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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 22 g (95% CI: 8, 37), 57 g (95% CI: 32, 81), and 194 g (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 a moderate increase in weight growth velocity during early childhood that resulted in a moderately 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.

1. Introduction

Childhood obesity is a large public health challenge worldwide (de Onis et al., 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 et al., 2015; Tang-Peronard et al., 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

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sugar molecule (Dybing and Sanner, 2003; Tareke et al., 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 et al., 2012). Acrylamide is also found in cigarette smoke, and smoking can contribute extensively to acrylamide exposure (Mojska et al., 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 0.4–1.9 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 (Zodl et al., 2007). Acrylamide is a known neurotoxicant (Ferguson et al., 2010; IARC, 1994) and can exert reproductive and developmental toxicity effects (Yilmaz et al., 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 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 via blood through the placenta to the fetus (Annola et al., 2008; Sorgel et al., 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 et al., 2013; Kadawathagedara et al., 2016; Pedersen et al., 2012). In Duarte-Salles et al., the adjusted OR for SGA was 1.11 (95% CI: 1.02, 1.21) and the birth weight change was −25.7 g (95% CI: −35.9, −15.4), for the highest vs. the lowest quartile of maternal acrylamide intake (Duarte-Salles et al., 2013). In Pedersen et al., the change on birth weight was −132 g (95% CI: −207, −56), for infants in the highest vs. the lowest quartile of acrylamide hemoglobin adduct (Pedersen et al., 2012). In Kadawathagedara et al., the adjusted OR for SGA was 1.11 (95% CI: 1.03, 1.21) and the change in birth weight was −9.8 g (95% CI: −21.3, 1.7) per 10 μg/day increase in maternal acrylamide intake (Kadawathagedara et al., 2016). 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 have 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 et al., 2008; Stout et al., 2015). However, there is currently no epidemiological study that has examined the potential association between prenatal acrylamide exposure and postnatal growth.

Therefore, the aim of the present study was to investigate the association between maternal dietary acrylamide intake during pregnancy and postnatal growth in children up to age 8 years in a large population-based cohort study in Norway, the Norwegian Mother and Child Cohort Study (MoBa).

2. Material and methods

2.1. Study population

Our study was conducted within MoBa, which is a prospective population-based pregnancy cohort study conducted by the Norwegian Institute of Public Health (Magnus et al., 2016). In brief, participants from all over Norway were recruited by postal invitation prior to their 1st ultrasound visit (17-18th gestational week) during the years 1999 to 2008. The women consented to participation in 40.6% of the pregnancies. MoBa now encompasses 114,500 children, 95,200 mothers and 75,200 fathers. 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 eligible study population included 80,453 women with singleton, live born babies without malformations and chromosomal anomalies and available acrylamide intake 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 and > 20 MJ, 2% excluded), paternal weight (5% missing), gestational age (0.4% missing), child gender (no missing), birth weight (0.1% missing) and length (3% missing), the population with non-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 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 detail by Duarte-Salles et al. (Duarte-Salles et al., 2013) and Brantsaeter et al. (Brantsæter et al., 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 et al., 2008a). The validation study 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 validation study also reported fair agreement between acrylamide metabolite concentrations in 24-hour urine and estimated acrylamide intake (Brantsæter et al., 2008b).

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), cooked potatoes, fried potatoes, coffee (coffee, decaffeinated coffee, fig coffee, milk based coffee), chocolate, sweets, salty snacks (potato crisps, potato snacks, peanuts and popcorn, pretzels), milk desserts (yoghurt with cereals, chocolate milk and chocolate pudding), and other (poultry, pizza and tacos, breaded fish, olives, dried fruits, chocolate/hazelnut spread).

2.3. Children's diet

We further assessed the exposure to acrylamide via the children's diet, by defining acrylamide food-scores that included possible contributors to the children's acrylamide intake, using previously applied methodology (Pedersen et al., 2012). The dietary information was collected via short food frequency questionnaires answered by the mother at child's age 3 and 7 years. At 3 years, the possible contributors of acrylamide intake included: biscuits, buns, chips and bread. We further defined an acrylamide-food score by giving 0 points if the child did not consume and 1 point if the child did consume the item (non-consumers: biscuits: 64%, buns: 60%, chips: 67%), while for bread, we assigned 0 points for consumption once per day or less (76%) and 1 point for more frequent consumption. The sub-scores for the different food items were summarizing and the acrylamide-food score grouped into 3-categories: low exposed children (n = 5511, 25%), average exposed (n = 7659, 34%) and high exposed (n = 9181, 41%).

At 7 years, the possible contributors of acrylamide intake included: soft bread, crispbread, breakfast cereals, pancakes, buns and chips. To define the acrylamide food-score, 0 points were assigned when the child's intakes were: soft bread ≤median (4 slices/day, 67%), crispbread ≤median (1 slice/day, 69%), breakfast cereals ≤3 times/month (74%), pancakes ≤3 times/month (88%), buns ≤3 times/month (78%), chips ≤3 times/month (61%), and 1 point was assigned for higher intake frequencies. The sub-scores for the different food items were summarizing and the acrylamide-food score grouped into 3-categories score: low exposed children (n = 4169, 19%), average exposed children (n = 7998, 36%) and high exposed children (n = 10,184, 46%).

2.4. 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 no specification was provided for measurements from 2 to 8 years. From birth to 5 years, weight and height of Norwegian children are screened in scheduled free voluntarily appointments at the public health centers. On average, seven repeated measurements of weight and height (10th and 90th 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 these, 2101 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 Fig. 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-Maximization (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 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 values 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 et al., 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 et al., 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).

2.5. Covariates

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 intake in pregnancy and fetal 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, 25.0–29.9, ≥30.0 kg/m^2), 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 (kcal, assessed concomitantly with acrylamide), and paternal BMI (kg/m^2) and height (m) were tested as potential confounders. We also tested for interaction between acrylamide intake 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 < .05. In addition, confounding by postnatal acrylamide exposure was explored by further adjustment for children's acrylamide food-scores at 3 years and 7 years described above.

2.6. Statistical analysis

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

Logistic regression models were used to investigate the association between maternal 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 children'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, v) examining acrylamide intake as three independent variables reflecting the amounts from the principal contributors (crispbread, sweet bakery items and bread) and vi) we have further explored the association between maternal acrylamide intake and risk for overweight at 3, 5 and 8 years after conditioning for children's acrylamide food-score. First, the association was explored with no adjustment for the children's acrylamide food-score but in the same number of mother-child pairs with available information on the food score. Second the acrylamide food-score was added in the model and third stratified analysis for low and high exposed children was performed.

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 (R Development Core Team, 2016).

3. Results

The mean maternal age at delivery was 30.3 years. Forty-six percent of the women were primiparous and 65% of the women had a normal BMI. The average weight gain during pregnancy was 14.8 kg. A large majority (93%) of the women in our study were non-smokers. Their babies had an average birth weight of 3620 kg and were born at 40 weeks of amenorrhea (Table 1).The median and interquartile range (IQR) of dietary acrylamide intake was 24.7 μg/day (IQR 18.4, 33.2), corresponding to 0.011 μg/kcal/day (IQR 0.008, 0.014) in 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 (Fig. 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 from crispbread increased to 25% (9% in the 1st quartile) and the contribution from bread decreased to 14%. 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 2). 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 associations were weaker at 5 and 8 years but similar positive trends were observed. Maternal acrylamide intake increased the ORs for obesity at 3 and 5 years and similar dose-response trends were observed, while only the association for the highest acrylamide (Q4) intake and obesity at 3 years was statistically significant. At 8 years, non-significant reduced odds were observed for Q2 and Q3 and increased odds for Q4. 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 (Fig. 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 effect-measure modification 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 (Fig. 3a). Regarding weight growth velocity, maternal acrylamide intake in the 4th quartile was associated with higher weight gain velocity from 1st month to 5 years (Fig. 3b). Finally, maternal energy-adjusted acrylamide intake higher than the 1st quartile was associated with higher BMI throughout the whole childhood (Fig. 3c).

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 3). At eight years, children highly exposed during the prenatal period weighed between 110 g to 278 g more than their low exposed peers, while the effect estimates were of small magnitude (~0.4–1% higher than the average weight at 8 years). Further adjustment for children's height did not change the results (data not shown). In combination with the observed association with BMI trajectories, this indicates that the association between acrylamide and weight trajectory is independent of height. 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 the exposure variable (in μg/day) the associations with overweight and obesity were similar, while for obese children 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).

When exploring the association between maternal acrylamide intake and risk of overweight after conditioning (adjustment and stratification) for children's acrylamide food-scores, the results were similar (Supplementary Figs. 2, 3 and 4). At 3 years, further adjustment for the acrylamide food-score did not modify the estimates (Supplementary Fig. 2). After restricting to low or high exposed children, maternal acrylamide intake was still associated with child overweight, indicating no effect of postnatal diet. At 5 years, in line with the results at 3 years, adjustment for children's acrylamide food-score did not modify the association between prenatal acrylamide exposure and child overweight (Supplementary Fig. 3). In addition, children with low exposure to acrylamide from their own diet, still were at higher risk for overweight due to high maternal acrylamide intake during pregnancy. After adjustment for acrylamide food-score at 8 years, the association between maternal acrylamide intake and overweight risk was attenuated, as also seen at the main analysis included in our manuscript (Supplementary Fig. 4).

4. Discussion

We found that prenatal acrylamide exposure was associated with a moderate increase in the prevalence of children being overweight or obese and moderately increased 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 studies have examined postnatal growth. The first study reporting an association with fetal growth was in 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 two assessed acrylamide exposure through diet (Duarte-Salles et al., 2013; Kadawathagedara et al., 2016). All three studies showed that high prenatal exposure to acrylamide was associated with impaired fetal growth. These results are 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).

Our findings of increased prevalence of overweight associated with high prenatal acrylamide exposure are in line with the Fetal

Table 1
Characteristics of study population overall and by quartile of acrylamide intake.

	All		Energy adjusted acrylamide intake during pregnancy (quartiles-in μg/kcal/day)							
			Q1 (≤18.3)		Q2 (18.4–24.6)		Q3 (26.7–33.1)		Q4 (≥33.2)	
	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD
Maternal age (years)	30.3	4.4	30.0	4.5	30.2	4.3	30.4	4.4	30.5	4.5
Gestational weight gain (kg)	14.8	5.8	14.8	6.0	14.7	5.7	14.8	5.7	14.7	5.9
Birth weight (g)	3620	520	3626	521	3623	521	3618	521	3620	520
Gestational age (weeks)	40.0	1.6	40.0	1.6	40.0	1.6	40.0	1.6	40.1	1.5

	All		Energy adjusted acrylamide intake during pregnancy (quartiles-in μg/kcal/day)							
			Q1 (≤18.3)		Q2 (18.4–24.6)		Q3 (26.7–33.1)		Q4 (≥33.2)	
	N	%	N	%	N	%	N	%	N	%
Maternal education										
Low (≤12 years)	14,405	28	3634	29	3392	26	3470	26	3909	30
Medium (13–16 years)	22,993	44	5356	42	5904	45	6009	46	5724	44
High (≥17 years)	14,554	28	3636	29	3853	29	3699	28	3366	26
Pre-pregnancy BMI										
< 18.5	1287	3	357	3	326	3	304	2	300	2
18.5–25	33,929	65	8234	65	8722	66	8626	66	8347	64
25–30	11,947	23	2829	22	2905	22	3057	23	3156	25
> 30	4789	9	1206	10	1196	9	1191	9	1196	9
Parity										
Nulliparous	24,060	46	6252	50	6129	47	5959	45	5720	44
Multiparous	27,892	54	6374	50	7020	53	7219	55	7279	56
Smoking during pregnancy										
No	48,439	93	11,861	94	12,420	95	12,320	94	11,838	91
Occasionally	1227	2	246	2	270	2	317	2	394	3
Daily	2286	5	519	4	459	3	541	4	767	6
Exposure to 2nd hand smoking										
No	47,107	91	11,368	90	12,013	91	12,304	91	11,692	90
Yes	4845	9	1258	10	1136	9	1144	9	1307	10
Alcohol consumption during pregnancy										
No	45,803	88	11,398	90	11,682	89	11,520	87	11,203	86
Yes	6149	12	1228	10	1467	11	1658	13	1796	14
Children's diet										
Acrylamide food-score at 3 years[a]										
Low	5511	25	1541	29	1428	25	1367	24	1175	21
Average	7659	34	1889	35	2083	26	1907	33	1780	32
High	9181	41	1894	36	2260	39	2492	43	2535	46
Acrylamide food-score at 7 years[a]										
Low	4169	19	1124	21	1171	20	1008	17	866	16
Average	7998	36	2042	38	2073	36	2005	35	1878	34
High	10,184	45	2158	41	2527	44	2753	48	2746	50

[a] N = 22,351 mother-child pairs.

Programming (Barker, 1998) and the Developmental Origins of Health and Disease hypotheses (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 fetal growth.

There are only few studies showing that early life chemical exposure may be obesogenic (Botton et al., 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 et al., 2007). Acrylamide is not known to be an EDC and the CONTAM panel of EFSA concluded that the epidemiological 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 et al., 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 et al., 2016; Nazarpour et al., 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 et al., 2017). During pregnancy, high acrylamide exposure can result in increased oxidative stress through increased expression of CYP2E1, resulting further in a heightened perinatal

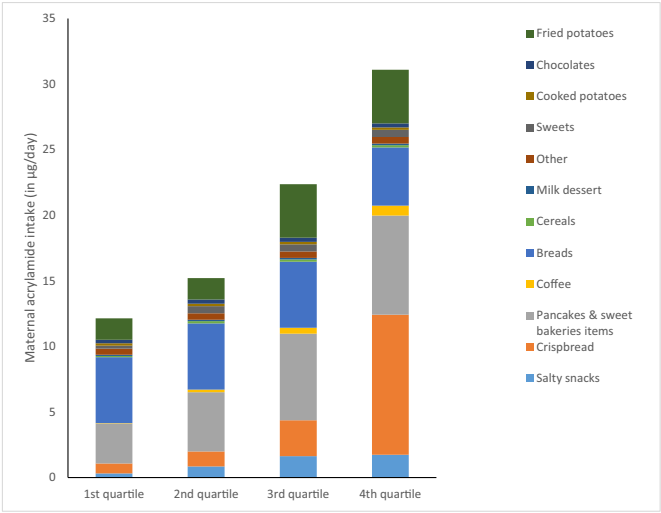

Fig. 1. Sources of maternal acrylamide intake according to quartiles of total acrylamide intake (n = 51,952) women in MoBa.

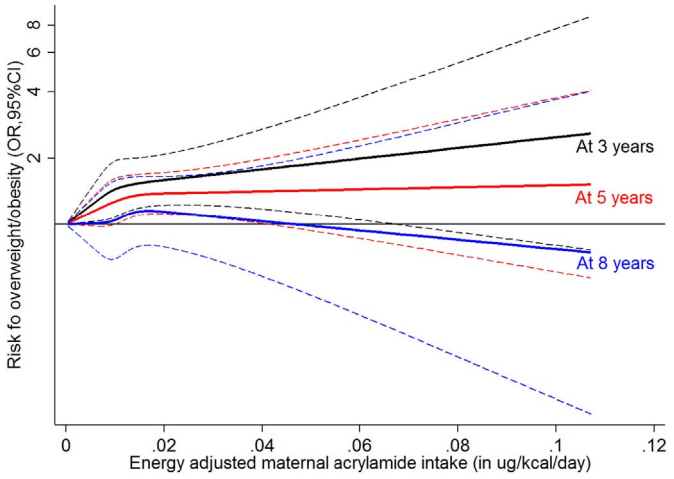

Fig. 2. Maternal acrylamide intake (µg/kcal/day) in pregnancy (in continuous scale) and child overweight/obesity at 3 (black lines), 5 (red lines) and 8 (blue lines) years (n = 51,952). Solid lines represent Odd Ratios (OR) and dotted lines represent 95% Confidence Intervals (CI). (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

inflammatory status (Nguyen et al., 2015; Wang et al., 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 et al., 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 et al., 2017). The negative association of both types of prenatal exposure on birth weight has been well described (Pedersen et al., 2013; Valero De Bernabe et al., 2004), and the mechanisms involved might be similar for acrylamide. Unfortunately, information on inflammation status was not available in our study.

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 et al., 2015), while in the present population of Norwegian women high acrylamide exposure was driven by crispbread intake. Chrispbread has a high content of dietary fiber and is 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. Another major source of acrylamide in our study population was dark bread, which is also high in fiber. Intakes of both whole-grain foods and fiber are recommended as components of a healthy diet and are included in the Norwegian food guidelines and Nordic Nutrition Recommendations (von Ruesten et al., 2014). In addition, fiber-rich bread, including dark bread and crispbread, has been identified as a component of a "prudent diet" in the same population (Englund-Ogge et al., 2014).

4.1. Strengths 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 et al., 2013). These two studies assessed acrylamide exposure via

Table 2
Maternal acrylamide intake in pregnancy and children's overweight/obesity and obesity only at age 3, 5 and 8 years (n = 51,952).

Maternal energy-adjusted acrylamide intake (µg/kcal/day)	Risk for overweight and/or obesity [a]								
	At 3 years			At 5 years			At 8 years		
	N cases/N total	OR	95% CI	N cases/N total	OR	95% CI	N cases/N total	OR	95% CI
Quartiles of intake									
Q1 (≤18.3)	1259/12,801	1.00		1954/12,801	1.00		577/12,801	1.00	
Q2 (18.4–24.6)	1354/13,012	1.10	1.02, 1.20	2088/13,012	1.08	1.01, 1.16	583/13,012	1.02	0.91, 1.15
Q3 (26.7–33.1)	1456/13,063	1.12	1.04, 1.22	2223/13,063	1.11	1.04, 1.19	662/13,063	1.12	0.99, 1.25
Q4 (≥33.2)	1461/13,076	1.21	1.11, 1.31	2240/13,076	1.17	1.10, 1.26	681/13,076	1.12	1.00, 1.26
p for trend		*< 0.001*			*< 0.001*			*0.023*	
Acrylamide intake, 1-IQR increase		1.07 (1.04, 1.11)			1.06 (1.03, 109)			1.04 (1.00, 1.09)	
Risk for obesity only[a]									
Q1 (≤18.3)	109/12,801	1.00		308/12,801	1.00		29/12,801	1.00	
Q2 (18.4–24.6)	116/13,012	1.09	0.84, 1.41	306/13,012	1.07	0.92, 1.26	27/13,012	0.76	0.46, 1.25
Q3 (26.7–33.1)	152/13,063	1.11	0.86, 1.44	381/13,063	1.13	0.96, 1.32	46/13,063	0.96	0.60, 1.53
Q4 (≥33.2)	141/13,076	1.35	1.06, 1.73	356/13,076	1.16	0.99, 1.36	52/13,076	1.46	0.96, 2.23
p for trend		*0.018*			*0.048*			*0.045*	
Acrylamide intake, 1-IQR increase		1.12 (1.03, 1.22)			1.06 (1.00, 1,13)			1.25 (1.09, 1.42)	

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.

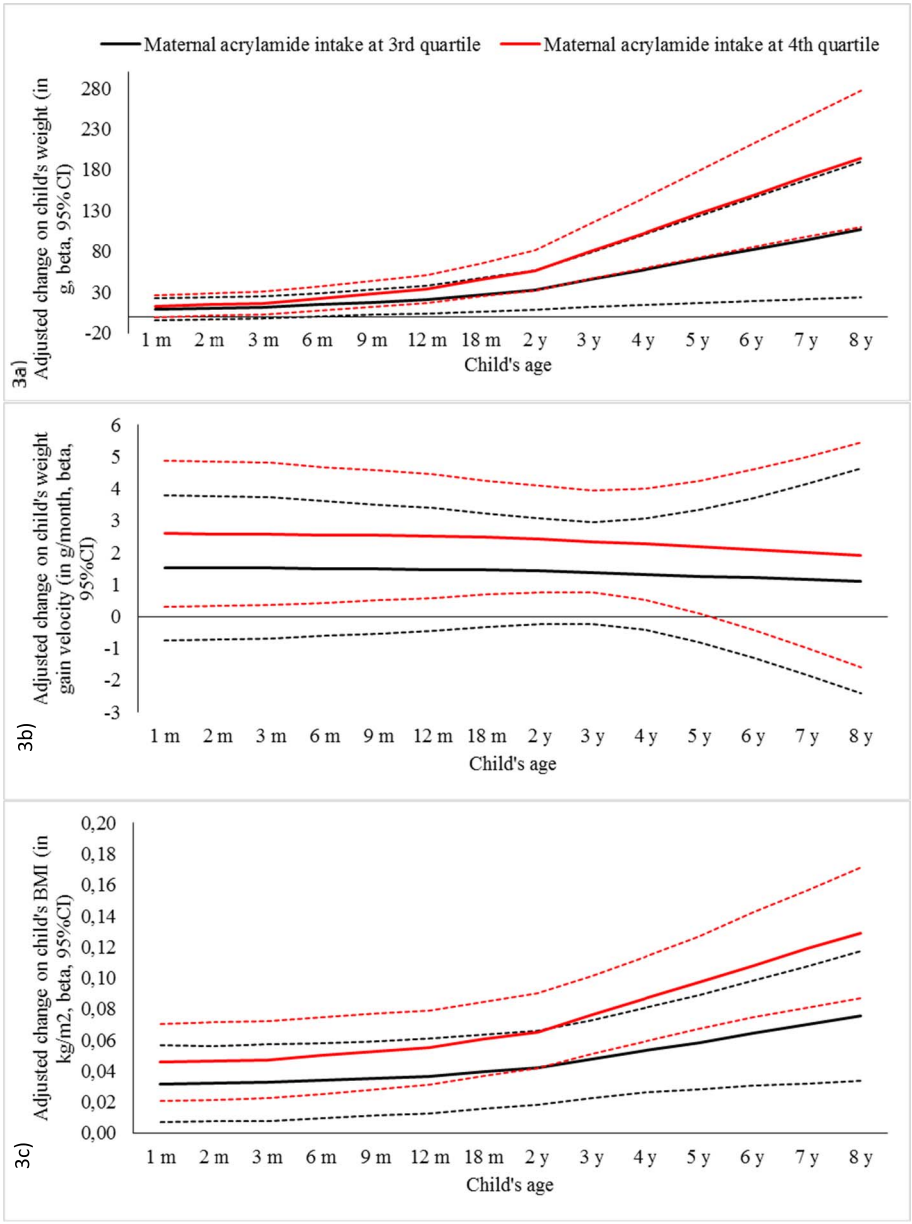

Fig. 3. Adjusted changes in children's A) weight, B) weight gain velocity and C) BMI from 1st month to 8 years, associated with 3rd and 4th maternal acrylamide intake quartiles (energy-adjusted).
All models are adjusted for maternal age, parity, maternal education, pre-pregnancy BMI, gestational weight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

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 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 (i.e. biomarkers) would be more 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 et al., 2005) and < 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 et al., 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 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). When conducting the longitudinal analysis in a subsample of children with many measurements (≥7) and up to 5 years only, similar

Table 3
Association between maternal acrylamide intake in pregnancy and children's weight, weight gain velocity and BMI from 1st month to 8 years. The 1st quartile of maternal acrylamide intake is used as the reference.

	Energy-adjusted maternal dietary acrylamide exposure (μg/kcal/day) in quartile			
	1st quartile	2nd quartile	3rd quartile	4th quartile
	Mean (SD)	β (95% CI)	β (95% CI)	β (95% CI)
Weight (in g)[a]				
3 months	6328 (613)	−0.1 (−14, 14)	11 (−2.7, 25)	17 (2.5, 31)
6 months	7976 (794)	2.6 (−12, 17)	14 (−0.2, 29)	22 (7.7, 37)
12 months	9904 (989)	8.2 (−8.7, 25)	21 (3.6, 37)	34 (17, 51)
2 years	12,558 (1265)	19 (−5.0, 44)	33 (8.4, 57)	57 (32, 81)
5 years	19,799 (2470)	53 (−0.4, 106)	70 (17, 123)	125 (73, 179)
8 years	27,000 (3942)	86 (2.5, 169)	107 (23, 190)	194 (110, 278)
Weight gain velocity (in g/month)[a]				
3 months	711 (98)	0.8 (−1.4, 3.1)	1.5 (−0.7, 3.7)	2.6 (0.4, 4.8)
6 months	429 (70)	0.9 (−1.2, 3.0)	1.5 (−0.6, 3.6)	2.6 (0.4, 4.7)
12 months	256 (43)	0.9 (−1.0, 2.8)	1.5 (−0.5, 3.4)	2.5 (0.6, 4.5)
2 years	206 (41)	1.0 (−0.7, 2.7)	1.4 (−0.2, 3.1)	2.4 (0.8, 4.1)
5 years	200 (44)	1.2 (−0.8, 3.3)	1.3 (−0.8, 3.3)	2.2 (0.1, 4.3)
8 years	200 (44)	1.5 (−2.0, 5.0)	1.1 (−2.4, 4.6)	1.9 (−1.6, 5.5)
BMI (in kg/m^2)[a]				
3 months	16.8 (1.1)	0.03 (0.00, 0.05)	0.03 (0.01, 0.06)	0.05 (0.02, 0.07)
6 months	17.4 (1.2)	0.03 (0.00, 0.05)	0.03 (0.01, 0.06)	0.05 (0.03, 0.07)
12 months	16.8 (1.2)	0.03 (0.01, 0.05)	0.04 (0.01, 0.06)	0.06 (0.03, 0.08)
2 years	16.3 (1.2)	0.04 (0.01, 0.06)	0.04 (0.02, 0.07)	0.07 (0.04, 0.09)
5 years	16.1 (1.4)	0.06 (0.03, 0.09)	0.06 (0.03, 0.09)	0.10 (0.07, 0.13)
8 years	15.3 (1.7)	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.

conclusions were drawn. We also acknowledge that the effect estimates in the longitudinal growth analysis are of small magnitude, pointing into cautionary interpretation of our findings. Nevertheless, the magnitude of the effect estimates does not reduce the importance of our findings. We found consistent associations between high maternal acrylamide intake during pregnancy and increases in all the studied weight status- and growth parameters (continuous and categorical) and we consider this as a strength of our observational study. In addition, 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 the large sample size, it is unlikely that we missed important confounders (Rothman et al., 2008). Controlling for confounding by postnatal exposure to acrylamide can be considered a strength of our study. We used an acrylamide food-score to account for children's acrylamide intake at 3 and 7 years. Conditioning on child acrylamide intake did not modify the observed associations between maternal acrylamide intake during pregnancy and weight status in childhood. In addition, the acrylamide food-score could also be interpreted as a proxy of an unhealthy diet, as it reflects consumption of sweet bakery products and chips. In this case, through the above mentioned analysis, we can still argue that an unhealthy diet during childhood cannot entirely explain our observed associations between prenatal acrylamide exposure and postnatal growth. Overall, it is less likely that the associations between high maternal acrylamide intake during pregnancy and the increased risk for overweight in childhood, as well as a modified growth trajectory, can be explained by maternal or child adherence to an unhealthy diet.

The association between acrylamide exposure during pregnancy with child 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 indication of a significant association between prenatal dietary exposure to acrylamide and a moderate increase of the prevalence of being overweight or obese and moderately increased risk of being in higher growth trajectories during early childhood and preschool age. These findings need to be confirmed in other studies.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.envint.2018.01.004.

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