Maternal Diet During Pregnancy and Early Growth : Focus on Diet Duality and Food Chemicals Exposure

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université PARIS-SACLAY

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UNIVERSITÉ PARIS SUD
Comprendre le monde, construire l'avenir

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Thèse de doctorat de l'Université Paris-Saclay
préparée à l'Université Paris Sud

École doctorale n°570 Santé Publique EDSP
Spécialité de doctorat: Santé publique – épidémiologie

Thèse présentée et soutenue à Villejuif, le 16 janvier 2018, par

Manik Kadawathagedara

Composition du Jury :

Mme M-C. Boutron-Ruault Directrice de recherche, INSERM (U 1018)	Présidente
Mme K. Castetbon Professeure, Université Libre Bruxelles	Rapportrice
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Mme M. Vrijheid Professeure, IS Global Barcelonne	Rapportrice
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M. J-F. Huneau Professeur, Agro Paris Tech (U 914)	Examinateur
Mme B. de Lauzon-Guillain Chargée de Recherche, INSERM (U 1153)	Directrice de thèse

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Thèse de doctorat

L'amitié double les joies et réduit de moitié les peines.

Francis Bacon

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Summary

Introduction

Maternal diet is the only prenatal source of nutrients and the major source for non-nutrients (such as chemicals) and can influence foetal growth and offspring's long-term health. Chemicals known as "obesogens" might also play a role in increasing obesity risk. One of the main routes of exposure to these chemicals is through foods. After a description of diet quality during pregnancy, the aim of this thesis was to study the association between prenatal exposure to food chemicals and prenatal and postnatal growth among children.

Methods

We used the data of three birth cohort studies: two French studies (EDEN and ELFE) and a Norwegian study (MoBa). We first described the compliance to dietary guidelines of French pregnant women and the association between a better diet quality and birth outcomes using the data of the ELFE study. Secondly, we studied the relationship of a specific food contaminant, acrylamide, on birth size in the EDEN and postnatal growth in MoBa. Finally, we extended analyses to all available food chemicals available in the second French Total Diet Study (TDS).

Results

The nutritional guidelines for pregnant women were rather well followed in ELFE. The *Diet Quality* score was associated with higher birth weight and lower risk of having a small-for-gestational-age (SGA) baby. We showed that prenatal dietary exposure to acrylamide was associated with reduced birth size in EDEN, and increased postnatal growth in MoBA. In EDEN, on the 99 selected food chemicals, birth weight was associated only with eight chemicals (four negatively and four positively). BMI at 5 years was associated only with one food chemical. These results were not significant after correction for multiple testing. When using the mixture approach, one mixture of chemicals was positively associated with birth weight. No association was observed between the mixtures and 5-y BMI.

Conclusions

The *Diet Quality* score was associated with higher birth size. Whereas dietary exposure to acrylamide was associated with impaired foetal growth. When looking at a larger number of food chemicals, we found only limited associations with child's prenatal or postnatal growth. Exposure to food chemicals assessed by TDS did not appear to be of major concern for growth but other windows of susceptibility, such as early childhood, and other outcomes, such as cognitive development, should be considered in future studies.

Résumé

Introduction

L'alimentation maternelle durant la grossesse est cruciale pour le développement du fœtus et plus tard pour la santé de l'enfant. Elle est la seule source prénatale de nutriments et la source majoritaire d'éléments non nutritifs (tels que certains contaminants) qui peuvent influencer la croissance fœtale. Des études épidémiologiques et animales ont montré qu'une restriction nutritionnelle pendant la grossesse pouvait conduire à une réponse adaptative du fœtus, favorisant la croissance des organes nobles au détriment des autres organes et conduisant à une altération durable du métabolisme. Ainsi, les enfants nés avec un petit poids de naissance sont plus à risque de développer des maladies cardiovasculaires, un diabète ou un syndrome métabolique à l'âge adulte que leurs homologues ayant un poids de naissance plus élevé. De plus en plus d'études suggèrent que l'exposition à des contaminants obésogènes pourrait également jouer un rôle dans l'augmentation du risque d'obésité, l'une des principales voies d'exposition à ces contaminants étant l'alimentation. Après une description de la qualité de l'alimentation pendant la grossesse, l'objectif de cette thèse était d'étudier l'association entre l'exposition prénatale aux contaminants alimentaires et la croissance des enfants.

Méthodes

Pour répondre à cet objectif, les données de trois cohortes de naissance ont été utilisées : deux études françaises (EDEN et ELFE) et une étude norvégienne (MoBa). Ces trois cohortes sont très riches et complémentaires : EDEN a inclus moins de sujets (n=2002) mais dispose de données détaillées sur la croissance et le développement ; ELFE est une étude plus large (n=18329) et représentative des naissances en France métropolitaine ; MoBa est une étude norvégienne, représentative et avec un nombre élevé de participants (n=110 000). Dans ces trois cohortes, les femmes ont rempli un questionnaire de fréquence alimentaire (QFA) portant sur leur alimentation pendant la grossesse.

L'évaluation des contaminants dans l'alimentation a été réalisée en combinant les données du QFA et des bases de données de contamination : la deuxième Etude de l'Alimentation Total (EAT2) française pour EDEN et ELFE et plusieurs bases de données de contamination (norvégienne, suédoise et européenne) pour MoBa. Dans un premier temps, nous avons décrit l'adéquation des consommations aux recommandations alimentaires du Programme National Nutrition Santé (PNNS) des femmes enceintes françaises en utilisant les données de l'étude ELFE. Nous avons créé un score de qualité globale de l'alimentation pendant la grossesse et un score portant sur les recommandations spécifiquement destinés aux femmes enceintes, puis nous avons étudié les facteurs associés à une meilleure qualité alimentaire pendant la grossesse. Ensuite, nous avons examiné l'association entre la qualité de l'alimentation et la croissance prénatale (poids et taille de naissance ainsi que le risque d'être petit pour l'âge gestationnel : PAG). Dans un deuxième temps, nous avons étudié la relation entre un contaminant alimentaire spécifique, l'acrylamide, et la croissance prénatale, dans EDEN, puis la croissance postnatale, dans EDEN et MoBa. Dans une troisième partie, nous avons étendu nos analyses à tous les contaminants alimentaires dosés dans l'EAT2, en utilisant deux approches : une analyse des composés pris individuellement et puis une analyse de ces composés considérés en mélange.

Résultats

Dans la première partie, nous avons montré que les recommandations du PNNS étaient globalement bien suivies par les femmes enceintes (score médian de 7,8 sur une échelle de 0 à 11). Les recommandations les moins bien suivies pour le score de qualité globale de l'alimentation étaient celles portant sur la consommation de «fruits et légumes», «pain complet» et «poissons et fruits de mer». Les recommandations spécifiques de la grossesse étaient également globalement bien suivies par les femmes enceintes (score médian de 7,7 sur une échelle de 0 à 9). Parmi les caractéristiques familiales étudiées, certaines étaient associées de façon identique à la fois au score de qualité de l'alimentation et au score de respect des recommandations spécifiques de la grossesse telles que certaines caractéristiques socioéconomiques ou démographiques (âge à l'accouchement, niveau

d'étude et revenu du foyer) et des facteurs pouvant représenter le rapport à la santé des femmes (tabagisme). Certains facteurs étaient spécifiquement associés au score de qualité de l'alimentation, reflétant probablement des habitudes culturelles et des traditions culinaires spécifiques (région, pays de naissance). Enfin, d'autres facteurs ont été associés spécifiquement au score de respect des recommandations spécifiques de la grossesse résumant l'exposition et l'attention portée aux recommandations (nombre d'enfants). Un score élevé de qualité de l'alimentation était associé à un poids de naissance plus élevé et un risque plus faible d'avoir un enfant petit pour l'âge gestationnel.

Dans la deuxième partie, nous avons montré une association significative entre l'exposition alimentaire à l'acrylamide et le risque de petit poids pour l'âge gestationnel : plus l'exposition pendant la grossesse était importante, plus la taille de naissance était faible et plus le risque de PAG était élevé. L'association avec le poids à la naissance était fortement atténuée après ajustement sur la taille de naissance. Dans l'étude EDEN, nous n'avons pas trouvé d'association entre l'exposition prénatale à acrylamide et l'indice de masse corporelle à cinq ans. Dans la cohorte norvégienne MoBa, nous avons constaté que l'exposition prénatale à l'acrylamide était associée à une prévalence accrue d'enfants en surpoids ou obèses dès l'âge de 3 ans et à une plus grande vitesse de croissance du poids durant la petite enfance. À notre connaissance, il s'agit de la première étude mettant en relation l'exposition prénatale à l'acrylamide et la croissance postnatale.

Dans EDEN, sur les 99 composés chimiques sélectionnés, le poids de naissance était associé négativement à l'exposition à quatre contaminants alimentaires (acrylamide, sulfites, DBahA, DON) et positivement à l'exposition à quatre métaux (baryum, chrome VI, plomb, strontium). L'IMC à 5 ans était associé négativement à l'exposition au DbaeP mais pas lié aux autres composés chimiques alimentaires dosés dans l'EAT2. Aucune de ces associations n'était statistiquement significative après prise en compte de la multiplicité des tests. Lorsque les composés chimiques étaient considérés en mélanges, seul le mélange de contaminants principalement composé de perfluorés et de métaux était positivement associé au poids de naissance et aucun mélange n'était associé à l'IMC à 5 ans.

Conclusion

Une qualité de l'alimentation élevée pendant la grossesse est associée à un poids de naissance plus élevé et une diminution du risque de PAG, alors que l'exposition alimentaire à l'acrylamide est associée à une altération de la croissance fœtale. L'exposition prénatale aux contaminants alimentaires, évaluée à partir des données d'EAT, ne semble pas préoccupante vis-à-vis de la croissance prénatale et postnatale précoce car les effets retrouvés sont de faible amplitude et ne sont plus significatifs après prise en compte des tests multiples. Néanmoins, il convient d'évaluer dans de futures études le lien entre ces expositions et d'autres évènements de santé comme le développement cognitif, ou lors d'autres périodes d'exposition comme la petite enfance.

Teams

This thesis took place within the "Early determinants of the child's health and development" team led by Marie-Aline Charles at the Epidemiology and Statistics Research Centre Sorbonne Paris Cité (CRESS) of the French National Institute of Health and Medical Research (INSERM), in Villejuif, France and a part of it was realized in the "Department of Environmental Exposure and Epidemiology" team led by Catherine Thomsen, at Division of Infection Control and Environmental Health, of the Norwegian Institute of Public Health (NIPH), Oslo, Norway. This thesis was conducted under the supervision of Blandine de Lauzon-Guillain and co-supervised by Jérémie Botton, assistant professor of epidemiology and biostatistics at Paris-Sud University, who is the principal investigator of the COCTELL project, and Eleni Papadopoulou, post-doctoral fellow at NIPH.

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List of papers

- Published papers

Paper I: **M Kadawathagedara**, A Chan Hon Tong, B Heude, A Forhan, MA Charles, V Sirot, J Botton. Dietary acrylamide exposure during pregnancy and anthropometry at birth in the EDEN mother-child cohort. Environ Res. 149: 189-96; 2016, http://dx.doi.org/10.1016/j.envres.2016.05.019

Paper II: **M Kadawathagedara,** C Kersuzan, S Wagner, C Tichit, S Gojard, MA Charles, S Lioret, B de Lauzon-Guillain. 2017. Adéquation des consommations alimentaires des femmes enceintes de l'étude ELFE aux recommandations du Programme national nutrition santé. Cah Nutr Diet, 78-88 ; 2017, http://dx.doi.org/10.1016/j.cnd.2016.12.001

J Botton, **M Kadawathagedara,** B de Lauzon-Guillain. Endocrine disrupting chemicals and growth of children. Ann Endocrinol (Paris); 2017, http://dx.doi.org/10.1016/j.ando.2017.04.009

T Traoré, A Forhan, V Sirot, **M Kadawathagedara**, B Heude, M Hulin, B de Lauzon-Guillain, J Botton, MA Charles, A Crépet, on behalf of the EDEN Mother-Child Cohort Study Group. To which mixtures are the French pregnant women mainly exposed? A combination of the second French Total Diet Study with the EDEN and ELFE cohort studies. Food and Chem Toxicol. 2017 Nov 12;111:310-328. doi: 10.1016/j.fct.2017.11.016

- Submitted papers

Paper III: **M Kadawathagedara,** J Botton, B de Lauzon-Guillain, HM Meltzer, AL Brantsaeter, M Haugen, E Papadopoulou. Dietary acrylamide exposure during pregnancy and postnatal growth and obesity: results from the Norwegian Mother and Child Cohort Study (MoBa), Environment International (under review)

M Kadawathagedara, B de Lauzon-Guillain, J Botton. Environmental contaminants and child's growth: evidence from epidemiological studies. Submitted to Journal of Developmental Origins of Health and Disease.

- Paper in preparation

Paper IV: **M Kadawathagedara**, T Traoré, S Carles, MA Charles, B Heude, M Hulin, A Crépet, V Sirot, B de Lauzon-Guillain*, Jérémie Botton*; on behalf of the EDEN Mother-Child Cohort Study Group. Use of total diet studies in epidemiology: application in the EDEN mother-child cohort. Submission planned to Environment International

L Fábelová, **M Kadawathagedara**, T Traoré, A Crépet, V Sirot, A Forhan, JY Bernard, MA Charles, B de Lauzon-Guillain, B Heude, J Botton; on behalf of the EDEN Mother-Child Cohort study group. Exposure to mixtures of dietary contaminants in pregnancy and cognitive development of preschool aged children. Submission planned to Environment International

Paper V: **M Kadawathagedara***, S Lioret*, C Kersuzan, C Tichit, S Nicklaus, MA Charles, B de Lauzon-Guillain. A priori and a posteriori maternal dietary pattern of the ELFE study and associations with offspring's birth weight. Submission planned to the American Journal of Clinical Nutrition.

Papers not directly related to the thesis

- Published papers

S Gorecki, N Bemrah, AC Roudot, E Marchioni, B Le Bizec, F Faivre, **M Kadawathagedara**, J Botton, and G Rivière on behalf of the EDEN mother-child cohort study group. Human health risks related to the consumption of foodstuffs of animal origin contaminated by bisphenol A, Food Chem Toxicol. 2017 Dec;110:333-339. doi: 10.1016/j.fct.2017.10.045. Epub 2017 Oct 28.

- Submitted papers

B Heude, M Le Guern,A Forhan, P Scherdel, **M Kadawathagedara**, MN Dufourg, C Bois, M Cheminat, J Botton, MA Charles, J Zeitlin. Can Intergrowth-21st fetal growth standards be used for all fetuses? A study of all births and births fulfilling Intergrowth's "healthy pregnancy" criteria in the French national Elfe birth cohort. European Journal of Epidemiology

- Paper in preparation

A Camier, **M Kadawathagedara**, S Lioret, MA Charles, B de Lauzon-Guillain. Social inequalities in perinatal folic acid supplementation: results from the ELFE cohort.

Oral communications

M Kadawathagedara, J Botton, B de Lauzon-Guillain, HM Meltzer, AL Brantsaeter, M Haugen, E Papadopoulou, Dietary acrylamide exposure during pregnancy and postnatal growth and obesity: results from the Norwegian mother and child cohort study (MoBa), 10th World Congress on Development Origins of Health and Disease, Rotterdam, Netherlands, 2017

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M Kadawathagedara, C Kersuzan, C Tichit, S Gojard, MA Charles, S Lioret, B de Lauzon-Guillain Respect des recommandations PNNS chez les femmes enceintes de l'enquête Elfe. French Nutrition Days (Journées francophone de nutrition), Bruxelles, Belgium, 2014

M Kadawathagedara, C Kersuzan, C Tichit, S Gojard, MA Charles, S Lioret, B de Lauzon-Guillain. Respect des recommandations PNNS chez les femmes enceintes de l'enquête Elfe. 2nd conference of the French society of developmental origins of health and disease (SF-dohad), Nantes, France, 2014

M Kadawathagedara, A Chan Hon Tong, B Heude, A Forhan, MA Charles, V Sirot, J Botton. Dietary acrylamide exposure during pregnancy and anthropometry at birth in the EDEN mother-child cohort. 2nd international conference on nutrition and growth, Barcelona, Spain, 2014

Invited communications

M Kadawathagedara, C Kersuzan, C Tichit, S Gojard, MA Charles, S Lioret, B de Lauzon-Guillain. Respect des recommandations PNNS chez les femmes enceintes de l'enquête Elfe. French Food and Health Fund (FFAS), Paris, France, 2017

M Kadawathagedara, J Botton, B de Lauzon-Guillain, HM Meltzer, AL Brantsaeter, M Haugen, E Papadopoulou, Dietary acrylamide exposure during pregnancy and postnatal growth and obesity: results from the Norwegian mother and child cohort study (MoBa), MoBa-seminar on Environmental Contaminants; Status and Future Perspectives, Oslo, Norway, 2017

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Poster presentations

M Kadawathagedara, C Kersuzan, C Tichit, S Gojard, MA Charles, S Lioret, B de Lauzon-Guillain. Respect des recommandations PNNS chez les femmes enceintes de l'étude Elfe. French Midwifery conference, Paris, France, 2017, **Price of the best abstract**

M Kadawathagedara, T Traoré, S Carles, MA Charles, B Heude, A Crépet, M Hulin, V Sirot, B de Lauzon-Guillain, J Botton. Maternal exposure to mixtures of food chemicals in relation with offspring birth weight and postnatal growth. International Society of Environmental Epidemiology, Rome, Italy, 2016

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Appendix

Abbreviations

ANSES: Agence nationale de sécurité sanitaire de l'alimentation, de l'environnement et du travail (French Agency for Food, Environmental and Occupational Health & Safety)

BMI: Body Mass Index

BFRs: Brominated Flame Retardants

BPA: Bisphenol A

CONTAM: Contaminant in the Food Chain

DDE: Dichlorodiphenyldichloroethylene

DDT: Dichlorodiphenyltrichloroethane

DON: Deoxynivalenol

EDCs: Endocrine Disrupting Compounds

EDEN: Etude des Déterminants pré- et post natals précoces du développement psychomoteur et de la santé de l'Enfant (study on the pre- and early postnatal determinants of child health and development)

EFSA: European Food and Safety Agency

ELFE: Etude Longitudinale depuis l'Enfance (French Longitudinal Study since Childhood)

FFQ: Food Frequency Questionnaire

IARC: International Agency for Research on Cancer

HCB: Hexacholorobenzene

LB: Lower Bound

MoBa: Norwegian Mother and Child Cohort Study

NMU: Non negative Matrix Under approximation

PAHs: Polycyclic Aromatic Hydrocarbons

PCBs: Polychlorinated biphenyls

PCDFs: Polychlorinated dibenzofurans

PCDDs: Polychlorinated dibenzo-p-dioxins

PFCs: Perfluorinated Compounds

PNNS: Programme National Nutrition Santé (French National Nutrition and Health Program)

POP: Persistent Organic Pollutant

SGA: Small for Gestational Age

TDS: Total Diet Study

UB: Upper Bound

1. BACKGROUND AND AIM

1.1. Maternal nutrition during pregnancy and offspring's growth

Childhood obesity is a major public health challenge (de Onis et al., 2010; The Global Burden of Disease Obesity Collaborators et al., 2017). In 2015, the prevalence of overweight (including obesity) was 17% among French children and adolescents (from 6 to 17 years), while the respective prevalence by gender was 16% for boys and 18% for girls (Verdot et al., 2017). Poor nutrition and lack of physical activity throughout life have been identified as the main driver of long-term elevated body weight, while advances in scientific research contributed to the understanding of complex causes of obesity (Yang et al., 2017). The "Barker hypothesis", suggesting that prenatal environment can influence the development of diseases in adulthood, now called the Developmental Origin of Health and Disease (DOHaD), had been investigated in various epidemiological studies to explain the increase of childhood obesity over the last decades. In fact, Barker showed in 1989 that children born with a lower birth weight were more likely to develop cardiovascular diseases, diabetes and metabolic syndrome in adulthood than their counterparts with higher birth weight (Barker et al., 1989). Baker and Hales hypothesized that nutritional restriction during pregnancy would lead to an adaptive response of foetus, favouring growth of noble organs (e.g. brain and kidney) to the detriment of others organs and ending up to a lasting alteration of the metabolism. These adaptations would be even more deleterious for children who were malnourished in-utero but exposed high nutritional intakes during the postnatal period (Hales and Barker, 1992). Some historical examples, such as the Dutch famine in 1944-45, have linked maternal under-nutrition during pregnancy with low birth weight, to incidence of cardiovascular diseases in adulthood (Painter et al., 2006). More recently, studies indicated that the reverse situation of excessive caloric intake during pregnancy also has implications for foetal development and long-term health (e.g. childhood and adolescence adiposity, higher body mass index [BMI] during adulthood), as demonstrated for maternal obesity or excessive gestational weight gain (Lawlor et al., 2011; Sharp et al., 2015).

Maternal nutrition during pregnancy appears therefore to be crucial for foetal development and later child's health (McMillen et al., 2008). More generally, the link between early life factors and long-term health is now well established (Gluckman et al., 2005). Epigenetic mechanisms provide a biological plausibility to these associations (Boekelheide et al., 2012).

Well-studied risk factors of childhood obesity, such as childhood diet and sedentary physical activity, do not completely account for its increasing prevalence worldwide. Hence, researchers have been focusing on alternate potential risk factors of childhood obesity, including the exposure to endocrine disrupting chemicals (EDCs). According to World Health Organization (WHO) (Bergman et al., 2015): “An endocrine disruptor is an exogenous substance or mixture that alters function(s) of the endocrine system and consequently causes adverse health effects in an intact organism, or its progeny, or (sub) populations. A potential endocrine disruptor is an exogenous substance or mixture that possesses properties that might be expected to lead to endocrine disruption in an intact organism, or its progeny, or (sub) populations.” Emerging evidence suggests that exposure to obesogenic chemicals might also play a role in increasing obesity risk, beyond traditional risk factors (Heindel et al., 2015; Tang-Peronard et al., 2011). The foetal and early postnatal periods would be of high susceptibility to these environmental exposures (De Long and Holloway, 2017; Diamanti-Kandarakis et al., 2009). The use of chemicals in consumer products and food stuffs has increased tremendously in the past decades, many of which can act as EDCs. EDCs can potentially affect all the human hormonal systems ranging from metabolism to growth, neurodevelopment or reproduction (Bergman et al., 2015; Kabir et al., 2015; Maqbool et al., 2016). In the recent years, there is compelling evidence revealing that these chemicals may act as obesogens and play a role in increasing obesity risk, especially when exposure occurs during pregnancy and early life (Darbre, 2017; Heindel et al., 2015; Legler et al., 2015; Tang-Peronard et al., 2011). A scientific expert panel concluded that “EDC exposures in the EU contribute substantially to obesity and diabetes, with a moderate probability of >€18 billion costs per year” (Legler et al., 2015).

1.2. Food chemicals during pregnancy

1.2.1. *Food contamination*

Exposure to chemicals through diet is an important pathway to consider in environmental epidemiology. For instance, diet contributes to 90% of total human exposure to dioxins and polychlorinated biphenyls (PCBs) (Liem et al., 2000). It is also the main source of exposure to hexacholorobenzene (HCB) and dichlorodiphenyltrichloroethane (DDT) (ATSDR, 2002a). A contaminant is a substance that is detected in matrix where it does not occur naturally. Indeed, many contaminants may be present in foods and exposure to these contaminants vary considerably with dietary habits (Baker and Nieuwenhuijsen, 2008). Some chemicals can be added (like pesticides and antibiotics) or can be naturally present in the food. They can be present at trace or even undetectable levels (Klaassen, 2013). In the rest of the thesis, we will use the term of chemicals as it is more general one.

The presence of chemicals in food items can be consecutive to different processes:

- natural origin: case of inorganic chemicals, minerals, phytoestrogens,
- natural contamination: case of mycotoxins,
- long-term contamination of water or soils due to human activities (industrial, agricultural or domestic contamination): case of persistent organic pollutants and heavy metals,
- technological or agronomic processes: case of authorized substances such as phytosanitary products or plant protection products (i.e. pesticides, herbicides, insecticides),
- processing or conservation of raw material or ready-to-eat food: case of neoformed compounds such as acrylamide and polycyclic aromatic hydrocarbons (PAHs) and case of authorized food additives or bisphenols, phthalates.

Historical examples of accidental contamination of foods to high dose of chemicals are well documented. Contamination to polychlorinated biphenyls (PCBs) and mercury are some of the most

famous: these acute contamination events were due to pollution of water or pollution occurring during the extraction process of rice oil (Guo et al., 1994; Harada, 1995; Yen et al., 1989) and could provide knowledge on the potential influence of high dose of exposure to a chemical on health. For example, birth weight restriction related to PCBs exposure was first described in humans after the 1968 Yusho incident in Japan, where thousands of pregnant women were intoxicated by PCB-contaminated rice oil. Their infants were born with specific characteristics: dark brown pigmentation of the skin and the mucous membrane, gingival hyperplasia, exophthalmic oedematous eye, dentition at birth, abnormal calcification of the skull as demonstrated by X-ray, rocker bottom heel and high incidence of low birth weight babies (Yamashita and Hayashi, 1985). These acute contamination events could also lead to hypothesis in the context of lower dose of exposure or chronic exposure as, for most of chemicals, relevant information on human toxicity remain unavailable (Baker and Nieuwenhuijsen, 2008).

To address the issue of food contamination, many countries have a food safety and security agency that provides reports and scientific advices to help to regulate the contamination of the food chain. After the food crisis of the 1990s, due to several episodes of Salmonella contamination, dioxin contamination or the bovine spongiform encephalopathy infection, the European Food and Safety Agency (EFSA) has been created. EFSA produces scientific opinion and advice that provides groundwork for European policies and legislation. The use of several persistent organic pollutants (POPs) has been prohibited since the 1980s in the United States and, in most countries, since the Stockholm convention in 2001. However, these pollutants can still be found in the environment (water or soils) and consequently in foods. Moreover, most of them are lipophilic and can bioaccumulate throughout the food chain.

1.2.2. *Maternal exposure during pregnancy in French women*

New-born babies have detectable concentrations of numerous environmental chemicals (Aylward et al., 2014). Studies have shown that many environmental contaminants can pass the placenta barrier

and in utero exposure occurs (Giaginis et al., 2012; Myren et al., 2007). Hence it is of primary importance to monitor exposures before and during pregnancy.

The French human biomonitoring program has been implemented by the French national public health agency (Santé publique France) in 2010 (Dereumeaux et al., 2016a). This program consisted in two cross-sectional national population-based biomonitoring surveys: the perinatal component was based on a random selection of pregnant women enrolled in the French Longitudinal Study since Childhood (the ELFE study, described in chapter 2) and the more general component was based on a study with a representative sample of adults aged 18-74 years and children aged 6-17 years, the Esteban study (Verdot et al., 2017). Findings from the perinatal component of the program (Dereumeaux et al., 2016b) indicated that bisphenol A (BPA), phthalates, pesticides (mainly pyrethroids), dioxins and furans, PCBs, brominated flame retardants (BFRs), perfluorinated compounds (PFCs) and metals (except uranium) were quantified in almost all collected samples. However, the exposure levels for some chemicals (e.g. phthalates, BPA, pesticides) were lower in the ELFE participants to those found in previous studies conducted on pregnant women in France or abroad. For total BPA and phthalates, exposure levels were similar to those reported in the most recent studies conducted among pregnant women and using spot urine samples. The authors explained these decreases by policies prohibiting or favouring substitution of these compounds in industrial processes. For BFRs, exposure levels were lower than in northern American pregnant women and, for PFCs, exposure levels were quite similar to those previously found in pregnant women in France or abroad. On the opposite, for pyrethroid and PCBs, exposure levels measured in the ELFE subsample were higher than those found in other studies among pregnant women. Finally, when no comparable data exist among pregnant women, results were compared to those found in the general population: dioxins and furans exposure levels highlighted in the ELFE subsample were lower than those observed in previous studies conducted in the French general population.

Complementary to data from the biomonitoring program, some observational studies provide data on food chemical exposure among pregnant women by combining data from food frequency questionnaires (FFQ) to data from the second French Total Diet Study (TDS, described in chapter 2) (Sirot et al., 2009). In the EDEN mother-child cohort (described in chapter 2) (Chan-Hon-Tong et al., 2013), food chemical exposure was assessed at two periods: the year prior the pregnancy and the last three months of the pregnancy. For most chemicals, significant changes in exposure were highlighted according to timing (before pregnancy or last three months of pregnancy) or seasons. Some chemical exposures appeared to be of concern and could have health impact, and margins of exposure to acrylamide, inorganic arsenic, lead, and a brominated flame retardant BDE-99 were too low to exclude all risks. For non-dioxin like PCBs, T-2 and HT-2 toxins, and deoxynivalenol (DON), quite high rates of intake above the toxicological reference values were highlighted before pregnancy but not during the last trimester of pregnancy. More recently, dietary exposure to pesticides was also investigated in detail in the ELFE study. Among 317 pesticides evaluated, under the upper bound (UB) scenario (undetected results were set to the LOD and unquantified, but detected, results were set to the limit of quantification), 14 pesticides exceeded the acceptable daily intake, while, under the lower bound (LB) scenario (results below the limit of detection were assigned a value of zero and unquantified, but detected, results were set to the LOD), only lindane exceeded the acceptable daily intake (de Gavelle et al., 2016). Another French study that focuses on potential impact of environmental and occupational exposure to chemicals on pregnancy and child development, the PELAGIE cohort (Chevrier et al., 2011), showed that herbicides were quantified in 5.3% (atrazine) to 39.7% (triazine hydroxylated metabolites) of maternal urine samples collected during pregnancy. The quantification frequency of herbicides in urine was higher for chloroacetanilide herbicides (especially for acetochlor) among women living in rural areas than women living in urban areas, while the frequency of triazine herbicide quantification was similar in both groups (Chevrier et al., 2014).

1.3. Environmental contaminants and child's growth

Infants can be exposed either prenatally, by trans-placental passage of chemicals, or postnatally by breastfeeding, their own diet and by other external pathways (air inhalation, dust, hand-to-mouth exposure) after birth.

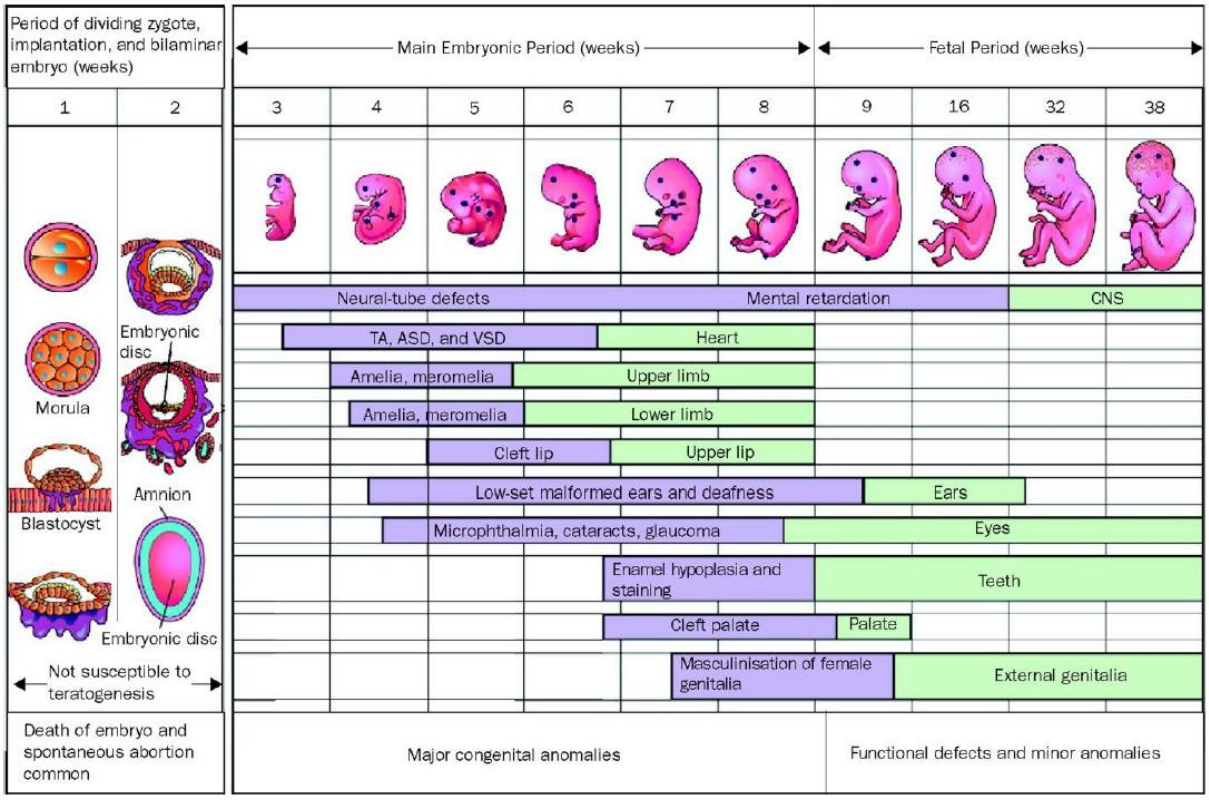
The placenta is the link between mothers and foetuses, and has multiple function, including transport of nutrients or oxygen and elimination of metabolic waste products. It was thought to be a barrier for drugs and chemicals but, during the last decades, evidence has accumulated that drugs and chemicals can be transferred across the placenta, by passive diffusion mechanism or active transporters (Giaginis et al., 2012; Myren et al., 2007). Most of the chemicals detected in food can pass the placental barrier, and can reach the developing internal organs of the foetus, especially the brain, and some of them can accumulate.

Several pieces of evidence suggest that foetuses and infants may be more sensitive to pollutants than adults (Landrigan et al., 2003). First, children's metabolic pathways are immature — especially during the foetal period and the first year after birth — suggesting that metabolism and detoxification are not as efficient in infants as they are in adults. Furthermore, development processes during these periods are also more easily disturbed. Due to their smaller body surface area, even low exposure levels during this window could have detrimental effects, sometimes asymptomatic at the time of exposure but appearing later on (Barouki et al., 2012).

To add some complexity to this issue, the effects of environmental contaminants on children's health can be highly dependent on exposure timing (Liu et al., 2017). Many sequential developmental processes exist in early life exist. The development of the foetus is unidirectional and specifically-timed. It is a complex and coordinate subsequent cellular events **see Figure 1** (Nowakowski and Hayes, 1999). Several studies have investigated the effect of prenatal exposure to environmental contaminants can negatively affect foetal growth and a wide range of health defects. Birth weight has been extensively studied as a proxy of foetal growth and low birth weight (LBW) less than 2500g is a

marker of intrauterine growth retardation (Schoeters et al., 2011; Slama and Cordier, 2013; Wigle et al., 2008).

Figure 1: Crucial periods in prenatal development from (Cardonick and Iacobucci, 2004)



Dots on the developing foetus show common sites of action of teratogens (agents that can disturb the development of an embryo or foetus). Horizontal bars indicate foetal development during a highly sensitive period (purple) and a less sensitive period (green). Abbreviations: CNS, central nervous system; TA, truncus arteriosus; ASD, atrial septal defect; VSD, ventricular septal defect.

In order to provide a summary of epidemiological evidence on the association between prenatal exposure to chemicals and prenatal and postnatal growth, we presented systematic review articles and international meta-analyses, when available, or recent research articles when summarising articles were not available. We are going to present first persistent organic pollutants, then, non-persistent pollutants (i.e. phthalates, BPA and environmental phenols), toxic heavy metals (i.e. cadmium, lead, arsenic and mercury) and, finally, other chemicals (i.e. mycotoxins and acrylamide). Literature evidence on prenatal exposure to environmental contaminants and pre or post-natal growth is presented below and summarize in **Table 1**.

1.3.1. *Persistent organic pollutants*

Persistent organic pollutants (POPs) are carbon-based chemical substances. They have a long half-life, are found throughout the environment and are toxic for humans and wildlife (Stockholm Convention, 2001). Most POPs are results of human activities, related to the use of pesticides or generated as by-products of industrial or combustion processes. Once in the environment, POPs accumulate in fatty tissue of living organisms, reaching the greatest concentrations at the top of the food chain (large fish, mammals and predatory birds). For non-accidentally and non-occupationally exposed populations, the major pathway of human exposure is from the ingestion of contaminated food. The main source (around 95%) of POPs intake is through dietary intake of animal fats (Magliano et al., 2014).

In 2001, the Stockholm convention has listed twelve POPs, the list has been extended further in 2017 with the addition of 16 chemicals classes. This section is focused on exposure to POPs that have been have been linked to child growth, namely:

- polychlorinated biphenyls (PCBs),
- polychlorinated dibenzo-p-dioxins (PCDD), polychlorinated dibenzofurans (PCDF),
- dichlorodiphenyl trichloroethane (DDT) and its metabolite dichlorodiphenyl dichloroethene (DDE),
- hexaclhorobenzene (HCB),
- brominated flame retardants (BFRs),
- perfluoroalkyl substances (PFAS).

Polychlorinated biphenyls (PCBs)

PCBs were used in industry as heat exchange fluids, in electric transformers and capacitors, and as additives in paint, carbonless copy paper and plastics. Of the 209 different types of PCBs, 13 exhibit a dioxin-like toxicity (Giesy and Kannan, 1998). Their persistence in the environment corresponds to the degree of chlorination, with higher chlorinated PCBs having longer half-lives (ATSDR, 2000). PCBs are listed as probable human carcinogens (IARC, 2016).

Large numbers of people have been accidentally exposed to PCBs through two cases of PCB food contamination of rice bran cooking oil during manufacture. Consumption of PCB-contaminated rice oil in Japan in 1968 and in Taiwan in 1979 caused pigmentation of nails and mucous membranes and swelling of the eyelids, along with fatigue, nausea and vomiting (Lu and Wong, 1984). Prenatally exposed Taiwanese children showed developmental delays and behavioural problems seven years after the accident (Chen et al., 1994). Another incidence of accidental exposure was the PCB contamination by industrial waste of the Lake Michigan in 1976. Children of mothers who consumed large amounts of contaminated fish from Lake Michigan showed poorer short-term memory function at age 4-y (Jacobson et al., 1990).

In non-accidentally exposed population, a large meta-analysis showed that prenatal exposure to PCB‑153 has been inversely associated with birth weight. More specifically, they reported a 150-g (95% CI: –240, –50 g) reduction per 1 µg/L increase in cord serum PCB‑153 (Govarts et al., 2012). Nevertheless, prenatal exposure to PCBs does not have an established negative association with low-birth weight, defined as a newborn with birth weight less than 2,500 (El Majidi et al., 2012). Concerning postnatal growth, a study pooling the data of seven birth cohorts showed did not show any association between prenatal exposure to PCB 153 and postnatal growth from birth to 24 months (Iszatt et al., 2015).

Dioxins and Furans

Dioxins (Polychlorinated dibenzo-p-dioxins, PCDDs) and furans (Polychlorinated dibenzofurans, PCDFs) are classes of POPs and refer to a group of toxic chemical compounds that share certain physico-chemical characteristics. Dioxins are produced unintentionally due to incomplete combustion or during the manufacture of pesticides and other chlorinated substances. The main sources of dioxins are the burning of hospital, municipal or hazardous wastes as well as automobile emissions, peat, coal, and wood (ATSDR, 1998). There are 75 different dioxins, of which seven are considered to be of concern, according to who the American Agency for Toxic Substances and Disease Registry (ATSDR, 1998).

Furans (PCDF) are produced unintentionally from many of the same processes that produce dioxins or PCBs. They have been detected in emissions from waste incinerators and automobiles. Furans are structurally similar to dioxins and share many of their toxic effects. There are 135 different types, and their toxicity varies (ATSDR, 1994).

Dioxins and furans have been associated with a number of adverse effects in humans (such as immune and enzyme disorders or chloracne), and are classified as possible human carcinogens (IARC, 1987). Diet, particularly animal products, is the major source of exposure for humans to dioxins and furans for humans.

Furans persist in the environment for long periods (several days in the air), and are classified as possible human carcinogens (IARC, 1995). Diet, particularly animal products, is the major source of exposure for humans. Furans have also been detected in breast-fed infants.

A small meta-analysis including only two case-control studies showed an increased risk of low birth weight after prenatal exposure to dioxins (Pan et al., 2015). A recent pooled analysis of three birth cohorts examined the effect of prenatal exposure to dioxins and dioxins like compounds and BMI at seven years in Norway, Belgium and Slovakia (Iszatt et al., 2016). Dioxins (PCDD, TCDD), furans (PCDF) and dioxin-like compounds (some PCBs) appeared to be associated with higher growth between 0 and 24 months (adjusted estimate for change in z-score: β = 0.07, 95% (confidence interval) CI: −0.01, 0.14). At 7 years, dioxins exposure was associated with a significant increase in BMI in girls but not in boys. Furthermore, girls had a 54% increased risk of being overweight at 7 years.

Dichlorodiphenyl Trichloroethane (DDT) and Dichlorodiphenyl Dichloroethene (DDE)

DDT was widely used as insecticide during World War II to protect soldiers and civilians from malaria, typhus, and other diseases transmitted by insects. After the war, DDT continued to be used to control these infectious diseases, and it was sprayed on a variety of agricultural crops, especially cotton. DDT is still applied to protect against the transmission of disease from mosquitoes, such as malaria, in several developing countries (ATSDR, 2002a). Its chemical stability, its persistence (as much as 50% can

remain in the soil 10-15 years after application), and its past widespread use result to present detection of DDT residues in the environment, even in remote regions of the planet, such as the Arctic (AMAP, 2009). Although residues in domestic animals have declined steadily over the last two decades, food-borne DDT remains the greatest source of exposure for the general population. Dichlorodiphenyldichloroethene (DDE) is the primary metabolite of DDT.

The short-term acute effects of DDT on humans are limited, but long-term exposures have been associated with chronic health effects (ATSDR, 2002a). Findings regarding an association between exposure to DDT and DDE and birth weight have been inconsistent. Several studies reported a negative association between DDT levels and birth weight (Longnecker et al., 2001; Rogan et al., 1986a; Siddiqui et al., 2003; Weisskopf et al., 2005). On the other hand, several studies did not find any association between level of prenatal or postnatal exposure to DDT or DDE and infant birth weight (Bjerregaard and Hansen, 2000; Dewailly et al., 1993; Farhang et al., 2005; Gladen et al., 2003; Karmaus and Zhu, 2004; Ribas-Fito et al., 2002; Rogan et al., 1986b). In the meta-analysis of 12 European birth cohorts (Govarts et al., 2012), the relation between cord serum p,p´-DDE and birth weight was not statistically significant. Concerning postnatal growth, Iszatt et al. showed a positive association between prenatal exposure to DDE and growth from birth to 24 month from the pooled analysis of seven European birth cohorts (Iszatt et al., 2015).

Hexachlorobenzene (HCB)

HCB was first introduced as a fungicide in 1945 to treat seeds and crops and was widely used to control wheat bunt. It is also a by-product of the manufacture of certain industrial chemicals and exists as an impurity in several pesticide formulations (ATSDR, 2015b). The primary route of exposure to HCB for the general population is from foods such as fatty fish.

Several studies reported a negative association between HCB levels and birth weight (Guo et al., 2014; Lopez-Espinosa et al., 2011; Vafeiadi et al., 2014). On the other hand, several studies did not find any association between levels of prenatal or postnatal exposure to HCB and infant birth weight

(Fenster et al., 2006; Ribas-Fito et al., 2002; Sagiv et al., 2007). After reviewing the literature, Tang-Peronard et al. reported an inconsistent association between HCB exposure during pregnancy and obesity risk (Tang-Peronard et al., 2011). One study found that prenatal exposure to HCB increased the risk of overweight among children aged 6 years (Smink et al., 2008) and the association was stronger for children whose mothers smoked during pregnancy. Another study, showed a positive association with rapid growth in the first 6 months of life and obesity in infancy (14 months of age) (Valvi et al., 2014). The prospective study of Verhulst et al., on the contrary, found no effect of prenatal exposure on growth among children aged 1 to 3 years (Verhulst et al., 2009). However, the small sample (n = 138) and the lack of adjustment for several potential confounders in this study may have affected the result.

Polybrominated diphenyl ethers (PBDEs)

PBDEs are a group of bromide-containing compounds. Although there are approximatively 209 PBDE congeners, only 3 major commercial mixtures (which contain a limited number of congeners, present in penta-, octa-, or deca-brominated forms) have been used as flame-retardants since 1965. PBDEs have very low water solubility, and when these substances are released to water, they typically bind to sediment. Humans can be exposed to PBDEs in a wide variety of ways, including consumption of contaminated foods, inhalation or skin contact (ATSDR, 2017).

A recent review (Zheng et al., 2016) stated that there is not enough evidence to support or refute the relationship between PBDEs and low birth weight (LBW). To date, 5 epidemiological studies have examined whether PBDE exposure during pregnancy affects birth weight, with 3 studies (Chao et al., 2007; Harley et al., 2011; Wu et al., 2010) reporting an increased risk for LBW and 2 studies (Mazdai et al., 2003; Tan et al., 2009) reporting no association. The link between PBDEs and postnatal growth and obesity was classified by Vrijheid et al. as “no evidence” as only one study showed an positive association in girls, and negative in boys between maternal prenatal exposure to PBDEs and BMI at 7 years (Vrijheid et al., 2016).

Perfluorinated compounds (PFCs)

Perfluorinated compounds, also known as poly- and perfluoroalkyl substances (PFAS), are a category of man-made organofluorinated compounds. Fluorocarbons are both lipophobic and hydrophobic (ATSDR, 2015a). The most abudant PFCs are perfluorooctanoic acid (PFOA) and perfluorooctanesulfonic acid (PFOS), they are resistant to degradation processes, and have long half-lives (3.8 and 5.4 years, respectively) (Olsen et al., 2007), which allow them to persist indefinitely in the environment (Lindstrom et al., 2011). Humans are exposed to PFCs through intake of contaminated foods or through water, air and dermal exposure due to widespread use since the 1950s as surfactants and emulsifiers in consumer and industrial products. Their unique water- and oil-repelling characteristics make them suitable for diverse applications in manufacturing of food packaging and containers (eg, microwave popcorn bags) or non-stick cookware etc. Evidence suggests that the primary route of exposure in non-occupationally exposed populations is through the food sources (Fromme et al., 2009; Haug et al., 2011; Lindstrom et al., 2011). PFASs have been detected in human blood, breast milk, and cord blood.

Regarding the association between prenatal PFAS exposure and foetal growth, two recent meta-analysis (Bach et al., 2015; Johnson et al., 2014), found a decrease of birth weight, birth length or ponderal index for the increase in maternal serum or plasma PFOA or PFOS. One study reported a negative association between maternal PFOA or PFOS levels and postnatal growth in early infancy (5 month and 12 month, weight and BMI), (Andersen et al., 2010), later results from the same study showed no association at 7 years for BMI and waist circumference (Andersen et al., 2013). While, another studies found a positive association between levels of prenatal exposure to PFOS and 20 month old infant weight (Maisonet et al., 2012).

1.3.2. *Non persistent pollutants*

Parabens, bisphenols, oxybenzone/benzophenone-3, triclosan and triclocarban are man-made chemicals used in various consumer products. Apart from triclocarban, all these compounds have a

phenol group in their chemical structure and can be referred to as “environmental phenols”. Environmental phenols and phtalates are a class of chemicals that do not persist in the environment or into the body once absorbed but are also EDCs (Philippat et al., 2014). The potential influence of each category of non-persistent pollutants is described below. We have focused on the most abundant and frequently studied non-persistent pollutants: phthalates, bisphenol A and other environmental phenols.

Phthalates

Phthalates, or diesters of 1,2-benzenedicarboxylic acid (phthalic acid), are used in manufacturing of cellulose ester films, consumer articles such as toothbrushes, tool handles and toys, medical devices and drugs, ingredients in cosmetic (ATSDR, 2002b; Hauser et al., 2004). Due to their widespread use, phthalates enter the environment by a variety of routes, and exposure to these compounds in industrialized countries is ubiquitous (ATSDR, 2002b; Blount et al., 2000).

Two reviews of the literature (Marie et al., 2015; Vrijheid et al., 2016) do not support an association of phthalates and body size at birth, mainly because of limitations and methodological differences between studies. Vrijheid et al. had classified the evidence for an effect of phthalates on foetal growth as “insufficient” (Vrijheid et al., 2016). Some epidemiological studies showed that prenatal or childhood phthalate exposures were associated with child adiposity but, overall, the associations remain inconsistent (Braun, 2017). One prospective study reported negative associations between prenatal urinary concentrations of metabolites of high molecular weight phthalates and body mass index (BMI) gain during childhood in boys (Valvi et al., 2015). In another study, prenatal maternal urinary concentrations of non-DEHP metabolites were negatively associated with BMI in boys at 5 years (Maresca et al., 2016). In a pooled analysis of three prospective cohort studies representing 707 US children, Buckley et al. reported a sex-specific association between monoethyl phthalate (MEP) during pregnancy and BMI at 4–7 years, which was negative in girls and positive (although not statistically significant) in boys (Buckley et al., 2016). In a population of boys, maternal urinary

concentrations of MEP was positively associated with weight growth velocity from two years onwards, with weight at 3 and 5 years and with BMI at five years (Botton et al., 2016). A study relying on a multi-pollutants analysis did not find any association between prenatal phthalates exposure and BMI at 7 years (Agay-Shay et al., 2015).

Bisphenol A (BPA)

Bisphenol A (BPA) is a synthetic monomer that was first developed in the 1890s and is used in many consumer products, including plastics (as a polymer, i.e. polycarbonate plastic), polyvinyl chloride (PVC), food packaging, dental sealants, and thermal receipts (Le et al., 2008; Munguia-Lopez et al., 2005). Humans are exposed to BPA through their diet, inhalation of household dust, and dermal exposure (Geens et al., 2012; Vandenberg et al., 2007).

A review (Rochester, 2013) showed that the evidence of BPA affecting birth weight is equivocal. The authors stated that the literature does not support a clear link between prenatal BPA exposure and altered birth weight in the offspring and conclude that more studies, examining exposures at several time points during gestation, are needed. Snijder et al. showed in their study, where maternal urinary BPA levels were assessed, that the negative association between BPA and foetal growth was sensitive to the numbers of BPA measurements (Snijder et al., 2013). Another review had classified the evidence for an effect of BPA on foetal growth as “insufficient” (Vrijheid et al., 2016). The epidemiological studies on the relationship between BPA and overweight or obesity in children are also inconclusive. Results from cross-sectional studies mainly show that higher urinary BPA concentrations are positively associated with obesity (Bhandari et al., 2013; Eng et al., 2013; Trasande et al., 2012; Wang et al., 2012), but the direction of the relationship cannot be established using such a design. Few prospective cohort studies examined early-life BPA exposure in association with later childhood BMI (Braun et al., 2014; Harley et al., 2013; Philippat et al., 2014; Vafeiadi et al., 2016; Valvi et al., 2013). Two studies found that higher prenatal BPA exposure was associated with higher BMI or weight-for-height among children (Philippat et al., 2014; Valvi et al., 2013), while one other reported

higher exposure in early childhood was related with lower BMI later in childhood (Braun et al., 2014). The most recent study found that higher BPA concentrations in children's urine at 4 years of age were associated with higher BMI z-score, whereas prenatal urinary BPA concentrations were negatively associated with BMI and adiposity measures in girls and positively in boys (Vafeiadi et al., 2016).

Other Environmental Phenols

Commonly studied environmental phenols, other than BPA, include parabens, oxybenzone/benzophenone-3 (OXBE), triclosan (TRCS) and triclocarban (TRCB). Parabens are alkyl or aryl esters of para-hydroxy benzoic acid (PHBA) and have mainly been used as antimicrobial preservatives in food, personal care products and pharmaceuticals (Boberg et al., 2010). OXBE is mainly used as UV filters in sunscreens and as UV stabilizer in some food packaging (Krause et al., 2012). TRCS and TRCB are used as antimicrobial and antifungal agent in products like toothpaste, soaps, detergents and other hygiene and PCPs (Witorsch and Thomas, 2010). Although these environmental phenols are non-persistent chemicals and have short elimination half-lives in humans (parabens: 1-7 hours, OXBE: < 24 hours (Kim and Choi, 2014) and TRCS: 2 days (Sandborgh-Englund et al., 2006)), their widespread use and potential endocrine disrupting properties have made them chemicals of concern (Bergman et al., 2013; Ghazipura et al., 2017).

Environmental phenols can be found in air and water after release from the manufacture, use, and disposal of products containing these compounds. In soil, they are likely to move to groundwater. Low levels of phenol have been found in foods such as smoked summer sausage, smoked pork belly, mountain cheese, fried bacon, fried chicken, and black fermented tea (ATSDR, 2008).

Evidence concerning the effect of phenol exposure on a lower size at birth is limited (Slama and Cordier, 2013). In the French EDEN mother-child cohort, exposure to these chemicals and pre and post-natal growth has been studied. Triclosan concentration in maternal mid-pregnancy urine sample was negatively associated with growth parameters measured at the third ultrasound examination but not earlier in pregnancy (Philippat et al., 2014). At birth, this phenol exposure tended to be negatively

associated with head circumference but not with weight or height. Parabens concentration in maternal mid-pregnancy urine was positively associated with weight at birth. This positive association remained until 3 years for methylparaben.

1.3.3. *Toxic heavy metals*

Toxic heavy metals, such as cadmium, lead, arsenic and mercury, are a group of toxic compounds among which endocrine disrupting activities have been described for some, but not all, of them. They are ubiquitous environmental pollutants. The most common sources of exposure for the general population are through air inhalation and dietary intake. Exposure to heavy metals can occur through inhalation of contaminated air. Air contamination occurs through gasoline and coal combustion, industrial emissions, and the spraying of metal-based pesticides.

Cadmium (Cd)

Cadmium is a heavy metal which occurs both naturally and as a pollutant associated with many modern industrial processes throughout the world. In the general population, the main exposure sources of cadmium are smoking, due to high cadmium content in tobacco leaves, and cadmium-contaminated foods resulting from production in contaminated soil (ATSDR, 2012). Cadmium is known to have endocrine disrupting activities (Slama and Cordier, 2013) and is also a human carcinogen, classified as group I by the IARC (IARC, 2012b).

Lead (Pb)

Lead occurs naturally in the environment. However, most of the high levels found throughout the environment come from human activities (ATSDR, 2007b). Pb is a highly toxic compound to the human body. Since the earliest recorded times, lead has been widely used in human life. The metal has been smelted, applied as a cosmetic, painted on buildings, and glazed on ceramic pots. On the other hand, lead may be the oldest recognized chemical toxin (Chisolm, 1985).

Arsenic (As)

Arsenic is a naturally occurring element that is widely distributed in the Earth's crust and exists in several forms. Arsenic combined with oxygen, chlorine or sulfur is called inorganic As. When combined with carbon and hydrogen is referred to organic arsenic (ATSDR, 2007a). Arsenic is a potent toxicant and carcinogen (IARC, 2012a). Drinking water is one of the major sources of As exposure in some parts of the world and it is present in a wide variety of foods including fish and rice (Carlin et al., 2016).

Mercury (Hg)

Mercury occurs naturally in the environment and exists in several forms. These forms can be organized under three headings: metallic mercury (also known as elemental mercury), inorganic mercury, and organic mercury (ATSDR, 1999). Hg is formed mainly by bacterial methylation of inorganic mercury (IHg) into the organic form methylmercury (MeHg). This transformation occurs in aquatic sediments with bioaccumulation in the food web. Fish and other seafood contain the highest concentrations of Hg, with only small amounts in other food groups (Clemens et al., 2011).

A number of studies have reported a negative association between in utero lead exposure and birth weight, but the literature is more limited for the other metal (Slama and Cordier, 2013). Nevertheless, a recent review (Vrijheid et al., 2016) including prospective studies and meta-analysis published after the 1st of September 2015, reported for prenatal growth a negative association between heavy metals (lead, mercury, cadmium and arsenic and had classified the evidence as "moderate". Concerning postnatal growth, they have reported ten studies with prenatal or postnatal exposure to heavy metals (cadmium, arsenic, mercury or lead) associated with slower postnatal growth in children but, due to a limited number of studies per specific heavy metals they classified evidence as "insufficient" (Vrijheid et al., 2016).

1.3.4. *Others chemicals*

Mycotoxins

A mycotoxin is a toxic metabolite produced by fungi colonizing crops (Marin et al., 2013). One of the most studied mycotoxin is aflatoxin, known to be a human carcinogens (IARC, 2002). Milk and dairy products are the most important food sources of aflatoxin. Zearalenone is another type of mycotoxin, present in grains and other plant foods through fungal contamination by Fusarium species (Marin et al., 2013), and in animal products (e.g., meat, eggs, and dairy products) through deliberate introduction of zeranol into livestock to promote growth and improve beef/meat production. Zeranol is a synthetic derivate of zearalenone. Finally, trichothecene mycotoxin deoxynivalenol (DON) is a mycotoxin produced in wheat, barley and corn following infestation by Fusarium species in the weld and during storage (Marin et al., 2013).

A review reported six studies with significant associations or correlations between low birth weight and aflatoxin while one study did not find any correlation (Shuaib et al., 2010). In a longitudinal study of 137 Gambian infants, exposure to aflatoxin during pregnancy was inversely associated with height-for-age and weight-for-age Z-score in the first year of life (Turner et al., 2007). Another longitudinal study of 200 infants from Benin showed a negative association between aflatoxin-albumin adducts in infants blood at recruitment, and height-for-age Z-score and weight-for-height Z-score 4 to 8 months later (Gong et al., 2004).

To our knowledge no epidemiological study has investigated the association between zearalenone and prenatal growth. In a case-control study of girls, where cases had precocious pregnancy, no significant correlation between urinary zearalenone levels and BMI was found in any group (Asci et al., 2014). Another cross sectional study showed that girls with detectable urinary zearalenone levels tended to be shorter (Bandera et al., 2011).

Experimental animal studies on DON's chronic toxic effects indicated that growth was the parameter most likely to be affected by DON (Pestka, 2010). To our knowledge no previous

epidemiological study has linked the effect of DON exposure to prenatal or postnatal growth (Smith et al., 2012; Wu et al., 2014).

Acrylamide

Acrylamide is a colourless, odourless, low molecular weight, highly water-soluble organic compound. It is a known neurotoxic for humans and animals and was classified as probably carcinogenic in humans (group 2A) by the International Agency for Research on Cancer (IARC, 1994). It is a chemical arising in a wide variety of carbohydrate-containing foods during frying or baking at high temperatures. This chemical will be presented more deeply in the chapter 4.

Two longitudinal studies have shown a relationship between higher maternal acrylamide exposure and lower birth weight or higher risk of having a SGA baby (Duarte-Salles et al., 2013; Pedersen et al., 2012). To our knowledge no study has linked acrylamide exposure and postnatal growth.

Table 1: Summary of the literature on prenatal exposure to environmental contaminant's and child growth

Prenatal exposure		Prenatal growth	Postnatal growth
Persistent Organic Pollutants (POPs)			
	PCBs	Not consistent	No association
	Dioxins and furans	Negative association	Positive association
	DDT/DDE	Not consistent	Positive association
	HCB	Not consistent	Not consistent
	PBDEs	Not consistent	Not consistent
	PFCs	Negative association	Not consistent
Non POPs			
	Phtalates	Not consistent	Not consistent
	BPA	Not consistent	Not consistent
	Other environmental phenols	Not consistent	?
Toxic heavy metals			
	Cadmium	Negative association	Not consistent
	Lead	Negative association	Not consistent
	Arsenic	Negative association	Not consistent
	Mercury	Negative association	Not consistent
Other chemicals			
	Mycotoxins (Aflatoxin)	Not consistent	Not consistent
	Acrylamide	Negative association	?

? : Association not studied to our knowledge

1.4. Objectives

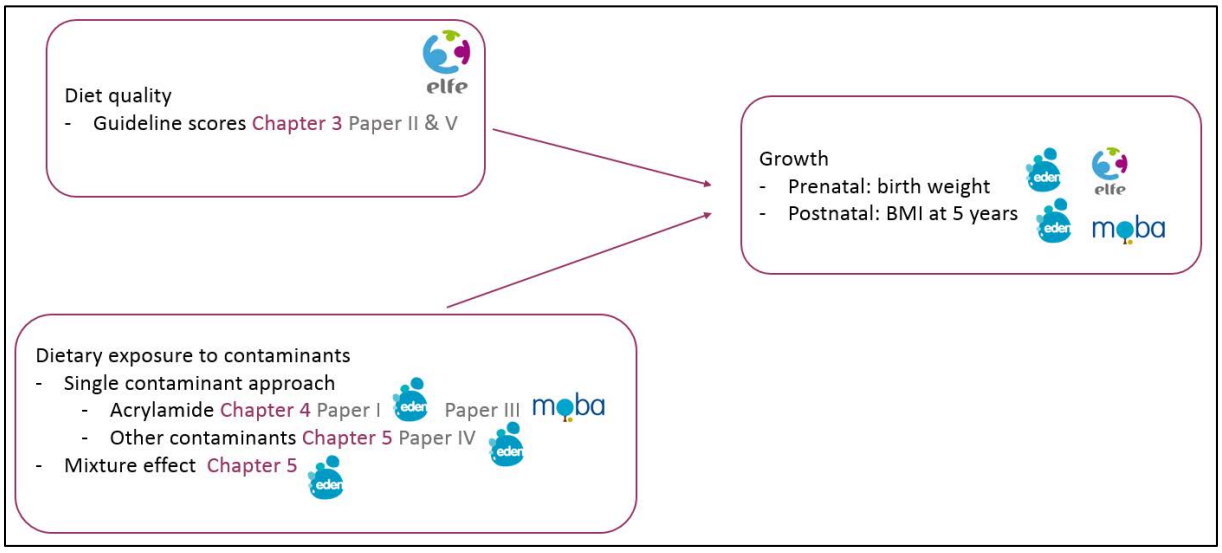
Maternal diet appears to be a vector of both nutrients and chemicals as reviewed in the first chapter of this thesis, their relationships with growth are inconsistent. Even if, for many of them, biological mechanisms have been evoked, substantial gaps in knowledge are remaining about the relationship between prenatal environmental exposures and foetal or early childhood growth (Zheng et al., 2016). In this context, the diet of the pregnant women can't be addressed without dealing with this two issues.

Therefore, after a description of diet quality during pregnancy, the general aim of this thesis was to study the influence of prenatal diet on growth, while taking into account both aspects: the global diet quality and exposure to food chemicals:

1. Description of the diet quality among pregnant women using a dietary score, and its association with prenatal growth in ELFE **(chapter 3)**
2. Influence of acrylamide exposure during pregnancy on prenatal or postnatal growth first in EDEN and replication strategy in MoBa **(chapter 4)**
3. Enlargement to a wide range of food chemicals in EDEN **(chapter 5**).

In the next (and second) chapter, I will present the methods of the study, including the study populations in which the analyses were performed, the main variables, and the statistical methods used **(Figure 2**). The last part presents the general conclusion of the thesis, and discusses the implications of the thesis for future research regarding methodological challenges and public health, the main limitations of the performed analyses, and finally, several perspectives from the thesis.

Figure 2: Specific objectives of the thesis



2. METHODS

2.1. Data sources

2.1.1. *TDS study*

2.1.1.1. Study presentation

Total Diet Studies (TDS) are carried out nationally and follow a standard methodology recommended by the World Health Organization (WHO). Their primary aim is to monitor exposure of populations to chemical substances present in foods, including residues of plant protection products, environmental chemicals, neoformed compounds, natural toxins, additives, trace elements and minerals. A unique aspect of the TDS is that, prior to analysis, foods are prepared as usually consumed (e.g. cooked, microwave heated), so the analytical results provide the basis for realistic estimates of the dietary intake of these chemicals (EFSA/FAO/WHO, 2011).

2.1.1.2. Data collection

Sampling

Two TDS were conducted in France, the first one between 2000 and 2004 and the second one (TDS2), used in the present thesis, in 2006. The TDS2 (Sirot et al., 2009) provided the concentration level of 440 substances in 212 core foods (Arnich et al., 2012; Bemrah et al., 2012; Nougadere et al., 2012; Riviere et al., 2014; Sirot et al., 2013; Sirot et al., 2012a; Sirot et al., 2012b; Veyrand et al., 2013). These core foods, defined from the classification of the 1,280 food items included in the second French national food consumption survey (INCA 2) (Dubuisson et al., 2010; Lioret et al., 2010), covered about 90% of the whole diet of the French population. In order to be representative of French dietary habits, each sample was composed by 15 sub-samples of the same core food, covering different varieties, purchase locations, preparation methods and cooking methods. In total, 19,785 different food products were purchased, in eight French regions over different seasons from 2007 to 2009, to make up the 1,319 composite samples of core foods to be analysed for additives, environmental chemicals, pesticide residues, trace elements and minerals, mycotoxins, phytoestrogens and acrylamide.

Detection limits

Concentrations below the analytical limits of detection (LOD) or quantification (LOQ) could not be detected or quantified, respectively. These data are left-censored and a solution is to replace censored data by a fixed value (GEMS/Food-EURO, 2013) according to different scenarios. In order to focus on substances with a detected value, an LB (Lower Bound) scenario derived from the one recommended in GEMS/Food-EURO (2013) was used in this thesis. This consists in replacing non-detected values by 0 and detected values unable to be quantified, by the LOD value. Under the LB scenario, the exposure of the whole population was equal to zero for 51% of the food chemicals (223 chemicals: 212 pesticides, four perfluorinated compounds and seven mycotoxins).

Chemicals available

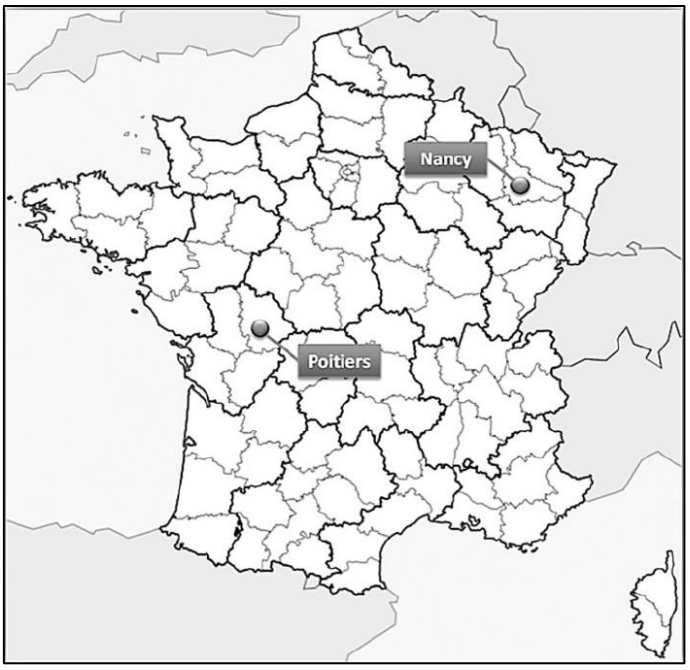
In this thesis, we have focused on chemicals or neoformed components and have not included ten minerals (Ca, Cu, Fe, K, Mg, Mn, Mo, Na, Se, Zn). Then, 207 out of 440 initial substances were included in the present study **(Appendix 1)**

2.1.2. *EDEN mother-child cohort*

2.1.2.1. Study presentation

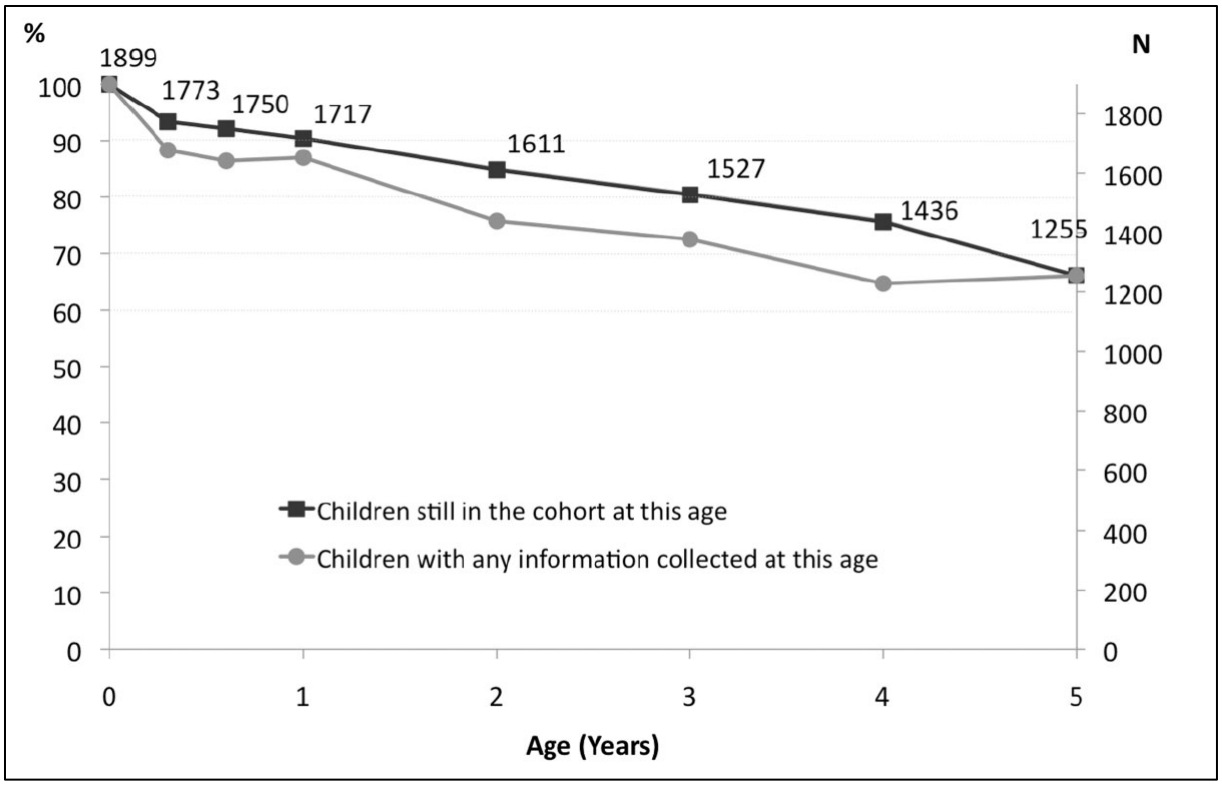
The overall objective of the EDEN study (study on the pre- and early postnatal determinants of child health and development) was to examine the relations and potential interactions between maternal exposures and health status during pregnancy, foetal development, health status of the new-born and the child's health and development (Heude et al. 2015). The exclusion criteria were twin pregnancy, known medical history of diabetes, plan to move outside of the region in the three following years and French illiteracy. Among women who fulfilled these inclusion criteria, 55% agreed to participate (Deschamps et al. 2009). This mother-child cohort had recruited 2002 pregnant women from February 2003 to January 2006, before their 24th week of gestation in two French university hospitals in the cities of Poitiers and Nancy **(Figure 3)**.

Figure 3: Geographic location of the study centre of EDEN study



From the 2002 recruited women, 95 had left the study upon delivery due to personal reasons. Among the 1907 remaining women, birth weight was not available for 8 of the children and 117 did not have a clinical examination at birth, mainly due to transfer to another service or delivery in another maternity department. **Figure 4** illustrates the attrition rate from birth to 5–6 years for the 1899 children with birth weight available: 66% of them were followed up to 5–6 years. Mothers of children lost to follow-up were younger at delivery (28.3 ± 5.2 vs 29.2 ± 4.8 years, $P<10^{-3}$) and had less frequently attained a high school diploma (49% vs 74%, $P<10^{-3}$) than included mothers; however, no difference was observed for maternal pre-pregnancy BMI, child's birth weight or preterm birth rate (Heude et al., 2015).

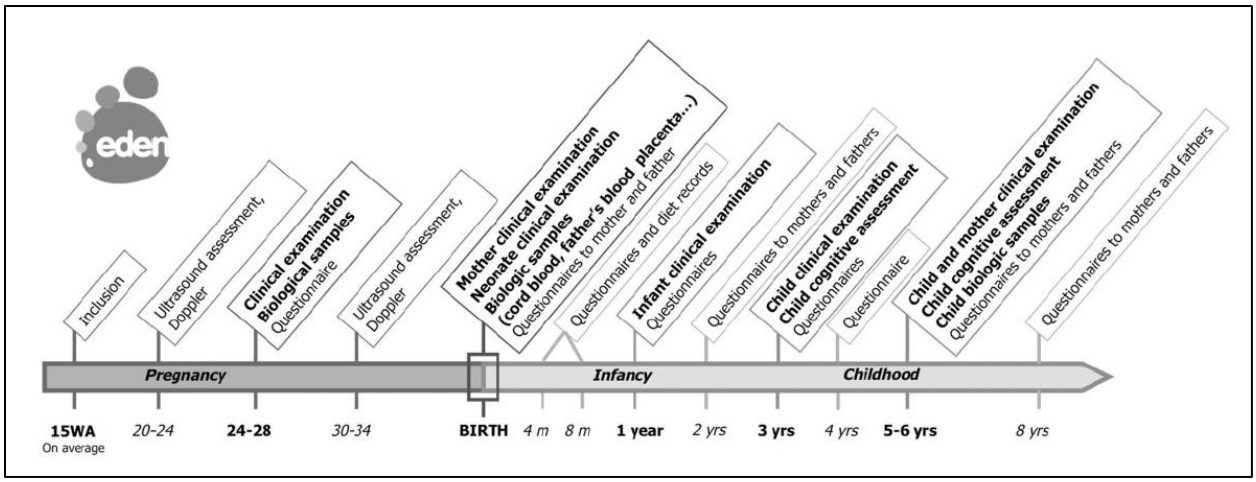
Figure 4: Percent and number of children followed-up from birth to five-six years from (Heude et al., 2015)



Mothers had three clinical examinations, one between 24 and 28 weeks of amenorrhea, one at delivery and one 5–6 years after delivery **(Figure 5)**. The child was examined clinically four times: at birth, at 1 year and 3 years and at 5–6 years. Concomitantly and in-between clinical visits, mothers and fathers answered questionnaires, administered by midwives or self-administered about their offspring, themselves and their household. Biological samples were collected from the mother during pregnancy and at birth, and from the child (or cord) at birth and at 5–6 years. Blood samples were also collected from fathers after the child's birth **(Figure 5)**.

The study has received the approval from the ethics committee of Kremlin-Bicêtre and from the National Commission for Data Protection and Liberties (CNIL).

Figure 5: Study follow up diagram from (Heude et al., 2015)



2.1.2.2. Data collection

At the 24-28thweek examination, maternal height was measured by research midwives, and pre-pregnancy weight (g), education level (highest degree attained) was reported by the participants during the interview. Maternal smoking during first and second trimester was collected through interview at inclusion. Mothers reported their current smoking status (used to characterize the 2nd trimester status), as well as smoking habits at the beginning of pregnancy (used for the 1st trimester status), both including daily cigarette consumption. After delivery, similar information was collected by the research midwives concerning smoking at the end of the 3rd trimester of pregnancy (used for the 3rd trimester status). Mothers were weighed after the delivery using electronic Terraillon SL 351 scales (Hanson Ltd, UK) to the nearest 0.1 kg. Maternal parity (primiparous / multiparous) and the gestational age (weeks), weight (g), length (cm), head circumference (cm) at birth were collected from medical records.

The three variables on smoking status were used to create the average number of cigarettes smoked during all the pregnancy, used as a categorical variable (none, 1 to 9, ≥10 per day). Maternal pre-pregnancy body mass index (BMI) was calculated as weight (in kg) for height (in m) squared. The education level was classified as high school diploma attained or not. Maternal specific weight gain

during pregnancy was calculated by subtracting reported weight before pregnancy from measured weight after delivery.

2.1.2.3. Characteristics of women and new-borns

The mean age of the women included was 29 years (range: 18–44) and 30% of the women were pregnant for the first time. The mean BMI was 23 kg/m² (standard deviation (SD): 4.5) and 53% of the women in the cohort attained high school diploma. The mean birth weight of their child was 3279 g (SD: 512). 52.6% of the newborns of the cohort were males and 94.4% were born at 37 weeks or more. Compared with the 2003 French National Perinatal Survey (Enquête National Perinatale, ENP) (Blondel et al., 2012), a national sample of births, women included in EDEN and still followed up at delivery had a higher level of education **(Table 2)**. Rates of preterm births or admissions of the new-born to a neonatal or intensive care unit were, however, similar in both studies (Heude et al., 2015).

Table 2: Characteristics of mothers and their children followed up until delivery in the EDEN study and comparison with the 2003 National Perinatal survey (table from (Heude et al., 2015)).

		EDEN (2003–06)		ENP 2003
		N	% (*N*) or mean ± SD	% or mean ± SD
Mother's age at delivery	<25 years	1899	15.7 (299)	18.8
	25–34 years	1899	68.6 (1302)	65.3
	≥35 years	1899	15.7 (298)	15.9
Maternal education	Attained high-school diploma	1884	53.6 (1010)	42.6
Employment	Employed during pregnancy	1882	73.1 (1413)	66.0
Parity	Primiparous	1896	44.5 (843)	43.7
Maternal smoking	Non-smokers	1859	63.2 (1192)	64.1
	Smokers during 3rd trimester	1859	16.7 (310)	21.8
Weight before pregnancy	kg	1884	62.2 ± 12.7	61.6 ± 12.5
BMI before pregnancy	kg/m²	1860	23.2 ± 4.6	22.9 ± 4.4
Offspring gender	Male	1899	52.6 (998)	51.2
Preterm birth	<37 weeks of amenorrhoea	1899	5.6 (107)	6.3
Birthweight	g	1899	3279 ± 512	3231 ± 584
Low birthweight	<2500 g	1899	5.4 (102)	8
Caesarean section		1895	15.8 (299)	20.2
Admission to neonatal care unit		1893	7.0 (133)	7.9

2.1.2.4. Food frequency questionnaire

A self-administered food frequency questionnaire (FFQ) was available at two time points in the EDEN study. One was completed at the inclusion and is related to the diet in the year prior to pregnancy and the other one was completed few days following delivery at the maternity and is related to the diet

during the last three months of pregnancy. This FFQ was slightly modified from a FFQ developed and validated in another French study (Deschamps et al. 2009). Consumption frequencies were recorded for 137 different food items, with a 7-item scale from "never" to "more than once a day". We first generated a frequency from the midpoint of the category (i.e. two servings/month for the category of 1 – 3 servings/month). However, some changes were made after a validation step for the questionnaire by comparing it to repeated 24-hour recalls: a minimum assignment was performed for groups of 7 or more items (e.g. fruits, vegetables) or high energy density foods (e.g. "Boiled potatoes", "Fried potatoes"). For these categories, if the frequency reported was between 1 to 3 times per month, we assigned 1 time per month rather than 2 times. Usual portion sizes were estimated using photos for different food types on a 3-level scale, derived from the Supplémentation en Vitamines et Minéraux Antioxydants (SU.VI.MAX) portion book (SU.VI.MAX., 2002) for the 12 food groups (e.g. meat, French fries, pasta, raw vegetables, cooked vegetables, cakes, cheese, beverages) corresponding to FFQ photographs. The portion size of the remaining food groups was estimated from the middle portion of the corresponding item in the SU.VI.MAX portion book. To calculate individual intake for each food item, the portion consumed (in g) was multiplied by the frequency declared (per day). The 137 food items were then grouped into 37 food groups. Women for which more than 3 items of the FFQ were missing were excluded and, when at the most 3 items were missing, missing values were imputed by the sample median.

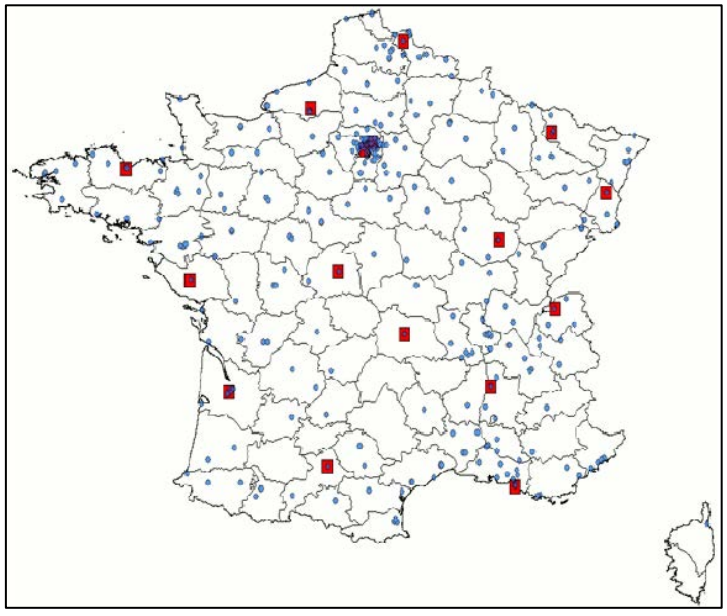
Individual total energy intakes were calculated for all subjects by multiplying the intake (in g per day) by the energy content of each food item, derived from the SU.VI.MAX nutrient composition database (SU.VI.MAX., 2006). Subjects with likely misreport of their food intake, i.e. with an estimated total energy intake under 1000 kcal/day (68 participants) or over 5000 kcal/day (30 participants), were excluded in some analysis (*cf* Chapter 4).

2.1.3. *ELFE study*

2.1.3.1. Study presentation

The purpose of the ELFE (Etude Longitudinale Française depuis l'Enfance) study was to build a nationally representative cohort of 20,000 children to be followed from birth to adulthood using a multidisciplinary approach in order to characterize the relationship between environmental exposures and the socio-economic context on health and behaviours more thoroughly (Vandentorren et al., 2009). It is a multidisciplinary, nationally representative, birth cohort, which included 18,329 children born in a random sample of 349 maternity units in France in 2011. From April 2011, all babies born in the included maternity wards on given recruitment days could be included with parental consent. Inclusion criteria were as follows: children born after 33 weeks of gestation, of mothers aged 18 years or older, not planning to move outside Metropolitan France in the following 3 years. Foreign families could also participate in the study, if mothers were able to read French, Arabic, Turkish or English. The recruitment phase took place during 4 waves of 4 to 8 days distributed along the year to take into account seasonal variability (Pirus et al., 2010). Among the 349 selected maternity units, 320 agreed to participate **(Figure 6)**.

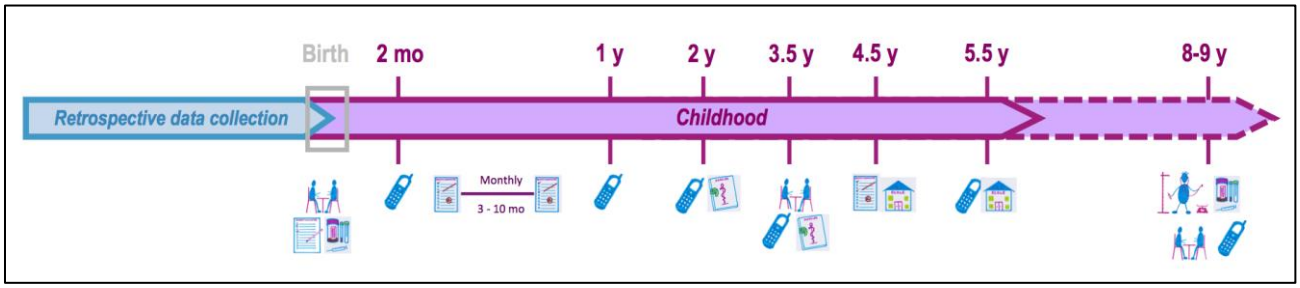
Figure 6: Geographic location of the study centre of ELFE study (Blue dots: maternity units, red rectangles: French Blood Agency)



Participating mothers and children were recruited in maternity wards (51% participation rate). Infants born out of the days of inclusion (n = 71) and those whose parents withdrew consent within first year (n=55) were excluded from the analyses. Infants for whom it was not possible to verify the eligibility criteria due to missing data were also excluded (n = 350). Thus, 17,853 infants were actually eligible. Data were collected in standardized interviews conducted by trained interviewers and through self-completed questionnaires. Mothers were interviewed at the maternity ward after delivery and biological samples were taken during the delivery. Clinical and medical data related to pregnancy and delivery were also accessible from medical records. Two months after delivery, telephone interviews took place with the mothers and fathers. The family was contacted again by phone around the child's first birthday, and again on his or her second birthday. At 3 years old, an interview was held in the child's home. Medical information was recorded and non-invasive samples were taken. In this thesis, we used the data collected at birth and at the 2-month interview **(Figure 7)**.

Families signed a consent form presenting the general aim of the study and all data were analysed anonymous. The ELFE study received approval of bodies overseeing ethical data collection in France (Comité Consultatif sur le Traitement des Informations pour la Recherche en Santé: CCTIRS, Commission National Informatique et Libertés: CNIL).

Figure 7: ELFE study follow up diagram



2.1.3.2. Data collection

Mothers were interviewed at the maternity ward for information about their pregnancy, their new-born, and their general characteristics. Information was completed with records from obstetric and

pediatric medical files. Mothers also completed a self-administered questionnaire on eating habits and exposure to cosmetics during pregnancy. A telephone interview took place 6-8 weeks (called 2-month interview) after delivery and included different types of questions, in particular detailed demographic and socioeconomic variables including country of birth, educational level, employment, monthly income, number of family members. As socio-demographic characteristics were more detailed in the 2-month interview than in the maternity interview, we used first data collected at two months and data collected during maternity stay were used only in case of missing value at 2 months.

Maternal socio-demographic characteristics included in our analyses were: maternal country of birth (France vs. another country), age at delivery (18-25 y, 25-29 y, 30-34 y, ≥35 y), number of older children (none, 1, 2, 3 or more), type of family (traditional, stepfamily, one-parent family), maternal highest education level attained (<Secondary school: less than 11 years, Secondary school: 12 years, high school: 13 years, 2-y university degree: 15 years, ≥3-y university degree: more than 15 years of schooling), smoking status (never smoker, smoker only before pregnancy, smoker until early pregnancy, smoker during the whole pregnancy), maternal region of residence and family income (≤1500 €/month, 1501-2300 €/month, 2301-3000 €/month, 3001-4000 €/month, 4001-5000 €/month, >5000 €/month).

Maternal health characteristics included reported maternal height (cm) and pre-pregnancy weight (kg), and attendance to birth preparation classes (None, 1-5 classes, 6 classes or more). New-born characteristics were collected in the medical record: sex, twin birth, birth weight (g) and gestational age.

2.1.3.3. Characteristics of women and new-borns

The mean age of the women included was 30 years (range: 18–44) and 44% of the women were pregnant for the first time, 66% of the women had a BMI between 18.5 and 25 kg/m² classified as normal, 38% had complete more than 15 years of schooling. The mean birth weight of the children in this cohort was 3327 g (SD: 486 g), 51% were males and 95.2% were born at 37 weeks or more.

Compared with the 2010 French National Perinatal Survey (Blondel et al. 2012), a national sample of births, women included in ELFE were comparable for age at delivery (mean age at delivery 29.7 years, SD: 5.3), parity (43% primiparous) and BMI (65% with normal BMI *vs.* 66% in ELFE). Compared to participants of the ELFE study, women included in the ENP were less educated (28.3% completed 15 years of schooling *vs.* 38% in ELFE), and had newborns with lower birth weight (mean birth weight: 3254 g *vs.* 3327 in ELFE).

2.1.3.4. Food frequency questionnaire

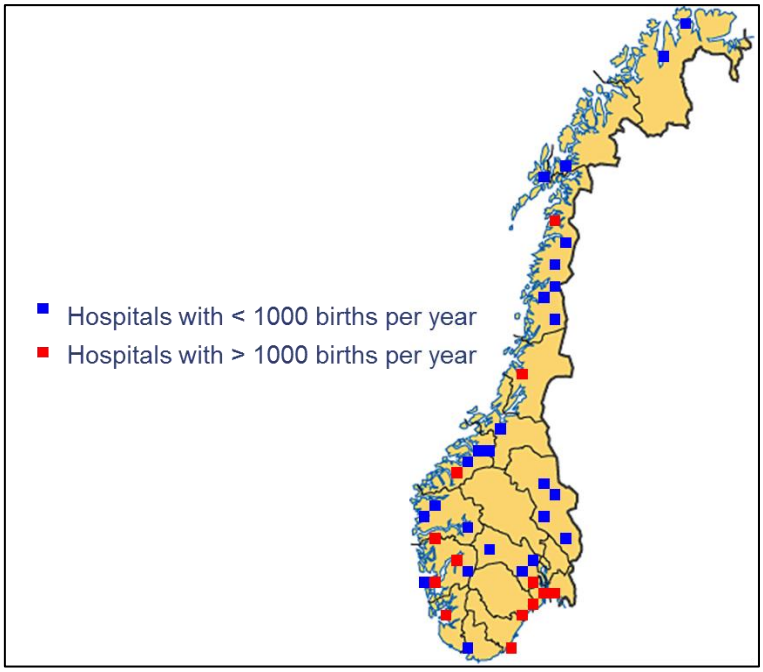
Mothers were asked to complete, during maternity stay, a self-administered FFQ to describe the dietary habits of their last three months of pregnancy. The frequency of consumption of 125 food items was collected, including 12 non-alcoholic beverages and four alcoholic beverages with a 7-item scale from "never" to "more than once a day". Usual portion sizes were estimated using photos for different food types on a 5-level scale, derived from the SU.VI.MAX portion book (SU.VI.MAX., 2002) for the 75 food items corresponding to FFQ photographs. The portion size of the 50 remaining food items was estimated from the middle portion of the corresponding item in the SU.VI.MAX portion book. After the transformation of FFQ frequency categories into annual frequencies, daily intake was assessed for each food item, by combining frequency of intake and portion size. Individual nutrient intakes were then calculated for all subjects by multiplying the daily intake by the nutritional value of each food item, using the SU.VI.MAX nutrient composition database (SU.VI.MAX., 2006). Women for which more than 10 items of the FFQ were missing were excluded and, when at the most 10 items were missing, missing values were imputed by sample median. A validation study was performed comparing the FFQ to three 24-hour recalls (one per month during the last three months of pregnancy) on an ad hoc sample of 62 pregnant women. The validation study showed that, for some food groups, 92.9% (for pasta rice and potatoes lowest percentage) to 100% (for milk) of women were classified in the same quintile or the adjacent one by both methods. Subjects with likely misreport of their food intake, i.e. with an estimated total energy intake under 933 kcal/day (3rd percentile, 464 participants) or over 5072 kcal/day (97th percentile, 464 participants), were excluded.

2.1.4. *MoBa study*

2.1.4.1. Study presentation

The Norwegian Mother and Child Cohort study (MoBa) is a prospective population-based pregnancy cohort conducted by the Norwegian Institute of Public Health. The main aim of MoBa is to detect causes of serious diseases through estimation of specific exposure-outcome associations especially among the children but also among parents (Magnus et al., 2016; Magnus et al., 2006). In brief, participants were recruited from hospitals all over Norway (50 hospitals among 52 Norway's hospitals with maternity units, **Figure 8**) by postal invitation after they signed up for a routine ultrasound examination (17-18th gestational week) in their local hospital from 1999–2008.

Figure 8: Geographic location of the study center of MoBa study



In total, 40.6% of the invited women participated in MoBa. 100 families have decided to leave the cohort and to have their data deleted. The cohort includes 114,479 children, 95,244 mothers and 75,500 fathers **(Table 3)**.

Table 3: Numbers of pregnancies, mothers, fathers and children participating in MoBa from (Magnus et al., 2016)

	Recruited[a]	All participants[b]	Active participants[c]
Pregnancies	112908	112762	101545
Pregnancies, fathers included	87436	87302	78726
Mothers	95369	95244	86169
Fathers	75618	75500	68314
Children	114622	114479	103219
Pairs of twins	1950	1946	1705
Sets of triplets	21	21	17

[a]All recruited participants from 1999 through 2008.
[b]Participants who can be followed through linkage with health registries.
[c]Participants who are sent questionnaires and can be invited to sub-studies.

The participants were asked to provide blood samples (at 17 weeks) and to fill out the baseline questionnaire (at approximatively 17, 22 and 30 weeks) when they came to the hospital for the ultrasound scans. Additional information was collected via questionnaire send by post around 22 and 30 weeks of gestation. Cord blood was collected at birth. Follow-up was conducted by self-administered questionnaires send by post at regular intervals (at 6 months, 18 months, 3, 5, 7 and 8 years old) until the 8 years of the child and through linkage to national registries (medical birth registry, national patient registry, cause of death registry, vaccination registry and cancer registry). Data used in this study are based on version 9 of the quality-assured data files, released for research in November 2015. All MoBa participants provided written informed consent before enrolment into the study. The MoBa study was approved by the Regional Committee for Ethics in Medical Research (S-95113 and S-97045) and the Norwegian Data Inspectorate. The study conducted within this thesis was approved by the Regional Committee of Medical Research Ethics for South-Eastern Norway (2016/377).

2.1.4.2. Data collection

The Medical Birth Registry of Norway (MBRN) was used to collect different information: mother's age at delivery (years), parity (nulliparous vs multiparous), gestational age at delivery, sex of the child and birth weight (g). Maternal education level (highest degree attained), smoking (number of cigarettes per week or per day) status and passive smoking (exposition to passive smoking at home, work) during pregnancy, alcohol consumption during pregnancy (frequency in the 3 first month of the pregnancy) and maternal and paternal anthropometric measures (weight (kg) and height (m)) were self-reported at the baseline questionnaire (15th week's questionnaire). Passive smoking exposure was self-reported again at the third questionnaire (30^{th} week questionnaire). Gestational weight gain (kg) was calculated as the difference between the pre-pregnancy weight, reported at the baseline questionnaire and the weight before delivery, reported 6 months after delivery.

Maternal education level was categorized as years of schooling (≤ 9 years, 13-16 years, ≥ 17 years), maternal pre-pregnancy BMI and paternal BMI were calculated in kg/m^2. Maternal smoking status during pregnancy was categorized as no, occasional or daily consumption of tobacco.

2.1.4.1. Characteristics of women and new-borns

The mean maternal age at delivery was 30.0 years (SD: 4.6 years) and 40.9% of the women were pregnant for the first time. 66.0% of the women had a normal BMI (18.5 – 25 kg/m^2) and 70.0% had completed more than 12 years of schooling. The mean birth weight of the children in the cohort was 3570 g (SD: 611 g). 52.6% were males and 93.2% were born at 37 weeks or more. Nilsen et al. (Nilsen et al., 2009) studied the differences in prevalence estimates and association measures between study participants and all women giving birth in Norway. Women who agreed to participate in the Norwegian Mother and Child Cohort Study (43.5% of invited; n = 73 579) were compared with all women giving birth in Norway (n = 398 849) using data from the population-based MBRN in 2000–2006. They found a strong under-representation of the youngest women (<25 years), those living alone, mothers with more than two previous births and with previous stillbirths (relative deviation 30–

45%). In addition, smokers, women with stillbirths and neonatal death were markedly under-represented in the cohort (relative deviation 22–43%), while multivitamin and folic acid supplement users were over-represented (relative deviation 31–43%).

2.1.4.2. Food frequency questionnaire

The MoBa FFQ was specifically designed for the MoBa study and was introduced in March 2002. It is a semi-quantitative self-administered questionnaire designed to capture dietary habits during the first half of pregnancy (answered at 22 weeks of pregnancy) and included questions about intake of 255 food items or dishes (Meltzer et al. 2008). The frequencies were divided in three subgroups: daily, weekly or monthly frequency, with for each one of 6, 3, or 4 frequencies to choose respectively. Intake of specific foods and nutrients were calculated based on standard Norwegian portion sizes (for dinner, vegetable, cakes and snack), the Norwegian food composition table, analysis of food samples and data on the content of more than 1000 food supplements collected from suppliers (Haugen et al. 2008). A validation study in 119 women in MoBa recruited on average 24 days (SD: 12 days) after completion of the MoBa FFQ showed that, relative to a dietary reference method (4-day weighted food diary) and several biological markers, the MoBa FFQ produces a realistic estimate of habitual intake and is a valid tool for ranking pregnant women according to high and low intakes of energy, nutrients and foods (Brantsaeter et al. 2008a). Subjects with likely misreport of their food intake, i.e. with an estimated total energy intake below 1,075 kcal (4.5 MJ)/day (278 participants excluded) or above 4,777 kcal (20.0 MJ)/day (400 participants excluded), were excluded.

2.1.5. *Summary of main characteristics of birth cohorts*

Table 4 presents a comparison of main characteristics of each cohort used in this thesis.

Table 4: Principal characteristics of the three cohorts

Cohorts			
Target	General population	General population	General population
Objectives	Health and development	Health, development and socialization	Health and development
Coverage	Regional	National	National
Recruitment	Prenatal	Birth	Prenatal
Effective	2000	18,329	95,369
Inclusion period	2003-2006	2011 (4 waves)	1999-2008
Center	2 maternity	349 maternity	50 maternity
Maternal diet	137-item FFQ validated 3 last months of pregnancy	125-item FFQ validated 3 last months of pregnancy	225-item FFQ validated 22 weeks of pregnancy
Growth	Clinical examination (1, 3, and 5y), Child health booklet	Child health booklet	Reported

2.2. Assessment of prenatal exposure to environmental chemicals

The aim of an exposure assessment of populations is to obtain accurate, precise and biologically relevant estimates in the most efficient and cost-effective way (Nieuwenhuijsen, 2015). To assess exposures to chemicals, direct methods or indirect methods can be used. Direct methods measure the level of exposure for each subject through biological sample or through personal monitoring such as outdoor or indoor air pollution sensors. Indirect methods are based on data from environmental monitoring or general measurements (e.g. stationary ambient air monitors or water pollution

measurements) then combined to individual characteristics (e.g. questionnaires, diaries that can collect information on presence of exposure, duration, frequency etc.)(Baker and Nieuwenhuijsen, 2008).

As biomarkers can be expensive, epidemiological studies are increasingly trying to evaluate the exposition to certain chemicals using indirect methods. In particular, for food chemicals, the indirect method would be the combination of food consumption data to exposure data from tested foods, potentially derived from total diet studies (TDS) (Papadopoulou et al., 2017).

2.2.1. *In Eden: TDS combined with FFQ*

Since some differences are observed between food items from the TDS 2 and those from the EDEN FFQ, a matching between nomenclatures of these studies was conducted by ANSES (Chan-Hon-Tong et al., 2013). For most food items, a food item from the FFQ was closed to a food item from TDS 2. When it was not the case, different scenarios were assumed:

- Approached scenario: the food items from the FFQ were more detailed than in TDS 2. For example carrots were separated into “cooked carrot” and “raw carrot” in the FFQ, while, in TDS 2, the food item “carrots” grouped together cooked and raw carrots. In this case, the concentration of the TDS 2 food item “carrots” was used for both detailed EDEN food items.
- Grouping scenario: the EDEN food item was covered by several TDS 2 food items. In this case, the weighted mean of the concentrations of related TDS 2 food items was attributed to this EDEN food item. The weights were estimated by the ratio of intake of each food item among women aged 18 to 45 years from the INCA 2 study. This scenario was applied, for example, to the category “dried vegetables” in EDEN and equivalent to both “white bean” and “lentil” in TDS 2.
- Recipes scenario: this case concerned only the category considered as dishes in the FFQ. For those products, the concentrations were calculated by using recipes. For example, it was

applied to the EDEN item “gratin dauphinois” composed by “potatoes”, “semi-skimmed milk”, “eggs”, “butter” and “cream” items from TDS 2.

After the matching, five food items from EDEN FFQ (avocado, pumpkin, cooked lighter, sweetener and whisky) remained without correspondence with TDS 2 items and were excluded. Finally, 207 substances were detected.

2.2.2. *In MoBa: acrylamide exposure*

A TDS study was not available in Norway but values for acrylamide exposure came from different contamination databases reporting acrylamide concentration of specific food items (Brantsaeter et al., 2008b; Duarte-Salles et al., 2013). Therefore, values of acrylamide concentration reported from Norwegian food items (Norwegian Food Safety Authority, 2002; Norwegian Food Safety Authority, 2006; Scientific Committee of the Norwegian Food Control Authority, 2002) were mostly used for calculating dietary acrylamide exposure. However, when acrylamide values were not available for Norwegian food samples, relevant values were selected from the European Union database (Institute for Reference Materials and Measurements, 2005) or, third, from the Swedish National Food Administration database (Livsmedelsverket, 2002). These data were ready before my arrival in Norway.

2.2.3. *Exposure calculations*

In both cohorts, exposure was assessed by combining concentration values with quantities consumed by each woman. The exposure to the substances was calculated following the formula:

$$e_{ij} = \sum_{f=1}^{F} q_{if} \times c_{fj},$$

where e_{ij} is the exposure to chemical j of subject i; q_{if} is the daily quantity of food f consumed by subject i (f=1 to F,F is the total number of different foods consumed by subject i during the week); c_{fj} is the concentration level of chemical j in food f.

2.3. Growth parameters

Prenatal growth parameters

Weight, length and head circumferences at birth were reported in each cohort either from medical records (EDEN and ELFE) or from the national birth registry (MoBA). Small-for-gestational-age and large-for-gestational-age status in EDEN and ELFE studies were defined by a weight lower than the 10th percentile or higher to 90th percentile. Two definitions were used, the first one according to gestational and sex. And the second one was a customized definition adapted from Gardosi et al. (Gardosi et al., 1995). This definition of SGA took parity, maternal height and weight and baby's sex into account. Conversely to these characteristics assumed to influence foetal growth physiologically, maternal smoking was only included in the customization model to get the independent effect of other variables on weight, but, SGA definition was not corrected for maternal smoking status because of its non-physiological impact on birth weight. For instance, a new-born with a low birth weight will be less likely SGA if its mother is smaller and lighter. On the contrary, a new-born with a low birth weight will have the same probability to be SGA whatever the smoking status of its mother.

Postnatal growth

Growth trajectories were obtained by modelling the individual growth from 1 month to 5 years in EDEN (Carles et al., 2016) and 8 years in MoBa, using the Jenss-Bayley growth curve model. This is a structural growth model, meaning that it implies a basic functional form of the growth and it is suitable for describing growth of weight or length up to 8 years, before growth starts to accelerate due to the start of puberty (Jenss and Bayley, 1937). By this non-linear mixed effects model (with random effect on each parameter) and by applying the Stochastic Approximation of Expectation-Maximisation (SAEM) algorithm (Berkey, 1982; Comets et al., 2014), individual weight and height were calculated using the Jenss-Bayley equation and individual weight and height growth velocities were calculated using the first derivative of the growth model, at several time points (1, 2, 3, 6, 9, 12, 18 months, 2, 3, 4, 5, 6, 7,

8 years). Body mass index (BMI) was calculated as weight (in kg) divided by squared height (in m) using the predicted growth values (Botton et al., 2014). The growth data modelling was conducted by other researchers from each team.

Using the International Task Force cut-offs, in EDEN, the prevalence of overweight was 5.8% and 6.3%, of obesity only 0.7% and 1% at 3 and 5 years respectively. In the included population from MoBa, the prevalence of overweight (including obesity) was 12.2%, 11.1% and 11.5% and, of obesity only 1.5%, 1.3% and 0.7% at 3, 5 and 8 years, respectively.

3. DIET QUALITY AMONG PREGNANT WOMEN AND PRENATAL GROWTH

3.1. Introduction and aim

Maternal diet is the only prenatal source of nutrients and can influence foetal growth and offspring's long-term health. Moreover, mothers play the role of the main regulating organs for the foetus (e.g. liver, kidneys) via the placenta. Optimal nutrient flux from the mother to the foetus is protective for pregnancy complications as preterm birth, preeclampsia and gestational diabetes, and for adverse birth outcomes, such as low birth weight (Chatzi et al., 2012; Meltzer et al., 2011; Rodriguez-Bernal et al., 2010). Therefore, maternal diet during pregnancy appears to be crucial for the developing foetus and later life health disease onset.

Initiated in 2001, the French National Nutrition and Health Program (PNNS) aims to improve the health status of the population by acting on one of its major determinants: nutrition (Hercberg et al., 2008). This plan proposed 9 guidelines (8 guidelines for foods and 1 guideline for physical activity) for the general population and additional guidelines for specific populations, such as pregnant women. Several national surveys aimed to describe diet quality of the French adult population and its evolution, such as INCA (Etude Individuelle National des Consummations Alimentaires, individual and national food survey) in 1998-1999 (Lioret et al., 2008; Volatier J-L, 2000), INCA 2 in 2006-2007 (Dubuisson et al., 2010) and INCA 3 in 2014-2015, conducted by the French Agency for Food Safety and Occupational Health; or ENNS in 2006-2007 (Castetbon et al., 2009) and ESTEBAN in 2014-2016 (Verdot et al., 2017), conducted by the French National Public Health Agency. However, these studies included few pregnant women and were not designed to assess diet quality of this specific population. Studying the diet of pregnant women is a public health issue because it identifies the most vulnerable groups that can benefit from more in-depth information and advice.

Using the data from the ELFE study, the first objective of this analysis was to assess how diet of French pregnant women comply with the PNNS guidelines, and the second objective was to identify the main demographic and socio-economic factors associated with a good or poor compliance. Finally,

the third objective was to analyse the relationship between maternal diet quality during pregnancy and foetal growth.

3.2. Methods

3.2.1. *Dietary scores*

Additionally to the food frequency questionnaire presented in details previously, women were asked to report dietary changes occurring during pregnancy, including raw vegetables, raw or bloody meat and raw milk cheese. For each food item, women indicated whether they had consumed more, less, equally, or had never consumed even before pregnancy this food item. Moreover, the frequency of main meals and snacks (breakfast, lunch, snack, dinner, and snacks between meals) during the last three months of pregnancy was collected using a 5-point scale ranging from "never" to "every day or almost every day".

As, some PNNS guidelines have several components, such as the “Meat, Poultry, Fish and Eggs” group, which proposes to consume them 1 to 2 times a day, but also to consume fish twice a week, the guidelines for the adult population are based on 8 nutritional quantitative benchmarks (daily frequency or daily quantity). In order to evaluate the adequacy of the intake of PNNS guidelines for adults, we adapted for the pregnant women (in particular for alcohol and dairy products) the PNNS Guideline Score (PNNS-GS), developed by Estaquio et al. in 2009 (Estaquio et al., 2009). Hence, guidelines for alcohol intake stipulate that adult women should not exceed two glasses of alcohol per day, while pregnant women are encouraged not to consume any alcohol. For guidelines on wholegrain cereals, intake was available only for bread, so we calculated a wholegrain/white bread ratio. For guidelines on added fat, we focused on plant/animal added fat ratio, as added fat were not reported with sufficient detail to assess energy provided by added fat.

Our *Diet Quality* score was thus based on 11 items described in the **Table 5**.

Table 5: PNNS guidelines for the adult population and construction of the score

General PNNS Guidelines	Limit to obtain a score of 1
Fruits and vegetables	At least 5 times/day
Starchy food	3 to 6 times/day
Whole food	Whole/white bread ratio ≥ 2/3
Dairy products	At least 3 times/day
Meet, fish, poultry and eggs	1 to 2 times/day
Fish and seafood	At least 2 times/week
Added fat	No use of added fat or plant/animal added fat ratio ≥0.5
Added sugar	Energy intake from sugar-rich foods ≤10% of total energy intake
Alcohol	No alcohol
Beverages	At least 1 l/day for water (score 0.5) + at the most 250 ml/day for sweet beverages (score 0.5)
Salt intake* (only from food, not added salt)	At the most 8 g/day

* Reconstituted from sodium intake: sodium intake x 1.25 (Agence Française de Sécurité Sanitaire Alimentaire (French Food Safety Agency), 2002; Estaquio et al., 2009)

Due to difficulties in estimation of energy needs among pregnant women, we did not correct our diet quality score for energy intake.

To assess guidelines specifically addressed to pregnant women, we constructed a second score, the *Pregnancy* score, of which the 9 items are described in the **Table 6**. For guidelines based on nutrients, we used the Estimated Average Requirement (EAR) for pregnant women to define an adequate intake (de Lauzon et al., 2004), except for iron, for which we used the EAR used for adult women.

Table 6: PNNS guidelines specific of pregnancy and construction of the score

PNNS pregnancy guidelines	**Limit to obtain a score of 1**
Folate	At least 308 mg/day
Folic acid supplement	Supplementation in the periconceptional period
Calcium	At least 770 mg/day
Iron	At least 12,32 mg/day
Iodine	At least 154 µg/day
Soy and soy-based products	Less than 1 time/day
Coffee/tea	Less than 3 times/day
Meal frequency	At least 4 meals or snack/day
Listeria	Score established by the number of guidelines attained: decreased intake of - raw milk cheese - pork meat products - raw or bloody meat
Toxoplasmosis	Score established by the number of guidelines attained: decreased intake of - raw or bloody meat - raw vegetables

In order to get a progressive score, we applied to both scores a methodology based on the principle of a percentage of the guideline followed by women, developed by von Ruesten et al. (von Ruesten et al., 2014). Thus, for each item, we used the following method:

1/ when the guideline was a minimum (e.g. at least 5 fruits and vegetables a day), a score of 1 point was given to all women with a usual intake equal or greater to this minimum. Otherwise, the score was equal to the usual intake, divided by the minimum recommended intake (Equation 1);

$$Score = \frac{Reported\ intake}{Recommended\ intake}$$

2/ when the guideline was a maximum (e.g. limit salt intake to less than 8 g/d), a score of 1 point was given to all women with a usual intake lower or equal to that maximum. Otherwise, the score was equal to the maximum recommended intake divided by the usual intake (Equation 2);

$$Score = \frac{Recommended\ intake}{Reported\ intake}$$

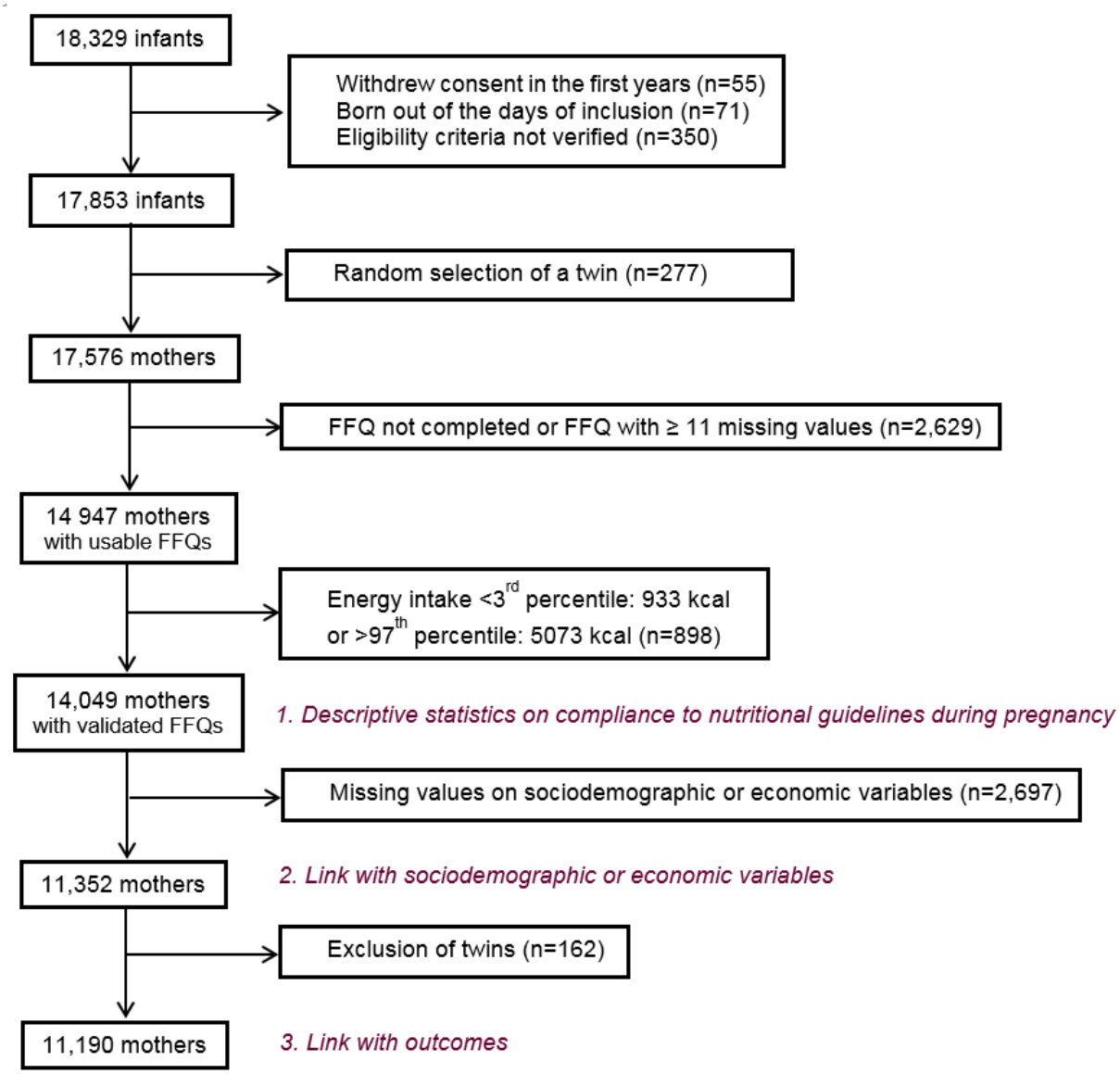
3/ the guideline was an interval (e.g. consume the food group "meat, poultry, fish and eggs" 1-2 times a day), a score of 1 point was given to all women with a usual intake within this interval. Otherwise, equation 1 was used when the usual intake did not reach the lower limit of the interval and the equation 2 was used when the usual intake exceeded the upper limit of the interval.

Then, the overall score was obtained as the sum of scores on each item.

3.2.2. *Population selection*

From the 17,853 eligible children in the ELFE cohort, we randomly selected a single twin in the event of a twin pregnancy (n = 277 exclusions), so that each woman was represented only once in the sample. From the 14,947 women with an available FFQ, 898 pregnant women were considered to have implausible energy intake and were withdrawn from the analyses. For analyses of the links between demographic or socioeconomic variables and consumption adequacy scores to the guidelines, subjects with at least one missing data on the variables considered were excluded (n = 1529) and for the analysis with birth outcomes the premature new-borns were excluded (n = 1168) see **Figure 9**.

Figure 9: Flow chart for the analysis of the diet quality



3.2.3. *Statistical analyses*

To be able to produce national statistics on diet quality among pregnant women, a weighting was applied to account for the sampling design and the bias resulting from refusal to participate at the inclusion in the study and non-response to the FFQ. This weighting was calculated, on one hand, by adjustment from the variables common to the consenting and the non-consenting and, on the other hand, by adjustment using margins of several variables (age, region, marital status, immigrant status, education level and parity) from civil registry data and from the 2010 National Perinatal Survey (Juillard et al., 2014).

The associations between maternal characteristics and each score were analysed using linear regressions including simultaneously the characteristics under study and adjusting for variables related to study design (maternity ward size, recruitment wave and region). Sensitivity analyses were carried out first using weighting to account for selection bias and, second, without exclusion of women with implausible energy intake (n = 898).

Concerning our objective on influence of diet quality on foetal growth, we used birth weight (g), birth length (cm) and weight-for-gestational-age categories (small/ appropriate/large for gestational age) as proxies of foetal growth. Associations with diet quality were tested by linear regression models, for birth weight and birth length, and multinomial logistic regression for weight-for-gestational-age categories (with adequate-for-gestational-age category as a reference). According to the literature, the following confounders were considered: maternal age at delivery, parity, pre-pregnancy BMI, weight gain during pregnancy, maternal height, smoking during pregnancy, highest education level attained, household income, type of family, new-born's sex and gestational age at delivery.

We have performed several complementary analysis:

(1) without excluding the new-born's before 37 weeks of amenorrhea,

(2) without weight gain during pregnancy as confounders since weight gain could be in the causal pathway between diet quality and foetal growth,

(3) adding energy intake in the model,

(4) without the women having gestational diabetes mellitus or previous history of diabetes, as diabetes during pregnancy could be in the causal pathway between diet quality adherence and foetal growth but could also influence both diet quality in late pregnancy and birth weight.

For weight-for-gestational-age analyses, we performed a sensitivity analysis using:

(5) customized definition (see chapter 2.3).

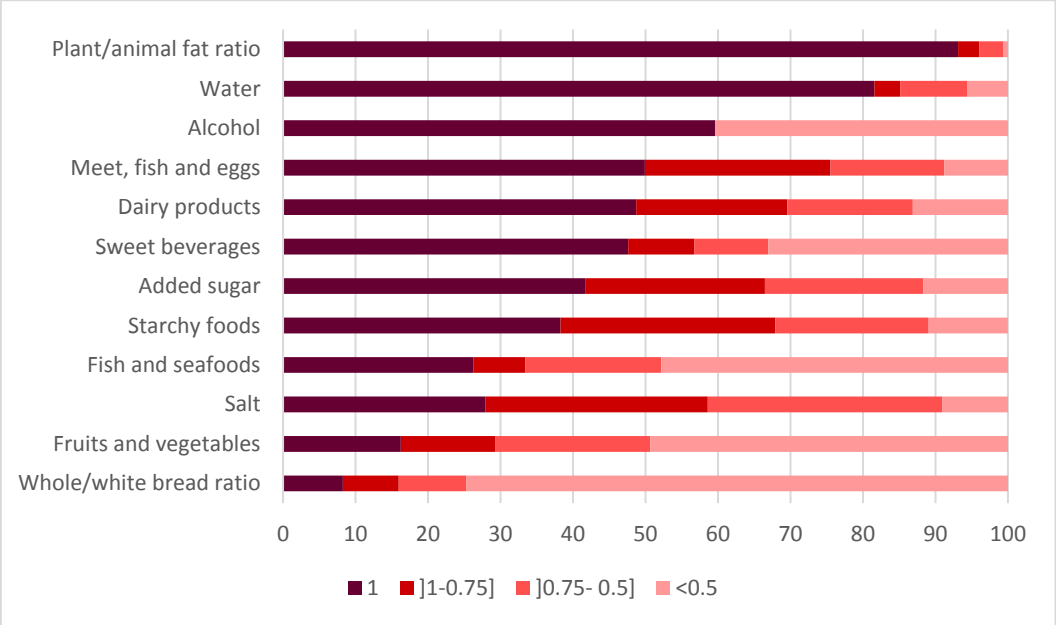
The significance level was set at 5%. All statistical analyses were performed using SAS software version 9.3 (SAS Institute, Cary, NC).

3.3. Results

3.3.1. *Descriptive statistics on diet quality*

For the 14049 women included in the analysis, the median *Diet Quality* score was 7.8 (IQR: interquartile range quartile 1 (Q1): 7.0 to quartile 3 (Q3): 8.5) for a maximum score of 11 points. The compliance to each guideline included in the *Diet Quality* score is presented in **Figure 10**. The PNNS guidelines with higher achievement rates were "Starches", "Dairy products", "Meat, fish, eggs", "Fat ratio of vegetable to animal", "Added sugar ", "Alcohol", “Water and Sweet Drink "and" Salt ". The guidelines in the *Diet Quality* score for which less than 50% of the women had a score of 0.75 were "Fruits and vegetables", "Wholemeal bread" and "Fish and seafood".

Figure 10: Compliance to general PNNS guidelines, among pregnant women from the ELFE study (n = 14,049)

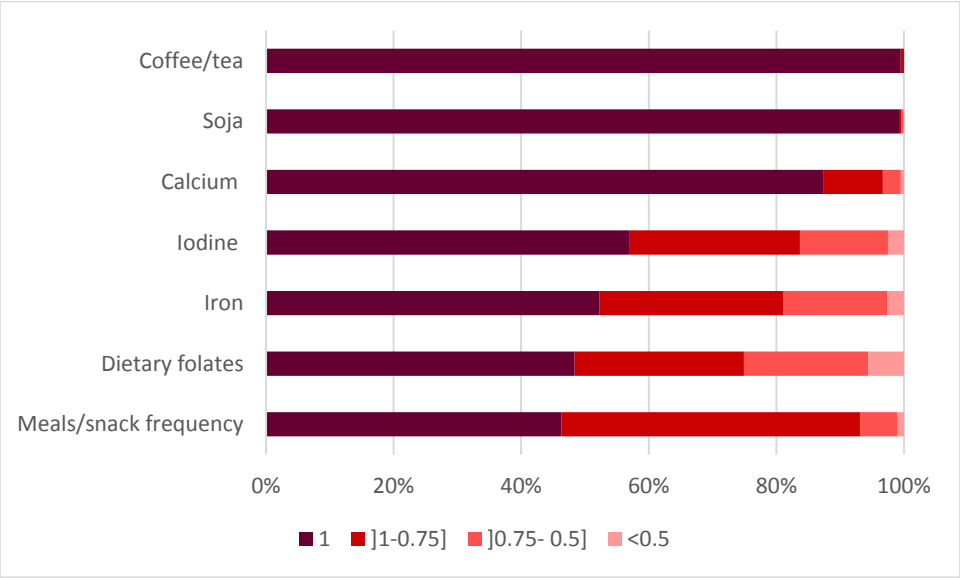


Red scale: percentage of women achieving a score = 1, score [0.75 - 1[score [0.5 - 0.75[and score <0.5 for the item considered, * the salt item only takes into account the salt contained in the foods or dishes (quiche, couscous ..) from food composition table (n = 14,049).

The average *Pregnancy* score was 7.7 (Q1: 7.2 - Q3: 8.1) for a maximum score of 9 points. The distribution of the pregnancy-score is presented in **Figure 11**. The guidelines of the *Pregnancy* score for which 50% of the women had a score higher than 0.75 (good adequacy) were the following: intakes of "Dietary folate", "Calcium", "Iron", "Iodine" , "Coffee / tea" and "Meal/snack frequency". In addition,

54% of women followed all the specific guidelines for listeriosis and only 23% of women were supplemented with folic acid before pregnancy or in the first trimester of pregnancy. From the 9401 seronegative women for toxoplasmosis, 61% followed at least one of the two specific guidelines for toxoplasmosis (21% of which followed both).

Figure 11: Compliance to guidelines specifically addressed to pregnant women, among pregnant women from the ELFE study (n = 14,079)



Red scale: percentage of women achieving a score = 1 score [0.75 - 1[score [0.5 - 0.75[and score <0.5 for the item considered (n = 14,049).

3.3.2. *Maternal characteristics and diet quality*

Both scores, *Diet Quality* and *Pregnancy*, were higher when women were in a traditional type of family, with higher household incomes and a higher level of education. They were also higher for women who did not smoke during pregnancy **(Table 7)**.

Table 7: Maternal characteristics and diet during pregnancy, (n = 11,532)

	***Diet Quality* score**		***Pregnancy* score**	
	β (95% CI)	**p**	**β (95% CI)**	**p**
Age at delivery		<.001		<.001
Less than 25 years	**-0.38 (-0.45 ; -0.30)**		**-0.19 (-0.24 ; -0.14)**	
25-29 years	**-0.12 (-0.17 ; -0.07)**		**-0.06 (-0.09 ; -0.03)**	
30-34 years	1 (REF)		1 (REF)	
35 years and more	**0.15 (0.09 ; 0.20)**		0.00 (-0.04 ; 0.03)	
Country of birth		<.001		0.80
France	1 (REF)		1 (REF)	
Other countries	**0.25 (0.18 ; 0.32)**		-0.01 (-0.06 ; 0.04)	
Years of schooling		<.001		<.001
<11 years	**-0.42 (-0.52 ; -0.33)**		**-0.28 (-0.35 ; -0.22)**	
12 years	**-0.28 (-0.35 ; -0.21)**		**-0.23 (-0.28 ; -0.18)**	
13 years	**-0.23 (-0.29 ; -0.18)**		**-0.15 (-0.19 ; -0.11)**	
15 years	**-0.14 (-0.19 ; -0.09)**		**-0.11 (-0.15 ; -0.07)**	
>15 years	1 (REF)		1 (REF)	
Household income		0.01		<.001
1500 €/month or less	**-0.09 (-0.18 ; -0.01)**		**-0.08 (-0.13 ; -0.02)**	
1501 - 2300 €/month	-0.04 (-0.10 ; 0.02)		-0.03 (-0.08 ; 0.01)	
2301 - 3000 €/month	1 (REF)		1 (REF)	
3001 - 4000 €/month	0.01 (-0.04 ; 0.06)		0.03 (-0.00 ; 0.07)	
4001 - 5000 €/month	0.06 (-0.01 ; 0.13)		0.03 (-0.02 ; 0.08)	
≥5000 €/month	**0.09 (0.02 ; 0.17)**		**0.07 (0.01 ; 0.12)**	
Region		<.001		<.001
East-Parisian basin	0.03 (-0.05 ; 0.12)		0.00 (-0.05 ; 0.06)	
West-Parisian basin	**0.10 (0.02 ; 0.18)**		-0.04 (-0.10 ; 0.01)	
Parisian region	1 (REF)		1 (REF)	
East	0.05 (-0.02 ; 0.13)		0.03 (-0.02 ; 0.09)	
North	-0.01 (-0.09 ; 0.07)		-0.02 (-0.08 ; 0.03)	
West	**0.15 (0.08 ; 0.22)**		**0.06 (0.02 ; 0.11)**	
South-east	**0.14 (0.07 ; 0.22)**		0.02 (-0.04 ; 0.07)	
South-west	**0.19 (0.11 ; 0.28)**		0.02 (-0.04 ; 0.08)	
Type of family		0.01		0.02
Traditional	1 (REF)		1 (REF)	
One-parent family	**-0.12 (-0.23 ; -0.00)**		**-0.11 (-0.19 ; -0.03)**	
Stepfamily	**-0.09 (-0.17 ; -0.02)**		0.00 (-0.05 ; 0.05)	
Parity		0.71		<.001
1st child	1 (REF)		1 (REF)	
2nd child	0.02 (-0.03 ; 0.06)		**-0.11 (-0.15 ; -0.08)**	
3rd child	0.03 (-0.03 ; 0.10)		**-0.16 (-0.21 ; -0.12)**	
4th child or more	-0.01 (-0.11 ; 0.09)		**-0.23 (-0.30; -0.16)**	

Multivariate linear regression models also adjusted for study design (wave and maternity size)

Table 6 continues: Maternal characteristics and diet during pregnancy, (n = 11,532)

	***Diet Quality* score**		***Pregnancy* score**	
	β (95% CI)	**p**	**β (95% CI)**	**p**
Smoking status		<.001		<.001
Non smokers	1 (REF)		1 (REF)	
Smoker before pregnancy	**-0.14 (-0.18 ; -0.09)**		**0.01 (-0.02 ; 0.05)**	
Smoker at beginning of the pregnancy	**-0.22 (-0.32 ; -0.12)**		**-0.09 (-0.16 ; -0.02)**	
Smoker during the last trimester	**-0.39 (-0.45 ; -0.33)**		**-0.12 (-0.16 ; -0.08)**	
Maternal pre-pregnancy BMI		0.12		<.001
<18.5 kg/m2	-0.04 (-0.11 ; 0.04)		0.03 (-0.02 ; 0.09)	
[18.5 - 25 kg/m2[	1 (REF)			
[25 - 30 kg/m2[	**-0.05 (-0.1 ; -0.00)**		**-0.07 (-0.10 ; -0.03)**	
At least 30 kg/m2[	-0.06 (-0.12 ; 0.01)		**-0.13 (-0.18 ; -0.08)**	
Diabetes		<.001		0.16
No	1 (REF)			
Previous history of diabetes	**0.67 (0.47 ; 0.87)**		0.05 (-0.10 ; 0.19)	
Gestational diabetes mellitus	**0.65 (0.57 ; 0.73)**		0.05 (-0.00 ; 0.11)	

Multivariate linear regression models also adjusted for study design (wave and maternity size)

Some characteristics were more specifically related to one of the two scores. The *Diet Quality* score was higher in foreign-born women, aged 35 or older, living in southern France, and those with diabetes before or during pregnancy. The *Pregnancy* score was lower for women under 30 years of age, obese before pregnancy, having a large number of children **(Table 7)**.

3.3.3. *Diet quality and foetal growth*

The analysis studying the relationship between diet quality and birth weight on continuous scale showed positive association after adjustment for the main confounders chosen from the literature. The birth weight increased by 8g (95%CI 0.86 ; 14) per increase of one point of the *Diet Quality* score. The results were similar when excluding preterm birth. When the women who had a previous history of diabetes or GDM only a positive trend was observed. The additional adjustment for gestational weight gain or energy intake did not change the results **(Table 8)**.

The prevalence of SGA, AGA, and LGA were 9.2%, 76.4%, and 14.2%, respectively. Having a low *Diet Quality* score was associated with increased risk of having a small for gestational age new-born but it wasn't associated with being large for gestational age, when compared to appropriate for gestational age new-born. These results were similar when we used more customize definition for weight-for-

gestational age (data not shown) and for the other analysis: after exclusion of preterm births, of women with previous history of diabetes or GDM, without adjustment for gestational weight gain or when energy intake was added in the model **(Table 8)**.

The association between diet quality and birth length were not significant. The results were similar when excluding preterm birth, or women had a previous history of diabetes or GDM. The additional adjustment for energy intake or taking out the adjustment for gestational weight gain did not change the results **(Table 8)**.

Table 8: Multivariate associations between the Diet Quality score and anthropometry at birth.

	Birth weight (g) [a]		**Birth length (cm) [a]**		**Weight for gestational age (ref=AGA n = 8,553)**			
					SGA (n = 1,038)		**LGA (n = 1599)**	
	beta	**95% CI**	**beta**	**95% CI**	**OR**	**95% CI**	**OR**	**95% CI**
Model 1, n = 11,190	**7.50**	**(0.76 ; 14.24)**	0.02	(-0.01 ; 0.05)	**0.92**	**(0.87 ; 0.98)**	1.04	(0.99 ; 1.10)
Model 2, n = 10,797	**7.65**	**(0.83 ; 14.55)**	0.01	(-0.02 ; 0.04)	**0.92**	**(0.87 ; 0.98)**	1.04	(0.99 ; 1.10)
Model 3, n = 11,190	6.62	(-0.24 ; 14.49)	0.01	(-0.02 ; 0.04)	**0.92**	**(0.87 ; 0.98)**	1.03	(0.98 ; 1.08)
Model 4, n = 11,190	**7.35**	**(0.57 ; 14.13)**	0.02	(-0.01 ; 0.05)	**0.92**	**(0.86 ; 0.98)**	1.04	(0.99 ; 1.10)
Model 5, n = 10,362	5.98	(-1.06 ; 13.05)	0.01	(-0.02 ; 0.05)	**0.93**	**(0.87 ; 0.99)**	1.02	(0.96 ; 1.08)

Model 1: Adjusted for: maternal age at delivery, parity, pre-pregnancy BMI, maternal height, maternal weight gain during pregnancy, smoking status, years of schooling, household income, country of birth, family type, region, wave and maternity size
Model 2: model 1 in the subsample after exclusion of pre-term births (weight for gestational age and sex SGA n = 1,038, AGA n = 8,338, LGA = 1,527)
Model 3: model 1 without adjustment for maternal weight gain during pregnancy
Model 4: model 1 additionally adjusted for total energy intake (kcal)
Model 5: model 1 in the subsample after exclusion of women with personal history of diabetes or gestational diabetes mellitus (weight for gestational age and sex SGA n = 1,027, AGA n = 8,048, LGA = 1,430)
[a] Additionally adjusted for: sex and gestational age

3.4. Discussion

The *Diet Quality* and *Pregnanc*y scores are synthesis variables characterizing the quality of the diet and the compliance to the nutritional guidelines. The PNNS guidelines were rather well followed in our

population. The specific guidelines with lower adherence for the *Diet Quality* score were the guidelines on "Fruits and vegetables", "Wholemeal bread" and "Fish and seafood" consumption. Several factors were identically associated with the *Pregnanc*y and *Diet Quality* scores as demographic variables (age, education and income) or behaviours related to health concerns (tobacco). Some factors were specifically associated with the *Diet Quality* score, probably reflecting cultural habits and culinary traditions (region, country of birth). Finally, other factors were associated specifically with the *Pregnanc*y score summarizing the exposure and the attention given to the guidelines (number of children). The *Diet Quality* score was associated with increase birth weight and a decrease of the odds of having a small for gestational age baby.

To our knowledge, there is no description of the diet of pregnant women in France from a study able to provide national statistics, as the number of pregnant women in ENNS or INCA studies was too small to derive statistics for this sub-sample. This first study provides elements for assessing dietary and nutritional risks and a better understanding of the demographic and socio-economic factors associated with the nutritional behaviours of pregnant women, which could lead to the orientation of national prevention and health education programs.

Comparison with other studies

In Europe, despite an alignment of diets and lifestyles, there are important differences between countries, particularly in terms of eating habits and associated health issues. Therefore, EFSA proposes that each country develops its own "Dietary Guidelines according to its particular diet" expressed in terms of food based dietary guidelines (FDBG) (EFSA, 2010).

Several studies around the world have created dietary score to assess country specific guidelines. In the United States, the DQI-P (Diet Quality Index for Pregnancy), was developed in the Carolina's Pregnancy, Infection and Nutrition cohort study (Bodnar and Siega-Riz, 2002). The score was based on the data from a FFQ filled by 2063 women. The guidelines used in this score were adapted from the Dietary Guidelines for Americans and the Food Guide Pyramid. In Australia, a score of

compliance to guidelines, the Australian Recommended Food Score (ARFS) was constructed in the ALSWH (Australian Longitudinal Study on Women's Health) cohort, focusing on Australian's women diet quality (Hure et al., 2009). It was based on the data from a validated FFQ assessing diet quality in 7,486 women. In Spain, a FFQ on diet during the first trimester of pregnancy was filled by 822 women from the INMA-Valencia study (Spanish acronym for Childhood and Environment) (Rodriguez-Bernal et al., 2010). They have assessed the proportion of women not reaching the minimum recommended daily intake for several food items based on the recommendation specific to pregnancy of the Spanish Society of Community Nutrition and for nutrients on the US Institute of Medicine guidelines. In Norway, the Norwegian health directorate published the Norwegian food guidelines (NFG) that is mainly based on food groups. The NFG incorporates quantitative guidelines on the following dietary components: fresh fruit, vegetables, whole-grain, fish, fatty fish, red meat, salt, and added sugar. The Nordic Nutrition Recommendations (NNR) is solely based on (macro-) nutrients. The compliance to dietary guidelines was assessed in the MoBa study (von Ruesten et al., 2014), using two Healthy Eating Index (HEI) scores based on NFG and NNR guidelines.

Australian pregnant women complied with most but not all guidelines: for folate, iron and dietary fibre the required levels were not reached (Hure et al., 2009). The lowest compliance rates were found for protein-rich foods (especially fish) and cereal consumption. These results are quite similar to ours, as we also see insufficient consumption of "fish and seafood".

In the Spanish INMA cohort, the authors were able to show that 76.6% of women did not reach the recommended intake for starchy foods, which was a bit higher compared to our study 61.7%. The food groups with higher compliance rate were "meat, poultry, fish and eggs", "fruits", "vegetables", and "non-alcoholic low-sugar drinks" with 69.8%, 52.1%, 53.8% % and 88.4% of women reaching the recommended intake (Rodriguez-Bernal et al., 2010). These results are not completely comparable to ours as for these same guidelines only 49.9% for "meat, fish and eggs", 16.3% for "fruit and vegetables", 47.6% for "sweet beverages" and 59.6% for "alcohol" women reached the recommended

intake. In terms of folic acid supplementation, our findings are very different from those in the INMA cohort, as more than 90% of women received folic acid supplementation in the first trimester of pregnancy (Rodriguez-Bernal et al., 2010), contrary to 23% in ELFE. This difference may be related to a difference in prescription of folic acid between these two countries or to a cultural difference in pregnancy planning.

In MoBa, the participants showed good adherence to the guidelines for whole-grain, red meat and added sugar intake, whereas the adherence to guidelines on vegetable intake was low. Interestingly, concerning nutrient intake, there was a high proportion of women showing compliance with the guidelines for nearly all macronutrients, except of saturated fat. Our results were not in line for wholemeal food consumption and were comparable with the low consumption of vegetables.

When looking at the determinants of dietary score in different countries, in the American study (Bodnar and Siega-Riz, 2002), a high score for DQI-P was positively associated with women's age, education and income, and primiparity. Similar relationships between women's characteristics and quality of diet during pregnancy were found in Norway (Hillesund et al., 2014; von Ruesten et al., 2014) and Spain (Rodriguez-Bernal et al., 2010). We showed similar association in our study for age at delivery, income, but only the *Pregnancy* score was associated with parity. In the Norwegian study, both HEI scores increased slightly with increasing age, socio-economic status, exercise frequency, and breastfeeding duration, whereas the HEI scores tended to decrease with increasing pre-pregnancy BMI, gestational weight gain (GWG), and smoking frequency. Again, we found similar association, with higher scores for older women, for women with higher attained years of schooling and household income but lower scores for women who smoked during pregnancy and, only for the *Pregnancy* score, with higher BMI.

Diet quality and foetal growth

In our analysis, diet quality during pregnancy was related to higher birth weight and lower risk of SGA In agreement with these results, high adherence to the New Nordic Diet, that implies higher intakes of

fruits and vegetables, potatoes, whole grain bread, fish, game, milk and water, was associated with reduced risk of SGA (OR=0·92; 95% CI 0·86, 0·99; P=0·025) and increased risk of LGA (OR=1·07; 95% CI 1·00, 1·15; P=0·048) in the MoBA study (Hillesund et al., 2014). In the INMA study (Rodriguez-Bernal et al., 2010), the Alternate HEI (AHEI) during pregnancy was positively related to birth weight (P for trend = 0.009) and birth length (P for trend = 0.013).

The *Diet Quality* score was derived from the PNNS-GS score, developed in the SU.VI.MAX study (Estaquio et al., 2009). This score allows for consideration of the diet as a whole rather than focusing on particular nutrients or food groups. This PNNS-GS score has already been used in several studies to characterize diet in the general population and to highlight demographic and socio-economic factors related to adequacy of diet to French guidelines (Alles et al., 2012; Estaquio et al., 2009; Malon et al., 2010). In the general population, it was shown that those who followed PNNS guidelines were less likely to become overweight over six years of follow-up (Kesse-Guyot et al., 2009).

It is important to note that the results of the association between diet quality and prenatal growth might be explained by residual confounding. Indeed, the *Diet Quality* score is explained by social factors that are as well know predictors of birth weight (Astone et al., 2007; Fairley, 2005; Mortensen, 2013), despite adjustment on several sociodemographic and economic variable some bias could be remaining.

Strengths and limitations

To create the *Pregnancy* score, we used the EAR as a cut-off to define adequate intake for nutrients. Indeed, at the population level, this threshold minimize the bias in estimation of prevalence of inadequate intake (de Lauzon et al., 2004). For iron, the EAR for adult women (12.32 g/day) was

considered instead of the EAR for the pregnant women (23.1 g/day) (Martin, 2001). In fact, the dietary recommended intake for iron was identical for pregnant women and for childbearing age in the United Kingdom (26), Nordic countries (Nordic Nutrition Recommendation, 2012), Germany (Koletzko et al., 2013) and WHO (World Health Organization, 2004), while they are multiplied by 1.5 or 2 in the United States, Canada (Institute of Medicine (IOM), 2001) and France. Although we selected this lower threshold, the prevalence of adequate intake for iron in pregnancy was only 51.9% in the ELFE study. Iron supplementation may be proposed depending on the results of the full blood count carried out at the beginning of pregnancy and at 6th month of pregnancy (Collège National des Gynécologues et Obstétriciens Français, 1997; HAS, 2009; Programme National Nutrition Santé, 2007). Furthermore, although there is a guideline for vitamin D for pregnant women, it was not possible to include it in our score because sun exposure and biological status of women were not available in ELFE.

Moreover, because the energy needs of pregnant women are difficult to assess, we have chosen not to penalize the scores for high-energy intakes, but sensitivity analyses adjusted for energy intake showed similar association with new-born anthropometric measurements, suggesting that this choice did not strongly impact our results. In addition, for the toxicological guidelines, our questionnaire did not allow to assess the removal of specific food groups (e.g. raw-milk cheese or bloody meat) from the diet, but only the decrease in intake since the beginning of the pregnancy, which may lead to an overestimation of compliance to these guidelines. Finally, instead of determining thresholds to define a score of 0.5 or 1 point for each item, the rate of compliance to each guideline was assessed, allowing a closer examination of compliance to guidelines among pregnant women.

To our knowledge, so far, most diet quality scores and guidelines did not take into account the 'food chemical' dimension of diet. However, recent advances in research highlighted emerging concern on health effects of food chemicals. The Directorate General for Health asked the French Agency for food Safety and Occupational Health (ANSES) in April 2012 to update the guidelines of the French PNNS while taking into account the issue of food chemicals. Published in 2016 (ANSES, 2016) for the general

adult population, the report highlighted the need for research to reduce uncertainties in nutritional and toxicological references. The report has also highlighted the difficulty in identifying combinations of foods that both cover the population's nutritional needs and cover exposure to chemicals. Levels of exposure remain a concern for a limited number of chemicals, including inorganic arsenic, acrylamide and lead. Finally, the report also recommended consumers to diversify diet and sources of supply. As the guidelines were not yet updated for pregnant women, it would be of great importance to provide new insight on the influence of food chemical exposure during pregnancy and offspring's health.

3.5. Conclusion

In this chapter we showed that the PNNS guidelines were met for a good proportion of women in our study. However, some specific guidelines remain of concern such as the consumption of fruit and vegetables, wholemeal food and fish and seafood. We were able to identify several demographic and socioeconomic factors associated with both the *Pregnancy* and *Diet Quality* scores. Finally, we showed a positive association between the *Diet Quality* score and birth weight and a decreased risk of having an SGA infant with higher *Diet Quality* score. In the next chapter we are going to study more deeply a food chemical that forms during cooking process and has been associated in other epidemiological and animal studies to prenatal growth.

4. FOOD CHEMICAL: CASE OF ACRYLAMIDE

4.1. Introduction and aim

Acrylamide does not occur naturally and has been industrially produced since the 1950s for various uses, including water and wastewater treatment, as gels in laboratories or in grout for tiling. Recent research highlighted that acrylamide can form as a by-product during the heating of starch-rich foods at high temperatures (>200 °C), by the Maillard reaction between asparagine and a sugar molecule (Dybing and Sanner, 2003; Tareke et al., 2002). Acrylamide is also found in cigarette smoke and smoking can contribute extensively to acrylamide exposure (Mojska et al., 2016).

In occupationally exposed populations, the main routes of acrylamide exposure are inhalation and dermal absorption, while, in non-occupationally exposed populations, diet remains the main source of exposure for non-smokers (Vikstrom et al., 2012). According to the Scientific Opinion from the European Food Safety Authority (EFSA), based on data from 24 European countries and approximately 43,000 acrylamide concentrations in foods, the main dietary sources of acrylamide exposure among adults are fried potatoes, bread, breakfast cereals, biscuits, crackers, crispbread and coffee, and the average exposure was 0.4 µg/kg body weight/day (EFSA, 2015). After ingestion, acrylamide is extensively absorbed from the gastrointestinal tract and, after reaching the systemic circulation, it is rapidly distributed into the tissues. Acrylamide is recognized as a neurotoxicant (Ferguson et al., 2010; IARC, 1994), can exert reproductive and developmental toxicity effects (Yilmaz et al., 2016) and is classified as “probably carcinogenic” in humans (group 2A) by the International Agency for Research on Cancer (IARC, 1994). In the human body, a significant portion of ingested acrylamide is converted to glycidamide, a chemically reactive epoxide with genotoxic activity (Sweeney et al. 2010). Glycidamide is likely to play an important role in the carcinogenicity of acrylamide (Hogervorst et al., 2010).

During pregnancy, 10-50% of dietary acrylamide is transferred through the placenta to the foetus (Annola et al., 2008; Sorgel et al., 2002). Taking into consideration the scarce epidemiological evidence, EFSA’s CONTAM panel (Contaminant in the Food Chain) recommended that further

epidemiological studies should be conducted to confirm or refute the inverse relationship between acrylamide exposure and impaired foetal growth (EFSA 2015).

Acrylamide is probably a chemical that presents good characteristics to be studied using the TDS data. First, acrylamide arises during the cooking process and TDSs are a good tool to assess acrylamide in foods, as they use food products as consumed (after conservation and heating or cooking). Second, this chemical is found in various types of food that are not so much correlated between them (e.g. coffee, crisps, bread…).

In this context, the aim of the present chapter was to investigate the association between maternal dietary exposure to acrylamide during pregnancy and, first, birth size in the EDEN mother-child cohort and, second, child's growth up to 8 years in the EDEN and MoBa studies. We will first describe the main acrylamide contributors in both studies.

4.2. Acrylamide and diet quality

In France, results from the TDS2 showed that the highest levels of acrylamide were found in fried-potato products (crisps, French fries and fried potatoes), bread, biscuits and coffee (Sirot et al., 2012a). The main sources of acrylamide in previous studies in Norway and Sweden were fried-potato products (potato crisps, French fries and fried potatoes), crisp bread, bread and breakfast cereals. Additionally, acrylamide from coffee was found to contribute substantially to the total dietary acrylamide exposure in the general population (Granby and Fagt, 2004; Scientific Committee of the Norwegian Food Control Authority, 2002; Svensson et al., 2003). A strong positive correlation was found between urinary acrylamide and coffee intake in a non-pregnant sample of Norwegian adults (Bjellaas et al., 2007). Less is known on determinants of acrylamide exposure in pregnant women.

4.2.1. *Methods*

4.2.1.1. Main contributors to acrylamide exposure

In MoBa, the 225 food items of the FFQ were aggregated into 100 detailed food groups. Twenty-seven out of hundred food groups contributed to dietary acrylamide exposure. In order to identify the main contributors of dietary acrylamide exposure during pregnancy, these 27 detailed food groups were further grouped into 12 main food groups. The 12 food groups were: cereals (porridge, cornflakes), bread (white bread, wholemeal bread, rolls), crispbread (crispbread and crackers), pancakes and sweet bakery (waffle and pancakes, buns, cakes, sweet biscuits), boiled potatoes, fried potatoes, coffee (coffee, decaffeinated coffee, figs coffee, milk coffee), chocolate, sweets, salty snacks (potato crisps, potato snacks, peanuts and popcorn, pretzels), dairy products (yoghurt, dairy dessert, milk and cream), other (poultry, pizza and tacos, prepared fish, raw vegetables, dried fruit, hazelnut spreads).

In EDEN, 27 food items out of 137 items from the FFQ contributed to the estimation of dietary acrylamide exposure. They were then further grouped into 10 main food groups: bread (white and wholemeal bread), rusk, breakfast cereals, cakes (pastries, tarts, cakes, biscuits, cereal bars), salty snacks (crisps and salty biscuits), French fries (French fries and fried potatoes), milk dessert, chocolates, coffee and other (savoury pies, croquet-monsieur, sandwich, pizza, hamburgers, poultry, fresh and frozen fish, oily fish, fried fish, fish dishes, tea).

4.2.1.2. Statistical analysis

We described the specific sources of acrylamide by quartiles of intake and identified the main contributors for different levels of exposure. The Spearman's correlation between dietary acrylamide exposure and diet quality was calculated. In Eden, we used the *Diet Quality* score, previously described, and, in MoBa, the intake of fibre. In EDEN, Spearman's correlation coefficients were calculated as well between the main categories of acrylamide contributors and continuous sociodemographic and economic factors, for dichotomous variable, Student's t-test was used.

4.2.2. *Results*

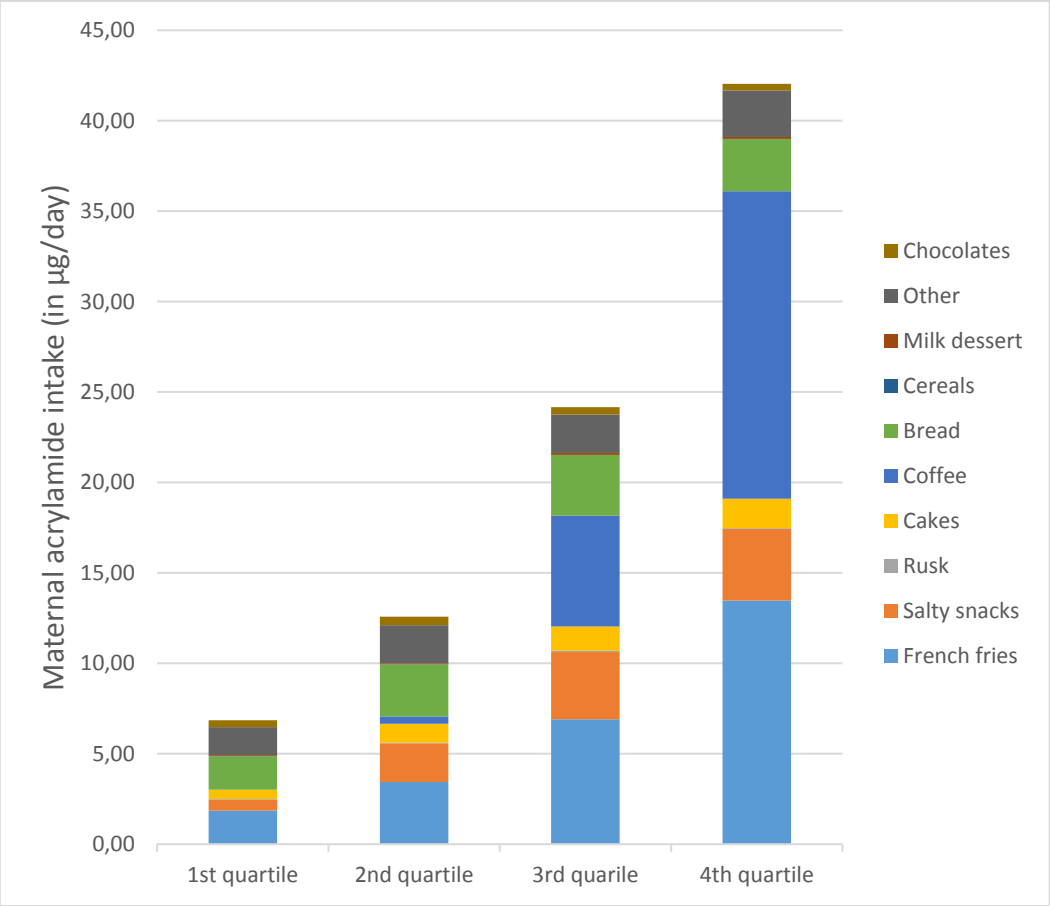
In EDEN, the estimated median and interquartile range (IQR) of dietary acrylamide exposure were 19.2 µg/day (IQR: 11.8, 30.3). The main contributors to dietary acrylamide exposure were French fries (29%) and bread (21%), and the contribution of each food differed from low to high exposure **(Figure 12)**. Namely, in the 1st quartile of exposure, the main contributors were French fries (27%) and bread (27%), while in the 4th upper quartile, the contribution of coffee increased to 40% (0% in the 1st quartile) and the contribution of the bread decreased to 7%.

As expected, the correlations between dietary acrylamide exposure and the main categories of contributors were positive and significant. The highest correlation was found with fried potatoes (French fries and crisps, Spearman's rho=0.70), then with tea and coffee (Spearman's rho=0.42) and the lowest with bread and biscuits (Spearman's rho=0.37).

The Spearman's correlation between the *Diet Quality* score and dietary acrylamide exposure (using the LB estimation) was -0.14 ($p<0.0001$).

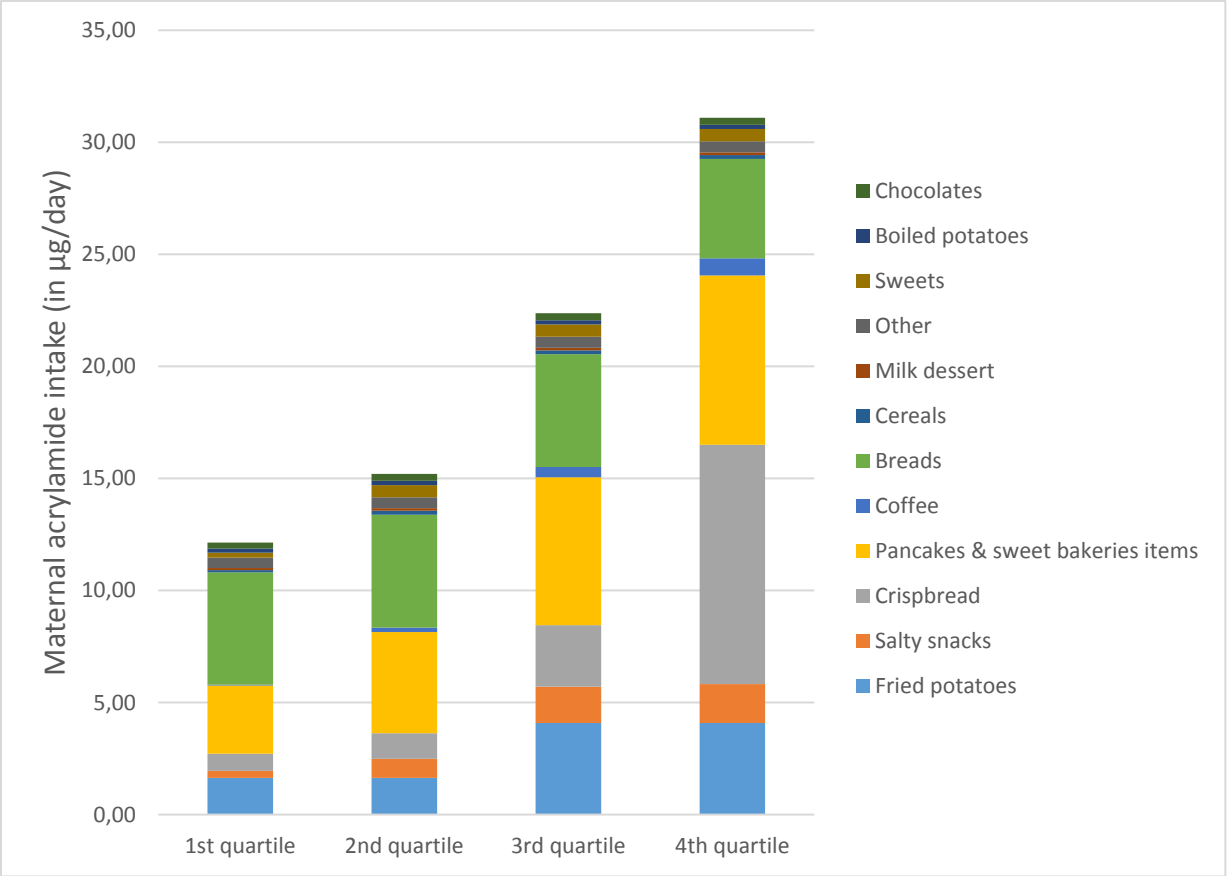
Dietary acrylamide exposure was significantly associated with the mean number of cigarettes smoked during pregnancy (Spearman's rho=0.22; $p<0.001$), maternal age (Spearman's rho=-0.05; $p=0.04$), education (low versus high: $\Delta=3.0$ µg/day; $p<0.001$), parity (multiparous versus primiparous: $\Delta=4.0$ µg/day; $p<0.001$) and study centre (Nancy *versus* Poitiers: $\Delta=2.3$ µg/day; $p=0.01$). After multivariable adjustment, centre, parity, maternal age and smoking remained significantly associated with acrylamide exposure.

Figure 12: Sources of maternal dietary acrylamide exposure according to quartiles of total dietary acrylamide exposure in women from EDEN (n = 1666).



In MoBa, the median and interquartile range (IQR) of dietary acrylamide exposure was 24.7 µg/day (IQR 18.4, 33.2), 0.011 µg/kcal/day (IQR 0.008, 0.014) among the 51,952 pregnant women. The main contributors to acrylamide were pancakes or sweet bakeries items (25%), bread (20%) and crispbread (18%), and the contribution of each food group to acrylamide exposure differed from low to high exposure **(Figure 13)**. Namely, in the lower quartile of exposure, the main contributors were pancakes and sweet bakeries items (22%) and bread (29%), while in the upper quartile, the contribution of crispbread increased to 25% (9% in the 1st quartile) and the contribution of the bread decreased to 14%. The Spearman's correlation between acrylamide intake and total fibre intake (considered as a marker of a healthy diet) was r=0.50 p<0.0001. In the same population, dietary acrylamide exposure was positively associated with maternal age, smoking during pregnancy and lower education level (Duarte-Salles et al., 2013).

Figure 13: Sources of maternal dietary acrylamide exposure according to quartiles of total dietary acrylamide exposure in women from MoBa (n = 51,952).



4.3. Acrylamide and growth in the EDEN study

4.3.1. *Methods*

4.3.1.1. Main variables

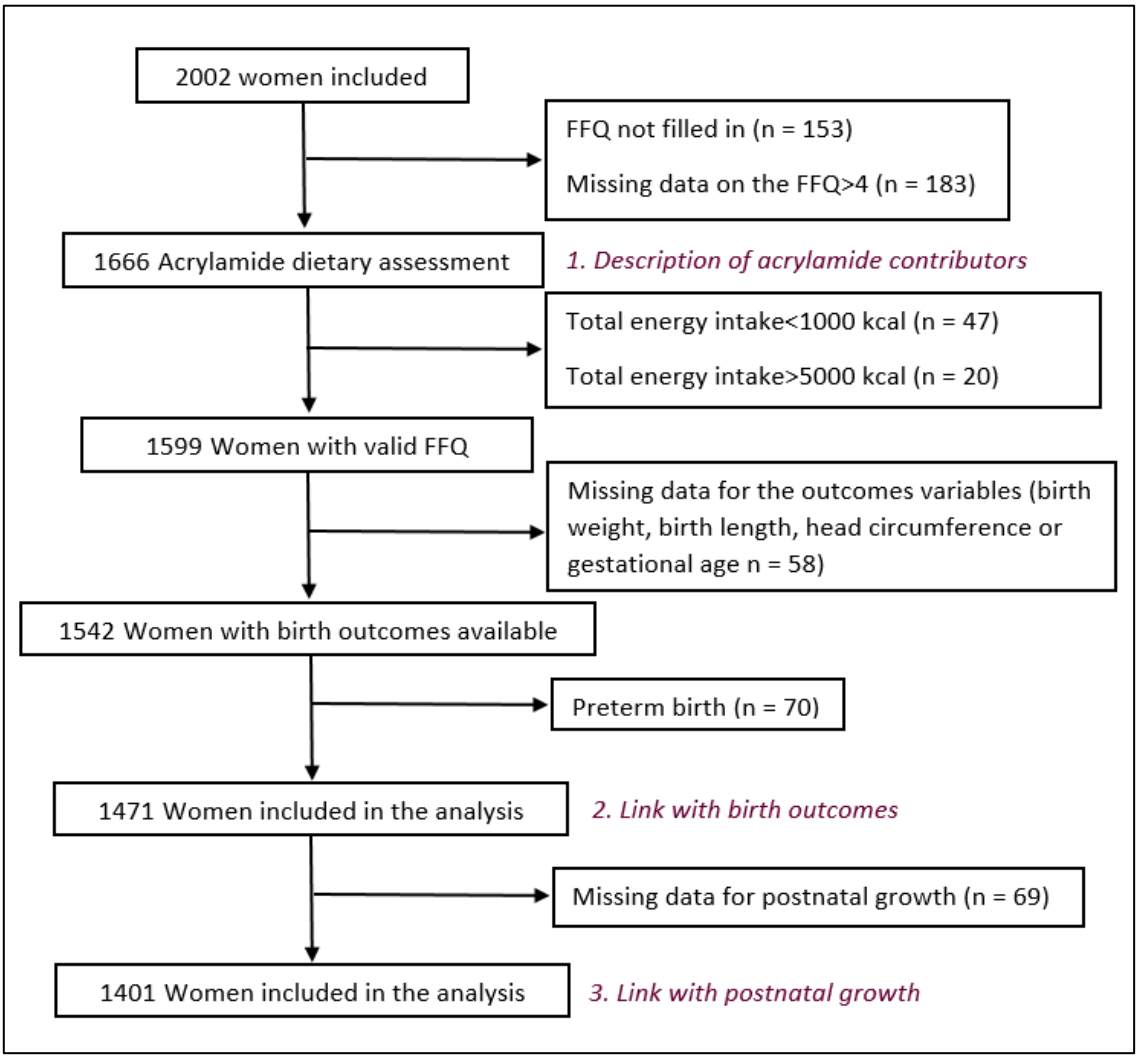
The association between maternal dietary acrylamide exposure and foetal growth was studied per 10 µg/day increase in acrylamide exposure.

Prenatal growth was assessed using birth weight (g), length (cm), head circumference (cm), and weight-for-gestational-age (SGA/AGA/LGA). Postnatal growth was assessed using predicted BMI at one, three and five years.

4.3.1.1. Sample selection

For these analysis, subjects with a daily energy intake under 1000 kcal/day or over 5000 kcal/day were excluded (n=47 and 20, respectively). Among the 1599 women with a validated FFQ, 1471 women with a full-term baby (delivery ≥ 37 weeks of amenorrhea) and complete data on birth weight and length were then included in our analyses on birth size. Among them, 1401 had sufficient data to assess postnatal growth **(Figure 14)**.

Figure 14: Flow chart of the analysis of dietary acrylamide exposure and growth in EDEN



4.3.1.2. Statistical analyses

At least one missing data on potential confounders variables (education, parity, pre-pregnancy BMI, tobacco smoke and specific weight gain during pregnancy) was observed in 8.4% of our population and

we imputed these data either from other information available during the follow-up (51%) or by the median when no other information was available (maternal height, education level, pre-pregnancy BMI, weight gain during pregnancy and height).

Associations between acrylamide and birth size were tested by multiple linear regressions for weight, length and head circumference and multiple logistic regressions for weight-for-gestational-age.

Deviation from linearity for the relations between birth size and acrylamide concentration was tested by comparing nested models using a Fisher's test (for the linear models) and a likelihood ratio test (for logistic models), with exposure variable in quartiles, declared either as ordinal (restricted model) or as dummy variable (full model).

The confounders have been selected *a priori*, based on the literature. All models (except for SGA) were adjusted for study centre, maternal age at delivery (years), height (cm) and education level (± high school diploma), primiparity (yes/no), smoking during pregnancy (average numbers of cigarette smoked per day), gestational age (weeks) at birth and new-born sex. We tested for each model the best way to adjust for gestational age either gestational age and gestational age squared, or adding a cubic term. For SGA models, we did not adjust on the variables already used in its definition (i.e. maternal height, parity, gestational age at birth and new-born sex). Additional adjustment for maternal BMI, pregnancy weight gain, total energy intake, passive smoking and interaction between BMI and pregnancy weight gain were also considered, as they have been described as potentially associated with anthropometry at birth, and were included in the final model if the p-value was less than 0.05 (or less than 0.20 for the interaction term). As acrylamide is found in cigarettes as well, we presented the results separately for children born to non-smokers (n=1075) and smokers (n=396), in addition to the results for the both populations gathered, and we tested the interaction between smoking and dietary acrylamide exposure. For each model, we analysed the residuals of the model and the presence of

influential observations. For the analysis with post-natal growth the same model as the birth weight model was applied.

We calculated the attributable fraction (AF) for SGA of being exposed to the fourth quartile compared to the other ones, using the method provided by Rückinger et al (Ruckinger et al., 2009) to take into account the adjustment factors. We compared this attributable fraction with the one of being exposed to tobacco consumption (ever smoked during pregnancy). 95% confidence intervals were calculated using bootstrap estimates from the SAS PROC SURVEYSELECT (Cassell, 2010).

The association between prenatal acrylamide exposure and postnatal growth was analysed using as outcomes both BMI at 3 and 5 years or being overweight (IOTF definition) at 3 and 5 years. We used the same models are the one specified for the birth weight analyses. The analyses were performed as well separately for children born to non-smokers (n=1042) and smokers (n=359) mothers, in addition to the results for the both groups gathered, and we tested the interaction between smoking and dietary acrylamide exposure.

We performed several complementary analysis:

(1) we analysed the associations using log-transformed acrylamide exposure because the distribution of acrylamide concentration was skewed to the right,

(2) we tested the adjustment on the main acrylamide contributor group (i.e. French fries, fries potatoes, crisps)

We performed as well some sensitivity analysis:

(3) we ran analysis excluding subjects with imputed variables.

We ran specific complementary analysis for the birth weight model:

(4) we ran the analysis with additional adjustment on paternal BMI and total energy intake,

(5) we used energy intake adjusted acrylamide (in µg/kcal/day),

(6) we ran the models without adjusting for weight gain during pregnancy as it could be influenced by acrylamide exposure and considered as an intermediate variable.

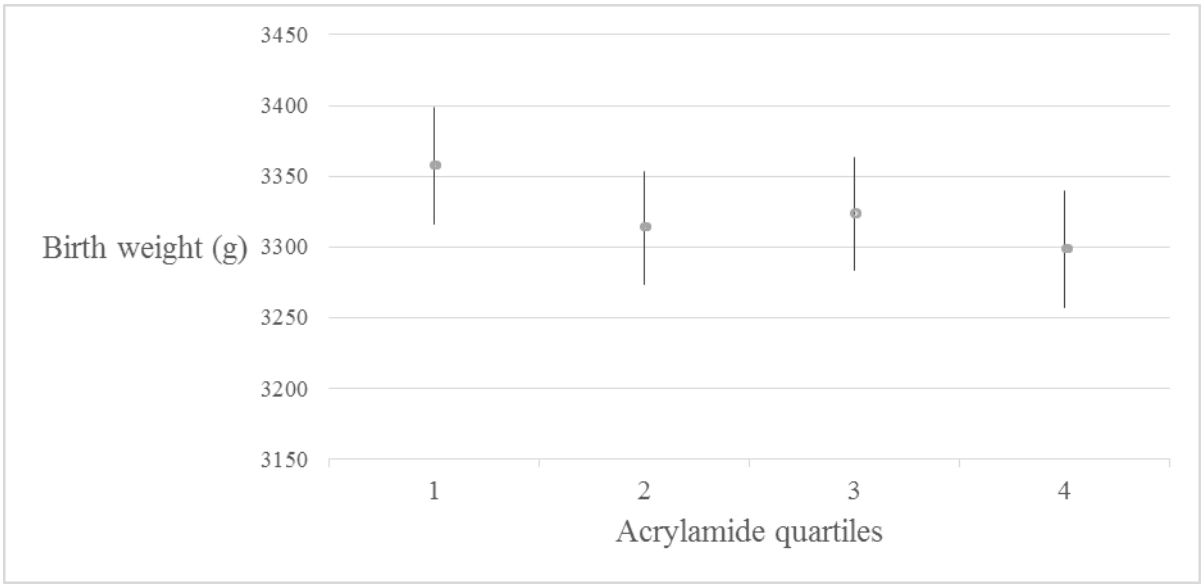
P-values were considered significant when <0.05. Data were analysed using SAS version 9.3 (SAS Institute, Inc., Cary, NC, USA).

4.3.2. *Results*

In multivariate analyses **(Table 9)**, an increase in exposure to acrylamide of 10 µg/day tend to be associated with a reduced birth length of 0.05 cm (95% CI: -0.11 ; 0.00) with a linear relationship ($p_{for\ non\text{-}linearity}$=0.80). The association tended to be stronger in smoking women than in non-smoking women, although the interaction term was not significant (p=0.11).

Birth weight decreased of 9.8g (95% CI: -21.3 ; 1.7) for 10µg/day increase in exposure to acrylamide **(Table 9)**. In our study population, although the second quartile was somewhat departing from the linear trend **(Figure 15)**, the test of non-linearity was not significant ($p_{for\ non\text{-}linearity}$ =0.80) and we observed a negative trend (p-trend=0.07). After adjusting for birth length, the negative trend with birth weight was non-significant (-1.0g, 95% CI: -15.4 ; 13.4). We did not show any significant difference in the associations according to active smoking (p-for-interaction=0.41 and 0.94 before and after adjustment for birth length respectively).

Figure 15 Means of birth weight (n = 1471) by quartiles of acrylamide (µg/day)



Multivariate linear regression adjusted for study centre, maternal age at delivery, parity, height, education level, tobacco consumption during pregnancy, gestational age at delivery, sex, maternal weight gain during pregnancy, maternal BMI before pregnancy and the interaction between maternal BMI and weight gain (p trend=0.07)

The association between head circumference and dietary acrylamide exposure, after adjustment for confounders in a linear regression model was not significant (0.00 cm, 95% CI: -0.04 ; 0.04) **(Table 9)**. The association was somewhat different according to smoking status during pregnancy (p-for-interaction= 0.01).

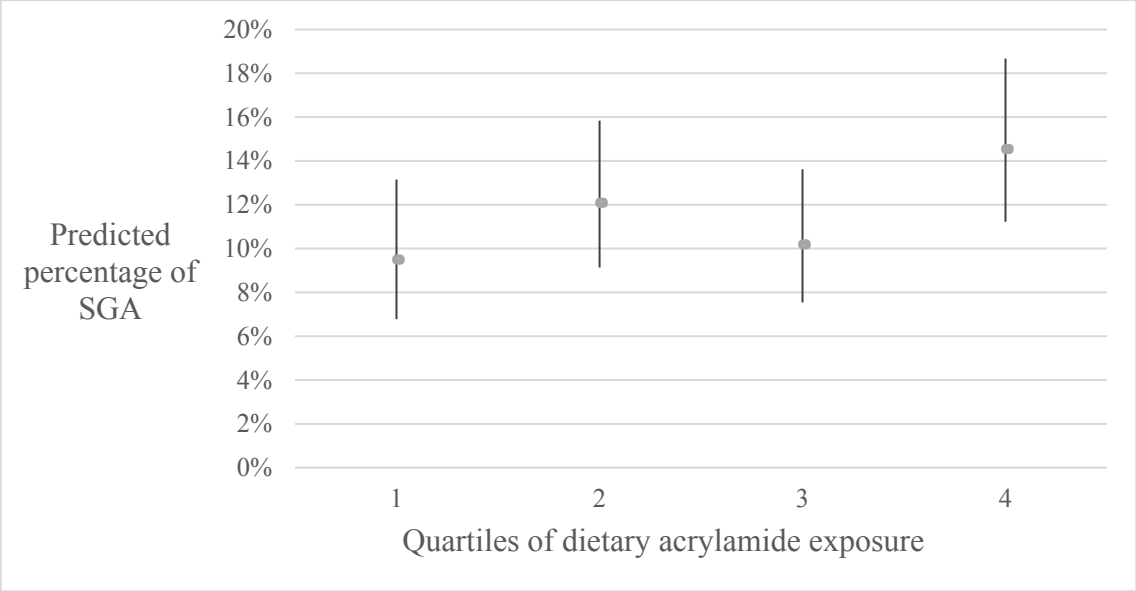
Table 9: Associations between dietary exposure to acrylamide (10µg/day) and anthropometry at birth.

	Birth size									
	Weight (g) [a, b, c, d]		**Length (cm)[a, d]**		**Weight-for-length [b, c, d]**		**SGA (vs AGA+LGA)[b]**		**Head circumference (cm) [a, b, c, e]**	
	β (95% CI)	**p**	**β (95% CI)**	**p**	**β (95% CI)**	**p**	**OR (95% CI)**	**p**	**β (95% CI)**	**p**
All women										
Model 1 (n = 1471)	-9.79 (-21.3 ; 1.69)	0.09	-0.05 (-0.11 ; 0.00)	0.06	-1.03 (-15.4 ; 13.4)	0.89	**1.11 (1.03 ; 1.21)**	**0.001**	-0.002 (-0.04 ; 0.04)	0.95
Model 2 (n = 1471)	**-28.6 (-54.4 ; -0.79)**	**0.04**	**-0.16 (-0.29 ; -0.03)**	**0.02**	-7.99 (-30.3 ; 14.4)	0.48	**1.31 (1.04 ; 1.66)**	**0.02**	-0.03 (-0.13 ; 0.08)	0.62
Model 3 (n = 1471)	-15.9 (-33.0 ; 1.14)	0.07	**-0.10 (-0.18 ; -0.02)**	**0.01**	-2.94 (-16.7 ; 10.8)	0.67	1.12 (0.99 ; 1.26)	0.08	-0.01 (-0.08 ; 0.05)	0.69
Model 4 (n = 1347)	-10.3 (-22.5 ; 1.89)	0.10	**-0.07 (-0.12 ; -0.01)**	**0.02**	-3.57 (-11.7 ; 4.55)	0.39	**1.12 (1.03 ; 1.22)**	**0.01**	-0.01 (-0.05 ; 0.04)	0.75
Non-smoking women										
Model 1 (n = 1075)	-7.69 (-23.0 ; 7.67)	0.33	-0.01 (-0.08 ; 0.05)	0.68	-5.46 (-17.7 ; 6.81)	0.38	**1.16 (1.04 ; 1.30)**	**0.01**	0.04 (-0.02 ; 0.10)	0.15
Smoking women										
Model 1 (n = 396)	-9.85 (-27.8 ; 8.11)	0.28	**-0.09 (-0.18 ; 0.00)**	**0.04**	0.46 (-14.1 ; 15.0)	0.95	1.05 (0.92 ; 1.19)	0.32	-0.06 (-0.13 ; 0.01)	0.09

Model 1: (except SGA) adjusted for study centre, maternal age at delivery, parity, height, maternal education level, tobacco consumption during pregnancy, gestational age at delivery, sex
Model 1 for SGA: adjusted for study centre, maternal age at delivery, maternal education level, tobacco consumption during pregnancy, and specific maternal weight gain during pregnancy
Model 2: acrylamide exposure log transformed
Model 3: adjusted on acrylamide main contributors: French fries, fries potatoes, crisps
Model 4: excluding the subjects with imputed variables (8.4%)
$p_{\text{for interaction}}$ between dietary acrylamide exposure and smoking status: 0.41 for birth weight, 0.11 for birth length, 0.94 for birth weight adjusted for birth length, 0.01 for head circumference, 0.27 for SGA
a: additionally adjusted for BMI
b: additionally adjusted for specific maternal weight gain during pregnancy
c: additionally adjusted for the interaction between maternal BMI and weight gain
d: gestational age and gestational age squared
e: gestational age, gestational age squared and gestational age cubed
SGA: small for gestational age, AGA: appropriate for gestational age, LGA: large for gestational age

After adjustments in a logistic model, dietary acrylamide exposure was significantly associated with an increased risk of SGA at birth (OR=1.11 for 10 µg/day increase, 95% CI: 1.03 ; 1.21). The association was not significantly different between smokers (OR=1.05, 95% CI: 0.92 ; 1.19) and non-smokers (OR=1.16, 95% CI: 1.04 ; 1.30, p-for-interaction=0.27). When intake was classified as quartiles, we did not observe a departure of the relationship from linearity ($p_{\text{for linearity}}$=0.31). The respective OR for each quartile Q2, Q3 and Q4, when compared to the first, were 1.31 (95% CI: 0.81 ; 2.12), 1.08 (95%CI 0.66 ; 1.77) and 2.16 (95% CI: 1.01 ; 2.62) respectively. The corresponding predicted percentages of SGA by acrylamide quartiles are presented on **Figure 16**.

Figure 16: Predicted percentage of SGA (n = 1471) by acrylamide quartiles (per 10 µg/day)



Multivariate logistic regression adjusted for study centre, maternal age at delivery, education level, tobacco consumption during pregnancy, and specific maternal weight gain during pregnancy (p trend=0.31)

Considering a causal relationship between dietary acrylamide exposure and SGA, and considering the adjustment factors including tobacco consumption, the attributable fraction of being exposed to the highest quartile of acrylamide on SGA was 10% (95% CI: 0% ; 19%). The attributable fraction of tobacco consumption on SGA in our population was 16% (95% CI: 4% ; 28%) after taking into account the same adjustment factors including dietary acrylamide exposure.

We did not find any association between dietary acrylamide exposure and BMI at 1, 3 and 5 years after adjustment in linear regression models **(Table 10)**. We did not show any significant

difference in the associations according to active smoking (p-for-interaction=0.86, 0.72 and 0.64 for predicted BMI at 1, 3 and 5 years respectively). The prevalence of overweight children in our population was 5.6% and 6.2% at 3 and 5 years respectively. We did not find any association between dietary acrylamide exposure and being overweight at 3 and 5 years after adjustment in logistic regression models **(Table 11)**. We did not show any significant difference in the associations according to active smoking (p-for-interaction= 0.45 and 0.72 for overweight at 3 and 5 years respectively).

Table 10: Associations between dietary exposure to acrylamide (per 10µg/day) and predicted BMI at 1, 3 and 5 years..

	Predicted postnatal growth					
	1-y BMI		3-y BMI		5-y BMI	
	β (95% CI)	p	β (95% CI)	p	β (95% CI)	p
All women (n = 1401)						
Model 1	0.01 (-0.03 ; 0.05)	0.69	-0.01 (-0.04 ; 0.03)	0.81	-0.01 (-0.04 ; 0.04)	0.82
Non-smoking women (n = 1042)						
Model 1	0.02 (-0.03 ; 0.07)	0.48	0.01 (-0.03 ; 0.06)	0.62	0.01 (-0.04 ; 0.06)	0.67
Smoking women (n = 359)						
Model 1	0.01 (-0.05 ; 0.08)	0.69	-0.02 (-0.08 ; 0.04)	0.56	-0.02 (-0.10 ; 0.05)	0.51

Model 1: adjusted for study centre, maternal age at delivery, parity, height, maternal education level, tobacco consumption during pregnancy, gestational age at delivery and gestational age squared, sex, BMI, specific maternal weight gain during pregnancy, as well as interaction between maternal BMI and weight gain

Table 11: Associations between dietary exposure to acrylamide (per 10µg/day) and overweight at 3 and 5 years.

	Prevalence (%)	Overweight	
		OR (95% CI)	p
All women (n = 1401)			
Overweight 3-y	5.6	1.03 (0.89 ; 1.19)	0.67
Overweight 5-y	6.2	0.98 (0.86 ; 1.12)	0.78
Non-smoking women (n = 1042)			
Overweight 3-y	5.2	1.03 (0.83 ; 1.29)	0.19
Overweight 5-y	5.4	0.91 (0.82 ; 1.20)	0.45
Smoking women (n = 359)			
Overweight 3-y	7.0	0.86 (0.72 ; 1.07)	0.78
Overweight 5-y	8.9	0.93 (0.79 ; 1.12)	0.93

Adjusted for study centre, maternal age at delivery, parity, height, maternal education level, tobacco consumption during pregnancy, gestational age at delivery and gestational age squared, sex, BMI, specific maternal weight gain during pregnancy, as well as interaction between maternal BMI and weight gain

Complementary and sensitivity analyses showed similar results when we excluded subjects with imputed variables and without adjusting for gestational weight gain during pregnancy. The associations using the log-transformed exposure variable and adjusting for acrylamide contributors were slightly stronger **(Table 9)**. The specific sensitivity analysis of birth weight showed similar results **(Table 12)**. When we used energy intake adjusted acrylamide (in µg/kcal/day) in the birth weight model and expressing the increase for 1 standard deviation the association, the magnitude and the strength were higher. For the birth weight model the analysis, with additional adjustment on paternal BMI and total energy intake the results remained in the same magnitude but were not significant anymore.

Table 12: Complementary and sensitivity analysis for birth weight and dietary acrylamide exposure (n = 1471)

	Weight (g)	
	β (95% CI)	**p**
Model 1[a]	-8.00 (-20.98 ; 4.98)	0.23
Model 2: acrylamide considered in µg/kcal/day (per 1 SD increase)	**-23.67 (-43.52 ; -3.82)**	**0.02**
Model 3: without adjustment on maternal weight gain	-9.35 (-20.90 ; 2.20)	0.11

Linear regression model adjusted for study centre, maternal age at delivery, parity, height, maternal education level, tobacco consumption during pregnancy, gestational age and gestational age squared, sex, additionally adjusted for maternal BMI, maternal weight gain during pregnancy and the interaction between maternal BMI and maternal weight gain

a: additionally adjusted for paternal BMI and maternal total energy intake

4.4. Acrylamide and postnatal growth in the MoBa study

Acrylamide exposure in Norwegian pregnant women has been studied before. The study by Duarte-Salles et al. explored the association with birth outcomes, including birth weight and SGA, (Duarte-Salles et al., 2013). In addition, Pedersen et al. studied a similar objective in a multi-country population of mother-child pairs from Norway, Spain, Greece, United Kingdom and Denmark (Pedersen et al., 2012). Therefore, I have focused my analyses on the effect of prenatal dietary acrylamide exposure on postnatal growth.

4.4.1. *Methods*

4.4.1.1. Main variables

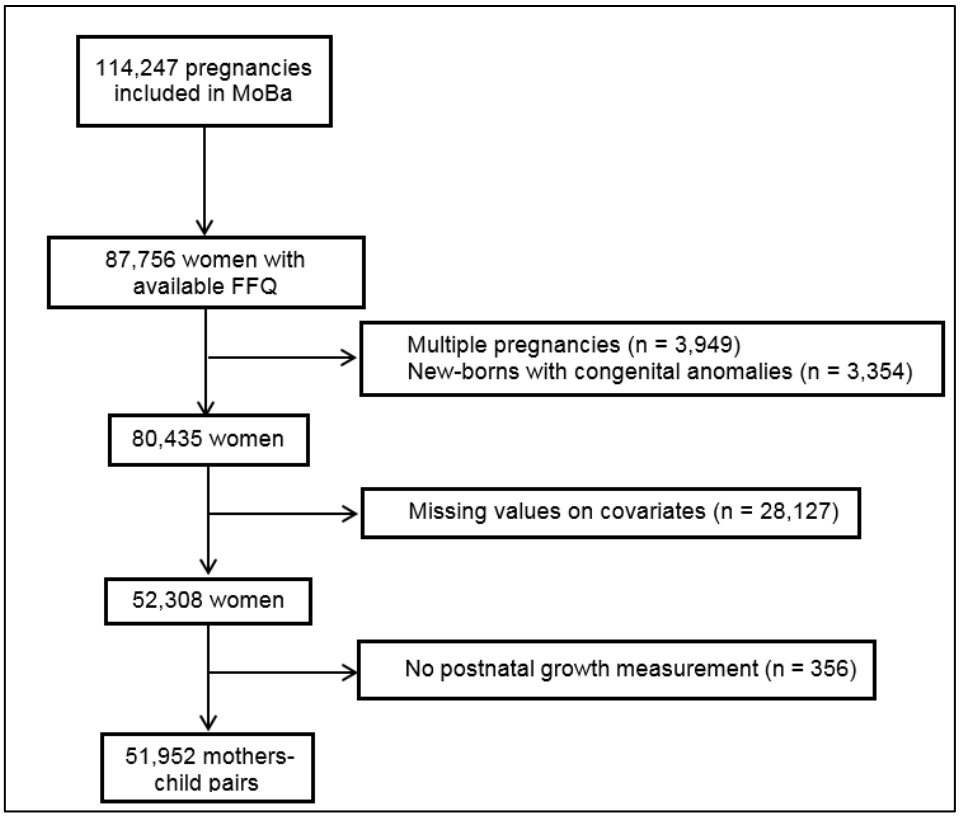
Energy intake adjusted acrylamide (in µg/kcal/day) was calculated by dividing dietary acrylamide exposure in (µg/day) by energy intake (kcal).

Body mass index (BMI) was calculated as weight (in kg) divided by squared height (in m) using the predicted growth values (Botton et al. 2014). Furthermore, we defined childhood overweight and obesity at 3, 5 and 8 years using the International Obesity Task Force (IOTF) cut-offs for boys and girls (Cole and Lobstein, 2012).

4.4.1.2. Sample selection

The data included 80,453 women with singleton, live born babies without malformations and chromosomal anomalies and available dietary acrylamide exposure estimates. After excluding mother-child pairs with missing information on parity (no missing), maternal age (no missing), maternal education (3% missing), pre-pregnancy BMI (3% missing), gestational weight gain (18% missing), maternal active (1% missing) and passive (1% missing) smoking during pregnancy, maternal alcohol consumption during pregnancy (14% missing), implausible energy intake (i.e. <4.5 MJ (1075 kcal) and >20 MJ (4777 kcal), 2% excluded), paternal weight (5% missing), gestational age (0.4% missing), child's gender (no missing), birth weight (0.1% missing) and length (3% missing), the population without missing information was 52,308 mother-child pairs. Additional mother-child pairs were excluded when no postnatal growth measurement was available, resulting in a final study sample of 51,952 mother-child pairs (65% of the source population) see **Figure 17**.

Figure 17: Flow chart for the analysis of Acrylamide and growth in MoBa



4.4.1.3. Statistical analyses

Logistic regression models were used to investigate the association between maternal dietary acrylamide exposure (in quartiles) and the risk of overweight including obesity or the risk of obesity only, at 3, 5 and 8 years separately. Further, we used restricted cubic splines with four knots at percentiles 5, 35, 65 and 95, to assess the linearity of the association, visually and statistically, using the exposure variable in a continuous scale. The logistic regression models were adjusted for random effects of sibling clusters since some mothers participated with more than one pregnancy.

Linear mixed effect models were used to investigate the association between maternal dietary acrylamide exposure during pregnancy (in quartiles) and child's postnatal growth from 1 month to 8 years. The effect estimates for each outcome were presented in line plots by quartiles of dietary acrylamide exposure.

Variables considered as potential confounders in this study were maternal and pregnancy-related characteristics previously identified as adjustment factors for the association between dietary acrylamide exposure in pregnancy and foetal growth (Duarte-Salles et al., 2013; Kadawathagedara et al., 2016; Pedersen et al., 2012). The variables included: parity (nulliparous vs multiparous), maternal age (years), maternal education (≤ 9 years, 13-16 years, ≥ 17 years), maternal pre-pregnancy BMI (<18.5, 18.5-24.9, 25-29.9, ≥30 kg/m²), gestational weight gain (kg), smoking during pregnancy (no, occasional, daily) and gestational age (weeks). In addition, maternal alcohol consumption during pregnancy (yes vs no), exposure to passive smoking during pregnancy (yes vs no), total energy intake (KJ, assessed concomitantly with acrylamide) and paternal BMI (kg/m^2) and height (m) were tested as potential confounders. We also tested for interaction between dietary acrylamide exposure and gender or birth weight. Variables were included in the model if the association with both the exposure variable and the outcome variable (overweight/obesity at 3 years) had a p-value less than 0.05. Only gender was not included in the final models

The association between maternal dietary acrylamide exposure in pregnancy and postnatal growth was tested by using both crude dietary acrylamide exposure (in µg/day) and energy intake adjusted dietary acrylamide exposure (in µg/kcal/day). The energy-adjusted analysis is presented as the main analysis and the non-adjusted in supplemental analysis. We performed the following complementary analyses (1) without adjustment for birth weight, (2) using only reported anthropometric data (not predicted values), (3) using acrylamide crude intake in µg/day with total energy intake as a covariate in the model, and (4) examining dietary acrylamide exposure as three independent variables reflecting the amounts from the principal contributors (crispbread, sweet bakeries items and bread).

The main analyses were performed using Stata 14 statistical software (Stata Corporation, College Station, Texas)

4.4.2. *Results*

Increasing maternal dietary acrylamide exposure during pregnancy was associated with higher prevalence of children being overweight/obese at 3, 5 and 8 years of age, after adjustment for confounders **(**Table 13**)**. Children born to mothers with dietary acrylamide exposure at 2nd, 3rd and 4th quartile had 10%, 12% and 21% higher odds of being overweight/obese at 3 years, compared to their low exposed peers. The association was weakened at 5 years and no significant association was found at 8 years. We found increased odds for obesity only at 3 years associated with the highest level of dietary acrylamide exposure, and a similar dose-response trend was also observed at 5 years. Assessing the exposure on a continuous scale, we found that the prevalence of overweight at 3 and 5 years (but not at 8 years) increased from no intake to an intake of 0.01 µg/kcal/day (~95th percentile of dietary acrylamide exposure) and then reached a plateau **(Figure 18)**. There was no interaction between birth weight and acrylamide exposure on postnatal growth and no substantial difference when removing birth weight from the covariates **(Table 14)**. There was no interaction between gender and acrylamide exposure on postnatal growth (data not shown). When using the reported anthropometric data to define the outcome, the estimates were similar compared to predicted anthropometric values, but with greater variances **(Table 15)**.

Figure 18: Maternal dietary acrylamide exposure (µg/kcal/day) in pregnancy (in continuous scale) and overweight/obesity at 3 (black lines), 5 (red lines) and 8 (blue lines) years (n = 51,952). Solid lines represent Odds Ratios (OR) and dotted lines represent 95% Confidence Intervals (CI).

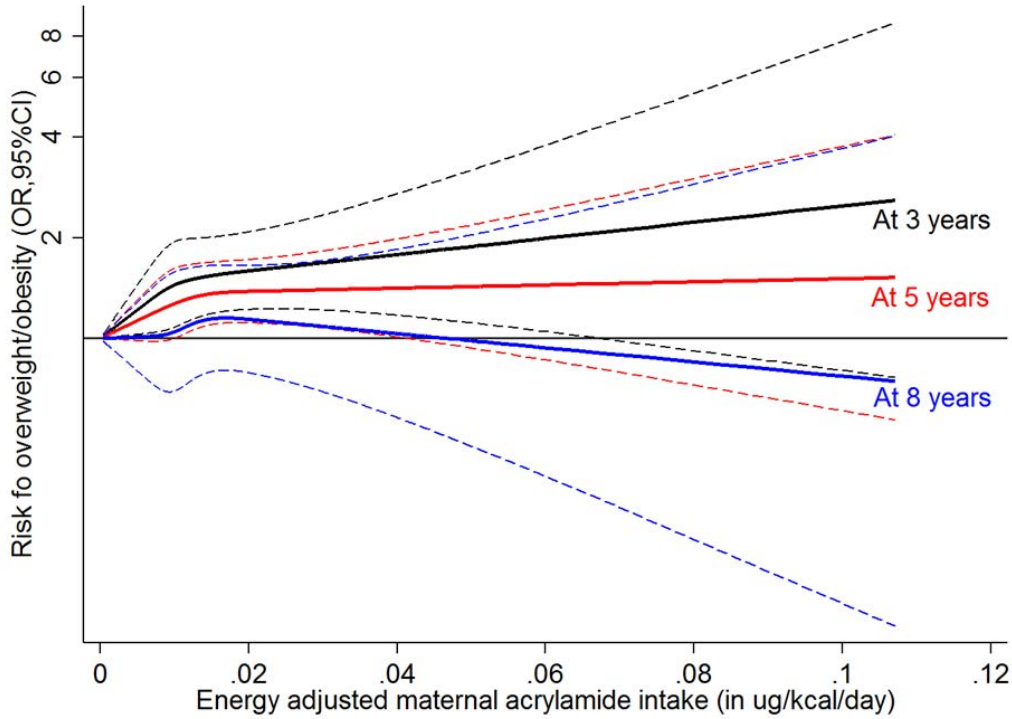


Table 13: Maternal dietary exposure to acrylamide in pregnancy and overweight/obesity or obesity only at 3, 5 and 8 years (n = 51,952).

Maternal energy-adjusted dietary acrylamide exposure (µg/kcal/day)	Risk for overweight and obesity [a]					
	At 3 years		At 5 years		At 8 years	
	Prevalence (%)	OR (95% CI)	Prevalence (%)	OR (95% CI)	Prevalence (%)	OR (95% CI)
Quartiles of exposure						
Q1	9.77		15.24		4.55	
Q2	10.54	**1.10 (1.02 ; 1.20)**	16.14	**1.08 (1.01 ; 1.16)**	4.57	1.02 (0.91 ; 1.15)
Q3	10.77	**1.12 (1.04 ; 1.22)**	16.59	**1.11 (1.04 ; 1.19)**	5.02	1.12 (0.99 ; 1.25)
Q4	11.55	**1.21 (1.11 ; 1.31)**	17.49	**1.17 (1.10 ; 1.26)**	5.12	1.12 (1.00 ; 1.26)
$p_{for\ trend}$		***<0.001***		***<0.001***		***0.023***
	Risk for obesity only [a]					
Q1	0.88		2.39		0.28	
Q2	0.94	1.09 (0.84 ; 1.41)	2.52	1.07 (0.92 ; 1.26)	0.21	0.76 (0.46 ; 1.25)
Q3	0.96	1.11 (0.86 ; 1.44)	2.67	1.13 (0.96 ; 1.32)	0.27	0.96 (0.60 ; 1.53)
Q4	1.21	**1.35 (1.06 ; 1.73)**	2.82	1.16 (0.99 ; 1.36)	0.44	1.46 (0.96 ; 2.23)
$p_{for\ trend}$		***0.018***		***0.048***		***0.045***

All models are adjusted for maternal age, parity, maternal education, pre-pregnancy BMI, gestational weight gain, maternal smoking during pregnancy, gestational age, maternal alcohol consumption during pregnancy, second hand smoking and birth weight.

[a] Overweight and/or obese children were defined according to IOTF definition, using the predicted anthropometric measurements.

Table 14: Complementary analysis: associations between maternal acrylamide intake in pregnancy and overweight/obesity and obesity only at 3, 5 and 8 years, without adjustment for birth weight (n = 51,952).

Maternal energy-adjusted dietary acrylamide exposure (µg/kcal/day)	**Risk for overweight and obesity [a]**		
	At 3 years OR (95% CI)	**At 5 years OR (95% CI)**	**At 8 years OR (95% CI)**
Quartiles of exposure			
Q1	1.00	1.00	1.00
Q2	**1.09 (1.01 ; 1.19)**	**1.07 (1.00 ; 1.15)**	1.02 (0.90 ; 1.14)
Q3	**1.11 (1.02 ; 1.20)**	**1.10 (1.03 ; 1.18)**	1.11 (0.99 ; 1.24)
Q4	**1.18 (1.09 ; 1.28)**	**1.15 (1.08 ; 1.24)**	1.11 (0.98 ; 1.24)
p for trend	***<0.001***	***<0.001***	***0.038***
		Risk for obesity only [a]	
Q1	1.00	1.00	1.00
Q2	1.08 (0.84 ; 1.40)	1.07 (0.91 ; 1.25)	0.76 (0.46 ; 1.26)
Q3	1.10 (0.85 ; 1.42)	1.12 (0.95 ; 1.31)	0.96 (0.60 ; 1.53)
Q4	**1.33 (1.04 ; 1.70)**	1.14 (0.98 ; 1.34)	1.47 (0.96 ; 2.24)
p for trend	***0.026***	*0.075*	***0.043***

All models are adjusted for maternal age, parity, maternal education, pre-pregnancy BMI, gestational weight gain, maternal smoking during pregnancy, gestational age, maternal alcohol consumption during pregnancy, second hand smoking.

[a] Overweight and/or obese children were defined according to IOTF definition, using the predicted anthropometric measurements.

Table 15: Supplementary analysis: maternal energy-adjusted dietary acrylamide exposure in pregnancy and overweight/obesity and obesity only at 3, 5 and 8 years, using reported anthropometric measurements.

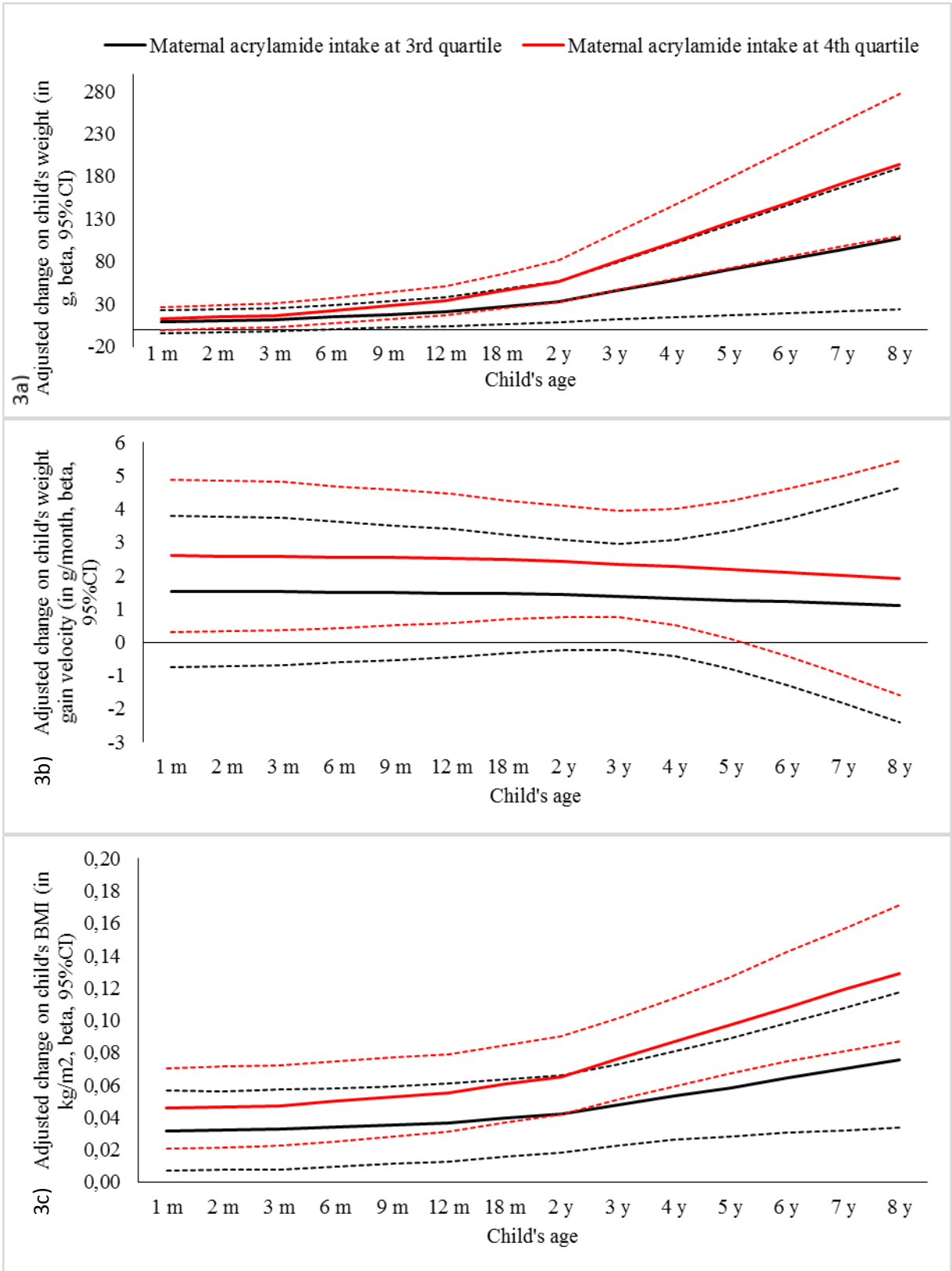
Energy adjusted maternal dietary acrylamide exposure (µg/day)	At 3 years (N = 22,856)		At 5 years (N = 22,481)		At 8 years (N = 13,068)	
	Prevalence (%)	OR (95% CI)	Prevalence (%)	OR (95% CI)	Prevalence (%)	OR (95% CI)
			Risk for overweight and obesity [a]			
Quartiles of exposure						
Q1	11.12	1.00	10.57	1.00	10.94	1.00
Q2	11.83	1.07 (0.96 ; 1.21)	10.89	1.05 (0.93 ; 1.18)	11.84	1.11 (0.95 ; 1.30)
Q3	12.01	1.09 (0.97 ; 1.22)	11.42	1.10 (0.97 ; 1.24)	11.34	1.04 (0.89 ; 1.22)
Q4	13.92	**1.28 (1.15 ; 1.44)**	11.55	1.09 (0.97 ; 1.23)	11.85	1.07 (0.92 ; 1.26)
p for trend		***<0.001***		*0.119*		*0.579*
			Obesity only [a]			
Q1	1.33	1.00	1.28	1.00	0.78	1.00
Q2	1.25	0.94 (0.68 ; 1.30)	1.27	1.02 (0.73 ; 1.43)	0.60	0.79 (0.44 ; 1.43)
Q3	1.76	1.32 (0.98 ; 1.79)	1.47	1.17 (0.85 ; 1.62)	0.60	0.77 (0.42 ; 1.39)
Q4	1.80	1.36 (1.00 ; 1.84)	1.35	1.05 (0.75 ; 1.46)	0.97	1.21 (0.71 ; 2.06)
p for trend		***0.009***		*0.602*		*0.493*

All models are adjusted for maternal age, parity, maternal education, pre-pregnancy BMI, gestational weight gain, maternal smoking during pregnancy, gestational age, maternal alcohol consumption during pregnancy, second hand smoking and birth weight.

[a] Overweight and/or obese children were defined according to IOTF definition, using the measured anthropometric measurements.

When assessing weight up to 8 years, we found that energy-adjusted dietary acrylamide exposure in the 3rd and 4th quartile was associated with higher weight from the first months onwards **(Figure 19)**. Regarding weight growth velocity, maternal dietary acrylamide exposure in the 4th quartile was associated with higher weight gain velocity from 1st month to 5 years. Finally, maternal dietary acrylamide exposure higher than the 1st quartile was associated with higher BMI throughout the whole childhood.

Figure 19: Adjusted changes in child's A) weight, B) weight gain velocity and C) BMI from 1st month to 8 years, associated with 3rd and 4th maternal dietary acrylamide exposure quartiles (energy-adjusted).



Footnote: All models are adjusted for maternal age, parity, maternal education, pre-pregnancy BMI, gestational weight gain, maternal smoking during pregnancy, gestational age, maternal alcohol consumption during pregnancy, second hand smoking and birth weight.

More specifically and focusing on the highest exposure level, 1 year old children prenatally exposed to high acrylamide levels weighed 34 g more, gained 2.5 g more per month and had 0.06 kg/m^2 higher BMI than their low exposed peers **(Table 16)**. At eight years after the exposure, highly exposed children weighed between 110 g to 278 g more than their low exposed peers did (~0.4-1% higher than the average weight at 8 years).

Table 16: Association between maternal dietary acrylamide exposure in pregnancy and child's weight, weight gain velocity and BMI from 1st month to 8 years. The 1st quartile of maternal dietary acrylamide exposure is used as the reference.

	Energy-adjusted maternal dietary acrylamide exposure (µg/kcal/day) in quartile		
	2nd quartile	**3r^{d} quartile**	**4th quartile**
	β (95% CI)	**β (95% CI)**	**β (95% CI)**
Weight (in g) [a]			
3months	-0.1 (-14 ; 14)	11 (-2.7 ; 25)	**17 (2.5 ; 31)**
6months	2.6 (-12 ; 17)	14 (-0.2 ; 29)	**22 (7.7 ; 37)**
12months	8.2 (-8.7 ; 25)	**21 (3.6 ; 37)**	**34 (17 ; 51)**
2years	19 (-5.0 ; 44)	**33 (8.4 ; 57)**	**57 (32 ; 81)**
5years	53 (-0.4 ; 106)	**70 (17 ; 123)**	**125 (73 ; 179)**
8years	**86 (2.5 ; 169)**	**107 (23 ; 190)**	**194 (110 ; 278)**
Weight gain velocity (in g/month) [a]			
3months	0.8 (-1.4 ; 3.1)	1.5 (-0.7 ; 3.7)	**2.6 (0.4 ; 4.8)**
6months	0.9 (-1.2 ; 3.0)	1.5 (-0.6 ; 3.6)	**2.6 (0.4 ; 4.7)**
12months	0.9 (-1.0 ; 2.8)	1.5 (-0.5 ; 3.4)	**2.5 (0.6 ; 4.5)**
2years	1.0 (-0.7 ; 2.7)	1.4 (-0.2 ; 3.1)	**2.4 (0.8 ; 4.1)**
5years	1.2 (-0.8 ; 3.3)	1.3 (-0.8 ; 3.3)	**2.2 (0.1 ; 4.3)**
8years	1.5 (-2.0 ; 5.0)	1.1 (-2.4 ; 4.6)	1.9 (-1.6 ; 5.5)
BMI (in kg/m^2) [a]			
3months	0.03 (0.00 ; 0.05)	**0.03 (0.01 ; 0.06)**	**0.05 (0.02 ; 0.07)**
6months	0.03 (0.00 ; 0.05)	**0.03 (0.01 ; 0.06)**	**0.05 (0.03 ; 0.07)**
12months	**0.03 (0.01 ; 0.05)**	**0.04 (0.01 ; 0.06)**	**0.06 (0.03 ; 0.08)**
2years	**0.04 (0.01 ; 0.06)**	**0.04 (0.02 ; 0.07)**	**0.07 (0.04 ; 0.09)**
5years	**0.06 (0.03 ; 0.09)**	**0.06 (0.03 ; 0.09)**	**0.10 (0.07 ; 0.13)**
8years	**0.08 (0.04 ; 0.12)**	**0.08 (0.03 ; 0.12)**	**0.13 (0.09 ; 0.17)**

All linear mixed models are adjusted for maternal age, parity, maternal education, pre-pregnancy BMI, gestational weight gain, maternal smoking during pregnancy, gestational age, maternal alcohol consumption during pregnancy, second hand smoking and birth weight.

[a] Predicted anthropometric measurements were used to define outcomes.

When using the crude dietary acrylamide exposure as an exposure variable (in µg/day) the associations with overweight and obesity were similar, while for obese only, the associations were stronger for the 3rd quartile at 3 and 5 years and for the 4th quartile at 8 years **(Table 17)**. When investigating the associations of the main acrylamide dietary contributors with the outcomes, similar associations were observed **(Table 18)**.

Table 17: Supplementary analysis: maternal dietary acrylamide exposure (µg/day) in pregnancy and overweight/obesity at 3, 5 and 8 years, using predicted anthropometric measurements (n = 51,952).

Maternal dietary acrylamide exposure (µg/day)	**Risk for overweight and obesity [a]**					
	At 3 years		**At 5 years**		**At 8 years**	
	Prevalence (%)	**OR (95% CI)**	**Prevalence (%)**	**OR (95% CI)**	**Prevalence (%)**	**OR (95% CI)**
Quartiles of exposure						
Q1	9.84	1.00	15.26	1.00	4.51	1.00
Q2	10.41	1.06 (0.98 ; 1.15)	16.05	1.06 (0.99 ; 1.13)	4.48	0.99 (0.88 ; 1.12)
Q3	11.21	**1.16 (1.07 ; 1.25)**	17.02	**1.14 (1.06 ; 1.22)**	5.07	**1.13 (1.01 ; 1.27)**
Q4	11.17	**1.14 (1.05 ; 1.24)**	17.13	**1.14 (1.06 ; 1.22)**	5.21	**1.15 (1.02 ; 1.29)**
p for trend		***<0.001***		***<0.001***		***0.010***
	Risk for obesity only [a]					
Q1	0.85	1.00	2.41	1.00	0.23	1.00
Q2	0.89	1.05 (0.80 ; 1.36)	2.35	0.98 (0.83 ; 1.15)	0.21	0.92 (0.54 ; 1.55)
Q3	1.16	**1.37 (1.07 ; 1.76)**	2.92	**1.22 (1.05 ; 1.42)**	0.35	1.54 (0.96 ; 2.45)
Q4	1.08	1.22 (0.95 ; 1.58)	2.72	1.11 (0.95 ; 1.30)	0.40	**1.62 (1.02 ; 2.56)**
p for trend		***0.033***		***0.032***		***0.008***

All models are adjusted for maternal age, parity, maternal education, pre-pregnancy BMI, gestational weight gain, maternal smoking during pregnancy, gestational age, maternal alcohol consumption during pregnancy, second hand smoking and birth weight.

[a] Overweight and obesity children were defined according to IOTF definition, using the predicted anthropometric measurements.

Table 18: Supplementary analysis: maternal acrylamide intake from crispbread, sweet bakery items and bread and overweight/obesity at 3, 5 and 8 years.

	Overweight and obesity [a]		
	3 years	**5 years**	**8 years**
	OR (95%CI)	**OR (95%CI)**	**OR (95%CI)**
Model 1: Energy-adjusted acrylamide exposure			
from crispbread			
<75th percentile	1.00	1.00	1.00
>75th percentile	**1.08 (1.01 ; 1.15**)	1.04 (0.99 ; 1.10)	1.09 (0.99 ; 1.20)
from sweet bakery items			
<75th percentile	1.00	1.00	1.00
>75th percentile	**1.09 (1.02 ; 1.16)**	**1.11 (1.05 ; 1.17)**	1.06 (0.96 ; 1.16)
from bread			
<75th percentile	1.00	1.00	1.00
>75th percentile	1.02 (0.99 ; 1.04)	1.02 (1.00 ; 1.04)	1.02 (0.99 ; 1.05)
Model 2: Acrylamide exposure			
from crispbread			
<75th percentile	1.00	1.00	1.00
>75th percentile	**1.08 (1.01 ; 1.15)**	1.04 (0.99 ; 1.10)	1.08 (0.98 ; 1.18)
from sweet bakery			
<75th percentile	1.00	1.00	1.00
>75th percentile	**1.09 (1.02 ; 1.17)**	**1.09 (1.03 ; 1.15)**	1.05 (0.96 ; 1.16)
from bread			
<75th percentile	1.00	1.00	1.00
>75th percentile	1.01 (1.00 ; 1.01)	1.00 (1.00 ; 1.01)	1.01 (1.00 ; 1.02)

All models are adjusted for maternal age, parity, maternal education, pre-pregnancy BMI, gestational weight gain, maternal smoking during pregnancy, gestational age, maternal alcohol consumption during pregnancy, second hand smoking and birth weight. Models are also mutually adjusted for the 3 food groups.

[a] Overweight/obesity were defined according to IOTF definition, using the predicted anthropometric measurements.

4.5. Discussion

It is interesting to note that the profiles of dietary exposure to acrylamide in both studies are quite different. In MoBa, unhealthy foods contribute less to total dietary acrylamide exposure compared to EDEN. The main differences are the contribution of French fries (higher in EDEN), coffee (higher in EDEN) and crispbread (higher in MoBa) to acrylamide exposure. Consequently, similar associations between acrylamide exposure and child's anthropometric measurements in both studies would be in favour of the influence of acrylamide itself and not its main contributor.

Our epidemiological study is the third to show a significant association between SGA status and dietary acrylamide exposure (Duarte-Salles et al., 2013; Pedersen et al., 2012): the greater the intake during pregnancy, the lower the birth length and the higher the risk of SGA. The association with birth weight was strongly attenuated after adjustment for birth length. In the EDEN study we did not find any association between dietary acrylamide and postnatal growth up to five years. In the analysis of the larger Norwegian MoBa cohort, we found that prenatal acrylamide exposure was associated with an increased risk of children being overweight or obese and having higher weight growth velocity during early childhood. To our knowledge, this is the first study to examine the relationship between prenatal acrylamide exposure and postnatal growth.

In several developed countries, an unexplained decrease over time in birth weight of term babies has been observed, despite the rising prevalence of maternal overweight and the average weight gain in pregnancy (Diouf et al., 2011; Donahue et al., 2010; Schiessl et al., 2009). Adverse environmental exposures could be an explanation (Barouki et al., 2012; Katić et al., 2010; Slama and Cordier, 2013). In fact, two previous epidemiological studies underlined associations between prenatal acrylamide exposure and impaired foetal growth. The first one was a consortium of five European mother-child cohort studies, including a subsample from MoBa, using biomarkers of acrylamide exposure during gestation (Pedersen et al., 2012), and the other one assessed acrylamide exposure through diet (Duarte-Salles et al., 2013). In line with these previous results, high dietary exposure to acrylamide was related to increased risk of SGA in the EDEN mother-child cohort. These results were consistent with animal studies showing a decrease in offspring body weight following maternal acrylamide exposure during gestation (El-Sayyad et al., 2011; Manson et al., 2005; Tyl and Friedman, 2003).

No previous animal or epidemiological study examined the relationship between prenatal exposure to acrylamide and postnatal growth. In MoBa, higher exposure to acrylamide was related to higher risk of overweight in childhood but this result was not found in EDEN. This discrepancy might

be due to a larger number of participants and higher prevalence of overweight in MoBa than in EDEN and therefore a lack of power in the EDEN study. In fact, to highlight an increase odds of being overweight of 20% with the prevalence of overweight in EDEN study (6%), we would need 24000 children at five years (sample size calculated using Kelsey et al method (Fleiss, 1981; Kelsey et al., 1996.). The increased risk of overweight in MoBa associated with high prenatal acrylamide exposure are in line with the Developmental origins of Disease hypothesis (Gluckman et al., 2008). Considering the absence of interaction between birth weight and prenatal exposure to acrylamide and that adjustment for birth weight did not change the association, the association between acrylamide exposure and postnatal growth is likely independent from the one with foetal growth, which suggest a direct effect.

We acknowledge that maternal dietary pattern related to high acrylamide exposure, rather than the acrylamide exposure itself, might confound the observed association. In other populations, dietary acrylamide exposure has been related with high intake of fast-foods, like chips (Pedersen et al., 2015), while in the Norwegian women high acrylamide exposure was driven by crispbread intake, that is high in fibre and not associated with an unhealthy dietary pattern. Hence, in this population, it is less likely that an unhealthy dietary pattern during pregnancy would explain our findings. To add to the evidence, in French pregnant women from the EDEN study, dietary intake was associated to a lower dietary score. Despite two different patterns of dietary acrylamide exposure, dietary acrylamide exposure was associated to negative health impacts.

Strengtsh and limitations

In EDEN and MoBa studies, acrylamide exposure was assessed through diet, as estimated using a FFQ and a food-chemical concentration database. Duarte-Salles et al. reported a positive correlation between estimated dietary acrylamide exposure and Hb adducts in maternal blood (Spearman's rho: 0.24, 95% CI: 0.00, 0.44) in the same Norwegian population as MoBa (Duarte-Salles et al., 2013). This level of correlation is in agreement with previous reports (Kutting et al., 2008; Tran et al., 2010; Wilson

et al., 2009a; Wilson et al., 2009b; Wirfalt et al., 2008). The use of dietary intake estimations to assess acrylamide exposure can be seen as a strength of our study, as an alternative method such as biomarkers would be more invasive, burdensome and expensive to be applied in a large population. In addition, dietary assessment is highly relevant as food is the primary source of acrylamide exposure in non-smokers and non-occupationally exposed populations (Dybing et al., 2005) and only 8 % and 27% of women smoked during pregnancy in MoBa and EDEN respectively.

Another strength of our study, in EDEN, is the use of customized growth curves to evaluate SGA and growth modelling. Customized growth curves limit misclassification bias, as the curves take better account of the physiological small birth weight. Also, the use of growth modelling takes attrition bias into account and handles the missing body size measurements. In MoBa, the correlations between the measured and the predicted body size measurements were strong at all ages ($r>0.93$ except one coefficient at 0.85). However, we still acknowledge the potential for outcome misclassification bias as only 26% of the study population had anthropometric data at 8 years, though in part because all our population (17%) had still not reached the age of 8 years. In sensitivity analyses restricted to the measured data, similar associations were found as with the predicted body size data. Similarly in EDEN, the use of measured BMI from clinical examination did not modified the associations (data presented in chapter 5). This provides some reassurance on the validity of the predicted anthropometrics. The mixed-effect growth modelling will predict the values also for the children lost to follow-up balancing between their previous observed values and the average population trajectory. The shrinkage due to this approach is likely to predict values closer to the mean compared to the actual child's growth, leading again to a loss of power and attenuation in the associations with acrylamide exposure (McCulloch et al., 2008).

4.6. Conclusion

In conclusion, the first part of our results showed a relationship between dietary acrylamide exposure and the risk of SGA, consistent with both experimental and other epidemiological studies. They suggest an effect on foetal growth, affecting both weight and length. We were not able to highlight a link between prenatal exposure and postnatal growth in EDEN. However, results from Moba, a large population-based study, provide the first epidemiological evidence of a significant association between prenatal dietary exposure to acrylamide and higher prevalence of overweight or obese and being in higher growth trajectories during early childhood and pre-school age. The association between acrylamide exposure during pregnancy with child's adiposity and other metabolic markers can provide more insight into the negative developmental programming effects of acrylamide and should be investigated by future studies.

5. CONSIDERING A LARGE NUMBER OF FOOD CHEMICALS

5.1. Introduction and aim

In the previous chapter, we studied in detail the influence of a specific food contaminant (i.e. acrylamide) on child growth. Nevertheless, foods convey, in addition to nutrients, a large number of chemicals which may have consequences on health, and the evidence to support this argument was extensively presented in the introduction of this thesis. TDSs have revealed that food commodities can be simultaneously contaminated with several compounds, with some contaminants having exposure levels of concern.

The objective of this section is to extend analyses to all the detectable compounds as reported in the French TDS and to study the associations with child's growth. We have focused our analysis into birthweight and 5-y BMI.

5.2. Methods

5.2.1. *Outcome*

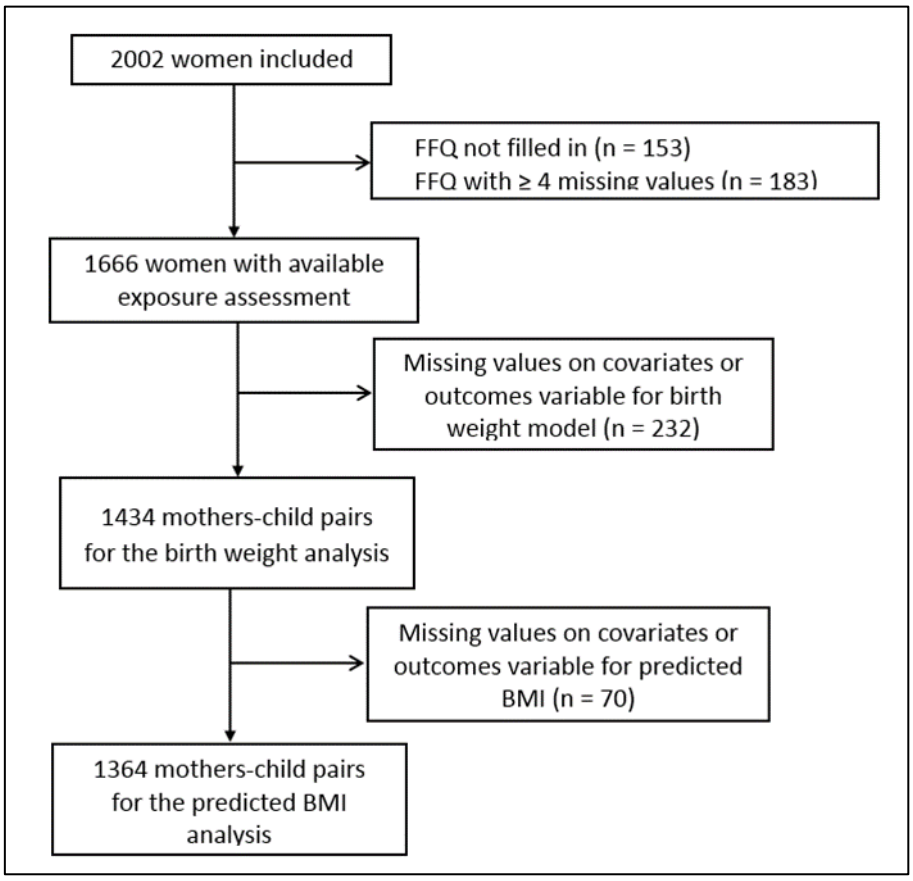
Birth weight z-score was adjusted for gestational age and sex (see chapter 2.3). Body mass index (BMI) was calculated as weight (in kg) divided by squared height (in m) using the predicted growth values (Botton et al., 2014).

5.2.2. *Sample selection*

In this analysis we have included subjects from the EDEN mother-child cohort study with available estimation of exposure to food chemical available (n=1666). These women had fill-in the FFQ completely (no missing questions) or almost completely (≤4 missing questions out of 137). For the analysis with birth weight as an outcome, n=1434 (86% of the women with available data on exposure to chemicals) women were included with additional information on birth weight, and no missing information on important confounders. For the analysis with BMI at 5 years, n= 1364 (82% of the

women with available data on exposure to chemicals) women were included in the analysis with additional postnatal growth information (**Figure 20).**

Figure 20: Flow chart of the large number of chemicals approach



5.2.3. *Statistical analysis*

The association between maternal exposure to each selected food chemical and birth weight z-score or child's 5-y predicted BMI was explored with linear regression models. For both birth weight and child's BMI, the following confounders have been selected a priori, based on the literature: study centre (Nancy vs Poitiers), maternal age at delivery, parity, maternal pre-pregnancy BMI, gestational weight gain, maternal height, education level (years of schooling), tobacco consumption during the pregnancy (3 categories: none, 1 to 9, ≥10 cigarettes per day in average), child's sex, paternal BMI. The birth weight model was additionally adjusted for maternal energy intake, as energy intake is a strong predictor of birth weight as well as probably related to high exposure to food chemicals, while the 5-y predicted BMI model was additionally adjusted for breastfeeding duration.

5.3. Single contaminant approach

In this section, we will first analyse the effect of single chemicals using an exploratory approach without any a priori hypothesis for all chemicals detected in TDS2.

5.3.1. *Methods*

5.3.1.1. Method for food chemicals selection

From the 445 food chemicals assessed in the TDS2, only 207 were detected in EDEN, in the TDS. We calculated the Spearman correlation between these food chemicals and each food item and pointed out, for each chemical, the highest correlation across all the food items. Above a certain correlation level, the effect of the chemical cannot be disentangle from the effect of one specific food item. We arbitrarily set the cut-off at the value 0.8 to put aside chemicals that cannot be studied in relation to outcomes. We illustrated Spearman's correlations between food chemicals in **Appendix 2**.

5.3.1.2. Statistical analyses

The exposure variables were transformed in logarithm to the base 2 to favour comparison of effect size across all chemicals. Therefore, the results are expressed for a doubling of the exposure.

Sensitivity analysis was conducted in the population with available measurements of weight and height at 5 years (n=965, 58%), rather than the predicted weight and height values included in the main analysis. Also similar sensitivity analysis was conducted using the predicted weight and height but in the n=965 children who also had their weight and height measured.

P-values were considered significant when <0.05. We used False Discovery Rate (FDR) procedure with q-value cut-off of 0.10 to account for multiple testing. Data were analysed using SAS version 9.3 (SAS Institute, Inc., Cary, NC, USA).

5.3.2. *Results*

Food chemicals selection

For 21 food chemicals, detected in only one food item, the highest correlation was obviously 1.0, because the variability of this chemical exposure was due only to variability in intake of the concerned food item. These 21 food chemicals and their contributor are listed in **Table 19**.

Table 19: Chemicals with a maximal correlation with one food item equals to one

Types	Chemicals	Food item
Mycotoxines		
	Azea	Wholemeal bread
	Azee	Wholemeal bread
	diacetoxyscirpenol (DAS)	Wholemeal bread
	de-epoxy deoxynivalenol (DOM1)	Cassoulet
	3-acethyl-deoxynivalenol (DON3)	Wholemeal bread
	Fusarenon-X (FusX)	Wholemeal bread
Perfluorinated compound		
	Perfluorododecanoic Acid (PFDoA)	Shellfish
	Perfluorotetradecanoic acid (PFTeDA)	Shellfish
Pesticides		
	Carbaryl	Raspberries
	Chlorfenvinphos	Vegetables
	Chlorothalonil	Raw vegetables
	Chlortal	Vegetables
	Cyproconazole	Salad
	Diazinon	Chipolatas sausages
	Diethofencarb	Raw vegetables
	Fenitrothion	Vegetables
	Malathion	Ravioli
	Permethrin	Green beens
	Vinclozolin	Green beens
Phytoestrogen		
	Biochanine A	Milk
Polycyclic Aromatic hydrocarbons		
	Dibenzo[a,h]pyrene (DbahP)	Coffee

For 87 other food chemicals, the highest correlation with a food items was at least 0.80 **(Table 20)**.

Table 20: Chemical with a maximal correlation with food items between 1 and 0.80

Maximal correlation with a food item	Types	Chemicals	Food item
0.98	**Perfluorinated compound**		
		PFBS	Water
		PFHxS	Water
	Pesticides		
		Azinphos_methyl	Apple
		Captan	Apple
		Diflubenzuron	Apple
		Diphenylamine	Apple
		Ethoxyquin	Apple
		Folpet	Apple
		Phosalone	Apple
		Pyrimicarb	Apple
		Pyriproxyfen	Raw vegetables
		Sulfur	Salad
		Tebufenozid	Apple
		Tetradifon	Salad
		Triflumuron	Apple
0.97	**Perfluorinated compound**		
		PFHpA	Water
		PFHxA	Water
	Pesticides		
		Bupirimate	Strawberry
		Dichlorvos	Strawberry
		Fenbuconazole	Peach
	Phytoestrogens		
		Resveratrol	Dried pulses
	Perfluorinated compound		
		PFTrDA	Fresh/frozen fish
	Pesticides		
		Lindane	Poultry

Table 20 continues: Chemical with a maximal correlation between 1 and 0.80

Maximal correlation with a food item	Types	Chemicals	Food item
0.96	**Pesticides**	Cyfluthrin	Raisin
		Dimethoate	Peach
		Endosulfan	Strawberry
		Etofenprox	Raisin
		Quinoxyfen	Raisin
		Spiroxamine	Raisin
		Tebuconazole	Peach
		Tebufenpyrad	Raisin
		Tetraconazole	Raisin
		Trifloxystrobin	Raisin
	Phytoestrogens	Matairesinol	Semi-skimmed milk
	Brominated flame retardants	PBB101	Fresh/frozen fish
	Metals and trace elements	MeHg	Fresh/frozen fish
	Perfluorinated compound	PFUnA	Fresh/frozen fish
0.95	**Pesticides**	Kresoxim_methyl	Strawberry
0.94		p2_Phenylphenol	Orange juice
		Ethion	Soup
	Brominated flame retardants	PBB52	Fresh/frozen fish
		PBDE100	Fresh/frozen fish
0.93	**Pesticides**	Flutriafol	Vegetables
		Propargite	Apple
		Triadimenol	Raisin
	Perfluorinated compound	PFOS	Fresh/frozen fish
	Brominated flame retardants	PBDE154	Fresh/frozen fish
0.92	**Pesticides**	Acrinathrin	Strawberry
		Carbendazim	Apple
	Dioxins and PCBs	PCB_123	Fresh/frozen fish
0.91	**Pesticides**	Thiabendazole	Apple
	Brominated flame retardants	PBDE28	Fresh/frozen fish
	Non-dioxin like PCBs	PCB_101	Fresh/frozen fish
	Dioxins and PCBs	PCB_189	Fresh/frozen fish
0.90	**Phytoestrogens**	Genisteine	Green beans
	Non-dioxin like PCBs	PCB_180	Fresh/frozen fish
	Brominated flame retardants	PBB153	Fresh/frozen fish
	Dioxins and PCBs	PCB_167	Fresh/frozen fish

Table 20 continues: Chemical with a maximal correlation between 1 and 0.80

Maximal correlation with a food item	Types	Chemicals	Food item
0.89	**Non-dioxin like PCBs**	PCB_153	Fresh/frozen fish
	Brominated flame retardants	PBDE47	Fresh/frozen fish
0.88	**Non-dioxin like PCBs**	PCB_138	Fresh/frozen fish
	Pesticides	Hexachlorobenzene	Sausages
	Dioxins and PCBs	PCB_156	Fresh/frozen fish
0.87	**Dioxins and PCBs**	PCB_157	Fresh/frozen fish
	Mycotoxines	FB2	Salty snacks
	Metals and trace elements	Aso	Fresh/frozen fish
0.86	**Mycotoxines**	DON15	Salty snacks
	Pesticides	Penconazole	Strawberry
	Phytoestrogens	Daidzeine	Green beans
	Phytoestrogens	Formononetine	Semi-skimmed milk
	Phytoestrogens	Enterolactone	Semi-skimmed milk
0.85	**Polycyclic Aromatic hudrocarbons**	MCH	Water
	Phytoestrogens	Secoisolariciresinol	Green beans
0.84	**Pesticides**	Mepanipyrim	Strawberry
	Metals and trace elements	HgI	Fresh/frozen fish
0.83	**Dioxins and PCBs**	PCB_77	Fresh/frozen fish
	Dioxins and PCBs	PCB_169	Fresh/frozen fish
	Pesticides	Methomyl	Apple
	Pesticides	Teflubenzuron	Apple
	Phytoestrogens	Equol	Semi-skimmed milk
	Perfluorinated compound	PFDA	Offal
0.82	**Dioxins and PCBs**	PCB_105	Fresh/frozen fish
0.81	**Dioxins and PCBs**	TCDF_2378	Fresh/frozen fish
	Mycotoxines	Pat	Orange juice
	Pesticides	Azoxystrobin	Strawberry
	Pesticides	Fludioxonyl	Salad
	Dioxins and PCBs	PCB_114	Fresh/frozen fish

Therefore, we analysed the 99 remaining food chemicals in relation to growth parameters. The **Table 21** presents the distribution of the 99 food chemicals selected.

For the 99 remaining food chemicals, the highest correlation across all the food items was ranging between 0.32 and 0.8 (0.8 excluded). These 99 food chemicals were then considered further in our analyses.

Table 21: Distribution of the 99 selected food chemicals (n = 1666)

Types	Food chemical	Min	25th centile	50th centile	75th centile	Max
Acrylamide (ng/j)						
	Acrylamide	141.46	11427.00	18772.02	30358.60	219742.69
Additives (µg/j)						
	Tartaric acid	57.17	984.59	1683.64	2777.35	30872.09
	Nitrites	0.10	14.12	23.48	37.48	262.55
	Sulphites	1.89	423.72	1630.30	3565.55	62272.73
BPA (ng/j)						
	BPA	458.89	2370.71	3404.24	4705.23	29386.79
Dioxins Furans (pg/j)						
	1,2,3,4,6,7,8-Hexachlorodibenzo-p-dioxin (HCDD)	3.26	17.32	23.67	31.50	122.11
	1,2,3,4,7,8-HCDD	0.23	1.41	1.95	2.64	9.24
	1,2,3,6,7,8-HCDD	0.87	5.45	7.52	10.17	33.36
	1,2,3,7,8,9-HCDD	0.25	1.85	2.58	3.54	12.01
	1,2,3,4,6,7,8-Hexachlorodibenzofuran (HCDF)	1.65	8.95	11.74	15.33	53.79
	1,2,3,4,7,8,9-HCDF	0.87	4.99	6.63	8.62	30.26
	1,2,3,4,7,8-HCDF	1.14	7.07	9.45	12.58	38.44
	1,2,3,6,7,8-HCDF	0.61	4.15	5.63	7.52	23.80
	1,2,3,7,8,9-HCDF	0.17	0.95	1.34	1.80	6.29
	2,3,4,6,7,8-HCDF	0.30	1.87	2.54	3.37	11.08
	Octchlorodibenzo-p-dioxin (OCDD)	14.29	71.18	98.53	135.13	589.92
	Octochlorodibenzofuren (OCDF)	4.09	24.30	31.99	41.94	157.78
	PCB 81	2.18	20.13	28.04	40.12	159.65
	PCB 126	19.85	183.28	265.82	370.55	1679.52
	PCB 118	2314.65	21440.81	31448.25	43182.76	200032.69
	1,2,3,7,8-Polychlorodibenzo-p-dioxin (PCDD)	0.42	3.10	4.34	5.98	21.59
	1,2,3,7,8-Polychlorinated dibenzofuran (PCDF)	0.17	1.68	2.34	3.33	15.57
	2,3,4,7,8-PCDF	1.06	8.23	11.32	15.61	57.18
	2,3,7,8-Tetrachlorodibenzodioxin (TCDD)	0.14	1.08	1.55	2.12	7.84
Non dioxins like Polychlorinated biphenyls (PCB) (pg/j)						
	PCB 28	958.83	7139.50	9705.42	13785.74	54502.54
	PCB 52	733.43	6904.50	10140.99	14449.02	67203.47

Table 21 continues: Distribution of the 99 selected food chemicals (n = 1666)

Types	Food chemical	Min	25th centile	50th centile	75th centile	Max
Metals and trace elements (µg/j)						
	Silver (Ag)	20.07	63.50	84.27	113.18	741.95
	Aluminum (Al)	741.97	2133.22	2790.96	3606.81	20022.21
	Inorganic arsenic (Asi)	6.81	22.17	26.90	32.59	102.92
	Barium (Ba)	134.02	401.77	513.58	670.81	3116.39
	Cadmium (Cd)	2.28	7.81	10.01	12.74	78.01
	Cobalt (Co)	4.06	11.19	14.37	18.48	69.23
	Chromium III (CrIII)	80.23	243.46	312.00	390.75	1372.76
	Chromium VI (CrVI)	11.65	34.84	42.74	51.80	152.04
	Galium (Ga)	0.00	0.01	0.03	0.14	1.91
	Germanium (Ge)	0.94	3.58	4.33	5.25	13.91
	Lithium (Li)	7.60	31.31	40.00	52.07	302.06
	Nickel (Ni)	45.47	130.98	168.62	225.37	1009.42
	Lead (Pb)	3.28	10.17	12.83	16.08	65.52
	Antimony (Sb)	0.44	1.42	1.85	2.57	11.67
	Tin (Sn)	10.34	53.92	79.53	118.99	2840.33
	Strontium (Sr)	475.48	2351.90	2894.26	3516.12	12021.80
	Tellurim (Te)	0.49	1.54	2.01	2.55	7.24
	Vanadium (V)	18.76	55.11	67.46	81.81	273.15
Polycyclic Aromatic Hydrocarbons (ng/j)						
	Anthracene (AN)	0.25	4.67	7.25	10.85	112.83
	Bibenzo[a,h]anthracene (BaA)	2.34	9.94	13.95	19.75	142.27
	Benzo[a]pyrene (BaP)	1.34	6.83	9.19	12.07	55.83
	Benzo[b]fluoranthene (BbF)	2.01	10.76	14.61	21.70	125.81
	Benzo[c]fluorene (BcFL)	0.24	1.42	2.09	3.08	19.57
	Benzo[g,h,i]perylene (BghiP)	3.08	18.47	25.91	32.63	112.97
	Benzo[j]fluoranthene (BjF)	1.10	5.39	7.43	10.81	55.08
	Benzo(k)fluoranthene (BkF)	0.58	3.97	5.39	8.25	49.33
	Chrysene (CHR)	4.90	24.16	33.36	47.03	293.49
	Cyclopenta[cd]pyrene (CPP)	2.38	15.08	21.19	27.26	118.42
	Dibenzo[a,e]pyrene (DbaeP)	0.26	1.90	2.50	3.27	15.42
	Dibenzo[a,h]anthracene (DBahA)	0.10	0.45	0.64	0.91	3.88
	Dibenzo[a,i]pyrene (DbaiP)	0.00	0.05	0.09	0.14	1.08
	Dibenzo[a,l]pyrene (DbalP)	0.00	0.03	0.10	0.25	89228.00
	Fluoranthene (FA)	29.23	132.39	172.11	224.48	1149.70
	Indeno[1,2,3-cd]pyrene (IP)	1.51	7.69	10.08	13.16	49.79
	Phenanthrene (PHE)	99.56	396.91	547.56	747.35	3048.34
	Pyrene (PY)	84.76	361.37	475.86	619.70	2387.45
Mycotoxins (ng/j)						
	Deoxynivalenol (DON)	1844.44	15630.60	21689.44	28030.46	108999.21
	Fumonisin B1 (FB1)	0.30	428.88	744.78	1142.41	1509845.50
	HT-2toxin (HT2)	22.32	299.95	409.61	529.08	3315.97
	Monoacetoxyscirpenol (MAS)	0.02	5.73	13.02	26.65	172.34

Table 21 continues: Distribution of the 99 selected food chemicals (n = 1666)

Types	Food chemical	Min	25th centile	50th centile	75th centile	Max
Mycotoxins (ng/j)						
	Nivalenol (Niv)	95.57	813.60	1177.41	1868.60	20628.05
	Ochratoxin A (OTA)	0.93	10.04	15.00	19.04	88.52
	Ochratoxin B (OTB)	0.01	0.80	1.45	2.64	12.58
	T-2toxin (T2)	8.79	83.55	122.26	188.91	1690.43
	Zearalenone (Zer)	22.08	253.92	339.83	449.70	2171.06
Perfluorinated compounds (ng/j)						
	Perfluorononanoic acid (PFNA)	0.00	0.03	0.09	0.27	5.65
	Perfluorooctanoic acid (PFOA)	0.01	0.72	0.93	1.15	5.39
Pesticides (µg/j)						
	Bifenthrin	0.00	0.05	0.13	0.23	1.88
	Boscalid	0.00	0.52	1.07	1.95	18.05
	Chlorpropham	0.01	2.59	4.96	8.75	133.30
	Chlorpyrifos_ethyl	0.00	0.21	0.55	1.28	12.18
	Chlorpyrifos_methyl	0.01	0.26	0.44	0.54	1.29
	Cyprodinyl	0.02	0.77	1.65	2.88	26.47
	Fenhexamid	0.00	0.23	1.00	2.86	52.55
	Imazalil	0.21	3.48	7.05	11.71	80.04
	Iprodione	0.00	4.05	9.26	17.03	116.99
	Lambda_Cyhalothrin	0.00	0.14	0.35	0.66	5.46
	Metalaxyl_M	0.00	0.14	0.26	0.44	2.98
	Myclobutanil	0.00	0.02	0.06	0.19	3.15
	Phosmet	0.00	0.10	0.22	0.43	3.23
	Piperonyl	0.96	7.88	10.44	14.08	80.93
	Pirimiphos_methyl	0.29	3.71	5.21	6.74	25.25
	Procymidone	0.00	0.53	1.20	2.05	13.27
	Pyrimethanil	0.01	0.50	1.11	2.04	18.85
Phytoetrogens (µg/j)						
	Coumestrol	0.06	0.44	1.92	3.85	1100.4
	Glyciteine	25.21	1.27	2.56	4.09	17.81
Flame retardants (ng/j)						
	Hexabromocyclododecane (HBCD) alpha	1.35	7.60	11.19	15.77	84.02
	HBCD beta	0.04	0.26	0.36	0.52	1.68
	HBCD gamma	0.05	0.40	0.56	0.80	2.91
	Polybrominated diphenyl esther (PBDE) 153	0.14	0.68	0.94	1.29	4.82
	PBDE 183	0.11	0.88	1.25	1.71	6.52
	PBDE 209	3.18	18.46	26.8	38.19	139.76
	PBDE 99	0.48	2.79	3.82	5.31	20.10

Association with 99 selected food chemicals

Among the 99 selected food chemicals, eight were significantly associated with birth weight. For a doubling of acrylamide, sulfite, Dibenzo[a,h]anthracene (DBahA) and deoxynivalenol (DON) dietary exposure during pregnancy the birth weight z-score was decreasing (acrylamide: β(95% CI)= -0.06 (-0.12 ; -0.01), sulphites: β= -0.03 (-0.05 ; -0.002), DBahA: β= -0.15 (-0.28 ; -0.02) and DON: β= -0.11 (-0.21 ; -0.01)). For a doubling of barium, chrome VI, lead and strontium dietary exposure during pregnancy the birth weight z-score was increasing (barium: β= 0.16 (0.01 ; 0.32), chrome VI: β= 0.25 (0.01 ; -0.50), lead: β= 0.20 (0.01 ; 0.39) and strontium (β= 0.16 (0.03 ; 0.30) (**Table 22** for significant associations and **Figure 21 to Figure 27** for detail of all associations).

Among the 99 food chemicals tested in association with BMI at 5 years, one negative significant association was found with a PAH: Dibenzo[a,e]pyrene (DbaeP, β= -0.09 (-0.17 ; -0.01)) **(Table 22)**. All these associations were not significant after correcting for multiple comparisons (q value for FDR) **(Table 22)**.

Table 22: Associations between the 99 selected food chemicals and birth weight z-score (n = 1434) and 5-y predicted BMI (kg/m²) (n = 1364), only significant associations are presented here

Types	Chemicals[c]	β	95% CI	p	q (FDR)
Birth weight z-score[a] (N = 1434)					
Acrylamide	Acrylamide	-0.06	(-0.12 ; 0.00)	0.05	0.38
Additives	Sulphites	-0.03	(-0.05 ; -0.00)	0.03	0.38
Metals and trace elements					
	Ba	0.16	(0.01 ; 0.32)	0.04	0.38
	CrVI	0.25	(0.01 ; 0.50)	0.04	0.38
	Pb	0.20	(0.01 ; 0.39)	0.04	0.38
	Sr	0.16	(0.03 ; 0.30)	0.02	0.38
PAH	DBahA	-0.15	(-0.28 ; -0.02)	0.03	0.38
Mycotoxins	DON	-0.11	(-0.21 ; -0.01)	0.03	0.38
5-y predicted BMI[b] (kg/m²) (N = 1364)					
PAH	DbaeP	-0.09	(-0.17 ; -0.01)	0.04	0.95

All the models adjusted for study centre, parity, maternal pre-pregnancy BMI, gestational weight gain, maternal height, maternal smoking during pregnancy, education level, paternal BMI, maternal age at delivery and child's sex

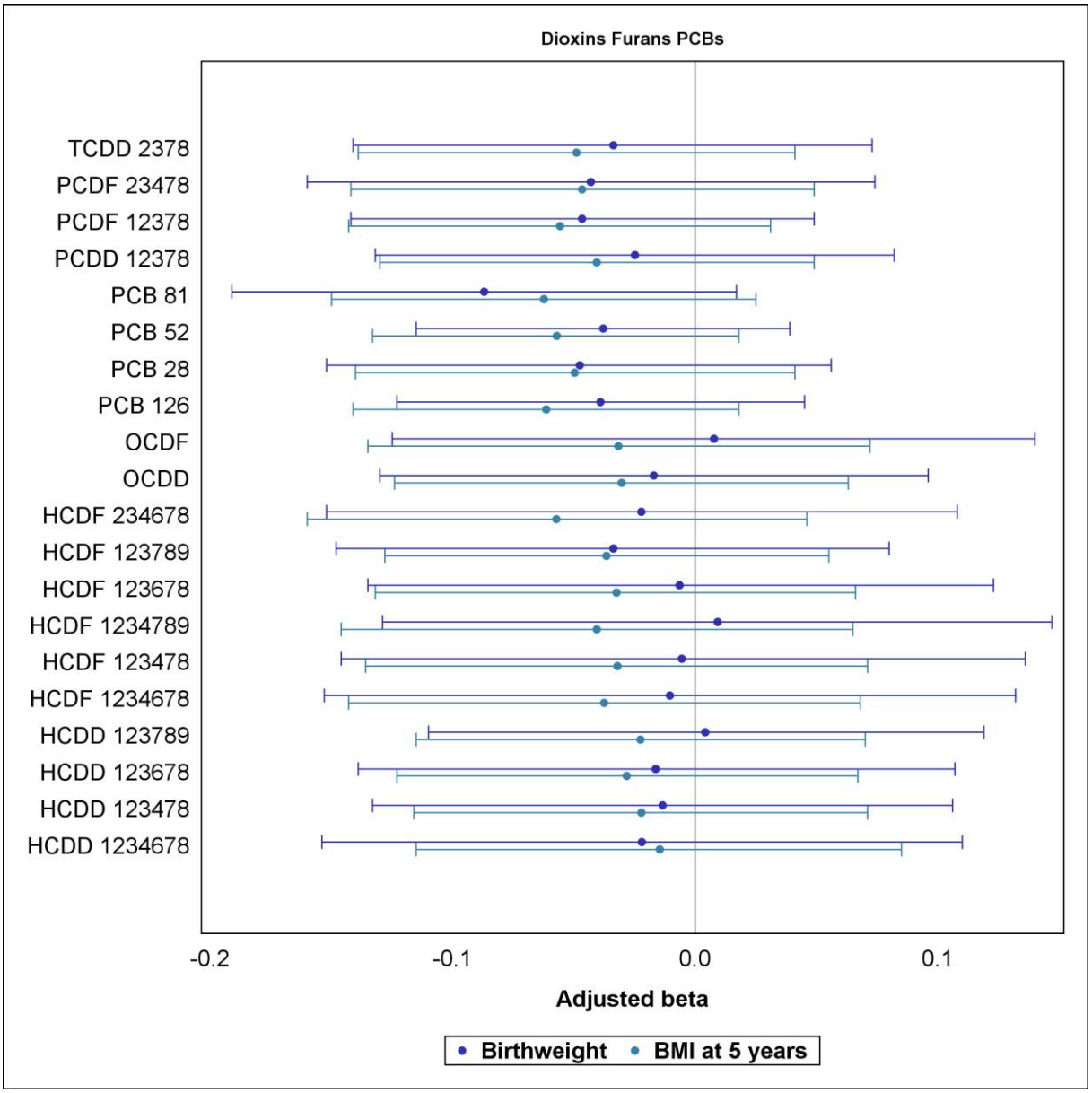
[a] energy intake

[b] breastfeeding duration

[c] chemicals significantly associated with at least birth weight z-score or predicted BMI

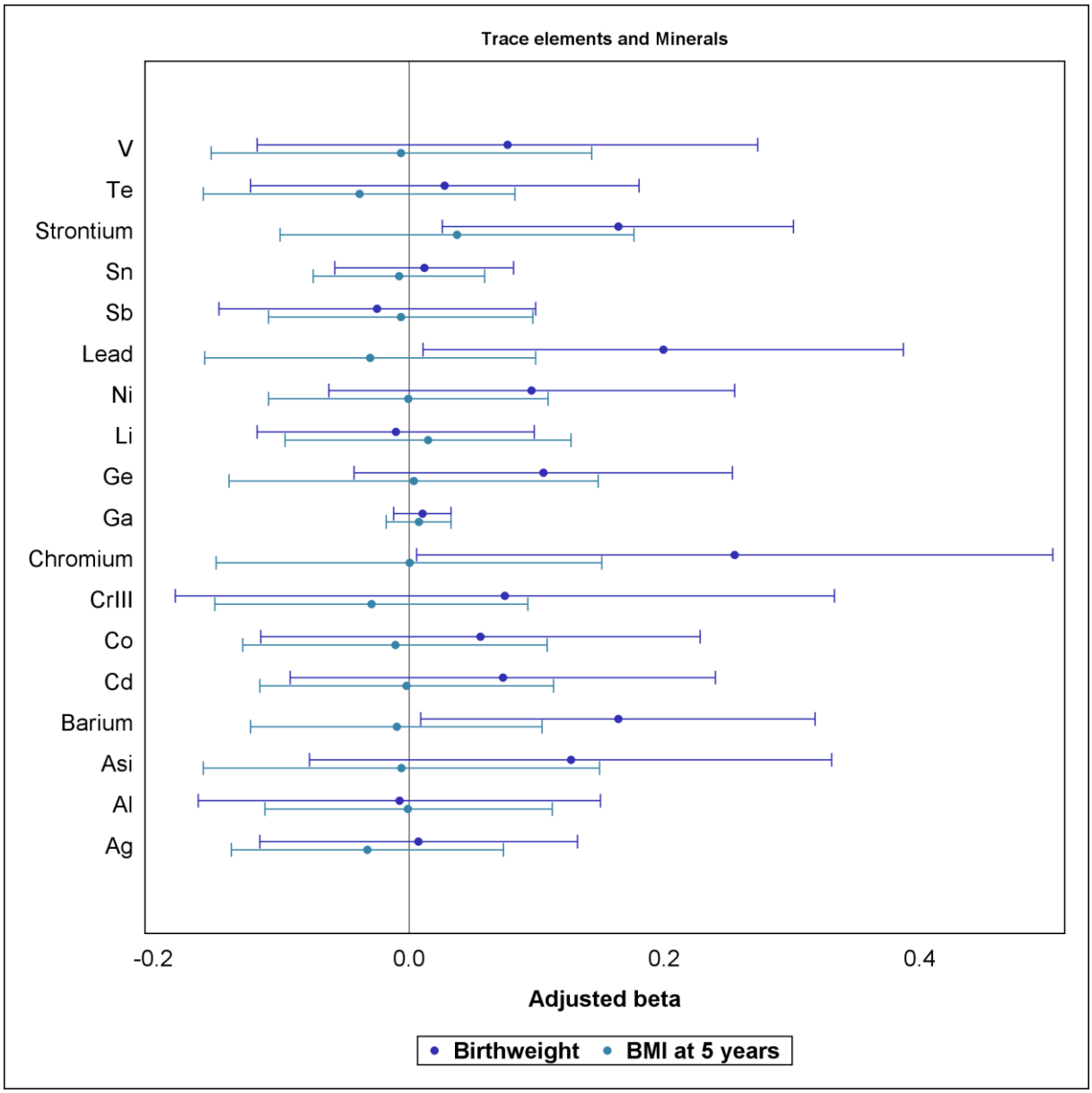
FDR: False discovery rate

Figure 21: Associations with birth weight z-score (n = 1434) or child's 5-y BMI (kg/m²) (n = 1364) and dietary exposure to dioxins furans or PCBs



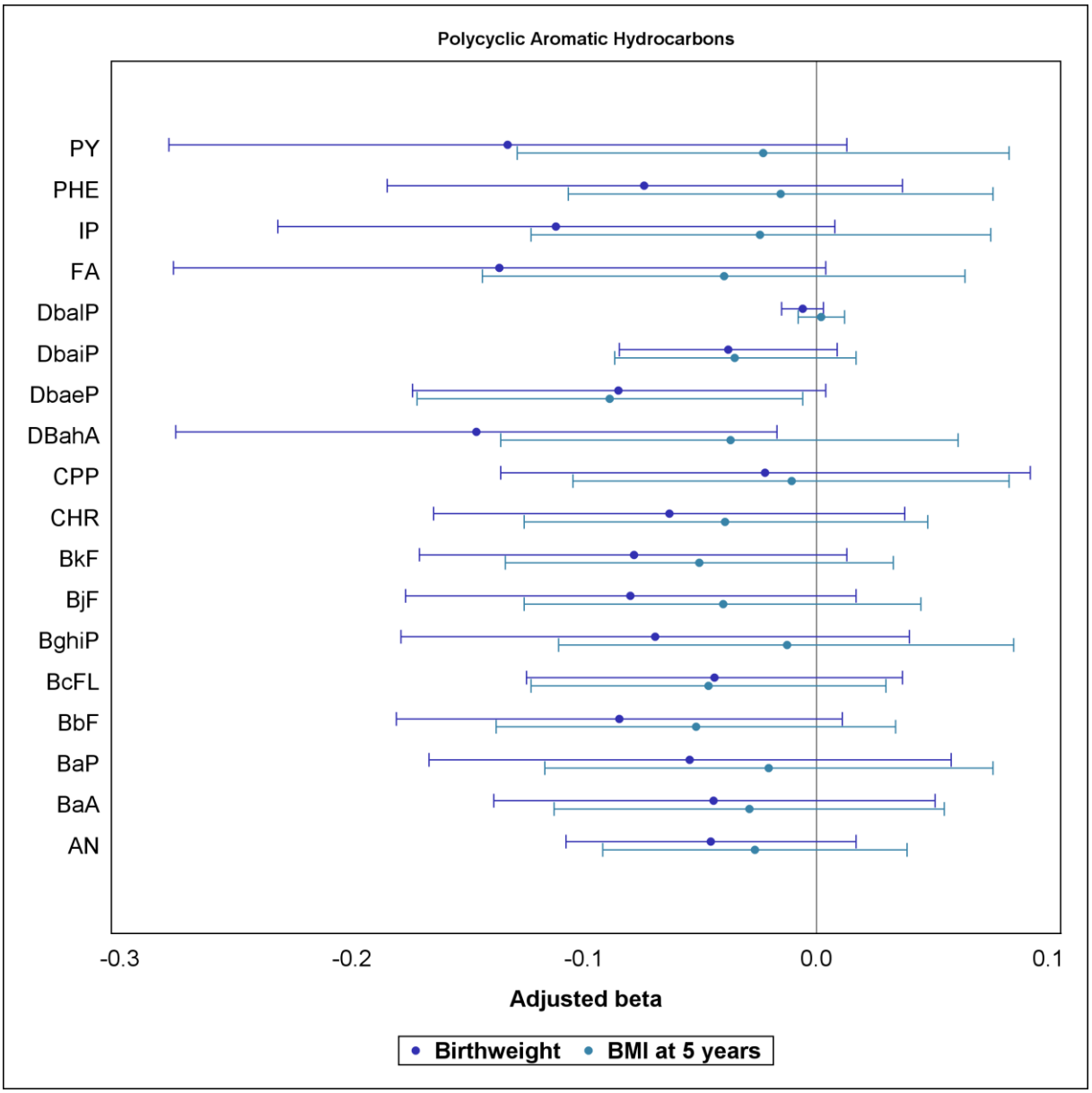
All the models adjusted for study centre, parity, maternal pre-pregnancy BMI, gestational weight gain, maternal height, maternal smoking during pregnancy, education level, paternal BMI, maternal age at delivery and child's sex. Birth weight additionally adjusted for energy intake and predicted BMI for breastfeeding duration

Figure 22: Associations with birth weight z-score (n = 1434) or child's 5-y BMI (kg/m²) (n = 1364) and dietary exposure to trace elements and minerals.



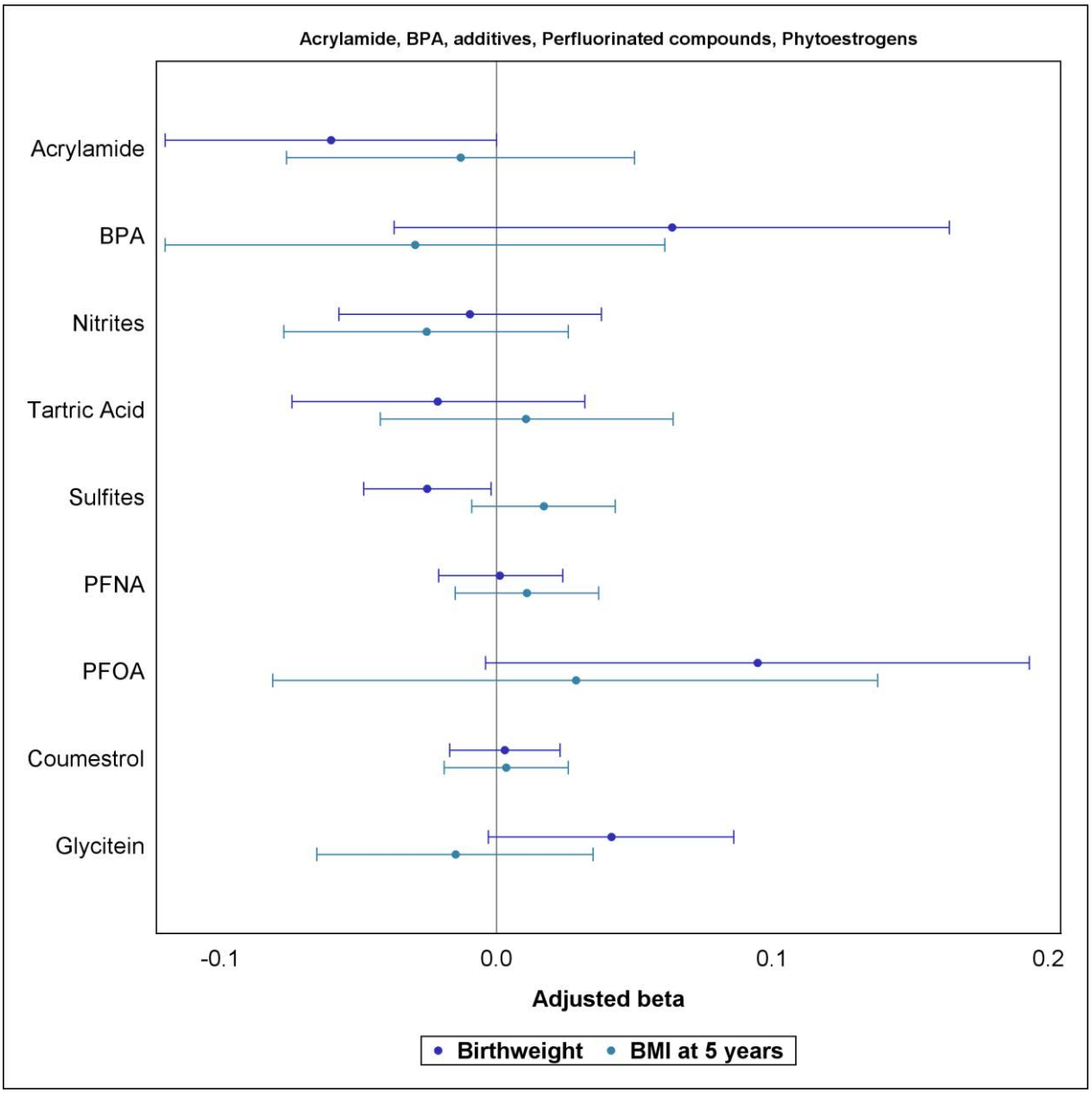
All the models adjusted for study centre, parity, maternal pre-pregnancy BMI, gestational weight gain, maternal height, maternal smoking during pregnancy, education level, paternal BMI, maternal age at delivery and child's sex. Birth weight additionally adjusted for energy intake and predicted BMI for breastfeeding duration

Figure 23: Associations with birth weight z-score (n = 1434) or child's 5-y BMI (kg/m²) (n = 1364) and dietary exposure to polycyclic aromatic hydrocarbons.



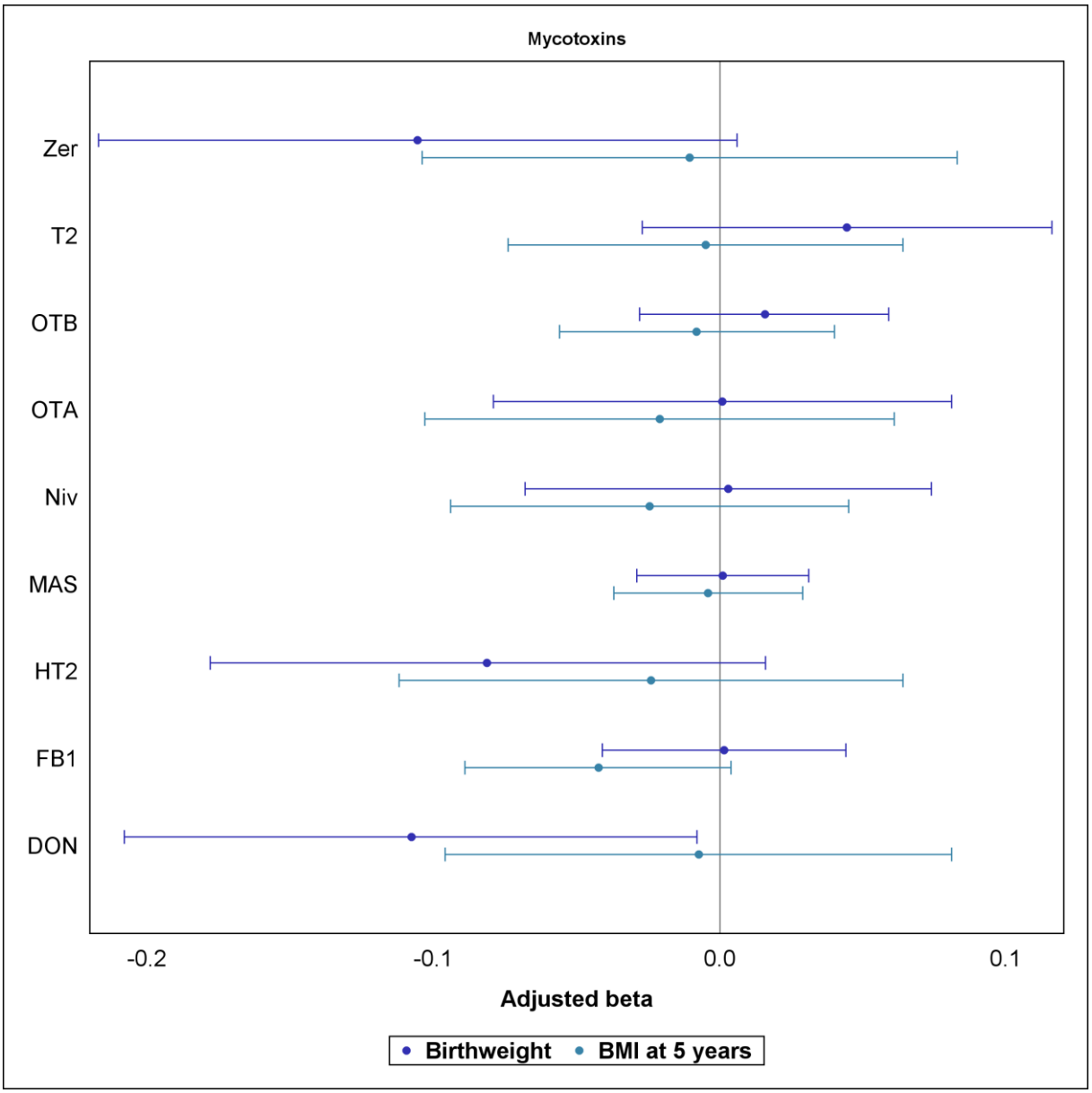
All the models adjusted for study centre, parity, maternal pre-pregnancy BMI, gestational weight gain, maternal height, maternal smoking during pregnancy, education level, paternal BMI, maternal age at delivery and child's sex. Birth weight additionally adjusted for energy intake and predicted BMI for breastfeeding duration

Figure 24: Associations with birth weight z-score (n = 1434) or child's 5-y BMI (kg/m²) (n = 1364) and dietary exposure to BPA, acrylamide, additives, perfluorinated compounds and phytoestrogens.



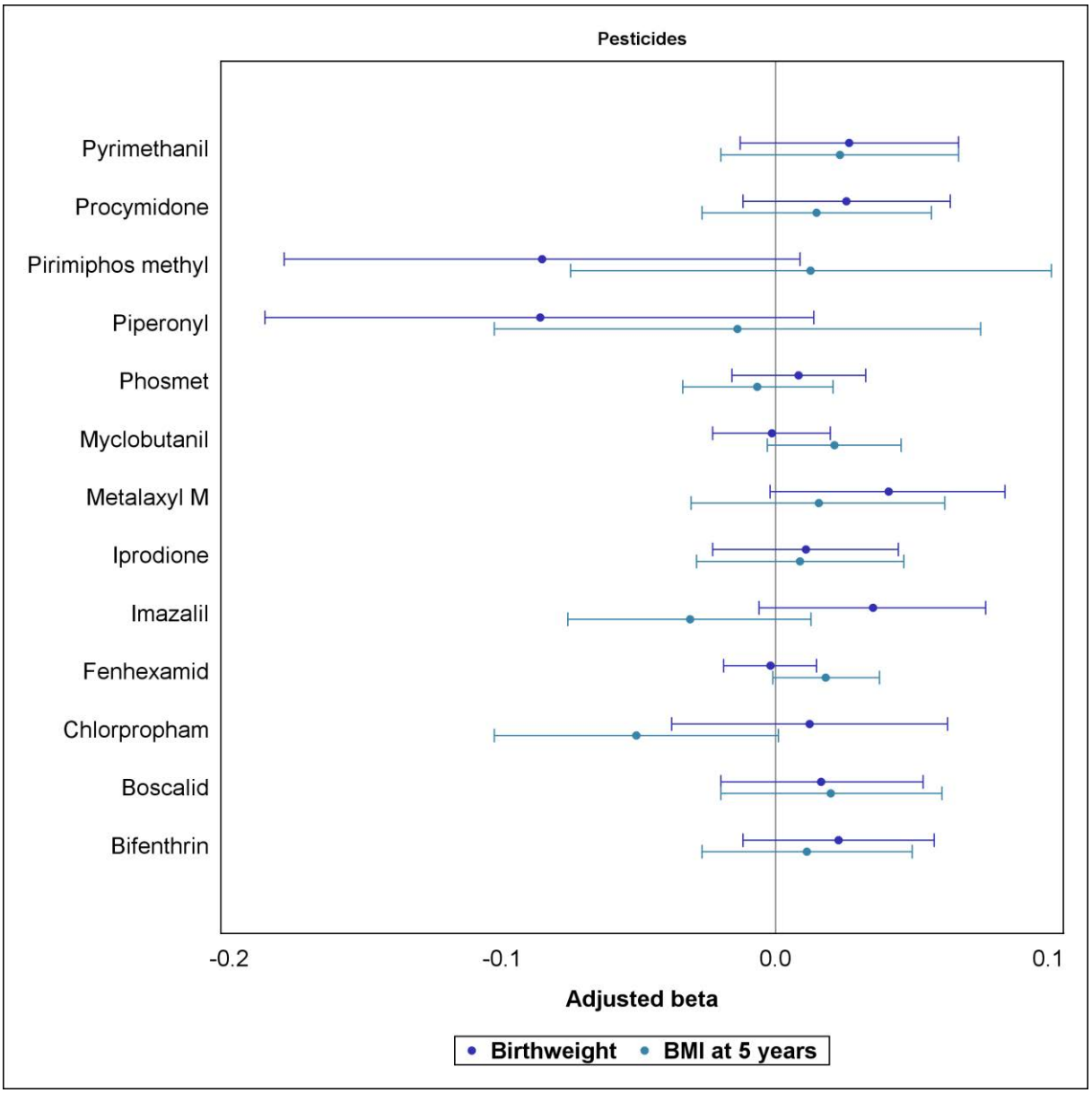
All the models adjusted for study centre, parity, maternal pre-pregnancy BMI, gestational weight gain, maternal height, maternal smoking during pregnancy, education level, paternal BMI, maternal age at delivery and child's sex. Birth weight additionally adjusted for energy intake and predicted BMI for breastfeeding duration

Figure 25: Associations with birth weight z-score (n = 1434) or child's 5-y BMI (kg/m²) (n = 1364) and dietary exposure to mycotoxins.



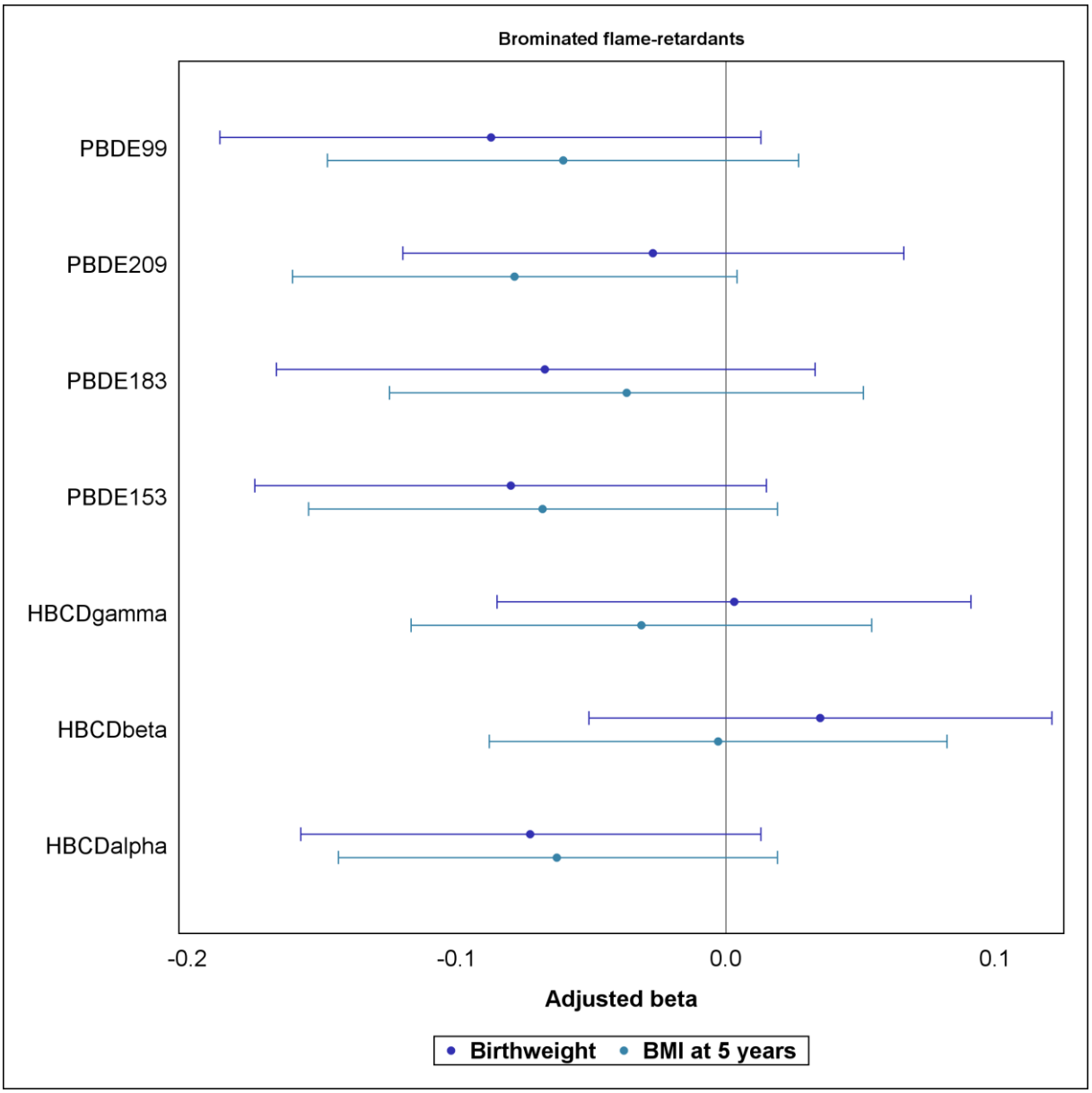
All the models adjusted for study centre, parity, maternal pre-pregnancy BMI, gestational weight gain, maternal height, maternal smoking during pregnancy, education level, paternal BMI, maternal age at delivery and child's sex. Birth weight additionally adjusted for energy intake and predicted BMI for breastfeeding duration

Figure 26: Associations with birth weight z-score (n = 1434) or child's 5-y BMI (kg/m²) (n = 1364) and dietary exposure to pesticides.



All the models adjusted for study centre, parity, maternal pre-pregnancy BMI, gestational weight gain, maternal height, maternal smoking during pregnancy, education level, paternal BMI, maternal age at delivery and child's sex. Birth weight additionally adjusted for energy intake and predicted BMI for breastfeeding duration

Figure 27: Associations with birth weight z-score (n = 1434) or child's 5-y BMI (kg/m²) (n = 1364) and dietary exposure to brominated flame retardants.



All the models adjusted for study centre, parity, maternal pre-pregnancy BMI, gestational weight gain, maternal height, maternal smoking during pregnancy, education level, paternal BMI, maternal age at delivery and child's sex. Birth weight additionally adjusted for energy intake and predicted BMI for breastfeeding duration

The sensitivity analysis using the measured BMI instead of the predicted BMI showed similar results. Although the negative significant association with DbaeP was not statistically significant anymore, the beta coefficient was very close. In addition, negative trends observed for two other chemicals became significant (one mycotoxin, the fumonisin B1 (FB1) β= -0.08 (-0.13 ; -0.02), and a pesticide: Chlorpropham β= -0.07 (-0.14 ; -0.01)). In the sensitivity analysis using predicted BMI on the

subsample of children with measured BMI at 5 years, the results were similar to the results using the total population.

5.4. Mixture of contaminant approach

Exposure to chemical mixtures, rather than to individual chemicals, reflect better the real-world scenarios. Moreover two or more environmental chemical exposures can have an additive (i.e., synergistic) or subadditive (i.e., antagonistic) association with the health outcome of interest. Another issue is the potential cumulative effect of chemicals. We are generally exposure to low levels of chemicals but the combination of low levels of chemicals might be associated with negative health outcomes (Braun et al., 2016).

Epidemiological studies are increasingly focusing on the impact on health of individual substance or of substances grouped by chemical similarity. The American National Institute of Environmental Health Sciences (NIEHS) has defined as priority the evaluations of the health risks due to the exposure to environmental mixtures (Carlin et al., 2013). Some studies examined several contaminants together (by adjusting one for the other) using statistical methods to select the exposure that can be examined together (Lenters et al., 2016). Many statistical approaches are proposed to identify the mixtures to which populations are more often exposed, their level of exposure, and their associated health effects, especially in more susceptible groups (Taylor et al., 2016). Using epidemiological approaches by combining quantified data on chemicals exposure during foetal and early postnatal periods and information on children growth and development can help us to better understand the potential impact of mixtures on health during these crucial periods.

5.4.1. *Methods*

Mixture identifications

Mixtures were identified, by ANSES partners, using Sparse Non-negative Matrix Under approximation (SNMU) (Gillis and Plemmons, 2013) on the 207 detected food chemicals (Traore et al., 2017). This

method allows to deal with large rates of null exposure. As expected, the Spearman correlations between identified mixtures and some food items were high. So, we tried several methods to address this issue.

The first method used was a hierarchical clustering method to identify chemicals that were highly correlated together with a 100 groups clustering. Among these 100 groups, 51 consist of one chemical each, 26 groups consist of 2 chemicals and 23 groups consist of at least 3 chemicals. Then, the SNMU method was applied to 100 chemicals (the 51 chemicals identified alone in a group and the first chemical identified in each group with at least 2 chemicals).

The second method was to apply the method described in the first part of the chapter with an a priori selection of 99 chemicals with correlation below 0.80 for each food item. The SNMU method was then applied to 99 selected chemicals.

For each method (base on 207, 100 or 99 food chemicals), eight mixtures were identified.

5.4.2. *Results*

5.4.2.1. Mixtures identification

Mixtures on 207 chemicals without preliminary selection

Eight mixtures were identified. Mixture 1 was composed predominantly of 11 metals, 6 PCBs, PAH pyrene and perfluorooctanoic acid. Mixture 2 included 7 PAHs, 1 BFRs, 8 PCBs, BPA and 2,3,7,8-TCDF. Mixture 3, 4 and 6 were mostly consisted of pesticides, and mixture 5 combined 3 perfluoroalkyl substances, Methylmercury and 8 BFRs. Mixture 7 was composed mainly of 12 mycotoxins, 2 pesticides and 5 PAHs. Mixture 8 consisted of 5 PFAS, 6 metals, and 5 phytoestrogens. The maximum correlation between these mixtures and food items ranged from 0.37 to 0.97 **(Table 23)**.

Mixtures on 99 food chemicals with preliminary selection based on correlation with food items

Mixture 1 was composed predominantly of 11 metals, 6 furans, 1 PAH pyrene and perfluorooctanoic acid. Mixture 2 included 7 PAHs, 6 BFRs, 3 PCBs, HT-2-toxin and BPA. Mixture 3 was mostly consisted

of 15 pesticides, and mixture 4 combined 5 pesticides and 7 mycotoxins. Mixture 5 was composed mainly of PCBs, 16 dioxins and furans, mixture 6 of 15 PAHs and mixture 7 of 12 metals and 2 PFAS and BPA Mixture 8 consisted of 3 mycotoxins, acrylamide, 3 PAHs and 6 pesticides. The maximum correlation between these mixtures and food items ranged from 0.36 to 0.68 **(Table 23)**.

Mixtures on 100 food chemicals with preliminary selection based hierarchical clustering

Mixture 1 was composed predominantly of 10 metals, 4 furans and dioxins, 3 PAH and perfluorooctanoic acid. Mixture 2 included 6 PCBs and furans, arsenic, methylmercury. Mixture 3 was mostly consisted of 15 pesticides, and mixture 4 combined 3 phytoestrogens, 5 PAHs and 3 mycotoxins. Mixture 5 was composed mainly of acrylamide, 5 mycotoxins and 8 PAHs, mixture 6 of 2 PFAS, 3 metals and mixture 7 of 4 phytoestrogens, 5 pesticides and BPA. Mixture 8 consisted of 6 PAHs, acrylamide. The maximum correlation between these mixtures and food items ranged from 0.37 to 0.90 **(Table 23**).

Table 23: Mixtures identified and maximal correlation with food items

	Maximal correlation* with food items	**Food item**
Mixtures on 207 chemicals without preliminary selection		
1. Metals, polycyclic aromatic hydrocarbons (PAHs) and furans	0.37	Poultry
2. PCBs, PAHs, BPA, brominated flame retardants (BFR)	0.76	Fresh/frozen fish
3. Some pesticides	0.96	Apple
4. Other pesticides	0.89	Grapes
5. PFAS, methyl mercury and BFR	0.85	Fresh/frozen fish
6. Other pesticides	0.86	Strawberry
7. Mycotoxins	0.93	Wholemeal bread
8. PFAS (other) and metals	0.78	Water
Mixtures on 99 selected chemicals		
1. Metals, furans	0.36	Poultry
2. BFR, PAHs, PCB 28	0.48	Fresh/frozen fish
3. Pesticides	0.63	Raw vegetables
4. Mycotoxins and pesticides	0.46	Pastas
5. PCBs, dioxins and furans	0.44	Fresh/frozen fish
6. PAHs	0.40	Shellfish
7. PFOA, metals and BPA	0.56	Water
8. Mycotoxins and acrylamide	0.68	Salty snacks

Table 23 continues: Mixtures identified and maximal correlation with food items

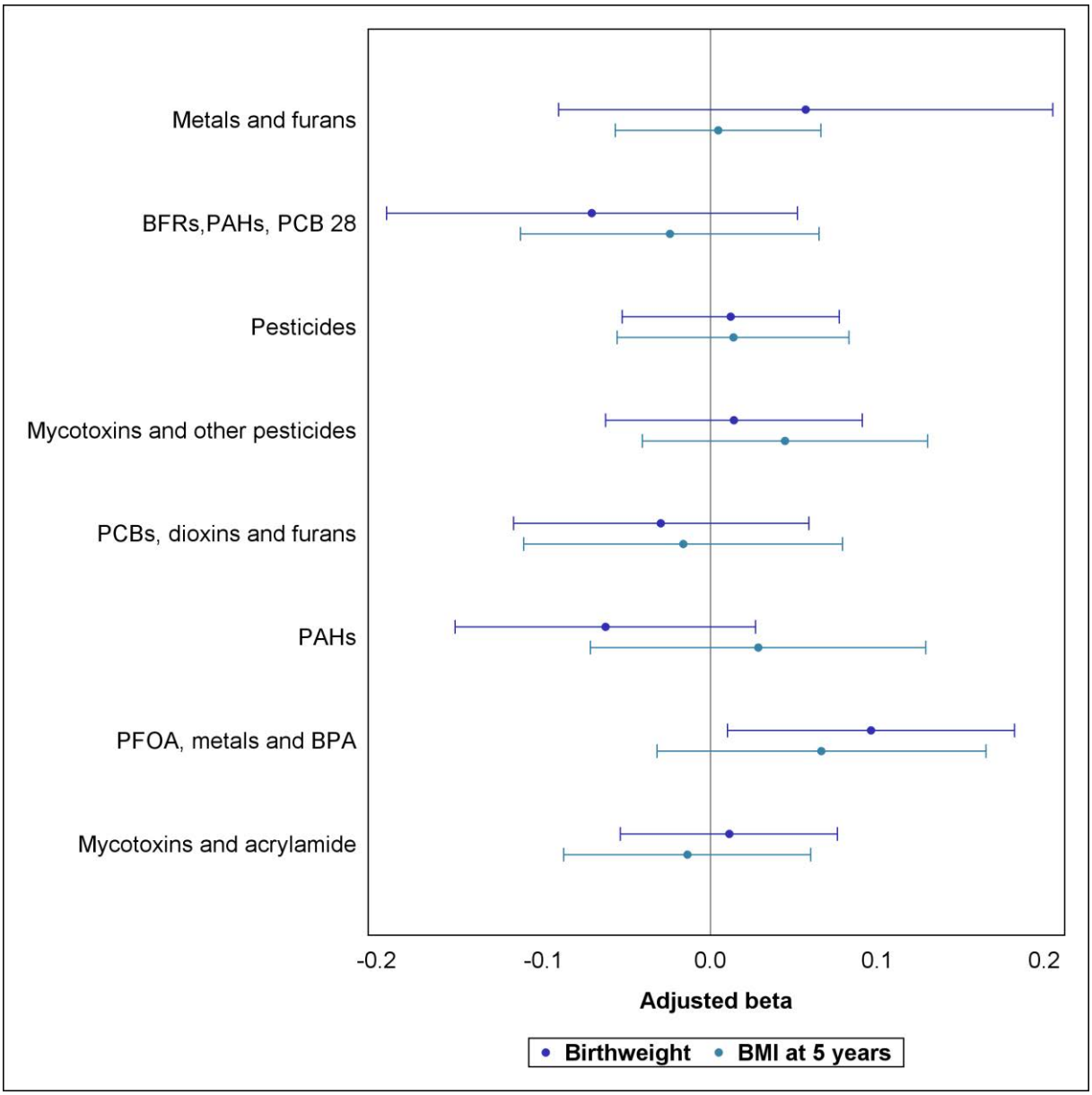
	Maximal correlation* with food items	Food item
Mixtures on 100 food chemicals with preliminary selection based hierarchical clustering		
1. Metals	0.37	Poultry
2. PCBs, Methylmercury, Arsenic	0.90	Fresh/frozen fish
3. Pesticides	0.60	Salad
4. Phytoestrogens	0.82	Semi skimmed milk
5. Acrylamide, mycotoxin, PAHs	0.74	Salty snacks
6. PFAS, metals	0.77	Water
7. Other phytoestrogens, permethrin, BPA	0.85	Green beans
8. PAHs and acrylamide	0.80	Coffee

5.4.2.2. Association with growth outcomes

For the analysis of the association between outcomes and mixtures, we have chosen to present as main analyses mixtures based on the 99 food chemicals previously selected from correlation with food items. The results for mixtures identified without preliminary selection of food chemical or mixtures identified with a preliminary selection of food chemical by hierarchical clustering are presented in complementary analysis.

For prenatal growth, the mixture composed by PFOA, metals and BPA (mixture 7) was positively associated with birth weight z-score, but not the other mixtures identified **(Figure 28)**. For postnatal growth, none of the mixtures was associated with predicted BMI at 5 years **(Figure 28)**.

Figure 28: Results from linear regression analysis between mixtures of 99 chemicals and birth weight z-score (n = 1434) and predicted BMI at 5 years b (n = 1364)



All the models adjusted for study centre, parity, maternal pre-pregnancy BMI, gestational weight gain, maternal height, maternal smoking during pregnancy, education level, paternal BMI, maternal age at delivery and child's sex
Birth weight additionally adjusted for energy intake and predicted BMI for breastfeeding duration

The analysis using either all chemicals detected or the chemicals selected with hierarchical showed the same results: the mixture composed mainly by perfluoroalkyl substances and metals was positively associated to birth weight z-score and no association was found between identified mixtures and predicted BMI at 5 years **(Table 24).**

Table 24: Supplementary analyses. Association between mixtures based on 207 or 100 chemicals and birth weight z-score (n = 1434) or predicted BMI at 5 years (n = 1364)

	Birth weight z-score [a]			Predicted BMI 5y [b]		
	beta	**95% CI**	**p**	**beta**	**95% CI**	**p**
Mixtures without preliminary selection, on 207 chemicals						
1. Metals, polycyclic aromatic hydrocarbons (PAHs) and furans	0 .058	(-0.071 ; 0.187)	0.38	0.001	(-0.061 ; 0.064)	0.97
2. PCBs, PAHs, BPA, brominated flame retardants (BFR)	-0.008	(-0.097 ; 0.081)	0.86	-0.020	(-0.098 ; 0.058)	0.61
3. Some pesticides	0.049	(-0.007 ; 0.105)	0.09	0.007	(-0.057 ; 0.071)	0.83
4. Other pesticides	0.001	(-0.060 ; 0.061)	0.98	-0.001	(-0.068 ; 0.067)	0.99
5. Perfluoalkyl acids (PFAS), methyl mercury and BFR	-0.029	(-0.096 ; 0.038)	0.39	-0.001	(-0.080 ; 0.078)	0.98
6. Other pesticides	-0.025	(-0.083 ; 0.034)	0.41	0.009	(-0.057 ; 0.076)	0.78
7. Mycotoxins	0.021	(-0.039 ; 0.080)	0.50	0.036	(-0.032 ; 0.104)	0.30
8. PFAS (other) and metals	**0.085**	**(0.020 ; 0.150)**	**0.01**	0.051	(-0.019 ; 0.121)	0.15
Mixtures with hierarchical clustering first, on 100 chemicals						
1. Metals	0.012	(-0.131 ; 0.155)	0.87	0.002	(-0.062 ; 0.065)	0.96
2. PCBs, Methylmercury, Arsenic	-0.014	(-0.061 ; 0.034)	0.57	-0.011	(-0.065 ; 0.044)	0.71
3. Pesticides	0 .013	(-0.041 ; 0.066)	0.64	0.013	(-0.045 ; 0.071)	0.65
4. Phytoestrogens	0 .037	(-0.011 ; 0.085)	0.13	-0.036	(-0.090 ; 0.019)	0.20
5. Acrylamide, mycotoxin, PAHs	-0.038	(-0.110 ; 0.034)	0.31	0.004	(-0.070 ; 0.079)	0.91
6. PFAS, metals	**0.074**	**(0.011 ; 0.137)**	**0.02**	0.050	(-0.019 ; 0.119)	0.15
7. Other phytoestrogens, permethrin, BPA	0.059	(-0.013 ; 0.130)	0.11	0.010	(-0.067 ; 0.087)	0.80
8. PAHs and acrylamide	-0.054	(-0.116 ; 0.008)	0.09	-0.009	(-0.081 ; 0.064)	0.81

All the models adjusted for study centre, parity, maternal pre-pregnancy BMI, gestational weight gain, maternal height, maternal smoking during pregnancy, education level, paternal BMI, maternal age at delivery and child's sex

[a] energy intake

[b] breastfeeding duration

5.5. Discussion

In the chemical-by-chemical analyses, dietary intake of acrylamide, sulfites, DBahA and DON was negatively associated with birth weight. Maternal dietary intake of barium, chromium VI, lead and strontium was positively associated with birth weight. Maternal dietary intake of DbaeP was negatively associated with the child's BMI at 5 years. These associations were no more statistically significant after taking to account multiple testing. When applying the mixture approach, one mixture of contaminants mainly composed by PFAS and metals was positively associated with birth weight. No association was observed with the BMI at 5 years.

Exposure assessment via TDS

The importance of TDS for the population exposure assessment to food contaminants is well established and its use of TDSs in epidemiological studies is very appealing. Indeed, the chemicals are measured in the food that is prepared as consumed and food sampling is focus on representative food commodities for the diet of the general population. Moreover, in the setting of large population based cohort studies, using biomarkers to assess the exposure to certain chemicals can be expensive, have practical drawbacks such as the difficulty in biological sample from infants. In addition, one measure might not be representative of usual exposure for short half-life chemicals (e.g. bisphenol A, phthalates or pyrethroid pesticides) (Perrier et al., 2016). Furthermore, when using the biomarkers approach, the measured exposure is an integrated measure of exposure through different routes of exposure (e.g. air, dust, water, food…) and is not specific to dietary exposure (Nieuwenhuijsen, 2015), a source that could be more easily targeted for recommendations and policies.

We used a selection criterion to choose the food chemicals that could be studied in relation with health outcomes. We analysed the correlations between food chemicals intake and food items, and a cut-off was set to 0.80. Indeed, when the correlation between the food item and the food chemical intake is too high, it is not possible to disentangle the effect of one from the other.

The use of TDS studies could be of interest in epidemiology, but some precaution should be taken when handing these data. We here tried to present some recommendations to apply TDS in relation to health outcomes.

Recommendation for the use of TDS combined with FFQ in exposure assessment for epidemiology studies

- Use the data only when a chemical has been tested/detected in several food items and therefore when the correlation between the food items and the chemical are not too high (e.g. below 0.8);
- Define which kind of analysis to perform, a priori based on previous evidence from literature (on specific chemicals) or exploratory analysis;
- Think about correction for multiple comparisons.

Individual contaminant approach

In our analysis, associations were observed with foetal growth (i.e. birth weight z-score) rather than with 5-y BMI. The associations with acrylamide were previously described in chapter 4. By including more contaminants we observed that maternal dietary exposure to DBahA, DON and sulphites were negatively associated with birth weight z-score. Some studies have reported an association between exposure to airborne PAHs and a decreased birth weight (Choi et al., 2008b; Jedrychowski et al., 2012) but another one reported no association in a study of more than 1500 women (Al-Saleh et al., 2013). To our knowledge, the relationship between exposure to sulphites or deoxynivalenol (DON) and birth weight has never been investigated in humans and would necessitate replication studies. In addition, maternal dietary exposure to four metals was associated with increase in birth weight (i.e. barium, chromium VI, lead, strontium). These results are not in line with previous literature in this field using mainly biomarkers. Lead exposure has been studied extensively in relation with birth outcomes. Most of the studies reported a negative association (Nishioka et al., 2014; Perkins et al., 2014; Taylor et al.,

2015; Xie et al., 2013; Zhang et al., 2015) whereas some others reported no association (Al-Saleh et al., 2014; Hu et al., 2015; Mirghani, 2010; Rahman et al., 2012; Sun et al., 2014). Barium and chromium VI have been less investigated. A Spanish study has found no significant relationship between chromium and barium analysed in 54 paired blood samples of cord blood and maternal blood (collected after delivery) and birth weight (Bermudez et al., 2015). This inconsistency compared to our results might be due our assessment of contamination through food intake. The correlation for each one of these chemicals with their main food contributors was 0.42 between lead and orange juice, 0.41 between barium and citrus fruits, 0.41 between chromium IV and water and finally 0.76 between strontium and water. When using the same methods as for acrylamide or phosalone, the models using the main food contributors' intake were positive with lower magnitude than those using the estimated food chemical intake and not significant. The residual method approach showed for these chemicals an association of the same magnitude than the main analysis but not significant either. Chance finding cannot be excluded either. In fact, these positive associations were not significant after applying the false discovery rate correction to take into account multiple testing.

Concerning postnatal growth, the DbaeP (a PAH) was the only one chemical associated with 5-y BMI and the association was negative. A recent study showed a negative association with height gain from birth to nine years (β= -1.07 (-2.10 , -0.05)), after high prenatal exposure to airborne PAHs (>34.7ng/m^3) when compared to lower exposure levels ≤9.2 ng/m^3 (Jedrychowski et al., 2015). However, in EDEN, we were not able to highlight significant association between prenatal exposure to DbaeP and predicted height at 5 years (β=-0.10 (-0.30 , 0.09)).

Testing several null hypotheses in a single study results in an increased risk of detecting a significant finding just by chance (Streiner, 2015). Whether or not to correct for multiple comparisons is an issue that under discussion. Correcting for multiple comparisons could result to potentially interesting observations being discarded as chance findings (Streiner, 2015). In our analysis, all the results were not significant after taking into account the correction for multiple comparisons using the

FDR approach. Here, we can argue that some associations, as the association with acrylamide, were already observed previously in the literature. To confirm our exploratory analysis, replication is needed in other studies.

Mixture approach

The use of the mixture approach enable to reduce the numbers of tests performed while enabling to study large number of chemical. Despite this strength, it is still not easy to disentangle the effect of the chemical of the effect of the food as strong correlation persisted. We tried different selections of chemicals before applying the mixture identification procedure, but the results were quite similar.

The results of mixtures analysis in relation to growth parameters are comparable to the analysis using the individual contaminant approach. First, we observed that maternal dietary exposure of 4 metals 4 metals (barium, chromium, lead and strontium) were positively associated with birth weight z-score. When we applied the selection criteria based on correlation with each food item below 0.80, only two PFAS were selected: PFOA and PFOS. A positive trend could be seen with PFOA with birth weight z-score (β=0.09, p=0.06) but this result was not significant after correcting for multiple testing (q (FDR)= 0.38). Moreover, no significant association was found between food chemical and predicted BMI at 5 years using either the individual contaminant approach or the mixture approach. As in the previous analysis, this association may be explained by food habits associated with these specific exposures as strong correlation were found between some food items and some mixtures. The mixture "PFAS and metals" had a correlation of 0.56 with water. When we use the water consumption as the exposure variable no association was observed (β=0.04, p=0.11). The different methods to select chemicals to use for the characterization of mixture showed similar results.

Our study is among the first to examine the effect of mixtures of contaminants on growth. Nevertheless, the mixture approach is essential for better assessment of real-life exposure, where we are exposed, at the same time, to many different chemicals and groups of chemicals, potentially interacting together. Recently, a study showed significant mixture effects of androgen receptor (AR)

antagonism (e.g. parabens, bisphenol A, pesticides, benzo(a)pyrene) when chemicals were combined at concentrations that individually not inducing observable AR antagonistic effects (Orton et al., 2014). Due to the wide range of contaminants present in food, studying the effect of these contaminants on health is not easy. Indeed, it still remains a challenge to know which substances must be studied together. For example, EFSA proposed cumulative assessment groups based on grouping pesticides by their organ toxicity or specific effects (EFSA, 2013). However, those groups do not account for the probability to be co-exposed to the grouping pesticides.

5.6. Conclusion

This analysis intends to show that using exposure assessment based on coupling the FFQ with the TDS in epidemiological analysis presents an important limitation that is the possible strong correlation between chemical intake assessment and some food item. We advise, first, to select the chemicals that are not collinear with the main food contributor to their exposure and, second, for these selected chemicals, to interpret carefully the results of associations with health outcomes. Indeed, the associations may be highly driven by the main food contributor rather than by the chemical per se. On the other hand, one of the main advantages for the use of TDS in exposure assessment are the number of available chemicals and that the source of exposure could be easily targeted for recommendation and policies.

6. DISCUSSION

6.1. Summary of main results

In a context of a worldwide increase in childhood obesity, the general aim of this thesis was to examine the associations between maternal diet a source of beneficial nutrients and toxic food chemicals and growth among children.

In the first part (chapter 3), we described the diet of French pregnant women and examined the links between maternal diet quality and prenatal growth, using birth weight, birth length and birth weight-for-gestational age as markers of prenatal growth. Using data from the ELFE study, we showed that pregnant women had a good compliance with dietary guidelines in general. The guidelines with the highest compliance rates were “origin of added fats”, “water” and “meat, fish and eggs”. The guidelines with the lowest compliance rates were “fruits and vegetable” and “use of whole-grain cereals”. Higher *Diet Quality* score was found among older women, non-smoking during pregnancy, with higher education level and higher household income. Higher compliance to the dietary guidelines was also positively associated with birth higher weight and with lower risk of having a SGA baby.

Later, we explored the influence of prenatal exposure to food chemicals on child’s growth (chapters 4 and 5). First, we focused in a particular food chemical, acrylamide that is produced during cooking process at high temperature (chapter 4). In the French EDEN study, we highlighted that high prenatal exposure to dietary acrylamide was associated with lower birth weight and higher risk of being SGA. These results were consistent with those previously highlighted in the Norwegian MoBa cohort. In both cohorts, we also examined the association between prenatal exposure to acrylamide and postnatal growth. In MoBa, we found that prenatal exposure to acrylamide was associated with an increased risk of overweight or obesity in children up to 5 years and higher weight growth velocity in early childhood. However, we couldn’t replicate these results in the EDEN cohort probably due to a lack of power.

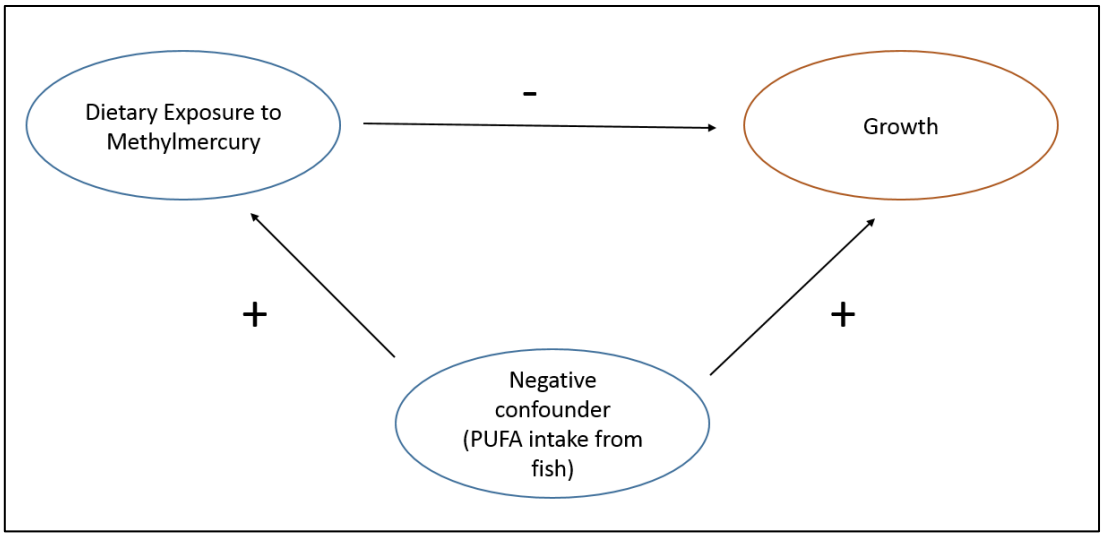
Secondly, we decided to enlarge our analyses to food chemicals available in TDS2 (chapter 5). In a first step, we selected food chemicals that could be analysed in relation to health outcomes. Then,

we analysed their individual association with birth weight and 5-y BMI in the EDEN cohort. We found that birth weight was negatively associated with maternal dietary exposure to four food chemicals (acrylamide, sulphites, DBahA, DON) and positively with maternal dietary exposure to four metals (barium, chromium VI, lead, strontium). The 5-y BMI was associated negatively with DbaeP but not associated with the other food chemicals. However, none of these associations remained statistically significant after correction for multiple comparisons. In a last part, we used a mixture of chemicals approach to characterize global exposure to food chemicals. Eight chemical mixtures were identified. Only the mixture mainly composed by PFAS and metals was positively associated with birth weight and none of the mixtures was associated with 5-y BMI.

6.2. Beneficial nutrients vs environmental contaminants from maternal diet

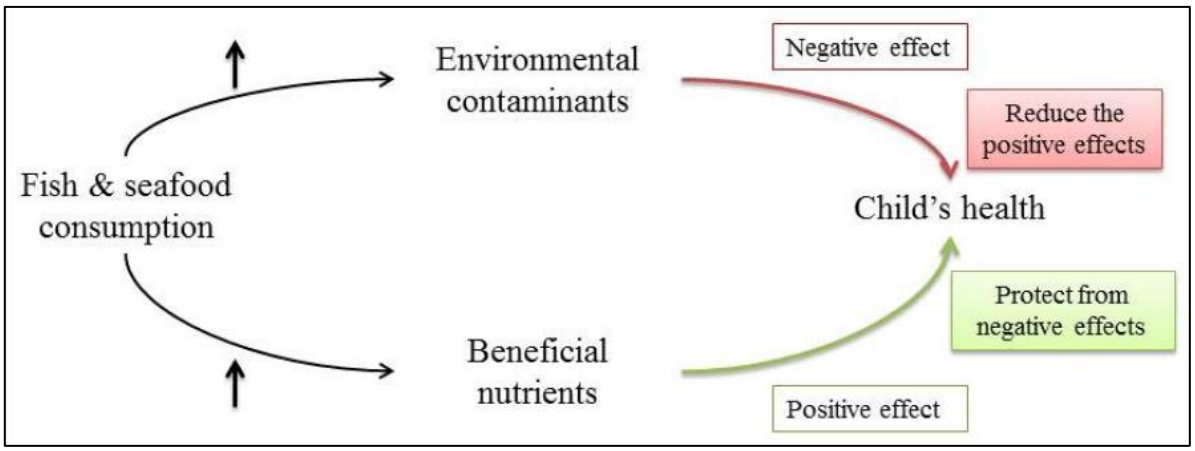
Foods consumed during pregnancy can carry of both beneficial nutrients and harmful compounds for the foetus. Seafood (fish and shellfish) consumption during pregnancy is a famous example for this benefit-risk balance in food consumption, as it simultaneously exposes the foetus to toxic chemicals (e.g. PCBs, PFAS, arsenic) and beneficial nutrients (e.g. polyunsaturated fatty acids, vitamins, minerals) (Stern and Korn, 2011; Strom et al., 2011). Often, toxicants and nutrients have opposite effects on the same outcome. Therefore, the potential effect of methylmercury on growth is confounded by the effect of simultaneous PUFAs benefits (Bernard et al., 2017). And the opposite, is also true: the beneficial effects of essential nutrients can be confounded by the competing adverse effects of the toxicants (Strom et al., 2011). This type of confounding where two variables are affecting the outcome in opposite directions has been described as negative confounding (**Figure 29)** (Choi et al., 2008a).

Figure 29: Negative confounding, figure adapted from (Choi et al., 2008a)



Under the effect of negative confounding, the potential negative association between environmental contaminants in seafood and child's health is under-estimated, because there is an additional negative effect that is masked by the positive effect of the PUFAs in seafood. A similar under-estimation of the beneficial effects of PUFAs occurs due to the competing negative effects with environmental contaminants in seafood **(Figure 30)**.

Figure 30: Competing effects of beneficial nutrients and environmental toxicants on child's health from (Papadopoulou, 2013)



In this thesis, when we identified mixtures, the first type of mixture without any selection criteria on chemicals, the mixture found were linked to only one food item or almost. For example, the second mixture comprised mainly PCBs, inorganic mercury and PAHs and was correlated with fresh/frozen fish at 0.76. For this reason, it was decided to exclude contaminants that were too related to a particular

food item. In this context, our results describing similar associations between chemical exposure and health outcome in different populations, where the exposure to the contaminant is due to different food vectors, as for the acrylamide in EDEN and MoBa, are of great interest.

6.3. Strengths and limitation

6.3.1. *Dietary assessment*

A major limitation of assessing exposure to contaminants using a food frequency questionnaire is the chance of inaccurate estimation. In fact, the use of FFQ may potentially induce errors related to: representiveness of the total diet in the listed foods, accuracy of frequency intervals as well as participants' capacity to recall and report frequencies, appropriateness of the portion sizes. FFQs are known to overestimate the overall contribution, especially when the number of items is important (Willett, 2013). However, validation studies showed that it is possible to classify women in relation to each other (Deschamps et al., 2009). Within the French ELFE study, a validation study was performed comparing the FFQ to three 24-hour recall (one per month during the last three months of pregnancy) on an *ad hoc* sample of 62 pregnant women. For major food groups most women were classified in the same quintile or adjacent quintile by both methods (92.9% for meat to 100% for milk). The energy-adjusted correlation between FFQ and the 24-hour recalls ranged from 0.12 (cake pastries) to 0.65 (milk) for foods, and from 0.21 (monounsaturated fatty acid) to 0.59 (Fibre) for nutrients, which is accepted as an overall good agreement. In the Norwegian MoBa study, the FFQ was also validated against food diaries and measured biomarkers of nutrients or food groups. The energy-adjusted correlation between FFQ and the food diary ranged from 0.21 (meat) to 0.80 (coffee) for foods, and from 0.19 (retinol) to 0.54 (fibre) for nutrients, which is accepted as an overall good agreement. Urinary biomarkers and serum/plasma concentration biomarkers confirmed that the MoBa FFQ was able to distinguish between high and low intake of nutrients and foods (Brantsaeter et al., 2008a).

In this study, the estimated exposures to contaminants are not to be used as accurate measurements of maternal exposure, but rather as relative exposure metrics, in order to classify high and low exposed populations. In addition, the assessment of the diet using FFQs bears the risk that either conscious or unconscious misreporting errors occur. The risk of over and underestimation is stronger for certain foods and in certain population groups. It has been shown that the intake of foods which are perceived as "unhealthy", tends to be under-reported in women with higher BMI (Olafsdottir et al., 2006). This was not formally evaluated in the French ELFE study but after exclusion of women with extreme energy intakes, in sensitivity analyses, the results were similar. Moreover, by the time the women completed the FFQ, they did not know the planned exposure-health associations to be explored, thus, a random measurement error is more probable for the dietary assessment. Random measurement error associated with intake estimates from FFQ tend to lead to underestimations of effect estimates (Rothman et al., 2008).

FFQ was completed at the maternity ward and covered the last three months of pregnancy for EDEN and ELFE, and the second trimester for MoBa, therefore not representative of the overall pregnancy consumption in both studies. In EDEN, a FFQ relative to the diet of the year pregnancy was available and the identified chemical mixtures were similar.

6.3.2. *Exposure assessment*

One limitation in the use of TDS studies in exposure assessment is the fact that the data are impacted by Berckson error. This type of measurement error is due to the use of the same approximate exposure for many subjects as a "proxy" to the true exposure that varies randomly between this proxies, with a mean equal to it (Nieuwenhuijsen 2015). It results in limited or no bias but reduces the power of a study, making it more likely that real associations are not detected (Armstrong 1998). This error impacts both the measured concentrations of nutrients or toxicants in the food items, as they come either from food composition databases or contamination databases. On the other hand the use of biomarkers has important limitation, when assaying non-persistent chemicals: short half-life for some

chemicals and high within-subject variability. Therefore the use of biomarkers is likely to imperfectly reflect the average exposure throughout long time periods. In most of the studies using biomarkers only a single sample is available which raise the question of reliability of the measure (Perrier et al., 2016; Pollack et al., 2016).

The use of TDSs as a food contamination database is less expensive compared to the use of biomarkers especially in large cohort. Due to the large number of chemicals tested, the issue of multiple comparisons rises. To deal with this issue, first, we used the false discovery rate correction and then, identification of mixtures.

The other main limitation is the difficulty to disentangle the effect from the food and the one from the chemical. Even if we used a selection criteria to try to address this issue, some chemicals were still strongly related to diet.

Finally, the chance of a misclassification (bias of the exposure), related to the dietary recall through the self-administered FFQ or the representativeness of the food contamination database, cannot be excluded. However, the classification bias is unlikely to be differential and, although the loss of power is compensated by the large sample size in MoBa study, the size of the associations is likely underestimated (Pearce et al., 2007).

6.3.3. *Generalizability of results*

Due to the design of mother-child cohorts used in this work, we have to acknowledge a selection bias: the study samples are not representative of the general population of each country, especially in terms of socioeconomic status.

Despite the high number of participants, the MoBa sample is not truly representative of all pregnant Norwegian women since only 40.6% of those pregnant women who are invited to this study agreed to participate. A comparison with non-participating pregnant Norwegian women showed that participating women comprise of less young mothers (<25 years) and less women living alone as well

as less women with two or more previous pregnancies (Nilsen et al., 2009). Nevertheless, a study of potential self-selection bias showed that despite a different prevalence of exposures and outcomes compared to the total population of pregnant women, no statistically relevant differences regarding eight selected exposure-outcome associations were found (Nilsen et al., 2009).

In EDEN, the participation rate was 42% and when we compared women in our analyses to women from the representative 2003 French National Perinatal Survey (NPS), the mother-child pairs included were quite similar for obstetrical data such as maternal age at delivery, baby's weight and length. However, the EDEN participants were more educated (55.8% had a higher education versus 42.6% in the NPS), more frequently from a European nationality (97.0% of them versus 90.9% in the NPS) and fewer were active smokers during pregnancy (e.g. 15.9% versus 20.8% in the NPS during the third trimester) (Blondel et al., 2012).

We do not expect this to create a bias in the associations between exposure and outcomes. The concordance of our results, for acrylamide and prenatal growth, with those found in other epidemiological and animal studies was the most convincing argument that our results are not biased or chance findings. Replicating the analysis of chemical exposure and growth in ELFE, a national representative cohort, could help to limit this bias and therefore have some estimates that integer wider levels of SES levels participants.

6.3.4. *Methodological considerations*

6.3.4.1. Adjustment variables

We choose our set of adjustment variable using prior knowledge or knowledge based on the literature review. For some of the analyses we used also Directed Acyclic Graphs to define the minimal adjustment set. The results using these models were similar (data not shown).

Residual confounding, i.e. confounding by factors that were not measured in the study, can never be ruled out in epidemiological studies (Rothman et al., 2008). In nutritional studies, where

socioeconomic status is strongly related to both the exposure variable (e.g. micronutrient intake) and child health outcomes, residual confounding may be of specific concern.

Different methods have been proposed to take into account residual confounding in epidemiology: instrumental variable, difference-in-difference method or fixed effects models (Streeter et al., 2017). Some of these methods seems difficult to apply in the context of this thesis, such as, the use of instrumental variable. In fact, an instrumental variable need to be a strong predictor of the exposure without being related to the outcome. These types of analysis need to be realised with caution as it can open "back door" paths and therefore include more bias.

6.3.4.2. Total energy intake adjustment

Adjustment for total energy intake is common in nutritional epidemiology. The main reason for this adjustment is the assumption that the amount of food consumed is roughly proportional to each person's own energy and nutrient requirements. When examining nutrient-disease relationships, the main exposure is the nutrient intake (or density) independently of energy intake (Rothman et al., 2008). The relevance of this same approach when dealing with non-nutritive and potentially harmful food substances remains under question as the absolute intake may be of more interest that the energy-adjusted intake.

Willett et al. described four different strategies to take energy into account in epidemiological studies (Willett, 2013):

- "Residual method": to use the residuals of a simple linear regression of the nutrient or chemical (explained variable) on total energy intake (explanatory variable).
- Standard multivariate method: adjusting for energy in the model
- "energy decomposition" or energy partition method the nutrient or in our case the chemical is divided by total energy intake
- Multivariate nutrient density method: to adjust the model for both energy and the following term, nutrient/energy.

In this thesis, we used two different approaches to take into account energy intake. In MoBa the exposure variable (dietary acrylamide exposure) divided by energy and the sensitivity analyses with crude exposure showed similar results. In EDEN we used the standard multivariate method in the analyses with all chemicals available in the TDS. Regarding the acrylamide analyses in EDEN, we performed the sensitivity analyses with the energy decomposition and the results were similar to those from our main analyses and the magnitude of the association was stronger for the energy decomposition analyses.

6.3.5. *Evidence of causality*

Different types of studies are used in observational epidemiology (e.g. cross-sectional, case-control or cohort studies). Each type contributes differently to epidemiological evidence for a specific causal relationship. In prospective cohort studies, participants are followed over time and exposures are assessed prior to the incidence of the health outcome (Rothman et al., 2008). This type of study is more efficient to assess causal relationships than the others. The studies presented in this thesis are all based on prospective cohort studies, and therefore temporality between exposure and outcome is respected, which is one of Hill's criteria for causality (Hill, 1965). The specific aim of our analysis was not known by the participant or the investigators at the moment of data collection.

Epidemiological studies, as the ones included in this thesis, can demonstrate statistically significant associations between contaminant exposure and health outcomes, but it should be noted that statistical significance does not imply a causal relationship. In the same way, absence of a statistically significant association does not prove the absence of a potential relationship. Causal inference methods are developed to try to limit the bias due to cohort study design and to approach a randomized control design. Different methods has been proposed: propensity score, inverse probability weighting, and instrumental variable (Ding et al., 2017). In this thesis, these methods has not been applied but this could be interesting to look more into them for future publications.

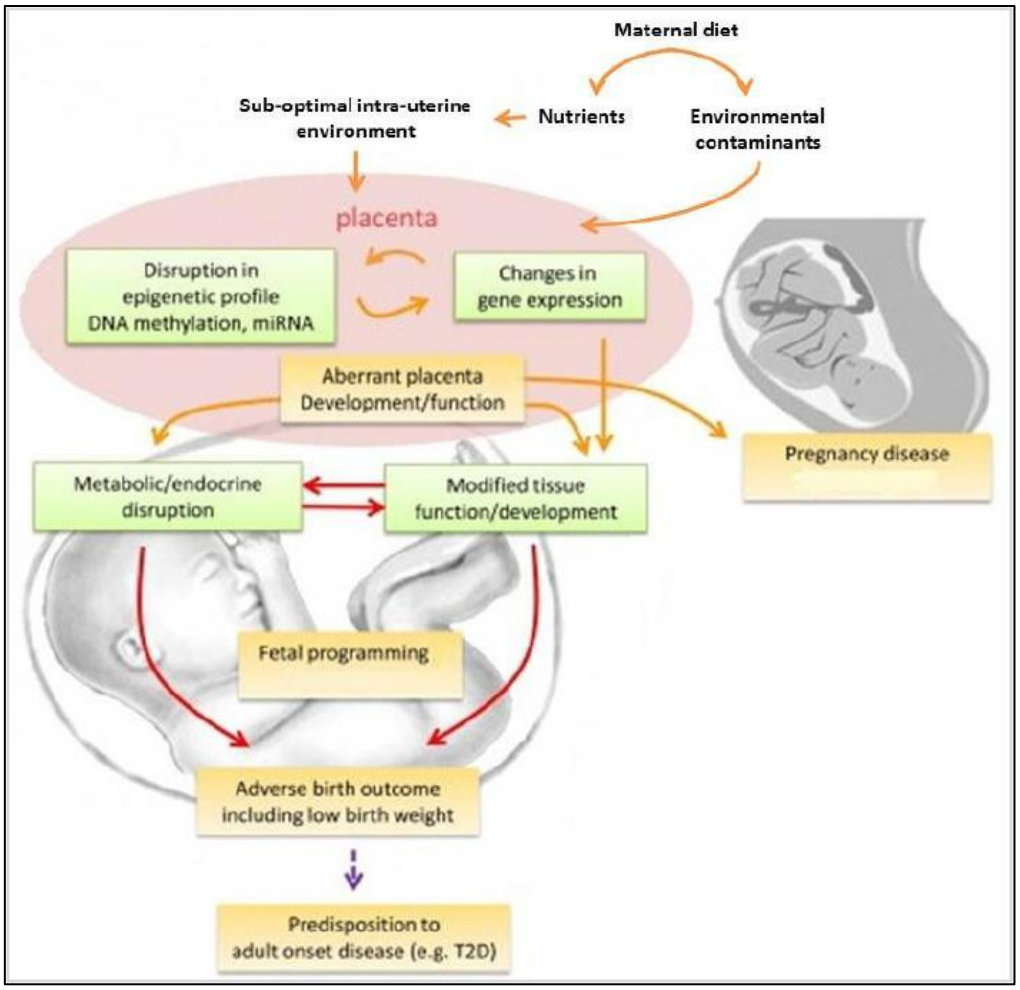
Another aspect to take into account is the strength of the association studied and their public health significance which does not imply a corresponding degree of etiologic significance (Rothman et al., 2008). Statistical and clinical significance are different concept. For one, the statistical significance, usually a threshold is used to identify when associations are supposed to be “of significance”. This approach is questioned by some researchers (McShane et al., 2017), and is even more relevant in big data studies or genome wide association studies (Concato and Hartigan, 2016). In contrast, no single threshold for clinical significance exist due to different context for clinical significance. In the context of growth, clinically relevant outcomes can be used as weight-for-gestational age z-score or the categorisation of BMI. Indeed, it is difficult to grasp the effect of 10g decrease of birth weight compared to a 10% increase in the risk of being some-for-gestational age. In this thesis growth outcomes were used in different ways continuously or with relevant clinical categorisation.

6.4. Potential mechanisms

6.4.1. *Epigenetic*

In studies related to the DOHaD hypothesis, the epigenetic modifications due to adverse environmental exposure are often cited as a possible mechanism (Desai et al., 2015). These modifications could induce heritable and persistent changes in gene expression without altering the DNA sequence. The three major molecular substrates that are involved in this process are the DNA, proteins that form the core around which the DNA wraps (histones) and a specific form of RNA molecules (noncoding RNA). Epigenetic changes include DNA methylation, chromatin folding or binding and packaging of DNA around nucleosomes and, finally covalent modifications of the histone proteins (Desai et al., 2015). The **Figure 31** present some mechanism involve in the DOHaD hypothesis.

Figure 31: Mechanism involved in the DOHaD hypothesis from (Papadopoulou, 2013)



A recent review found that in the context of child health, the impact of environmental modification on the epigenome are of small magnitude. However, these small environmental effects (maternal smoking, exposure to heavy metals or phthalates and phenols) on the epigenome have been replicated across populations and across time. Therefore, the authors conclude about the need of having critical discourse on findings such small effects. Meanwhile they advocate the research to emphasis the studies on the dynamic nature of the epigenome with the help of longitudinal studies (Breton et al., 2017).

6.4.2. *Endocrine disrupting chemicals*

As described in the first chapter, endocrine disrupting chemicals are environmental chemicals that can mimic or interfere with the effects of endogenous hormones (Newbold et al., 2007). Many studies are

suggesting that these chemicals could have an obesogenic effect, known as the "environmental obesogenic hypothesis" (Iszatt et al., 2015; Vafeiadi et al., 2016; Valvi et al., 2013).

Acrylamide is not known to be an EDC and the CONTAM panel of EFSA concluded that the evidence from the available studies in the literature on hormonal and endocrine effects of acrylamide is equivocal (EFSA 2015). In a cross-sectional study from Lin et al., urinary acrylamide metabolites were negatively associated with free thyroxine (T4) (Lin and others 2015). Although this result is coming from a cross-sectional study so we cannot exclude reverse causation, it provides an interesting new insight for a possible mechanism involved. Indeed, thyroid hormones are essential for an optimal growth but the literature is divergent regarding their effect on maternal hypothyroidism and prenatal growth (Hou and others 2016; Nazarpour and others 2015). A recent study showed an association between air pollution and foetal thyroid function that could have led to reduced birth weight (Janssen et al., 2017). A negative association between EDCs biomarkers (e.g. DDE, DEHP, HCB, PCB, PFOA, PFOS) and foetal thyroid hormones has already been showed (Maervoet et al., 2007). Foetal thyroid function might as well have an impact on foetal growth (Shields et al., 2011).

In our analysis, the mixture composed mainly with PFOA, metals and BPA was somewhat positively associated with birth weight. Most of the compounds of this mixture are known to be endocrine disruptors. The positive association underlined in our analysis might be due to residual confounding due to beneficial nutrients of maternal diet.

Another window of susceptibility should be investigated, and child's postnatal exposition should be considered in addition to prenatal exposition. This will be possible soon, as infant exposure to food chemicals is now available. Moreover, we examined child's growth up to 5 years in EDEN. It would be of great interest to confirm the absence of association later in childhood, such as during the puberty period.

6.4.3. *Oxidative stress and inflammation*

Another possible biological mechanism between acrylamide exposure and growth is through oxidative stress and inflammation. Recently, acrylamide exposure was found to be inversely associated with several body composition measures in a sample of adults from the NHANES, and high oxidative stress was suggested a potential mechanism involved (Chu and others 2017). During pregnancy, high acrylamide exposure can result in increased oxidative stress through increased expression of CYP2E1, resulting further in a heightened perinatal inflammatory status (Nguyen and others 2015; Wang and others 2003). Indeed, elevated maternal plasma C-reactive protein has been associated with a higher risk of childhood overall adiposity and central adiposity in the American cohort Project Viva, providing evidence that maternal inflammatory status might also contribute to explain our findings (Gaillard and others 2016). Oxidative stress and inflammation are also mechanisms that are suspected to influence the relation between exposure to air pollution or to tobacco smoke during pregnancy and low birth weight (Aycicek and Ipek 2008; Westergaard and others 2017). The negative association between both types of prenatal exposure and birth weight has been well described (Pedersen and others 2013; Valero De Bernabe and others 2004), and the mechanisms involved might be similar for acrylamide.

6.5. Public health implications

6.5.1. *Guidelines update*

In most of industrialized countries dietary guidelines are implemented to improve the health status of the population. Lately, the public concern of contaminants in food has been rising in France. Therefore, the recent update of French nutritional guidelines for the adult population highlighted this issue, but nutritional guidelines still need to be updated for specific population such as pregnant women and children. It is of great importance to identify combinations of foods that both cover the population's nutritional needs while limiting exposure to contaminants. In fact, for a limited number of contaminants, including inorganic arsenic, acrylamide and lead, levels of exposure remain of concern. In a recent study from 1,100 Germans on risk perception of foods, the most well-known chemicals in

foods were mercury in fish (78%) and dioxin in egg or milk (70%)(BfR, 2017). Within the frame of available data in this thesis, for some chemicals, the risk on later life health cannot be excluded; nevertheless, the results of our analysis are not alarming.

6.5.2. *Adding extra burden to mothers-to be*

Some researchers address concerns due to implication of DOHaD research on pregnant women (Richardson et al., 2014). Indeed, DOHaD research situates the maternal body as a central site of epigenetic programming and transmission, as well as a significant target of medical and public health interventions. Epigenetic studies of maternal effects on foetal development raise vital social, ethical, and philosophical questions. Therefore, this research field induces questioning on the possible impact of our research. First, we can question the impact of DOHaD research, on the role of the mother in normal and pathological development. Secondly, it raises the concern of the implication of a research focused on maternal, and therefore the necessity of taking into account a larger social environment. Many of the intrauterine stressors that DOHaD identified as having adverse intergenerational effects correlate with social gradients, race and gender. This points out the need for societal changes rather than individual solutions. Therefore, the pregnancy should be seen as a window of opportunities rather than a window of susceptibility in the communication of our research to the public. The role of fathers in the DOHaD research should be as well be more investigated. Animal studies are already showing epigenetic changes in sperm cells due to the hepatic lipid metabolism after under-nutrition that passes to the second generation male mice (Fullston et al., 2013).

6.6. Perspectives

To add to the complexity of the issue of exposure to chemicals, in the real-world, children are not exposed to a single chemical at a time but to complex mixtures of chemicals. Epidemiological studies are still mainly focused on the impact on health of individual chemicals or structurally-similar groups of chemicals, while the study of mixture of contaminants remains limited (Agay-Shay et al., 2015). Since

a decade, a new concept called the exposome is increasingly studied. The exposome approach try to encompass the totality of human environmental exposures from conception onwards (Vrijheid, 2014). EDEN and MoBa study are both part of the HELIX (The Human Early Life Exposome) project which is an EU funded project including six existing birth cohorts and starting in 2013. The link between the exposome and the child health outcomes are yet to come, but it this approach could help to better understand the role of environment on child health.

It would be of interest to have TDS studies that differentiate samples according to cultivation mode of the products (organic vs traditional) to look at the impact of this type of consumption on health outcomes. Bionutrinet, an ongoing French project based on the Nutrinet-Santé study, is already assessing the consumption of organic food in adults from online-based questionnaire (Kesse-Guyot et al., 2013).

Assessment of child exposure through their own diet could allow studying another window of susceptibility for postnatal growth. This assessment is part of the COCTELL project lead by Jérémie Botton, the infant exposure to food chemicals has just been assessed and the mixture identification is ongoing. Therefore, this new window of susceptibility could be studied, using a more integrative approach of prenatal and postnatal growth exposures to food chemicals and their association with child's growth, using for example structural equation modelling.

In EDEN, probably due to a lack of power, the positive relationship between prenatal dietary acrylamide exposure and postnatal growth was not possible to be highlighted. ELFE is larger representative birth cohort (more than 18,000 women included) and this sample size could allow to bring to light the association. Therefore, the next step of the COCTELL project will be to study the association between prenatal exposure to food chemicals and growth in this larger and nationwide cohort.

6.7. Conclusion

In this thesis, we showed that maternal diet quality during pregnancy was associated with better perinatal outcomes, whereas dietary acrylamide exposure was associated with impaired foetal growth and higher weight gain in childhood. When exploring a larger number of food chemicals, we found only limited associations with child's prenatal or postnatal growth, when using the single contaminant approach. When using the mixture approach, one mixture of chemical was positively associated with birth weight. Exposure to food chemicals assessed by TDS, did not appeared to be of major concern for growth, but other windows of susceptibility and other outcomes, such as cognitive development, should be considered in future studies.

As in all observational studies, only associations, and not causation, can be inferred from the results of this thesis alone. Therefore, our findings should be evaluated in light of existing evidence. Furthermore, future research is warranted to confirm and extend the findings of this thesis.

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APPENDICES

Appendix 1: List of chemicals used fromTDS2

- 21 trace elements and minerals: aluminium (Al), antimony (Sb), barium (Ba), cadmium (Cd), cobalt (Co), gallium (Ga), germanium (Ge), lithium (Li), lead (Pb), nickel (Ni), silver (Ag), strontium (Sr), tellurium (Te), tin (Sn), vanadium (V). Separate analyses were performed to take into account the proportion of inorganic and organic arsenic (As) and mercury (Hg), and the proportion of trivalent and hexavalent chromium (Cr). Inorganic and organic arsenic (Asi and Aso), trivalent and hexavalent chromium (CrIII and CrVI) and inorganic and organic mercury (HgI and MeHg) were therefore considered instead of total arsenic, chromium and mercury;
- 17 congeners of polychlorinated dibenzo-p-dioxins (or dioxins) and polychlorinated dibenzofurans (or furans) (PCCD/F) (HCDD/F-123478, HCDD/F-123678, HCDD/F-123789, HCDD/F-1234678, OCDD/F, PCDD/F-12378, TCDD/F-2378, HCDF-1234789, HCDF-234678, PCDF-23478);
- 12 congeners of 'dioxin-like' polychlorinated biphenyls (PCBs) (PCB-77, 81, 105, 114, 118, 123, 126, 156, 157, 167, 169, 189);
- six congeners of 'non dioxin-like' polychlorinated biphenyls (PCB-28, 52, 101, 138, 153, 180);
- 12 perfluoroalkyl acids (PFAAs): nine carboxylates (PFDA, PFDoA, PFHpA, PFHxA, PFNA, PFOA, PFTeDA, PFTrDA, PFUnA) and three sulfonates (PFBS, PFHxS, PFOS);
- 14 brominated flame retardants (BFRs): eigth polybrominated diphenyl ether congeners (PBDE-28, 47, 99, 100, 153, 154, 183, 209), three polybrominated biphenyl congeners (PBB-52, 11, 153) and three hexabromocyclododecane congeners (HBCD-alpha, beta, gamma);
- 18 mycotoxins: fumonisins B1 and B2 (FB1, FB2), ochratoxin A, B (OTA, OTB) and patuline (Pat), trichothecenes from group A includes T2-toxin, HT2-toxin, diacetoxyscirpenol (DAS) and monoacetoxyscirpenol (MAS; group B includes nivalenol (NIV), deoxynivalenol (DON), de-epoxy derivative of DON (DOM-1), 3-acetyldeoxynivalenol (DON3), 15-acetyldeoxynivalenol (DON15), and fusarenon X (FusX), zearalenone (Zea) and its metabolites: alpha zearalanol and alpha zearalenol;
- 11 phytoestrogens: biochanin A, coumestrol, daidzein, enterolactone, equol, , formononetin, genistein, glycitein, matairesinol, resveratrol, and secoisolariciresinol;
- 73 active pesticide residues respectively;
- 4 additives: nitrites, sulfites, tartaric acid and annatto;
- 1 heat-induced chemicals including acrylamide and 20 congeners of polycyclic aromatic hydrocarbons (PAHs): anthrancene (AN), benzo[a]anthracene (BaA), benzo[a]pyrene (BaP), benzo[b]Fluoranthene (BbF), benzo[c]fluorine (BcFL), benzo[g,h,i]perylene (BghiP), benzo[j]Fluoranthene (BjF), benzo[k]Fluoranthene (BkF), chrysene (CHR),

cyclopenta(c,d)pyrene (CPP), dibenzo[a,h]anthracene (DBahA), dibenzo[a,e]pyrene (DbaeP), dibenzo[a,h]pyrene (DbahP), dibenzo[a,i]pyrene (DbaiP), dibenzo[a,l]pyrene (DbalP), Fluoranthene (FA), indeno[1,2,3-cd]pyrene (IP), 5-methylchrysene (MCH), Phenanthrene (PHE) and pyrene (PY);

- bisphenol A (BPA) provided by (Bemrah et al., 2014) from the same food samples.

Appendix 2: Correlation matrix between a subsample of food chemicals

	Acrylamide	Nitrites	BPA	HCDD 1,2,3,4,6,7,8	PCB 81	PCDD 1,2,3,7,8	PCDF 1,2,3,7,8	TCDD 2,3,7,8	PCB 28	Asi	Cd	Pb	DbaeP	DbaiP	DON	PFNA	PFOA	BDE 99
Acrylamide																		
Nitrites	0,30																	
BPA	0,22	0,27																
HCDD 1,2,3,4,6,7,8	0,27	0,45	0,54															
PCB 81	0,20	0,31	0,53	0,80														
PCDD 1,2,3,7,8	0,17	0,23	0,41	0,81	0,84													
PCDF 1,2,3,7,8	0,12	0,25	0,55	0,75	0,89	0,72												
TCDD 2,3,7,8	0,14	0,20	0,44	0,78	0,89	0,98	0,81											
PCB 28	0,12	0,27	0,54	0,75	0,91	0,77	0,96	0,85										
Asi	0,31	0,25	0,57	0,60	0,54	0,54	0,56	0,55	0,59									
Cd	0,36	0,31	0,73	0,60	0,57	0,51	0,59	0,52	0,56	0,75								
Pb	0,24	0,20	0,65	0,58	0,51	0,54	0,55	0,54	0,56	0,85	0,81							
DbaeP	0,49	0,44	0,42	0,54	0,49	0,36	0,48	0,37	0,46	0,43	0,50	0,40						
DbaiP	0,48	0,42	0,27	0,38	0,24	0,24	0,26	0,23	0,24	0,32	0,27	0,26	0,36					
DON	0,32	0,31	0,33	0,43	0,44	0,40	0,39	0,39	0,41	0,44	0,62	0,43	0,42	0,10				
PFNA	0,07	0,06	0,38	0,39	0,24	0,21	0,34	0,22	0,25	0,21	0,39	0,28	0,15	0,15	0,08			
PFOA	0,07	0,12	0,44	0,31	0,37	0,32	0,43	0,36	0,43	0,65	0,45	0,46	0,21	0,18	0,19	0,22		
PBDE 99	0,17	0,32	0,53	0,75	0,92	0,81	0,93	0,88	0,96	0,54	0,55	0,52	0,45	0,28	0,41	0,25	0,43	

Spearman's correlation, N=1471

Appendix 3: Paper I- Dietary acrylamide intake during pregnancy and anthropometry at birth in the French EDEN mother-child cohort study

Dietary acrylamide intake during pregnancy and anthropometry at birth in the French EDEN mother-child cohort study

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Abbreviations:
AF: Attributable Factor, BMI: Body Mass Index, FFQ: Food Frequency Questionnaire, Hb: Haemoglobin, IARC: International Agency for Research on Cancer, IQR: Interquartile Range, LMP: Last Menstrual Period, SGA: Small for Gestational Age, TDS: Total Diet Study, US: Ultrasound

Abstract

Background and aim:

Acrylamide is a contaminant formed in a wide variety of carbohydrate-containing foods during frying or baking at high temperatures. Recent studies have suggested reduced foetal growth after exposure to high levels of acrylamide during pregnancy.

Objective:

To study the relationship between maternal dietary acrylamide intake during pregnancy and their offspring's anthropometry at birth.

Design:

In our population of 1471 mother-child pairs from two French cities, Nancy and Poitiers, dietary acrylamide intake during pregnancy was assessed by combining maternal food frequency questionnaires with data on food contamination at the national level, provided by the second "French Total Diet study". Newborns weighing less than the 10th percentile, according to a customized definition, were defined as small for gestational age (SGA). Linear and logistic regression models were used to study continuous and binary outcomes respectively, adjusting for the study centre, maternal age at delivery, height, education, parity, smoking during pregnancy, the newborn's gestational age at birth and sex.

Results:

The median and interquartile range of dietary acrylamide intake were 19.2 µg/day (IQR, 11.8;30.3). Each 10 µg/day increase in acrylamide intake was associated with an odds-ratio for SGA of 1.11 (95% Confidence Interval: 1.03,1.21), birth length change of -0.05 cm (95% CI: -0.11,0.00) and birth weight change of -9.8 g (95% CI: -21.3,1.7).

Conclusions:

Our results, consistent with both experimental and epidemiological studies, add to the evidence of an effect of acrylamide exposure on the risk of SGA and suggest an effect on foetal growth, for both weight and length.

Key Words: Acrylamide, foetal growth, SGA, food contaminant**,** pregnancy

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1. Introduction

A low birth weight or being small for a gestational age (SGA) have been associated with an increased risk of mortality and morbidity and can have major implications on later health (Dessì et al., 2012). Barker et al. showed that a low birth weight was associated with high systolic blood pressure and the risk of cardiovascular disease in adulthood (Barker et al., 1989). Since this initial work, low birth weight has been associated with a number of chronic diseases (Barker et al., 2002; Barouki et al., 2012; Gluckman et al., 2005). Many environmental exposures such as tobacco smoking, air pollution or chemicals have been shown to affect foetal growth (Nieuwenhuijsen et al., 2013; Schoeters et al., 2011; Slama and Cordier, 2013).

Acrylamide is a known neurotoxic for humans and animals (Ferguson et al., 2010; IARC, 1994) and was classified as "probably carcinogenic" in humans (group 2A) by the International Agency for Research on Cancer, IARC (Hogervorst et al., 2008; IARC, 1994). It does not occur as a natural product and has been produced since the 1950s to be used, for example, in water and wastewater treatment, as gels in laboratories or in grout for tiling. In these cases, the main routes of occupational exposure are inhalation and dermal. In 2002, studies showed that acrylamide can appear in foodstuffs containing carbohydrates when they are cooked at high temperatures, higher than 200°C (Dybing and Sanner, 2003; Tareke et al., 2002). They are produced by a reaction between asparagine and a sugar molecule. Acrylamide is also found in cigarette smoke and diet is the first source of exposure to acrylamide in non-smokers (Vikström et al., 2012).

Total Diet Studies (TDS) aim to measure levels of various contaminants and nutrients in foods at the national level (Sirot et al., 2012). A unique aspect of the TDS is that foods are prepared as they would be consumed (e.g. cooked), so the analytical results provide the basis for realistic estimates of the dietary intake of these contaminants. This is crucial for

acrylamide as it appears during the cooking process.. In France, fried potato products (crisps, French fries, pan-fried), bread, biscuits and coffee showed the highest levels (Sirot et al., 2012).

Acrylamide has been shown to pass the placental barrier in humans (Annola et al., 2008). Two epidemiological studies have shown a relationship between an increased maternal acrylamide exposure and a lower foetal weight at birth or an increased risk of having a SGA baby (Duarte-Salles et al., 2013; Pedersen et al., 2012). The analysis of the NewGeneris consortium, a European prospective mother-child study, was based on haemoglobin adducts of acrylamide and glycidamide (its metabolite) measured in maternal and cord blood (Pedersen et al., 2012). In MoBa, a Norwegian mother-child cohort study, dietary acrylamide was estimated using data provided from Norway, Sweden and the European Union on dietary contamination and compared with a biomarker of exposure in a small subsample (Duarte-Salles et al., 2013).

Our aim was to provide additional epidemiological evidence on the association, expected to be negative, between maternal dietary acrylamide intake, assessed for the first time using data from a national TDS, with offspring length, weight, head circumference and the risk of SGA at birth.

2. Subjects and methods

2.1.Population and study design

EDEN is an ongoing mother-child cohort study that recruited 2002 pregnant women from February 2003 to January 2006, before their 24th week of gestation in two French university hospitals in the cities of Poitiers and Nancy (Heude et al., 2015). The exclusion criteria were twin pregnancies, known medical history of diabetes, plan to move outside the region in the next three years and French illiteracy (Deschamps et al., 2009). From the 2002 women recruited, 96 left the study on delivery for personal reasons, 4 left because of intra-uterine death, 3 because they delivered outside the study hospitals. After delivery, the mother completed questionnaires and a clinical examination and her child had a clinical examination. Our analysis includes the 1471 women with a validated FFQ (detailed below), having a full term pregnancy and information available on parameters at birth: weight, length, head circumference and gestational age (see supplementary materials). The study was approved by the ethics committee of Kremlin-Bicêtre and the National Commission for Data Protection and Liberties (CNIL).

2.2.Dietary information

The FFQ was available at two time points in the EDEN study. The first was completed at inclusion and documents the diet in the year prior to pregnancy. The second FFQ was completed in the few days following delivery at the maternity hospital and documents the diet during the last three months of pregnancy. The latter was used in the main analyses and the former in sensitivity analyses. The FFQ used was slightly modified from a FFQ developed and validated in another French study (Deschamps et al., 2009). Consumption frequencies were recorded for 137 different food items, with a 7-item scale from “never” to “more than once a day”. We generated the frequency from the midpoint of the categories (i.e. 2 for the

category of 1 – 3 servings/month). For each food item, the sizes of portions usually consumed by the mothers were also recorded, using pictures for several food types (e.g. meat, French fries, pasta, vegetables, cakes, cheeses) on a 3-level scale. For other foods, the portion consumed was assumed to be a standard portion assessed for the French adult population (Lafay et al., 2002). To calculate the food intake for each item, the portion consumed (in g) was multiplied by the frequency declared (per day). Some changes were made after a validation step for the questionnaire by comparing it to repeated 24-hour recalls. As calorie intakes were too high by comparing the FFQ to the 24-hour recall, a minimum assignment was performed for groups of 7 or more items (e.g. fruits and vegetables) or high energy density foods (e.g. "Boiled potatoes", "Fried potatoes"). For these categories if the consumption was between 1 to 3 times per month, we assigned 1 time per month rather than 2 times before taking into account the validation step.

Individual total energy intakes were calculated for all women by multiplying the intake (in g per day) by the energy value of each food. Energy values were obtained from the SU.VI.MAX nutrient composition database (Hercberg, 2003; Le Moullec et al., 1996). Women with an estimated total energy intake under 1000 kcal/day or over 5000 kcal/day were excluded (47 and 20 respectively), leaving 1599 women with a validated FFQ, and 1471 women had full term babies (delivery $\geq$ 37 weeks of gestation) with information available on birth weight and length (see supplementary materials). After exclusion of preterm babies (N=110, 5.8% in the EDEN study), 2% of the newborns had a birth weight < 2500g and 12% were declared as SGA according to the customized definition (detailed below).

Three groups of acrylamide contributors were created from the food with the highest acrylamide levels: (1) French fries, pan-fried potatoes, crisps, (2) coffee, tea, and (3) bread, pastries, biscuits, crackers, cakes, pizzas. In each group, we calculated the sum of the food intake corresponding to each item.

2.3. Acrylamide assessment

Food contamination data came from the second French TDS, conducted in 2006-2010 by the French Agency for Food, Environmental and Occupational Health and Safety (ANSES). Details on sampling methodology of the TDS have been published elsewhere (Sirot et al., 2012), in particular for acrylamide exposure (Sirot et al., 2009). To combine individual consumption data with contamination data, all the food items in the EDEN FFQ were linked with the closest food items of the TDS (Chan-Hon-Tong et al., 2013). Individual dietary exposures (in µg/day) were calculated by summing for each food item, the cross-product between total daily intake (in g/day) and concentration of acrylamide (in µg/g). In order to describe levels in our population, we also calculated exposure in ng/kg body weight/day by dividing by the mother's mean body weight during the last trimester (the weight at the third trimester visits were retrieved from medical records and if these information were not available the mean of the population 74.27 kg was imputed).

2.4.Anthropometry at birth and other variables

The birth weight (g), length (cm), head circumference (cm) and parity (primiparous / multiparous) were collected from medical records. Gestational age was indicated in the medical record and was determined from the 12 week ultrasound scan (US, 76.4%), by the last menstrual period (LMP, 20.4%) or by basal body temperature (0.6%). Gestational age is expressed in weeks of amenorrhea. Two percent of births were conceived by in-vitro fertilisation. Slama et al. in 2014 suggest to preferably estimate gestational age by using both last menstrual period and ultrasound information, because of the possibility of errors tied to both methods (Slama et al., 2014). The method probably less prone to bias uses ultrasound measures to correct the date of the last menstrual period, but only when the discrepancy with LMP exceeds two weeks. In our sample, 1245 (93.1%) women had a difference of less than

two weeks, 92 had a difference of more than 2 weeks (6.9%) and information on the LMP was missing for 134 women.

SGA was defined by a weight lower than the 10th percentile according to a customized definition adapted from Gardosi et al. (Gardosi et al., 1995). This definition of SGA takes parity, maternal height and weight and the baby's sex into account. Conversely to these characteristics assumed to influence fetal growth physiologically, maternal smoking was only included in the customization model to get the independent effect of other variables on weight, but, the SGA definition was not corrected for maternal smoking status because of its non-physiological impact on birth weight. For instance, a newborn with a low birth weight will be less likely to be SGA if its mother is smaller and lighter. In contrast, a newborn with a low birth weight will have the same probability to be SGA whatever the smoking status of its mother.

At the 24^{th}-28^{th} week examination, maternal height was measured by research midwifes, and pre-pregnancy weight (g), education (classified as higher or lower than the baccalaureat, A level), smoking habits during first and second trimester were collected through interview. For smoking habits, the mothers reported their current smoking status (2nd trimester status), by providing average daily cigarette consumption, as well as habits at the beginning (1st trimester) of pregnancy. After delivery, similar information for smoking at the end of the 3rd trimester of pregnancy was collected by the research midwives (3rd trimester habits). These three variables were used to calculate the average number of cigarettes smoked during pregnancy, which was used in the analyses as a categorical variable (none, 1 to 9, $\geq$10 per day). Maternal body mass index (BMI) was calculated as weight (in kg) for height (in m) squared. Weight gain during pregnancy was calculated by subtracting the reported weight before pregnancy from measured weight two-to-three days after delivery. Mothers were weighed using electronic Terraillon SL 351 scales (Hanson Ltd, UK) to the nearest 0.1 kg.

2.5. Statistical Analysis

Student *t*, χ^2 and Mann-Whitney tests were used to compare differences between excluded and non-excluded mother-child pairs. Spearman correlation coefficients (r_{Sp}) were calculated between dietary acrylamide intake and continuous variables, including the main categories of acrylamide contributors.

Linear and logistic regression models studied continuous and binary outcomes respectively. We tested deviation from linearity for the relations between birth outcomes and acrylamide concentration by comparing nested models using a Fisher test (for the linear models) and a likelihood ratio test (for logistic models), with the exposure variable in quartile groups, declared either as ordinal (restricted model) or as dummy variable (full model), respectively. We present graphically the predicted percentage of SGA (obtained using the "lsmeans" statement from the SAS PROC LOGISTIC) according to acrylamide quartile groups.

The confounders have been selected *a priori*, based on the literature. We took into account in all the models (except for SGA) the study centre, maternal age at delivery, height, education, parity, smoking during pregnancy, and the newborn's gestational age at birth and sex. For each model we tested the best way to adjust for gestational age, by linear, squared or cubic terms. For SGA, we did not adjust on the variables already used in its definition (i.e. maternal height, parity, the newborn's gestational age at birth or sex). Additional adjustment for maternal BMI, pregnancy weight gain, total energy intake, passive smoking and interaction between BMI and pregnancy weight gain, were also considered, as they have also been described as potentially associated with anthropometry at birth, and were included in the final model if the corresponding p-value was less than 0.05 (or less than 0.20 for the interaction term). As acrylamide is found in cigarettes, we present the results separately for children born to non-smokers (n=1075) and smokers (n=396); in addition for the entire

population, we tested the interaction between smoking and dietary acrylamide exposure. For each model, we analysed the residuals of the model and the presence of influential observations.

In 8.4% of our population there was at least one missing data on potential confounder variables (education, parity, pre-pregnancy BMI, tobacco smoke and specific weight gain during pregnancy). We imputed these data either from other information available during the follow-up (51%) or by the median when no other information was available.

We calculated the attributable fraction (AF) for SGA due to dietary acrylamide exposure being above *versus* below the third quartile, using the method provided by Rückinger et al. (Ruckinger et al., 2009) to take into account adjustment factors. We compared this AF with the one of being exposed to tobacco (ever smoked during pregnancy). Ninety five percent confidence intervals were calculated using bootstrap estimates from the SAS PROC SURVEYSELECT (Cassell, 2010).

In sensitivity analyses, we analyzed the associations using log-transformed acrylamide exposure because of a right skewed distribution. We re-ran all models excluding people with imputed variables. We ran as well the analysis using a corrected variable in which we prioritize the gestational age calculated via LMP as compared to US. We also ran the models excluding mothers who developed gestational diabetes or hypertension. We tested the interaction between newborn's sex and acrylamide intake in all the models, and we present the analysis by sex in the supplementary material. We tested whether using FFQ corresponding to the diet during the year before pregnancy to evaluate acrylamide exposure changed our results. We tested the adjustment for the main acrylamide contributor group (i.e. French fries, pan-fried potatoes, crisps). Finally, we ran the models without adjusting for weight gain during pregnancy as it could be influenced by acrylamide exposure and considered as a mediating variable.

P-values were considered significant when <0.05. Data were analysed using SAS version 9.3 (SAS Institute, Inc., Cary, NC, USA).

3. Results

Compared to the representative 2003 French National Perinatal Survey (NPS) (Blondel et al., 2012), mother-child pairs included in our study were similar for obstetrical data such as maternal age at delivery, baby's weight and length. However, they were more educated (55.8% had a higher education *versus* 42.6% in the NPS), more frequently of European nationality (97.0% of them *versus* 90.9% in the NPS) and fewer smoked during pregnancy (e.g. 15.9% *versus* 20.8% in the NPS during the third trimester). The women from the EDEN study that were excluded from these analyses had a lower education, a lower income, a higher BMI and had gained less weight during the pregnancy; this weight gain was more frequently adequate using the recommendation for weight gain during pregnancy according to pre-pregnancy BMI (Table 1).

The estimated median and interquartile range (IQR) of dietary acrylamide intake were 19.2 µg/day (IQR 11.8,30.3) (Table 1). Dietary acrylamide intake was significantly associated with the mean number of cigarettes smoked during pregnancy (r_{Sp}=0.22; p<0.001), maternal age (r_{Sp} =-0.05; p=0.04), education (low *versus* high: Δ=3.0 µg/day; p<0.001), parity (multiparous *versus* primiparous: Δ=4.0 µg/day; p<0.001) and study centre (Nancy *versus* Poitiers: Δ=2.3 µg/day; p=0.01). After multivariable adjustment, centre, parity, maternal age and smoking remained significantly associated with acrylamide intake.

As expected, the correlation between acrylamide intake and its main contributors were positive and significant. The highest correlation was found with fried potatoes (French fries, pan-fried and crisps, r_{Sp} =0.70), lower for tea and coffee (r_{Sp} =0.42) and lowest for bread and biscuits (r_{Sp} =0.37).

The coefficient between dietary acrylamide intake and birth length was negative and significant (r_{Sp} =-0.11, p= <.0001). After adjustment in a linear regression model (Table 2), a 10µg/day higher intake of acrylamide was associated with a lower birth length of 0.05cm

(95% Confidence Interval (95% CI): -0.11,0.00). The association tended to be stronger in smokers (-0.09 cm (95% CI: -0.18,0.00), p-for-interaction= 0.11).

The correlation between dietary acrylamide intake and birth weight was negative and significant (r_{Sp} =-0.06, p=0.02). After adjustment in a linear regression model (Table 2), birth weight was lower by 9.8g (95% CI: -21.3,1.7) for each 10µg/day higher dietary acrylamide intake. In our study population, although the second quartile group departed from a linear trend (**Figure 1**), the test of non-linearity was not significant (p=0.80) and we observed a negative trend (p-trend=0.07). After adjusting for birth length, the negative trend with birth weight became non significant (-1.0g, 95% CI: -15.4,13.4). We did not show any significant difference in the associations according to active smoking (p-for-interaction=0.41 and 0.94 before and after adjustment for birth length respectively).

Dietary acrylamide intake and head circumference at birth were not significantly associated (r_{Sp}=-0.03, p=0.20). After adjustment in a linear regression model (Table 2), the association was still not significant (0.00 cm, 95% CI: -0.04,0.04). However, the association differed according to smoking status during pregnancy (p-for-interaction= 0.01) being -0.06 cm (95% CI: -0.13,0.01) in smokers and 0.04 cm (95% CI: -0.02,0.10) in non-smokers.

In a crude analysis, the level of dietary acrylamide was significantly higher in SGA newborns (Δ=0.49µg/day, p=0.0004). After adjustments in a logistic model, the intake was significantly associated with an increased risk of SGA at birth (OR=1.11 for 10µg/day increase, 95% CI: 1.03, 1.21). The association was not significantly different between smokers (OR=1.05, 95% CI: 0.92,1.19) and non-smokers (OR=1.16, 95% CI: 1.04,1.30, p-for-interaction=0.27). When intake was classified into quartile groups, we did not observe a departure of the relationship from linearity (p=0.31). The respective OR for each quartile group Q2, Q3 and Q4, when compared to the first group, were 1.31 (95% CI: 0.81,2.12), 1.08

(95%CI 0.66,1.77) and 2.16 (95% CI: 1.01,2.62) respectively. The corresponding predicted percentages of SGA by acrylamide quartiles are presented on **Figure 2**.

Considering a causal relationship between dietary acrylamide intake and SGA, with adjustment factors including tobacco consumption, the attributable fraction of being exposed above the higher quartile of acrylamide on SGA was AF=0.10 (95% CI: 0.00,0.19). The attributable fraction of tobacco consumption on SGA in our population was 0.16 (95% CI: 0.04, 0.28) after taking into account the same adjustment factors including dietary acrylamide intake.

Sensitive analyses showed similar results when we excluded people with imputed variables, with gestational diabetes or hypertension as well as with and without adjusting for gestational weight gain during pregnancy (see supplementary materials). The analyses using the gestational age, giving priority to LMP were similar for every outcome although no longer statistically significant for SGA. A significant interaction was found between acrylamide intake and the newborn's sex in relation with birth length, the association was negative and significant for girls but not for boys. The associations using the log-transformed exposure variable and adjusting for acrylamide contributors were generally slightly stronger (see supplementary materials). When we used the FFQ data from the year prior to pregnancy, the associations were somewhat attenuated.

4. Discussion

Our epidemiological study is the third to show a significant association between SGA status and dietary acrylamide intake (Duarte-Salles et al., 2013; Pedersen et al., 2012): the greater the intake during pregnancy, the lower the birth length and the higher the risk of SGA. The association with birth weight was strongly attenuated after adjustment for birth length.

In the MoBa cohort study, that combined a FFQ with a database containing values of acrylamide concentration reported from Norwegian, Swedish or European Union analyses of food items, the mean acrylamide level estimated in 50651 mothers was 0.41 ± 0.2 μg/kg bw/day, compared to 0.38 ± 0.2 μg/kg bw/day in our study when we used pre-pregnancy weight as in MoBa, instead of weight at the last trimester. Likewise, we found an effect size of the association between dietary acrylamide and birth weight that was very close to that seen in MoBa: they found a lower birth weight of -9.9 g (95% CI: -13.5,-6.3) for one SD (4.6 ng/kcal/day) increase in their adjusted model, compared to -16.9 g (95% CI: -36.7,2.9) for a change in one Standard Deviation (SD) (17.3 μg/day, i.e. 7.8 ng/kcal/day) in our study, after expressing our regression coefficient for a same change would lead to a coefficient equal to -10.0 g. A relationship was also found between low birth weight, defined as birth weight below the 10^{th} percentile (gestational age and parity specific) in MoBa and the dietary acrylamide intake with an OR=1.03 (95% CI: 1.00,1.06) for an increase of one SD though the OR was higher in our study (OR=1.20 (95% CI: 1.04,1.38 for a change in one SD). This difference seemed not fully explained by the higher exposure variability in our population (as for birth weight), because expressing our OR for a same change would lead to an OR equal to 1.11.

The second epidemiological study is a multicentric study of 1001 mother-child pairs (NewGeneris) from England, Denmark, Greece, Norway and Spain. Exposure to acrylamide was assessed by measures of haemoglobin (Hb) adducts, a biomarker correlated with an

"acrylamide-rich food score". A significant relationship with birth weight was seen in a model adjusted only for gestational age and country. The mean birth weight was decreased by 35g (95% CI: -51,-19) for an increase in 10pmol/g Hb acrylamide. When the model was adjusted for more variables (active and passive smoking, sex, BMI, parity, maternal age at birth, education, consumption of fruits and vegetables to characterize a healthy diet), the level of the association was weakened (β= -23g (95% CI: -51,5). A negative association was also found between acrylamide Hb or glycidamide Hb adducts and head circumference (β= -0.06, 95% CI: -0.12,0.00 and -0.10, 95% CI: -0.20,0.00, respectively). These associations were not significant after further adjustment for active and passive smoking, sex, BMI, parity, maternal age at birth, education and consumption of fruits and vegetables. In our analysis, we did not find any significant association between dietary acrylamide intake and decreased head circumference.

One limitation of our study is the use of self-administered FFQs, which may provide an over or under statement bias (e.g. social pressure for a healthy diet) (Joachim, 1997; Shu et al., 2004.). Moreover, when matching FFQ data from EDEN and contamination data from the TDS, some items did not correspond (e.g. in TDS, several kinds of biscuits were tested (chocolate, fruit), whereas in EDEN's FFQ this level of detail was not available; conversely, EDEN's FFQ, but not the TDS, detailed whether the potatoes were deep-fried or pan-fried). However, the classification bias is unlikely to be differential, and would rather lead to underestimated associations. Furthermore, in contrast to the two previous epidemiological studies (Duarte-Salles et al., 2013; Pedersen et al., 2012), we had no biological measure to validate our estimation of intake. However, Vikström et *al*. showed that well-designed FFQ were good proxies for estimating average levels of acrylamide for non-smokers (Vikström et al., 2012). Observed Spearman correlation coefficients between exposure to acrylamide estimated by FFQ and the bioassay were shown to be r_{Sp}=0.24 (95% CI: 0.02,0.44) for

acrylamide and r_{Sp} =0.48 (95% CI: 0.29,0.63) for its metabolite glycidamide (Duarte-Salles et al., 2013). We may also discuss the generalizability of our results because our population is not representative of the French mother-child pairs especially in terms of socioeconomic status. We do not expect this to create a bias in the associations between exposure and outcomes. The concordance of our results with those of the other studies was the most convincing argument that our results are not biased or chance findings.

Assessing dietary intake through a TDS has also strong advantages. This is a standardized method recommended by the World Health Organisation and European Food and Safety Authority, that takes into account food "as consumed" (European Food Safety Authority, 2011). This is particularly important to allow a good estimate for acrylamide, formed during cooking at high temperatures. The estimation of dietary acrylamide intake is independent of active and passive smoking, in contrast to an estimation by biomarkers, and this could facilitate eventual specific food recommendations. Another strength of our study is the use of customized growth curves to evaluate SGA, which limits misclassification bias, as the curves take better account of the physiological small birth weight. Of note, despite the quite high correlation between the dietary acrylamide intakes assessed from the FFQs for the year prior to pregnancy and that during the last trimester (r_{Sp}=0.53), the associations using the pre-pregnancy FFQ were slightly lower. This may further suggest a more specific association with acrylamide, rather than an effect related to general dietary habits, potential uncontrolled factors or residual confounding.

We additionally showed that adjusting birth weight for birth length, that was also associated with acrylamide intake, weakened the association that became non-significant. This suggests that acrylamide intake may have an overall effect on foetal growth. This result is in line with animal studies that show an effect of acrylamide on the ossification process (El-Sayyad et al., 2011). However, the significant relationship found between dietary

acrylamide intake and reduced birth length warrants confirmation in other human studies, as it is the first time that the relation has been shown. The differences observed in the associations between smokers and non-smokers were not consistent between outcomes. These analyses should be repeated in other studies before postulating a synergistic effect between smoking and dietary acrylamide intake. The association between acrylamide intake and birth length was negative and significant for girls but not for boys. To our knowledge there is no biological hypothesis supporting a difference in the associations by sex, and this analysis need to be replicated.

The mechanism of the action of acrylamide on the risk of low birth weight is not clearly established. The only hypothesis that has been suggested is that acrylamide, and its metabolite glycidamide, could create specific adducts on nucleophilic sites of DNA implicated in the regulation of growth (Duarte-Salles et al., 2013). Several animal studies, mainly in rodents, show a decrease in offspring body weight following maternal acrylamide exposure during gestation (El-Sayyad et al., 2011; Manson et al., 2005; Tyl and Friedman, 2003) and a panel of experts from the American National Toxicology Program endorsed this statement in 2005 (Manson et al., 2005). One of these studies suggested that the effect of fried potatoes or chips might be even more detrimental than acrylamide *per se*, since mice fed with a diet containing 30% fried potatoes or chips gave birth to offspring with a lower birth weight than the group fed with acrylamide (25µg/kg bw) dissolved in water (El-Sayyad et al., 2011). This effect has been hypothesized to be due to a joint effect with other substances (Duarte-Salles et al., 2013). In our analysis, there might be uncontrolled confounding due to lack of information on potential dietary co-exposure such as trans fatty acids, although their independent effect on birth outcomes are inconsistent across the studies (Cohen et al., 2011; Dirix et al., 2009a; Dirix et al., 2009b).

The results of our study add to the evidence that dietary acrylamide intake is associated with an increased risk of SGA and a decrease in both birth length and birth weight. Approximating RR by OR, which is reasonable here because the outcome is not very frequent (prevalence expected to be 10%) and the OR is modest, we calculated the AF. The aim of the AF is to assess the public health impact of an exposure by measuring its contribution to the observed outcome incidence under the hypothesis of a causal effect (Rothman et al., 2008). This AF, as calculated, can be interpreted as follows: in case of causality and adjusting for the considered confounders, if we could reduce the maximum level of acrylamide in the diet of pregnant women to below the cut-point of the observed higher quartile, we would prevent 10 % of SGA newborns. By comparison, if no women smoked, 16% of SGA newborns would be prevented.

In several developed countries, an unexplained decrease over time in birth weight of term babies has been observed, despite the rising prevalence of maternal overweight and the average weight gain in pregnancy (Diouf et al., 2011; Donahue et al., 2010; Schiessl et al., 2009). Adverse environmental exposures could be an explanation (Barouki et al., 2012; Katić et al., 2010; Slama and Cordier, 2013).

Finally, it will be important to study the longer term effects of dietary acrylamide intake during pregnancy on the children's health, in particular on cognitive development, as coffee consumption, one of the main contributors of acrylamide in the diet, was recently shown to be negatively associated with IQ in the EDEN study (Galera et al., 2015).

In conclusion, our results showed a relationship between dietary acrylamide intake and the risk of SGA, consistent with both experimental and other epidemiological studies. They suggest an effect on foetal growth, affecting both weight and length.

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The authors' responsibilities were as follows MK: conducted the data analyses and drafted the manuscript; BH and JB: provided statistical expertise; M-AC, JB, BH: supervised the study; MK, JB: participated in the interpretation of the results and the writing of the manuscript; ACHT, AF: exposure assessment; VS, ACHT: exposure assessment expertise; AF: data-management and BH, VS, and M-AC: provided critical input and advice concerning the analyses. All authors contributed to the revision of the manuscript.

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FIGURE LEGENDS

Fig. 1. Means of birth weight (N=1471) by quartile groups of dietary acrylamide (µg/day), adjusted for study centre, maternal age at delivery, parity, height, education level, tobacco consumption during pregnancy, gestational age at delivery, sex, maternal weight gain during pregnancy, maternal BMI before pregnancy and the interaction between maternal BMI and weight gain, (p trend=0.07). The EDEN study

Fig. 2. Predicted percentage of SGA (N=1471) by quartile groups of dietary acrylamide (µg/day) adjusted for study centre, maternal age at delivery, education level, tobacco consumption during pregnancy, and specific maternal weight gain during pregnancy (p trend=0.31). The EDEN study

Table 1
Characteristics of the study population and comparison between the women included and non-included; The EDEN study

		Women Included (N=1471)		**Women Excluded (N=531)**	**p-value***
		N (%), mean ± SD or quartiles	**Missing values**	**N (%), mean ± SD or quartiles**	
Recruitment centre	Poitiers	728 (49.5)	0	240 (45.2)	0.09
	Nancy	743 (50.5)		291 (54.8)	
Maternal characteristics					
Age at delivery (years)		29.5 ± 4.80	78	29.5 ± 5.19	0.90
Education	≤ A level	638 (44.2)	90	250 (55.8)	<.001
	>A level	806 (55.8)		198 (44.2)	
Nationality	French	1450 (98.6)		430 (81.0)	<.001
	Other	16 (1.1)		20 (3.8)	
	Missing	0.3 (5)		81 (15.2)	
Primiparous	No	819 (55.7)	107	236 (54.4)	0.63
	Yes	652 (44.3)		198 (45.6)	
BMI before pregnancy (kg/m²)		23.2 ± 4.4	94	23.7 ± 5.2	0.04
BMI (kg/m²)	<18.5	69 (4.7)	84	26 (5.8)	0.04
	18.5-24.9	1026 (69.7)		289 (64.6)	
	25.0-29.9	259 (17.6)		79 (17.7)	
	>30	117 (8.0)		53 (11.9)	
Specific maternal weight gain during pregnancy (kg)		9.1 ± 5.0	115	8.5 ± 5.9	0.03
Weight gain (kg) during pregnancy according to IOM's recommendation, depending on pre-pregnancy BMI	Inadequate (<recommendation)	576 (39.2)	108	135 (31.9)	<.001
	Appropriate (=recommendation)	333 (22.4)		138 (32.6)	
	Excessive	562 (38.2)		150 (35.5)	

	(>recommendation)				
Height (cm)		163.6 ± 6.1	80	163.0 ± 6.2	0.09
Tobacco consumption during pregnancy (cig/day)	No	1075 (73.1)	123	308 (73.7)	0.67
	1-9	324 (22.0)		86 (20.6)	
	≥10	72 (4.9)		24 (5.7)	
Energy intake (kcal/day)		2213.3 ±751.8	413	2213.3 ± 726.7	0.99
Newborn's data					
Gestational age (weeks of amenorrhea)		39.5 ± 1.2	107	38.2 ± 2.7	<.001
Birth weight (g)[a]		3345 ± 432	103	3051 ± 674	<.001
Birth length (cm)[a]		49.8 ± 2.09	169	48.6 ± 3.1	<.001
Head circumference (cm)[b]		34.3 ± 1.5	159	33.6 ± 1.9	<.001
SGA	No	1294 (88.0)	119	348 (82.5)	0.003
	Yes	177 (12.0)		74 (17.5)	
Newborn's sex	Boys	777 (52.8)		223 (51.6)	0.66
	Girls	694 (47.2)		209 (48.4)	
Maternal dietary acrylamide intake					
Acrylamide (µg/day)		23.8 ± 17.3	336	27.4 ± 32.7	0.13
Acrylamide (µg/day)	(min, Q1, median, Q3, max)	(0.16, 11.8, 19.2, 30.3, 183.5)	336	(2.7, 8.7, 16.7, 33.3, 220)	
Acrylamide (µg/kg bw/day)		0.33± 0.25	336	0.37 ± 0.43	0.15
Acrylamide (ng/kg bw /day)	(min Q1, median, Q3, max)	(2.4, 163.4, 260.5, 422, 2594.2)	336	(33.1, 128, 234,4 35.6, 2895)	

* p-value for t-, chi-squared or Mann-Whitney tests as appropriate

[a] the differences for birth weight, length and head circumference was due to the exclusion of preterm babies

Table 2
β regression coefficients or odds-ratio (OR) between dietary acrylamide intake (10µg/day) and anthropometry at birth. The EDEN study

All N=1471	**β or OR**	**(95% CI)**	**p**
Birth weight (g) [a, b, c, d]	-9.79	(-21.3 ; 1.69)	0.09
Birth length (cm) [b, d]	-0.05	(-0.11 ; 0.001)	0.06
Birth weight (g) for length (cm) [a, c, d]	-1.03	(-15.4 ; 13.4)	0.89
SGA (n=177) [c]	1.11	(1.03 ; 1.21)	0.001
Head circumference (cm) [a, b, c, e]	-0.002	(-0.04 ; 0.04)	0.95
Non smokers N=1075	**β or OR**	**(95% CI)**	**p**
Birth weight (g) [a, b, c, d]	-7.69	(-23.0 ; 7.67)	0.33
Birth length (cm) [b, d]	-0.01	(-0.08 ; 0.05)	0.68
Birth weight (g) for length (cm) [a, b, c, d]	-5.46	(-17.7 ; 6.81)	0.38
SGA (n=113) [c]	1.16	(1.04 ; 1.30)	0.01
Head circumference (cm) [a, b, c, e]	0.04	(-0.02 ; 0.10)	0.15
Smokers N=396	**β or OR**	**(95% CI)**	**p**
Birth weight (g) [a, b, c, d]	-9.85	(-27.8 ; 8.11)	0.28
Birth length (cm) [b, d]	-0.09	(-0.18 ; 0.00)	0.04
Birth weight (g) for length (cm) [a, b, c, d]	0.46	(-14.1 ; 15.0)	0.95
SGA (n=64) [c]	1.05	(0.92 ; 1.19)	0.32
Head circumference (cm) [a, b, c, e]	-0.06	(-0.13 ; 0.01)	0.09

All models (except SGA) are adjusted for study centre, maternal age at delivery, parity, height, maternal education level, tobacco consumption during pregnancy, gestational age at delivery, sex.

Models for SGA are adjusted for study centre, maternal age at delivery, maternal education level, tobacco consumption during pregnancy, and specific maternal weight gain during pregnancy

p-for-interaction between acrylamide intake and smoking status: 0.41 for birth weight, 0.11 for birth length, 0.94 for birth weight adjusted for birth length, 0.01 for head circumference and 0.27 for SGA

[a]: additionally adjusted for the interaction between maternal BMI and weight gain

[b]: additionally adjusted for BMI

[c]: additionally adjusted for specific maternal weight gain during pregnancy

[d]: gestational age and gestational age squared

[e]: gestational age, gestational age squared and gestational age cubed

Appendix 4: Paper II- Adéquation des consommations alimentaires des femmes enceintes de l'étude ELFE aux recommandations du Programme national nutrition santé

Adéquation des consommations alimentaires des femmes enceintes de l'étude ELFE aux recommandations du Programme National Nutrition Santé

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Résumé :

Objectifs: Evaluer l'adéquation des consommations alimentaires des femmes enceintes aux recommandations du Programme National Nutrition Santé (PNNS) et identifier les principaux facteurs démographiques et socioéconomiques associés.

Méthodes: A partir du questionnaire en maternité de 14051 femmes de l'étude ELFE, un score d'adéquation des apports vis-à-vis des recommandations adultes (score-PNNS) et un score d'adéquation des apports vis-à-vis des recommandations spécifiques de la grossesse (score-grossesse) ont été construits puis mis en relation avec les caractéristiques démographiques et socioéconomiques des femmes à l'aide de régressions linéaires multivariées.

Résultats: Le score-PNNS médian (échelle de 0 à 11) était de 7,8 et le score-grossesse médian (échelle de 0 à 10) était de 7,7. Ces deux scores étaient associés positivement à l'âge de la femme, son niveau d'étude, de revenus et le suivi des cours de préparation à la naissance. Les deux scores étaient également plus élevés chez les femmes nées à l'étranger, primipares et avec un IMC faible.

Conclusion: Ces résultats soulignent l'importance de tenir compte des facteurs démographiques et socioéconomiques pour renforcer la communication autour des messages du PNNS auprès des groupes à risque.

Mots-clés: Apport alimentaire - Femmes enceintes - Cohorte de naissance - Recommandations nutritionnelles

Title

Adherence to PNNS guidelines among pregnant women from the ELFE study

Abstract

Objectives: To assess the adherence of dietary intake to PNNS guidelines among French pregnant women and to identify the main demographic and socioeconomic factors associated.

Methods: From the maternity questionnaire of 14 051 women from the ELFE study, a score of adherence to adult guidelines (PNNS-score) and a score of adherence to guidelines specific to pregnant women (pregnancy-score) were built and related to demographic and socioeconomic characteristics by multivariable linear regressions.

Results: The median PNNS-score (0-11 scale) was 7.8 and the median pregnancy-score (0-10 scale) was 7.7. Both scores were positively associated with woman's age, education level, income and attendance to birth preparation courses. Both scores were higher among women born abroad, primiparous and with low BMI.

Conclusion: These findings highlight the need to take demographic and socioeconomic characteristics into account to enhance communication on PNNS guidelines among at risk groups.

Key words: Food intake – Pregnancy – Birth cohort – Nutritional guidelines

Introduction

De nombreux travaux ont mis en évidence un lien entre l'environnement prénatal et la survenue de pathologies à l'âge adulte. Autrefois appelé « hypothèse de Barker », ce concept est aujourd'hui connu sous le nom d'origine développementale de la santé (DOHaD, Developmental Origins of Health and Diseases). Ainsi, Barker avait montré en 1989 que les enfants nés avec un petit poids de naissance étaient plus souvent atteints de maladies cardiovasculaires, diabète et syndrome métabolique à l'âge adulte (1). D'autres exemples historiques, comme celui de la famine Hollandaise en 1944-45, ont permis de mettre en évidence un lien entre sous-nutrition maternelle durant la grossesse, faible poids de naissance et pathologies à l'âge adulte (2). Baker et Hales avaient émis l'hypothèse selon laquelle une restriction nutritionnelle durant la grossesse engendrerait une réponse adaptative de l'organisme du fœtus, favorisant la croissance des organes nobles (par exemple le cerveau et le rein) aux détriments des autres et pouvant ainsi aboutir à une altération durable du métabolisme. Ces adaptations seraient d'autant plus délétères que l'enfant est soumis à des apports nutritionnels élevés durant la période postnatale (3, 4). La situation inverse, d'un apport calorique excessif pendant la grossesse a également des conséquences pour le développement fœtal et la santé de l'enfant à long terme qui sont largement démontrées pour l'obésité maternelle, le gain de poids gestationnel excessif (5, 6). Les apports en micronutriments ont également leur importance. En particulier, l'apport en acide folique en période périconceptionnelle et en début de grossesse joue un rôle dans la prévention des anomalies de fermeture du tube neural. L'alimentation maternelle apparaît donc comme un élément crucial pour le développement fœtal avec des conséquences sur la santé ultérieure de l'enfant (7).

Initié en 2001, le Programme National Nutrition Santé (PNNS) vise l'amélioration de l'état de santé de la population en agissant sur l'un de ses déterminants majeurs : la nutrition (8). Ce

plan propose 9 repères (8 repères pour les aliments et 1 repère pour l'activité physique) pour la population générale et des repères supplémentaires pour des populations spécifiques, telles que les femmes enceintes. L'étude de l'alimentation des femmes enceintes constitue un enjeu de santé publique car elle permet d'identifier les groupes plus vulnérables pouvant bénéficier d'une information et de conseils plus approfondis. Néanmoins, il n'existe à ce jour aucun état de lieux sur l'alimentation des femmes enceintes en France à une échelle nationale.

A partir des données de l'Etude Longitudinale Française depuis l'Enfance (ELFE), l'objectif de cette analyse était d'évaluer l'adéquation des consommations alimentaires des femmes enceintes vis-à-vis des recommandations du PNNS et d'identifier les principaux facteurs démographiques et socioéconomiques associés à une meilleure ou moins bonne adéquation des consommations alimentaires aux recommandations.

Matériel et méthodes

Présentation de l'étude

L'étude ELFE constitue la première cohorte française de naissance de grande envergure, avec 18 329 enfants recrutés parmi un échantillon aléatoire de 320 maternités de France métropolitaine. Le recrutement des enfants a été mené sur 25 jours répartis sur l'année 2011 en quatre vagues d'enquête. Les nourrissons étaient éligibles lorsqu'ils étaient nés à 33 semaines d'aménorrhée au moins, singletons ou jumeaux et issus d'une mère majeure résidant en France métropolitaine. Les mères ont signé un consentement éclairé et toutes les données collectées ont été anonymisées. L'étude ELFE a été approuvée par le Comité Consultatif pour le Traitement de l'Information pour la Recherche en Santé (CCTIRS) et la Commission Nationale Informatique et Libertés (CNIL). Elle a reçu le label d'intérêt général du Comité National de l'Information Statistique.

Données Recueillies

Alimentation maternelle

Un questionnaire de fréquence alimentaire (QFA), rempli par les femmes à la maternité, a permis d'évaluer l'alimentation des trois derniers mois de la grossesse. Il comprenait 122 items. Les femmes pouvaient répondre parmi sept fréquences allant de « jamais » à « plus d'une fois par jour ». Un manuel photos, issu de l'étude SU.VI.MAX (9), a permis d'estimer les portions consommées pour 77 aliments et des portions standard ont été appliquées pour les 45 aliments restants. Les quantités journalières consommées ont été obtenues pour chaque item en multipliant, pour chaque individu, les fréquences de consommation par la taille de portion. Ensuite, le croisement de ces quantités journalières avec une table de composition nutritionnelle, également issue de l'étude SU.VI.MAX. (10), a permis le calcul des apports nutritionnels journaliers.

Seuls les QFA avec moins de 11 données manquantes ont été considérés comme exploitables. Parmi les questionnaires considérés comme exploitables, les fréquences manquantes pour un item donné ont été remplacées par la fréquence médiane de cet item.

Une enquête de validation a été effectuée par comparaison à trois rappels de 24 heures (un par mois pendant les trois derniers mois de la grossesse) sur un échantillon *ad-hoc* de 62 femmes enceintes. Elle a montré que, selon les groupes d'aliments, 92,9% (pour les viandes) à 100 % (pour le lait) des femmes étaient classées dans le même quintile ou le quintile adjacent par les deux méthodes. L'application des formules d'identification des sur- ou sous-déclarants étant peu adaptée à l'utilisation de QFA, notamment chez les femmes enceintes, il a été décidé d'exclure les femmes avec un apport énergétique hors alcool inférieur au 3ème percentile (933 kcal) ou supérieur au 97ème percentile (5072 kcal).

Un questionnaire additionnel a permis d'évaluer les modifications de consommation de certains groupes d'aliments, tels que les crudités, la viande saignante ou le fromage au lait cru, au cours de la grossesse. Pour chaque groupe d'aliments, les femmes devaient préciser

si pendant la grossesse elles en avaient consommé plus, autant, moins ou si elles n'en avaient jamais consommé même avant la grossesse.

La fréquence de consommation des différents repas et collation hebdomadaire (petit déjeuner, déjeuner, goûter, dîner, et collations entre ces repas) durant les trois derniers mois de la grossesse était mesurée via une échelle à 5 points allant de « jamais » à « tous les jours ou presque ».

Variables démographiques et socioéconomiques

Lors du séjour en maternité, des entretiens ont permis de recueillir des renseignements sur la situation sociodémographique des parents (pays de naissance, niveau d'étude, région d'habitation, statut marital), le déroulement de la surveillance prénatale, la consommation de tabac et la prise de supplément médicamenteux en acide folique. La présence d'un diabète préexistant ou gestationnel et le rang de l'enfant ont été extraits du dossier médical. La situation démographique et socioéconomique des femmes (revenus du foyer) a également été évaluée lors de l'entretien téléphonique qui a eu lieu 2 mois après l'accouchement. Pour ces variables, nous avons utilisé préférentiellement les données du suivi à 2 mois, plus détaillées que celles collectées à la maternité, complétées en cas de donnée manquante par les données de la maternité.

Mesure de l'adéquation aux recommandations

Les recommandations alimentaires du PNNS pour les adultes reposent sur 9 repères quantitatifs (nombre de prises par jour ou quantité par jour). Certaines recommandations ont plusieurs composantes, comme celle correspondant au groupe « Viandes et volailles, produits de la pêche et œufs » qui propose de consommer ce groupe 1 à 2 fois par jour, mais également de consommer du poisson 2 fois par semaine. Pour évaluer le degré d'adéquation des apports vis-à-vis des recommandations nutritionnelles du PNNS pour les adultes, nous avons utilisé le PNNS-GS (Programme National Nutrition Santé Guideline Score), développé par Estaquio et al. en 2009 (11), adapté à population des femmes enceintes (notamment pour l'alcool et les

produits laitiers). Les recommandations pour la consommation d'alcool, les femmes adultes ne doivent pas excéder deux verres d'alcool par jour, alors que pour les femmes enceintes il est recommandé de ne pas boire d'alcool pendant la grossesse. Concernant les produits laitiers, nous ne voulions pas pénaliser les femmes qui avaient une consommation de produits laitiers supérieure à 3,5 portions par jour. En effet dans le score tel qu'établi par Estaquio et collaborateur, entre il y avait une pénalisation d'une consommation excessive de produits laitiers (11). Pour ces deux items nous avons donc modifié les bornes pour une meilleure adéquation avec les recommandations spécifiques aux femmes enceintes. Le score-PNNS ainsi construit repose sur 11 items décrits dans le **Matériel additionnel.** Dans notre étude, nous avons été amenés à modifier ce score pour l'adapter aux données disponibles dans l'étude ELFE et aux spécificités de la grossesse. Tout d'abord, la consommation d'aliments complets n'a pu être évaluée qu'à partir de la consommation de pain, nous avons donc calculé un ratio pain complet sur pain total. De plus, pour les matières grasses ajoutées, cette recommandation a été évaluée seulement par le fait de privilégier les matières grasses d'origine végétale par rapport aux matières grasses d'origine animale. La limitation de matières grasses, qui constitue le deuxième élément de la recommandation sur les matières grasse ajoutées n'a pas pu être prise en compte, car nous ne disposions pas de l'information dans l'étude sur le pourcentage de l'énergie totale apporté par les lipides des matières grasses ajoutées. Notre QFA ne comportant pas de question sur le sel de table, seul le sel contenu dans les aliments ou les plats (quiche, couscous..) figurant dans les tables de consommation alimentaire a été pris en compte. Nous avons également appliqué la méthodologie proposée par Estaquio et collaborateur pour une meilleure prise en compte du sel. En effet, il est estimé que 80% de l'apport alimentaire du sel en France est lié aux aliments contenant du sel. Nous avons ainsi multiplié l'apport calculé grâce au QFA par 1,25 (11, 12). Par ailleurs, notre score-PNNS n'a pas été corrigé pour l'apport énergétique, car il est difficile de déterminer les besoins énergétiques des femmes enceintes. Enfin, nous avons fait le choix de construire un score essentiellement alimentaire, l'item sur l'activité physique n'a donc pas été pris en compte.

Pour évaluer l'adéquation des consommations vis-à-vis des recommandations adressées spécifiquement aux femmes enceintes, nous avons construit un deuxième score, le score-grossesse, dont les 9 items sont décrits dans le **Matériel additionnel**. Pour les recommandations portant sur des nutriments, nous avons utilisé comme borne le besoin nutritionnel moyen (BNM) de la population considérée (13). Dans le cas de l'apport en fer, le BNM utilisé a été celui des femmes adultes (12,32 g/j).

Afin d'obtenir un score très progressif, nous avons appliqué aux deux scores une méthodologie reposant sur le principe du pourcentage de la recommandation atteint par les consommations alimentaires, développée dans le cadre de la cohorte MOBA (14). Ainsi, pour chacun des items, nous avons utilisé la méthode suivante :

- Lorsque la recommandation correspondait à un minimum (par exemple au moins 5 fruits et légumes par jour), un score de 1 point était attribué si la consommation de l'individu était supérieure ou égale à ce minimum. Dans le cas contraire, le score était égal à la consommation de l'individu, divisée par la consommation minimale recommandée (équation 1).
- Lorsque la recommandation correspondait à un maximum (par exemple limiter la consommation de sel à moins de 8 g/j), un score de 1 point était attribué si la consommation de l'individu était inférieure ou égale à ce maximum. Dans le cas contraire, le score était égal à la consommation maximale recommandée, divisée par la consommation de l'individu (équation 2).
- Lorsque la recommandation correspondait à un intervalle (par exemple consommer le groupe d'aliments « viande, volaille, poisson et œufs » 1 à 2 fois par jour), un score de 1 point était attribué si la consommation de l'individu se situait dans cet intervalle. Dans le cas contraire, l'équation 1 était utilisée lorsque la consommation n'atteignait pas la borne inférieure de l'intervalle et l'équation 2 était utilisée lorsque la consommation dépassait la borne supérieure de l'intervalle.

Pour les recommandations concernant les risques infectieux, toxoplasmose et listéria, ainsi que pour la recommandation sur la prise de supplément médicamenteux en acide folique, il ne s'agissait pas de recommandation correspondant à un minimum, un intervalle ou un maximum : nous avons donc attribué un score selon le nombre de recommandations suivies. Les modifications de fréquences de consommation de certains aliments ont pu être prise en compte, pour la toxoplasmose : viande saignante, crudités et pour la listériose viande saignante, charcuterie et fromage au lait cru. Le score toxoplasmose a été calculé uniquement chez les femmes séronégatives en début de grossesse (N=9401).

Le score global correspond ensuite à la somme des scores obtenus pour chacun des items.

Sélection de la population

Les différentes étapes de sélection de la population sont présentées dans la figure 1. Parmi les 17 855 enfants éligibles de la cohorte ELFE, nous avons sélectionné au hasard un seul jumeau en cas de grossesse gémellaire (n=277 exclusions), afin que chaque femme ne soit représentée qu'une seule fois dans l'échantillon. Parmi les 14 950 femmes avec un QFA exploitable, 899 femmes enceintes ont été considérées comme ayant un apport énergétique improbable et retirées des analyses.

Pour les analyses sur les liens entre les variables démographiques ou socioéconomiques et les scores d'adéquation des consommations vis-à-vis des recommandations, nous avons exclu des analyses les sujets avec au moins une donnée manquante sur les variables considérées (**Figure 1**).

Analyses statistique

Les analyses descriptives ont été pondérées afin de tenir compte du plan de sondage stratifié et du biais résultant du refus de participation à l'étude en maternité et de la non-réponse au QFA. La pondération a été calculée, d'une part, par ajustement à partir des variables communes aux consentantes et aux non-consentantes et, d'autre part, par redressement à l'aide d'un calage sur les marges de plusieurs variables (âge, région, statut matrimonial, statut

d'immigré, niveau d'étude et primiparité) à partir de données d'état civil et de l'Enquête Nationale Périnatale 2010 (15).

L'étude des relations entre les scores et les variables démographiques et socioéconomiques a été menée à l'aide de régressions linéaires multiples. Ainsi un modèle de régression a été réalisé pour chacun des scores : score-PNNS et score-grossesse, ajustant simultanément sur l'ensemble des variables démographiques et socioéconomiques étudiées. Des analyses de sensibilité ont été réalisées d'une part en ne faisant pas d'exclusion sur l'apport énergétique et d'autre, part en utilisant les pondérations pour tenir compte des non-réponses. Le seuil de significativité a été fixé à 5%. Toutes les analyses statistiques ont été réalisées à l'aide du logiciel SAS version 9.3 (SAS Institute, Cary, NC).

Résultats

Les caractéristiques des femmes sélectionnées sont présentées dans le **Tableau 1**.

Description du score

Pour les 14051 femmes incluses dans l'analyse, la médiane du score PNNS était de 7,8 (EIQ : étendue interquartile quartile 1 (Q1) à quartile 3 (Q3)) (Q1 :7,0 - Q3 : 8,5) pour un score maximal de 11 points. La distribution du score PNNS est présentée sur **la Figure 2**. La moyenne du score grossesse était de 7,7 (Q1 : 7,2 - Q3 : 8,1) pour un score maximal de 9 points. La distribution du score grossesse est présentée sur la Figure 3.

Les **figures 2 et 3** montrent, pour chaque item des scores, le pourcentage de femmes ayant atteint un score de 1 point (adéquation parfaite) ou ayant un score compris entre 0,75 et 1 point (bonne adéquation). Les items du score-PNNS les mieux suivis correspondaient aux consommations suivantes : « Féculents », « Produits laitiers », « Viandes, poisson, œufs », « Ratio matières grasses végétales/animales», « Sucres ajoutés », « Alcool », « Eau et boisson sucrée » et « Sel ». Les items du score-PNNS pour lesquels moins de 50% des femmes avaient obtenus un score de 0,75 étaient « Fruits et légumes », « Aliments complets » et « Poisson et produits de la mer ».

Les items du score-grossesse pour lesquels 50% des femmes avaient un score supérieur à 0,75 (bonne adéquation) étaient les suivants: apport alimentaires en « Folates », « Calcium », « Fer », « Iode», « Soja », « Café/thé » et « Fréquences des prises alimentaires ». Par ailleurs, 54% des femmes suivaient toutes les recommandations spécifiques pour la listériose et 23% des femmes seulement étaient supplémentées en acide folique avant la grossesse ou au premier trimestre de la grossesse. Parmi les 9401 femmes séronégatives pour la toxoplasmose, 61% suivaient au moins une des deux recommandations spécifiques pour la toxoplasmose (dont 21% suivaient les deux).

Relation entre les scores et les variables démographiques et socioéconomiques

Les deux scores, PNNS et grossesse, étaient plus élevés lorsque les femmes étaient mariées, avec des revenus élevés et un niveau d'étude élevé. Ils étaient également supérieurs pour les femmes n'ayant pas fumé pendant la grossesse et pour celles ayant assisté à un nombre important de cours de préparation à la naissance (Tableau 2).

Certaines caractéristiques étaient liées plus spécifiquement à l'un des deux scores. Le score-PNNS était plus élevé chez les femmes âgées d'au moins 35 ans, nées à l'étranger, vivant dans les régions du sud de la France et pour celles ayant un diabète avant ou pendant la grossesse. Le score-grossesse était, quant à lui, plus faible pour les femmes âgées de moins de 30 ans, obèses avant la grossesse, ayant un grand nombre d'enfants et ayant eu peu de consultations prénatales (Tableau 2).

Les analyses de sensibilité ont montré des résultats similaires.

Discussion

Construction des scores :

Les scores PNNS et grossesse sont des variables de synthèse caractérisant la qualité de l'alimentation et l'adéquation des consommations vis-à-vis des recommandations.

Le score d'adéquation des consommations vis-à-vis des recommandations nutritionnelles du PNNS pour les adultes repose principalement sur le score PNNS-GS, développé dans le cadre de l'étude SU.VI.MAX. (11). Ce score permet une prise en compte de l'alimentation dans sa globalité au lieu de se focaliser sur des nutriments ou des groupes d'aliments particuliers. Ce score global a déjà été utilisé dans plusieurs études pour caractériser l'alimentation de la population générale et en comprendre les déterminants facteurs associés démographiques et socioéconomiques (11, 16-25). Il a également permis de mettre en évidence que les personnes qui suivaient le mieux les recommandations du PNNS étaient moins à risque de développer un surpoids au cours de six ans de suivi (19).

Lors de la création du score-grossesse, nous avons utilisés le BNM pour considérer un apport comme adéquat ou non. En effet, il a été montré, au niveau d'une population que ce seuil était celui qui biaisait le moins la prévalence de l'inadéquation des apports (13). Pour évaluer l'adéquation des apports en fer, nous avons utilisé le BNM des femmes adultes et non celui des femmes enceintes. En effet, les apports nutritionnels conseillés en fer pendant la grossesse sont identiques à ceux des femmes en âge de procréer au Royaume-Uni (26), dans les pays nordiques (27), en Allemagne (28) et selon l'OMS (29), alors qu'ils sont multipliés par 1,5 ou 2 aux Etats-Unis, au Canada (30) et en France. Bien que nous ayons retenu ce seuil minimal, seules 51,9% des femmes de l'étude ELFE avaient un apport en fer considéré comme adéquat. Une prise de supplément médicamenteux en fer peut être proposée en fonction des résultats de la numération formule sanguine réalisée en début de grossesse et au 6ème mois (31-33). Par ailleurs, bien qu'il existe une recommandation pour l'apport en vitamine D chez les femmes enceintes, il n'était pas possible de l'intégrer dans notre score car l'apport lié à l'exposition solaire et le statut de biologique des femmes n'étaient pas des informations disponibles dans ELFE.

L'estimation des apports alimentaires à partir d'un questionnaire de fréquence ne permet pas une estimation précise. Les chiffres d'adéquation des consommations selon les différents critères évalués qui reposent sur une estimation des apports ne doivent donc pas être considérés dans l'absolu mais plutôt en relatif pour comparer les femmes enceintes de l'étude ELFE entre elles et évaluer si les tendances observées sont similaires avec d'autres études ayant adopté la même méthodologie. Le QFA de l'étude ELFE a été rempli à la maternité et portait sur les trois derniers mois de la grossesse : il n'est donc pas représentatif des consommations sur l'ensemble de la grossesse. De plus, les besoins énergétiques des femmes enceintes étant difficiles à évaluer, nous avons choisi de ne pas effectuer de pénalisation des scores pour des apports énergétiques trop élevés. Par ailleurs, pour les recommandations de nature toxicologique, notre questionnaire ne permettait pas d'évaluer complétement la suppression de certains aliments du régime alimentaire mais uniquement la

diminution de leur consommation depuis le début de la grossesse, ce qui a pu conduire à une surestimation du respect de ces recommandations. L'étude de validation du QFA a été réalisée uniquement sur trois rappels des 24 heures. Il n'y a pas eu de dosage de biomarqueurs. Enfin, au lieu de déterminer des bornes pour définir un score de 0,5 ou de 1 point pour chaque item, nous avons choisi d'utiliser un pourcentage d'adéquation des consommations à chacune des recommandations, en faisant l'hypothèse que ce choix nous permettait une analyse plus fine de l'adéquation des apports de la population aux recommandations. Cependant, cette méthode présente une limite importante car lorsque la recommandation correspond à un maximum et que la consommation est beaucoup plus importante que celle préconisée il est quasiment impossible d'obtenir un score de 0. De même, lorsque la recommandation correspond à un minimum on n'obtient pas plus de points si on consomme six fruit et légumes par jour que si on en consomme dix.

Quelles femmes enceintes suivent le mieux les recommandations nutritionnelles en France ?

A notre connaissance, il n'existe aucun état des lieux de l'alimentation des femmes enceintes en France. Cette première étude permet d'apporter des éléments d'évaluation des risques alimentaires et nutritionnels et de mieux comprendre les facteurs démographiques et socioéconomiques associés aux comportements nutritionnels des femmes enceintes, ce qui pourrait permettre l'orientation des programmes nationaux de prévention et d'éducation à la santé.

Plusieurs facteurs étaient associés de manière identique aux scores grossesse et PNNS comme des variables démographiques et socioéconomiques (âge, éducation, revenu) ou des comportements liés aux préoccupations de santé (tabac, préparation à la naissance). Certains facteurs étaient associés spécifiquement au score-PNNS, traduisant vraisemblablement les habitudes culturelles et les traditions culinaires (région, pays de naissance). Enfin, d'autres facteurs étaient associés spécifiquement au score-grossesse résumant l'exposition et

l'attention portée aux recommandations (nombre d'enfants, nombre de consultations prénatales). Certaines données de la littérature montrent que les femmes nullipares ont des meilleurs scores alimentaires durant la grossesse que les femmes multipares (34-37). Dans nos analyses nous retrouvons un effet inverse, plus les femmes ont d'enfants plus le score-PNNS est élevé, cette relation peut être dû à la population d'étude, qui a un niveau d'études élevé par rapport à la population générale. Néanmoins, nos analyses tiennent compte du niveau d'études des femmes. Une autre interprétation possible serait l'amélioration de la qualité nutritionnelle par la présence des enfants dans le foyer. En effet les mères ayant déjà un ou plusieurs enfants pourraient modifier leurs habitudes alimentaires pour respecter davantage les recommandations dès lors qu'elles ont des enfants. Ainsi elles pourraient faire bénéficier à leurs enfants d'une alimentation plus saine et leurs inculquer de meilleures habitudes alimentaires. Cet effet a également été retrouvé dans d'autres études sur les déterminants de la qualité nutritionnelles de l'alimentation des femmes enceintes aux Canada (38, 39). L'effet de l'âge de la femme à l'accouchement sur la qualité de l'alimentation est dans notre étude cohérent avec les données de la littérature, les femmes les plus jeunes ayant des score-PNNS et score-grossesse plus faibles que les femmes plus âgées (34, 40).

Il a été montré en 2006 que les femmes en âge de procréer ne constituait pas un groupe particulièrement à risque d'inadéquation des apports en calcium en France (41). Ce rapport est en accord avec nos résultats qui montrent que la recommandation sur les apports en calcium est satisfaite pour une large majorité des femmes enceintes de notre étude.

La prise de supplément médicamenteux en acide folique permet de réduire le risque d'anomalies de fermeture du tube neural (par exemple : spina-bifida, anencéphalie). Les recommandations varient selon les pays européens mais la plupart préconisent une prise de supplément médicamenteux en période périconceptionnelle et au 1er trimestre de la grossesse (42). Dans notre population, l'adéquation à cette recommandation reste faible. En effet, si 42,4% des femmes ont reçu un supplément médicamenteux en acide folique au cours de la grossesse, seules 23% ont été supplémentée durant la période recommandée.

Comparaison à d'autres études étrangères

Un autre indice de qualité du régime alimentaire des femmes enceintes, le DQI-P (Diet Quality Index for Pregnancy) a été développé dans l'étude de cohorte PIN (Pregnancy, Infection and Nutrition) menée en Caroline du Nord aux Etats-Unis (34). Un score élevé pour cet indice de qualité était positivement associé à l'âge des femmes, à leur niveau d'études et de revenus, ainsi qu'à la primiparité (34). Des relations similaires entre caractéristiques des femmes et qualité de l'alimentation pendant la grossesse ont été mis en évidence en Norvège (14, 43) et en Espagne (44).

La cohorte ALSWH (Australian Longitudinal Study on Women's Health), portant notamment sur la qualité de l'alimentation des femmes australiennes (N= 7486) en 2003, montrait que les femmes enceintes ne respectaient pas l'ensemble des recommandations. A partir des données d'un QFA validé, ils ont construit un score de respect des recommandations alimentaires australiennes ARFS (Australian Recommended Food Score) et ainsi montré que pour les folates, le fer et les fibres alimentaires, les niveaux requis n'étaient pas atteints (45). Ils ont également montré que les deux items ayant les plus faibles scores étaient la consommation de protéines (particulièrement de poisson) et de céréales. Ces résultats sont assez similaires aux nôtres dans la mesure où nous observons également une consommation insuffisante de « poissons et de produits de la mer ».

Dans l'étude espagnole INMA-Valencia (acronyme espagnol pour Enfance et Environnement), un QFA portant sur l'alimentation au cours du 1er trimestre de grossesse a été rempli par 822 femmes. Les auteurs ont pu montrer que 76,6% de femmes n'atteignaient pas les recommandations alimentaires pour la consommation de féculents. Les groupes d'aliments pour lesquels les recommandations étaient les mieux suivies étaient : les viandes-volailles-poissons-œufs, fruits, légumes, et les boissons non alcooliques peu sucrées avec respectivement 69,8%, 52,1%, 53,8% et 88,4% des femmes dont les consommations atteignaient les recommandations (44). Concernant la prise d'un supplément médicamenteux en acide folique, nos résultats sont très différents de ceux observés dans la cohorte INMA,

dans laquelle la prise d'un supplément médicamenteux en acide folique concernait plus de 90% des femmes au premier trimestre de grossesse (44). Cette différence pourrait être liée à une différence de prescription de l'acide folique entre ces deux pays ou à une différence culturelle dans la planification de la grossesse.

Conclusion

Cette étude apporte des éléments de compréhension des habitudes alimentaires des femmes enceintes vivant en France. Elle permet de mettre en avant les facteurs associés à une bonne adéquation des consommations avec les recommandations du PNNS et pourrait ainsi permettre de renforcer la communication autour des messages du PNNS auprès des femmes les plus jeunes et les moins éduquées mais aussi des femmes multipares.

Au-delà de cet enjeu opérationnel, le travail méthodologique de construction de scores présente une vocation plus large : les scores PNNS et Grossesse pourront être utilisés comme variables de caractérisation de la qualité de l'alimentation maternelle dans d'autres analyses. Ces scores pourront permettre d'analyser les relations entre alimentation maternelle et croissance fœtale et développement de l'enfant.

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Tableaux et figures

Figure 1: Diagramme de flux

Figure 2 : Descriptif de l'adéquation des consommations alimentaires de femmes enceintes * au regard des différentes recommandations PNNS à destination de la population adulte, Nuancier de gris : pourcentage des femmes qui atteignent un score= 1, score [0,75 – 1[, score [0,5 – 0,75[et score< 0,5 pour l'item considéré, * l'item sel ne tient compte que du sel contenu dans les aliments ou les plats (quiche, couscous..) figurant dans les tables de consommation alimentaire

Figure 3 : Descriptif de l'adéquation des consommations alimentaires de femmes enceintes au regard des différentes recommandations PNNS spécifique à la grossesse à destination des femmes enceintes, Nuancier de gris: pourcentage des femmes qui atteignent un score= 1 score [0,75 – 1[, score [0,5 – 0,75[et score< 0,5 pour l'item considéré

Matériel additionnel : Recommandation PNNS à destination de la population adulte et construction du score-PNNS

Repère PNNS	**Recommandation**	**Seuil pour un score de 1 point**
Fruits et légumes	Augmenter la consommation de fruits et légumes, quelles qu'en soient les formes (crus, cuits, nature, préparés, frais, surgelés ou en conserve) pour atteindre une consommation d'au moins 5 fruits et légumes par jour	Fréquence de consommation ≥5 /jour
Féculents	Augmenter la consommation des féculents sources d'amidon, notamment des aliments céréaliers (et particulièrement des aliments céréaliers complets qui ont l'intérêt d'apporter des quantités appréciables de fibres), des pommes de terre, des légumineuses, etc. ; ils doivent être présents à chaque repas	Fréquence de consommation entre 3 et 6 par jour
Aliments complets		Ratio quantité pain complet / pain total ≥2/3
Lait et produits laitiers	Consommer des aliments sources de calcium (essentiellement les produits laitiers et, en complément, les légumes voire les eaux minérales riches en calcium pour les consommateurs d'eaux minérales) en quantité suffisante pour atteindre les apports conseillés, soit 3 produits laitiers par jour	Fréquence de consommation ≥3 /jour
Viandes, volailles, œufs	Consommer de la viande, du poisson et d'autres produits de la pêche ou des œufs 1 à 2 fois par jour en alternance (en quantité inférieure à l'accompagnement), en privilégiant pour les viandes les morceaux les moins gras et en favorisant la consommation de poisson (au moins deux fois par semaine)	Fréquence de consommation des viandes/volailles/œufs/poisson entre 1 et 2 par jour
Produits de la pêche		Fréquence de consommation des produits de la pêche ≥2 /semaine
Matière grasse ajoutées	Pour un meilleur équilibre, privilégiez les matières grasses végétales	Pas d'utilisation de MG[a] ajoutées ou ratio MGV[b]/ (MGV+MGA[c]) ≥0,5

Produits sucrées	Limiter la consommation de sucre et d'aliments riches en sucre (sodas, confiserie, chocolat, pâtisseries, desserts sucrés, etc.)	Apport énergie provenant des aliments riches en sucre ≤10% de l'apport énergétique total
Alcool	L'alcool est un toxique et il n'y a aucune dose limite connue actuellement pour fixer un seuil de risque pour le développement neurologique de votre enfant. Quel qu'il soit (vin, bière, alcool fort), l'alcool constitue un danger pour l'enfant que vous attendez. Il convient donc d'éviter toute boisson alcoolisée pendant la grossesse.	Aucune consommation d'alcool pendant la grossesse
Boissons	Pour se désaltérer, l'eau est la seule boisson indispensable ; de plus, c'est la moins chère. Il faudrait en boire au moins un litre et demi par jour, pendant et entre les repas, telle quelle ou sous forme de boissons chaudes (thé, tisane, infusion…). Si vous êtes amateur de sodas ou de boissons sucrées, essayez de vous contenter d'un verre par jour, voire deux ou trois à l'occasion d'une soirée.	Consommation d'eau ≥1l/jour et consommation de boissons sucrées ≤250ml/jour
Sel des aliments (hors sel ajouté)	Pour atteindre les objectifs nutritionnels du PNNS, il faut également limiter la consommation de sel et toujours préférer le sel iodé	Quantité de sel (reconstituée à partir de l'apport en sodium) ≤8g/jour

[a]MG : Matière Grasse, [b]MGV : Matière Grasse d'origine végétale, [c]MGA : Matière Grasse d'origine Animale

Matériel additionnel: Conseils nutritionnels adressés spécifiquement aux femmes enceintes dans le cadre du PNNS et construction du score-grossesse

Repère PNNS-Grossesse	Recommandation	Seuil pour un score de 1 point
Folates	Vous savez que les fruits et légumes sont importants pour leurs apports en vitamines, minéraux et fibres. Avant même que vous soyez enceinte, ils vous apportent, ainsi que d'autres aliments, des folates qui joueront un rôle très important dans le développement du système nerveux de l'embryon. Une alimentation variée apporte normalement suffisamment de folates.	Apport en folates ≥308 mg/j
Supplément médicamenteux en acide folique	Par précaution, votre médecin ou votre sage-femme vous prescriront un supplément médicamenteux de folates, dès votre projet de grossesse et pendant les premières semaines de votre grossesse.	Supplémentation en période périconceptionnelle ou au 1er trimestre de grossesse
Calcium	Vous savez qu'il est important d'avoir des apports suffisants en calcium pour la « santé » de ses os. Cela est particulièrement important au moment de la grossesse (et pendant l'allaitement), pour assurer à la fois votre santé et la construction du squelette de votre bébé. Le calcium est apporté par l'alimentation, essentiellement par le lait et les produits laitiers. Pour assurer vos besoins et ceux de votre enfant, consommez 3 produits laitiers par jour, à varier : lait, yaourts, fromage blanc, fromage...	Apport en calcium ≥770 mg
Fer	Même si vos besoins en fer augmentent pendant la grossesse, ils sont normalement couverts par votre alimentation si elle est proche des repères de ce guide	Apport en fer ≥12,32 mg

Iode	L'iode joue un rôle essentiel pour le bon fonctionnement de votre glande thyroïde et le développement du cerveau de votre enfant. Vos besoins augmentent pendant la grossesse.	Apport en iode ≥ 154 µg
Soja et produits à base de soja	Ils contiennent des phyto-estrogènes. Des expériences chez l'animal montrent qu'ils peuvent avoir des effets indésirables sur les petits. Cela n'a pas été observé jusqu'à présent chez l'humain mais, par prudence, il est recommandé pendant la grossesse : - d'éviter de consommer des compléments alimentaires contenant des extraits de soja ; - de limiter les aliments à base de soja (par exemple, tonyu ou jus de soja, tofu, desserts à base de soja) : pas plus d'un par jour.	Fréquence des produits à base de soja <1/j
Café/thé	Aucun effet néfaste pendant la grossesse n'est à mettre sur le compte de la caféine, mais il est toutefois déconseillé de consommer plus de 3 tasses de café par jour	Fréquence du café/thé <3/j
Alimentation	Mangez plus souvent dans la journée, mais sans manger plus, au total : trois petits repas, un goûter plus une ou deux collations.	Fréquence des prises alimentaires ≥4/j
Listériose	Pendant votre grossesse, il est donc recommandé d'éviter : - les fromages à pâte molle à croûte fleurie (type camembert, brie) et à croûte lavée (type munster, pont-l'évêque), surtout s'ils sont au lait cru ; les fromages râpés industriels. Enlevez la croûte de tous les fromages ; - certains produits de charcuterie, notamment rillettes, pâtés, foie gras, produits en gelée ; - la viande crue ou peu cuite, les coquillages crus, le poisson cru (sushi, sashimi, tarama), les poissons fumés (saumon, truite), et les crustacés décortiqués vendus cuits.	Score en fonction du nombre de recommandations dont les consommations sont adéquates: - diminution de la consommation de fromages au lait cru - diminution de la consommation de charcuterie - diminution de la consommation de viande saignante ou crue

Toxoplasmose	Si vous n'êtes pas protégée de la toxoplasmose : - ne mangez pas de viande crue ou de la viande peu cuite ; - évitez les viandes fumées ou marinées (gibier) sauf si elles sont bien cuites ; - lavez très soigneusement les légumes, fruits et herbes aromatiques, afin de leur ôter tout résidu de terre. N'en mangez pas si vous ne savez pas comment ils ont été lavés.	Score en fonction du nombre de recommandations dont les consommations sont adéquates: - diminution de la consommation de viande saignante ou crue - diminution de la consommation de crudités, légumes crus

Tableau 1 : Caractéristiques de la population

		N (%*)
Age Maternel	Moins 25 ans	1520 (14,1)
	25-29 ans	4375 (31,2)
	30-34 ans	5154 (33,4)
	35 ans et plus	3002 (21,3)
Niveau d'étude de la mère	Au plus primaire	51 (0,90)
	Collège	401 (6,44)
	CAP/BEP	1818 (18,7)
	Lycée général	1035 (8,10)
	Lycée technique	1779 (12,2)
	Etudes sup.	8940 (53,7)
Pays de naissance	France	12689 (82,1)
	Etranger	1355 (17,9)
Statut marital	Mariée	6321 (43,4)
	Pacsée	2233 (13,1)
	Cohabitation	4866 (36,7)
	Seule	579 (6,81)
Région	Région parisienne	2344 (21,4)
	Nord	1317 (7,15)
	Est	1429 (7,90)
	Bassin Parisien est	1214 (8,14)
	Bassin Parisien ouest	1235 (9,56)
	Ouest	2090 (13,1)
	Sud-Ouest	1144 (7,66)
	Centre-Est	1604 (10,7)
	Méditerranée	1674 (11,4)
Revenu du foyer	<1501 euros/mois	1033 (12,6)
	1501-2300 euros/mois	1876 (17,7)
	2301-3000 euros/mois	3619 (27,9)
	3001-4000 euros/mois	3484 (24,7)
	4001-5000 euros/mois	1411 (9,61)
	>5000 euros/mois	1140 (7,47)
IMC avant grossesse	<18.5 kg/m2	1033 (7,80)
	18.5-24.9 kg/m2	9117 (63,3)
	25-29.9 kg/m2	2391 (18,1)
	30 kg/m2 et plus	1369 (10,8)
Consommation de tabac pendant la grossesse	Non fumeuse	7897 (56,9)
	Fumeuse avant grossesse	3361 (21,2)
	Fumeuse avant 3^{e} trimestre	549 (4,19)
	Fumeuse pdt 3^{e} trimestre	2199 (17,7)
Sérologie toxoplasmose	Non immunisée	9043 (65,3)
	Immunisée	4650 (33,9)

IGM+ seul ou spécifique	83 (0,57)
Séroconversion suspecté ou documentée	30 (0,20)

*Pourcentage pondéré estimé à partir des 14051 femmes avec un questionnaire de fréquence alimentaire valide

Tableau 2 : Associations entre les variables sociodémographiques ou paramètres de santé des femmes et les scores d'adhésion aux recommandations nutritionnelles à destination des adultes ou spécifiques de la grossesse, régressions linéaires multiples (n=11820)

	Score PNNS N=11820		Score Grossesse N=11820	
	β (IC 95%)	P	β(IC 95%)	P
Age maternel		<0,0001		<0,0001
Moins de 25 ans	**-0,36 (-0,43 ; -0,28)**		**-0,17 (-0,22 ; -0,12)**	
25-29 ans	**-0,12 (-0,17 ; -0,07)**		**-0,06 (-0,09 ; -0,03)**	
30-34 ans	0 (REF)		0 (REF)	
35 ans et plus	**0,15 (0,10 ; 0,21)**		0,01 (-0,03 ; 0,05)	
Pays de naissance		<.0001		0,33
France	0 (REF)		0 (REF)	
Etranger	**0,24 (0,17 ; 0,31)**		0,02 (-0,02 ; 0,07)	
Niveau d'étude		<.0001		<.0001
Au plus primaire	-0,26 (-0,62 ; 0,09)		-0,05 (-0,30 ; 0,20)	
Collège	**-0,26 (-0,40 ; -0,13)**		**-0,17 (-0,26 ; -0,07)**	
CAP/BEP	**-0,22 (-0,29 ; -0,15)**		**-0,14 (-0,18 ; -0,09)**	
Lycée général	**-0,11 (-0,19 ; -0,04)**		**-0,09 (-0,14 ; -0,03)**	
Lycée technique	**-0,19 (-0,26 ; -0,13)**		**-0,13 (-0,18 ; -0,09)**	
Etudes sup	0 (REF)		0 (REF)	
Revenus du foyer		0,002		0,02
<1501 euros/mois	-0,07 (-0,15 ; 0,01)		-0,05 (-0,08 ; 0,04)	
1501-2300 euros/mois	-0,01 (-0,07 ; 0,06)		-0,01 (-0,06 ; 0,03)	
2301-3000 euros/mois	0 (REF)		0 (REF)	
3001-4000 euros/mois	0,03 (-0,02 ; 0,08)		0,03 (-0,01 ; 0,06)	
4001-5000 euros/mois	**0,08 (0,02 ; 0,15)**		0,03 (-0,02 ; 0,08)	
>5000 euros/mois	**0,13 (0,05 ; 0,21)**		**0,07 (0,02 ; 0,12)**	
Région		<.0001		0,05
Région parisienne	0 (REF)		0 (REF)	
Nord	-0,03 (-0,11 ; 0,05)		-0,02 (-0,08 ; 0,04)	
Est	0,02 (-0,05 ; 0,10)		0,02 (-0,03 ; 0,07)	
Bassin Parisien est	0,03 (-0,05 ; 0,11)		-0,02 (-0,08 ; 0,04)	
Bassin Parisien ouest	**0,08 (0,01 ; 0,16)**		**-0,06 (-0,11 ; 0,00)**	
Ouest	**0,13 (0,06 ; 0,20)**		0,02 (-0,02 ; 0,07)	
Sud-Ouest	**0,18 (0,10 ; 0,26)**		0,00 (-0,05 ; 0,06)	
Sud-Est	**0,12 (0,05 ; 0,20)**		-0,01 (-0,06 ; 0,04)	
Méditerranée	**0,20 (0,12 ; 0,27)**		-0,05(-0,10 ; 0,00)	
Statut Matrimonial		0,005		<.0001
Mariée	0 (REF)		0 (REF)	
Pacsée	-0,01 (-0,06 ; 0,05)		0,02 (-0,02 ; 0,06)	
Cohabitation	**-0,08 (-0,12 ; -0,03)**		**-0,05 (-0,08 ; -0,01)**	
Seule	-0,10 (-0,21 ; 0,02)		**-0,14 (-0,22 ; -0,06)**	
Rang de l'enfant		0,14		<.0001
Un	0 (REF)		0 (REF)	
Deux	**0,05 (0,00 ; 0,10)**		**-0,06 (-0,09 ; -0,02)**	
Trois	**0,07 (0,00 ; 0,14)**		**-0,09 (-0,13 ; -0,04)**	

Quatre et plus	0,04 (-0,06 ; 0,14)		**-0,15 (-0,22 ; -0,08)**	
Tabagisme maternel pendant la grossesse		<.0001		<.0001
Non fumeuse	0 (REF)		0 (REF)	
Fumeuse avant grossesse	**-0,13 (-0,18 ; -0,09)**		0,02 (-0,02 ; 0,05)	
Fumeuse avant 3e tri.	**-0,17 (-0,27 ; 0,07)**		**-0,08 (-0,15 ; -0,02)**	
Fumeuse pendant 3e tri.	**-0,37 (-0,42 ; 0,31)**		**-0,09 (-0,13 ; -0,05)**	
IMC avant grossesse		0,38		<.0001
<18.5 kg/m2	-0,04 (-0,12 ; 0,03)		0,03 (-0,02 ; 0,08)	
18.5-24.9 kg/m2	0 (REF)		0 (REF)	
25-29.9 kg/m2	-0,04 (-0,09 ; 0,01)		**-0,07 (-0,11 ; -0,03)**	
30 kg/m2 et plus	-0,01 (-0,07 ; 0,06)		**-0,14 (-0,19 ; -0,09)**	
Diabète		<.0001		0,24
Non	0 (REF)		0 (REF)	
Diabète préexistant	**0,66 (0,46 ; 0,86)**		0,07 (-0,07 ; 0,21)	
Diabète gestationnel	**0,40 (0,33 ; 0,46)**		0,03 (-0,01 ; 0,08)	
Nombre de consultations prénatales		0,01		<.0001
0-5 consultations	-0,11 (-0,22 ; 0,01)		**-0,12 (-0,20 ; -0,04)**	
6-9 consultations	0 (REF)		0 (REF)	
10-14 consultations	0,04 (0,00 ; 0,09)		**0,05 (0,02 ; 0,09)**	
15 consultations et plus	0,10 (0,00 ; 0,20)		**0,08 (0,01 ; 0,15)**	
Nombre de séances de préparation à la naissance		<.0001		<.0001
Aucune séance	0 (REF)		0 (REF)	
1-2 séances	**0,17 (0,08 ; 0,27)**		**0,10 (0,04 ; 0,17)**	
3-5 séances	**0,08 (0,02 ; 0,14)**		**0,11 (0,07 ; 0,15)**	
6-9 séances	**0,15 (0,10 ; 0,21)**		**0,17 (0,14 ; 0,21)**	
10 séances et plus	**0,25 (0,10 ; 0,39)**		**0,21 (0,11 ; 0,31)**	

Appendix 5: Paper III- Dietary acrylamide intake during pregnancy and postnatal growth and obesity: results from the Norwegian Mother and Child Cohort Study (MoBa)

Manuscript Details

Manuscript number	ENVINT_2017_1325
Title	Dietary acrylamide intake during pregnancy and postnatal growth and obesity: results from the Norwegian Mother and Child Cohort Study (MoBa)
Article type	Research Paper

Abstract

Background: Prenatal acrylamide exposure has been negatively associated with fetal growth but the association with child growth is unknown. Objectives: We studied the association between prenatal acrylamide exposure and child postnatal growth up to 8 years in the Norwegian Mother and Child Cohort Study (MoBa). Methods: In 51,952 mother-child pairs from MoBa, acrylamide intake during pregnancy was estimated by combining maternal food intake with food concentrations of acrylamide. Mothers reported their child's weight and length/height up to 11 times between 6 weeks and 8 years. Weight and height growth trajectories were modelled using Jenss-Bayley's growth model. Logistic regression models were used to study the association with overweight/obese status at 3, 5 and 8 years, as identified using the International Obesity Task Force cut-offs. Linear mixed-effect models were used to explore associations with overall growth. Results: At 3 years, the adjusted odds ratios (95% Confidence Intervals (CI)) of being overweight/obese were 1.10 (1.02 – 1.20), 1.12 (1.04 – 1.22) and 1.21 (1.11 – 1.31) by increasing prenatal acrylamide exposure quartile. Similar dose-response associations were found at 5 and 8 years. Acrylamide intake during pregnancy was associated with higher weight growth velocity in childhood. Children exposed at the highest level had 22g (95%CI: 8 – 37), 57g (95%CI: 32 – 81), and 194g (95%CI: 110 – 278) higher weight at 0.5, 2, and 8 years, respectively, compared to their low exposed peers. Conclusions: Children prenatally exposed to acrylamide in the highest quartile experienced higher weight growth velocity during early childhood that resulted in an increased prevalence of overweight/obesity compared to peers in the lowest quartile. Our study is the first to link prenatal acrylamide exposure and postnatal growth.

Keywords	Acrylamide, pregnancy, postnatal growth, obesity, MoBa
Taxonomy	Dietary Exposure, Child Obesity, Acrylamide, Pregnancy

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Highlights (3 to 5, 85 characters including spaces)

- Prenatal dietary acrylamide exposure was assessed combining FFQ and contamination data
- Prenatally exposed children were more likely to be overweight or obese
- Prenatally exposed children were more likely to have higher weight growth velocity
- First study on prenatal dietary exposure and postnatal growth that need replication

Title: Dietary acrylamide intake during pregnancy and postnatal growth and obesity: results from the Norwegian Mother and Child Cohort Study (MoBa)

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Abstract

Background: Prenatal acrylamide exposure has been negatively associated with fetal growth but the association with child growth is unknown.

Objectives: We studied the association between prenatal acrylamide exposure and child postnatal growth up to 8 years in the Norwegian Mother and Child Cohort Study (MoBa).

Methods: In 51,952 mother-child pairs from MoBa, acrylamide intake during pregnancy was estimated by combining maternal food intake with food concentrations of acrylamide. Mothers reported their child's weight and length/height up to 11 times between 6 weeks and 8 years. Weight and height growth trajectories were modelled using Jenss-Bayley's growth model. Logistic regression models were used to study the association with overweight/obese status at 3, 5 and 8 years, as identified using the International Obesity Task Force cut-offs. Linear mixed-effect models were used to explore associations with overall growth.

Results: At 3 years, the adjusted odds ratios (95% Confidence Intervals (CI)) of being overweight/obese were 1.10 (1.02 – 1.20), 1.12 (1.04 – 1.22) and 1.21 (1.11 – 1.31) by increasing prenatal acrylamide exposure quartile. Similar dose-response associations were found at 5 and 8 years. Acrylamide intake during pregnancy was associated with higher weight growth velocity in childhood. Children exposed at the highest level had 22g (95%CI: 8 – 37), 57g (95%CI: 32 – 81), and 194g (95%CI: 110 – 278) higher weight at 0.5, 2, and 8 years, respectively, compared to their low exposed peers.

Conclusions: Children prenatally exposed to acrylamide in the highest quartile experienced higher weight growth velocity during early childhood that resulted in an increased prevalence of overweight/obesity compared to peers in the lowest quartile. Our study is the first to link prenatal acrylamide exposure and postnatal growth.

Keywords: Acrylamide, pregnancy, postnatal growth, obesity, MoBa

1. Introduction

Childhood obesity is a large public health challenge worldwide (de Onis and others 2010). The major risk factors for obesity are poor nutrition and lack of physical activity. New evidence suggests that exposure to obesogenic chemicals, i.e. chemicals that alter adipogenesis or metabolism, could play a role in obesity development (Heindel and others 2015; Tang-Peronard and others 2011). The fetuses and infants may be especially sensitive to exposure to obesogens, even in low concentrations, due to their immature detoxification pathways and developmental plasticity (Janesick and Blumberg 2012).

Acrylamide is a colourless, odourless, low molecular weight, highly water-soluble organic compound. Acrylamide does not occur naturally and has been industrially produced since the 1950s for various uses, including water and wastewater treatment, as gels in laboratories or in grout for tiling. More recently, it was found that acrylamide can form as a byproduct during the heating of starch-rich foods at high temperatures (>200 °C), by the Maillard reaction between asparagine and a sugar molecule (Dybing and Sanner 2003; Tareke and others 2002). In occupationally exposed populations, the main routes of acrylamide exposure are inhalation and dermal absorption, while, in non-occupationally exposed populations, diet is the main source of exposure for non-smokers (Vikstrom and others 2012). Acrylamide is also found in cigarette smoke, and smoking can contribute extensively to acrylamide exposure (Mojska and others 2016). According to the Scientific Opinion by the European Food Safety Authority (EFSA), based on data from 24 European countries and approximately 43,000 acrylamide concentrations in foods, the main sources of exposure to adults are fried potatoes, bread, breakfast cereals, biscuits, crackers, crispbread and coffee, and the average exposure was 0.4 µg/kg body weight/day (EFSA 2015). After ingestion, acrylamide is extensively absorbed from the gastrointestinal tract, and after reaching the systemic circulation, it is rapidly distributed

into the tissues. Acrylamide is a known neurotoxicant (Ferguson and others 2010; IARC 1994) and can exert reproductive and developmental toxicity effects (Yilmaz and others 2016). It is classified as “probably carcinogenic” in humans (group 2A) by the International Agency for Research on Cancer (IARC 1994). In the body, a significant fraction of ingested acrylamide is converted metabolically to the chemically reactive and genotoxic epoxide, glycidamide (Sweeney and others 2010). Glycidamide is likely to play an important role in the carcinogenicity of acrylamide (Hogervorst and others 2010).

During pregnancy, 10-50% of dietary acrylamide is transferred via blood through the placenta to the fetus (Annola and others 2008; Sorgel and others 2002). Three epidemiological studies have shown a negative association between prenatal acrylamide exposure and birth weight or height or increased risk of having a small for gestational age (SGA) newborn (Duarte-Salles and others 2013; Kadawathagedara and others 2016; Pedersen and others 2012). Taking into consideration the scarce epidemiological evidence, the CONTAM panel (Contaminant in the Food Chain) of EFSA recommended that further epidemiological studies should be conducted to confirm or refute the inverse relationship between dietary acrylamide intake and impaired fetal growth (EFSA 2015).

Several epidemiological studies indicated that small size at birth is a risk factor for a range of metabolic disorders, including higher body mass index (BMI) in adulthood, insulin resistance, increased visceral adiposity and impaired glucose tolerance (Barker 1998; Calkins and Devaskar 2011; Gluckman and others 2008; Stout and others 2015). However, there is no epidemiological evidence on the association between prenatal exposure to acrylamide and postnatal growth.

The aim of the present study was to investigate the association between maternal dietary acrylamide intake during pregnancy and child’s postnatal growth up to 8 years in a large

97 population-based cohort study in Norway, the Norwegian Mother and Child Cohort Study
98 (MoBa).
99
100 **2. Material and methods**
101 **2.1 Study population**
102 Our study was conducted within MoBa, which is a prospective population-based pregnancy
103 cohort study conducted by the Norwegian Institute of Public Health (Magnus and others
104 2016). In brief, participants were recruited from all over Norway during their 1st ultrasound
105 visit (17-18th gestational week) from 1999 to 2008. The women consented to participation in
106 40.6% of the pregnancies. MoBa now encompasses 114,500 children, 95,200 mothers and
107 75,200 fathers. Data used in this study are based on version 9 of the quality-assured data files,
108 released for research in November 2015. All MoBa participants provided written informed
109 consent before enrollment into the study.
110 The data included 80,453 women with singleton, live born babies without malformations
111 and chromosomal anomalies and available acrylamide intake estimates. After excluding
112 mother-child pairs with missing information on parity (no missing), maternal age (no missing),
113 maternal education (3% missing), pre-pregnancy BMI (3% missing), gestational weight gain
114 (18% missing), maternal active (1% missing) and passive (1% missing) smoking during
115 pregnancy, maternal alcohol consumption during pregnancy (14% missing), implausible
116 energy intake (i.e. <4.5 MJ and >20 MJ, 2% excluded), paternal weight (5% missing),
117 gestational age (0.4% missing), child's gender (no missing), birth weight (0.1% missing) and
118 length (3% missing), the population with non-missing information was 52,308 mother-child
119 pairs. Additional mother-child pairs were excluded when no postnatal growth measurement

was available, resulting in a final study population of 51,952 mother-child pairs (65% of the source population).

The MoBa study was approved by the Regional Committee for Ethics in Medical Research (S-95113 and S-97045) and the Norwegian Data Inspectorate. The current study was approved by the Regional Committee of Medical Research Ethics for South-Eastern Norway (2016/377).

2.2 Maternal dietary acrylamide intake

The MoBa food frequency questionnaire (FFQ) was used to estimate the daily intake of acrylamide (in µg/day) as previously described in details by Duarte-Salles et al (Duarte-Salles and others 2013) and Brantsaeter et al. (Brantsæter and others 2008b). In brief, food consumption data, assessed by the FFQ, and food contamination data, comprising concentrations of acrylamide in various food items (data from Norwegian, Swedish and European food safety authorities), were combined (Institute for Reference Materials and Measurements 2005; Livsmedelsverket 2002; Norwegian Food Safety Authority 2002; Norwegian Food Safety Authority 2006; Scientific Committee of the Norwegian Food Control Authority 2002). Energy-adjusted acrylamide intake (in µg/kcal/day) was calculated by dividing acrylamide intake (in µg/day) by total daily energy intake (kcal). The MoBa FFQ has been validated in 119 pregnant women using a 4-day weighed food record and biological markers as reference methods (Brantsæter and others 2008a). The validation demonstrated that it provides valid estimates of dietary intakes and is a valid tool for ranking pregnant women along the distribution of energy, nutrients and foods.

The FFQ contains 225 food items that were aggregated into 100 detailed food groups. Twenty seven out of 100 food groups contributed to acrylamide intake. In order to identify the main contributors to acrylamide intake during pregnancy, these 27 were further grouped into 12 main food groups. The 12 food groups were: cereals (porridge, cornflakes), bread

(white bread, dark bread, rolls), crispbread (crispbread and crackers), pancakes and sweet bakery items (waffle and pancakes, buns, cakes, sweet biscuits), boiled potatoes, fried potatoes, coffee (coffee, decaffeinated coffee, figs coffee, milk coffee), chocolate, sweets, salty snacks (potato crisps, potato snacks, peanuts and popcorn, pretzels), milk desserts (yoghurt, milk dessert, milk and cream), and other (poultry, pizza and tacos, prepared fish, raw vegetables, dried fruits, hazelnut spreads).

2.3 Children's postnatal growth

Anthropometric measurements of the children were reported by the mothers at eleven time-points and in six different questionnaires: around the age of 6 weeks, 3 months and 6 months (Questionnaire administered at 6 months), around the age of 8 months, 1 year and 18 months (Questionnaire administered at 18 months), around the age of 2 years and 3 years (Questionnaire administered at 3 years), around the age of 5 years (Questionnaire administered at 5 years), the age of 7 years (Questionnaire administered at 7 years) and 8 years (Questionnaire administered at 8 years). From 6 weeks to 18 months, mothers were asked to refer to their child's health card, while for measurements from 2 to 8 years no specification was provided. From birth to 5 years, weight and height of Norwegian children are screened in scheduled voluntarily appointments at the public health centers. On average, seven repeated measurements of weight and height (10^{th} and 90^{th} percentiles for weight as for height were 3 and 10 measurements) and a total of 373,261 weight measurements and 365,578 height measurements were reported for the children included in our study. Of them, 2,101 children had all 11 reported values for both weight and height. The response rate of anthropometric measurements went down as the children grew older (**Supplementary Figure 1**).

We obtained growth trajectories by modelling the individual growth from 1 month to 8 years, using the Jenss-Bayley growth curve model. This is a structural growth model, meaning that it implies a basic functional form of the growth and it is suitable for describing growth of weight or length up to 8 years, before growth starts to accelerate due to the start of puberty (Jenss and Bayley 1937). By this non-linear mixed effects model (with random effect on each parameter) and by applying the Stochastic Approximation of Expectation-Maximisation (SAEM) algorithm (Berkey 1982; Comets and others 2014), individual weight and height were calculated using the Jenss-Bayley equation and individual weight and height growth velocities were calculated using the first derivative of the model, at several time points (1, 2, 3, 6, 9, 12, 18 months, 2, 3, 4, 5, 6, 7, 8 years). The predicted anthropometric values as well as their correlation with the measured ones are presented in Supplemental material (**Supplementary table 1**). Implausible anthropometrics were identified and excluded by separately implementing two different methods: i) by identifying measured values with a >|3SD| difference from the predicted value as derived from the Jenss-Bayley growth curve model, and ii) by the conditional growth percentiles method (Yang and Hutcheon 2016). In total, 2% of weight and 2% of length/height measurements were excluded as implausible. In order to define growth trajectories independent of birth size and to be able to further assess the effect of acrylamide on early growth independent of the effect on birth size (Duarte-Salles and others 2012), birth weight and length were not included in the growth models.

Body mass index (BMI) was calculated as weight (in kg) divided by squared height (in m) using the predicted growth values (Botton and others 2014). Further, we defined childhood overweight and obesity at 3, 5 and 8 years using the extended International Obesity Task Force (IOTF) cut offs for boys and girls (Cole and Lobstein 2012).

190 **2.4 Covariates**

191 Variables considered as potential confounders in this study were maternal and pregnancy-
192 related characteristics previously identified as adjustment factors for the association between
193 dietary acrylamide intake in pregnancy and fetal growth (Duarte-Salles and others 2013;
194 Kadawathagedara and others 2016; Pedersen and others 2012). The variables included parity
195 (nulliparous vs multiparous), maternal age (years), maternal education (≤ 9 years, 13-16 years,
196 ≥ 17 years), maternal pre-pregnancy BMI (<18.5, 18.5-24.9, 25.0-29.9, ≥30.0 kg/m^2),
197 gestational weight gain (kg), smoking during pregnancy (no, occasional, daily) and gestational
198 age (weeks). In addition, maternal alcohol consumption during pregnancy (yes vs no),
199 exposure to passive smoking during pregnancy (yes vs no), total energy intake (KJ, assessed
200 concomitantly with acrylamide) and paternal BMI (kg/m^2) and height (m) were tested as
201 potential confounders. We also tested for interaction between acrylamide intake and gender
202 or birth weight. Variables were included in the model if the association with both the exposure
203 variable and the outcome variable (overweight/obesity at 3 years) had a *p*-value less than
204 0.05. In addition, confounding by postnatal acrylamide exposure was explored by further
205 adjustment for child's bread consumption (in slices/day) at 3 years (median: 4 slices/day, 5th -
206 95th percentile: 2-6 slices/day) and 7 years (median: 3 slices/day, 5th-95th percentile: 0-7
207 slices/day) as assessed by a two short food frequencies questionnaires (with one items for
208 bread consumption at 3 and 4 items at 7 years).

209 **2.5 Statistical analysis**

210 We described the specific sources of acrylamide by quartiles of intake and identified the
211 main contributors for different levels of exposure.

212 Logistic regression models were used to investigate the association between maternal
213 acrylamide intake (in quartiles) and the risk of overweight including obesity or the risk of

obesity only, at 3, 5 and 8 years separately. Further, we used restricted cubic splines with four knots at percentiles 5, 35, 65 and 95, to assess the linearity of the association, visually and statistically, using the exposure variable in a continuous scale. The logistic regression models were adjusted for random effects of sibling clusters since some mothers participated with more than one pregnancy.

Linear mixed effect models were used to investigate the association between maternal acrylamide intake during pregnancy (in quartiles) and child's postnatal growth from 1 month to 8 years. The effect estimates for each outcome were presented in line plots by quartiles of acrylamide intake.

The association between maternal acrylamide intake in pregnancy and postnatal growth was tested by using crude acrylamide intake (in µg/day) and energy intake adjusted acrylamide intake (in µg/kcal/day). The energy-adjusted analysis is presented as the main analysis and the non-adjusted in Supplemental material. We performed the following sensitivity analyses i) with and without adjustment for birth weight, ii) using only measured anthropometric data (not predicted values), iii) including only the children with a high number of anthropometric measurements (>7, the median) and limiting the age range to <5 years, iv) using acrylamide crude intake in µg/day with energy intake as a covariate in the model, and v) examining acrylamide intake as three independent variables reflecting the amounts from the principal contributors (crispbread, sweet bakery items and bread).

The analyses were performed using Stata 14 statistical software (Stata Corporation, College Station, Texas) except growth modelling that was conducted in R version 3.2.2 (Team 2016).

3. Results

The median and interquartile range (IQR) of dietary acrylamide intake was 24.7 µg/day (IQR 18.4, 33.2), 0.011 µg/kcal/day (IQR 0.008, 0.014) among the 51,952 pregnant women. The

main contributors to acrylamide intake were pancakes or sweet bakery items, bread and crispbread, and the contribution of each food differed from low to high exposure (Figure 1). Namely, in the 1st quartile of exposure, the main contributors were pancakes and sweet bakery items (22%) and bread (29%), while in the 4th upper quartile, the contribution of crispbread increased to 25% (9% in the 1st quartile) and the contribution of the bread decreased to 14%. The characteristics of the population have been described previously; in brief, the mean age at delivery was 30 years of age, 52% of the women were nulliparous, 66% of the women had a normal BMI (18.5 – 25 kg/m^2), and 92% of the women were non-smokers during pregnancy. In children, the prevalence of overweight was 10.6%, 14.8% and 7.8% and, of obesity only 0.8%, 1.6% and 0.4% at 3, 5 and 8 years, respectively (**Supplementary table 2**).

Increasing maternal acrylamide intake during pregnancy was associated with higher odds of children being overweight/obese at 3, 5 and 8 years of age, after adjustment for confounders (**Table 1**). Children born to mothers with acrylamide intake at 2nd, 3rd and 4th quartile had 10%, 12% and 21% higher odds of being overweight/obese at 3 years, compared to their low exposed peers. The association was weakened at 5 years and no significant association was found at 8 years. We found an increased odds for obesity only at 3 years associated with the highest level of acrylamide intake, and a similar dose-response trend was observed at 5 years. Assessing the exposure on a continuous scale, we found that the prevalence of overweight at 3 and 5 years (but not at 8 years) increased from no intake to an intake of 0.01 µg/kcal/day (~95th percentile of acrylamide intake) and then reached a plateau (**Figure 2**). There was no interaction between birth weight and acrylamide exposure on postnatal growth and no substantial difference when removing birth weight from the covariates (**Supplementary Table 3**). There was no interaction between gender and

acrylamide exposure on postnatal growth (data not shown). When using the reported anthropometric data to define the outcome, the estimates were similar compared to predicted anthropometric values, but with greater variances (**Supplementary table 4**).

When assessing weight up to 8 years, we found that energy-adjusted acrylamide intake in the 3rd and 4th quartile was associated with higher weight from the first months onwards (**Figure 3**). Regarding weight growth velocity, maternal acrylamide intake in the 4th quartile was associated with higher weight gain velocity from 1st month to 5 years. Finally, maternal energy-adjusted acrylamide intake higher than the 1st quartile was associated with higher BMI throughout the whole childhood.

More specifically and focusing on the highest exposure level, 1 year old children prenatally exposed to high acrylamide levels weighed 34 g more, gained 2.5 g more per month and had 0.06 kg/m^2 higher BMI than their low exposed peers (**Table 2**). At eight years, highly exposed children during prenatal period weighed between 110 g to 278 g more than their low exposed peers did (~0.4-1% higher than the average weight at 8 years). Restricting the analysis to children with seven or more measurements and assessing growth up to 5 years, we observed similar associations (**Supplementary Table 5**).

When using the crude acrylamide intake as an exposure variable (in µg/day) the associations with overweight and obesity were similar, while for obese only, the associations were stronger for the 3rd quartile at 3 and 5 years and for the 4th quartile at 8 years (**Supplementary table 6**). When investigating the associations of the main acrylamide dietary contributors with the outcomes, consistent associations were observed (**Supplementary table 7**).

Child's bread consumption at 3 and 7 years was used as a proxy for acrylamide exposure in childhood and further adjustment for it did not modify our findings on prenatal acrylamide exposure (**Supplementary Table 8**).

4. Discussion

We found that prenatal acrylamide exposure was associated with an increased prevalence of children being overweight or obese and having higher weight growth velocity very early during childhood. To our knowledge, this is the first study on the relationship between prenatal acrylamide exposure and postnatal growth.

There are three previous epidemiological studies on the association between prenatal acrylamide exposure and fetal growth, while no previous animal or epidemiological study on postnatal growth. The first one was a consortium of five European mother-child cohort studies, including a subsample from MoBa, using biomarkers of acrylamide exposure during gestation (Pedersen and others 2012), and the other two assessed acrylamide exposure through diet (Duarte-Salles and others 2013; Kadawathagedara and others 2016). All three studies showed that high prenatal exposure to acrylamide was associated with impaired fetal growth. These results were consistent with animal studies showing a decrease in offspring body weight following maternal acrylamide exposure during gestation (El-Sayyad and others 2011; Manson and others 2005; Tyl and Friedman 2003).

Our findings of increased prevalence of overweight associated with high prenatal acrylamide exposure are in line with the Fetal Programming (Barker 1998) and Developmental Origins of Health and Disease hypothesis (Gluckman and others 2008). Considering the absence of interaction between birth weight and prenatal exposure to acrylamide and that adjustment for birth weight did not change the association, the association between acrylamide exposure and postnatal growth is likely independent from the one with fetal growth, which suggest a direct effect.

There are only few studies showing that early life chemical exposure may be obesogenic (Botton and others 2017), and they mainly focused on persistent organic pollutants that can

act as endocrine disrupting chemicals (EDCs). EDCs are environmental compounds that can mimic or interfere with the effects of endogenous hormones such as estrogens, androgens, progestins, and thyroid, hypothalamic, and pituitary hormones (Newbold and others 2007). Acrylamide is not known to be an EDC and the CONTAM panel of EFSA concludes that the evidence from the available studies in the literature on hormonal and endocrine effects of acrylamide is equivocal (EFSA 2015). In a cross-sectional study from Lin et al., urinary acrylamide metabolites were negatively associated with free thyroxine (T4) (Lin and others 2015). Although this result is coming from a cross-sectional study so we cannot exclude reverse causation, it provides an interesting new insight for a possible mechanism involved. Indeed, thyroid hormones are essential for an optimal growth but the literature is divergent regarding their effect on hypothyroidism and prenatal growth (Hou and others 2016; Nazarpour and others 2015).

Another possible biological mechanism between acrylamide exposure and growth is through oxidative stress and inflammation. Recently, acrylamide exposure was found to be inversely associated with several body composition measures in a sample of adults from the NHANES, and high oxidative stress was suggested as the mechanism involved (Chu and others 2017). During pregnancy, high acrylamide exposure can result in increased oxidative stress through increased expression of CYP2E1, resulting further in a heightened perinatal inflammatory status (Nguyen and others 2015; Wang and others 2003). Indeed, elevated maternal plasma C-reactive protein has been associated with a higher risk of childhood overall adiposity and central adiposity in the American Project Viva cohort, providing evidence that maternal inflammatory status might also contribute to explain our findings (Gaillard and others 2016). Oxidative stress and inflammation are also mechanisms that are suspected to influence the relation between air pollution or exposure to tobacco smoke during pregnancy

and low birth weight (Aycicek and Ipek 2008; Westergaard and others 2017). The negative association of both types of prenatal exposure on birth weight has been well described (Pedersen and others 2013; Valero De Bernabe and others 2004), and the mechanisms involved might be similar for acrylamide.

We acknowledge that the maternal dietary pattern related to high acrylamide exposure, rather than the acrylamide exposure itself, might confound the observed association. In other populations, acrylamide intake has been related with high intake of fast-foods, like chips (Pedersen and others 2015), while in the present population of Norwegian women high acrylamide exposure was driven by crispbread intake, that is high in fiber and not associated with an unhealthy dietary pattern. Hence, in this population, it is less likely that an unhealthy dietary pattern during pregnancy would explain our findings.

Strength and limitations

This study is the first to assess the relationship between prenatal acrylamide intake and postnatal growth in a large population based study (N=51,952). It is a follow up of a previous study describing the link between prenatal exposure to acrylamide and fetal growth (Duarte-Salles and others 2013). These two studies assessed acrylamide exposure *via* diet, as estimated using a FFQ and a food-chemical concentration database in the same population. Duarte-Salles et al. reported a positive correlation between estimated acrylamide intake and Hb adducts in maternal blood (Spearman correlation: 0.24, 95% CI: 0.00, 0.44). This level of correlation is in agreement with previous reports (Kutting and others 2008; Tran and others 2010; Wilson and others 2009a; Wilson and others 2009b; Wirfalt and others 2008). The use of dietary intake estimations to assess acrylamide exposure can be seen as a strength of our study, as an alternative method (i.e biomarkers) would be more invasive, burdensome and expensive to be applied in such a large population. In addition, dietary assessment is highly

relevant as food is the primary source of acrylamide exposure in non-smokers and non-occupationally exposed populations (Dybing and others 2005) and less than 8 % of women smoked during pregnancy in our study. Nevertheless, the chance of a misclassification (bias of the exposure), related to the dietary recall through the self-administered FFQ or the representativeness of the food contamination database, cannot be excluded. However, the classification bias is unlikely to be differential and, although the loss of power is compensated by the large sample size in our study, the size of the associations is likely underestimated (Pearce and others 2007).

An additional strength is the use of growth modelling that takes attrition bias into account and handles the missing body size measurements. The correlations between the measured and the predicted body size measurements were strong at all ages ($r>0.93$ except one coefficient at 0.85, see Supplementary Table 1). In sensitivity analyses restricted to the measured data, similar associations were found as with the predicted body size data (Supplementary Table 4). This provides some reassurance on the validity of the predicted anthropometrics. However, we still acknowledge the potential for outcome misclassification bias as only 26% of the study population had anthropometric data at 8 years (Supplementary Table 1), though in part because all our population (17%) had still not reached the age of 8 years. The mixed-effect growth modeling will predict the values also for the children lost to follow-up balancing between their previous observed values and the average population trajectory. The shrinkage due to this approach is likely to predict values closer to the mean compared to the actual child's growth, leading again to a loss of power and attenuation in the associations with acrylamide exposure (McCulloch and others 2008). When conducting the longitudinal analysis in a subsample of children with many measurements (≥7) and up to 5 years only, similar conclusions were drawn.

In addition, a possible attenuation of the observed association with overweight after 5 years might be explained by possible misclassification of the outcome through another source. The development of all Norwegian children is assessed, from birth to 5 years, in voluntarily scheduled appointments with a public health nurse. Hence, parental misreporting of the child's weight and height after 5 years might induce misclassification of the outcome.

Finally, we decided to consider potential confounders when the variable was associated with both the exposure and the outcomes. Although this practice has been criticized, given our high sample size, it is quite unlikely that we missed important confounders (Rothman and others 2008). Controlling for confounding by postnatal exposure to acrylamide can be considered a strength of our study. Child's bread consumption available at 3 and 7 years was used as a proxy to child's dietary acrylamide exposure and adjustment for this did not modify our results on prenatal acrylamide exposure and the risk for childhood overweight and obesity.

The association between acrylamide exposure during pregnancy with child's adiposity and other metabolic markers can provide more insight into the negative developmental programming effects of acrylamide and should be investigated by future studies.

5. Conclusion

In summary, this large population-based study provides the first epidemiological evidence of a significant association between prenatal dietary exposure to acrylamide and increased prevalence of being overweight or obese and being in higher growth trajectories during early childhood and pre-school age. These findings need to be confirmed in other studies.

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603 **Tables**

604 **Table 1. Maternal acrylamide intake in pregnancy and overweight/obesity and obesity only at 3, 5 and 8 years (n=51,952).**

	Risk for overweight and/or obesity [a]								
Maternal energy-adjusted acrylamide intake (µg/kcal/day)	At 3 years			At 5 years			At 8 years		
	Prevalence (%)	OR	95% CI	Prevalence (%)	OR	95% CI	Prevalence (%)	OR	95% CI
Quartiles of intake									
Q1	9.77	1.00		15.24	1.00		4.55	1.00	
Q2	10.54	1.10	1.02,1.20	16.14	1.08	1.01,1.16	4.57	1.02	0.91,1.15
Q3	10.77	1.12	1.04,1.22	16.59	1.11	1.04,1.19	5.02	1.12	0.99,1.25
Q4	11.55	1.21	1.11,1.31	17.49	1.17	1.10,1.26	5.12	1.12	1.00,1.26
p for trend		*<0.001*			*<0.001*			*0.023*	
	Risk for obesity only [a]								
Q1	0.88	1.00		2.39	1.00		0.28	1.00	
Q2	0.94	1.09	0.84,1.41	2.52	1.07	0.92, 1.26	0.21	0.76	0.46,1.25
Q3	0.96	1.11	0.86,1.44	2.67	1.13	0.96,1.32	0.27	0.96	0.60,1.53
Q4	1.21	1.35	1.06,1.73	2.82	1.16	0.99,1.36	0.44	1.46	0.96,2.23
p for trend		*0.018*			*0.048*			*0.045*	

All models are adjusted for maternal age, parity, maternal education, pre-pregnancy BMI, gestational weight gain, maternal smoking during pregnancy, gestational age, maternal alcohol consumption during pregnancy, second hand smoking and birth weight.

[a] Overweight and/or obese children were defined according to IOTF definition, using the predicted anthropometric measurements.

605

606 **Table 2.** Association between maternal acrylamide intake in pregnancy and child's weight,
607 weight gain velocity and BMI from 1st month to 8 years. The 1st quartile of maternal
608 acrylamide intake is used as the reference.

	Energy-adjusted maternal acrylamide intake (µg/kcal/day) in quartiles								
	2nd quartile			3rd quartile			4th quartile		
	Beta	(95%	CI)	Beta	(95%	CI)	Beta	(95%	CI)
Weight (in g) [a]									
3months	-0.1	(-14	, 14)	11	(-2.7	, 25)	17	(2.5	, 31)
6months	2.6	(-12	, 17)	14	(-0.2	, 29)	22	(7.7	, 37)
12months	8.2	(-8.7	, 25)	21	(3.6	, 37)	34	(17	, 51)
2years	19	(-5.0	, 44)	33	(8.4	, 57)	57	(32	, 81)
5years	53	(-0.4	, 106)	70	(17	, 123)	125	(73	, 179)
8years	86	(2.5	, 169)	107	(23	, 190)	194	(110	, 278)
Weight gain velocity (in g/month) [a]									
3months	0.8	(-1.4	, 3.1)	1.5	(-0.7	, 3.7)	2.6	(0.4	, 4.8)
6months	0.9	(-1.2	, 3.0)	1.5	(-0.6	, 3.6)	2.6	(0.4	, 4.7)
12months	0.9	(-1.0	, 2.8)	1.5	(-0.5	, 3.4)	2.5	(0.6	, 4.5)
2years	1.0	(-0.7	, 2.7)	1.4	(-0.2	, 3.1)	2.4	(0.8	, 4.1)
5years	1.2	(-0.8	, 3.3)	1.3	(-0.8	, 3.3)	2.2	(0.1	, 4.3)
8years	1.5	(-2.0	, 5.0)	1.1	(-2.4	, 4.6)	1.9	(-1.6	, 5.5)
BMI (in kg/m^2) [a]									
3months	0.03	(0.00	, 0.05)	0.03	(0.01	, 0.06)	0.05	(0.02	, 0.07)
6months	0.03	(0.00	, 0.05)	0.03	(0.01	, 0.06)	0.05	(0.03	, 0.07)
12months	0.03	(0.01	, 0.05)	0.04	(0.01	, 0.06)	0.06	(0.03	, 0.08)
2years	0.04	(0.01	, 0.06)	0.04	(0.02	, 0.07)	0.07	(0.04	, 0.09)
5years	0.06	(0.03	, 0.09)	0.06	(0.03	, 0.09)	0.10	(0.07	, 0.13)
8years	0.08	(0.04	, 0.12)	0.08	(0.03	, 0.12)	0.13	(0.09	, 0.17)

All linear mixed models are adjusted for maternal age, parity, maternal education, pre-pregnancy BMI, gestational weight gain, maternal smoking during pregnancy, gestational age, maternal alcohol consumption during pregnancy, second hand smoking and birth weight.

[a] Predicted anthropometric measurements were used to define outcomes.

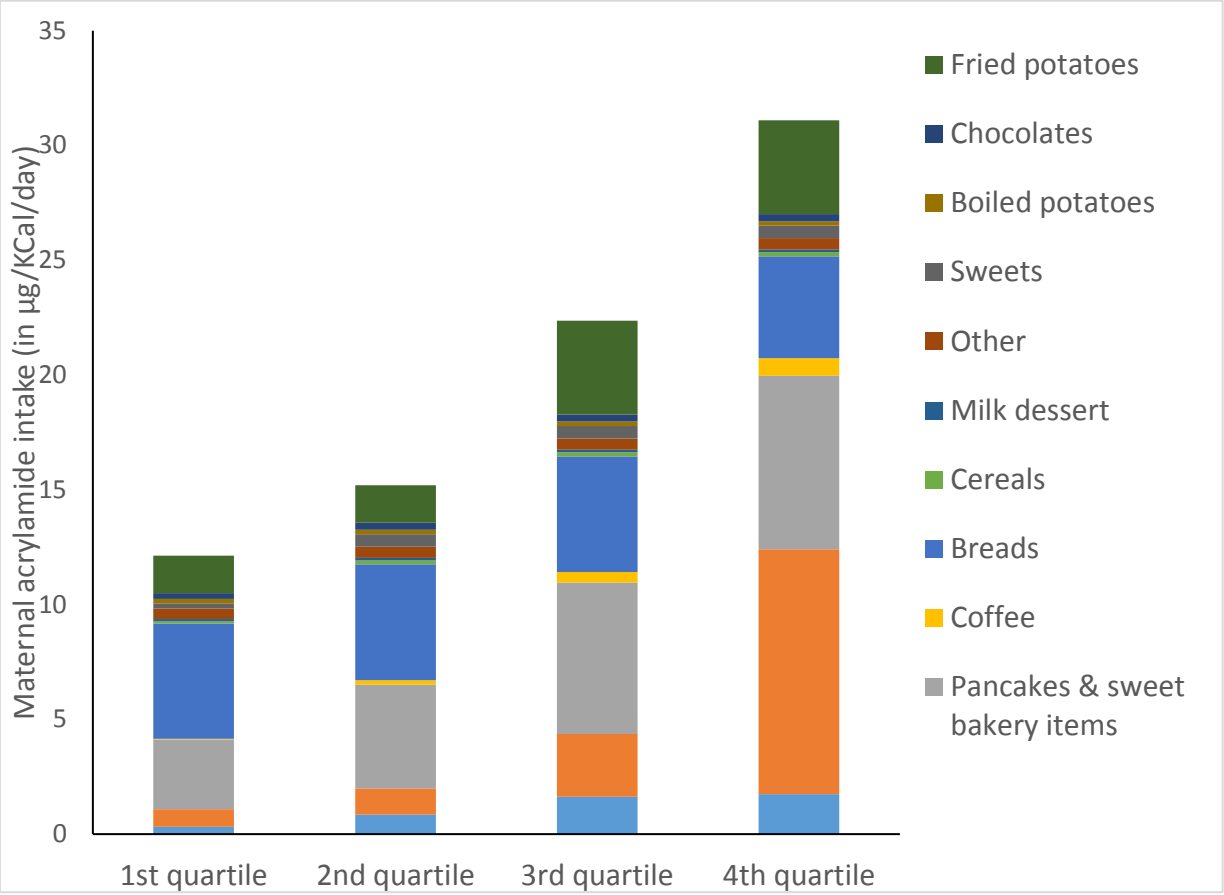
609

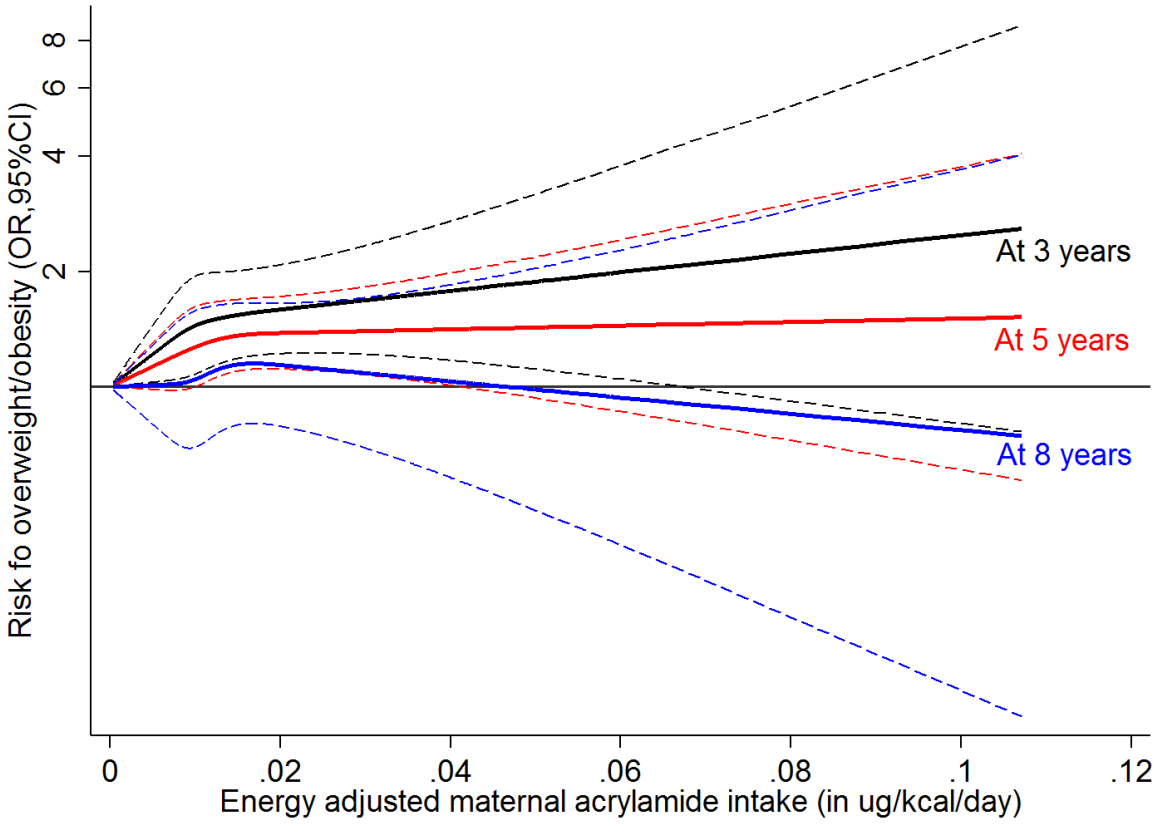
610 **Figure 1.** Sources of maternal acrylamide intake according to quartiles of total acrylamide

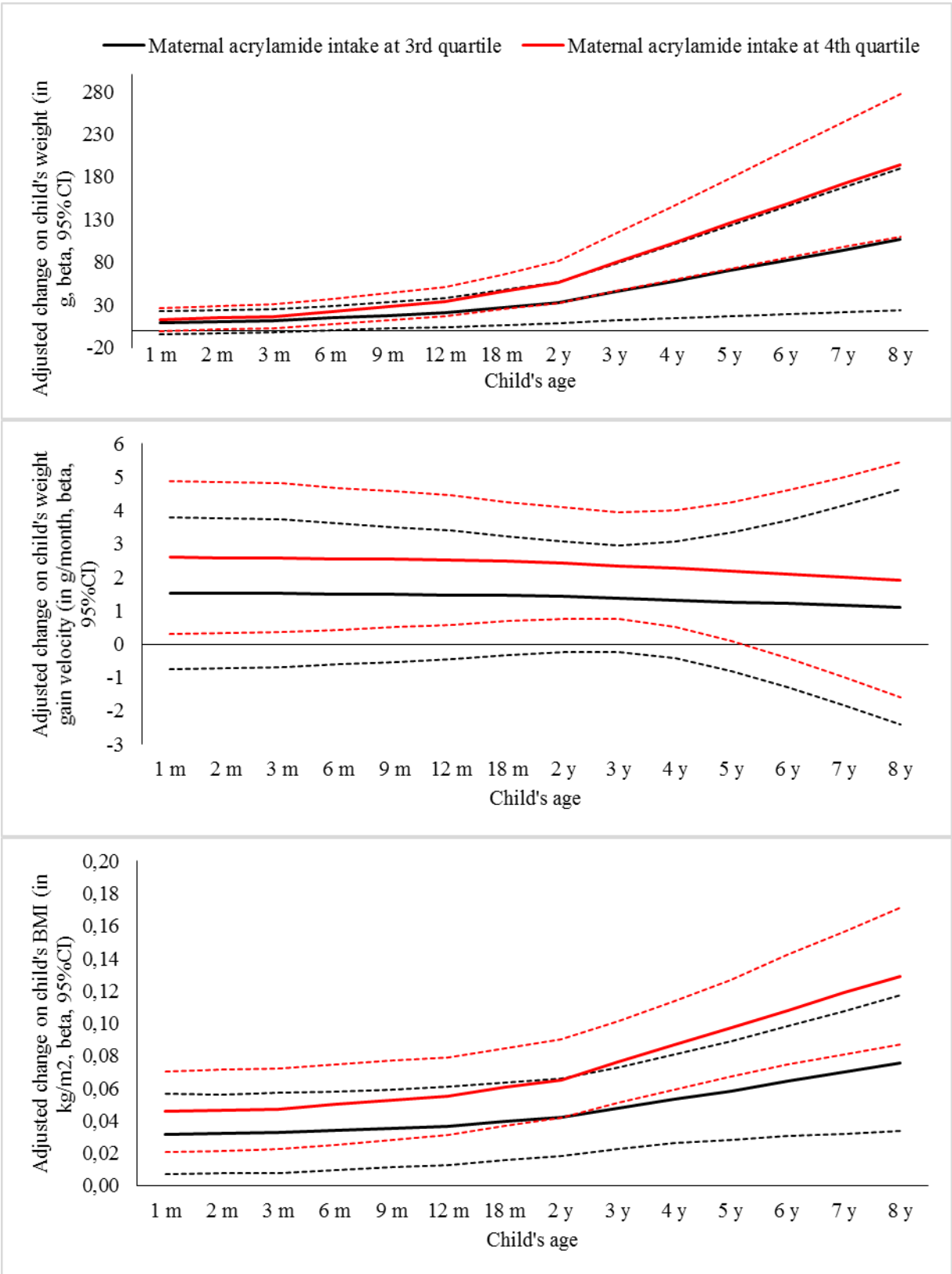
611 intake (n=51,952) women in MoBa.

612 **Figure 2.** Maternal acrylamide intake (μg/kcal/day) in pregnancy (in continuous scale) and
613 overweight/obesity at 3 (black lines), 5 (red lines) and 8 (blue lines) years (n=51,952). Solid
614 lines represent Odd Ratios (OR) and dotted lines represent 95% Confidence Intervals (CI).

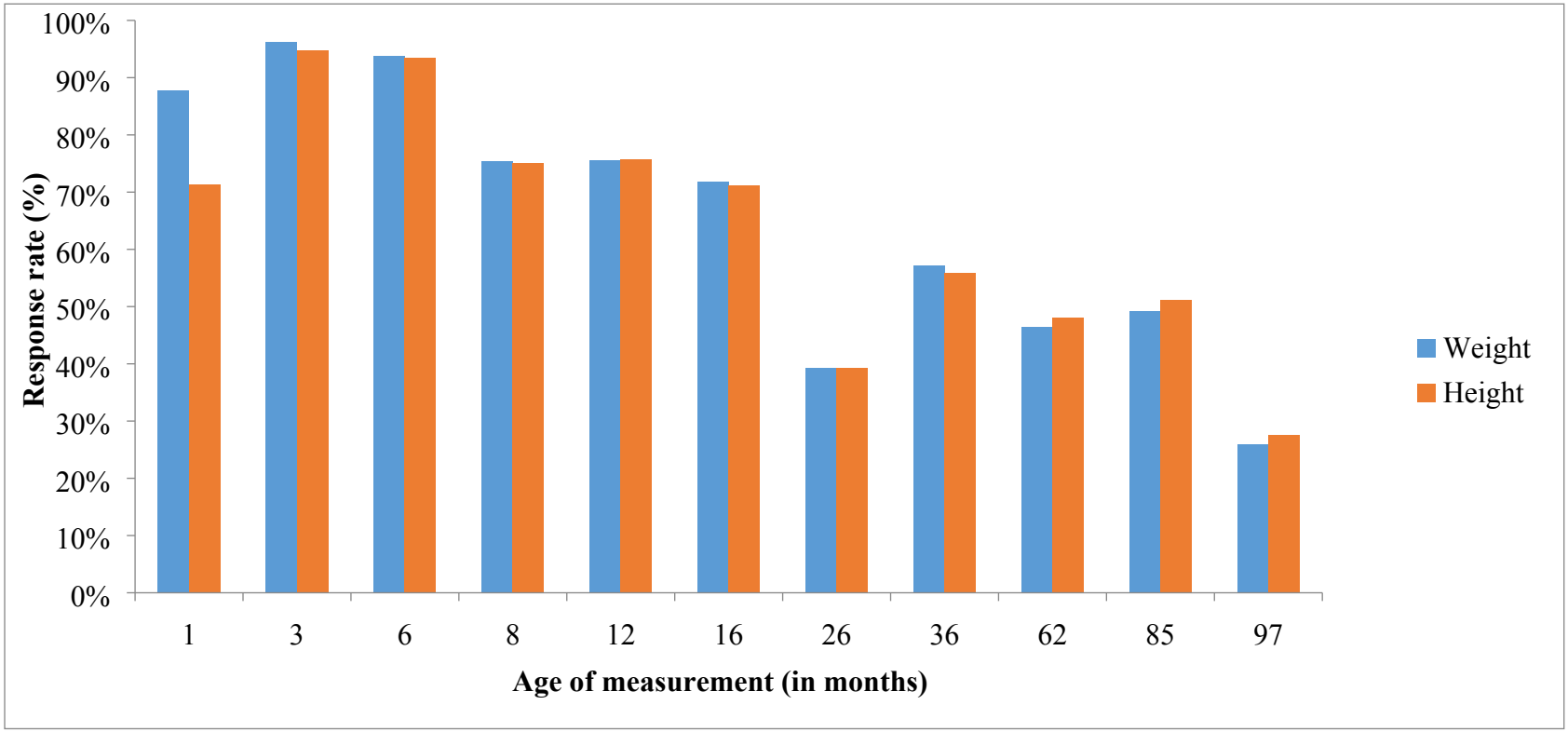
615 **Figure 3.** Adjusted changes in child's A) weight, B) weight gain velocity and C) BMI from 1st
616 month to 8 years, associated with 3rd and 4th maternal acrylamide intake quartiles (energy-
617 adjusted).
618 Footnote: All models are adjusted for maternal age, parity, maternal education, pre-
619 pregnancy BMI, gestational weight gain, maternal smoking during pregnancy, gestational age,
620 maternal alcohol consumption during pregnancy, second hand smoking and birth weight.


35
30
25
20
15
10
5
0
Maternal acrylamide intake (in µg/KCal/day)
1st quartile
2nd quartile
3rd quartile
4th quartile
Fried potatoes
Chocolates
Boiled potatoes
Sweets
Other
Milk dessert
Cereals
Breads
Coffee
Pancakes & sweet bakery items


Risk fo overweight/obesity (OR,95%CI)
2
4
6
8
At 3 years
At 5 years
At 8 years
0
.02
.04
.06
.08
.1
.12
Energy adjusted maternal acrylamide intake (in ug/kcal/day)


Maternal acrylamide intake at 3rd quartile
Maternal acrylamide intake at 4th quartile
Adjusted change on child's weight (in g, beta, 95%CI)
280
230
180
130
80
30
-20
1 m
2 m
3 m
6 m
9 m
12 m
18 m
2 y
3 y
4 y
5 y
6 y
7 y
8 y
Child's age
Adjusted change on child's weight gain velocity (in g/month, beta, 95%CI)
6
5
4
3
2
1
0
-1
-2
-3
Child's age
Adjusted change on child's BMI (in kg/m2, beta, 95%CI)
0,20
0,18
0,16
0,14
0,12
0,10
0,08
0,06
0,04
0,02
0,00
Child's age

Supplemental figure 1. Response rate of anthropometric measurements for 51,952 mother-child pairs.



Supplementary Table 1. Measured and predicted growth measurements (weight and height) in children, based on maternal reports, at 11 time points in the Norwegian Mother and Child Cohort Study (MoBa).

		Measured growth				Predicted growth		Correlation between measured and predicted growth	
	Age (months)	Weight (in kg) N=373,261		Height (in cm) N=365,578		Weight (in kg) N=571,472	Height (in cm) N=571,472	Weight	Height
Time point	Mean (SD)	Measurements distribution (%)	Mean (SD)	Measurements distribution (%)	Mean (SD)	Mean (SD)	Mean (SD)	Pearson's r	Pearson's r
1	1.4 (0.2)	12	5.0 (0.7)	10	56.9 (2.3)	5.0 (0.5)	57.3 (1.9)	0.85	0.95
2	3.1 (0.3)	13	6.4 (0.8)	13	62.1 (2.4)	6.4 (0.7)	61.7 (2.1)	0.94	0.95
3	5.8 (0.5)	13	7.9 (0.9)	13	67.9 (2.5)	7.9 (0.8)	67.5 (2.3)	0.95	0.96
4	8.1 (0.8)	11	8.8 (1.0)	11	71.3 (2.7)	8.8 (0.9)	71.3 (2.5)	0.96	0.96
5	12.2 (0.6)	11	9.9 (1.1)	11	76.5 (2.7)	10.0 (1.0)	76.8 (2.5)	0.96	0.96
6	16 (1.2)	10	10.9 (1.2)	10	80.6 (2.9)	10.9 (1.1)	80.9 (2.7)	0.96	0.96
7	25.5 (2)	5	12.9 (1.5)	6	88.7 (3.5)	12.9 (1.4)	88.9 (3.3)	0.94	0.95
8	36.2 (1.4)	8	15.0 (1.7)	8	96.6 (3.7)	15.1 (1.6)	96.4 (3.5)	0.93	0.96
9	62.4 (3.4)	6	19.9 (2.6)	7	113.1 (5.1)	20.2 (3.5)	112.6 (4.6)	0.96	0.97
10	85.2 (1.6)	7	24.9 (3.7)	7	125.8 (5.3)	25.0 (3.5)	125.8 (5.0)	0.98	0.98
11	96.9 (1)	4	28.0 (4.3)	4	131.9 (5.5)	27.7 (4.1)	132.4 (5.3)	0.99	0.98

Supplementary Table 2. Prevalence of overweight/obesity and obesity only at age 2-8 years in our study population, defined by using measured or predicted anthropometric data.

	Child's age						
	2 years	3 years	4 years[a]	5 years	6 years[a]	7 years	8years
Using measured anthropometric data							
N total	20,151	22,856	181	22,481	1,032	24,803	13,068
% cases of overweight/obesity	10.5	12.2	9.9	11.1	8.2	11.3	11.5
% cases of obesity only	1.2	1.5	2.2	1.3	0.6	1.1	0.7
Using predicted anthropometric data							
N total (with measured data available)	20,151	22,856	181	22,481	1,032	24,803	13,068
% cases of overweight/obesity	5.7	10.6	12.7	14.8	10.6	10.7	7.8
% cases of obesity only	0.2	0.8	2.2	1.6	0.8	0.8	0.4
N total	51,952	51,952	51,952	51,952	51,952	51,952	51,952
% cases of overweight/obesity	5.3	10.7	15.5	16.4	13.2	8.6	4.8
% cases of obesity only	0.3	1.0	2.3	2.6	1.7	0.9	0.3
% Overlap of cases of overweight/obesity[b]	82	69	61	63	69	86	96
% Overlap of cases of obesity only[b]	80	58	50	54	50	85	94

[a] The number of children at 4 and 6 years is low because the follow-up was conducted at 3, 5 and 7 years.

[b] % Overlap represents the percentage of the cases defined by the predicted anthropometric data who rank as cases also by using measured anthropometric data.

Supplementary Table 3. Associations between maternal acrylamide intake in pregnancy and overweight/obesity and obesity only at 3, 5 and 8 years, without adjustment for birth weight.

	Risk for overweight and/or obesity [a]					
Maternal energy-adjusted	At 3 years		At 5 years		At 8 years	
acrylamide intake (µg/kcal/day)	OR	95% CI	OR	95% CI	OR	95% CI
Quartiles of intake						
Q1	1.00		1.00		1.00	
Q2	1.09	1.01,1.19	1.07	1.00,1.15	1.02	0.90,1.14
Q3	1.11	1.02,1.20	1.10	1.03,1.18	1.11	0.99,1.24
Q4	1.18	1.09,1.28	1.15	1.08,1.24	1.11	0.98,1.24
p for trend		*<0.001*		*<0.001*		*0.038*
	Risk for obesity only [a]					
Q1	1.00		1.00		1.00	
Q2	1.08	0.84,1.40	1.07	0.91,1.25	0.76	0.46,1.26
Q3	1.10	0.85,1.42	1.12	0.95,1.31	0.96	0.60,1.53
Q4	1.33	1.04,1.70	1.14	0.98,1.34	1.47	0.96,2.24
p for trend		*0.026*		*0.075*		*0.043*

All models are adjusted for maternal age, parity, maternal education, pre-pregnancy BMI, gestational weight gain, maternal smoking during pregnancy, gestational age, maternal alcohol consumption during pregnancy, second hand smoking.

[a] Overweight and/or obese children were defined according to IOTF definition, using the predicted anthropometric measurements.

Supplementary Table 4. Maternal energy-adjusted acrylamide intake in pregnancy and overweight/obesity and obesity only at 3, 5 and 8 years, using measured anthropometric measurements.

	Risk for overweight and/or obesity [a]								
Energy adjusted maternal acrylamide intake (μg/day)	At 3 years			At 5 years			At 8 years		
	Prevalence (%)	OR	95% CI	Prevalence (%)	OR	95% CI	Prevalence (%)	OR	95% CI
Quartiles of intake									
Q1	11.12	1.00		10.57	1.00		10.94	1.00	
Q2	11.83	1.07	0.96,1.21	10.89	1.05	0.93,1.18	11.84	1.11	0.95,1.30
Q3	12.01	1.09	0.97,1.22	11.42	1.10	0.97,1.24	11.34	1.04	0.89,1.22
Q4	13.92	1.28	1.15,1.44	11.55	1.09	0.97,1.23	11.85	1.07	0.92,1.26
p for trend			*<0.001*			*0.119*			*0.579*
	Obesity only [a]								
Q1	1.33	1.00		1.28	1.00		0.78	1.00	
Q2	1.25	0.94	0.68,1.30	1.27	1.02	0.73,1.43	0.60	0.79	0.44,1.43
Q3	1.76	1.32	0.98,1.79	1.47	1.17	0.85,1.62	0.60	0.77	0.42,1.39
Q4	1.80	1.36	1.00,1.84	1.35	1.05	0.75,1.46	0.97	1.21	0.71,2.06
p for trend			*0.009*			*0.602*			*0.493*

All models are adjusted for maternal age, parity, maternal education, pre-pregnancy BMI, gestational weight gain, maternal smoking during pregnancy, gestational age, maternal alcohol consumption during pregnancy, second hand smoking and birth weight.

[a] Overweight and/or obese children were defined according to IOTF definition, using the measured anthropometric measurements.

Supplementary Table 5. Association between maternal acrylamide intake in pregnancy and child's weight, weight gain velocity and BMI from 1st month to 5 years, for 31,358 children with more than 6 measurements. The 1st quartile of maternal acrylamide intake is used as the reference.

	Energy-adjusted maternal acrylamide intake (µg/kcal/day) in quartiles								
		2nd quartile			3rd quartile			4th quartile	
	Beta	(95%	CI)	Beta	(95%	CI)	Beta	(95%	CI)
Weight (in g) [a]									
3months	-12	(-28	, 5)	8.6	(-8.0	, 25)	12	(-5.0	, 29)
6months	-8.7	(-27	, 9.2)	12	(-6.0	, 30)	18	(0.1	, 36)
12months	-2.7	(-25	, 19)	19	(-3.4	, 40)	31	(8.8	, 53)
2years	9.3	(-24	, 42)	32	(-1.2	, 65)	56	(23	, 90)
5years	45	(-27	, 118)	72	(-0.6	, 144)	133	(59	, 206)
Weight gain velocity (in g/month) [a]									
3months	0.3	(-2.8	, 3.5)	1.7	(-1.4	, 4.8)	2.5	(-0.6	, 5.7)
6months	0.5	(-2.4	, 3.3)	1.7	(-1.0	, 4.4)	2.5	(-0.2	, 5.2)
12months	0.7	(-1.9	, 3.2)	1.6	(-0.9	, 4.2)	2.5	(-0.1	, 5.0)
2years	1.1	(-1.3	, 3.5)	1.5	(-0.9	, 3.9)	2.4	(0.0	, 4.8)
5years	2.4	(-3.1	, 7.8)	1.2	(-4.2	, 6.6)	2.3	(-3.2	, 7.7)
BMI (in kg/m^2) [a]									
3months	0.002	(-0.03	, 0.03)	0.03	(-0.002	, 0.06)	0.03	(-0.004	, 0.06)
6months	0.006	(-0.03	, 0.04)	0.03	(0.0002	, 0.06)	0.03	(0.0003	, 0.06)
12months	0.01	(-0.02	, 0.04)	0.03	(0.004	, 0.07)	0.04	(0.009	, 0.07)
2years	0.02	(-0.007	, 0.06)	0.04	(0.01	, 0.07)	0.06	(0.02	, 0.09)
5years	0.06	(0.02	, 0.19)	0.06	(0.01	, 0.11)	0.11	(0.06	, 0.15)

All linear mixed models are adjusted for maternal age, parity, maternal education, pre-pregnancy BMI, gestational weight gain, maternal smoking during pregnancy, gestational age, maternal alcohol consumption during pregnancy, second hand smoking and birth weight.

[a] Predicted anthropometric measurements were used to define outcomes.

Supplementary Table 6. Maternal acrylamide intake in pregnancy and overweight/obesity at 3, 5 and 8 years, using predicted anthropometric measurements (n=51,952).

	Risk for overweight and/or obesity [a]								
Maternal acrylamide	At 3 years			At 5 years			At 8 years		
intake (µg/day)	Prevalence (%)	OR	95% CI	Prevalence (%)	OR	95% CI	Prevalence (%)	OR	95% CI
Quartiles of intake									
Q1	9.84	1.00		15.26	1.00		4.51	1.00	
Q2	10.41	1.06	0.98,1.15	16.05	1.06	0.99,1.13	4.48	0.99	0.88,1.12
Q3	11.21	1.16	1.07,1.25	17.02	1.14	1.06,1.22	5.07	1.13	1.01,1.27
Q4	11.17	1.14	1.05,1.24	17.13	1.14	1.06,1.22	5.21	1.15	1.02,1.29
p for trend			*<0.001*			*<0.001*			*0.010*
	Risk for obesity only [a]								
Q1	0.85	1.00		2.41	1.00		0.23	1.00	
Q2	0.89	1.05	0.80,1.36	2.35	0.98	0.83,1.15	0.21	0.92	0.54,1.55
Q3	1.16	1.37	1.07,1.76	2.92	1.22	1.05,1.42	0.35	1.54	0.96,2.45
Q4	1.08	1.22	0.95,1.58	2.72	1.11	0.95,1.30	0.40	1.62	1.02,2.56
p for trend			0.033			0.032			0.008

All models are adjusted for maternal age, parity, maternal education, pre-pregnancy BMI, gestational weight gain, maternal smoking during pregnancy, gestational age, maternal alcohol consumption during pregnancy, second hand smoking and birth weight.

[a] Overweight and obesity children were defined according to IOTF definition, using the predicted anthropometric measurements.

Supplementary table 7. Maternal acrylamide intake from crispbread, sweet bakery items and bread and overweight/obesity at 3, 5 and 8 years.

	Overweight/obesity [a]					
	3 years		5 years		8 years	
	OR	95%CI	OR	95%CI	OR	95%CI
Energy adjusted acrylamide intake from crispbread						
<75th percentile	1.00		1.00		1.00	
>75th percentile	1.08	1.01,1.15	1.04	0.99,1.10	1.09	0.99,1.20
Energy adjusted acrylamide intake from sweet bakery items						
<75th percentile	1.00		1.00		1.00	
>75th percentile	1.09	1.02,1.16	1.11	1.05,1.17	1.06	0.96,1.16
Energy adjusted acrylamide intake from bread						
<75th percentile	1.00		1.00		1.00	
>75th percentile	1.02	0.99,1.04	1.02	1.00,1.04	1.02	0.99,1.05
Acrylamide intake from crispbread						
<75th percentile	1.00		1.00		1.00	
>75th percentile	1.08	1.01,1.15	1.04	0.99,1.10	1.08	0.98,1.18
Acrylamide intake from sweet bakery						
<75th percentile	1.00		1.00		1.00	
>75th percentile	1.09	1.02,1.17	1.09	1.03,1.15	1.05	0.96,1.16
Acrylamide intake from bread						
<75th percentile	1.00		1.00		1.00	
>75th percentile	1.01	1.00,1.01	1.00	1.00,1.01	1.01	1.00,1.02

All models are adjusted for maternal age, parity, maternal education, pre-pregnancy BMI, gestational weight gain, maternal smoking during pregnancy, gestational age, maternal alcohol consumption during pregnancy, second hand smoking and birth weight. Models are also mutually adjusted for the 3 food groups.

[a] Overweight/obesity were defined according to IOTF definition, using the predicted anthropometric measurements.

Supplementary Table 8. Maternal acrylamide intake during pregnancy and child overweight/obesity, after adjustment for child's bread intake, as a proxy for postnatal acrylamide exposure.

	Risk for overweight and/or obesity [a]							
	At 3 years		At 5 years		At 8 years			
Energy-adjusted maternal acrylamide intake (μg/kcal/day) in quartiles	Adjusted for bread intake at 3 years (slices/day)		Adjusted for bread intake at 3 years (slices/day)		Adjusted for bread intake at 3 years (slices/day)		Adjusted for bread intake at 7 years (slices/day)	
	OR	95%CI	OR	95%CI	OR	95%CI	OR	95%CI
Q1	1.00		1.00		1.00		1.00	
Q2	1.07	0.97, 1.18	1.06	0.97, 1.14	0.97	0.85,1.11	1.01	0.90,1.14
Q3	1.07	0.98,1.18	1.08	0.99,1.17	1.03	0.90,1.18	1.10	0.98,1.24
Q4	1.16	1.06,1.28	1.16	1.07,1.26	1.06	0.93,1.21	1.11	0.99,1.25
p-for-trend	*0.003*		*<0.001*		*0.242*		*0.033*	

All models are adjusted for maternal age, parity, maternal education, pre-pregnancy BMI, gestational weight gain, maternal smoking during pregnancy, gestational age, maternal alcohol consumption during pregnancy, second hand smoking and birth weight.

[a] Overweight/obesity were defined according to IOTF definition, using the predicted anthropometric measurements.

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Titre : Alimentation maternelle pendant la grossesse et croissance précoce : qualité de l'alimentation et exposition aux contaminants alimentaires

Mots clés : Grossesse, qualité de l'alimentation, croissance précoce, contaminants alimentaires

Résumé :

Après une description de la qualité de l'alimentation pendant la grossesse, l'objectif était d'étudier l'association entre l'exposition prénatale aux contaminants alimentaires et la croissance des enfants. Les analyses ont été menées dans trois cohortes de naissance : deux études françaises (EDEN et ELFE), et une étude norvégienne (MoBa).

Premièrement, nous avons montré que les recommandations générales et spécifiques étaient globalement bien suivies par les femmes enceintes. Un score élevé de qualité de l'alimentation était associé à un poids de naissance plus élevé et un risque plus faible d'avoir un enfant petit pour l'âge gestationnel (PAG).

Deuxièmement, nous avons montré que plus l'exposition pendant la grossesse à l'acrylamide (AA) est importante, plus la taille de naissance était faible et plus le risque de PAG est élevé. Dans MoBa, nous avons constaté que l'exposition prénatale à l'AA était associée à une prévalence accrue d'enfants en surpoids ou obèses et à une plus grande vitesse de croissance du poids durant l'enfance.

Enfin, dans EDEN, en élargissant à 99 contaminants, l'exposition prénatale aux contaminants alimentaires ne semble pas préoccupante vis-à-vis de la croissance prénatale et postnatale précoce car les effets retrouvés sont de faible amplitude et ne sont plus significatifs après prise en compte des tests multiples.

Title : Maternal diet during pregnancy and early growth: focus on diet quality and food chemicals exposure

Keywords : Pregnancy, diet quality, early growth, food chemicals

Abstract:

After a description of diet quality during pregnancy, the aim of this thesis was to study the association between prenatal exposure to food chemicals and prenatal and postnatal growth among children. The analyses were conducted in three birth cohort studies: two French studies (EDEN and ELFE) and a Norwegian study (MoBa).

First, we showed that the nutritional guidelines for pregnant women were rather well followed in ELFE. The Diet Quality score was associated with higher birth weight and lower risk of having a small-for-gestational-age (SGA) baby.

Then, we showed that prenatal dietary exposure to acrylamide was associated with reduced birth size in EDEN, and increased postnatal growth in MoBA.

Finally, in EDEN, when looking at a larger number of food chemicals, we found that exposure to food chemicals did not appear to be of major concern for growth. The size of the effects found were of low amplitude and no longer significant after taking into account multiple tests.

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