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RESEARCH REPORT

ADDICTION SSA

# Safety of e-cigarettes and nicotine patches as stop-smoking aids in pregnancy: Secondary analysis of the Pregnancy Trial of E-cigarettes and Patches (PREP) randomized controlled trial

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## Abstract

**Aims:** The aim of this study was to examine the safety of e-cigarettes (EC) and nicotine patches (NRT) when used to help pregnant smokers quit.

**Design:** A recent trial of EC versus NRT reported safety outcomes in the randomized arms. We conducted a further analysis based on product use.

**Setting:** Twenty-three hospitals in England and a stop-smoking service in Scotland took part.

**Participants:** The participants comprised 1140 pregnant smokers.

**Interventions:** We compared women using and not using EC and NRT regularly during pregnancy.

**Measurements:** Measurements included nicotine intake compared with baseline, birth weight, other pregnancy outcomes, adverse events, maternal respiratory symptoms and relapse in early abstainers.

**Findings:** Use of EC was more common than use of NRT (47.3% vs 21.6%, $P < 0.001$). Women who stopped smoking (abstainers) and used EC at the end-of-pregnancy (EOP) reduced their salivary cotinine by 45% [49.3 ng/ml, 95% confidence interval (CI) = −79.8 to −10]. Only one abstainer used NRT at EOP. In dual users, cotinine increased by 19% (24 ng/ml, 95% CI = 3.5–68). In women reporting a reduction of at least 50% in cigarette consumption, cotinine levels increased by 10% in those using nicotine products and by 9% in those who did not. Birth weights in dual users and exclusive smokers were the same (3.1 kg). Birth weight in abstainers using either nicotine product was higher than in smokers [3.3 kg, standard deviation (SD) = 0.7] versus 3.1 kg, SD = 0.6; difference = 0.15 kg, 95% CI = 0.05–0.25) and not different from abstainers not using nicotine products (3.1 kg, SD = 0.8). Abstainers and smokers using nicotine products had no worse pregnancy outcomes or more adverse events than abstainers and smokers not

using them. EC users reported more improvements than non-users in cough [adjusted relative risk (aRR) = 0.59, 95% CI = 0.37–0.93] and phlegm (aRR = 0.53, 95% CI = 0.31–0.92), controlling for smoking status. EC or NRT use had no association with relapse.

**Conclusions:** Regular use of e-cigarettes or nicotine patches by pregnant smokers does not appear to be associated with any adverse outcomes.

KEYWORDS
Birth weight, e-cigarettes, nicotine, pregnancy, safety, smoking, vaping

## INTRODUCTION

Smoking is associated with a range of adverse pregnancy outcomes [1,2], but the role of nicotine in these effects is currently not clear. In animal studies, forced chronic high doses of nicotine during pregnancy have been shown to have a range of serious adverse effects, but it is not clear if this generalizes to intermittent nicotine doses self-administered by human smokers [3].

Nicotine replacement therapy (NRT), mainly in the form of nicotine patches, is widely used to help pregnant smokers quit [4]. Two recent systematic reviews of studies of the effects of NRT on pregnancy outcomes identified no clear evidence of adverse effects, but commented that only limited data were available [5,6]. A narrative review reported some concerns, but also recommended NRT use [4].

E-cigarettes (EC) are another nicotine product that some pregnant smokers use as an aid to stopping smoking [7]. EC have a wider reach than traditional NRT products [8,9] and also appear more effective for smoking cessation [10]. Unlike NRT, however, EC are a consumer product, rather than a medicinal product, and data on their safety in pregnancy are even more limited.

An earlier systematic review of existing literature reported insufficient evidence to draw conclusions, but noted some indications that vaping has little or no effect on birth weight [6]. One study found a greater number of abnormal reflexes in infants of both smokers and EC users compared with non-smokers [11]. This could be due to smoking in early pregnancy, or genetic and familial factors or could be due to nicotine exposure. Two studies reported associations between EC use in late pregnancy and preterm birth and low birth weight, but it was not clear whether these associations were due to previous smoking [12,13]. Two more recent studies did not find an association between EC use during pregnancy and adverse pregnancy outcomes [14] or with low gestational weight gain [15], but the level of EC use was not established.

Randomized controlled trials (RCTs) can be expected to provide the best causal evidence of drug safety, but their usefulness in assessing safety of nicotine products in pregnancy is limited. This is because most participants usually continue to smoke; and among those who stop smoking, only some use the assigned products, while some use the products assigned to the comparison group. An alternative is to use the data from such studies to compare participants who did or did not use nicotine products regularly during pregnancy. As these groups are not randomized, unmeasured confounders can influence the result, but less than in cohort studies, where spontaneous quitters may differ substantially from those using nicotine in, for example, baseline smoke intake and dependence and whether they quit in early pregnancy or later. In RCTs, participants are relatively homogenous, in that they all smoked during the first trimester, sought help with stopping smoking and met inclusion criteria; also, information is available on baseline measures and on nicotine product use during pregnancy that cohort studies usually do not have.

We completed a large RCT comparing EC and nicotine patches given to pregnant smokers (PREP trial) [16]. Regarding smoking cessation, the results were affected by EC use in the NRT arm. When this was controlled for, EC were more effective than NRT in all efficacy outcomes. Regarding product safety, the two study arms did not differ in pregnancy outcomes apart from low birth weight, that was less frequent in the EC arm.

We present a secondary analysis of this data set that, instead of comparing the randomized groups, compares outcomes in participants who did and did not regularly use these two nicotine products during their pregnancy.

## METHODS

### Design

In the PREP trial, pregnant women motivated to stop smoking were randomized to either nicotine patches or EC and received up to six weekly telephone support calls. They were contacted again at 35 weeks gestation (end of pregnancy, EOP). An additional follow-up collecting safety data was conducted at 3 months post-partum. For full trial procedures, see the PREP report [16].

Assessments of product safety in randomized groups can be affected by the fact that only some participants use their assigned product regularly and some use products assigned to the comparison group. To complement the analysis based on the randomized groups that was presented in the PREP report, in this study we compare participants who did and did not use nicotine products regularly during pregnancy, regardless of randomization.

We aimed to compare women who did and did not use EC or NRT (nicotine products) regularly during their pregnancy in the following:

1. Changes in salivary cotinine levels at EOP compared with baseline, to see whether product use increases or decreases nicotine intake compared to smoking.

2. Baseline characteristics, to identify variables that are associated with such use, so these can be controlled for.
3. Birth weight and other birth outcomes, to see if product use poses any risks or negates benefits of stopping smoking.
4. Respiratory symptoms in women, to verify the previous counterintuitive finding of better respiratory outcomes with EC use [16].
5. Rate of relapse to smoking in early abstainers. If product use increases the risk of relapse, this would represent a negative safety outcome.

The study was approved by the National Research Ethics Service Committee London–South East (ref: 17/LO/0962) and the Medicines and Healthcare Regulatory Agency via the Clinical Trial of an Investigational Medicinal Product Notification Scheme. A Data Monitoring and Ethics Committee and a Trial Steering Committee supervised the study. The study was pre-registered on International Standard Randomized Controlled Trial Number, ref.: ISRCTN 62025374.

## Participants

PREP recruited 1140 pregnant (12–24 weeks gestation) daily smokers, wanting help with stopping smoking, having no strong preference for EC or NRT and not currently using these products.

The analysis of birth and maternal outcomes includes data from 1095 participants, as in the main report [16]. The analyses exclude participants who withdrew from the study prior to delivery ($n$ = 6), had undergone elective termination ($n$ = 2), gave birth outside study sites and have missing birth and maternal outcomes information ($n$ = 24) or had twins ($n$ = 13).

## Study products

### E-cigarettes

Participants received a refillable EC starter kit (One Kit by the UK Ecig Store; Wembley, UK) and two 10-ml bottles of tobacco-flavoured e-liquid (18 mg/ml nicotine). Further supplies of e-liquid were posted on request for up to 8 weeks. Participants were asked to source and pay for any supplies after 8 weeks.

### Nicotine Replacement therapy

Participants received an initial 2-week supply of Nicorette Invisi 15 mg/16-hour nicotine patches. Further supplies were posted on request for up to 8 weeks. Participants were encouraged to access further supplies of patches and/or other NRT products via their general practitioner (GP) or local stop smoking service. In the United Kingdom, pregnant smokers receive NRT free.

## Measures

At baseline, demographic and smoking history variables were collected and participants provided a saliva sample. During telephone calls at weeks 1–4 post-target quit date (TQD) and at EOP, participants reported on their smoking status and use of nicotine products. At EOP only, participants reported any onset of four respiratory symptoms since starting treatment: phlegm, shortness of breath, cough and wheezing and on any changes in these symptoms if pre-existent [17].

At EOP, saliva samples for cotinine analysis were collected from three groups of participants: self-reported abstainers, those reporting a reduction in cigarette consumption by at least 50% and those reporting currently both smoking and using nicotine products. This was to validate self-reported abstinence and self-reported smoking reduction and to see any effects of dual use on nicotine intake.

Health status was monitored, and serious adverse events (SAEs), other adverse events (AEs) and adverse reactions (ARs) were recorded at each contact.

Research midwives collected birth and maternal outcomes via hospital records relating to termination, miscarriage (non-live birth prior to 24 weeks gestation), stillbirth (non-live birth at 24 weeks gestation or later), neonatal death (from live birth to 28 days), post-neonatal death (from 29 days), preterm birth (< 37 weeks gestation), low birth weight (< 2500 g), neonatal intensive care (NICU) admissions, congenital abnormalities, caesarean-section delivery, gestational age and birth weight.

## Definitions

Regular use of EC or NRT was defined as per main trial analysis [16]; that is, as a self-report of having used the product for at least 5 consecutive days during the first 4 weeks, using regularly for at least 1 week, or occasionally for at least 3 weeks or currently using the product at EOP. Participants who reported regular use of both products were included among EC or NRT users according to the predominant product use. If both products were used to the same extent, participants were included among EC users to reduce the number of comparison groups and because health effects of EC use were of particular interest. Participants meeting this definition are labelled as 'regular users of EC', 'regular users of NRT' or 'regular users of nicotine products' if the two previous categories are analysed together.

Current use of EC or NRT at EOP was defined as self-report of currently using the product at EOP. Participants meeting this definition are labelled as 'current users of EC', 'current users of NRT' or 'current users of nicotine products' if the two previous categories are analysed together.

The main study report describes the problems we encountered with collecting postal saliva samples. Studying the instructions, providing the samples, packaging them and mailing them back proved

challenging for women in late pregnancy or with newborn babies. Because of the lack of samples we are using self-reported point-prevalence abstinence in this report; that is, reporting no smoking at all in the past 7 days at EOP. Participants meeting these criteria are labelled as 'abstainers'. Participants who reported smoking or had missing information were classified as smokers.

Participants who reported at EOP that they reduced their daily cigarette consumption by at least 50% are labelled as 'reducers'.

Relapse was defined as self-reported abstinence at 4 weeks, followed by non-abstainer status at EOP. When looking at links between relapse and nicotine product use at 4 weeks, product use was defined as using EC or NRT on at least 1 day at week 4.

## Statistical methods

Birth, maternal outcomes and SAE analyses include the full sample. AE analyses include only participants who were reached and asked the relevant questions.

Rates of relapse, presence of respiratory symptoms and categorical birth and maternal outcomes were analysed using binomial regression with a logarithmic link to estimate risk ratios (RR). Birth weight and gestational age, which were reasonably normally distributed, were analysed using linear regression.

We report both median (interquartile range, IQR) for cotinine readings and estimate median differences and 95% confidence intervals (CIs), as the difference scores were symmetrical. We estimated 95% CIs by bootstrapping the median differences between EOP and baseline using 10 000 replications.

Differences in birth weight across smoking status groups were estimated using regressions to estimate differences and their corresponding 95% CIs.

Analyses of birth and maternal outcomes, AEs and relapse rates were adjusted for baseline characteristic associated with the outcome in which the groups differed (see Supporting information, Tables S1 and S2). Where baseline characteristics used to adjust the models were missing, we imputed the value using the multiple imputation model described in the main paper [16]. Participants were recruited throughout 23 sites, but because treatment was provided centrally by the study team at Queen Mary University of London (QMUL) rather than at the sites, analyses were not adjusted for sites. Analyses comparing incidence of respiratory symptoms between nicotine product users and non-users were adjusted for smoking status.

As treatment was provided centrally by the study team at QMUL we did not anticipate heterogeneity across study sites, but we looked into checking this assumption via mixed-effect logistic models, with site included as random effect. However, cluster size was too small.

The analyses reported here were not pre-specified and should be considered exploratory. All analyses were run using Stata version 17.0.

# RESULTS

## Use of nicotine products

Regular use of EC during pregnancy ($n$ = 539, 47.3%) was more common than regular use of NRT ($n$ = 235, 20.6%; $z$ = 21.6, $P$ < 0.001). The difference was more pronounced in the proportions who used EC and NRT at the time of EOP follow-up: $n$ = 232 (21.2%) versus $n$ = 28 (2.5%; $z$ = 0.03, $P$ < 0.001). Among abstainers, there were 131 (66.8%) regular users of EC and 40 (20.4%) regular users of NRT ($z$ = 41.4, $P$ < 0.001), while 25 (12.8%) abstainers did not use nicotine products regularly.

## Differences in baseline characteristics between abstainers using and not using nicotine products and smokers

Abstainers using EC and abstainers using NRT did not differ in baseline characteristics (Supporting information, Table S1) and so were combined into one group (i.e. nicotine users) for analyses (Supporting information, Table S2). There were no significant differences between abstainers using and not using nicotine products (Supporting information, Table S2). Compared to smokers, both groups of abstainers (using and not using nicotine products regularly) had lower cigarette dependence scores and were lighter smokers at baseline, as indexed by salivary cotinine levels. In addition, abstainers using nicotine products had a higher level of education and were more likely to be employed than smokers.

Based on these results, analyses for pregnancy outcomes (i.e. birth and maternal outcomes, SAE and AE) were adjusted for baseline cotinine levels, occupation and Fagerström Test of Cigarette Dependence (FTCD) [18].

## Nicotine intake from cigarettes and from nicotine products

Due to problems with collecting saliva samples at EOP discussed above, analyses of changes in salivary cotinine levels included only 297 (48.9%) of 607 eligible participants. Participants who did and did not provide saliva samples were balanced on cigarette consumption, baseline cotinine levels and tobacco dependence scores (Supporting information, Table S3).

We examined effects of current use of nicotine products on cotinine levels in three groups of participants.

1. Abstainers: abstainers who used EC at the time of EOP ($n$ = 41) reduced their cotinine levels from 109.0 (IQR = 57.2–137.0) to 59.7 ng/ml (26.4–186.0); that is, by 45% (median difference = 49.3, bootstrapped 95% CI = −79.8 to −10). The one abstainer using NRT and providing full data increased their cotinine intake from 63.1 to 128.0 ng/ml (the increase seems due to a low baseline reading).

2. Dual users: those smoking and using EC at EOP ($n$ = 104) increased their cotinine levels by 19% from 127 ng/ml (82.4–192.0) at baselines to 151 ng/ml (89.0–258.0) at EOP (median difference = 24 ng/ml, bootstrapped 95% CI = 3.5–68). Those smoking and using NRT ($n$ = 10) increased their cotinine levels by 16%, from 120 (64.5–191.0) to 140 ng/ml (50.4–194.0; median difference = 20 ng/ml, bootstrapped 95% CI = −34.1 to 103.5).
3. Reducers: those who self-reported reducing their cigarette consumption by at least 50% (i.e. reducers). Reducers not using EC or NRT ($n$ = 83) increased their cotinine levels by 9.3% [from 108 ng/ml (74.1–162.0) to 118 ng/ml (65.1–214.0); median difference = 10, bootstrapped 95% CI = −7.0–41.0]. Reducers using EC ($n$ = 77) increased their cotinine levels by 10% from 123 (86.6–178.0) to 135 ng/ml (85.9–248.0; median difference = 12 ng/ml, bootstrapped 95% CI = −11.0 to 36.0. Reducers using NRT ($n$ = 8) increased their cotinine levels by 17%, from 120 (63.6–163.0) to 140 ng/ml (42.5–211.5; median difference = 20, bootstrapped 95% CI = −61.9 to 121.0).

Table 1 shows the results with EC and NRT users combined. Abstainers using nicotine products reduced their cotinine levels by 38%, while dual users increased them by 19%. Reducers increased their cotinine levels by 9–10%, whether or not they used nicotine products (Table 1).

## Use of nicotine products and birth weight

Birth weight of infants born to abstainers who were regularly using EC or NRT did not differ (3.3 kg, SD = 0.7 versus 3.3 kg, SD = 0.5; see Supporting information, Table S4), so the two groups were combined as abstainers regularly using nicotine products.

Birth weight of infants born to abstainers regularly using nicotine was higher than birth weight of smokers (3.3 kg, SD = 0.7 versus 3.1 kg, SD = 0.6; difference = 0.15 kg, 95% CI = 0.05–0.25) and not different from abstainers not regularly using nicotine products (3.1 kg, SD = 0.8).

The last row of Table 2 shows additional comparisons in subgroups defined by smoking status and use of nicotine products. There was no difference between birth weight of infants of women who continued to smoke and did not use nicotine products and birth weight of infants of dual users; that is, women who continued to smoke and in addition used nicotine products regularly.

## Use of nicotine products and other pregnancy outcomes

Table 2 shows adverse pregnancy outcomes and gestational age in groups defined by their smoking status and regular use of nicotine products. Abstainers using EC and NRT did not differ in these outcomes (Supporting information, Table S4), and so are merged as nicotine product users.

The small sample of abstainers not using nicotine products ($n$ = 25) had more preterm births than abstainers using nicotine, which also translated into a higher proportion with any adverse pregnancy outcome (see Table 2). Among women who did not manage to stop smoking there were no differences between those who did not use nicotine products and those who did (dual users).

In the complete sample (combining abstainers and smokers), nicotine product users ($n$= 774) did not differ from non-users ($n$ = 156) in SAEs (12.1 versus 14.7%, RR = 0.84, 95% CI = 0.55–1.29) or in AEs (25.5 versus 22.4%; RR = 1.14, 95% CI = 0.83–1.56; comparisons adjusted for employment).

## EC use and respiratory symptoms

Information on respiratory symptoms was collected only towards the end of the study and was available for 143 participants.

For this subset of participants, there were no differences in the onset of four respiratory symptoms since starting treatment between women regularly using and not using EC (see Supporting information, Table S5).

**TABLE 1** Changes in cotinine levels from baseline in abstainers, smokers and reducers using and not using nicotine products at end of pregnancy.

| | Baseline ng/ml, median (IQR) | EOP ng/ml, median (IQR) | Difference and bootstrapped 95% CI[a] |
|---|---|---|---|
| Abstainers using nicotine products at EOP ($n$ = 42) | 109 (57.2–137.0) | 67.5 (26.4–186.0) | −41.6 **(−38%)**[b] (−74.6–1) |
| Smokers using nicotine products at EOP (dual users) ($n$ = 114) | 127 (81.3–191.0) | 151 (85.9–250.0) | 24 **(+19%)**[b] (3.5–58.5) |
| Reducers using nicotine products at EOP ($n$ = 85) | 123 (86.6–178.0) | 135 (82.3–247.0) | 12 **(+9.8%)**[b] (−12.0–36.0) |
| Reducers not using nicotine products an EOP ($n$ = 83) | 108 (74.1–162.0) | 118 (65.1–214.0) | 10 **(+9.3%)**[b] (−7.0–41.0) |

*Note*: Bold type indicates p < 0.05.
Abbreviations: CI = confidence interval; EOP = end of pregnancy; IQR = interquartile range.
[a]10 000 bootstrap replications.

**TABLE 2** Adverse and other pregnancy outcomes and adverse events by nicotine products use and smoking status.

| | Abstinent did not use nicotine products regularly *n* = 25 | Abstinent used nicotine products regularly *n* = 166 | RR (95% CI)[a] | Smoking did not use nicotine products regularly *n* = 322 | Smoking used nicotine products regularly *n* = 582 | RR (95% CI)[a] |
|---|---|---|---|---|---|---|
| Adverse maternal and pregnancy outcomes | | | | | | |
| Miscarriage *n* (%) | 0 | 1 (0.6) | NC | 2 (0.6) | 2 (0.3) | NC |
| Stillbirth *n* (%) | 0 | 0 | NC | 0 | 2 (0.3) | NC |
| Neonatal death *n* (%) | 1 (5.6) | 0 | NC | 0 | 4 (0.7) | NC |
| Postnatal death *n* (%) | 0 | 0 | NC | 1 (0.3) | 2 (0.3) | NC |
| Maternal death *n* (%) | 0 | 0 | NC | 0 | 0 | NC |
| Preterm birth *n* (%) | 6 (24.0) | 11 (6.6) | **0.29 (0.12–0.70)** | 36 (11.2) | 56 (9.6) | 0.89 (0.60–1.34) |
| Low birth weight *n* (%)<br>*n* = 25–162–320-575 | 4 (16.0) | 16 (9.9) | 0.64 (0.24–1.72) | 36 (11.3) | 76 (13.2) | 1.24 (0.85–1.81) |
| NICU admission *n* (%) | 4 (16.0) | 15 (9.0) | 0.57 (0.21–1.59) | 22 (6.8) | 56 (9.6) | 1.42 (0.87–2.30) |
| Congenital abnormalities *n* (%) | 0 | 4 (2.4) | NC | 10 (3.1) | 26 (4.5) | 1.38 (0.66–2.87) |
| Terminations *n* (%)<br>Due to congenital abnormalities<br>Due to premature rupture of membranes | 0<br>0 | 0<br>0 | NC | 1 (0.3)<br>0 | 2 (0.3)<br>2 (0.3) | NC |
| Number of women with any adverse pregnancy outcome[b] *n* (%) | 9 (36.0) | 26 (15.7) | **0.45 (0.24–0.84)** | 60 (18.6) | 136 (23.4) | 1.29 (0.98–1.69) |
| Number of women with other adverse events | | | | | | |
| Serious adverse events (SAE) *n* (%) | 4 (16.0) | 25 (15.1) | 0.72 (0.28–1.84) | 65 (11.2) | 36 (11.2) | 0.65 (0.41–1.05) |
| Adverse events *n* (%)<br>19–162–560-124 | 3 (15.8) | 50 (30.9) | 2.00 (0.69–5.79) | 143 (25.5) | 31 (25.0) | 1.04 (0.74–1.46) |
| Other pregnancy outcomes | | | | | | |
| Delivery by caesarean section | 9 (36.0) | 45 (27.1) | 0.72 (0.41–1.29) | 81 (25.2) | 144 (24.7) | 0.91 (0.71–1.16) |
| Gestational age in weeks Mean (SD)<br>*n* = 25–165–322–580[c] | 37.6 (4.0) | 38.6 (2.7) | 0.93 (−0.34 to 2.21) | 38.4 (2.9) | 38.2 (3.2) | −0.26 (−0.68 to 0.16) |
| Birth weight<br>Mean (SD)<br>*n* = 25–162–320–575[c] | 3.1 (0.8) | 3.3 (0.7) | 0.20 (−0.05 to 0.45) | 3.1 (0.6) | 3.1 (0.5) | −0.05 (−0.14 to 0.03) |

*Notes*: The samples comprise *n* = 1095 participants with singleton births for whom birth and maternal outcomes were available (this applies to the whole table). Bold type indicates $p < 0.05$.
Abbreviations: 95% CI = 95% confidence interval; FTCD = Fagerström Test of Cigarette Dependence; NC = not calculated due to small cell size; NICU = neonatal intensive care; RR = relative risk; SAE = serious adverse event; SD = standard deviation.
[a]Models adjusted for FTCD, baseline cotinine levels and occupation.
[b]Women who experienced one or more of the outcomes listed in the rows above.
[c]Mean differences [95% confidence interval (CI)].

Table 3 shows changes in symptoms in women who experienced them prior to the start of treatment. EC users reported better outcomes for cough and phlegm than non-users. Controlling for smoking status did not change the results.

The respiratory symptoms questions were included to check the previous findings of favourable effects of EC use on pre-existing cough and phlegm [17], but we also checked this in NRT users and non-users for completeness. The two groups did not differ (Supporting information, Table S6).

## Use of nicotine products and relapse

In participants who were abstinent from smoking at 4 weeks, relapse rates at 6 months were similar in those who used EC and NRT and those not using nicotine products at 4 weeks (Table 4).

# DISCUSSION

We did not detect any major risk associated with using EC and NRT during late pregnancy.

Abstainers using EC at EOP reduced their salivary cotinine levels compared with baseline by 45%. Levels in dual users increased by 19%, while women who reported reducing their cigarette consumption by at least 50% increased their cotinine levels by 9.3% if they did not also regularly use nicotine products or by 9.8% if they did. Finding increased cotinine levels in reducers was unexpected, especially as pregnancy is known to speed up nicotine metabolism [19]. We did not collect samples from women who did not report a reduction in their cigarette consumption and so could not check whether their salivary cotinine levels also increased. We identified only one study that reported cotinine levels in early and late pregnancy, but the samples were not identical and the later sample included women who stopped

**TABLE 3** Change in respiratory symptoms in participants who did not and did use EC regularly.

| Change in pre-existing symptoms[a] | Used EC regularly (*n* = 39–54) *n* (%) | Did not use EC regularly (*n* = 20–40) *n* (%) | Unadjusted RR (95% CI)[b] | Adjusted RR (95% CI)[b,c] |
|---|---|---|---|---|
| Phlegm | | | | |
| Worse | 12 (30.8) | 13 (65.0) | **0.47 (0.27–0.84)** | **0.53 (0.31–0.92)** |
| Same | 12 (30.8) | 4 (20.0) | | |
| Better | 15 (38.5) | 3 (15.0) | | |
| Shortness of breath | | | | |
| Worse | 21 (38.9) | 17 (42.5) | 0.92 (0.56–1.50) | 1.00 (0.62–1.61) |
| Same | 28 (51.9) | 20 (50.0) | | |
| Better | 5 (9.3) | 3 (7.5) | | |
| Cough | | | | |
| Worse | 16 (35.6) | 19 (65.5) | **0.54 (0.34–0.87)** | **0.59 (0.37–0.93)** |
| Same | 14 (31.1) | 6 (20.7) | | |
| Better | 15 (33.3) | 4 (13.8) | | |
| Wheezing | | | | |
| Worse | 12 (30.0) | 16 (48.5) | 0.62 (0.34–1.12) | 0.64 (0.35–1.16) |
| Same | 24 (60.0) | 14 (42.4) | | |
| Better | 4 (10.0) | 3 (9.1) | | |

*Note*: Bold type indicates p < 0.05.
Abbreviations: CI = confidence interval; EC = electronic cigarette; EOP = end of pregnancy; RR = relative risk.
[a]Symptoms were measured on a 5-point scale: much better, somewhat better, the same, somewhat worse and much worse; worse = somewhat worse and much worse, same = same, better = somewhat better and much better.
[b]RR are for symptoms deterioration (somewhat worse and much worse versus same, much better and somewhat better).
[c]Adjusted for smoking status at EOP.

**TABLE 4** Relapse rates at EOP in 4-week abstainers who did and did not use EC and NRT at 4 weeks.

| | Not using nicotine (*n* = 29) | Using EC (*n* = 86) | Using NRT (*n* = 30) | Using either or both (*n* = 121) |
|---|---|---|---|---|
| Relapsed by EOP *n* (%) | 9 (31.0) | 29 (33.7) | 10 (33.3) | 41 (33.9) |
| RR (95% CI)[a] | | 1.08 (0.57–2.04) | 1.03 (0.48–2.21) | 1.09 (0.59–2.00) |

Abbreviations: CI = confidence interval; EC = electronic cigarette; EOP = end of pregnancy; FTCD = Fagerström Test of Cigarette Dependence; NRT = nicotine replacement therapy; RR = relative risk.
[a]The group not using nicotine products is the reference. Model adjusted for FTCD, baseline cotinine levels and occupation.

smoking [20]. Future studies that collect cotinine data in early and late pregnancy can clarify this issue.

The key adverse effect of smoking on pregnancy concerns restricted prenatal growth [21,22]. Overall, the use of nicotine products in later pregnancy was not associated with infant birth weight, while in abstainers, those using nicotine products had infants with a higher birth weight than smokers and not different from infants of abstainers not using nicotine. The birth weight of infants of dual users did not differ from that of smokers. This suggests that use of EC and NRT after the first trimester may not affect intrauterine growth in women who continue to smoke and that it does not reduce the benefits of stopping smoking in women who quit.

Users of EC and users of NRT did not differ in any safety outcomes, and use of these products was not associated with any of the adverse events that we monitored. It should be noted, however, that these findings only concern nicotine use in the later stages of pregnancy, as all participants were smoking in the first trimester. Future research should examine pregnancy outcomes in daily vapers who never smoked, provided such use becomes more common.

Unexpectedly, the small sample of abstainers not using nicotine products had more adverse outcomes than abstainers using them and also more than smokers. It is possible that this group included women who avoided nicotine products because of pregnancy complications or that this was a chance finding.

In a previous large randomized trial involving non-pregnant smokers, participants allocated to EC experienced less cough and phlegm during 1-year follow-up than those allocated to NRT, and the effect was independent of smoking cessation [17]. The same phenomenon was observed in this study. The observation seems counter-intuitive, but several previous reports noted improvements in upper respiratory tract infections associated with EC use [23–25]. The main ingredients in EC aerosol are propylene glycol and glycerine, both of which have antibacterial effects [26], and it is possible that inhaling them regularly may reduce bacterial infections. Further studies, such as a trial of usual care plus nicotine-free EC versus usual care only in patients with chronic upper airways infections, is needed to clarify the issue.

Smokers who stop smoking with the help of EC are more likely to continue using their product than is the case with licensed stop-smoking medications [27]. This raises an important question of how such use affects relapse to smoking. In this sample, post-cessation EC use had no association with relapse. Evidence from other sources is needed to establish whether use of EC prevents or facilitates relapse over longer time-periods.

The key limitation of this study is that nicotine product use was not randomized. Analysing the effects of nicotine products based on their actual use avoids the problem that randomization does not guarantee product use, but product use is a self-selected behaviour. We controlled for any baseline differences between users and non-users, but the study findings could still have been influenced by differences we did not detect. It is reassuring that the findings broadly tally with those from the randomized comparison that did not detect any risk signals in the EC arm, where nicotine use was much higher than in the NRT arm. Nevertheless, the results need to be interpreted with caution. Another limitation is the reliance upon self-reported abstinence. The statistical power in some comparisons was limited; for example, there were only 25 abstainers not using nicotine products. Effects on any rare pregnancy complications could have been missed. Also, the women and infants were only followed-up to 3 months post-delivery. Saliva samples were obtained from only a subsample of eligible participants, although those who did and did not provide the samples did not differ in the key baseline variables.

In summary, abstainers using EC and NRT had infants with significantly higher birth weight than smokers and not different from abstainers not using nicotine. The previous finding of an association of EC use with positive changes in respiratory symptoms was replicated. We did not detect any risks to pregnancy from EC nor NRT use by smokers trying to quit. These new findings could alleviate some concerns about use of nicotine-containing products to help pregnant smokers quit, but further studies are needed to verify these results.

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## DECLARATION OF INTERESTS

The authors have no conflicts of interest to declare.

## DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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## SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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