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Pesticide residue intake from fruits and vegetables and fecundability in a North American preconception cohort study

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ABSTRACT

Intake of conventionally-grown fruits and vegetables with higher levels of pesticide residue contamination has been associated with poorer semen quality and lower probability of live birth among couples undergoing fertility treatment. We examined the association between dietary intake of pesticide residues and fecundability, the per cycle probability of conception, in a preconception cohort of pregnancy planners. We enrolled women aged 21–45 years who were attempting to conceive without use of fertility treatment into Pregnancy Study Online (PRESTO) from June 2013 through September 2019. Participants completed a baseline questionnaire on demographics, lifestyle factors, and medical and reproductive histories, and bimonthly follow-up questionnaires for up to 12 months or until reported conception. Ten days after baseline, participants completed the National Cancer Institute's Diet History Questionnaire II, a validated food frequency questionnaire. Using data from the USDA Pesticide Data Program, we classified fruits and vegetables as having high or low pesticide residues using a validated method. We examined the relation between greater intake of high- and low-pesticide residue fruits and vegetables with fecundability using proportional probabilities regression models, adjusted for potential confounders and accounting for consumption of organic produce. We restricted our analysis to 5234 women who had been attempting conception for ≤ 6 cycles at study entry, and further stratified by pregnancy attempt time at study entry (< 3 vs. 3–6 cycles) to evaluate potential for reverse causation. Intakes of high- and low-pesticide residue fruits and vegetables were not appreciably related to fecundability in the full sample, or among women trying to conceive for < 3 cycles at study entry. However, among women trying to conceive for 3–6 cycles at study entry, both high- and low-pesticide residue fruit and vegetable intakes were strongly inversely related to fecundability, indicating potential reverse causation bias. These results do not support the hypothesis that intake of pesticide residues from conventionally-grown fruits and vegetables is harmful to fertility, although non-differential exposure misclassification may have attenuated our findings.

1. Introduction

Pesticides—substances used to repel, prevent, or destroy pests—are commonly applied to fruit and vegetable crops worldwide (Zhang et al., 2011). Intake of conventionally-grown (*i.e.*, not organic) fruits and vegetables is a major source of pesticide exposure in the general population (Bradman et al., 2015; Lu et al., 2006; Oates et al., 2014), and biomonitoring studies in the United States and Canada have found that pesticides and their metabolites are commonly detected in human biospecimens (Centers for Disease Control and Prevention, 2017; Haines et al., 2017). Although dietary guidelines emphasize that individuals should increase their consumption of fruits and vegetables to prevent chronic diseases (U.S., 2015), consumers have raised concerns regarding increased exposure to pesticide residues from produce consumption (Williams and Hammitt, 2001).

Measuring concentrations of pesticides and their metabolites in biospecimens (*i.e.*, blood and urine) is the best metric currently available for assessing pesticide exposure. However, there are several challenges to using this method in epidemiologic studies. Collecting and analyzing biospecimens is logistically challenging, expensive, and invasive to participants, thereby limiting the size, diversity, and geographic variability of study populations. Recent studies have utilized food frequency questionnaires (FFQ) to assess dietary intake of pesticide residues in relation to reproductive health, a tool that overcomes

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many of the challenges of directly measuring pesticide levels in blood and urine (Chiu et al., 2015; Chiu et al., 2016; Chiu et al., 2018; Chiu et al., 2018; Chiu et al., 2018; Hu et al., 2016). Specifically, the Pesticide Residue Burden Score (PRBS), calculated using data from the United States Department of Agriculture (USDA) Pesticide Data Program (USDA, 2018), classifies common fruits and vegetables based on their likelihood of pesticide contamination and calculates participants' intakes of high- and low-pesticide fruits and vegetables. It has been validated among 3679 participants from the National Health and Nutrition Examination Survey (NHANES), where PRBS scores in the top quintile were associated with 13.0% higher urinary pesticide metabolite concentrations compared with scores in the bottom quintile (Hu et al., 2016).

In the Rochester Young Men's Study, a population of healthy men aged 18–22 years, low-pesticide residue fruit and vegetable intake, defined using the PRBS, was associated with improved semen quality, whereas high-pesticide residue fruit and vegetable intake was unrelated to semen quality (Chiu et al., 2016). In the Environment and Reproductive Health (EARTH) Study, a study of couples undergoing fertility treatment, high intake of high-pesticide residue fruits and vegetables was associated with poorer semen quality, but high intake of low-pesticide residue fruits and vegetables was not meaningfully related to semen quality (Chiu et al., 2015). Likewise, in the EARTH study, intake of high- but not low-pesticide residue fruits and vegetables was associated with lower probability of live birth among couples receiving fertility treatment (Chiu et al., 2018). There has been no prospective study of pesticide residue intake defined using the PRBS and fertility among couples attempting to conceive spontaneously.

In the present work, we applied this FFQ-based approach to categorize pesticide exposure in a preconception cohort study of pregnancy planners from North America. We examined the association between greater intake of high- and low-pesticide residue fruits and vegetables with fecundability, the per-cycle probability of conception among non-contracepting couples.

2. Methods

2.1. Study design

Pregnancy Study Online (PRESTO) is an ongoing internet-based preconception cohort study (Wise et al., 2015). Eligible women are age 21–45 years, residents of the United States or Canada, and attempting to conceive without use of fertility treatment. Participation involves completion of a baseline questionnaire on demographic, lifestyle, medical, and reproductive factors and follow-up questionnaires every 8 weeks for up to 12 months. Ten days after completion of the baseline questionnaire, we invite women to complete an optional FFQ, the National Cancer Institute's Diet History Questionnaire II (Subar et al., 2001). The study was approved by the institutional review board at Boston University Medical Campus. All participants provided online informed consent.

From June 2013 through September 2019, 11,120 women completed the baseline questionnaire. We excluded 169 women who had not had a menstrual period in at least six months, 30 women with no prospectively-reported last menstrual period (LMP) dates, and 2181 women who had been trying to conceive for more than six menstrual cycles at enrollment. Of the 8701 remaining women, 5455 completed the FFQ (62.7%), and we additionally excluded 129 women with estimated total caloric intake < 600 or > 3800 kcal/day. Most women (89%) completed their FFQ within one month of baseline; we excluded the 92 women who completed the FFQ more than six months after baseline for a final analytic sample of 5234 women.

2.2. Dietary assessment

The Diet History Questionnaire II is a validated FFQ that assesses dietary intake over the past 12 months (Millen et al., 2006; Subar et al., 2001). Using Diet*Calc software, we obtained daily intake and nutrient information on 277 individual food items, including 40 fruits and vegetables. In a validation study, deattenuated correlation coefficients comparing the FFQ data with repeat 24-hour food diaries were 0.66 for total vegetables and 0.66 for total fruits (Millen et al., 2006). For subgroups of vegetables, deattenuated correlation coefficients were 0.52 for white potatoes, 0.43 for other starchy vegetables, 0.67 for dark green vegetables, 0.58 for deep yellow vegetables, 0.49 for tomatoes, 0.62 for legumes, and 0.63 for other vegetables. For subgroups of fruits, deattenuated correlation coefficients were 0.63 for citrus fruit, melon, and berries and 0.64 for other fruit.

2.3. Primary definition of pesticide residue intake

The PRBS is a cost-effective, non-invasive metric designed to assess pesticide residue intake from fruits and vegetables, and has been described in detail elsewhere (Chiu et al., 2018). Briefly, the PRBS uses data from the USDA Pesticide Data Program database to identify fruits and vegetables with high likelihood of pesticide contamination. The Pesticide Data Program, launched in 1991, randomly samples fruits and vegetables every year for measurement of over 300 pesticide residues. Fresh samples of some foods are washed and peeled before measurement to emulate typical consumer practices. The PRBS combines three measures of pesticide exposure from the Pesticide Data Program database for each fruit and vegetable into one metric: (1) the proportion of samples with any detectable pesticides, (2) the proportion of samples with pesticides above the tolerance level, and (3) the proportion of samples with three or more detectable pesticides. To calculate the PRBS, intakes of individual fruits and vegetable are ranked into tertiles for each of these measures and assigned a score for each (0 for the lowest tertile, 1 for the middle tertile, and 2 for the highest tertile). Scores are summed across all three measures for a total score that ranges from 0 (least contaminated) to 6 (most contaminated). For example, a fruit or vegetable in the lowest tertile for samples with any detectable pesticides, the middle tertile for samples above the tolerance level, and the highest tertile for samples with three or more detectable pesticides would have a score of 3 $(0 + 1 + 2)$. Fruits and vegetables with scores ≥ 4 are considered high-pesticide residue foods; those with scores < 4 are considered low-pesticide residue foods. In the present study, we used the Pesticide Data Program database from 2012 to 2017 to define high- and low-pesticide residue fruits and vegetables using the PRBS. The exposure metric accounts for the quantity of individual fruits and vegetables consumed by participants and the likelihood that those individual fruits and vegetables contain pesticide residues. Our defined list of high-pesticide residue fruits and vegetables (Table 1) was similar to those from previous studies (Chiu et al., 2015; Chiu et al., 2016; Chiu et al., 2018; Chiu et al., 2018) and to the "dirty dozen" fruits and vegetables developed by an advocacy group (Environmental Working Group, 2019).

2.4. Secondary definitions of pesticide residue intake

While the PRBS as a method of ranking participants by pesticide residue intake has shown adequate validity when compared with urinary and serum concentrations of pesticide residues in NHANES and a cohort of men undergoing fertility treatment (Chiu et al., 2018; Hu et al., 2016), there are a few potential weaknesses in its design. First, the PRBS defines high- and low-pesticide residue fruits and vegetables using tertiles of exposure metrics from the Pesticide Data Program database. This practice, while not problematic for assessing rank scores within a study, can make comparisons across studies difficult, especially when studies ascertain different lists of fruits and vegetables. In addition, the PRBS weighs the three measures of pesticide exposure equally, despite the fact that they represent three different types of exposure. The resulting score is at best a rough approximation to an idealized

Table 1
Distribution of fruit and vegetable intake in PRESTO and pesticide residue data from USDA Pesticide Data Program.

	PRESTO		USDA Pesticide Data Program			
			Percentage of samples with:			
Fruit or vegetable	% women with any intake	Mean intake (SD) cup equiv/week	any detectable pesticides	pesticides above tolerance level	≥3 detectable pesticides	PRBS[a]
Peaches, nectarines, plums	42.1	0.22 (0.49)	96.5	8.4	55.1	6
Raw or cooked greens	85.9	1.13 (1.54)	96.3	26.2	86.0	6
Strawberries	72.8	0.37 (0.56)	95.6	6.6	92.6	6
Hot peppers	20.0	0.04 (0.08)	71.7	8.3	41.6	5
Grapes	69.9	0.28 (0.52)	94.9	1.5	81.0	5
Pickled vegetables	39.6	0.08 (0.10)	87.0	4.9	43.6	5
Sweet peppers	77.8	0.26 (0.36)	89.8	2.2	61.3	5
Tomatoes	92.7	0.76 (1.05)	75.8	7.0	61.3	5
White potatoes	97.5	1.12 (1.07)	99.8	0.6	52.0	5
Apples	91.0	1.49 (2.08)	97.0	0.0	80.7	4
Applesauce	47.6	0.13 (0.41)	93.0	0.0	81.2	4
Carrots	88.1	0.41 (0.56)	72.3	4.9	31.6	4
Mango	14.6	0.11 (0.27)	75.4	24.6	14.9	4
Pears	53.5	0.19 (0.48)	88.0	0.2	73.4	4
String beans	84.6	0.46 (0.60)	73.9	5.4	27.9	4
Dried fruit	45.2	0.17 (0.36)	35.9	9.8	3.8	3
Grapefruit	27.3	0.09 (0.32)	93.8	0.1	18.4	3
Lettuce	91.0	0.80 (0.83)	80.2	1.6	31.3	3
Melon	61.8	0.28 (0.61)	57.9	2.3	8.3	3
Oranges, tangerines, clementines	62.5	0.45 (0.74)	94.6	0.2	9.5	3
Sweet potatoes	61.4	0.19 (0.34)	56.9	2.3	3.2	3
Winter squash	59.0	0.15 (0.30)	70.0	3.6	20.6	3
Asparagus	62.4	0.19 (0.31)	18.3	7.2	2.0	2
Bananas, plantains	88.7	1.34 (1.59)	81.5	0.1	8.9	2
Broccoli	92.5	0.67 (0.74)	32.7	1.6	4.4	2
Cauliflower, Brussel sprouts	67.7	0.27 (0.45)	45.2	1.0	0.8	2
Olives	29.1	0.04 (0.06)	33.3	8.3	1.1	2
Orange and grapefruit juice	81.0	0.67 (1.89)	27.3	7.9	0.0	2
Avocado, guacamole	55.8	0.23 (0.21)	1.1	1.1	0.0	1
Cantaloupe	29.7	0.09 (0.28)	36.6	0.0	2.4	1
Peas	62.2	0.20 (0.35)	19.1	3.5	0.4	1
Beans	81.8	0.16 (0.21)	3.3	0.5	0.0	0
Cabbage/sauerkraut/coleslaw	64.7	0.16 (0.34)	24.3	0.0	2.0	0
Corn	72.2	0.30 (0.43)	1.7	0.0	0.0	0
Onions	81.7	0.30 (0.28)	16.8	0.4	0.5	0
Pineapple	53.9	0.13 (0.32)	0.0	0.1	0.0	0

[a] PRBS = Pesticide Residue Burden Score. Fruits and vegetables with PRBS scores of 4–6 are classified as "high-pesticide residue", and those with scores of 0–3 are classified as "low-pesticide residue".

scale that measures meaningfully spaced increments of biological exposure. Lastly, the pesticide contamination data from the database are continuous measures (*e.g.*, the proportion of samples with any detectable pesticides). The PRBS, by defining each fruit and vegetable as "high" or "low" based on a binary cut point, does not utilize the full range of the underlying continuous data.

To address these limitations, in a secondary analysis, we calculated six additional metrics of pesticide residue intake. First, we examined the three measures contributing to the PRBS individually, by defining high-pesticide residue fruits and vegetables as those where (1) ≥90% of samples had any detectable pesticides, (2) ≥5% of samples had pesticide levels above the tolerance level or (3) ≥50% of samples had three or more detectable pesticides. Second, we created a new pesticide residue score variable that used the full range of continuous data from the Pesticide Data Program database for each of the three measures of pesticide exposure. To create the score, we multiplied the intake of each fruit and vegetable in our cohort by the proportion of samples from the database with (4) any detectable pesticides, (5) pesticides above the tolerance level and (6) three or more detectable pesticides. These scores represent fruit and vegetable intake weighted by the level of pesticide contamination. The absolute value of the scores is not biologically meaningful, but the score orders participants according to pesticide residue intake. This score has not been validated with measures in human biospecimens.

Four of the 40 fruit and vegetable items on our FFQ were "other fruits", "other vegetables", "other juices", and "vegetable medley". We excluded intake of these items from our definitions of high- and low-pesticide residue intake (accounting for 9% of total intake in our cohort) in all analyses.

2.5. *Assessment of fecundability*

On each follow-up questionnaire, we asked women if they were currently pregnant and if they had experienced any pregnancy losses since their previous questionnaire. If they were not currently pregnant, we asked them if they were still trying to conceive. We also asked all women if they had initiated fertility treatment. For women who were lost to follow-up, we attempted to ascertain pregnancy status by linking with birth registries in selected states, searching for baby announcements and baby registries online, and contacting participants via telephone.

We collected information on cycle regularity and typical cycle length on the baseline questionnaire. We asked about the date of the first day of the LMP at baseline and on each follow-up. We calculated time to pregnancy, in discrete menstrual cycles, as: cycles of attempt at study entry + [(LMP date from most recent follow-up questionnaire –

date of baseline questionnaire completion)/usual cycle length] + 1.

2.6. Assessment of covariates

We ascertained information on demographics (*e.g.*, age, race/ethnicity, education, geographic region of residence), lifestyle (*e.g.*, height, weight, alcohol intake, cigarette smoking history, physical activity, intake of multivitamins), and reproductive history (*e.g.*, parity, history of infertility, intercourse frequency, last method of contraception) on the baseline questionnaire. We also asked what proportion of the food consumed was organic ("almost none", "less than half", "more than half", "almost all"), separately for individual food groups (*e.g.*, breads & cereals, eggs, milk, yogurt, cheese, vegetables, fruits, fish, poultry, other meat). We calculated the Healthy Eating Index (2010) from the FFQ (Guenther et al., 2013), and removed components related to fruit and vegetable intake to avoid overcontrol (modified score ranges from 0 to 80, with higher scores indicating better diet quality).

2.7. Statistical analysis

We used life-table methods to calculate the proportion of women who conceived during follow-up (Cox, 1972). We used the Andersen-Gill data structure (Therneau and Grambsch, 2000), with one observation per menstrual cycle, to update pregnancy status over time and to account for left truncation due to delayed entry into the risk set (Schisterman et al., 2013). Women contributed menstrual cycles to the analysis from study entry until pregnancy (regardless of outcome) or until one of the following censoring events: initiation of fertility treatment, cessation of pregnancy attempt, 12 cycles, or loss to follow-up.

We categorized intake of high- and low-pesticide fruits and vegetables as < 0.5, 0.5–0.9, 1.0–1.4, 1.5–1.9, and ≥ 2.0 cup-equivalents/day. We used proportional probabilities regression models to estimate fecundability ratios (FR) and 95% confidence intervals (CI) comparing each category of intake to the reference level (Weinberg et al., 1989). The FR estimates the ratio of the per-cycle probability of conception comparing exposed with unexposed women; exposures with FRs < 1 are associated with reduced fecundability. We controlled for indicator variables for cycle at risk in the regression models to account for the decline in baseline fecundability over time and delayed entry into the risk set. In all models, we created a separate category for women who reported that they eat organic fruit and vegetables "most of the time" or "more than half of the time" ($n = 479$, 9.3%); the PRBS metric likely measures pesticide residue intake more accurately among women eating mostly conventionally-grown produce.

Final models were adjusted for age (< 25, 25–29, 30–34, ≥ 35 years), race/ethnicity (non-Hispanic White vs. not), education (≤ 12, 13–15, 16, ≥ 17 years), annual household income ($<$ \$50,000, \$50,000–99,999, \$100,000–149,999, $\geq$ \$150,000 USD), BMI (< 25, 25–29, 30–34, ≥ 35 kg/m^2), smoking history (never, former, current occasional, current regular smoker), sugar-sweetened soda intake (0, 1, 2–6, ≥ 7 drinks/week), physical activity (< 10, 10–19, 20–39, ≥ 40 metabolic equivalent of task (MET)-hours/week), daily use of multivitamins or folic acid (yes vs. no), Healthy Eating Index score (with fruit and vegetable components excluded; < 40, 40–49, 50–59, ≥ 60), intercourse frequency (< 1, 1, 2–3, ≥ 4 times/week), doing something to improve chances of conception (yes vs. no), last method of birth control (hormonal methods, barrier methods, withdrawal/rhythm methods), month of enrollment, geographic region of residence (Northeastern U.S., Southern U.S., Midwestern U.S., Western U.S., and Canada), and total fruit and vegetable intake.

We stratified final models by attempt time at study entry (< 3 vs. 3–6 cycles) to assess the potential for reverse causation, where women trying for longer have changed their diet in response to perceived subfertility. We also stratified final models by calendar year of study participation (2013–2015 vs. 2016–2019), as changes in pesticide regulations and use during the study period could affect the association between high- and low-pesticide residue fruit and vegetable intake and fecundability. We conducted sensitivity analyses restricting to participants residing in the United States, because pesticide residue levels were calculated using a United States database. Although the stringency of regulations in the United States and Canada are generally similar, (Boyd, 2006) maximum residue levels for individual pesticides vary substantially, limiting our ability to apply our exposure metrics to Canadian participants. We conducted additional sensitivity analyses restricted to (a) women who reported "almost never" consuming organic fruits and vegetables and (b) women without occupational pesticide exposure. Lastly, because a validation study found little association between organic food intake and urinary pesticide metabolite concentrations (Chiu et al., 2018) and the Pesticide Data Program samples some organic produce, we conducted a sensitivity analysis not accounting for organic fruit and vegetable intake.

We used multiple imputation to impute missing covariate and outcome data using fully conditional specification methods. (Liu and De, 2015) We combined point estimates and standard errors across five imputation data sets according to Rubin's rule. We had complete dietary intake data on all women included in the present analysis. Covariate missingness ranged from 0% (age) to 3.4% (household income). The question on organic food intake was added to the questionnaire in October 2017; therefore, 76.0% of the data for this question were imputed. However, simulation studies have shown that the proportion of missing data is not a strong predictor of the performance of the imputation model and should not be used to guide decisions on the handling of missing data. (Madley-Dowd et al., 2019) Women with no follow-up (2.4%) were assigned one cycle of follow-up and had their pregnancy status (pregnant vs. not pregnant) imputed at the end of that cycle.

3. Results

Overall, 5234 women contributed 21,634 menstrual cycles to the analysis. Pregnancy was identified for 3369 women (74.2% of the population when accounting for loss to follow-up). The remaining women were censored for the following reasons: initiated fertility treatment (8.9%), stopped trying to conceive (3.3%), completed 12 cycles of attempt time without conception (14.0%), or were lost to follow-up (6.7%). The remaining women (2.8%) were still actively contributing follow-up to the study at the time of analysis.

Patterns of participant characteristics by intake of high- and low-pesticide residue fruits and vegetables are shown in Table 2. Women with higher intake of fruits and vegetables, regardless of the pesticide residue classification, were slightly older, more likely to be non-Hispanic White, and had higher income and educational attainment. They generally had lower BMI and healthier lifestyle practices, including higher physical activity, lower smoking prevalence, lower sugar-sweetened soda intake, higher Healthy Eating Index scores, and higher prevalence of daily multivitamin or folic acid intake. High consumers of fruits and vegetables were also less likely to be parous, have a history of infertility, have infrequent intercourse, or report a hormonal last method of contraception. Fruit and vegetable intake was also positively associated with eating "almost all" organic fruits and vegetables.

In unadjusted models, higher intake of fruits and vegetables, regardless of pesticide residue contamination, was associated with improved fecundability (Table 3). After adjustment for potential confounders, associations were substantially attenuated: the FRs comparing 0.5–0.9, 1.0–1.4, 1.5–1.9, and ≥ 2.0 with < 0.5 cup-equivalents/day of total fruits and vegetables were 1.03 (95% CI: 0.94, 1.14), 1.12 (95% CI: 1.01, 1.25), 1.09 (95% CI: 0.95, 1.24), and 1.05 (95% CI: 0.88, 1.25), respectively. The attenuation was primarily due to adjustment for income, education, BMI, sugar-sweetened soda intake, and HEI score.

We did not observe a meaningful difference in associations between intake of high- or low-pesticide residue fruits and vegetables and

Table 2
Baseline characteristics of 5234 female pregnancy planners by intake of fruits and vegetables with high- and low-pesticide residues.

	High-pesticide residue fruit & vegetable intake (cup equivalents/day)					Low-pesticide residue fruit & vegetable intake (cup equivalents/day)				
Characteristic[a,b]	< 0.5	0.5–0.9	1.0–1.4	1.5–1.9	≥2.0	< 0.5	0.5–0.9	1.0–1.4	1.5–1.9	≥2.0
Number of women	1133	1867	1275	565	394	1126	1920	1287	584	317
Age at baseline, years (mean)	29.4	30.1	30.4	30.4	30.2	29.2	30.1	30.5	30.6	30.3
White, non-Hispanic (%)	86.9	87.5	87.2	88.2	86.8	86.2	88.3	87.3	88.1	83.0
Household income < $50,000/year (%)	20.6	16.1	13.4	14.8	17.0	23.1	13.9	15.3	14.0	17.1
Less than college degree (%)	30.0	19.7	18.9	19.8	20.2	31.5	19.6	17.9	18.9	21.2
Geographic region of residence										
Northeast U.S.	22.0	23.7	23.6	25.5	24.7	20.2	23.2	26.5	24.3	23.2
Southern U.S.	25.8	22.4	21.2	19.1	20.4	27.3	22.7	18.7	19.5	20.8
Midwestern U.S.	24.3	22.2	18.7	16.7	15.0	26.1	20.9	18.8	17.0	17.0
Western U.S.	17.3	18.0	17.4	15.0	15.2	15.9	17.8	17.4	18.6	14.5
Canada	10.8	13.7	19.3	23.7	24.7	10.5	15.4	18.7	20.7	24.4
BMI, kg/m^2 (mean)	28.0	27.3	26.8	26.9	25.9	29.1	27.0	26.5	26.2	26.4
MET-hours/week physical activity (mean)	26.9	33.1	37.2	42.4	49.9	25.9	33.2	37.9	44.7	47.8
Current regular cigarette smoker (%)	6.8	4.5	3.1	3.2	2.6	7.3	4.6	2.8	2.6	3.0
Sleep duration < 7 hours/night (%)	25.9	20.7	22.2	18.8	22.2	26.3	22.1	19.2	19.6	23.0
Occupational pesticide exposure, %	1.7	1.2	2.1	1.2	1.3	1.6	1.7	1.3	1.4	1.6
Almost all fruit intake is organic, %	9.8	12.0	13.6	14.1	16.8	10.0	12.1	13.0	15.9	15.9
Almost all vegetable intake is organic, %	10.5	12.3	12.8	14.9	17.5	10.5	11.6	13.7	16.0	17.1
Total caloric intake, kcal/day (mean)	1280	1500	1700	1820	2010	1320	1480	1680	1830	2110
Alcohol, drinks/week (mean)	2.9	3.4	3.3	3.4	3.0	2.8	3.4	3.6	3.3	2.6
Sugar-sweetened soda, drinks/week (mean)	1.6	1.1	0.9	0.8	0.7	2.0	1.1	0.7	0.6	0.9
Daily multivitamin or folic acid use (%)	80.2	85.0	87.3	84.6	85.6	80.7	84.9	85.9	85.6	87.4
Healthy Eating Index score (mean)[c]	46.2	50.0	52.3	54.0	55.7	44.5	50.4	52.9	55.5	55.3
Parous (%)	33.8	30.6	31.1	26.6	28.5	34.4	31.6	28.4	29.0	27.9
Intercourse frequency < 1 time/week (%)	23.2	21.2	19.8	21.0	18.3	24.2	21.0	20.4	19.6	15.1
Doing something improve chances of conception (%)	76.8	77.7	75.8	74.4	75.9	77.3	76.5	76.3	76.7	76.9
Hormonal last method contraception (%)	43.2	38.8	36.9	33.7	35.1	44.2	38.4	37.0	34.1	32.5
≥3 cycles of attempt at study entry (%)	31.6	30.8	30.9	29.9	29.2	32.9	29.1	30.3	30.2	37.4

BMI = body mass index; MET = metabolic equivalent of task.

[a] Characteristics standardized by age of cohort at baseline.

[b] After imputation; data presented in this table are from first imputation data set only.

[c] Excluding components related to fruit and vegetable intake.

Table 3
Association between high- and low- pesticide residue fruit and vegetable intake and fecundability.

					Attempt time at study entry			
					< 3 cycles (n = 3626)		3–6 cycles (n = 1608)	
Intake (cup equivalents/day)	No. of Cycles	No. of Preg	Unadjusted[a] FR (95% CI)	Adjusted[b] FR (95% CI)	No. of Preg	Adjusted[b] FR (95% CI)	No. of Preg	Adjusted[b] FR (95% CI)
Total fruit and vegetables								
< 0.5	4114	558	Reference	Reference	417	Reference	141	Reference
0.5–0.9	8387	1281	1.12 (1.03, 1.23)	1.03 (0.94, 1.14)	969	1.08 (0.96, 1.20)	312	0.93 (0.76, 1.14)
1.0–1.4	5670	970	1.27 (1.15, 1.41)	1.12 (1.01, 1.25)	742	1.20 (1.06, 1.36)	228	0.90 (0.72, 1.12)
1.5–1.9	2291	381	1.25 (1.10, 1.42)	1.09 (0.95, 1.24)	299	1.18 (1.01, 1.37)	82	0.89 (0.67, 1.19)
≥2.0	1172	179	1.24 (1.06, 1.46)	1.05 (0.88, 1.25)	127	1.16 (0.95, 1.43)	52	0.78 (0.55, 1.09)
High-pesticide residue fruits and vegetables								
Almost all organic	3166	464	1.05 (0.88, 1.24)	0.91 (0.75, 1.09)	360	0.96 (0.77, 1.19)	104	0.76 (0.55, 1.04)
< 0.5	4223	609	Reference	Reference	453	Reference	156	Reference
0.5–0.9	6717	1026	1.06 (0.97, 1.16)	0.97 (0.86, 1.09)	777	1.00 (0.87, 1.14)	249	0.87 (0.66, 1.15)
1.0–1.4	4432	728	1.15 (1.03, 1.28)	0.98 (0.84, 1.15)	541	1.03 (0.87, 1.22)	187	0.85 (0.57, 1.26)
1.5–1.9	1830	327	1.25 (1.10, 1.42)	1.08 (0.91, 1.28)	252	1.13 (0.93, 1.37)	75	0.97 (0.65, 1.46)
≥2.0	1266	215	1.23 (1.04, 1.45)	1.09 (0.87, 1.38)	171	1.18 (0.90, 1.56)	44	0.77 (0.47, 1.28)
Low pesticides residue fruits and vegetables								
Almost all organic	3166	464	1.08 (0.91, 1.27)	0.87 (0.72, 1.05)	360	0.92 (0.74, 1.14)	104	0.75 (0.54, 1.05)
< 0.5	4311	589	Reference	Reference	434	Reference	155	Reference
0.5–0.9	6757	1067	1.12 (1.02, 1.24)	0.96 (0.85, 1.09)	812	0.98 (0.84, 1.14)	255	0.91 (0.71, 1.17)
1.0–1.4	4330	752	1.23 (1.11, 1.36)	0.97 (0.84, 1.13)	576	1.02 (0.86, 1.22)	176	0.81 (0.60, 1.10)
1.5–1.9	2014	323	1.17 (1.01, 1.34)	0.93 (0.77, 1.13)	248	0.97 (0.78, 1.20)	75	0.86 (0.56, 1.30)
≥2.0	1056	174	1.24 (1.04, 1.49)	1.00 (0.77, 1.28)	124	1.09 (0.83, 1.43)	50	0.78 (0.47, 1.28)

[a] Adjusted for total energy intake.

[b] Adjusted for total energy intake, age, race/ethnicity, education, income, BMI, smoking history, sugar-sweetened soda intake, physical activity, daily use of multivitamin/folic acid, HEI score, sleep duration, intercourse frequency, doing something to improve chances, last method of birth control, geographic region, season of enrollment. Models for high- and low-pesticide residue fruit and vegetables intake were additionally adjusted for total fruit and vegetable intake.

fecundability in the full sample (Table 3, Supplemental Figure 1). The adjusted FR comparing intake of ≥2.0 with < 0.5 cup-equivalents/day of high-pesticide residue fruits and vegetables was 1.09 (95% CI: 0.87, 1.38); the corresponding FR for low-pesticide residue fruits and vegetables was 1.00 (95% CI: 0.77, 1.28). Consumption of organic produce “most of the time” or “more than half of the time” was not appreciably associated with fecundability: the FR in the high-pesticide residue fruit and vegetable model was 0.91 (95% CI: 0.75, 1.09) and in the low-pesticide residue fruit and vegetable model was 0.87 (95% CI: 0.72, 1.05). When we included women who consumed organic produce “most of the time” or “more than half of the time” in their respective fruit and vegetable intake categories, rather than their own separate category, adjusted FRs comparing ≥2.0 with < 0.5 cup-equivalents/day of high- and low-pesticide residue fruits and vegetables were 0.97 (95% CI: 0.77, 1.20) and 0.94 (95% CI: 0.75, 1.18), respectively.

Associations varied by attempt time at study entry. Among women who had been attempting pregnancy for < 3 cycles at study entry, total fruit and vegetable intake was associated with improved fecundability: adjusted FRs comparing 0.5–0.9, 1.0–1.4, 1.5–1.9, and ≥2.0 with < 0.5 cup-equivalents/day were 1.08 (95% CI: 0.96, 1.20), 1.20 (95% CI: 1.06, 1.36), 1.18 (95% CI: 1.01, 1.37), and 1.16 (95% CI: 0.95, 1.43), respectively (Table 3). There was a slight positive association between high-, but not low-pesticide residue fruit and vegetable intake (Table 3). However, among women who had been attempting pregnancy for 3–6 cycles at study entry, total, high- and low-pesticide residue fruit and vegetable intakes were associated with reduced fecundability, although results were imprecise. The FR comparing intake of ≥2.0 with < 0.5 cup-equivalents/day of total fruits and vegetables was 0.78 (95% CI: 0.77, 1.09); the corresponding FRs for high- and low-pesticide residue fruits and vegetables were 0.77 (95% CI: 0.47, 1.28) and 0.78 (95% CI: 0.47, 1.28), respectively. Among women attempting pregnancy for 3–6 cycles at study entry, consumption of organic produce “most of the time” or “more than half of the time” was also associated with reduced fecundability (FR = 0.76 [95% CI: 0.55, 1.04] in the high-pesticide fruit and vegetable models and 0.75 [95% CI: 0.54, 1.05] in the low-pesticide fruit and vegetable models).

When defining pesticide residue intake using other metrics, results were similar to those using the PRBS (Supplemental Table 1). Our findings did not differ materially when restricting to women from the United States (Supplemental Table 2), women who reported eating organic fruits and vegetables “almost none of the time” (Supplemental Table 3), or women without occupational pesticide exposure (Supplemental Table 4). Results were similar among women who participated from 2013–2015 and 2016–2019, with the exception of high-pesticide residue fruit and vegetable intake, which was slightly more positively associated with improved fecundability in 2016–2019 (data not shown).

4. Discussion

In this North American preconception cohort study, we found little evidence that intake of pesticide residues from conventionally-grown fruits and vegetables was associated with reduced fecundability. In fact, we observed strong evidence of reverse causation in this cohort among those with longer pregnancy attempt times. Specifically, among women attempting pregnancy for < 3 menstrual cycles at study entry, neither high- nor low-pesticide residue fruit and vegetable intake was associated with fecundability. However, among women attempting pregnancy for 3–6 cycles at study entry, greater fruit and vegetable intake, regardless of pesticide contamination, and frequent organic food intake were inversely associated with fecundability. This pattern is consistent with the hypothesis that women who had been trying longer to conceive at study entry may have already changed their behaviors (*i.e.*, increased their fruit and vegetable consumption or started eating more organic foods) because of subfertility, inducing a spurious inverse association between produce intake and fecundability. The results confined to women with shorter attempt times at study entry are less likely to be influenced by diet change in response to failure to conceive, because women are less likely to have changed their diet after only a few months of trying.

We observed a positive association between total fruit and vegetable intake and improved fecundability. Although there has been limited study of fruit and vegetable intake in relation to fertility, support for an association between the two comes from studies of micronutrients and dietary patterns (Gaskins and Chavarro, 2018). Intake of folate has been associated with improved fertility in both preconception cohorts of couples attempting to conceive spontaneously (Cueto et al., 2016) and infertility cohorts (Gaskins et al., 2014; Gaskins et al., 2015; Haggarty et al., 2006). Evidence for other micronutrients is less consistent. A Cochrane review of randomized controlled trials (Showell et al., 2017) found only low-quality evidence to support the hypothesis that antioxidant supplementation improves fertility treatment outcomes. However, there was high variability in interventions across trials, making drawing a conclusion on overall antioxidant intake difficult. Studies of dietary patterns and fertility consistently show that healthier diets (including higher intake of fruits and vegetables) are related to improved fertility (Gaskins and Chavarro, 2018).

Our results are not consistent with previous studies that have demonstrated an adverse effect of high-pesticide residue fruit and vegetable intake on markers of fertility. In the EARTH Study, a prospective cohort study of 325 couples seeking fertility treatment at a Massachusetts hospital, women in the highest quartile of intake of high-pesticide residue fruits and vegetables, defined using the PRBS, had 18% lower odds of clinical pregnancy and 26% lower odds of live birth compared with women in the lowest quartile (Chiu et al., 2018). Low-pesticide residue fruit and vegetable intake, on the other hand, was associated with higher odds of clinical pregnancy and live birth. In our study, we observed little difference in the association between fruit and vegetable intake and fecundability by pesticide residue contamination. The EARTH study is a cohort of women seeking treatment for infertility at a Massachusetts hospital, whereas our study enrolls women early on in their pregnancy attempt (70% trying for < 3 cycles at enrollment). It is possible that factors related to underlying fertility (infertility diagnosis, severity of infertility, parity) influenced fruit and vegetable intake at enrollment in the EARTH study, creating a spurious inverse association. This does not, however, explain why results differed for high- and low-pesticide residue fruits and vegetables. Increased intake of individual fruits and vegetables is likely influenced by their availability, taste, and perceived health benefits. If any of these factors differed across categories of pesticide contamination (and specifically, if women are more likely to increase intake of high-pesticide residue fruits and vegetables in response to health concerns), then reverse causation could bias one group more than the other.

The groups of fruits and vegetables defined as high- and low-pesticide residue groups via the PRBS also have different nutritional content. For example, the average amount of several macro- and micronutrients per 100 g of food varied across high- and low-pesticide groups: 1.16 vs. 2.30 g protein, 1.17 vs. 0.58 μg retinol, 21.5 vs. 31.6 mg calcium, and 1.76 vs. 2.21 g dietary fiber. Therefore, differences in nutrient intake could have confounded the observed associations.

There is evidence in the literature that genetic polymorphisms may influence susceptibility to the health effects of pesticide exposure. Interindividual variation in cytochrome P450 and paraoxonase gene families leads to altered metabolism of pesticides in the body (Costa et al., 2003; Kaur et al., 2017). Therefore, some sub-populations may be particularly susceptible to pesticide toxicity. We were unable to account for genetic variation in our cohort; differences in genetic polymorphisms (and therefore pesticide susceptibility) in our study compared with others could partially account for our discrepant findings.

We attempted to improve on the PRBS by accounting for organic food intake, which is associated with low pesticide residue intake, as has been demonstrated by intervention studies that found a reduction in pesticide biomarkers after adherence to an organic diet (Bradman et al., 2015; Curl et al., 2019; Hyland et al., 2019). The exposure metrics we defined are presumably better measures of pesticide residue intake among women who do not eat a lot of organic food. Thus, we created a separate category for frequent consumers of organic produce. Because we added the question on organic food intake to our questionnaire four years after the study began, we had a high proportion of missing data (76%). However, simulation studies have shown that the proportion of missing data is not a strong predictor of the performance of the imputation model and should not be used to guide decisions on the handling missing data (Madley-Dowd et al., 2019). In addition, women may not report organic diet practices accurately. Given the phrasing of our question ("What proportion of the food that you eat is organic?"), they were not able to report if they ate organic for only certain fruits and vegetables (*i.e.*, "the dirty dozen," produce identified by an advocacy organization as highly contaminated with pesticides). Despite these limitations, our use of information on organic diet likely improved the specificity of our exposure metrics.

We attempted to overcome some of the limitations of the PRBS by examining additional measures of pesticide contamination (*e.g.*, continuous score). However, our results were similar across exposure metrics.

A major limitation of our analysis is that we did not measure pesticide residue intake or exposure directly, but instead used fruit and vegetable intake as a proxy. We also did not conduct a validation study in our population but instead relied on validations from other populations. Previous work in NHANES and the EARTH study compared PRBS scores with urinary biomarkers of pesticide exposure and concluded that the PRBS is a valid tool to rank participants by pesticide residue exposure (Chiu et al., 2018; Hu et al., 2016). High-, but not low-pesticide residue fruits and vegetables were associated with increased pesticide biomarker concentrations, which is consistent with the idea that only certain fruits and vegetables are likely contaminated. However, correlations between class-specific PRBS scores and biomarker measures were generally low ($r < 0.25$). Thus, while useful and cost-effective, the PRBS is likely a metric with low specificity. Another factor that contributes to the lack of specificity is that all pesticides (over 700 measured through the Pesticide Data Program) are grouped together for calculation of these metrics. Pesticides comprise a chemically-diverse group of compounds that likely differ in the mechanism of action and extent to which they could affect human reproduction. Use of a non-specific exposure can substantially attenuate exposure-response relations (Friesen et al., 2007).

The Pesticide Data Program samples fruits and vegetables from select states with the goal of estimating the national distribution of pesticide residue contamination in fruits and vegetables. Because individuals consume fruits and vegetables that are primarily imported from other states we do not expect that sampling fruits and vegetables from only certain states indicates that our exposure metric is only valid in those states. If there were a more direct correlation between state of origin and state of sale/intake, this might be a more important issue, but this is not the case. It does raise concerns, however, about the validity of results among our Canadian participants, as agricultural practices and pesticide regulations differ in Canada (Boyd, 2006). However, when we conducted a sensitivity analysis restricted to U.S. participants, results were similar to the overall results.

Intakes of fruits and vegetables, as well as organic foods, are highly correlated with socioeconomic status, healthcare access, neighborhood, and more healthful behaviors (*e.g.*, less sugar-sweetened soda intake, less smoking), and as expected, we observed strong confounding in this analysis. However, the direction of the confounding was similar for both high- and low-pesticide residue fruit and vegetable intake, indicating that any unmeasured confounding by these and related factors is unlikely to explain differences by high- vs. low-pesticide residue fruit and vegetable intake.

5. Conclusions

We found that fruit and vegetable intake, regardless of pesticide contamination, was associated with strong reductions in fecundability among women who had been trying to conceive for 3–6 cycles at study entry, but not among women trying for shorter time periods. Because fruit and vegetable intake is modifiable and perceived to be healthful by the general population, studies examining the association between fruit and vegetable intake and health are highly susceptible to reverse causation. Even prospective studies, where the outcome is measured after ascertainment of exposure, are susceptible to this bias if participants have any knowledge or concerns about their chances of an adverse health outcome.

CRediT authorship contribution statement

Amelia K. Wesselink: Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Writing - original draft. **Elizabeth E. Hatch:** Conceptualization, Funding acquisition, Investigation, Project administration, Supervision, Methodology, Writing - review & editing. **Kenneth J. Rothman:** Funding acquisition, Investigation, Project administration, Supervision, Methodology, Writing - review & editing. **Sydney K. Willis:** Data curation, Investigation, Methodology, Writing - review & editing. **Olivia R. Orta:** Data curation, Investigation, Methodology, Writing - review & editing. **Lauren A. Wise:** Conceptualization, Data curation, Funding acquisition, Investigation, Project administration, Supervision, Methodology, Writing - review & editing.

Declaration of Competing Interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: PRESTO has received in-kind donations from FertilityFriend.com, Kindara.com, Sandstone Diagnostics, and Swiss Precision Technologies for primary data collection. Dr. Lauren Wise serves as a consultant to AbbVie, Inc. for her work on uterine fibroids.

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Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.envint.2020.105693.

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