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Master thesis

一、母親手機使用與孩童神經認知行為發展
Exposure to maternal mobile phone use and children's neurocognitive development
二、臍帶血中酚類化合物與胎兒生長發育之相關性
Association between phenolic compounds in umbilical cord blood and child growth

吳佩璇

Pei-Hsuan Wu

指導教授：陳保中 博士

Advisor: Pau-Chung Chen, Ph.D.

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「終於要開始寫致謝了！」，這大概是這時候最貼切也最想大喊的一句話。這個部分終於可以比較輕鬆的書寫，也不用再為了內容而想破頭，唯一要擔心的反而是漏掉任何一位我要感謝的人。碩班這兩年過得很充實也很忙碌，很快地，兩年的碩班生活即將告一段落，真的要感謝很多鼓勵和幫助我的人，因為你們的陪伴，讓我的碩班生活很精彩。

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佩璇 民國 101 年 6 月

Part I

一、母親手機使用與孩童神經認知行為發展

Exposure to maternal mobile phone use and children's neurocognitive development

中文摘要

研究背景與目的：現今社會中手機使用已越趨頻繁，然而手機之電磁波暴露對於孩童健康發展之不良影響仍有爭議。少數研究已探討手機暴露與孩童神經行為發展間之相關性，但目前仍未有研究探討手機暴露與孩童智力之影響。本研究之目的為，先描述從妊娠期到產後一年之母親手機使用情形，並進一步探討其手機使用量和孩童神經行為發展與智力間之影響。

材料與方法：自 2004 年 5 月至 2005 年 2 月間，收集來自台灣北部地區不同醫療院所的產婦及其新生兒為研究對象,最終納入133對的產婦及其新生兒進行分析。我們使用「嬰幼兒綜合發展測驗」(Comprehensive Developmental Inventory for Infants and Toddlers, 簡稱 CDIIT) 以及「魏氏兒童智力量表第四版」(Wechsler Intelligence Scale for Children-Fourth edition, 簡稱 WISC-IV) 評估孩童之神經行為發展與智力分數。另外，我們也使用「瑞文氏圖形推理測驗」(Standard Progressive Matrices, 簡稱 SPM)評估母親的智力。藉由自填式問卷評估母親的手機使用量，再使用迴歸模式(regression model)進行統計分析。

結果：本研究發現，從妊娠期至產後一年，多數的母親每天手機的接聽通數皆少於 3 通，且每通電話之通話時間皆少於 3 分鐘。研究結果並未發現手機暴露對於孩童的神經行為發展有不良之影響。

結論：目前仍未有明確的證據足以證明手機之暴露會造成孩童神經行為之不良影響，未來仍需要更多的研究針對此議題進行探討。

關鍵字：手機，孩童神經行為發展，孩童智力

Abstract

Background and objective: In today's world, mobile phone use has been commonly and increased rapidly in many countries. Health effects of exposure to mobile phone use on the children are controversial. An association between exposure to mobile phone use and children's neurodevelopment was reported but there are still no studies investigating the effect on children's intelligence. We described the maternal mobile phone use from pregnancy to 12 months, and examined the association between exposure to mobile phone use and children's neurocognitive development in young children from the general population in Taipei, Taiwan.

Methods: The study was a part of the Taiwan Birth Panel Study. A total of 133 pairs of parents and their singleton child were recruited into this study. We used the Comprehensive Developmental Inventory for Infants and Toddlers (CDIIT) and Wechsler Intelligence Scale for Children-Fourth edition (WISC-IV) to assess child neurocognitive development. We also assessed the intelligence of the mothers using the Standard Progressive Matrices Plus (SPM^{+}). Mothers completed the questionnaires to report their mobile phone use. Regression model was used to estimate the association between mobile phone exposure and children's neurocognitive development.

Results: Most of the mothers took less than 3 phone calls per days, and the call duration

was less than 3 minutes in each phone call from pregnancy to 12 months. In this study, we found no significant association between maternal mobile phone use and neurocognitive development in young children.

Conclusions: There is no convincing evidence that maternal mobile phone use had an adverse effect on the neurocognitive development of children. Further studies are needed to explore the association of mobile phone use and children's neurocognitive development.

Key words: prenatal exposure, mobile phone, neurocognitive development, young children

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Introduction

In today's world, mobile phone use has been commonly and increased rapidly in many countries. In globally, there were nearly 5 billion mobile phone subscribers in 2010 (International Telecommunication Union 2010). And then in Taiwan, there were more than 90% people have mobile phone (Directorate-General of Budget, Accounting and Statistics, Executive Yuan 2010). Therefore, the risk of exposure to radiofrequency fields is increasingly, especially in children. Children are more susceptible to radiofrequency fields, and may be more vulnerable than adults because of their developing nervous systems. Furthermore, children expose the radiofrequency fields at earlier age, and they will have longer lifetime of exposure than adults (Divan et al., 2010; Kheifets et al., 2005).

The World Health Organization emphasized that the studies which investigate the effects of children mobile phone use on cognitive effect are high priority and necessary (World Health Organization 2007). Only few studies evaluated the association between mobile phone use and child neurodevelopment, but the results were not consistent. Divan et al. (2008) showed that prenatal and postnatal exposure to the mobile phone was associated with emotional and hyperactivity problems at 7 years of age. And another study found little evidence of maternal mobile phone use and early

neurodevelopment at 14 months (Vrijheid et al., 2010). On the other hand, some studies didn't find specific evidence for adverse effect of maternal mobile phone use on the early neurodevelopment of children (Divan et al., 2011; Divan et al., 2010).

The purpose of this study is to describe the maternal mobile phone use during pregnancy, and at postnatal ages up to 12 months. Furthermore, the adverse developmental effects of mobile phone use on the children are scanty and contentious. Another purpose of this study is to examine the association between prenatal and postnatal mobile phone use and early-childhood neurodevelopment and intelligence in young children.

Materials and Methods

Study population

This study was based on the Taiwan Birth Panel Study (TBPS), a prospective cohort study, which was conducted between April 2004 and January 2005 (Hsieh et al., 2011). Informed consents were obtained from study participants before delivery to collect maternal blood, umbilical cord blood, and questionnaires. After delivery, all subjects were interviewed by trained interviewers to obtain the information during prenatal life style. Then, we followed up these children at 2, 5 and 7 years old. The postnatal questionnaires were completed by main caregivers in each follow-up. Moreover, the neurodevelopment and intelligence test were conducted at the age of 2 and 7 years, respectively. The protocols used in this study were approved by the Ethical Committee of National Taiwan University Hospital.

In this study, we only included singleton infants and there were no active smoking mothers in these participants. We also excluded preterm infants, subjects who didn't complete the neurodevelopment and intelligence test at 2 and 7 years of age and subjects without mobile phone data. Finally, there were 133 subjects remained in our study.

Mobile phone exposure

At 5 years of age, we modified the questionnaires for mobile phone exposure of the Danish National Birth Cohort (DNBC) study (Danish National Birth Cohort 2010). The questionnaires focused on mobile phone use among mothers during pregnancy (three trimesters of pregnancy), and at postnatal ages up to 12 months. Mothers reported their use of mobile phone (average daily phone calls, average times spoken per phone calls), and use of hands-free equipment from pregnancy to 12 months, and the location of mobile phone during pregnancy (clothing pocket or bag). In the questionnaires, daily number of calls were divided into three groups (below 3 calls, 4 to 10 calls, and over 10 calls) and times spoken per phone calls were divided into four groups (below 1 minute, 1 to 3 minutes, 4 to 10 minutes, and over 10 minutes). In order to estimate the cumulative dose of mobile phone use, we used the median to represent each exposure group, and multiplied daily phone calls and times spoken per phone together. The dose of pregnancy was sum of three trimesters and the postnatal dose at 1-year-old was sum of 12 months per year. Therefore, the cumulate dose was used for estimating the prenatal and postnatal mobile phone exposure.

Child neurodevelopment

Child neurodevelopment was assessed at 2 years of age using the Comprehensive Developmental Inventory for Infants and Toddlers (CDIIT) (Liao and Pan, 2005). The CDIIT was designed to assess development in the area of cognitive, motor, gross motor, fine motor, language, social, and self-help. And the available age range of the CDIIT is from 3 to 71 months. The standardization used 3703 infants of aged 3 to 71 months who were randomly selected in Taiwan and the CDIIT has good test-retest reliabilities (Liao and Pan, 2005). Also, the CDIIT has the acceptable concurrent validity with the Bayley scales of Infant Development-II (BSID-II) which is commonly used in the international (Liao et al., 2005).

The assessment of the CDIIT was divided into two parts, the physical therapists and questionnaires. The cognitive and motor subtests, and part of the language subtest were individually and directly evaluated by the testers. In addition, the social and self-help subtests and some items of the language subtest were scored from the questionnaires which completed by the main caregivers. The results of the CDIIT test, developmental quotients (DQ) were obtained for the whole test (whole DQ), five subtests (cognitive DQ, motor DQ, language DQ, social DQ, and self-help DQ), as well as for the two subdomains (gross motor DQ and fine motor DQ). In the norm, the mean

DQ is 100 (Liao and Pan, 2005). According to the manual of CDIIT, a DQ of 85 or above is within normal limits, and the children whose DQ below 70 and within 70-84 were classified as delay and borderline, respectively (Liao et al., 2005).

Children's and Maternal Intelligence

We used the Chinese version of the Wechsler Intelligence Scale for Children-Fourth edition (WISC-IV) (David, 2007), the universally acknowledged tools, to evaluate the children's intelligence in 6-7 years old children. The WISC-IV has five domains of Full Scale (FSIQ), Verbal Comprehension Index (VCI), Perceptual Reasoning Index (PRI), Working Memory Index (WMI), and Processing Speed Index (PSI). The assessment of WISC-IV was tested by trained testers, and we used the age-corrected scores of 5 domains. In the norm, the mean score of the WISC-IV is 100 and the standard deviation is 15.

Mother's intelligence was assessed by the Standard Progressive Matrices Plus (SPM^+) (Raven et al., 2006). There are 60 questions in the SPM^+ test, and the subjects have to do their best to answer the most numbers of the questions in 30 minutes. The available age of SPM^+ is from 12 to adults, and full score of the SPM^+ test is 60. In the regression models, we adjusted the total score of the mother's intelligence.

Home Observation for Measurement of the Environment Inventory (HOME Inventory)

At 2 years of age, we also took the HOME Inventory to measure the caregiving environment. The Home Inventory is designed to measure the quality and quantity of stimulation and support available to a child in the home environment (Caldwell and Robert, 2003). The Infant/Toddler HOME Inventory (IT-HOME) is used for birth to age three children, and comprises 45 items clustered into six subscales: parental responsivity, acceptance of child, organization of the environment, learning materials, parental involvement, and variety of experience. For the HOME Inventory, the subjects were observed and the main caregivers were interviewed by the trained visitors. The missing data were substituted by the mode of the HOME scores in this study.

Statistical Analysis

We used linear regression models and logistic regression models to estimate the association between mobile phone use and child neurodevelopment. The maternal mobile phone use was divided into two groups, during pregnancy and birth to 12 months. According to the samples distribution, high exposure was defined as the fourth

quartile of the cumulative dose, and low exposure was defined as all other quartiles. In the logistic regression models, the cut-points of the 8 areas of the CDIIT DQ and the 5 domains of the WISC-IV test were the first quartile of the distribution.

We adjusted some potential confounders in the models, including maternal age, maternal education, family income, infant gender, lead levels in the cord blood, HOME score, prenatal ETS exposure as reported on a questionnaire. The models of postnatal mobile phone exposure, we also adjusted postnatal ETS exposure and the hours that mothers accompany with child per day. Moreover, we adjusted the maternal intelligence in the models of mobile phone use and children's intelligence. All statistical analysis was conducted with SAS 9.2.

Results

In this analysis, only 133 pairs of mothers and children had complete mobile phone use data and finished the CDIIT and the WISC-IV test. Most mothers have higher education level, and only 5% mothers consumed alcohol during pregnancy. In addition, all the infants are full-term birth and only 2 infants' birth weight below the normal limits. These subjects were from general population, the mean DQ of 8 tests of the CDIIT and the mean score of the WISC-IV are all within normal limits (Table 1, p16). Either prenatal or postnatal mobile phone use, most of the mothers took less than 3 phone calls per days, and the call duration was less than 3 minutes per call. Furthermore, more than 85% of the mothers didn't use the hands-free equipment, and 94% mothers put their phone in the bags during pregnancy (Table 2, p17). However, there were no significant findings between maternal mobile phone use and child neurodevelopment and intelligence (Table 3 and Table 4, p18 and 19).

Discussion

Our study didn't find an evidence to support that maternal mobile phone use from pregnancy to 12 months after birth were adversely affected the children's neurocognitive development. There were two studies published the similar results reporting no association between prenatal mobile phone use and early-childhood neurodevelopment at 6, 14 and 18 months (Divan et al., 2011; Vrijheid et al., 2010). However, these results were expected, and various potential confounders for neurodevelopment were analyzed and adjusted.

Most of these mothers took less than 3 phone calls per days during pregnancy, but the proportion of heavier user (≥ 4 phone calls per day) in our study is slightly higher than the population in western countries (Divan et al., 2011; Vrijheid et al., 2010; Divan et al., 2010; Divan et al., 2008). And the mothers used the mobile phone directly, only few mothers had ever used the hands-free equipment. Even though the cumulative dose was high, these children's neurodevelopment and intelligence are still within normal limits.

So far, we have no specific biologic mechanism to explain the association between mobile phone use and adverse effect on neurodevelopment. Some studies focused on the molecular and cellular effect of radiofrequency exposure. Electromagnetic frequency

may affect cell cycle and causing cell damage (Panagopoulos et al., 2007; Zmyslony et al., 2004). According to a recent letter to the editor (Hocking, 2009), Brzezinski (1997) suggested that mobile phone is close to the head when talking on, and the radiofrequency fields from a mobile phone may affect signaling in the unmyelinated nerves and in turn influence melatonin secretion. Furthermore, diverse changes in maternal metabolism or the sex hormone environment may affect development of the fetal brain leading to behavioral problems (Brzezinski, 1997). Only one animal study found that the mice exposed *in-utero* to radiofrequency were hyperactive, had decreased memory, and decreased anxiety, because the electromagnetic frequency impaired the nervous transmission (Aldad et al., 2012). But the exposure dose was used in animal study is higher and not identical to the human, the extrapolation of this animal model to humans is limited.

During pregnancy, more than 90% of the mothers put their mobile phone in the bag when not in use, so the mobile phone didn't close to the fetus. To our knowledge, the intensity of radiofrequency field would reduce with distance. In addition, the call duration per phone calls of most mothers was less than 3 minutes. Accordingly, the prenatal exposure to mobile phone use may not high enough to affect the children's neurocognitive development in this study. There are more highly educated mothers in our study, and they spend more time to accompany with children. These mothers might

take more attention and better care to their children, so the children have better neurocognitive development in the postnatal age.

An important limitation of this study is recall bias, because we used the retrospective questionnaires to estimate the past maternal mobile phone use. We considered that mobile phone use might be a habit, and the users didn't change a lot in different periods. A previous study has shown good accuracy for recalled self-reporting mobile phone use, although the individuals tend to underestimate the number of calls and overestimate the call duration (Vrijheid et al., 2006). Another limitation is that we didn't ask the children's use of mobile phone. A study found that the high risk for adverse health effects were for children who both prenatal exposure and use mobile phone directly in postnatal age (Divan et al., 2008). But in this study, mobile phone should be rarely used by these young children, so their postnatal dose of mobile phone exposure might be lower.

Conclusion

Based upon the results of this study, although the dose of maternal mobile phone use is slightly higher than other studies and using the objective tools to estimate the children's neurocognitive development. However, among these young children, we

didn’t find an evidence to support an association between maternal mobile phone use and children’s neurocognitive development. Our study focused on the 2 and 6-7 years old children and we recruited small sample size, we hope others will be able to explore this question on different age of children or in the large sample size study in the future.

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Table 1. Characteristics of the study population

Characteristic	All population (n = 133) mean ± standard deviation
Maternal characteristics	
Age (years)	33.0 ± 3.9
Maternal education (%)	
High school and below	36.1
University and above	63.9
Prenatal ETS [a] exposure (%)	24.1
SPM+ [b] total score	39.6 ± 4.5
Family characteristics	
Annual family income	
≥ NT$ 1,000,000	34.6
< NT$ 1,000,000	65.4
HOME score [c] (point)	41.2 ± 2.3
Mother accompany with child per day (hr)	7.4 ± 5.2
Infant characteristics	
Gender (%)	
Male	52.6
Female	47.4
Birth weight (g)	3279.8 ± 396.1
Gestational age (week)	39.0 ± 1.1
Lead in cord blood (μg/L)	1.26 ± 0.66
Postnatal ETS exposure (%)	31.6
CDIIT [d] (DQ [e])	
Whole Test	100.0 ± 12.1
Cognitive	99.7 ± 21.0
Language	101.8 ± 12.8
Motor	88.5 ± 11.8
Gross-motor	86.0 ± 13.7
Fine-motor	95.6 ± 10.9
Social	108.8 ± 14.8
Self-help	100.6 ± 14.1
WISC-IV [f]	
FSIQ (Full Scale IQ)	109.4 ± 12.0
VCI (Verbal Comprehension Index)	107.8 ± 13.4
PRI (Perceptual Reasoning Index)	110.0 ± 15.0
WMI (Working Memory Index)	110.0 ± 14.6
PSI (Processing Speed Index)	100.5 ± 12.2

[a] ETS, environmental tobacco smoke [b] Standard Progressive Matrices [c] HOME, Home Observation for Measurement of the Environment [d] CDIIT, Comprehensive Developmental Inventory for Infants and Toddlers [e] DQ, developmental quotients [f] WISC-IV, Wechsler Intelligence Scale for Children, 4th edition

Table 2. Distribution of maternal mobile phone use from pregnancy to 12 months (N = 133)

	During pregnancy No. (%)	Birth to 12 months No. (%)
Daily phone calls		
< 3	73 (54.9)	74 (55.6)
4-10	49 (36.8)	49 (36.8)
> 10	11 (8.3)	10 (7.5)
Time spoken per phone calls (min)		
< 1	39 (29.3)	39 (29.3)
1-3	80 (60.2)	75 (56.4)
4-10	13 (9.8)	18 (13.5)
> 10	1 (0.7)	1 (0.8)
Prenatal cumulative dose of mobile phone use (hr)		
≤ 63	114 (85.7)	--
> 63	19 (14.3)	--
Postnatal cumulative dose of mobile phone use (hr)		
≤ 84	--	111 (83.5)
> 84	--	22 (16.5)
Use of hands-free equipment		
Yes	19 (14.3)	
No	114 (85.7)	
Location of mobile phone		
Clothing pocket	8 (6.0)	
In the bag	125 (94.0)	

Values are numbers and percentages.

Table 3. Linear regression models of the child neurodevelopment and mobile phone use (N=133)

Mobile phone use	During pregnancy (≤ 63 hr vs. >63 hr)				Birth to 12 months (≤ 84 hr vs. >84 hr)			
	Crude β (SE)	P value	Adjusted [a] β (SE)	P value	Crude β (SE)	P value	Adjusted [b] β (SE)	P value
CDIIT DQ								
Whole DQ	-2.18 (2.99)	0.4669	-0.74 (2.77)	0.7910	1.61 (2.62)	0.5390	1.41 (2.67)	0.5993
Cognitive DQ	-3.93 (5.32)	0.4618	-2.05 (5.38)	0.7042	0.30 (5.08)	0.9523	0.50 (5.15)	0.9234
Language DQ	-6.03 (3.13)	0.0562	-3.79 (2.97)	0.2158	-0.43 (2.83)	0.8800	-0.28 (2.89)	0.9237
Motor DQ	2.22 (3.00)	0.4615	2.56 (3.01)	0.3969	-0.28 (2.85)	0.9214	-0.10 (2.89)	0.9717
Gross-motor DQ	1.30 (3.42)	0.7046	1.43 (3.49)	0.6825	-1.50 (3.30)	0.6498	-1.26 (3.34)	0.7066
Fine-motor DQ	1.03 (2.78)	0.7126	1.79 (2.68)	0.5068	-0.03 (2.54)	0.9910	0.29 (2.57)	0.9097
Social DQ	-0.85 (3.67)	0.8171	0.07 (3.55)	0.9850	0.48 (3.36)	0.8857	-0.74 (3.35)	0.8262
Self-help DQ	-0.39 (3.52)	0.9128	0.62 (3.37)	0.8549	4.34 (3.17)	0.1729	4.41 (3.23)	0.1756
WISC-IV								
Full Scale IQ	-2.37 (2.99)	0.4294	-2.32 (2.94)	0.4317	-3.93 (2.82)	0.1662	-2.80 (2.81)	0.3222
Verbal Comprehension Index	3.05 (3.38)	0.3680	3.83 (3.25)	0.2416	1.32 (3.20)	0.6817	2.46 (3.19)	0.4407
Perceptual Reasoning Index	-4.91 (3.67)	0.1836	-5.46 (3.69)	0.1416	-4.99 (3.47)	0.1535	-3.92 (3.54)	0.2705
Working Memory Index	-3.99 (3.65)	0.2767	-4.30 (3.65)	0.2411	-6.47 (3.43)	0.0616	-6.20 (3.48)	0.0768
Processing Speed Index	-0.74 (3.12)	0.8119	-0.80 (3.06)	0.7950	-1.84 (2.94)	0.5342	-1.19 (2.98)	0.6917

[a] Models adjusted for maternal education, maternal age, family income, infant sex, lead levels in the cord blood, HOME score, prenatal ETS exposure as reported on a questionnaire, and mothers intelligence.

[b] Models adjusted for maternal education, maternal age, family income, infant sex, lead levels in the cord blood, HOME score, prenatal ETS exposure and postnatal ETS exposure as reported on a questionnaire, mother accompany with child per day (hr), and mothers intelligence.

Table 4. Logistic regression models of the child neurodevelopment and mobile phone use (N=133)

Mobile phone use	During pregnancy (≤ 63 hr vs. >63 hr)				Birth to 12 months (≤ 84 hr vs. >84 hr)			
	Crude OR (95%CI)	P value	Adjusted [a] OR (95%CI)	P value	Crude OR (95%CI)	P value	Adjusted [b] OR (95%CI)	P value
CDIIT DQ								
Whole DQ	2.19 (0.78-6.16)	0.1383	1.92 (0.59-6.19)	0.2776	1.29 (0.46-3.65)	0.6308	1.07 (0.32-3.53)	0.9170
Cognitive DQ	1.00 (0.30-3.29)	1.0000	0.92 (0.25-3.33)	0.8960	1.13 (0.38-3.37)	0.8330	0.81 (0.22-2.91)	0.7405
Language DQ	3.56 (1.30-9.78)	0.0137*	3.38 (1.00-11.42)	0.0504	2.65 (1.01-6.96)	0.0481*	1.75 (0.54-5.71)	0.3509
Motor DQ	1.21 (0.40-3.67)	0.7379	1.06 (0.31-3.60)	0.9316	2.19 (0.82-5.84)	0.1186	2.21 (0.72-6.82)	0.1670
Gross-motor DQ	1.33 (0.40-4.46)	0.6405	1.35 (0.37-4.89)	0.6476	2.77 (0.98-7.85)	0.0552	2.89 (0.90-9.28)	0.0747
Fine-motor DQ	1.25 (0.38-4.18)	0.7131	1.22 (0.31-4.81)	0.7813	1.01 (0.31-3.31)	0.9854	0.69 (0.16-2.93)	0.6111
Social DQ	1.21 (0.40-3.67)	0.7379	1.09 (0.33-3.68)	0.8842	0.96 (0.32-2.86)	0.9441	0.86 (0.26-2.90)	0.8102
Self-help DQ	1.15 (0.38-3.49)	0.8039	0.99 (0.30-3.26)	0.9881	0.45 (0.12-1.62)	0.2202	0.38 (0.09-1.55)	0.1753
WISC-IV								
Full Scale IQ	1.64 (0.57-4.76)	0.3601	1.36 (0.44-4.18)	0.5902	1.69 (0.62-4.62)	0.3050	1.07 (0.36-3.21)	0.9041
Verbal Comprehension Index	0.40 (0.09-1.84)	0.2379	0.36 (0.08-1.71)	0.1982	0.33 (0.07-1.49)	0.1490	0.28 (0.06-1.34)	0.1099
Perceptual Reasoning Index	2.73 (0.99-7.53)	0.0529	2.89 (0.96-8.68)	0.0581	**2.65 (1.01-6.96)**	**0.0481***	2.17 (0.75-6.27)	0.1546
Working Memory Index	2.04 (0.70-6.00)	0.1933	2.12 (0.68-6.64)	0.1978	2.77 (1.02-7.52)	0.0459	2.63 (0.89-7.77)	0.0807
Processing Speed Index	0.83 (0.22-3.11)	0.7827	0.67 (0.17-2.65)	0.5715	1.01 (0.31-3.31)	0.9854	0.70 (0.20-2.49)	0.5860

Cut-points of the CDIIT DQ and the WISC-IV test were the first quartile.

[a] Models adjusted for maternal education, maternal age, family income, infant sex, lead levels in the cord blood, HOME score, prenatal ETS exposure as reported on a questionnaire, and mothers intelligence.

[b] Models adjusted for maternal education, maternal age, family income, infant sex, lead levels in the cord blood, HOME score, prenatal ETS exposure and postnatal ETS exposure as reported on a questionnaire, mother accompany with child per day (hr), and mothers intelligence.

* $p < 0.05$

Appendix 1

Appendix 1. Paper reviews of exposure to prenatal and postnatal cell phone use and child neurodevelopment

Country	Population	Study year	Exposure assessment	Findings	Reference
Denmark	General population	March 1996 to November 2002	Retrospective questionnaires	No evidence of developmental milestone delays among infants	Divan HA et al., 2011
Denmark	General population	March 1996 to November 2002	Retrospective questionnaires	↑ Risk of behavioural problems (both prenatal and postnatal exposure)	Divan HA et al., 2010
Spain	General population	July 2004 to July 2006	Prospective questionnaires	↓ Psychomotor score at 14 months (Heaviest users)	Vriheid et al., 2010
Denmark	General population	March 1996 to November 2002	Retrospective questionnaires	Emotional and hyperactivity problems at 7 years of age	Divan HA et al., 2008

Appendix 2

Questionnaires of mobile phone use

G.電磁波概況

G1.請問**<u>您(孩子母親) 懷孕前一年到現在</u>**是否曾使用手機？□1 沒有【跳答至 G12.】 □2 有

手機使用頻率	**G2.** 是否有使用手機		**G3.** 每天約幾通			**G4.** 每通平均幾分鐘				**G5.** 使用哪一耳接聽電話	
	否	是	3 通以下	4-10 通	10 通以上	1 分鐘內	1-3 分鐘	3-10 分鐘	10 分鐘以上	右耳	左耳
a.懷孕前一年以上	□1	□2	□1	□2	□3	□1	□2	□3	□4	□1	□2
b.懷孕前半年	□1	□2	□1	□2	□3	□1	□2	□3	□4	□1	□2
c.懷孕第 1～3 個月	□1	□2	□1	□2	□3	□1	□2	□3	□4	□1	□2
d.懷孕第 4～6 個月	□1	□2	□1	□2	□3	□1	□2	□3	□4	□1	□2
e.懷孕第 7 個月～分娩	□1	□2	□1	□2	□3	□1	□2	□3	□4	□1	□2
f.兒童 0～1 歲	□1	□2	□1	□2	□3	□1	□2	□3	□4	□1	□2
g.兒童 1～2 歲	□1	□2	□1	□2	□3	□1	□2	□3	□4	□1	□2
h.兒童 3～5 歲	□1	□2	□1	□2	□3	□1	□2	□3	□4	□1	□2

G6. 請問**您(孩子母親)除了直接接聽手機外，使用手機免持聽筒接聽的頻率？**

使用頻率	使用**手機免持聽筒**接聽的頻率				
	一直都是	經常	有時	很少	從不
a.懷孕前一年以上	□1	□2	□3	□4	□5
b.懷孕前半年	□1	□2	□3	□4	□5
c.懷孕第 1～3 個月	□1	□2	□3	□4	□5
d.懷孕第 4～6 個月	□1	□2	□3	□4	□5
e.懷孕第 7 個月～分娩	□1	□2	□3	□4	□5
f.兒童 0～1 歲	□1	□2	□3	□4	□5
g.兒童 1～2 歲	□1	□2	□3	□4	□5
h.兒童 3～5 歲	□1	□2	□3	□4	□5

G7. 請問**您(孩子母親)除了直接接聽手機外，使用耳機接聽的頻率？**

使用頻率	使用**耳機**接聽的頻率				
	一直都是	經常	有時	很少	從不
a.懷孕前一年以上	□1	□2	□3	□4	□5
b.懷孕前半年	□1	□2	□3	□4	□5
c.懷孕第 1～3 個月	□1	□2	□3	□4	□5
d.懷孕第 4～6 個月	□1	□2	□3	□4	□5
e.懷孕第 7 個月～分娩	□1	□2	□3	□4	□5
f.兒童 0～1 歲	□1	□2	□3	□4	□5
g.兒童 1～2 歲	□1	□2	□3	□4	□5
h.兒童 3～5 歲	□1	□2	□3	□4	□5

G8. 請問**您(孩子母親)除了直接接聽手機外，使用藍芽接聽的頻率？**

使用頻率	使用**藍芽**接聽的頻率				
	一直都是	經常	有時	很少	從不
a.懷孕前一年以上	□1	□2	□3	□4	□5
b.懷孕前半年	□1	□2	□3	□4	□5
c.懷孕第 1～3 個月	□1	□2	□3	□4	□5
d.懷孕第 4～6 個月	□1	□2	□3	□4	□5
e.懷孕第 7 個月～分娩	□1	□2	□3	□4	□5
f.兒童 0～1 歲	□1	□2	□3	□4	□5
g.兒童 1～2 歲	□1	□2	□3	□4	□5
h.兒童 3～5 歲	□1	□2	□3	□4	□5

G9. 在**您(孩子母親)**懷孕時, 您的手機通常置於何處？

使用頻率	**上衣口袋**	**洋裝或裙子口袋**	**包包裡**
c.懷孕第 1～3 個月	□1	□2	□3
d.懷孕第 4～6 個月	□1	□2	□3
e.懷孕第 7 個月～分娩	□1	□2	□3

G10. 您(孩子母親)是否隨時帶著您的行動電話

□1 是的，隨時

□2 是的百分之五十以上的時機間都帶著

□3 是的大約百分之五十的時間帶著

□4 是的但低於百分之五十的時間

□5 幾乎都不帶在身上

G11. 請問**您的寶貝**除了直接接聽手機外，使用手機**免持聽筒**接聽的頻率？

使用頻率	使用手機免持聽筒				
	一直都是	經常	有時	很少	從不
a.兒童 0～1 歲	□1	□2	□3	□4	□5
b.兒童 1～2 歲	□1	□2	□3	□4	□5
c.兒童 3～5 歲	□1	□2	□3	□4	□5

G12. 請問**您的寶貝**除了直接接聽手機外，使用**耳機**接聽的頻率？

使用頻率	使用**耳機**接聽的頻率				
	一直都是	經常	有時	很少	從不
a.兒童 0～1 歲	□1	□2	□3	□4	□5
b.兒童 1～2 歲	□1	□2	□3	□4	□5
c.兒童 3～5 歲	□1	□2	□3	□4	□5

G13. 請問**您的寶貝**除了直接接聽手機外，使用**藍芽**接聽的頻率？

使用頻率	使用**藍芽**接聽的頻率				
	一直都是	經常	有時	很少	從不
a.兒童 0～1 歲	□1	□2	□3	□4	□5
b.兒童 1～2 歲	□1	□2	□3	□4	□5
c.兒童 3～5 歲	□1	□2	□3	□4	□5

G14. 請問**您(孩子母親)懷孕前一年到現在，家中是否使用無線電話？**

□1 否 【跳答至 G16.】 □2 是

G15a 何時開始使用？
□1 懷孕前一年以上 □2 懷孕前半年 □3 懷孕第 1～3 個月 □4 懷孕第 4～6 個月
□5 懷孕第 7 個月～分娩 □6 兒童 0～1 歲 □7 兒童 1～2 歲 □8 兒童 3～5 歲

G15. 您家中是否使用**無線上網**？

□1 否 【跳答至 G17.】 □2 是

G16a 何時開始使用？
□1 懷孕前一年以上 □2 懷孕前半年 □3 懷孕第 1～3 個月 □4 懷孕第 4～6 個月
□5 懷孕第 7 個月～分娩 □6 兒童 0～1 歲 □7 兒童 1～2 歲 □8 兒童 3～5 歲

G16. 您住家附近是否有**行動電話基地台**？

□1 否　【跳答至 G18.】 □2 是　□3 不清楚

□4 其他電磁波產生器，如高壓電塔，廣播電台發射塔，變電所等，請說明_____

G18a 何時開始有行動電話基地台？
□1 懷孕前一年以上 □2 懷孕前半年　□3 懷孕第 1～3 個月　□4 懷孕第 4～6 個月
□5 懷孕第 7 個月～分娩　□6 兒童 0～1 歲　□7 兒童 1～2 歲　□8 兒童 3～5 歲

G17. 您工作場所是否使用**無線電話**？

□1 **否**　【跳答至 G19.】 □2 **是**

G18a 何時開始使用？
□1 懷孕前一年以上 □2 懷孕前半年　□3 懷孕第 1～3 個月　□4 懷孕第 4～6 個月
□5 懷孕第 7 個月～分娩　□6 兒童 0～1 歲　□7 兒童 1～2 歲　□8 兒童 3～5 歲

G18. 您工作場所是否使用**無線上網**？

□1 否　【跳答至 G20.】 □2 是

G19a 何時開始使用？
□1 懷孕前一年以上 □2 懷孕前半年　□3 懷孕第 1～3 個月　□4 懷孕第 4～6 個月
□5 懷孕第 7 個月～分娩　□6 兒童 0～1 歲　□7 兒童 1～2 歲　□8 兒童 3～5 歲

G19. 您工作場所附近是否有**行動電話基地台**？

□1 否　**【跳答至下一頁】** □2 是　□3 不清楚

□4 其他電磁波產生器，如高壓電塔，廣播電台發射塔，變電所等，請說明_____

G20a 何時開始有行動電話基地台？
□1 懷孕前一年以上 □2 懷孕前半年　□3 懷孕第 1～3 個月　□4 懷孕第 4～6 個月
□5 懷孕第 7 個月～分娩　□6 兒童 0～1 歲　□7 兒童 1～2 歲　□8 兒童 3～5 歲

Part II

二、臍帶血中酚類化合物與胎兒生長發育之相關性

Association between phenolic compounds in umbilical cord blood and child growth

中文摘要

研究背景與目的：雙酚 A(BPA)、壬基酚(NP)與辛基酚(OP)為工業上常用之化學物質，也時常存在日常生活的用品中。塑膠奶瓶、玩具、水瓶、罐頭食品、清潔劑…等，皆會釋放出微量的酚類化合物。一般來說，這些酚類物質大多經由飲食而進入人體，飲食攝入也是日常生活中最主要的暴露途徑。這些酚類物質也被歸類為環境賀爾蒙之汙染物，研究指出此種物質可能會影響生殖系統之發育或胎兒之生長與發育。然而，目前對於產前暴露酚類物質與其胎兒之出生結果與往後生長發育之相關性仍不清楚。因此，本研究目的為分析臍帶血中雙酚 A、壬基酚與辛基酚濃度，並探討其與胎兒出生結果與往後生長發育之相關性。

材料與方法：本研究之 401 位產後婦女與其單胞胎之胎兒，皆選自於台北出生世代追蹤研究(Taiwan Birth Panel Study)。產後利用結構式問卷收集產婦產前之生活習慣調查，並於生產時收集胎兒臍帶血。以極致液相層析—串聯質譜儀(UPLC-MS/MS)分析臍帶血中酚類化合物之濃度。並進一步使用迴歸模式分析臍帶血中酚類化合物與其胎兒之出生結果與往後生長發育之相關性。

結果：臍帶血中雙酚 A、壬基酚與辛基酚之中位數濃度分別為 1.50、60.97 以及 2.30 ng/mL。在迴歸模式中，調整相關之潛在干擾因子後，發現壬基酚和出生時的頭圍(per ln unit: β = -0.13, 95% CI: -0.23, -0.03)呈顯著之負相關；關於往後生長發育的部分，發現壬基酚和頭圍(per ln unit: β = -0.10, 95% CI: -0.19, -0.01 for 0-18 months)與身高(per ln uint: β = -0.05, 95% CI: -0.10, -0.002 for 0-6 years)呈負相關。

結論：本研究結果顯示，臍帶血中壬基酚濃度和胎兒之出生頭圍與其往後的頭圍和身高之發展呈負相關。但仍需要更多完整且長期的研究來進一步探討產前酚類化合物與胎兒出生結果與生長發育之相關。

關鍵字：產前暴露、酚類化合物、胎兒與孩童生長發育

Abstract

Background and objective: Bisphenol A, nonylphenol, and octylphenol are widely used in our life, and they all classified as endocrine-disrupting compounds (EDCs) which could lead the adverse effect on children's growth. Previous studies investigated the association between prenatal phenols exposure and birth outcomes, and the findings were inconsistent. In addition, most of these studies measured the levels of phenols in maternal blood or urine during pregnancy to regard as the prenatal exposure. Few studies measured the phenols levels in cord blood to represent the prenatal exposure of fetus. The objective of this study was to measure the phenols levels in cord blood and explore the effects of prenatal phenols exposure on birth size and growth.

Methods: The study was a part of the Taiwan Birth Panel Study. A total of 401 pairs of parents and their infants were recruited in this study. We used the ultra-performance liquid chromatography – tandem mass spectrometry (UPLC/MS/MS) to measure the free form BPA, NP and OP in cord blood. Birth outcomes were obtained after delivery, and we followed up these children to obtain the growth data up to 6 years old. The association between phenols levels in cord blood and child growth was assessed using linear regression and mixed models.

Results: The median of BPA, NP, and OP concentration in cord blood were 3.10, 74.4, and 2.30 ng/mL, respectively. For birth outcomes, after adjusting the confounders, head circumference decreased by 0.13 cm (95% CI: -0.23, -0.03) in association with a 1-unit increase in ln-transformed NP concentration. Regarding the child growth, a 1-unit increase of ln-NP was significantly associated with a decrease in head circumference (β = -0.11, 95% CI: -0.21, -0.02 for 0-18 months), and height z-score (β = -0.06, 95% CI: -0.11, -0.01 for 0-6 years).

Conclusion: In this study, we observed an evidence of prenatal NP exposure may have an adverse effect on head circumference at birth and child growth in the early childhood. However, among these young children, we didn't find an effect of prenatal BPA and OP exposure on child growth. Therefore, further studies are needed to explore the association between prenatal phenols exposure and child growth

Key words: prenatal exposure, phenol, fetal and child growth, young children

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Introduction

Bisphenol A (BPA) used in the manufacture of polycarbonate plastics (PC) and epoxy resins. BPA had been found to release from the plastic products, including toys, baby bottles, dental sealant, food and water containers, also the lining of beverages and food cans (Cao et al., 2009; Maragou et al., 2008). Nonylphenol (NP) and octylphenol (OP) are widely used and the most common surfactants in domestic detergents, pesticide formulations, industrial products, and release from the wax used for coating fruits and vegetables, plastic food packaging (Ying et al., 2002). BPA, NP, and OP are widely spread in the environment, they all classified as endocrine-disrupting compounds (EDCs). Endocrine disruptors are the chemicals that can interfere with hormone system in animals and humans, and then affect the natural hormones in the body responsible for the maintenance of homeostasis and the regulation of developmental processes (Kavlock, 1999).

Exposure sources and routes are ubiquitous make human exposure nearly universal, especially in dietary ingestion. Specific products or activities had been examined for potential exposure of human, including canned food, microwave containers (Mariscal-Arcas et al., 2009), soft drinks (Cao et al., 2009), smoking and alcohol consumption (Braun et al., 2011; He et al., 2009). The main exposure route of BPA is

dietary ingestion for general population, especially for preschool children. Dietary ingestion of BPA accounted for > 95% of the children excreted amounts of urinary BPA (Morgan et al., 2011). The average daily NP intake in Taiwan is at least 4-fold higher than daily intake in western countries due to the dietary habit of Taiwanese (Lu et al., 2007). However, phenols exposure of pregnant mothers is an important issue and should be concerned about.

Phenols levels had been measured in maternal blood, placental tissue and cord blood of pregnant mothers in previous studies (Chen et al., 2008; Schönfelder et al., 2002). These findings supported that phenols can accumulate in the maternal-fetal-placental unit, and have the maternal-fetal transfer when the barrier of placenta does not exist. Placental transfer can lead to the prenatal exposure to fetus, and the potential effect of prenatal phenols exposure on fetal and children growth is a concern.

Previous studies which investigated the association between prenatal phenols exposure and birth outcomes were limited and inconsistent. In the general population, few studies found the adverse effect of prenatal BPA exposure on birth outcomes such as gestational age and birth weight (Chou et al., 2011; Cantonwine et al., 2010). Increased BPA exposure was associated with slightly increase in head circumference (Philippat et al., 2012). Another study didn't find the association between prenatal BPA

exposure and birth outcomes (Wolff et al., 2008). In addition, the effect of prenatal NP exposure on the birth size of offspring was only shown in the animal studies (Jie et al., 2010). Regarding the body growth at postnatal age, the effect of prenatal BPA exposure on body weight was only shown in animal studies (Honma et al., 2002; Rubin et al., 2001). Overall, the association between prenatal phenols exposure and child growth is not explicit. Additionally, most of these previous studies measured the levels of phenols in maternal blood or urine during pregnancy to regard as the prenatal exposure of fetus. Few studies used the phenols levels in cord blood to represent the prenatal exposure.

According to the metabolism of bisphenol A in human, BPA were rapidly absorbed from the gastrointestinal tract in human. Conjugation with glucuronic acid in the liver, and rapidly cleared from blood by elimination with urine (Völkel et al., 2002). The half-life of BPA and NP from the blood was 5.3 and 2-3 hours, respectively (Völkel et al., 2002; Müller et al., 1998). Although the half-life of phenols is short, the exposure sources and routes are ubiquitous in our life. BPA glucuronide does not exert hormonal activity (Matthews, 2001; Snyder et al., 2000), therefore only unconjugated BPA is possibly expected the hormonal effects and cause the health effect. Also, there were no studies shown the estrogenic potency of NP-conjugates. Volkel et al (2002) assumed that the determination of free BPA may serve as a biomarker more related to

potential estrogenic effects. Furthermore, the deconjugation of BPA glucuronide *in utero* by β-glucuronidase, an enzyme that is present in high concentrations in placenta and various other tissues (Ginsberg and Rice, 2009). This creates the potential for local activation of the conjugated from back to free BPA in numerous tissues and may be important to resultant fetal exposure. The risk of phenols exposure does not be negligible despite the rapid metabolism in human.

In this study, we measured the free form BPA, NP and OP levels in cord blood. Moreover, we explored the effect of prenatal phenols exposure on birth size and child growth among the young children.

Materials and Methods

Study population

This study was based on the Taiwan Birth Panel Study (TBPS), a prospective cohort study, which was conducted between April 2004 and January 2005 (Hsieh et al., 2011). Informed consents were obtained from study participants before delivery to collect umbilical cord blood at birth and stored at -80℃ until laboratory analysis. After delivery, all subjects were interviewed by trained interviewers to obtain the information during prenatal life style. The protocols used in this study were approved by the Ethical Committee of National Taiwan University Hospital.

In this study, five mothers who reported smoking over 5 months during pregnancy, four mothers who reported drinking more than 100 mL during pregnancy, four infants who were very preterm (gestational age < 32 weeks), and six twin babies were excluded from the analysis. Combined with the appropriate cord blood for phenols measurement, finally, a total of 401 mother-infant pairs were remained in our study.

Measurement of BPA, NP, OP in cord blood

Chemicals and reagents

Bisphenol A was supplied by AccuStandard (New Haven, Connecticut, USA). Bisphenol A-D_{16}, 4-tert-octylphenol and the technical mixture of nonylphenol were obtained from Sigma/Aldrich (Saint Louis, MO, USA). 4-n-Octyl-d17-phenol was supplied by C/D/N Isotopes (Pointe-Claire, Quebec, Canada; purity > 98%). Stock solutions of each compound were prepared at a concentration of 500 μg/mL in methanol and stored at -20℃. Milli-Q water was obtained from a Millipore water purification system (Milford, MA,USA). N-methylmorpholine (purity > 99.5%) were provided by J.T. Baker (Phillipsburg, NJ, USA). Solvents including methanol and acetonitrile were all LC/MS grade (J.T. Baker). Bovine plasma were purchased from Sigma-Aldrich (St. Louis, MO, USA).

Sample preparation and calibration experiments

All glassware was rinsed with methanol before being used for experiments. The concentration of BPA, NP, and OP in the cord blood were quantified using modified analytical methods previously described (Anari et al., 2002). We conducted a small

experiment to compare two methods of derivatized with Dansyl chloride and underivatized analysis. We chose the better method by comparing the linear range of calibration and the feasibility between derivatization and non derivatization (the results showed in Appendix1). Finally, the underivatization method was used in this study.

A 50 μL aliquot plasma was diluted with 0.5 mL of water and added in 50 μL of internal standard (Bisphenol A-D_{16} and 4-n-Octyl-d17-phenol; 200 ng/mL in methanol). After gentle mixing, samples were added in 2 mL of ethyl acetate to each test tube. The samples were vortex-mixed and the organic phase (1.5 mL) of the samples was transferred to another tube, then filtrated through 0.22 μm PVDF syringe filters into a 2 mL auto-sampler vial, and evaporated to dryness by SpeedVac concentrator (Thermo Savant SPD 1010, Holbrook, NY, USA). The residues were reconstituted with 50 μL of methanol and transferred to 150-μL insert for UPLC/MS/MS analysis.

Matrix-matched standard calibration solution was prepared in bovine plasma and through the same procedure of sample preparation. The linear range were 0.5-500 ng/mL for BPA, 10-750 ng/mL for NP, 2.5-200 ng/mL for OP, and spiked 200 ng/mL of internal standard (BPA-d16 and 4-n-Octyl-d17-phenol) in each solution.

Instrumental analysis

We measured the concentration of bisphenol A (BPA), nonylphenol (NP), and octylphenol (OP) in cord bloods using ultra-performance liquid chromatography tandem mass spectrometry (UPLC/MS/MS). The UPLC/MS/MS was performed using a Waters Acquity UPLC system (Waters Corporation, Milford, MA, USA) and controlled by MassLynx V4.1 with QuanLynx Application Manager. An ACQUITY UPLC BEH C18 column (2.1 mm × 50 mm, 1.7μm) was used, the temperature and the flow rate were maintained at 60℃ and 0.5 mL/min, respectively. The mobile phase was composed of 10 mM N-methylmorpholine (pH 9.5) and acetonitrile. The initial composition of gradient program was 40% acetonitrile for 0.5 min, followed by a linear gradient to 60% acetonitrile in 0.5 min, then 95% acetonitrile in 2 min and held at 95% acetonitrile for 1 min before being returned to the initial condition. At last, the column was re-equilibrated at 40% acetonitrile for 1 min. The total run time of gradient program was 5 minutes and the sample injection volume was 5 μL.

To achieve maximal analyte signal intensities, the instrumental parameters were referenced to previously described (Lien et al., 2009). The mass spectrometer was performed in native electrospray ionization (ESI-) and the capillary voltage was maintained at 3.0 kV. The desolvation gas flow, con gas flow, desolvation temperature,

and source temperature were set at 900 L/hr, 50 L/hr, 400℃ and 120℃, respectively. Extractor voltage was 3.0 V and RF lens voltage was 0 V. Collision gas was argon at 3.13×10^{-3} mbar. Ion energy 1 and 2 were set at 0.3 and 3, respectively. Both LM 1 and LM 2 resolution were set at 12. The multiplier voltage was set at 650 V. The dwell time for NP and OP were 0.08 second, then for BPA was 0.1 second. Ions were monitored by selected reaction monitoring (SRM) as shown in Table 1 (p55) as well as the individual collision energy and cone voltage.

Evaluation of matrix effect and extraction efficiency of sample pretreatment

Three duplicates of bovine plasma which were spiked three different levels of BPA, NP and OP (10, 25 and 100 ng/mL) before or after the procedure of sample preparation. For matrix effect, the same levels of all analytes were spiked into solvent solutions. The percent matrix effect was calculated by the following formula: matrix effect% = (area of post-extraction spike / area of standard) × 100. Then, the extraction efficiency was tested to measure the analytes loss during sample preparation. We used the following formula to calculate the extraction efficiency: absolute recoveries% = (area of pre-extraction spike / area of post-extraction spike) × 100.

Method validation and quantification

The sample preparation of plasma with UPLC/MS/MS method was validated regarding the precision, accuracy, and detection limit. For intra- and inter-day precision and accuracy, the calibration standards in bovine plasma were analyzed on the same day (n=3) and on three different days. The recovery of the method was determined by three duplicates of bovine plasma spiked known amounts (10, 25 and 100 ng/mL) of BPA, NP and OP with fixed levels of internal standard, and was calculated by dividing the measured quantities with the theoretical (spiked) quantities. BPA and NP were found in blanks, almost all the human plasma were detected the peak but some signal intensities were below the background level, it is impractical to calculate their limits of detection (LODs), therefore we used the lowest concentration of calibration curve to define their LOQs. In addition, limits of detection (LODs) and quantification (LOQs) were defined as the minimum concentration of OP in the calibration curve by using the peak-to-peak option of MassLynx software and was defined as signal-to-noise ratios (S/N ratios) equaling to 3 and 10.

For quantification accuracy, the quality control (QC) samples were prepared from a plasma pool obtained from multiple cord blood plasma which provide from those were not recruit in this study. The plasma pool was divided into four subpools, one

subpool was used to analyze the phenols levels of the samples (no spike), and the three different concentration (5, 20 and 100 ng/mL) were spiked into the other three subpools.

All glassware was rinsed with methanol before being use for experiments. A solvent blank sample spiked fixed level of internal standard with each batch of samples to check experimental contamination and background level of native analytes. The quality control (QC) samples were prepared from human plasma, and the matrices were mixed uniformly and divided into three subpools. Two subpools were used to spiked with fixed level of internal standard to detect the level of analytes, then another subpool was spiked with known level (50 ng/mL) of BPA, NP and OP standard to check the stability of method. These QC samples were chose from every twenty-five samples.

The linear ranges in plasma with 1/ *x* weighted were as follow: 0.5-500 ng/mL for BPA; 10-750 ng/mL for NP; 2.5-200 ng/mL for OP. The square of the correlation coefficient (R^2) was equal to or greater than 0.997. The data acquired and processed using MassLynx V4.1 Software.

Infant's birth outcomes and child growth

Birth outcomes used in this analysis included infant's gestational age (weeks), birth weight (grams), length (centimeters) and head circumference (centimeters), which were obtained by researchers abstracting from medical records. Growth data were recorded from Child Healthcare Handbook which was created and published by Bureau of Health Promotion, Department of Health, Taiwan. The height, weight and head circumference of the child were measured at visits to clinics for health examinations and were recorded in the Child Healthcare Handbook. We also measured child's height and weight in every times of follow-up at different age.

Statistical analysis

The backgrounds of BPA and NP were deducted, then phenols concentrations were natural log-transformed to fit the normal distribution before linear/mixed regression analysis. We used t-test and ANOVA to assess the phenols concentration distribution in different characteristics of mothers and infants. The univariable linear/mixed models analysis were used to define the potential confounders of birth outcomes and child growth parameters. Furthermore, any potential confounders which were significantly related to at least one of the growth parameters or phenols levels in

cord blood were included in the multivariable models.

Linear regression models were used to assess the association between prenatal phenols exposure and birth outcomes of newborns. According to the statistics and literature review, the potential confounders were infant gender, gestational age, lead and cotinine level in cord blood, maternal education, maternal BMI during pregnancy, and annual household income.

Mixed models were used to assess the effect of prenatal phenols exposure and child growth from birth to 6 years of age. All pairs, no matter how many growth measurements from birth to 6 years they had, were included in the analysis. We also analyzed age- and sex-specific height and weight z-scores according to the growth norm of preschool children in Taipei City (Lee et al., 2009). Because of the growth measurements time of every subjects are not consistent, we adjusted the measurements time in the mixed models. Other potential confounders in models included infant gender, gestational age, lead and cotinine level in cord blood, and maternal education. Furthermore, the phenols levels in cord blood were classified by quartile to assess the dose-response of prenatal phenols and child growth.

Statistical analysis was conducted with SAS version 9.2. All tests were two-sided and a p-value < 0.05 was considered statistically significant.

Results

Method performance, matrix effect, recovery and method validation

The matrix effects in different spiking levels in bovine plasma of the analytes were shown in Table 3. For NP, the matrix effect was from 81.5% to 97.9%, and ion enhancement effect was found of BPA and OP. The extraction efficiencies of the three phenols in bovine plasma were 64.4% to 123.3% (Table 3, p57). Using the quantitative method of matrix-matched calibration with one internal standard, the recoveries of three analytes were 94.3%-107.0% as shown in Table 3. The accuracy and precision of intra- and inter-day of matrix-matched calibration were shown in Table 4 (p58).

Three different concentrations (5, 20, 100 ng/mL) were spiked into the human cord blood samples to evaluate the method accuracy and precision. We found that the measured concentrations were very close to the spiked levels if the backgrounds (no spike) were not deducted (Table 5, p59).

Because BPA and NP were found in the blanks, their LOQs were defined as the lowest concentration of calibration curve, 0.5 and 10 ng/mL, respectively. Moreover, the LOD and LOQ of OP were 0.89 and 2.96 ng/mL, which was defined as the signal-to-noise (S/N) ratios equaling to 3 and 10.

Phenols levels in cord blood

A total of 401 subjects' cord bloods were used in this study and the detection rate of BPA, NP and OP were 55.86%, 77.56% and 68.33%, respectively. If BPA or NP levels were below the background level, half of LOQ (0.25 ng/mL for BPA; 5 ng/mL for NP) would be regarded as the BPA or NP levels in cord blood. Also, half of LOD (0.45 ng/mL) would be regarded as the OP levels if OP levels were lower than the LOD. The range of BPA was from 0.25 to 211.40 ng/mL, NP was from 5.0 to 561.57 ng/mL, and OP was from 0.45 to 183.4 ng/mL. Then, the median of BPA, NP and OP were 1.50, 60.97, and 2.30 ng/mL, respectively (Table 6, p60).

The phenols concentration distribution in different characteristics of mothers and infants were shown in Table 7 (p61). For NP levels, young mothers had lowest geometric mean concentration than other older mother; mothers who had low annual household income had higher NP concentration. BPA concentration of the mothers who had ETS-exposure during pregnancy was higher than those who didn't have prenatal ETS-exposure. But, we didn't find the correlation between cotinine level in cord blood and prenatal phenols exposure in this study.

Prenatal phenols exposure and child growth

A total of 401 mother-infants pairs were recruited in this study (Figure 1, p51). The characteristics of these 401 mother-infants pairs were shown in Table 8 (p62). Half of mothers had lower education level, and about 30% of mothers had ETS-exposure during pregnancy. The geometric means of lead level and cotinine level in cord blood were 1.07 and 0.15 ng/ml, respectively. We excluded the vary preterm infants, so the mean of gestational age and birth weight are all within normal limits.

The relationship between infant and maternal factors, and growth parameters were shown in Table 9 (p63). Infant's gender, gestational age, cotinine level in cord blood, maternal age at delivery, and maternal education were important determinants of birth size at birth and growth from birth to 6 months. Because maternal age was highly correlated with maternal education, we only adjusted maternal education in multivariable models to avoid over-adjustment.

Table 10 shows that the linear regression models of natural log-transformed phenols concentration and birth outcomes. After adjusting, there was a negative association between ln-NP in cord blood and head circumference at birth. Head circumference decreased by 0.15 cm (95% CI: -0.25, -0.05) in association with a 1-unit increase in natural log-transformed NP concentration (Table 10, p64).

Table 11 to 14 shows that the effects of prenatal phenols exposure on child growth between birth to different age. After adjusting the growth measurements time and other confounders, there was a significantly negative association between cord blood NP and head circumference up to 18 months (Table 11 and Table 12, p65 and 66). Regarding other growth parameters, an increase in cord blood NP was significantly associated with a decrease in height z-score from birth up to 6 years when controlling the confounders (Table 12 to Table 14, p66-68). A 1-unit increase of ln-NP was significantly associated with a decrease in head circumference (β = -0.12, 95% CI: -0.20, -0.04 for 0-6 months; β = -0.11, 95% CI: -0.21, -0.02 for 0-18 months), and height z-score (β = -0.06, 95% CI: -0.12, -0.01 for 0-6 years). Although the estimates suggested that no significant dose-response between prenatal NP exposure and child growth, children who in the high dose group had smaller head circumference and height than those children who in the low dose group (Table 15, p69).

Discussion

Our findings indicated that prenatal exposure to nonylphenol was adversely related to the birth outcome and child growth at early childhood, especially for head circumference and height. However, no effects were found for exposure to bisphenol A and octylphenol.

Compared with previous studies, the BPA, NP and OP levels in cord blood in our study were slightly higher than other countries and the general population in Northern Taiwan (Chou et al., 2011; Chen et al., 2008; Lee et al., 2008; Schönfelder et al., 2002). In the US population, concentrations of BPA for those in low annual household income were higher than those in high household income (Calafat et al., 2008). Although we didn't find the significant inverse trend with annual household income, the mothers whose annual household income was below NT$ 1,000,000 had high BPA level in this study. Furthermore, we found the significant inverse trend for NP concentration with mother's education level and annual household income.

To our knowledge, this is the first study to investigate the association between NP levels in cord blood and child growth. Our study found that head circumference and height were decreased with the increase in the prenatal NP exposure. Similar results were found in animal studies, Hirano et al found an adverse effect of NP exposure on

body length among aquatic invertebrate species, and the results indicated that the body length to be the most sensitive to NP exposure (Hirano et al., 2009). Another study found that birth length was decreased with the increase in the gestational exposure of NP concentration (Jie et al., 2010). After categorizing NP exposure in quartile, we observed that children's head circumference and height in higher exposure group were smaller and shorter than low exposure group. These findings suggested that higher prenatal NP exposure may lead to the adverse effect on child growth. Although the half-life of NP from the blood was 2-3 hour (Müller et al., 1998), the exposure rout of NP is ubiquitous in the environment and repeated exposure of fetus due to increased amount taken by pregnant mothers is possibly lead to the adverse effect on children's growth and development.

We didn't find the prenatal BPA exposure affect birth sizes and child growth, also the inconsistent findings were shown in previous studies either in rodent or in human. Perinatal low dose BPA exposure to rate was associated with increase in body weight after birth and continued into adulthood (Rubin et al., 2001), another study found the effect on perinatal BPA exposure with decrease in body weight in postnatal days (Honma et al., 2002). Moreover, previous human studies had shown that prenatal BPA is associated with decrease in gestational age and birth weight (Chou et al., 2011; Cantonwine et al., 2010), and increase in head circumference (Philippat et al., 2012).

Regarding the BPA exposure and obesity, the association between BPA exposure and obesity in adults and elderly adults had been shown in previous studies (Wang et al., 2012; Carwile and Michels, 2011). So far the association was found in adults rather than the young children. Furthermore, the half-life of BPA from blood was less than 6 hours and rapidly excreted with urine (Völkel et al., 2002).

Several potential limitations in our study should be discussed. First, the most important limitation in our study, a single plot blood collection has the potential to misclassify exposure. The concentration of BPA in urine is variable over time during pregnancy, and many environmental factor are related with BPA exposure (Braun et al., 2011). In this study, we assumed the phenols exposure sources of theses pregnant mothers are regular and sustained during pregnancy, although the half-life of phenols is short. In addition, all the cord blood was collected at delivery. We standardized the timing of cord blood collection to reduce the variability over time. Second, we didn't measure the postnatal exposure to phenols of these children. Phenols exposure routes of young children are ubiquitous in the environment such as dietary ingestion, non-dietary ingestion, and inhalation route. Postnatal exposure is also important for exposure assessment of children and may lead to the adverse effect on child growth. Additionally, measurement errors of birth outcomes may exist in this study, especially for birth length and head circumference. The measurement of head circumference is

likely to have errors due to head modeling. The measurement errors were expected to be random, and we excluded the irrational measurements of growth data for each subjects.

However, this is a prospective and longitudinal birth cohort study, and we had repeated measurements of child growth at different age to follow up the child's growth and development. Also, we had lead and cotinine levels in cord blood and adjusted these potential confounders in the models to control the effect of lead and cotinine exposure on child growth. Braun et al (2011) found that the urinary BPA concentrations were positively associated with serum cotinine levels among the pregnant mothers. Exposure to BPA from tobacco smoking because BPA comprises 25% of the weight of some cigarette filters (Jackson and Darnell, 1985). Therefore, Braun et al (2011) suggested that further studies should examine the joint effect of BPA and tobacco smoke exposure and adjust for on another.

Conclusion

According to the results of this study, we observed the consistent effect of prenatal NP exposure on head circumference and body height from birth to 18 months and 6 years, respectively. This evidence supported the association between prenatal NP exposure and child growth. However, among these young children, we didn't find an

effect of prenatal BPA and OP exposure on birth sizes and child growth. Because of the inconsistent findings and finite researches in the young children, we hope further studies will have more comprehensive exposure assessment data and explore the potential effect of phenols exposure and child growth.

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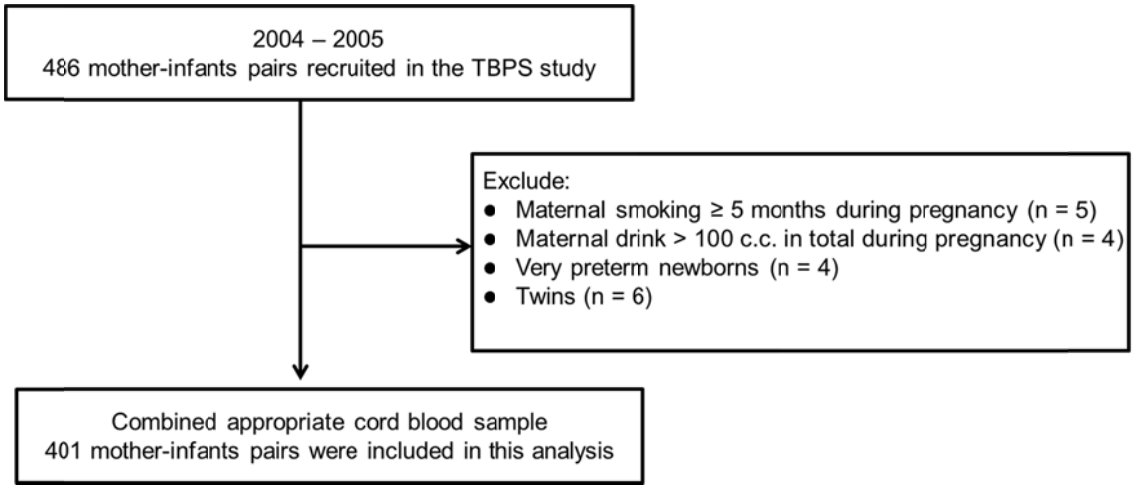


Figure 1. The flow chart of study population

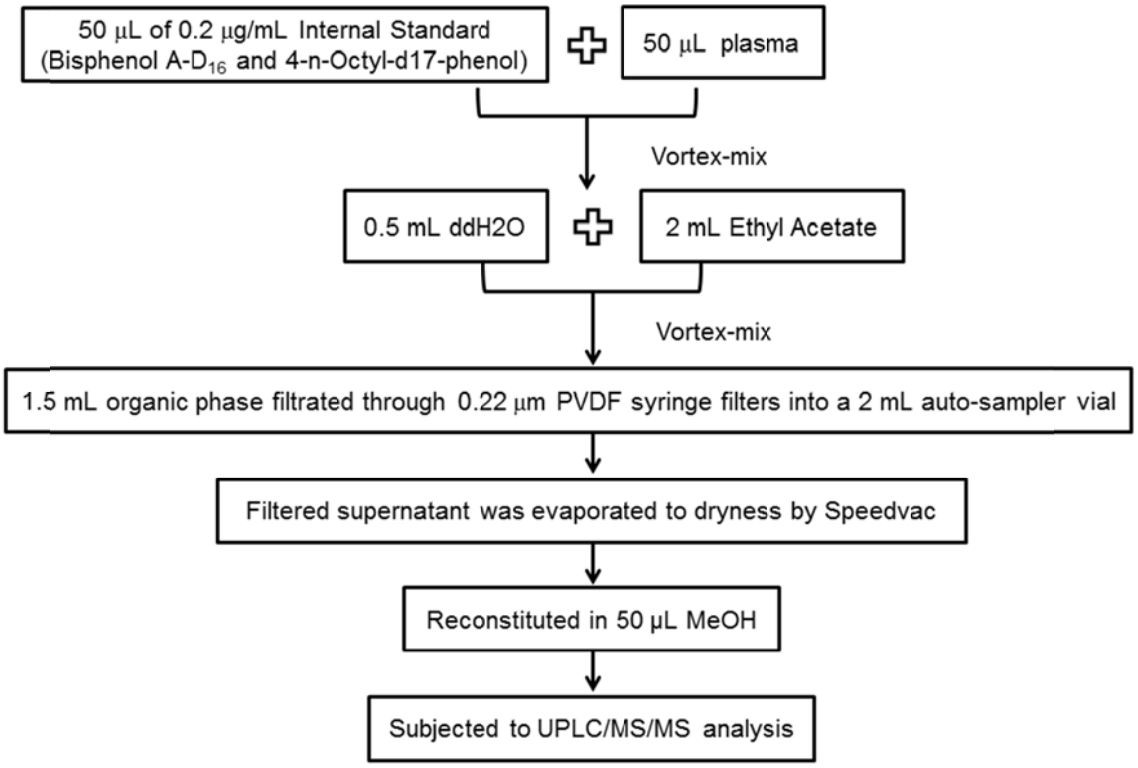


Figure 2. The flow chart of sample preparation

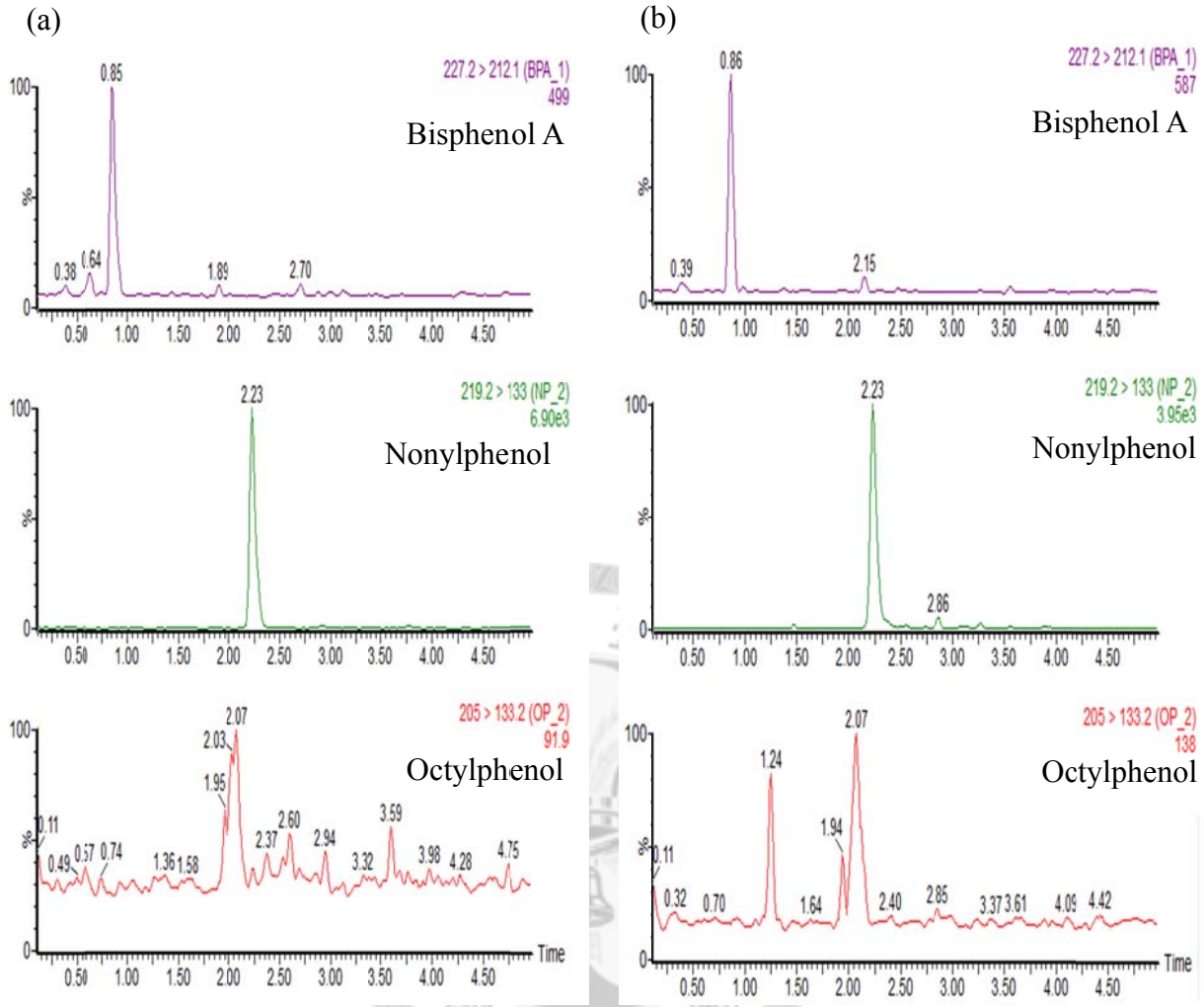


Figure 3. UPLC/MS/MS chromatogram of solvent blank and matrix blank: (a) solvent blank: MeOH, (b) matrix blank: bovine plasma

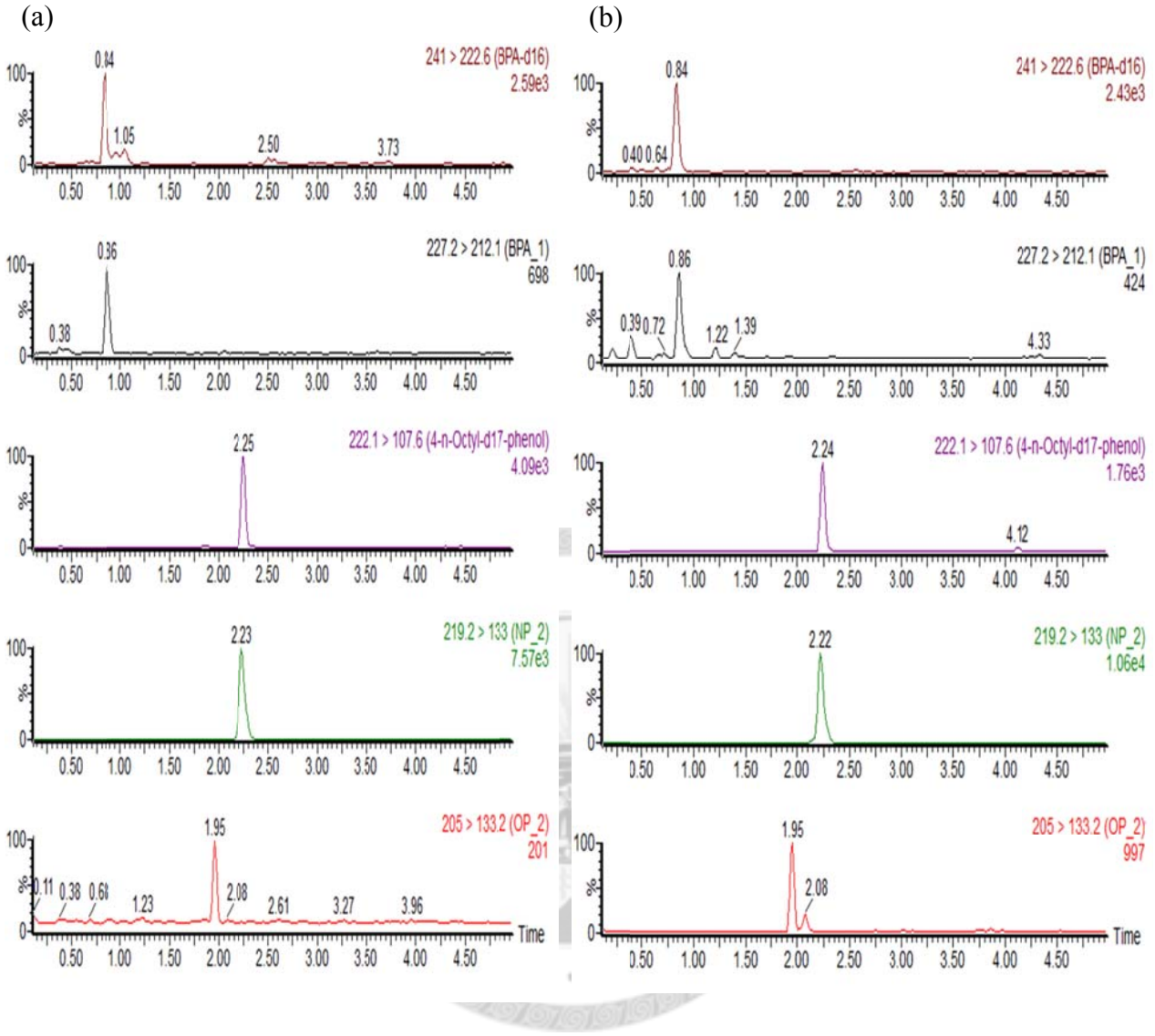
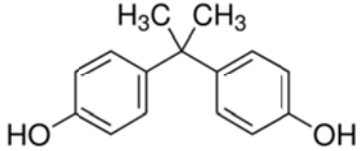
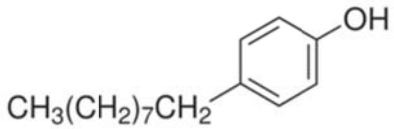
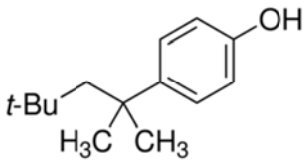
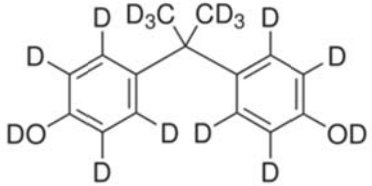
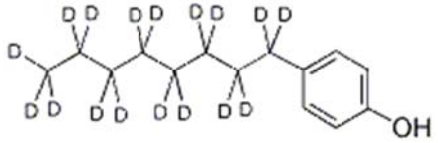


Figure 4. UPLC/MS/MS chromatogram of bovine plasma and human cord blood: (a) bovine plasma spiked with 50 ng/mL of BPA, NP, OP and the 200 ng/mL of internal standard. (b) human cord blood plasma

Table 1. Selected reaction monitoring (SRM) transitions, individual collision energy and cone voltage of the analytes

Analytes	MW	Precursor ion (m/z)	Product ion (m/z)	Cone voltage (V)	Collision energy (V)
BPA 	228.3	227.2	212.1 132.8	35	18
NP 	220.4	219.2	133.0 147.0	35	30
OP 	206.3	205.0	133.2 147.0	35	25
BPA-d16 	244.4	241.0	222.6	35	22
4-n-Octyl-d17-phenol 	223.4	222.1	107.6	35	25

BPA-d16 was used as internal standard of BPA

4-n-Octyl-d17-phenol was used as internal standard of NP and OP

Table 2. Instrumental parameters of the mass spectrometer

Parameter	Value
Ionization Mode	ESI-
Voltages	
Capillary (kV)	3.0
Extractor (V)	3
RF Lens (V)	0
Temperature	
Source temperature (℃)	120
Desolvation temperature (℃)	400
Column Oven (℃)	60
Gas Flow	
Desolvation gas flow (L/hr)	900
Cone gas flow (L/hr)	50
Analyzer	
LM 1 resolution	12
HM 1 resolution	12
Ion Energy 1 (V)	0.3
Entrance 1 (V)	1
Exit 1 (V)	1
LM 2 resolution	12
HM 2 resolution	12
Ion Energy 2 (V)	3.0
Multiplier voltage (V)	650
Gas Cell Pirani Pressure (mbar)	3.13×10^{-3}

Table 3. Matrix effect factor (%), extraction efficiency and recovery percentages of analytes with different concentration in bovine plasma (n=3)

	BPA			NP			OP		
	10 ng/mL	25 ng/mL	100 ng/mL	10 ng/mL	25 ng/mL	100 ng/mL	10 ng/mL	25 ng/mL	100 ng/mL
Matrix effect factor	147.7 ± 16.4	111.8 ± 13.07	114.3 ± 1.46	88.1 ± 17.4	81.5 ± 6.37	97.9 ± 4.71	104.7 ± 3.8	85.0 ± 11	117.7 ± 16.45
Extraction efficiency	67.5 ± 9.01 (13.35)	102.2 ± 7.84 (7.64)	64.4 ± 16.39 (25.46)	123.3 ± 2.60 (2.11)	105.3 ± 8.34 (7.29)	92.9 ± 18.36 (19.77)	76.1 ± 18.15 (23.85)	87.4 ± 14.58 (16.68)	96.3 ± 6.39 (6.63)
Recovery	105 ± 13.89 (13.23)	99.5 ± 2.72 (2.74)	98.2 ± 2.41 (2.46)	102 ± 11.53 (11.31)	94.3 ± 1.89 (2.01)	100.8 ± 0.71 (0.70)	107 ± 13.53 (12.64)	101.6 ± 5.66 (5.57)	99.4 ± 1.11 (1.11)

Values are mean ± SD (RSD%)

Matrix effect% = (area of post-extraction spike / area of standard) x 100%

Extraction efficiency (%) = (area of pre-extraction spike / area of post-extraction spike) x 100%

Recovery (%) = (measured value / theoretical value) x 100%

Table 4. Intra- and Inter-day and precision for BPA, NP, and OP in bovine plasma (n=3)

Concentration (ng/mL)		BPA		NP		OP	
		Intra-day	Inter-day	Intra-day	Inter-day	Intra-day	Inter-day
0.5	Mean	0.47	0.43				
	RSD%	12.37	13.32				
	Bias%	-6.67	-13.33				
2.5	Mean	2.33	2.40			2.45	2.53
	RSD%	4.95	11.02			2.89	2.79
	Bias%	-6.67	-4.00			-2.00	1.33
5	Mean	4.97	4.67			5.37	5.05
	RSD%	6.47	8.11			10.60	4.20
	Bias%	-0.67	-6.67			7.33	1.00
10	Mean	11.95	11.63	9.85	9.53	10.10	10.17
	RSD%	7.69	10.75	0.72	1.60	4.32	1.14
	Bias%	19.50	16.33	-1.50	-4.67	1.00	1.67
25	Mean	25.50	25.30	25.45	25.57	22.35	23.15
	RSD%	1.18	1.81	0.28	2.22	7.91	2.75
	Bias%	2.00	1.20	1.80	2.27	-10.60	-7.40
50	Mean	50.90	52.23	51.33	50.73	52.40	51.03
	RSD%	1.11	2.01	1.62	1.86	0.54	2.47
	Bias%	1.80	4.47	2.60	1.47	4.80	2.07
100	Mean	97.00	99.13	99.65	100.63	94.00	100.93
	RSD%	4.84	0.67	0.07	1.14	4.81	8.29
	Bias%	-3.00	-0.87	-0.35	0.63	-6.00	0.93
200	Mean	200.93	201.20	199.13	201.70	204.33	204.40
	RSD%	0.50	0.42	1.23	0.37	3.03	1.99
	Bias%	0.47	0.60	-0.43	0.85	2.17	2.20
500	Mean	500.70	503.33	505.85	498.63		
	RSD%	0.18	0.28	1.10	0.25		
	Bias%	0.14	0.67	1.17	-0.27		
750	Mean			753.85	748.83		
	RSD%			0.98	0.14		
	Bias%			0.51	-0.16		

RSD% = (standard deviation / mean) x 100%

Bias% = [(measured value – theoretical value) / theoretical value] x 100%

Table 5. Quantification of the spiked samples in human cord blood plasma (n=3)

Analyte	No spike (ng/mL)	Low [a] level (ng/mL)	Medium [b] level (ng/mL)	High [c] level (ng/mL)
BPA	5.17 ± 1.70 (32.98%)	13.07 ± 3.38 (25.90%)	23.47 ± 4.46 (19.01%)	136.80 ± 11.95 (8.74%)
NP	10.00 ± 2.33 (23.26%)	13.67 ± 0.81 (5.96%)	29.83 ± 2.24 (7.50%)	112.60 ± 8.84 (7.85%)
OP	2.63 ± 0.32 (12.21%)	7.33 ± 1.27 (17.37%)	21.33 ± 4.61 (21.59%)	106.77 ± 7.51 (7.03%)

Values are mean ± SD (RSD%)

[a] Spike at 5 ng/mL for phenols

[b] Spike at 20 ng/mL for phenols

[c] Spike at 100 ng/mL for phenols

Table 6. The detection rate and concentration of BPA, NP, OP in cord blood plasma (n=401)

Analytes	Detection rate % (> LOQ)	Median (range) (ng/mL)	Mean (SD) (ng/mL)	90th percentile (ng/mL)
BPA	55.86%	1.50 (0.25 - 211.40)	8.33 (18.02)	21.50
NP	77.56%	60.97 (5.00 - 561.57)	83.26 (87.43)	187.47
OP	68.33%	2.30 (0.45 - 183.4)	10.20 (20.65)	24.3

The backgrounds of BPA and NP (1.60 and 13.34 ng/mL) were deducted

The LOD of OP was 0.89 ng/mL

The LOQ of BPA, NP and OP were 0.5, 10 and 2.96 ng/mL, respectively

Table 7. Characteristics of 401 mother-infants pairs included in this study

Characteristic	All women and children
Maternal characteristics	
Age (years)	30.8 ± 4.6
Pregnancy BMI (kg/m^2)	26.8 ± 3.8
Maternal education (%)	
High school and below	228 (56.9)
University and above	173 (43.1)
Prenatal ETS [a] exposure (%)	
Yes	116 (28.9)
No	285 (71.1)
Parity	
0	192 (47.9)
≥1	209 (52.1)
Family characteristics	
Annual household income	
< NT$ 1,000,000	242 (60.4)
≥ NT$ 1,000,000	159 (39.7)
Infant characteristics	
Gender (%)	
Male	207 (51.6)
Female	194 (48.3)
Lead levels in cord blood (ng/mL) [b]	1.07 ± 1.91
Cotinine levels in cord blood (ng/mL) [b]	0.15 ± 4.46
Birth outcomes	
Gestational age (weeks)	38.6 ± 1.4
Birth weight (g)	3187.2 ± 424.3
Birth length (cm)	49.1 ± 2.0
Head circumference (cm)	33.6 ± 1.6

Values are mean ± standard deviation or percent.

[a] ETS, environmental tobacco smoke

[b] Values are GM ± GSD

Table 8. Phenols levels distribution in maternal and infant's characteristics

		BPA (ng/mL)			NP (ng/mL)			OP (ng/mL)		
	No. (%)	GM	GSD	P-value	GM	GSD	P-value	GM	GSD	P-value
Maternal characteristics										
Age (years)				0.6007			**0.0327**			0.1244
< 30	176 (43.9)	1.80	7.33		47.23	3.96		2.10	4.98	
30-34	122 (30.4)	1.60	6.18		30.90	4.57		2.66	6.04	
≥ 35	103 (25.7)	1.42	6.75		34.43	4.43		3.20	5.64	
Body mass index (kg/m^2)				0.5719			0.8891			0.5100
< 24	81 (20.2)	1.38	6.19		36.48	4.19		2.07	4.66	
24-28.6	222 (55.4)	1.64	7.02		38.00	4.39		2.65	5.89	
≥ 28.7	98 (24.4)	1.87	6.89		40.47	4.25		2.64	5.32	
Maternal education				0.1209			0.0538			**0.0353**
High school and below	228 (56.9)	1.86	7.17		43.25	4.10		2.15	5.22	
University and above	173 (43.1)	1.38	6.29		32.57	4.53		3.09	5.76	
Prenatal ETS exposure				**0.0216**			0.4845			0.0645
No	285 (71.1)	1.42	6.31		39.54	4.36		2.78	5.70	
Yes	116 (28.9)	2.31	7.86		35.33	4.17		1.97	4.89	
Parity				0.9221			0.0696			0.2783
0	192 (47.9)	1.65	7.04		43.93	3.99		2.28	5.32	
≥ 1	209 (52.1)	1.62	6.63		33.72	4.56		2.75	5.64	
Family characteristics										
Annual family income				0.3694			**0.0092**			**0.0007**
< NT$ 1,000,000	242 (60.4)	1.75	7.09		44.62	4.14		1.99	5.03	
≥ NT$ 1,000,000	159 (39.7)	1.47	6.40		30.30	4.44		3.58	5.90	
Infant characteristics										
Gender				0.3576			0.3452			0.0717
Male	207 (51.6)	1.78	6.84		35.81	4.59		2.92	5.81	
Female	194 (48.3)	1.49	6.78		41.10	4.00		2.15	5.10	

Table 9. Results from univariable linear/mixed model analysis

Covariate	Newborns [a]			0-6 months [b]		
	N	Crude β	95% CI	N	Crude β	95% CI
Length or height (cm)	399			401		
Gender§		**-0.53#**	**(-0.91, -0.15)**		**-1.14***	**(-1.77, -0.52)**
Parity§		-0.10	(-0.48, 0.29)		-0.21	(-0.85, 0.44)
Gestational age (weeks)		**0.59****	**(0.47, 0.71)**		**0.71****	**(0.49, 0.94)**
Breastfeeding§		0.38	(-0.22, 0.98)		0.05	(-0.78, 0.88)
Maternal age (years)		0.04	(-0.004, 0.08)		**0.15****	**(0.08, 0.22)**
Maternal education§		0.22	(-0.17, 0.61)		**0.79#**	**(0.15, 1.44)**
Pregnancy BMI (kg/m^2)		**0.12****	**(0.07, 0.17)**		0.06	(-0.03, 0.16)
Annual family income§		-0.21	(-0.61, 0.18)		-0.47	(-1.12, 0.18)
Lead levels in cord blood (ng/mL)†		0.27	(-0.03, 0.56)		0.04	(-0.45, 0.53)
Cotinine levels in cord blood (ng/mL) †		**-0.15#**	**(-0.28, -0.02)**		**-0.34***	**(-0.58, -0.11)**
Weight (g)	400			401		
Gender§		**-155.52***	**(-237.68, -73.37)**		**-0.36****	**(-0.52, -0.21)**
Parity§		27.21	(-56.36, 110.77)		-0.09	(-0.26, .07)
Gestational age (weeks)		**143.56****	**(117.69, 169.43)**		**0.15****	**(0.09, 0.21)**
Breastfeeding§		71.62	(-53.70, 196.93)		0.07	(-0.15, 0.29)
Maternal age (years)		**15.87***	**(6.94, 24.80)**		**0.03***	**(0.01, 0.05)**
Maternal education§		**101.12#**	**(17.42, 184.83)**		0.13	(-0.04, 0.29)
Pregnancy BMI (kg/m^2)		**36.09****	**(25.52, 46.66)**		0.02	(-0.0004, 0.05)
Annual family income§		21.88	(-63.43, 107.19)		-0.02	(-0.19, 0.15)
Lead levels in cord blood (ng/mL)†		53.03	(-11.26, 117.32)		0.03	(-0.09, 0.15)
Cotinine levels in cord blood (ng/mL) †		**-41.79***	**(-69.44, -14.15)**		**-0.08***	**(-0.14, -0.02)**
Head circumference (cm)	399			401		
Gender§		**-0.67****	**(-0.97, -0.37)**		**-0.91****	**(-1.26, -0.57)**
Parity§		0.23	(-0.08, 0.54)		-0.13	(-0.49, 0.23)
Gestational age (weeks)		**0.32****	**(0.22, 0.43)**		**0.35****	**(0.22, 0.47)**
Breastfeeding§		-0.12	(-0.54, 0.30)		0.03	(-0.44, 0.49)
Maternal age (years)		**0.10****	**(0.07, 0.13)**		**0.09****	**(0.05, 0.13)**
Maternal education§		**0.83****	**(0.54, 1.13)**		**0.57***	**(0.21, 0.94)**
Pregnancy BMI (kg/m^2)		**0.09****	**(0.05, 0.13)**		0.05	(-0.004, 0.11)
Annual family income§		**0.48***	**(0.17, 0.79)**		-0.18	(-0.55, 0.19)
Lead levels in cord blood (ng/mL)†		0.15	(-0.09, 0.39)		0.21	(-0.09, 0.52)
Cotinine levels in cord blood (ng/mL) †		**-0.20****	**(-0.30, -0.10)**		**-0.22***	**(-0.35, -0.09)**

†Lead and cotinine levels in cord blood were natural log-transformed

[a] Linear regression; [b] Mixed model; # p-value < 0.05, * p-value < 0.01, ** p-value < 0.0001

§Coding of covariates: gender: 1=boy, 2=girl; parity: 1=0, 2=≥1; duration of breastfeeding: 1=<6, 2=≥6 months; maternal education: 1=high school and below, 2=university and above; annual family income: 1=< NT$ 1,000,000, 2=≥ NT$ 1,000,000.

Table 10. Linear regression models of phenols levels in cord blood and birth outcomes (n = 401)

	ln BPA (ng/mL)		ln NP (ng/mL)		ln OP (ng/mL)	
	Crude β (95% CI)	Adjusted β (95% CI)	Crude β (95% CI)	Adjusted β (95% CI)	Crude β (95% CI)	Adjusted β (95% CI)
Gestational age [a] (weeks)	-0.03 (-0.10, 0.04)	-0.02 (-0.10, 0.05)	0.003 (-0.09, 0.10)	0.01 (-0.08, 0.11)	**0.09* (0.01, 0.17)**	0.07 (-0.01, 0.15)
Birth weight [b] (g)	-2.56 (-24.36, 19.24)	-1.97 (-20.17, 16.23)	-11.27 (-39.87, 17.34)	-13.59 (-37.64, 10.46)	20.85 (-3.62, 45.32)	3.70 (-17.12, 24.53)
Birth length [b] (cm)	0.02 (-0.08, 0.12)	0.02 (-0.06 0.11)	-0.02 (-0.15, 0.11)	-0.04 (-0.16, 0.068)	0.01 (-0.11, 0.12)	-0.05 (-0.15, 0.06)
Head circumference [b] (cm)	0.02 (-0.06, 0.10)	0.03 (-0.04, 0.10)	**-0.15** (-0.25, -0.04)**	**-0.13** (-0.23, -0.03)**	**0.11* (0.03, 0.20)**	0.05 (-0.03, 0.14)

All phenols, lead, and cotinine concentrations in cord blood were natural log-transformed.

[a] Adjusted gender, lead and cotinine levels in cord blood, maternal education, maternal BMI during pregnancy, and annual household income

[b] Adjusted gender, gestational age, lead and cotinine levels in cord blood, maternal education, maternal BMI during pregnancy, and annual household income

* p-value < 0.05, ** p-value < 0.01

Table 11. Mixed models of phenols levels in cord blood and child growth from birth to 12 months (n = 401)

	Age 0-6 months						Age 0-12 months					
	Crude model		Adjusted Model 1[a]		Adjusted Model 2[b]		Crude model		Adjusted Model 1[a]		Adjusted Model 2[b]	
	β	95% CI	β	95% CI	β	95% CI	β	95% CI	β	95% CI	β	95% CI
Length or height (cm)												
ln BPA	-0.04	(-0.21, 0.13)	-0.01	(-0.12, 0.10)	0.0005	(-0.10, 0.10)	0.05	(-0.15, 0.24)	-0.04	(-0.16, 0.07)	-0.04	(-0.15, 0.07)
ln NP	-0.06	(-0.28, 0.15)	-0.11	(-0.26, 0.03)	-0.10	(-0.27, 0.03)	-0.12	(-0.37, 0.13)	-0.10	(-0.25, 0.06)	-0.08	(-0.22, 0.07)
ln OP	0.10	(-0.09, 0.28)	0.05	(-0.07, 0.17)	-0.01	(-0.12, 0.10)	0.11	(-0.10, 0.32)	0.05	(-0.08, 0.18)	-0.01	(-0.13, 0.11)
Weight (g)												
ln BPA	-0.01	(-0.06, 0.03)	-0.01	(-0.04, 0.02)	-0.01	(-0.04, 0.01)	0.00003	(-0.06, 0.06)	-0.02	(-0.06, 0.01)	-0.03	(-0.06, 0.01)
ln NP	0.02	(-0.04, 0.07)	0.001	(-0.04, 0.04)	0.01	(-0.03, 0.04)	-0.02	(-0.09, 0.05)	-0.01	(-0.06, 0.04)	-0.01	(-0.05, 0.04)
ln OP	0.02	(-0.02, 0.07)	0.014	(-0.02, 0.04)	-0.003	(-0.03, 0.03)	0.03	(-0.03, 0.09)	0.01	(-0.03, 0.05)	-0.004	(-0.04, 0.03)
Head circumference (cm)												
ln BPA	-0.04	(-0.14, 0.06)	-0.03	(-0.10, 0.04)	-0.03	(-0.09, 0.03)	-0.001	(-0.10, 0.10)	-0.04	(-0.12, 0.03)	-0.05	(-0.11, 0.02)
ln NP	-0.05	(-0.17, 0.07)	**-0.13****	**(-0.22, -0.05)**	**-0.10****	**(-0.18, -0.03)**	-0.09	(-0.22, 0.05)	**-0.11***	**(-0.20, -0.02)**	**-0.08***	**(-0.16, -0.001)**
ln OP	0.02	(-0.08, 0.12)	0.03	(-0.05, 0.10)	-0.02	(-0.08, 0.05)	0.02	(-0.09, 0.13)	0.01	(-0.07, 0.09)	-0.03	(-0.10, 0.03)
Weight z-score												
ln BPA	-0.01	(-0.05, 0.03)	-0.01	(-0.04, 0.03)	-0.01	(-0.04, 0.03)	-0.02	(-0.06, 0.02)	-0.02	(-0.06, 0.02)	-0.02	(-0.05, 0.02)
ln NP	0.01	(-0.04, 0.05)	0.002	(-0.04, 0.05)	0.005	(-0.04, 0.05)	-0.02	(-0.07, 0.04)	-0.01	(-0.06, 0.04)	-0.01	(-0.06, 0.04)
ln OP	0.02	(-0.02, 0.06)	0.017	(-0.02, 0.05)	0.003	(-0.03, 0.04)	0.03	(-0.01, 0.08)	0.02	(-0.02, 0.06)	0.005	(-0.04, 0.05)
Height z-score												
ln BPA	-0.004	(-0.04, 0.03)	-0.001	(-0.03, 0.03)	0.004	(-0.03, 0.03)	-0.005	(-0.04, 0.03)	-0.01	(-0.04, 0.03)	-0.004	(-0.04, 0.03)
ln NP	-0.03	(-0.08, 0.02)	-0.03	(-0.08, 0.01)	-0.03	(-0.07, 0.01)	-0.04	(-0.08, 0.01)	-0.03	(-0.07, 0.01)	-0.03	(-0.07, 0.01)
ln OP	0.02	(-0.02, 0.06)	0.01	(-0.02, 0.05)	0.0002	(-0.03, 0.03)	0.03	(-0.02, 0.07)	0.01	(-0.03, 0.05)	0.0001	(-0.04, 0.04)

All phenols, lead, and cotinine concentrations in cord blood were natural log-transformed.

[a] Adjusted measurements time; [b] Adjusted measurements time, gender, gestational age, lead and cotinine levels in cord blood, and maternal education

* p-value < 0.05, ** p-value < 0.01

Table 12. Mixed models of phenols levels in cord blood and child growth from birth to 2 years (n = 401)

	Age 0-18 months						Age 0-2 years					
	Crude model		Adjusted Model 1[a]		Adjusted Model 2[b]		Crude model		Adjusted Model 1[a]		Adjusted Model 2[b]	
	β	95% CI	β	95% CI	β	95% CI	β	95% CI	β	95% CI	β	95% CI
Length or height (cm)												
ln BPA	-0.03	(-0.27, 0.20)	-0.04	(-0.17, 0.10)	-0.04	(-0.16, 0.09)	-0.02	(-0.30, 0.26)	-0.06	(-0.21, 0.09)	-0.06	(-0.20, 0.09)
ln NP	-0.11	(-0.41, 0.19)	-0.18*	(-0.36, -0.01)	-0.16	(-0.32, 0.002)	-0.23	(-0.58, 0.12)	**-0.21***	**(-0.41, -0.02)**	**-0.19***	**(-0.38, -0.004)**
ln OP	0.17	(-0.08, 0.42)	0.06	(-0.09, 0.20)	-0.003	(-0.14, 0.14)	0.31*	(0.01, 0.60)	0.07	(-0.10, 0.23)	0.005	(-0.15, 0.16)
Weight (g)												
ln BPA	-0.02	(-0.09, 0.04)	-0.02	(-0.07, 0.02)	-0.02	(-0.07, 0.02)	-0.01	(-0.09, 0.07)	-0.03	(-0.08, 0.02)	-0.03	(-0.08, 0.02)
ln NP	-0.02	(-0.10, 0.06)	-0.04	(-0.09, 0.02)	-0.03	(-0.08, 0.03)	-0.05	(-0.15, 0.05)	-0.05	(-0.11, 0.02)	-0.04	(-0.10, 0.03)
ln OP	0.04	(-0.03, 0.11)	0.01	(-0.04, 0.06)	-0.01	(-0.05, 0.04)	0.08	(-0.01, 0.16)	0.02	(-0.03, 0.08)	0.003	(-0.05, 0.06)
Head circumference (cm)												
ln BPA	-0.04	(-0.15, 0.08)	-0.02	(-0.10, 0.06)	-0.03	(-0.10, 0.04)	-0.03	(-0.16, 0.10)	-0.02	(-0.10, 0.07)	-0.03	(-0.11, 0.05)
ln NP	-0.02	(-0.16, 0.13)	**-0.13***	**(-0.23, -0.02)**	**-0.10***	**(-0.19, -0.01)**	-0.05	(-0.21, 0.11)	-0.12*	(-0.23, -0.01)	-0.09	(-0.19, 0.01)
ln OP	0.05	(-0.07, 0.17)	0.02	(-0.07, 0.11)	-0.02	(-0.10, 0.05)	0.10	(-0.04, 0.23)	0.03	(-0.06, 0.12)	-0.02	(-0.10, 0.07)
Weight z-score												
ln BPA	-0.02	(-0.07, 0.02)	-0.02	(-0.06, 0.02)	-0.02	(-0.06, 0.02)	-0.02	(-0.07, 0.02)	-0.03	(-0.07, 0.02)	-0.02	(-0.06, 0.02)
ln NP	-0.03	(-0.08, 0.03)	-0.03	(-0.08, 0.03)	-0.02	(-0.08, 0.03)	-0.04	(-0.09, 0.02)	-0.04	(-0.09, 0.02)	-0.03	(-0.09, 0.02)
ln OP	0.02	(-0.02, 0.07)	0.02	(-0.03, 0.06)	0.002	(-0.04, 0.04)	0.03	(-0.02, 0.08)	0.02	(-0.02, 0.07)	0.01	(-0.04, 0.05)
Height z-score												
ln BPA	-0.01	(-0.05, 0.03)	-0.01	(-0.05, 0.03)	-0.01	(-0.04, 0.03)	-0.01	(-0.05, 0.03)	-0.02	(-0.05, 0.02)	-0.01	(-0.05, 0.03)
ln NP	-0.05	(-0.10, 0.004)	-0.05	(-0.09, 0.002)	-0.05	(-0.09, 0.0005)	**-0.06***	**(-0.11, -0.01)**	**-0.06***	**(-0.10, -0.01)**	**-0.05***	**(-0.10, -0.01)**
ln OP	0.02	(-0.02, 0.07)	0.01	(-0.03, 0.05)	0.001	(-0.04, 0.04)	0.03	(-0.02, 0.07)	0.02	(-0.02, 0.06)	0.004	(-0.04, 0.05)

All phenols, lead, and cotinine concentrations in cord blood were natural log-transformed.

[a] Adjusted measurements time; [b] Adjusted measurements time, gender, gestational age, lead and cotinine levels in cord blood, and maternal education

* p-value < 0.05, ** p-value < 0.01

Table 13. Mixed models of phenols levels in cord blood and child growth from birth to 5 years (n = 401)

	Age 0-3 years						Age 0-5 years					
	Crude model		Adjusted Model 1[a]		Adjusted Model 2[b]		Crude model		Adjusted Model 1[a]		Adjusted Model 2[b]	
	β	95% CI	β	95% CI	β	95% CI	β	95% CI	β	95% CI	β	95% CI
Length or height (cm)												
ln BPA	-0.12	(-0.42, 0.18)	-0.06	(-0.22, 0.11)	-0.05	(-0.21, 0.11)	-0.19	(-0.57, 0.19)	-0.06	(-0.25, 0.13)	-0.05	(-0.24, 0.13)
ln NP	-0.20	(-0.58, 0.18)	**-0.24***	**(-0.45, -0.02)**	**-0.21***	**(-0.41, -0.01)**	-0.19	(-0.68, 0.29)	-0.23	(-0.48, 0.02)	-0.20	(-0.44, 0.04)
ln OP	0.22	(-0.09, 0.54)	0.11	(-0.07, 0.30)	0.04	(-0.13, 0.21)	0.35	(-0.06, 0.75)	0.10	(-0.11, 0.31)	0.03	(-0.17, 0.23)
Weight (g)												
ln BPA	-0.03	(-0.12, 0.05)	-0.03	(-0.09, 0.03)	-0.03	(-0.09, 0.02)	-0.07	(-0.18, 0.05)	-0.03	(-0.10, 0.03)	-0.03	(-0.09, 0.03)
ln NP	-0.03	(-0.14, 0.09)	-0.05	(-0.12, 0.03)	-0.04	(-0.11, 0.04)	0.001	(-0.14, 0.15)	-0.06	(-0.14, 0.03)	-0.04	(-0.12, 0.04)
ln OP	0.05	(-0.04, 0.15)	0.03	(-0.04, 0.09)	0.01	(-0.06, 0.07)	0.07	(-0.05, 0.19)	0.03	(-0.04, 0.10)	0.01	(-0.06, 0.08)
Weight z-score												
ln BPA	-0.03	(-0.08, 0.01)	-0.03	(-0.07, 0.01)	-0.03	(-0.07, 0.02)	-0.03	(-0.08, 0.01)	-0.03	(-0.07, 0.01)	-0.03	(-0.07, 0.01)
ln NP	-0.03	(-0.09, 0.02)	-0.03	(-0.09, 0.02)	-0.03	(-0.08, 0.03)	-0.03	(-0.09, 0.02)	-0.03	(-0.09, 0.02)	-0.03	(-0.08, 0.03)
ln OP	0.03	(-0.02, 0.08)	0.02	(-0.02, 0.07)	0.01	(-0.04, 0.05)	0.03	(-0.02, 0.08)	0.02	(-0.02, 0.07)	0.01	(-0.04, 0.06)
Height z-score												
ln BPA	-0.02	(-0.06, 0.02)	-0.02	(-0.06, 0.02)	-0.01	(-0.05, 0.02)	-0.02	(-0.06, 0.02)	-0.02	(-0.06, 0.02)	-0.02	(-0.06, 0.02)
ln NP	**-0.06***	**(-0.11, -0.005)**	**-0.06***	**(-0.11, -0.01)**	**-0.05***	**(-0.10, -0.01)**	**-0.05***	**(-0.11, -0.002)**	**-0.05***	**(-0.11, -0.002)**	**-0.05***	**(-0.10, -0.002)**
ln OP	0.02	(-0.02, 0.07)	0.02	(-0.03, 0.06)	0.003	(-0.04, 0.04)	0.02	(-0.03, 0.06)	0.01	(-0.03, 0.06)	-0.001	(-0.04, 0.04)

All phenols, lead, and cotinine concentrations in cord blood were natural log-transformed.

[a] Adjusted measurements time; [b] Adjusted measurements time, gender, gestational age, lead and cotinine levels in cord blood, and maternal education

* p-value < 0.05, ** p-value < 0.01

Table 14. Mixed models of phenols levels in cord blood and child growth from birth to 6 years (n = 401)

	Age 0-6 years					
	Crude model		Adjusted Model 1[a]		Adjusted Model 2[b]	
	β	95% CI	β	95% CI	β	95% CI
Length or height (cm)						
ln BPA	-0.39	(-0.87, 0.09)	-0.05	(-0.25, 0.16)	-0.04	(-0.24, 0.16)
ln NP	-0.11	(-0.72, 0.50)	-0.327*	(-0.653, -0.01)	-0.25	(-0.50, 0.001)
ln OP	0.47	(-0.04, 0.98)	0.10	(-0.12, 0.32)	0.03	(-0.18, 0.24)
Weight (g)						
ln BPA	-0.14	(-0.28, 0.004)	-0.03	(-0.10, 0.04)	-0.03	(-0.10, 0.04)
ln NP	0.02	(-0.16, 0.20)	-0.06	(-0.15, 0.03)	-0.05	(-0.14, 0.04)
ln OP	0.09	(-0.06, 0.25)	0.03	(-0.05, 0.10)	0.001	(-0.07, 0.08)
Weight z-score						
ln BPA	-0.04	(-0.08, 0.01)	-0.03	(-0.08, 0.01)	-0.03	(-0.07, 0.01)
ln NP	-0.03	(-0.09, 0.03)	-0.03	(-0.09, 0.02)	-0.03	(-0.07, 0.01)
ln OP	0.03	(-0.02, 0.08)	0.02	(-0.02, 0.07)	0.01	(-0.04, 0.05)
Height z-score						
ln BPA	-0.03	(-0.07, 0.01)	-0.03	(-0.07, 0.02)	-0.02	(-0.06, 0.02)
ln NP	**-0.05***	**(-0.11, -0.001)**	**-0.05***	**(-0.11, -0.002)**	**-0.05***	**(-0.10, -0.002)**
ln OP	0.02	(-0.03, 0.06)	0.01	(-0.03, 0.06)	-0.002	(-0.04, 0.04)

All phenols, lead, and cotinine concentrations in cord blood were natural log-transformed.

[a] Adjusted measurements time

[b] Adjusted measurements time, gender, gestational age, lead and cotinine levels in cord blood, and maternal education

* p-value < 0.05, ** p-value < 0.01

Table 15. Dose-response of prenatal NP exposure and child growth

	Head circumference (cm)				Height (cm)			
	Age 0-18 months				Age 0-6 years			
NP (ng/mL)	Crude β	95% CI	Adjusted [a] β	95% CI	Crude β	95% CI	Adjusted [a] β	95% CI
< 5.00	0		0		0		0	
5.00 -60.94	0.16	(-0.46, 0.78)	-0.14	(-0.52, 0.24)	0.22	(-2.80, 2.37)	-0.67	(-1.73, 0.38)
60.95 -126.47	-0.18	(-0.78, 0.43)	-0.29	(-0.66, 0.08)	-1.26	(-3.76, 1.24)	-1.09*	(-2.11, -0.07)
> 126.47	-0.01	(-0.59, 0.57)	-0.29	(-0.65, 0.07)	-0.08	(-2.53, 2.37)	-0.93	(-1.94, 0.07)

All phenols, lead, and cotinine concentrations in cord blood were natural log-transformed.

[a] Adjusted measurement time, gender, gestational age, lead and cotinine levels in cord blood, maternal education

* p-value < 0.05, ** p-value < 0.01

Appendix 1

Comparison of two methods of sample preparations

A small experiment was conducted to compare two methods of derivatized with Dansyl chloride and underivatized analysis. For Dansyl derivatives, the signal intensity of phenols had been improved (Figure 1, p71). The signal intensity of NP background had also been improved, but high signal intensity of NP background would affect the low concentrations in the linear range (Figure 2, p71). The linear range of calibration curve would be too narrow. Furthermore, we couldn't use highly concentrated in the procedure of sample preparation because of the limited sample volume. Based on these reasons, underivatized method was used in this study.

Table 1. The flow chart of derivatized with Dansyl chloride and underivatized analysis

Derivatized with Dansyl chloride	**Underivatized**
50 µL plasma + 50 µL 0.4ppm IS	**50 µL plasma + 50 µL 0.1ppm IS**
↓ Vortex mixed	↓ Vortex mixed
+ 500 µL ddH_2O + 2 mL of ethyl acetat	**+ 500 µL ddH_2O + 2 mL of ethyl acetat**
↓ Vortex mixed	↓ Vortex mixed
1.5 mL organic phase filtrated through 0.22 µm syringe filter	**1.5 mL organic phase filtrated through 0.22 µm syringe filter**
↓ Speedvac	↓ Speedvac
100 µL of Sodium bicarbonate ($NaHCO_3$)，(100 mM, pH adjusted with NaOH to 10.5)	**Reconstituted in 50 µL MeOH**
↓ Vortex-mixing 1 min	↓
100 µL of dansyl chloride (1 mg/mL in acetone)	**UPLC/MS/MS**
↓ Vortex-mixing 1 min	
The mixture was kept at 60℃ for 3 min	
↓	
UPLC/MS/MS	

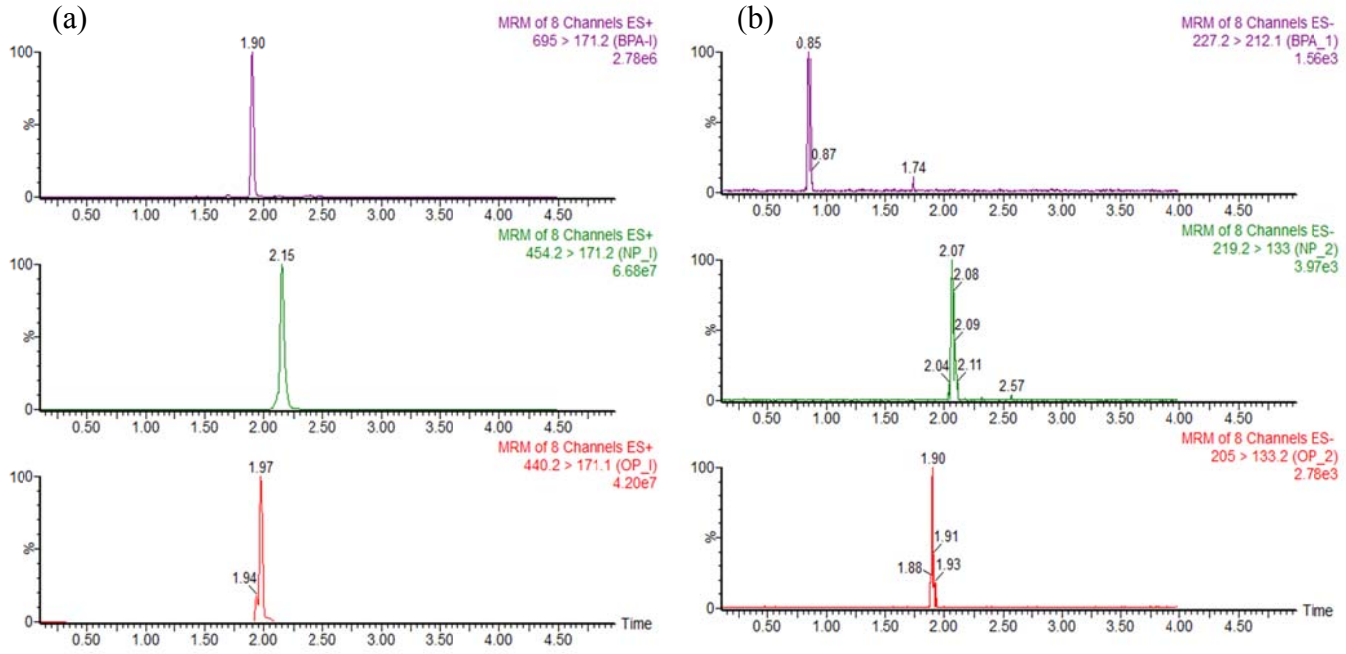


Figure 1. UPLC/MS/MS chromatogram of 50 ng/mL phenols in solvent: (a) Dansyl chloride; (b) Underivatized

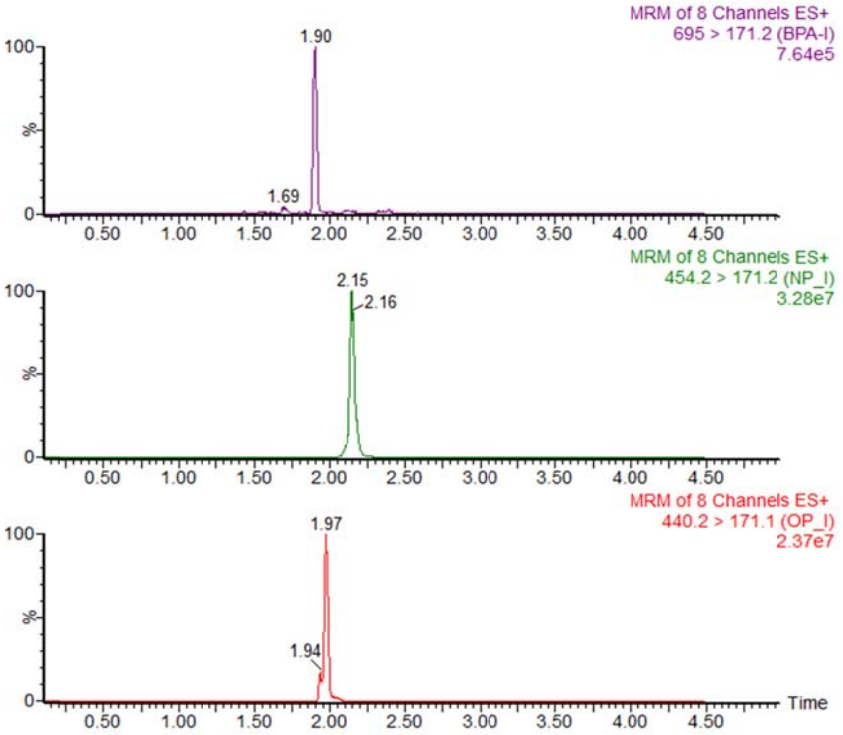


Figure 2. UPLC/MS/MS chromatogram of derivatized with Dansyl chloride in solvent blank (MeOH)

Appendix 2

Appendix 2. Paper reviews of phenols concentrations in umbilical cord blood

Analytes	Country	Study Year	No. subjects	Concentration (ng/mL)				References
				Mean (SD)	Median	GM	Range	
Bisphenol A	**Taiwan (Taipei)**	**April 2004 to January 2005**	**401**	**8.33 (18.02)**	**1.50**	**1.63**	**0.25 - 211.40**	**This study**
	Taiwan (Hsinchu)	January 2006 to August 2007	97			1.06	0.30 – 18.50	Chou et al., 2011
	Korea (Seoul, Cheongju, Gumi)	August 2008 to March 2009	25	< 0.6			< 0.60 - 0.70	Wan et al., 2010
	Korea	-	300	1.13 (1.43)	< 0.63	0.65	N.D. - 8.86	Lee et al., 2008
	Malaysia	-	180				N.D. - 4.05	Tan et al., 2003
	Germany (Berlin)	October 2000 to May 2001	37		2.3		0.20 - 9.20	Schönfelder et al., 2002
	Japan	-	32	2.20 (1.80)				Ikezuki et al., 2002
Nonylphenol	**Taiwan (Taipei)**	**April 2004 to January 2005**	**401**	**83.26 (87.43)**	**60.97**	**37.71**	**5.0 – 561.57**	**This study**
	Taiwan (Central)	-	124		0.91	2.69	N.D. – 182.0	Chen et al., 2008
	Taiwan (Northen)		50		41.80	12.90	N.D. – 211.0	
	Malaysia	-	180				N.D. – 15.17	Tan et al., 2003
Octylphenol	**Taiwan (Taipei)**	**April 2004 to January 2005**	**401**	**10.20 (20.65)**	**2.30**	**2.51**	**0.45 – 184.30**	**This study**
	Malaysia	-	180				N.D/ – 1.15	Tan et al., 2003

Appendix 3

Appendix 3. Paper reviews of prenatal exposure to BPA and birth outcomes

Country	Population	Study Year	Exposure assessment	Median / GM [a]	Findings	References
France	General population	2002 - 2006	Maternal urine	2.7	↑ Head circumference	Philippat et al., 2012
Taiwan (Hsinchu)	General population	January 2006 to August 2007	Maternal blood	2.5	↑ Risk of LBW (low birth weight) ↑ Risk of SGA (small for gestational age)	Chou et al., 2011
China	Occupational exposure	2004 - 2008	Personal air sampling	-	↓ Birth weight	Miao et al., 2011
Mexico	General population	2001 - 2003	Maternal urine	1.38	Gestational age ≤ 37 weeks had higher BPA concentration	Catonwine et al., 2010
New York	General population	March 1998 to March 2002	Maternal urine	1.3	No significant findings	Wolff et al., 2008

[a] Values are ng/mL; μg/g creatinine