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Title	Advanced glycation end product intake during pregnancy and offspring allergy outcomes: prospective cohort study
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Publication date	2021-10-05
Original Citation	Venter, C., Pickett , K., Starling, A., Maslin, K., Smith, P. K., Palumbo, M. P., O'Mahony, L., Ben Abdallah, M. and Dabelea, D. (2021) 'Advanced glycation end product intake during pregnancy and offspring allergy outcomes: prospective cohort study', Clinical and Experimental Allergy, 51(11), pp.1459-1470. https://doi.org/10.1111/cea.14027
Type of publication	Article (peer-reviewed)
Link to publisher's version	10.1111/cea.14027
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Download date	2026-11-16 19:34:25
Item downloaded from	https://hdl.handle.net/10468/12081



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Accepted Article

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Article type : Original Article

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Advanced glycation end product intake during pregnancy and offspring allergy outcomes: prospective cohort study

Running title: Maternal AGEs intake and offspring allergies

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This article has been accepted for publication and undergone full peer review but has not been through the copyediting, typesetting, pagination and proofreading process, which may lead to differences between this version and the Version of Record. Please cite this article as doi: 10.1111/CEA.14027

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Declarations of interest

Dr. Venter reports grants from Reckitt Benckiser, grants from Food Allergy Research and Education, grants from National Peanut Board, during the conduct of the study; personal fees from Reckitt Benckiser, personal fees from Nestle Nutrition Institute, personal fees from Danone, personal fees from Abbott Nutrition, personal fees from Else Nutrition, and personal fees from Before Brands, outside the submitted work. Dr Smith reports personal fees from the Nestle Nutrition Institute and speaker fee from Danone and Bayer outside of the submitted work.
Dr. O'Mahony reports personal fees from Alimentary Health, grants from GSK, outside the submitted work. The other authors declare no interests.

Author contributions:

CV initiated the paper and drafted the first version of the paper. KP performed the data analysis with guidance and review by MP. AS guided on the epidemiological aspects of the study. PS and LOM advised on interpretation of AGEs intake and cytokine data. MAB extracted the allergy data from the electronic medical records. KM assisted with interpretation of the dietary and AGEs intake. DD is the principal investigator and assessed and guided the data analysis plan. All authors reviewed and commented on various drafts of the paper.

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Informed consent

Informed consent was obtained from all subjects involved in the study.

Institutional review board

The Healthy Start study protocol was approved by the Colorado Multiple Institutional Review Board. (IRB number: 09-0563; Healthy Start 1; 2009-2014 and Healthy Start 2; 2015-present).

Data availability statement

Data available on request from the authors from https://coloradosph.cuanschutz.edu/research-and-practice/centers-programs/lead.

Funding/ Acknowledgements:

This work was supported by the of Health, grant numbers: R01 DK076648/DK/NIDDK NIH HHS/United States, R01 GM121081/GM/NIGMS NIH HHS/United States, UG3 OD023248/OD/NIH HHS/United States, UH3 OD023248/OD/NIH HHS/United States, R25GM111901-S1, R25GM11190, NIH grant R00ES025817

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Abstract

Background

Associations have been shown between concurrent assessment of dietary intake of AGEs and childhood allergic outcomes. We examined the association between maternal AGEs intake and development of offspring asthma, wheeze, atopic dermatitis, allergic rhinitis, and food allergies, and sought to determine whether intake of AGEs was associated with cord sera cytokines/chemokines.

Methods

Pregnant women ≥ 16 years were recruited in the Healthy Start study, a prospective pre-birth cohort from Colorado (N =1410). The analysis included 962 dyads with adequate diet (≥2 recalls) and allergy outcome details. AGEs intake was estimated for each mother by matching intakes reported using 24-hour dietary recalls during pregnancy to a reference database of commonly consumed foods' AGEs values. Child diagnoses of asthma and allergies up to 8 years were obtained from electronic medical records. Cord sera cytokines and chemokines were analyzed in a subset (N = 462) of children.

Results

The median [IQR] AGEs intake for the overall sample was 11919 kU/day [8293, 16573]. Unadjusted analysis showed a positive association between maternal AGEs intake in pregnancy and rhinitis up to 8 years of age (HR = 1.03; 95% CI: 1.01, 1.06), but the association was attenuated and no longer significant in adjusted models (HR = 1.01; 95% CI: 0.98, 1.04). Both adjusted and unadjusted models showed no associations between AGEs intake in pregnancy and any of the other outcomes ($p>0.05$). There were no significant associations between any cytokine or chemokine measured and AGEs intake or any of the outcomes studied ($p>0.05$).

Conclusion

The study showed that maternal AGEs intake was not associated with offspring asthma and allergy outcomes. AGEs exposure during pregnancy may not have the same impact on child development to postnatal exposure.

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Key messages

- AGEs exposure during postnatal life has been associated with multiple adverse health outcomes.
- Maternal intake of AGEs during pregnancy was not associated with offspring allergies.
- Maternal intake of AGEs during pregnancy was not associated with cord blood cytokine or chemokine levels.

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Introduction

Allergic diseases are an increasing public health concern.[1,2] The four major presentations of allergic diseases include asthma, atopic dermatitis, allergic rhinitis, and food allergies. Atopic dermatitis is usually the first manifestation of allergic diseases, followed by food allergies, asthma and allergic rhinitis, a process of allergic disease development referred to as the atopic march.[3] Although allergic diseases share a common immunological profile involving T-helper 2 (Th2) and inflammatory cells and their cytokines and chemokines, each condition may also appear separately with its own individual gene/environment interactions.[4]

Early life factors, including maternal diet during pregnancy, have been studied as a possible risk factor for offspring allergic diseases. However, despite the large number of studies focusing on maternal dietary intake in pregnancy and offspring allergic outcomes, the results do not give clear guidance on which dietary factors to address.[5,6] The European Academy of Allergy and Clinical Immunology also concludes that the role of the maternal diet in the development of offspring allergy outcomes is unclear.[7] Much more progress has been made in terms of the infant diet and allergy prevention, with most international allergy prevention guidelines advising against delaying introduction of food allergens, particularly peanut and egg. [8,7,9,10]

Observational data indicates that increased intake in childhood of foods typical of the Western diet, such as burgers, sugar and high fructose corn syrup,[11] and food preparations, such as frying, may be associated with the increase in allergic diseases.[12] Advanced glycation end products (AGEs) are compounds formed when sugar binds to protein or it is formed via lipoxidation.[11] It is postulated that the Western diet is high in AGEs and via its effect on both Th2 and inflammatory cytokines, may contribute to the increase in allergic outcomes. This is also referred to as the false alarm hypothesis.[12]

Inflammatory cytokines and chemokines include, but are not limited to IL-1, IL-6, IL-8, IL-4, IL-5, IL-13, alarmins (IL-25, IL-33 and TSLP), and TNF-α.[13,14] The Receptor for Advanced Glycation End Products (RAGE) is activated by ligands, including endogenous pathogen associated molecular patterns (PAMPs), and also dietary derived AGEs, which are high in the western diet. The AGEs receptor (RAGE) is linked to up-regulation of TNF-α, IL-1, IL-6 and IL-8.[13] Induction of alarmins (IL25, IL33, TSLP) and the importance of this is reinforced by models of atopic dermatitis and allergic

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asthma that show RAGE and its activation ligands are central to the development of sensitization and allergic responses.[12,15,16] In addition, higher levels of soluble RAGE (a decoy ligand) is protective against asthma.[17] Further inflammatory mechanisms related to AGEs products are: 1) induction of glycation of intracellular proteins including transcription factors, 2) alteration of the pericellular matrix, resulting in signaling changes and cellular dysfunction, 3) oxidative stress and mitochondrial dysfunction, 4) methylglyoxal – an archetypal AGE binds to lysine on DNA and induces oxidative/nitrogen induced damage and DNA cleavage. Each of the fore-mentioned mechanisms may have more impact on a developing fetus than a child/adult and is worthy of investigation in the context of development of atopic disease. In animal models of food allergy, resveratrol, a well-defined anti-oxidant, reduces development of ovalbumin allergy in a cholera-toxin adjuvant model with both reduced sensitization of ovalbumin and a reduction in dendritic cell activation.[18] Soy isoflavones, daidzien and genistein, have been shown to suppress allergic reactions in a murine model of peanut allergy.[19] Furthermore, in-vitro studies of resveratrol have shown a reduction of AGEs induced dendritic cell (DC) maturation, decreased dendritic cell RAGE receptor activation in response to AGE-albumin, and reduced dendritic cell activation to AGE-albumin stimulated DC (cytokines, co-stimulatory cells, mitogen activated protein kinases and NF-kB).[20]

Based on the underlying inflammatory processes in allergic conditions, particularly asthma and wheeze, we previously studied the association between the maternal diet and asthma/wheeze in the child. We concluded that the inflammatory profile of the maternal diet was not associated with cytokine and chemokine levels at birth. However, the results suggested that a maternal diet that scored higher on the dietary inflammatory index (DII) was associated with increased odds of offspring asthma and/or wheeze by age 4 years.[21] The DII is a complex index that provides an estimate of the inflammatory potential of the diet based on the inflammatory potential of foods and nutrients in single index.[22] AGEs are proteins or lipids that become glycated after exposure to sugars during heating and is considered to be one aspect of an inflammatory diet.[11]

In our pursuit to find the specific dietary factors in pregnancy that are associated with offspring outcomes, we investigated the role of maternal dietary AGEs intake and offspring asthma, wheeze, atopic dermatitis, allergic rhinitis and food allergy. The primary aim of this study was to assess the associations between maternal AGEs intake during pregnancy and offspring diagnosis of asthma, wheeze, allergic rhinitis, atopic dermatitis, and food allergy up to 8 years. We hypothesized that

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increased maternal AGEs intake during pregnancy would be associated with an increased rate of development of these outcomes in offspring. The secondary aim of this study was to examine associations between maternal AGEs intake and cord sera levels of cytokines and chemokines. We hypothesized that maternal AGEs intake would be associated with cord sera cytokines and chemokines, and that the effect might be exacerbated by maternal obesity, as both AGEs and obesity are related to inflammatory processes.[12,23]

Methods

Study sample

This analysis included data from a longitudinal pre-birth cohort of 1410 mother-child dyads. Pregnant women aged 16 years or older with singleton pregnancies were recruited from obstetrics clinics at the local hospital from 2009 to 2014. The Healthy Start study protocol was approved by the Colorado Multiple Institutional Review Board (IRB number: 09-0563; Healthy Start 1; 2009-2014 and Healthy Start 2; 2015-present) and was registered as an observational study at clinicaltrials.gov as NCT02273297. Further details regarding the study have been published elsewhere.[23]

At recruitment, the cohort included 1410 mother-child dyads. Following written consent, pregnant women completed questionnaires on medical history at enrollment in early pregnancy and were asked to give consent for the review of offspring electronic medical records up to age 4 years. Additional consent for review of offspring electronic medical records up to age 8 was requested when mothers and children came in for a follow-up visit after age 4.

Participants were excluded from this analysis if they did not provide consent for child medical record review from birth up to 4 years of age (n=9), had offspring who died prior to birth (n=6), or who had insufficient data available to search for the child in the electronic medical records system (n=66). Among the 1329 participants eligible for inclusion in the electronic medical record search, 68 children had no records in the electronic medical record system, resulting in a total of 1261 participants with allergy outcome information. Mothers were asked to complete 1 dietary recall per month during pregnancy. The analytic cohort included 962 mother-offspring dyads that completed ≥2 dietary recalls over the course of pregnancy and had valid offspring allergy outcome information. For the

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immunological analysis, data from N=462 mother-offspring dyads with data on cord sera cytokine and chemokine levels were used (Supplemental Figure 1).

Maternal daily AGEs intake

Maternal dietary intake was measured 2-8 times throughout pregnancy, from the second trimester onward, using the Automated Self-Administered 24-hour dietary recall (ASA24).[24] To estimate AGEs intake from the reported dietary intake, a reference database of commonly consumed foods' AGEs values (in kU/100g) built by Uribarri et al.[11] was used. Food descriptions from the ASA24 diaries were matched to the AGEs database by name and cooking process where possible. Foods without simple matches as well as complex multi-ingredient foods were decomposed into gram equivalents for 23 food components specified in My Pyramid,[243] e.g. 1 cup of broccoli = 1 dark-green vegetable and 1 English muffin = 1 grain equivalent. The gram equivalents for each code were estimated from My Pyramid by decomposing food codes using the USDA food and nutrient database for dietary studies 3.0 ingredient list.[256] Average AGEs (kU/g) values were then created from the Uribarri et al.[11] AGEs list for each of the 23 components based on general cooking type (fried, baked, stewed, or fresh), as cooking method is the main determinant of AGEs scores. Components for discretionary fats and sugars were excluded from this step due to difficulties with calculating accurate AGEs scores. Finally, daily dietary AGEs intake was calculated (in kU) based on quantity of the food/food component consumed. Median daily AGEs intake (kU/day) was calculated for each individual based on total number of dietary recalls available due to the right skewed nature of the AGEs distribution. Median daily AGEs were also standardized to amount per daily caloric intake (kU/1000kcal/day) to compare to previous literature.

Child allergy outcomes

The outcomes of interest for the present paper were child diagnosis of allergic diseases (asthma, wheeze, allergic rhinitis, atopic dermatitis, food allergy) up to 8 years of age based on data obtained from the electronic medical records. "Any outcome" was defined as diagnosis of one or more of the following diseases: asthma, wheeze, allergic rhinitis, atopic dermatitis, food allergy. Children's medical record data was abstracted for participants who consented to child medical record review and whose records were available in the Epic medical records system, as described previously.[23] In short, the following search terms were used: 1) allergic rhinitis: "allergic rhinitis", "allergic rhinoconjunctivitis", "hay fever", "rhinitis", "seasonal allergies"; 2) asthma: "asthma"; 3) atopic

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dermatitis/eczema: “atopic dermatitis”, “eczema”; 4) wheeze: “wheeze.” Search terms related to IgE-mediated food allergies and food allergens included: “food allergy”, “almond”, “cashew”, “clam”, “crab”, “egg”, “fin fish”, “fish”, “milk”, “pecan”, “peanut”, “salmon”, “sesame seed”, “scallop”, “shellfish”, “shrimp”, “soy”, “sunflower seed”, “tree nut”, “tuna”, “wheat”. The electronic medical records were reviewed by two clinician researchers, who assigned diagnoses for asthma, wheeze, allergic rhinitis, atopic dermatitis/eczema, and food allergies, after extensive review of medical notes.

For any participant with suspected food allergy, we recorded whether the child had IgE-mediated food allergy, the age of diagnosis, and the age at development of tolerance to the food if tolerance had been developed. Children with Eosinophilic Esophagitis (EoE) or Food Protein induced enterocolitis (FPIES) were not considered to have IgE-mediated food allergies unless they also had co-existing IgE-mediated food allergies.

Cord blood collection

Cord blood samples were obtained at delivery, stored on ice for up to 20 minutes, and processed by centrifugation. Serum aliquots were stored at 4°C for up to 24 hours before being transported (on ice) to an 80°C freezer for long-term storage. [267]

Cord sera cytokines and chemokines

Under a separate ancillary study (NIH: R00ES025817) focusing on sera analysis from maternal-offspring dyads with available sera and cord blood, stored frozen umbilical cord sera extracted at birth was analyzed for a range of cytokines and chemokines. Cord blood inflammatory biomarkers were processed by the University of Colorado Cancer Center Flow Cytometry Shared Resource. Plasma cytokine/chemokine concentrations were determined by multiplex panel immunoassay according to manufacturer’s instructions (EMD Millipore Corporation, Billerica, MA 01821). Cytokines including IL-1β, IL-4, IL-6, IL-10, and TNF-α; and chemokines IL-8 and MCP-1, were measured in units of pg/mL. For each analysis, samples were run in duplicate, and the percent coefficient of variation was computed as a quality control measure. If both replicates were out of range, the value was designated as being below (or above) the limit of detection. Values that were below the lower limit of detection were marked as “out-of-range low” and values that were above the upper limit of detection were marked as “out-of-range high”.[21] The cytokines and chemokines studied were previously selected to be analyzed for an NIH grant (R00ES025817) and included those that were related to either air pollution exposure or pregnancy/birth outcomes.

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Covariate data

Data regarding maternal race/ethnicity, parity, maternal history of allergy (asthma and/or allergic rhinitis), and age of introduction of solid foods were obtained through self-reported questionnaires. Maternal history of asthma was assessed using the following question, *"Has a health professional such as a doctor, physician assistant, or nurse practitioner ever told you that you have asthma?"* Maternal history of allergic rhinitis was assessed using the following question, *"Has a health professional such as a doctor, physician assistant, or nurse practitioner ever told you that you have hay fever, seasonal allergies or allergic rhinitis?"* Mothers were considered to have a history of allergy if they answered yes to one or both of the preceding questions. Pre-pregnancy weight was obtained from either medical records or self-reported early in pregnancy. Maternal height was measured at the first research visit via stadiometer. Pre-pregnancy body mass index (BMI) was calculated using pre-pregnancy weight (kg) divided by height (m) squared. Pre-pregnancy BMI was categorized as follows: lean (BMI <25 kg/m^2), overweight (BMI 25-29.99 kg/m^2), and obese (BMI ≥30 kg/m^2).[24] Observed gestational weight gain was calculated as the difference between the last available weight recorded during pregnancy and the pre-pregnancy weight.[278] Gestational weight gain was categorized as less than recommended, within the recommended range, or more than recommended (excessive weight gain) based on pre-pregnancy BMI categories, as described by the 2009 Institute of Medicine (IOM) guidelines.[289] Information on total caloric intake during pregnancy (kcal/day) was obtained using repeated 24-hour recalls, as described above. Breastfeeding duration was computed as breastmilk months, a product of breastfeeding duration and intensity, using feeding information reported by mothers at the 18 months postnatal interview. For exclusively breastfed infants, breastmilk months is equivalent to the duration of breastfeeding (e.g., 8 months of breastfeeding = 8 breastmilk months). For infants fed both breastmilk and formula, breastmilk months is the duration of exclusive breastfeeding plus the weighted duration of mixed feeding (e.g., 4 months of exclusive breastfeeding + 2 months of 50% breastmilk and 50% formula = 5 breastmilk months.) For infants fed formula exclusively, breastmilk months is 0.[30]

Statistical Analysis

Descriptive statistics were calculated for maternal and offspring characteristics, including means and standard deviations or median and interquartile range (IQR) for continuous variables dependent on distribution. Categorical variables were presented as frequencies and percentages. Demographic

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variables were compared between those with or without available cytokine data using statistical tests, including t-tests for normally distributed continuous variables, Wilcoxon rank sum tests for non-normally distributed continuous variables, and chi-square tests for categorical variables. We computed cumulative incidence of the medical record verified respiratory and allergy outcomes up to 1 year, 2 years, 3 years, and 4 years of age to describe the burden of these diseases in the cohort. Hypothesis testing was conducted at an alpha level of 0.05. In the final models, we reported, where appropriate, beta estimates, hazard ratios, 95% confidence intervals, and p-values and for the associations.

Associations between maternal AGEs intake during pregnancy and offspring diagnosis of asthma, wheeze, allergic rhinitis, atopic dermatitis, and food allergy

Cox proportional hazards models were fit to examine the associations between maternal daily AGEs intake (kU) and development of child allergic diseases (asthma, atopic dermatitis/eczema, food allergy, allergic rhinitis, wheeze, and any allergy) up to age 8 years. A literature review[29] identified a set of covariates used in previous publications seeking to identify associations between maternal diet during pregnancy and offspring allergy and respiratory outcomes. Two models were performed for the outcome: a base adjusted model 1, and an expanded adjusted model 2. Adjusted Model 1 was the base model with factors most commonly associated with allergy outcomes[2,30] and included child race/ethnicity, child sex, nulliparity, gestational smoking, and energy intake during pregnancy. Adjusted Model 2 was based on factors previously included when studying maternal diet and childhood allergy outcomes.[29] These included all variables in model 1, and additionally: mode of delivery, maternal history of allergy, breastfeeding duration, age of introduction of solid foods, maternal pre-pregnancy BMI category (Supplemental Figure 2). We constructed a directed acyclic graph to represent hypothesized causal relationships and confirmed that none of the covariates were either intermediates or colliders. To test the hypothesis that the effect of maternal AGEs intake on allergy onset may be exacerbated by maternal obesity and excessive gestational weight gain, we included interaction terms between maternal AGEs intake with pre-pregnancy BMI category and IOM gestational weight gain category into Adjusted model 2. Non-significant interactions ($p > 0.05$) were removed from the final adjusted models. The follow-up age was different for each child. This occurred for one of two reasons: 1) consent was only given to review child medical records from birth up to age 4 years, but not from age 4 to 8 years; or 2) consent was given to review child medical records from birth up to age 8 years, but the child had not yet reached 8 years of age at the time of

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the electronic medical record search (e.g. the child was only 6 years old when the search was conducted). The Cox proportional hazards modeling approach allowed us to censor participants at the latest follow-up age for which they had available electronic medical record data, due to one of the two reasons described. For children with multiple recorded diagnoses of a disease outcome, their age at their first diagnosis was used. We checked that the assumption of proportional hazards was met for the "any outcome" prior to interpreting the results of these models. A sensitivity analysis was also performed dividing AGEs intake into quartiles to test for non-linear associations.

Associations between maternal AGEs intake and cord sera levels of cytokines and chemokines.

To examine the associations between maternal intake of AGEs and cytokines, two separate modeling strategies were used depending on the detection rate of the values. For each of the cytokines and chemokines, we determined the number and percentage of values that were outside the detection range. In addition, we calculated the median and IQR for each of the cytokines and chemokines. Cord sera cytokines and chemokines with <20% of values outside the detection range were treated as continuous variables (IL-6, IL-8, TNF-α, MCP-1).[1] When the cytokines or chemokines were treated as continuous variables, values below the limit of detection were assigned values equal to half the lowest value observed on the standard curve[28 29] and values above the limit of detection were assigned values equal to 1.5 times the highest value on the standard curve. Cord sera cytokines and chemokines with ≥20% of values outside the detection range were treated as categorical variables and dichotomized as detectable or not detectable (IL-1β, IL-4).

For chemokines with <20% of values outside of the detection range, separate general linear univariate models were fit. Prior to fitting models for each of the cytokines and chemokines, the values of these cytokines and chemokines (IL-6, IL-8, TNF-α, MCP-1) were natural log transformed to account for the positively skewed distributions . For cytokines with ≥20% values outside of the detection range (IL-1β, IL-4), separate logistic regression models were fit to estimate the odds that the value of the cytokine or chemokine was detectable. For both cytokines and chemokines with <20% or ≥20% of values outside the detection range, unadjusted models included maternal intake of AGEs as the only predictor. Adjusted models were fit for each cytokine/chemokine, with the covariates and hypothesized interactions tested determined a priori. The adjusted models for the inflammatory cytokines (IL-1β, IL-6, TNF-α) and chemokines (IL-8, MPC-1) included nulliparity, child race/ethnicity, child sex, pre-pregnancy BMI category, IOM gestational weight gain category, and total caloric intake (kcal/day) as covariates (Supplemental Figure 3). The adjusted models for the T-regulatory cytokine (IL-10) and Th2 cytokine (IL-4) included the same covariates as were included for

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the inflammatory cytokines, in addition to maternal history of allergy. To test the hypothesis that the effect of maternal AGEs intake on inflammatory cytokines and chemokines may be exacerbated by maternal obesity and excessive gestational weight gain, we included interaction terms between maternal AGEs intake with pre-pregnancy BMI category and with IOM gestational weight gain category. Non-significant interactions ($p > 0.05$) were removed from the final adjusted models. A sensitivity analysis was again performed dividing AGEs intake into quartiles to test for non-linear associations.

Results

Descriptive statistics

Table 1 reports descriptive statistics for maternal and offspring characteristics of the overall sample of Healthy Start participants who had both maternal AGEs intake and offspring electronic medical record data. Table 1 also compares maternal and offspring characteristics between the subset of participants with cytokine/chemokine data and the subset without cytokine/chemokine data. There were no significant demographic differences in the cohort included in analysis (N = 962, Supplemental Figure 1) and those excluded (data not shown). The median [IQR] AGEs intake for the overall sample was 11919 kU/day [8293, 16573]. Accounting for daily caloric intake, the median [IQR] AGEs intake was 6485.0 kU/1000kcal [4669.6, 8546.6]. Birthweight (g) was statistically, but not clinically, significantly higher in participants with cytokine and chemokine data compared to participants without cytokine and chemokine data (3290±433 vs. 3196±541, p=0.002), as was gestational age at birth (weeks) (39.48±1.24 vs. 39.21±1.95, p=0.01). Maternal age (years) at delivery was also statistically, while not substantially, different at 28.25±6.03 for those with cytokine and chemokine data compared to 29.17±5.84 for those without (p=0.02). AGEs intake, total caloric intake, breastfeeding duration, gestational age, age of introduction of solids, nulliparity, gestational smoking, ethnicity, pre-pregnancy BMI, IOM gestational weight gain, maternal history of allergy, and child sex were not significantly different between those with and without cord sera cytokine and chemokine data. Supplemental Table 1 shows cumulative incidence of allergy outcomes in the offspring. There were no statistically significant differences between those participants with or without cytokine data for any of the outcomes studied: any outcome, wheeze, asthma, atopic dermatitis, allergic rhinitis, and food allergy ($p > 0.05$, data not shown).

Associations between maternal AGEs intake and offspring diagnosis of allergic outcomes

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Unadjusted analysis showed a positive association between a 1000kU/day increase in maternal AGEs intake in pregnancy and development of allergic rhinitis up to 8 years of age (HR = 1.034; 95% CI:1.012, 1.057), but the association was attenuated and no longer significant in adjusted model 1 (HR = 1.01 (95% CI: 0.986, 1.043). In the base adjusted analysis for any outcome, asthma, atopic dermatitis, food allergy, and wheeze, there were no statistically significant associations between AGEs scores and childhood allergy outcomes up to 8 years of age, with all Hazard Ratio values nearing 1 ($p>0.05$, Table 2). For these allergic outcomes, fully adjusted regression models gave similar results (Figure 1). There was also no evidence of a non-linear relationship between AGEs intake and any outcome ($p > 0.05$, Supplemental Table 4). There were no significant interactions between AGEs and BMI category ($p > 0.05$) for any of outcomes except for allergic rhinitis ($p = 0.01$) and wheeze ($p = 0.02$), and thus interactions are not reported in the adjusted model 2 in Table 2. For allergic rhinitis, women with a pre-pregnancy BMI categorized as "lean" were the only group with a significant AGEs effect with a hazard ratio of 1.054 for a 1000kU/day increase in AGEs (95% CI: 1.014, 1.095; $p = 0.008$). For wheeze, only women with a pre-pregnancy BMI categorized as "obese" had a significant AGEs effect with a hazard ratio of 0.934 for a 1000kU/day increase in AGEs (95% CI: 0.883, 0.989; $p = 0.02$) (Supplemental Table 3).

Associations between maternal AGEs intake and cord sera cytokine/chemokine levels

Supplemental Table 2 reports the frequency and percentage of values outside of the detection range for each cytokine/chemokine, and records whether the out-of-range values were low (below the lower limit of detection) or high (above the upper limit of detection). The median and IQR for levels of each cytokine/chemokine are also reported.

The hypothesized interaction between AGEs intake and pre-pregnancy BMI category for each of the cytokines/chemokines examined was non-significant (all $p>0.05$). After removing all non-significant interaction terms, the associations between continuous maternal AGEs scores and cord sera levels of the cytokines/chemokines remained non-significant in the final adjusted models (all $p>0.05$; Tables 3 and 4). There was also no evidence of a non-linear relationship between AGEs intake and any cord sera levels of the cytokines/chemokines ($p > 0.05$, Supplemental Table 5)

Discussion

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Previous studies have indicated that AGEs intake may be implicated in non-communicable diseases such as diabetes,[31,32] chronic kidney disease,[33] non-alcoholic fatty liver disease,[34] coronary heart disease,[32] obstructive airway diseases,[35] cancer,[36] dementia and aging[37], arthritis,[38] asthma/wheeze,[39,40] chronic bronchitis. [41] [37,42,43] Studies focusing on allergy outcomes, showed an association between the childhood diet, studied at a similar time as allergic outcomes.[12,44,45] In this study, we examined the association between maternal AGEs intake during pregnancy and offspring allergy outcomes. The unadjusted analysis showed a positive association between maternal AGEs intake in pregnancy and offspring allergic rhinitis up to 8 years of age, but the association was no longer significant in adjusted models. For all other offspring allergy outcomes, we did not find a significant association with maternal AGEs intake, before or after adjusting for potential confounders. For allergic rhinitis, a significant interaction between maternal pre-pregnancy BMI and AGEs intake was observed, showing that the association between increased AGEs intake and "lean"based on their pre-pregnancy BMI. A significant interaction between AGEs intake and pre-pregnancy BMI was also observed for wheeze, indicating increased intake of AGEs was associated with reduced risk of offspring wheeze only among women categorized as obese based on their pre-pregnancy BMI. Immunological data from previous studies[12,15,16] indicates that intake of AGEs may be associated with development of allergic disease via its effect on RAGE receptors, leading to a cascade of inflammatory processes. In the study presented here, no significant associations between maternal AGEs intake and cord sera levels any of the cytokines or chemokines studied were observed.

Studies examining the relationship between AGEs intake and allergy outcomes, have been conducted in children, focusing on the child's diet and the child's concurrent allergic symptoms. The International Study of Asthma and Allergies in Children (ISAAC) study reported that eating fast foods ≥ 3 times a week by adolescents was associated with asthma, rhino-conjunctivitis and eczema in these study participants.[45] The authors hypothesized this this effect may be due to the AGEs content of the food. Another prospective study reported on intake of AGEs in children and found that higher fast food consumption rates in urban children in South Africa was associated with atopic dermatitis than those with lower consumption rates. Urban children with high fried/microwaved meat consumption also had higher rates of any allergy compared to those with lower intakes.[44] These foods were once again used as a proxy for AGEs intake, rather than using a robust measurement of AGEs content of the whole diet, as was done for the Healthy Start cohort in the study presented here. More recently, a study from the US indicated that increased AGEs intake was significantly

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associated with increased odds of wheezing, wheeze-disrupted sleep, and wheezing requiring prescription medication.[40]

Following on from the results of these studies,[40,44,45] we sought to test whether maternal AGEs intake during pregnancy was associated with offspring allergic outcomes. In both the unadjusted and adjusted models for any outcome, asthma, atopic dermatitis, and food allergy up to 8 years, we found no statistically significant findings for the association between maternal AGEs intake and offspring allergy outcomes. The primary reason we suspect may explain the discrepancy between our study findings and the findings of the previous studies listed, is that previous studies examined concurrent AGEs intake of the child in which allergic disease was also studied, whereas we prospectively studied maternal intake of AGEs during pregnancy and examined allergy in offspring. This may indicate that AGEs intake in pregnancy may not affect child allergy outcomes. The results of our study indicated that among women with a pre-pregnancy BMI categorized as lean weight women, increased AGEs intake during pregnancy was associated with increased risk of offspring allergic rhinitis; and among women with a pre-pregnancy BMI categorized as obese, increased AGEs intake was associated reduced risk of offspring wheeze. These findings are difficult to interpret and further studies may be able to clarify these results.

The discrepancy in findings between our study and previous studies may also be explained by different measures and methods used to determine AGEs intake, or different methods for assessment of allergy outcomes. Previous studies investigating the association between AGEs and disease outcomes, used serum levels of AGEs,[31,46] or activity of the age receptor (RAGE)[37,42,43] rather than dietary intake of AGEs as in our study. Some studies measured reported high-fructose corn syrup sweetened soft drinks, fruit drinks[38] or apple juice, apple juice, fruit drinks and soda intake.[39,41] It is postulated that intake high fructose corn syrup, leads to *in situ* formation of AGEs, hence making these foods a suitable proxy for studying AGEs intake.[47]

Only three studies used dietary intake of AGEs measured by food frequency questionnaires to define AGEs intake; one study defined AGEs intake by food group[35] and two studies quantified AGEs intake based on FFQs measuring AGEs intake of commonly eaten foods.[3337] Our study is the first study to our knowledge that investigated AGEs intake in pregnancy and its association with child health outcomes. We have used detailed 24 hour recalls completed 2-8 times over the course of pregnancy

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to calculate average AGEs intake throughout pregnancy. The median AGEs intake of the women in the Healthy Start study was 6485.0 kU/1000 kcal. In our cohort, the median [IQR] AGEs intake for the overall sample was 11919 kU/day [8293, 16573]. There are no studies reporting AGEs intake in pregnant women, but a review paper by Nowotny et al.[48] indicates that AGEs intakes in adults can range from 6 000 – 27 000 kU/day, which indicates that our calculated AGES intake falls within this range.

No previous studies have explored the relationship between maternal AGEs intake during pregnancy and cord blood cytokines and chemokines. We had expected to see that higher maternal AGEs intake would be positively associated with proinflammatory cytokines and chemokines (IL-1β, IL-6, TNF-α, MCP-1, IL-8) [49] and negatively associated with anti-inflammatory cytokines such as IL-10.[4] In particular, we expected to see some association between AGEs intake and TNF-α and MCP-1 levels. TNF-α is a known pro-inflammatory cytokine and higher levels of TNF-α has been associated with increased expression of RAGE.[50] MCP-1 is thought to play a role in cell-surface expression of adhesion molecules[51] and RAGE is closely related to other genes coding for cell adhesion molecules. However, we saw no significant associations between maternal AGEs intake and cord sera cytokine or chemokine levels.

A strength of this study is that we present information from a well-characterized cohort with a large sample size, which enabled us to take various relevant covariates into account. We were able to study the association between a comprehensive and detailed measure of dietary AGEs intake during pregnancy, physician diagnosed recorded outcomes, and a range of cytokines and chemokines in cord sera. We are also the first research group to study the association between maternal AGEs and cord sera cytokine levels as a possible underlying mechanism for the development of offspring allergies.

We have used detailed 24 hour recalls completed 2-8 times over the course of pregnancy to calculate average AGEs intake throughout pregnancy. Approximately 76% of the participants completed ≥2 dietary recalls over the pregnancy, with a median of 3 recalls. Two recalls can be representative of the entire pregnancy, given that dietary intake is relatively stable across pregnancy[52] and two or more recalls are sufficient to estimate usual dietary intake, per the National Cancer Institute Dietary Assessment Primer.[53] In addition, we also compared the estimated daily AGEs values for those with below the median number of intakes (<3) to those with 4 or more entries.

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The distributions were not statistically different with those with 3 or less entries (N = 556) having a median estimated daily AGEs intake of 12104 (IQR: 7400-17148) and those with 4+ entries (N = 406) with a median of 11824 (IQR: 8978-15577) (p = 0.49). We have used a robust method to calculate AGEs intake, but the AGEs content of many foods is unknown and calculation of the AGEs scores of composite foods is difficult to standardize. One particular limitation of the dietary AGEs calculation may be that discretionary fats and sugars were excluded due to difficulties with calculating accurate AGEs scores. These issues may partially explain the null associations.

Future studies may benefit from using an AGEs food frequency questionnaire, validated against reliable biomarkers, such as AGEs serum levels, and other forms of dietary intake to measure AGEs instead. This information will enable us to assess if current levels of foods are indeed correct, especially composite foods and provide us with validated measures of dietary intake. There are currently no studies reporting on validating measurement of AGEs intake by using biological samples such as blood[12] or skin.[33,54] Some covariate information was collected through self-report rather than objective measures, which might have influenced data quality.

Our results are limited as only one Th2 and one T-regulatory cytokine were measured. Measuring cytokines in cord blood mononuclear cells, after sufficient stimulation with antigen, is preferable to using frozen cord sera. Future studies should focus on measuring a wider range of cord sera cytokines and chemokines, using antigen stimulation of cord blood mononuclear cells.

Other limitations included the potential bias associated with the self-report of dietary intake.[55,56] In addition, the sensitivity and specificity of using electronic medical record data for allergy outcomes is not known, but this approach has been used in European cohort studies to report and validate on asthma outcomes.[57] We also acknowledge that the mechanistic consequences of the AGE/RAGE interaction could either impact on immune responses increasing a tendency to allergic sensitization and/or enhancing susceptibility to inflammation independent of allergy. The latter may have been impacted by pregnancy intake of AGEs and future studies should focus on separating “allergic” from “inflammatory” outcomes. In particular, wheezing in infancy may not indicate an allergic phenotype, though its inflammatory characteristics[58] have been well described. Most of the findings have wide confidence intervals, highlighting the fact that further studies are required.

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Conclusion

In this study, we did not observe significant associations between maternal AGEs intake during pregnancy, and offspring allergy outcomes or cord blood cytokines and chemokines. These findings suggest that maternal AGEs intake during pregnancy may not impact development of allergic diseases in offspring. Exposure to AGEs during pregnancy may not have the same impact on child development as postnatal AGEs exposure.

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Figure Legends/Text:

Figure 1. Hazard ratios with confidence intervals for the associations between continuous maternal AGE (kU/day) intake and Offspring Allergy Outcomes up to 8 years; adjusted for maternal race/ethnicity, child sex, nulliparity, maternal smoking prior to pregnancy, maternal history of allergy, mode of delivery, breastfeeding duration, age of introduction of solid foods, maternal pre-pregnancy BMI category, and energy intake during pregnancy (all models exclude interactions).

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Table 1. Maternal and offspring characteristics in the Healthy Start cohort

	Overall sample	Subset with cytokine/chemokine data	Subset without cytokine/chemokine data	
Sample size (N)	962	462	500	
Continuous variables	**Mean* ± SD[a]**	**Mean* ± SD[a]**	**Mean* ± SD[a]**	**p-value[b]**
Maternal characteristics				
Advanced Glycation End Product Intake (AGEs) (kU/day)(Median [IQR])	11919 [8293, 16573]	11921.2 [7875.5, 15998.7]	11918.7 [8648.2, 16890.9]	0.21
AGEs (kU/1000kcal) (Median [IQR])	6485.0 [4669.6, 8546.6]	6434.0 [4510.2, 8448.9]	6434.0 [4510.2, 8448.9]	0.17
Age at delivery (years)	28.7 ± 5.9	28.25 ± 6.03	29.17 ± 5.84	0.02
Total caloric intake (kcal/day)	2070 ± 390	2055.58 ± 378.81	2083.66 ± 399.48	0.26
Breastfeeding duration (breastmilk months)[34]	8.7 ± 6.7	8.28 ± 6.64	9.11 ± 6.71	0.08
Nulliparous	475 (49%)	239 (52%)	236 (47%)	0.18
Smoking in pregnancy	64 (7%)	32 (7%)	32 (6%)	0.84
Pre-pregnancy body mass index[31]				0.28

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Underweight (<18.5 kg/m^2)	24 (2%)	14 (3%)	10 (2%)	
Lean (25 kg/m^2)	510 (53%)	232 (50%)	278 (56%)	
Overweight (25-29.99 kg/m^2)	245 (25%)	120 (26%)	125 (25%)	
Obese (≥30 kg/m^2)	183 (19%)	96 (21%)	87 (17%)	
IOM[d] gestational weight gain[33]				0.25
Less than recommended	213 (22%)	92 (20%)	121 (24%)	
Within recommended range	286 (30%)	143 (31%)	143 (29%)	
More than recommended	460 (48%)	227 (49%)	233 (47%)	
Maternal history of allergy	334 (35%)	160 (35%)	174 (35%)	1
Offspring characteristics				
Race/ethnicity				0.94
Non-Hispanic white	548 (57%)	262 (57%)	285 (57%)	
Non-Hispanic black	98 (10%)	50 (11%)	48 (10%)	
Hispanic	213 (22%)	101 (22%)	112 (22%)	
Other[c]	104 (11%)	49 (11%)	55 (11%)	
Sex – female	503 (52%)	247 (53%)	256 (51%)	0.52
Birthweight (grams)	3242 ± 595	3290.4 ± 432.8	3196.3 ± 541.12	0.002
Gestational age at birth (weeks)	39.3 ± 1.7	39.48 ± 1.24	39.21 ± 1.95	0.01

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Age solid foods introduced (months)	6.1 ± 2.0	6.1 ± 1.9	6.2 ± 2.0	0.12

a) SD: Standard deviation

b) p-value for hypothesis test comparing demographic variables between those with or without any cytokine data. Statistical tests included t-tests for normally distributed continuous variables, Wilcoxon rank sum tests for non-normally distributed continuous variables, and chi-square tests for categorical variables.

c) Other race/ethnicity includes non-Hispanic Asian, American Indian/Alaska Native, Hawaiian/Pacific Islander, and multi-racial

d) IOM: Institute of Medicine

***AGE intake was expressed as median [IQR] as a non-normally distributed variable.**

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Table 2. Results of Cox proportional hazard models examining the association between maternal daily AGE intake and child allergy diagnosis

	Unadjusted Model ((N = 9		Adjusted Model 1± ((N = 9		Adjusted Model 2≠ (N = 782)	
Outcome	***HR*(95% CI)***	***p-value***	***HR*(95% CI)***	***p-value***	***HR*(95% CI)***	***p-value***
Any Allergy	1.007 (0.993, 1.02	0.32	0.995 (0.978, 1.01	0.56	0.997 (0.978, 1.01	0.74
Asthma	1.014 (0.993, 1.03	0.19	1.009 (0.984, 1.03	0.48	1.008 (0.98, 1.037	0.57
Atopic Dermatitis	1.003 (0.986, 1.02	0.70	0.993 (0.972, 1.01	0.49	0.999 (0.976, 1.02	0.93
Food Allergy	1.012 (0.971, 1.05	0.56	0.978 (0.928, 1.03	0.41	0.975 (0.915, 1.03	0.44
Rhinitis	1.034 (1.012, 1.057)	0.002	1.014 (0.986, 1.04	0.34	1.012 (0.98, 1.045	0.58#
Wheeze	0.99 (0.969, 1.011	0.35	0.975 (0.951, 1.00	0.05	0.981 (0.955, 1.00	0.17#

* Hazard ratio's (HR) given for 1000kU increase in AGE value.

±adjusted for maternal race/ethnicity, child sex, nulliparity, maternal smoking prior to pregnancy and energy intake during pregnancy.

≠adjusted for maternal race/ethnicity, child sex, nulliparity, maternal smoking prior to pregnancy, maternal history of allergy, mode of delivery, breastfeeding duration, age of introduction of solid foods, maternal pre-pregnancy BMI category, and energy intake during pregnancy

#Significant interaction between AGE and BMI category observed. Results from models including interactions shown in Supplemental Table 3.

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Table 3. Associations between maternal AGE intake (kU) and natural log levels of cord sera cytokines and chemokines

	Unadjusted (N= 462)			Adjusted+ (N= 462)		
Outcome	β*	SE	p-value	β*	SE	p-value
IL-6	-0.001	0.01	0.95	0.009	0.011	0.43
IL-8	-0.01	0.008	0.18	-0.005	0.009	0.57
TNF-α	-0.0003	0.003	0.91	0.004	0.004	0.27
MCP-1	0.004	0.004	0.23	0.007	0.004	0.09
IL-10	-0.007	0.006	0.22	-0.001	0.013	0.92

*The beta estimate represents the change in log-pg/mL of each outcome per each 1000kU increase in maternal AGE intake.

+ Adjusted for child race/ethnicity, child sex, nulliparity, energy intake during pregnancy, IOM gestational weight gain category, BMI Category. The model for IL-10 additionally adjusts for maternal history of allergy.

Table 4. Associations between maternal AGE intake (kU) and the odds of the cord sera cytokine and chemokine value being detectable

	Unadjusted Model (N= 462)			Adjusted Model+ (N= 462)		
Outcome	OR*	95% CI	p-value	OR*	95% CI	p-value
IL-1β	0.992	(0.966, 1.019)	0.57	0.981	(0.949, 1.014)	0.26
IL-4	0.998	(0.97, 1.026)	0.87	1.015	(0.98, 1.051)	0.41

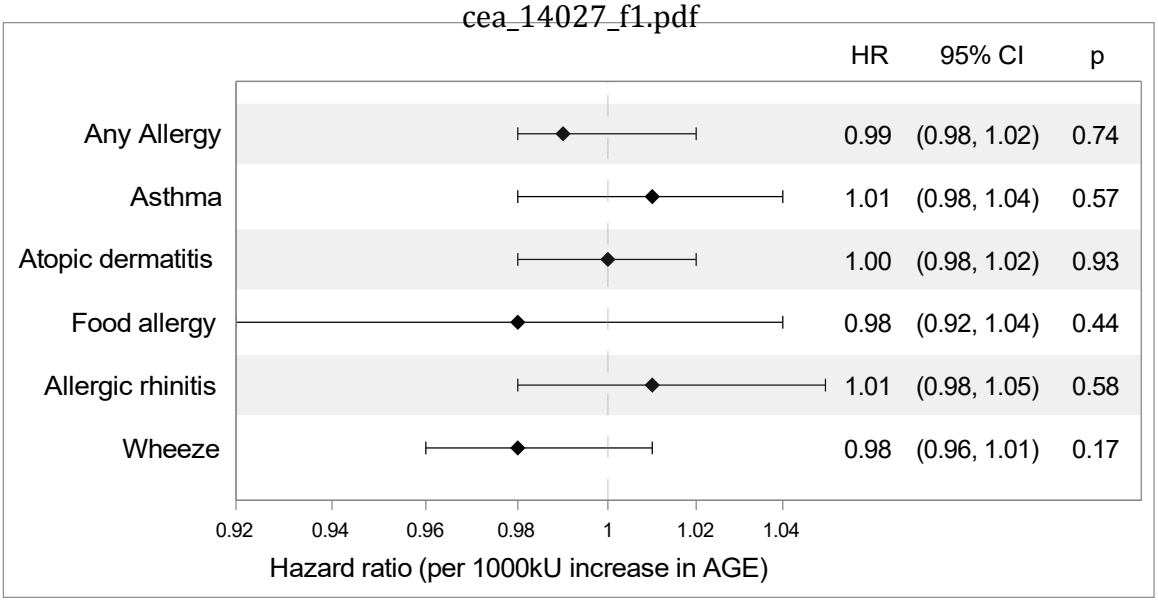
* The odds ratio (OR) represents the change in the odds that the outcome is detectable per each 1000kU increase in maternal AGE intake.

+ Adjusted for child race/ethnicity, child sex, nulliparity, energy intake during pregnancy, IOM gestational weight gain category, BMI Category. The model for IL-4 additionally adjusts for maternal history of allergy.

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