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Original Contribution

Electronic Cigarettes and Fecundability: Results From a Prospective Preconception Cohort Study

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Although electronic cigarette (e-cigarette) aerosol contains similar toxicants to combustible cigarettes, few studies have examined their influence on fecundability. We assessed the association between e-cigarette use and fecundability, overall and according to combustible cigarette smoking history, in a cohort of 4,586 North American women (aged 21–45 years) enrolled during 2017–2020 in Pregnancy Study Online, a Web-based prospective preconception study. Women reported current and former e-cigarette use on baseline and follow-up questionnaires, and they completed bimonthly follow-up questionnaires until self-reported pregnancy or censoring. Fecundability ratios and 95% confidence intervals were calculated using proportional probabilities models, controlling for potential confounders. Overall, 17% of women had ever used e-cigarettes and 4% were current users. Compared with never use of e-cigarettes, current e-cigarette use was associated with slightly lower fecundability (fecundability ratio = 0.84, 95% confidence interval (CI): 0.67, 1.06). Compared with current nonusers of e-cigarettes and combustible cigarettes, fecundability ratios were 0.83 (95% CI: 0.54, 1.29) for current dual users of e-cigarettes and combustible cigarettes, 0.91 (95% CI: 0.70, 1.18) for current e-cigarette users who were nonsmokers of combustible cigarettes, and 1.01 (95% CI: 0.85, 1.20) for nonusers of e-cigarettes who were current smokers of combustible cigarettes. Current e-cigarette use was associated with slightly reduced fecundability, but estimates of its independent and joint associations with combustible cigarette smoking were inconsistent and imprecise.

combustible cigarettes; electronic cigarettes; fecundability; preconception cohort; time to pregnancy

Abbreviations: CI, confidence interval; e-cigarette, electronic cigarette; FR, fecundability ratio; LMP, last menstrual period; PRESTO, Pregnancy Study Online.

Editor's note: *An invited commentary on this article appears on page 362.*

Electronic cigarettes (e-cigarettes) have gained substantial popularity in the United States. Approximately 3.4% of reproductive aged women in the United States currently use e-cigarettes exclusively, and 11.3% use e-cigarettes in combination with combustible cigarettes (1). A recent analysis of the nationally representative Population Assessment of Tobacco and Health study found that 5% of pregnant women in the United States are current e-cigarette users, and 18% are former e-cigarette users (2). According to data from the 2015 state-level Pregnancy Risk Assessment Monitoring System survey, approximately 10% of pregnant women in Oklahoma and Texas, the 2 states in which data were available, used e-cigarettes in the 3 months before pregnancy (3). Women planning to conceive might use e-cigarettes to help quit or reduce smoking, to sustain cigarette cessation, or for recreational use (4). The extent to which preconceptional use of e-cigarettes affects a woman's ability to conceive is unknown.

E-cigarette aerosol contains toxicants found in combustible cigarettes, including nicotine, ultrafine particles, heavy metals, polycyclic aromatic hydrocarbons, and volatile organic compounds (5). Combustible cigarette smoking is a risk factor for adverse pregnancy outcomes (6–8) and is associated with reduced fecundability in several studies (9–14). Fertility-related mechanisms include oocyte damage and alteration of endogenous hormone concentrations from

exposure to nicotine, polycyclic aromatic hydrocarbons, and cadmium (8). We hypothesize a similar effect for women who vape during the period before conception, given that implicated constituents are also found in most e-cigarette products (15–19). E-cigarette liquids can contain high levels of nicotine; in some cases nicotine delivery by e-cigarettes is comparable with combustible cigarette smoking (15). Cadmium has been detected in the aerosol of several e-cigarette brands, in addition to other metals including lead, nickel, and chromium (16, 17). Studies of polycyclic aromatic hydrocarbons exposure from e-cigarettes are limited (16, 18, 19), although one biomarker study found higher concentrations of polycyclic aromatic hydrocarbons among e-cigarette users compared with never users (18). In addition, e-cigarette liquid often contains flavoring compounds, humectants, and propellants not found in combustible cigarettes. When heated these constituents convert to toxic and carcinogenic by-products, but any independent effect on reproductive health is unknown (5, 20, 21). Importantly, e-cigarette aerosols contain lower levels of toxicants than combustible cigarettes, particularly chemicals such as formaldehyde and metals, and the amount of toxicants in e-cigarette liquid is variable across products (5, 16). In addition, only combustible cigarettes contain carbon monoxide and nitrosamines. To our knowledge, no study has examined the association of e-cigarette exposure with fecundability, either independently or jointly with combustible cigarettes.

Dual use of e-cigarettes and combustible cigarettes might influence health differently from use of e-cigarettes alone. If smokers who use e-cigarettes reduce their combustible cigarette exposure, then dual use of e-cigarettes might be less harmful to fecundity by reducing overall toxicant exposure. However, if dual users do not reduce cigarette exposure, or if there is a synergistic effect of e-cigarettes and combustible cigarettes, dual use could cause more harm to fecundity than use of either product alone.

In a North American prospective cohort study of female pregnancy planners, we evaluated the association between preconceptional e-cigarette use and fecundability, the average per-cycle probability of conception. We additionally assessed the extent to which the association between e-cigarette use and fecundability varies according to cigarette smoking behaviors.

METHODS

Study design and sample

Pregnancy Study Online (PRESTO) is an ongoing Web-based preconception prospective cohort study of pregnancy planners, described previously (22). Eligible participants include women aged 21–45 years who are residents of the United States or Canada, not using fertility treatments or contraception at study entry, in a stable relationship with a male partner, and are actively trying to get pregnant. At baseline, women report demographic information, medical history, and lifestyle factors, and they are invited to complete the National Cancer Institute's Dietary Health Questionnaire II, a Web-based food frequency questionnaire (23). Women then complete bimonthly follow-up surveys for up to 12 months, reporting on pregnancy status and factors that might change over follow-up. PRESTO was approved by the Boston University Medical Campus Institutional Review Board. All participants provided informed consent.

Questions on e-cigarettes were added to the baseline questionnaire on June 22, 2017. From that date through January 2, 2020, 5,971 eligible women completed the baseline questionnaire. We excluded women who had last menstrual period (LMP) dates >6 months before baseline and those with missing or implausible LMP dates ($n = 91$), those with no prospective LMP dates during follow-up ($n = 14$), and those trying to conceive for >6 menstrual cycles at baseline (to limit the possibility of reverse causation from women changing their behaviors in response to difficulty conceiving; $n = 1{,}280$). The final study population included 4,586 women.

Exposure assessment: e-cigarette use

E-cigarette use was measured on the baseline and follow-up questionnaires. At baseline, participants were asked, "Have you ever used e-cigarettes, e-hookahs, vaping pens, personal vaporizers, or any other battery-powered device that simulates smoking?" Those who reported "yes" were asked how many milliliters of liquid they currently vape per day, and whether the device they used contains nicotine. At each follow-up assessment, participants reported any e-cigarette use in the previous 4 weeks.

Covariate assessment

At baseline, we ascertained information on potential risk factors for fecundability, including age (24), education (25, 26), annual household income (26), race/ethnicity (25, 26), body mass index (27), caffeine intake (28), alcohol- and marijuana-use frequency (29, 30), secondhand and in-utero cigarette smoke exposure (9), sleep duration (31), daily use of multivitamins and/or folic acid (32), hours of work per week (31), Perceived Stress Scale score (33), physician-diagnosed depression/anxiety (34), depression symptoms via the Major Depression Inventory (34), intercourse frequency, and parity. Women additionally reported whether they were doing anything to improve chances of pregnancy (e.g., ovulation testing, basal body temperature) and last contraception method used. A measure of overall diet quality (35), the Healthy Eating Index, was calculated based on the food frequency questionnaire data.

Combustible cigarette smoking status and history were ascertained from baseline and follow-up questionnaires. Participants were classified as current regular smokers (smoked ≥1 cigarette/day), current occasional smokers (smoked <1 cigarette/day), past smokers (smoked cigarettes regularly for ≥6 months in lifetime), or never smokers. We calculated cumulative pack-years of cigarette smoking by multiplying smoking duration by intensity (packs smoked per day). Never smokers ($n = 3{,}432$) and occasional smokers who were never regular smokers ($n = 48$) were assigned a pack-year value of zero.

Time to pregnancy

On each follow-up questionnaire, participants reported their most recent LMP date and whether they conceived or had any pregnancy losses since the previous questionnaire. Among nonrespondents, we obtained pregnancy information via phone interviews, online baby announcements/baby registries, fertility tracking software data, and birth registry linkage in selected states (California, Florida, Massachusetts, Michigan, Ohio, Pennsylvania, and Texas).

Time to pregnancy was calculated using baseline and follow-up questionnaire data. At baseline, participants reported the number of menstrual cycles they had been attempting to conceive, their LMP date, and the length of their usual menstrual cycle. Women were considered to have irregular cycles if they reported not being able to "predict from one menstrual period to the next about when the next menstrual period would start." For women with irregular cycles, we estimated cycle length using LMP data ascertained during follow-up. Time to pregnancy was calculated in discrete cycles as follows: menstrual cycles of attempt time at baseline + ((LMP date from the most recent follow-up assessment − baseline questionnaire date)/usual menstrual cycle length) + 1.

Statistical analysis

Participants contributed menstrual cycles of attempt time until pregnancy or censoring, whichever came first. Censoring events included loss to follow-up, no longer attempting to conceive, initiation of fertility treatment, or 12 cycles of attempt time. We compared age-standardized baseline characteristics across baseline e-cigarette use. We computed the proportion of women who conceived over follow-up using life-table methods to account for censoring. We analyzed observed cycles only and utilized an Anderson-Gill data structure to generate time-varying exposure and covariates and account for left truncation due to variation in pregnancy attempt times at study entry (ranging from 0–6 cycles) (36). We estimated fecundability ratios and 95% confidence intervals for the association between e-cigarette use and time to pregnancy by fitting proportional probabilities regression models (14). Fecundability ratios represent the ratio of average per-cycle probability of conception in each e-cigarette category compared with never e-cigarette use.

We operationalized e-cigarette exposure as ever versus never use and as current, former, and never use. Current use was defined as having ever used an e-cigarette and currently vaping >0 mL of e-liquid/day, or currently using a device containing nicotine (e-cigarettes with no nicotine might still contain other potentially harmful chemicals and metals). In a sensitivity analysis, we excluded women who currently used a device not containing nicotine. Former users had ever used an e-cigarette but did not meet the current-use definition. We classified baseline current e-cigarette users by intensity of use, distinguishing between vaping <3 mL/day and ≥3 mL/day (the average daily dose in some prior studies) (37, 38). We analyzed baseline-only and time-varying e-cigarette exposure.

To adjust for confounding, we included covariates in our model that were potential confounders (risk factors for impaired fecundability that are associated with e-cigarette use, excluding causal intermediates). Certain variables were associated with e-cigarette use in our data but were not associated with time to pregnancy in prior PRESTO studies (e.g., in-utero cigarette exposure (9), caffeine intake (39), marijuana use (30), anxiety diagnosis (34)). To preserve precision and avoid model convergence problems, we did not adjust for these covariates. Final models adjusted for age, annual household income (in $: <50,000, 50,000–99,000, 100,000–149,000, ≥150,000), education (up to some high school, high-school diploma or equivalency, some college, college degree, graduate degree), baseline smoking status (current regular smoker, current occasional smoker, former smoker, never smoker), pack-years of cigarette smoking (intensity × duration), weekly alcohol intake (drinks/week: <1, 1–6, 7–13, ≥14), intercourse frequency (times/week: <1, 1, 2–3, ≥4), using methods to improve pregnancy chances (yes/no), body mass index, Major Depression Inventory score (continuous), multivitamin/prenatal supplement use (yes/no), Healthy Eating Index score (continuous), and parity. If parity is a marker of underlying fertility, adjusting for parity might induce bias (40, 41). We therefore examined models with and without parity adjustment.

In secondary analyses, we created mutually exclusive joint-exposure categories based on time-varying current use of both e-cigarettes and combustible cigarettes, classifying participants as exclusive e-cigarette users, exclusive cigarette smokers, dual users of e-cigarettes and cigarettes, and current nonusers of either product (referent). We then further expanded categories to differentiate former and never use, with women who never used e-cigarettes or cigarettes as the referent. We replicated our primary analysis among never cigarette smokers, because this analysis is less likely to be affected by residual confounding by cigarette smoking. In these analyses, we adjusted for the same covariates mentioned above, except for baseline cigarette smoking status.

In additional models, we stratified by age (<30 vs. ≥30 years at baseline) and pregnancy attempt time at study entry (<3 vs. ≥3 cycles) to assess potential for reverse causation (i.e., subfertile women might quit cigarette smoking and start using e-cigarettes). In an additional sensitivity analysis, we reclassified conceptions resulting in pregnancy loss as no conception to examine the association between e-cigarette use and time to viable pregnancy.

We used multiple imputation with 5 imputed data sets to impute missing data on exposure, outcome, and covariates. Women who completed no follow-up questionnaires ($n = 1{,}159$) were assigned 1 cycle of observation, with pregnancy status imputed at that cycle. No variable was missing information for more than 1% of participants, except for income (3.3%), hours worked per week (3.5%), and Healthy Eating Index score (43.2%). Analyses were performed using SAS, version 9.4 (SAS Institute, Inc., Cary, North Carolina).

RESULTS

Our study population of 4,586 women contributed 14,489 menstrual cycles of attempt time and 2,604 pregnancies

Table 1. Baseline Characteristics of 4,586 Female Pregnancy Planners According to Baseline Electronic Cigarette Use, Pregnancy Study Online, United States and Canada, 2017–2020[a]

Baseline Characteristic	Never User ($n = 3,805$)		Former User ($n = 609$)		Current User[b] ($n = 172$)	
	Mean	%	Mean	%	Mean	%
% of total sample		83.0		13.3		3.8
Age at baseline, years	29.8		29.2		29.1	
≤12 years of education		6.3		10.4		15.4
Household income below $50,000/year		19.3		32.7		42.5
Not currently employed		14.3		20.0		25.3
Race/ethnicity						
Non-Hispanic White		85.1		82.0		84.4
Non-Hispanic Black		3.3		3.6		1.3
Non-Hispanic other race		5.6		7.0		5.5
Hispanic		6.0		7.5		8.8
Body mass index[c]	28.6		30.3		31.0	
Caffeine intake, mg/day	120.8		161.8		176.3	
Alcohol intake, no. of drinks/week	2.8		4.4		2.8	
Marijuana use ≥1 times/week		5.2		2.1		16.8
Sleep duration <7 hours/night		25.4		20.0		25.3
Daily use of multivitamins or folic acid		80.8		71.9		77.2
Healthy Eating Index score	63.7		58.9		56.8	
Perceived Stress Score	16.4		18.0		18.8	
Ever diagnosed with depression		25.0		40.8		41.8
Ever diagnosed with anxiety		25.1		39.8		42.2
Major Depression Inventory score	11.1		15.0		15.8	
Parous		37.0		38.2		45.6
Gravid		52.9		61.9		71.5
Using methods to improve pregnancy chances		78.3		78.2		82.3
Last form of contraception: hormonal		36.9		40.6		40.6
Intercourse frequency of <1 time/week		20.1		24.0		15.4
Combustible cigarette smoking history						
Never cigarette smoker		83.1		37.3		23.0
Former cigarette smoke		10.3		27.6		45.3
Occasional cigarette smoker		2.2		9.9		12.9
Current cigarette smoker		4.3		25.2		19.5
Partner currently smokes cigarettes		2.8		2.4		2.3
In utero exposure to cigarette smoke		10.0		17.5		19.2
Total pack-years	0.54		2.6		3.6	

[a] All characteristics except for age are standardized to baseline age of cohort.
[b] Current electronic cigarette users are participants who have ever used an electronic cigarette and who reported using >0 mL of liquid/day at baseline or report currently using a device that contains >0 mg of nicotine.
[c] Weight (kg)/height(m)^2.

(73.4% conceived during 12 cycles of follow-up after accounting for censoring). At baseline, 17% of women ever used an e-cigarette, and 4% were current users. Comparing baseline and last follow-up questionnaire, 10% of current e-cigarette users became former users over follow-up, 4% of former users became current users, and 0.5% of never users became current or former users.

Table 1 presents baseline characteristics stratified by baseline e-cigarette use. E-cigarette use was associated with lower education, income, Healthy Eating Index, use of

Table 2. Fecundability Ratios According to Baseline and Time-Varying Electronic Cigarette Use, Pregnancy Study Online, United States and Canada, 2017–2020

Exposure	No. of Pregnancies	No. of Cycles	Unadjusted		Adjusted[a]	
			FR	95% CI	FR	95% CI
Baseline e-cigarette use						
Never e-cigarette user	2,238	11,997	1.00	Referent	1.00	Referent
Ever e-cigarette user	366	2,492	0.82	0.74, 0.91	0.88	0.78, 0.99
Former e-cigarette user	289	1,945	0.83	0.74, 0.93	0.89	0.78, 1.00
Current e-cigarette user	77	547	0.79	0.63, 0.99	0.85	0.68, 1.07
E-liquid, mL/day[b]						
<3	41	292	0.76	0.54, 1.07	0.82	0.58, 1.15
≥3	36	255	0.82	0.61, 1.11	0.89	0.65, 1.21
Time-varying e-cigarette use						
Never e-cigarette user	2,232	11,944	1.00	Referent	1.00	Referent
Ever e-cigarette user	372	2,545	0.82	0.74, 0.91	0.88	0.78, 0.99
Former e-cigarette user	286	1,921	0.84	0.75, 0.94	0.89	0.79, 1.01
Current e-cigarette user	86	624	0.78	0.63, 0.97	0.84	0.67, 1.06
Time-varying e-cigarette use among never cigarette smokers[c]						
Never e-cigarette user	1,898	10,031	1.00	Referent	1.00	Referent
Ever e-cigarette user	141	880	0.85	0.72, 1.00	0.90	0.76, 1.07
Former e-cigarette user	119	731	0.86	0.72, 1.02	0.91	0.76, 1.08
Current e-cigarette user	22	149	0.79	0.51, 1.21	0.87	0.57, 1.32

Abbreviations: CI, confidence interval; e-cigarette, electronic cigarette; FR, fecundability ratio.

[a] Adjusted for age, annual household income, education, baseline smoking status, pack-years of cigarette smoking, weekly alcohol intake, intercourse frequency, doing anything to improve conception chances, body mass index, Major Depression Inventory score, multivitamin or supplement use, Healthy Eating Index, and parity.

[b] Question on mL of liquid/day asked only on baseline questionnaire.

[c] Includes 3,432 women who had never smoked cigarettes by the end of follow-up. Model adjusted for all variables listed under footnote a, except for baseline smoking status and pack-years of cigarette smoking.

multivitamins, higher body mass index, and greater caffeine intake, marijuana use, physician-diagnosed depression and anxiety, Major Depression Inventory score, parity, and intercourse frequency. E-cigarette use was strongly associated with combustible cigarette smoking history. Approximately 83% of never e-cigarette users were never cigarette smokers, compared with 37% of former and 23% of current e-cigarette users. Current e-cigarette use was positively associated with pack-years of combustible cigarette smoking (Table 1).

Women retained in the study (n = 3,427) and those lost to follow-up (n = 1,115) were similar according to mean age (29.8 vs. 29.5 years), alcohol intake (3.1 vs. 2.8 drinks/week), having partners who smoke combustible cigarettes (4.2% vs. 5.4%), intercourse frequency (20.6% vs. 21.2%, <1 time/week), and depression (27.9% vs. 27.8%) or anxiety (28.3% vs. 26.4%) diagnoses. They differed by e-cigarette use (84.7% vs. 77.7%, never users), current combustible cigarette smoking (5.4% vs. 14.3%), mean body mass index (calculated as weight (kg)/height (m)^2; 28.2 vs. 31.0), use of multivitamins/prenatal supplements (83.6% vs. 67.4%), marijuana use (7.2% vs. 9.1%, use ≥1 time/week), education (4.6% vs. 14.8%, ≤12 years), and annual income (18.0% vs. 33.7%, less than $50,000).

E-cigarette use was associated with small reductions in fecundability (Table 2). Baseline current and former e-cigarette use were associated small reductions in fecundability after confounder adjustment (current-use fecundability ratio (FR) = 0.85, 95% confidence interval (CI): 0.68, 1.07; former-use FR = 0.89, 95% CI: 0.78, 1.00). The association did not get stronger with greater intensity of e-cigarette use (<3 mL per day, FR = 0.82, 95% CI: 0.58, 1.15; ≥3 mL per day, FR = 0.89, 95% CI: 0.65, 1.21). Time-varying estimates for current and former users were similar to baseline estimates (current-use FR = 0.84, 95% CI: 0.67, 1.06; former-use FR = 0.89, 95% CI: 0.79, 1.01). Confidence intervals for current-use and intensity estimates were wide and consistent with a broad range of associations, including none. Among never cigarette smokers, among whom residual confounding by cigarette smoking is unlikely, associations between e-cigarette use and fecundability were slightly attenuated and more imprecise (current-use FR = 0.87, 95% CI: 0.57, 1.32) (Table 2).

Table 3. Fecundability Ratios According to Time-Varying Current Electronic Cigarette Use and Combustible Cigarette Smoking, Pregnancy Study Online, United States and Canada, 2017–2020

Exposure Category of Use	No. of Pregnancies	No. of Cycles	Unadjusted		Adjusted[a]	
			FR	95% CI	FR	95% CI
Exclusive current e-cigarette user	61	424	0.83	0.64, 1.07	0.91	0.70, 1.18
Exclusive current cigarette smoker	193	1,265	0.90	0.78, 1.04	1.01	0.85, 1.20
Dual current user of e-cigarettes and cigarettes	25	200	0.72	0.47, 1.09	0.83	0.54, 1.29
Noncurrent user of e-cigarettes and cigarettes[b]	2,325	12,600	1.00	Referent	1.00	Referent

Abbreviations: CI, confidence interval; e-cigarette, electronic cigarette; FR, fecundability ratio.

[a] Adjusted for age, annual household income, education, pack-years of cigarette smoking, weekly alcohol intake, intercourse frequency, doing anything to improve conception chances, body mass index, Major Depression Inventory score, multivitamin or supplement use, healthy eating index, and parity.

[b] Noncurrent use includes never and former users.

Compared with noncurrent users of both e-cigarettes and combustible cigarettes (Table 3), there was essentially no association among exclusive cigarette smokers (FR = 1.01, 95% CI: 0.85, 1.20); exclusive current e-cigarette use was associated with slightly lower fecundability (FR = 0.91, 95% CI: 0.70, 1.18) and dual current use of e-cigarettes and cigarettes was associated with reduced fecundability (FR = 0.83, 95% CI: 0.54, 1.29), all with wide confidence intervals. Compared with never users of e-cigarettes and cigarettes (Web Table 1, available at https://academic.oup.com/aje), estimates remained imprecise due to small numbers within strata. Fecundability ratios suggested a nearly null association for current cigarette smokers who were never e-cigarette users (FR = 1.01, 95% CI: 0.83, 1.24) and small but imprecise inverse associations for current e-cigarette users who were never smokers (FR = 0.87, 95% CI: 0.57, 1.32) and dual current users of e-cigarettes and cigarettes (FR = 0.82, 95% CI: 0.52, 1.27).

Adjusted fecundability ratios for current e-cigarette use were slightly stronger among women with shorter pregnancy attempt times at study entry (<3 cycles, FR = 0.75, 95% CI: 0.56, 1.02; ≥3 cycles, FR = 1.04, 95% CI: 0.69, 1.57) and women <30 years old at baseline (<30 years, FR = 0.78, 95% CI: 0.55, 1.10; ≥30 years, FR = 0.89, 95% CI: 0.64, 1.25) (Web Tables 2 and 3). Excluding e-cigarette users with devices containing 0 mg nicotine ($n = 28$ women; Web Table 4), the adjusted fecundability ratio for time-varying current e-cigarette use was consistent with our primary analysis (FR = 0.83, 95% CI: 0.66, 1.04). Reclassifying pregnancies to include only viable pregnancies led to slightly attenuated results (Web Table 5; current-use FR: 0.87, 95% CI: 0.68, 1.10). Models that did not adjust for parity were similar to models adjusting for parity (data not shown).

DISCUSSION

In this prospective cohort study of North American women planning pregnancies, after adjusting for cigarette smoking and other covariates, we found that women who ever used e-cigarettes had small reductions in fecundability compared with women who never used e-cigarettes. The association was slightly stronger for current compared with former e-cigarette use but did not increase with greater intensity of e-cigarette use. Estimates of the independent and joint associations of e-cigarette use with combustible cigarette smoking were imprecise and inconsistent.

To our knowledge, there is no other study on female e-cigarette use and fecundability for comparison of results, nor have there been many investigations of other alternative/e-merging tobacco products on fecundability. Animal studies indicate that maternal e-cigarette exposure during pregnancy is associated with respiratory and neurological disorders of offspring (42–44). Use of combustible cigarettes might cause lower fecundability through disruption of intrauterine hormones (45), alteration of folliculogenesis (8), and reductions in oocyte quantity and quality (8, 46, 47). Similar mechanisms due to exposure to nicotine, metals, flavorings, or other chemicals found in e-cigarette aerosol are plausible. However, because e-cigarette toxicants and behavior are highly correlated with combustible cigarettes, it is difficult to parse out independent associations of e-cigarette use on fecundability.

When examining independent and joint associations of e-cigarette and combustible cigarette exposure, we found that, compared with current nonusers of either product, dual users of e-cigarettes and cigarettes had the greatest reduction in fecundability, followed by exclusive e-cigarette users, with no adverse association found among exclusive cigarette smokers. Contrary to most published literature, we found only small associations of cigarette smoking in a prior analysis of smoking and fecundability in PRESTO (9). Women using e-cigarettes during preconception might be doing so as a means to quit cigarettes or reduce harmful cigarette-related toxicant exposure. If these results truly indicate interaction between e-cigarettes and cigarette smoking exposure (i.e., through synergism), this finding might prompt questions about whether smokers attempting to conceive should seek alternative methods for smoking cessation. However, exist-

ing evidence indicates that substitution of e-cigarettes for combustible cigarettes results in substantial reductions in toxicant exposure (48). Further, there appears to be no association between smoking alone and fecundability in our data (9), and thus synergism with e-cigarettes is difficult to interpret. Finally, the confidence intervals of our estimates were wide and compatible with a broad range of associations, including no association. Systematic error such as residual confounding or misclassification, coupled with chance variation, could explain some or all of our findings.

Residual confounding by cigarette smoking remains a concern in our primary analysis as well as the analysis of joint associations of e-cigarettes and cigarettes. We did not adjust for nicotine addiction, and it is possible that reduced fecundability in our data for current e-cigarette users is due to residual confounding (i.e., smokers who use e-cigarettes might have a current or past history of heavier cigarette smoking than nonusers of e-cigarettes). We do adjust for intensity and duration of combustible cigarette smoking in all models, but self-reported smoking behaviors are prone to misclassification (49), and thus cigarette smoking history could account for a systematic departure of the fecundability ratio from 1.0. On the other hand, among never smokers we also found a small albeit imprecise association that should have minimal confounding by combustible cigarette smoking.

The magnitude of associations between combustible cigarette smoking and fecundability varies by duration, dose, and recency of cigarette exposure (9). Therefore, we might expect associations of e-cigarette use and fecundability to vary by recency or intensity of use. This was not the case in our primary analysis. Rather than increase, the association decreased with e-cigarette intensity, detracting from a causal interpretation. In our study, participants self-reported e-cigarette use, and current use was defined based on self-reported e-liquid vaped per day, which could lead to exposure misclassification between current and former use categories. Misclassification might also be exacerbated by heterogeneity of e-cigarette products. Assuming nondifferential misclassification, if true current e-cigarette users were misclassified as former users, then fecundability ratios would be underestimated for current use, and overestimated for former use.

Among some women, experiencing subfertility could increase e-cigarette use resulting in reverse-causation bias. Thus, we stratified our models by pregnancy attempt time at study entry, given that women with shorter pregnancy attempt times are less likely to change vaping behaviors in response to subfertility. The inverse association between current e-cigarette use and fecundability was slightly stronger among women with shorter pregnancy attempt times, allaying concerns about reverse causation. We also found a slightly stronger inverse association among women <30 years old at baseline. Younger women might use e-cigarettes more often or more intensely than older women. However, in our data, distribution of e-liquid vaped per day was similar across age categories.

Limitations of this study include potential for exposure misclassification, residual confounding, and imprecision. Another concern is possible selection bias leading to an overestimate of associations for current e-cigarette use, because women lost to follow-up were more likely than retained women to have characteristics associated with reduced fecundability (e.g., lower socioeconomic status) and to use e-cigarettes. Finally, not all women have male-partner data available, and we were not able to include male-reported variables that might be important influences on fecundability in the analysis.

It is estimated that 15% of couples experience infertility (25), which is associated with psychological distress and financial hardship (50). Identifying modifiable factors that affect fertility is important to help couples improve chances of pregnancy. Women planning a pregnancy, particularly smokers who wish to reduce or substitute combustible cigarette exposure, might seek guidance on the safety of using e-cigarettes during the preconception period. In our data, e-cigarette use was associated with slightly reduced fecundability, but it remains unclear whether this represents a causal effect. If internally valid, these results should be applicable to any population exposed to e-cigarettes and tobacco products similar to those used in this population.

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