STUDIES INTO THE CARDIOVASCULAR AND RESPIRATORY EFFECTS OF ELECTRONIC CIGARETTES

By

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For Natalie and Scott

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Publications

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ABBREVIATIONS AND DEFINITIONS

AHP	Allied healthcare professional
AI	Augmentation Index
BAL	Bronchoalveolar-lavage
BHF	British Heart Foundation
BMI	Body Mass Index
BP	Blood pressure
CDC	Centers for Disease Control and Prevention
CFTR	Cystic fibrosis transmembrane conductance regulator
CRF	Clinical Research Facility
CRP	C-reactive protein
COPD	Chronic obstructive pulmonary disease
COSHH	Control of substances hazardous to health
DBP	Diastolic blood pressure
E-cigarettes	Electronic cigarettes
eCO	Exhaled carbon monoxide
ECG	Electrocardiogram
eGFR	Estimated glomerular filtration rate
EMP	Endothelial microparticle
END	Electronic nicotine delivery system
eNO	Exhaled nitric oxide
eNOS	Endothelial nitric oxide synthase
EPC	Endothelial progenitor cell
EVALI	E-cigarette, or vaping, product use-associated lung injury
FDA	Food and Drug Administration
FeNO	Fractional exhaled nitric oxide
$FEF_{25–75\%}$	Forced expiratory flow at 25–75% of forced vital capacity
$FEV_{1,}$	Forced expiratory volume in one second
FDG-PET/CT	18F-flurorodeoxyglucose positron emission tomography/computer tomography
FMD	Flow mediated dilation
FTND	Fragerström Test of Nicotine Dependence
FVC	Forced vital capacity
GC	Gas chromatography
GC–NPD	Gas chromatography nitrogen–phosphorus detector
GRI	Glasgow Royal Infirmary
GP	General Practice
HR	Heart rate
HRV	Heart rate variability

IQR	Interquartile range
ITT	Intention-to-treat
MCC	Mucocilary clearance
MHRA	Medicines and Healthcare Products Regulatory Agency
MP	Microparticle
MUC5AC	Mucin-5AC
nAChRs	Nicotinic acetylcholine receptors
NCSCT	National Centre for Smoking Cessation and Training
NET	Neutrophil extracellular trap related protein
NHS	National Health Service
NHSGGC	National Health Service Greater Glasgow and Clyde
NICE	National Institute for Health and Care Excellence
NicoTAR	Nicotine and Tobacco Product Assessment Shared Resource
NNA	New Nicotine Alliance
NO	Nitric oxide
NRP	Nicotine Replacement Patch
NRT	Nicotine Replacement Therapy
O_2 Sats	Oxygen saturations
PAOD	Peripheral arterial occlusive disease
PAT	Peripheral arterial tonometry
PECAM-1	Platelet endothelial cell adhesion molecule
PEF	Peak expiratory flow
PFP	Platelet free plasma
PHE	Public Health England
PM	Particulate matter
PMP	Platelet microparticle
PP	Per protocol
PPM	Parts per million
PWA	Pulse wave amplitude
PWV	Pulse wave velocity
QEUH	Queen Elizabeth University Hospital
RCF	Relative centrifugal force
ROS	Reactive oxygen species
RPCI	Roswell Park Cancer Institute
RHI	Reactive hyperaemia index
SBP	Systolic blood pressure
SD	Standard deviation
sE-selectin	Soluble endothelial leukocyte adhesion molecule-1
sICAM-1	Soluble intercellular adhesion molecule 1

SIMD	Scottish index of multiple deprivation.
SNA	Sympathetic nerve activity
sP-selectin	Soluble platelet selectin
SREC	Standardised research e-cigarette
sVCAM-1	Soluble vascular adhesion molecule 1
TC	Tobacco cigarettes
THC	Tetrahydro-cannabinol
TPD	European Union Tobacco Products Directive
UK	United Kingdom
US	United States of America
VAPOUR	CardioVAscular imPacts of electrOnic cigarettes in comparison to the Use of nicotine Replacement patches
WHO FCTC	World Health Organisation Framework Convention on Tobacco Control

SUMMARY

Tobacco smoking remains the single largest preventable cause of social health inequalities, morbidity and deaths in the United Kingdom (UK), accounting for approximately 122,000 deaths in the UK each year (Royal Collage of Physicians, 2016). Tobacco smokers lose an average of 3 months of life expectancy for every year smoked after the age of 35, dying around 10 years younger than a non-smoker (Doll et al., 2004). Annually, smoking related illness is estimated to cost the National Health Service (NHS) £2.6 billon (Public Health England, 2017).

Despite tobacco smoking being entirely preventable and a widely known modifiable risk factor, with significant risk reduction benefits in morbidity and mortality (Doll et al., 2004, Freund et al., 1993), one billion adults worldwide continue to smoke (World Lung Foundation, 2018), primarily because their desire to smoke is driven by nicotine addiction. Although nicotine is the principle addictive chemical within tobacco smoke and produces withdrawal symptoms on discontinuation, it is the exposure from the toxins and carcinogens found in the tobacco smoke which are predominately deleterious to health, rather than nicotine itself.

The importance of "harm reduction" cannot be overemphasised. Tobacco harm reduction strategies in relation to smoking cessation, have focused on delivering nicotine without the products of combustion to support quit attempts. It is widely accepted that nicotine replacement therapy (NRT) reduces the motivation to smoke and NRT is recommend to individuals seeking pharmacological help to stop smoking (National Institute for Health and Care Excellance, 2018). Data from a Cochrane review published in 2012, concluded that all commercially available forms of NRT (gum, transdermal patch, nasal spray, inhaler and sublingual tablets and lozenges) increase the likelihood of smoking cessation by 50-70% amongst smokers. There is no evidence that NRT increases the risk of major cardiovascular events in patients with cardiovascular disease (Stead et al., 2012a).

Since 2011, the use of electronic cigarettes (e-cigarettes) as a smoking cessation aid has gained unprecedented popularity. Within the UK it is estimated that there are 2.9 million e-cigarettes users (Action on Smoking and Health, 2019b). Subsequently e-cigarettes have replaced medicinal NRT as the preferred nicotine replacement product to support quit attempts (Smoking in England, 2015). Unlike conventional NRT, nicotine containing e-cigarettes are hand-held devices capable of emulating both the physicality and modality of nicotine delivery associated with tobacco smoking without the products of combustion.

Despite the potential harm reduction associated with e-cigarettes, their use remains controversial and has raised global debate and public health concerns regarding their effectiveness and safety. UK health policy considers e-cigarettes as a safer alternative to tobacco smoking, which offers a viable harm-reduction option (Public Health England, 2017). Other nations such as the United

States (US) and Australia have adopted a more precautionary stance; as there are concerns regarding their safety and concern that e-cigarettes may act as a gateway to tobacco smoking (Leventhal et al., 2015). This predicament has arisen mainly because the use of e-cigarettes has evolved far faster than the scientific understanding of their potential biological health effects.

In the "real life setting" patients are 1.6 times more likely to attempt quitting if they are advised to quit smoking by their physician (Pignone M and Salazar R, 2017). The National Institute for Health and Care Excellence (NICE) is concerned that the uncertainties surrounding the safe use of e-cigarettes makes it challenging for healthcare professionals to have informed discussions with their patients on the use of e-cigarettes, and as such this may discourage some tobacco smokers from switching to e-cigarettes (NICE, 2018).

This thesis seeks to evaluate the cardiovascular and respiratory health effects of e-cigarettes which can be translated into "real-world" practice. A multifaceted approach was taken to address several key themes.

1. Conducting research within a framework governed by tobacco control policy.

2. Understanding healthcare professionals' perceptions of nicotine, NRT and e-cigarettes.

3. Investigating the acute cardiorespiratory effects of e-cigarettes compared to tobacco cigarettes.

4. Investigating the short-term cardiorespiratory effects of e-cigarettes compared to NRT.

The emphasis of this work was directed to finding a pragmatic and patient-centred approach to help direct future e-cigarette research and the healthcare professionals' everyday practice.

Chapter 2, highlights how in the context of the ongoing e-cigarette debate, and major investments by the tobacco industry, it is crucial that independent researchers provide regulators and the public with evidence-based guidance. The key ethical, legislative and regulatory issues are discussed and the extent to which they influenced the research design and methodology of the studies presented in the subsequent chapters.

Chapter 3 focuses on exploring the attitudes and risk perceptions concerning nicotine, tobacco cigarettes, NRT and e-cigarettes amongst healthcare professionals. Our study demonstrates that whilst the majority of healthcare professionals view e-cigarettes as a harm reduction product, there is a discrepancy amongst their perceptions and their clinical practice. There is an urgent need for evidence-based guidelines and education to establish congruence between healthcare professionals' beliefs and tobacco harm reduction policy, so that smokers wishing to stop smoking are provided with both effective and consistent practitioner advice.

Chapter 4 reports a cross-over study which evaluates the acute effects of e-cigarettes versus tobacco smoking on vascular and respiratory function and circulating microparticles (MPs),

particularly platelet MPs (PMPs, biomarkers of thrombosis) and endothelial MPs (EMPs, biomarkers of endothelial function). Twenty healthy male tobacco smokers were recruited and randomised into one of two study arms after which they crossed over into the other study arm on a separate day. The interventions comprised of smoking one tobacco cigarette or taking 15 vapes of an e-cigarette with e-liquid containing 18mg/ml of nicotine. Vascular and respiratory function studies and venous blood sampling were performed before and following each intervention. The number of MPs was determined by flow cytometry. The vascular and respiratory function tests demonstrated that following e-cigarette exposure there was a significant increase in reactive hyperaemia index, (a measure of endothelial function) (p =.006), augmentation index (a measure of vascular stiffness) (p =.010), and a decrease in peak expiratory flow (p = .03), which was not demonstrated after tobacco cigarette use. Following tobacco cigarette exposure, the number of EMPs and PMPs significantly increased (all p < .001). Following e-cigarette exposure, no significant change in EMPs was observed, whereas the number of PMPs were significantly increased (p < .001). Our results demonstrate that e-cigarette and tobacco cigarette exposure elicit differential effects on the cardiovascular and respiratory system. Where tobacco smoking significantly increased microparticle formation, indicative of possible endothelial injury, e-cigarette use induced vasoreactivity and decreased peak expiratory flow. These findings suggest that both e-cigarettes and tobacco smoking negatively impact vascular function.

Chapter 5 reports a randomised controlled trial investigating the short-term cardiovascular effects of e-cigarettes in comparison to nicotine replacement patches (NRPs) (The VAPOUR study). The primary aim of the study was to assess the 12-week effects of e-cigarettes versus nicotine replacement patches upon endothelial function as assessed by flow mediated dilation (FMD). Secondary outcomes included changes in blood pressure, heart rate, pulmonary function and weight. Fifty-five smokers with no established history of cardiovascular disease were recruited. Among the participants who were "smokefree" at 12 weeks there was a significant improvement in FMD (e-cigarettes 1.09 ± 0.61%; NRPs 1.10 ± 0.52%) and an associated decrease in blood pressure, systolic (e-cigarettes -7 ± 8mmHg; NRPs -6 ± 3 mmHg) and diastolic blood pressure (e-cigarettes -3 ± 5mmHg; NRPs -4 ± 4mmHg) in both the e-cigarette and NRP study arms (all p < .05). Significant increases in post cessation weight gain were observed following the use of NRPs (78.6 ± 17.6 vs 76.3 ± 14.5 kg, p = .027), but not following the use of e-cigarettes (70.7 ± 11.7 vs 70.1 ± 12 kg, p = .271). No significant changes were observed in pulmonary function in either the e-cigarette or NRP arms (all p > .05). These data demonstrate that within the context of a 12 week smoking cessation programme the use of both e-cigarettes and nicotine replacement patches have comparable and beneficial effects upon cardiovascular health. Although the long-term health effects of e-cigarettes await further clarification, the VAPOUR study provides evidence to support the use of e-cigarettes as a short-term smoking cessation intervention, which in turn may help inform evidence-based discussion between healthcare professionals and patients wishing to stop smoking.

To conclude, the work presented in this thesis has highlighted that biomarker studies, such as ours, have an important role in predicting potential cardiovascular and respiratory risks of e-cigarettes, and developing an understanding of any potential cardiovascular and respiratory risks associated with long-term e-cigarette use. However, the judgement as to whether the observed associations represent a cause-effect relationship between the exposure of vaping and development of cardiovascular and respiratory disease requires inferences far beyond the data of the studies presented in this thesis. Our findings provide the preliminary evidence which supports the harm reduction role of e-cigarettes when used as a temporary short-term smoking cessation intervention. Although our findings suggest that e-cigarettes may be less harmful, it is important to recognise that our research findings also suggest that e-cigarette use may not be devoid from cardiovascular risk and the implications of these findings on long-term health need further exploration.

INTRODUCTION

1.1 E-cigarettes

E-cigarettes were invented and developed as an alternative to tobacco smoking. The invention of the e-cigarette is often credited to Chinese pharmacist Hon Lik who invented the first commercially available e-cigarette device in 2003. However, the principle of e-cigarette function, the evaporation of liquid and the delivery of aerosol can be tracked backed to published patents as earlier as the 1930s'. The first documented reference to an e-cigarette is a patent granted to the inventor J Robinson in 1930 (filed in 1927), describing an e-cigarette "for holding medicinal compounds which are electronically or otherwise headed to produce vapour for inhalation" (Robinson, 1930). In 1965, Herbert A. Gilbert was granted a patent for a "Smokeless non-tobacco cigarette" and described a battery-operated device "to provide a safe and harmless means for and method of smoking by replacing burning tobacco paper with heated, moist, flavoured air" (Gilbert, 1965). Furthermore, in 1990, Philip Morris International started developing a nicotine aerosol device, similar to the modern e-cigarette to address the health concerns and decreased social acceptability of smoking that were leading smokers to switch to nicotine replacement therapy (Dutra et al., 2017). The term e-cigarettes refers to a diverse group of devices that allow users to inhale an aerosol, which is commonly referred to as vapour, by heating a liquid (e-liquid) commonly composed of a mixture of water, propylene glycol, vegetable glycerine, flavourings and nicotine. Common forms are first-generation disposable 'ciga-like', second-generation rechargeable e-cigarettes, and third- generation large tank devices. The most recent iteration of e-cigarettes are pod-based devices such as the popularised 'JUUL', which are smaller than other types of e-cigarettes and are able to deliver nicotine 1.25–2.7 times faster than competing e-cigarettes (Voos et al., 2019). Despite the diverse range of e-cigarettes, all e-cigarettes generally operate in a similar manner and are composed of similar components; a lithium battery, an atomiser composed of a wick or a metal coil, e-liquid and depending on the e-cigarette design the e-liquid is either sealed within cartridges, pods or added to a tank system. Where the early e-cigarette devices were designed to resemble cigarettes, technological advancements to improve sensory satisfaction and nicotine delivery mean that newer generation e-cigarettes are generally larger, look less like cigarettes and have improved capabilities to deliver nicotine at a rate and dose comparable to tobacco cigarettes (Etter, 2014b, Flouris et al., 2013).

E-cigarettes are known by many different names. They are sometimes called "e-cigs," "e-hookahs", "mods", "vape pens", "vapes", "tank systems" and "electronic nicotine delivery systems (ENDS)". However, it is now recognised that the current terminology is no longer appropriate as it does not accurately represent the whole spectrum of e-cigarette devices and range of substances delivered via e-cigarettes which include non-nicotine liquids, nicotine containing liquids and tetrahydro-cannabinol (THC) containing liquids (McNeill A, 2019). While there are broader discussions ongoing in the UK and internationally to develop a common terminology and classification; for the

purposes of this thesis, the term e-cigarettes will be used to describe nicotine containing e-cigarettes, unless otherwise specified. I will refer to people who regularly use e-cigarettes as vapers and the act of using an e-cigarette as vaping.

1.2 Tobacco harm reduction

Harm reduction is a strategy, policy and philosophy of reducing risk, morbidity and mortality associated with an action or condition. There are few practices that are more addictive and harmful to individuals or society than tobacco smoking. Approximately half of all lifelong tobacco smokers will die as a direct cause of their tobacco smoking, losing an average of 10 years of life expectancy compared with never smokers (Doll et al., 2004). Within the UK, smoking is the primary cause of preventable illness and premature deaths, and one of the largest causes of health inequalities. In 2017/18 tobacco-related illness accounted for in excess of 489,300 hospital admissions and 77,800 preventable deaths in England (NHS Digital, 2019). Although due to a wide range of diseases, 70% of these deaths arise from 3 main causes: lung cancer, chronic obstructive pulmonary disease (COPD), and vascular disease (Peto R et al., 2012). The resultant financial impact of tobacco smoking on our economy is in excess of £11 billion per annum of which an estimated £2.5 billion falls to the NHS (Department of Health, 2017). As there is no risk-free level of exposure to tobacco smoke, the direct and passive consequences of inhaling tobacco smoke result in harm and a reduction in quality of life to individuals across all age groups from the moment of conception (Royal Collage of Physicians, 2010). Clear links have been established between the prevalence of smoking and deprivation, with the prevalence of smoking and smoking related deaths being three times more common amongst socioeconomically disadvantaged populations within our society (Office for National Statistics, 2019).

Tobacco harm reduction seeks to reduce the net damage to health associated with the use of combustible tobacco smoking. To minimise the clinical and financial burden of tobacco smoking, national tobacco control strategies aim to create a "tobacco-free" generation by 2030, with the prevalence of smoking in the adult population reduced to ≤5 % (Royal Collage of Physicians, 2010, Department of Health and Social Care, 2019). This multifaceted approach focuses upon tobacco prevention, protection, cessation and policy enforcement. Although over recent decades the prevalence of tobacco smoking amongst high-income countries has fallen markedly, smoking remains common practice. Within the UK, an estimated 7.2 million adults still smoke; out of the constituent countries, Scotland continues to have the highest proportion of adult smokers (16.3%), followed by Wales (15.9%), Northern Ireland (15.5%) and England (14.4%) (Office for National Statistics, 2019). Across all ages, men are more likely to smoke than women, with the incidence of smokers being most common amongst young adults and those from socioeconomically disadvantaged populations (Office for National Statistics, 2019).

Current tobacco control policies have proved more effective in preventing the uptake of smoking than in helping established smokers to quit (Department of Health, 2017). Although surveys consistently show that a majority of smokers want to stop smoking, the overall successful quit rate remains low (Office for National Statistics, 2019). This is primarily because quit attempts are undermined by the highly addictive effect of nicotine. To sustain tobacco use, tobacco cigarettes have been purposefully engineered to be highly efficient nicotine delivery devices with the capabilities to deliver doses of nicotine at rates that exceed those achieved by intravenous injection, making tobacco smoking as addictive as drugs such as heroin or cocaine (Britton et al., 2016). The mechanisms of nicotine addiction are multifactorial; with smokers experiencing an initial sensation of reward from the exposure to nicotine within 15-20 seconds from the point tobacco smoke is inhaled. After sustained use and consequent desensitisation to nicotine's effects, smokers seek nicotine through the means of tobacco smoking to temporarily relieve the symptoms of nicotine withdrawal (Benowitz and Fraiman, 2017).

Although sustained tobacco smoking is driven by nicotine addiction, most of the harm to health from smoking is caused by exposure to the toxic products of combustion contained within tobacco smoke rather than nicotine itself. Of the three leading causes of mortality from smoking, direct exposure to the carcinogens contained in tobacco smoking primarily cause lung cancer; the proinflammatory effects of smoke cause COPD (Durham and Adcock, 2015); and the prothrombotic, proinflammatory and endothelial effects of smoke cause cardiovascular disease (Ambrose and Barua, 2004). Although nicotine may not be entirely harmless, several studies which have evaluated the effects of non-combustible nicotine products have shown that nicotine itself is unlikely to contribute to smoking-relating cancers and cardiovascular diseases (Lee and Hamling, 2009, Huhtasaari et al., 1999, Hansson et al., 2012), supporting the harm reduction principle proposed my Michael A.H. Russell, that "people smoke for the nicotine but die from the tar" (Russell, 1976). Most of the harm caused by tobacco smoking can be reduced by encouraging smokers to switch to a smoke-free source of nicotine. Through the delivery of smoke-free nicotine, NRT aims to reduce the motivation to consume tobacco and the physiological and psychomotor withdrawal symptoms. In the context of smoking cessation, clinical trials have demonstrated that a combination of NRT and behavioural support can increase the chance of a successful quit attempt by 50-70% (Stead et al., 2012b). The safety profile of NRT for smoking cessation has been well established and studies have demonstrated that NRT is not associated with an increased risk of heart attack, stroke or death, and is considered safe to use in pregnancy and in stable cardiac disease (Hubbard et al., 2005). Although there is a paucity of evidence relating to the long-term health effects of NRT, data from the 5-year Lung Health Study demonstrates that extended use is not associated with the occurrence of cancer or cardiovascular disease (Murray et al., 2009, Murray et al., 1996). Notably, it is widely accepted that any long-term effects of sustained NRT use are likely to be of minimal consequence in relation to those associated with continued tobacco use (Schnoll et al., 2015). Therefore as part a harm reduction strategy to transition smokers onto

smokeless form of nicotine, many clinical guidelines recommend NRT as a first line treatment for people seeking pharmacological help to stop smoking, with both the UK Medicines and Healthcare products Regulatory Agency (MHRA) and NICE approving the long-term use of NRT (NICE, 2018).

However, outside the confinements of clinical trials, population studies demonstrate that efficiency rates are low, and only 1 in 20 individuals who try NRT are successful in their quit attempt (Kotz et al., 2014). Although there is a myriad of reasons for NRT failure and relapse rates, it is important to recognise that many NRTs are unable to replicate many of the sensorimotor cues and behavioural rituals of tobacco smoking and fail to deliver nicotine to the brain at a comparable dose and rate experienced with tobacco smoking (Rose and Levin, 1991, Hajek et al., 1989). Unlike conventional NRT, e-cigarettes are the only nicotine replacement product capable of replicating both the physicality and modality of nicotine delivery associated with tobacco smoking, but without the products of combustion. Consequently, the emergence of e-cigarettes has revolutionised the choice of nicotine replacement products available to smokers.

1.3 E-cigarettes: harm reduction or exacerbation?

Internationally there is a lack of consensus regarding the harm reduction role for e-cigarettes. Some of the many disputes against the use of e-cigarettes stem from the fact the e-cigarettes have evolved far faster than the scientific understanding of their potential health effects. On a population level, there are several concerns that e-cigarettes may enhance the attractiveness of smoking itself and perpetuate the smoking epidemic through (1) dual tobacco and e-cigarette use, which will not only reduce the number of successful quit attempts but it also sustain tobacco smoking amongst individuals who would otherwise have quit; (2) acting as a gateway to nicotine addiction and tobacco smoking by attracting individuals who would not otherwise have used nicotine to become regular users, and then in due course become tobacco smokers; (3) diverting smokers away from evidence based smoking cessation treatments and services; (4) providing the tobacco industry with an ideal opportunity to manipulate its position to be seen as an advocator of harm-reduction; (5) renormalising the acceptability of inhaling nicotine and tobacco smoking; and (6) undermining smokefree legislation.

The concern regarding the renormalisation effect of tobacco smoking caused by e-cigarettes is best understood by first considering denormalisation. In public health policy, tobacco denormalisation strategies seek to make smoking less visible and less acceptable than it currently is. The underlying strategy has roots in social learning theory and emphasises the how the role of social constructs or "norms" can influence an individual's beliefs and behaviours on tobacco smoking and how changing the norms surrounding tobacco smoking will help, over time, to change smoking behaviours. Over a course of just a few decades the implementation of many tobacco control initiatives which include smokefree legislation, the legislation banning point-of-sale advertising;

introduction of mandatory plain packaging and pictorial health warnings on tobacco products, mass media campaigns which challenge positive social norms about smoking have been integral to the decline in smoking prevalence and uptake. Many of the principles of tobacco smoking denormalisation strategies are incompatible with e-cigarette use, as e-cigarettes mimic many of the behavioural rituals associated with tobacco smoking. Therefore, there is a concern that over a period of time pro-vaping campaigns, e-cigarette advertisements and smokefree legislations which permits the use of e-cigarette, threaten to reverse the successful, decades-long public health campaign to denormalise tobacco smoking, leading to an exponential rise in tobacco smoking amongst never smokers (Fairchild et al., 2014). In turn, e-cigarettes have generated a divergent range of public health values, policies and regulations amongst nations.

As such, despite all three evidence reviews undertaken by Public Health England, the Royal College of Physicians and the US National Academies of Sciences, Engineering and Medicine concluding that e-cigarettes are likely far less harmful than smoking (Royal College of Physicians, 2016, McNeill A et al., 2015a, National Academy of Sciences, 2018); the UK and US public health campaigns could not stand in sharper contrast (Figure 1.1), with Public Health England leading a pro-vaping campaign, aimed at protecting the health of current smokers and the US Food and Drug Administration (FDA) leading an anti-vaping campaign, aimed at protecting children, adolescents and non-smokers.

Figure 1.1 E-cigarette campaigns. (a) The Food and Drug Administration's "An epidemic is spreading" antivaping campaign. (b) Public Health England's 2018 Stoptober campaign.

The polarised messages driven by these public health campaigns reflect the differences which exist between how the two nations have chosen to balance the risk and opportunities presented by e-cigarettes against the impact that e-cigarettes are currently having at a population level.

Against this backdrop, the US is seeing what can be considered as two distinct but related epidemics connected with e-cigarette use, which predominantly affect young people: an epidemic of youth vaping which threatens to engulf a new generation into nicotine addiction, and a national outbreak of e-cigarette, or vaping, product use-associated lung injury (EVALI).

In August 2019, the US saw a multistate outbreak of EVALI associated with the use of e-cigarettes delivering a range of substances including nicotine and tetrahydro-cannabinol (THC, the psychoactive ingredient in marijuana). As of the 18th February 2020, a total of 2,807 hospitalised EVALI cases or deaths have been reported to the Centers for Disease Control and Prevention (CDC) from all 50 states, the District of Columbia, and two U.S. territories (Puerto Rico and U.S. Virgin Islands) and 68 deaths have been confirmed (Centers for Disease Control and Prevention, 2020). All of the patients with EVALI had reported using vaping products. Some patients reported exclusively using nicotine-containing e-cigarettes, but the majority of patients reported the use of THC-containing e-cigarettes. Laboratory testing of bronchoalveolar-lavage (BAL) fluid samples from 51 patients (median age 24 years) with EVALI revealed THC in most samples and vitamin E acetate in all samples but did not identify these substances in BAL fluid samples from a control group (Blount et al., 2019). So far, the identification of vitamin E acetate, which is a thickening agent in THC-containing vaping products has been thought to be the primary cause of EVALI, however at present there is insufficient evidence to rule out the contribution of other e-cigarette chemicals which could lead to the development of EVALI (Centers for Disease Control and Prevention, 2020). Therefore, until more is known about the specific cause(s) of EVALI, the CDC and FDA advice is to completely avoid THC-containing e-cigarettes. Furthermore, they advise avoidance of all e-cigarette or vaping products amongst individuals who do not currently use tobacco products, and EVALI remains a reportable disease to the CDC.

Between 2011 and 2015 the US has seen a 900% rise in e-cigarette use among young people, an increase at a rate of epidemic proportions (Cullen et al., 2019). In 2019, according to National Youth Tobacco Survey, more than 5.2 million adolescents had reported to having used e-cigarettes in the past 30 days, compared to 3.8 million in 2018 (The Food and Drug Administration, 2019). Although there are numerous reasons accounting for why young people may be incited to use e-cigarettes, the recently developed pod devices, such as the popularised ‘JUUL’ are believed to especially appeal to adolescents because of their discrete design, high nicotine concentrations, flavourings and marketing (Centers for Disease Control and Prevention, 2019, Cullen et al., 2019). For the US the youth vaping epidemic is a matter of concern as studies have demonstrated that nicotine exposure during this time can harm brain development (Tobore, 2019). In addition adolescents who use e-cigarettes have an increased risk of experimenting with tobacco cigarettes (Barrington-Trimis et al., 2016) and e-cigarettes have had an undermining effect on the nation's progress at reducing overall tobacco use (The Food and Drug Administration, 2019). Therefore, to tackle the youth vaping epidemic, the FDA’s antivaping campaign targets adolescents who have used or might be tempted to use e-cigarettes, and includes implementation of novel strategies to make e-cigarettes less enticing to young people (e.g. placing restrictions on certain flavours) (The Food and Drug Administration, 2020).

Whereas in contrast to the US, within the UK the prevalence of vaping is almost entirely limited to adults who are or have been smokers (Action on Smoking and Health, 2019b). Public Health England has embraced e-cigarettes to address tobacco smoking related morbidity and mortality. In 2015, Public Health England reported what it described as a "landmark review" of evidence about e-cigarettes which concluded that that e-cigarette use is around 95% less harmful than smoking, based on the rationale that firstly the constituents of tobacco smoke that harm health are either absent in e-cigarette vapour or, if present, are mostly at levels much below 5% of smoking doses; and second, that the principal chemicals present in e-cigarettes have not been associated with any serious risk (McNeill et al., 2015). In the absence of robust scientific evidence, Public Health England were criticised by the scientific community following the endorsement and publishment of the "95% less harmful" (Lancet, 2015), given that the origin of the "95% less harmful" statistic was derived from a single study entitled "Estimating the Harms of Nicotine-Containing Products Using the Multiple-Criteria Decision Analysis Approach" (Nutt et al., 2014). In this paper Nutt and colleagues describe how in July 2013, a group of 12 individuals with no prespecified expertise in tobacco control reviewed the context of perceived harms from nicotine products, the range of products, and the criteria of harms. The group, some of whom had conflicts of interest with the tobacco industry scored the products for harm, and weightings were applied to the results. Based on the opinions of this group, cigarettes were ranked as the most harmful nicotine product with a score of 99·6. E-cigarettes were estimated to have only 4% of the maximum relative harm (Nutt et al., 2014).

Within the UK, e-cigarettes have already overtaken NRT as the primary aid used in attempts to quit smoking. E-cigarette use continues to grow, with an estimated 7.1% of the adult population reporting their use. This amounts to approximately 3.6 million people, of whom just under 2 million are ex-smokers; 1.4 million are current smokers (known as dual users); and 200,000 are never smokers (Action on Smoking and Health, 2019b). In 2019, the Smokefree Great Britain annual survey demonstrated that since 2014 the proportion of vapers who were ex-smokers had risen from 33.0% to 54.1%, while the proportion of vapers who also smoke (known as dual users) had declined from 65.1% to 39.8% (Action on Smoking and Health, 2019b). The three most commonly cited reasons for e-cigarette use were to (1) quit tobacco smoking; (2) prevent relapse; and (3) to save money. Unlike the US, the UK has not had a national outbreak of vaping related illnesses nor has it seen a surge in e-cigarette use amongst adolescents. National surveys of 11-16 year-olds indicate that the prevalence of regular e-cigarette use amongst never smokers of this age group is negligible (between 0.1% and 0.5%) and that e-cigarette experimentation amongst young people does not result in regular e-cigarette use or progress to tobacco smoking (Bauld et al., 2017).

To support the harm-reduction role of e-cigarettes as a smoking cessation aid, observational studies have demonstrated that smokers are more likely to have a successful quit attempt with an e-

cigarette than individuals who chose not to or who use over-the-counter NRT (Rahman et al., 2015). A large UK multicentre randomised control trial demonstrated that e-cigarettes were almost twice as effective for smoking cessation as NRT (18.0% vs 9.9%) when both products were accompanied by behavioural support provided by the NHS stop-smoking services (Hajek et al., 2019). Out of the successful quit attempts, it is important to note that sustained product use at 1-year was significantly greater amongst participants using an e-cigarette compared to NRT (80% vs 4%) (Hajek et al., 2019). Although dual use of e-cigarettes and tobacco cigarettes is common practice, there is no evidence that this has negatively impacted upon the number of quit attempts; or that the effect of dual use of tobacco and e-cigarettes differs from dual use of tobacco smoking and NRT.

With the evidence supporting the prominent and beneficial role that e-cigarettes are having in assisting smoking cessation attempts within the UK, the pattern of current use demonstrates that e-cigarettes have potential to the reduce the burdens borne by current smokers and support the UK's ambition to create a "tobacco-free" generation by 2030. Therefore, Public Health England's core message, to act in the present moment and encourage smokers to make the switch on to e-cigarettes and not wait for the publication of more conclusive research, is rationalised.

Although I have focused on the US and UK drawing two very different conclusions from existing evidence, in terms of public health policy the UK may be considered an outlier according to the Global State of Tobacco Harm Reduction Report, with 39 countries having banned or restricted the sale of e-cigarettes or nicotine containing liquids (Shapiro H, 2018).

1.4 Potential impact of e-cigarette usage on human health.

It is widely believed that e-cigarettes are less harmful than tobacco smoking because they have "lower" levels of harmful constituents. However, there are concerns that chronic exposure to aerosol constituents, nicotine, carbonyl compounds, particulate matter, metals, and flavourings, many induce adverse health effects and therefore, the safety of e-cigarettes remains a legitimate concern. Investigation of the health effects of e-cigarettes is challenged by product diversity and technological advancements and until the long-term population data emerges to clarify if e-cigarettes are causally linked to adverse health outcomes, biomarker studies of exposure, risk and harm are required. As the majority of tobacco smoking related deaths are attributable to cardio-respiratory disease, it can be argued, in the first instance that it is important to prioritise efforts into understanding the cardio-respiratory effects of e-cigarettes.

1.4.1 Potential cardiovascular and respiratory effects of e-cigarette constituents

1.4.1.1 Nicotine

Nicotine exerts its biological effects through nicotinic acetylcholine receptors (nAChRs), which are located in the brain, autonomic ganglia, and adrenal medulla. The binding of nicotine to nAChRs results in the activation of the sympathetic nervous system through the release of catecholamines, both locally (neuronal) and systemically (adrenal). Nicotine addiction is mediated by α4β2 nAChRs; cardiovascular effects are mediated predominantly by α3β4 nAChRs3, and the non-neuronal effects are mediated primarily by homomeric α7 nAChRs. Non-neuronal nAChRs are found on endothelial cells, inflammatory cells, macrophages and keratinocytes. From a cardiovascular perspective activation of the nAChRs promotes haemodynamic changes, endothelial dysfunction, insulin resistance, dyslipidaemia, arrhythmogenesis, inflammation, and changes in the myocardium (Benowitz and Fraiman, 2017). Whereas in the lung, activation of various nAChR-mediated signalling pathways, have been implicated in the pathophysiology of lung cancer and susceptibility to respiratory tract infections (Scott et al., 2018, Lam et al., 2007, Paleari et al., 2008). Specifically airway exposure to nicotine has been found to adversely impact several host defence mechanisms by (1) inhibiting cough reflexes through perceptual and motor responses to irritant cough stimulants (Dicpinigaitis, 2017); (2) inducing mucociliary dysfunction through the down regulation of α7 nAChR and subsequent impairment of the cystic fibrosis transmembrane conductance regulator (CFTR) (Maouche et al., 2013); and (3) impairing viral and bacterial clearance through the downregulation of type 1 T helper cell (Th1) immune responses (Yanagita et al., 2012).

Nicotine is most addictive when delivered to the brain quickly and in high doses. The systemic effects of nicotine differ across the range of nicotine containing products, as a consequence of the differences which exist between the mode of nicotine delivery, dosage and absorptions rates. As such when nicotine is inhaled following e-cigarette or tobacco cigarette use, nicotine is passed directly through the alveolar membranes of the lungs into the pulmonary venous circulation, then carried into the arterial circulation and rapidly delivered to the brain in high doses. Although initial studies reported that first-generation e-cigarettes delivered comparatively lower concentrations of nicotine to the bloodstream than tobacco cigarettes. More recent studies have demonstrated that newer generation e-cigarette devices are more efficient in nicotine delivery and are capable of reaching comparable plasma nicotine levels to tobacco smoking, especially amongst experienced smokers who can adjust their vaping topography (Shahab et al., 2017). Furthermore consistent with its systemic uptake, comparable levels of the nicotine metabolite, cotinine have been found in the saliva and plasma levels of both vapers and smokers (Etter, 2014b, Flouris et al., 2013). In comparison, when nicotine is absorbed via the transdermal or buccal routes (as in the case with conventional NRT including patches, gums and lozenges) the nicotine absorption into the systemic circulation is far slower, generating lower arterial nicotine levels.

While one may conclude that switching from tobacco cigarettes to less harmful forms of nicotine is "safer" and poses less risk to an individual than tobacco smoking, it has been suggested that due to the differing pharmacokinetics and highly addictive nature of inhaled nicotine, e-cigarettes are more likely to induce adverse health effects and sustain nicotine dependence long-term (Middlekauff, 2020). As such, prolonged exposure to inhaled nicotine through e-cigarettes use may not have the same safety profile as other licensed forms of NRT, and further investigation is warranted to understand the long-term effects of nicotine delivered by e-cigarettes.

1.4.1.2 Particulate matter

The terms fine particles, or particulate matter ($PM_{2.5}$), refer to tiny particles or droplets in the air that are two and a half microns or less in diameter. Owing to their small size, $PM_{2.5}$ are able to easily penetrate the airways and be delivered into the systemic circulation to induce adverse biological responses. Epidemiological and clinical studies suggest a strong association between human exposure to $PM_{2.5}$ and the risk of developing cardiovascular disease, with $PM_{2.5}$ exposure from ambient air pollution and/or tobacco smoking having been linked to the development of a number of health conditions including hypertension, coronary artery disease, myocardial infarction, atherosclerosis, thrombosis and arrhythmias (Qasim et al., 2017). Furthermore, there is evidence of a nonlinear dose-response relationship between $PM_{2.5}$ exposure and cardiovascular mortality, which means that exposure to low levels of $PM_{2.5}$ can result in adverse outcomes (Pope et al., 2009).

E-cigarettes have been found to generate large amounts of $PM_{2.5}$, with vapers exhaling significant levels of $PM_{2.5}$ comparable to levels found in tobacco smokes (Fernandez et al., 2015). Studies which have evaluated the impact of e-cigarettes on indoor air quality to estimate the possible effect of passive vaping, have found that $PM_{2.5}$ concentrations increased dramatically in the indoor space where e-cigarette use was allowed for 2 days, at concentrations higher than the reported values from tobacco smoking in indoor bars (Soule et al., 2017). Therefore, exposure to e-cigarettes generated $PM_{2.5}$ represents a potential health concern not just to e-cigarette users but also to innocent bystanders, as vaping exposes non-users to secondhand e-cigarette $PM_{2.5}$ emissions.

Inhalation of $PM_{2.5}$ has been found to induce endothelial dysfunction, oxidative stress and inflammatory and thrombogenic responses through two main pathways; the direct and indirect pathways (Tanwar et al., 2018). The direct pathway is mediated when $PM_{2.5}$ pass through the alveolar endothelium interface into the systemic circulation, to target multiple organs and the vasculature. Mechanistically, via the direct pathway $PM_{2.5}$ induce cardiac contractile dysfunction and arrhythmias via interference with calcium ions (Nelin et al., 2012), and vascular dysfunction and thrombus formation through oxidative stress and inflammation (van Eeden et al., 2001, Gurgueira et al., 2002). The indirect pathway is triggered by the deposition of $PM_{2.5}$ in the respiratory tree which gives rise to activation of the autonomic nervous system and pulmonary

inflammation (Martinelli et al., 2013). Collectively the translocation of proinflammatory mediators, vasoactive molecules and reactive oxygen species (ROS) from the lung into the circulation and modulation of the autonomic nervous system increases the risk of developing arrhythmias and thrombosis through the promotion of oxidative stress, thrombogenesis, vasoconstriction and change in heart rate variability (HRV) (Magari et al., 2002, Gurgueira et al., 2002). Therefore $PM_{2.5}$ generated from e-cigarettes have the potential to induce harm through the activation of both the direct and indirect pathways, and studies have demonstrated that exposure from a single puff of an e-cigarette is sufficient to deliver $PM_{2.5}$ into the systemic circulation and deposit significant levels of $PM_{2.5}$ into the lungs (Zhang et al., 2013b, Manigrasso et al., 2015). Therefore, it is imperative that further studies evaluating the $PM_{2.5}$ induced health effects of e-cigarettes are conducted, to establish the level of risk posed by the direct and passive effects of vaping.

1.4.1.3 Carbonyl compounds and oxidising agents

Although the heating and vaporisation of e-liquids does not involve combustion, e-cigarettes have been found to emit volatile carbonyls, such as formaldehyde, acetaldehyde, and acrolein (Wang et al., 2017, Ogunwale et al., 2017). Recent e-cigarette studies of carbonyl compounds have demonstrated that generation of aldehydes is primarily related to the battery power output of the e-cigarette device and thermal decomposition of the e-liquid solvents propylene glycol and glycerol (Wang et al., 2017, Kosmider et al., 2014). As e-cigarette technology advances, studies of newer generation devices have reported that high-voltage devices produce comparable levels of carbonyls to that of tobacco cigarettes, in both “dry-puff” and normal puffing conditions (Hutzler et al., 2014, Kosmider et al., 2014, Qasim et al., 2017). Furthermore, biomarker studies have confirmed the delivery of carbonyls into the systemic circulation following e-cigarette use, with biomarker studies reporting the presence of measurable levels of acrolein metabolites, 3-hydroxypropylmercapturic acid (3-HPMA) in the urine samples from e-cigarette users. Although levels of 3-HPMA are elevated amongst e-cigarette users compared to never users (Hecht et al., 2015), an 83% reduction in 3-HPMA levels has been seen when tobacco smokers switched to e-cigarettes, which was comparable to the reductions seen in those who quit smoking (O'Connell et al., 2016).

While the contribution of e-cigarettes to carbonyl exposure is not yet fully understood, the presence of carbonyls in e-cigarette aerosols is a major concern due to their known adverse effects on human health when inhaled at sufficient concentrations. Formaldehyde is classified by the International Agency for Research of Cancer as a human carcinogen (Group 1); acetaldehyde is classified as a possible human carcinogen (Group 2B); and acrolein is listed as a hazard air pollutant by the US Environmental Protection Agency, as it causes irritation of the nasal cavity and damages the lining of the lung.

Aside from their cytotoxic effects, in-vivo studies suggest that through the promotion of oxidative stress, inflammation and thrombogenesis, exposure to aldehydes and acrolein can lead to the

development of cardiovascular events (Park and Taniguchi, 2008). With regards to formaldehyde exposure, murine studies have reported significant increases in platelet counts in mice (Zhang et al., 2013a); and increases in cardiac oxidative stress (Gulec et al., 2006), alongside decreases in left ventricular end-systolic pressure, heart rate and cardiac output indicating acute heart failure which have been seen in rats (Takeshita et al., 2009, Gulec et al., 2006). As for acetaldehyde, exposure to acetaldehyde has been found to give rise to elevations in blood pressure and heart rate (Egle, 1972), in addition to adversely affecting cardiac mitochondria to induce myocardial mitochondrial dysfunction and damage (Jin et al., 2014, Brandt et al., 2016). Exposure to acrolein has been shown to induce oxidative stress, upregulate proinflammatory cytokines and inhibit cardioprotective signalling pathways; increasing the risk of thrombosis and atherogenesis (Wang et al., 2008a, Luo et al., 2007). Acute acrolein exposure has also been shown to impair the antiatherogenic function of apolipoprotein A1 in high-density lipoprotein to induce lipoprotein modification and systemic dyslipidaemia (Shao et al., 2005). In human endothelial cells, through the oxidation of thioredoxins (critical proteins involved in the regulation of redox homeostasis), acrolein has been found to induce endothelial dysfunction and apoptosis (Szadkowski and Myers, 2008), whereas acrolein exposure in murine studies has been shown to increase platelet activation and establish a pro-thrombotic state (Sithu et al., 2010), in addition to inducing left ventricle dilation and dysfunction, and dilated cardiomyopathy (Luo et al., 2007).

1.4.1.4 Metals

The presence of metals including tin, lead, copper, chromium, aluminium, nickel, iron, and zinc have been found in e-cigarette aerosols (Williams et al., 2013). The metal contaminates are likely to originate from the e-cigarette device itself such as the coil or soldered joints or from some e-liquids. The concentration level of metals emitted by e-cigarettes varies depending on the e-cigarette design, e-liquid, nicotine concentration, puffing topography and users experience (Zhao et al., 2020).

Although it has been reported that the levels of metals found in e-cigarette aerosols fall below exposure guidelines (Farsalinos et al., 2015b). The direct comparison of metal aerosol levels to human biosample levels samples obtained from vapers, provides confirmation that the inhaled metals presented in the e-cigarette aerosol are absorbed through the respiratory tract and delivered into the systemic circulation (Aherrera et al., 2017, Goniewicz et al., 2018). The International Agency for Research of Cancer classifies lead as probable carcinogen which has also been associated with increased risk of cardiovascular and kidney disease (Navas-Acien et al., 2007); and both nickel and chromium as carcinogens which have been associated with decreased lung function and increased risk of asthma and bronchitis (Zhang et al., 2009); therefore the presence of metals and metalloids in e-cigarette aerosols remains a concern and warrants further investigation.

1.4.1.5 Flavourings

E-cigarettes have been found to contain over 7000 different e-cigarette flavours including aldehydes (vanillin, vanilla; benzaldehyde, berry/fruit; cinnamaldehyde, cinnamon; damascenone, tobacco), benzyl alcohol, terpenes (linalool, flowery; farnesol, apple), pyrazines (coffee, chocolate), menthol, menthone and other minty compounds, and sweet flavours including ethyl maltol (Gotts et al., 2019). Although many of these flavours are used as food additives and are deemed safe for indigestion, the inhaled effects of flavoured e-liquids and individual flavouring agents on the cardiorespiratory system remain uncertain. Although the pulmonary concentrations of flavours following e-cigarette use are unknown, the thermal decomposition of flavouring compounds have been found to dominate the formation of aldehydes during vaping, at levels which exceed occupational safety standards (Khlystov and Samburova, 2016, Klager et al., 2017). Therefore, the lack of regulation regarding e-cigarette flavourings is a concern given that aldehydes exert hazardous effects when inhaled at sufficient concentrations. As such particular concerns have been raised over exposure to diacetyl, 2, 3-pentanedione, a buttery flavouring in e-liquids, after exposure to the diacetyl containing aerosolised flavourings have been demonstrated to cause bronchiolitis obliterans, which is a severe and irreversible obstructive lung disease (Allen et al., 2016, Klager et al., 2017).

A number of in-vivo studies have demonstrated that flavours in e-liquids exert proinflammatory and cytotoxic effects (Clapp et al., 2019, Muthumalage et al., 2017, Gerloff et al., 2017, Leigh et al., 2016). Form a respiratory perspective, the inhaled effects of cinnamaldehyde flavoured e-cigarette aerosols have been found to impair respiratory immune cell function, by inducing ciliary dysfunction in epithelia through the immunosuppression of alveolar macrophages and natural killer cells and inflammation mediated by ROS production (Muthumalage et al., 2017, Clapp et al., 2019). Furthermore dose-dependent cytotoxic effects were demonstrated when monocytes were exposed to nicotine free flavouring, with the flavourings cinnamaldehyde, vanillin, and pentanedione exerting the most toxic effects (Muthumalage et al., 2017). Although the cardiotoxic effects of flavourings are largely unknown, a recent study of human endothelial cells found that exposure to low concentrations of vanillin, menthol and cinnamaldehyde was associated with increased inflammatory responses and impaired nitric oxide (NO) production, suggestive of endothelial dysfunction (Fetterman et al., 2018).

1.4.2 Potential biological mechanisms by which e-cigarettes cause cardiovascular risk

Four main mechanisms have been proposed by which e-cigarettes may increase the risk of cardiovascular disease including: systemic nerve activation; oxidative stress; endothelial activation and platelet activation (Middlekauff, 2020) (Figure 1.2).

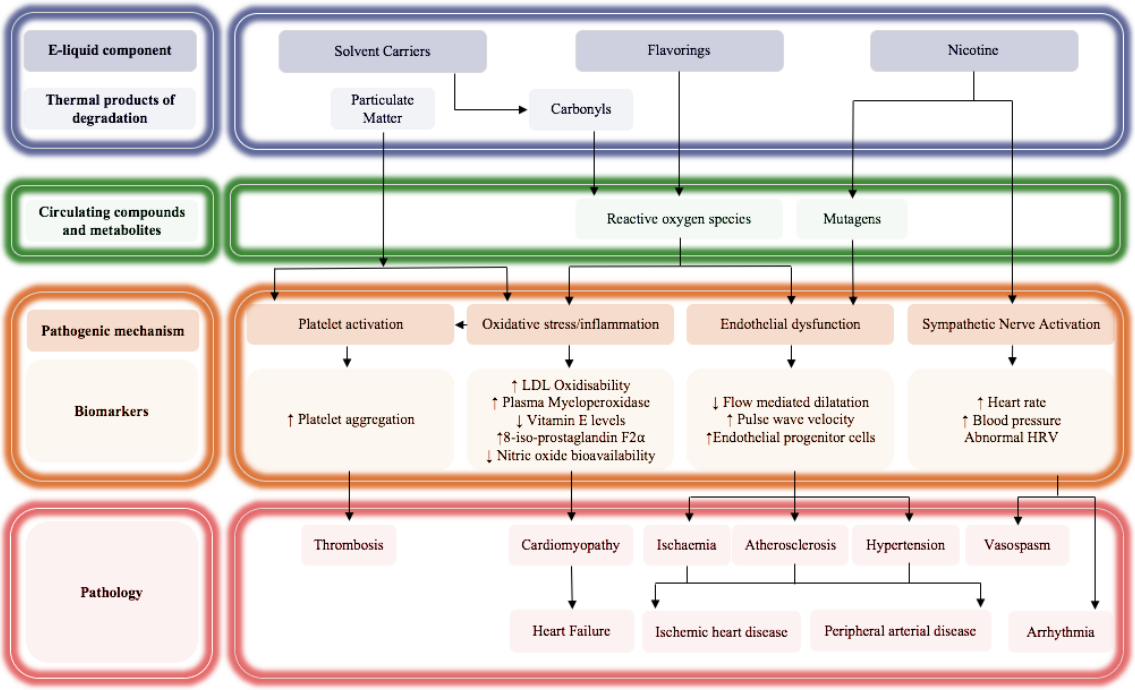


Figure 1.2 Potential adverse cardiovascular effects induced by various constitutes of e-cigarette aerosol. Adapted from Middlekauff (2020).

1.4.2.1 Sympathetic nerve activity

Numerous studies have demonstrated that the acute use of nicotine containing e-cigarettes, like tobacco cigarettes increases sympathetic nerve activity (SNA), giving rise to elevations in in blood pressure, heart rate and HRV (Moheimani et al., 2017a, Moheimani et al., 2017b Vlachopoulos et al., 2016). While the assessments of the acute changes in heart rate and blood pressure may have limited prognostic value, a shift in the cardiac sympathovagal balance toward sympathetic predominance as assessed by HRV has been associated with increased cardiovascular risk (Middlekauff et al., 2014). Increased SNA, as assessed by HRV has been reported amongst habitual nicotine containing e-cigarette users, but not in nicotine free e-cigarette users (Moheimani et al., 2017). Although the acute sympathomimetic effect of e-cigarettes are typically attributed to the vasoactivity of nicotine, it is important to recognise that (1) the HRV pattern that was observed amongst habitual e-cigarette users has been associated with increased cardiac risk in multiple populations with and without pre-existing cardiac disease (Hillebrand et al., 2013); and (2) in the study where regular e-cigarette users displayed a sympathetic pre-dominance, all of the e-cigarette users had abstained from vaping and nicotine was not detectable in e-cigarette users at the time of the HRV recordings (Moheimani et al., 2017). The latter finding is consistent with a mechanism beyond the acute pharmacological effect of nicotine. Activation of the splenocardiac axis (an inflammatory signalling network initiated by increased SNA which underlies the development of atherosclerosis and acute myocardial infarction (Libby et al., 2016) has been reported amongst habitual e-cigarette and tobacco cigarette users (Boas et al., 2017). Using 18F-flurorodeoxyglucose positron emission tomography/computer tomography (FDG-PET/CT), Boas et al. detected an increased uptake of 18F-flurorodeoxyglucose in splenic and aortic tissue following chronic exposure to e-cigarette and tobacco cigarette emissions (Boas et al., 2017). This is a concern, given that clinical studies have demonstrated that increased metabolic activity of haematopoietic tissues correlates with vascular inflammation, and has been shown to confer with increased cardiovascular risk (Libby et al., 2016, Emami et al., 2015, Tarkin et al., 2014). Although this activation is suggestive of a potential mechanism by which e-cigarettes may lead to increased risk of future cardiovascular events; it is important to recognise that nicotine is likely to have a prominent role in the activation of the splenocardiac axis; given that the carcinogenic toxins present in e-cigarette aerosols are lower than those in tobacco smoke (Goniewicz et al., 2014) and the plasma nicotine levels achieved by newer generation e-cigarettes are similar to tobacco cigarettes (Goniewicz et al., 2017).

1.4.2.2 Oxidative stress

Oxidative stress refers to elevated intracellular levels of ROS (Schieber and Chandel, 2014). ROS are reactive intermediates of molecular oxygen that are physiologically formed in cells as a by-product of cellular metabolism. Although homeostatic ROS concentrations play a crucial role as secondary messengers in many intracellular signalling pathways in both the innate and adaptive

immune responses, the physiological role of ROS becomes pathophysiological when the ROS bioavailability overwhelms the cellular antioxidant defence mechanism, due to either excessive ROS production or defective antioxidant enzymes. Under these conditions, the oxidative modification of lipids, proteins and nucleic acids leads to cellular damage, tissue injury, and inflammation (Holmstrom and Finkel, 2014). Oxidative stress has been associated with the pathogenesis of several diseases including lung cancer, COPD, diabetes, hypercholesterolemia, and atherosclerosis (Pizzino et al., 2017).

Tobacco smoke can be divided into two phases: a particulate (tar) phase and a gaseous phase. Both phases contains high concentrations of harmful ROS (hydrogen peroxide, epoxides, NO, nitrogen dioxide, peroxynitrite) (Pryor and Stone, 1993). As such the exogenous delivery of the free radicals present in tobacco smoke play a crucial role in upsetting the oxidative balance and inducing oxidative stress (Varela-Carver et al., 2010). At a vascular level, tobacco induced oxidative stress creates a pro-atherosclerotic and inflammatory environment, as the upset in oxidative balance triggers systemic inflammation via immune activation, and the exposure of free radicals leads to a smoking-related reduction in NO bioavailability and endothelial dysfunction (Raij et al., 2001). In addition, the free radicals oxidize and deplete tetrahydrobiopterin, a critical co-factor of endothelial NO synthase (eNOS), resulting in eNOS uncoupling and superoxide production (Alp and Channon, 2004).

Concerns regarding the oxidative potential of e-cigarettes to provide a favourable condition for the development of atherosclerosis and subsequent adverse cardiovascular outcomes have been raised after comparable levels of oxidant species have been found in e-cigarette aerosols which are capable of producing measurable oxidative stress (Lerner et al., 2015). With several studies reporting unfavourable changes in biomarkers of oxidative stress following the use of nicotine containing e-cigarettes (Moheimani et al., 2017, Carnevale et al., 2016, Chaumont et al., 2018, Biondi-Zoccai et al., 2019), and cross-over studies reporting that the single use of nicotine containing e-cigarettes has led to the increase in markers of oxidative stress (NOX2-derived peptide, 8-isoProstaglandin F2, plasma myeloperoxidase and vitamin E) and decreases in NO bioavailability (Biondi-Zoccai et al., 2019, Carnevale et al., 2016). Furthermore, when e-cigarettes are compared to (1) tobacco cigarettes, e-cigarettes have been found to have a lesser impact on markers of oxidative stress (Carnevale et al., 2016); (2) nicotine free e-cigarettes and a sham control, acute increases in plasma myeloperoxidase (an oxidative biomarker, positively correlated with an increased cardiovascular risk and atherogenesis (Daugherty et al., 1994, Rudolph et al., 2012)) were only associated with the use of nicotine containing e-cigarettes (Chaumont et al., 2018); and (3) non-user controls, e-cigarette use is associated with significant increases in low-density lipoprotein oxidizability (indicative of the susceptibility of apolipoprotein B containing lipoproteins to cause oxidation (Moheimani et al., 2017)). Therefore, given these findings, e-

cigarette induced oxidative stress is a potential precursor to the development of atherosclerosis and its clinical sequelae.

1.4.2.3 Endothelial dysfunction and arterial stiffness

The vascular endothelium is a continuous layer of flat polygonal endothelial cells lining the blood luminal surface of the entire circulatory system. The endothelium plays a pivotal role in vascular haemostasis and is involved in the control of thrombosis and thrombolysis, platelet and leukocyte interaction with the vessel wall, and the regulation of vascular tone and growth of blood vessels (Verhamme and Hoylaerts, 2006). In the case of a "healthy" endothelium, the phenotypic characteristics include (1) a vasodilatory phenotype; consisting of high levels of vasodilators such as NO and prostacyclin and low levels of ROS and uric acid; (2) an anticoagulative phenotype; consisting of low levels of plasminogen activator inhibitor 1, von Willebrand factor, and P-selectin; (3) a low inflammatory state; consisting of low levels of soluble vascular cell adhesion molecule (sVCAM), soluble intercellular adhesion molecule (sICAM), E-selectin, C-reactive protein (CRP), tumour necrosis factor alpha, and interleukin-6; and (4) a regenerative capacity; consisting of high levels of endothelial progenitor cells (EPCs, indicative of vascular repair capacity) and low levels of endothelial microparticles (EMPs) and circulating endothelial cells (indicative of endothelial stress/damage) (Rajendran et al., 2013).

Tobacco smoking induces endothelial dysfunction which is one of the earliest events in atherogenesis and precedes structural disorders, plaque build-up and clinical events (Ross, 1986). Endothelial dysfunction is characterised by a shift in the actions of the endothelium to include; impaired vasodilation, increased oxidative stress, and a pro-coagulant, -thrombogenic and -inflammatory phenotype with a decreased vascular repair capacity (Rajendran et al., 2013). In terms of pathophysiology, tobacco smoking induces endothelial dysfunction through the reduction of NO bioavailability in the endothelial cells resulting in an impairment of endothelium-dependent dilation. The endothelial production of NO and endothelium dependent response can be augmented by a variety of physiological stimuli, including an increase in blood flow. Subsequently brachial artery flow-mediated dilation (FMD) is used as the standard non-invasive measurement of endothelial function and has been shown to have prognostic value for future cardiovascular disease (Widlansky et al., 2003). Using this method, active and passive tobacco smoking have been associated with a causative and dose-related impairment of endothelium-dependent arterial dilation, and smoking cessation has been found to lead to the reversibility of endothelial dysfunction (Celermajer et al., 1992, Celermajer et al., 1996, Celermajer et al., 1993).

With regards to e-cigarettes, two cross-over studies have evaluated the acute effect of nicotine containing e-cigarettes on endothelial function (Carnevale et al., 2016). When endothelial function was assessed using FMD, the single use of a nicotine containing e-cigarette led to a significant reduction in FMD, which was comparable to the reduction seen immediately after participants

smoked a single tobacco cigarette (Carnevale et al., 2016). In contrast, when acetylcholine-mediated dilation was used as measure of endothelial function to compare the acute endothelial effects of nicotine containing e-cigarettes, nicotine-free e-cigarettes and a sham control, only nicotine containing e-cigarettes were found to acutely impair endothelial function (Chaumont et al., 2018). It remains unknown whether this acute endothelial dysfunction translates into sustained endothelial dysfunction.

EPCs are stem cells which have a key role in regeneration of endothelial cells following vascular injury. In response to acute endothelial damage, EPCs are released from the bone marrow. Therefore, elevated levels of EPCs are indicative of vascular injury and subsequently serve as a biomarker of endothelial dysfunction (Antoniewicz et al., 2016). An acute exposure study investigating the acute effects of nicotine containing e-cigarettes demonstrated that levels of EPCs significantly increased following 10 puffs of an e-cigarette (Antoniewicz et al., 2016). Given that the acute effects were comparable to acute increases in EPCs which have previously been demonstrated after the active smoking of one cigarette (Mobarrez et al., 2014), it is possible that e-cigarettes could have the potential, like tobacco cigarettes, to have an injurious effect on the endothelium.

Arterial stiffness, as estimated by aortic pulse wave velocity (PWV), is a strong independent predictor of cardiovascular disease and all-cause mortality (Vlachopoulos et al., 2010). Like tobacco cigarettes, acute exposure studies have demonstrated that nicotine containing e-cigarettes (but not nicotine free e-cigarettes) are associated with increases in aortic stiffness (Vlachopoulos et al., 2016, Chaumont et al., 2018).

1.4.2.4 Platelet function

In the development of atherosclerosis, platelets have a pivotal role in thrombus formation and plaque rupture (Csordas and Bernhard, 2013). As a consequence of increased inflammation, matrix metalloproteinases expression and platelet activation, tobacco smoking is well known to accelerate the progression of atherosclerosis and destabilisation of atherosclerotic plaques (Pamukcu et al., 2011). At present there is limited published data concerning the impact of e-cigarette use on platelet function with only one in-vivo study comparing the acute effects of tobacco cigarettes and nicotine containing e-cigarettes on platelet function reported in the literature so far (Nocella et al., 2018). Although this cross-over study found that both the use of e-cigarettes and tobacco cigarettes were associated with unfavourable increases in platelet aggregation, consistent with those seen amongst chronic smokers, the effects of e-cigarettes were less pronounced than those of tobacco cigarettes (Nocella et al., 2018).

In summary, while e-cigarettes, in particular nicotine containing e-cigarettes, appear to induce acute negative effects on SNA, oxidative stress, endothelial function, arterial stiffness and platelet

aggregation, the chronic effects of these phenomena and association with atherogenesis await clarification and are urgently needed.

1.4.3 Potential biological mechanisms whereby e-cigarettes cause respiratory risk

Currently there is a lack of information regarding the short- and long-term effects of e-cigarettes on the respiratory system. However, chronic exposure to e-cigarette vapour may contribute to the development of respiratory disease by inducing airway remodelling, inflammation, injury and impaired immunity (Figure 1.3).

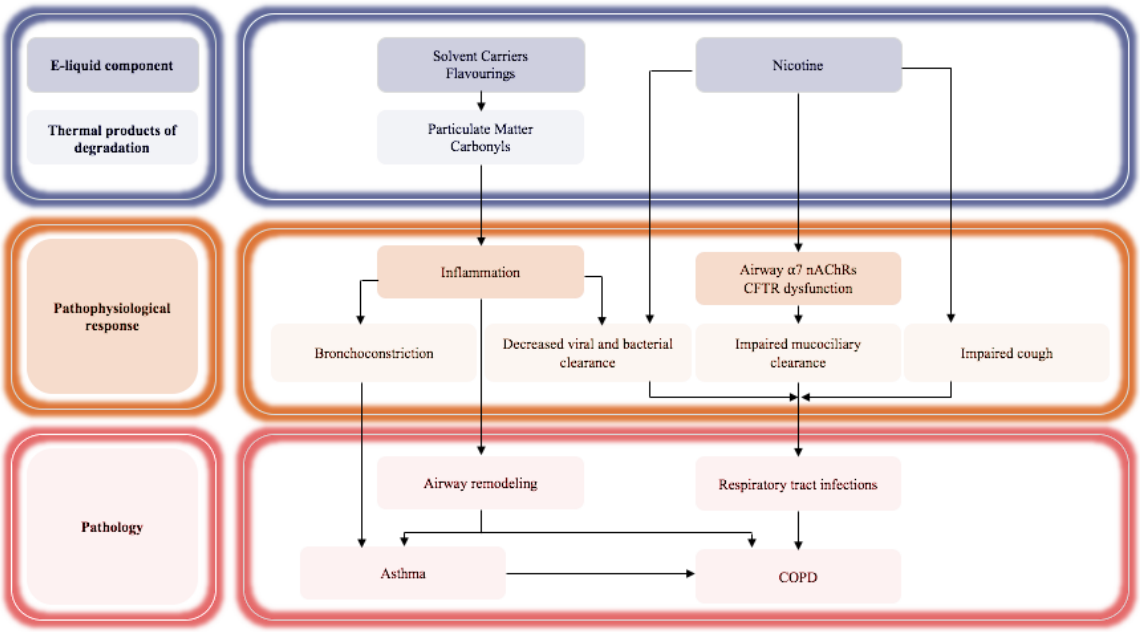


Figure 1.3 Potential adverse respiratory effects induced by various constitutes of e-cigarette aerosol.

1.4.3.1 Airway inflammation, injury and remodelling

Preclinically, pro-inflammatory effects on the lungs are observable in healthy smokers before the onset of disease (Shields et al., 2017). Persistent airway inflammation in both large and small airways is a hallmark of COPD, causing progressive airflow limitation, emphysema, airway remodelling and an irreversible decline in lung function (Malinovschi et al., 2015). As discussed earlier, exposure to the various e-cigarette aerosol constituents from vaping is likely to exert injurious and inflammatory airway and pulmonary effects which may have clinical implications for the development of chronic lung disease.

Fractional exhaled nitric oxide (FeNO) is a validated biomarker which correlates with the presence of inflammation in the lungs and is used for monitoring conditions characterised by airway eosinophilia (See and Christiani, 2013, Turner et al., 2019). Several cross-sectional studies have reported that baseline FeNO measurements are decreased by almost 50% in smokers compared to non-smokers (Shields et al., 2017). The data relating to e-cigarette induced FeNO changes are

limited, and the results are inconsistent, with acute exposure studies reporting either increases, decreases or no changes in FeNO levels following e-cigarette use (Vardavas et al., 2012, Campagna et al., 2016, Ferrari et al., 2015a).

Although neutrophil activation plays an essential role in the innate immune system against infection, excessive neutrophil activation which gives rises to increased levels of neutrophil-extracellular-trap (NET)-related proteins, neutrophil elastase, and matrix metalloproteinase have been demonstrated to induce emphysematous lung tissue damage and accelerate disease progression in smokers and patients with asthma and COPD (Liu et al., 2017, Sharafkhaneh et al., 2008, Overbeek et al., 2013). The expression of CD11b and CD66b are regarded as markers of neutrophil activation (Higham et al., 2016). Proteomic studies of e-cigarette users' sputum and blood samples suggest that as in the case with tobacco smoking, e-cigarette exposure activates the neutrophil inflammatory responses; as demonstrated by increased neutrophil CD11b and CD66b expression, NETs, myeloperoxidase, neutrophil elastase, and proteinase-3 (Reidel et al., 2018, Clapp et al., 2019, Ghosh et al., 2018, Higham et al., 2016).

Secondary to chronic airway inflammation, airway remodelling is a well-established structural feature observed in asthma and COPD (Dournes and Laurent, 2012). Pathologically, airway remodelling consists of structural changes within the airway wall, which features increased epithelium basal membranous thickness, hypertrophy of the smooth muscle cell, and peribronchial fibrosis. As it often takes a number of years or decades for the clinical endpoints of airway remodelling to manifest, spirometric testing serves as a fundamental intermediate outcome measurement of airflow limitation/obstruction caused by smooth muscle contraction or structural changes that may predict overt disease (Reddel et al., 2009). The most common measurements of lung function include: forced vital capacity (FVC), the maximum amount of air that can be exhaled when blowing out as fast as possible; forced expiratory volume in one second (FEV1), a measure of air clearance from the large/cartilaginous airways; FEV1/FVC ratio; forced expiratory flow at 25–75% of FVC ($FEF_{25–75\%}$), a sensitive measure of obstruction in the peripheral airways; and peak expiratory flow (PEF), the maximal flow that can be exhaled when blowing out at a steady rate.

To date several studies have examined the effects of vaping upon pulmonary function. While the collective evidence from acute exposure studies on pulmonary function remains inconclusive, with some studies reporting evidence of airflow obstruction and others not (Boulay et al., 2017, Vardavas et al., 2012, Ferrari et al., 2015b, Flouris et al., 2013, Staudt et al., 2018). A short-term randomised control study of smokers with no pre-existing respiratory disease reported no difference in lung function in subjects who switched to nicotine containing e-cigarettes or continued to smoke over 3 months (Cravo et al., 2016). Longer term data from the ECLAT study (a 12-month prospective randomised smoking cessation control trial of "healthy" smokers) detected early improvements in $FEF_{25–75\%}$ at 3 months and no obstructive pulmonary changes as measured by FVC, FVC1 and FEV1/FVC at 3, 6 and 12 months amongst smokers who switched completely

to e-cigarettes (Cibella et al., 2016, Campagna et al., 2016). While smoking cessation has been found to have beneficial effects on the pulmonary function of patients with COPD and asthma, limited data is available regarding the pulmonary effects of vaping in users with pre-existing obstructive pulmonary diseases. From this limited data, a 3-year retrospective-prospective follow up study of forty-four COPD patients who switched to e-cigarettes (single or dual users) found no deterioration in pulmonary function and significantly fewer COPD exacerbations (Polosa et al., 2018). Importantly the absence of spirometric changes following sustained e-cigarette use does not mean that e-cigarettes are harmless, with large data of almost 4000 COPD patients, from The Lung Health Study reporting that smoking cessation in COPD patients is associated with improvements in FEV_1 within 1 year (Kanner et al., 1999, Scanlon et al., 2000). In contrast, a similar retrospective-prospective study of 18 mild-moderate asthmatic smokers who had switched to e-cigarettes (either single or dual users) demonstrated significant and stable improvements in FEV_1, $FEF_{25–75\%}$ and no significant changes in acute exacerbation rates at 1 and 2 year follow up (Polosa et al., 2016a, Polosa et al., 2014). The authors concluded that e-cigarette use ameliorates objective and subjective asthma outcomes and that these beneficial effects may persist in the long term (Polosa et al., 2016a).

1.4.3.2 Effects on immunity

As previously mentioned, e-cigarette use may predispose users to respiratory tract infections through a variety of mechanism including suppression of the innate immune system and impairment of mucocilary clearance (MCC) and the cough stimulus, which are integral defence mechanisms that help clear pathogens and environmental pollutants from the respiratory tract (Dicpinigaitis, 2017, Maouche et al., 2013, Yanagita et al., 2012).

The airway epithelial mucosal barrier is part of the innate immune system and protects the underlying epithelia when faced with microbial, physical, and chemical challenges including smoking and vaping (Reidel et al., 2018, Kesimer et al., 2013). Secreted gel-forming mucins form a major protein component of the mucus responsible for its viscoelasticity and effective MCC (Lillehoj et al., 2013). Increased mucin concentrations, in particular mucin-5AC (MUC5AC), are associated with smoking and chronic inflammatory lung diseases such as bronchial asthma, COPD, bronchiectasis and cystic fibrosis (Rose and Voynow, 2006, Ghosh et al., 2018). Increased levels of MUC5AC have been found both in bronchial epithelia and in airway secretions of vapers (Lillehoj et al., 2013, Ghosh et al., 2018), with in-vitro and in-vivo data suggesting that changes in e-cigarette induced MUC5AC levels are driven by exposure to propylene glycol and vegetable glycerine, rather than nicotine (Ghosh et al., 2018). As elevated mucin concentrations are an important hallmark of failed mucus transport in mucoobstructive disease, it has been suggested that alterations in the mucin expression profile following e-cigarette use may also serves as a biomarker of harm (Lillehoj et al., 2013).

Consistent with the deleterious effects of inhaled nicotine on the cough reflex, acute exposure studies investigating the effects of e-cigarettes and tobacco cigarette use have reported significant reductions in cough reflex in response to a capsaicin cough challenge following the use of nicotine containing e-cigarette and tobacco cigarettes, but not after nicotine-free e-cigarette use (Dicpinigaitis et al., 2016 (Dicpinigaitis et al., 2016, Dicpinigaitis, 2017). Furthermore, the inhalation of nicotine e-cigarette aerosols has been associated with impairment of nasal and bronchial MCC function in-vitro and in-vivo. Clinically, e-cigarette use has been associated with significantly worsening sino-nasal symptoms and nasal MCC, compared to non-e-cigarette users in a 3 month prospective randomised smoking cessation trial (Kumral et al., 2016). In-vitro studies have identified that e-cigarette exposure has a suppressive effect on immune and inflammatory-response genes in nasal and bronchial epithelial cells involved in ciliogenesis (Clapp et al., 2019, Carson et al., 2017, Martin et al., 2016, Kumral et al., 2016, Ghosh et al., 2018). Furthermore, in-vitro studies have demonstrated that e-cigarette use induces airway dehydration of the epithelia through the inhibition of CFTR mediated chloride secretions (Lin et al., 2019).

Cell culture and experimental animal data suggest that vapers may be more susceptible to bacterial and viral infections through increased alveolar macrophage apoptosis, pro-inflammatory cytokine secretions, impaired macrophage and neutrophil phagocytosis and alterations in microbiome diversity (Clapp et al., 2019, Scott et al., 2018). In a mouse-model, when mice were infected with Streptococcus pneumonia, the alveolar macrophages in the e-cigarette aerosol-exposed mice had reduced phagocytic function and impaired bacterial clearance compared to air-exposed mice (Sussan et al., 2015). Similarly, chronic e-cigarette aerosol exposure has been found to enhance the colonisation and virulence of Staphylococcus aureus (Miyashita et al., 2018, Hwang et al., 2016), while in-vitro, independent of the effects of nicotine, suppression of respiratory immune cell function has been reported when alveolar macrophages, neutrophils, and natural killer cells were exposed to a number of nicotine free flavoured e-liquids and individual flavouring agents (Clapp et al., 2019). It remains uncertain whether these findings can be translated from the bench to bedside.

1.5 Clinical challenges

Although in the UK several influential organisations such as Public Health England, the Royal College of Physicians and NICE have published official statements and guidelines pertaining to the use of e-cigarettes (McNeill A, 2018, Royal College of Physicians, 2016, NICE, 2018), the patterns of e-cigarette use and technological advancements continue to evolve at a rate far faster than our scientific understanding of their potential pathophysiological health effects. In a time when evidence-based practice is advocated, the uncertainty about the short- and long-term health risks of e-cigarettes and their therapeutic role as a nicotine replacement product for smoking cessation poses a challenge to clinicians.

Therefore, this thesis seeks to undertake the preliminary work to evaluate the cardiovascular and respiratory health effects of e-cigarettes which can be translated into "real-world" practice. A multifaceted approach was taken to address several key themes:

1. Conducting research within the framework governed by tobacco control policy.

2. Understanding healthcare professionals' perceptions of nicotine, NRT and e-cigarettes.

3. Investigating the acute cardiorespiratory effects of e-cigarettes compared to tobacco cigarettes.

4. Investigating the short-term cardiorespiratory effects of e-cigarettes compared to NRT.

The emphasis of this work was directed to finding a pragmatic and patient-centred approach to help direct future e-cigarette research and the healthcare professionals' everyday practice.

RESEARCH STRATEGY AND APPORACH TO UNDERTAKING E-CIGARETTE RESEARCH

2.1 INTRODUCTION

If we consider the overall public health impact of e-cigarettes to be the product of the damage e-cigarettes cause or prevent, multiplied by the number of individuals who chose to use them to stop tobacco smoking, it will take several decades to determine if e-cigarettes are causally linked to adverse health outcomes. Therefore, in the interim, public health policy makers have a pivotal role in shaping the e-cigarette conversation, through the implementation of tobacco control policies, jurisdictions and recommendations, whilst the scientific community is challenged to propose and undertake the necessary studies to provide the evidence. A major difficulty for researchers lies in the fact that we are chasing a moving target. Technological advancements, legislations and regulations pertaining to e-cigarettes are constantly changing, and research findings are often obsolete by the time short-term studies are published, which in turn, questions the futility and investment in long-term studies. In the race to produce clinically relevant and informative research, e-cigarettes present researchers with many methodological and ideological challenges. In this regard, the aim of this chapter is to explain the rationale behind the research strategy and methodological approaches employed in this thesis.

2.2 RESEARCH STRATEGY

In 2015, when I embarked upon e-cigarette research, this coincided with Public Health England's landmark review of evidence about e-cigarettes which endorsed and publicised the estimate derived from the paper by Nutt et al., that e-cigarette use is "95% less harmful" compared to tobacco smoking. As previously discussed, although this estimate came under scrutiny from the scientific community due to the absence of robust clinical studies (Polosa, 2015, Lancet, 2015), from a regulatory point of view, Public Health England established that their priority was to lead a campaign to protect the health of current smokers from the harms of tobacco smoke by encouraging smokers to make the switch to "less harmful" nicotine containing e-cigarettes. In order to provide regulators with data to inform future evidence-based regulations, the research strategy underlying this thesis was designed to be congruent with Public Health England's values. The overarching aim was to design and conduct a series of studies which would provide the preliminary evidence examining the impact of e-cigarettes relative to tobacco smoking and NRT.

2.3. METHODOLOGICAL CONSIDERATIONS

2.3.1 Selection of an e-cigarette and e-liquid

Selecting an e-cigarette device and e-liquid represented a major methodological challenge, given the vast range of e-cigarette devices and e-liquids, lack of regulation and potential conflicts of interest with the tobacco industry.

2.3.1.1 The tobacco industry, a potential conflict of interest

Following the increase in e-cigarette use and decline in tobacco consumption, the tobacco industry has strategically expanded its ownership and control of e-cigarette brands and companies, in addition to investing billions of pounds into the development of e-cigarette (Britton et al., 2016). Consequently, the tobacco industry's involvement and domination of the e-cigarette market is a concern for public health and underscores the importance for independent research to inform policies and educate consumers about these products.

One concern is that e-cigarettes offer the tobacco industry with an opportunity to perpetuate tobacco smoking, whilst exploiting the concept of harm-reduction to manipulate the industry's position to be seen as a "partner" of public health addressing the tobacco epidemic, rather than causing it. The 'e-Voke', an e-cigarette manufactured by British American Tobacco provides the prime example. In 2015, the e-Voke made headlines as it became the first e-cigarette to be granted a medicinal licence by the authority of the Medicines and Healthcare Products Regulatory Agency (MHRA). Although the e-Voke never made it to market, the authorisation – or licence – would have allowed the e-Voke to be available on the NHS for smoking cessation. Should this have happened, it would be considered a public health outcry, as the tobacco industry would be profiteering from providing a treatment for the tobacco epidemic. Consequently, Article 5.3 of the World Health Organisation Framework Convention on Tobacco Control (WHO FCTC) sets out to protect tobacco control policies from the harmful influences of the tobacco industry, to ensure that public health is prioritised over the tobacco industry's profit margins. Specifically, Article 5.3 legally obligates that the tobacco industry is not, and could not, be a partner of governments in the implementation of tobacco control measures and that any party which chooses to accept the tobacco industry as a stakeholder in addressing the tobacco epidemic is in breach of this treaty (World Health Organisation, 2008).

The sentiments shared by Article 5.3 to protect tobacco control policy development from the tobacco companies interference, emphasises the need for independent research. Nevertheless, the tobacco industry's domination of the e-cigarette market, makes it challenging for researchers and institutions to conduct independent research. In the endeavour to preserve the integrity of independent research and circumvent any conflicts of interests with the tobacco industry, the conscious decision was made to source an independently manufactured and retailed e-cigarette and

e-liquid. Although I was successful in achieving this, it was not without challenge, as many of the remaining independent e-cigarette manufacturers were reluctant to support our research studies, for fear that any negative research findings could prove too costly for their business to survive. This is a concern for e-cigarette research, because should the tobacco industry continue to dominate the e-cigarette market, many researchers may have little choice and may have to consider using products affiliated to the tobacco industry. Going forward, it is inevitable that e-cigarette researchers will be unable to avoid conflicts of interest with the tobacco industry. Therefore, to preserve the integrity of the research in this field, it is imperative that researchers are transparent in declaring how they have approached and managed such conflicts of interests.

2.3.1.2 Regulation of the e-cigarette device and e-liquid

In the UK, e-cigarettes are regulated as general consumer products (MHRA, 2017). When e-cigarettes first appeared on the market, there was limited regulation of these devices and concerns were raised over the variable quality and safety of e-cigarettes and e-liquids, as well as the marketing and promotion of these devices (British Medical Association, 2014, The Association of Directors of Public Health, 2015). Since 2015, to address these concerns the European Union Tobacco Products Directive (TPD), and other regulatory authorities have set out a number of regulations (summarised in Table 2.1) to govern the manufacture, sale and advertising of e-cigarettes and e-liquids (Tobacco Products Directive, 2014, British Medical Association, 2017).

In addition to TPD regulations for e-cigarettes to be sold under the remit of consumer products, there is a separate framework to allow these devices to be licensed as medicines through the MHRA (MHRA, 2017). Any e-cigarette products, which are licensed as medicine would have to meet the MHRA stringent standards and regulations for medicines. As previously discussed, the main advantage for a company to hold a medicinal licence for a product, is that it would enable healthcare professionals to recommend their e-cigarette for use as a smoking cessation aid and it would be able to be provided to patients in the same way that NRTs (e.g. gum and patches) currently are. To date, the aforementioned e-Voke has been the only approved e-cigarette product to have received MHRA approval, although it has never been brought to market. Although all e-cigarette manufacturers can apply through the MHRA for a medicinal licence, the high costs and delays that this process involves serves as a deterrent for many e-cigarette manufacturers.

For e-cigarette research, achieving the right balance of regulation is not easy: too much regulation can be stifling and compromise research attempts at answering the questions of need, while too little regulation can compromise the ethics and safety of research, by exposing research participants to products that are ineffective, unduly hazardous, or both. Consequently, the process of identifying and sourcing an independently manufactured e-cigarette and e-liquid which was TPD compliant and satisfied the study sponsors pharmacovigilance regulatory framework, was incredibly challenging and led to delays in our research being approved and undertaken.

Table 2.1 Summary of key legislation/regulation for e-cigarettes

Tobacco Product Directive
In 2016, the European Union Tobacco Product Directive (TPD) came into effect and was subsequently transposed into UK law via the Tobacco and Related Products Regulations (2016). The legislations introduced the following measures: • Restrict e-cigarette tanks to a capacity of no more than 2ml. • Restrict the maximum volume of e-liquid for sale in one refill container to 10ml. • Restrict e-liquids to a nicotine strength of no more than 20mg/ml. • Require nicotine-containing products or their packaging to be child-resistant and tamper evident. • Ban certain ingredients including colourings, caffeine and taurine. • Product information, including health warnings that the product contains nicotine on the front and back of packs. • Require all e-cigarettes and e-liquids to be notified to the Medicines and Healthcare products Regulatory Authority (MHRA) before they can be sold. • E-cigarettes and re-fill containers cannot be advertised on television, radio or through information society services, or in certain printed publications including newspapers, magazines and periodicals. Domestic advertising (billboards, buses etc) is permitted. • Medicinal advertisement claims are not permitted.
Domestic Legislation
In 2015, the Children and Families Act (2014) introduced the following measures in England and Wales to make it illegal to: • Sell e-cigarettes or e-liquids to children and young people under the age of 18. • Purchase e-cigarettes on behalf of under 18s. In 2016, The Health (Tobacco, Nicotine etc. and Care) (Scotland) Act 2016. This introduced the following measures: • A ban on the sale of e-cigarettes to under 18s. • Inclusion of e-cigarettes on the Scottish Tobacco Retailer Register. • Powers for Scottish Ministers to introduce restrictions on e-cigarette advertising.

Table adapted from E-cigarettes: Balancing risks and opportunities, British Medical Association (British Medical Association, 2017).

2.3.1.3 E-cigarette device and e-liquid used in clinical studies

To control for the differences in the nicotine delivery kinetic between differing e-cigarette technologies and variation of e-liquids, the use of the same e-cigarette device and e-liquid in each of the studies in this thesis was chosen. The chosen e-cigarette device was a commercially-available second generation e-cigarette device. The device consisted of a 1300mAh variable voltage rechargeable battery, a tank and an atomiser (SmokeMax, Groove Trading Ltd, Glasgow). Each tank contained approximately 1.5ml of e-liquid. The e-liquid used in the study was reported by the manufacturer to contain 18mg/ml nicotine, and was tobacco flavoured (Pillbox38 UK Ltd, Totally Wicked, Blackburn, UK). All the e-liquid used in the study was manufactured from the same batch. The e-liquid Control of Substances Hazardous to Health (COSHH) assessment report from the manufacture stated that the contents per 10ml bottle were: 360mg nicotine, 12.6ml propylene glycol, 6.2ml vegetable glycerine, 120mg vanillin, 48mg furaneol and 80mg ethyl vanillin.

Furthermore, an independent analysis of the e-liquid was performed at the Nicotine and Tobacco Product Assessment Shared Resource (NicoTAR), Roswell Park Cancer Institute, Buffalo, New York, US. Nicotine concentrations were determined using gas chromatography (GC) with a nitrogen–phosphorus detector (GC–NPD). Flavouring compounds were also identified in each liquid using a GC/mass spectrometry method. The methods for determining the concentrations of nicotine and flavouring compounds are described in previous publications (Goniewicz et al., 2015, Goniewicz et al., 2013, Leigh et al., 2016). According to the laboratory report presented in Table 2.2, the average nicotine content was 17.27 mg/ml and the identified flavouring compounds correlated closely with the manufacturer's COSHH report.

Table 2.2 Nicotine and chemical compounds found in Totally Wicked Red Label American Red Tobacco flavoured e-liquid

Flavour brand name	Labelled nicotine concentration (mg/ml)	Determined nicotine concentration (mg/ml)	Identified chemicals	CAS Registry Number
American Red Tobacco	18	17.27	Pyridine, 3-(1-methyl-2-pyrrolidinyl)-, (S)-	54-11-5
			Propylene Glycol	57-55-6
			Glycerin	56-81-5
			Vanillin	121-33-5
			Vanillin propylene glycol acetal	68527-74-2
			Ethyl Vanillin	121-32-4
			Ethyl Vanillin propylene glycol acetal, cis-	68527-76-4
			2(3H)-Furanone, 5-butyldihydro-	104-50-7
			2(3H)-Furanone, dihydro-5-pentyl-	104-61-0

2.3.1.3.1 Declaration of conflicts of interest and disclaimers

All of the research presented in this thesis, including the purchase of the e-cigarettes and e-liquid used in the clinical studies were funded by a grant from the British Heart Foundation (Centre of Research Excellence Award, reference number RE/13/5/30177). There were no conflicts of interest with the tobacco industry.

When choosing the e-cigarette device and e-liquid to use for our research studies, the TPD regulations and Article 5.3 of the WHO FCTC were taken into consideration. In regard to Article 5.3, advice and guidance was sought from Professor Linda Bauld, Bruce and John Usher Professor of Public Health, University of Edinburgh; President of the Society for Research on Nicotine and Tobacco Europe; and Deputy Director of the UK Centre for Tobacco and Alcohol Studies. Furthermore, I approached the New Nicotine Alliance (NNA) for independent advice and guidance on e-cigarettes to support the product selection and how to educate study participants on their use. The NNA, is a registered charity (Charity Number: 1160481), which is completely independent of commercial interests in relevant industries (e-cigarette, tobacco, pharmaceutical companies), and operates on a not-for-profit basis. The charity campaigns for a public and organisational understanding of the potential of safer nicotine products for reducing tobacco smoking. Andy Morrison, Lead Board Member for NNA provided guidance on e-cigarettes as a technology, and their use. This advice equipped me with the skills and knowledge to educate study participants on how to use an e-cigarette.

For my research studies I successfully manged to identify and purchase e-cigarette devices and e-liquid from two independent UK-based e-cigarette manufacturers (Smokemax and Totally Wicked). These manufacturers were specifically chosen on the grounds that neither company nor their products had any affiliations with the tobacco industry, they complied with the current TPD regulations, and both companies were able to meet the research requirements. For example, Mr Tom Russell, Director of SmokeMax helped me devise the e-cigarette device participant information leaflet and Mr Stuart Mercer, Operations Director for Totally Wicked supplied me with the COSHH form for the e-liquid which I used, and co-ordinated for all of the e-liquid which has been purchased to be produced from one batch.

Furthermore, all study participants were informed that “we” (the institution, sponsor and funders) did not endorse any e-cigarette or e-liquid over any other similar products which are available on the market. Furthermore, NHS Greater Glasgow and Clyde (NHSGGC), the sponsor of the VAPOUR study requested that all study participants were aware that NHSGGC had not performed any additional testing or quality assessment and do not recommend these products over any others that are available in the UK.

2.3.2 Smokefree legislation

The evidence is clear that exposure to secondhand smoke is harmful (Royal College of Physicians, 2005), which is why under the Health Act 2006, the UK has laws prohibiting smoking in enclosed public places and workplaces. Since 2006, the implementation of smokefree legislation has resulted in positive outcomes on both child and adult health; leading to reductions in preterm deaths; childhood admissions to hospital with asthma; and adult admissions for myocardial infarction (Pell et al., 2008, Millett et al., 2013, Been et al., 2014). E-cigarette use, known as vaping, is not covered by smokefree legislation and organisations are free to make their own policies on the use of e-cigarettes on their premises. While the debate continues about the potential of e-cigarette to undermine the public health impact of smokefree legislation, alongside the unknown risks imposed by passive vaping, many organisations' smokefree policies are precautionary and subject e-cigarette to the same tobacco smoking restrictions.

In 2015, on the back of Public Health England's review that concluded that e-cigarettes are significantly safer for tobacco smokers than tobacco cigarettes (McNeill A et al., 2015a), NHSGGC became the first NHS organisation in the UK to revise their smoke policy to allow the use of e-cigarettes in specified areas within hospital grounds. The rationale to lift the ban on e-cigarettes, was to support smokers to stop smoking and stay smokefree, by making vaping an easier choice than smoking. In particular, it was felt that smoking cessation attempts should not be undermined by making vapers use the same space as smokers (Greater Glasgow and Clyde NHS Board, 2015).

My studies had to be designed around smokefree legislation. As smoking is prohibited on NHSGGC premises I was unable to conduct an exposure study which involved the use of tobacco smoking within the Clinical Research Facility (CRF). As such the acute exposure study (presented in Chapter 4) had to be conducted in a dedicated facility within a research centre where smoking outside the building was permitted. However, as smoking was not permitted indoors, participants had to be taken outdoors to smoke or vape and then moved indoors for assessment. To keep the delays between exposure and assessment as short as possible, the investigatory studies had to be limited to parameters that could be assessed relatively quickly, and a limited range of vascular function tests had to be selected for this project. For the short-term exposure study ("the VAPOUR study" presented in Chapter 5) which investigated the effects of e-cigarettes versus nicotine replacement patches over 12-weeks, I recognised that participants randomised to the e-cigarette intervention would require educating and training on how to use an e-cigarette. As the study was to be conducted at the CRF, approval from the NHSGGC Interim Director of Public Health had to be sought. The request was approved and as part of the VAPOUR study I was permitted and allocated a designated room within the CRF to educate research participants on how to use an e-cigarette.

2.3.3 Protection of research participants

When conducting experimental research with human participants, investigators have a primary responsibility to protect participants from physical and mental harm during the investigation. Normally, the risk of harm must be no greater than in ordinary life, i.e. participants should not be exposed to risks greater than or additional to those encountered in their normal lifestyles (The British Psychological Society, 2014). In this context, when designing the experimental studies, the following question was asked: Would any of the following interventions; tobacco cigarettes, nicotine containing e-cigarettes and/or NRT expose research participants to unnecessary risks if they were (a) never or former smokers or (b) smokers?

For never or former smokers, the answer was "yes"; all of these interventions would pose an unnecessary risk that was greater than or additional to those encountered in their normal lifestyles. On this basis, it was considered unethical to recruit never or former smokers into such studies. Whereas for habitual tobacco smokers, who routinely expose themselves to the harms of tobacco smoking, the answer was "no" as while the use of e-cigarettes and NRT may not be risk free, the risk presented by obtaining nicotine from tobacco smoke remains substantially greater. Therefore, I could ethically justify the recruitment of smokers into such studies.

A more delicate situation concerned experimental studies centred on the investigation of outcomes of smoking interventions, and more precisely the use of tobacco smoking control groups. In this circumstance the following question was asked: as part of a trial, such as the VAPOUR study investigating the effects of smoking cessation interventions, are research participants exposed to unnecessary physical and mental harm if they are denied a smoking cessation intervention and asked to continue to smoke? The answer was "yes". While the scientific merits of having a control group, which would provide a useful baseline comparison to compare groups and assess the effects of tobacco smoking interventions, had been considered, in this circumstance my primary responsibility to protect the patient from harm had to take priority. In this context it was considered unethical to have a "tobacco smoking" control arm, where one would actively withhold a smoking cessation intervention from a participant and request that they continued to expose themselves to the harms of tobacco smoke.

2.4 CONCLUSIONS

In the context of the ongoing e-cigarette debate, and major investments by the tobacco industry, it is essential that independent researchers conduct the relevant research to inform evidence-based guidance and public health policy. In a research field which is governed by tobacco control policy and is evolving all the time, the intention of this chapter was not to serve as an exhaustive account of challenges, but rather to highlight the key ethical, legislative and regulatory issues which have influenced the research design and methodology of the studies presented in the subsequent chapters.

A REGIONAL SURVEY OF THE KNOWLEDGE AND PERCEPTIONS ABOUT NICOTINE, TOBACCO SMOKING, NICTOINE REPLACEMENT THERAPIES AND E-CIGARETTES AMONGST HEALTHCARE PROFESSIONALS

3.1 INTRODUCTION

In Scotland, tobacco-related illness is associated with over 10,000 deaths and around 128,000 hospital admissions each year (The Scottish Public Health Observatory, 2018). Although the smoking prevalence in Scotland has gradually declined from 31% of adults in 2003 to 21% in 2016 (The Scottish Public Health Observatory, 2018), reducing smoking further remains a priority for improving health in Scotland. In 2013, the Scottish Government's 5 year tobacco control strategy, set a target to create a "tobacco-free" generation by 2034, and reduce the smoking prevalence to 5% or less (APS Group Scotland, 2013). The multifaceted approach to this focuses upon tobacco prevention, protection and cessation.

With the evidence demonstrating that brief smoking cessation interventions are both a cost-effective and effective preventive strategy (NHS Health Scotland, 2017); and numbers needed to treat for smoking cessation interventions compare favourably with other primary preventive interventions such as the use of statins (Van Schayck et al., 2017), healthcare professionals are well placed to reduce the health burden associated with smoking. At an individual level they are able to educate the population on the harms of tobacco smoking and offer brief interventions and refer patients on to smoking cessation services, whereas at a community level, healthcare professionals can be influential exemplars of tobacco control, by acting as positive role models, in addition to supporting and promoting local and national smoke-free policies. At a societal level the opinions of healthcare professionals are often captured and communicated across a vast range of social, economic and political arenas which in turn can be instrumental in the shaping of public opinion and tobacco control policies. Furthermore, healthcare organisations can act as flagship to other professional organisations by proactively embracing the principles of the Health Professional Code of Practice on Tobacco Control (World Health Organisation, 2005), in addition to the modernisation of their approaches to address the new tobacco control challenges and opportunities following the emergence of e-cigarettes.

The emergence of e-cigarettes as a smoking cessation aid has dramatically changed the landscape of tobacco harm reduction. E-cigarettes have generated some strongly polarised views, as they are a consumer led technology which currently push the limits of scientific knowledge and accepted moral standards (Hobden and Cunningham, 2006). The e-cigarette debates have largely focused on the estimated relative harm-reduction benefit of e-cigarette use compared to tobacco smoking; the unknown long-term health risks from both active and passive exposure to the e-cigarette aerosol; and effectiveness for tobacco cessation. The use of e-cigarettes may promote tobacco smoking by

(1) undermining smoke-free legislation; (2) renormalising tobacco smoking; and (3) acting as a gateway to tobacco smoking.

Within the UK there is growing consensus that is endorsed by prominent health organisations such as Public Health England, the Royal College of Physicians and NHS Scotland, that the use of e-cigarettes is significantly less harmful than smoking, and that e-cigarettes use should be advocated in the context of smoking cessation. At the time this research was conducted, the National Centre for Smoking Cessation and Training (NCSCT) recommended that smoking cessation services should be e-cigarette friendly and supportive of individuals wishing to stop smoking with the use of e-cigarettes; especially in those that have tried, but not succeeded in stopping smoking with the use of licensed smoking cessation medicines (McEwen A, 2016). Furthermore there was evidence published in a Cochrane review from two randomised trials (Bullen et al., 2013, Caponnetto et al., 2013) that demonstrated that e-cigarettes were effective at helping smokers to stop smoking in the long term compared with placebo e-cigarettes (Hartmann-Boyce et al., 2016).

The prevalence of tobacco smoking for NHS Greater Glasgow and Clyde (NHSGGC) has been a longstanding issue and ongoing challenge. With 24% of all adults identifying as regular tobacco smokers, the Scottish Health Survey identified NHSGGC as the Scottish Health Board with the highest tobacco smoking prevalence (The Scottish Public Health Observatory, 2018). Following the Public Health England report which advocated that e-cigarettes are 95% safer than tobacco cigarettes (McNeill A et al., 2015b), NHSGCC recognised that e-cigarettes may present a harm reduction opportunity to significantly reduce smoking rates. Subsequently NHSGGC made the landmark decision to modernise their smokefree policies and allow the use of e-cigarettes in specified areas within hospital grounds, in addition to their smoking cessation service offering an e-cigarette friendly service (Greater Glasgow and Clyde NHS Board, 2015). Although several NHS organisations have subsequently adopted the same approach, this is by no means universal and in many NHS organisations e-cigarette use remains subject to the same restrictions as tobacco smoking. The lack of consensus between NHS organisations, portrays a conflicting message to both healthcare professionals and the public, adding to the controversy surrounding e-cigarettes. Rogers (1995) identified five theoretical stages involved in the processes underlying healthcare professionals' successful adoption of a new technology: knowledge (a basic understanding of the process), persuasion (attitudes), decision (the choice to adopt or reject the innovation), implementation (putting it into practice), and confirmation (evaluating the results of the decision) (Rogers EM, 1995).

Given the exponential growth in awareness and use of e-cigarettes, healthcare professionals are increasingly engaging in conversations with their patients relating to the use of e-cigarettes (Hiscock et al., 2014). A prerequisite for all healthcare professionals to be able to effectively counsel patients on the use of e-cigarettes is to be aware of and understand the relative harms of tobacco smoking and the harm reduction principles of NRT. Concerningly studies have

demonstrated that healthcare professionals tend to overestimate the harmful effects of nicotine replacement products compared to tobacco smoking (Moysidou et al., 2016), with one study demonstrating that 40% of physicians incorrectly thought nicotine was one of the most important causes of smoking related diseases (Ramesh Patwardhan and Murphy, 2013). Research has also suggested that within clinical practice there is significant variation in the use of e-cigarettes, with the percentage of healthcare professionals who advise the use of e-cigarettes for smoking cessation ranging from 3.7% to 46% (Kanchustambham et al., 2017). Although the variations in clinical practice will be multifactorial, one of the commonly stated barriers to recommending e-cigarettes to their patients is that physicians feel as though they lack the required knowledge to provide informed advice regarding their use (El-Shahawy et al., 2016, Sherratt et al., 2016, Hiscock et al., 2014, Pepper et al., 2014).

Therefore, the primary aim of this study is to explore the attitudes and risk perceptions concerning nicotine, tobacco cigarettes, NRT and e-cigarettes amongst healthcare professionals within a regional health care delivery model and gain an understanding of how receptive healthcare professionals are to the role of e-cigarettes within tobacco harm reduction. Secondary aims sought to investigate whether an individual's occupational role or smoking status influenced these beliefs.

3.2 METHODOLOGY

3.2.1 Study design

A cross-sectional survey of healthcare professionals working within NHSGGC was performed from 3rd October to 31st October 2017.

A structured questionnaire (Appendix 1) was developed from a pre-existing e-cigarette research survey, which was conducted in Greece, with permission of the principal investigator, and in conjunction with national and local NHSGGC smokefree policy. To identify potential sources of response error and improve survey items, six healthcare professionals reviewed the survey and a pilot test was performed. The healthcare professionals involved in reviewing the questionnaire were excluded from the study to avoid any bias.

Ethical approval and NHSGGC sponsorship for this study were granted by the University of Glasgow College of Medical, Veterinary and Life Sciences Research Ethics Committee (Reference Number 200170018), and NHSGGC Research and Development Department (Reference Number GN17HS556), respectively.

3.2.2 Sampling and data collection

Healthcare professionals working within NHSGGC health board were selected by convenience sampling. A mixed-mode approach of online and paper surveys was used, to help to ensure adequate coverage of the intended population, and to reduce coverage error.

Inclusion criteria included all members of NHS staff who had an email account with the domain @ggc.scot.nhs.uk. This included clinical and non-clinical staff. Completed paper questionnaires that were returned to the study investigators by internal mail were included. There were no specific exclusion criteria.

Before starting the survey, participants were presented with an invitation paragraph, which included a brief description of the research purpose, confirmation of anonymity; a consent statement, and contact details of the research team. Informed consent was obtained through virtue of completion.

The online survey was uploaded to the research tool (www.surveymonkey.com). The invitation paragraph which contained a hyperlink to the survey, was distributed by NHSGGC Corporate Communications to all users with a ggc.scot.nhs.uk email account. To account for the healthcare professionals within NHSGGC without a ggc.scot.nhs.uk email account, paper questionnaires of the survey (with a return self-addressed envelope) were systematically distributed to healthcare professionals throughout the following NHSGGC hospitals: the Queen Elizabeth University Hospital (QEUH), Gartnavel General Hospital, Glasgow Royal Infirmary (GRI), the Royal Alexandra Hospital, Inverclyde Royal Hospital, the Royal Hospital for Children in Glasgow, the Beatson West of Scotland Cancer Centre and the West Glasgow Ambulatory Care Hospitals. For all of the named hospitals, the study investigators systematically visited and recruited NHS employees present in all accessible areas including: inpatient wards; emergency departments; outpatients departments; ambulatory care facilities; pharmacies; diagnostic laboratories; radiology departments; office blocks; and estate and domestic service facilities. Recruitment of individual staff by paper questionaries involved direct face-to-face discussions with staff present. Additional paper questionnaires were left at clinical locations for additional staff to complete who were not currently on-site, such as night-shift workers. Healthcare professionals who completed a paper version were asked to return the completed survey to the research team via internal mail using the return envelope provided.

3.2.3 Questionnaire

The survey consisted of 20 questions. Question styles included closed, multiple choice and Likert scale questions, in addition to optional free text responses. For the questions which used a Likert scale, participants were asked to score a statement on either a five or ten-point scale ranging from: "strongly disagree" to "strongly agree", "lowest risk" to "highest risk", "not addictive" to "highly addictive" and "no concern" to "very concerned".

Questions 1 to 15 were designed to capture responses from all healthcare professionals, whereas questions 16 to 20 were designed to capture responses from healthcare professionals with patient contact.

3.2.3.1 Questionnaire themes and questions

The survey questions asked healthcare professionals for information centred around the following five themes:

1. Demographics.
2. Knowledge and beliefs regarding tobacco cigarettes, NRT and e-cigarettes.
3. Attitudes towards e-cigarettes acting as a gateway to tobacco smoking.
4. Awareness and attitudes towards e-cigarette regulation and workplace policy.
5. Preparedness for informing patients about e-cigarette use.

3.2.3.1.1 Demographics

To identify the respondent's occupational role, respondents were asked *"what is your occupation?*" Participants were given seven options: (1) General Practitioner; (2) Physician; (3) Surgeon; (4) Dentist; (5) Nurse; (6) Healthcare assistant and (7) other (please state).

To identify the respondent's speciality, respondents were asked to: *"describe [their] speciality."*

Participants were given 30 options: (1) General Practice; (2) Nursing; (3) Pharmacology; (4) Dentistry; (5) Research/Science; (6) Clinical trials; (7) Lecturer/Medical education; (8) Dermatology; (9) Cardiology; (10) Respiratory; (11) Diabetes and Endocrinology; (12) Smokefree Services; (13) General Medicine; (14) Care of the Elderly; (15) Palliative Care; (16) Public Health; (17) Radiology; (18) General Surgery; (19) Vascular Surgery; (20) Paediatric; (21) Anaesthetics; (22) Cardiothoracics; (23) Plastic Surgery; (24) Oral and Maxillofacial Surgery; (25) Neurology; (26) Trauma and Orthopaedics; (27) Urology; (28) Nephrology; (29) Accident and Emergency; (30) Neurosurgery; and (31) Other, please state.

To identify the respondent's smoking status, respondents were asked *"do you currently or have you ever smoked tobacco cigarettes?"* Participants were given three options: (1) No, never smoker; (2) Yes, but no longer smoke tobacco cigarettes; and (3) Yes, currently smoke tobacco cigarettes.

To identify the smoking cessation methods that the former tobacco smokers had previously used, respondents were asked *"if you are a former smoker, how did you stop smoking?"* Participants were given seven options: (1) Oral medications e.g. varenicline, bupropion; (2) NRT e.g. patches, gum, spray; (3) E-cigarettes; (4) Psychological support; (5) Other methods e.g. acupuncture, hypnotherapy (6) Without using any aids; and (7) Not applicable.

3.2.3.1.2 Knowledge and beliefs regarding tobacco cigarettes, NRT and e-cigarettes

To gauge the general attitude towards e-cigarettes, respondents were asked *"do you agree with the following statement: E-cigarettes are a good thing?"* The five response options were: (1) Strongly disagree; (2) Disagree; (3) Neutral; (4) Agree; and (5) Strongly agree.

To identify the respondent's perceived health risk of tobacco and non-tobacco products, respondents were asked to score the risk to health they perceived for tobacco cigarettes, snus (a traditional Scandinavian oral smokeless tobacco product which is usually placed behind the upper lip, either in a loose form or in portioned sachets), e-cigarettes, NRT and oral smoking cessation medications; using a 10-point Likert scale (1=lowest risk to 10=highest risk).

To identify the respondent's perceived health risk from the different components of a tobacco cigarette, respondents were asked to score the risk to health they perceived in relation to the following tobacco cigarette components: nicotine, inhaled smoke, carbon monoxide, tar and tobacco; using a 10-point Likert scale (1=lowest risk to 10=highest risk).

To identify how addictive the respondents perceived tobacco cigarettes, NRT and e-cigarettes to be, respondents were asked to score how addictive they considered each product to be; using a 10-point Likert scale (1=not addictive to 10=highly addictive).

To identify how harmful to health the respondents considered both nicotine replacement patches and e-cigarettes to be compared to tobacco cigarettes, the respondents were asked to rank individually how harmful to health, they considered nicotine replacement patches and e-cigarettes to be compared to tobacco cigarettes. The response options included: "Don't know", "less harmful", "equally harmful" and "more harmful".

3.2.3.1.3 Attitudes towards e-cigarettes acting as a gateway to tobacco smoking

To identify how concerned respondents were that e-cigarettes may encourage non-smokers to take up tobacco cigarette smoking amongst the following 3 age groups: adults (>19 years); adolescents (10-19 years) and children (<10 years), respondents were asked to score their level of concern using the 10-point Likert scale (1=no concern to 10=very concerned).

3.2.3.1.4 Awareness and attitudes towards e-cigarette regulation and workplace policy

To gauge the respondent's awareness of NHSGGC workplace policy on e-cigarettes, respondents were asked *"are you aware of your workplace policy on e-cigarette use?"* The three response options were: (1) Yes, e-cigarette use is allowed; (2) Yes, e-cigarette use is not allowed; and (3) Not sure.

To gauge the respondent's attitudes on NHSGCC policy which allowed the use of e-cigarettes on hospital grounds, respondents were asked *"to what extend did they agree with the decision that some hospitals within the UK allow the use of e-cigarettes on hospital grounds?"* The five response options were: (1) Strongly disagree; (2) Disagree; (3) Neutral; (4) Agree; and (5) Strongly agree.

3.2.3.1.5 Preparedness for informing patients about e-cigarette use

To identify amongst the clinical healthcare professional respondents how often they see tobacco smoking patients as part of their clinical practice they were asked *"how often do you see patients who smoke in your working environment?"* The five response options were: (1) Never; (2) Less than one day a week; (3) 1-2 days a week; (4) Daily; and (5) I do not have patient contact (Questionnaire completed)

To identify amongst the clinical healthcare professional respondents how often they see patients who use e-cigarettes as part of their clinical practice they were asked *"how often do you see patients who use e-cigarettes in your working environment?"* The four response options were: (1) Never; (2) Less than one day a week; (3) 1-2 days a week; and (4) Daily.

To identify amongst the clinical healthcare professional respondents how often they are asked by patients about e-cigarettes they were asked *"how often are you asked by patients about e-cigarettes?"* The four response options were: (1) Never; (2) Less than one day a week; (3) 1-2 days a week; and (4) Daily.

To identify amongst the clinical healthcare professional respondents if they had received training from NHSGGC about what advice they should give to patients about e-cigarettes they were asked *"has your workplace advised you on what advice you should give to patients if they ask about e-cigarettes?"* The response options were either *"yes"* or *"no"*.

To identify amongst the clinical healthcare professional respondents how confident they felt in advising patients about e-cigarettes, and if they felt they required more information and guidance regarding e-cigarettes, they were asked to what extent they agreed with each of the following statements: *"I feel confident advising patients about e-cigarettes" and "I feel I need more information and guidance regarding e-cigarettes."* The five response options were: (1) Strongly disagree; (2) Disagree; (3) Neutral; (4) Agree; and (5) Strongly agree.

To identify amongst the clinical healthcare professional respondents if they would recommend e-cigarettes to patients as a method to stop smoking they were asked *"would you recommend e-cigarettes to patients as a method to stop smoking?"* The response options were either *"yes"* or *"no"*.

3.2.4 Data Analysis

3.2.4.1 Data classification and analysis

The data were classified and analysed according the following groups of respondents:

1. All respondents.
2. Smokers vs never smokers.
3. Patient facing vs non-patient facing healthcare professionals.
4. Allied healthcare professionals (AHPs), doctors and nurses.

Pre-planned analysis included the descriptive statistics of all responses and the inferential statistics of differences according to groups by (1) smokers and never smokers; and (2) AHPs, doctors and nurses. Additional post hoc analysis included the inferential statistics of differences between patient facing and non-patient facing healthcare professionals.

3.2.4.1.1 All respondents

The data from respondents' given occupation and speciality was categorised into 12 healthcare professional groups and corresponding sub specialisms: nursing; doctors; AHPs; wider healthcare team; public health; pharmacy; midwifery; dental team and psychological therapists; healthcare science; health informatics; and management (NHS Health Education, 2017).

The data from the respondents' smoking status, was classified into two groups which consisted of: (1) smokers (current and former tobacco smokers) or (2) never smokers.

The data from the former smoker respondents' smoking cessation methods, was classified into four smoking cessation groups which included: no medications; oral medications e.g. varenicline, bupropion; e-cigarettes and NRT.

3.2.4.1.2 Smokers and never smokers

Group comparisons were made between *"smokers"* and *"never smokers"* responses. This was based on the expectation that personal tobacco smoking experience may elicit differences in the knowledge and perceptions regarding nicotine, nicotine containing products and tobacco smoking.

3.2.4.1.3 Patient facing vs non-patient facing healthcare professionals

Group comparisons were made between *"patient facing"* and *"non-patient facing"* healthcare professionals.

The reason for dividing the sample into these sub groups is related to the expectation that irrespective of their discipline, *"patient facing"* healthcare professionals would have a better

knowledge about the study subject and education of the health issues relating to tobacco smoking and have experience of how harm reduction strategies such as smoking cessation can be effective in minimising the burden of disease at a patient and population level.

Figure 3.1 illustrates how the responses were classified. According to the respondent's healthcare professional group classification, all of the respondents were classified into either a *"patient facing"* group or a *"non-patient facing*" group. *"Patient facing"* occupations included the following professional groups: nurses; doctors; AHPs; public health; midwives; members of a dental team and psychological therapists. The *"patient facing"* group also included the sub group of clinical support staff from the wider healthcare team and also the sub group of pharmacist from the pharmacy group. The *"non-patient facing"* occupations included: the wider healthcare team (administration, corporate services, support services, estates services and domestic services only), pharmacy (pharmacist technician and pharmacy assistant only), dental team (dental technician only), healthcare science, health informatics and management.

In response to the questions which focused on eliciting how prepared clinical healthcare professionals felt about informing patients about the use of e-cigarette use. The *"patient facing"* group was further classified into a *"non-clinical"* healthcare professional group and *"clinical"* healthcare professional group, on the basis that some *"patient facing"* healthcare professionals may not have regular patient contact within the clinical setting for example a pathologist or microbiologist.

Figure 3.1 illustrates how question 15 of the survey was further used to sub classify the *"patient facing"* group into a *"non-clinical"* healthcare professional group and a *"clinical"* healthcare professional group. The *"non-clinical healthcare professional group"* is defined as healthcare professionals with a *"patient facing"* occupational role, who do not have direct clinical contact with patients. This included all of the respondents who responded to question 15 and ticked the response *"I do not have patient contact"*. Whereas, the *"clinical*" healthcare professional group is defined as healthcare professionals with a *"patient facing"* role that involves having direct clinical contact with patients. This included all of respondents who responded to question 15 and did not select the response option *"I do not have patient contact"*.

3.2.4.1.4 Allied healthcare professionals, doctors and nurses

Group comparisons were specifically made between AHPs, doctors and nurses. This is because collectively AHPs, doctors and nurses represent a cohort of autonomous healthcare practitioners with complementary roles, which when combined account for 61% of NHS Scotland's workforce (Audit Scotland, 2017). Within the context of policy and education it is critical to understand if there are any similarities or differences in the responses from these 3 healthcare professional groups.

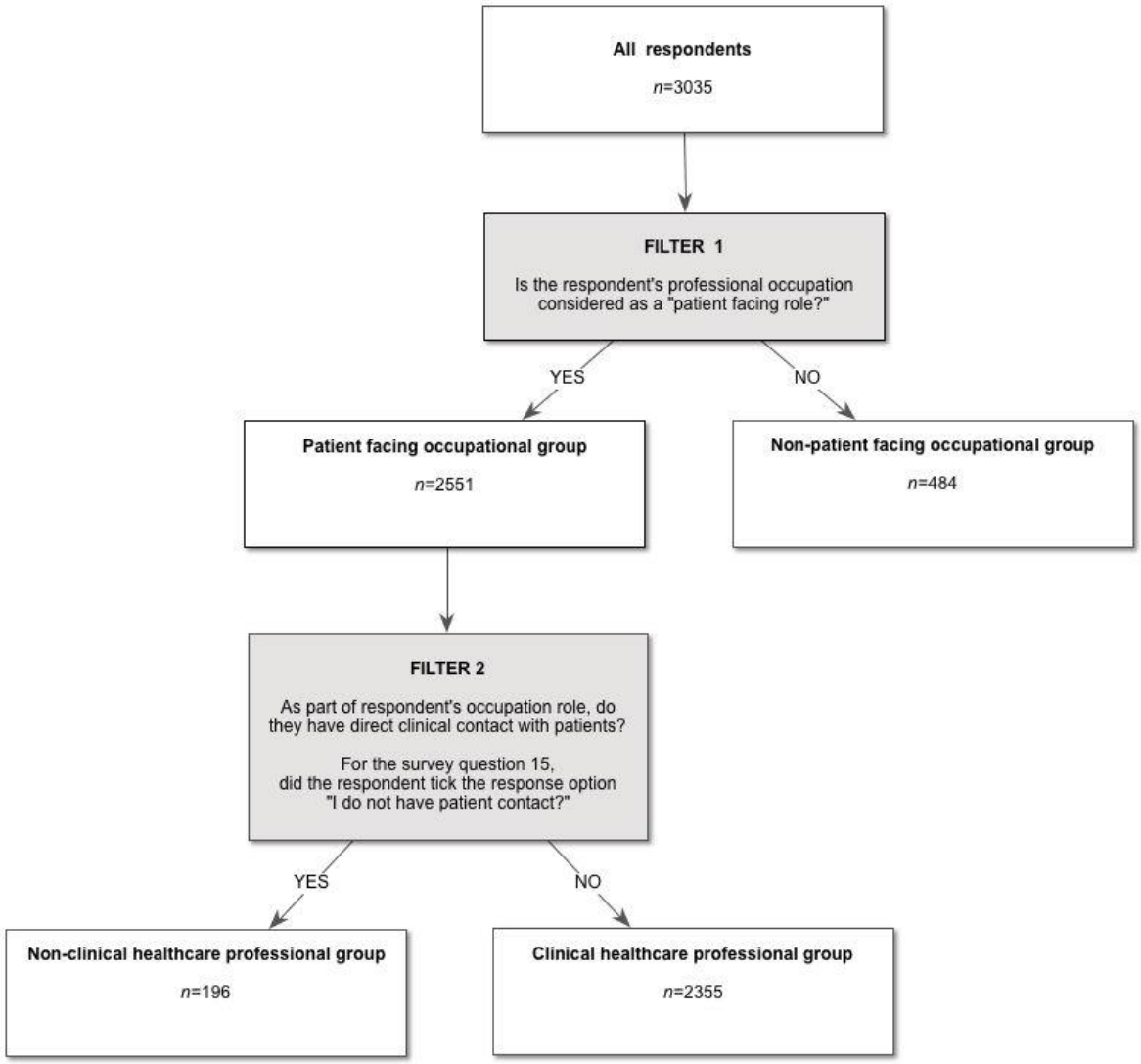


Figure 3.1 A flowchart illustrating how the survey data was filtered and grouped into *"patient facing*" and *"non-patient facing"* occupational groups and *"clinical"* and *"non-clinical"* healthcare professional groups.

3.2.4.2 Statistical Analysis

Categorical variables are presented as frequency and percentage and ordinal variables as median (25th-75th percentiles), and/or the mean rank. Non-parametric tests were used as appropriate to analyse the categorical and ordinal ranked data. *P*-values are reported as asymptotic (2-sided test) significance. Statistical significance was accepted at the level $p < .05$, unless otherwise stated. Statistical analyses were conducted using SPSS statistical software (IBM SPSS Statistics, Version 24.0. Armonk, NY: IBM Corp)

The Wilcoxon signed-rank test and Sign test were used as appropriate to determine whether there was a median difference between paired observations.

The Friedman test was used to determine whether there were any statistically significant differences between the distributions of three or more related groups. If statistical significance was demonstrated, a Bonferroni correction was performed to account for multiple pairwise comparisons, using the formula: adjusted alpha level = original alpha level ÷ number of comparisons. Depending on the number of pairwise comparisons statistical significance was accepted at the following levels: 1 pairwise comparison = $p < .05$; 2 pairwise comparisons = $p < .025$; 3 pairwise comparisons = $p < .017$; 4 pairwise comparisons = $p < .013$; 5 pairwise comparison = $p < .01$.

The Mann-Whitney U test and Kruskal-Wallis H test were used as appropriate to determine if there were statistically significant group differences between groups of an independent categorical variable on an ordinal dependent variable. For both tests, distributions of responses for each group were assessed by visual inspection of histograms and boxplots, as appropriate. If the Kruskal-Wallis H test reached statistical significance, a post hoc test of medians was performed. Pairwise comparisons with a Bonferroni correction were performed using Dunn's (1964) procedure. The *p*-value was adjusted in accordance with the number of pairwise comparisons.

For the Mann-Whitney U test the confidence intervals for the effect size (r) was calculated using the following formula:

$$r = \frac{z}{\sqrt{N}}$$

Cohen's guidelines are that an *r* score of 0.1 to 0.3 represents a small strength of association; 0.3 to 0.5, a medium strength of association; and 0.5 to 1, a large strength of association. (Fritz et al., 2012).

For the Kruskal-Wallis test, the Epsilon square (ε^2) was calculated to measure the effect size. An Epsilon square of 0.00 < 0.01 would mean that the difference was negligible, 0.01 < 0.04 = weak; 0.04 < 0.16 = moderate; 0.16 < 0.36 = relatively strong; 0.36 < 0.64 = strong, 0.64 < 1.00 =very strong (Tomczak A and Tomczak E, 2014).

The chi-square test of homogeneity (r x 2) was used, with an adequate sample size according to Cochran (1954), to determine if there was a statistically significant difference in the probabilities between two independent groups (e.g. never smokers and ever smokers) in terms of a multinomial dependent variable. The chi-square test of homogeneity (2 x c) was used, with an adequate sample size according to Cochran (1954), to determine if any statistically significant difference existed between the binomial proportions of three or more independent groups (e.g. AHPs, doctors and nurses) on a dichotomous dependent variable. If the multinomial probability distribution reached statistical significances between groups, a post hoc test of multiple z-test of two proportions, with a Bonferroni correction was performed. The *p*-value was adjusted in accordance with the number of pairwise comparisons. For the chi-square test of homogeneity, Cramer's V was calculated to measure the effect size. A Cramer's V of 0 to 0.05 would mean no or a very weak effect size; >0.05 to 0.1, a weak effect size; >0.1 to 0.15, a moderate effect size; >0.15 to 0.25, a strong effect size; and >0.25, a very strong effect size (Akoglu, 2018).

A Spearman's rank-order correlation was used to calculate a coefficient (r_s) to measure the strength and direction of the association between the group responses for two ordinal variables.

3.3 RESULTS

3.3.1 Descriptive analysis of the survey respondents

3.3.1.1 Healthcare professional group and sub-specialisms

3.3.1.1.1 All respondents

The results of the descriptive analysis of the whole study sample are presented in Table 3.1. A total of 3035 healthcare professionals completed the survey. The respondent's given healthcare occupation and speciality was categorised according to 12 healthcare professional occupations and corresponding sub specialisms and the observed frequencies and percentages are presented in Appendix 2.

Out of the 3035 respondents, nurses accounted for 35.6% (n=1081) of responses, doctors 19.9% (n=605), wider healthcare team 17.8% (n=539), AHPs 10.5% (n=318), public health 3.8% (n=116); healthcare science, 3.5% (n=107), pharmacy 3.5% (n=107), health informatics 1.6% (n=49), management 1.2% (n=36), midwifery 1.2% (n=35), dental team 0.8% (n=22) and psychological therapies 0.6% (n=20), (Figure 3.2).

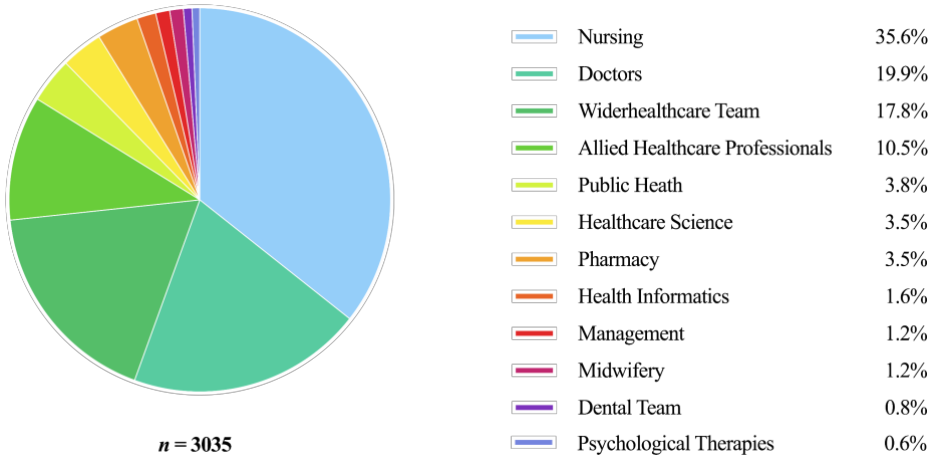


Figure 3.2 Survey respondents classified according to healthcare professional group. Data presented as percentage.

Table 3.1 Characteristics of all survey responses

Characteristics and survey responses	All Responses
Healthcare occupation	***n* = 3035**
Nursing	1081 (35.6)
Doctor	605 (19.9)
Wider Healthcare Team	539 (17.8)
AHPs	318 (10.5)
Public Health	116 (3.8)
Healthcare Science	107 (3.5)
Pharmacy	107 (3.5)
Health Informatics	49 (1.6)
Management	36 (1.2)
Midwifery	35 (1.2)
Dental Team	22 (0.8)
Psychological Therapies	20 (0.6)
Smoking Status	***n* = 3035**
Never Smoker	1822 (60.0)
Former Smoker	959 (31.6)
Current Smoker	254 (8.4)
Smoking Cessation Method	***n* = 959**
No medications	505 (52.7)
Oral Medications	39 (4.1)
E-cigarettes	287 (29.9)
NRT	117 (12.2)
No response	11 (1.1)
Patient facing occupation	***n* = 3035**
Patient facing occupation group	2551 (84.1)
Non-patient facing occupation group	484 (15.9)
Clinical healthcare professionals	***n* = 2551**
Clinical healthcare professional group	2355 (92.3)
Non-clinical healthcare professional group	196 (7.7)

Data presented as frequency (percentage).

3.3.1.1.2 Patient facing vs non-patient facing

The results of the descriptive analysis for *"patient facing"* and *"non-patient facing"* occupational groups according to healthcare professional group, smoking status, and smoking cessation methods are presented in Table 3.2.

Out of the 3035 respondents, 84.1% (*n*=2551) were considered to have a *"patient facing"* occupational role and 15.9% (*n*=484) were considered to have *"non-patient facing"* occupational role. The observed frequencies and percentages of *"patient facing"* and *"non-patient facing"* respondents corresponding to healthcare occupation are presented in Table 3.2 and Figure 3.3.

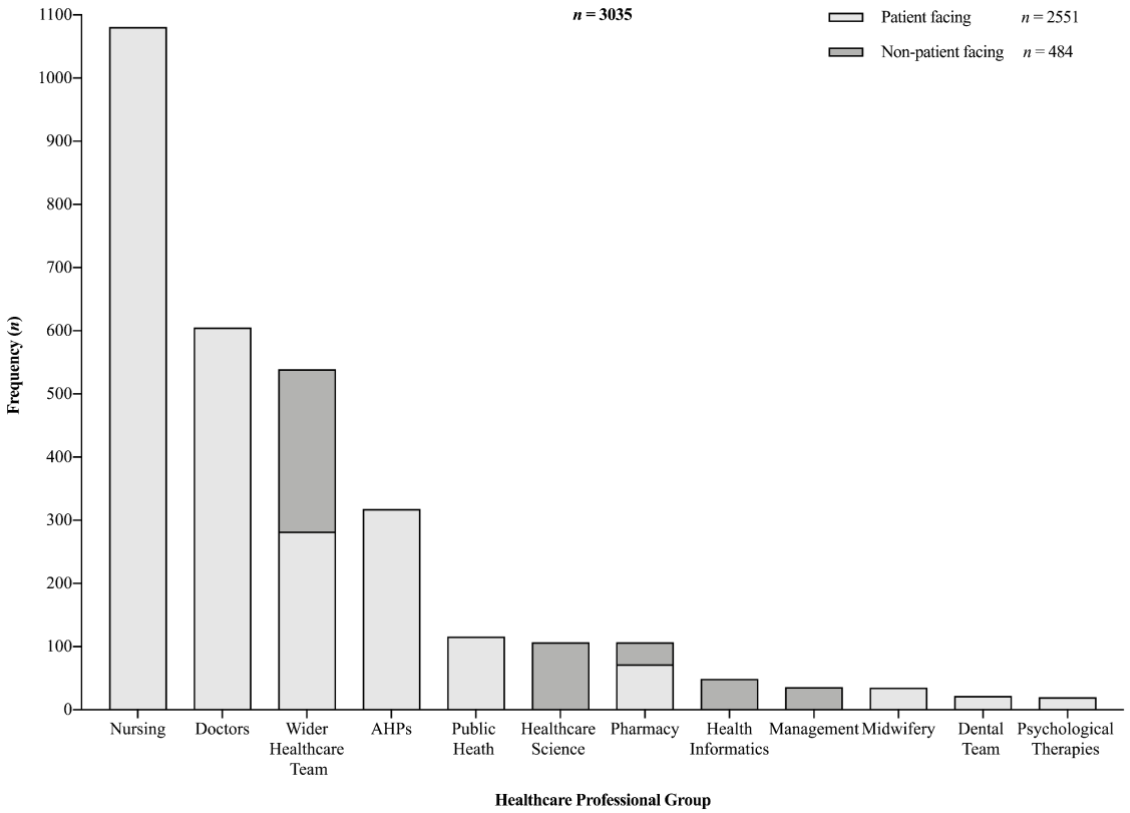


Figure 3.3 Patient facing and non-patient facing responses classified according to healthcare professional group. Data presented as frequency.

Table 3.2 Comparisons of demographics survey responses between patient facing and non-patient facing occupations.

Survey responses	**Patient Facing** ***n*** **= 2551**	**Non-Patient Facing** ***n*** **= 484**	***p*-value**
Healthcare occupation			
Nursing	1081 (42.3)	0 (0)	-
Doctor	605 (23.7)	0 (0)	-
Wider Healthcare Team	282 (11.1)	257 (53.1)	-
AHPs	318 (12.5)	0 (0)	-
Public Health	116 (4.5)	0 (0)	-
Healthcare Science	0 (0)	107 (22.1)	-
Pharmacy	72 (2.8)	35 (7.3)	-
Health Informatics	0 (0)	49 (10.1)	-
Management	0 (0)	36 (7.4)	-
Midwifery	35 (1.4)	0 (0)	-
Dental Team	22 (0.9)	0 (0)	-
Psychological Therapies	20 (0.8)	0 (0)	-
Smoking Status	***n*** **= 2551**	***n*** **= 484**	***p*-value**
Never Smoker	1590 (62.3)	232 (47.9)	**< .001**
Former Smoker	760 (29.8)	199 (41.1)	**< .001**
Current Smoker	201 (7.9)	53 (11.0)	**< .001**
Smoking Cessation Method	***n*** **= 760**	***n*** **= 199**	***p*-value**
No medications	421 (55.4)	84 (42.2)	**< .001**
Oral Medications	30 (3.9)	9 (4.5)	n/s
E-cigarettes	202 (26.6)	85 (42.7)	**< .001**
NRT	97 (12.8)	20 (10.1)	n/s
No response	10 (1.3)	1 (0.5)	-

Data are presented as frequency (percentage). P-values derived from Chi-Square test of Homogeneity.

3.3.1.1.3 Clinical healthcare professionals vs non clinical healthcare professionals

Out of the 2551 respondents with patient facing occupations, 92.3% (*n*=2355) of respondents had clinical roles with direct patient contact (clinical healthcare professional group) and 7.7% (*n*=196) had clinical roles without direct patient contact (non-clinical healthcare professional group).

Out of the 2355 respondents in the clinical healthcare professional group, nurses accounted for 42.5% (*n*=1002) of respondents; doctors 24.9% (*n*=586); wider healthcare team (clinical support staff only) 10.3% (*n*=243); AHPs 12.3% (*n*=290), public health 4.2% (*n*=100); pharmacy (pharmacists only) 2.8% (*n*=66), midwifery 1.4% (*n*=32); dental team 0.8% (*n*=19) and psychological therapies 0.7% (*n*=17).

3.3.1.1.4 Smokers vs never-smokers

The results of the descriptive analysis for the *"smoker"* and *"never smoker"* groups according to healthcare professional group are presented in Table 3.3 and Figure 3.4.

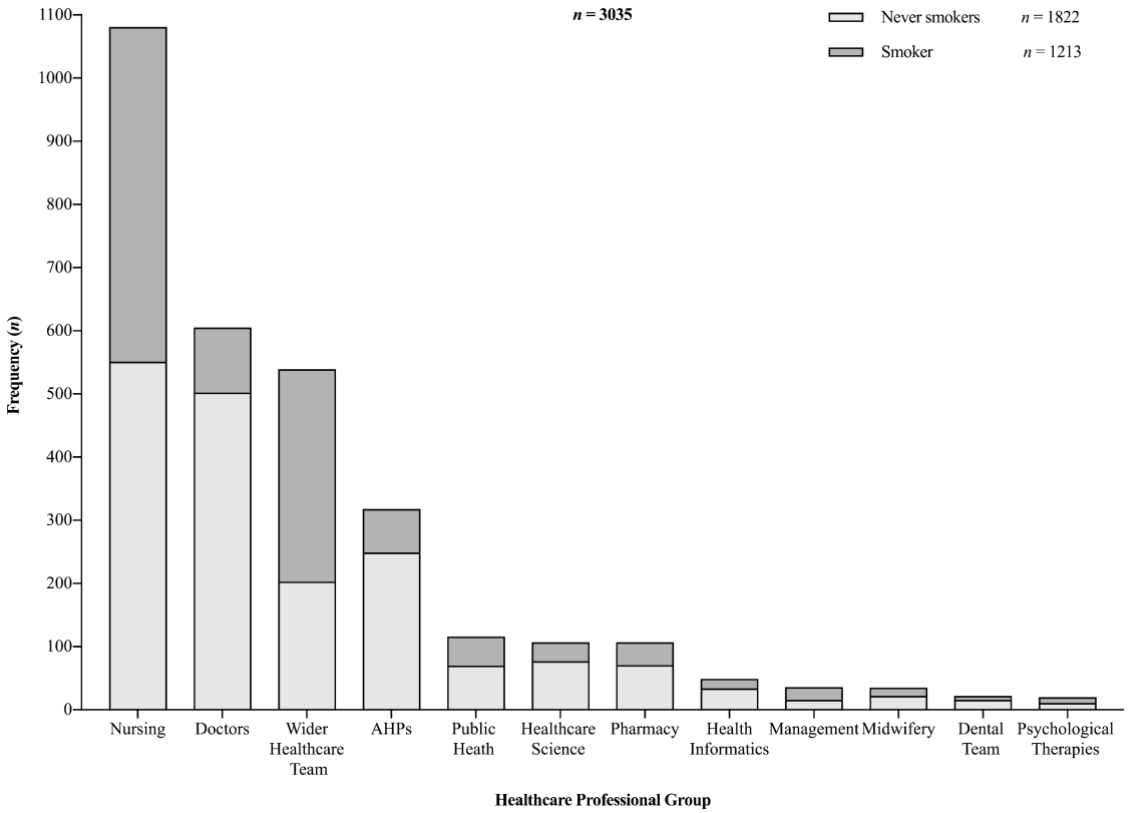


Figure 3.4 Responses from healthcare professional who are smokers or never smokers, according to their healthcare professional group. Data presented as frequency.

Table 3.3 Comparisons of demographics survey responses between never smokers and smokers.

Characteristics and survey responses	Never Smokers *n* = 1822	Smokers *n* = 1213
Healthcare occupation		
Nursing	551 (30.2)	530 (43.7)
Doctor	502 (27.6)	103 (8.5)
Wider Healthcare Team	203 (11.1)	336 (27.7)
AHPs	249 (13.7)	69 (5.7)
Public Health	70 (3.8)	46 (3.8)
Healthcare Science	77 (4.2)	30 (2.5)
Pharmacy	71 (3.9)	36 (3.0)
Health Informatics	34 (1.9)	15 (1.2)
Management	16 (0.9)	20 (1.6)
Midwifery	22 (1.2)	13 (1.1)
Dental Team	16 (0.9)	6 (0.5)
Psychological Therapies	11 (0.6)	9 (0.7)
Patient facing occupation		
Patient facing occupation group	1590 (87.3)	961 (79.2)
Non-patient facing occupation group	232 (12.7)	252 (20.8)
Clinical healthcare professionals	***n* = 1590**	***n* = 961**
Clinical healthcare professional group	1471 (92.5)	884 (92.0)
Non-clinical healthcare professional group	119 (7.5)	77 (8.0)

Data are presented as frequency (percentage).

3.3.1.2 Smoking status

3.3.1.2.1 All respondents

All of the healthcare respondents were asked the question *"do you currently or have you ever smoked tobacco cigarettes?"*. In total, 100% (*n*=3035) of respondents answered the question. The observed frequencies and percentages of respondents who were *"never smokers"*, *"former smokers"* and *"current smokers"* are presented in Table 3.1 and Figure 3.5.

In total 60% (*n*=1822) of respondents were *"never smokers"* and 40% (*n*=1213) were *"smokers"*, with 8.4% (*n*=254) of respondents identifying as *"current smokers"* and 31.6% (*n*=959) identifying as *"former smokers"*.

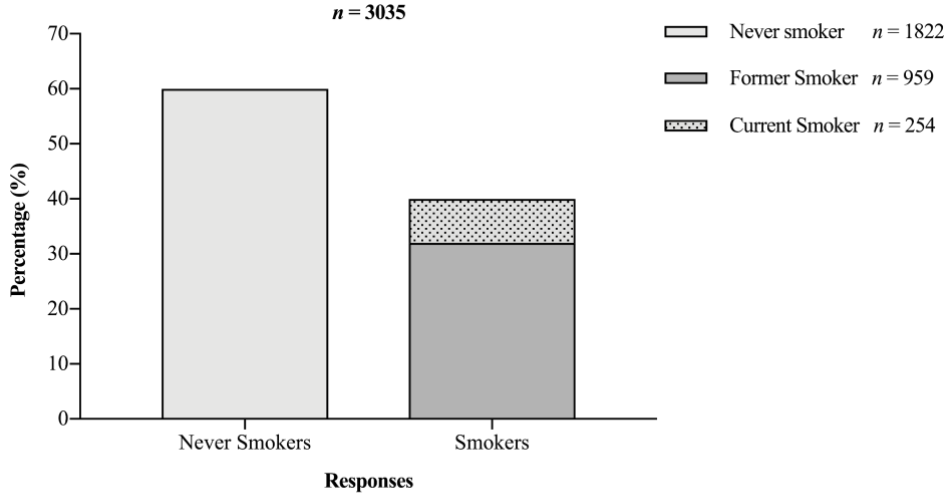


Figure 3.5 Smoking status of survey respondents. Data presented as percentage.

3.3.1.2.2 Patient facing vs non-patient facing

The observed frequencies and percentages of respondents who were *"never smokers"*, *"former smokers"* and *"current smokers"* according to the *"patient facing"* and *"non-patient facing"* groups are presented in Table 3.2 and Figure 3.6.

The proportion of respondents who were *"current smokers"* was significantly greater amongst the *"non-patient facing"* group (11.0% *n*=53) compared to the *"patient facing"* group (7.9% *n*=201), $p < .05$. Furthermore, the proportion of *"former smokers"* was also significantly greater amongst the *"non-patient facing"* group (41.1% *n*=199), in comparison to the *"patient facing"* group (29.8% *n*=760), $p < .05$. However, the proportion of *"never smokers"* was significantly greater amongst the *"patient facing"* group (62.3% *n*=1590), in comparison to the *"non-patient facing"* group (47.9%, *n*=232), $p < .05$.

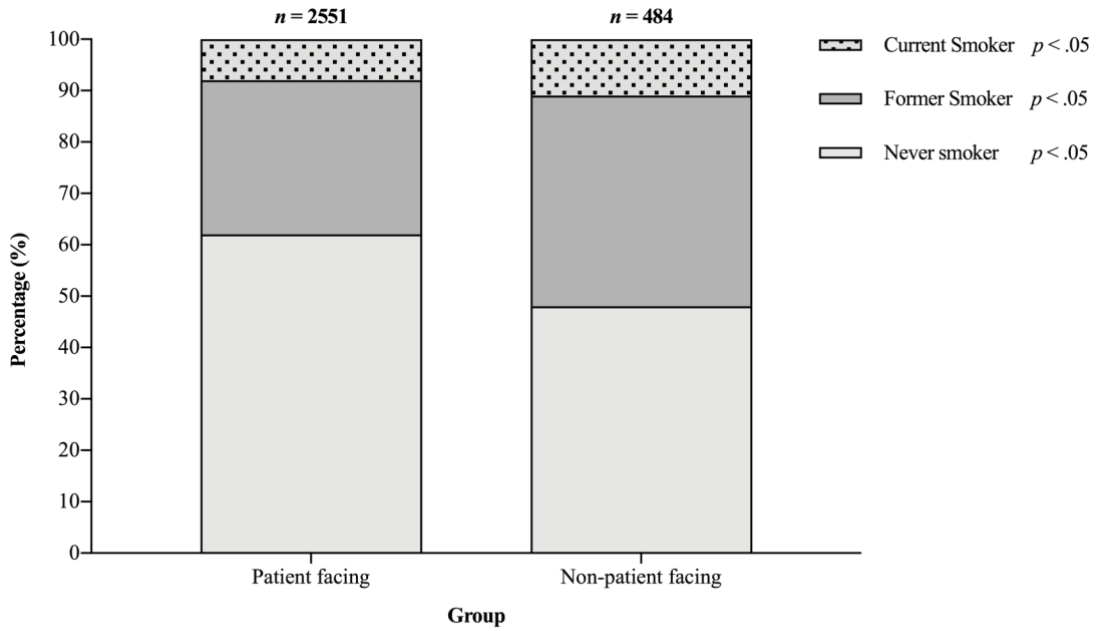


Figure 3.6 A comparison of smoking status between patient facing and non-patient facing respondents. Data presented as percentage. A chi-square test of homogeneity demonstrated statistically significant differences in smoking status between the *"patient facing"* and *"non-patient facing"* respondents, $p < .001$. Post hoc analysis demonstrated significant differences in the proportions of each smoking status group between the *" patient facing"* and *"non-patient facing"* respondents, all $p < .05$.

3.3.1.2.3 Allied healthcare professionals, doctors and nurses

The observed frequencies and percentages of AHPs, doctors and nurses who were *"never smokers"*, *"former smokers"* and *"current smokers"* are presented in Table 3.4 and Figure 3.7.

The number of *"never smokers"* was lower amongst the nurses (51%, *n*=551) as compared to either doctors (83%, *n*=502,) or AHPs (78.3%, *n*=249) both $p < .017$. In comparison, the number of *"current smokers"* was greater amongst the nurses (11.2%, *n*=121) compared to either doctors (3.3%, *n*=20) or AHPs (1.9%, *n*=6,) both $p < .017$. The proportion of *"former smokers"* was statistically different across all three healthcare professional groups: nurses (37.8%, *n*=409), doctors (13.7%, *n*=83) and AHPs (19.8%, *n*=63), all $p < .017$.

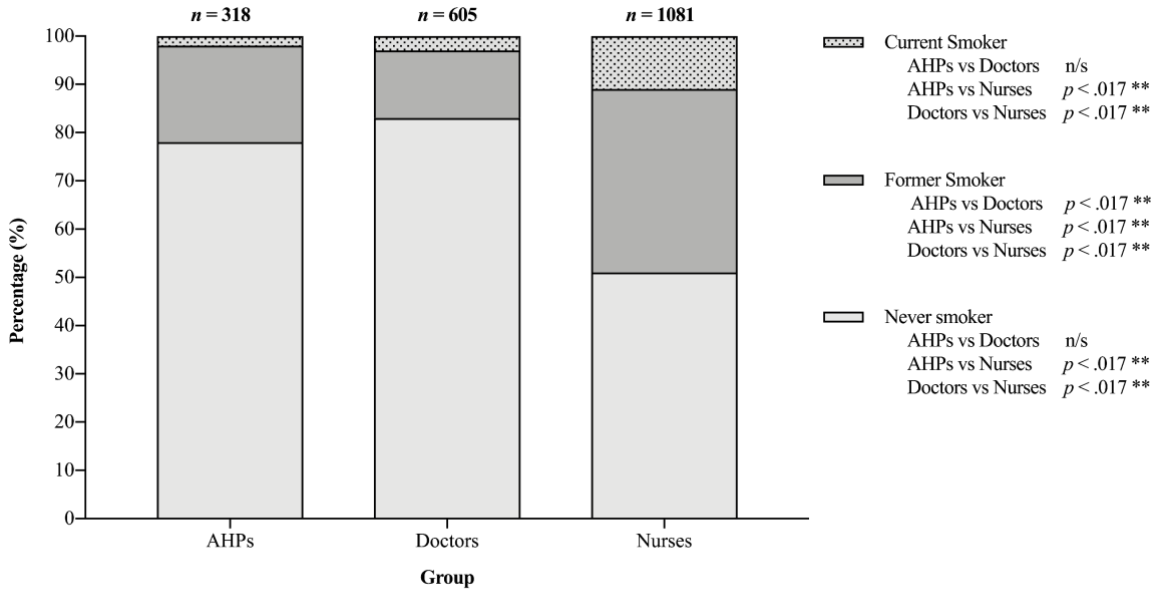


Figure 3.7 A comparison of smoking status between AHPs, doctors and nurses. Data presented as percentage. A chi-square test of homogeneity demonstrated statistically significant differences in smoking status between each of the healthcare professional group, $p < .001$. For each smoking status, post hoc analysis with a Bonferroni correction, demonstrated significant differences between the pairwise comparisons between the proportion of AHPs, doctors and nurses who were *"current smokers", "former smokers"* and *"never smokers"*.

Table 3.4 Comparisons of demographics survey responses between AHPs, doctors and nurses.

Characteristics and survey responses	AHPs	Doctors	Nurses	*p*-values
Smoking Status	***n* = 318**	***n* = 605**	***n* = 1081**	
Never Smoker	249 (78.3)	502 (83.0)	551 (51.0)	**< .001**
Former Smoker	63 (19.8)	83 (13.7)	409 (37.8)	
Current Smoker	6 (1.9)	20 (3.3)	121 (11.2)	
Smoking Cessation Method	***n* = 63**	***n* = 83**	***n* = 409**	
No medications	46 (73.0)	59 (71.1)	210 (51.3)	**< .001**
E-cigarettes	6 (9.5)	12 (14.5)	125 (30.6)	
NRT	8 (12.7)	10 (12.0)	52 (12.7)	
Oral Medications	1 (1.6)	1 (1.2)	19 (4.6)	-
No response	2 (3.2)	1 (1.2)	3 (0.7)	-
Clinical healthcare professionals	***n* = 318**	***n* = 605**	***n* = 1081**	
Clinical healthcare professional group	290 (91.2)	586 (96.9)	1002 (92.7)	-
Non-clinical healthcare professional group	28 (8.8)	19 (3.1)	79 (7.3)	-

Data are presented as frequency (percentage). P-values derived Chi-Square test of Homogeneity.

3.3.1.3 Smoking cessation method

3.3.1.3.1 All respondents

Out of the 959 respondents who identified as *"former smokers"*, 98.9% (*n*=948) reported their smoking cessation method. Of which 53.3% (*n*=505) used no medications, 4.1% (n=39) used oral smoking cessation medications, 30.3% (*n*=287) used e-cigarettes and 12.3% (*n*=117) used NRT (Figure 3.8 and Table 3.1).

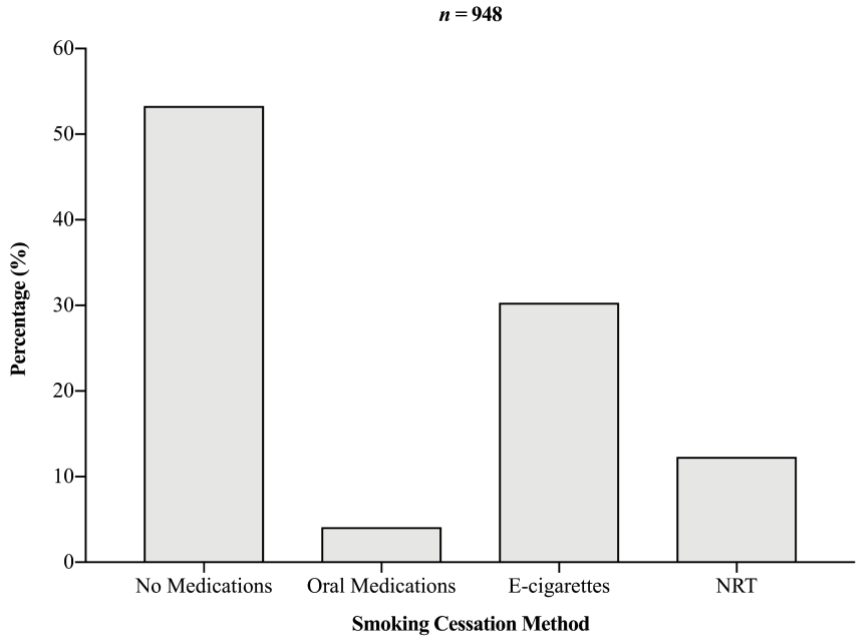


Figure 3.8 Smoking cessation methods used by former smokers. Data presented as percentage.

3.3.1.3.2 Patient facing vs non-patient facing

The observed frequencies and percentages of smoking cessation methods used by *"former smokers"* according to *"patient facing"* and *"non-patient facing"* groups are presented in Table 3.2 and Figure 3.9.

The proportion of former smokers who used e-cigarettes as a smoking cessation method was significantly greater amongst the *"non-patient facing"* group (42.9%, *n*=85) in comparison to the *"patient facing"* group (26.9%, *n*=202) $p < .05$. The use of no smoking cessation medications was significantly greater amongst the *"patient facing"* group (56.1%, *n*=421) in comparison to *"non-patient facing"* (42.4%, *n*=84,) $p < .05$. The use of NRT and oral medications was not significantly different between *"patient facing"* and *"non-patient facing"* groups, (both $p > .05$).

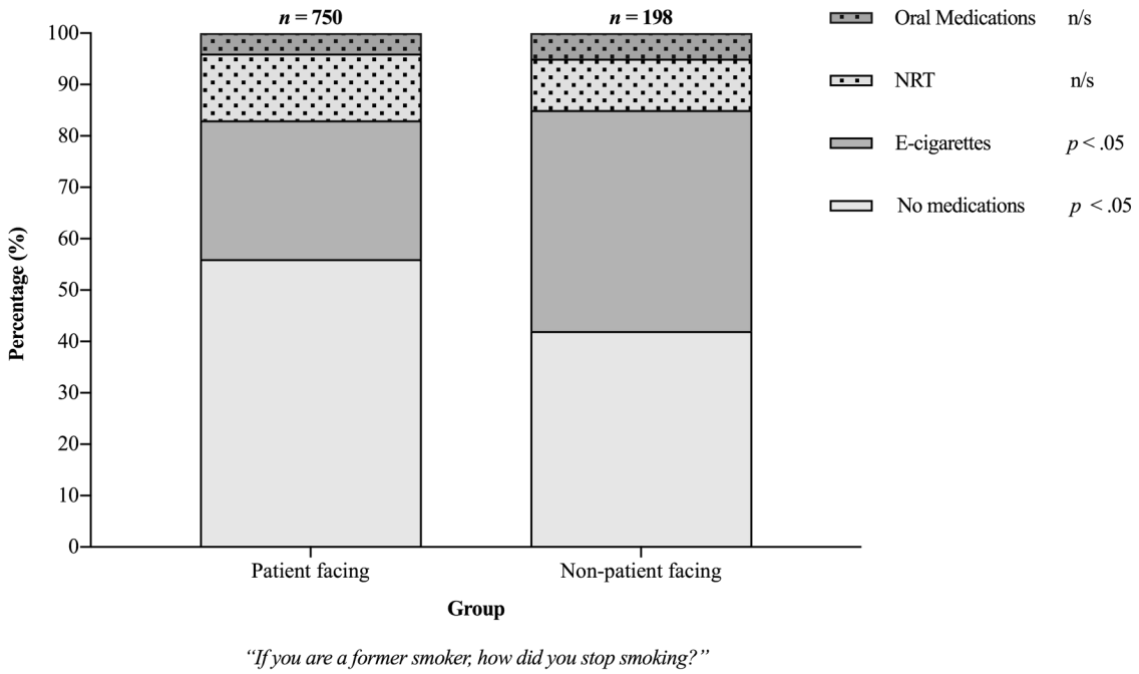


Figure 3.9 A comparison of smoking cessation methods used by patient facing and non-patient facing former smokers. Data presented as percentage. A chi-square test of homogeneity demonstrated statistically significant differences in smoking status between the *"patient facing"* and *"non-patient facing"* respondents, $p < .001$. Post hoc analysis demonstrated significant differences in the proportion of *"patient facing"* and *"non-patient facing"* respondents who used e-cigarettes or no medications to stop smoking, both $p < .05$. A greater proportion of *"patient facing"* respondents used no medications to stop smoking, compared to *"non-patient facing"* respondents. A greater proportion of *"non-patient facing"* respondents used e-cigarettes to stop smoking, compared to *"patient facing"* respondents.

3.3.1.3.3 Allied healthcare professionals, doctors and nurses

The observed frequencies and percentages of smoking cessation methods used by AHPs, doctors and nurses who were *"former smokers"* are presented in Table 3.4 and Figure 3.10.

A significantly greater proportion of nurses (30.8%, *n*=125) used e-cigarettes to stop smoking, in comparison to either doctors (14.6%, *n*=12) or AHPs (9.8%, *n*=6), both $p < .017$. A significantly greater proportion of doctors (72%, *n*=59) and AHPs (75.4%, *n*=46) used no medications to stop smoking compared to nurses (51.7%, *n*=210), both $p < .017$. The use of NRT was proportionally similar across all three healthcare professional groups, nurses (12.8%, *n*=52), doctors (12.2%, *n*=10) and AHPs (13.1%, *n*=8), all $p > .017$.

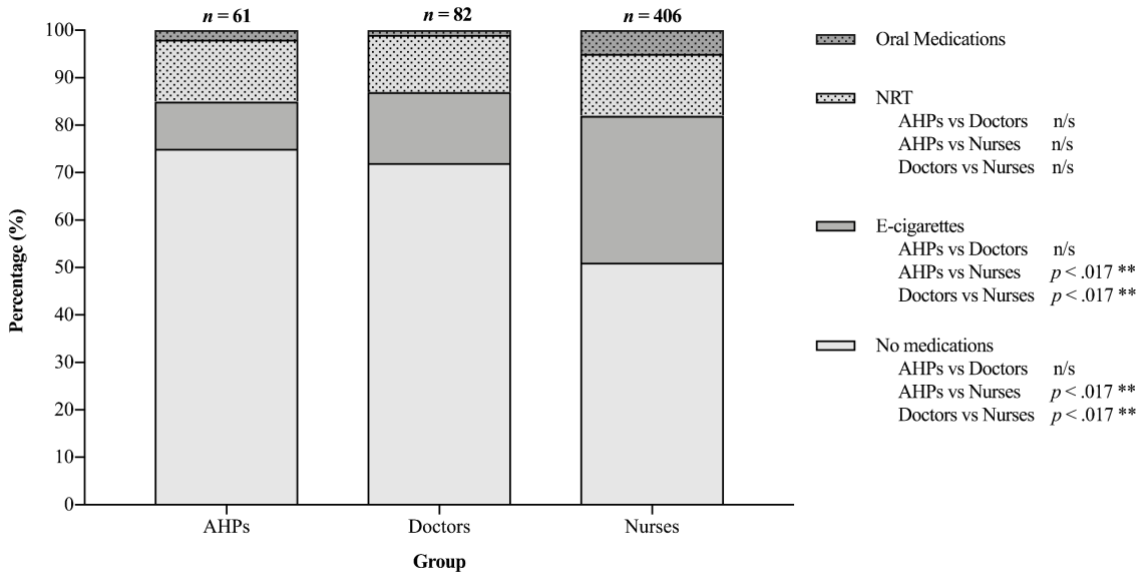


Figure 3.10 A comparison of smoking cessation method used between AHPs, doctors and nurses who were former smokers. Data presented as percentage. A chi-square test of homogeneity demonstrated statistically significant differences in smoking cessation method used between each of the healthcare professional group, $p < .001$. For NRT, e-cigarettes and no medications a post hoc analysis with a Bonferroni correction demonstrated significant differences between the proportion of AHPs, doctors and nurses who used each smoking cessation method.

3.3.2 Knowledge and beliefs of tobacco cigarettes, nicotine replacement therapies and e-cigarettes

3.3.2.1 Global perception of e-cigarettes

3.3.2.1.1 All respondents

Respondents were asked *"do you agree with the following statement: e-cigarettes are a good thing?"*. In total, 100% (*n*=3035) of respondents answered the question. The observed frequencies and percentages of responses from all respondents are presented in Table 3.5. Overall, 10.9% (*n*=331) strongly disagreed, 27.5% (*n*=834) disagreed, 33.6% (*n*=1019) were neutral, 22.4% (*n*=681) agreed and 5.6% (*n*=170) strongly agreed (Figure 3.11).

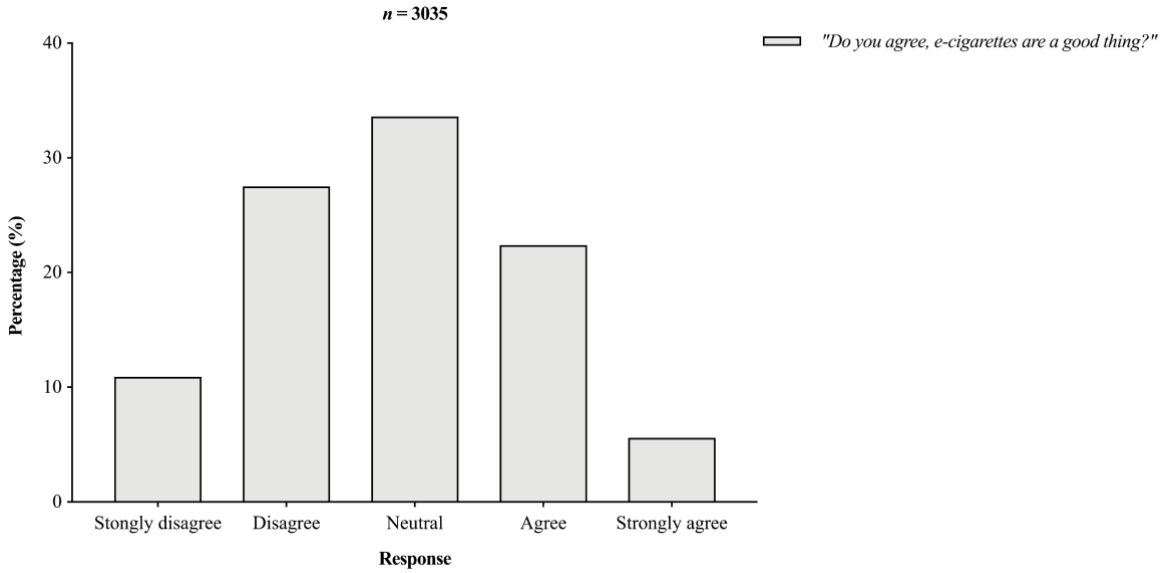


Figure 3.11 Healthcare professional respondents' level of agreement on whether they considered e-cigarettes to be *"a good thing."* Data presented as percentage.

Table 3.5 Perceived level of risk and harm associated with tobacco and non-tobacco products.

Survey responses	All Responses
Do you agree e-cigarettes are a good thing?	
Strongly agree	170 (5.6)
Agree	681 (22.4)
Neutral	1019 (33.6)
Disagree	834 (27.5)
Strongly disagree	331 (10.9)
Risk score for tobacco and non-tobacco products	
Tobacco cigarettes	10 (10;10)
Suns	9 (7;10)
E-cigarettes	5 (4;7)
NRT	4 (2;5)
Oral medications (varenicline, bupropion)	4 (3;5)
Risk score for components of tobacco cigarettes	
Nicotine	8 (5;10)
Inhaled Smoke	10 (8;10)
Carbon Monoxide	10 (9;10)
Tar	10 (9;10)
Tobacco	9 (7;10)
Perceived level of addictiveness for tobacco cigarettes, NRT and e-cigarettes	
Tobacco cigarettes	10 (10;10)
E-cigarettes	8 (7;10)
NRT	6 (4;8)
Perceived risk of harm from NRT exposure compared to tobacco cigarettes	
More harmful	10 (0.3)
Equally harmful	216 (7.1)
Less harmful	2695 (88.8)
Don't know	114 (3.8)
Perceived risk of harm from e-cigarette exposure compared to tobacco cigarettes	
More harmful	45 (1.5)
Equally harmful	592 (19.5)
Less harmful	2047 (67.4)
Don't know	351 (11.6)

Data are presented as frequency (percentage) and median (25^{th}-75^{th} percentiles).

3.3.2.1.2 Patient facing vs non-patient facing

In response to the question *"do you agree e-cigarette are a good thing?,* the observed frequencies and percentages for each group are presented in Table 3.6 and Figure 3.12.*"* The median agreement scores were *"neutral"* for both the *"patient facing"* and *"non-patient facing"* groups. No statistically significant differences in responses was demonstrated between the groups, $p = .148$.

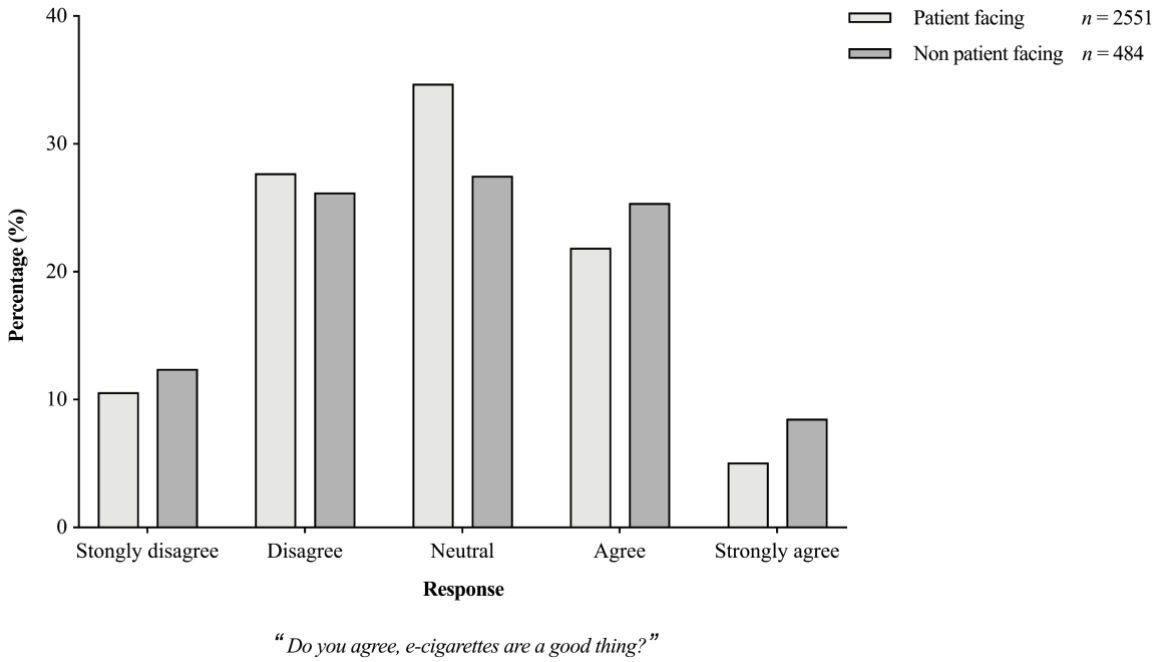


Figure 3.12 A comparison between the patient facing and non-patient facing respondents' level of agreement on whether they considered e-cigarettes to be "a good thing". Data presented as percentage. The median level of agreement was *"neutral"* for both groups. A Mann-Whitney U test demonstrated no statistically significant differences between the median level of agreement between the *"patient facing"* and *"non-patient facing"* group, $p = .148$.

Table 3.6 Comparisons of survey responses between patient facing and non-patient facing occupations upon the perceived level of risk associated with tobacco and non-tobacco products.

Survey responses	Patient Facing *n* = 2551	Non-Patient Facing *n* = 484	*p*-value
Do you agree e-cigarettes are a good thing?			
Strongly agree	129 (5.1)	41 (8.5)	
Agree	558 (21.9)	123 (25.4)	
Neutral	886 (34.7)	133 (27.5)	.148[a]
Disagree	707 (27.7)	127 (26.2)	
Strongly disagree	271 (10.6)	60 (12.4)	
Risk score for tobacco and non-tobacco products			
Tobacco cigarettes	10 (10;10)	10 (10;10)	.826
Suns	9 (7;10)	9 (7;10)	.852
E-cigarettes	5 (4;7)	5 (4;8)	.963
NRT	4 (2;5)	4 (2;6)	.179
Oral medications (varenicline,	4 (3;5)	5 (3;6)	**.002**
Risk score for components of tobacco cigarettes			
Nicotine	8 (5;10)	8 (5;10)	**.004**
Inhaled Smoke	10 (8;10)	10 (8;10)	.389
Carbon Monoxide	10 (9;10)	10 (10;10)	**< .001**
Tar	10 (9;10)	10 (9;10)	.494
Tobacco	9 (8;10)	10 (7;10)	.743
Perceived level of addictiveness for tobacco cigarettes, NRT and e-cigarettes			
Tobacco cigarettes	10 (10;10)	10 (10;10)	.062
E-cigarettes	9 (7;10)	8 (7;10)	**.033**
NRT	6 (4;8)	6 (5;8)	.345
Perceived risk of harm from NRT exposure compared to tobacco cigarettes			
More harmful	8 (0.4)	2 (0.4)	
Equally harmful	167 (6.5)	49 (10.1)	.852
Less harmful	2297 (90.0)	398 (82.2)	
Don't know	79 (3.1)	35 (7.2)	
Perceived risk of harm from e-cigarette exposure compared to tobacco cigarettes			
More harmful	38 (1.5)	7 (1.4)	
Equally harmful	479 (18.8)	113 (23.3)	**.039**
Less harmful	1734 (68.0)	313 (64.7)	
Don't know	300 (11.8)	51 (10.5)	

Data are presented as median (25^{th}-75^{th} percentiles), and frequency (percentage). *P*-values derived from Independent Samples Mann-Whitney U test.

3.3.2.1.3 Allied healthcare professionals, doctors and nurses

When healthcare professionals were asked *"do you agree e-cigarette are a good thing?"*, the observed frequencies and percentages responses from AHPs, doctors and nurses are presented in Table 3.7 and Figure 3.13.

Although the median agreement score was *"neutral"* for all 3 groups of healthcare professionals (AHPs, doctors and nurses), the distribution of responses was different $\chi^2(2) = 21.883$, $p < .001$, the effect size for this finding was relatively strong, $\varepsilon^2 = .11$. Doctors had a stronger tendency towards agreeing that e-cigarettes were a "good thing" (*mean rank* = 1084.33) in comparison to either nurses (*mean rank* = 981.23) or AHPs (*mean rank* = 919.12), both $p < .017$).

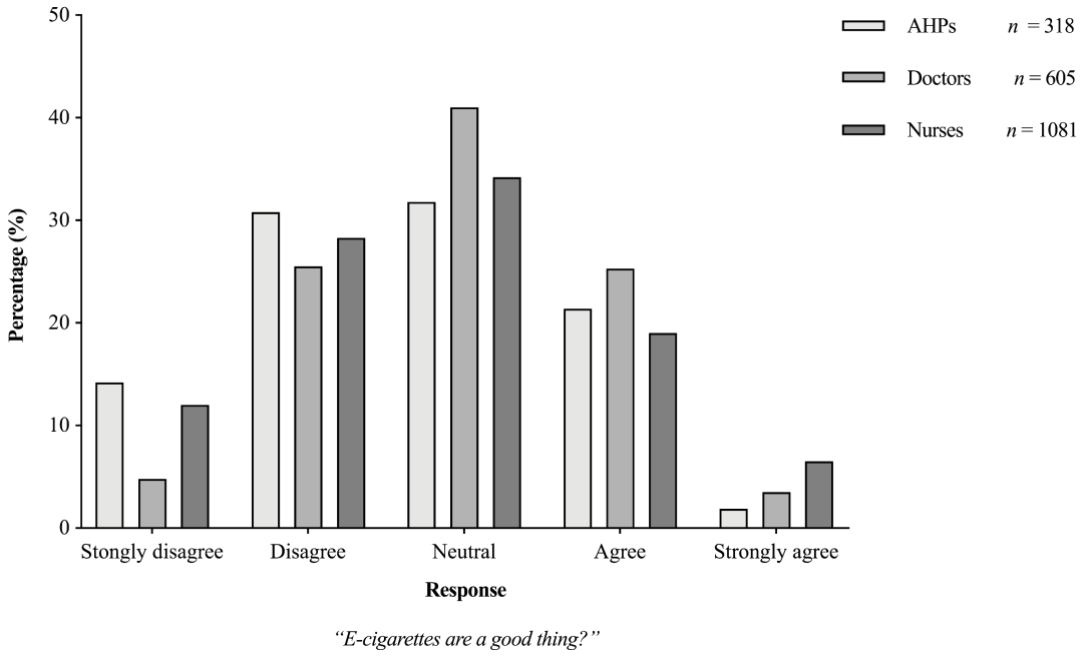


Figure 3.13 A comparison between AHPs', doctors' and nurses' level of agreement on whether they considered e-cigarettes to be "a good thing". A Kruskal-Wallis test demonstrated that there were statistically significant differences in the median agreement scores across all three groups, $p < .001$. Post hoc analysis with a Bonferroni correction demonstrated statistically significant differences between the level of agreement of doctors (*mean rank* = 1084.33) compared to either nurses (*mean rank* = 981.23) or AHPs (*mean rank* = 919.12), both $p < .017$.

Table 3.7 Comparisons of survey responses between AHPs, doctors and nurses upon the perceived level of risk associated with tobacco and non-tobacco products.

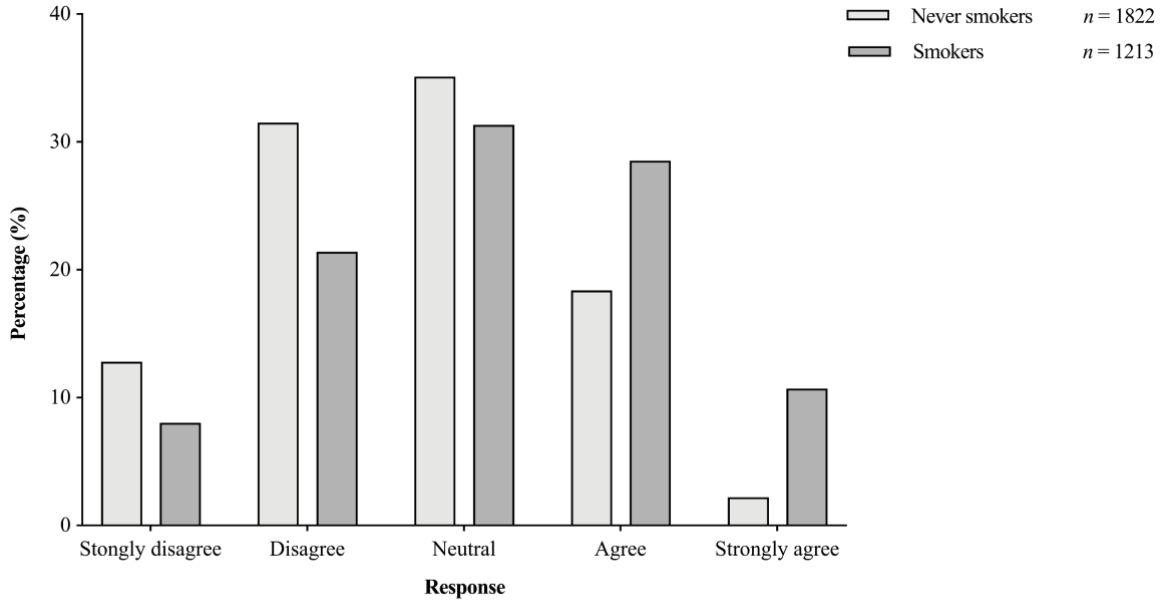
Survey responses	AHPs *n* = 318	Doctors *n* = 605	Nurses *n* = 1081	*p*-values
Do you agree e-cigarettes are a good thing?				
Strongly agree	6 (1.9)	21 (3.5)	70 (6.5)	
Agree	68 (21.4)	153 (25.3)	205 (19.0)	
Neutral	101(31.8)	248 (41.0)	370 (34.2)	**< .001**[a]
Disagree	98 (30.8)	154 (25.5)	306 (28.3)	
Strongly disagree	45 (14.2)	29 (4.8)	130 (12.0)	
Risk score for tobacco and non-tobacco products				
Tobacco cigarettes	10 (10;10)	10 (10;10)	10 (10;10)	.310
Suns	9 (8;10)	8 (7;9)	9 (7;10)	**< .001**
E-cigarettes	6 (4;8)	5 (4;6)	6 (4:8)	**< .001**
NRT	4 (3;5)	3 (2;4)	4 (2;5)	**< .001**
Oral medications (varenicline,	4 (3;5)	3 (2;5)	4 (3;6)	**< .001**
Risk score for components of tobacco cigarettes				
Nicotine	8 (5;10)	6 (4;8)	8 (5;10)	**< .001**
Inhaled Smoke	10 (8;10)	10 (8;10)	10 (8;10)	.120
Carbon Monoxide	10 (9;10)	9 (8;10)	10 (9;10)	**< .001**
Tar	10 (9;10)	10 (9;10)	10 (9;10)	**< .001**
Tobacco	9 (7;10)	9 (7;10)	10 (8;10)	**< .001**
Perceived level of addictiveness for tobacco cigarettes, NRT and e-cigarettes				
Tobacco cigarettes	10 (10;10)	10 (9;10)	10 (10;10)	**< .001**
E-cigarettes	8 (7;10)	8 (7;10)	9 (7;10)	**< .001**
NRT	7 (5;8)	5 (3;7)	6 (5;8)	**< .001**
Perceived risk of harm from NRT exposure compared to tobacco cigarettes				
More harmful	1 (0.3)	0 (0)	5 (0.5)	
Equally harmful	17 (5.3)	4 (0.7)	97 (9.0)	**< .001**
Less harmful	292 (91.8)	592 (97.9)	941 (87.0)	
Don't know	8 (2.5)	9 (1.5)	38 (3.5)	
Perceived risk of harm from e-cigarette exposure compared to tobacco cigarettes				
More harmful	2 (0.6)	1 (0.2)	22 (2.0)	
Equally harmful	66 (20.8)	47 (7.8)	261 (24.1)	**< .001**
Less harmful	214 (67.3)	508 (84.0)	669 (61.9)	
Don't know	36 (11.3)	49 (8.1)	129 (11.9)	

Data are presented as median (25^{th}-75^{th} percentiles), and frequency (percentage). P-values derived from Independent Samples Kruskal-Wallis test.

3.3.2.1.4 Smokers vs never-smokers

When *"smokers"* and *"never-smokers"* were asked *"do you agree e-cigarette are a good thing?",* the observed frequencies and percentages of responses from *"smokers"* and *"never-smokers"* are presented in Table 3.8 and Figure 3.14.

Although the median agreement scores were *"neutral"* for both groups, the level of agreement that *"e-cigarettes were a good thing"* was statistically significant higher amongst the *"smokers" (Mdn*=3, *mean rank* =1734.89) compared to *"never-smokers"* (*Mdn*=3, *mean rank* = 1373.60), U = 1368136, z = 11.546, $p < .001$, the effect size for this finding was small, r = .2.



"Do you agree, e-cigarettes are a good thing?"

Figure 3.14 A comparison between the smokers' and never smokers' level of agreement on whether they considered e-cigarettes to be "a good thing". Data presented as percentage. The median level of agreement was *"neutral"* for both groups. A Mann-Whitney U test demonstrated statistically significant differences between the median level of agreement between smokers and never smokers, $p < .001$. With smokers (*mean rank* = 1734.89) having a higher level of agreement that e-cigarettes are a "good thing" compared to never smokers (*mean rank* = 1373.60).

Table 3.8 Comparisons of survey responses between never smokers and smokers upon the perceived level of risk associated with tobacco and non-tobacco products.

Survey responses	Never smokers *n* = 1822	Smokers *n* = 1213	*p*-value
Do you agree e-cigarettes are a good thing?			
Strongly agree	40 (2.2)	130 (10.7)	**<.001**[a]
Agree	335 (18.4)	346 (28.5)	
Neutral	639 (35.1)	380 (31.3)	
Disagree	574 (31.5)	260 (21.4)	
Strongly disagree	234 (12.8)	97 (8.0)	
Risk score for tobacco and non-tobacco products			
Tobacco cigarettes	10 (10;10)	10 (10;10)	.517
Suns	9 (8;10)	9 (6;10)	**< .001**
E-cigarettes	6 (4;8)	5 (3;7)	**< .001**
NRT	4 (3;5)	3 (2;5)	**< .001**
Oral medications (varenicline, bupropion)	4 (3;5)	4 (3;5)	.796
Risk score for components of tobacco cigarettes			
Nicotine	8 (5;10)	7 (4;10)	**< .001**
Inhaled Smoke	10 (8;10)	10 (8;10)	.282
Carbon Monoxide	10 (9;10)	10 (9;10)	**< .001**
Tar	10 (9;10)	10 (9;10)	**.026**
Tobacco	9 (8;10)	9 (7;10)	.527
Perceived level of addictiveness for tobacco cigarettes, NRT and e-cigarettes			
Tobacco cigarettes	10 (10;10)	10 (10;10)	.565
E-cigarettes	9 (7;10)	8 (7;10)	**< .001**
NRT	6 (5;8)	6 (4;8)	**< .001**
Perceived risk of harm from NRT exposure compared to tobacco cigarettes			
More harmful	9 (0.5)	1 (0.1)	.309
Equally harmful	137 (7.5)	79 (6.5)	
Less harmful	1606 (88.1)	1089 (89.8)	
Don't know	70 (3.8)	44 (3.6)	
Perceived risk of harm from e-cigarette exposure compared to tobacco cigarettes			
More harmful	29 (1.6)	16 (1.3)	**.023**
Equally harmful	387 (21.2)	205 (16.9)	
Less harmful	1195 (65.6)	852 (70.2)	
Don't know	211 (11.6)	140 (11.5)	

Data are presented as median (25^{th}-75^{th} percentiles), and frequency (percentage). P-values derived from Independent Samples Mann-Whitney U test.

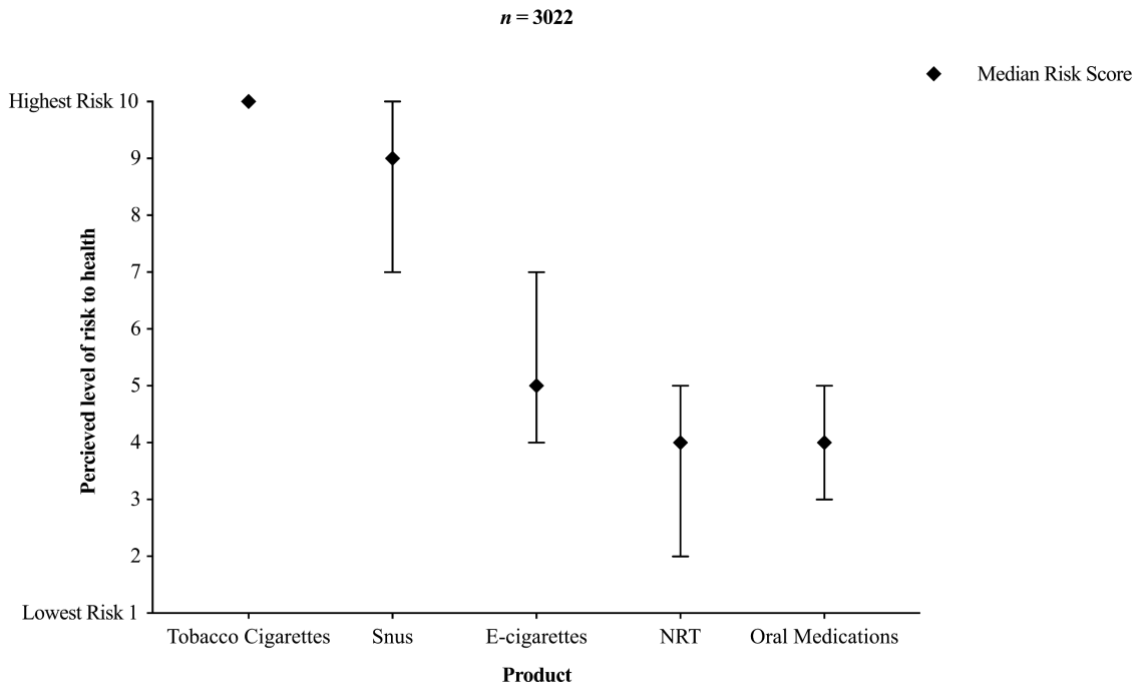
3.3.2.2 Perceived relative harm of e-cigarettes compared to tobacco containing products and smoking cessation medications

3.3.2.2.1 All respondents

Respondents were asked to score the risk to health (1=lowest risk to 10=highest risk) they perceived with tobacco cigarettes, snus, e-cigarettes, NRT and oral medication.

Out of the 3035 survey respondents, 100% (*n*=3035) gave a risk score for tobacco cigarettes, 99.7% (*n*=3027) snus, 99.9% (*n*=3033) e-cigarettes, 99.9% (*n*=3034) NRT and 99.8% (*n*=3030) for oral smoking cessation medications. The observed medians are presented in Table 3.5.

In total 99.6% (*n*=3022) of all respondents, gave a risk score for all five products (Figure 3.15). The median perceived health risk scores for each product had statistically significantly different distributions $\chi 2(4) = 8947.257$, $p < .001$. There was a significant difference in the perceived health risk scores across all products (tobacco cigarettes (*Mdn*=10), snus (*Mdn*=9), e-cigarettes (*Mdn*=5), NRT (*Mdn*=4) and oral smoking cessation medications (*Mdn*=4)), $p < .01$. Tobacco cigarettes (*Mdn*=10) were perceived to have the greatest health risk, whereas oral smoking cessation products (*Mdn*=4) were considered as having the least health risk. E-cigarettes were considered more harmful in comparison to NRT, but less harmful than either tobacco cigarettes or snus, all $p < .01$. Both oral smoking cessation medications and NRT had the lowest perceived health risk scores with similar medians and distribution of scores among respondents, however NRT (*Mdn*=4, *mean rank* =1.76) was perceived as a slightly less harmful product than oral smoking cessation medications (*Mdn*=4, *mean rank* = 1.91), $p = .002$.



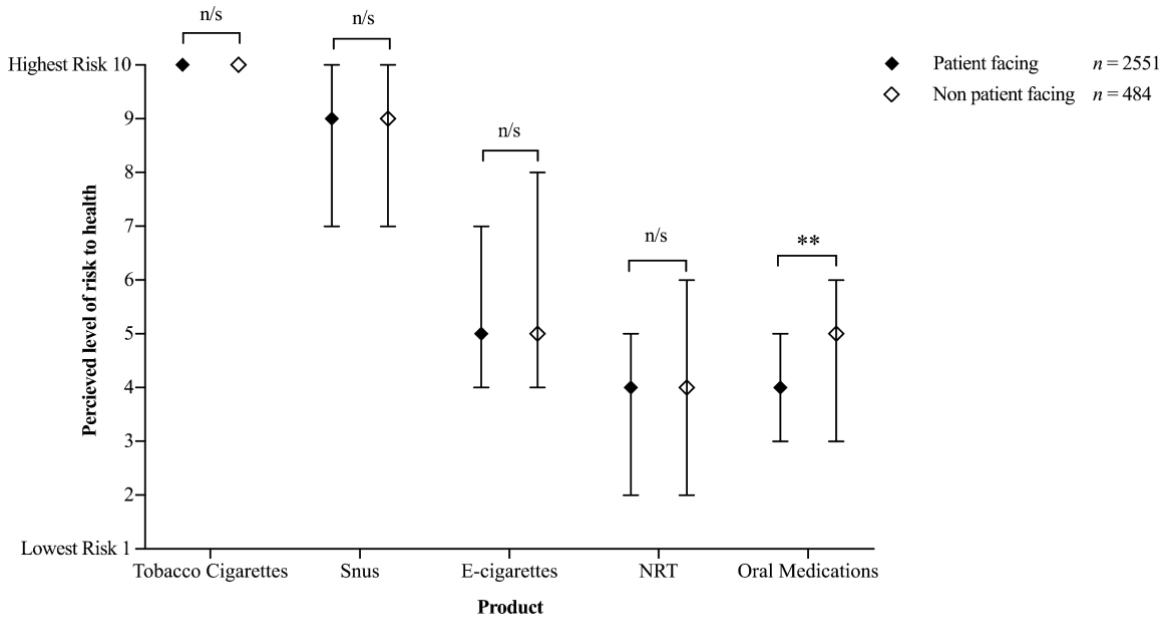
"Based on your knowledge, please score the health risk of each of the following product?"

Figure 3.15 The level of risk to health the survey respondents associated with tobacco cigarettes, suns, e-cigarettes, NRT and oral smoking cessation medications. Data presented as median (25th-75th percentiles). For each product, all 5 pairwise comparisons with a Bonferroni correction were statistically significant, $p < .01$. The median harm scores demonstrated that respondents considered tobacco cigarettes to be most harmful product followed by snus, e-cigarettes, NRT and oral medications.

3.3.2.2.2 Patient facing vs non-patient facing

The observed medians for the health risk scores for tobacco cigarettes, snus, e-cigarette, NRT and oral medications provided by *"patient facing"* and *"non-patient facing"* respondents are presented in Table 3.6. and Figure 3.16.

The health risk scores for tobacco cigarettes, snus, e-cigarettes and NRT were not statistically significantly different between *"patient facing"* and *"non-patient facing"* groups, all $p > .05$. The health risk score for oral medications was statistically significant higher amongst *"non-patient facing"* respondents (*Mdn*=5, *mean rank* = 1627.88) compared to *"patient facing"* respondents (*Mdn*=4, *mean rank* = 1464.24), $U = 668233.5$, $z = 3.111$, $p = .002$, the effect size for this finding was negligible, $r = .05$.



"Based on your knowledge, please score the health risk of each of the following product?"

Figure 3.16 A comparison between the patient facing and non-patient facing respondents' perceived level of harm to health they associate with tobacco cigarettes, snus, e-cigarettes, NRT and oral medications. Data presented as median (25th-75th percentiles). The median harm scores demonstrated that both *"patient facing"* and *"non-patient facing"* respondents considered tobacco cigarettes to be most harmful to health, followed by snus, e-cigarettes, oral medications and NRT. For each product a Mann-Whitney U test demonstrated statistically significant differences between the median harm score between the groups for oral medications, $p < .05$. With the *"non patient facing"* group perceiving oral medications to be more harmful to health in comparison to the respondents who are *"patient facing"*.

3.3.2.2.3 Allied healthcare professionals, doctors and nurses

The observed medians for the health risk scores for tobacco cigarettes, snus, e-cigarette, NRT and oral medications provided by AHPs, doctors and nurses are presented in in Table 3.7 and Figure 3.17.

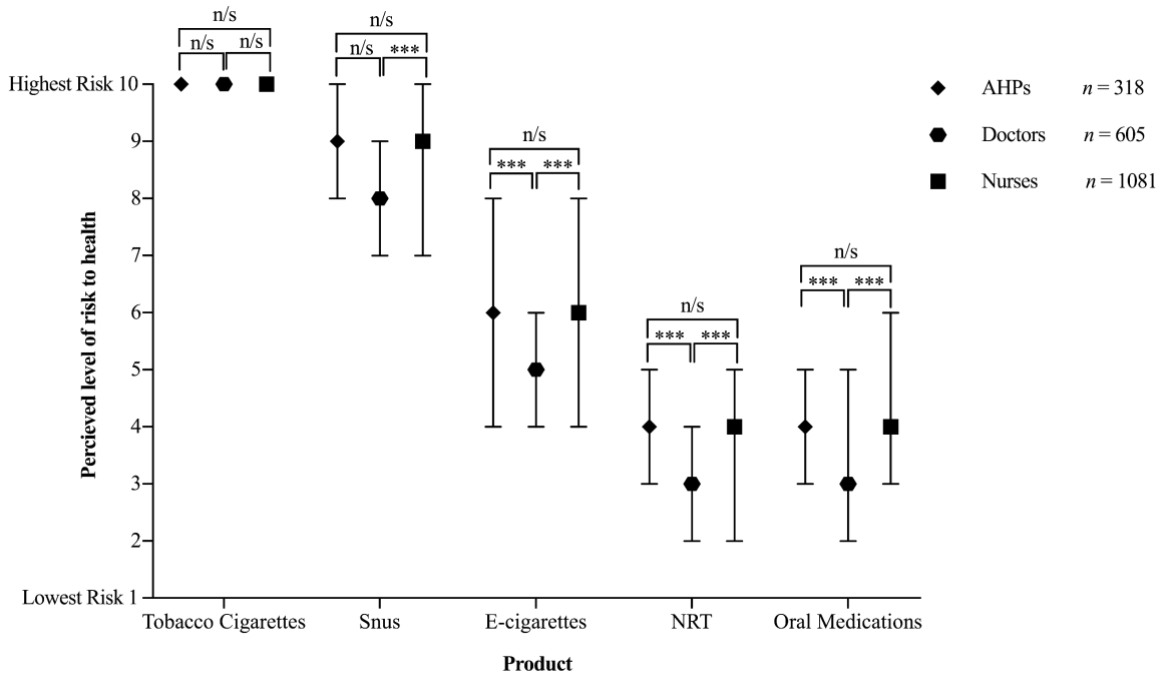
For tobacco cigarettes, the perceived level of harm was the same between AHPs (*Mdn*=10), nurses (*Mdn*=10) and doctors (*Mdn*=10), $p = .310$.

For snus, the perceived level of harm was lowest amongst doctors (*Mdn*=8), as compared to AHP (*Mdn*=9) or nurses (*Mdn*=9). The score from the perceived harm from snus was different across all 3 healthcare professional groups, $\chi^2(2) = 32.370$, $p < .001$, the effect size for this finding was weak, $\varepsilon^2 = .003$. Doctors perceived snus to be less harmful to health (*mean rank* = 891.89), compared to nurses (*mean rank* = 1043.48) or AHPs *(mean rank* = 1056.52), both $p < .017$.

For e-cigarettes, the perceived level of harm was lowest amongst doctors (*Mdn*=5), compared to AHP (*Mdn*=6) or nurses (*Mdn*=6). The perceived level of harm from e-cigarette was different across all 3 healthcare professional groups, $\chi^2(2) = 55.159$, $p < .001$, the effect size for this finding was relatively strong, $\varepsilon^2 = .029$. Doctors perceived e-cigarettes to be less harmful to health (*mean rank* = 858.20), compared to either nurses (*mean rank* = 1058.52) or AHPs (*mean rank* = 1083.63), both $p < .017$.

For NRT, the perceived level of harm was lowest amongst doctors (*Mdn*=3), compared to AHP (*Mdn*=4) or nurses (*Mdn*=4). The perceived level of harm from NRT was different across all 3 healthcare professional groups, $\chi^2(2) = 43.826$, $p < .001$, the effect size for this finding was relatively strong, $\varepsilon^2 = .025$. Doctors perceived NRT to be less harmful to health (*mean rank* = 874.26), compared to either nurses (*mean rank* = 1050.60) or AHPs (*mean rank* = 1079.41), both $p < .017$.

For oral medications, the perceived level of harm was lowest amongst doctors (*Mdn*=3), compared to AHP (*Mdn*=4) or nurses (*Mdn*=4). The perceived level of harm from oral tobacco score was different across all 3 healthcare professional groups, $\chi^2(2) = 73.552$, $p < .001$, the effect size for this finding was strong, $\varepsilon^2 = .039$. Doctors perceived oral medications to be less harmful to health (*mean rank* = 840.74), compared to either nurses (*mean rank* = 1089.29) or AHPs (*mean rank* = 1005.82), both $p < .017$.



"Based on your knowledge, please score the health risk of each of the following product?"

Figure 3.17 A comparison between AHPs', doctors' and nurses' perceived level of harm to health they associate with tobacco cigarettes, snus, e-cigarettes, NRT and oral medications. Data presented as median (25th-75th percentiles). A Kruskal-Wallis test demonstrated that there were statistically significant differences in the median health risk scores across all three healthcare professional groups for the following products: snus, e-cigarettes, NRT and oral medications, all $p < .001$. For each of these products post hoc analysis with a Bonferroni correction demonstrated statistically significant differences in the perceived harm score between the healthcare professional groups.

3.3.2.2.4 Smokers vs never smokers

The observed medians for the perceived health risk scores for tobacco cigarettes, snus, e-cigarettes, NRT and oral medications provided by *"never smokers"* and *"smokers"* are presented in Table 3.8 and Figure 3.18.

The perceived health risk scores for tobacco cigarettes and oral medications were not statistically significantly different between *"never smoker"* and *"smoker"* groups, all $p > .05$. The perceived health risk score for snus (never smokers: *Mdn*=9, *mean rank* =1561.32; smokers: *Mdn*=9, *mean rank* = 1443.05, $U = 1013662.5$, $z = -3.788$, $p < .05$, negligible effect size, $r = -0.07$), NRT (never smokers: *Mdn*=4, *mean rank* = 1617.75; smokers: *Mdn*=3, *mean rank* =1367.00, $U = 921876.0$, $z = -7.808$, $p < .05$, small effect size, $r = -0.14$), and e-cigarettes (never smokers: *Mdn*=6, *mean rank* =1615.76; smokers *Mdn*=5, *mean rank* = 1368.81, $U = 924079.5$, $z = -7.684$, $p < .05$, small effect size, $r = -0.14$) were all statistically significantly higher amongst *"never smoker"* group compared to *"smoker"* group.

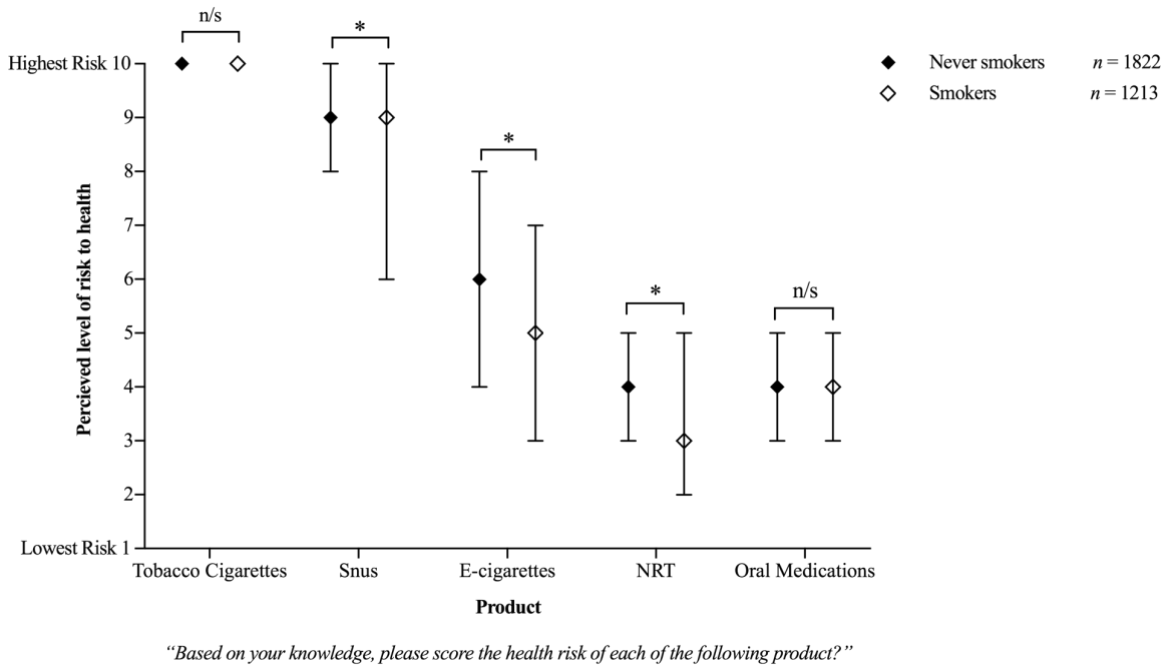


Figure 3.18 A comparison between the smokers' and never smokers' perceived level of harm to health they associate with tobacco cigarettes, snus, e-cigarettes. Data presented as median (25th-75th percentiles). The median harm scores demonstrated that both *"smokers" and "never smokers"* considered tobacco cigarettes to be most harmful to health, followed by snus, e-cigarettes, oral medications and NRT. A Mann-Whitney U test demonstrated statistically significant differences between the median harm score between *"smokers"* and *"never smokers"* for snus, e-cigarettes and NRT, all $p < .05$. With *"never smokers"* perceiving snus, e-cigarettes and NRT to be more harmful to health in comparison to the *"smokers"*.

3.3.2.3 Perceived level of harm associated with the components of tobacco cigarettes

3.3.2.3.1 All respondents

Respondents were asked to score the risk to health they perceived with each of the listed tobacco cigarette components (1=lowest risk to 10=highest risk).

Of the 3035 respondents, 100% gave a risk score for nicotine, 99.9% (*n*=3034) inhaled smoke, 100% (*n*=3035) carbon monoxide, 99.9% (*n*=3034) tar and 99.9% (*n*=3033) for tobacco. The observed medians are presented in Table 3.5.

In total, 99.6% (*n*=3022) of all respondents, gave a risk score for all five components (Figure 3.19). There was a statistically significant difference in distributions across the perceived health risk scores associated with the different components of tobacco cigarettes, $\chi 2(4) = 2796.290$, $p < .001$. There were differences in the perceived health risk scores between all of the tobacco cigarette component category pairings with nicotine perceived as the component with the lowest risk and tar as the component with the highest health risk (nicotine (*Mdn*=8, *mean rank* =2.11), inhaled smoke (*Mdn*=10, *mean rank* = 3.11), carbon monoxide (*Mdn*=10, *mean rank* = 3.4), tar (*Mdn*=10, *Mean rank* = 3.59) and tobacco (*Mdn*=9, *mean rank* =2.79)), all $p < .01$

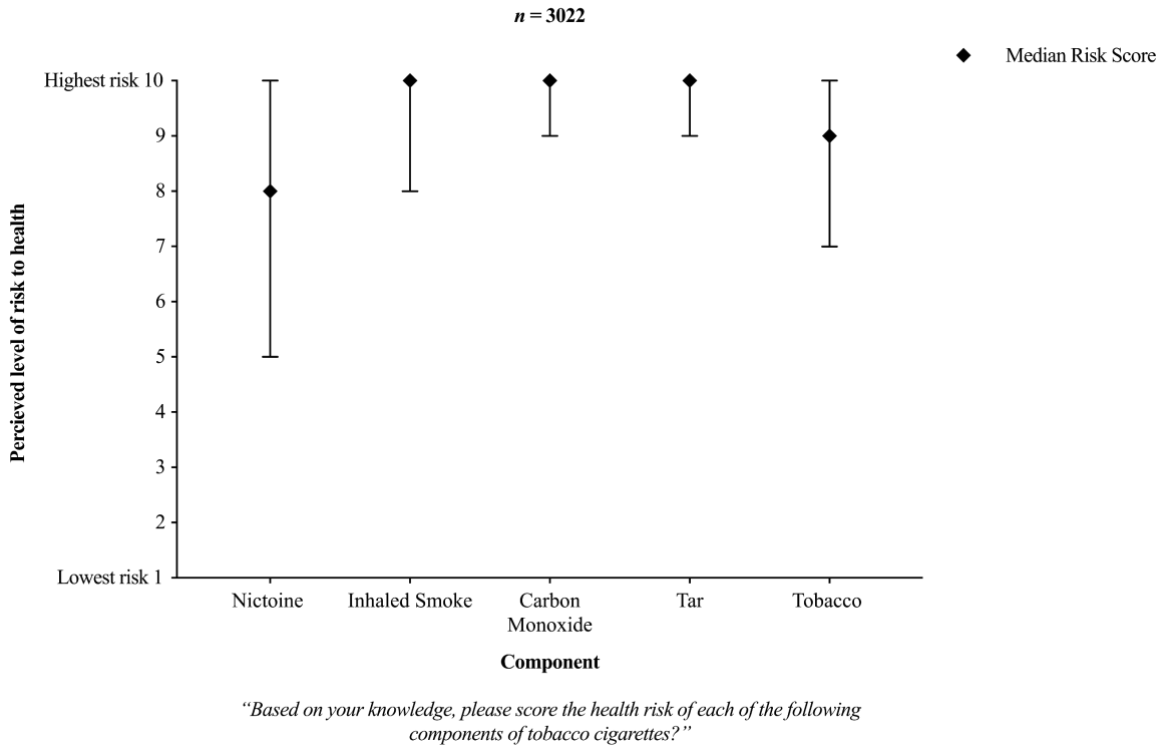


Figure 3.19 The level of risk to health the survey respondents associated with the tobacco cigarette components: nicotine, inhaled smoke, carbon monoxide, tar and tobacco. Data presented as median (25th-75th percentiles). For each of the tobacco cigarette components, all 5 pairwise comparisons with a Bonferroni correction were statistically significant, $p < .01$. The mean rank scores demonstrated that respondents considered tar to be most harmful to health and nicotine to be the least harmful to health.

3.3.2.3.2 Patient facing vs non-patient facing

The observed medians for the health risk scores for nicotine, inhaled smoke, carbon monoxide, tar and tobacco between the *"patient facing"* and *"non-patient facing"* groups are presented in Table 3.6. and Figure 3.20.

The health risk scores for inhaled smoke, tar and tobacco were not statistically significantly different between *"patient facing"* and *"non-patient facing"* groups, all $p > .05$. While the median health risk scores for nicotine and carbon monoxide were similar, the scores were statistically significant different amongst *"patient facing"* and *"non-patient facing"* groups. The *"non-patient facing"* groups perceived nicotine (*Mdn*=8, *mean rank* = 1620.12) to be more harmful than the *"patient facing group"* (*Mdn*=8, *mean rank* = 1498.62), $U = 666770.5$, $z = 2.860$, $p = .004$, the effect size for this finding was negligible, $r = 0.05$. The *"non-patient facing"* group also perceived carbon monoxide (*Mdn*=10, *mean rank* = 1654.18) to be more harmful in comparison to the *"patient facing"* group (*Mdn*=10, *mean rank* = 1492.16), $U = 683253$, $z = 4.455$, $p < .001$, the effect size for this finding was negligible, $r = 0.08$.

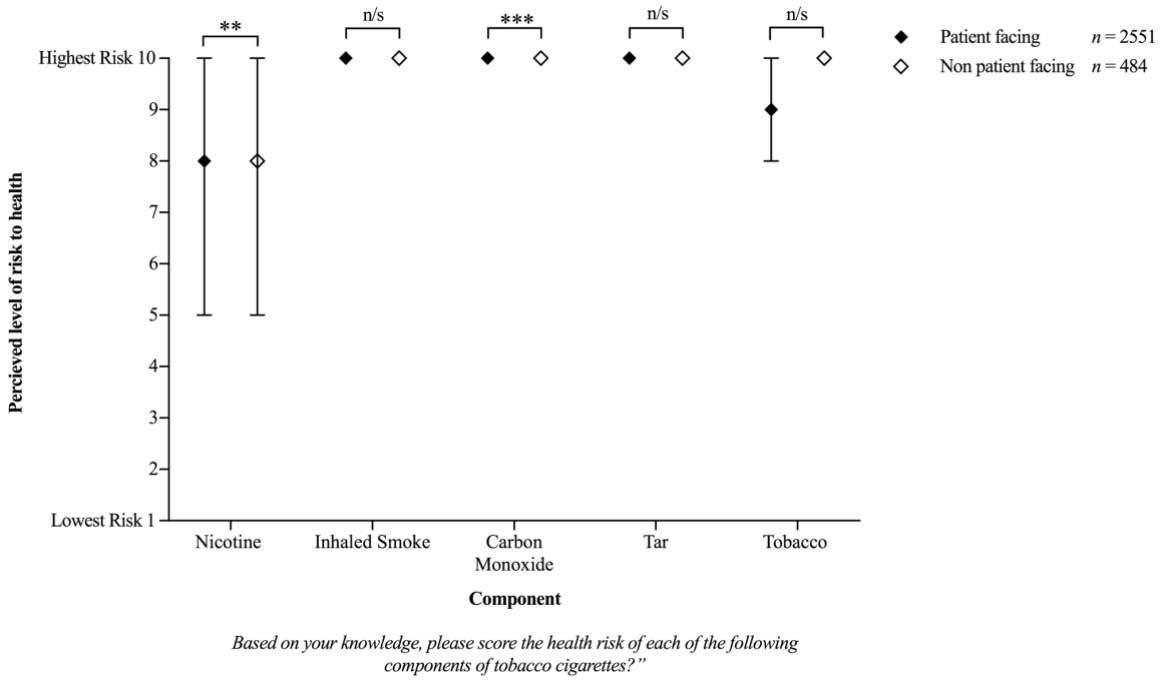


Figure 3.20 A comparison between the patient facing and non-patient facing respondents' perceived level of harm to health they associate with the tobacco cigarette components: nicotine, inhaled smoke, carbon monoxide, tar and tobacco. Data presented as median (25th-75th percentiles). The median harm scores demonstrated that both the *"patient facing"* and *"non-patient facing"* respondents considered nicotine to be the least harmful component of tobacco cigarettes. A Mann-Whitney U test demonstrated statistically significant differences between the median harm score between the *"patient facing"* and *"non-patient facing"* respondents for nicotine and carbon monoxide, both $p < .05$. The *"non-patient facing"* group perceived nicotine and carbon monoxide be more harmful in comparison to the *"patient facing"* group.

3.3.2.3.3 Allied healthcare professionals, doctors and nurses

The observed medians for the health risk scores for nicotine, inhaled smoke, carbon monoxide, tar and tobacco between AHPs, doctors and nurses. are presented in Table 3.7. and Figure 3.21.

The nicotine harm score was different across healthcare professional groups, $\chi^2(2) = 128.140$, $p < .001$, the effect size for this finding was strong, $\varepsilon^2 = .052$. Doctors (*Mdn*=6, *mean rank* = 784.85), perceived nicotine to be less harmful to health in comparison to either nurses (*Mdn*=8 *mean rank* = 1105.28) or AHPs (*Mdn*=8, *mean rank* = 1067.18), $p < .017$.

The inhaled smoke harm score was not statistically significantly different between the doctor (*Mdn*=10), nursing (*Mdn*=10) and AHP (*Mdn*=10) groups, $p = .120$.

The carbon monoxide harm score was statistically significantly different across healthcare professional groups, $\chi^2(2) = 211.551$, $p < .001$, the effect size for this finding was very strong, $\varepsilon^2 = .085$. Doctors perceived carbon monoxide to be less harmful to health (*Mdn*= 9, *mean rank* = 755.29), in comparison to either nurses (*Mdn*=10, *mean rank* = 1116.61) or AHPs (*Mdn*=10, *mean rank* = 1084.93), both $p < .017$.

The tar harm score was statistically significantly different across healthcare professional groups, $\chi^2(2) = 25.284$, $p < .001$, the effect size for this finding was moderate, $\varepsilon^2 = .009$. Nurses perceived tar to be more harmful to health (*Mdn*=10, *mean rank* = 1050.25), in comparison to either doctors (*Mdn*=10, *mean rank* = 949.32), or AHPs (*Mdn*=10, *mean rank* = 938.04), both $p < .017$.

The tobacco harm score was statistically significantly different across healthcare professional groups,$\chi^2(2) = 37.952$, $p < .001$, the effect size for this finding was moderate, $\varepsilon^2 = .008$. Nurses perceived tobacco to be more harmful to health (*Mdn*=10, *mean rank* = 1070.30), in comparison to doctors (*Mdn*=9, *mean rank* = 907.86), *(p* <.001) and AHPs (*Mdn*=9, *mean rank* = 945.70), both $p < .017$.

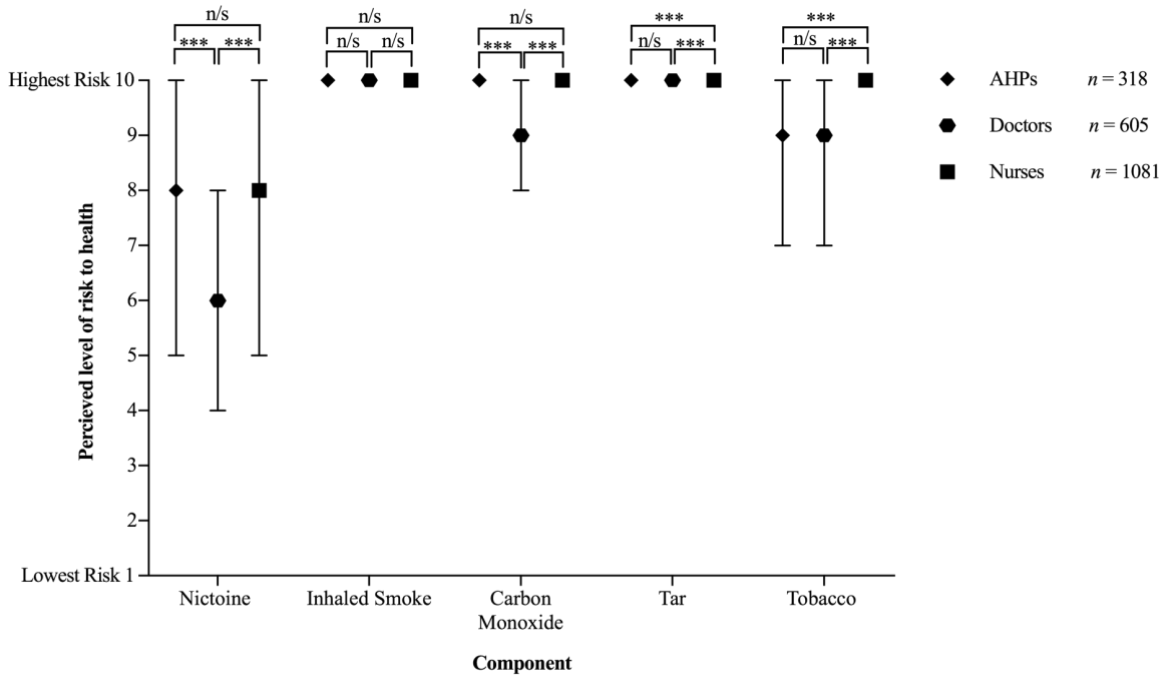


Figure 3.21 A comparison between AHPs', doctors' and nurses' perceived level of harm to health they associate with the tobacco cigarette components: nicotine, inhaled smoke, carbon monoxide, tar and tobacco. Data presented as median (25th-75th percentiles). A Kruskal-Wallis test demonstrated that there were statistically significant differences in the median health risk scores across all three healthcare professional groups for the following tobacco cigarette components: nicotine, carbon monoxide, tar and tobacco, all $p < .001$. For each of these components the post hoc analysis with a Bonferroni correction demonstrated statistically significant differences in the harm score between the three groups of healthcare professionals.

3.3.2.3.4 Smokers vs never-smokers

The observed medians for the health risk scores for nicotine, inhaled smoke, carbon monoxide, tar and tobacco between *"never smokers"* and *"smokers"* are presented in Table 3.8. and Figure 3.22.

The health risk scores for inhaled smoke and tobacco were not statistically significantly different between the *"never smoker"* and *"smoker"* groups, all $p > .05$. The health risk score for nicotine was statistically significant higher amongst *"never smoker"* group *(Mdn*=8, *mean rank* =1595.96) compared to *"smoker"* group (*Mdn*=7, *mean rank* = 1400.91), $U = 963007$, $z = -6.143$, $p < .05$, the effect size for this finding was small $r = -0.11$. Whereas, the health risk for carbon monoxide (never smokers: *Mdn*=10, *mean rank* = 1455.47, versus smokers: *Mdn*=10, *mean rank* =1611.92) and tar (never smokers: *Mdn*=10, *mean rank* =1494.54, versus smokers: *Mdn*=10, *mean rank* =1551.97) was statistically significantly lower amongst the *"never smokers"* in comparison to *"smoker"* group both, $p < .05$. The effect size for carbon monoxide was small, $r = 0.10$ and the effect size for tar was negligible, $r = 0.04$.

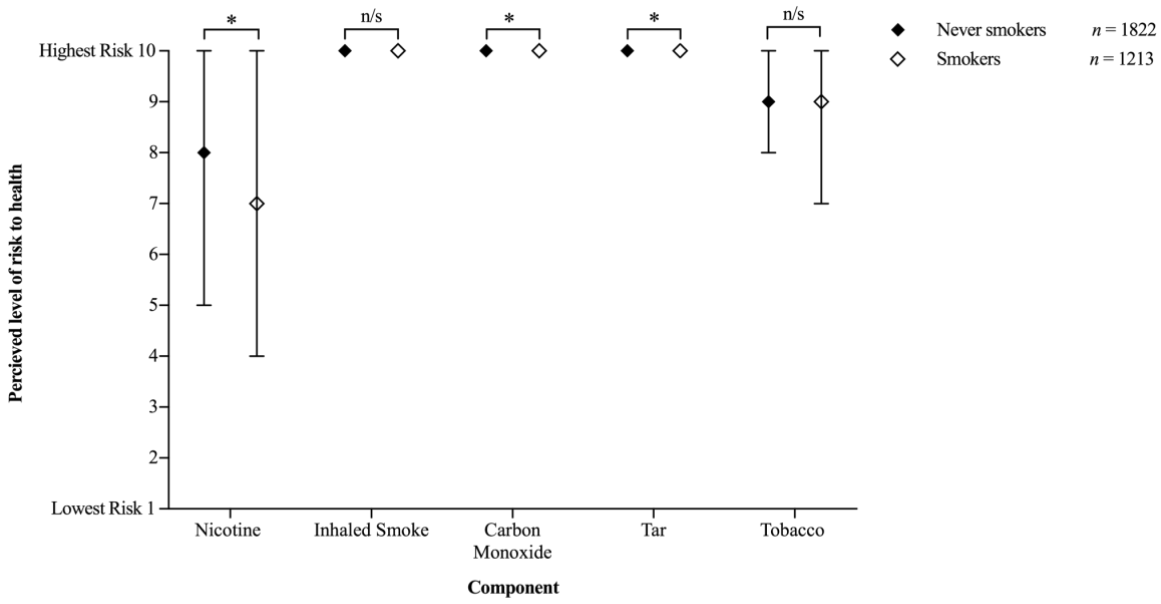


Figure 3.22 A comparison between the smokers' and never smokers' perceived level of harm to health they associate with the tobacco cigarette components: nicotine, inhaled smoke, carbon monoxide, tar and tobacco. Data presented as median (25th-75th percentiles). The median harm scores demonstrated that both *"never smokers"* and *"smokers"* considered nicotine to be the least harmful component of tobacco cigarettes. For each component a Mann-Whitney U test demonstrated statistically significant differences between the median harm score between *"never smokers"* and *"smokers"* for nicotine, carbon monoxide and tar, all $p < .05$. *"Never smokers"* perceived nicotine to be more harmful in comparison to *"smokers"*. Whereas *"smokers"* considered carbon monoxide and tar to be more harmful to health compared to *"never smokers"*.

3.3.2.4 Perceived level of addiction associated with tobacco cigarettes, e-cigarettes and nicotine replacement therapies

3.3.2.4.1 All respondents

Respondents were asked to score how addictive they considered tobacco cigarettes, NRT and e-cigarettes (1=not addictive to 10=highly addictive) to be. The observed medians from all respondents are presented in Table 3.5.

In total 99.9% (n=3034) of all respondents, gave an addictiveness score for all three products (Figure 3.23). The perceived addictiveness score had different distributions for the different products, $\chi 2(2) = 4016.842$, $p < .001$. Statistically significant differences were demonstrated in the perceived addictiveness score between all three products. Tobacco cigarettes (*Mdn*=10), were perceived as the most addictive product, followed by e-cigarettes (*Mdn*=8), and then NRT (*Mdn*=6), $p < .017$.

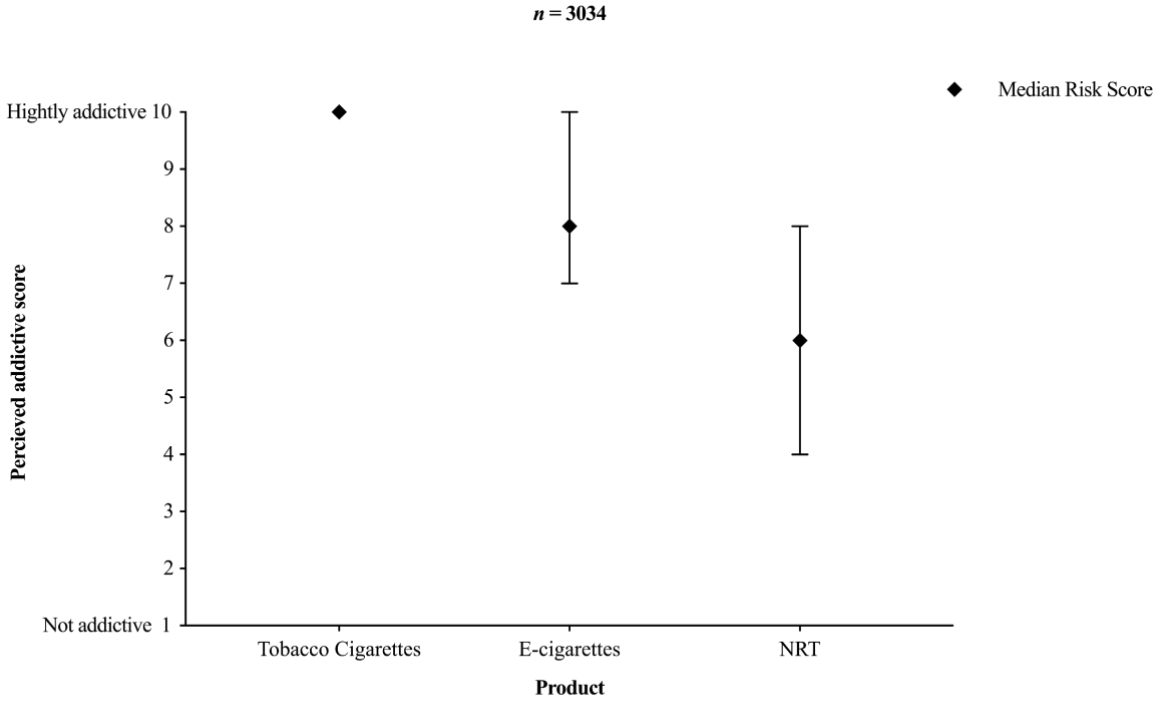
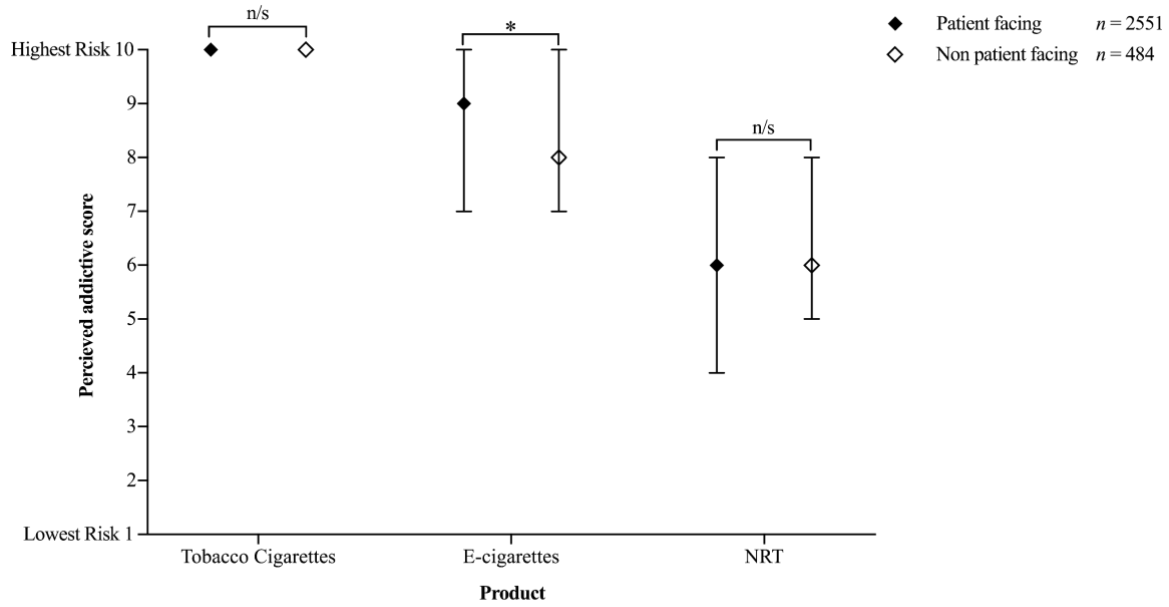


Figure 3.23 The level addictiveness for tobacco cigarettes, e-cigarettes and NRT perceived by survey respondents. Data presented as median (25th-75th percentiles). For each product, all 3 pairwise comparisons with a Bonferroni correction were statistically significant, $p < .017$. E-cigarettes were perceived as less addictive than tobacco cigarettes but more addictive than NRT.

3.3.2.4.2 Patient facing vs non-patient facing

The observed medians for the addictive scores for tobacco cigarettes, NRT and e-cigarettes between the *"patient facing"* and *"non-patient facing"* groups are presented in Table 3.6. and Figure 3.24.

Between the *"patient facing"* and *"non-patient facing"* groups, median addictive scores for tobacco cigarettes (*Mdn*=10) and NRT (*Mdn*=6) were not statistically significantly different, both $p > .05$. For e-cigarettes, the median additive score for *"patient facing"* groups (*Mdn*=9), was statistically significantly higher compared to *"non-patient facing"* group (*Mdn*=8), $U = 580670.5$, $z = -2.126$, $p = .033$, the effect size for this finding was negligible, $r = -0.04$.



"How addictive do you consider the following products?"

Figure 3.24 A comparison between the patient facing and non-patient facing respondents' perceived level of addiction they associate with tobacco cigarettes, e-cigarettes and NRT. Data presented as median (25th-75th percentiles). The median addictive scores demonstrated that both the *"patient facing"* and *"non-patient facing"* groups considered tobacco cigarettes to be the most addictive product, followed by e-cigarettes and NRT. A Mann-Whitney U test demonstrated statistically significant differences between the median addictive score between the *"non-patient facing"* groups for e-cigarettes, $p = .033$. The *"patient facing"* group perceived e-cigarettes to be more addictive compared to the *"non-patient facing"* group.

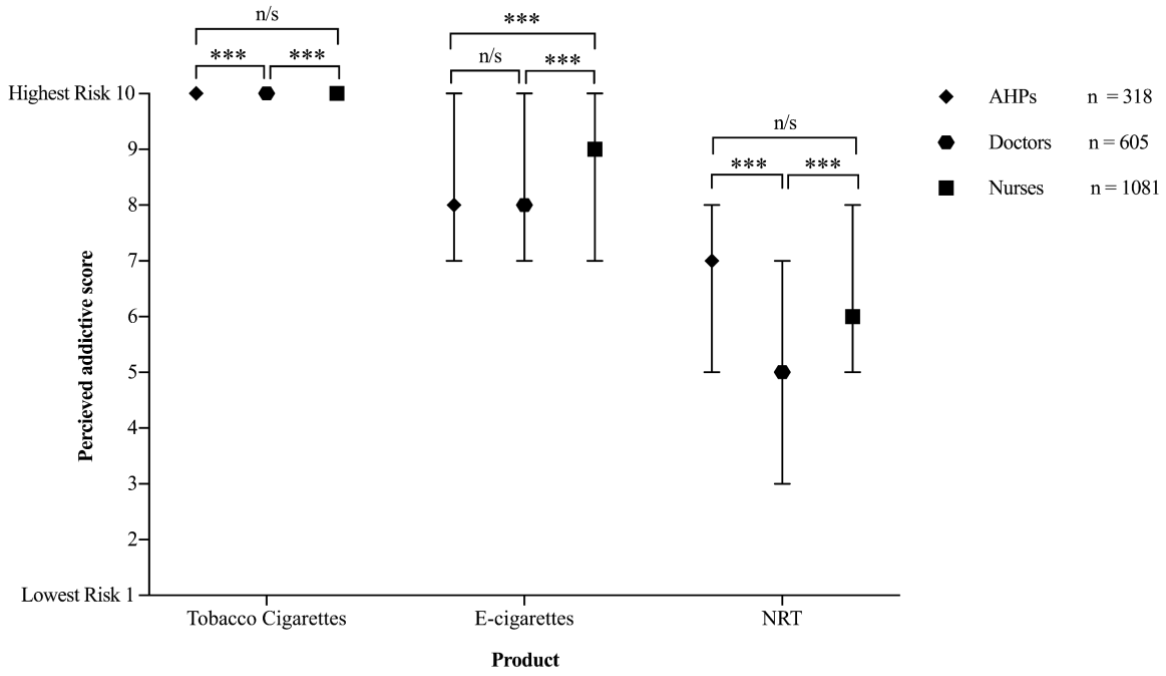
3.3.2.4.3 Allied healthcare professionals, doctors and nurses

The observed medians for the addictive scores for tobacco cigarettes, NRT and e-cigarettes between AHPs, doctors and nurses are presented in Table 3.7 and Figure 3.25.

For tobacco cigarettes although the median addictiveness score was the same across the 3 groups, (*Mdn*=10), there was a notable difference in distributions resulting in a significant difference between the mean rank scores for all 3 healthcare professional groups $\chi^2(2) = 32.575$, $p < .001$, the effect size for this finding was moderate, $\varepsilon^2 = .009$. Overall, doctors considered tobacco cigarettes to be less addictive (*mean rank* = 925.42) in comparison to either AHPs (*mean rank* =1011.06) or nurses (*mean rank* =1043.12), both $p < .017$.

For NRT the median addictiveness score was different across all groups; AHPs (*Mdn*=7); nurses (*Mdn*=6); and doctors (*Mdn*=5), $\chi^2(2) = 73.636$, $p < .001$, the effect size for this finding was strong, $\varepsilon^2 = .037$. Doctors considered NRT to be less addictive (*mean rank* =836.89) in comparison to either AHPs (*mean rank* =1109.36) or nurses (*mean rank* =1063.75), both $p < .017$.

For e-cigarettes the median addictiveness score was greater amongst nurses (*Mdn*=9) in comparison to AHPs (*Mdn*=8) or doctors (*Mdn*=8). There was a notable difference in distribution for each group resulting in a difference between the mean rank scores, $\chi^2(2) = 16.323$, $p < .001$, the effect size for this finding was weak, $\varepsilon^2 = .003$ In comparison to nurses (*mean rank* =1048.53), both AHPs (*mean rank* =937.80) and doctors (*mean rank* =952.53) considered e-cigarettes to be less addictive, both $p < .017$.



"How addictive do you consider the following products?"

Figure 3.25 A comparison between AHPs', doctors' and nurses' perceived level of addiction they associate with tobacco cigarettes, e-cigarettes and NRT. Data presented as median (25th-75th percentiles). A Kruskal-Wallis test demonstrated that there were statistically significant differences in the median addictiveness scores across all three products, $p < .001$. For all 3 products, the post hoc analysis with a Bonferroni correction, demonstrated statistically significant differences in the pairwise comparisons addictive scores between the healthcare professional groups.

3.3.2.4.4 Smokers vs never-smokers

The observed medians for the addictive scores for tobacco cigarettes, NRT and e-cigarettes between the *"never smokers"* and *"smokers"* groups are presented in Table 3.8. and Figure 3.26.

There was no difference in the addictive score given to tobacco cigarettes (*Mdn*=10) between the *"never smokers"* and *" smokers"* groups, $p = .565$. Whereas, the additive scores for NRT (never smokers: *Mdn*=6, *mean rank* = 1573.40, versus smokers: *Mdn*=6, *mean rank* = 1433.58, $U = 1002646$, $z = -4.340$, $p < .001$, negligible effect size, $r = -0.07$.) and e-cigarettes (never smokers: *Mdn*=9, *mean rank* = 1567.44, versus smokers: *Mdn*=8, *mean rank* = 1422.53, $U = 1013493$, $z = -3.967$, $p < .001$, negligible effect size, $r = -0.08$.) were statistically significantly higher amongst *"never smoker"* group compared to *"smoker"* group, both $p < .001$.

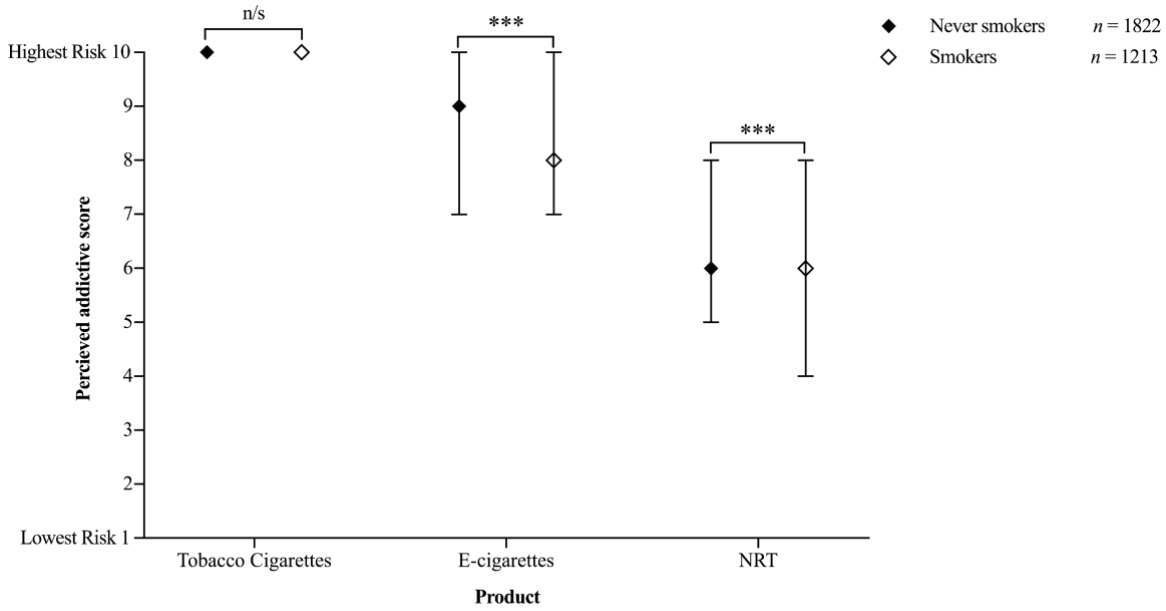


Figure 3.26 A comparison between the smokers' and never smokers' perceived level of addiction they associate with tobacco cigarettes, e-cigarettes and NRT. Data presented as median (25th-75th percentiles). The median addictive scores demonstrated that both *"smokers"* and *"never smokers"* considered tobacco cigarettes to be the most addictive product, followed by e-cigarettes and NRT. A Mann-Whitney U test demonstrated statistically significant differences between the median addictive score between *"smokers"* and *"never smokers"* for e-cigarettes and NRT, both $p < .001$. For both e-cigarettes and NRT the perceived level of addiction was greatest amongst the *"never smokers"* compared to the *"smokers"*.

3.3.2.5 Perceived level of harms from e-cigarettes and nicotine replacement patches compared to tobacco cigarettes

3.3.2.5.1 All respondents

Respondents were asked to rank how harmful to health they considered nicotine replacement patches and e-cigarettes to be in comparison to tobacco cigarettes. In total, 100% (n=3035) of respondents answered both parts of the question. The observed frequencies and percentages are presented in Table 3.5 and Figure 3.27.

In comparison to tobacco cigarettes, 88.8% (*n*=2695) of respondents considered nicotine replacement patches to be *"less harmful"*, 7.1% (*n*=216) *"equally harmful",* 0.3% (*n*=10) *"more harmful"* and 3.8% (*n*=114) responded as *"don't know"*.

In relation to the harm perceived from e-cigarettes in comparison to tobacco cigarettes, 67.4% (*n*=2047) of respondents considered e-cigarettes to be *"less harmful"*, 19.5% (*n*=592) "*equally harmful"*, 1.5% (*n*=45) *"more harmful"* and 11.6% (*n*=351) responded as *"don't know"*.

Out of the 3035 respondents, 86.9% (*n*=2638) provided a *"less harmful"*, *"equally harmful"* or *"more harmful"* response to both questions. Although the majority of respondents perceived both e-cigarettes and nicotine replacement patches to be less harmful than tobacco cigarettes, nicotine replacement patches were perceived to be less harmful product than e-cigarettes, $z = -18.271$, $p < .001$, with 17% (*n*=459) viewing nicotine replacement patches to be relatively less harmful than e-cigarettes.

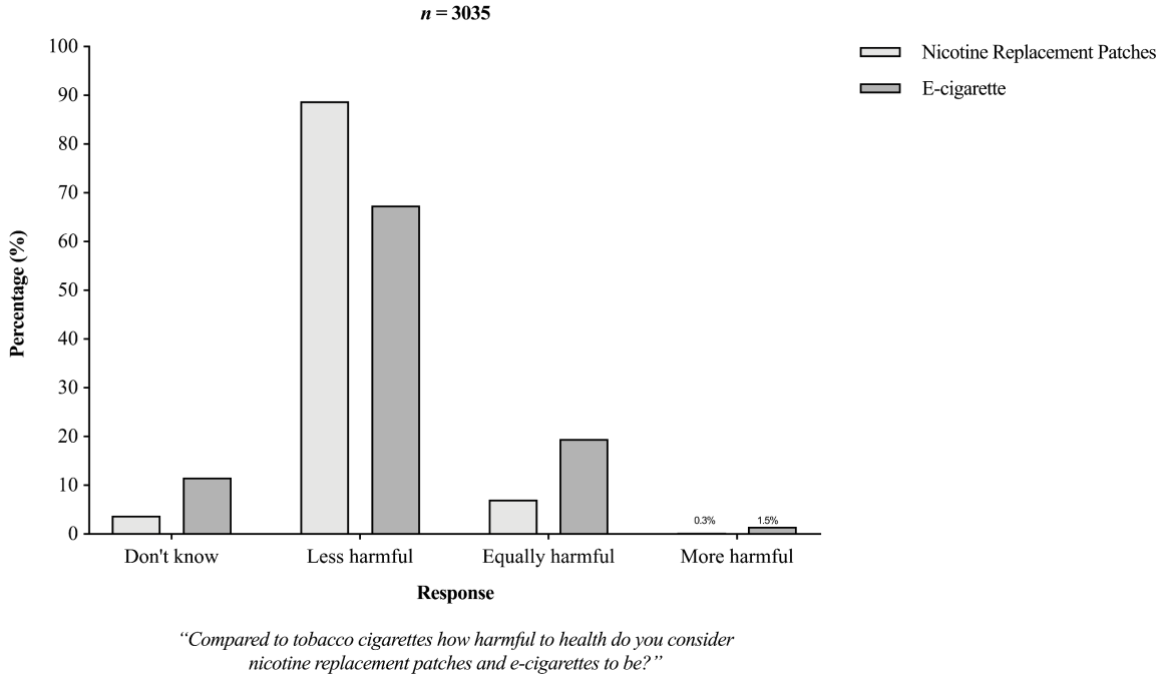


Figure 3.27 Healthcare professional respondents' perception of how harmful to health they perceive nicotine replacement patches and e-cigarettes to be, when compared to tobacco cigarettes. Data presented as percentage. The median level of agreement was that nicotine replacement patches and e-cigarettes are *"less harmful"* in comparison to tobacco cigarettes.

3.3.2.5.2 Patient facing vs non-patient facing

In response to the question *"in comparison to tobacco cigarettes how harmful to health, do you consider nicotine replacement patches and e-cigarettes to be?",* the observed frequencies and percentages for the *"patient facing"* and *"non-patient facing"* group responses are presented in Table 3.6 and Figures 3.28 and 3.29.

Overall the *"patient facing"* and *"non-patient facing"* groups perceived both e-cigarettes and nicotine replacement patches to be *"less harmful"* than tobacco cigarettes. For each product the responses from both groups had similar distributions $p < .05$.

For nicotine replacement patches no significant difference in the median level of harm was demonstrated between the *"patient facing"* and *"non-patient facing"* groups, $p = .852$. In contrast the *"non-patient facing"* group tended to perceived e-cigarettes as more harmful (*mean rank* = 1580.41) than the *"patient facing"* group (*mean rank* = 1506.16) $U = 647500.5$, $z = 2.066$, $p = .039$, the effect size for this finding was negligible, $r = .04$.

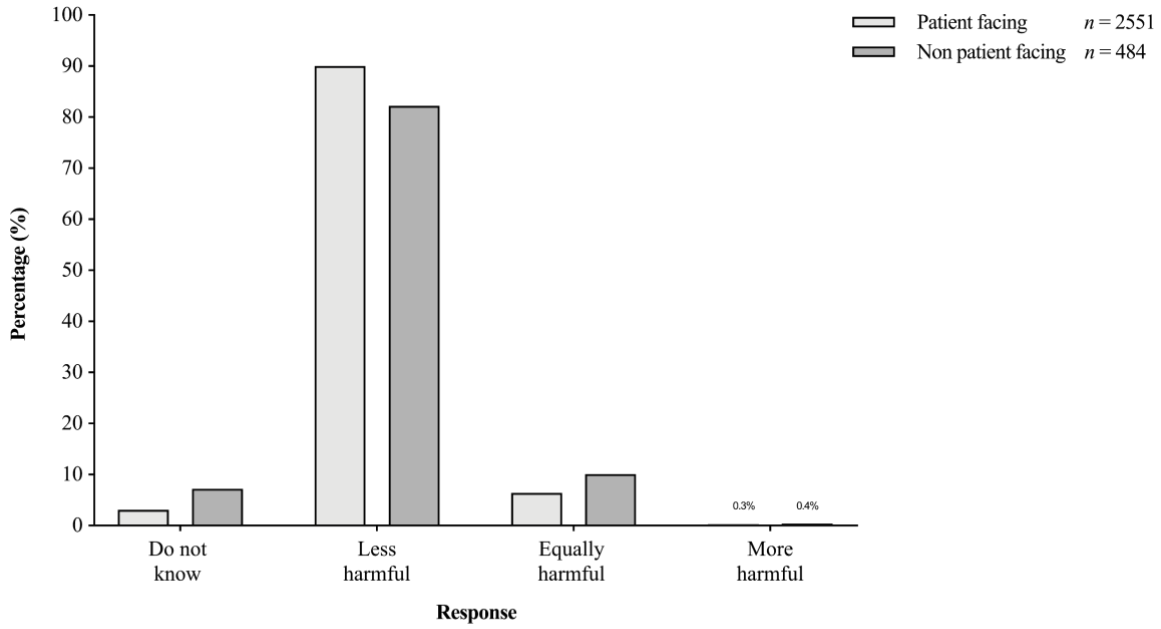


Figure 3.28 A comparison between the patient facing and non-patient facing respondents' perception of how harmful to health they consider nicotine replacement patches to be in comparison to tobacco cigarettes. Data presented as percentage. The median level of agreement was that nicotine replacement patches are *"less harmful"* in comparison to tobacco cigarettes amongst the *"patient facing"* and *"non-patient facing"* groups. A Mann-Whitney U test did not demonstrate any statistically significant differences between the median level of agreement between the *"patient facing"* and *"non-patient facing"* groups, $p = .852$.

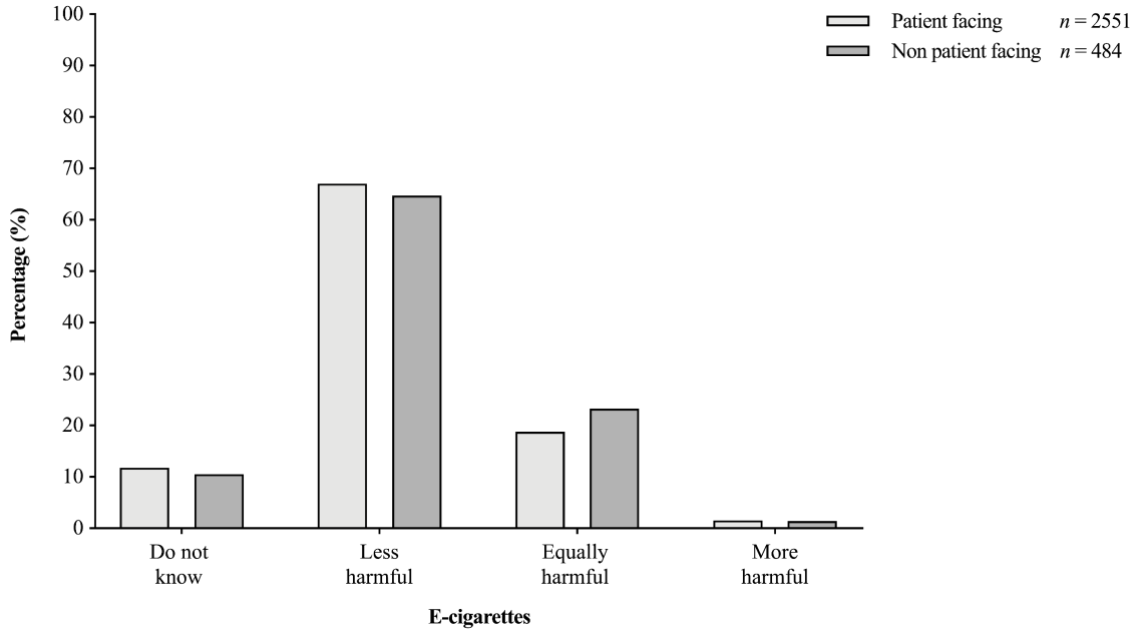


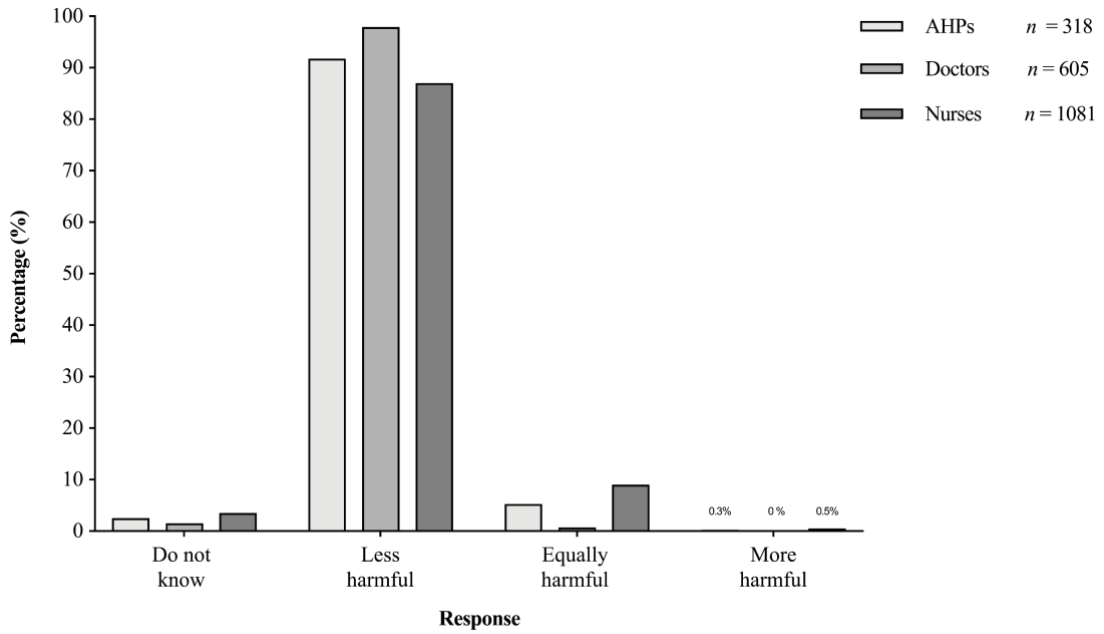
Figure 3.29 A comparison between the patient facing and non-patient facing respondents' perception of how harmful to health they consider e-cigarettes to be in comparison to tobacco cigarettes. Data presented as percentage. The median level of agreement was that e-cigarettes are *"less harmful"* in comparison to tobacco cigarettes amongst both the *"patient facing"* and *"non-patient facing"* groups. A Mann-Whitney U test demonstrated that there were statistically significant differences between the median level of agreement between the *"patient facing"* and *"non-patient facing"* groups, $p = .039$. With the *"non-patient facing"* group (*mean rank* = 1580.41) perceiving the harm from e-cigarettes to be greater compared to the *"patient facing" group* (*mean rank* = 1506.16).

3.3.2.5.3 Allied healthcare professionals, doctors and nurses

In responses to the question *"in comparison to tobacco cigarettes how harmful to health, do you consider nicotine replacement patches and e-cigarettes to be?"*, the observed frequencies and percentages of responses from healthcare professionals groups compromising of AHPs, doctors and nurses are presented in Table 3.7 and Figures 3.30 and 3.31.

The median agreement score for both nicotine replacement patches and e-cigarettes was *"less harmful"* for all three healthcare professional groups. However, there were notable differences in the distributions of the agreement scores between the different healthcare professional groups for both nicotine replacement patches, $\chi^2(2) = 20.975$, $p < .001$, the effect size for this finding was relatively strong, $\varepsilon^2 = .010$ and e-cigarettes $\chi^2(2) = 31.685$, $p < .001$, the effect size for this finding was moderate, $\varepsilon^2 = .015$

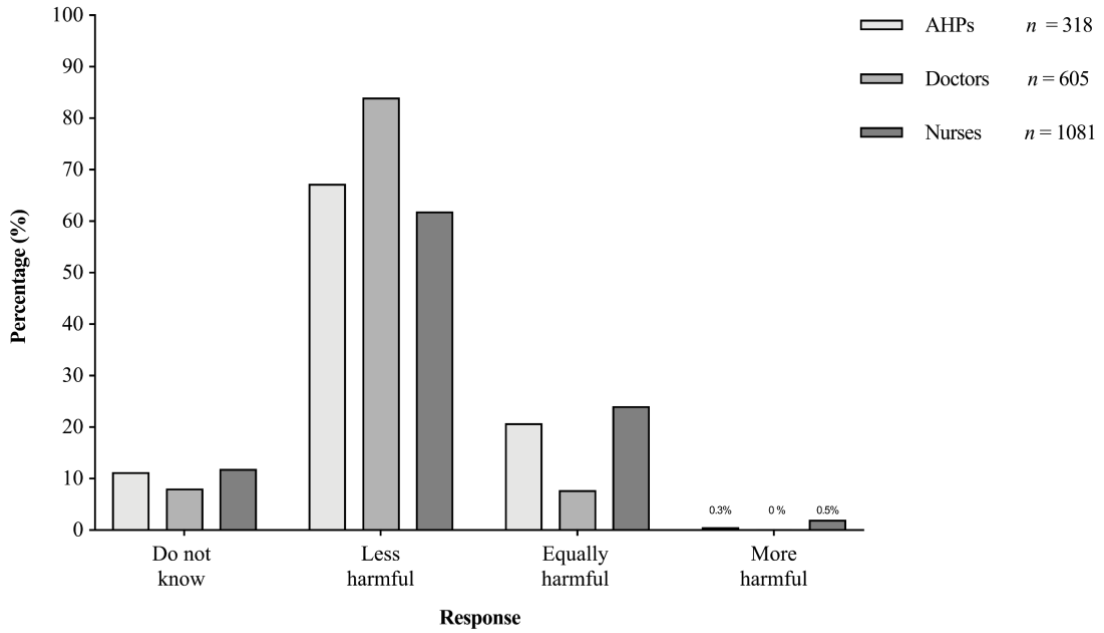
For nicotine replacement patches, overall doctors perceived nicotine replacement patches to be less harmful (*mean rank* = 960.44) in comparison to either AHPs (*mean rank* = 999.54) and nurses (*mean rank* = 1026.91), $p < .017$. Whereas for e-cigarettes, doctors considered e-cigarettes to be less harmful (*mean rank* = 915.35), in comparison to either AHPs (*mean rank* = 1009.12, $p = 0.12$) or nurses (*mean rank* = 1049.33, $p < .017$).



"In comparsion to tobacco cigarettes how harmful to health do you consider nictone replacement patches to be?"

Figure 3.30 A comparison between AHPs', doctors' and nurses' perception of how harmful to health they consider nicotine replacement patches to be in comparison to tobacco cigarettes. Data presented as percentage. A Kruskal-Wallis test demonstrated that there were statistically significant differences in the median agreement scores across all three groups, $p < .001$. For nicotine replacement patches, the post hoc analysis with a Bonferroni correction demonstrated statistically significant differences in median response of less harmful between doctors and nurses, $p < .017$. With doctors (*mean rank* = 960.44) perceiving nicotine replacement patches to be less

harmful in comparison to tobacco cigarettes compared to AHPs (*mean rank* = 999.54) and nurses (*mean rank* = 1026.91).



"In comparsion to tobacco cigarettes how harmful to health do you consider e-cigarettes to be?"

Figure 3.31 A comparison between AHPs', doctors' and nurses' perception of how harmful to health they consider e-cigarettes to be in comparison to tobacco cigarettes. Data presented as percentage. A Kruskal-Wallis test demonstrated that there were statistically significant differences in the median agreement scores across all three groups, $p < .001$. For e-cigarettes, the post hoc analysis with a Bonferroni correction demonstrated statistically significant differences in the pairwise comparisons differences in the median response of less harmful between doctors and both AHPs and nurses, both $p < .017$, with doctors (*mean rank* = 915.35) perceiving e-cigarettes to be less harmful in comparison tobacco cigarettes compared to AHPs (*mean rank* = 1009.12) and nurses (*mean rank* = 1049.33).

3.3.2.5.4 Smokers vs never-smokers

In response to the question *"in comparison to tobacco cigarettes how harmful to health, do you consider nicotine replacement patches and e-cigarettes to be?"*, the observed frequencies and percentages for the *"smoker"* and *"never smoker "* group responses are presented in Table 3.8 and Figures 3.32 and 3.33.

Overall the *"smoker"* and *"never smoker"* groups perceived both e-cigarettes and nicotine replacement patches to be *"less harmful"* than tobacco cigarettes. For each product the responses from both groups had similar distributions $p < .05$.

For nicotine replacement patches no significant difference in the median level of harm was demonstrated between the *"smokers"* and *"never smoker"* groups, $p = .309$. However, the *"never smoker"* group tended to perceived e-cigarettes as more harmful (*mean rank* = 1542.49) than the *"smoker"* group (*mean rank* = 1481.22), $U = 1060429.5$, $z = -2.281$, $p = .023$, the effect size for this finding was negligible, $r = -0.04$.

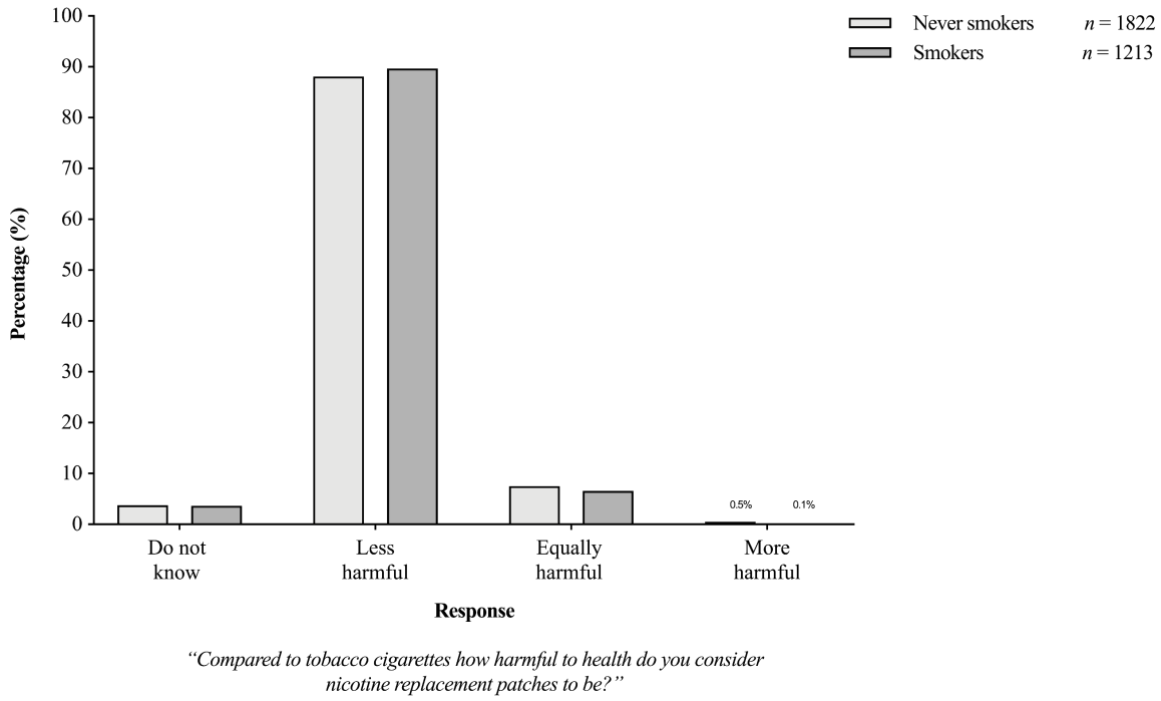
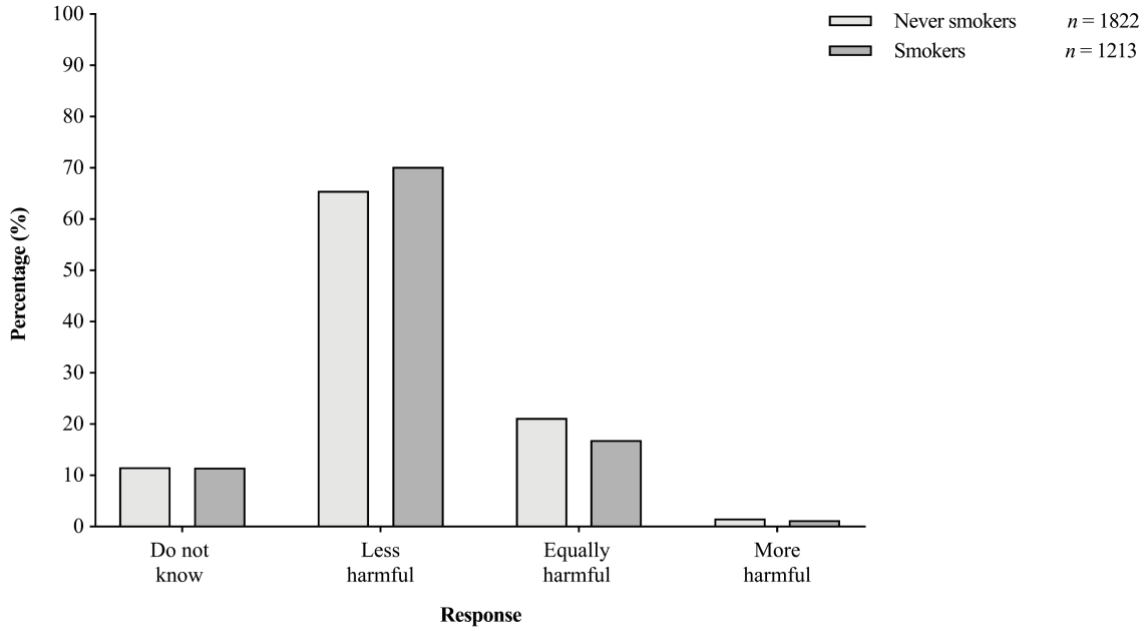


Figure 3.32 A comparison between the smokers' and never smokers' perception of how harmful to health they consider nicotine replacement patches to be in comparison to tobacco cigarettes. Data presented as percentage. The median level of agreement that nicotine replacement patches are *"less harmful"* in comparison to tobacco cigarettes amongst *"smokers"* and *"never smokers"*. A Mann-Whitney U test did not demonstrate any statistically significant differences between the median level of agreement between *"smokers"* and *"never smokers"*, $p = .309$.



"Compared to tobacco cigarettes how harmful to health do you consider e-cigarettes to be?"

Figure 3.33 A comparison between the smokers' and never smokers' perception of how harmful to health they consider e-cigarettes to be in comparison to tobacco cigarettes. Data presented as percentage. The median level of agreement was that e-cigarettes are *"less harmful"* in comparisons to tobacco cigarettes amongst both *"smokers"* and *"never smokers"*. A Mann-Whitney U test demonstrated that there were statistically significant differences between the median level of agreement between *"smokers"* and *"never smokers"*, $p = .023$, with the *"never smokers"* (*mean rank* = 1542.49) perceiving the harm from e-cigarettes to be greater in comparison to the *"smokers"* (*mean rank* = 1481.22).

3.3.3 Attitudes towards e-cigarettes acting as a gateway to tobacco smoking

3.3.3.1 Concern that e-cigarettes may act as gateway to tobacco smoking

3.3.3.1.1 All respondents

Respondents were asked to score how concerned they were that e-cigarettes may encourage non-smokers to take up tobacco smoking (1=no concern to 10=very concerned) for each of the following age groups: Adults >19 years, adolescents 10-19 years, children <10 years. In total 100%, (*n*=3035) of respondents answered the question. The observed medians for each group are presented in Table 3.9 and Figure 3.34.

A notable difference in the distributions in the concern score for each age groups was observed $\chi^2(2) = 1070.239$, $p < .001$. Respondents were most concerned that e-cigarettes may encourage non-smoking adolescents to take up tobacco smoking (*Mdn*=8, *mean rank* = 2.37), in comparison to either non-smoking adults (*Mdn*=5, *mean rank* = 1.76) or non-smoking children (*Mdn*=5, *mean rank* = 1.86), all $p < .017$.

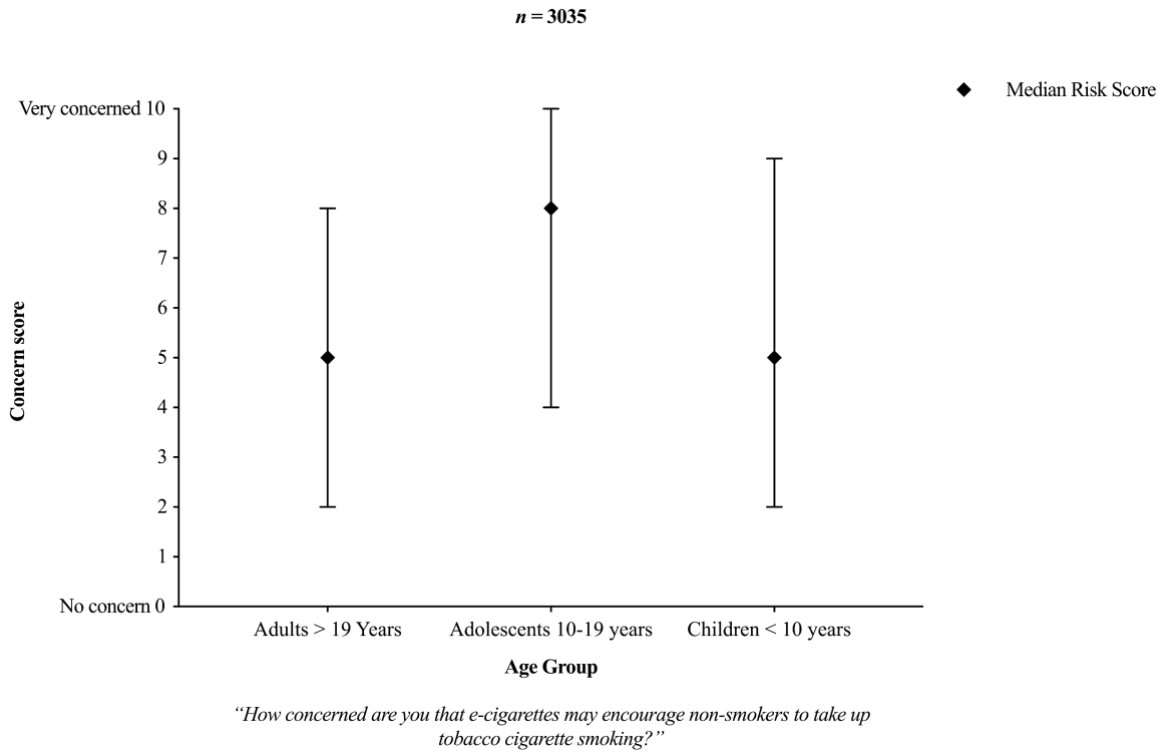


Figure 3.34 Healthcare professional respondents' level of concern that e-cigarettes may act as a gateway to tobacco smoking amongst non-smoking: adults, adolescents and children. Data presented as median (25^{th}-75^{th} percentiles).

Table 3.9 Level of concern that e-cigarettes may act as a gateway to tobacco smoking

Survey responses	All Responses
Concern that e-cigarettes may act as a gateway to tobacco smoking in never smokers	
Adults > 19 years	5 (2;8)
Adolescents 10-19 years	8 (4;10)
Children <10 years	5 (2;9)

Data are presented as frequency (percentage) and median (25^{th}-75^{th} percentiles).

3.3.3.1.2 Patient facing vs non-patient facing

The observed median concern scores that e-cigarettes may encourage non-smokers to take up tobacco smoking between the *"patient facing"* and *"non-patient facing"* groups are presented in Table 3.10. and Figure 3.35.

Out of all of the age groups, both the *"patient facing"* and *"non-patient facing"* groups were most concerned that e-cigarettes may encourage non-smoking adolescents to take up tobacco smoking. However, the median level of concern was greater amongst the *"patient facing"* group (*Mdn* =8) in comparison to the *"non-patient facing"* (*Mdn*=7), *U*=629892.0, *z* =-2.102, *p* =.036, the effect size for this finding was negligible, *r* = -0.04.

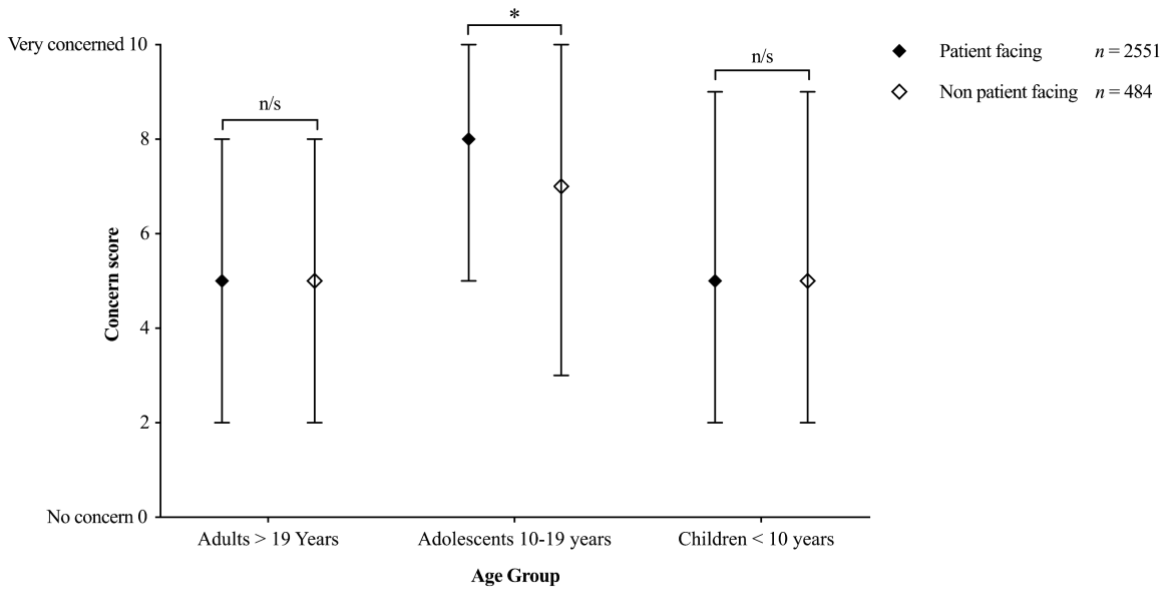


Figure 3.35 A comparison between the patient facing and non-patient facing respondents' level of concern that e-cigarettes may act as a gateway to tobacco smoking amongst non-smoking: adults, adolescents and children. Data presented as median (25th-75th percentiles). Out of all 3 age groups, both the *"patient facing"* and *"non-patient facing"* groups were most concerned that e-cigarettes may act a gateway to tobacco smoking amongst adolescents. A Mann-Whitney U test demonstrated statistically significant differences between the median concern score between the *"patient facing"* and *"non-patient facing* groups for adolescents, all *p* =.036.

Table 3.10 Comparisons of survey responses between patient facing and non-patient facing occupations upon the level of concern that e-cigarettes may act as a gateway to tobacco smoking.

Survey responses	Patient Facing ***n* = 2551**	Non-Patient Facing ***n* = 484**	*p*-value
Concern that e-cigarettes may act as a gateway to tobacco smoking in never smokers			
Adults > 19 years	5 (2;8)	5 (2;8)	.475
Adolescents 10-19 years	8 (5;10)	7 (3;10)	**.036**
Children <10 years	5 (2;9)	5 (2;9)	.338

Data are presented as median (25^{th}-75^{th} percentiles), and frequency (percentage). *P*-values derived from Independent Samples Mann-Whitney U test.

3.3.3.1.3 Allied healthcare professionals, doctors and nurses

The observed median concern scores that e-cigarettes may encourage non-smokers to take up tobacco smoking between the 3 healthcare professional groups of AHPs, doctors and nurses are presented in Table 3.11. and Figure 3.36.

For the adult age group, the median level of concern was the same across all 3 healthcare professional groups (*Mdn*=5). The median concern scores that e-cigarettes may encourage adult non-smokers to take up tobacco smoking was statistically significantly different between the healthcare professional groups, $\chi^2(2) = 6907$, $p = .032$, the effect size for this finding was moderate, $\varepsilon^2 = .005$. Nurses were more concerned that e-cigarettes would encourage non-smoking adults to take up tobacco smoking (*Mdn*=5, *mean rank* =1026.46) compared to doctors (*Mdn*=5, *mean rank* =951.36), $p = .030$.

For the adolescent age group, the median level of concern amongst nurses (*Mdn*=7), was less than doctors (*Mdn*=8) and AHPs (*Mdn*=8). The median concern scores that e-cigarettes may encourage non-smokers who are adolescents to take up tobacco smoking was statistically significantly different across the healthcare professional groups, $\chi^2(2) = 21.171$, $p < .001$, the effect size for this finding was moderate, $\varepsilon^2 = .014$. Doctors were most concerned that e-cigarettes may encourage non-smoking adolescents to take up tobacco smoking *Mdn*=8, *mean rank* = 1091.49), in comparison to either AHPs (*Mdn*=8, *mean rank* =972.41, $p = .008$), or nurses (*Mdn*=7, *mean rank* = 961.55, $p < .017$).

For the child age group, the median level of concern amongst doctors (*Mdn*=6), was higher than nurses (*Mdn*=5) and AHPs (*Mdn*=5). The median concern scores that e-cigarettes may encourage non-smokers who are children to take up tobacco smoking was statistically significantly different across the healthcare professional groups, $\chi^2(2) = 10.611$, $p = .005$, the effect size for this finding was moderate, $\varepsilon^2 = .005$. Doctors were most concerned that e-cigarettes may encourage non-smoking children to take up tobacco smoking (*Mdn*=6, *mean rank* = 1062.30), in comparison nurses (*Mdn*=5, *mean rank* = 967.58), $p = .003$.

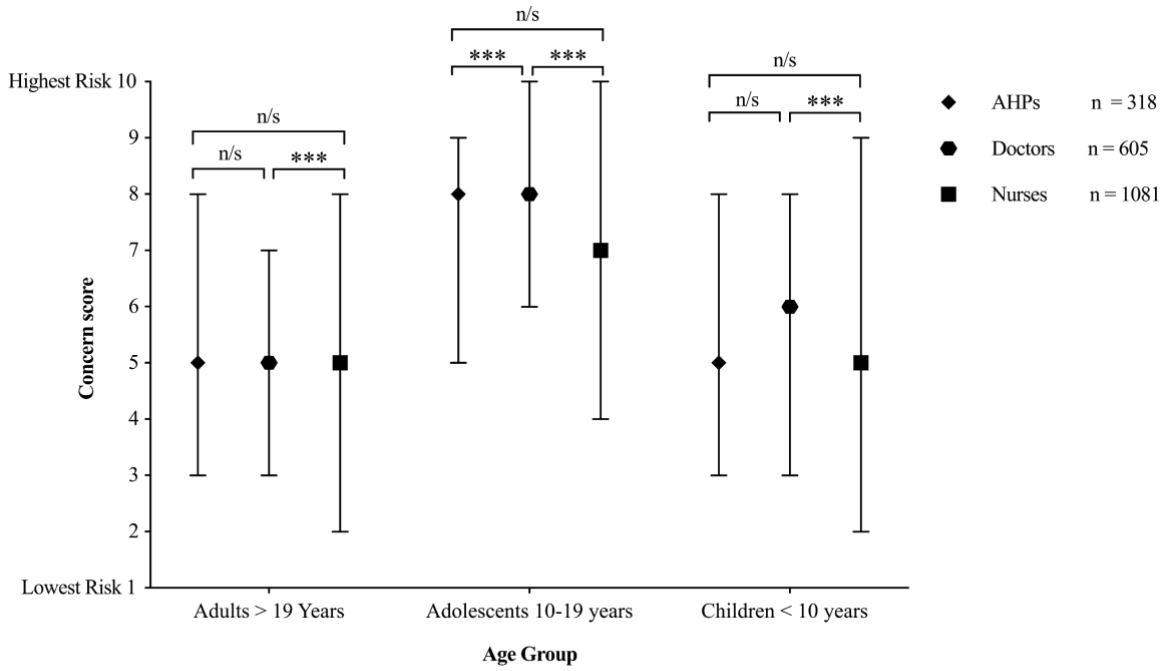


Figure 3.36 A comparison between AHPs', doctors' and nurses' perceived level of concern that e-cigarettes may act as a gateway to tobacco smoking amongst non-smoking adults, adolescents and children. Data presented as median (25th-75th percentiles). A Kruskal-Wallis test demonstrated that there were statistically significant differences in the median agreement scores across all three groups, $p < .001$. For all 3 age groups, the post hoc analysis (with a Bonferroni correction) demonstrated statistically significant differences ($p < .017$) in the pairwise comparisons between the healthcare professional groups.

Table 3.11 Comparisons of survey responses between AHPs, doctors and nurses upon the level of concern that e-cigarettes may act as a gateway to tobacco smoking.

Survey responses	AHPs *n* = 318	Doctors *n* = 605	Nurses *n* = 1081	*p*-values
Concern that e-cigarettes may act as a gateway to tobacco smoking in never smoker's				
Adults > 19 years	5 (3;8)	5 (3;7)	5 (2;8)	**.032**
Adolescents 10-19 years	8 (5;9)	8 (6;10)	7 (4;10)	**.001**
Children <10 years	5 (3;8)	6 (3;8)	5 (2;9)	**.005**

Data are presented as median (25^{th}-75^{th} percentiles), and frequency (percentage). *P*-values derived from Independent Samples Kruskal-Wallis test.

3.3.3.1.4 Smokers vs never-smokers

The observed median concern scores that e-cigarettes may encourage non-smokers to take up tobacco smoking between the *"smoker"* and *"never smoker"* groups are presented in Table 3.12. and Figure 3.37.

Out of all of the age groups, both the *"smoker"* and *"never smoker"* groups were most concerned that e-cigarettes may encourage non-smoking adolescents to take up tobacco smoking. However, between the *"smoker"* and *"never smoker"* groups there were notable differences in the median agreement scores for all of the age groups, $p < .001$. Overall the *"never smoker"* group expressed more concern than the *"smoker"* group that e-cigarettes, may encourage non-smoking adults, adolescents and children to become tobacco smokers, all $p < .001$, all $r = -0.1$ to -0.3 (small effect size).

Figure 3.37 A comparison between the smokers' and never smokers' level of concern that e-cigarettes may act as a gateway to tobacco smoking amongst non-smoking adults, adolescents and children. Data presented as median (25th-75th percentiles). Out of all 3 age groups, both the *"smokers"* and *"never smokers"* were most concerned that e-cigarettes may act a gateway to tobacco smoking amongst adolescents. A Mann-Whitney U test demonstrated statistically significant differences between the median concern score between *"smokers"* and *"never smokers"* for each age group, all $p < .001$. For all age groups the median level of concern that e-cigarettes would act as a gateway to tobacco smoking was greater amongst the *"never smokers"* compared to the *" smokers"*.

Table 3.12 Comparisons of survey responses between never smokers and smokers upon the level of concern that e-cigarettes may act as a gateway to tobacco smoking

Survey responses	Never smokers ***n* = 1822**	Smokers ***n* = 1213**	***p*-value**
Concern that e-cigarettes may act as a gateway to tobacco smoking in never smokers			
Adults > 18 years	5 (3;8)	4 (2;7)	**< .001**
Adolescents 10-18 years	8 (5;10)	6 (3;9)	**< .001**
Children <10 years	6 (3;9)	4 (1;8)	**< .001**

Data are presented as median (25^{th}-75^{th} percentiles) *P*-values derived from Independent Samples Mann-Whitney U test.

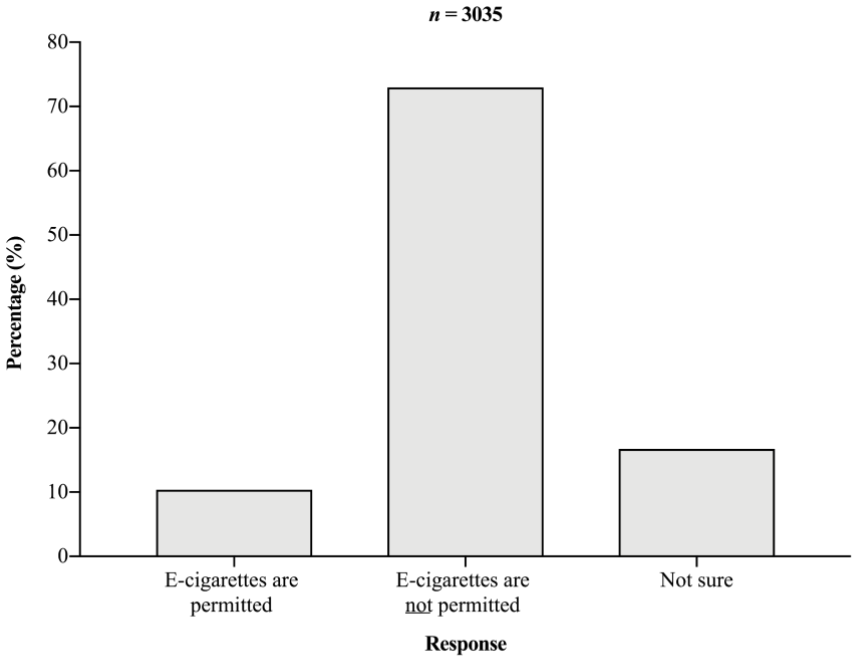
3.3.4 Awareness and attitudes towards e-cigarette regulation and workplace policy

3.3.4.1 Awareness of e-cigarette workplace policy

3.3.4.1.1 All respondents

All healthcare respondents were asked *"are you aware of your workplace policy on e-cigarette use?"*. In total 100% (*n*=3035) of respondents answered the question. The observed frequencies and percentages of responses from all respondents are presented in Table 3.13.

Overall, 16.7% (*n*=507) of respondents were *"not sure"* of the e-cigarette workplace policy. Whereas 83.2% (*n*=2528) said they were aware of the e-cigarette workplace policy, of which 72.9% (*n*=2214) thought that e-cigarettes use was not allowed and 10.3% (*n*=314) thought that e-cigarette use was allowed (Figure 3.38).



"Are you aware of your workplace policy on e-cigarette use?"

Figure 3.38 Survey respondents' perception upon NHSGGC workplace policy on e-cigarette use. Data presented as percentage.

Table 3.13. E-Cigarettes and workplace policy

Survey responses	All Responses *n*= 3035
"Are you aware of your workplace policy on e-cigarette use?"	
Yes, e-cigarette use is allowed	314 (10.3)
Yes, e-cigarette use is **not** allowed	2214 (72.9)
Not sure	507 (16.7)
"To what extent do you agree with the decision that some hospitals within the UK allow the use of e-cigarettes on hospital grounds?"	
Strongly agree	300 (9.9)
Agree	707 (23.3)
Neutral	738 (24.3)
Disagree	730 (24.1)
Strongly disagree	560 (18.5)

Data are presented as frequency (percentage).

3.3.4.1.2 Patient facing vs non-patient facing

In response to the question *"are you aware of your workplace policy on e-cigarette use?"* The observed frequencies and percentages for the *"patient facing"* and *"non-patient facing"* group are presented in Table 3.14 and Figure 3.39.

The proportion of respondents who answered *"yes, e-cigarette use is permitted"* was statistically significant greater amongst the *"non-patient facing"* group (15.5% n=75), in comparison to the *"patient facing"* group (9.4%, n=239), $p < .05$. The effect size for this finding, Cramer's V, was weak, .074. There were no statistical differences found between the groups responses who answered either *"yes, e-cigarette use is not permitted"* and *"not sure"*.

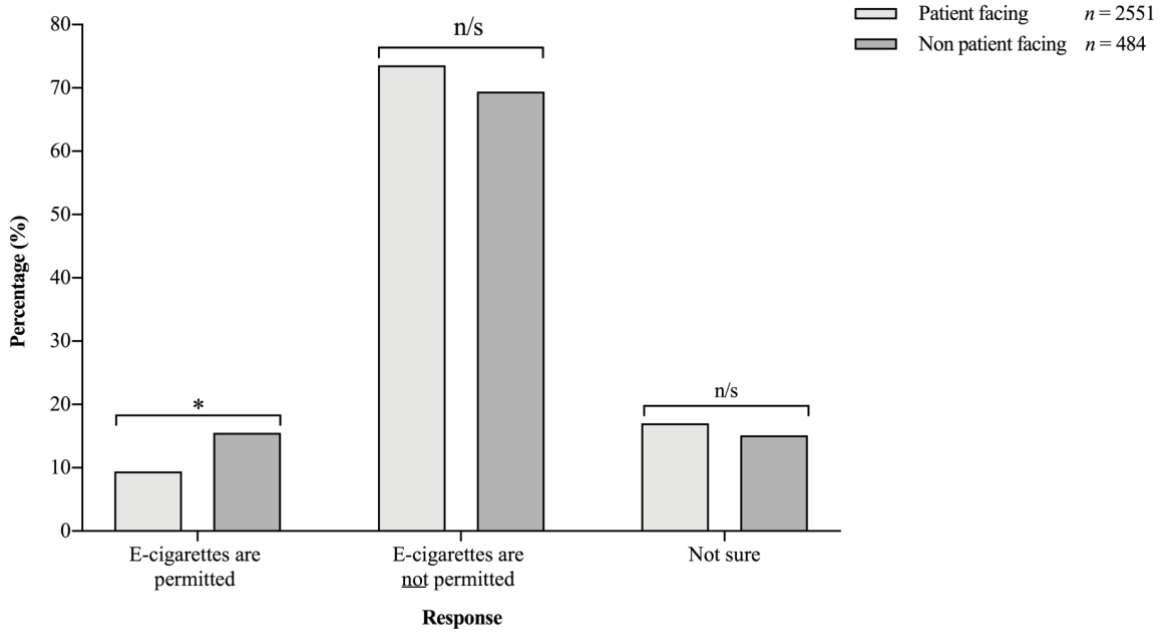


Figure 3.39 A comparison between the patient facing and non-patient facing respondents' awareness of NHSGCC e-cigarette workplace policy. Data presented as percentage. A chi-square test of homogeneity demonstrated statistically significant differences in opinions between the *"patient facing"* and *"non-patient facing"* group, $p < .001$. For those who answered *"yes, e-cigarettes are permitted"* post hoc analysis of pairwise comparisons demonstrated statistically significant proportional differences in the response between the *"patient facing"* and *"non-patient facing"* groups for each opinion, both $p < .05$.

Table 3.14. Comparisons of survey responses between patient facing and non-patient facing occupations upon e-cigarettes and workplace policy.

Survey responses	Patient Facing ***n* = 2551**	Non-Patient Facing ***n* = 484**	***p*-value**	
"Are you aware of your workplace policy on e-cigarette use?"				
Yes, e-cigarette use is allowed	239 (9.4)	75 (15.5)		**< .05**[c]
Yes, e-cigarette use is **not**	1878 (73.6)	336 (69.4)	**< .001**[b]	> .05[c]
Not sure	434 (17.0)	73 (15.1)		> .05[c]
"To what extent do you agree with the decision that some hospitals within the UK allow the use of e-cigarettes on hospital grounds?"				
Strongly agree	226 (8.9)	74 (15.3)		
Agree	596 (23.4)	111 (22.9)		
Neutral	624 (24.5)	114 (23.6)	**.013**[a]	
Disagree	639 (25.0)	91 (18.8)		
Strongly disagree	466 (18.3)	94 (19.4)		

Data are presented as frequency (percentage). *P*-values derived from Independent Samples Mann-Whitney U test[a], Chi-Square Test of Homogeneity[b] and post hoc analysis pairwise comparisons using multiple z-tests of two proportions [c].

3.3.4.1.3 Allied healthcare professionals, doctors and nurses

In response to the question *"are you aware of your workplace policy on e-cigarette use?",* the observed frequencies and percentages for each healthcare professional group (AHPs, doctors and nurses) are presented in Table 3.15 and Figure 3.40.

Statistically significant proportional differences on the understanding of the e-cigarette workplace policy between the healthcare professional groups was observed, $p < .001$. The effect size for this finding, Cramer's V, was moderate, .142. A significantly smaller proportion of the doctors (3.5%, n=21) thought that according to the workplace policy, e-cigarette use was allowed, in comparison to either nurses (11.7%, n=126) or AHPs (7.9%, n=25), both $p < .017$. Whereas, the proportion of healthcare professionals who did not think that the use of e-cigarettes was allowed, was significantly greater amongst the nurses (76.7%, n=826) in comparison to AHPs (68.2%, n=217) $p < .017$. The proportion of healthcare professionals who unsure of the e-cigarette workplace policy was significantly lower amongst nurses (11.7%, n=126), in comparison to either AHPs (23.9%, n=79) or doctors (25%, n=151), both $p < .017$.

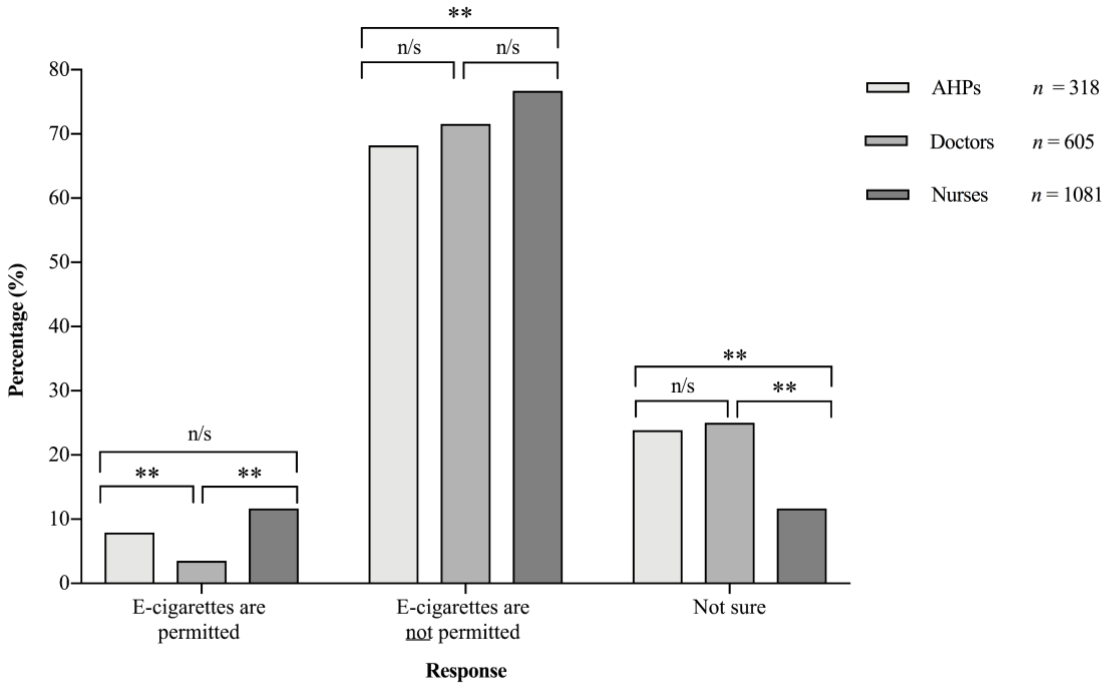


Figure 3.40 A comparison between AHPs', doctors' and nurses' levels of awareness of NHSGCC e-cigarette workplace policy. Data presented as percentage. A chi-square test of homogeneity demonstrated statistically significant differences in opinion between each of the healthcare professional group, $p < .001$. Post hoc analysis (with a Bonferroni correction, $p < .017$) demonstrated statistically significant proportional differences in the response between AHPs, doctors and nurses for each opinion.

Table 3.15 Comparisons of survey responses between AHPs, doctors and nurses upon e-cigarettes and workplace policy.

Survey responses	AHPs *n* = 318	Doctors *n* = 605	Nurses *n* = 1081	*p*-values
"Are you aware of your workplace policy on e-cigarette use?"				
Yes, e-cigarette use is allowed	25 (7.9)	21 (3.5)	126 (11.7)	**< .001**[b]
Yes, e-cigarette use is **not** allowed	217 (68.2)	433 (71.6)	829 (76.7)	**< .001**[b]
Not sure	76 (23.9)	151 (25.0)	126 (11.7)	**< .001**[b]
"To what extent do you agree with the decision that some hospitals within the UK allow the use of e-cigarettes on hospital grounds?"				
Strongly agree	11 (3.5)	23 (3.8)	139 (12.9)	
Agree	57 (17.9)	119 (19.7)	275 (25.4)	
Neutral	82 (25.8)	127 (21.0)	285 (26.4)	**< .001**[a]
Disagree	91(28.6)	222 (36.7)	204 (18.9)	
Strongly disagree	77 (24.2)	114 (18.8)	178 (16.5)	

Data are presented as frequency (percentage). *P*-values derived from Independent Samples Kruskal-Wallis test[a] and Chi-Square test of Homogeneity[b].

3.3.4.1.4 Smokers vs never-smokers

In response to the question *"are you aware of your workplace policy on e-cigarette use?",* the observed frequencies and percentages for the *"smoker"* and *"never-smoker"* groups are presented in Table 3.16 and Figure 3.41.

The proportion of respondents who answered *"yes, e-cigarette use is permitted"* was greater amongst the *"smoker"* group (13.9%, n=169) in comparison to the *"never smoker"* group (8.0%, n=145), $p < .05$. The proportion of respondents who answered *"unsure"* was greater amongst the *"never smoker"* group (19.6%, n=357) in comparison to the *"smoker"* group (12.4%, n=150), $p <$ .05. The effect size for this finding, Cramer's V, was weak .058. There were no statistical differences found between the groups' responses who answered *"yes, e-cigarette use is not permitted"*, $p >$.05.

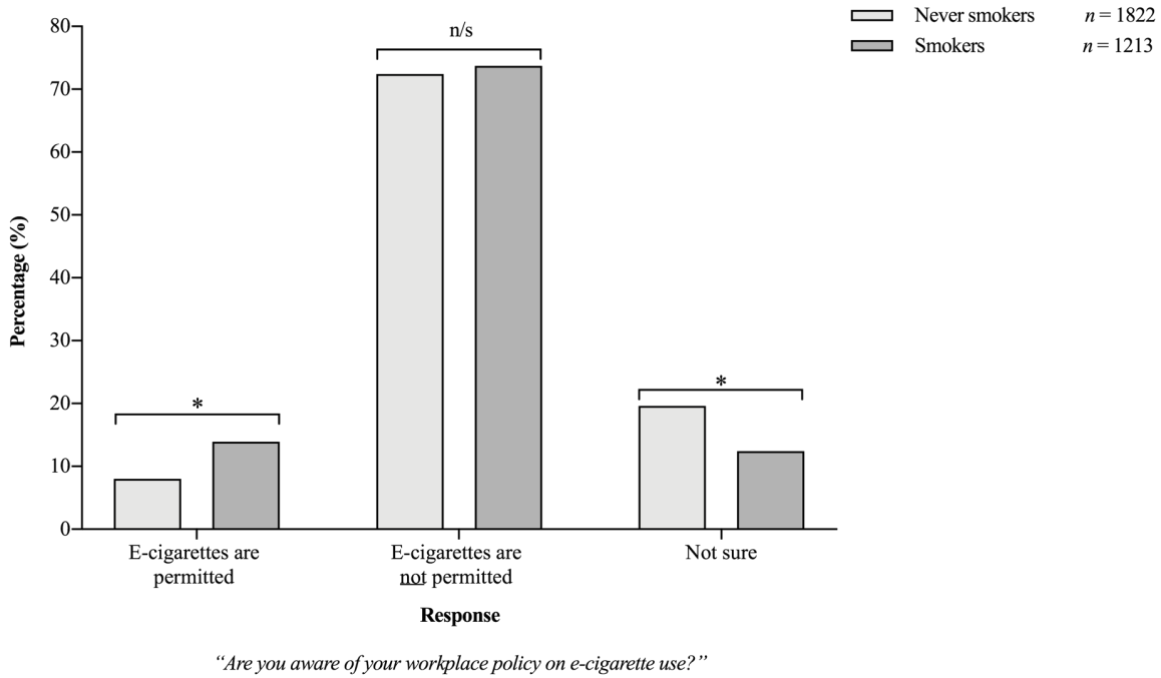


Figure 3.41 A comparison between the smokers' and never smokers' levels of awareness of NHSGCC e-cigarette workplace policy. Data presented as percentage. A chi-square test of homogeneity demonstrated statistically significant differences in opinions between the *"never smoker"* and *"smoker"* groups, $p < .001$. For those who answered *"yes, e-cigarettes are permitted"* and *"not sure"* post hoc analysis of pairwise comparisons demonstrated statistically significant proportional differences in the response between *"never smokers"* and *"smokers"*, both $p < .05$.

Table 3.16 Comparisons of survey responses between never smokers and ever smokers upon e-cigarettes and workplace policy.

Survey responses	Never smokers *n* = 1822	Ever smokers *n* = 1213	*p*-value	
"Are you aware of your workplace policy on e-cigarette use?"				
Yes, e-cigarette use is permitted	145 (8.0)	169 (13.9)		**< .05**[c]
Yes, e-cigarette use is **not** permitted	1320 (72.4)	894 (73.7)	**< .001**[b]	> .05[c]
Not sure	357 (19.6)	150 (12.4)		**< .05**[c]
"To what extent do you agree with the decision that some hospitals within the UK allow the use of e-cigarettes on hospital grounds?"				
Strongly agree	67 (3.7)	233 (19.2)	**< .001**[a]	
Agree	314 (17.2)	393 (32.4)		
Neutral	456 (25.0)	282 (23.2)		
Disagree	555 (30.5)	175 (14.4)		
Strongly disagree	430 (23.6)	130 (10.7)		

Data are presented as frequency (percentage). *P*-values derived from Independent Samples Mann-Whitney U test[a], Chi-Square Test of Homogeneity[b] and post hoc analysis pairwise comparisons using multiple z-tests of two proportions[c].

3.3.4.2 Attitudes towards the policy permitting e-cigarettes use on hospital grounds

3.3.4.2.1 All respondents

The respondents were asked *"to what extent do you agree with the decision that some hospitals within the UK allow the use of e-cigarettes* on *hospital grounds"*. In total 100% (*n*=3035) of respondents answered the question. The observed frequencies and percentages of responses are presented in Table 3.13. Overall, 18.5% (*n*=560) strongly disagreed, 24.1% (*n*=730) disagreed, 24.3% (*n*=738) were neutral, 23.3% (*n*=707) agreed and 9.9% (*n*=300) strongly agreed (Figure 3.42).

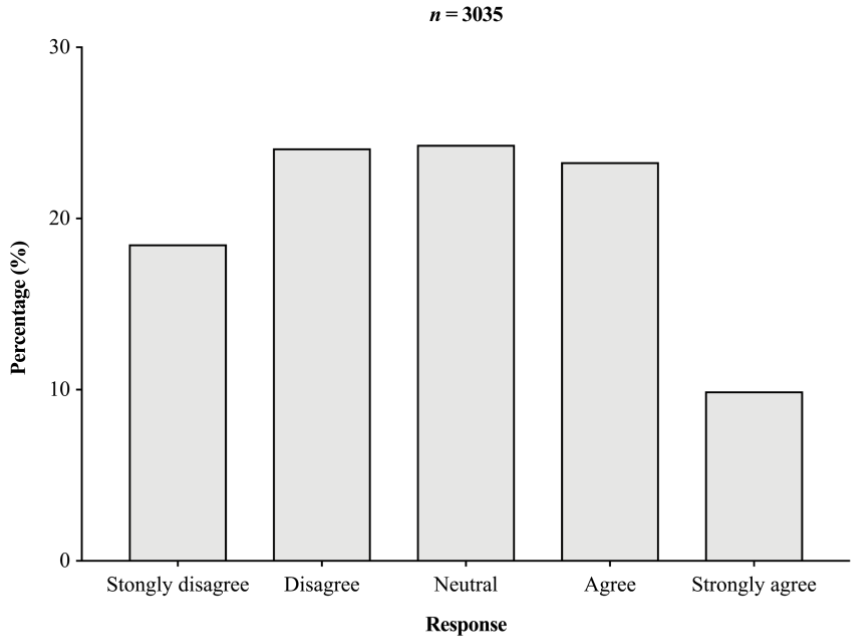


Figure 3.42 Survey respondents' level of agreement that some hospitals within the UK allowed the use of e-cigarettes on hospital grounds. Data presented as percentage.

A Spearman's rank-order correlation was run to assess the relationship between the responses for the questions where respondents were asked *"do you agree with the following statement: e-cigarettes are a good thing?"* and *"to what extent did they agree with the decision that some hospitals within the UK allow the use of e-cigarettes on hospital grounds."* Preliminary analysis showed the relationship to be monotonic, as assessed by visual inspection of a scatterplot. There was a positive correlation between the agreement responses for those who considered e-cigarettes to be a *"good thing"* and to what extend they agreed with the decision that some hospitals within the UK allow the use of e-cigarettes on hospital grounds, $r_s = .572$, $p < .001$ (figure 3.43).

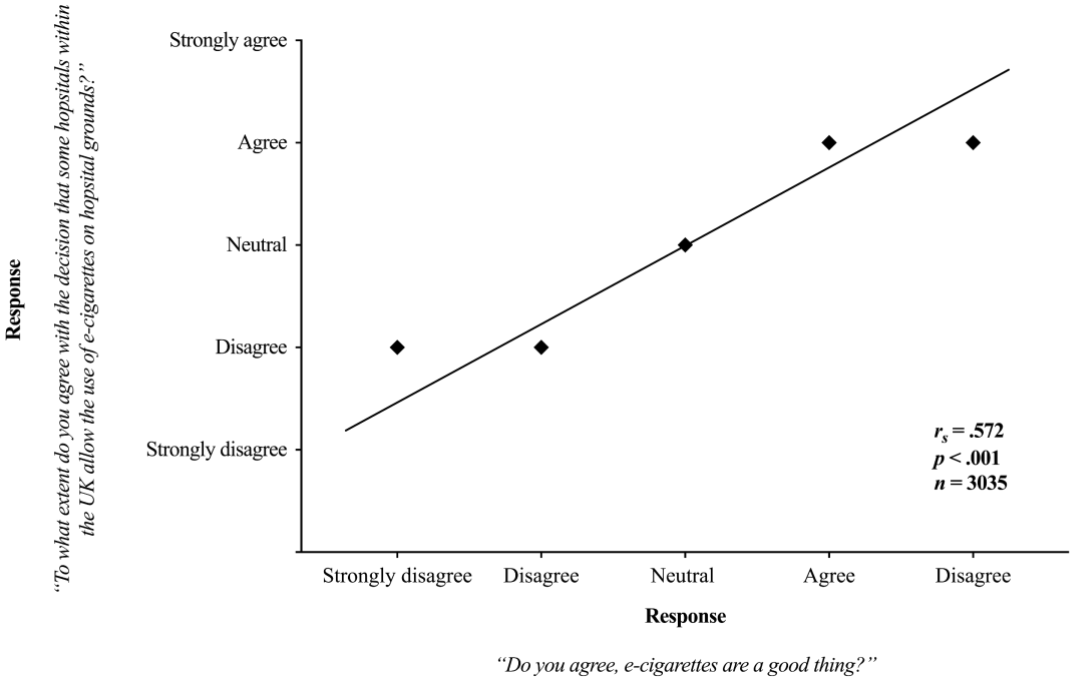


Figure 3.43 A Spearman's correlation comparing healthcare professional respondents' level of agreement on whether they considered e-cigarettes to be *"a good thing"* and level of agreement with the decision that some hospitals within the UK allowed the use of e-cigarettes on hospital grounds. Data presented as median.

3.3.4.2.2 Patient facing vs non-patient facing

In response to the question *"to what extent do you agree with the decision that some hospitals within the UK allow the use of e-cigarettes on hospital grounds",* the observed frequencies and percentages for the *"patient facing"* and *"non-patient facing"* group are presented in Table 3.14 and Figure 3.44.

Although the median agreement scores were *"neutral"* for both groups, the *"non-patient facing"* group had a greater tendency to agree with the decision that some hospitals within the UK allow the use of e-cigarettes on hospital grounds (*mean rank* = 1606.82), than the *"patient facing"* group (*mean rank* = 1501.15) $U = 660329.5$, $z = 2.493$, $p = .013$ the effect size for this finding was negligible, $r = .06$.

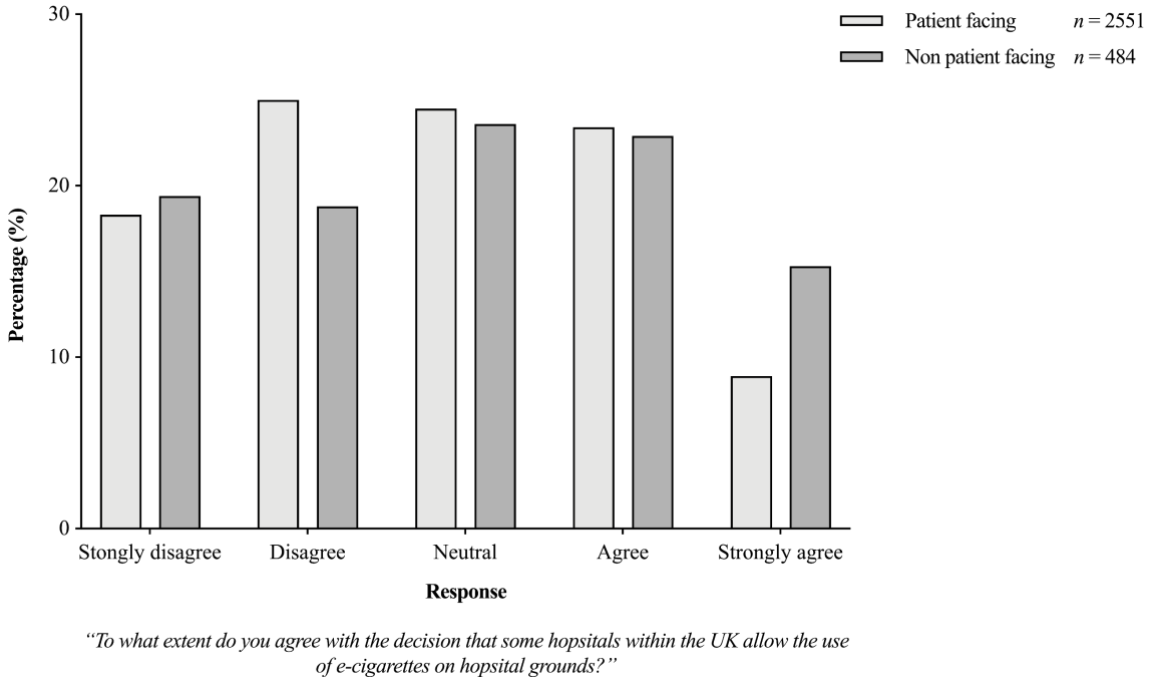


Figure 3.44 A comparison between the patient facing and non-patient facing respondents' level of agreement as to what extent they agree with the decision that some hospitals within the UK allow the use of e-cigarettes on hospital grounds". Data presented as percentage. The median level of agreement was *"neutral"* for both the *"patient facing"* and *"non-patient facing"* group. A Mann-Whitney U test demonstrated statistically significant differences between the level of agreement between both groups, $p = .013$, with the *"non-patient facing"* group (*mean rank* = 1606.82) having a more favourable opinion towards the decision that some UK hospitals allow the use the of e-cigarettes on hospital grounds, compared to the *"patient facing"* group (*mean rank* = 1501.15).

3.3.4.2.3 Allied healthcare professionals, doctors and nurses

In response to the question "*to what extent do you agree with the decision that some hospitals within the UK allow the use of e-cigarettes on hospital grounds",* the observed frequencies and percentages for each healthcare professional group (AHPs, doctors and nurses) are presented in Table 3.15 and Figure 3.45.

The median agreement score was *"disagree"* for both AHPs and doctors, and *"neutral"* for nurses. There was a notable difference in the distributions of the agreement scores for healthcare professional groups $\chi^2(2) = 74.847$, $p < .001$, the effect size for this finding was strong, $\varepsilon^2 = .038$. Whereby AHPs (*mean rank* = 871.01) and doctors (*mean rank* = 892.05) both disagreed with the decision, nurses had a neutral stance (*mean rank* =1103), $p < .017$.

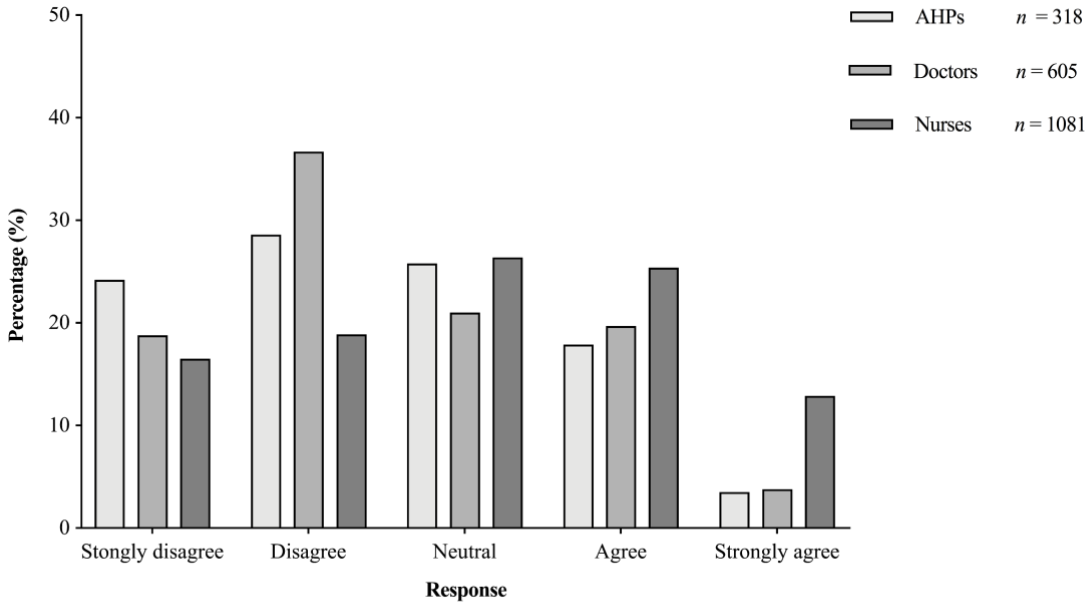


Figure 3.45 A comparison between AHPs', doctors' and nurses' level of agreement on whether they agree with the decision that some hospitals within the UK allow the use of e-cigarettes on hospital grounds. A Kruskal-Wallis test demonstrated that there were statistically significant differences in the median agreement scores across all three groups, $p < .001$. Post hoc analysis with a Bonferroni correction demonstrated statistically significant differences, with nurses having a neutral stance, and both doctors and AHPs disagreeing with the decision, $p < .017$.

3.3.4.2.4 Smokers vs never-smokers

In response to the question *"to what extent do you agree with the decision that some hospitals within the UK allow the use of e-cigarettes on hospital grounds",* the observed frequencies and percentages for the *"smoker"* and *"never-smoker"* groups are presented in Table 3.16 and Figure 3.46.

There a notable difference in the median agreement scores between both groups, with the *"never smokers,"* disagreeing with the decision that some hospitals within the UK allow the use of e-cigarettes on hospital grounds, and the *"smokers"* agreeing with the decision, $U = 1538563.0$, $z = 18.792$, $p < .001$ the effect size for this finding was medium, $r = .34$.

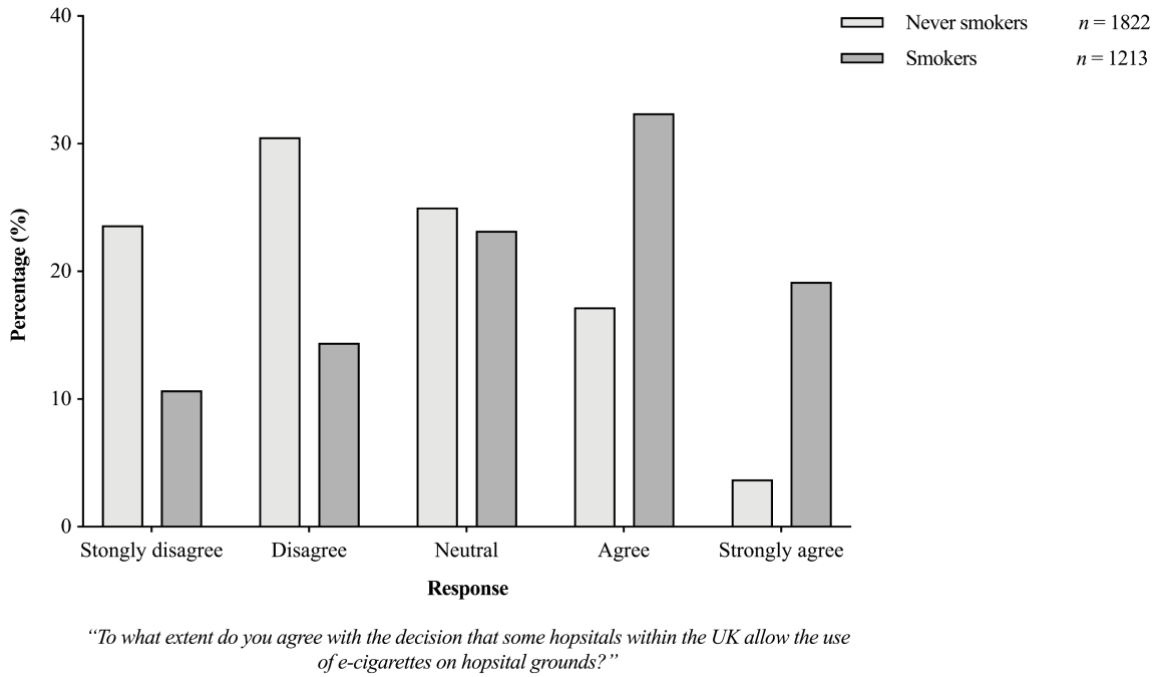


Figure 3.46 A comparison between the smokers' and never smokers' level of agreement on whether they agreed with the decision that some hospitals with the UK allowed the use e-cigarettes on hospital grounds. Data presented as percentage. The median level of agreement was *"disagree"* for never smokers and *"agree"* for smokers. A Mann-Whitney U test demonstrated statistically significant differences between the median level of agreement between smokers and never smokers, $p < .001$.

3.3.5 Clinical healthcare professional's preparedness for informing patients about e-cigarettes use

3.3.5.1 Frequency of clinical healthcare professionals that encounter patients who smoke tobacco cigarettes and use e-cigarettes

3.3.5.1.1 All clinical healthcare professional respondents

Clinical healthcare professional respondents (*n*=2355) were asked *"how often do you see patients who smoke tobacco cigarettes in your working environment?",* in total 100% *(n*=2355) of the clinical healthcare professional respondents answered the question. The observed frequencies and percentages are presented in Table 3.17. Of these 46.2% (*n*=1087) of respondents reported that they encounter patients who smoke tobacco cigarettes on a daily basis, 37.1% (*n*=873) 1-2 days a week, 8% (*n*=189) less than 1-day per week and 8.7% (*n*=206) never encounter smokers (figure 3.47).

Clinical healthcare professional respondents (*n*=2355) were asked *"how often do you see patients who use e-cigarettes in your working environment?",* in total 96.5% *(n*=2272) of the clinical healthcare professional respondents answered the question. The observed frequencies and percentages are presented in Table 3.17. Of these, 36.9% (*n*=838) of respondents reported that they encounter patients who use e-cigarettes on a daily basis, 26.2% (*n*=596) 1-2 days a week, 21.9% (*n*=498) less than 1-day per week and 15% (*n*=340) never encounter patients who use e-cigarettes (Figure 3.46).

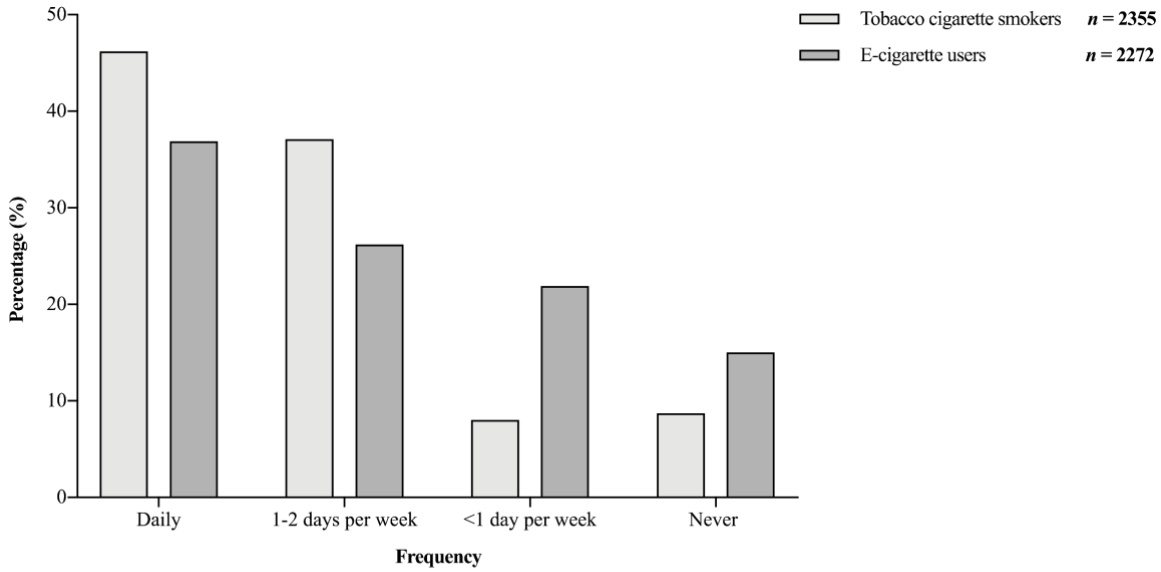


Figure 3.47 Frequency of how often clinical healthcare professional respondents see patients who use tobacco and e-cigarettes as part of their clinical practice. Data presented as percentage.

Table 3.17 Preparedness for recommending patients about the use of e-cigarettes

Survey questions and responses	Clinical Healthcare Professionals
"How often do you see patients who smoke in your working environment?"	
Daily	1087 (46.2)
1-2 days per week	873 (37.1)
Less than 1 day per week	189 (8.0)
Never	206 (8.7)
"How often do you see patients who use e-cigarettes in your working environment?"	
Daily	838 (35.6)
1-2 days per week	596 (25.3)
Less than 1 day per week	498 (21.1)
Never	340 (14.4)
No response	83 (3.5)
"How often are you asked by patients questions about e-cigarettes?"	
Daily	96 (4.1)
1-2 days per week	244 (10.4)
Less than 1 day per week	608 (25.8)
Never	1320 (56.1)
No response	87 (3.7)
"Has your workplace advised you on what advice you should give to patients if they ask you about e-cigarettes?"	
Yes	422 (17.9)
No	1932 (82.0)
No response	1 (0)
"I feel confident advising patients about e-cigarettes"	
Strongly agree	62 (2.6)
Agree	186 (7.9)
Neutral	437 (18.6)
Disagree	893 (37.9)
Strongly disagree	680 (28.9)
No response	97 (4.1)
"I feel I need more information and guidance regarding e-cigarettes"	
Strongly agree	783 (33.2)
Agree	1018 (43.2)
Neutral	256 (10.9)
Disagree	112 (4.8)
Strongly disagree	89 (3.8)
No response	97 (4.1)
"Would you recommend e-cigarettes to patients as a method to stop smoking?"	
Yes	969 (41.1)
No	1276 (54.2)
No response	110 (4.7)

Data are presented as frequency (percentage).

3.3.5.2 Frequency that clinical healthcare professionals encounter patients who use e-cigarettes

3.3.5.2.1 All clinical healthcare professional respondents

Clinical healthcare professional respondents (*n*=2355) were asked *"how often are you asked by patients about e-cigarettes?",* in total, 96.3% (*n*=2268) of the clinical healthcare professional respondents answered the question. The observed frequencies and percentages are presented in Table 3.17. Of which 4.2% (*n*=96) of respondents stated that patients ask e-cigarette questions on a daily basis, 10.8% (*n*=244) 1-2 days a week, 26.8% (*n*=608) less than 1-day per week and 58.2% (*n*=1320) have never been asked e-cigarettes question by their patients (Figure 3.48).

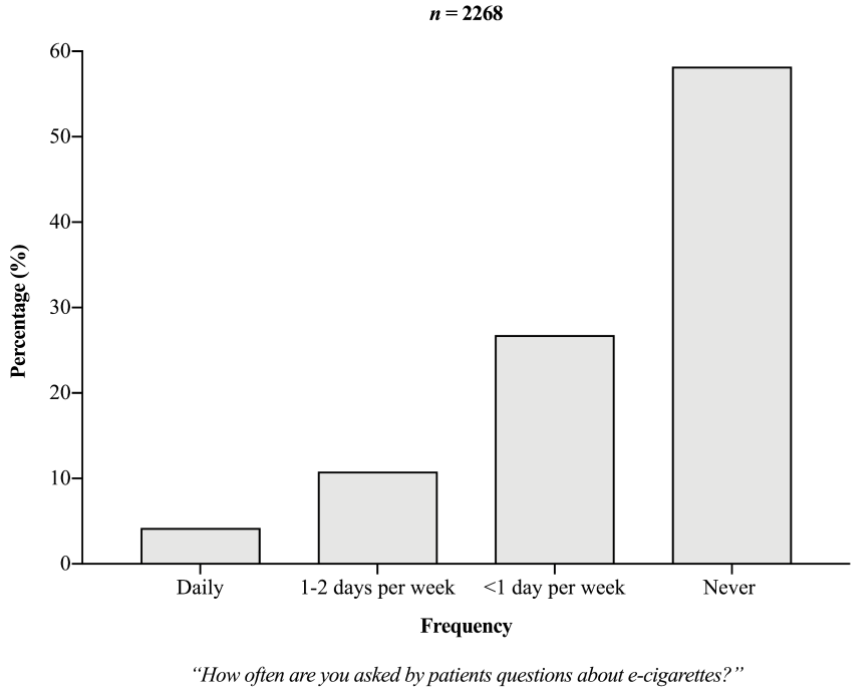
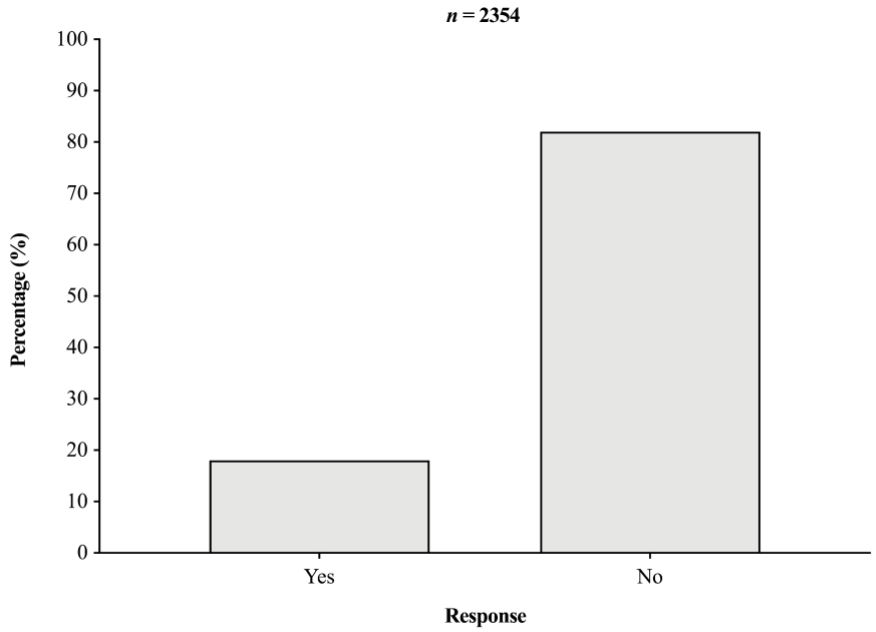


Figure 3.48 Frequency of how often the clinical healthcare professional respondents are asked e-cigarette questions by their patients. Data presented as percentage.

3.3.5.3 Clinical healthcare professionals' perceptions of the whether they have received workplace advice regarding patient information relating to e-cigarettes use

3.3.5.3.1 All clinical healthcare professional respondents

All 2355 clinical healthcare professional respondents were asked *"has your workplace advised you on what advice you should give to patients if they ask about electronic cigarettes?"*. In total, 99.9% (*n*=2354) of respondents answered the question. The observed frequencies and percentages of responses are presented in Table 3.17. Overall, the majority of respondents answered *"no"* (82%, *n*=1932) their workplace had not advised them, and 18% (*n*=422) answered *"yes",* their workplace had provided them with advice (Figure 3.49).



"Has your workplace advised you on what advice you should give to patients if they ask about electronic cigarettes?"

Figure 3.49 Percentage of clinical healthcare professionals who have received e-cigarette advice from their workplace on what e-cigarette information they should give to patients. Data presented as percentage.

3.3.5.4 Healthcare professional self-perception of ability to advise patient regarding e-cigarettes

3.3.5.4.1 All clinical healthcare professional respondents

The clinical healthcare professional respondents (*n*=2355) were asked *"to what extent do you agree with the statement: I feel confident advising patients about e-cigarettes?"*. The observed frequencies and percentages are presented in Table 3.17. In total, 95.9% (*n*=2258) of the clinical healthcare professional respondents answered the question, of which 30.1% (*n*=680) strongly disagreed, 39.5% (*n*=893) disagreed, 19.4% (*n*=437) were neutral, 8.2% (*n*=186) agreed and 2.7% (*n*=62) strongly agreed.

The clinical healthcare professional respondents (*n*=2355) were asked *"to what extent do you agree with the statement: I feel I need more information and guidance regarding e-cigarettes?"* In total, 95.9% (*n*=2258) of the clinical healthcare professional respondents answered the question, of which 3.9% (*n*=89) strongly disagreed, 5% (*n*=112) disagreed, 11.3% (*n*=256) were neutral, 45.1% (*n*=1018) agreed and 34.7% (n=783) strongly agreed.

In total, 95% (*n*=2239) of the clinical healthcare professional respondents answered both parts of the question (Figure 3.50). The median score of agreement was *"disagree"* in response to the statement "*I feel confident advising patients about e-cigarettes?"* and *"agree"* in response to the statement "*I feel I need more information and guidance regarding e-cigarettes?"* The difference in median scores between both statements was statistically significant, $z = 37.110$, $p < .001$.

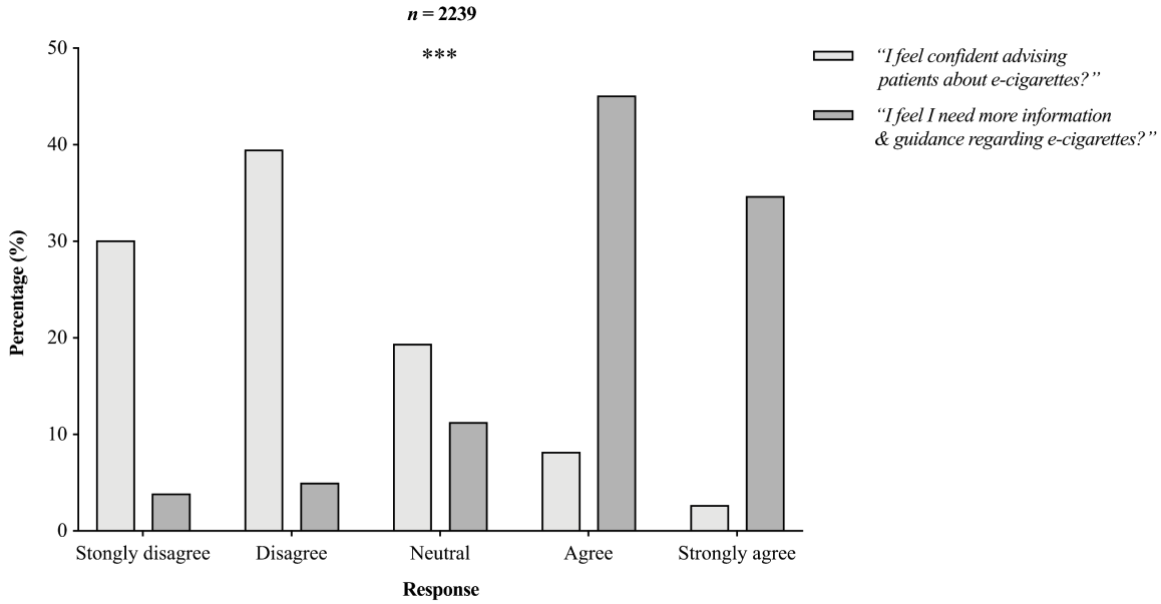


Figure 3.50 Healthcare professional respondents' level of agreement in response to the statements *"I feel confident advising patients about e-cigarettes"* and *"I feel I need more information and guidance regarding e-cigarettes"* Data presented as percentage. Statistical significance was demonstrated between the median level of agreement for both questions, p < .001.

A strong negative correlation was observed in relation to healthcare professionals' level of confidence at discussing e-cigarettes with their patients and their wish for more information and guidance regarding e-cigarettes. r_s = -.358, p < .001 (figure 3.51).

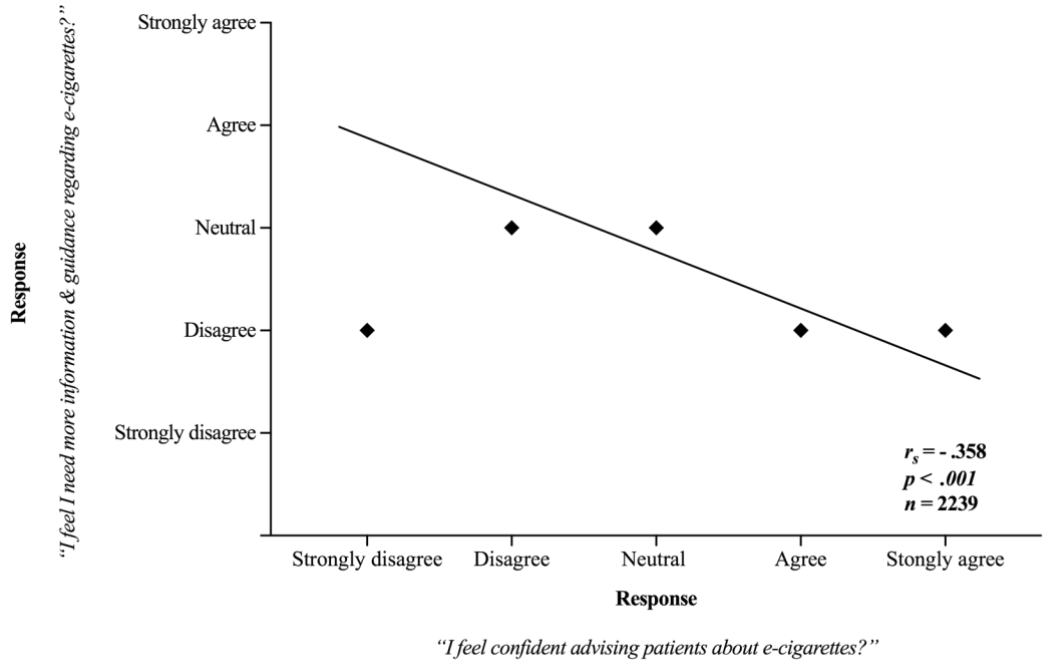


Figure 3.51 A Spearman's correlation comparing level of agreement on whether clinical healthcare professionals felt confident advising patients about e-cigarette cigarettes, in relation to whether they felt they needed more information and guidance regarding e-cigarettes. Data presented as median.

3.3.5.4.2 Allied healthcare professionals, doctors and nurses

In response to the statement *"I feel confident advising patients about e-cigarettes"*. The observed frequencies and percentages of responses from healthcare professionals' groups compromising of AHPs, doctors and nurses are presented in Table 3.18 and Figure 3.52.

Although the median agreement score was *"disagree"* for all three groups, there was a notable difference in the distributions of the agreement scores between the healthcare professional groups $\chi^2(2) = 48.362$, $p < .001$, the effect size for this finding was relatively strong, $\varepsilon^2 = .024$. Overall AHPs (*mean rank* = 723.99) felt less confident at advising patients about e-cigarettes in comparison to either doctors (*mean rank* = 934.14) or nurses (*mean rank* = 955.25), both $p < .017$.

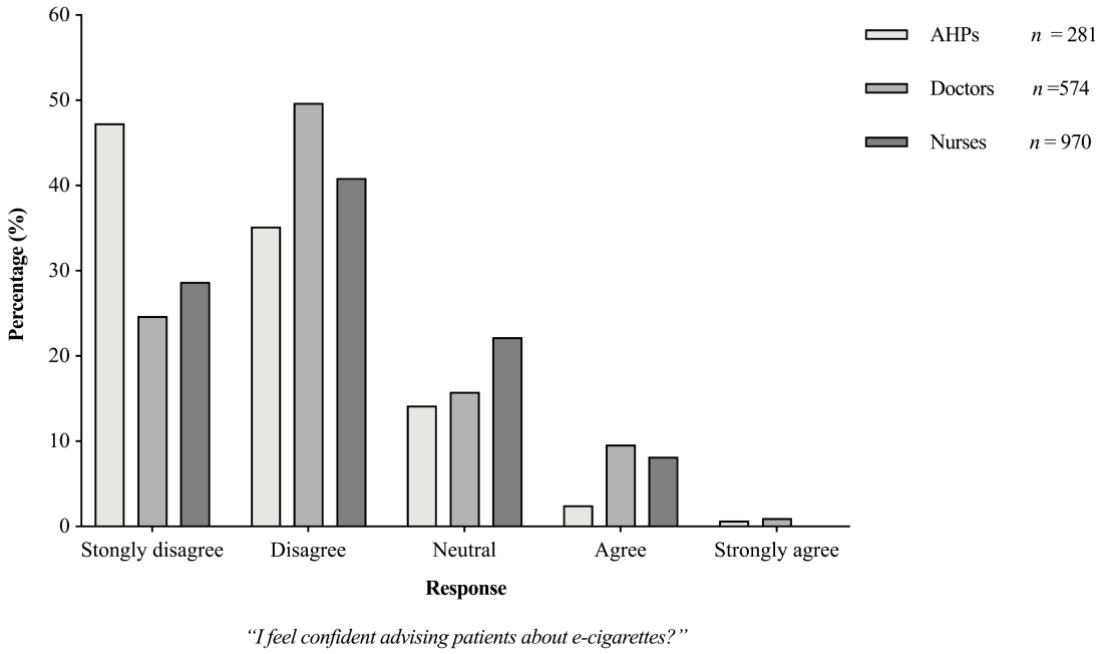


Figure 3.52 A comparison between AHPs', doctors' and nurses' level of agreement on whether they feel confident advising patients about e-cigarettes. A Kruskal-Wallis test demonstrated that there were statistically significant differences in the median *"disagree"* agreement scores across all three groups, $p < .001$. Post hoc analysis with a Bonferroni correction demonstrated that AHPs had lower levels of confidence when advising patients about e-cigarettes compared to both doctors and nurses, both $p < .017$.

In response to the statement *"I feel need more information and guidance regarding e-cigarettes"*, the observed frequencies and percentages of responses from healthcare professionals' groups compromising of AHPs, doctors and nurses are presented in Table 3.18 and Figure 3.53.

The median agreement score was *"agree"* for all three groups, with no statistically significant difference demonstrated between the different healthcare professional groups opinion, $\chi^2(2) = .102$, $p = .950$.

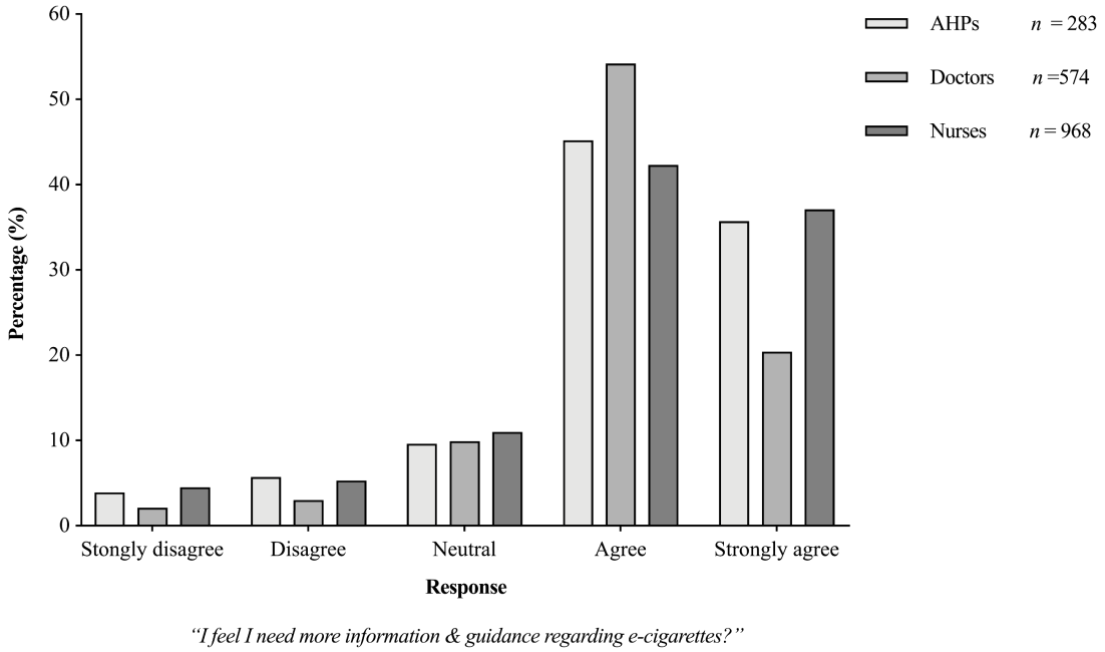


Figure 3.53 A comparison between AHPs', doctors' and nurses' level of agreement on whether they feel they need more information and guidance regarding e-cigarettes. Data are presented as percentage. The median agreement score for all 3 groups was *"agree"*. A Kruskal-Wallis test demonstrated that there were no statistically significant differences in the median agreement scores across all three groups, $p = .950$.

Table 3.18 Comparisons between the AHPs, doctors and nurses upon their preparedness for recommending patients upon the use of e-cigarettes.

Survey responses	AHPs *n* = 290	Doctors *n* = 586	Nurses *n* = 1002	*p*-values
"I feel confident advising patients about e-cigarettes"				
Strongly agree	2 (0.7)	6 (1.0)	30 (3.0)	**< .001**[a]
Agree	7 (2.4)	55 (9.4)	80 (8.0)	
Neutral	40 (13.8)	86 (14.7)	215 (21.5)	
Disagree	99 (34.1)	285 (48.6)	367 (36.6)	
Strongly disagree	133 (45.9)	142 (24.2)	278 (27.7)	
No response	9 (3.1)	12 (2.0)	32 (3.2)	
"I feel I need more information and guidance regarding e-cigarettes"				
Strongly agree	101 (34.8)	177 (30.2)	359 (35.8)	.950[a]
Agree	128 (44.1)	311 (53.1)	408 (40.7)	
Neutral	27 (9.3)	57 (9.7)	106 (10.6)	
Disagree	16 (5.5)	17 (2.9)	51 (5.1)	
Strongly disagree	11 (3.8)	12 (2.0)	44 (4.4)	
No response	7 (2.4)	12 (2.0)	34 (3.4)	
"Would you recommend e-cigarettes to patients as a method to stop smoking?"				
Yes	92 (31.7)	293 (50.0)	411 (41.0)	**< .001**[a]
No	184 (63.4)	278 (47.4)	552 (55.1)	**< .001**[a]
No response	14 (4.8)	15 (2.6)	39 (3.9)	**-**

Data are presented as frequency (percentage). P-values derived from Independent Samples Kruskal-Wallis Test[a] and Chi-Square test of Homogeneity[b].

3.3.5.4.3 Smokers vs never-smokers

In response to the statement *"I feel confident advising patients about e-cigarettes",* the observed frequencies and percentages for the *"smoker"* and *"never smoker "* group responses are presented in Table 3.19 and Figures 3.54.

Although the median agreement score was *"disagree"* for both groups, the level of agreement was statistically significant higher amongst the *"never smokers"* (*Mdn*=2, *mean rank* = 1060.13) compared to *"smokers" (Mdn*=2, *mean rank* =1246.12), $U = 694366.5$, $z = 6.900$, $p < .001$ the effect size for this finding was small, $r = .16$.

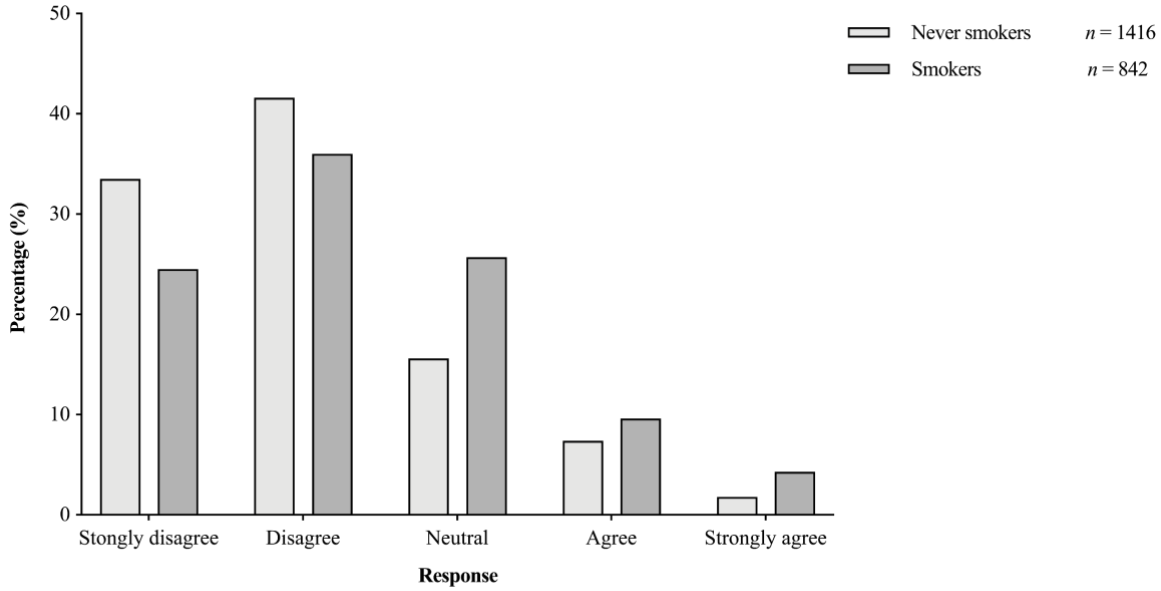


Figure 3.54 A comparison of the level of agreement from healthcare professionals who are smokers and never smokers in response to the statement *"I feel confident advising patients about e-cigarettes"* Data presented as percentage. The median level of agreement was *"disagree"* for both groups. A Mann-Whitney U test demonstrated statistically significant differences between the median level of agreement between *"smokers"* and *"never smokers", p* < .001. With *"never smokers",* (*mean rank* = 1060.13) having lower levels of confidence at advising patients about e-cigarettes compared to *"smokers"* (*mean rank* =1246.12).

In response to the statement *"I feel need more information and guidance regarding e-cigarettes",* the observed frequencies and percentages for the *"smoker"* and *"never smoker"* group responses are presented in Table 3.19 and Figures 3.55.

The median agreement score was *"agreed"* for both groups, with no statistically significant difference demonstrated between groups, $p = .086$.

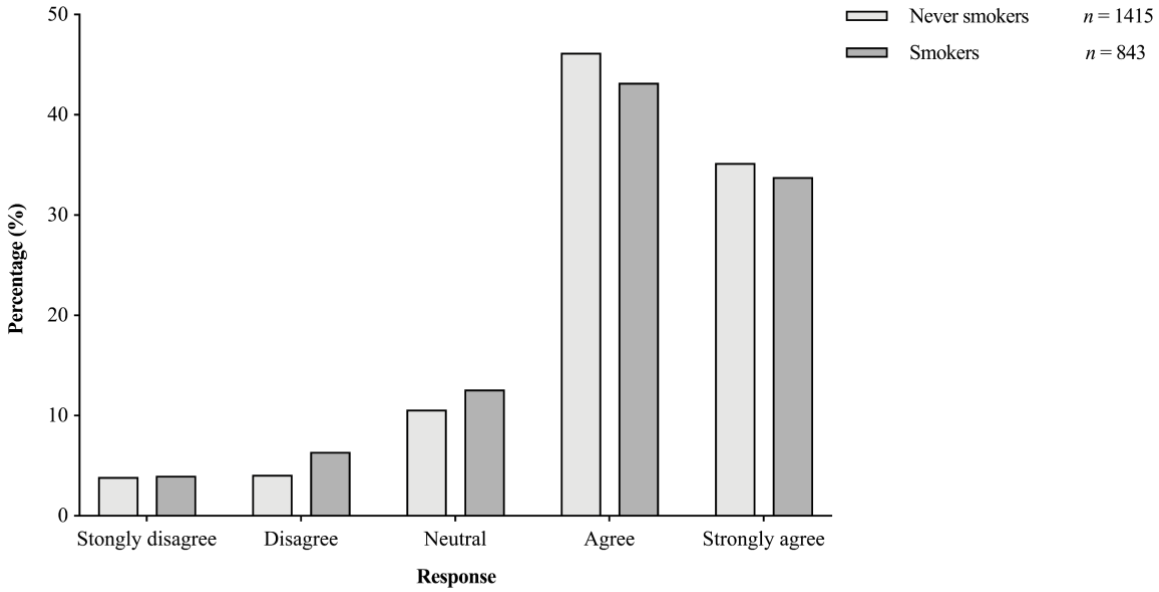


Figure 3.55 A comparison of the level of agreement from healthcare professionals who are smokers and never smokers in response to the statement *"I feel I need more information and guidance regarding e-cigarettes"* Data presented as percentage. The median level of agreement was *"agree"* for both groups. A Mann-Whitney U Test did not demonstrate statistical significance between the median level of agreement between *"smokers"* and *"never smokers"*. $p = .086$

Table 3.19 Comparisons between the clinical healthcare professional respondents were never smokers and smokers upon their preparedness for recommending patients upon the use of e-cigarettes.

Survey responses	Never smokers *n* = 1471	Smokers *n* = 884	*p*-value	
"I feel confident advising patients about e-cigarettes"				
Strongly agree	26 (1.8)	36 (4.1)	**< .001**[a]	
Agree	105 (7.1)	81 (9.2)		
Neutral	221 (15.0)	216 (24.4)		
Disagree	590 (40.1)	303 (34.3)		
Strongly disagree	474 (32.2)	206 (23.3)		
No response	55 (3.7)	42 (4.8)		
"I feel I need more information and guidance regarding e-cigarettes"				
Strongly agree	498 (33.9)	285 (32.2)	.086[a]	
Agree	654 (44.5)	364 (41.2)		
Neutral	150 (10.2)	106 (12.0)		
Disagree	58 (3.9)	54 (6.1)		
Strongly disagree	55 (3.7)	34 (3.8)		
No response	56 (3.8)	41 (4.6)		
"Would you recommend e-cigarettes to patients as a method to stop smoking?"				
Yes	529 (36.0)	440 (49.8)	**< .001**[b]	**< .05**[c]
No	870 (59.1)	406 (45.9)		**< .05**[c]
No response	72 (4.9)	38 (4.3)	-	-

Data are presented as frequency (percentage). P-values derived from Independent Samples Mann-Whitney U test[a], Chi-square test of Homogeneity[b] and post hoc analysis pairwise comparisons using multiple z-tests of two proportions [c]

3.3.5.5 Recommending e-cigarette as a smoking cessation method to patient

3.3.5.5.1 All clinical healthcare professional respondents

All clinical healthcare professional respondents (*n*=2355) were asked *"would you recommend e-cigarettes as a method to stop smoking?",* in total, 95.3% (*n*=2245) of the clinical healthcare professional respondents answered the question. The observed frequencies and percentages are presented in Table 3.17, of which, 43.2% (*n*=969) answered *"yes"* they would recommend e-cigarettes as a method to stop smoking, and 56.8% (*n*=1276) answered *"no"* they would not recommend e-cigarettes to their patients as a method to stop smoking (Figure 3.56).

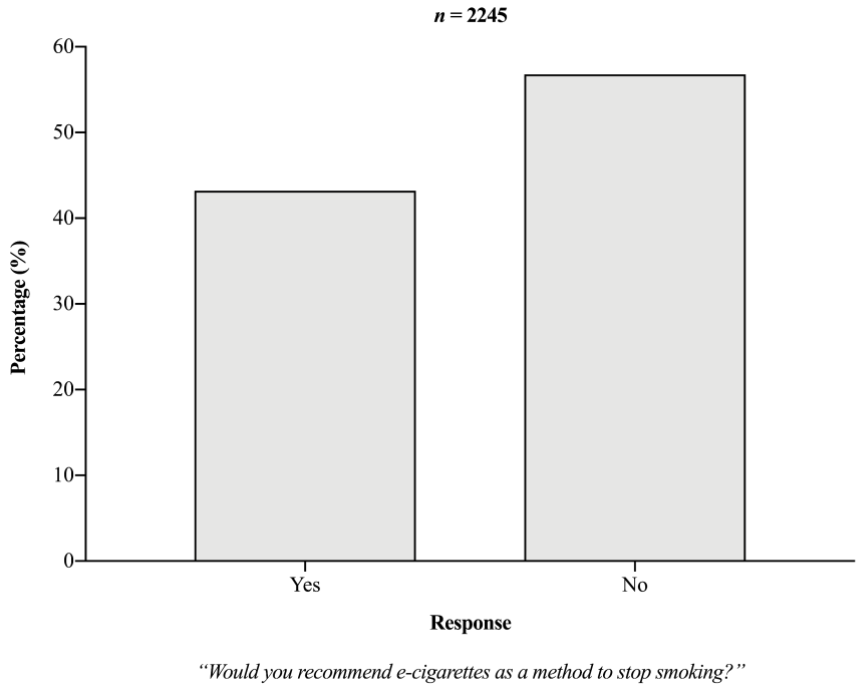
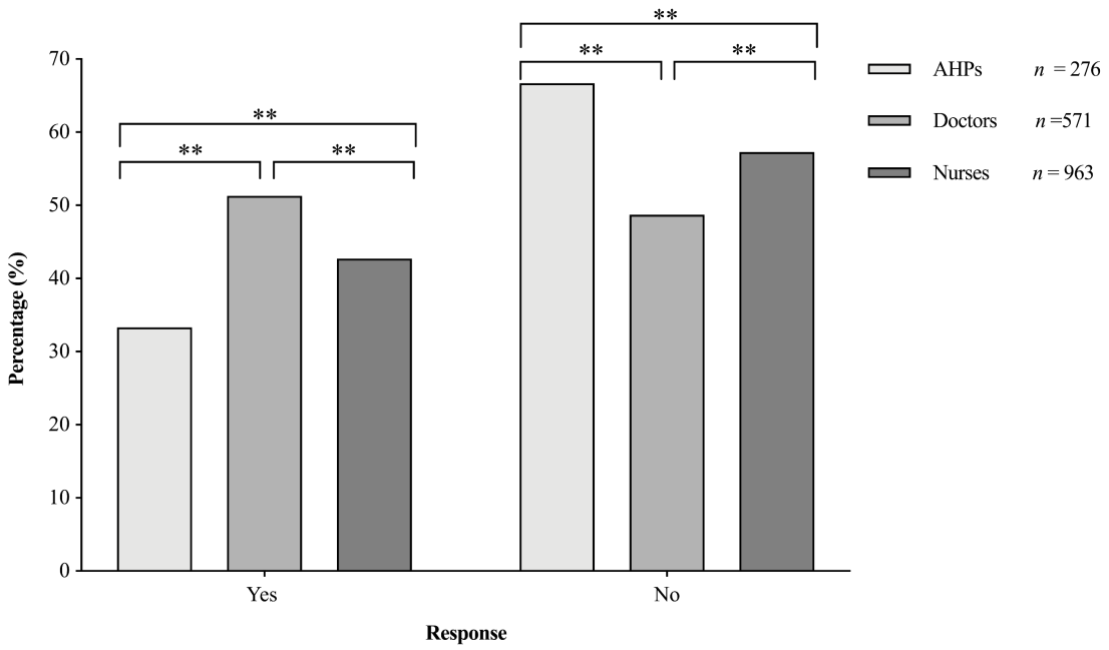


Figure 3.56 Percentage of clinical healthcare respondents who would recommend e-cigarettes to patients as a method to stop smoking. Data presented as percentage.

3.3.5.5.2 Allied healthcare professionals, doctors and nurses

In response to the question *"would you recommend e-cigarettes to patients as a method to stop smoking?",* the observed frequencies and percentages for each healthcare professional group (AHPs, doctors and nurses) are presented in Table 3.18 and Figure 3.57.

Notable differences were observed in the healthcare professional group responses $\chi^2(2) = 25.824$, $p < .001$. The effect size for this finding, Cramer's V, was moderate, .122. The group with the highest proportion of professionals saying *"yes"* they would recommend e-cigarettes as a method to stop smoking was doctors (51.3%, *n*=293), followed by nurses (42.7%, *n*=411, 41.0%) and AHPs (33.3, *n*=92), all $p < .017$ level. The group with the highest proportion of professionals saying *"no"* they would not recommend e-cigarettes to patients was AHPs (66.7%, *n*=184), followed by nurses (57.3%, *n*=552) and then doctors (48.7%, *n*=278), all $p < .017$ level.



"Would you recommend e-cigarettes to patients as a method to stop smoking?"

Figure 3.57 A comparison between AHPs', doctors' and nurses' opinion as to whether they would recommend e-cigarettes to patients as a method to stop smoking. Data presented as percentage. A chi-square test of homogeneity demonstrated statistically significant differences in opinions between each of the healthcare professional group, $p < .001$. Post hoc analysis with a Bonferroni correction demonstrated statistically significant proportional differences in the response between AHPs, doctors and nurses for each opinion, all $p < .017$.

3.3.5.5.3 Smokers vs never-smokers

In response to the question *"would you recommend e-cigarettes to patients as a method to stop smoking?",* the observed frequencies and percentages for the *"smoker"* and *"never-smoker"* groups are presented in Table 3.19 and Figure 3.58.

Notable differences were observed between the *"never smoker"* and *"smoker"* group responses $\chi^2(1) = 70.018$, $p < .001$. The effect size for this finding, Cramer's V, was weak, .003. The proportion of respondents who answered *"yes",* to recommending e-cigarettes to patients as a method to stop smoking, was greatest amongst the *"smokers"* (52%, n=440) in comparison to the *"never smokers"* (37.8%, n=529), $p < .05$. Conversely, the proportion of respondents who answered *"no"* was greater amongst the *"never smokers"* (62.2%, n=870) group in comparison to the *"smokers"* (48%, n=406), $p < .05$.

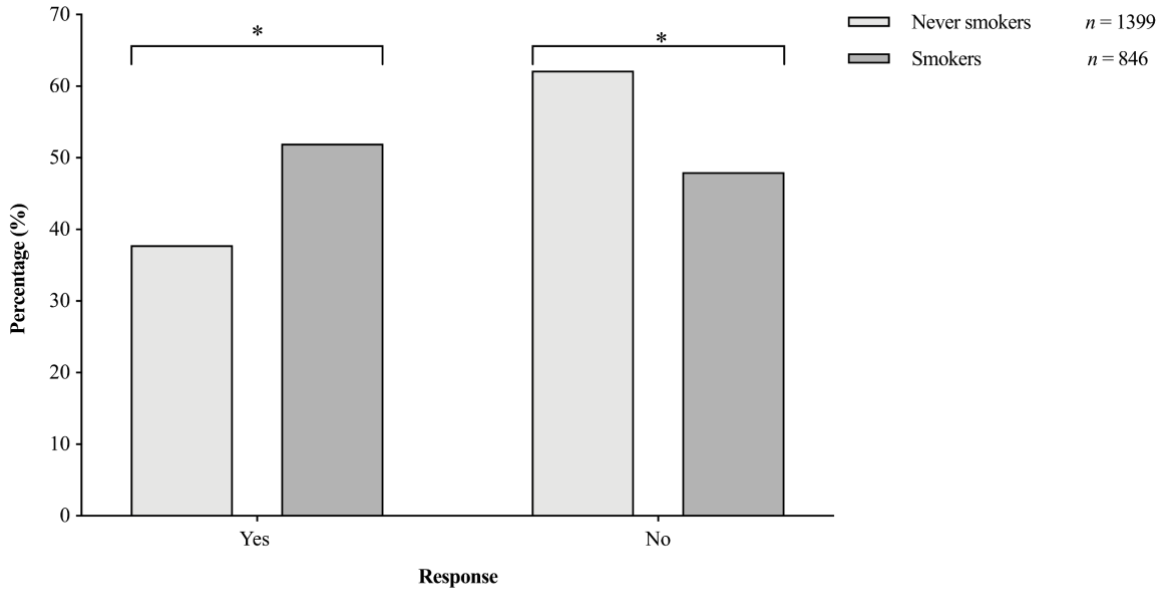


Figure 3.58 A comparison between the responses from clinical healthcare professionals who were smokers and never smokers on whether they would recommend e-cigarettes to patients as a method to stop smoking. Data presented as percentage. A chi-square test of homogeneity demonstrated statistically significant differences in opinions between the *"never smoker"* and *"smoker"* groups, $p < .001$. Post hoc analysis demonstrated statistically significant proportional differences in the response between *"never smokers"* and *"smokers"* for each opinion, all $p < .05$.

3.4 DISCUSSION

With 3035 individual respondents, this survey represents approximately 7% of the 44,000 healthcare professional employed by NHSGGC Health Board, by both number of respondents and as a percentage of the health region. Within the UK to our knowledge this is the largest survey relating to healthcare professionals' knowledge and perceptions of e-cigarettes, NRT and tobacco cigarettes.

The survey respondents and their responses can be analysed and interpreted across 6 main themes to help to understand the influences on beliefs and attitudes towards e-cigarettes in healthcare. These themes are: Descriptive analysis of respondents; knowledge and beliefs; gateway theory; awareness and attitudes towards e-cigarette regulation and workplace policy; and preparedness for informing patients about e-cigarette use.

3.4.1 Descriptive analysis of respondents

Tobacco smoking amongst healthcare professionals is a recognised barrier to tobacco interventions with patients (Sarna et al., 2014). Studies have demonstrated that health professionals have more success in convincing patients to stop smoking if they are not smokers themselves (Smith and Leggat, 2007). For effectual change to arise from policy within clinical practice, policy enactment is dependent on the "discretionary" application by the frontline *"patient facing"* healthcare professionals (Lipsky M, 1980). Therefore, how much a healthcare professionals personal smoking behaviour affects their professional attitude and clinical behaviour represents a critical issue in tobacco control (Smith and Leggat, 2007).

In our study 40% of the respondents were *"smokers",* with 8.4% of respondents identifying as *"current smokers"* and 31.6% of respondents identified as *"former smokers"*. Within our data, group comparisons demonstrated that the incidence of *"current smokers"* was greatest amongst the *"non-patient facing"* group compared to the *"patient facing"* group. In relation to tobacco control, doctors and nursing staff are seen by patients as the main "frontline" exemplars (Adriaanse and van Reek, 1989). In our study amongst the *"patient facing"* healthcare professionals, the smoking prevalence was greatest amongst nursing staff (11.2%) in comparison to doctors (3.3%). Our data is consistent with previous studies, which have demonstrated that (1) smoking prevalence of medical professionals tends to be lower than the general population (Smith and Leggat, 2007); and (2) within the medical profession smoking prevalence tends to be lowest amongst doctors and highest amongst nurses (Sarna et al., 2014). The lower tobacco smoking prevalence amongst the *"patient facing"* healthcare professionals may be a direct result of their professional role. Research has demonstrated that frontline medical professionals, in particular doctors are less likely to take up, and more likely to give up tobacco smoking earlier than the general population (Davis, 1993). This is because *"patient facing"* healthcare professionals tend be more aware of the dangers of tobacco smoking, as a direct result of their education and clinical exposure to tobacco-related

morbidity and mortality (Davis, 1993). Furthermore, the stigmatism associated with tobacco smoking and the unacceptability of engaging in contradictory behaviours to health promotion, often manifests itself within in the healthcare long before it does in society (Davis, 1993).

In comparison to other medical professionals, the heightened prevalence of smoking amongst nursing staff is a concern, given that nurses represent the largest healthcare professional group and are a powerful but potentially under-utilised smoking cessation resource (Juranić et al., 2017). Studies have suggested that the main potential reason for the large smoking prevalence among nursing staff might be linked to occupational stress, nurse education, peer influence and lack of support (O'Donovan, 2009, Strobl and Latter, 1998).

In our study the prevalence of *"former smokers"* (31.6%) provides a reassuring indication of estimation of quitting among health care professionals. In parallel with current smoking cessation trends within the UK, e-cigarettes were also the preferred smoking cessation aid to support quit attempts (Beard et al., 2016), with group comparisons demonstrating that the use of e-cigarettes to support quit attempts was greatest amongst the *"non-patient facing"* healthcare professionals. Given that we have already established that levels of education and personal behaviours can affect professional attitudes and clinical behaviour these group differences may be of interest. The paucity of evidence relating to the short- and long-term risks of e-cigarettes and non-medicinal nature of e-cigarettes could potentially explain why the use of e-cigarettes to support individuals own quit attempts is less popular amongst *"patient facing"* healthcare professionals, compared to *"non-patient facing"* healthcare professionals.

3.4.2 Knowledge and beliefs of tobacco cigarettes, NRT and e-cigarettes

Within clinical practice the implementation of evidence-based guidance on tobacco harm reduction is dependent on healthcare professionals having a basic knowledge and understanding of the principles which underpin why tobacco harm reduction strategies focus upon delivering nicotine without the products of combustion.

It is therefore essential that healthcare professionals understand that although nicotine is the primarily addictive component within tobacco cigarettes responsible for perpetuating nicotine dependence and persistent tobacco use, the harm caused by tobacco smoking is mostly related to the carcinogens, carbon monoxide, and thousands of other toxins contained with tobacco smoke, rather than nicotine itself. This is why smoking cessation tobacco harm reduction strategies have focused upon the use of pharmacotherapy to deliver nicotine without the products of combustion (e.g. nicotine replacement products, including patches, lozenges, microbats, inhalators and e-cigarettes), or medications designed to reduce or inhibit nicotine withdrawal symptoms (e.g. varenicline and bupropion); in order to provide tobacco smokers with practical means to engage in healthier and safer behaviours.

In accordance with these principles our data demonstrate that although nicotine was appropriately recognised as the least harmful tobacco smoke component by our survey respondents, both doctors and smokers considered nicotine to be less harmful to health, relative to the risk scores provided by their group comparators. However, with an overall median score of 8 our data suggests our survey respondents, like many other healthcare professionals tend to overestimate the harms of nicotine and still view nicotine as a relatively harmful component (Moysidou et al., 2016). With research demonstrating that there is no increased risk of cardiovascular disease associated with the long-term nicotine exposure from the use of snus or NRT (Lee, 2011, Lee, 2013a, Lee, 2013b, Mills et al., 2014). Such misconceptions relating to harms of nicotine amongst healthcare professionals is concerning as it represents a major obstacle in the implementation of tobacco harm reduction indicatives, as it can deter healthcare professionals from recommending NRT to stop smoking (Moysidou et al., 2016).

In line with the international research, our data demonstrate that e-cigarettes were perceived to be a less harmful alternative to tobacco smoking but more harmful and more addictive than NRT and oral medications (Beard et al., 2014, Nutt et al., 2014). With the subgroup analysis revealing that in comparison to their respective group comparators, doctors and smokers had a lower risk perception of both the harms and addictiveness posed by e-cigarettes, NRT and oral medications. Despite these differences, the relative ranking of the perceived level of risk and addictiveness for tobacco products, e-cigarettes, NRT was the same across all subgroups, which demonstrates that as an organisation there is a degree of congruence between the employee's values and the health boards philosophy that e-cigarettes are a product aimed at reducing tobacco produced harm. However, it is important to recognise that healthcare professionals perceive NRT to be safer and less addictive alternative to e-cigarettes. Therefore although NHSGGC may have an 'e-cigarette friendly' ethos, at the coalface, as seen in English smoking cessation staff, healthcare professionals maybe reluctant to recommend e-cigarettes over NRT (Hiscock et al., 2014, Beard et al., 2014).

Despite e-cigarettes being the only nicotine replacement product on the market capable of emulating both the physicality and modality of nicotine delivery associated with tobacco smoking, the acceptance and use of e-cigarettes as a smoking cessation aid amongst the healthcare profession has not been universally adopted. Research tracking the attitude changes of NCSCT stop smoking service staff towards e-cigarettes suggests that although the majority of staff did not view e-cigarettes to be a 'good thing', attitudes are transitioning towards a more favourable outlook; with 15% of smoking cessation practitioners agreeing or strongly agreeing that e-cigarettes are a 'good thing' in 2011, to 26% in 2013, and 24.4% in 2014 (Hiscock et al., 2014, Hiscock et al., 2015). In response to the same question, our data across all survey respondents demonstrates similar findings, with 28% agreeing or strongly agreeing that e-cigarettes are a 'good thing', 33.6% taking a neutral stance and 38.4% disagreeing or strongly disagreeing. Furthermore, in comparison to the other healthcare professional groups, both doctors and smokers had a significantly lower risk

perception in relation to the harms to health posed by nicotine and e-cigarettes and were more likely to view e-cigarettes as a 'good thing'.

It is important to recognise that smoking behaviours and occupational roles appeared to be influential factors in shaping risk perceptions and overall outlook on the use of e-cigarettes. With both doctors and smokers (current or former) having comparably lower risk perceptions in relation to the harms and addictiveness of nicotine and e-cigarettes, compared to the other healthcare professional groups. As risk perception is a highly personal process of decision making, based on an individual's frame of reference developed over a lifetime, among many other factors (Brown V, 2014), it is important to acknowledge that while the risk perception between smokers and doctors may be similar, the rationale behind the doctors' risk perception maybe fundamentally different to that of the smokers. Due to the survey collecting limited data regarding opinion we can only speculate as to why this relationship and differences in risk perception exists between the healthcare professional groups.

3.4.3 Attitudes towards e-cigarettes acting as a gateway to tobacco smoking.

In addition to the harm reduction benefits of e-cigarettes as a smoking cessation aid, concerns have been raised that e-cigarettes may act as an 'entry portal' for never smokers into nicotine use, addiction and subsequent tobacco use, in addition to renormalising smoking behaviours. With the World Health Organisation and many others raising concerns that adolescents or "young people" are the group of individuals most at risk from the gateway effect (World Health Organisation, 2016). In accordance with this concern all of the healthcare professionals we surveyed also expressed a level of concern that e-cigarettes may act as a gateway to tobacco smoking amongst never smokers, with the most concern being focused on adolescents. This was an opinion which was shared across all of the sub-groups.

Some studies have suggested that adolescents are most at risk of the "gateway effect" because by nature adolescents are more likely to undertake risky behaviours (Hilton et al., 2016), and may be more susceptible to the tobacco and e-cigarette industries' influential marketing and advertisements (Hansen et al., 2018). However, despite the "gateway effect" frequently being cited as a concern, to date, there is no strong evidence that indicates that e-cigarettes are acting as a gateway to tobacco smoking within the UK. With data from five large scale surveys conducted between 2015 and 2017 involving over 60,000 11-16 year-olds demonstrating that not only was the prevalence of regular e-cigarette use amongst never smokers negligible (between 0.1% and 0.5%) but that e-cigarette experimentation amongst young people did not result in regular e-cigarette use (Bauld et al., 2017).

3.4.4 Awareness and attitudes towards e-cigarette regulation and workplace policy.

Exposure to secondhand tobacco smoke is associated with adverse health effects, which include lung cancer, cardiorespiratory diseases, and low birth weights (Khader et al., 2011, Asomaning et

al., 2008, He et al., 1999). To protect the public from the harmful effects of secondhand smoke, smokefree legislation which prohibits smoking in enclosed public places and workplaces has been implemented in many countries and are part of policy in many jurisdictions. The impact of smokefree legislation has resulted in major public health benefits, including significantly reducing the rates of heart attacks and childhood asthma hospitalisations as well as pregnancy-related complications (Pell et al., 2008, Mackay et al., 2012, Mackay et al., 2010), in addition to influencing the changes in social attitudes and norms towards smoking by reducing the acceptability of smoking (Frazer et al., 2016).

In this regard, concerns have been expressed that the use of e-cigarettes might re-establish the act of inhaling nicotine and renormalise the act of tobacco smoking thereby undermining the success of smokefree legislation (Britton et al., 2016). The counter argument to this opinion is that given that e-cigarette use is almost entirely limited to those who are or have been smokers (Action on smoking and health, 2018), prohibitive policies which treat vaping in the same way as smoking, are overlooking the potential of e-cigarettes to support smokefree compliance and reduce the need for policy enforcement and in doing so may continue to expose people to the harms of tobacco smoke. This is why organisations such as NHSGGC have modernised their smokefree strategies to operate an e-cigarette policy which also allows the use of e-cigarettes in specified areas within hospital grounds (Greater Glasgow and Clyde NHS Board, 2015).

The existing research on NHSGGC healthcare professionals' attitudes towards e-cigarettes was conducted eight months following NHSGGC Core Brief which provided guidance on the use of e-cigarettes on NHS grounds smokefree (NHSGGC, 2017). The guidelines sanctioned that (1) staff, patients and visitors were allowed to use e-cigarettes on NHS healthcare facility grounds; (2) staff may only use e-cigarettes during rest breaks; (3) there are no additional breaks for smokers or those using e-cigarettes; and (4) e-cigarettes cannot be used within buildings or at entrances or exits to buildings. The premise of this guidance was to ensure that NHSGGC grounds remained smokefree and there was a more consistent approach to e-cigarette use, following the adoption of smoking cessation services "e-cigarette friendly approach".

In relation to these guidelines our data demonstrate that although the vast majority of NHSGGC employees felt they were aware of the e-cigarette policy, there was considerable variation in the interpretation of the guidelines, with only 12% of those respondents correctly identifying that e-cigarettes use was permitted. However a limitation of this study is that it does not help to clarify whether this finding was due to differences in the interpretation of whether the survey question was relating to e-cigarette use inside buildings, outside or in designated areas, and therefore the difference in the respondents' understanding of the guidance is difficult to interpret. Although a positive correlation was found to exist between healthcare professionals' perception of e-cigarettes being *"a good thing"* and their level of agreement towards smokefree legislation which permits the use of e-cigarettes on hospital grounds, two thirds of the respondents did not agree that e-cigarettes

should be permitted on hospital grounds. Our findings are consistent with a similar study conducted in Belgium which reported that two-thirds of all respondents were concerned that there was a risk of secondhand exposure from e-cigarette use and that 80% of healthcare professionals disagreed with allowing the use of e-cigarettes in public spaces, with the majority of respondents citing that they were concerned that e-cigarettes may renormalise tobacco smoking and lead to an increased uptake of smoking (Van Gucht and Baeyens, 2016).

Within our data, group comparisons demonstrated that *"smokers"* who were either current or former smokers had a greater awareness that e-cigarettes were permitted on hospital grounds and were more supportive of the decision for e-cigarettes to be used on hospital grounds. In contrast a greater proportion of *"never smokers"* stated they were unsure of the policy relating to the use of e-cigarettes on hospital grounds and opposed the decision that some hospitals within the UK allow the use of e-cigarettes on hospital grounds. The increased awareness of smokefree policy amongst smokers may reflect the direct impact that smokefree policy imposes upon their own personal smoking behaviours. Furthermore the heighted awareness of smokefree policy amongst smokers may have a positive impact, given that smokefree environments have been evidenced to protect smokers by creating an environment which (1) supports and sustains quit attempts; and (2) reduces tobacco cigarette consumption (Callinan et al., 2010, Fichtenberg and Glantz, 2002).

Together these data provides some insight into the disconnect that exists between policy initiatives and its interpretation at a grass root level. For alignment to occur between the organisations top-down edicts and what happens at the coal face in day-to-day practice, it may be prudent that NHSGGC uses a range of dissemination methods which provide healthcare professionals with the opportunity to understand the rationale behind the changes to policy.

3.4.5 Preparedness for informing patients about e-cigarettes use.

Healthcare professionals have the potential to make a large contribution to reducing smoking rates, by providing brief interventions and acting as a vital source of referrals to smoking cessation; in addition to influencing beliefs and attitudes towards e-cigarettes. While the effectiveness of brief interventions might appear small in percentage or absolute terms, as seen with our data the cumulative public health effect can be significant due to the frequency with which healthcare professionals encounter tobacco smokers within clinical practice (NHS Health Scotland, 2017). Therefore to maximise the effectiveness of the brief interventions offered by healthcare professionals, NICE recommend that healthcare professionals should be able to offer smoking cessation advice on using nicotine-containing products on general sale, including NRT and nicotine-containing e-cigarettes (NICE, 2018).

Given the increasing use of e-cigarettes as a smoking cessation aid, it is not unforeseen that this has coincided with an increasing number of patient enquiries about the use of e-cigarettes (Kandra et

al., 2014, Hiscock et al., 2014, Cummins et al., 2016), with 40% of healthcare professionals reporting that they regularly received inquiries about e-cigarettes. With less than 15% of our clinical healthcare professional respondents stating that they had received guidance on how to advise patients regarding e-cigarette use, it was not surprising that healthcare professionals' levels of confidence in advising patients on e-cigarettes use, inversely correlated with their self-reported need for further information ($r=-0.358$, $p<0.001$), with only 10.9% of respondents in agreeing with the statements that they felt confident to advise patients on the use of e-cigarettes; and 79.8% agreeing that that they felt they required more information on e-cigarettes.

Following the reported low levels of clinical guidance, confidence and familiarity and a clinical demand for more e-cigarette information and guidance, our data are consistent with previously published studies which have demonstrated that the majority of healthcare professionals said they would not recommend e-cigarettes as a method for smoking cessation (Kanchustambham et al., 2017). Although from our data we are unable to establish why healthcare professional are reluctant to recommend e-cigarettes; a study evaluating the views of smoking cessation practitioners has identified that the majority of smoking cessation practitioners do not recommend e-cigarettes because they are not medically licenced and as such the health service cannot provide them to patients (Hiscock et al., 2014). Furthermore, as e-cigarette technology advances and the nicotine delivery kinetics are likely to grow closer to those of cigarettes (Etter, 2014a), there is a growing concerns that individuals will become dependent on e-cigarettes (Hiscock et al., 2014). Nevertheless in the context of smoking cessation, e-cigarette dependence may not necessarily be a negative thing, as it may improve the effectiveness of successful quit attempts. In this regard a large UK based randomised control trial has demonstrated that e-cigarettes are almost twice as effective than nicotine-replacement therapy, at achieving 1-year smoking abstinence when both products were accompanied by behavioural support provided by NHS stop-smoking services (Hajek et al., 2019).

Although only 43.2% of healthcare professionals said they would recommend e-cigarettes as a method to stop smoking, a key finding in our data lies in the group comparisons which demonstrates that in addition to both doctors and smokers having lower risk perceptions regarding the levels of harms and addictiveness of nicotine and e-cigarettes, doctors (51.3%) and smokers (52%) were more likely to recommend e-cigarettes compared to the other healthcare professional groups. In keeping with previous studies which have demonstrated that healthcare professionals who view e-cigarettes as a harm reduction tool are 4.45 times more likely to recommend e-cigarettes (Kanchustambham et al., 2017), the harm perception of nicotine appears to be an influencing factor in the clinical recommendation of e-cigarettes.

Therefore, to increase the likelihood that healthcare professionals would encourage smokers to make the switch to e-cigarettes, it is crucial that any misperceptions relating to the harms of nicotine and e-cigarettes are addressed in a dove-tailed fashion which combines education with

training. This training should firstly educate healthcare professionals upon the harms of smoking as a disease rather than an addiction, and detail how health benefits are gained through the use of nicotine replacement which separates addiction from toxicity. Following this, all healthcare professionals should be provided with training regarding smoking cessation advice on all nicotine-containing products on general sale, including NRT and e-cigarettes. This is why the open access online course on e-cigarettes for healthcare professionals provided by the NCSCT will be a welcomed and valuable resource (NCSCT, 2018). In addition to this, it is also important that medical education about e-cigarette use is not confined to a single lecture or workshop but should be integrated throughout the medical curriculum and practicums.

3.4.6 Limitations

Our study has several limitations which should be acknowledged. Although numerically our response rate which represents approximately 7% of all healthcare professionals employed by NHSGGC, may appear low with the potential for non-response bias, our response rate is concordant and comparable with other healthcare professional surveys (Dykema et al., 2011)

While this survey was open to all NHS healthcare professionals working within the NHSGGC Health Board, our sampling frame defined by our methods means that our responses were predominately from healthcare professionals working within either secondary or tertiary healthcare and that primary care healthcare professionals' responses are likely to be underrepresented. As primary care healthcare professionals are not routinely provided nor have access to a ggc.scot.nhs.uk email account they would have been unlikely to have had access to the online survey. Similarly, primary care healthcare professionals would have been unlikely to have been present within the hospitals when the paper questionnaires were disturbed.

As the survey returns only represent approximately 7% of those invited to be survey participants, there is the potential that the active respondents represent a non-random sub-population who have engaged with the survey due to potential unknown factors influencing engagement and active participation. This incomplete response rate with potential for factors influencing engagement might represent a selection bias. Accordingly, collider bias has to be considered when interpreting these survey results particularly with regards to any associations or non-association demonstrated between participant groups and survey responses.

Comparison of the details of the respondents to that of the distribution of the demographics of the whole of the group invited to participate in a survey can help identify any demographic selection bias with over or underrepresentation of identified demographic groups. However, while this may help identify whether the demographic groups have equal engagement and representation in the survey, it will not demonstrate whether the responses given by those who do engage from any particular demographic group is truly representative of a random selection of their demographic

group or influenced by other potentially unknow factors. While certain sensitivity analysis methods have been described to adjust data for collider bias, it is difficult to accurately demonstrate, control or adjust for such bias when the data that represents the true distribution of responses within the population and sub-populations sampled is not available to use as a reference.

It is important to acknowledge that the external validity of findings may have been limited by our sample size, cross sectional design and non-probability sampling methods. Where in our efforts to reduce the impact of coverage bias and non-response error, we made the purposeful decision to identify survey respondents through a mixed-mode approach of online and paper surveys. We are aware that some healthcare professionals may have completed both a paper and an online survey, and without the ability to uncover duplicate paper responses, this may have subjected our findings to a response bias. It is also inevitable that self-selection bias will exist within our resulting data, given the fact that participation in the study was optional and we recognise that the propensity of survey participation (or not) will be influenced to a certain extent by an individual's own interest in the research topic. Therefore, caution should be taken when generalising the reported findings to all NHSGGC healthcare professionals. In addition to this our study was geographically limited to healthcare professionals working within NHSGGC, and therefore the generalisation of our findings to other healthcare professionals working in other organisations would need the use of discretion.

It is also important to acknowledge that although our survey was developed from a pre-existing e-cigarette research survey with the involvement and input from other healthcare professionals and researchers, this survey has not been formally validated. In addition to this, it is therefore critical to mention that we did receive feedback from two respondents who considered the wording of the question *"how often do you see patients who smoke in your working environment?"* to be ambiguous, as the words *"see"* and *"in your working environment"* could be interpreted as physically "seeing" a patient smoking, opposed to a clinical healthcare professional directly "seeing" a patient who smokes. To address this concern all of the responses to this question were individually cross referenced to the healthcare professional's occupational role, and responses from non-patient facing healthcare professionals and non-clinical patient facing healthcare professionals were removed, for the analysis of this question and subsequent questions which were aimed only at clinical healthcare professionals. Although we did not receive any direct participation feedback regarding the statement *"do you agree e-cigarettes are a good thing?"* it is worthwhile to note that Hiscock et al. cited the same survey question as limitation of their research on smoking practitioners' attitudes towards e-cigarettes (Hiscock et al., 2014). Through the inspection of verbatim comments Hiscock et al. identified the reason for this was because the comparator of e-cigarettes had not been clearly established within the survey question, therefore respondents could be comparing e-cigarettes to combustible cigarettes or to no products at all.

In looking to gain an understanding of the views of clinicians and other healthcare professionals with regards to e-cigarettes and nicotine replacement therapies and its place in healthcare, choosing

a cross-sectional survey approach was considered the most appropriate method to generate a broad understanding of current views amongst a diverse healthcare workforce. The benefit of the survey approach utilising the NHSGGC email network, was that it allowed a rapid distribution of the survey to a large number of healthcare professionals within a short period of time. Accompanied by the simultaneous distribution of a paper version of the survey, this allowed the survey to reach a significant breadth of the of the healthcare workforce including most of the different workforce sub-groups. Importantly this mass survey allowed the survey to reach the range of the workforce within each different sub-group which would likely not have been possible via other measures. In undertaking a survey approach, the survey was not only accessible to the various workforce groups surveyed but it helped reduce the risk of potential bias on the part of the study investigators in choosing individuals to survey, while also allowing respondents to participate with anonymity. E-cigarettes is a subject not without some controversy and with the potential for anonymised responses which could be completed in private, individuals who may not be entirely comfortable with discussing their views on a topic such as e-cigarettes via an interview could feel enabled to participate in the survey and express their personal views. The downside of this method of survey however is that it is reliant on self-selecting engagement on the part of the survey participant and this allowed for potential self-selection bias in those engaging with the study. The structured use of closed questions and Likert scale type questions with the limited use of free text responses helped standardise the responses to a format compatible with quantitative analysis of the respondents' data. Ideally, in order to gain a better understanding of the beliefs and motivating factors behind the views of different groups within the healthcare workforce, a further series of focused and structured interviews to probe and clarify the views and influences supporting the beliefs of individuals would have been of interest. This would have provided better qualitative data, however structured interviews across a broad and diverse workforce to follow the survey would have required a considerable investment of resources beyond the means of this research to ensure a diverse purposive sample was achieved from across all different subgroups. In summary the survey approach allowed a relatively quick, efficient and very cost-effective method of investigating the views of the NHSGGC healthcare workforce relating to e-cigarettes while allowing the widest opportunity for any individual to participate. Across such a large and diverse demographic, this data would simply would not have been possible to obtain with other techniques such as structured interviews.

Finally, it is likely that our survey findings relating to healthcare professional knowledge and perceptions of e-cigarettes are likely to have evolved in response to the dynamic changes following the development of e-cigarette technology, research, regulation and policy.

3.4.7 Conclusions

This survey suggests that given the substantial interest amongst smokers who are reliant upon healthcare professionals as a source of guidance regarding e-cigarettes, healthcare professionals are in a prominent position to offer brief interventions and influence how smokers view e-cigarettes, which could improve smoking cessation rates and subsequently improve patient outcomes. While it is reassuring that healthcare professionals view e-cigarettes and nicotine replacement patches as a less harmful alternative to tobacco smoking, misconceptions relating to harms of nicotine, alongside low levels of confidence and familiarity with guidance on how to advise patients on the use of e-cigarettes exist. Therefore, it is imperative that education is provided to establish congruence between healthcare professionals' beliefs and tobacco harm reduction policy in order that smokers wishing to stop smoking are provided with both effective and consistent practitioner advice. Healthcare professionals should have readily available access to educational resources and evidence-based guidelines which are regularly updated to reflect the rapidly expanding body of emerging research and technological advancements relating to e-cigarettes.

A CROSS-OVER STUDY INVESTIGATING THE ACUTE EFFECTS OF E-CIGARETTES AND TOBACCO CIGARETTES ON VASCULAR AND RESPIRATORY FUNCTION IN HEALTHY VOLUNTEERS

4.1 INTRODUCTION

Within the UK, e-cigarette use is largely confined to current and ex-smokers and use amongst never smokers remains low. Of the 3.6 million e-cigarette users, just under 2 million are ex-smokers; 1.4 million are current smokers; and 200,000 are never smokers (Action on Smoking and Health, 2019a). Current smokers have a high degree of interest in using e-cigarettes, because of the perception that e-cigarettes are a healthier alterative to tobacco smoking, and unlike conventional NRT, e-cigarettes are capable of emulating both the physicality and modality of nicotine delivery associated with tobacco smoking. Consequently, e-cigarettes have become the preferred smoking cessation product to support their quit attempts (Beard et al., 2016). In the absence of credible and validated science which quantifies the comparative risks of cardiovascular disease and lung disease, there is concern that e-cigarettes may be nothing more than a more sophisticated version of the "light" cigarette, which smokers mistakenly believed to be safer than regular cigarettes and to offer meaningful reductions in tar or nicotine (National Cancer Institute, 2001).

Rather than waiting several decades for observational studies to determine whether or not e-cigarettes are causally linked to adverse health outcomes, researchers are challenged to develop a science base to inform public health policies and educate consumers about these products. Several investigatory steps are required to determine the disease risk associated with e-cigarettes. To circumvent the observational time lag, biomarker studies may provide insights into potential cardiovascular and respiratory risks.

Therefore, in this study our aim was to investigate the acute physiological and biochemical effects following e-cigarette use in comparison to tobacco smoking. Parameters investigated included: vascular function; respiratory function; circulating microparticles (MPs), particularly platelet MPs (PMPs, a biomarker of haemostasis and thrombosis) and endothelial MPs (EMPs, a biomarker of endothelial function and injury); and levels of circulating soluble adhesion and selectin molecules. In this study it was hypothesised that both e-cigarettes and tobacco cigarettes would elicit acute cardiorespiratory effects; however, the effects would be less pronounced following e-cigarette use.

4.2 METHODOLOGY

4.2.1 Study design and participants

A single-centre prospective randomised cross-over study was conducted at the Institute of Cardiovascular and Medical Sciences, University of Glasgow between June 2016 and December 2016.

Participants were included if they were male, at least 18 years of age and a habitual tobacco smoker of one or more tobacco cigarettes per day. Exclusion criteria included an established history of cardiovascular, respiratory or renal disease; a lack of ability to provide written consent; and history of allergy to any substance within the e-liquid (nicotine, propylene glycol, vegetable glycerol, vanillin, furaneol and ethyl vanillin).

All participants attended for two study visits at the same time of day, with a minimum of 24 hours between each visit. Prior to each study visit participants were asked to fast and to refrain from tobacco smoking and e-cigarette use for a minimum of 4 hours, and refrain from consuming caffeinated and alcoholic products for a minimum of 12 hours. Participants were exposed to each intervention (either tobacco cigarette smoking or e-cigarette use) on separate study days. Study investigations were performed pre and post intervention (Figure 4.1).

Ethical approval for this study was granted by the University of Glasgow College of Medical, Veterinary and Life Sciences Research Ethics Committee (Reference Number 200150108) and complied with the Declaration of Helsinki. All participants provided informed written consent.

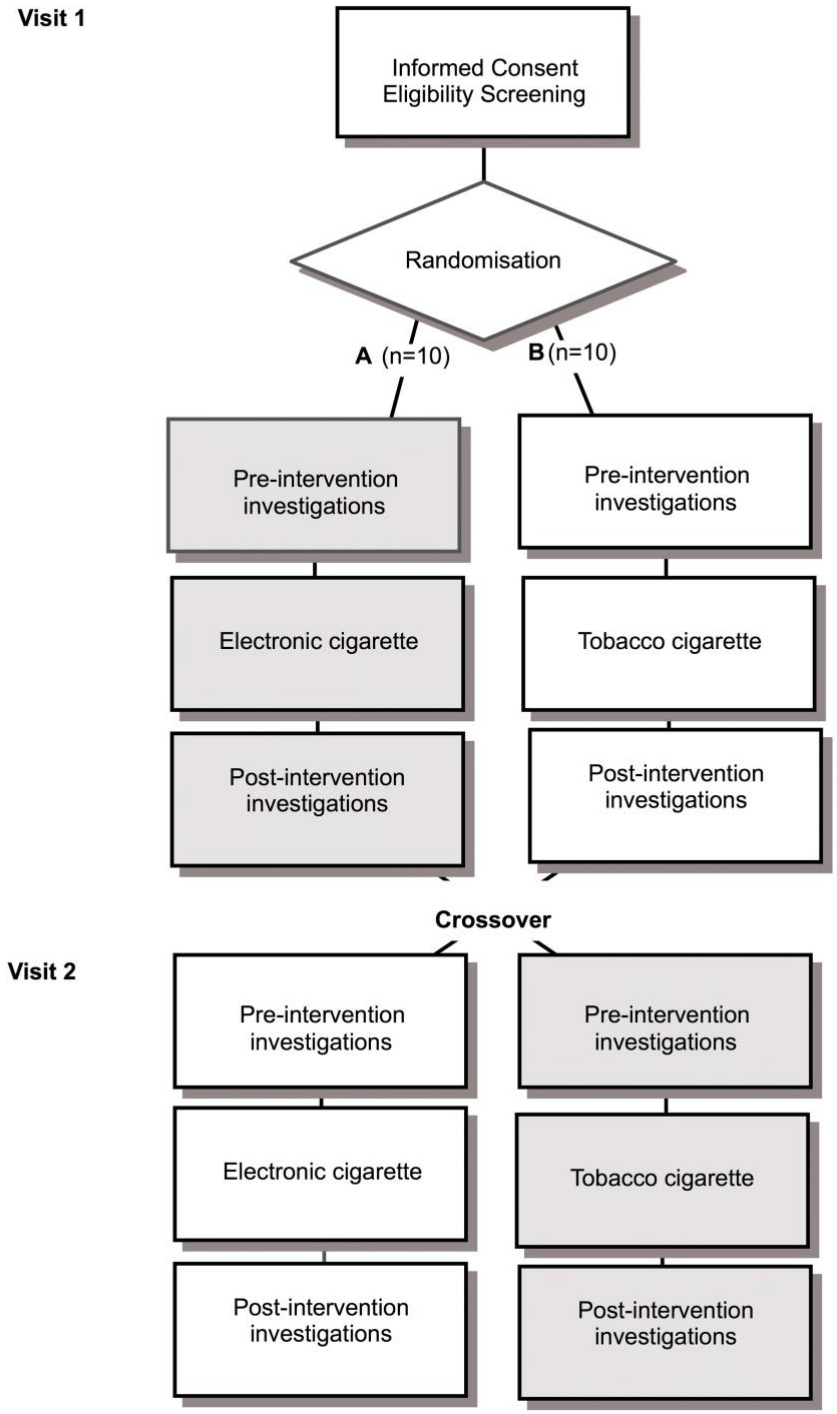


Figure 4.1 Study Design. 20 healthy male smokers were randomised in a crossover fashion to e-cigarette and tobacco cigarette study arms. Study investigations were performed before and after each intervention. The washout period between study visits was a minimum of 24 hours.

4.2.2 Recruitment

Twenty male participants were sequentially screened and recruited into the study from a poster campaign. All of the participants were considered healthy if they self-reported that they had no cardiovascular, respiratory or renal disease.

4.2.3 Randomisation

Participants were randomised in a 1:1 fashion to either study arms "A" or "B", which determined the order that the participants received each intervention. The randomisation sequence was generated using a secure web-based random sequence generator. The investigator and participants were not blinded to the randomisation.

4.2.4 Recompense

Upon completion of the study all participants were offered a £20 shopping voucher as recompense for their time and efforts for taking part in the study. Participants were able to keep the e-cigarette device and e-liquid which they used in the study if they chose to. All participants were offered an optional referral to NHSGGC Smokefree Services for smoking cessation support.

4.2.5 Interventions

For the tobacco smoking intervention, participants were asked to smoke one of their regular tobacco cigarettes.

For the e-cigarette intervention participants were asked to use a commercially-available second generation e-cigarette device with nicotine-containing e-liquid. The device consisted of a 1300mAh variable voltage rechargeable battery, a tank and an atomiser (SmokeMax, Groove Trading Ltd, Glasgow). Each tank contained approximately 1.5 ml of e-liquid. The e-liquid used in the study was Totally Wicked Red Label, American Red Tobacco with a reported 18mg/ml nicotine. All of the e-liquid used in the study was manufactured from the same batch. Specific details relating to the characterisation and analysis of the e-cigarette device and e-liquid are presented in Chapter 2.

Each participant was provided with a new e-cigarette device, which was prepared by the study investigator. The investigator filled the tank with e-liquid and set the battery voltage to 3.3 volts. When asked to use the e-cigarette participants were required to take 15 "puffs" of the e-cigarette. This is considered to be comparable to the amount of nicotine obtained from smoking a conventional tobacco cigarette, approximately 0.5mg (Geiss et al., 2015).

4.2.6 Study Investigations

All study investigations were performed before and after each intervention. One trained investigator (myself) performed all of the investigations.

4.2.6.1 Assessment of vascular function

Non-invasive blood pressure measurements were taken using the auscultatory method on the participant's dominant arm using a blood pressure cuff and sphygmomanometer (Hokanson SC12, Cuff, Hokanson DS400 Aneroid sphygmomanometer, DE Hokanson, Inc, Belleve, WA, USA). Three repetitive blood pressure recordings were taken and the mean systolic blood pressure (SBP) and diastolic blood pressure (DBP) recordings were calculated. Post intervention blood pressure measurements were taken 10 minutes following the intervention.

Heart rate was measured immediately before and one minute following the intervention. The radial pulse was palpated, and the arterial pulse was counted for 60 seconds.

Reactive hyperaemia index (RHI), a measure of endothelial function via peripheral arterial tonometry (PAT); and augmentation index (AI), a measure of arterial stiffness, were assessed using a non-invasive plethysmographic method (EndoPAT-2000; Itamar Medical Ltd, Caesarea, Israel) in accordance with the manufacturers recommendations. Participants were studied in the supine position in a quiet, temperature controlled room. After a ten-minute equilibrium period a blood pressure cuff was placed on the participant's non-dominant upper arm (the experimental arm) while the contralateral arm served as a control. Pneumatic probes were fitted to the index fingers of each hand. Baseline pulse wave amplitude (PWA) was measured for five minutes. The blood pressure cuff was then rapidly inflated in the experimental arm 60 mmHg plus SBP (the occlusion pressure did not exceed 200 mmHg) for a duration of five minutes. After exactly five minutes of occlusion the blood pressure cuff was rapidly deflated to induce flow mediated reactive hyperaemia. A post-occlusion recording was then measured for a further five minutes. Post intervention PAT was recorded 15 minutes following the intervention. The PAT data was automatically analysed using proprietary software (EndoPAT-2000; Itamar Medical Ltd, Caesarea, Israel) in an operator-independent manner. The RHI was calculated as the ratio of the of the post-occlusion average pulse amplitude to the baseline average pulse amplitude. The values were normalised to the measurements in the contralateral arm which served as a control to compensate for non-endothelium dependent systemic effects. AI was calculated from the PAT waveform and functioned as a measure of medium and large arterial wall elasticity. As AI is related to heart rate, the AI was corrected to a standard heart rate of 75 beats per minute ($AI_{@75}$).

4.2.6.2 Blood sampling

Blood sampling was obtained from 18 of the 20 study participants. Blood samples were collected from the participant's dominant arm using sodium citrate 3.2% and Z serum separator clot activator VACUETTE® tubes, before and five minutes following intervention. To obtain platelet free plasma (PFP) the samples were centrifuged at 2000 relative centrifugal force (RCF) for 10 minutes, before removing the plasma and centrifuging at 1500 RCF for 20 minutes. The serum samples were

obtained by centrifuging whole blood at 2000 RCF for 10 minutes after which the serum was transferred into storage tubes. All samples were stored at -80°C until analysis.

4.2.6.3 Measurement of serum soluble adhesion and selectin molecules

For assessment of the serum soluble adhesion and selectin molecules measurements were performed in duplicate. The serum samples were thawed and then centrifuged at 1000 RCF at 4°C for 10 minutes. The molecules were measured using MILLIPLEX® MAP Kit Human Cardiovascular Diseases Magnetic Bead Panel 2 (Cat. No HCVD2MAG-67K, Merck) and MILLIPLEX® MAP Human Cardiovascular Disease Panel 4 (Cat. No. HCVD4MAG-67K, Merck) in accordance with the manufacturers recommendations. The serum soluble adhesion and selectin molecules quantified were sICAM-1 (soluble intercellular adhesion molecule 1), sVCAM-1 (soluble vascular adhesion molecule 1), sE-selectin (soluble endothelial leukocyte adhesion molecule 1), sP-selectin (soluble platelet selectin), and PECAM-1 (platelet endothelial cell adhesion molecule 1). To qualify the assay performance two quality controls were performed with each plate. The biomarkers for each sample were quantified using Luminex®, XMAP®, MAGPIX® instrument (MAGPX12027001). The results were then analysed using the Luminex® xPONENT® software (v4.2). Statistical analysis was performed on the derived from the means from the duplicates.

4.2.6.4 Measurement of microparticles

For MP measurements, technical triplicates were performed for all samples. The PFP was thawed and 50µl of PFP was incubated on ice and in the dark for 30 minutes with 5µl of anti-CD42b-FITC (1:600) (clone HIP1, BD-Pharmingen) and 6µl of anti-CD31-APC/Cy7 (1:600) (clone WM59, Biolegend). Subsequently 2.5µl of Annexin-V-alexa 647 (Biolegend); 3µL of 0.5mol/L $CaCl_2$(aq) (Sigma); and 233.5 µl of NaCl(aq) 0.9 % were added to make a final reaction volume of 300µl. FITC- and APC/Cy7-conjugated isotype-matched monoclonal antibodies (Biolegend) were used for negative controls. MPs were defined as particles identified between 0.1-1 µm in diameter. MP events were measured using flow cytometry (FACS Canto II – BD Biosciences) at constant medium flow for 4 minutes. The MP events were gated according to size (0.1-1 µm) at forward scatter and side scatter, both in log scale, using 1 µm size beads as a reference (Flow cytometry sub-micron size reference kit – Molecular Probes, Life Technologies). MPs were identified as total MPs (Annexin V+), PMPs (Annexin V+ CD31+ CD42b+) and EMPs (Annexin V+ CD31+ CD42b-). The concentrations of MPs were calculated using the counting beads (flow cytometry sub-micron size reference kit – Molecular Probes Lyfe Technologies) as a known standard with 1 ml of PFP used for normalisation. FACS data was analysed using Flow Jo™ software (v10.0.7, Tree Star, Inc., Oregon, USA). The absolute number of MPs, EMPs and PMPs were calculated using the following formula: MP/mL = A x (B/C) x 20 where A = total number of MP events observed in the constant flow of 4 min; B = total number of counting beads added in the FACS

tube before acquisition; C = total number of beads counted in the constant flow of 4 min; and 20 is the correction factor for 1 mL of plasma. Statistical analysis was performed on the means of MPs, EMPs and PMPs derived from the technical triplicates.

4.2.6.5 Assessment of respiratory function

A MicroLab^{TM} spirometer (Micro Medical Limited, Kent, England) which complies with both the American Thoracic Society and European Respiratory Society 2005 standards was used. Spirometry measurements were taken including FEV_1, FVC, FEV_1/FVC ratio and PEF. The machine was calibrated before spirometry recordings. Height and weight were recorded. All participants were asked to take a deep breath (as large as possible) and blow out as hard and as fast as possible until there was no air left. Spirometry was repeated a minimum of 3 times until the British Thoracic Society quality criteria were met. The procedure was performed before and 25 minutes following the intervention. The "best" spirometry readings were then used for further analysis.

4.2.6.6 Assessment of exhaled carbon monoxide

Exhaled carbon monoxide (eCO) was measured using the Bedfont Micro^{+TM} Smokerlyzer eCO monitor (Bedfont® Scientific Ltd, Kent, England) according to the manufacturers recommendations. The Smokerlyser measures eCO levels in parts per million (ppm) based on the conversion of eCO to carbon dioxide over a catalytically active electrode. An eCO level $\leq$ 6 ppm is considered normal and equates <1% of CO in blood. Participants were asked to hold their breath for 15 seconds before exhaling slowly and fully into the mouth piece during which the eCO was measured. eCO levels were recorded after each breath. Measurements were taken at baseline and three minutes following the intervention.

4.2.7 Outcome measures

The primary end point of this acute exposure study was to investigate the immediate effects upon endothelial function following tobacco cigarette use in comparison to e-cigarette use. Secondary end points were to assess the acute differences in the haemodynamic, pulmonary and biomarker responses following exposure from tobacco cigarettes in comparison to e-cigarettes.

4.2.8 Statistical Analysis

Visual inspection of box-plots and the Shapiro-Wilk test was applied to assess normality of the data and identify outlier data points. Parametric and non-parametric tests were used as appropriate. Continuous variables were expressed as mean ± SD or median and 25^{th}-75^{th} percentiles. Comparisons of the baseline characteristics between study arms "A" and "B" were made using Student's t-test and Mann-Whitney U-test. Paired Student's t-tests and related samples Wilcoxon signed rank tests were used to compare continuous variables between pre- and post intervention, as

appropriate. A Two-Way Repeated Measures ANOVA of intervention (e-cigarette and tobacco cigarette) and time point relative to intervention (pre- and post-intervention) was also performed, relating to all dependent variables (Appendix 3). Statistical significance was set at 0.05 and analyses were conducted using SPSS statistical software (IBM SPSS Statistics, Version 24.0. Armonk, NY: IBM Corp) and GraphPad Prism version 7.00 for Mac OS X (GraphPad Software, La Jolla California USA, www.graphpad.com).

4.3 RESULTS

4.3.1 Study Cohort

Baseline characteristics are summarised in Table 4.1. All participants (mean age 31.6 ± 10.5 years) were regular tobacco smokers and consumed an average of 7 tobacco cigarettes per day. Statistical analysis demonstrated that these characteristics were similar between participants who had been randomised to start with study arm A and those who started with study arm B.

There was heterogeneity in the brand of tobacco cigarettes used; although all were commercially available cigarettes. In total, there were six different brands: 10 participants smoked Marlboro Gold, 4 Golden Virginia, 2 Amber Leaf, 2 Café Crème, 1 American Sprit, 1 Mayfair.

Table 4.1 Baseline characteristics

Characteristics	All (n=20)
Age (years)	31.6 ± 10.5[a]
Body Mass Index (kg/m^2)	25.7 ± 5[a]
Smoking duration (years)	13 (7-22)[b]
Number of tobacco cigarettes smoked (per day)	7 (1-30)[c]
Number of days between study visits	6 (1-13)[b]
SBP (mmHg)	123 ± 13[a]
DBP(mmHg)	79 ± 10[a]
HR (bpm)	64 ± 9[a]
RHI	1.91 ± 0.41[a]
PWA occluded arm (AU)	833 ± 387[a]
PWA control arm (AU)	871 ± 423[a]
AI (%)	-8.2 ± 10.9[a]
$AI_{@75}$	-15.0 ± 12.1[a]
eCO (ppm)	5 (2-11)[b]
FEV_1 (L)	4.2 ± 0.6[a]
FVC (L)	5.3 (4.9-5.8)[b]
FEV_1/FVC (%)	81.5 ± 6.9[a]
PEF (L/min)	570 ± 66[a]

Data are presented as mean ± SD[a], median (25^{th}-75^{th} percentiles)[b] or mode (range)[c] as appropriate.

4.3.2 Vascular function

Table 4.2 summarises the cardiovascular changes following the use of both interventions. One minute following the use of both an e-cigarette and tobacco cigarette, heart rate significantly increased (Figure 4.2). However, tobacco smoking elicited a significantly greater increase in heart rate (15 ± 12 bpm; $p < .001$) in comparison to the increase following e-cigarette use (Table 4.3). Whilst no statistical significant difference was observed in either systolic or diastolic blood pressure following the use of an e-cigarette or tobacco cigarette in comparison to the baseline parameters, the changes in systolic blood pressure were greater following tobacco cigarette use (4 ± 9 mmHg) compared to e-cigarette use (-1 ± 6 mmHg) ($p = .046$) (see Table 4.3).

A statistically significant increase in RHI ($p = .006$) and an increase in AI ($p = .010$) were seen immediately after using an e-cigarette. Changes in these parameters were not statistically significant after using a tobacco cigarette ($p > .05$). When the changes in AI were compared between e-cigarettes and tobacco cigarettes pre and post intervention, there were statistically significant differences between the interventions (5.6 ± 8.0%, $p = .006$) (Figures 4.2b, 4.3a and table 4.3). However, when the AI was standardised to $AI_{@75,}$ no significant difference was seen following either e-cigarette or tobacco cigarette use or between interventions (all $p > .05$).

Exposure to e-cigarettes and tobacco cigarettes led to a significant reduction in PWA in both the occluded arm (both interventions $p < .001$) and the control arm (e-cigarette $p = .001$, tobacco cigarette $p < .001$) (Figure 4.3b and 4.3c).

4.3.3 Circulating Biomarkers

Table 4.3 summarises the change in circulating biomarker changes following the use of both interventions. The serum concentrations of sP-selectin decreased following e-cigarette exposure ($p = .026$). However, no significant changes in the concentrations of sP-selectin were seen following tobacco cigarette exposure ($p > .05$). Conversely, serum concentrations of PECAM-1 decreased following tobacco cigarette use ($p = .028$). No significant changes in the concentration of PECAM-1 levels were demonstrated following e-cigarette use ($p > .05$). In addition, no significant changes were detected in the serum concentrations of sICAM-1, sVCAM-1 or sE-selectin following either interventions (all $p > .05$).

Five minutes following tobacco cigarette use, the total number of circulating MPs and EMPs significantly increased ($p < .001$). In contrast, no significant changes in either the total number of MPs or EMPs were detected five minutes following e-cigarette use ($p > .05$) (Figures 4.4a and 4.4b). The total number of PMPs five minutes following both interventions significantly increased ($p < .001$) (Figure 4.4c).

4.3.4 Respiratory Function

Table 4.4 summaries the changes observed in the respiratory function and eCO levels at baseline and following the use of both interventions. No statistically significant changes were seen for FEV1, FVC or FEV1/FVC following either the use of an e-cigarette or a tobacco cigarette. PEF significantly decreased following the use of an e-cigarette ($p = .019$) but not following the use of a tobacco cigarette ($p > .05$). Exhaled CO increased following tobacco cigarette use ($p < .001$) whereas an overall reduction in eCO levels was seen following e-cigarette use ($p = .007$).

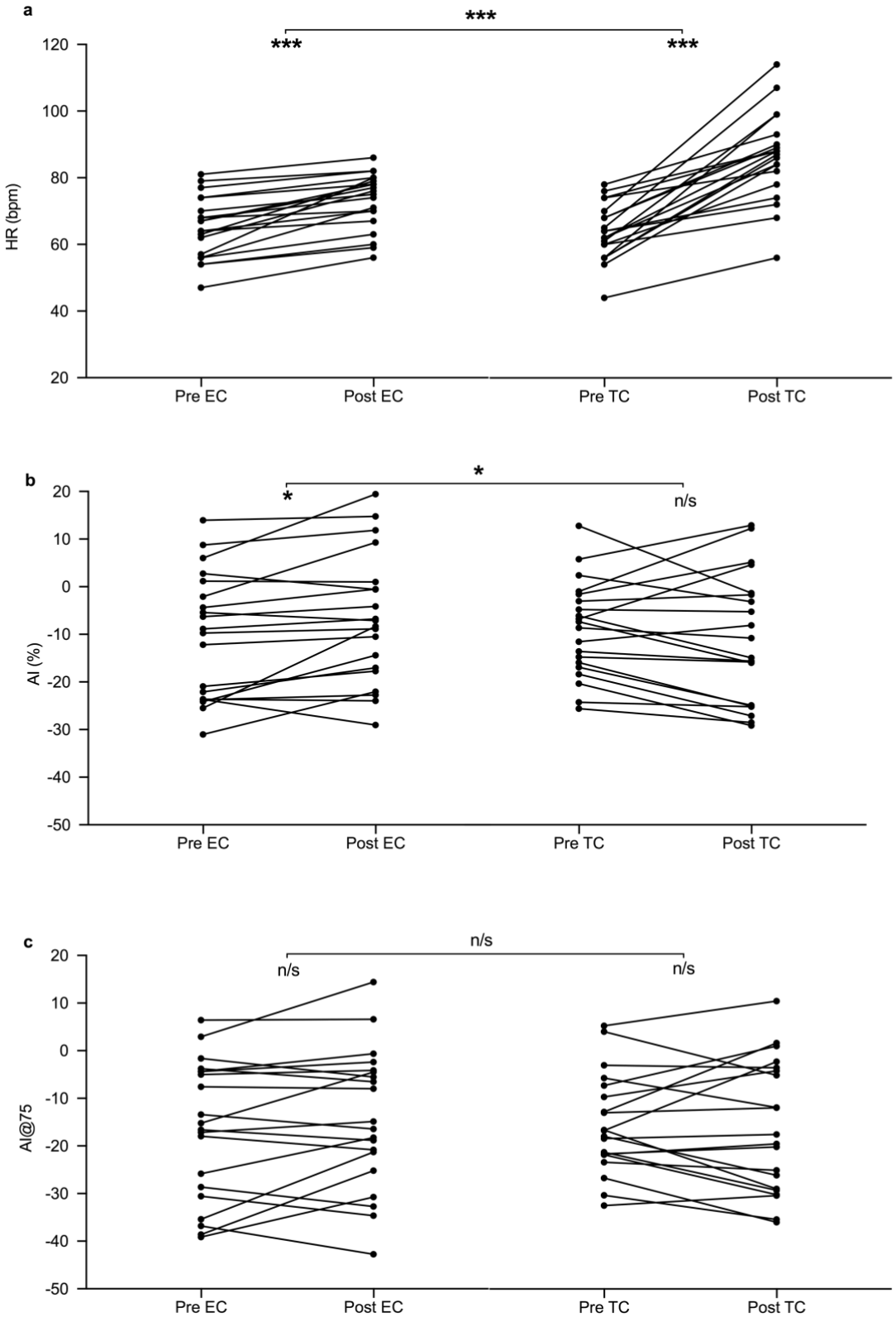


Figure 4.2 Comparison of changes in heart rate (HR) and augmentation index (AI) parameters before and after e-cigarette (EC) and tobacco cigarette (TC) use. (a) HR; (b) AI; (c) AI@75

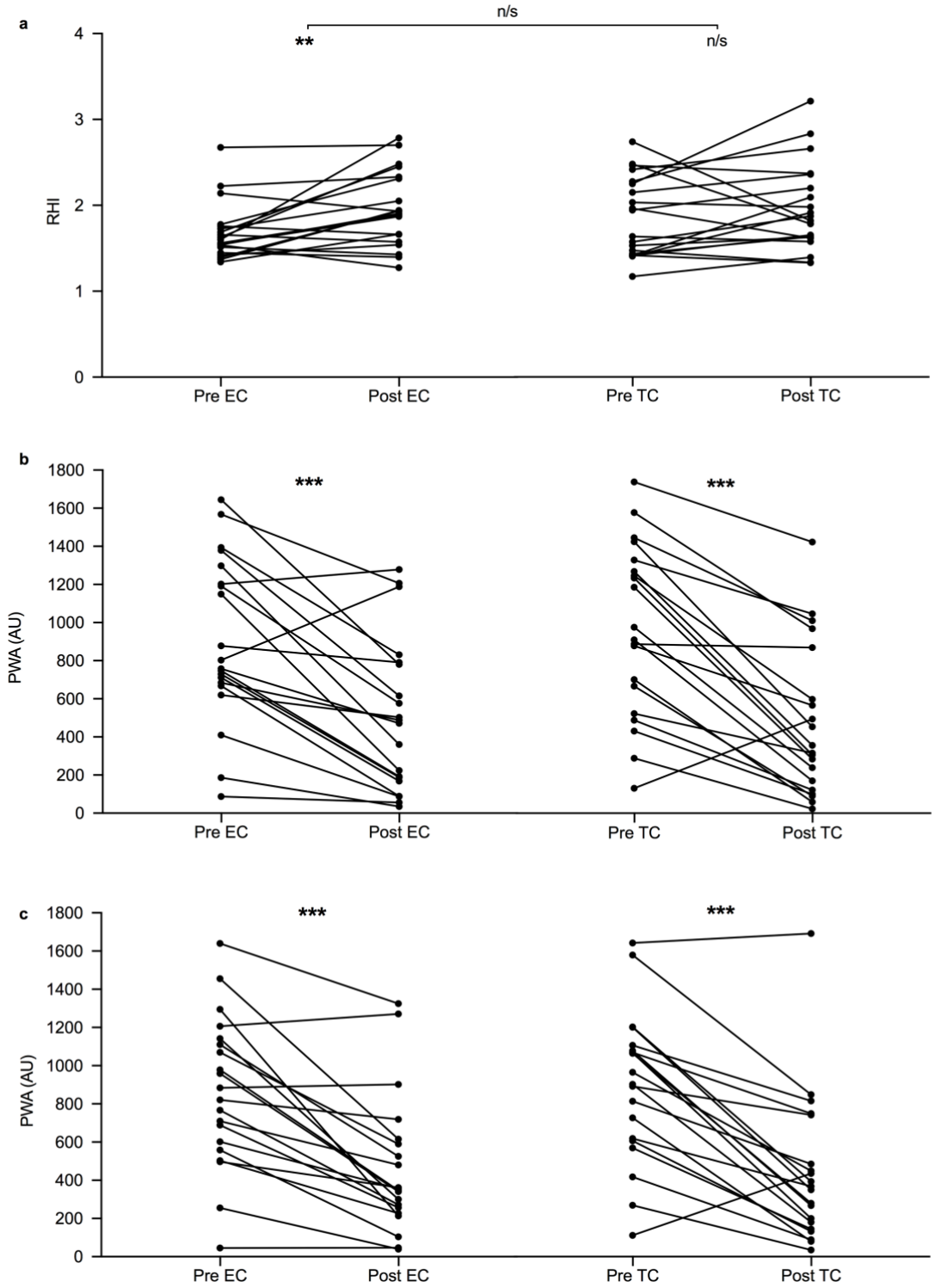


Figure 4.3 Comparison of changes in vascular function parameters before and after e-cigarette and tobacco cigarette use. (a) Reactive hyperaemia index (RHI); (b) Control arm baseline pulse wave amplitude (PWA); (c) Occluded arm baseline PWA.

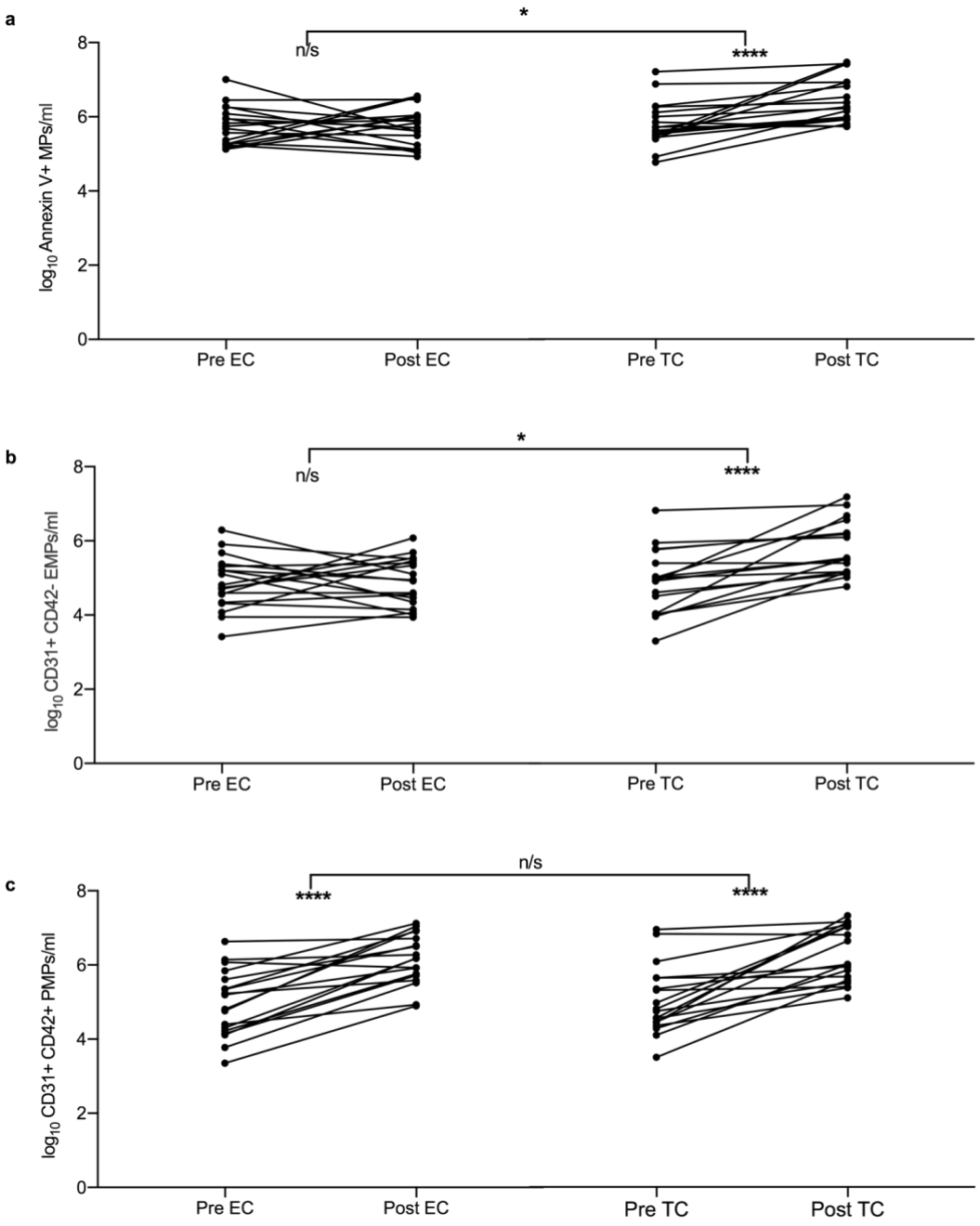


Figure 4.4: Comparison of changes in circulating microparticles (MPs) before and after e-cigarette use. (a) Total MPs; (b) Endothelial MPs (EMPs); (b)Platelet MPs (PMPs).

Table 4.2 Cardiovascular parameters of vascular function at baseline and following e-cigarette and tobacco cigarette use.

Parameter	Intervention	Pre-Intervention	Post-intervention	Change following intervention	P-value
HR (bpm)	E-cigarette	65 ± 9	73 ± 8	8 ± 5	**< .001**[b]
	Tobacco Cigarette	64 ± 8	86 ± 13	23 ± 12	**< .001**[b]
SBP (mmHg)	E-cigarette	124 ± 12	123 ± 11	-1 ± 6	.431[a]
	Tobacco Cigarette	121 ± 14	125 ± 14	4 ± 9	.058[a]
DBP (mmHg)	E-cigarette	80 ± 11	80 ± 10	0 ± 5	.950[b]
	Tobacco Cigarette	75 ± 11	77 ± 10	2 ± 5	.167[b]
RHI	E-cigarette	1.68 ± 0.33	1.96 ± 0.44	0.28 ± 0.38	**.006**[b]
	Tobacco Cigarette	1.86 ± 0.47	1.96 ± 0.51	0.10 ± 0.44	.156[b]
PWA occluded arm (AU)	E-cigarette	860 ± 397	465 ± 359	-395 ± 310	**< .001**[b]
	Tobacco Cigarette	895 ± 392	437 ± 387	-458 ± 324	**< .001**[b]
PWA control arm (AU)	E-cigarette	906 ± 434	507 ± 399	-399 ± 353	**.001**[b]
	Tobacco Cigarette	966 ± 451	475 ± 396	-492 ± 340	**< .001**[b]
AI (%)	E-cigarette	-10.5 ± 13.2	-6.9 ± 13.5	3.7 ± 5.7	**.010**[a]
	Tobacco Cigarette	-9.0 ± 10.0	-10.9 ± 13.5	-1.9 ± 7.4	.265[a]
$AI_{@75}$ (%)	E-cigarette	-16.6 ± 14.5	-14.3 ± 14.6	2.3 ± 6.5	.131[a]
	Tobacco Cigarette	-15.6 ± 10.4	-16.2 ± 13.9	0.7 ± 7.8	.709[a]

Data are presented as mean ± SD and median (25^{th}-75^{th} percentiles). P-values derived from paired t-test[a] and related-samples Wilcoxon signed ranked test[b]

Table 4.3 Difference (Δ) in physiological parameters following study interventions

Parameters	Difference following e-cigarette use (Post-Pre)	Difference following tobacco cigarette use (Post-Pre)	Difference between ΔEC and ΔTC (ΔEC - ΔTC)	P-value
ΔHR (bpm)	8 ± 5	23 ± 12	-15 ± 12	**< .001**
ΔSBP (mmHg)	-1 ± 6	4 ± 9	-5 ± 11	**.046**
ΔDBP (mmHg)	0 ± 5	2 ± 5	-1 ± 7	.333
ΔRHI	0.28 ± 0.38	0.10 ± 0.44	0.18 ± 0.52	.178
ΔAI (%)	3.7 ± 5.7	-1.9 ± 7.4	5.6 ± 8.0	**.006**
$\Delta AI_{@75}$	2.3 ± 6.5	-0.7 ± 7.8	-2.9 ± 9.1	.191
sICAM-1 (ng/ml)	-4.0 (-9.0;5.3)	-1.5 (-4.3;4.5)	-6.0 (-11.3; 6.8)	.286
sP-selectin (ng/ml)	-19.5 (-33.0;5.5)	-12.5 (-19.0;9.0)	-20 (-31.3;16.5)	.177
sVCAM-1 (ng/ml)	-25.0 (-85.3;73.3)	-3.0 (-50.3;78.3)	-45.0 (-156.8;87.5)	.267
sE-selectin(ng/ml)	-0.9 (-3.2;5.8)	-0.8 (-6.6;2.6)	0.3 (-4.1;6.7)	.433
PECAM-1 (ng/ml)	-0.04 (-0.07;0.05)	-0.06 (-0.12;0.00)	0.04 (-0.08;0.17)	.201
$\Delta\log_{10}$MPs/ml	-0.2 (-0.5;0.7)	0.4 (0.2;1.1)	-0.7 (-1.6;0.2)	**.024**
$\Delta\log_{10}$EMPs/ml	0.0 (-0.5;0.7)	0.6 (0.3;1.6)	-0.7 (-1.9;0.2)	**.016**
$\Delta\log_{10}$PMPs/ml	1.4 (0.6;1.8)	1.0 (0.3;2.1)	-0.1 (-1.1;1.0)	.799
ΔFEV_1 (L)	-0.1 ± 0.2	0.0 ± 0.2	0.0 ± 0.3	.754
ΔFVC (L)	-0.1 ± 0.3	0.0 ± 0.3	-0.1 ± 0.5	.721
ΔFEV/FVC (%)	-0.2 ± 2.0	-0.3 ± 4.8	0.1 ± 4.3	1.000
ΔPEF (L/min)	-31 ± 54	-22 ± 53	-9 ± 71	.709
ΔeCO (ppm)	-2 ± 3	11 ± 2	-13 ± 4	**< .001**

EC, e-cigarette, TC, tobacco cigarette. Data are presented as mean ± SD or median (25^{th}-75^{th} percentile). P-values derived from Related Samples Wilcoxon signed ranked test

Table 4.4 Circulating biomarkers of vascular function at baseline and following e-cigarette and tobacco cigarette use.

Parameter	Intervention	Pre-Intervention	Post-intervention	Change following intervention	P-value
sICAM-1 (ng/ml)	E-cigarette	42.0 (21;60)	35.0 (24.3;62.3)	-4.0 (-9.0;5.3)	.381[b]
	Tobacco Cigarette	46.0 (17.8;54.8)	42.0 (25.0;57.0)	-1.5 (-4.3;4.5)	.868[b]
sP-selectin (ng/ml)	E-cigarette	95.0 (70.8;125.3)	84.0 (60.5;107.5)	-19.5 (-33.0;5.5)	**.026[b]**
	Tobacco Cigarette	87.0 (65.8;116.5)	79.0 (57.0;97.0)	-12.5 (-19.0;9.0)	.117[b]
sVCAM-1 (ng/ml)	E-cigarette	713.0 (617.3;841.0)	722.0 (609.0;788.0)	-25.0 (-85.3;73.3)	.349[b]
	Tobacco Cigarette	698.0 (585.8;797.3)	710.5 (613.5;826.5)	3.0 (-50.3;78.3)	.647[b]
sE-selectin (ng/ml)	E-cigarette	65.5 (48.4;108.1)	63.4 (55.4;101.1)	-0.9 (-3.2;5.8)	.948[b]
	Tobacco Cigarette	71.8 (50.7;109.6)	64.4 (40.2;108.2)	-0.8 (-6.6;2.6)	.372[b]
PECAM-1 (ng/ml)	E-cigarette	0.95 (0.83;1.04)	0.91 (0.79;1.20)	-0.04 (-0.07;0.05)	.554[b]
	Tobacco Cigarette	1.04 (0.83;1.28)	0.93 (0.74;1.27)	-0.06 (-0.12;0.00)	**.028[b]**
$\log_{10}$ MPs/mL	E-cigarette	5.7 (5.3;6.1)	5.8 (5.2;6.1)	-0.2 (-0.5;0.7)	.766[b]
	Tobacco Cigarette	5.7 (5.5;6.2)	6.3 (5.9;6.9)	0.4 (0.2;1.1)	**< .001**[b]
$\log_{10}$ EMPs/mL	E-cigarette	4.8 (4.3;5.3)	4.9 (4.3;5.5)	0.0 (-0.5;0.7)	.966[b]
	Tobacco Cigarette	4.9 (4.1;5.5)	5.5 (5.2;6.3)	0.6 (0.3;1.6)	**< .001**[b]
$\log_{10}$ PMPs/mL	E-cigarette	5.0 (4.2;5.7)	6.2 (5.7;6.8)	1.4 (0.6;1.8)	**< .001**[b]
	Tobacco Cigarette	4.8 (4.4;5.6)	6.0 (5.7;7.1)	1.0 (0.3;2.1)	**< .001**[b]

Data are presented as mean ± SD and median (25^{th}-75^{th} percentiles). P-values derived from paired t-test[a] and related-samples Wilcoxon signed ranked test[b].

Table 4.5 Respiratory physiological parameters at baseline and following e-cigarette and tobacco cigarette

Parameter	Intervention	Pre-Intervention	Post-intervention	Change following intervention	P-value
FEV_1 (L)	E-cigarette	4.2 ± 0.6	4.1 ± 0.7	-0.1 ± 0.2	.132[a]
	Tobacco Cigarette	4.3 ± 0.7	4.2 ± 0.6	0.0 ± 0.2	.373[a]
FVC (L)	E-cigarette	5.2 ± 0.7	5.1 ± 0.7	-0.1 ± 0.3	.433[b]
	Tobacco Cigarette	5.3 ± 0.9	5.2 ± 0.8	0.0 ± 0.3	.723[b]
FEV_1/FVC (%)	E-cigarette	81.1 ± 6.8	80.9 ± 7.3	-0.2 ± 2.0	.629[b]
	Tobacco Cigarette	81.3 ± 7.0	81.0 ± 7.2	-0.3 ± 4.8	.501[b]
PEF (L/min)	E-cigarette	562 ± 62	531 ± 96	-31 ± 54	**.019[a]**
	Tobacco Cigarette	567 ± 72	545 ± 81	-22 ± 53	.074[a]
eCO (ppm)	E-cigarette	9 ± 10	7 ± 7	-2 ± 3	**.007[b]**
	Tobacco Cigarette	9 ± 10	20 ± 10	11 ± 2	**< .001[b]**

Data are presented as mean ± SD. P-values derived from paired t-test[a] and related-samples Wilcoxon signed ranked.

4.4 DISCUSSION

In this cross-over randomised study in 20 healthy male smokers we explored the immediate effects of e-cigarettes and tobacco cigarettes on endothelial function, arterial stiffness, cardiovascular haemodynamic parameters, pulmonary function and circulating MPs.

4.4.1 Cardiovascular Effects

We observed a significant increase in heart rate following the use of both interventions. This effect was more pronounced following exposure to tobacco smoking. This haemodynamic response was expected as nicotine is known to activate the sympathetic nervous system, resulting in a transient rise in heart rate, blood pressure and systemic vasoconstriction (Benowitz and Burbank, 2016). This explanation is supported by a previous study by Grassi et al which demonstrated significant increases in heart rate, systolic and diastolic blood pressure which were accompanied by increases in plasma noradrenaline and adrenaline levels (Grassi et al., 1994). In our study, the significantly greater rise in heart rate following tobacco cigarette use, compared to e-cigarette use, may be explained by a faster nicotine absorption rate from tobacco cigarettes in comparison to e-cigarettes (Farsalinos et al., 2014a, Farsalinos et al., 2015a, Vansickel et al., 2010).

Reports on the blood pressure effects in other acute exposure studies comparing e-cigarettes to tobacco cigarettes studies are inconsistent (Yan and D'Ruiz, 2015, Farsalinos et al., 2014c, Czogala et al., 2012). In our study we did not observe any significant changes in systolic or diastolic blood pressure following tobacco cigarette exposure or e-cigarette exposure. Differences between our results and previously reported data by Grassi et al. may be due to differences in the tobacco cigarettes used and in assessment of blood pressure (Grassi et al., 1994). Different levels of nicotine exposure will impact on the levels of catecholamines and subsequently affect the pressor response. In our study participants smoked one of their own tobacco cigarettes, and the nicotine content of each tobacco cigarette was unknown. In addition, blood pressure was measured at a single time point (ten minutes following exposure). In contrast, in the study by Grassi et al findings were derived from continuous haemodynamic measurements for 15 minutes following exposure to a standardised tobacco cigarette containing 1.1mg nicotine.

We observed an acute increase in AI following e-cigarette use. It may appear that our data suggest that vascular function deteriorates following e-cigarette use relative to tobacco cigarette use. However, when we corrected AI for heart rate (Wang et al., 2008b), we found no significant differences in $AI_{@75}$, suggesting that effects on AI are due to changes in heart rate rather than acute changes in vascular stiffness. As previously mentioned, this difference in heart rate could be explained by a difference in the efficiency of the nicotine delivery systems between e-cigarette and tobacco cigarettes (Farsalinos et al., 2014a, Farsalinos et al., 2015a, Vansickel et al., 2010). Conversely to our findings, Vlachopoulos et al. recently published a study using carotid-femoral

pulse wave velocity as a direct method to study aortic stiffness in 24 healthy habitual smokers. They demonstrated that pulse wave velocity increased five minutes following the use of a tobacco cigarette and an e-cigarette (Vlachopoulos et al., 2016). Given the fact that aortic stiffness is known to be an independent predictor of cardiovascular risk (Laurent et al., 2001) further long-term studies are warranted to explore the potential impact of e-cigarettes on aortic stiffness.

In our study RHI increased following the use of an e-cigarette suggesting an improvement in endothelial function. The mean RHI response following tobacco smoking demonstrated an increase, however this failed to reach statistical significance. In contrast the baseline PWAs (recorded prior to cuff occlusion during PAT measurements before and after each intervention) were significantly reduced following both interventions. While a decrease in RHI was not demonstrated, the changes in PWA, which are suggestive of an acute vasoconstrictive response following nicotine exposure, may provide an explanation for this. A vessel in its constricted state has greater capacity to vasodilate relative to its pre-constricted state. The inverse of this phenomenon has been reported in pregnancy where the RHI response paradoxically suggested a deterioration in endothelial function. However, in keeping with the vasodilatory response in pregnancy, the baseline PWA was significantly increased, suggesting that in the later stages of pregnancy the vasculature was less able to vasodilate as it had already reached its vasodilatory capacity (Carty et al., 2012). Furthermore, it would be counter-intuitive if an improvement was seen in endothelial function following either product. Mechanistically the exposure of endothelial cells to tobacco smoke is known to increase the production of superoxide and ROS. This leads to oxidative stress along with uncoupling of endothelial NO synthase. Uncoupling of endothelial NO synthase decreases the bioavailability of NO which results in impaired endothelium dependent vasodilation. Carnevale et al. demonstrated in 40 healthy subjects (20 smokers and 20 non-smokers) deterioration in markers of oxidative stress and FMD 30 minutes following a single exposure to either e-cigarettes or tobacco cigarettes (Carnevale et al., 2016). Furthermore, their findings question whether FMD is a more optimal technique over PAT to assess the endothelial response following acute exposure to both e-cigarette and tobacco cigarette research.

At a molecular level, it is known that proinflammatory stimuli such as tobacco smoking, hypertension, diabetes mellitus and hypertriglyceridemia can stimulate the expression of adhesion molecules (ICAM-1, VCAM-1 and E-selectin) on the surface of vascular endothelial cells (Gaal et al., 2000, DeSouza et al., 1997, Hackman et al., 1996, Nair et al., 2001), suggesting that elevated levels of soluble adhesion molecules may serve as surrogate markers to detect pre-clinical endothelial dysfunction (Ridker et al., 1998, Hwang et al., 1997). Therefore, as an adjunct to assessment of endothelium-dependent vasodilation, we measured concentrations of serum soluble adhesion and selectin molecules. In our study serum concentrations of these molecules did not demonstrate any consistent pattern of activation following both e-cigarette and tobacco cigarette

exposure. In this context, however, it is important to note that there is controversy about the utility of these markers to act as a surrogate of endothelium-dependent vasodilation (John et al., 2000).

For the cardiovascular risk of e-cigarettes to be estimated, data from longitudinal observational studies need to emerge. As it may take several decades for the cardiovascular impact from long term e-cigarette exposure to be fully understood, biomarkers of cardiovascular disease may have a role in assessing the probability of whether e-cigarette exposure is likely to be associated with cardiovascular disease. Therefore, biomarker studies may have an important role in developing an understanding of any potential cardiovascular risks associated with long term e-cigarette use. Improvements in the understanding of the relationship between e-cigarettes and the cardiovascular system will enable healthcare professionals and individuals to make more informed health decisions regarding the use of e-cigarettes. MPs are emerging as a possible biomarker for early detection of endothelial dysfunction, vascular inflammation and thrombotic state (Burger et al., 2013). MPs are defined as membrane-bound vesicles which are between 0.1-1 μm in diameter; which are formed from the outward blebbing and shedding of the plasma membrane of cells undergoing activation, stress or apoptosis (Boulanger, 2010). MPs are released from several cell types including leukocytes, erythrocytes, endothelial cells and platelets.

Our study demonstrates that the number of EMPs and PMPs significantly increased following exposure from smoking a single tobacco cigarette. We also observed a comparable significant increase in numbers of PMPs following e-cigarette exposure. However, no significant rise in EMPs was detected following e-cigarette use. Mobarrez and Antoniewicz et al. conducted a study that focused on acute exposure of healthy volunteers to a single tobacco cigarette and identified a significant acute release of EMPs and PMPs (Mobarrez et al., 2014). When they repeated the same study design but substituted tobacco cigarettes for e-cigarettes they identified that E-selectin positive MPs of endothelial origin were the only MP elevated (p = .038) (Antoniewicz et al., 2016). Since the relationship between e-cigarette exposure and atherosclerotic disease remains largely unknown it is important to consider the potential significance of our data where both tobacco and e-cigarette exposure were associated with a significant increase in numbers of PMPs. In-vivo studies have demonstrated increased levels of PMPs in those with coronary heart disease (Ueba et al., 2010). It is suggested that increased PMPs may have a role in the thrombotic and atherogenic processes leading to cardiovascular events (Viera et al., 2012). Numerous studies have demonstrated that increased EMP levels correlate with impaired FMD and arterial stiffness (Amabile et al., 2005, Wang et al., 2009) and are considered independent predictors of cardiovascular events (Sinning et al., 2011). Therefore, even though our data did not detect any significant changes in EMPs or deterioration in endothelial function following e-cigarette exposure, the positive findings presented in the studies by Antoniewicz and Mobarrez et al. and Carnevale et al. need to be considered and further research is required to explore these phenomena in more detail (Antoniewicz et al., 2016).

4.4.2 Respiratory Effects

From a respiratory perspective, we did not observe any significant changes relating to FEV_1, FVC and FEV_1/FVC. However, we did observe an immediate reduction in PEF following e-cigarette use, which was not seen following the use of a tobacco cigarette. This may be suggestive of a defensive physiological response against the irritants from the e-cigarette aerosol. E-cigarette users report that this irritative psychosomatic effects (also referred to as "throat hit") are associated with an increased perception of efficacy as it replicates the sensation associated with tobacco cigarette use (Etter, 2016). This effect may be secondary to e-liquid solvent propylene glycol (1,2 propanediol), which when inhaled is known to cause throat airway irritation (Wieslander et al., 2001). Our study presents a novel finding of acutely reduced PEF following e-cigarette use in tobacco smokers which has not previously been identified. This important acute change in respiratory function warrants additional research to quantify this effect and identify the causative pathophysiology which may have important clinical implications.

4.4.3 Limitations

Our study has several limitations which should be acknowledged. Prior to this study being conducted there were no previously published data sets available to allow sample size and power calculation based on similar studies. A convenience sample of 20 participants and the cross-over design appeared appropriate for this exploratory study. With hindsight, a power calculation could have been undertaken with regards to an effect-size target based on recognised control group outcome measure means and associated standard deviations. This would have been helpful in the interpretation of the significance (or lack of) the treatment group results. All study subjects were male and were restricted to using only one specific e-cigarette device and e-liquid. Therefore, our data cannot be generalised to the wider population, and are not necessarily applicable to the use of different e-liquids and e-cigarettes which are available. All study subjects were male and were restricted to using only one specific e-cigarette device and e-liquid. Therefore, our data cannot be generalised to the wider population, and are not necessarily applicable to the use of different e-liquids and e-cigarettes which are available.

We relied on participant self-reporting to confirm abstinence from tobacco smoking, e-cigarette use and ingestion of caffeinated and alcoholic products prior to the study investigation. As we were unable to control the study participants' behaviour out with the study environment, we acknowledge that the self-reporting accounts are vulnerable to misrecollection (Connor Gorber et al., 2009). The average eCO data at baseline, provides some reassurance that there was no tobacco cigarette use immediately prior to the study visits.

In our study blood sampling was performed at baseline and five minutes following exposure to e-cigarettes or tobacco cigarettes. As serial blood sampling was not performed we are naïve as to trajectory and timings relating to peak values of circulating MPs and levels of serum soluble

adhesion and selectin molecules, and the differences between e-cigarette and tobacco cigarette exposure. This point is further illustrated by the previously discussed acute exposure studies conducted by Mobarrez et al. and Antoniewicz et al. In both studies which performed serial blood sampling at 1, 2, 4 and 24 hours following tobacco cigarette or e-cigarette exposure, the time of peak detection of PMPs and EMPs differed between interventions (Antoniewicz et al., 2016, Mobarrez et al., 2014).

It is likely that participants will have been exposed to variable amounts of nicotine, as participants in the study used their own brand of tobacco cigarettes and exhibited different smoking and vaping techniques. Although plasma nicotine levels were not measured, the physiological changes seen in heart rate are consistent with the haemodynamic responses that have been reported and validated in other studies, demonstrating that tobacco cigarettes deliver nicotine at a faster rate than e-cigarettes (Vansickel et al., 2010, Farsalinos et al., 2014a).

4.4.4 Conclusions

In conclusion, to our knowledge this is the first reported study to use PAT to assess the endothelial function response following the use of e-cigarettes with comparison to tobacco cigarettes. We have postulated that the RHI response may have arisen following the vasoconstrictive response to nicotine. This is an important methodological consideration for future researchers in this field. Furthermore, we have demonstrated that both e-cigarettes and tobacco cigarettes elicit differential effects on circulating MPs. Our findings suggest that e-cigarette use induces a thrombogenic response and stimulates an obstructive airway response, whereas tobacco cigarette use induces both a thrombogenic and endothelial inflammatory response. Underlying mechanisms for these differential responses are unclear but should be investigated. With regards to e-cigarettes, the long-term effects of these phenomena and their potential association with atherogenesis and cardiovascular risk await further clarification.

A RANDOMISED CONTROLLED TRIAL INVESTIGATING THE CARDIOVASCULR EFFECTS OF E-CIGARETTES IN COMPARISON TO NICOTINE REPLACEMNT PATCHES

5.1 INTRODUCTION

Smoking is a major risk factor for cardiovascular morbidity and mortality and is considered to be the leading preventable cause of death worldwide (Centers for Disease Control and Prevention, 2018). Smoking, either active or passive, can cause cardiovascular disease by mediating many independent pathological processes which have a deleterious effect on endothelial function, sympathetic tone, metabolism, and the coagulation and fibrinolytic systems (Csordas and Bernhard, 2013). The long-term cardiovascular benefits of smoking cessation are well established, with epidemiological and clinical studies demonstrating that the harm from tobacco smoking is dose-dependent and smoking cessation can lead to the reversibility of endothelial dysfunction (Celermajer et al., 1993, Poredos et al., 1999, Celermajer et al., 1996).

Although the ultimate tobacco harm reduction goal would be the complete cessation of all tobacco and nicotine-containing products, sustained tobacco use is primarily driven by nicotine addiction, and each year only 2-3% of all tobacco smokers who try to stop smoking succeed (Volpp et al., 2009, Baumeister, 2017). Nicotine is highly addictive and has potent sympathomimetic effects which result in a transient increase in heart rate and blood pressure. The nicotine doses absorbed following tobacco smoke causes minimal harm, in contrast to the carcinogens, carbon monoxide and thousands of toxins contained in tobacco smoke (Csordas and Bernhard, 2013, Britton et al., 2016). It is the distinction between toxicity and addition which underpins the reasoning why many tobacco cessation policies and initiatives advocate that tobacco smokers should be encouraged to use less harmful smoke-free forms of nicotine, with NRT forming the cornerstone of this approach (McNeill A et al., 2015b, Royal College of Physicians, 2016).

In the context of smoking cessation, clinical trials have demonstrated that NRT is (1) effective and can increase the chance of a successful quit attempt by 50-70%; and (2) safe, and can be used alone or in combination, concurrently with smoking, and amongst smokers with established cardiovascular disease (Stead et al., 2012b, Mills et al., 2014). The evidence-based guidance on tobacco harm reduction published by NICE recommend the replacement of tobacco smoking with medically licenced NRT for smokers who are otherwise or unable or unwilling to quit (NICE, 2013).

The emergence of e-cigarettes has disrupted and changed the landscape of smoking cessation. Unlike NRT, e-cigarettes are a consumable product, capable of delivering nicotine via the oral inhalation route and reproducing many of the sensorimotor cues and behavioural rituals associated

with tobacco smoking. E-cigarettes have overtaken NRT to become the preferred nicotine replacement product to support quit attempts (Beard et al., 2016).

Despite the potential harm reduction associated with e-cigarettes, the role of e-cigarettes as a smoking cessation aid remains controversial and has raised global debate. This predicament has arisen mainly because the use of e-cigarettes and their technological advancements are evolving far faster than the scientific understanding of their potential pathophysiological health effects. Public Health England and the Royal College of Physicians have taken the stance that relative to the well-established harm caused by tobacco smoking, e-cigarettes are a far safer alternative to tobacco smoking (McNeill A et al., 2015b, Royal College of Physicians, 2016).

In 2018, NICE updated their evidence-based guidance on tobacco harm reduction and provided healthcare professionals with recommendations on the use of e-cigarettes. The guidelines concluded that healthcare professionals should advise patients that although the evidence suggests that e-cigarettes are less harmful than smoking, they are not risk-free, and the evidence relating to their short and long-term health impacts is still emerging (NICE, 2018).

Therefore, to facilitate healthcare professionals' evidence-based decisions concerning tobacco control policies and the use of nicotine-containing e-cigarettes as an alternative nicotine replacement product for smoking cessation amongst tobacco smokers wishing to stop smoking we conducted the VAPOUR study, investigating the cardioVAscular imPacts of electrOnic cigarettes in comparison to the Use of nicotine Replacement patches. The primary outcome of the study was to access physiological effects on cardiovascular function amongst tobacco smokers undergoing a 12-week smoke-free quit attempt following the use of nicotine-containing e-cigarettes combined with behavioural support in comparison to nicotine replacement patches and behavioural support.

The specific objectives of the study included:

1. The comparison of the short-term (3 month) physiological effects that nicotine-containing e-cigarettes combined with behavioural support in comparison to nicotine replacement patches and behavioural support, have upon cardiovascular function, assessed by FMD, blood pressure and heart rate using non-invasive haemodynamic measurements.

2. The comparison of the short-term (3 month) physiological effects that nicotine-containing e-cigarettes combined with behavioural support in comparison to nicotine replacement patches and behavioural support have upon respiratory function by using spirometry to assess pulmonary function.

3. To assess the feasibility of the study design concerning recruitment and retention rates.

5.2 METHODOLOGY

5.2.1 Study design and participants

We conducted a pragmatic, two-armed, single centre, randomised controlled pilot study between 1st December 2015 and 13th July 2018 (Figure 5.1). Our study was developed in discussion with NHSGCC Smokefree Services to run in parallel with the smoke-free community pathway.

Ethical approval and NHSGGC sponsorship for this study were granted by the East of Scotland Research Ethics Services (Reference Number 16/WS/0103), and NHSGGC Research and Development Department (Reference Number GN16CH051). Our study complied with the Declaration of Helsinki. Informed written consent was obtained from all participants. The trial was registered with the ClinicalTrials.gov database (NCT03358953).

Between December 2015 and March 2018, the study aimed to recruit a total of 100 participants. Following telephone screening, participants were included in the study if they were aged between 18 and 65 years old; habitual tobacco smokers (smoking on average 1-15 tobacco cigarettes per day for more than six months); willing to quit tobacco smoking; with either the use of nicotine replacement patches or an e-cigarette with nicotine-containing e-liquid, in addition to engaging with NHSGGC Community Smokefree Service's 12-week behavioural support programme.

Participants were excluded if they declined participation in the study or were unable to provide informed consent; pregnant or breast feeding; had used an e-cigarette or nicotine replacement patch in the last 3 months; were allergic to the active substances in either of the nicotine replacement products; had an established history of illicit drug use, major depressive illness or other psychiatric conditions, peripheral arterial occlusive disease (PAOD), COPD, renal impairment (eGFR < 45 mL/min), uncontrolled hypertension (BP $\geq 165/95$ mmHg), or cardiovascular disease (defined as unstable angina, heart failure New York Heart Association functional classification classes III–IV, or a recent stroke, myocardial infarction, coronary artery bypass graft or percutaneous coronary angiogram within the last 3 months). Ineligible participants who failed to meet the pre-specified inclusion and exclusion criteria were offered a referral into NHSGGC Community Smokefree Services so that they could access smoking cessation support for their quit attempt, without progressing in the trial.

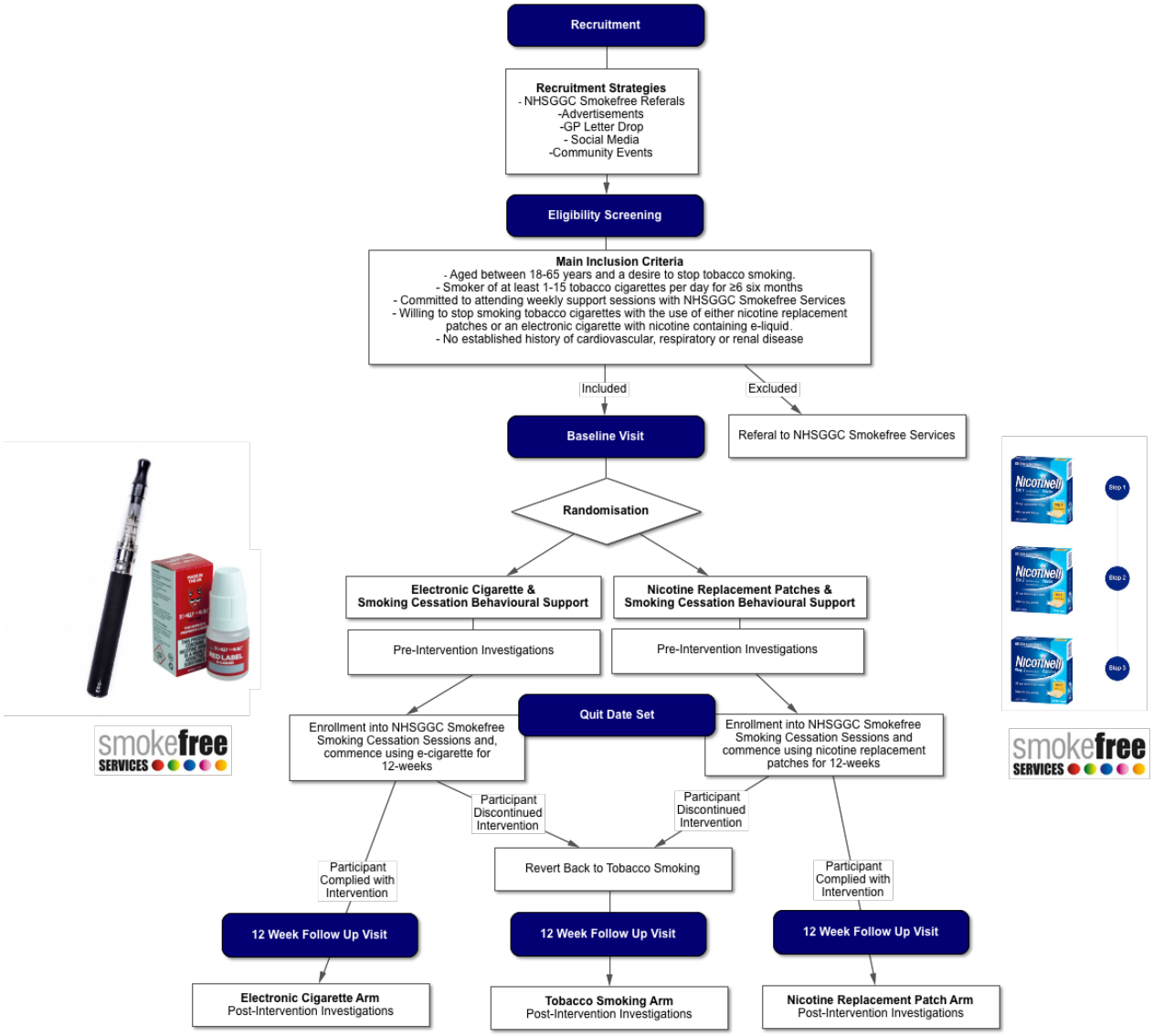


Figure 5.1 Study Design. A randomised, single centre, 2-armed study, comparing e-cigarettes with nicotine replacement patches. Study investigations were performed at the baseline visit (pre-intervention) and 12-weeks following the participant's "quit date" (post-intervention). Participants randomised to the e-cigarette arm received two second generation e-cigarette devices with a 12-week supply (12 bottles) of tobacco flavoured e-liquid containing 18mg/ml nicotine. Participants randomised to the nicotine replacement patch arm received a 12-week reducing nicotine regime (21mg, 14mg, 7mg) of Nicotinell® Patches. All participants received 12-weeks of behavioural support. Participants who resumed tobacco smoking were followed up at 12-weeks, to become the "control" tobacco smoking arm.

5.2.2 Sample size

Prior to this study being conducted, we were unaware of any similar studies available to allow sample size and power calculations.

As the primary outcome of the study is the change in endothelial function at 3-months following the "quit date" as measured by FMD, we took into consideration data which measured FMD of the brachial artery to evaluate the effects of smoking on endothelial function between chronic smokers and non-smokers (Esen et al., 2004). Based on this data we calculated that we would need 17 participants in each group to detect a power of 80% when using a 0.05 significance level. Accounting for NHSGGC Smokefree Community Services dropout rate, a convenience sample of 100 participants; of which 50 participants would be recruited into each group was deemed appropriate for this study.

5.2.3 Recruitment

Between December 2015 and March 2018, a variety of local and regional recruitment strategies were ethically approved and employed to identify potential participants (Figure 5.2). All of the recruitment strategies conveyed the necessary information about the study and detailed study-specific contact details (email address, telephone number). Following initial contact with the study team, participants received a participant information leaflet, and a telephone screening appointment was arranged.

5.2.3.1 Advertisement through local media

Numerous local media platforms were used to advertise the study, and capture interest amongst the general population. In December 2015, the British Heart Foundation, University of Glasgow and NHSGGC released a joint press release, which generated media coverage in four newspapers. Intermittently throughout the study advertisements were placed in a variety of local newspapers, community magazines and on Gumtree.

5.2.3.2 Recruitment from NHSGGC Smokefree Services

Approval was granted for the NHSGGC Smokefree services to advertise the VAPOUR study via their approved social media platform, in addition to informing new clients about the VAPOUR study if they wished to stop tobacco smoking with either nicotine replacement patches and/or an e-cigarette. If any of these clients declared an interest, depending on the client's preference the practitioner could directly refer them into the study or provide them with study contact details to self-refer. Furthermore, to promote smoking cessation, public engagement "pop up stands", were held collaboratively with smokefree services and the VAPOUR study team in the entrance foyer of the QEUH and the at the Celtic Football Club Healthy Hoops Event.

5.2.3.3 Recruitment from primary care

One of the research strategies was to recruit patients from general practices (GPs) affiliated with the NHSGGC CRF. This recruitment strategy has been formally established between NHSGGC Research and Development team and the local GPs, to identify potential recruits into clinical trials via several approved mechanisms including “letter drops”. A letter drop is a recruitment strategy, where the Practice Manager and or the principal General Practitioner from supporting GPs, grant permission for research nurses to search the patient database with a view to generating a list of individuals who may potentially fulfil the trial's inclusion in the absence of exclusion criteria. The database search enabled us to search for patients who were tobacco smokers, between 18 to 65 years old and had no recorded history of cardiovascular, respiratory, renal or psychiatric illness. Once the list was generated, it was reviewed and approved by the principal General Practitioner. Invitation packs comprising of an invitation letter, a participant information leaflet, a reply slip and a pre-paid stamped addressed envelope were then sent out. Upon receipt of the invitation pack, interested participants were able to contact the study team.

As the process was labour intensive and we were naïve to how successful this recruitment strategy would be we opted to pilot this recruitment strategy at Govan Health Centre based on its geographical proximity to the CRF, and NHSGGC Smokefree Services. In October 2018, 280 invitation packs were distributed to patients screened from Govan Health Centre database.

5.2.3.4 Recruitment from secondary care

Roll up banner stands to advertise the study were placed in the entrance foyers of the QEUH, GRI, New Victoria Hospital and Glasgow Dental School from March 2017 to March 2018. On three separate occasions the VAPOUR study was advertised on NHSGGC Staff Payslips.

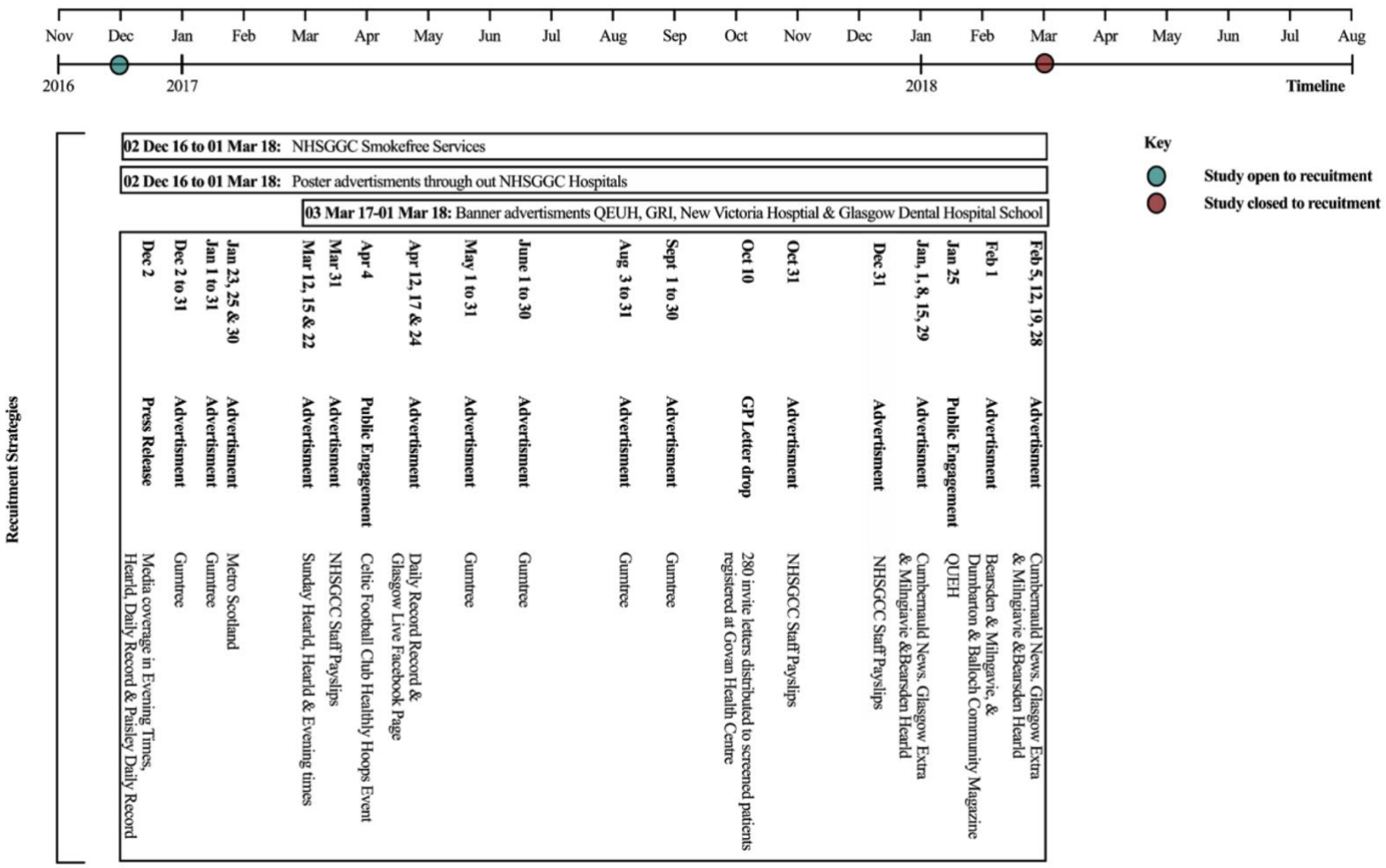


Figure 5.2 Recruitment strategy timeline. A timeline of the recruitment strategies employed during the VAPOUR study.

5.2.4 Study visits

The study comprised of two study visits; a baseline study visit, and a follow-up visit. All study visits were undertaken at NHSGGC CRF, QEUH, Glasgow. The same trained investigator (myself) performed all of the study visits.

5.2.4.1 Baseline visit

At the baseline visit, all of the participants were randomised and enrolled into NHSGGC Community Smokefree Services to receive 12-weeks of behavioural support. The online NHSGGC Smokefree Services postcode finder was used to identify and book the smoking cessation which the participant would be able to attend. Simultaneously the study team also contacted the NHSGCC Smokefree Services co-ordinator to inform them that a study participant would be attending the Smokefree Services and which arm of the trial they have been assigned to.

5.2.4.2 NHSGGC Smokefree Services

All participants received the same 12-week behavioural support provided by NHSGGC Smokefree Services. A trained smoking cessation health improvement practitioner provided weekly face to face support sessions and monitored weekly exhaled carbon monoxide (eCO) levels. The behavioural support sessions took place in a number of venues across the NHSGGC catchment area. On attendance at each smokefree session, participants were asked to show the health improvement practitioner their study participant card (to make the health improvement practitioner aware that the participant was in the study, and which arm of the study they had been randomised to), and to complete a smoking cessation diary with the health improvement practitioner. The diary was designed to collect information on three key elements (1) the number of smokefree visits attended (2) record weekly eCO readings; and (3) record the use of additional nicotine replacement products or tobacco smoking during the "quit attempt".

5.2.4.3 Quit Date

Following the baseline visit, participants were asked to define their "quit date". Participants were recommended to set their quit date with the support of smoking cessation healthcare practitioner at the first smoking cessation support session. The "quit date" defined the date the participant stopped smoking and commenced using their assigned nicotine replacement product, and from which the 12-week follow-up visit was made. To confirm the "quit date," the study investigators contacted the participant and Smokefree Services, within seven days from the date they were due to attend their first smokefree session.

5.2.4.4 Follow-up visit

The follow-up visit was scheduled 12 weeks after the participants “quit date”, irrespective of the participant's smokefree outcome. Participants were considered as having withdrawn from the study if they requested to leave the trial or were lost to follow up.

5.2.5 Randomisation

Randomisation took place at the baseline visit. Using a secure website (Sealed Envelope Ltd, 2016), participants were randomised in a 1:1 fashion, to either the e-cigarettes combined with behavioural support or nicotine replacement patch group combined with behavioural support. Using a permuted block design with a computer random number generator, block randomisation with block sizes of 4, 6 and 8 was used to reduce bias and achieve balance in the allocation of participants to treatment arms.

5.2.6 Interventions

5.2.6.1 Behavioural Support

All participants received 12 weeks of behavioural support provided by NHSGGC Smokefree Community Services. The smoking cessation support sessions were held at various venues across NHSGGC.

5.2.6.2 Nicotine-Replacement Group

Participants randomised to the nicotine replacement patch arm received a smoking advisor referral form recommending a 12-week reducing nicotine regime (21mg, 14mg, 7mg) of Nicotinell® Patches. Participants were then asked to take the form to their local community pharmacist who would review it and complete an Unscheduled Care Community Pharmacy Scotland form, enabling a weekly supply of nicotine replacement patches to be dispensed to the participant in accordance with the regime. If required, participants were also permitted to use additional other licensed nicotine replacement products (gum, lozenges, nasal spray, inhalers and micro tabs), in combination with the nicotine replacement patches.

5.2.6.3 E-cigarette Group

At the baseline visit participants randomised to the e-cigarette group, were provided with an e-cigarette starter pack. The starter pack was custom made for the study and contained two commercially available-second generation e-cigarette devices with a charging device, 11 replacement atomisers, and 12 x 10ml bottles of nicotine-containing e-liquid. Each e-cigarette device consisted of a 1300mAh variable voltage rechargeable battery, a tank and an atomiser, and the charging device comprised of USB e-c-cigarette charger and USB mains adapter (SmokeMax; Groove Trading Ltd,

Glasgow UK), and written instructions. All of the e-liquid used in this study was manufactured from the same batch. The e-liquid was tobacco flavoured and reported by the manufacturer to contain 18mg/ml nicotine. Independent analysis of the e-liquid nicotine content and flavourings was performed at the NicoTAR, Rosewell Park Cancer Institute Buffalo, New York, USA, as discussed in Chapter 2. At the baseline visit, participants received oral and written information on how to operate the e-cigarette, and for the duration of the study were asked only to use the study e-cigarette and e-liquid they were provided with. Participants were able to contact the study team directly if any technical problems in relation to the e-cigarette devices and e-liquid were encountered. If the technical issues could not be resolved via troubleshooting, supplementary e-cigarette devices and e-liquid were provided to accommodate for any losses or breakages.

5.2.6.4 Tobacco smoking group

Participants whose smokefree quit attempt was unsuccessful and reverted back to tobacco smoking were invited back to the final study visit to become the "tobacco smoking controls" as it was considered unethical to randomise individuals who wished to stop smoking to a tobacco cigarette study arm.

5.2.7 Study investigations

5.2.7.1 General testing conditions

All of the study investigations were performed by the same trained investigator (myself), in the same temperature-controlled room (between 22 and 24ºC), at a similar time of day. Unless otherwise stated, all of the study investigations were performed at the baseline and follow up study visits. The equipment used in this study was maintained by the staff at the CRF.

Participants were asked to fast and to refrain from tobacco smoking and using nicotine-containing products for 4 hours prior to each study visit, and from consuming any caffeinated or alcoholic beverages for a minimum of 12 hours before each study visit. During the vascular studies participants were asked not to speak during the studies and were placed in the supine position. Height and weight were recorded at the start of each study, and participants were asked a questionnaire to identify confounding factors that might affect the clinical studies which included fasting status, smoking and menstrual cycle (for women).

At the baseline study visit demographic data were obtained from all participants and clinical history, (including past medical history, medications, smoking history), and nicotine dependence assessed by Fragerström Test of Nicotine Dependence (FTND).

5.2.7.2 Assessment of vascular function

Non-invasive blood pressure, heart rate and oxygen saturations were measured following 10 minutes of rest, with participants lying in the supine position using Philips IntelliVue MP30 monitor and compatible multi-measurement extensions (Philips, Leopardstown, Dublin, Ireland)

FMD of the brachial artery was used to measure endothelial function, in adherence to published guidelines to measure nitric oxide-mediated endothelium relaxation (Thijssen et al., 2011, Corretti et al., 2002). The participant was placed in the supine position. ECG leads were attached to the participant's chest. This allowed an ECG recording to be taken throughout the study enabling R-wave triggering to record the images captured at the end of diastole. The right arm was then extended and abducted to 90º and supported in position with a semi-cylindrical frame, at a level consistent with the level of the heart. A blood pressure cuff and sphygmomanometer (Hokanson SC12, Cuff, Hokanson DS400 Aneroid sphygmomanometer; DE Hokanson, Inc, Bellevue, Washington, USA) were placed on the right forearm. A 7MHz liner ultrasound transducer and a Siemens Acuson, Sequoia ultrasound system (Siemens AG, Erlangen, Germany) were used to locate the brachial artery in the 2D longitudinal plane, 10-15cm superior to the antecubital fossa. The ultrasound probe was held in place using a stereotactic clamp (RKC 80/189, Rose & Krieger, Potsdam, Germany). Figure 5.3 illustrates the timings of the procedure. After a rest period, baseline images were recorded for 3 minutes. Arterial occlusion was created by rapidly inflating the blood pressure cuff on the experimental arm to 50mmHg above systolic blood pressure, with the occlusion pressure not exceeding 200 mmHg, for a duration of 5 minutes. The cuff was then rapidly deflated and a 5 minute “post-cuff” recording was made.

FMD analysis was performed once all of the participants had completed the study. To try to eliminate the bias of expectation influencing the research findings, all of the recordings were saved in duplicate, and each recording was assigned a randomised computer-generated number, which was linked to the participant unique identifier and study visit date. The investigator performing the analysis of the recording was blinded to the allocation of treatment, study visit and smoking cessation outcome.

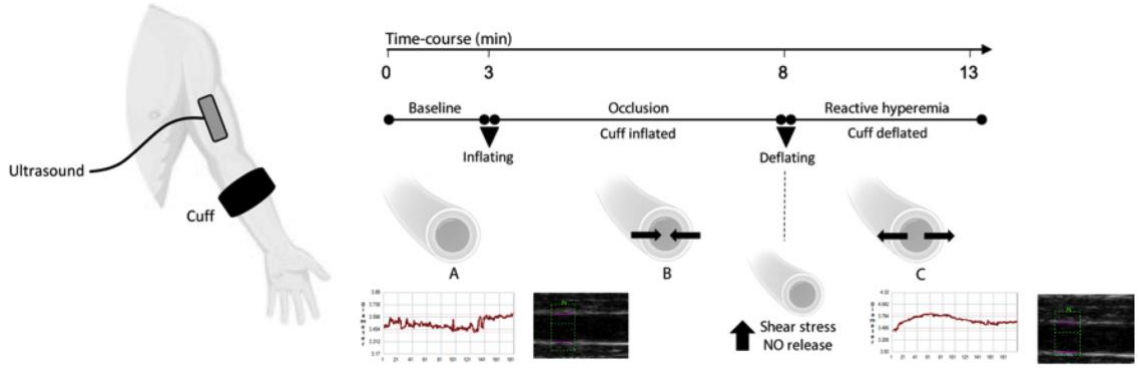


Figure 5.3 Measurement of flow-mediated dilation (FMD). FMD was measured using a non-invasive technique using a high-resolution ultrasound of the brachial artery. The three key steps involved: A) 3 minute baseline arterial diameter B) 5 minute cuff inflation, to create a nitric oxide (NO) mediated stimulus the C) 5 minute post-cuff brachial arterial diameter measurements. Image adapted form (Jarrete et al., 2016).

Each of the recordings were analysed by one trained investigator (myself) using specialised automated edge detection software (Brachial Analyzer, MIA LLC, Coralville, IA, USA). The principle measurement of FMD was calculated as the percentage maximum change in the arterial diameter pre and post occlusion, relative to the baseline diameter. All of the automated analysed images were reviewed and when required were edited to ensure the image outline the intima-lumen interface. Images were rejected if the diameter measurement confidence was less than 70%. The baseline diameter was determined as the mean of 30 baseline images. The post-cuff maximal diameter was determined as the mean of the 3 readings taken around the "peak" diameter. Each recording was analysed twice. Once all recordings were analysed, the recordings were unblinded according to the participant's unique identifier and study visit. As each FMD study recording was analysed twice, the mean average was used for further analysis.

5.2.7.3 Assessment of respiratory function

The MicroLab spirometer (Micro Medical Limited, Kent, England), which complies with both the American Thoracic Society and European Respiratory Society 2005 standards was used to measure pulmonary function. Standard spirometry measurements were taken, including FEV_1, FVC, FEV_1/FVC and PEF. The device was calibrated before spirometry recordings. All participants were asked to take a large deep breath and blow out as hard and as fast as possible until there was no air left. Spirometry was repeated a minimum of three times until the British Thoracic Society quality criteria were met. The "best" spirometry readings were then used for further analysis.

5.2.7.4 Assessment of exhaled carbon monoxide and abstinence

The eCO levels measured using the Bedfont Micro$^+$ Smokerlyzer carbon monoxide monitor (Bedfont Scientific Ltd, Kent, England) according to the manufacture's recommendations. Participants were asked to hold their breath for 15 seconds before exhaling slowly and fully into the mouthpiece during

which time the eCO was measured. The eCO levels were recorded after each breath at the baseline visit and follow up visit. The eCO levels were measured in ppm based on the conversion of carbon monoxide to carbon dioxide over a catalytically active electrode. An eCO level of 6 ppm or less was considered normal and equates to less than 1% of carbon monoxide in blood; 7ppm to 10ppm was indicative of a light tobacco smoker, or a non-smoker breathing in poor air quality or passive smoke inhalation; and 11ppm to 30ppm was indicative of a regular tobacco smoker. Abstinence at 12 weeks was considered by participant self-reporting as having smoked no more than 5 tobacco cigarettes from 2 weeks after the target quit date, validated by an eCO level of less than 7ppm at the 12-week follow up visit.

5.2.8 Analysis strategy

An intention-to-treat (ITT) analysis and per protocol (PP) analysis was performed as shown in Figure 5.4. The PP analysis included analysis of all the study participants who complied fully with the study protocol. Participants who were lost to follow up, or those who deviated from the study protocol, were not included in the PP analysis. For the ITT analysis all study participants were included in the analysis according to the study arm the participant was originally randomised to and irrespective of the individual participant's compliance with the study protocol. Missing follow-up data for the ITT analysis was managed by substituting the individual participants baseline data.

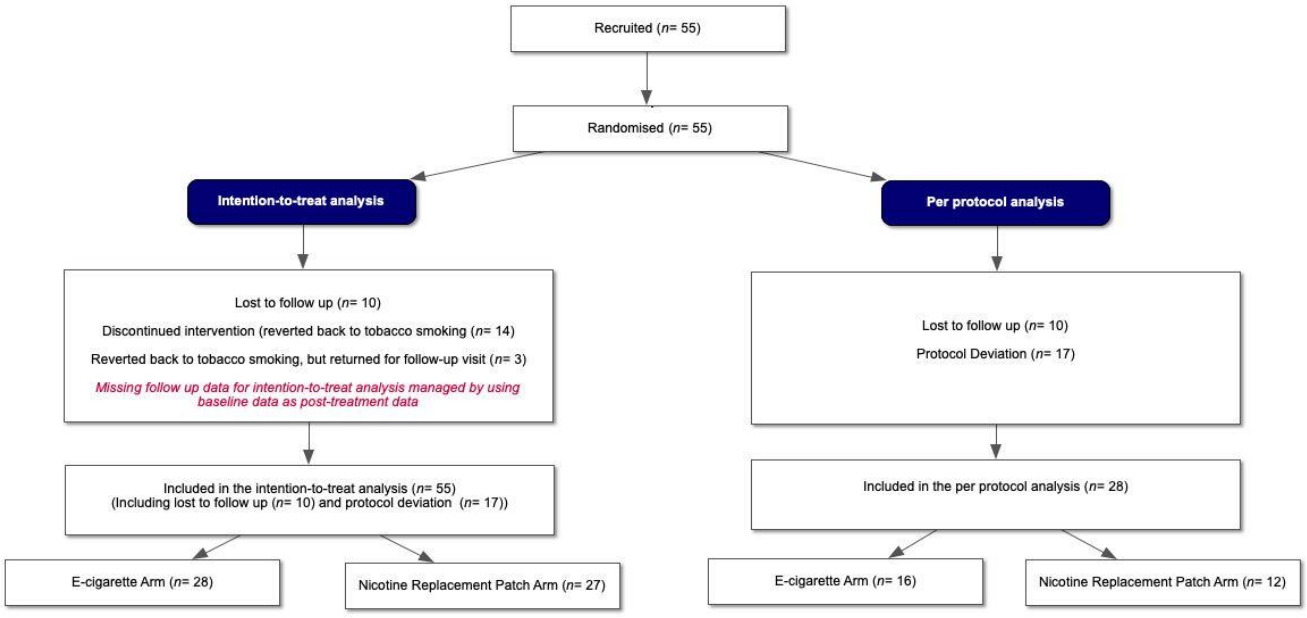


Figure 5.4 Overview of intention-to-treat and per protocol analysis

5.2.9 Statistical analysis

Visual inspection of box-plots and the Shapiro–Wilks test was applied to assess normality of the data and identify outlier data points. Parametric and nonparametric tests were used as appropriate. Continuous variables were expressed as mean ± SD or median and 25th–75th percentiles, ordinal variables were expressed as mode and range. Comparisons of the baseline characteristics between the e-cigarette and nicotine replacement study groups were made using Student's *t* test and Mann–Whitney *U* test. Paired Student's *t* tests and related samples Wilcoxon signed rank tests were used to compare continuous variables between pre and post intervention, as appropriate. Statistical significance was set at 0.05 and analyses were conducted using SPSS statistical software (IBM SPSS Statistics, version 24.0; IBM Corp, Armonk, New York, USA) and GraphPad Prism, version 7.00 for Mac OS X (GraphPad Software, La Jolla, California, USA, www.graphpad.com).

5.3 RESULTS

5.3.1 Study cohort

The CONSORT diagram for the study is shown in Figure 5.5. In total of 563 participants registered their interest in the study and were screened for inclusion. Of these, 55 (9.3%) participants fulfilled the inclusion criteria and underwent randomisation; 28 participants were randomised assigned to the e-cigarette group, and 27 participants to the nicotine replacement patch group. The most frequent reason for exclusion was an unwillingness to be randomised to either e-cigarettes or nicotine replacement patch study groups, allergy to the nicotine replacement patches, followed by an established history of cardiovascular and or respiratory disease, or smoking more than 15 cigarettes per day.

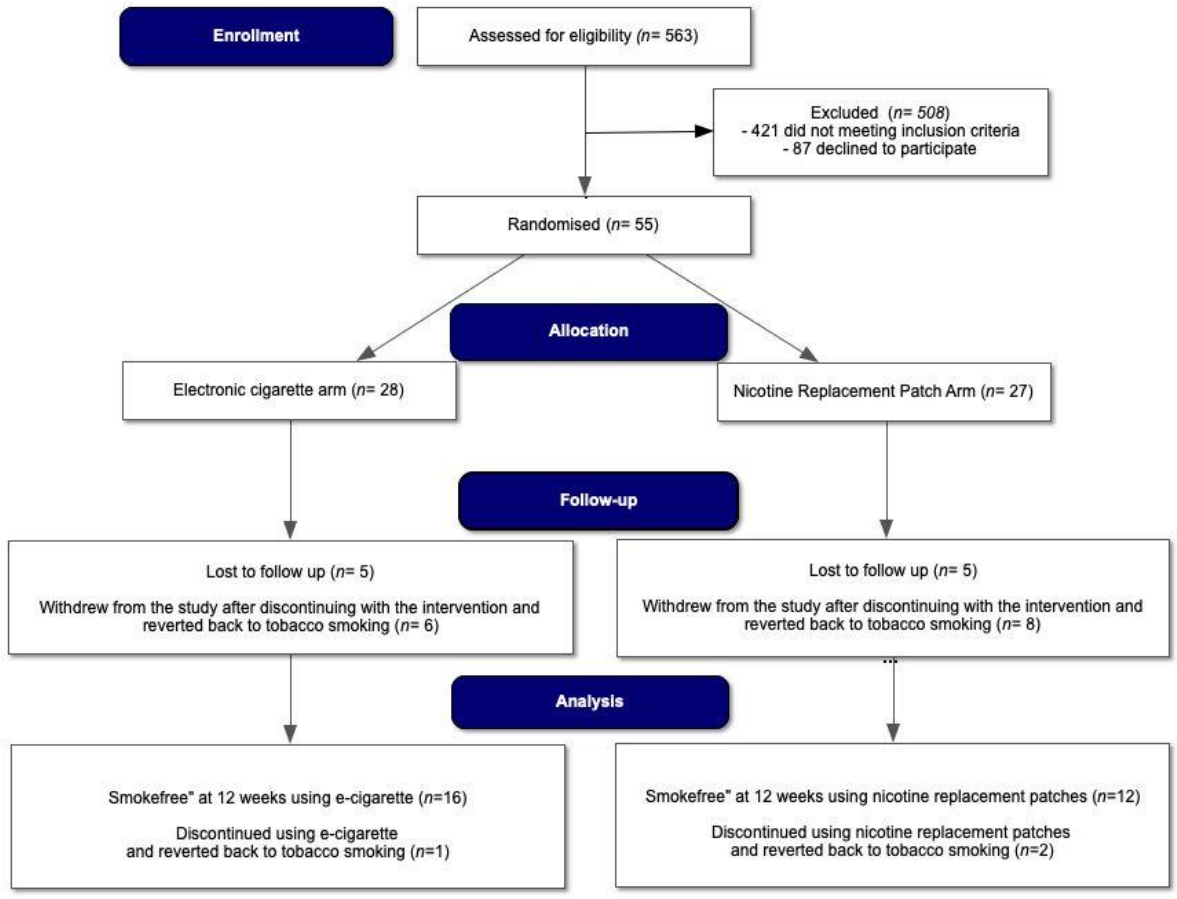


Figure 5.5 Trial flow and CONSORT diagram of screening, randomisation, follow up and analysis.

Baseline characteristics are summarised in Table 5.1. All participants (mean age of 44.2 ± 10.9 years) were Caucasian, 52.7% were male and 43.7% were female, with no established history of cardiorespiratory disease. The Scottish Index of Multiple Deprivation (SIMD) 2016 based on postcode identified that there was a bimodal distribution in relation to the study population's socioeconomic status. Figure 5.6 illustrates how the two peaks centered upon the 2nd and 8th decile, which respectively corresponded to the "most deprived" and "least deprived" deciles. In accordance with SIMD 2016, 62% of the recruited participants were from a socially deprived background (deciles 1-5). All of the participants were regular tobacco smokers, averaging a 20-pack year history with an averaged eCO breath test of 17 ± 7 ppm. The individual participants' FTND scores demonstrated that 16.4% (*n*=9) had a low nicotine dependence score, 25.5% (*n*=14) had a low to moderate nicotine dependence score, 43.6% (*n*=24) had a moderate nicotine dependence score and 14.5% (n=8) had a high nicotine dependence score. Statistical analysis demonstrated that the study group baseline characteristics were comparable for age, sex, smoking history, socioeconomic status, cardiorespiratory parameters, body mass index and eCO levels.

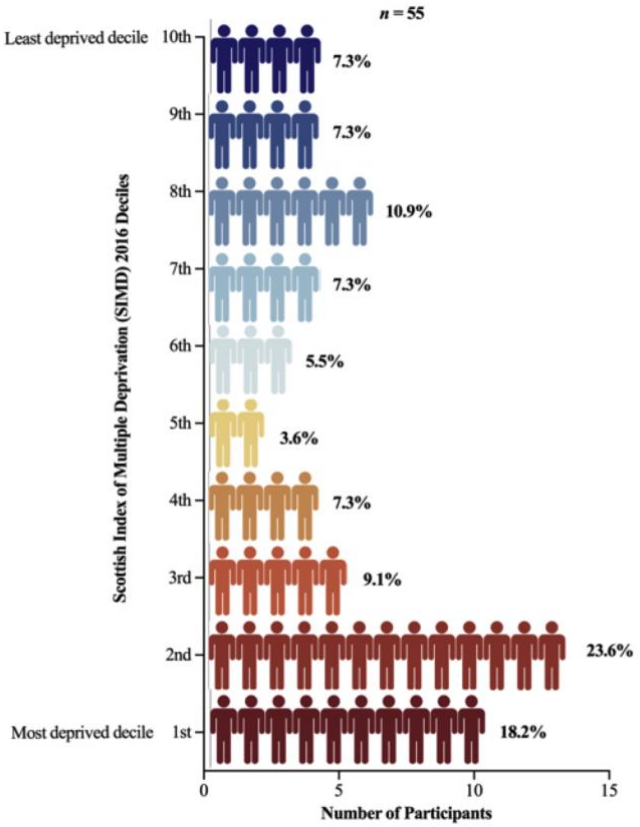


Figure 5.6 Demographic background of the study population according to the Scottish Index of Multiple Deprivation (SIMD) 2016 Deciles.

Table 5.1 Baseline Characteristics for whole sample and randomisation groups

Characteristics	All (*n*=55)	EC Group (*n*=28)	NRP Group (*n*=27)	*p*-value
Age (years) [a]	44.2 ± 10.9	45.4 ± 9.3	43 ± 12.4	.414^
Gender (*n*) [b] Male	29 (52.7%)	13 (46.4%)	16 (59.3%)	1.00‘
Female	26 (47.3%)	15 (53.6%)	11 (40.7)	1.00‘
Number of cigarettes per day (*n*) [c]	15 (5-15)	15 (10-15)	15 (10-15)	.542‘
Pack year history (years) [a]	20 ± 9.3	20 ± 8	19 ± 10	.077^
FTND [c]	7 (1-8)	5 (1-8)	5 (1-8)	.156^
SIMD[c]	2 (1-10)	2 (1-10)	1 (1-10)	.079‘
HR (bpm) [a]	64 ± 9	62 ± 9	65 ± 9	.179^
SBP (mmHg)[a]	118 ± 10	118 ± 10.4	118 ± 9.2	.930^
DBP (mmHg) [a]	71 ± 7	71 ± 6.7	70 ± 6.5	.645^
FMD (%)[d]	4.28 (3.55;6.25)	4.32 (3.60;5.92)	4.06 (3.09;6.49)	.416‘
O_2 Sats (%)[a]	98 ± 2	98 ± 2	98 ± 2	.830^
FEV1[a]	3.30 ± 0.93	3.13 ± 0.81	3.28 ± 1.05	.535^
FVC [a]	4.07 ± 1.04	3.97 ± 0.91	4.16 ± 1.17	.510^
FEV1/FVC [a]	78.2 ± 6.8	78.0 ± 7.1	78.4 ± 6.6	.841^
PEF [a]	459 ± 116	444 ±104	473 ± 127	.361^
eCO (ppm)[a]	17 ± 7	17 ± 8	16 ± 7	.667^
BMI[a]	25.7 ± 4.26	25.6 ± 4.1	25.9 ± 4.5	.718^

Data are presented mean ± SD[a], frequency (percentage)[b], mode (range)[c] and median (25^{th}-75^{th} percentiles)[d]. *P*-values derived from independent samples t-test^, Mann Whitney U test. BMI, body mass index; DBP, diastolic blood pressure; eCO, exhaled carbon monoxide; FEV_1, forced expiratory volume in one second; FVC, forced vital capacity; FEV_1/FVC, forced expiratory volume in one second/ forced vital capacity ratio; FMD, flow mediated dilatation; FTND, Fragerström nicotine dependence score; HR, heart rate; O_2 Sats, oxygen saturations; PEF, peak expiratory flow; SBP, systolic blood pressure; SIMD, Scottish index of multiple deprivation.

5.3.2 Adherence

Out of the 55 participants randomised, 31 (56.3%) participants completed the study protocol. In total 28 (50.9%) participants adhered to the nicotine replacement product they were assigned and were "smokefree" at 12 weeks. The "smokefree" quit attempt was unsuccessful for 17 (30.9%) participants who took part in the study, all of whom self-reported that they had reverted back to tobacco smoking and had discontinued the intervention they had been assigned. Although all of the participants who had reverted back to smoking were invited to return to a follow up visit, the majority declined and only 3 of the participants who had reverted back to smoking returned and attended the follow up visit. Overall the study dropout rate (i.e. those participants who were lost to follow up or decline to return to a follow up visit) was 43.6% (24 of 55).

When comparing the adherence, follow up and dropout rates between the study groups, the overall adherence to the assigned nicotine replacement product and successful smokefree attempts at 12 weeks was proportionally greater in the e-cigarette group in comparison to the nicotine replacement patch group. With 57% (16 of 28) of participants in the e-cigarette group been smokefree at 12 weeks compared to 44% (12 of 27) of participants in the nicotine replacement patch group. The proportion of participants who reverted back to tobacco smoking was proportionally greater amongst the nicotine replacement patches group (37%, 10 of 27) compared to the e-cigarette group (25%, 7 of 28). Out of the 3 participants who had reverted back to tobacco smoking during the study and attended the follow up study visit, one participants was from the e-cigarette group, and two participants were from the nicotine replacement patch group. The nicotine replacement patch group had an almost a 10% increased drop-out rate in comparison to the e-cigarette group (nicotine replacement patch group: 48%, 13 of 27 versus e-cigarette group: 39%, 11 of 28).

5.3.3 Cardiovascular function

Figure 5.7 and Table 5.2 summarise the changes in cardiovascular function at baseline and 12 weeks following the use of e-cigarettes, nicotine replacement patches and tobacco cigarettes for the PP analysis. Table 5.3 summarise the changes in cardiovascular function at baseline and 12 weeks following the use of e-cigarettes, nicotine replacement patches and tobacco cigarettes as per the ITT analysis.

For the PP analysis, non-invasive blood pressure measurement following 12 weeks of abstinence from tobacco smoking demonstrated significant reductions in both systolic and diastolic blood pressure in both e-cigarette and nicotine replacement patch groups. There was a systolic blood pressure reduction of 7 ± 8 mmHg in the e-cigarette group and 6 ± 3 mmHg in the nicotine replacement group. Evaluation of the changes in FMD following 12 weeks of abstinence from tobacco smoking, demonstrated the FMD on average increased from 5.12 ± 2.15 to 6.24 ± 2.45 in subjects who abstained from tobacco smoking using an e-cigarette (p <.001), and from 4.56 ± 2.22 to 5.60 ± 2.22 using the nicotine replacement patches (p = .003). There was no significant difference in the physiological improvements in endothelial function and non-invasive blood pressure measurements between the two groups (p >.05).

No statistically significant changes were identified in resting heart rate following either treatment group (all p >.05).

Compared to the PP analysis, overall the results of the ITT analysis demonstrated similar trends, but of lesser magnitudes. There were no significant changes in HR detected in either study arm in either analysis. Statistically significant changes in SBP and FMD were seen in both the e-cigarette and nicotine replacement patch study-arms in both the PP and ITT analysis. DBP changes, with a reduction in pressure, were seen in both study-arms in both analyses, however the reduction of DBP in the e-cigarette arm failed to reach statistical significance in the ITT analysis whereas as it was statistically significant in the PP analysis.

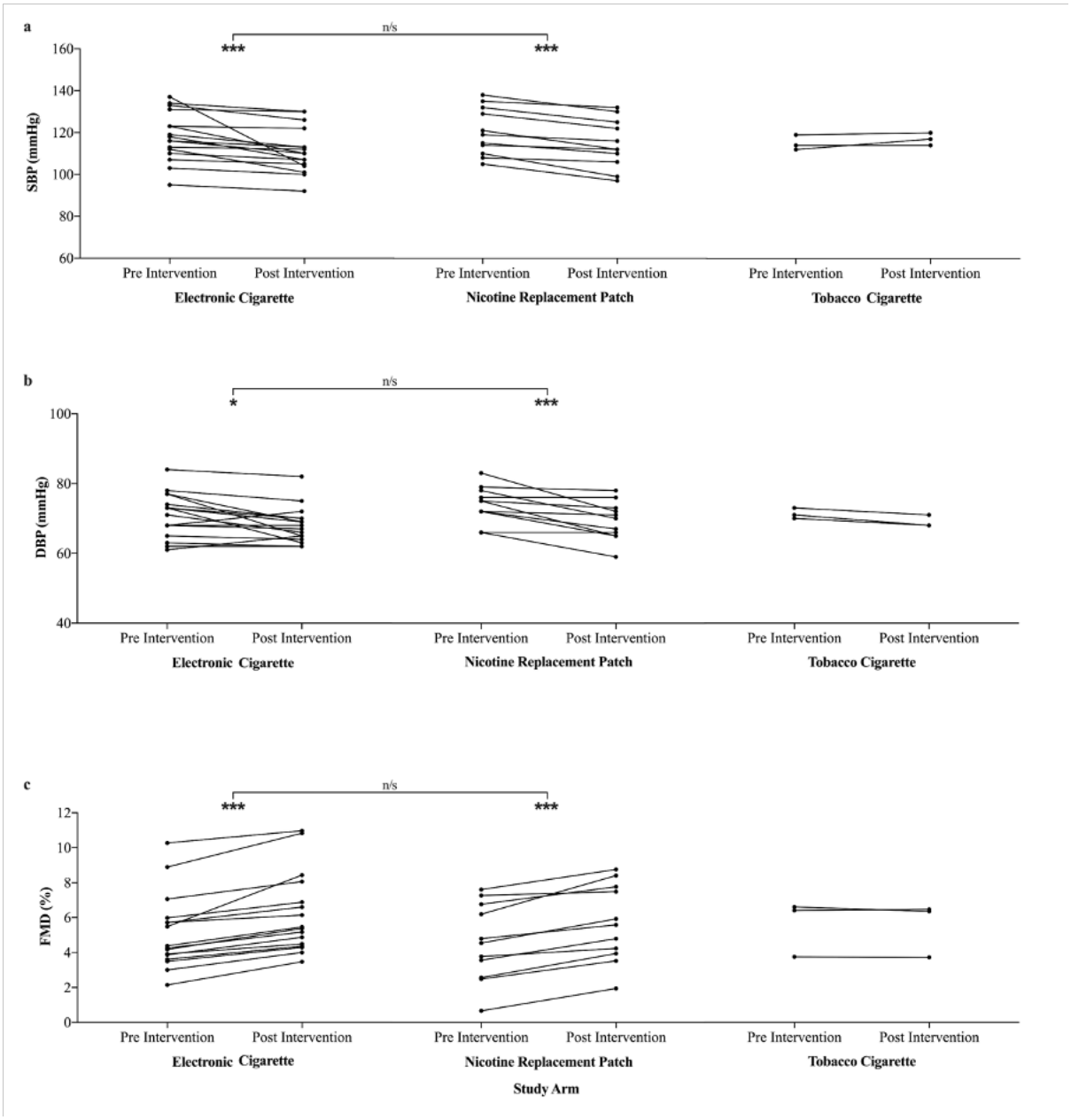


Figure 5.7 Cardiovascular changes before and 12 weeks after e-cigarettes, nicotine replacement patches and tobacco cigarette use. (a) Systolic blood pressure (b) Diastolic blood pressure (c) Flow mediated dilation. Data presented as per protocol analysis.

Table 5.2 Per protocol analysis: Changes in cardiovascular function between baseline and 12 weeks following intervention

Parameter	Study Arm	Pre-Intervention	Post-Intervention	Change	*P*-value
HR (bpm)	E-cigarette	61 ± 9	61 ± 11	0 ± 8	.214[b]
	Nicotine Replacement Patch	64 ± 7	60 ± 8	-3 ± 5	.050[b]
	Tobacco smoking	64 ± 8	65 ± 8	1.± 4	-
SBP (mmHg)	E-cigarette	118 ± 12	111 ± 11	-7 ± 8	**< .001**[a]
	Nicotine Replacement Patch	120 ± 11	115 ± 12	-6 ± 3	**< .001**[a]
	Tobacco smoking	115 ± 4	117 ± 3	2 ± 3	-
DBP (mmHg)	E-cigarette	71 ± 7	68 ± 5	-3 ± 5	**.029**[a]
	Nicotine Replacement Patch	73 ± 6	69 ± 6	-4 ± 4	**< .001**[a]
	Tobacco smoking	68 ± 3	66 ± 2	1 ± 3	-
FMD (%)	E-cigarette	5.12 ± 2.15	6.34 ± 2.45	1.09 ± 0.61	**< .001**[b]
	Nicotine Replacement Patch	4.56 ± 2.22	5.60 ± 2.22	1.10 ± 0.52	**.003**[b]
	Tobacco smoking	5.59 ± 1.59	5.60 ± 1.63	-0.08 ± 0.16	-

Data are presented as mean ± SD. P-values derived from paired t-test[a], related-samples Wilcoxon signed ranked test[b]. Abbreviations are reported as in previous tables.

Table 5.3 Intention-to-treat analysis: Changes in cardiovascular function between baseline and 12 weeks by study arm randomisation

Parameter	Study Arm	Pre-Intervention	Post-Intervention	Change	*P*-value
HR (bpm)	E-cigarette	62 ± 9	62 ± 10	0 ± 6	.177
	Nicotine Replacement Patch	65 ± 9	64 ± 9	-1 ± 4	.101
SBP (mmHg)	E-cigarette	118 ± 10	115 ± 11	-4 ± 7	**<.001**
	Nicotine Replacement Patch	119 ± 9	116 ± 9	-2 ± 4	**.007**
DBP (mmHg)	E-cigarette	71 ± 7	69 ± 6	-2 ± 4	.055
	Nicotine Replacement Patch	70 ± 6	68 ± 6	-2 ± 4	**.016**
FMD (%)	E-cigarette	5.15 ± 2.26	5.77 ± 2.39	0.61 ± 0.72	**<.001**
	Nicotine Replacement Patch	4.62 ± 2.19	5.09 ± 2.25	0.47 ± 0.65	**.002**

Data are presented as mean ± SD. P-values derived from related-samples Wilcoxon signed ranked test. Missing follow up data for intention-to-treat analysis managed by using baseline data as post-treatment data. Abbreviations are reported as in previous tables.

5.3.4 Body weight

Table 5.4 and Table 5.5 summarises the changes in body mass index (BMI) at baseline and 12 weeks following the use of e-cigarettes, nicotine replacement patches and tobacco cigarettes for the PP analysis and ITT analysis respectively.

Significant increases were observed in weight for nicotine replacement patch arm in both the PP analysis (78.6 ± 17.6 vs 76.3 ± 14.5 kg, $p = .027$) and ITT analysis (77.9 ± 15.0 vs 77.0 ± 14.6 kg, $p = .028$). Whereas, no significant changes in weight were observed in the e-cigarette arm following either the PP analysis (70.7 ± 11.7 vs 70.1 ± 12 kg, $p = .271$), or ITT analysis (72.9 ± 13.1 vs 72.6 ± 13.3 kg, $p = .315$).

For BMI, compared to the PP analysis the results of the ITT analysis demonstrated similar trends and significant findings. No significant changes in BMI were seen in the e-cigarette arm in either analysis. A significant increase in BMI was seen in the nicotine replacement patch study arm in both analyses.

5.3.5 Respiratory function and exhaled carbon monoxide breath test

Table 5.4 and Table 5.5 summarise the changes in respiratory function and eCO levels at baseline and 12 weeks following the use of e-cigarettes, nicotine replacement patches and tobacco cigarettes for the PP analysis and ITT analysis respectively.

Compared to the PP analysis, overall the results of the ITT analysis demonstrated similar trends and significant findings.

No significant changes were seen in FEV_1, FVC, FEV_1/FVC or PEF for either the e-cigarette or nicotine replacement study arms in either analysis.

The eCO validation tests performed at the final study visit demonstrated a significant reduction in eCO levels from 18 ± 7 ppm at the baseline visit to 1 ± 1 ppm at the final study, confirming abstinence from tobacco smoking for all participants in the e-cigarette and nicotine replacement patch groups (both $p < .001$) for the PP analysis. A significant reduction in eCO was also demonstrated in the ITT analysis for both study arm groups.

Table 5.4 Per protocol analysis: Changes in body mass index, exhaled carbon monoxide and respiratory function at baseline and 12 weeks following intervention

Parameter	Study Arm	Pre-Intervention	Post-Intervention	Change	*P*-value
BMI	E-cigarette	24.7 ± 3.7	25.1 ± 3.6	0.2 ± 0.8	.326[a]
	Nicotine Replacement Patch	26.1 ± 5.7	26.9 ± 5.6	0.8 ± 1.0	**.027**[a]
	Tobacco smoking	22.8 ± 4.7	23.1 ± 5.1	0.3 ± 0.5	-
eCO (ppm)	E-cigarette	18 ± 7	1 ± 1	-17 ± 7	**<.001**[a]
	Nicotine Replacement Patch	18 ± 7	1 ± 1	-17 ± 7	**<.001**[a]
	Tobacco smoking	18 ± 9	19 ± 6	1 ±3	-
FEV1	E-cigarette	3.19 ± 0.68	3.13 ± 0.72	-0.06 ± 0.18	.118[a]
	Nicotine Replacement Patch	3.07 ± 0.86	3.01 ± 0.79	-0.04 ± 0.17	.422 [a]
	Tobacco smoking	3.61 ± 1.05	3.45 ± 1.12	-0.16 ± 0.27	-
FVC	E-cigarette	4.01 ± 0.83	3.90 ± 0.98	-0.10 ± 0.38	.487 [b]
	Nicotine Replacement Patch	3.91 ± 0.99	3.86 ± 0.92	-0.04 ± 0.29	.350[b]
	Tobacco smoking	4.77 ± 0.80	4.65 ± 1.16	-0.12 ± 0.37	-
FEV1/FVC	E-cigarette	79.2 ± 7.1	79.4 ± 6.9	0.1 ± 3.1	.887[b]
	Nicotine Replacement Patch	78.3 ± 6.6	78.1 ± 6.4	-0.1 ± 5.3	.286[b]
	Tobacco smoking	74.8 ± 8.7	73.3 ± 6.5	-1.5 ± 6.1	-
PEF	E-cigarette	447 ± 104	443 ± 113	-4 ± 59	.394[b]
	Nicotine Replacement Patch	470 ± 106	476 ± 107	6 ± 50	.656[b]
	Tobacco smoking	510 ± 145	481 ± 249	-29 ± 116	-
O_2 Sats (%)	E-cigarette	97 ± 3	98 ± 2	1 ± 2	.201[b]
	Nicotine Replacement Patch	97 ± 2	98 ± 1	1 ± 2	.398[b]
	Tobacco smoking	98 ± 2	98 ± 2	0 ± 1	-

Data are presented as mean ± SD. P-values derived from paired t-test[a], related-samples Wilcoxon signed ranked test[b]. Abbreviations are reported as in previous tables.

Table 5.5 Intention-to-treat analysis: Changes in body mass index, exhaled carbon monoxide and respiratory function by study arm randomisation

Parameter	Study Arm	Pre-Intervention	Post-Intervention	Change	*P*-value
BMI	E-cigarette	25.6 ± 4.1	25.7 ± 4.1	0.1 ± 0.6	.433
	Nicotine Replacement Patch	25.9 ± 4.5	26.0 ± 4.4	0.4 ± 0.7	**.028**
eCO (ppm)	E-cigarette	17 ± 8	8 ± 9	-10 ± 10	**<.001**
	Nicotine Replacement Patch	16 ± 7	9 ± 9	-7 ± 10	**.002**
FEV1	E-cigarette	3.13 ± 0.81	3.09 ± 0.82	-0.04 ± 0.14	.092
	Nicotine Replacement Patch	3.28 ± 1.06	3.32 ± 1.01	0.03 ± 0.14	.506
FVC	E-cigarette	3.97 ± 0.91	3.93 ± 1.01	-0.05 ± 0.29	.679
	Nicotine Replacement Patch	4.16 ± 1.16	4.20 ± 1.09	0.04 ± 0.20	.142
FEV1/FVC	E-cigarette	78.0 ± 7.1	77.9 ± 6.9	-0.2 ± 2.6	.623
	Nicotine Replacement Patch	78.4 ± 6.6	78.4 ± 6.8	0.0 ± 3.6	.345
PEF	E-cigarette	445 ± 105	447 ± 130	2 ± 49	.255
	Nicotine Replacement Patch	474 ± 128	477 ± 128	5 ± 42	.600
O_2 Sats (%)	E-cigarette	98 ± 2	98 ± 2	0 ± 2	.201
	Nicotine Replacement Patch	98 ± 2	98 ± 2	0 ± 1	.676

Data are presented as mean ± SD. P-values derived from paired related-samples Wilcoxon signed ranked test. Missing follow up data for intention-to-treat analysis managed by using baseline data as post-treatment data. Abbreviations are reported as in previous tables.

5.4 DISCUSSION

Within the UK, the standard length of smoking cessation programmes supported by the NHS is 12 weeks (NHS, 2016). This study was designed to complement the standard 12 week smoking cessation programme offered by NHSGGC Smokefree Community Services. Within the context of smoking cessation, we investigated effects of nicotine-containing e-cigarettes in comparison to nicotine replacement patches over 12 weeks. We studied the effects on endothelial function, cardiovascular haemodynamic parameters, pulmonary function and weight.

5.4.1 Effects on the cardiovascular system

Several acute-exposure studies investigating the immediate effects of e-cigarettes have demonstrated adverse cardiovascular effects with regards to heart rate, blood pressure, endothelial dysfunction, oxidative stress and arterial stiffening (Kerr et al., 2019, Vlachopoulos et al., 2016, Carnevale et al., 2016, Ikonomidis et al., 2018). However, the effects demonstrated in these studies do not necessarily constitute as cardiovascular harm; instead they represent a sympathetic transient vascular response to nicotine. To our knowledge, this is the first study to report the cardiovascular effects of e-cigarettes in comparison to nicotine replacement patches within the context of smoking cessation.

Following 12 weeks of smoking cessation, using either nicotine-containing e-cigarettes or nicotine replacement patches, we observed a significant reduction in systolic and diastolic blood pressure along with an improvement in endothelial function.

5.4.1.1 Effects on endothelial function

The changes observed in the endothelial function parameters measured are consistent with the literature which demonstrates that smoking-induced endothelial dysfunction is dose-dependent and that smoking cessation can lead to the reversibility of endothelial dysfunction (Celermajer et al., 1996, Celermajer et al., 1993, Poredos et al., 1999). Following the use of e-cigarettes or nicotine replacement patches, we demonstrated a 1% absolute increase in FMD following 12 weeks of smoking cessation. Within the context of smoking cessation, our data are consistent with previous studies which have investigated the effects of NRT on endothelial function (Johnson et al., 2010). These studies have not, however, included the use of e-cigarettes. Johnson et al. reported a large prospective trial which evaluated the 1-year outcomes of NRT and smoking cessation on endothelial function in tobacco smokers with no pre-existing cardiovascular disease. This double-blind randomised placebo-controlled trial demonstrated that endothelial function significantly improved amongst the subjects who quit smoking, with FMD increasing from 6.2 ± 4.4 to 7.2 ± 4.2% after one year (p = .005). While a 1% increase in FMD may appear to be small, studies have demonstrated that a 1% increase in FMD is associated with a significant reduction in the incidence

of cardiovascular events (Yeboah et al., 2007). In order to fully evaluate the association between FMD changes at 12 weeks following smoking cessation supported by e-cigarette use and the incidence of long term adverse cardiovascular events, extended follow-up studies would be required.

5.4.1.2 Effects on blood pressure and heart rate.

Hypertension and tobacco smoking are cardiovascular risk factors and the leading causes of preventable mortality worldwide (Benjamin E et al., 2018). The interactions between smoking and blood pressure are complex, and there is uncertainty surrounding the independent effects of chronic tobacco smoking and hypertension (Primatesta P et al., 2001). Epidemiological studies have reported lower blood pressures amongst habitual tobacco smokers compared to non-smokers (Karvonen et al., 1959, Handa et al., 1990). This finding is regarded as a paradox given that nicotine is an adrenergic agonist, with potent sympathomimetic effects, responsible for the transient rise in blood pressure and heart rate following tobacco cigarette use (Lee et al., 2001). The data relating to smoking cessation induced blood pressure changes are limited, and the results are inconsistent, with studies reporting lower, higher or equivocal blood pressures in tobacco smokers compared with non-smokers (Oncken et al., 2001, Mann et al., 1991, Takami and Saito, 2011).

Given the well-established pressor effect of nicotine, concerns have been raised that nicotine replacement medications might adversely affect blood pressure. Several studies have demonstrated that in patients with and without pre-existing cardiovascular disease, the use of transdermal nicotine as part of a smoking cessation regime does not elicit adverse effects on blood pressure (Zevin et al., 1998, Silva et al., 2016, Tanus-Santos et al., 2001). It is hypothesised that the lack of any sustained cardiovascular effects from transdermal nicotine replacement patches may be explained by a tolerance to nicotine (Pickering, 2001).

Within the literature, few studies have investigated smoking cessation induced blood pressure changes following the use of e-cigarettes (Farsalinos et al., 2016, Ikonomidis et al., 2018). Farsalinos et al. conducted a prospective randomised control trial, which investigated the changes in blood pressure and heart rate amongst normotensive smoker who were invited to either reduce or abstain from tobacco smoking by switching to e-cigarettes. In this study, irrespective of the smoking phenotype classification (e.g. abstainers, reducers or failures) a small, but significant reduction was seen in systolic blood pressure (122.6 ±.13.3 vs 126.0 ± 15.6 mmHg $p < .001$), with no changes in diastolic blood pressure or heart rate at week 52 compared to baseline following e-cigarettes use. Iknonomidis et al. investigated 70 normotensive smokers enrolled in an e-cigarette-assisted smoking cessation programme. The results of this study demonstrated that as part of a 1-month smoking cessation programme, replacement of conventional cigarettes with nicotine containing e-cigarettes resulted in significant reductions in central systolic blood pressure (122.2 ±.8.0 vs 124.1 ± 9.0 mmHg $p < .04$), brachial systolic blood pressure (124.5 ±.9.0 vs 127.1 ± 6.0

mmHg p < .03) and AI@75 (23.9 ±.7.0 vs 28.9± 9.0% p < .001) and malondialdehyde (a marker of oxidative stress;1.09 ±.0.1 vs 1.28.0 ± 0.1 nmol/L p < .001), with no significant changes seen in diastolic blood pressure, heart rate or PWV compared to baseline measurements.

In our study, we observed small reductions in systolic and diastolic blood pressure and no change in heart rate following 12 weeks of smoking cessation in both the e-cigarette and nicotine replacement patch group. While the observed reductions in blood pressure were of statistical significance, the clinical benefit of a reduction in blood pressure amongst individuals who were normotensive at baseline (mean systolic blood pressure 118 ± 10, mean diastolic blood pressure 71 ± 7) may be limited. There is evidence which supports that a high to normal blood pressure (systolic pressure of 130 to 139 mm Hg, diastolic pressure of 85 to 89 mm Hg, or both) is associated with an increased risk of cardiovascular disease, including myocardial infarction and coronary artery disease (Qureshi et al., 2005). When Farsalions et al. repeated the same analysis in 66 subjects with a high-normal pressure blood pressure at baseline, a significant reduction in systolic blood pressure was observed at week 53 compared to baseline (132 ± 12.0 vs 141.2 ± 10.5 mmHg, $p < .001$), amongst those who reduced their tobacco smoking consumption or who quit smoking following tobacco cigarette use.

5.4.2 Effects on body weight

In the interpretation of the changes in blood pressure after smoking cessation, it is important to consider changes in body weight. Post-cessation weight gain has been shown to lessen some of the health benefits of stopping smoking, increasing the risk of hypertension and type 2 diabetes (Niskanen et al., 2004, Yeh et al., 2010). A meta-analysis demonstrated that 80% of individuals who are successful in quitting smoking experience post-cessation weight gain, gaining on average 2.9, 4.2 and 4.7 kg at 3, 6, and 12 months after quitting (Aubin et al., 2012). Although the health benefits of smoking cessation outweigh the health risks associated with post-cessation weight gain, the consequences of post-cessation weight gain are a recognised barrier to the initiation of quit attempts and increases relapse rates (Pomerleau et al., 2001, Bush et al., 2008).

Most of the effects contributing to post-cessation weight gain are thought to be brought about by the nicotine withdrawal, resulting in a decreased metabolic rate and increased appetite, which is often accompanied by increased caloric intake but no increase in physical activity (Audrain-McGovern and Benowitz, 2011). Therefore, given this theory, the use of NRT therapy should be associated with reductions in post cessation weight gain.

A Cochrane review that examined the effectiveness of NRT in preventing post-cessation weight gain demonstrated that NRT reduced the expected post-cessation weight gain by 0.5 kg (Farley et al., 2012). However, this small reduction in weight was not sustained after the NRT was discontinued. Although there is a paucity of evidence relating to the metabolic effects of e-cigarette

use and post-cessation weight gain following e-cigarettes use, the lack of post cessation weight gain following e-cigarette use has previously been reported (Russo et al., 2016, Russo et al., 2018). Russo et al. conducted a 1-year randomised control trial and evaluated post-cessation weight gain in "healthy" tobacco smokers who were invited to quit or reduce their tobacco smoking by switching to a first-generation "cig-a-like" e-cigarette. In this study, post-cessation weight gain was reported as 2.4 kg at 12 weeks after quitting following the use of an e-cigarette. Furthermore, a retrospective study investigating 1-year post cessation weight changes following e-cigarette use (where over 85% of participants were reported to use a second or third generation e-cigarette device) reported significantly lower post-cessation weight gain amongst e-cigarette users compared to quitters (1.6 ± 3.6 kg vs. 3.4 ± 3.0 kg; $p = .009$) (Russo et al., 2018).

In our study, post-cessation weight gain was observed to a greater extent following the use of nicotine replacement patches, with those using nicotine replacement patches gaining on average 2.3 kg, compared to 0.6 kg following the use of a second-generation e-cigarette. The reported weight gain following the use of nicotine replacement patches is in keeping with the post-cessation weight gain trajectories reported within the literature (Farley et al., 2012, Russo et al., 2018). Although the lack of post cessation weight gain following e-cigarette use is consistent with previous e-cigarette studies, there is a discrepancy in amount of weight gained between the studies. The discrepancy in weight gain between the two studies may be explained by the differences in nicotine delivery efficacy between the first and second generation e-cigarettes used in the studies. Second and third generation e-cigarettes have been reported to deliver nicotine at a rate similar to tobacco cigarettes (Farsalinos et al., 2014b, Fearon et al., 2017).

The apparent lack of post-cessation weight gain following e-cigarettes use compared nicotine replacement patches is a complicated process, which is confounded by nicotine addiction sensorimotor stimuli and behavioural rituals of tobacco smoking (Rose and Levin, 1991). Quit attempts are often associated with compulsive eating behaviours as individuals substitute eating for "hand to mouth" behaviour and "oral gratification" associated with smoking; which can lead to an increase in caloric intake (Bush et al., 2016). In contrast to nicotine replacement patches, vaping replicates the initial sensation of reward from exposure to nicotine; the sense of "smoke" in the throat (commonly known as a "throat hit"), in addition to the physical acts of tobacco smoking, such as the hand-to-mouth, and handling of tobacco cigarettes. Consequently, by substituting tobacco cigarettes with e-cigarettes, post-cessation weight gain may be minimised as individuals are provided with a coping mechanism which perpetuates their smoking rituals, rather than defaulting to food and overeating.

The finding that e-cigarettes minimise weight gain during cessation attempts is significant, for two main reasons. Firstly, the lack of weight gain following e-cigarette use may incentivise and sustain quit attempts amongst individuals who are concerned about cessation-related weight gain. Secondly, e-cigarettes may have the potential to reduce the negative health consequences

associated with increases in weight gain that may trigger the development of chronic diseases. Smoking and obesity are both independent and often co-existing risk factors for the development of chronic diseases such as cardiovascular disease, type II diabetes, respiratory disease and some cancers (Murugan and Sharma, 2008). Therefore, by reducing tobacco consumption and post-cessation weight gain, e-cigarettes may represent a weight-controlled tobacco cessation intervention which has a dual benefit in tackling the harms from smoking and obesity.

5.4.3 Effects on the respiratory system

5.4.3.1 Effects on pulmonary function

Concern has been raised over the effects of e-cigarettes on the respiratory system. Our short-term study demonstrated no significant changes in respiratory function, following 12 weeks of smoking cessation, using either nicotine-containing e-cigarettes or nicotine replacement patches. Our findings are not unexpected, given that our study participants were "healthy smokers" with no pre-existing lung disease. Across the numerous studies which have investigated the long-term respiratory effects of e-cigarette use, no clinically significant adverse effects in relation to pulmonary function have been identified amongst healthy smokers (Cibella et al., 2016, Campagna et al., 2016, Polosa et al., 2017), or smokers with asthma or COPD (Polosa et al., 2016a, Polosa et al., 2016b). Furthermore, progressive improvements in peripheral airway function (assessed by forced expiratory flow at 25-75 % (FEF25-75)), were observed at 3, 6 and 12 months amongst individuals who stopped smoking after switching to an e-cigarette as part of a 1-year prospective randomised control trial (Cibella et al., 2016). Although no deterioration of lung function has been identified in these studies, it is important to acknowledge that pulmonary function tests may be insensitive to detect the sub-clinical lung pathology that may occur in response to chronic inhalation of e-cigarette aerosols (Regan et al., 2015). High-resolution computed tomography is considered to be a more sensitive tool to detect early signs of lung damage, such as parenchymal micronodules, ground glass attenuation and emphysematous changes (Remy-Jardin et al., 1993). In a small prospective 3.5 year observational study of a cohort study of nine e-cigarette users, no significant abnormalities were identified following high-resolution computed tomography or pulmonary function tests (Polosa et al., 2017).

5.4.3.2 Effects on exhaled carbon monoxide levels

Given that the delivery of nicotine associated with both e-cigarettes and nicotine replacement patch use does not involve the burning of tobacco, it is not unexpected that we observed the normalisation of eCO levels amongst those who ultimately gave up smoking with the use of either an e-cigarette or nicotine replacement patch. Our data is consistent with previous studies which have reported normalisation in both eCO and exhaled nitric oxide (eNO) levels amongst "healthy smokers" who have abstained from tobacco smoking through e-cigarette use at 3, 6 and 12 months (Campagna et al., 2016). With regards to lung health, both eNO and eCO are considered as

inflammatory and carcinogenic biomarkers. NO is known to have antimicrobial actions by inhibiting the replication of respiratory pathogens (Nathan and Hibbs, 1991), and eCO is linked to airway inflammation (Zhang et al., 2010), and emerging data has revealed that both eCO and eNO have mechanistic roles in tumour biology (Szabo, 2016). Therefore, the observed normalisation of eNO and eCO levels may potentially have a harm reduction role in lowering the incidence of respiratory tract infections and lung cancer. While further long-term studies over an extended period are warranted to establish if chronic cigarette use has a causal effect on the respiratory system, within the context of a 3-month smoking cessation programme our data provide some preliminary evidence that for "healthy" individuals the use of e-cigarettes is unlikely to have a significant impact on lung health if they are used as a temporary bridge from tobacco smoking to abstinence.

5.4.4 Intention-to-treat analysis versus per protocol analysis

The discussion above is predominantly based on a PP analysis. While the PP analysis may provide estimates of the biological impact of the interventions, it is expected that in real world clinical practice, 100% compliance with the use of NRT interventions as prescribed would not be realistic. The ITT analysis helped preserve the baseline comparability and provide a control of confounding by known and unknown confounders, reduce the potential for bias of non-compliance with the study protocol and help provide an estimate of an effect that might be closer to that seen in real clinical practice.

The use of an individual participant's baseline data to replace missing data, would be expected to reduce any effect seen in that study arm and the ITT analysis did show more modest changes compared to the PP analysis.

Importantly, the changes seen in the ITT analysis, while more modest, still demonstrated significant changes in the same direction as the PP analysis for SBP, FMD and BMI in both the e-cigarette and nicotine replacement patch study arms.

While a significant reduction in DBP was seen in the PP analysis for the e-cigarette arm, the more modest reduction in DBP demonstrated in the ITT analysis was not statistically significant. This supports an argument that the clinical changes in DBP with e-cigarettes may not be experienced in clinical practice to the magnitude suggested by the PP analysis and further research would be required to explore this relationship.

5.4.5 Limitations

Our study has several limitations which should be acknowledged. The small sample size, in the e-cigarette, nicotine replacement patch and smoking subgroup cohort reduces the power to show

significant changes which occurred between the two-time points measured, which can cause Type II errors. Our sample size was confounded by recognised recruitment challenges and high attrition rates associated with smoking cessation studies. In our study, 43.6% of study participants were lost to follow up which is consistent with the dropout rates reported in other smoking cessation trials (Johnson et al., 2010). A lack of blinding is a known limitation which is associated with selection, performance and detection biases (Patsko et al., 2017). Even though all participants enrolled in the study, were willing to trial a quit attempt using either an e-cigarette or nicotine replacement, if participants lacked equipoise, selection bias might have arisen once participants were made aware of their assigned nicotine replacement, influencing participant co-operation and motivation. Our study may have been subject to performance bias, as we relied on participant self-reporting to confirm compliance with the study procedures, adherence to the assigned nicotine replacement products and abstinence from tobacco smoking. However, the eCO measurements which were performed at the weekly smokefree service sessions and study visits provide some reassurance to confirm the reported smoking status over the 12-week study period. To minimise the impact of detection biases, when analysing the FMD measurements I was blinded to the subject, treatment allocation, study visit and outcome. Finally, our findings cannot be generalised as our study participants represent a self-selected sample of healthy, Caucasian, tobacco smokers, who as part of a quit attempt were restricted to using a specific type of nicotine replacement patches or e-cigarettes provided by the study. Therefore, our study sample is not representative of all smokers attempting a quitting attempt with the use of the vast array of nicotine-containing e-cigarette devices and/or nicotine replacement patches available on the market.

5.4.6 Conclusions

Replication of our findings is required in larger prospective studies, using a more representative population and including a range of nicotine e-cigarette devices and e-liquids which are available on the market. Within the limitations of this study, however, the benefits of nicotine-containing e-cigarette interventions as part of a 12-week smoking cessation programme include minimising post-cessation weight gain and similar improvements in cardiovascular function and eCO levels to that of nicotine replacement patches. Although long-term health effects of e-cigarettes await further clarification, within the context of 12-week of smoking cessation programmes our findings support the harm reduction role of e-cigarette use as a temporary short-term smoking cessation interventions. Therefore, our research findings may help inform evidence-based discussion between healthcare professionals and smokers wishing to stop smoking, future research and policies.

CONCLUSIONS

6.1 Research aims and key findings

The tobacco epidemic is one of the biggest public health threats the world has ever faced, and remains the leading avoidable cause of death, illness and impoverishment (World Health Organisation, 2019). Despite smoking being one of the most important modifiable risk factors for the development of cardio-respiratory diseases, many patients will continue to smoke as a consequence of their nicotine addiction. Tobacco harm reduction acknowledges that the health harms from smoking can be significantly reduced by replacing cigarettes with a less toxic source of nicotine. Within the UK the emergence of e-cigarettes has dramatically changed and disrupted the smoking cessation landscape. Since 2014, e-cigarettes have remained the public's preferred smoking cessation aid with recently published randomised controlled data demonstrating that e-cigarettes are almost twice as effective as NRTs (18.0% vs 9.9%) in achieving smoking abstinence at one year (Hajek et al., 2019).

Over the last decade the harm reduction role of e-cigarettes has generated some strongly divergent views. While in opposition to some international policy positions, on the basis that e-cigarettes are likely to be 95% less harmful than smoking, Public Health England have been leading a pro-vaping campaign aimed at protecting the health of current smokers from the harms of tobacco smoke by encouraging smokers to switch on to nicotine containing e-cigarettes (McNeill A et al., 2015a). The recommendation was made with the acknowledgment of the existing knowledge gap surrounding the potential adverse health effects of e-cigarettes, with Public Health England concluding in an evidence based review that *"the comparative risks of cardiovascular disease and lung disease have not been quantified, and as such, research regarding biomarkers of exposure, risk and harm are required"* (McNeill A, 2018). Back in 2015 when I embarked on this research, the paucity of existing evidence regarding the cardiorespiratory effects of e-cigarettes presented a blank canvas and unique research opportunity for the work presented in this thesis. The overarching aim of this thesis was to design and conduct a series of studies which would provide the preliminary evidence on the harm reduction role of e-cigarettes (as an alternative nicotine replacement product) in reducing the subclinical cardio-respiratory health-related harms of tobacco smoking in "healthy smokers". As the clinical application of Public Health England's top-down edicts are centred on healthcare professionals having an understanding of harm-reduction, additional aims were to explore the attitudes and risk perceptions concerning nicotine, tobacco cigarettes, NRT and e-cigarettes amongst healthcare professionals.

I investigated this hypothesis firstly by designing and conducting a randomised acute exposure cross-over study to assess the acute effects of vaping in comparison to tobacco smoking, on endothelial function, arterial stiffness, cardiovascular haemodynamic parameters, pulmonary function and circulating MPs in "healthy" tobacco smokers (Chapter 4). The key findings from this

study demonstrated that both e-cigarette and tobacco cigarettes elicited differential cardiorespiratory effects on RHI, circulating MPs and PEF, suggesting that vaping induces a thrombogenic response and stimulates an obstructive airway response, whereas tobacco smoking induces both a thrombogenic and endothelial inflammatory response. Although the underlying mechanisms for these differential responses are unclear and further studies to investigate this are warranted, we postulated that:

- The immediate reduction in PEF following vaping, may be suggestive of a defensive physiological response against the irritants from the e-cigarette aerosol.
- The observed changes in RHI, which were observed following vaping only, may have arisen due to the vasoconstrictive response to nicotine, as demonstrated by the reductions in PWA. Given that our study was the first reported study to use PAT to assess the endothelial function response following the use of e-cigarettes, this an important methodological consideration regarding the utility of PAT to assess vascular function in future e-cigarette studies.
- The rise in EMPs and PMPs following tobacco cigarette exposure correlated with our understanding of the mechanisms involved in how tobacco smoking causes endothelial dysfunction and thrombosis. In times of uncertainly regarding the safe use of e-cigarettes, the rise in platelet MPs may mean that e-cigarettes could potentially be associated with a thrombotic risk and MP biomarker studies may have an assistive role in predicting the cardiovascular risk of e-cigarettes. This is important in the context of harm-reduction, as although e-cigarettes may be less harmful than tobacco smoking, they may not be devoid from cardiovascular risk and further studies are warranted.

To facilitate healthcare professionals' evidence-based decisions concerning the use of nicotine-containing e-cigarettes as an alternative nicotine replacement product for smoking cessation, with input from Smokefree services, I then designed and conducted a novel two-armed, pragmatic, single centre randomised control trial which mimicked real-world smoking cessation conditions, known as the VAPOUR study (Chapter 5). The primary outcome of this study was to assess physiological effects on endothelial function as studied by FMD amongst tobacco smokers undergoing a 12-week smoke-free quit attempt following the use of nicotine-containing e-cigarettes with behavioural support in comparison to nicotine replacement patches and behavioural support. Secondary outcomes included changes in cardiovascular haemodynamic parameters, pulmonary function and weight. Within the limitations of our study, our novel findings demonstrated that as part of a 12-week smoking cessation programme the use of both e-cigarettes and nicotine replacement patches have comparable and beneficial effects upon cardiovascular health, and no adverse effects on pulmonary functions. In contrast to nicotine replacement patches, no significant post cessation weight gain changes were observed following e-cigarette use. Although the

replication of our findings is required in larger studies the VAPOUR study provides some preliminary evidence to support the use of nicotine containing e-cigarettes as a short-term smoking cessation intervention. In turn this may help inform evidence-based discussion between healthcare professionals and smokers wishing to stop smoking with nicotine replacement products.

Finally, as the NHS healthcare professionals are the site of policy enactment, and it is their 'discretionary' application that determines whether or not changes occur in clinical practice (Lipsky M, 1980), it is key that congruence regarding the harm reduction role of e-cigarettes is established between healthcare professionals' beliefs and the top-down edicts arising from policy and clinical recommendations. Therefore, to establish if congruence existed at an organisational level, I conducted a regional cross-sectional survey of NHSGCC healthcare professionals' attitudes and risk perceptions concerning nicotine, tobacco cigarettes, NRT and e-cigarettes (Chapter 3). The key findings taken from the 3035 survey respondents identified that a discrepancy existed amongst healthcare professionals' perceptions and what they would clinically recommend to patients. At a grass route level, while the general consensus (in line with the NHSGGC harm reduction philosophy) across all healthcare professional groups was that e-cigarettes offered a tobacco harm reduction option; with doctors and smokers congruently holding a lower risk perception regarding the levels of harms and addictiveness of nicotine and e-cigarettes, compared to the other healthcare professional groups. In clinical practice, only 43.2% of healthcare professionals said they would recommend e-cigarettes as a method to stop smoking, with the sub-group analysis demonstrating that doctors and smokers were almost 10% more likely to recommend e-cigarettes, when compared to the other healthcare professional groups. While such divergence between the harm perception of e-cigarettes and clinical recommendations is likely to reflect the paucity of conclusive evidence. Our survey findings demonstrated that misconceptions relating to the harms of nicotine, alongside low levels of confidence and familiarity of the guidance on how to advise patients on the use of e-cigarettes, are likely to have a pivotal role in effecting changes in day-to-day clinical practice. Highlighting the urgent need for the development and integration of e-cigarette evidence based medical teaching and training across both undergraduate and postgraduate medical curriculums and practicums, so that patients wishing to stop smoking are provided with both effective and consistent practitioner advice on the harm reduction role of e-cigarettes.

6.2 Challenges and limitations of this thesis

It is important to recognise while the relative dearth of existing evidence regarding the health effects of e-cigarettes presented an exciting opportunity to pioneer clinically relevant and informative e-cigarette research, numerous ethical, methodological, legislative and regulatory challenges were encountered in the setting up and running of these e-cigarette studies. We were required to employ pragmatic solutions and make scientifically compromising modifications to the design of our trials, as a pre-requisite to the attainment of the necessary approvals to conduct

research, which subsequently imposed limitations on our research methodology and the internal and external validity of our findings.

Owing mainly to the challenges of identifying and sourcing an independently manufactured e-cigarette and e-liquid which was TPD compliant and satisfied the study sponsors pharmacovigilance regulatory framework, the VAPOUR study incurred a time lag of 12 months. As the total time available to conduct this research was 3 years, these delays reduced the time available for recruitment and furthermore a rapid expansion was seen in e-cigarettes both as a technology and as a research subject. In fact, most of the scientific literature which has provided some insights into the potential biological mechanisms by which e-cigarettes may induce cardiovascular and respiratory effects has emerged during this time frame. While the recent development of a standardised research e-cigarette (SREC) by the US National Institutes of Drug Abuse may offer a pragmatic pharmacovigilance solution for future e-cigarette studies and enable more meaningful comparisons between different research studies, the generalisability of the research findings would continue to be limited and may not be reflective of the e-cigarette marketplace and technology as successive "generational" changes are inevitable.

In keeping with the experience of many smoking cessation studies, the VAPOUR study encountered difficulties with recruitment and high levels of attrition. Despite intensive researcher efforts and financial resources to enrol more individuals into the study to make up for those who withdrew, in addition to attempting to reduce attrition by putting in additional efforts to follow up participants and provide 24/7 e-cigarette troubleshooting device support to circumvent the challenges posed by device breakages and failures, for the time-period we had to complete this study we were unable to achieve our desired sample size. Consequently, this resulted in a sample size that was marginally smaller than necessary on the basis of our power analysis.

Moving forward, as high attrition rates are likely to pose the same methodological dilemmas for the development of future research in this field, it is important to explore and understand the predictors of attrition. Therefore, in hindsight it may have been useful if I had undertaken qualitative research aimed at understanding the participants' lived experience of taking part in the VAPOUR study in relation to their smoking cessation journey, rather than depending on researcher experiences which are subject to inherent personal bias and speculation.

While the focus of the body of the work presented in this thesis relied on the use of validated physiological and biomarker studies to explore if there is an association between the exposure of vaping and the development of subclinical cardiovascular and respiratory disease in "healthy" tobacco smokers. It had been our intention, as part of a sub-study to the VAPOUR study, to conduct ex-vivo studies of resistance arteries obtained from gluteal biopsies of research participants to develop an understanding of the mechanistic vascular changes that occur at a cellular and tissue level. We proposed that the data generated from myography studies would have

enabled us to develop an understanding of the complex mechanisms involved in blood pressure regulation, and to see if the vessels' structural and functional properties changed after vaping which could affect the regulation of blood pressure. Furthermore, the remaining vascular tissue from the gluteal resistant arterioles would have then been used to culture cell lines on which further laboratory experiments could have been performed to facilitate our understanding of any cardiovascular changes at the cellular level between the study arms. Unfortunately, despite obtaining ethical approval for this research, only two research participants volunteered to take part in the sub-study. As the utility of such a small sample was unlikely to yield any meaningful findings we did not pursue this sub-study any further. Furthermore, while it is recognised that in vitro and murine studies have a valuable role in exploring the responses to vaping, these approaches also have inherent flaws, mainly due to the fact that the testing conditions are unable to replicate human vaping topography and aerosol exposure conditions (which as two research entities are not yet fully understood). As such caution must be taken when projecting the findings to humans for the risk of either overestimating or underestimating the harms of vaping.

Further challenges were encountered as all of these studies were set up and run almost exclusively by one investigator (myself), with very limited clinical or administrative support. Even with a relatively small number of participants, it was extremely challenging to balance the competing pressures of recruitment, eligibility screening, study visits/procedures, smokefree service referrals, provide 24/7 e-cigarette troubleshooting device support, in addition to completing the necessary trial administration to ensure that each of these studies ran in accordance with the protocol, smoke-free services and the expectations of the participants.

6.3 Conclusions for practice – a personal perspective

From the perspective as both a clinician and a researcher, my observations and interactions with the VAPOUR study participants undergoing their “real-life experience” of attempting smoking cessation, has provided me with valuable insights into the overlapping areas of clinical research and clinical practice in this field. The comparisons and interactions with individuals using either e-cigarettes or nicotine patches during quit attempts has considerably shaped my views particularly with regards e-cigarettes as a clinical tool for smoking cessation quit attempts.

In the VAPOUR study we identified significant challenges relating to recruitment and retention. The apparent motivation for many participants to take part in the study was through a strong personal desire to stop smoking. From my interactions, discussions and observations with the participants, study drop-out was linked to a relapse to smoking tobacco cigarettes and thus retention appeared to be linked to a behavioural change which supported smoking cessation.

During the VAPOUR screening, recruitment and study visits, this theme became apparent to me as the principle researcher. Participants' motivation for taking part in the study appeared to include an

expression of hope that, by being part of the study, they would be more likely to be successful at stopping smoking. This motivation may have acted as the “carrot” which facilitated recruitment, not only because the trial offered smoking cessation support, but because participants believed that a successful smoking cessation attempt would not only benefit themselves but would also benefit the study researchers and thus participation on the study provided additional incentive to engage in a quit attempt. It was clear from the engagement with the participants that, despite discussing the purpose of the study, participants considered the trial as a smoking cessation study rather than a study aimed at investigating the physiological outcomes of e-cigarettes compared to both nicotine replacement patches and to those people who resumed tobacco smoking.

All of the participants who were recruited into the study had previously tried to stop smoking. In considering why participants specifically wanted to take part in this study, participants frequently used phrases which contained the words “help”, “support”, “need”, “guilt”, “failure” and “disappointment”. These terms suggest that the emotional state of participants recruited into a study was heightened relating to smoking cessation attempts, with participants being acutely aware of the smoking cessation challenges ahead. Therefore, the same factors linked to the hope of a successful smoking cessation attempts which may have acted as the “carrot” to recruitment, may conversely have acted as the “stick” to retention amongst those who resumed tobacco smoking and felt negative guilt-related feelings prompting their drop-out from the study. It was apparent in discussing continued study participation with the individuals who resumed tobacco smoking that they found it emotionally difficult to attend the final study visit due to a sense of shame at their inability to complete the cessation programme. This emphasised the importance that in studies in which smoking cessation is a component or possible motivator, the strong emotional “push and pull” individual participants experience demands specific support and recognition that irrespective of a participants desired personal outcome, from the researchers perspective, attendance at the final visit is of great value.

I believe that researcher response times are an important recruitment factor. Several participants expressed that although they had considered stopping smoking for several months or years, they had never acted upon this notion. Subsequently, when they saw the advertisement for the study, many of the participants eluded to "acting" on an impulse, describing it as a “now or never moment”. Participants often said they contacted the research team within moments of seeing the advert, and it was vitally important that they were able to speak to the study team promptly because if they had allowed a time lapse, the notion might have passed. From a recruitment perspective, this highlights the critical importance of the research team to be flexible to the participants needs and to be equipped with the resources and availability to respond to the immediacy of a potentially time-bound notion.

Although all of the participants recruited into this trial had to accept randomisation into either the nicotine replacement patch or e-cigarette arm, the participants' randomisation preference leaned

towards e-cigarettes with participants perceiving that cessation attempts would be easier with an e-cigarette due to shared similarities with tobacco cigarettes (e.g. the hand to mouth action and the oral inhalation delivery of nicotine). Following randomisation and smoking cessation product assignment, participants randomised to receive e-cigarettes often reported feelings of elation and were confidence that they could stop smoking with an e-cigarette as they perceived e-cigarettes to be similar to tobacco cigarettes. Whereas participants randomised to nicotine replacement patches, often expressed words of disappointment and concerns that they would find the quit attempt harder with a nicotine replacement patch, as they had to change their habits and behaviours. It is possible this emotional response to assigned intervention could have an impact on both study engagement and outcomes. While blinding of participants and researchers is preferable, the blinding of participants and researchers as to the active nicotine delivery method used in a study such as VAPOUR is difficult to achieve without complex study designs including simultaneous multi-modal interventions with placebo controls.

At the final study visit research participants expressed conflicting views relating to the benefits of taking part in the 12-week smokefree behavioural sessions depending on which study arm they were assigned to. The participants in the e-cigarette group tended to state they didn't find the smokefree support sessions of much value because e-cigarettes emulated similar behaviours to tobacco smoking, making the switch from tobacco smoking to vaping much more manageable. Participants in the nicotine replacement patch group on the other hand tended to express that as part of their quit attempt they felt that the behavioural support sessions where integral to the success of there smokefree attempt as the use of patches required a dramatic behavioural change in their tobacco smoking habits. Amongst those who had a successful quit attempt, users of the nicotine replacement patch were subsequently pleased that they had been assigned patches because they felt they were forced to break the habits associated with tobacco smoking and were no longer dependent on nicotine. Those in the e-cigarette group who stopped tobacco smoking, while delighted that they had stopped using tobacco, often expressed concerns that they felt they had swapped one addiction to another and asked what medical guidance and support was available to help them become e-cigarette free. In the absence of any clinical guidance on the aftercare to support patients who have quit tobacco smoking via the use of an e-cigarette, this request for additional help presented to me by my study participants illustrated the real-life clinical dilemma relating to the lack of guidance available to clinicians to help provide continued onward support of e-cigarette users who wish to become e-cigarette free.

The significant emotional factors involved with tobacco smoking, initiation of cessation attempts, cessation attempt outcomes and habit-breaking, are clearly major factors for consideration in e-cigarette research and in the use of e-cigarettes in the clinical practice of supporting cessation of tobacco smoking. This highlights the need in developing clinical recommendations of e-cigarettes for smoking cessation, that healthcare professionals and patients must be aware that e-cigarette

users may have different behavioural support requirements during *and* after their quit attempts. Secondly the dearth of clinical guidance to support e-cigarette users to become e-cigarette free needs to be urgently addressed, supported by well-designed and focused research.

6.4 Future directions

Moving forward it is important that the findings of prospective biomarker studies such as ours are replicated in much larger studies using a more representative sample and range of nicotine e-cigarette devices and e-liquids, to detect if e-cigarette use is associated with any subclinical injury in "heathy" smokers switching to e-cigarettes, or changes in patients with pre-existing cardiovascular and respiratory diseases. In the absence of knowing the long term health risks associated with e-cigarettes, health benefits can still be gained from research efforts focusing on understanding the short term cardiovascular and respiratory risks. This includes (1) any tobacco smokers who as part of a successful quit attempt uses an e-cigarette as a short term nicotine replacement measure; or (2) for patient cohorts where despite having a reduced life expectancy, smoking cessation is associated with significant improvements in their disease related morbidity and morbidity. An example of this is provided in the management of PAOD, where although the disease burden of critical limb ischemia is associated with a reduced life expectancy and a mortality typically exceeding 50% by 5 years (Duff et al., 2019), there is substantial evidence which identifies that smoking cessation leads to significant reductions in the risk of disease progression, major limb amputation and premature death (Action on Smoking and Health, 2017). As such, NICE identifies smoking cessation as the single most important modifiable risk factor in the management of PAOD, and as first line management recommends smoking cessation with the aid of medicinal and behavioural support (NICE, 2012).

As previously discussed in Chapter 2, in the race to produce clinically relevant and informative research, a major difficulty for e-cigarette researchers lies in the fact that we are chasing a moving target. This leads to the situation that by the time the research findings of short-term studies are published, they are often obsolete due to constant technological advancements and legislative and regulatory changes. Consequently, the futility of whether or not long term studies will be able to determine if e-cigarettes are causally linked to adverse health outcome is questioned. Given these limitations, the development of large prospective biomarker studies which take advantage of the UK Biobank, or large collaborative datasets may allow for e-cigarette research to be turned around at a faster rate and conducted in much bigger and broader populations than were available for this thesis.

Finally, at the same time the nicotine delivery kinetics of e-cigarettes have been engineered to become more effective in alleviating the nicotine withdrawal symptoms associated with quitting tobacco cigarette smoking. The consequences are that e-cigarettes are likely to become more addictive and will be used in the long-term. To some extent this has already been demonstrated by

the data presented in the randomised controlled trial by Hajek et al, where e-cigarettes were almost twice as effective for smoking cessation compared to NRT (18.0% vs 9.9%), but among participants with the successful quit attempts, sustained product use at 1-year was significantly greater in the e-cigarette compared to the NRT group (80% vs 4%) (Hajek et al., 2019). Therefore, in the absence of knowing the long-term health consequences of e-cigarette use and Public Health England's recommendation for smokers to switch on to e-cigarettes, the concerns of swapping one addiction for another remains a legitimate concern and should be managed. It is my opinion that to manage the immediate threat of e-cigarette addiction together with the unknown long-term risks of e-cigarette use, pre-emptive measures in clinical practice and research efforts should also focus on managing e-cigarette addiction and cessation, with a view to exploring and developing "e-cigarette friendly" smokefree cessation services to provide tobacco smokers with the cessation support on firstly becoming smokefree and then e-cigarette free.

6.5 Closing remarks

To conclude, this thesis demonstrated that biomarker studies, such as ours, have an important role in predicting potential cardiovascular and respiratory risks of e-cigarettes and developing an understanding of any potential cardiovascular and respiratory risks associated with long term e-cigarette use. However, the judgement as to whether our observed associations represent a cause-effect relationship between the exposure of vaping and the development of cardiovascular and respiratory disease requires inferences far beyond the data of studies presented in this thesis. For this to happen it will require the consideration of criteria that include the magnitude of the association from large long-term epidemiological studies, and the consistent replication of findings from large prospective controlled trials. Nevertheless, this body of research provides the preliminary evidence which supports the harm reduction role of e-cigarettes when used as a temporary short-term smoking cessation intervention. Although our findings suggest that e-cigarettes may be less harmful, it is important to recognise that significant rises in PMPs, which are a surrogate biomarker of thrombosis suggest that e-cigarettes may not be devoid from cardiovascular risk and further studies are warranted. In the meantime, consideration should be given to research and its role to help direct future research and facilitate evidence-based decisions with regards to smoke-free policies and the use of e-cigarettes as a smoking cessation tool, thereby having an impact at an individual, local, national and global scale.

APPENDIX

Appendix 1: Healthcare Professional Survey

HEALTHCARE PROFESSIONAL SURVEY QUESTIONNAIRE VERSION 1.3_05/10/2017_12.00

Knowledge and Perceptions about Nicotine, Nicotine Replacement Therapies and Electronic Cigarettes amongst Healthcare Professionals in UK

Investigators: Miss Daniele Kerr MBBS. MRCS and Professor Christian Delles MD, FRCP, FAHA, FBIHS

As part of our programme of research investigating the health effects of electronic cigarettes. We would like to invite you to take part in this 10-minute questionnaire survey. Our aim is to better understand the knowledge and perceptions about nicotine, nicotine Replacement Therapies and electronic cigarettes amongst healthcare professionals in United Kingdom. By completing this questionnaire, you are consenting to participate in this research study. Your decision to take part in this research is entirely voluntary. By completing this questionnaire, it is important you understand that you will be consenting to participate in this research study. All questionnaires reviewed will be fully anonymised, therefore it will not be possible to withdraw once you have submitted a completed questionnaire. This questionnaire has been approved by the following bodies: University of Glasgow College of Medical, Veterinary and Life Sciences Ethics Committee and NHS Greater Glasgow and Clyde Research & Development department. Once the data from this questionnaire has been collected the research findings will be disseminated to healthcare professionals and public health specialists through Staffnet and newsletters; and to the wider scientific community through peer reviewed publications, presentations and research student dissertations. No identifiable participant information will be detailed within the research finding. If you have any questionnaire relating to the questionnaire please do not hesitate to contact Miss Daniele Kerr on 07570047819 or 0141 330 2627 or email Cams-INS-Vapour@glasgow.ac.uk

Questions about you:

1. **What is your occupation?**

☐ General practitioner ☐ Physician ☐ Surgeon ☐ Dentist
☐ Nurse ☐ Healthcare Assistant ☐ Other (Please state) _____

2. **Please describe your speciality (Please tick only one)?**

☐ General practice	☐ Nursing	☐ Pharmacology	☐ Dentistry
☐ Research/science	☐ Clinical Trials	☐ Lecturer/Medical Education	☐ Dermatology
☐ Cardiology	☐ Respiratory	☐ Diabetes and Endocrinology	☐ Smokefree Services
☐ General Medicine	☐ Care of the Elderly	☐ Palliative Care	☐ Public Health
☐ Radiology	☐ General surgery	☐ Vascular Surgery	☐ Paediatrics
☐ Cardiothoracics	☐ Urology	☐ Trauma & Orthopaedics	☐ Neurosurgery
☐ Neurology	☐ Plastic Surgery	☐ Oral & Maxillofacial Surgery	☐ Anaesthetics
☐ Nephrology	☐ Accident and Emergency		

☐ Other (Please state) _____

3. **Do you currently or have you ever smoked tobacco cigarettes?**
   - ☐ No, never smoked
   - ☐ Yes, but no longer smoke tobacco cigarettes
   - ☐ Yes, currently smoke tobacco cigarettes

4. **If you are a former smoker how did you stop?**
   - ☐ By using oral medications (e.g. varenicline, bupropion)
   - ☐ By using nicotine replacement therapies (e.g. patches, chewing gum, spray)
   - ☐ By using an electronic cigarette
   - ☐ By using psychological support
   - ☐ By using other methods (acupuncture, hypnotherapy)
   - ☐ Without using any aids
   - ☐ Not applicable

Questions about your views:

4. **Based on your opinion/knowledge, please score the health risk of each of the following products:**

	Lowest Risk									Highest Risk
Tobacco cigarettes	1	2	3	4	5	6	7	8	9	10
Snus (smokeless tobacco)	1	2	3	4	5	6	7	8	9	10
Electronic cigarettes	1	2	3	4	5	6	7	8	9	10
Nicotine replacement therapies	1	2	3	4	5	6	7	8	9	10
Oral smoking cessation medications (e.g. varenicline, bupropion)	1	2	3	4	5	6	7	8	9	10

5. **Based on your opinion/knowledge, please score the health risk of each of the following components of tobacco cigarettes:**

	Lowest Risk									Highest Risk
Nicotine	1	2	3	4	5	6	7	8	9	10
Inhaled Smoke	1	2	3	4	5	6	7	8	9	10
Carbon Monoxide	1	2	3	4	5	6	7	8	9	10
Tar	1	2	3	4	5	6	7	8	9	10
Tobacco	1	2	3	4	5	6	7	8	9	10

6. **When compared to tobacco cigarettes how harmful to health do you consider the following:**

Nicotine Replacement Patches	☐Don't know	☐Less harmful	☐Equally harmful	☐More harmful
Electronic cigarettes	☐Don't know	☐Less harmful	☐Equally harmful	☐More harmful

7. **Do you agree with the following statement, "Electronic cigarettes are a good thing"?**

☐Strongly disagree ☐Disagree ☐ Neutral ☐Agree ☐Strongly agree

8. **How addictive do you consider the following product:**

	Not addictive									Highly addictive
Tobacco cigarettes	1	2	3	4	5	6	7	8	9	10
Electronic cigarettes	1	2	3	4	5	6	7	8	9	10
Nicotine replacement therapies	1	2	3	4	5	6	7	8	9	10

Questions about your workplace:

10. Are you aware of your workplace policy on electronic cigarette use?

☐Yes, electronic cigarette use is permitted
☐Yes, electronic cigarette use is not permitted
☐Not sure

11. Does your workplace have a system to record use of electronic cigarettes among patients?

☐Yes ☐No

Please provide comments in the space below

12. Has your workplace advised you on what advice you should give to patients if they ask about electronic cigarettes?

☐Yes ☐No

If yes, what is the recommended advice on electronic cigarettes?

13. To what extent do you agree with the decision that some hospitals within the United Kingdom permit the use of electronic cigarettes on hospital grounds?

☐Strongly disagree ☐Disagree ☐ Neutral ☐Agree ☐Strongly agree

14. Please rank how concerned are you that electronic cigarettes may encourage non-smokers to take up tobacco cigarette smoking

	No concern									very concerned
Adults > 19 years	1	2	3	4	5	6	7	8	9	10
Adolescents 10-19 years	1	2	3	4	5	6	7	8	9	10
Children <10 years	1	2	3	4	5	6	7	8	9	10

Questions about your patients:

15. How often do you see patients who smoke in your working environment?

☐I do not have patient contact (Questionnaire completed)
☐Never
☐Less than 1 day per week
☐1–2 days per week
☐Daily

16. Do you routinely ask patients if they;

Use tobacco cigarettes: ☐Yes ☐No
If yes, do you document this in the medical records: ☐Yes ☐No

Use nicotine replacement therapies e.g. patches, gum: ☐Yes ☐No
If yes, do you document this in the medical records: ☐Yes ☐No

Use electronic cigarettes: ☐Yes ☐No
If yes, do you document this in the medical records: ☐Yes ☐No
Please state what terminology you would use for electronic cigarette use:

17. How often do you see patients who use electronic cigarettes in your working environment?

☐Never
☐Less than 1 day per week
☐1–2 days per week
☐Daily

18. How often are you asked by patient's questions about electronic cigarettes?

☐Never ☐Less than 1 day per week ☐1–2 days per week ☐Daily

19. To what extent do you agree with the following statements:

"I feel confident advising patients regarding electronic cigarettes"

☐Strongly disagree ☐Disagree ☐ Neutral ☐Agree ☐Strongly agree

"I feel I need more information and guidance regarding electronic cigarettes"

☐Strongly disagree ☐Disagree ☐ Neutral ☐Agree ☐Strongly agree

20.Would you recommend electronic cigarettes to patients as a method to stop smoking?

☐Yes ☐No

Please provide any comments in the space below:

Thank you very much for taking the time to complete this questionnaire

Appendix 2: Classification of healthcare professional respondents by occupation

Characteristics and survey responses			All Responses
Occupation	**n**	**valid %**	**total %**
Doctor			
Physicians	229	(37.9)	(7.5)
Surgeons	118	(19.5)	(3.9)
General Practitioners	102	(16.9)	(3.4)
Psychiatrists	44	(7.3)	(1.4)
Emergency Medicine	31	(5.1)	(1.0)
Anaesthetics	30	(5.0)	(1.0)
Paediatrics and Child Health	26	(4.3)	(0.9)
Radiologists	12	(2.0)	(0.4)
Public Health	5	(0.8)	(0.2)
Obstetrician and Gynaecologists	4	(0.7)	(0.1)
Pathology	4	(0.7)	(0.1)
Total	**605**	**(100)**	**(19.9)**
Nursing			
Adult Nurse	448	(41.1)	(14.8)
Mental Health Nurse	74	(6.8)	(2.4)
Paediatric Nurse	36	(3.3)	(1.2)
Theatre Nurse	28	(2.6)	(0.9)
District Nurse	7	(0.6)	(0.2)
Neonatal Nurse	8	(0.7)	(0.3)
Learning Disability Nurse	5	(0.5)	(0.2)
General Practice Nurse	3	(0.3)	(0.1)
Nurse (Unspecified)	472	(43.7)	(15.6)
Total	**1081**	**(100)**	**(35.7)**
AHPs			
Physiotherapist	104	(32.7)	(3.4)
Occupational Therapist	52	(16.4)	(1.7)
Podiatrist	30	(9.4)	(1.0)
Diagnostic Radiographer	29	(9.1)	(1.0)
Dietitian	26	(8.2)	(0.9)
Speech and Language Therapist	22	(6.9)	(0.7)
Prosthetist/Orthotist	6	(1.9)	(0.2)
Therapeutic Radiographer	5	(1.6)	(0.2)
Operating Department Practitioner	2	(0.6)	(0.1)
Orthoptist	2	(0.6)	(0.1)
AHP (Unspecified)	40	(12.6)	(1.3)
Total	**318**	**(100)**	**(10.6)**

Occupation	n	valid %	total %
Psychological Therapies			
Clinical Psychologist	12	(60.0)	(0.4)
Assistant Clinical Psychologist	7	(35.0)	(0.2)
Psychotherapist	1	(5.0)	(0.0)
Total	**20**	**100**	**(0.6)**
Dental Team			
Dentist	11	(50.0)	(0.4)
Dental Nurse	8	(36.4)	(0.3)
Dental Technician	2	(9.1)	(0.1)
Dental Hygienist	1	(4.5)	(0.0)
Total	**22**	**100**	**(0.8)**
Pharmacy			
Pharmacist	72	(67.3)	(2.4)
Pharmacist Technician	31	(29.0)	(1.0)
Pharmacy Assistant	4	(3.7)	(0.1)
Total	**107**	**(100)**	**(3.5)**
Wider Healthcare Team			
Clinical Support Staff	282	(40.6)	(9.3)
Administration	219	(52.3)	(7.2)
Corporate Services	16	(3.0)	(0.5)
Support Services	13	(2.4)	(0.4)
Estate Services	7	(1.3)	(0.2)
Domestic Services	2	(0.4)	(0.1)
Total	**539**	**(100)**	**(17.7)**
Public Health			
Public Health Practitioner	94	(81.0)	(3.1)
Health Visitor	22	(19.0)	(0.7)
Total	**116**	**(100)**	**(3.8)**
Midwifery			
Midwife	35	(100)	(1.2)
Total	**35**	**(100)**	**(1.2)**
Healthcare Science			
Life Sciences	53	(49.5)	(1.7)
Physiological Sciences	16	(15.0)	(0.5)
Clinical Informatics	9	(8.4)	(0.3)
Clinical Bioinformatics	2	(1.9)	(0.1)
Clinical Scientist (Unspecified)	27	(25.2)	(0.9)
Total	**107**	**(100)**	**(3.5)**

Data are presented as frequency (percentage)

Appendix 3: Two-Way Repeated Measures ANOVA for physiological and biomarker parameters following e-cigarette and tobacco cigarette

Parameter	Two-way RM ANOVA interaction of Intervention (EC or TC) with time point	Intervention	Pre-Intervention	Post-intervention	Change following intervention	P-value
HR (bpm)	<0.001	E-cigarette	65 (2.1)	73 (1.9)	8 (1.2)	<0.001
		Tobacco Cigarette	64 (1.9)	86 (2.9)	23 (2.7)	<0.001
		EC and TC Difference	1.5 (1.7)	13.1 (2.5)		
		EC and TC Difference P-value	0.381	<0.001		
SBP (mmHg)	0.048	E-cigarette	124 (2.6)	123 (2.5)	1 (1.2)	0.431
		Tobacco Cigarette	121 (3.1)	125 (3.0)	4 (2.1)	0.058
		EC and TC Difference	3.2(1.4)	2(1.7)		
		EC and TC Difference P-value	0.034	0.267		
DBP* (mmHg)	0.405	E-cigarette	80 (2.4)	80 (2.3)*	0 (1.2)	0.805
		Tobacco Cigarette	75 (2.4)	77 (2.2)	2 (1.1)	0.166
		EC and TC Difference	-4 (2.0)	-3 (1.5)		
		EC and TC Difference P-value	0.044	0.067		
RHI*	0.153	E-cigarette	1.68 (0.07)*	1.96 (0.10)	0.28 (0.09)	0.004
		Tobacco Cigarette	1.86 (0.10)	1.97 (0.11)	0.10 (0.10)	0.302
		EC and TC Difference	0.18 (0.12)	0.01 (0.08)		
		EC and TC Difference P-value	0.140	0.921		

PWA occluded arm* (AU)	0.501	E-cigarette	860 (89)	465 (80)	-395 (69)	<0.001
		Tobacco Cigarette	895 (88)	437 (87)*	-458 (72)	<0.001
		EC and TC Difference	35 (84)	-28 (52)		
		EC and TC Difference P-value	0.679	0.592		
PWA control arm * (AU)	0.379	E-cigarette	906 (97)	507 (89)	-399 (79)	<0.001
		Tobacco Cigarette	966 (101)	475* (88)	-492 (76)	<0.001
		EC and TC Difference	61 (97)	-32 (60)		
		EC and TC Difference P-value	0.540	0.598		
AI (%)	0.005	E-cigarette	-10.5 (2.9)	-6.9 (3.0)	3.7 (1.3)	0.010
		Tobacco Cigarette	-9.0 (2.2)	-10.9 (3.0)	-1.9 (1.7)	0.265
		EC and TC Difference	1.6 (1.7)	-4.0 (1.7)		
		EC and TC Difference P-value	0.368	0.026		
AI@75 (%)	0.165	E-cigarette	-16.6 (3.2)	-14.3 (3.3)	2.3 (1.4)	0.131
		Tobacco Cigarette	-15.5 (2.3)	-16.2 (3.1)	-0.7 (0.7)	0.709
		EC and TC Difference	-1.1 (1.8)	-1.9 (0.4)		
		EC and TC Difference P-value	0.558	0.358		
sICAM-1* (ng/ml)	0.280	E-cigarette	61.6* (21.8)	44.4* (6.9)	-17.2 (16.2)	0.302
		Tobacco Cigarette	42.4* (5.8)	41.4 (4.6)	-0.9 (2.2)	0.673
		EC and TC Difference	-19.2 (17.5)	-2.9 (3.9)		
		EC and TC Difference P-value	0.286	0.457		

sP-selectin* (ng/ml)	0.202	E-cigarette	117.8* (23.8)	84.7 (6.1)	-33.11 (21.1)	0.135
		Tobacco Cigarette	89.1 (7.2)	82.4* (6.9)	-6.7 (4.4)	0.145
		EC and TC Difference	-28.7 (21.8)	-2.3 (6.8)		
		EC and TC Difference P-value	0.204	0.737		
sVCAM-1* (ng/ml)	0.214	E-cigarette	787.1* (96.0)	701.8 (27.9)	-85.3 (88.2)	0.347
		Tobacco Cigarette	687.3 (31.0)	710.4 (31.4)	23.1 (27.5)	0.414
		EC and TC Difference	-99.8 (94.5)	8.6 (29.1)		
		EC and TC Difference P-value	0.306	0.774		
sE-selectin(ng/ml)	0.395	E-cigarette	72.2 (7.1)	73.1 (7.1)	0.9 (2.0)	0.660
		Tobacco Cigarette	76.1 (7.6)	74.3 (7.9)	-1.8 (1.9)	0.347
		EC and TC Difference	3.9 (2.9)	1.2 (2.7)		
		EC and TC Difference P-value	0.195	0.660		
PECAM-1* (ng/ml)	0.234	E-cigarette	0.97* (0.07)	0.96 (0.07)	-0.02 (0.04)	0.664
		Tobacco Cigarette	1.06 (0.07)	1.00 (0.07)	-0.07 (0.03)	0.018
		EC and TC Difference	0.09 (0.40)	0.04 (0.05)		
		EC and TC Difference P-value	0.045	0.468		
$\log_{10}$ MPs/mL*	0.018	E-cigarette	5.8 (0.1)	5.7 (0.1)	-0.0 (0.2)	0.862
		Tobacco Cigarette	5.8 (0.1)	6.4 (0.1)*	0.6 (0.2)	<0.001
		EC and TC Difference	0.0 (0.2)	0.7 (0.2)		
		EC and TC Difference P-value	0.802	0.001		

log_{10} EMPs/mL	0.008	E-cigarette	4.9 (0.2)	4.9 (0.2)	0.0 (0.2)	0.896
		Tobacco Cigarette	4.9 (0.2)	5.8 (0.2)	0.9 (0.2)	<0.001
		EC and TC Difference	0.0 (0.2)	0.9 (0.2)		
		EC and TC Difference P-value	0.919	<0.001		
log_{10} PMPs/mL	0.856	E-cigarette	5.0 (0.2)	6.2 (0.2)	1.2 (0.2)	<0.001
		Tobacco Cigarette	5.0 (0.2)	6.3 (0.2)	1.2 (0.2)	<0.001
		EC and TC Difference	0.1 (0.3)	0.1 (0.3)		
		EC and TC Difference P-value	0.813	0.644		
FEV_1 (L)	0.564	E-cigarette	4.2 (0.1)	4.1 (0.2)	-0.1 (0.1)	0.132
		Tobacco Cigarette	4.3 (0.1)	4.2 (0.3)	0.0 (0.0)	0.373
		EC and TC Difference	0.1 (0.0)	0.1 (0.1)		
		EC and TC Difference P-value	0.105	0.214		
FVC (L)	0.541	E-cigarette	5.2 (0.2)	5.1 (0.2)	-0.1 (0.1)	0.187
		Tobacco Cigarette	5.3 (0.2)	5.2 (0.2)	0.0 (0.1)	0.609
		EC and TC Difference	0.1 (0.1)	0.1 (0.1)		
		EC and TC Difference P-value	0.221	0.197		
FEV_1/FVC (%)	0.918	E-cigarette	81.1 (1.5)	80.9 (1.6)	-0.2 (0.4)	0.654
		Tobacco Cigarette	81.3 (1.6)	81.0 (1.6)	-0.3 (1.2)	0.782
		EC and TC Difference	0.2 (0.8)	0.1 (0.8)		
		EC and TC Difference P-value	0.796	0.875		

PEF (L/min)	0.594	E-cigarette	562 (14)	531 (22)	-31 (12)	0.019
		Tobacco Cigarette	567 (16)	545 (18)	-22 (12)	0.074
		EC and TC Difference	5 (9)	13 (12)		
		EC and TC Difference P-value	0.565	0.270		
CO (ppm)*	<0.001	E-cigarette	9 (2)*	7 (2)*	-2 (1)	0.024
		Tobacco Cigarette	9 (2)*	20 (2)*	11 (0)	<0.001
		EC and TC Difference	0 (1)	13 (1)		
		EC and TC Difference P-value	0.676	<0.001		

EC, e-cigarette, TC, tobacco cigarette, SBP, systolic blood pressure; DBP, diastolic blood pressure; HR, heart rate; RHI, reactive hyperaemia index; PWA, pulse wave amplitude, AU, arbitrary units, AI, augmentation index; AI@75, AI at heart rate of 75bpm; sICAM-1, soluble intercellular adhesion molecule 1; sP-selectin, soluble platelet selectin; sVCAM-1, soluble vascular adhesion molecule 1; sE-selectin, endothelial leukocyte adhesion molecule-1; PECAM-1, platelet endothelial cell adhesion molecule; MPs, microparticles; EMPs, endothelial microparticles, PMPs, platelet microparticles; CO, exhaled carbon monoxide; FEV_1, forced expiratory volume in one second; FVC, forced vital capacity; FEV_1/FVC, forced expiratory volume in one second/ forced vital capacity ratio PEF, peak expiratory flow. Normality assessed by Shapiro-Wilks test of normality. Outliers assessed as studentized residuals with a value greater than 3 or less than -3. Data are presented as mean with standard error. *Data contains outliers and/or is not normally distributed, which may affect validity of the ANOVA results.

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