Endocrine disrupting chemicals and Risk of Type 2 diabetes and Cardiovascular Health: focused on PFOS and phthalates exposures

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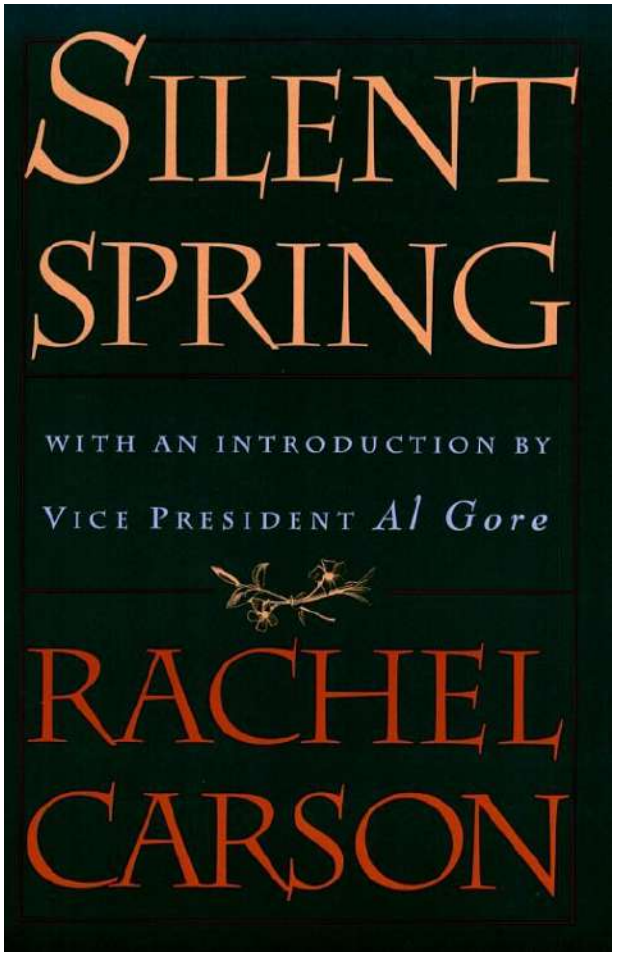
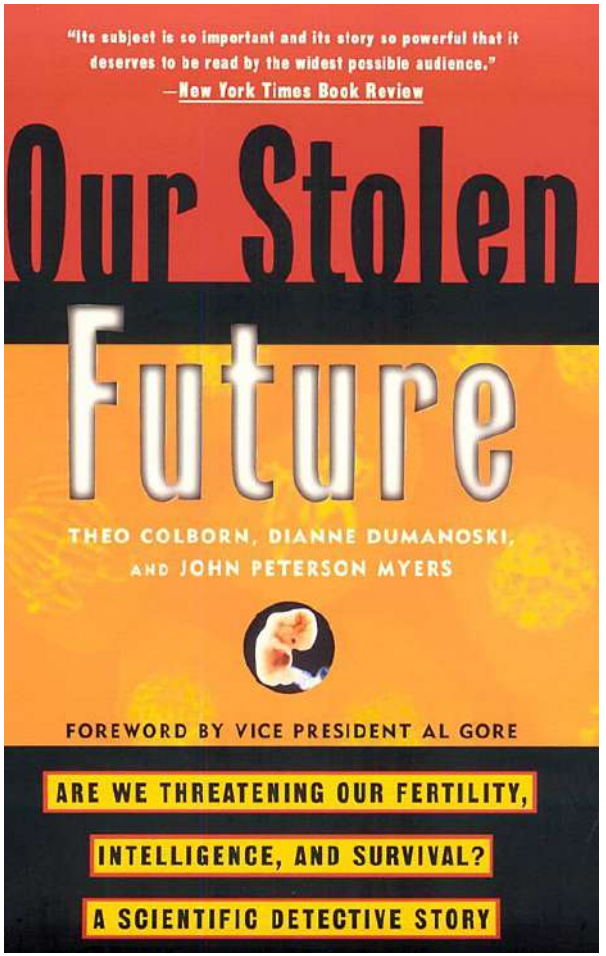
COI

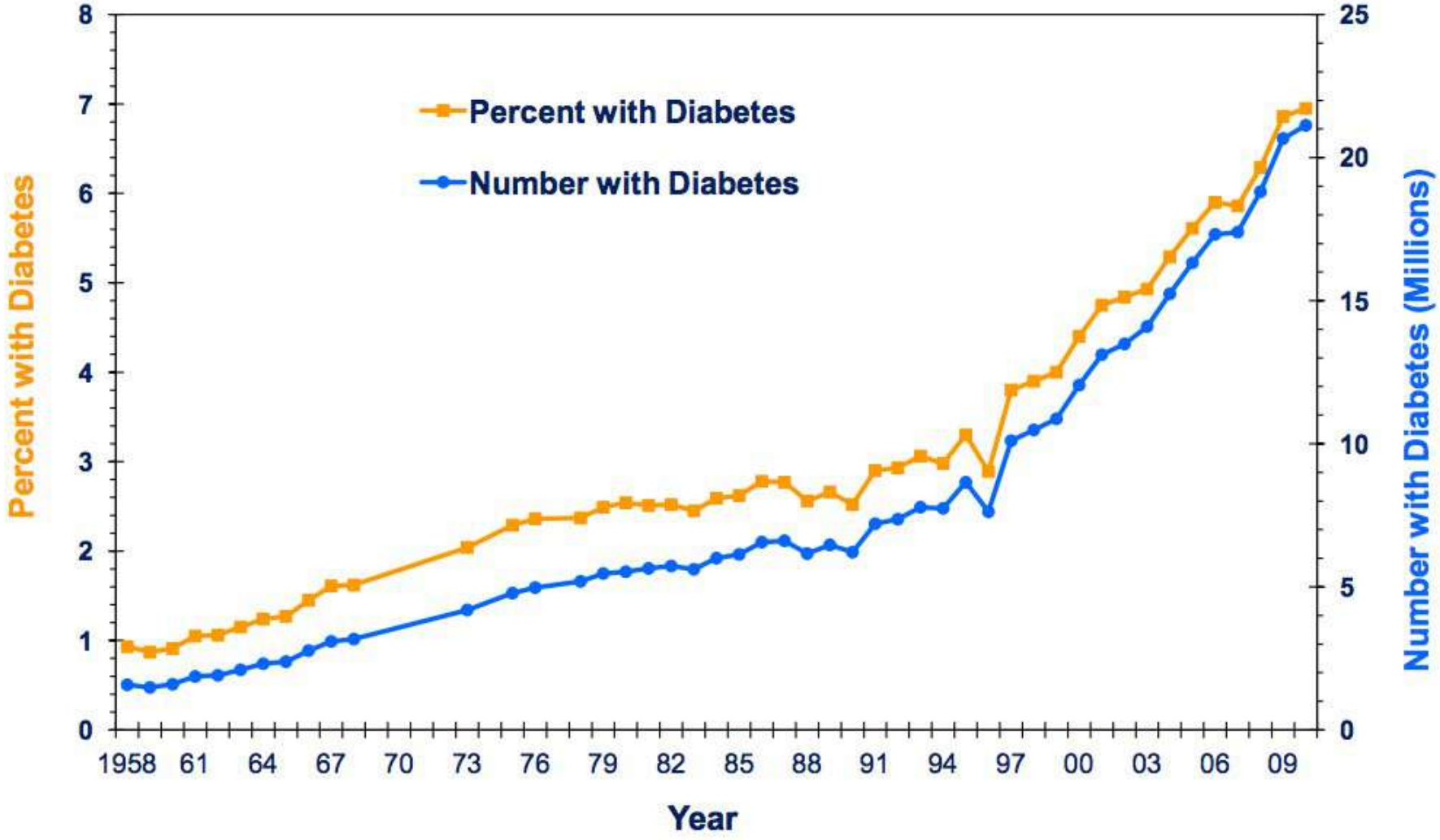
- I declare there are no conflict of interest in this study, including study subjects, authors, and grant.

Silent Spring to Silent Sperm?

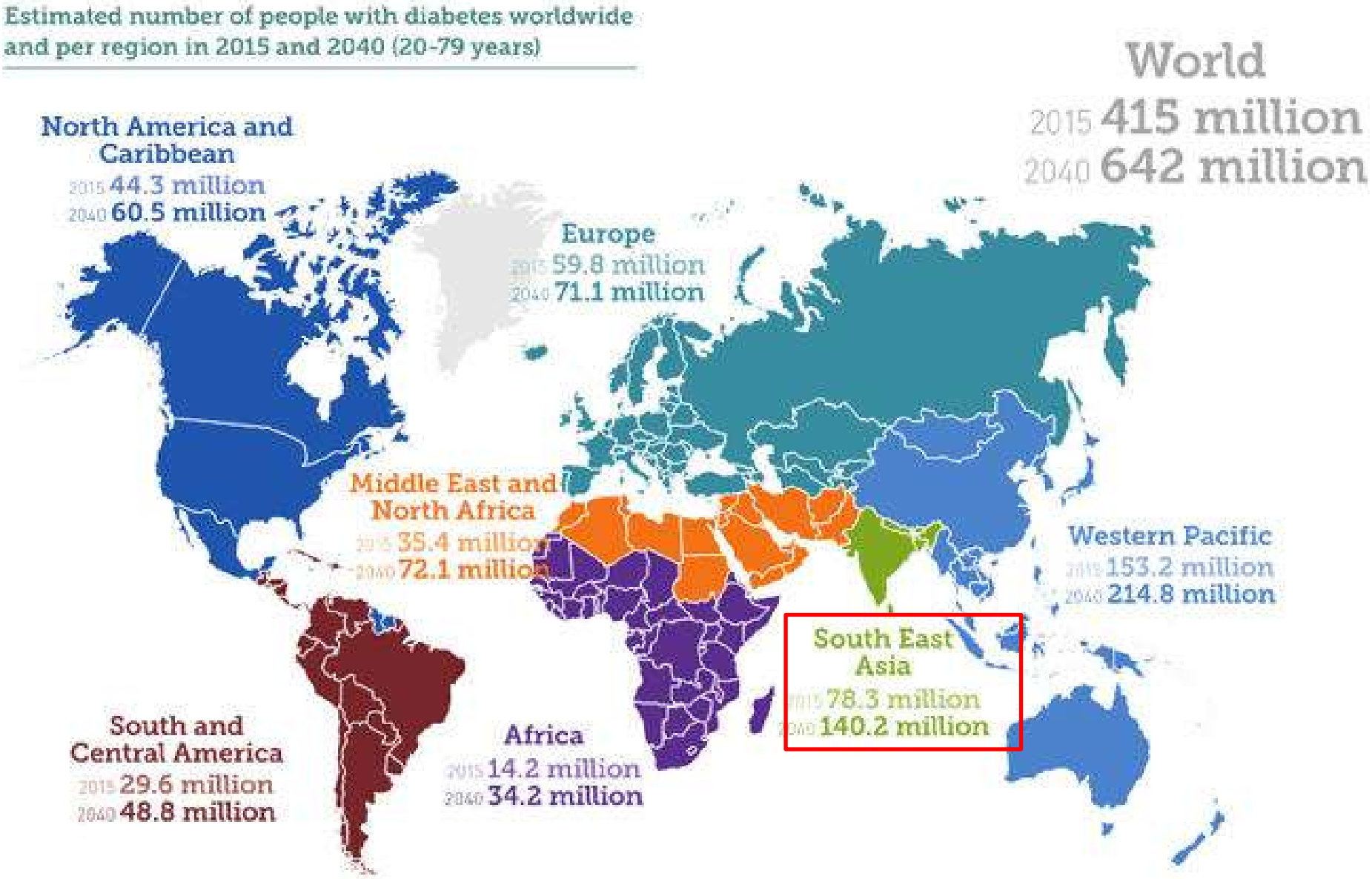




Number and Percentage of U.S. Population with Diagnosed Diabetes, 1958-2010



Numbers of Type 2 Diabetes



Future Research Questions:

1. What is the overall health burden of these chemicals with long-term, cumulative exposure over a life-time, versus short-term use?
2. What proportion of susceptibility to obesity is explained by chemicals in the environment

American Heart Association | American Stroke Association

Policy Statement on Environmental Endocrine Disrupting Chemicals & the Impact on Obesity and Cardiovascular Disease

Position

2010 September

The American Heart Association (AHA) recognizes that the causes of obesity are multi-factorial and complex, and therefore, must be addressed on multiple levels. Recently, endocrine disrupting chemicals (EDCs) such as diethylstilbestrol, bisphenol A, phthalates and organotins have been proposed as potential "obesogens" that contribute to a toxic chemical burden that may initiate or exacerbate the development of obesity and its related comorbitites.[1-7] EDCs are found in a variety of products including plastics, cosmetics, shampoos, soaps, lubricants, pesticides, paints and flame-retardant materials.[2, 8] Laboratory studies are still elucidating the exact mechanisms by which these substances affect weight, but current evidence suggests that they disrupt developmental and homeostatic controls over fat production and energy balance.[9-12] However, determining the link with obesity can be especially challenging because obese people might be eating more and therefore exposing themselves to more of the chemicals in food packaging. Teasing out causality can be challenging. Although limited research exists on the effect of these environmental chemicals on human populations, several epidemiological studies have found that chemical exposure, particularly during critical developmental periods, is positively correlated with increased weight, cardiovascular disease and diabetes.[8, 13-18] Additional research is needed to clarify these results and establish a causal link between exposure to EDCs and adverse health effects in humans as well as discern the physiological/cellular/metabolic impact of exposure. The AHA recommends further research before taking a proactive advocacy position.

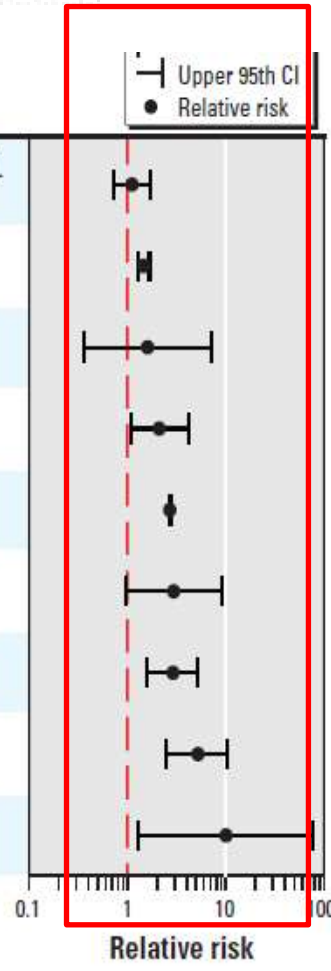
Environmental Factors of Type 2 Diabetes

- Smoking
- Arsenic
- PCBs
- POPs
- Phthalates
- Bisphenol A

Environ Health Perspect 2012 Review

Figure 2. Association between arsenic and diabetes in areas of relatively high exposures (> 150 ppm drinking water).

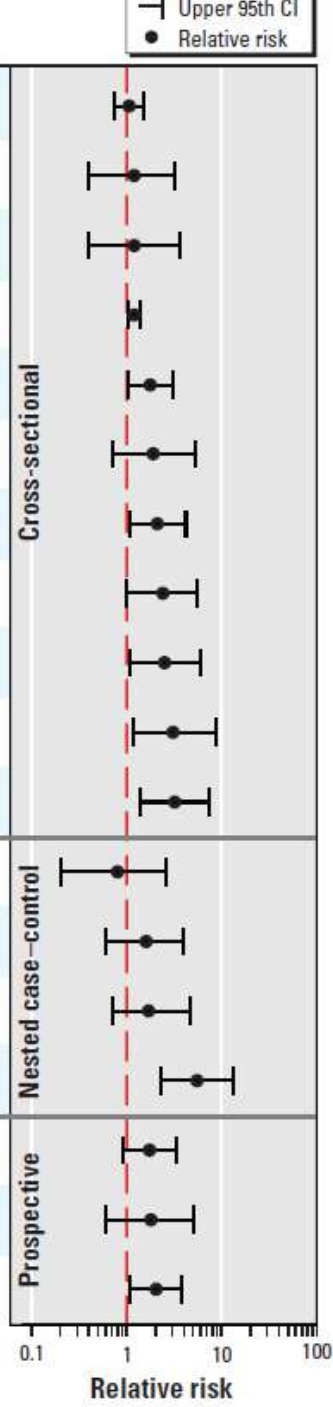
Reference	Study description (*n*)	Diagnostic	Relative risk adj OR (95% CI)	Exposure
Chen et al. 2010	Bangladesh (Araihazar) CS HEALS, ♂♀ (11,319)	Self-report prior to baseline	1.11 (0.73, 1.69)	176.2–864 (Qn5) vs. 0.1-8 (Qn1) µg/L (drinking water, CEI)
Tsai et al. 1999	Taiwan (Chiayi County) Retro blackfoot region, ♂♀ (19,536 deaths)	Death certificate	1.46 (1.28, 1.67) SMR[a]	Blackfoot endemic region vs. national reference
Tollestrup et al. 2003	USA (Ruston, WA) Retro, lived near smelter as children, ♂♀ (1,074 deaths)	Death certificate	1.6 (0.4, 7.2) RR[a]	≥ 10 vs. < 1 year
Tseng et al. 2000a, 2000b	Taiwan (southwestern) Pros industrial region, ♂♀ (446)	FBG, OGGT	2.1 (1.1, 4.2) RR	≥ 17 vs. < 17 mg/L-year (drinking water, CEI)
Wang et al. 2003	Taiwan (southwestern) CS As endemic reg., ♂♀ (706,314)	Insurance claims	2.69 (2.65, 2.73)	Endemic vs. nonendemic region
Nabi et al. 2005	Bangladesh (Chapainowabganj) CC 115 arsenicosis cases, ♂♀ (235)	Glucose, blood	2.95 (0.95, 9.28) OR[a]	218.1 vs. 11.3 (avg) µg/L (drinking water)
Rahman et al. 1999	Bangladesh (multi-site) CS w/skin lesions, ♂♀ (134)	Glucosuria	2.9 (1.6, 5.2) adj PR	> 10 vs. < 1 mg-year/L (drinking water, CEI)
Rahman et al. 1998	Bangladesh (Dhaka) CS 163 keratosis cases, ♂♀ (1,107)	Self-report, OGGT, glucosuria	5.2 (2.5, 10.5) adj PR	Keratosis vs. non-keratosis
Lai et al. 1994	Taiwan (Southern) CS As endemic region, ♂♀ (891)	Self-report, OGGT, treatment history	10.1 (1.3, 77.9)	≥ 15 vs. 0 ppm-year (drinking water, CEI)



Arsenic and Diabetes

Environ Health Perspect 2012 Review

Reference	Study description (*n*)	Chemical	Diagnostic	Relative risk adj OR (95% CI)	Exposure
Rylander et al. 2005	Sweden (national registry), CS fisherman's wives, ♀ (184)	PCB153	Self-report	1.06 (0.75, 1.5) per 100 ng/g ↑	230 (110–810) [med (5th–95th), cases] ng/g lipid (serum)
Jørgensen et al. 2008	Greenland (west coast) Inuit, CS ♂♀ (692)	PCBs, non-dioxin	OGTT, FBG	1.2 (0.4, 3.2)	Q4 vs. Q1 ng/g lipid (plasma)
Jørgensen et al. 2008	Greenland (west coast) Inuit, CS ♂♀ (692)	PCBs, dioxin-like	OGTT, FBG	1.2 (0.4, 3.6)	Q4 vs. Q1 ng/g lipid (plasma)
Rylander et al. 2005	Sweden (national registry), CS fishermen, ♂ (196)	PCB153	Self-report	1.20 (1.04, 1.39) per 100 ng/g ↑	560 (360–1,600) [med (5th–95th), cases] ng/g lipid (serum)
Ukropec et al. 2010	Slovakia (eastern, "polluted"), CS ≥ 21 year, ♂♀ (2,047)	PCBs	FBG	1.77 (1.05, 3.02)	1,341–2,330 (Q4) vs. 148–627 (Q1) ng/g lipid (serum)
Turyk et al. 2009b	USA (Great Lakes), CS fish eaters, ♂♀ (503)	PCBs	Self-report, HbA1c	1.9 (0.7, 5.2)	3.6–24.4 (Q4) vs. < 0.8 (Q1) ng/g (serum)
Turyk et al. 2009b	USA (Great Lakes), CS fish eaters, ♂♀ (503)	PCBs, dioxin-like	Self-report, HbA1c	2.1 (1.1, 4.2)	0.3–1.6 (T3) vs. < LOD (T1) ng/g (serum)
Codru et al. 2007	USA (Akwesasne) Mohawks, CS ♂♀ (352)	PCB153	FBG, medication	2.4 (1.0, 5.6)	104.1 (T3) vs. 59.8 (T1) ng/g lipid (serum)
Lee et al. 2006	USA (NHANES 1999–2002) ≥ 20 year, CS ♂♀ (2,106)	PCB153	FBG, self-report	2.5 (1.1, 6)	14.3 (< 25th) vs. ND ng/g lipid (serum)
Uemura et al. 2008	Japan (multisite), CS ♂♀ (1,374)	PCBs, dioxin-like	Self-report, HbA1c	3.07 (1.16, 8.81)	≥ 7.60 to < 13 vs. ≤ 7.60 pg TEQ/g lipid (serum)
Codru et al. 2007	USA (Akwesasne) Mohawks, CS ♂♀ (352)	PCBs	FBG, medication	3.2 (1.4, 7.5)	756.2 (T3) vs. 448.6 (T1) ng/g lipid (serum)
Lee et al. 2010	USA (multisite) CARDIA, nested CC ≥ 18 year, ♂♀ (180)	PCB153	FBG, medication	0.8 (0.2, 2.6)	> 466 (Q4) vs. ≤ 204 (Q1) pg/g (serum)
Rignell-Hydbom et al. 2009	Sweden (Lund) WHILA, nested CC ♀ (742)	PCB153	OGTT	1.6 (0.61, 4)	> 1,790 vs. ≤ 1,790 pg/ml (serum)
Wang et al. 2008	Taiwan (Yucheng), nested CC ≥ 30 year, ♂ (167)	PCBs	Self-report	1.7 (0.7, 4.6)	99.4 vs. 53.9 ppb (serum)
Wang et al. 2008	Taiwan (Yucheng), nested CC ≥ 30 year, ♀ (244)	PCBs	Self-report	5.5 (2.3, 13.4)	121.4 vs. 72.6 ppb (serum)
Vasiliu et al. 2006	USA (Michigan) PBB cohort, Pros ♂ (688)	PCBs	Self-report	1.74 (0.91, 3.34) IDR	> 10 vs. ≤ 5.0 ng/mL (serum)
Turyk et al. 2009a	USA (Great Lakes), Pros fish eaters, ♂♀ (471)	PCBs	Self-report	1.8 (0.6, 5) IRR	4.3–29.8 (T3) vs. < 1.6 (T1) ng/g ww (serum)
Vasiliu et al. 2006	USA (Michigan) PBB cohort, Pros ♀ (696)	PCBs	Self-report	2.04 (1.10, 3.78) IDR	5.1–7.0 vs. ≤ 5.0 ng/mL (serum)

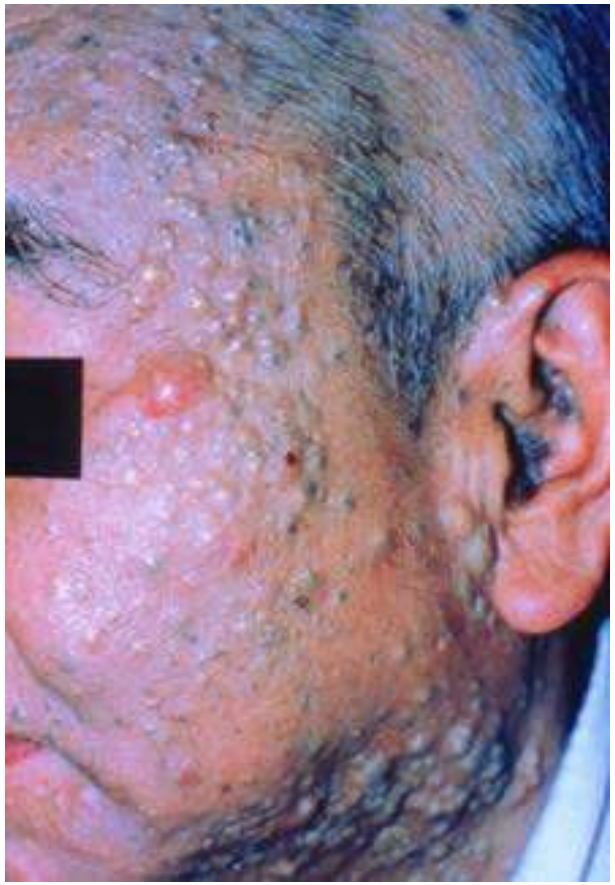


PCBs and Diabetes Mellitus

Environ Health Perspect
2012 Review

Polychlorinated Biphenyls and Dibenzofurans 1978~1979

- About 2,000 **Yucheng** (oil-disease) victims were Taiwanese people exposed to **polychlorinated biphenyls (PCBs)** and their heat-degradation products, mainly polychlorinated dibenzofurans (**PCDFs**), from the ingestion of contaminated rice oil in 1978-79.
- OR of **5.5** for DM and **3.5** for hypertension for Yucheng women 24 years later



Increased Risk of Diabetes and Polychlorinated Biphenyls and Dioxins

A 24-year follow-up study of the Yucheng cohort

Wang SL and Kuo YL. *Diabetes Care* 31:1574–1579, 2008

RESULTS — The diabetes risk to members of the Yucheng cohort relative to their reference subjects was significantly increased for women (odds ratio [OR] 2.1 [95% CI 1.1–4.5]) but not for men after considering age, BMI, cigarette smoking, and alcohol intake. Yucheng women diagnosed with chloracne had adjusted ORs of 5.5 (95% CI 2.3–13.4) for diabetes and 3.5 (1.7–7.2) for hypertension compared with those who were chloracne free.

Atherosclerosis 241 (2015) 657–663

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journal homepage: www.elsevier.com/locate/atherosclerosis

Association between levels of serum bisphenol A, a potentially harmful chemical in plastic containers, and carotid artery intima-media thickness in adolescents and young adults

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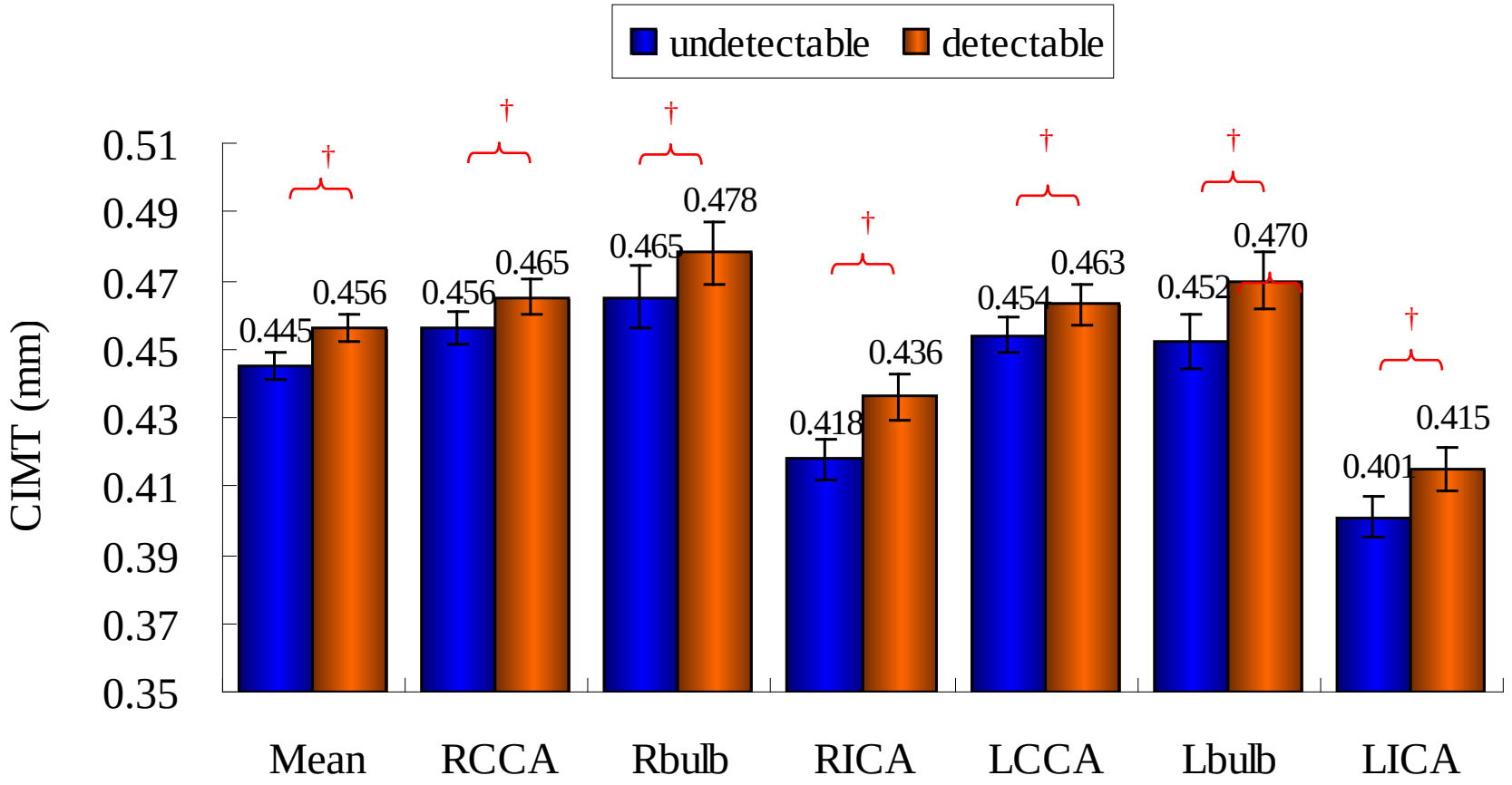
Conclusion: Higher serum concentrations of BPA were associated with increased CIMT in this cross-sectional study of adolescents and young adults. Studies to clarify the mechanisms of these associations are needed.

Figure 1.
Bisphenol A and carotid intima-media thickness



p-value: * <0.05, † <0.01, ‡ <0.005

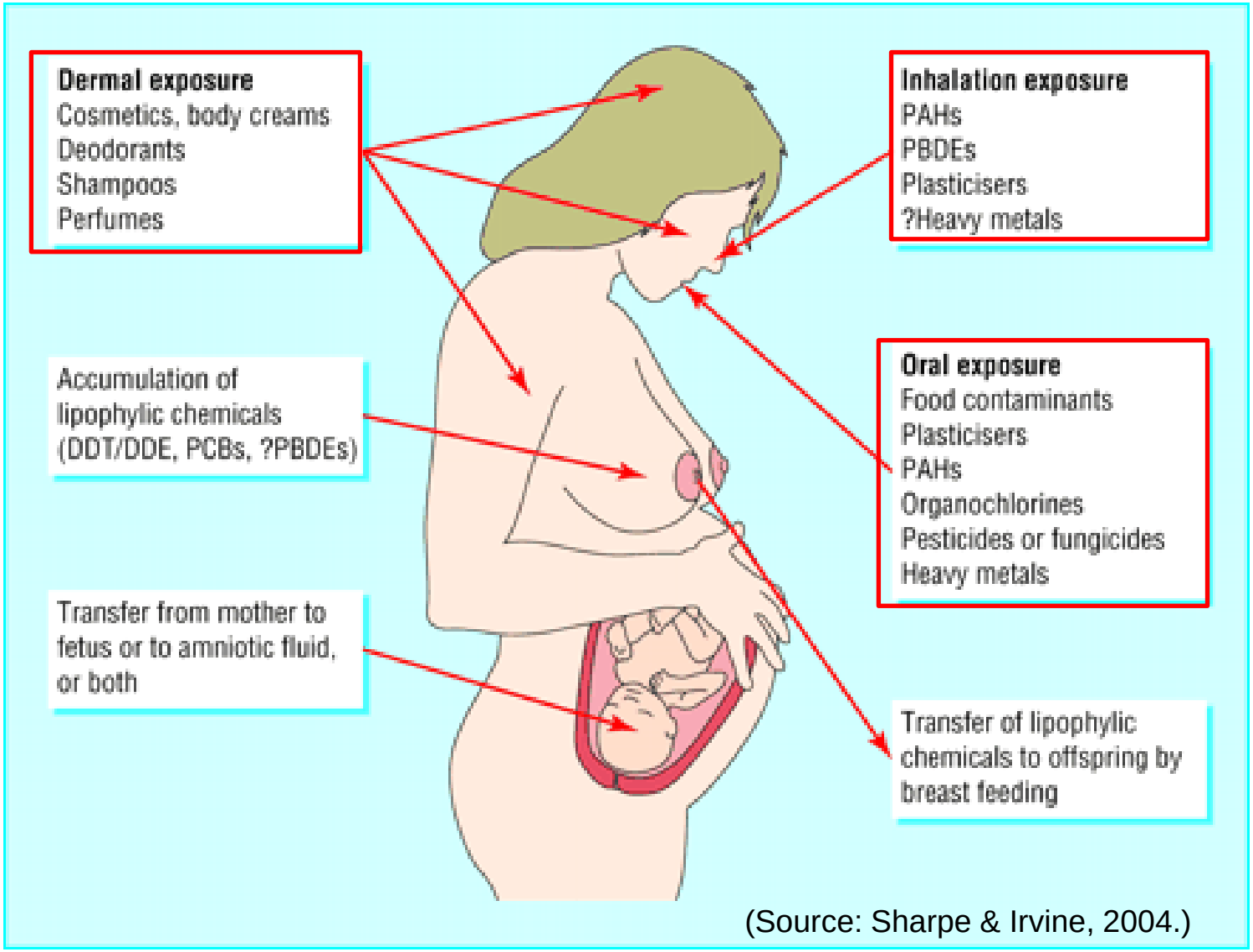
Lin & Su et al. Atherosclerosis 2015; 241: 657-663.

Environmental Exposures That Affect the Endocrine System

- **Pesticides** (insecticides such as o,p'-DDT, endosulfan, dieldrin, methoxychlor, kepone, dicofol, toxaphene, chlordane; herbicides such as alachlor, atrazine and nitrofen; fungicides such as benomyl, ferbam, and maneb; and fumigants such as aldicarb and dibromochloropropane)
- **Industrial chemicals** (polychlorinated biphenyls (PCBs), dioxin and benzo(a)pyrene)
- **Brominated flame retardants** (polybrominated diphenyl ethers, PBDEs)
- **Perfluoroalkylated substances**
- **Products associated with plastics (bisphenol A, phthalates)**
- **Ordinary household products** (breakdowns products of detergents and associated surfactants, including nonylphenol and octylphenol);
- **Pharmaceuticals** (drug estrogens - birth control pills, diethylstilbestrol (DES), cimetidine)
- **Heavy metals** (lead, mercury, arsenic , cadmium, and tin)

Persistent Organic Pollutants (POPs)

Routes of Human Exposure to Some Common Environmental Chemicals



(Source: Sharpe & Irvine, 2004.)

Phthalate Plasticizer Event in Taiwan 2011

A major incident of phthalate-contaminated foodstuffs happened in Taiwan between April and July, 2011. Phthalates were deliberately added to foodstuffs as a substitute of emulsifier (Clouding agent).

Wu et al. Environ Int. 2012 Sep;44:75-9. **The public health threat of phthalate-tainted foodstuffs in Taiwan: the policies the government implemented and the lessons we learned.**

What is Phthalates?

- Phthalates are **diesters of phthalic acids**, a class of industrial chemicals extensively used since the early 20th century as softeners of plastics, solvents in perfumes, and additives to hairsprays and lubricants and as insect repellents.
- Di-2-ethylhexyl phthalate (DEHP) is used primarily as a plasticizer for polyvinyl chloride (PVC) and can therefore be found in a variety of products such as **floor and wall coverings, vinyl gloves, toys, child care articles, food packaging materials, and medical devices** (Green et al. 2005).

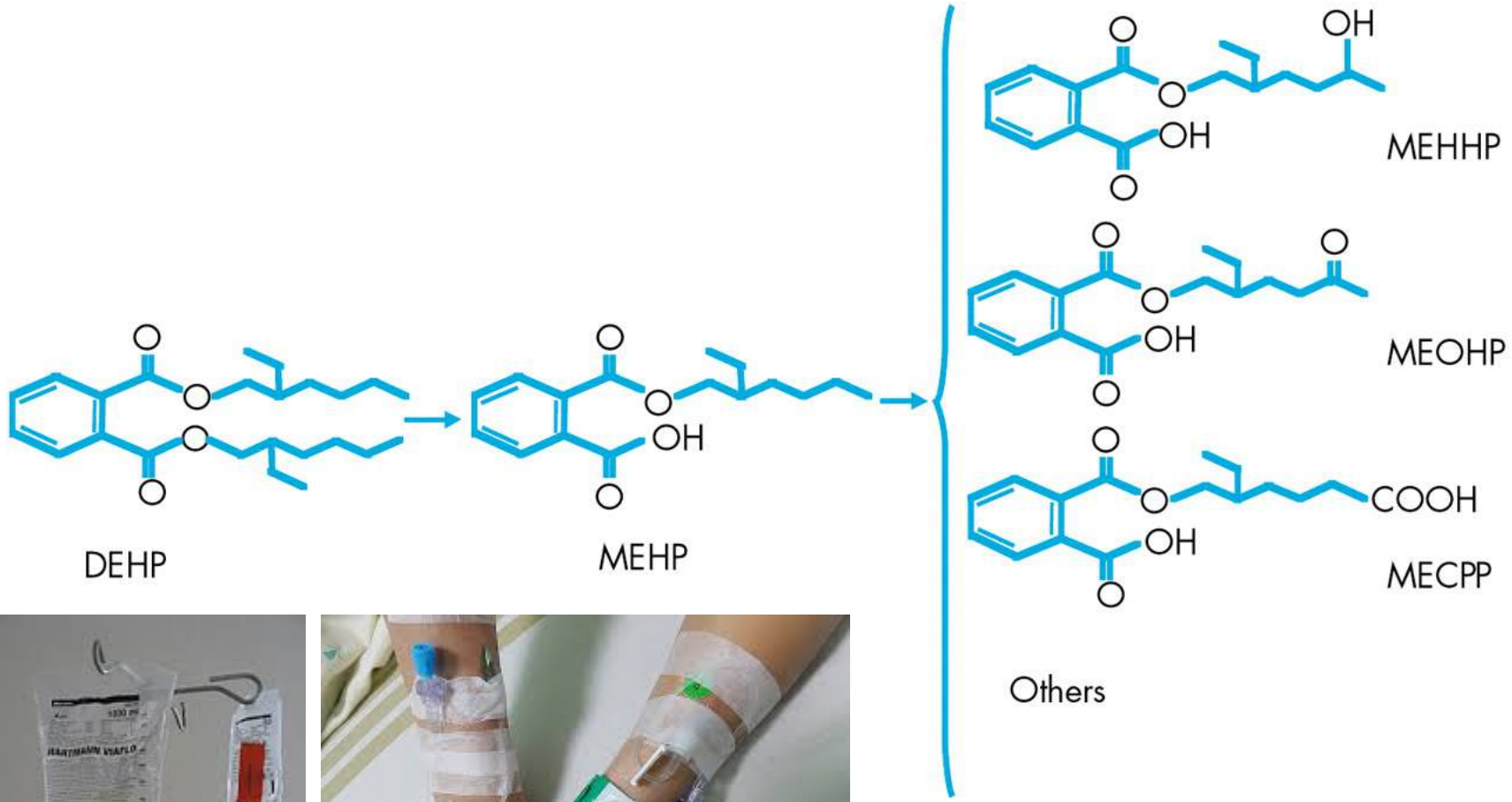
Intake, absorption and excretion

- Intake via **food, food packaging and water, polluted dust**
- After absorption, the parent diester phthalates are rapidly hydrolyzed to the corresponding **monoesters**, some of which are then further metabolized, with the metabolites excreted in **urine and feces**. In humans, phthalates are eliminated mostly within hours, with **excretion complete by a day or two; half-lives in the body are in hours** (Koch and Calafat 2009).
- For phthalates with short alkyl chains, monoesters represent the major human metabolite, but in the case of phthalates with long alkyl chains, including **DEHP, diisononyl phthalate (DINP) and diisodecyl phthalate (DIDP)**, the monoesters are further metabolized via ω- and ω-1-oxidation of the aliphatic side chain (Agency for Toxic Substances and Disease Registry 2002).

Eating Phthaltes Everyday

Lifestyles and daily life

Selected metabolites of di[2-ethylhexyl) phthalate) (DEHP) in humans: mono(2-ethylhexyl) phthalate (MEHP), mono(2-ethyl-5-hydroxyhexyl) phthalate (MEHHP), mono(2-ethyl-5-oxohexyl) phthalate (MEOHP), and mono(2-ethyl-5-carboxypentyl) phthalate (MECPP).



Hauser R , and Calafat A M Occup Environ Med 2005;62:806-818

OEM

Heating Plastic Wrap release Phthalates

Table 4 Phthalate concentrations in lunch meal under different heating conditions

Unit: μg/g

Treatment	Sample no.	DMP	DEP	DBP	DEHP	BBzP
Control	1 [a]	0.048±0.023 [b]	0.009±0.009	0.048±0.023	**0.275±0.023**	0.100±0.009
	2	0.062±0.011	0.007±0.003	0.072±0.017	0.245±0.068	0.097±0.005
	3	0.083±0.005	0.010±0.010	0.047±0.008	0.282±0.032	0.102±0.007
	Mean±SD	0.064±0.018	0.009±0.002	0.056±0.014	0.267±0.020	0.100±0.003
Heating 1 [c]	1	**0.117±0.024**	**0.229±0.260**	**1.914±1.084**	**2.113±0.389**	**ND (< 0.003)**
	2	0.156±0.009	0.274±0.274	3.124±0.311	3.428±1.118	0.129±0.223
	3	0.105±0.020	0.036±0.018	0.513±0.236	3.223±0.830	0.214±0.134
	Mean±SD	0.126±0.027	0.180±0.126	1.850±1.307	2.921±0.708 [d]	0.172±0.060
Heating 2 [c]	1	**0.247±0.033**	**0.190±0.038**	**2.579±0.284**	**4.956±0.623**	**0.284±0.161**
	2	**0.203±0.016**	**0.125±0.027**	**2.294±0.169**	**4.622±0.180**	0.097±0.168
	3	0.138±0.008	0.033±0.001	0.434±0.007	**3.214±0.198**	0.134±0.020
	Mean±SD	0.196±0.055 [e]	0.116±0.079	1.769±1.615	**4.264±0.925** [f]	0.172±0.099

[a] Tested in triplicate. [b] Mean±SD.

[c] **Heating 1:** the food in bowl was **not contacting plastic wrap** during 3 min heating; **heating 2**: the food on plate was **contacting plastic wrap** during 3 min heating.

[d] Statistically different compared with control (P=0.009) (student t-test). [e] (P=0.013) (student t-test). [f] (P=0.001) (student t-test).

Chen et al. Environment International 34 (2008) 79–85

Phthalate Concentrations and Dietary Exposure from Food Purchased in New York State

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Environ Health Perspect 2013; 121: 473-9.

Table 3. Mean and median food group concentrations (ng/g whole weight)[a] of phthalate esters from Albany, New York.

Food	Statistic	DMP	DEP	DiBP	DBP	DnHP	BBzP	DCHP	DEHP	DnOP
Beverages	Mean	0.13/0.06	0.1/0	0.29/0.23	0.7/0	0.1/0	0.1/0	0.1/0	3.89/2.28	0.5/0
	Median	0.1/0	0.1/0	0.1/0	0.7/0	0.1/0	0.1/0	0.1/0	1.85/0	0.5/0
Milk	Mean	0.1/0	0.17/0.12	0.2/0.15	1.5/1.15	0.1/0	0.55/0.5	0.1/0	48.6/48.6	1.51/1.26
	Median	0.1/0	0.17/0.12	0.2/0.15	1.5/1.15	0.1/0	0.55/0.5	0.1/0	48.6/48.6	1.51/1.26
Other dairy	Mean	0.48/0.42	1.37/1.34	1.91/1.89	105/104.4	1.25/1.18	4.22/4.19	0.3/0.21	144/144	2.76/2.31
	Median	0.1/0	0.66/0.66	0.79/0.79	4.77/4.77	0.1/0	1.2/1.2	0.1/0	92.8/92.8	0.5/0
Fish	Mean	0.21/0.15	0.6/0.56	1/0.94	11/10.6	0.13/0.05	1.61/1.55	0.1/0	31.7/31.4	0.5/0
	Median	0.1/0	0.86/0.86	0.1/0	0.7/0	0.1/0	0.1/0	0.1/0	39.6/39.6	0.5/0
Fruit/vegetables	Mean	0.1/0	0.12/0.04	0.55/0.53	0.7/0	0.1/0	0.67/0.61	0.1/0	6.2/5.09	0.5/0
	Median	0.1/0	0.1/0	0.48/0.48	0.7/0	0.1/0	0.1/0	0.1/0	1.85/0	0.5/0
Grain	Mean	0.3/0.27	12.6/12.6	3.54/3.52	15.9/15.8	0.23/0.17	5.92/5.92	0.1/0	61.6/61.6	0.5/0
	Median	0.34/0.34	1.17/1.17	1.64/1.64	5.14/5.14	0.1/0	4.65/4.65	0.1/0	50.6/50.6	0.5/0
Beef	Mean	0.18/0.13	0.64/0.64	0.1/0	0.7/0	2.47/2.42	0.61/0.56	0.1/0	1.85/0	3.57/3.32
	Median	0.18/0.13	0.64/0.64	0.1/0	0.7/0	2.47/2.42	0.61/0.56	0.1/0	1.85/0	3.57/3.32
Pork	Mean	0.33/0.28	0.55/0.55	6.25/6.18	0.7/0	0.1/0	0.23/0.15	0.1/0	300/300	2.86/2.49
	Median	0.16/0.11	0.59/0.59	0.1/0	0.7/0	0.1/0	0.1/0	0.1/0	20.6/20.6	0.5/0
Poultry	Mean	0.15/0.1	0.41/0.4	0.1/0	0.7/0	0.21/0.12	0.66/0.6	0.1/0	18.6/18.3	0.5/0
	Median	0.15/0.1	0.33/0.33	0.1/0	0.7/0	0.1/0	0.1/0	0.1/0	14.8/14.8	0.5/0
Meat and meat products	Mean	0.22/0.17	0.49/0.48	1.99/1.9	0.7/0	0.51/0.43	0.48/0.41	0.1/0	101.8/101	1.7/1.28
	Median	0.2/0.2	0.45/0.45	0.1/0	0.7/0	0.1/0	0.1/0	0.1/0	7/7	0.5/0
Vegetable oils	Mean	1.2/1.14	0.1/0	3.2/3.17	3.53/3.07	0.19/0.12	154/154	14.27/14.2	117/116.3	0.84/0.5
	Median	0.1/0	0.1/0	0.25/0.25	0.7/0	0.1/0	2.2/2.2	0.1/0	48.9/48.9	0.5/0
Condiments	Mean	0.33/0.28	0.77/0.72	1/0.98	15.4/15	0.1/0	1.99/1.96	0.13/0.05	30.4/30.1	1.19/0.77
	Median	0.2/0.15	0.16/0.11	0.81/0.81	1.6/1.25	0.1/0	1.33/1.33	0.1/0	20.6/20.6	0.5/0
Infant food	Mean	0.1/0	0.35/0.31	0.77/0.74	1.14/0.64	0.1/0	3.36/3.35	0.18/0.1	75.1/75.1	2.5/2.14
	Median	0.1/0	0.28/0.28	0.22/0.22	0.7/0	0.1/0	2.37/2.37	0.1/0	29.4/29.4	0.5/0

[a]Concentrations are displayed as the phthalate ester concentration in a food group when substituting one-half the LOD for each nondetect ÷ the phthalate ester concentration in a food group when substituting 0 for each nondetect.

Comparison of Phthalate Food Concentrations, reported elsewhere

Table 4. Comparison of phthalate food concentrations reported elsewhere in the literature with food concentrations found in the present study (ng/g wet weight).

Food	Source	DEHP	DBP	BBzP	DiBP
Beverages	This study (mean)	3.9	0.7	0.1	0.3
	Wormuth et al. (2006)[a]	14	18	0.1	2
	Page and Lacroix (1995)[b]	ND	—	ND	—
	FSA (2012)[c]: MK	—	—	—	—
	FSA (2012)[c]: TDS	ND	ND	ND	ND
	Fierens et al. (2012)[d]	0.1	0.1	0.1	0.1
All dairy	This study (mean)	126.5	85.9	3.6	1.6
	Wormuth et al. (2006)[a]	211	22	14	0.4
	Page and Lacroix (1995)[b]	830	—	260	—
	FSA (2012)[c]: MK	159	ND	ND	12
	FSA (2012)[c]: TDS	71	ND	ND	ND
	Fierens et al. (2012)[d]	27.5	2.0	ND	2.4
Fish	This study (mean)	31.7	11.0	1.6	1.0
	Wormuth et al. (2006)[a]	13	8	5	1
	Page and Lacroix (1995)[b]	67	—	ND	—
	FSA (2012)[c]: MK	59	ND	ND	ND
	FSA (2012)[c]: TDS	789	9	ND	1
	Fierens et al. (2012)[d]	86.0	ND	ND	ND

Food	Source	DEHP	DBP	BBzP	DiBP
Beef	This study (mean)	1.9	0.7	0.6	0.1
	Wormuth et al. (2006)[a]	207	75	0	7
	Page and Lacroix (1995)[b]	50	—	ND	—
	FSA (2012)[c]: MK	34	0.5	ND	ND
	FSA (2012)[c]: TDS	90	ND	ND	ND
	Fierens et al. (2012)[d]	44.5	1.5	ND	2.0
Pork	This study (mean)	300	0.7	0.2	6.3
	Wormuth et al. (2006)[a]	64	4	0	0
	Page and Lacroix (1995)[b]	250	—	ND	—
	FSA (2012)[c]: MK	34	0.5	ND	ND
	FSA (2012)[c]: TDS	90	ND	ND	ND
Poultry	This study (mean)	18.6	0.7	0.7	0.1
	Wormuth et al. (2006)[a]	518	100	15	30
	Page and Lacroix (2005)[b]	2,600	—	ND	—
	FSA (2012)[c]: MK	34	0.5	ND	ND
	FSA (2012)[c]: TDS	322	ND	ND	ND

Environ Health Perspect 2013; 121: 473-9.

Phthalates in Indoor Dust and Their Association with Building Characteristics

Carl-Gustaf Bornehag,[1,2,3] Björn Lundgren,[1] Charles J. Weschler,[2,4] Torben Sigsgaard,[5] Linda Hagerhed-Engman,[1] and Jan Sundell[2]

[1]Swedish National Testing and Research Institute, Borås, Sweden; [2]International Centre for Indoor Environment and Technology, Technical University of Denmark, Lyngby, Denmark; [3]Department of Public Health Sciences, Karlstad University, Karlstad, Sweden; [4]Environmental and Occupational Health Sciences Institute, University of Medicine and Dentistry of New Jersey/Robert Wood Johnson Medical School and Rutgers University, Piscataway, New Jersey, USA; [5]Department of Environmental and Occupational Medicine, Aarhus University, Aarhus, Denmark

Table 2. Concentrations (mg/g dust) for different phthalates in settled dust from 346 bedrooms.

Phthalate	Above detection limit[b] [*n* (%)]	All samples (*n* = 346)				Type of flooring[a] (median mg/g dust)		
		Mean	Median	Min–Max	95th percentile	No PVC (*n* = 157)	PVC (*n* = 187)	*p*-Value[c]
DEP	32 (9.2)	0.031	0.000	0.000–2.425	0.115	0.000	0.000	0.241
DINP	173 (50.0)	0.639	0.041	0.000–40.667	1.930	0.000	0.082	0.394
DIBP	188 (54.3)	0.097	0.045	0.000–3.810	0.311	0.042	0.050	0.120
BBzP	272 (78.6)	0.319	0.135	0.000–45.549	0.599	0.089	0.192	< 0.001
DnBP	308 (89.0)	0.226	0.150	0.000–5.446	0.568	0.133	0.159	0.138
DEHP	343 (99.1)	1.310	0.770	0.000–40.459	4.069	0.700	0.868	0.001

Abbreviations: Max, maximum; Min, minimum.
[a]Type of flooring in the child's bedroom. [b]Number of samples with a concentration greater than the detection limits (0.040 mg/g dust). [c]Mann-Whitney *U*-test regarding differences in phthalate concentration between bedrooms with and without PVC as flooring material.

Environ Health Perspect 113:1399–1404 (2005).


木纹系列：
地毯纹系列：
大理石纹系列：

Evidence of Phthalates Exposure and Cardiovascular Risk Factors

- A growing number of reports show that phthalates are associated with cardiovascular disease risk factors.
- Most studies are from the National Health and Nutrition Examination Survey (NHANES) data, with **increased risk** of
- Obesity and altered glucose homeostasis (Huang et al. 2014; Stahlhut et al. 2007; Trasande et al. 2013)
- Diabetes mellitus (James-Todd et al. 2012; Lind et al. 2012)
- Albuminuria (Trasande et al. 2014)
- Higher systolic blood pressure (Trasande et al. 2013)
- Inflammation markers including absolute neutrophil counts, alkaline phosphatase and ferritin levels (Ferguson et al. 2012), and CRP (Ferguson et al. 2011).

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Positive association between concentration of phthalate metabolites in urine and microparticles in adolescents and young adults

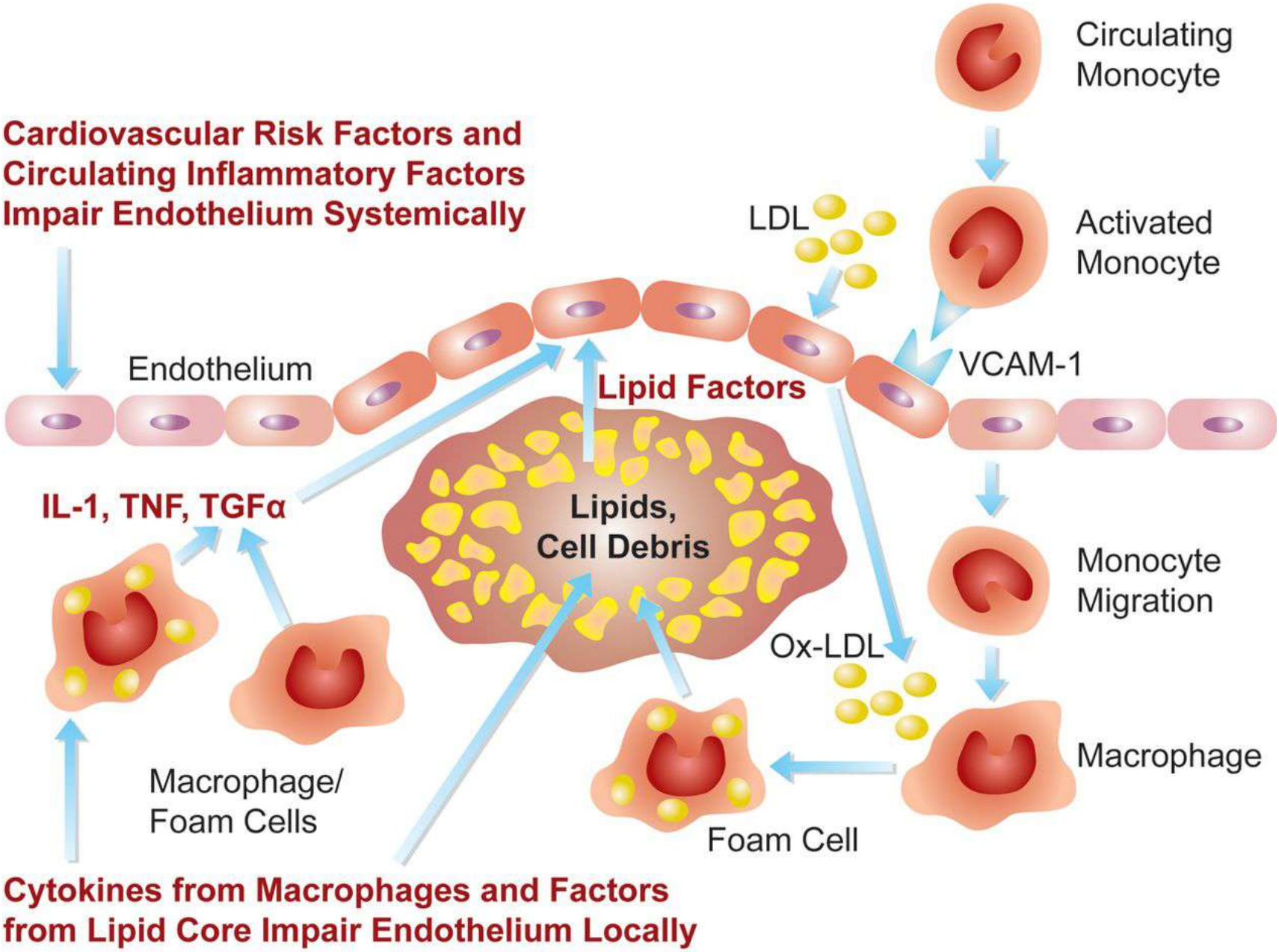
Chien-Yu Lin [a,b], Chia-Jung Hsieh [c], Shyh-Chyi Lo [d], Pau-Chung Chen [e,f,g,l], Pao-Ling Tomg [h,l], Anren Hu [i], Fung-Chang Sung [j], Ta-Chen Su [e,k,*]

- In this study, we test the possible associations between endothelial and platelet microparticles and phthalates exposure in adolescents and young adults.

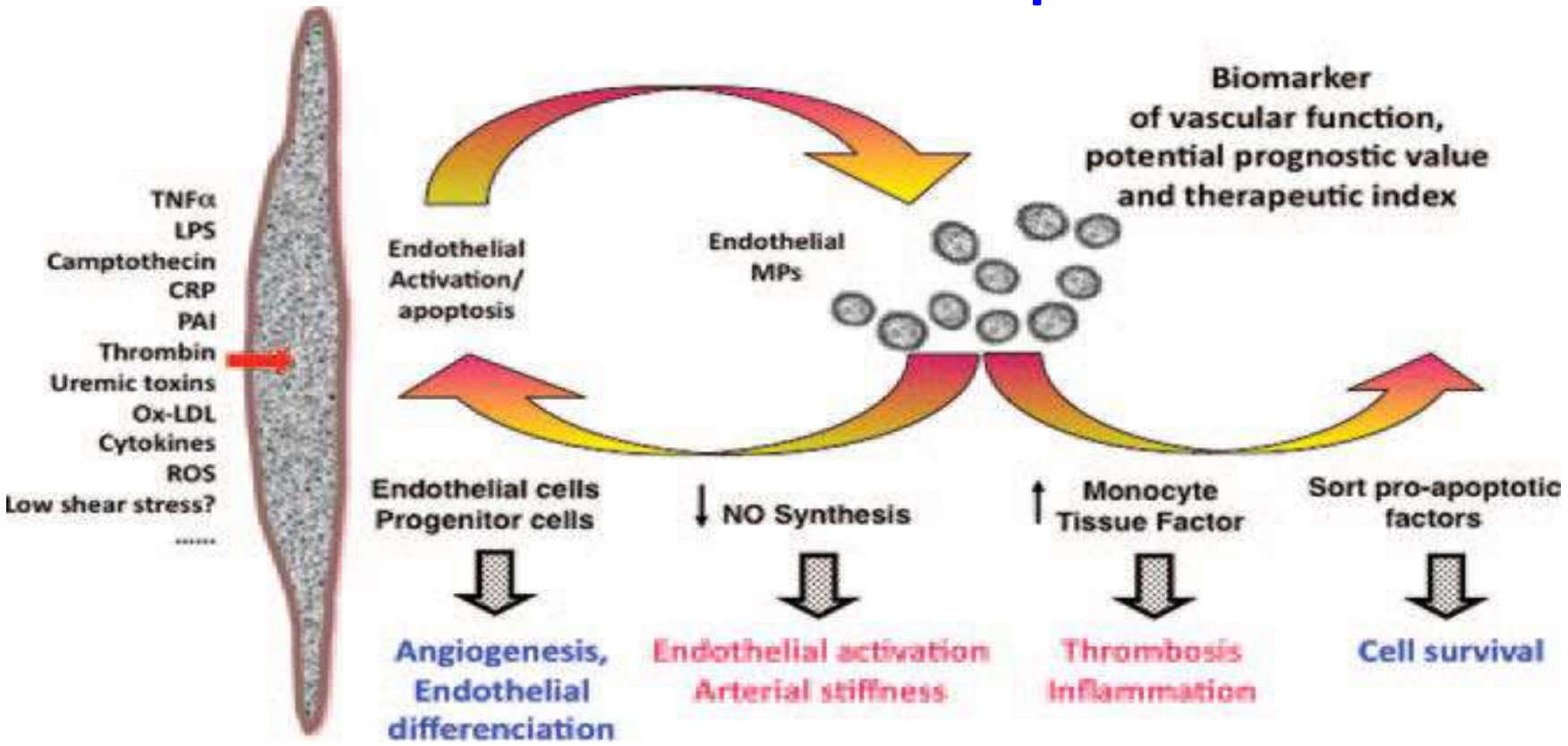
Microparticles and Atherosclerosis

- Atherosclerosis, which predisposes to CVD, is often accompanied by endothelial dysfunction and associated endothelium injury.
- Cell apoptosis, inflammatory activation occurring during atherosclerosis development **induce the formation of microparticles.**
- The attachment of monocytes to the endothelium, followed by their migration into the intima, is a crucial step in the development of atherosclerotic lesions (Lutterotti et al. 2006).
- Because CD31 was expressed on apoptotic platelet and endothelial cells and CD42a was expressed only on apoptotic platelet cells, CD31+/CD42a− was defined as a marker on **endothelial microparticles (EMPs)** that were shed from apoptotic endothelial cells (Dignat-George and Boulanger 2011)

Endothelial Dysfunction in Vulnerable Plaques



Endothelial microparticles



- Microparticles are small vesicles, between 0.1 and 1 µm in diameter.
- Microparticles concentrations are increased in patients with cardiovascular risk factors after cardiovascular events (Baron, 2012).
- **A recent study has focused on endothelial microparticles (EMPs) and platelet microparticles (PMPs) as emerging surrogate markers of chronic endothelial dysfunction (Werner et al. 2006).**

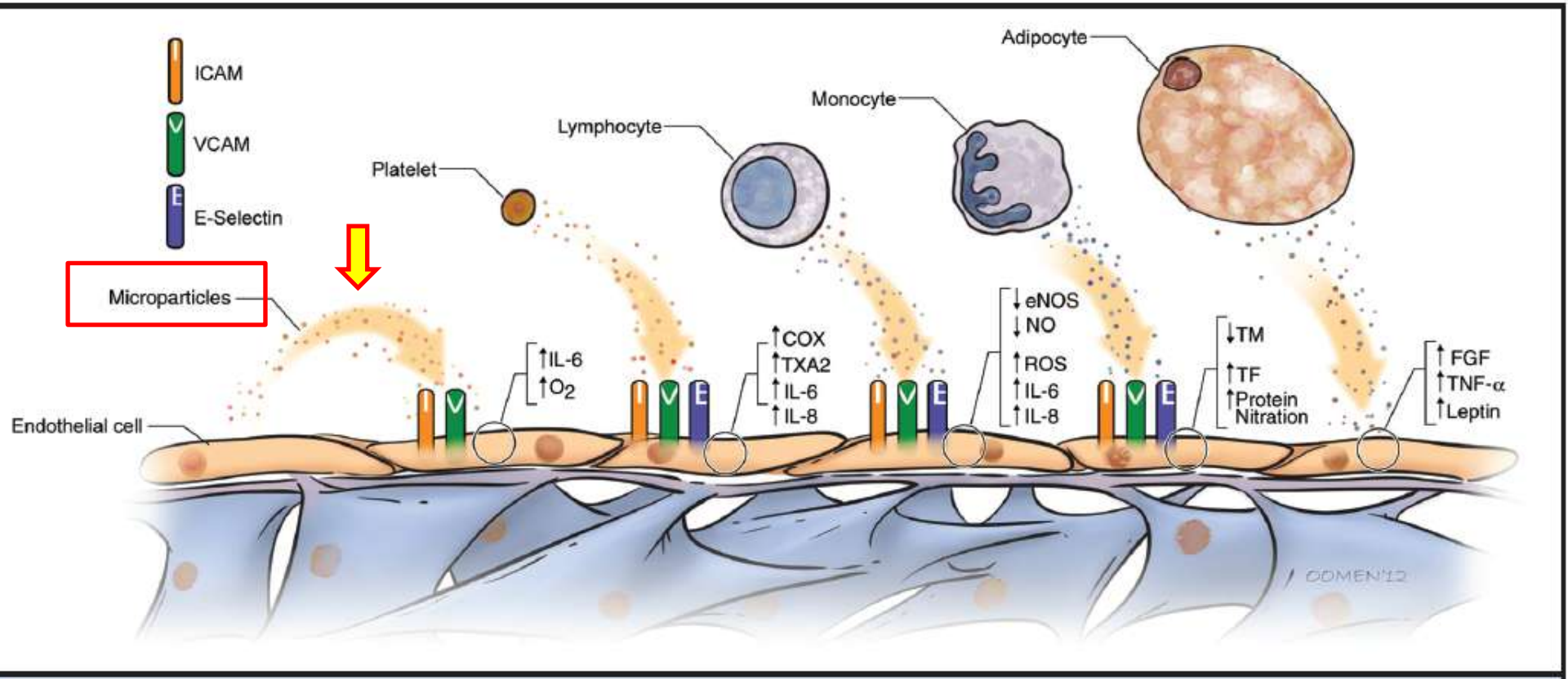


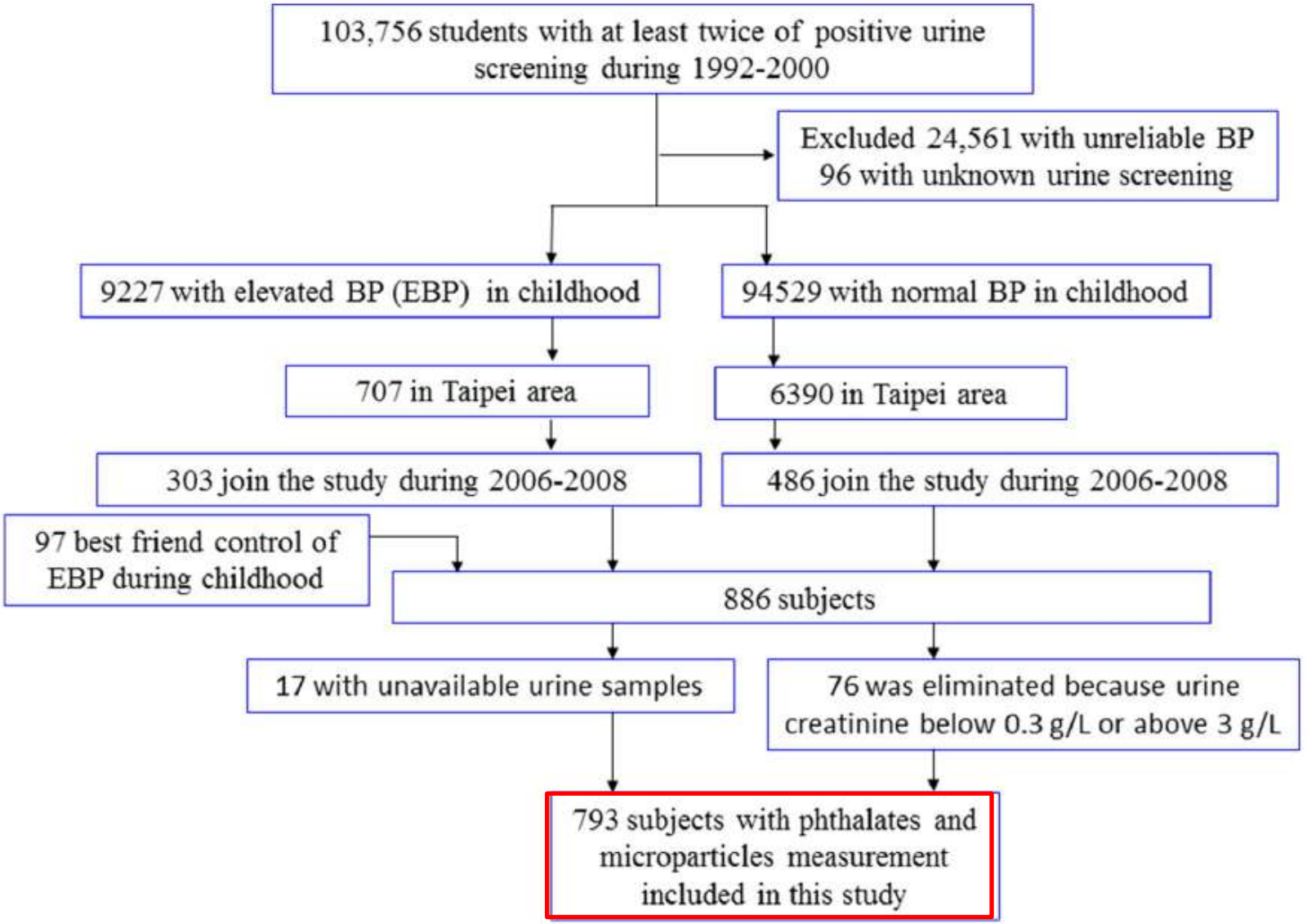
Fig. 1. Implication of circulating MPs on endothelial dysfunction.

Microparticles elicit endothelial dysfunction by disrupting NO production, promoting inflammation and coagulation and altering angiogenesis and apoptosis. TXA2, thromboxane A2; TM, thrombomodulin. ©2012 Glen Oomen. Reproduced with permission.

Fina Lovren, Subodh Verma. Evolving Role of Microparticles in the Pathophysiology of Endothelial Dysfunction. Clin Chem 2013; 59:1166-74.

Methods

- **The endothelial microparticles (EMPs), platelet microparticles (PMPs) and CD14** were measured with a **flow cytometer method** (Chirinos et al. 2005).
- In brief, the microparticles were measured simultaneously in citrated serum by a pair of fluorescent monoclonal antibodies: phycoerythrin-labeled anti-CD31, fluorescein isothiocyanate-labeled anti CD42a and fluorescein isothiocyanate-labeled anti CD14 (BD bioscience). The values of the microparticles are reported as counts/µL.
- **Urinary metabolites of phthalates** were measured by standard method with **LC-MS/MS system**.



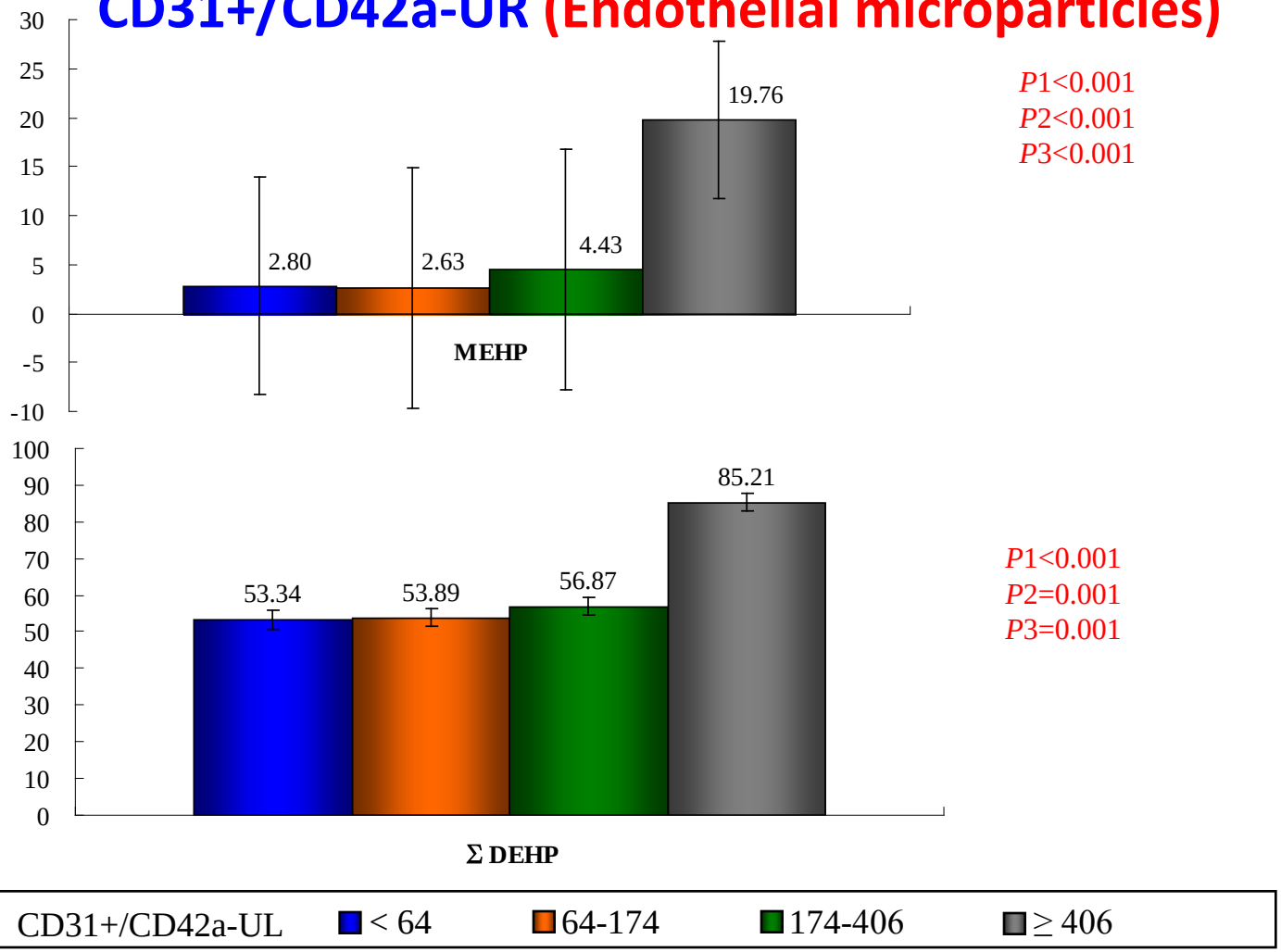
From 2006 to 2008 we established a cohort, the YOung TAiwanese Cohort (YOTA) Study, based on students with and without childhood EBP selected from the 1992-2000 mass urine screening population (Su, et al. JAT 2014 Nov.).

Table 1. Geometric mean and standard deviation of urinary phthalates metabolites concentration by quartile distribution of CD31+/CD42a- (Endothelial microparticles)

	CD31+/CD42a-						
	< 64 N=215	64-174 N=195	174-406 N=182	≥ 406 N=173	P-value 1	P-value 2	P-value 3
Creatinine adjusted							
MEHP	**2.80±11.1**	**2.63±12.3**	**4.43±12.3**	**19.76±7.96**	**<.001**	**<.001**	**<.001**
MEHHP	26.60±2.5	26.40±2.6	24.42±2.1	25.72±2.44	0.731	0.256	0.095
MEOHP	16.22±2.7	17.12±2.3	15.24±2.3	15.73±2.26	0.695	0.096	0.045
∑DEHP	53.34±2.5	53.89±2.5	56.87±2.3	85.21±2.22	<.001	0.001	0.001
MMP	7.42±2.03	7.01±2.10	7.59±1.94	7.67±2.12	0.776	0.397	0.362
MEP	31.43±3.6	29.95±3.4	33.44±3.2	31.81±3.43	0.912	0.493	0.637
MnBP	21.01±2.4	34.0±2.53	40.62±2.4	48.82±2.32	<.001	0.001	0.001
MBzP	1.93±2.86	1.90±3.05	1.87±2.93	1.97±3.08	0.879	0.888	0.832
MiNP	0.46±2.05	0.50±2.40	0.49±2.39	0.72±3.30	0.006	<.001	<.001

Data was Geometric mean and standard deviation. Unit of urinary phthalates metabolites is µg/g creatinine.
P-value 1 is Kruskal Wallis test for medians.
P-value 2 is for Endothelial microparticles quartile 4 compared with Endothelial microparticles quartile 1.
P-value 3 is test for trend.

Figure 1. Geometric mean and standard deviation of urinary phthalates metabolites concentration by quartile distribution of CD31+/CD42a-UR (Endothelial microparticles)



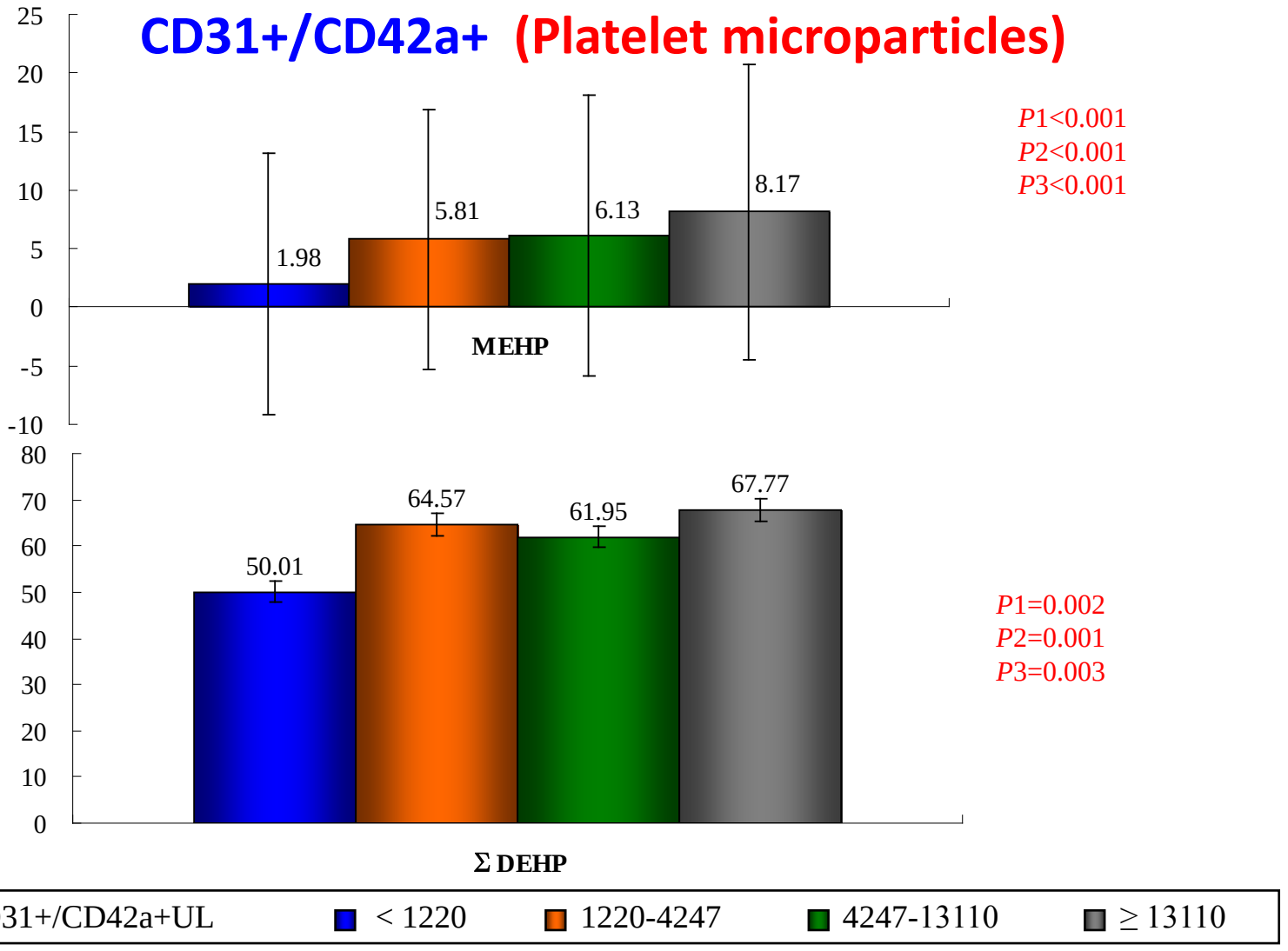
Data was Geometric mean and standard deviation. Unit of urinary phthalates metabolites is µg/g creatinine.
P-value 1 is Kruskal Wallis test for medians.
P-value 2 is for Endothelial microparticles quartile 4 compared with Endothelial microparticles quartile 1.
P-value 3 is test for trend.

Table 2. Geometric mean and standard deviation of urinary phthalates metabolites concentration by quartile distribution of CD31+/CD42a+ (Platelets microparticles)

	CD31+/CD42a+						
	< 1220 N=211	1220-4247 N=194	4247-13110 N=184	≥ 13110 N=175	P-value 1	P-value 2	P-value 3
Creatinine adjusted							
MEHP	**1.98±11.11**	**5.81±11.10**	**6.13±12.03**	**8.17±12.59**	**<.001**	**<.001**	**<.001**
MEHHP	25.30±2.32	28.82±2.31	24.65±2.61	24.59±2.41	0.238	0.631	0.511
MEOHP	15.75±2.26	17.31±2.66	15.73±2.45	15.63±2.20	0.355	0.731	0.587
∑DEHP	50.01±2.30	64.57±2.43	61.95±2.38	67.77±2.54	0.002	0.001	0.003
MMP	7.66±2.08	7.30±2.0	7.53±2.0	7.09±2.10	0.716	0.473	0.546
MEP	34.51±3.49	28.83±3.34	30.72±3.14	32.37±3.61	0.730	0.651	0.500
MnBP	34.50±2.48	38.69±2.49	41.71±2.43	36.94±2.35	0.441	0.577	0.389
MBzP	1.94±2.95	2.04±2.72	1.93±2.73	1.73±3.54	0.486	0.875	0.667
MiNP	0.44±1.98	0.53±2.62	0.54±2.51	0.64±3.02	0.015	<.001	0.003

Data was Geometric mean and standard deviation. Unit of urinary phthalates metabolites is µg/g creatinine.
P-value 1 is Kruskal Wallis test for medians.
P-value 2 is for Endothelial microparticles quartile 4 compared with Endothelial microparticles quartile 1.
P-value 3 is test for trend.

Figure 2. Geometric mean and standard deviation of urinary phthalates metabolites concentration by quartile distribution of CD31+/CD42a+ (Platelet microparticles)



Data was Geometric mean and standard deviation. Unit of urinary phthalates metabolites is µg/g creatinine.
P-value 1 is Kruskal Wallis test for medians.
P-value 2 is for Endothelial microparticles quartile 4 compared with Endothelial microparticles quartile 1.
P-value 3 is test for trend.

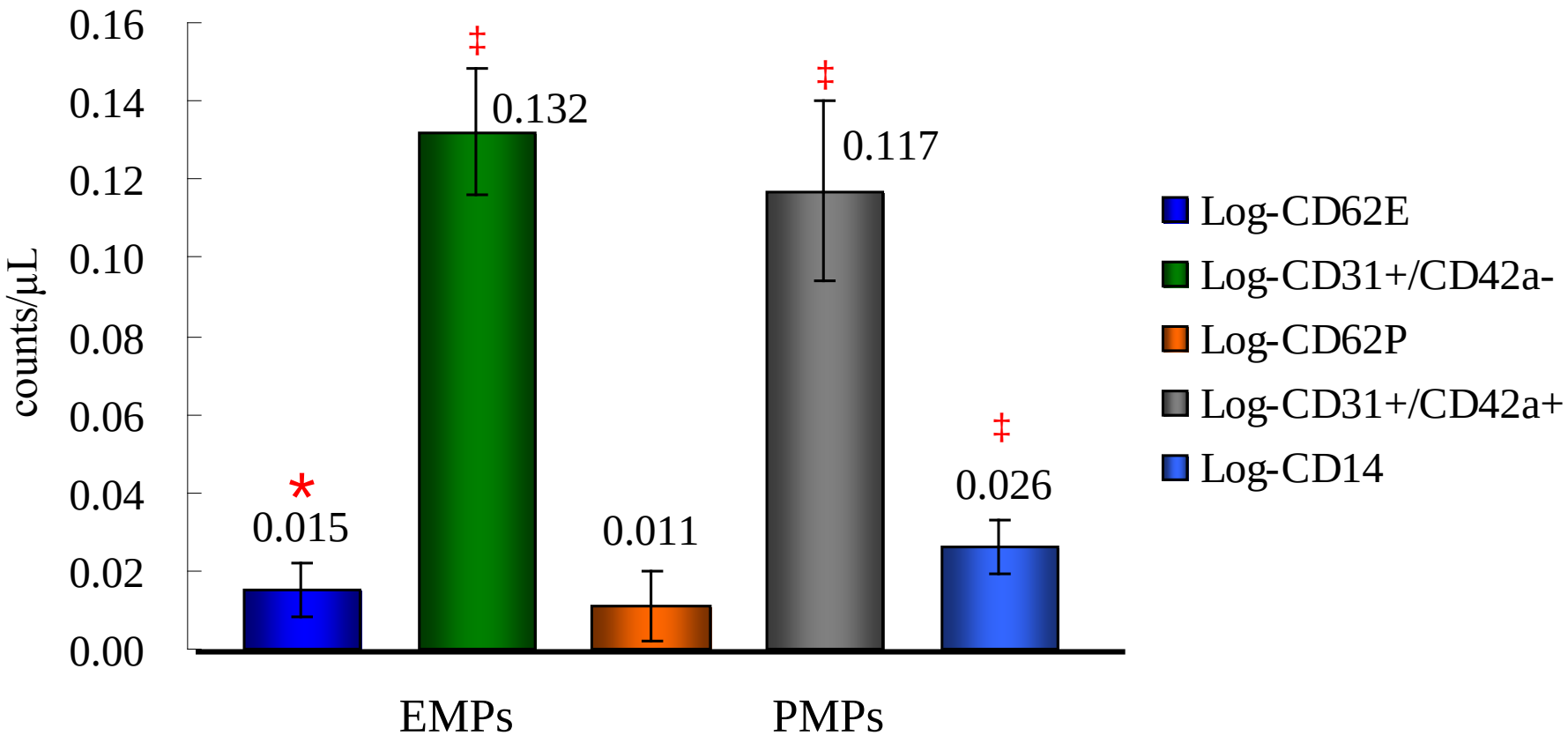
Microparticles associated with cardiovascular risk factors

Table 2
Linear regression coefficients (standard error) of cardiovascular risk factors with a unit increase in natural log-transformed microparticles in multiple linear regression models ($n = 792$).

	SBP mm Hg	BMI kg/m^2	LDL-C mg/dL	HDL-C mg/dL	log-TG mg/dL	UA mg/dL	log-HOMA-IR
Log-CD62E (counts/μL)	0.757 (0.918)	0.534 (0.276)	0.924 (2.170)	−0.715 (0.646)	0.008 (0.032)	−0.026 (0.081)	0.127 (0.068)
P value	0.410	0.053	0.670	0.269	0.807	0.747	0.063
Log-CD31+/CD42a− (counts/μL)	1.021 (0.363)	0.587 (0.108)	3.262 (0.855)	−0.901 (0.255)	0.065 (0.013)	0.044 (0.032)	0.224 (0.026)
P value	0.005	<0.001	<0.001	<0.001	<0.001	0.173	<0.001
Log-CD62P (counts/μL)	1.636 (0.697)	0.440 (0.210)	2.741 (1.650)	−0.743 (0.492)	0.068 (0.025)	0.077 (0.062)	0.002 (0.052)
P value	0.019	0.036	0.097	0.131	0.005	0.216	0.963
Log-CD31+/CD42a+ (counts/μL)	0.199 (0.272)	0.166 (0.081)	0.998 (0.641)	−0.012 (0.191)	−0.019 (0.010)	0.020 (0.024)	0.140 (0.020)
P value	0.465	0.042	0.120	0.949	0.052	0.412	<0.001
Log-CD14 (counts/μL)	2.310 (0.893)	1.224 (0.266)	6.205 (2.108)	−1.502 (0.629)	0.108 (0.031)	0.118 (0.079)	0.315 (0.066)
P value	0.010	<0.001	0.003	0.017	0.001	0.138	<0.001

Adjusted for age, gender, smoking status.
Abbreviations: BMI, body mass index; HOMA-IR, homeostasis model assessment of insulin resistance; LDL-C, low density lipoprotein cholesterol; SBP, systolic blood pressure; TG, triglyceride; UA, uric acid.

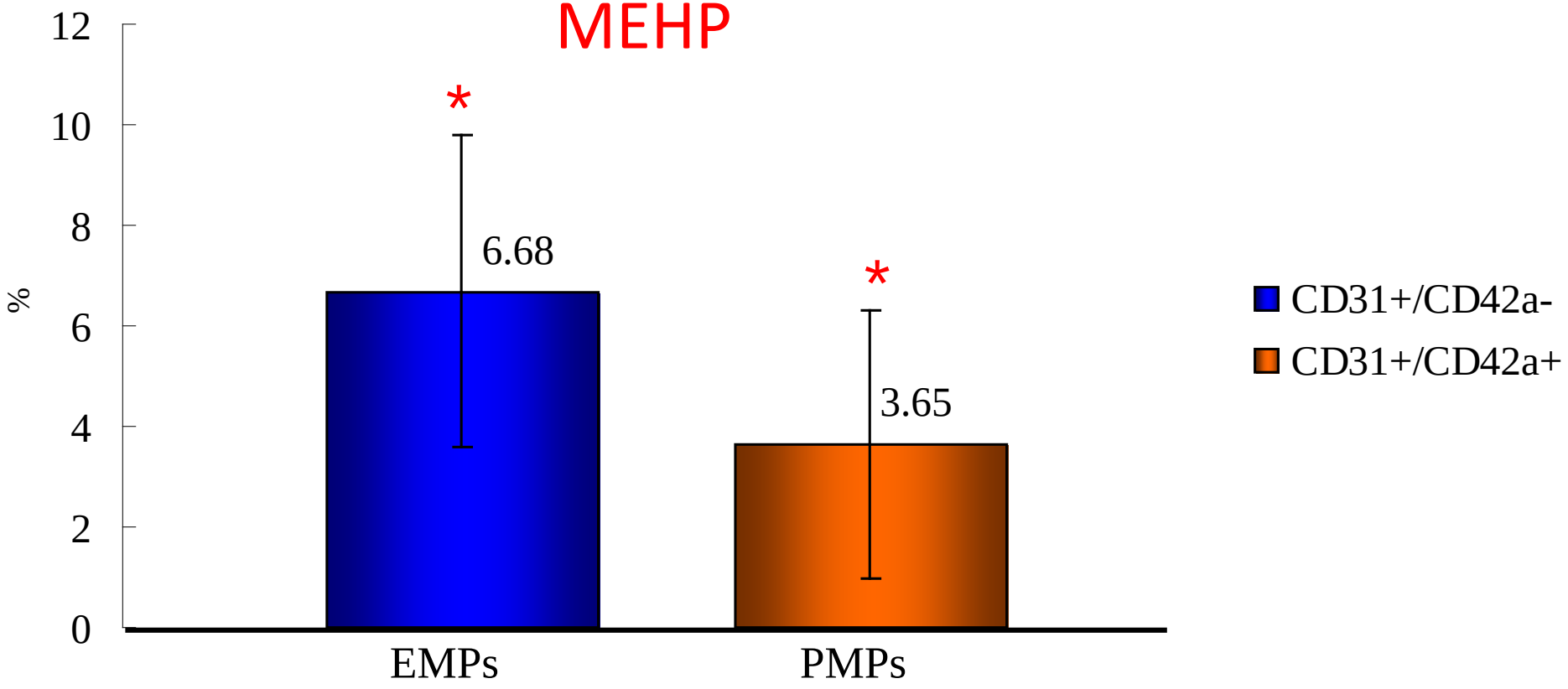
Figure 1. For every increase one Log-MEHP the increase of microparticles.



Adjusted for age, gender and other risk factors (smoking status, BMI, systolic BP, LDL-C, triglyceride, and HOMA-IR).

p-value: * <0.05, † <0.01, ‡ <0.005.

Figure 2. Estimated percentage (95% CI) in EMPs, PMPs for an IQR increase in the DEHP metabolites (adjusted Cr) in multiple linear regression models



Adjusted for age, gender and other risk factors (smoking status, BMI, systolic BP, LDL-C, triglyceride, and HOMA-IR). * p <0.05.

Conclusions and Perspectives

- A clear positive association was found between urinary concentrations of MEHP and microparticles from endothelium and platelets in adolescents or young adults.
- This study provides the scientific evidence of atherogenic effects of DEHP phthalates exposure.

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Mono-2-ethylhexyl phthalate associated with insulin resistance and lower testosterone levels in a young population☆

Szu-Ying Chen [a, b], Jing-Shiang Hwang [c], Fung-Chang Sung [d], Chien-Yu Lin [e, f], Chia-Jung Hsieh [g, h], Pau-Chung Chen [h, i, j], Ta-Chen Su [h, k, *]

Positive Association between MEHP and Insulin Resistance and Lower Testosterone Levels

Environmental Pollution 2017 June .

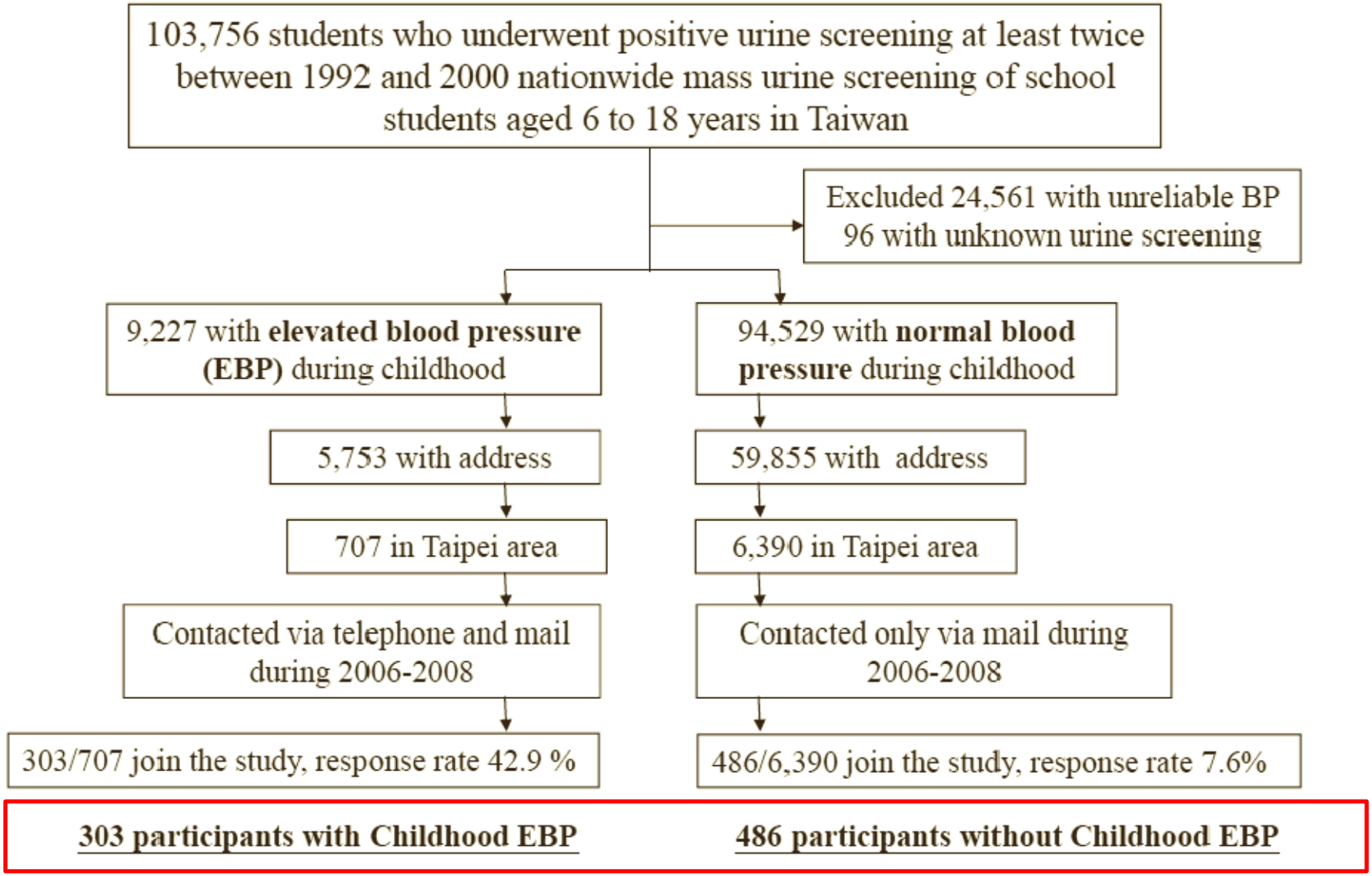
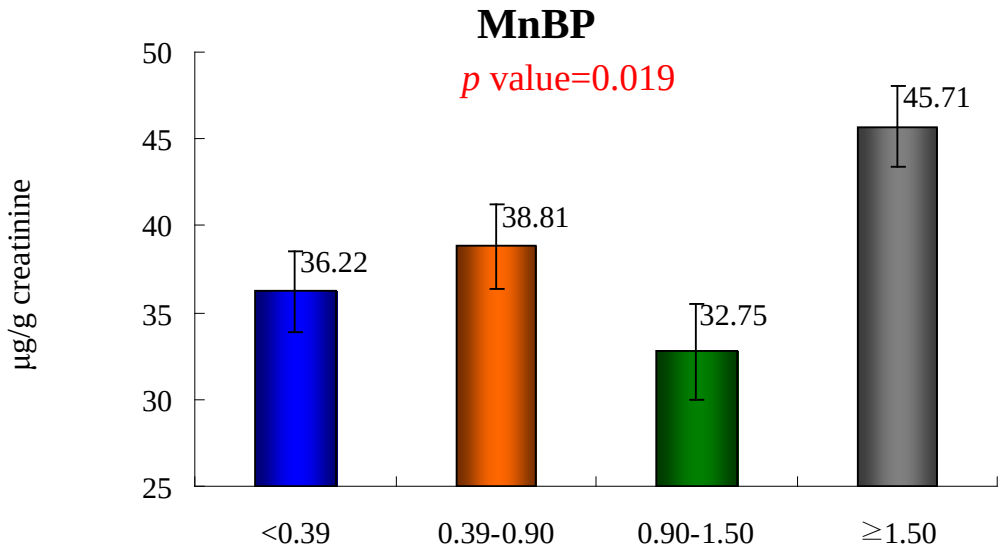


Fig. 1. Flowchart of participant recruitment based on the selection of patients with and without an elevated blood pressure (EBP) in childhood in the YOung TAiwanese Cohort (YOTA) study conducted during the period of 2006-2008.

Su TC, JAT 2014 **Nov**; 21:1170-1182.

Figure 2. Concentrations of creatinine adjusted urinary phthalate metabolites in 786 study subjects divided by quartiles of HOMA-IR indices.



<0.39, n=213;
0.39-0.90, n=193;
0.90-1.50, n=191;
≥1.50, n=190

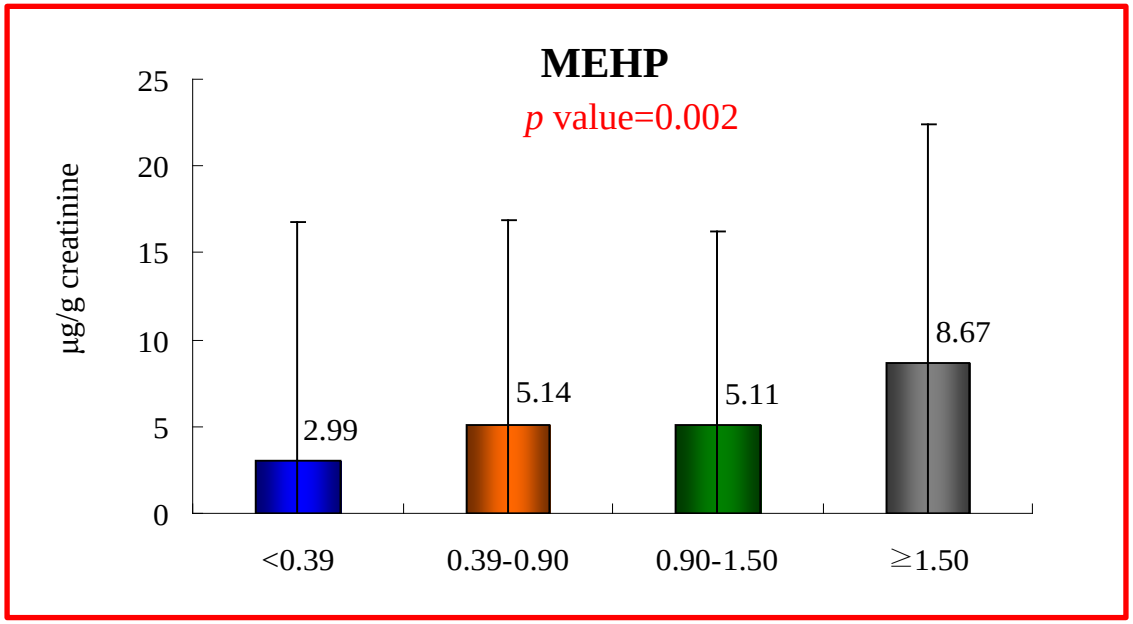
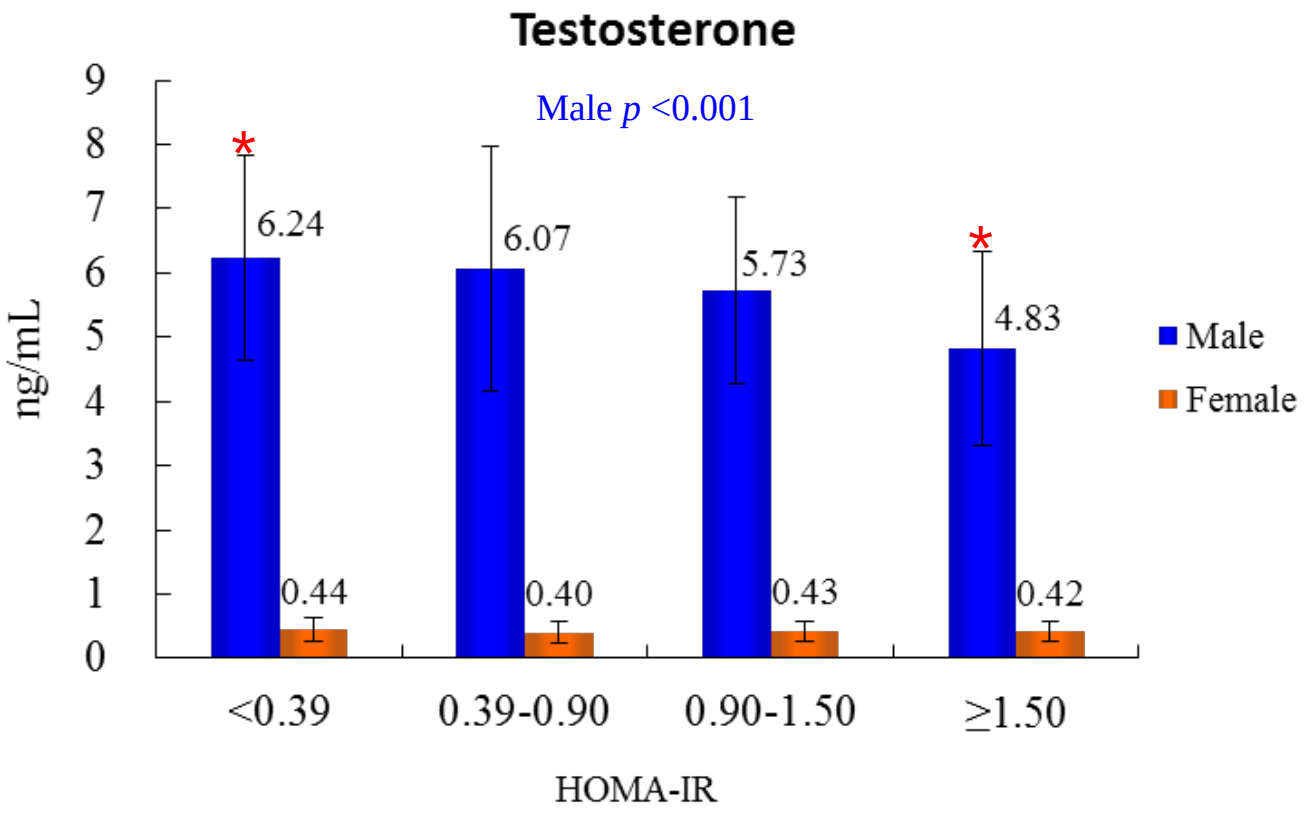
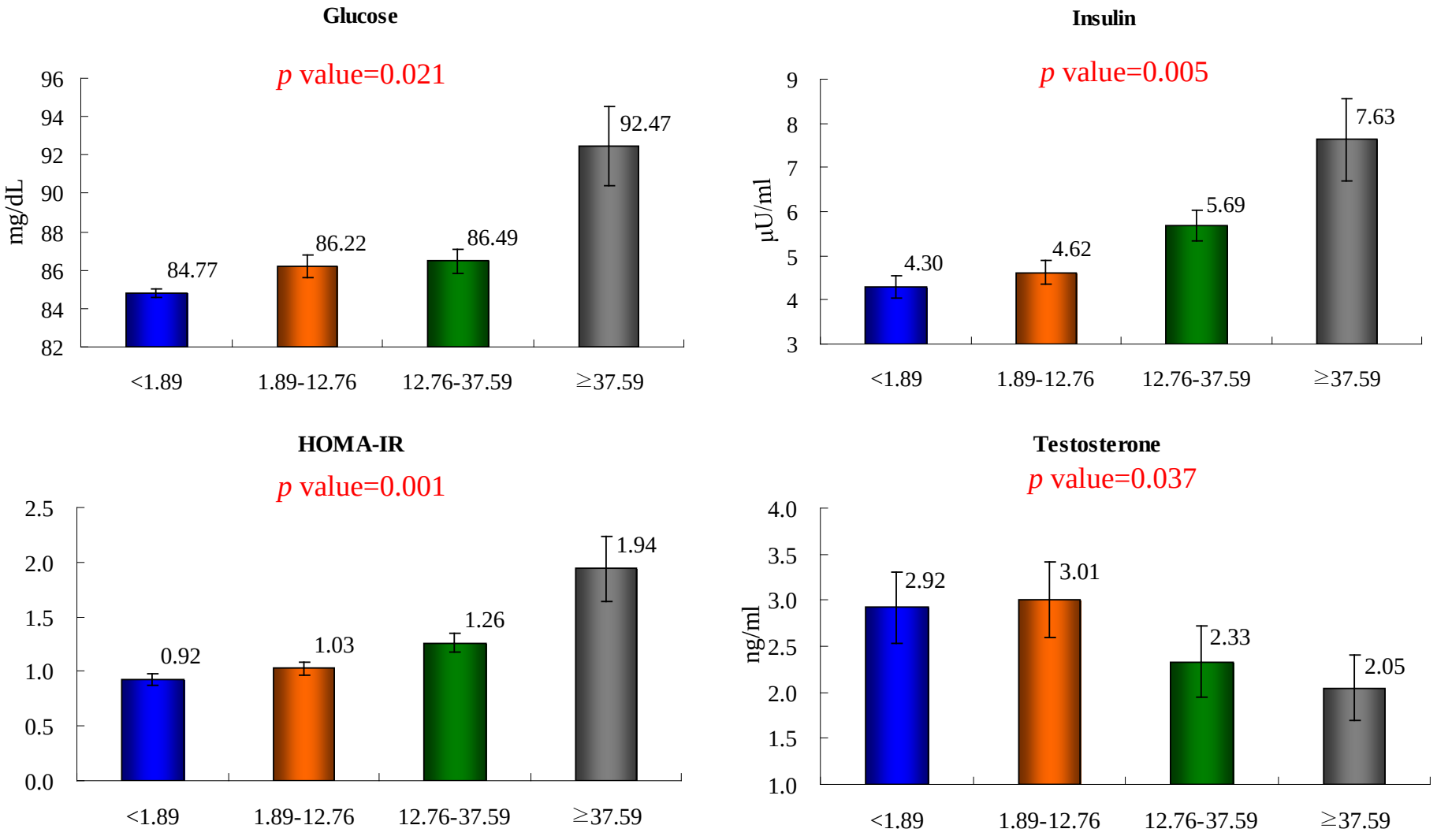


Figure 1. Descriptive analyses of basic characteristics of 786 study subjects divided by quartiles of HOMA-IR indices.



* *p*-value<0.05 for 1st quartile vs. 4th quartile.

Figure 3-2. Adjusted estimates and 95% confidence intervals (Cis) for fasting glucose, insulin, HOMA-R, and testosterone for study subjects divided by quartiles of MEHP.



Glucose N=787; insulin N=787; HOMA-IR N=787; testosterone N=732.

Figure 2. Glycemic indices change for every one unit increase in seven log-transformed urinary phthalate metabolites among adolescents and young adults.

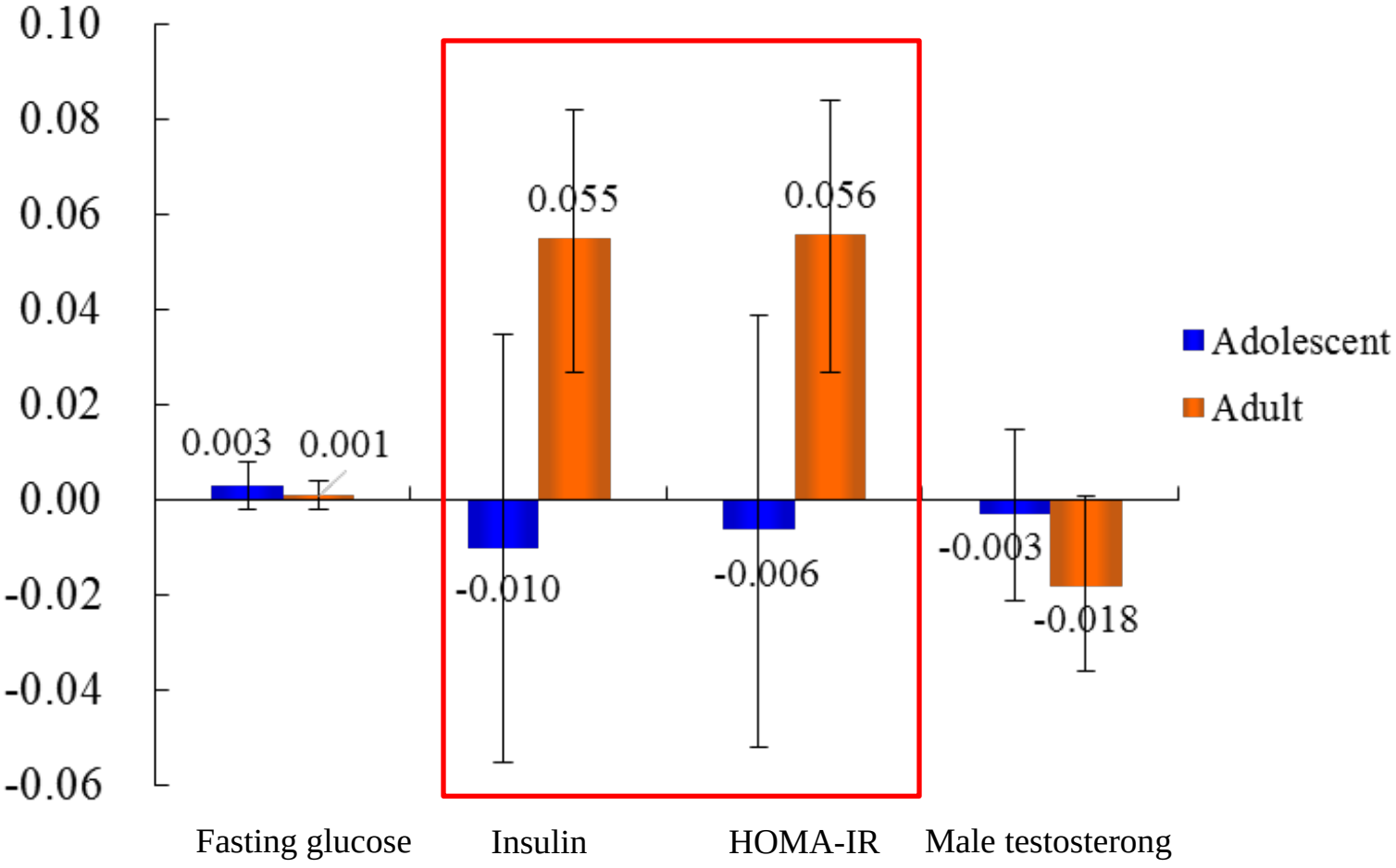


Fig 2. Schematic interconnections between urinary MEHP, male testosterone, and insulin resistance in young adults

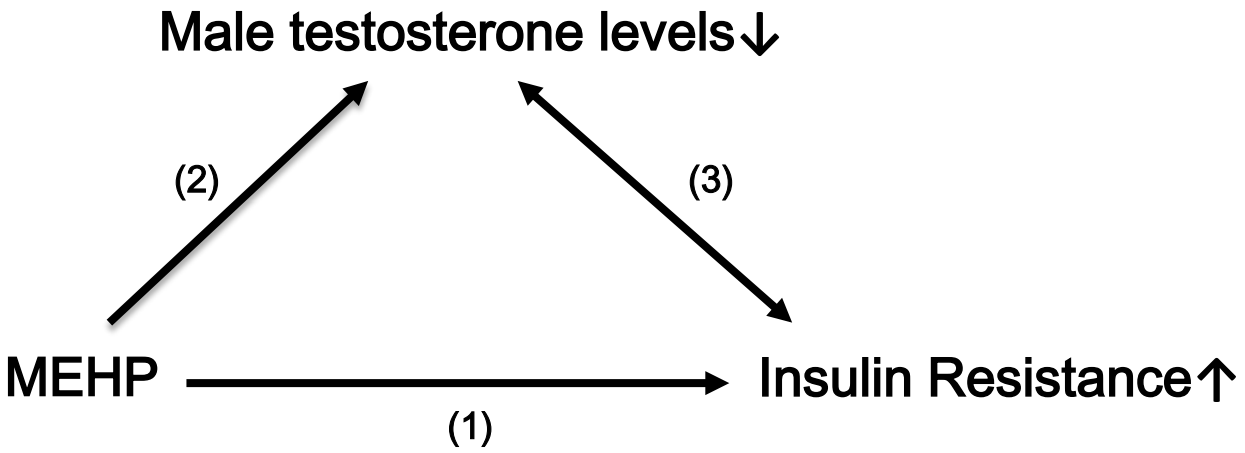


Fig. 2. Schematic interconnections between urinary MEHP metabolites, male testosterone, and insulin resistance in young adults. (1) Urinary MEHP metabolites are associated with increased insulin resistance. (2) Urinary MEHP metabolites are associated with lower male testosterone levels. (3) The male testosterone levels are inversely associated with increased insulin resistance.

Discussions

- Urinary **DEHP** metabolite, MEHP associate **with fasting insulin and HOMA-IR**, independent of covariates in young adults.
- Those of low risk subjects are susceptible groups, such as women, non-HTN, No smoking, No alcohol, and non-APOE4 carriers.
- This study highlighted the **diabetogenic potential** of phthalates exposure.

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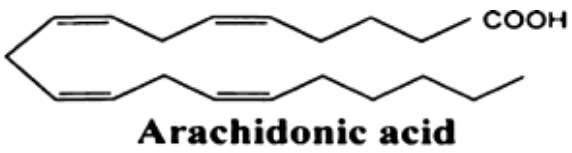
Positive Association between Urinary Concentration of Phthalate Metabolites and Oxidation of DNA and Lipid in Adolescents and Young Adults

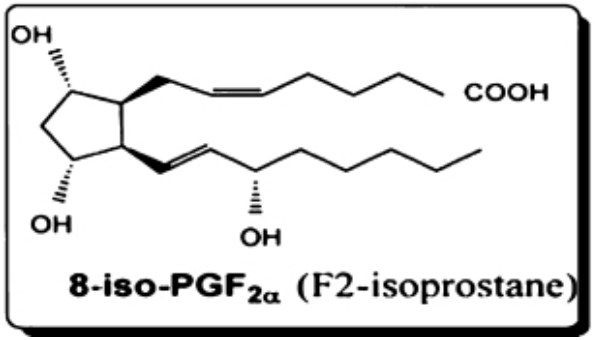
Chien-Yu Lin[1,2], Pau-Chung Chen[3,4,5], Chia-Jung Hsieh[6], Chao-Yu Chen[7], Anren Hu[8], Fung-Chang Sung[9], Hui-Ling Lee[7] & Ta-Chen Su[3,10]

Phthalate has been used worldwide in various products for years. Little is known about the association between phthalate exposure and biomarkers of oxidative stress in adolescents and young adults. Among 886 subjects recruited from a population-based cohort during 2006 to 2008, 751 subjects (12–30 years) with complete phthalate metabolites and oxidation stress measurement were enrolled in this study. Nine urine phthalate metabolites, 8-hydroxydeoxyguanosine (8-OHdG), and 8-iso prostaglandin F2α (8-isoPGF2α) were measured in urine to assess exposure and oxidative stress to DNA and lipid, respectively. Multiple linear regression analysis revealed that an ln-unit increase in mono-methyl phthalate (MMP) concentration in urine was positively associated with an increase in urine biomarkers of oxidative stress (in μg/g; creatinine of 0.098 ± 0.028 in 8-OHdG; and 0.253 ± 0.051 in 8-isoPGF2α). There was no association between other eight phthalate metabolite concentrations and oxidative stress. In conclusion, a higher MMP concentration in urine was associated with an increase in markers of oxidative stress to DNA and lipid in this cohort of adolescents and young adults. Further studies are warranted to clarify the causal relationship between exposure to phthalate and oxidative stress.

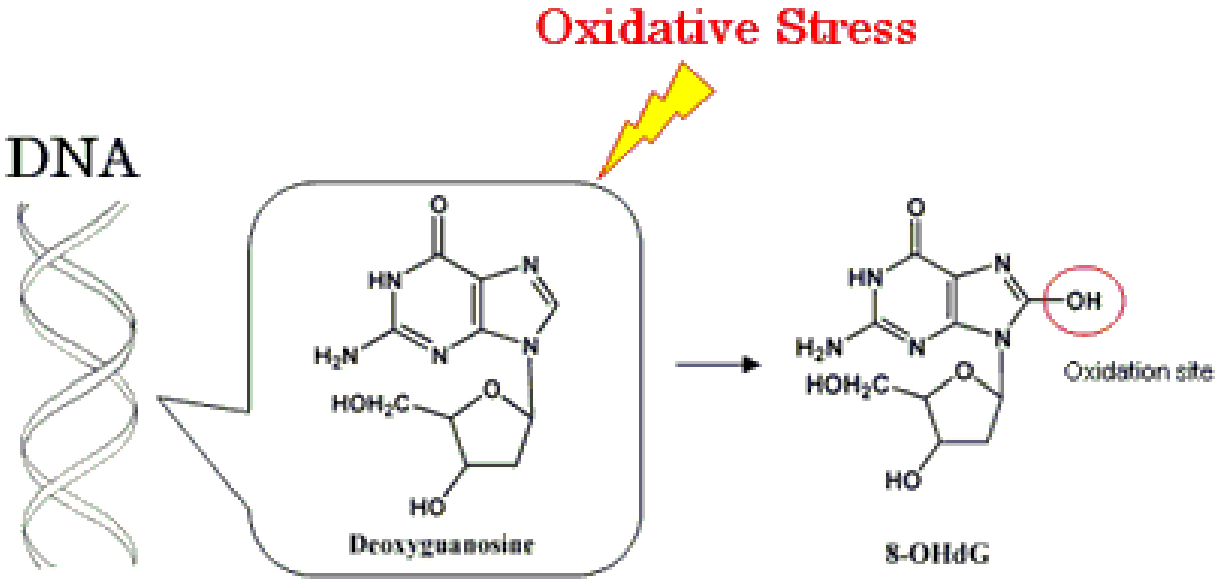


Arachidonic acid

Oxidative stress ⇌ ROS



8-iso-$PGF_{2\alpha}$ (F2-isoprostane)



8-OHdG was measured by LC-MS/MS

Figure 1. Algorithm used to select the participants.

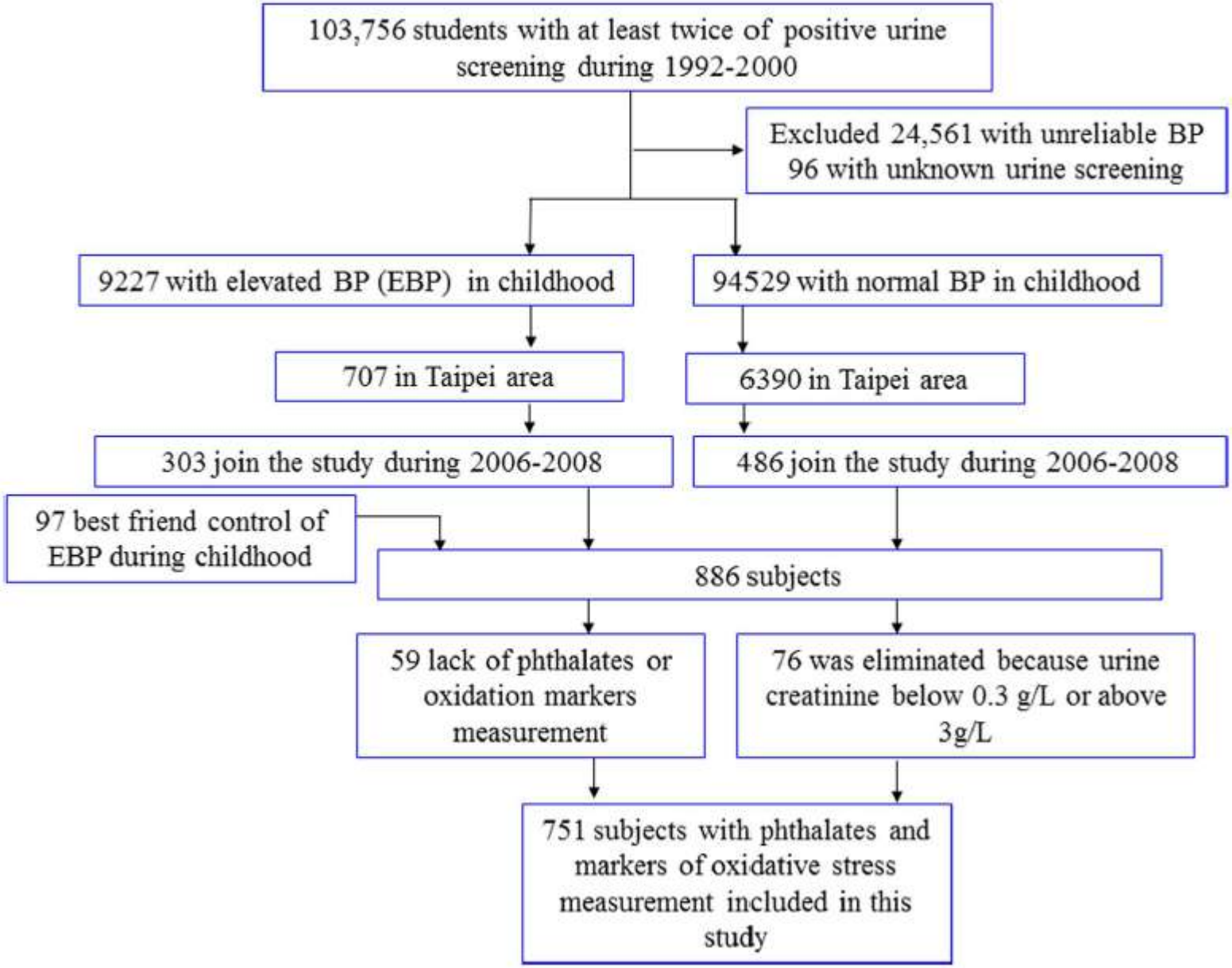


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Table 3. Linear regression coefficients (standard error) of 8-OHdG and 8-isoPGF2α with a unit increase in natural log-transformed phthalate metabolintes in multiple linear regression models (n=751).

	Ln 8-OHdG (μg/g creatinine)	P value	Ln 8-isoPGF$_{2\alpha}$ (μg/g creatinine)	P value
Ln ∑MEHP (μmol/g creatinine)				
Model 1	0.000(0.020)	0.997	0.070(0.037)	0.060
Model 2	0.008(0.020)	0.694	0.065(0.037)	0.081
Ln MMP (μg/g creatinine)				
Model 1	0.098(0.028)	<0.001	0.251(0.050)	<0.001
Model 2	0.096(0.028)	0.001	0.253(0.051)	<0.001
Ln MiBP (μg/g creatinine)				
Model 1	0.044(0.020)	0.029	0.069(0.037)	0.063
Model 2	0.044(0.020)	0.026	0.064(0.037)	0.084
Ln MEP (μg/g creatinine)				
Model 1	0.024(0.017)	0.152	-0.005(0.031)	0.869
Model 2	0.021(0.017)	0.215	-0.003(0.031)	0.914
Ln MnBP (μg/g creatinine)				
Model 1	0.028(0.022)	0.202	0.006(0.040)	0.878
Model 2	0.033(0.022)	0.141	-0.004(0.041)	0.914
Ln MBzP (μg/g creatinine)				
Model 1	0.024(0.018)	0.178	0.076(0.033)	0.022
Model 2	0.022(0.018)	0.227	0.073(0.033)	0.029

∑MEHP, sum of (MEHP/278)+(MEHHP/294)+(MEOHP/292)
Model 1: adjusted for age and gender.
Model 2: adjusted for age, gender and other risk factors (smoking status, body mass index, systolic blood pressure, low density lipoprotein, triglyceride, and homeostasis model assessment of insulin resistance).

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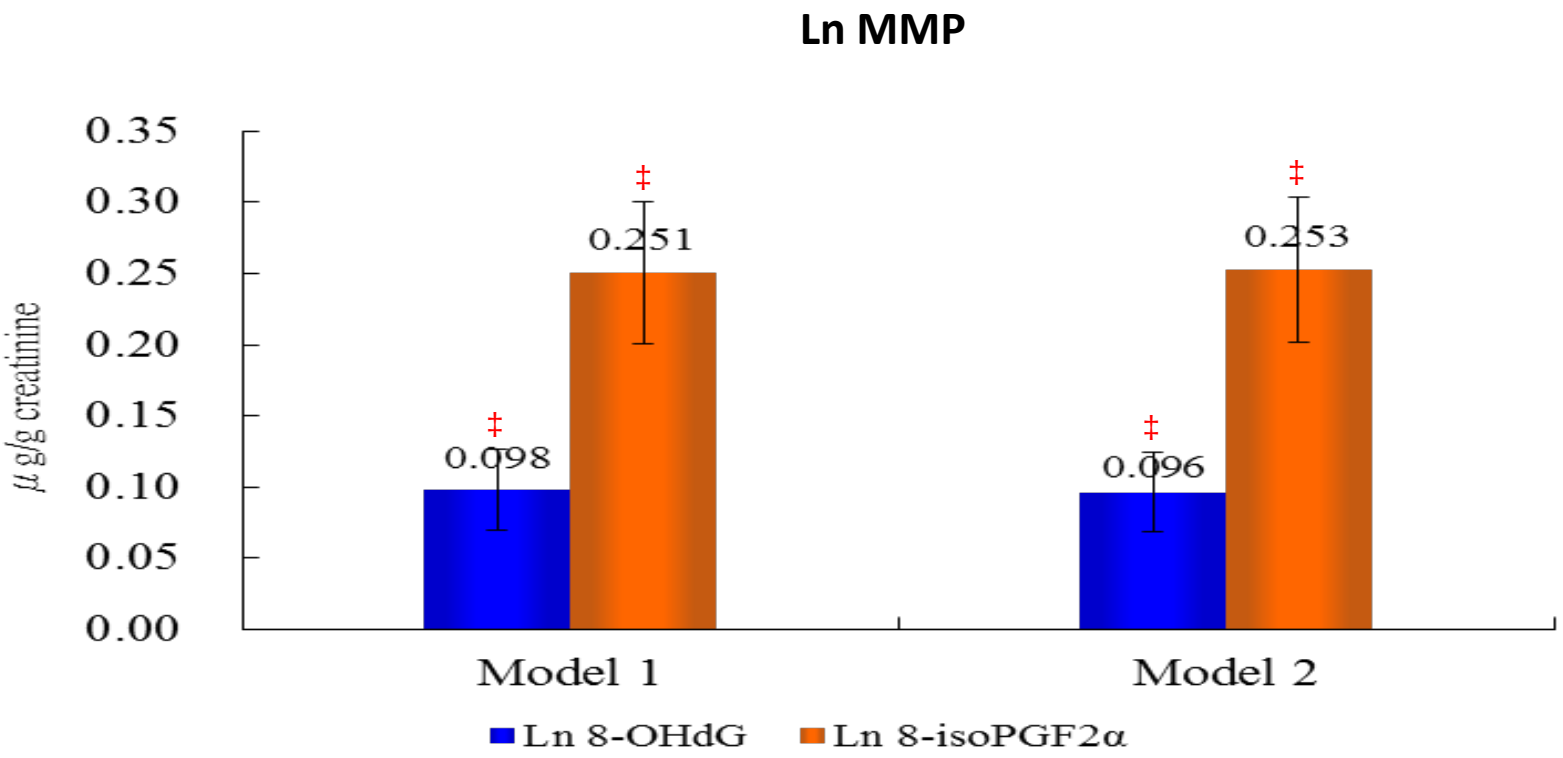
Figure 3-1. Linear regression coefficients (standard error) of 8-OHdG and 8-isoPGF2α with a unit increase in natural log-transformed phthalate metabolites in multiple linear regression models.



Model 1: adjusted for age and gender.
Model 2: adjusted for age, gender and other risk factors (smoking status, body mass index, systolic blood pressure, low density lipoprotein, triglyceride, and homeostasis model assessment of insulin resistance).
p-value: * <0.05, † <0.01, ‡ <0.005.

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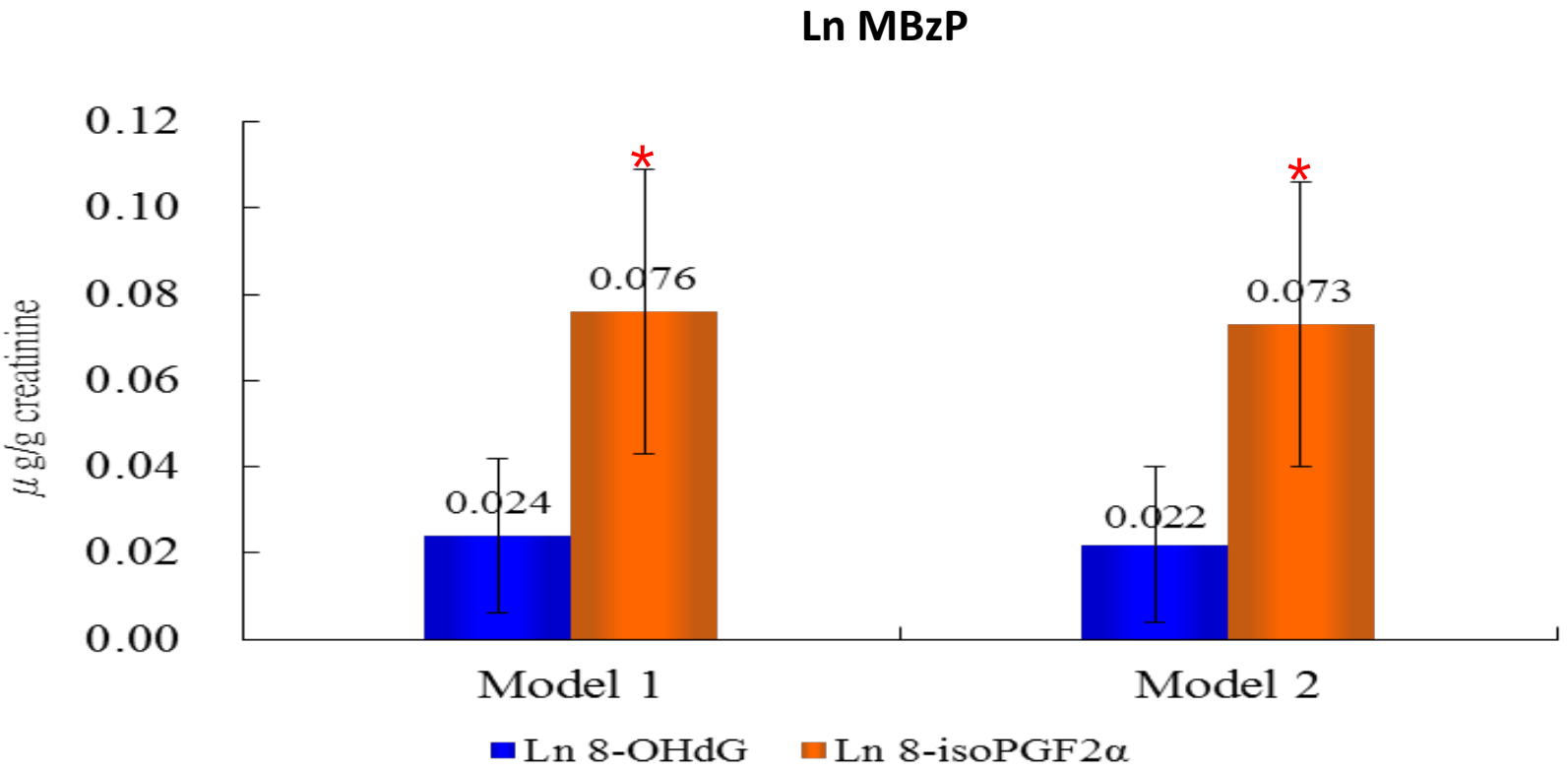
Figure 3-2. Linear regression coefficients (standard error) of 8-OHdG and 8-isoPGF2α with a unit increase in natural log-transformed phthalate metabolites in multiple linear regression models (n=751).



Model 1: adjusted for age and gender.
Model 2: adjusted for age, gender and other risk factors (smoking status, body mass index, systolic blood pressure, low density lipoprotein, triglyceride, and homeostasis model assessment of insulin resistance).
p-value: * <0.05, † <0.01, ‡ <0.005.

Lin and Su et al. Scientific Reports 2017;7:44318 | DOI: 10.1038/srep44318

Associations between urinary phthalate metabolites and subclinical atherosclerosis in adolescents and young adults

Stroke 2017; under revision

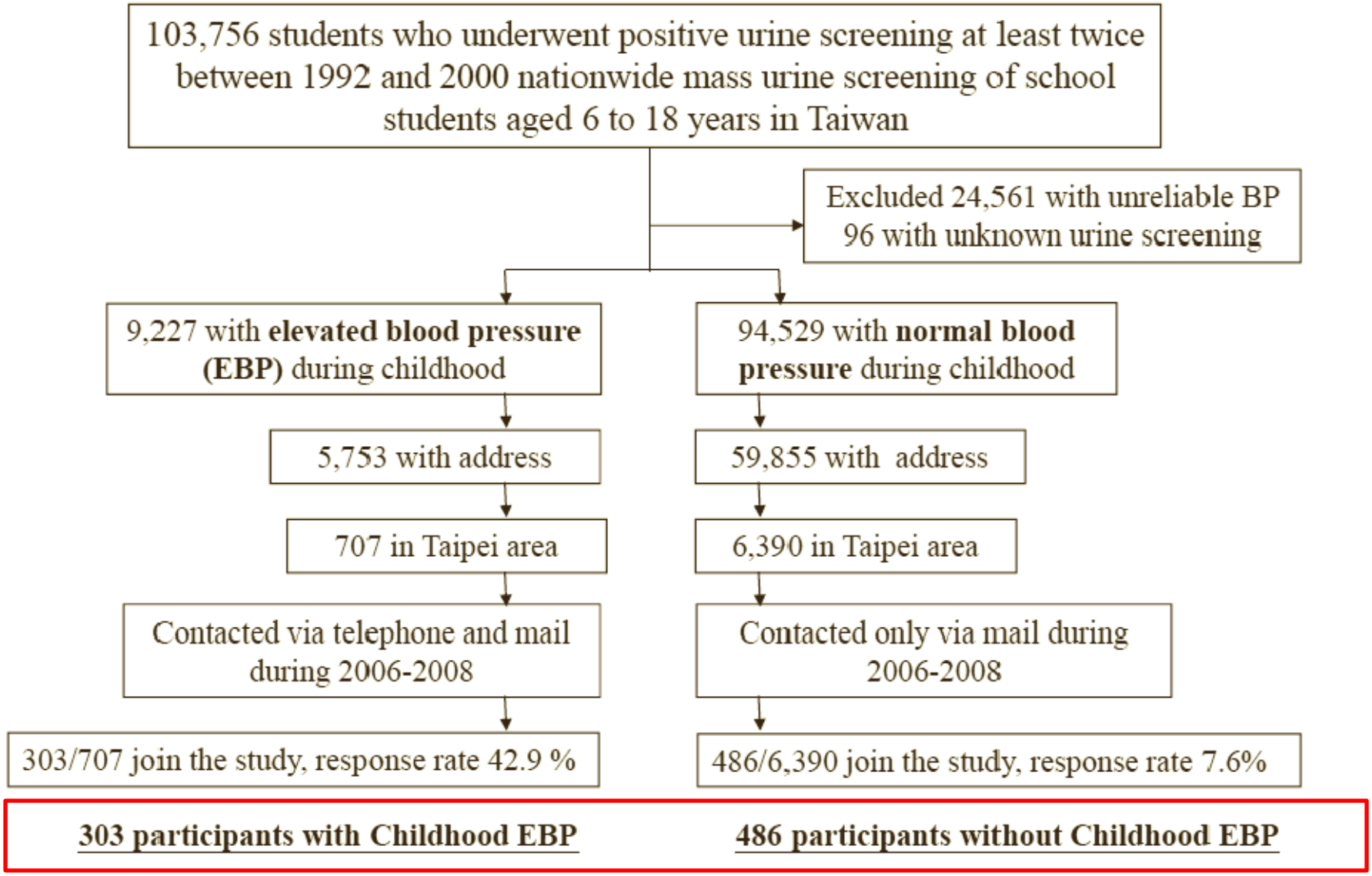
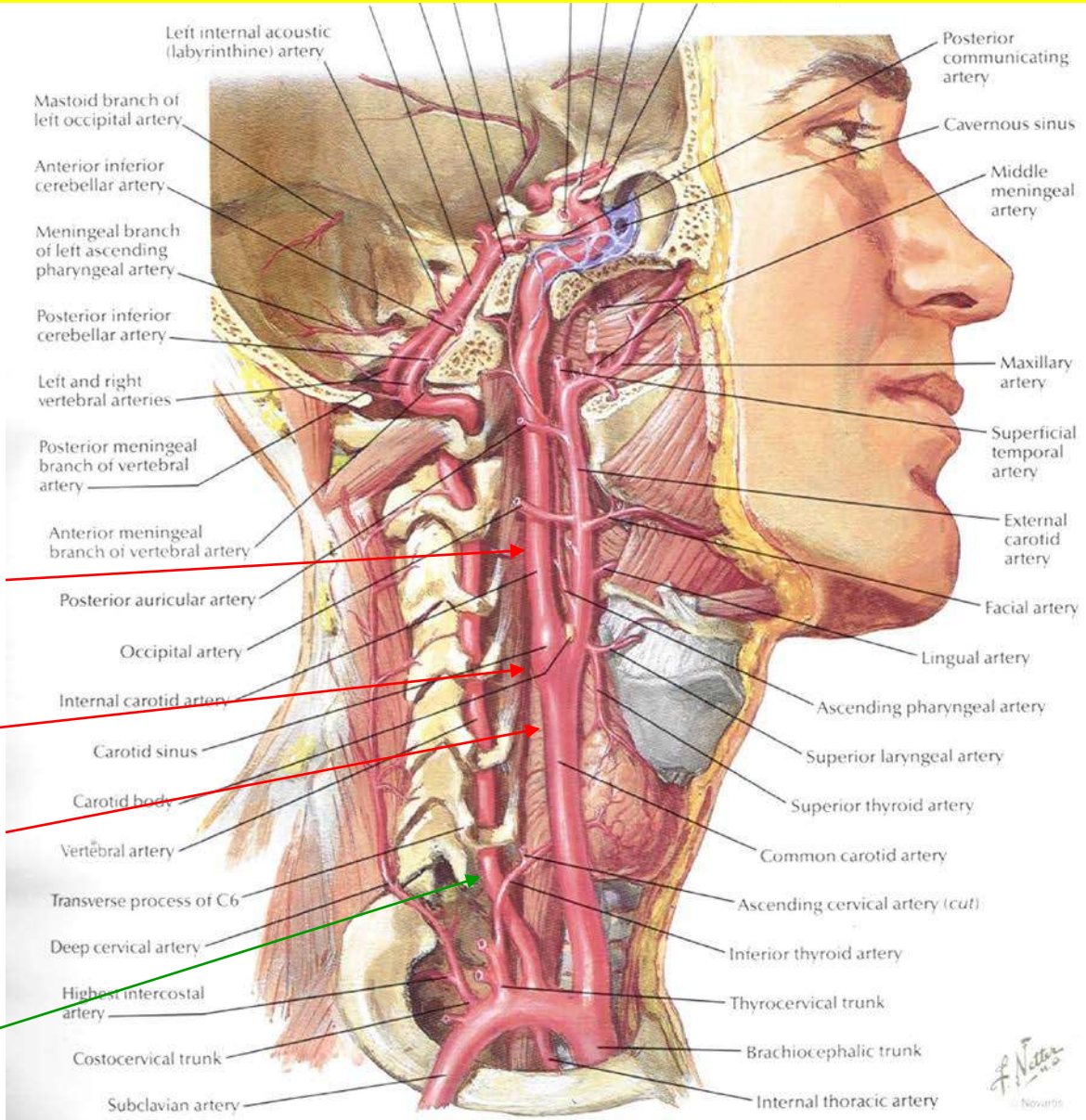


Fig. 1. Flowchart of participant recruitment based on the selection of patients with and without an elevated blood pressure (EBP) in childhood in the YOung TAiwanese Cohort (YOTA) study conducted during the period of 2006-2008.

Su et al., J Atheroscl T hromb2014; 21:1170-1182.

Why we choose carotid atherosclerosis as surrogate outcome for preclinical atherosclerosis?



Internal carotid artery

Carotid bulb

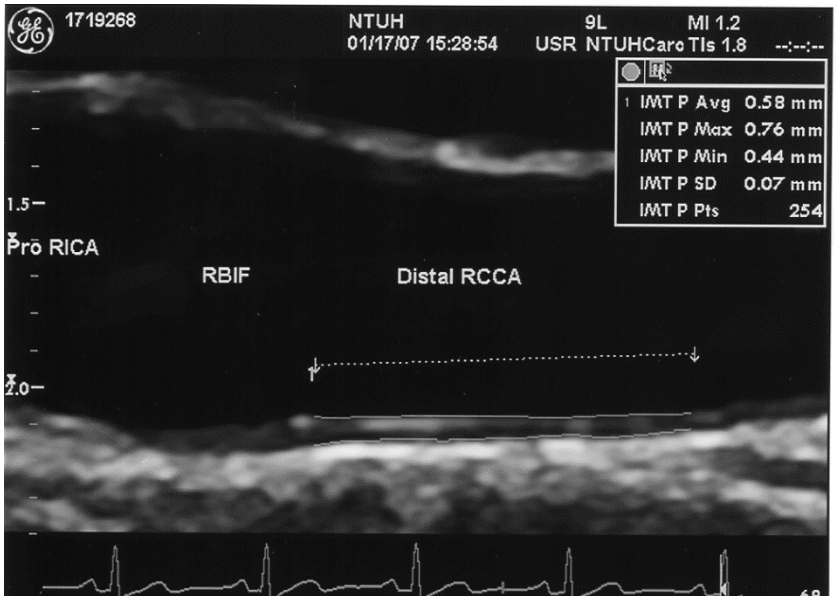
Common Carotid artery

Vertebral a

Extracranial Carotid Artery (ECCA) Intima-Media Thickness (IMT)

- Maximal and Average Carotid IMT
- **IMT** indicates the thickness between lumen-intima interface and media-adventitia interface at far wall of common carotid artery
- IMT maximal and mean value at bilateral CCA, ICA, and bulb.

(Su et al, Stroke 2001, 2016 Atherosclerosis 2006, 2007, 2009, 2015, JAT 2009, 2012, 2014, PLoS One 2014; Chien et al PLoS One 2009; Lin and Su, Int J Cardiol. 2013, Environ Int 2016)



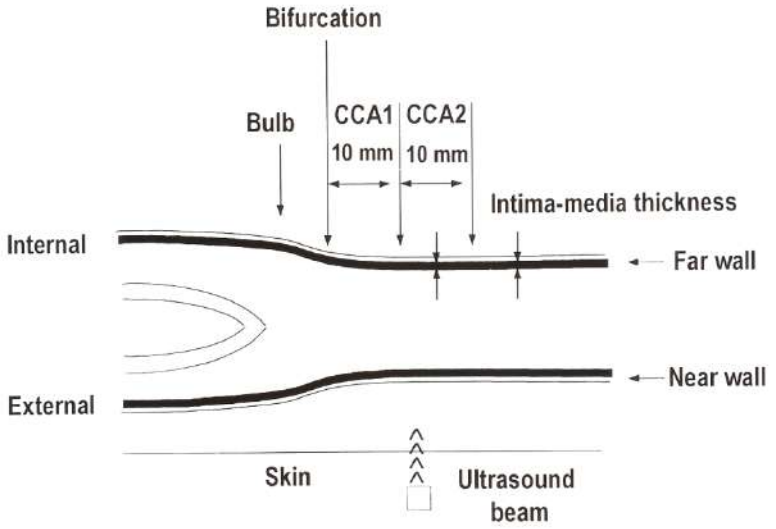


Table 1 Characteristics of Adolescents and Young Adults

	Intima-Media Thickness, mm						
Variables	< 0.40	0.40-0.43	0.43-0.46	≥0.46	P 1	P 2	P 3
	N=197	N=200	N=193	N=197			
Age, year	20.79±3.37	21.23±3.20	21.65±3.02	21.61±3.58	0.033	0.014	0.004
Male, %	28.93	35.5	44.04	50.76	<.001	<.001	<.001
Waist, cm	66.9±8.6	67.9±8.3	71.4±10.7	76.4±15.3	<.001	<.001	<.001
BMI, kg/m^2	21.0±3.4	20.9±3.1	22.0±3.7	23.7±5.3	<.001	<.001	<.001
SBP, mmHg	104.8±12.4	104.4±12.6	108.3±13.6	113.0±17.6	<.001	<.001	<.001
DBP, mmHg	65.0±9.8	64.7±8.6	65.8±9.7	72.2±14.0	<.001	<.001	<.001
HTN, %	3.55	7	8.81	21.32	<.001	<.001	<.001
Sugar, mg/dL	85.3±9.1	84.7±13.5	85.7±10.0	93.3±36.1	<.001	<.001	<.001
DM, %	0.51	1	1.04	2.54	0.303	0.138	0.086
TCHO, mg/dL	173.4±35.9	170.9±34.2	173.1±28.9	183.3±39.2	0.002	0.005	0.002
HDL, mg/dL	51.9±10.2	50.7±10.1	50.2±10.6	48.54±9.41	0.01	<.001	0.001
LDL, mg/dL	98.0±29.4	95.79±29.3	101.3±27.9	111.6±35.7	<.001	<.001	<.001
TG, mg/dL	80.5±44.9	83.4±93.4	81.4±40.6	98.3±106.2	0.074	0.022	0.031
Smoking, %	11.68	11	14.51	15.74	0.451	0.243	0.146
Alcohol, %	6.6	7.5	7.77	13.71	0.053	0.022	0.017
Hs-CRP, mg/L	0.07±0.12	0.08±0.16	0.10±0.17	0.12±0.27	0.031	0.008	0.006
Albumin, g/dL	4.93±0.26	4.94±0.23	4.93±0.23	4.87±0.32	0.018	0.012	0.006
Cr, mg/dL	0.97±0.46	0.93±0.15	0.96±0.18	1.05±0.80	0.078	0.084	0.045
ECCr, ml/min	89.4±21.5	91.4±18.9	96.9±21.87	104.03±30.6	<.001	<.001	<.001
UA, mg/dL	5.64±1.35	5.63±1.31	5.83±1.49	6.20±1.61	<.001	<.001	<.001

Figure Gender difference of urinary phthalate metabolites levels

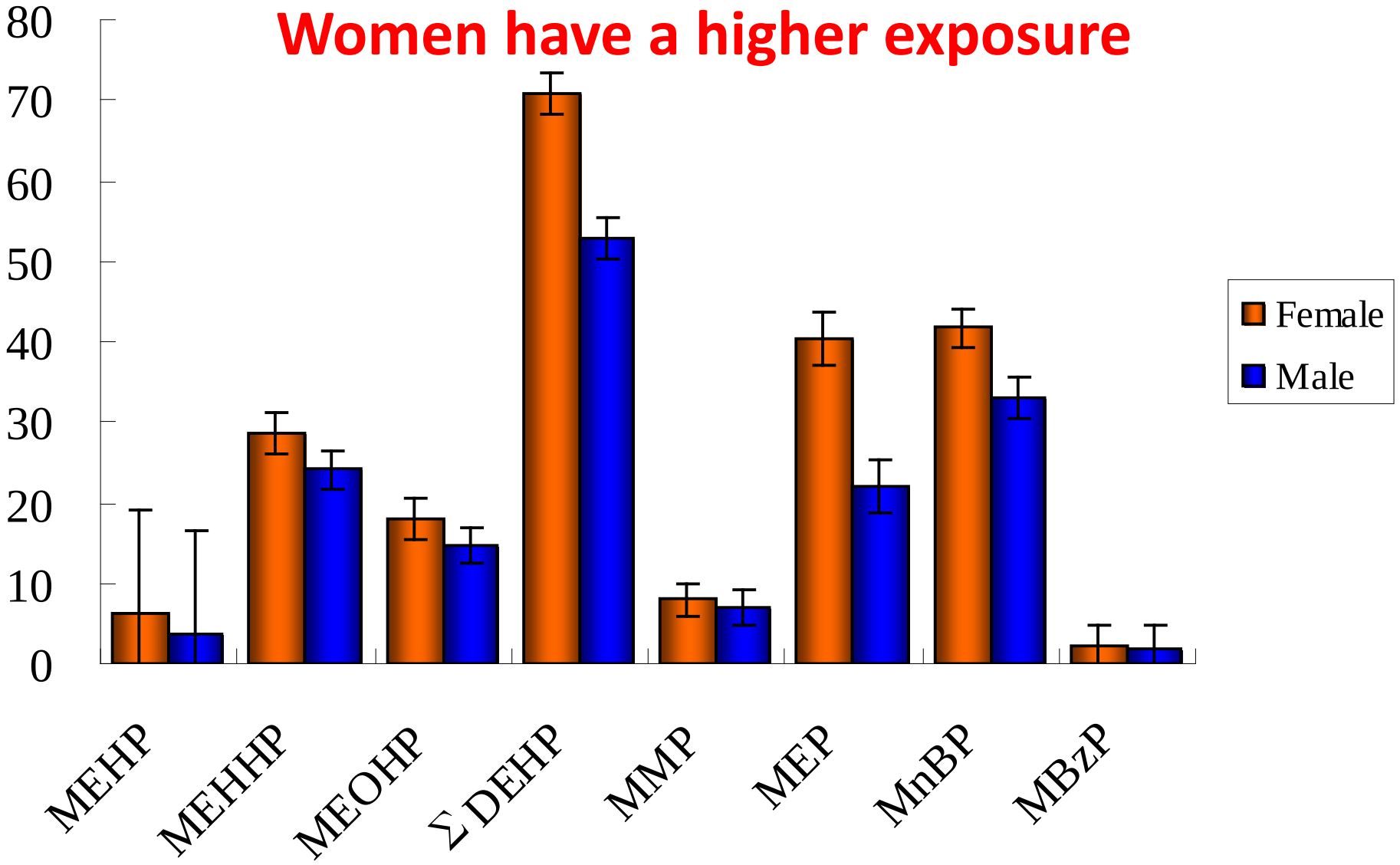


Figure BMI and urinary phthalate metabolites

Overweight have a higher exposure

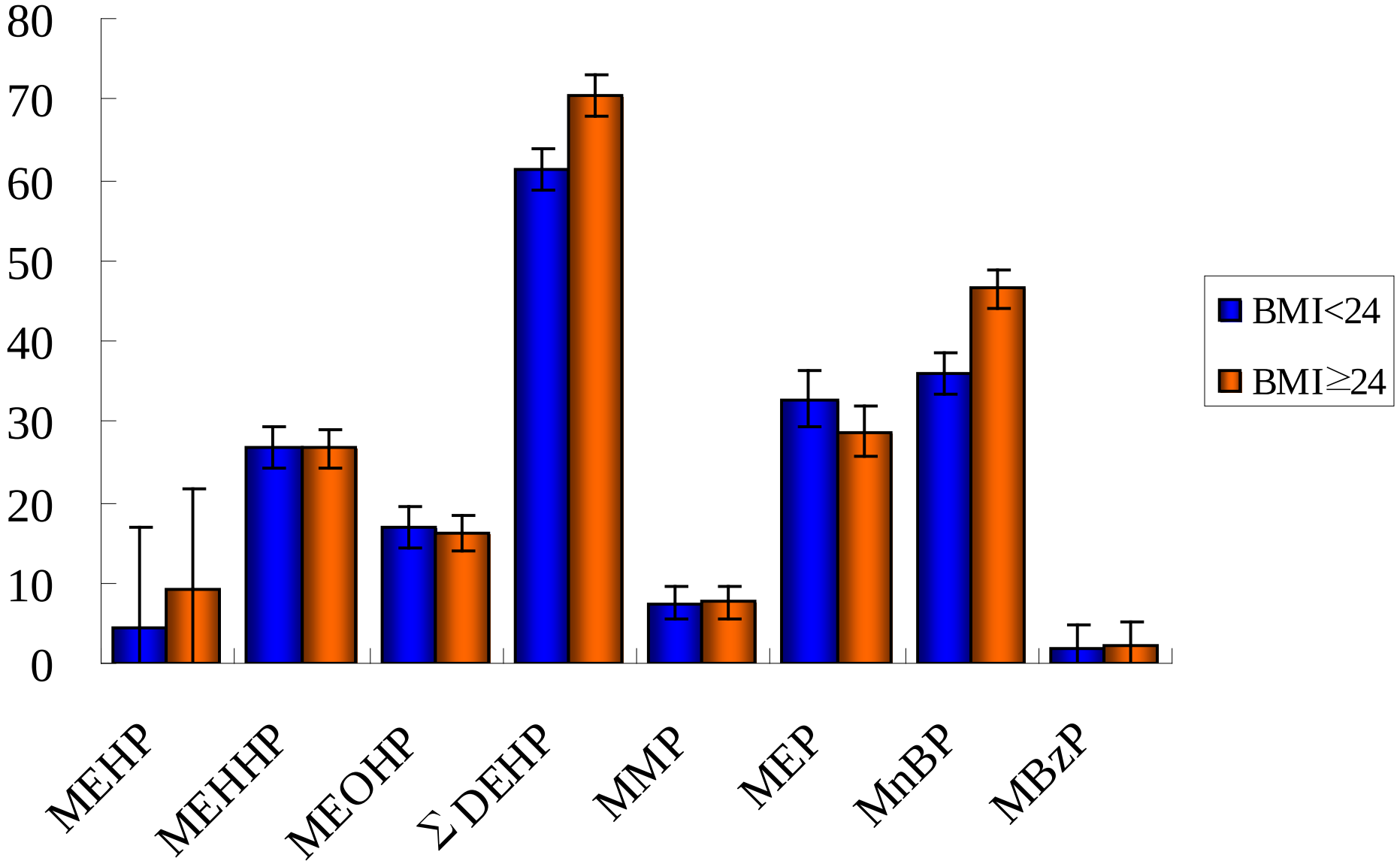


Figure 2. Creatinine-adjusted concentration of urinary phthalate metabolites by quartiles distribution of carotid IMT

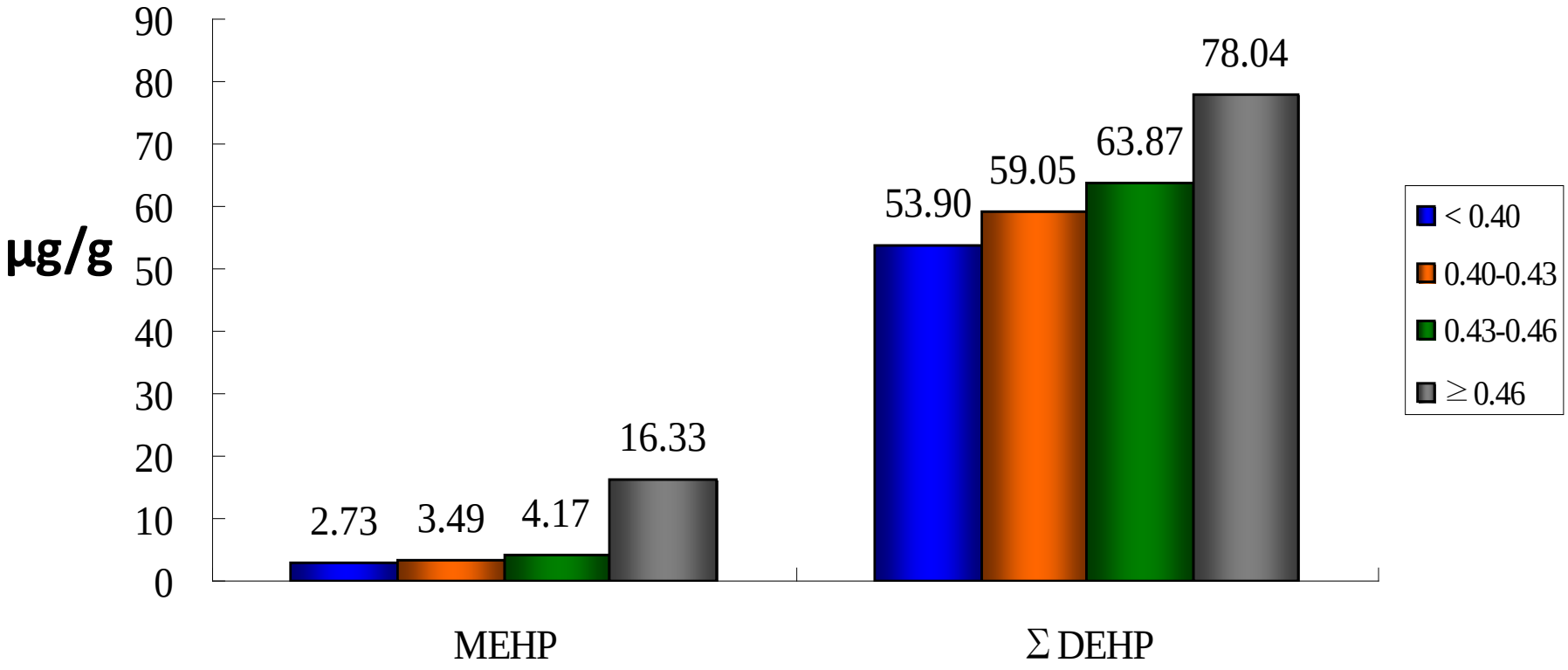
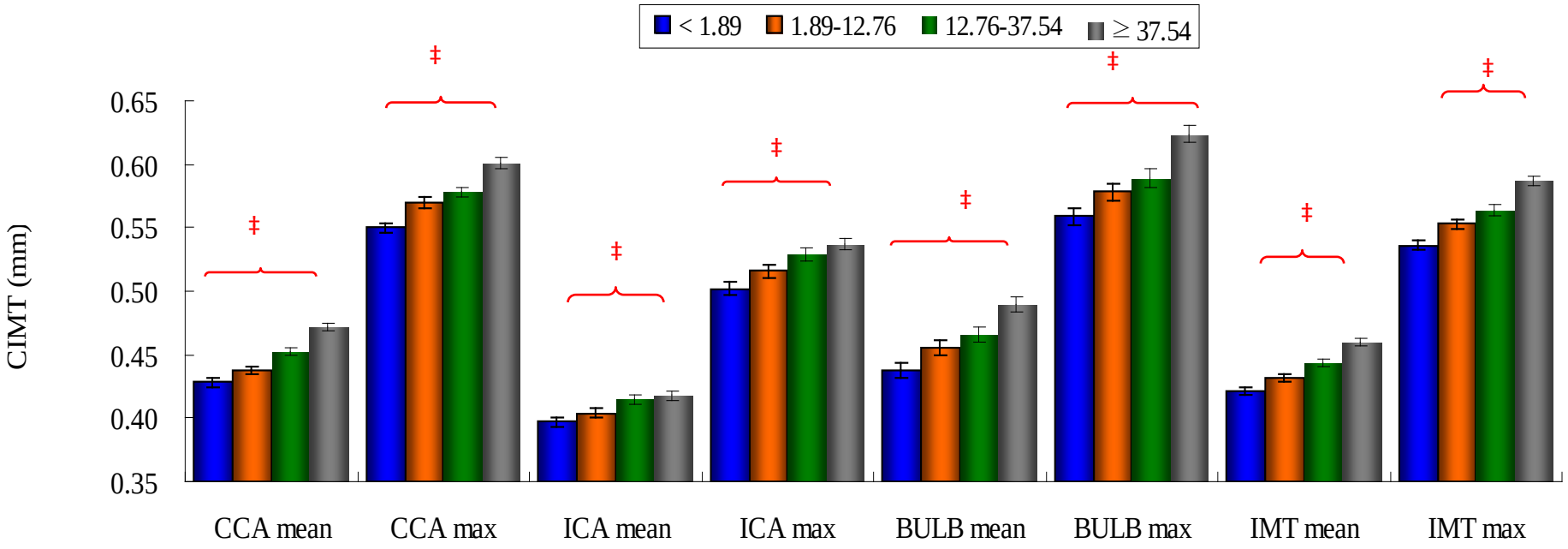


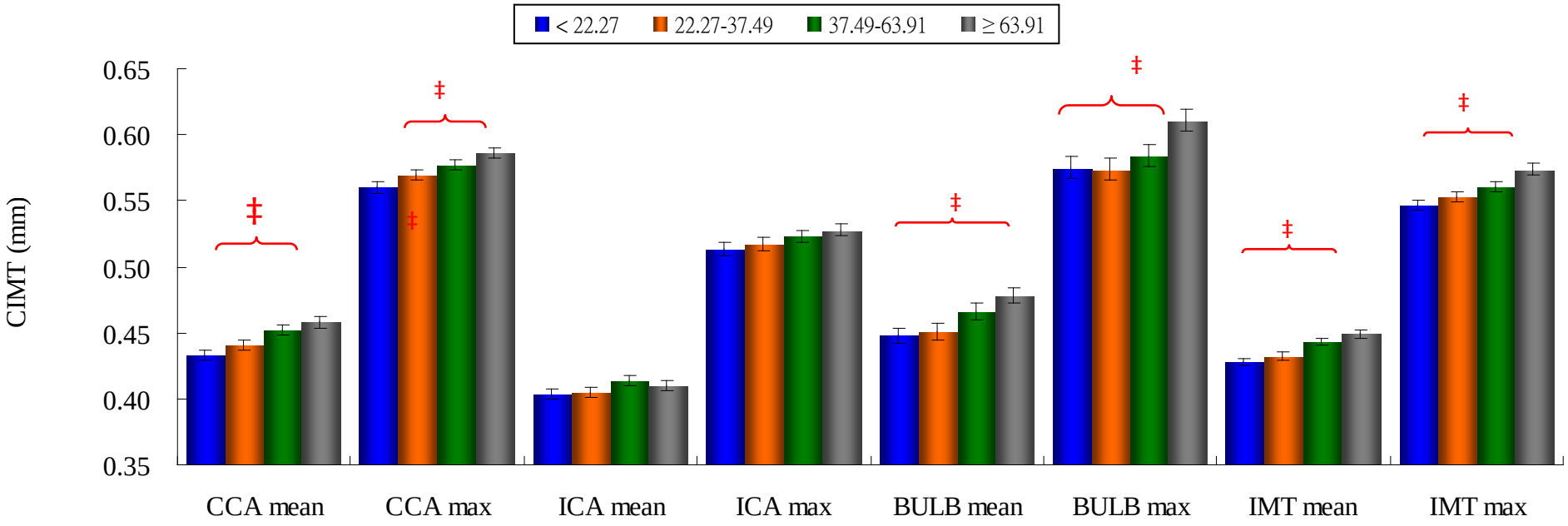
Figure 4-1. Carotid intima-media thickness across quartiles of MEHP concentration in linear regression models



p-value: * <0.05, † <0.01, ‡ <0.005.

Least square mean and standard error after adjustment for age, gender, body mass index, glucose, cholesterol, hypertension, smoking and drinking habit, hs-CPR, household income.

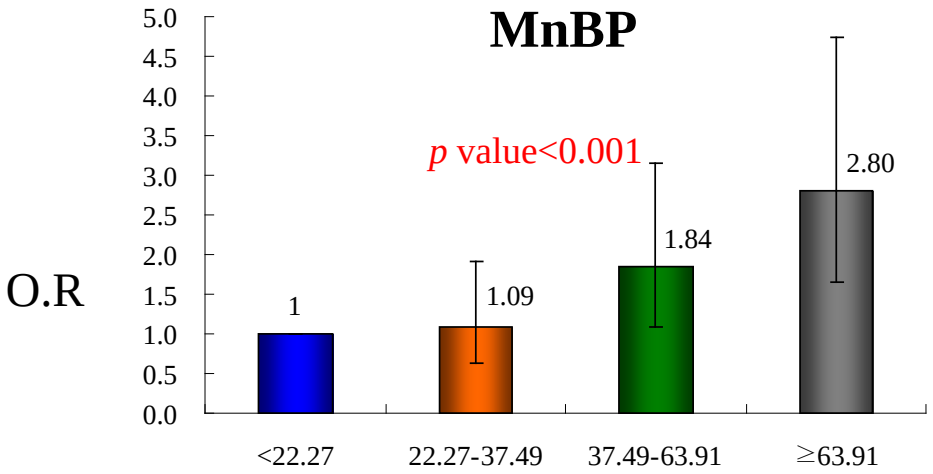
Figure 4-3. Carotid intima-media thickness (CIMT) in mm across quartiles of MnBP concentration in linear regression models.



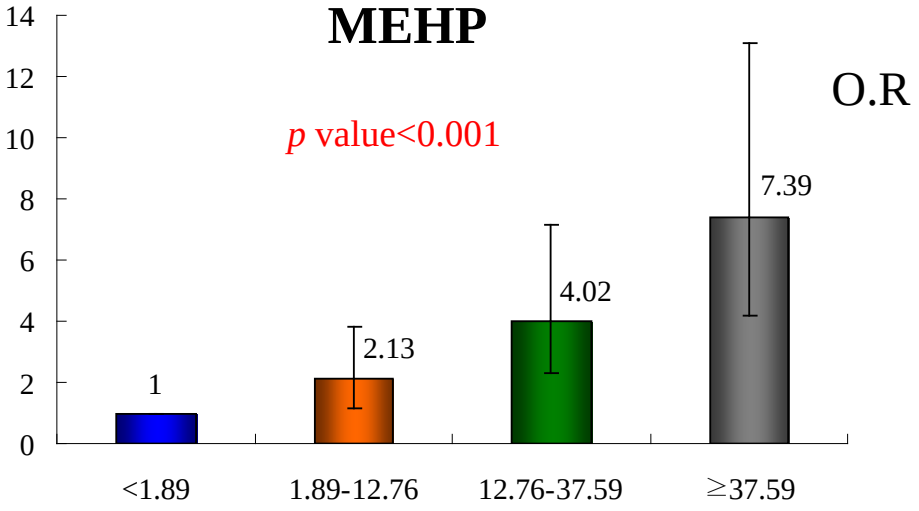
p-value: * <0.05, † <0.01, ‡ <0.005.

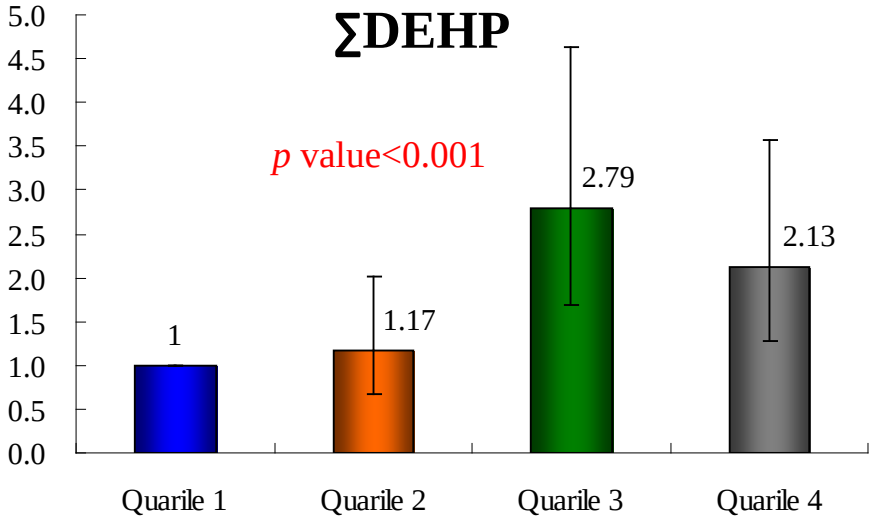
Least square mean and standard error after adjustment for age, gender, body mass index, glucose, cholesterol, hypertension, smoking and drinking habit, hs-CPR, household income.

Figure 4. Multivariate logistic regression analysis for the risk of thicker carotid intima-thickness (CIMT ≥75th percentile) by quartile distribution of urinary phthalate metabolites.



Models were adjusted for age, gender, body mass index, cholesterol, hypertension, smoking and drinking habit, hs-CPR, household income.





Discussions

- Urinary phthalate (**DEHP)** metabolites are significantly and positively associated with **carotid IMT, including CCA, ICA, and bulb, and mean IMT** after controlling associated covariates.
- The major phthalate esters related with subclinical atherosclerosis are **MnBP, MEHP and ΣDEHP**.
- The associations in relative healthy young adults and adolescents indicate the evidence is very important and not by chance.

Urinary Phthalate Metabolite Concentrations and Diabetes among Women in the National Health and Nutrition Examination Survey (NHANES) 2001–2008

Tamarra James-Todd,[1] Richard Stahlhut,[2] John D. Meeker,[3] Sheena-Gail Powell,[1] Russ Hauser,[4,5] Tianyi Huang,[1] and Janet Rich-Edwards[1,4]

Table 2. Association [OR (95% CI)] between urinary phthalate metabolites and diabetes among women 20–79 years of age (NHANES 2001–2008).

Urinary phthalate metabolite	Model 1[a]	Model 2[b]	Model 3[c]	Model 4[d]
MEP				
Q1				
Q2	1.04 (0.65–1.68)	1.00 (0.63–1.59)	0.95 (0.60–1.51)	0.93 (0.58–1.49)
Q3	1.08 (0.62–1.88)	1.17 (0.64–2.13)	1.09 (0.61–1.96)	1.19 (0.65–2.20)
Q4	1.10 (0.58–2.06)	0.94 (0.49–1.80)	0.89 (0.47–1.67)	0.89 (0.48–1.68)
MnBP				
Q1				
Q2	1.37 (0.84–2.24)	1.32 (0.80–2.18)	1.29 (0.78–2.13)	1.31 (0.78–2.22)
Q3	2.01 (1.21–3.36)	1.76 (1.05–2.94)	1.71 (1.04–2.81)	1.73 (1.01–2.96)
Q4	1.32 (0.76–2.28)	1.06 (0.59–1.89)	1.06 (0.61–1.85)	1.14 (0.63–2.04)
MiBP				
Q1				
Q2	1.04 (0.66–1.66)	1.06 (0.67–1.68)	1.04 (0.66–1.67)	1.03 (0.64–1.67)
Q3	1.47 (0.85–2.53)	1.65 (0.91–2.98)	1.69 (0.93–3.06)	1.71 (0.92–3.16)
Q4	1.85 (1.04–3.27)	1.97 (0.99–3.93)	1.95 (0.99–3.85)	1.80 (0.89–3.65)
MBzP				
Q1				
Q2	0.81 (0.43–1.51)	0.85 (0.45–1.60)	0.78 (0.41–1.49)	0.84 (0.44–1.60)
Q3	1.73 (1.12–2.66)	1.84 (1.18–2.88)	1.80 (1.16–2.81)	1.90 (1.18–3.08)
Q4	1.60 (0.86–2.97)	1.95 (1.09–3.48)	1.96 (1.11–3.47)	1.99 (1.14–3.49)
MCPP[e]				
Q1				
Q2	0.78 (0.46–1.33)	0.85 (0.50–1.44)	0.83 (0.49–1.43)	0.76 (0.44–1.33)
Q3	1.46 (0.95–2.25)	1.54 (0.98–2.42)	1.55 (0.98–2.44)	1.47 (0.90–2.41)
Q4	1.45 (0.84–2.49)	1.62 (0.97–2.71)	1.68 (1.03–2.75)	1.64 (0.96–2.79)
∑DEHP (MEHP, MEHHP, and MEOHP)[f]				
Q1				
Q2	1.53 (0.92–2.54)	1.58 (0.97–2.57)	1.53 (0.95–2.48)	1.47 (0.90–2.40)
Q3	1.81 (1.10–2.99)	1.85 (1.13–3.02)	1.73 (1.03–2.91)	1.70 (0.96–3.03)
Q4	1.45 (0.84–2.51)	1.66 (0.90–3.05)	1.53 (0.82–2.87)	1.43 (0.75–2.75)

Q, quartile. For each of the metabolites, Q1 is the reference.

Environ Health Perspect. 2012; 120: 1307-13.

Table 3. Association [difference in median value (95% CI)] between urinary phthalate metabolites and FBG, ln-HOMA-IR, and A1c among women 20–79 years of age without self-reported diabetes (NHANES 2001–2008).[a]

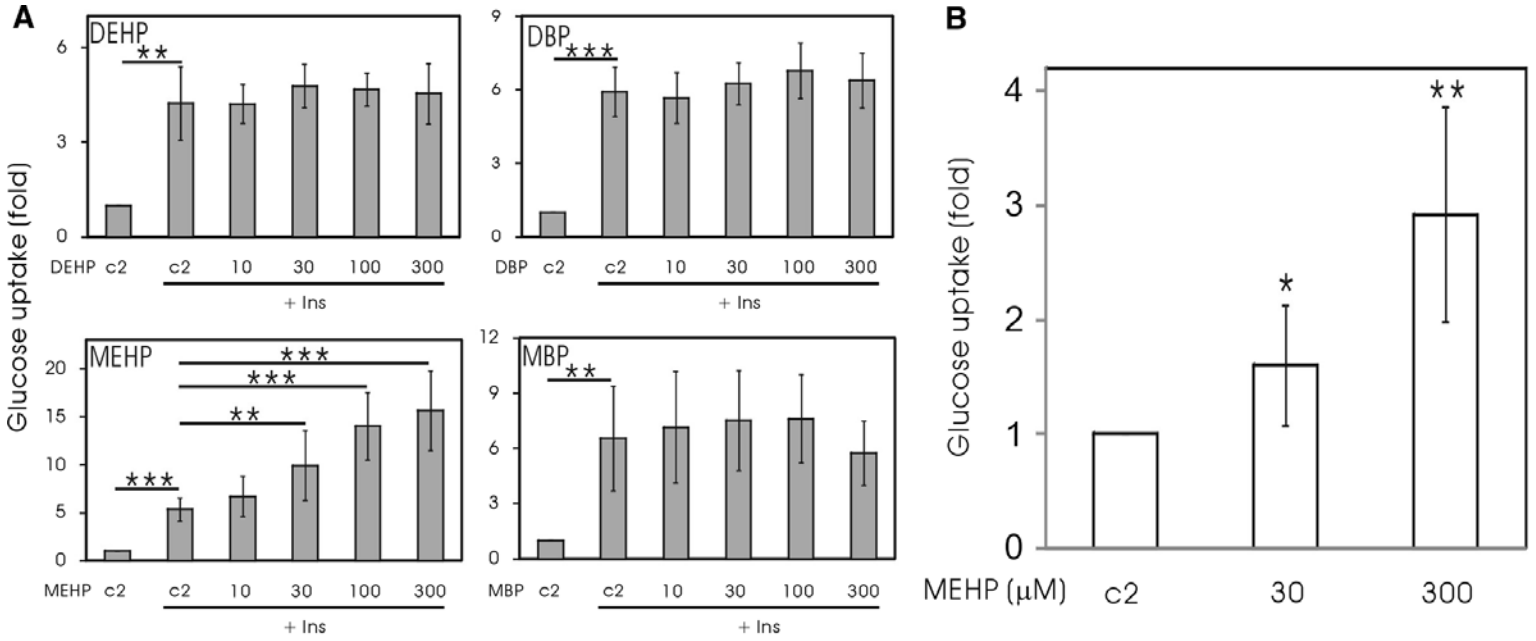
	FBG (mg/dL)		ln(HOMA-IR)		A1c (%)	
Phthalates	Model 1[b]	Model 2[c]	Model 1[b]	Model 2[c]	Model 1[b]	Model 2[c]
MEP	*n* = 979		*n* = 965		*n* = 2,074	
Q1						
Q2	0.95 (–0.94, 2.85)	1.10 (–0.83, 3.04)	0.06 (–0.10, 0.23)	0.03 (–0.09, 0.14)	0.01 (–0.04, 0.06)	–0.02 (–0.07, 0.02)
Q3	1.18 (–0.91, 3.27)	0.38 (–1.91, 2.67)	0.07 (–0.08, 0.23)	0.01 (–0.11, 0.14)	–0.02 (–0.07, 0.03)	–0.03 (–0.07, 0.02)
Q4	–0.03 (–2.16, 2.09)	–0.61 (–2.99, 1.78)	0.10 (–0.07, 0.26)	–0.04 (–0.17, 0.09)	–0.03 (–0.08, 0.02)	–0.05 (–0.10, 0.00)
MnBP	*n* = 985		*n* = 971		*n* = 2,092	
Q1	REF	REF	REF	REF	REF	REF
Q2	–0.35 (–2.07, 1.38)	–0.62 (–2.62, 1.38)	0.09 (–0.06, 0.25)	0.04 (–0.08, 0.16)	0.01 (–0.04, 0.06)	0.00 (–0.04, 0.04)
Q3	–0.19 (–2.22, 1.83)	0.19 (–2.05, 2.43)	0.09 (–0.06, 0.24)	0.11 (–0.01, 0.23)	–0.02 (–0.08, 0.03)	–0.03 (–0.08, 0.02)
Q4	–0.03 (–2.35, 2.30)	–0.05 (–2.47, 2.36)	0.14 (–0.04, 0.31)	0.10 (–0.04, 0.24)	–0.03 (–0.09, 0.02)	–0.02 (–0.07, 0.03)
MBzP	*n* = 985		*n* = 971		*n* = 2,092	
Q1						
Q2	0.00 (–1.70, 1.70)	0.77 (–1.11, 2.64)	0.09 (–0.07, 0.25)	–0.01 (–0.12, 0.11)	0.01 (–0.04, 0.06)	–0.01 (–0.05, 0.04)
Q3	–1.13 (–3.24, 0.98)	–1.08 (–3.34, 1.18)	0.13 (–0.02, 0.28)	0.06 (–0.07, 0.19)	0.00 (–0.05, 0.05)	–0.03 (–0.08, 0.01)
Q4	–2.27 (–4.76, 0.21)	–2.80 (–5.32, –0.28)	0.10 (–0.09, 0.29)	–0.07 (–0.22, 0.09)	–0.03 (–0.09, 0.03)	–0.03 (–0.09, 0.02)
MCPP	*n* = 985		*n* = 971		*n* = 2,092	
Q1						
Q2	1.06 (–0.90, 3.02)	0.98 (–1.20, 3.15)	0.04 (–0.13, 0.20)	0.01 (–0.11, 0.13)	–0.04 (–0.09, 0.00)	–0.04 (–0.09, 0.00)
Q3	0.65 (–1.42, 2.73)	0.01 (–2.23, 2.24)	0.02 (–0.14, 0.17)	–0.03 (–0.16, 0.10)	–0.02 (–0.07, 0.03)	–0.01 (–0.06, 0.04)
Q4	–0.06 (–2.24, 2.12)	–0.49 (–3.01, 2.04)	–0.07 (–0.23, 0.10)	–0.01 (–0.15, 0.13)	–0.06 (–0.12, –0.01)	–0.07 (–0.12, –0.01)
MiBP	*n* = 985		*n* = 971		*n* = 2,092	
Q1						
Q2	3.08 (1.22, 4.93)	3.03 (1.05, 5.00)	0.13 (–0.02, 0.28)	0.13 (0.01, 0.25)	0.03 (–0.01, 0.08)	0.03 (–0.01, 0.08)
Q3	3.50 (1.45, 5.54)	3.17 (1.17, 5.17)	0.08 (–0.08, 0.25)	0.10 (–0.01, 0.21)	0.03 (–0.02, 0.09)	0.04 (0.00, 0.09)
Q4	5.86 (3.55, 8.17)	6.04 (3.81, 8.28)	0.22 (0.06, 0.38)	0.18 (0.06, 0.31)	0.01 (–0.05, 0.07)	0.01 (–0.04, 0.07)
∑DEHP	*n* = 976		*n* = 962		*n* = 2,074	
Q1						
Q2	0.35 (–1.50, 2.19)	–0.13 (–2.08, 1.82)	0.12 (–0.04, 0.29)	0.01 (–0.11, 0.13)	0.04 (–0.01, 0.08)	0.02 (–0.02, 0.06)
Q3	–1.24 (–3.37, 0.89)	–1.75 (–3.93, 0.44)	0.10 (–0.04, 0.24)	0.05 (–0.07, 0.16)	–0.01 (–0.06, 0.04)	–0.03 (–0.07, 0.02)
Q4	0.25 (–1.94, 2.44)	0.01 (–2.34, 2.36)	0.19 (0.02, 0.35)	0.13 (0.01, 0.25)	0.01 (–0.05, 0.07)	–0.02 (–0.07, 0.03)

Q, quartile. For each of the phthalate categories, Q1 is the reference.

Mono(2-ethylhexyl)phthalate accumulation disturbs energy metabolism of fat cells

(Chiang H.C. et al., *Arch Toxicol* 2016;90(3):589–601.)

- In vitro evidence of MEHP impacts on lipolysis, glucose uptake/glycolysis, and mitochondrial respiration/biogenesis demonstrates that MEHP accumulation disturbs energy metabolism of fat cells.

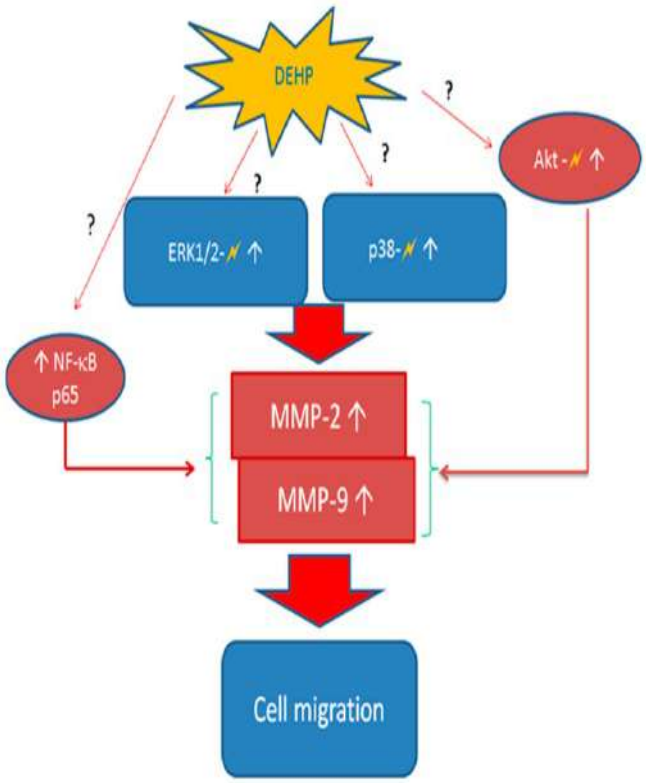


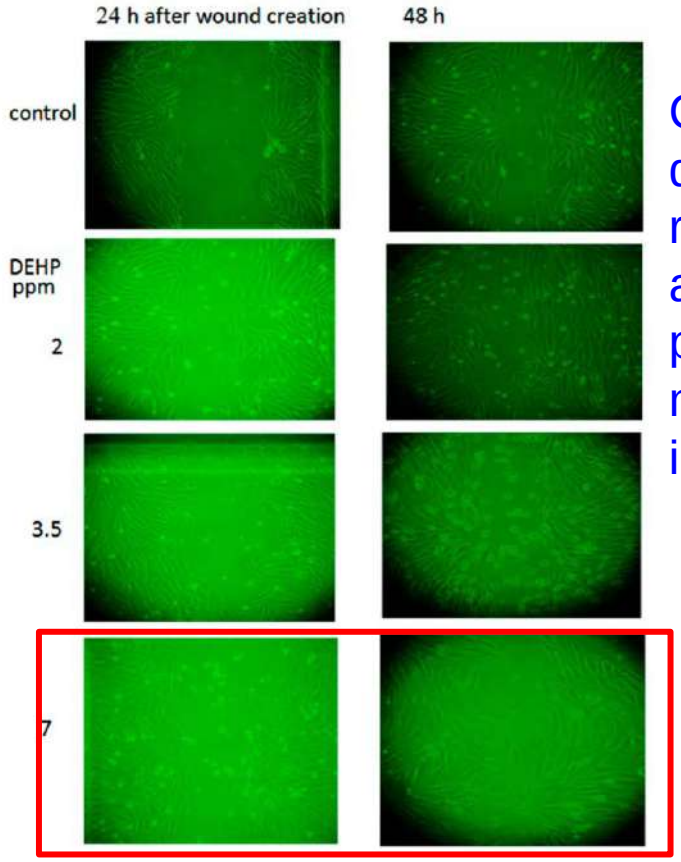
-MEHP-treated adipocytes displayed significant increases in glucose uptake.
-MEHP treatment during adipogenesis might alter the normal gene expression pattern and led to the consequent changes in insulin sensitivity.

Possible Mechanisms of Di(2-ethylhexyl) Phthalate-Induced MMP-2 and MMP-9 Expression in A7r5 Rat Vascular Smooth Muscle Cells

(Shih M.F. et al., *Int. J. Mol. Sci.* 2015;16(12):28800–28811)

- DEHP can be a potent inducer of atherosclerosis by increasing MMP-2 and MMP-9 expression at least through the regulations of p38 MAPK, ERK1/2, Akt, and NF-κB.





Cardiovascular disorders is often related to the abnormal proliferation and migration of VSMC in arterial wall

DEHP at doses higher than 3.5 ppm would induce cell migration

DEHP

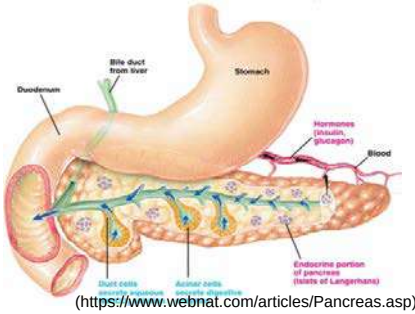
-MMP -MnBP
-DMP -DEP

Systolic BP

BMI

Waist

Pancreas

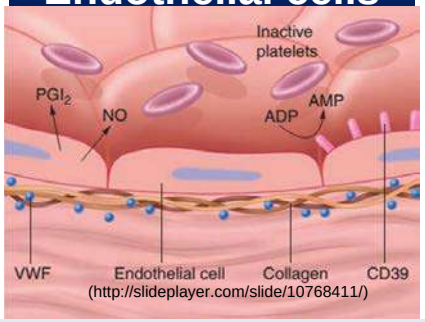


(https://www.webnat.com/articles/Pancreas.asp)

Insulin resistance

Env. Poll., 2017

Platelet & Endothelial cells



Endothelial microparticles

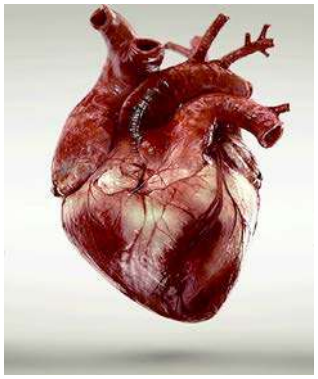
Platelet microparticles

Environ Int., 2016

(http://www.wisegeek.org/what-is-vasoconstriction.htm)

?

Carotid IMT ⇒ **CHD**

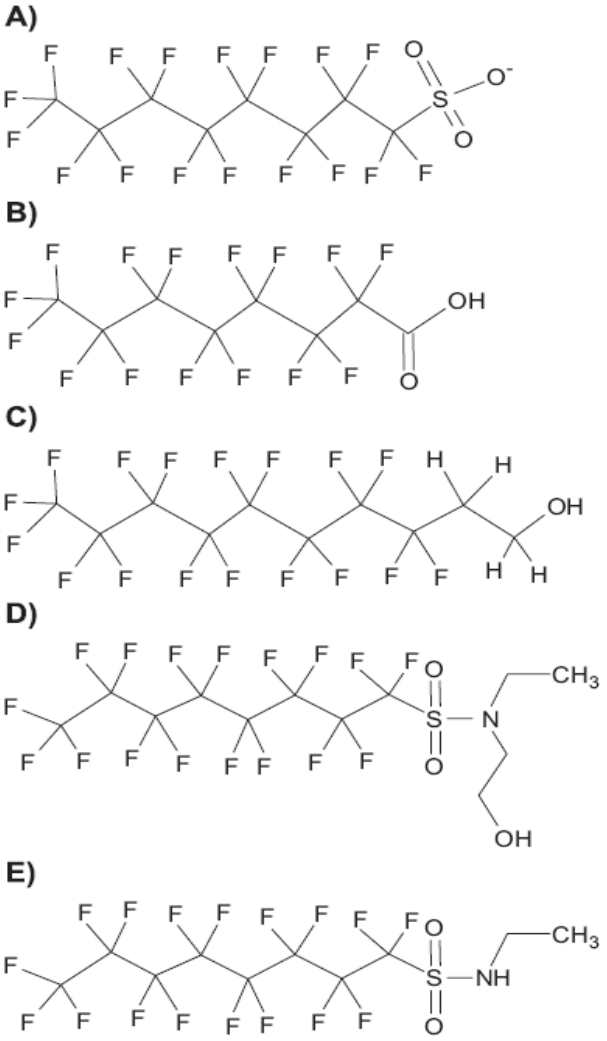


Perfluorinated Chemicals and Cardiometabolic Health

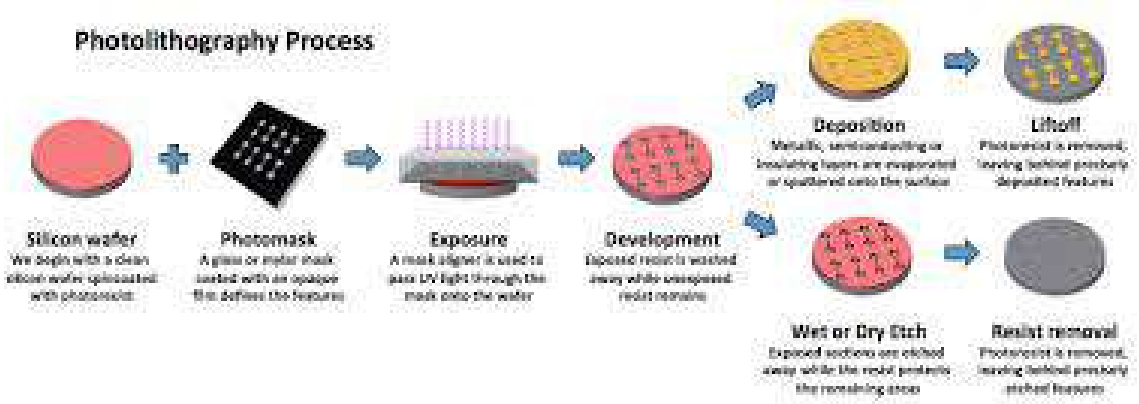
Ta-Chen Su

Introduction

- Perfluorinated chemicals (PFCs) consist of a 4 to 14 carbon backbone and a charged functional moiety (primarily carboxylate, sulfonate, or phosphonate).
- PFCs are man-made chemicals that have only been used in the last half century.
- The two most widely known PFCs are perfluorooctane sulfate (**PFOS**) **and perfluorooctanoic acid (PFOA)**



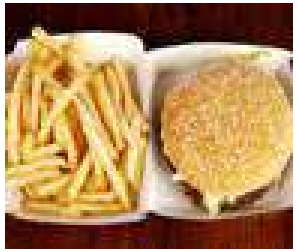
Chemical structure of PFCs.
(A) Perfluorooctane sulfonate (PFOS),
(B) perfluorooctanoate (PFOA),
(C) 1-hydroxyethane-2-perfluorooctanol(8:2 FTOH),
(D) N-ethyl perfluorooctane sulfonamidothanol (NEtFOSE),
(E) N-ethyl perfluorooctane sulfonamide (NEtFOSA).



Perfluorinated chemicals, PFCs

- Stable in air, nonflammable, not degraded by strong acids, alkalis or oxidizing agents.
- Surfactants, lubricants, polishes, food packaging, and fire-retardant foams

- The unique stability: nonbiodegradable and very persistent in the environment

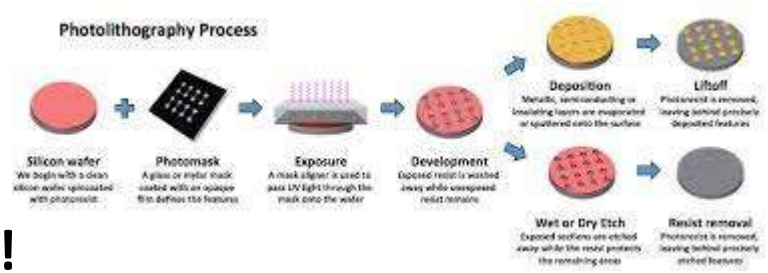


Perfluorinated chemicals, PFCs

- PFCs are a large group of manufactured compounds that are widely used to make everyday products more resistant to stains, grease, and water.
- For example, PFCs may be used to keep food from sticking to cookware, to make sofas and carpets resistant to stains, to make clothes and mattresses more waterproof, and may also be used in some food packaging, as well as in some firefighting materials.
- Because they help reduce friction, they are also used in a variety of other industries, including aerospace, automotive, building and construction, and electronics.
- **Semiconductive Company:**

  Photolithography

  (Many factories in Taiwan)



- **Long half life and bioaccumulative!!**
- PFCs have been demonstrated to associate with insulin resistance and glucose homeostasis (Lin CY, Diabetes Care 2009).

Introduction

- Possible exposure pathways:
  Drinking water
  Food
  Dust in homes
  Migration from food packaging and cookware

- **Half life:**

The longer the carbon chain length, the longer PFCs persists in the body.

4-carbon: perfluorobutane sulfonate = 1 month

8-carbon: PFOA = 3.8 years

PFOS = 5.4 years

Enviorn Health Perspect 2007; 115.1298-305

Contents lists available at ScienceDirect

Environmental Pollution

journal homepage: www.elsevier.com/locate/envpol

The impact of semiconductor, electronics and optoelectronic industries on downstream perfluorinated chemical contamination in Taiwanese rivers

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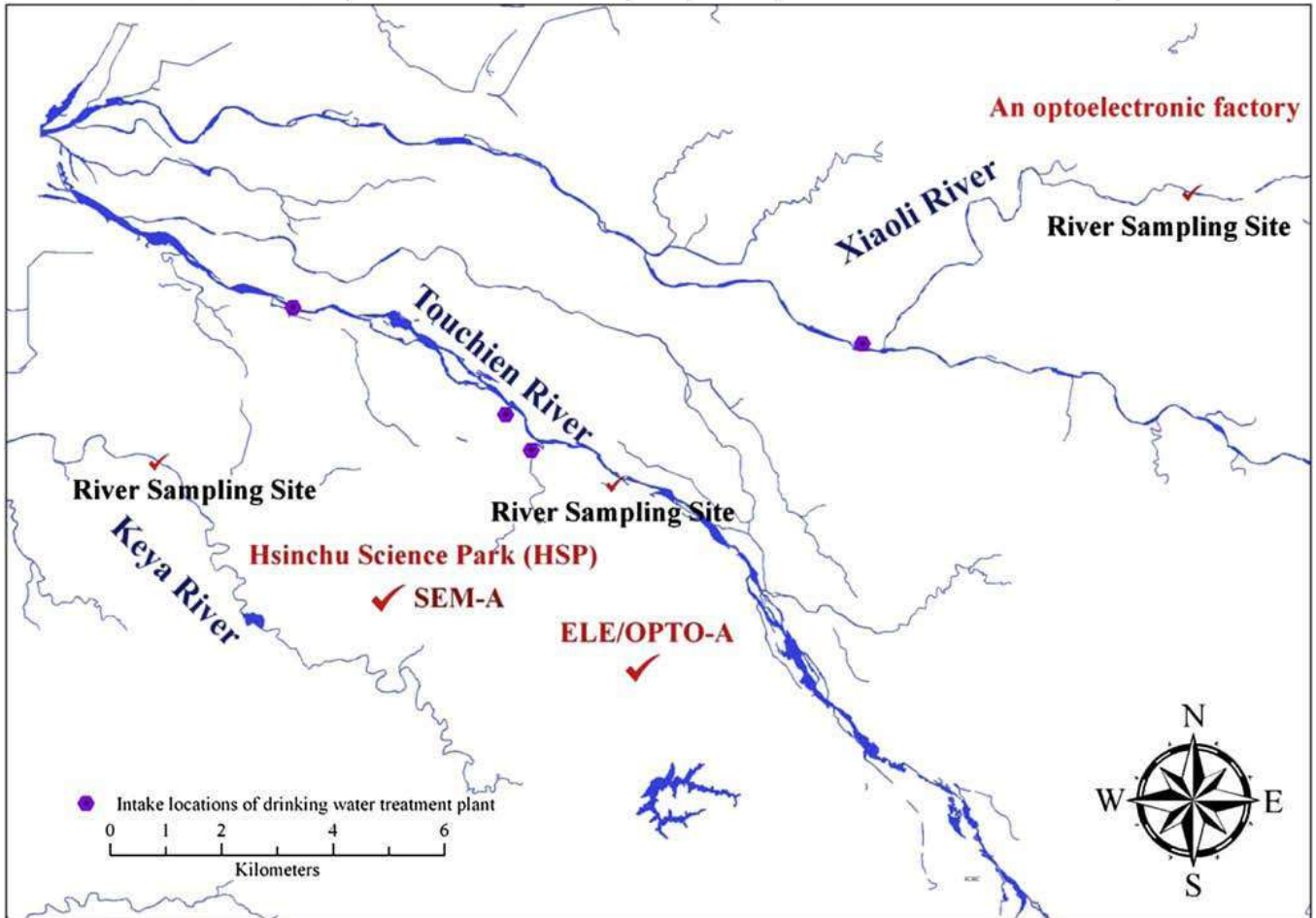
National Taiwan University, Graduate Institute of Environmental Engineering, No. 1, Sec. 4, Roosevelt Road, Taipei 10617, Taiwan

The semiconductor, electronics and optoelectronic industries are the primary source of PFC contamination in downstream aqueous environments.



PFOA, PFOS, and PFDA levels in Hsin-Chu Rivers

Table 4
PFOA, PFOS, and PFDA concentrations detected in Taiwanese River waters and compared with previous studies around the globe.

Region	Occurrence area	Impact	PFOA (ng/L)	PFOS (ng/L)	PFDA (ng/L)	Ref.
Taiwan	Xiaoli	I	17.3	82	11.3	Present study
Taiwan	Touchien	I	10.9	48.9		Present study
Taiwan	Keya	I	310	5440		Present study
Japan	Tsurumi River	STP	13.4–15.9	179.6–179.9	2.1–3.9	Zushi et al. (2008)
Japan	Uji River	I, P	100–110	8.7–10	–	Senthilkumar et al. (2007)
China	Yangtze River	I, U, P	2.0–260	<0.01–14	<0.01–3.8	So et al. (2007)
China	Pearl River Guangzhou	I, U, P	0.85–13	0.9–99	<0.13–0.57	So et al. (2007)
Germany	Rivers	WWTP	1.0–14	0.7–15		Becker et al. (2008)
N-Italy	Po River	I	337	<0.1–25	–	Loos et al. (2008)
	Tánaro River		1270	2	–	
U.S.A	Tannessee River	Highest by fluorochemical manufacturing facility	nd–598	16.8–144	–	Hansen et al. (2002)

I, industrial discharge; STP, sewage treatment plants; U, urban discharge; WWTP, wastewater plant; P, populated area.

Table 3
Perfluorinated chemicals (PFCs) concentrations determined in a semiconductor fabrication plant (SEM-A) waters (pure water, wafer photolithographic wastewater, and final effluent).

Compounds	Pure water (ng/L)	Photolithographic wastewater (ng/L)	Final effluent (ng/L)
PFBS	5.7	5,153,330	75,430
PFHxS	24.2	9,930,000	133,330
PFOS	36.7	12,566,670	128,670
PFHxA	nd	na	76.4
PFHpA	0.1	na	8.8
PFOA	1.4	na	118.3
PFNA	nd	na	7.7
PFDA	0.2	na	7.5
PFUnA	nd	na	9.1
PFDoA	0.2	na	2.9

na, Not available; nd, Not detected.

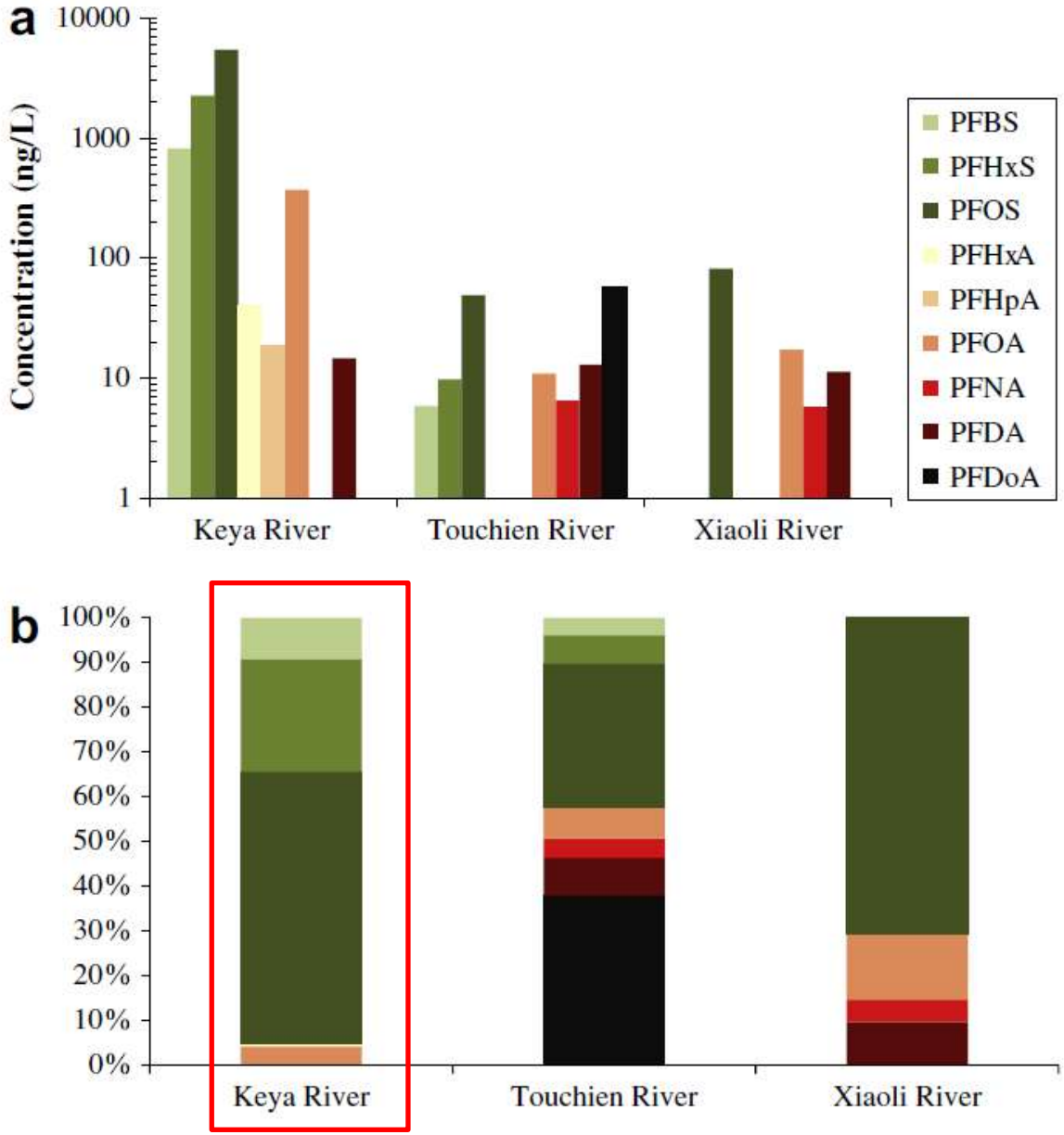


Fig. 3. (a) The logarithmic concentrations of the perfluorinated chemicals (PFCs) detected in the Keya, Touchien, and Xiaoli rivers; (b) percent distribution (scaling up to 100%) of PFCs in each of the three rivers.

Chemosphere 80 (2010) 1167–1174

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High levels of perfluorochemicals in Taiwan's wastewater treatment plants and downstream rivers pose great risk to local aquatic ecosystems

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Graduate Institute of Environmental Engineering, National Taiwan University, 71, Chou-Shan Rd., Taipei 106, Taiwan

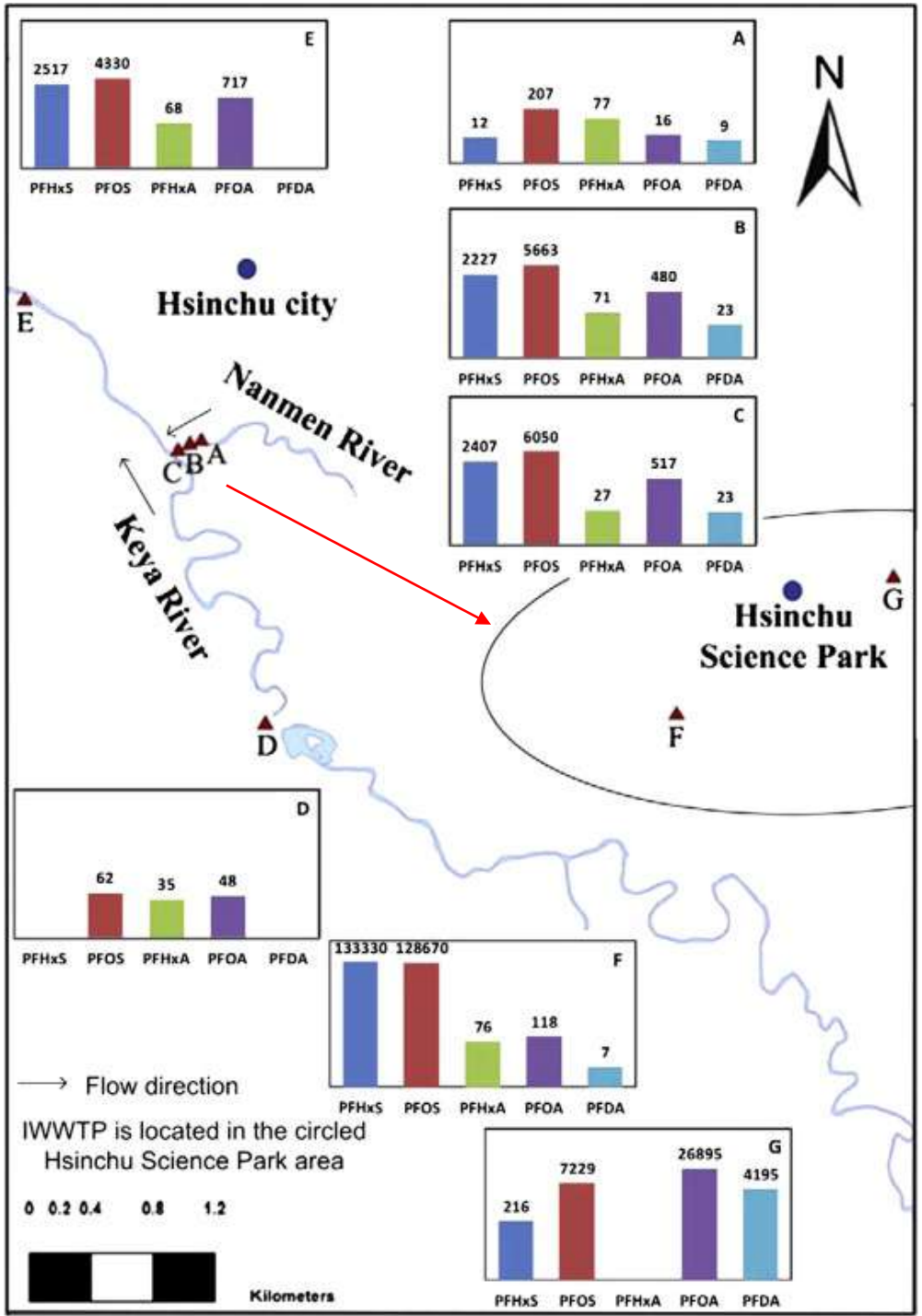

E
2517
4330
68
717
PFHxS PFOS PFHxA PFOA PFDA
A
12
207
77
16
9
PFHxS PFOS PFHxA PFOA PFDA
N
B
2227
5663
71
480
23
PFHxS PFOS PFHxA PFOA PFDA
Hsinchu city
E
Nanmen River
C
B
A
C
2407
6050
27
517
23
PFHxS PFOS PFHxA PFOA PFDA
Keya River
Hsinchu
Science Park
G
F
D
D
62
35
48
PFHxS PFOS PFHxA PFOA PFDA
133330 128670
F
76
118
7
PFHxS PFOS PFHxA PFOA PFDA
Flow direction
IWWTP is located in the circled
Hsinchu Science Park area
0 0.2 0.4 0.8 1.2
Kilometers
G
216
7229
26895
4195
PFHxS PFOS PFHxA PFOA PFDA

Table 3
Perfluorochemical (PFCs) concentrations (ng L^{-1}) in wastewater treatment plants.

PFC	Municipal WWTP1		Municipal WWTP2		Industrial WWTP Effluent
	Influent	Effluent	Influent	Effluent	
PFBS	16.3 ± 4.9	2.6 ± 1.3	3.3 ± 0.8	4.8 ± 1.5	960 ± 35.2
PFHxS	6.4 ± 2.1	6.3 ± 3.7	14.9 ± 7.8	35 ± 4.2	2226.7 ± 120.6
PFOS	175 ± 70.4	162.7 ± 28	216.7 ± 35	264.7 ± 34	5663.3 ± 427.4
PFHxA	348.3 ± 66.2	180.7 ± 15.8	80.1 ± 29.5	155 ± 8.7	71.1 ± 16.5
PFHpA	1.9	<0.1	0.8	<0.1	14.5 ± 0.3
PFOA	23.6 ± 8.4	25.4 ± 6	17.6 ± 2.7	19.3 ± 6.2	480.3 ± 28.2
PFNA	10.6 ± 0.8	<0.1	0.4 ± 0.1	0.3 ± 0.1	10.4 ± 0.8
PFDA	20.6 ± 16.2	1.8 ± 0.8	1.2 ± 0.1	1.4 ± 0.1	22.6 ± 1.3
PFUnA	83.5 ± 6.9	<0.1	<0.1	<0.1	4.8 ± 1.2
PFDoA	<0.1	<0.1	<0.1	0.7 ± 0.2	2.8 ± 0.3

Fig. 2. Perfluorochemical (PFCs) contamination in upstream and downstream of industrial wastewater treatment plant discharge in Nanmen River.

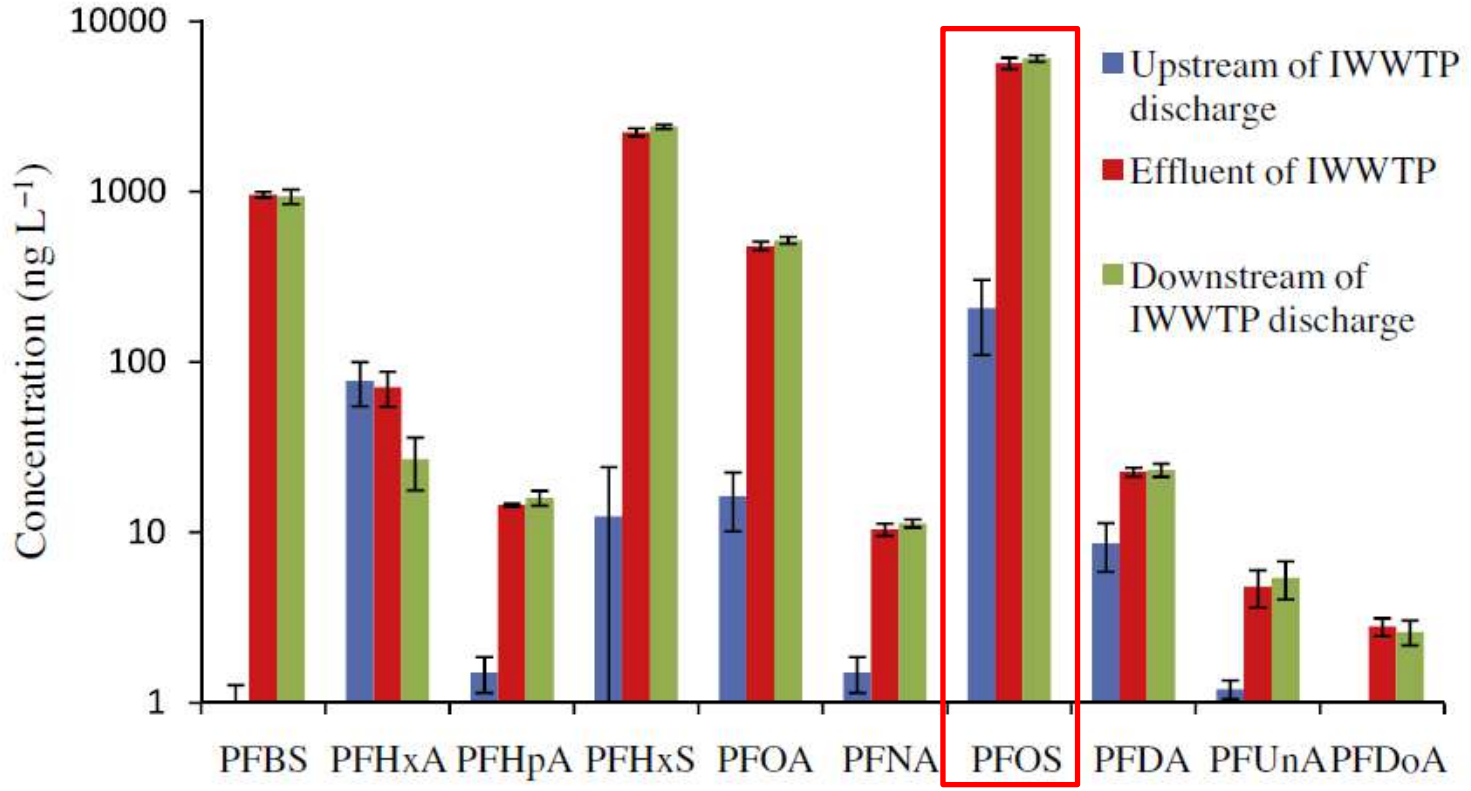


Table 4
Ratio of sediment-to-water concentration of detected perfluorochemicals in sediments.

Sampling location	Compounds	Sediment ($ng\ kg^{-1}$)	Water ($ng\ L^{-1}$)	Ratio ($ng\ kg^{-1}/ng\ L^{-1}$)
Upstream of IWWTP effluent discharge	PFOS	<LOQ	207.2	nc
	PFOA	<LOQ	16.3	nc
	PFUnA	3.3×10^3	1.2	2738
	PFDoA	5×10^3	<LOQ	nc
Effluent discharge of IWWTP	PFOS	89.7×10^3	5663.3	15.8
	PFOA	<LOQ	480.3	nc
	PFUnA	3.7×10^3	4.8	778
	PFDoA	11.5×10^3	2.8	4093
Downstream of IWWTP effluent discharge	PFOS	159.4×10^3	6050	26.3
	PFOA	2×10^3	517.3	4
	PFUnA	4.1×10^3	5.4	766
	PFDoA	15.8×10^3	2.6	6088

nc: Not calculable.

Occurrence of perfluorinated compounds in the aquatic environment as found in science park effluent, river water, rainwater, sediments, and biotissues

Angela Yu-Chen Lin · Sri Chandana Panchangam · Yu-Ting Tsai · Tsung-Hsien Yu

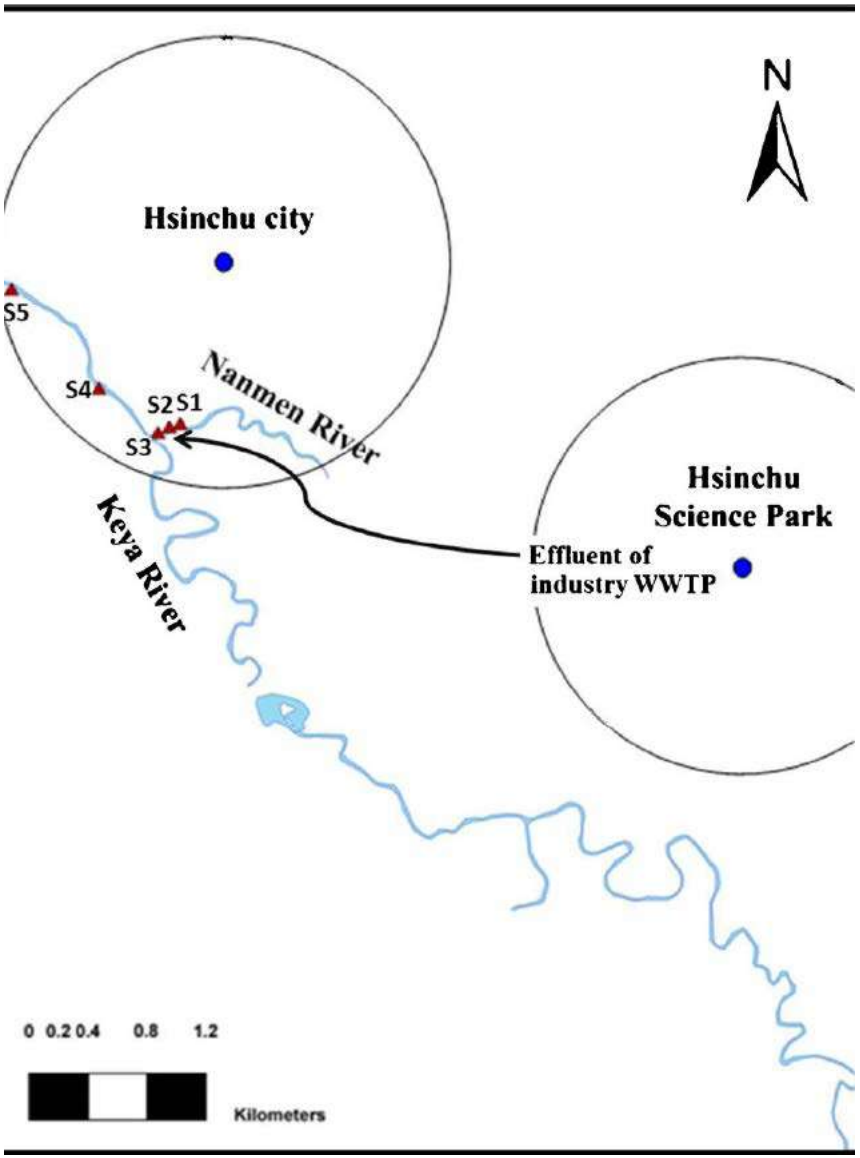
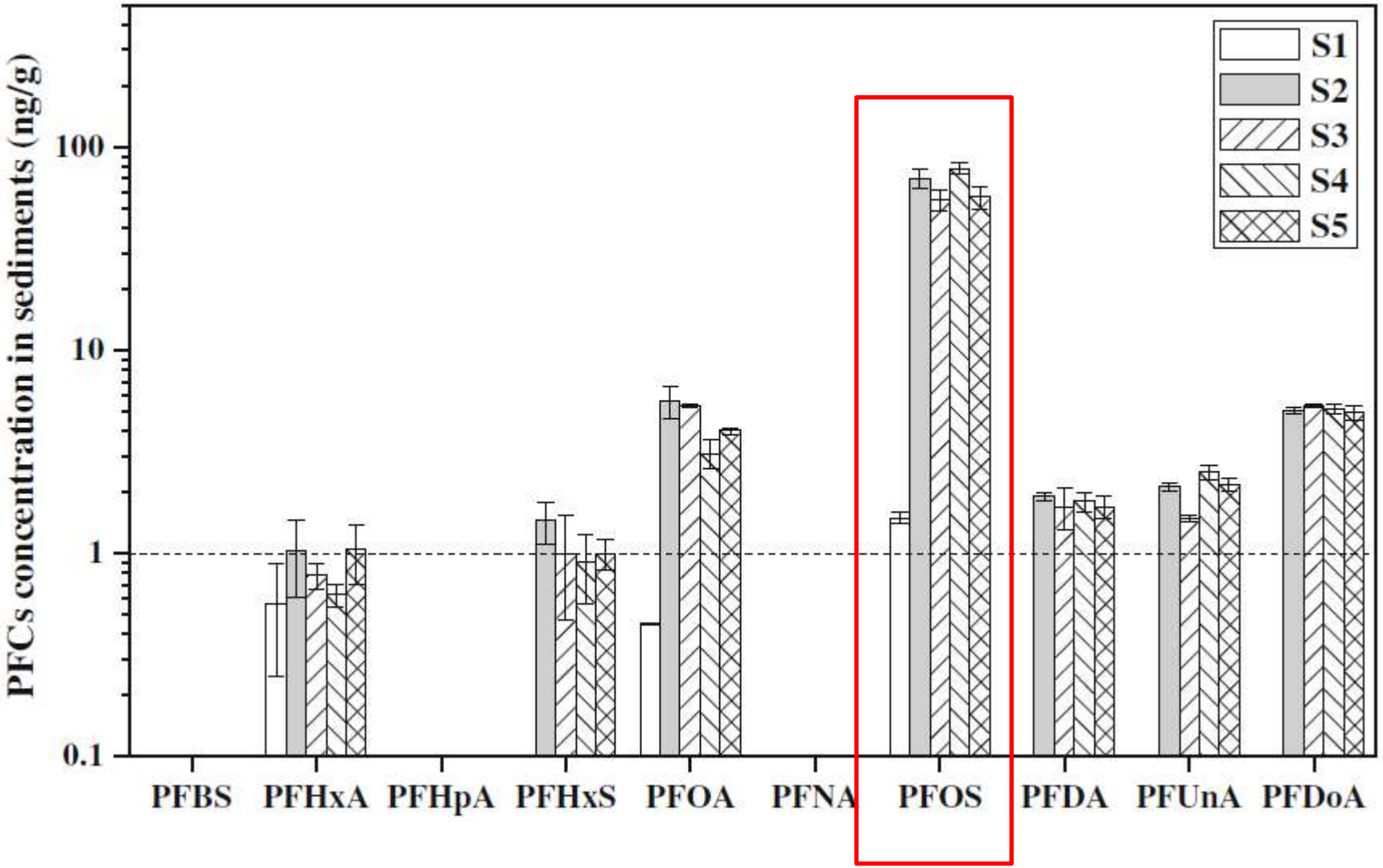


Fig. 3 Concentration and distribution of perfluoroalkyl acids detected in sediments



Muscle tissue of Tilpin and Catfish

Table 1 Perfluoroalkyl acid (PFAA) concentrations in muscle tissue samples

Source	Class (number)	Length (cm)	Weight (g)	Muscle tissue (ng/g) (n=3)									
				PFBS	PFHxA	PFHpA	PFHxS	PFOA	PFNA	PFOS	PFDA	PFUnA	PFDoA
Keya River[a]	Tilapia -1 (A1)	24	351	nd	nd	nd	14±3	109±14	3±1	1,386±45	8±0	43±5	185±8
	Tilapia -2 (A2)	26	334	nd	nd	nd	17±2	97±13	10±2	1,828±33	12±3	52±3	163±4
	Tilapia -3 (A3)	18	202	nd	4±0	nd	7±1	102±10	7±2	1,209±47	11±2	55±6	199±12
Keelung River[b]	Tilapia -1 (B1)	25	384	nd	nd	nd	nd	24±3	6±1	113±8	7±2	22±3	34±8
	Tilapia -2 (B2)	24	355	nd	nd	nd	nd	15±3	4±0	111±12	7±1	12±1	25±3
	Catfish -1 (B3)	54 (male)	886	nd	nd	nd	nd	14±3	8±1	108±5	6±1	11±2	33±2
	Catfish -2 (B4)	53 (female)	901	nd	nd	nd	nd	16±2	nd	95±6	5±0	16±4	38±5

[a] Sampling site between S4 and S5

[b] Receiving river (Keelung River) of wastewater treatment plant discharge

PFCs in Liver Tissue Samples

Table 2 Perfluoroalkyl acid (PFAA) concentrations in liver tissue samples

Source	Class (number)	Length (cm)	Weight (g)	Liver tissue (ng/g) (n=3)									
				PFBS	PFHxA	PFHpA	PFHxS	PFOA	PFNA	PFOS	PFDA	PFUnA	PFDoA
Keya River[a]	Tilapia -1 (A1)	24	351	9±2	7±2	nd	440±13	142±15	24±3	28,933±667	38±4	124±10	773±24
	Tilapia -2 (A2)	26	334	3±0	nd	2±0	327±25	114±9	55±6	23,680±352	67±8	112±9	506±21
	Tilapia -3 (A3)	18	202	4±1	5±1	nd	416±11	118±10	50±8	19,307±213	46±4	117±5	586±14
Keelung River[b]	Tilapia -1 (B1)	25	384	nd	nd	nd	4±1	111±7	12±2	258±17	16±4	60±3	130±9
	Tilapia -2 (B2)	24	355	nd	nd	nd	nd	108±13	12±4	260±11	17±3	45±6	72±5
	Catfish -1 (B3)	54 (male)	886	nd	nd	nd	nd	48±8	8±2	110±13	10±1	25±2	51±6
	Catfish -2 (B4)	53 (female)	901	nd	nd	nd	nd	61±3	11±1	133±13	10±0	29±2	48±3

[a] Sampling site between S4 and S5

[b] Receiving river (Keelung River) of wastewater treatment plant discharge

Association Among Serum Perfluoroalkyl Chemicals, Glucose Homeostasis, and Metabolic Syndrome in Adolescents and Adults

Lin et al., Diabetes Care 2009; 32: 702-7.

Table 2—*Linear regression coefficients with 1-unit increase in log PFCs in adolescents and adults*

	β coefficient			
	Log PFHS	Log PFNA	Log PFOA	Log PFOS
Adolescent				
Glucose				
Model 1	−0.02 ± 0.03	0.04 ± 0.04	−0.04 ± 0.05	−0.03 ± 0.06
Model 2	−0.02 ± 0.03	0.05 ± 0.05	−0.04 ± 0.05	−0.04 ± 0.06
Model 3	−0.01 ± 0.03	0.07 ± 0.04	−0.03 ± 0.05	−0.03 ± 0.06
Log insulin				
Model 1	0.02 ± 0.04	−0.09 ± 0.05	0.05 ± 0.08	0.06 ± 0.07
Model 2	0.03 ± 0.04	−0.10 ± 0.05	0.07 ± 0.09	0.07 ± 0.07
Model 3	0.06 ± 0.03	−0.10 ± 0.05*	0.08 ± 0.07	0.15 ± 0.08
Log HOMA-IR				
Model 1	0.02 ± 0.04	−0.09 ± 0.05	0.04 ± 0.08	0.05 ± 0.07
Model 2	0.02 ± 0.05	−0.09 ± 0.05	0.06 ± 0.09	0.07 ± 0.07
Model 3	0.05 ± 0.03	−0.08 ± 0.04	0.08 ± 0.05	0.15 ± 0.07
Log β-cell function				
Model 1	0.03 ± 0.04	−0.12 ± 0.07	0.06 ± 0.10	0.06 ± 0.08
Model 2	0.03 ± 0.04	−0.12 ± 0.06	0.08 ± 0.10	0.08 ± 0.08
Model 3	0.05 ± 0.03	−0.12 ± 0.06*	0.08 ± 0.08	0.13 ± 0.09

Adult	β coefficient			
	Log PFHS	Log PFNA	Log PFOA	Log PFOS
Glucose				
Model 1	−0.07 ± 0.09	−0.05 ± 0.04	−0.11 ± 0.10	−0.03 ± 0.08
Model 2	−0.05 ± 0.09	−0.02 ± 0.05	−0.11 ± 0.11	−0.23 ± 0.09
Model 3	−0.02 ± 0.06	0.00 ± 0.04	−0.09 ± 0.08	−0.03 ± 0.07
Log insulin				
Model 1	−0.04 ± 0.05	−0.06 ± 0.04	0.08 ± 0.04	0.13 ± 0.05*
Model 2	−0.04 ± 0.05	−0.05 ± 0.04	0.08 ± 0.04	0.13 ± 0.05*
Model 3	0.01 ± 0.03	−0.04 ± 0.03	0.07 ± 0.03*	0.14 ± 0.05†
Log HOMA-IR				
Model 1	−0.05 ± 0.05	−0.06 ± 0.04	0.06 ± 0.05	0.12 ± 0.05*
Model 2	−0.04 ± 0.05	−0.06 ± 0.05	0.07 ± 0.05	0.12 ± 0.05*
Model 3	0.00 ± 0.04	−0.04 ± 0.04	0.06 ± 0.04	0.14 ± 0.05†
Log β-cell function				
Model 1	−0.02 ± 0.04	−0.05 ± 0.03	0.09 ± 0.04*	0.14 ± 0.06*
Model 2	−0.02 ± 0.04	−0.05 ± 0.04	0.09 ± 0.04*	0.14 ± 0.06*
Model 3	0.01 ± 0.03	−0.04 ± 0.03	0.07 ± 0.03*	0.15 ± 0.05†

Data are means ± SEM. *$P < 0.05$; †$P < 0.01$. Model 1 adjusted for age, sex, race; model 2 adjusted for model 1 + health behaviors (smoking status, alcohol intake, and household income); model 3 adjusted for model 2 + measurement data (waist circumference, CRP, and insulin/glucose/HOMA) + medications.

Environmental Science & Technology

ARTICLE

pubs.acs.org/est

Associations between Levels of Serum Perfluorinated Chemicals and Adiponectin in a Young Hypertension Cohort in Taiwan

Chien-Yu Lin,[†,‡] Li—Li Wen,[§] Lian-Yu Lin,[∥] Ting-Wen Wen,[⊥] Guang-Wen Lien,[⊥] Chia-Yang Chen,[#] Sandy H.J. Hsu,[▽] Kuo-Liong Chien,[○] Fung-Chang Sung,[◆] Pau-Chung Chen,[*,⊥] and Ta-Chen Su[*,∥]

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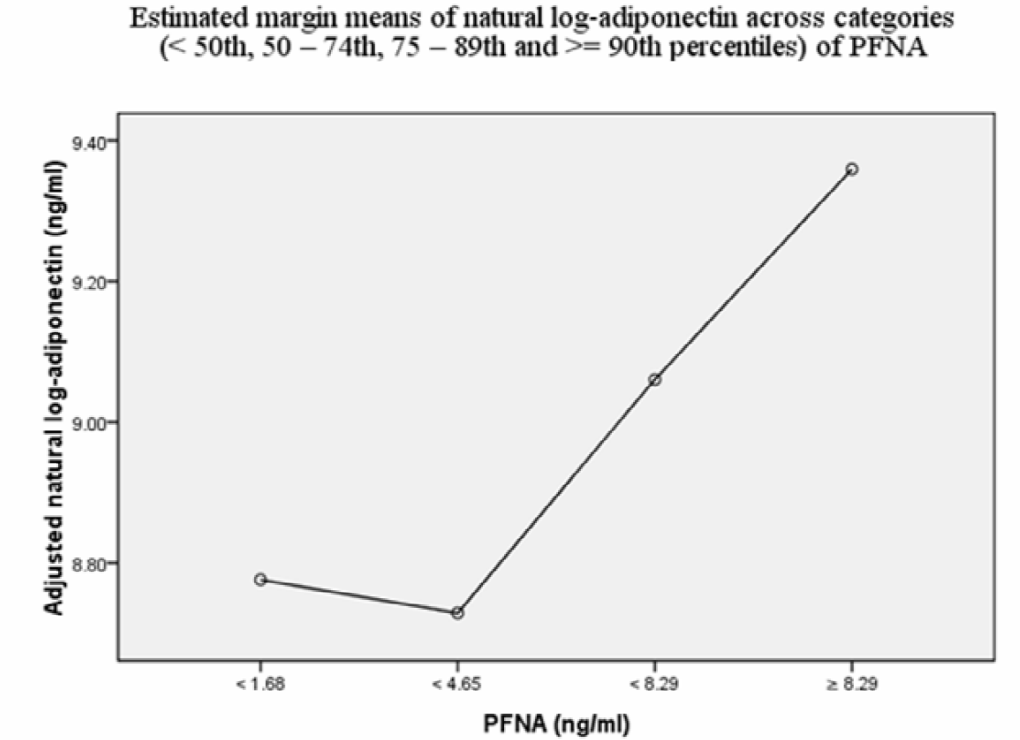
[‡]School of Medicine, Fu Jen Catholic University, Taipei County 242, Taiwan

[§]Department of Clinical Laboratory, En Chu Kong Hospital, New Taipei City 237, Taiwan

[∥]Department of Internal Medicine, National Taiwan University Hospital, Taipei 100, Taiwan

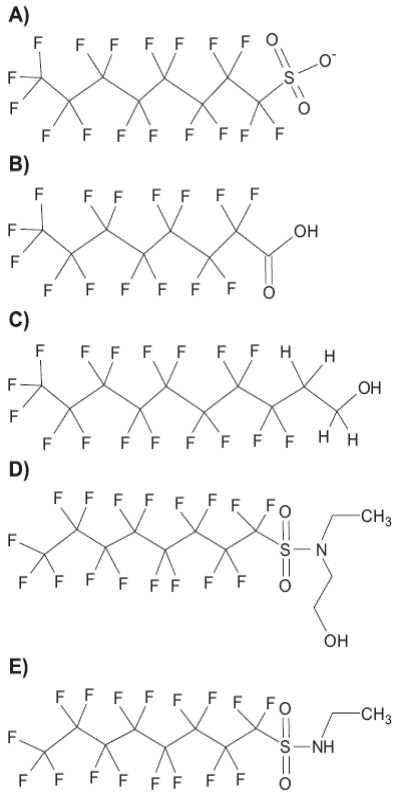
[⊥]Institute of Occupational Medicine and Industrial Hygiene, College of Public Health, National Taiwan University, Taipei 100, Taiwan



Model of the endocrine systems targeted by endocrine-disrupting chemicals

Perfluorinated chemicals (PFCs)

PFNA (perfluorononanoic acid)



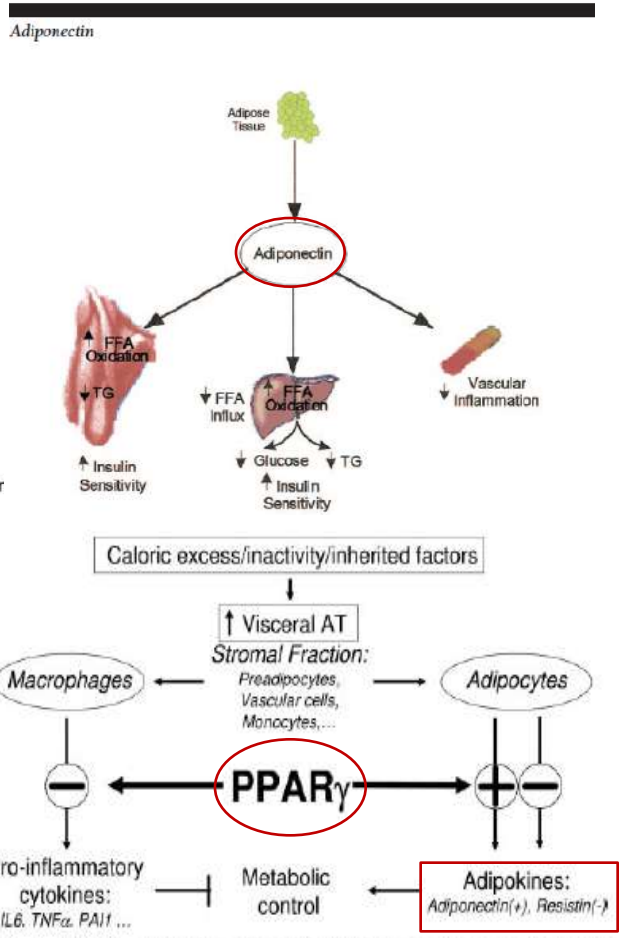


FIG. 6. PPARγ activation. Beneficial effects on both macrophages and visceral adipocytes in adipose tissue (Refs. 14, 15, 32). AT, Adipose tissue.

Diamanti-Kandarakis E et al. Endocrine Reviews 2009;30:293-342

ENDOCRINE REVIEWS

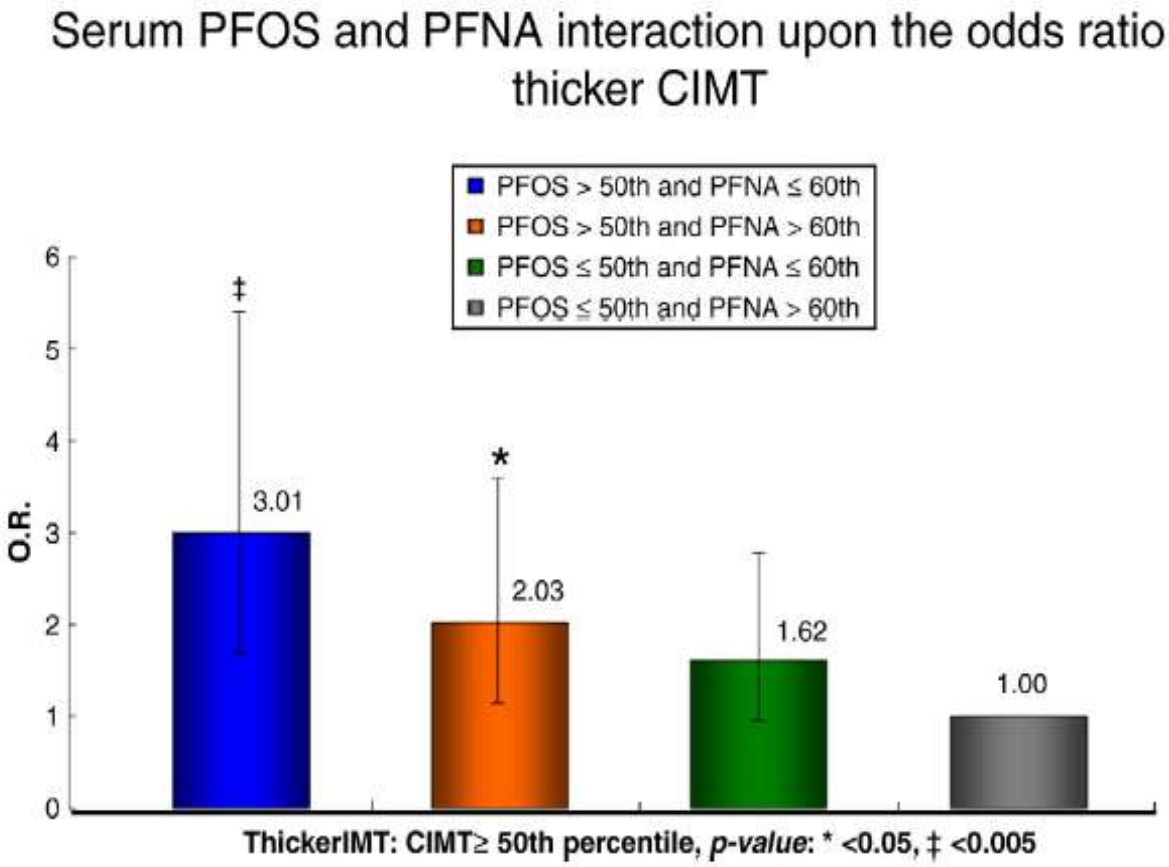
International Journal of Cardiology 168 (2013) 3309–3316

Contents lists available at ScienceDirect

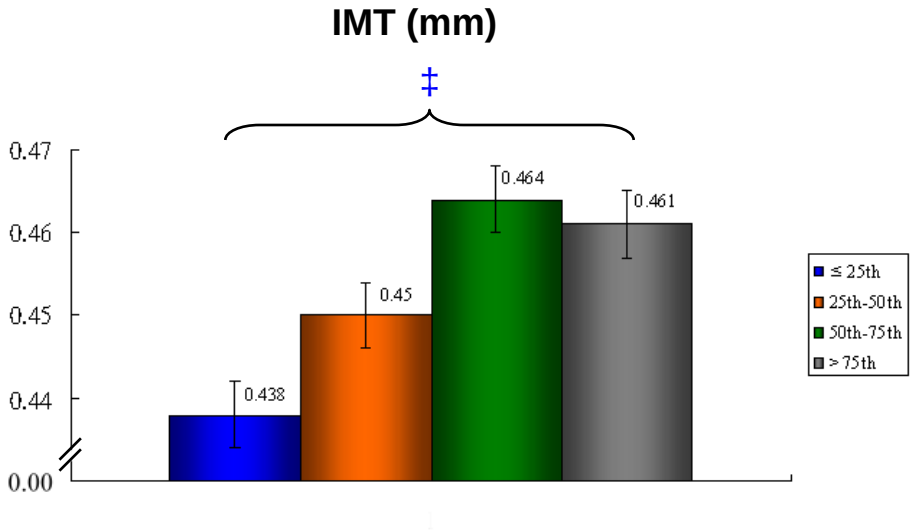
International Journal of Cardiology

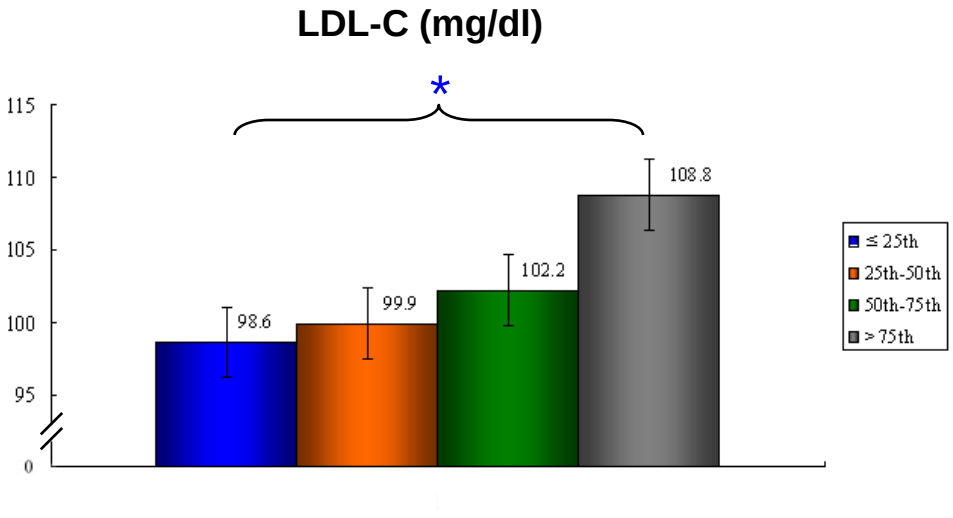
journal homepage: www.elsevier.com/locate/ijcard

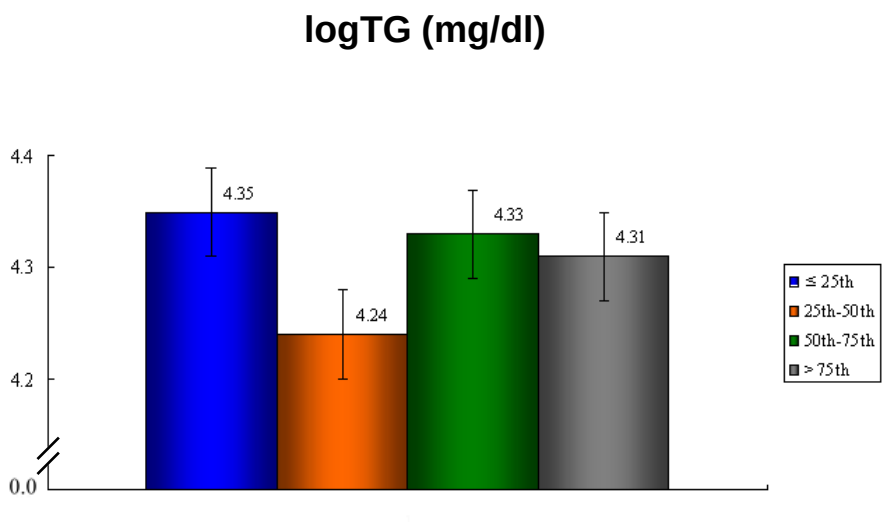
Association between levels of serum perfluorooctane sulfate and carotid artery intima–media thickness in adolescents and young adults

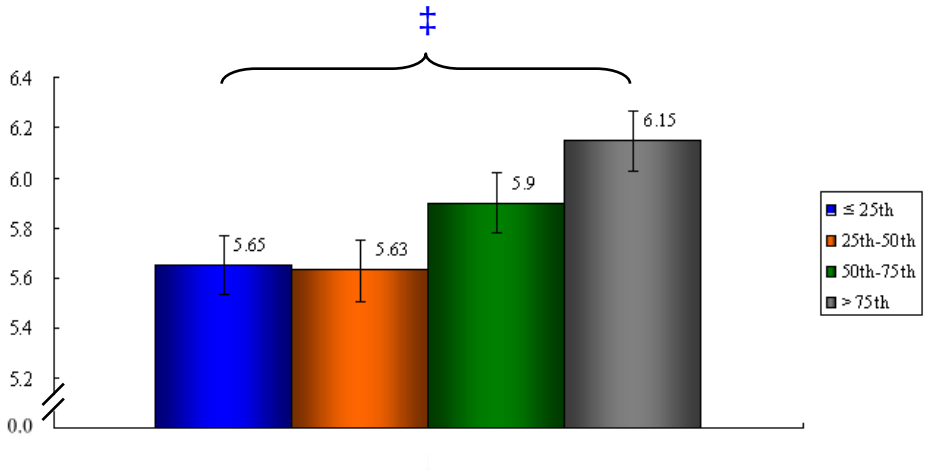


Mean and standard error of unadjusted cardiovascular risk factors across categories of PFOS in linear regression models (n = 644)



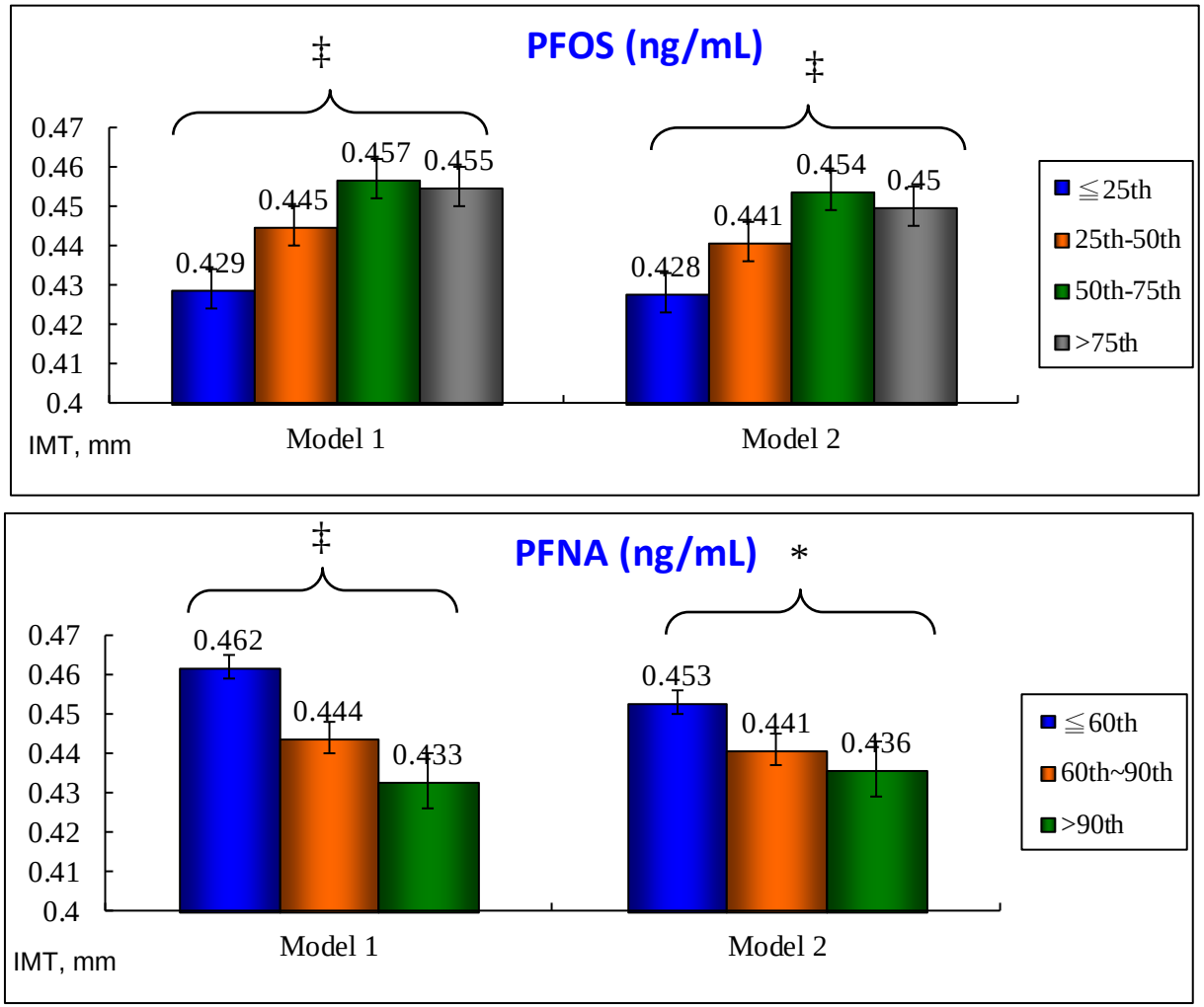






p-value: * <0.05, † <0.01, ‡ <0.005

Table 4. Carotid IMT across different categories of serum PFOS and PFNA level in linear regression models



Model 1: adjusted for age, gender

Model 2: adjusted for age, gender, smoking status, SBP, BMI, LDL-C, TG, hs-CRP, HOMA

p-value for these parameters * P <0.05, † <0.01, ‡ <0.005

Contents lists available at ScienceDirect

Environment International

journal homepage: www.elsevier.com/locate/envint

Serum perfluorinated chemicals, glucose homeostasis and the risk of diabetes in working-aged Taiwanese adults ☆

Ta-Chen Su [a,b,*,1], Chin-Chi Kuo [c,d,e,1], Juey-Jen Hwang [a], Guang-Wen Lien [b], Ming-Fong Chen [e,f], Pao-Chung Chen [b,g]

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[b] Institute of Occupational Medicine and Industrial Hygiene, National Taiwan University College of Public Health, Taipei, Taiwan
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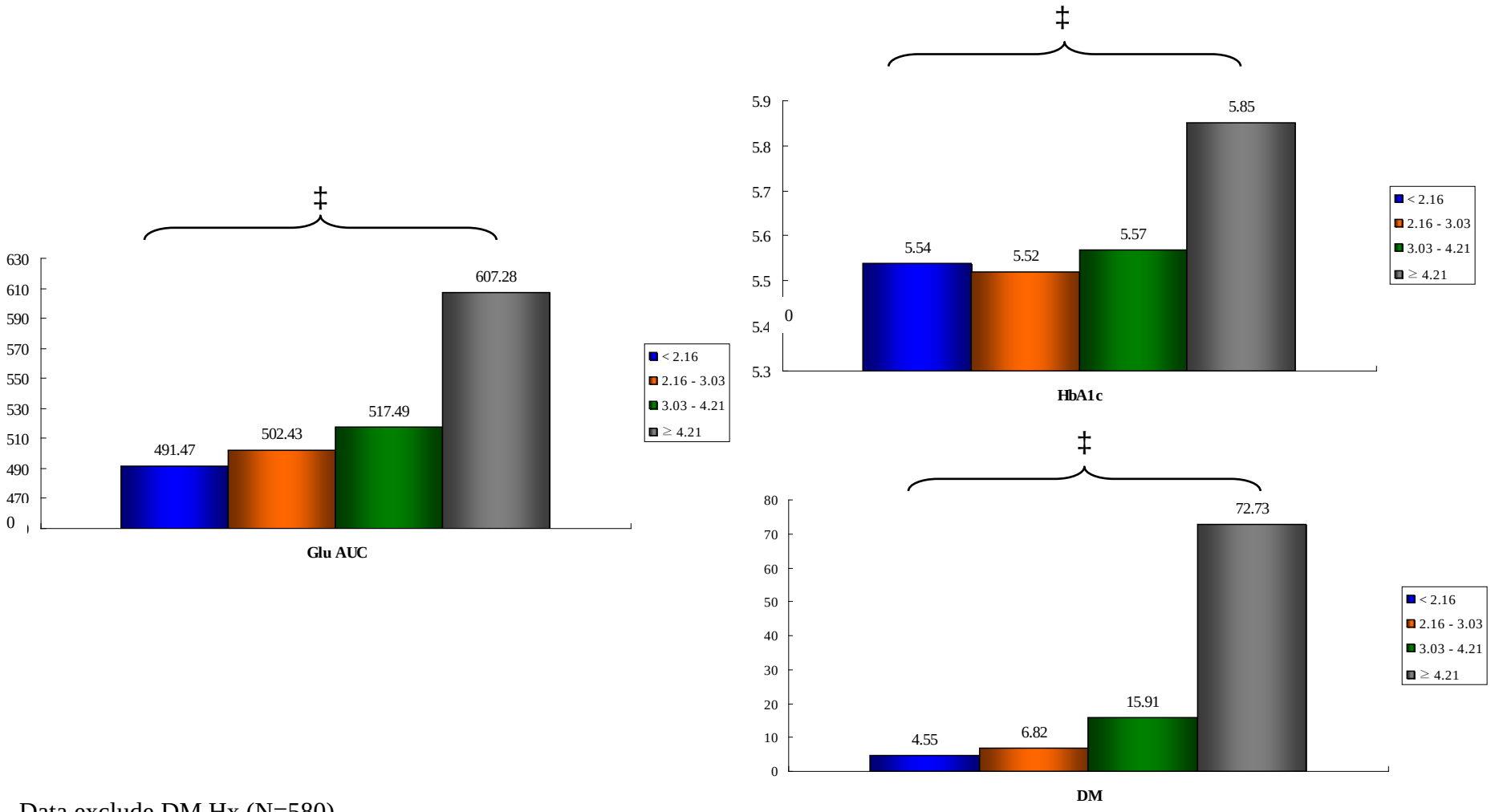
[d] Kidney Institute and Division of Nephrology, Department of Internal Medicine, China Medical University Hospital, College of Medicine, China Medical University, Taichung, Taiwan
[e] Clinical Outcome Research and Training Center, China Medical University Hospital, College of Medicine, China Medical University, Taichung, Taiwan
[f] Cardiovascular Center, China Medical University Hospital, College of Medicine, China Medical University, Taichung, Taiwan
[g] Department of Environmental and Occupational Medicine, National Taiwan University Hospital, Taipei, Taiwan

Su et al., Environmental International 2016 March

Material and Methods

- Between 2009 and 2011, 592 adults aged 35–65 years who attended a cohort study of work- and environment-related cardiovascular diseases as the control subjects of acute CHD in National Taiwan University Hospital.
- 571 middle-aged (age range, 20–60 years old) adults without clinical diabetes (fasting levels < 7.0 mmol/L) or known history of CHD or stroke completed a **standard 2-h oral glucose tolerance test** (OGTT) (75-g glucose in 300 mL water) and had **plasma PFCs** measurements were included in this analysis.

Figure 1. Trend Test of Glycemic Indices According to Quartile Distribution of Serum PFOS Levels

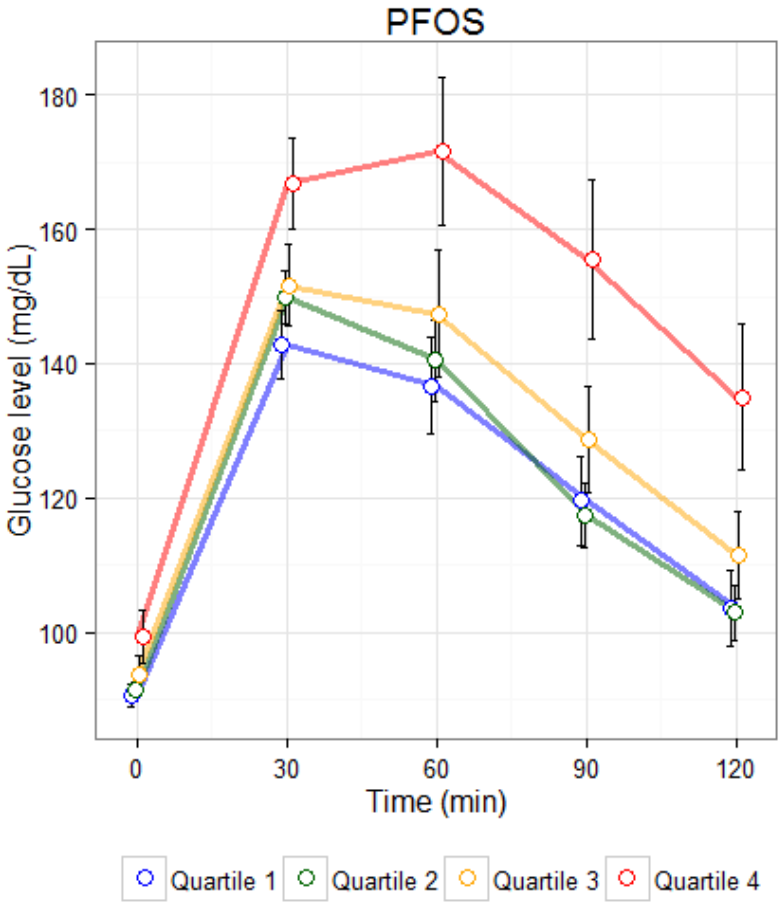


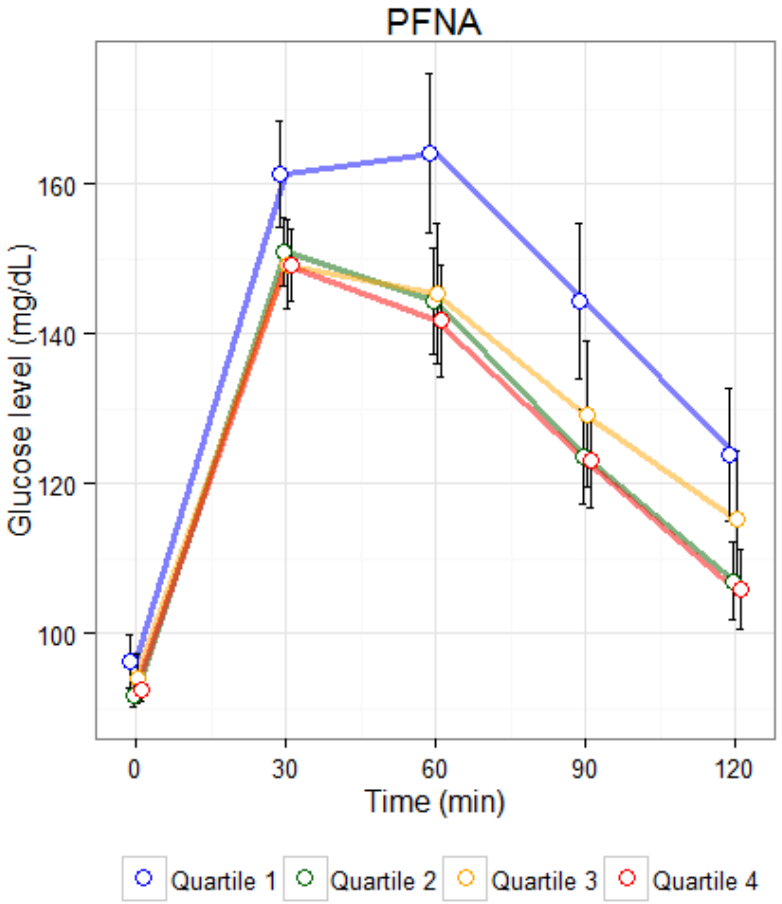
Data exclude DM Hx (N=580)

Glu AUC and HbA1c were adjusted for age, gender, BMI, hypertension, hypercholesterolemia, smoking, drinking and individual income.

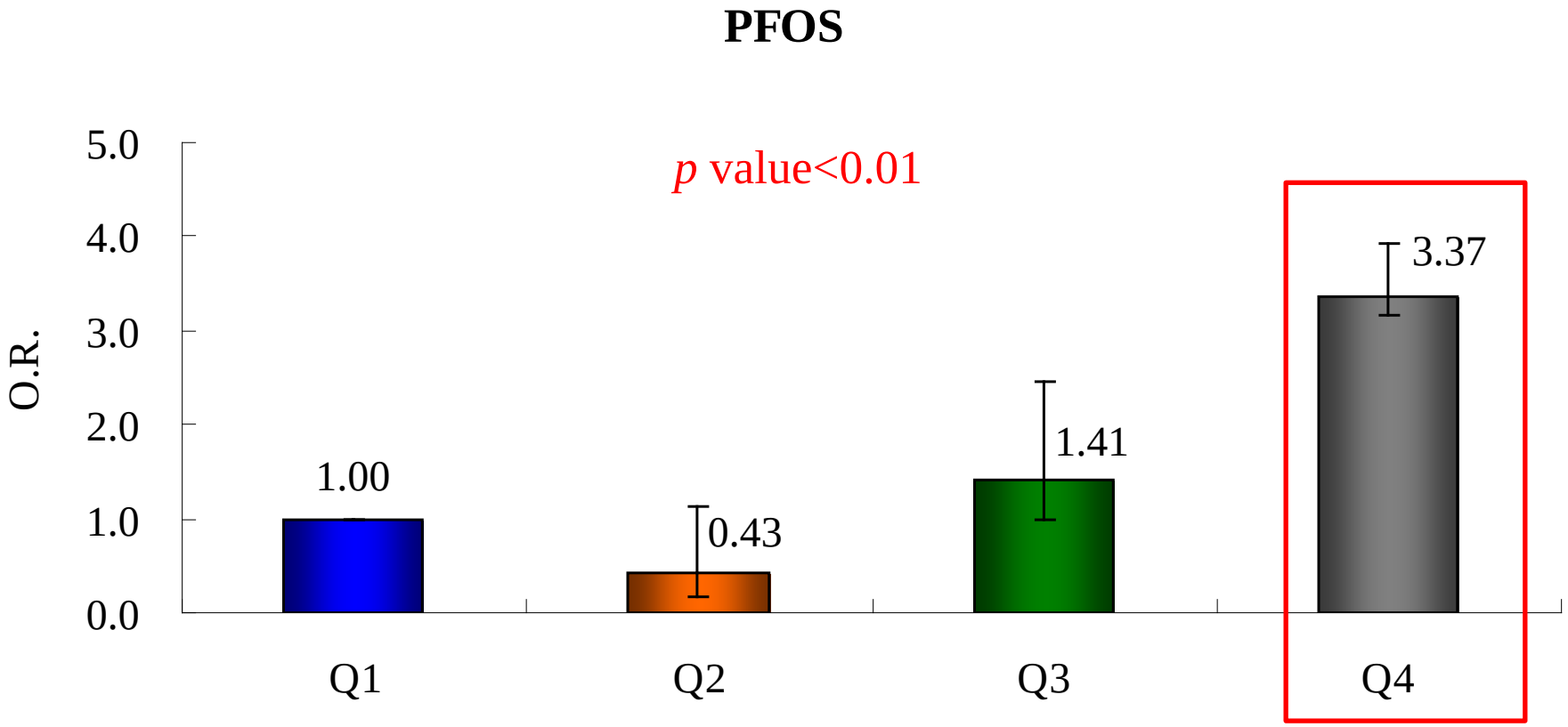
p-value for these parameters * P <0.05, † <0.01, ‡ <0.005

OGTT results and PFOS, PFNA





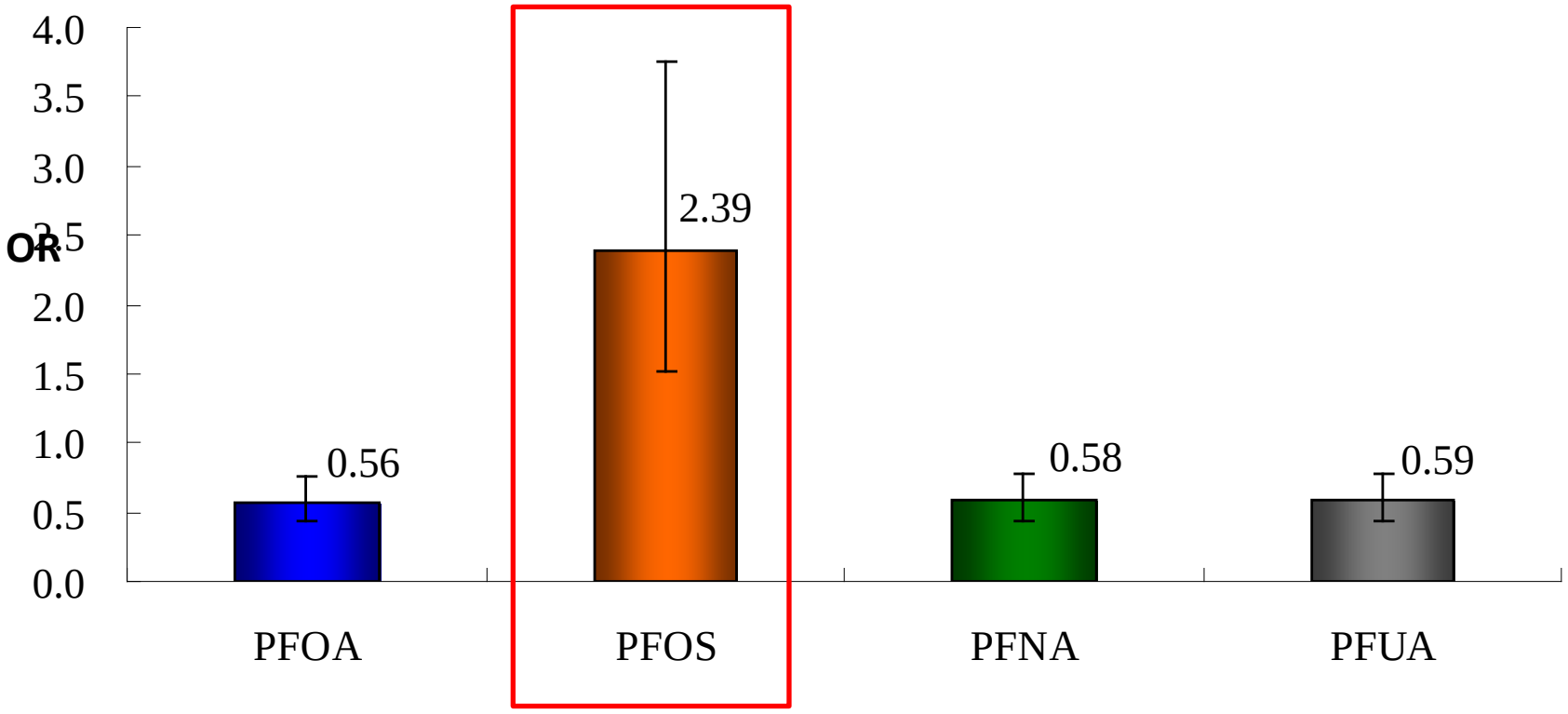
Risk of Type 2 Diabetes for Quartile Increase in PFCs



After adjusting associated variables.

Q1: <2.4 ng/ml, Q2: 2.4-3.2 ng/ml, Q3: 3.2-4.8 ng/ml, Q4: >4.8 ng/ml.

Risk of Type 2 Diabetes for every doubling increase in PFCs



After adjusting associated variables.

Environment International 94 (2016) 292–299

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journal homepage: www.elsevier.com/locate/envint

The association of carotid intima-media thickness with serum Level of perfluorinated chemicals and endothelium-platelet microparticles in adolescents and young adults

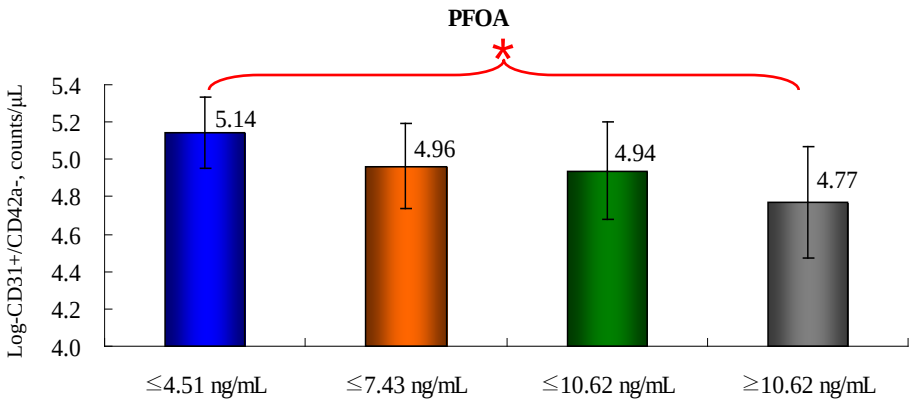
Chien-Yu Lin [a,b], Pau-Chung Chen [c,d,e], Shyh-Chyi Lo [f], Pao-Ling Torng [g], Fung-Chang Sung [h], Ta-Chen Su [c,i,*]

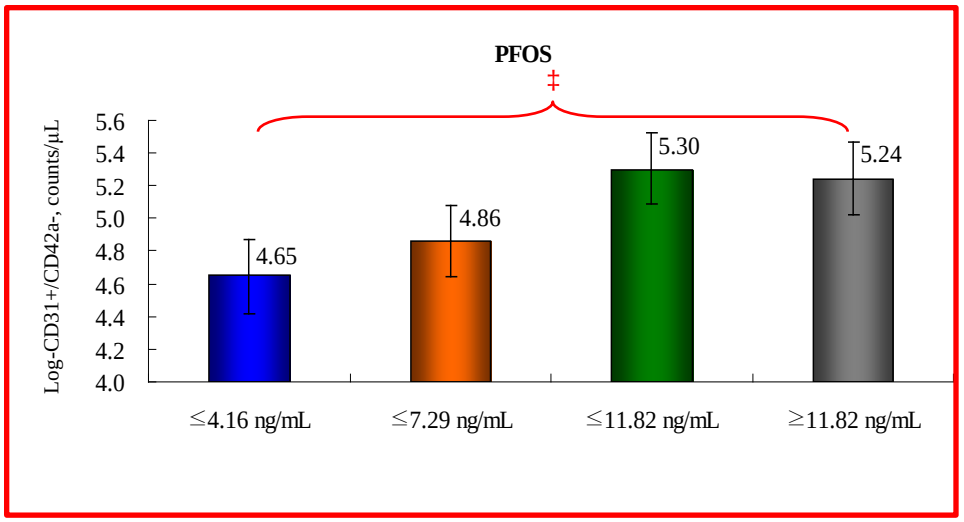
[a] Department of Internal Medicine, En Chu Kong Hospital, New Taipei City 237, Taiwan
[b] School of Medicine, Fu Jen Catholic University, New Taipei City 242, Taiwan
[c] Institute of Occupational Medicine and Industrial Hygiene, College of Public Health, National Taiwan University, Taipei 10020, Taiwan
[d] Department of Public Health, College of Public Health, National Taiwan University, Taipei 10020, Taiwan
[e] Department of Environmental and Occupational Medicine, National Taiwan University College of Medicine and National Taiwan University Hospital, Taipei 10002, Taiwan
[f] Department of Laboratory Medicine, National Taiwan University Hospital, Taipei 10002, Taiwan
[g] Department of Obstetrics and Gynecology, National Taiwan University Hospital, Taipei 10002, Taiwan
[h] Department of Health Services Administration, College of Public Health, China Medical University, Taichung 404, Taiwan
[i] Department of Internal Medicine and Cardiovascular Center, National Taiwan University Hospital, Taipei 10002, Taiwan

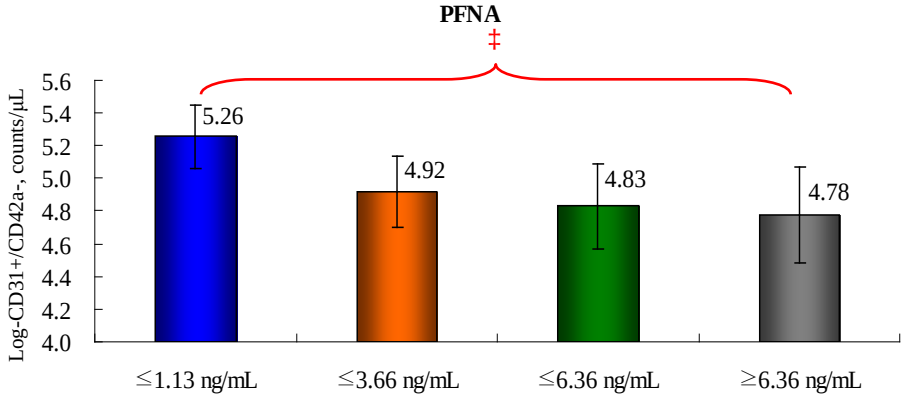
and 8-OHdG. In conclusion, we found the positive association between PFOS and CIMT that was more evident when serum levels of EMPs (CD31 +/CD42a −) and PMPs (CD31 +/CD42a +) were elevated. Further studies are warranted to investigate the causal inference of PFOS exposure on endothelial cell damage and atherosclerosis.

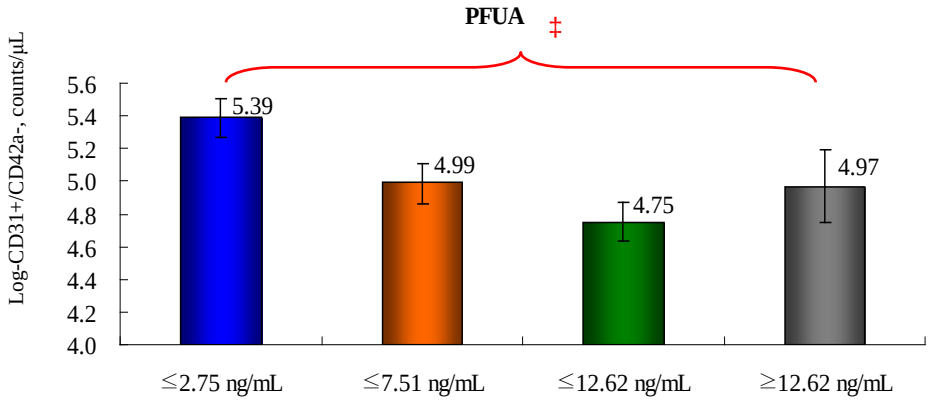
Environment International 94 (2016), 292–299

Figure 1. Mean and 95% C. I. of adjusted markers of EMPs across categories of PFCs in linear regression models (n = 848).





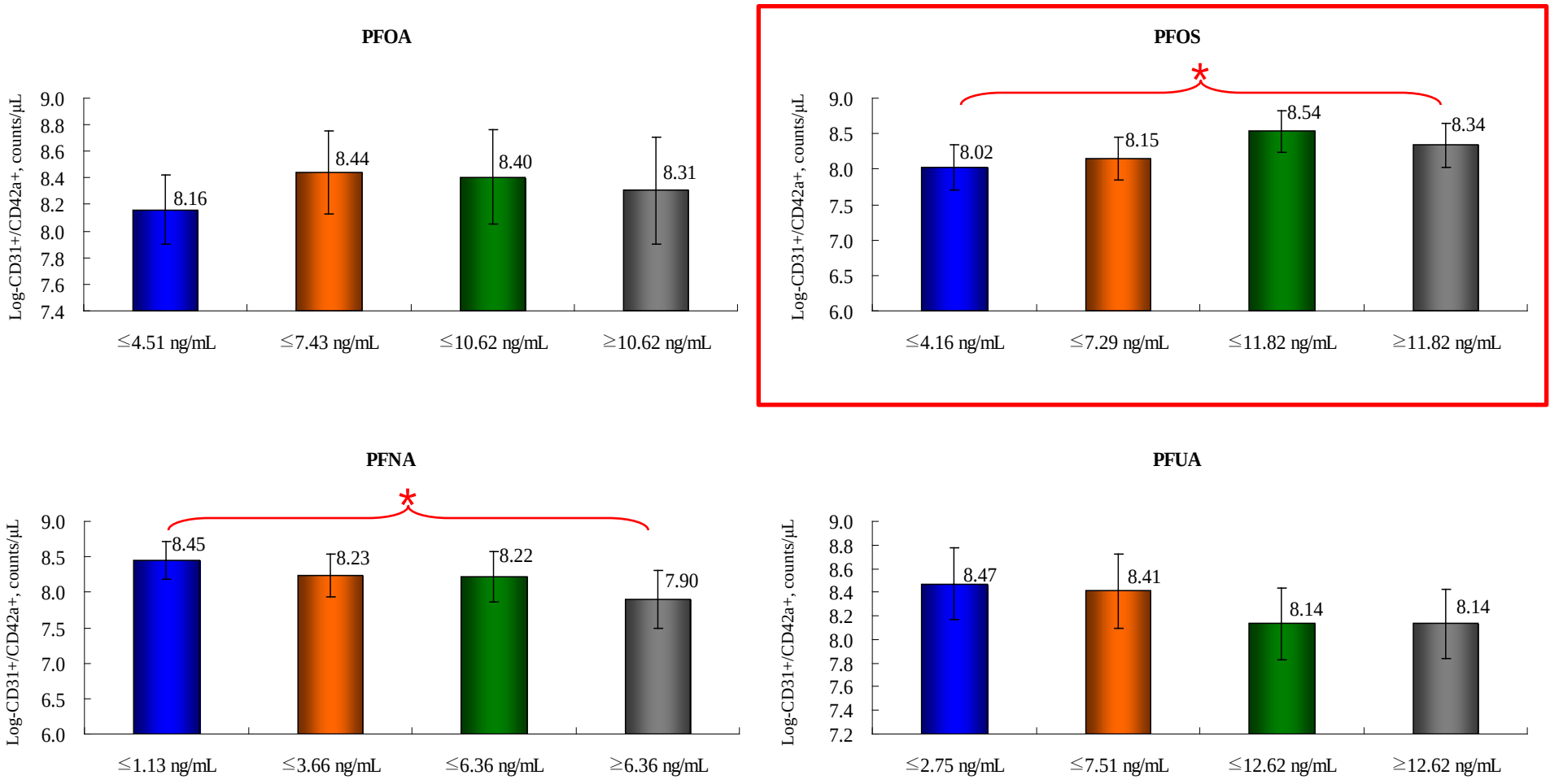




p-value: * <0.05, † <0.01, ‡ <0.005

Adjusted for age, gender and other risk factors (smoking status, body mass index, systolic blood pressure, low density lipoprotein, triglyceride, homeostasis model assessment of insulin resistance, and high sensitivity C-reactive protein).

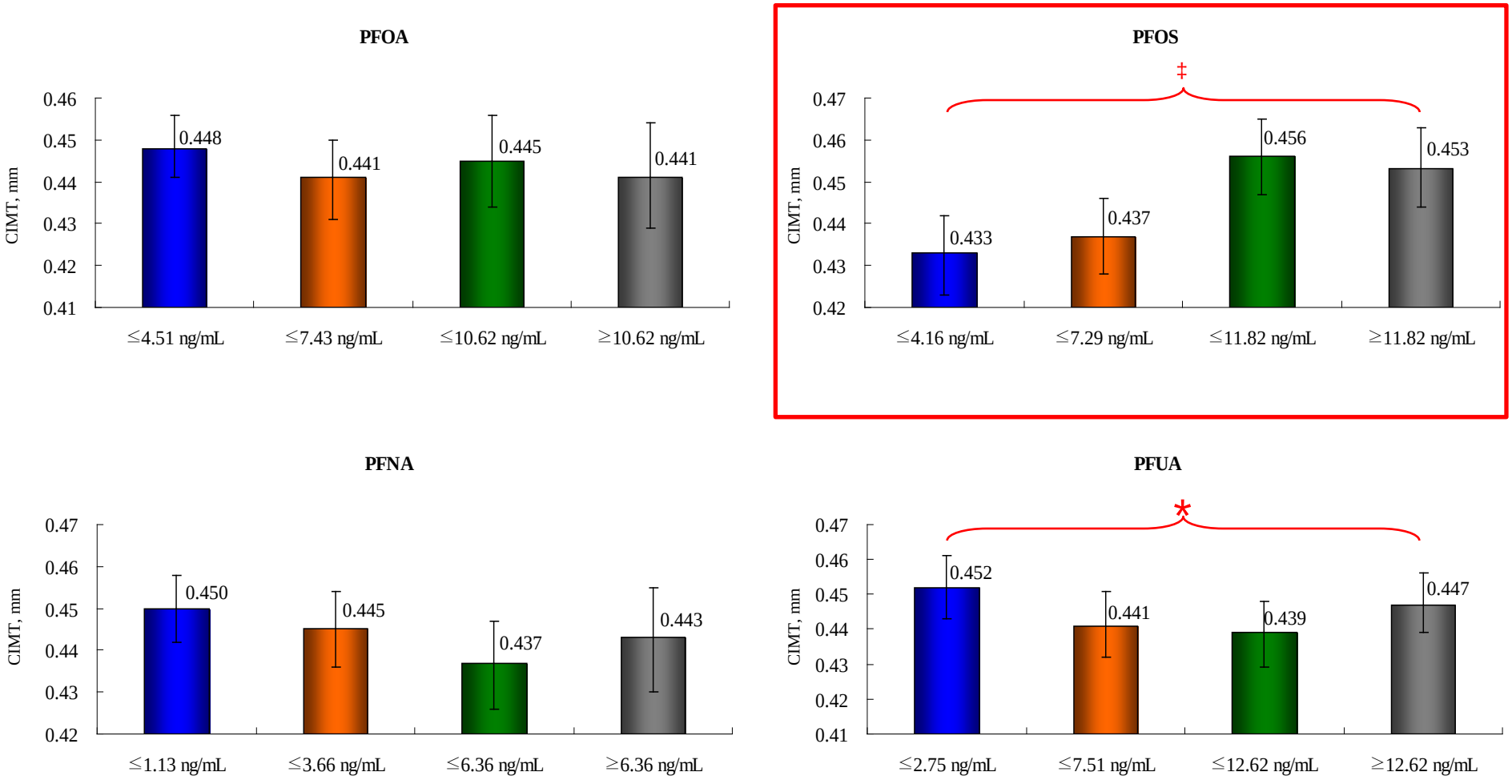
Figure 2. Mean and 95% C. I. of adjusted markers of PMPs across categories of PFCs in linear regression models (n = 848).



p-value: * <0.05, † <0.01, ‡ <0.005

Adjusted for age, gender and other risk factors (smoking status, body mass index, systolic blood pressure, low density lipoprotein, triglyceride, homeostasis model assessment of insulin resistance, and high sensitivity C-reactive protein).

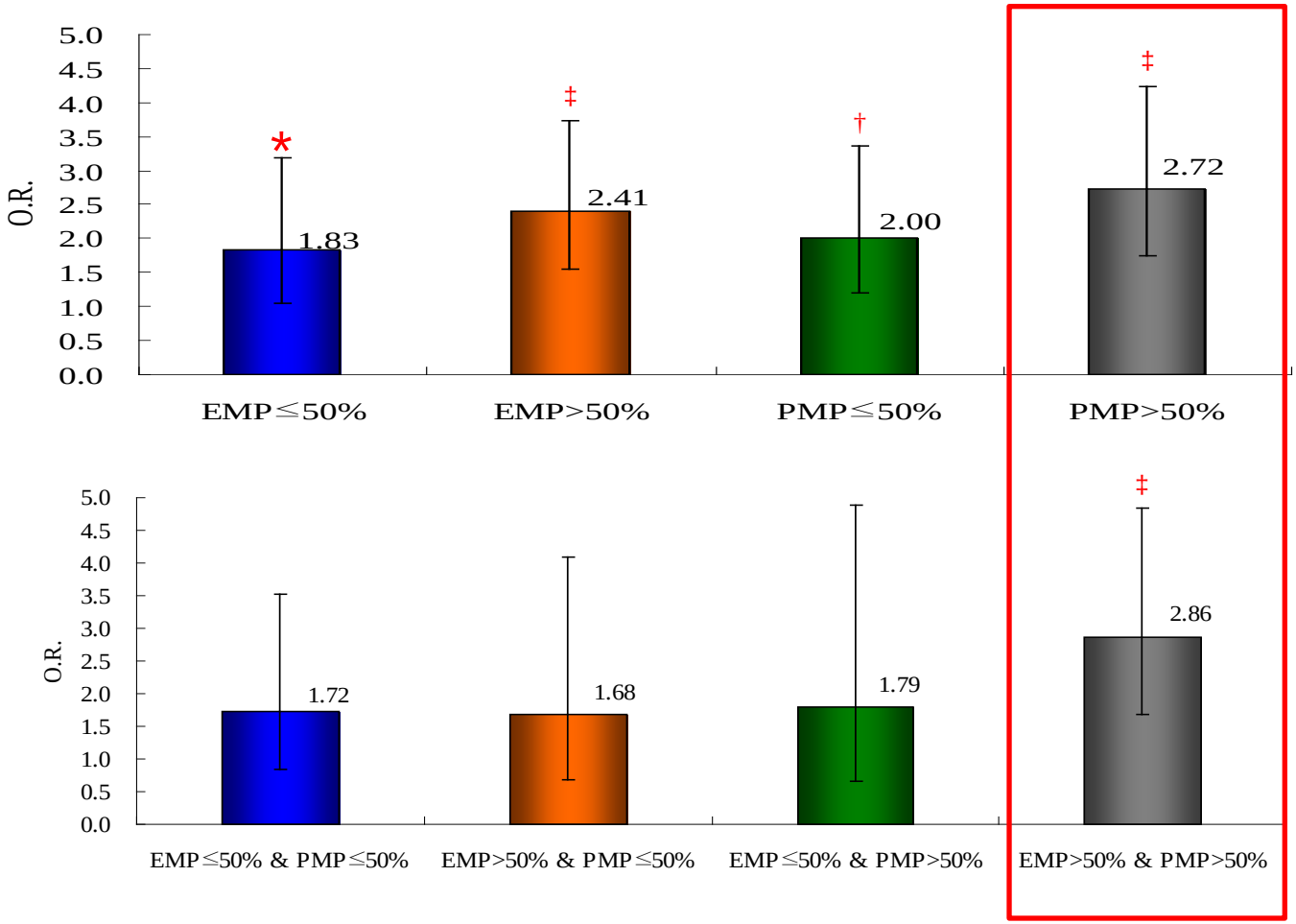
Figure 4. Mean and 95% C. I. of adjusted markers of CIMT across categories of PFCs in linear regression models (n = 848).



p-value: * <0.05, † <0.01, ‡ <0.005

Adjusted for age, gender and other risk factors (smoking status, body mass index, systolic blood pressure, low density lipoprotein, triglyceride, homeostasis model assessment of insulin resistance, and high sensitivity C-reactive protein).

Figure 5. Odds ratios (ORs) (95% C.I.) of thicker CIMT (greater than 50th percentile) with higher serum PFOS concentration (greater than 50%) by different categories of EMPs and PMPs concentrations.



p-value: * <0.05, † <0.01, ‡ <0.005

Adjusted for age, gender, smoking status, body mass index, systolic blood pressure, low density lipoprotein, triglyceride, homeostasis model assessment of insulin resistance, and high sensitivity C-reactive protein.

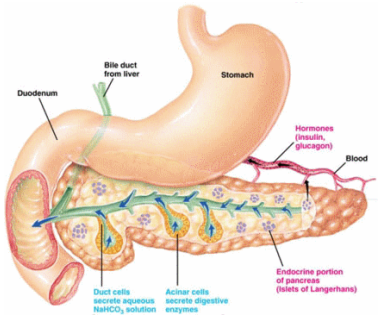
PFOS

SBP

BMI

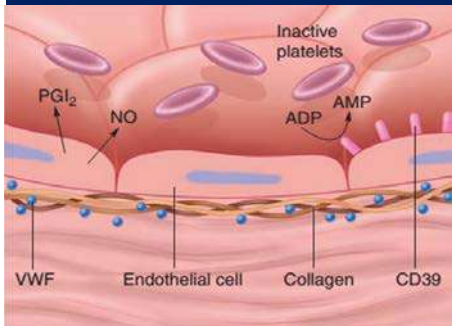
Waist

Pancreas



(https://www.webnat.com/articles/Pancreas.asp)

Platelet & Endothelial cells



(http://slideplayer.com/slide/10768411/)

Diabetes mellitus
Glucose

Environ Int., 2016

Endothelial microparticles

Platelet microparticles

Environ Int., 2016

?

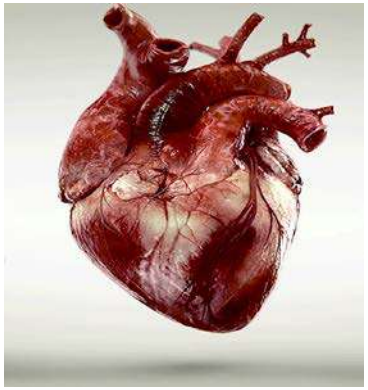
(http://www.wisegeek.org/what-is-vasoconstriction.htm)

Carotid IMT ↑

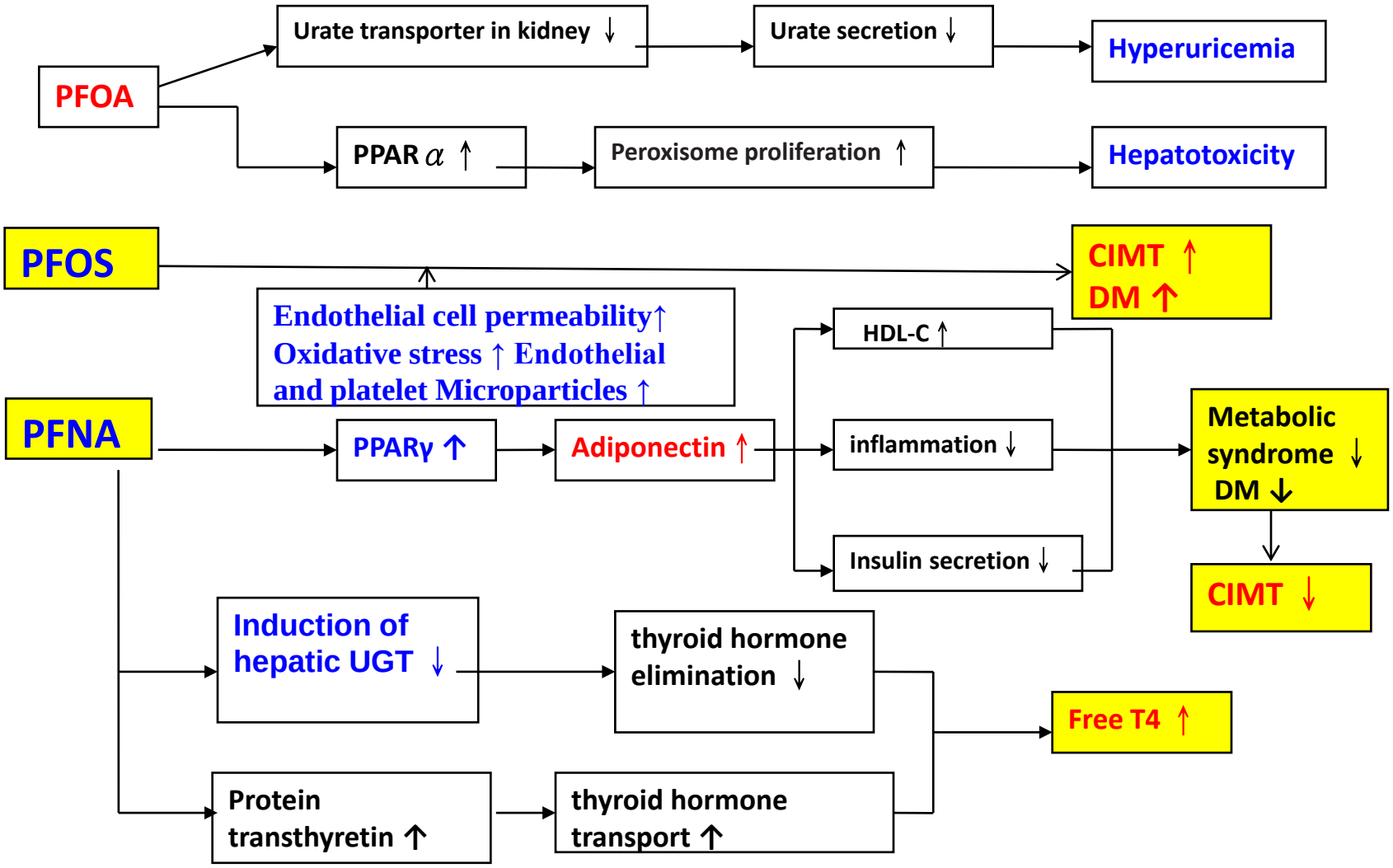
Environ Int., 2016

IJC, 2013

CHD



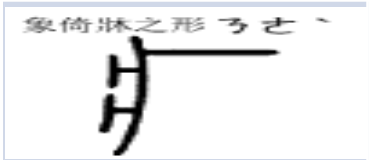
Proposed Mechanism of PFCs on Health



Conclusions

- Plasticizers and PFCs are common pollutants around us.
- **The diabetogenic and atherogenic potentials of DEHP and PFOS was demonstrated in our series of studies.**
- How to prevent exposure to DEHP and PFOS in our daily life and dietary habits are very important for primary prevention of diabetes and cardiovascular disease.

病（Diseases)

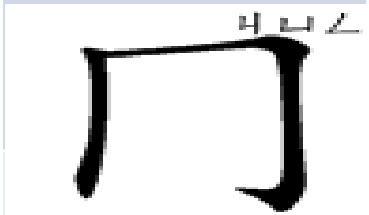


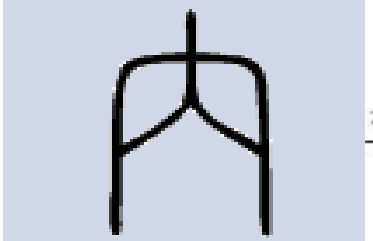
象倚牀之形

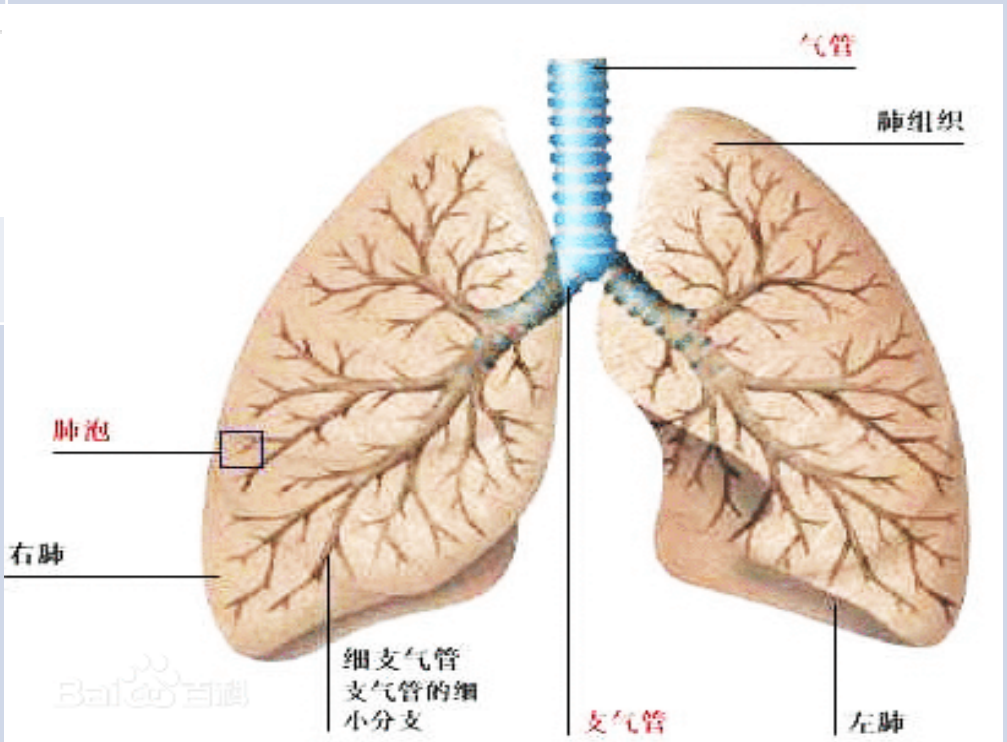
主

一是【橫線】
Transverse line

由東向西【東西】向是也
春播秋收 **(East to West)**
所以說**吃東西(Food)** 不說吃南北







左肺＋右肺
→冂（Door）
氣管→人
細枝氣管如同
樹枝不斷繁衍
人亦如是
肺在身體裡
∴為內
∵吃東西入內
→病→倚牀

You inhale bad air and eat contaminated food and you get the diseases.

Many Thanks for your attention!!

E-mail: tachensu@ntu.edu.tw