significant in the disease's incidence (p>0.05) in both groups. It is found that diet and phthalate exposure are indicators in various studies on diabetes and obesity due to the assumption that phthalate exposure is often followed by an unsuitable calorie intake, such as frequent consumption of packaged/processed foods or fatty foods [14].

Phthalate metabolites are also related to increased glucose concentration, cell function indicator, and insulin resistance. Phthalate exposure can disturb blood glucose control and influence pre-diabetes. The progressive decrease in insulin sensitivity plays an essential role in pathogenesis syndrome metabolic (MetS). The compensation of disturbed beta-cell as a response to the increased insulin resistance is a pathophysiology factor related to poor glucose tolerance. Besides, the pre-diabetes condition, impaired glucose tolerance (IGT), and impaired fasting glucose are descriptions of pathology insulin resistance in insulin-sensitive organs.

MEP, MEHHP, Methylbenzylpiperazine (MBzP), and mono(2-ethyl-5-oxohexyl) phthalate (MEOHP) were associated with increased abdominal circumference [32]. Meanwhile, the metabolites related to HOMA-IR (an indicator of the presence of insulin resistance) are MEP, MBP, and MBzP. MEHHP was only associated with increased abdominal circumference and not with HOMA-IR. It is revealed that dermal phthalate exposure has a relationship with impaired glucose metabolism in respondents with and without DM [33]. Phthalate in urine have a positive association with increased insulin resistance and oxidative stress, which are risk factors of insulin resistance in diabetic patients [44].

Some recent studies observed that urinary concentrations of phthalates were positively associated with the risk of DM [45], [46], and the chemical is positively associated with diabetes and its risk factors. Phthalates alter normal glucose metabolism in non-DM respondents as they have the ability to bind PPAR-alpha and PPAR-gamma. Furthermore, PPAR-gamma agonists have tremendous therapeutic potential in treating T2DM as they have insulin-sensitizing activity and anti-diabetic effects [47].

This study is limited to the variable obtained at the same time. Moreover, the urine sample for phthalate examination is only done once because of the limitation of money. But if the result shows the concentration content of MEP and MEHHP is relatively extreme, then the laboratory will repeat the measurement, known as the Duplo examination. The possibility of contact between urine and plastic

compounds during the examination process leads to overestimated results on the phthalate levels in the examination results. However, since the phthalate compound examined in this study is not the primary compound but a metabolite product that is the result of metabolism in the human body, which is excreted through the urine, so will be very different from the primary compound.

4. CONCLUSION

The study revealed that the urinary MEP of T2DM has a higher content than MEHHP. The urinary MEP level was the independent risk factor for T2DM in Indonesian adults. While age, gender, nutrition status, family history, dietary status, and physical activity are not confounding factors in urinary MEP effect for T2DM. It is also proved that phthalate (MEP and MEHHP) through phthalate exposure (dermal and ingestion) has a higher proportion in T2DM patients, and phthalate exposure is one of the risks that cause T2DM. A further study with other phthalates in different setting areas and combined exposure is suggested.

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