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Association of Lifetime Exposure to Glyphosate and Aminomethylphosphonic Acid (AMPA) with Liver Inflammation and Metabolic Syndrome at Young Adulthood: Findings from the CHAMACOS Study

Brenda Eskenazi,[1] Robert B. Gunier,[1] Stephen Rauch,[1] Katherine Kogut,[1] Emily R. Perito,[2,3] Xenia Mendez,[1] Charles Limbach,[4] Nina Holland,[1] Asa Bradman,[1,5] Kim G. Harley,[1] Paul J. Mills,[6] and Ana M. Mora[1]

[1]Center for Environmental Research and Community Health (CERCH), School of Public Health, University of California, Berkeley, Berkeley, California, USA
[2]Department of Pediatrics, University of California, San Francisco, San Francisco, California, USA
[3]Department of Epidemiology and Biostatistics, University of California, San Francisco, San Francisco, California, USA
[4]Monterey County Health Department, Salinas, California, USA
[5]Department of Public Health, University of California, Merced, Merced, California, USA
[6]Department of Family Medicine and Public Health, University of California, San Diego, La Jolla, California, USA

Background: The prevalence of liver disorders and metabolic syndrome has increased among youth. Glyphosate, the most widely used herbicide worldwide, could contribute to the development of these conditions.

Objective: We aimed to assess whether lifetime exposure to glyphosate and its degradation product, aminomethylphosphonic acid (AMPA), is associated with elevated liver transaminases and metabolic syndrome among young adults.

Methods: We conducted a prospective cohort study ($n = 480$ mother–child dyads) and a nested case–control study ($n = 60$ cases with elevated liver transaminases and 91 controls) using data from the Center for the Health Assessment of Mothers and Children of Salinas (CHAMACOS). We measured glyphosate and AMPA concentrations in urine samples collected during pregnancy and at child ages 5, 14, and 18 y from cases and controls. We calculated glyphosate residue concentrations: [glyphosate + (1.5 × AMPA)]. We estimated the amount of agricultural-use glyphosate applied within a 1-km radius of every residence from pregnancy to age 5 y for the full cohort using California Pesticide Use Reporting data. We assessed liver transaminases and metabolic syndrome at 18 y of age.

Results: Urinary AMPA at age 5 y was associated with elevated transaminases [relative risk (RR) per 2-fold increase = 1.27, 95% confidence interval (CI): 1.06, 1.53] and metabolic syndrome (RR = 2.07, 95% CI: 1.38, 3.11). Urinary AMPA and glyphosate residues at age 14 y were associated with metabolic syndrome [RR = 1.80 (95% CI: 1.10, 2.93) and RR = 1.88 (95% CI: 1.03, 3.42), respectively]. Overall, a 2-fold increase in urinary AMPA during childhood was associated with a 14% and a 55% increased risk of elevated liver transaminases and metabolic syndrome, respectively. Living near agricultural glyphosate applications during early childhood (birth to 5 y of age) was also associated with metabolic syndrome at age 18 y in the case–control group (RR = 1.53, 95% CI: 1.16, 2.02).

Discussion: Childhood exposure to glyphosate and AMPA may increase risk of liver and cardiometabolic disorders in early adulthood, which could lead to more serious diseases later in life. https://doi.org/10.1289/EHP11721

Introduction

The prevalence of childhood obesity and metabolic syndrome has increased at an alarming rate in the United States,[1,2] particularly among populations of color.[1–3] Accompanying this, has been an increase in nonalcoholic fatty liver disease (NAFLD),[4] a condition that can lead to cirrhosis and hepatocellular carcinoma later in life.[5] Although diet and physical activity play an important role in cardiometabolic and liver disorders, some hypothesize that exposure to synthetic chemicals may also be involved.[6,7]

Use of the herbicide glyphosate has markedly increased in the United States in the last two decades and currently is the most commonly used broad-spectrum herbicide worldwide.[8,9] It is used to control broadleaf grasses and weeds in agriculture, forestry, and right-of-way clearances, in parks, and in yards as a component in home weed killers (e.g., Round-up®). Exposure to glyphosate and its prime degradation product, aminomethylphosphonic acid (AMPA), can occur through consumption of contaminated food,[10,11] air,[12] dust,[12] and water.[13] In food, glyphosate has been detected primarily in grains[14] and legumes, including soybeans,[15] but it has also been detected in other fruits and vegetables[10,16] and in baby formula.[17] AMPA is also the degradation product of amino-polyphosphonates, which are extensively used in detergents, fire retardants, and other compounds.[18]

The potential impact of glyphosate on human health is controversial and widely debated.[19–22] Like glyphosate, AMPA raises toxicologic concern.[23] In 2015, the International Agency for Research on Cancer (IARC) classified glyphosate as probably carcinogenic to humans (Group 2A),[21] but to date the U.S. Environmental Protection Agency (U.S. EPA) has found no evidence of risk to human health.[20] Animal[24–28] and human[29–31] studies have suggested that exposure to glyphosate may be related to liver disease, and some researchers have hypothesized a potential relationship with metabolic disorders.[32,33] In the current study, we investigated the association of prenatal and childhood exposure to glyphosate and AMPA—as indicated by urinary concentrations and registry data of nearby agricultural use of glyphosate—with markers of liver inflammation and metabolic syndrome in young adults.

Methods

Study Population

Participants are mother–child dyads enrolled in the Center for the Health Assessment of Mothers and Children of Salinas

Address correspondence to Brenda Eskenazi, Center for Environmental Research and Community Health (CERCH), School of Public Health, University of California at Berkeley, 1995 University Ave., Suite 265, Berkeley, CA 94704 USA. Telephone: +1 (510) 517-2831. Email: eskenazi@berkeley.edu

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(CHAMACOS) longitudinal cohort of children born between 2000 and 2002 in California's Salinas Valley.[34] Briefly, pregnant women receiving prenatal care at community clinics primarily serving farmworker families were eligible for enrollment if they were at least 18 y old, <20 wk gestation, spoke English or Spanish, met income requirements for public health insurance (Medi-Cal), and planned to deliver at the county hospital. Of 601 CHAMACOS women enrolled, 527 remained in the study at delivery ($n = 537$ live-born children, including twins) in the period 2000–2001 (CHAMACOS1 participants). In 2009–2010 we enrolled a second wave of 305 mother–child dyads of children born in 2000–2002 (CHAMACOS2 participants), using similar selection criteria. CHAMACOS1 mothers completed visits during pregnancy and delivery, and children were followed at approximately 1- to 2-y intervals. CHAMACOS2 mother–child dyads completed a baseline data collection visit at 9 y. Thereafter, CHAMACOS1 and CHAMACOS2 families completed the same study visits.

The present analyses included 480 CHAMACOS1 and CHAMACOS2 participants who completed the 18-y follow-up visit prior to our March 2020 COVID-19 closure and a subset of these who were selected for a nested case–control study of liver inflammation at age 18 y (Supplementary Figure 1). Cases ($n = 60$) were defined by having an alanine transaminase (ALT) >44 IU/L or an aspartate aminotransferase (AST) >40 IU/L for males or >32 IU/L for females (cutoffs are based on LabCorp reference ranges); controls ($n = 91$) had normal ALT and AST levels and were randomly selected and frequency-matched to cases on sex. Cases and controls were required to have maternal pregnancy and/or child urine specimens collected and stored from earlier study waves ($n = 415$ were eligible for selection).

Mothers provided written informed consent; children provided verbal assent starting at age 7 y, written assent starting at age 12 y, and full written consent at age 18 y. All study activities were approved by the University of California, Berkeley Office for the Protection of Human Subjects.

Study Procedures

The specific data and sample collection procedures are described below:

Maternal and youth interviews. Mothers were interviewed in English or Spanish by trained bilingual bicultural research assistants who used structured questionnaires at each study visit, including the prenatal visit at 26 wk gestation, and the child follow-up visits at 5, 14, and 18 y. We collected information on family occupation history, socioeconomic status, medical history, and lifestyle factors. Youth were interviewed in English at ages 14 and 18 y.

Dietary assessments. Mothers were interviewed using a validated food frequency questionnaire (FFQ) of their diet at 26 wk gestation[35–37] and their child's diet at age 5 y.[38,39] Youth completed a validated food screener at 14 y[40] and basic diet questions at 18 y.[41,42] In the FFQ administered during pregnancy, women were asked how often they ate various food items in the previous 3 months and how much they consumed each time. In the FFQ at 5 y, mothers were asked about the number of times their child ate various foods in the previous 4 wk. In the food screener at 14 y, the youth were asked the number of days in the previous week they ate or drank different food items and how much in 1 day. The validated FFQs and screener underwent proprietary data processing (Pregnancy[35–37] and 14-y FFQL Nutritionquest[40]; 5-y FFQ: Harvard Nutrition Questionnaire Service Center)[38,39,43] to convert reported dietary intake into summary variables and individual food items. We selected *a priori* those dietary variables that included foods commonly treated with glyphosate. We dichotomized continuous summary variables (i.e., total calories, total carbohydrates, whole grains, bran, fruits, and vegetables) into being above or below the median observed in our sample; we also dichotomized reported intake of individual foods (i.e., cold cereal, hot cereal, bread, tortillas, legumes) (e.g., <1 time per day vs. ≥1 time per day). In addition to the administration of the validated FFQs and screener, we asked mothers how frequently their 5-y-old children consumed fast food; we directly asked young adults this question at the 14-y and 18-y visits. We asked the 14- and 18-y-olds to report on their overall alcohol consumption; for 18-y-olds, we also asked about recent binge drinking (≥4 drinks in a row for females, ≥5 for males). At the 5-, 14-, and 18-y visits, we queried the mothers about family food security (U.S. Department of Agriculture Food Security Scale, Short Form).[44]

Body measurements. At the 18-y visit, we recorded young adult participants' height in triplicate using a wall-mounted stadiometer and their weight (a single measurement) using a Tanita bioimpedance scale (Tanita TBF-300A Body Composition Analyzer; Tanita Corporation). We calculated body mass index (BMI) based on the average recorded height and the single weight measurement. We measured waist circumference three times with a measuring tape wrapped around the abdomen, parallel to the floor, at the iliac crest. We present the average of these three measurements as the waist circumference. We measured blood pressure in triplicate using an automated oscillometric monitor (Dinamap Carescape V100). Participants sat and rested for two minutes prior to the first reading and had a 1-min rest between each subsequent reading. We present the average of the second two systolic and diastolic blood pressure readings, respectively, as the measured blood pressure.

Blood collection for clinical chemistries. At the 18-y visit, a fasting blood sample was collected from the young adults via venipuncture and analyzed for ALT, AST, glucose, high-density lipoprotein (HDL) cholesterol, and serum triglycerides (LabCorp). For those with elevated ALT, we also measured bilirubin and Hepatitis B and C (LabCorp) as well as ceruloplasmin and actin smooth muscle antibodies (LabCorp) to rule out common causes of liver disease other than NAFLD.

Urinary measurements of glyphosate and AMPA. For the case–control subgroup, we analyzed maternal urine collected at approximately 26 wk gestation and child urine collected at the 5-y, 14-y, and 18-y visits. All urine specimens were aliquoted into clean glass containers with Teflon caps and stored at −80°C at our Salinas research field office until shipment on dry ice to our University of California Berkeley–based biorepository, where they were stored at −80°C. Aliquots were kept in a frozen state until analysis with no intermediate freeze-thaw cycle. For prenatal, 5-y, and 14-y visits, spot urine samples were collected when participants had not fasted. However, at the 18-y visit, 40% ($n = 48$ out of 121) of participants provided a nonfirst morning void spot urine sample under fasting conditions to coincide with a fasting blood draw.

Aliquots of maternal prenatal and child urine samples for our selected cases and controls were shipped on dry ice to the Center de Toxicologie du Québec, Institut National de Santé Publique du Québec (INSPQ). Glyphosate and AMPA were measured in a single extraction by ultraperformance liquid chromatography (UPLC)–mass spectroscopy/mass spectroscopy (MSMS) at INSPQ. This method was performed as previously published.[45] External quality control for glyphosate and/or AMPA was ensured by INSPQ's successful participation in the Quebec External Quality Assessment Scheme for Organic Substances in Urine (OSEQAS), German External Quality Assessment Scheme (G-EQUAS), and Human Biomonitoring for Europe (HBM4EU, reference laboratory) program (see certificates of participation in the Supplementary Material). Limits of detection (LOD) were 0.08 μg/L for glyphosate and 0.09 μg/L for AMPA. Specific gravity was measured by a refractometer (Atago Company Ltd.).

California Pesticide Use Reporting (PUR) data. For the full cohort, we recorded families' residential addresses each time they attended a study visit. In addition, at the 16-y visit, mothers completed a detailed residential history interview in which all residences from the start of their pregnancy through their child's 16-y visit were obtained.

To characterize potential exposure, we estimated agricultural glyphosate use near each participant's residence during the prenatal and postnatal (birth to 5-y visit) time periods using PUR data from 1999 to 2007.[46–48] PUR data include the amount (kilograms) of active ingredient applied, application date, and location to a 1-square-mile section (1.6 km × 1.6 km) defined by the U.S. Public Land Survey System (PLSS).[47–49] We weighted the amount of glyphosate applied in each section by the proportion of land area that was included in a 1-km radius and accounted for the potential downwind transport of glyphosate from the application site using wind direction from the closest meteorological station[50] based on the daily proportion of time the wind blew from each of eight directions. We summed all glyphosate agricultural applications to determine estimates of the wind-weighted amount of glyphosate (kg) applied around all residences for each participant during pregnancy and from birth to the 5-y visit.

Data Analysis

We used chi-square tests to compare the detection frequencies of glyphosate and AMPA concentrations measured in urine samples collected from the mother during pregnancy and from the child at 5, 14, and 18 y. We fitted crude and multivariable Poisson regression models using robust standard errors for specific-gravity adjusted urinary glyphosate and AMPA concentrations, as well as total glyphosate residue concentrations, in relationship to *a*) case–control status defined by liver transaminases, *b*) metabolic syndrome, and *c*) other clinical chemistry and anthropometry measures measured at 18 y of age (dichotomized as within or outside normal clinical limits; see more details below). We estimated exposure to total glyphosate residues using the formula [glyphosate + (1.5 × AMPA)].[29,51,52] This formula, proposed by the Joint Meeting on Pesticide Residues,[53] is derived from the ratio of the AMPA molecular weight to the glyphosate molecular weight ($\sim$1.52) and assumes that AMPA and glyphosate have similar human toxicity. We used $\log_2$-transformed glyphosate, AMPA, and total glyphosate residue concentrations to reduce the influence of outliers. Values below the LOD were randomly imputed based on a log-normal distribution using maximum likelihood estimation.[54] Models were run for time points when at least half of participants had concentrations above the LOD, which included 14- and 18-y glyphosate and glyphosate residue concentrations, and 5-, 14-, and 18-y AMPA concentrations. We fitted models for 18-y nonfasting urinary concentrations and for all 18-y urinary concentrations.

In the models for metabolic syndrome and other clinical chemistry and anthropometry measures collected at 18 y, we corrected for oversampling of individuals with elevated markers of liver inflammation (and by extension, males) using stratum-specific weights for elevated ALT/AST and sex, based on the ratio of the proportions of each group in the case–control subset and full study population (i.e., male controls: 0.887; male cases: 0.373; female controls: 2.668; and female cases: 0.364).[55,56] The following clinical cutoffs for adults were used for these models: high-density lipoprotein (HDL) cholesterol <40 mg/dL for males or <50 mg/dL for females, serum triglycerides ≥150 mg/dL, fasting glucose ≥100 mg/dL, BMI ≥25 kg/m^2, waist circumference ≥40 inches for males or ≥35 inches for females, and systolic blood pressure >130 mm Hg and diastolic >85 mm Hg.[57–59] The presence of metabolic syndrome was indicated by having at least three of the following five factors: *a*) high systolic blood pressure or diastolic blood pressure; *b*) large waist circumference; *c*) elevated fasting serum glucose; *d*) elevated serum triglycerides; and *e*) low HDL cholesterol.[59]

To approximate lifetime glyphosate exposure, we fitted multiple informant models with repeated urinary concentrations at the 5-y, 14-y, and 18-y visits, using mixed-effects Poisson models with a random intercept for each participant[60] (we did not include urinary concentrations during pregnancy because the detection frequency was low). For participants who provided a fasting urine sample at 18 y, their 18-y measurement was excluded, but their 5-y and 14-y measurements were retained in the models. To determine whether exposure–outcome associations differed across the visits at which samples were collected and thus the appropriateness of multiple informant models, we also ran models that included exposure × visit interaction terms.

We examined whether BMI (continuous) at 14 y mediated the observed associations of urinary AMPA and glyphosate residue concentrations with the outcomes of interest using Structural Equation Models (SEMs).[61] In the case–control study group, we conducted sensitivity analyses excluding eight cases who had high actin (>19 U) or low ceruloplasmin (<16 mg/dL male, <19 mg/dL female) levels (based on LabCorp adult reference ranges) and/or who reported recent binge drinking in the past 30 d. We also used *t*-tests to examine the associations of dietary factors (dichotomous summary variables and individual food items) with glyphosate, AMPA, and glyphosate residues, measured concurrently.

We examined the correlation of maternal and child urinary concentrations of glyphosate and AMPA and PUR data from birth to 5 y. We constructed models of prenatal and postnatal PUR data in relationship to dichotomized clinical chemistry measures, anthropometric measures, and metabolic syndrome for the case–control subset ($n = 151$) and the entire 18-y sample ($n = 415$ for clinical chemistries, $n = 480$ for anthropometry). Because only 50.1% of the women lived within 1 km of an agricultural glyphosate application during pregnancy, we modeled prenatal exposure to glyphosate as a binary measure (zero vs. nonzero use within 1 km). Because 95.2% of children lived near agricultural glyphosate between birth and age 5 y, we modeled postnatal exposure using the sum ($\log_2$-transformed) of all agricultural glyphosate used during this period.

Covariates for multivariable models using urinary concentrations and PUR data were selected using a directed acyclic graph (DAG) (Supplemental Figure 2) and included youths' sex and any alcohol consumption at 18 y (yes vs. no), maternal prepregnancy BMI (continuous), parental work in agriculture during the prenatal period (yes vs. no), as well as household poverty (above the poverty line vs. below)[62] and food security (high/marginal food security vs. low/very low food security)[44] at the time of sample collection (for models of urinary concentrations) or at the 18-y visit (for models of PUR data).

All statistical analyses were conducted using Stata 15.0 (StataCorp) and ArcMap 10.6.1 (Esri Corp.).

Results

In Table 1, we present demographic information of the study participants. Most mothers were overweight or obese before pregnancy. Seventy percent of the young adult cases were male in comparison with 47.5% in the full 18-y cohort. At the 18-y visit, 42.5% of the families were living at or below the federal poverty line, and 28.2% were at low or very low food security. Among the 18-y young adults, 10.6% fulfilled the criteria for metabolic syndrome, and 57.2% were overweight or obese (Table 2). In the case–control subset, 28.8% of cases vs. 4.4% of controls fulfilled

Table 1. Demographic characteristics of participants in the liver disease nested case–control study and all 18-y-old participants, CHAMACOS study, 1999–2020 [*n* (%)].

	All 18-y-old participants[a] ($n=480$)	Cases[b] ($n=60$)	Controls[b] ($n=91$)
Maternal age at delivery (y)			
18–24	200 (41.7)	30 (50.0)	32 (35.2)
25–29	148 (30.8)	15 (25.0)	35 (38.5)
30–34	84 (17.5)	7 (11.7)	11 (12.1)
35–45	48 (10.0)	8 (13.3)	13 (14.3)
Maternal education			
≤6th grade	207 (43.1)	25 (41.7)	47 (51.6)
7th–12th grade	162 (33.8)	24 (40.0)	31 (34.1)
High school graduate	111 (23.1)	11 (18.3)	13 (14.3)
Marital status at pregnancy			
Not married/living as married	70 (14.6)	8 (13.6)	16 (17.6)
Married/living as married	408 (85.4)	51 (86.4)	75 (82.4)
Missing	2	1	0
Years in U.S. prior to delivery			
≤1 y	81 (16.9)	7 (11.7)	22 (24.2)
2–5 y	139 (29.0)	17 (28.3)	22 (24.2)
6–10 y	121 (25.2)	22 (36.7)	26 (28.6)
≥11 y, nonnative	96 (20.0)	12 (20.0)	16 (17.6)
Entire life	43 (9.0)	2 (3.3)	5 (5.5)
Language spoken at home (during pregnancy)			
Spanish primarily	438 (91.6)	57 (96.6)	84 (92.3)
Spanish and English equally	17 (3.6)	1 (1.7)	4 (4.4)
English primarily	19 (4.0)	1 (1.7)	2 (2.2)
Other	4 (0.8)	0 (0.0)	1 (1.1)
Missing	2	1	0
Maternal prepregnancy BMI			
Normal or underweight (<25.0 kg/m^2)	160 (33.4)	14 (23.3)	34 (37.4)
Overweight (25–29.9 kg/m^2)	201 (42.0)	22 (36.7)	38 (41.8)
Obese (≥30 kg/m^2)	118 (24.6)	24 (40.0)	19 (20.9)
Missing	1	0	0
Parental work in agriculture during pregnancy			
Yes	356 (74.5)	41 (69.5)	70 (76.9)
No	122 (25.5)	18 (30.5)	21 (23.1)
Missing	2	1	0
Participant sex			
Male	228 (47.5)	42 (70.0)	64 (70.3)
Female	252 (52.5)	18 (30.0)	27 (29.7)
Any alcohol consumption at 18 y			
Yes	249 (52.1)	27 (45.8)	48 (52.7)
No	229 (47.9)	32 (54.2)	43 (47.3)
Missing	2	1	0
Household poverty at 18 y			
At or below poverty line	196 (42.5)	31 (52.5)	37 (41.1)
Above the poverty line	265 (57.5)	28 (47.5)	53 (58.9)
Missing	19	1	1
Food security at 18 y			
High or marginal	338 (71.8)	42 (70.0)	61 (67.0)
Low	97 (20.6)	13 (21.7)	21 (23.1)
Very low	36 (7.6)	5 (8.3)	9 (9.9)
Missing	9	0	0

Note: BMI, body mass index; CHAMACOS, Center for the Health Assessment of Mothers and Children of Salinas; U.S., United States.
[a]Participants with blood draw and clinical chemistry at 18-y visit prior to onset of COVID-19 shelter in place (March 2020).
[b]Participants with urinary glyphosate measurements.

the criteria for metabolic syndrome, and 85.0% of cases were overweight or obese vs. 57.2% of controls.

Urinary Glyphosate and AMPA Concentrations

Few prenatal samples had detectable concentrations of glyphosate (4.2% >LOD) or AMPA (14.1% >LOD), and these percentages did not differ between cases and controls (Supplemental Tables 1 and 2). Overall, detection frequencies of glyphosate and AMPA were higher for children than for pregnant mothers (Supplemental Table 1).

The detection frequency of glyphosate was low at age 5 y (35.2% >LOD) and differed somewhat between cases and controls (46.9% vs. 28.6%, $p=0.08$) (Supplemental Table 2), whereas the detection frequency of AMPA was higher than for glyphosate at age 5 y (76.9% >LOD) with a specific gravity-corrected geometric mean (GM_{sg}) of 0.22 μg/L and a geometric standard deviation (GSD_{sg}) of 2.53 (Supplemental Table 1) but did not differ between cases and controls (Supplemental Table 2).

At 14 and 18 y, cases and controls did not differ in the proportion of urine samples with detectable levels of glyphosate or AMPA (Supplemental Table 2). Both glyphosate and AMPA had higher detection frequencies and geometric means at age 14 y than at all other ages [78.9% >LOD; GM_{sg} (GSD_{sg}) = 0.28 μg/L (2.37); and 93.3% >LOD; GM_{sg} (GSD_{sg}) = 0.72 μg/L (2.27); respectively] (Supplemental Table 1). Specifically, 18-y-olds overall had lower detection frequencies and geometric means of glyphosate [54.6% >LOD; GM_{sg} (GSD_{sg}) = 0.16 μg/L (2.77)] and AMPA [66.9% >LOD; GM_{sg} (GSD_{sg}) = 0.25 μg/L (2.46)] than at 14 y, even among those who had not fasted [glyphosate: 65.8% >LOD; GM_{sg} (GSD_{sg}) = 0.17 μg/L (2.80) and AMPA: 75.3% >LOD; GM_{sg} (GSD_{sg}) = 0.27 μg/L (2.76)]. In comparison with 18-y-olds who had fasted, those who had not fasted had a greater proportion of samples above the detection limit for glyphosate (65.8% vs. 37.5%) and AMPA (75.3% vs. 54.2%).

Urinary concentrations of glyphosate and AMPA were correlated within each study wave ($r=0.35$–0.66) (Supplemental Table 3). Dietary factors were only modestly associated with urinary glyphosate and AMPA concentrations (Supplemental Table 4): Higher consumption of cold cereal was associated with somewhat higher AMPA and glyphosate residue concentrations at 5 y; higher total caloric and carbohydrate intake and higher consumption of hot cereal, bread, and fruits and vegetables were associated with higher concentrations of glyphosate at 14 y.

Residential Proximity to Glyphosate Use

Agricultural applications of glyphosate were low during the time of pregnancy (~Year 2000) and age 5 y visits (~Year 2005) but higher at ages 14 (~Year 2014) and 18 (~Year 2018) (Figure 1; Supplemental Table 5). Glyphosate use near the child's residence

Table 2. Liver clinical chemistry measures and metabolic outcomes of all 18-y-old CHAMACOS participants and those in the nested case–control subset {GM [GSD] or *n* (%)}.

Outcome	All 18-y-old participants ($n=405$–474)	Cases ($n=60$)	Controls ($n=91$)
Elevated liver transaminases	61 (14.7)	60 (100.0)	0 (0.0)
ALT (IU/L)[a]	18.9 [1.9]	57.8 [1.6]	17.1 [1.5]
AST (IU/L)[a]	19.0 [1.5]	35.6 [1.5]	17.8 [1.3]
BMI category	—	—	—
Normal (<25 kg/m^2)	203 (42.8)	9 (15.0)	39 (42.9)
Overweight (25–29.9 kg/m^2)	130 (27.4)	13 (21.7)	30 (33.0)
Obese (≥30 kg/m^2)	141 (29.8)	38 (63.3)	22 (24.2)
Metabolic syndrome	43 (10.6)	17 (28.8)	4 (4.4)
Blood pressure (systolic ≥130 or diastolic ≥90 mm Hg)	52 (11.0)	15 (25.4)	8 (8.8)
Waist circumference (≥40 in for male, ≥35 in for female)	185 (39.2)	42 (70.0)	24 (26.4)
Fasting glucose (≥100 mg/dL)	20 (4.8)	8 (13.3)	4 (4.4)
Triglycerides (≥150 mg/dL)	50 (12.1)	18 (30.0)	6 (6.6)
HDL cholesterol (<40 mg/dL male, <50 mg/dL female)	158 (38.1)	29 (48.3)	29 (31.9)

Note: —, no data; ALT, alanine transaminase; AST, aspartate aminotransferase; BMI, body mass index; CHAMACOS, Center for the Health Assessment of Mothers and Children of Salinas; GM, geometric mean; GSM, geometric standard deviation; HDL, high-density lipoprotein; in, inches.
[a]Geometric mean (geometric standard deviation).

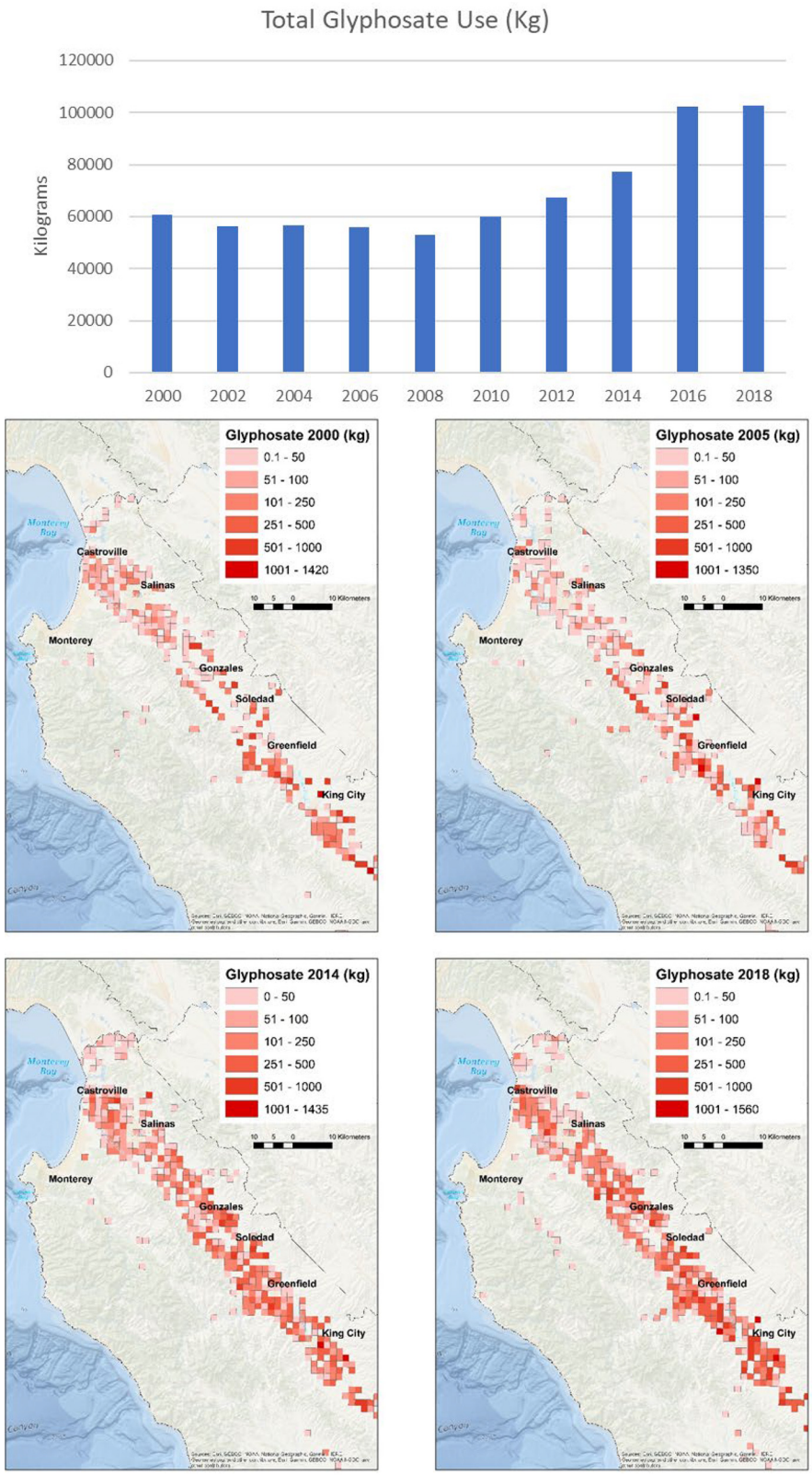

Figure 1. Agricultural use of glyphosate in Monterey County, California, 2000–2018. Note: Sources: Esri, General Bathymetric Chart of the Oceans (GEBCO), National Oceanic and Atmospheric Administration, National Geographic, Garmin, HERE, Geonames.org, and other contributors.

during early childhood (birth to 5 y) was not correlated with urinary glyphosate concentrations at age 5 ($r = -0.007$) and weakly correlated with urinary AMPA concentrations at this same age ($r = 0.12$) (Supplemental Table 3).

Associations of Urinary Glyphosate and AMPA Concentrations with Liver and Cardiometabolic Outcomes

We observed associations of urinary AMPA and glyphosate residues with markers of liver inflammation (Table 3; Supplemental

Table 3. Adjusted[a] RRs and 95% CI for 2-fold increases in child urinary glyphosate, AMPA, and glyphosate residue concentrations (specific gravity-corrected, μg/L) and abnormal markers of liver inflammation and metabolic syndrome (and its components) in CHAMACOS young adults in case–control group.

	Glyphosate		AMPA			Glyphosate residues[b]	
Outcome	14 y ($n = 103$–104)	18 y[c] ($n = 72$–73)	5 y ($n = 90$–91)	14 y ($n = 104$–105)	18 y[c] ($n = 72$–73)	14 y ($n = 103$–104)	18 y[c] ($n = 72$–73)
Elevated liver transaminases	1.07 (0.89, 1.29)	1.11 (0.97, 1.27)	1.27 (1.06, 1.53)	1.16 (0.96, 1.39)	1.13 (0.98, 1.32)	1.15 (0.93, 1.42)	1.16 (1.00, 1.35)
Metabolic syndrome	1.22 (0.76, 1.96)	1.20 (0.71, 2.02)	2.07 (1.38, 3.11)	1.80 (1.10, 2.93)	1.59 (0.99, 2.54)	1.88 (1.03, 3.42)	1.54 (0.94, 2.52)
High blood pressure	1.30 (0.83, 2.04)	0.98 (0.70, 1.37)	1.29 (0.80, 2.10)	1.50 (0.98, 2.30)	1.28 (0.88, 1.86)	1.55 (0.93, 3.60)	1.23 (0.85, 1.79)
Large waist circumference	0.88 (0.71, 1.10)	1.19 (0.94, 1.50)	1.11 (0.88, 1.40)	1.15 (0.87, 1.53)	1.26 (0.96, 1.65)	1.06 (0.74, 1.52)	1.33 (1.02, 1.73)
High glucose	0.95 (0.57, 1.60)	1.75 (0.20, 15.49)	2.95 (1.70, 5.14)	1.63 (0.92, 2.88)	4.29 (0.31, 59.55)	1.55 (0.75, 3.20)	3.16 (0.30, 33.36)
High triglycerides	0.95 (0.70, 1.31)	1.18 (0.92, 1.52)	1.39 (0.81, 2.37)	1.51 (1.03, 2.22)	1.45 (1.07, 1.96)	1.40 (0.90, 2.18)	1.39 (1.04, 1.88)
Low HDL cholesterol	0.86 (0.70, 1.05)	1.16 (0.94, 1.42)	0.90 (0.72, 1.12)	1.19 (0.96, 1.48)	1.15 (0.89, 1.48)	1.11 (0.84, 1.45)	1.20 (0.93, 1.54)

Note: AMPA, aminomethylphosphonic acid; BMI, body mass index; CHAMACOS, Center for the Health Assessment of Mothers and Children of Salinas; CI, confidence interval; HDL, high-density lipoprotein; RR, relative risk.
[a]Models adjusted for sex, any alcohol consumption at 18 y (yes/no), maternal prepregnancy BMI, parental work in agriculture during pregnancy (yes/no), household poverty status at time of visit (above vs. below the poverty threshold), and food security at time of visit (high/marginal security vs. low and very low security).
[b]Calculated using the formula: [Glyphosate + (1.5 × AMPA)].
[c]Limited to participants with nonfasting urine samples.

Table 6). Higher AMPA concentrations at 5 y were associated with elevated liver transaminases at 18 y [relative risk (RR) = 1.27; 95% confidence interval (CI): 1.06, 1.53]. Higher AMPA and glyphosate residue concentrations at 18 y among nonfasting participants were marginally associated with elevated liver enzymes [RR = 1.13 (95% CI: 0.98, 1.32) and RR = 1.16 (95% CI: 1.00, 1.35), respectively]; these associations were further attenuated when fasting 18-y-olds were included (Supplemental Table 7). RRs remained similar when we excluded the eight cases with high actin, with low ceruloplasmin, and/or who binge-drank alcohol (Supplemental Table 8).

We also found associations of urinary AMPA and total glyphosate residue concentrations with metabolic syndrome and related conditions. Two-fold increases in AMPA at 5 y (RR = 2.07, 95% CI: 1.38, 3.11) and in AMPA and glyphosate residues at 14 y [RR = 1.80 (95% CI: 1.10, 2.93) and RR = 1.88 (95% CI: 1.03, 3.42), respectively] and at 18 y (among nonfasters) [RR = 1.59 (95% CI: 0.99, 2.54) and RR = 1.54 (95% CI: 0.94, 2.52), respectively] were associated with a 50% or greater increased risk of metabolic syndrome at 18 y (Table 3; Supplemental Table 6). In addition, higher AMPA concentrations at age 5 y were associated with elevated glucose levels (RR = 2.95, 95% CI: 1.70, 5.14), and higher AMPA concentrations at ages 14 y and 18 y (among nonfasters) were associated with elevated triglycerides [RR = 1.51 (95% CI: 1.03, 2.22) and RR = 1.45 (95% CI: 1.07, 1.96) respectively]. Higher urinary glyphosate residue concentrations at age 18 y (among nonfasters) were associated with elevated triglycerides (RR = 1.39, 95% CI: 1.04, 1.88) and large waist circumference (RR = 1.33, 95% CI: 1.02, 1.73).

In multiple informant models, we did not find evidence of interaction by visit in the associations of glyphosate, AMPA, or glyphosate residue concentrations with our outcomes (Supplemental Table 9). Therefore, we fitted models without interaction terms, using repeated measurements to approximate lifetime exposure (Table 4). In these models, a 2-fold increase in childhood urinary concentrations of AMPA was associated with a 14% increased risk of elevated liver transaminases (95% CI: 1.05, 1.23) and a 55% increased risk of metabolic syndrome (95% CI: 1.19, 2.02) at age 18 y. Higher childhood urinary concentrations of AMPA were also associated with elevated blood pressure, glucose, and triglycerides and with larger waist circumference. Higher childhood glyphosate residue concentrations were also associated with increased risks of elevated liver transaminases (RR per 2-fold increase in concentrations = 1.13, 95% CI: 1.05, 1.22), metabolic syndrome (RR = 1.52, 95% CI: 1.12, 2.06), and elevated triglycerides (RR = 1.22, 95% CI: 1.01, 1.46) (Table 4).

In the SEM models, we found no evidence that associations of urinary AMPA or glyphosate residues with elevated liver transaminases or metabolic syndrome were mediated by young adult BMI (Supplemental Table 10).

Association of Residential Proximity to Glyphosate Use with Liver and Cardiometabolic Outcomes

Any agricultural use of glyphosate near the home during pregnancy was associated with an increased risk of metabolic syndrome in the case–control subset (RR = 3.42, 95% CI: 1.12, 10.42) but not in the full sample (RR = 1.16, 95% CI: 0.66, 2.05)

Table 4. Multiple informant models (RRs and 95% CI) for repeated child urinary glyphosate, AMPA, and glyphosate residue concentrations (specific gravity-corrected, μg/L) at the 5-y, 14-y, and 18-y visits and abnormal markers of liver inflammation and metabolic syndrome (and its components), using mixed-effects Poisson models with a random intercept for each CHAMACOS participant.[a,b]

	Glyphosate ($n = 121$–122)	AMPA ($n = 121$–122)	Glyphosate residues[c] ($n = 121$–122)
Elevated liver transaminases	1.05 (0.98, 1.13)	1.14 (1.05, 1.23)	1.13 (1.05, 1.22)
Metabolic syndrome	1.14 (0.82, 1.59)	1.55 (1.19, 2.02)	1.52 (1.12, 2.06)
High blood pressure	1.08 (0.85, 1.38)	1.23 (1.01, 1.50)	1.22 (0.99, 1.51)
Large waist circumference	1.02 (0.94, 1.12)	1.06 (0.99, 1.14)	1.06 (0.99, 1.14)
High glucose	1.11 (0.82, 1.49)	1.35 (1.02, 1.77)	1.30 (0.96, 1.77)
High triglycerides	0.99 (0.86, 1.14)	1.27 (1.07, 1.52)	1.22 (1.01, 1.46)
Low HDL cholesterol	0.94 (0.87, 1.02)	1.01 (0.96, 1.07)	0.99 (0.93, 1.06)

Note: AMPA, aminomethylphosphonic acid; BMI, body mass index; CHAMACOS, Center for the Health Assessment of Mothers and Children of Salinas; CI, confidence interval; HDL, high-density lipoprotein; RR, relative risk.
[a]Fasting urine samples taken at 18 y are not included in models, but 5-y and 14-y samples are still included for those participants.
[b]Models adjusted for sex, any alcohol consumption at 18 years (yes/no), maternal prepregnancy BMI, parental work in agriculture during pregnancy (yes/no), household poverty status at 18 y (above vs. below the poverty threshold), and food security at 18 y (high/marginal security vs. low and very low security).
[c]Calculated using the formula: [Glyphosate + (1.5 × AMPA)].

Table 5. Adjusted[a] RRs and 95% CI for living within 1 km of agricultural glyphosate use during maternal pregnancy (any use) and from birth to age 5 y (all use, in kilograms, $\log_2$) based on the California Pesticide Use Reporting (PUR) data and presence of elevated markers of liver inflammation or metabolic syndrome (and its components) among all CHAMACOS young adult participants and in case–control subset.

	Any PUR use near home residence during pregnancy (yes/no)		Sum of PUR use near home residence from birth to age 5 y ($\log_2$)	
Outcome	All 18-y-old participants ($n = 397$–464)	Case–control subset ($n = 149$–150)	All 18-y-old participants ($n = 327$–373)	Case–control subset ($n = 129$–130)
Elevated liver transaminases	0.83 (0.53, 1.30)	1.14 (0.77, 1.71)	0.93 (0.80, 1.08)	0.98 (0.86, 1.11)
Metabolic syndrome	1.16 (0.66, 2.05)	3.42 (1.12, 10.42)	1.15 (0.97, 1.35)	1.53 (1.16, 2.02)
High blood pressure	1.00 (0.60, 1.67)	0.89 (0.40, 1.99)	0.95 (0.78, 1.16)	1.11 (0.85, 1.46)
Large waist circumference	1.04 (0.84, 1.29)	1.23 (0.74, 2.05)	1.05 (0.97, 1.13)	0.97 (0.82, 1.15)
High glucose	0.78 (0.31, 1.95)	0.39 (0.10, 1.54)	0.87 (0.65, 1.15)	0.79 (0.56, 1.11)
High triglycerides	0.99 (0.58, 1.67)	3.37 (1.36, 8.33)	1.09 (0.90, 1.32)	1.45 (1.11, 1.88)
Low HDL cholesterol	1.04 (0.81, 1.32)	1.07 (0.64, 1.78)	1.00 (0.91, 1.09)	0.91 (0.76, 1.07)

Note: BMI, body mass index; CHAMACOS, Center for the Health Assessment of Mothers and Children of Salinas; CI, confidence interval; HDL, high-density lipoprotein; PUR, Pesticide Use Reporting; RR, relative risk.
[a]Models adjusted for sex, alcohol use at 18 y (never/ever), maternal prepregnancy BMI, parental work in agriculture during pregnancy (yes/no), household poverty status at 18 y (above vs. below the poverty threshold), and food security at 18 y (high/marginal security vs. low and very low security).

(Table 5; Supplemental Table 11). A 2-fold increase in nearby glyphosate use during early childhood was also associated with an increased risk of metabolic syndrome in the case–control group (RR = 1.53, 95% CI: 1.16, 2.02), and with a somewhat elevated risk in the full sample (RR = 1.15, 95% CI: 0.97, 1.35) (Table 5, Supplemental Table 11). In the case–control group, we also observed increased risk of elevated triglyceride levels with any nearby agricultural glyphosate use during pregnancy (RR per 2-fold increase = 3.37, 95% CI: 1.36, 8.33) as well as with all agricultural glyphosate use during early childhood (RR = 1.45, 95% CI: 1.11, 1.88) (Table 5).

Discussion

We observed associations of glyphosate or AMPA exposure during childhood with liver inflammation and metabolic syndrome at young adulthood. More specifically, after accounting for multiple potential confounders, we found that higher urinary concentrations of AMPA, a degradation product of glyphosate and aminopolyphosphonates, and glyphosate residues between ages 5 and 18 y were associated with both elevated liver transaminases and metabolic syndrome at age 18 y. This association could not be explained by mediation by body mass. In addition, we found that agricultural glyphosate use during the prenatal period and/or childhood (from birth to age 5 y) was associated with metabolic syndrome at 18 y.

Our findings are consistent with Mills et al.,[29] who observed that urinary concentrations of AMPA and total glyphosate residues were elevated in 34 patients with nonalcoholic steatohepatitis (NASH) in comparison with 63 controls and more elevated in cases with more advanced fibrosis than those with less. These findings are also consistent with hepatotoxicity noted at much higher doses in glyphosate poisoning cases and with occupational exposures.[30,31] In rodent studies, even low dosages of glyphosate or glyphosate-based herbicide formulations produced signs of NAFLD,[24] as evidenced by fibrosis, steatosis, and necrosis of the liver.[25] Glyphosate and glyphosate-based herbicide formulations have been found to alter the metabolome, proteome,[24] transcriptome,[26] epigenome,[27] and DNA[28] of the liver in rodent studies. Exposure to glyphosate, glyphosate-based herbicides, and AMPA has also induced epigenetic modifications in *in vitro* studies of human peripheral blood mononuclear cells.[27]

In a study of male rats, Prasad et al.[33] found a dose-related increase in fasting blood glucose and serum insulin in glyphosate-exposed groups in comparison with controls. To our knowledge, the association of glyphosate with insulin resistance and other metabolic disorders has not been previously explored in human populations, although researchers have hypothesized that glyphosate has the potential to induce metabolic disease because of its ability to induce oxidative stress in preadipocytes and in other tissues.[32,33,63–65] A second hypothesis for glyphosate's etiologic role in metabolic disorders is its adverse effect on the gut microbiota, which have been shown in animal studies to be a source of oxidative stress.[66] Recent investigations in rats have shown that glyphosate-containing herbicides inhibit the shikimate pathway in the gut microbiome.[66] A third hypothesis for the association is through endocrine disruption,[67] with evidence that glyphosate and glyphosate-containing herbicides can disrupt endocrine-signaling systems.[33,68,69] Although the association of exposure to AMPA with metabolic disorders has been neither explored nor hypothesized, a recent *in vitro* study based on induced pluripotent stem cells (iPSCs) found changes in glucose metabolism following treatment to glyphosate or AMPA.[70]

Most of our prenatal urine samples, all collected around year 2000, had nondetectable levels of glyphosate and AMPA, consistent with the low use of glyphosate in agriculture around that time.[8] With this exception, detection frequencies and concentrations in urine samples collected during childhood were within the range of those reported in other studies of children.[71–74] Adolescents (12- to 19-y-olds) participating in the 2013–2014 National Health and Nutrition Examination Survey (NHANES) had a higher weighted detection frequency (87.2% >LOD) and wet weight geometric mean (GM = 0.48 μg/L) of urinary glyphosate concentrations than the 14-y-olds included in our study (who provided urine samples collected around the same time) (78.9% >LOD, GM = 0.18 μg/L, respectively)[75]; urinary AMPA concentrations were not measured in NHANES adolescents. However, our 14-y-old participants had higher urinary glyphosate and AMPA detection frequencies (78.9 and 93.3% >LOD, respectively) and wet weight geometric means (GM = 0.18 and 0.45 μg/L, respectively) than 14- to 17-y-old children participating in the 2015–2017 German Environmental Survey for Children and Adolescents (glyphosate: 46% >LOQ, GM <LOQ, respectively; AMPA: 42% >LOQ, GM <LOQ, respectively) (LOQ = 0.1 μg/L for both glyphosate and AMPA).[72] It is likely that diet was a major source of glyphosate and AMPA exposure among our study participants at age 14 y, as indicated by higher urinary glyphosate or AMPA concentrations among those who ate more cereal, fruits, vegetables, bread, and in general, carbohydrates. We observed lower urinary concentrations of glyphosate and AMPA at age 18 y, even among the participants who had not fasted, than at age 14 y, despite increases in agricultural glyphosate use. It is possible that differences in diet may explain the lower concentrations at age 18 y; unfortunately, our 18-y dietary questionnaire was too limited to test this hypothesis. Similar to our findings at age 18 y,

the NHANES data revealed lower urinary glyphosate concentrations in those who had fasted more than 8 h in comparison with those who fasted less, supporting the importance of dietary intake in glyphosate exposure.[75]

A strength of our study was that we could characterize agricultural glyphosate use near homes using California's unique PUR database. However, our estimates do not reflect the full extent of ambient glyphosate exposure; they do not account for agricultural use near participants' schools, workplaces, or nonagricultural uses (e.g., homes, roadways, parks).[46] We also did not consider use of specific formulations of glyphosate-based pesticides, which may differ in their toxicity.[76] Despite these limitations, we observed associations between PUR-assessed agricultural glyphosate exposure and metabolic syndrome that are interesting and merit additional research.[77]

An important limitation of our study is that a single measure of glyphosate or AMPA concentrations in the urine, and even multiple measures at different developmental periods, might not accurately reflect exposure, given the short half-life of glyphosate and AMPA in humans of between 3.5 and 14.5 h.[78] This possibility, along with inaccuracy in dietary recall, could explain the modest associations of urinary AMPA and glyphosate residue concentrations with dietary factors that we observed. The short half-life of glyphosate in the human body[78] as well as in the environment[79] (unlike AMPA, which has been classified as persistent in soil[80] and groundwater[81]) may have contributed to the weak correlations we observed between glyphosate use near residences and urinary glyphosate or AMPA concentrations. It can also explain the lower detection and urinary concentrations among those 18-y-olds who had fasted (vs. the nonfasters), given that food was likely an important route of exposure and that the maximum concentration of glyphosate and AMPA in urine is 1–3 h and 5–6 h after exposure, respectively.[82] Given these short half-lives, the urinary concentrations measured concurrently with the outcomes at 18 y might not accurately reflect the exposure to glyphosate and AMPA preceding the onset of disease, which would be important criterion to establish a causal relationship.

Although we observe some associations of nearby agricultural use of glyphosate during the prenatal period and childhood with metabolic syndrome, urinary glyphosate concentrations were not associated with any health outcomes in the present study. Nevertheless, we observed associations of urinary AMPA and glyphosate residue concentrations (with the latter largely driven by AMPA) with elevated liver transaminases and/or metabolic syndrome. It is likely that urinary AMPA was derived from degradation of glyphosate in the environment. For example, microbial degradation of glyphosate in soil results in the accumulation of AMPA in soil, plants, and animal products.[18] AMPA is highly soluble in water, more persistent in the environment than glyphosate,[83] and therefore frequently detected at higher concentrations than glyphosate in most hydrological settings, with groundwater and soil water samples having the highest values.[81] Tracer studies in Canada have shown that AMPA in groundwater is mainly derived from glyphosate degradation rather than wastewater sources, such as those contaminated with phosphonates.[84] Although few studies have measured urinary AMPA concentrations in human populations, it is known that AMPA is poorly metabolized in the human body. For example, in a study of volunteers who ingested glyphosate,[82] total dose recovered as unchanged glyphosate was low (1%–6%) but extremely low for AMPA—0.01%–0.04% of the total dose of glyphosate. This low excretion of AMPA in urine after glyphosate exposure has also been demonstrated in other studies.[31,85] Thus, urinary AMPA likely results from direct exposure to AMPA from food residues and water, with a lesser extent from the metabolism of glyphosate *in vivo*. However, additional research is needed to identify the major pathways of AMPA exposure.

Our research suggests that lifetime exposure to glyphosate and AMPA may increase risk of liver and metabolic disease in early adulthood, which could lead to more serious diseases later in life, such as liver cancer,[86] diabetes, and cardiovascular disease.[87] Longitudinal lifelong studies in humans, such as CHAMACOS, are necessary to connect potential impact of glyphosate and AMPA on organ damage and other intermediate outcomes to chronic illness in adulthood. Future research should include frequent measurements of exposure biomarkers during fetal and child development to determine windows of susceptibility; examine the effects of glyphosate and AMPA in the context of exposure to pesticide mixtures[88,89]; and explore associations with other outcomes, such as reproductive and endocrine function.[67,90] In addition, studies with sufficient sample size should examine differences in susceptibility by sex, as seen in animal studies.[91,92]

Conclusions

Metabolic and liver diseases are increasing among youth and young adults.[93] Our study suggests that glyphosate, the most commonly used herbicide worldwide, and AMPA, a degradation product of glyphosate and amino-phosphonates, may increase risk of liver inflammation and/or cardiometabolic disease in young adulthood. Although previous research on glyphosate in humans has largely focused on its potential carcinogenicity, this study indicates the need for further investigation of its association with metabolic and liver outcomes.

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