

Toxicant and carcinogen exposure associated with long-term e-cigarette use

17. Deutsche Konferenz für Tabakkontrolle DEUTSCHES KREBSFORSCHUNGSZENTR IN DER HELMHOLTZ-GEMEINSCH

Forschen für ein Leben ohne Krebs

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WHO-Kollaborationszentrum für Tabakkontrolle

17th German Conference on Tobacco Control

Forschen für ein Leben ohne Krebs

Please, mark the answers applying to you:	Conflict of Interest /Yes – No (if yes, which)	
Within the past 5 years, have you received speaker compensation fees from the pharmaceutical industry, tobacco industry or e-cigarette industry or their lobby organizations?	No	
Within the past 5 years, have you received consultation fees from the pharmaceutical industry, tobacco industry or e-cigarette industry or their lobby organizations (Advisory Boards)?	Yes – Johnson & Johnson (advisory board)	
Within the past 5 years, have you received financial support for projects of the pharmaceutical industry, tobacco industry or e-cigarette industry or their lobby organizations?	Yes – GRAND research grant from Pfizer	
Do you have commercial connections with manufacturers or distribution organizations for tobacco products, nicotine substitute products or e-inhalation products which are mentioned within the scope of the 16th German Conference on Tobacco Control (if relevant)?	No	
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Herewith I declare that I have no conflicts of interest within the scope of the 17th German Conference on Tobacco Control.

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SURNAME, FIRST NAME (Capitals) SHAHAB, LION

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Declaration of interest

- I have received research funds and have undertaken consultancy for companies that develop and manufacture smoking cessation medications and advise the pharmaceutical industry (Pfizer, Johnson & Johnson, and Atlantis Health Care)
- My salary is funded by UCL via the Higher Education Funding Council for England
- I have never received any funding from the tobacco or e-cigarette industry
- I am a vaper

Background



Controversy surrounding safety claims

Public Health England

August 2015

Protecting and improving the nation's health

E-cigarettes: an evidence update A report commissioned by Public Health England

Authors:

McNeill A, Brose LS, Calder R, Hitchman SC Institute of Psychiatry, Psychology & Neuroscience, National Addiction Centre, King's College London UK Centre for Tobacco & Alcohol Studies

Hajek P, McRobbie H (Chapters 9 and 10) Wolfson Institute of Preventive Medicine, Barts and The London School of Medicine and Dentistry Queen Mary, University of London UK Centre for Tobacco & Alcohol Studies

There has been an overall shift towards the inaccurate perception of EC being as harmful as cigarettes [...] in contrast to the current expert estimate that **using EC is around 95% safer than smoking**.

Royal College of Physicians



Nicotine without smoke Tobacco harm reduction

A report by the Tobacco Advisory Group of the Royal College of Physicians

April 2016

'...the hazard to health arising from long-term vapour inhalation from the e-cigarettes available today is unlikely to exceed 5% of the harm from smoking tobacco...'

Background



Controversy surrounding safety claims AJPH PERSPECTIVES

THE LANCET Editorial

E-cigarettes: Public Health England's evidence-based confusion

it described as a "landmark review" of evidence about the criteria of harms. The group scored the products e-cigarettes. The headline in their press release quoted for harm, and weightings were applied to the results. their top-line finding-"E-cigarettes around 95% less Based on the opinions of this group, cigarettes were harmful than tobacco". Kevin Fenton, Director of Health ranked as the most harmful nicotine product with a and Wellbeing at PHE, commented that, "E-cigarettes score of 99.6. E-cigarettes were estimated to have are not completely risk free but when compared to only 4% of the maximum relative harm. It is this result smoking, evidence shows they carry just a fraction of that yields the "95% less harmful" figure reported the harm". Indeed, the 95% figure was widely picked last week. up in news media. The BBC, for example, reported with

evidence that e-cigarettes are so safe? "There is a need to publicise the current best estimate this work. that using EC is around 95% safer than smoking." PHE

undue haste nicotine products, the range of products (including short of its mission.
The Lancet

Last week, Public Health England (PHE) reported what "electronic nicotine delivery system products"), and

But neither PHE nor McNeill and Haiek report certainty that "E-cigarettes are 95% less harmful than the caveats that Nutt and colleagues themselves tobacco". So what was the allegedly "game-changing" emphasised in their paper. First, there was a "lack of hard evidence for the harms of most products on most In the "evidence update" published by PHE, of the criteria", Second, "there was no formal criterion written by Ann McNeill (King's College London) and for the recruitment of the experts". In other words, Peter Hajek (Queen Mary University of London), the the opinions of a small group of individuals with no safety of e-cigarettes "in the light of new evidence" prespecified expertise in tobacco control were based is summarised in this way: "While vaping may not be on an almost total absence of evidence of harm. It is 100% safe, most of the chemicals causing smoking- on this extraordinarily flimsy foundation that PHE related disease are absent and the chemicals that are based the major conclusion and message of its report. present pose limited danger. It had previously been The study led by Nutt was funded by Euroswiss estimated that EC [e-cigarettes] are around 95% safer Health and Lega Italiana Anti Fumo (LIAF). than smoking (10, 146). This appears to remain a Riccardo Polosa, one of the authors of the Nutt paper, reasonable estimate." The headline conclusion of the is the Chief Scientific Advisor to LIAF. In the paper, he PHE report was a judgment relying on two references reports serving as a consultant to Arbi Group Srl, an from 2014. One (reference 146) was a briefing report e-cigarette distributor. His research on e-cigarettes is to the UK All-Party Parliamentary Group on Pharmacy. currently supported by LIAF. Another author reports The other (reference 10) was a paper by David Nutt and serving as a consultant to manufacturers of smoking colleagues published in European Addiction Research. It cessation products. The editors of the journal added is from this paper that the 95% figure derives. McNeill a note at the end of the paper warning readers about and Hajek are clear about the importance of this work: the "potential conflict of interest" associated with

Tobacco is the largest single cause of preventable immediately acted on this recommendation. But with deaths in England-e-cigarettes may have a part

It is worth reading the paper on which PHE has PHE on work that the authors themselves accept is based its latest advice carefully. Nutt and colleagues methodologically weak, and which is made all the describe how the Independent Scientific Committee more perilous by the declared conflicts of interest on Drugs, which Nutt founded in 2010, convened an surrounding its funding, raises serious questions not international expert panel to consider the "relative only about the conclusions of the PHE report, but also importance of different types of harm related to about the quality of the agency's peer review process. the use of nicotine-containing products". During a PHE claims that it protects and improves the nation's For the Public Health England two-day workshop in July, 2013, the panel met in health and wellbeing. To do so, it needs to rely on the report set https://www.gou.ug/ London to review the context of perceived harms from highest quality evidence. On this occasion, it has fallen

to play to curb tobacco use. But the reliance by

publications/euclearettes.an evidence-update

neering, and Medicine (NASEM), the other from Public Health England n September 2018, the Food (PHE)—were issued back to back in and Drug Administration the winter of 2018. While some have (FDA) launched a \$60 million read these analyses as broadly concampaign targeted at adolescents sistent, providing support for the who had used or might be view that e-cigarettes could play a tempted to use e-cigarettes. role in smoking harm reduction, in Employing graphic imagery, every major respect, they come to

Two major public health evaluations

of e-cigarettes-one from the Na-

tional Academies of Science, Engi-

worm-like creatures crawling unwhat the evidence suggests in terms der the skin and into the lungs and of public health policy. How is that brains of otherwise blemishpossible free adolescents. The ads sound an The explanation rests in what the

2 reports see as the central challenge

posed by e-cigarettes, which helped dence. For NASE No Que have the biogrand the interest of the sector of t from the potential risks of exp to nicotine and or from the bustible cia alization. A precaut mcCONSENSUS and Sent Autors of Sent Autors of Sent Autors and could speak question of causality paramount. For a chatbot (Figure A, available as a PHE, the priority was how to reduce supplement to the online version of the burdens now borne by current this article at http://www.ajph. smokers, burdens reflected in meaorg). The approach was a muscular surable patterns of morbidity and counter to e-cigarette advertising mortality. With a focus on immediate that blurred the boundary between

an addictive product and candy or was "relevant and meaningful." cereal (Figure 2).2 Thus, competing priorities deter-Making this forceful challenge mined what counted as evidence when it came to the impact of e-cigarettes on current smokers, nonsmoking bystanders, and children and adolescents A new clinical trial demonstrating the efficacy of e-cigarettes as a cessation tool makes understanding how values. and framing shape core questions and conclusive evidence imperative. (Am J Public Health. 2019;109:1000-1006. doi:10.2105/AJPH.2019.305107) responding not only to a per-

from the National Academies

of Science, Engineering, and on the evidence. The 2 agencies Medicine (NASEM) that it had issued their evaluations of the evidence nearly back to back in The FDA approach could not the winter of 2018. Some have stand in sharper contrast with the read these analyses as broadly Public Health England (PHE) consistent, providing support strategy. For PHE, which has for the view that e-cigarettes ublished its own reviews the could play a role in smoking harm

evidence provided additional reduction. Yet, in every major support for a national policy in respect, they come to very difwhich e-cigarettes had become ferent conclusions about what an official part of a campaign to the evidence suggests in terms address morbidity and mortality of public health policy. The idemic spreading" and "vaping can from tobacco smoking. In Ocdifferences between the 2 reports put dangerous chemicals into your tober 2017, England's expert turn on the profoundly important question of what should count as evidence for policymakers.

Fundamentally, the 2 reports and other containants campaign evolus Rever Madness, e new state of the state of th this analysis on the divide that how to protect the health of current smokers. For the United States, the pivotal issue was the global outlier on the question protection of children and nonof e-cigarettes. Australia's national smokers-innocent bystanders. The formulation of the questions science research agency, for example, has taken a very different and inclusion and exclusion cristance and maintains a ban on teria is always a value-based nicotine sales.4 Indeed, some have process. Understanding these argued that, at its very origins, different values is critical to funds from the tobacco industry mapping the politics of smoking tainted the English conviction that harm reduction as debate inpeople "smoke for the nicotine but tensifies about disruptive highdie from the tar."5,6(p1431) impact nicotine products like Underpinning the 2 ap-Juul,⁷ which has been at the proaches are very different takes center of a storm of concern over

ABOUT THE AUTHORS

The E-Cigarette Debate: What Counts as Evidence?

See also McKee, p. 965.

on denicts hideor

urgent warning: "There is an ep-

Amy Lauren Fairchild, PhD, MPH, Ronald Bayer, PhD, and Ju Sung Lee, MHA

commissioned.

- Amy Lauren Fairchild is with the Department of Health Policy and Management. Texas A&M School of Public Health, College Station. Ronald Bayer is with the Department of Sociomedical Sciences, Mailman School of Public Health, Columbia University, New York, NY. Ju Sung Lee is a doctoral candidate in the Department of Health Policy and Management, Texas A&M University
- Correspondence should be sent to Amy Lauren Fairchild, 212 Adriance Lab Rd, College Station, TX 77843 (e-mail: fairchild@sph.tamhsc.edu). Reprints can be ordered at http:// ceived epidemic of youth vaping www.ajph.org by clicking the "Reprints" link. but also to an evidence review This article was accepted March 14, 2019. doi: 10.2105/AIPH.2019.305107

1000 Perspectives From the Social Sciences Peer Reviewed Fairchild et al.

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BMJ 2015;351:h4863 doi: 10.1136/bmj.h4863 (Published 15 September 2015)

the**bmj**

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ANALYSIS

Evidence about electronic cigarettes: a foundation built on rock or sand?

Public Health England recently endorsed the use of e-cigarettes as an aid to guitting smoking. Martin McKee and Simon Capewell question the evidence on safety and efficacy underpinning the recommendations

Martin McKee professor of European public health¹, Simon Capewell professor of clinical epidemiology

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often tackle complex and controversial issues. Public Health England (PHE) has been courageous in entering the debate on the role of electronic cigarettes in tobacco control. In a new report it concludes that e-cigarettes are much safer than conventional cigarettes,1 and one of its author is quoted as describing them as a potential "game changer" in tobacco control.2 Media coverage suggests that the debate is now over, with a BBC correspondent describing the evidence as "unequivocal."2 However, although British organisations such as the Royal College of Physicians of London3 and ASH UK,4 have endorsed some of the report's conclusions, albeit with caveats, many others have come to the opposite opinion. These include the British Medical Association, the UK Faculty of Public Health, the US Centers for Disease Control and Prevention, the American Lung Association, the World Health Organization,5 the European Commission,6 and other leading international health bodies.7 The available evidence about e-cigarettes suggests that the debate is far from over and questions remain about their benefits and harms

Those responsible for safeguarding the health of the public must

Defining the role of e-cigarettes

Fundamental divisions seem to exist between those engaged in this debate. Supporters of e-cigarettes focus narrowly on existing smokers, comparing the devices' effects with those of smoking conventional cigarettes. As well as being an aid to quitting, e-cigarettes are seen as having a role for people who do not want to quit, offering a safer substitute for some of the cigarettes they would otherwise smoke.

Meanwhile, those on the other side of the debate express concern about uptake of e-cigarettes among people, especially children and adolescents, who would not otherwise smoke and about their long term health effects. They argue that although e-cigarettes do not contain some of the most harmful substances found in conventional cigarettes, such as tar, they do contain

other substances such as formaldehyde (a carcinogen) and diverse flavourines. Thus, it is equally important to include non-smoking as a comparator. They also draw attention to important epidemiological evidence that contrary to what is widely believed, reduced smoking (as opposed to quitting) may not reduce overall risk of death.8 The expression "dual use," which acknowledges that two thirds of e-cigarette users also smoke, rarely occurs in the PHE report. Although some dual use is inevitable during the quitting process, if this persists long term health concerns remain. A recent cohort study by McNeill and colleagues showed that dual use among daily "vapers" apparently remained above 80% after 12 months follow-up, which is worrying.9

Quality of the evidence

A fundamental principle of public health is that policies should be based on evidence of effectiveness. So does the available evidence show clearly that e-cigarettes are as effective as established quitting aids? Unfortunately not. The recent Cochrane review is widely cited,10 but it included only two randomised controlled trials, both with important limitations. and concluded that the evidence was of "low or very low quality by GRADE standards." The PHE report authors concede the weakness of the evidence, noting how a single observational study with substantial limitations offers "some of the best evidence to date on the effectiveness of e-cigarettes for use in quit attempts.'

Where there is uncertainty about risks, the precautionary principle should apply. Thus, in the absence of scientific consensus that the substance is not harmful to the public, the burden of proof that it is not harmful falls on those taking an action. The quality of the evidence cited by PHE therefore becomes crucial. The headline message from the PHE report. widely quoted in the media, is that "best estimates show

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harms. PHE turned to evidence that

829

to e-cigarettes remarkable is that. when he took office, FDA Commissioner Scott Gottlieb announced a new approach to tobacco control. A continuum of risk would define FDA policy: products involving lesser harms should edge out deadly combustible products. In making this sharp turn, the FDA was

Background



Controversy surrounding safety claims



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A priori considerations: which outcome to choose?

• Look at actual health outcomes in cohorts?



- A priori considerations: which outcome to choose?
- Look at actual health outcomes in cohorts? lacksquare







A priori considerations: which outcome to choose?

• Look at actual health outcomes in cohorts?



- A priori considerations: which outcome to choose?
- Look at actual health outcomes in cohorts?
 - Takes a long time to see effect not enough data
 - Some smoking-related health effects are irreversible



Former tobacco user

Current tobacco user

S

Base: Total Population

Smoking

Toolkit Study



A priori considerations: which outcome to choose?

- Look at actual health outcomes in cohorts?
 - Takes a long time to see effect not enough data
 - Some smoking-related health effects are irreversible
 - Health outcomes confounded with past smoking behaviour of most EC users
- Look at biomarkers of actual harm?
 - Evidence of harm might occur more quickly
 - Acute vs. chronic effects



A priori considerations: which outcome to choose?

Letters

Electronic Cigarette Smoking Increases Aortic Stiffness and Blood Pressure in Young Smokers

Smoking increases aortic stiffness and blood pressure (BP) (1), which are both important predictors of cardiovascular risk and all-cause mortality (2.3). Electronic cigarettes (EC) simulate tobacco cigarettes (TC) and have been advocated as a less harmful alternative (4). The effect of EC on aortic stiffness has not been defined. We investigated the acute effects of EC smoking on aortic stiffness and BP and compared them with the effects of TC smoking

We studied 24 smokers (age: 30 ± 8 years) otherwise free of cardiovascular risk factors on 4 separate occasions (total 96 sessions): 1) TC over 5 min; 2) EC over 5 min; 3) EC for a period of 30 min; and 4) nothing (sham procedure) for 60 min. EC5min was chosen as a direct comparison with TC (nicotine delivery rate from EC is far lower and slower than with TC), and EC30min to mimic the common pattern of EC smoking (nicotine delivered obtained plasma levels comparable with those after 5 min of TC smoking) (5). Carotid-femoral pulse-wave velocity (PWV) was used to assess aortic stiffness. Our Institutional Research Ethics Committee approved the study protocol, and all subjects provided written informed consent. The results at various time points were compared with the baseline measurements within each arm, and between the 4 arms using paired and unpaired t-tests, respectively. The composite effect of TC or EC versus sham over time was investigated with an analysis of variance for repeated measures, Regarding PWV, the composite effect of smoking sessions versus sham over time was investigated by using mean BP as covariate

There were no differences in all baseline measurements between the sessions. Heart rate increased in both the TC and EC 30-min sessions (by 4.0 beats/ min after 5 min, p < 0.05, and by 3.1 beats/min after 30 min, respectively), whereas the effect of EC5min smoking on heart rate was minimal (p = 0.57), B(TC and EC increased systolic BP (Figure 1A) and t differences in changes of BP responses between th smoking forms were not significant. Diastolic exhibited similar patterns of changes. PWV increased immediately (by 0.44 m/s) after end of TC smoking and remained increas

throughout the whole period (Figure 1B). EC5n smoking induced a significant PWV increase af 15 min (by 0.19 m/s). EC30 min smoking provoke

FIGURE 1 Systolic BP and PWV Responses



Systolic BP (A) and PWV (B) responses. Each line represents response defined as net TC/EC smoking effect minus sham procedure effect at each time point, BL - baseline; NS - non-significant. The p values refer to the composite effect of TC/EC at 5 and 30 min versus sham during the whole study duration. The composite effect of TC/EC versus sham was determined by using mean pressure as covariate. *TC versus sham, ¶EC at 5 min versus sham, †EC at 30 min versus sham, **p < 0.001, PWV change between EC 5 min session and sham session after 15 min smoking using the Student t test for paired measures.

Effect of caffeine on aortic elastic properties and wave reflection

Charalambos Vlachopoulos, Kozo Hirata and Michael F. O'Rourke

Objective Caffeine is the most widely used pharmacologically active substance. Aortic elastic properties and arterial wave reflection are important factors for the efficient performance of the cardiovascular system, as well as prognosticators of cardiovascular risk. We investigated the effect of caffeine on aortic elastic properties and wave reflection.

Design We studied the effect of caffeine (250 mg) in 20 healthy subjects according to a randomized, placebocontrolled, double-blind, cross-over design.

Methods Aortic stiffness was evaluated with carotidfemoral pulse wave velocity and wave reflection with augmentation index of the aortic pressure waveform.

Results Pulse wave velocity increased (by 0.51 m/s, P < 0.001) denoting an increase in a tic stiffness. Augmentation index and augmented pressure increased (by 6.8%, and by 4.4 mmHg, respectively, P < 0.001 for both) denoting increased wave reflections. Concurrently, both radial and aortic systolic, diastolic and pulse pressure increased significantly. However, this increase was 20 and 9% larger for aortic systolic pressure (at 30 and 60 min,

Introduction

Despite the extensive consumption of caffeine worldwide, determination of its true impact on human health remains a challenge for the medical community. Epidemiological studies on the effect of caffeine intake on cardiovascular disease cover the whole spectrum from a strong, positive association [1], to no association [2]. The role of caffeine in raising blood pressure is also a controversial issue. Caffeine has a strong, persistent, acute pressor effect [3], but the effect of habitual caffeine on blood pressure is less clear. However, studies with a positive association are continuously increasing [4] and a meta-analysis [5] of 11 controlled clinical trials demonstrated increased systolic and diastolic blood pressure in chronic coffee drinkers.

The elastic properties of the aorta, as well as the magnitude and timing of wave reflection, are important determinants of left ventricular function, coronary blood flow and mechanical integrity of arteries [6-8]. Furthermore, aortic stiffness, increased wave reflection, and their pathophysiological manifestations such as

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P < 0.001 and P < 0.05, respectively) and 56% larger for aortic pulse pressure (at 30 min, P < 0.001) compared with the corresponding upper limb values. This indicates that peripheral pressure measurements are not an accurate guide for the pressor effect of caffeine in central arteries.

Conclusions Caffeine affects unfavorably aortic stiffness and enhances wave reflections. This finding has implications for the impact of caffeine consumption on cardiovascular risk. J Hypertens 21:563-570 © 2003 Lippincott Williams & Wilkins.

Journal of Hypertension 2003, 21:563-570

Keywords: aorta, arteries, caffeine, stiffness, wave reflection

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See editorial commentary page 491

increased systolic pressure and pulse pressure (and especially central pulse pressure) and reduced diastolic pressure have been identified as independent factors of

We have previously shown that caffeine increases aortic stiffness and wave reflection in hypertensive subjects investigate the acute effect of caffeine on both aortic

We studied 20 subjects (17 men) aged 50 ± 16 (range 20 to 70) years; all had normal blood pressure, did not have diabetes, or family history of premature vascular disease. Four subjects were smokers. All but two subjects had no history of hyperlipidemia. They were clinically well and taking no regular cardiovascular medications (except for two who were on lipid-lowering drugs). All subjects were regular caffeine consumers

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Effects of High Intensity Resistance Training on Arterial Stiffness and Wave Reflection in Women

Miriam Y. Cortez-Cooper, Allison E. DeVan, Maria M. Anton, Roger P. Farrar, Kimberly A. Beckwith, Janice S. Todd, and Hirofumi Tanaka

Background: Cross-sectional studies reported that chronic resistance training is associated with arterial stiffening in men. These findings are in marked contrast to those found with aerobic exercise and may have important clinical relevance with regard to cardiovascular disease risk. However, the effect of resistance training on arterial stiffness has not been confirmed by interventional studies nor has this relation been investigated in women.

Methods: To determine whether a strength training program increases regional and central arterial stiffness in women, 23 healthy young women (29 \pm 1 years; mean \pm SD) participated in a high-intensity strength and power training program for 11 weeks. Ten other women (27 \pm 2 years) served as time controls.

Results: In the intervention group, one repetition maximal strength increased 12% to 17% (P < .0001), and leg fat-free mass (via DEXA) increased significantly. Brachial blood pressure (BP) and fasting plasma lipid and lipopro-

ardiovascular disease is the number one cause of mortality in women, and coronary heart disease is the predominant cardiovascular event comprising more than half of the events in women.¹ According to the Framingham Heart Study, 63% of women who died suddenly of coronary heart disease, had no previous symptoms of this disease. Therefore, there is mounting interest in finding new risk factors to better predict the presence of occult coronary heart disease. Emerging evidence indicates that elevated arterial stiffness may play a role in the pathogenesis of coronary heart disease and serve as an early marker for the detection of asymptomatic atherosclerotic lesions.2

It is widely accepted that regular participation in phys-

Received September 28, 2004. First decision January 13, 2005. Accepted January 16, 2005. From the Department of Kinesiology and Health Education, Univer-

- sity of Texas at Austin, Austin, Texas.
- This study was supported by the grant from the City of Austin Fire Department and the NIH grant (AG20966). MYC-C was supported by

wave velocity, a segmental measure of peripheral arterial stiffness. Conclusions: We concluded that a high-intensity resistance training program increases arterial stiffness and wave reflection in young healthy women. Our present interventional results are consistent with the previous cross-sectional studies in men in which high-intensity strength training is associated with arterial stiffening. Am J Hypertens 2005; 18:930-934 © 2005 American Journal of Hypertension, Ltd.

tein concentrations did not change across the 11 weeks.

Carotid augmentation index, a measure of arterial wave

reflection and arterial stiffness, increased from -8% ±

13% to 1% \pm 18% (P < .05), and carotid-femoral pulse

wave velocity increased (791 ± 88 v 833 ± 96 cm/sec;

P < .05). There were no changes in femoral-ankle pulse

Key Words: Arterial compliance, strength training, exercise, C-reactive protein,

ical activity confers protective effects against coronary heart disease.3 However, the type of the physical activity that has been examined in these epidemiologic studies is generally confined to aerobic exercises, and it is not clear whether strength training exerts similar cardioprotective effects. The benefits of strength training, including increased bone and muscle mass and increased strength of connective tissue, are being increasingly recognized.4 Strength training could become an even more essential component of overall exercise and fitness programs if it was shown to have positive effects on the cardiovascular system as well. However, in marked contrast to regular aerobic exercise, we5 and other investigators6 have previously reported that strength training is associated with

the NIH predoctoral fellowship (HL072729), and MMA was supported by the fellowship from the government of Spain.

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[20,21]. The purpose of the present study was to elastic properties and wave reflection in healthy sub-

iects.

cardiovascular risk [9-19].

Methods

Subjects



A priori considerations: which outcome to choose?

FEV₁ DECLINE





DNA adducts may persist for decades after exposure (e.g. Schmeisser et al, 2014)

Fletcher & Peto Curve (1977)



A priori considerations: which outcome to choose?

- Look at actual health outcomes in cohorts?
 - Takes a long time to see effect not enough data
 - Some smoking-related health effects are irreversible
 - Health outcomes confounded with past smoking behaviour of most EC users
- Look at biomarkers of actual harm?
 - Evidence of harm might occur more quickly
 - Acute vs. chronic effects
 - Effects may again be long-lasting and confounded with past smoking
- Look at biomarkers of risk?
 - Evidence accumulates quickly
 - Short-term / reversible
 - Have decades of research on tobacco products to guide us!



A priori considerations: which design to chose?

- Humans not animals
 - Failure to replicate animal studies (poor design but also important physiological differences) : 8% successful translation from animal models to human cancer trials (Mak et al, 2011)

Electronic-cigarette smoke induces lung adenocarcinoma and bladder urothelial hyperplasia in mice

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Edited by Bert Vogelstein, Johns Hopkins University, Baltimore, MD, and approved September 9, 2019 (received for review July 2, 2019)

Electronic-cigarettes (E-cigs) are marketed as a safe alternative to tobacco to deliver the stimulant nicotine, and their use is gaining in popularity, particularly among the younger population. We recently showed that mice exposed to short-term (12 wk) E-cig smoke (ECS) sustained extensive DNA damage in lungs, heart, and bladder mucosa and diminished DNA repair in lungs. Nicotine and its nitrosation product, nicotine-derived nitrosamine ketone, cause the same deleterious effects in human lung epithelial and bladder urothelial cells. These findings raise the possibility that ECS is a lung and bladder carcinogen in addition to nicotine. Given the fact that E-cig use has become popular in the past decade, epidemiological data on the relationship between ECS and human cancer may not be known for a decade to come. In this study, the carcinogenicity of ECS was tested in mice. We found that mice exposed to ECS for 54 wk developed lung adenocarcinomas (9 of 40 mice, 22.5%) and bladder urothelial hyperplasia (23 of 40 mice, 57.5%). These lesions were extremely rare in mice exposed to vehicle control or filtered air. Current observations that ECS induces lung adenocarcinomas and bladder urothelial hyperplasia, combined with our previous findings that ECS induces DNA damage in the lungs and bladder and inhibits DNA repair in lung tissues, implicate ECS as a lung and potential bladder carcinogen in mice. While it is well established that tobacco smoke poses a huge threat to human health, whether ECS poses any threat to humans is not yet known and warrants careful investigation.

human and animal carcinogens (2, 3, 7). Hence, measuring nitrosamine levels in body fluids has become a gold standard for assessing the potential carcinogenic effect of TS (7, 8). This method has been adapted to address the potential carcinogenic effects of E-cig smoke (ECS) (9). It has been found that the level of 4-(methylnitrosoamino)-4-(3-pyidyl)-1-butanol (NNAL), an NNK derivative, in the urine and saliva of E-cig smokers is only 5% of the levels found in comparable tobacco smokers (9). This has led to the assumption that nicotine nitrosation does not take place in ECS and that only a minute quantity of nitrosamines is present in ECS (9). This finding has supported the recommendation from public health experts, including Public Health England, that E-cigs are 95% safer than conventional cigarettes (10), and has prompted many epidemiologists to speculate that switching from TS to ECS could save millions of lives (11). Likely as a result of this reasoning, the popularity of E-cig

Likely as a result of this reasoning, the popularity of E-cig smoking is rising rapidly. Currently 3.2% of adults in the United States and 3.6 million junior-high and high-school students have embraced E-cig smoking (10). Given the widespread use of E-cigs, their health effects—particularly their carcinogencidy deserve careful scrutiny (10). Assessing the safety of E-cigs must examine 3 critical issues. First, is the level of nitrosamines in Mouse bread that spontaneously developed cancer within 1 year (11.1% "fresh air" vs 22.5% in EC nicotine condition)

- Were exposed continuously for 4h for 5 days a week at 36 mg/ml (3 mice died due to noncancer causes) ~ 7 years in 1 year
- Constant voltage used for 4h likely induced overheating (carbonyls) and undermines homeostatic responses
- Additional exposure due to nicotine deposits on fur and surface > can oxidise to NNK
- No evidence that nicotine causes cancer in humans (IARC)!



A priori considerations: which design to chose?

- Humans not animals
 - Failure to replicate animal studies (poor design but also important physiological differences) : 8% successful translation from animal models to human cancer trials (Mak et al, 2011)
- Body-level exposure
 - Machine yield deceptive > user characteristics



Location of filter vent holes



Location of filter vent holes outside ISO testing machine





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- Body-level exposure
 - Machine yield deceptive > user characteristics
- Appropriate comparator: smokers not never smokers
 - Claim is about reduced risk compared with smokers
 - Most EC users are current / past smokers

Suitable biomarkers of subsequent risk in humans

- 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanol (NNAL)
 - Marker for nitrosamine exposure (NNK) > potent lung carcinogens (IARC)
 - Specific to tobacco use; linked to subsequent cancer risk (Yuan et al, 2011)
 - Urinary half-life ~10 days (Goniewicz, 2009)
- 1-hydroxypyrene (1-HOP)
 - Marker of polycyclic aromatic hydrocarbon exposure (pyrene) > potent carcinogens (IARC)

OH

COOH

OH

- Relatively specific to tobacco use; linked to subsequent cancer risk (Yuan et al, 2014)
- Urinary half-life ~20 hours (Buchet et al, 1992)
- 3-hydroxypropylmercapturic acid (3-HPMA)
 - Marker of volatile organic compound (acrolein) > potent respiratory irritant (US EPA)
 - Relatively specific to tobacco use; aldehydes have been linked to cancer (IARC) ; c 0 `
 - Urinary half-life ~ 1 day (Carmella et al, 2009)
- Carbon monoxide
 - For simplicity only looking at exhaled CO > highly toxic (WHO)
 - Relatively specific to tobacco use; linked to cardiovascular diseases (Lee et al, 2015)
 - Half-life ~5 hours (Sandberg et al, 2011)

UCL

Impact of EC use on NNAL

- 10 published papers (8 studies) with 658 participants
- Mostly second/third generation EC evaluated



Impact of EC use on NNAL

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Mostly second/third generation EC evaluated lacksquare



DCL

Impact of EC use on NNAL

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Impact of EC use on NNAL





Health effects: beyond cancer

Generally see similar levels to non-smokers



Impact of dual use (1) Dual use only beneficial in non-daily smokers; (2) Less impact of EC on metals; (3) Residual increase in some biomarkers compared with non-smokers 180 Dual Use (Daily Smoker/Non-daily EC use) Dual Use (Daily EC use/Non-daily Smoker) 160 % of cigarette-only smoker levels EC-only use Never users 140 120 100 9.8% 41.3*% **60.2*%** 80 * 97.6*% 60 40 20 0 NNK (NNAL) Lead (Pb) Pyrene (1-HOP) Acrolein (CEMA) **Brain/Heart/Kidney** Cancer Cancer **Respiratory Diseases**



New trial evidence: cardiovascular and respiratory function

- George et al (2019)
 - Randomised smokers (N=145) to either continued smoking, EC with or without nicotine, with 1 month follow-up
 - Improvements in endothelial function and vascular stiffness (irrespective of nicotine use)





New trial evidence: cardiovascular and respiratory function

- George et al (2019)
 - Randomised smokers (N=145) to either continued smoking, EC with or without nicotine, with 1 month follow-up
 - Improvements in endothelial function and vascular stiffness (irrespective of nicotine use)
- Hajek et al (2019)
 - Randomised smokers (N=866) to receive either NRT or EC, with 1 year follow-up
 - Improvements in cough and phlegm production



New trial evidence: cardiovascular and respiratory function

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 - Randomised smokers (N=145) to either continued smoking, EC with or without nicotine, with 1 month follow-up
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Table 5. Respiratory Symptoms at Baseline and at 52 Weeks.*							
Symptom	om E-Cigarettes (N=315) Nicotine Replacement (N=27		cement (N=279)	Relative Risk (95% CI)†			
	Baseline	52 Weeks	Baseline	52 Weeks			
number (percent)							
Shortness of breath	120 (38.1)	66 (21.0)	92 (33.0)	64 (22.9)	0.9 (0.7–1.1)		
Wheezing	102 (32.4)	74 (23.5)	86 (30.8)	59 (21.1)	1.1 (0.8–1.4)		
Cough	173 (54.9)	97 (30.8)	144 (51.6)	111 (39.8)	0.8 (0.6–0.9)		
Phlegm	137 (43.5)	79 (25.1)	121 (43.4)	103 (36.9)	0.7 (0.6–0.9)		



Health effects: outstanding questions

- Clearly e-cigarettes are not completely safe
 - Nicotine has a *Low* Risk, not a *No* Risk profile (e.g. Dempsey & Benowitz, 2001)
 - Threshold effects (is XX% reduction in exposure= XX% reduction in harm?)
 - E-cigarette specific risks not captured by tobacco-related outcomes
 - Route of administration > most research on oral not pulmonary administration
 - Changing use pattern may produce unique risks (e.g. cloud-chasing, newer products)
 - Novel biomarkers necessary
- However, toxicological analyses have shown cigarettes to be uniquely dangerous product, compared with which, e-cigarettes are clearly a reduced risk products
 Cigarette



Health effects: outstanding questions

- Clearly e-cigarettes
 - **OPEN ACCESS** - Nicotine has a *Low*
 - Threshold effects (is: ished online only. To view sase visit the journal online http://dx.dolorg/10.1136/ baccocontrol-2017-0537591
 - E-cigarette specific
 - Route of administrati norehensive Cancer Center town University Medical ter 3300 Whitehoven St W. Suite 4100, Washington
 - Changing use patter .777@georgetown.edu evised 11 July 2017 cepted 5 August 2017
 - Novel biomarkers ne
- However, toxicologic dangerous product, reduced risk produc Nothing EC

NRT 95% risk reduction = 6.6*million fewer deaths*

Research pape

Potential deaths averted in USA by replacing cigarettes with e-cigarettes

David B Abrams^{1,8}

ABSTRACT

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Introduction US tobacco control policies to reduce cigarette use have been effective, but their impact has been relatively slow. This study considers a strategy of switching cigarette smokers to e-cigarette use ('vaping') in the USA to accelerate tobacco control progress. Methods A Status Quo Scenario, developed to project smoking rates and health outcomes in the absence of vaping, is compared with Substitution models, whereby cigarette use is largely replaced by vaping over a 10-year period. We test an Optimistic and a Pessimistic Scenario, differing in terms of the relative harms of e-cigarettes compared with cigarettes and the impact on overall initiation, cessation and switching. Projected mortality outcomes by age and sex under the Status Quo and E-Cigarette Substitution Scenarios are compared from 2016 to 2100 to determine public health impacts. Findings Compared with the Status Quo, replacement of cigarette by e-cigarette use over a 10-year period yields 6.6 million fewer premature deaths with 86.7 million fewer life years lost in the Optimistic Scenario. Under the Pessimistic Scenario, 1.6 million premature deaths are averted with 20.8 million fewer life years lost. The largest gains are among younger cohorts, with a 0.5 gain in average life expectancy projected for the age 15 years cohort in 2016. Conclusions The tobacco control community has been

divided regarding the role of e-cigarettes in tobacco control. Our projections show that a strategy of replacing cigarette smoking with vaping would yield substantial life year gains, even under pessimistic assumptions regarding cessation, initiation and relative harm.

INTRODUCTION

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Harms from cigarette smoking remain unacceptably high even though smoking prevalence in the USA has decreased markedly over the past 50 years." Two of three long-term smokers will likely die prematurely by a potent switching-based strategy. To address of a smoking-attributable disease.5-5 Although many tobacco control policies, such as higher cigarette taxes, smoke-free public places, media campaigns, cessation treatment programmes and advertising restrictions, have already been implemented with substantial effectiveness, their pace in averting preventable deaths has been relatively slow and their potential to secure quick and substantial new smoking declines is limited.⁶⁷ Accordingly, some smokers who would otherwise have quit tobacco control experts and national governments all tobacco and nicotine use to instead use e-cighave begun considering what might be done to arettes. To distinguish the effect of policies on accelerate declines in tobacco-caused health harms younger and older cohorts, we present separate and eventually eliminate all tobacco consumption analyses for the cohorts age 15 years and age 35 (often termed an 'endgame'). The 2014 US Surgeon years in 2016.

General Report recommended an endgame strategy for the tobacco epidemic." Finland, New Zealand, Hong Kong and Ireland have already set the goal of reaching an endgame.

While some refer to an endgame for all tobacco, plan to minimise cigarette use has yet to be implemented. At the same time, emerging nicotine-debetter address new opportunities and threats that they present.1

Rather than focusing on policies designed excluexperts suggest a complementary approach to encourage the use of less harmful nicotine deliver products, such as e-cigarettes, as a substitute for cigarettes. * 9 18-21 Some public health experts and officials fear that e-cigarette use ('vaping') may increase overall tobacco-related harms by serving as a gateway to smoking or prompting smokers to vape or engage in dual use instead of quitting all use.12-15 However, evidence is mounting that e-cigarettes deliver only a small percentage of the toxi cants delivered by cigarettes.26-52 In addition, newer e-cigarettes models have been shown to more effi ciently deliver nicotine29 50 55 than older models and The goal of this paper is to show the potentia

health impact from an endgame strategy directed at replacing all or most cigarette smoking by e-cigarette use over a 10-year period. The 10-year time frame is used for illustrative purposes to show the potential health gains that could be secured the major concerns about switching smokers to e-cigarettes, some of the projections assume a much smaller net reduction in health harms from switching to e-cigarette from cigarette use that existing research suggests, and that the switching strategy will increase initiation into regular vaping by youth and others who would not otherwise use any nicotine delivery products and will prompt

David T Levy,¹ Ron Borland,² Eric N Lindblom,³ Maciej L Goniewicz,⁴ Rafael Meza,⁵ Theodore R Holford,⁶ Zhe Yuan,⁷ Yuying Luo,⁷ Richard J O'Connor,⁴ Raymond Niaura,⁸ **G.** Dempsey & Benowitz, 2001)

XX% reduction in harm?)

most appear to focus on cigarettes as a more real-istic and most important target, since they cause related outcomes

livery products, such as e-cigarettes, call for an nonary administration

Rather than focusing on policies designed exclus-sively to reduce cigarette use, some public health) ud-chasing, newer products)

cigarettes to be uniquely provide sensocimotor experiences and 'throat-hir' similar to smoking,⁴ thus increasing their potential to serve as effective substitutes for cigarettes.



60% risk reduction = 1.6 *million fewer deaths*

Levy DT, et al. Tob Control 2017;0:1-8. doi:10.1136/tobaccocontrol-2017-053759 BMJ Copyright Article author (or their employer) 2017. Produced by BMJ Publishing Group Ltd under licence



What does this mean?

- Combustion is key
 - Cigarette smoke (600 compounds, including 70 carcinogens, turned it 7,000+ through burning at ~800 °C) vs aerosol (e-cigarettes mainly nicotine, PG/VG, flavourings)
 - Would assume e-cigarettes are safer based on simple chemistry
- Statement that we do not know long-term health consequences ignores substantial research based on decades of insights from work on tobacco
 - Consensus in academic community: e-cigarettes are <u>much less harmful</u> than cigarettes based on both evaluation of e-liquid/aerosol carcinogenicity and exposure profile of users
 - This should translate into reduced long-term risk of smoking-related diseases (especially cancer) when switching completely
- However, unknown unknowns exist (e.g. novel risks specific to e-cigarettes) and absolute risks (vis à vis not smoking) cannot be determined so need more data:
 - Ideal approach: compare disease incidence in cohorts of never smokers with long-term EC use, never smokers without any product use and long-term smokers (but <u>will take</u> <u>time</u>)

Conclusions



What does this mean?

- Combustion is key
 - Cigarette smoke (600 compounds, including 70 carcinogens, turned it 7,000+ through burning at ~800 °C) vs aerosol (e-cigarettes mainly nicotine, PG/VG, flavourings)

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k on tobacco

And finally...

VAPING DEATHS ACROSS THE US



O

And finally...



Putting recent events in context: what's going on?

- Worldwide, there are over 40 million e-cigarette users and devices have been on the market for over a decade with very few problems reported
- Since July/August there has been a sudden outbreak of 'vapingrelated lung disease', primarily in the US
- These are <u>acute</u> events, so likely have an <u>acute</u> cause (i.e. it's not vaping per se but what is vaped that may be the problem)
 - Most cases involve younger users of bootlegged, illicit products (cannabis)
 - Cannabis unlike nicotine is not easily water-soluble so in part disease may be due to addition of solvents to make it easier to vape THC oils (bad for lungs)
 - Since e-liquids in US not as tightly regulated as in Europe (EU TPD) also likely to include other adulterants (especially black market products)
 - Possibility that people used products wrongly (dry puff/high voltage)

And finally...



Putting recent events in context: what's going on?

- with cigarettes

 - are a much less harmful alternative to smoking 📕 (I.e. it's not

Advice include other Possibility that people used products wrongly (dry puff/high voltage)

Conclusions: a warning



Unintended consequences of misinformation



Conclusions: a warning



Unintended consequences of misinformation





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Public Health England



Maciej Goniewicz

SPECTRUM

Shaping Public hEalth poliCies

To Reduce ineqUalities and harM



CANCER RESEARCH UK

