Early life predictors of child growth trajectories and early adolescent cardiovascular health

Parisa Montazeri

TESI DOCTORAL UPF / 2021

Thesis supervisor:

Dr. Martine Vrijheid

ISGLOBAL, Barcelona Institute for Global Health

DEPARTMENT OF EXPERIMENTAL AND HEALTH SCIENCES UNIVERSITAT POMPEU FABRA

For Salma

"Children are one third of our population and all of our future."
– Select Panel for the Promotion of Child Health, 1981

Acknowledgements

This work started in 2017 at the Institute for Global Health (ISGlobal) in Barcelona. Many people have contributed to the project design and execution in several different ways. I would like to express my thanks and gratitude over the next few lines to those people.

To the participants of the INMA and HELIX birth cohort studies. Thank you for making this PhD thesis a possibility, and so many of the other studies that have been possible because of your continued participation.

To my supervisor Dr. Martine Vrijheid. I am extremely grateful for all of your guidance, support and encouragement over the last years. I was lucky enough to have you as a co-supervisor for my master's thesis, and very appreciative when you thought of me for a PhD position you had available. Working with you has taught me to be a more critical thinker and a better researcher. You are an inspiration to work with both professionally and personally, and I have learned so much under your guidance.

To all of my colleagues from the INMA team and at ISGlobal, thank you for making this work possible. Gracias a Silvia Fochs y Nuria Pey por recoger todos los datos de los participantes INMA y guiarme a través de los procesos de trabajo de campo. Gracias a Lourdes Cirugeda, sin tu ayuda no tendríamos las trayectorias tan importantes en esta tesis. Gracias a Charline Warembourg y Maribel Casas por estar siempre disponibles para consultas y dudas. Gracias a Sandra Márquez por siempre encontrar tiempo para ayudarme con preguntas estadísticas relacionadas con esta tesis y más allá.

To Alicia Abellan, Gabi Prado-Peralto, Carmen de Keijzer, and Cristina Vert. I'm so glad to have been able to begin this PhD journey with all of you, even though I'm the last to finish. The PhD experience was definitely more fun being able to share it with all of you.

To my parents and sister, I am deeply grateful for your unconditional love and support even from thousands of miles away.

Last but not least, thank you to my husband Shadi for your endless support, words of encouragement and patience through this PhD process. It hasn't always been easy to juggle work, a PhD and taking care of a baby, but we made it!

Abstract

Research over the previous decades has shown us that early life influences have long-term effects on health and disease. Under the Developmental Origins of Health and Disease (DOHaD) hypothesis several factors have been shown to increase risk for chronic diseases in later life. Rates of obesity and cardiovascular diseases (CVD) have increased at an astounding rate over recent decades. Lifestyle factors alone fail to fully account for the magnitude of this epidemic. Emerging science supports a role in the pathogenesis of obesity and CVD for novel risk factors like maternal metabolic health, socioeconomic position (SEP), and endocrine disrupting chemicals (EDCs). The main aim of this thesis was to examine the role of early life predictors, focusing on maternal, chemical and social factors, on child growth and early adolescent cardiovascular health using traditional and novel measures of preclinical phenotypes.

We used data from two longitudinal birth cohort studies: the INfancia y Medio Ambiente (INMA, "Environment and Childhood") Project and the Human Early-Life Exposome (HELIX) Project. A variety of non-persistent and persistent EDCs were included to characterize chemical exposure. SEP was included as maternal education and employment status, family affluence score, and social class. Child growth was analyzed using child body mass index (BMI) growth trajectories from birth to 4 or 9 years, and cardiovascular health was measured at 11 years old using traditional and novel measures of macro- and microvascular health.

We found that maternal prepregnancy BMI and gestational weight gain were associated with offspring's BMI trajectories characterized by accelerated growth during early childhood, and these same trajectories were related to macrovascular health function during early adolescence. Regarding EDCs, we found that chemical exposure differs by SEP, and those of higher SEP are potentially at greater risk of exposure. Further, we found that prenatal exposure to EDCs, particularly organochlorine compounds (DDE, HCB, PCBs) are related to BMI trajectories characterized by accelerated growth in childhood. However, prenatal exposure to non-persistent EDCs

(phthalates, phenols) does not appear to be associated with early adolescent cardiovascular health.

In conclusion, the findings of this thesis suggest that early life exposure to maternal metabolic parameters and EDCs appear to have a potentially adverse effect on child growth and early adolescent cardiovascular health, which may be modified by SEP. Given how widespread exposure to EDCs is, the importance of maternal health status prior to pregnancy, and the increasing rates of obesity and CVD, these findings are of critical importance.

Resumen

Las investigaciones realizadas durante las décadas anteriores nos han demostrado que las influencias de la vida temprana tienen efectos a largo plazo sobre la salud y la enfermedad. Según la hipótesis de los orígenes del desarrollo de la salud y la enfermedad (DOHaD), se ha demostrado que varios factores aumentan el riesgo de enfermedades crónicas en la edad adulta. Las tasas de obesidad y enfermedades cardiovasculares (ECV) han aumentado a un ritmo asombroso en las últimas décadas. Los factores del estilo de vida por sí solos no pueden explicar completamente la magnitud de esta epidemia. La ciencia emergente apoya un papel en la patogénesis de la obesidad y las ECV para nuevos factores de riesgo como la salud metabólica materna, la posición socioeconómica (SEP) y los químicos disruptores endocrinos (EDCs). El objetivo principal de esta tesis fue examinar el papel de los predictores de la vida temprana, centrándose en factores maternos, químicos y sociales, en el crecimiento infantil y la salud cardiovascular durante la adolescencia temprana a través de medidas tradicionales y novedosas de fenotipos preclínicos.

Utilizamos datos de dos estudios longitudinales de cohortes de nacimiento: el Proyecto INfancia y Medio Ambiente (INMA) y el Proyecto Human Early-Life Exposome (HELIX). Se incluyó una variedad de EDCs persistentes y no persistentes para caracterizar la exposición química. La SEP se incluyó como educación materna y situación laboral, puntaje de riqueza familiar y clase social. El crecimiento infantil se analizó utilizando trayectorias de crecimiento del índice de masa corporal (IMC) desde el nacimiento hasta los 4 o 9 años, y la salud cardiovascular se midió a los 11 años utilizando medidas tradicionales y novedosas de salud macro- y microvascular.

Encontramos que el IMC materno previo al embarazo y el aumento de peso gestacional se asociaron con trayectorias del IMC caracterizadas por un crecimiento acelerado durante la infancia, y estas mismas trayectorias se relacionaron con la función de salud macrovascular durante la adolescencia temprana. Con respecto a los EDCs, encontramos que la exposición a sustancias químicas difiere según el SEP, y los de un SEP más alto tienen potencialmente un

mayor riesgo de exposición. Además, encontramos que la exposición prenatal a los EDCs, en particular los compuestos organoclorados (DDE, HCB, PCB), están relacionados con trayectorias de IMC caracterizadas por un crecimiento acelerado en la niñez. Sin embargo, la exposición prenatal a los EDCs no persistentes (ftalatos, fenoles) no parecen estar asociados con la salud cardiovascular de la adolescencia temprana.

En conclusión, los hallazgos de esta tesis sugieren que la exposición temprana a los parámetros metabólicos maternos y a los EDCs parecen tener un efecto potencialmente adverso sobre el crecimiento infantil y la salud cardiovascular durante la adolescencia temprana, que puede ser modificado por la SEP. Dado lo generalizada que es la exposición a los EDC, la importancia del estado de salud materna antes del embarazo y las crecientes tasas de obesidad y ECV, estos hallazgos son de vital importancia.

Preface

This thesis was conducted at the Barcelona Institute for Global Health (ISGlobal) and supervised by Dr. Martine Vrijheid. The thesis was carried out and written between September 2017 and September 2021. The thesis consists of a compilation of five original articles (3 published, 1 under review and 1 in preparation), and complies with the Department of Experimental and Health Sciences of the Universitat Pompeu Fabra, Barcelona, Spain.

The main aim of this thesis was to examine the role of early life predictors, focusing on maternal, chemical, and social factors, on child growth trajectories and early adolescent cardiovascular health through traditional and novel measures of preclinical phenotypes. The thesis begins with an introductory chapter that summarizes the current evidence related to the main thesis topic: the possible early life predictors of growth trajectories and cardiovascular health. It continues on to identify the current knowledge gaps, and justifies the aim of the thesis. Following, the main results of the thesis are presented as 5 original articles, based on two birth cohorts studies. The first two articles focus on childhood growth trajectories; firstly evaluating prenatal maternal metabolic predictors of childhood growth trajectories, and secondly assessing associations between the growth trajectories and early adolescent cardiovascular health. The third article focuses on the socioeconomic determinants of chemical exposure during pregnancy and childhood. The final two articles examine the associations between multiple prenatal chemical exposures and childhood growth trajectories and early adolescent cardiovascular health. To conclude, the thesis provides a general discussion of the main findings, methodological considerations, contributions to current research, implications for public health, and contemplates future research.

Throughout the duration of the thesis, the author participated in field work (assisting with the child visits for the INMA Sabadell cohort at 11 years old), biobank activities and data management activities as they pertained to this thesis. Further, the author actively participated in national and international research projects and conferences, in particular the HBM4EU project which is a collaborative effort under Horizon 2020 to advance human

biomonitoring in Europe by analyzing chemical exposure and the possible health effects of European citizens in order to support policy making. As a part of HBM4EU the author took lead roles in work packages to write the Statistical Analysis Plans used by HBM4EU Study and analyze the exposure patterns of UV filter chemicals. A summary of further activities is provided in the Annex.

Abbreviations (*in alphabetical order*)

AIC	Akaike Information Criteria
As	arsenic
BIC	Bayesian Information Criteria
BKMR	Bayesian kernel machine regression
BMI	body mass index
BP-3/OXBE	benzophenone-3/oxybenzone
BPA	bisphenol-A
BUPA	butyl paraben
BWQS	Bayesian weighted quantile sum regression
Cd	cadmium
CRAE	central retinal arteriole equivalent
CRP	C-reactive protein
CRVE	central retinal venular equivalent
CVD	cardiovascular disease
DBP	diastolic blood pressure
DDE	dichlorodiphenyldichloroethylene
DDT	dichlorodiphenyltrichloroethane
DOHaD	Developmental Origins of Health and Disease
EDCs	endocrine disrupting chemicals
ETPA	ethyl paraben
FAS	family affluence score
GDM	gestational diabetes
GWG	gestational weight gain
HCB	hexachlorobenzene
HDL-C	high-density lipoprotein cholesterol
HELIX	Human Early-Life Exposome
Hg	mercury
HMW	high molecular weight
INMA	INfancia y Medio Ambiente (Environment and Childhood)
LCGA	latent class growth analysis
LDL-C	low-density lipoprotein cholesterol
LGA	large-for-gestational-age

LMW	low molecular weight
MBzP	mono benzyl phthalate
MECPP	mono-2-ethyl 5-carboxypentyl phthalate
MEHHP	mono-2-ethyl-5-hydroxyhexyl phthalate
MEHP	mono-2-ethylhexyl phthalate
MEOHP	mono-2-ethyl-5-oxohexyl phthalate
MEP	monoethyl phthalate
MEPA	methyl paraben
MiBP	mono-iso-butyl phthalate
MICE	multivariate imputation by chained equations
MnBP	mono-n-butyl phthalate
OP	organophosphate
Pb	lead
PC	principal components
PCA	principal component analysis
PCB	polychlorinated bisphenols
PCB	polychlorinated bisphenol
PFAS	perfluoroalkyl substances
PFHxS	perfluorohexane sulfonate
PFNA	perfluorononanoate
PFOA	perfluorooctanoate
PFOS	perfluorooctane sulfonate
POPs	persistent organic pollutants
PPAR	peroxisome proliferator-activated receptor
PRPA	propyl paraben
PVC	polyvinyl chloride
PWV	pulse wave velocity
SBP	systolic blood pressure
SEP	social economic position
SES	socioeconomic status
TRCS	triclosan
UV	ultraviolet
μm	micrometers

Table of Contents

1. INTRODUCTION

1.1. Cardiovascular Health

Cardiovascular diseases (CVDs) are a group of conditions related to the heart and blood vessels, the most common of which is coronary heart disease; a buildup of plaque in one's arteries (i.e. atherosclerosis) that limits blood flow to the heart (World Health Organization (WHO), 2021). CVDs are the primary causes of death globally, and a leading contributor to disability (World Health Organization (WHO), 2021). The latest Global Burden of Disease study in 2019 reported that from 1990 to 2019 prevalent cases of CVD nearly doubled from 271 to 523 million, while CVD related death increased from 12.1 to 18.6 million during the same period (Roth et al., 2020). It is estimated that 80% of premature CVD is preventable by improving modifiable risk factors (World Health Organization (WHO), n.d.), such as high blood pressure, high cholesterol, and obesity (Roth et al., 2020).

1.1.1.Cardiovascular Health Measurement

The cardiovascular system is a complex system that facilitates the transportation of blood by which beneficial nutrients are delivered, and conversely removes waste products from the body. It accomplishes these processes through the macrovascular and microvascular systems. The macrovascular system is comprised of large arteries and veins that move blood quickly to and from organs, while the microvascular system consists of small vessels (arterioles, capillaries, and venules) of a diameter <150 μm that regulate local perfusion (Yuan and Rigor, 2010). Measures of cardiovascular health have more traditionally focused on measurements of the macrovascular system, such as blood pressure, in addition to body mass index (BMI), adiposity measures (e.g. waist circumference), and lipids (e.g. cholesterol, triglycerides). A large body of evidence exists to show that increased systolic and diastolic blood pressure are strongly associated with cardiovascular diseases (Payne, 2012). The same can be said for high cholesterol, specifically high low-density lipoprotein cholesterol (LDL-C) and low high-density lipoprotein cholesterol (HDL-C) (Payne, 2012). Obesity is a risk factor for and can further exasperate high blood pressure and cholesterol. Several novel markers of cardiovascular health have

been introduced over the last decade, such as C-reactive protein (CRP), a biomarker of systemic inflammation positively associated with cardiovascular outcomes (Payne, 2012). Additionally, non-invasive measures have been introduced, namely pulse wave velocity (PWV) and retinal imaging. Aortic PWV is an indicator of arterial stiffness (macrovasculature) that independently predicts cardiovascular mortality in adults, and has been validated for use in children (Thurn et al., 2015). The retina is the only spot where the microvascular structure can be analyzed non-invasively through the use of imaging (Newman et al., 2017). Structural changes to the microvasculature can be measured by the diameter of the venules and arterioles. Retinal venular widening is indicative of inflammation and atherosclerosis, while arterial narrowing is indicative of damage (Li et al., 2016).

1.1.2. Cardiovascular Health in Children

Cardiovascular disease and its risk factors are often discussed only for the adult and typically older adult population, however a part of the origin to these illnesses is likely to lie in fetal and early life. Similar risk factors found in adults can be traced back to childhood, including obesity, high blood pressure, and additional risk factors like rapid growth during infancy (Franks et al., 2010; Juonala et al., 2011). Recent research shows that cardiovascular risk factors in young and middle-aged adults can be traced back to higher risk in childhood and adolescence (Franks et al., 2010; Juonala et al., 2011). Measures of obesity and adiposity, blood pressure, and other markers of macro- and microvascular function during childhood have been associated with later cardiovascular morbidity and mortality (Charakida et al., 2012; Donald et al., 2010; Juonala et al., 2011; Lurbe et al., 2012). Childhood blood pressure has been shown to predict adult blood pressure as well as other markers of cardiovascular disease (Magnussen and Smith, 2016), while childhood obesity has been associated with increased arterial stiffening, a precursor to atherosclerosis, during childhood and adulthood (Cote et al., 2015; Hudson et al., 2015). Microvascular changes observed in the retina through imaging have been linked to arterial hypertension, coronary heart disease, diabetes mellitus and obesity in adulthood (Li et al., 2016; Newman et al., 2017).

1.2. Growth Trajectories

It has been established that having a BMI outside of normal range significantly worsens cardiovascular disease risk in children and adolescents (Friedemann et al., 2012). However, a challenge of many of these studies is that BMI is assessed at only one point in time, which ignores the change of BMI over time and thus may misrepresent one's BMI over a longer period. In addition to BMI, other growth factors like birthweight and growth velocity have been associated with adverse health outcomes in later life (Mook-Kanamori et al., 2011; Oken and Gillman, 2003; Ziyab et al., 2014). Longitudinal growth trajectories integrate information on multiple aspects of growth, such as birthweight, growth velocity and BMI peaks (Adair, 2007; Pizzi et al., 2014), which may improve prediction and uncover greater effects of BMI and child growth on health risk and outcomes (Ziyab et al., 2014). A growth trajectory is a defined path that describes a pattern of growth and its evolution over time based on certain parameters. Different statistical modeling approaches exist to estimate longitudinal growth trajectories. For the purposes of this thesis we focus on modeling trajectories through latent class growth analysis (LCGA). With this type of modeling each participant is assigned to a particular trajectory "class" which most closely fits their specific growth pattern (Slining et al., 2012). This facilitates easier interpretation as each child belongs to a class with specific characteristics of growth. Additionally, LCGA allows for non-linear growth patterns and a heterogeneous population, which means that classes do not need to be defined a priori and predictors (e.g. sex and time) can act differently on the outcome by each latent class (Duncan and Duncan, 2004).

1.3. Early Life Programming: Developmental Origins of Health and Disease

The Developmental Origins of Health and Disease (DOHaD) hypothesis proposes that exposure to certain environmental influences during critical periods of development (e.g. in-utero and infancy) may increase risk to adverse health outcomes during later life (Barker, 2007). The foundation for this hypothesis originated from a study by Barker and Osmund which demonstrated an ecological association between increased infant mortality rates in

the 1920's and ischemic heart disease rates between 1968 and 1978 (Barker and Osmond, 1986). They proposed that this association was due to differences in early life factors such as poor nutrition and adverse living conditions. This research sparked the DOHaD hypothesis and led to future research on the roles of early life environmental exposures and critical periods of development in future disease onset (Wadhwa et al., 2009). The DOHaD hypothesis is now widely accepted in the field of public health and epidemiology. The objective is to explain *how* and *what* environmental factors during the prenatal and early postnatal periods increase risk for adverse health consequences in later life (Barouki et al., 2012). Research centered on this hypothesis has found that nutrition, stress, exposure to environmental chemicals, smoking and certain infections can lead to developmental changes in the fetus that predispose them to diseases in later life (Heindel and Vandenberg, 2015). These diseases comprise of a range of disorders including adult hypertension, obesity, diabetes and immunological and reproductive diseases (Heindel and Vandenberg, 2015).

Critical periods of development are characterized by a high degree of plasticity, a phenomenon where a single genotype can produce a range of physiological states in response to different environmental conditions during development (Silveira et al., 2007). The prenatal period, childhood, and adolescence are critical periods considered to be particularly sensitive phases of growth and development given that cell division, and tissue and organ development are taking place (Barouki et al., 2012). Exposure to a significant factor could have consequences that lead to alterations in normal bodily functions (Silveira et al., 2007). The following sections describe some of the exposures and underlying mechanisms that have been suggested to influence growth and cardiovascular health at critical periods.

1.3.1. Maternal Metabolic Health, Child Growth, and Cardiovascular Health

Metabolic health can be measured through aspects of body composition like obesity status, triglyceride levels, cholesterol levels, blood pressure, and glucose levels. When put together these parameters create a holistic picture of one's metabolic health.

Increased levels of several parameters measured during pregnancy have been associated with multiple aspects of child growth. For example, prepregnancy overweight/obesity and higher gestational weight gain (GWG) have been associated with higher risk to giving birth to a large-for-gestational-age (LGA) newborn, a risk that is increased for those pregnant women with gestational diabetes and hypertension (Heude et al., 2012). Prepregnancy overweight/obesity and GWG have also been linked to obesity status in the child during infancy and carrying on through childhood and early adulthood (Haga et al., 2012; van Rossem et al., 2014; Voerman et al., 2019; Ziyab et al., 2014). On the contrary, women with lower GWG had higher odds of preterm birth that was stronger when accounting for women with gestational diabetes and high blood pressure (Heude et al., 2012). A study analyzing child growth parameters outside of weight status found that prepregnancy underweight was associated with smaller birth size and higher growth velocity, while prepregnancy overweight/obesity was associated with higher birth size, decreased growth velocity and delayed tempo (speed of growth) (Pizzi et al., 2014).

It is clear that prepregnancy weight status increases the risk of pregnancy complications and health outcomes of the mother and newborn, specifically birth size and later growth parameters. This is of particular importance as children with overweight/obesity are more likely to stay that way throughout their life course and face increased health risks for type 2 diabetes, certain cancers, and CVD (World Health Organization (WHO), n.d.). When investigating childhood growth patterns and trajectories, those with accelerated growth velocity, particularly when starting at a low birthweight, have been found to be at the highest risk for cardiovascular diseases later in life (Barker et al., 2005; Victora et al., 2008).

Studies examining the relationship between parameters of growth like birthweight, accelerated growth and obesity, have found that they are correlated with several risk factors for CVD in later life such as; increased cholesterol, blood pressure, PWV, and adverse changes to the retinal microvascular structure (Adair and Cole, 2003; Horta et al., 2003; Huxley et al., 2000; Leunissen et al., 2009; Li et al., 2016; Nordman et al., 2020). Some studies have taken this a step further and investigated these relationships using growth trajectories to combine these different growth parameters. Children

with growth trajectories characterized by overweight/obesity and/or accelerated growth patterns were found to be at increased risks for higher blood pressure, augmentation index (a measure of arterial stiffness), and CVD risk during adolescence and early adulthood (Boyer et al., 2015; Buffarini et al., 2018; Hanvey et al., 2017; Toemen et al., 2016; Ziyab et al., 2014).

The literature presented shows a potential link between adverse maternal metabolic markers during pregnancy (e.g. prepregnancy weight status, gestational weight gain) and increased risk of their child experiencing accelerated growth velocity which later studies have correlated with higher risk for CVD and its precursors in later life. However, most of these studies utilized growth parameters separately rather than combining them into a growth trajectory for a more accurate identification of those at risk, and/or utilized only traditional markers of cardiovascular health in children (e.g. blood pressure).

1.3.2. Endocrine Disrupting Chemicals, Child Growth, and Cardiovascular Health

Exposure to endocrine disrupting chemicals (EDCs) is a public health concern as millions of tons of plastics and other consumer products produced worldwide leave humans increasingly exposed to their properties (Gore et al., 2015; Landrigan and Goldman, 2011). EDCs can alter the hormonal and homeostatic systems thus interfering with natural body processes (Diamanti-Kandarakis et al., 2009), and several EDCs are known to be able to cross the placental barrier (Gingrich et al., 2020). Exposure to EDCs during pregnancy may cause irreversible damage to the fetus resulting in increased disease susceptibility in later life (Lunder et al., 2010; Mamsen et al., 2017; Vrijheid et al., 2016). This section describes the EDCs that have been studied within the scope of this thesis in relation to child growth and cardiovascular health. These include **persistent organic pollutants:** organochlorine compounds (DDE: dichlorodiphenyldichloroethylene, HCB: hexachlorobenzene), polychlorinated bisphenols (PCB congeners –138, −153, −180), perfluoroalkyl substances (PFOA: perfluorooctanoate, PFNA: perfluorononanoate, PFHxS: perfluorohexane sulfonate, PFOS: perfluorooctane sulfonate); and **non-persistent pollutants:**

phthalate metabolites (MEP: monoethyl phthalate, MiBP: mono-iso-butyl phthalate, MnBP: mono-n-butyl phthalate, MBzP: mono benzyl phthalate, MEHP: mono-2-ethylhexyl phthalate, MEHHP: mono-2-ethyl-5-hydroxyhexyl phthalate, MEOHP: mono-2-ethyl-5-oxohexyl phthalate, MECPP: mono-2-ethyl 5-carboxypentyl phthalate), phenols (MEPA: methyl paraben, ETPA: ethyl paraben, PRPA: propyl paraben, BPA: bisphenol-A, BUPA: butyl paraben, BP-3/OXBE: benzophenone-3/oxybenzone, TRCS: triclosan).

1.3.2.1. Persistent Organic Pollutants

Persistent organic pollutants (POPs) are a broad term for certain types of synthetic organic chemicals including pesticides (dichlorodiphenyltrichloroethane (**DDT**)) and industrial chemicals (**HCB** and **PCBs**) (World Health Organization (WHO), 2008). These chemicals are lipophilic, persist in the environment for years, and bioaccumulate through the food web (i.e. they accumulate in an animals system as they eat smaller animals over time). The use of DDT, HCB and PCBs was restricted or banned in many countries during the 1970s and 80s due to concerns about adverse effects to the environment and human health, though DDT is still used in some countries as vector control for malaria (World Health Organization (WHO), 2004). However, due to their persistence in the environment and bioaccumulation, humans are still exposed to these pollutants today. Exposure occurs mostly through diet, mainly from fatty fish, meat and dairy products. Exposure during prenatal and early life occurs in utero via the placenta or through breast milk (World Health Organization (WHO), 2008).

POPs have been hypothesized to have obesogenic properties, meaning they promote obesity through certain biological mechanisms (Casals-Casas and Desvergne, 2011). Prenatal exposure to certain POPs like DDT, HCB and PCBs may promote obesity and affect growth by upsetting the endocrine system (La Merrill and Birnbaum, 2011). The exact mechanisms are unknown, however in vivo research points to an adipogenic effect. For example, DDT has been found to induce adipogenic differentiation, the process by which immature fat cells (preadipocytes) develop into mature fat cells called adipocytes, while DDE (the primary metabolite of DDT) has been shown to increase proliferation of preadipocytes (Cano-Sancho et al., 2017).

Epidemiological studies investigating DDE have generally found that prenatal exposure was associated with excess adiposity measures via BMI, body fat percent or skinfold thickness, while results are more inconsistent for HCB and PCBs exposure (Güil-Oumrait et al., 2021; Krönke et al., 2021; Vafeiadi et al., 2015; Valvi et al., 2012). Few studies have examined the relationship between prenatal POPs exposure and childhood growth. Of those that have, DDE and HCB were positively associated with rapid growth during the first 6 months of life (Mendez et al., 2011; Valvi et al., 2014). Additionally, DDE was associated with increased growth while a congener of PCB (congener 153) was associated with decreased growth during the first 24 months (Iszatt et al., 2015).

Additionally, **perfluoroalkyl substances (PFAS)** are another type of POP. They are similar to the aforementioned persistent pollutants in that they persist in the environment for several years, however they are not lipophilic. PFAS are used in commercial products due to their strong and stable carbon-fluorine bond that when combined with a polar structure becomes a surfactant. This characteristic makes PFAS very useful in a variety of applications such as, textiles as a water and oil repellent, food contact materials, cosmetics, medical devices, pharmaceuticals, biocides and paints (European Commission, 2020). Like the previously mentioned POPs, PFASs also bioaccumulate in animals. However, humans are primarily exposed through their use in textiles, paints and inks, and food contact materials. Some PFAS, like PFOA and PFOS, have been regulated in recent years, and additional PFAS are currently under review due to their potentially toxic effects. In pregnant women, PFAS may have a toxic effect through interaction with the peroxisome proliferator-activated receptors (PPARs), which regulate lipid metabolism, healthy placenta function, and fetal and child development (Szilagyi et al., 2020).

Some epidemiological evidence exists for PFAS and child adiposity and obesity. The results are largely mixed with some studies reporting positive associations between prenatal exposure to PFAS and others indicating no associations (Braun et al., 2011; Høyer et al., 2015; Lauritzen et al., 2018; Maisonet et al., 2012; Mora et al., 2017). Very few studies have examined other parameters of child growth. A study examining rapid growth during infancy found that

one PFAS was associated with greater odds for experiencing rapid growth (Starling et al., 2019), while two additional studies investigating growth rate during infancy found no associations (Manzano-Salgado et al., 2017; Shoaff et al., 2018).

1.3.2.2. Non-persistent Organic Pollutants

Phthalates and **phenols** are synthetic organic chemicals ubiquitous in today's environment (Diamanti-Kandarakis et al., 2009). Different than POPs, phthalates and phenols have a short half-life of hours and do not bioaccumulate. Rather, they are metabolized and eliminated quickly via urine. However, they are so widespread in their use that human exposure is constant, making them of concern (Diamanti-Kandarakis et al., 2009). Phthalates can be split into two main groups; high molecular weight (HMW) and low molecular weight (LMW). HMW phthalates are used as additives in polyvinyl chloride (PVC) plastics commonly used for medical tubing, food packaging, waterproof clothing, and children's toys among others (Wang et al., 2019). They are not covalently bonded to plastic, which causes them to leach into the environment (Husøy et al., 2019) exposing humans. LMW phthalates are used in personal care products like nail polish and fragrances (Committee on the Health Risks of Phthalates, 2008). Similarly, phenols (e.g., bisphenols, parabens, benzophenones) are used widely in personal care products as antimicrobial and antifungal agents (Husøy et al., 2019; Olujimi et al., 2010). BPA has several applications, but it is primarily used to manufacture polycarbonate plastics used for impact-resistant safety equipment, automobile parts and toys (CDC, 2017). Parabens and triclosan are used as preservatives and antimicrobial agents in personal care products like lotions, toothpaste and hand sanitizer (Gosens et al., 2014; Weatherly and Gosse, 2017). Benzophenones are primarily found in sunscreens given their ability to absorb ultraviolet (UV) light (Wang and Kannan, 2013).

Exact mechanisms by which prenatal exposure to phthalates and phenols may alter childhood growth and cardiovascular disease are not well understood, and have only been studied for certain phthalate metabolites and BPA. Little is known for other phenols. However, evidence points to oxidative stress as a major factor (Ferguson et al., 2017). Oxidative stress has been linked to obesity, diabetes, hypertension and atherosclerosis (Pignatelli et al., 2018;

Senoner and Dichtl, 2019). The inflammation due to oxidative stress appears to the driven through the stimulation of the PPARs (Gingrich et al., 2020).

Increasing evidence suggests a possible relationship between early life exposure to phthalates and BPA, and cardiovascular risk and obesity during adulthood (Fu et al., 2020; Mariana et al., 2016; Nidens et al., 2020). Very few studies have analyzed these exposures with parameters of growth outside of BMI or obesity. One study found weak negative associations with some phthalate metabolites and change in height and weight z-score during infancy (Berman et al., 2021), while the only study investigating the associations using growth trajectories found a relationship between varying tertiles of phthalate exposure and belonging to the highest BMI trajectory, and no relationship for BPA (Yang et al., 2020). Regarding macro- and microvascular health, previous research has not examined associations between phthalates and phenols (primarily BPA) with measures other than blood pressure. Studies examining blood pressure have reported mixed findings. A review on phthalates concluded a positive association with systolic blood pressure (SBP) and diastolic blood pressure (DBP) (Golestanzadeh et al., 2019), while two other studies reported a negative association with DBP in girls only (Sol et al., 2020; Valvi et al., 2015). Similarly mixed results have been reported for BPA. Positive associations have been observed between prenatal phthalate exposure and blood pressure (Bae et al., 2017; Ouyang et al., 2020; Warembourg et al., 2019), though one study reported a negative association with DBP (Sol et al., 2020). Further, a birth cohort found that prenatal phthalates and BPA were not associated with childhood blood pressure (Vafeiadi et al., 2018, 2015).

1.4. Gaps in Knowledge

1.4.1. Study Design

Study design depends primarily on the research question at hand. In epidemiological studies aiming to investigate the health effects of certain exposures, a longitudinal study design is the best fit. As data is collected over a period of time statistical methods can be used to analyze changes over this time, or analyze health outcomes

(Caruana et al., 2015). This is particularly useful when examining the effect of prenatal and early life exposures on health effects in later years. For example, collecting multiple height and weight measurements over several ages, allows for the calculation of growth trajectories which may identify more accurately children at higher risks for certain conditions. This would otherwise not be possible in a cross-sectional study design which only takes a "snap-shot" at a single point in time. Further, while cross-sectional studies may be quick and easier to carry-out they provide no information on the influence of time and thus are less valid for investigating cause-and-effect. That being said, longitudinal studies also have some drawbacks, namely they can be prone to selection bias due to loss to follow up of participants over time leading to biased effect estimates.

1.4.2.Novel Measures of Cardiovascular Health

Recent evidence has shown that cardiovascular risk during adulthood can be traced back to higher levels of risk factors during childhood and early adolescence (Juonala et al., 2011). Given this, there is great interest in measuring cardiovascular health early in life when risk factors may be modifiable. In children and young adolescents the most promising measures are those that are non-invasive and that have proven to be accurate during these younger ages. Conventionally, studies have used blood pressure, lipid profile, and/or adiposity measurements as markers for cardiovascular risk. More recently, non-invasive tools have become available to characterize health of the macro- and microvascular structures. PWV is a measure of macrovascular health and arterial stiffness which has been associated with increased cardiovascular risk and atherosclerosis in adulthood (Cote et al., 2015; Hudson et al., 2015). This measure is non-invasive, simple to perform and has been validated in healthy children (Thurn et al., 2015). Further, structural changes in the microvasculature via retinal vessel diameter during childhood can be evaluated by using fundus images (Wong and Mitchell, 2007). Retinal vessel diameter is considered an independent risk factor for cardiovascular disease with venular widening indicative of inflammation and atherosclerosis, and arterial narrowing indicative of arterial damage (Li et al., 2016; Newman et al., 2017). While these measures have had some use in the general population, there use with children and in conjunction

with prenatal exposures is lacking (Charakida et al., 2012; Juonala et al., 2011; Siegrist et al., 2014).

1.4.3. Multiple Exposures: Mixture Analysis

In real life, people are exposed to a wide variety of environmental chemicals simultaneously. However, until recently, many studies have focused on examining only single chemical exposures which ignores the combined effect of multiple exposures. Investigating multiple exposures greatly increases the complexity of the analysis, however it is also a better reflection of real life. Over recent years, several statistical techniques have been developed to analyze these complex mixtures. Mixture models can reduce confounding by other chemicals, help to identify which chemical most strongly affects the outcome, assesses interactions between chemicals, and assesses the joint effects (i.e. mixture). Some popular multiple exposure methods include dimension reducing techniques like principal component analysis (PCA) which reduces the number of correlated variables into a small number of new variables thus minimizing information loss (Jolliffe and Cadima, 2016). Other methods include Bayesian kernel machine regression (BKMR) which flexibly models dose-response relations of many exposures including interactions (Bobb et al., 2018) and Bayesian weighted quantile sum regression (BWQS) which estimates the net effect of a mixture and identifies "bad actor" pollutants within said mixture (Colicino et al., 2020).

1.4.4. The Role of Socioeconomic Position

Socioeconomic position (SEP) is typically measured through income, occupation, education level, or a combination of the three factors (Winkleby et al., 1992). When it comes to illnesses like cardiovascular disease, social disparities like low SEP, low education, and limited access to care have long shown to play a role in more negative health outcomes (Winkleby et al., 1992). Likewise, in environmental health, social determinants have long been studied and shown to play a role in a wide variety of health outcomes, including the unequal distribution of environmental risk to exposures (Pampel et al., 2010). However, recent studies have found varying results that contradict the traditional hypothesis of disadvantaged groups as being systematically classified as the "high

risk" group when it comes to chemical exposure (Hicken et al., 2012). Epidemiological evidence has been mixed with some studies reporting higher concentrations of certain chemicals in those of higher SEP, while other studies have reported the opposite (Lim et al., 2015; Tyrrell et al., 2013; Vrijheid et al., 2012). These contradictory findings challenge the traditional hypothesis and elicit further exploration.

2. RATIONALE

Cardiovascular diseases are a global health problem and a part of their origin is likely to begin in prenatal and early postnatal life. The same risk factors found in adults can be traced back to childhood; obesity, high blood pressure, and rapid growth during infancy. Prenatal and early life exposure to environmental chemicals, maternal metabolic factors, and social determinants may all play a role in adversely effecting child growth and cardiovascular health.

Environmental chemicals are increasingly problematic as there are tens of thousands in production, and humans are continually exposed from common everyday items. A growing body of evidence indicates that developmental adaptations due to adverse environmental exposures during vulnerable time periods like pregnancy and early life may alter molecular pathways leading to high risk growth trajectories and/or increased cardiovascular risk. Identifying chemicals with potentially adverse effects is particularly important amongst already vulnerable groups like pregnant women to better the health of children and future generations.

At the same time, there is need to discover novel research tools to detect those at higher risk for developing cardiovascular diseases in the future. Despite this, some previous research studies have predominantly analyzed only one parameter of growth, or only traditional measures of cardiovascular health like blood pressure and adiposity. By using tools like longitudinal growth trajectories and novel measures of cardiovascular health we may be more able to accurately identify children at higher disease risk during an age when adverse risk factors are still preventable and/or reversible. This will help gain new insights in to the environmental origins of cardiovascular disease risk, and help identify those at the highest risk so that prevention efforts can be tailored for those groups.

3. OBJECTIVES

The overall aim of this thesis was to examine the role of early life predictors, focusing on maternal, chemical, and social factors, on child growth trajectories and early adolescent cardiovascular health measured through traditional and novel preclinical phenotypes (Figure 1). This is addressed through the following specific objectives:

1. To evaluate the associations between markers of maternal metabolic health during pregnancy and their offspring's longitudinal BMI growth trajectories during childhood (0 to 4 years).

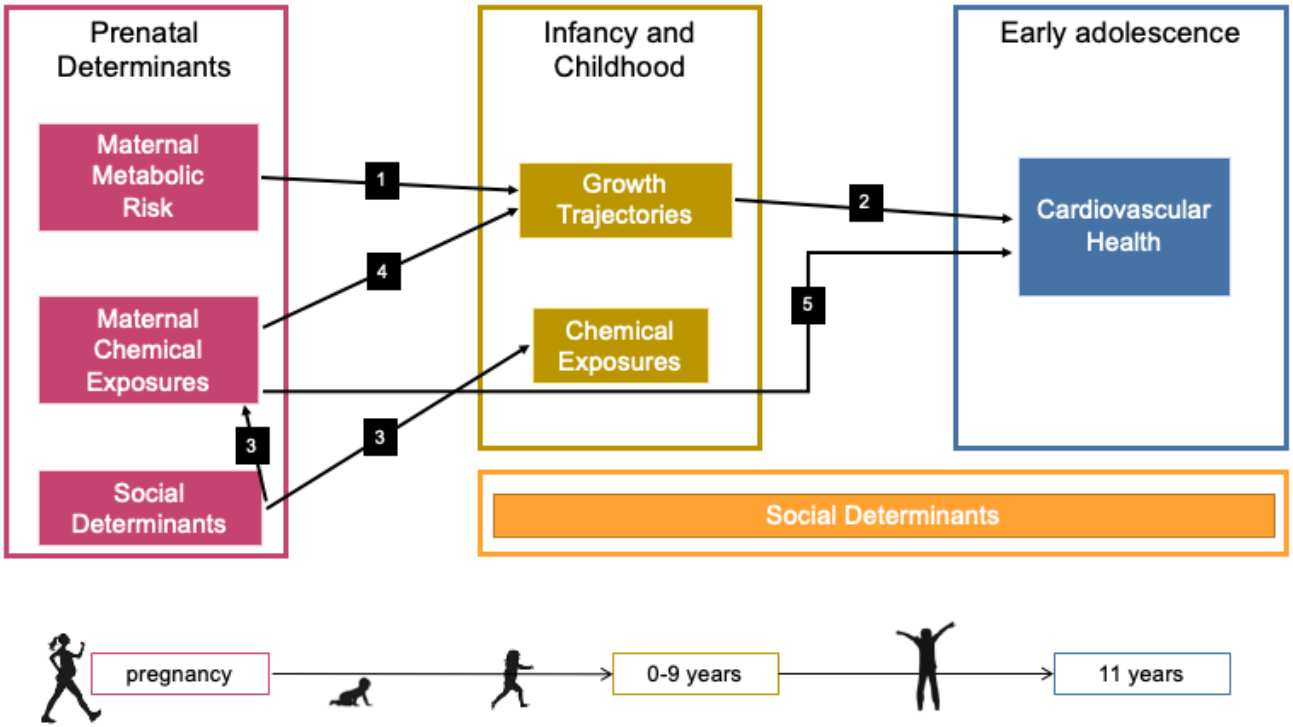
2. To evaluate the associations between childhood longitudinal BMI growth trajectories (0 to 9 years) and early adolescent cardiovascular health at 11 years.

3. To investigate the associations between indicators of social economic position and several chemical concentrations in pregnant women and their children (6 to 12 years).

4. To examine the associations between prenatal chemical exposures and childhood longitudinal BMI growth trajectories (0 to 9 years).

5. To examine the associations between selected prenatal chemical exposures and early adolescent cardiovascular health at 11 years.

Figure 1. Graphical layout of specific objectives labeled by objective number.



4. METHODS

This section provides a general overview of the methods used in this thesis to evaluate the research hypotheses. A summary of the study populations, prenatal characteristics, chemical concentrations, childhood growth trajectories, and early adolescent cardiovascular measurements are detailed in Table 1. More detailed descriptions of the methods and analyses utilized are given in each of the papers included in Chapter 5 (Results).

4.1. Description of the Birth Cohorts

Two birth cohorts were used for this thesis; the INMA-"INfancia y Medio Ambiente" (Environment and Childhood) project and the HELIX (Human Early Life Exposome) study (Figures 2a-2b). Both studies are birth cohorts that followed pregnant women through the prenatal period and their offspring through childhood.

4.1.1.INMA

The INMA project includes data from seven prospective population based birth cohorts from different regions throughout Spain. This thesis used data from the four "new" birth cohorts located in; Asturias, Gipuzkoa, Sabadell and Valencia. Women were recruited during the first prenatal visit (10-13 weeks) at their local hospital or health center. The recruitment periods were from May 2004 to July 2007 in Asturias (n=494), from April 2006 to January 2008 in Gipuzkoa (n=638), from July 2004 to July 2006 in Sabadell (n=657), and from November 2003 to June 2005 in Valencia (n=855). Inclusion criteria were; >=16 years of age, singleton pregnancy, intention to deliver at reference hospital, and no assisted conception or communication issues. Mother-child pair were followed-up with during the 3rd trimester (28-32 weeks), at birth, and at child aged 6 months, and 1, 4, 7, 9 and 11 years of age using the same study protocol in each cohort (Guxens et al., 2012). Information was collected through medical registries, interview-based questionnaires with parents and the child, and physical examinations of the children by trained INMA personnel. Interview based questionnaires conducted during each visit collected information of parental and child characteristics such as,

sociodemographic, lifestyle and behavioral factors, as well as medical history. Maternal metabolic parameters (prepregnancy BMI, GWG, gestational diabetes (GDM), and concentrations of cholesterol, triglycerides, and CRP), were estimated from questionnaire data and serum extracted during the first prenatal visit. Prenatal chemical concentrations were determined in maternal serum samples taken during the first prenatal visit and urine samples taken during the first and third prenatal visits. Child weight and height information was collected from medical registries and trained INMA personnel at study visits. In the Sabadell cohort, cardiovascular measures, blood pressure, PWV, and retinal images, were taken by trained INMA personnel at the 11 year visit.

Figure 2a. Geographical locations of the INMA birth cohorts in Spain.

4.1.2. HELIX

This thesis used data from the HELIX sub-cohort study which is comprised of 1,301 mother-child pairs. Sub-cohort subjects were recruited from six different European birth cohorts; BiB (Born in Bradford UK (n=205) (Wright et al., 2013), EDEN (Study of determinants of pre- and postnatal developmental, France, n=198) (Drouillet et al., 2009), INMA (Environment and Childhood, Spain, n=223) (Guxens et al., 2012), KANC (Kaunas Cohort, Lithuania n=204) (Grazuleviciene et al., 2009), MoBa (The Norwegian Mother and Child Cohort Study, Norway (Oslo region) n=272) (Magnus et al., 2016) and RHEA (Mother–Child Cohort in Crete, Greece n=199) (Chatzi et al., 2009). Eligibility criteria were; child aged 6-11 years at study visit, stored prenatal blood and urine samples for biomarker measurements, complete address history available, no serious health issues, and data available on certain lifestyle factors such as diet and SES. Chemical concentration measurements for archived maternal samples were performed at one laboratory or their contract laboratories. In three cohorts, EDEN, INMA and RHEA maternal samples had been previously analyzed for certain contaminants. As such, select samples were re-analyzed with each sample batch to ensure comparability. Women completed questionnaires during pregnancy in each cohort which included information on lifestyle factors and SES. These data were later harmonized between cohorts. Clinical assessments of the children were carried out between December 2013 and February 2016. The assessments were done using the same protocol for all participating cohorts, and they included blood and urine sample collection for the children as well as additional data on lifestyle factors and other social determinants (Maitre et al., 2018).

Figure 2b. Geographical locations of the HELIX birth cohorts in Europe.

Table 1. Summary of the prenatal exposures, childhood growth trajectories, and early adolescent cardiovascular measurements assessed at different ages by paper.

	Paper I	Paper II	Paper III	Paper IV	Paper V
Population Characteristic	INMA (AST, GIP, SAB, VAL) N = 2251	INMA (SAB) N = 489	HELIX N = 1301	INMA (GIP, SAB, VAL) N = 1911	INMA (SAB) N = 416
Familial:					
Socioeconomic position			✓ (exposure)		
Maternal metabolic:					
Prepregnancy BMI, GWG, GDM	✓ (exposure)				
Cholesterol, triglycerides, CRP	✓ (exposure)				
Chemical concentration:					
Phthalates			✓ (outcome)	✓ (exposure)	✓ (exposure)
Phenols			✓ (outcome)	✓ (exposure)	✓ (exposure)
POPs			✓ (outcome)	✓ (exposure)	
PFASs			✓ (outcome)	✓ (exposure)	
Heavy metals			✓ (outcome)		
OP Pesticide Metabolites			✓ (outcome)		
Child BMI growth trajectories:					
0 – 4 years old	✓ (outcome)				
0 – 9 years old		✓ (exposure)		✓ (outcome)	
Early adolescent cardiovascular health (11 years):					
Blood pressure		✓ (outcome)			✓ (outcome)
Pulse Wave Velocity		✓ (outcome)			✓ (outcome)
Retinal images		✓ (outcome)			✓ (outcome)

Abbreviations: AST: Asturias, GIP: Gipuzkoa, SAB: Sabadell, VAL: Valencia, BMI: body mass index, GWG: gestational weight gain, GDM: gestational diabetes mellitus, POPs: persistent organic pollutants, PFASs: perfluoroalkyl substances, OP: organophosphate

5. RESULTS

Paper I: Maternal Metabolic Health Parameters During Pregnancy in Relation to Early Childhood BMI Trajectories

Paper II: Early-childhood BMI trajectories in relation to preclinical cardiovascular measurements in adolescence

Paper III: Socioeconomic position and exposure to multiple environmental chemical contaminants in six European mother-child cohorts

Paper IV: Prenatal exposure to multiple endocrine disrupting chemicals and childhood BMI trajectories

Paper V: Prenatal exposure to phthalates and phenols and preclinical vascular health during early adolescence

5.1. Paper I

Montazeri P, Vrijheid M, Martinez D, Basterrechea M, Fernandez-Somoano A, Guxens M, Iñiguez C, Lertxundi A, Murcia M, Tardon A, Sunyer J, Valvi D. Maternal Metabolic Health Parameters During Pregnancy in Relation to Early Childhood BMI Trajectories. Obesity. 2018;26(3):588-596. doi: 10.1002/oby.22095.

Original Article
PEDIATRIC OBESITY

Obesity

Maternal Metabolic Health Parameters During Pregnancy in Relation to Early Childhood BMI Trajectories

Parisa Montazeri[1,2,3], Martine Vrijheid[1,2,3], David Martinez[1,2,3], Mikel Basterrechea[3,4,5], Ana Fernandez-Somoano[3,6], Monica Guxens[1,2,3], Carmen Iñiguez[3,7], Aitana Lertxundi[3,4,5], Mario Murcia[3,7], Adonina Tardon[3,6], Jordi Sunyer[1,2,3], and Damaskini Valvi[1,2,3,8]

Objective: The objective of this study was to evaluate the associations between maternal metabolic parameters and early childhood BMI trajectories.
Methods: Two thousand two hundred fifty-one children born in Spain between 2004 and 2008 were analyzed. Five BMI *z* score trajectories from birth to age 4 years were identified by using latent class growth analysis. Multinomial regression assessed the associations between maternal metabolic parameters and offspring's BMI trajectories.
Results: Children in the reference BMI trajectory had average size at birth followed by a slower BMI gain. Maternal prepregnancy obesity was associated with trajectories of accelerated BMI gain departing from either higher (relative risk ratio [RRR] = 1.77; 95% CI: 1.07-2.91) or lower size at birth (RRR = 1.91; 95% CI: 1.17-3.12). Gestational weight gain (GWG) above clinical guidelines was associated with a trajectory of higher birth size followed by accelerated BMI gain (RRR = 2.14; 95% CI: 1.53-2.97). Maternal serum triglycerides were negatively associated with BMI trajectories departing from lower birth sizes. Gestational diabetes, maternal serum cholesterol, and C-reactive protein were unrelated to children's BMI trajectories.
Conclusions: Maternal prepregnancy obesity, GWG, and serum triglycerides are associated with longitudinal BMI trajectories in early childhood that may increase disease risk in later life. Health initiatives should promote healthy weight status before and during pregnancy to improve maternal and child health.

Obesity (2017) **00**, 00-00. doi:10.1002/oby.22095

Introduction

Childhood obesity worldwide has more than doubled in the past 4 decades (1), with more than 42 million preschool-aged children currently estimated to be classified with overweight or obesity (2). Children with overweight or obesity are more likely to remain in trajectories of excessive weight throughout their life course, facing health consequences that include increased risks for type 2 diabetes, cardiovascular disease, certain cancers, and mortality (3). Maternal

[1] ISGlobal, Barcelona Institute for Global Health, Barcelona, Spain [2] Department of Experimental and Health Sciences, Pompeu Fabra University, Barcelona, Spain [3] Center for Biomedical Research in the Network of Epidemiology and Public Health, Madrid, Spain [4] Public Health Division of Gipuzkoa, Basque Government, San Sebastián, Spain [5] Biodonostia Health Research Institute, San Sebastián, Spain [6] University Institute of Oncology of the Principality of Asturias and Area of Preventive Medicine and Public Health, Department of Medicine, University of Oviedo, Oviedo, Asturias, Spain [7] Epidemiology and Environmental Health Joint Research Unit, Foundation for the Promotion of Health and Biomedical Research of the Valencia Region, Jaume I University, and University of Valencia, Valencia, Spain [8] Department of Environmental Health, T.H. Chan School of Public Health, Harvard University, Boston, Massachusetts, USA. Correspondence: Damaskini Valvi (dvalvi@hsph.harvard.edu)

Funding agencies: This work was funded by grants from The Spanish Ministry of Health and the European Commission. The funding sources that follow have been listed by subcohort. Asturias: FIS-FEDER 04/2018, 09/02311, and 13/02429; Hospital San Agustin, Aviles, Asturias; Cajastur Social Work/Liberbank Foundation; and University of Oviedo. Gipuzkoa: Carlos III Health Institute (FIS-PI06/0867 and FIS-PS09/00090), Basque Government (2005111093 and 2009111069), and Provincial Government of Gipuzkoa (DFG06/004 and DFG08/001). Sabadell: Pregnancy and birth: Carlos III Health Institute (Red INMA G03/176), Government of Catalonia, Catalan National Science Foundation (1999SGR 00241); 6 months to 2 years of age examinations: Carlos III Health Institute (Red INMA G03/176, CB06/02/0041, and PI041436), Government of Catalonia, Catalan National Science Foundation (1999SGR 0024); Child examinations at 4 years: Carlos III Health Institute (Red INMA G03/176, CB06/02/0041, PI041436, and PI081151, including FEDER funds), Government of Catalonia, Catalan National Science Foundation (1999SGR 00241), and TV3 La Marató Foundation (090430); Growth trajectories: PI15/00118. Valencia: European Union (FP7-ENV-2011 cod 282957 and HEALTH.2010.2.4.5-1). Spain: Carlos III Health Institute (G03/176; FIS-FEDER: PI11/01007, PI11/02591, PI11/02038, PI13/1944, PI13/2032, PI14/00891, PI14/01687, PI16/1288, and Miguel Servet-FEDER CP11/00178 and CP15/00025) and the Valencian Government, Foundation for the Promotion of Health and Biomedical Research of the Valencia Region (UGP 15-230, UGP 15-244, and UGP 15-249).
Disclosure: The authors declared no conflict of interest.
Author contributions: MV and DV designed this research. PM and DM performed the statistical analyses under the supervision of DV. MV, MB, AF, MG, CI, AT, JS, and DV were responsible for designing the INfancia y Medio Ambiente ("Environment and Childhood") study follow-up protocols and data collection. PM wrote the first manuscript draft and shares primary responsibility with MV and DV. All authors critically reviewed the manuscript and approved the final version for submission.
Additional Supporting Information may be found in the online version of this article.
Received: 30 May 2017; **Accepted:** 19 November 2017; **Published online 00 Month 2017. doi:10.1002/oby.22095**

prepregnancy BMI and metabolic health parameters in pregnancy, such as gestational diabetes mellitus (GDM), have been associated with multiple aspects of child growth, including birth weight, growth velocity, BMI peak, BMI status, and adiposity (4-6); however, few prospective studies have integrated repeated growth measurements to assess the role of maternal metabolic health on offspring's growth trajectories over time.

Longitudinal BMI trajectories integrate information on multiple aspects of growth, like birth size, BMI gain velocity, and BMI peaks, which have previously been associated with higher risks for asthma, obesity, and elevated blood pressure (7,8). For example, robust evidence from cohort studies has demonstrated that both children who are born relatively smaller and experience rapid growth during the first year of life and children born with higher birth weights have increased risks for diseases in later life (9,10). These findings suggest that adverse growth patterns linked to disease may be apparent in early childhood. Longitudinal BMI trajectories may permit a more accurate identification of young children at higher disease risk, in comparison to growth outcomes assessed at a single time point, and may be valuable for investigation into early life health determinants (8).

Studies evaluating maternal determinants of offspring's BMI trajectories are few and have focused primarily on maternal sociodemographic data (8,11), lifestyle factors (12,13), and prepregnancy overweight (8,12). The association of maternal metabolic parameters, beyond prepregnancy BMI, in relation to offspring's longitudinal BMI trajectories remains unexplored. Therefore, we utilized a large prospective birth cohort to evaluate the associations between multiple maternal metabolic parameters (prepregnancy BMI, gestational weight gain [GWG], GDM, and metabolic biomarkers) and offspring's BMI trajectories during the first 4 years of postnatal life.

Methods

Population and design

We studied mother-child pairs from the Spanish birth cohort studies of the INfancia y Medio Ambiente (INMA, "Environment and Childhood") Project (14). Women were recruited at 10 to 13 weeks of gestation through regional hospitals, Sabadell ($N = 657$), Valencia ($N = 855$), Asturias ($N = 494$), and Gipuzkoa ($N = 638$), between 2003 and 2008 (14). The inclusion criteria were as follows: ≥ 16 years of age, singleton pregnancy, intention to deliver at reference hospital, and no assisted conception or communication issues. Mother-child pairs were followed up at 28 to 32 weeks' gestation, at birth, and at the child ages of 6 months and 1, 2, and 4 years (15). Information was collected though medical registries, interview-based questionnaires with the mothers, and physical examinations of the children conducted by specially trained personnel (15). The study has been approved by the ethics review boards of the hospitals involved in the study. All mothers signed a written consent for themselves and for their child's participation.

Maternal metabolic parameters

Maternal metabolic parameters assessed included prepregnancy BMI, GWG, GDM, and nonfasting serum concentrations of cholesterol, triglycerides, and C-reactive protein (CRP). Maternal prepregnancy BMI was estimated from self-reported weight and measured height. BMI status was defined by using World Health Organization (WHO) cutoffs for adults (normal weight including underweight if BMI < 25 kg/m^2; overweight if BMI 25-30 kg/m^2; and obesity if BMI > 30 kg/m^2) (3). Maternal GWG was calculated as the difference between the weight measured during the third trimester visit and self-reported prepregnancy weight. GWG was defined as inadequate, recommended, or excessive by using the Institute of Medicine classification (16).

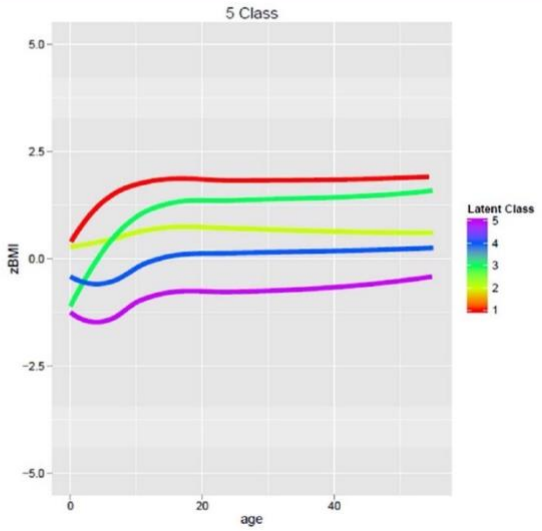
GDM diagnosis information (no/yes) was extracted from medical records. In Spain, pregnant women are routinely screened for GDM at 24 to 28 weeks of gestation with a 50-g, 1-hour oral glucose challenge test (OGCT). If their blood glucose concentration is $\geq$140 mg/dL, they are administered a 100-g, 3-hour oral glucose tolerance test 2 to 3 weeks later to confirm a GDM diagnosis based on National Diabetes Data Group criteria (17). Pregnant women at low risk for GDM (age < 24 years, normal weight, and with no family or personal history of diabetes or prior pregnancy complications) did not undertake OGCTs and are included in the nondiagnosed for GDM category.

Maternal concentrations of total cholesterol, triglycerides, and CRP were measured in nonfasting serum extracted during the first prenatal visit. For the Gipuzkoa and Sabadell subcohorts, lipid analyses were performed at the Basque Country Public Health Laboratory by using the CHOD-POD and GPO-POD enzymatic colorimetric assays (Spinreact S.A., Girona, Spain) for total cholesterol and triglycerides, respectively (18). For the Valencia subcohort, lipid analyses were performed at the General Biochemistry Laboratory of La Fe Hospital by using OSR6116 and OSR6x118 enzymatic colorimetric assays (Beckman Coulter Inc., Brea, California) for total cholesterol and triglycerides, respectively. Concentration values were within the detection range for all analyzed samples at both laboratories. CRP was measured by using immunoturbidimetric assays and standardized analytical procedures at the Consulting Quimico Sanitario Laboratory in Madrid for the Gipuzkoa subcohort and at the Reference Laboratory of Catalonia for the Sabadell subcohort, as detailed elsewhere (19). Quality controls including intra- and interplate coefficients of variance ($< 10\%$) confirmed the absence of analytical batch effects for lipid and CRP determinations.

Childhood BMI trajectories

Repeated measurements of child height and weight from birth until 4 years of age were extracted from medical records. BMI was calculated as weight in kilograms divided by squared height in centimeters, and age- and sex-specific BMI z scores were calculated by using the WHO Child Growth Standards (20). We defined overweight as a specific BMI for age and sex $\geq$ the 85th percentile BMI of the WHO reference population (21).

We estimated BMI z score trajectories using latent class growth analysis (22), which allows parameter differences to be captured across unobserved subpopulations by assuming a number of discrete latent classes. The mean number of BMI z score measurements from 0 to 55 months was 11 (SD = 3.4) per child. We tested from two to seven possible trajectory classes, and the Akaike and Bayesian information criteria were used to define the best data fit. Five distinct BMI z score trajectories from birth to 4 years of age were identified as the best fit (Figure 1).



Child BMI z-score Trajectory	Frequency (%)	Description
Class 1	11.9	Higher birth size and subsequent accelerated BMI gain
Class 2	26.0	Higher birth size and subsequent slower BMI gain
Class 3	13.4	Lower birth size and subsequent accelerated BMI gain
Class 4	35.9	Average birth size and subsequent slower BMI gain (reference category)
Class 5	12.8	Lower birth size and subsequent slower BMI gain

Figure 1 Child BMI *z* score trajectory classes from birth to 4 years of age in the INMA children ($N = 2,251$). [Color figure can be viewed at wileyonlinelibrary.com]

Statistical analysis

Our analysis included 2,251 mother-child pairs (82% of those initially recruited) who had available data for at least one maternal metabolic parameter being studied and repeated weight and height measurements of the child permitting the calculation of BMI trajectories. Analyses of metabolic biomarkers had fewer observations, as this information was not available for all subcohorts ($n = 1,707$ for maternal serum lipids measured in Sabadell, Guipuzkoa, and Valencia; and $n = 1,002$ for maternal serum CRP measured in Sabadell and Guipuzkoa).

Concentrations of triglycerides and CRP were $\log_2$-transformed to normalize right skewed distributions. The associations between maternal metabolic parameters and child longitudinal BMI trajectories were assessed by using multinomial logistic regression, as the outcome variable has five categories. We present herein the coefficients from the multinomial models exponentiated to relative risk ratios (RRRs). First, we evaluated associations in statistical models adjusted for subcohort only; second, we evaluated associations in multivariate-adjusted models including the subcohort and additional confounders.

We considered a wide list of covariates obtained from interview-based questionnaires administered at the first and third trimesters, which included the following: maternal sociodemographic data (country of origin, education, social class coded based on occupation according to the International Standard Classification of Occupations 88 system, working status, and parity), lifestyle factors (smoking, alcohol), and self-reported perception of physical activity. Energy intake was calculated based on information from a 101-item food frequency questionnaire validated for use in pregnant women (23). Potential confounders were initially selected by using directed acyclic graphs. Covariates that changed the multinomial regression coefficients by more than 10% for at least one of the maternal metabolic parameters using a forward selection procedure were retained in the final multivariate-adjusted models. Covariates retained were as follows: subcohort, maternal age, maternal education, parity, smoking status during pregnancy, country of origin, working situation at first trimester, and paternal BMI. Effect estimates were not adjusted for gestational age, birth weight, and predominant breastfeeding because these factors may mediate the associations between maternal metabolic parameters and child postnatal growth (24,25).

TABLE 1 Population characteristics overall and according to child BMI *z* score trajectory class

	All children, *N* = 2,251	Class 1, 269 (12.0%)	Class 2, 585 (26.0%)	Class 3, 301 (13.4%)	Class 4, 809 (35.9%)	Class 5, 287 (12.8%)	
	Mean ± SD or *n* (%)	Mean ± SD or *n* (%)	Mean ± SD or *n* (%)	Mean ± SD or *n* (%)	Mean ± SD or *n* (%)	Mean ± SD or *n* (%)	*P*[a]
Maternal characteristics							
Country of origin							
Spain	2,075 (92.4)	239 (88.9)	533 (91.1)	281 (94.0)	747 (92.6)	275 (95.8)	0.017
Other	172 (7.6)	30 (11.1)	52 (8.9)	18 (6.0)	60 (7.4)	12 (4.2)	
Age in pregnancy	32 ± 4.2	31.8 ± 4.1	32.0 ± 4.3	32.3 ± 3.9	32.0 ± 4.2	32.2 ± 4.2	0.523
Education							
Primary school or less	514 (22.9)	70 (26.0)	137 (23.5)	61 (20.4)	185 (22.9)	61 (21.2)	0.659
Secondary school	933 (41.5)	109 (40.5)	247 (42.3)	118 (39.5)	332 (41.1)	127 (44.2)	
University degree	800 (35.6)	90 (33.5)	200 (34.2)	120 (40.1)	291 (36.0)	99 (34.5)	
Social class							
Professionals and managers	510 (22.7)	52 (19.3)	129 (22.1)	80 (26.6)	184 (22.7)	65 (22.6)	0.597
Skilled manual/nonmanual	597 (26.5)	71 (26.4)	157 (26.9)	71 (23.6)	226 (27.9)	72 (25.1)	
Semiskilled/unskilled	1,143 (50.8)	146 (54.3)	298 (51.0)	150 (49.8)	399 (49.3)	150 (52.3)	
Working situation at first trimester							
Working	1,593 (70.8)	190 (70.6)	418 (71.6)	218 (72.4)	559 (69.2)	208 (72.5)	0.709
Not working	488 (21.7)	61 (22.7)	124 (21.2)	63 (20.9)	188 (23.3)	52 (18.1)	
Leave	168 (7.5)	18 (6.7)	42 (7.2)	20 (6.6)	61 (7.5)	27 (9.4)	
Parity							
Nulliparous	1,277 (56.8)	143 (53.4)	289 (49.4)	200 (66.4)	456 (56.4)	189 (66.1)	< 0.001
Multiparous	972 (43.2)	125 (46.6)	296 (50.6)	101 (33.5)	353 (43.6)	97 (33.9)	
Type of delivery							
Vaginal	1,364 (62.0)	146 (54.1)	375 (65.4)	171 (58.0)	505 (63.9)	167 (59.0)	0.021
Instrumental	449 (20.4)	49 (18.9)	111 (19.4)	67 (22.7)	159 (20.1)	63 (22.3)	
Cesarean	388 (17.6)	65 (25.0)	87 (15.2)	57 (19.3)	126 (15.9)	53 (18.7)	
Smoking status during pregnancy							
Never	1,526 (69.1)	180 (67.9)	402 (69.7)	197 (67.2)	551 (69.1)	196 (71.0)	0.497
Until first trimester	324 (14.7)	36 (13.6)	87 (15.1)	38 (13.0)	118 (14.8)	45 (16.3)	
Until third trimester	358 (16.2)	49 (18.5)	88 (15.2)	58 (19.8)	128 (16.1)	35 (12.7)	
Alcohol use at first trimester							
No	1,562 (69.9)	185 (69.3)	395 (68.0)	216 (72.2)	580 (72.3)	186 (65.5)	0.153
Yes	671 (30.1)	82 (30.7)	186 (32.0)	83 (27.8)	222 (27.7)	98 (34.5)	
Total EI at first trimester, kcal/d	2,094.4 ± 530	2,126.8 ± 560	2,106.8 ± 566	2,037.6 ± 457	2,094.3 ± 528	2,098.4 ± 498	0.481
Mediterranean diet score at first trimester							
Low	692 (31.8)	86 (32.9)	171 (30.0)	90 (31.0)	256 (32.6)	89 (32.7)	0.261
Medium	1,050 (48.2)	138 (52.9)	273 (47.9)	148 (51.0)	366 (46.7)	125 (45.9)	
High	435 (20.0)	37 (14.2)	126 (22.1)	52 (17.9)	162 (20.7)	58 (21.3)	
Perception of physical activity							
Sedentary	147 (6.6)	16 (6.0)	32 (5.5)	20 (6.8)	59 (7.4)	20 (7.0)	0.912
A little active	567 (25.5)	78 (29.2)	145 (25.0)	78 (26.3)	190 (23.8)	76 (26.8)	
Moderately active	909 (40.9)	103 (38.6)	239 (41.2)	122 (41.2)	334 (41.9)	111 (39.1)	
Quite active	601 (27.0)	70 (26.2)	164 (28.2)	76 (25.7)	214 (26.8)	77 (27.1)	
Child characteristics							
Sex							
Female	1,085 (48.3)	111 (41.4)	279 (47.7)	146 (48.7)	425 (52.5)	124 (43.5)	0.009
Male	1,162 (51.7)	157 (58.6)	306 (52.3)	154 (51.3)	384 (47.5)	161 (56.5)	
Gestational age, wk	39.6 ± 0.3	39.7 ± 1.3	39.8 ± 1.3	39.3 ± 1.7	39.7 ± 1.5	39.3 ± 2.0	0.004

TABLE 1. (continued).

	All children, $N = 2,251$	Class 1, 269 (12.0%)	Class 2, 585 (26.0%)	Class 3, 301 (13.4%)	Class 4, 809 (35.9%)	Class 5, 287 (12.8%)	
	Mean ± SD or *n* (%)	Mean ± SD or *n* (%)	Mean ± SD or *n* (%)	Mean ± SD or *n* (%)	Mean ± SD or *n* (%)	Mean ± SD or *n* (%)	*P*[a]
Birth weight, g	3,260 ± 467	3,498 ± 432	3,431 ± 400	3,123 ± 446	3,225 ± 420	2,930 ± 515	< 0.001
Birth length, cm	49.6 ± 2.2	49.9 ± 1.9	49.9 ± 1.9	49.3 ± 2.2	49.6 ± 2.1	48.8 ± 2.6	< 0.001
BMI status at 4 y, kg/m^2	16.2 ± 1.6	18.1 ± 1.7	16.4 ± 1.2	17.3 ± 1.7	15.7 ± 1.2	14.7 ± 1.0	< 0.001
Overweight/obesity at 4 years (WHO)							
No	1,326 (70.4)	50 (22.2)	339 (70.9)	108 (43.6)	599 (86.1)	230 (97.5)	< 0.001
Yes	557 (29.6)	175 (77.8)	139 (29.1)	140 (56.4)	97 (13.9)	6 (2.5)	
Obesity at 4 years (IOTF)							< 0.001
Grade 3 thinness	7 (0.4)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)	6 (2.5)	
Grade 2 thinness	14 (0.7)	0 (0.0)	0 (0.0)	0 (0.0)	3 (0.4)	11 (4.7)	
Grade 1 thinness	85 (4.5)	0 (0.0)	2 (0.4)	0 (0.0)	31 (4.5)	52 (22.0)	
Normal weight	1,406 (74.0)	75 (33.3)	403 (84.3)	152 (61.3)	600 (86.2)	164 (69.5)	
Overweight	278 (14.6)	101 (44.9)	58 (12.1)	59 (23.8)	55 (7.9)	2 (0.8)	
Obesity	109 (5.7)	49 (21.8)	15 (3.1)	37 (14.9)	6 (0.9)	1 (0.4)	
Predominant breastfeeding, wk							
0	488 (22.8)	72 (28.5)	126 (22.4)	53 (18.5)	191 (24.7)	46 (17.0)	< 0.001
> 0-16	682 (31.8)	73 (28.8)	154 (27.4)	122 (42.7)	235 (30.4)	98 (36.2)	
> 16-24	733 (34.2)	78 (30.8)	207 (36.8)	83 (29.0)	260 (33.7)	105 (38.7)	
> 24	241 (11.2)	30 (11.9)	75 (13.3)	28 (9.8)	86 (11.1)	22 (8.1)	
Paternal characteristics							
BMI status, kg/m^2							
Under-normal weight: < 18.5-25	975 (44.0)	104 (39.5)	243 (42.2)	109 (36.6)	378 (47.7)	141 (49.5)	< 0.001
Overweight: 25-30	978 (44.2)	105 (39.9)	267 (46.3)	151 (50.7)	334 (42.1)	121 (42.5)	
Obesity: > 30	262 (11.8)	54 (20.5)	66 (11.5)	38 (12.7)	81 (10.2)	23 (8.1)	

χ^2 and Fisher's exact tests used for categorical explanatory variables, and Kruskal-Wallis test used for continuous explanatory variables. BMI trajectory classes defined as follows: Class 1, higher birth size followed by accelerated BMI gain; Class 2, higher birth size followed by slower BMI gain; Class 3, lower birth size followed by accelerated BMI gain; Class 4 (reference), average birth size followed by slower BMI gain; and Class 5, lower birth size followed by slower BMI gain.
[a]*P* value denotes comparison of mean or percentage of each characteristic by BMI trajectory class.
EI, energy intake; IOTF, International Obesity Task Force; WHO, World Health Organization.

We created a separate model for each maternal metabolic parameter to minimize overadjustment due to the correlation between metabolic covariates. We also performed sensitivity analyses, adjusting each model for prepregnancy BMI to evaluate whether this is a confounder in the associations of other metabolic parameters. Multiple imputation generating 20 data sets was performed to handle missing observations in covariates (< 3% of observations), and we further conducted complete case analyses excluding observations with missing information.

A two-sided $P \leq 0.05$ determined statistically significant associations. Latent class growth analysis for determining the BMI *z* score trajectories was performed using the "lcmm" function in R package software (2). All other analyses were conducted by using Stata version 12 (StataCorp, College Station, Texas).

Results

The analysis population consisted of mothers predominantly of Spanish origin (92.4%) with a mean age of 32 years at pregnancy. Most mothers received secondary education or higher (77.1%) and were working during the first pregnancy trimester (70.8%) (Table 1). About half of mothers were nulliparous (56.8%), and more than half (69.1%) reported not to have smoked during pregnancy. The prevalences of maternal prepregnancy overweight and obesity were 18.5% and 7.6%, respectively, and weight gain during pregnancy was classified as inadequate for 24.1% of mothers and excessive for 37.5%, whereas 4.4% of mothers were diagnosed for GDM (Table 2).

One-third of children (35.9%) fell into a BMI trajectory characterized by average size at birth followed by a slower BMI gain (Class 4, reference category) compared with the other BMI trajectories (Figure 1): Class 1, higher birth size followed by accelerated BMI gain (12.7%); Class 2, higher birth size followed by slower BMI gain (26.0%); Class 3, lower birth size followed by accelerated BMI gain (13.4%); and Class 5, lower birth size followed by slower BMI gain (12.8%). By age 4 years, 29.6% of children had overweight (which includes obesity), with the highest prevalence of overweight seen in children of the two trajectories characterized by accelerated BMI gain (Classes 1 and 3) (Table 1).

TABLE 2 Maternal metabolic parameters overall and according to child BMI z score trajectory class

	All children, 100%	Class 1, 11.9%	Class 2, 26.0%	Class 3, 13.4%	Class 4, 35.9%	Class 5, 12.8%	
	Mean ± SD or *n* (%)	Mean ± SD or *n* (%)	Mean ± SD or *n* (%)	Mean ± SD or *n* (%)	Mean ± SD or *n* (%)	Mean ± SD or *n* (%)	*P*[a]
Prepregnancy BMI status, kg/m² (n = 2,251)							
Under[b]-normal weight: < 18.5-25	1,664 (73.9)	178 (66.2)	426 (72.8)	208 (69.1)	617 (76.3)	235 (81.9)	< 0.001
Overweight: 25-30	416 (18.5)	60 (22.3)	115 (19.7)	61 (20.3)	140 (17.3)	40 (13.9)	
Obesity: > 30	171 (7.6)	31 (11.5)	44 (7.5)	32 (10.6)	52 (6.4)	12 (4.2)	
Gestational weight gain (n = 2,177)							
Recommended	836 (38.4)	76 (29.5)	225 (39.8)	103 (35.9)	322 (40.8)	110 (39.6)	< 0.001
Inadequate	525 (24.1)	41 (15.9)	121 (21.4)	78 (27.2)	194 (24.6)	91 (32.7)	
Excessive	816 (37.5)	141 (54.6)	219 (38.8)	106 (36.9)	273 (34.6)	77 (27.7)	
Gestational diabetes (n = 2,217)							
No	2,119 (95.6)	250 (94.3)	559 (96.7)	278 (94.6)	762 (95.1)	270 (96.8)	0.312
Yes	98 (4.4)	15 (5.7)	19 (3.3)	16 (5.4)	39 (4.9)	9 (3.2)	
Cholesterol, mg/dL (n = 1,707)[c]	195.7 ± 33.5	197.9 ± 30.6	197.6 ± 34.0	193.9 ± 31.2	195.2 ± 33.7	193.3 ± 35.9	0.071
Triglycerides, mg/dL (n = 1,705)[c]	106.2 ± 43.7	111.2 ± 47.8	108.9 ± 45.3	99.6 ± 38.6	107.4 ± 43.3	99.5 ± 41.1	0.031
C-reactive protein, mg/L (n = 1,002)[c]	0.6 ± 0.7	0.6 ± 0.6	0.6 ± 0.7	0.7 ± 0.9	0.6 ± 0.7	0.6 ± 0.6	0.029

BMI trajectory classes defined as follows: Class 1, higher birth size followed by accelerated BMI gain; Class 2, higher birth size followed by slower BMI gain; Class 3, lower birth size followed by accelerated BMI gain; Class 4 (reference), average birth size followed by slower BMI gain; and Class 5, lower birth size followed by slower BMI gain.
[a]*P* value denotes comparison of mean or percentage of each characteristic by growth trajectory class.
[b]Prevalence of underweight separately is 4.4%.
[c]There were fewer observations because cholesterol and triglyceride concentrations were measured in only three (Sabadell, Gipuzkoa, and Valencia) of the four INMA subcohorts, and C-reactive protein concentrations were measured in only two (Sabadell and Gipuzkoa) of the subcohorts.
INMA, INfancia y Medio Ambiente ("Environment and Childhood").

Child BMI trajectories significantly differed according to maternal country of origin, parity, type of delivery, paternal BMI (Table 1), and maternal metabolic parameters, including prepregnancy BMI, GWG, and triglyceride and CRP levels (Table 2). In the multivariate-adjusted models (Table 3), defining the group of children with average sizes at birth followed by slower BMI gain as the reference category (Class 4), maternal prepregnancy overweight was marginally associated with the BMI trajectory of higher birth size followed by accelerated BMI gain (Class 1 vs. Class 4: RRR = 1.36; 95% CI: 0.96-1.95). Prepregnancy obesity was positively associated with the two BMI trajectories characterized by accelerated BMI gain departing from either higher (Class 1 vs. Class 4: RRR = 1.77; 95% CI: 1.07-2.91) or lower birth size (Class 3 vs. Class 4: RRR = 1.91; 95% CI: 1.17-3.12). Excessive GWG was positively associated with the BMI trajectory of higher birth size and subsequent accelerated BMI gain (Class 1 vs. Class 4: RRR = 2.14; 95% CI: 1.53-2.97), whereas inadequate GWG was associated with the BMI trajectory of lower birth size and slower BMI gain (Class 5 vs. Class 4: RRR = 1.50; 95% CI: 1.07-2.10). Higher maternal triglyceride concentrations were negatively associated with the two trajectories of lower birth size followed by either accelerated (Class 3 vs. Class 4: RRR = 0.68; 95% CI: 0.50-0.93) or slower BMI gain (Class 5 vs. Class 4: RRR = 0.68; 95% CI: 0.51-0.91). No clear associations were observed with GDM, total cholesterol, or CRP concentrations (Table 3).

Associations between maternal metabolic parameters and child BMI trajectories did not differ significantly between the multivariate-adjusted models (Table 3) and the models adjusted for subcohort only (Supporting Information Table S1). Analyses after excluding observations with missing values in additional covariates led to similar coefficients (Supporting Information Table S2). In sensitivity analyses, adding prepregnancy BMI to the models, the coefficients for the associations of GWG, GDM, cholesterol, triglycerides, CRP levels, and child BMI trajectories remained unchanged in magnitude and significance (data not shown).

Discussion

In this prospective study of children born in Spain, we found that maternal prepregnancy BMI and GWG are associated with offspring's BMI trajectories from birth through early childhood. Specifically, we found that maternal prepregnancy obesity is associated with early childhood BMI trajectories characterized by accelerated BMI gain, regardless of birth size. Further, children of mothers who gained weight above the clinical recommendations, compared with children of mothers within the recommended range, had a higher probability to follow a BMI trajectory of higher birth size and accelerated BMI gain. Conversely, the children of mothers with lower than recommended GWG had a higher probability to depart from a lower birth size followed by a slower BMI gain. Maternal nonfasting serum triglyceride concentrations in early pregnancy were negatively associated with the two BMI trajectories of lower birth size followed by either an accelerated or slower BMI gain. GDM diagnosis and early pregnancy serum cholesterol and CRP concentrations were not clearly associated with the BMI trajectories.

TABLE 3 Adjusted associations between maternal metabolic parameters and child BMI *z* score trajectory class

	Class 1	Class 2	Class 3	Class 5
	Higher birth size, accelerated BMI gain[a]	Higher birth size, slower BMI gain[a]	Lower birth size, accelerated BMI gain[a]	Lower birth size, slower BMI gain[a]
	RRR (95% CI)	RRR (95% CI)	RRR (95% CI)	RRR (95% CI)
Prepregnancy BMI (n = 2,251)				
Underweight-normal	1.00	1.00	1.00	1.00
Overweight	1.36 (0.96-1.95)	1.15 (0.87-1.53)	1.30 (0.92-1.84)	0.76 (0.52-1.13)
Obesity	1.77 (1.07-2.91)	1.17 (0.76-1.81)	1.91 (1.17-3.12)	0.63 (0.33-1.23)
Gestational weight gain (n = 2,177)				
Recommended	1.00	1.00	1.00	1.00
Inadequate	0.84 (0.55-1.29)	0.87 (0.65-1.16)	1.23 (0.87-1.75)	1.50 (1.07-2.10)
Excessive	2.14 (1.53-2.97)	1.14 (0.89-1.47)	1.17 (0.84-1.62)	0.80 (0.57-1.12)
Gestational diabetes (n = 2,217)				
No	1.00	1.00	1.00	1.00
Yes	1.26 (0.66-2.34)	0.68 (0.39-1.19)	1.12 (0.61-2.05)	0.61 (0.29-1.28)
Cholesterol (n = 1,707)[a]	1.00 (1.00-1.01)	1.00 (1.00-1.01)	1.00 (0.99-1.00)	1.00 (0.99-1.00)
Triglycerides (n = 1,705)[a]	1.07 (0.78-1.45)	1.02 (0.81-1.28)	0.68 (0.50-0.93)	0.68 (0.51-0.91)
C-reactive protein (n = 1,002)[b]	1.11 (0.92-1.33)	1.09 (0.95-1.24)	1.14 (0.96-1.36)	1.01 (0.85-1.19)

[a]Reference outcome category is Class 4: average birth size and subsequent slower BMI gain. All models adjusted for subcohort, maternal age, maternal education, parity, smoking status during pregnancy, country of origin, working situation at first trimester, and paternal BMI.
[b]There were fewer observations because cholesterol and triglyceride concentrations were measured in only three (Sabadell, Gipuzkoa, and Valencia) of the four INMA subcohorts, and C-reactive protein concentrations were measured in only two (Sabadell and Gipuzkoa) of the subcohorts.
INMA, INfancia y Medio Ambiente ("Environment and Childhood"); RRR, relative risk ratio.

Children in this study followed at least five distinct BMI-averaged trajectories characterized by main differences in their size at birth (defined for comparison as "lower," "average," or "higher" birth size) and by differences in BMI gain velocity, which were more prominent during the first year of age (defined as "accelerated" or "slower" BMI gain). These BMI patterns are similar to the BMI- or weight-adjusted-for-height trajectories previously reported in children born in the Netherlands, United Kingdom, Japan, United States, and Australia (8,11,13,26,27). However, our study is the first to identify two distinct accelerated BMI gain trajectories in early infancy departing from either lower or higher birth sizes. Low birth size babies with a thrifty "catch-up" fat phenotype are known to be at higher risk for insulin resistance, type 2 diabetes, and cardiovascular disease (28), whereas larger size at birth is associated with increased BMI at later ages (10), accelerated growth in infancy, and adverse health outcomes in later life, including obesity and hypertension (29-31). Thus, the children in the accelerated BMI gain trajectories departing from either lower or higher birth size (Classes 1 and 3) may face increased risk for cardiometabolic disease in later life (28-31). Future research in the INMA birth cohorts through puberty, and adulthood is warranted to elucidate the health risks associated with altered early infancy growth patterns as well as the combined impact of birth size and growth acceleration on disease pathogenesis.

Maternal prepregnancy obesity was associated with increases in children's risk to present a trajectory of accelerated BMI gain departing from either a higher or lower size at birth by 77% and 91%, respectively. These associations were less evident, although they moved in the same direction for maternal prepregnancy overweight. In agreement with our results, previous longitudinal studies have reported positive associations between maternal prepregnancy or early pregnancy BMI and childhood trajectories characterized by accelerated BMI gain (13,26) and/or overweight/obesity (8,11). Our findings expand the state of evidence showing that maternal prepregnancy obesity is associated with postnatal trajectories of accelerated growth regardless of a child's size at birth. These associations may be explained by shared genetic and environmental factors between the mothers and their offspring and/or by long-lasting alterations of fetal endocrine and metabolic programming in the children of mothers with obesity (10,32). Fetal overnutrition in the offspring of mothers with obesity may explain in part the association observed with the trajectory of accelerated BMI gain departing from higher birth sizes (32). This is also supported by the strong association we found between excessive GWG and the higher birth size–accelerated BMI gain trajectory. However, it is likely that different mechanisms and/or mediating factors (e.g., a shorter gestational duration and/or breastfeeding duration in some of the mothers with prepregnancy obesity (25)), may explain the observed association of maternal BMI with a trajectory of accelerated BMI gain in children at the lower end of birth sizes. It is therefore of interest to confirm the associations seen in this study between maternal prepregnancy BMI and diverse childhood growth trajectories with other large populations and to elucidate further potentially implicated mechanisms. Our findings also highlight the utility of assessing longitudinal BMI trajectories to acquire a more in-depth understanding of early-life growth determinants. Further, the high prevalence of overweight/obesity (26%) and the low prevalence of mothers with adequate GWG (38%) both underscore the urgent need for effective

lifestyle interventions to promote a healthy weight status and GWG in Spain and elsewhere, so as to improve the health outcomes in women of childbearing age and their offspring (33).

Maternal nonfasting serum triglyceride concentrations in early pregnancy were negatively associated with the two BMI trajectories of lower birth size followed by either accelerated or slower BMI gain, and the associations were not confounded by maternal prepregnancy BMI. Higher fasting and nonfasting triglyceride levels in either early or late pregnancy have been associated with higher birth weight in previous studies (34-36), and these findings support our results that suggest that there is a lower risk in children of following a trajectory departing from lower birth sizes. However, findings from this first study evaluating the associations between maternal triglyceride levels and postnatal BMI trajectories suggest that maternal triglyceride levels in early pregnancy, though associated with birth size, are not associated with trajectories of accelerated BMI gain later in infancy and are worthy of further exploration in other populations. Maternal cholesterol and CRP levels in early pregnancy were not associated with child BMI trajectories; however, future studies assessing lipids and inflammation markers at later pregnancy stages are needed to fully understand the impact of maternal lipid profiles and/or inflammation on children's growth patterns. Moreover, despite the known relationships of GDM with high birth size and increased obesity risk (37), we found no clear association between GDM and children's BMI trajectories. The prevalence of the clinical diagnosis of GDM in this cohort was relatively low (4.4%), which may be due to the fact that in Spain, as well as in other European regions (38), only women considered at high risk (based on their age and clinical history) undertake an OGCT. Misclassification of GDM cases is therefore likely and could have attenuated associations toward the null.

A major strength of this study is the large sample size and prospective design that permitted the collection of repeated weight and height measurements and the evaluation of longitudinal childhood BMI trajectories. Furthermore, the wide list of covariates measured allowed us to examine simultaneously the associations of several maternal metabolic parameters and child BMI trajectories while accounting for important confounders. Our study also has limitations, which include the lack of more direct measures of maternal and child adiposity (e.g., skinfold thicknesses) and of repeated maternal fasting lipid measures. According to recent international clinical guidelines, fasting is not required for an accurate determination of lipid profiles (39), and both fasting and nonfasting maternal lipid levels have been associated with offspring's growth outcomes (34-36). However, the nondifferential measurement error in the nonfasting lipid variables could distort associations either toward or against the null (40). Future studies may therefore benefit from the assessment of lipids at fasting, as well as at multiple time points during pregnancy, to more accurately capture the lipid profile over the entire course of pregnancy. Finally, we cannot rule out residual confounding due to self-reported data (e.g., maternal smoking and physical activity) and/or unmeasured confounders, such as common genetic risk factors in the mothers and their children, which could explain in part the observed associations.

Conclusion

This study provides evidence that maternal metabolic parameters during pregnancy contribute to the determination of offspring's BMI trajectories in early childhood, possibly associated with disease risk in later life. Maternal prepregnancy obesity was associated with early childhood trajectories characterized by accelerated BMI gain, regardless of birth size, whereas excessive GWG was associated with a child's higher size at birth followed by accelerated BMI gain. Further, higher maternal triglyceride serum levels in early pregnancy were associated with lower risk of the children to depart from a BMI trajectory of low birth size followed by either accelerated or slower BMI gain. Health initiatives and interventions aiming to improve maternal and child health should be intensified to promote healthy weight status and GWG in women of childbearing age. O

Acknowledgments

We thank all of the study participants and personnel for their collaboration, and we thank the listed funding sources for supporting the INMA birth cohort studies. We also thank Michelle Ann Mendez and Amy Herring for scientific advice and thank Cristina Bocos Hernandez for assistance with data analysis at the early stages of this research.

References

1. NCD Risk Factor Collaboration. Trends in adult body-mass index in 200 countries from 1975 to 2014: a pooled analysis of 1698 population-based measurement studies with 19.2 million participants. *Lancet* 2016;387:1377-1396.
2. de Onis M, Blössner M, Borghi E. Global prevalence and trends of overweight and obesity among preschool children. *Am J Clin Nutr* 2010;92:1257-1264.
3. World Health Organization. *Obesity: Preventing and Managing the Global Epidemic*. Report of a WHO consultation. WHO Technical Report Series 894. Geneva: WHO; 2000.
4. Heude B, Thiébaugeorges O, Goua V, et al. Pre-pregnancy body mass index and weight gain during pregnancy: relations with gestational diabetes and hypertension, and birth outcomes. *Matern Child Health J* 2012;16:355-363.
5. Godoy GAF, Korevaar TIM, Peeters RP, et al. Maternal thyroid hormones during pregnancy, childhood adiposity and cardiovascular risk factors: the Generation R Study. *Clin Endocrinol (Oxf)* 2014;81:117-125.
6. Pizzi C, Cole TJ, Richiardi L, dos-Santos-Silva I, Corvalan C, De Stavola B. Prenatal influences on size, velocity and tempo of infant growth: findings from three contemporary cohorts. *PLoS One* 2014;9:e90291. doi:10.1371/journal.pone.0090291
7. Adair L. Size at birth and growth trajectories to young adulthood. *Am J Hum Biol* 2007;19:327-333.
8. Ziyab AH, Karmaus W, Kurukulaaratchy RJ, Zhang H, Arshad SH. Developmental trajectories of body mass index from infancy to 18 years of age: prenatal determinants and health consequences. *J Epidemiol Community Health* 2014;68:934-941.
9. Mook-Kanamori DO, Durmuş B, Sovio U, et al. Fetal and infant growth and the risk of obesity during early childhood: the Generation R Study. *Eur J Endocrinol* 2011;165:623-630.
10. Oken E, Gillman MW. Fetal origins of obesity. *Obes Res* 2003;11:496-506.
11. van Rossem L, Wijga AH, Brunekreef B, et al. Overweight in infancy: which pre- and perinatal factors determine overweight persistence or reduction? A birth cohort followed for 11 years. *Ann Nutr Metab* 2014;65:211-219.
12. Suzuki K, Sato M, Zheng W, Shinohara R, Yokomichi H, Yamagata Z. Childhood growth trajectories according to combinations of pregestational weight status and maternal smoking during pregnancy: a multilevel analysis. *PLoS One* 2015;10: e0118538. doi: 10.1371/journal.pone.0118538
13. Haga C, Kondo N, Suzuki K, et al. Developmental trajectories of body mass index among Japanese children and impact of maternal factors during pregnancy. *PLoS One* 2012;7:e51896. doi:10.1371/journal.pone.0051896
14. Ribas-Fitó N, Ramón R, Ballester F, et al. Child health and the environment: the INMA Spanish study. *Paediatr Perinat Epidemiol* 2006;20:403-410.
15. Guxens M, Ballester F, Espada M, et al. Cohort Profile: The INMA--INfancia y Medio Ambiente--(Environment and Childhood) Project. *Int J Epidemiol* 2012;41: 930-940. doi:10.1093/ije/dyr054
16. Institute of Medicine (US), National Research Council (US) Committee to Reexamine IOM Pregnancy Weight Guidelines; Rasmussen KM, Yaktine AL, eds. *Weight Gain During Pregnancy: Reexamining the Guidelines*. Washington, DC: National Academies Press; 2009.

17. The Expert Committee on the Diagnosis and Classification of Diabetes Mellitus. Report of the Expert Committee on the Diagnosis and Classification of Diabetes Mellitus. *Diabetes Care* 2003;26(suppl 1):5-20.
18. Alvarez-Pedrerol M, Guxens M, Ibarluzea J, et al. Organochlorine compounds, iodine intake, and thyroid hormone levels during pregnancy. *Environ Sci Technol* 2009;43:7909-7915.
19. Morales E, Guerra S, Garca-Esteban R, et al. Maternal C-reactive protein levels in pregnancy are associated with wheezing and lower respiratory tract infections in the offspring. *Am J Obstet Gynecol* 2011;204:1-9.
20. de Onis M. 4.1 The WHO Child Growth Standards. *World Rev Nutr Diet* 2015;113: 278-294.
21. World Health Organization. *WHO Child Growth Standards: Length/height-for-Age, Weight-for-Age, Weight-for-Length, Weight-for-Height and Body Mass Index-for-Age: Methods and Development*. Geneva: WHO; 2006.
22. Slining MM, Herring a. H, Popkin BM, Mayer-Davis EJ, Adair LS. Infant BMI trajectories are associated with young adult body composition. *J Dev Orig Health Dis* 2012;4:56–68.
23. Vioque J, Navarrete-Muñoz EM, Gimenez-Monzó D, et al. Reproducibility and validity of a food frequency questionnaire among pregnant women in a Mediterranean area. *Nutr J* 2013;12:26. doi:10.1186/1475-2891-12-26
24. Heerman W, Bian A, Shintani A, Barkin S. The interaction between maternal pre-pregnancy BMI and gestational weight gain shapes infant growth. *Acad Pediatr* 2014;14:463-470.
25. Crume TL, Ogden LG, Mayer-Davis EJ, et al. The impact of neonatal breast-feeding on growth trajectories of youth exposed and unexposed to diabetes *in utero*: the EPOCH Study. *Int J Obes (Lond)* 2012;36:529-534.
26. Giles LC, Whitrow MJ, Davies MJ, Davies CE, Rumbold a R, Moore VM. Growth trajectories in early childhood, their relationship with antenatal and postnatal factors, and development of obesity by age 9 years: results from an Australian birth cohort study. *Int J Obes (Lond)* 2015;39:1049–1056.
27. Li C, Goran MI, Kaur H, Nollen N, Ahluwalia JS. Developmental trajectories of overweight during childhood: role of early life factors. *Obesity (Silver Spring)* 2007;15:760-771.
28. Dulloo AG, Jacquet J, Seydoux J, Montani J-P. The thrifty "catch-up fat" phenotype: its impact on insulin sensitivity during growth trajectories to obesity and metabolic syndrome. *Int J Obes (Lond)* 2006;30:S23-S35.
29. Chrestani MA, Santos IS, Horta BL, Dumith SC, de Oliveira Dode MAS. Associated factors for accelerated growth in childhood: a systematic review. *Matern Child Health J* 2013;17:512-519.
30. Eriksson JG, Kajantie E, Lampl M, Osmond C. Trajectories of body mass index amongst children who develop type 2 diabetes as adults. *J Intern Med* 2015;278: 219-226.
31. Perng W, Hajj H, Belfort M, et al. Birth size, early weight gain, and midchildhood cardiometabolic health. *J Pediatr* 2016;173:122-130.
32. Penfold NC, Ozanne SE. Developmental programming by maternal obesity in 2015: Outcomes, mechanisms, and potential interventions. *Horm Behav* 2015;76: 143-152.
33. Clifton R, Evans M, Cahill A, et al. Design of lifestlye intervention trials to prevent excessive gestational weight gain in women with overweight or obesity. *Obesity (Silver Spring)* 2016;24:305-313.
34. Misra VK, Trudeau S, Perni U. Maternal serum lipids during pregnancy and infant birth weight: the influence of prepregnancy BMI. *Obesity (Silver Spring)* 2011;19: 1476-1481.
35. Vrijkotte TGM, Algera SJ, Brouwer IA, van Eijsden M, Twickler MB. Maternal triglyceride levels during early pregnancy are associated with birth weight and postnatal growth. *J Pediatr* 2011;159:736-742.e1.
36. Liu B, Geng H, Yang J, et al. Early pregnancy fasting plasma glucose and lipid concentrations in pregnancy and association to offspring size: a retrospective cohort study. *BMC Pregnancy Childbirth* 2016;16:56. doi:10.1186/s12884-016-0846-7
37. Crume T, Ogden L, Daniels S, Hamman R, Norris J, Dabelea D. The impact of *in utero* exposure to diabetes on childhood body mass index growth trajectories: the EPOCH study. *J Pediatr* 2011;158:941-946.
38. Valvi D, Oulhote Y, Weihe P, et al. Gestational diabetes and offspring birth size at elevated environmental pollutant exposures. *Environ Int* 2017;107:205-215.
39. Nordestgaard BG, Langsted A, Mora S, et al. Fasting is not routinely required for determination of a lipid profile: clinical and Laboratory implications including flagging at desirable concentration cutpoints-a joint consensus statement from the European Atherosclerosis Society and European Federation of Clinical Chemistry and Laboratory Medicine. *Clin Chem* 2016;62:930-946.
40. Brenner H, Loomis D. Varied forms of bias due to nondifferential error in measuring exposure. *Epidemiology* 1994;5:510-517.

Supplementary Material
Paper I

Table S1. Unadjusted associations between maternal metabolic health parameters and child´s BMI z-score trajectory class (multinomial logistic regression coefficients adjusted for subcohort only).

Maternal metabolic parameter	Class 1 higher birth size-accelerated BMI gain [a]	Class 2 higher birth size-slower BMI gain [a]	Class 3 lower birth size-accelerated BMI gain [a]	Class 5 lower birth size-slower BMI gain [a]
	RRR (95% CI)	*RRR (95% CI)*	*RRR (95% CI)*	*RRR (95% CI)*
Prepregnancy BMI (n=2251)				
Underweight-normal	1.00	1.00	1.00	1.00
Overweight	1.48 (1.04-2.09)	1.19 (0.90-1.57)	1.27 (0.90-1.79)	0.75 (0.51-1.09)
Obesity	2.10 (1.30-3.38)	1.23 (0.81-1.87)	1.87 (1.16-2.99)	0.59 (0.31-1.13)
Gestational Weight Gain (n=2177)				
Recommended	1.00	1.00	1.00	1.00
Inadequate	0.87 (0.57-1.33)	0.89 (0.67-1.18)	1.22 (0.86-1.73)	1.43 (1.02-1.99)
Excessive	2.22 (1.60-3.07)	1.15 (0.90-1.48)	1.21 (0.88-1.67)	0.81 (0.58-1.13)
Gestational Diabetes (n=2217)				
No	1.00	1.00	1.00	1.00
Yes	1.18 (0.64-2.18)	0.66 (0.38-1.16)	1.14 (0.62-2.08)	0.65 (0.31-1.36)
Cholesterol (n=1707) [b]	1.00 (0.99-1.01)	1.00 (0.99-1.01)	1.00 (0.99-1.00)	1.00 (0.99-1.00)
Triglycerides (n=1705) [b]	1.16 (0.86-1.55)	1.05 (0.84-1.31)	0.70 (0.51-0.94)	0.65 (0.49-0.86)
C-Reactive Protein (n=1002) [b]	1.14 (0.96-1.35)	1.09 (0.96-1.24)	1.08 (0.92-1.27)	0.97 (0.82-1.15)

[a] The reference outcome category is Class 4: average birth size and subsequent slower BMI gain. All models are adjusted for subcohort.

[b] Fewer observation because cholesterol and triglyceride concentrations were measured in only 3 (Sabadell, Gipuzkoa and Valencia) and C-Reactive Protein concentrations in only 2 (Sabadell, Gipuzkoa) of the 4 INMA subcohorts.

Abbreviation: BMI, body mass index. Reference group for the outcome is Class 4 (average birth size-slower growth) trajectory.

Table S2. Adjusted associations between maternal metabolic health parameters and child´s BMI z-score trajectory class from the complete case analysis (excludes observations with missing values).

Maternal metabolic parameter	Class 1	Class 2	Class 3	Class 5
	higher birth size-accelerated BMI gain [a]	higher birth size-slower BMI gain [a]	lower birth size-accelerated BMI gain [a]	lower birth size-slower BMI gain [a]
	RRR (95% CI)	*RRR (95% CI)*	*RRR (95% CI)*	*RRR (95% CI)*
Prepregnancy BMI (n=2149)				
Underweight-normal	1.00	1.00	1.00	1.00
Overweight	1.48 (1.03-2.11)	1.16 (0.87-1.55)	1.29 (0.90-1.85)	0.75 (0.50-1.12)
Obesity	2.04 (1.23-3.39)	1.25 (0.80-1.95)	2.06 (1.24-3.41)	0.69 (0.36-1.35)
Gestational Weight Gain (n=2091)				
Recommended	1.00	1.00	1.00	1.00
Inadequate	0.77 (0.49-1.19)	0.86 (0.64-1.15)	1.18 (0.82-1.69)	1.43 (1.01-2.03)
Excessive	2.04 (1.45-2.85)	1.16 (0.90-1.50)	1.15 (0.82-1.60)	0.78 (0.55-1.10)
Gestational Diabetes (n=2126)				
No	1.00	1.00	1.00	1.00
Yes	1.34 (0.72-2.51)	0.71 (0.68-2.08)	1.21 (0.65-1.23)	0.65 (0.31-1.37)
Cholesterol (n=1654) [b]	1.00 (1.00-1.01)	1.00 (1.00-1.01)	1.00 (0.99-1.00)	1.00 (0.99-1.00)
Triglycerides (n=1652) [b]	1.09 (0.80-1.49)	1.03 (0.81-1.30)	0.68 (0.50-0.94)	0.70 (0.52-0.94)
C-Reactive Protein (n=958) [b]	1.12 (0.94-1.35)	1.10 (0.96-1.26)	1.17 (0.98-1.39)	1.02 (0.85-1.21)

[a] The reference outcome category is Class 4: average birth size and subsequent slower BMI gain. All models are adjusted for subcohort, maternal age, maternal education, parity, smoking status during pregnancy, country of origin, working situation at 1st trimester, and paternal BMI.

[b] Fewer observation because cholesterol and triglyceride concentrations were measured in only 3 (Sabadell, Gipuzkoa and Valencia) and C-Reactive Protein concentrations in only 2 (Sabadell, Gipuzkoa) of the 4 INMA subcohorts.

Abbreviation: BMI, body mass index.

5.2. Paper II

Montazeri P, Fossati S, Clemente DBP, Cirugeda L, Elosua R, Fernández-Barrés S, Fochs S, Garcia-Esteban R, Marquez S, Pey N, Nawrot TS, Vrijheid M. Early-childhood BMI trajectories in relation to preclinical cardiovascular measurements in adolescence. J Dev Orig Health Dis. 2021 Jul 26:1-8. doi: 10.1017/S2040174421000441. Epub ahead of print. PMID: 34308826.

Journal of Developmental Origins of Health and Disease

www.cambridge.org/doh

Early-childhood BMI trajectories in relation to preclinical cardiovascular measurements in adolescence

Parisa Montazeri[1,2,3], Serena Fossati[1,2,3], Diana B.P. Clemente[4], Lourdes Cirugeda[1,2,3], Roberto Elosua[5,6,7], Silvia Fernández-Barrés[1,2,3], Silvia Fochs[1,2,3], Raquel Garcia-Esteban[1,2,3], Sandra Marquez[1,2,3], Nuria Pey[1,2,3], Tim S Nawrot[4,8] and Martine Vrijheid[1,2,3]

[1]ISGlobal, Barcelona, Spain; [2]Universitat Pompeu Fabra (UPF), Barcelona, Spain; [3]CIBER Epidemiología y Salud Pública (CIBERESP), Spain; [4]Centre for Environmental Sciences, Hasselt University, Hasselt, Belgium; [5]Hospital del Mar Medical Research Institute (IMIM), Barcelona, Spain; [6]CIBER Enfermedades Cardiovasculares (CIBERCV), Barcelona, Spain; [7]Medical School, University of Vic-Central University of Catalonia (UVic-UCC), Vic, Spain and [8]Department of Public Health and Primary Care, Leuven University, Leuven, Belgium

Original Article

Cite this article: Montazeri P, Fossati S, Clemente DBP, Cirugeda L, Elosua R, Fernández-Barrés S, Fochs S, Garcia-Esteban R, Marquez S, Pey N, Nawrot TS, and Vrijheid M. Early-childhood BMI trajectories in relation to preclinical cardiovascular measurements in adolescence. *Journal of Developmental Origins of Health and Disease* doi: 10.1017/S2040174421000441

Received: 20 January 2021
Revised: 16 June 2021
Accepted: 17 June 2021

Keywords:
Growth; growth trajectories; body mass index (BMI); blood pressure; cardiovascular health

Address for correspondence:
Martine Vrijheid, ISGlobal, Barcelona, Spain.
E-mail: martine.vrijheid@isglobal.org

Abstract

Cardiovascular diseases are the leading causes of morbidity and mortality. Overweight, obesity, and accelerated growth during early childhood have been associated with adverse cardiovascular outcomes in later life. Few studies have assessed whether trajectories of accelerated growth in early childhood are associated with preclinical cardiovascular measurements. We aimed to evaluate the associations between childhood body mass index (BMI) growth trajectories and measures of macro- and microvascular function in early adolescence. Measurements of macrovascular function (systolic and diastolic blood pressure (SBP and DBP), pulse wave velocity (PWV), and microvascular function (central retinal arteriolar/veinular equivalent) were assessed at 11 years old in a Spanish birth cohort study ($n = 489$). BMI trajectories from birth to 9 years were identified using latent class growth analysis. Multiple linear regression assessed the associations between the BMI trajectories and macro- and microvascular function. Compared to children with average birth size and slower BMI gain (reference), children with a lower birth size and accelerated BMI gain had increased SBP [$\beta = 6.57$; (95% CI 4.00, 9.15)], DBP [$\beta = 3.65$; (95% CI 1.45, 5.86)], and PWV [$\beta = 0.14$; (95% CI 0.01, 0.27)]. Children with higher birth size and accelerated BMI gain had increased SBP [$\beta = 4.75$; (95% CI 1.79, 7.71) compared to the reference. No significant associations between BMI trajectories and the microvascular measurements were observed. In conclusion, we found that childhood BMI trajectories characterized by accelerated growth are associated with preclinical macrovascular measurements in young adolescents.

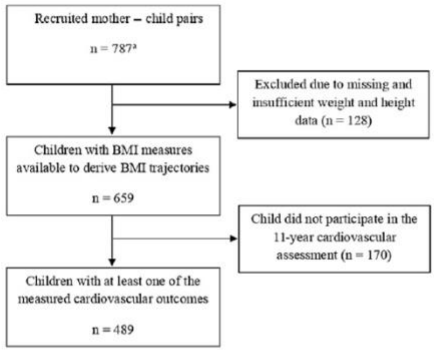
Introduction

Cardiovascular diseases are the leading causes of morbidity and mortality, and a considerable part of their origin is likely to lie in fetal and childhood life. Recent research shows that cardiovascular risk in young and middle-aged adults can be traced back to higher risk in childhood and adolescence.[1,2] Measures of obesity and adiposity, blood pressure, and other markers of macro- and microvascular function during childhood have been associated with later cardiovascular morbidity and mortality[2–5] For example, childhood blood pressure predicts adult blood pressure and other markers of cardiovascular disease,[6] and obesity during childhood has been shown to be associated with increased arterial stiffening, a potential precursor to atherosclerosis, during childhood and adulthood.[7,8] Further, structural changes in the microvasculature during childhood, as measured through retinal vein and arteriole diameters, have been linked to arterial hypertension, coronary heart disease, diabetes mellitus, and obesity in adulthood.[9,10] Retinal venular widening is indicative of inflammation and atherosclerosis, while arteriolar narrowing is indicative of damage.[10]

The developmental origins of health and disease hypothesis states that developmental programming during the pre- and early postnatal periods is sensitive to certain exposures that appear to play a critical role in future disease risk.[11] Accelerated growth during the postnatal period is one such exposure, suggested to play a role in adverse cardiovascular health over the life course, particularly among those with low birth weight.[12,13] Studies examining the relationship between individual aspects of growth (e.g. birth weight, accelerated growth, obesity, and adiposity status) have found that these different aspects are associated with risk factors for cardiovascular disease in later life such as increased cholesterol, blood pressure, pulse wave

velocity (PWV), and adverse changes to the retinal microvascular structure.[10,14–19] Fewer studies have utilized growth trajectories which integrate growth information over a period of time, thereby permitting a more accurate identification of children at a higher disease risk than just growth assessed at a single time point.[20–24] These studies found associations between growth trajectories characterized by accelerated growth or early overweight/obesity and increased blood pressure, augmentation index (a measure of arterial stiffness), and cardiovascular risk during adolescence and early adulthood.[20–24]

As previous studies primarily focused on measures of macrovascular health (e.g. blood pressure) or examined cross-sectional associations between infant growth or obesity and vascular health, there is need to examine the relationship between growth trajectories and a wider range of cardiovascular health measures. Therefore, in the present study, we aimed to evaluate the associations between childhood body mass index (BMI) growth trajectories from 0 to 9 years and preclinical cardiovascular measurements of macrovascular function (systolic and diastolic blood pressure, PWV) and microvascular function (central retinal arteriolar and venular equivalent) in young adolescents at 11 years old.



[a] recruited either during pregnancy (n=657) or at birth (n=130)

Fig. 1. Flowchart of the study sample.

Method

Study population

We studied children from the INMA (INfancia y Medio Ambiente, Environment and Childhood) birth cohort study from Sabadell, Spain. A total of 787 women were recruited at 10–13 weeks of gestation or at birth through regional hospitals from 2004 to 2007. The inclusion criteria were ≥16 years of age, singleton pregnancy, intention to deliver at reference hospital, and no assisted conception or communication issues.[25] Children and their families were followed up with at 28–32 weeks gestation, birth, and child's age of 6 months, 1, 2, 4, 7, 9, and 11 years.[25] Information was collected though medical registries, interview-based questionnaires with the mothers, and physical examinations of the children conducted by specially trained personnel.[25] The present analysis was limited to children who participated in the 11-year follow-up and who had both a BMI trajectory and at least one cardiovascular measurement available ($N = 454–489$, depending on outcome) (Fig. 1). This study was approved by the Ethics Review Boards of the hospitals involved in the study. All mothers signed a written consent for themselves and their child's participation.

Growth trajectories

Repeated measurements of child's height and weight from birth to 9 years of age were extracted from medical records and measurements taken by trained INMA staff. Children were measured using standardized protocols, always without shoes and in lightweight clothing. BMI was calculated using the standard equation (kg/m^2), and age- and sex-specific BMI z-scores were calculated using the WHO Child Growth Standards.[26,27]

BMI z-score trajectories (referred to as BMI trajectories hereafter) were previously estimated from 0 to 4 years using latent class growth analysis (LCGA).[28,29] Following the same methods, the trajectories were extended to 9 years (mean = 9.9 years) with an average of 14.3 measurement points per child. Five distinct BMI trajectories from birth to 9 years of age were identified as the best fit. Extending the trajectories to 9 years did not change the classes from the previously identified trajectories. The trajectories differed in birth size (defined as "lower", "average," or "higher") and in BMI gain velocity (defined as "slower" or "accelerated") (Fig. 2). Based on these differences, the five trajectories are class 1, larger birth size with subsequent accelerated BMI gain, class 2, larger birth size with subsequent slower BMI gain, class 3, smaller birth size with subsequent accelerated BMI gain, class 4, average birth size with subsequent slower BMI gain, and class 5, smaller birth size with subsequent slower BMI gain. For analysis, we used class 4 as the reference category.

Cardiovascular measurements

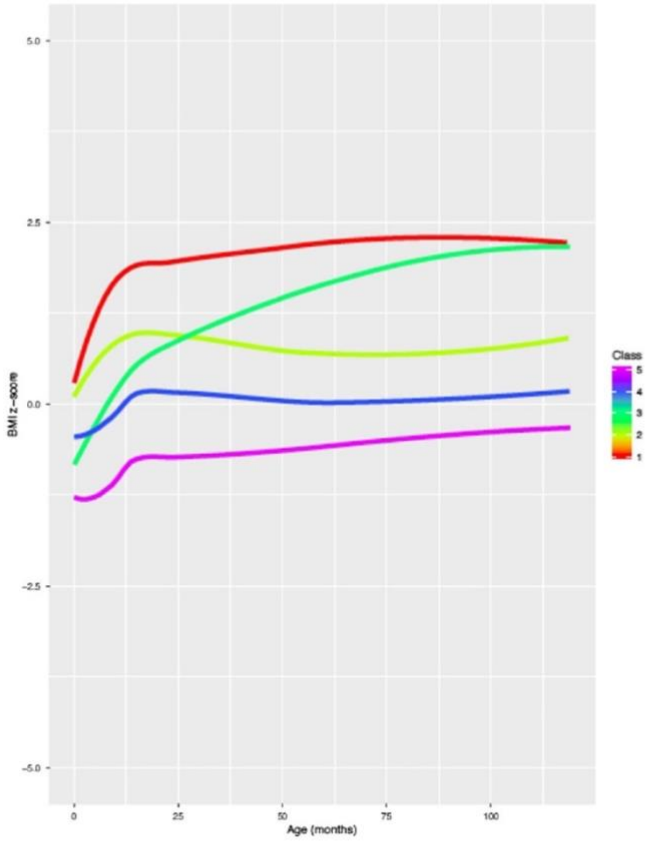
INMA research nurses trained to use the necessary technology carried out the cardiovascular measurements. Children were visited during school time for the assessment.

Blood pressure

Systolic blood pressure (SBP) and diastolic blood pressure (DBP) were measured using an automated oscillometric device OMRON 705IT with brachial cuff attached. Children were asked to sit down in a chair and positioned with their arm and back supported and their legs uncrossed with both feet on the floor. The cuff was placed on the child's arm positing the artery index marker over the child's brachial artery. After 5 min of rest, three consecutive measurements were taken with 1-min intervals between. SBP and DBP measures were averaged using the second and third measures taken. Values are presented in millimeter of mercury (mmHg).

Pulse wave velocity

PWV was recorded using VICORDER®, an arterial stiffness testing system with neck cuff and femoral thigh cuff attached in combination with the VICORDER® vascular diagnostic program package. To do this, the child laid in the supine position with a support to raise their head and shoulders 30º above their heart level. The thigh cuff was placed on their upper right thigh as high as possible, and the neck cuff was placed after palpating the pulse of the right common carotid artery. The 80% method was used (80% of the measured direct distance between the carotid and femoral recording sites) to ensure the smallest possible measurement error. With the child relaxed and still, three waveform measurements were recorded with the nurse observing a stable wave pattern. PWV



Description of the BMI z-score trajectory classes

Class 1	higher birth size – accelerated gain
Class 2	higher birth size – slower gain
Class 3	lower birth size – accelerated gain
Class 4	average birth size – slower gain (reference)
Class 5	lower birth size – slower gain

Fig. 2. BMI z-score growth trajectories from 0 to 9 years old.

measures were averaged using the three initial measurements. Values are given in meter per second (m/s).

Central retinal arteriolar/venular equivalent

Retinal images were photographed using a Canon CR2-Plus Non-Mydriatic Retinal Camera which provides information on retina changes not visible with standard photography. The child was seated behind the camera with their chin on the chin rest and their forehead pressed to the overhead bar (glasses were removed if needed). The child was asked to look straight into the camera lens, while the operator used software guides to properly align the child's eye using the joystick, finally taking the retina image. Photos were taken from both the left and right eyes and saved in high resolution for later analysis with the IFlexis software (version 2.1.1, VITO Health, Mol, Belgium). This software calculates the Central Retinal Venular Equivalent (CRVE) and Central Retinal

Arteriolar Equivalent (CRAE) using the Parr–Hubbard–Knudtson formula.[30] Average CRVE and CRAE were calculated using the Big 6 methodology; an average of the six widest arterioles and venules running through a zone between 0.5 and 1 disk diameter from the optic disk margin.[31] Processing of these measurements was carried out by one trained researcher to limit observer variability. CRAE and CRVE measures were averaged between the right and left eyes. Values are denoted in micrometer (μm).

Statistical analysis

Our analysis included a maximum of 489 children. After confirming normality of residuals, homoscedasticity, and outliers, associations between child BMI trajectories and cardiovascular measurements were assessed using multiple linear regression. Covariates were selected using directed acyclic graphs (DAGs). Models were adjusted for child age at cardiovascular measurement (years), child sex (male/female), gestational age (weeks), family socioeconomic status (SES) (low/middle/high) based on occupation using the Goldthorpe model, maternal smoking during pregnancy (none/until first trimester/until third trimester), maternal prepregnancy BMI (kg/m2), paternal BMI (kg/m2), and parental cardiovascular history (neither parent has diagnosis/one parent has at least one diagnosis/both parents have at least one diagnosis) based on questionnaire data from parents on previous cardiovascular events: heart attack, angina, hemorrhage or stroke, arthrosclerosis in legs, high cholesterol, high blood sugar, and high blood pressure. SBP, DBP, and PWV were additionally adjusted for child's height (cm) at cardiovascular measurement. BMI was not included in the models because the DAG indicated that it was a mediator rather than a covariate. Further variable descriptions can be found in Supplemental Material Table S1.

In order to maximize sample size, multiple imputation generating 20 datasets was performed to handle missing covariate observations (missing values between 1% and 13%). Imputation was carried out using the multiple imputation by chained equations (MICE) approach using the *ice* command in STATA 14. This approach assumes that data are missing at random, thus additional covariates were added to the predictive models for more accurate imputation. The imputed data were used for our main analyses and results were combined using Rubin's combination rules.

To assess any differences by sex, we stratified the associations. Further, we conducted the following sensitivity analyses: a) not adjusting for height for associations with SBP, DBP, and PWV; b) removing those children with incomplete measures (less than two measures for SBP and DBP or less than three measures for PWV) or less than good quality measures (as assessed by a trained researcher and computer software) for CRAE and CRVE; c) a complete case analysis using the non-imputed dataset; and d) cross-sectional analysis of zBMI and cardiovascular measurements.

Statistical significance was defined at P-value <0.05. LCGA analysis for determining the BMI z-score trajectories was performed using the "lcmm" function in Rstudio. All other analyses were conducted using STATA version 14 (College Station, TX).

Results

Study population characteristics are presented in Table 1. There was virtually no difference between SES categories. On

Table 1. Characteristics of the study population ($n = 489$)

	N missing	*Percent or mean ± sd*
Child characteristics		
Sex (female)	0	48.3%
Birth weight (g)	0	3278.8 ± 409.1
Height at birth (cm)	13	49.6 ± 1.9
Gestational age (weeks)	0	39.8 ± 1.3
BMI trajectories from birth to 9 years	0	
Class 1: higher birth size – accelerated gain		9.8%
Class 2: higher birth size – slower gain		27.0%
Class 3: lower birth size – accelerated gain		13.7%
Class 4: average birth size – slower gain (ref.)		35.0%
Class 5: lower birth size – slower gain		14.5%
Age[a]	0	11.0 ± 0.6
Weight[a] (kg)	0	42.0 ± 10.5
Height[a] (cm)	0	146.1 ± 8.0
zBMI[a]	0	0.70 ± 1.24
Systolic blood pressure (mmHg)	0	101.6 ± 9.9
Diastolic blood pressure (mmHg)	1	59.9 ± 7.7
Pulse wave velocity (PWV) (m/s)	22	4.4 ± 0.5
Central Retinal Arteriolar Equivalent (CRAE) (μm)	35	180.6 ± 12.9
Central Retinal Venular Equivalent (CRVE) (μm)	35	252.0 ± 17.1
Family characteristics		
Family SES (during pregnancy)	60	
High		35.4%
Middle		30.5%
Low		34.0%
Maternal BMI (prepregnancy)	11	23.8 ± 4.5
Maternal smoking (during pregnancy)	65	
None		73.1%
Until first trimester		14.4%
Until third trimester		12.5%
Paternal BMI (pregnancy first trimester)	10	25.8 ± 3.5
Parental cardiovascular history[b]	4	
Neither parent has diagnosis		47.2%
One parent has at least one diagnosis		42.7%
Both parents have at least one diagnosis		10.1%

[a]Taken at the time of cardiovascular measurement.
[b]Doctor diagnosis of cardiovascular disease (coronary heart disease, cerebrovascular disease, and peripheral vascular disease) or cardiovascular risk factors (hypercholesterolemia, hypertension, and diabetes).

Table 2. Cardiovascular measurements by BMI z-score growth trajectory

BMI z-score trajectory	Systolic blood pressure (mmHg)	Diastolic blood pressure (mmHg)	Pulse wave velocity (m/s)	Central Retinal Arteriolar Equivalent (μm)	Central Retinal Venular Equivalent (μm)
	n = 489	*n* = 488	*n* = 467	*n* = 454	*n* = 454
Class 1	107.0 ± 11.5	61.0 ± 9.5	4.5 ± 0.5	176.8 ± 13.0	250.7 ± 18.9
Class 2	100.0 ± 8.8	58.9 ± 6.7	4.3 ± 0.4	182.2 ± 13.4	252.1 ± 17.3
Class 3	108.9 ± 10.3	64.1 ± 8.6	4.6 ± 0.5	180.6 ± 11.4	252.5 ± 17.3
Class 4	99.6 ± 8.7	59.4 ± 7.2	4.3 ± 0.4	180.3 ± 12.5	252.4 ± 17.0
Class 5	98.5 ± 8.1	58.6 ± 6.7	4.4 ± 0.4	180.6 ± 14.0	250.8 ± 15.8

BMI z-score trajectory description: Class 1: higher birth size – accelerated gain; Class 2: higher birth size – slower gain; Class 3: lower birth size – accelerated gain; Class 4: average birth size – slower gain; Class 5: lower birth size – slower gain.

Table 3. Adjusted associations between BMI z-score trajectory class and cardiovascular measurements

BMI z-score trajectory	Systolic blood pressure	Diastolic blood pressure	Pulse wave velocity	Central Retinal Arteriolar Equivalent	Central Retinal Venular Equivalent
	n = 489	*n* = 488	*n* = 467	*n* = 454	*n* = 454
	β (95% CI)	*β* (95% CI)	*β* (95% CI)	*β* (95% CI)	*β* (95% CI)
Class 1	4.75 (1.79, 7.71)*	0.53 (−2.01, 3.07)	0.02 (−0.14, 0.17)	−2.66 (−7.26, 1.93)	−1.42 (−7.59, 4.76)
Class 2	−0.20 (−2.18, 1.79)	−0.98 (−2.68, 0.72)	−0.03 (−0.13, 0.07)	1.91 (−1.16, 4.98)	−0.49 (−4.62, 3.63)
Class 3	6.57 (4.00, 9.15)*	3.65 (1.45, 5.86)*	0.14 (0.01, 0.27)*	0.85 (−2.98, 4.67)	0.53 (−4.61, 5.67)
Class 4	Ref.	Ref.	Ref.	Ref.	Ref.
Class 5	−1.46 (−3.86, 0.95)	−0.98 (−3.04, 1.08)	0.05 (−0.08, 0.17)	0.71 (−2.89, 4.31)	−1.17 (−6.01, 3.67)

BMI z-score trajectory description: Class 1: higher birth size – accelerated gain; Class 2: higher birth size – slower gain; Class 3: lower birth size – accelerated gain; Class 4: average birth size – slower gain; Class 5: lower birth size – slower gain.
Coefficients marked with *are significant at $P < 0.05$.
Models using imputed data and adjusted for: child age at cardiovascular measurement, child sex, gestational age, family SES, maternal smoking (during pregnancy), maternal prepregnancy BMI, paternal BMI (during pregnancy), and parental cardiovascular history. Systolic blood pressure, diastolic blood pressure, and pulse wave velocity were additionally adjusted for child's height at cardiovascular measurement.

average, both parent's had a normal prepregnancy BMI, and the majority of mother's (73%) did not smoke during pregnancy. Approximately 40% of children had one parent with at least one diagnosed cardiovascular condition (Table 1). At the time of cardiovascular measurement, on average, children were 11 years old, weighed 42 kg, and were 146 cm tall. Imputed study population data can be found in Supplementary Material Table S2.

Children were most likely to belong to the reference trajectory, class 4, characterized by average birth size and slower BMI gain (35%). Subsequently; class 1, higher birth size and accelerated BMI gain (9.8%); class 2, higher birth size and slower BMI gain (27%); class 3, lower birth size and accelerated BMI gain (13.7%); and class 5, lower birth size and slower BMI gain (14.5%) (Table 1 and Fig. 1).

Average SBP and DBP were 101.6 mmHg and 59.5 mmHg, respectively (Table 1). Average PWV was 4.4 m/s, and average CRAE and CRVE measures were 180.6 μm and 252.0 μm, respectively. Averages and standard deviations for each cardiovascular measurement by BMI trajectory can be found in Table 2. Correlation coefficients between cardiovascular measurements can be found in Supplementary Material Table S3 and Fig. S1.

In covariate-only analysis, boys had higher SBP and PWV, and smaller CRAE and CRVE measurements than girls (Supplementary Material Table S4). Those children with lower family SES had higher SBP and DBP than those with higher SES. Height and maternal prepregnancy BMI were positively correlated with SBP and PWV, while gestational age was positively correlated with CRAE. Children of mothers who smoked through the third trimester had higher SBP and PWV compared to those whose mothers did not smoke, and children with one parent with a cardiovascular event in their history had higher PWV compared to those with parents with no history.

Table 3 shows the adjusted associations between BMI trajectories and cardiovascular measurements. Compared to children with average birth and slower BMI gain (class 4, reference trajectory), children with a lower birth size and accelerated BMI gain (class 3) had a higher SBP [$\beta = 6.57$; (95% CI 4.00, 9.15)], DBP [$\beta = 3.65$; (95% CI 1.45, 5.86)], and PWV [$\beta = 0.14$; (95% CI 0.01, 0.27)]. The BMI trajectory with children with higher birth size and accelerated BMI gain (class 1) showed an increase in SBP [$\beta = 4.75$; (95% CI 1.79, 7.71) compared to the reference trajectory. We found no significant associations between BMI trajectories and the retinal measurements, CRAE or CRVE. Crude associations were similar although higher, and all significant associations remained the same (Supplementary Material Table S5).

Overall, results were similar to main analyses when stratifying by sex. We found that both boys and girls with accelerated BMI gain (class 1 and 3) had a higher SBP (Supplementary Material S5). However, we found that the observed associations for children with a lower birth size and accelerated BMI gain (class 3) with DBP

and PWV were only significant for boys. Furthermore, girls from class 2 characterized by higher birth size and slower BMI gain had a decreased PWV when compared to the reference.

In sensitivity analyses, not adjusting for height strengthened all associations (Supplemental Material Table S7). No significant differences were found between children with complete measures and those with incomplete measures for DBP, PWV, or those with less than good measures for CRAE and CRVE (Supplemental Material Table S8-S9). Complete case analyses showed similar results to analysis with imputed data (Supplementary Material Table S10). Cross-sectional analysis showed similar significant relationships between zBMI and the cardiovascular measurements; however, associations were stronger with the BMI trajectories (Supplementary Material Table S11).

Discussion

In this prospective population-based study in Spain, we found that BMI trajectories from birth to 9 years were associated with preclinical macrovascular measurements in young adolescents at 11 years. Specifically, we found that children with a lower birth size and accelerated BMI gain (class 3) had increased SBP, DBP, and PWV, when compared to the reference class. Children with a higher birth size and accelerated BMI gain (class 1) had increased SBP. We found no associations between BMI trajectories and retinal microvascular measurements.

Macrovasculature

We found that a trajectory characterized by lower birth size and accelerated BMI gain during infancy and early childhood was associated with increased measurements of macrovascular function. Previous longitudinal studies using growth trajectories have found similar results.[21–24] One study that analyzed pre-/postnatal growth trajectories found that those with decreased or normal fetal growth and accelerated infant growth had higher blood pressure.[24] Other studies found that rapid weight gain from the first year onward and early persistent obesity were positively associated with SBP and DBP in young adults of 18 years old.[20,22] While an Australian birth cohort that identified growth trajectories from birth to 14 years did not find associations between growth trajectories and blood pressure or PWV, they did find that augmentation index was higher in consistently overweight children.[21] Augmentation index is an independent measure to PWV, but they are both measures of macrovascular structure function and specifically arterial stiffness. Lycett *et al.* found that those in an "always very high" zBMI trajectory from 2 to 11 years had higher PWV at 11–12 years old.[32] Additionally, in our study, we observed that those with a higher birth size followed by accelerated BMI gain had higher SBP. Likewise, Boyer *et al.* calculated trajectories from 15 months to 10.5 years of age and found that higher BMI at 15 months coupled with slower declines before adiposity rebound and faster BMI rebound after adiposity rebound, predicted higher adolescent cardiovascular risk as calculated using waist-to-height ratio, skinfold thickness, SBP, and BMI.[23]

Blood pressure and PWV are closely related measures of the macrovascular system. Young people with hypertension have been shown to have similar heart damage as the elderly,[33] and hypertension, once developed early in life, is irreversible.[34] Further, PWV is an indicator of early vascular alterations and is considered the most precise noninvasive measurement of arterial stiffness related to cardiovascular events and mortality in adults.[5] From the aforementioned studies, including our own, there is a pattern of higher blood pressure and PWV (or other arterial stiffness marker) associated with accelerated growth during infancy or afterward. Given that childhood blood pressure tracks into adulthood and hypertension is a risk factor for cardiovascular disease,[6] identifying early risk factors should be a priority to avoid adverse health outcomes in later life. Identification of children and/or adolescents at high-risk through the use of growth trajectories may be helpful for preventative strategies targeting the reduction of cardiovascular events. One of the most important modifiable risk factors for cardiovascular health is overweight and obesity. Juonala *et al.* observed that children who had overweight or obesity but achieved normal weight status by adulthood had a similar cardiovascular risk to those who never had overweight or obesity.[2] These results show that children's bodies are still flexible and developing, which may imply that their cardiovascular system is more adaptable than during adulthood indicating a point of reversibility during childhood.

Microvasculature

There are a limited number of studies that have used retinal measurements to assess cardiovascular outcomes in healthy children and adolescents. In our study, childhood growth trajectories were not associated with microvasculature measured through retinal imaging. Comparably, an Australian study did not observe an association between their calculated growth trajectories and microvasculature measured by the arteriole-to-venule ratio (AVR = CRAE/CRVE).[21] To our knowledge, this is the only other study to have assessed retinal microvascular measurements with growth trajectories. However, a systematic review of cross-sectional studies found that adverse retinal vascular changes were associated with childhood overweight and obesity.[10] This cross-sectional relationship was not found in our study.

Given that we took measures of both micro- and macrovasculature, we had initially hypothesized to find changes in the microvasculature structure associated with the child growth trajectories if changes in the macrovasculature were observed. In diabetic individuals, it has been shown that microvascular disease plays a causative role in the development of macrovascular disease, and the two diseases being highly intertwined.[35] However, in many instances, changes in the micro- and macrovascular structures are observed together, and it remains unclear whether microvascular changes precede macrovascular changes or occur concurrently. This is even less clear in the case of healthy children. The small body of research in this area does seem to indicate a relationship between overweight and obesity and adverse changes in the retinal microvasculature; however, we did not find this in our study. Given that the observed differences in previous studies were small, perhaps our study lacks sufficient variability and/or sample size to observe such changes.

Strengths and limitations

Major strengths of this study were the longitudinal study design that permitted the collection of repeated weight and height measurements to be able to calculate the distinct BMI trajectories, and the detailed measures of micro- and macrovasculature structure utilized. Further, the strong follow-up in the INMA study permitted us to measure micro- and macrovascular function in a pediatric population that is otherwise infrequently measured. This study also had some limitations. Our small sample size was prohibitive in that we were not able to stratify groups further by

potentially important modifying factors like SES. Although we controlled for SES in our regression models, there may still be some residual confounding given that SES was based solely on occupation. In initial models, we tested SES based on occupation and maternal education as potential markers of SES and found similar results with both variables. Nevertheless, we cannot exclude residual confounding by unmeasured social factors related to cardiovascular measures in young adolescents. Further, longitudinal studies are prone to selection bias and our study is no exception. Those with an interest in research and of higher SES tend to agree to participate and continue. However, follow-ups were done in the school setting, making it more easily accessible for children to participate. Lastly, there was little variation for all cardiovascular measurements. This is most likely due to the fact that these measurements were taken in healthy children during early adolescence. Nevertheless, we still found significant differences with macrovascular measurements across BMI trajectories.

Implications

Our study offers an important contribution to the current literature, as we were able to demonstrate two distinct patterns of accelerated BMI gain (departing from higher and lower birth size) and show that both patterns of accelerated growth are associated with the measures of preclinical macrovascular health. A study by Barker *et al.* previously found that the risk of coronary events in later life is more related to tempo (i.e. rate or speed) of childhood BMI gain rather than BMI at any particular age.[12] Like Barker's findings, other studies concluded that chronic diseases were most common in children who experienced weight gain after infancy, and weight gain during infancy (0–2 years old) had less impact on cardiovascular risk than weight gained during later childhood years.[13,19] While these findings relate to participants of lower birth size and accelerated growth after infancy, our study shows that the same may in part be true for those born at higher birth size and experience accelerated BMI gain during infancy. One potential explanation for the reported differences could be the income level of the study population country. The aforementioned studies reported results from low- to middle-income countries where rapid/catch-up growth during the first 2 years in otherwise small infants may be protective.[36] This may not be the case in high-income countries like Spain where our study population is from.

To further quantify our results on the population level, knowing that blood pressure tracks from childhood to adulthood,[6] a reduction of SBP as little as 2 mmHg could result in a 10% decrease in stroke and a 7% decrease in coronary heart disease during middle age.[37] Being able to identify those at the highest risk for coronary events at the earliest age possible may be possible through BMI trajectories. BMI trajectories are noninvasive and easily calculated measures. Additionally, using blood pressure and PWV screening in those children with higher risk growth trajectories (i.e. those who have an accelerated growth trajectory pattern) may be a novel way to identify those at greatest risk for cardiovascular disease during adulthood, early in life, while damage may be reversible and set the child on a healthier trajectory.

Conclusion

We conclude that BMI trajectories from birth to 9 years are associated with preclinical macrovascular measurements in young adolescents at 11 years. This study provides evidence that accelerated growth, especially in those of lower birth size, during infancy is a risk factor for higher SBP and DBP, and PWV in early adolescence. This subset of the population may be at greater risk for cardiovascular disease later in life. This knowledge could be used to help prevent future cardiovascular disease by targeting individuals at need for extra monitoring and lifestyle interventions. Prevention strategies for future mothers and throughout infancy and childhood should be a priority to avoid adverse health outcomes in later life.

Supplementary material. To view supplementary material for this article, please visit https://doi.org/10.1017/S2040174421000441

Acknowledgments. We thank all of the study participants for their support with the INMA Sabadell birth cohort study.

Financial support. The Instituto de Salud Carlos III (Red INMA G03/176; CB06/02/0041; PI041436; PI081151 incl. FEDER funds; PI12/01890 incl. FEDER funds; CP13/00054 incl. FEDER funds; PI15/00118 incl. FEDER funds; CP16/00128 incl. FEDER funds; PI16/00118 incl. FEDER funds; PI16/00261 incl. FEDER funds; PI18/00547 incl. FEDER funds), CIBERESP, Generalitat de Catalunya-CIRIT 1999SGR 00241, Generalitat de Catalunya-AGAUR (2009 SGR 501, 2014 SGR 822), Fundació La marató de TV3 (090,430), Spanish Ministry of Economy and Competitiveness (SAF2012–32,991 incl. FEDER funds), Agence Nationale de Securite Sanitaire de l'Alimentation de l'Environnement et du Travail (1262C0010; EST-2016 RF-21), EU Commission (261,357, 308,333, 603,794 and 634,453).
ISGlobal is a member of the CERCA Programme, Generalitat de Catalunya.

Conflicts of interest. The authors have no conflict of interest.

References

1. Franks P, Hanson R, Knowler W, Sievers M, Bennett M, Looker H. Childhood obesity, other cardiovascular risk factors, and premature death. *N Engl J Med*. 2010; 362, 485–493.
2. Juonala M, Magnussen CG, Berenson GS, *et al.* Childhood adiposity, adult adiposity, and cardiovascular risk factors. *N Engl J Med*. 2011; 365, 1876–1885.
3. Charakida M, Jones A, Falaschetti E, *et al.* Childhood obesity and vascular phenotypes: a population study. *J Am Coll Cardiol*. 2012; 60, 2643–2650.
4. Donald AE, Charakida M, Falaschetti E, *et al.* Determinants of vascular phenotype in a large childhood population: the avon longitudinal study of parents and children (ALSPAC). *Eur Heart J*. 2010; 31, 1502–1510.
5. Lurbe E, Torro I, Garcia-Vicent C, Alvarez J, Fernández-Fornoso JA, Redon J. Blood pressure and obesity exert independent influences on pulse wave velocity in youth. *Hypertension*. 2012; 60, 550–555.
6. Magnussen CG, Smith KJ. Pediatric blood pressure and adult preclinical markers of cardiovascular disease. *Clin Med Insights Blood Disord*. 2016; 9, 1–8.
7. Hudson LD, Rapala A, Khan T, Williams B, Viner RM. Evidence for contemporary arterial stiffening in obese children and adolescents using pulse wave velocity: a systematic review and meta-analysis. *Atherosclerosis*. 2015; 241, 376–386.
8. Cote AT, Phillips AA, Harris KC, Sandor GGS, Panagiotopoulos C, Devlin AM. Obesity and arterial stiffness in children: systematic review and meta-analysis. *Arterioscler Thromb Vasc Biol*. 2015; 35, 1038–1044.
9. Newman AR, Andrew NH, Casson RJ. Review of paediatric retinal microvascular changes as a predictor of cardiovascular disease. *Clin Exp Ophthalmol*. 2017; 45, 33–44.
10. Li LJ, Ikram MK, Wong TY. Retinal vascular imaging in early life: insights into processes and risk of cardiovascular disease. *J Physiol*. 2016; 594, 2175–2203.
11. Heindel JJ, Vandenberg LN. Developmental origins of health and disease: a paradigm for understanding disease cause and prevention. *Curr Opin Pediatr*. 2015; 27, 248–253.
12. Barker DJP, Osmond C, Forsén TJ, Kajantie E, Eriksson JG. Trajectories of growth among children who have coronary events as adults. *N Engl J Med*. 2005; 353, 1802–1809.

13. Victora CG, Adair L, Fall C, *et al.* Maternal and child undernutrition: consequences for adult health and human capital. *Lancet.* 2008; 371, 340–357.
14. Spiotta R, Luma G. Evaluating obesity and cardiovascular risk factors in children and adolescents. *Am Fam Physician.* 2008; 78, 1052–1058.
15. Nordman H, Jääskeläinen J, Voutilainen R. Birth size as a determinant of cardiometabolic risk factors in children. *Horm Res Paediatr.* 2020; 93, 144–153.
16. Leunissen RWJ, Kerkhof GF, Stijnen T, Hokken-Koelega A. Timing and tempo of first-year rapid growth in relation to cardiovascular and metabolic risk profile in early adulthood. *J Am Med Assoc.* 2009; 301, 2234–2242.
17. Horta BL, Barros FC, Victora CG, Cole TJ. Early and late growth and blood pressure in adolescence. *J Epidemiol Community Health.* 2003; 57, 226–230.
18. Huxley RR, Shiell AW, Law CM. The role of size at birth and postnatal catch-up growth in determining systolic blood pressure: a systematic review of the literature. *J Hypertens.* 2000; 18, 815–831.
19. Adair LS, Cole TJ. Rapid child growth raises blood pressure in adolescent boys who were thin at birth. *Hypertension.* 2003; 41, 451–456.
20. Ziyab AH, Karmaus W, Kurukulaaratchy RJ, Zhang H, Arshad SH. Developmental trajectories of Body Mass Index from infancy to 18 years of age: prenatal determinants and health consequences. *J Epidemiol Community Health.* 2014; 68, 934–941.
21. Hanvey AN, Mensah FK, Clifford SA, Wake M. Adolescent cardiovascular functional and structural outcomes of growth trajectories from infancy: prospective community-based study. *Child Obes.* 2017; 13, 154–163.
22. Buffarini R, Restrepo-Méndez MC, Silveira VM, *et al.* Growth across life course and cardiovascular risk markers in 18-year-old adolescents: the 1993 Pelotas birth cohort. *BMJ Open.* 2018; 8, 1–8.
23. Boyer BP, Nelson JA, Holub SC. Childhood body mass index trajectories predicting cardiovascular risk in adolescence. *J Adolesc Heal.* 2015; 56, 599–605.
24. Toemen L, De Jonge LL, Gishti O, *et al.* Longitudinal growth during fetal life and infancy and cardiovascular outcomes at school-age. *J Hypertens.* 2016; 34, 1396–1406.
25. Guxens M, Ballester F, Espada M, *et al.* Cohort profile: the INMA—INfancia y Medio Ambiente—(Environment and Childhood) project. *Int J Epidemiol.* 2012; 41, 930–940.
26. Group. WMGRS. WHO Child Growth Standards: Length/Height-for-Age, Weight-for-Age, Weight-for-Length, Weight-for-Height and Body Mass Index-for-Age: Methods and Development; 2006.
27. de Onis M, Onyango AW, Borghi E, Siyam A, Nishida C, Siekmann J. Development of a WHO growth reference for school-aged children and adolescents. *Bull World Health Organ.* 2007; 85, 660–667.
28. Montazeri P, Vrijheid M, Martinez D, *et al.* Maternal metabolic health parameters during pregnancy in relation to early childhood BMI trajectories. *Obesity.* 2018; 26, 588–596.
29. Slining MM, Herring AH, Popkin BM, Mayer-Davis EJ, Adair LS. Infant BMI trajectories are associated with young adult body composition. *J Dev Orig Health Dis.* 2012; 4, 1–13.
30. Knudtson MD, Lee KE, Hubbard LD, Wong TY, Klein R, Klein BEK. Revised formulas for summarizing retinal vessel diameters. *Curr Eye Res.* 2003; 27, 143–149.
31. De Boever P, Louwies T, Provost E, Int Panis L, Nawrot TS. Fundus photography as a convenient tool to study microvascular responses to cardiovascular disease risk factors in epidemiological studies. *J Vis Exp.* 2014; 92, 1–9.
32. Lycett K, Juonala M, Magnussen CG, *et al.* Body mass index from early to late childhood and cardiometabolic measurements at 11 to 12 years. *Pediatrics.* 2020; 146, 1–10.
33. Mangena P, Saban S, Hlabyago KE, Rayner B. An approach to the young hypertensive patient. *South African Med J.* 2016; 106, 36–38.
34. McEniery CM, Franklin SS, Cockcroft JR, Wilkinson IB. Isolated systolic hypertension in young people is not spurious and should be treated: pro side of the argument. *Hypertension.* 2016; 68, 269–275.
35. Chawla A, Chawla R, Jaggi S. Microvasular and macrovascular complications in diabetes mellitus: Distinct or continuum? *Indian J Endocrinol Metab.* 2016; 20, 546–551.
36. Singhal A. Long-term adverse effects of early growth acceleration or catch-up growth. *Ann Nutr Metab.* 2017; 70, 236–240.
37. Lewington S, Clarke R, Qizilbash N, Peto R, Collins R. Age-specific relevance of usual blood pressure to vascular mortality: A meta-analysis of individual data for one million adults in 61 prospective studies. *Lancet.* 2002; 360, 1903–1913.

Supplementary Material
Paper II

Table S1. Covariate description

Variable	Equipment/Tool Used	Protocol Followed
Child's age at cardiovascular measurement	--	Calculated from birth date and date of measurement.
Child´s height at cardiovascular measurement (cm)	Stadiometer: Seca 214, d=1mm	Measured without shoes and the child standing upright and centrically with legs straight and weight evenly distributed on the floorboard of the stadiometer. The examiner took the height by going down face level with the child and child´s head maintained in the Frankfort Horizontal Plane.
Child Sex	Medical record	Taken from medical record file as male or female.
Gestational Weeks	Medical record	Taken from medical record file in weeks and days of gestation at birth.
Family socioeconomic status	Questionnaire	Based on occupation, using the Goldthorpe model as a reference. Social class was ranked according to the more privileged partner. Possible allocations were "low", "middle", "high".
Maternal smoking status during pregnancy	Questionnaire	Mother asked about tobacco use at 12 weeks and 32 weeks. Possible response included: "yes" or "no".
Maternal prepregnancy BMI	Questionnaire	Calculated using the standard formula (kg/m^2) from two questions. "How much did you weigh before this pregnancy? (Kg)" and "Height in cm."
Paternal BMI during pregnancy	Questionnaire	Calculated using the standard formula (kg/m^2) from two questions asked to the mother. "How much does the father weigh (Kg)?" and "How tall is the father (cm)."
Parental Cardiovascular History	Questionnaire	Both mother and father asked about previous cardiovascular events, such as: "heart attack, angina, hemorrhage or stroke, arthrosclerosis in legs, high cholesterol, high blood sugar, and high blood pressure." These factors were combined into a scored variable: "parents have 1+ diagnosis", "one parent has 1+ diagnosis", "neither parent has diagnosis".

Table S2. Characteristics of the study population (n=489)

	N missing	Original data set *percent or mean±sd*	Imputed data set *percent or mean±sd*
Child Characteristics			
Sex (female)	0	48.3%	-
Birth weight (g)	0	3278.8±409.1	-
Height at birth (cm)	13	49.6±1.9	-
Gestational age (weeks)	0	39.8±1.3	-
BMI trajectories from birth to 9 years	0		
Class 1: higher birth size – accelerated gain		9.8%	-
Class 2: higher birth size – slower gain		27.0%	-
Class 3: lower birth size – accelerated gain		13.7%	-
Class 4: average birth size – slower gain		35.0%	-
Class 5: lower birth size – slower gain		14.5%	-
Age[a]	0	11.0±0.6	-
Weight[a] (kg)	0	42.0±10.5	-
Height[a] (cm)	0	146.1±8.0	-
zBMI[a]	0	0.70±1.24	-
Systolic blood pressure (mmHg)	0	101.6±9.9	-
Diastolic blood pressure (mmHg)	1	59.9±7.7	-
Pulse wave velocity (PWV) (m/s)	22	4.4±0.5	-
Central retinal artery equivalent (CRAE) (μm)	35	180.6±12.9	-
Central retinal vein equivalent (CRVE) (μm)	35	252.0±17.1	-
Family Characteristics			
Family SES (during pregnancy)	60		
High		35.4%	36.1%
Middle		30.5%	30.3%
Low		34.0%	33.7%
Maternal BMI (prepregnancy)	11	23.8±4.5	23.8±4.5
Maternal smoking (during pregnancy)	65		
None		73.1%	73.3%
Until 1st trimester		14.4%	14.2%
Until 3rd trimester		12.5%	12.5%
Paternal BMI (pregnancy 1st trimester)	10	25.8±3.5	25.8±3.5
Parental cardiovascular history[b]	4		
Neither parent has diagnosis		47.2%	47.2%
1 parent has at least one diagnosis		42.7%	42.6%
Both parents have at least one diagnosis		10.1%	10.2%

[a] Taken at the time of cardiovascular measurement.

[b] Doctor diagnosis of cardiovascular disease (coronary heart disease, cerebrovascular disease, and peripheral vascular disease) or cardiovascular risk factors (hypercholesterolemia, hypertension, and diabetes).

Table S3. Pearson correlation coefficients between cardiovascular measurements

	Systolic Blood Pressure	**Diastolic Blood Pressure**	**Pulse Wave Velocity**	**Central Retinal Artery Equivalent**	**Central Retinal Vein Equivalent**
	Coefficient (p-value)	Coefficient (p-value)	Coefficient (p-value)	Coefficient (p-value)	Coefficient (p-value)
Systolic Blood Pressure	1.00				
Diastolic Blood Pressure	0.66 (<0.01)	1.00			
Pulse Wave Velocity	0.36 (<0.01)	0.43 (<0.01)	1.00		
Central Retinal Artery Equivalent	-0.12 (0.01)	-0.05 (0.26)	-0.13 (0.01)	1.00	
Central Retinal Vein Equivalent	-0.01 (0.82)	0.08 (0.10)	-0.06 (0.25)	0.57 (<0.01)	1.00

Figure S1: Correlation graphs between cardiovascular measurements

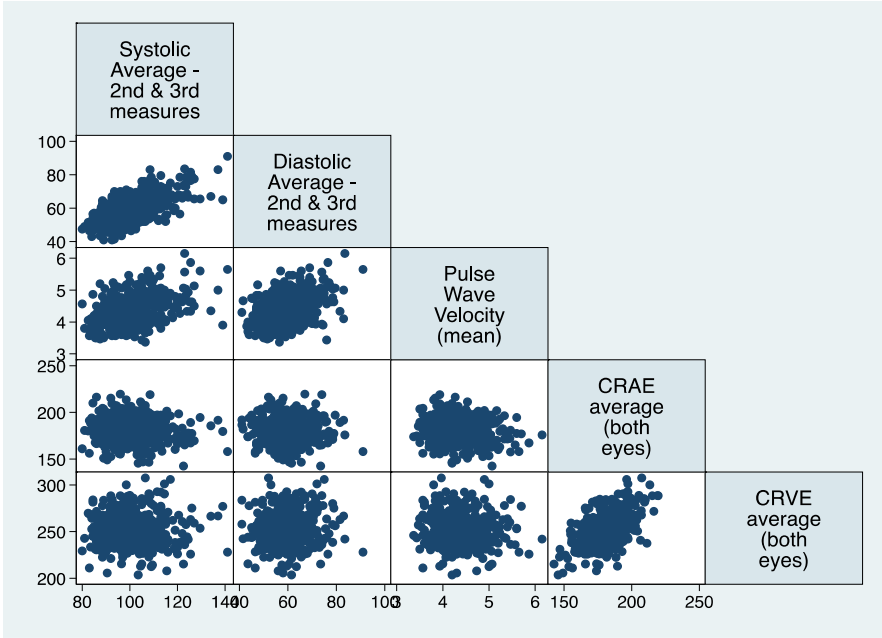


Table S4. Associations between covariates and cardiovascular measurements, using imputed data.

Covariate	**Systolic Blood Pressure**	**Diastolic Blood Pressure**	**Pulse Wave Velocity**	**Central Retinal Artery Equivalent**	**Central Retinal Vein Equivalent**
	n=489	*n=488*	*n=467*	*n=454*	*n=454*
	β (95% CI)	*β (95% CI)*	*β (95% CI)*	*β (95% CI)*	*β (95% CI)*
Age at CV measure	1.25 (-0.25, 2.75)	0.26 (-0.99, 1.52)	-0.03 (-0.10, 0.04)	0.84 (-1.13, 2.82)	-0.85 (-3.50, 1.80)
Sex male (vs female)	1.96 (0.37, 3.55)	0.11 (-1.23, 1.44)	0.16 (0.09, 0.24)	-4.47 (-6.83, -2.11)	-4.11 (-7.28, -0.94)
Height at CV measure	0.43 (0.32, 0.55)	0.17 (0.07, 0.26)	0.02 (0.01, 0.02)	--	--
Gestational age	-0.25 (-0.84, 0.35)	0.08 (-0.42, 0.58)	-0.01 (-0.04, 0.02)	0.96 (0.05, 1.86)	0.19 (-1.02, 1.41)
Family SES middle (vs high)	1.28 (-0.74, 3.30)	0.90 (-0.82, 2.62)	0.05 (-0.05, 0.15)	0.03 (-2.99, 3.05)	1.22 (-2.77, 5.21)
Family SES low (vs high)	3.30 (1.28, 5.32)	2.99 (1.27, 4.70)	0.08 (-0.02, 0.18)	-0.57 (-3.58, 2.43)	1.77 (-2.22, 5.75)
Smoking 1st trimester (vs none)	0.54 (-1.88, 2.96)	0.16 (-1.89, 2.21)	-0.05 (-0.17, 0.08)	-0.17 (-3.73, 3.38)	-0.84 (-5.45, 3.76)
Smoking 3rd trimester (vs none)	2.51 (-0.11, 5.13)	0.68 (-1.57, 2.92)	-0.01 (-0.13, 0.13)	-2.41 (-6.38, 1.57)	-0.26 (-5.55, 5.03)
Maternal prepregnancy BMI	0.22 (0.03, 0.40)	0.15 (-0.01, 0.30)	0.01 (0.00, 0.02)	-0.07 (-0.34, 0.21)	0.07 (-0.30, 0.44)
Paternal pregnancy BMI	0.01 (-0.23, 0.25)	-0.05 (-0.25, 0.16)	-0.01 (-0.02, 0.00)	0.20 (-0.17, 0.56)	0.08 (-0.40, 0.57)
Parental CVD - 1 parent with 1+ diagnosis (vs no diagnosis)	-0.01 (1.71, 1.70)	0.25 (-1.18, 1.68)	0.09 (0.01, 0.18)	1.72 (-0.82, 4.27)	2.08 (-1.35, 5.50)
Parental CVD - both parents with 1+ diagnosis (vs no diagnosis)	2.38 (-0.45, 5.21)	1.82 (-0.55, 4.19)	0.09 (-0.05, 0.23)	-2.34 (-6.55, 1.86)	-0.94 (-6.64, 4.76)

Table S5. Crude associations between BMI z-score trajectory class and cardiovascular measurements.

BMI *z*-score trajectory	**Systolic Blood Pressure**	**Diastolic Blood Pressure**	**Pulse Wave Velocity**	**Central Retinal Artery Equivalent**	**Central Retinal Vein Equivalent**
	n=489	*n=488*	*n=467*	*n=454*	*n=454*
	β (95% CI)	*β (95% CI)*	*β (95% CI)*	*β (95% CI)*	*β (95% CI)*
Class 1: higher birth size-accelerated BMI gain	7.32 (4.37, 10.26)	1.63 (-0.77, 4.03)	0.14 (-0.01, 0.29)	-3.50 (-7.91, 0.90)	-1.64 (-7.47, 4.19)
Class 2: higher birth size-slower BMI gain	0.33 (-1.76, 2.41)	-0.55 (-2.26, 1.15)	-0.02 (-0.12, 0.08)	1.89 (-1.19, 4.97)	-0.26 (-4.34, 3.82)
Class 3: lower birth size-accelerated BMI gain	9.30 (6.70, 11.90)	4.71 (2.59, 6.83)	0.26 (0.13, 0.39)	0.29 (-3.49, 4.06)	0.10 (-4.90, 5.10)
Class 4: Average birth size- slower gain	Ref.	Ref.	Ref.	Ref.	Ref.
Class 5: lower birth size-slower BMI gain	-1.14 (-3.68, 1.41)	-0.80 (-2.88, 1.27)	0.07 (-0.05, 0.20)	0.31 (-3.31, 3.92)	-1.56 (-6.36, 3.23)

Table S6. Adjusted associations between BMI z-score trajectory class and cardiovascular outcomes stratified by sex, *imputed*.

BMI *z*-score trajectory	**Systolic Blood Pressure**	**Diastolic Blood Pressure**	**Pulse Wave Velocity**	**Central Retinal Artery Equivalent**	**Central Retinal Vein Equivalent**
	Female; n=236 *Male; n=253*	*Female; n=235* *Male; n=253*	*Female; n=229* *Male; n=238*	*Female; n=217* *Male; n=237*	*Female; n=217* *Male; n=237*
	β (95% CI)	*β (95% CI)*	*β (95% CI)*	*β (95% CI)*	*β (95% CI)*
Class 1: higher birth size-accelerated BMI gain					
Female	7.08 (2.19, 11.97)	-0.26 (-4.62, 4.09)	-0.22 (-0.46, 0.03)	0.63 (-7.62, 8.87)	1.65 (-9.15, 12.44)
Male	4.51 (0.62, 8.41)	1.59 (-1.64, 4.83)	0.16 (-0.04, 0.28)	-4.69 (-10.34, 0.97)	-3.77 (-11.58, 4.04)
Class 2: higher birth size-slower BMI gain					
Female	-1.66 (-4.26, 0.94)	-1.81 (-4.14, 0.52)	-0.15 (0.28, -0.02)	4.03 (-0.29, 8.35)	2.60 (-3.05, 8.26)
Male	1.69 (-1.42, 4.81)	-0.22 (-2.80, 2.37)	0.12 (-0.04, 0.28)	-1.33 (-5.85, 3.18)	-5.92 (-12.16, 0.32)
Class 3: lower birth size-accelerated BMI gain					
Female	5.65 (1.80, 9.51)	1.94 (-1.50, 5.38)	-0.01 (-0.20, 0.18)	0.73 (-5.54, 7.01)	1.52 (-6.70, 9.74)
Male	7.69 (4.07, 11.32)	5.04 (2.03, 8.05)	0.25 (0.07, 0.44)	-0.53 (-5.51, 4.46)	-2.52 (-9.42, 4.38)
Class 4: Average birth size-slower gain	Ref.	Ref.	Ref.	Ref.	Ref.
Class 5: lower birth size-slower BMI gain					
Female	-1.11, (-4.50, 2.29)	-2.10 (-5.14, 0.94)	0.03 (-0.14, 0.19)	-0.08 (-5.53, 5.36)	-1.36 (-8.50, 5.77)
Male	-2.05 (-5.53, 1.44)	-0.37 (-3.26, 2.51)	0.09 (-0.09, 0.28)	1.04 (-3.81, 5.88)	-1.96 (-8.67, 4.75)
Models using imputed data and adjusted for: child age at cardiovascular measurement, gestational age, family SES, maternal smoking (during pregnancy), maternal prepregnancy BMI, paternal BMI (during pregnancy), and parental cardiovascular history. Systolic blood pressure, diastolic blood pressure and pulse wave velocity were additionally adjusted for child´s height at cardiovascular measurement.					

Table S7. Adjusted associations between BMI z-score trajectory class and systolic blood pressure, diastolic blood pressure and pulse wave velocity not adjusting for height, *imputed*.

BMI *z*-score trajectory	**Systolic Blood Pressure**	**Diastolic Blood Pressure**	**Pulse Wave Velocity**
	n=489	*n=488*	*n=467*
	β (95% CI)	*β (95% CI)*	*β (95% CI)*
Class 1: higher birth size-accelerated BMI gain	5.92 (2.88, 8.95)	0.92 (-1.60, 3.45)	0.06 (-0.09, 0.22)
Class 2: higher birth size-slower BMI gain	-0.10 (-2.16, 1.95)	-0.95 (-2.66, 0.75)	-0.03 (-0.13, 0.08)
Class 3: lower birth size-accelerated BMI gain	8.38 (5.78, 10.97)	4.27 (2.11, 6.43)	0.21 (0.08, 0.34)
Class 4: Average birth size-slower gain	Ref.	Ref.	Ref.
Class 5: lower birth size-slower BMI gain	-1.26 (-3.75, 1.22)	-0.92 (-2.99, 1.15)	0.05 (-0.08, 0.18)

Models using imputed data and adjusted for: child age at cardiovascular measurement, child sex, gestational age, family SES, maternal smoking (during pregnancy), maternal prepregnancy BMI, paternal BMI (during pregnancy), and parental cardiovascular history.

Table S8. Descriptive statistics for cardiovascular measures separated by those children with complete measurements and those with only partial.

	Complete Measurements	**Partial Measurements**
	mean (sd) *n*	mean (sd) *n*
Systolic Blood Pressure[a]	-	-
Diastolic Blood Pressure[b]	59.9 (7.6) *486*	60.5 (9.2) *2*
Pulse Wave Velocity[c]	4.4 (0.4) *407*	4.3 (0.5) *60*
Central Retinal Artery Equivalent[d]	180.9 (12.7) *359*	179.2 (13.6) *95*
Central Retinal Vein Equivalent[d]	251.5 (16.8) *359*	253.6 (17.9) *95*

[a] All children had two measures for systolic blood pressure.
[b] Two children had one usable measures for diastolic blood pressure.
[c] 60 children had less than three measures for pulse wave velocity.
[d] 95 children had only one usable measure or two measures with one being recorded as less than good quality.

Table S9. Adjusted associations between BMI z-score trajectory class and pulse wave velocity using only children with three measurements, and with CRAE and CRVE using only children with two good measurements, ***imputed***.

BMI *z*-score trajectory	**Diastolic Blood Pressure**	**Pulse Wave Velocity**	**Central Retinal Artery Equivalent**	**Central Retinal Vein Equivalent**
	n=486	*n=407*	*n=359*	*n=359*
	β (95% CI)	*β (95% CI)*	*β (95% CI)*	*β (95% CI)*
Class 1: higher birth size-accelerated BMI gain	0.47 (-2.07, 3.01)	0.01 (-0.18, 0.15)	-2.43 (-7.70, 2.83)	0.63 (-6.46, 7.71)
Class 2: higher birth size-slower BMI gain	-1.08 (-2.79, 0.62)	-0.03 (-0.13, 0.08)	2.37 (-0.99, 5.73)	0.62 (-3.90, 5.15)
Class 3: lower birth size-accelerated BMI gain	3.59 (1.38, 5.80)	0.15 (0.01, 0.29)	-0.25 (-4.49, 4.00)	0.01 (-5.71, 5.71)
Class 4: Average birth size- slower gain	Ref.	Ref.	Ref.	Ref.
Class 5: lower birth size-slower BMI gain	-1.02 (-3.08, 1.04)	0.02 (-0.11, 0.14)	0.99 (-3.11, 5.09)	-0.53 (-6.05, 5.00)
Models using imputed data and adjusted for: child age at cardiovascular measurement, child sex, gestational age, family SES, maternal smoking (during pregnancy), maternal prepregnancy BMI, paternal BMI (during pregnancy), and parental cardiovascular history. Systolic blood pressure, diastolic blood pressure and pulse wave velocity were additionally adjusted for child´s height at cardiovascular measurement.				

Table S10. Adjusted associations between BMI z-score trajectory class and cardiovascular outcomes, *complete case*.

BMI *z*-score trajectory	**Systolic Blood Pressure**	**Diastolic Blood Pressure**	**Pulse Wave Velocity**	**Central Retinal Artery Equivalent**	**Central Retinal Vein Equivalent**
	n=415	*n=414*	*n=396*	*n=384*	*n=384*
	β (95% CI)	*β (95% CI)*	*β (95% CI)*	*β (95% CI)*	*β (95% CI)*
Class 1: higher birth size- accelerated BMI gain	5.21 (1.92, 8.51)	1.05 (-1.77, 3.86)	0.05 (-0.12, 0.22)	-2.01 (-7.04, 3.02)	-0.34 (-7.30, 6.63)
Class 2: higher birth size-slower BMI gain	0.09 (-2.11, 2.30)	-0.87 (-2.75, 1.01)	-0.03 (-0.14, 0.08)	2.03 (-1.30, 5.36)	-0.44 (-5.06, 4.17)
Class 3: lower birth size-accelerated BMI gain	6.21 (3.39, 9.04)	3.31 (0.90, 5.72)	0.16 (0.01, 0.30)	0.46 (-3.64, 4.56)	0.20 (-5.49, 5.88)
Class 4: Average birth size- slower gain	Ref.	Ref.	Ref.	Ref.	Ref.
Class 5: lower birth size-slower BMI gain	-1.86 (-4.51, 0.80)	-0.84 (-3.11, 1.42)	0.06 (-0.08, 0.19)	0.66 (-3.22, 4.55)	-0.03 (-5.42, 5.35)
Models adjusted for: child age at cardiovascular measurement, child sex, gestational age, family SES, maternal smoking (during pregnancy), maternal prepregnancy BMI, paternal BMI (during pregnancy), and parental cardiovascular history. Systolic blood pressure, diastolic blood pressure and pulse wave velocity were additionally adjusted for child´s height at cardiovascular measurement.					

Table S11. Adjusted associations between zBMI at 11 years and cardiovascular outcomes (cross-sectional), *imputed*.

	Systolic Blood Pressure	**Diastolic Blood Pressure**	**Pulse Wave Velocity**	**Central Retinal Artery Equivalent**	**Central Retinal Vein Equivalent**
	n=489	*n=488*	*n=467*	*n=454*	*n=454*
	β (95% CI)	*β (95% CI)*	*β (95% CI)*	*β (95% CI)*	*β (95% CI)*
zBMI	3.59 (2.92, 4.26)*	1.61 (1.00, 2.22)*	0.01 (-0.03, 0.04)	-0.52 (-1.57, 0.53)	0.14 (-1.39, 1.42)
Models using imputed data and adjusted for: child age at cardiovascular measurement, child sex, gestational age, family SES, maternal smoking (during pregnancy), maternal prepregnancy BMI, paternal BMI (during pregnancy), and parental cardiovascular history.					

5.3. Paper III

Montazeri P, Thomsen C, Casas M, de Bont J, Haug LS, Maitre L, Papadopoulou E, Sakhi AK, Slama R, Saulnier PJ, Urquiza J, Grazuleviciene R, Andrusaityte S, McEachan R, Wright J, Chatzi L, Basagaña X, Vrijheid M. Socioeconomic position and exposure to multiple environmental chemical contaminants in six European mother-child cohorts. Int J Hyg Environ Health. 2019;222(5):864-872. doi: 10.1016/j.ijheh.2019.04.002.

International Journal of Hygiene and Environmental Health 222 (2019) 864–872

Contents lists available at ScienceDirect

International Journal of Hygiene and Environmental Health

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

Socioeconomic position and exposure to multiple environmental chemical contaminants in six European mother-child cohorts

Parisa Montazeri[a,b,c], Cathrine Thomsen[d], Maribel Casas[a,b,c], Jeroen de Bont[a,b,c], Line S. Haug[d], Léa Maitre[a,b,c], Eleni Papadopoulou[d], Amrit K. Sakhi[d], Rémy Slama[e], Pierre Jean Saulnier[f,g,h], Jose Urquiza[a,b,c], Regina Grazuleviciene[i], Sandra Andrusaityte[i], Rosie McEachan[j], John Wright[j], Leda Chatzi[k,l,m], Xavier Basagaña[a,b,c], Martine Vrijheid[a,b,c,*]

[a] ISGlobal, Barcelona, Spain
[b] Universitat Pompeu Fabra (UPF), Barcelona, Spain
[c] CIBER Epidemiología y Salud Pública (CIBERESP), Spain
[d] Norwegian Institute of Public Health, Oslo, Norway
[e] Team of Environmental Epidemiology, IAB, Institute for Advanced Biosciences, Inserm, CNRS, CHU-Grenoble-Alpes, University Grenoble-Alpes, Grenoble, France
[f] University of Poitiers Medical School, Centre Investigation Clinique, Poitiers, France
[g] CHU Poitiers, Centre Investigation Clinique, Poitiers, France
[h] INSERM, CIC1402, Poitiers, France
[i] Department of Environmental Sciences, Vytautas Magnus University, Kaunas, Lithuania
[j] Bradford Institute for Health Research, Bradford Teaching Hospitals NHS Foundation Trust, Bradford, UK
[k] Department of Social Medicine, University of Crete, Heraklion, Greece
[l] Department of Preventive Medicine, Keck School of Medicine, University of Southern California, Los Angeles, CA, USA
[m] Department of Genetics and Cell Biology, Faculty of Health, Medicine and Life Sciences, Maastricht University, Maastricht, Netherlands

A B S T R A C T

Background: Human exposure to environmental chemical contaminants at critical periods of development can lead to lifelong health consequences. Traditionally, socioeconomically disadvantaged groups are thought to experience higher contaminant exposures; however, this relationship may not hold for all contaminants.

Methods: Using data from six European birth cohorts (1301 mother-child pairs), we determined biomarkers of exposure to 41 contaminants in biological samples from children (6–12 years) and their mothers during pregnancy, including organochlorine compounds (OCs), polybrominated diphenyl ethers (PBDEs), per- and polyfluoroalkyl substances (PFASs), metals, phthalate metabolites, phenols, and organophosphate (OP) pesticide metabolites. We analyzed these biomarkers with several socioeconomic position (SEP) indicators (maternal education, employment status and family affluence scale).

Results: Higher SEP was associated with higher concentrations of several chemicals during pregnancy, including certain PFASs, mercury, arsenic, several phenols, and OP pesticides. Similarly, childhood concentrations of OCs, PFASs, mercury, arsenic, and bisphenol A were higher in higher SEP groups. Conversely, cadmium exposure during pregnancy and exposure to lead and phthalate metabolites in childhood were higher in lower SEP. Principal components representing multiple pollutant exposures showed similar association with SEP.

Conclusions: This study demonstrates that environmental chemical contaminant exposure during fetal and childhood life is not exclusively associated to lower SEP and that for several contaminants higher SEP groups incur higher exposure levels.

1. Introduction

The development and use of synthetic chemicals has grown immensely over the last century with tens of thousands of chemicals currently in production (Landrigan and Goldman, 2011). These chemicals range in use from plastics for convenience use, pesticides for food production and flame retardants for safety. Recent scientific literature has highlighted widespread human exposure to many of these chemicals (Gore et al 2015). Depending on the chemical, exposure can occur through food, water, air, dust, and/or physical contact with common household items (Landrigan and Goldman, 2011).

Exposures to environmental contaminants are of particular concern in pregnant women and children as many chemicals have been shown to transfer in-utero from the mother to the fetus, and higher levels of certain chemicals have been observed in children due to frequent hand-to-mouth/object activity (Lunder et al 2010; Mamsen et al 2017). The

* Corresponding author. ISGlobal, Institute for Global Health, C/ Doctor Aiguader 88, 08003, Barcelona, Spain.
E-mail address: martine.vrijheid@isglobal.org (M. Vrijheid).

https://doi.org/10.1016/j.ijheh.2019.04.002
Received 17 January 2019; Received in revised form 2 April 2019; Accepted 11 April 2019
1438-4639/

gestational and childhood period are both critical periods of growth and development that when interrupted by outside sources like environmental contaminants can lead to lifelong health consequences such as, asthma, obesity, neurodevelopmental disabilities and cardiovascular disease (Vrijheid et al 2016).

In environmental health, socioeconomic position (SEP) has long been studied and shown to play a role in a wide variety of health outcomes, including the unequal distribution of environmental risk to exposures (Pampel et al., 2010). This unequal distribution is often related to SEP indicators such as income, social status, employment and education. Depending on the environmental risk and the group(s) being studied, the direction and magnitude of inequality can vary (Hicken et al 2012).

Scientific evidence has reported varying results that both support and contradict the traditional hypothesis of disadvantaged groups as being systematically classified as the "high risk" group. A study in the United States using NHANES data found that individuals with higher SEP had higher burdens of certain metals, per- and polyfluoroalkyl substances (PFASs), phthalates, and oxybenzone (OXBE/BP3), whilst lower SEP was associated with higher levels of bisphenol A (BPA) and three different phthalates (Tyrrell et al 2013). Similarly, a Spanish birth cohort found that polychlorinated biphenyls (PCB), hexachlorobenzene (HCB) and mercury (Hg) were higher in higher social classes (Vrijheid et al 2012). A Korean study examining metals in children found that lead levels where higher in those of lower SEP, while mercury was higher in high socioeconomic position children (Lim et al 2015). This incongruence challenges the traditional hypothesis prompting further exploration.

As outlined in the Sixth Ministerial Conference on Environment and Health in Czech Republic in June 2017, "reducing the exposure of vulnerable groups to hazardous chemicals, particularly during the early stages of human development" is a priority area to better the health of children and future generations. Studying the social determinants of an already vulnerable group like pregnant women and children is of critical importance to minimizing the health burden of chemical contaminants. Our understanding of the role that social determinants play in dictating a person's exposure to environmental contaminants is limited. This study aimed to investigate the associations between indicators of SEP and measured levels of several environmental contaminants in a population of pregnant women and their children (6–12 years old) in six European birth cohorts.

2. Material and methods

2.1. Study population and sample collection

The study population has been previously described in detail (Maitre et al 2018; Vrijheid et al 2014). Briefly, data used was from The Human Early-Life Exposome (HELIX) subcohort which comprises of 1301 mother-child pairs. The participants were recruited from six different European birth cohorts; BiB (Born in Bradford UK (n = 205) (Wright et al 2013), EDEN (Study of determinants of pre- and postnatal developmental, France, n = 198) (Drouillet et al 2009), INMA (Environment and Childhood, Spain, n = 223) (Guxens et al 2012), KANC (Kaunas Cohort, Lithuania n = 204) (Grazuleviciene et al 2009), MoBa (The Norwegian Mother and Child Cohort Study, Norway (Oslo region) n = 272) (Magnus et al 2016) and RHEA (Mother–Child Cohort in Crete, Greece n = 199) (Chatzi et al 2009).

For all cohorts, women were recruited during pregnancy and blood and urine samples were collected (Maitre et al 2018), except for KANC where no urine was collected. As part of the HELIX subcohort follow-up, clinical assessments of their children were carried out between December 2013 and February 2016 and these included blood and urine collection (Maitre et al 2018). These assessments were done in a completely harmonized manner (children only) between the cohorts using the same protocol for sample collection and clinical measures (Maitre et al 2018). All women signed a written consent at initial recruitment during pregnancy, and either the mother and/or father signed a written consent for the participation of their child at the time of clinical assessment. Ethical approval was obtained for this project from the relevant authorities in each of the six participating countries.

2.2. Indicators of socioeconomic position

Women completed questionnaires during pregnancy at the time of recruitment in each cohort. Collected data on maternal characteristics included age, education attained (low = primary school, middle = secondary school, high = university degree or higher), employment status during pregnancy (employed or unemployed), parity (nulliparous = 0 children, primiparous = 1 child, multiparous = 2 or more children), and breastfeeding of any previous children (ever/never and duration). These data were later harmonized between cohorts. At the children's assessments, cohorts used the same study questions for participants. Data on child's age, sex, and breastfeeding (yes/no and duration) were collected. Additionally, family affluence scale (FAS), a four-item measure of family wealth was calculated based on four questions regarding car ownership, bedroom sharing, family travel, and computer ownership. From this a composite FAS score was calculated using a three point ordinal scale; low affluence (FAS low = score of 0,1,2), middle affluence (FAS middle = score of 3,4,5), or high affluence (FAS high = score of 6,7,8,9) (Andersen et al 2008; Boyce et al 2006).

2.3. Environmental contaminants

Concentrations of environmental contaminants were determined in serum, plasma, whole blood, and urine using maternal samples collected during pregnancy or at birth and stored by the cohorts, and in newly collected samples from the children during childhood (Supplementary Material S1-2; Haug et al 2018). Samples were frozen at −80 °C under optimized and standardized procedures (Maitre et al 2018). Environmental contaminants measured (see full names in Table 1) included organochlorine compounds (DDE, DDT, HCB), polychlorinated bisphenyls (PCB-118, -138, −153, −170, −180), polybrominated diphenylethers (PBDE-47, -153), per- and polyfluoroalkyl substances (PFASs) (PFOA, PFNA, PFUnDA, PFHxS, PFOS), and metals and elements (As, Cd, Hg, M, Pb) in blood, and phthalate metabolites (MEP, MiBP, MnBP, MBzP, MEHP, MEHHP, MEOHP, MECPP, oh-MiNP, oxo-MiNP), phenols (MEPA, ETPA, PRPA, BPA, BUPA, OXBE, TCS), and non-specific organophosphate (OP) pesticide metabolites (DMP, DMTP, DMDTP, DEP, DETP, DEDTP) in urine. Lipophilic compounds measured in blood were adjusted by plasma/serum lipids and urine samples were adjusted by creatinine to account for variation in urine dilution, no adjustment was done for PFASs or metals as they are non-lipophilic.

Analyses for archived maternal samples from pregnancy and childhood were performed at one laboratory, the Department of Environmental Exposure and Epidemiology at the Norwegian Institute of Public Health (NIPH) or their contract laboratories, for comparability purposes and to reduce uncertainty. For certain cohorts (EDEN, INMA, and RHEA), maternal samples had been previously analyzed at different laboratories and results were available for select contaminants. To ensure high quality, internal quality control (QC) samples were analyzed with each sample batch and results were plotted in quality control charts by contaminant. The results were found satisfactory and no batch correction was applied. Details regarding laboratories, analytical techniques, quality control measures, inter-laboratory comparison analyses, and limit of detection (LOD) and limit of quantification (LOQ) for each laboratory can be found in Haug et al (2018) and correlations in Supplementary Material S3-4.

Concentrations measured by NIPH or their contract laboratories were reported whenever a signal was observed on the instrument even when below LOQ, these results were used in the statistical calculations.

Table 1
Social Determinants collected during prenatal and postnatal periods of 1301 pregnant women and their children in the HELIX subcohort, original and imputed data sets.

Characteristic	N Missing	Original data set	Imputed data set
		mean ± SD or percent	mean ± SD or percent
Prenatal Characteristics			
Cohort	0		
BiB		15.8(205)	15.8(205)
EDEN		15.2(198)	15.2(198)
INMA		17.1(223)	17.1(223)
KANC		15.7(204)	15.7(204)
MoBa		20.9(272)	20.9(272)
Rhea		15.3(199)	15.3(199)
Maternal Age at delivery (mean ± SD)	16	30.8 ± 4.9	30.8 ± 4.9
Maternal Education	44		
Low (primary)		13.8(173)	14.1
Middle (secondary)		34.4(433)	34.3
High (university or higher)		51.8(651)	51.7
Maternal Working Status	113		
Unemployed		17.4(207)	17.8
Employed		82.6(981)	82.2
Parity	31		
Nulliparous (0)		45.9(583)	45.9
Primiparous (1)		36.2(460)	36.2
Multiparous(> =2)		17.9(227)	17.9
Breastfeeding with previous child	49		
No previous child		46.3(580)	46.3
No		8.9(112)	8.9
Yes		44.7(560)	44.7
Breastfeeding duration with previous child (days) (mean ± SD)	64	104.7 ± 178.8	104.7 ± 178.7
Postnatal Characteristics			
Child's Age (years) (mean ± SD)	0	8.0 ± 1.6	8.0 ± 1.6
Child's Sex	0		
Female		45.3(590)	45.3
Male		54.7(711)	54.7
Family Affluence Scale	8		
Low		10.5(136)	10.5
Middle		38.6(499)	38.7
High		50.9(658)	50.9
Breastfeeding with study child	6		
No		15.4(200)	15.4
Yes		84.6(1095)	84.6
Breastfeeding duration with study child (days) (mean ± SD)	29	217.0 ± 244.6	217.0 ± 244.6

For samples where no concentrations were generated, defined as below LOD, values were singly imputed using a quantile regression approach for the imputation of left-censored missing data implemented in the *imputeLOD* function in the rexposome package in the R software (The R Project (Computing TRPfS, 2016)).

Most contaminants were detected in a high proportion of samples (> 90% quantifiable for 33 contaminants during pregnancy and 32 during childhood). Two contaminants (DMDTP and DEDTP) were not included for analysis due to > 40% of observations being below the LOD, leaving 41 contaminants for the final analysis.

2.4. Statistical analysis

To handle missing values in the SEP and covariate variables, a multiple imputation approach was followed under the assumption of missing at random (van Buuren and Groothuis-Oudshoorn, 2011. In total, 20 imputed data sets were generated using the *ice* command in Stata with imputation models that included additional covariates not included in the analyses models to enhance prediction (Royston and White, 2011).

All environmental contaminants showed non-normal distributions in graphical evaluations and normality tests (qqplot, histogram, Shapiro-Wilk test) and were thus transformed using the base-2 logarithm; the geometric mean (GM), median and interquartile range were used to describe their distributions.

Firstly, multivariable linear regression models were used to examine how levels of environmental contaminants during pregnancy and childhood varied by selected indicators of SEP, for each of the 41 contaminants separately using both complete-case and imputed data sets. SEP was defined as maternal education and maternal employment status for pregnant women, and maternal education and FAS score for children. In the multivariate adjusted models, covariates included were chosen a-priori as those reported to influence environmental contaminant concentrations in the literature. In order to keep models as parsimonious as possible the same covariates were used across all contaminants. Multivariable adjusted models during pregnancy included cohort, parity, previous breastfeeding, and age of mother at chemical measurement (Caspersen and Ida, 2016; Manzano-Salgado and Cyntia, 2015), while models for childhood were adjusted for cohort, parity (of mother), previous breastfeeding (of mother), breastfeeding, and child age at measurement (Fisher et al 2016; Mondal et al 2014; Morck et al 2015). A sensitivity analysis further adjusting pregnancy models for fish consumption and smoking was carried out (Brandhagen et al 2014; Mondal et al 2014).

Given the large number of environmental contaminants, we conducted principal component analysis (PCA) to reduce the dimensionality of our data. PCA reduces the number of correlated variables into a small number of new variables called components, which capture as much variance of the original variables as possible while still remaining uncorrelated with one another (SAS Institute n.d.). PCA was applied separately to the imputed datasets for mothers and their children using the R function *prcomp*. After examining the scree plot and using Kaiser's rule, all components with an eigenvalue greater than 1 were retained, resulting in 13 components for pregnancy and 12 components for childhood. Next, varimax rotation was applied and after examining the data only those components that accounted for 5% or more of variance in the data were retained for further analysis. This resulted in 5 components for pregnancy and 4 components for childhood. In order to conduct regression analysis with the components, scores were calculated for each subject based on the component weight in conjunction with the original variable values. Finally, multivariate linear regression models were run to investigate the relationship between socioeconomic position and the new components. A sensitivity analysis taking out one cohort at a time was carried out to understand any differences between the cohorts.

Statistical significance was defined as p-value < 0.05. Preliminary and regression analyses were performed using STATA version 12.0 (StataCop, College Station, TX, USA), and principal component analysis was carried out using RStudio version 3.4.1 (The R Foundation for Statistical Computing).

3. Results

In our study population, pregnant women were on average 30.8 years old at delivery, 82.6% were employed during pregnancy and for 45.9% of them this was their first child. About half of pregnant women had a high level of education (51.8%), while 34.4% had a mid level and 13.8% had a low level education. On average children were 8 years old at the time of sample collection (age range: 5.4–12.1), 54.7% were male and 84.6% of them were breastfed. Half (50.9%) of the families were classified as having high affluence, 38.6% as middle and 10.5% as low affluence (Table 1). The mean and frequency of demographic characteristics were generally similar in the original and imputed data sets

Table 2
Median concentrations of biomarkers of 41 chemical contaminants (detailed distributions and percent detected in Supplementary Material Table S6).

Chemical Contaminants	Abbrev.	Unit	Pregnancy			Childhood		
			N	Median (p25-75)	PC	N	Median (p25-75)	PC
Persistent Pesticides:								
4,4′dichlorodiphenyldichloroethylene	DDE	ng/g lipid	1048	52.3 (25.9–110.7)	PC4	1279	21.7 (11.5–45.6)	–
4,4′dichlorodiphenyltrichloroethane	DDT	ng/g lipid	826	1.3 (0.8–3.0)	PC4	1279	0.7 (0.3–1.6)	–
Hexachlorobenzene	HCB	ng/g lipid	1048	8.2 (5.6–12.9)	–	1279	8.2 (6.3–11.4)	–
2,2′,4,4′-Tetrabromodiphenyl Ether	PBDE-47	ng/g lipid	684	0.4 (0.3–0.7)	PC4	1279	0.2 (0.1–0.4)	–
2,2′,4,4′,5,5′-Hexabromodiphenyl ether	PBDE-153	ng/g lipid	648	0.4 (0.03–0.7)	–	1279	0.2 (0.03–0.4)	–
2,3′,4,4′,5-Pentachlorobiphenyl	PCB-118	ng/g lipid	829	2.6 (1.6–4.8)	PC1	1279	2.0 (1.5–2.9)	–
2,2′,3,4,4′,5′-Hexachlorobiphenyl	PCB-138	ng/g lipid	1048	9.1 (5.5–16.1)	PC1	1279	5.4 (3.4–8.7)	PC2
2,2′,4,4′,5,5′-Hexachlorobiphenyl	PCB-153	ng/g lipid	1048	17.6 (10.4–30.5)	PC1	1279	11.6 (7.3–18.6)	PC2
2,2′,3,3′,4,4′,5-Heptachlorobiphenyl	PCB-170	ng/g lipid	826	3.7 (1.8–7.1)	PC1	1279	1.3 (0.6–2.7)	PC2
2,2′,3,4,4′,5,5′-Heptachlorobiphenyl	PCB-180	ng/g lipid	1048	10.4 (5.8–18.5)	PC1	1279	3.7 (1.6–8.0)	PC2
Per- and Polyfluoroalkyl Substances:								
Perfluorooctanoate	PFOA	µg/L	1240	2.3 (1.4–3.3)	–	1301	1.5 (1.2–2.0)	PC3
Perfluorononanoate	PFNA	µg/L	1240	0.7 (0.4–1.1)	PC4	1301	0.5 (0.3–0.7)	PC3
Perfluoroundecanoate	PFUnDA	µg/L	1032	0.2 (0.1–0.3)	PC4	1301	0.03 (0.02–0.1)	PC3
Perfluorohexane sulfonate	PFHxS	µg/L	1240	0.5 (0.3–0.9)	–	1301	0.4 (0.2–0.6)	PC3
Perfluorooctane sulfonate	PFOS	µg/L	1240	6.4 (4.1–9.6)	–	1301	2.0 (1.3–3.2)	PC3
Metals:								
Arsenic	As	µg/L	833	1.2 (0.3–2.3)	–	1298	1.4 (0.3–2.3)	–
Cadmium	Cd	µg/L	833	0.2 (0.1–0.3)	–	1298	0.1 (0.04–0.1)	–
Mercury	Hg	µg/L	1020	1.9 (1.0–3.4)	–	1298	0.9 (0.4–1.7)	–
Manganese	Mn	µg/L	833	11.1 (8.5–14.3)	–	1298	8.6 (7.1–10.5)	–
Lead	Pb	µg/L	833	9.7 (7.1–13.2)	–	1298	8.5 (6.4–11.1)	–
Phthalate Metabolites:								
Monoethyl phthalate	MEP	µg/g crt.	1080	178.9 (72.1–468.4)	–	1301	32.8 (15.0–79.4)	–
Mono-iso-butyl phthalate	MiBP	µg/g crt.	1088	38.7 (23.3–60.6)	–	1301	40.3 (24.6–71.5)	–
Mono-n-butyl phthalate	MnBP	µg/g crt.	1089	29.6 (18.3–47.3)	–	1301	22.7 (14.5–38.8)	–
Mono benzyl phthalate	MBzP	µg/g crt.	1088	7.3 (3.6–15.2)	–	1300	4.8 (2.7–8.7)	–
Mono-2-ethylhexyl phthalate	MEHP	µg/g crt.	1085	8.7 (4.4–15.2)	PC3	1260	2.9 (1.6–5.1)	PC1
Mono-2-ethyl-5-hydroxyhexyl phthalate	MEHHP	µg/g crt.	1089	18.2 (10.5–31.2)	PC3	1298	19.4 (11.4–33.2)	PC1
Mono-2-ethyl-5-oxohexyl phthalate	MEOHP	µg/g crt.	1089	14.1 (8.3–23.7)	PC3	1300	12.3 (7.1–20.5)	PC1
Mono-2-ethyl 5-carboxypentyl phthalate	MECPP	µg/g crt.	913	33.6 (22.4–52.3)	PC3	1300	32.9 (19.9–57.8)	PC1
Mono-4-methyl-7-hydroxyoctyl phthalate	oh-MiNP	µg/g crt.	914	0.9 (0.6–1.5)	–	1301	5.0 (3.1–9.3)	–
Mono-4-methyl-7-oxooctyl phthalate	oxo-MiNP	µg/g crt.	914	1.0 (0.6–1.7)	–	1301	2.7 (1.7–5.0)	–
Phenols:								
Methyl paraben	MEPA	µg/g crt.	815	166.8 (39.5–389.4)	–	1299	6.3 (3.1–24.3)	PC4
Ethyl paraben	ETPA	µg/g crt.	817	6.3 (1.1–26.7)	–	1298	0.7 (0.4–1.2)	PC4
Propyl paraben	PRPA	µg/g crt.	1083	44.2 (8.9–134.2)	–	1284	0.2 (0.02–1.6)	PC4
Bisphenol-A	BPA	µg/g crt.	1084	2.8 (1.6–6.6)	PC2	1289	3.8 (2.3–7.0)	–
N-Butyl paraben	BUPA	µg/g crt.	1083	3.4 (0.4–14.4)	PC2	1296	0.1 (0.05–0.1)	–
Oxybenzone	OXBE	µg/g crt.	1085	4.9 (1.5–27.4)	PC2	1301	2.0 (0.8–6.7)	–
Triclosan	TCS	µg/g crt.	1085	6.9 (1.5–79.7)	–	1301	0.6 (0.3–1.5)	–
OP Pesticide Metabolites:								
Dimethyl phosphate	DMP	µg/g crt.	1080	8.4 (4.1–16.4)	PC5	1295	0.4 (0.3–4.7)	–
Dimethyl thiophosphate	DMTP	µg/g crt.	1084	5.0 (2.0–12.3)	PC5	1300	2.8 (1.2–6.3)	–
Diethyl phosphate	DEP	µg/g crt.	1082	3.3 (1.9–6.4)	PC5	1299	1.8 (0.4–4.7)	–
Diethyl thiophosphate	DETP	µg/g crt.	1037	0.6 (0.1–2.6)	PC5	1280	0.1 (0.1–1.7)	–

Abbreviations: Abbrev. = abbreviation, ng = nanogram, g = gram, µg = microgram, L = liter, crt. = creatinine, PC = principal component.

Detailed SEP indicators by cohort in Supplementary Material S5.

Environmental contaminant distributions are shown in Table 2 and in more detail in Supplementary Material S6. For most contaminants, concentrations were somewhat higher during pregnancy than childhood (Haug et al 2018).

3.1. Socioeconomic position and single environmental contaminants

Fig. 1 shows the associations between SEP indicators and 41 environmental contaminants analyzed during pregnancy and in childhood (see Supplementary Material S7-10 for complete regression output, complete-case and imputed). During pregnancy, concentrations of several contaminants measured were lower in low or middle education groups when compared to the high education group (Fig. 1; Supplementary Material S7). PFUnDA concentrations were 10% lower in the low education group [Geometric Mean Ratio(GMR) = 0.90; 95%CI 0.80, 1.00] and Hg concentrations were 17% lower [GMR = 0.83; 95%CI 0.72, 0.95]. In low educated women, concentrations of several phenols were around half of those in high educated women (GMRs for MEPA, ETPA, PRPA and BUPA between 0.49 and 0.59). BPA concentrations were reduced only in the middle education group [GMR = 0.86; 95%CI 0.74, 0.99] compared to high education. OP pesticide metabolites also showed lower concentrations in pregnant women of lower education with significant differences observed for DMP [GMR = 0.79; 95%CI 0.67, 0.94] and DMTP [GMR = 0.70; 95%CI 0.54, 0.90]. Conversely, Cd concentrations were 30% higher in the low education group [GMR = 1.30; 95%CI 1.12, 1.50] when compared to high education; the sensitivity analysis additionally adjusting for smoking reduced this to 12% higher (no longer statistically significant). Further adjustment for fish consumption did not change the effect estimates (Supplementary Material S19-S20).

Associations between maternal employment status and environmental contaminant exposures were generally weaker than those for maternal education, with GMRs closer to 1 and fewer statistically significant associations (Fig. 1; Supplementary Material S8). We observed lower exposure to all measured PFASs in unemployed pregnant women compared to employed, with GMRs between 0.97 and 0.92 (for example PFOA [GMR = 0.89; 95%CI 0.83, 0.96]). Conversely, DDE

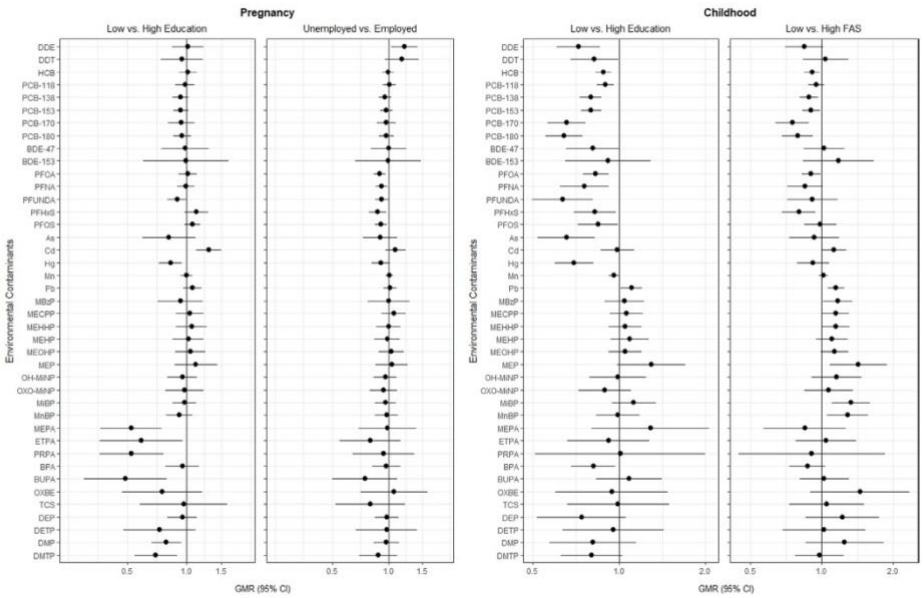


Fig. 1. Adjusted associations (Geometric Mean Ratio (95% CI) between maternal education and employment status and concentrations of chemicals in pregnant women (Pregnancy) and between maternal education and family affluence scale (FAS) and concentrations of chemicals in children (Childhood), ages 6–12 years during childhood, imputed data (n = 1301). Pregnancy models were adjusted for cohort, parity, previous breastfeeding, and age at chemical measurement. Childhood models were adjusted for cohort, parity, previous breastfeeding, breastfeeding of study child, and child age at chemical measurement (years). For interpretation: GMR values < 1 signify lower exposure and GMR values > 1 signify higher exposure in comparison to the reference category.

concentrations were 21% higher in unemployed pregnant women compared to those who were employed [GMR = 1.21; 95%CI 1.03, 1.42]. Sensitivity analysis adjusting pregnancy models for fish consumption or smoking did not change associations for employment status.

In children, lower maternal education was associated with lower concentrations of several groups of contaminants. All organochlorine compounds (DDE, DDT, HCB, and PCBs) showed lower concentrations in children of mothers with low education compared to those whose mothers with a high education, with GMRs between 0.64 and 0.90 (Fig. 1; Supplementary Material S9. For example, DDE concentrations were 28% lower [GMR = 0.72; 95%CI 0.61, 0.86]. PFASs also showed lower childhood concentrations in the low education group (GMRs between 0.64 and 0.84), as did As [GMR = 0.66; 95%CI 0.52, 0.82], Hg [GMR = 0.70; 95%CI 0.60, 0.81], and BPA [GMR = 0.81; 95%CI 0.68, 0.97]. On the other hand, Pb concentrations were 10% higher [GMR = 1.10; 95%CI 1.01, 1.20] in children with mothers with low education.

Significant associations with FAS score indicating lower exposure in children with families in the lower FAS score groups were observed, although less pronounced than with maternal education (Fig. 1; Supplementary Material S10). For example, HCB concentrations were 9% lower in the FAS low group when compared to high. A similar trend was observed for several PCBs (for example PCB-170 [GMR = 0.75; 95%CI 0.64, 0.89]), and certain PFASs (for example PFOA [GMR = 0.90; 95%CI 0.82, 0.99]). Low FAS was associated with higher concentrations of phthalates with GMRs between 1.15 and 1.43 (for example MiBP [GMR = 1.33; 95%CI 1.11, 1.60]) and heavy metals with GMRs between 1.03 and 1.15 (for example Pb [GMR = 1.15; 95%CI 1.06, 1.24]).

3.2. Socioeconomic position and components combining environmental contaminants

In pregnant women, the five components retained for regression analysis accounted for 42.8% of the total variance of the data. After varimax rotation the components were defined by the following contaminants and loadings; component 1 was highly loaded with PCBs: PCB-118 (0.34), PCB-138 (0.45), PCB-153 (0.43), PCB-170 (0.42), PCB-180 (0.42); component 2 was highly loaded with phenols: OXBE (0.51), BPA (0.49), BUPA (0.39); component 3 was highly loaded with DEHP metabolites: MECPP (0.52), MEOHP (0.51), MEHHP (0.49), MEHP (0.45); component 4 was highly loaded with persistent organic pollutants (POPs mixture): DDE (0.50), DDT (0.34), PBDE-47 (0.40), PFNA (0.38), PFUNDA (0.37); and component 5 was highly loaded with pesticide metabolites: DMTP (0.52), DEP (0.49), DMP (0.49), DETP (0.48) (Supplementary Material S11-12 for detailed loadings).

In pregnancy, linear regression models showed a significant negative association between middle level maternal education and PCB exposure when compared to the high education group (component 1) [β = −0.15; 95%CI -0.30, 0.00] (Table 3). Similarly, significant negative associations were observed between both low and middle level maternal education and phenols (component 2) [low vs high (β = −0.25; 95%CI -0.44, −0.05); middle vs high (β = −0.14; 95%CI -0.27, −0.01)] and OP pesticide metabolites (component 5) [low vs high (β = −0.40; 95%CI -0.66, −0.14); middle vs high (β = −0.30;

Table 3
Association between components from principal-component analysis and selected social determinants for pregnant women (Pregnancy). Adjusted models shown (imputed data, n = 1301).

Pregnancy					
Component		Maternal Education		Maternal Employment Status	
		Cat.	Beta (95%CI)	Cat.	Beta (95%CI)
PC1[a]	: PCBs	low	−0.19 (−0.42, 0.03)	unemployed	−0.10 (−0.28, 0.08)
		middle	−0.15 (−0.30, −0.00)*	employed	reference
		high	reference	–	–
PC2[b]	: phenols	low	−0.25 (−0.44, −0.05)*	unemployed	−0.12 (−0.28, 0.04)
		middle	−0.14 (−0.27, −0.01)*	employed	reference
		high	reference	–	–
PC3[c]	: DEHP metabolites	low	0.13 (−0.21, 0.46)	unemployed	0.10 (−0.17, 0.37)
		middle	0.10 (−0.12, 0.32)	employed	reference
		high	reference	–	–
PC4[d]	: POPs	low	−0.11 (−0.29, 0.06)	unemployed	0.07 (−0.08, 0.21)
		middle	−0.07 (−0.19, 0.05)	employed	reference
		high	reference	–	–
PC5[e]	: OP pesticide metabolites	low	−0.40 (−0.66, −0.14)*	unemployed	−0.11 (−0.33, 0.10)
		middle	−0.30 (−0.48, −0.12)*	employed	reference
		high	reference	–	–

Abbreviations: PC = principal component, Cat. = category of independent variable, CI = confidence interval.
Pregnancy models were adjusted for cohort, parity, previous breastfeeding, and age at chemical measurement.
* indicates p-value significant at < 0.05.
[a] PC1 loaded with PCBs: PCB-118, PCB-138, PCB-153, PCB-170, PCB-180.
[b] PC2 loaded with phenols: OXBE, BPA, BUPA.
[c] PC3 loaded with DEHP metabolites: MECPP, MEOHP, MEHHP, MEHP.
[d] PC4 loaded with a mixture of POPs: DDE, DDT, PBDE-47, PFUNDA, PFNA.
[e] PC5 loaded with OP pesticide metabolites: DMTP, DMP, DETP, DEP.

95%CI -0.48, −0.12)] (Table 3). The observed directions were similar to associations found in the single contaminant models. No significant associations were observed between maternal employment and the components (Table 3).

In sensitivity analysis the observed associations were generally similar between the cohorts and went in the same direction. We observed some heterogeneity (i.e. $I^2 > 25\%$ and p-value < 0.00.5) with maternal education and PC2 (low vs. high: $I^2 = 59\%$) and PC5 (middle vs. high $I^2 = 60.6\%$) (Supplementary Material S15-16).

In children, the four components retained for further analysis accounted for 40.3% of the total variance of the data. The components and their loadings were as follows; component 1 was highly loaded with DEHP metabolites: MEHHP (0.50), MEOHP (0.50), MECPP (0.48), MEHP (0.47); component 2 was highly loaded with PCBs: PCB-138 (0.42), PCB-153 (0.46), PCB-170 (0.44), PCB-180 (0.45), component 3 was highly loaded with PFASs: PFOS (0.51), PFOA (0.48), PFNA (0.45), PFUnDA (0.38), PFHxS (0.34); and component 4 loaded highly with parabens: MEPA (0.60), PRPA (0.52), ETPA (0.43) (Supplementary Material S13-14 for detailed loadings).

In children, a significant negative relationship was found for both low and middle maternal education when compared to high and PCBs (component 2) [low (β = −0.90; 95%CI -1.20, −0.59); middle (β = −0.74; 95%CI -0.95, −0.54)], and PFASs (component 3) [low (β = −0.64; 95%CI -0.90, −0.37); middle (β = −0.44; 95%CI -0.62, −0.26)]. Similar trends were observed with FAS score and PCBs (component 2) [low (β = −0.53; 95%CI -0.86, −0.20)], and PFASs (component 3) [middle (β = −0.21; 95% −0.39, −0.03)]. On the contrary, low FAS score was found to have a positive association with DEHP metabolites (component 1) [low (β = 0.35; 95%CI 0.02, 0.67)] (Table 4). These associations are consistent with findings from single contaminant models.

In sensitivity analysis the observed estimates and directionality were similar to all cohort models. We observed some heterogeneity with maternal education and PC2 (middle vs. high: $I^2 = 66.3\%$) and PC3 (low vs. high: $I^2 = 62.5\%$), and with FAS and PC3 (middle vs. high: $I^2 = 71.3\%$) (Supplementary Material S17-18). Given the low frequency of families for low FAS in MoBa and EDEN cohorts, we removed these cohorts for sensitivity analysis. We observed a loss of significance with PC1 however the coefficient remained similar, and stronger associations for PC2 and PC3 (Supplementary Material S18.1).

4. Discussion

In this large study of a wide variety of environmental chemical contaminants measured during pregnancy and childhood, higher SEP was associated with higher levels of several groups of contaminants, including substances banned decades ago (such as PCBs) and contaminants currently or recently in production (such as PFASs, parabens, pesticides). Of the 41 analyzed contaminants, 29% showed higher concentrations in higher SEP group compared to lower during pregnancy, and this number increased to 39% during childhood. Fewer environmental contaminants (5% in pregnant women and 22% in children) showed higher concentrations in the lower SEP groups, most notably Cd in pregnant women, and phthalates and metals (Cd, Pb) in children.

4.1. Persistent pesticides (DDE, DDT, HCB, PCBs, PBDEs)

In pregnancy and childhood a clear tendency indicating higher concentrations of persistent pesticides with higher SEP was seen. These findings are broadly consistent with existing literature. Two studies on pregnant women reported higher PCB concentrations with higher education levels in Canada (Fisher et al 2016) and higher social class in Spain (Vrijheid et al 2012). A study on adolescents in Belgium found that the mean exposure of PCBs significantly increased with increasing SEP (Morrens et al 2012). On the other hand, a study on African-American women found that higher income was associated with an increase in PCB concentrations, while education was not, and they observed no associations with education or income and DDE concentrations (Borrell, 2004). A study on pregnant women in Canada found similar differences by education for several persistent pesticides including DDE (Fisher et al 2016). Associations in this study were

Table 4
Association between components from principal-component analysis and selected social determinants for children (6–12 years) (Childhood). Adjusted models shown (imputed data, n = 1301).

Childhood					
Component		Maternal Education		Family Affluence Scale (FAS)	
		Cat.	Beta (95%CI)	Cat.	Beta (95%CI)
PC1[a]	: DEHP metabolites	low	0.16 (−0.15, 0.46)	low	0.35 (0.02, 0.67)*
		middle	0.15 (−0.05, 0.36)	middle	0.11 (−0.10, 0.31)
		high	reference	high	reference
PC2[b]	: PCBs	low	−0.90 (−1.20, −0.59)*	low	−0.53 (−0.86, −0.20)*
		middle	−0.74 (−0.95, −0.54)*	middle	−0.05 (−0.25, 0.16)
		high	reference	high	reference
PC3[c]	: PFASs	low	−0.64 (−0.90, −0.37)*	low	−0.27 (−0.55, 0.02)
		middle	−0.44 (−0.62, −0.26)*	middle	−0.21 (−0.39, −0.03)*
		high	reference	high	reference
PC4[d]	: parabens	low	0.01 (−0.25, 0.26)	low	−0.07 (−0.34, 0.20)
		middle	−0.09 (−0.26, 0.08)	middle	−0.10 (−0.26, 0.07)
		high	reference	high	reference

Abbreviations PC = principal component, Cat. = category of independent variable, CI = confidence interval.
Childhood models were adjusted for cohort, parity, previous breastfeeding, breastfeeding of study child, and child age at chemical measurement (years).
* indicates p-value significant at < 0.05.
[a] PC1 loaded with DEHP metabolites: MEHHP, MEOHP, MECPP, MEHP.
[b] PC2 loaded with PCBs: PCB-153, PCB-180, PCB-170, PCB-138.
[c] PC3 loaded with PFASs: PFOS, PFOA, PFNA, PFUnDA, PFHxS.
[d] PC4 loaded with parabens: MEPA, PRPA, ETPA.

stronger for children than pregnant women. Breastfeeding and dietary intake of dairy, meat, and fish affect concentration levels of several persistent pollutants and are also related to SEP. Our analyses adjusted for breastfeeding and fish consumption so these are unlikely to explain the observed SEP gradients, and they may be explained by other dietary or indoor factors. However, it is possible that our breastfeeding and fish measurements may not have been precise enough to capture the difference.

4.2. Per- and polyfluoroalkyl substances (PFASs: PFOA, PFNA, PFUnDA, PFHxS, PFOS)

No associations were observed in principal component models that included PFASs for pregnant women. However in single models we observed higher concentrations of PFUnDA in pregnant women with high education status, and with employed women and all PFASs. One explanation may be higher concentrations of PFASs in offices as found in one study (Fraser et al 2013); however another study found higher levels in household and personal air (Padilla-Sánchez et al 2017). Both studies had low sample sizes and the study by Fraser sampled new and renovated buildings which may increase PFASs levels. Two studies on pregnant women found that PFASs concentrations increased with maternal education (Fisher et al 2016) and household income (Brantsæter et al 2013). However, a Spanish study on pregnant women did not find any association with social class or education (Manzano-Salgado and Cyntia, 2016). In childhood we observed a significant negative association between PFASs concentrations in childhood and level of maternal education in both component and single contaminant models. We did not identify any studies on the social determinants of PFASs in children, however PFASs have been shown to transfer in-utero through the placenta and through breastfeeding (Manzano-Salgado and Cyntia, 2015; Mondal et al 2014). Levels of PFASs have also been found to vary by breastfeeding and diet, most notably higher levels with higher fish and shellfish intake (Brandhagen et al 2014; Manzano-Salgado and Cyntia, 2016), however in this study adjustment for breastfeeding and fish consumption did not alter results. In the US, national biomonitoring data from the National Health and Nutrition Examination Survey (NHANES) indicates that exposure to PFASs is positively associated with family income (Nelson et al 2012), and higher burdens of PFASs with increased SES (Tyrrell et al 2013).

4.3. Metals (As, Cd, Hg, Mn, Pb)

We observed higher concentrations of Hg in mothers and children of higher maternal education, and As for children only. Conversely we observed higher concentrations of Cd in mothers of lower education and children with middle FAS. In children we also found higher Pb concentrations with decreasing maternal education and FAS score. Diet (fish, seafood, cereal-based products) and/or lifestyle factors (smoking) are likely to be the main routes of exposure (Castaño et al 2015; EFSA, 2014; EFSA CONTAM Panel, 2015). These behaviors are also highly related to social status as a systematic review concluded that Pb is higher in children with lower SEP (Bolte et al., 2010). Hg has been more related to fish and seafood consumption, with higher consumption associated with higher education (Schober et al 2003) and social class (Vrijheid et al 2012). In this study, adjusting for fish consumption did not alter the findings, however adjusting for smoking explained part of the association with Cd in pregnant women.

4.4. Phthalate metabolites (MEP, MiBP, MnBP, MBzP, MEHP, MEHHP, MEOHP, MECPP, oh-MiNP, oxo-MiNP)

In single contaminant and component analysis we observed higher levels of DEHP metabolites with lower FAS in children. Other studies report similar positive relationships as well as negative relationships depending on the phthalate analyzed (Casas et al 2011; Tyrrell et al 2013). DEHP levels, like other phthalates have been found to decrease with age. This may explain in part why we only observe this association in children. Children may have higher burdens due to their smaller size and increased play activity, putting them into contact with flooring, wall-coverings, and toys (Becker et al 2004). Additionally, phthalates have a short half-life and are eliminated from the body in a few hours or days; thus it is difficult to accurately characterize exposure. A biomarker measurement at one point in time only provides very recent exposure making misclassification more likely.

4.5. Phenols (MEPA, ETPA, PRPA, BPA, BUPA, OXBE, TCS)

We reported a negative association between levels of phenols and maternal education for pregnant women in component and single models. The phenols component was loaded most highly with OXBE (BP3), an environmental contaminant commonly found in sunscreen and cosmetics, both of which are more likely to be used by those of higher social status (Park et al 2018). In children we observed lower concentrations of OXBE with middle FAS. We also observed lower concentrations of BPA in middle level education in pregnancy and low education in childhood. This is contrary to other studies that have reported a relationship between higher BPA concentrations and lower education (Casas et al 2013; Covaci et al 2015), or income groups (Geens et al 2014). Phenols have been associated with a greater cosmetic and personal care product use (Larsson et al 2014), which may in part explain the observed difference. Another explanation could be misclassification as phenols have short half-lives, similar to phthalates (Larsson et al 2014).

4.6. OP pesticide metabolites (DMP, DMTP, DEP, DETP)

In pregnant women we observed higher concentrations of OP pesticide metabolites with higher education in component models, consistent with the single contaminant models for both pregnant women and children. Similar to other non-persistent compounds, OP pesticide metabolites have a short half-life thus making it difficult to accurately measure exposure and in using dialkylphosphates (DAPs) as biomarkers the levels shown may also reflect preformed DAPs further clouding exposure assessment (Lu et al 2011; Weerasekera et al 2009). However, similar findings have been reported in pregnant women in Canada (Sokoloff et al 2016) and the Netherlands (van den Dries et al 2018). Recent studies have cited higher fruit and vegetable consumption, associated with high social position, as a key for increasing exposure (van den Dries et al 2018; Lewis et al 2015; Llop et al 2017).

4.6.1. Strengths and limitations

Major strengths of this study include the prospective cohort design consisting of 1301 mother-child pairs and the harmonized sample collection and analysis across six cohorts for the childhood samples. Also, we defined SEP in this study according to several indicators rather than just one. Especially unique is the use of the family affluence measure, which does not take into account education or occupation. Although the four item FAS score has been indicated not to be discriminatory within very rich or poor countries, we found a good distribution overall in our population. Additionally, our results with this measure and education were similar, further strengthening our associations. Although we were not able to study further SEP indicators like occupation or income, our analysis showed that maternal education gave the strongest social gradients, both during pregnancy and in childhood, thus it seems to be a good predictor of environmental contaminants. Lastly, the use of PCA enabled us to evaluate the combined effect of SEP on many environmental contaminants by creating components that represent a weighted combination of the individual contaminants in its group. In this analysis we used PCA to complement the single contaminant models, as PCA reduces the dimensionality and takes into account correlations between the contaminants. As such, our conclusions are based on the consistency of the results between single contaminant and component models.

In this study, urine and blood collection of the maternal samples were not collected nor stored in a harmonized manner, nor were they analyzed at the same lab. This between-laboratory variability can later cause problems with result interpretation. To reduce this variability samples were chosen at random and sent to the different labs to evaluate any differences, of which results were positive (Supplementary Material S3-4). Further, we cannot completely exclude the possibility of residual confounding by factors such as diet and breastfeeding as it is possible that the included measures are too crude to capture all confounding. Although we analyzed 41 environmental contaminants, we are exposed to many more in our environment and may have missed major environmental contaminants. Additionally, there were missing values for several environmental contaminants. To deal with this issue we used single imputation, which provides valid results under the MAR assumption (Bernhardt et al., 2015). To support the results from the imputed data set we fit the single contaminant models using the original data set and found few differences in significant estimates (Supplementary Material S7-10). Finally, although the study sample is population-based, it is likely to under represent families of lower SEP and rural areas. This is unlikely to have led to false associations, but may have diminished contrast between low and high SEP groups. Future studies should consider including those from non-urban settings and lower SEP. This would also be an opportunity to include area-level SEP indicators, as this study focused on individual indicators, and relationships may differ.

5. Conclusions

Overall these findings provide one of the most comprehensive overviews of the burden of exposure to environmental chemical contaminants by SEP indicators in pregnant women and their children from six different European countries. In this mostly urban European population, among the compounds tested, we more frequently observed families of higher social position to be at higher risk to be exposed to persistent pesticides, PFASs, phenols, OP pesticides, BPA, Hg and As whereas families of lower social position were at risk of higher exposures to Cd, Pb, and phthalates, particularly DEHP metabolites. Many of the contaminants studied are suspected of negatively impacting child health and have been linked to adverse health outcomes in later life (Gore et al 2015). These same health outcomes have also been independently linked to social disparity (Marmot et al 2008). Thus, in future work it is important that researchers looking into health effects of environmental contaminants not only adjust for SEP but rather examine modification to better understand the role of socioeconomic position within health effects.

Declarations of interest

None.

Funding

The research leading to these results has received funding from the European Community's Seventh Framework Programme (FP7/2007–2013) under grant agreement no 308333 – the HELIX project. Dr. Maribel Casas received funding from Instituto de Salud Carlos III (Ministry of Economy and Competitiveness) (MS16/00128). The INMA (Environment and Childhood) Sabadell cohort and biomarker measurements were funded by grants from Instituto de Salud Carlos III (Red INMA G03/176; CB06/02/0041; PI041436; PI081151 incl. FEDER funds; PI12/01890 incl. FEDER funds; CP13/00054 incl. FEDER-funds), CIBERESP, Generalitat de Catalunya-CIRIT 1999SGR 00241, Generalitat de Catalunya-AGAUR (2009 SGR 501, 2014 SGR 822), Fundació La marató de TV3 (090430), Spanish Ministry of Economy and Competitiveness (SAF2012-32991 incl. FEDER funds).

Acknowledgements

We are grateful to all the participating children, parents, practitioners and researchers in the six cohorts who took part in this study, especially to those families in addition donated blood and urine to this specific HELIX study. More details can be found in Supplementary Material S21.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ijheh.2019.04.002.

References

Andersen, A., et al., 2008. "High Agreement on Family Affluence between Children ' S and Parents ' Reports : International Study of. 1092–94.

Becker, Kerstin, et al., 2004. DEHP metabolites in urine of children and DEHP in house dust. Int. J. Hyg Environ. Health 207 (5), 409–417.

Bernhardt, Paul W., Wang, H., Zhang, D., 2015. Statistical methods for generalized linear models with covariates subject to detection limits. Stat Biosci. 7 (1), 68–89.

Bolte, Gabriele, Tamburlini, Giorgio, Kohlhuber, Martina, 2010. Environmental inequalities among children in europe - evaluation of scientific evidence and policy implications. Eur. J. Public Health 20 (1), 14–20.

Borrell, L.N., Factor-Litvak, P., Wolff, M.S., Susser, E., Matte, T.D., 2004. Effect of socioeconomic status on exposures to polychlorinated biphenyls (PCBs) and dichlorodiphenyldichloroethylene (DDE) among pregnant African-American women. Arch. Environ. Health 59 (5), 250–255.

Boyce, William, Torsheim, Torbjorn, Currie, Candace, Zambon, Alessio, 2006. The family affluence scale as a measure of national wealth: validation of an adolescent self-report measure. Soc. Indicat. Res. 78 (3), 473–487.

Brandhagen, Martin, et al., 2014. Breast-feeding in relation to weight retention up to 36 Months postpartum in the Norwegian mother and child cohort study: modification by socio-economic status? Publ. Health Nutr. 17 (7), 1514–1523.

Brantsæter, A.L., et al., 2013. Determinants of plasma concentrations of perfluoroalkyl substances in pregnant Norwegian women. Environ. Int. 54, 74–84.

van Buuren, Stef, Groothuis-Oudshoorn, Karin, 2011. "MICE : multivariate imputation by chained equations in R. J. Stat. Softw. 45 (3).

Casas, Lidia, et al., 2011. Urinary concentrations of phthalates and phenols in a population of Spanish pregnant women and children. Environ. Int. 37 (5), 858–866. Retrieved. https://doi.org/10.1016/j.envint.2011.02.012.

Casas, Maribel, et al., 2013. Dietary and sociodemographic determinants of bisphenol a urine concentrations in pregnant women and children. Environ. Int. 56, 10–18. Retrieved. https://doi.org/10.1016/j.envint.2013.02.014.

Caspersen, Ida, Henriette, et al., 2016. Determinants of plasma PCB, brominated flame retardants, and organochlorine pesticides in pregnant women and 3 Year old children in the Norwegian mother and child cohort study. Environ. Res. 146, 136–144. Retrieved. https://doi.org/10.1016/j.envres.2015.12.020.

Castaño, Argelia, et al., 2015. Fish consumption patterns and hair mercury levels in children and their mothers in 17 EU countries. Environ. Res. 141, 58–68. Retrieved. https://doi.org/10.1016/j.envres.2014.10.029.

Chatzi, Leda, et al., 2009. Metabolic syndrome in early pregnancy and risk of preterm birth. Am. J. Epidemiol. 170 (7), 829–836.

Covaci, Adrian, et al., 2015. Urinary BPA measurements in children and mothers from six european member States: overall results and determinants of exposure. Environ. Res. 141, 77–85. Retrieved. https://doi.org/10.1016/j.envres.2014.08.008.

van den Dries, Michiel A., et al., 2018. Determinants of organophosphate pesticide exposure in pregnant women: a population-based cohort study in The Netherlands. Int. J. Hyg Environ. Health 221 (3), 489–501. Retrieved. https://doi.org/10.1016/j.ijheh.2018.01.013.

Drouillet, Peggy, et al., 2009. Association between maternal seafood consumption before pregnancy and fetal growth: evidence for an association in overweight women. The EDEN mother-child cohort. Paediatr. Perinat. Epidemiol. 23 (1), 76–86.

EFSA, 2014. Dietary Exposure to Inorganic Arsenic in the European Population. Retrieved. http://doi.wiley.com/10.2903/j.efsa.2014.3597.

EFSA CONTAM Panel, 2015. European Food Safety Authority. Scientific Opinion on Lead in Food. Retrieved. http://www.efsa.europa.eu/en/efsajournal/doc/1570.pdf.

Fisher, Mandy, et al., 2016. Concentrations of persistent organic pollutants in maternal and cord blood from the maternal-infant research on environmental chemicals (MIREC) cohort study. Environ. Health: A Global Access Science Source 15 (1), 59. Retrieved. http://www.ncbi.nlm.nih.gov/pubmed/27142700.

Fraser, Alicia J., et al., 2013. Polyfluorinated compounds in dust from homes, offices, and vehicles as predictors of concentrations in office workers' serum. Environ. Int. 60, 128–136.

Geens, Tinne, et al., 2014. Determinants of bisphenol a and phthalate metabolites in urine of flemish adolescents. Environ. Res. 134, 110–117. Retrieved. https://doi.org/10.1016/j.envres.2014.07.020.

Gore, A.C., et al., 2015. Executive summary to EDC-2: the endocrine society's second scientific statement on endocrine-disrupting chemicals. Endocr. Rev. 36 (6), 593–602.

Grazuleviciene, Regina, Danileviciute, Asta, Nadisauskiene, Ruta, Vencloviene, Jone, 2009. Maternal smoking, GSTM1 and GSTT1 polymorphism and susceptibility to adverse pregnancy outcomes. Int. J. Environ. Res. Public Health 6 (3), 1282–1297.

Guxens, M., et al., 2012. Cohort profile: the INMA–INfancia Y medio ambiente–(environment and childhood) project. Int. J. Epidemiol. 41 (4), 930–940. Retrieved. http://www.ije.oxfordjournals.org/cgi/doi/10.1093/ije/dyr054.

Haug, Line S., et al., 2018. In-utero and childhood chemical exposome in six european mother-child cohorts. Environ. Int (in press)(September):751–63. Retrieved. https://doi.org/10.1016/j.envint.2018.09.056.

Hicken, Margaret T., et al., 2012. A novel look at racial health disparities: the interaction between social disadvantage and environmental health. Am. J. Public Health 102 (12), 2344–2351.

Landrigan, Philip J., Goldman, Lynn R., 2011. Children S vulnerability to toxic chemicals: a challenge and opportunity to strengthen health and environmental policy. Health Aff. 30 (5), 842–850.

Larsson, Kristin, et al., 2014. Exposure determinants of phthalates, parabens, bisphenol a and triclosan in Swedish mothers and their children. Environ. Int. 73, 323–333.

Lewis, Ryan C., et al., 2015. Distribution and determinants of urinary biomarkers of exposure to organophosphate insecticides in Puerto Rican pregnant women. Sci. Total Environ. 512–513, 337–344.

Lim, Sinye, Ha, Mina, Hwang, Seung Sik, Son, Mia, Kwon, Ho Jang, 2015. "Disparities in children's blood lead and mercury levels according to community and individual socioeconomic positions. Int. J. Environ. Res. Public Health 12 (6), 6232–6248.

Llop, Sabrina, et al., 2017. Distributions and determinants of urinary biomarkers of organophosphate pesticide exposure in a prospective Spanish birth cohort study. Environ. Health: A Global Access Science Source 16 (1), 46.

Lu, C., Bravo, R., Caltabiano, L.M., Irish, R.M., 2011. "The presence of dialkylphosphates in fresh fruit Juices : implication for organophosphorus pesticide exposure and risk assessments. J. Toxicol. Environ. Health 68 (3), 209–227.

Lunder, Sonya, Hovander, Lotta, Athanassiadis, Ioannis, Bergman, Ake, 2010. Significantly higher polybrominated diphenyl ether levels in young U.S. Children than in their mothers. Environ. Sci. Technol. 44 (13), 5256–5262. Retrieved. http://www.ncbi.nlm.nih.gov/pubmed/20540541.

Magnus, Per, et al., 2016. Cohort profile update: the Norwegian mother and child cohort study (MoBa). Int. J. Epidemiol. 45 (2), 382–388.

Maitre, L., et al., 2018. Cohort profile: the human early life exposome (HELIX) study - a european population-based exposome cohort. BMJ Open (1), 1–17.

Mamsen, Linn Salto, et al., 2017. Concentration of perfluorinated compounds and cotinine in human foetal organs, placenta, and maternal plasma. Sci. Total Environ. 596–597, 97–105. Retrieved. https://doi.org/10.1016/j.scitotenv.2017.04.058.

Manzano-Salgado, Cyntia, B., et al., 2015. Transfer of perfluoroalkyl substances from mother to fetus in a Spanish birth cohort. Environ. Res. 142, 471–478. Retrieved. https://doi.org/10.1016/j.envres.2015.07.020.

Manzano-Salgado, Cyntia, B., et al., 2016. Variability of perfluoroalkyl substance concentrations in pregnant women by socio-demographic and dietary factors in a Spanish birth cohort. Environ. Int. 92–93, 357–365. Retrieved. https://doi.org/10.1016/j.envint.2016.04.004.

Michael, Marmot, Friel, Sharon, Bell, Ruth, Houweling, Tanja AJ., Taylor, Sebastian, 2008. Closing the gap in a generation: health equity through action on the social determinants of health. Lancet 372 (9650), 1661–1669.

Mondal, Debapriya, et al., 2014. Breastfeeding: a potential excretion route for mothers and implications for infant exposure to perfluoroalkyl acids. Environ. Health Perspect. 122 (2), 187–192.

Morck, Thit A., et al., 2015. PFAS concentrations in plasma samples from Danish school children and their mothers. Chemosphere 129, 203–209.

Morrens, Bert, et al., 2012. Social distribution of internal exposure to environmental pollution in flemish adolescents. Int. J. Hyg Environ. Health 215 (4), 474–481. Retrieved. https://doi.org/10.1016/j.ijheh.2011.10.008.

Nelson, Jessica W., Scammell, Madeleine Kangsen, Hatch, Elizabeth E., Webster, Thomas F., 2012. Social disparities in exposures to bisphenol a and polyfluoroalkyl chemicals: a cross-sectional study within NHANES 2003-2006. Environ. Health: A Global Access Science Source 11 (1), 10. Retrieved. http://www.scopus.com/inward/record.url?eid=2-s2.0-84859131389&partnerID=tZOtx3y1.

Padilla-Sánchez, Juan, A., Papadopoulou, Eleni, Poothong, Somrutai, Haug, Line S., 2017. Investigation of the best approach for assessing human exposure to poly- and perfluoroalkyl substances through indoor air. Environ. Sci. Technol. 51 (21), 12836–12843.

Pampel, Fred C., Krueger, P.M., Denney, J.T., 2010. Socioeconomic disparities in health behaviors. In: Annual Review of Sociology, vol. 36. pp. 349–370. Retrieved. http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3169799/.

Park, Gyeong-Hun, et al., 2018. Socioeconomic factors influencing cosmetic usage patterns. J. Expo. Sci. Environ. Epidemiol. 28, 242–250.

Royston, Patrick, White, Ian R., 2011. Multiple imputation by chained equations (MICE): implementation in Stata. J. Stat. Softw. 45 (4).

SAS Institute Principal Component Analysis. n.d, pp. 1–56 in. Retrieved. support.sas.com/publishing/pubcat/chaps/55129.pdf.

Schober, S.E., et al., 2003. Blood mercury levels in US children and women of childbearing age, 1999-2000. Jama 289 (13), 1667–1674. Retrieved. http://www.ncbi.nlm.nih.gov/pubmed/12672735.

Sokoloff, Katia, et al., 2016. Determinants of urinary concentrations of dialkyl phosphates among pregnant women in Canada - results from the MIREC study. Environ. Int. 94, 133–140. Retrieved. https://doi.org/10.1016/j.envint.2016.05.015.

TRPfS, Computing, 2016. R: A Language and Environment for Statistical Computing. R Foundation for Statistical Computing, Vienna, Austria 2016.

Tyrrell, Jessica, Melzer, David, Henley, William, Galloway, Tamara S., Osborne, Nicholas J., 2013. Associations between socioeconomic status and environmental toxicant concentrations in adults in the USA: NHANES 2001-2010. Environ. Int. 59, 328–335. Retrieved. https://doi.org/10.1016/j.envint.2013.06.017.

Vrijheid, M., et al., 2014. The human early-life exposome (HELIX): project rationale and design. Environ. Health Perspect. 122 (6), 535–545.

Vrijheid, Martine, et al., 2012. Socioeconomic status and exposure to multiple environmental pollutants during pregnancy: evidence for environmental inequity? J. Epidemiol. Community Health 66 (2), 106–113. Retrieved. http://jech.bmj.com/lookup/doi/10.1136/jech.2010.117408.

Vrijheid, Martine, Casas, Maribel, Gascon, Mireia, Valvi, Damaskini, Nieuwenhuijsen, Mark, 2016. Environmental pollutants and child health-A review of recent concerns. Int. J. Hyg Environ. Health 219 (4–5), 331–342. Retrieved. https://doi.org/10.1016/j.ijheh.2016.05.001.

Weerasekera, Gayanga, et al., 2009. A mass spectrometry-based method to measure dialkylphosphate degradation products of organophosphorous insecticides in dust and orange juice †. J. Environ. Monit. 11, 1345–1351.

Wright, John, et al., 2013. Cohort profile: the born in Bradford multi-ethnic family cohort study. Int. J. Epidemiol. 42 (4), 978–991.

Supplementary Material
Paper III

Table S1. Matrix used for each biomarker and study population (pregnant women by cohort and children)

Population /Cohort	Persistent pesticides	PFASs	Metals	Phthalates metabolites	Phenols	OP pesticide metabolites
Sub-cohort pregnant women						
BIB	Serum	Serum	Whole blood	Urine	Urine	Urine
EDEN	Serum	Serum	Whole blood	Urine	Urine	Urine
KANC	-	Whole blood	Whole blood	-	-	-
MOBA	Plasma	Plasma	Whole blood	Urine	Urine	Urine
RHEA	Serum	Serum	Whole blood	Urine	Urine	Urine
INMA	Serum	Plasma	Cord blood (Hg)	Urine	Urine	Urine
Sub-cohort children	Serum	Plasma	Whole blood	Urine	Urine	Urine

Table S2. Time when maternal samples were collected during pregnancy

Cohort	Collection Year(s)	Persistent Pesticides	PFASs	Metals	Phthalates metabolites	Phenols	OP pesticide metabolites
BIB	2007-08	3rd T	3rd T	3rd T	3rd T	3rd T	3rd T
EDEN	2003-05	2nd T	2nd T	2nd T	2nd T	2nd T	2nd T
KANC	2006-08	-	Birth	Birth	-	-	-
MOBA	2004-07	2nd T	2nd T	2nd T	2nd T	2nd T	2nd T
RHEA	2007-08	1st T	1st T	1st T	1st T	1st T	1st T
INMA	2004-06	1st T	1st T	Birth (Hg only)	3rd T	3rd T	3rd T

T = trimester

Table S3. Spearman correlations between 10 samples analyzed in NIPH and INMA labs – sub-cohort pregnant women

							NIPH					
INMA	PFOA	PFOS	PFHxS	PFNA	MEP	MiBP	MnBP	MBzP	MEHP	MEHHP	MEOHP	Cotinine
PFOA	0.65	-	-	-	-	-	-	-	-	-	-	-
PFOS	-	0.85	-	-	-	-	-	-	-	-	-	-
PFHxS	-	-	0.90	-	-	-	-	-	-	-	-	-
PFNA	-	-	-	0.50	-	-	-	-	-	-	-	-
MEP	-	-	-	-	0.95	-	-	-	-	-	-	-
MiBP	-	-	-	-	-	0.90	-	-	-	-	-	-
MnBP	-	-	-	-	-	-	0.89	-	-	-	-	-
MBzP	-	-	-	-	-	-	-	0.97	-	-	-	-
MEHP	-	-	-	-	-	-	-	-	0.68	-	-	-
MEHHP	-	-	-	-	-	-	-	-	-	0.95	-	-
MEOHP	-	-	-	-	-	-	-	-	-	-	0.79	-
Cotinine	-	-	-	-	-	-	-	-	-	-	-	0.95

Table S4. Spearman correlations between 10 samples analyzed in NIPH and EDEN labs – sub-cohort pregnant women

	NIPH						
EDEN	MEPA	ETPA	PRPA	BUPA	BPA	OXBE	TRCS
MEPA	1.0	-	-	-	-	-	-
ETPA	-	0.98	-	-	-	-	-
PRPA	-	-	0.90	-	-	-	-
BUPA	-	-	-	1.0	-	-	-
BPA	-	-	-	-	0.90	-	-
OXBE	-	-	-	-	-	0.91	-
TRCS	-	-	-	-	-	-	0.99

Table S5. Indicators of Socioeconomic Position (SEP) by sub-cohort

SEP Indicator	**Cohort** percent (N)						
	BiB	**EDEN**	**INMA**	**KANC**	**MoBa**	**Rhea**	**All cohorts**
Maternal Education							
Low (primary)	48.1 (87)	6.1 (12)	23.9 (53)	6.3 (12)	0 (0.0)	4.6 (9)	13.8(173)
Middle (secondary)	17.7 (32)	37.2 (73)	41.4 (92)	35.7 (71)	21.0 (55)	55.8 (110)	34.4(433)
High (university or higher)	34.3 (62)	56.6 (111)	34.7 (77)	58.3 (116)	79.0 (207)	39.6 (78)	51.8(651)
Maternal Working Status							
Unemployed	37.7 (43)	16.2 (32)	8.6 (19)	16.6 (33)	4.2 (11)	35.4 (69)	17.4(207)
Employed	62.3 (71)	83.8 (166)	91.4 (201)	83.4 (166)	95.8 (251)	64.6 (126)	82.6(981)
Family Affluence Scale							
Low	27.5 (56)	1.0 (2)	6.8 (15)	14.4 (29)	1.5 (4)	15.1 (30)	10.5(136)
Middle	43.1 (88)	21.3 (42)	39.6 (87)	53.2 (107)	26.8 (73)	51.3 (102)	38.6(499)
High	29.4 (60)	77.7 (153)	53.6 (118)	32.3 (65)	71.7 (195)	33.7 (67)	50.9(658)

Table S6. Concentrations of environmental contaminants in blood and urine samples from mothers and children in the HELIX sub-cohort

Compound		Pregnant Women Samples						Children Samples					
Abbreviation	**Unit**	**N**	**%>LOD**	**GM**	**p25**	**p50**	**p75**	**N**	**%>LOD**	**GM**	**p25**	**p50**	**p75**
DDE	ng/g lipid	1048	99.9	55.76	25.88	52.29	110.68	1279	79.8	24.73	11.55	21.75	45.58
DDT	ng/g lipid	826	65.6	1.49	0.82	1.33	3.05	1279	100	0.49	0.28	0.71	1.65
HCB	ng/g lipid	1048	99.1	9.07	5.59	8.16	12.95	1279	99.9	8.88	6.27	8.19	11.37
PBDE 47	ng/g lipid	684	80.8	0.47	0.27	0.43	0.75	1279	90.8	0.21	0.15	0.23	0.37
PBDE 153	ng/g lipid	648	72.9	0.24	0.03	0.45	0.66	1279	54.4	0.11	0.03	0.16	0.42
PCB 118	ng/g lipid	829	79.1	2.79	1.57	2.64	4.82	1279	99.8	2.14	1.51	1.98	2.94
PCB 138	ng/g lipid	1048	96.5	9.18	5.54	9.10	16.13	1279	99.8	5.40	3.36	5.37	8.70
PCB 153	ng/g lipid	1048	99.6	17.89	10.39	17.62	30.48	1279	100	11.87	7.28	11.65	18.61
PCB 170	ng/g lipid	826	99.5	3.6	1.84	3.69	7.06	1279	90.7	1.09	0.56	1.26	2.75
PCB 180	ng/g lipid	1048	97.6	10.29	5.78	10.38	18.54	1279	99.2	3.61	1.62	3.68	8.02
PFOA	µg/L	1240	99.7	2.08	1.38	2.30	3.34	1301	100	1.53	1.19	1.55	1.97
PFNA	µg/L	1240	97.9	0.62	0.43	0.69	1.08	1301	99.5	0.46	0.30	0.47	0.72
PFUnDA	µg/L	1032	95.4	0.15	0.10	0.19	0.29	1301	68.6	0.04	0.02	0.03	0.09

PFHxS	µg/L	1240	97.5	0.54	0.31	0.55	0.91	1301	99.7	0.33	0.19	0.36	0.61
PFOS	µg/L	1240	100	6.14	4.12	6.41	9.63	1301	99.8	1.95	1.26	2.03	3.22
As	µg/L	833	58.5	1.93	0.28	1.19	2.27	1298	67.1	1.06	0.28	1.37	2.34
Cd	µg/L	833	99.6	0.23	0.15	0.22	0.33	1298	86.5	0.05	0.04	0.07	0.09
Hg	µg/L	1020	98.9	1.8	0.98	1.90	3.45	1298	97.7	0.79	0.42	0.86	1.75
Mn	µg/L	833	64.4	11.15	8.46	11.10	14.30	1298	99.8	8.68	7.13	8.57	10.50
Pb	µg/L	833	100	9.87	7.14	9.66	13.20	1298	100	8.54	6.39	8.53	11.10
MEP	µg/g creatinine	1080	99.0	191.05	72.12	178.94	468.40	1301	100	36.79	15.04	32.77	79.45
MiBP	µg/g creatinine	1088	99.9	38.88	23.30	38.69	60.63	1301	100	41.80	24.57	40.27	71.47
MnBP	µg/g creatinine	1089	100	30.92	18.35	29.64	47.28	1301	100	23.96	14.48	22.76	38.81
MBzP	µg/g creatinine	1088	99.7	7.83	3.63	7.33	15.25	1300	99.9	5.11	2.67	4.82	8.75
MEHP	µg/g creatinine	1085	99.5	8.4	4.42	8.73	15.25	1260	96.8	2.90	1.56	2.86	5.11
MEHHP	µg/g creatinine	1089	100	18.94	10.53	18.19	31.19	1298	99.8	19.99	11.45	19.40	33.19
MEOHP	µg/g creatinine	1089	100	14.39	8.29	14.08	23.66	1300	99.9	12.35	7.06	12.26	20.52
MECPP	µg/g creatinine	913	99.9	36.05	22.39	33.57	52.32	1300	99.9	35.01	19.88	32.93	57.79
oh-MiNP	µg/g creatinine	914	92.6	0.85	0.61	0.91	1.47	1301	100	5.73	3.12	5.00	9.26
oxo-MiNP	µg/g creatinine	914	95.7	1.01	0.62	1.03	1.75	1301	100	3.06	1.68	2.72	4.96

MEPA	µg/g creatinine	815	99.8	133.5	39.51	166.78	389.41	1299	99.7	10.29	3.08	6.35	24.26
ETPA	µg/g creatinine	817	97.4	5.73	1.14	6.26	26.69	1298	99.3	0.84	0.41	0.66	1.24
PRPA	µg/g creatinine	1083	97.3	28.79	8.87	44.22	134.18	1284	67.3	0.25	0.02	0.24	1.61
BPA	µg/g creatinine	1084	99.4	3.32	1.56	2.82	6.59	1289	98.3	4.17	2.31	3.83	7.00
BUPA	µg/g creatinine	1083	97.0	2.27	0.36	3.37	14.38	1296	96.6	0.09	0.05	0.07	0.14
OXBE	µg/g creatinine	1085	99.3	7.41	1.46	4.90	27.45	1301	99.9	2.57	0.79	2.05	6.66
TCS	µg/g creatinine	1085	98.5	10.29	1.50	6.28	79.69	1301	100	0.77	0.28	0.60	1.51
DMP	µg/g creatinine	1080	90.8	7.17	4.13	8.37	16.41	1295	49.3	1.13	0.30	0.36	4.66
DMTP	µg/g creatinine	1084	88.9	3.77	2.05	4.96	12.35	1300	90.4	2.26	1.23	2.81	6.27
DEP	µg/g creatinine	1082	97.8	3.34	1.86	3.33	6.44	1299	80.9	1.27	0.43	1.82	4.71
DETP	µg/g creatinine	1037	50.0	0.61	0.12	0.58	2.56	1280	43.5	0.38	0.10	0.13	1.68

n analysed: samples with biomarker measurements and fat/creatinine measurements
%>LOD: % of the biomarker measurements with concentrations reported greater than the limit of detection (LOD)

Table S7. Adjusted geometric mean ratios, 95% confidence intervals and p-values for complete case and imputed regression analysis of maternal education with 41 biomarkers for chemical contaminants in pregnant women.

Pregnant Women			
	Maternal Education (complete case, adjusted)		Maternal Education (imputed, adjusted)
Chemical	GM ratio (95% CI)	N	GM ratio (95% CI)
DDE		991	
low	1.01 (0.84, 1.21)		1.01 (0.84, 1.22)
middle	0.98 (0.88, 1.1)		0.97 (0.86, 1.08)
high	reference		reference
DDT		774	
low	0.96 (0.71, 1.28)		0.95 (0.74, 1.21)
middle	0.99 (0.84, 1.17)		0.97 (0.81, 1.17)
high	reference		reference
HCB		991	
low	1.03 (0.92, 1.16)		1.02 (0.92, 1.13)
middle	1.05 (0.98, 1.12)		1.02 (0.95, 1.09)
high	reference		reference
PBDE47		637	
low	0.86 (0.66, 1.12)		0.98 (0.75, 1.3)
middle	1.04 (0.88, 1.22)		1.06 (0.86, 1.31)
high	reference		reference
PBDE153		601	
low	0.89 (0.52, 1.51)		0.99 (0.6, 1.64)
middle	0.72 (0.5, 1.03)		0.92 (0.65, 1.3)
high	reference		reference
PCB118		777	
low	0.97 (0.85, 1.09)		0.98 (0.88, 1.09)
middle	0.96 (0.89, 1.03)		0.95 (0.88, 1.02)
high	reference		reference
PCB138		991	
low	0.93 (0.85, 1.01)		0.93 (0.85, 1.02)
middle	0.96 (0.9, 1.02)		0.96 (0.9, 1.03)
high	reference		reference
PCB153		991	
low	0.93 (0.86, 1.02)		0.93 (0.86, 1.02)
middle	0.96 (0.91, 1.02)		0.97 (0.91, 1.03)
high	reference		reference
PCB170		774	
low	0.98 (0.86, 1.13)		0.94 (0.81, 1.1)
middle	0.98 (0.9, 1.07)		0.95 (0.86, 1.05)
high	reference		reference
PCB180		991	
low	0.96 (0.87, 1.06)		0.95 (0.86, 1.05)

middle	0.97 (0.91, 1.03)	0.97 (0.9, 1.05)
high	reference	reference
PFOA	1176	
low	1.02 (0.92, 1.13)	1.01 (0.91, 1.13)
middle	1 (0.95, 1.06)	1 (0.94, 1.06)
high	reference	reference
PFNA	1176	
low	1 (0.9, 1.1)	0.99 (0.9, 1.1)
middle	0.99 (0.93, 1.05)	0.99 (0.93, 1.05)
high	reference	reference
PFUnDA	973	
low	0.85 (0.76, 0.95)	0.9 (0.8, 1)
middle	0.88 (0.82, 0.95)	0.92 (0.86, 0.99)
high	reference	reference
PFHxS	1176	
low	1.13 (0.98, 1.3)	1.12 (0.97, 1.29)
middle	1.01 (0.93, 1.09)	1.01 (0.93, 1.09)
high	reference	reference
PFOS	1176	
low	1.08 (0.99, 1.18)	1.07 (0.98, 1.18)
middle	1.01 (0.95, 1.08)	1.01 (0.95, 1.07)
high	reference	reference
As	799	
low	0.64 (0.45, 0.91)	0.81 (0.6, 1.11)
middle	0.76 (0.63, 0.92)	0.84 (0.69, 1.02)
high	reference	reference
Cd	799	
low	1.41 (1.15, 1.72)	1.3 (1.12, 1.5)
middle	1.22 (1.1, 1.36)	1.17 (1.06, 1.29)
high	reference	reference
Hg	982	
low	0.79 (0.68, 0.92)	0.83 (0.72, 0.95)
middle	0.85 (0.78, 0.93)	0.87 (0.79, 0.95)
high	reference	reference
Mn	799	
low	0.98 (0.91, 1.07)	1 (0.93, 1.07)
middle	1.01 (0.96, 1.05)	1.01 (0.97, 1.05)
high	reference	reference
Pb	799	
low	1.15 (0.99, 1.34)	1.07 (0.96, 1.19)
middle	1.07 (1, 1.16)	1.04 (0.98, 1.1)
high	reference	reference
MBzP	1029	
low	0.95 (0.77, 1.17)	0.93 (0.71, 1.21)
middle	1.03 (0.89, 1.19)	1.01 (0.84, 1.23)
high	reference	reference
MECPP	857	

low	1.03 (0.84, 1.25)	1.04 (0.88, 1.22)
middle	1.09 (0.97, 1.21)	1.03 (0.93, 1.14)
high	reference	reference
MEHHP	1030	
low	1.03 (0.86, 1.25)	1.06 (0.88, 1.27)
middle	1.01 (0.89, 1.14)	1.02 (0.91, 1.16)
high	reference	reference
MEHP	1026	
low	1.02 (0.84, 1.24)	1.02 (0.85, 1.22)
middle	1.03 (0.91, 1.17)	1.03 (0.91, 1.15)
high	reference	reference
MEOHP	1030	
low	1.04 (0.86, 1.25)	1.04 (0.87, 1.25)
middle	1.01 (0.9, 1.14)	1.02 (0.9, 1.14)
high	reference	reference
MEP	1021	
low	1.14 (0.88, 1.47)	1.11 (0.87, 1.43)
middle	1.16 (0.96, 1.41)	1.12 (0.93, 1.33)
high	reference	reference
oh-MiNP	858	
low	0.92 (0.8, 1.06)	0.95 (0.8, 1.13)
middle	0.97 (0.86, 1.1)	0.97 (0.87, 1.09)
high	reference	reference
oxo-MiNP	858	
low	0.99 (0.81, 1.22)	0.97 (0.78, 1.21)
middle	1.02 (0.89, 1.17)	1.01 (0.87, 1.17)
high	reference	reference
MiBP	1030	
low	0.96 (0.83, 1.11)	0.97 (0.85, 1.12)
middle	0.9 (0.81, 0.99)	0.92 (0.83, 1.01)
high	reference	reference
MnBP	1030	
low	0.92 (0.79, 1.07)	0.92 (0.79, 1.07)
middle	0.99 (0.87, 1.13)	0.98 (0.86, 1.12)
high	reference	reference
MEPA	766	
low	0.53 (0.38, 0.74)	0.52 (0.36, 0.74)
middle	0.98 (0.73, 1.32)	0.96 (0.73, 1.27)
high	reference	reference
ETPA	768	
low	0.49 (0.31, 0.78)	0.59 (0.36, 0.95)
middle	0.83 (0.6, 1.16)	0.9 (0.66, 1.24)
high	reference	reference
PRPA	1024	
low	0.47 (0.33, 0.68)	0.52 (0.36, 0.76)
middle	0.88 (0.67, 1.15)	0.92 (0.7, 1.21)
high	reference	reference

BPA	1025	
low	0.95 (0.79, 1.14)	0.95 (0.78, 1.16)
middle	0.85 (0.74, 0.97)	0.86 (0.74, 0.99)
high	reference	reference
BUPA	1024	
low	0.37 (0.24, 0.58)	0.49 (0.3, 0.79)
middle	0.78 (0.58, 1.06)	0.85 (0.63, 1.15)
high	reference	reference
OXBE	1026	
low	0.71 (0.44, 1.16)	0.75 (0.47, 1.2)
middle	1.04 (0.73, 1.48)	1.05 (0.75, 1.48)
high	reference	reference
TCS	1026	
low	0.9 (0.52, 1.54)	0.97 (0.58, 1.61)
middle	0.94 (0.64, 1.4)	0.97 (0.67, 1.4)
high	reference	reference
DEP	1023	
low	0.96 (0.79, 1.16)	0.95 (0.8, 1.13)
middle	0.9 (0.79, 1.03)	0.91 (0.8, 1.03)
high	reference	reference
DETP	980	
low	0.76 (0.51, 1.13)	0.73 (0.48, 1.11)
middle	0.92 (0.68, 1.25)	0.87 (0.65, 1.17)
high	reference	reference
DMP	1021	
low	0.76 (0.64, 0.91)	0.79 (0.67, 0.94)
middle	0.82 (0.71, 0.94)	0.85 (0.75, 0.97)
high	reference	reference
DMTP	1025	
low	0.66 (0.5, 0.86)	0.7 (0.54, 0.9)
middle	0.74 (0.61, 0.89)	0.78 (0.65, 0.94)
high	reference	reference

For interpretation: GMR values < 1 signify lower exposure and GMR values > 1 signify higher exposure in comparison to the reference category.

Table S8. Adjusted geometric mean ratios, 95% confidence intervals and p-values for complete case and imputed regression analysis of maternal employment status with 41 biomarkers for chemical contaminants in pregnant women.

Pregnant Women			
	Maternal Employment Status (complete case, adjusted)		Maternal Employment Status (imputed, adjusted)
Chemical	GM ratio (95% CI)	N	GM ratio (95% CI)
DDE		935	
unemployed	1.26 (1.06, 1.5)		1.21 (1.03, 1.42)
employed	reference		reference
DDT		720	
unemployed	1.24 (0.98, 1.56)		1.17 (0.95, 1.43)
employed	reference		reference
HCB		935	
unemployed	0.97 (0.91, 1.05)		0.99 (0.92, 1.06)
employed	reference		reference
PBDE47		583	
unemployed	0.99 (0.8, 1.23)		1 (0.8, 1.24)
employed	reference		reference
PBDE153		548	
unemployed	1.01 (0.62, 1.64)		0.99 (0.66, 1.47)
employed	reference		reference
PCB118		723	
unemployed	0.98 (0.91, 1.06)		1 (0.92, 1.09)
employed	reference		reference
PCB138		935	
unemployed	0.94 (0.87, 1.01)		0.95 (0.88, 1.03)
employed	reference		reference
PCB153		935	
unemployed	0.97 (0.89, 1.04)		0.97 (0.9, 1.04)
employed	reference		reference
PCB170		720	
unemployed	0.98 (0.88, 1.09)		0.97 (0.86, 1.08)
employed	reference		reference
PCB180		935	
unemployed	0.97 (0.88, 1.06)		0.97 (0.88, 1.06)
employed	reference		reference
PFOA		1120	
unemployed	0.89 (0.83, 0.96)		0.89 (0.83, 0.96)
employed	reference		reference
PFNA		1120	
unemployed	0.92 (0.86, 0.99)		0.91 (0.85, 0.98)
employed	reference		reference

PFUnDA	919	
unemployed	0.91 (0.84, 0.99)	0.92 (0.84, 1)
employed	reference	reference
PFHxS	1120	
unemployed	0.89 (0.81, 0.98)	0.87 (0.78, 0.97)
employed	reference	reference
PFOS	1120	
unemployed	0.92 (0.85, 0.99)	0.91 (0.84, 0.97)
employed	reference	reference
As	795	
unemployed	0.83 (0.67, 1.03)	0.9 (0.73, 1.11)
employed	reference	reference
Cd	795	
unemployed	1.08 (0.93, 1.26)	1.08 (0.95, 1.23)
employed	reference	reference
Hg	975	
unemployed	0.89 (0.8, 1)	0.9 (0.81, 1.01)
employed	reference	reference
Mn	795	
unemployed	1 (0.95, 1.06)	1 (0.95, 1.06)
employed	reference	reference
Pb	795	
unemployed	1.03 (0.95, 1.12)	1.01 (0.93, 1.09)
employed	reference	reference
MBzP	972	
unemployed	1.01 (0.84, 1.22)	1 (0.77, 1.29)
employed	reference	reference
MECPP	802	
unemployed	1.02 (0.89, 1.18)	1.06 (0.91, 1.23)
employed	reference	reference
MEHHP	973	
unemployed	0.99 (0.84, 1.17)	0.99 (0.85, 1.15)
employed	reference	reference
MEHP	970	
unemployed	0.94 (0.8, 1.1)	0.98 (0.84, 1.14)
employed	reference	reference
MEOHP	973	
unemployed	1.02 (0.87, 1.2)	1.03 (0.88, 1.2)
employed	reference	reference
MEP	964	
unemployed	1.03 (0.82, 1.29)	1.04 (0.85, 1.26)
employed	reference	reference
oh-MiNP	803	
unemployed	0.91 (0.78, 1.07)	0.95 (0.83, 1.1)
employed	reference	reference
oxo-MiNP	803	
unemployed	0.92 (0.77, 1.1)	0.94 (0.79, 1.11)

employed	reference	reference
MiBP	973	
unemployed	0.94 (0.83, 1.06)	0.95 (0.84, 1.08)
employed	reference	reference
MnBP	973	
unemployed	0.97 (0.83, 1.13)	0.97 (0.85, 1.11)
employed	reference	reference
MEPA	709	
unemployed	1.13 (0.77, 1.65)	0.98 (0.69, 1.39)
employed	reference	reference
ETPA	711	
unemployed	0.71 (0.47, 1.08)	0.8 (0.55, 1.15)
employed	reference	reference
PRPA	968	
unemployed	1 (0.68, 1.47)	0.94 (0.64, 1.36)
employed	reference	reference
BPA	968	
unemployed	0.98 (0.81, 1.18)	0.97 (0.81, 1.15)
employed	reference	reference
BUPA	967	
unemployed	0.66 (0.44, 1)	0.75 (0.5, 1.11)
employed	reference	reference
OXBE	969	
unemployed	1.15 (0.74, 1.8)	1.06 (0.7, 1.59)
employed	reference	reference
TCS	969	
unemployed	0.73 (0.45, 1.2)	0.8 (0.52, 1.22)
employed	reference	reference
DEP	966	
unemployed	0.95 (0.82, 1.11)	0.97 (0.84, 1.13)
employed	reference	reference
DETP	924	
unemployed	1 (0.69, 1.45)	0.97 (0.67, 1.4)
employed	reference	reference
DMP	964	
unemployed	0.91 (0.77, 1.07)	0.97 (0.83, 1.13)
employed	reference	reference
DMTP	968	
unemployed	0.82 (0.65, 1.04)	0.88 (0.7, 1.1)
employed	reference	reference

For interpretation: GMR values < 1 signify lower exposure and GMR values > 1 signify higher exposure in comparison to the reference category.

Table S9. Adjusted geometric mean ratios, 95% confidence intervals and p-values for complete case and imputed regression analysis of maternal education with 41 biomarkers for chemical contaminants in children (6-12 years).

Children			
	Maternal Education (complete case, adjusted models)		Maternal Education (imputed, adjusted models)
Chemical	GM ratio (95% CI)	N	GM ratio (95% CI)
DDE		1210	
low	0.7 (0.59, 0.82)		0.72 (0.61, 0.86)
middle	0.76 (0.69, 0.84)		0.77 (0.69, 0.85)
high	reference		reference
DDT		1210	
low	0.79 (0.65, 0.96)		0.82 (0.68, 1)
middle	0.84 (0.73, 0.96)		0.84 (0.73, 0.96)
high	reference		reference
HCB		1210	
low	0.87 (0.81, 0.92)		0.88 (0.83, 0.94)
middle	0.89 (0.85, 0.92)		0.89 (0.85, 0.93)
high	reference		reference
PBDE47		1210	
low	0.79 (0.64, 0.98)		0.81 (0.65, 1.01)
middle	0.92 (0.82, 1.03)		0.93 (0.83, 1.04)
high	reference		reference
PBDE153		1210	
low	0.92 (0.65, 1.32)		0.91 (0.65, 1.29)
middle	0.86 (0.69, 1.06)		0.86 (0.7, 1.06)
high	reference		reference
PCB118		1210	
low	0.89 (0.83, 0.96)		0.9 (0.84, 0.96)
middle	0.87 (0.83, 0.91)		0.88 (0.83, 0.92)
high	reference		reference
PCB138		1210	
low	0.79 (0.73, 0.86)		0.8 (0.73, 0.87)
middle	0.82 (0.77, 0.87)		0.82 (0.77, 0.88)
high	reference		reference
PCB153		1210	
low	0.79 (0.73, 0.85)		0.8 (0.74, 0.87)
middle	0.82 (0.78, 0.87)		0.83 (0.78, 0.88)
high	reference		reference
PCB170		1210	
low	0.63 (0.54, 0.74)		0.66 (0.56, 0.76)
middle	0.72 (0.64, 0.8)		0.72 (0.65, 0.81)
high	reference		reference
PCB180		1210	
low	0.62 (0.53, 0.72)		0.64 (0.55, 0.74)

middle	0.72 (0.65, 0.8)	0.72 (0.65, 0.8)
high	reference	reference
PFOA	1232	
low	0.82 (0.73, 0.91)	0.83 (0.75, 0.92)
middle	0.88 (0.82, 0.94)	0.88 (0.82, 0.94)
high	reference	reference
PFNA	1232	
low	0.75 (0.62, 0.91)	0.76 (0.62, 0.92)
middle	0.85 (0.76, 0.96)	0.85 (0.75, 0.96)
high	reference	reference
PFUnDA	1232	
low	0.62 (0.48, 0.8)	0.64 (0.5, 0.81)
middle	0.72 (0.6, 0.85)	0.71 (0.6, 0.85)
high	reference	reference
PFHxS	1232	
low	0.83 (0.7, 0.98)	0.82 (0.69, 0.98)
middle	0.81 (0.72, 0.91)	0.8 (0.72, 0.9)
high	reference	reference
PFOS	1232	
low	0.8 (0.69, 0.94)	0.84 (0.72, 0.99)
middle	0.82 (0.74, 0.91)	0.83 (0.74, 0.92)
high	reference	reference
As	1230	
low	0.64 (0.51, 0.81)	0.66 (0.52, 0.82)
middle	0.79 (0.67, 0.92)	0.79 (0.68, 0.92)
high	reference	reference
Cd	1230	
low	1.01 (0.88, 1.16)	0.99 (0.86, 1.13)
middle	0.96 (0.88, 1.04)	0.96 (0.88, 1.04)
high	reference	reference
Hg	1230	
low	0.68 (0.57, 0.8)	0.7 (0.6, 0.81)
middle	0.76 (0.68, 0.84)	0.76 (0.68, 0.84)
high	reference	reference
Mn	1230	
low	0.96 (0.92, 1)	0.96 (0.92, 1)
middle	1 (0.97, 1.03)	1 (0.97, 1.03)
high	reference	reference
Pb	1230	
low	1.1 (1.01, 1.2)	1.1 (1.01, 1.2)
middle	1.07 (1.02, 1.12)	1.06 (1.02, 1.12)
high	reference	reference
MBzP	1231	
low	1.07 (0.9, 1.26)	1.04 (0.89, 1.22)
middle	1.05 (0.94, 1.16)	1.04 (0.94, 1.15)
high	reference	reference
MECPP	1231	

low	1.06 (0.92, 1.21)	1.06 (0.93, 1.21)
middle	1.06 (0.98, 1.14)	1.06 (0.98, 1.14)
high	reference	reference
MEHHP	1229	
low	1.04 (0.91, 1.2)	1.05 (0.92, 1.2)
middle	1.06 (0.98, 1.15)	1.06 (0.98, 1.14)
high	reference	reference
MEHP	1192	
low	1.11 (0.95, 1.3)	1.09 (0.94, 1.27)
middle	1.08 (0.98, 1.19)	1.07 (0.97, 1.18)
high	reference	reference
MEOHP	1231	
low	1.04 (0.91, 1.19)	1.05 (0.92, 1.2)
middle	1.07 (0.99, 1.16)	1.06 (0.99, 1.15)
high	reference	reference
MEP	1232	
low	1.28 (0.96, 1.69)	1.3 (0.99, 1.7)
middle	1.22 (1.01, 1.46)	1.21 (1.01, 1.45)
high	reference	reference
oh-MiNP	1232	
low	0.96 (0.76, 1.21)	0.99 (0.79, 1.24)
middle	1.01 (0.86, 1.18)	1.01 (0.87, 1.18)
high	reference	reference
oxo-MiNP	1232	
low	0.89 (0.72, 1.1)	0.89 (0.72, 1.1)
middle	0.98 (0.84, 1.15)	0.98 (0.84, 1.14)
high	reference	reference
MiBP	1232	
low	1.15 (0.96, 1.37)	1.13 (0.94, 1.35)
middle	1.09 (0.97, 1.24)	1.09 (0.97, 1.23)
high	reference	reference
MnBP	1232	
low	0.99 (0.83, 1.18)	0.99 (0.83, 1.18)
middle	1.02 (0.91, 1.15)	1.02 (0.91, 1.15)
high	reference	reference
MEPA	1230	
low	1.38 (0.87, 2.21)	1.29 (0.8, 2.06)
middle	1.04 (0.81, 1.33)	1.01 (0.78, 1.29)
high	reference	reference
ETPA	1230	
low	0.95 (0.7, 1.29)	0.92 (0.66, 1.28)
middle	0.91 (0.76, 1.08)	0.91 (0.75, 1.09)
high	reference	reference
PRPA	1216	
low	1.03 (0.53, 2.01)	1.01 (0.51, 1.99)
middle	1.03 (0.68, 1.56)	0.99 (0.64, 1.51)
high	reference	reference

BPA	1221	
low	0.81 (0.68, 0.96)	0.81 (0.68, 0.97)
middle	0.94 (0.83, 1.07)	0.95 (0.83, 1.09)
high	reference	reference
BUPA	1228	
low	1.08 (0.82, 1.44)	1.08 (0.83, 1.41)
middle	0.94 (0.81, 1.1)	0.95 (0.81, 1.1)
high	reference	reference
OXBE	1232	
low	0.93 (0.61, 1.42)	0.94 (0.6, 1.48)
middle	1.2 (0.91, 1.59)	1.17 (0.89, 1.55)
high	reference	reference
TCS	1232	
low	1 (0.65, 1.54)	0.99 (0.66, 1.5)
middle	0.93 (0.73, 1.18)	0.95 (0.75, 1.2)
high	reference	reference
DEP	1230	
low	0.8 (0.58, 1.11)	0.74 (0.52, 1.05)
middle	0.89 (0.73, 1.09)	0.86 (0.7, 1.06)
high	reference	reference
DETP	1212	
low	1.01 (0.66, 1.53)	0.96 (0.64, 1.44)
middle	0.77 (0.6, 0.98)	0.77 (0.6, 0.98)
high	reference	reference
DMP	1226	
low	0.81 (0.57, 1.16)	0.81 (0.57, 1.15)
middle	0.86 (0.68, 1.08)	0.85 (0.68, 1.06)
high	reference	reference
DMTP	1231	
low	0.79 (0.61, 1.01)	0.8 (0.62, 1.03)
middle	0.83 (0.71, 0.98)	0.84 (0.71, 0.98)
high	reference	reference

For interpretation: GMR values < 1 signify lower exposure and GMR values > 1 signify higher exposure in comparison to the reference category.

Table S10. Adjusted geometric mean ratios, 95% confidence intervals and p-values for complete case and imputed regression analysis of family affluence scale with 41 biomarkers for chemical contaminants in children (6-12 years).

Children			
	Family Affluence Scale (complete case, adjusted)		Family Affluence Scale (imputed, adjusted)
Chemical	GM ratio (95% CI)	N	GM ratio (95% CI)
DDE		1210	
low	0.86 (0.71, 1.04)		0.84 (0.7, 1.02)
middle	1.1 (0.99, 1.22)		1.06 (0.96, 1.18)
high	reference		reference
DDT		1210	
low	1.04 (0.83, 1.31)		1.04 (0.83, 1.3)
middle	1.07 (0.94, 1.22)		1.07 (0.94, 1.21)
high	reference		reference
HCB		1210	
low	0.91 (0.84, 0.97)		0.91 (0.85, 0.98)
middle	1 (0.95, 1.04)		0.99 (0.94, 1.03)
high	reference		reference
PBDE47		1210	
low	0.99 (0.81, 1.22)		1.02 (0.84, 1.25)
middle	1.02 (0.92, 1.15)		1.03 (0.92, 1.15)
high	reference		reference
PBDE153		1210	
low	1.14 (0.8, 1.63)		1.18 (0.83, 1.67)
middle	0.88 (0.72, 1.07)		0.87 (0.72, 1.07)
high	reference		reference
PCB118		1210	
low	0.96 (0.88, 1.04)		0.95 (0.88, 1.02)
middle	1 (0.95, 1.06)		1 (0.95, 1.05)
high	reference		reference
PCB138		1210	
low	0.89 (0.81, 0.98)		0.88 (0.81, 0.97)
middle	1.01 (0.95, 1.08)		1 (0.94, 1.06)
high	reference		reference
PCB153		1210	
low	0.91 (0.83, 0.99)		0.9 (0.83, 0.98)
middle	1 (0.94, 1.07)		0.99 (0.94, 1.06)
high	reference		reference
PCB170		1210	
low	0.76 (0.64, 0.9)		0.75 (0.64, 0.89)
middle	1.02 (0.91, 1.14)		1 (0.9, 1.12)
high	reference		reference
PCB180		1210	
low	0.8 (0.69, 0.93)		0.79 (0.68, 0.92)

middle	1.01 (0.91, 1.12)	0.98 (0.89, 1.09)
high	reference	reference
PFOA	1232	
low	0.91 (0.82, 1)	0.9 (0.82, 0.99)
middle	0.96 (0.89, 1.02)	0.95 (0.89, 1.01)
high	reference	reference
PFNA	1232	
low	0.88 (0.73, 1.04)	0.85 (0.71, 1.01)
middle	0.86 (0.76, 0.97)	0.85 (0.75, 0.96)
high	reference	reference
PFUnDA	1232	
low	0.9 (0.7, 1.16)	0.91 (0.71, 1.17)
middle	0.97 (0.82, 1.15)	0.96 (0.82, 1.14)
high	reference	reference
PFHxS	1232	
low	0.83 (0.7, 0.98)	0.8 (0.68, 0.94)
middle	0.88 (0.78, 0.98)	0.86 (0.77, 0.96)
high	reference	reference
PFOS	1232	
low	0.99 (0.84, 1.17)	0.99 (0.84, 1.15)
middle	0.94 (0.84, 1.04)	0.93 (0.84, 1.03)
high	reference	reference
As	1230	
low	0.94 (0.74, 1.21)	0.93 (0.73, 1.18)
middle	1.13 (0.97, 1.32)	1.11 (0.95, 1.29)
high	reference	reference
Cd	1230	
low	1.13 (1, 1.28)	1.13 (1, 1.27)
middle	1.11 (1.02, 1.21)	1.1 (1.02, 1.2)
high	reference	reference
Hg	1230	
low	0.91 (0.77, 1.07)	0.92 (0.79, 1.08)
middle	0.95 (0.86, 1.06)	0.95 (0.86, 1.05)
high	reference	reference
Mn	1230	
low	1 (0.96, 1.05)	1.02 (0.97, 1.06)
middle	1.03 (1, 1.06)	1.03 (1, 1.06)
high	reference	reference
Pb	1230	
low	1.14 (1.05, 1.23)	1.15 (1.06, 1.24)
middle	1.05 (1.01, 1.09)	1.05 (1, 1.1)
high	reference	reference
MBzP	1231	
low	1.18 (1.02, 1.37)	1.17 (1.01, 1.35)
middle	1.15 (1.04, 1.28)	1.14 (1.03, 1.26)
high	reference	reference
MECPP	1231	

low	1.13 (0.98, 1.29)	1.15 (1, 1.31)
middle	1.03 (0.96, 1.11)	1.04 (0.97, 1.12)
high	reference	reference
MEHHP	1229	
low	1.13 (0.99, 1.3)	1.15 (1, 1.31)
middle	1.04 (0.96, 1.12)	1.04 (0.97, 1.12)
high	reference	reference
MEHP	1192	
low	1.1 (0.94, 1.29)	1.11 (0.95, 1.29)
middle	1.02 (0.93, 1.13)	1.02 (0.93, 1.12)
high	reference	reference
MEOHP	1231	
low	1.12 (0.98, 1.28)	1.13 (0.99, 1.29)
middle	1.05 (0.97, 1.13)	1.05 (0.98, 1.13)
high	reference	reference
MEP	1232	
low	1.43 (1.07, 1.9)	1.43 (1.08, 1.89)
middle	1.09 (0.92, 1.3)	1.07 (0.9, 1.26)
high	reference	reference
oh-MiNP	1232	
low	1.12 (0.88, 1.43)	1.15 (0.91, 1.47)
middle	0.93 (0.8, 1.07)	0.92 (0.8, 1.07)
high	reference	reference
oxo-MiNP	1232	
low	1.04 (0.82, 1.32)	1.07 (0.84, 1.36)
middle	1.02 (0.88, 1.19)	1.01 (0.87, 1.18)
high	reference	reference
MiBP	1232	
low	1.32 (1.09, 1.6)	1.33 (1.11, 1.6)
middle	1.18 (1.05, 1.33)	1.17 (1.04, 1.31)
high	reference	reference
MnBP	1232	
low	1.3 (1.06, 1.6)	1.29 (1.06, 1.57)
middle	1.18 (1.05, 1.32)	1.15 (1.03, 1.29)
high	reference	reference
MEPA	1230	
low	0.96 (0.64, 1.44)	0.85 (0.57, 1.27)
middle	1.04 (0.8, 1.34)	0.96 (0.75, 1.25)
high	reference	reference
ETPA	1230	
low	1.1 (0.82, 1.48)	1.04 (0.78, 1.4)
middle	0.94 (0.79, 1.1)	0.9 (0.77, 1.07)
high	reference	reference
PRPA	1216	
low	1.08 (0.53, 2.21)	0.91 (0.45, 1.85)
middle	0.98 (0.65, 1.48)	0.89 (0.59, 1.34)
high	reference	reference

BPA	1221	
low	0.88 (0.73, 1.05)	0.87 (0.73, 1.04)
middle	0.99 (0.87, 1.12)	0.98 (0.87, 1.11)
high	reference	reference
BUPA	1228	
low	1.06 (0.83, 1.35)	1.03 (0.81, 1.31)
middle	0.95 (0.82, 1.11)	0.94 (0.81, 1.09)
high	reference	reference
OXBE	1232	
low	1.5 (0.92, 2.46)	1.45 (0.9, 2.35)
middle	0.81 (0.61, 1.06)	0.76 (0.58, 1)
high	reference	reference
TCS	1232	
low	1.08 (0.74, 1.56)	1.05 (0.73, 1.52)
middle	1.01 (0.8, 1.28)	1.01 (0.8, 1.28)
high	reference	reference
DEP	1230	
low	1.24 (0.87, 1.77)	1.23 (0.86, 1.75)
middle	1.12 (0.91, 1.38)	1.09 (0.89, 1.33)
high	reference	reference
DETP	1212	
low	1.11 (0.74, 1.67)	1.02 (0.68, 1.53)
middle	1.06 (0.83, 1.36)	1.05 (0.82, 1.35)
high	reference	reference
DMP	1226	
low	1.28 (0.87, 1.89)	1.25 (0.86, 1.83)
middle	1.14 (0.91, 1.43)	1.13 (0.9, 1.4)
high	reference	reference
DMTP	1231	
low	0.97 (0.76, 1.23)	0.98 (0.77, 1.24)
middle	1.13 (0.96, 1.32)	1.11 (0.95, 1.31)
high		

For interpretation: GMR values < 1 signify lower exposure and GMR values > 1 signify higher exposure in comparison to the reference category.

Principal Component Analysis in pregnant women.

Figure S1: Scree plot for components (dimensions) from principal components analysis in pregnant women.

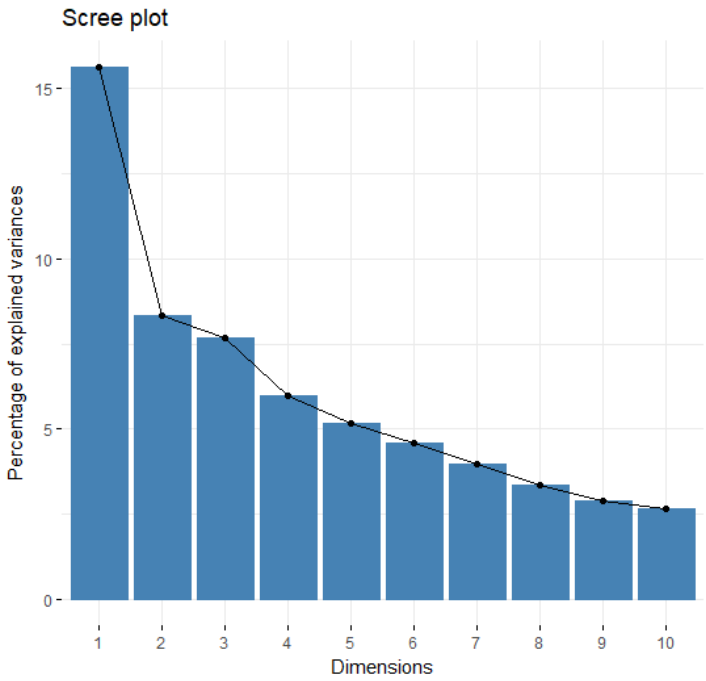


Table S11: Eigenvalues for 12 retained components from principal components analysis in pregnant women.

Factor	Eigenvalue	Variance percent	Cumulative variance percent
Dim.1	6.40531962	15.6227308	15.62273
Dim.2	3.40798026	8.31214698	23.93488
Dim.3	3.14737607	7.67652701	31.6114
Dim.4	2.44753595	5.96959988	37.581
Dim.5	2.12350286	5.17927526	42.7603
Dim.6	1.87791732	4.58028616	47.34057
Dim.7	1.62773854	3.97009401	51.31066
Dim.8	1.3727995	3.34829146	54.65895
Dim.9	1.19051979	2.90370681	57.56266
Dim.10	1.09531976	2.6715116	60.23417
Dim.11	1.04377728	2.54579824	62.77997
Dim.12	1.03476938	2.52382776	65.3038

Table S12: Loadings after varimax rotation for 12 retained components from principal components analysis in pregnant women.

	PC1	PC2	PC3	PC4	PC5	PC6	PC7	PC8	PC9	PC10	PC11	PC12
bpa		**0.486**						-0.196		-0.141		
bupa		**0.387**					**0.299**					
dde				**0.495**		-0.138				0.102		
ddt	0.120			**0.338**						0.126	-0.243	
dep					**0.494**					0.107	-0.164	
detp					**0.479**				-0.106	0.184	-0.168	
dmp					**0.489**					-0.142	0.197	
dmtp					**0.523**					-0.126	0.135	-0.112
etpa		0.254					0.325	0.107			0.143	
hcb	0.232	-0.123		0.139				**0.322**			0.162	0.171
mbzp									**0.448**	-0.186		
mecpp			**0.518**									
mehhp			**0.485**									
mehp		0.148	**0.446**									
meohp			**0.511**									
mep		0.164						**0.504**				
mepa		-0.219					**0.633**					
mibp									**0.550**	0.128		
mnbp									**0.628**			
ohminp												**0.586**
oxbe		**0.509**						0.201		0.146	-0.177	

oxominp												**0.672**
pbde153				0.289				**0.315**		-0.221	-0.181	0.202
pbde47	-0.109			**0.403**				0.105			0.157	
pcb118	**0.338**							-0.199			-0.112	
pcb138	**0.453**											
pcb153	**0.433**											
pcb170	**0.421**											
pcb180	**0.423**											
pfhxs				-0.158		**0.483**						
pfna				**0.384**		**0.381**		-0.104				
pfoa						**0.548**						
pfos						**0.473**		-0.131				
pfunda		0.117		**0.372**		0.119	0.107	-0.276			-0.163	
prpa		0.106					**0.562**					
tcs		-0.122		-0.112			0.135	**0.349**				
as		0.117								0.125	**0.549**	
cd								0.227	-0.119	**0.522**	0.118	
hg											**0.509**	
mn		-0.219					0.178	-0.220	0.123	**0.307**	-0.124	0.160
pb								-0.132		**0.575**		

Pregnant Women		
PC	**Variable (loading >=0.3)** listed from highest to lowest loading value	**% variance**
PC1	**PCB118, PCB138, PCB153, PCB170, PCB180**	**15.6**
PC2	**OXBE, BPA, BUPA**	**8.3**
PC3	**MECPP, MEOHP, MEHHP, MEHP**	**7.7**
PC4	**DDE, DDT, PBDE47, PFUNDA, PFNA**	**6**
PC5	**DMTP, DMP, DETP, DEP**	**5.2**
PC6	PFOA, PFHXS, PFOS, PFNA	4.6
PC7	MEPA, PRPA, ETPA, BUPA	4
PC8	MEP, TCS, HCB, PBDE153	3.3
PC9	MNBP, MIBP, MBZP	2.9
PC10	Pb, Cd, Mn	2.7
PC11	As, Hg	2.5
PC12	OXOMINP, OHMINP	2.5

Principal Component Analysis in children.

Figure S2: Scree plot for components (dimensions) from principal components analysis in children (6-12 years).

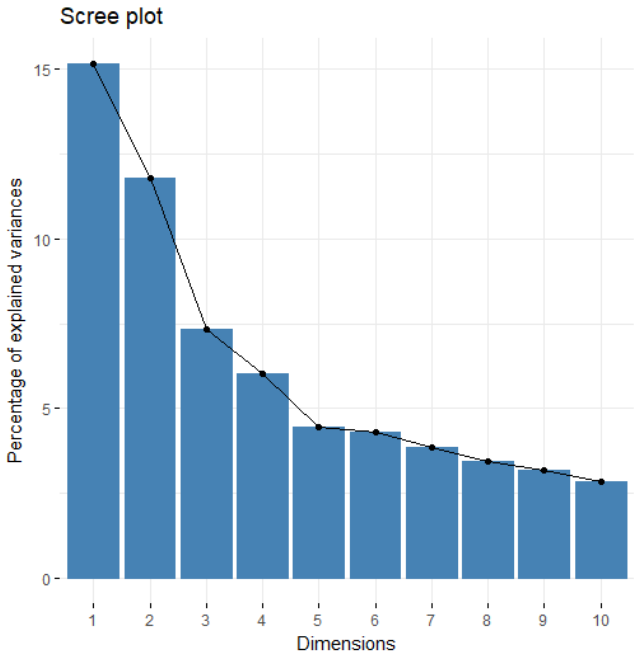


Table S13: Eigenvalues for 13 retained components from principal components analysis in children (6-12 years).

Factor	Eigenvalue	Variance percent	Cumulative variance percent
Dim.1	6.2172981	15.1641417	15.16414
Dim.2	4.83691243	11.7973474	26.96149
Dim.3	3.00523939	7.32985218	34.29134
Dim.4	2.47073986	6.02619478	40.31754
Dim.5	1.82878927	4.46046164	44.778
Dim.6	1.75833469	4.28862119	49.06662
Dim.7	1.57834784	3.84962887	52.91625
Dim.8	1.41041953	3.44004764	56.3563
Dim.9	1.30768109	3.18946608	59.54576
Dim.10	1.16013251	2.82959148	62.37535
Dim.11	1.11877734	2.72872522	65.10408
Dim.12	1.10417554	2.69311108	67.79719
Dim.13	1.05425423	2.57135177	70.36854

Table S14: Loadings after varimax rotation for 13 retained components from principal components analysis in children (6-12 years).

	PC1	PC2	PC3	PC4	PC5	PC6	PC7	PC8	PC9	PC10	PC11	PC12	PC13
bpa											**0.498**		
bupa				0.200							**0.415**		
dde												**0.517**	
ddt												**0.584**	
dep													**0.630**
detp					0.124								**0.599**
dmp					**0.677**								
dmtp					**0.603**								0.162
etpa				**0.428**							0.284		
hcb		0.278				-0.142						0.249	
mbzp				0.149	0.210	0.205	**0.408**				0.127		-0.227
mecpp	**0.482**												
mehhp	**0.504**												
mehp	**0.470**												
meohp	**0.501**												
mep				0.185		0.129	**0.354**			-0.128	-0.212	-0.241	
mepa				**0.595**									
mibp							**0.466**						
mnbp				-0.135			**0.462**				0.214		
ohminp									**0.704**				

oxbe					-0.235		0.168				**0.423**		0.233
oxominp									**0.688**				
pbde153								**0.649**					
pbde47								**0.726**					
pcb118		0.281					0.152					0.201	
pcb138		**0.423**											
pcb153		**0.456**											
pcb170		**0.441**											
pcb180		**0.449**											
pfhxs		0.107	**0.335**								-0.150	**-0.311**	
pfna			**0.452**								0.109		
pfoa			**0.482**	0.117		-0.255							
pfos			**0.505**										
pfunda			**0.378**			0.298							
prpa				**0.523**									
tcs				0.169			**0.331**			-0.180		-0.114	0.179
as						**0.602**							
cd										**0.661**			
hg						**0.570**							
mn										**0.630**	-0.111		
pb					-0.147		0.255			0.241	**-0.325**		0.140

Children		
PC	**Variable (loading >=0.3)** listed from highest to lowest loading value	**% variance**
PC1	**MEHHP, MEOHP, MECPP, MEHP**	**15.2**
PC2	**PCB153, PCB180, PCB170, PCB138**	**11.8**
PC3	**PFOS, PFOA, PFNA, PFUNDA, PFHXS,**	**7.3**
PC4	**MEPA, PRPA, ETPA**	**6**
PC5	DMP, DMTP	4.5
PC6	As, Hg	4.3
PC7	MIBP, MNBP, MBZP, MEP, TRCS	3.8
PC8	PBDE47, PBDE153	3.4
PC9	OHMINP, OXOMINP	3.2
PC10	Cd, Mn	2.8
PC11	BPA, OXBE, BUPA, Pb	2.7
PC12	DDT, DDE, PFHXS	2.7
PC13	DEP, DETP	2.6

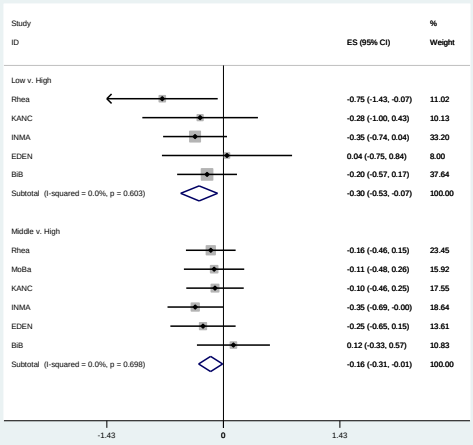
Table S15: Sensitivity analysis removing one cohort at a time for estimates (Beta (95%CI)) with principal components and maternal education in pregnant women.

Maternal Education								
			Cohort Removed:					
Component	Cat.	All Cohorts	BiB (UK)	EDEN (France)	INMA (Spain)	KANC (Lithuania)	MoBa (Norway)	RHEA (Greece)
PC1[a]: PCBs								
	low	-0.19 (-0.42, 0.03)	-0.18 (-0.47, 0.12)	-0.26 (-0.49, -0.04)*	-0.15 (-0.43, 0.12)	-0.20 (-0.44, 0.03)	-0.23 (-0.45, -0.00)*	-0.14 (-0.38, 0.10)
	middle	-0.15 (-0.30, -0.00)*	-0.16 (-0.32, .01)	-0.15 (-0.31, 0.01)	-0.11 (-0.28, 0.06)	-0.16 (-0.32, 0.01)	-0.18 (-0.34, -0.01)	-0.15 (-0.32, 0.02)
	high	reference	reference	reference	reference	reference	reference	reference
PC2[b]: phenols								
	low	-0.25 (-0.44, -0.05)*	-0.25 (-0.50, 0.01)	-0.20 (-0.42, 0.02)	-0.19 (-0.42, 0.05)	-0.35 (-0.55, -0.15)*	-0.23 (-0.42, -0.03)*	-0.24 (-0.45, -0.04)*
	middle	-0.14 (-0.27, -0.01)*	-0.16 (-0.30, -0.02)	-0.13 (-0.28, 0.02)	-0.14 (-0.29, 0.00)*	-0.14 (-0.28, 0.00)*	-0.11 (-0.25, 0.04)	-0.14 (-0.29, 0.00)*
	high	reference	reference	reference	reference	reference	reference	reference
PC3[c]: DEHP metabolites								
	low	0.13 (-0.21, 0.46)	0.30 (-0.13, 0.74)	0.04 (-0.31, 0.38)	0.01 (-0.37, 0.39)	0.10 (-0.26, 0.47)	0.11 (-0.23, 0.45)	0.19 (-0.15, 0.52)
	middle	0.10 (-0.12, 0.32)	0.16 (-0.08, 0.41)	-0.07 (-0.31, 0.17)	0.26 (0.03, 0.50)	0.05 (-0.20, 0.31)	0.07 (-0.17, 0.32)	0.11 (-0.12, 0.35)

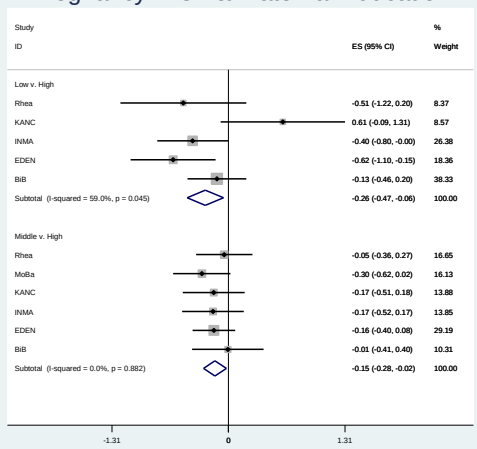
	high	reference	reference	reference	reference	reference	reference	reference
PC4[d]: POPs								
	low	-0.11 (-0.29, 0.06)	0.01 (-0.21, 0.23)	-0.13 (-0.32, 0.06)	-0.16 (-0.36, 0.05)	-0.11 (-0.30, 0.08)	-0.12 (-0.31, 0.06)	-0.12 (-0.30, 0.05)
	middle	-0.07 (-0.19, 0.05)	-0.06 (-0.18, 0.07)	-0.07 (-0.20, 0.06)	-0.09 (-0.22, 0.03)	-0.01 (-0.14, 0.11)	-0.08 (-0.21, 0.06)	-0.09 (-0.22, 0.03)
	high	reference	reference	reference	reference	reference	reference	reference
PC5[e]: OP pesticide metabolites								
	low	-0.40 (-0.66, -0.14)*	-0.52 (-0.86, -0.18)*	-0.46 (-0.74, -0.18)*	-0.26 (-0.57, 0.05)	-0.41 (-0.70, -0.12)*	-0.37 (-0.63, -0.12)*	-0.39 (-0.66, -0.12)*
	middle	-0.30 (-0.48, -0.12)*	-0.26 (-0.45, -0.07)*	-0.43 (-0.63, -0.24)*	-0.28 (-0.48, -0.09)*	-0.32 (-0.52, -0.11)*	-0.22 (-0.41, -0.04)*	-0.30 (-0.49, -0.10)*
	high	reference	reference	reference	reference	reference	reference	reference

Mother´s models were adjusted for cohort, parity, previous breastfeeding, and age at chemical measurement.
* indicates p-value significant at <0.05.
[a]PC1 loaded with PCBs: PCB118, PCB138, PCB153, PCB170, PCB180. [b]PC2 loaded with phenols: OXBE, BPA, BUPA. [c]PC3 loaded with DEHP metabolites: MECPP, MEOHP, MEHHP, MEHP. [d]PC4 loaded with a mixture of POPs: DDE, DDT, PBDE47, PFUNDA, PFNA. [e]PC5 loaded with OP pesticide metabolites: DMTP, DMP, DETP, DEP.

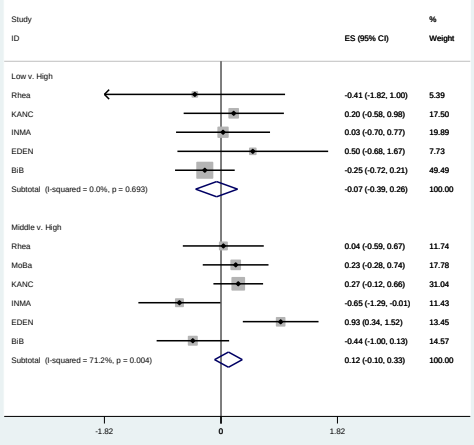
Pregnancy: PC1 & Maternal Education



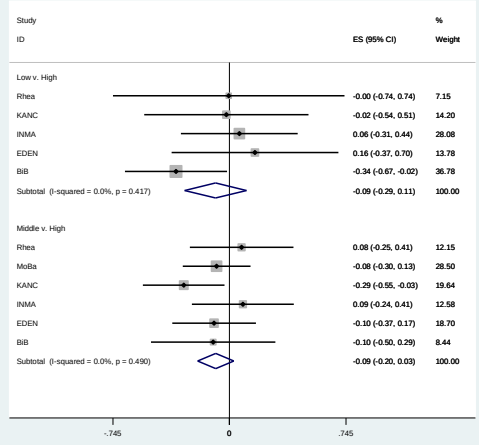
Pregnancy: PC2 & Maternal Education



Pregnancy: PC3 & Maternal Education



Pregnancy: PC4 & Maternal Education



Pregnancy: PC5 & Maternal Education

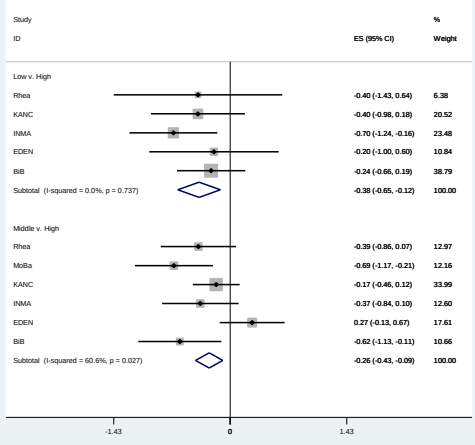


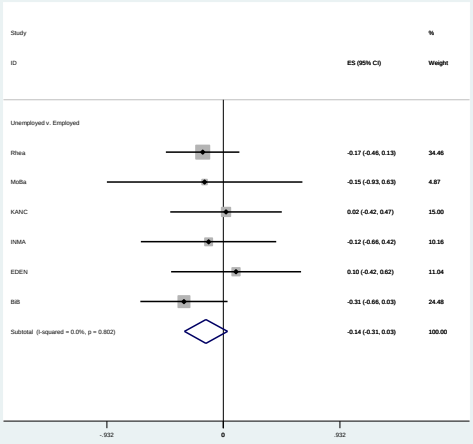
Table S16: Sensitivity analysis removing one cohort at a time for estimates (Beta (95%CI)) with principal components and maternal working status in pregnant women.

Maternal Education								
			Cohort Removed:					
Component	Cat.	All Cohorts	BiB (UK)	EDEN (France)	INMA (Spain)	KANC (Lithuania)	MoBa (Norway)	RHEA (Greece)
PC1[a]: PCBs								
	unemp	-0.10 (-0.28, 0.08)	-0.03 (-0.25, 0.18)	-0.14 (-0.33, 0.05)	-0.10 (-0.29, 0.10)	-0.14 (-0.34, 0.06)	-0.12 (-0.31, 0.06)	-0.07 (-0.29, 0.15)
	emp	reference	reference	reference	reference	reference	reference	reference
PC2[b]: phenols								
	unemp	-0.12 (-0.28, 0.04)	-0.12 (-0.31, 0.06)	-0.15 (-0.33, 0.03)	-0.17 (-0.34, -0.01)*	-0.06 (-0.23, 0.11)	-0.11 (-0.27, 0.06)	-0.11 (-0.30, 0.07)
	emp	reference	reference	reference	reference	reference	reference	reference
PC3[c]: DEHP metabolites								
	unemp	0.10 (-0.17, 0.37)	0.10 (-0.22, 0.42)	0.11 (-0.18, 0.39)	0.05 (-0.22, 0.33)	0.11 (-0.20, 0.41)	0.05 (-0.23, 0.33)	0.22 (-0.09, 0.52)
	emp	reference	reference	reference	reference	reference	reference	reference
PC4[d]: POPs								
	unemp	0.07 (-0.08, 0.21)	0.04 (-0.12, 0.20)	0.08 (-0.07, 0.24)	0.10 (-0.04, 0.25)	0.10 (-0.06, 0.25)	0.04 (-0.12, 0.19)	0.01 (-0.15, 0.17)
	emp	reference	reference	reference	reference	reference	reference	reference

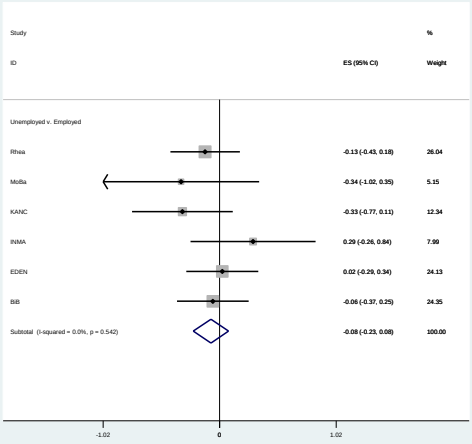
PC5[e]: OP pesticide metabolites								
	unemp	-0.11 (-0.33, 0.10)	-0.12 (-0.37, 0.13)	-0.23 (-0.47, -0.00)*	-0.31 (-0.25, 0.19)	-0.13 (-0.38, 0.11)	-0.17 (-0.38, 0.04)	0.02 (-0.23, 0.27)
	emp	reference	reference	reference	reference	reference	reference	reference

Mother´s models were adjusted for cohort, parity, previous breastfeeding, and age at chemical measurement.
* indicates p-value significant at <0.05.
[a]PC1 loaded with PCBs: PCB118, PCB138, PCB153, PCB170, PCB180. [b]PC2 loaded with phenols: OXBE, BPA, BUPA. [c]PC3 loaded with DEHP metabolites: MECPP, MEOHP, MEHHP, MEHP. [d]PC4 loaded with a mixture of POPs: DDE, DDT, PBDE47, PFUNDA, PFNA. [e]PC5 loaded with OP pesticide metabolites: DMTP, DMP, DETP, DEP.

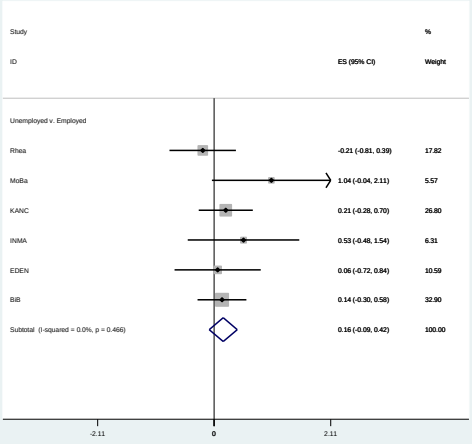
Pregnancy: PC1 & Maternal Employment



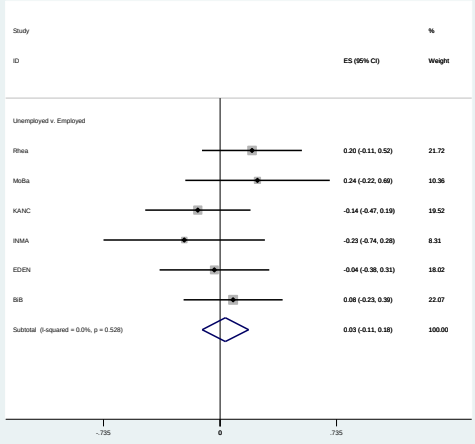
Pregnancy: PC2 & Maternal Employment



Pregnancy: PC3 & Maternal Employment



Pregnancy: PC4 & Maternal Employment



Pregnancy: PC5 & Maternal Employment

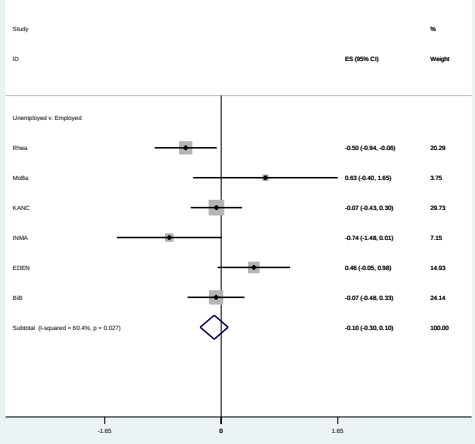


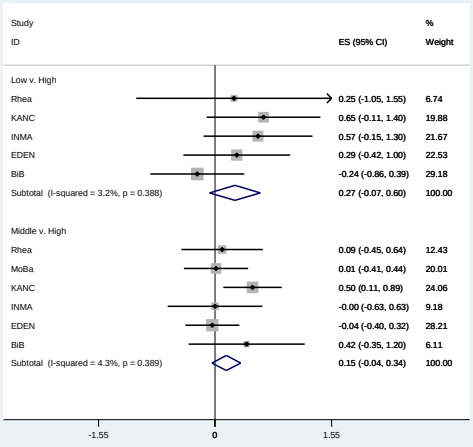
Table S17: Sensitivity analysis removing one cohort at a time for estimates (Beta (95%CI)) with principal components and maternal education in children (6-12 years).

Maternal Education								
			Cohort Removed:					
Component	Cat.	All Cohorts	BiB (UK)	EDEN (France)	INMA (Spain)	KANC (Lithuania)	MoBa (Norway)	RHEA (Greece)
PC1[a]: DEHP metabolites								
	low	0.16 (-0.15, 0.46)	0.48 (0.10, 0.86)*	0.16 (-0.18, 0.50)	-0.05 (-0.40, 0.30)	0.09 (-0.25, 0.42)	0.16 (-0.15, 0.48)	0.16 (-0.16, 0.47)
	middle	0.15 (-0.05, 0.36)	0.14 (-0.07, 0.35)	0.18 (-0.06, 0.41)	0.20 (-0.02, 0.41)	0.06 (-0.17, 0.30)	0.17 (-0.06, 0.41)	0.17 (-0.05, 0.40)
	high	reference	reference	reference	reference	reference	reference	reference
PC2[b]: PCBs								
	low	-0.90 (-1.20, -0.59)*	-0.98 (-1.38, -0.57)*	-0.96 (-1.28, -0.63)*	-0.73 (-1.08, -0.37)*	-0.92 (-1.21, -0.62)*	-0.93 (-1.24, -0.61)*	-0.88 (-1.20, -0.56)*
	middle	-0.74 (-0.95, -0.54)*	-0.81 (-1.03, -0.59)*	-0.83 (-1.06, -0.60)*	-0.64 (-0.86, -0.42)*	-0.70 (-0.91, -0.49)*	-0.78 (-1.01, -0.55)*	-0.71 (-0.94, -0.48)*
	high	reference	reference	reference	reference	reference	reference	reference
PC3[c]: PFASs								
	low	-0.64 (-0.90, -0.37)*	-0.65 (-0.99, -0.31)*	-0.71 (-0.99, -0.42)*	-0.36 (-0.68, -0.04)*	-0.72 (-0.99, -0.44)*	-0.65 (-0.93, -0.37)*	-0.68 (-0.95, -0.41)*
	middle	-0.44 (-0.62, -0.26)*	-0.43 (-0.62, -0.24)*	-0.46 (-0.65, -0.26)*	-0.43 (-0.62, -0.23)*	-0.47 (-0.66, -0.27)*	-0.47 (-0.67, -0.26)*	-0.39 (-0.59, -0.20)*

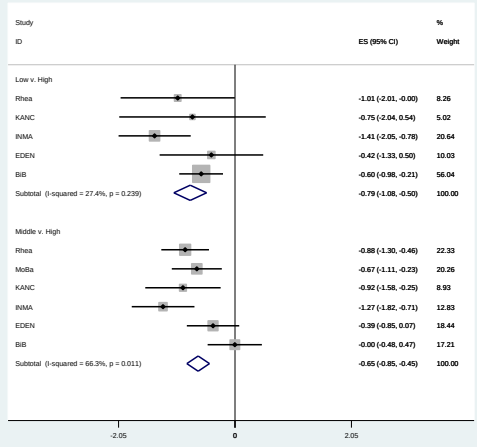
	high	reference	reference	reference	reference	reference	reference	reference
PC4[d]: parabens								
	low	0.01 (-0.25, 0.26)	0.01 (-0.31, 0.32)	0.04 (-0.22, 0.31)	-0.05 (-0.35, 0.25)	0.05 (-0.23, 0.32)	-0.02 (-0.29, 0.25)	0.01 (-0.26, 0.28)
	middle	-0.09 (-0.26, 0.08)	-0.05 (-0.23, 0.12)	-0.07 (-0.25, 0.12)	-0.16 (-0.34, 0.03)	-0.08 (-0.27, 0.11)	-0.14 (-0.34, 0.06)	-0.04 (-0.23, 0.15)
	high	reference	reference	reference	reference	reference	reference	reference

Children´s models were adjusted for cohort, parity, previous breastfeeding, breastfeeding of study child, and child age at chemical measurement (years).
* indicates p-value significant at <0.05.
fPC1 loaded with DEHP metabolites: MEHHP, MEOHP, MECPP, MEHP. gPC2 loaded with PCBs: PCB153, PCB180, PCB170, PCB138. hPC3 loaded with PFASs: PFOS, PFOA, PFNA, PFUnDA, PFHxS. iPC4 loaded with parabens: MEPA, PRPA, ETPA.

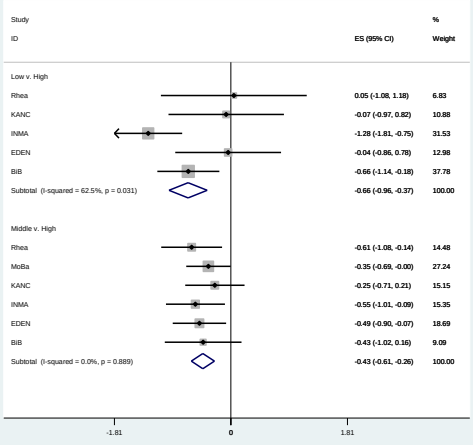
Childhood: PC1 & Maternal Education



Childhood: PC2 & Maternal Education



Childhood: PC3 & Maternal Education



Childhood: PC4 & Maternal Education

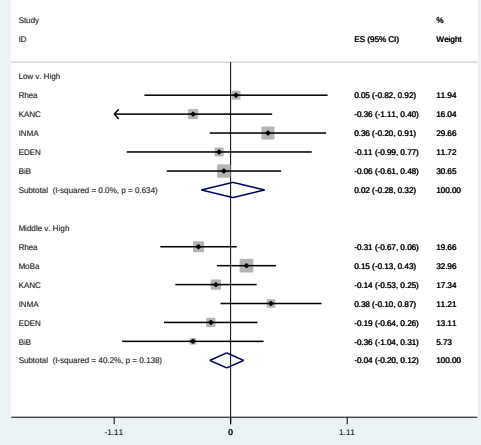


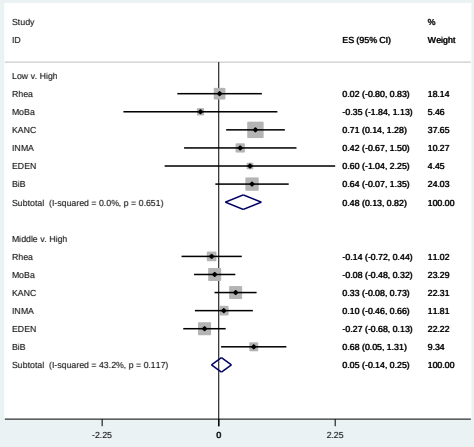
Table S18: Sensitivity analysis removing one cohort at a time for estimates (Beta (95%CI)) with principal components and family affluence scale (FAS) in children (6-12 years).

Family Affluence Scale								
			Cohort Removed:					
Component	Cat.	All Cohorts	BiB (UK)	EDEN (France)	INMA (Spain)	KANC (Lithuania)	MoBa (Norway)	RHEA (Greece)
PC1[a]: DEHP metabolites								
	low	0.35 (0.02, 0.67)*	0.33 (-0.06, 0.71)	0.36 (0.02, 0.71)*	0.34 (0.01, 0.67)*	0.25 (-0.13, 0.63)	0.40 (0.05, 0.74)*	0.41 (0.05, 0.77)*
	middle	0.11 (-0.10, 0.31)	0.01 (-0.20, 0.22)	0.16 (-0.07, 0.38)	0.10 (-0.12, 0.31)	0.06 (-0.17, 0.28)	0.16 (-0.08, 0.39)	0.16 (-0.05, 0.38)
	high	reference	reference	reference	reference	reference	reference	reference
PC2[b]: PCBs								
	low	-0.53 (-0.86, -0.20)*	-0.64 (-1.06, -0.22)*	-0.53 (-0.87, -0.19)*	-0.58 (-0.93, -0.24)*	-0.49 (-0.83, -0.14)*	-0.57 (-0.92, -0.22)*	-0.39 (-0.77, -0.01)*
	middle	-0.05 (-0.25, 0.16)	-0.01 (-0.24, 0.22)	-0.07 (-0.30, 0.15)	-0.09 (-0.31, 0.13)	-0.05 (-0.26, 0.16)	-0.09 (-0.32, 0.15)	0.02 (-0.21, 0.24)
	high	reference	reference	reference	reference	reference	reference	reference
PC3[c]: PFASs								
	low	-0.27 (-0.55, 0.02)	-0.27 (-0.62, 0.08)	-0.31 (-0.61, -0.02)*	-0.26 (-0.57, 0.04)	-0.22 (-0.54, 0.10)	-0.30 (-0.61, 0.01)	-0.25 (-0.57, 0.06)
	middle	-0.21 (-0.39, -0.03)*	-0.11 (-0.31, 0.08)	-0.29 (-0.48, -0.09)*	-0.21 (-0.41, -0.02)*	-0.24 (-0.43, -0.05)*	-0.31 (-0.52, -0.10)*	-0.12 (-0.31, 0.07)

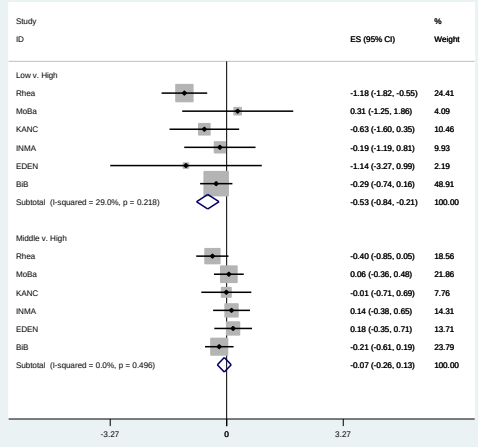
	high	reference	reference	reference	reference	reference	reference	reference
PC4[d]: parabens								
	low	-0.07 (-0.34, 0.20)	-0.15 (-0.47, 0.16)	-0.04 (-0.31, 0.23)	-0.01 (-0.29, 0.27)	-0.09 (-0.40, 0.22)	-0.08 (-0.38, 0.22)	-0.04 (-0.35, 0.27)
	middle	-0.10 (-0.26, 0.07)	-0.12 (-0.29, 0.05)	-0.10 (-0.28, 0.07)	-0.10 (-0.28, 0.09)	-0.11 (-0.29, 0.08)	-0.09 (-0.29, 0.11)	-0.06 (-0.25, 0.12)
	high	reference	reference	reference	reference	reference	reference	reference

Children´s models were adjusted for cohort, parity, previous breastfeeding, breastfeeding of study child, and child age at chemical measurement (years).
* indicates p-value significant at <0.05.
fPC1 loaded with DEHP metabolites: MEHHP, MEOHP, MECPP, MEHP. gPC2 loaded with PCBs: PCB153, PCB180, PCB170, PCB138. hPC3 loaded with PFASs: PFOS, PFOA, PFNA, PFUnDA, PFHxS. iPC4 loaded with parabens: MEPA, PRPA, ETPA.

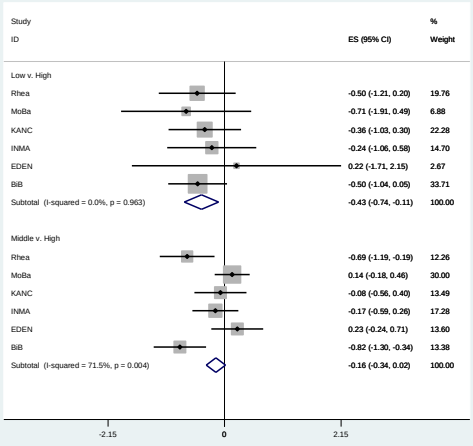
Childhood: PC1 & FAS



Childhood: PC2 & FAS



Childhood: PC3 & FAS



Childhood: PC4 & FAS

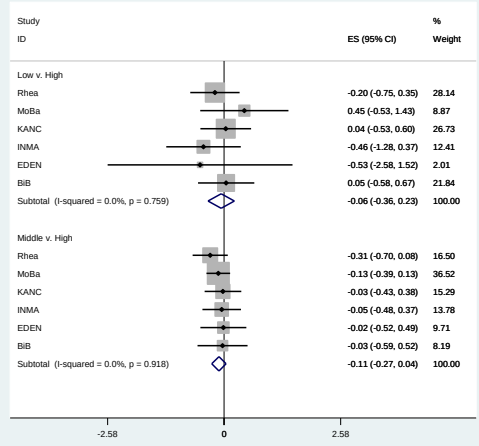


Table S18.1: Sensitivity analysis removing EDEN and MoBa for estimates (Beta (95%CI)) with principal components and family affluence scale (FAS) in children (6-12 years).
Given the limitations of the FAS measure and the low percentages of representation of low FAS in EDEN (1%) and MoBa (1.5%), we removed these two cohorts simultaneously.

Family Affluence Scale			
Component	Cat.	All Cohorts	Cohort Removed EDEN (France) + MoBa (Norway)
PC1[f] : DEHP metabolites			
	low	0.35 (0.02, 0.67)*	0.33 (-0.06, 0.71)
	middle	0.11 (-0.10, 0.31)	0.23 (-0.05, 0.51)
	high	reference	reference
PC2[g] : PCBs			
	low	-0.53 (-0.86, -0.20)*	-0.83 (-1.25, -0.41)*
	middle	-0.05 (-0.25, 0.16)	-0.13 (-0.43, 0.18)
	high	reference	reference
PC3[h] : PFASs			
	low	-0.27 (-0.55, 0.02)	-0.32 (-0.65, 0.01)
	middle	-0.21 (-0.39, -0.03)*	-0.43 (-0.67, -0.20)*
	high	reference	reference
PC4[i] : parabens			
	low	-0.07 (-0.34, 0.20)	0.02 (-0.29, 0.33)
	middle	-0.10 (-0.26, 0.07)	-0.13 (-0.36, 0.09)
	high	reference	reference

Children´s models were adjusted for cohort, parity, previous breastfeeding, breastfeeding of study child, and child age at chemical measurement (years).
* indicates p-value significant at <0.05.
[f]PC1 loaded with DEHP metabolites: MEHHP, MEOHP, MECPP, MEHP. [g]PC2 loaded with PCBs: PCB153, PCB180, PCB170, PCB138. [h]PC3 loaded with PFASs: PFOS, PFOA, PFNA, PFUnDA, PFHxS. [i]PC4 loaded with parabens: MEPA, PRPA, ETPA.

Table S19: Sensitivity Analysis further adjusting for fish consumption and smoking independently for adjusted geometric mean ratios, 95% confidence intervals and p-values for imputed regression analysis of maternal education with 41 biomarkers for chemical contaminants in pregnant women.

	Smoking	Fish Consumption
Chemical	GM ratio (95% CI)	GM ratio (95% CI)
DDE		
low	1.04 (0.87, 1.25)	1.01 (0.84, 1.21)
middle	0.98 (0.88, 1.1)	0.96 (0.86, 1.08)
high	reference	reference
DDT		
low	0.99 (0.77, 1.26)	0.94 (0.73, 1.2)
middle	1 (0.83, 1.2)	0.96 (0.8, 1.16)
high	reference	reference
HCB		
low	1.02 (0.92, 1.13)	1.01 (0.91, 1.13)
middle	1.02 (0.95, 1.1)	1.02 (0.95, 1.09)
high	reference	reference
PBDE47		
low	0.98 (0.74, 1.29)	0.98 (0.74, 1.29)
middle	1.05 (0.85, 1.3)	1.06 (0.86, 1.3)
high	reference	reference
PBDE153		
low	0.98 (0.6, 1.61)	0.99 (0.6, 1.63)
middle	0.91 (0.65, 1.28)	0.91 (0.64, 1.3)
high	reference	reference
PCB118		
low	1.01 (0.9, 1.12)	0.98 (0.88, 1.1)
middle	0.97 (0.9, 1.04)	0.95 (0.88, 1.02)
high	reference	reference
PCB138		
low	0.94 (0.85, 1.03)	0.93 (0.85, 1.02)
middle	0.96 (0.9, 1.03)	0.96 (0.9, 1.03)
high	reference	reference
PCB153		
low	0.93 (0.86, 1.02)	0.94 (0.86, 1.02)
middle	0.96 (0.9, 1.03)	0.97 (0.91, 1.03)
high	reference	reference
PCB170		
low	0.94 (0.8, 1.1)	0.94 (0.81, 1.1)
middle	0.95 (0.86, 1.05)	0.95 (0.86, 1.05)
high	reference	reference
PCB180		
low	0.95 (0.85, 1.05)	0.95 (0.86, 1.06)
middle	0.97 (0.9, 1.05)	0.97 (0.9, 1.05)

high	reference	reference
PFOA		
low	1.01 (0.91, 1.12)	1.01 (0.91, 1.13)
middle	0.99 (0.93, 1.05)	1 (0.94, 1.06)
high	reference	reference
PFNA		
low	1 (0.91, 1.11)	0.99 (0.9, 1.1)
middle	0.99 (0.93, 1.06)	0.99 (0.93, 1.05)
high	reference	reference
PFUnDA		
low	0.91 (0.81, 1.01)	0.9 (0.81, 1.01)
middle	0.93 (0.86, 1)	0.92 (0.86, 0.99)
high	reference	reference
PFHxS		
low	1.1 (0.96, 1.27)	1.12 (0.97, 1.29)
middle	1 (0.92, 1.08)	1.01 (0.93, 1.09)
high	reference	reference
PFOS		
low	1.08 (0.98, 1.18)	1.07 (0.98, 1.18)
middle	1.01 (0.95, 1.07)	1.01 (0.95, 1.07)
high	reference	reference
As		
low	0.82 (0.59, 1.12)	0.83 (0.61, 1.13)
middle	0.84 (0.69, 1.03)	0.85 (0.7, 1.02)
high	reference	reference
Cd		
low	1.12 (0.98, 1.28)	1.3 (1.12, 1.51)
middle	1.06 (0.97, 1.16)	1.17 (1.06, 1.29)
high	reference	reference
Hg		
low	0.83 (0.72, 0.95)	0.84 (0.73, 0.96)
middle	0.87 (0.8, 0.96)	0.88 (0.8, 0.96)
high	reference	reference
Mn		
low	1 (0.93, 1.07)	1 (0.93, 1.07)
middle	1.01 (0.97, 1.05)	1.01 (0.97, 1.05)
high	reference	reference
Pb		
low	1.06 (0.95, 1.18)	1.07 (0.96, 1.19)
middle	1.03 (0.97, 1.09)	1.04 (0.98, 1.1)
high	reference	reference
MBzP		
low	0.94 (0.71, 1.23)	0.93 (0.71, 1.21)
middle	1.02 (0.84, 1.24)	1.01 (0.84, 1.22)
high	reference	reference
MECPP		
low	1.06 (0.9, 1.25)	1.04 (0.88, 1.22)

middle	1.04 (0.94, 1.16)	1.03 (0.93, 1.14)
high	reference	reference
MEHHP		
low	1.07 (0.89, 1.29)	1.06 (0.88, 1.27)
middle	1.03 (0.91, 1.17)	1.02 (0.9, 1.16)
high	reference	reference
MEHP		
low	1.03 (0.86, 1.24)	1.02 (0.85, 1.22)
middle	1.04 (0.92, 1.17)	1.03 (0.91, 1.16)
high	reference	reference
MEOHP		
low	1.06 (0.88, 1.27)	1.04 (0.87, 1.25)
middle	1.03 (0.91, 1.16)	1.02 (0.9, 1.14)
high	reference	reference
MEP		
low	1.12 (0.87, 1.44)	1.12 (0.87, 1.43)
middle	1.12 (0.93, 1.34)	1.12 (0.94, 1.33)
high	reference	reference
oh-MiNP		
low	0.96 (0.8, 1.15)	0.95 (0.8, 1.13)
middle	0.98 (0.87, 1.1)	0.97 (0.87, 1.09)
high	reference	reference
oxo-MiNP		
low	0.99 (0.79, 1.23)	0.97 (0.78, 1.21)
middle	1.02 (0.88, 1.18)	1.01 (0.87, 1.17)
high	reference	reference
MiBP		
low	0.98 (0.85, 1.12)	0.97 (0.85, 1.12)
middle	0.92 (0.83, 1.01)	0.92 (0.83, 1.01)
high	reference	reference
MnBP		
low	0.94 (0.8, 1.1)	0.91 (0.78, 1.07)
middle	1 (0.88, 1.14)	0.98 (0.86, 1.11)
high	reference	reference
MEPA		
low	0.53 (0.37, 0.75)	0.53 (0.37, 0.75)
middle	0.97 (0.74, 1.28)	0.97 (0.73, 1.27)
high	reference	reference
ETPA		
low	0.6 (0.37, 0.97)	0.59 (0.36, 0.95)
middle	0.92 (0.67, 1.26)	0.9 (0.66, 1.24)
high	reference	reference
PRPA		
low	0.52 (0.36, 0.76)	0.53 (0.36, 0.77)
middle	0.92 (0.7, 1.21)	0.92 (0.7, 1.21)
high	reference	reference
BPA		

low	0.94 (0.77, 1.15)	0.95 (0.78, 1.16)
middle	0.85 (0.73, 0.99)	0.86 (0.74, 0.99)
high	reference	reference
BUPA		
low	0.51 (0.31, 0.83)	0.49 (0.3, 0.81)
middle	0.88 (0.64, 1.19)	0.86 (0.63, 1.16)
high	reference	reference
OXBE		
low	0.77 (0.48, 1.24)	0.75 (0.47, 1.2)
middle	1.07 (0.76, 1.51)	1.06 (0.75, 1.48)
high	reference	reference
TCS		
low	0.93 (0.55, 1.57)	0.98 (0.59, 1.64)
middle	0.94 (0.64, 1.37)	0.97 (0.67, 1.41)
high	reference	reference
DEP		
low	0.97 (0.81, 1.16)	0.95 (0.8, 1.14)
middle	0.92 (0.81, 1.05)	0.91 (0.8, 1.03)
high	reference	reference
DETP		
low	0.77 (0.5, 1.17)	0.73 (0.48, 1.12)
middle	0.9 (0.68, 1.21)	0.87 (0.65, 1.17)
high	reference	reference
DMP		
low	0.8 (0.68, 0.95)	0.79 (0.67, 0.94)
middle	0.86 (0.75, 0.98)	0.85 (0.75, 0.97)
high	reference	reference
DMTP		
low	0.73 (0.56, 0.94)	0.7 (0.54, 0.9)
middle	0.81 (0.67, 0.97)	0.79 (0.66, 0.94)
high	reference	reference

Table S20: Sensitivity Analysis further adjusting for fish consumption and smoking independently for adjusted geometric mean ratios, 95% confidence intervals and p-values for imputed regression analysis of maternal employment status with 41 biomarkers for chemical contaminants in pregnant women.

	Smoking	Fish Consumption
Chemical	GM ratio (95% CI)	GM ratio (95% CI)
DDE		
unemployed	1.21 (1.04, 1.42)	1.2 (1.03, 1.41)
employed	reference	reference
DDT		
unemployed	1.17 (0.95, 1.44)	1.16 (0.94, 1.43)
employed	reference	reference
HCB		
unemployed	0.99 (0.92, 1.06)	0.99 (0.92, 1.06)
employed	reference	reference
PBDE47		
unemployed	0.99 (0.8, 1.24)	0.99 (0.8, 1.24)
employed	reference	reference
PBDE153		
unemployed	0.99 (0.66, 1.47)	0.98 (0.66, 1.47)
employed	reference	reference
PCB118		
unemployed	1.01 (0.93, 1.09)	1 (0.92, 1.09)
employed	reference	reference
PCB138		
unemployed	0.95 (0.88, 1.03)	0.95 (0.88, 1.03)
employed	reference	reference
PCB153		
unemployed	0.97 (0.9, 1.04)	0.97 (0.9, 1.05)
employed	reference	reference
PCB170		
unemployed	0.97 (0.86, 1.08)	0.97 (0.86, 1.08)
employed	reference	reference
PCB180		
unemployed	0.97 (0.88, 1.06)	0.97 (0.88, 1.07)
employed	reference	reference
PFOA		
unemployed	0.89 (0.83, 0.96)	0.89 (0.83, 0.96)
employed	reference	reference
PFNA		
unemployed	0.91 (0.85, 0.98)	0.91 (0.85, 0.98)
employed	reference	reference
PFUnDA		
unemployed	0.92 (0.84, 1)	0.92 (0.85, 1)
employed	reference	reference

PFHxS		
unemployed	0.87 (0.78, 0.96)	0.87 (0.79, 0.97)
employed	reference	reference
PFOS		
unemployed	0.91 (0.84, 0.98)	0.91 (0.84, 0.98)
employed	reference	reference
As		
unemployed	0.9 (0.73, 1.11)	0.91 (0.74, 1.12)
employed	reference	reference
Cd		
unemployed	1.06 (0.94, 1.18)	1.08 (0.95, 1.23)
employed	reference	reference
Hg		
unemployed	0.91 (0.81, 1.01)	0.91 (0.82, 1.02)
employed	reference	reference
Mn		
unemployed	1 (0.95, 1.06)	1 (0.95, 1.06)
employed	reference	reference
Pb		
unemployed	1.01 (0.93, 1.09)	1.01 (0.93, 1.09)
employed	reference	reference
MBzP		
unemployed	1 (0.77, 1.29)	1 (0.77, 1.29)
employed	reference	reference
MECPP		
unemployed	1.06 (0.92, 1.23)	1.06 (0.91, 1.23)
employed	reference	reference
MEHHP		
unemployed	1 (0.86, 1.16)	0.99 (0.85, 1.15)
employed	reference	reference
MEHP		
unemployed	0.98 (0.84, 1.14)	0.98 (0.84, 1.14)
employed	reference	reference
MEOHP		
unemployed	1.03 (0.89, 1.2)	1.03 (0.88, 1.2)
employed	reference	reference
MEP		
unemployed	1.03 (0.85, 1.26)	1.04 (0.85, 1.26)
employed	reference	reference
oh-MiNP		
unemployed	0.96 (0.83, 1.1)	0.96 (0.83, 1.1)
employed	reference	reference
oxo-MiNP		
unemployed	0.94 (0.79, 1.11)	0.94 (0.79, 1.11)
employed	reference	reference
MiBP		
unemployed	0.95 (0.84, 1.08)	0.95 (0.84, 1.08)

employed	reference	reference
MnBP		
unemployed	0.97 (0.85, 1.12)	0.97 (0.84, 1.11)
employed	reference	reference
MEPA		
unemployed	0.98 (0.69, 1.4)	0.98 (0.69, 1.4)
employed	reference	reference
ETPA		
unemployed	0.8 (0.55, 1.16)	0.8 (0.55, 1.16)
employed	reference	reference
PRPA		
unemployed	0.94 (0.64, 1.36)	0.94 (0.65, 1.37)
employed	reference	reference
BPA		
unemployed	0.97 (0.81, 1.15)	0.97 (0.82, 1.15)
employed	reference	reference
BUPA		
unemployed	0.75 (0.51, 1.12)	0.76 (0.51, 1.12)
employed	reference	reference
OXBE		
unemployed	1.06 (0.71, 1.6)	1.06 (0.71, 1.6)
employed	reference	reference
TCS		
unemployed	0.79 (0.52, 1.21)	0.8 (0.53, 1.23)
employed	reference	reference
DEP		
unemployed	0.98 (0.84, 1.13)	0.97 (0.84, 1.13)
employed	reference	reference
DETP		
unemployed	0.98 (0.68, 1.42)	0.97 (0.67, 1.41)
employed	reference	reference
DMP		
unemployed	0.97 (0.83, 1.14)	0.97 (0.83, 1.13)
employed	reference	reference
DMTP		
unemployed	0.88 (0.7, 1.11)	0.88 (0.7, 1.11)
employed	reference	reference

Table S21: Additional acknowledgements of some of the cohorts included in HELIX

BiB:	Born in Bradford is only possible because of the enthusiasm and commitment of the Children and Parents in BiB. We are grateful to all the participants, health professionals and researchers who have made Born in Bradford happen.
EDEN:	We thank all the children and families participating in the EDEN-HELIX mother-child cohort. We thank Sonia Brishoual, Angelique Serre and Michele Grosdenier (Poitiers Biobank, CRB BB-0033-00068, Poitiers, France) for biological sample management and Prof Frederic Millot (principal investigator), Elodie Migault, Manuela Boue and Sandy Bertin (Clinical Investigation Center, Inserm CIC1402, CHU de Poitiers, Poitiers, France) for planification and investigational actions. We are also grateful to Veronique Ferrand-Rigalleau, Celine Leger and Noella Gorry (CHU de Poitiers, Poitiers, France) for administrative assistance. We thank Lise Giorgis-Allemand and Joane Quentin for the study management (Inserm, IAB Grenoble and CHU Grenoble-Alpes).
INMA:	The authors would like to thank Silvia Fochs, Nuria Pey, Cecilia Persavento and Susana Gros for field work, sample management and overall management in INMA.
MOBA:	We thank Ingvild Essen for thorough field work, Heidi Marie Nordheim for biological sample management and the MoBa administrative unit (MoBa).

5.4. Paper IV

Montazeri P, Valvi D, Casas M, Cirugeda L, Beneito A, Guxens M, Lertxundi A, Lopez-Espinosa MJ, Marina LS, Sunyer J, Vrijheid M. Prenatal exposure to multiple endocrine disrupting chemicals and childhood BMI trajectories. *Manuscript in process*.

ABSTRACT

INTRODUCTION: Prenatal exposure to endocrine disrupting chemicals (EDCs) may predispose individuals to develop obesity. Studies evaluating the effects of prenatal EDC exposure on child growth have mainly focused on individual aspects of growth using single chemical exposure models. However, in real life humans are exposed to multiple EDCs simultaneously and growth is a dynamic process. Thus, this study aimed to evaluate the associations between prenatal exposure to EDCs and children's body mass index (BMI) growth trajectories using single exposure and mixture modeling approaches.

METHODS: Using data from Spanish birth cohorts (n=1,911), prenatal exposure to persistent chemicals (organochlorines, perfluoroalkyl substances) and non-persistent chemicals (phthalates, phenols) was assessed using serum and spot-urine concentrations taken during pregnancy. BMI growth trajectories were calculated from 0 to 9 years old using latent class growth analysis. Multinomial regression models assessed associations for individual chemicals and Bayesian weighted quantile sum regression (BWQS) evaluated the overall association of the EDC mixture with child growth trajectories.

RESULTS: In single exposure models, prenatal exposure to hexachlorobenzene (HCB), dichlorodiphenyldichloroethylene (DDE), polychlorinated biphenyls (PCBs) and perfluorononanoic acid (PFNA) increased risk of belonging to a BMI growth trajectory characterized by lower birth size and subsequent accelerated BMI gain [e.g. (PCB-180: RRR = 1.20; 95% CI: 1.01-1.43), (HCB: RRR = 1.25; 95% CI: 1.09-1.42)]. HCB and DDE exposure were also associated with higher probability to belong to a trajectory of higher birth size and accelerated BMI gain. In mixture models, a mixture of 23 EDCs was associated with lower birth size and subsequent accelerated BMI gain. This association was strongest in males and those of lower social class.

CONCLUSION: This study provides evidence that prenatal exposure to EDCs may lead to a BMI trajectory in childhood characterized by lower or higher birth size and accelerated BMI gain. In single exposure and mixture models, organochlorine compounds were of most concern. To prevent adverse growth trajectories and their consequences, limiting EDC exposure in pregnant women to protect the growth and development of the growing fetus should be advised.

INTRODUCTION

Infant and early childhood growth and adiposity status are important factors in promoting healthy childhood development and well-being during adulthood. Children with overweight or obesity are more likely to continue in trajectories of excess weight during adulthood, putting them at an increased risk for complications such as diabetes, cardiovascular disease and increased mortality [1-3].

One risk factor of concern are endocrine disrupting chemicals (EDCs) as they may predispose individuals to develop obesity by interfering with normal endocrine function [4-5]. Several EDCs are persistent and remain in the environment for many years through bioaccumulation (e.g. dichlorodiphenyldichloroethylene (DDE), hexaclorobenzene (HCB), polychlorinated bisphenyls (PCBs), and perfluoroalkyl substances (PFAS)) [6]. Others are non-persistent (e.g. phthalates and phenols) and are metabolized quickly, but are so widespread in their use that human exposure in constant [7-8]. Exposure to EDCs occurs through use of plastic convenience items, consumption of food and water, and application of personal care products, to name a few [9-10]. Exposure is particularly concerning for pregnant women as many EDCs have been shown to transfer in-utero from the mother to the fetus [11-12]. As demonstrated by the developmental origins of health and disease (DOHaD) hypothesis, the gestational period is a critical stage of growth and development when exposure to EDCs may cause irreversible damage to the fetus resulting in increased disease susceptibility in later life [11-13].

While studies have evaluated the impact of prenatal EDC exposure on birth size and later body mass index (BMI) in childhood, fewer studies have utilized growth trajectories which integrate repeated measurements of growth over time [14-23]. By integrating multiple measures of growth from birth onwards, the more dynamic aspects of growth can be captured, particularly during the first two years of life which is a period of exponential growth that may impact later disease risk [24]. For example, previous evidence has shown that children who experience accelerated growth during infancy have increased risks for multiple diseases in adulthood, such as hypertension, cardiovascular diseases, diabetes and cancer [2,25-28]. These findings indicate that adverse growth patterns linked to disease may be evident in early childhood. By determining these

growth patterns and their determinants, we may be able to intervene during early life thus lessening future disease burden.

Studies evaluating the effects of prenatal EDC exposure on child growth have mainly focused on individual aspects of growth using single chemical exposure models. However, in real life humans are exposed to multiple EDCs simultaneously and growth is a dynamic process. Investigating multiple exposures increases the complexity of the analysis, but it is also a better reflection of real world circumstances. To better reflect real world exposure to EDCs and the dynamic patterns of childhood growth we aimed to evaluate the associations between prenatal exposure to persistent and non-persistent EDCs and children's BMI growth trajectories from 0 to 9 years old using single exposure and mixture modeling approaches.

METHODS

Study Population

The present study includes 1,911 mother-child pairs from the INfancia y Medio Ambiente (INMA) Spanish birth cohort studies in: Gipuzkoa (n=556), Sabadell (n=659), and Valencia (n=696) (Ribas-Fito). Pregnant women were recruited during the first trimester through regional hospitals between 2003 and 2008. The inclusion criteria were: ≥16 years of age, singleton pregnancy, intention to deliver at reference hospital, and no assisted conception or communication issues [29]. Mother child pairs were followed-up with during the third trimester, at birth, and at child ages 6 months, 1, 2, 4, 7, and 9 years. Information was collected through written questionnaires and physical examinations [29]. This study was approved by the ethics review boards of the hospitals involved in the study, and mother's signed a written consent for their and their child's participation.

Measurement of chemicals

Concentrations of chemicals were determined using maternal serum, plasma, and urine samples taken during pregnancy. Concentrations of organochlorines (OC: DDE, HCB, and PCB -138, -150, and -180) were measured in first trimester maternal serum samples. Samples were analyzed using gas chromatography with electron capture detection (GC-ECD) at the Gipuzkoa Basque Government Public Health Laboratory for Sabadell and Gipuzkoa

and the IDAEA/CSIC (Barcelona) for Valencia, as described previously [30,31]. As OCs are lipophilic, all concentrations were adjusted for maternal serum lipid content. PFAS concentrations were analyzed in first trimester maternal plasma samples at the Institute for Occupational Medicine, Rheinisch-Westfälische Technische Hochschule (RWTH) Aachen University using column-switching high performance liquid chromatography (HPLC) coupled to tandem mass spectrometry (MS-MS), as previously described [32]. Phthalate metabolites were measured at NIPH for Gipuzkoa and Valencia using pooled samples (1st and 3rd trimesters) with column-switching liquid chromatography-tandem mass spectrometry (LC-MS-MS), and at IMIM for Sabadell using spot urine samples taken separately during the first and third trimesters with HPLC-MS/MS. Phenols were measured at Instituto de Investigación Biosanitaria ibs.GRANADA for Gipuzkoa using pooled samples (1st and 3rd trimesters), and at NIPH for Sabadell and Valencia using spot urine samples taken separately during the first and third trimesters with on-line solid phase extraction (SPE) prior to ultra-high performance liquid chromatography (UPLC) coupled to MS-MS. Phthalate metabolites and phenols were adjusted for variation in urinary dilution by creatinine, and concentrations derived from separate first and third trimesters samples were averaged for analyses. Details regarding laboratories, and limit of detection (LOD) or quantification by cohort and sampling period can be found in Supplementary Material Tables S1a-c. For all concentrations a value equal to half the LOD was set to samples with concentrations below LOD, and concentrations were transformed using the base-2 logarithm to achieve more normal distributions.

Growth Trajectories

Repeated measurements of child's height and weight from birth to 9 years of age were obtained from medical records and measurements taken by trained INMA staff. Children were measured using standardized protocols, without shoes and in lightweight clothing. Age and sex specific BMI z-scores were calculated using the WHO Child Growth Standards [33,34]. BMI z-score trajectories (referred to as BMI trajectories hereafter) were estimated using latent class growth analysis (LCGA) [35,36]. The trajectories include measurements from 0 to 9 years (mean age=9.9 years) with an average of 14.3 measurement points per child. Five distinct BMI

trajectories were identified as the best fit for our data using Akaike information criterion (AIC) and Bayesian information criterion (BIC). The trajectories differed in birth size (defined as "lower", "average" or "higher") and in BMI gain velocity (defined as "slower" or "accelerated") (Figure 1). Based on these definitions the classes are labeled as: Class 1, larger birth size with subsequent accelerated BMI gain; Class 2, larger birth size with subsequent slower BMI gain; Class 3, smaller birth size with subsequent accelerated BMI gain; Class 4, average birth size with subsequent slower BMI gain; and Class 5, smaller birth size with subsequent slower BMI gain. For analysis, Class 4 was used as the reference category.

Statistical Analysis

Descriptive statistics were used to summarize population averages. Before running regression models, and to handle missing values for the chemical exposures (missing ranged from 11.3% in the OCs to 48.7% in the phthalate metabolites) and covariates (missing ranged from 0.1% in maternal age to 5.9% in paternal BMI), we followed a multiple imputation approach under the assumption of missing at random [37]. We generated 20 imputed data sets using the ice command in Stata, using imputation models that included additional covariates not included in the analyses models to improve prediction [38]. Covariates included in the main models were chosen using a directed acyclic graph (DAG), and all models were adjusted for sub-cohort (Gipuzkoa, Sabadell, Valencia), maternal age at delivery (years), prepregnancy BMI (kg/m^2), maternal smoking during pregnancy (none/yes), parity (0/1+), maternal Mediterranean diet score during pregnancy, paternal BMI, social class (higher, middle, lower), and child sex.

Associations between chemical concentrations and BMI trajectories were analyzed by running single exposure models using multinomial logistic regression. Next, we tested the association between a mixture including all chemical concentrations and the BMI trajectories using Bayesian weighted quantile sum regression (BWQS). BWQS is an extension on WQS regression that summarizes the overall exposure to the mixture by estimating a single weighted index while accounting for the individual contribution of each concentration of the mixture using weights [39].

Triclosan (TRCS) was not included in the mixture as it was not measured in Gipuzkoa.

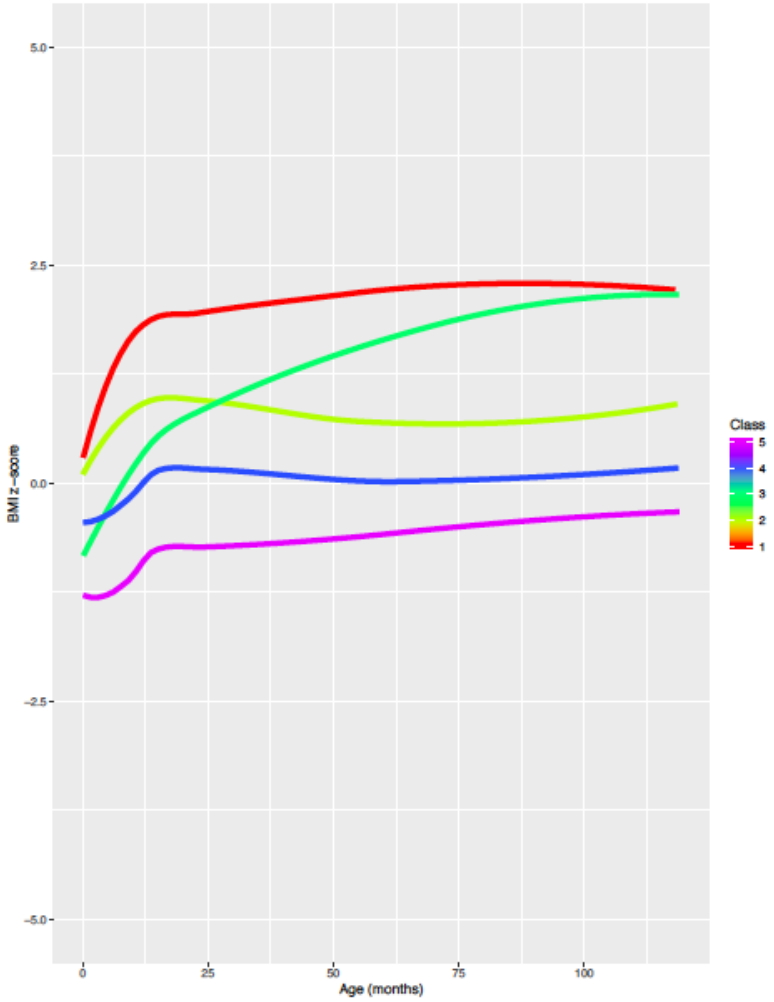
Additionally, we conducted sensitivity analyses: 1) complete case analysis for single exposure models; 2) stratifying single exposure models by child sex and social class; 3) stratifying multiple exposure models by child sex and social class (only for significant results in unstratified analysis). Statistical significance was defined as p-value <0.05. Regression analyses and imputation were carried out with STATA version 14 (College Station, TX). BWQS was conducted using RStudio version 4.0.3 (RStudio Team 2020).

RESULTS

Study Population

Figure 1 and Table 1 show the distribution of BMI trajectories and the main characteristics for the study population. The majority of children (32%) belonged to the reference trajectory, Class 4: average birth size and slower BMI gain, while the least number of children (11%) belonged to Class 1: larger birth size and accelerated BMI gain (Figure 1). There were no differences in main characteristics between the original and imputed datasets (Table S2). Population characteristics were generally consistent across the BMI trajectories with a few differences. When compared to all BMI trajectories combined, Class 1 had a higher percentage belonging to the lower social class group and mothers who smoked during pregnancy. Additionally, more mothers with children in Class 5 were nulliparous, and maternal and paternal prepregnancy BMI were slightly higher in Classes 1 and 3 (Table 1). The geometric mean (GM) of the EDC concentrations were generally similar between the original and the imputed data sets (Table 2). Correlations between the chemical exposures were generally high within distinct classes of chemicals, namely phthalate metabolites, PFASs, and PCBs, but not between one another (Supplementary Material Figure S1a-b).

Figure 1. BMI z-score growth trajectories from 0 to 9 years old



Class	Description	Frequency
Class 1	higher birth size – accelerated BMI gain	11.1%
Class 2	higher birth size – slower BMI gain	26.8%
Class 3	lower birth size – accelerated BMI gain	15.3%
Class 4	average birth size – slower BMI gain (reference)	31.8%
Class 5	lower birth size – slower BMI gain	15.0%

Table 1. Characteristics of the study population (n = 1,911)

Characteristic	Missing	Original Data	Class 1: higher birth size – accelerated BMI gain	Class 2: higher birth size – slower BMI gain	Class 3: lower birth size – accelerated BMI gain	Class 4: average birth size – slower BMI gain	Class 5: lower birth size – slower BMI gain
	(N)	N (%) or Mean (SD)	N (%) or Mean (SD)	N (%) or Mean (SD)	N (%) or Mean (SD)	N (%) or Mean (SD)	N (%) or Mean (SD)
Sub-cohort	0						
Gipuzkoa		556 (29.1)	59 (27.8)	168 (32.8)	83 (28.4)	173 (28.5)	73 (25.4)
Sabadell		659 (34.5)	68 (32.1)	170 (33.1)	88 (30.1)	226 (37.2)	107 (37.3)
Valencia		696 (36.4)	85 (40.1)	175 (34.1)	121 (41.44)	208 (34.3)	107 (37.3)
Social Class	94						
Higher		594 (32.7)	47 (23.5)	154 (31.8)	97 (34.6)	202 (34.8)	94 (34.6)
Middle		477 (26.2)	57 (28.5)	129 (26.6)	66 (23.6)	157 (27.1)	68 (25.0)
Lower		746 (41.1)	96 (48)	202 (41.7)	117 (41.8)	221 (38.1)	110 (40.4)
Smoking during pregnancy	33						
None		1293 (68.9)	125 (59.8)	360 (71.0)	194 (67.4)	417 (69.7)	197 (71.4)
Yes		585 (31.1)	84 (40.2)	147 (29.0)	94 (32.6)	181 (30.3)	79 (28.6)
Parity	96						
0		1012 (55.8)	109 (54.5)	234 (48.4)	173 (61.8)	316 (54.5)	180 (66.4)
1+		803 (44.2)	91 (45.5)	250 (51.7)	107 (38.2)	264 (45.5)	91 (33.6)
Maternal age (at delivery) (years)	2	31.8 (4.2)	31.6 (4.2)	31.9 (4.2)	32.0 (4.0)	31.7 (4.2)	31.8 (4.2)

Maternal prepregnancy BMI (kg/m2)	17	23.5 (4.2)	25.2 (5.0)	23.3 (3.6)	24.6 (5.2)	23.0 (4.1)	22.6 (3.6)
Paternal BMI (prepregnancy) (kg/m2)	112	25.8 (3.4)	26.7 (4.0)	25.8 (3.1)	26.7 (3.5)	25.2 (3.3)	25.1 (3.1)
Maternal Mediterranean diet score	94	8.0 (2.7)	7.9 (2.6)	8.2 (2.7)	8.0 (2.6)	7.9 (2.7)	7.9 (2.8)
Child sex	0						
Female		927 (48.5)	85 (40.1)	242 (47.2)	143 (49.0)	326 (53.7)	131 (45.6)
Male		984 (51.5)	127 (59.9)	271 (52.8)	149 (51.0)	281 (46.3)	156 (54.4)
Abbreviations: N = number of observations, SD = standard deviation, BMI = body mass index							

Table 2. Geometric mean (GM) concentrations for the EDCs in the original and imputed datasets

EDC	Original Data		Imputed Data (N=1,911)
	N	GM (95% CI)	GM (95% CI)
MEP	983	243.33 (226.88, 260.97)	249.90 (247.15, 252.68)
MiBP	983	31.81 (30.45, 33.23)	34.43 (34.19, 34.67)
MnBP	983	31.49 (29.53, 33.58)	33.64 (33.30, 33.98)
MBzP	982	9.45 (8.95, 9.99)	10.47 (10.38, 10.56)
MEHP	981	8.43 (8.00, 8.88)	10.31 (10.23, 10.39)
MEHHP	983	25.24 (24.07, 26.47)	32.21 (31.98, 32.44)
MEOHP	983	17.23 (16.44, 18.05)	21.77 (21.62)
MECPP	983	38.22 (36.67, 39.84)	46.83 (46.54, 47.13)
MEPA	1148	185.06 (168.53, 203.20)	180.98 (178.12, 183.87)
ETPA	1148	13.17 (11.90, 14.58)	13.05 (12.82, 13.27)
PRPA	1146	36.08 (32.43, 40.14)	34.49 (33.87, 35.12)
BPA	1147	2.98 (2.74, 3.24)	2.87 (2.83, 2.91)
BUPA	1146	2.09 (1.86, 2.35)	2.05 (2.01, 2.09)
BP-3	1148	6.51 (5.76, 7.35)	6.45 (6.32, 6.58)
TRCS[a]	893	30.04 (26.53, 34.01)	29.70 (29.07, 30.35)
HCB	1695	41.02 (39.21, 42.91)	40.95 (40.58, 41.34)
DDE	1695	132.69 (127.08, 138.54)	134.64 (133.45, 135.85)
PFHxS	1236	0.57 (0.55, 0.58)	0.55 (0.55, 0.55)
PFOA	1236	2.31 (2.24, 2.38)	2.26 (2.24, 2.27)
PFOS	1236	5.78 (5.63, 5.93)	5.69 (5.66, 5.72)
PFNA	1236	0.65 (0.63, 0.67)	0.64 (0.64, 0.64)
PCB 138	1694	24.68 (23.80, 25.59)	24.43 (24.25, 24.61)
PCB 153	1694	40.29 (38.85, 41.78)	39.62 (39.32, 39.91)
PCB 180	1695	28.89 (27.84, 29.97)	28.40 (28.19, 28.62)

Abbreviations: EDC = endocrine disrupting chemical, GM = geometric mean, N = number of observations, CI = confidence interval
MEP, MiBP, MnBP, MBzP, MEHP, MEHHP, MEOHP, MECPP, MEPA, ETPA, PRPA, BPA, BP-3, TRCS in ug/g creatinine
HCB, DDE, PCB -138, -153, -180 in ng/g lipid
PFHxS, PFOA, PFOS, PFNA in ng/mL
[a] TRCS is only available for Sabadell and Valencia, n imputed = 1355

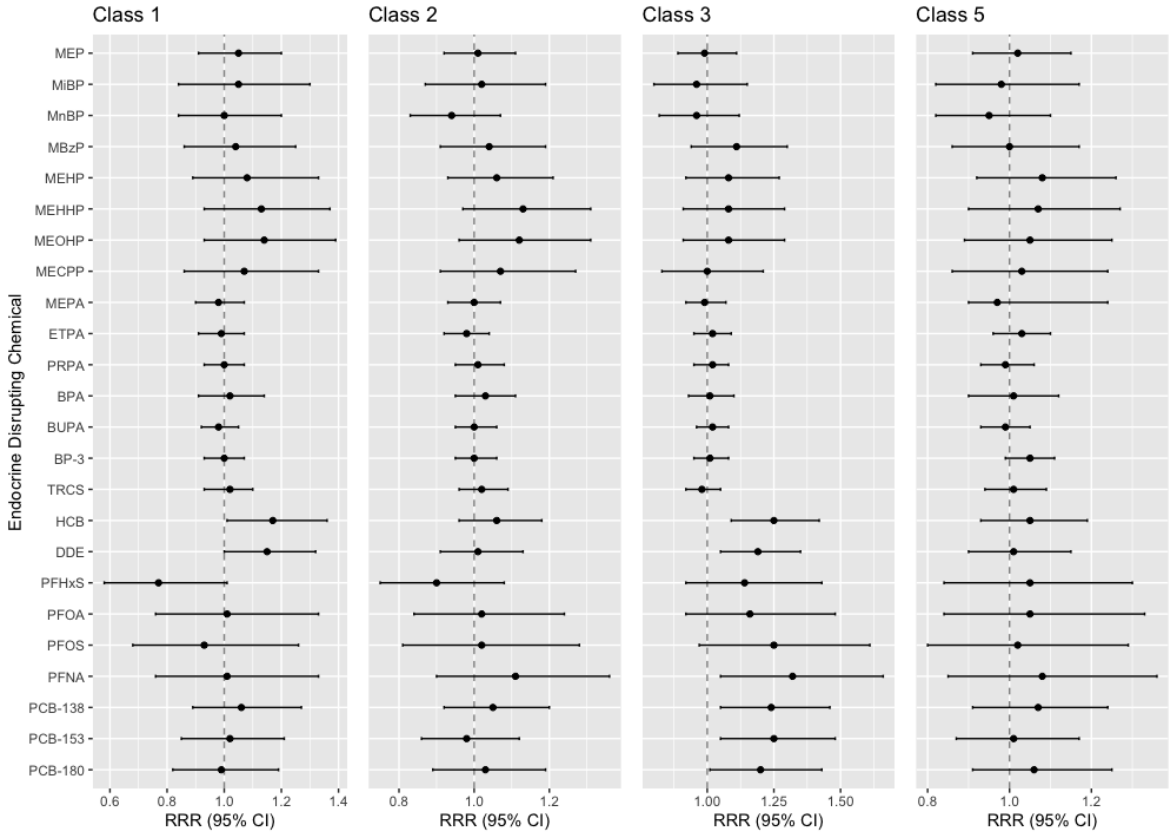
Single Exposure Models

Associations from single exposure models and BMI trajectories, in reference to Class 4 (average birth size followed by slower BMI gain), are shown in Figure 2 and Table S3. Prenatal exposure to all OCs (HCB, DDE, PCBs -138, -153, -180) was associated with a statistically significant 19 to 25% increase in risk of belonging to the BMI trajectory characterized by lower birth size and accelerated BMI gain (Class 3) per doubling of exposure concentration [e.g. Class 3 vs. 4: (PCB-180: RRR = 1.20; 95% CI: 1.01-1.43), (HCB: RRR = 1.25; 95% CI: 1.09-1.42)]. Additionally, HCB and DDE concentrations were associated with an increased risk of belonging to the BMI trajectory characterized by higher birth size and accelerated BMI gain (Class 1) [Class 1 vs. 4: (HCB: RRR = 1.17; 95% CI: 1.01-1.36), (DDE: RRR = 1.15; 95% CI: 1.00-1.32)]. Regarding PFAS, a doubling of prenatal PFNA exposure was associated with a 32% increase in risk of belonging to Class 3 (Class vs. 4: RRR = 1.32; 95% CI: 1.05-1.66); for other PFAS, RRR estimates for this class were increased but did not reach statistical significance.

In complete case analyses, results were somewhat stronger than imputed models, and had the same directionality (Supplementary Material Table S4). In addition to the statistically significant findings of the imputed models, the complete case analyses showed statistically significant associations between MBzP, MEHP, PFOA and PFOS concentrations and increased probability of belonging to Class 3.

In stratified analyses by sex, associations generally followed a similar patterns as in the overall population, with increases in risk of belonging to Class 3 seen for OCs and PFAS in females and males, although these did not always reach statistical significance (Supplementary Material Table S5). Statistically significantly increased RRRs for Class 3 were observed in males for HCB, DDE and PCB-153, and in females for HCB. For boys, Class 1 membership was statistically significantly increased for DDE. While not significant in overall analyses, MEHHP exposure was associated with an increased probability of belonging to a trajectory characterized by higher birth size and slower BMI gain (Class 2) in girls [Class 2 vs. 4: (RRR = 1.23; 95% CI: 1.01, 1.51)].

Figure 2. Associations (Relative Risk Ratios and 95% Confidence Intervals) between prenatal EDC exposure and BMI trajectories: single exposure models



Abbreviations: EDC = endocrine disrupting chemical, RRR = relative risk ratio, CI = confidence interval
BMI trajectory descriptions: Class 1 = higher birth size – accelerated BMI gain, Class 2 = higher birth size – slower BMI gain, Class 3 = lower birth size – accelerated BMI gain, Class 5 = lower birth size – slower BMI gain. All RRRs are in reference to Class 4 = average birth size – slower BMI gain.

In stratified analyses by social class, associations varied and not one particular social class was consistently at a higher risk than others; rather, differences were observed by social class depending on EDC (Supplementary Material Table S6). Statistically significant risk increases of belonging to Class's 1 and 3 were seen for HCB in those of middle social class, while increased RRRs were found for DDE and Class 1 in those of lower social class and Class 3 in those of higher social class. Associations for PCBs were generally higher in the higher social class, with PCB-138 and -153 and Class 3 reaching statistical significance. PFAS had higher RRRs for Class's 1 and 3 for both lower and higher social classes, and PFNA reached statistical significance with Class 3 for those of lower social class. Although not significant in overall analyses, in those of lower social class exposure to MEHP, MEHHP and MEOHP was associated with increased probability of belonging to a BMI trajectory characterized by lower birth size and slower BMI gain (Class 5), and Class 2 for MEHHP and MEOHP only [e.g. Class 5 vs. 4 (MEHP: RRR = 1.30; 95% CI: 1.01, 1.67), Class 2 vs. 4 (MEOHP: RRR = 1.37; 95% CI: 1.03, 1.81)].

Multiple Exposure Models

In mixture models using BWQS, a positive association was observed between the mixture of 23 EDCs and BMI trajectory Class 3 in reference to Class 4 ($\beta = 0.53$; credible interval [CrI]: 0.03, 0.96) (Table 3). Components of HCB, DDE, PCB-138, -153, -180, and BP-3 had somewhat higher weights (in that order), and thus contributed slightly more to the overall mixture (Supplementary Material Table S7). No associations between the EDC mixture and the other BMI trajectory classes were observed (Table 3). When stratified by sex the mixture was not statistically significantly associated with Class 3 in either boys or girls, but was somewhat stronger in boys ($\beta = 0.61$; CrI: -0.13, 1.31) than in girls ($\beta = 0.36$; CrI: -0.21, 0.95) (Supplementary Material Table S8). In stratification by social class, the EDC mixture was associated with the Class 3 BMI trajectory in those of lower social class ($\beta = 0.84$; CrI: 0.25, 1.49), whereas there was no evidence for an association in middle or higher social class ($\beta = 0.09$ and 0.05, respectively) (Supplementary Material Table S9).

Table 3. Association between exposure to prenatal EDC mixture and BMI trajectories from BWQS regression (imputed data; n = 1.911)

BMI Trajectory	Beta (CrI)
Class 1: higher birth size – accelerated BMI gain	0.14 (-0.38, 0,68)
Class 2: higher birth size – slower BMI gain	0.15 (-0.15, 0.46)
Class 3: lower birth size – accelerated BMI gain	0.53 (0.03, 0.96)
Class 4: average birth size – slower BMI gain	Ref.
Class 5: lower birth size – slower BMI gain	0.21 (-0.19, 0.63)
Abbreviations: BMI = body mass index, CrI = credible interval, Ref. = reference	

DISCUSSION

In this large prospective cohort of mother – child pairs in Spain, OCs, PFNA, and a mixture of 23 EDCs were associated with childhood BMI growth trajectories. Specifically, prenatal concentrations of HCB, DDE, PCBs and PFNA were associated with an increased risk of belonging to a BMI growth trajectory characterized by lower birth size and subsequent accelerated BMI gain. Further, HCB and DDE exposure was associated with higher probability to belong to a trajectory of higher birth size and accelerated BMI gain. In addition, our study results suggest that a mixture of EDCs is associated with lower birth size and subsequent accelerated BMI gain, and the chemicals of highest concern are similar to those previously mentioned in single exposure analyses. This association was the strongest in males and those of lower social class.

Our findings suggest that prenatal exposure to DDE and HCB is associated with the two trajectories that are characterized by accelerated BMI gain (from lower and higher birth size), and that PCB exposure is associated with the trajectory of lower birth size and subsequent accelerated BMI gain. These findings are largely in line with the literature, especially for DDE and HCB. An earlier study using INMA data also found that prenatal exposure to DDE and HCB was associated with rapid growth during the first 6

months of life, however associations were null for prenatal exposure to PCBs [19]. A pooled study from seven European cohorts found that prenatal DDE exposure was associated with increased weight-for-age growth rate, whereas PCBs were associated with decreased growth rate [22]. A review highlighted that exposure to DDE and HCB is consistently associated with increased adiposity during childhood, but that evidence is less clear for PCBs [13].

A review which included seven studies on prenatal PFAS exposure and postnatal growth parameters concluded that PFAS are associated with a rapid increase in BMI during childhood [16], and two additional reviews reported an association between PFAS and excess adiposity and risk of obesity during childhood [13,40]. Further, a recent review highlighted that PFAS levels during pregnancy are associated with decreases in birthweight, which may be mediated by maternal glucose [41]. Our findings are in line with literature on birthweight and childhood growth, suggesting that PFAS, especially PFNA, exposure is associated with a higher probability of belonging to a trajectory of lower birth size and accelerated BMI gain.

Regarding the non-persistent EDCs, phthalates and phenols, studies have reported largely mixed results with regards to prenatal exposure and later BMI [13,40]. The INMA study previously reported a negative association with rapid growth during infancy in boys, while other studies reported positive associations with rapid growth during infancy and higher probability of following an overweight trajectory from infancy to adolescence in a sex-specific and dose-specific manner [20,42-44]. We did not observe any results with any of the phenols. BPA is the most frequently studied phenol, but results are inconsistent [13,40].

The only previous study that investigated an EDC mixture (which included phthalates, plasticizers, bisphenols, TRCS, polycyclic aromatic hydrocarbons, pesticides, PFAS, OCs and PCBs) with children's growth trajectory parameters found a positive association with a mixture including 41 metabolites (26 after summation) and lower birthweight z-scores and slower weight gain parameters until 5.5 years old [21]. They reported that TRCS and PFOA were primary drivers of these associations as they had the highest WQS weights. Similar to our study Svensson et al. (2021) found an association

with lower birth size, however, whereas we found our mixture was associated with subsequent accelerated growth they found their mixture was associated with slower or delayed growth. This difference could be due several factors such as; 1) slight differences in metabolites included in the mixture, Svensson et al. (2021) included 41 metabolites while we included 23, although chemicals were from similar chemical groups; 2) calculation of the growth parameters, we used LCGA to estimate growth trajectories whereas they used a double-logistic growth model and extracted growth parameters (infant growth spurt rate and peak growth velocity); and 3) mixture model selected, they chose WQS while we selected BWQS which adds an additional layer to WQS regression in that it allows for bidirectionality of the coefficient associated with the mixture thus increasing model flexibility. Given that our studies are the first to analyze EDC mixtures with growth trajectories, it is important for other studies from diverse populations to replicate the findings.

Additionally, we stratified our results by sex and social class. In single exposure models we did not observe strong patterns between the stratified groups, however in the mixture exposure models we found the observed significant positive association with the trajectory of lower birth size and accelerated BMI gain to be stronger in males and those of lower social class. Differences in sex may be attributable to effects on sex hormones (e.g. estrogens and androgens) that play a role in adipogenesis. Regarding social class, previous work on the social determinants of EDC exposure has reported results that support higher exposure to OCs in higher social class groups [45-47]. However, research has reported mixed results with PFAS and phthalates and social class [48-50]. Given that our mixture was driven by OCs and research has shown OC concentrations are higher in higher social classes we may have expected to find stronger results with the higher social class, however we found the opposite. This may indicate that although higher social classes may have higher levels of certain EDCs, those of lower social classes may be more vulnerable to the effects of EDCs due to other factors in their environment.

The exact mechanism by which prenatal exposure to EDCs may affect childhood growth is unclear, and may differ depending on the chemical in question. Nonetheless, the obesogen hypothesis states

that EDCs interfere with the endocrine and metabolic systems thus altering normal growth patterns, weight gain and obesity [51]. Supporting literature has identified the peroxisome proliferator activated receptor (PPAR)-alpha and -gamma pathways as key contributors. These receptors regulate lipid metabolism, healthy placenta function, and fetal and child development indicating their ability to influence child growth starting from prenatal life [52]. Additionally, EDCs have been found to be able to induce adipogenic differentiation, and decrease metabolic efficiency, both of which can lead to obesity [40,53,54].

This study has some strengths worth mentioning. The data used is part of a large collaborative longitudinal study in Spain that began following mother – child pairs from the beginning of pregnancy. The multiple follow-up points throughout infancy and childhood up to 9 years of age enabled the calculation of BMI trajectories, another strength of this study. By using LCGA we were able to assign BMI trajectory classes to our population, defined by specific growth parameters that could be used for later regression analyses. This kind of method offers ease of interpretation, but may assign a child to a BMI trajectory they do not really follow, although that would be the minority. We also included a mixture of EDCs that included phthalates, phenols, OCs, and PFAS. This wide variety of chemicals does not include all potentially EDCs. However, it offers a good representation of those that may affect childhood growth and that humans are commonly exposed to. Additionally, we were able to use a novel mixture approach, BWQS, which allowed us to analyze an EDC mixture more representative of real life exposure, and identify those chemicals that were driving the associations (e.g. those with the highest weights).

Our study should be interpreted with the following limitations in mind. The non-persistent chemicals in this study were analyzed using only 1 to 2 spot-urine samples or a pooled urine sample. These types of chemicals have large variability in sample concentrations which can lead to measurement error on the exposure variable and ultimately bias associations towards the null due to regression dilution bias [55]. This is not the case for the persistent EDCs in our study (OCs, PFAS) which have long half-lives and likely give a reliable estimate of exposure. Further, there were missing values for many exposures in our study. In order to

correct for this we used multiple imputation under the MAR assumption which has been proven to give valid results, rather than use complete case analysis which can lead to selection bias [38]. By imputing the exposures we were also able to maintain sufficient sample for BWQS regression. Multiple imputation should be a technique considered by future studies aiming to use mixture analysis, but may have missing exposure values. Finally, multiple comparison issues are important in single exposure models. We did not adjust for multiple testing in our study which can be over conservative, instead we complimented those models with a mixture approach that reduces co-pollutant confounding by taking into account the exposure variables simultaneously. When looking at our results we found similar results between the significant EDCs in the single exposure models and those with the highest weights in BWQS regression, which gave us greater confidence in our results.

Our results provide further support for the DOHaD hypothesis, as they demonstrate that early life exposure to environmental factors can influence a child's growth trajectory. Our study found that chemical exposures and their mixture were related to an increased risk of belonging to a trajectory characterized by lower birth size and accelerated BMI gain, and for some chemicals (DDE and HCB) by higher birth size and accelerated BMI growth. Given that accelerated growth has been linked to adverse health consequences (e.g. hypertension, obesity, cardiovascular diseases, diabetes, and cancers) in later life, it would be important for future research to evaluate the health impacts of prenatal EDC exposure over the life course [26].

This study provides evidence that prenatal exposure to EDCs may lead to a BMI trajectory in childhood characterized by lower birth size and accelerated BMI gain. In both a mixture of EDCs as well as single EDC exposure models, OCs seemed to be those of most concern. To help prevent future adverse growth trajectories and their consequences, it may be prudent to limit EDC exposure in pregnant women to protect the growth and development of the growing fetus.

ACKNOWLEDGMENTS

We thank all of the study participants for their support with the INMA birth cohort studies. We also thank the dedicated INMA research nurses and staff for their work in conducting the study visits.

FUNDING

Gipuzkoa: This study was funded by grants from Instituto de Salud Carlos III (FIS-PI06/0867, FIS-PI09/00090, FIS-PI13/02187 and FIS-PI18/01142 incl. FEDER funds), CIBERESP, Department of Health of the Basque Government (2005111093, 2009111069, 2013111089 and 2015111065), and the Provincial Government of Gipuzkoa (DFG06/002, DFG08/001 and DFG15/221) and annual agreements with the municipalities of the study area (Zumarraga, Urretxu , Legazpi, Azkoitia y Azpeitia y Beasain).

Valencia: This study was funded by Grants from UE (FP7-ENV-2011 cod 282957 and HEALTH.2010.2.4.5-1), Spain: ISCIII (Red INMA G03/176, CB06/02/0041; FIS-FEDER: PI03/1615, PI04/1509, PI04/1112, PI04/1931, PI05/1079, PI05/1052, PI06/1213, PI07/0314, PI09/02647, PI11/01007, PI11/02591, PI11/02038, PI13/1944, PI13/2032, PI14/00891, PI14/01687, PI16/1288, and PI17/00663; Miguel Servet-FEDER CP11/00178, CP15/00025, and CPII16/00051), Generalitat Valenciana: FISABIO (UGP 15-230, UGP-15-244, and UGP-15-249), and Alicia Koplowitz Foundation 2017.

Sabadell: This study was funded by grants from Instituto de Salud Carlos III (Red INMA G03/176; CB06/02/0041; PI041436; PI081151 incl. FEDER funds; PI12/01890 incl. FEDER funds; CP13/00054 incl. FEDER funds; PI15/00118 incl. FEDER funds; CP16/00128 incl. FEDER funds; PI16/00118 incl. FEDER funds; PI16/00261 incl. FEDER funds; PI17/01340 incl. FEDER funds; PI18/00547 incl. FEDER funds), CIBERESP, Generalitat de Catalunya-CIRIT 1999SGR 00241, Generalitat de Catalunya-AGAUR (2009 SGR 501, 2014 SGR 822), Fundació La marató de TV3 (090430), Spanish Ministry of Economy and Competitiveness (SAF2012-32991 incl. FEDER funds), Agence Nationale de Securite Sanitaire de l'Alimentation de l'Environnement et du

Travail (1262C0010; EST-2016 RF-21), EU Commission (261357, 308333, 603794 and 634453). We acknowledge support from the Spanish Ministry of Science and Innovation and the State Research Agency through the “Centro de Excelencia Severo Ochoa 2019-2023” Program (CEX2018-000806-S), and support from the Generalitat de Catalunya through the CERCA Program.

REFERENCES

1. World Health Organization (WHO). Fact sheet: Cardiovascular diseases (CVDs). (2021).
2. Barker, D. J. P., Osmond, C., Forsén, T. J., Kajantie, E. & Eriksson, J. G. Trajectories of growth among children who have coronary events as adults. N. Engl. J. Med. 353, 1802–1809 (2005).
3. Victora, C. G. et al. Maternal and child undernutrition: consequences for adult health and human capital. Lancet 371, 340–357 (2008).
4. Heindel, J. & Blumberg, B. Environmental Obesogens: Mechanisms and Controversies. Annu Rev Pharmacol Toxicol. 6, 89–106 (2019).
5. Heindel, J., Newbold, R. & Schug, T. Endocrine disruptors and obesity. Nat. Rev. Endocrinol. 11, 653–661 (2015).
6. World Health Organization (WHO). Hexachlorobenzene in drinking water. (2004).
7. Diamanti-Kandarakis, E. et al. Endocrine-Disrupting Chemicals: An Endocrine Society Scientific Statement. Endocr Rev. 30, 293–342 (2009).
8. Wittassek, M., Koch, H. M., Angerer, J. & Brüning, T. Assessing exposure to phthalates – The human biomonitoring approach. Mol Nutr Food Res 55, 7–31 (2011).
9. Landrigan, P. J. & Goldman, L. R. Children s Vulnerability To Toxic Chemicals: A Challenge And Opportunity To Strengthen Health And Environmental Policy. Health Aff. 30, 842–850 (2011).
10. Gore, A. C. et al. Executive Summary to EDC-2: The Endocrine Society’s second Scientific Statement on endocrine-disrupting chemicals. Endocr. Rev. 36, 593–602 (2015).

11. Lunder, S., Hovander, L., Athanassiadis, I. & Bergman, A. Significantly higher polybrominated diphenyl ether levels in young U.S. children than in their mothers. Environ. Sci. Technol. 44, 5256–62 (2010).
12. Mamsen, L. S. et al. Concentration of perfluorinated compounds and cotinine in human foetal organs, placenta, and maternal plasma. Sci. Total Environ. 596–597, 97–105 (2017).
13. Vrijheid, M., Casas, M., Gascon, M., Valvi, D. & Nieuwenhuijsen, M. Environmental pollutants and child health-A review of recent concerns. Int. J. Hyg. Environ. Health 219, 331–342 (2016).
14. Govarts, E. et al. Early-life exposure to multiple persistent organic pollutants and metals and birth weight: Pooled analysis in four Flemish birth cohorts. Environ. Int. 145, 106149 (2020).
15. Vafeiadi, M. et al. Association of prenatal exposure to persistent organic pollutants with obesity and cardiometabolic traits in early childhood: The rhea mother–child cohort (Crete, Greece). Environ. Health Perspect. 123, 1015–1021 (2015).
16. Liew, Z., Goudarzi, H. & Oulhote, Y. Developmental Exposures to Perfluoroalkyl Substances (PFASs): An Update of Associated Health Outcomes. Current environmental health reports vol. 5 (2018).
17. Güil-Oumrait, N., Valvi, D., Garcia-Esteban, R. & Guxens, M. Prenatal exposure to persistent organic pollutants and markers of obesity and cardiometabolic risk in Spanish adolescents. Environ. Int. 151, 1–12 (2021).
18. Lauritzen, H. B. et al. Prenatal exposure to persistent organic pollutants and child overweight/obesity at 5-year follow-up: a prospective cohort study. Environ. Heal. 17, 1–12 (2018).
19. Valvi, D. et al. Prenatal exposure to persistent organic pollutants and rapid weight gain and overweight in infancy. Obesity 22, 488–496 (2014).
20. Yang, T. C. et al. Exposure to Bisphenol A and phthalates metabolites in the third trimester of pregnancy and BMI trajectories. 13, 550–557 (2020).
21. Svensson, K. et al. Prenatal exposures to mixtures of endocrine disrupting chemicals and children's weight

trajectory up to age 5.5 in the SELMA study. Sci. Rep. 11, 1–12 (2021).
22. Iszatt, N. et al. Prenatal and Postnatal Exposure to Persistent Organic Pollutants and Infant Growth : A Pooled Analysis of Seven European Birth Cohorts. Env. Heal. Perspect 123, 730–736 (2015).
23. Agay-Shay, K. et al. Multi-pollutant EDCs and childhood weight. Environ. Health Perspect. 123, 1030–1037 (2015).
24. Bier, D. Growth in the first two years of life. Nestle Nutr. 61, 135–44 (2008).
25. Druet, C. et al. Prediction of childhood obesity by infancy weight gain: an individual-level meta-analysis. Paediatr Perinat Epidemiol. 26, 19–26 (2012).
26. Zheng, T. et al. Effects of environmental exposures on fetal and childhood growth trajectories. Ann Glob Heal. 82, 41–99 (2016).
27. Mook-Kanamori, D. O. et al. Fetal and infant growth and the risk of obesity during early childhood: the Generation R Study. Eur J Endocrinol 165, 623–30 (2011).
28. Oken, E. & Gillman, M. W. Fetal origins of obesity. Obes. Res. 11, 496–506 (2003).
29. Guxens, M. et al. Cohort Profile: The INMA--INfancia y Medio Ambiente--(Environment and Childhood) Project. Int. J. Epidemiol. 41, 930–940 (2012).
30. Goñi, F., López, R., Etxeandia, A., Millán, E. & Amiano, P. High throughput method for the determination of organochlorine pesticides and polychlorinated biphenyls in human serum. J Chromatogr B Anal. Technol Biomed Life Sci 852, 15–21 (2007).
31. Grimalt, J. et al. Integrated analysis of halogenated organic pollutants in sub-millilitre volumes of venous and umbilical cord blood sera. Anal Bioanal Chem 396, 2265–72 (2010).
32. Manzano-Salgado, C. B. et al. Transfer of perfluoroalkyl substances from mother to fetus in a Spanish birth cohort. Environ. Res. 142, 471–478 (2015).
33. Group., W. M. G. R. S. WHO Child Growth Standards: Length/height-for-age, weight-for-age, weight-for-length, weight-for-height and body mass index-for-age: Methods and development. (2006).

34. de Onis, M. et al. Development of a WHO growth reference for school-aged children and adolescents. Bull. World Health Organ. 85, 660–667 (2007).
35. Montazeri, P. et al. Maternal Metabolic Health Parameters During Pregnancy in Relation to Early Childhood BMI Trajectories. Obesity 26, 588–596 (2018).
36. Slining, M. M., Herring, a. H., Popkin, B. M., Mayer-Davis, E. J. & Adair, L. S. Infant BMI trajectories are associated with young adult body composition. J. Dev. Orig. Health Dis. 4, 1–13 (2012).
37. van Buuren, S. & Groothuis-Oudshoorn, K. MICE : Multivariate Imputation by Chained Equations in R. J. Stat. Softw. 45, (2011).
38. Royston, P. & White, I. R. Journal of Statistical Software Multiple Imputation by Chained Equations (MICE): Implementation in Stata. J. Stat. Softw. 45, 1–20 (2011).
39. Colicino, E., Pedretti, N. F., Busgang, S. & Gennings, C. Per- And poly-fluoroalkyl substances and bone mineral density: Results from the Bayesian weighted quantile sum regression. Environ. Epidemiol. 4, e092 (2020).
40. Braun, J. M. Early-life exposure to EDCs: role in childhood obesity and neurodevelopment. Nat. Rev. Endocrinol. 13, 161–173 (2016).
41. Kahn, L. G., Philippat, C., Nakayama, S. F. & Trasande, L. Endocrine-disrupting chemicals : implications for human health. Lancet Diabetes Endocrinol. 8, 703–718 (2020).
42. Valvi, D. et al. Prenatal phthalate exposure and childhood growth and blood pressure: Evidence from the spanish inma-sabadell birth cohort study. Environ. Health Perspect. 123, 1022–1029 (2015).
43. Botton, J. et al. Phthalate pregnancy exposure and male offspring growth from the intra-uterine period to five years of age. Env. Res. 151, 601–609 (2021).
44. Heggeseth, B., Holland, N., Eskenazi, B., Kogut, K. & Harley, K. Heterogeneity in Childhood Body Mass Trajectories in relation to Prenatal Phthalate Exposure. Env. Res. 175, 22–33 (2019).
45. Montazeri, P. et al. Socioeconomic position and exposure to multiple environmental chemical contaminants in six European mother-child cohorts. Int. J. Hyg. Environ. Health 222, 864–872 (2019).

46. Vrijheid, M. et al. Socioeconomic status and exposure to multiple environmental pollutants during pregnancy: evidence for environmental inequity? J. Epidemiol. Community Health 66, 106–113 (2012).
47. Fisher, M. et al. Concentrations of persistent organic pollutants in maternal and cord blood from the maternal-infant research on environmental chemicals (MIREC) cohort study. Environ. Health 15, 59 (2016).
48. Nelson, J. W., Scammell, M. K., Hatch, E. E. & Webster, T. F. Social disparities in exposures to bisphenol A and polyfluoroalkyl chemicals: a cross-sectional study within NHANES 2003-2006. Environ. Health 11, 10 (2012).
49. Casas, L. et al. Urinary concentrations of phthalates and phenols in a population of Spanish pregnant women and children. Environ. Int. 37, 858–866 (2011).
50. Tyrrell, J., Melzer, D., Henley, W., Galloway, T. S. & Osborne, N. J. Associations between socioeconomic status and environmental toxicant concentrations in adults in the USA: NHANES 2001-2010. Environ. Int. 59, 328–335 (2013).
51. Thayer, K. A., Heindel, J. J., Bucher, J. R. & Gallo, M. A. Role of environmental chemicals in diabetes and obesity: A national toxicology program workshop review. Environ. Health Perspect. 120, 779–789 (2012).
52. Szilagyi, J. T., Avula, V. & Fry, R. C. Perfluoroalkyl Substances (PFAS) and Their Effects on the Placenta, Pregnancy, and Child Development: a Potential Mechanistic Role for Placental Peroxisome Proliferator – Activated Receptors (PPARs). Curr. Environ. Heal. Reports (2020) doi:10.1007/s40572-020-00279-0 EARLY.
53. Cano-Sancho, G., Salmon, A. G. & La Merrill, M. A. Association between Exposure to p,p-DDT and Its Metabolite p,p-DDE with Obesity: Integrated Systematic Review and Meta-Analysis. Env. Heal. Perspect 1–15 (2017).
54. Gingrich, J., Ticiani, E. & Veiga-Lopez, A. Placenta Disrupted: Endocrine Disrupting Chemicals and Pregnancy. Trends Endocrinol. Metab. 31, 508–524 (2020).
55. Hutcheon, J. A., Chiolero, A. & Hanley, J. A. Random measurement error and regression dilution bias. BMJ c2289 (2010).

Supplementary Material
Paper IV

Tables S1a-c. Details regarding laboratories, and limit of detection (LOD) or quantification by cohort and sampling period

Table S1a: Gipuzkoa

EDC			1st Trimester		3rd Trimester		Pooled	
	Lab	LOD/Q	N	% <LOD/Q	N	% <LOD/Q	N	% <LOD/Q
MEP	NIPH	0.15	20	0%	5	0%	229	0%
MiBP	NIPH	0.15	20	0%	5	0%	229	0%
MnBP	NIPH	0.15	20	0%	5	0%	229	0%
MBzP	NIPH	0.06	20	0%	5	0%	228	0%
MEHP	NIPH	0.15	20	0%	5	0%	228	0%
MEHHP	NIPH	0.12	20	0%	5	0%	229	0%
MEOHP	NIPH	0.12	20	0%	5	0%	229	0%
MECPP	NIPH	0.61	20	0%	5	0%	229	0%
MEPA	Granada	0.06	20	0%	6	0%	229	0%
ETPA	Granada	0.06	20	0%	6	0%	229	1.3%
PRPA	Granada	0.06	20	0%	6	0%	229	0%
BPA	Granada	0.12	20	20.0%	6	0%	229	19.7%
BUPA	Granada	0.04	20	25.0%	6	0%	229	10.0%
BP-3	Granada	0.07	20	5.0%	6	0%	229	3.1%
TRCS	not measured							
HCB	Gipuzkoa	0.071	549	9.3%				
DDE	Gipuzkoa	0.071	549	2.2%				
PFHxS	RWTH	0.2	324	7.4%				
PFOA	RWTH	0.2	324	0%				
PFOS	RWTH	0.2	324	0%				
PFNA	RWTH	0.1	324	0.3%				
PCB 138	Gipuzkoa	0.071	548	6.8%				
PCB 153	Gipuzkoa	0.071	548	2.2%				
PCB 180	Gipuzkoa	0.071	549	3.6%				

Abbreviation: EDC = endocrine disrupting chemical, LOD/Q = limit of detection/quantification, N = number of observations

Table S1b: Sabadell

EDC			1st Trimester		3rd Trimester		Pooled	
	Lab	LOD/Q	N	% <LOD/Q	N	% <LOD/Q	N	% <LOD/Q
MEP	IMIM	1	395	0%	403	0.2%		
MiBP	IMIM	0.5	395	0%	403	0%		
MnBP	IMIM	1	395	0.8%	403	0.5%		
MBzP	IMIM	0.5	395	0.8%	403	0.7%		
MEHP	IMIM	1	395	0.5%	403	0.5%		
MEHHP	IMIM	0.5	395	0%	403	0%		
MEOHP	IMIM	0.5	395	0%	403	0%		
MECPP	IMIM	1	395	0%	403	0.2%		
MEPA	NIPH	0.03	99	0%	456	0%		
ETPA	NIPH	0.03	99	0%	456	0.7%		
PRPA	NIPH	0.03	99	1.0%	454	0.2%		
BPA	NIPH	0.03	99	0%	455	0.9%		
BUPA	NIPH	0.06	99	5.1%	454	5.1%		
BP-3	NIPH	0.03	99	0.0%	456	0%		
TRCS	NIPH	0.03	99	0.0%	456	0%		
HCB	Gipuzkoa	0.071	548	8.4%				
DDE	Gipuzkoa	0.071	548	0.2%				
PFHxS	RWTH	0.2	407	2.2%				
PFOA	RWTH	0.2	407	0%				
PFOS	RWTH	0.2	407	0%				
PFNA	RWTH	0.1	407	0.7%				
PCB 138	Gipuzkoa	0.071	548	22.1%				
PCB 153	Gipuzkoa	0.071	548	7.8%				
PCB 180	Gipuzkoa	0.071	548	16.6%				

Abbreviation: EDC = endocrine disrupting chemical, LOD/Q = limit of detection/quantification, N = number of observations

Table S1c: Valencia

EDC			1st Trimester		3rd Trimester		Pooled	
	Lab	LOD/Q	N	% <LOD/Q	N	% <LOD/Q	N	% <LOD/Q
MEP	NIPH	0.15	6	0%	45	0%	270	0%
MiBP	NIPH	0.15	6	0%	45	0%	270	0%
MnBP	NIPH	0.15	6	0%	45	0%	270	0%
MBzP	NIPH	0.06	6	0%	45	0%	270	0%
MEHP	NIPH	0.15	6	0%	44	0%	270	0%
MEHHP	NIPH	0.12	6	0%	45	0%	270	0%
MEOHP	NIPH	0.12	6	0%	45	0%	270	0%
MECPP	NIPH	0.61	6	0%	45	0%	270	0%
MEPA	NIPH	0.03	437	0%	437	0%		
ETPA	NIPH	0.03	437	0%	437	0%		
PRPA	NIPH	0.03	437	1.1%	437	0.5%		
BPA	NIPH	0.03	437	0%	437	0%		
BUPA	NIPH	0.07	437	10.3%	437	11.0%		
BP-3	NIPH	0.03	437	0%	437	0%		
TRCS	NIPH	0.07	437	0%	437	0%		
HCB	CSIC	0.029	598	5.5%				
DDE	CSIC	0.015	598	0.3%				
PFHxS	RWTH	0.2	505	2.6%				
PFOA	RWTH	0.2	505	0%				
PFOS	RWTH	0.2	505	0%				
PFNA	RWTH	0.1	505	0.8%				
PCB 138	CSIC	0.028	598	4.0%				
PCB 153	CSIC	0.017	598	3.8%				
PCB 180	CSIC	0.015	598	2.8%				

Abbreviation: EDC = endocrine disrupting chemical, LOD/Q = limit of detection/quantification, N = number of observations

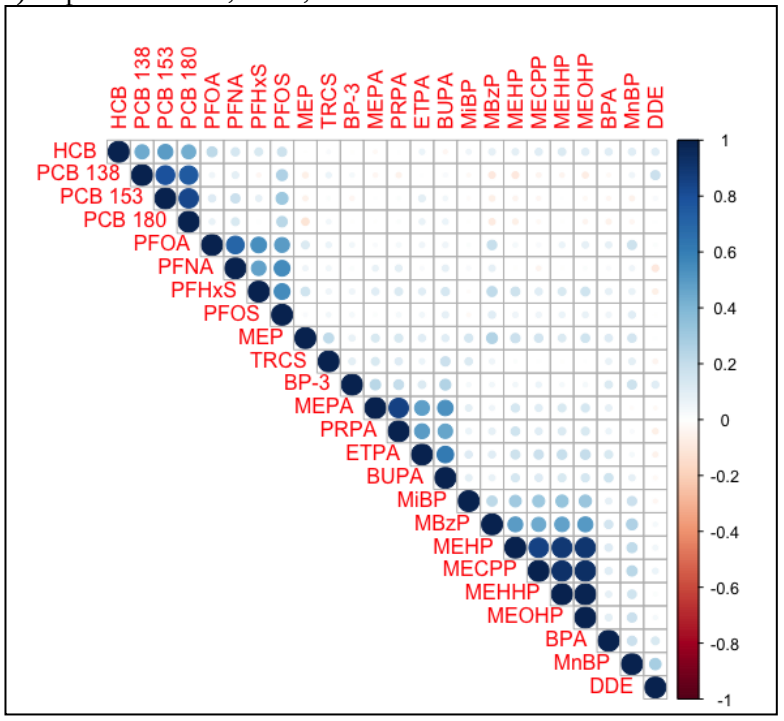
Table S2. Characteristics of the study population, original and imputed data

Characteristic	Missing	Original Data	Imputed Data
	(N)	N (%) or Mean (SD)	% or Mean (SD)
Sub-cohort	0		
Gipuzkoa		556 (29.1)	-
Sabadell		659 (34.5)	-
Valencia		696 (36.4)	-
Social Class	94		
Higher		594 (32.7)	32.6
Middle		477 (26.2)	26.3
Lower		746 (41.1)	41.2
Smoking during pregnancy	33		
None		1293 (68.9)	68.9
Yes		585 (31.1)	31.1
Parity	96		
0		1012 (55.8)	55.4
1+		803 (44.2)	44.6
Maternal age (at delivery)	2	31.8 (4.2)	31.8 (4.2)
Maternal prepregnancy BMI	17	23.5 (4.2)	23.5 (4.3)
Paternal BMI (prepregnancy)	112	25.8 (3.4)	25.8 (3.4)
Maternal Mediterranean diet score	94	8.0 (2.7)	8.0 (2.7)
Child sex	0		
Female		927 (48.5)	-
Male		984 (51.5)	-

Abbreviations: N = number of observations, SD = standard deviation, BMI = body mass index

Figures S1a-b. Pairwise Correlations of EDC exposures

a) Imputed data set, n = 1,911



b) Original data set, complete case

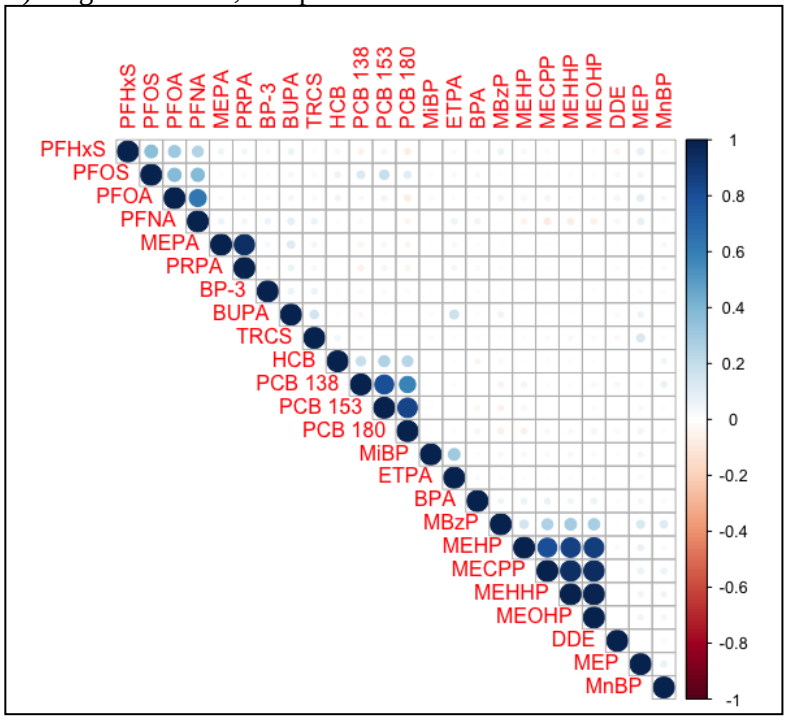


Table S3. Associations between EDCs and childhood BMI growth trajectory classes from single exposure models

	Class 1	Class 2	Class 3	Class 5
EDC	RRR (95% CI)	RRR (95% CI)	RRR (95% CI)	RRR (95% CI)
MEP	1.05 (0.91, 1.20)	1.01 (0.92, 1.11)	0.99 (0.89, 1.11)	1.02 (0.91, 1.15)
MiBP	1.05 (0.84, 1.30)	1.02 (0.87, 1.19)	0.96 (0.80, 1.15)	0.98 (0.82, 1.17)
MnBP	1.00 (0.84, 1.20)	0.94 (0.83, 1.07)	0.96 (0.82, 1.12)	0.95 (0.82, 1.10)
MBzP	1.04 (0.86, 1.25)	1.04 (0.91, 1.19)	1.11 (0.94, 1.30)	1.00 (0.86, 1.17)
MEHP	1.08 (0.89, 1.33)	1.06 (0.93, 1.21)	1.08 (0.92, 1.27)	1.08 (0.92, 1.26)
MEHHP	1.13 (0.93, 1.37)	1.13 (0.97, 1.31)	1.08 (0.91, 1.29)	1.07 (0.90, 1.27)
MEOHP	1.14 (0.93, 1.39)	1.12 (0.96, 1.31)	1.08 (0.91, 1.29)	1.05 (0.89, 1.25)
MECPP	1.07 (0.86, 1.33)	1.07 (0.91, 1.27)	1.00 (0.83, 1.21)	1.03 (0.86, 1.24)
MEPA	0.98 (0.90, 1.07)	1.00 (0.93, 1.07)	0.99 (0.92, 1.07)	0.97 (0.90, 1.06)
ETPA	0.99 (0.91, 1.07)	0.98 (0.92, 1.04)	1.02 (0.95, 1.09)	1.03 (0.96, 1.10)
PRPA	1.00 (0.93, 1.07)	1.01 (0.95, 1.08)	1.02 (0.95, 1.08)	0.99 (0.93, 1.06)
BPA	1.02 (0.91, 1.14)	1.03 (0.95, 1.11)	1.01 (0.93, 1.10)	1.01 (0.90, 1.12)
BUPA	0.98 (0.92, 1.05)	1.00 (0.95, 1.06)	1.02 (0.96, 1.08)	0.99 (0.93, 1.05)
BP-3	1.00 (0.93, 1.07)	1.00 (0.95, 1.06)	1.01 (0.95, 1.08)	1.05 (0.99, 1.11)
TRCS[a]	1.02 (0.93, 1.10)	1.02 (0.96, 1.09)	0.98 (0.92, 1.05)	1.01 (0.94, 1.09)
HCB	1.17 (1.01, 1.36)	1.06 (0.96, 1.18)	1.25 (1.09, 1.42)	1.05 (0.93, 1.19)
DDE	1.15 (1.00, 1.32)	1.01 (0.91, 1.13)	1.19 (1.05, 1.35)	1.01 (0.90, 1.15)
PFHxS	0.77 (0.58, 1.01)	0.90 (0.75, 1.08)	1.14 (0.92, 1.43)	1.05 (0.84, 1.30)
PFOA	1.01 (0.76, 1.33)	1.02 (0.84, 1.24)	1.16 (0.92, 1.48)	1.05 (0.84, 1.33)
PFOS	0.93 (0.68, 1.26)	1.02 (0.81, 1.28)	1.25 (0.97, 1.61)	1.02 (0.80, 1.29)
PFNA	1.01 (0.76, 1.33)	1.11 (0.90, 1.36)	1.32 (1.05, 1.66)	1.08 (0.85, 1.36)
PCB 138	1.06 (0.89, 1.27)	1.05 (0.92, 1.20)	1.24 (1.05, 1.46)	1.07 (0.91, 1.24)
PCB 153	1.02 (0.85, 1.21)	0.98 (0.86, 1.12)	1.25 (1.05, 1.48)	1.01 (0.87, 1.17)
PCB 180	0.99 (0.82, 1.19)	1.03 (0.89, 1.19)	1.20 (1.01, 1.43)	1.06 (0.91, 1.25)

Reference outcome category is Class 4. Abbreviations: BMI = body mass index, RRR = relative risk ratio, CI = confidence interval. All models adjusted for sub-cohort, social class, smoking during pregnancy, parity, maternal age at delivery, maternal prepregnancy BMI, paternal prepregnancy BMI, maternal Mediterranean diet score, child sex.

[a] TRCS only included two cohorts (Sabadell, Valencia) as such sample size was smaller (n = 1,355)

Table S4. Associations between EDCs and childhood BMI growth trajectory classes from single exposure models, complete case analysis

		Class 1	Class 2	Class 3	Class 5
EDC	N	RRR (95% CI)	RRR (95% CI)	RRR (95% CI)	RRR (95% CI)
MEP	958	1.10 (0.94, 1.28)	1.01 (0.90, 1.13)	0.95 (0.83, 1.08)	0.99 (0.85, 1.14)
MiBP	958	1.09 (0.87, 1.36)	0.99 (0.83, 1.17)	0.96 (0.79, 1.16)	0.96 (0.79, 1.18)
MnBP	958	1.03 (0.87, 1.22)	0.89 (0.77, 1.02)	0.94 (0.81, 1.09)	0.91 (0.78, 1.07)
MBzP	957	1.05 (0.85, 1.28)	0.99 (0.85, 1.16)	1.19 (1.00, 1.40)	0.93 (0.78, 1.12)
MEHP	956	1.17 (0.94, 1.45)	1.05 (0.89, 1.24)	1.20 (1.00, 1.44)	1.02 (0.83, 1.25)
MEHHP	958	1.19 (0.95, 1.50)	1.13 (0.95, 1.35)	1.18 (0.97, 1.43)	0.98 (0.79, 1.23)
MEOHP	958	1.21 (0.95, 1.54)	1.13 (0.94, 1.36)	1.20 (0.98, 1.47)	0.97 (0.77, 1.22)
MECPP	958	1.10 (0.85, 1.42)	1.06 (0.88, 1.29)	1.04 (0.83, 1.29)	0.93 (0.73, 1.19)
MEPA	1121	0.98 (0.89, 1.08)	1.00 (0.93, 1.07)	0.99 (0.92, 1.08)	0.97 (0.89, 1.06)
ETPA	1121	1.01 (0.93, 1.10)	0.98 (0.92, 1.05)	1.03 (0.95, 1.10)	1.05 (0.97, 1.13)
PRPA	1119	1.01 (0.93, 1.09)	1.02 (0.96, 1.09)	1.03 (0.96, 1.11)	1.01 (0.94, 1.09)
BPA	1120	1.03 (0.92, 1.15)	1.04 (0.96, 1.12)	1.00 (0.91, 1.09)	0.98 (0.88, 1.08)
BUPA	1119	0.98 (0.91, 1.06)	1.00 (0.95, 1.06)	1.04 (0.97, 1.11)	0.98 (0.92, 1.05)
BP-3	1121	1.01 (0.94, 1.08)	1.01 (0.96, 1.06)	1.02 (0.96, 1.09)	1.05 (0.98, 1.11)
TRCS[a]	880	1.02 (0.93, 1.11)	1.03 (0.97, 1.10)	0.99 (0.91, 1.06)	1.03 (0.95, 1.11)
HCB	1649	1.19 (1.03, 1.39)	1.05 (0.95, 1.17)	1.24 (1.08, 1.41)	1.04 (0.92, 1.17)
DDE	1649	1.19 (1.03, 1.37)	1.01 (0.90, 1.12)	1.24 (1.09, 1.40)	1.06 (0.93, 1.20)
PFHxS	1205	0.82 (0.62, 1.08)	0.96 (0.77, 1.18)	1.27 (0.99, 1.64)	1.01 (0.79, 1.30)
PFOA	1205	1.18 (0.88, 1.59)	1.10 (0.88, 1.37)	1.29 (1.00, 1.65)	1.09 (0.84, 1.42)
PFOS	1205	0.98 (0.73, 1.33)	1.09 (0.87, 1.38)	1.33 (1.02, 1.74)	1.05 (0.80, 1.37)
PFNA	1205	1.08 (0.82, 1.43)	1.22 (0.98, 1.52)	1.50 (1.17, 1.92)	1.11 (0.86, 1.43)
PCB 138	1648	1.06 (0.88, 1.27)	1.05 (0.92, 1.21)	1.24 (1.05, 1.47)	1.06 (0.91, 1.25)
PCB 153	1648	1.02 (0.85, 1.22)	0.98 (0.86, 1.12)	1.24 (1.04, 1.48)	1.00 (0.86, 1.16)
PCB 180	1649	0.99 (0.82, 1.19)	1.03 (0.90, 1.19)	1.20 (1.00, 1.43)	1.04 (0.88, 1.23)

Reference outcome category is Class 4. Abbreviations: BMI = body mass index, RRR = relative risk ratio, CI = confidence interval. All models adjusted for sub-cohort, social class, smoking during pregnancy, parity, maternal age at delivery, maternal prepregnancy BMI, paternal prepregnancy BMI, maternal Mediterranean diet score, child sex.

[a] TRCS only included two cohorts (Sabadell, Valencia) as such sample size was smaller (n = 1,355)

Table S5. Associations between EDCs and childhood BMI growth trajectory classes from single exposure models by sex, females (n = 927) / males (n = 984)

		Class 1	Class 2	Class 3	Class 5
EDC	Sex	RRR (95% CI)	RRR (95% CI)	RRR (95% CI)	RRR (95% CI)
MEP	F	1.03 (0.83, 1.29)	1.01 (0.89, 1.15)	1.02 (0.87, 1.19)	1.05 (0.88, 1.25)
	M	1.06 (0.90, 1.25)	1.02 (0.88, 1.17)	0.97 (0.83, 1.13)	0.99 (0.84, 1.18)
MiBP	F	1.02 (0.75, 1.39)	1.06 (0.84, 1.34)	0.95 (0.74, 1.21)	0.97 (0.76, 1.25)
	M	1.08 (0.82, 1.43)	0.99 (0.80, 1.22)	0.98 (0.77, 1.25)	0.99 (0.76, 1.28)
MnBP	F	1.04 (0.79, 1.36)	0.91 (0.76, 1.09)	0.95 (0.78, 1.15)	0.94 (0.77, 1.14)
	M	0.98 (0.79, 1.22)	0.97 (0.82, 1.15)	0.97 (0.79, 1.18)	0.96 (0.78, 1.19)
MBzP	F	1.11 (0.83, 1.47)	1.07 (0.87, 1.32)	1.11 (0.89, 1.40)	0.95 (0.76, 1.18)
	M	1.00 (0.79, 1.25)	1.01 (0.85, 1.21)	1.10 (0.90, 1.35)	1.04 (0.82, 1.31)
MEHP	F	1.17 (0.89, 1.54)	1.11 (0.93, 1.34)	1.15 (0.93, 1.43)	1.10 (0.88, 1.37)
	M	1.02 (0.79, 1.33)	1.02 (0.82, 1.26)	1.02 (0.81, 1.29)	1.06 (0.85, 1.31)
MEHHP	F	1.29 (0.96, 1.73)	**1.23 (1.01, 1.51)**	1.21 (0.95, 1.52)	1.13 (0.88, 1.46)
	M	1.01 (0.77, 1.31)	1.03 (0.82, 1.29)	0.96 (0.73, 1.25)	1.01 (0.8, 1.27)
MEOHP	F	1.26 (0.95, 1.68)	1.21 (0.99, 1.48)	1.20 (0.95, 1.51)	1.13 (0.88, 1.46)
	M	1.03 (0.78, 1.36)	1.04 (0.82, 1.31)	0.97 (0.73, 1.28)	0.98 (0.77, 1.23)
MECPP	F	1.14 (0.81, 1.61)	1.15 (0.92, 1.44)	1.14 (0.88, 1.48)	1.10 (0.83, 1.45)
	M	1.00 (0.75, 1.35)	1.00 (0.78, 1.28)	0.87 (0.65, 1.16)	0.97 (0.75, 1.25)
MEPA	F	0.97 (0.85, 1.10)	0.99 (0.90, 1.09)	1.01 (0.91, 1.13)	0.94 (0.84, 1.06)
	M	1.00 (0.89, 1.13)	1.00 (0.92, 1.09)	0.98 (0.88, 1.10)	1.00 (0.91, 1.11)
ETPA	F	1.00 (0.89, 1.11)	1.00 (0.92, 1.08)	1.03 (0.93, 1.14)	1.03 (0.93, 1.14)
	M	0.98 (0.89, 1.09)	0.96 (0.88, 1.05)	1.00 (0.91, 1.10)	1.02 (0.93, 1.13)
PRPA	F	0.98 (0.88, 1.09)	1.01 (0.93, 1.09)	1.03 (0.94, 1.13)	0.96 (0.87, 1.06)
	M	1.02 (0.92, 1.14)	1.02 (0.94, 1.11)	1.01 (0.91, 1.11)	1.03 (0.93, 1.14)
BPA	F	1.03 (0.89, 1.18)	1.07 (0.96, 1.20)	1.06 (0.94, 1.20)	1.03 (0.89, 1.19)
	M	1.00 (0.86, 1.15)	0.99 (0.90, 1.09)	0.96 (0.85, 1.08)	0.98 (0.85, 1.13)
BUPA	F	1.02 (0.92, 1.14)	1.01 (0.94, 1.09)	1.05 (0.96, 1.14)	1.00 (0.91, 1.10)
	M	0.95 (0.87, 1.03)	0.99 (0.92, 1.06)	1.00 (0.92, 1.08)	0.98 (0.90, 1.06)
BP-3	F	1.03 (0.92, 1.15)	1.01 (0.94, 1.08)	1.00 (0.92, 1.09)	1.05 (0.97, 1.15)
	M	0.97 (0.89, 1.07)	0.99 (0.92, 1.07)	1.02 (0.94, 1.11)	1.04 (0.97, 1.12)
TRCS[a]	F	1.07 (0.93, 1.23)	1.06 (0.96, 1.16)	1.03 (0.93, 1.15)	1.06 (0.96, 1.18)
	M	0.98 (0.88, 1.09)	0.99 (0.90, 1.08)	0.94 (0.85, 1.04)	0.96 (0.87, 1.08)

HCB	F	1.21 (0.96, 1.52)	1.08 (0.92, 1.27)	**1.23 (1.01, 1.49)**	0.96 (0.81, 1.14)
	M	1.17 (0.96, 1.41)	1.05 (0.91, 1.20)	**1.27 (1.06, 1.52)**	1.14 (0.96, 1.34)
DDE	F	1.09 (0.87, 1.36)	0.95 (0.81, 1.11)	1.08 (0.89, 1.30)	1.01 (0.84, 1.20)
	M	**1.21 (1.01, 1.46)**	1.08 (0.93, 1.26)	**1.30 (1.10, 1.54)**	1.03 (0.86, 1.22)
PFHxS	F	0.75 (0.51, 1.11)	0.94 (0.72, 1.23)	1.29 (0.92, 1.82)	1.13 (0.81, 1.57)
	M	0.76 (0.54, 1.06)	0.86 (0.67, 1.09)	1.02 (0.77, 1.35)	0.97 (0.73, 1.28)
PFOA	F	1.04 (0.69, 1.56)	1.12 (0.85, 1.47)	1.24 (0.87, 1.78)	1.21 (0.87, 1.68)
	M	0.95 (0.68, 1.33)	0.92 (0.70, 1.21)	1.06 (0.78, 1.45)	0.91 (0.65, 1.26)
PFOS	F	0.85 (0.54, 1.34)	1.07 (0.77, 1.49)	1.26 (0.85, 1.88)	1.06 (0.75, 1.52)
	M	0.97 (0.65, 1.44)	0.97 (0.72, 1.31)	1.24 (0.89, 1.72)	0.97 (0.70, 1.33)
PFNA	F	0.99 (0.67, 1.45)	1.20 (0.89, 1.61)	1.28 (0.91, 1.79)	1.27 (0.93, 1.74)
	M	0.99 (0.69, 1.43)	1.02 (0.78, 1.33)	1.35 (0.99, 1.86)	0.92 (0.66, 1.27)
PCB 138	F	1.18 (0.89, 1.55)	1.08 (0.89, 1.33)	1.26 (0.98, 1.61)	1.12 (0.88, 1.42)
	M	0.98 (0.78, 1.24)	1.03 (0.86, 1.23)	1.21 (0.97, 1.50)	1.02 (0.83, 1.26)
PCB 153	F	1.02 (0.76, 1.36)	0.95 (0.77, 1.17)	1.21 (0.93, 1.58)	0.98 (0.77, 1.24)
	M	1.02 (0.82, 1.27)	1.01 (0.86, 1.20)	**1.26 (1.00, 1.59)**	1.03 (0.85, 1.25)
PCB 180	F	1.00 (0.75, 1.32)	1.03 (0.83, 1.27)	1.18 (0.91, 1.53)	1.04 (0.82, 1.31)
	M	0.98 (0.77, 1.25)	1.04 (0.87, 1.26)	1.21 (0.95, 1.54)	1.09 (0.87, 1.36)

Reference outcome category is Class 4. Abbreviations: BMI = body mass index, RRR = relative risk ratio, CI = confidence interval, F = female, M = male.. All models adjusted for sub-cohort, social class, smoking during pregnancy, parity, maternal age at delivery, maternal prepregnancy BMI, paternal prepregnancy BMI, maternal Mediterranean diet score.

[a] TRCS only included two cohorts (Sabadell, Valencia) as such sample size was smaller (n = 647 for females, n = 708 for males).

Table S6. Associations between EDCs and childhood BMI growth trajectory classes from single exposure models by social class, higher (n = 613) / middle (n = 497) / lower (n = 777)

		Class 1	Class 2	Class 3	Class 5
EDC	Social Class	RRR (95% CI)	RRR (95% CI)	RRR (95% CI)	RRR (95% CI)
MEP	H	1.14 (0.89, 1.48)	1.04 (0.89, 1.21)	1.00 (0.83, 1.22)	1.02 (0.83, 1.25)
	M	1.12 (0.89, 1.41)	0.98 (0.81, 1.17)	0.93 (0.75, 1.14)	1.06 (0.86, 1.30)
	L	0.96 (0.77, 1.18)	1.04 (0.89, 1.21)	1.04 (0.87, 1.25)	1.02 (0.85, 1.21)
MiBP	H	0.92 (0.64, 1.33)	0.91 (0.70, 1.18)	0.87 (0.63, 1.19)	0.97 (0.74, 1.27)
	M	1.23 (0.83, 1.82)	1.07 (0.78, 1.47)	1.14 (0.81, 1.61)	1.07 (0.75, 1.53)
	L	1.04 (0.76, 1.43)	1.09 (0.85, 1.40)	0.95 (0.72, 1.25)	0.94 (0.68, 1.30)
MnBP	H	1.15 (0.84, 1.57)	0.90 (0.72, 1.14)	1.01 (0.78, 1.32)	0.89 (0.69, 1.15)
	M	0.97 (0.71, 1.32)	0.96 (0.76, 1.21)	0.94 (0.72, 1.23)	1.03 (0.76, 1.39)
	L	0.95 (0.76, 1.19)	0.95 (0.79, 1.14)	0.91 (0.74, 1.13)	0.95 (0.75, 1.20)
MBzP	H	1.10 (0.80, 1.52)	1.01 (0.81, 1.25)	1.17 (0.91, 1.51)	0.97 (0.77, 1.23)
	M	0.92 (0.65, 1.30)	1.09 (0.84, 1.40)	1.12 (0.85, 1.48)	0.93 (0.68, 1.26)
	L	1.09 (0.82, 1.44)	1.05 (0.83, 1.32)	1.06 (0.82, 1.39)	1.09 (0.83, 1.42)
MEHP	H	1.10 (0.78, 1.57)	1.04 (0.83, 1.29)	1.07 (0.84, 1.36)	0.93 (0.72, 1.22)
	M	0.99 (0.70, 1.40)	0.94 (0.73, 1.20)	1.02 (0.74, 1.40)	1.04 (0.77, 1.40)
	L	1.19 (0.88, 1.60)	1.23 (0.97, 1.56)	1.20 (0.91, 1.57)	**1.30 (1.01, 1.67)**
MEHHP	H	1.17 (0.84, 1.63)	1.06 (0.85, 1.33)	1.01 (0.78, 1.31)	0.97 (0.75, 1.25)
	M	1.10 (0.76, 1.58)	1.00 (0.77, 1.30)	1.03 (0.73, 1.46)	0.95 (0.68, 1.32)
	L	1.19 (0.88, 1.61)	**1.36 (1.03, 1.80)**	1.24 (0.92, 1.67)	**1.35 (1.01, 1.80)**
MEOHP	H	1.17 (0.84, 1.63)	1.06 (0.85, 1.33)	1.00 (0.78, 1.29)	0.92 (0.71, 1.19)
	M	1.06 (0.73, 1.54)	0.98 (0.75, 1.28)	1.01 (0.72, 1.43)	0.95 (0.68, 1.33)
	L	1.24 (0.91, 1.68)	**1.37 (1.03, 1.81)**	1.28 (0.95, 1.72)	**1.35 (1.02, 1.80)**
MECPP	H	1.12 (0.79, 1.60)	0.99 (0.77, 1.27)	0.90 (0.68, 1.20)	0.91 (0.69, 1.22)
	M	0.98 (0.64, 1.51)	0.96 (0.71, 1.30)	1.00 (0.68, 1.45)	0.97 (0.66, 1.41)
	L	1.15 (0.80, 1.66)	1.29 (0.94, 1.78)	1.17 (0.82, 1.66)	1.27 (0.93, 1.73)
MEPA	H	0.96 (0.82, 1.13)	0.96 (0.86, 1.08)	0.92 (0.81, 1.04)	0.92 (0.80, 1.05)
	M	0.99 (0.84, 1.15)	1.04 (0.92, 1.17)	0.96 (0.83, 1.11)	0.99 (0.84, 1.16)
	L	1.01 (0.88, 1.16)	1.01 (0.91, 1.13)	1.10 (0.98, 1.23)	1.02 (0.90, 1.16)
ETPA	H	0.99 (0.84, 1.16)	0.96 (0.86, 1.08)	0.97 (0.86, 1.09)	1.00 (0.87, 1.14)
	M	0.99 (0.86, 1.15)	0.98 (0.88, 1.09)	0.99 (0.87, 1.13)	1.02 (0.88, 1.18)

	L	1.01 (0.90, 1.12)	1.00 (0.91, 1.09)	1.07 (0.96, 1.20)	1.06 (0.95, 1.18)
PRPA	H	0.98 (0.85, 1.13)	0.98 (0.89, 1.09)	0.95 (0.85, 1.05)	0.96 (0.86, 1.08)
	M	0.98 (0.85, 1.14)	1.02 (0.91, 1.14)	0.99 (0.87, 1.13)	1.00 (0.86, 1.16)
	L	1.04 (0.93, 1.16)	1.04 (0.95, 1.14)	1.10 (0.99, 1.23)	1.02 (0.92, 1.14)
BPA	H	0.98 (0.83, 1.15)	1.06 (0.95, 1.19)	1.06 (0.92, 1.21)	1.01 (0.87, 1.18)
	M	0.99 (0.81, 1.21)	1.01 (0.88, 1.17)	1.04 (0.87, 1.25)	0.93 (0.77, 1.13)
	L	1.06 (0.90, 1.25)	1.02 (0.89, 1.16)	0.96 (0.82, 1.12)	1.06 (0.89, 1.26)
BUPA	H	0.98 (0.84, 1.13)	1.00 (0.90, 1.11)	1.00 (0.90, 1.12)	0.95 (0.85, 1.06)
	M	0.98 (0.87, 1.11)	1.00 (0.91, 1.10)	0.98 (0.87, 1.10)	1.02 (0.90, 1.16)
	L	0.99 (0.90, 1.09)	1.01 (0.93, 1.09)	1.06 (0.97, 1.16)	1.00 (0.91, 1.10)
BP-3	H	1.02 (0.90, 1.16)	0.99 (0.90, 1.08)	1.00 (0.90, 1.10)	1.03 (0.94, 1.14)
	M	0.94 (0.83, 1.05)	1.00 (0.92, 1.08)	0.99 (0.88, 1.11)	1.03 (0.93, 1.15)
	L	1.04 (0.93, 1.16)	1.03 (0.93, 1.12)	1.05 (0.96, 1.16)	1.08 (0.98, 1.20)
TRCS[a]	H	1.16 (0.96, 1.41)	1.05 (0.92, 1.18)	1.03 (0.90, 1.18)	1.03 (0.90, 1.16)
	M	0.96 (0.83, 1.12)	1.02 (0.90, 1.15)	1.00 (0.86, 1.17)	1.06 (0.89, 1.26)
	L	1.00 (0.88, 1.12)	1.01 (0.92, 1.11)	0.94 (0.85, 1.05)	0.98 (0.88, 1.10)
HCB	H	1.26 (0.91, 1.74)	1.06 (0.87, 1.30)	1.15 (0.90, 1.45)	1.22 (0.97, 1.53)
	M	**1.52 (1.08, 2.15)**	1.21 (0.98, 1.51)	**1.53 (1.13, 2.07)**	1.13 (0.88, 1.44)
	L	1.00 (0.82, 1.22)	0.99 (0.85, 1.15)	1.18 (0.97, 1.43)	0.93 (0.78, 1.12)
DDE	H	0.95 (0.70, 1.29)	1.08 (0.88, 1.33)	**1.39 (1.07, 1.80)**	1.16 (0.92, 1.47)
	M	1.11 (0.82, 1.49)	0.92 (0.73, 1.16)	1.11 (0.85, 1.44)	0.84 (0.63, 1.12)
	L	**1.23 (1.03, 1.48)**	1.00 (0.85, 1.17)	1.13 (0.94, 1.35)	1.01 (0.85, 1.20)
PFHxS	H	0.84 (0.53, 1.35)	0.94 (0.67, 1.31)	1.17 (0.80, 1.70)	0.96 (0.67, 1.38)
	M	0.78 (0.45, 1.37)	0.85 (0.59, 1.23)	0.95 (0.61, 1.49)	0.98 (0.60, 1.62)
	L	0.71 (0.50, 1.01)	0.93 (0.70, 1.23)	1.28 (0.93, 1.76)	1.17 (0.84, 1.63)
PFOA	H	1.27 (0.75, 2.14)	1.03 (0.72, 1.47)	1.14 (0.73, 1.78)	1.07 (0.74, 1.54)
	M	0.99 (0.58, 1.69)	1.12 (0.77, 1.63)	1.12 (0.69, 1.83)	0.90 (0.53, 1.51)
	L	0.90 (0.59, 1.36)	0.98 (0.72, 1.33)	1.21 (0.87, 1.69)	1.15 (0.81, 1.62)
PFOS	H	1.03 (0.58, 1.81)	1.25 (0.87, 1.79)	1.31 (0.82, 2.07)	0.97 (0.65, 1.45)
	M	0.91 (0.53, 1.57)	1.01 (0.67, 1.53)	0.99 (0.60, 1.61)	0.92 (0.55, 1.56)
	L	0.86 (0.57, 1.30)	0.92 (0.66, 1.28)	1.37 (0.95, 1.98)	1.16 (0.80, 1.66)
PFNA	H	0.91 (0.57, 1.46)	1.12 (0.79, 1.59)	1.13 (0.72, 1.78)	1.00 (0.71, 1.41)
	M	0.95 (0.58, 1.55)	1.04 (0.70, 1.54)	1.35 (0.84, 2.17)	0.94 (0.57, 1.55)
	L	1.10 (0.72, 1.69)	1.18 (0.87, 1.60)	**1.49 (1.07, 2.07)**	1.26 (0.89, 1.79)
PCB 138	H	1.18 (0.81, 1.71)	1.12 (0.88, 1.42)	**1.39 (1.02, 1.89)**	1.17 (0.89, 1.54)

	M	1.20 (0.82, 1.74)	1.06 (0.80, 1.41)	1.15 (0.81, 1.64)	1.00 (0.72, 1.39)
	L	0.94 (0.73, 1.20)	1.01 (0.83, 1.23)	1.18 (0.93, 1.51)	1.04 (0.82, 1.31)
PCB 153	H	1.22 (0.78, 1.89)	1.07 (0.82, 1.40)	**1.48 (1.02, 2.14)**	1.00 (0.77, 1.30)
	M	1.27 (0.82, 1.98)	0.99 (0.75, 1.33)	1.09 (0.77, 1.56)	0.98 (0.70, 1.37)
	L	0.87 (0.70, 1.09)	0.95 (0.80, 1.13)	1.21 (0.94, 1.55)	1.05 (0.84, 1.31)
PCB 180	H	1.33 (0.84, 2.10)	1.11 (0.84, 1.46)	1.35 (0.95, 1.92)	0.98 (0.75, 1.29)
	M	1.19 (0.75, 1.88)	1.02 (0.77, 1.37)	1.10 (0.75, 1.61)	1.16 (0.79, 1.70)
	L	0.83 (0.65, 1.05)	1.00 (0.83, 1.22)	1.15 (0.90, 1.48)	1.11 (0.87, 1.41)

Reference outcome category is Class 4. Abbreviations: BMI = body mass index, RRR = relative risk ratio, CI = confidence interval, H = higher, M = middle, L = lower. All models adjusted for sub-cohort, smoking during pregnancy, parity, maternal age at delivery, maternal prepregnancy BMI, paternal prepregnancy BMI, maternal Mediterranean diet score, child sex.

[a] TRCS only included two cohorts (Sabadell, Valencia) as such sample size was smaller (n = 375 for higher, n = 374 for middle, n = 606 for lower).

Table S7. Associations between EDC mixture and childhood BMI growth trajectory classes from mixture models using BWQS regression (n = 1,911)

	Class 1	Class 2	Class 3	Class 5
	Beta (CrI)	Beta (CrI)	Beta (CrI)	Beta (CrI)
beta 1 (BWQS index)	0.144 (-0.383, 0.678)	0.146 (-0.152, 0.462)	0.534 (0.027, 0.955)	0.212 (-0.193, 0.625)
Chemical weight for:				
MEP	0.048 (0.001, 0.169)	0.044 (0.001, 0.152)	0.03 (0.001, 0.106)	0.051 (0.001, 0.182)
MiBP	0.039 (0.001, 0.136)	0.041 (0.001, 0.144)	0.022 (0.001, 0.084)	0.039 (0.001, 0.14)
MnBP	0.046 (0.001, 0.162)	0.042 (0.001, 0.152)	0.028 (0.001, 0.097)	0.039 (0.001, 0.139)
MBzP	0.041 (0.001, 0.137)	0.042 (0.001, 0.142)	0.029 (0.001, 0.101)	0.034 (0.001, 0.127)
MEHP	0.044 (0.001, 0.151)	0.042 (0.001, 0.154)	0.037 (0.001, 0.128)	0.039 (0.001, 0.146)
MEHHP	0.042 (0.001, 0.157)	0.045 (0.001, 0.154)	0.031 (0.001, 0.112)	0.038 (0.001, 0.141)
MEOHP	0.04 (0.001, 0.146)	0.041 (0.001, 0.147)	0.026 (0.001, 0.101)	0.036 (0.001, 0.128)
MECPP	0.039 (0.001, 0.144)	0.04 (0.001, 0.146)	0.029 (0.001, 0.101)	0.039 (0.001, 0.128)
MEPA	0.039 (0.001, 0.141)	0.043 (0.001, 0.15)	0.027 (0.001, 0.099)	0.041 (0.001, 0.145)
ETPA	0.039 (0.001, 0.155)	0.038 (0.001, 0.135)	0.026 (0.001, 0.092)	0.042 (0.001, 0.152)
PRPA	0.041 (0.001, 0.147)	0.048 (0.001, 0.163)	0.032 (0.001, 0.115)	0.044 (0.001, 0.151)
BPA	0.045 (0.001, 0.163)	0.049 (0.002, 0.17)	0.043 (0.001, 0.14)	0.047 (0.001, 0.163)

BUPA	0.04 (0.001, 0.139)	0.039 (0.001, 0.14)	0.029 (0.001, 0.099)	0.039 (0.001, 0.143)
BP-3	0.05 (0.001, 0.179)	0.046 (0.001, 0.157)	0.051 (0.002, 0.161)	0.066 (0.002, 0.215)
HCB	0.059 (0.002, 0.212)	0.052 (0.002, 0.172)	0.108 (0.004, 0.283)	0.044 (0.001, 0.158)
DDE	0.055 (0.002, 0.197)	0.048 (0.002, 0.168)	0.094 (0.002, 0.261)	0.055 (0.002, 0.187)
PFHxS	0.039 (0.001, 0.156)	0.037 (0.001, 0.137)	0.04 (0.001, 0.132)	0.042 (0.001, 0.143)
PFOA	0.04 (0.001, 0.147)	0.039 (0.001, 0.144)	0.034 (0.001, 0.125)	0.042 (0.001, 0.149)
PFOS	0.039 (0.001, 0.15)	0.039 (0.001, 0.142)	0.047 (0.001, 0.161)	0.045 (0.001, 0.15)
PFNA	0.039 (0.001, 0.139)	0.045 (0.001, 0.158)	0.043 (0.001, 0.134)	0.05 (0.001, 0.177)
PCB 138	0.045 (0.001, 0.156)	0.048 (0.001, 0.171)	0.075 (0.003, 0.235)	0.043 (0.001, 0.148)
PCB 153	0.045 (0.001, 0.157)	0.045 (0.001, 0.158)	0.063 (0.002, 0.197)	0.042 (0.001, 0.146)
PCB 180	0.046 (0.001, 0.165)	0.047 (0.001, 0.168)	0.058 (0.002, 0.192)	0.045 (0.001, 0.157)

Reference outcome category is Class 4.
Abbreviations: BMI = body mass index, CrI = credible interval
All models adjusted for sub-cohort, smoking during pregnancy, parity, maternal age at delivery, maternal prepregnancy BMI, paternal prepregnancy BMI, maternal Mediterranean diet score, social class, child sex.

Table S8. Associations between EDC mixture and childhood BMI growth trajectory Class 3 vs. Class 4 from BWQS regression, by sex

	Female (n = 469)			Male (n = 430)		
	mean	lower CrI	upper CrI	mean	lower CrI	upper CrI
beta 1 (BWQS index)	0.364	-0.205	0.953	0.610	-0.126	1.309
Chemical weight for:						
MEP	0.040	0.002	0.153	0.033	0.001	0.114
MiBP	0.036	0.001	0.120	0.027	0.001	0.107
MnBP	0.036	0.001	0.130	0.035	0.001	0.123
MBzP	0.037	0.001	0.136	0.036	0.001	0.123
MEHP	0.048	0.002	0.169	0.034	0.001	0.121
MEHHP	0.041	0.001	0.144	0.030	0.001	0.110
MEOHP	0.040	0.001	0.142	0.028	0.001	0.108
MECPP	0.041	0.001	0.143	0.029	0.001	0.112
MEPA	0.035	0.001	0.119	0.030	0.001	0.114
ETPA	0.035	0.001	0.124	0.033	0.001	0.119
PRPA	0.039	0.001	0.126	0.033	0.001	0.124
BPA	0.047	0.001	0.161	0.039	0.001	0.127
BUPA	0.034	0.001	0.124	0.038	0.001	0.137
BP-3	0.042	0.001	0.147	0.059	0.002	0.189
HCB	0.070	0.002	0.247	0.074	0.003	0.221
DDE	0.052	0.002	0.181	0.092	0.003	0.269
PFHxS	0.040	0.001	0.144	0.046	0.002	0.148
PFOA	0.043	0.001	0.148	0.035	0.001	0.120
PFOS	0.043	0.001	0.147	0.051	0.001	0.165
PFNA	0.037	0.001	0.127	0.055	0.001	0.175
PCB 138	0.061	0.002	0.205	0.054	0.002	0.180
PCB 153	0.057	0.002	0.190	0.047	0.001	0.157
PCB 180	0.045	0.002	0.159	0.061	0.001	0.198

Abbreviations: BMI = body mass index, CrI = credible interval
All models adjusted for sub-cohort, smoking during pregnancy, parity, maternal age at delivery, maternal prepregnancy BMI, paternal prepregnancy BMI, maternal Mediterranean diet score, social class.

Table S9. Associations between EDC mixture and childhood BMI growth trajectory Class 3 vs. Class 4 from BWQS regression, by social class

	Higher (n = 310)			Middle (n = 234)			Low (n = 355)		
	mean	lower CrI	upper CrI	mean	lower CrI	upper CrI	mean	lower CrI	upper CrI
beta 1 (BWQS index)	0.050	-0.707	0.888	0.092	-0.754	0.999	0.843	0.247	1.486
Chemical weight for:									
MEP	0.043	0.001	0.151	0.043	0.001	0.165	0.044	0.001	0.150
MiBP	0.041	0.001	0.148	0.043	0.001	0.166	0.025	0.001	0.086
MnBP	0.043	0.001	0.154	0.043	0.001	0.152	0.033	0.001	0.118
MBzP	0.043	0.001	0.153	0.042	0.001	0.148	0.031	0.001	0.113
MEHP	0.042	0.001	0.146	0.040	0.001	0.136	0.048	0.002	0.152
MEHHP	0.043	0.001	0.153	0.040	0.001	0.136	0.036	0.001	0.130
MEOHP	0.042	0.001	0.152	0.040	0.001	0.144	0.039	0.001	0.135
MECPP	0.042	0.001	0.150	0.043	0.001	0.147	0.033	0.001	0.116
MEPA	0.043	0.001	0.158	0.043	0.001	0.167	0.048	0.002	0.159
ETPA	0.042	0.002	0.152	0.041	0.001	0.150	0.035	0.001	0.120
PRPA	0.043	0.001	0.161	0.045	0.001	0.158	0.051	0.001	0.163
BPA	0.045	0.002	0.168	0.043	0.001	0.148	0.033	0.001	0.114
BUPA	0.043	0.001	0.147	0.042	0.001	0.151	0.036	0.001	0.123
BP-3	0.043	0.001	0.156	0.045	0.001	0.157	0.048	0.002	0.155
HCB	0.046	0.001	0.167	0.055	0.002	0.215	0.065	0.002	0.202
DDE	0.049	0.001	0.191	0.046	0.001	0.169	0.060	0.002	0.178
PFHxS	0.042	0.001	0.149	0.041	0.001	0.141	0.050	0.002	0.163
PFOA	0.043	0.001	0.144	0.044	0.001	0.155	0.032	0.001	0.118
PFOS	0.042	0.001	0.140	0.044	0.001	0.152	0.044	0.001	0.146
PFNA	0.042	0.001	0.153	0.046	0.001	0.162	0.049	0.001	0.159
PCB 138	0.046	0.001	0.167	0.044	0.001	0.165	0.059	0.002	0.201
PCB 153	0.047	0.001	0.175	0.042	0.001	0.142	0.052	0.002	0.180
PCB 180	0.045	0.002	0.161	0.045	0.001	0.156	0.050	0.001	0.165

Abbreviations: BMI = body mass index, CrI = credible interval
All models adjusted for sub-cohort, smoking during pregnancy, parity, maternal age at delivery, maternal prepregnancy BMI, paternal prepregnancy BMI, maternal Mediterranean diet score, social class.

5.5. Paper V

Montazeri P, Fossati S, Warembourg C, Casas M, Clemente DBP, Garcia-Esteban R, Nawrot TS, Vrijheid M. Prenatal exposure to phthalates and phenols and preclinical vascular health during early adolescence. *Under review at International Journal of Hygiene and Environmental Health (since July 2021).*

ABSTRACT

Background and Aim: Exposure to endocrine-disrupting chemicals may increase cardiovascular risk from early life, but studies in children have shown inconsistent results, most focused on analysis of single chemicals, and none included measures of micro-vascularization as early preclinical markers. This study aimed to evaluate the association between prenatal exposure to phthalates and phenols and macro- and microvascular health during early adolescence.

Methods: Using data from a Spanish birth cohort (n=416), prenatal exposure to eight phthalate metabolites and seven phenols (bisphenol A, four parabens, benzophenone-3, triclosan) were assessed using first and/or third trimester spot-urine concentrations. Macrovascular health (systolic and diastolic blood pressure (SBP and DBP, mmHg), pulse wave velocity (PWV, m/s)) and microvascular health (central retinal artery/vein equivalent (CRAE/CRVE, μm)), were measured at 11 years old. Linear regression models assessed associations for individual chemicals and Bayesian weighted quantile sum regression (BWQS) evaluated the overall association of the phthalate and phenol mixture with cardiovascular health.

Results: In single exposure models, bisphenol-A was associated with decreased PWV (β per doubling of exposure = –0.06; 95% CI: –0.10, -0.01). Mono-iso-butyl phthalate was associated with an increase in CRAE (β = 1.89; 95% CI: 0.34, 3.44). Methyl- and butyl-parabens were associated with a decrease in CRVE (β = -0.71; 95% CI: -1.41, -0.01) and (β = -0.96; 95% CI: -1.57, -0.35), respectively. No statistically significant associations were observed between any of the exposures and SBP or DBP. BWQS models showed no evidence of associations between the phthalate and phenol mixture and any of the outcomes.

Conclusions: Our results provide little evidence to suggest that prenatal exposure to phthalates and phenols is associated with macro- or microvascular health during early adolescence, except a few associations with certain compounds. Errors in exposure measurement and reduced variability in cardiovascular measures at this early age limit our ability to draw strong conclusions.

INTRODUCTION

Widespread exposure to environmental contaminants is a public health concern as each year millions of tons of plastics and other consumer products are produced around the world (Gore et al., 2015; Landrigan and Goldman, 2011). Several of these contaminants are known as endocrine disrupting chemicals (EDCs), meaning they can alter the hormonal and homeostatic systems thus interfering with natural body processes (Diamanti-Kandarakis et al., 2009). Some EDCs have long half-lives, in turn wreaking havoc on humans and animals alike for decades after production, while others are non-persistent and have shorter half-lives but are so widespread in their use that human exposure is constant making them of concern (Diamanti-Kandarakis et al., 2009). These non-persistent chemicals, including phthalates and phenols, are of concern given their widespread use in building materials, clothing, food containers, personal care products and medical devices (Meeker, 2012; Wittassek et al., 2011; Wormuth et al., 2006).

Pregnant women are of particular concern as exposure to EDCs may cause irreversible damage to the fetus resulting in increased disease susceptibility in later life (Lunder et al., 2010; Mamsen et al., 2017; Vrijheid et al., 2016). Cardiovascular disease risk can be traced from adulthood back to early childhood and vascular changes during childhood have been associated with arterial hypertension, coronary heart disease, diabetes mellitus and obesity in later life (Franks et al., 2010; Juonala et al., 2011; Li et al., 2016; Newman et al., 2017). Increasing evidence has suggested a relationship between early life exposure to EDCs, including phthalates and bisphenol-A (BPA), and development and progression of cardiovascular disease over the life course (Fu et al., 2020; Mariana et al., 2016; Nidens et al., 2020). However, the majority of previous work has evaluated the association between EDCs and cardiovascular risk cross-sectionally and using only blood pressure, lipid profile, and/or adiposity measurements as markers for cardiovascular risk. Measures of the vascular system outside of blood pressure have yet to be studied.

Examining additional vascular measures associated with cardiovascular disease would be beneficial to create a more complete picture of cardiovascular risk. In addition to blood

pressure, pulse wave velocity (PWV), a measure of macrovascular health and arterial stiffness, has been associated with increased cardiovascular risk and atherosclerosis in adulthood (Cote et al., 2015; Hudson et al., 2015). Microvascular changes can be assessed through retinal vein and artery diameters, whereby venular widening is indicative of inflammation and atherosclerosis, and arterial narrowing is indicative of arterial damage (Newman et al., 2017). Such measures have been associated with cardiovascular and metabolic disease in adults (Newman et al., 2017), and related to elevated blood pressure, obesity, and type 1 diabetes during childhood (Li et al., 2016; Newman et al., 2017). To the best of our knowledge, no studies have assessed the relationship between prenatal urinary concentrations of phthalates and phenols and cardiovascular markers beyond blood pressure, such as PWV or retinal imaging.

To create a more complete assessment of cardiovascular risk related to prenatal phthalate and phenol exposure this study aimed to: 1) analyze the association between prenatal exposure to phenols and phthalates and measurements of macro- and microvascular structure during early adolescence; 2) consider multiple chemical exposures by using a statistical approach that accounts for chemical mixtures; and 3) explore if these associations may be altered by sex and social class.

METHODS

Study Population

The participants in this study were from the INMA (INfancia y Medio Ambiente, Environment and Childhood) study, a longitudinal birth cohort study from Sabadell, Spain that included 657 women who were recruited at 10-13 weeks of gestation through regional hospitals from 2004 to 2006. The inclusion criteria were: ≥16 years of age, singleton pregnancy, intention to deliver at reference hospital, and no assisted conception or communication issues (Guxens et al., 2012). Children and their families participated in regular follow-up visits in which data was collected via questionnaires and biological samples. The present analysis was limited to mother – child pairs in which the mother gave at least one spot urine sample during pregnancy and their child participated in the 11-year follow-up with at least one cardiovascular measurement

available (N = 416). This study was approved by the Ethics Review Committee and all mothers signed a written consent for themselves and their child's participation.

Measurement of phthalates and phenols

Spot urine samples were collected from pregnant women during the first and third trimesters of pregnancy in 100mL polypropylene containers. These samples were aliquoted in 10mL polyethylene tubes and stored at −20ºC.

Phthalates

Phthalate analyses were carried out in the Bioanalysis Research Group at the Hospital del Mar Medical Research Institute (Spain). This study uses data for eight measured phthalate metabolites: MBzP (mono-benzyl phthalate), MEP (mono-ethyl phthalate), MiBP (mono-iso-butyl phthalate), MnBP (mono-n-butyl phthalate), MEHP (mono-(2-ethylhexyl) phthalate), MEHHP (mono-(2-ethyl-5-hydroxyhexyl) phthalate), MEOHP (mono-(2- ethyl-5-oxohexyl) phthalate), MECPP (mono-(2-ethyl-5-carboxypentyl) phthalate). Analysis was performed by ultraperformance liquid chromatography coupled to tandem mass spectrometry (UPLC-MS/MS) (Valvi et al., 2015b). The limit of detection (LOD) values were: 0.5 g/L for MEHHP, MEOHP, MBzP and MiBP, and 1 ng/mL for MEHP, MECPP, MEP and MnBP. Phthalate concentrations were determined in the first and third trimesters of pregnancy and averaged for analyses.

Phenols

Seven phenols were analyzed in this study: MEPA (methyl paraben), ETPA (ethyl paraben), PRPA (propyl paraben), BPA, BUPA (n-butyl paraben), BP-3 (benzophenone-3), TRCS (triclosan). Total BPA (free plus conjugated) determination was carried out in the Department of Analytical Chemistry laboratory – University of Cordoba (Spain) using UPLC-MS/MS (Casas et al., 2013). The remaining phenols were analyzed at the Norwegian Institute of Public Health (NIPH) laboratory using on-line solid phase extraction (SPE) prior to UPLC-MS/MS (Sakhi et al., 2018). The LOD values were: 1 μg/L for BPA, 0.07 μg/L for BUPA, and 0.04 μg/L for all remaining phenols. BPA was measured during the first and third trimesters and averaged for analyses. All other phenols were measured only in the third trimester.

Creatinine
Creatinine concentrations were measured at the Echevarne Laboratory of Barcelona (Spain) using the Jaffé method (kinetic measurement, compensated method) with Beckman Coulter© reactive in AU5400 (IZASA®). Creatine adjusted phthalate and phenol concentrations were calculated for each trimester and then averaged. The creatinine adjusted concentrations were used in all the statistical analysis (hereafter, in μg/g creatinine).

Cardiovascular Measurements
During the 11-year follow-up visit, cardiovascular measurements were taken by INMA nurses trained to use the appropriate device. Children were visited during school hours. Measures of blood pressure and PWV were taken to assess the macrovascular structure while images of the retina were taken to assess the microvascular structure.

Blood Pressure
Systolic blood pressure (SBP) and diastolic blood pressure (DBP) were taken using an automated oscillometric device OMROM 705IT with brachial cuff attached. Children sat in a chair with their legs uncrossed, both feet flat on the floor, and their arm and back supported. The cuff was positioned on the child´s resting arm placing the artery index marker over the brachial artery. After five minutes of relaxation, three consecutive measurements were taken with one-minute intervals. An average of the second and third measurements were used for analyses and values are presented are in millimeter of mercury (mmHg).

Pulse Wave Velocity
PWV was recorded using VICORDER® in combination with the VICORDER® vascular diagnostic program package. To take the measurement the child laid down in the supine position using a support to raise their head and shoulders 30º above their heart level. The thigh cuff was placed on their upper right thigh as high as possible, and the neck cuff was placed after palpating the pulse of the right common carotid artery. The 80% method was used (80% of the measured direct distance between the carotid and femoral recording sites) to ensure the smallest possible measurement error. After the child was still and relaxed, the nurse watched the system

for stable wave patterns and recorded three waveform measurements. An average of the three measurements were used for analyses and values are given in meter per second (m/sec).

Central Retinal Arteriolar/Venular Equivalent

Images of the retina were photographed using a Canon CR2-Plus Non Mydriatic retinal camera, which provides information on retinal changes not visible with standard photography. The child sat behind the device with their chin on the chin rest and forehead pressed to the overhead bar (glasses removed if needed), and looked straight into the camera lens while the nurse aligned the child´s eye using the joystick and software guides. Photos were taken from both the left and right eyes and saved in high resolution for later analysis with the IFlexis software (version 2.1.1, VITO Health, Mol, Belgium). This software calculates the Central Retinal Venular Equivalent (CRVE) and Central Retinal Arteriolar Equivalent (CRAE) using the Parr-Hubbard-Knudtson formula (Knudtson et al., 2003). Average CRVE and CRAE were calculated using the big 6 methodology; an average of the six widest arterioles and venules running through a zone between 0.5 and 1 disc diameter from the optic disc margin (De Boever et al., 2014). Processing of these measurements was carried out by one trained researcher to limit observer variability. Measurements from the right and left eye were averaged for analyses and values are denoted in micrometer (μm).

Statistical Analyses

For statistical analyses concentrations of phthalates and phenols with values below the LOD were substituted by LOD/2 (% < LOD ranged from 0-3%). As initial exposure distributions were right skewed all concentrations were log2-transformed to normalize distributions. To check linearity between log2-transformed concentrations and cardiovascular outcomes we performed generalized additive models (GAMs) using the “mgcv” package in Rstudio. If the effective degrees of freedom were equal or close to 1, the relationship was considered linear. Given that some of the GAMs showed evidence of non-linearity we modelled concentrations as both continuous and categorical (tertiles) in single exposure models. Covariates included in the models were chosen using a directed acyclic graphs (DAG) (Figure S1) and all final models were adjusted for: maternal age at delivery (years), pre-pregnancy BMI (kg/m2), gestational weight gain (kg), maternal

smoking during pregnancy (none/until 1st trimester/until 3rd trimester), social class (high/middle, low), parental cardiovascular history (neither parent has diagnosis/1 parent has at least one diagnosis/both parents have at least one diagnosis), child sex, gestational age, and child age at cardiovascular measurement. SBP, DBP, and PWV were additionally adjusted for child height at cardiovascular measurement.

To maximize sample size and handle missing covariate observations, multiple imputation was carried out using the multiple imputation by chained equations (MICE) using the "ice" command in STATA generating 20 datasets. The MICE approach assumes that data is missing at random, as such, additional variables that were not included in the final model were added to the predictive models for more accurate results. The imputed data was used for multiple linear regression models and results were combined using Rubin's combination rules.

Associations between the chemical concentrations and the outcomes were analyzed in two steps. First, we ran single exposures models, using linear regression. Then, we tested the association between a chemical mixture including all phthalates and phenols and the outcomes using Bayesian weighted quantile sum regression (BWQS). BWQS is an extension on WQS regression which summarizes the overall exposure to the mixture by estimating a single weighted index while accounting for the individual contribution of each concentration of the mixture using weights. BWQS is a novel approach that extends this method to overcome certain limitations, specifically it does not require selection of the directionality of the coefficient associated with the mixture. This allows more flexibility to the model, improving statistical power (Colicino et al., 2020).

Additionally, we conducted the following sensitivity analyses. To further explore the role of effect modifiers, stratification by child sex and social class was carried out for both single exposure and mixture models. In single exposure models we tested for interactions with sex and social class by inserting cross-product terms (exposure*sex or exposure*social class) into the model. To explore time windows of exposure, we ran analyses separately for first and third trimester concentrations of phthalates and BPA.

Further, we ran models excluding gestational weight gain and gestational age as they could be potential mediators. Lastly, mixture models were additionally divided into separate mixtures for phthalates and phenols.

Statistical significance was defined as p-value <0.05. For interaction terms, a less stringent p-value of 0.10 was used. Regression analyses and imputation were carried out with STATA version 14 (College Station, TX). GAMs and BWQS were conducted using RStudio version 4.0.3 (RStudio Team 2020).

RESULTS

Study Population

Study population characteristics are presented in Table 1. There were no differences in main characteristics between the original and imputed datasets. Children had a mean SBP and DBP of 102.1 and 60.1 mmHg, respectively, and their average PWV was 4.4 m/sec (Table 1). Children's retinal measures were 181.1 μm on average for CRAE and 252.3 μm for CRVE (Table 1). Correlations between cardiovascular measures were weak or showed no correlation overall with the exceptions of SBP and DBP (r = 0.66), and CRAE and CRVE (r = 0.55) which were moderately correlated (Figure S2a).

Phthalate metabolites and phenols were detected in almost all samples (97-100%>LOD) (Table 2). The correlations between these chemicals was strongest between the metabolites of di(2-ethylhexyl) phthalate (DEHP); MEHP, MEHHP, MEOHP and MECPP, whose correlations ranged from (r = 0.67 to 0.95) (Figure S2b). Among phenols, MEPA was strongly correlated with PRPA (0.89) and moderately with BUPA (0.46), while BUPA was also moderately correlated with ETPA (0.59) (Figure S2b).

GAMs examining the shape of the relationship between prenatal concentrations and cardiovascular outcomes were mixed (Figure S3a-e). The strongest deviations from linearity for outcomes were observed for: SBP with MEHP; DBP with MEHP and BPA; PWV with TRCS; CRAE with MBzP, MEOHP and MECPP; and CRVE with MEHP and MEPA. (Figure S3a-e).

Table 1. Study Population Characteristics, n = 416

	Missing	Non-imputed data Mean (sd) or n (%)	Imputed data Mean (sd) or %
Maternal/Familial characteristics			
Maternal age (years)	1	31.9 (4.1)	31.9 (4.1)
Pre-pregnancy BMI	0	23.8 (4.5)	-
Gestational Weight Gain (kg)	12	14.0 (5.0)	14.0 (5.0)
Smoking during pregnancy	4		
None		303 (73.5)	73.6
Until 1st trimester		56 (13.6)	13.6
Until 3rd trimester		53 (12.9)	12.9
Socioeconomic Status	0		
High/middle		273 (65.6)	-
Low		143 (34.4)	-
Parental Cardiovascular History	4		
None		196 (47.6)	47.6
1 parent has 1+ diagnosis		178 (43.2)	43.1
Both parents have 1+ diagnosis		38 (9.2)	9.2
Child Characteristics			
Sex	0		
Female		197 (47.4)	-
Male		219 (52.6)	-
Gestational age at birth (weeks)	0	39.8 (1.3)	-
Age at cardio measure (years)	1	11.1 (0.5)	11.1 (0.5)
Height at cardio measure (cm)	1	146.6 (7.8)	146.6 (7.8)
Systolic blood pressure (mmHg)	2	102.1 (9.9)	-
Diastolic blood pressure (mmHg)	3	60.1 (7.7)	-
Pulse wave velocity (m/s)	19	4.4 (0.5)	-
Central retinal arteriolar equivalent (μm)	34	181.1 (12.8)	-
Central retinal venular equivalent (μm)	34	252.3 (17.2)	-

Abbreviations: sd: standard deviation, n: sample size, %: percent, BMI: body mass index, kg: kilograms, cm: centimeters, mmHg: millimeter of mercury, m/s: meters per second, μm: micrometer

Table 2. Prenatal exposure to phthalates (averaged between 1st and 3rd trimester) and phenols (3rd trimester only), summary statistics in µg/g creatinine adjusted

	n	LOD (µg/L)	n (% >LOD) 1 tr.	n (% >LOD) 3rd tr.	Min	P25	P50	P75	Max
MEHP	334	1	332 (99)	332 (99)	1.79	7.28	10.78	17.13	69.41
MEHHP	334	0.5	334 (100)	334 (100)	5.29	17.54	26.88	41.21	503.41
MEP	334	1	334 (100)	333 (99)	37.45	199.84	389.76	746.88	9379.85
MiBP	334	0.5	334 (100)	334 (100)	5.08	22.09	31.53	48.19	334.23
MnBP	334	1	331 (99)	332 (99)	5.77	20.09	30.75	47.53	835.66
MBzP	334	0.5	331 (99)	331 (99)	1.54	7.09	11.78	19.84	405.08
MEOHP	334	0.5	334 (100)	334 (100)	4.11	13.83	20.62	29.99	378.28
MECPP	334	1	334 (100)	333 (99)	7.74	27.05	38.97	58.07	718.85
MEPA	407	0.04	-	407 (100)	1.77	82.16	248.57	536.75	45927.10
ETPA	407	0.04	-	404 (99)	0.01	4.74	18.22	57.97	3753.74
PRPA	405	0.04	-	405 (100)	0.06	15.97	54.95	143.91	14132.27
BPA	331	1	331 (100)	328 (99)	5.52	0.33	1.69	2.53	69.44
BUPA	405	0.07	-	394 (97)	0.00	0.65	4.16	12.60	217.25
BP-3	407	0.04	-	407 (100)	0.12	1.15	3.24	20.00	10028.70
TRCS	407	0.04	-	407 (100)	0.31	4.08	28.36	149.03	1909.51

Abbreviations: µg/g: microgram per gram, µg/L: microgram per liter, LOD: limit of detection; min: minimum value max: maximum value; P: percentile; MEHP: Mono-2-ethylhexyl phthalate; MEHHP: Mono-2-ethyl-5-hydroxyhexyl phthalate; MEP: Monoethyl phthalate; MiBP: Mono-iso-butyl phthalate; MnBP: Mono-n-butyl phthalate; MBzP: Mono benzyl phthalate; MEOHP: Mono-2-ethyl-5-oxohexyl phthalate; MECPP: Mono-2-ethyl 5-carboxypentyl phthalate; MEPA: Methyl paraben; ETPA: Ethyl paraben; PRPA: Propyl paraben; BPA: Bisphenol-A; BUPA: N-Butyl paraben; BP-3: Benzophenone-3; TRCS: Triclosan

Single Exposure Models

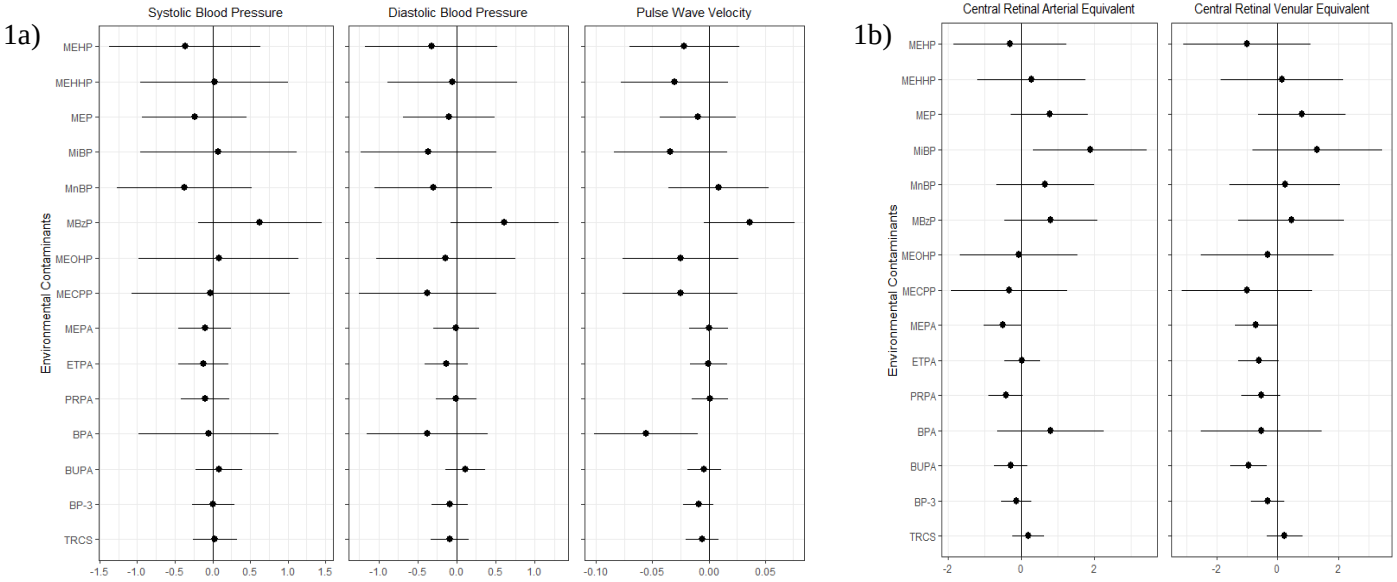
Figures 1a and 1b show the associations from single exposure models using continuous measures of prenatal phthalate and phenol concentrations and cardiovascular outcome measurements in early adolescence. Regarding macrovascular outcomes, no statistically significant associations were observed between any of the chemical concentrations and SBP or DBP when using continuous exposure measures. When using categorical exposure measures, MEPA concentrations in the 2nd tertile were associated with an increase in SBP (β 2nd vs 1st tertile = 2.48; 95%CI: 0.31, 4.66) (Table S1). Phenols tended to be associated with decreases in PWV, and of these only the association for continuous BPA reached statistical significance (β per doubling of exposure = -0.06; CI: -0.10, -0.01) (Figure 1a, Table S1). When exposures were classified in tertiles, MBzP concentrations in the 2nd tertile were statistically significantly associated with an increase in PWV (β 2nd vs 1st tertile = 0.14; CI: 0.02, 0.25) (Table S1).

Regarding microvascular measures, phthalates tended to be associated with increases in both CRAE and CRVE, however only the association between MiBP and CRAE reached statistical significance (β per doubling of exposure = 1.89; CI: 0.34, 3.44) (Figure 1b, Table S1). Conversely, phenols tended to be related with decreases in retinal measures with three reaching statistical significance: MEPA (β per doubling of exposure = -0.71; CI: -1.41, -0.01), BUPA (β per doubling of exposure = -0.96; CI: -1.57, -0.35), and BPA (β 2nd vs 1st tertile = -4.98; CI: -9.98, 0.01) (Figure 1b, Table S1).

Mixture Models

In mixture models using BWQS there was no evidence of associations between the phthalates and phenols mixture and SBP (β = 0.50; Credible Interval (CrI): -1.44, 2.37), DBP (β = 0.43; CrI: -1.20, 2.09), PWV (β = -0.03; CrI: -0.12, 0.07), CRAE (β = -0.49; CrI: -3.47, 2.59) or CRVE (β = -1.33; CrI: -5.43, 2.69) (Table 3). Components of the mixture contributed about equally to the mixture (Table S2).

Figures 1a-b. Associations (Beta and 95% CI) between individual phthalate and phenol exposures and macrovascular (1a) and microvascular (1b) measurements from linear regression models.



Using covariate imputed data, m=20. Models adjusted for child age, child sex, mother's age at delivery, prepregnancy BMI, gestational weight gain, social class, parental cardiovascular history, smoking during pregnancy and gestational age. Macrovascular measures additionally adjusted for child height. Abbreviations: MEHP: Mono-2-ethylhexyl phthalate; MEHHP: Mono-2-ethyl-5-hydroxyhexyl phthalate; MEP: Monoethyl phthalate; MiBP: Mono-iso-butyl phthalate; MnBP: Mono-n-butyl phthalate; MBzP: Mono benzyl phthalate; MEOHP: Mono-2-ethyl-5-oxohexyl phthalate; MECPP: Mono-2-ethyl 5-carboxypentyl phthalate; MEPA: Methyl paraben; ETPA: Ethyl paraben; PRPA: Propyl paraben; BPA: Bisphenol-A; BUPA: N-Butyl paraben; BP-3: Benzophenone-3; TRCS: Triclosan

Table 3. Associations between phthalates and phenols mixture and cardiovascular measurements using BWQS regression

Mixture		Systolic Blood Pressure		Diastolic Blood Pressure		Pulse Wave Velocity		Central Retinal Arteriolar Equivalent		Central Retinal Venular Equivalent
	n	beta 1 (BWQS index) (95% CI)	n	beta 1 (BWQS index) (95% CI)	n	beta 1 (BWQS index) (95% CI)	n	beta 1 (BWQS index) (95% CI)	n	beta 1 (BWQS index) (95% CI)
Unstratified[a]	305	0.50 (-1.44, 2.37)	304	0.43 (-1.20, 2.09)	292	-0.03 (-0.12, 0.07)	280	-0.49 (-3.47, 2.59)	280	-1.33 (-5.43, 2.69)
Social Class[b]										
High/middle	209	0.34 (-1.72, 2.31)	209	-0.19 (-2.02, 1.68)	199	-0.04 (-0.14, 0.08)	191	-0.63 (-4.31, 3.37)	191	-2.77 (-7.80, 2.04)
Low	96	1.12 (-2.77, 5.05)	95	1.24 (-2.11, 4.85)	93	-0.01 (-0.21, 0.20)	89	1.09 (-4.74, 6.63)	89	5.11 (-3.05, 13.02)
Sex[c]										
Female	141	0.42 (-2.31, 3.08)	140	0.56 (-1.76, 3.02)	139	-0.01 (-0.15, 0.13)	127	2.36 (-2.56, 7.20)	127	0.80 (-5.69, 6.79)
Male	164	0.86 (-1.91, 3.57)	164	0.75 (-1.62, 3.13)	153	-0.02 (-0.16, 0.11)	153	-2.28 (-6.12, 1.37)	153	-1.72 (-7.27, 3.71)

Data is from the 1st set of imputed data

[a] Models adjusted for child age at visit, child sex, mother's age at delivery, prepregnancy BMI, gestational weight gain, social class, parental cardiovascular history, smoking during pregnancy and gestational age. SBP, DBP and PWV were additionally adjusted for child height at visit.

[b] Models adjusted for the same as unstratified with the exception of social class.

[c] Models adjusted for the same as unstratified with the exception of sex.

Sensitivity analyses

Associations between chemical concentrations and cardiovascular outcomes were mostly consistent between sexes, with a few associations found to be statistically significant only in boys or only in girls in single exposure models (Table S3). For example: the relationship between BPA and PWV was only significant in boys (β =-0.08; CI: -0.15, -0.01); and MiBP and PWV was only significant in girls (β = 2.73; CI: 0.10, 5.36) (Table S3). However, there was little evidence for interaction with these results (p interaction>0.10) (Table S3). Similarly, in the mixture models there was little evidence for differences by sex (Table 3, Table S2).

When we stratified by social class, we did not observe a consistent pattern of interaction for most exposure-outcome associations in single exposure models (Table S4). BPA was associated with decreased PWV among those of low social class (β = -0.10; CI: -0.19, -0.02, p interaction=0.09), but not high/middle social class. MiBP and TRCS were associated with increased CRVE measures in those of low social class (β = 6.12; CI: 2.06, 10.18, p interaction=0.02) and (β = 0.94; 95% CI: 0.01, 1.87, p interaction=0.04), respectively. While one paraben, BUPA was associated with decreased CRVE in those of high/middle social class (β = -1.40; CI: -2.16, -0.64, p interaction=0.08) (Table S4). In mixture models these was no evidence for differences by social class (Table 3, Tables S2).

When analyzing the separate trimester time points for phthalates and BPA, we observed similar associations as in single exposure models for MBzP and PWV in the 1st trimester (β = 0.04; CI: 0.00, 0.07) and MiBP and CRAE in the 3rd trimester (β = 1.23; CI: -0.01, 2.46) (Table S5). The observed associations between BPA and PWV and CRVE were no longer significant in models separated by trimester, however the coefficients were in a similar direction for PWV in both trimesters and CRVE in the 1st trimester. We found an association between MBzP and DBP in the 1st trimester which was not significant in single exposure models, however coefficients were similar (β = 0.59; CI: 0.02, 1.15) (Table S5). Excluding gestational weight gain and gestational age from the continuous single exposure models did not change the results (Table S6). In mixture models separately for phthalates and phenols no significant associations were observed (Tables S7-S8).

DISCUSSION

In this Spanish birth cohort, we found little evidence to suggest that prenatal urinary concentrations of phthalates and phenol metabolites are associated with parameters of macro- and microvascular health during early adolescence. A few statistically significant associations were found between certain chemical exposures and measures of SBP, PWV, CRAE and CRVE. None of the exposures showed associations with DBP and there was no evidence of associations between the phthalates and phenols mixture and any of the outcomes.

Several studies have examined the relationship between exposure to phthalates during pregnancy and/or childhood and blood pressure in children. Consistent with our mostly null findings, a birth cohort in Greece found that prenatal urinary phthalate metabolites and BPA were not associated with childhood blood pressure (Vafeiadi et al., 2018, 2015). In contrast other studies have found significant associations with blood pressure. Two studies observed an association between prenatal phthalate exposure and decreased SBP during childhood in girls only (Sol et al., 2020; Valvi et al., 2015). A systematic review and meta-analysis on phthalates concluded a positive association between several phthalate metabolites and both SBP and DBP in children and adolescents (Golestanzadeh et al., 2019). Regarding phenols, recent studies found a positive association between prenatal BPA and childhood SBP in girls (Ouyang et al., 2020) and boys (Sol et al., 2020). Similar positive associations were also observed with DBP and both sexes combined (Bae et al., 2017; Warembourg et al., 2019) and girls only (Ouyang et al., 2020). However, one study identified a negative relationship between BPA and DBP in girls (Sol et al., 2020). While several studies found a significant association between phthalate and/or BPA exposure and blood pressure, often sex dependent, our results were mostly null, even when stratified by sex. Aside from BPA, the HELIX study analyzed prenatal BP-3 and TRCS and observed no association with blood pressure (Warembourg et al., 2019).

We found that an increase in prenatal BPA exposure was related to a decrease in PWV in children, which remained significant for boys and those of low social class in our stratified analyses. Additionally, we observed a positive association with the phthalate metabolite

MBzP and PWV for those of higher social class. Two other studies in children have examined the relationship between phthalate exposure and a measure of arterial stiffness, though both were cross-sectional studies, measuring phthalate exposure and arterial stiffness at the same time point (Kataria et al., 2017; Su et al., 2019). Su et al. (2019) found higher phthalate concentrations to be associated with higher risk of increased carotid intima-media thickness in an adolescent population (Su et al., 2019). Kataria et al. (2017), found that DEHP metabolites were associated with decreased brachial artery distensibility and they found no relevant associations between phthalates and PWV (Kataria et al., 2017).

We did not identify any previous studies that assessed the relationship between phthalates, phenols and retinal measurements (CRAE and CRVE), so our study is the first. We observed that one phthalate metabolite, MiBP, was associated with increased CRAE, and this association was also observed for girls and those of lower social class in stratified analyses. CRAE assesses artery width, whereby narrowing is indicative of arterial damage. However, it is unclear how MiBP may mitigate arterial narrowing. Additionally, two parabens, MEPA and PRPA, were associated with reduced CRAE for boys, indicative of arterial narrowing. MiBP and TRCS were associated with an increase in CRVE for those of lower social class, which could indicate some venular widening or potential inflammation. However, the parabens BUPA, MEPA and ETPA were all found to be associated with reduced CRVE, implying the mitigation of any venular widening. These findings give an indication that phthalate and phenol compounds may play a role in altering the microvascular structure. However, these are the very first results and require replication in further studies.

While the mechanism(s) underlying the associations of phthalates and phenols are not well understood, oxidative stress, a key indicator of cardiovascular disease, may play a central role (Ferguson et al., 2017). Oxidative stress in regards to cardiovascular health describes injury caused to cells from the increased formation of reactive oxygen species (ROS) which ultimately overwhelms the ability to eliminate ROS or repair ROS-induced damage (Dhalla et al., 2000). Oxidative stress from increased levels of ROS have been connected to several risk factors for cardiovascular disease including hypertension, diabetes, obesity, arrhythmia and

atherosclerotic plaque formation (Pignatelli et al., 2018; Senoner and Dichtl, 2019). A study on phthalate exposure and markers of oxidative stress found a positive association between phthalate metabolites and increased body weight, risk of insulin resistance and F2-isoprostane levels (systemic oxidative stress biomarker) (Kataria et al., 2017). Additionally, BPA exposure was correlated with the expression of pro-inflammatory genes related to c-reactive protein, a marker indicative of CVD risk (Tsen et al., 2021). Also, phthalates and BPA have been related to changes in placental micro-RNA expression, DNA methylation, and genomic imprinting (Mose et al., 2007; Strakovsky and Schantz, 2018). Given that the placenta plays a vital role in fetal growth and development these changes may result in adverse health outcomes for the child. Findings from a 2020 in vitro study found that exposure to the phthalate metabolite MEHP on human endometrial microvascular endothelial cells, resulted in apoptosis and pyroptosis, forms of cell death that can lead to impairment of normal tissue and organ function (An, 2021). These few studies point to the mechanism(s) by which chemicals like phthalates and phenols may induce oxidative stress in the body thus interrupting normal development and increasing cardiovascular risk. However, further studies are needed, both longitudinal cohort studies and in vivo studies, to elucidate the mechanisms involved in the development of cardiovascular risk.

Our study has several strengths. The longitudinal nature of this study helps to detect potential relationship better than that of a cross-sectional study. We included novel measures of vascular health, as well as phenolic compounds not previously studied in relation to cardiovascular outcomes. Additionally, while many studies have accounted for sex through stratification, ours is the first to stratify by social class. Social class is an important factor given that it plays a large role in dictating to which chemicals and in what quantity exposure occurs (Montazeri et al., 2019). As our study demonstrates, merely adjusting for social class or similar variable does not completely disentangle these complex associations. Lastly, our study included a novel statistical approach, BWQS, which complimented single exposure models by accounting for the high dimensionality among phthalates and phenols that the single exposure models alone cannot account for (Carrico et al., 2015; Colicino et al., 2020).

Our study also has some limitations. Non-persistent chemicals such as phthalates and phenols have short half-lives leading to large variability in sample concentrations relying on spot urine samples (Casas et al., 2018). This type of measurement error on the exposure variable can lead to null associations due to regression dilution bias (Hutcheon et al., 2010). One way to minimize this bias is by obtaining repeated measures to better estimate the true exposure values (Hutcheon et al., 2010). For phthalate metabolites and BPA, we had two measurements during pregnancy and averaged those to lessen this bias somewhat. For the other phenols we had only one sample during pregnancy which could lead to an attenuation bias as high as 69% (Vernet et al., 2019). New cohort studies measuring nonpersistent chemicals like phthalates and phenols should aim to collect and pool three samples per day at minimum to more effectively estimate weekly exposure (Vernet et al., 2019). Another limitation was that our sample size was small, particularly for the stratified analyses (sex and social class), limiting our ability to detect significant associations and draw firm conclusions. Additionally, it is unclear how sensitive the measured cardiovascular outcomes are during early adolescence. While, several studies have examined health effects using blood pressure, fewer have used PWV and this is the first to use retinal imaging. Studies using these outcome measures at different age points are needed to further understand at which age these measures are most useful. Further, although we attempted to control for factors such as sex, social class and parental cardiovascular history, we cannot exclude residual confounding by unmeasured factors related to cardiovascular measures in young adolescents. Lastly, multiple comparison is a concern in multi-pollutant studies. Rather than apply an overly conservative adjustment for multiple comparison, we complemented our single exposure models with mixture models and draw our final conclusions on the consistency between the results.

Conclusion

This is the first birth cohort study to evaluate prenatal exposure to urinary phthalate metabolites and phenols, and their mixture during pregnancy with novel measures of vascular health during early adolescence. Our results provide little evidence to suggest that prenatal exposure to phthalates and phenols is associated with early adolescent measures of macro- and microvascular health. Future

longitudinal studies would benefit from using similar novel measures of vascular health as well as repeat urinary measurements for exposure assessment.

ACKNOWLEDGMENTS

We thank all of the study participants for their support with the INMA Sabadell birth cohort study. We also thank the dedicated INMA research nurses, Silvia Fochs and Núria Pey, for their work in conducting the study visits.

FUNDING

This study was funded by grants from Instituto de Salud Carlos III (Red INMA G03/176; CB06/02/0041; PI041436; PI081151 incl. FEDER funds; PI12/01890 incl. FEDER funds; CP13/00054 incl. FEDER funds; PI15/00118 incl. FEDER funds; CP16/00128 incl. FEDER funds; PI16/00118 incl. FEDER funds; PI16/00261 incl. FEDER funds; PI17/01340 incl. FEDER funds; PI18/00547 incl. FEDER funds), CIBERESP, Generalitat de Catalunya-CIRIT 1999SGR 00241, Generalitat de Catalunya-AGAUR (2009 SGR 501, 2014 SGR 822), Fundació La marató de TV3 (090430), Spanish Ministry of Economy and Competitiveness (SAF2012-32991 incl. FEDER funds), Agence Nationale de Securite Sanitaire de l'Alimentation de l'Environnement et du Travail (1262C0010; EST-2016 RF-21), EU Commission (261357, 308333, 603794 and 634453). CW held a Sara Borrell postdoctoral grant (CD18/00132) from the Instituto de Salud Carlos III. We acknowledge support from the Spanish Ministry of Science and Innovation and the State Research Agency through the "Centro de Excelencia Severo Ochoa 2019-2023" Program (CEX2018-000806-S), and support from the Generalitat de Catalunya through the CERCA Program.

REFERENCES

An, L., 2021. Exposure to mono (2-ethylhexyl) phthalate facilitates apoptosis and pyroptosis of human endometrial microvascular endothelial cells through NLRP3 inflammasome. J Appl Toxicol. 41, 755–64. https://doi.org/10.1002/jat.4106

Bae, S., Lim, Y.H., Lee, Y.A., Shin, C.H., Oh, S.Y., Hong, Y.C., 2017. Maternal Urinary Bisphenol A Concentration during Midterm Pregnancy and Children's Blood Pressure at Age 4. Hypertension 69, 367–374. https://doi.org/10.1161/HYPERTENSIONAHA.116.08281

Carrico, C., Gennings, C., Wheeler, D.C., Factor-Litvak, P., 2015. Characterization of a Weighted Quantile Score Approach for Highly Correlated Data in Risk Analysis Scenarios. J Agric Biol Env. Stat. 20, 100–20. https://doi.org/10.1007/s13253-014-0180-3.Characterization

Casas, M., Basagaña, X., Sakhi, A.K., Haug, L.S., Philippat, C., Granum, B., Manzano-Salgado, C.B., Brochot, C., Zeman, F., de Bont, J., Andrusaityte, S., Chatzi, L., Donaire-Gonzalez, D., Giorgis-Allemand, L., Gonzalez, J.R., Gracia-Lavedan, E., Grazuleviciene, R., Kampouri, M., Lyon-Caen, S., Pañella, P., Petraviciene, I., Robinson, O., Urquiza, J., Vafeiadi, M., Vernet, C., Waiblinger, D., Wright, J., Thomsen, C., Slama, R., Vrijheid, M., 2018. Variability of urinary concentrations of non-persistent chemicals in pregnant women and school-aged children. Environ. Int. 121, 561–573. https://doi.org/10.1016/j.envint.2018.09.046

Casas, M., Valvi, D., Luque, N., Ballesteros-Gomez, A., Carsin, A.E., Fernandez, M.F., Koch, H.M., Mendez, M.A., Sunyer, J., Rubio, S., Vrijheid, M., 2013. Dietary and sociodemographic determinants of bisphenol A urine concentrations in pregnant women and children. Environ. Int. 56, 10–18. https://doi.org/10.1016/j.envint.2013.02.014

Colicino, E., Pedretti, N.F., Busgang, S., Gennings, C., 2020. Per-And poly-fluoroalkyl substances and bone mineral density: Results from the Bayesian weighted quantile sum regression. Environ. Epidemiol. 4, e092. https://doi.org/10.1101/19010710

Cote, A.T., Phillips, A.A., Harris, K.C., Sandor, G.G.S., Panagiotopoulos, C., Devlin, A.M., 2015. Obesity and arterial stiffness in children: Systematic review and meta-analysis. Arterioscler. Thromb. Vasc. Biol. 35, 1038–1044. https://doi.org/10.1161/ATVBAHA.114.305062

De Boever, P., Louwies, T., Provost, E., Int Panis, L., Nawrot, T.S., 2014. Fundus photography as a convenient tool to study microvascular responses to cardiovascular disease risk factors in epidemiological studies. J. Vis. Exp. 1–9. https://doi.org/10.3791/51904

Dhalla, N.S., Temsah, R.M., Netticadan, T., 2000. Role of oxidative stress in cardiovascular diseases. J. Hypertens. 655–73.

Diamanti-Kandarakis, E., Bourguignon, J., Giudice, L., Hauser, R., Prins, G., Soto, A., Zoeller, R., Gore, A., 2009. Endocrine-Disrupting Chemicals: An Endocrine Society Scientific Statement. Endocr Rev. 30, 293–342.

Ferguson, K.K., Chen, Y.H., Vanderweele, T.J., McElrath, T.F., Meeker, J.D., Mukherjee, B., 2017. Mediation of the relationship between maternal phthalate exposure and preterm birth by oxidative stress with repeated measurements across pregnancy. Environ. Health Perspect. 125, 488–494. https://doi.org/10.1289/EHP282

Franks, P., Hanson, R., Knowler, W., Sievers, M., Bennett, M., Looker, H., 2010. Childhood Obesity, Other Cardiovascular Risk Factors, and Premature Death. N. Engl. J. Med. 362, 485–493. https://doi.org/10.1056/NEJMoa0904130.Childhood

Fu, X., Xu, J., Zhang, R., Yu, J., 2020. The association between environmental endocrine disruptors and cardiovascular diseases: A systematic review and meta-analysis. Environ. Res. 187, 109464. https://doi.org/10.1016/j.envres.2020.109464

Golestanzadeh, M., Riahi, R., Kelishadi, R., 2019. Association of exposure to phthalates with cardiometabolic risk factors in children and adolescents: a systematic review and meta-analysis. Environ. Sci. Pollut. Res. 26, 35670–35686. https://doi.org/10.1007/s11356-019-06589-7

Gore, A.C., Chappell, V.A., Fenton, S.E., Flaws, J.A., Nadal, A., Prins, G.S., Toppari, J., Zoeller, R.T., 2015. Executive Summary to EDC-2: The Endocrine Society's second Scientific Statement on endocrine-disrupting chemicals. Endocr. Rev. 36, 593–602. https://doi.org/10.1210/er.2015-1093

Guxens, M., Ballester, F., Espada, M., Fernández, M.F., Grimalt, J.O., Ibarluzea, J., Olea, N., Rebagliato, M., Tardón, A., Torrent, M., Vioque, J., Vrijheid, M., Sunyer, J., 2012. Cohort profile: The INMA-INfancia y Medio Ambiente-(environment and childhood) project. Int. J. Epidemiol. 41, 930–940. https://doi.org/10.1093/ije/dyr054

Hudson, L.D., Rapala, A., Khan, T., Williams, B., Viner, R.M., 2015. Evidence for contemporary arterial stiffening in obese children and adolescents using pulse wave velocity: A systematic review and meta-analysis. Atherosclerosis 241, 376–386. https://doi.org/10.1016/j.atherosclerosis.2015.05.014

Hutcheon, J.A., Chiolero, A., Hanley, J.A., 2010. Random measurement error and regression dilution bias. BMJ c2289.

Juonala, M., Magnussen, C.G., Berenson, G.S., Venn, A., Burns, T.L., Sabin, M.A., Srinivasan, S.R., Daniels, S.R., Davis, P.H., Chen, W., Sun, C., Cheung, M., Viikari, J.S., Dwyer, T., Raitakari, O.T., 2011. Childhood adiposity, adult adiposity, and cardiovascular risk factors. N. Engl. J. Med. 365, 1876–1885. https://doi.org/10.1056/NEJMoa1010112

Kataria, A., Levine, D., Wertenteil, S., Vento, S., Xue, J., Rajendiran, K., Kannan, K., Thurman, J.M., Morrison, D., Brody, R., Elaine Urbina, M., Attina, T., Trasande, L., Trachtman, H., 2017. Exposure to Bisphenols and Phthalates and Association with Oxidant Stress, Insulin Resistance, and Endothelial Dysfunction in Children. Pediatr Res. 81, 857–64. https://doi.org/10.1093/ajcp/24.11.1259

Knudtson, M.D., Lee, K.E., Hubbard, L.D., Wong, T.Y., Klein, R., Klein, B.E.K., 2003. Revised formulas for summarizing retinal vessel diameters. Curr. Eye Res. 27, 143–149. https://doi.org/10.1076/ceyr.27.3.143.16049

Landrigan, P.J., Goldman, L.R., 2011. Children s Vulnerability To Toxic Chemicals: A Challenge And Opportunity To Strengthen Health And Environmental Policy. Health Aff. 30, 842–850. https://doi.org/10.1377/hlthaff.20.2.225

Li, L.J., Ikram, M.K., Wong, T.Y., 2016. Retinal vascular imaging in early life: Insights into processes and risk of cardiovascular disease. J. Physiol. 594, 2175–2203. https://doi.org/10.1113/JP270947

Lunder, S., Hovander, L., Athanassiadis, I., Bergman, A., 2010. Significantly higher polybrominated diphenyl ether levels in young U.S. children than in their mothers. Environ. Sci. Technol. 44, 5256–62. https://doi.org/10.1021/es1009357

Mamsen, L.S., Jönsson, B.A.G., Lindh, C.H., Olesen, R.H., Larsen, A., Ernst, E., Kelsey, T.W., Andersen, C.Y., 2017. Concentration of perfluorinated compounds and cotinine in human foetal organs, placenta, and maternal plasma. Sci. Total Environ. 596–597, 97–105. https://doi.org/10.1016/j.scitotenv.2017.04.058

Mariana, M., Feiteiro, J., Verde, I., Cairrao, E., 2016. The effects of phthalates in the cardiovascular and reproductive systems: A review. Environ. Int. 94, 758–776. https://doi.org/10.1016/j.envint.2016.07.004

Meeker, J., 2012. Exposure to environmental endocrine disruptors and child development. Arch. Pediatr. Adolesc. … 166, E1–E7. https://doi.org/10.1001/archpediatrics.2012.241.Exposure

Montazeri, P., Thomsen, C., Casas, M., de Bont, J., Haug, L.S., Maitre, L., Papadopoulou, E., Sakhi, A.K., Slama, R., Saulnier, P.J., Urquiza, J., Grazuleviciene, R., Andrusaityte, S., McEachan, R., Wright, J., Chatzi, L., Basagaña, X., Vrijheid, M., 2019. Socioeconomic position and exposure to multiple environmental chemical contaminants in six European mother-child cohorts. Int. J. Hyg. Environ. Health 222, 864–872. https://doi.org/10.1016/j.ijheh.2019.04.002

Mose, T., Knudsen, L.E., Hedegaard, M., Mortensen, G.K., 2007. Transplacental transfer of monomethyl phthalate and mono(2-ethylhexyl) phthalate in a human placenta perfusion system. Int. J. Toxicol. 26, 221–229. https://doi.org/10.1080/10915810701352721

Newman, A.R., Andrew, N.H., Casson, R.J., 2017. Review of paediatric retinal microvascular changes as a predictor of

cardiovascular disease. Clin. Exp. Ophthalmol. 45, 33–44. https://doi.org/10.1111/ceo.12773

Nidens, N., Vogel, M., Körner, A., Kiess, W., 2020. Prenatal exposure to phthalate esters and its impact on child development. Best Pr. Res Clin Endocrinol Metab 101478. https://doi.org/10.1016/j.beem.2020.101478

Ouyang, F., Zhang, G.-H., Du, K., Shen, L., Ma, R., Wang, Xia, Wang, Xiaobin, Zhanga, J., 2020. Maternal prenatal urinary bisphenol A level and child cardio-metabolic risk factors: A prospective cohort study. Env. Pollut. 265(Pt A). https://doi.org/10.1016/j.envpol.2020.115008

Pignatelli, P., Menichelli, D., Pastori, D., Violi, F., 2018. Oxidative stress and cardiovascular disease: new insights. Kardiol Pol. 76, 713–22. https://doi.org/10.5603/KP.a2018.0071

Sakhi, A.K., Sabaredzovic, A., Papadopoulou, E., Cequier, E., Thomsen, C., 2018. Levels, variability and determinants of environmental phenols in pairs of Norwegian mothers and children. Environ. Int. 114, 242–251. https://doi.org/10.1016/j.envint.2018.02.037

Senoner, T., Dichtl, W., 2019. Oxidative stress in cardiovascular diseases: Still a therapeutic target? Nutrients 11. https://doi.org/10.3390/nu11092090

Sol, C.M., Santos, S., Asimakopoulos, A.G., Duijts, L., Kannan, K., Trasande, L., Jaddoe, V.W. V, Group, G.R.S., City, N.Y., City, N.Y., City, N.Y., City, Y., City, N.Y., 2020. Associations of maternal phthalate and bisphenol urine concentrations during pregnancy with childhood blood pressure in a population-based prospective cohort study. Env. Int. 138. https://doi.org/10.1016/j.envint.2020.105677

Strakovsky, R.S., Schantz, S.L., 2018. Impacts of bisphenol A (BPA) and phthalate exposures on epigenetic outcomes in the human placenta. Environ. Epigenetics 4, 1–18. https://doi.org/10.1093/eep/dvy022

Su, T.-C., Hwang, I.-S., Torng, P.-L., Wu, C., Lin, C.-Y., Sung, F.-C., 2019. Phthalate exposure increases subclinical atherosclerosis in young population. Env. Pollut. 586–93. https://doi.org/10.1016/j.envpol.2019.04.006.

Tsen, C.-M., Liu, J.-H., Yang, D.-P., Chao, H.-R., Chen, J.-L., Chou, W.-C., Ho, Y.-C., Chuang, C.-Y., 2021. Study on the correlation of bisphenol A exposure, pro-inflammatory gene expression, and C-reactive protein with potential cardiovascular disease symptoms in young adults. Env. Sci Pollut Res Int. Online ahe. https://doi.org/10.1007/s11356-021-12805-0

Vafeiadi, M., Georgiou, V., Chalkiadaki, G., Rantakokko, P., Kiviranta, H., Karachaliou, M., Fthenou, E., Venihaki, M., Sarri, K., Vassilaki, M., Kyrtopoulos, S.A., Oken, E., Kogevinas, M., Chatzi, L., 2015. Association of prenatal exposure to persistent organic pollutants with obesity and cardiometabolic traits in early childhood: The rhea mother–child cohort (Crete, Greece). Environ. Health Perspect. 123, 1015–1021. https://doi.org/10.1289/ehp.1409062

Vafeiadi, M., Myridakis, A., Roumeliotaki, T., Margetaki, K., Chalkiadaki, G., Dermitzaki, E., Venihaki, M., Sarri, K., Vassilaki, M., Leventakou, V., Stephanou, E.G., Kogevinas, M., Chatzi, L., 2018. Association of early life exposure to phthalates with obesity and cardiometabolic traits in childhood: Sex specific associations. Front. Public Heal. 6, 1–11. https://doi.org/10.3389/fpubh.2018.00327

Valvi, D., Casas, M., Romaguera, D., Monfort, N., Ventura, R., Martinez, D., Sunyer, J., Vrijheid, M., 2015a. Prenatal phthalate exposure and childhood growth and blood pressure: Evidence from the spanish inma-sabadell birth cohort study. Environ. Health Perspect. 123, 1022–1029. https://doi.org/10.1289/ehp.1408887

Valvi, D., Monfort, N., Ventura, R., Casas, M., Casas, L., Sunyer, J., Vrijheid, M., 2015b. Variability and predictors of urinary phthalate metabolites in Spanish pregnant women. Int. J. Hyg. Environ. Health 218, 220–231. https://doi.org/10.1016/j.ijheh.2014.11.003

Vernet, C., Philippat, C., Agier, L., Calafat, A.M., Ye, X., Lyon-Caen, S., Hainaut, P., Siroux, V., Schisterman, E.F., Slama, R., 2019. An Empirical Validation of the Within-subject Biospecimens Pooling Approach to Minimize Exposure Misclassification in Biomarker-based Studies. Epidemiology 30, 756–767. https://doi.org/10.1097/EDE.0000000000001056

Vrijheid, M., Casas, M., Gascon, M., Valvi, D., Nieuwenhuijsen, M., 2016. Environmental pollutants and child health-A review of recent concerns. Int. J. Hyg. Environ. Health 219, 331–342. https://doi.org/10.1016/j.ijheh.2016.05.001

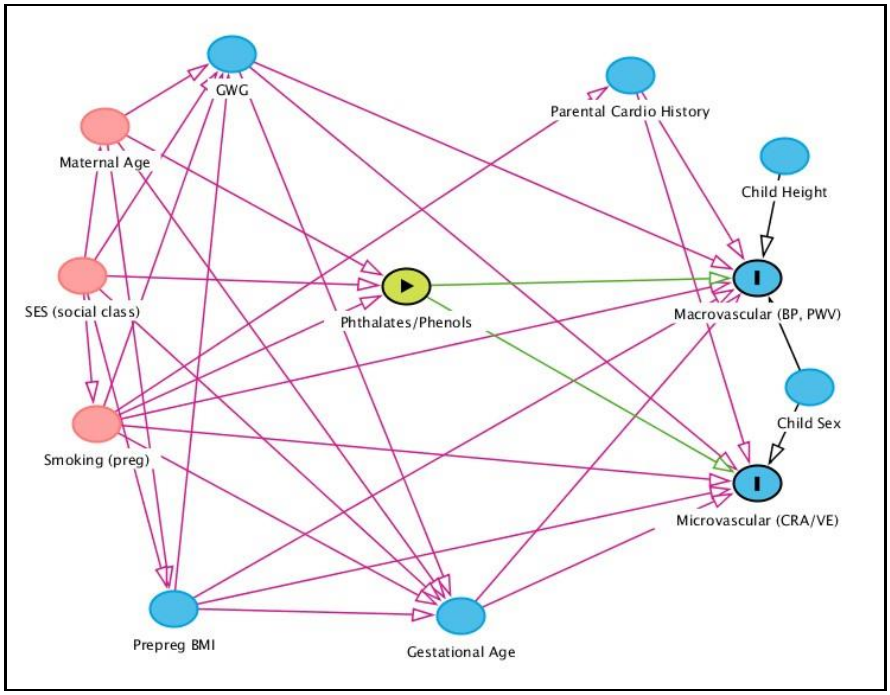
Warembourg, C., Maitre, L., Tamayo-Uria, I., Fossati, S., Roumeliotaki, T., Aasvang, G.M., Andrusaityte, S., Casas, M., Cequier, E., Chatzi, L., Dedele, A., Gonzalez, J.R., Gražulevičienė, R., Haug, L.S., Hernandez-Ferrer, C., Heude, B., Karachaliou, M., Krog, N.H., McEachan, R., Nieuwenhuijsen, M., Petraviciene, I., Quentin, J., Robinson, O., Sakhi, A.K., Slama, R., Thomsen, C., Urquiza, J., Vafeiadi, M., West, J., Wright, J., Vrijheid, M., Basagaña, X., 2019. Early-Life Environmental Exposures and Blood Pressure in Children. J. Am. Coll. Cardiol. 74, 1317–1328. https://doi.org/10.1016/j.jacc.2019.06.069

Wittassek, M., Koch, H.M., Angerer, J., Brüning, T., 2011. Assessing exposure to phthalates – The human biomonitoring approach. Mol Nutr Food Res 55, 7–31.

Wormuth, M., Scheringer, M., Vollenweider, M., Hungerbühler, K., 2006. What are the sources of exposure to eight frequently used phthalic acid esters in Europeans? Risk Anal. 26, 803–24. https://doi.org/10.1111/j.1539-6924.2006.00770.x.

Supplementary Material
Paper V

Figure S1. Directed Acyclic Graph (DAG)



Figures S2a-b. Correlation Matrices

Figure S2a. Cardiovascular Outcomes

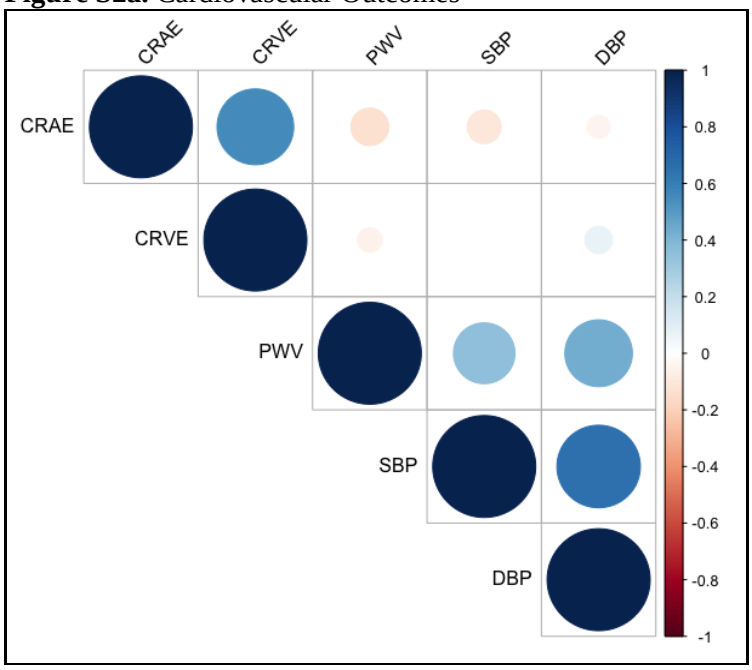


Figure S2b. Phthalates and Phenols:

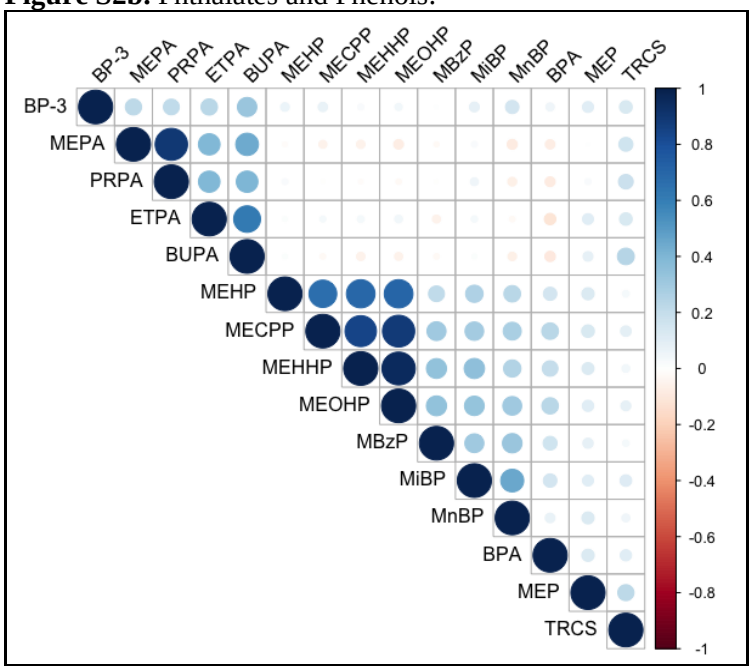
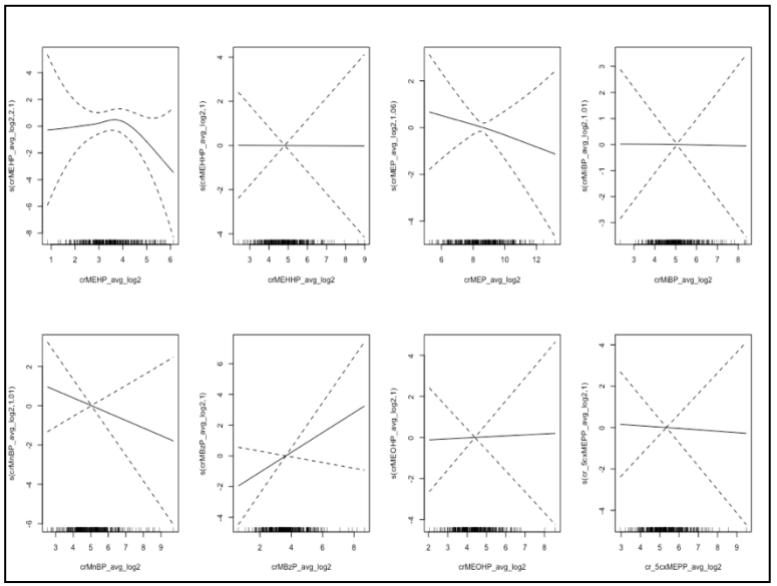


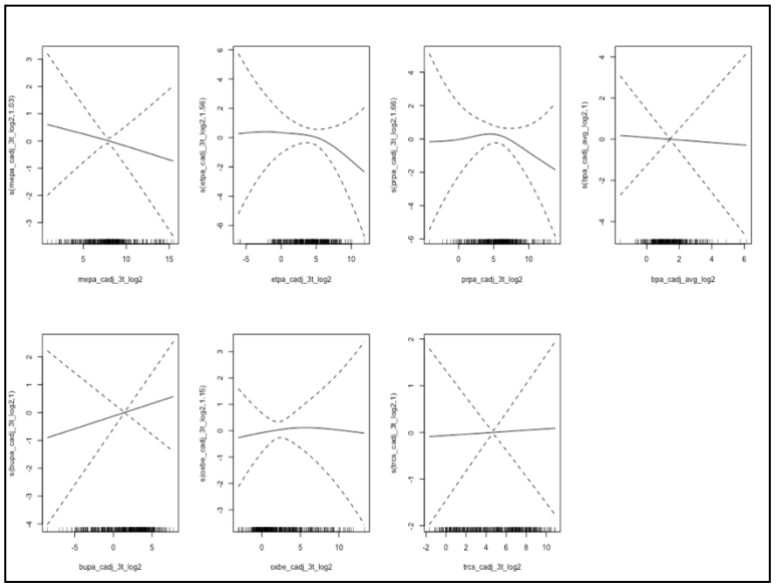
Figure S3a-e. Generalized Additive Models (GAMs): Smooth associations between prenatal log-transformed phthalate and phenol concentrations and early adolescent cardiovascular measures.

a) Systolic Blood Pressure

Phthalates

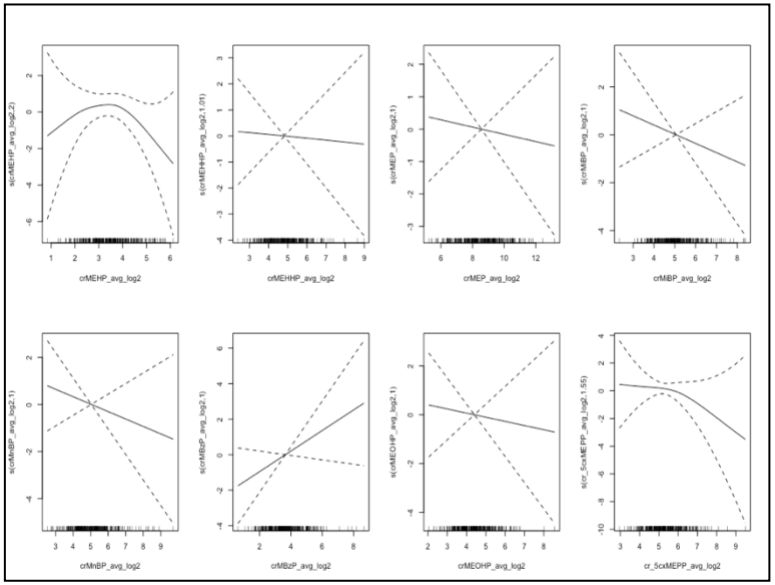


Phenols

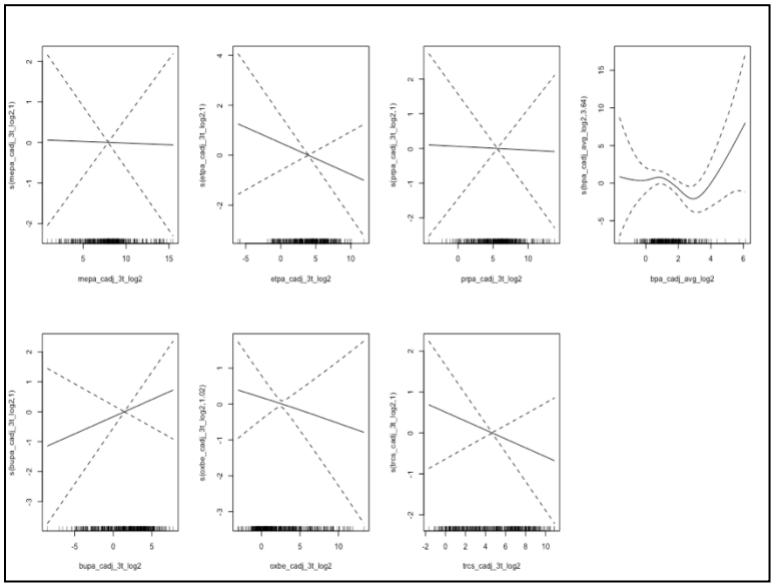


b) Diastolic Blood Pressure

Phthalates

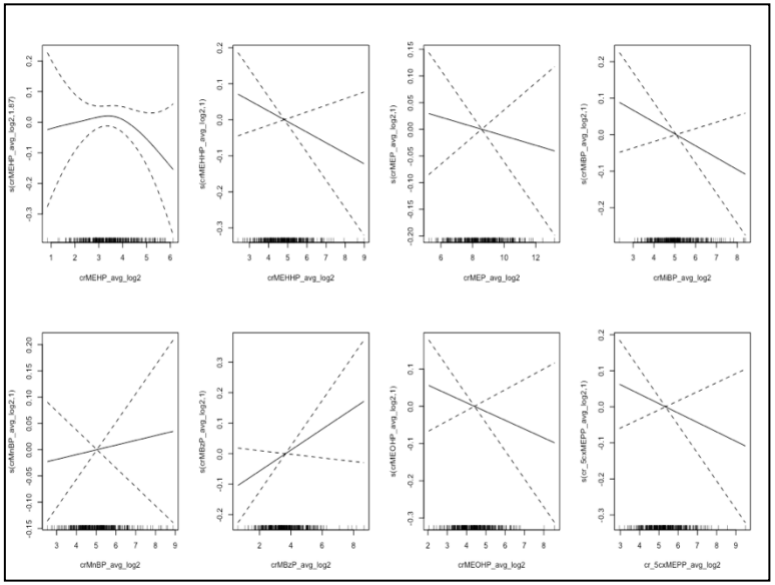


Phenols

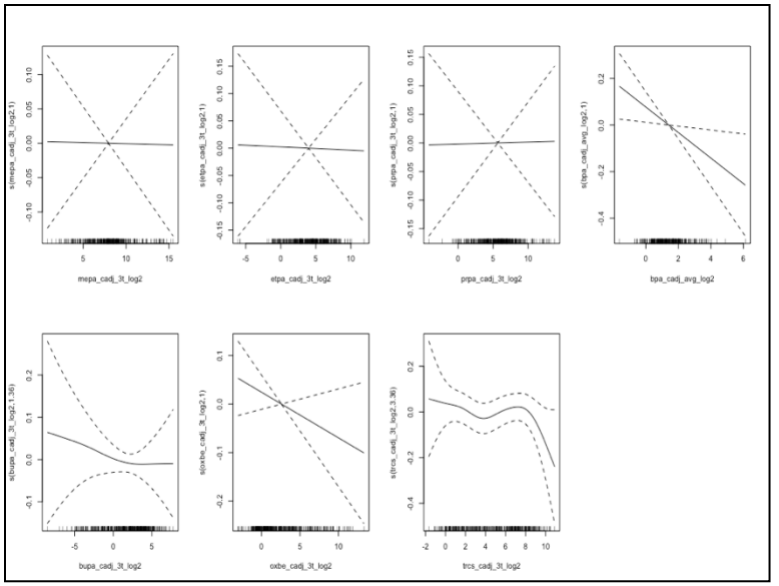


c) Pulse Wave Velocity

Phthalates

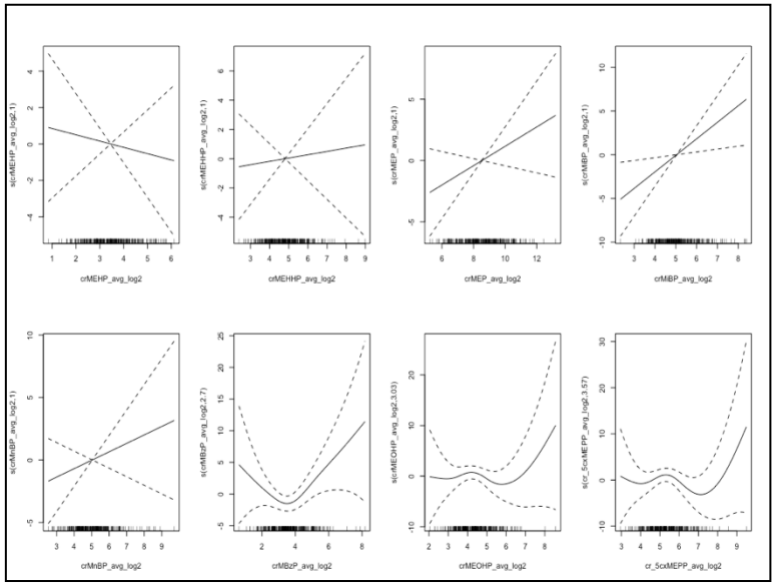


Phenols

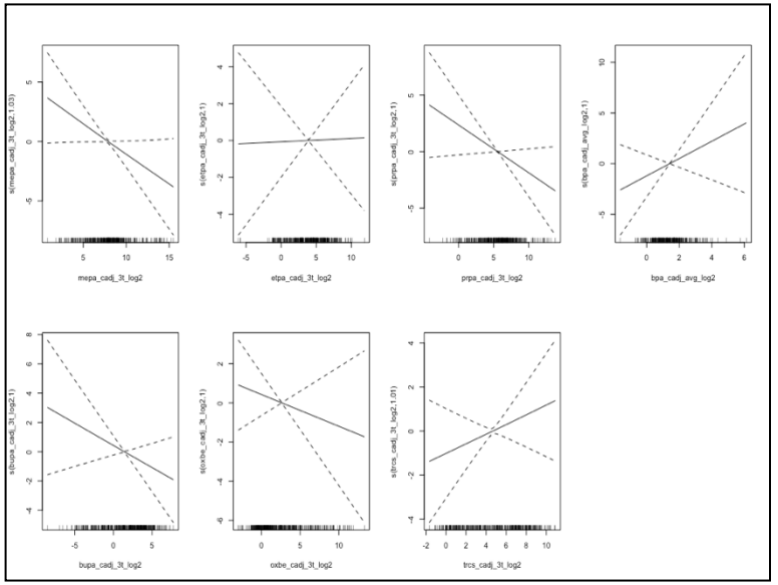


d) Central Retinal Arteriole Equivalent

Phthalates

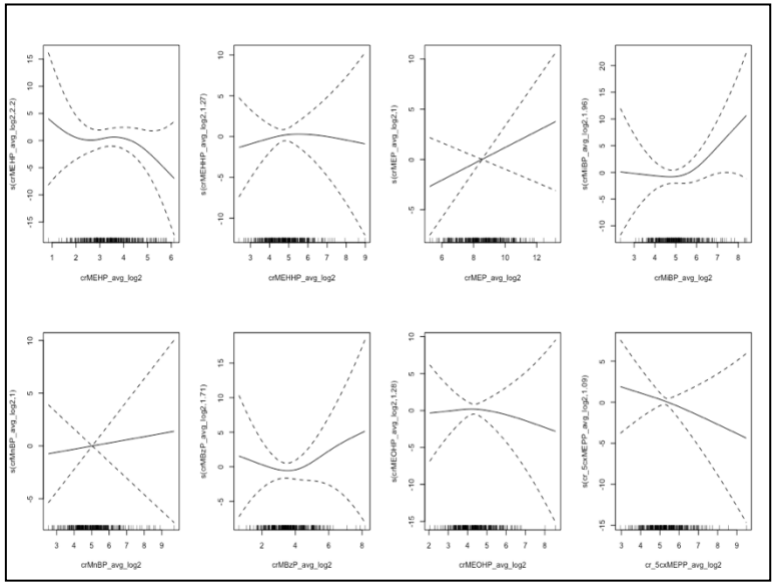


Phenols



e) Central Retinal Venular Equivalent

Phthalates



Phenols

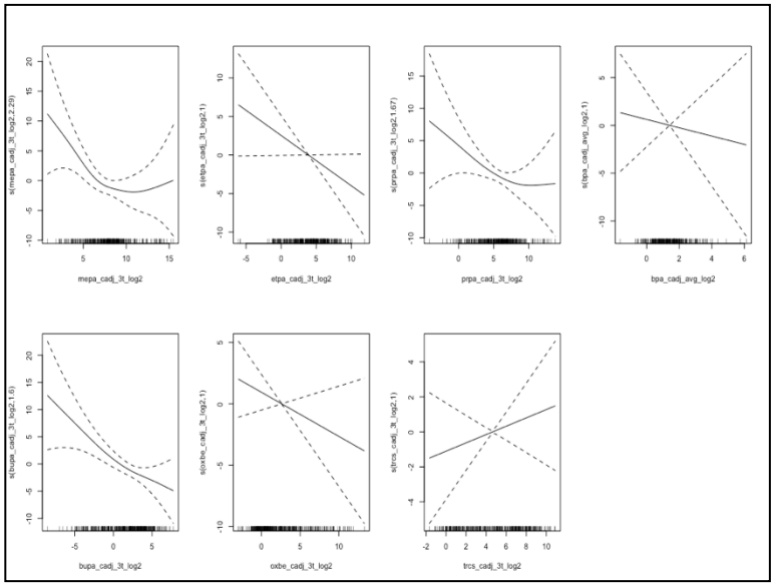


Table S1. Associations between individual prenatal phthalate and phenol exposures and early adolescent cardiovascular measurements from regression models, continuous and tertile exposure.

	Systolic Blood Pressure		Diastolic Blood Pressure		Pulse Wave Velocity		Central Retinal Arteriole Equivalent		Central Retinal Venular Equivalent	
Chemical	n	Beta (95% CI)	n	Beta (95% CI)	n	Beta (95% CI)	n	Beta (95% CI)	n	Beta (95% CI)
MEHP	332		331		317		304		304	
1st tertile		Ref.		Ref.		Ref.		Ref.		Ref.
2nd tertile		1.30 (-1.05, 3.64)		0.45 (-1.53, 2.43)		0.08 (-0.04, 0.19)		1.35 (-2.23, 4.93)		2.84 (-2.03, 7.71)
3rd tertile		-0.25 (-2.57, 2.07)		-0.46 (-2.41, 1.50)		-0.04 (-0.15, 0.07)		-0.02 (-3.54, 3.49)		0.47 (-4.32, 5.25)
continuous		-0.37 (-1.37, 0.64)		-0.33 (-1.17, 0.52)		-0.02 (-0.07, 0.03)		-0.31 (-1.85, 1.23)		-1.02 (-3.11, 1.08)
MEHHP	332		331		317		304		304	
1st tertile		Ref.		Ref.		Ref.		Ref.		Ref.
2nd tertile		0.40 (-1.91, 2.71)		1.16 (-0.79, 3.10)		-0.05 (-0.16, 0.07)		1.62 (-1.89, 5.14)		3.27 (-1.50, 8.05)
3rd tertile		0.56 (-1.78, 2.91)		0.63 (-1.34, 2.60)		-0.07 (-0.19, 0.04)		0.05 (-3.48, 3.58)		1.25 (-3.56, 6.05)
continuous		0.02 (-0.96, 1.01)		-0.05 (-0.88, 0.78)		-0.03 (-0.08, 0.02)		0.29 (-1.20, 1.77)		0.14 (-1.88, 2.16)
MEP	332		331		317		304		304	
1st tertile		Ref.		Ref.		Ref.		Ref.		Ref.
2nd tertile		1.83 (-0.50, 4.15)		-0.47 (-2.44, 1.50)		-0.09 (-0.20, 0.03)		0.70 (-2.81, 4.21)		3.20 (-1.58, 7.97)
3rd tertile		-0.30 (-2.63, 2.04)		-0.28 (-2.26, 1.70)		-0.03 (-0.14, 0.08)		2.12 (-1.45, 5.70)		3.33 (-1.53, 8.19)
continuous		-0.24 (-0.94, 0.45)		-0.10 (-0.69, 0.49)		-0.01 (-0.04, 0.02)		0.77 (-0.29, 1.84)		0.81 (-0.64, 2.25)
MiBP	332		331		317		304		304	

1st tertile		Ref.		Ref.		Ref.		Ref.		Ref.
2nd tertile		2.23 (-0.08, 4.55)		0.55 (-1.42, 2.51)		0.03 (-0.08, 0.14)		2.87 (-0.64, 6.38)		-0.10 (-4.90, 4.71)
3rd tertile		0.17 (-2.15, 2.49)		-0.46 (-2.43, 1.50)		-0.04 (-0.16, 0.07)		2.55 (-0.98, 6.07)		0.60 (-4.22, 5.43)
continuous		0.08 (-0.96, 1.12)		-0.36 (-1.24, 0.52)		-0.03 (-0.08, 0.02)		1.89 (0.34, 3.44)		1.31 (-0.82, 3.44)
MnBP	332		331		317		304		304	
1st tertile		Ref.		Ref.		Ref.		Ref.		Ref.
2nd tertile		1.34 (-0.98, 3.65)		0.07 (-1.89, 2.02)		-0.01 (-0.12, 0.11)		0.08 (-3.44, 3.60)		1.41 (-3.39, 6.20)
3rd tertile		-0.60 (-2.92, 1.72)		-0.89 (-2.85, 1.08)		0.00 (-0.12, 0.11)		0.97 (-2.60, 4.55)		-1.21 (-6.07, 3.65)
continuous		-0.37 (-1.27, 0.52)		-0.30 (-1.05, 0.46)		0.01 (-0.04, 0.05)		0.66 (-0.68, 2.01)		0.24 (-1.59, 2.07)
MBzP	332		331		317		304		304	
1st tertile		Ref.		Ref.		Ref.		Ref.		Ref.
2nd tertile		0.07 (-2.26, 2.39)		0.62 (-1.34, 2.58)		0.14 (0.02, 0.25)		-2.90 (-6.34, 0.55)		-0.25 (-4.99, 4.50)
3rd tertile		1.27 (-1.05, 3.60)		1.33 (-0.63, 3.29)		0.08 (-0.03, 0.19)		1.62 (-1.88, 5.12)		1.17 (-3.65, 5.99)
continuous		0.63 (-0.20, 1.46)		0.61 (-0.08, 1.31)		0.04 (0.00, 0.08)		0.81 (-0.46, 2.09)		0.45 (-1.29, 2.19)
MEOHP	332		331		317		304		304	
1st tertile		Ref.		Ref.		Ref.		Ref.		Ref.
2nd tertile		0.56 (-1.79, 2.90)		1.79 (-0.19, 3.76)		0.05 (-0.06, 0.16)		1.15 (-2.38, 4.67)		2.18 (-2.62, 6.98)
3rd tertile		0.53 (-1.82, 2.88)		0.36 (-1.61, 2.32)		-0.08 (-0.19, 0.03)		-0.93 (-4.46, 2.61)		-0.36 (-5.17, 4.46)
continuous		0.08 (-0.98, 1.15)		-0.14 (-1.04, 0.75)		-0.02 (-0.08, 0.03)		-0.07 (-1.67, 1.53)		-0.34 (-2.52, 1.85)
MECPP	332		331		317		304		304	
1st tertile		Ref.		Ref.		Ref.		Ref.		Ref.
2nd tertile		-0.41 (-2.76, 1.94)		-0.56 (-2.54, 1.42)		0.02 (-0.09, 0.14)		2.18 (-1.33, 5.68)		0.97 (-3.82, 5.76)

3rd tertile		0.22 (-2.13, 2.56)		-0.27 (-2.24, 1.71)		-0.04 (-0.16, 0.07)		-0.59 (-4.13, 2.95)		-1.19 (-6.04, 3.65)
continuous		-0.03 (-1.08, 1.02)		-0.38 (-1.26, 0.51)		-0.03 (-0.08, 0.03)		-0.32 (-1.91, 1.27)		-1.01 (-3.17, 1.15)
MEPA	405		404		389		373		373	
1st tertile		Ref.		Ref.		Ref.		Ref.		Ref.
2nd tertile		2.48 (0.31, 4.66)		-0.05 (-1.88, 1.78)		0.00 (-0.11, 0.10)		-0.46 (-3.69, 2.76)		-2.10 (-6.47, 2.27)
3rd tertile		-0.86 (-3.03, 1.30)		-0.28 (-2.10, 1.54)		0.00 (-0.11, 0.10)		-2.09 (-5.32, 1.15)		-2.93 (-7.32, 1.45)
continuous		-0.10 (-0.45, 0.25)		-0.01 (-0.30, 0.28)		0.00 (-0.02, 0.02)		-0.49 (-1.00, 0.03)		-0.71 (-1.41, -0.01)
ETPA	405		404		389		373		373	
1st tertile		Ref.		Ref.		Ref.		Ref.		Ref.
2nd tertile		0.04 (-2.19, 2.27)		-0.07 (-1.92, 1.78)		-0.01 (-0.11, 0.10)		0.87 (-2.43, 4.18)		-1.72 (-6.19, 2.75)
3rd tertile		-0.65 (-2.85, 1.54)		-0.49 (-2.31, 1.34)		0.00 (-0.11, 0.10)		-0.49 (-3.75, 2.76)		-3.79 (-8.19, 0.61)
continuous		-0.13 (-0.46, 0.21)		-0.13 (-0.40, 0.15)		0.00 (-0.02, 0.02)		0.03 (-0.45, 0.52)		-0.63 (-1.28, 0.03)
PRPA	403		402		387		371		371	
1st tertile		Ref.		Ref.		Ref.		Ref.		Ref.
2nd tertile		1.19 (-0.99, 3.38)		0.64 (-1.18, 2.46)		-0.02 (-0.13, 0.08)		1.49 (-1.74, 4.72)		0.31 (-4.07, 4.70)
3rd tertile		-0.54 (-2.72, 1.65)		0.37 (-1.45, 2.19)		0.02 (-0.09, 0.13)		-1.34 (-4.58, 1.89)		-2.34 (-6.73, 2.05)
continuous		-0.10 (-0.42, 0.22)		-0.01 (-0.27, 0.26)		0.00 (-0.01, 0.02)		-0.42 (-0.89, 0.05)		-0.54 (-1.18, 0.09)
BPA	331		330		317		305		305	
1st tertile		Ref.		Ref.		Ref.		Ref.		Ref.
2nd tertile		-0.10 (-2.44, 2.23)		-0.14 (-2.09, 1.81)		-0.08 (-0.20, 0.03)		-1.01 (-4.66, 2.64)		-4.98 (-9.98, 0.01)
3rd tertile		-0.54 (-2.90, 1.82)		-1.36 (-3.33, 0.6)		-0.08 (-0.20, 0.03)		0.93 (-2.75, 4.61)		-2.77 (-7.80, 2.27)

continuous		-0.05 (-0.99, 0.88)		-0.38 (-1.16, 0.4)		-0.06 (-0.10, -0.01)		0.80 (-0.65, 2.25)		-0.54 (-2.54, 1.46)
BUPA	403		402		387		371		371	
1st tertile		Ref.		Ref.		Ref.		Ref.		Ref.
2nd tertile		0.78 (-1.43, 2.99)		0.24 (-1.61, 2.08)		-0.09 (-0.20, 0.01)		-1.25 (-4.52, 2.03)		-5.57 (-9.97, -1.17)
3rd tertile		0.66 (-1.58, 2.89)		0.91 (-0.95, 2.77)		-0.02 (-0.13, 0.09)		-1.19 (-4.53, 2.14)		-5.11 (-9.59, -0.64)
continuous		0.09 (-0.22, 0.39)		0.11 (-0.14, 0.37)		0.00 (-0.02, 0.01)		-0.28 (-0.74, 0.17)		-0.96 (-1.57, -0.35)
BP-3	405		404		389		373		373	
1st tertile		Ref.		Ref.		Ref.		Ref.		Ref.
2nd tertile		-1.12 (-3.31, 1.07)		-0.28 (-2.10, 1.53)		-0.06 (-0.16, 0.05)		-0.83 (-4.07, 2.41)		-0.85 (-5.24, 3.55)
3rd tertile		0.27 (-1.93, 2.47)		-0.49 (-2.32, 1.34)		-0.1 (-0.21, 0.00)		-1.61 (-4.83, 1.62)		-1.57 (-5.94, 2.81)
continuous		0.01 (-0.27, 0.29)		-0.08 (-0.32, 0.15)		-0.01 (-0.02, 0.00)		-0.12 (-0.53, 0.28)		-0.32 (-0.87, 0.23)
TRCS	405		404		389		373		373	
1st tertile		Ref.		Ref.		Ref.		Ref.		Ref.
2nd tertile		-0.83 (-3.01, 1.34)		-0.51 (-2.32, 1.30)		-0.04 (-0.15, 0.06)		-0.11 (-3.34, 3.11)		-0.43 (-4.80, 3.95)
3rd tertile		0.70 (-1.48, 2.88)		-0.55 (-2.36, 1.26)		-0.04 (-0.15, 0.06)		1.45 (-1.76, 4.67)		1.35 (-3.01, 5.71)
continuous		0.03 (-0.26, 0.32)		-0.09 (-0.33, 0.16)		-0.01 (-0.02, 0.01)		0.20 (-0.23, 0.63)		0.23 (-0.36, 0.82)

Using covariate imputed data, m=20. Models adjusted for child age at visit, child sex, mother's age at delivery, prepregnancy BMI, gestational weight gain, social class, parental cardiovascular history, smoking during pregnancy and gestational age. SBP, DBP and PWV were additionally adjusted for child height at visit.

Table S2. Associations between phthalates and phenols mixture and cardiovascular measurements using BWQS regression

	Systolic BP		Diastolic BP		Pulse Wave Velocity		Central Retinal Arteriole Equivalent		Central Retinal Venular Equivalent	
	n	Beta (CrI)	n	Beta (CrI)	n	Beta (CrI)	n	Beta (CrI)	n	Beta (CrI)
Unstratified										
beta 1	305	0.5 (-1.44, 2.37)	304	0.43 (-1.2, 2.09)	292	-0.03 (-0.12, 0.07)	280	-0.49 (-3.47, 2.59)	280	-1.33 (-5.43, 2.69)
Weight for:										
MEHP		0.06 (0.00, 0.21)		0.07 (0.00, 0.23)		0.07 (0.00, 0.23)		0.07 (0.00, 0.22)		0.06 (0.00, 0.21)
MEHHP		0.06 (0.00, 0.22)		0.07 (0.00, 0.22)		0.07 (0.00, 0.26)		0.07 (0.00, 0.22)		0.06 (0.00, 0.22)
MEP		0.07 (0.00, 0.23)		0.07 (0.00, 0.24)		0.06 (0.00, 0.21)		0.07 (0.00, 0.23)		0.06 (0.00, 0.21)
MiBP		0.06 (0.00, 0.22)		0.06 (0.00, 0.22)		0.07 (0.00, 0.24)		0.07 (0.00, 0.22)		0.06 (0.00, 0.21)
MnBP		0.06 (0.00, 0.22)		0.06 (0.00, 0.22)		0.07 (0.00, 0.23)		0.06 (0.00, 0.21)		0.07 (0.00, 0.22)
MBzP		0.07 (0.00, 0.25)		0.08 (0.00, 0.27)		0.06 (0.00, 0.23)		0.06 (0.00, 0.23)		0.07 (0.00, 0.22)
MEOHP		0.07 (0.00, 0.23)		0.07 (0.00, 0.22)		0.07 (0.00, 0.23)		0.06 (0.00, 0.22)		0.06 (0.00, 0.22)
MECPP		0.07 (0.00, 0.24)		0.06 (0.00, 0.22)		0.06 (0.00, 0.22)		0.06 (0.00, 0.22)		0.06 (0.00, 0.22)
MEPA		0.07 (0.00, 0.24)		0.07 (0.00, 0.24)		0.06 (0.00, 0.23)		0.08 (0.00, 0.27)		0.07 (0.00, 0.24)
ETPA		0.07 (0.00, 0.24)		0.07 (0.00, 0.22)		0.07 (0.00, 0.24)		0.07 (0.00, 0.26)		0.07 (0.00, 0.24)
PRPA		0.07 (0.00, 0.24)		0.07 (0.00, 0.23)		0.06 (0.00, 0.22)		0.07 (0.00, 0.24)		0.08 (0.00, 0.26)
BPA		0.06 (0.00, 0.22)		0.06 (0.00, 0.24)		0.08 (0.00, 0.27)		0.07 (0.00, 0.22)		0.07 (0.00, 0.25)
BUPA		0.07 (0.00, 0.24)		0.07 (0.00, 0.25)		0.06 (0.00, 0.23)		0.07 (0.00, 0.23)		0.08 (0.00, 0.27)
BP-3		0.07 (0.00, 0.23)		0.06 (0.00, 0.23)		0.07 (0.00, 0.23)		0.07 (0.00, 0.25)		0.07 (0.00, 0.24)
TRCS		0.07 (0.00, 0.24)		0.06 (0.00, 0.22)		0.07 (0.00, 0.23)		0.06 (0.00, 0.22)		0.06 (0.00, 0.21)
Social Class: High/Middle										
beta 1	209	0.34 (-1.72, 2.31)	209	-0.19 (-2.02, 1.68)	199	-0.04 (-0.14, 0.08)	191	-0.63 (-4.31, 3.37)	191	-2.77 (-7.8, 2.04)

Weight for:										
MEHP		0.07 (0.00, 0.23)		0.06 (0.00, 0.23)		0.06 (0.00, 0.22)		0.07 (0.00, 0.24)		0.06 (0.00, 0.22)
MEHHP		0.07 (0.00, 0.23)		0.06 (0.00, 0.21)		0.06 (0.00, 0.22)		0.07 (0.00, 0.24)		0.06 (0.00, 0.21)
MEP		0.07 (0.00, 0.21)		0.07 (0.00, 0.22)		0.07 (0.00, 0.25)		0.07 (0.00, 0.23)		0.05 (0.00, 0.19)
MiBP		0.07 (0.00, 0.23)		0.07 (0.00, 0.24)		0.07 (0.00, 0.25)		0.06 (0.00, 0.23)		0.07 (0.00, 0.25)
MnBP		0.06 (0.00, 0.22)		0.07 (0.00, 0.24)		0.08 (0.00, 0.25)		0.07 (0.00, 0.25)		0.06 (0.00, 0.21)
MBzP		0.07 (0.00, 0.25)		0.07 (0.00, 0.24)		0.06 (0.00, 0.25)		0.06 (0.00, 0.23)		0.06 (0.00, 0.21)
MEOHP		0.07 (0.00, 0.24)		0.07 (0.00, 0.22)		0.06 (0.00, 0.2)		0.07 (0.00, 0.23)		0.06 (0.00, 0.22)
MECPP		0.07 (0.00, 0.22)		0.07 (0.00, 0.23)		0.06 (0.00, 0.21)		0.06 (0.00, 0.22)		0.06 (0.00, 0.2)
MEPA		0.07 (0.00, 0.23)		0.07 (0.00, 0.23)		0.06 (0.00, 0.22)		0.07 (0.00, 0.23)		0.07 (0.00, 0.23)
ETPA		0.07 (0.00, 0.24)		0.07 (0.00, 0.24)		0.07 (0.00, 0.24)		0.07 (0.00, 0.23)		0.08 (0.00, 0.27)
PRPA		0.07 (0.00, 0.23)		0.07 (0.00, 0.24)		0.06 (0.00, 0.22)		0.07 (0.00, 0.25)		0.08 (0.00, 0.25)
BPA		0.07 (0.00, 0.23)		0.07 (0.00, 0.25)		0.07 (0.00, 0.23)		0.07 (0.00, 0.22)		0.08 (0.00, 0.26)
BUPA		0.06 (0.00, 0.21)		0.06 (0.00, 0.22)		0.07 (0.00, 0.24)		0.07 (0.00, 0.22)		0.08 (0.00, 0.27)
BP-3		0.06 (0.00, 0.21)		0.07 (0.00, 0.23)		0.07 (0.00, 0.22)		0.07 (0.00, 0.24)		0.07 (0.00, 0.24)
TRCS		0.07 (0.00, 0.22)		0.07 (0.00, 0.23)		0.08 (0.00, 0.25)		0.06 (0.00, 0.23)		0.06 (0.00, 0.21)
Social Class: Low										
beta 1	96	1.12 (-2.77, 5.05)	95	1.24 (-2.11, 4.85)	93	-0.01 (-0.21, 0.2)	89	1.09 (-4.74, 6.63)	89	5.11 (-3.05, 13.02)
Weight for:										
MEHP		0.06 (0.00, 0.22)		0.06 (0.00, 0.21)		0.07 (0.00, 0.21)		0.07 (0.00, 0.23)		0.08 (0.00, 0.26)
MEHHP		0.06 (0.00, 0.21)		0.07 (0.00, 0.23)		0.06 (0.00, 0.23)		0.07 (0.00, 0.23)		0.07 (0.00, 0.23)
MEP		0.07 (0.00, 0.23)		0.07 (0.00, 0.23)		0.07 (0.00, 0.24)		0.07 (0.00, 0.22)		0.07 (0.00, 0.22)
MiBP		0.06 (0.00, 0.21)		0.07 (0.00, 0.24)		0.06 (0.00, 0.22)		0.07 (0.00, 0.25)		0.1 (0.00, 0.31)
MnBP		0.06 (0.00, 0.21)		0.06 (0.00, 0.21)		0.06 (0.00, 0.22)		0.06 (0.00, 0.23)		0.06 (0.00, 0.2)
MBzP		0.07 (0.00, 0.24)		0.07 (0.00, 0.24)		0.06 (0.00, 0.23)		0.07 (0.00, 0.22)		0.06 (0.00, 0.21)
MEOHP		0.06 (0.00, 0.22)		0.07 (0.00, 0.22)		0.07 (0.00, 0.23)		0.07 (0.00, 0.24)		0.06 (0.00, 0.21)
MECPP		0.07 (0.00, 0.24)		0.06 (0.00, 0.2)		0.07 (0.00, 0.23)		0.06 (0.00, 0.21)		0.05 (0.00, 0.18)

MEPA		0.07 (0.00, 0.24)		0.07 (0.00, 0.24)		0.07 (0.00, 0.25)		0.07 (0.00, 0.23)		0.06 (0.00, 0.2)
ETPA		0.06 (0.00, 0.22)		0.06 (0.00, 0.2)		0.07 (0.00, 0.23)		0.07 (0.00, 0.23)		0.07 (0.00, 0.22)
PRPA		0.07 (0.00, 0.23)		0.08 (0.00, 0.25)		0.07 (0.00, 0.26)		0.06 (0.00, 0.22)		0.06 (0.00, 0.2)
BPA		0.07 (0.00, 0.25)		0.06 (0.00, 0.22)		0.07 (0.00, 0.26)		0.07 (0.00, 0.23)		0.07 (0.00, 0.23)
BUPA		0.07 (0.00, 0.23)		0.08 (0.00, 0.27)		0.07 (0.00, 0.23)		0.06 (0.00, 0.22)		0.07 (0.00, 0.23)
BP-3		0.07 (0.00, 0.25)		0.07 (0.00, 0.23)		0.07 (0.00, 0.22)		0.07 (0.00, 0.23)		0.06 (0.00, 0.2)
TRCS		0.07 (0.00, 0.23)		0.07 (0.00, 0.24)		0.07 (0.00, 0.22)		0.07 (0.00, 0.24)		0.07 (0.00, 0.23)
Sex: Female										
beta 1	141	0.42 (-2.31, 3.08)	140	0.56 (-1.76, 3.02)	139	-0.01 (-0.15, 0.13)	127	2.36 (-2.56, 7.2)	127	0.8 (-5.69, 6.79)
Weight for:										
MEHP		0.07 (0.00, 0.23)		0.06 (0.00, 0.21)		0.06 (0.00, 0.22)		0.07 (0.00, 0.23)		0.07 (0.00, 0.24)
MEHHP		0.06 (0.00, 0.22)		0.07 (0.00, 0.23)		0.07 (0.00, 0.23)		0.07 (0.00, 0.22)		0.07 (0.00, 0.25)
MEP		0.07 (0.00, 0.22)		0.07 (0.00, 0.23)		0.07 (0.00, 0.23)		0.07 (0.00, 0.24)		0.07 (0.00, 0.23)
MiBP		0.07 (0.00, 0.22)		0.06 (0.00, 0.21)		0.07 (0.00, 0.22)		0.08 (0.00, 0.26)		0.07 (0.00, 0.22)
MnBP		0.07 (0.00, 0.24)		0.07 (0.00, 0.22)		0.07 (0.00, 0.23)		0.08 (0.00, 0.26)		0.06 (0.00, 0.21)
MBzP		0.07 (0.00, 0.24)		0.07 (0.00, 0.23)		0.07 (0.00, 0.26)		0.08 (0.00, 0.27)		0.07 (0.00, 0.23)
MEOHP		0.07 (0.00, 0.24)		0.07 (0.00, 0.22)		0.06 (0.00, 0.22)		0.07 (0.00, 0.24)		0.06 (0.00, 0.23)
MECPP		0.06 (0.00, 0.23)		0.06 (0.00, 0.21)		0.06 (0.00, 0.22)		0.06 (0.00, 0.21)		0.06 (0.00, 0.22)
MEPA		0.07 (0.00, 0.24)		0.07 (0.00, 0.24)		0.07 (0.00, 0.23)		0.06 (0.00, 0.2)		0.07 (0.00, 0.23)
ETPA		0.06 (0.00, 0.21)		0.07 (0.00, 0.23)		0.07 (0.00, 0.23)		0.06 (0.00, 0.22)		0.06 (0.00, 0.22)
PRPA		0.07 (0.00, 0.24)		0.07 (0.00, 0.24)		0.06 (0.00, 0.22)		0.06 (0.00, 0.21)		0.07 (0.00, 0.23)
BPA		0.07 (0.00, 0.22)		0.06 (0.00, 0.22)		0.07 (0.00, 0.24)		0.06 (0.00, 0.22)		0.07 (0.00, 0.23)
BUPA		0.06 (0.00, 0.23)		0.07 (0.00, 0.21)		0.07 (0.00, 0.23)		0.06 (0.00, 0.21)		0.07 (0.00, 0.25)
BP-3		0.07 (0.00, 0.24)		0.07 (0.00, 0.22)		0.07 (0.00, 0.22)		0.06 (0.00, 0.21)		0.06 (0.00, 0.21)
TRCS		0.06 (0.00, 0.22)		0.06 (0.00, 0.22)		0.07 (0.00, 0.25)		0.07 (0.00, 0.21)		0.07 (0.00, 0.24)
Sex: Male										
beta 1	164	0.86 (-1.91, 3.57)	164	0.75 (-1.62, 3.13)	153	-0.02	153	-2.28	153	-1.72

			(-0.16, 0.11)	(-6.12, 1.37)	(-7.27, 3.71)
Weight for:					
MEHP	0.06 (0.00, 0.23)	0.07 (0.00, 0.22)	0.07 (0.00, 0.24)	0.07 (0.00, 0.24)	0.07 (0.00, 0.24)
MEHHP	0.06 (0.00, 0.22)	0.06 (0.00, 0.22)	0.07 (0.00, 0.24)	0.07 (0.00, 0.25)	0.07 (0.00, 0.23)
MEP	0.07 (0.00, 0.23)	0.07 (0.00, 0.24)	0.06 (0.00, 0.23)	0.06 (0.00, 0.21)	0.06 (0.00, 0.24)
MiBP	0.06 (0.00, 0.22)	0.06 (0.00, 0.21)	0.07 (0.00, 0.22)	0.06 (0.00, 0.2)	0.06 (0.00, 0.2)
MnBP	0.06 (0.00, 0.22)	0.06 (0.00, 0.22)	0.07 (0.00, 0.23)	0.06 (0.00, 0.2)	0.06 (0.00, 0.21)
MBzP	0.07 (0.00, 0.23)	0.08 (0.00, 0.27)	0.06 (0.00, 0.23)	0.07 (0.00, 0.23)	0.07 (0.00, 0.24)
MEOHP	0.06 (0.00, 0.21)	0.06 (0.00, 0.23)	0.07 (0.00, 0.23)	0.06 (0.00, 0.21)	0.07 (0.00, 0.23)
MECPP	0.06 (0.00, 0.23)	0.06 (0.00, 0.22)	0.07 (0.00, 0.23)	0.06 (0.00, 0.22)	0.07 (0.00, 0.23)
MEPA	0.06 (0.00, 0.22)	0.07 (0.00, 0.23)	0.06 (0.00, 0.23)	0.08 (0.00, 0.28)	0.07 (0.00, 0.23)
ETPA	0.07 (0.00, 0.23)	0.07 (0.00, 0.23)	0.07 (0.00, 0.23)	0.07 (0.00, 0.22)	0.07 (0.00, 0.24)
PRPA	0.07 (0.00, 0.26)	0.07 (0.00, 0.23)	0.06 (0.00, 0.22)	0.08 (0.00, 0.27)	0.07 (0.00, 0.24)
BPA	0.06 (0.00, 0.22)	0.06 (0.00, 0.22)	0.07 (0.00, 0.24)	0.06 (0.00, 0.2)	0.07 (0.00, 0.23)
BUPA	0.08 (0.00, 0.27)	0.08 (0.00, 0.27)	0.06 (0.00, 0.21)	0.06 (0.00, 0.21)	0.07 (0.00, 0.22)
BP-3	0.07 (0.00, 0.23)	0.07 (0.00, 0.23)	0.07 (0.00, 0.26)	0.07 (0.00, 0.23)	0.07 (0.00, 0.22)
TRCS	0.07 (0.00, 0.25)	0.06 (0.00, 0.21)	0.07 (0.00, 0.23)	0.07 (0.00, 0.23)	0.06 (0.00, 0.22)

Table S3. Associations between individual prenatal phthalate and phenol exposures and early adolescent cardiovascular measurements from regression models, by sex.

Chemical	Sex	Systolic Blood Pressure	Diastolic Blood Pressure	Pulse Wave Velocity	Central Retinal Arteriolar Equivalent	Central Retinal Venular Equivalent
		Beta (95% CI)	Beta (95% CI)	Beta (95% CI)	Beta (95% CI)	Beta (95% CI)
MEHP	F	0.15 (-1.35, 1.65)	-0.22 (-1.53, 1.10)	-0.01 (-0.08, 0.06)	1.44 (-1.20, 4.07)	1.61 (-1.74, 4.97)
	M	-0.62 (-2.03, 0.80)	-0.29 (-1.42, 0.85)	-0.03 (-0.10, 0.04)	-1.36 (-3.26, 0.54)	-2.50 (-5.22, 0.21)
	int.	*0.73*	*0.96*	*0.55*	*0.33*	*0.11*
MEHHP	F	0.42 (-1.08, 1.93)	0.32 (-1.01, 1.64)	-0.03 (-0.10, 0.04)	1.27 (-1.38, 3.91)	2.14 (-1.21, 5.49)
	M	-0.28 (-1.63, 1.08)	-0.31 (-1.40, 0.78)	-0.03 (-0.10, 0.03)	-0.29 (-2.09, 1.51)	-1.02 (-3.60, 1.55)
	int.	*0.81*	*0.58*	*0.87*	*0.47*	*0.19*
MEP	F	-0.33 (-1.34, 0.68)	0.05 (-0.86, 0.95)	-0.03 (-0.08, 0.02)	0.99 (-0.75, 2.72)	0.79 (-1.43, 3.00)
	M	-0.03 (-1.04, 0.99)	-0.12 (-0.93, 0.70)	0.01 (-0.04, 0.06)	0.59 (-0.81, 2.00)	0.97 (-1.05, 2.98)
	int.	*0.56*	*0.95*	*0.24*	*0.63*	*0.86*
MiBP	F	0.64 (-0.89, 2.16)	-0.38 (-1.73, 0.96)	-0.05 (-0.12, 0.02)	2.73 (0.10, 5.36)	0.39 (-3.01, 3.79)
	M	-0.28 (-1.77, 1.22)	-0.29 (-1.49, 0.91)	-0.01 (-0.08, 0.07)	1.58 (-0.40, 3.55)	2.31 (-0.52, 5.14)
	int.	*0.47*	*0.94*	*0.48*	*0.33*	*0.51*
MnBP	F	0.43 (-0.75, 1.61)	0.13 (-0.91, 1.17)	0.02 (-0.03, 0.08)	1.29 (-0.75, 3.32)	-0.27 (-2.87, 2.34)
	M	-1.12 (-2.55, 0.31)	-0.68 (-1.83, 0.47)	0.01 (-0.06, 0.08)	0.32 (-1.58, 2.21)	0.91 (-1.80, 3.63)

	int.	*0.39*	*0.77*	*0.99*	*0.55*	*0.51*
MBzP	F	0.80 (-0.42, 2.02)	0.34 (-0.74, 1.42)	0.05 (-0.01, 0.10)	1.76 (-0.45, 3.98)	2.29 (-0.53, 5.11)
	M	0.51 (-0.65, 1.67)	0.86 (-0.07, 1.79)	0.03 (-0.03, 0.09)	0.25 (-1.31, 1.82)	-0.81 (-3.06, 1.44)
	int.	*0.75*	*0.53*	*0.73*	*0.32*	*0.05*
MEOHP	F	0.67 (-0.95, 2.3)	0.24 (-1.19, 1.67)	-0.02 (-0.09, 0.06)	0.33 (-2.57, 3.23)	0.98 (-2.70, 4.66)
	M	-0.34 (-1.79, 1.11)	-0.41 (-1.58, 0.75)	-0.03 (-0.10, 0.04)	-0.33 (-2.27, 1.60)	-1.25 (-4.01, 1.52)
	int.	*0.55*	*0.52*	*0.74*	*0.81*	*0.35*
MECPP	F	0.18 (-1.39, 1.74)	0.07 (-1.31, 1.45)	-0.02 (-0.10, 0.05)	-0.41 (-3.18, 2.36)	0.77 (-2.75, 4.29)
	M	-0.19 (-1.66, 1.28)	-0.76 (-1.93, 0.41)	-0.03 (-0.11, 0.04)	-0.30 (-2.26, 1.66)	-2.20 (-4.99, 0.59)
	int.	*0.87*	*0.62*	*0.91*	*0.74*	*0.32*
MEPA	F	-0.07 (-0.54, 0.41)	0.03 (-0.39, 0.44)	0.00 (-0.02, 0.02)	-0.18 (-0.96, 0.59)	-0.59 (-1.57, 0.39)
	M	0.02 (-0.53, 0.58)	0.05 (-0.39, 0.50)	0.01 (-0.02, 0.04)	-0.76 (-1.50, -0.02)	-0.65 (-1.70, 0.40)
	int.	*0.66*	*0.96*	*0.89*	*0.34*	*0.84*
ETPA	F	-0.23 (-0.69, 0.24)	-0.09 (-0.49, 0.32)	0.01 (-0.01, 0.04)	-0.17 (-0.91, 0.56)	-0.69 (-1.62, 0.24)
	M	-0.02 (-0.51, 0.48)	-0.14 (-0.52, 0.25)	-0.01 (-0.03, 0.02)	0.26 (-0.41, 0.94)	-0.37 (-1.32, 0.58)
	int.	*0.36*	*0.9*	*0.05*	*0.39*	*0.98*
PRPA	F	-0.19 (-0.62, 0.25)	0.00 (-0.38, 0.39)	-0.01 (-0.03, 0.01)	-0.12 (-0.85, 0.60)	-0.43 (-1.35, 0.49)
	M	0.11 (-0.39, 0.60)	0.06 (-0.33, 0.45)	0.02 (-0.01, 0.04)	-0.65 (-1.32, 0.01)	-0.56 (-1.50, 0.38)
	int.	*0.19*	*0.66*	*0.36*	*0.4*	*0.85*
BPA	F	0.27 (-1.06, 1.60)	0.16 (-0.99, 1.30)	-0.04 (-0.10, 0.03)	0.27 (-2.05, 2.60)	-0.98 (-3.98, 2.02)

	M	-0.23 (-1.60, 1.14)	-0.79 (-1.90, 0.31)	-0.08 (-0.15, -0.01)	1.18 (-0.77, 3.14)	-0.10 (-2.92, 2.71)
	int.	*0.42*	*0.19*	*0.29*	*0.58*	*0.74*
BUPA	F	-0.24 (-0.69, 0.22)	-0.11 (-0.51, 0.29)	-0.01 (-0.04, 0.01)	-0.44 (-1.18, 0.30)	-0.98 (-1.91, -0.05)
	M	0.37 (-0.06, 0.80)	0.33 (-0.02, 0.67)	0.00 (-0.02, 0.03)	-0.12 (-0.72, 0.48)	-0.82 (-1.65, 0.01)
	int.	*0.12*	*0.33*	*0.84*	*0.53*	*0.9*
BP-3	F	0.02 (-0.37, 0.41)	-0.08 (-0.41, 0.26)	0.00 (-0.02, 0.02)	0.06 (-0.57, 0.70)	-0.11 (-0.92, 0.71)
	M	0.02 (-0.40, 0.44)	0.01 (-0.33, 0.34)	-0.01 (-0.03, 0.01)	-0.20 (-0.76, 0.36)	-0.27 (-1.05, 0.52)
	int.	*0.88*	*0.72*	*0.53*	*0.65*	*0.83*
TRCS	F	-0.04 (-0.45, 0.37)	-0.07 (-0.43, 0.29)	-0.02 (-0.04, 0.00)	0.45 (-0.21, 1.12)	0.11 (-0.74, 0.95)
	M	0.13 (-0.30, 0.57)	-0.11 (-0.46, 0.23)	0.01 (-0.01, 0.03)	-0.06 (-0.65, 0.54)	0.29 (-0.55, 1.12)
	int.	*0.5*	*0.69*	*0.12*	*0.43*	*0.41*

Abbreviation: F = female, M = male, int. = p for interaction from Wald test.
Models adjusted for Models adjusted for child age at visit, child sex, mother's age at delivery, prepregnancy BMI, gestational weight gain, parental cardiovascular history, smoking during pregnancy and gestational age. SBP, DBP and PWV were additionally adjusted for child height at visit.

Table S4. Associations between individual prenatal phthalate and phenol exposures and early adolescent cardiovascular measurements from regression models, by social class.

Chemical	Social Class	Systolic Blood Pressure	Diastolic Blood Pressure	Pulse Wave Velocity	Central Retinal Arteriolar Equivalent	Central Retinal Venular Equivalent
		Beta (95% CI)	Beta (95% CI)	Beta (95% CI)	Beta (95% CI)	Beta (95% CI)
MEHP	H/M	-0.11 (-1.26, 1.04)	-0.24 (-1.20, 0.72)	0.01 (-0.04, 0.07)	-1.44 (-3.30, 0.41)	-2.04 (-4.55, 0.46)
	L	-1.08 (-3.25, 1.10)	-0.74 (-2.58, 1.10)	-0.09 (-0.20, 0.01)	2.79 (-0.08, 5.66)	2.79 (-1.22, 6.80)
	int.	*0.5*	*0.71*	*0.01*	*0.02*	*0.09*
MEHHP	H/M	0.43 (-0.69, 1.55)	-0.08 (-1.02, 0.86)	0 (-0.05, 0.06)	-0.24 (-2.02, 1.54)	-0.60 (-3.01, 1.81)
	L	-1.07 (-3.21, 1.08)	-0.07 (-1.90, 1.75)	-0.10 (-0.20, 0.00)	1.42 (-1.42, 4.26)	3.00 (-0.91, 6.90)
	int.	*0.27*	*0.93*	*0.01*	*0.27*	*0.17*
MEP	H/M	-0.05 (-0.87, 0.78)	-0.15 (-0.84, 0.54)	-0.01 (-0.05, 0.03)	0.95 (-0.37, 2.28)	1.32 (-0.47, 3.11)
	L	-0.19 (-1.62, 1.25)	0.42 (-0.81, 1.65)	0.01 (-0.06, 0.08)	1.02 (-0.94, 2.98)	0.12 (-2.61, 2.84)
	int.	*0.8*	*0.31*	*0.73*	*0.75*	*0.4*
MiBP	H/M	0.43 (-0.75, 1.61)	-0.31 (-1.29, 0.68)	-0.04 (-0.09, 0.02)	1.53 (-0.33, 3.40)	-0.37 (-2.91, 2.17)
	L	-0.82 (-3.11, 1.48)	-0.10 (-2.04, 1.85)	-0.03 (-0.14, 0.08)	2.93 (-0.10, 5.95)	6.12 (2.06, 10.18)
	int.	*0.39*	*0.84*	*0.91*	*0.63*	*0.02*
MnBP	H/M	-0.23 (-1.29, 0.83)	-0.25 (-1.13, 0.64)	-0.02 (-0.07, 0.04)	1.34 (-0.36, 3.03)	0.91 (-1.39, 3.21)
	L	-0.61 (-2.39, 1.17)	-0.25 (-1.77, 1.27)	0.05 (-0.03, 0.14)	-0.77 (-3.07, 1.54)	-1.68 (-4.85, 1.50)

	int.	*0.72*	*0.51*	*0.09*	*0.2*	*0.39*
MBzP	H/M	0.84 (-0.07, 1.74)	0.59 (-0.17, 1.34)	0.05 (0.00, 0.09)	1.06 (-0.42, 2.54)	0.31 (-1.70, 2.32)
	L	-0.06 (-2.11, 1.99)	0.47 (-1.26, 2.21)	0 (-0.09, 0.10)	0.50 (-2.35, 3.36)	1.40 (-2.54, 5.33)
	int.	*0.22*	*0.81*	*0.54*	*0.85*	*0.58*
MEOHP	H/M	0.50 (-0.69, 1.69)	-0.17 (-1.17, 0.83)	0 (-0.05, 0.06)	-0.52 (-2.42, 1.38)	-0.77 (-3.34, 1.80)
	L	-1.03 (-3.43, 1.37)	-0.06 (-2.10, 1.97)	-0.08 (-0.20, 0.03)	0.83 (-2.37, 4.03)	1.59 (-2.83, 6.02)
	int.	*0.29*	*0.97*	*0.04*	*0.44*	*0.42*
MECPP	H/M	0.36 (-0.83, 1.55)	-0.21 (-1.20, 0.79)	0.02 (-0.04, 0.07)	-0.5 (-2.41, 1.41)	-1.09 (-3.67, 1.48)
	L	-0.60 (-2.93, 1.73)	-0.62 (-2.59, 1.35)	-0.10 (-0.21, 0)	-0.3 (-3.44, 2.83)	-0.27 (-4.61, 4.06)
	int.	*0.4*	*0.62*	*0.04*	*0.98*	*0.73*
MEPA	H/M	-0.17 (-0.59, 0.24)	-0.10 (-0.45, 0.26)	-0.01 (-0.03, 0.01)	-0.63 (-1.28, 0.03)	-0.98 (-1.85, -0.11)
	L	0.06 (-0.60, 0.72)	0.17 (-0.36, 0.7)	0.02 (-0.01, 0.06)	-0.49 (-1.36, 0.38)	-0.28 (-1.51, 0.95)
	int.	*0.39*	*0.27*	*0.05*	*0.66*	*0.58*
ETPA	H/M	-0.09 (-0.52, 0.34)	-0.10 (-0.47, 0.27)	-0.02 (-0.04, 0.01)	-0.02 (-0.70, 0.66)	-0.96 (-1.86, -0.06)
	L	-0.31 (-0.86, 0.23)	-0.23 (-0.67, 0.20)	0.02 (-0.01, 0.05)	0.16 (-0.54, 0.86)	-0.23 (-1.21, 0.76)
	int.	*0.87*	*0.6*	*0.03*	*0.62*	*0.41*
PRPA	H/M	-0.10 (-0.48, 0.29)	-0.1 (-0.43, 0.22)	-0.01 (-0.03, 0.01)	-0.51 (-1.11, 0.09)	-0.77 (-1.57, 0.02)
	L	-0.05 (-0.65, 0.55)	0.21 (-0.28, 0.69)	0.02 (-0.01, 0.05)	-0.46 (-1.25, 0.34)	-0.08 (-1.20, 1.05)
	int.	*0.75*	*0.16*	*0.06*	*0.63*	*0.69*
BPA	H/M	-0.16 (-1.3, 0.97)	-0.48 (-1.41, 0.46)	-0.02 (-0.08, 0.04)	0.98 (-0.89, 2.85)	-0.69 (-3.22, 1.85)

	L	0.64 (-1.17, 2.46)	-0.15 (-1.69, 1.38)	-0.10 (-0.19, -0.02)	0.80 (-1.80, 3.40)	0.61 (-3.08, 4.30)
	int.	*0.57*	*0.53*	*0.09*	*0.47*	*0.95*
BUPA	H/M	0.01 (-0.36, 0.38)	0.05 (-0.27, 0.37)	-0.01 (-0.03, 0.01)	-0.52 (-1.10, 0.06)	-1.40 (-2.16, -0.64)
	L	0.07 (-0.50, 0.65)	0.17 (-0.29, 0.64)	0.01 (-0.02, 0.04)	0.12 (-0.62, 0.87)	-0.09 (-1.14, 0.97)
	int.	*0.35*	*0.57*	*0.17*	*0.11*	*0.08*
BP-3	H/M	-0.02 (-0.35, 0.31)	-0.04 (-0.32, 0.24)	-0.01 (-0.03, 0.01)	-0.42 (-0.93, 0.09)	-0.56 (-1.24, 0.12)
	L	0.16 (-0.39, 0.70)	-0.21 (-0.65, 0.23)	0 (-0.03, 0.02)	0.38 (-0.33, 1.08)	0.22 (-0.78, 1.21)
	int.	*0.62*	*0.49*	*0.73*	*0.06*	*0.25*
TRCS	H/M	0.08 (-0.28, 0.44)	-0.10 (-0.40, 0.21)	-0.01 (-0.03, 0.01)	0.11 (-0.47, 0.68)	-0.18 (-0.94, 0.59)
	L	-0.03 (-0.54, 0.49)	-0.05 (-0.47, 0.37)	0 (-0.03, 0.02)	0.23 (-0.44, 0.89)	0.94 (0.01, 1.87)
	int.	*0.98*	*0.77*	*0.62*	*0.38*	*0.04*

Abbreviation: H/M = high/middle, L = low, int. = p for interaction from Wald test.
Models adjusted for child age at visit, child sex, mother's age at delivery, prepregnancy BMI, gestational weight gain, parental cardiovascular history, smoking during pregnancy and gestational age. SBP, DBP and PWV were additionally adjusted for child height at visit.

Table S5. Associations between individual prenatal phthalate and BPA exposures and early adolescent cardiovascular measurements from linear regression models, by trimester

Chemical	Systolic Blood Pressure	Diastolic Blood Pressure	Pulse Wave Velocity	Central Retinal Arteriole Equivalent	Central Retinal Venular Equivalent
	First Trimester				
MEHP	-0.15 (-1.00, 0.70)	-0.09 (-0.81, 0.63)	0.00 (-0.04, 0.04)	-0.11 (-1.41, 1.20)	-0.60 (-2.38, 1.18)
MEHHP	0.09 (-0.67, 0.85)	-0.01 (-0.65, 0.63)	-0.01 (-0.05, 0.03)	0.38 (-0.77, 1.52)	0.39 (-1.18, 1.95)
MEP	0.10 (-0.50, 0.69)	0.00 (-0.50, 0.50)	0.00 (-0.03, 0.03)	0.63 (-0.28, 1.55)	0.92 (-0.32, 2.16)
MiBP	-0.07 (-0.96, 0.81)	-0.02 (-0.77, 0.73)	-0.02 (-0.06, 0.03)	0.81 (-0.52, 2.14)	0.83 (-0.97, 2.64)
MnBP	-0.22 (-1.00, 0.56)	0.04 (-0.61, 0.70)	0.01 (-0.03, 0.05)	0.60 (-0.56, 1.76)	0.57 (-1.01, 2.16)
MBzP	0.51 (-0.16, 1.19)	0.59 (0.02, 1.15)	0.04 (0.00, 0.07)	0.53 (-0.50, 1.56)	0.42 (-0.98, 1.82)
MEOHP	0.10 (-0.73, 0.93)	-0.05 (-0.75, 0.65)	0.00 (-0.04, 0.04)	-0.02 (-1.27, 1.24)	-0.13 (-1.83, 1.58)
MECPP	0.10 (-0.80, 0.99)	-0.22 (-0.97, 0.53)	-0.01 (-0.05, 0.03)	-0.25 (-1.59, 1.10)	-0.76 (-2.59, 1.07)
BPA	0.16 (-0.62, 0.94)	-0.16 (-0.81, 0.49)	-0.03 (-0.07, 0.01)	0.51 (-0.71, 1.74)	-0.57 (-2.26, 1.11)
	Third Trimester				
MEHP	-0.06 (-0.86, 0.74)	-0.21 (-0.88, 0.47)	-0.02 (-0.06, 0.01)	-0.34 (-1.56, 0.87)	-0.68 (-2.34, 0.98)
MEHHP	-0.19 (-1.01, 0.62)	-0.17 (-0.86, 0.52)	-0.04 (-0.08, 0.00)	0.05 (-1.18, 1.29)	-0.41 (-2.09, 1.27)
MEP	-0.03 (-0.61, 0.55)	0.06 (-0.43, 0.55)	-0.01 (-0.04, 0.02)	0.44 (-0.44, 1.33)	-0.04 (-1.25, 1.18)
MiBP	0.03 (-0.80, 0.86)	-0.48 (-1.18, 0.21)	-0.03 (-0.07, 0.01)	1.23 (-0.01, 2.46)	0.52 (-1.17, 2.20)
MnBP	-0.14 (-0.84, 0.57)	-0.21 (-0.81, 0.38)	0.00 (-0.03, 0.04)	0.27 (-0.8, 1.33)	-0.06 (-1.51, 1.39)
MBzP	0.29 (-0.41, 1.00)	0.24 (-0.35, 0.83)	0.01 (-0.03, 0.04)	0.43 (-0.65, 1.50)	-0.32 (-1.79, 1.15)

MEOHP	-0.07 (-0.92, 0.78)	-0.18 (-0.90, 0.53)	-0.03 (-0.07, 0.01)	0.06 (-1.22, 1.35)	-0.27 (-2.02, 1.48)
MECPP	-0.15 (-0.99, 0.69)	-0.20 (-0.90, 0.51)	-0.03 (-0.07, 0.01)	-0.38 (-1.65, 0.88)	-0.65 (-2.38, 1.08)
BPA	-0.22 (-0.99, 0.55)	-0.36 (-1.00, 0.28)	-0.03 (-0.07, 0.01)	0.84 (-0.35, 2.04)	0.09 (-1.56, 1.74)
Using covariate imputed data, m=20 Models adjusted for child age at visit, child sex, mother's age at delivery, prepregnancy BMI, gestational weight gain, social class, parental cardiovascular history, smoking during pregnancy and gestational age. SBP, DBP and PWV were additionally adjusted for child height at visit.					

Table S6. Associations between individual prenatal phthalate and phenol exposures and early adolescent cardiovascular measurements from regression models, continuous models, not adjusting for GWG and gestational age.

Chemical	Systolic Blood Pressure	Diastolic Blood Pressure	Pulse Wave Velocity	Central Retinal Arteriole Equivalent	Central Retinal Venular Equivalent
	Beta (95% CI)	Beta (95% CI)	Beta (95% CI)	Beta (95% CI)	Beta (95% CI)
MEHP	-0.39 (-1.40, 0.62)	-0.33 (-1.18, 0.52)	-0.02 (-0.07, 0.03)	-0.31 (-1.84, 1.23)	-1.02 (-3.11, 1.06)
MEHHP	0.04 (-0.95, 1.02)	-0.05 (-0.88, 0.78)	-0.03 (-0.08, 0.02)	0.28 (-1.20, 1.76)	0.14 (-1.87, 2.16)
MEP	-0.23 (-0.92, 0.47)	-0.07 (-0.66, 0.52)	-0.01 (-0.04, 0.03)	0.79 (-0.26, 1.85)	0.80 (-0.64, 2.24)
MiBP	0.08 (-0.96, 1.12)	-0.33 (-1.21, 0.54)	-0.03 (-0.08, 0.02)	1.91 (0.36, 3.46)	1.30 (-0.82, 3.42)
MnBP	-0.35 (-1.25, 0.54)	-0.26 (-1.02, 0.49)	0.01 (-0.03, 0.06)	0.69 (-0.64, 2.03)	0.23 (-1.59, 2.05)
MBzP	0.64 (-0.19, 1.46)	0.60 (-0.10, 1.29)	0.03 (-0.01, 0.07)	0.78 (-0.49, 2.05)	0.46 (-1.27, 2.19)
MEOHP	0.12 (-0.94, 1.18)	-0.12 (-1.01, 0.77)	-0.02 (-0.07, 0.03)	-0.09 (-1.69, 1.51)	-0.32 (-2.50, 1.85)
MECPP	0.00 (-1.05, 1.05)	-0.39 (-1.27, 0.49)	-0.03 (-0.08, 0.02)	-0.38 (-1.96, 1.20)	-0.97 (-3.12, 1.18)
MEPA	-0.12 (-0.47, 0.23)	-0.02 (-0.31, 0.27)	0.00 (-0.02, 0.02)	-0.50 (-1.02, 0.01)	-0.71 (-1.40, -0.01)
ETPA	-0.12 (-0.45, 0.21)	-0.13 (-0.40, 0.15)	0.00 (-0.02, 0.02)	0.02 (-0.47, 0.50)	-0.62 (-1.27, 0.04)
PRPA	-0.11 (-0.43, 0.21)	-0.01 (-0.28, 0.25)	0.00 (-0.02, 0.02)	-0.42 (-0.89, 0.05)	-0.55 (-1.18, 0.09)
BPA	-0.04 (-0.97, 0.89)	-0.34 (-1.11, 0.43)	-0.05 (-0.10, -0.01)	0.88 (-0.56, 2.32)	-0.52 (-2.51, 1.46)
BUPA	0.08 (-0.23, 0.39)	0.11 (-0.15, 0.37)	0.00 (-0.02, 0.01)	-0.28 (-0.74, 0.17)	-0.96 (-1.56, -0.35)
BP-3	0.00 (-0.28, 0.27)	-0.10 (-0.33, 0.13)	-0.01 (-0.02, 0.00)	-0.13 (-0.54, 0.27)	-0.32 (-0.86, 0.23)
TRCS	0.02 (-0.27, 0.31)	-0.09 (-0.33, 0.16)	-0.01 (-0.02, 0.01)	0.22 (-0.21, 0.65)	0.22 (-0.36, 0.81)

Using covariate imputed data, m=20
Models adjusted for child age at visit, child sex, mother's age at delivery, prepregnancy BMI, social class, parental cardiovascular history, and smoking during pregnancy. SBP, DBP and PWV were additionally adjusted for child height at visit.

Table S7. Associations between phthalates mixture and cardiovascular measurements using BWQS regression

		Systolic BP		Diastolic BP		Pulse Wave Velocity		CRVE		CRAE
	n	Beta (CrI)	n	Beta (CrI)	n	Beta (CrI)	n	Beta (CrI)	n	Beta (CrI)
Unstratified										
beta 1 (BWQS index)	332	-0.11 (-1.41, 1.18)	331	-0.19 (-1.33, 1.03)	317	-0.03 (-0.09, 0.04)	304	0.61 (-1.35, 2.74)	304	0.37 (-2.23, 3.04)
Weight for:										
MEHP		0.12 (0.00, 0.4)		0.12 (0.00, 0.39)		0.12 (0.00, 0.38)		0.11 (0.00, 0.38)		0.12 (0.00, 0.41)
MEHHP		0.12 (0.00, 0.38)		0.12 (0.00, 0.39)		0.15 (0.00, 0.47)		0.12 (0.00, 0.4)		0.12 (0.00, 0.4)
MEP		0.13 (0.00, 0.44)		0.13 (0.00, 0.41)		0.13 (0.00, 0.39)		0.14 (0.00, 0.43)		0.13 (0.00, 0.44)
MiBP		0.13 (0.01, 0.4)		0.13 (0.00, 0.42)		0.13 (0.00, 0.4)		0.14 (0.00, 0.44)		0.13 (0.00, 0.42)
MnBP		0.13 (0.00, 0.45)		0.14 (0.01, 0.44)		0.12 (0.00, 0.36)		0.13 (0.00, 0.43)		0.12 (0.00, 0.42)
MBzP		0.12 (0.00, 0.41)		0.12 (0.00, 0.42)		0.1 (0.00, 0.39)		0.13 (0.00, 0.43)		0.12 (0.00, 0.4)
MEOHP		0.12 (0.00, 0.41)		0.12 (0.00, 0.37)		0.13 (0.00, 0.4)		0.11 (0.00, 0.4)		0.12 (0.00, 0.4)
MECPP		0.12 (0.00, 0.4)		0.12 (0.00, 0.38)		0.12 (0.00, 0.4)		0.12 (0.00, 0.39)		0.12 (0.00, 0.41)
Social Class: High/Middle										
beta 1 (BWQS index)	226	0.31 (-1.26, 1.8)	226	-0.22 (-1.54, 1.07)	214	0.02 (-0.07, 0.11)	207	0.72 (-1.79, 3.45)	207	-0.03 (-3.29, 3.69)
Weight for:										
MEHP		0.12 (0.00, 0.4)		0.12 (0.00, 0.39)		0.12 (0.00, 0.39)		0.11 (0.00, 0.38)		0.13 (0.00, 0.41)
MEHHP		0.12 (0.00, 0.38)		0.12 (0.00, 0.42)		0.11 (0.00, 0.38)		0.11 (0.00, 0.38)		0.12 (0.00, 0.39)
MEP		0.13 (0.00, 0.41)		0.13 (0.00, 0.42)		0.12 (0.00, 0.4)		0.14 (0.00, 0.45)		0.14 (0.00, 0.46)
MiBP		0.12 (0.00, 0.4)		0.12 (0.00, 0.4)		0.11 (0.00, 0.38)		0.13 (0.00, 0.42)		0.12 (0.00, 0.43)

MnBP		0.12 (0.00, 0.42)		0.13 (0.00, 0.45)		0.12 (0.00, 0.41)		0.13 (0.00, 0.41)		0.13 (0.00, 0.41)
MBzP		0.14 (0.00, 0.45)		0.12 (0.00, 0.41)		0.18 (0.00, 0.56)		0.13 (0.00, 0.41)		0.12 (0.00, 0.41)
MEOHP		0.12 (0.00, 0.42)		0.12 (0.00, 0.38)		0.11 (0.00, 0.39)		0.12 (0.00, 0.40)		0.12 (0.00, 0.39)
MECPP		0.12 (0.00, 0.41)		0.12 (0.00, 0.4)		0.12 (0.00, 0.39)		0.12 (0.00, 0.38)		0.12 (0.00, 0.4)
Social Class: Low										
beta 1 (BWQS index)	106	-0.6 (-3.25, 2.03)	105	-0.16 (-2.35, 1.96)	103	-0.07 (-0.18, 0.06)	97	1.74 (-1.87, 5.42)	97	2.76 (-2.56, 7.84)
Weight for:										
MEHP		0.12 (0.00, 0.39)		0.12 (0.00, 0.4)		0.14 (0.00, 0.43)		0.14 (0.00, 0.47)		0.13 (0.00, 0.41)
MEHHP		0.13 (0.00, 0.42)		0.12 (0.00, 0.4)		0.15 (0.00, 0.46)		0.14 (0.00, 0.45)		0.13 (0.00, 0.43)
MEP		0.12 (0.00, 0.4)		0.12 (0.00, 0.4)		0.11 (0.00, 0.33)		0.13 (0.00, 0.41)		0.11 (0.00, 0.39)
MiBP		0.13 (0.00, 0.42)		0.12 (0.00, 0.4)		0.12 (0.00, 0.38)		0.15 (0.01, 0.44)		0.2 (0.01, 0.54)
MnBP		0.13 (0.00, 0.41)		0.13 (0.00, 0.42)		0.1 (0.00, 0.34)		0.11 (0.00, 0.38)		0.1 (0.00, 0.34)
MBzP		0.13 (0.00, 0.41)		0.13 (0.00, 0.43)		0.12 (0.00, 0.39)		0.11 (0.00, 0.37)		0.11 (0.00, 0.37)
MEOHP		0.13 (0.00, 0.41)		0.12 (0.00, 0.39)		0.13 (0.00, 0.39)		0.12 (0.00, 0.38)		0.11 (0.00, 0.37)
MECPP		0.11 (0.00, 0.36)		0.13 (0.00, 0.42)		0.13 (0.00, 0.42)		0.11 (0.00, 0.37)		0.1 (0.00, 0.35)
Sex: Female										
beta 1 (BWQS index)	155	0.47 (-1.25, 2.26)	154	-0.08 (-1.64, 1.49)	152	-0.02 (-0.12, 0.08)	140	2.28 (-0.94, 5.46)	140	1.76 (-2.31, 5.64)
Weight for:										
MEHP		0.13 (0.00, 0.39)		0.12 (0.00, 0.39)		0.11 (0.00, 0.38)		0.11 (0.00, 0.38)		0.13 (0.00, 0.43)
MEHHP		0.12 (0.00, 0.37)		0.12 (0.00, 0.41)		0.13 (0.00, 0.42)		0.11 (0.00, 0.38)		0.13 (0.00, 0.41)
MEP		0.13 (0.00, 0.43)		0.13 (0.00, 0.40)		0.14 (0.00, 0.45)		0.14 (0.00, 0.39)		0.13 (0.00, 0.38)
MiBP		0.13 (0.00, 0.43)		0.13 (0.00, 0.42)		0.13 (0.00, 0.41)		0.15 (0.01, 0.47)		0.11 (0.00, 0.38)

MnBP		0.13 (0.00, 0.41)		0.12 (0.00, 0.39)		0.12 (0.00, 0.41)		0.14 (0.00, 0.42)		0.11 (0.00, 0.37)
MBzP		0.12 (0.00, 0.41)		0.12 (0.00, 0.4)		0.12 (0.00, 0.42)		0.14 (0.00, 0.45)		0.14 (0.00, 0.43)
MEOHP		0.13 (0.00, 0.43)		0.13 (0.00, 0.42)		0.12 (0.00, 0.41)		0.1 (0.00, 0.36)		0.13 (0.00, 0.42)
MECPP		0.12 (0.00, 0.4)		0.13 (0.00, 0.42)		0.12 (0.00, 0.38)		0.1 (0.00, 0.35)		0.12 (0.00, 0.41)
Sex: Male										
beta 1 (BWQS index)	177	-0.55 (-2.55, 1.39)	177	-0.33 (-1.9, 1.17)	165	-0.03 (-0.12, 0.07)	164	-0.72 (-3.18, 1.96)	164	-0.64 (-4.31, 3.46)
Weight for:										
MEHP		0.12 (0.00, 0.39)		0.13 (0.00, 0.41)		0.13 (0.00, 0.41)		0.13 (0.01, 0.43)		0.13 (0.00, 0.42)
MEHHP		0.12 (0.00, 0.37)		0.12 (0.00, 0.4)		0.14 (0.01, 0.47)		0.14 (0.00, 0.44)		0.13 (0.00, 0.41)
MEP		0.12 (0.00, 0.37)		0.13 (0.01, 0.4)		0.11 (0.00, 0.4)		0.12 (0.00, 0.38)		0.13 (0.00, 0.42)
MiBP		0.13 (0.00, 0.42)		0.13 (0.01, 0.41)		0.12 (0.00, 0.39)		0.12 (0.00, 0.38)		0.12 (0.00, 0.38)
MnBP		0.16 (0.01, 0.48)		0.15 (0.00, 0.45)		0.12 (0.00, 0.39)		0.12 (0.00, 0.38)		0.12 (0.00, 0.4)
MBzP		0.12 (0.00, 0.36)		0.11 (0.00, 0.39)		0.11 (0.00, 0.4)		0.12 (0.00, 0.42)		0.13 (0.00, 0.42)
MEOHP		0.12 (0.00, 0.39)		0.12 (0.00, 0.39)		0.13 (0.00, 0.39)		0.13 (0.00, 0.41)		0.12 (0.00, 0.39)
MECPP		0.12 (0.00, 0.38)		0.12 (0.00, 0.42)		0.13 (0.00, 0.42)		0.12 (0.00, 0.4)		0.13 (0.00, 0.4)

Data is from the 1st set of covariate imputed data
Models adjusted for child age at visit, child sex, mother's age at delivery, prepregnancy BMI, gestational weight gain, social class, parental cardiovascular history, smoking during pregnancy and gestational age. SBP, DBP and PWV were additionally adjusted for child height at visit.
Models stratified by social class adjusted for child age at visit, child sex, mother's age at delivery, prepregnancy BMI, gestational weight gain, parental cardiovascular history, smoking during pregnancy and gestational age. SBP, DBP and PWV were additionally adjusted for child height at visit.
Models stratified by child sex adjusted for child age at visit, mother's age at delivery, prepregnancy BMI, gestational weight gain, social class, parental cardiovascular history, smoking during pregnancy and gestational age. SBP, DBP and PWV were additionally adjusted for child height at visit.

Table S8. Associations between phenols mixture and cardiovascular measurements using BWQS regression

		Systolic BP		Diastolic BP		Pulse Wave Velocity		CRVE		CRAE
	n	Beta (CrI)	n	Beta (CrI)	n	Beta (CrI)	n	Beta (CrI)	n	Beta (CrI)
Unstratified										
beta 1 (BWQS index)	317	0.3 (-1.26, 1.73)	316	0.12 (-1.32, 1.39)	304	-0.02 (-0.1, 0.06)	291	-0.91 (-3.09, 1.44)	291	-2.25 (-5.65, 0.8)
Weight for:										
MEPA		0.15 (0.00, 0.46)		0.14 (0.00, 0.47)		0.13 (0.00, 0.47)		0.17 (0.01, 0.49)		0.13 (0.00, 0.42)
ETPA		0.14 (0.01, 0.44)		0.13 (0.00, 0.44)		0.15 (0.00, 0.47)		0.13 (0.00, 0.45)		0.13 (0.00, 0.42)
PRPA		0.14 (0.00, 0.45)		0.14 (0.01, 0.45)		0.13 (0.00, 0.43)		0.15 (0.01, 0.47)		0.15 (0.01, 0.44)
BPA		0.14 (0.00, 0.47)		0.16 (0.00, 0.51)		0.18 (0.01, 0.53)		0.14 (0.00, 0.44)		0.18 (0.01, 0.48)
BUPA		0.14 (0.00, 0.43)		0.15 (0.00, 0.49)		0.13 (0.00, 0.42)		0.14 (0.00, 0.43)		0.15 (0.01, 0.46)
BP-3		0.14 (0.00, 0.46)		0.14 (0.00, 0.43)		0.14 (0.00, 0.44)		0.15 (0.00, 0.45)		0.14 (0.00, 0.45)
TRCS		0.16 (0.00, 0.48)		0.14 (0.00, 0.43)		0.13 (0.00, 0.42)		0.13 (0.00, 0.43)		0.11 (0.00, 0.4)
Social Class: High/Middle										
beta 1 (BWQS index)	213	-0.06 (-1.74, 1.55)	213	-0.28 (-1.81, 1.11)	203	-0.04 (-0.12, 0.04)	194	-1.36 (-4.1, 1.52)	194	-3.65 (-7.29, 0.12)
Weight for:										
MEPA		0.14 (0.00, 0.45)		0.13 (0.00, 0.43)		0.13 (0.00, 0.43)		0.16 (0.01, 0.48)		0.13 (0.01, 0.41)
ETPA		0.14 (0.00, 0.47)		0.14 (0.00, 0.45)		0.16 (0.01, 0.48)		0.14 (0.00, 0.43)		0.15 (0.00, 0.46)
PRPA		0.14 (0.00, 0.44)		0.14 (0.00, 0.44)		0.13 (0.01, 0.4)		0.16 (0.01, 0.47)		0.14 (0.00, 0.43)
BPA		0.15 (0.00, 0.49)		0.17 (0.00, 0.5)		0.13 (0.00, 0.41)		0.13 (0.00, 0.42)		0.17 (0.01, 0.47)
BUPA		0.14 (0.01, 0.44)		0.14 (0.00, 0.46)		0.14 (0.00, 0.46)		0.13 (0.00, 0.41)		0.16 (0.00, 0.47)

BP-3		0.14 (0.01, 0.46)		0.14 (0.00, 0.45)		0.15 (0.01, 0.45)		0.16 (0.00, 0.47)		0.15 (0.00, 0.44)
TRCS		0.14 (0.00, 0.44)		0.14 (0.00, 0.44)		0.16 (0.01, 0.47)		0.13 (0.00, 0.42)		0.11 (0.00, 0.33)
Social Class: Low										
beta 1 (BWQS index)	104	1.22 (-1.61, 4.26)	103	0.99 (-1.88, 3.73)	101	0.05 (-0.13, 0.2)	97	0.36 (-3.58, 4.42)	97	2.18 (-3.52, 8.09)
Weight for:										
MEPA		0.15 (0.00, 0.46)		0.14 (0.01, 0.44)		0.16 (0.00, 0.48)		0.13 (0.00, 0.43)		0.13 (0.00, 0.44)
ETPA		0.12 (0.00, 0.39)		0.12 (0.00, 0.41)		0.13 (0.00, 0.42)		0.14 (0.00, 0.46)		0.16 (0.00, 0.48)
PRPA		0.13 (0.00, 0.43)		0.16 (0.00, 0.48)		0.16 (0.01, 0.48)		0.14 (0.00, 0.42)		0.13 (0.00, 0.43)
BPA		0.16 (0.00, 0.47)		0.14 (0.00, 0.44)		0.14 (0.00, 0.51)		0.16 (0.01, 0.47)		0.15 (0.01, 0.45)
BUPA		0.15 (0.00, 0.46)		0.16 (0.00, 0.47)		0.13 (0.00, 0.41)		0.14 (0.00, 0.45)		0.15 (0.00, 0.45)
BP-3		0.16 (0.00, 0.45)		0.13 (0.00, 0.44)		0.14 (0.00, 0.44)		0.15 (0.00, 0.45)		0.13 (0.00, 0.45)
TRCS		0.14 (0.00, 0.42)		0.16 (0.01, 0.48)		0.15 (0.01, 0.46)		0.14 (0.00, 0.44)		0.15 (0.01, 0.46)
Sex: Female										
beta 1 (BWQS index)	147	-0.58 (-2.79, 1.57)	146	0.03 (-1.85, 1.97)	145	0 (-0.11, 0.11)	132	-0.62 (-4.4, 3.19)	132	-2.73 (-8.14, 2.55)
Weight for:										
MEPA		0.13 (0.00, 0.43)		0.14 (0.00, 0.45)		0.14 (0.00, 0.45)		0.15 (0.00, 0.47)		0.13 (0.00, 0.4)
ETPA		0.15 (0.00, 0.46)		0.14 (0.00, 0.44)		0.14 (0.00, 0.44)		0.14 (0.00, 0.45)		0.13 (0.00, 0.44)
PRPA		0.13 (0.00, 0.43)		0.15 (0.00, 0.48)		0.14 (0.01, 0.44)		0.14 (0.00, 0.44)		0.13 (0.00, 0.39)
BPA		0.15 (0.00, 0.45)		0.15 (0.01, 0.46)		0.16 (0.00, 0.49)		0.15 (0.00, 0.46)		0.19 (0.01, 0.51)
BUPA		0.15 (0.00, 0.49)		0.14 (0.00, 0.43)		0.14 (0.00, 0.44)		0.15 (0.00, 0.46)		0.16 (0.01, 0.46)
BP-3		0.15 (0.00, 0.47)		0.14 (0.00, 0.47)		0.15 (0.00, 0.45)		0.14 (0.00, 0.47)		0.14 (0.00, 0.43)
TRCS		0.14 (0.00, 0.42)		0.14 (0.00, 0.43)		0.14 (0.00, 0.48)		0.14 (0.00, 0.46)		0.12 (0.00, 0.42)

Sex: Male										
beta 1 (BWQS index)	170	1.22 (-0.93, 3.27)	170	0.57 (-1.43, 2.43)	159	-0.02 (-0.15, 0.1)	159	-1.3 (-4.52, 2.01)	159	-1.11 (-5.65, 2.98)
Weight for:										
MEPA		0.13 (0.00, 0.4)		0.14 (0.00, 0.44)		0.12 (0.00, 0.43)		0.17 (0.01, 0.51)		0.14 (0.00, 0.44)
ETPA		0.13 (0.00, 0.42)		0.14 (0.00, 0.45)		0.15 (0.00, 0.48)		0.13 (0.00, 0.4)		0.14 (0.00, 0.45)
PRPA		0.14 (0.01, 0.45)		0.13 (0.00, 0.44)		0.13 (0.00, 0.45)		0.15 (0.00, 0.47)		0.15 (0.00, 0.48)
BPA		0.12 (0.00, 0.43)		0.13 (0.00, 0.5)		0.17 (0.01, 0.51)		0.13 (0.00, 0.44)		0.15 (0.01, 0.47)
BUPA		0.17 (0.01, 0.49)		0.18 (0.00, 0.54)		0.13 (0.00, 0.45)		0.12 (0.00, 0.41)		0.14 (0.00, 0.45)
BP-3		0.16 (0.01, 0.48)		0.15 (0.00, 0.45)		0.16 (0.01, 0.49)		0.14 (0.00, 0.43)		0.14 (0.00, 0.46)
TRCS		0.16 (0.00, 0.46)		0.13 (0.00, 0.42)		0.13 (0.00, 0.47)		0.16 (0.01, 0.45)		0.14 (0.00, 0.44)

Data is from the 1st set of covariate imputed data
Models adjusted for child age at visit, child sex, mother's age at delivery, prepregnancy BMI, gestational weight gain, social class, parental cardiovascular history, smoking during pregnancy and gestational age. SBP, DBP and PWV were additionally adjusted for child height at visit.
Models stratified by social class adjusted for child age at visit, child sex, mother's age at delivery, prepregnancy BMI, gestational weight gain, parental cardiovascular history, smoking during pregnancy and gestational age. SBP, DBP and PWV were additionally adjusted for child height at visit.
Models stratified by child sex adjusted for child age at visit, mother's age at delivery, prepregnancy BMI, gestational weight gain, social class, parental cardiovascular history, smoking during pregnancy and gestational age. SBP, DBP and PWV were additionally adjusted for child height at visit.

6. DISCUSSION

6.1. Main Findings

Using data from European based birth cohort studies we found that early life exposure to maternal metabolic parameters and EDCs appear to have an effect on child BMI growth trajectories and early adolescent cardiovascular health, which may be modified by socioeconomic position. Maternal prepregnancy BMI and gestational weight gain were associated with offspring's BMI trajectories characterized by accelerated growth during early childhood, and these same trajectories were related to macrovascular health function during early adolescence. When examining EDCs, we found that chemical exposure differs by SEP, and those of higher SEP are potentially at greater risk of exposure. Further, prenatal exposure to EDCs, particularly organochlorine compounds (DDE, HCB, PCBs) are related to BMI trajectories characterized by accelerated growth in childhood. While, prenatal exposure to non-persistent EDCs (phthalates, phenols) does not appear to be associated with early adolescent cardiovascular health.

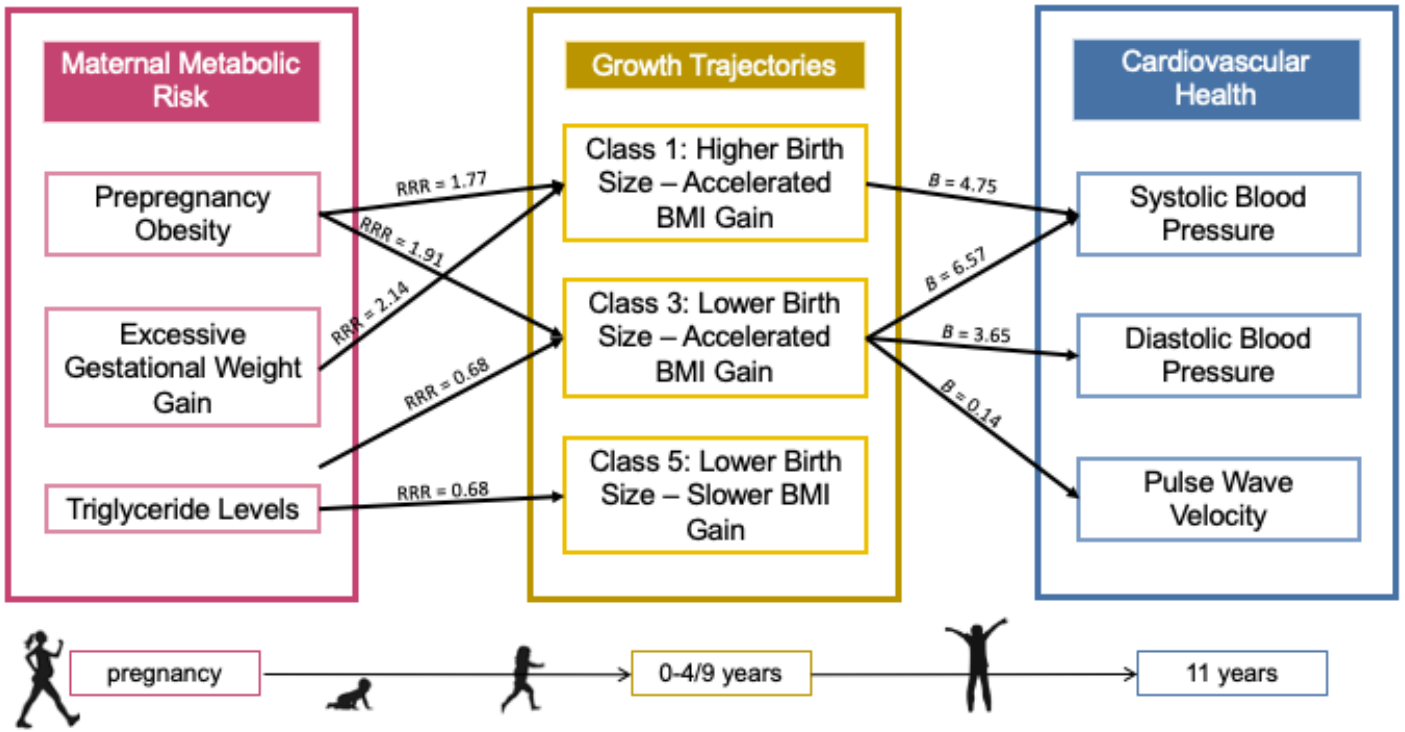
6.1.1. Determinants of BMI Trajectories and Association with Cardiovascular Health

In the first study (Paper I) we used data from four of the INMA birth cohorts to evaluate associations between markers of maternal metabolic health status during pregnancy and their offspring's BMI trajectories during early childhood (0 to 4 years). Firstly, we identified five unique trajectories, two of which were characterized by accelerated BMI gain, which could be classified as potentially higher risk trajectories as children who experience accelerated growth have been shown to face increased risk for several diseases in later life. Analyzing the maternal metabolic parameters with the BMI trajectories, we found that prepregnancy obesity was associated with BMI trajectories characterized by accelerated BMI gain, departing from either higher or lower birth size. Further, children of mothers who gained more than the recommended amount of weight during pregnancy had a higher probability to follow a BMI trajectory characterized by higher birth size and accelerated BMI gain, while children of mothers who gained less

than the recommended had a higher probability of belonging to a BMI trajectory characterized by lower birth size followed by slower BMI gain. Additionally, maternal triglyceride concentrations were negatively associated with the two BMI trajectories characterized by lower birth size followed by either slower or accelerated BMI gain.

In Paper II we evaluated the associations between childhood BMI trajectories (0 to 9 years) and early adolescent cardiovascular health at 11 years using data from the INMA Sabadell cohort. We found evidence that accelerated growth, especially in those of lower birth size, is a risk factor for higher systolic and diastolic blood pressure (SBP and DBP), and pulse wave velocity (PWV) in early adolescence. Specifically, we observed that children with a lower birth size and accelerated BMI gain had increased SBP, DBP and PWV, and children with a higher birth size and accelerated BMI gain had increased SBP. We did not observe any associations between the BMI trajectories and retinal microvascular measurements. Although we extended the trajectories to 9 years for use in Paper II, the trajectories and their descriptions remained the same. As such, we can link the two works to discern that; 1) prepregnancy obesity increased risk of the offspring belonging to a BMI trajectory of lower birth size and accelerated BMI gain which was then associated with increased SBP, DBP and PWV in early adolescence, and 2) prepregnancy obesity and excessive GWG increased risk of the offspring belonging to a BMI trajectory of higher birth size and accelerated BMI gain which was then associated with increased SBP in early adolescence (Figure 3). Given that accelerated growth has been linked to future adverse health consequences in adulthood, our findings are important. They demonstrate early modifiable determinants (prepregnancy obesity, excessive GWG) of accelerated growth, and early preclinical macrovascular changes related to accelerated growth.

Figure 3. Associations between maternal metabolic risk factors during pregnancy and childhood growth trajectories and early adolescent cardiovascular health



Abbreviations: RRR = relative risk ratio, B = beta estimate

6.1.2. Socioeconomic Determinants of Chemical Exposure

In Paper III we evaluated the social determinants of chemical exposures utilizing markers of socioeconomic position (SEP) (maternal education, maternal employment status, family affluence score) and measured concentrations of 41 chemicals during pregnancy and childhood in 1,301 mother-child pairs from six different European populations (HELIX study). We observed that families of higher SEP were at higher risk to be exposed to persistent pesticides, PFASs, phenols, organophosphate (OP) pesticides, BPA, mercury (Hg) and arsenic (As), whereas families of lower SEP were at risk of higher exposures to cadmium (Cd), lead (Pb), and phthalates. We found that these trends were similar in single chemical exposure models and regression analysis using principal components (PC). These findings challenge the traditional hypothesis that disadvantaged groups should be classified as the "high exposure risk" group.

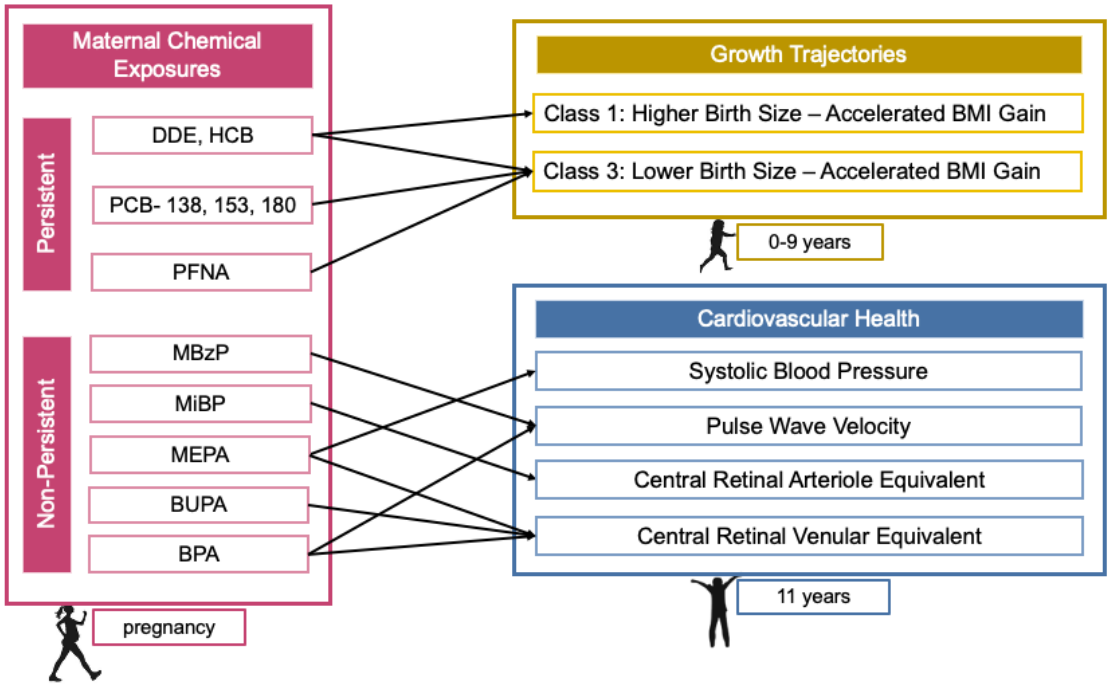
6.1.3. Chemical Exposures and BMI Trajectories and Cardiovascular Health

In the final studies of the thesis we examined the associations between prenatal exposure to chemical contaminants and BMI trajectories (0 to 9 years) and early adolescent cardiovascular health (11 years). In Paper IV we examined the associations between prenatal exposure to POPs, PFAS, phthalates and phenols and BMI trajectories using data from three of the INMA birth cohorts. We found that prenatal exposure to HCB and DDE was associated with BMI trajectories characterized by accelerated BMI gain, departing from either higher or lower birth size. Additionally, prenatal exposure to PCBs and PFNA was associated with a higher probability of the child belonging to the BMI trajectory characterized by lower birth size and accelerated BMI gain. Lastly, using mixture models, we found a significant positive association with children belonging to the lower birth size-accelerated BMI gain trajectory when exposed to a mixture of all analyzed chemicals. Chemicals with the most weight in the mixture model were similar to those previously mentioned; DDE, HCB, PCB-138, -153, -180 and BP-3 (Figure 4). In Paper V we analyzed the

associations between prenatal phthalate and phenol exposures and early adolescent cardiovascular health using data from the INMA Sabadell cohort. We observed statistically significant positive associations between MEPA and SBP, and central retinal arteriole equivalent (CRAE) and MiBP; and negative associations between BPA and PWV, and MEPA, BPA, BUPA and central retinal venular equivalent (CRVE) (Figure 4). We did not find any evidence of association with mixture models. Overall, we found little evidence to suggest that prenatal urinary concentrations of phthalates and phenol metabolites were associated with macro- and microvascular health during early.

Drawing on our research in Paper III, we attempted to account for SEP not only through adjustment, but also by stratifying by social class in Papers IV and V. We found that certain associations only remained significant for certain social classes. For example, the association between OCs and a BMI trajectory characterized by lower birth size and accelerated BMI gain remained significant only for those of higher social class, while the association between BPA and decreased PWV remained significant only in those of lower social class. This demonstrates the importance of examining associations by potentially modifying factors (e.g. SEP), when possible, to further disentangle these complex relationships.

Figure 4. Associations between prenatal chemical exposures and child growth trajectories and early adolescent cardiovascular health



Abbreviations: DDE = dichlorodiphenyldichloroethylene, HCB = hexachlorobenzene, PCB = polychlorinated biphenyl, PFNA = perfluorononanoic acid, MBzP = monobenzyl phthalate, MiBP = mono-isobutyl phthalate, MEPA = methyl paraben, BUPA = butyl paraben, BPA = bisphenol A

6.2. Methodological Considerations

6.2.1.Study Design

Use of the INMA birth cohort studies is a major strength of this thesis. The prospective longitudinal design minimizes the risk of reverse causation between the exposures and outcomes. Longitudinal studies allow researchers to look at changes over time which is particularly useful when looking at developmental changes over the lifespan. The long follow-up of the INMA study permitted us to examine the associations between early life exposures beginning in the first trimester of pregnancy through childhood and early adolescence. This gave us the opportunity to construct BMI trajectories rather than analyzing growth at one point in time (Papers I, II and IV), and analyze prenatal concentrations of several chemicals with growth and cardiovascular health assessed at different ages through childhood and early adolescence (Papers IV and V). Like all studies, longitudinal studies also have some disadvantages, the main one being loss to follow-up. This may bias effect estimation if there are differences in the groups that are related to the exposure and the outcomes (i.e. data are not missing at random). In our studies using INMA data, participation rates ranged from 63-89% of the originally included population (Paper 1: 82%; Paper 2: 75%; Paper 4: 89%; Paper 5: 63%). When loss to follow-up is due to missing at random mechanisms there does not seem to be any important bias, however, when lost to follow-up is based on a missing not at random mechanism estimates may be extremely biased (Kristman et al., 2004). Recommended follow-up thresholds are between 60-80%, of which our studies fall within or of above the range. In cohort studies, participants lost to follow-up tend to be the less advantaged and less healthy, which can lead to a healthier and wealthier study population. However, several studies have shown that this leads to minimal bias even when SEP is the exposure of interest (Howe et al., 2016).

6.2.2.Sample Size

Sample size is a key issue in epidemiological research, and of particular concern for stratified analyses. Samples should not be either too big or too small since both have limitations that can compromise the conclusions drawn from the studies. Too small of a

sample can cause a Type II error, which is the failure to reject a false null hypothesis (false negative). Too large of a sample size can cause the opposite, a Type I error which emphasizes statistical differences that are not clinically relevant (false positive) (Faber and Fonseca, 2014). In our studies, sample size ranged from 416 to 2,251 (Paper I: 2,251, Paper II: 495; Paper III: 1,301, Paper IV: 1,911, Paper V: 416). Even though sample size was smaller in two of the papers (Papers II and V), by limiting the study to only those in Sabadell we were able to use novel measures of cardiovascular health (PWV, CRAE, CRVE) not measured in other INMA cohorts or many previous studies. To gain some statistical power, we analyzed associations using the continuous scale, and imputed data for mixture models to limit data loss. To impute missing data we utilized the multivariate imputation by chained equations (MICE) approach of multiple imputation (Azur et al., 2010). This method has several advantages: 1) results in unbiased estimates assuming the observed variables are predictive missing data, 2) allows for use of all available data thus preserving the sample size and increasing study power, and 3) regression models are easily carried out with standard software and interpreted (McCleary, 2002). To ensure imputed data was similar to the original dataset we always evaluated any differences in the main study population characteristics and ran a complete case analysis.

6.2.3. Assessment of Metabolic Markers

Self-reported data was used for prepregnancy BMI and GWG calculation. Self-reported data may pose a threat to the validity of the measurements, however by ensuring the questions are easily understood and appropriate for the population being questioned validity is greatly increased. In addition, height and weight data, as used in INMA, has been validated for identifying relationships in epidemiological studies (Spencer et al., 2001). Additionally, we used non-fasting lipid concentrations in Paper I, which may be subject to non-differential (random) misclassification thus distorting the associations. However, both fasting and non-fasting samples are valid for measuring lipid levels, and both have been associated with offspring growth parameters. Moreover, there are no reference ranges defined for lipid levels during a normal pregnancy, and it is known that cholesterol and triglyceride levels rise during pregnancy (Bartels and O'Donoghue, 2011). This is mostly due to the lack of

evidence on the implication of elevated lipids during pregnancy. Future studies may benefit from taking multiple measures of lipids during the different trimesters to more accurately assess the lipid profile.

6.2.4. Assessment of Chemical Concentrations

Exposure misclassification in the studies evaluating chemical contaminants (Papers IV and V) is primarily a concern for non-persistent rather than persistent chemicals. Persistent chemicals have a long half-life in the human body as such, one single blood measurement in any trimester is considered sufficient for estimating exposure throughout pregnancy (Longnecker et al., 1999). Nevertheless, some interindividual variation may still occur during pregnancy due to individual behavioral differences, metabolic differences, and the natural metabolic changes that occur during pregnancy given the lipophilic nature of POPs (Savitz, 2014). Research has shown that POPs are primarily stored in adipose tissue which serves as a source of chronic POP exposure (La Merrill et al., 2013). However, much of this data comes from studies on weight loss in obese participants rather than during pregnancy, which is a period known for weight gain rather than loss. Nonetheless, we cannot estimate to what extent maternal metabolism may have influenced associations between POPs and their offspring's growth and cardiovascular health.

In our studies evaluating the health effects of non-persistent chemicals, exposure misclassification is a major limitation. Non-persistent chemicals have short half-lives as they are metabolized rapidly and excreted through urine. In studies relying on spot urine samples this leads to large variability in concentrations (Casas et al., 2018). This can lead to regression dilution bias which can cause null associations (Hutcheon et al., 2010). One method to minimize this bias is to collect multiple urine samples (Hutcheon et al., 2010). If repeated measurements are not available, recent work proposes that using pooled samples (combining multiple measures) or regression calibration (a statistical method for adjusting concentration estimates) can be used and both perform similarly (Agier et al., 2020). In Papers IV and V, we had two spot urine samples during pregnancy (1st and 3rd trimester averaged or pooled) for phthalates, and for BPA in Paper V, which may have helped to lessen this bias

somewhat. However, to most accurately estimate exposure during pregnancy recent work estimates that three samples per day or four weekly pools of 15–20 urines each would be necessary (Casas et al., 2018; Vernet et al., 2019).

6.2.5. Assessment of BMI Growth Trajectories

A strength of this thesis is the use of height and weight measurements taken repeatedly for the children, from birth to 9 years old. This allowed us to construct longitudinal BMI growth trajectories for the INMA children, which have the advantage of encompassing multiple growth parameters that single time-point measures do not. The studies in this thesis (Papers I, II and IV) used growth trajectories modeled from LCGA. This method has the advantage of being able to model non-linear growth patterns and estimate individual trajectories that are then assigned to a "latent class" grouping. This facilitates the ease of interpretation in the analysis between the calculated trajectories and health outcomes at different time points. However, this method also has some disadvantages. Namely, height and weight needs to be measured at roughly the same time points for all children. In INMA, standardized protocols were established for measurements at similar age groups, so this was not an issue. Additionally, defining the trajectories may be done in several different ways, leading to different interpretations. For the INMA growth trajectories we used commonly applied criterion; Akaike Information Criteria (AIC) and Bayesian Information Criteria (BIC), with the aim of making our trajectories more comparable to others. Although we chose the LCGA approach for our data, other approaches are available (e.g. multilevel modeling, growth mixture modeling), and all have their own advantages and disadvantages. To understand the complexities in life course research as it pertains to growth, several of these approaches may be necessary as they each answer slightly different research questions and therefore complement one another (Tu et al., 2013).

6.2.6. Assessment of Cardiovascular Health

To assess cardiovascular health in this thesis we used measures of blood pressure, PWV, and retinal venular and arteriole diameters. Blood pressure has long been used in all age groups as a marker for

cardiovascular health, and has been shown to track from childhood into adulthood (Juonala et al., 2011). PWV is known as the gold standard to evaluate aortic stiffness, and is non-invasive making it a good choice for children. Recently, studies have validated its use in health children and adolescents (Reusz et al., 2010; Thurn et al., 2015). However, it has not been utilized in many studies evaluating children's cardiovascular risk profiles. Retinal imaging is a new technology that allows detailed non-invasive assessment of the microvasculature. Increasing evidence supports that structural changes in the retinal microvasculature are associated with CVD risk factors. While these measurements are still fairly new and understudied, they may help predict those at greater risk for developing CVD later in life (Li et al., 2016; Newman et al., 2017). More research is still needed at different age groups and study populations to better understand when these measures may be most useful.

6.2.7.Socioeconomic Position

Socioeconomic position (SEP) played an important role throughout this thesis. In Paper III we found that those of lower SEP are not always those that are the highest exposed as the traditional hypothesis would suggest. We aimed to use a variety of SEP indicators in Paper III to confirm this; maternal education, maternal employment status and family affluence score (FAS). For those over 25 years of age, education is considered an excellent measure of SEP (Oakes, 2010), but it is not without some disadvantages. The percentage of college graduates has greatly increased over the last decades, and educational attainment is not always equivalent to income. Even still, we detected strong patterns with maternal education similar to other studies in developed countries. In Papers IV and V we stratified by familial social class, which was calculated based on the Goldthorpe class schema which uses occupation to measure social class. The validity of this method has been tested, finding strong indicators between occupation and one's social class with the exception of minor differences between those of the highest and lowest classes (Evans, 1992).

In our studies these classes were combined as we used either two or three categories for social class (depending on study sample size). In Paper IV, we did not find that one social class was consistently at

higher risk than others in single exposure models, rather associations were stronger depending on the EDC in question. For example, associations between DDE and PCBs and the trajectory characterized by lower birth size and accelerated BMI gain were statistically significant only for those of higher social class, whereas associations between DDE and the trajectory of higher birth size and accelerated BMI gain and PFNA and the trajectory of lower birth size and accelerated BMI gain were only statistically significant for those of lower social class. At the same time, in mixture models when EDCs were combined we found a strong positive association with the trajectory characterized by lower birth size and accelerated BMI gain for those of lower social class, and no evidence of an association in the middle and higher social class groups. A limitation in Paper IV was that we were not able to test for interaction by social class (only stratify), so although we found that some estimates were stronger in one group when compared to another through stratification we cannot say anything about whether these differences are statistically significant. In Paper V, we did not observe any consistent patterns in single exposure or mixture models, however this is most likely due to the small sample size of the study.

Overall, these results suggest that there is no clear pattern of effect modification by social class for individual EDCs, but that the effects of EDC mixtures on growth trajectories may occur predominantly in lower social classes. Further work in needed to disentangle the interactions between SEP and chemical exposures influencing child growth and cardiovascular health.

6.2.8.Multiple Exposures

The majority of knowledge on chemical exposures and health effects comes from the study of single exposure models (i.e. a single input with a single outcome). However, the real world is a mixture of several chemicals that humans are exposed to simultaneously. Mixture models aim to take this into consideration by accounting for multiple exposures together in one model. In this thesis we used two different methods to evaluate exposure mixtures: PCA and BWQS. In Paper III, we used PCA to examine the relationship between SEP indicators and chemical contaminants. PCA allowed us to evaluate the combined effect of many

environmental contaminants by creating components which represented the weighted combination of the individual chemicals in the group. In Papers IV and V we used BWQS regression which builds upon WQS regression. This type of modeling summarizes overall exposure to a chemical mixture by estimating a weighted index that accounts for the individual contribution of each chemical included in the mixture (Colicino et al., 2020). By using these kinds of techniques we are able to assess the effects of a combination(s) of chemicals which is more closely related to how humans are exposed in real life. In each paper using mixture models we also ran single exposure models, as they complement one another, and use these similarities to draw our conclusions. We found that the single exposure and mixture models yielded similar results, giving us further confidence in our conclusions.

6.3. Contribution to the Current Evidence

This PhD thesis has given insight into the role of early life predictors play on influencing childhood growth and cardiovascular health, and provides further evidence to support the DOHaD hypothesis. According to our aforementioned objectives, our finding contribute to: 1) understand the role of maternal metabolic health on offspring's postnatal BMI growth trajectories during early childhood, 2) explain the relationship between childhood growth trajectories and early adolescent cardiovascular health, 3) identify socioeconomic group at increased risk for higher chemical exposure, and 4) understand the effects of prenatal exposure to persistent and non-persistent chemicals on childhood growth and cardiovascular health. The specific contributions to the current evidence are listed in Table 2 and discussed in the following sub-sections.

6.3.1. Maternal Metabolic Health and Child Growth Trajectories

This study was one of the first to examine maternal metabolic health with childhood BMI trajectories. Previous studies had largely used only singular measures of growth; birthweight and/or BMI. Through this we were able to identify two distinct trajectories of accelerated growth. As accelerated growth during infancy has been

associated with adverse health outcomes in later life such as, obesity, hypertension and CVD we considered these two trajectories to be higher risk (Chrestani et al., 2013; Dulloo et al., 2006; Eriksson et al., 2015; Perng et al., 2016). Previous studies had found positive associations between maternal prepregnancy BMI and excessive gestational weight gain, and higher risk of later accelerated BMI gain and/or later overweight in their offspring (Deierlein et al., 2012; Diesel et al., 2015; Giles et al., 2015; Haga et al., 2012; van Rossem et al., 2014; Ziyab et al., 2014). Our study was the first to examine maternal lipid concentrations with child growth trajectories, although previous studies had examined birthweight (Liu et al., 2016; Misra et al., 2011; Vrijkotte et al., 2011). Our findings provide further evidence for these associations and expanded on them. We demonstrated that prepregnancy overweight is associated with growth trajectories of accelerated growth independently of a child's size at birth. Further, by using trajectories rather than growth at a single time point our study also highlighted the benefit of assessing BMI trajectories to gain a more comprehensive understanding of early life predictors of childhood growth patterns.

6.3.2. Child Growth Trajectories and Cardiovascular Health

Few studies have evaluated the association between childhood BMI growth trajectories and measures of preclinical cardiovascular health. Those that have primarily focused on macrovascular measures (e.g. blood pressure). These studies observed associations between growth trajectories characterized by early overweight/obesity or accelerated growth and increased blood pressure, augmentation index (a measure of arterial stiffness), and cardiovascular risk during adolescence and early adulthood (Boyer et al., 2015; Buffarini et al., 2018; Hanvey et al., 2017; Ziyab et al., 2014). Our study expanded on this by not only utilizing longitudinal BMI growth trajectories, but also including a wider range of cardiovascular outcomes that encompassed the macro- and microvascular systems.

Our results from Paper II, combined with existing research on the subject, provides evidence that accelerated growth, especially in those of lower birth size, is associated with measures of preclinical

macrovascular health (SBP, DBP, PWV) in early adolescence. However, our findings are slightly different to previous studies in that we found accelerated growth to happen during infancy (0-2 years) whereas, other studies found that weight gain after infancy was more related to cardiovascular risk (Adair and Cole, 2003; Victora et al., 2008). Additionally, our study found that those born at higher birth size and experience accelerated BMI gain during infancy may experience similar risks. These differences in findings may be due in part to differences in the income levels of the study populations. Our study comes from Spain, a high income country, while the aforementioned studies reported results from low to middle income countries where accelerated growth during infancy may be protective (Singhal, 2017).

We were able to include novel measures of microvasculature through retinal imaging, but we did not observe any associations with the BMI trajectories, which is similar to another study (Hanvey et al., 2017). The limited research in this area does seem to indicate a relationship between overweight/obesity and adverse changes in the retinal microvasculature, however it is not clear at what age these measurements may be most useful (Li et al., 2016). Studies using retinal imaging should continue to conduct these measurements at different ages to help assess this issue.

6.3.3. Socioeconomic Position and Chemical Exposure

Our findings from Paper III provide one of the most comprehensive reviews on the burden of exposure to environmental chemicals by SEP in a European population. We analyzed 41 chemicals, of which 29% were higher in higher SEP groups compared to lower in pregnant women, increasing to 39% in children. On the contrary, only 5% of chemicals were higher in low SEP groups for pregnant women, and 22% for children. We found families of higher SEP had increased exposure to persistent pesticides, PFASs, phenols, OP pesticides, BPA, Hg and As, while families of lower SEP had greater exposure to Cd, Pb, and phthalates. These findings were broadly consistent with existing literature (Brantsæter et al., 2013; Fisher et al., 2016; Morrens et al., 2012; Nelson et al., 2012; Schober et al., 2003; Sokoloff et al., 2016; Tyrrell et al., 2013; van den Dries et al., 2018; Vrijheid et al., 2012). Although, some studies

reported null findings or findings to the contrary (Borrell et al., 2004; Casas et al., 2011; Manzano-Salgado et al., 2016). Our findings challenge the traditional hypothesis, that those of lower SEP should be systematically classified as the higher risk group. However, as exposure to the chemicals is ubiquitous, those of lower SEP are still exposed. Given that low SEP is a consistent and reliable predictor of a vast array of outcomes across the life span, including cardiovascular health and growth parameters, even if they are less exposed the effect may be greater as they may face lower quality or inadequate access to health care, an inability to navigate the health care system, face bias or prejudice from medical staff, or stress (Bahls, 2011; Fiscella et al., 2000).

6.3.4. Chemical Exposures, Child Growth and Cardiovascular Health

Previous studies have evaluated the effects of chemical exposures on certain aspects of child growth and cardiovascular health; primarily birthweight, obesity and blood pressure. Few studies have examined growth trajectories or measures of accelerated growth, and none have examined more novel measures of cardiovascular health like PWV or retinal imaging of the microvasculature. On the subject of growth trajectories, previous work is consistent with our own results. Findings have consistently shown positive associations between prenatal exposure to DDE and accelerated growth and increased adiposity during childhood while associations are less consistent for HCB, PCBs and PFAS (Braun, 2016; Iszatt et al., 2015; Liew et al., 2018; Valvi et al., 2014; Vrijheid et al., 2016). We found PCBs to be positively associated with a growth trajectory characterized by accelerated growth, while another study found the opposite (Iszatt et al., 2015). We further assessed these relationships using mixture models, which to our knowledge only one other study has done. While we found a mixture of persistent and non-persistent chemicals to be positively associated with a trajectory characterized by lower birth size and accelerated BMI gain, the other study found a similar mixture to be associated with slower infant growth spurt rate and delayed age at infant peak growth velocity (Svensson et al., 2021). Our findings with accelerated growth are important as previous research has concluded that low birthweight followed by accelerated growth is associated with multiple diseases in adulthood, including hypertension, obesity, cardiovascular diseases,

diabetes, and cancers (Barker et al., 2005; Druet et al., 2012; Zheng et al., 2016). The use of novel mixture models may give us a more comprehensive technique to examine chemical exposure as it would occur in real life, but as these are the first studies using such methods, more studies are needed to elucidate the associations.

Previous work examining prenatal exposure to non-persistent chemicals (e.g. phthalates and phenols) have observed both positive and negative associations with blood pressure, often sex dependent, while some have found mostly null associations similar to our results (Bae et al., 2017; Golestanzadeh et al., 2019; Ouyang et al., 2020; Sol et al., 2020; Vafeiadi et al., 2018, 2015; Valvi et al., 2015b; Warembourg et al., 2019). Ours was the first study to examine prenatal exposure to non-persistent chemicals with PWV and retinal imaging measures. We observed that an increase in prenatal BPA exposure was related to a decrease in PWV, which remained significant for boys and those of low social class. Our results for retinal imaging measures were mixed, in both positive and negative directions. One phthalate metabolite, MiBP, was associated with increased CRAE, which remained significant for girls and those of lower social class. Whereas the parabens, MEPA and PRPA, were associated with reduced CRAE for boys. MiBP and TRCS were associated with an increase in CRVE for those of lower social class, while BUPA, MEPA and ETPA were all found to be associated with reduced CRVE. In mixture analysis, including all phthalate metabolites and phenols together, no associations were observed. Thus, overall, our results are mostly null. However, as these are the very first results in the case of the more novel measures, more studies are needed to explore these associations, or lack thereof, further.

Table 2. Main results of the studies included in this thesis

Paper	Exposure	Outcome	Main Results
I	Maternal metabolic health (prenatal)	BMI growth trajectories (0 – 4 yrs.)	▪ Maternal prepregnancy overweight was associated with childhood BMI trajectories characterized by accelerated BMI gain, independently of size at birth. ▪ Gestational weight gain above widely used clinical guidelines was associated with higher child's size at birth followed by accelerated BMI gain. ▪ Higher maternal concentrations of triglycerides were associated with offspring's BMI trajectories characterized by a lower size at birth and a slower or accelerated BMI gain. ▪ Gestational diabetes, maternal concentrations of cholesterol and C-reactive protein were not associated with children's BMI trajectories.
II	BMI growth trajectories (0 – 9 yrs.)	Cardiovascular health (11 yrs.)	▪ Children belonging to a BMI trajectory characterized by lower birth size and accelerated BMI gain had increased SBP, DBP and PWV. ▪ Children belonging to a BMI trajectory characterized by higher birth size and accelerated BMI gain had increased SBP. ▪ No significant associations between BMI trajectories and the retinal microvascular measurements were observed.
III	Socioeconomic position (prenatal and ~8 yrs.)	Chemical concentrations (prenatal and ~8 yrs.)	▪ Mother – child pairs of higher social position were at greater risk of increased exposure to persistent pesticides, PFASs, phenols, OP pesticides, BPA, Hg and As. ▪ Mother – child pairs of lower social position were at greater risk of increased exposure to Cd, Pb, and phthalates; particularly DEHP metabolites.
IV	Chemical concentrations (prenatal)	BMI growth trajectories (0 – 9 yrs.)	▪ In single exposure models, prenatal exposure to higher concentrations of OCs (DDE, HCB, PCBs) and PFNA was associated with increased risk for belonging to trajectories characterized by accelerated BMI gain, departing from either lower or higher birth size. ▪ In multiple exposure models, exposure to a mixture of 23 chemicals was positively associated with belonging to a BMI trajectory characterized by lower birth size and accelerated BMI gain.
V	Chemical concentrations (prenatal)	Cardiovascular health (11 yrs.)	▪ Overall, prenatal concentrations of phthalates and phenols were not associated with measures of cardiovascular health during early adolescence in single exposure or mixture models.

Abbreviations: BMI: body mass index; PFAS: Per- and polyfluoroalkyl substances; OP: organophosphate; BPA: bisphenol-A; Hg: mercury; As: arsenic; Cd: cadmium; Pb: lead; DEHP: Di(2-ethylhexyl) phthalate; SBP: systolic blood pressure; DBP: diastolic blood pressure; PWV: pulse wave velocity; OC: organochlorine, DDE: dichlorodiphenyldichloroethylene, HCB: hexachlorobenzene

6.4. Implications for Public Health

Cardiovascular diseases are a major cause of disability, premature death, and escalating health care costs worldwide. Early identification of predisposing risk factors is fundamental given that lifestyle and genetic factors explain only a portion of cardiovascular disease risk (Kelishadi and Poursafa, 2014). Recent research, including the work in this thesis, now points to early life risk factors in the underlying pathology of later cardiovascular disease development (Murray et al., 2015). This knowledge gives rise to the idea that prevention should start from the beginning by aiming for optimal fetal and infant development. A primordial prevention strategy, which addresses health from infancy to old age, is one approach to achieve significant health benefits over the long term. It would involve a combination of lifestyle interventions (e.g. physical activity, good nutrition, no tobacco), and regulatory strategies (e.g. regulation of high salt/fat foods, high quality health care). While health promotion strategies focused at changing individual behaviors have been traditionally promoted, behavior change is complex and difficult to begin or maintain in the face of social or environmental adversity. On a population level, these interventions can be expensive to implement with only moderate benefit that does not last. Changes that affect policy, the environment, and cultural attitudes have been more successful. A positive example of this are the anti-tobacco laws which have reduced cardiovascular events (Castellano et al., 2014).

At the same time, this thesis along with other work has demonstrated that chemical exposure is ubiquitous and not restricted to any one socioeconomic group. Prenatal chemical exposure, even in low doses, has the potential to affect long term growth, development and disease risk. We demonstrated that several chemicals were associated with potential at risk growth trajectories characterized by accelerated growth and those same trajectories were associated with early adolescent cardiovascular health risk factors. Recommendations to avoid or limit chemical exposure exist at the individual and population level. Regulations that ban or limit the use of certain chemicals coming from a governmental level would be the most effective way to reduce exposure. Several chemicals have been banned or limited in certain products (e.g. DDT as a pesticide, BPA in child-care products),

while others are on a watch-list (e.g. BP-3, PFAS). Regulators should support research evaluating human health effects to these chemicals as well as research seeking to identify new chemicals with disruptive properties. Additionally, policy that requires products to be labeled as an endocrine disruptor and list the offending chemicals may promote behavior change thus forcing companies to seek healthier alternatives. On an individual level, behavior changes should be promoted such as, washing fruits and vegetables to reduce pesticide exposure, avoid using plastic and canned foods and drinks to limit phthalate and phenol exposure, choose personal care products free of parabens, avoid products labeled "fire-retardant" or "non-stick" to reduce PFAS exposure and remove shoes when entering the home (Endocrine Society, 2021). Moreover, as many chemicals are introduced via food, recommendations on the consumption of fish and seafood, which are important sources of POP and mercury exposure, could reduce levels. These individual behavior changes are especially important during pregnancy, as the developing fetus is exposed during a critical stage in development.

Pregnancy may be a key moment for change over the life course. During pregnancy and the post-natal period women have repeated contact with health care professionals (e.g. midwives, gynecologists, pediatricians), and there is encouraging evidence to suggest positive health behavior changes during this time (Crozier et al., 2009; Olander et al., 2018). Concentrating health promotion efforts during this time period, when women are more accepting to positive behavior change, may be a more cost-effective and impactful approach. Undertaking positive health changes during this period may have benefits to pregnancy BMI, weight gain, lipid levels and environmental exposures. This could carry-on by benefiting their child; avoiding a higher risk growth trajectory during childhood, reducing cardiovascular risk during early adolescence, and preventing future cardiovascular disease in adulthood.

6.5. Future Research

This thesis has advanced research in the field of early life exposures on growth and cardiovascular risk over the life course. While there is already sufficient evidence to support the DOHaD hypothesis,

there are still challenges for future research such as; 1) continue to identify early life exposures that influence growth and cardiovascular health; 2) identify the most critical windows of susceptibility to these exposures; 3) elucidate the relationships between early life risk factors (e.g. EDCs, genetic and lifestyle factors, growth patterns, SEP) and later cardiovascular risk; 4) understand the mechanisms that underline these outcomes.

While this thesis identified certain early life risk factors associated with child growth and cardiovascular risk, there are likely more factors to uncover. This is particular true in the case of EDCs. In order to identify EDCs that most influence growth and cardiovascular health, exposure assessment can be greatly improved particularly for non-persistent chemicals. Future cohort studies aiming to evaluate non-persistent chemicals should aim to collect three samples per day and/or four weekly pools of 15–20 urines each in order to accurately assess exposure (Casas et al., 2018; Vernet et al., 2019). It may be more expensive and time-consuming to collect several measurements from each participant, as such this type of research could be undertaken by smaller cohort studies or carried out for only a subset of the study population.

In addition, more studies are needed to evaluate critical time windows of exposure that are more likely to have an effect of child growth and cardiovascular health. Repeated measures during pregnancy of lipids as well as EDCs would be beneficial. Lipid profiles, particularly cholesterol and triglycerides, naturally increase during pregnancy. Taking measurements during each trimester as well as repeated measures of weight and cardiovascular health would help to identify critical windows of susceptibility.

The relationships between early life exposures and child growth and cardiovascular health is complex. As this thesis has shown, several early life parameters are risk factors for adverse growth patterns and cardiovascular health. However, more work is needed to understand how these early life parameters are related to one another and could compound on one another potentially increasing risk even further. Recent advances in statistics is starting to help answer this through the use of mixture models (e.g. BKMR, BWQS) and the "exposome" approach which considers the combined effects of several factors (e.g. chemical, lifestyle, social, urban). This type of

research will require continuous innovation and development of new methods to analyze multiple exposures that will create a more comprehensive picture of real world human exposure.

In recent years work has been conducted to better understand the mechanisms behind the rise of lipid levels during pregnancy which occur primarily to increase nutrient availability for the growing placenta and fetus (von Versen-Hoeynck and Power, 2007). However, information is still lacking on understanding the mechanisms underlining the effects of EDC exposure on growth and cardiovascular health. Research points to mechanisms implicated in the oxidative stress response such as the PPARs (Houben et al., 2017). However, further studies are needed, both longitudinal cohort studies and in vivo studies, to identify biomarkers related to these effects.

7. CONCLUSIONS

- Maternal metabolic parameters, prepregnancy BMI, gestational weight gain, and triglyceride concentrations, may be associated with their offspring's BMI growth trajectories during early childhood. Prepregnancy obesity and excessive gestational weight gain may lead to BMI trajectories characterized by accelerated growth, regardless of birth size. Conversely, inadequate gestational weight gain may increase the probability of belonging to a trajectory of lower birth size followed by a slower BMI gain. Higher maternal triglyceride concentrations may decrease the probability of belonging to BMI trajectories of lower birth size followed by accelerated or slower BMI gain.

- Early life growth may influence cardiovascular health during early adolescence. Specifically, children with a growth trajectory characterized by accelerated growth, particularly those born at a lower birth size, may be more likely to have higher levels of systolic and diastolic blood pressure and increased pulse wave velocity during early adolescence.

- Exposure to environmental chemicals is ubiquitous, and those of higher socioeconomic position may be at higher risk of exposure than those of lower socioeconomic position. Families of higher social position may be at higher risk of exposure to persistent pesticides, PFASs, phenols, OP pesticides, BPA, Hg and As. While families of lower social position may be at risk of higher exposure to Cd, Pb, and phthalates; particularly DEHP metabolites.

- Early life exposure to prenatal OCs, PFNA, and a mixture of 23 chemicals may increase the risk of belonging to BMI trajectories characterized by accelerated growth, departing from either higher or lower birth size.

- Early life exposure to prenatal urinary phthalate metabolites and phenols, and their mixture does not seem to be associated with early adolescent measures of cardiovascular health. Future longitudinal studies assessing these

associations would benefit from using repeat urinary measurements for exposure assessment.

- Early life exposure to maternal metabolic parameters and chemical contaminants appear to have a potentially adverse effect of child growth and cardiovascular health, which may be modified by socioeconomic position. Health initiatives aimed at improving maternal and child health should be intensified to promote healthy weight status in women of childbearing age. Further, environmental regulations should be reviewed and behavior changes should be encouraged to reduce the levels of chemical exposure in the general population.

REFERENCES

Adair, L., 2007. Size at Birth and Growth Trajectories to Young Adulthood. Am. J. Hum. Biol. 19, 327–333. https://doi.org/10.1002/ajhb

Adair, L.S., Cole, T.J., 2003. Rapid child growth raises blood pressure in adolescent boys who were thin at birth. Hypertension 41, 451–6. https://doi.org/10.1161/01.HYP.0000054212.23528.B2

Agier, L., Slama, R., Basagaña, X., 2020. Relying on repeated biospecimens to reduce the effects of classical-type exposure measurement error in studies linking the exposome to health. Env. Res. 186. https://doi.org/10.1016/j.envres.2020

Azur, M., Stuart, E., Frangakis, C., Leaf, P., 2010. Multiple imputation by chained equations: what is it and how does it work? Int. J. Methods Psychiatr. Res. 20, 40–9. https://doi.org/10.1002/mpr.329

Bae, S., Lim, Y.H., Lee, Y.A., Shin, C.H., Oh, S.Y., Hong, Y.C., 2017. Maternal Urinary Bisphenol A Concentration during Midterm Pregnancy and Children's Blood Pressure at Age 4. Hypertension 69, 367–374. https://doi.org/10.1161/HYPERTENSIONAHA.116.08281

Bahls, C., 2011. Health policy brief: Achieving equity in health, Health Affairs.

Barker, D., 2007. The origins of the developmental origins theory. J. Intern. Med. 261, 412–417. https://doi.org/10.1111/j.1365-2796.2007.01809.x

Barker, D., Osmond, C., 1986. Infant mortality, childhood nutrition, and ischaemic heart disease in England and Wales. Lancet 1, 1077–81. https://doi.org/10.1016/s0140-6736(86)91340-1

Barker, D.J.P., Osmond, C., Forsén, T.J., Kajantie, E., Eriksson, J.G., 2005. Trajectories of growth among children who have coronary events as adults. N. Engl. J. Med. 353, 1802–1809. https://doi.org/10.1056/NEJMoa044160

Barouki, R., Gluckman, P.D., Grandjean, P., Hanson, M., Heindel, J.J., 2012. Developmental origins of non-communicable disease : Implications for research and public health. Environ. Heal. 11, 1–9.

Bartels, Ä., O'Donoghue, K., 2011. Cholesterol in pregnancy: a review of knowns and unknowns. Obstet. Med. 4, 147–151. https://doi.org/10.1258/om.2011.110003

Berman, Y.E., Doherty, D.A., Main, K.M., Frederiksen, H., Hickey, M., Keelan, J.A., Newnham, J.P., Hart, R.J., 2021. Associations between prenatal exposure to phthalates and timing of menarche and growth and adiposity into adulthood: A twenty-years birth cohort study. Int. J. Environ. Res. Public Health 18, 1–20. https://doi.org/10.3390/ijerph18094725

Bobb, J.F., Claus Henn, B., Valeri, L., Coull, B.A., 2018. Statistical software for analyzing the health effects of multiple concurrent exposures via Bayesian kernel machine regression. Environ. Heal. A Glob. Access Sci. Source 17, 1–10. https://doi.org/10.1186/s12940-018-0413-y

Borrell, L.N., Factor-Litvak, P., Wolff, M.S., Susser, E., Matte, T.D., 2004. Effect of socioeconomic status on exposures to polychlorinated biphenyls (PCBs) and dichlorodiphenyldichloroethylene (DDE) among pregnant African-American women. Arch. Environ. Health 59, 250–255. https://doi.org/10.3200/AEOH.59.5.250-255

Boyer, B.P., Nelson, J.A., Holub, S.C., 2015. Childhood body mass index trajectories predicting cardiovascular risk in adolescence. J. Adolesc. Heal. 56, 599–605. https://doi.org/10.1016/j.jadohealth.2015.01.006

Brantsæter, A., Whitworth, K., Ydersbond, T., Haug, L., Haugen, M., Knutsen, H., Thomsen, C., Meltzer, H., Becher, G., Sabaredzovic, A., Hoppin, J., Eggesbø, M., Longnecker, M., 2013. Determinants of plasma concentrations of perfluoroalkyl substances in pregnant Norwegian women. Env. Int. 54, 74–84. https://doi.org/10.1007/s12020-009-9266-z.A

Braun, J.M., 2016. Early-life exposure to EDCs: role in childhood obesity and neurodevelopment. Nat. Rev. Endocrinol. 13, 161–173. https://doi.org/10.1038/nrendo.2016.186

Braun, J.M., Kalkbrenner, A.E., Calafat, A.M., Bernert, J.T., Ye, X., Silva, M.J., Barr, D.B., Sathyanarayana, S., Lanphear, B.P., 2011. Variability and predictors of urinary bisphenol a concentrations during pregnancy. Environ. Health Perspect. 119, 131–137. https://doi.org/10.1289/ehp.1002366

Buffarini, R., Restrepo-Méndez, M.C., Silveira, V.M., Gonçalves, H.D., Oliveira, I.O., Menezes, A.M., Formoso Assunção, M.C., 2018. Growth across life course and cardiovascular risk markers in 18-year-old adolescents: The 1993 Pelotas birth cohort. BMJ Open 8, 1–8. https://doi.org/10.1136/bmjopen-2017-019164

Cano-Sancho, G., Salmon, A.G., La Merrill, M.A., 2017. Association between Exposure to p,p-DDT and Its Metabolite p,p-DDE with Obesity: Integrated Systematic Review and Meta-Analysis. Env. Heal. Perspect 1–15.

Caruana, E.J., Roman, M., Hernández-Sánchez, J., Solli, P., 2015. Longitudinal studies. J. Thorac. Dis. 7, E537–E540. https://doi.org/10.3978/j.issn.2072-1439.2015.10.63

Casals-Casas, C., Desvergne, B., 2011. Endocrine Disruptors : From Endocrine to Metabolic Disruption. Annu. Rev. Physiol. 73, 135–62. https://doi.org/10.1146/annurev-physiol-012110-142200

Casas, L., Fernández, M.F., Llop, S., Guxens, M., Ballester, F., Olea, N., Irurzun, M.B., Rodríguez, L.S.M., Riaño, I., Tardón, A., Vrijheid, M., Calafat, A.M., Sunyer, J., 2011. Urinary concentrations of phthalates and phenols in a population of Spanish pregnant women and children. Environ. Int. 37, 858–866. https://doi.org/10.1016/j.envint.2011.02.012

Casas, M., Basagaña, X., Sakhi, A.K., Haug, L.S., Philippat, C., Granum, B., Manzano-Salgado, C.B., Brochot, C., Zeman, F., de Bont, J., Andrusaityte, S., Chatzi, L., Donaire-Gonzalez, D., Giorgis-Allemand, L., Gonzalez, J.R., Gracia-Lavedan, E., Grazuleviciene, R., Kampouri, M., Lyon-Caen, S., Pañella, P., Petraviciene, I., Robinson, O., Urquiza, J., Vafeiadi, M., Vernet, C., Waiblinger, D., Wright, J., Thomsen, C., Slama, R., Vrijheid, M., 2018. Variability of urinary concentrations of non-persistent chemicals in pregnant women and school-aged children. Environ. Int. 121, 561–573. https://doi.org/10.1016/j.envint.2018.09.046

Castellano, J.M., Narula, J., Castillo, J., Fuster, V., 2014. Promoting Cardiovascular Health Worldwide: Strategies, Challenges, and Opportunities. Rev. Española Cardiol. (English Ed. 67, 724–730. https://doi.org/10.1016/j.rec.2014.01.023

CDC, 2017. Bisphenol A (BPA) Factsheet [WWW Document].

Charakida, M., Jones, A., Falaschetti, E., Khan, T., Finer, N., Sattar, N., Hingorani, A., Lawlor, D.A., Smith, G.D., Deanfield, J.E., 2012. Childhood obesity and vascular phenotypes: A population study. J. Am. Coll. Cardiol. 60, 2643–2650. https://doi.org/10.1016/j.jacc.2012.08.1017

Chrestani, M.A., Santos, I.S., Horta, B.L., Dumith, S.C., de Oliveira Dode, M.A.S., 2013. Associated Factors for Accelerated Growth in Childhood: A Systematic Review. Matern. Child

Health J. 17, 512–519. https://doi.org/10.1007/s10995-012-1025-8
Colicino, E., Pedretti, N.F., Busgang, S., Gennings, C., 2020. Per- And poly-fluoroalkyl substances and bone mineral density: Results from the Bayesian weighted quantile sum regression. Environ. Epidemiol. 4, e092. https://doi.org/10.1101/19010710
Committee on the Health Risks of Phthalates, 2008. Phthalate Exposure Assessment in Humans, in: Phthalates and Cumulative Risk Assessment: The Tasks Ahead. p. 2.
Cote, A.T., Phillips, A.A., Harris, K.C., Sandor, G.G.S., Panagiotopoulos, C., Devlin, A.M., 2015. Obesity and arterial stiffness in children: Systematic review and meta-analysis. Arterioscler. Thromb. Vasc. Biol. 35, 1038–1044. https://doi.org/10.1161/ATVBAHA.114.305062
Crozier, S.R., Robinson, S.M., Borland, S.E., Godfrey, K.M., Cooper, C., Inskip, H., SWS Study Group, 2009. Europe PMC Funders Group Do women change their health behaviours in pregnancy ? Findings from the Southampton Women ' s Survey. Paediatr Perinat Epidemiol. 23, 446–453. https://doi.org/10.1111/j.1365-3016.2009.01036.x
Deierlein, A.L., Siega-Riz, A.M., Herring, A.H., Adair, L.S., Daniels, J.L., 2012. Gestational weight gain and predicted changes in offspring anthropometrics between early infancy and 3 years. Pediatr. Obes. 7, 134–142. https://doi.org/10.1111/j.2047-6310.2011.00025.x
Diamanti-Kandarakis, E., Bourguignon, J., Giudice, L., Hauser, R., Prins, G., Soto, A., Zoeller, R., Gore, A., 2009. Endocrine-Disrupting Chemicals: An Endocrine Society Scientific Statement. Endocr Rev. 30, 293–342.
Diesel, J.C., Eckhardt, C.L., Day, N.L., Brooks, M.M., Arslanian, S.A., Bodnar, L.M., 2015. Gestational weight gain and offspring longitudinal growth in early life. Ann. Nutr. Metab. 67, 49–57. https://doi.org/10.1159/000437149
Donald, A.E., Charakida, M., Falaschetti, E., Lawlor, D.A., Halcox, J.P., Golding, J., Hingorani, A.D., Smith, G.D., Deanfield, J.E., 2010. Determinants of vascular phenotype in a large childhood population: The avon longitudinal study of parents and children (ALSPAC). Eur. Heart J. 31, 1502–1510. https://doi.org/10.1093/eurheartj/ehq062
Druet, C., Stettler, N., Sharp, S., Simmons, R., Cooper, C., Smith, G., Ekelund, U., Lévy-Marchal, C., Jarvelin, M., Kuh, D., Ong,

K., 2012. Prediction of childhood obesity by infancy weight gain: an individual-level meta-analysis. Paediatr Perinat Epidemiol. 26, 19–26. https://doi.org/10.1111/j.1365-3016.2011.01213

Dulloo, A.G., Jacquet, J., Seydoux, J., Montani, J.-P., 2006. The thrifty 'catch-up fat' phenotype: its impact on insulin sensitivity during growth trajectories to obesity and metabolic syndrome. Int. J. Obes. 30, S23–S35. https://doi.org/10.1038/sj.ijo.0803516

Duncan, T.E., Duncan, S.C., 2004. An Introduction to Latent Growth Curve Modeling. Behav. Ther. 35, 333–363.

Endocrine Society, 2021. What You Can Do About EDCs [WWW Document].

Eriksson, J.G., Kajantie, E., Lampl, M., Osmond, C., 2015. Trajectories of body mass index amongst children who develop type 2 diabetes as adults. J. Intern. Med. 278, 219–226. https://doi.org/10.1111/joim.12354

European Commission, 2020. Poly- and perfluoroalkyl substances (PFAS).

Evans, G., 1992. Testing the Validity of the Goldthorpe Class Schema. Eur. Sociol. Rev. 8, 211–232.

Faber, J., Fonseca, L.M., 2014. How sample size influences research outcomes. Evidence-based Orthod. 19, 27–29. https://doi.org/10.1590/2176-9451.19.4.027-029.ebo

Ferguson, K.K., Chen, Y.H., Vanderweele, T.J., McElrath, T.F., Meeker, J.D., Mukherjee, B., 2017. Mediation of the relationship between maternal phthalate exposure and preterm birth by oxidative stress with repeated measurements across pregnancy. Environ. Health Perspect. 125, 488–494. https://doi.org/10.1289/EHP282

Fiscella, K., Franks, P., Gold, M., Clancy, C., 2000. Inequality in quality: addressing socioeconomic, racial, and ethnic disparities in health care. JAMA 283, 2579–84.

Fisher, M., Arbuckle, T.E., Liang, C.L., LeBlanc, A., Gaudreau, E., Foster, W.G., Haines, D., Davis, K., Fraser, W.D., 2016. Concentrations of persistent organic pollutants in maternal and cord blood from the maternal-infant research on environmental chemicals (MIREC) cohort study. Environ. Health 15, 59. https://doi.org/10.1186/s12940-016-0143-y

Franks, P., Hanson, R., Knowler, W., Sievers, M., Bennett, M., Looker, H., 2010. Childhood Obesity, Other Cardiovascular

Risk Factors, and Premature Death. N. Engl. J. Med. 362, 485–493. https://doi.org/10.1056/NEJMoa0904130.Childhood

Friedemann, C., Heneghan, C., Mahtani, K., Thompson, M., Perera, R., Ward, A., 2012. Cardiovascular disease risk in healthy children and its association with body mass index: systematic review and meta-analysis. BMJ e4759. https://doi.org/10.1136/bmj.e4759

Fu, X., Xu, J., Zhang, R., Yu, J., 2020. The association between environmental endocrine disruptors and cardiovascular diseases: A systematic review and meta-analysis. Environ. Res. 187, 109464. https://doi.org/10.1016/j.envres.2020.109464

Giles, L.C., Whitrow, M.J., Davies, M.J., Davies, C.E., Rumbold, a R., Moore, V.M., 2015. Growth trajectories in early childhood, their relationship with antenatal and postnatal factors, and development of obesity by age 9 years: results from an Australian birth cohort study. Int. J. Obes. 39, 1–8. https://doi.org/10.1038/ijo.2015.42

Gingrich, J., Ticiani, E., Veiga-Lopez, A., 2020. Placenta Disrupted: Endocrine Disrupting Chemicals and Pregnancy. Trends Endocrinol. Metab. 31, 508–524. https://doi.org/10.1016/j.tem.2020.03.003

Golestanzadeh, M., Riahi, R., Kelishadi, R., 2019. Association of exposure to phthalates with cardiometabolic risk factors in children and adolescents: a systematic review and meta-analysis. Environ. Sci. Pollut. Res. 26, 35670–35686. https://doi.org/10.1007/s11356-019-06589-7

Gore, A.C., Chappell, V.A., Fenton, S.E., Flaws, J.A., Nadal, A., Prins, G.S., Toppari, J., Zoeller, R.T., 2015. Executive Summary to EDC-2: The Endocrine Society's second Scientific Statement on endocrine-disrupting chemicals. Endocr. Rev. 36, 593–602. https://doi.org/10.1210/er.2015-1093

Gosens, I., Delmaar, C.J.E., Ter Burg, W., De Heer, C., Schuur, A.G., 2014. Aggregate exposure approaches for parabens in personal care products: A case assessment for children between 0 and 3 years old. J. Expo. Sci. Environ. Epidemiol. 24, 208–214. https://doi.org/10.1038/jes.2013.33

Güil-Oumrait, N., Valvi, D., Garcia-Esteban, R., Guxens, M., 2021. Prenatal exposure to persistent organic pollutants and markers of obesity and cardiometabolic risk in Spanish adolescents. Environ. Int. 151, 1–12.

https://doi.org/10.1016/j.envint.2021.106469
Haga, C., Kondo, N., Suzuki, K., Sato, M., Ando, D., Yokomichi, H., Tanaka, T., Yamagata, Z., 2012. Developmental Trajectories of Body Mass Index Among Japanese Children and Impact of Maternal Factors during Pregnancy. PLoS One 7, e51896. https://doi.org/10.1371/journal.pone.0051896
Hanvey, A.N., Mensah, F.K., Clifford, S.A., Wake, M., 2017. Adolescent cardiovascular functional and structural outcomes of growth trajectories from infancy: Prospective community-based study. Child. Obes. 13, 154–163. https://doi.org/10.1089/chi.2016.0263
Heindel, J.J., Vandenberg, L.N., 2015. Developmental origins of health and disease: A paradigm for understanding disease cause and prevention. Curr. Opin. Pediatr. 27, 248–253. https://doi.org/10.1097/MOP.0000000000000191
Heude, B., Thiébaugeorges, O., Goua, V., Forhan, A., Kaminski, M., Foliguet, B., Schweitzer, M., Magnin, G., Charles, M.A., 2012. Pre-Pregnancy Body Mass Index and Weight Gain During Pregnancy: Relations with Gestational Diabetes and Hypertension, and Birth Outcomes. Matern. Child Health J. 16, 355–363. https://doi.org/10.1007/s10995-011-0741-9
Hicken, M.T., Gee, G.C., Morenoff, J., Connell, C.M., Snow, R.C., Hu, H., 2012. A novel look at racial health disparities: The interaction between social disadvantage and environmental health. Am. J. Public Health 102, 2344–2351. https://doi.org/10.2105/AJPH.2012.300774
Horta, B.L., Barros, F.C., Victora, C.G., Cole, T.J., 2003. Early and late growth and blood pressure in adolescence. J. Epidemiol. Community Health 57, 226–230. https://doi.org/10.1136/jech.57.3.226
Houben, A., Martens, R., Stehouwer, C., 2017. Assessing Microvascular Function in Humans from a Chronic Disease Perspective. J. Am. Soc. Nephrol. 28, 3461–3472. https://doi.org/10.1681/ASN.2017020157
Howe, L., Tilling, K., Galobardes, B., Lawlor, D., 2016. Loss to Follow-up in Cohort Studies Bias in Estimates of Socioeconomic Inequalities. Epidemiology 24, 1–9. https://doi.org/10.1097/EDE.0b013e31827623b1
Høyer, B., Ramlau-Hansen, C., Vrijheid, M., Valvi, D., Pedersen, H., Zviezdai, V., Jönsson, B., Lindh, C., Bonde, J., Toft, G., 2015. Anthropometry in 5- to 9-Year-Old Greenlandic and

Ukrainian Children in Relation to Prenatal Exposure to Perfluorinated Alkyl Substances. Environ. Health Perspect. 123, 841–846.

Hudson, L.D., Rapala, A., Khan, T., Williams, B., Viner, R.M., 2015. Evidence for contemporary arterial stiffening in obese children and adolescents using pulse wave velocity: A systematic review and meta-analysis. Atherosclerosis 241, 376–386. https://doi.org/10.1016/j.atherosclerosis.2015.05.014

Husøy, T., Andreassen, M., Hjertholm, H., Carlsen, M.H., Norberg, N., Sprong, C., Papadopoulou, E., Sakhi, A.K., Sabaredzovic, A., Dirven, H.A.A.M., 2019. The Norwegian biomonitoring study from the EU project EuroMix: Levels of phenols and phthalates in 24-hour urine samples and exposure sources from food and personal care products. Environ. Int. 132, 1–13. https://doi.org/10.1016/j.envint.2019.105103

Hutcheon, J.A., Chiolero, A., Hanley, J.A., 2010. Random measurement error and regression dilution bias. BMJ c2289.

Huxley, R.R., Shiell, A.W., Law, C.M., 2000. The role of size at birth and postnatal catch-up growth in determining systolic blood pressure: A systematic review of the literature. J. Hypertens. 18, 815–831. https://doi.org/10.1097/00004872-200018070-00002

Iszatt, N., Stigum, H., Verner, M., White, R.A., Govarts, E., Murinova, L.P., 2015. Prenatal and Postnatal Exposure to Persistent Organic Pollutants and Infant Growth : A Pooled Analysis of Seven European Birth Cohorts. Env. Heal. Perspect 123, 730–736.

Jolliffe, I.T., Cadima, J., 2016. Principal component analysis : a review and recent developments. Phil.Trans.R.Soc.A 374, 1–16.

Juonala, M., Magnussen, C.G., Berenson, G.S., Venn, A., Burns, T.L., Sabin, M.A., Srinivasan, S.R., Daniels, S.R., Davis, P.H., Chen, W., Sun, C., Cheung, M., Viikari, J.S., Dwyer, T., Raitakari, O.T., 2011. Childhood adiposity, adult adiposity, and cardiovascular risk factors. N. Engl. J. Med. 365, 1876–1885. https://doi.org/10.1056/NEJMoa1010112

Kelishadi, R., Poursafa, P., 2014. A Review on the Genetic, Environmental, and Lifestyle Aspects of the Early-Life Origins of Cardiovascular Disease. Curr. Probl. Pediatr. Adolesc. Health Care 44, 54–72. https://doi.org/10.1016/j.cppeds.2013.12.005

Kristman, V., Manno, M., Côté, P., 2004. Loss to follow-up in cohort studies: how much is too much? Eur J Epidemiol. 19, 751–60. https://doi.org/10.1023/b:ejep.0000036568.02655.f8.

Krönke, A.A., Jurkutat, A., Schlingmann, M., Poulain, T., Nüchter, M., Hilbert, A., Kiviranta, H., 2021. Persistent organic pollutants in pregnant women potentially affect child development and thyroid hormone status. Pediatr. Res. Online ahe. https://doi.org/10.1038/s41390-021-01488-5

La Merrill, M., Birnbaum, L., 2011. Childhood obesity and environmental chemicals. Mt Sinai J Med 78, 22–48. https://doi.org/10.1002/msj.20229.CHILDHOOD

La Merrill, M., Emond, C., Kim, M.J., Antignac, J.P., Le Bizec, B., Clément, K., Birnbaum, L.S., Barouki, R., 2013. Toxicological function of adipose tissue: Focus on persistent organic pollutants. Environ. Health Perspect. 121, 162–169. https://doi.org/10.1289/ehp.1205485

Landrigan, P.J., Goldman, L.R., 2011. Children s Vulnerability To Toxic Chemicals: A Challenge And Opportunity To Strengthen Health And Environmental Policy. Health Aff. 30, 842–850. https://doi.org/10.1377/hlthaff.20.2.225

Lauritzen, H.B., Larose, T.L., Øien, T., Sandanger, T.M., Odland, J.Ø., Bor, M. Van De, Jacobsen, G.W., 2018. Prenatal exposure to persistent organic pollutants and child overweight/obesity at 5-year follow-up: a prospective cohort study. Environ. Heal. 17, 1–12. https://doi.org/10.1186/s12940-017-0338-x

Leunissen, R.W.J., Kerkhof, G.F., Stijnen, T., Hokken-Koelega, A., 2009. Timing and tempo of first-year rapid growth in relation to cardiovascular and metabolic risk profile in early adulthood. JAMA - J. Am. Med. Assoc. 301, 2234–2242. https://doi.org/10.1001/jama.2009.761

Li, L.J., Ikram, M.K., Wong, T.Y., 2016. Retinal vascular imaging in early life: Insights into processes and risk of cardiovascular disease. J. Physiol. 594, 2175–2203. https://doi.org/10.1113/JP270947

Liew, Z., Goudarzi, H., Oulhote, Y., 2018. Developmental Exposures to Perfluoroalkyl Substances (PFASs): An Update of Associated Health Outcomes, Current environmental health reports. https://doi.org/10.1007/s40572-018-0173-4

Lim, S., Ha, M., Hwang, S.S., Son, M., Kwon, H.J., 2015. Disparities in children’s blood lead and mercury levels

according to community and individual socioeconomic positions. Int. J. Environ. Res. Public Health 12, 6232–6248. https://doi.org/10.3390/ijerph120606232

Liu, B., Geng, H., Yang, J., Zhang, Y., Deng, L., Chen, W., Wang, Z., 2016. Early pregnancy fasting plasma glucose and lipid concentrations in pregnancy and association to offspring size: a retrospective cohort study. BMC Pregnancy Childbirth 16, 56. https://doi.org/10.1186/s12884-016-0846-7

Longnecker, M., Klebanoff, M., Gladen, B., Berendes, H., 1999. Serial levels of serum organochlorines during pregnancy and postpartum. Arch Env. Heal. 54, 110–4. https://doi.org/10.1080/00039899909602244

Lunder, S., Hovander, L., Athanassiadis, I., Bergman, A., 2010. Significantly higher polybrominated diphenyl ether levels in young U.S. children than in their mothers. Environ. Sci. Technol. 44, 5256–62. https://doi.org/10.1021/es1009357

Lurbe, E., Torro, I., Garcia-Vicent, C., Alvarez, J., Fernández-Fornoso, J.A., Redon, J., 2012. Blood pressure and obesity exert independent influences on pulse wave velocity in youth. Hypertension 60, 550–555. https://doi.org/10.1161/HYPERTENSIONAHA.112.194746

Magnussen, C.G., Smith, K.J., 2016. Pediatric blood pressure and adult preclinical markers of cardiovascular disease. Clin. Med. Insights Blood Disord. 9, 1–8. https://doi.org/10.4137/CMBD.S18887

Maisonet, M., Terrell, M.L., Mcgeehin, M.A., Christensen, K.Y., Holmes, A., 2012. Maternal Concentrations of Polyfluoroalkyl Compounds during Pregnancy and Fetal and Postnatal Growth in British Girls. Environ. Health Perspect. 120, 1432–1437.

Mamsen, L.S., Jönsson, B.A.G., Lindh, C.H., Olesen, R.H., Larsen, A., Ernst, E., Kelsey, T.W., Andersen, C.Y., 2017. Concentration of perfluorinated compounds and cotinine in human foetal organs, placenta, and maternal plasma. Sci. Total Environ. 596–597, 97–105. https://doi.org/10.1016/j.scitotenv.2017.04.058

Manzano-Salgado, C.B., Casas, M., Lopez-Espinosa, M.J., Ballester, F., Iñiguez, C., Martinez, D., Romaguera, D., Fernández-Barrés, S., Santa-Marina, L., Basterretxea, M., Schettgen, T., Valvi, D., Vioque, J., Sunyer, J., Vrijheid, M., 2017. Prenatal exposure to perfluoroalkyl substances and cardiometabolic risk in children from the spanish INMA birth

cohort study. Environ. Health Perspect. 1–10. https://doi.org/10.1289/EHP1330

Manzano-Salgado, C.B., Casas, M., Lopez-Espinosa, M.J., Ballester, F., Martinez, D., Ibarluzea, J., Santa-Marina, L., Vioque, J., Sunyer, J., Vrijheid, M., 2016. Variability of perfluoroalkyl substance concentrations in pregnant women by socio-demographic and dietary factors in a Spanish birth cohort. Environ. Int. 92–93, 357–365. https://doi.org/10.1016/j.envint.2016.04.004

Mariana, M., Feiteiro, J., Verde, I., Cairrao, E., 2016. The effects of phthalates in the cardiovascular and reproductive systems: A review. Environ. Int. 94, 758–776. https://doi.org/10.1016/j.envint.2016.07.004

McCleary, L., 2002. Using multiple imputation for analysis of incomplete data in clinical research. Nurs Res. 51, 339–43. https://doi.org/10.1097/00006199-200209000-00012

Mendez, M.A., Garcia-Esteban, R., Guxens, M., Vrijheid, M., Kogevinas, M., Goñi, F., Fochs, S., Sunyer, J., 2011. Prenatal Organochlorine Compound Exposure , Rapid Weight Gain , and Overweight in Infancy. Env. Heal. Perspect 119, 272–278. https://doi.org/10.1289/ehp.1002169

Misra, V.K., Trudeau, S., Perni, U., 2011. Maternal serum lipids during pregnancy and infant birth weight: the influence of prepregnancy BMI. Obesity (Silver Spring). 19, 1476–1481. https://doi.org/10.1038/oby.2011.43

Mook-Kanamori, D.O., Durmuş, B., Sovio, U., Hofman, A., Raat, H., Steegers, E.A.P., Jarvelin, M.-R., Jaddoe, V.W. V, 2011. Fetal and infant growth and the risk of obesity during early childhood: the Generation R Study. Eur J Endocrinol 165, 623–30. https://doi.org/10.1530/EJE-11-0067

Mora, A.M., Oken, E., Rifas-shiman, S.L., Webster, T.F., Gillman, M.W., Calafat, A.M., Ye, X., Sagiv, S.K., 2017. Prenatal Exposure to Perfluoroalkyl Substances and Adiposity in Early and Mid-Childhood. Environ. Health Perspect. 125, 467–473.

Morrens, B., Bruckers, L., Hond, E. Den, Nelen, V., Schoeters, G., Baeyens, W., Van Larebeke, N., Keune, H., Bilau, M., Loots, I., 2012. Social distribution of internal exposure to environmental pollution in Flemish adolescents. Int. J. Hyg. Environ. Health 215, 474–481. https://doi.org/10.1016/j.ijheh.2011.10.008

Murray, R., Godfrey, K., Lillycrop, K., 2015. The Early Life

Origins of Cardiovascular Disease. Genet. Environ. Behav. Risk Reduct. 9.
Nelson, J.W., Scammell, M.K., Hatch, E.E., Webster, T.F., 2012. Social disparities in exposures to bisphenol A and polyfluoroalkyl chemicals: a cross-sectional study within NHANES 2003-2006. Environ. Health 11, 10. https://doi.org/10.1186/1476-069X-11-10
Newman, A.R., Andrew, N.H., Casson, R.J., 2017. Review of paediatric retinal microvascular changes as a predictor of cardiovascular disease. Clin. Exp. Ophthalmol. 45, 33–44. https://doi.org/10.1111/ceo.12773
Nidens, N., Vogel, M., Körner, A., Kiess, W., 2020. Prenatal exposure to phthalate esters and its impact on child development. Best Pr. Res Clin Endocrinol Metab 101478. https://doi.org/10.1016/j.beem.2020.101478
Nordman, H., Jääskeläinen, J., Voutilainen, R., 2020. Birth Size as a Determinant of Cardiometabolic Risk Factors in Children. Horm. Res. Paediatr. 93, 144–153. https://doi.org/10.1159/000509932
Oakes, M., 2010. NIH: Introductory Social and Behavioral Science Training Materials "Measuring socioeconomic status."
Oken, E., Gillman, M.W., 2003. Fetal origins of obesity. Obes. Res. 11, 496–506. https://doi.org/10.1038/oby.2003.69
Olander, E.K., Smith, D.M., Darwin, Z., 2018. Health behaviour and pregnancy: a time for change. J. Reprod. Infant Psychol. 36, 1–3. https://doi.org/10.1080/02646838.2018.1408965
Olujimi, O.O., Fatoki, O.S., Odendaal, J.P., Okonkwo, J.O., 2010. Endocrine disrupting chemicals (phenol and phthalates) in the South African environment: A need for more monitoring. Water SA 36, 671–682. https://doi.org/10.4314/wsa.v36i5.62001
Ouyang, F., Zhang, G.-H., Du, K., Shen, L., Ma, R., Wang, Xia, Wang, Xiaobin, Zhanga, J., 2020. Maternal prenatal urinary bisphenol A level and child cardio-metabolic risk factors: A prospective cohort study. Env. Pollut. 265(Pt A). https://doi.org/10.1016/j.envpol.2020.115008
Pampel, F.C., Krueger, P., Denney, J., 2010. Socioeconomic disparities in health behaviors. Annu. Rev. Sociol. 36, 349–370. https://doi.org/10.1146/annurev.soc.012809.102529.Socioeconomic

Payne, R.A., 2012. Cardiovascular risk. Br. J. Clin. Pharmacol. 74, 396–410. https://doi.org/10.1111/j.1365-2125.2012.04219.x

Perng, W., Hajj, H., Belfort, M., Rifas-Shiman, S., Kramer, M., Gillman, M., Oken, E., 2016. Birth size, early weight gain, and mid-childhood cardiometabolic health. J.Pediatr. 122–130. https://doi.org/10.3109/10253890.2015.1094689.Post-Traumatic

Pignatelli, P., Menichelli, D., Pastori, D., Violi, F., 2018. Oxidative stress and cardiovascular disease: new insights. Kardiol Pol. 76, 713–22. https://doi.org/10.5603/KP.a2018.0071

Pizzi, C., Cole, T.J., Richiardi, L., dos-Santos-Silva, I., Corvalan, C., De Stavola, B., 2014. Prenatal Influences on Size, Velocity and Tempo of Infant Growth: Findings from Three Contemporary Cohorts. PLoS One 9, e90291. https://doi.org/10.1371/journal.pone.0090291

Reusz, G., Cseprekal, O., Temmar, M., Kis, E., Cherif, A., Thaleb, A., Fekete, A., Szabó, A., Benetos, A., Salvi, P., 2010. Reference values of pulse wave velocity in healthy children and teenagers. Hypertension 56, 217–24. https://doi.org/10.1161/HYPERTENSIONAHA.110.152686

Roth, G., Mensah, G., Johnson, C., Addolorato, G., Ammirati, E., Baddour, L., Barengo, N., Beaton, A., Benjamin, E., Benziger, C., Global Burden of Cardiovascular Diseases Writing Group, 2020. Global Burden of Cardiovascular Diseases and Risk Factors, 1990-2019. J. Am. Coll. Cardiol. 76. https://doi.org/10.1016/j.jacc.2020.11.010

Savitz, D., 2014. Invited commentary: interpreting associations between exposure biomarkers and pregnancy outcome. Am. J. Epidemiol. 179, 545–7. https://doi.org/10.1093/aje/kwt314

Schober, S.E., Sinks, T.H., Jones, R.L., Bolger, P.M., McDowell, M., Osterloh, J., Garrett, E.S., Canady, R.A., Dillon, C.F., Sun, Y., Joseph, C.B., Mahaffey, K.R., 2003. Blood mercury levels in US children and women of childbearing age, 1999-2000. Jama 289, 1667–1674. https://doi.org/10.1001/jama.289.13.1667

Senoner, T., Dichtl, W., 2019. Oxidative stress in cardiovascular diseases: Still a therapeutic target? Nutrients 11. https://doi.org/10.3390/nu11092090

Shoaff, J., Papandonatos, G.D., Calafat, A.M., Chen, A., Lanphear, B.P., Ehrlich, S., Kelsey, K.T., Braun, J.M., 2018. Prenatal exposure to perfluoroalkyl substances. Environ. Epidemiol. 2,

1–7. https://doi.org/10.1097/ee9.0000000000000010
Siegrist, M., Hanssen, H., Neidig, M., Fuchs, M., Lechner, F., Stetten, M., Blume, K., Lammel, C., Haller, B., Vogeser, M., Parhofer, K.G., Halle, M., 2014. Association of leptin and insulin with childhood obesity and retinal vessel diameters. Int. J. Obes. 38, 1241–1247. https://doi.org/10.1038/ijo.2013.226
Silveira, P.P., Portella, A.K., Goldani, M.Z., Barbieri, M.A., 2007. Developmental origins of health and disease (DOHaD). J. Pediatr. (Rio. J). 83, 494–504. https://doi.org/10.2223/JPED.1728
Singhal, A., 2017. Long-Term Adverse Effects of Early Growth Acceleration or Catch-Up Growth. Ann. Nutr. Metab. 70, 236–240. https://doi.org/10.1159/000464302
Slining, M.M., Herring, a. H., Popkin, B.M., Mayer-Davis, E.J., Adair, L.S., 2012. Infant BMI trajectories are associated with young adult body composition. J. Dev. Orig. Health Dis. 4, 1–13. https://doi.org/10.1017/S2040174412000554
Sokoloff, K., Fraser, W., Arbuckle, T.E., Fisher, M., Gaudreau, E., LeBlanc, A., Morisset, A.S., Bouchard, M.F., 2016. Determinants of urinary concentrations of dialkyl phosphates among pregnant women in Canada - Results from the MIREC study. Environ. Int. 94, 133–140. https://doi.org/10.1016/j.envint.2016.05.015
Sol, C.M., Santos, S., Asimakopoulos, A.G., Duijts, L., Kannan, K., Trasande, L., Jaddoe, V.W. V, Group, G.R.S., City, N.Y., City, N.Y., City, N.Y., City, Y., City, N.Y., 2020. Associations of maternal phthalate and bisphenol urine concentrations during pregnancy with childhood blood pressure in a population-based prospective cohort study. Env. Int. 138. https://doi.org/10.1016/j.envint.2020.105677
Spencer, E.A., Appleby, P.N., Davey, G.K., Key, T.J., 2001. Validity of self-reported height and weight in 4808 EPIC–Oxford participants. Public Health Nutr. 5, 561–565. https://doi.org/10.1079/phn2001322
Starling, A.P., Adgate, J.L., Hamman, R.F., Kechris, K., Calafat, A., Dabelea, D., 2019. Prenatal exposure to per- and polyfluoroalkyl substances and infant growth and adiposity: the Healthy Start Study. Environ. Int. 131, 1–26. https://doi.org/10.1016/j.envint.2019.104983.Prenatal
Svensson, K., Tanner, E., Gennings, C., Lindh, C., Kiviranta, H., Wikström, S., Bornehag, C.G., 2021. Prenatal exposures to

mixtures of endocrine disrupting chemicals and children's weight trajectory up to age 5.5 in the SELMA study. Sci. Rep. 11, 1–12. https://doi.org/10.1038/s41598-021-89846-5

Szilagyi, J.T., Avula, V., Fry, R.C., 2020. Perfluoroalkyl Substances (PFAS) and Their Effects on the Placenta, Pregnancy, and Child Development: a Potential Mechanistic Role for Placental Peroxisome Proliferator – Activated Receptors (PPARs). Curr. Environ. Heal. Reports. https://doi.org/10.1007/s40572-020-00279-0 EARLY

Thurn, D., Doyon, A., Sözeri, B., Bayazit, A.K., Canpolat, N., Duzova, A., Querfeld, U., Schmidt, B.M.W., Schaefer, F., Wühl, E., Melk, A., Consortium, S., 2015. Aortic Pulse Wave Velocity in Healthy Children and Adolescents : Reference Values for the Vicorder Device and Modifying Factors. Am. J. Hypertens. 28, 1480–1488. https://doi.org/10.1093/ajh/hpv048

Toemen, L., De Jonge, L.L., Gishti, O., Van Osch-Gevers, L., Taal, H.R., Steegers, E.A.P., Hofman, A., Helbing, W.A., Jaddoe, V.W.V., 2016. Longitudinal growth during fetal life and infancy and cardiovascular outcomes at school-age. J. Hypertens. 34, 1396–1406. https://doi.org/10.1097/HJH.0000000000000947

Tu, Y., Tilling, K., Sterne, J., Gilthorpe, M., 2013. A critical evaluation of statistical approaches to examining the role of growth trajectories in the developmental origins of health and disease. Int. J. Epidemiol. 42, 1327–39. https://doi.org/10.1093/ije/dyt157

Tyrrell, J., Melzer, D., Henley, W., Galloway, T.S., Osborne, N.J., 2013. Associations between socioeconomic status and environmental toxicant concentrations in adults in the USA: NHANES 2001-2010. Environ. Int. 59, 328–335. https://doi.org/10.1016/j.envint.2013.06.017

Vafeiadi, M., Georgiou, V., Chalkiadaki, G., Rantakokko, P., Kiviranta, H., Karachaliou, M., Fthenou, E., Venihaki, M., Sarri, K., Vassilaki, M., Kyrtopoulos, S.A., Oken, E., Kogevinas, M., Chatzi, L., 2015. Association of prenatal exposure to persistent organic pollutants with obesity and cardiometabolic traits in early childhood: The rhea mother–child cohort (Crete, Greece). Environ. Health Perspect. 123, 1015–1021. https://doi.org/10.1289/ehp.1409062

Vafeiadi, M., Myridakis, A., Roumeliotaki, T., Margetaki, K., Chalkiadaki, G., Dermitzaki, E., Venihaki, M., Sarri, K.,

Vassilaki, M., Leventakou, V., Stephanou, E.G., Kogevinas, M., Chatzi, L., 2018. Association of early life exposure to phthalates with obesity and cardiometabolic traits in childhood: Sex specific associations. Front. Public Heal. 6, 1–11. https://doi.org/10.3389/fpubh.2018.00327

Valvi, D., Casas, M., Romaguera, D., Monfort, N., Ventura, R., Martinez, D., Sunyer, J., Vrijheid, M., 2015a. Prenatal phthalate exposure and childhood growth and blood pressure: Evidence from the spanish inma-sabadell birth cohort study. Environ. Health Perspect. 123, 1022–1029. https://doi.org/10.1289/ehp.1408887

Valvi, D., Mendez, M.A., Garcia-Esteban, R., Ballester, F., Ibarluzea, J., Goñi, F., Grimalt, J.O., Llop, S., Marina, L.S., Vizcaino, E., Sunyer, J., Vrijheid, M., 2014. Prenatal exposure to persistent organic pollutants and rapid weight gain and overweight in infancy. Obesity 22, 488–496. https://doi.org/10.1002/oby.20603

Valvi, D., Mendez, M.A., Martinez, D., Grimalt, J.O., Torrent, M., Vrijheid, M., 2012. Prenatal Concentrations of Polychlorinated Biphenyls, DDE, and DDT and Overweight in Children: A Prospective Birth Cohort Study. Env. Heal. Perspect 120, 451–457.

Valvi, D., Monfort, N., Ventura, R., Casas, M., Casas, L., Sunyer, J., Vrijheid, M., 2015b. Variability and predictors of urinary phthalate metabolites in Spanish pregnant women. Int. J. Hyg. Environ. Health 218, 220–231. https://doi.org/10.1016/j.ijheh.2014.11.003

van den Dries, M.A., Pronk, A., Guxens, M., Spaan, S., Voortman, T., Jaddoe, V.W., Jusko, T.A., Longnecker, M.P., Tiemeier, H., 2018. Determinants of organophosphate pesticide exposure in pregnant women: A population-based cohort study in the Netherlands. Int. J. Hyg. Environ. Health 221, 489–501. https://doi.org/10.1016/j.ijheh.2018.01.013

van Rossem, L., Wijga, A.H., Brunekreef, B., de Jongste, J.C., Kerkhof, M., Postma, D.S., Gehring, U., Smit, H.A., 2014. Overweight in Infancy: Which Pre- and Perinatal Factors Determine Overweight Persistence or Reduction? A Birth Cohort Followed for 11 Years. Ann. Nutr. Metab. 65, 211–219. https://doi.org/10.1159/000360305

Vernet, C., Philippat, C., Agier, L., Calafat, A.M., Ye, X., Lyon-Caen, S., Hainaut, P., Siroux, V., Schisterman, E.F., Slama, R.,

2019. An Empirical Validation of the Within-subject Biospecimens Pooling Approach to Minimize Exposure Misclassification in Biomarker-based Studies. Epidemiology 30, 756–767. https://doi.org/10.1097/EDE.0000000000001056

Victora, C.G., Adair, L., Fall, C., Hallal, P.C., Martorell, R., Richter, L., Sachdev, H.S., 2008. Maternal and child undernutrition: consequences for adult health and human capital. Lancet 371, 340–357. https://doi.org/10.1016/S0140-6736(07)61692-4

Voerman, E., Santos, S., Golab, B.P., Amiano, P., Ballester, F., Barros, H., Bergström, A., Charles, M.A., Chatzi, L., Chevrier, C., Chrousos, G.P., Corpeleijn, E., Costet, N., Crozier, S., Devereux, G., Eggesbø, M., Ekström, S., Fantini, M.P., Farchi, S., Forastiere, F., Georgiu, V., Godfrey, K.M., Gori, D., Grote, V., Hanke, W., Hertz-Picciotto, I., Heude, B., Hryhorczuk, D., Huang, R.C., Inskip, H., Iszatt, N., Karvonen, A.M., Kenny, L.C., Koletzko, B., Küpers, L.K., Lagström, H., Lehmann, I., Magnus, P., Majewska, R., Mäkelä, J., Manios, Y., McAuliffe, F.M., McDonald, S.W., Mehegan, J., Mommers, M., Morgen, C.S., Mori, T.A., Moschonis, G., Murray, D., Chaoimh, C.N., Nohr, E.A., Andersen, A.M.N., Oken, E., Oostvogels, A.J.J.M., Pac, A., Papadopoulou, E., Pekkanen, J., Pizzi, C., Polanska, K., Porta, D., Richiardi, L., Rifas-Shiman, S.L., Ronfani, L., Santos, A.C., Standl, M., Stoltenberg, C., Thiering, E., Thijs, C., Torrent, M., Tough, S.C., Trnovec, T., Turner, S., van Rossem, L., von Berg, A., Vrijheid, M., Vrijkotte, T.G.M., West, J., Wijga, A., Wright, J., Zvinchuk, O., Sørensen, T.I.A., Lawlor, D.A., Gaillard, R., Jaddoe, V.W.V., 2019. Maternal body mass index, gestational weight gain, and the risk of overweight and obesity across childhood: An individual participant data meta-analysis. PLoS Med. 16, 1–22. https://doi.org/10.1371/journal.pmed.1002744

von Versen-Hoeynck, F., Power, R., 2007. Maternal-fetal metabolism in normal pregnancy and preeclampsia. Front. Biosci. 12, 2457–2470.

Vrijheid, M., Casas, M., Gascon, M., Valvi, D., Nieuwenhuijsen, M., 2016. Environmental pollutants and child health-A review of recent concerns. Int. J. Hyg. Environ. Health 219, 331–342. https://doi.org/10.1016/j.ijheh.2016.05.001

Vrijheid, M., Martinez, D., Aguilera, I., Ballester, F., Basterrechea, M., Esplugues, A., Guxens, M., Larrañaga, M., Lertxundi, A.,

Mendez, M., Murcia, M., Marina, L.S., Villanueva, C.M., Sunyer, J., 2012. Socioeconomic status and exposure to multiple environmental pollutants during pregnancy: evidence for environmental inequity? J. Epidemiol. Community Health 66, 106–113. https://doi.org/10.1136/jech.2010.117408

Vrijkotte, T.G.M., Algera, S.J., Brouwer, I.A., van Eijsden, M., Twickler, M.B., 2011. Maternal Triglyceride Levels during Early Pregnancy are Associated with Birth Weight and Postnatal Growth. J. Pediatr. 159, 736-742.e1. https://doi.org/10.1016/j.jpeds.2011.05.001

Wadhwa, P., Buss, C., Entringer, S., Swanson, J.M., 2009. Developmental Origins of Health and Disease: Brief History of the Approach and Current Focus on Epigenetic Mechanisms. Semin Reprod Med 27, 358–68. https://doi.org/10.1055/s-0029-1237424

Wang, L., Kannan, K., 2013. Characteristic profiles of benzonphenone-3 and its derivatives in urine of children and adults from the United States and China. Environ. Sci. Technol. 47, 12532–12538. https://doi.org/10.1021/es4032908

Wang, Y., Zhu, H., Kannan, K., 2019. A review of biomonitoring of phthalate exposures. Toxics 7, 1–28. https://doi.org/10.3390/TOXICS7020021

Warembourg, C., Maitre, L., Tamayo-Uria, I., Fossati, S., Roumeliotaki, T., Aasvang, G.M., Andrusaityte, S., Casas, M., Cequier, E., Chatzi, L., Dedele, A., Gonzalez, J.R., Gražulevičienė, R., Haug, L.S., Hernandez-Ferrer, C., Heude, B., Karachaliou, M., Krog, N.H., McEachan, R., Nieuwenhuijsen, M., Petraviciene, I., Quentin, J., Robinson, O., Sakhi, A.K., Slama, R., Thomsen, C., Urquiza, J., Vafeiadi, M., West, J., Wright, J., Vrijheid, M., Basagaña, X., 2019. Early-Life Environmental Exposures and Blood Pressure in Children. J. Am. Coll. Cardiol. 74, 1317–1328. https://doi.org/10.1016/j.jacc.2019.06.069

Weatherly, L., Gosse, J.A., 2017. Triclosan Exposure, Transformation, and Human Health Effects. J Toxicol Env. Heal. B Crit Rev. 20, 447–69. https://doi.org/10.1080/10937404.2017.1399306.Triclosan

Winkleby, M.A., Jatulis, D.E., Frank, E., Fortmann, S.P., 1992. Socioeconomic status and health: How education, income, and occupation contribute to risk factors for cardiovascular disease. Am. J. Public Health 82, 816–820.

https://doi.org/10.2105/AJPH.82.6.816
Wong, T., Mitchell, P., 2007. The eye in hypertension. Lancet 369, 425–35. https://doi.org/10.1016/S0140-6736(07)60198-6
World Health Organization (WHO), 2021. Fact sheet: Cardiovascular diseases (CVDs) [WWW Document].
World Health Organization (WHO), 2008. Persistent Organic Pollutants (POPs).
World Health Organization (WHO), 2004. Hexachlorobenzene in drinking water.
World Health Organization (WHO), n.d. Cardiovascular diseases: Data and statistics [WWW Document]. URL https://www.euro.who.int/en/health-topics/noncommunicable-diseases/cardiovascular-diseases/data-and-statistics
Yang, T.C., Peterson, K.E., Meeker, J.D., Zhang, Z., Cantoral, A., Solano, M., Tellez-rojo, M.M., Arbor, A., Infirmary, B.R., Kingdom, U., Arbor, A., Arbor, A., Arbor, A., 2020. Exposure to Bisphenol A and phthalates metabolites in the third trimester of pregnancy and BMI trajectories 13, 550–557. https://doi.org/10.1111/ijpo.12279.Exposure
Yuan, S., Rigor, R., 2010. Chapter 2, Structure and Function of Exchange Microvessels., in: Regulation of Endothelial Barrier Function. Morgan & Claypool Life Sciences.
Zheng, T., Zhang, J., Sommer, K., Bassig, B., Zhang, X., Braun, J., Xu, S., Boyle, P., Zhang, B., Shi, K., Buka, S., Liu, S., Li, Y., Qian, Z., Dai, M., Romano, M., Zou, A., Kelsey, K., 2016. Effects of environmental exposures on fetal and childhood growth trajectories. Ann Glob Heal. 82, 41–99. https://doi.org/10.1016/j.aogh.2016.01.008.
Ziyab, A.H., Karmaus, W., Kurukulaaratchy, R.J., Zhang, H., Arshad, S.H., 2014. Developmental trajectories of Body Mass Index from infancy to 18 years of age: prenatal determinants and health consequences. J. Epidemiol. Community Heal. 68, 934–941. https://doi.org/10.1136/jech-2014-203808

APPENDIX

About the Author

Parisa Montazeri graduated with a Bachelor of Science in Health Science from San Jose State Univerity (2006 – 2011) and a Master of Public Health from Pompeu Fabra University and Autonoma University of Barcelona (2014 – 2016). She joined the Barcelona Institute for Global Health (ISGlobal) in 2017 where the present thesis has been carried out. A summary of the research activity of the author during the thesis is provided below.

Other co-authored papers

- Peralta GP, Abellan A, **Montazeri P**, Basterrechea M, Esplugues A, González-Palacios S, Roda C, Santa-Marina L, Sunyer J, Vrijheid M, Casas M, Garcia-Aymerich J. Early childhood growth is associated with lung function at 7 years: a prospective population-based study. Eur Respir J. 2020;56(6):2000157. doi: 10.1183/13993003.00157-2020.

- Gilles L, Govarts E, Rambaud L, Vogel N, Castaño A, Esteban López M, Rodriguez Martin L, Koppen G, Remy S, Vrijheid M, **Montazeri P**, Birks L, Sepai O, Stewart L, Fiddicke U, Loots I, Knudsen LE, Kolossa-Gehring M, Schoeters G. HBM4EU combines and harmonises human biomonitoring data across the EU, building on existing capacity - The HBM4EU survey. Int J Hyg Environ Health. 2021 Aug 26;237:113809. doi: 10.1016/j.ijheh.2021.113809. Epub ahead of print. PMID: 34455198.

Oral Presentations

- **Montazeri P**, Vrijheid M, Martinez D, Basterrechea M, Fernandez-Somoano A, Guxens M, Iñiguez C, Lertxundi A, Murcia M, Tardon A, Sunyer J, Valvi D. "Maternal metabolic health parameters during pregnancy in relation to early childhood body mass index trajectories". 14ª Jornadas Científicas INMA. Granada, Spain, November 2017.

- **Montazeri P**, Thomsen C, Casas M, de Bont J, Haug LS, Maitre L, Papadopoulou E, Sakhi AK, Slama R, Saulnier PJ, Urquiza J, Grazuleviciene R, Andrusaityte S, McEachan R,

Wright J, Chatzi L, Basagaña X, Vrijheid M. "Social disparities of environmental chemical exposures in pregnant women and their children". ISGlobal Annual Scientific Retreat. Barcelona, Spain, June, 2018.

- **Montazeri P**, Fossati S, Clemente DBP, Cirugeda L, Elosua R, Fernández-Barrés S, Fochs S, Garcia-Esteban R, Marquez S, Pey N, Nawrot TS, Vrijheid M. "Early childhood BMI trajectories in relation to pre-clinical cardiovascular measurements in adolescence". 16ª Jornadas Científicas INMA. Online. November-December 2020.

Poster Communications

- **Montazeri P**, Thomsen C, Casas M, de Bont J, Haug LS, Maitre L, Papadopoulou E, Sakhi AK, Slama R, Saulnier PJ, Urquiza J, Grazuleviciene R, Andrusaityte S, McEachan R, Wright J, Chatzi L, Basagaña X, Vrijheid M. "Social disparities of environmental chemical exposures in pregnant women and their children". Prenatal Programming and Toxicity (PPTOX) VI Conference. Faroe Islands. May, 2018.

- **Montazeri P**, Thomsen C, Casas M, de Bont J, Haug LS, Maitre L, Papadopoulou E, Sakhi AK, Slama R, Saulnier PJ, Urquiza J, Grazuleviciene R, Andrusaityte S, McEachan R, Wright J, Chatzi L, Basagaña X, Vrijheid M. "Social disparities of environmental chemical exposures in pregnant women and their children". ISGlobal PhD Symposium. November, 2017.

- **Montazeri P**, Thomsen C, Casas M, de Bont J, Haug LS, Maitre L, Papadopoulou E, Sakhi AK, Slama R, Saulnier PJ, Urquiza J, Grazuleviciene R, Andrusaityte S, McEachan R, Wright J, Chatzi L, Basagaña X, Vrijheid M. "Associations between social position and environmental contaminants in six European mother-child cohorts". ISGlobal PhD Symposium. November, 2018.

- **Montazeri P**, Fossati S, Warembourg C, Casas M, Clemente DBP, Garcia-Esteban R, Nawrot TS, Vrijheid M. "Prenatal

exposure to phthalates and phenols and preclinical cardiovascular health during early adolescence". 33rd Annual Conference of the International Society for Environmental Epidemiology (ISEE). August, 2021.

Reviews for Peer-Reviewed Scientific Journals

- Environmental Pollution (1x)
- Environmental Health (3x)