



# JOURNAL CLUB

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## Association of electronic cigarette use with subsequent initiation of tobacco cigarettes in US youths

Berry KM, Fetterman JL, Benjamin EJ, et al.

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Use of cigarettes by young people has fallen in recent years, but the number of US youths using e-cigarettes has increased substantially. There are now concerns that the increased use of e-cigarettes could lead to the normalisation of smoking among young people.

There is a growing body of evidence that e-cigarette use may be associated with initiation of cigarette smoking in young people, with a recent meta-analysis finding that young e-cigarette users were more than three times as likely to subsequently start smoking. Use of other non-cigarette tobacco products also increases the risk of smoking later in life; however, few studies compare the use of these products and e-cigarettes in the same population, making direct comparisons between different non-cigarette products more difficult. Furthermore, previous studies are also open to methodological limitations; therefore, the aggregate effect of such products on subsequent cigarette use remains uncertain.

For this study, data were obtained from waves 1-3 of The Population Assessment of Tobacco and Health (PATH) Study to assess the association of e-cigarettes and non-cigarette tobacco products (e.g. shisha, snuff, cigars) on subsequent cigarette use in young people.

The study was comprised of youths who completed questions on current and prior nicotine product use at three timepoints between 2013 and 2016. Analysis was restricted to those aged 12-15 who had never used any tobacco product at the first timepoint (N=6123, mean age = 13.4 years). Study participants were further subclassified into those at high risk and at low risk for smoking initiation, according to their responses to questions on prior substance use and attitudes towards cigarettes.

The study authors found that youths who used e-cigarettes as their first nicotine product were more than four times as likely to ever smoke cigarettes and nearly three times more likely to currently use cigarettes over two years of follow-up, compared with nicotine-naïve individuals. Interestingly, prior non-cigarette tobacco product use was associated with a similar risk. In a subanalysis, the authors found that the association between e-cigarette use and subsequent cigarette smoking behaviours was particularly pronounced in youths that were at low risk for smoking initiation. It was estimated that a substantial proportion of new cigarette use and current cigarette use may be attributable to the use of e-cigarettes – more than non-cigarette tobacco products.

These results are consistent with other studies suggesting that the use of e-cigarettes and non-cigarette tobacco products is associated with increased cigarette smoking initiation and use in young people. These findings corroborate the arguments for strict regulation of youth access to e-cigarettes and they also have implications for their marketing.

## Screening heroin smokers attending community drug services for COPD

Burhan H, Young R, Byrne T, et al.

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More heroin users now administer the drug by inhalation than by injection, which has led to an increase in respiratory disease in this population. Heroin smokers typically engage poorly with screening and disease prevention initiatives, contributing to poor health outcomes compared to non-heroin smokers including more severe respiratory symptoms, undertreatment and high rates of hospitalisation for COPD exacerbations. In contrast, attendance at key worker appointments remains very high as the receipt of methadone prescriptions is dependent on regular attendance at community drug services. These meetings present an opportunity for increased engagement of heroin smokers in screening and treatment programmes for respiratory diseases.

The aim of this cross-sectional study was to establish whether COPD screening of a large population of heroin smokers at community drug centres is deliverable and whether the initiative would be acceptable to drug users. Furthermore, this study sought to investigate the relationship between heroin inhalation and lung damage.

The study recruited 1,082 heroin smokers who were visiting community drug services in Liverpool between December 2015 and June 2016. Of these, 753 (73% of those approached) completed spirometry screening for COPD and completed questionnaires assessing quality of life, respiratory symptoms and use of other substances.

The study found that most heroin smokers had either COPD (39%) or combined features of COPD and asthma (15%). The length of time that individuals had been smoking heroin, crack and cigarettes were strongly associated with respiratory disease diagnosis; however, spirometric measures were not associated with tobacco/drug exposure. Heroin smokers largely considered combining healthcare appointments with drug key worker appointments to be an acceptable initiative, with 92% responding that they happy with this arrangement.

In conclusion, pairing healthcare assessments with drug key worker appointments could be an effective measure in increasing engagement with respiratory disease screening in heroin smokers. Such an initiative would provide increased opportunity to treat respiratory symptoms and reduce the risk of long-term respiratory complications in this high-risk population.

## Eosinophilic airway inflammation is a main feature of unstable asthma in adolescents

Ciółkowska J, Emeryk A, Hydzik P, et al.

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Stability of asthma is based not only on the long-term control of symptoms and exacerbations, but also on clinical phenotype. ICS are widely used for long-term control of asthma and previous research has established an association between a patient's response to ICS and their cytological inflammatory phenotype. Eosinophilic inflammatory asthma, for example, is relatively resistant to high-dose ICS. In mild asthma, management of symptoms using ICS is usually sufficient to achieve stable asthma,

but ICS alone is not sufficient for moderate and severe asthma.

This cross-sectional study aimed to characterise the inflammatory profile of stable and unstable asthma in adolescents treated with moderate- and high-dose ICS.

The study participants were children and adolescents (N=139, mean age = 16.8 years) with active asthma, who were non-smokers receiving treatment with moderate- to high-dose ICS for at least one year. Between January 2012 and February 2014, participants completed a three-month observation period, during which patients recorded their symptoms and medication use and completed a number of diagnostic and observational tests. Of 139 participants, 72 were classified as having stable asthma and 67 as having unstable asthma. Clinical and spirometric measurements in both groups were compared, as well as inflammatory markers including fractional exhaled nitric oxide, sputum cytology and bronchial hyperresponsiveness following provocation with hypertonic saline and exercise.

The study found that patients with unstable asthma had more eosinophilic inflammation, bronchial hyperresponsiveness and lower spirometry parameters compared with the stable asthma group. Elevated percentages of eosinophils in induced sputum were seen in the sputum of 75% of patients in the unstable group and a multivariate analysis found that the eosinophil count was significantly associated with asthma instability.

The study relied on self-reporting for medication compliance, a subjective method and limitation of the study, although this approach has been previously used in similar studies. The authors also only performed one sputum eosinophil count, which may not be reflective of the patient's long-term asthma stability.

In summary, the authors concluded that eosinophilic inflammation is the dominant type of inflammation in unstable asthma. Elevated bronchial hyperresponsiveness and lower spirometric parameters were also associated with asthma instability, which highlights the usefulness of determining the inflammatory phenotype of unstable asthma patients.

## A randomized trial of e-cigarettes versus nicotine-replacement therapy

Hajek P, Phillips-Walter A, Przulj D, et al.

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E-cigarettes and NRT are commonly used in attempts to stop smoking. However, evidence is limited regarding how effective e-cigarettes are in facilitating smoking cessation, especially compared with NRT.

There are several studies highlighting that nicotine-containing e-cigarettes are more effective than nicotine-free e-cigarettes in facilitating smoking cessation. However, previous studies directly comparing e-cigarettes and NRT have typically compared low-nicotine first-generation e-cigarettes and did not include any face-to-face contact.

This multicentre randomised controlled trial evaluated the 52-week efficacy of refillable second-generation e-cigarettes compared with NRT in facilitating smoking cessation in adults. Sustained abstinence was defined as a self-report of ≤5 cigarettes from two weeks after the target quit date, validated by expired carbon monoxide levels at 52-week follow-up. Secondary outcomes included abstinence at other timepoints, cigarette use in participants without sustained abstinence, respiratory symptoms, withdrawal symptoms and adverse reactions.

886 adults attending NHS stop-smoking services between May 2015 and February 2018 were randomly assigned to either an e-cigarette starter pack or an NRT of their choice. Participants in the e cigarette group were provided with a refillable second-generation e-cigarette and a bottle of nicotine e-liquid and were encouraged to experiment with e-liquids of different strengths and flavours. The NRT group could select products such as patches, gums, lozenges, nasal sprays, inhalers, mouth sprays and microtabs and were encouraged to combine products. Both groups received the same multisession behavioural support.

The study authors found that 52-week abstinence rates in the e-cigarette group were almost double that of the NRT group. Among the participants who were abstinent at 52 weeks, those randomised to e-cigarettes were more than eight times as likely to still be using their product. E-cigarettes caused more throat/mouth irritation and NRT caused more nausea. Greater decreases in the incidence of cough and excess phlegm were reported in the e-cigarette group, but there were no significant differences between groups for shortness of breath, wheeze and adverse events. E cigarettes were more effective in reducing tobacco withdrawal symptoms and were rated higher than NRTs by participants. Some participants did not achieve full abstinence, but those randomised to e-cigarettes were more likely to reduce their cigarette use than those using NRT.

Strengths of this study included: (1) participant autonomy in choice of e-liquids and NRT, (2) inclusion of behavioural support for both groups, (3) inclusion of many participants from multiple centres. Its limitations included: (1) inability to blind product assignment, (2) carbon monoxide validation only detects smoking in the last 24 hours; therefore, false negatives are a possibility.

The authors concluded that e-cigarettes are more effective for smoking cessation than NRT and may allow better tailoring of nicotine dose to individual needs.

## Impact of chronic obstructive pulmonary disease on the outcomes of patients with peripheral artery disease

Keller K, Hobohm L, Münzel T, et al.

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Smoking is one of the leading causes of PAD and COPD, both of which have high mortality rates.

In smokers with COPD, cardiovascular disease is one of the leading causes of death. Associations between COPD in smokers and coronary artery disease, myocardial infarction and pulmonary embolism are well established. Moreover, there is a growing body of evidence that COPD and smoking are associated with lower limb artery cardiovascular disease, which can contribute to PAD.

Data from a nationwide German patient sample was used in this retrospective cohort study to investigate the impact of COPD on in-hospital outcomes of PAD patients, especially death. PAD patients were classified into two groups based on COPD status and compared for comorbidities and in-hospital outcomes.

Between January 2005 and December 2015, a total of 5,611,827 patients aged ≥18 years were treated for PAD in hospitals in Germany. Of these, 761,011 had COPD and 4,850,816 did not, from which a total of 277,894 PAD patients died in hospital across both groups. Secondary outcomes during in-hospital stays, such as myocardial infarction, pulmonary embolism and deep vein thrombosis, were also assessed.

thrombosis, were also recorded.

The study authors found in-hospital mortality to be significantly higher in PAD patients with concomitant COPD compared with those without COPD. It was also found that COPD in PAD patients was associated with a higher prevalence of myocardial infarction, pulmonary embolism, deep vein thrombosis and cancer. Interestingly, PAD patients with COPD typically showed lower PAD stages than those without COPD. A statistical analysis found COPD to be an independent predictor of in hospital death and pulmonary embolism in PAD patients, although PAD patients with COPD had a lower risk of amputation.

The authors conclude that there is an increased risk of in-hospital death in PAD patients with COPD, most likely driven by higher frequencies of pulmonary embolism and cancer. This has two major implications for treatment: (1) PAD patients with a history of smoking may benefit from COPD screening, (2) PAD patients diagnosed with comorbid COPD are at an increased risk of complications; therefore, they should be monitored more closely.

## Inaccurate diagnosis of COPD: the Welsh National COPD Audit

Fisk M, McMillan V, Brown J, et al.

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COPD is the leading cause of poor health, disability and mortality in the UK. In Wales, the prevalence of COPD is 2.2% and rates of hospital admissions and mortality due to COPD are higher than the UK average.

Making an accurate diagnosis of COPD is challenging and spirometry should be used to confirm diagnosis and demonstrate persistent airflow obstruction. Previous studies have demonstrated that when COPD is not confirmed by post bronchodilator spirometry, diagnosis accuracy may be as low as 50%. Misdiagnosis may lead to incorrect management of a patient's respiratory symptoms, which can have an impact on their quality of life.

Data from the Welsh National COPD Primary Care Audit were used to evaluate the clinical symptoms and management of patients with spirometry incompatible with COPD.

The Welsh National COPD Primary Care Audit collected data from 48,105 patients across 280 General practices in Wales between January 2014 and March 2015. Only patients on the register with recorded post-bronchodilator FEV<sub>1</sub>/FVC were included in this analysis (n=8957). 25% of the sample had spirometry incompatible with COPD diagnosis (FEV<sub>1</sub>/FVC ratio ≥0.70), who were compared with the remaining 75% of patients with compatible spirometry (FEV<sub>1</sub>/FVC <0.70).

Patients with incompatible spirometry were more likely to be never-smokers and female, and on average had better mean FEV<sub>1</sub> and higher body mass index scores. On measures of respiratory symptoms, groups were similar for breathlessness scores and exacerbation frequency. Asthma co-diagnosis was similar in both groups and patients in the groups were equally likely to be taking long-acting beta-agonists and ICS. However, patients with incompatible spirometry were less likely to receive a combination of both medication types or long-acting muscarinic agonists. Moreover, the researchers observed that spirometry

was misinterpreted in around a quarter of cases, which implies an estimated 16,000 misdiagnoses across the whole of Wales, if extrapolated.

Among the strengths of this study was the insight into the real-world diagnosis and management of COPD on a national level. The study does have its limitations: notably the authors not having access to information on patients' comorbidity diagnoses, which may have provided alternative explanations for clinical features of patients with incompatible spirometry.

The authors conclude that the poor documentation of spirometry and incorrect interpretation of spirometry results leads to a significant proportion of COPD patients receiving inaccurate diagnoses. They also call for healthcare providers and commissioners to increase their efforts to improve the accuracy of COPD diagnosis in primary care because there are significant costs to the NHS that will continue if the problem remains unsolved.

### Abbreviations/acronyms:

**e-cigarettes** = electronic cigarettes

**COPD** = chronic obstructive pulmonary disease

**ICS** = inhaled corticosteroids

**FeNO** = fractional exhaled nitric oxide

**FEV<sub>1</sub>** = forced expiratory lung volume in 1 second

**FVC** = forced vital capacity

**NRT** = nicotine replacement therapy

**PAD** = peripheral artery disease

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