# Prenatal Phthalate Exposures and Anogenital Distance in Swedish Boys

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**Running title:** Prenatal exposure to phthalates and AGD in boys

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## Abstract

**Background:** Phthalates are used as plasticizers in soft polyvinyl chloride (PVC) and in a large number of consumer products. Due to reported health risks, di-isononyl phthalate (DiNP) has been introduced as a replacement for diethyl hexyl phthalate (DEHP) in soft PVC. This raises concerns since animal data suggest that DiNP may have anti-androgenic properties similar to DEHP. The anogenital distance (AGD) - the distance from the anus to the genitals - has been used to assess reproductive toxicity.

**Objective:** The objective of this study was to examine the associations between prenatal phthalate exposure and AGD in Swedish infants.

**Methods:** AGD was measured in 196 boys at age 21 months and first trimester urine was analyzed for ten phthalate metabolites of DEP, DBP, DEHP, BBzP as well as DiNP and creatinine. Data on covariates were collected by questionnaires.

**Results:** The most significant associations were found between the shorter of two AGD measures (anoscrotal distance, AGDas) and DiNP metabolites and strongest for oh-MMeOP and oxo-MMeOP. However, the AGDas reduction was small (4%) in relation to more than an interquartile increase in DiNP exposure.

**Conclusions:** These findings call into question the safety of substituting DiNP for DEHP in soft PVC, particularly since a shorter male AGD has been shown to relate to male genital birth defects in children and impaired reproductive function in adult males and the fact that human levels of DiNP are increasing globally.

## Introduction

Diesters of 1,2-benzenedicarboxylic acid (phthalic acid), commonly referred to as phthalates, belong to a group of chemicals with endocrine disrupting properties, meaning that they can interfere with our normal hormonal balance, potentially resulting in adverse human health effects. A recent state of the art report from WHO provides new evidence for several human health risks from exposure to phthalates and other endocrine disrupters (EDCs) including reproductive health and sexual development (Bergman et al. 2012).

Phthalates are used as plasticizers in soft polyvinyl chloride (PVC) and found in a large number of commonly used consumer products including food, building materials, plastics, cosmetics, cleaning products, packages, toys, etc. (Bornehag et al. 2005; Dodson et al. 2012; Rudel et al. 2011). Often, the fraction of phthalates in the plastics is as high as 30% or more. Because they are not covalently bound to the product matrix, phthalates can leach into the surrounding environment. As a result they are routinely found in indoor air (Bergh et al. 2011; Rudel and Perovich 2009) and dust ( Abb et al. 2009; Bornehag et al. 2005; Bornehag et al. 2004; Langer et al. 2010; Zhang et al. 2013) as well as in food and water (Shi et al. 2012).

Phthalates are ubiquitous in the environment and humans are exposed by multiple routes (oral, dermal and inhalation), the pathway varying by phthalate. It has recently been shown, for example, that exposure to di-2-ethylhexyl phthalate (DEHP) is primarily via food and for children also via mouthing of plastics, while exposure to diethyl phthalate (DEP) and benzyl butyl phthalate (BBzP) is primarily via dermal and inhalation pathways (Carlstedt et al. 2013; Koch et al. 2013; Wittassek et al. 2011). Robust biomonitoring data show phthalate metabolites in human fluids such as urine, both in children (Langer et al. 2014) and adults (Wittassek et al. 2011), blood (Fredriksen et al. 2010; Wan et al. 2013) and breast milk (Fromme et al. 2011).

These compounds have also been found in amniotic fluid, suggesting that they cross the placental barrier and convey foetal exposure (Jensen et al. 2012).

One complication in studying phthalate exposure is that replacement of phthalates is continuously on going as risks are reported for older formulations. One example of this is the introduction of di-isononyl phthalate (DiNP), and more recently di-isononyl cyclohexane-1, 2-dicarboxylate (DINCH), to replace DEHP in soft PVC (ECHA 2013). Recent bio monitoring data show that urinary levels of DEHP metabolites are decreasing while DiNP-metabolites are increasing in European (Göen et al. 2011) and American populations (Silva et al. 2013).

**Phthalates and reproductive health**

The impact of endocrine disrupting chemicals on male reproductive health has been a research focus for almost 20 years. During that time, multiple studies in laboratory animals (since 1995) (Sharpe et al. 1995) and humans (since 2005) (Swan et al. 2005) have demonstrated the sensitivity of the developing male reproductive system to several phthalates. Phthalates may reduce the production of androgens by the testis and rodent studies have demonstrated that DEHP and dibutyl phthalate (DBP) disrupt androgen signaling when administered in the critical window for the development of the reproductive tract (MacLeod et al. 2010; Van den Driesche et al. 2011). In humans, there are similar findings where phthalates (e.g., DEHP and DBP) are suspected to be related to male reproductive and developmental abnormalities (ECHA 2013).

**Anogenital distance and phthalate exposure**

The anogenital distance (AGD) - the distance from the anus to the genitals - is a marker that has been used in animal studies to assess reproductive toxicity (USEPA 1996). AGD is a sexually dimorphic trait that develops *in utero* under androgen control and is 50-100% longer in males

than females.

Numerous studies have shown that prenatal phthalate exposure (notably DEHP, DBP, BBzP) shortens male AGD in rodents (Foster 2005; van den Driesche et al. 2011). Only a few human studies have examined prenatal phthalate exposure and AGD. The first to examine this association in humans reported significant inverse relationships between male AGD and DEP, DBP BBzP and monoisobutyl phthalate (MiBP) metabolites (Swan et al. 2005), and a later publication with a larger sample size and more powerful statistical methods found associations between male endpoints and metabolites of DEHP (Swan 2008). Recently a relationship between prenatal DEHP exposure and shorter AGD in male newborns was reported from Japan (Suzuki et al. 2012) and from Mexico (Bustamante-Montes et al. 2013). However, a study from Taiwan found a negative association between prenatal monobutyl phthalate (MBP) exposure and AGD in newborn girls but not in boys (Huang et al. 2009). To date no studies in humans have included metabolites of DiNP.

**Aim of the study**

Animal data suggest that DiNP may have anti-androgen properties similar to DEHP (Boberg et al. 2011). This raises concern, since DiNP has been introduced to replace DEHP and consequently DiNP exposure is rapidly increasing in populations globally. While several studies have examined phthalates and AGD in humans, none has included DiNP. Therefore, in the current study we examine the relationship between 1$^{st}$ trimester urinary metabolite concentrations of DEP, DBP, DEHP, BBzP as well as DiNP in relation to anogenital distance in boys at 21 months of age.

## Method

### Description of the SELMA study

The Swedish Environmental Longitudinal, Mother and child, Asthma and allergy (SELMA) study is a prospective birth cohort study in Sweden including more than 2,000 mother-child pairs followed from early pregnancy (Bornehag et al. 2012). The study aim is to investigate the impacts of early life exposure to endocrine disrupting chemicals and other exposures, for multiple outcomes of growth, development and chronic diseases.

The SELMA cohort was established by recruiting women in the 10th week of pregnancy in the county of Värmland, Sweden, between September 2007 and March 2010. Out of 8,394 reported pregnant women, 6,658 were invited to participate in the study. Among the invited women, 2,582 agreed to participate, corresponding to a participating rate of 39%. Of the 4,076 non-participants, 2,091 women were invited to complete a non-respondent questionnaire in order to examine possible selection bias. We found a self-selection bias in the established cohort when compared with the non-participant group, e.g. participating families did smoke less (14% vs. 19%), had more frequent asthma and allergy symptoms in the family (58% vs. 38%), as well as higher education (university level) among the mothers (51% vs. 36%) and more often lived in single-family houses (67% vs. 60%). However, there is no obvious reason that this selection bias will have an impact on identification of environmental risk factors for health effects. Detailed recruitment procedures, selection criteria as well as data relating to selection bias have been reported and discussed elsewhere (Bornehag et al. 2012). Biological samples (blood and urine) have been collected from the 2,582 pregnant women and their children. Information related to life styles, socioeconomic status, living conditions, diet, and medical history etc. has been collected using annual questionnaires (Bornehag et al. 2012).

**Measurements of AGD in baby boys**

Boys born between September 1st 2009 and November 20th 2010 (i.e., those who were younger than 18 months in the SELMA-study) (n=325) and their parents were invited to participate in the study and of these 228 participated (70%). Of these we were able to measure AGD in 225 boys, and of these, 196 children are included in the current analyses. Mean age of the 196 boys was 20.8 months. AGD was measured by two nurses (one pediatric staff nurse and one midwife) from the County Council of Värmland who were trained by research staff from The Infant Development and the Environment Study (TIDES), (Barret et al. 2014). The nurses had no knowledge of the mother´s phthalate concentrations. All AGD measurements were made in the baby's home or at a pediatric clinic.

We obtained two measurements of AGD using measurement methods that have been described elsewhere (Sathyanarayana et al. 2010). Briefly, the longer AGD measurement (AGDap) was measured from the center of the anus to the anterior base of the penis and the shorter (AGDas) from the center of the anus to the posterior base of the scrotum. The infant was placed on his back on a flat surface with his hips relaxed outward and pulled back towards his shoulders by his mother or an assistant. The examiner stood in front of the infant and made three measurements of both long and short AGD with a dial caliper and the coefficient of variation (CV) was calculated for each AGD measure. Only one measurement was made for 12 boys regarding AGDas and for 24 boys regarding AGDap.

**Phthalate metabolites in 1st trimester urine**

Of the 2,582 pregnant women participating in the SELMA-study, a first morning urine sample was obtained from 2,356 women (91%) in week 9-11 of the pregnancy. The urine samples were stored frozen at -20°C. These samples were analysed for the 10 phthalate metabolites listed in

Table 1. Briefly, 0.2 ml of urine were added with 0.1 ml of ammonium acetate (pH 6.5) and 0.01 ml glucoronidase (E-coli) and thereafter incubated at 37°C in 30 min. Then 0.05 ml of a 50:50 (v:v) water and acetonitrile solution of labelled (3H or 13C) internal standards of all analysed compounds were added. A C18 column (2.1 mm i.d. x 50 mm, Genesis Lightn; Grace, Deerfield, IL, USA) was used prior to the injector to reduce the interferences of contaminants in the mobile phase. The phthalate metabolites in the samples were separated on a C18 column (1.5 µm, 2.0 mm i.d. x 30 mm VisionHT; Grace, Deerfield, IL, USA). The mobile phases were water and acetonitrile with 0.08% formic acid. The samples were analysed on a Shimadzu UFLC system (Shimadzu Corporation, Kyoto, Japan) coupled to a QTRAP5500 triple quadrupole linear ion trap mass spectrometer equipped with a TurboIon Spray source (LC-MS/MS; AB Sciex, Foster City, CA, USA). The samples were analysed in triplicates and the mean of the two closest were reported. All samples were analysed in a randomized order. For quality control of the analyses, chemical blanks and two different in-house prepared quality control samples were analysed in all sample batches. The limit of detection (LOD) was defined as the concentration corresponding to a peak area ratio of three times the standard deviation of the chemical blanks and is shown in Table 1. The laboratory at Lund University is a reference laboratory for analyses of urinary phthalate metabolites in a European bio monitoring project (www.eu-hbm.info/cophes). The creatinine concentrations were analysed according to an enzymatic method described by (Mazzachi et al. 2000). The sum of DEHP and DiNP metabolites were calculated by summing the metabolite concentrations on a molar basis.

**Statistical analyses**

Urinary levels of phthalate metabolites were log-transformed to normalize distributions and geometric means (GM) with 95% confidence interval (CI). Associations between log-

transformed phthalate metabolite concentrations and AGD were estimated using a general linear model and we present the beta-coefficients with 95% CI. We also categorized covariate-adjusted AGD (AGDas and AGDap) into "short" (below the 25$^{th}$ percentile), "medium" (25$^{th}$-75$^{th}$ percentile) and "long" (75$^{th}$ percentile and above) as a reference. We then used logistic regression models to estimate the odds ratio (OR) of having a boy with a short (adjusted) AGD (below the 25$^{th}$ percentile) compared to a long AGD (75$^{th}$ percentile and above) as a function of log-transformed concentrations of phthalate metabolites in prenatal urine. Finally we examined the ORs for having a short AGD compared to a long AGD as a function of quartiles of phthalate metabolite concentration in the pregnant women's urine with the lowest quartile as a reference. Therefore, using these models we examined the relation between prenatal phthalate exposure and AGD in three ways: 1) both AGD and phthalate metabolite concentrations modeled as continuous variables (results in Table 5); 2) categorical AGDs vs. continuous phthalate metabolite concentrations (results in Table 6), and 3) both AGD and phthalate metabolite concentrations modeled as categorical variables (results in Figure 1).

The literature indicates that both age and body size can influence measures of AGD. Thus, we controlled for body size by using weight-for-age percentiles by the use of WHO standards (WHO 2009). Weight for age percentiles are correlated with age, but much less correlated than weight and age (Swan 2008). Finally, in addition to weight-for-age, all models were adjusted for the boy's age at examination (months), gestational week of urine sampling, and urinary creatinine concentration. A p-value less than 0.05 was considered statistically significant.

**Ethical approval**

The research ethics committee at Uppsala University, Sweden approved the study and informed consent was obtained from all participating adults.

## Results

*Study population*: The study population for this analysis was quite similar to the entire SELMA study population. The 196 families included in the final analysis were somewhat better educated, smoked less, and were more likely to live in a single family house and in a rural setting (Table 2).

*Anogenital distance* was measured on 225 boys (19-21 months of age) between June 2011 and August 2012 and prenatal phthalates metabolites were available for 199 of them. Of these, 1 child was excluded due to an error in weight measurements and 2 children were excluded due to a CV for the AGD measurements >10%, resulting in a study population of 196 children. These 196 boys had a mean age of 20.8 months and a mean weight of 12.6 kg. In addition, AGDap was not measured on 4 of these boys, so for those analyses n=192 (Table 3).The median AGDas was 40.7 mm (inter-quartile-range 37.8-45.0 mm) while the median AGDap was 82.6 mm (inter-quartile-range 78.0-87.4 mm). The mean CV was 2.3% for AGDas and 1.6% for AGDap (Table 3).

*Phthalate metabolites*: Ten phthalate metabolites and creatinine were measured in urine collected in weeks 9-11. The geometric mean and 95% confidence interval for the concentration of the 10 metabolites as well as the sum of DEHP- and DiNP-metabolites are presented in Table 4. All phthalate metabolites were identified above limit of detection (LOD) in all urine samples (Table 1). The distribution of the metabolite concentrations in the AGD study population was comparable to the distribution in the entire SELMA-cohort (n=2,356) (data not shown). In Table 4 we also provide unpublished data reflecting urinary levels of phthalate metabolites in pregnant women of boys and girls from the Study for Future Families (SFF) while published data reflect boys only (Swan et al. 2005; Swan 2008) as well as from the US National Health and Nutrition

Examination Survey (NHANES) study where data is from women in child bearing age (CDC 2014).

*Anogenital distance in relation to phthalate exposure:* Most of the phthalate metabolites were negatively associated with AGD both before and after adjusting for covariates in multiple linear regression models, however most of the associations did not reach significance. Strongest and most significant inverse associations were found between AGDas and DiNP metabolites and most strongly for oh-MMeOP and oxo-MMeOP and the sum of DiNP metabolites (Table 5).

These associations were also seen when AGD was stratified and phthalate concentrations compared by adjusted AGD quartile (Table 6). The odds ratios for having an AGDas in the 2$^{nd}$-3$^{rd}$ quartile when compared with the 4$^{th}$ quartile as a function of (log transformed) DiNP metabolite concentrations were in the range of 1.1-1.2 but non-significant, while the ORs for having an AGDas in the 1$^{st}$ quartile when compared with the 4$^{th}$ quartile was in the range of 2.6-3.1 and significant. We also saw weaker inverse associations between AGDap and DINP metabolites, which did not reach statistical significance. Associations between prenatal DEHP-metabolite exposure and shorter AGDas were also seen, however, these associations did not reach statistical significance.

Finally, the odds of having a short AGDas (in the 1$^{st}$ quartile) when compared to a long AGDas (4$^{th}$ quartile) as a function of quartile of phthalate metabolite concentration showed a linear dose response relationship for prenatal DiNP metabolite exposure (Figure 1A). Similar but somewhat weaker associations were seen between AGDas and DEHP metabolites, as well as well as MBzP metabolites, while no associations were seen with MEP and MBP metabolites. No consistent patterns were seen between AGDap and any of the phthalate metabolites (Figure 1B).

## Discussion

Our finding that prenatal phthalate exposure is associated with shorter male AGD is consistent with several earlier studies. However, Swan (2008) found associations between a shorter male AGD and prenatal exposure, particularly for DEHP metabolites, in mothers recruited in 2000-2003, while we saw a stronger association to DiNP metabolites. Mothers of the 196 boys included in the current analysis were pregnant in 2009-2010. Phthalates in commerce changed considerably between 2000 and 2010. Since then DiNP has largely replaced DEHP in soft PVC applications such as flooring materials, and was measureable in 100% of the current mothers. Additionally, in the current study we observed associations primarily with the shorter AGD measure (AGDas) while in SFF associations were stronger for AGDap (Swan 2008), a difference that may in part be due to subtle differences in measurement methods between the two studies, but is largely unexplained.

The inverse association between prenatal DiNP exposure and AGDas was significant as expressed in Table 5 but the AGDas reduction was small in relation to the quite large increase in exposure. For example, more than an interquartile increase in DiNP exposure (Table 4) was related to a 4% (1.69 mm) reduction in AGDas in the used model (Table 5). About the same effect size have been found for DEHP exposure and AGD reduction in the SFF study (Swan 2008). However, such small relative differences have been associated to male genital birth defects and impaired reproductive function in adult males as described below.

Our finding of an association between AGD and prenatal exposure to DiNP, and to a lesser extent to DEHP (not significant) is not unexpected. DEHP is a known anti-androgen (Foster 2005; Gray et al. 2000) and DiNP may be as well. Prenatal DiNP reduces testosterone production in Harlan rats pups (Hannas et al. 2011), although it is reported to be a less potent anti-androgen

than DEHP. Furthermore, DINP exposure to rats during gestation and perinatally increased the incidence of reproductive malformations in male offspring and caused alterations in foetal testicular testosterone production (Borch et al. 2004; Gray et al. 2000). In addition, DiNP is an analogue of DEHP, i.e., the reason for replacing DEHP with DiNP in soft PVC is that the two molecules have common chemical properties, which maybe also include anti-androgenic action. Our finding is also in line with some animal data. Prenatal exposure to DiNP has been found to reduce anogenital distance in male offspring rats in three studies; in Wistar rats (Boberg et al., 2011), in Wistar Imamichi rats (Lee et al. 2006) and in Sprague-Dawley (SD) rats (Ostby et al. 2001). In another study by Clewell et al. AGD was reported to be reduced, but only on postnatal day 14 and at the highest exposure level (Clewell et al. 2013b). Boberg et al. (2011) found similar dose-related effects of DiNP as previously shown for DEHP and DBP. They stated that their finding supports the conclusion that DINP has anti-androgen properties and is, therefore, a reproductive toxicant. However, they also stated that DiNP appears less potent than DEHP and DBP. On the other hand, in three other studies no association were found between prenatal DiNP exposure and AGD in offspring rats (Clewell et al. 2013a; Gray et al. 2000; Masutomi et al. 2004).

AGD measurements in SELMA boys were longer than those in SFF (Swan et al. 2005; Swan 2008). Median AGDap was 82.6 mm in SELMA and 70.2 mm in SFF; median AGDas was 40.7 mm in SELMA and 36.8 mm in SFF. This is, in part at least, due to difference in age at exam; boys in SELMA averaged 20.8 months compared to 12.8 months in SFF. The other three studies reporting associations between prenatal phthalate exposure and AGD in offspring children are not comparable to ours, since AGD measurements in those studies was measured at birth (Bustamante-Montes et al. 2013; Sathyanarayana et al. 2010; Suzuki et al. 2012).

Prenatal urinary levels of phthalate metabolites in the 196 mothers were comparable to those in the entire SELMA cohort suggesting that there was no substantial selection bias (data not shown). The urinary levels of most phthalate metabolites are comparable to those in SFF and NHANES but there are differences. MBP metabolite levels are higher in Swedish pregnant women (SELMA) while MEP is higher in pregnant women in USA (SFF, NHANES). MBzP-metabolites levels are slightly higher in Sweden while the picture for DEHP metabolites is more unclear with both higher and lower levels in Swedish data (Table 4). Regarding DiNP metabolites there are no data in SFF. However, based on more recent data for the DINP metabolite cx-MMeHP, concentrations in pregnant women in Sweden and the USA were similar in 2008 (Silva et al. 2013).

The associations we observed between prenatal DiNP metabolites and a shorter AGD in baby boys raises concern for at least two reasons. *Firstly*, anogenital distance has been shown to be associated with adverse health effects in humans. Three studies reported that male infants and boys with hypospadias or undescended testis had reduced AGD (Hsieh et al. 2012; Jain and Singal 2013; Thankamony et al. 2013). Moreover, a shorter AGD in adult men has been related to decreased fertility (Eisenberg et al. 2011), impaired semen quality (Mendiola et al. 2011) and lower serum testosterone levels (Eisenberg et al. 2012). Shortened AGD has also been suggested as a biomarker of testicular dysgenesis syndrome (Sharpe 2005). *Secondly*, the use of DiNP is increasing as it is used to replace DEHP in soft PVC and as a consequence the human urinary levels of DiNP metabolites are rapidly increasing globally. The total global market for phthalates have been estimated by European Chemicals Agency (ECHA) to about 6 million ton, with 1.4 million tons in Europe, the Middle East and Africa, 1.1 million tons in the Americas and 3.5 million tons in Asia, and phthalates represent 84% of the global plasticizer market (ECHA 2013).

Of the global market of plasticizers, DiNP and DIDP was reported to represent about 32% (ECHA 2013). Based on data from the American Chemistry Council the annual world production of DiNP was estimated to be about 1.5 million tons in 2013, assuming a production growth of 2.5% during the last years (ACC 2012). Biomonitoring data from Europe and the USA also show that human urinary levels of DEHP metabolites are decreasing while DiNP-metabolite concentrations are increasing (Göen et al. 2011; Silva et al. 2013).

## Conclusions

The use of DiNP in soft PVC is increasing and biomonitoring data show that human DiNP metabolite levels are rapidly increasing globally. Our data suggest that this substitute phthalate may not be safer than the chemical it is replacing. We find that DiNP is associated with a shorter anogenital distance in boys at the age of 21 months, which is of concern since AGD has been shown to be related to male genital birth defects and impaired reproductive function in adult males.

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**Table 1.** Analysed phthalate metabolites in the urine of 196 pregnant women, their mother compounds including CAS number, and limit of detections.

| Parent compounds | | Metabolites | | | Limit of detection (LOD) |
|---|---|---|---|---|---|
| **Diester name (acronym)** | **CAS NO** | **Monoester name** | **Acronym** | **CAS NO** | **ng/ml** |
| Diethyl Phthalate (DEP) | 84-66-2 | Mono-ethyl phthalate | MEP | 2306-33-4 | 0.01 |
| Dibutyl Phthalate (DBP) | 84-74-2 | Mono-n-butyl phthalate | MnBP | 131-70-4 | 0.10 |
| Butylbenzyl Phthalate (BBzP) | 85-68-7 | Mono-benzyl phthalate | MBzP | 2528-16-7 | 0.04 |
| Di-2-ethylhexyl Phthalate (DEHP) | 117-81-7 | Mono-(2-ethylhexyl) phthalate | MEHP | 4376-20-9 | 0.10 |
| | | Mono-(2-ethyl-5-hydroxylhexyl) phthalate | oh-MEHP | 40321-99-1 | 0.02 |
| | | Mono-(2-ethyl-5-oxohexyl) phthalate | oxo-MEHP | 40321-98-0 | 0.03 |
| | | Mono-(2-ethyl-5-carboxypentyl) phthalate | cx-MEPP | 40809-41-4 | 0.02 |
| Diisononyl Phthalate(DiNP) | 68515-48-0 | Mono-(4-methyl-7-hydroxyloctyl) phthalate | oh-MMeOP | 936021-98-6 | 0.02 |
| | | Mono-(4-methyl-7-oxo octyl) phthalate | oxo-MMeOP | 936022-00-3 | 0.01 |
| | | Mono-(4-methyl-7-carboxyheptyl) phthalate | cx-MMeHP | 936022-02-5 | 0.02 |

**Table 2.** Characteristics of the study population of 196 boys and the families in the entire SELMA study.

| **Variable** | **The current study (n=196)** | **SELMA[a] (n=1,974)** |
|---|---|---|
| | **(%)** | **(%)** |
| Surrounding for the home | | |
| Urban | 16.8 | 19.3 |
| Suburban | 47.1 | 47.9 |
| Rural | 36.1 | 32.9 |
| Type of home | | |
| Single family house | 64.2 | 60.8 |
| Row house | 7.1 | 7.9 |
| Apartment in multifamily house | 26.4 | 29.5 |
| Other | 2.4 | 1.8 |
| Education for the mother (highest) | | |
| Elementary school | 2.8 | 3.9 |
| High school (Gymnasium) | 33.5 | 36.0 |
| University | 58.5 | 54.0 |
| Other | 5.2 | 6.0 |
| Smoking in family | | |
| Any smoker in the family | 16.0 | 18.4 |

[a]Data from a questionnaire at week 10 of pregnancy when the urine samples from the pregnant women were taken (n=1,974).

**Table 3.** Description of the measurements of the 196 boys including AGD measurements and other characteristics.

| | Mean (SD) | Percentiles | | |
|---|---|---|---|---|
| | | 25th | 50th | 75th |
| Age of the children (months) | 20.8 ± 1.6 | 19.7 | 20.7 | 21.8 |
| Weight of the children (kg) | 12.6 ±1.3 | 11.7 | 12.6 | 13.3 |
| Gestational week for urine sampling | 10.0 ±2.3 | 9.0 | 10.0 | 11.0 |
| Anogenital distance (mm) | | | | |
| AGDas | 41.4 ±5.98 | 37.8 | 40.7 | 45.0 |
| AGDap (n=192) | 82.2 ±6.94 | 78.0 | 82.6 | 87.4 |
| CV (%)[a] | | | | |
| AGDas (n=184) | 2.28 | 1.03 | 1.59 | 2.91 |
| AGDap (n=168) | 1.58 | 0.66 | 1.13 | 1.84 |

[a]For 12 boys only one measurement were made regarding AGDas and for 24 boys only one AGDap measurement were done.

**Table 4.** Distribution of urinary levels of phthalate metabolites (ng/mL) in 196 women in the current study and in two American studies, SFF and NHANES.

| Phthalate | Metabolite | The current study 2008-2009 (1st trimester) (n=196) | | | | SFF[a] 2000-2003 (2nd trimester) (n=380) | NHANES[b] 2005-2010 (women 20-40 years) (n=1,069) |
|---|---|---|---|---|---|---|---|
| | | GM (95% CI) | 25th | 50th | 75th | GM (95% CI) | GM (95% CI) |
| DEP | MEP | 63.64 (54.35, 74.52) | 30.67 | 60.56 | 134.12 | 149.00 (124.66, 178.10) | 100.99 (89.28, 114.24) |
| DBP | MBP | 67.62 (60.02, 76.17) | 43.13 | 66.03 | 111.78 | 15.04 (13.49, 16.77) | 18.98 (17.34, 20.77) |
| BBzP | MBzP | 15.99 (13.50, 18.95) | 7.85 | 15.08 | 35.58 | 9.97 (8.64, 11.50) | 7.37 (6.63, 8.19) |
| DEHP | MEHP | 3.27 (2.87, 3.73) | 1.91 | 3.30 | 5.86 | 3.23 (2.82, 3.70) | 2.61 (2.31, 2.95) |
| | oh-MEHP | 14.42 (12.82, 16.22) | 8.69 | 15.28 | 22.85 | 11.74 (10.28, 13.40) | 18.30 (16.14, 20.73) |
| | oxo-MEHP | 9.68 (8.59, 10.91) | 5.67 | 9.99 | 15.60 | 10.51 (9.26, 11.93) | 11.67 (10.36, 13.14) |
| | cx-MEPP | 14.21 (12.63, 15.98) | 8.00 | 14.53 | 22.50 | 19.97 (16.45, 24.24) | 28.78 (25.71, 32.21) |
| | SumDEHP[c] | 142.61 (126.99, 160.16) | 84.56 | 148.13 | 220.71 | 118.33 (104.37, 134.17) | - |
| DiNP | oh-MMeOP | 6.81 (5.60, 8.28) | 2.83 | 6.27 | 14.23 | - | - |
| | oxo-MMeOP | 3.05 (2.56, 3.63) | 1.33 | 2.75 | 6.22 | - | - |
| | cx-MMeHP | 10.81 (9.16, 12.75) | 4.95 | 8.26 | 16.43 | - | - |
| | SumDiNP[3] | 67.74 (57.00, 80.52) | 28.28 | 55.91 | 124.92 | - | - |
| Creatinine (mmol/L) | | 9.55 (8.94, 10.20) | 7.00 | 9.60 | 13.10 | - | - |

[a]Unpublished data from mothers of boys and girls, while published data reflect boys only (Swan et al. 2005, Swan 2008). [b]Based on pooled 2005-2010 NHANES cycles, and women of ages 20-40 years (CDC 2014). [c]The unit is nmol/L.

**Table 5.** Association between AGD in boys and log-transformed concentrations of phthalate metabolites in prenatal urine expressed as a beta-coefficient with a 95% CI from an adjusted[a] linear regression model.

| Phthalate | Metabolite | AGDas | | AGDap | |
|---|---|---|---|---|---|
| | | Beta (95%CI) | p-value | Beta (95%CI) | P-value |
| DBP | MBP | -1.41 (-4.39, 1.57) | 0.351 | -2.06 (-5.29, 1.18) | 0.211 |
| DEP | MEP | 0.63 (-1.29, 2.54) | 0.518 | -1.30 (-3.40, 0.81) | 0.225 |
| BBzP | MBzP | -1.66 (-3.56, 0.25) | 0.088 | -0.65 (-2.74, 1.44) | 0.542 |
| DEHP | MEHP | -1.28 (-3.74, 1.17) | 0.304 | -1.74 (-4.43, 0.95) | 0.203 |
| | oh-MEHP | -1.24 (-3.99, 1.51) | 0.374 | -1.50 (-4.50, 1.49) | 0.324 |
| | oxo-MEHP | -0.77 (-3.48, 1.94) | 0.576 | -1.25 (-4.19, 1.70) | 0.406 |
| | cx-MEPP | -0.89 (-3.69, 1.92) | 0.534 | -0.64 (3.69, 2.40) | 0.677 |
| | SumDEHP | -1.16 (-4.01, 1.68) | 0.420 | -1.39 (-4.49, 1.70) | 0.375 |
| DiNP | oh-MMeOP | -1.61 (-3.06, -0.16) | **0.029** | -1.23 (-2.83, 0.37) | 0.131 |
| | oxo-MMeOP | -1.82 (-3.47, -0.17) | **0.031** | -1.67 (-3.49, 0.15) | 0.072 |
| | cx-MMeHP | -1.51 (-3.26, 0.24) | **0.091** | -1.39 (-3.32, 0.53) | 0.156 |
| | SumDiNP | -1.69 (-3.35, -0.02) | **0.047** | -1.46 (-3.29, 0.38) | 0.119 |

[a]Adjusted for age (months), gestational week of urine sampling, weight-for-age percentile, and creatinine

**Table 6.** Association between AGD (short, medium and long as reference) and log-transformed concentrations of phthalate metabolites in prenatal urine expressed as an odds ratio (OR) with 95% CI calculated in an adjusted[a] logistic regression model.

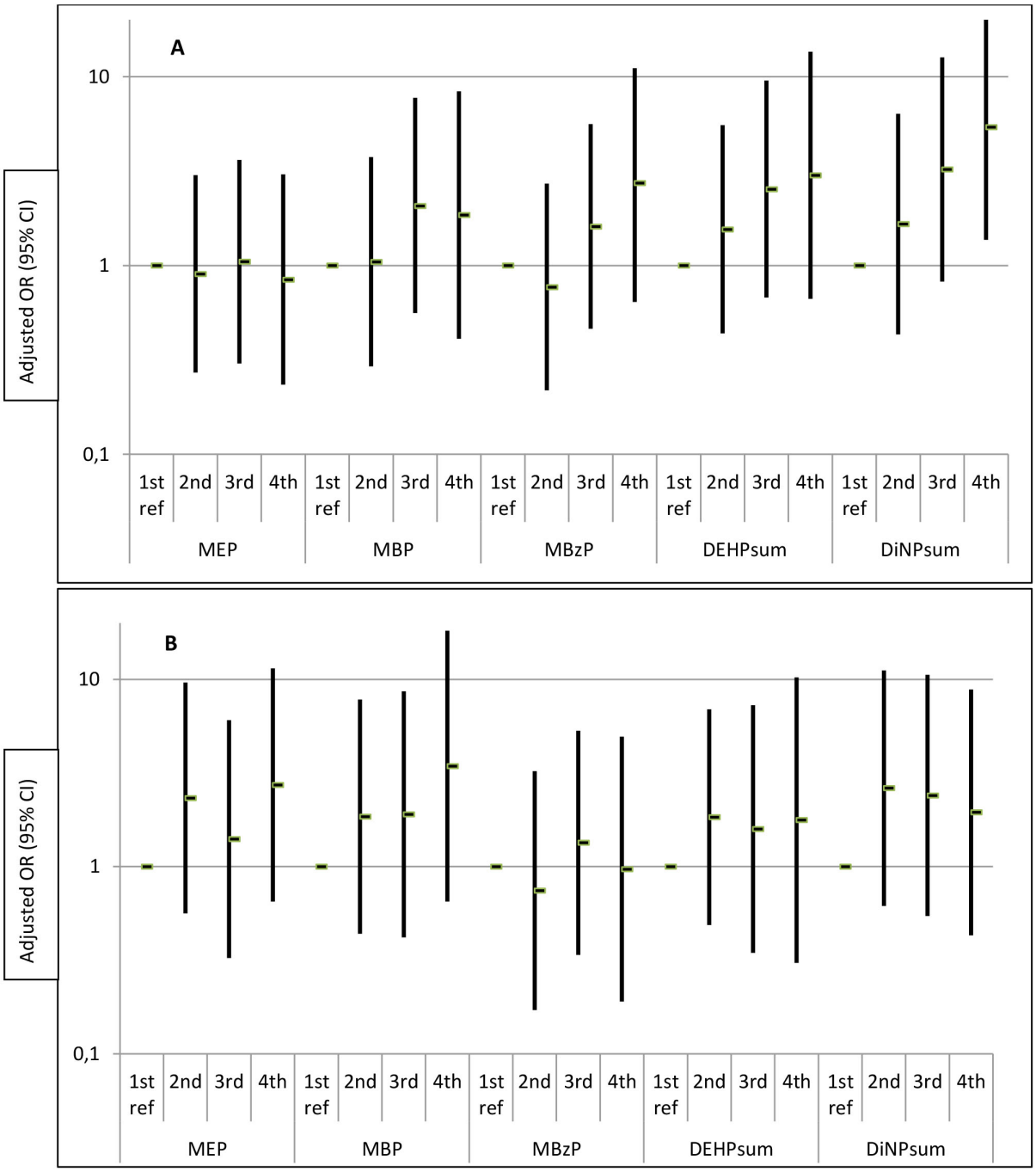
| | | AGDas | | | AGDap | | |
|---|---|---|---|---|---|---|---|
| **Phthalate** | **Metabolite** | **Short 1st quartile** | **Medium 2nd-3rd quartile** | **Long 4th quartile (ref)** | **Short 1st quartile** | **Medium 2nd-3rd quartile** | **Long 4th Quartile (ref)** |
| DBP | MBP | 1.84 (0.43, 7.91) | 0.73 (0.21, 2.60) | 1.0 | 1.83 (0.37, 9.02) | 0.84 (0.23, 3.01) | 1.0 |
| DEP | MEP | 1.06 (0.47, 2.40) | 0.84 (0.32, 2.16) | 1.0 | 2.23 (0.80, 6.24) | 1.11 (0.47, 2.62) | 1.0 |
| BBzP | MBzP | 1.92 (0.74, 5.00) | 0.75 (0.33, 1.79) | 1.0 | 1.49 (0.53, 4.17) | 1.21 (0.52, 2.81) | 1.0 |
| DEHP | MEHP | 1.71 (0.52, 5.64) | 1.04 (0.37, 2.93) | 1.0 | 1.98 (0.51, 7.66) | **4.01 (1.32, 12.20)** | 1.0 |
| | oh-MEHP | 1.85 (0.50, 6.95) | 0.89 (0.27, 2.92) | 1.0 | 2.62 (0.58, 11.78) | 3.05 (0.91, 10.16) | 1.0 |
| | oxo-MEHP | 1.47 (0.40, 5.37) | 0.72 (0.22, 2.32) | 1.0 | 2.23 (0.50, 9.87) | 3.05 (0.93, 10.07) | 1.0 |
| | cx-MEPP | 1.76 (0.46, 6.70) | 0.98 (0.30, 3.28) | 1.0 | 1.76 (0.38, 8.27) | 2.80 (0.82, 9.57) | 1.0 |
| | SumDEHP | 1.82 (0.47, 7.06) | 0.88 (0.26, 3.00) | 1.0 | 2.44 (0.51, 11.72) | 3.36 (0.96, 11.82) | 1.0 |
| DiNP | oh-MMeOP | **2.61 (1.24, 5.48)** | 1.08 (0.55, 2.09) | 1.0 | 1.47 (0.67, 3.22) | 1.17 (0.61, 2.24) | 1.0 |
| | oxo-MMeOP | **2.99 (1.28, 7.00)** | 1.17 (0.54, 2.53) | 1.0 | 1.73 (0.70, 4.23) | 1.28 (0.61, 2.70) | 1.0 |
| | cx-MMeHP | **3.11 (1.27, 7.66)** | 1.21 (0.52, 2.78) | 1.0 | 1.77 (0.67, 4.65) | 1.41 (0.62, 3.21) | 1.0 |
| | SumDiNP | **3.02 (1.28, 7.09)** | 1.16 (0.52, 2.56) | 1.0 | 1.69 (0.68, 4.20) | 1.32 (0.61, 2.84) | 1.0 |

[a]Adjusted for age (months), gestational week for urine sampling, weight for age percentile, and creatinine.

## Figure Legend

**Figure 1.** Odds ratio for having a short AGD (in the 1st quartile) compared to a long AGD (4th quartile) as a function of quartile of phthalate metabolite concentration in the pregnant women's urine [(A) AGDas, (B) AGDap]. Adjustments made for age (months), gestational week of urine sampling, weight-for-age percentile, and creatinine.

Figure 1.


A
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