Cigarette consumption in adult dual users of cigarettes and e-cigarettes: a review of the evidence, including new results from the PATH study [version 1; peer review: 1 approved with reservations]

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Abstract

Background: Modelling disease risk from e-cigarette use requires knowing how much e-cigarette uptake affects a smoker's cigarette consumption. From Waves 1-3 of the US PATH study and other evidence, we sought answers to three questions: (Q1) Does consumption differ between dual users and exclusive smokers? (Q2) Does initiating e-cigarettes affect cigarette consumption? (Q3) Is baseline consumption related to later initiation of e-cigarettes?

Methods: Consumption data from PATH were corrected for clear recording errors, with e-cigarette use classified as established or every day, and adjustment made for demographics, use of alcohol, drugs and other tobacco products, and age of starting smoking. Searches identified other studies published since 2008, with Q1 answered from cross-sectional studies, and Q2 and Q3 also from prospective studies.

Results: (Q1) In PATH, consumption in current every day e-cigarette users was 2-3 cigarettes per day lower in dual users, with no difference seen in established users. From 31 published studies, consumption was no lower in dual users for current or ever e-cigarette users. (Q2) In PATH study consistent decreases in consumption occurred in those becoming every day dual users with increases seen in those reverting to exclusive smoking. Thirteen published studies consistently showed reduced consumption in those becoming dual users. (Q3) Three studies consistently showed greater consumption in smokers subsequently initiating e-cigarettes, but no significant difference was seen for PATH.
Conclusions: Assessment is complicated by the few every day e-cigarette users in PATH, and between-study variability in quantifying e-cigarette use and presentation of results. As taking up e-cigarettes is associated with reducing consumption, finding no clear cross-sectional difference between dual users and exclusive smokers suggests smokers taking up e-cigarettes had higher consumption initially, limited evidence supporting this. Given the much lower disease risk of e-cigarettes vs. cigarettes, smokers becoming dual users should somewhat reduce their disease risk.

Keywords
Smoking, E-cigarettes, Dual use, Cigarette consumption
**Abbreviations**

CC, cigarette consumption; CI, confidence interval; OR, odds ratio; PATH, Population Assessment of Tobacco and Health; RRTP, reduced-risk tobacco product; SE, standard error.

**Introduction**

Various population health impact models have been developed to estimate the extent to which mortality is reduced following the introduction of a reduced-risk tobacco product (RRTP). In many applications of one approach (Lee et al., 2017) it is assumed that adult dual users of cigarettes and RRTPs have a mean cigarette consumption (CC) per day that is half that of cigarette smokers who do not use RRTPs. A substantial reduction in CC in dual users is also assumed in another similar modelling exercise (Poland & Teisringer, 2017). However, other approaches (e.g. (Bachand et al., 2018; Hill & Camacho, 2017; Vugrin et al., 2015)) have assumed that dual users and cigarette-only smokers have the same or a very similar CC. While conclusions regarding CC in dual users may depend on the specific type of RRTP, there is very little evidence available on very recently introduced types, such as heated tobacco products. However, as we demonstrate, a considerable number of papers have published evidence relating to e-cigarettes.

The objective of the work described here is to review and summarize evidence in adults comparing CC by dual users of cigarettes and e-cigarettes with CC by cigarette-only smokers. More specifically, this study attempts to answer three interrelated questions.

Q1. Does CC differ between dual users and exclusive smokers?

Q2. Does take-up of e-cigarettes change CC?

Q3. Does baseline CC differ by subsequent take-up of e-cigarettes?

Answers to Q1 may be obtained from cross-sectional studies carried out at one point in time, or from prospective studies at separate follow-ups. Answers to Q2 and Q3 will usually require information from prospective studies, though cross-sectional studies asking questions on the history of tobacco use might also provide relevant results.

We derive answers to the three questions from Waves 1, 2 and 3 of the publicly available adult data from the Population Assessment of Tobacco and Health (PATH) study (Hyland et al., 2017), a longitudinal cohort study in the U.S. supported by Federal funds, some previous publications (Berry et al., 2019; Buu et al., 2018) having only considered data from Waves 1 and 2. We also derive results from a detailed review of other published literature. We restrict attention to adults as they are most relevant to the estimation of the impact on mortality of RRTP introduction, and as the level of CC in cigarette smoking youths is less firmly established.

**Methods**

**Analysis of adult data from waves 1, 2 and 3 of the PATH study**

To be included in the analyses, individuals had to satisfy four criteria:

1. Be aged 18 to 54 years at Wave 1 (as e-cigarette use proved to be very uncommon in those aged 55+ years).
2. Be current every day cigarette smokers at each Wave with data available on CC.
3. Have data available on current and former established e-cigarette use at each Wave.
4. Have data available at Wave 1 on nine variables considered as potential predictors of CC (referred to subsequently simply as “predictors” – sex (male, female), age range (18–24, 25–34, 35–44, 45–54 years), highest grade of schooling (less than High School, GED, High School graduate, some college (no degree) or associates degree, bachelor’s degree, advanced degree), Hispanic origin (yes, no), race (white alone, black alone, other), age range when first started smoking cigarettes every day (<18, 18–24, 25–34, 35–44, 45–54, 55+ years), ever used alcohol (yes, no) ever used cocaine or crack (yes, no), ever use of other tobacco products (yes, no) – based on separate variables for traditional cigars, cigarillos, filtered cigars, pipes, hookah, smokeless tobacco, snus and dissolvable tobacco.

In the PATH dataset, the data on CC were recorded by two variables, a number and a unit (cigarettes per day or packs per day), the intention being to derive daily consumption directly from the number variable if the unit was cigarettes per day and by multiplying the number by 20 if the unit was packs per day. However, for some individuals the consumption data recorded in this way was highly implausible. For example, one individual had a recorded CC of 15 packs per day at Wave 1, 10 cigarettes per day at Wave 2 and 15 cigarettes per day at Wave 3. Here the implied consumption of 300 cigarettes per day is highly implausible and it seems much more likely that the Wave 1 consumption was actually 15 cigarettes per day. Accordingly, as described more fully in Extended data, Additional File 1 (Lee, 2020), a detailed investigation of the CC data at each Wave was carried out, and corrections were made for 84 individuals. There were 75 corrections relating to individuals where the consumption at one Wave was seven or more times the average consumption at the other two Waves. However, there were nine individuals where corrections were applied for other reasons, as described in the Additional File (see Extended data; Lee, 2020). All the analyses reported are based on the corrected CC data.

Analyses were carried out relating to current and ever established e-cigarette use, based on data for a current established
e-cigarette user (one who has ever used, has used fairly regularly, and uses every day or some days) and a former established e-cigarette user (one who has ever used, has used fairly regularly, and currently does not use at all), with ever users being those who were either current or former users. Analyses were also carried out relating to current day e-cigarette use. Note that for Wave 3, the data used were for e-product use (which also includes e-cigarettes, e-pipes and e-hookahs) rather than e-cigarette use, data for e-cigarette use not being available for this Wave.

All the analyses were weighted, based on the weighting factors for Wave 1, and used weighted linear regression analyses. Analyses were carried out with no adjustment for other variables and with adjustment for the other nine predictor variables selected, using a forward stepwise approach, including variables significant at p<0.05.

To answer Q1, the corrected CC was compared in exclusive cigarette smokers and in dual users, separately at each Wave.

To answer Q2 (and to provide some additional information), the change in corrected CC between two Waves was compared in four groups – exclusive cigarette smokers at both Waves, dual users at both Waves, dual users only at the second Wave, and dual users only at the first Wave. Separate analyses were carried out for each pair of Waves.

To answer Q3, the corrected CC at the first of two Waves in those who were then exclusive cigarette smokers was compared in those who did or did not become dual users. Separate analyses were carried out for each pair of Waves.

Software used to analyse data from the PATH study
Relevant data were transferred for analysis to a ROELEE database, and analysed using the ROELEE program (Release 59, Build 49). All these analyses could be run using the R-program (https://www.r-project.org), using the “lm” function including the “weights=” option for weighted linear regression, and for stepwise regression using the “step” function specifying “method=forward” and test=”F”.

Literature searches
The search was limited to publications from 2008 onwards, e-cigarette usage not being widely established before then (Barrington-Trimis et al., 2015; Bauld et al., 2014; Bell & Keane, 2014). Potential publications were initially obtained from a search on PubMed on 22 October 2018:

(e-cig*[tiab] OR e cig*[tiab] or electronic cig*[tiab] OR electronic nicotine [tiab] OR "vaping"[MeSH Terms] OR "Electronic nicotine delivery systems"[MeSH Terms]) AND (Epidemiologic studies[MeSH Terms] OR Epidemiology OR Surveys and questionnaires[MeSH Terms] OR survey*[TIAB])

Subsequently, on 26th July 2019, the search was repeated, using the same keywords as before, but restricted to papers published since 1st January 2018.

An initial trial was undertaken on the first 100 papers for which free copies were available via PubMed, with PNL screening using the abstract only, and BAF independently screening using the full paper. Based on the high level of agreement between the two methods, it was decided that initial screening on the abstract was satisfactory, but that where there was any doubt the papers would need to be obtained and examined in full. In particular, any paper apparently reporting an epidemiological survey in a general adult population which had enquired about both cigarettes and e-cigarettes should be obtained, even if there was no mention in the abstract of dual use or of the number of cigarettes smoked.

All papers were then screened by BAF or AJT, with the full paper obtained wherever necessary. Papers were accepted as having data, or as being relevant reviews. No restriction was made as to the type of device referred to by the original papers, whether e-cigarettes, ENDS, ANDS, cigalike or other terminology, or whether containing nicotine or not, except that results specifically referring to heated tobacco products were excluded.

For each paper, rejected papers were marked in two ways. First, whether they were rejected on the basis of the full paper, abstract or title, this final option only being used where no abstract was available through PubMed and the title and publication type clearly indicated it was not relevant. Papers which were at all debatable or borderline for acceptance were also examined by KJC and PNL before being finally rejected.

Second, the reason for rejection was coded as follows:
1. Not a study asking individuals about their smoking and e-cigarette usage
2. Study of adolescents, young adults (age 25 or under), or students
3. Study in persons with a pre-existing medical condition
4. Study in persons likely to have unusual smoking and/ or e-cigarette habits (e.g. studies of illicit drug users, prisoners, homeless persons, e-cigarette retail employees, medical personnel)
5. Trial of smoking cessation methods or of switching to e-cigarettes
6. Study with <100 participants
7. Study restricted to e-cigarette users (or dual users), or inappropriately restricted on smoking habits or quitting status/intention
8. No results presented distinguishing exclusive cigarette smokers and dual users
9. No results on CC
10. Results on CC not in a useable format (e.g. studies which reported amount smoked overall, but not by exclusive/dual use).
11. Report on the PATH study.
Only one reason was recorded per paper, usually (but not necessarily) the first from the list above. A note on the reason for rejection was also usually recorded.

The papers identified as review papers from the PubMed search were examined, looking for references to papers apparently describing an epidemiological survey which had enquired about both cigarettes and e-cigarettes. Except where either the context of the review paper or the title of the secondary paper indicated that the survey was in an ineligible population (corresponding to rejection codes 2–7), new papers were added to the list of candidate papers and at least the abstract was examined. As previously, unless the abstract made clear that the study population was ineligible, the full paper was obtained, regardless of whether dual use or amount smoked were mentioned in the abstract. Further review papers cited in the original set of reviews were also considered, but only if the context in the original review indicated that they referred to amount smoked.

Extraction and analysis of information from the accepted papers
For each publication, information was collected on the study location, title and type (prospective or cross-sectional), the period when the study was conducted, the age of the population considered, the number of smokers, the definition of e-cigarette use (and whether it contained nicotine) and which of the three questions it could provide answers to. For Q1, the data extracted (separately for current and ever e-cigarette use) included the numbers of dual users of cigarettes and e-cigarettes, and of exclusive cigarette smokers, the CC for each group and the difference, with its statistical significance, where possible. Where distributions were given by grouped amount smoked, the estimates of CC were derived using assumed midpoints. For studies where differences could be estimated, comparisons were made, again separately for current and ever e-cigarette use, of the number showing positive and negative differences, with unweighted means and standard errors estimated overall, and separately for US and European studies. For Q2, data were extracted for studies comparing changes in CC in those becoming or not becoming current e-cigarette users, with the number showing significant differences in each direction summarized. Data were also extracted for studies reporting changes in CC only in those becoming current dual users, with the numbers showing reductions or increases summarized. For Q3, evidence was summarised comparing CC in exclusive cigarette smokers according to whether they later used e-cigarettes, there being too few studies to allow more than a description of the results.

**Results**

**Results from the PATH study**
A total of 3,543 adults were eligible for the analysis. Table 1 summarises the results relating to Q1. They show no significant tendency for CC to be associated with current or ever established e-cigarette use, with six of the differences being positive and six negative. In contrast, though based on much smaller numbers of dual users, current every day e-cigarette use is associated with a consistently lower CC, with five of the six estimates significant at p<0.05, and the estimated difference ranging from 1.50 to 2.92 cigarettes per day.

Table 2 summarizes the results relating to changes in e-cigarette status between Waves, with those who are exclusive cigarette smokers at each Wave (“No No”) used as the base for comparisons. The analyses comparing the “No Yes” with the “No No” group are directly relevant to Q2 as defined, while those comparing “Yes No” with “No No” provide information on the reverse association.

The results relating to established e-cigarette use, with one marginal exception, show no significant tendency for changes in CC to be associated with changes in e-cigarette use. The results for every day e-cigarette use show more evidence of a

| Wave | Mean CC (95% CI) | Current established e-cigarette use Dual users | Unadjusted difference | Adjusted difference | Ever established e-cigarette use Dual users | Unadjusted difference | Adjusted difference | Current every day e-cigarette use Dual users | Unadjusted difference | Adjusted difference |
|------|------------------|---------------------------------------------|----------------------|-------------------|--------------------------------------------|----------------------|-------------------|--------------------------------------------|----------------------|-------------------|
| 1    | 16.68 (16.37-16.98) | 306 | -0.63<sup>a</sup> | -0.65<sup>a</sup> | 463 | -0.22<sup>a</sup> | -0.16<sup>a</sup> | 66 | -2.45<sup>b</sup> | -2.86<sup>b</sup> |
| 2    | 16.06 (15.77-16.36) | 432 | +0.30<sup>a</sup> | +0.15<sup>a</sup> | 817 | +0.29<sup>a</sup> | +0.23<sup>a</sup> | 74 | -1.50<sup>a</sup> | -2.26<sup>a</sup> |
| 3    | 16.12 (15.82-16.41) | 331 | -0.61<sup>a</sup> | -0.51<sup>a</sup> | 1,034 | +0.51<sup>a</sup> | +0.55<sup>a</sup> | 73 | -2.75<sup>a</sup> | -2.92<sup>a</sup> |

<sup>a</sup> Mean cigarette consumption (CC) for all 3,543 selected individuals.

<sup>b</sup> The number of those with no e-cigarette use is always equal to 3,543 minus the number of dual users.

<sup>c</sup> Differences in cigarette consumption are always between dual users and those with no e-cigarette use, according to the definition of e-cigarette use. Significance codes used are + p<0.05 ++ p<0.01 +++ p<0.001 NS p≥0.05.

<sup>d</sup> In Waves 1 and 3 the differences in cigarette consumption are adjusted for sex, age range, school grade, race, Hispanic origin, ever used other tobacco products, and age at starting to smoke. In Wave 2 the differences are adjusted for the same list of factors except ever used other tobacco products. Significance codes are as for unadjusted differences.
relationship. While they show no consistent tendency for changes to differ between those who are exclusive cigarette smokers at each Wave (“No No”), and those who are dual users at each Wave (“Yes Yes”), there is a consistent decrease in CC in those who became dual users at the second Wave (“No Yes”), and a consistent increase in those who switch from dual use to exclusive smoking (“Yes No”). While none of the decreases are significant (at p<0.05), four of the increases are highly significant (p<0.001). However, the numbers becoming or ceasing to be dual users are small.

Table 3 summarizes the results relating to Q3. The results do not show any consistent difference in baseline CC in those who were not e-cigarette users at baseline according to their subsequent e-cigarette use, whether based on current or ever established or current every day use.

Other published results

Literature search

Our original PubMed search identified 1,403 publications, a number which extended to 1,434 from examination of reference lists in review papers and secondary references. From these 55 papers were identified as relevant, which described results from 45 apparently relevant studies. The later search identified 697 publications, of which 342 had already been identified by the first search. Nine of the remaining 355 were selected as relevant, with eight describing new studies and one providing additional results from a study identified earlier.

Further examination of the papers led to seven of the 53 studies being rejected: the Smoking Toolkit Survey (Beard et al., 2018) a time-series analysis linking prevalence of e-cigarette use with average CC in England; a paper (Morean et al., 2018)...
describing results from four studies, with the data for dual use and for cigarette use coming from two different surveys (and the other two not concerning tobacco); analyses of multiple internet and mail surveys (Etter & Eissenberg, 2015) where the surveys of e-cigarette users and of smokers were conducted at different times and in different national populations; the Mexico ITC survey (Lozano et al., 2019) as its analysis relating to Q2 was not restricted to those not using e-cigarettes at baseline; the Korea KCHS study (Han, 2019) which only related smoking to use of e-cigarettes due to a price increase; a US GFK study (Weaver et al., 2018) which did not relate CC to e-cigarette use at the same time point; and the California CSC study (Al Delaimy et al., 2015) which only compared smokers who either reported they have used e-cigarettes or will never use e-cigarettes at both surveys.

Study characteristics
Table 4 summarizes the characteristics of the 46 studies considered, in order of country within continent. Of the 46 studies, 22 were conducted in the US, five in multiple countries, three in the United Kingdom, three in Italy, two in France and one in each of 11 other countries. Of these, 16 studies involved an element of follow-up, the remaining 30 being of cross-sectional design, with three of these involving multiple cross-sectional studies. The studies mainly covered the whole adult population though some were restricted to younger adults. The number of smokers included varied considerably between studies with 10 involving more than 4,000 and seven less than 250. As will become evident, the studies varied in how e-cigarette use was defined and the questions they could answer. All the papers described the product as e-cigarettes, and it has been

| Waves considered | Definition of use | Adjusted/ unadjusted | Number of individuals | Difference in baseline cigarette consumption (SE) |
|------------------|------------------|----------------------|-----------------------|-----------------------------------------------|
| 1 to 2           | Current established | Unadjusted          | 3237 253              | 0.93 (0.61)                                   |
|                  |                   | Adjusted            |                       |                                               |
|                  | Ever established  | Unadjusted          | 3080 354              | 0.55 (0.54)                                   |
|                  |                   | Adjusted            |                       |                                               |
|                  | Current every day | Unadjusted          | 3477 60               | 0.30 (1.20)                                   |
|                  |                   | Adjusted            |                       | −0.41 (1.12)                                  |
| 1 to 3           | Current established | Unadjusted          | 3237 233              | −0.70 (0.64)                                  |
|                  |                   | Adjusted            |                       | −0.61 (0.60)                                  |
|                  | Ever established  | Unadjusted          | 3080 571              | 0.23 (0.44)                                   |
|                  |                   | Adjusted            |                       | 0.25 (0.42)                                   |
|                  | Current every day | Unadjusted          | 3477 64               | 0.02 (1.20)                                   |
|                  |                   | Adjusted            |                       | 0.05 (1.11)                                   |
| 2 to 3           | Current established | Unadjusted          | 3111 155              | −0.42 (0.73)                                  |
|                  |                   | Adjusted            |                       | −0.09 (0.69)                                  |
|                  | Ever established  | Unadjusted          | 2726 217              | 0.78 (0.64)                                   |
|                  |                   | Adjusted            |                       | 0.88 (0.61)                                   |
|                  | Current every day | Unadjusted          | 3469 56               | −0.15 (1.19)                                  |
|                  |                   | Adjusted            |                       | −0.30 (1.12)                                  |

SE – standard error. None of the differences were statistically significant at p<0.05

\[ a \] Adjusted for sex, age range, school grade, race, Hispanic origin, age of starting to smoke and ever use of other tobacco products

\[ b \] Adjusted for sex, age range, school grade, race, Hispanic origin and age of starting to smoke cigarettes

Table 3. Answering Q3 using PATH study: baseline cigarette consumption among baseline non e-cigarette users by subsequent e-cigarette use.
| Study | Reference(s) | Study title | Location | Study type | Period | Age | Number of smokers | Definition of e-cigarette use | Questions answered |
|-------|--------------|-------------|----------|------------|--------|-----|--------------------|-------------------------------|-------------------|
| 1     | Vardavas et al. (2015) | Eurobarometer | Europe | CS | 2012 | 15+ | 7,412 | E | Q1 |
| 2     | Farsalinos et al. (2016), Kulik et al. (2018), Farsalinos et al. (2017) | Eurobarometer | 28 countries | CS | 2014 | 15+ | 7,243 | C, E | Q1, Q2 |
| 3     | Laverty et al. (2018) | Eurobarometer | 28 countries | MCS | 2014, 17 | 15+ | ≈15,000 | CR, E | Q1 |
| 4     | Kralkova et al. (2013) | Health Barometer | 17 city study | CS | 2012 | M 33.5 | 1,738 | ER | Q1, Q2 |
| 5     | Andler et al. (2016) | Study of e-cigarette and tobacco shops | Munich, Germany | CS | 2014, 17 | 15-85 | 2,057 | CR | Q1, Q2 |
| 6     | Brown et al. (2014), Brose et al. (2015) | IPSS | Great Britain | P | 2014-15 | 18-73 | 208 | C | Q1 |
| 7     | Kilibarda et al. (2016) | Lifestyle survey | Serbia | CS | 2014 | 18-64 | 2,164 | C, E | Q1 |
| 8     | Hummel et al. (2015) | ITC | Netherlands | P | 2008-14 | 15+ | 1,820 | C, E | Q1 |
| 9     | Office for National Statistics (2017) | Opinions and lifestyle surveys | Great Britain | MCS | 2014-16 | 16+ | Large | C | Q1 |
| 10    | Prokopowicz et al. (2019) | Volunteer study | Sosnowiec, Poland | CS | 2017 | 19-39 | 57 | C | Q1 |
| 11    | Richardson et al. (2014) | Eight area cohort study | Minnesota, US | P | 2014 | 18-35 | 867 | C, E | Q1 |
| 12    | Choi & Forster (2014b) | Adolescent community cohort study | Minnesota, US | P | 2010-12 | 18+ | 1,567 | E | Q1 |
| 13    | Choi & Forster (2014a) | Three area survey | Charlotte, Denver, Topeka, US | CS | 2013 | 18-35 | 867 | C, E | Q1 |
| 14    | Biener et al. (2015) | American Indian study | Oklahoma, US | P | 2015-17 | 18+ | 367 | C, E | Q1 |
| 15    | LeVault et al. (2016) | Springfield survey | Oklahoma, US | CS | 2014 | 18+ | 200 | C | Q1 |
| Study | Reference(s) | Study title | Location | Study type | Period | Age | Number of smokers | Definition of e-cigarette use | Questions answered |
|-------|--------------|-------------|----------|------------|--------|-----|------------------|------------------------------|---------------------|
| 26    | Wang et al. (2018) | Health eHeart study | US | P | 2013-17 | 18+ | 2,207 | C | Q1 |
| 27    | Shi et al. (2016) | TUS-CPS 2010 cohort | US | P | 2010-11 | 18+ | 2,454 | E | Q1, Q2 |
| 28    | Levy et al. (2017) | TUS-CPS surveys | US | MCS | 2014-15 | 18+ | 20,350 | E, C, CR | Q1 |
| 29    | Pearson et al. (2015) | BecomeAnEX cessation trial | US | P | 2012-2013 | 18+ | 2,123 | C | Q1, Q2 |
| 30    | Olsson et al. (2019) | NESARC III | US | CS | 2012-13 | 18-35 | 3,487 | C (PY) | Q1 |
| 31    | Bloom et al. (2019) | SWEET | US | CS | ? | 18+ | 577 | C | Q1 |
| 32    | Jaber et al. (2018) | NHANES 2013-14 | US | CS | 2013-14 | 18+ | 1,049 | C | Q1 |
| 33    | Rostron et al. (2016) | NATS 2012-13 | US | CS | 2012-13 | 18+ | 4,867 | CR | Q1 |
| 34    | Chivers et al. (2016) | AMT users 2014 | US | CS | 2014 | 24-44 | 400 | CR | Q1 |
| 35    | English et al. (2018) | AMT users 2017 | US | CS | 2017 | 21+ | 245 | C | Q3 |
| 36    | Stein et al. (2018) | AMT users | US | CS | ? | 18+ | 396 | C | Q1 |
| 37    | Kalkhoran et al. (2015) Grana et al. (2014) | GFK 2011 | US | P | 2011-12 | 18+ | 1,324 | C | Q1, Q2 |
| 38    | Wackowski et al. (2016) | GFK 2014 | US | CS | 2014 | 18+ | 519 | C, E | Q1 |
| 39    | Zhuang et al. (2016) | GFK 2012 | US | P | 2012-14 | 18+ | 2,028 | C | Q1 |
| 40    | Rutten et al. (2015) | GFK 2014 | US | CS | 2014 | 18+ | 2,254 | C | Q2 |
| 41    | Seto et al. (2016) | Telephone survey | Hawaii, US | CS | 2014 | 18+ | ? | E | Q2 |
| 42    | Twyman et al. (2016) | Disadvantaged smokers | New South Wales, Australia | CS | 2013-14 | 18+ | 369 | C | Q1 |
| 43    | Wu et al. (2018) | QTW | Hong Kong | P | 2014-15 | 18+ | 956 | E | Q1, Q2 |
| 44    | Etter & Bullen (2014) | Internet | Multiple | P | 2011-13 | 18+ | 273 | C | Q2 |
| 45    | Adkison et al. (2013) Chan et al. (2019) | ITC Four country survey | US, Canada, Australia, UK | P | 2008-16 | 18+ | 4,717 | C | Q1, Q2 |
| 46    | Sung (2018) | 6th Korea National Health and Nutrition Examination Survey | South Korea | CS | 2013-15 | 19+ | 2,782 | C | Q1 |

*a* CS = cross-sectional, MCS = multiple cross-sectional, P = prospective

*b* M = mean

*c* C = current, C (PY) = current (past year), E = ever, ER = ever regular, R = regular

*d* Q1 = Does CC differ between dual users and exclusive smokers?

Q2 = Does take-up of e-cigarettes affect time changes in CC?

Q3 = Does baseline CC differ by subsequent take-up of e-cigarettes?

*e* Not given but estimated from results for one survey

*f* Not given but around 2,000 households are interviewed per month

*g* 1,820 were interviewed in 2008, with 1,802 in 2010, 1,530 in 2013 and 1,550 in 2014. Note that in this cohort study, respondents are surveyed each year, with drop-outs replenished by inviting new smokers

*h* Date not stated. 2017 assumes the study was completed the year before publication

*i* 46% were aged under 21

*j* The respondents were stated to be “Mainly from the United States” with no further details given

*k* Number of smokers not stated, the total participants numbered 937

*l* 34% of respondents from US, 24% France, 8% UK, 6% Switzerland, 28% other countries
assumed that all the products contained nicotine, no study stating otherwise, though many did not give details.

Table 4 also gives references for the publications considered in our analyses. For some studies there were additional publications which provided no useful extra results to those cited: Study 2 (Laverty et al., 2018), study 5 (Andler et al., 2015; INPES, 2014), study 9 (Office for National Statistics, 2016), study 10 (Nelson et al., 2015), and study 27 (Shi et al., 2015).

Results related to Q1
Table 5 summarizes the results from the 39 studies that presented evidence comparing CC in dual users with that in exclusive cigarette smokers. Of these studies, the evidence related to current e-cigarette use in 25, to ever e-cigarette use in eight and to both current and ever use in six. In some studies, results were presented in terms of the distribution of the subjects by broad categories of cigarette consumption and (as described in the footnotes to Table 5) the overall mean CC could only be estimated by making assumptions about the mean CC for each category.

Of the 30 studies providing estimates relating to current e-cigarette use, two studies (18 and 22) merely stated there was a lack of association between e-cigarette use and amount smoked. In the other studies, estimates of the difference in CC between dual users and exclusive e-cigarette use could be derived, with two being from study 38 at two different time points. The evidence was conflicting, with 11 estimates showing a lower CC in dual users and 18 a higher CC. Omitting the estimate from study 29 (Pearson et al., 2015) (as it only related to e-cigarette use as a cessation aid) and the earlier estimate from study 37 (Grana et al., 2014) to avoid double-counting, the unweighted mean difference was estimated as +0.03 cigarettes per day reduction (Standard error [SE] 0.36). While there was some evidence of a reduction in the 11 estimates from Europe (1.04 cigarettes per day reduction, standard error [SE] 0.72), the 14 estimates from the USA did not confirm this (0.56 increase, SE 0.29).

The 14 studies providing estimates relating to ever e-cigarette use were equally inconsistent, with four of the ten estimated differences showing a reduction, and six an increase.

Results related to Q2
Our searches revealed 17 studies that presented evidence on whether cigarette-only smokers who become dual users change their CC. The top half of Table 6 summarizes results for five studies, all of prospective design, where dual use refers to current use and where changes are compared in those who remain exclusive cigarette smokers (“No No”) and those who become dual users (“No Yes”). All these studies present evidence that reductions in CC are significantly greater in dual users. The bottom half of Table 6 also presented evidence from a further eight studies (one prospective and seven cross-sectional), where changes were only recorded in those who became dual users. Of these, seven showed large reductions, which seem likely to be substantially greater than in those remaining exclusive cigarette smokers, although lack of the relevant data prevents this from being tested, while the other (study 41 (Seto et al., 2016)) showed a smaller reduction. The evidence from these 13 studies clearly indicates that becoming a current e-cigarette user leads to a reduction in CC.

The other four studies provided less useful results. Study 22 (Choi & Forster, 2014a) reported that changes in CC were almost identical between those who had never used e-cigarettes and those who had used e-cigarettes for at least one day in the past 30 days at baseline, after adjustment for demographics and baseline CC. These results neither relate to a proper definition of current e-cigarette use, nor to taking up e-cigarettes between baseline and follow-up. Study 27 (Shi et al., 2016) concluded that “among early adopters, ever-use of first generation e-cigarettes to aid quitting cigarette smoking was not associated with improved cessation or with reduced CC, even among heavier smokers” but the basis for this conclusion is most unclear, with no formal statistical analysis described and it being unclear when the e-cigarette use occurred, and whether those who quit during follow-up were excluded. Study 37 (Grana et al., 2014) reported that “e-cigarette use at baseline was not associated with a change in cigarette consumption, controlled for baseline cigarette consumption”. In study 43 (Wu et al., 2015), no difference was seen between exclusive cigarette smokers and dual users at six months follow-up in individuals who continued to smoke. These analyses related to ever rather than current use of e-cigarettes.

It can also be noted that, as studies restricted to dual users were excluded (see Literature searches, rejection reason 7), the results shown in the bottom half of Table 6 may not be comprehensive.

Results related to Q3
Our searches revealed only three published studies that presented evidence relevant to whether CC in exclusive cigarette smokers differed according to whether they later used e-cigarettes. Study 5 (Andler et al., 2016), a cross-sectional study which involved 4,752 current smokers of whom 759 also currently used e-cigarettes, noted that, before they started to vape, these individuals smoked 21 cigarettes per day as compared to 11.3 in those who continued to smoke. Though the results presented did not allow precise estimation of the difference in CC between smokers according to whether they later used e-cigarettes, the results clearly suggested that heavier smokers were more likely to start vaping. Study 35 (English et al., 2018), a cross-sectional study involving 245 current smokers, of whom 103 also currently used e-cigarettes, reported that, for each additional cigarette smoked per day prior to using e-cigarettes, individuals were 4.0% (p = 0.001) more likely to use e-cigarettes. Study 45 (Chan et al., 2019), a prospective study, presented results from a logistic regression predicting uptake of vaping in 3,797 smokers. After adjustment for a range of smoking-related and demographic variables, they reported an increasing likelihood of uptake with increasing cigarette consumption, with ORs of 1.13 (95%
Table 5. Results relating to Q1 from 38 published studies other than PATH.

| Study | Publication | Number of smokers | CC Dual | CC Cigs only | Difference | Estimated |
|-------|-------------|--------------------|---------|--------------|------------|-----------|
| 2     | Kulik et al. (2018) | Total 6,865 | 15.6 | 14.4 | +1.2 | Given |
| 6     | Pasquereau et al. (2017) | 252 | 8.7 | 10.0 | −1.3 | Estimated |
| 7     | Rüther et al. (2016) | 94 | 12.3 | 15.7 | −3.4 | Estimated |
| 8     | Brown et al. (2014) | 775 | 13.9 | 12.6 | +1.3 | Given |
| 9     | Office for National Statistics (2017) | Large | 10.9 | 11.5 | −0.6 | Estimated |
| 10    | Shahab et al. (2017) | 36 | 11.9 | 13.9 | −2.0 | Given |
| 12    | Manzoli et al. (2015) | 232 | 14.9 | 14.1 | +0.8 | Given |
| 14    | Hummel et al. (2015) | ? | 15.0 | 16.5 | −1.5 | Estimated |
| 15    | Prokopowicz et al. (2019) | 29 | 8.8 | 14.7 | −5.9 | Given |
| 16    | Klibarda et al. (2016) | 106 | 15.8 | 18.0 | −2.2 | Given |
| 17    | Hedman et al. (2018) | 339 | 12.3 | 10.1 | +2.2 | Estimated |
| 18    | Doupcheva et al. (2013) | 25 | 1,064 | - | - | “No statistically significant difference between vapers and non-vapers ...” |
| 19    | Zavala-Arciniega et al. (2018) | 151 | 11.5 | 9.8 | +1.7 | Estimated |
| 21    | Richardson et al. (2014) | Total 1,270 | - | - | +2.4 | Given |
| 22    | Choi & Forster (2014a) | - | - | - | - | “More frequent use of e-cigarettes does not ... reduce cigarette consumption” |
| 24    | Comiford et al. (2018) | 59 | 17.8 | 17.4 | +0.4 | Estimated |
| 25    | LeVaul et al. (2016) | 121 | 12.5 | 13.5 | −1.0 | Estimated |
| 26    | Wang et al. (2018) | 514 | 10.0 | 9.0 | +1.0 | Given |
| 28    | Levy et al. (2017) | 2,153 | 13.5 | 13.8 | −0.3 | Estimated |
| 29    | Pearson et al. (2015) | 672 | 17 | 15 | +2.0 | Given |
| 30    | Ofsson et al. (2019) | 571 | 13.2 | 12.0 | +1.2 | Given |
| 31    | Bloon et al. (2019) | 158 | 17.8 | 16.6 | +1.2 | Given |
| 32    | Jaber et al. (2018) | 64 | 9.9 | 11.6 | −1.7 | Given |
| 33    | Rostron et al. (2016) | 904 | 15.6 | 15.8 | −0.2 | Estimated |
| 34    | Chivers et al. (2016) | 233 | 13.6 | 12.5 | +1.3 | Given |
| 36    | Stein et al. (2018) | 198 | 15.8 | 15.7 | +0.1 | Given |
| 37    | Kalkhoran et al. (2015) | 104 | 14.0 | 12.9 | +1.1 | Estimated |
| 38    | Wackowski et al. (2016) | 97 | 10.7 | 11.6 | −0.9 | Estimated |
| 39    | Zhuang et al. (2016) | 528 | 15.3 | 14.2 | +0.1 | Estimated |
| 42    | Twyman et al. (2016) | 103 | 17.7 | 15.2 | +2.5 | Given |
| 46    | Sung (2018) | 209 | 16.6 | 17.4 | −0.8 | Estimated |
| Study | Publication | Number of smokers | CC Dual Cigs only | CC Dual Cigs only | Difference* or given |
|-------|-------------|-------------------|------------------|------------------|---------------------|
| 1     | Vardavas et al. (2015) | 1,505 | 5,907 | Adjusted ORs (95% CI) for ever e-cigarette use vs ≤5 cigs/day were 1.53 (1.10 to 2.13), 2.07 (1.52 to 2.81) and 1.48 (0.97 to 2.27) for 6-10, 11-20 and 21+ cigs/day |
| 3     | Laverty et al. (2018) | Total 6,153 | Adjusted ORs (95% CI) for ever e-cigarette use vs <10 cigs/day and 26.59 (23.12 to 30.59) for 10+ cigs/day |
| 4     | Kralikova et al. (2013) | 863 | 868 | 13 | 14 | −1* | Given |
| 9     | Office for National Statistics (2017) | Large | 12.5 | 10.9 | −1.6 | Estimateddb |
| 14    | Hummel et al. (2015) | ? | ? | 19.7 | 16.5 | +3.2 | Estimatedda |
| 19    | Zavala-Arciniega et al. (2018) | 542 | 2,190 | 10.8 | 9.7 | +1.1 | Estimatedda |
| 20    | Pokhrel et al. (2013) | 202 | 1,365 | 17.8 | 18.3 | −0.5 | Given |
| 23    | Biener et al. (2015) | - | - | “…. does not …. reduce cigarette consumption”. Level of daily smoking was not a significant predictor of e-cigarette trial or use in the past month |
| 24    | Comiford et al. (2018) | 233 | 134 | 18.0 | 16.6 | +1.4 NS | Estimatedda |
| 27    | Shi et al. (2016) | Total 2,454 | 15.1% of smokers of 15+ cigs/day and 9.9% of smokers of <15 cigs/day had ever used e-cigarettes |
| 28    | Levy et al. (2017) | 7,695 | 12,655 | 14.2 | 13.5 | +0.7 | Estimatedda |
| 38    | Wackowski et al. (2016) | 294 | 225 | 11.4 | 11.3 | +0.1 | Estimatedda |
| 43    | Wu et al. (2018) | 163 | 793 | 19+ | 15+ | +4+++ | Given |
| 45    | Chan et al. (2019) | Total 3,797 | Adjusted ORs (95% CI) for ever e-cigarette use vs 0-10 cigs/day were 1.13 (0.95-1.35), 1.41 (1.12-1.78) and 1.69 (1.19-2.39) for 11-20, 21-30 and 31+ cigs/day |

* *, - p<0.05; **, - p<0.01; ***, - p<0.001 NS p≥0.05

Where a code is not given, the significance level was not reported.

d Estimated assuming midpoints of 5, 15 and 30 cigs/day for 0-10, 11-20 and 21+ cigs/day
d Estimated assuming midpoints of 5, 15, 25 and 40 cigs/day for 0-10, 11-20, 21-30 and 31 cigs/day
d Estimated from separate data for current, former and never e-cigarette users
d Estimated from adjusted ORs for forced entry analysis assuming midpoints of 5, 13, 18 and 30 cigs/day for 10 or fewer, 11-15, 16-20 and more than 20

e Estimated assuming midpoints of 2.5, 10 and 25 cigs/day for <5, 5-14 and 15+ cigs/day
e Estimated from adjusted ORs assuming midpoints of 2 and 15 cigs/day for <5 and 5+ cigs/day
e Estimated assuming midpoints of 10 and 30 cigs/day for <1, 1+ packs/day
e Estimated assuming midpoints of 5.5 and 21 cigs/day for <11, 11+ cigs/day
f Results relate to use in the last 30 days
g Estimated assuming midpoints of 2.5, 10, 20 and 35 cigs/day for 1-4, 5-14, 15-24 and 25+ cigs/day
h Median consumption
i E-cigarette users were those using them to quit cigarettes
j Estimated from figure combining results for cigs + ecigs and cigs + cigars + ecigs into dual users
k Estimated assuming midpoints of 2.5, 8, 15 and 30 cigs/day for <5, 6-10, 11-20 and 21+ cigs/day
l Estimated assuming midpoints of 5 and 20 cigs/day for 10 or fewer and >10 cigs/day
m Estimated assuming midpoints of 8 and 25 cigs/day for 1-15 and >15 cigs/day
n Estimated assuming midpoints of 5 and 20 cigs/day for light (<10) and heavy (>10) cigs/day
Discussion

Based on the analyses of the PATH study, there was no evidence from the analysis of Q1 (Table 1) that cigarette smokers who were also current or ever established e-cigarette users had a lower CC than exclusive cigarette smokers. However, cigarette smokers who were also current every day e-cigarette users did have a lower CC by about two to three cigarettes per day. This is consistent with CC in dual users being more likely to be affected in adults who use e-cigarettes more often, occasional e-cigarette use being less likely to affect cigarette smoking habits. These results, based on cross-sectional analysis, are less relevant to the effect that e-cigarette use might have on CC than those based on changes over time (Q2). Here again the results for every day e-cigarette use (Table 2) showed more evidence of an effect, with those becoming dual users consistently decreasing CC and those switching from dual use to exclusive smoking consistently increasing their CC, although only the second result was statistically significant. It is possible that those who decided

Table 6. Results relating to Q2 from the other studies.

| Study | Publication | Numbers | “No"  | “Yes" | Finding |
|-------|-------------|---------|-------|-------|---------|
| 6     | Pasquereau et al. (2017) | 1,805   | 257   |       | Adjusted OR 2.6 (95% CI 1.8 to 3.8) for reduction of cigarette consumption of 50% or more in those taking up e-cigarettes |
| 8     | Brose et al. (2015) | 769     | 72    |       | Adjusted OR 2.49 (95% CI 1.14 to 5.45) for reduction of cigarette consumption of 50% or more in those taking up e-cigarettes |
| 12    | Manzoli et al. (2017)c | 369     | 165   |       | Mean reductions in cigarette consumption (SE) are 1.6 (6.4) and 5.3 (3.3), p = 0.2. 14.1% and 66.7% reduced by 50% or more, p<0.001 |
| 29    | Pearson et al. (2015) | <1,451a | <672b |       | Mean reductions in cigarette consumption (SE) are 5.1 (7.9) and 7.1 (8.3), p = 0.05 |
| 45    | Adkison et al. (2013) | 5,765   | 174   |       | Mean reductions in cigarette consumption are 3.78 and 1.85, p<0.05 |

Studies comparing changes in CC in those becoming or not becoming current e-cigarette users

Studies reporting changes in CC only in those becoming current dual users

a Adjusted for education, income, occupational status, socio-professional category and size of urban unit
b Adjusted for age, sex, education, follow-up NRT use and baseline strengths of urge to smoke
c Results based on 24-month follow-up. Some earlier results are also available for 12-month follow-up (Manzoli et al., 2015)
d Numbers include those who quit during follow-up
e Estimated from data provided
f The 82% who reduced had a mean reduction of 8.9 cigarettes per day, so, assuming the remaining 18% had no reduction, the mean reduction would be 7.3 cigarettes per day
g The terms “drastically” and “slightly” were undefined
h The terms “substantially” and “slightly” were undefined

0.95-1.35), 1.41 (1.12-1.78) and 1.69 (1.19-2.39) for smokers of 11-20, 21-30 and 31+ cigarettes per day, as compared to 0-10 cigarettes per day.
to take up e-cigarettes might have had a different baseline CC than those who continued to smoke cigarettes exclusively (Q3), but our analyses (Table 3) showed no evidence of this.

Two limitations of our analyses should be noted. One is the small number of cigarette smokers who were also current every day e-cigarette users, ranging from about 50 to 70 in the relevant analyses. The other is the weakness of the CC data itself. While we have made our best attempt to correct obvious errors in the data, some doubts must remain about the validity of our correction.

Two previous publications (Berry et al., 2019; Buu et al., 2018) have presented results from the PATH study using data from Waves 1 and 2, neither making any mention of correcting the clearly erroneous CC data. Buu et al. (2018) restricted attention to those who, at Wave 1, had in the past 12 months smoked cigarettes and not used e-cigarettes, and who at Waves 1 and 2 had not used tobacco products other than cigarettes or e-cigarettes. Comparisons were made between those who had or had not used e-cigarettes some day or every day in the past 30 days. The authors reported that a higher frequency of e-cigarette use was associated with a lower CC after controlling for baseline CC and other confounding variables. This finding, though based on different statistical procedures, seems consistent with our finding for Q2.

Based on current cigarette smokers aged 25+ years who were not current e-cigarette users at Wave 1, Berry et al. (2019) presented odds ratios (ORs) and 95% confidence intervals (CIs), adjusted for 12 potential confounding variables, relating at least a 50% reduction in CC between Waves 1 and 2 to new e-cigarette use at Wave 2. While no material difference was noted for experimental e-cigarette use (OR 1.08, 95% CI 0.78 to 1.48) or for some day e-cigarette use (OR 1.00, 95% CI 0.58 to 1.74), a highly significant (p<0.001) effect was noted for every day e-cigarette use (OR 5.70, 95% CI 3.47 to 9.35). Their analyses defined current smokers as smoking every day or some days, whereas ours restricted attention to every day smokers. Nevertheless, though differently expressed, their analyses support our findings for Q2, with those switching to every day e-cigarette use reducing their cigarette consumption.

As regards Q1, the other published studies identified by the literature search (see Table 5) provide no clear evidence of a relationship of current or ever e-cigarette use to CC. The lack of consistent association seen in the literature aligns with the findings from the PATH study shown in Table 1 for current and ever established e-cigarette use, but not with the results for current every day use. A problem is that very few of the reviewed studies provided results for current regular e-cigarette use, which may be considered comparable to the results for every day e-cigarette use from the PATH study. Also many of the studies only presented results for grouped cigarette consumption, making it difficult to accurately quantify CC.

The results from the other published studies regarding Q2 shown in Table 6 clearly demonstrate that becoming a current e-cigarette user is associated with a reduction in CC. While this conclusion is consistent with that from the PATH study, the actual decrease in CC associated with uptake of e-cigarettes cannot be directly compared, as few of the 13 studies actually presented estimates of the mean reduction, with others simply giving the numbers reducing (or increasing) consumption, or presenting odds ratios for the probability of reducing cigarette consumption by 50% or more, and only five allowing the reduction to be tested against a suitable control group of continuing exclusive smokers.

As noted above, only three of the other published studies provided evidence relating to Q3. While these results are all consistent with those who choose to start using e-cigarettes being heavier smokers than those who do not choose to do so, our analyses of the PATH study data found no clear relationship. Given the limited number of studies, more evidence is clearly needed to answer Q3.

Assessment of the overall evidence is unclear, partly due to the between-study differences in how e-cigarette use is quantified, and how the results are presented. Given the quite clear evidence from the analyses addressing Q2 that those taking up e-cigarettes and becoming dual users do reduce their CC, the failure to find any very clear difference in CC between current dual users and exclusive cigarette smokers from the analyses of Q1 would suggest that smokers who subsequently take up e-cigarettes had somewhat higher CC to start with. While the analyses at Q3 are rather limited they do tend to support this view.

Although the overall evidence is somewhat difficult to interpret, it appears that exclusive cigarette smokers who become dual users tend to decrease their CC, especially if they use e-cigarettes regularly. The level of reduction in CC is generally fairly modest, and seemingly inconsistent with the assumption that those becoming dual users replace half their cigarettes with e-cigarettes. However, given the much lower claimed disease risks of e-cigarettes relative to cigarettes (Nutt et al., 2014), it seems quite possible that smokers who become dual users will reduce their disease risk to some extent.

Overall, it can be concluded that there is clear evidence that exclusive cigarette smokers who become dual users of cigarettes and e-cigarettes reduce their daily CC. The reduction seen is quite modest in most studies (e.g. two or three cigarettes per day), though some studies show greater reductions. The fact that cross-sectional analyses show little difference in CC between dual users and exclusive cigarette smokers may be due to those who take up e-cigarettes tending to be somewhat heavier cigarette smokers to start with, though more evidence is needed to confirm this. Obtaining accurate overall estimates is made difficult by the different way that studies present their results.
Harmonization in the way data on patterns of use of different tobacco products are collected and analysed across studies is warranted.

Data availability

Source data

PATH study data: National Addiction & HIV Data Archive Program: Population Assessment of Tobacco and Health (PATH) Study [United States] Public-Use Files (ICPSR 36498). https://www.icpsr.umich.edu/icpsrweb/NAHDAP/studies/36498/
versions/V9 (United States Department of Health and Human Services (USDHHS)).

The data are available under the Terms of Use as set out by ICPSR, which can be accessed when users start the process of downloading the data.

Extended data

Open Science Framework: Cigarette consumption in adult dual users of cigarettes and e-cigarettes. A review of the evidence, including new results from the PATH study. https://doi.org/10.17605/OSF.IO/QHBZN (Lee, 2020).

This project contains the following extended data file:

- CC in dual users - additional file (DOCX).

Extended data are available under the terms of the Creative Commons Zero “No rights reserved” data waiver (CC0 1.0 Public domain dedication).

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**Summary:** The authors conducted secondary analysis of cross-sectional and longitudinal PATH data to compare cigarette consumptions among dual users of cigarettes and e-cigarettes. The authors also present a review of published literature on this topic.

These reviewers have the following comments.

1. The authors describe e-cigarettes as “reduced-risk tobacco products (RRP)”. While there is no doubt that e-cigs have considerably lower exposure to many of the HPHCs compared to combustible cigarettes and therefore present lower risks relative to cigarettes, the evidence is still emerging regarding these products. The authors should therefore consider identifying these products as “Potential Reduced-Risk Products” (PRRP).

2. While we understand that recall bias may complicate inferences on tobacco product use history and the “correction” applied by the authors seems reasonable, the authors should consider including a results table for descriptive statistics (with and without correction) in the Supplement, to allow the reader judge for themselves regarding impact of this correction.

3. The authors conclude that “smokers who become duals users will reduce their disease risk to some extent”. This is an extremely broad generalization, particularly given the authors own conclusion that the reduction in cigarettes is “fairly modest”. There is no empirical evidence to support this statement of risk reduction among the entire category of dual users, even to “some extent”. A recent report indicates that dual users are a very heterogenous group[ref-1][ref-2]. Indeed, established every day frequent e-cigarette users may smoke far fewer cigarettes than current smokers thereby substantially reducing exposure to many of the HPHCs. This may lead to lowering of disease risks. In order to
achieve the optimum outcome of reducing smoking related diseases, adult smokers must switch completely from cigarettes to e-cigs. We recommend that the authors either delete or modify the statement with appropriate caveats.

4. There are several points for consideration to refine the methodology used in this manuscript:

1. In the method section, the authors describe that the analysis is limited to every day cigarette smokers. The authors described “all the analyses were weighted, based on weighting factors for Wave 1”. In PATH user guide (Section 5), there are various types of weights. It is not clear whether the cross-sectional analysis (Q1) was conducted separately using cross-sectional weights of each wave to ensure the representativeness of the results. Longitudinal analysis should be conducted using longitudinal weights. In this case, wave 3 weights should be applied to answer research questions 2 and 3. The authors must clearly specify which weight was used for each analysis (Q1-Q3).

2. The data is limited to ‘current everyday cigarette smokers at each Wave with data available on CC’. As reported by Borland et. al. (2019)[ref-3] and Smith et al. (2021)[ref-1] cigarette consumption differs significantly between every day and some day cigarette smokers and different segment of dual users. To obtain a complete picture of the current cigarette smoker population, the authors should consider including some day smokers in the analysis. This group more likely represents a larger proportion of dual users and provides a more comprehensive view of the cigarette consumption data for dual users. We note that indeed, there are cigarette consumption data in PATH for some day smokers.

3. To answer Q3, the cigarette consumption was “compared in those who did or did not become dual users”. However, since Q3 is asking “is baseline consumption related to later initiation of e-cigarettes”. A logistic regression model with e-cigarette initiation as the outcome measure and cigarette consumption being the covariate would be more appropriate to answer Q3.

4. Based on the current analysis description for Q3, the analysis will compare exclusive cigarette smokers who did or did not become dual users. A clearer description of ‘dual user’ needs to be given as it is shown in Table 3 there are three types of ‘Definition of Use’. Does the heading ‘Became users’ in the ‘Ever Established’ row mean exclusive daily smokers who became ever established users of e-cigarette? Please clarify.

5. The authors should clearly describe if R survey package is used in the analysis. While the R-program is appropriate to conduct statistical analysis, R survey package allows the researcher to utilize the full-sample weight, variance estimation method, BRR-Fay replicate weights, and that Fay's factor are correctly specified (See PATH User Guide, Appendix B for example R program code). The authors must specify whether replicate weights and Fay's correction factor were used in current analyses.

6. Authors state that “nine predictor variables [were] selected, using a forward stepwise approach, including variables significant at p<0.05”. It is not clear what variables were considered and the rationale for selection of the variables... The age range category “55+ years” for the variable ‘age range when first started smoking cigarettes every day’ should not be included as the data analysis is limited to 18 to 54 years.

7. Authors only included respondents “aged 18 to 54 years at Wave 1 (as e-cigarette use proved to be very uncommon in those aged 55+ years”. A quick analysis revealed that
by excluding individuals aged 55 or older, around 14% of the sample size is excluded among both current established and former established e-cigarette users at Wave 1. This phrase “(as e-cigarette use proved to be very uncommon in those aged 55+ years)” should be deleted since the data does not appear to support the statement.

1. In the result section, the table captions should include more detail descriptions and definitions. For all result tables, the phrase ‘among every day smokers’ should be added if the analysis is only conducted among every day smokers. Does the table footnote ‘NS’ mean ‘not significant’? If yes, the corresponding footnote should be ‘p>0.05’ instead of ‘p<=0.05’. The ‘dual use’ term becomes very confusing when it is corresponding to three meanings (i.e., current establish e-cigarette use, ever established e-cigarette use and current every day e-cigarette use). The authors should be more precise.
   1. Table 1. Table caption should include ‘among every day smokers’ if the analysis is only conducted among every day smokers. There are three columns of ‘dual users’. The author needs to clarify the definitions of these three types of ‘dual users’.
   2. Table 2. The word ‘e-cigarette’ should be added to ‘current established use’, ‘ever established use’, and ‘current every day use’. The ‘No No’, ‘Yes Yes’, ‘No Yes’, ‘Yes No’ combinations should be clearly labeled with CS and ECIG to clearly identify the groups being considered.
   3. Table 3. The word “e-cigarette” should be specified in the ‘Definition of Use’ column. And the dual use needs to be clearly defined (see previous comments in the method section).

2. Literature review results
   1. Results related to Q2
      In the literature review section, some of the findings were drawn from studies with adolescent data. Five out of 13 studies (Table 6) referenced in the results include adolescent data. The authors should be consistent with the literature search criteria and either exclude studies on youth as that was considered out of scope for the review, modify their search criteria or provide a rationale regarding inclusion of only select publications with adolescent data.
   2. Results related to Q3.
      Based on Andler et al. 2016, the authors state that ‘heavier smokers were more likely to start vaping’. However, this does not accurately represent the results from the publication. Andler et al. 2016, state that “82 % of dual users reported that vaping had enabled them to reduce their cigarette consumption, with a mean reduction of 8.9 cigarettes per day. These individuals were initially heavy smokers, smoking 21 cigarettes per day on average (the mean overall among smokers was 11.3 in 2014).” Just because the participants in the study were heavy smokers that does not establish causality. Furthermore, Andler et al. 2016, included adolescents (age 15+) in their study. The authors should consider providing more context around the statement on heavy smokers.

Is the work clearly and accurately presented and does it cite the current literature?
Yes

Is the study design appropriate and is the work technically sound?
Partly

Are sufficient details of methods and analysis provided to allow replication by others?
If applicable, is the statistical analysis and its interpretation appropriate?
Yes

Are all the source data underlying the results available to ensure full reproducibility?
Yes

Are the conclusions drawn adequately supported by the results?
Partly

**Competing Interests:** The primary reviewer and co-reviewers are employed by Altria Client Services LLC.

**Reviewer Expertise:** Tobacco use behavior research.

We confirm that we have read this submission and believe that we have an appropriate level of expertise to confirm that it is of an acceptable scientific standard, however we have significant reservations, as outlined above.

**Author Response 29 Mar 2021**

**Peter Lee**, P.N.Lee Statistics and Computing Ltd, Sutton, UK

Reply to comments from Drs Wei, Lizhnyak and Sarkar on March 16 2021

We thank the three reviewers for the time they spent and their helpful comments. Our responses are shown in italics below each comment. We hope that the changes we have made to the paper will allow the reviewers to approve the revision without reservations.

Approved With Reservations

**Summary:** The authors conducted secondary analysis of cross-sectional and longitudinal PATH data to compare cigarette consumptions among dual users of cigarettes and e-cigarettes. The authors also present a review of published literature on this topic. These reviewers had the following comments.

- The authors describe e-cigarettes as “reduced-risk tobacco products (RRP)”. While there is no doubt that e-cigs have considerably lower exposure to many of the HPHCs compared to combustible cigarettes and therefore present lower risks relative to cigarettes, the evidence is still emerging regarding these products. The authors should therefore consider identifying these products as “Potential Reduced-Risk Products” (PRRP).

*We actually used the abbreviation RRTP. As the abbreviation is only used in the introduction section in a general context, not specific to e-cigarettes, we think it remains valid. Though we accept that there is currently no good epidemiological evidence relating to e-cigarettes, the statements we make in the paper concerning risk, which are few, are still valid. Thus in the discussion we only state “However, given the much lower claimed disease risks of e-cigarettes relative to cigarettes (Nutt et al., 2014), it seems possible that smokers who become dual users*
will reduce their disease risk to some extent,” and in the abstract we say “Given the much lower disease risk of e-cigarettes vs. cigarettes, smokers becoming dual users should somewhat reduce their disease risk.”

○ While we understand that recall bias may complicate inferences on tobacco product use history and the “correction” applied by the authors seems reasonable, the authors should consider including a results table for descriptive statistics (with and without correction) in the Supplement, to allow the reader judge for themselves regarding impact of this correction.

As specified in the paper, some of the reported cigarette values are clearly wrong and by a factor of 20. This is not due to recall bias, but to errors by the participant regarding the units used, for example wrongly recording they smoked 20 packs a day, when they meant 20 cigarettes a day. We would certainly not wish to present any results based on the uncorrected values and strongly recommend that no-one else does so.

○ The authors conclude that “smokers who become dual users will reduce their disease risk to some extent”. This is an extremely broad generalization, particularly given the authors own conclusion that the reduction in cigarettes is “fairly modest”. There is no empirical evidence to support this statement of risk reduction among the entire category of dual users, even to “some extent”. A recent report indicates that dual users are a very heterogenous group[ref-1][ref-2]. Indeed, established every day frequent e-cigarette users may smoke far fewer cigarettes than current smokers thereby substantially reducing exposure to many of the HPHCs. This may lead to lowering of disease risks. In order to achieve the optimum outcome of reducing smoking related diseases, adult smokers must switch completely from cigarettes to e-cigs. We recommend that the authors either delete or modify the statement with appropriate caveats.

It is important to note that the phrase cited by the reviewers, from the abstract, “smokers who become dual users will reduce their disease risk to some extent, is preceded by the conditional statement “Given the much lower disease risk of e-cigarettes vs. cigarettes”. This links back to our answer to point 1. Given that e-cigarettes are much less risky than current cigarettes (the generally accepted view) and given that smokers switching to dual use replace some of their cigarettes by e-cigarettes, then smokers who become dual users will indeed reduce their disease risk. The reviewers recommended that we modify the statement with an appropriate caveat, but we had already done so.

○ There are several points for consideration to refine the methodology used in this manuscript:
  1. In the methods section, the authors describe that the analysis is limited to every day cigarette smokers. The authors described “all the analyses were weighted, based on weighting factors for Wave 1”. In PATH user guide (Section 5), there are various types of weights. It is not clear whether the cross-sectional analysis (Q1) was conducted separately using cross-sectional weights of each wave to ensure the representativeness of the results. Longitudinal analysis should be conducted using longitudinal weights. In this case, wave 3 weights should be applied to answer research questions 2 and 3. The authors must clearly specify which weight was used for each analysis (Q1-Q3).

As the population analysed was restricted to those with relevant data at all three Waves, it seemed appropriate to us to use the Wave 1 person weights throughout both for simplicity and to ensure comparability between all our findings. Clearly, some of the analyses could have used
other weights, but we prefer to keep to what we did.

- The data is limited to ‘current everyday cigarette smokers at each Wave with data available on CC’. As reported by Borland et. al. (2019) and Smith et al. (2021) cigarette consumption differs significantly between every day and some day cigarette smokers and different segment of dual users. To obtain a complete picture of the current cigarette smoker population, the authors should consider including some day smokers in the analysis. This group more likely represents a larger proportion of dual users and provides a more comprehensive view of the cigarette consumption data for dual users. We note that indeed, there are cigarette consumption data in PATH for some day smokers.

The problem is that the reporting of cigarette consumption in the PATH study for someday smokers is not comparable to that for everyday smokers. Whereas everyday smokers were asked the average number of cigarettes now smoked per day, someday smokers were only asked about the average number of cigarettes smoked in the past 30 days on the days they were smoking, so we do not know their average daily consumption. While it is possible that some extra information might have been derived using also data for someday smokers (or different weights) we prefer to describe what we did, and let others report alternative analyses they might think are preferable.

- To answer Q3, the cigarette consumption was “compared in those who did or did not become dual users”. However, since Q3 is asking “is baseline consumption related to later initiation of e-cigarettes”. A logistic regression model with e-cigarette initiation as the outcome measure and cigarette consumption being the covariate would be more appropriate to answer Q3.

In response to this point, we ran analyses equivalent to those used to answer Q3, but using weighted logistic regression as suggested by the reviewers rather than weighted linear regression as we had done. The unadjusted results were identical, and the adjusted results gave such similar results that it seems unnecessary to revise our results.

- Based on the current analysis description for Q3, the analysis will compare exclusive cigarette smokers who did or did not become dual users. A clearer description of ‘dual user’ needs to be given as it is shown in Table 3 there are three types of ‘Definition of Use’. Does the heading ‘Became users’ in the ‘Ever Established’ row mean exclusive daily smokers who became ever established users of e-cigarette? Please clarify.

We have amended Table 3 to make it clear (in a footnote) that all the analyses concerned those who were current everyday cigarette smokers at all three waves, and to make it clear that the column “Definition of use” relates to use of e-cigarettes. The heading already makes it clear that we are concerned with baseline non e-cigarette users who became e-cigarette users at follow-up.

- The authors should clearly describe if R survey package is used in the analysis. While the R-program is appropriate to conduct statistical analysis, R survey package allows the researcher to utilize the full-sample weight, variance estimation method, BRR-Fay replicate weights, and that Fay’s factor are correctly specified (See PATH User Guide, Appendix B for example R program code). The authors must specify whether replicate weights and Fay’s correction factor were used in current analyses.

No we have not used this technique. We state in the methods section that “All the analyses were weighted, based on the weighting factors for Wave 1, and used weighted linear regression analyses”. We also state that: **Software used to analyse data from the PATH study.** Relevant data were transferred for analysis to a ROELEE database, and analysed using the ROELEE program (Release 59, Build 49). All these analyses could be run using the R-program (
https://www.r-project.org), using the "lm" function including the "weights=" option for weighted linear regression, and for stepwise regression using the "step" function specifying "method="forward" and test="F".

- Authors state that “nine predictor variables [were] selected, using a forward stepwise approach, including variables significant at p<0.05”. It is not clear what variables were considered and the rationale for selection of the variables...

The first paragraph of the methods section, sub-section 4, lists the nine predictor variables (sex, age, education, Hispanic origin, race, age starting cigarettes, alcohol, cocaine/crack, and other tobacco products. These were included into the final model, including the endpoint of interest, using forwards stepwise approach. These candidate variables were selected from a general consideration of the literature and not from stepwise regression from some longer list. The section of the methods says “Analyses were carried out with no adjustment for other variables and with adjustment for the other nine predictor variables selected, using a forward stepwise approach, including variables significant at p<0.05.” We have changed this sentence to read “Analyses were carried out with no adjustment for other variables and with adjustment for those of the nine predictor variables described above which were selected using a forward stepwise approach to include variables significant at p<0.05.”

- The age range category “55+ years” for the variable ‘age range when first started smoking cigarettes every day’ should not be included as the data analysis is limited to 18 to 54 years.

In fact the analyses included those aged 18 to 64 years, as we now make clear in the revised version of the paper.

- Authors only included respondents “aged 18 to 54 years at Wave 1 (as e-cigarette use proved to be very uncommon in those aged 55+ years”. A quick analysis revealed that by excluding individuals aged 55 or older, around 14% of the sample size is excluded among both current established and former established e-cigarette users at Wave 1. This phrase “(as e-cigarette use proved to be very uncommon in those aged 55+ years)” should be deleted since the data does not appear to support the statement.

We have amended the sentence for point 1 of paragraph 1 of the methods to read “Be aged 18 to 64 years at Wave 1, as preliminary analysis showed e-cigarette use to be rare at older ages. Thus, for example, only 9 out of 472 (1.9%) ever established users at Wave 1 were aged 65+ years, and only 18 out of 835 (2.2%) were.” We have also added 55-64 years to the categories of the age range in point 4 of paragraph 1.

- In the result section, the table captions should include more detail descriptions and definitions. For all result tables, the phrase ‘among every day smokers’ should be added if the analysis is only conducted among every day smokers. Does the table footnote ‘NS’ mean ‘not significant’? If yes, the corresponding footnote should be ‘p>0.05’ instead of ‘p<=0.05’.

We have corrected the relevant parts of footnotes in Tables 1 and 2 to read “NS (not significant) p >0.05”

- The ‘dual use’ term becomes very confusing when it is corresponding to three meanings (i.e., current establish e-cigarette use, ever established e-cigarette use and current every day e-cigarette use). The authors should be more precise.

Table 1. Table caption should include ‘among every day smokers’ if the analysis is only conducted among every day smokers.

We have amended the footnote of Table 1 to emphasise that the analyses are based on those who were everyday cigarette smokers at all three waves, though this is already stated in the Methods
There are three columns of ‘dual users’. The author needs to clarify the definitions of these three types of ‘dual users’.

We have amended the footnote of Table 1 to make it clearer that dual users are those who are both everyday cigarette smokers and e-cigarette users as defined in the column headings.

Table 2. The word ‘e-cigarette’ should be added to ‘current established use’, ‘ever established use’, and ‘current every day use’.

We have done this.

The ‘No No’, ‘Yes Yes’, ‘No Yes’, ‘Yes No’ combinations should be clearly labeled with CS and ECIG to clearly identify the groups being considered.

The labels ‘No No’ etc only apply to e-cigarette use, as all the individuals considered are everyday cigarette smokers at all three waves. This has been made clearer in the Table.

We have done this.

The word “dual” is not used. Each column is labelled by one of the three e-cigarette use categories, and the results are all within everyday cigarette smokers at all three waves, as has been made clear.

We have done this.

The dual use needs to be clearly defined (see previous comments in the method section).

Literature review results

1. Results related to Q2

In the literature review section, some of the findings were drawn from studies with adolescent data. Five out of 13 studies (Table 6) referenced in the results include adolescent data. The authors should be consistent with the literature search criteria and either exclude studies on youth as that was considered out of scope for the review, modify their search criteria or provide a rationale regarding inclusion of only select publications with adolescent data.

In the methods section, we have clarified the second reason for rejection as “Study only of adolescents, young adults (age 25 or under), or students”. We did not want to exclude studies that included adolescents as well as adults.

Results related to Q3.

Based on Andler et al. 2016, the authors state that ‘heavier smokers were more likely to start vaping’. However, this does not accurately represent the results from the publication. Andler et al. 2016, state that “82 % of dual users reported that vaping had enabled them to reduce their cigarette consumption, with a mean reduction of 8.9 cigarettes per day. These individuals were initially heavy smokers, smoking 21 cigarettes per day on average (the mean overall among smokers was 11.3 in 2014.” Just because the participants in the study were heavy smokers that does not establish causality. Furthermore, Andler et al. 2016, included adolescents (age 15+) in their study. The authors should consider providing more context around the statement on heavy smokers.

We have amended the statement “the results clearly suggested that heavier smokers were more likely to start vaping” to read “the results clearly suggested that vapers were more likely to be heavier smokers.

Competing Interests: No competing interests were disclosed.
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