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Cohort Profile

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Cohort Profile: The EDEN mother-child cohort on the prenatal and early postnatal determinants of child health and development

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Why was the cohort set up?

Barker's hypothesis suggests that health in adulthood can be influenced by events occurring during the developmental period.[1] Studies from various parts of the world have shown associations between low birthweight with adult pathological conditions such as hypertension, insulin-resistance, type 2 diabetes and osteoporosis. In animals, experiments have also corroborated that events occurring at an early stage in an organism still immature, such as the fetus or the infant, can affect health later on.[2] During the late 1990s and early 2000s, more and more emphasis has been placed on the role of nutrition in the first months of life, in addition to or rather than prenatal nutrition and environmental pollutants, as a potential determinant of later health in humans.[3,4] The increase in the prevalence of obesity in most countries has also raised concerns as more and more young women enter pregnancy with excessive weight. Overweight in future mothers is a risk factor for gestational diabetes, a condition that has also been associated with obesity and glucose intolerance in the offspring later in life.[5]

Some of the early factors, such as alcohol consumption or smoking during pregnancy, or restricted intrauterine growth, influence many aspects of the health and development of the child.[6–8] A better knowledge of the prenatal factors affecting later health and of the potential interactions between pre- and postnatal factors requires prospective studies starting from pregnancy.

In this context, 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, fetal development, health status of the infant at birth and the child's health and development.

Where is it located? Who set it up? How has it been funded

EDEN was set up in 2003 in two university maternity clinics, in Nancy and Poitiers, France, (see Figure 1), by the

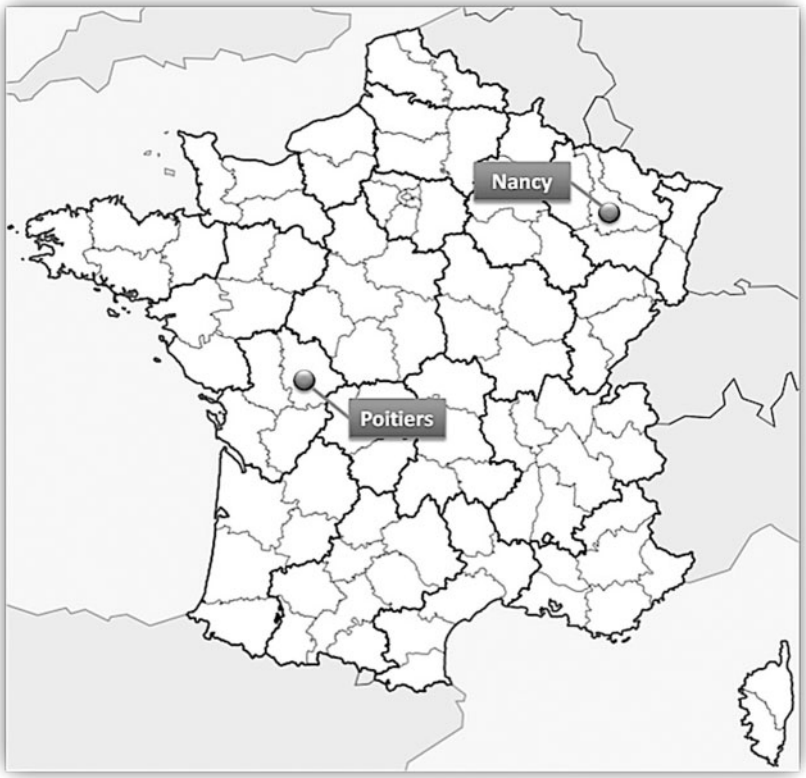

Figure 1. Localisation of the two maternity recruitment centres for the EDEN study.

local clinical teams from the local university hospitals in collaboration with research teams from the National Institute of Health and Medical Research (Inserm). The study relied on many different sources of funding including Inserm, University Paris 11, the French Medical Research Foundation and the National Research Agency and also from national and European programmes and project grants. A more comprehensive list of funders can be found on the EDEN website, along with other information.[9]

Inserm is the 'promoter' of the EDEN study. The study received approval from the ethics committee (CCPPRB) of Kremlin Bicêtre on 12 December 2002 and from CNIL (Commission Nationale Informatique et Liberté), the French data privacy institution.

Who is in the cohort?

Study participation was proposed to all women visiting the prenatal clinic before their 24th week of amenorrhoea (WA). Exclusion criteria were multiple pregnancies, known diabetes before pregnancy, French illiteracy or planning to move out of the region within the next 3 years.

Among the 3758 women invited to participate, 2002 (53%) were enrolled in the study (1034 women from Nancy and 968 from Poitiers). Recruitment extended from 2003 to 2006. On average, women were included at 15 WA (range: 8–26). Their mean age was 29 years (range: 18–44) and 30% of the women were pregnant for the first time.

Compared with the 2003 French National Perinatal Survey (Enquête National Perinatale, ENP), a national sample of births,[10] women included in EDEN and still followed up at delivery had a higher level of education (Table 1); percentages of preterm births or admissions of the newborn to a neonatal or intensive care unit were, however, similar.

How often have they been followed up?

Children have been followed-up for up to 8 years, by visits to research centres and questionnaires mailed to parents. Clinical examinations from pregnancy to 5–6 years of age have been performed by specifically trained midwives. As the 8-year data collection is still ongoing, it will not be presented further in this paper.

Assessments schedule

Mothers had three clinical examinations, one between 24 and 28 weeks of amenorrhea, one at delivery and one 5–6 years after delivery (Figure 2). The child was examined clinically four times: at birth, at 1 year and 3 years and during the 6th year (at 5 years and 8 months, on average), with specific cognitive assessments by psychologists at

Table 1. Data description for mothers and their children followed up until delivery and comparison with the 2003 National Perinatal Survey (ENP2003).[10] The EDEN Study

		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/m^2	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

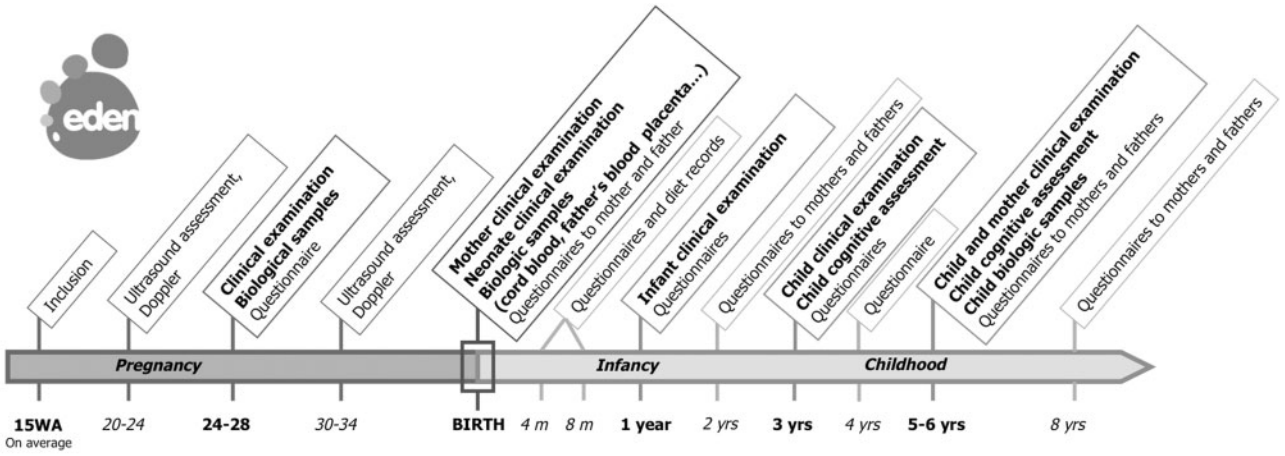

Figure 2. Assessments and data collection -from mothers included during pregnancy to children 8 years after birth. The EDEN Study.

3 and 5–6 years. Concomitantly and in between clinical visits, mothers and fathers answered questionnaires, self-administered or administered by midwives, about their offspring, themselves and their household. Questionnaires were filled up twice during the first year (at 4 and 8 months), at 1 year and every year thereafter until 5–6 years. At 4, 8 and 12 months, the parents provided a 3-day food record for their infants. 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 at the child's birth.

Attrition

In all, 95 women (4.7%) withdrew from the study during pregnancy, mainly for reasons of convenience. These women were on average 2 years younger at inclusion than women followed up to delivery (27 vs 29 years) and they were also less educated (50% attained high school diploma vs 72% for women still in the cohort at delivery). Among the 1907 remaining women, birthweight was unavailable 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 3 illustrates the attrition rate from birth to 5–6 years for the 1899 children with birthweight 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%, $P < 10^{-3}$); however, no differences were observed for maternal body mass index (BMI), child's birthweight or preterm birth rate.

What has been measured?

Health phenotype and exposure assessments

Many phenotypes and exposures have been assessed, either from parental questionnaires or clinical investigations but also from biological samples and DNA. Tables 2 and 3 display specific assessments for the mother and the child, respectively. Table 4 describes more general information collected on pregnancy, delivery, household characteristics and fathers, and this table also provides a non-exhaustive list of biomarkers already measured in the cohort. There are other more specific measures of health and exposure, sometimes only in subsamples, that are presented below.

Bone density

Bone status has been measured at 3 and 5–6 years by specially trained midwives using a quantitative ultrasound (QUS) technique at the proximal phalanges of the hand. The ultrasound device was a DBM Sonic BP (IGEA, Capri, Italy) equipped with a probe specially adapted to young infants.[11] The device provides information on Bone Transmission Time (BTT) in μs, which corresponds to the difference between total transmission time through the phalanges and transmission time through soft tissue.

Prenatal and postnatal growth

Usual clinical measures at 20–24 WA and 30–34 WA, and as well as ultrasound assessments recorded by a limited number of echography technicians who used standardized procedures, were collected. Ultrasound measures included femoral length, biparietal diameter, head circumference, transversal abdominal diameter and abdominal circumference as well as Doppler recordings of the uterine artery at 20–24 WA, and of the umbilical artery at 30–34 WA.

At each clinical examination, the child's weight and height were measured. In between, weight and height data were collected from self-administered questionnaires and

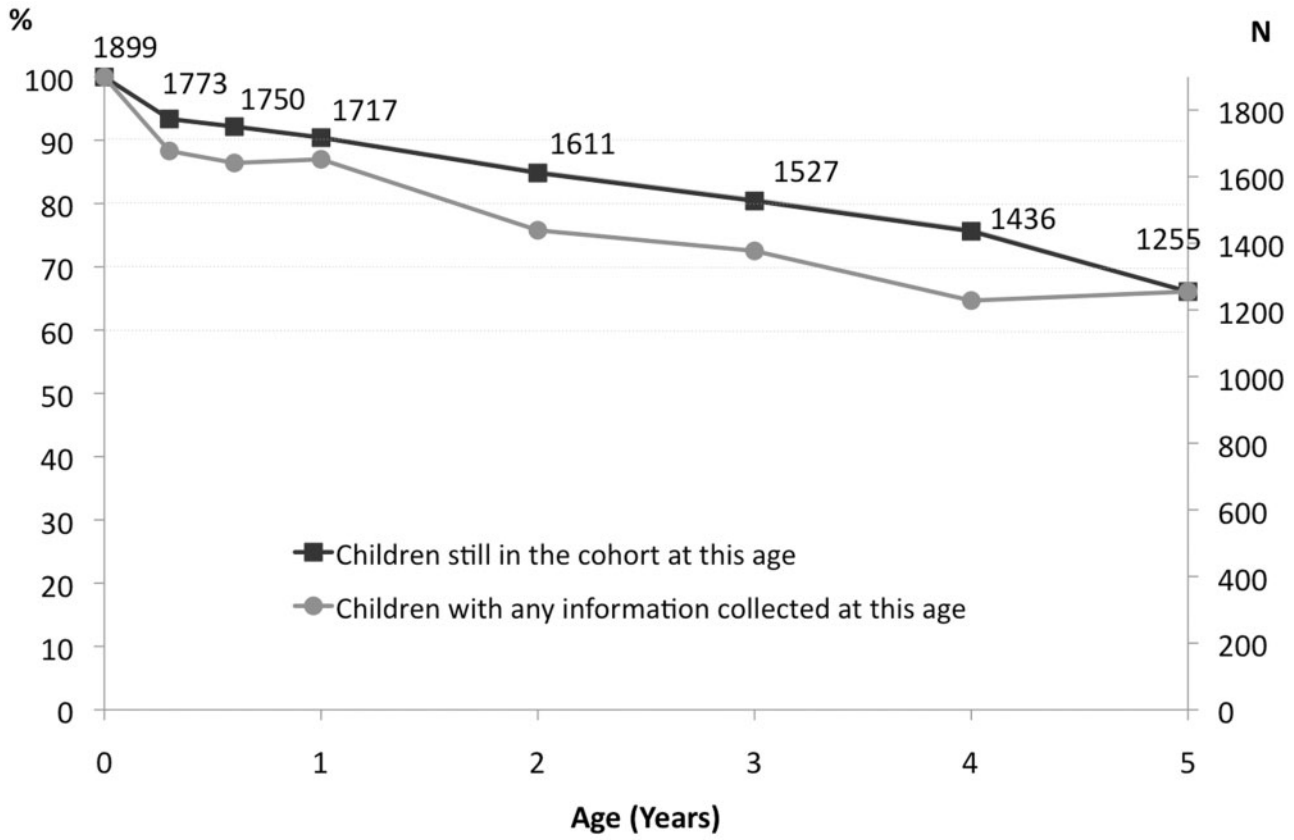

Figure 3. Percent and number of children followed-up from birth to five-six years (with some data collected at this age: grey dots and lines; and not lost to follow-up, i.e. still in the cohort but with no information at this age: black squares and lines). The EDEN Study.

Table 2. Data collected on maternal health and exposures. The EDEN study

	24–26 WA	Delivery	4 months	8 months	1 year	2 years	3 years	4 years	5–6 years
Health									
Weight	♙✍	♙	–	–	♙	–	♙	–	♙
Height	♙	–	–	–	–	–	–	–	♙
Body composition (BIA)	–	–	–	–	–	–	–	–	♙
Blood pressure	♙	♙	–	–	–	–	–	–	♙
Heart rate	♙	♙	–	–	–	–	–	–	♙
Asthma/allergy	✍	✍	–	–	–	–	–	–	–
Infectious disease	✍	❐	–	–	–	–	–	–	–
Mental health	✍	♙	✍	✍	✍	✍	✍	✍	✍
Exposures									
Tobacco smoking	✍	✍	✍	✍	✍	✍	✍	✍	✍
Passive smoking	✍	✍	✍	✍	✍	✍	✍	✍	✍
Alcohol consumption	✍	✍	✍	✍	✍	✍	✍	–	–
Binge drinking	✍	✍	–	–	–	–	–	–	–
Substance misuse	✍	✍	–	–	–	✍	–	–	–
Medicine intake	–	✍	✍	✍	✍	✍	✍	–	–
Diet and dietary behaviour	✍	✍	–	–	–	✍	–	–	–
Stress/depression	✍	–	–	–	–	–	✍	–	✍
Occupational hazards	✍	✍	–	–	–	–	–	–	–
Outdoor air pollution	✍	✍	–	–	✍	✍	✍	–	–
Indoor contaminants	–	✍	–	–	–	–	–	–	–

The table specifies whether information was not collected at this follow-up (–), collected through health records (❐), self-administered questionnaires (✍) or from the midwives during clinical examinations (♙).

BIA, bio impendance analysis; WA, weeks of amenorrhoea. At 24–26 WA, many questions also concerned the pre-pregnancy period: on weight before pregnancy, weight evolution since age 20 years, diet during the year preceding pregnancy, alcohol consumption, tobacco use before and at the beginning of pregnancy and health antecedents.

at clinical visits when reported by health professionals in the child's health booklet. Thus, children had on average 22 weight measurements (interquartile range 16–26) from birth to 5–6 years. Individual growth curves were obtained using the Jenss growth curve model.[12] This method allows parameters on individual growth patterns to be estimated, such as growth velocities at any age.[13]

Atopy and asthma

An enriched version of the International Study on Asthma and Allergies in Childhood (ISAAC) questionnaire was used to identify single phenotypes of asthma, allergic rhinitis and eczema (atopic dermatitis) between birth and 5–6 years.[14,15] Multidimensional phenotypes (bronchiolitis with wheezing, doctor-diagnosed asthma with a history of bronchiolitis, doctor-diagnosed asthma with wheezing and doctor-diagnosed asthma with wheezing and a history of bronchiolitis) were also introduced for asthma in the first year of life.[16] Lung function was assessed at 5–6 years of age according to the European Respiratory Society guidelines for children, using an MIR device. Lung function parameters included forced expiratory volume in 1 s (FEV_1), vital capacity (VC) and forced expiratory flow 25–75 (FEF_{25-75}). Manoeuvres were repeated three times and the best value will be considered for analysis.

Atmospheric pollutants

Several air pollution models have been developed in the study areas. These include a model based on air quality monitoring stations (NO_2, PM_{10}), a land-use regression model (NO_2)[17,18] and two dispersion models (based on ADSM-Urban software ADMS for NO_2 and PM_{10}; STREET for NO_2, PM_{10}, CO, volatile organic compounds and benzene) at the home address.[14,16,19–22] In addition, for a subsample of 271 non-smoking women, their personal exposure to seven volatile organic compounds (including benzene, toluene, xylenes, chloroform and a glycol ether) were obtained using passive air samplers (Radiello, Fondazione Salvatore Maugeri, Padova, Italy) carried by the pregnant women over 7 days around the 24th gestational week.[23]

The EDEN biobank and DNA bank

Special biological centres were set up for the study in the two locations under the supervision of local biologists. Preparation and storage of all biological samples during

Table 3. Data collected on childrens' health, development and exposures. The EDEN Study

	Birth	4 months	8 months	1 year	2 years	3 years	4 years	5–6 years
Health								
Weight	👤❐	✍	✍	👤	✍	👤	✍	👤
Height	👤❐	✍	✍	👤	✍	👤	✍	👤
Head circumference	👤❐	✍	✍	👤	✍	👤	✍	👤
Waist circumference	–	–	–	👤	–	👤	–	👤
Skinfolds	👤	–	–	👤	–	👤	–	👤
Ultrasound	❐	–	–	–	–	–	–	–
Body composition (BIA)	–	–	–	–	–	–	–	👤
Asthma/allergy	–	✍	✍	✍	✍	✍	✍	✍
Lung function	–	–	–	–	–	–	–	👤
Infectious diseases	–	✍	✍	✍	✍	✍	✍	✍
Blood pressure	–	–	–	–	–	👤	–	👤
Heart rate	–	–	–	–	–	👤	–	👤
Sleep	–	✍	✍	✍	✍	✍	✍	✍
Hearing/vision	–	–	✍	✍	✍	✍	✍	✍
Hospitalizations	–	✍	✍	✍	✍	✍	✍	✍
Behaviour and cognitive development								
IQ	–	–	–	–	–	–	–	👤
Other cognitive assessments	–	✍	✍	👤✍	✍	👤✍	✍	👤✍
Behaviour	–	–	–	✍	✍	✍	–	✍
Exposures								
Breastfeeding	❐	✍	✍	✍	✍	–	–	–
Diet	–	✍	✍	✍	✍	✍	✍	👤✍
Indoor pollution	–	–	–	✍	✍	✍	–	–
Pet contact	–	–	✍	✍	✍	✍	–	✍
Physical activity	–	–	–	✍	✍	✍	–	✍
Medicine intake	–	✍	✍	✍	✍	✍	✍	✍
Vaccinations	–	✍	✍	✍	✍	✍	✍	✍
Others								
Child care and school attendance	–	–	✍	✍	✍	✍	✍	✍

The table specifies whether information was not collected at this follow-up (–), collected from health records (❐), through parental questionnaires (✍) or from the midwives or psychologists during clinical and cognitive examinations (👤).

BIA, bio impendance analysis.

the pregnancy period were performed by up to two laboratory technicians in each location. All biological material is stored in −80°C freezers with alarm control. The types and origins of the biological samples obtained during the three phases of biological collection are listed in Table 5. DNA has been extracted from 1755 pregnancy blood samples, 1312 paternal samples, 1367 cord blood samples, 668 placenta samples and 836 blood samples in 5–6-year-old children; 682 children had DNA both from cord blood and at 5–6 years. Amplified and genomic DNA samples are now stored in 96-well plates at −80°C. More than 40 single nucleotide polymorphisms (SNPs) have been genotyped either from genomic or from amplified DNA. Epigenetic analyses in cord blood on candidate locations have been performed,[24] and methylome analysis was conducted on the 668 placentas.

What has it found? Key findings and publications

More than 60 articles based on EDEN data have been published up to April 2015, on EDEN alone or in collaboration with other cohorts. Details and updates of these results can be found on the EDEN study website.[9] Many different fields of exposure and health outcomes have been covered by these publications, and some examples are summarized below.

Maternal diet and nutrition

We have shown fish intake during pregnancy to be associated with a higher birthweight but only in overweight mothers,[25] a finding later confirmed by the meta-analysis of several European cohorts, including the EDEN study.[26]

Table 4. Other data collected on pregnancy, delivery, households, fathers and biomarkers measured so far. The EDEN Study

Pregnancy and delivery	Child's sex, gestational age at birth, mode of delivery, Apgar score, malformations, congenital malformations, stillbirth, prenatal diagnosis, preeclampsia, gestational diabetes
Obstetric and medical history	Induced abortions, spontaneous abortions, previous deliveries, chronic diseases, all antenatal visits and previous pregnancies' antecedents
Parents/household	Planned pregnancy, parental ages at birth, fertility treatment, time to pregnancy, education, occupations, single parenthood
Fathers	Weight, height, diabetes, smoking habits, alcohol consumption, substance misuse, occupational hazards
Biomarkers[a]	Phenols, phthalates, albumin, fatty acids, allergens, methylation, lead, cadmium, about 50 candidate SNPs

[a]A non exhaustive list of biomarkers measured so far either in the whole population or on smaller samples, either in the mother or in children or both.

Table 5. Biological samples collected during pregnancy, at birth and at 5–6 years. The EDEN Study

	During pregnancy	*Birth*	*5–6 years*
DNA	Mother	Father, Cord	Child
Plasma	Mother	Father, Cord	Child
Serum	Mother (Fasting and 1 h post charge)	Cord	Child
Platelets	–	Cord	–
Urine	Mother	–	Child
Erythrocytes	Mother	Cord	–
Colostrum	–	Mother	–
Cord samples	–	Cord	–
Meconium	–	Child	–
Placenta samples	–	Placenta	–
Hair[a]	Mother	Mother, Child	Child
Saliva	Mother	–	–

The table specifies whether information was not collected at this follow-up (–).
[a]also collected at 3 years.

A lower ratio between maternal dietary n6 and n3 PUFA intake was shown to be associated with better cognitive development in children who were not breastfed.[27]

Concerning maternal nutritional status and its changes over time,[28–30] we found that in mothers with a BMI below 25 kg/m^2 when starting pregnancy, weight loss in the years preceding pregnancy was associated with a higher risk of the newborn being undersized for his gestational age (SGA). On the other hand, regardless of pre-pregnancy BMI, an average weight gain of more than 0.5 kg/year between the age of 20 years and pregnancy was positively associated with a maternal risk of gestational diabetes and hypertension.[31]

Infant nutrition, growth and development

We underlined an association with paternal BMI emerging progressively in the first months of life, contrasting with a lack of association between maternal BMI and growth velocity at 3 months.[32] In an individual meta-analysis with three other cohorts, a genetic score of obesity susceptibility was shown to be associated with an increase in early postnatal and global growth, but not prenatal growth.[33]

In a subsample of the cohort we showed that cord insulin concentration was negatively associated with growth during the first year in girls but not in boys, suggesting that early growth patterns may be programmed by fetal hyperinsulinemia, and that girls may be more susceptible than boys to its consequences.[34]

A longer breastfeeding duration was associated with a lower increase in weight and length between birth and 4 months but no difference was observed among bottlefed babies regarding the different types of formula used.[35] Lastly, we showed that even in the French context, characterized by a shorter average breastfeeding duration than in most other European countries, breastfeeding for a longer duration was associated with a better cognitive development at 2 and 3 years.[36]

Environment, including Atmospheric Pollution

Air pollution effects have been studied using a variety of approaches ranging from monitoring-station data[21] and

fine-scale exposure models[19,22,37] to volatile air compounds (VOC) personal passive air samplers.[23] Maternal exposure to airborne benzene during pregnancy was associated with lower weight and smaller biparietal diameter during pregnancy and lower head circumference at birth.[23] Maternal exposure to ambient air pollution before and during pregnancy was associated with an alteration of the distribution of cord blood lymphocyte phenotypes in newborns.[16] In addition, results showed that gestational exposure to ambient urban air pollution, especially during late pregnancy, may contribute to lower vitamin D levels in offspring.[20] Possible effects of atmospheric pollutants on maternal blood pressure[21] and placental weight[19] have also been suggested, and possible effects on neurodevelopment have been considered in the context of the ESCAPE EU project.[38,39] Contamination with lead (blood levels) was associated with a higher risk of gestational hypertension.[40] Based on pregnancy maternal urine samples, triclosan (an organochlorine pesticide found in soap and tooth paste) and parabens concentrations were associated with pre- and postnatal growth.[41]

Both single and multidimensional asthma phenotypes were related positively to reported heavy parental smoking, traffic-related air pollution and dampness, and negatively to cat exposure and domestic wood heating in the first year of life.[14] Having suffered from bronchiolitis in the first year of life was associated with passive smoking and *in utero* exposure to traffic-related air pollution reported during pregnancy,[14] but not with NO_2 levels assessed by a dispersion model.[17] Vitamin D deficit at birth was related to eczema from 1 to 5–6 years and transient wheezing but not asthma.[15]

Mental Health, Behaviour

We showed that the combination of maternal depression and anxiety during pregnancy was associated with an increased risk of spontaneous preterm birth.[42] Social withdrawal, assessed in 1-year-old infants by midwives using the Alarm Distress Baby Scale, predicted relational and behavioural disorders at 3–5 years.[43,44]

Collaborations and perspectives

The large array of phenotypic, clinical and biological material collected in the EDEN cohort has led to a number of national and international collaborations. For example, the HABEAT project, a multidisciplinary approach for studying determinants of food habits in early childhood, has involved six different European countries [http://www.habeat.eu/]. EDEN was included in the MEDAll (Mechanisms of the Development of Allergy), CHICOS (Developing a Child Cohort Research Strategy for Europe [http://www.chicosproject.eu/], ENRIECO and HELIX exposome projects,[45] four projects conducted within the European Union's 7th Framework Programme.[46,47] Regarding atmospheric pollutants, EDEN is involved in ESCAPE (European Study of Cohorts of Air Pollution Effects, FP7) [http://www.escapeproject.eu/][37] and ICAPPO (International Collaboration on Air Pollution and Pregnancy Outcomes).[48,49]

At the national level, EDEN helps in developing the objectives and design of the first national French birth cohort ELFE [http://www.elfe-france.fr/index.php/en/], launched in April 2011, that will examine every aspect of the lives of more than 18 000 children, from health, social and environmental perspectives.[50]

What are the main strengths and weaknesses?

The main strengths of EDEN are its general population basis with the inclusion of women very early in pregnancy. It offers a large variety of data with frequent collection, especially in infancy, and fine phenotyping through three clinical examinations for the mother (during pregnancy, at delivery and 5–6 years after delivery) and four clinical examinations for the child from birth to 5–6 years, including cognitive assessments at three and 5–6 years. Moreover, standardized questionnaires and extensive DNA and biological collections enrich the data collection. Another positive specificity of EDEN is the quantity of data collected from fathers.

Because of the area-based mode of recruitment and the selective acceptance of participation in the study, urban, well-educated and high-income households are over-represented in the EDEN mothers compared with the national population. This characteristic of the cohort is accentuated by attrition during follow-up. This may have introduced some bias in the estimation of associations and may impact on the external validity of some of the results. Finally, our sample size does not allow the study of rare diseases and extreme values for continuous traits unless data are pooled with those of other cohorts, as we have done, for example, to study the environmental risks of low birthweight.[37]

Can I get hold of the data? Where can I find out more?

As mentioned earlier, further details on the study can be found on the EDEN website: [https://eden.vjf.inserm.fr/index.php?lang=en].[9]

EDEN profile in a nutshell

- EDEN is a mother-child cohort study investigating the prenatal and early postnatal determinants of child health and development.
- Pregnant women ($n = 2002$) were recruited before 24 weeks of amenorrhoea in two maternity clinics from middle-sized French cities (Nancy and Poitiers). Deliveries occurred from May 2003 to September 2006, and 1907 newborns were then included.
- Detailed information on phenotypes and exposures were collected through questionnaires from pregnancy until 8 years and through clinical examinations of the mother (at 24 weeks of amenorrhoea, at delivery and 5–6 years after delivery) and the child (at birth and 1, 3 and 5–6 years, including cognitive assessments at 3 and 5–6 years). At 5–6 years, 1255 children were still followed up.
- The main outcomes of interest are fetal (via ultrasound) and postnatal growth, adiposity development, respiratory health, atopy, behaviour and bone, cognitive and motor development. The main early-life determinants studied are maternal nutrition, diet, eating behaviour, environmental pollutants (atmospheric pollutants, phenols, phthalates, heavy metals and allergens) and socioeconomic and psycho-emotional factors. Biological samples have been collected. Genetic and epigenetic data are available.
- Any researcher interested in exploring EDEN data should contact directly the corresponding author of this paper [barbara.heude@inserm.fr] or [etude.eden@inserm.fr].

The Birth Cohort project and its website is another resource where useful information can be found: [http://www.birthcohorts.net/bch2/].[47] The web page dedicated to EDEN provides a basic description of the cohort, a list of data and biological samples collected for assessment of exposures and disease in children, mothers and fathers, for each follow-up.

EDEN is involved in many national and international collaborations and is keen to develop new ones. Any researcher interested in exploring EDEN data should contact directly the corresponding author [barbara.heude@inserm.fr] and [etude.eden@inserm.fr] to complete a dedicated project form for evaluation by the EDEN steering committee.

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