

Smoking, the heart and circulation

August 2021

Introduction

Cardiovascular disease (CVD) is a general term for conditions affecting the heart or circulatory system.¹ These include coronary heart disease (angina, heart attacks and CHD), cerebrovascular disease (embolism, aneurysms, and stroke), heart valve disease, congenital heart disease and peripheral arterial disease.¹ Cardiovascular diseases (CVDs), principally coronary heart disease and stroke, are the leading cause of global mortality and a major contributor to disability.² Tobacco use is the leading behavioural risk factor for CVD.¹

CVD is responsible for about 4.1 million deaths each year across European countries.³ In the UK alone, there are 7.6 million people living with CVD, which contributes to around 163,000 deaths each year – or one death every three minutes.⁴ It is estimated that about 20,000 of these deaths – or 1 in 8 – can be attributed to smoking.⁴ Since 1961, the annual number of deaths from heart and circulatory diseases in the UK has fallen by around a half.⁴ The economic cost of premature death, disability, informal costs, hospital treatment and prescription for CVD in the UK is estimated at £15.8 billion ⁴ and over €210 billion a year for the EU.³

In 2019, CVD was responsible globally for an estimated 19 million mortalities, 9.8 million men and 9.2 million women ⁵ illustrating an upward trend as already predicted by the World Health Organisation (WHO).⁶ The global annual number of deaths from heart and circulatory diseases is projected to rise to more than 23 million by 2030 and more than 34 million by 2060.⁵

This factsheet examines the links between smoking and CVD, the mechanisms by which smoking causes CVD and how a person's risk may be reduced by quitting.

SMOKING, CARDIOVASCULAR DISEASE AND COVID-19

COVID-19 is a respiratory viral infection that affects the lungs and airways. It is caused by a novel virus called Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2).⁷ This virus has been responsible for millions of infections and deaths worldwide since it emerged in December 2019 and was declared a pandemic in March 2020.⁸ 9

Although evidence of the impact of smoking on COVID-19 is still mixed and developing, a UK study published in January 2021 suggests that current smokers who get coronavirus are twice as likely to attend hospital and tend to report more symptoms than non-smokers. The analysis, by researchers from Imperial

College London, King's College London, and ZOE (a health symptom tracking app) looked at data from 2.4 million people in the UK who self-reported their symptoms and test results.¹⁰

Available evidence suggests that patients with pre-existing cardiovascular diseases appear to have a higher risk of more severe complications from COVID-19.¹¹ Smoking increases the risk of developing CVD and many serious health conditions, including chronic lung disease, and diabetes, all of which increase the risk of severe disease and death from coronavirus.

For further information see the British Heart Foundation webpage on smoking and COVID-19

SMOKING AND ITS CONTRIBUTION TO CARDIOVASCULAR DISEASE

Smoking ranks among the top causes of cardiovascular disease, including coronary heart disease, ischemic stroke, peripheral artery disease and abdominal aortic aneurysm.⁴ Smoking increases the risk of cardiovascular disease in several ways:

- Smoking damages the lining of the arteries, including the coronary arteries. One of the chemicals included in cigarettes, acrolein, affects the way the body processes cholesterol, allowing higher amounts to remain in the blood system.^{12 13} This compound, among others, decreases the normal functioning and the ratio of high-density lipoprotein HDL (the "good" cholesterol) to low-density lipoprotein LDL (the "bad" cholesterol) among tobacco users.^{12 13 14} HDL helps with the removal of excess cholesterol by transporting it back to the liver for disposal.^{14 15} Low-density lipoproteins and other fatty substances stick to the blood vessel walls and cause narrowing over time, a process known as atherosclerosis.^{12 14 15} The damage encourages the build-up of fatty material in the arteries. This can lead to a heart attack or a stroke.
- Smoking also increases the amount of fibrinogen (a protein that causes blood to clot) in the bloodstream, increasing the risk of blood clots and thrombosis.¹⁶ Smoking also causes an increase in platelet aggregation, which makes the blood a bit thicker, causing reduced blood flow within the blood vessels.¹⁶ ¹⁷ Finally, smoking has also been shown to make blood vessels constrict (vasoconstriction) which leads to high blood pressure and a reduction in blood supply to the heart.¹⁷
- Inhalation of carbon monoxide (CO) in cigarette smoke significantly reduces the amount of oxygen that can be carried by the blood, resulting in tissues being starved of oxygenated blood, which causes them to suffocate and die.¹⁹ This can lead to shortness of breath and increased heart rate.¹⁹
- Nicotine is the addictive chemical found in cigarettes. When someone smokes the nicotine in the cigarette increases their blood pressure and heart rate, causing their heart to work harder and increasing their risk of heart disease or stroke.¹⁹ Clinical trials on the sole use of nicotine in the form of Nicotine Replacement Therapy (NRT) in patients with underlying, stable coronary disease, suggest that use of therapeutic nicotine does not increase cardiovascular risk.^{20 21} A Cochrane review found that all of the commercially available forms of NRT (gum, transdermal patch, nasal spray, inhaler, lozenges) can help people quit successfully. It increases the rate of quitting by 50% to 60% and does not increase the risk of heart attacks.²¹ For information about the impact of e-cigarette use on CVD risk see page 4 'E-cigarettes and the heart.'

SMOKING, MORTALITY AND LIFE EXPECTANCY

Throughout the first half of the 20th century the hazards of smoking remained largely unsuspected.^{22 23} The British Doctors Study, conducted by researchers at the University of Oxford from 1951 to 2001, is considered to be the first study to demonstrate strong statistical proof of the correlation between tobacco smoking and cause-specific mortality.^{22 22} The study demonstrates a threefold higher overall mortality among doctors who smoke throughout their adult life relative to those who do not, resulting in an average loss of 10 years of life expectancy.^{22 23} The Million Women Study, a British cohort study, also documented comparable increases in mortality and estimates of years of life lost to lifelong smoking in women.²⁴ Research findings demonstrated that 1 year of life is lost for every 4 years of smoking after the age of 30.²⁴ The authors demonstrated that stopping smoking before age 40 years avoids more than 90% of the excess mortality caused by continuing smoking; stopping before age 30 years avoids more than 97% of it.²⁴

CARDIOVASCULAR RISKS OF CIGARETTE SMOKING

Research has clearly established cigarette smoking as a risk factor for cardiovascular disease incidence and mortality, with smoking increasing the risk of death from CVD by up to three times.^{25 26} Smoking related CVD risk has been shown to be substantively higher in current and recent smokers, compared to never smokers and those who have quit. CVD risk is also shown to be greater with increasing smoking duration and by the number of cigarettes smoked per day. ^{25 27 28 29}

A recent systematic review looking at the impact of smoking on CVD found that the risk of cardiovascular mortality in older adults who were current smokers is double that of non-smokers (RR 2.07, 95% Cl 1.82– 2.36).³⁰ The study found that in people aged 60 years and older, smoking strongly contributes to acute coronary events, stroke, and cardiovascular deaths.³⁰ The authors found that smoking advanced the risk of dying from cardiovascular disease by 5.5 years.³⁰

SMOKING AND CORONARY HEART DISEASE (CHD)

Coronary heart disease – also known as ischaemic heart disease – is what happens when the heart's blood supply is blocked or interrupted by a build-up of fatty substances in the coronary arteries, in a process is known as atherosclerosis. Eventually, the arteries may become so narrow that they cannot get enough oxygen rich blood to the heart, leading to a heart attack.

The 1990 US Surgeon General report firmly established that smoking is the "most important of the known modifiable risk factors for CHD."³¹ This relationship has been demonstrated across racial and ethnic groups and in women younger than 50 years of age, even though the incidence of CHD in this population is low.³²

In the UK, the British Regional Heart Study cited smoking as one of the three principle non-hereditary risk factors for coronary heart disease; the others are raised blood cholesterol level and high blood pressure.³⁴ Research analysis of US National Health Interview Survey reported a threefold risk for coronary heart disease in male smokers aged 35-64 years old (RR 3.18, 95% CI 2.34–4.33) and almost a four-fold risk for female smokers aged 35-64 years (RR 3.93, 95% CI 2.56–6.05).³⁵

SMOKING AND STROKE

A stroke is a serious life-threatening medical condition that happens when the blood supply to part of the brain is cut off. Stroke is the fifth biggest killer in the UK, causing around 34,000 deaths each year.⁴ Findings from the INTERSTROKE study revealed that the odds of having ischemic stroke (happens when a blockage cuts off the blood supply to the brain) more than doubled for smokers (RR 2.3, 99% CI 1.9– 2.8).^{36 37} The study, which was conducted across 32 different countries and involved over 3000 cases, was designed to establish the association between traditional and emerging risk factors and stroke. The risk of having a haemorrhagic stroke (bleeding into the brain) was 40% higher among smokers than among non-smokers (RR 1.4, 99% CI 1.1–1.9).^{36 37}

SMOKING AND PERIPHERAL ARTERIAL DISEASE (PAD)

Peripheral arterial disease (PAD) is a common condition where a build-up of fatty deposits in the arteries restricts blood supply to leg muscles. While not immediately life-threatening PAD increases the risk of developing other forms of CVD including coronary heart disease, stroke, and heart attack.

Smoking is the most important preventable risk factor for PAD in both high-income and low or middleincome countries.³⁸ Risks are cumulative, with smokers who also have high blood pressure or have high cholesterol being at the greatest risk. Some types of PAD are almost exclusively found in smokers, with the condition being a rare diagnosis in non-smokers. The European Prospective Investigation into Cancer and Nutrition (EPIC) Norfolk cohort study, which included 25,639 men and women aged 45–79 years, found that smoking increased the risk of peripheral arterial disease more than fourfold (RR 4.66, 95% CI 3.29– 6.61).³⁹ Another large scale study in the United Kingdom, including almost 2 million people reported a fivefold increased risk of developing PAD among smokers (RR 5.16, 95% CI 4.80–5.54).⁴⁰ Findings are consistent with a previous meta-analysis involving 55 studies.⁴¹

SECONDHAND SMOKE (SHS)

Breathing in other people's cigarette smoke is called passive, involuntary or secondhand smoking (SHS). Secondhand smoke, also called "environmental tobacco smoke", comprises "sidestream" smoke from the burning tip of the cigarette and "mainstream" smoke which is smoke that has been inhaled and then exhaled by the smoker. Recent research reported that exposure to SHS increases the risk of CVD by 23%²⁹ and specifically increases ischemic and coronary heart disease risk by 25–30%.⁴² A meta-analysis conducted in 2015 showed that non-smokers exposed to SHS had a 35% increased risk for stroke (RR 1.35, 95% CI 1.22–1.50) and 27% increased risk for ischaemic heart disease (RR 1.27, 95% CI 1.10–1.48).⁴³ The risks were higher in women than in men.⁴⁴

Globally, it was estimated that one third of adult never-smokers and 40% of children were exposed to secondhand smoke in 2004, contributing to 379,000 deaths from ischaemic heart disease.⁴⁴ A 2016 Cochrane review found that the introduction of smokefree legislation led to improved public health outcomes through reductions in exposure to SHS.⁴⁵ The review found strong evidence of a positive impact on cardiovascular health following the introduction of smokefree laws, most clearly demonstrated by reduced hospital admissions for acute coronary syndrome.

E-CIGARETTES AND THE HEART

Electronic cigarettes – also known as e-cigarettes or vaping products – are currently the most popular aid for quitting smoking in England. In 2020, 27.2% of English adults used a vaping product in a quit attempt in

the previous 12 months, compared with 15.5% who used NRT over the counter or on prescription (2.7%) and 4.4% who used varenicline.⁴⁶ Findings from the annual Smokefree GB survey commissioned by ASH show that among current vapers the three main reasons given for using an e-cigarette are as an aid to quitting (28%) followed by preventing relapse (18%) and to cut down the amount smoked (10%).⁴⁷ Evidence shows that e-cigarettes are considerably less harmful than smoking, though not completely risk-free.^{48 49} Although the long-term health effects of e-cigarette use are not yet known, they are likely to be much less harmful to users and bystanders than cigarettes. There is currently no evidence of harm to bystanders from exposure to e-cigarette vapour and any risks are likely to be extremely low.⁴⁸

Vaping is positively associated with quit success.46 According to the findings of a recent Cochrane review, nicotine-containing e-cigarettes are approximately 70% more effective in supporting smokers to quit successfully than NRT.⁵⁰ Public Heath England's advice remains that smokers are better off switching completely to vaping, but non-smokers should not take up vaping.⁵¹

Switching from smoking to vaping has substantial health benefits including improving cardiovascular function. A study funded by the British Heart Foundation at Dundee University found that within one month of switching from traditional cigarettes to e-cigarettes, there was a significant improvement in endothelial function and vascular stiffness.⁵²

SMOKING CESSATION

Giving up smoking significantly reduces the risk of developing cardiovascular diseases including heart attack and stroke.⁵³ A recent cohort study involving 8,770 individuals found that among heavy smokers, smoking cessation was associated with significantly lower risk of CVD within 5 years compared to current smokers.⁵⁴ Around 10-15 years after quitting former smokers showed a similar CVD risk to never smokers. Moreover, almost half of the decline in coronary heart disease mortality in England and Wales between 1981 and 2000 has been attributed to reductions in smoking prevalence.⁵⁵

It is particularly important for those who have other risk factors such as high blood pressure, raised blood cholesterol levels, diabetes, obesity, or are physically inactive to quit smoking. Smokers who wish to reduce their risk of CVD should be informed: 1) that the only reliable way of doing so is stopping smoking completely and 2) that smoking reduction alone is unlikely to reduce their risk significantly. However, if they are unable to stop smoking they may wish to attempt smoking reduction with the help of NRT or an e-cigarette, but that their ultimate goal should be to fully quit smoking in the near future when they feel they are able to do so.

For further information on quitting smoking see:

- ASH. Stopping smoking. March 2020
- <u>NHS advice and support on quitting</u>

When referring to this publication, please cite as:

Action on Smoking and Health (ASH). Smoking, the heart and circulation. 2021

References

References last checked August 2021

¹ World Health Organization (WHO). Factsheet: <u>Cardiovascular Diseases</u>. June 2021.

² Folegatti PM, Ewer KJ, Aley PK, Angus B, Becker S, Belij-Rammerstorfer S, Bellamy D, Bibi S, Bittaye M, Clutterbuck EA, Dold C. <u>Safety and immunogenicity of the ChAdOx1 nCoV-19 vaccine against SARS-CoV-2: a preliminary report of a phase</u> <u>1/2, single-blind, randomised controlled trial</u>. The Lancet. 2020 Aug 15;396(10249):467-78.

³ Timmis A, Townsend N, Gale CP, Torbica A, Lettino M, Petersen SE, Mossialos EA, Maggioni AP, Kazakiewicz D, May HT, De Smedt D. <u>European Society of Cardiology: cardiovascular disease statistics 2019</u>. European heart journal. 2020 Jan 1;41(1):12-85.

⁴ British Heart Foundation (BHF). Statistics Factsheet – UK. January 2021

⁵ British Heart Foundation (BHF). <u>Statistics Factsheet – Global</u> January 2021

⁶ World Health Organisation (WHO). World Health Statistics 2008.

⁷ Long B, Brady WJ, Koyfman A, Gottlieb M. <u>Cardiovascular complications in COVID-19.</u> The American journal of emergency medicine. 2020 Jul 1;38(7):1504-7.

⁸ Xu Z, Shi L, Wang Y, Zhang J, Huang L, Zhang C, Liu S, Zhao P, Liu H, Zhu L, Tai Y. <u>Pathological findings of COVID-19</u> associated with acute respiratory distress syndrome. The Lancet respiratory medicine. 2020 Apr 1;8(4):420-2.

⁹ Huang C, Wang Y, Li X, Ren L, Zhao J, Hu Y, Zhang L, Fan G, Xu J, Gu X, Cheng Z. <u>Clinical features of patients infected</u> with 2019 novel coronavirus in Wuhan, China. The lancet. 2020 Feb 15;395(10223):497-506.

¹⁰ Hopkinson NS, Rossi N, El-Sayed_Moustafa J, Laverty AA, Quint JK, Freidin M, Visconti A, Murray B, Modat M, Ourselin S, Small K. <u>Current smoking and COVID-19 risk: results from a population symptom app in over 2.4 million people</u>. Thorax. 2021 Jul 1;76(7):714-22.

¹¹ BHF. Coronavirus: what it means for you if you have heart or circulatory disease. July 2021.

¹² Henning RJ, Johnson GT, Coyle JP, Harbison RD. <u>Acrolein can cause cardiovascular disease: a review. Cardiovascular toxicology.</u> 2017 Jul;17(3):227-36.

¹³ Tamamizu-Kato S, Wong JY, Jairam V, Uchida K, Raussens V, Kato H, Ruysschaert JM, Narayanaswami V. <u>Modification by acrolein, a component of tobacco smoke and age-related oxidative stress, mediates functional impairment</u> of human apolipoprotein E. Biochemistry. 2007 Jul 17;46(28):8392-400.

¹⁴ Shao C, Wang J, Tian J, Tang YD. Coronary Artery Disease: <u>From Mechanism to Clinical Practice. Coronary Artery</u> <u>Disease: Therapeutics and Drug Discovery</u>. 2020 Jan 1:1-36.

¹⁵ Gossett LK, Johnson HM, Piper ME, Fiore MC, Baker TB, Stein JH. <u>Smoking intensity and lipoprotein abnormalities in</u> <u>active smokers</u>. Journal of clinical lipidology. 2009 Dec 1;3(6):372-8.

¹⁶ Pretorius E, Oberholzer HM, van der Spuy WJ, Meiring JH. <u>Smoking and coagulation: the sticky fibrin phenomenon.</u> <u>Ultrastructural Pathology.</u> 2010 Aug 1;34(4):236-9.

¹⁷ Barua RS, Ambrose JA. <u>Mechanisms of coronary thrombosis in cigarette smoke exposure</u>. Arteriosclerosis, thrombosis, and vascular biology. 2013 Jul;33(7):1460-7.

¹⁸ Falconi AM, Gold EB, Janssen I. <u>The longitudinal relation of stress during the menopausal transition to fibrinogen</u> <u>concentrations: results from the Study of Women's Health Across the Nation.</u> Menopause (New York, NY). 2016 May;23(5):518.

¹⁹ Papathanasiou G, Mamali A, Papafloratos S, Zerva E<u>. Effects of Smoking on Cardiovascular Function: The Role of Nicotine and Carbon Monoxide</u>. Health Science Journal. 2014; 8:272–88.

²⁰ Benowitz NL, Gourlay SG. <u>Cardiovascular toxicity of nicotine: implications for nicotine replacement therapy</u>. Journal of the American College of Cardiology. 1997 Jun;29(7):1422-31.

²¹Hartmann-Boyce J, Chepkin SC, Ye W, Bullen C, Lancaster T. <u>Nicotine replacement therapy versus control for smoking</u> <u>cessation</u>. Cochrane Database of Systematic Reviews Issue 5. Art. No. CD000146. 2018.

²²Di Cicco ME, Ragazzo V, Jacinto T. <u>Mortality in relation to smoking: the British Doctors Study.</u> Breathe. 2016 Sep 1;12(3):275-6.

²³ Doll R, Peto R. Mortality in relation to smoking: 20 years' observations on male British doctors. Br Med J. 1976; 2(6051):1525–36.

²⁴ Pirie K, Peto R, Reeves GK, Green J, Beral V, Million Women Study Collaborators. <u>The 21st century hazards of smoking</u> and benefits of stopping: a prospective study of one million women in the UK. Lancet. 2013; 381(9861):133–41.

²⁵ Jha P, Ramasundarahettige C, Landsman V, Rostron B, Thun M, Anderson RN, McAfee T, Peto R. <u>21st-century hazards</u> of smoking and benefits of cessation in the United States. New England Journal of Medicine. 2013 Jan 24;368(4):341-50.
²⁶ Thun MJ, Carter BD, Feskanich D, Freedman ND, Prentice R, Lopez AD, Hartge P, Gapstur SM. <u>50-year trends in</u> smoking-related mortality in the United States. N engl J med. 2013 Jan 24;368:351-64.

²⁷ Teo KK, Ounpuu S, Hawken S, Pandey MR, Valentin V, Hunt D, Diaz R, Rashed W, Freeman R, Jiang L, Zhang X. <u>Tobacco use and risk of myocardial infarction in 52 countries in the INTERHEART study: a case-control study.</u> The lancet. 2006 Aug 19;368(9536):647-58. ²⁸ Perk J, De Backer G, Gohlke H, Graham I, Reiner Z, Verschuren M, et al. op Reimer WJ S, Vrints C, Wood D, Zamorano JL, Zannad F: European guidelines on cardiovascular disease prevention in clinical practice (version 2012). The fifth joint Task force of the European Society of Cardiology and other societies on cardiovascular disease prevention in clinical practice (constituted by representatives of nine societies and by invited experts). Developed with the special contribution of the European Association for Cardiovascular Prevention & Rehabilitation (EACPR). Eur Heart J. 2012; 33(17):1635–701.

²⁹ Lv X, Sun J, Bi Y, Xu M, Lu J, Zhao L, Xu Y. <u>Risk of all-cause mortality and cardiovascular disease associated with</u> <u>secondhand smoke exposure: a systematic review and meta-analysis.</u> International journal of cardiology. 2015 Nov 15;199:106-15.

³⁰Mons U, Müezzinler A, Gellert C, Schöttker B, Abnet CC, Bobak M, de Groot L, Freedman ND, Jansen E, Kee F, Kromhout D. <u>Impact of smoking and smoking cessation on cardiovascular events and mortality among older adults: meta-analysis of individual participant data from prospective cohort studies of the CHANCES consortium.</u> bmj. 2015 Apr 20;350.

³¹ US Department of Health and Human Services. <u>Chapter 4: The Health Benefits of Smoking Cessation. Surgeon General's</u> <u>Report on Smoking and Health</u>. Atlanta: US Department of Health and Human Services, Public Health Service, Centers for Disease Control, Center for Chronic Disease Prevention and Health Promotion, Office on Smoking and Health; 1990. DHHS publication No. (CDC) 90–8416

³² US Department of Health and Human Services. Tobacco Use Among US Racial/Ethnic Minority Groups—African Americans, American Indians and Alaska Natives, Asian Americans and Pacific Islanders, and Hispanics. A Report of the Surgeon General. Atlanta: U.S. Department of Health and Human Services, Centers for Disease Control and Prevention, National Center for Chronic Disease Prevention and Health Promotion, Office on Smoking and Health; 1998.

³³ Croft P, Hannaford PC. <u>Risk factors for acute myocardial infarction in women: evidence from the Royal College of General</u> <u>Practitioners' oral contraception study. British Medical Journal</u>. 1989 Jan 21;298(6667):165-8.

³⁴ Capewell S, Allender S, Critchley J, Lloyd-Williams F, O'Flaherty M, Rayner M, Scarborough P. <u>Modelling the UK burden of</u> <u>cardiovascular disease to 2020</u> a research report for the cardio & vascular coalition and the British heart foundation. British Heart Foundation. 2008

³⁵ Rostron B. <u>Smoking-attributable mortality by cause in the United States: revising the CDC's data and estimates</u>. Nicotine & Tobacco Research. 2012 May 16;15(1):238-46.

³⁶ O'Donnell MJ, Chin SL, Rangarajan S, Xavier D, Liu L, Zhang H, Rao-Melacini P, Zhang X, Pais P, Agapay S, Lopez-Jaramillo P. <u>Global and regional effects of potentially modifiable risk factors associated with acute stroke in 32 countries</u> (INTERSTROKE): a case-control study. The lancet. 2016 Aug 20;388(10046):761-75.

³⁷ O'Donnell MJ, Xavier D, Liu L, Zhang H, Chin SL, Rao-Melacini P, Rangarajan S, Islam S, Pais P, McQueen MJ, Mondo C. <u>Risk factors for ischaemic and intracerebral haemorrhagic stroke in 22 countries (the INTERSTROKE study): a</u> <u>case-control study.</u> The Lancet. 2010 Jul 10;376(9735):112-23.

³⁸ ASH. <u>ASH Research Report: Smoking & Peripheral Arterial Disease (PAD)</u>. 2017

³⁹ Stoekenbroek RM, Boekholdt SM, Luben R, Hovingh GK, Zwinderman AH, Wareham NJ, Khaw KT, Peters RJ. <u>Heterogeneous impact of classic atherosclerotic risk factors on different arterial territories: the EPIC-Norfolk prospective</u> <u>population study</u>. European heart journal. 2016 Mar 14;37(11):880-9.

⁴⁰ Pujades-Rodriguez M, George J, Shah AD, Rapsomaniki E, Denaxas S, West R, Smeeth L, Timmis A, Hemingway H. <u>Heterogeneous associations between smoking and a wide range of initial presentations of cardiovascular disease in 1 937</u> <u>360 people in England: lifetime risks and implications for risk prediction</u>. International journal of epidemiology. 2015 Feb 1;44(1):129-41.

⁴¹ Lu L, Mackay DF, Pell JP. <u>Meta-analysis of the association between cigarette smoking and peripheral arterial disease.</u> Heart. 2014; 100(5):414–23.

⁴² Dunbar A, Gotsis W, Frishman W. <u>Second-hand tobacco smoke and cardiovascular disease risk: an epidemiological</u> <u>review.</u> Cardiology in review. 2013; 21(2):94–100.

⁴³ Fischer F, Kraemer A. <u>Meta-analysis of the association between second-hand smoke exposure and ischaemic heart</u> <u>diseases, COPD and stroke. BMC Public Health</u>. BioMed Central; 2015; 15(1):1–18.

⁴⁴ Öberg M, Jaakkola MS, Woodward A, Peruga A, Prüss-Ustün A. <u>Worldwide burden of disease from exposure to second-hand smoke: a retrospective analysis of data from 192 countries.</u> The lancet. 2011 Jan 8;377(9760):139-46.

⁴⁵ Frazer K, Callinan JE, McHugh J, van Baarsel S, Clarke A, Doherty K, Kelleher C. <u>Legislative smoking bans for reducing</u> <u>harms from secondhand smoke exposure, smoking prevalence and tobacco consumption</u>. Cochrane Database of Systematic Reviews. 2016(2).

⁴⁶ McNeill A, Brose LS, Calder R, Simonavicius E, Robson D. <u>Vaping in England: An evidence update including vaping for</u> <u>smoking cessation, February 2021: a report commissioned by Public Health England</u>. London: Public Health England. 2021 Feb;23

⁴⁷ ASH. <u>Use of e-cigarettes (vapes) among adults in Great Britain</u>. June 2021

⁴⁸ McNeill A, Brose LS, Calder R, Bauld L, Robson D. <u>Evidence review of e-cigarettes and heated tobacco products 2018.</u> A report commissioned by Public Health England. London: Public Health England. 2018 Feb;6.

⁴⁹ Royal College of Physicians. <u>Nicotine without smoke: Tobacco harm reduction</u>. London: RCP, 2016; 908.

⁵⁰ Hartmann-Boyce J, McRobbie H, Lindson N, Bullen C, Begh R, Theodoulou A, Notley C, Rigotti NA, Turner T, Butler AR, Fanshawe TR. <u>Electronic cigarettes for smoking cessation</u>. Cochrane database of systematic reviews. 2021(4).
⁵¹ Newton J. Public health matters. 8 things to know about e-cigarettes. Public Health England. March 2020

⁵² George J, Hussain M, Vadiveloo T, Ireland S, Hopkinson P, Struthers AD, Donnan PT, Khan F, Lang CC. <u>Cardiovascular</u> <u>effects of switching from tobacco cigarettes to electronic cigarettes</u>. Journal of the American College of Cardiology. 2019 Dec 24;74(25):3112-20.

⁵³ Carreras G, Pistelli F, Falcone F, Carrozzi L, Martini A, Viegi G, Gorini G. <u>Reduction of risk of dying from tobacco-related</u> <u>diseases after quitting smoking in Italy.</u> Tumori Journal. 2015 Nov;101(6):657-63.

⁵⁴ Duncan MS, Freiberg MS, Greevy RA, Kundu S, Vasan RS, Tindle HA. <u>Association of smoking cessation with subsequent</u> risk of cardiovascular disease. Jama. 2019 Aug 20;322(7):642-50.

⁵⁵ Unal B, Critchley JA, Capewell S. <u>Explaining the decline in coronary heart disease mortality in England and Wales between</u> <u>1981 and 2000.</u> Circulation. 2004 Mar 9;109(9):1101-7.