



## Review article

# Maternal acrylamide exposure during pregnancy and fetal growth: A systematic review and dose-response meta-analysis of epidemiological studies

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## ABSTRACT

**Background:** Acrylamide is a food contaminant linked to developmental toxicity in animals and possibly in humans.

**Objectives:** We performed a systematic review and dose-response meta-analysis of epidemiological studies evaluating the relationship between maternal acrylamide exposure during pregnancy and the risk of being small for gestational age (SGA) and birth weight, birth head circumference and birth length.

**Methods:** We performed the literature search in PubMed, Scopus, and Web of Science, until June 6th, 2022. Studies carried out in mother-newborn pairs, assessing maternal acrylamide exposure during pregnancy, either via dietary assessments or biomarkers i.e., hemoglobin adducts of acrylamide (AA-Hb) and glycidamide (GA-Hb), and evaluating birth outcomes were included. We employed a random-effects model to assess the pooled effect estimates and their 95% confidence intervals (CI) for the association between acrylamide exposure and birth outcomes. Risk of Bias for Nutrition Observational Studies tool was used for bias assessment.

**Results:** Out of 169 records identified, five original studies were eligible, including 53,870 mother-newborn pairs in total. Means were 21.9 µg/day for estimated dietary acrylamide exposure (3 studies), and 18.4 and 14.9 pmol/g for AA-Hb and GA-Hb, respectively (2 studies). Higher risk of SGA and lower birth weight and head circumference were observed in the highest quartile of AA-Hb [odds ratio (OR): 1.20 (95% CI: 1.08; 1.33); mean difference (MD): -131 g (95% CI: -204; -58) and -0.31 cm (95% CI: -0.58; -0.04), respectively], and GA-Hb [OR: 1.36 (95% CI: 1.13; 1.64), MD: -161 g (95% CI: -271; -52); and MD: -0.38 cm (95% CI: -0.66; -0.10), respectively], whereas a lower birth length was observed only in the highest quartile of GA-Hb (MD: -0.85 cm (95% CI: -1.38; -0.33)). Results from the dose-response meta-analysis between increasing maternal acrylamide exposure during pregnancy and birth weight showed no clear evidence of a deviation from linearity. **Conclusions:** Overall, our findings strengthen the evidence of an adverse effect of maternal acrylamide exposure during pregnancy on fetal growth. These results encourage to increase preventive actions towards lowering acrylamide exposure in the population.

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## 1. Introduction

Acrylamide is abundantly present in many foods. Starch-based foods, such as cookies, potato chips, French fries, and coffee can contain high levels of acrylamide, mainly because of the Maillard reaction between the amino acid asparagine and reducing sugars at high preparation temperatures (>120 °C) (Tareke et al., 2002). Acrylamide and its epoxide metabolite, glycidamide, are small, hydrophilic, reactive compounds exerting toxicity in all tissues of the body. Acrylamide is classified as a probable human carcinogen by the International Agency for Research on Cancer (class 2A) (IARC, 1994). In addition, acrylamide has been shown to cause neurotoxicity in animals and occupationally exposed individuals, as well as reproductive and developmental toxicity in animals (EFSA CONTAM Panel, 2015). Nevertheless, the observed lower offspring birth weight in animals has been considered a result of maternal toxicity, occurring at doses far exceeding those observed in the general population (>5 mg/kg body weight per day).

Acrylamide and glycidamide pass the placental barrier relatively unhindered, as shown in perfusion studies (Annola et al., 2008). In line with those findings, two studies, performed in 75 and 171 European mother-newborn pairs, showed a strong correlation ( $r \geq 0.7$ ) between acrylamide hemoglobin adducts measured in cord blood and those measured in maternal blood; and the same was observed for glycidamide hemoglobin adducts (Pedersen et al., 2012; von Stedingk et al., 2011). In its acrylamide health risk assessment of 2015, the European Food Safety Authority (EFSA) concluded that no health effects of acrylamide other than cancer, as assessed based on rodent studies, were expected at the doses that a general diet renders (EFSA CONTAM Panel, 2015). Recent meta-analyses of epidemiological studies on dietary acrylamide intake and cancer risk suggest an association between acrylamide intake and an increased risk of endometrial and ovarian cancer (Adani et al., 2020), particularly in never-smoking women, and an increased risk of premenopausal breast cancer risk (Adani et al., 2020), while no clear indications for associations with other site-specific cancers were found (Filippini et al., 2022a). In addition, emerging evidence from epidemiological studies points to a possible association between acrylamide intake and other health outcomes (e.g., cardiovascular disease, diabetes and depressive symptoms), though the number of studies on these outcomes is still limited and their results not entirely consistent (Guo et al., 2017; Huang et al., 2018; Li et al., 2021; Liu et al., 2017, 2021; Veronese et al., 2021; Wang et al., 2021, 2022; Yin et al., 2021). As a consequence of EFSA's risk assessment related to cancer, in 2017, the European Commission set benchmark levels and mitigation measures for acrylamide in different foods (as set out in regulation EC, 2017/2158), with the goal of lowering the dietary acrylamide exposure of the general public (EC, 2017; EU, 2017).

In its 2015 risk assessment, EFSA did not use the results of the two published epidemiological studies at the time that showed an association between high maternal acrylamide exposure during pregnancy and decreased fetal growth parameters, stating that these human data involved too many uncertainties pertaining to the causality of the observed associations, to perform a risk assessment (EFSA CONTAM Panel, 2015). However, EFSA did call for further epidemiological research on the association between acrylamide intake and birth anthropometric outcomes. The importance of studying prenatal growth is clear; according to the Developmental Origins of Health and Disease (DOHaD) hypothesis, suboptimal prenatal growth entails an increased risk of several illnesses such as type 2 diabetes, obesity, and cardiovascular disease throughout the lifespan (Aris et al., 2018; Nagata et al., 2019).

Since the publication of EFSA's report, new papers on acrylamide exposure of the mother during pregnancy and fetal growth have been published (Hogervorst et al., 2021; Kadawathagedara et al., 2016; Nagata et al., 2019).

In a meta-analysis from early 2020, Zhan et al. pooled the studies on acrylamide intake and fetal growth (four for birth weight, three for the

risk of being small for gestational age (SGA) and two for head circumference) published up to April 26, 2019. The authors concluded that higher maternal acrylamide exposure during pregnancy was associated with an increased risk of being SGA and a lower birth weight (Zhan et al., 2020). Due to the limited evidence in this field, there is the need to build stronger evidence to better understand and characterize the relationship between acrylamide exposure and fetal growth. We aimed to investigate the association between maternal acrylamide exposure during pregnancy and birth anthropometric outcomes i.e., the risk of SGA, birth weight, birth head circumference and birth length, performing a meta-analysis with newly published studies. Compared to the previous meta-analysis, we included an additional study (Hogervorst et al., 2021), and an additional anthropometric outcome (namely, birth length), and we performed a dose-response meta-analysis whenever possible. Contrary to the meta-analysis by Zhan et al., we pooled multivariable-adjusted effect estimates whereas they pooled unadjusted values. We hypothesized that high maternal acrylamide exposure during pregnancy is associated with a detrimental effect on fetal growth.

## 2. Methods

### 2.1. Literature search

PubMed, Scopus, and Web of Science databases were used for the literature search. Two sets of terms were used (medical subject headings [MeSH] terms were employed, whenever possible). The first set entailed terms related to exposure to acrylamide and the second included keywords with the health outcomes under study (i.e., fetal growth, birth outcomes, birth weight, birth length, birth head circumference, and SGA). The search string was then adapted according to each database. The protocol with the detailed search strategy used for each database is presented in the Supplementary Material (Table S1). The literature search was restricted to English language publications with no time limitation (from inception until June 6th, 2022), nor any other filter.

In addition, manual reference scanning of the previously published literature including meta-analysis and eligible papers was performed to identify additional reports to be included.

This systematic literature review followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) (Page et al., 2021) and the Meta-analysis Of Observational Studies in Epidemiology (MOOSE) guidelines (Stroup et al., 2000). The meta-analysis is registered in the International Prospective Register of Systematic Reviews (PROSPERO registration number: CRD42021284654).

### 2.2. Selection of papers

#### 2.2.1. Inclusion criteria

The following inclusion criteria were applied according to the PECOS framework (Morgan et al., 2018): Population - reports with mother-newborn pairs from the general population; Exposure - highest level of maternal acrylamide exposure during pregnancy, expressed as continuous and/or categories (i.e. quintiles, quartiles, or tertiles), either measured through dietary assessment methods (e.g., food frequency questionnaire) or through established biomarkers of acrylamide exposure (e.g., hemoglobin adducts of acrylamide (AA-Hb) and glycidamide [a metabolite of acrylamide] (GA-Hb)); Comparator - lowest levels of maternal acrylamide exposure during pregnancy; Outcomes - risk estimates (risk ratio [RR] or odds ratio [OR] with corresponding 95% confidence intervals [CIs]) for the risk of being small-for-gestational-age (SGA, defined as weight below the 10th percentile of birth weight according to sex and gestational age in the study population (de Onis and Habicht, 1996; WHO, 1995)) and/or mean difference (MD) with 95% CI for birth weight, birth head circumference and birth length, adjusted at least for smoking status, since smoking has been observed to increase the level of acrylamide and to be a detrimental factor for fetal growth and development (Sabra et al., 2017; Schettgen et al., 2004); Study design -

observational epidemiological studies with original data.

### 2.2.2. Eligibility assessment

All references resulting from the search were downloaded and duplicates were removed. Two authors (J.H. and A.V.) independently screened titles and abstracts for eligibility, and a third author (T.F.) resolved any disagreements.

### 2.3. Data extraction

One of the research team members (J.H) extracted the data from the selected papers and a second team member (A.V.) independently checked them. Whenever there were disagreements, a consensus was reached by both authors. When information for the meta-analysis was missing, the corresponding author of the paper was contacted to seek clarification.

The following data were extracted: author; year of publication; study design; country; year of the baseline assessment; follow-up; age of the mother; sex of the child; smoking status; doses of acrylamide and/or glycidamide exposure, overall, by smoking status and categories of exposure i.e. quintiles, quartiles, or tertiles (mean and/or median value; according to what was available); number of mother-newborn pairs; number of newborns with SGA; person-years; risk estimates for SGA and beta coefficients for birth weight, birth head circumference and birth length, and covariables and outcomes distribution. Regression estimates with their 95% CIs were extracted for the model that adjusted for the largest set of covariables.

The median or mean (when the median was not available) of acrylamide exposure in each category was assigned to the corresponding effect estimate. If the median or mean intake in each category of exposure was not reported, the midpoint of the upper and lower boundaries of the category was assigned. If the upper bound of the highest category or the lowest bound of the lowest category were not reported, these were estimated using  $\pm 20\%$  of the lower or higher open boundaries, respectively (Filippini et al., 2022b; Vinceti et al., 2016).

### 2.4. Risk of bias assessment

The risk of bias was assessed by A.V and checked by F.L. using the Risk of Bias for Nutrition Observational Studies (RoB-NObs) tool (<https://nesr.usda.gov/>), a modified version of the Cochrane Collaboration tool for assessing the risk of bias in non-randomized studies of interventions (ROBINS-I) (Morgan et al., 2019) adapted for observational studies of food, nutrition, and public health.

### 2.5. Data analysis

For each of the fetal growth related-outcomes, we used a restricted maximum likelihood random-effects meta-analysis to assess the pooled effect estimate along with the 95% CI for the highest versus the lowest category of acrylamide exposure.

A dose-response meta-analysis of the association between acrylamide exposure and birth anthropometric outcomes was performed using the one-stage approach recently employed in other research fields, whenever there were three or more reports available (Filippini et al., 2020, 2021). The shape of the associations was evaluated using cubic splines with knots at three fixed cut-points (10th, 50th and 90th percentiles) of the exposure through a multivariate random-effects meta-analysis using the restricted maximum likelihood method (Orsini, 2021) using the median value of the distributions as the reference category. We fitted a linear regression model reporting its slope alongside the non-linear relationship yielded by the spline analysis, and we also evaluated the effect of variation across studies through graphical overlay of study-specific predicted curves. To limit heterogeneity, we did not pool together all the five studies, but we stratified the analyses by exposure assessment method (i.e., dietary acrylamide estimation or

biomarkers).

We performed additional analyses for newborns from mothers that did not smoke during pregnancy, as smokers have on average a higher acrylamide exposure than non-smokers and smoking is also known to be an independent detrimental factor for fetal growth and development (Sabra et al., 2017; Schettgen et al., 2004). In sensitivity analyses, to check for the robustness of our results, we also performed leave-one-out meta-analysis, where there were three or more studies available.

We assessed the possible presence of publication bias using Egger's regression asymmetry test for studies reporting highest versus lowest exposure when at least five studies evaluated the same outcome (Egger et al., 1997; Lin et al., 2020). We also assessed heterogeneity using the  $I^2$  statistic (Crippa et al., 2019) and we calculated its 95% CI when less than five studies (but more than one) were included (Schmid et al., 2020; von Hippel, 2015). We used 'meta', 'mvmeta' and 'drmeta' routines for of Stata statistical software, version 17.0 (Stata Corp, College Station, TX, USA, 2021) for all statistical analyses.

## 3. Results

The different steps of the papers' selection for this systematic review and meta-analysis are depicted in Fig. 1. Out of 169 records identified, five papers from five original studies met the inclusion criteria. Table 1 shows the characteristics of the studies included (Duarte-Salles et al., 2013; Hogervorst et al., 2021; Kadawathagedara et al., 2016; Nagata et al., 2019; Pedersen et al., 2012). To evaluate maternal acrylamide exposure during pregnancy, three studies used self-reported dietary assessment of acrylamide with a total of 52,326 mother-child pairs (Duarte-Salles et al., 2013; Kadawathagedara et al., 2016; Nagata et al., 2019), whereas two other studies used validated biomarkers of internal acrylamide exposure (AA-Hb and GA-Hb) with a total of 1544 mother-child pairs (Hogervorst et al., 2021; Pedersen et al., 2012). These total numbers refer to the whole sample of included children, both from mothers who smoked during pregnancy and from mothers who did not smoke during pregnancy. Nagata et al. estimated maternal dietary acrylamide intake using a dietary record for five consecutive days in week 29 of the pregnancy (Nagata et al., 2019). The other two studies that estimated maternal acrylamide intake used food frequency questionnaires (FFQ). Duarte-Salles et al. estimated dietary acrylamide exposure in the Norwegian Mother and Child cohort Study (MoBa) assessed through an FFQ in week 23–24 of the pregnancy, which covered the intake of foods during the first four to five months of the pregnancy (Duarte-Salles et al., 2013). Participating mothers in the study of Kadawathagedara et al. were part of the French EDEN mother-child study and completed an FFQ in the first few days after delivery and this FFQ covered the last three months of the pregnancy (Kadawathagedara et al., 2016). The estimated dietary exposure to acrylamide was 21.9  $\mu\text{g}/\text{d}$ , and the internal acrylamide and glycidamide exposure, measured in cord blood, were 18.4 and 14.9 pmol/g hemoglobin on average, respectively. Five studies performed analyses for birth weight (Duarte-Salles et al., 2013; Hogervorst et al., 2021; Kadawathagedara et al., 2016; Nagata et al., 2019; Pedersen et al., 2012), four for birth head circumference (Hogervorst et al., 2021; Kadawathagedara et al., 2016; Nagata et al., 2019; Pedersen et al., 2012) and three studies for the risk of being SGA (Duarte-Salles et al., 2013; Kadawathagedara et al., 2016; Pedersen et al., 2012) and for birth length (Hogervorst et al., 2021; Kadawathagedara et al., 2016; Nagata et al., 2019) (Table 1). All studies were performed in both boys and girls except for one study where only girls were included (Nagata et al., 2019). Most of the mothers reported to have medium-high education and to be multiparous, and more than 73% were never smokers (Table 1).

Summary effect estimates from the five studies pooled by acrylamide exposure assessment method (i.e., dietary assessment method or biomarkers) and each of the birth anthropometric outcomes for the overall populations are shown in Figs. 2–5.

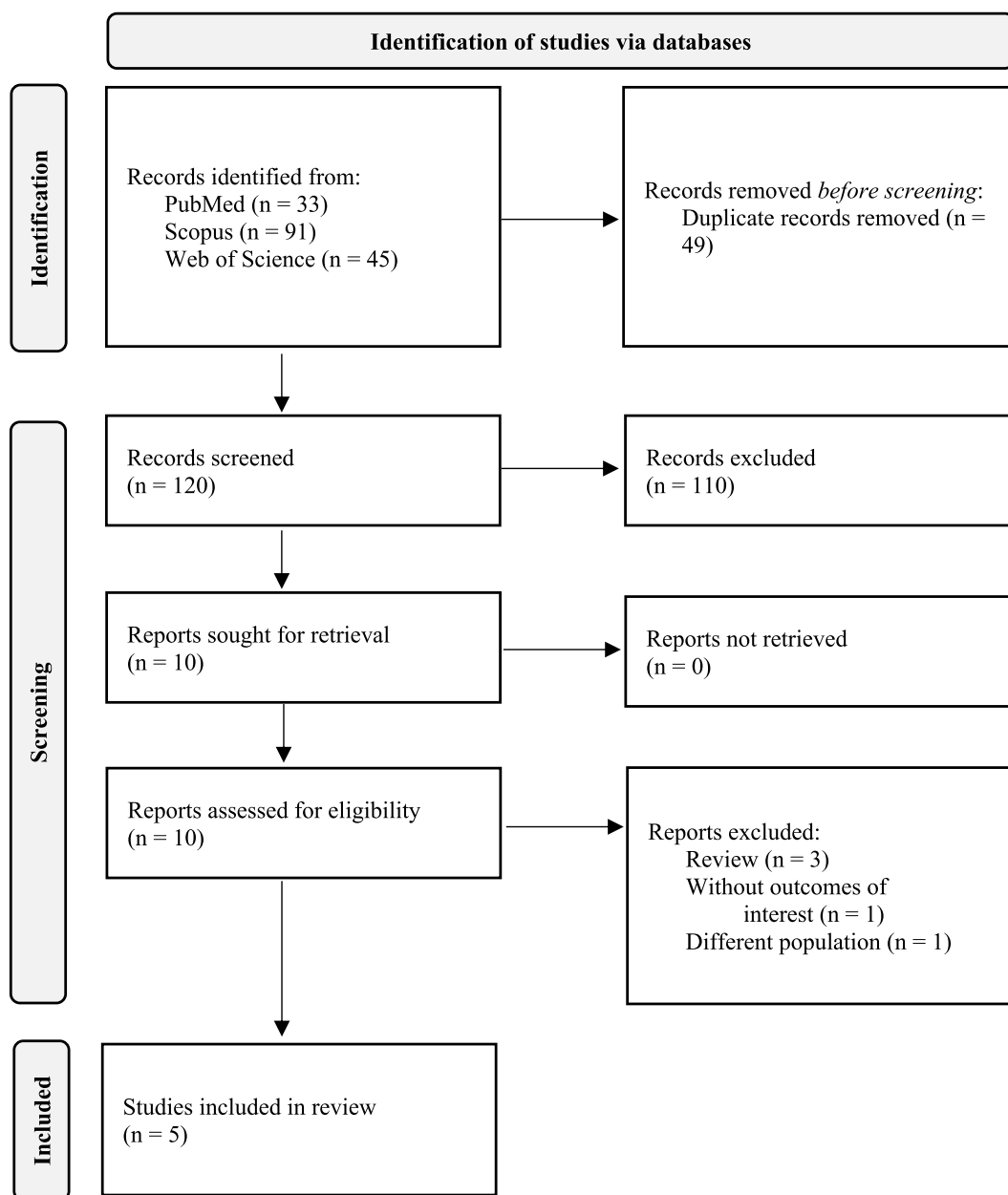


Fig. 1. PRISMA flow-diagram of study selection.

When the highest category of acrylamide exposure, as assessed by dietary assessment methods, was compared to the lowest, no clear association was found for any of the birth anthropometric outcomes considered (Figs. 3–5) except for a higher risk of SGA (OR: 1.14, 95% CI: 1.06; 1.22) (Fig. 2). Figure S1 showed lower birth weight in relation to the highest quintile of dietary acrylamide exposure when the report by Nagata et al. was left out in the leave-one-out meta-analysis (MD:  $-37.4$  g, 95% CI:  $-69.9$ ;  $-4.8$ ).

Pooled analyses on newborns from non-smoking mothers showed similar results to those in which newborns from smoking and non-smoking mothers were combined (Figs. 2–5). One exception was for lower birth weight (MD:  $-17.3$  g, 95% CI:  $-34.3$ ;  $-0.3$ ) in the highest category of acrylamide exposure as assessed by dietary assessment methods (Fig. 3).

When the highest category of acrylamide and glycidamide hemoglobin adducts was compared to the lowest category, we found a higher risk of SGA and lower birth weight and birth head circumference (Figs. 2–4). For AA-Hb, the pooled effect estimates were: OR: 1.20 (95%

CI: 1.08; 1.33); MD:  $-131$  g (95% CI:  $-204$ ;  $-58$ ); MD:  $-0.31$  cm (95% CI:  $-0.58$ ;  $-0.04$ ); and for GA-Hb the estimates were: OR: 1.36 (95% CI: 1.13; 1.64); MD:  $-161$  g (95% CI:  $-271$ ;  $-52$ ) and MD:  $-0.38$  cm (95% CI:  $-0.66$ ;  $-0.10$ ), respectively. Lower birth length (MD:  $-0.85$  cm, 95% CI:  $-1.38$ ;  $-0.33$ ) was observed in relation to the highest category (vs lowest) of GA-Hb, not of AA-Hb (Fig. 5).

Due to the limited number of studies and different quantiles of acrylamide exposure between the studies, we could only perform dose-response analysis for birth weight using the studies that assessed acrylamide exposure by dietary assessment methods (Fig. 6). Here, the shape of the association between acrylamide and weight seemed to be non-linear with an indication of a U-shaped relationship but the linear trend from regression analysis showed an inverse relation. When we plotted mean changes for each quintile of AA-Hb vs the lowest in relation to birth weight for the two individual studies that used AA-Hb as biomarker of exposure, we observed lower birth weight by increasing quartile of acrylamide exposure (Figure S1).

In general, between-study heterogeneity was high ( $I^2 > 70\%$ ) for

**Table 1**  
Descriptive characteristics and birth outcomes of the included studies by acrylamide exposure assessment method.

	Dietary assessment studies			Biomarker studies	
	(Duarte-Salles et al., 2013) <sup>a</sup>	Kadawathagedara et al., (2016)	Nagata et al., (2019)	(Pedersen et al., 2012) <sup>a</sup>	Hogervorst et al., (2021)
<b>Type of exposure assessment</b>	FFQ	FFQ	5-day diet records	Cord blood	Cord blood
<b>Time of exposure assessment</b>	First 5 months of pregnancy	Last 3 months of pregnancy	Week 29 of pregnancy	After the delivery	After the delivery
<b>Study population</b>	MoBa	EDEN	N.A.	NewGeneris consortium	ENVIRONAGE
<b>Country</b>	Norway	France	Japan	DK, GR, ES, NO, ENG <sup>c</sup>	Belgium
<b>Baseline (years)</b>	1999–2008	2003–2006	2000–2001	2006–2010	2010–2013
<b>Mother-child pairs (N)</b>	50,651	1471	204	1101	443
<b>Sex of the child, Male N (% male)</b>	25,906 (51.1)	777 (52.8)	0 (0.0)	550 (50.0)	229 (51.7)
<b>Age mother (years) mean (SD)</b>	30.1 (4.5)	29.5 (4.8)	28.9 (4.2)	30.9 (5.2)	30 (27–32) <sup>h</sup>
<b>Multiparity (&gt;1) (%)</b>	48	56	55	64	46.7
<b>Gestational age (weeks) mean (SD)</b>	39.5 (1.7)	39.5 (1.2)	39.5 (1.0)	38 (3.0)	40 (39–40) <sup>h</sup>
<b>Maternal weight gain (kg) mean (SD)</b>	14.9 (6.2)	9.1 (5.0)	9.6 (3.0)	–	14 (11.0–17.5) <sup>h</sup>
<b>Maternal education Low, Middle, High (%)</b>	30, 43, 25 <sup>e</sup>	44, 56 <sup>f</sup>	13.5 (1.9) <sup>g</sup>	26, 38, 36	11, 32, 57
<b>Exposure (µg/d   pmol/g)<sup>b</sup> mean (SD) minimum-maximum</b>	27.1 (13.4)   6.8–17.2	19.2 (17.3)   9.4–36.4	19.6 (9.9)   11.8–26.2	19.7 (16.5) (AA-Hb)   13.6 (10.1) (GA-Hb)   8.7–26.0 (AA-Hb)   6.3–18.8 (GA-Hb)	17.1 (13.2) (AA-Hb)   16.2 (11.6) (GA-Hb)   9.1–24.8 (AA-Hb)   8.6–23.4 (GA-Hb)
<b>Birth outcomes</b>	SGA, weight	SGA, weight, head circumference, length	Weight, head circumference length	SGA, weight, head circumference	Weight, head circumference, length
<b>SGA N (%)</b>	5188 (10.2)	177 (12.0)	–	72 (8.0)	–
<b>Weight (g) mean (SD)</b>	3600 (539)	3345 (432)	3007 (351)	1083 (98%) <sup>d</sup>	3430 (3140–3720) <sup>i</sup>
<b>Head circumference (cm) mean (SD)</b>	–	34.3 (1.5)	32.7 (1.9)	34.8 (1.5)	34.0 (33.0–35.0) <sup>i</sup>
<b>Length (cm) mean (SD)</b>	–	49.8 (2.09)	49.0 (2.20)	–	50.0 (49.0–52.0) <sup>i</sup>
<b>Smoking habits</b>	All, non-smokers and smokers	All, non-smokers and smokers	All	All, non-smokers	All, non-smokers
<b>Non-smokers (%)</b>	92	73	83	89	86
<b>Covariables</b>	Mother's age, parity, mother's BMI, mother's gestational weight gain, smoking during pregnancy gestational age, newborn's sex	Recruitment centre, mother's characteristics (age at delivery, education level, height, BMI, pregnancy weight gain, total energy intake, smoking during pregnancy, passive smoking), passive smoking and interaction between BMI and pregnancy weight gain, newborn's gestational age at birth and sex	Mother's age, parity, smoking status, pre pregnancy height and weight, gestational weight gain, weeks of gestation at the time of blood sampling, total energy intake	Country of the child's birth, gestational age, maternal smoking, passive smoking, newborn's sex, mother's pre pregnancy BMI, parity, mother's age, ethnicity, education and consumption of fruit and vegetables, fish, and soft drinks	Mother's pre-pregnancy BMI, weight gain during pregnancy, smoking during pregnancy and passive smoking, vegetable, fruit and fish intake, and consumption of soda drinks, parity, gestational age, newborn's sex, date of delivery

AA-Hb: acrylamide hemoglobin adducts; BMI: Body mass index; cm: centimeters; FFQ: food frequency questionnaire; G: grams; GA-Hb: glycidamide hemoglobin adducts; Hb adducts: hemoglobin adducts; kg: kilogram; n: count; %: proportion; N.A.: Not available; SGA: small for gestational age defined as birth weight less than the 10th percentile according to gestational age and sex.

<sup>a</sup> Studies in which the FFQ data were validated with acrylamide urine (n = 79 (Duarte-Salles et al., 2013)) or blood biomarkers against the FFQ (n = 726 (Pedersen et al., 2012)). In Pedersen et al., 2012, the results of the association between estimated acrylamide exposure and birth outcomes were not included in our pooled analysis since the estimates from the model with the largest set of covariables were not clearly reported.

<sup>b</sup> µg/d used for dietary acrylamide exposure, pmol/g for acrylamide and glycidamide hemoglobin adducts.

<sup>c</sup> Denmark, Greece, Norway, Spain, England.

<sup>d</sup> % with birth weight ≥2500 g.

<sup>e</sup> 2% were missing on maternal education.

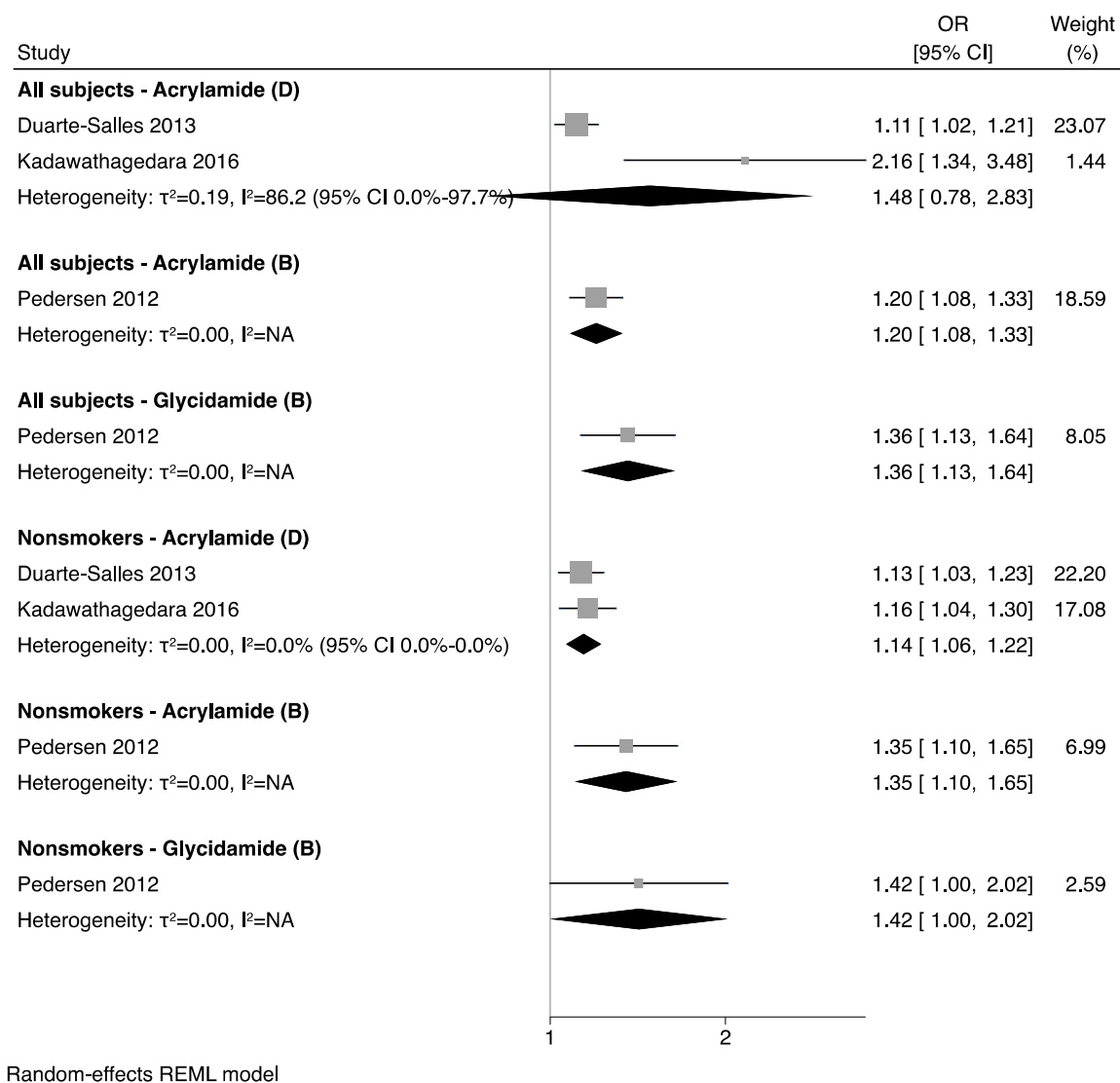
<sup>f</sup> ≥ or > bacculaureate.

<sup>g</sup> Years of education (mean and SD).

<sup>h</sup> Median (interquartile range).



<sup>i</sup> Median (interquartile range).



**Fig. 2.** Odd ratio (OR) with 95% confidence interval (CI) between exposure to acrylamide and glycidamide and the risk of small for gestational age comparing the highest versus the lowest exposure category in the overall and nonsmoking populations divided by compound and type of acrylamide exposure assessment. D: acrylamide exposure assessed by dietary assessment method. B: acrylamide exposure assessed by biomarker (hemoglobin adducts). NA: not assessed. The squares represent point estimates of change and horizontal lines represent the 95% CI. The area of each square is proportional with the weight of the study in the meta-analysis. Each study weight is computed according to the random-effects REML model. Ideally, the weight adds up to 100% when all studies were combined, but each stratified analysis is independent since weight considers study-specific variance and group-specific heterogeneity. The diamonds represent the combined change for each compound. The solid line represents null change.

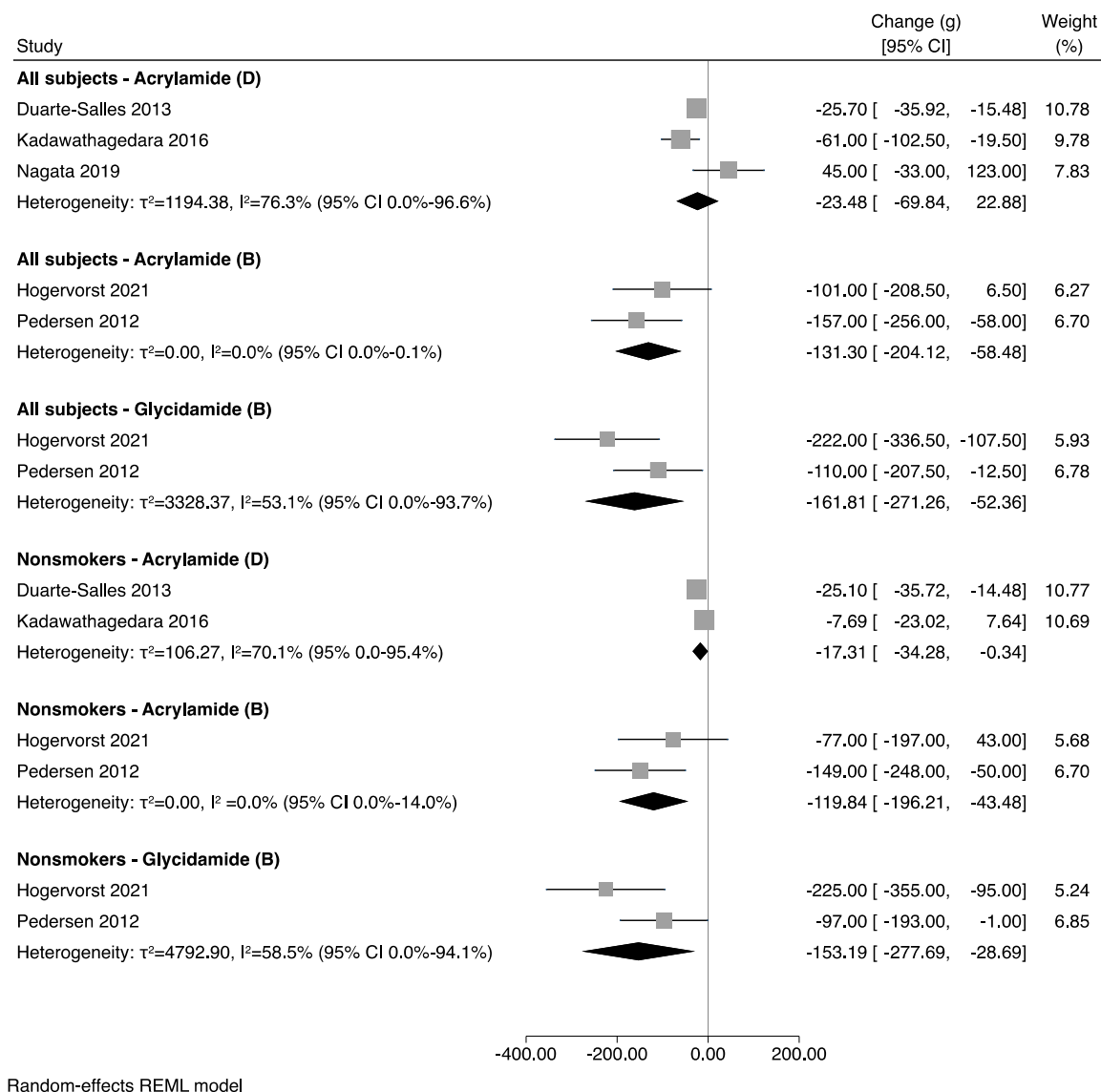
studies using a dietary assessment method, while it was low ( $I^2 < 50\%$ ) when pooling studies using Hb-adducts for exposure assessment (Figs. 2–5).

The risk of bias assessment of the included studies is presented in Supplementary Material, Figure S2-S3. All studies had a low risk of bias in the domain regarding the selection of the reported result and a moderate risk of bias in the domain related to the departure from intended results. On the other hand, following the RoB-NObs criteria, none of the studies reported detailed information on the domain of missing data and three out of the five included studies were scored as having a serious risk of bias in the domain concerning the selection of the participants. Due to missing information in different domains in several of the studies, the overall risk of bias was regarded as “no information”.

Due to the limited number of studies for each outcome (always less than five), we did not assess publication bias nor the Egger’s test.

#### 4. Discussion

We present the results of a meta-analysis evaluating the association between maternal acrylamide exposure during pregnancy and fetal growth as assessed by the risk of SGA, birth weight, birth head circumference, and birth length. Overall, our results show an association between increasing maternal acrylamide exposure during pregnancy and these birth outcomes when pooling the two studies that assessed hemoglobin adducts. However, when pooling the three studies that assessed the estimated maternal dietary exposure to acrylamide, we only observed an increased risk of SGA. In the dose-response meta-analysis,

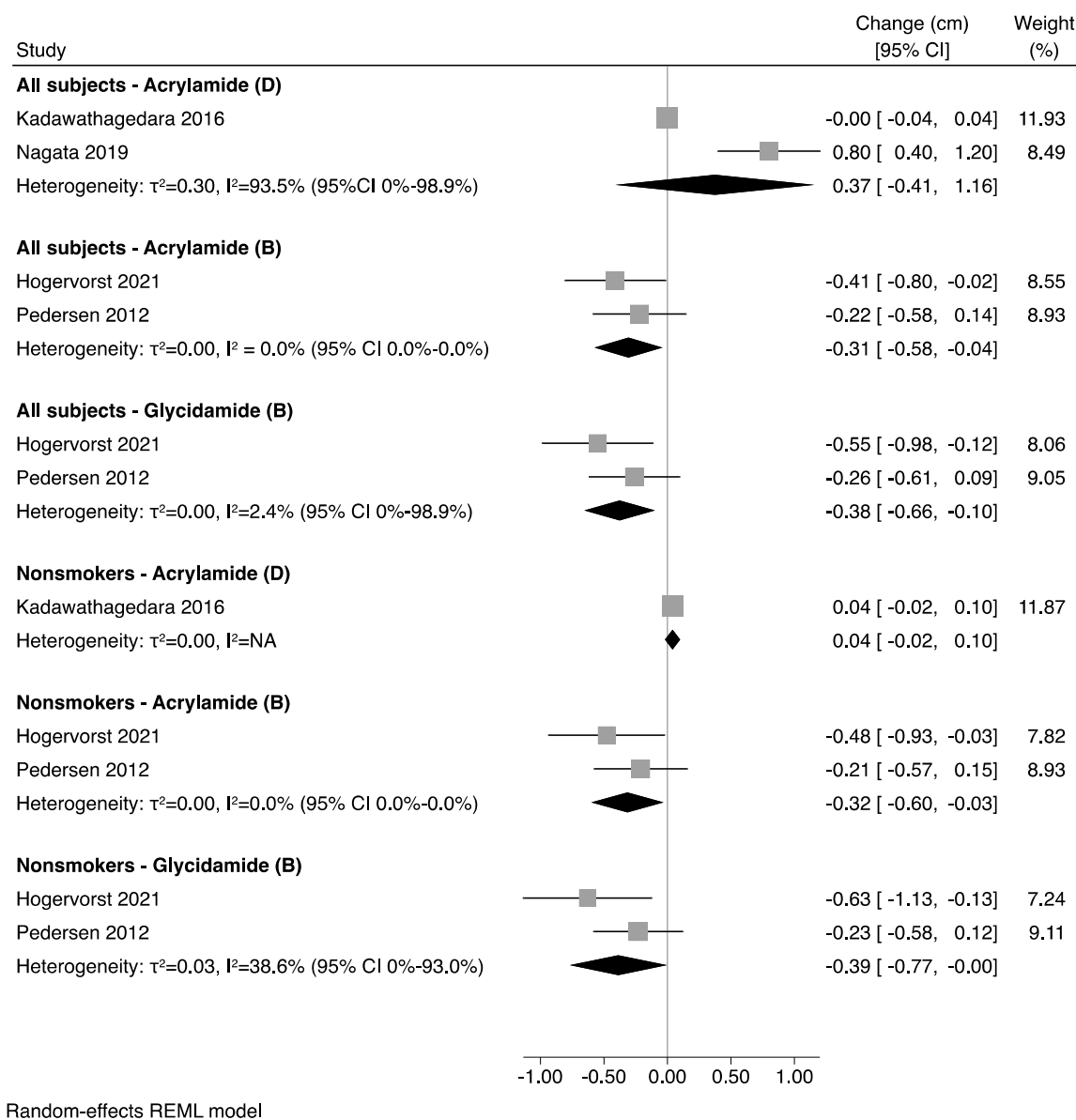


**Fig. 3.** Change with 95% confidence interval (CI) between exposure to acrylamide and glycidamide and weight at birth (g) comparing the highest versus the lowest exposure category in the overall and nonsmoking populations divided by compound and type of acrylamide exposure assessment. D: acrylamide exposure assessed by dietary assessment method. B: acrylamide exposure assessed by biomarker (hemoglobin adducts). The squares represent point estimates of change and horizontal lines represent the 95% CI. The area of each square is proportional with the weight of the study in the meta-analysis. Each study weight is computed according to the random-effects REML model. Ideally, the weight adds up to 100% when all studies were combined, but each stratified analysis is independent since weight considers study-specific variance and group-specific heterogeneity. The diamonds represent the combined change for each compound. The solid line represents null change.

we found no clear evidence of a deviation from linearity for the association with birth weight using the studies that assessed dietary acrylamide. In the two studies using biomarkers of acrylamide exposure, we could not perform a dose-response meta-analysis but there was an indication of a linear negative trend of birth weight in relation to increasing quartiles of AA-Hb and GA-Hb levels in the individual studies. When we restricted our analyses to newborns of non-smoking mothers, similar associations as in the overall group were observed for studies that used biomarkers to assess exposure. For studies that used dietary assessment methods, there was a lower birth weight in the highest category of exposure compared to the lowest category in the subgroup of newborns of mothers that did not smoke during the pregnancy.

Our results are in line to a certain extent with the results from the meta-analysis by Zhan et al. (2020). Compared to this previous review, we included one additional outcome (birth length) and one study (Hogervorst et al., 2021), but we did not combine studies with different

acrylamide exposure assessment methods (i.e., dietary assessments and biomarkers). Also, since we included only studies with multivariable-adjusted effect estimates as per our selection criterion, contrary to Zhan et al., we did not include the study of Kadawathagedara et al., (2018) in which only crude estimates of the association between acrylamide and birth weight were reported (Kadawathagedara et al., 2018). Zhan et al. pooled the effect estimates using two different statistical approaches: the interval collapse method (ICM) and the highest category versus lowest category method (HLM) approach, the latter method being the method that was used in the current study. Similarly to our results obtained for studies that used dietary assessment methods, they did not observe negative associations (with birth weight and the risk of SGA) with the HLM but they did when they compared all other categories of acrylamide exposure to the lowest category of exposure (i.e., using the ICM analysis). This might be due to the fact that the ICM analysis is less affected by underlying dose-response relationships,



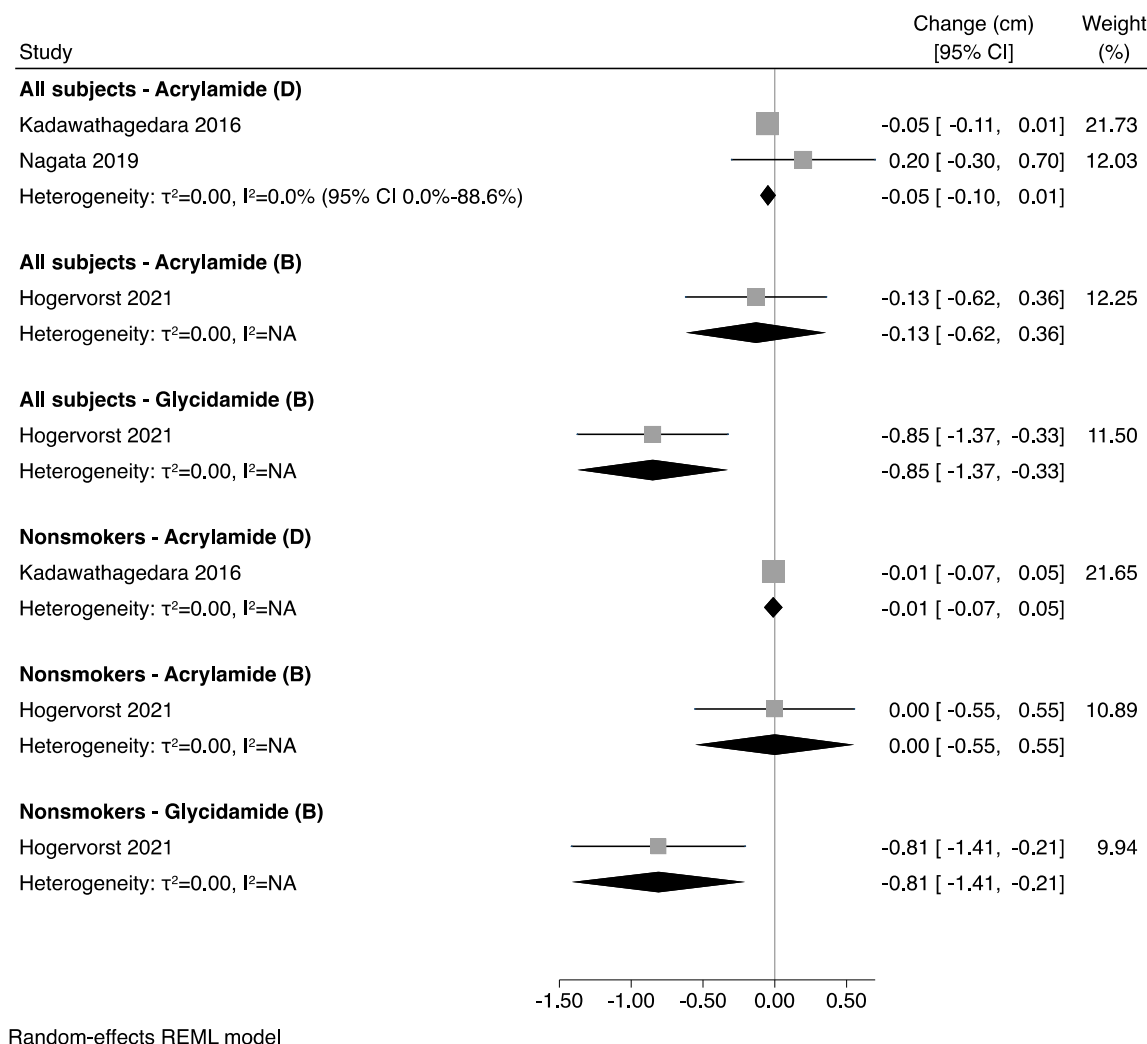
**Fig. 4.** Change with 95% confidence interval (CI) between exposure to acrylamide and glycidamide, and head circumference at birth (cm) comparing the highest versus the lowest exposure category in the overall and nonsmoking populations divided by compound and method of acrylamide exposure assessment. D: acrylamide exposure assessed by dietary assessment method. B: acrylamide exposure assessed by biomarker (hemoglobin adducts). NA: not applicable. The squares represent point estimates of change and horizontal lines represent the 95% CI. The area of each square is proportional with the weight of the study in the meta-analysis. Each study weight is computed according to the random-effects REML model. Ideally, the weight adds up to 100% when all studies were combined, but each stratified analysis is independent since weight considers study-specific variance and group-specific heterogeneity. The diamonds represent the combined change for each compound. The solid line represents null change.

lumping all exposure categories apart from the reference category together.

The possible curvilinearity found for birth weight and estimated dietary acrylamide exposure in our study might be explained by the inclusion of the Japanese study by Nagata et al. (2019). As shown in our leave-one-out meta-analysis, we only observed a decreased birth weight in relation to the highest quintile of dietary acrylamide exposure when the Japanese study was dropped from the analysis. When we left out this study, the dose-response relationship observed for birth weight was nearly linear. The Japanese study differs from the other studies included in this meta-analysis in several ways. Firstly, it is the only study in our meta-analysis to show a tendency of higher birth weight in relation to increasing acrylamide exposure, i.e., a tendency of a protective association between birth outcomes and increasing acrylamide exposure.

Secondly, the Japanese study included newborn girls only, and had a very small sample size, whereas the other studies included newborns of both sexes. Interestingly, Kadawathagedara et al. observed decreasing in fetal growth parameters in relation to increasing estimated dietary acrylamide exposure in girls only (Kadawathagedara et al., 2016). However, no effect modification of the association between acrylamide exposure and birth outcomes was observed in the ENVIRONAGE birth cohort study, also included in this meta-analysis (Hogervorst et al., 2021). Thirdly, the most important dietary sources of acrylamide, as well as cooking methods and the food processing, may differ between Asian regions and Europe. Considering this, it is possible that in Asian regions, dietary acrylamide exposure is associated more with a rather healthy diet, with acrylamide intake resulting largely from fried vegetables together with green tea, coffee, confectionery and potatoes





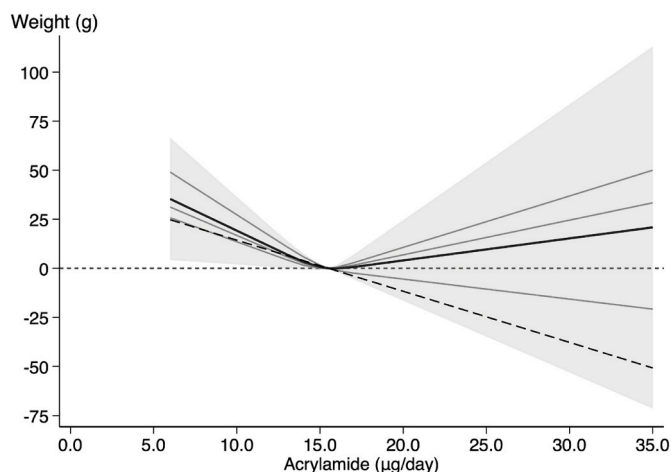
**Fig. 5.** Change with 95% confidence interval (CI) between exposure to acrylamide and glycidamide and length at birth (cm) comparing the highest versus the lowest exposure category in the overall and nonsmoking populations divided by compound and type of acrylamide exposure assessment. D: acrylamide exposure assessed by dietary assessment method. B: acrylamide exposure assessed by biomarker (hemoglobin adducts). NA: not applicable. The squares represent point estimates of change and horizontal lines represent the 95% CI. The area of each square is proportional with the weight of the study in the meta-analysis. Each study weight is computed according to the random-effects REML model. Ideally, the weight adds up to 100% when all studies were combined, but each stratified analysis is independent since weight considers study-specific variance and group-specific heterogeneity. The diamonds represent the combined change for each compound. The solid line represents null change.

(Kotemori et al., 2018) potentially offsetting the possible adverse effects of acrylamide (Gete et al., 2020), while in Europe, where the most important sources of acrylamide exposure are fried potatoes, cereal products and coffee (EFSA CONTAM Panel, 2015), acrylamide exposure correlates with a more unhealthy diet and the adverse effect of acrylamide is not offset. However, it is worth to mention that some of the main dietary acrylamide sources in Europe, such as crispy bread, whole meals and muesli, are considered to be healthy (EFSA CONTAM Panel, 2015). It might also be that the different results found in the Japanese study arise from the well-recognized differences in body weight and composition between European and Asian populations (WHO Expert Consultation, 2004). Finally, the Japanese study used a 5-day dietary record to assess acrylamide exposure, whereas the other two studies used an FFQ that in one study covered the first four to five months and in the other study covered the last three months of the pregnancy. Five days may be too short of a period to reliably capture the maternal acrylamide exposure during pregnancy in the relevant time window of exposure.

In the current review, associations between maternal acrylamide

exposure during pregnancy and birth outcomes were observed pooling studies that used biomarkers to assess exposure, but less strongly so when using dietary assessment methods, except for the risk of SGA. For fetal growth outcomes, Hb-adducts may be the best suitable method for acrylamide assessment because, as compared with dietary questionnaires, they represent the exposure during at least the last four months of pregnancy, during which most of fetal growth takes place and, thus, capturing the exposure during the relevant time window for disease etiology. The included studies that used dietary assessments greatly differed in the period of exposure that they covered, i.e., from the first semester to the last three months of pregnancy. Interestingly, the two biomarker studies (Hogervorst et al., 2021; Pedersen et al., 2012) were also those that observed a negative association with birth head circumference, whereas the two studies that used a dietary assessment method (Kadawathagedara et al., 2016; Nagata et al., 2019) did not, which may be due to the greater precision of biomarkers to assess acrylamide exposure as compared to the dietary assessment methods.

There is little data to inform the possible biological mechanism underlying the observed negative associations between gestational



**Fig. 6.** Dose-response meta-analysis between dietary acrylamide exposure and change in birth weight (Duarte-Salles et al., 2013; Kadawathagedara et al., 2016; Nagata et al., 2019). Spline curve (black solid line) with 95% confidence interval (light grey area), assuming a linear trend (black dashed line), and with indication of study-specific dose-response trend (dark grey solid lines). Reference: 15.5 µg/day (median value).

acrylamide intake and birth outcomes. Both acrylamide and glycidamide can bind to thiol groups in proteins, which may lead to their impaired function (Exon, 2006), playing an essential role in fetal development. In the ENVIRONAGE birth cohort, gestational acrylamide exposure was associated with lower cord blood insulin levels, and insulin mediated the association between cord blood glycidamide adducts and birth weight by 11.9% among all neonates and by 12.9% among neonates of non-smoking mothers (Hogervorst et al., 2021). These findings suggest that the association between acrylamide exposure and fetal growth may, to some extent, be explained by an effect on insulin levels, though there are other mechanisms that might play a role (Hogervorst et al., 2021). In 1356 adults in the cross-sectional National Health and Nutrition Examination Survey (NHANES) study, acrylamide hemoglobin adducts in blood were also negatively associated with insulin levels, with a significant trend across the quartiles of acrylamide exposure (Lin et al., 2009).

The results from this meta-analysis are important in light of the DOHaD hypothesis that stipulates that suboptimal prenatal growth likely increases the risk of health disorders such as type 2 diabetes, obesity and cardiovascular disease later in life (Aris et al., 2018; Fernandez-Twinn and Ozanne, 2006). Currently, there is only one study that has investigated the association between gestational acrylamide dietary exposure and postnatal development of children, suggesting that the highest gestational exposure to acrylamide (vs the lowest) increases the risk of being overweight or obese at 3, 5 and 8 years of age (Kadawathagedara et al., 2018).

Our review has some limitations. First, we cannot exclude the possibility of residual confounding by factors that are associated with both acrylamide exposure and fetal growth, such as another dietary exposure, e.g., fish intake or a generally less healthy lifestyle or diet. However, three of the studies (Hogervorst et al., 2021; Kadawathagedara et al., 2016; Pedersen et al., 2012) included in this meta-analysis adjusted, in sensitivity analyses, for variables that can be considered proxies for a healthy or unhealthy diet (consumption of vegetables, fruits, fish and soda drinks), and results were not importantly different from the main findings. To control for confounding in a different way, one of the included studies, the ENVIRONAGE birth cohort (Hogervorst et al., 2021), investigated interaction between acrylamide exposure during pregnancy and single nucleotide polymorphisms (SNPs) in acrylamide-metabolizing genes, such as cytochrome P450 Family 2 Subfamily E Member 1 (CYP2E1), the enzyme responsible for

metabolism of acrylamide to glycidamide. The observed interaction with CYP2E1 SNPs (Hogervorst et al., 2021) suggests that glycidamide might be more important with regard to fetal growth than acrylamide, which was indeed observed to be the case in both the ENVIRONAGE study and the current meta-analysis. The observed acrylamide-gene interactions need to be corroborated in other studies. These interactions suggest that the observed associations between acrylamide exposure and birth outcomes are not merely due to confounding and might indeed reflect causal relationship. That is because the CYP2E1 enzyme has a distinct limited set of substrates, which includes acrylamide, and if acrylamide was only a proxy for the truly causal factor, an interaction with the CYP2E1 enzyme would not have been likely. It is unlikely, though not entirely impossible, that the causal factor, if not acrylamide, is also a substrate of CYP2E1.

Second, the studies using biomarkers to assess acrylamide exposure during pregnancy that were included in this meta-analysis were by nature cross-sectional in design. This hampers the conclusion that the acrylamide exposure preceded the reduction in fetal growth. In theory, it is possible that the circumstances that resulted to reduced fetal growth led to the mother ingesting more acrylamide during pregnancy. However, we think that is highly unlikely. In addition, also the pooled estimates of the studies that used dietary assessment methods, estimating exposure during different periods of pregnancy, showed that increased acrylamide exposure was associated with fetal growth (birth weight and risk of SGA). These latter results are also strengthened by the fairly good correlation that was found between estimated dietary acrylamide exposure and Hb-adducts in a subset of the MoBa cohort ( $n = 79$ ) (Duarte-Salles et al., 2013). Finally, the small number of studies limited the interpretation and the precision of some estimates, also hampering the implementation of some stratified analyses as well as the assessment of publication bias.

Our meta-analysis has some important strengths. We performed an updated analysis of the relationship between maternal acrylamide exposure during pregnancy and fetal growth, as assessed by birth outcomes. Compared to a previous meta-analysis, we added birth length as an additional birth outcome (Hogervorst et al., 2021; Kadawathagedara et al., 2016; Nagata et al., 2019) and one more report on acrylamide hemoglobin adducts in cord blood (Hogervorst et al., 2021), and performed a dose-response meta-analysis for birth weight.

## 5. Conclusions

Our meta-analysis provides an indication for an adverse effect of maternal acrylamide exposure during pregnancy on fetal growth. In order to further strengthen the body of evidence, further epidemiological studies on the association between cord blood acrylamide hemoglobin adduct levels and insulin levels in cord blood would be useful as well as studies on the interaction between maternal acrylamide exposure during pregnancy and single nucleotide polymorphisms in genes involved in acrylamide metabolism, such as CYP2E1. Considering the DOHaD hypothesis, our meta-analysis suggests that prenatal acrylamide exposure may have detrimental effects at a later age. Thus, more studies are needed to shed light on whether maternal acrylamide exposure during pregnancy might lead to adverse effects on postnatal and later life development and health. In the meantime, based on the current body of evidence related to fetal growth and other adverse effect of acrylamide, the mitigation measures toward food producers (industry and restaurants) to limit the formation of acrylamide in foods are to be strengthened, and strategies to reduce acrylamide exposure by home-prepared foods through targeted public health education and awareness are warranted.

## Authors contribution

All authors contributed substantively to this work. J.H, A.V., T.F. and F.L. conceptualized the study and drafted the manuscript. T.F.

performed the statistical analyses. All authors were involved in the interpretation of results and the editing of the manuscript (J.H, A.V, T.I. H, M.V, A.Å, K.L, T.N, T.F and F.L). All authors approved manuscript submission (J.H, A.V, T.I.H, M.V, A.Å, K.L, T.N, T.F and F.L.).

### Data availability statement

All data generated or analyzed during this study are included in this published article and its supplementary information file.

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### Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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### Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.envres.2022.113705>.

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