Underage vaping spikes in the north of England

thebureauinvestigates.com/stories/2020-05-04/underage-vaping-spikes-in-north-of-england

More than a fifth of 15-year-olds in Yorkshire and the Humber vape, according to NHS figures that suggest a stark north-south divide in underage vaping.

The data – based on a survey of 13,000 children produced after inquiries by The Bureau – found that teenagers in Yorkshire were more than three times as likely to vape regularly as those in London.

Vaping has long been understood as a powerful tool in helping smokers quit, but with big tobacco companies spending billions getting e-cigarettes to market there is concern among campaigners and activists that these products could get a new generation hooked on nicotine. In the US more than one in four high school students regularly vape. In the UK, Public Health England has consistently said that relatively few teenagers vape. However the Bureau's research suggests that national data figures fail to recognise local hotspots.

The majority of 15-year-olds in Yorkshire and the Humber have tried e-cigarettes. Almost 10% vape at least once a week, and another 12% vape occasionally.

Separate figures produced by councils in Yorkshire highlighted the potential risk of teen vaping “hotspots” hidden in the national figures. A survey of 1,800 pupils aged 14 and 15 in Calderdale, West Yorkshire, found that 11% vaped at least once a week.

The northwest of England also has significantly higher underage vaping rates than the south, with 6% of 15-year-olds vaping at least once a week. In Blackpool, a local authority survey of children aged 14 and 15 revealed that 8% used e-cigarettes weekly and almost half had tried them.

In comparison, less than 3% of 15-year-olds in London and the southeast are regular vapers, according to the NHS-commissioned Smoking, Drinking and Drug Use Among Young People survey.

Public Health England – which recommends e-cigarettes, also known as vapes, as a tool for quitting smoking – insists that regular vaping among young people "remains low". Experts, however, believe the true figures could be higher than surveys suggest.

Dr Jennifer Quint, a reader in respiratory epidemiology at Imperial, fears that both the national and local surveys' methodology may be causing a massive under-reporting of youth vaping. "I suspect there are a lot of places that are just as bad … but you don't have the data to support it," she added.

More than a fifth of 15-year-olds regularly vape in Yorkshire and the Humber Andrew Yates/Getty Images

Paediatricians have previously said they fear the number of UK children who vape is being "grossly under-reported".

Dr Arif Rajpura, public health director for NHS Blackpool, said vaping could help smokers to quit, but is concerned that it could potentially lead to a new generation becoming addicted to nicotine. “We don’t want young people who have never smoked to start a new form of addiction,” he said.

Rachel Brown, a researcher at Cardiff University who has studied youth vaping, said: “The data shows young people who are trying e-cigarettes first are doing so because they found e-cigarettes easier to get hold of.”

Brown added: “Vaping is something that is very much centred around the social group. Where the experimentation happens it is almost always with peer groups and it is often the case that one person would turn up with a vape and everyone would try it.”

Vaping has divided the UK’s public health community. Professor Andrew Bush, a paediatrician specialising in respiratory disease, is concerned about the long-term impacts of vaping. “It took 30 or 40 years before we realised the damaging effects of tobacco,” he said. “We are sitting on a potential time bomb with all these kids getting hooked on this stuff.”

The northwest has significantly higher underage vaping rates than the south Getty Images

John Britton, a professor of epidemiology and director at the UK Centre for Tobacco & Alcohol Studies at the University of Nottingham, does not believe youth vaping is a critical issue.

The Medicines and Healthcare products Regulatory Agency has received reports of 26 serious respiratory reactions to vaping. In total, there have been five cases of patients dying from potentially e-cigarette-related illnesses. By contrast, smoking is believed to be responsible for 80,000 smoking deaths each year in England.

“Nobody I know in tobacco harm reduction has ever argued that vaping is safe,” said Britton. “We just argue that it is not as harmful as smoking and the level of risk is orders of magnitude less than smoking.”

When contacted by the Bureau about discrepancies in regional vaping data, Public Health England made no comment on that issue, but Martin Dockrell, the head of tobacco control, noted: “The research in the UK consistently finds some young people experiment but regular vaping among those who have never smoked is very rare and youth smoking rates continue to decline at an encouraging rate.”

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Header image: A young woman vaping. Credit: Getty Images

Are the UK's rules on e-cigarettes too lax?

FT ft.com/content/00706e4c-06dd-11ea-a984-fbbacad9e7dd

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Public Health England says vaping is 95 per cent safer than smoking © Getty Images/iStockphoto

If Adam Butler cannot have a regular nicotine hit, his mother describes his mood as "grim". The 15-year-old from London vapes an e-cigarette made by the popular brand Juul every half an hour. "It's the most simple and easy to use because you just buy them on eBay for cheap," he said.

Adam is among a small but growing number of UK teenagers who vape as a fashionable and, UK health authorities say, potentially safer alternative to smoking cigarettes.

Parents on the online forum Mumsnet said they would prefer their children to vape than smoke and Public Health England, a government body, says that vaping is 95 per cent safer than smoking. But this claim is based on 2014 data and scientists are increasingly rejecting the advice.

In recent years, more than 20 countries have banned vaping while others, including Canada and Australia, have tightened regulations.

The case of Ewan Fisher, a Nottinghamshire teenager who nearly died from a vaping-related illness reported in the Archives of Disease in Childhood, a medical journal, has prompted parents and campaigners to also ask whether vaping is as safe as PHE suggests.

Mr Fisher, now 19, took up vaping aged 16 and used e-cigarettes "fairly frequently". He was admitted to hospital soon afterwards with a fever and difficulty breathing, and had to use an artificial lung machine for three days to recover.

The article's key conclusion was that "we consider e-cigarettes as 'much safer than tobacco' at our peril".

The publicity around Mr Fisher's case follows more than 2,200 lung disease cases and 48 deaths associated with vaping in the US, which is expected to result in Washington banning fruity flavours in some e-cigarettes.

The cases have since been linked to vitamin E acetate, which is often used in vaping pods containing the cannabis compound THC.

PHE said that responses to the US outbreak risked spreading the "already widespread misunderstanding" that e-cigarettes were dangerous.

E-cigarettes work by creating a vapour from a liquid, which is then inhaled. The liquid usually contains nicotine, propylene glycol and glycerine — the latter two used for, among other things, antifreeze, sweetening food and flavourings.

> The flavourings may have been tested for safety as food additives but that tells us nothing about when they are combined with the chemicals that make up the vaping liquid

Euromonitor reported in July that total UK market value for heated tobacco, e-cigarettes and smokeless products such as oral nicotine pouches was £1.85bn in 2018 — an increase of 37 per cent on 2017.

In its most recent survey of youth vaping, in September, Action on Smoking and Health (Ash), a public health charity, found that since 2015, when it became illegal for under-18s to buy e-cigarettes or have an adult buy them on their behalf, the proportion of 11 to 18-year-olds that said they currently used an e-cigarette had doubled from 2.4 to 4.9 per cent.

The figures are much lower than in the US where 27.5 per cent of high school students use e-cigarettes, according to the government's Food and Drug Administration.

PHE's guidance that vaping is 95 per cent safer derives from research published in the journal European Addiction Research, which measured the relative harms of different nicotine-based products. The authors gave the research a caveat by saying that the experts used to survey the products were selected without "formal criterion" and that they were limited by a "lack of hard evidence for the harms of most products on most of the criteria".

Ash backs PHE and said Mr Fisher's case was rare, adding that vaping was "much less risky" than smoking, which kills 250 people a day in the UK.

But Martin McKee, professor of European public health at the London School of Hygiene and Tropical Medicine, said PHE's position was "indefensible" and that "England is way out of line with the rest of the world on this".

"There is not enough evidence that [e-cigarettes] are beneficial as a tool for quitting," he said. "The flavourings may have been tested for safety as food additives but that tells us nothing about when they are combined with the chemicals that make up the vaping liquid."

A study published last month by scientists at the University Medical Centre in Mainz, Germany, found that acrolein, a chemical produced when the liquid in e-cigarettes is vaporised, activated an enzyme that stiffens the arteries and increases heart rate.

PHE said that it kept evidence "under review" and that "UK regulated e-cigarettes carry a fraction of the risk of smoked tobacco".

Defenders of vaping say that teenagers in the UK are less likely to become addicted because EU regulations limit the amount of nicotine in a vape pod to 20mg. But Adam Butler, whose name has been changed, said that he and his friends get around this by buying pods online from the US, where there is no legal limit on the amount of nicotine.

Juul and the damage done to e-cigarettes

There has also been a move by the UK Vaping Industry Association, of which Juul is a member, to push for limits on nicotine to be removed post-Brexit.

Despite the backlash, London-headquartered tobacco company British American Tobacco announced last month that it would increase investment in e-cigarettes and extend a partnership with the Formula One motor racing team McLaren, first announced in February, to boost marketing of its reduced-risk products.

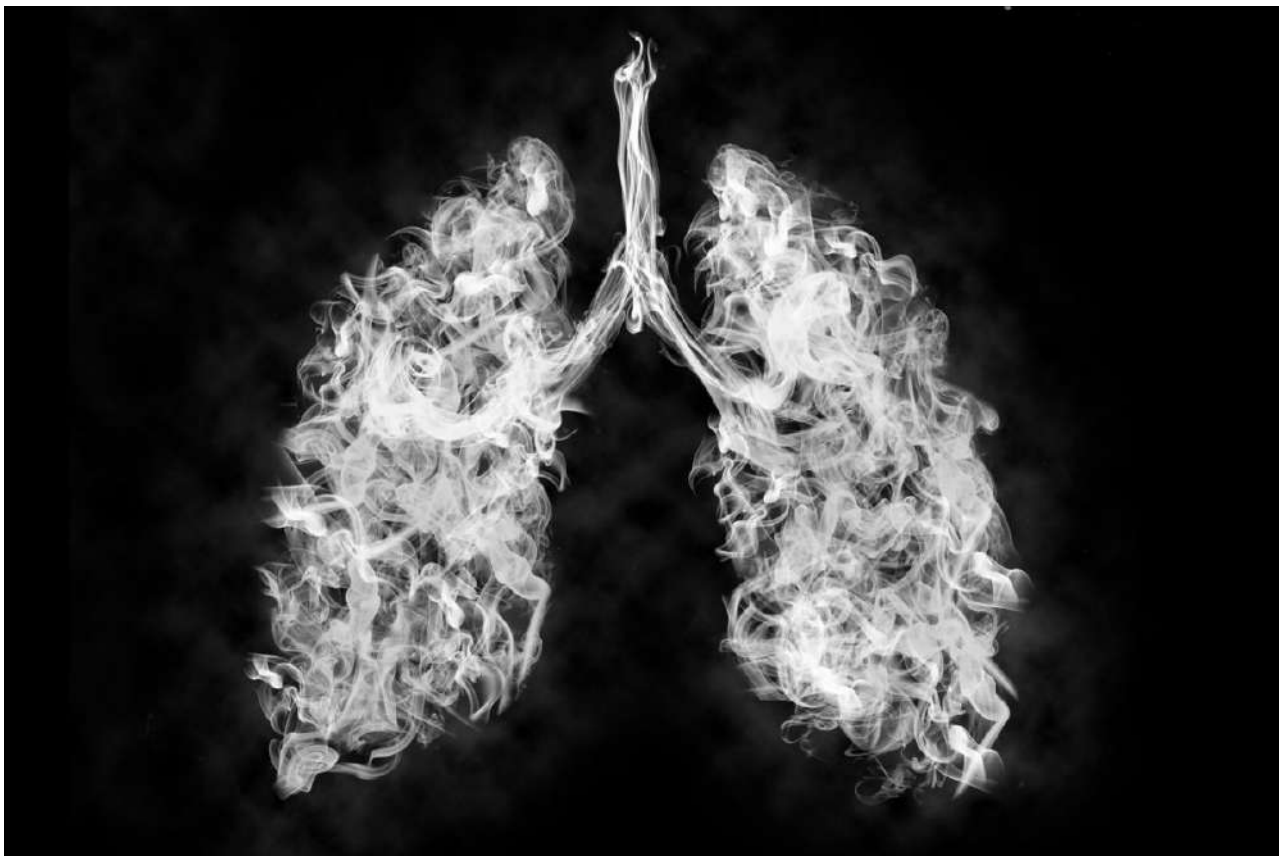
Kingsley Wheaton, BAT's chief marketing officer, denied claims it was targeting young people: "One of the reasons why Formula One was appealing was that it had a slightly higher age profile than some other options," he said.

This article has been amended to reflect that the US lung disease cases associated with vaping have been linked to vitamin E acetate

Using certain e-cigarette devices can lead to smoking more cigarettes

news.usc.edu/168364/vaping-combustive-cigarettes-smoking-usc-research

April 10, 2020



The type of device used for vaping may indicate higher or lower risk factors, with vape pen users generally using fewer cigarettes, says Jessica Barrington-Trimis. (Illustration/Pascal Kiszon, iStock)

A new USC study finds that teens who vape end up as heavier users of combustible cigarettes than smokers who never used e-cigarettes.

The study, which appears in Pediatrics, found that participants using a pen-like e-cigarette device smoked 2.83 times as many cigarettes as those who had never used e-cigarettes. Participants who used a modifiable e-cigarette device (often called "mods") smoked far more cigarettes — 8.38 times as many.

Mods have components that can be modified — such as the battery, temperature and power — which can change the relative amount of nicotine delivery and size of the vape cloud. Vape pens, however, generally deliver a consistent and often lower level of nicotine.

"The type of device that participants use may be an important risk factor for higher levels of cigarette smoking," said Jessica Barrington-Trimis, assistant professor of preventive medicine at the Keck School of Medicine of USC. "Device type may be an important target

for regulation to reduce the burden of tobacco-related disease stemming from e-cigarette use."

Vaping young adults are more likely to use combustible cigarettes

Barrington-Trimis and her colleagues collected data from 1,312 young adults participating in the Southern California Children's Health Study on specific characteristics of e-cigarette use from the past 30 days, between 2015 and 2016. The researchers followed up with the participants one year later.

They found that young adults who vaped were more likely to smoke combustible cigarettes after one year, and the amount they smoked depended on the e-cigarette device they used. Researchers concluded that young adults using modifiable e-cigarette devices smoked more than six times as many cigarettes a year later.

The researchers recommended that targeted regulation of mod e-cigarettes could help reduce heavy smoking patterns but added that additional research is needed to discover the reasons for these differences.

In addition to Barrington-Trimis, other study authors are Zhi Yang, Sara Schiff, Jennifer Unger, Tess Boley Cruz, Robert Urman, Junhan Cho, Adam M. Leventhal, Kiros Berhane and Rob McConnell, all of the Keck School; and Jonathan Samet of the University of Colorado.

The study was funded by the National Cancer Institute of the National Institutes of Health and the Food and Drug Administration Center for Tobacco Products (grants P50CA180905 and U54CA180905), the National Institute on Drug Abuse of the National Institutes of Health (grant K01DA042950) and the Tobacco-Related Disease Research Program (grant 27-IR-0034).

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E-cigarette Use and Subsequent Smoking Frequency Among Adolescents

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abstract

BACKGROUND AND OBJECTIVES: Electronic cigarette (e-cigarette) use is associated with cigarette initiation among adolescents. However, it is unclear whether e-cigarette use is associated with more frequent cigarette use after initiation. Also, the extent to which cigarette or dual cigarette and e-cigarette users transition to exclusive e-cigarette use or to the nonuse of either product is not yet known.

METHODS: Data were pooled from 3 prospective cohort studies in California and Connecticut (baseline: 2013–2014; follow-up: 2014–2016; *N* = 6258). Polytomous regression models were used to evaluate the association of baseline e-cigarette use (never or ever) with cigarette use frequency at follow-up (experimental: initiation but no past-30-day use; infrequent: 1–2 of the past 30 days; frequent: 3–5 or more of the past 30 days). Polytomous regression models were also used to evaluate transitions between baseline ever or past-30-day single or dual product use and past-30-day single or dual product use at follow-up.

RESULTS: Among baseline never smokers, e-cigarette users had greater odds of subsequent experimental (odds ratio [OR] = 4.58; 95% confidence interval [CI]: 3.56–5.88), infrequent (OR = 4.27; 95% CI: 2.75–6.62) or frequent (OR = 3.51; 95% CI: 1.97–6.24) cigarette use; the 3 OR estimates were not significantly different. Baseline past-30-day exclusive cigarette use was associated with higher odds at follow-up of exclusive cigarette or dual product use than of exclusive e-cigarette use.

CONCLUSIONS: Tobacco control policy to reduce adolescent use of both e-cigarettes and cigarettes is needed to prevent progression to more frequent tobacco use patterns and reduce combustible cigarette use (with or without concurrent e-cigarette use) to lessen the adverse public health impact of e-cigarettes.

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Dr Barrington-Trimis formulated the research question, interpreted the results, wrote and edited the manuscript, and is the guarantor; Ms Liu and Ms Mayer contributed to formulating the research question, conducted the analyses, interpreted the results, and edited the manuscript; Drs Kong and Cruz contributed to formulating the research question, the interpretation of results, and the editing of the manuscript; Drs Leventhal, Krishnan-Sarin, and McConnell designed the study (each cohort), collected data, contributed to formulating the research question and the interpretation of the results, and critically reviewed the manuscript; and all authors approved the final manuscript as submitted.

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WHAT'S KNOWN ON THIS SUBJECT: Electronic cigarette (e-cigarette) use is associated with cigarette initiation. However, it is unclear whether e-cigarette use is associated with more frequent cigarette use after initiation or whether adolescent cigarette or dual product users transition to exclusive e-cigarette use or nonuse.

WHAT THIS STUDY ADDS: Adolescent e-cigarette users appear to follow similar trajectories of cigarette smoking frequency as nonusers. Exclusive cigarette or dual product users are more likely to continue using cigarettes than to transition away from smoking to exclusive e-cigarette use or to nonuse.

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Recent studies of population trends in tobacco and alternative tobacco use prevalence among youth in the United States have revealed an indication that electronic cigarettes (e-cigarettes) are used by at least some youth who are unlikely to have started using tobacco products if e-cigarettes were unavailable.[1,2] Moreover, we[3–6] and others[7–20] have demonstrated that youth and young adults who have used e-cigarettes are more likely than those who have not used e-cigarettes to subsequently initiate combustible cigarette use, with a meta-analytic estimate of more than a threefold increase in the risk of subsequent cigarette initiation.[21]

Based in part on this evidence, in a 2016 report "E-cigarette Use among Youth and Young Adults," the Surgeon General concluded that e-cigarette use in this population is a public health concern.[22] However, others have suggested that this conclusion may be premature if e-cigarette users are disproportionately more likely to be merely experimenting temporarily with cigarettes and are unlikely to progress to more frequent smoking.[23] Because e-cigarettes have gained popularity only recently and the progression from cigarette initiation to regular use typically transpires over several years,[24–28] it could be argued that researchers in studies to date showing a risk of subsequent cigarette experimentation among e-cigarette users may not have followed e-cigarette users long enough or in sample sizes large enough to assess the risk of progression to regular smoking.

Another key question regarding the public health impact of the high e-cigarette use prevalence among youth and young adults is whether e-cigarettes facilitate smoking cessation. Although there has been considerable study of the potential for e-cigarettes to be a cigarette smoking cessation aid in adults,[29–31] there has been little study of transitions from cigarette or multiple tobacco product use to the exclusive use of e-cigarettes (or transition to the nonuse of cigarettes or e-cigarettes) among youth. We reported in an earlier publication that ever cigarette use was associated with a subsequent onset of e-cigarette use in adolescents.[3] A separate study revealed that past-30-day cigarette use was not associated with subsequent past-30-day e-cigarette use across 3 annual waves of data in adolescents.[16] Researchers in each of these studies have evaluated the use of cigarettes and e-cigarettes as separate variables, which cannot be used to distinguish whether the association of combustible cigarette use with subsequent e-cigarette use reflects youth who quit smoking and have completely transitioned to exclusive e-cigarette use or youth who are now dual product users of both cigarettes and e-cigarettes. Most youth do not use e-cigarettes to quit smoking; data from the National Youth Tobacco Survey (2016) revealed that only 7.8% (95% confidence interval [CI]: 6.5%–9.5%) of youth cited cessation as a reason for e-cigarette use.[32] In 1 of our cohort studies (unpublished data), we also observed that few young adults (12.8%) cited cessation as a reason for using e-cigarettes.[33] Although many youth (52.8%)[34] and young adult (62.3%)[35] smokers are interested in quitting using cigarettes, it is not clear that these populations are using e-cigarettes to do so or whether e-cigarettes are an effective aid in these populations. With no published evidence of the likelihood that adolescent and young adult smokers transition to the exclusive use of e-cigarettes or to complete abstention from both tobacco products, this possible positive public health impact of e-cigarettes in youth and young adults remain uninvestigated.

In the current study, we aimed to assess 2 critical questions that are central to the evaluation of the public health impact of e-cigarettes on youth. First, among baseline never smokers, we assessed the association of e-cigarette use with the frequency of smoking in the past 30 days at follow-up in a prospective study with a large pooled sample in which 3 cohorts of youth in California and Connecticut were combined. We aimed to evaluate whether e-cigarette users who initiate cigarette smoking are disproportionately represented by young people who are only temporarily experimenting, resulting in a reduced risk of progression to higher levels of smoking in contrast to nonusers of e-cigarettes, or whether the progression to more frequent cigarette use equals or exceeds the typical probability of transitioning observed among non–e-cigarette users, which would suggest that the e-cigarette–to–cigarette use transition is a significant public health concern. Second, we examined the rates of transition from cigarette use or the dual use of e-cigarettes and cigarettes to the exclusive use of e-cigarettes or no tobacco product use. Appreciable rates of transition away from cigarette use (to exclusive e-cigarette use or complete abstention) that are substantially lower than the likelihood of continued cigarette use, with or without concurrent e-cigarette use, may benefit the public health of the population of youth and young adult cigarette smokers.

METHODS

Participants

Southern California Children's Health Study

The Southern California Children's Health Study (CHS) is a population-based prospective cohort study of youth in 12 communities across Southern California.[36,37] The use

of e-cigarettes was first assessed when participants were in 11th or 12th grade between January 2014 and June 2014 by using a paper-and-pencil questionnaire completed under study staff supervision in school classrooms.[36,37] The present analyses are restricted to participants who completed an online follow-up questionnaire between February 2015 and July 2016 (N = 1553; response rate = 74.0%). All participants were ≥18 years of age at follow-up.

Happiness and Health Study

The Happiness and Health (H&H) Study is a population-based prospective cohort study of adolescents in 10 schools in the greater Los Angeles area.[3] Students were initially enrolled in the study in ninth grade in the fall of 2013 at participating schools; data were collected every semester by using a paper-and-pencil questionnaire under study staff supervision in school classrooms. In the current analysis, we use data from participants who completed the spring 2014 data collection (baseline, ninth grade) and spring 2015 data collection (follow-up, 10th grade; N = 3190; response rate = 93.9%).

Yale Adolescent Survey Study

The Yale Adolescent Survey Study (YASS) is a cohort study of ninth- to 12th-grade students in southeastern Connecticut.[38,39] An initial sample of students was recruited in the fall of 2013 from 3 high schools; data were collected by using a paper-and-pencil questionnaire under study staff supervision in school classrooms. Follow-up questionnaires were completed ∼6 months later (spring 2014) in the same high schools, and surveys were matched by using established procedures[40,41] to maintain the confidentiality of participants. The matching procedure for this study is described in detail elsewhere.[42] In the present analyses, we included participants who completed a follow-up questionnaire and were successfully matched with their baseline data at follow-up (N = 1404; match rate = 60.0%).

Ethics Statement

The study was approved by the University of Southern California Institutional Review Board and the Yale University Institutional Review Board. For the CHS and H&H Study, participants aged ≥18 years provided written informed consent; for participants <18 years of age at data collection, written or verbal parental informed consent was obtained, and students assented to participation. For the YASS, alternative consent procedures were used wherein investigators sent out an informational letter detailing the study to parents of eligible children who were enrolled in high schools at which data were collected; parents could opt their children out of the survey. Participants were informed before survey completion that participation was not mandatory; completion of the survey was considered to be assent by participants.

Measures

Tobacco and Alternative Tobacco Product Use

At each survey, participants were asked their age at first use of each product, which was used to classify participants as ever users. Participants who had "never tried" a product ("not even 1 or 2 puffs") were classified as never users. Those reporting an age at first use of each tobacco product or who reported having ever used a product were classified as ever users of that product. Participants were additionally asked the number of days that each product was used in the past 30 days (0, 1–2, 3–5, 6–9, 10–19, 20–29, or all 30 days). Among ever users of a product, participants were categorized as "experimenters" (ever use but no use in the past 30 days), "infrequent users" (use on 1–2 of the past 30 days), or "frequent users" (use on 3–5 or more of the past 30 days). Participants who reported using e-cigarettes, but not cigarettes, in the past 30 days (at baseline or follow-up) were classified as exclusive e-cigarette users; participants who reported using cigarettes, but not e-cigarettes, in the past 30 days were classified as exclusive cigarette users; and participants who reported using both products in the past 30 days were considered dual product users.

Sociodemographic Characteristics

Questionnaires were also used to assess gender, race/ethnicity (Hispanic, non-Hispanic white, and other), baseline grade in high school (ninth, 10th, 11th, and 12th), and parental education (less than high school, high school graduate, some college, or college graduate; CHS and H&H Study only because this information was not available in the YASS).

Statistical Analysis

On the basis of prospectively collected data, we used polytomous logistic regression models to evaluate the association between e-cigarette use at baseline and patterns of tobacco use at follow-up. In analytic models that were restricted to never smokers at baseline, odds ratios (ORs) and 95% CIs were used to estimate the odds of smoking (experimentation, infrequent use, or frequent use relative to never use) associated with e-cigarette use. A second set of models were used to evaluate the association of baseline past-30-day tobacco use (no use, exclusive e-cigarette use, exclusive cigarette use, or dual product use) with past-30-day use at follow-up (no past-30-day use, exclusive e-cigarette use, exclusive cigarette use, or dual product use). Post hoc tests were used to evaluate the heterogeneity of effects. All models were adjusted for gender, race/ethnicity, grade, and

TABLE 1 Demographic Characteristics of Subjects at Baseline

	CHS (CA)	H&H Study (CA)	YASS (CT)
	N = 1553	*N* = 3190	*N* = 1404
Sex			
Male	752 (48.4)	1467 (46.0)	637 (45.4)
Female	801 (51.6)	1723 (54.0)	767 (54.6)
Race/Ethnicity			
Non-Hispanic white	592 (38.1)	512 (16.0)	1198 (85.3)
Hispanic white	758 (48.8)	1505 (47.2)	66 (4.7)
Other	203 (13.1)	1173 (36.8)	140 (10.0)
Baseline grade			
Ninth	—	3190 (100.0)	417 (29.7)
10th	21 (1.3)	—	363 (25.9)
11th	866 (55.8)	—	340 (24.2)
12th	666 (42.9)	—	283 (20.2)
Baseline e-cigarette use			
No	1197 (77.3)	2211 (70.8)	1078 (76.9)
Yes	351 (22.7)	911 (29.2)	323 (23.1)
Baseline cigarette use			
No	1293 (83.5)	2660 (85.2)	1212 (86.3)
Yes	255 (16.5)	463 (14.8)	192 (13.7)

Data are presented as *n* (%). Totals may vary because of missing data. CA, California; CT, Connecticut; —, no participants.

cohort by using a missing indicator when appropriate with a random effect for school. We also assessed whether associations varied across cohorts (CHS, H&H Study, YASS) using appropriate interaction terms. Sensitivity analyses were additionally used to assess whether effect estimates differed after adjusting for parental education by using the CHS and H&H Study. All statistical analyses were based on 2-sided hypotheses tested at a .05 level of significance. Analyses were performed by using SAS 9.4 (SAS Institute, Inc, Cary, NC).

RESULTS

Descriptive Results

Demographic data at baseline for each of the 3 cohort studies are presented in Table 1. Both the CHS and H&H Study had ∼50% Hispanic white participants (the CHS had ∼38% white participants; the H&H Study had ∼16% white participants); the YASS had ∼5% Hispanic white participants and ∼85% white participants. The prevalence of e-cigarette use at baseline was slightly higher in the H&H Study (29.2%) than in the CHS and YASS (22.7%–23.1%, respectively). The prevalence of cigarette use at baseline was similar across all 3 studies.

Frequency of Cigarette Use

In the combined sample at follow-up, 9.2% of never smoking youth at baseline had initiated the use of cigarettes; 6.2% were classified as experimenters, 1.9% were infrequent smokers, and 1.1% were frequent smokers (Table 2). Compared with baseline never e-cigarette users, a higher proportion of baseline e-cigarette users reported each category of cigarette use at follow-up (Fig 1): experimentation (15.1% vs 4.4%), infrequent smoking (4.2% vs 1.4%), and frequent smoking (2.2% vs 0.9%). Elevated ORs were observed for baseline e-cigarette use (versus no use) for cigarette experimentation at follow-up (OR = 4.57; 95% CI: 3.56–5.87), infrequent smoking (OR = 4.27; 95% CI: 2.75–6.62), and frequent smoking (OR = 3.51; 95% CI: 1.97–6.24) versus maintaining never use of cigarettes by follow-up. In the sample of adolescents who had initiated cigarette use between baseline and follow-up, the proportion who reported infrequent or frequent use was similar for e-cigarette users and nonusers (see the inset of Fig 1); those who used e-cigarettes at baseline had similar odds of reporting past-30-day infrequent (OR = 0.98; 95% CI: 0.60–1.60) or frequent (OR = 0.76; 95% CI: 0.41–1.42) versus experimental cigarette use at follow-up compared with those who had not used e-cigarettes at baseline. Results did not differ by study (interaction: $P > .1$; results not shown) or in sensitivity analyses after additional adjustment for parental education.

Transitions Between Past-30-Day Nonuse, Single Product Use, and Dual Product Use From Baseline to Follow-up

Among the 2 cohorts for which past-30-day product use data at baseline ($N = 2705$) were collected, participants who reported that they had not used either product in the past 30 days at baseline were highly likely to remain nonusers (89.2%; Fig 2). Among baseline past-30-day exclusive e-cigarette users, 53.3% were nonusers of either product at follow-up, 28.5% were exclusive e-cigarette users, 5.5% were exclusive cigarette users, and 12.7% were dual product users (see the right inset of Fig 2). Logistic regression models were used to estimate the relative odds of each tobacco use pattern in the past 30 days at follow-up (reference: nonuse of either product). Baseline exclusive e-cigarette users had higher odds of reporting exclusive e-cigarette use at follow-up (OR = 7.28; 95% CI: 4.86–10.9), exclusive cigarette use at follow-up (OR = 3.84; 95% CI: 1.80–8.19), or dual product use at follow-up (OR = 8.86; 95% CI: 5.08–15.4). No statistical differences in the magnitude of the ORs were observed (difference in e-cigarette versus dual product use: $P = .53$; difference in cigarette versus dual product use: $P = .051$; difference in e-cigarette versus cigarette use: $P = .095$).

TABLE 2 E-cigarette Use and Risk of Subsequent Smoking Among Baseline Never Smokers

E-cigarette Use (Baseline)	Cigarette Use (Follow-up)			
	Never	Experimentation[a]	Infrequent[b]	Frequent[c]
Total, *N* (%)	4575 (90.8)	315 (6.2)	96 (1.9)	55 (1.1)
Never	3891 (93.3)	184 (4.4)	60 (1.4)	36 (0.9)
Ever	673 (78.5)	129 (15.1)	36 (4.2)	19 (2.2)
Versus never use, adjusted OR (95% CI)[d]	Reference	4.57 (3.56–5.87)	4.27 (2.75–6.62)	3.51 (1.97–6.24)
Versus previous use, adjusted OR (95% CI)[e]	—	Reference	0.98 (0.60–1.60)	0.76 (0.41–1.42)

—, not applicable.

[a] Experimentation is initiation between baseline and follow-up but no use in the past 30 days.

[b] Infrequent use is initiation and use on 1–2 of the past 30 days.

[c] Frequent use is initiation and use on 3–5 or more of the past 30 days.

[d] Adjusted for sex, race and/or ethnicity, grade, and study; restricted to never cigarette users at baseline with a random effect for school.

[e] Additionally restricted to ever cigarette initiators.

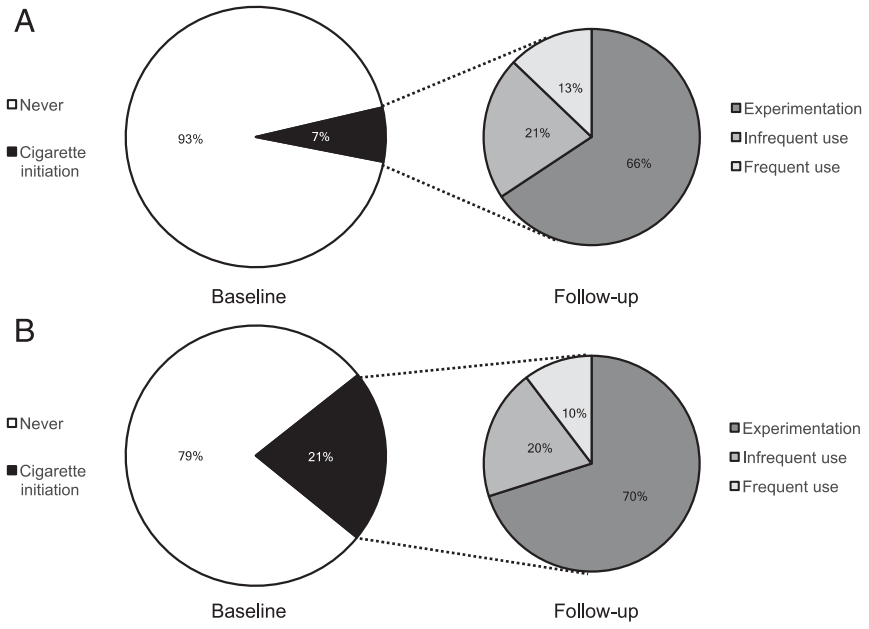

FIGURE 1
Prevalence of cigarette initiation between baseline and follow-up and, among initiators, frequency of cigarette use at follow-up for never e-cigarette users and e-cigarette users at baseline. A, Never e-cigarette users. B, E-cigarette users.

Baseline exclusive cigarette users were equally likely to be exclusive cigarette (27.9%) or dual (27.9%) users at follow-up, with 9.3% switching to exclusive e-cigarette use and 34.9% reporting no use of either product at follow-up. Relative to baseline nonusers of either product, baseline exclusive cigarette users had greater odds of reporting exclusive cigarette use (OR = 29.5; 95% CI: 12.3–70.8), dual product use (OR = 28.8; 95% CI: 12.6–66.1), or exclusive e-cigarette use (OR = 4.03; 95% CI: 1.30–12.6) versus nonuse of either product at follow-up; ORs were significantly greater for exclusive cigarette or dual product use relative to exclusive e-cigarette use at follow-up (difference in e-cigarette versus dual product use: $P = .002$; difference in e-cigarette versus cigarette use: $P = .002$), but no difference in the magnitude of ORs was observed for the likelihood of exclusive cigarette versus dual product use at follow-up (difference in cigarette versus dual product use: $P = .96$).

Participants who were dual past-30-day product users at baseline were likely to be using 1 or more products in the past 30 days at follow up (81.8%), with most remaining as dual product users (51%) and a smaller segment transitioning to exclusive cigarette use (16%). Few dual product users transitioned to exclusive e-cigarette use (15%) or no tobacco use (18%) at follow-up. Baseline dual product users were substantially more likely than those who were not using either product in the past 30 days at baseline to report dual product use (versus no use of either product) at follow-up (OR = 105; 95% CI: 56.6–194), with lower (but still elevated) odds of reporting exclusive cigarette use (OR = 44.3; 95% CI: 20.4–96.1) or exclusive e-cigarette use (OR = 11.3; 95% CI: 5.51–23.2) seen; all ORs were statistically different (difference for all contrasts: $P < .01$). Patterns were again similar by study, with generally higher ORs for the YASS (interaction: $P = .024$; results not shown), and did not differ in sensitivity analyses after additional adjustment for parental education.

Analyses in which we evaluated the transition from ever use of tobacco products at baseline to past-30-day use at follow-up are presented in the Supplemental Information (see also Supplemental Fig 3, Supplemental Table 4).

DISCUSSION

Previous results from our research group have revealed that e-cigarette

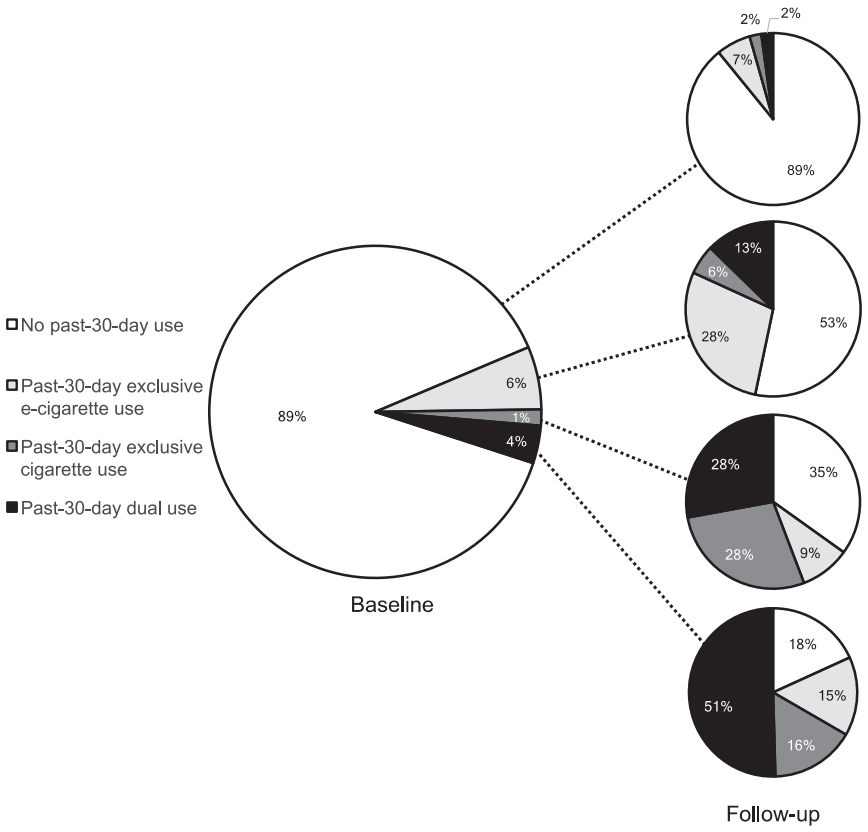

FIGURE 2
Prevalence of past-30-day tobacco product use at baseline and follow-up.

use is associated with subsequent cigarette initiation[4,16] and that the frequency of e-cigarette use was associated with the frequency of smoking at a 6-month follow-up in a sample of 10th-grade students.[6] Here, we provide new results in a pooled sample showing that the risk of past-30-day smoking and of more frequent smoking after initiation was higher in baseline e-cigarette ever versus never users. A smoking uptake pattern characterized by temporary experimentation without progression to more frequent smoking was not disproportionately represented in youth e-cigarette users versus nonusers who started smoking. Rather, among all smoking initiators, the smoking progression sequence was similar among those who used e-cigarettes at baseline and those who initiated cigarette use without a baseline history of e-cigarette use. Supplemental analyses revealed that the magnitude of associations did not significantly differ by cohort, suggesting that this is a generalizable phenomenon across age groups and locations.

Youth who initiate and quickly progress to more frequent smoking are at a high risk of becoming chronic smokers throughout adulthood,[24,27,43–45] resulting in an increased risk of developing tobacco-related diseases. If smoking trajectories of youth who begin cigarette use with or without a previous use of e-cigarettes continue to be similar,[44,45] the results from this study and others revealing a robust increase in the odds of smoking initiation due to e-cigarette use heighten concerns about recent trends in e-cigarette use. Because e-cigarettes are used by at least some youth who likely would not ever have begun smoking without having been exposed to e-cigarettes,[1,2] the potential negative impact of e-cigarettes on the health of youth via the effect of e-cigarettes on smoking uptake is concerning.

In an evaluation of the likelihood of transitioning from exclusive cigarette or dual product use to exclusive e-cigarette use or abstention from both tobacco products, we found that baseline cigarette and dual product users were at an exceedingly high risk of past-30-day cigarette use or dual product use at follow-up, with a lower likelihood of transition away from smoking seen (Table 3). An appreciable proportion of baseline past-30-day exclusive cigarette and dual product users did transition to no past-30-day use of either product at follow-up (34.9% [exclusive cigarette users] and 18.2%, [dual product users]; Fig 2), and a smaller segment transitioned to exclusive e-cigarette use at follow-up (9.3% [exclusive cigarette users] and 15.2% [dual product users]; Fig 2). However, the likelihood of transitioning from smoking to less harmful tobacco product use patterns (exclusive e-cigarette use or use of neither product) was moderate. Although it is possible that dual product users may be using e-cigarettes with the intention of transitioning away from smoking to exclusive e-cigarette use or no use, the probability of this sequence within 6 months to 1 year was modest. Whether some of the dual product users at follow-up in our study may eventually transition to exclusive e-cigarette use or abstention from both products is unknown and will require further surveillance.

It is possible that dual product use may be brief or rare for most who successfully transition from smoking to e-cigarette use, similar to those who successfully quit with Food and Drug Administration–approved nicotine replacement therapies, for whom the dual use of cigarettes and nicotine replacement therapy is limited. Therefore, some cases of successful cessation of smoking

TABLE 3 Use of E-cigarettes, Cigarettes, or Dual Product Use at Baseline and Odds of Past-30-Day Use at Follow-up

Baseline Product Use	Past-30-d Use at Follow-up		
	Exclusively E-cigarettes Versus None, OR (95% CI)	Exclusively Cigarettes Versus None, OR (95% CI)	Dual Use Versus None, OR (95% CI)
Past-30-d use[a,b,c]			
Neither product	Reference	Reference	Reference
Exclusively e-cigarettes	7.28 (4.86–10.9)[d]	3.84 (1.80–8.19)[d]	8.86 (5.08–15.4)[d]
Exclusively cigarettes	4.03 (1.30–12.6)[d]	29.5 (12.3–70.8)[e]	28.8 (12.6–66.1)[e]
Dual product	11.3 (5.51–23.2)[d]	44.3 (20.4–96.1)[e]	105 (56.6–194)[f]

Superscript letters denote a test of independence of effect estimates by row; estimates sharing letters are not statistically significantly different from one another ($P < .05$).
[a] Stability estimates of remaining in a use pattern (versus nonuse) on the diagonal.
[b] Adjusted for gender, race and/or ethnicity, grade, and study with a random effect for school.
[c] Restricted to the CHS and YASS.

with e-cigarettes may not have been identified in this analysis. However, we found that most adolescent dual product users remain dual product users within 6 months to 1 year, suggesting that dual product use is most often not a temporary state of transition for youth. Regardless, additional types of analyses and study methodologies are needed to clarify whether e-cigarettes may function as an effective cessation aid in this population. Observational studies of adults to date have generally revealed that e-cigarette use among smokers is associated with a lower likelihood of cigarette smoking cessation.[29,46,47] We are not aware of any studies in which researchers explicitly evaluate e-cigarettes as a cessation aid for youth, but studies to date have not found evidence for an association of e-cigarette use with a reduction in the frequency of smoking or for complete cessation.[8,13,48]

There were some limitations to the study. There were relatively few youth who reported levels of cigarette or e-cigarette use more often than 3 to 5 times in the previous month. Continued follow-up with these cohorts is needed to determine which youth progress to daily smoking in early adulthood. In addition, in the analysis evaluating dual product use, no data on past-30-day e-cigarette use were available at baseline for 1 of the cohorts. Although we adjusted for covariates that were hypothesized to confound the tested associations, we were unable to adjust for other factors that may be important but that were only collected in 1 of the 3 studies (for example, behavioral characteristics, including risk taking propensity or impulsivity or other factors, such as peer tobacco use or approval of use). Finally, the studies represent youth of varying ages in different geographical locations; all analyses were controlled for baseline grade, gender, race/ethnicity and study. Further research to examine factors that may influence regional differences in tobacco use transitions in youth could be useful for state and local tobacco control policy makers. Continued research to explore factors that may promote the transition to nicotine dependence (thus increasing the adverse public health impact of use) are warranted.

With our findings, we suggest that smoking uptake and progression is an adverse public health consequence of high rates of e-cigarette use among youth and young adults. The findings also did not reveal strong evidence of transitioning away from combustible cigarette use as a potential public health benefit of e-cigarette use in young people. Together, these findings reveal that adolescent e-cigarette use may result in an overall adverse impact on the public health of youth and young adults. Additional follow-up in large cohort studies along with data on factors that promote transitioning from e-cigarettes to cigarettes and that inhibit transitioning from cigarettes to e-cigarettes or nonuse are needed to develop targeted interventions to minimize the adverse public health impact of e-cigarettes in the adolescent population.

ABBREVIATIONS

CHS: Children's Health Study
CI: confidence interval
e-cigarette: electronic cigarette
H&H: Happiness and Health
OR: odds ratio
YASS: Yale Adolescent Survey Study

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E-cigarette Use and Subsequent Smoking Frequency Among Adolescents

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Journal of the American Heart Association

ORIGINAL RESEARCH

Alterations in Vascular Function Associated With the Use of Combustible and Electronic Cigarettes

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BACKGROUND: Electronic cigarettes (e-cigarettes) have been proposed as a potential harm reduction tool for combustible cigarette smokers. The majority of adult e-cigarette users continue to smoke combustible cigarettes and are considered dual users. The vascular impact of e-cigarettes remains incompletely defined.

METHODS AND RESULTS: We examined the association of e-cigarette use with measures of vascular function and tonometry, preclinical measures of cardiovascular injury. As part of the CITU (Cardiovascular Injury due to Tobacco Use) study, we performed noninvasive vascular function testing in individuals without known cardiovascular disease or cardiovascular disease risk factors who were nonsmokers (n=94), users of combustible cigarettes (n=285), users of e-cigarettes (n=36), or dual users (n=52). In unadjusted analyses, measures of arterial stiffness including carotid-femoral pulse wave velocity, augmentation index, carotid-radial pulse wave velocity, and central blood pressures differed across the use groups. In multivariable models adjusted for age, sex, race, and study site, combustible cigarette smokers had higher augmentation index compared with nonusers (129.8±1.5 versus 118.8±2.7, P=0.003). The augmentation index was similar between combustible cigarette smokers compared with sole e-cigarette users (129.8±1.5 versus 126.2±5.9, P=1.0) and dual users (129.8±1.5 versus 134.9±4.0, P=1.0). Endothelial cells from combustible cigarette smokers and sole e-cigarette users produced less nitric oxide in response to A23187 stimulation compared with nonsmokers, suggestive of impaired endothelial nitric oxide synthase signaling.

CONCLUSIONS: Our findings suggest that e-cigarette use is not associated with a more favorable vascular profile. Future longitudinal studies are needed to evaluate the long-term risks of sustained e-cigarette use.

Key Words: e-cigarettes ■ electronic cigarettes ■ smoking ■ vascular function

E-cigarettes have gained popularity among adult smokers seeking to reduce their consumption of or quit combustible cigarettes.[1–3] Many users and public health activists view e-cigarettes as safer alternatives to combustible cigarettes because these products contain a limited number of ingredients (nicotine, propylene glycol/glycerin, and in many cases flavoring additives) compared with combustible tobacco products. The perception that e-cigarettes are safer than combustible cigarettes is widespread, with the majority of adult e-cigarette users reporting that the primary reason for use is the perception that e-cigarettes pose less of a health risk than combustible cigarette smoking.[1] Consequently, e-cigarettes have drawn significant attention as a potential way to reduce harm. However, it is unclear whether e-cigarettes are a safer alternative to combustible cigarettes.

Cardiovascular disease (CVD) is the primary cause of morbidity and mortality among combustible cigarette smokers.[4,5] Smoking combustible cigarettes

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For Sources of Funding and Disclosures, please see page 8.

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CLINICAL PERSEPCTIVE

What Is New

- Augmentation index, a measure of vascular stiffness, was similar between sole combustible cigarette users compared with sole e-cigarette users and compared with dual users, suggesting that e-cigarette use is not associated with a more limited arterial stiffening impact than combustible cigarette smoking.
- In endothelial cells freshly collected from study participants, stimulated nitric oxide production was diminished in both combustible and e-cigarette users, suggesting the presence of endothelial cell dysfunction.

What Are the Clinical Implications?

- Our study suggests that e-cigarette use is associated with a similar vascular profile compared with combustible cigarette use.

Nonstandard Abbreviations and Acronyms

AIx	augmentation index
BP	blood pressure
CVD	cardiovascular disease
DAF-2	DA 4,5-diaminofluorescein diacetate
EC	endothelial cell
eNOS	endothelial nitric oxide synthase
NO	nitric oxide
PWV	pulse wave velocity

exposes the cardiovascular system to inhaled toxins and leads to widespread changes in vascular function that are associated with adverse cardiovascular outcomes.[6–9] Vascular dysfunction, associated with smoking combustible cigarettes, is characterized by impaired endothelial function and increased vascular stiffness, both of which are predictive of adverse cardiovascular outcomes and mortality.[10–12] Although smoke generated from combustible cigarettes generates a wide range of harmful or potentially harmful substances, the increased cardiovascular risk associated with smoking has largely been attributed to reactive aldehydes such as acrolein, formaldehyde, and acetaldehyde.[13] Importantly, such aldehydes have also been found in e-cigarette–generated aerosol,[13–16] although their contribution to the cardiovascular effects of e-cigarette use remains unknown.

To gain early evidence of the cardiovascular effects of e-cigarettes, we performed a cross-sectional study (the CITU [Cardiovascular Injury due to Tobacco Use] study) of nonsmokers, combustible cigarette users, e-cigarette users, and dual combustible and e-cigarette users. The objective of this study was to compare vascular function between combustible cigarette users and users of e-cigarettes, alone or with contemporaneous use of combustible cigarettes.

METHODS

Primary de-identified data supporting the findings of this study are available through the American Heart Association Tobacco Regulation and Addiction Center upon request.

Study Participants

We recruited male and female participants between the ages of 21 and 45 years from Boston University Medical School and the University of Louisville who were without established CVD or CVD risk factors (dyslipidemia, hypertension, diabetes mellitus), as previously described.[17] Participants were classified as nonsmokers if they were not current smokers or users of other tobacco products, smoked fewer than 100 cigarettes in their lifetime, and had a urinary cotinine level <10 ng/mL. Combustible cigarette smokers were defined based on current smoking of at least 5 days per week, having smoked ≥100 cigarettes in their lifetime, and no current e-cigarette use. E-cigarette users were defined as participants who currently use e-cigarettes at least 5 days per week and do not currently use combustible cigarettes. Dual combustible and e-cigarette users were defined as participants who reported current use of both combustible and e-cigarettes, at least 5 days per week, with a lifetime usage of ≥100 cigarettes. All inclusion and exclusion criteria can be found in Table S1. All participants gave written informed consent and all study protocols were approved by the Boston Medical Center and University of Louisville institutional review boards.

Vascular Function Testing

Noninvasive vascular function was measured as previously described to calculate 5 measures: baseline brachial artery diameter, baseline flow velocity, hyperemic flow velocity, flow-mediated dilation, and hyperemic shear stress.[9,17,18] Participants were asked to fast from food and tobacco products overnight, 8 to 12 hours before the study visit. Brachial artery diameter was measured at baseline and after a 5-minute occlusion (blood pressure [BP] cuff attached to the lower arm inflated to 200 or 50 mm Hg higher than the systolic pressure) to determine flow-mediated dilation, a noninvasive measure of conduit artery endothelial-dependent vasodilation. Resting and hyperemic flow velocities and shear stress were

measured in the brachial artery using Doppler ultrasound. Shear stress (dynes/cm^2) was calculated as 8 μV/diameter, where μ was blood viscosity (assumed to be 0.035 dyne-s/cm^2) and V was brachial velocity (cm/s) at baseline.[19] All vascular images were analyzed at Boston University using Vascular Research Tools Brachial Analyzer for Research V.6.8.5 (Medical Imaging Applications, LLC) by a technician blinded to tobacco product use group.

Tonometry Measurements

Arterial tonometry and waveform analysis were used to determine carotid-femoral pulse wave velocity (PWV), carotid-radial PWV, augmentation index (AIx), central systolic BP, central diastolic BP, and heart rate using (SphygmoCor, Atcor).[20,21] Participants rested supine for at least 5 minutes before measurement. A tonometer was used over 3 locations (radial, carotid, femoral arteries) sequentially and the R wave from the ECG was used to measure transit time with a caliper used to measure distance between locations. Pulse waveform analysis was performed from the radial artery recordings with a validated transfer function along with brachial BP readings used to determine central BPs. AIx was assessed from the radial artery waveform by comparing the augmentation pressure divided by the pulse pressure and is expressed as a percentage.[21]

EC Collection

Venous endothelial cells (ECs) were collected as previously described.[2] In brief, a 0.018 inch J-wire (Arrow International) was inserted into a forearm vein through a 20 or 22 gauge intravenous catheter and used to gently rub the endothelial surface. ECs were recovered from the wire in red blood cell lysis/dissociation buffer, centrifuged, and applied to poly-L-lysine–coated slides (Sigma). Nitric oxide (NO) bioavailability was assessed immediately after isolation as described below. All other cells were fixed onto the slides using 4% paraformaldehyde, dried, and frozen at −80°C before staining and immunofluorescence imaging to quantify protein expression as described below.

Fluorescence Imaging and Quantification

To evaluate NO production, freshly isolated ECs were incubated with 3 μmol/L 4,5-diaminofluorescein diacetate (DAF-2DA; Calbiochem) for 30 minutes. After 2 washes with Hanks balanced salt solution, cells were stimulated with 1 μmol/L A23187 (Sigma) for 15 minutes and fixed with 2% paraformaldehyde. Mean fluorescence intensity at an excitation of 498 nm was measured on a fluorescence microscope (Nikon Eclipse TE2000), quantified for 20 cells, and averaged for each condition. Data are expressed as percent increase in DAF-2DA fluorescence stimulated by A23187 compared with unstimulated cells.

Protein levels of endothelial NO synthase (eNOS) were quantified using immunofluorescence microscopy. Cells were permeabilized with 0.1% triton-X in 50 mmol/L glycine for 10 minutes, washed 3 times with 50 mmol/L glycine in 1X PBS, and blocked for 10 minutes with 0.5% bovine serum albumin in 50 mmol/L glycine/1X PBS. Slides were stained with primary antibody against eNOS (1:100 dilution, BD Transduction, catalog #610296) for 3 hours at 37°C. Following 3 washes with 50 mmol/L glycine/1X PBS, the cells were incubated with secondary antibody for 45 minutes at 37°C. The fluorescence intensity was quantified in 20 ECs and averaged for each condition. To control for batch-to-batch variability, fluorescence intensity was normalized to the intensity in human aortic ECs, which were stained simultaneously. Final intensity was calculated by dividing the average fluorescence intensity for the patient sample by the average fluorescence intensity of the human aortic EC sample and multiplying by 100. The intensity is expressed in arbitrary units. All quantification for all measures was performed blinded to participant identity and tobacco product status.

Statistical Analyses

Clinical characteristics and vascular function measures were compared across the 4 groups (nonsmokers, combustible cigarette users, e-cigarette users, and dual combustible and e-cigarette users) using 1-way ANOVA or chi-square testing for continuous or categorical data, respectively. Using a generalized linear model, we compared means while adjusting for age, sex, race, and study site. We performed post hoc analyses comparing combustible cigarette use with nonuse and with e-cigarette use alone or dual use with Bonferroni correction for multiple testing. Data are reported as mean±SD. Two-sided $P<0.05$ was considered statistically significant. All statistical analyses were peformed using SAS 9.4 (TS1M3; SAS Institute).

RESULTS

Clinical Characteristics

Combustible cigarette and dual users were older than nonsmokers and e-cigarette users (Table 1). E-cigarette users were more likely to be younger, men, and white. The number of pack-years or average number of cigarettes smoked per day were similar for both combustible cigarette smokers and dual users (15±13 versus 13±10, respectively; $P=1.0$). All e-cigarette users were former smokers.

Table 1. Clinical Characteristics and Vascular Measures of the CITU Study Cohort

	Nonsmokers (n=94)	Combustible Cigarette Users (n=285)	E-Cigarette Users (n=36)	Dual Users (n=52)	*P* Value
Clinical characteristics					
Age, y	29±6	32±7	29±6	33±7	<0.0001
Women, %	56	42	28	47	0.01
Black race, %	65	61	28	54	<0.01
Average number of cigarettes per d, %					
<5	100	10	100	16	<0.0001
≥5		90		84	
Urinary cotinine, mg/dL	3±2	917±879	856±959	775±740	<0.0001
Vascular function and tonometry measures					
Baseline brachial diameter, mm	3.8±0.8	4.0±0.7	3.8±0.7	3.9±0.6	0.28
Baseline mean flow velocity, cm/s	12.7±5.6	15.3±8.9	15.1±9.2	14.9±10.0	0.61
Hyperemic mean flow velocity, cm/s	77.6±19.1	72.8±19.0	70.3±17.5	73.9±20.2	0.21
Flow-mediated dilation, %	7.0±4.1	6.2±3.9	7.5±4.9	5.9±5.2	0.16
Shear stress, dyne/cm^2	60.3±19.6	53.8±18.3	53.6±14.2	54.7±20.1	0.14
Carotid-femoral PWV, m/s	5.6±1.1	6.0±1.2	5.8±0.6	6.4±1.2	0.004
Carotid-radial PWV, m/s	6.7±1.8	7.4±1.8	5.9±1.0	7.4±1.8	0.0001
AIx	116.7±17.5	130.9±25.8	113.3±9.0	137.2±29.3	<0.0001
Central systolic BP, mm Hg	119±12	122±13	118±10	127±15	0.003
Central diastolic BP, mm Hg	72±9	76±10	71±6	79±13	<0.001
Heart rate, beats per min	69±10	66±11	64±8	69±13	0.12

Values are expressed as mean±SD or percentage. AIx indicates augmentation index; BP, blood pressure; CITU, Cardiovascular Injury due to Tobacco Use; and PWV, pulse wave velocity.

E-Cigarette Product Characteristics

All e-cigarette users reported using second- or third-generation devices (Table 2). Among dual users, 9 participants reported using first-generation devices and 40 reported use of second- or third-generation devices. Only 2 e-cigarette users and 6 dual users reported never using e-liquids containing nicotine. Most e-cigarette and dual users reported using flavored e-liquids (Table 2). The majority of e-cigarette and dual users reported using fruit-flavored e-liquids. Use of menthol or mint flavored e-liquids were frequently reported among dual users. Among the e-cigarette users, 93% reported quitting smoking combustible cigarettes for months or years at the time of the study visit, with only 2 participants reporting quitting combustible cigarettes for weeks.

Vascular Function and Tonometry

In unadjusted analyses, baseline brachial diameter and flow velocity, flow-mediated dilation, shear stress, reactive hyperemia, and heart rate were similar across the tobacco product users and the nonsmokers (Table 1). Carotid-femoral PWV, carotid-radial PWV, and AIx were different across the groups suggestive of alterations in vascular stiffness. Both central systolic and diastolic BPs were different across the groups (P=0.003 and P<0.001, respectively). Heart rate was similar across all groups.

In multivariable models adjusting for age, sex, race, and study site, the association of AIx persisted with tobacco product use (overall P=0.0008) (Table 3). In post hoc analyses, combustible cigarette users had higher AIx values compared with nonsmokers (129.8±1.5 versus 118.8±2.7, respectively; P=0.003). Dual users had AIx values similar to combustible cigarette users (134.9±4.0 versus 129.8±1.5, respectively; P=1.0) as did sole e-cigarette users (126.2±5.9 versus 129.8±1.5, respectively; P=1.0) in post hoc analyses (Figure 1). Collectively, these data suggest that e-cigarette use is associated with measures of vascular stiffness, which has direct relevance to CVD.

Table 2. E-cigarette Product Characteristics

	E-Cigarette Users	Dual Users
Type of e-cigarette device used		
First-generation	0	9
Second- or third-generation	24	40
Types of flavored e-liquids used		
Unflavored	0	6
Tobacco	0	2
Fruit	12	17
Candy or other dessert	6	5
Vanilla	2	3
Mint or menthol	2	15
Other	2	1

EC Phenotype

In a cross-sectional cohort of nonsmokers (n=21), combustible cigarette users (n=22), and sole e-cigarette users (n=14), we evaluated EC phenotype of freshly collected ECs. All groups were similar for sex (P=0.7), and e-cigarette users were younger and the majority were former smokers (93%) (Table 4). Combustible cigarette smokers were more likely to be black.

In ECs, NO (DAF-2DA fluorescence) production in response to A23187 stimulation differed across the groups (P=0.03). In post hoc analyses, combustible cigarette users had lower A23187-induced NO production compared with nonsmokers (2.8±2.2% versus 14.1±1.5%, P=0.003) (Figure 2A) consistent with EC dysfunction. E-cigarette users also had lower A23187-induced NO production compared with nonsmokers (2.6±3.0% versus 14.1±1.5%, P=0.018). A23187-stimulated NO production in ECs from combustible and e-cigarette users was not different (P=0.828), suggesting similar impairment in NO signaling. eNOS levels quantified using immunofluorescence imaging differed across the groups (Figure 2B, P=0.033). E-cigarette users had lower eNOS levels compared with combustible cigarette users (10.7±2.2 arbitrary units versus 22.1±3.6 arbitrary units, P=0.03) and trended to have lower levels compared with nonsmokers (Figure 2B, P=0.122). Consequently, the differences in NO production could, in part, be caused by differential expression of eNOS. Collectively, these studies suggest that ECs from combustible and e-cigarette users have similar alterations in EC phenotype indicative of a loss of NO signaling.

DISCUSSION

We performed noninvasive vascular testing in a cohort of young adults without CVD risk factors or CVD, consisting of nonsmokers, combustible cigarette users, e-cigarette users, and dual users. In agreement with national surveys, adult e-cigarette users were predominately white and male who were current or former smokers. Many measures of vascular health did not differ between tobacco product users and nonusers including measures of large and small vessel vasodilator response. In unadjusted models, tobacco product use was associated with higher arterial stiffness by multiple measurements. Furthermore, in adjusted models, combustible cigarette use was associated with a higher AIx compared with nonusers. AIx was not different in users of e-cigarettes alone or in conjunction with combustible cigarette use compared with combustible cigarette use alone. ECs freshly collected from combustible cigarette smokers and sole e-cigarette users produced less NO in response to A23187 stimulation compared with nonsmokers, suggestive of impaired eNOS signaling. The lower NO

Table 3. Vascular Function and Tonometry Measures Adjusted for Age, Sex, Race, and Study Site

	Nonsmokers	Combustible Cigarette Users	E-Cigarette Users	Dual Users	*P* Value
Baseline brachial diameter, mm	3.8±0.08	3.9±0.04	3.8±0.1	3.9±0.1	0.63
Baseline mean flow velocity, cm/s	13.0±1.2	16.1±0.6	13.5±1.9	15.5±1.5	0.1
Hyperemic mean flow velocity, cm/s	73.8±2.7	72.2±1.4	68.9±4.1	73.0±3.3	0.79
Flow-mediated dilation, %	6.6±0.6	6.3±0.3	7.3±0.8	6.1±0.7	0.68
Shear stress, dyne/cm^2	57.0±2.4	54.1±1.3	54.4±3.7	54.8±3.0	0.73
Carotid-femoral PWV, m/s	5.7±0.1	6.0±0.08	6.1±0.3	6.3±0.2	0.12
Carotid-radial PWV, m/s	6.8±0.2	7.2±0.1	6.8±0.4	7.3±0.2	0.2
AIx	118.4±2.6	129.8±1.5	126.2±5.9	134.9±4.0	0.0008
Central systolic BP, mm Hg	105±2	110±1	106±4	114±2	0.007
Central diastolic BP, mm Hg	74±1	76±1	72±3	78±2	0.14
Heart rate, beats per min	69.6±1.2	66.6±0.7	66.5±2.0	68.8±1.6	0.1

Values are expressed as least square mean±SEM. AIx indicates augmentation index; BP, blood pressure; and PWV, pulse wave velocity.

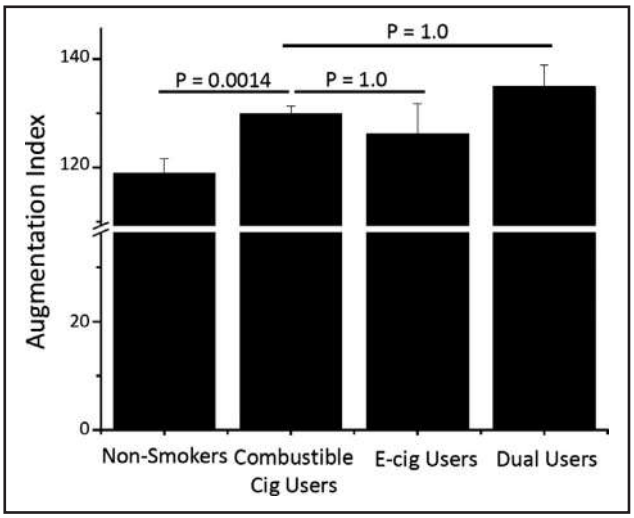

Figure 1. Augmentation index (AIx) is associated with tobacco product use.
AIx for nonsmokers, combustible cigarette users, e-cigarette users, and dual users following adjustment for age, sex, race, and study site. Data are expressed as least square mean±standard error.

production in the cells from e-cigarette users could, in part, be explained by lower eNOS expression. These findings suggest that there was not a vascular benefit to the addition or substitution of e-cigarettes. In addition, several measures of vascular function may be relatively insensitive to detect the vascular effects of chronic tobacco product use in healthy young individuals. Measures of vascular stiffness may be more sensitive than measures of vasodilation for detecting effects associated with chronic tobacco use, and measures of the response to acute use may be needed to enhance the detection of vascular effects of specific products.

Previous work has shown that increased vascular stiffness and sympathetic regulation of BP and heart rate are associated with the use of combustible cigarettes.[10–12,22–24] Among younger individuals, a higher AIx is associated with early alterations in vascular remodeling and is thought to be an early indicator of arterial remodeling and future central aortic stiffness.[25] In a cross-sectional study, AIx in young chronic smokers was found to be higher than that in age- and sex-matched nonsmokers, and smoking a single combustible cigarette led to an acute increase in the carotid-femoral PWV.[24] It has also been reported that in smokers acute use of an e-cigarette with nicotine or smoking a single combustible cigarette increased carotid-femoral PWV, when compared with the use of an e-cigarette without nicotine. These findings suggest that nicotine is a contributor to the hemodynamic effects associated with acute e-cigarette use.[23]

Our study provides additional insights into the chronic effects of e-cigarette use. We found that chronic e-cigarette use, alone or in conjunction with combustible cigarette use, was associated with a similar impairment of selected arterial stiffness measures. There is no evidence from our study that e-cigarettes are a harm reduction tobacco product as compared with combustible cigarettes. Our observation of the association of higher AIx and impaired eNOS signaling with e-cigarette use could indicate adverse vascular remodeling, which, with continued tobacco product use, may lead to hypertension. The cross-sectional nature of our study precludes direct evaluation of the effect of switching from combustable cigarette use to e-cigarette use. However, we required a minimum of 3 months of e-cigarette use to classify patients as e-cigarette users; e-cigarette use had to be exclusive for at least 3 months in the exclusive e-cigarette use group. Prior studies have shown a reduction in AIx with smoking cessation in healthy tobacco users in as litte as 4 weeks.[26] Thus, our findings are consistent with the possibility that e-cigarette use does not confer the same benefit as complete cessation of tobacco products.

Our finding that endothelial function was similar in tobacco product users compared with nonusers is in contrast to prior reports. Several large cohort studies, including the Framingham Heart Study, have shown lower flow-mediated dilation associated with active combustible cigarette use.[18,27] In addition, the acute use of combustible cigarettes or e-cigarettes has been reported to impair endothelial function that may be in part attributable to nicotine exposure.[28,29] In our study we did not observe a difference in flow-mediated dilation in tobacco product users. Many factors may account for the apparent contradiction of the prior literature. It may be, at least in part, attributable to tobacco product abstinence 8 to 12 hours before the study visit. Another reason for this lack of difference may be lower exposure (fewer pack-years)

Table 4. Clinical Characteristics of Participants With EC Phenotype Data

	Nontobacco Product Users (n=21)	Combustible Cigarette Users (n=22)	E-Cigarette Users (n=14)	*P* Value
Clinical characteristics				
Age, y	38±13	40±11	29±6	<0.01
Women, %	43	32	21	0.65
Black race, %	62	91	36	0.011

Values are expressed as mean±SD or percentage. EC indicates endothelial cell.

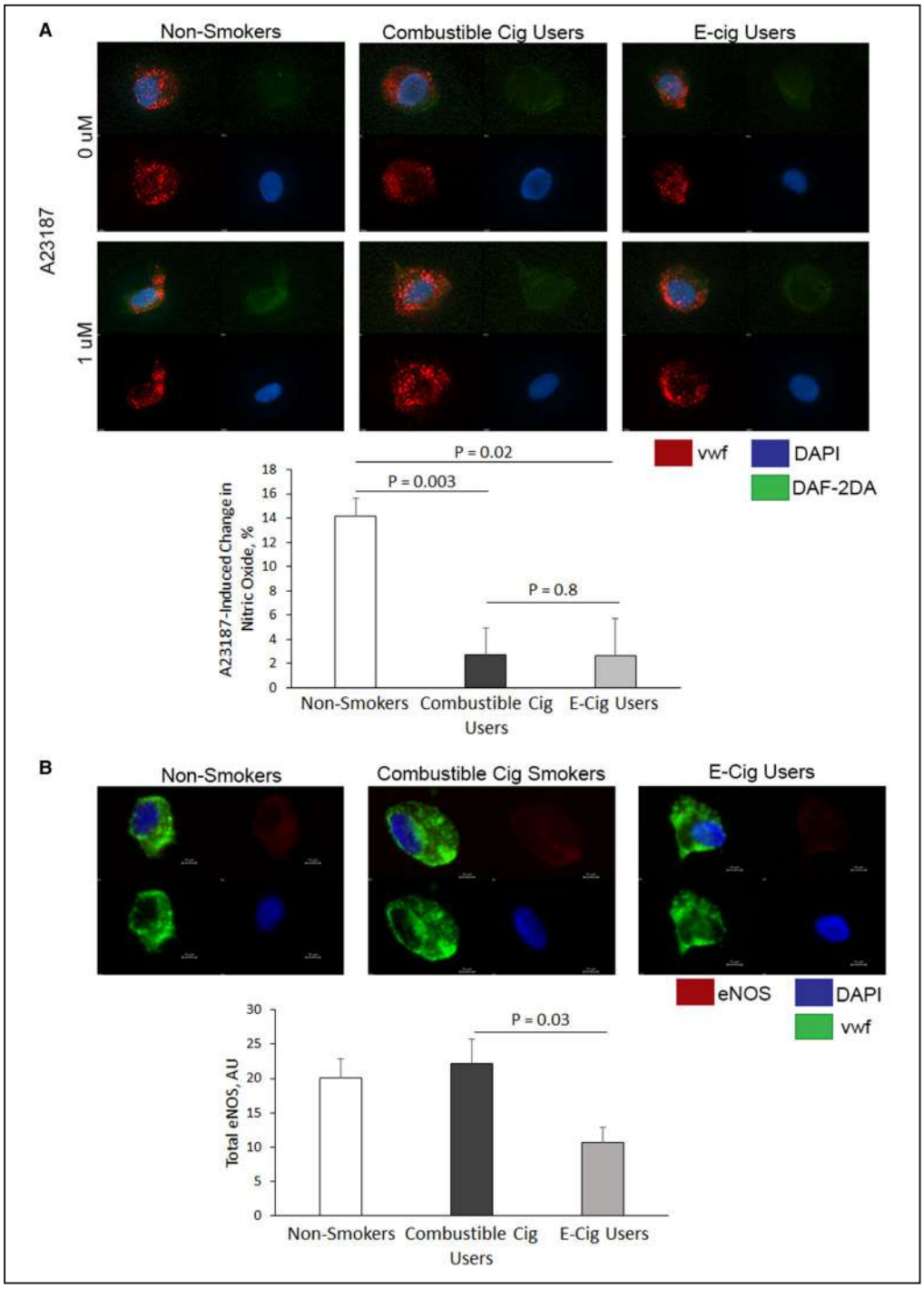

Figure 2. Tobacco product use is associated with impaired endothelial cell (EC) phenotype.
A, Nitric oxide (NO) production (4,5-diaminofluorescein diacetate [DAF-2DA] fluorescence) in response to A23187 stimulation in ECs freshly isolated from combustible cigarette users (n=11) and e-cigarette users (n=5) was lower compared with nontobacco product users (n=10). **B**, Endothelial NO synthase (eNOS) levels quantified by immunofluorescence in ECs from nontobacco product users (n=11), combustible cigarette users (n=13), and e-cigarette users (n=12) were similar. Data are expressed as mean±standard error.

in our cohort. Indeed, previous studies have found a consistent inverse association between flow-mediated dilation with the number of pack-years.[22] In addition, many of the prior studies involved cohorts with a greater burden of cardiovascular risk factors and more advanced age. However, in our study, the ECs from combustible cigarette and sole e-cigarette users had impaired NO production in response to A23187, suggestive of endothelial dysfunction. Nevertheless, further work is required to assess how

the duration and the intensity of use affect vascular function, and whether there is a threshold of exposure at which the use of tobacco products significantly and chronically affect endothelial function.

Despite its many strengths related to the concurrent evaluation of several vascular measures across users of tobacco products, our study has several limitations. The study groups were inherently different regarding age, race, and sex. For example, the sole e-cigarette users were predominantly white males and former smokers, which is consistent with national surveys of tobacco use.[1,2] Consequently, residual confounding can not be fully excluded. Additionally, it remains possible that longer time periods of exclusive e-cigarette use would be required to observe improvements in cardiovascular health metrics, although, as noted, prior studies have suggested that improvements in AIx occur in as little as 4 weeks. Further, most of the e-cigarette users in our study reported using nicotine in their devices and it is possible that products with less or no nicotine may be associated with reduced cardiovascular harm. However, a number of studies indicate that e-cigarette users self-titrate in order to obtain similar levels of nicotine, regardless of the product nicotine content. Moreover, even though we measured urinary cotinine to validate self-reported tobacco product use, we were unable to differentiate between combustible and e-cigarette use with urinary cotinine as both products contain nicotine. Therefore, we are unable to validate that sole e-cigarette users are completely abstaining from combustible cigarettes. Additionally, our study cohort consisted primarily of healthy, young adults, and it is likely that they may have responded differently compared with individuals with cardiovascular risk factors. We examined venous ECs rather than arterial ECs, which may be more relevant to CVD. However, previous studies have shown correlated findings in arterial and venous ECs collected using similar methodology.[30,31] Finally, e-cigarettes represent a diverse class of tobacco products with a wide range of operating conditions, use patterns, product characteristics, and e-liquid constituents, which often include varying levels of nicotine, several flavors, and different ratios of the vehicles—glycerin and propylene glycol. Thus, it appears likely that the use of different products may be associated with exposure to different toxicants that exert different toxicities.

CONCLUSIONS

Our study provides new insights into the effects of tobacco product use on measures of vascular function in young, healthy adult individuals without CVD risk factors. The most recent nationally representative sample shows that the majority of adult e-cigarette users are either former (36.5%) or current (22.1%) combustable cigarette smokers emphasizing the importance of understanding cardiovascular health measures in these groups.[32] Significantly, we found that e-cigarette use either with or without combustible cigarette use was associated with a similar elevation of AIx, a measure of vascular stiffness, as compared with users of combustible cigarettes alone. Several measures of vascular function did not distinguish between tobacco product users and nonusers in young healthy adults. These data suggest that the abnormalities in vascular stiffness persist in e-cigarette users and that, at least within the limitations of our cohort and measurement approaches, there was no evidence that the use of e-cigarettes reduces cardiovascular injury, dysfunction, or harm associated with the use of combustible tobacco products. Further, ECs from combustible cigarette and e-cigarette users had impaired A23187-induced NO production, suggestive of EC dysfunction. With the diversity of tobacco products available and continuing to increase, methods to evaluate tobacco product–induced cardiovascular toxicity are needed. Our study suggests that measures of vascular stiffness, such as AIx, may be useful methods in evaluating novel tobacco product cardiovascular toxicity.

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Disclosures

None.

Supplementary Materials

Table S1

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SUPPLEMENTAL MATERIAL

Table S1. Inclusion and Exclusion Criteria.

Inclusion Criteria for Non-Smokers
No current tobacco product use
Smoked <100 cigarettes in their lifetime
Urinary cotinine level <10 ng/mL
Inclusion Criteria for Combustible Cigarette Users
Smoked ≥100 cigarettes in their lifetime
Current combustible cigarette smoking of ≥ 5 cigarettes/day
Inclusion Criteria for E-Cigarette Users
No current combustible cigarette smoking for ≥3 months
Current e-cigarette smoking of ≥ 5 days/week
Inclusion Criteria for Dual Users
Current e-cigarette smoking of ≥ 5 days/week
Current traditional cigarette smoking of ≥ 5 cigarettes/day
Smoked ≥100 cigarettes in their lifetime
Exclusion Criteria for All Study Participants
No history of diabetes, hypertension, or cardiovascular disease. Fasting blood sugar <100 mg/dL, LDL<130mg/dL, triglycerides <150 mg/dL, blood pressure <140/90 mmHg.
Clinically evident major illness, including cancer, end-stage renal disease, hepatic failure.
Women who are lactating or pregnant. Pregnancy will be excluded by a urine pregnancy test.

First evidence that e-cigarettes may be prompting UK teens to try the real thing

bmj.com/company/newsroom/first-evidence-that-e-cigarettes-may-be-prompting-uk-teens-to-try-the-real-thing

Some signs that vaping may also escalate tobacco use

E-cigarettes may be prompting UK teens to start smoking the real thing, and to escalate tobacco consumption, finds the first UK study to report this trend, and published online in the journal **Tobacco Control**.

But the researchers call for caution in interpreting the survey data on which the findings are based: while vaping prevalence has increased in the UK, smoking prevalence has continued to fall, they point out.

Rates of e-cigarette use among teens are low, but the proportion of those who have tried them at least once are reasonably high, at 13-22%, and the trend is upwards. But the studies suggesting that experimentation with e-cigarettes may act as a gateway to smoking in adolescents have been carried out in the US.

The researchers therefore wanted to see if there were any similarities in patterns in the UK, as well as to explore several potential risk factors and influences that have not been looked at before.

They mined data from the survey responses of 2386 teens from 20 schools across England in 2014 (baseline), when respondents were aged 13 and 14, and again a year later.

At baseline, the teens were asked about their vaping and smoking behaviours—how much and how often. And they were asked whether any of their friends or family smoked; and what their attitude to smoking was—factors associated with smoking uptake among the young.

Levels of carbon monoxide in their breath were assessed: this gas indicates whether someone has been smoking. And information was also collected on whether they had free school meals—a measure of household financial hardship.

A year later they were asked whether they smoked cigarettes, and if so, how many; and their breath carbon monoxide levels were re-assessed.

At baseline, nearly two thirds (61.5%, 1726) of the sample had neither tried vaping nor smoking; 16% said they had only tried e-cigarettes; 4.4% had tried the real thing, but not e-cigarettes; and nearly one in five (18.1%) had tried both.

Starting to smoke over the next 12 months was significantly more common among those who had friends and two or three family members who smoked. And it was significantly less likely among those with negative attitudes towards smoking.

But it was strongly associated with e-cigarette use, particularly among those without friends who smoked—a group usually thought to be less vulnerable to taking up smoking.

Among those who had never smoked cigarettes but had tried e-cigarettes at baseline, a third (34.4%) said that they had tried cigarettes 12 months later compared with only 9% in the group who had not tried e-cigarettes at baseline.

After taking account of other potentially influential factors, those who vaped were four times as likely to start smoking conventional cigarettes as were those who didn't use e-cigarettes.

And occasional smokers at baseline were nearly twice as likely to escalate their habit if they had tried e-cigarettes as were those who hadn't experimented with vaping (just over 24% compared with just under 13%).

After taking account of other potentially influential factors, this was no longer significant, but the numbers involved were small, caution the researchers.

They suggest that there may be plausible explanations for their findings, including that e-cigarette use among teens may simply be an indicator of those who would have started smoking and escalated their habit anyway.

E-cigarette use may also have 'normalised' any kind of nicotine use through developing addiction to it, but they point out that there is no direct evidence as yet to back this up.

Despite attempts to account for a broad range of potential influences, there may be other as yet unexplored factors that are responsible, they add.

This is an observational study, so no firm conclusions can be drawn about cause and effect, something which the researchers are eager to emphasise.

"While acknowledging that a causal relationship may be plausible, we cannot confirm this, based on our findings and the trends observed over the same period in the UK," they write.

"Given the lack of clarity regarding the mechanism linking e-cigarette and cigarette use, we need to be cautious in making policy recommendations based on our findings," they insist.

Research: Do electronic cigarettes increase cigarette smoking in UK adolescents? Evidence from a 12 month prospective study doi 10.1136/tobaccocontrol-2016-053539

Journal: ***Tobacco Control***

Do electronic cigarettes increase cigarette smoking in UK adolescents? Evidence from a 12-month prospective study

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ABSTRACT

Background In cross-sectional surveys, increasing numbers of adolescents report using both electronic cigarettes (e-cigarettes) and cigarettes. This study assessed whether adolescent e-cigarette use was associated prospectively with initiation or escalation of cigarette use.

Methods Data were from 2836 adolescents (aged 13–14 years at baseline) in 20 schools in England. At baseline, breath carbon monoxide levels, self-reported e-cigarette and cigarette use, sex, age, friends and family smoking, beliefs about cigarette use and percentage receiving free school meals (measure of socioeconomic status) were assessed. At 12-month follow-up, self-reported cigarette use was assessed and validated by breath carbon monoxide levels.

Results At baseline, 34.2% of adolescents reported ever using e-cigarettes (16.0% used only e-cigarettes). Baseline ever use of e-cigarettes was strongly associated with subsequent initiation (n=1726; OR 5.38, 95% CI 4.02 to 7.22; controlling for covariates, OR 4.06, 95% CI 2.94 to 5.60) and escalation (n=318; OR 1.91, 95% CI 1.14 to 3.21; controlling for covariates, this effect became non-significant, OR 1.39, 95% CI 0.97 to 1.82) of cigarette use.

Conclusions This is the first study to report prospective relationships between ever use of e-cigarettes and initiation and escalation of cigarette use among UK adolescents. Ever use of e-cigarettes was robustly associated with initiation but more modestly related to escalation of cigarette use. Further research with longer follow-up in a broader age range of adolescents is required.

INTRODUCTION

Electronic cigarettes (e-cigarettes) deliver inhaled aerosol usually containing nicotine. E-cigarettes are thought to have minimal impact on morbidity and mortality[1 2] and are recognised as harm reducing for adult smokers.[2–4] Although rates of adolescent regular use of e-cigarettes are low, rates of ever use are substantial (13%–22%) and have increased over recent years, whereas rates of cigarette use have decreased over the same period both in the USA[5–7] and UK.[8–15] Nevertheless, the possible relationship between adolescent e-cigarette use and the initiation and escalation of cigarette use remains under-researched.

Longitudinal data on e-cigarette use and subsequent cigarette use are currently limited to US samples based on unverified self-reported measures.[16–19] For example, two US studies reported baseline e-cigarette use to be positively associated with the initiation of cigarette use 12 months later in 14-year olds controlling for various predictors of smoking (OR 1.75, 95% CI 1.10 to 2.77; OR 2.87, 95% CI 2.03 to 4.05).[17 18] Barrington-Trimis *et al*[16] reported similar findings over 16 months in 17-year-olds (OR 6.17, 95% CI 3.30 to 11.6), whereas Wills *et al*[19] reported that e-cigarette use was linked to initiation (OR 2.87, 95% CI 2.03 to 4.05) but not to escalation of smoking over 12 months in a sample of adolescents aged 14–15 years.

This study is novel in assessing these relationships between e-cigarette use and subsequent cigarette use in a sample of UK adolescents and in exploring a number of previously unexamined smoking risk factors as covariates and moderators. In particular, we investigated the extent to which baseline ever use of e-cigarettes was associated with the initiation or escalation of cigarette use (objectively validated) 12 months later in a sample of UK adolescents aged 13–14 years. The impact of controlling for various smoking risk factors such as friends and family smoking and their moderating effects was also explored.

METHODS

Participants and procedures

Data were collected as part of a 4-year cluster randomised controlled trial of a school-based smoking initiation intervention[20 21] based on implementation intentions.[22] Data from 2836 adolescents (13–14 years at baseline) in the 20 control schools are reported here. Head teachers consented to school participation with parents given the option to withdraw children from the study. Adolescents consented by completing questionnaires matched across time points using a personally generated code. The data reported here are from waves 3 (September–December 2014; referred to as *baseline*) and 4 (September–December 2015; referred to as *follow-up*) of the trial when e-cigarette use measures were added to the data collection.

The Faculty of Medicine, University of Leeds, UK, ethical review committee approved the study (reference 12–0155).

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Table 1 Descriptive data for the full sample and subsamples

		Cross-sectional sample (total N=2836)		Longitudinal sample of baseline never used cigarettes (total n=1726)		Longitudinal sample of baseline once/ used to use cigarettes (total n=318)	
		N/M	(%/SD)	N/M	(%/SD)	N/M	(%/SD)
Age		13.18	(0.39)	13.18	(0.39)	13.17	(0.39)
Sex	Boy	1411	(49.8%)	898	(48.0%)	164	(51.6%)
	Girl	1425	(50.2%)	898	(52.0%)	154	(48.4%)
Heard of e-cigarettes (baseline)	No	346	(12.2%)	227	(13.2%)	24	(7.5%)
	Yes	2383	(84.2%)	1381	(80.0%)	286	(90.0%)
	Don't know	103	(3.2%)	118	(6.8%)	8	(2.5%)
Ever used e-cigarettes (baseline)	No	1867	(65.8%)	1383	(80.1%)	70	(22.0%)
	Yes	969	(34.2%)	343	(19.9%)	248	(78.0%)
Ever used cigarettes (baseline)	No	2196	(77.4%)	1726)	(100.0%	0	(0.0%)
	Yes	640	(22.6%)	0	(0.0%)	318	(100.0%)
Family smokers = none		898	(31.7%)	666	(38.6%)	42	(13.2%)
Family smokers = one		852	(30.0%)	534	(30.9%)	88	(27.7%)
Family smokers = two		517	(19.2%)	298	(17.3%)	74	(23.2%)
Family smokers = three or more		569	(20.1%)	228	(13.2%)	114	(35.8%)
Friend smokers = none		1384	(48.8%)	1050	(60.8%)	67	(21.1%)
Friend smokers = a few		1135	(40.0%)	613	(35.5%)	189	(59.4%)
Friend smokers = most		317	(11.2%)	63	(3.7%)	62	(19.5%)
Intentions		4.69	(0.77)	4.87	(0.50)	4.48	(0.76)
Attitude		4.73	(0.57)	4.88	(0.32)	4.51	(0.65)
Perceived norms		4.81	(0.57)	4.91	(0.30)	4.66	(0.50)
Perceived behavioural control		4.61	(0.72)	4.78	(0.49)	4.43	(0.71)
Self-efficacy		4.64	(0.77)	4.83	(0.47)	4.41	(0.82)
Free school meals*		14.24	(6.63)	13.82	(6.55)	15.57	(6.35)

*Mean and SD for this variable based on school-level data.

Measures

Cigarette use was assessed using a standardised measure[23] at both time points; adolescents ticked one of the following: 'I have never smoked; I have only tried smoking once; I used to smoke sometimes, but I never smoke cigarettes now; I sometimes smoke cigarettes now, but I don't smoke as many as one a week; I usually smoke between one and six cigarettes a week; and I usually smoke more than six cigarettes a week'. Self-reported smoking was validated against a measure of breath carbon monoxide (CO) levels (using Micro+ Smokerlyzer CO Monitor; Bedfont Scientific Limited, Kent, England, UK). Such measures are reliable and valid ways of assessing regular cigarette smoking[24 25] but not occasional smoking due to the short half-life (4–6 hours) of breath CO.

E-cigarettes/vapourisers were described as 'a tube that sometimes looks like a normal cigarette and has a glowing tip. They all puff a vapour that looks like smoke but unlike normal cigarettes, they don't burn tobacco'. Awareness ('Have you ever heard of e-cigarettes or vapourisers?' yes I have; no I haven't; I don't know) and use ('Which ONE of the following is closest to describing your experience of e-cigarettes or vapourisers?' I have never used them; I have tried them once or twice; I use them sometimes (more than once a month but less than once a week); I use them often (more than once a week)) of e-cigarettes were tapped by single items.

Other measures were assessed as covariates/moderators. Percentage of children at a school eligible for free school meals was used as an indicator of socioeconomic status.[26] Sex and age were measured (age not used in analyses as adolescents from one school year). Family smoking was assessed using the question, 'Who smokes in your family now? Tick all the people who smoke at the moment', followed by a list of family members (zero to nine family members marked; scored as 0, 1, 2 or 3 or more). Friends' smoking was assessed using the question, 'How many of your friends smoke?' none of them; only a few; half and half; most but not all; all of them (scored as none of them, a few or most (last three categories)).

Baseline health cognitions about smoking[21] were assessed as mean of multiple items on five-point scales (high scores indicated negative views of smoking): intention was tapped by three statements ('I plan not to smoke', 'I don't want to smoke' and 'I will try not to smoke'; strongly disagree to strongly agree; Cronbach's alpha 0.90), attitude by seven statements ('For me, smoking would be… good–bad; beneficial–harmful; pleasant–unpleasant; enjoyable–unenjoyable; wise–foolish; fun–not fun; healthy–unhealthy'; Cronbach's alpha 0.87), norms by five statements ('Most of my friends think…'; 'My best male friend thinks…'; 'My best female friend thinks…'; 'My family think…'; 'People who are important to me think…'; I should smoke–I should not smoke; Cronbach's alpha 0.79), perceived behavioural control by three statements ('I am confident I could resist smoking', strongly disagree to strongly agree; 'For me to not smoke would be…', difficult–easy; 'How much control do you feel you have over not smoking?' no control–complete control; Cronbach's alpha 0.69) and self-efficacy by six statements ('I can say no to smoking, even at school'; 'I can say no to smoking even when I am offered a cigarette'; 'I can say no to smoking, even if my friends want me to smoke'; 'I can say no to smoking, even if I was the only one in the group not smoking'; 'I can say no to smoking, even if I feel a bit left out of the group'; 'I can say no to smoking, even if I feel like smoking'; strongly disagree-strongly agree; Cronbach's alpha 0.91).

Table 2 Relationships between cigarette and e-cigarette use: (A) cross-sectional relationships between baseline cigarette and e-cigarette use; (B) prospective relationships between cigarette use at 1-year follow-up and e-cigarette use at baseline among baseline never used cigarettes; (C) prospective relationships between cigarette use at 1-year follow-up and e-cigarette use at baseline among baseline used once or used to use cigarettes

	Baseline e-cigarette use			
	Never	Tried	Infrequent	Frequent
		(1–2 times)	(1/month–1/week)	(>1/week)
Cigarette Use	n (%)	n (%)	n (%)	n (%)
A. Cross-sectional relationships at baseline (n=2836)				
Never	1743 (61.5)	407 (14.4)	40 (1.4)	6 (0.2)
Once	90 (3.2)	201 (7.1)	57 (2.0)	10 (0.4)
Used to	20 (0.7)	59 (2.1)	38 (1.3)	22 (0.8)
Rarely (<1/week)	8 (0.3)	15 (0.5)	31 (1.1)	19 (0.7)
Occasional (1–6/week)	1 (0.0)	6 (0.2)	20 (0.7)	10 (0.4)
Frequent (>6/week)	5 (0.2)	7 (0.2)	6 (0.2)	15 (0.5)
B. Longitudinal relationships for baseline never users of cigarettes (n=1726)				
Never	1259 (72.9)	211 (12.2)	13 (0.8)	1 (0.1)
Once	86 (5.0)	65 (3.8)	8 (0.5)	0 (0.0)
Used to smoke	19 (1.1)	19 (1.1)	1 (0.1)	1 (0.1)
Rarely (<1/week)	11 (0.6)	12 (0.7)	1 (0.1)	0 (0.0)
Occasional (1–6/week)	5 (0.3)	3 (0.2)	2 (0.1)	0 (0.0)
Frequent (>6/week)	3 (0.2)	1 (0.1)	3 (0.2)	2 (0.1)
C. Longitudinal relationships for baseline triers of cigarettes (n=318)				
No change	61 (19.2)	131 (41.2)	43 (13.5)	14 (4.4)
Escalation	9 (2.8)	38 (11.9)	17 (5.3)	5 (1.6)

Data analysis

We tested for differences on each baseline measure between adolescents who had complete versus missing values on one or more measures using χ^2 tests and t-tests. Among respondents completing all measures, we report descriptives on baseline measures for three subsamples: full cross-sectional sample, longitudinal subsample of baseline never users of cigarettes and longitudinal subsample of baseline occasional users of cigarettes. The relationship between e-cigarette and cigarette use was examined next in the same three subsamples. Self-rated smoking was validated against breath CO levels at baseline and follow-up using Games–Howell post hoc tests based on 1000 bootstrapped resamples because the data were skewed and had unequal variances.

Given the problems with imputing values for outcome variables,[27] attrition analyses were used to assess biases in all baseline measures in those with and without matched follow-up data (at follow-up 1=data missing; 0=data available) in the two longitudinal subsamples using multilevel logistic regressions (in R) to assess model fit (Akaike Information Criterion) and, for each predictor, the odds ratios (OR), 95% CIs and p value. The main analyses used the same analysis to predict follow-up initiation (1=smoked; 0=never smoked) or escalation (0=never, once or used to smoke cigarettes; 1=rarely, occasional or frequent cigarette smoking) of smoking based on ever use of e-cigarettes and covariates. E-cigarette use was dichotomised into never versus ever use due to few regular users. Model 1 controlled for the clustering of adolescents within schools, and baseline e-cigarette ever use was a predictor; model 2 added baseline covariates; and model 3 tested interactions between each covariate and e-cigarettes ever use. To assess the impact of baseline missing values, we repeated the regressions with imputation.[28]

RESULTS

Sample description

At baseline, full data were available on 2836 adolescents, who did not differ (p>0.05) from those with missing data (N=58–92) on all measures except sex (p=0.001; boys less likely to have complete data) and norms (p=0.02; those with lower norms to not smoke less likely to have complete data).

Table 1 provides descriptive data on baseline measures for respondents who completed all measures. The cross-sectional sample (table 1) was mostly aged 13 years, approximately half boys, and a majority not having ever used e-cigarettes or cigarettes. Levels of e-cigarette awareness and use were lower in the never smoking subsample (table 1: 80.0% heard of, 19.9% used e-cigarettes) compared with the subsample reporting occasional smoking (table 1: 90.0% heard of, 78.0% used e-cigarettes).

At baseline and follow-up, CO levels were low and not significantly different between those reporting they never smoked, had only tried smoking once, used to smoke sometimes or smoked sometimes but not as many as one per week; CO levels were significantly higher (p<0.05) among those reporting they smoked 1–6 or >6 cigarettes per week but not significantly different across these latter two categories.

Simple relationships between use of e-cigarettes and cigarettes

Table 2 reports the relationship between e-cigarette and cigarette use in the three subsamples. Table 2A shows the cross-sectional relationship: 61.5% of the sample had tried neither e-cigarettes nor cigarettes, 16.0% had tried e-cigarettes but not cigarettes, 4.4% had tried cigarettes but not e-cigarettes and 18.2% had used both.

Table 2B shows the longitudinal relationship between baseline e-cigarette use and follow-up cigarette use in the baseline

Table 3 Association of baseline measures with missingness (1=absent) at follow-up for baseline never used cigarettes (n=2196; left-hand column) and baseline once or used to use cigarettes (n=497; right-hand column)

	Baseline never used cigarettes		Baseline once or used to use cigarettes	
Predictors	**OR (95% CI)**	**p Value**	**OR (95% CI)**	**p Value**
Never used e-cigarettes	1.00		1.00	
Ever used e-cigarettes	1.11 (0.85 to 1.46)	0.43	0.83 (0.51 to 1.35)	0.44
Friend smokers= none	1.00		1.00	
Friend smokers=a few	1.18 (0.93 to 1.49)	0.18	2.08 (1.12 to 3.82)	0.019
Friend smokers= most	1.36 (0.78 to 2.39)	0.28	4.33 (2.10 to 8.95)	<0.001
Male	1.00		1.00	
Female	0.70 (0.56 to 0.86)	<0.001	0.84 (0.6 to 1.26)	0.40
Family smokers = none	1.00		1.00	
Family smokers = one	1.29 (0.99 to 1.67)	0.057	0.90 (0.47 to 1.71)	0.74
Family smokers = two	1.10 (0.79 to 1.51)	0.58	0.97 (0.50 to 1.89)	0.93
Family smokers = three or more	1.53 (1.10 to 2.12)	0.01	0.81 (0.43 to 1.53)	0.51
Intentions	0.77 (0.62 to 0.96)	0.02	0.99 (0.71 to 1.38)	0.95
Attitudes	0.93 (0.65 to 1.31)	0.66	1.29 (0.86 to 1.93)	0.22
Norms	0.95 (0.66 to 1.37)	0.78	0.99 (0.65 to 1.52)	0.97
Perceived behavioural control	0.91 (0.73 to 1.14)	0.42	0.64 (0.46 to 0.88)	0.006
Self-efficacy	1.25 (0.95 to 1.64)	0.11	1.15 (0.79 to 1.67)	0.46
Free school meals	1.03 (0.97 to 1.08)	0.34	1.01 (0.97 to 1.06)	0.49

Baseline never used cigarettes, AIC=2222.6; baseline once or used to use cigarettes, AIC=658.7.

never smokers; initiation of cigarette use in the next 12 months rose from 9.0% to 34.4%, respectively, in baseline never versus ever used e-cigarettes. Baseline CO levels were low among the self-reported never smokers, and exclusion of adolescents with higher baseline CO levels (>2 ppm) did not substantively change the regression findings. CO levels at follow-up were significantly higher among those classified as initiating compared with not initiating cigarette use ($p<0.05$).

Table 2C shows the longitudinal relationship between e-cigarette use at baseline and escalation of cigarette use at follow-up among baseline occasional smokers; escalation in the next 12 months rose from 12.9% to 24.2%, respectively, in those never versus ever having used e-cigarettes at baseline. Baseline CO levels were low among those self-reporting that they had only once used or former smokers and exclusion of adolescents with higher baseline CO levels (>2 ppm) did not substantively change the regression findings. CO levels at follow-up were significantly higher among those classified as escalating versus not escalating smoking ($p<0.001$).

Attrition analyses

At baseline, 2196 adolescents (77.4%) reported never having smoked but only 1726 adolescents (78.6%) could be matched across time points. The similar number of adolescents completing questions at each time point (total N=2928 and 2747 at baseline and follow-up, respectively) suggests that attrition was principally due to a failure to match personally generated codes.

Analyses (table 3) indicated no significant effects for baseline ever used e-cigarettes, friends' smoking, attitude, norms, perceived behavioural control, self-efficacy or free school meals on missingness; however, there were significant effects for sex (OR 0.70, 95% CI 0.56 to 0.86; girls less likely to be missing), family smoking (OR 1.53, 95% CI 1.10 to 2.12; with three or more family members who smoked more likely to be missing) and intention (OR 0.77, 95% CI 0.62 to 0.96; with weaker intentions not to smoke more likely to be missing).

At baseline, 497 adolescents reported trying or past use of cigarettes. We matched 318 adolescents (64.0%) across time points. Analyses indicated no significant effects for baseline ever used e-cigarettes, sex, family smoking, intention, attitude, perceived behavioural control, self-efficacy and free school meals on missingness (table 3); however, there were significant effects for friends' smoking (OR 2.08, 95% CI 1.12 to 3.82 for few friends smoking; OR 4.33, 95% CI 2.10 to 8.95 for most friends smoking; with a few or most friends who smoked more likely to be missing) and perceived behavioural control (OR 0.64, 95% CI 0.46 to 0.88; with weaker perceived behavioural control over not smoking more likely to be missing).

Prospective analyses

Initiation of cigarette use at follow-up was predicted by having ever used e-cigarettes at baseline (table 4, model 1; OR 5.38, 95% CI 4.02 to 7.22) and remained so when controlling for covariates (table 4, model 2; OR 4.06, 95% CI 2.94 to 5.60). Initiation of cigarette use was significantly higher in adolescents who at baseline were ever users of e-cigarettes, had either a few or most friends who smoked and had one, two or three or more family members who smoked, but was significantly lower in adolescents with stronger intentions (not to smoke). Exploratory analyses revealed that baseline friends' smoking was a statistically significant moderator ($p<0.001$; all other moderators $p>0.43$). Decomposition of the moderation effect (table 4, model 3) indicated that the the impact of ever used e-cigarettes on likelihood of initiating cigarette use was attenuated among those with a few or most friends who smoked at baseline. Multiple imputation resulted in an additional 28 cases in this analysis. The estimated model coefficients showed very little change (mostly <1%), and there was no change in the interpretation.

Table 4 also reports the results of the regressions to predict escalation of cigarette use at follow-up. In model 1, ever use of e-cigarettes at baseline was a significant predictor of escalation of cigarette use (OR 2.16, 95% CI 1.01 to 4.62). In model 2, ever use of e-cigarettes at baseline became a non-significant predictor of escalation when controlling for covariates (OR 1.89, 95% CI 0.82 to 4.33). Escalation of cigarette use was significantly higher in adolescents who had most friends who

Table 4 Association of baseline ever used e-cigarettes with ever used cigarettes at follow-up (among never users of cigarettes at baseline; n=1726; left-hand column) or increased use of cigarettes at follow-up (among baseline once or used to use cigarettes; n=318; right-hand column) controlling for clustering by school

	Baseline never used cigarettes		Baseline once or used to use cigarettes	
Predictors	**OR (95% CI)**	**p Value**	**OR (95% CI)**	**p Value**
Model one without covariates				
Never used e-cigarettes	1.00		1.00	
Ever used e-cigarettes	5.38 (4.02 to 7.22)	<0.001	2.16 (1.01 to 4.62)	0.046
Model two with covariates				
Never used e-cigarettes	1.00		1.00	
Ever used e-cigarettes	4.06 (2.94 to 5.60)	<0.001	1.89 (0.82 to 4.33)	0.13
Friend smokers = none	1.00		1.00	
Friend smokers = a few	1.87 (1.35 to 2.58)	<0.001	1.15 (0.50 to 2.66)	0.75
Friend smokers = most	2.99 (1.52 to 5.87)	0.001	3.23 (1.19 to 8.77)	0.022
Male	1.00		1.00	
Female	1.32 (0.97 to 1.79)	0.08	0.83 (0.45 to 1.52)	0.55
Family smokers = none	1.00		1.00	
Family smokers = one	0.76 (0.51 to 1.13)	0.18	1.69 (0.61 to 4.68)	0.31
Family smokers = two	2.05 (1.37 to 3.06)	<0.001	1.41 (0.48 to 4.12)	0.53
Family smokers = three or more	1.90 (1.23 to 2.94)	0.004	1.23 (0.45 to 3.41)	0.69
Intentions	0.70 (0.52 to 0.96)	0.03	1.50 (0.87 to 2.57)	0.14
Attitudes	0.68 (0.44 to 1.04)	0.08	0.51 (0.28 to 0.90)	0.020
Norms	0.89 (0.57 to 1.39)	0.61	1.12 (0.56 to 2.23)	0.75
Perceived behavioural control	1.00 (0.73 to 1.37)	0.99	0.99 (0.58 to 1.69)	0.96
Self-efficacy	1.09 (0.75 to 1.57)	0.66	0.57 (0.35 to 0.94)	0.027
Free school meals	0.99 (0.97 to 1.02)	0.60	1.01 (0.96 to 1.07)	0.62
Model three with covariates and interactions				
Never used e-cigarettes and Friend smokers = none	1.00			
Ever used e-cigarettes and friend smokers = none	7.74 (4.68—12.79)	<0.001		
Never used e-cigarettes and Friend smokers = a few	2.57 (1.72 to 3.84)	<0.001		
Ever used e-cigarettes and friend smokers = a few	7.84 (5.08–12.09)	<0.001		
Never used e-cigarettes and friend smokers = most	6.32 (2.68 to 14.91)	<0.001		
Ever used e-cigarettes and friend smokers = most	8.75 (3.68–20.83)	<0.001		
Male	1.00			
Female	1.37 (1.01 to 1.86)	0.04		
Family smokers = none	1.00			
Family smokers = one	0.76 (0.51 to 1.14)	0.19		
Family smokers = two	2.02 (1.35 to 3.03)	<0.001		
Family smokers = three or more	1.87 (1.21 to 2.90)	0.005		
Intentions	0.70 (0.52 to 0.96)	0.03		
Attitudes	0.67 (0.44 to 1.01)	0.06		
Norms	0.91 (0.59 to 1.41)	0.69		
Perceived behavioural control	1.00 (0.73 to 1.37)	0.99		
Self-efficacy	1.09 (0.75 to 1.59)	0.65		
Free school meals	0.99 (0.96 to 1.02)	0.47		

Follow-up ever used cigarettes: model without covariates, AIC=1281.3; model with covariates, AIC=1226.5; model with covariates and interactions, AIC=1218.7; follow-up escalation of cigarette use: model without covariates, AIC=334.1; model with covariates, AIC=327.5.

smoked, but was significantly lower in those adolescents with stronger attitudes (not to smoke) and intentions (not to smoke). Exploration of moderation effects revealed that two interactions were statistically significant (attitudes, p=0.01; intentions, p=0.02), although decomposition of these effects did not reveal significant effects of e-cigarette use on escalation of cigarette use at different levels of either moderator (p>0.20). None of the other moderators approached statistical significance (p>0.16). Multiple imputation did not change any values or the analyses.

The ORs based on logistic regression analyses reported in table 4 may overestimate the degree of association between e-cigarette use and subsequent smoking because the prevalence of the outcome exceeds the usual 15% cut-off. To assess the degree of overestimation, we ran the initial models (model 1 in table 4) using a log binomial model. For the analyses of never smokers, the degree of association was reduced but remained statistically significant: incidence relative risk (IRR) was 3.85 (95% CI 3.07 to 4.82), p<0.001. For the analyses of smoking escalation, the degree of association was also reduced and no longer statistically significant: IRR=1.81 (95% CI 095 to 3.44), p=0.071.

DISCUSSION

We showed that ever use of e-cigarettes is associated with initiation of cigarette use; an effect that remains when controlling for various predictors of smoking. Our study in UK adolescents

(13–14 years old) found patterns similar to those reported in longitudinal studies among adolescents aged 13–14 years and older[16–19] in the USA with comparable sized ORs (the IRR was also of a comparable magnitude). Together, these studies suggest that it is unlikely that the high rates of dual use of e-cigarette and cigarette use observed in the USA[5–7] and UK[8–15] in cross-sectional surveys of adolescents are entirely attributable to cigarette users subsequently taking up e-cigarettes. A significant minority of adolescents try e-cigarettes first (19.9% here) and later initiate cigarette use. Our findings also indicated that the association between ever use of e-cigarettes and initiation of cigarette use was particularly strong among adolescents with no friends who smoked, a group usually considered to be less susceptible to smoking initiation (see the study by Barrington-Trimis *et al*[16] for similar moderation effect among those with low intentions to smoke). In relation to escalation of cigarette use, the OR showed that ever use of e-cigarettes is associated with subsequent escalation, although this effect was attenuated when using the IRR or when controlling for covariates. However, given the limited numbers escalating their cigarette use in this study and lack of support in other studies, these findings should be treated cautiously (eg, other studies either did not find e-cigarette use to be related to change in frequency of smoking among baseline ever-smokers,[19] or found that baseline frequency of use of e-cigarettes was only associated with follow-up smoking frequency among baseline non-smokers and not among baseline infrequent or frequent smokers[29]).

Our research provides limited insights into the mechanism relating ever use of e-cigarettes to subsequent initiation and escalation of cigarette use. In principle, it is possible that e-cigarette use in adolescents is a marker for those who would have initiated or escalated cigarette use even if e-cigarettes had not been available. Among such adolescents, the availability of e-cigarettes may have simply delayed initiation or escalation. However, at least in relation to initiation, the fact that e-cigarette use was a bigger risk factor in groups considered least at risk (ie, no friends who smoke at baseline) argues against this (see the study by Barrington-Trimis *et al*[19] for a similar moderator effect also difficult to reconcile with this explanation). It is also plausible that the use of e-cigarettes might lead to initiation and escalation in cigarette use by normalising any kind of nicotine use, by developing nicotine addiction (if the e-cigarettes contain nicotine) or by developing friendship networks with smokers and decreasing the perceived risks of smoking.[30–32] However, there is no direct evidence yet to suggest that ever use of e-cigarettes normalises cigarette use.

Given the lack of clarity regarding the mechanism linking e-cigarette and cigarette use, we need to be cautious in making policy recommendations based on our findings. We acknowledge that since our survey, UK legislation has been put in place, including bans on marketing and selling e-cigarettes to minors. UK agencies are required to enforce age of sale, child and tamper proof packaging and display age of sale signage and health warnings on e-cigarette packaging. Nevertheless, our findings emphasise the value of regulating the marketing and sale of e-cigarettes to minors in countries without such measures, particularly given that e-cigarette advertising has been shown to reduce perceived harm of occasional smoking.[33]

Our study's strengths include a large demographically diverse sample, measurement of e-cigarette and cigarette use over 12 months, exploration of initiation and escalation of cigarette use, validation of smoking measures and exploration of covariates and moderators not previously examined. There are also weaknesses. First, our study had a relatively high attrition. This was principally attributable to problems in matching participants' personally generated anonymous codes, although attrition analyses indicated relatively modest biases in the final compared with initial sample. Second, like other similar studies, we focused on self-reported e-cigarette and cigarette use. Although we validated the self-reported smoking against an objective measure of CO, we did not have a way of validating e-cigarette use. Third, we failed to distinguish types of e-cigarette use (e-cigarettes vary in a number of ways, including the delivery method and whether they contain nicotine). Furthermore, our description of e-cigarettes and the timing of our survey might have restricted our study to first-generation devices, in which their nicotine delivery profile mimic less closely to cigarettes than do more recent generations.[34] Exploring relationships between use of new generations of e-cigarettes both containing nicotine or not and subsequent cigarette use is an important issue for further research. The current research focused on cigarette use, although other studies have reported similar effects with various tobacco products.[18]

A fourth limitation concerns our main analyses (table 4), which were restricted to ever use of e-cigarettes, and we were unable to test whether more regular use of e-cigarettes was more strongly associated with initiating or escalating cigarette use (see table 2; see the study by Warner[6] for cross-sectional data). Relatedly, our analyses of impacts on escalation should be treated cautiously given the limited numbers escalating cigarette use during the period studied and the fact that our findings conflict with published work.[19] Fifth, our research was restricted to a limited geographical area (two English counties), although it did extend findings from several US states. Sixth, our research focused on a limited age range (baseline: 13–14 years; most published studies[17–19] are with this age group). Future studies should explore effects in different aged adolescents and over varying time periods. Finally, our research could only consider a finite number of covariates and moderators, and it is plausible that important factors were omitted. Previous related studies[16–19] have examined various other factors (eg, sensation seeking, impulsivity, other substance use, delinquent behaviour, academic performance and race/ethnicity). It would be valuable to test these additional covariates and moderating variables in future work.

In summary, this is the first study to report longitudinal relationships between ever use of e-cigarettes and initiation or escalation of cigarette use among UK adolescents. Despite measuring and accounting for the influence of a broad range of variables in this and other studies,[16–19] it is possible that any third variables could have been responsible for the observed relationships. Therefore, while acknowledging that a causal relationship may be plausible, we cannot confirm this based on our findings and the trends observed over the same time period in the UK; rates of e-cigarette use have increased, but the rates of cigarette use have continued to decline. Future research could seek to disentangle these apparently contrary findings and assess dose–response relationships between e-cigarette and cigarette use over longer-time periods in a broader age range of adolescents while controlling for a range of covariates and assessing the impact of antismoking interventions.

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What this paper adds

Previous research: In cross-sectional surveys of UK adolescents, electronic cigarette (e-cigarette) use is increasing, cigarette use is decreasing and increasing numbers of adolescents report using both e-cigarettes and cigarettes. Several studies among US adolescents suggest that self-reported e-cigarette use is associated with subsequent initiation of cigarette use, whereas one study in US adolescents found no association between e-cigarette use and escalation of cigarette use. However, these studies were all conducted in the USA, did not validate their self-reported smoking measures against objective measures and assessed only a limited range of risk factors for smoking as covariates and moderators of these relationships.
Interpretation: Associations similar to those found in the previous studies are reported in a sample of UK adolescents and are validated against breath CO measures. Data collected over a 12-month period confirmed a sizeable relationship between ever use of e-cigarettes and subsequent initiation of cigarette use and showed that e-cigarette use is modestly associated with subsequent escalation of cigarette use. The former but not the latter relationship remained after controlling for various other risk factors for smoking (eg, intentions to smoke), only some of which had been assessed in previous studies. These findings support the robustness of the relationship between ever use of e-cigarettes and initiation of cigarette use but suggest the relationship between ever use of e-cigarettes and escalation of cigarette use may be explainable by other factors. Ever use of e-cigarettes was a stronger predictor of initiation of cigarette use in those with no friends who smoked at baseline compared with those with a few or most friends who smoked at baseline. The latter finding would not appear to be consistent with the suggestion that e-cigarette use may simply be a marker for those who would go on to smoke cigarettes even without having tried e-cigarettes.

of major outputs. The authors of this article affirm that the manuscript is an honest, accurate and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been explained.

Contributors MC had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. Study concept and design: MC, SG, RL, CJA, CT, RW and KS . Acquisition, analysis or interpretation of data: MC, SG, RSE, KF, BSM, LC, RL, CJA, DM, CT, RW and KS . Drafting of the manuscript: MC and SG. Critical revision of the manuscript for important intellectual content: MC, SG, RL, CJA, DM, CT, RW and KS. Statistical analysis: RW and MC. Obtained funding: MC, SG, CJA, CT, RW and KS. Administrative, technical or material support: RS-E, KF, BSM and LC. Study supervision: MC, SG, RL and DM.

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Teens who use e-cigarettes are 'nearly five times more likely to smoke tobacco later in life'

dailymail.co.uk/health/article-8097927/Teens-use-e-cigarettes-nearly-five-times-likely-smoke-tobacco-later-life.html

March 10, 2020

- **Many health experts view e-cigarettes as crucial tool in fight against tobacco and Public Health England has repeatedly endorsed the devices**
- **But others are worried about safety concerns and their use by young people**
- **Schoolchildren in England are now more likely to have tried e-cigarettes than traditional cigarettes**
- **More than one in three 15-year-olds have used the devices despite the fact it has been illegal to sell them to under-18s since October 2015**

Youngsters who use e-cigarettes are nearly five times more likely to go on to try tobacco, research published yesterday says.

The study adds considerable evidence to the theory that 'vaping' can be a gateway to smoking cigarettes.

Many health experts view e-cigarettes as a crucial tool in the fight against tobacco and Public Health England has repeatedly endorsed the devices.

But others are worried about unresolved safety concerns and their use by young people.

Youngsters who use e-cigarettes are nearly five times more likely to go on to try tobacco, research published yesterday says. The study adds considerable evidence to the theory that 'vaping' can be a gateway to smoking cigarettes. (File photo)

Schoolchildren in England are now more likely to have tried e-cigarettes than traditional cigarettes. More than one in three 15-year-olds have used the devices despite the fact it has been illegal to sell them to under-18s since October 2015.

The research, led by scientists at the University of Bristol, combined the results of 17 studies to investigate whether non-smokers who tried e-cigarettes were more likely to go on to tobacco.

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The data, which included under-30s in the UK, US, the Netherlands, Germany, Canada and Mexico, found that using e-cigarettes increased the odds of subsequently smoking tobacco by a factor of 4.6, when compared with those who had never vaped.

The researchers said that after years of falling tobacco use, widespread uptake of e-cigarettes had created a new generation of smokers. Among the under-18s the effect was even greater, they said.

Data, which included under-30s in the UK, US, the Netherlands, Germany, Canada and Mexico, found that using e-cigarettes increased the odds of subsequently smoking tobacco by a factor of 4.6, when compared with those who had never vaped. (File photo)

If this age group was excluded from the data, the odds of taking up cigarettes was 3.17 times higher among vapers than non-vapers.

But if under-18s were included, the multiplier rose to 4.87.

The scientists, who are funded by the research arm of the NHS, the British Heart Foundation and Cancer Research UK, stressed that the findings were not definitive. For example, they said the link could be explained by the tendency of rebellious teenagers who try e-cigarettes to be more likely to experiment with smoking.

They wrote in the journal Tobacco Control: 'In adolescence, risk-taking is common and decision making for health-risk behaviours is influenced by peers, societal influences and parental monitoring.'

But they said there was some evidence of a causal link, with all the data going 'consistently in the same direction'.

They added: 'There are plausible causal pathways (e.g. nicotine addiction, similar hand-to-mouth actions for both behaviours).

'This suggests the results provide some support for a causal relationship between e-cigarette use and later smoking.

'This is in line with the theory that e-cigarettes act as a gateway to smoking.

'E-cigarettes have historically not delivered nicotine as effectively as cigarettes, so that e-cigarettes may not be adequate to satisfy users who become more heavily addicted to nicotine.'

How vaping has REVERSED the fall in nicotine use and tobacco giants are cashing in on the surprising trend

- **Documents published by British American Tobacco show the emergence of vaping has reversed a decline in nicotine use**
- **Both BAT and rival Imperial Brands state that vaping is 'additive' for their firms**
- **This indicates that e-cigarettes are helping tobacco firms to boost revenues**

By MATTHEW CHAPMAN, FINANCIAL MAIL ON SUNDAY
PUBLISHED: 21:51 BST, 20 July 2019 | **UPDATED:** 10:41 BST, 21 July 2019

The rise of e-cigarettes marketed as a safer alternative for smokers has led to more people getting hooked on nicotine products, research by a major tobacco company has revealed.

Documents published by FTSE 100 giant British American Tobacco show the emergence of vaping and the use of other less harmful tobacco products has reversed a decline in nicotine use.

Between 2007 and 2012, the number of nicotine users in BAT's top 40 markets outside of the US fell steadily from 366 million to 345 million as millions kicked smoking for health reasons. But its internal data showed the total had climbed to 362 million by 2017.

The rise of e-cigarettes marketed as a safer alternative for smokers has led to more people getting hooked on nicotine products, research by a major tobacco company has revealed

In documents unearthed by The Mail on Sunday, both BAT and rival Imperial Brands stated that vaping is 'additive' for their businesses.

This indicates that e-cigarettes are helping tobacco firms to boost revenues, as opposed to merely replacing lost income from falling cigarette sales.

The resurgence in nicotine use has coincided with the soaring popularity of vaping. A vaping device simulates smoking without burning tobacco.

Instead a liquid containing nicotine is heated electronically, producing a flavoured vapour that the user inhales.

The number of those who vape worldwide increased from about seven million in 2011 to 35 million in 2016, according to researcher Euromonitor.

Other alternatives to cigarettes include devices in which tobacco is heated rather than burned in order to reduce toxins.

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According to the independent Royal Society for Public Health, nicotine on its own is no more harmful than caffeine. E-cigarettes are promoted by Public Health England as aids for giving up smoking.

However, BAT's research found just 18 per cent of those who used its vaping devices were smokers who had quit.

In a briefing to financial analysts late last year, chief executive Nicandro Durante revealed that a study found 5 per cent of vapers had never smoked before, 8 per cent were relapsed smokers and 70 per cent both smoked and vaped.

Concern has also been raised that vaping is becoming increasingly popular among teenagers and other young people, creating a new market for tobacco companies.

In documents unearthed by The Mail on Sunday, both BAT and rival Imperial Brands stated that vaping is 'additive' for their businesses. This indicates that e-cigarettes are

helping tobacco firms to boost revenues

The devices have been tried by a quarter of children aged 11 to 15, according to the NHS. Some vaping liquids and devices are marketed using cartoon characters and images of sweets.

Linda Bauld, professor of public health at the University of Edinburgh and a government adviser on tobacco harm reduction, said it was 'potentially a good thing' that there were more options for those who want to quit smoking.

But she added: 'The main concern about nicotine is that it addicts you to a product that potentially has other stuff in it that is harmful.'

A BAT presentation to investors in March said the total nicotine revenue pool is 'growing rapidly' thanks to the rise of cigarette alternatives. It estimates revenues will grow 25 per cent between 2018 and 2023 to around £100 billion across its top 40 markets.

Earlier this month, tobacco firm Imperial Brands said it would abandon its policy of hiking its dividend to shareholders in order to reinvest money into the e-cigarette market.

Chief executive Alison Cooper has said the company's blu vaping devices are an 'additive business on top of that of tobacco delivery'.

Imperial Brands has predicted the global vaping market will grow between 300 and 500 per cent by 2025 with 'limited impact' on its revenue from cigarettes.

BAT has already seen a significant rise in sales from its non-cigarette lines. The tobacco giant's so-called 'Potentially Reduced Risk Products' business has grown to pull in annual revenues of £2 billion in just three years.

The Mail on Sunday has previously reported that vaping and tobacco heating devices generate higher profit margins than cigarette sales.

'Smokers who have struggled to kick the habit should try an

The shift towards new products comes as the Government seeks to eradicate smoking in England by 2030.

A spokesman for Imperial Brands said: 'The risks to smokers' health are caused by the toxicants released from burning tobacco, not by the naturally occurring nicotine.'

Andrej Kuttruf, board member of the UK Vaping Industry Association, said: 'Vaping is at least 95 per cent less harmful than smoking and you are three times more likely to quit smoking if you vape.

'Figures from Action on Smoking and Health show that of young people aged 11 to 18 who have never smoked, only 0.8 per cent are current vapers.'

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REVIEW ARTICLE

Harmful effects of nicotine

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ABSTRACT

With the advent of nicotine replacement therapy, the consumption of the nicotine is on the rise. Nicotine is considered to be a safer alternative of tobacco. The IARC monograph has not included nicotine as a carcinogen. However there are various studies which show otherwise. We undertook this review to specifically evaluate the effects of nicotine on the various organ systems. A computer aided search of the Medline and PubMed database was done using a combination of the keywords. All the animal and human studies investigating only the role of nicotine were included. Nicotine poses several health hazards. There is an increased risk of cardiovascular, respiratory, gastrointestinal disorders. There is decreased immune response and it also poses ill impacts on the reproductive health. It affects the cell proliferation, oxidative stress, apoptosis, DNA mutation by various mechanisms which leads to cancer. It also affects the tumor proliferation and metastasis and causes resistance to chemo and radio therapeutic agents. The use of nicotine needs regulation. The sale of nicotine should be under supervision of trained medical personnel.

Key words: *Addiction, cancer, cardiovascular, gastrointestinal, nicotine, respiratory*

INTRODUCTION

Tobacco is the leading cause of preventable cancers. WHO estimated around 1.27 billion tobacco users worldwide. Tobacco consumption alone accounts for nearly 5.4 million deaths per year and one billion people may die in this century if global tobacco consumption remained at the current levels.[1] An international treaty spearheaded by WHO in 2003 and signed by 170 countries, aims to encourage governments to reduce the production, sales, distribution advertisement and promotion of tobacco products. Despite strong opposition from the Industry, the treaty has been making steady progress in achieving its goal of comprehensive tobacco control around the world.[2] As tobacco consumption is being curbed, there is a growing demand for cessation. Pharmacological treatment of nicotine addiction remains an active area of research. There are many nicotine preparations (nicotine gums, patches, e cigarettes and inhalational agents) that are freely available in most parts of the world. These products are being heavily promoted and marketed as magical remedies. Nicotine gums are available in 2 mg and 4 mg preparation that deliver around 1 mg and 3 mg nicotine to the blood stream respectively. E-cigarette, a sophisticated nicotine delivery device, delivers nicotine in a vapor form and it closely mimics the act of smoking. Currently, these products constitute approximately 1% of total nicotine consumption and are showing an increasing trend in most countries.[3]

Nicotine is well known to have serious systemic side effects in addition to being highly addictive. It adversely affects the heart, reproductive system, lung, kidney etc. Many studies have consistently demonstrated its carcinogenic potential. [Table 1] The only other known use of nicotine has been as an insecticide since 17th century.[4] After World War II, its use has declined owing to the availability of cheaper, more potent pesticides that are less harmful to mammals. The environment Protection Agency of United States has banned use of nicotine as a pesticide from 1st January 2014.[4] India, one of the largest producer and exporter of nicotine sulphate, has progressively banned its use as agricultural pesticide.[5] We undertook this review to evaluate the systemic adverse effects of nicotine.

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MATERIALS AND METHODS

A computer aided search of the Medline and PubMed databases was done using different combination of the keywords "nicotine," "chemical composition," "history," "metabolism," "addiction," "cancer," "toxic," "endocrine system," "cardiovascular system," "respiratory system,"

Table 1: Studies showing nicotine as a carcinogen

Author	Model	System	References
Jensen *et al*., 2012	Animal	Gastrointestinal	[50]
Schuller *et al*., 1995	Animal	Lung cancer	[45]
Nakada *et al*. 2012	Human	Tumor promoter in lung cancer	[46]
Al-Wadei *et al*., 2009	Mice	Pancreatic cancer	[56]
Treviño *et al*., 2012	Animal	Pancreatic cancer	[58]
Crowley-Weber *et al*., 2003	Human	Pancreatc cancer	[57]
Chen *et al*., 2011	Human	Breast cancer	[59]
Wassenaar *et al*., 2013	Human	Lung	[44]

"lung carcinogenesis, "gastrointestinal system," "immune system," "ocular," " cataract," "central nervous system," "renal system," " reproductive system," "menstrual cycle," "oocytes," "foetus,". Initial search buildup was done using "Nicotine/adverse effects" [Mesh], which showed 3436 articles. Articles were analyzed and 90 relevant articles were included in the review. All the animal and human studies that investigated the role of nicotine on organ systems were analyzed. Studies that evaluated tobacco use and smoking were excluded. All possible physiological effects were considered for this review. We did not exclude studies that reported beneficial effects of nicotine. The objective was to look at the effects of nicotine without confounding effects of other toxins and carcinogens present in tobacco or tobacco smoke.

CHEMICAL PROPERTIES AND METABOLISM

Nicotine was first extracted from tobacco by German physicians Wilhelm Heinrich Posselt and Karl Ludwig Reimann. Nicotine, a strong alkaloid, in its pure form is a clear liquid with a characteristic odour. It turns brown on exposure to air. It is water soluble and separates preferentially from organic solvents. It is an amine composed of pyridine and pyrrolidine rings.

Nicotine is a dibasic compound and the availability and absorption in human body depends upon the pH of the solution.[7] The absorption can occur through oral mucosa, lungs, skin or gut.[6] The increase in pH of a solution causes an increase in concentrations of uncharged lipophilic nicotine, in this form it can actively pass through all biological membranes.[7] The addition of slaked lime and catechu to tobacco increases the absorption of nicotine from the oral cavity.

Nicotine once ingested, is absorbed and metabolized by the liver. The metabolic process can be categorized into two phases. In phase I there is microsomal oxidation of the nicotine via multiple pathways.[8] This leads to formation of various metabolites like cotinine and nornicotine, demethyl cotinine, trans-3-hydroxy-cotinine and d-(3-pyridyl)-g-methylaminobutyric acid.[9,10] Thereafter in phase II there is N'-and O'-glucuronidation of the metabolites and excretion via urine, feces, bile, saliva, sweat etc.[11,12] 5-10% of elimination is by renal excretion of unchanged nicotine, however there is reabsorption from the bladder when the urinary pH is high.[14] There is evidence that nitrosation of nicotine *in vivo* could lead to formation of N-nitrosonornicotine (NNN) and 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone (NNK).[13] which are known to be highly carcinogenic. Inflammation in the oral cavity increases risk of endogenous nitrosation.

MECHANISM OF ACTION

Nicotine acts via 3 major mechanisms, producing physiological and pathological effects on a variety of organ systems.[15,16]

1. Ganglionic transmission.
2. Nicotinic acetylcholine receptors (nAChRs) on chromaffin cells via catecholamines.
3. Central nervous system (CNS) stimulation of nAChRs.

Brain imaging studies demonstrate that nicotine acutely increases activity in the prefrontal cortex and visual systems. There is release of a variety of neurotransmitters important in drug-induced reward. Nicotine also causes an increased oxidative stress and neuronal apoptosis, DNA damage, reactive oxygen species and lipid peroxide increase. nAChRs were originally thought to be limited to neuronal cells, however, studies have identified functional nAChRs in tissues outside the nervous system. Actions on nicotinic receptors produce a wide variety of acute and long-term effects on organ systems, cell multiplication and apoptosis, throughout the body.

IMMEDIATE EFFECTS AND TOXICITY

Nicotine on direct application in humans causes irritation and burning sensation in the mouth and throat, increased salivation, nausea, abdominal pain, vomiting and diarrhea.[17] Gastrointestinal effects are less severe but can occur even after cutaneous and respiratory exposure.[18] Predominant immediate effects as seen in animal studies and in humans consist of increase in pulse rate and blood pressure. Nicotine also causes an increase in plasma free fatty acids, hyperglycemia, and an increase in the level of catecholamines in the blood.[19,20] There is reduced coronary blood flow but an increased skeletal muscle blood flow.[20,22] The increased rate of respiration causes hypothermia, a

hypercoagulable state, decreases skin temperature, and increases the blood viscosity.

Nicotine is one of the most toxic of all poisons and has a rapid onset of action. Apart from local actions, the target organs are the peripheral and central nervous systems. In severe poisoning, there are tremors, prostration, cyanosis, dypnoea, convulsion, progression to collapse and coma. Even death may occur from paralysis of respiratory muscles and/or central respiratory failure with a LD50 in adults of around 30-60 mg of nicotine. In children the LD50 is around 10 mg.[23]

GREEN TOBACCO SICKNESS

This is an acute form of nicotine toxicity that is known to occur due to handling of green tobacco leaves, with symptoms lasting from 12 to 24 h. The acute symptoms include headache, nausea, vomiting, giddiness, loss of appetite, fatigue and tachyarrythmias.[24] No significant mortality has been reported due to green tobacco sickness (GTS) but it significantly affects the health of workers in the tobacco industry.[25]

NICOTINE ADDICTION

Nicotine is one of the most addicting agent. The US surgeon general (2010) has concluded nicotine to be as addictive as cocaine or heroin. Nicotine interacts with the nicotinic acetyl choline receptors and stimulates the dopaminergic transmission.[26] This in turn stimulates the reward centre and is responsible for the mood elevation and apparent improvement in cognitive function.[27] With chronic stimulation by nicotine the GABAergic neurons are desensitized and thus lose their inhibitory effect on dopamine.[28] This in turn reinforces the addiction by inducing craving. This effect has been shown to affect the CYP2A6 gene and leads to heritable dependence to nicotine. Studies have shown the nicotine dependence to be transmitted maternally and grand maternally by epigenetic mechanism.[29]

EFFECTS ON METABOLISM

Nicotine causes catecholamine release and stimulates the autonomic system. There is increased glycogen synthesis due to α-adrenoceptor stimulation. This leads to reduction in the fasting blood glucose levels. It also causes lipolysis thus decreasing body weight. Nicotine affects insulin resistance and predisposes to metabolic syndrome. In an animal study prenatal exposure was toxic to pancreatic β-cell and leads to decreased B cell population, thus increasing the risk of diabetes.[30,31]

NICOTINE AND CANCER

The stimulation of nAChRs by nicotine has biologic effects on cells important for initiation and progression of cancer.[26] It activates signal transduction pathways directly through receptor-mediated events, allowing the survival of damaged epithelial cells. In addition, nicotine is a precursor of tobacco specific nitrosamines (TSNAs), through nitrosation in the oral cavity.[32,33] It is shown that nitrosation of nicotine could lead to formation of NNN and NNK. This effect of nicotine may be important because of its high concentration in tobacco and nicotine replacement products.[13] NNN and NNK are strongly carcinogenic.[34]

Nicotine forms arachidonic acid metabolites which cause increased cell division. Binding to Bcl-2 and action on vascular endothelial growth factor and cyclooxygenase-2 (COX-2) causes increased cancer proliferation and survival.[35,36] Promotion of tumor angiogenesis accelerates tumor growth which is mediated by β-adrenergic activation and stimulation of nAChRs.[35,37-39] Nicotine also suppresses apoptosis by phosphorylation mediated extracellular signal regulated kinases of Bcl-2.[40,41] Recent studies show that nicotine, activates nuclear factor kappa B (NF-kB)-dependent survival of cancer cell and proliferation.[42]

In normal cells, nicotine can stimulate properties consistent with cell transformation and the early stages of cancer formation, such as increased cell proliferation, decreased cellular dependence on the extracellular matrix for survival, and decreased contact inhibition. Thus, the induced activation of nAChRs in lung and other tissues by nicotine can promote carcinogenesis by causing DNA mutations[26] Through its tumor promoter effects, it acts synergistically with other carcinogens from automobile exhausts or wood burning and potentially shorten the induction period of cancers[43] [Table 2].

LUNG CARCINOGENESIS

A study relates lung carcinogenesis by nicotine due to genetic variation in CYP2B6.[44] Its simultaneous exposure with hyperoxia has been found to induce cancer in hamsters.[45] Cotinine has been found to promote lung tumorigenesis by inhibiting anti-apoptotic pathway.[46] Nuclear translocation of ARB1 gene by nicotine has found in proliferation and progression of nonsmall-cell lung cancer. Several Studies have shown that nicotine has significant role in tumor progression and metastasis via CXCR4 and increased angiogenesis.[36,47] Carriers of the lung-cancer-susceptibility loci in their DNA extract more nicotine. Smokers carrying the gene CHRNA3 and CHRNA5 were found to extract more nicotine and cells

Table 2: Studies showing the role of nicotine as tumor promoter

Author	System	References
Chu *et al.*, 2013	Gastrointestinal tumor growth	[71]
Improgo *et al.*, 2013	Lung	[47]
Heusch and Maneckjee, 1998	Lung	[40]
Mai *et al.*, 2003	Lung	[41]
Shin *et al.*, 2005	Gastric	[36]
Heeschen *et al.*, 2001	Tumor growth and angiogenesis	[35]
Zhu *et al.*, 2003	Tumor angiogenesis and growth	[39]
Heusch and Maneckjee, 1998	Lung	[40]
Le Marchand *et al.*, 2008	Lung	[48]
Perez-Sayans *et al.*, 2010	GIT	[51]
Zhang *et al.*, 2010	GIT	[49]
Petros *et al.*, 2012	Chemoresistance	[53]
Trevino *et al.*, 2012	Tumor growth and chemoresistance	[90]

GIT – Gastrointestinal tract

were thus exposed to a higher internal dose of carcinogenic nicotine-derived nitrosamines.[48] Additionally modulation of the mitochondrial signaling pathway leads to resistance to the chemotherapeutic agents.[49]

GASTRO INTESTINAL CARCINOGENESIS

The carcinogenic role may be mediated by the MAPK/COX-2 pathways, α-7 nAchR and β-adrenergic receptor expression, and mi RNAs α-BTX anatagonist.[50] Nicotine forms adducts with liver DNA which enhances its mutagenic potential.[49,51,52] activation of cell-surface receptors by nicotine stimulates downstream kinases that can mediate resistance to chemotherapy. It has been shown by the finding that smokers who continue to smoke during chemotherapy have a worse prognosis. Moreover they also have increased toxicity and lower efficacy of chemo therapeutic drugs.[53] Nicotine affects the periostin gene, α-7-nAChR and e-cadherin suppression which explains the mechanism of gastric cancer growth, invasion and metastasis.[54,55] Nicotine negatively impacts tumor biology by promoting angiogenesis, tumor invasion and increased risk of metastasis.[53]

PANCREATIC CANCER

Nicotine has been found to induce pancreatic adenocarcinoma in mice model, by stimulating the stress neurotransmitters.[56,57] In another study nicotine promoted the growth of nonsmall cell lung cancer and pancreatic cancer in a receptor dependent fashion. It also increased tumor metastasis, and resistance to gemcitabine induced apoptosis, causing chemoresistance.[58] The MUC-4 upregulation, NF-kB and GRP78 activation and Id1 expression by Src dependent manner are the probable mechanism leading to tumor growth, metastasis and chemotherapeutic drug resistance.[57,58]

BREAST CANCER

Nicotine causes α9-nAChR-mediated cyclin D3 overexpression which might cause transformation of normal breast epithelial cells and induce cancer. Nicotine and cotinine has been found to be present in the breast fluid of lactating women.[59] Several studies have found that α9-nAChR mediated mechanism leads to increased tumor growth, metastasis and tumor cells resistant to chemotherapeutic drugs in breast cancer.[59,60]

CARDIOVASCULAR SYSTEM

The acute hemodynamic effects of cigarette smoking or smokeless tobacco are mediated primarily by the sympathomimetic action. The intensity of its hemodynamic effect is greater with rapid nicotine delivery.[61] Nicotine causes catecholamine release both locally and systemically leading to an increase in heart rate, blood pressure and cardiac contractility. It reduces blood flow in cutaneous and coronary vessels; and increases blood flow in the skeletal muscles. Due to restricted myocardial oxygen delivery there is reduced cardiac work. In a study, chewing a low dose (4 mg) of nicotine gum by healthy nonsmokers blunted the increase in coronary blood flow that occurs with increased heart rate produced by cardiac pacing.[21] Thus, persistent stimulation by nicotine can contribute to Coronary Vascular Disease by producing acute myocardial ischemia. In the presence of coronary disease, myocardial dysfunction can be worsened. In a placebo-controlled experiment that produced transient ischemia in anesthetized dogs myocardial dysfunction was produced at doses, that did not alter heart rate, blood pressure, or blood flow or myocyte necrosis.[62]

Nicotine alters the structural and functional characteristics of vascular smooth muscle and endothelial cells.[63] It enhances release of the basic fibroblast growth factor and inhibits production of transforming growth factor-β1.[64] These effects lead to increased DNA synthesis, mitogenic activity, endothelial proliferation and increases atherosclerotic plaque formation.[65] Neovascularization stimulated by nicotine can help progression of atherosclerotic plaques.[66] These effects lead to myointimal thickening and atherogenic and ischemic changes, increasing the incidence of hypertension and cardiovascular disorders. A study on

dogs demonstrated the deleterious effects of nicotine on the heart.[67]

Nicotinic acetylcholine receptor's actions on vascular smooth muscle proliferation and plaque neovascularization increases the risk of peripheral arterial disorders. In a murine model of hind limb ischemia, short-term exposure to nicotine paradoxically increased capillary density and improved regional blood flow in the ischemic hind limb.[35] However, long-term exposure to nicotine for 16 weeks (about one-third of the life span of a mouse) before induction of ischemia obliterated angiogenic response to nicotine.[68]

RESPIRATORY SYSTEM

The effects of nicotine on respiratory system are twofold. One, directly by a local exposure of lungs to nicotine through smoking or inhaled nicotine, and second via a central nervous system mechanism. Nicotine plays a role in the development of emphysema in smokers, by decreasing elastin in the lung parenchyma and increasing the alveolar volume. Nicotine stimulates vagal reflex and parasympathetic ganglia and causes an increased airway resistance by causing bronchoconstriction.[69] Nicotine alters respiration through its effects on the CNS. The simultaneous effect of bronchoconstriction and apnea increases the tracheal tension and causes several respiratory disorders. In a study microinjection of nicotine were administered to the prebotzinger complex and adjacent nuclei in the brain. The firing pattern of the brain signals and breathing pattern were monitored. There was an increased frequency of bursts and decreased amplitude and a shallow and rapid rhythm of respiration.[70]

GASTROINTESTINAL SYSTEM

Nicotine use has been associated with Gastro Esophageal Reflux Disorder (GERD) and peptic ulcer disease (PUD).[36,71] This effect is mediated by increased gastric acid, pepsinogen secretion and stimulatory effects on vasopressin. The action on the cyclo-oxygenase pathway also increases the risk of GERD and PUD.[72] Nicotine causes smooth muscle relaxation by action of endogenous nitric oxide as a nonadrenergic noncholinergic neurotransmitter.[73] The decrease in tone of the colon and gastric motility and reduced lower esophageal sphincteric pressure might be the reason of increased incidence of GERD.[74]

There is an increased incidence of treatment resistant *Helicobacter pylori* infection in smokers. It potentiates the effects of toxins of *H. pylori* by its action on the gastric parietal cells.[75] This effect could be due to histamine mediated response of nicotine.

IMMUNOLOGICAL SYSTEM

Nicotine has been known to be immunosuppressive through central and peripheral mechanisms. It impairs antigen and receptor mediated signal transduction in the lymphoid system leading to decreased immunological response. The T-cell population is reduced due to arrest of cell cycle. Even the macrophage response, which forms the first line defense against tuberculosis becomes dysfunctional and causes increased incidence of tuberculosis.[76] The migration of fibroblasts and inflammatory cells to the inflamed site is reduced. There is decreased epithelialization and cell adhesion and thus there is a delayed wound healing as well as increased risk of infection in nicotine exposed individuals.

The action on the hypothalamo-pituitary adrenal axis and autonomic nervous system stimulation via sympathetic and parasympathetic pathways affects the immune system. The adrenocorticotropic hormone (ACTH) secretion pathway and corticotrophin release is affected and this causes immunosuppression.[77]

OCULAR SYSTEM

Nicotine promotes pathologic angiogenesis and retinal neovascularization in murine models. It causes age-related macular degeneration in mice.[78] In a clinical study, the most virulent form of age-related maculopathy was associated with retinal neovascularization that contributed to visual deterioration. Tobacco smokers are known to be at greater risk of age-related macular degeneration than are nonsmokers.[79] In animal model, spraguely Dawley rats with type 1 diabetes treated with nicotine, developed cataract.[80] Thus the syngergistic relationship between nicotine and glucose metabolism exaggerating diabetes might cause accelerated cataract formation. There is synergistic relationship between nicotine and glucose metabolism which increases the risk of diabetes mellitus. This might cause accelerated cataract formation.

RENAL SYSTEM

Risk of chronic kidney disease in smokers is high. Cigarette smoking has been found to increase albumin excretion in urine, decrease glomerular filtration rate, causes increased incidence of renal artery stenosis and is associated with an increased mortality in patients with end-stage renal disease. The pathogenesis of renal effects is due to the action of nicotine via COX-2 isoform induction. The COX-2

isoforms causes increased glomerular inflammation, acute glomerulonephritis and ureteral obstruction.[81] There is impaired response of kidneys to the increased systemic blood pressure in smokers. This loss of renoprotective mechanism in smokers also leads to pathogenetic effects of nicotine on the renal system.[82]

REPRODUCTIVE SYSTEM – MALES

Nitrous oxide liberated from parasympathetico-nergic nerves plays a pivotal role in generating immediate penile vasodilatation and corpus cavernosum relaxation, and NO derived from endothelial cells contributes to maintaining penile erection. Nicotine causes impairment of NO synthesis. This may lead to loss of penile erections and erectile dysfunction.[83]

Various animal studies suggest that nicotine causes seminiferous tubules degeneration, disrupts the spermatogenesis and at cellular level, affect germ cell structure and function in males.[84] It decreases testosterone levels which is secondary to decreased production of StAR.[85] StAR is the protein which plays an important role in testosterone biosynthesis.

REPRODUCTIVE SYSTEM – FEMALE

Menstrual cycle

Nicotine by inhibiting the 21 hydoxylase causes hypoestrogenic state. It shunts the metabolites to formation of androgen. This leads to chronic anovulation and irregular menstrual cycles. Nicotine can predispose the endometrium to inappropriate cytokine production and irregular bleeding.[86] There is consistent evidence that increase in follicle-stimulating hormone levels and decreases in estrogen and progesterone that are associated with cigarette smoking in women, is atleast in part due to effects of nicotine on the endocrine system.[26]

Effect on oocytes

Nicotine affects the ovaries and alters the production of oocytes in various animal studies. Nicotine-treated oocytes appeared nonspherical with rough surface and torn and irregular zona-pellucida. Nicotine also caused disturbed oocyte maturation. There is a decreased blood flow to the oviducts and thus impaired fertilization.[87]

Peri-natal effects

Maternal smoking has always been known to have deleterious effects on the fetal outcome. There is an increased incidence of intrauterine growth restriction, still birth, miscarriages and mental retardation.[88] Various animal studies show retarded fetal growth and lower birth weight when treated perinatally with nicotine. The lower levels of ACTH and cortisol due to nicotine are probable reasons for the incidence of lower birth weight in the newborns.[89]

Maternal as well as grand maternal smoking has been found to increase risk of pediatric asthma. Another serious and important effect is the transgenic transmission of the addictive pattern.[29]

CONCLUSION

Nicotine is the fundamental cause of addiction among tobacco users. Nicotine adversely affects many organs as shown in human and animal studies. Its biological effects are widespread and extend to all systems of the body including cardiovascular, respiratory, renal and reproductive systems. Nicotine has also been found to be carcinogenic in several studies. It promotes tumorigenesis by affecting cell proliferation, angiogenesis and apoptotic pathways. It causes resistance to the chemotherapeutic agents. Nicotine replacement therapy (NRT) is an effective adjunct in management of withdrawal symptoms and improves the success of cessation programs. Any substantive beneficial effect of nicotine on human body is yet to be proven. Nicotine should be used only under supervision of trained cessation personnel therefore its sale needs to be strictly regulated. Needless to say, that research for safer alternative to nicotine must be taken on priority.

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Dangers of ‘vaping are being ignored’ as evidence of harm mounts

metro.co.uk/2019/04/23/dangers-vaping-ignored-evidence-harm-mounts-9289165

Zoe Drewett

23 April 2019

The number of children and young people who are trying vaping is on the rise, according to latest PHE figures (Picture: PA)

Health chiefs have been accused of ignoring growing evidence that shows vaping is harmful to health and has created nicotine addiction in children and young people.

Public Health England (PHE) promote e-cigarettes as a safe alternative to smoking while choosing to ignore warnings over the risks, a leading health professor said.

Prof Martin McKee of the London School of Hygiene and Tropical Medicine said there are grounds for ‘serious concern’.

‘The nicotine in e-cigarettes is not a harmless drug and then there all these other things such as flavourings that are inhaled,’ he said.

‘We haven’t had e-cigarettes for long enough to know the true effects.

‘But when we look at the evidence we do have, there’s enough grounds for serious concerns.

‘Given the short-term effects on lung function and cardiovascular effects, there is enough evidence to say we should be very, very careful.’

Health professors argue long-term studies aren’t available as PHE is promoting e-cigarettes as an aid to stop smoking (Picture: PA)

The professor argues the UK is ‘out of step’ with other parts of the world on safety messages surrounding vaping.

He said San Francisco had adopted a ‘sensible’ policy to ban e-cigarettes until their health effects are fully evaluated.

The US has launched a drive to warn teenagers of the dangers of nicotine addiction from vaping.

Wizz Air to launch six new routes from Luton Airport starting in June

Increasing evidence shows young people are more likely to be targeted by marketing surrounding e-cigarette brands.

PHE figures published in February showed the number of UK children and teenagers trying vaping has doubled in recent years.

The professor said it was ‘worrying’ that vaping was being ‘pushed very hard to children’ creating the risk of a ‘new generation addicted to nicotine’.

One brand, Juul, introduced in the UK last summer, was blamed for a rise in nicotine addiction among children in the US, he said.

Professor Aaron Scott found that in the short-term, vaping was harmful (Picture: SWNS)

PHE has campaigned for cigarette smokers to switch to e-cigarettes, and has said they are 95 per cent less harmful than tobacco smoking.

Prof McKee disputes that figure and argued e-cigarettes cause damage in their own right.

Dr Aaron Scott, from the University of Birmingham, completed research that found vaporised e-liquid fluid has a similar effect on the lungs and body as seen in regular cigarette smokers.

He told the Press Association: ‘We don’t know what the long-term data is but we have shown that it’s cytotoxic and it’s pro-inflammatory, just like cigarette smoke is over the short-term.’

Long-term studies have been made difficult because PHE is pushing the promotion of e-cigarettes, he said.

Prof Scott added: ‘We only have evidence for short-term and in the short-term it’s definitely harmful.’

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Number of children vaping doubles in just four years

metro.co.uk/2019/02/27/number-children-vaping-doubles-just-four-years-8761072

Joe Roberts

27 February 2019

The number of children who are vaping has doubled in just four years, official figures have revealed.

Overall use of e-cigarettes among young people remains low but the habit is growing, with children as young as 11 admitting to using the gadgets.

Experts fear kids are being drawn in as they think it is 'cool' and do not realise flavoured e-cigarettes also contain nicotine.

Children as young as 11 have admitted using the gadgets (Picture: Shutterstock / Bulgn)
Public Health England (PHE) commissioned the report into surveys of e-cigarette use among young people.

The most recent was the Action on Smoking and Health YouGov survey of more than 2,000 children aged 11 to 18 in 2018.

It showed that 11.7% of 11 to 18-year-olds in 2018 had tried e-cigarettes once or twice at some point, almost double the 6.5% in 2014.

Awareness of vaping is also on the rise, with the proportion of kids who said they had never tried e-cigarettes falling from 91.5% in 2014 to 83.4% in 2018.

Some 3.4% of those polled in 2018 reported using e-cigarettes – more than double the 1.6% in 2014.

Experts fear the habit is on the rise among kids because they think it is 'cool' (Picture: PA)
The report said: 'Experimentation and use of e-cigarettes has been increasing steadily over time.'

There was also a definite link between vaping and smoking, researchers said, with smokers far more likely to try vaping than those who had never smoked.

When youngsters who had tried an e-cigarette were asked why, 57.2% said they wanted to give it a try, while 16.1% said they liked the flavours.

The survey also found the proportion of children trying vaping before a tobacco cigarette rose from 8% in 2014 to 21% in 2018.

Researchers said that while England 'continues to take small progressive steps towards ensuring vaping remains an accessible and appealing alternative to smoking', more can be done.

They said more smokers may be attracted to vaping if a licensed e-cigarette was available and barriers to 'licensing and the commercialising of licensed products need further exploration'.

Professor John Newton, health improvement director at PHE, said the UK was 'not seeing a surge in e-cigarette use among young people in Britain'.

He added: 'While more young people are experimenting with e-cigarettes, the crucial point is that regular use remains low and is very low indeed among those who have never smoked.

'We will keep a close watch on young people's vaping and smoking habits to ensure we stay on track to achieve our ambition of a smoke-free generation.'

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- Telegraph
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Health officials turning a blind eye to teenage vaping, experts claim

The number of UK children and teenagers trying vaping has doubled in recent years
Credit: Alamy

https://www.telegraph.co.uk/news/2019/04/22/health-officials-turning-blind-eye-teenage-vaping-experts-claim/

- Henry Bodkin, Health Correspondent

23 April 2019 • 12:01am

Health officials have been accused of downplaying the risk to teenagers from vaping by leading scientists, including one who identified that e-cigarettes cause lung damage.

Public Health England (PHE) is "ignoring evidence" that vaping is harmful, putting Britain "out of step" with countries such as the US where teenagers are actively warned off the products, the experts said.

Dr Aaron Scott, the University of Birmingham scientist who showed that vaporised e-liquid fluid has a similar effect on the lungs as regular cigarettes, said funding for long-term research into the harms of vaping was being stifled because "PHE wants to push the message that they [e-cigarettes] are not harmful".

His comments were echoed by Professor Martin Mckee, from the London School of Hygiene and Tropical Medicine, who warned PHE is turning a blind eye to increasing evidence that youngsters are trying vaping and are attracted to e-cigarette brands and marketing.

The organisation says the UK has some of the “world’s strictest e-cigarette” regulations when it comes to advertising and minimum age of sale.

However, PHE figures show the number of UK children and teenagers trying vaping has doubled in recent years.

Some 15.9 per cent of children aged 11 to 18 reported having tried vaping, according to 2018 data, a rise from 8.1 per cent in 2014.

The proportion who said they had never tried e-cigarettes fell from 91.5 per cent in 2014 to 83.4 per cent in 2018.

Prof McKee said PHE "seems to be doing everything it can to promote e-cigarettes" and was choosing to ignore warnings over the risks.

He said: "The nicotine in e-cigarettes is not a harmless drug and then there all these other things such as flavourings that are inhaled.

"We haven't had e-cigarettes for long enough to know the true effects.

"But when we look at the evidence we do have, there's enough grounds for serious concerns.

"Given the short-term effects on lung function and cardiovascular effects, there is enough evidence to say we should be very, very careful."

E-cigs and heated tobacco products are harmful and do not help smokers to quit

medicalxpress.com/news/2019-05-e-cigs-tobacco-products-smokers.html

MAY 28, 2019

by European Lung Foundation

In a new statement published by the European Respiratory Society (ERS) Tobacco Control Committee, an international coalition of respiratory doctors and scientists have warned that tobacco harm reduction strategies which support the use of alternative nicotine delivery products for smoking cessation are not effective and are based upon incorrect assumptions and undocumented claims.

They say there is a lack of proof to support claims that nicotine delivery devices such as e-cigarettes and heated tobacco products help people to quit smoking for good, and say that there is mounting evidence that their use is harmful to health.

As a result, they are calling for policymakers and public health bodies to reconsider programs that support the use of e-cigs and heated tobacco products, and say they cannot recommend tobacco harm reduction as a population-based strategy.

The statement brings together key arguments based on a number of scientific studies for why a tobacco harm reduction strategy should not be used as a population-based strategy in tobacco control.

Charlotta Pisinger is Chair of the ERS Tobacco Control Committee and clinical professor of tobacco control at Bispebjerg and Frederiksberg Hospital and University of Copenhagen, Denmark. She explained: "Tobacco harm reduction strategies are based on incorrect assumptions that smokers cannot or will not quit smoking, but in reality, the majority of smokers want to quit and they dislike being nicotine dependent. Most of the new products, including heated tobacco and e-cigarettes, are devices of nicotine inhalation, and therefore do not help smokers to beat their addiction to nicotine.

"There is also a lack of evidence to support the claims that e-cigarettes are more effective than established smoking cessation medications or nicotine replacement therapies, but the few independent studies that have been published indicate that e-cig and heated tobacco device use undermines quit attempts outside of a clinical setting, and show that most people use alternative nicotine delivery products alongside conventional cigarettes, rather than as a replacement."

The statement warns that e-cigs and heated tobacco products, which are largely produced and marketed by the tobacco industry, are just another example of the tobacco industry's long-established tactic to sell so-called safer products in a bid to deter smokers from quitting and to make smoking more socially acceptable.

The authors say several studies already confirm that e-cigs and heated tobacco products have short-term toxic effects on health, and warn that if we wait any longer to see the long-term effects, we risk facing consequences similar to those caused by ignoring the early warnings about how harmful conventional cigarettes are to health.

Professor Tobias Welte from Hannover University, Germany, is President of the European Respiratory Society. He said: "We understand that many health professionals, tobacco control professionals and policy makers who recommend harm reduction strategies may have good intentions, but there is very little evidence to support the claims that e-cigarettes and heated tobacco devices are helping smokers to quit conventional cigarettes for good.

"Although exposure to potentially harmful ingredients from e-cigarettes and heated tobacco devices may be lower than cigarettes, this does not mean that they are harmless. Until we know more about the long-term effects of their use on human health, it is irresponsible to recommend that they be used in population-wide tobacco control strategies. Evidence-based tobacco dependence treatments already exist and are safe and cost-effective, and we must utilise this. Nothing should enter the lungs besides clean air—we must not give up on smokers."

More information: The ERS Position paper on tobacco harm reduction statement was prepared by the ERS Tobacco Control Committee. Access in full: ers.box.com/v/ERSTCC-Harm-Reduction-Position

Provided by European Lung Foundation