Early life exposure to endocrine disrupting chemicals and child health

de Cock, M.

2014

document version
Publisher's PDF, also known as Version of record

4

LInking EDCs in maternal Nutrition to Child health (LINC study) – protocol for prospective cohort to study early life exposure to environmental chemicals and child health

Marijke de Cock, Ilona Quaak, Juliette Legler, and Margot van de Bor

Submitted to BMC Open, Public Health

Abstract

Introduction: The LINC study is a prospective birth cohort designed to study associations between early life environmental exposures and child health, including growth and neurodevelopment.

Methods and analysis: Women are included during the first trimester of pregnancy. Major congenital anomalies and twin births are reasons for exclusion. Information on pregnancy, maternal health, parental anthropometry, and birth (e.g. birth weight, gestational age) are collected through midwives. Women receive questionnaires each trimester regarding amongst others lifestyle, and mental state. At birth cord blood, placenta, meconium and vernix is collected. Parents collect urine of the child shortly after birth and breast milk in the second month after birth. Exposure to a broad range of endocrine disrupting chemicals (EDCs), including dioxins, organochlorine pesiticides, brominated flame retardants, and perfluorinated alkyl acids, will be determined in cord plasma and breast milk. Furthermore various hormones, including leptin and cortisone, are determined in cord plasma.

Ethics and dissemination: This study was approved by the medical ethics committee of the VU University Medical Centre. Consent for the infant is given by the mother, who is specifically required to give consent for both herself as well as her child. Results will be published regardless of the findings of this study, and will be widely disseminated among related medical stakeholders (e.g. midwives and pediatricians), policy makers, and the general public.

Introduction

Chemicals are used worldwide, making everyday life more comfortable. Their integration into modern day society extends to a level that consumers are often unaware of their presence. They are incorporated in common items, e.g. food packaging materials containing bisphenol a (BPA) and phthalates, which may transfer from the packaging material to the food item itself.[1] Furthermore food products and water may contain pesticides, including those banned from production but persistent in the environment.[2] This ubiquitous presence of chemicals inevitably results in human exposure.

Human biomonitoring studies in the United States detected several chemicals such as perfluorinated compounds (PFCs) and polychlorinated biphenyls (PCBs) in 90-100% of the population,[3] including pregnant women.[4] They have also been quantified in amniotic fluid [5 6] and cord blood,[7 8] which indicates that they may pass the placenta and reach the foetus. As the presence of contaminants has also been established in breast milk,[9] it is clear that exposure not only starts prenatally, it also continues in early life.

Research has shown that certain compounds may interfere with the function of hormones (endocrine disrupting chemicals, EDCs), including thyroid hormones, estrogen, and testosterone (reviewed by Bergman et al. [10]), which are involved in various processes in adults, but also in brain development early in life.[11 12] They may also interact with peroxisome proliferator activated receptor (PPAR) α and γ, involved in amongst others adipogenesis.[10] Furthermore, exposure early in life may cause epigenetic modifications, resulting in increased expression or silencing of genes – effects which may be trans-generational.[13] Another point to consider is that exposure early in life may have different effects than exposure in adulthood, as developmental plasticity is much higher in the first period of life.[14]

An increasing number of children nowadays face the diagnosis of diabetes type 2,[15] obesity,[16 17] attention deficit hyperactivity disorder,[18] and autism spectrum disorder.[19] Even though increased risks for each of these health problems have been observed with increased exposure to chemicals,[20-22] results are not unambiguous and variations in methodology complicate comparison between different studies. Furthermore, the focus in most observational research has been on non-dioxin-like PCBs and dichlorodiphenyldichloroethylene (DDE), while other compounds such as perfluorinated alkyl acids, and phthalates have been identified as potential health threats as well, but have not yet been investigated as thoroughly.

The increasing impact of non-communicable diseases in children on society and health care costs has created a need for more knowledge on the role of other factors, such as the environment, in the etiology of these diseases. This has led to a call from the European Union to motivate research on this particular topic. The LInking EDCs in maternal Nutrition to Child health (LINC) study is set up to investigate health effects of perinatal exposure to a variety of EDCs, and to study determinants of exposure, including child behaviors, dietary intake, and the residential and occupational environment.

Methods

The LINC study is a population-based, prospective birth cohort study. It has been initiated to study the effects of perinatal exposure to EDCs on various health outcomes later in life. The general aims of the study are:

- To relate early life exposure markers of EDCs with effect biomarkers, health outcome data and other parameters via multiple regression and multivariate analysis, while taking into account relevant confounders and covariates.
- To determine child behavior types, lifestyle factors, and factors in the residential and/or occupational area, which are relevant for exposure to EDCs.

Subjects

All children without major congenital anomalies who are born to women living in the area of Zwolle, Purmerend, or Den Helder (figure 1) are allowed to participate in the cohort. The area of Zwolle in particular was chosen because of the relatively low level of urbanization; about 59% of the Zwolle city area is used for agriculture. Purmerend and Den Helder differ substantially from Zwolle, both from an environmental and demographic perspective, which may offer the opportunity to compare results for different populations.

Pregnant women have been recruited through midwifery clinics in this area from 2011 and onwards. Women are considered eligible for participation if they are less than twelve weeks pregnant at their first visit to the clinic and if they are able to fill out questionnaires in Dutch. Decisionally incapacitated subjects are not asked to participate, and twin pregnancies are excluded.

Follow-up of subjects

Data from regular care provided by midwives and/or obstetricians is collected for information on women's health during pregnancy. Further information on the period before and during pregnancy is collected by means of questionnaires, which are sent out to women at inclusion, and at the end of each trimester (four weeks after birth for the last trimester). Follow-up of the child is done by youth healthcare organizations (at 1, 2, 3, 4, 6, 9, and 12 months of age), which monitor growth and development of children as part of the Dutch health care program. Questionnaires are sent to the mothers when the children are 3, 6, 9, 12, and 18 months of age.

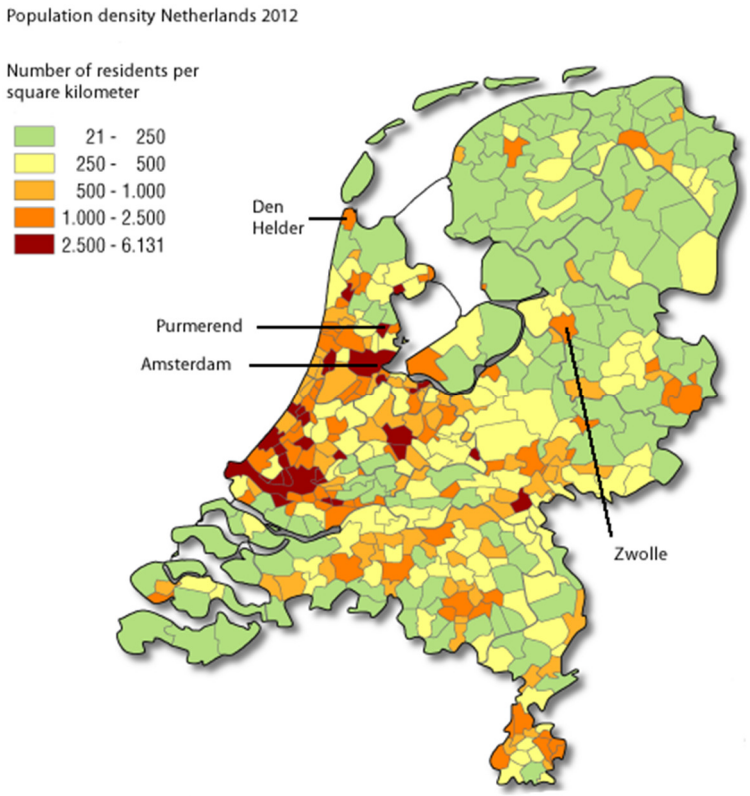

Figure 1. Population density in the Netherlands 2012.[53]

Measurements

A complete overview of measurements during pregnancy and the first 18 months after birth is given in table 4.1.

Assessment of exposure

The aim is to assess perinatal exposure. For this purpose cord blood is collected from each participant at birth, as it is considered a proxy for prenatal exposure and collection is non-invasive for both mother and child. To determine postnatal exposure, mothers are instructed to collect breast milk during one week, starting eight weeks after birth. Use of a breast pump is allowed, and when used, the brand of the pump is provided by the participant. Timing of breast milk collection was decided upon after feedback in a pilot study, in which mothers indicated that collection any earlier after birth was uncomfortable. Furthermore, a small piece from the fetal side of the placenta is collected for epigenetic studies.

Moreover, a sample of vernix and meconium is collected at birth, and parents collect a urine sample of the child during the first week after birth. Furthermore we will aim to collect multiple urine samples of the child during early childhood.

Table 4.1 Measurements in LINC during pregnancy and the first 18 months after birth.

Time	Questionnaires/sampling	Anthropometry
1st trimester of pregnancy	• Demographics • Previous pregnancies, fertility • Allergies (mother and father) • FFQ mother • Lifestyle • Mental state, stress • Occupational and residential exposure	• Weight (mother and father) • Length (mother and father)
2nd trimester of pregnancy	• Food diary mother • Lifestyle • Mental state, stress	-
3rd trimester of pregnancy	• General health, medication, family history • Lifestyle • Mental state, stress • Social support	• Weight (mother, 36 weeks of gestation)
Birth	• Cord blood • Placenta • Vernix (if present) • Meconium • Urine (1st week)	• Birth weight • Head and waist circumference
Month 1	-	• Weight and length • Head circumference
Month 2	• Breast milk	• Weight and length • Head circumference
Month 3	• Infant diet • Second hand smoke exposure • Mental state, stress • Crying/sleeping pattern	• Weight and length • Head circumference
Month 4	-	• Weight and length • Head circumference
Month 6	• Infant diet • Second hand smoke exposure • Mental state, stress • Social support • Crying/sleeping pattern • Occupational and residential exposure	• Weight and length • Head circumference
Month 9	• Infant diet • Second hand smoke exposure • Mental state, stress • Crying/sleeping pattern	• Weight and length • Head circumference
Month 12	• Infant diet • Child allergies	• Weight and length • Head circumference

	• Second hand smoke exposure • Mental state, stress • Crying/sleeping pattern • Child behavior • Occupational and residential exposure • Saliva • Hand, back, and mouth wipe • Dust sample	
Month 18	• Child behavior checklist	-

To assess whether dust is a relevant carrier for flame retardants and if contributes significantly to exposure during early childhood, home visits are performed when the child is 12 months of age. During these visits a saliva sample is collected from each child, as well as a hand, back, and mouth wipe to assess how much dust accumulates on the surface of the body and can potentially be degisted or absorbed through the skin. Furthermore an indoor dust sample from the home is collected.

Exposure to PCB-153, DDE, hexachlorobenzene (HCB), dioxins (CALUX), brominated diphenyl ether (BDE)-47, BDE-99, hexabromocyclododecane (HBCD), perfluorooctanesulfonic acid (PFOS), perfluorooctanoic acid (PFOA), and the secondary DEHP metabolites mono(2-ethyl-5-carboxypentyl) phthalate (MECPP), mono(2-ethyl-5-hydroxyhexyl) phthalate MEHHP, and mono(2-ethyl-5-oxohexyl) phthalate (MEOHP) will be assessed in cord blood and breast milk. Other chemicals will include organophosphates, carbamates, and pyrethroids. Additionally levels of resorcinol bis(diphenylphosphate) (RBDPP) and bisphenol A bis(diphenylphosphate) (BPA-BDPP) will be determined in the saliva samples as well as the indoor dust samples. These two flame retardants are used as alternatives for deca-BDE in TV or flat screen housings, as well as other electronic equipment. The other samples will be stored for additional analyses, and more compounds may be determined as the study progresses.

Health outcomes

There are various parameters early in life which are indicators for development later in life. Birth weight for example is inversely associated with hypertension and type 2 diabetes in adulthood,[23 24] and both high and low birth weight have been associated with obesity.[25 26] Rapid growth in infancy has been identified as an independent risk factor for childhood obesity.[27 28] A recent study by Gittner et al. showed that children who were obese at the age of five years already had distinct body mass index (BMI) patterns before 12 months of age, with children who had a normal BMI at age five always having a lower BMI from age 6 months and onwards compared to children who were obese at age five years.[29] They furthermore showed that BMI patterns over time differed between male and female children. Childhood obesity has also been related to exposure to endocrine disrupting chemicals early in life. Several studies have observed positive associations with BMI for chemicals such as organochlorine pesticides (e.g. DDE, HCB) [7 30 31] and perfluorinated alkyl acids,[32] although results are not unambiguous.[33 34]

Also brain development is regulated and influenced by hormones, and especially thyroid hormones are known to be essential for normal embryonal and foetal neurogenesis.[35] EDCs are known to affect thyroid hormonal function in particular. Therefore disruption of hormonal function during specific time periods important for brain development may have many consequences and may amongst others have adverse effects on neurodevelopment. Positive associations for prenatal EDC exposure and autism spectrum disorders have been reported,[36-39] however studies in this area are relatively scarce. For attention deficit hyperactivity disorder, study results seem to be more convincing of an association with early life exposure to endocrine disruptors.[20]

Given the physiological processes which may be affected by EDC exposure, it was decided to focus on physical growth as well as neurodevelopment. Both these outcomes are monitored by youth health care centres, which determine child weight, height, and head circumference, and which monitor psychomotor development by means of the van Wiechen scheme. Furthermore at 12 months, the Infant Behavior Questionnaire is administered,[40] followed by the Child Behavior CheckList at 18 months.[41]

Nutrition

Exposure to chemicals occurs in part through diet.[42] However, diet is a factor which is relatively easy to control or change and may therefore be a potential pathway through which daily exposure can be decreased. This was for example shown by Rudel et al. (2012) who observed a significant reduction after a 'fresh food' intervention, which implied that participants followed a three day diet containing no canned foods or foods packaged in plastic.[43] We therefore aim to assess the relevance of diet, and certain food groups in particular, in the contribution to the body burden of exposure for our population. Information on maternal dietary habits before pregnancy is collected by means of a food frequency questionnaire (FFQ),[44] which was validated for dioxin intake through diet.[45] As pregnancy may be a period in which dietary patterns may change because women may want to adopt a more healthy lifestyle, women also fill out a 2-day food diary at the start of the second trimester.

Effect biomarkers

Associations with health outcomes will be determined for each compound individually. However, the compound by compound approach is not an accurate representation of our body burden and fails to take into account that chemicals may interact and may potentially enhance or diminish the effects they would have individually. It may therefore be useful to study biomarkers of effect. These biomarkers should be able to reflect complex exposures as well as the accumulation of exposures over time.[46] They are furthermore able to relate cause and (health) effect. As we suspect these chemicals to be endocrine disruptors, hormone levels will be included as effect biomarkers.

Cord blood will also be used to determine various hormone levels, including leptin, adiponectin, ghrelin, insulin, cortisone, glucagon, insulin-like growth factor (IGF) 1, and sex hormone-binding globulin. The Dutch National Institute for Public Health and the Environment is approached in order to obtain data on thyroid hormones (total thyroxine) as measured in the neonatal screening programme.

Sample size

Sample size was calculated for BMI at 12 months of age. Karmaus et al. (2009) observed an increase in BMI of 1.65 kg/m^2 in offspring of mothers having maternal serum levels of DDE of 1.5 – 2.9 µg/L compared to offspring of mothers having levels of < 1.5 µg/L DDE.[47] Smink et al. (2008) measured the HCB in cord blood and related this to BMI at the age of six years. Children with levels higher than 1.03 ng/mL HCB had a BMI which was 0.95 kg/m^2 higher than that of children with levels lower than 0.46 ng/mL HCB.[48] Karmaus et al. did not measure DDE in cord blood and they only measured BMI in the offspring at adult age. Smink et al. on the other hand did measure BMI in children and determined exposure to HCB in cord blood.[31] Therefore we considered a difference in BMI of 1.0 kg/m^2 relevant.

Previous measurements of BMI in 12 month old Dutch children, performed by TNO,[49] showed that the variation in BMI among those children is 1.36 kg/m^2 (1 SD). Furthermore, based on data on DDE levels that already have been obtained in a Belgian cohort,[50] we expect that about 30% of our sample will have DDE levels of < 1.5 µg/L in cord blood.

In order to determine the required sample size for the present study, we entered two rows of data in Microsoft Excel (one with 30 zero's and one with 70 ones to resemble the estimated distribution of DDE levels dichotomised at 1.5 µg/L). Thereafter we simulated BMI scores to these rows. For the 30 observations, we sampled from a population with a mean BMI of 17.1 (average BMI of boys and girls aged 12 months [49]) and SD of 1.36 and for the 70 observations we sampled from a population with a mean BMI of 18.1 and SD of 1.36. The mean BMI of this latter population is the mean BMI in Dutch boys and girls at the age of twelve months, increased with 1 BMI point. For both groups we selected a sample that resembled the population parameters and we entered those data into SPSS 17. In the following step we conducted a regression analysis with the group variable as independent and BMI scores as outcome. This linear regression analysis resulted in an r^2 of 0.11. Finally, this r^2 was used to conduct a sample size calculation for multiple linear regression analysis in STATA 10.0. Assuming a change in r^2 by adding DDE levels to the model of 0.11, an alpha of 0.05, a power of 0.80 and 10 variables in the final model, the sample size needed is 42. A more conservative estimate of change in r^2 of 0.05 resulted in a sample size of 88.

The drop-out rate in the study of Karmaus et al. was 55%.[47] Koletzko et al. (2009) followed infants from birth until they were two years of age.[51] The drop-out rate was approximately 40% during the course of that study. To ensure the highest possibility of

good statistical power, the sample size in the present study for this outcome is set to N = 200. However, experience has indicated that from all participants, only 40% provides a complete set of body samples. Moreover, from many participants, the volume of the cord blood is too low to be used for measurement of the selected chemicals. For this reason, we would like to extend the sample size to 500 in order to have samples available for 200 participants.

Statistical analyses

For all analyses effect modification of the outcome by gender will be checked, as the included chemicals disrupt the endocrine system, and in particular steroid hormones. Linearity of exposure markers and outcome will furthermore be checked due to suspected nonmonotonic dose-response associations,[52] and for each compound exposure values below the limit of quantification (LOQ) will be replaced by LOQ/$\sqrt{2}$.[50]

In order to quantify the relation between exposure and BMI at the age of 12 and 18 months, we will use linear multilevel (mixed) models. These models take into account the dependency of repeated measures within the individuals. For each compound a separate model will be composed for weight, height, BMI, and head circumference. Exposure quartiles, time, and gender will be added to the models as fixed effects and a random effect will be added for subject. Various covariates, described in 2.5.1, will be tested and included in the model if significant (change in β-coefficient > 10%).

To study the relationship between exposure and behavior at the age of 18 months, linear regression analyses will be conducted. The scales 'Attention Deficit Hyperactivity Problems' and 'Pervasive Developmental Problems' of the CBCL will be used to measure behavioral outcomes and for each of these scales a separate model will be designed.

Covariates

Potential covariates were selected based on literature. Weight and length of both parents are measured by the midwife at inclusion, approximately 10-12 weeks in pregnancy. Measurement of maternal weight is repeated at 36 weeks of pregnancy to determine gestational weight gain. Midwives received a measuring tape as well as strict instructions on how to perform these measurements. Weighing scales are provided by the midwife and are calibrated daily. Gestational age is determined by means of ultrasound. Birth weight is measured by a midwife or a nurse and is obtained from registries of the midwives.

Questionnaires are administered at inclusion and the start of the second trimester to collect information on education (having a bachelor or master degree, yes or no), birth date of the mother, parity, and maternal smoking (yes or no) and alcohol intake during the first trimester (drinks per week). At inclusion, fish intake (grams per day) is determined by food frequency questionnaire which includes both frequencies and portion sizes.[44] One month after birth another questionnaire is administered to inquire on folic acid intake during pregnancy (yes or no).

Ethics and dissemination

Ethics and safety considerations

Conduction of this study will be according to the principles of the Declaration of Helsinki (version October 22nd, 2008) and in accordance with the Medical Research Involving Human Subjects Act (WMO). This study was approved by the medical ethics committee of the VU University Medical Centre.

The target group of this research is infants aged 0 – 18 months. Consent for the infant is given by the mother, who is specifically required to give consent for both herself as well as her child. Furthermore it will be stressed that participants may leave the project at any time if they desire to do so and that neither withdrawal nor the decision not to participate will affect the care provided to them by midwives or youth health care.

The LINC-study is a non-invasive study. The majority of the data will be collected through regular health care (midwives, obstetricians and youth health care). Furthermore, questionnaires will be administered, cord blood, placentas, breast milk, urine, saliva, vernix and meconium will be collected. In addition, hand-wipes, mouth-wipes, and back-wipes will be collected from each child, and waist circumference and head circumference will also be measured in children. All these measurements are non-invasive.

Dissemination

Results will be published in international peer reviewed journals and multiple doctoral theses, regardless of the findings of this study. Furthermore they will be presented at national and international scientific conferences.

Translation of results to society is considered high priority as this will create knowledge and awareness amongst various stakeholders. We will aim to share study results with professional groups related to the target population involved in the cohort, i.e. pregnant women and children. These professional groups will include midwives, obstetricians, and pediatricians, but other stakeholders may be involved as the study progresses. We will furthermore disseminate results to the general public as well as policy makers.

Conclusion

In conclusion, the LINC study, as a prospective cohort, will provide insight into the effects of early life exposure to EDCs on child health and development, including childhood obesity and neurodevelopmental disorders. Knowledge on the etiology of these childhood disorders is valuable as this may enable more effective prevention and intervention. Our aim is to extend follow-up of our participants throughout childhood and hopefully adolescence and adulthood to further study long-term health effects of environmental exposures.

Acknowledgements

We would like to acknowledge all the midwives for their help in recruitment of participants, as well as youth health care organizations in the area of Zwolle. Furthermore we are grateful to Marja Lamoree and Jacco Koekkoek from the Institute for Environmental Studies (IVM) for their contribution to the analysis of the samples, as well as to Michiel de Boer from the section Health and Life Sciences at the VU University for his advice regarding the statistical analysis. We would like to thank our participants for their commitment to the LINC study, which is not possible without them.

References

1. Rudel RA, Gray JM, Engel CL, Rawsthorne TW, Dodson RE, Ackerman JM, Rizzo J, Nudelman JL, Brody JG 2011 Food packaging and bisphenol A and bis(2-ethyhexyl) phthalate exposure: findings from a dietary intervention. Environ Health Perspect **119**:914-920. Epub 2011 Mar 2022.

2. Nougadere A, Sirot V, Kadar A, Fastier A, Truchot E, Vergnet C, Hommet F, Bayle J, Gros P, Leblanc JC 2012 Total diet study on pesticide residues in France: levels in food as consumed and chronic dietary risk to consumers. Environ Int **45**:135-150. Epub 2012 May 2015.

3. CDC 2009 Fourth Report on Human Exposure to Environmental Chemicals. U.S. Department of Health and Human Services, Centers for Disease Control and Prevention, Atlanta, GA.

4. Woodruff TJ, Zota AR, Schwartz JM 2011 Environmental chemicals in pregnant women in the United States: NHANES 2003-2004. Environ Health Perspect **119**:878-885. Epub 2011 Jan 2010.

5. Luzardo OP, Mahtani V, Troyano JM, Alvarez de la Rosa M, Padilla-Perez AI, Zumbado M, Almeida M, Burillo-Putze G, Boada C, Boada LD 2009 Determinants of organochlorine levels detectable in the amniotic fluid of women from Tenerife Island (Canary Islands, Spain). Environ Res **109**:607-613. Epub 2009 Apr 2029.

6. Foster W, Chan S, Platt L, Hughes C 2000 Detection of endocrine disrupting chemicals in samples of second trimester human amniotic fluid. J Clin Endocrinol Metab **85**:2954-2957.

7. Valvi D, Mendez MA, Martinez D, Grimalt JO, Torrent M, Sunyer J, Vrijheid M 2011 Prenatal concentrations of polychlorinated biphenyls, DDE, and DDT and overweight in children: a prospective birth cohort study. Environ Health Perspect **120**:451-457. Epub 2011 Oct 2025.

8. Verhulst SL, Nelen V, Hond ED, Koppen G, Beunckens C, Vael C, Schoeters G, Desager K 2009 Intrauterine exposure to environmental pollutants and body mass index during the first 3 years of life. Environ Health Perspect **117**:122-126.

9. Mikes O, Cupr P, Kohut L, Krskova A, Cerna M 2012 Fifteen years of monitoring of POPs in the breast milk, Czech Republic, 1994-2009: trends and factors. Environ Sci Pollut Res Int **19**:1936-1943.

10. Bergman A, Heindel JJ, Kasten T, Kidd KA, Jobling S, Neira M, Zoeller RT, Becher G, Bjerregaard P, Bornman R, Brandt I, Kortenkamp A, Muir D, Drisse MN, Ochieng R, Skakkebaek NE, Bylehn AS, Iguchi T, Toppari J, Woodruff TJ 2013 The impact of endocrine disruption: a consensus statement on the state of the science. Environ Health Perspect **121**:A104-106.

11. Ahmed OM, El-Gareib AW, El-Bakry AM, Abd El-Tawab SM, Ahmed RG 2008 Thyroid hormones states and brain development interactions. Int J Dev Neurosci **26**:147-209.

12. Weiss B 2012 The intersection of neurotoxicology and endocrine disruption. Neurotoxicology **2012**:31.

13. Zhang X, Ho SM 2011 Epigenetics meets endocrinology. J Mol Endocrinol **46**:R11-32.

14. Newbold RR 2010 Impact of environmental endocrine disrupting chemicals on the development of obesity. Hormones (Athens) **9**:206-217.

15. Bloomgarden ZT 2004 Type 2 diabetes in the young: the evolving epidemic. Diabetes Care **27**:998-1010.

16. Han JC, Lawlor DA, Kimm SY 2010 Childhood obesity. Lancet **375**:1737-1748.

17. EASO. The European Association for the Study of Obesity - Facts & Statistics. http://www.easo.org/childhood-obesity-cotf/facts-a-statistics. (Last accessed on 12-07-2013).

18. Pastor PN, Reuben CA 2008 Diagnosed attention deficit hyperactivity disorder and learning disability: United States, 2004-2006. Vital Health Stat 10:1-14.

19. ADDM, CDC 2012 Prevalence of autism spectrum disorders--Autism and Developmental Disabilities Monitoring Network, 14 sites, United States, 2008. MMWR Surveill Summ **61**:1-19.

20. de Cock M, Maas YG, van de Bor M 2012 Does perinatal exposure to endocrine disruptors induce autism spectrum and attention deficit hyperactivity disorders? Review. Acta Paediatr **101**:811-818.

21. Alonso-Magdalena P, Quesada I, Nadal A 2007 Endocrine disruptors in the etiology of type 2 diabetes mellitus. Nat Rev Endocrinol **7**:346-353. Epub 2011 Apr 2015.

22. Hatch EE, Nelson JW, Stahlhut RW, Webster TF 2009 Association of endocrine disruptors and obesity: perspectives from epidemiological studies. Int J Androl **33**:324-332. Epub 2010 Jan 2022.

23. Bergvall N, Iliadou A, Johansson S, de Faire U, Kramer MS, Pawitan Y, Pedersen NL, Lichtenstein P, Cnattingius S 2007 Genetic and shared environmental factors do not confound the association between birth weight and hypertension: a study among Swedish twins. Circulation **115**:2931-2938.

24. Hales CN, Barker DJ, Clark PM, Cox LJ, Fall C, Osmond C, Winter PD 1991 Fetal and infant growth and impaired glucose tolerance at age 64. BMJ **303**:1019-1022.

25. Yu ZB, Han SP, Zhu GZ, Zhu C, Wang XJ, Cao XG, Guo XR 2011 Birth weight and subsequent risk of obesity: a systematic review and meta-analysis. Obes Rev **12**:525-542.

26. Labayen I, Moreno LA, Ruiz JR, Gonzalez-Gross M, Warnberg J, Breidenassel C, Ortega FB, Marcos A, Bueno M 2008 Small birth weight and later body

composition and fat distribution in adolescents: the Avena study. Obesity (Silver Spring) **16**:1680-1686. Epub 2008 May 1688.

27. Monteiro PO, Victora CG 2005 Rapid growth in infancy and childhood and obesity in later life--a systematic review. Obes Rev **6**:143-154.

28. Odegaard AO, Choh AC, Nahhas RW, Towne B, Czerwinski SA, Demerath EW 2013 Systematic examination of infant size and growth metrics as risk factors for overweight in young adulthood. PloS one **8**:e66994.

29. Gittner LS, Ludington-Hoe SM, Haller HS 2013 Utilising infant growth to predict obesity status at 5 years. J Paediatr Child Health **49**:564-574.

30. Mendez MA, Garcia-Esteban R, Guxens M, Vrijheid M, Kogevinas M, Goni F, Fochs S, Sunyer J 2010 Prenatal Organochlorine Compound Exposure, Rapid Weight Gain and Overweight in Infancy. Environ Health Perspect.

31. Smink A, Ribas-Fito, N., Garcia, R., Torrent, M., Mendez, M.A., Grimalt, J.O., and Sunyer, J. 2008 Exposure to hexachlorobenzene during pregnancy increases the risk of overweight in children aged 6 years. Acta Pædiatrica **97**:1465-1469.

32. Halldorsson TI, Rytter D, Haug LS, Bech BH, Danielsen I, Becher G, Henriksen TB, Olsen SF 2012 Prenatal exposure to perfluorooctanoate and risk of overweight at 20 years of age: a prospective cohort study. Environ **120**:668-673. Epub 2012 Feb 2013.

33. Garced S, Torres-Sanchez L, Cebrian ME, Claudio L, Lopez-Carrillo L 2012 Prenatal dichlorodiphenyldichloroethylene (DDE) exposure and child growth during the first year of life. Environmental research **113**:58-62.

34. Pan IJ, Daniels JL, Herring AH, Rogan WJ, Siega-Riz AM, Goldman BD, Sjodin A 2010 Lactational exposure to polychlorinated biphenyls, dichlorodiphenyltrichloroethane, and dichlorodiphenyldichloroethylene and infant growth: an analysis of the Pregnancy, Infection, and Nutrition Babies Study. Paediatr Perinat Epidemiol **24**:262-271.

35. Patel J, Landers K, Li H, Mortimer RH, Richard K 2011 Thyroid hormones and fetal neurological development. J Endocrinol **209**:1-8. Epub 2011 Jan 2016.

36. Miodovnik A, Engel SM, Zhu C, Ye X, Soorya LV, Silva MJ, Calafat AM, Wolff MS 2011 Endocrine disruptors and childhood social impairment. Neurotoxicology **32**:261-267. Epub 2010 Dec 2021.

37. Roberts EM, English PB, Grether JK, Windham GC, Somberg L, Wolff C 2007 Maternal residence near agricultural pesticide applications and autism spectrum disorders among children in the California Central Valley. Environ Health Perspect **115**:1482-1489.

38. Volk HE, Hertz-Picciotto I, Delwiche L, Lurmann F, McConnell R 2011 Residential proximity to freeways and autism in the CHARGE study. Environ **119**:873-877. Epub 2010 Dec 2013.

39. Windham GC, Zhang L, Gunier R, Croen LA, Grether JK 2006 Autism spectrum disorders in relation to distribution of hazardous air pollutants in the san francisco bay area. Environ Health Perspect **114**:1438-1444.

40. Rothbart MK 1981 Measurement of Temperament in Infancy. Child Development **52**:569-578.

41. Achenbach TM, Ruffle TM 2000 The Child Behavior Checklist and related forms for assessing behavioral/emotional problems and competencies. Pediatr Rev **21**:265-271.

42. Schafer KS, Kegley SE 2002 Persistent toxic chemicals in the US food supply. Journal of epidemiology and community health **56**:813-817.

43. Rudel RA, Gray JM, Engel CL, Rawsthorne TW, Dodson RE, Ackerman JM, Rizzo J, Nudelman JL, Brody JG 2011 Food packaging and bisphenol A and bis(2-ethyhexyl) phthalate exposure: findings from a dietary intervention. Environ Health Perspect **119**:914-920.

44. van Dooren-Flipsen MMH, van Klaveren JD 1998 ANI-Voedselfrequentie vragenlijst: ontwikkeling vragenlijst naar de inname van vetoplosbare residuen en contaminanten. Rikilt-DLO, Wageningen, Netherlands.

45. Bilau M, Matthys C, Bellemans M, De Neve M, Willems JL, De Henauw S 2008 Reproducibility and relative validity of a semi-quantitative food frequency questionnaire designed for assessing the intake of dioxin-like contaminants. Environmental research **108**:327-333.

46. Silins I, Hogberg J 2011 Combined toxic exposures and human health: biomarkers of exposure and effect. International journal of environmental research and public health **8**:629-647.

47. Karmaus W, Osuch JR, Eneli I, Mudd LM, Zhang J, Mikucki D, Haan P, Davis S 2009 Maternal levels of dichlorodiphenyl-dichloroethylene (DDE) may increase weight and body mass index in adult female offspring. Occup Environ Med **66**:143-149.

48. Smink A, Ribas-Fito N, Garcia R, Torrent M, Mendez MA, Grimalt JO, Sunyer J 2008 Exposure to hexachlorobenzene during pregnancy increases the risk of overweight in children aged 6 years. Acta Paediatrica **97**:1465-1469.

49. Fredriks AM, van Buuren S, Wit JM, Verloove-Vanhorick SP 2000 Body index measurements in 1996â€“7 compared with 1980. Archives of Disease in Childhood **82**:107-112.

50. Govarts E, Nieuwenhuijsen M, Schoeters G, Ballester F, Bloemen K, de Boer M, Chevrier C, Eggesbo M, Guxens M, Kramer U, Legler J, Martinez D, Palkovicova L, Patelarou E, Ranft U, Rautio A, Petersen MS, Slama R, Stigum H, Toft G, Trnovec T, Vandentorren S, Weihe P, Kuperus NW, Wilhelm M, Wittsiepe J, Bonde JP 2012 Birth weight and prenatal exposure to polychlorinated biphenyls (PCBs) and dichlorodiphenyldichloroethylene (DDE): a meta-analysis within 12 European Birth Cohorts. Environ **120**:162-170. Epub 2011 Oct 2013.

51. Koletzko B, von Kries R, Closa R, Escribano J, Scaglioni S, Giovannini M, Beyer J, Demmelmair H, Gruszfeld D, Dobrzanska A, Sengier A, Langhendries J-P, Rolland Cachera M-F, Grote V 2009 Lower protein in infant formula is associated with lower weight up to age 2 y: a randomized clinical trial. Am J Clin Nutr **89**:1836-1845.

52. Vandenberg LN, Colborn T, Hayes TB, Heindel JJ, Jacobs DR, Jr., Lee DH, Shioda T, Soto AM, vom Saal FS, Welshons WV, Zoeller RT, Myers JP 2012 Hormones and endocrine-disrupting chemicals: low-dose effects and nonmonotonic dose responses. Endocr Rev **33**:378-455.

53. Mulder M. Volksgezondheid Toekomst Verkenning, Nationale Atlas Volksgezondheid. Bilthoven: RIVM, 2012.