The Effects of Vaping and Smoking on Respiratory Function and Inflammation; Can they be Reversed by Aerobic Exercise and Vaping and Smoking Cessation?

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The Effects of Vaping and Smoking on Respiratory Function and Inflammation; Can they be Reversed by Aerobic Exercise and Vaping and Smoking Cessation?

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tough time, she was amazing in supporting me and made everything possible for me. Thank you for bearing with me, for the tireless nights, you never left my side over the years and through every step of this journey. The successful completion of this work would have been impossible without your support, love and encouragement, my Babel Rose! I will always remember Aseels' words ''*things that passes, finishes!*''

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Abstract

Introduction: Vaping is marketed as a healthier alternative to smoking, but little is known about the effects of vaping on cardiorespiratory function. Smoking cessation (SC) is a strategy to stop and/or reverse the detrimental effects of smoking, and one of the techniques used to encourage smokers quit is aerobic exercise. The aim of this thesis was to assess the effects of vaping and smoking on respiratory and muscle function, and systemic inflammation, and whether effects can be reversed by SC with or without aerobic exercise. **Specific objectives are:** To 1) compare the respiratory function and respiratory muscle strength between vapers, smokers and non-smokers; 2) assess the effects of 14 days SC on respiratory and muscle function and low-grade systemic inflammation; and 3) determine the effects of aerobic exercise on vaping and smoking cessation. **Methods:** 1) In 12 vapers, 14 smokers and 18 non-smokers spirometry and respiratory muscle strength were measured; 2) in 48 cigarette smokers the impact of 14 days SC on spirometry, skeletal muscle function, markers of oxidative stress and serum cytokines were determined and 3) in a systematic review with meta-analysis the effects of aerobic exercise on vaping and SC and maximal or peak oxygen uptake were determined. **Results:** 1) Both vapers and smokers had a similarly lower respiratory function than non-smokers, but there was no evidence for a lower respiratory muscle strength. 2) Smoking cessation did not reverse the lower respiratory function, but it did reverse the low-grade systemic inflammation and impaired muscle function. 3) Aerobic exercise did not significantly increase the success rate of quitting, but it did improve cardiopulmonary fitness. **Conclusion:** Vaping causes similar detrimental effects as smoking on lung function. As little as 14 days of SC reversed the low-grade systemic inflammation and impaired muscle function in smokers. Aerobic exercise added to a SC programme did not increase the success rate of quitting, but it did improve the fitness of the quitters.

Table of Contents

List of Figures

List of Tables

List of abbreviations:

abbreviation	Full term	abbreviation	Full term
AGEs	Advanced glycation end products	IL-1	Interleukin-1
ATP	Adenosine triphosphate	KE	Knee extensor
BMI	Body mass index	LMW	Low molecular weight
BP	Blood pressure	MDA	Malondialdehyde
CO	Carbon monoxide	MeSH	Medical Subject Headings
CROB 2	Cochrane Risk of Bias tool 2	MEP	Maximal expiratory pressure
COPD	Chronic obstructive pulmonary disease	MIP	Maximal inspiratory pressure
CV	Coefficient of variation	MVC	Maximal voluntary contraction
CVD	Cardiovascular diseases	NRT	Nicotine replacement therapy
E-cigarette	Electronic cigarette	PEF	Peak Expiratory Flow
EOT	End-of-treatment	PICOS	Population, intervention, comparison, outcome measures and study design
ENDS	Electronic nicotine delivery systems	RCTs	Randomised controlled trials
EU	European Union	RR	Risk ratio
EVALI	E-cigarette, or vaping product use-associated lung injury	SC	Smoking cessation
FDA	Food and Drug Administration	SNIP	Sniff nasal inspiratory pressure
FEF	Maximum mid-expiratory flow	PRISMA	Systematic Reviews and Meta-Analyses
FEV_1	Forced Expiratory Volume in one second	TAS	Total antioxidant status
FI	Fatigue index	TNF-α	Tumour necrosis factor α
FVC	Forced Vital Capacity	UK	United Kingdom
Hb	Haemoglobin	US	United States
HbCO/COHb	Carboxyhaemoglobin	VA	Voluntary activation
Hct	Haematocrit	VO2max	Maximum oxygen consumption
HR	Heart Rate	VO2peak	Peak oxygen consumption
IFN-γ	Interferon gamma		

Chapter 1 : General Introduction

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1.1. Background

Cigarette packages contain warning labels like 'Smoking Kills' and 'Smoking clogs the arteries and causes heart attacks and stroke'. These labels illustrate the tragic truth that smoking is a major risk factor for the development of cancer, cardiovascular diseases (CVD) and respiratory disorders including chronic obstructive pulmonary disease (COPD). In addition, smoking causes systematic inflammation, as reflected by an increase in white blood cells (WBC) count and inflammatory cytokines (Abdul-Rasheed and Al-Rubayee, 2013; Aula and Qadir, 2013; Bloomer, 2007; Morrow et al., 1995). It causes more than 7 million deaths per year globally (World Health Organization, 2017) and in 2016, 77,900 deaths in the United Kingdom (UK) were directly or indirectly attributable to smoking (Office for National Statistics, 2017). Yet, these labels do not appear enough of a deterrent as about 7.2 million of the UK population are smokers (Office for National Statistics, 2019).

These disastrous effects of smoking develop unperceivably slowly and only later in life, the detrimental health issues become evident (Lopez et al., 1994), a phenomenon referred to as 'the smoking time-bomb'. To make matters worse, 'The beneficial cognitive effects of nicotine have implications for initiation of smoking and maintenance of tobacco dependence' (Heishman et al., 2010).

Any means to administer nicotine, but without the concomitant inhalation of the more than 4,000 toxic substances in cigarette smoke, such as acrolein, carbon monoxide (CO), acetaldehyde and cyanide, would thus be preferable to cigarette smoking. E-cigarettes containing nicotine are considered to do this. The success of e-cigarettes in reducing smoking is reflected by the fact that about 54.1% of the current 3.6 million adult e-cigarette users in the UK are ex-smokers (Action on Smoking and Health, 2019).

There is, however, concern that e-cigarettes may singularly stimulate uptake of smoking, particularly in youth, and have an acute effect on cardiorespiratory health, even in the absence of smoking (Korfei, 2018; Schraufnagel et al., 2014). Additionally, there are potential risks with vaping during pregnancy and lactation on the development of the child in the womb and health of the new born baby (Kuehn, 2019; McAlinden et al., 2017; Orzabal et al., 2019). Indeed, vapours from e-cigarettes contain, besides nicotine and the respiratory irritant propylene glycol, toxic substances also seen in cigarette smoke, such as acrolein, acetaldehyde, formaldehyde and reactive oxygen species. As seen in animal studies, these toxic substances may well cause oxidative stress and negative effects on cardiovascular and respiratory function after vaping (Korfei, 2018), casting doubt on the idea that e-cigarettes are a suitable 'healthy' alternative to normal cigarettes. Yet, there are only basic regulations for the composition of e-cigarette liquids (as described in https://www.gov.uk/guidance/e-cigarettes-regulations-for-consumer-products).

The potential health risk of e-cigarettes led the Forum of International Respiratory Societies to release a position statement that concluded: *'As a precaution, electronic nicotinic delivery devices should be restricted or banned until more information about their safety is available'* (Schraufnagel et al., 2014). There is, thus an unmet need to know the effects of vaping on respiratory function in humans, and how this is related to the daily vaping volume and/or for how long one has been vaping.

1.2. The dangers of nicotine in e-cigarettes

An e-cigarette is composed of a rechargeable lithium battery, vaporizing chamber and a cartridge that contains the vaping liquid that consists, among other substances, of nicotine, glycerol, propylene glycol, glycerine and tobacco flavouring (Cobb and Abrams, 2011; Westenberger, 2009), although some vaping liquids may be free of nicotine. Nicotine is easily absorbed by the mucus membrane, skin, gastrointestinal tract and

respiratory airways (Callahan-Lyon, 2014) and acts as a neurotransmitter that in turn stimulates the release of dopamine, which contributes to the feeling of pleasure and satisfaction as part of the reward pathway (Bressan and Crippa, 2005). It is this effect of nicotine that makes smoking so addictive (Benowitz, 2010). As mentioned above, the dose of nicotine in e-cigarettes can be very high; typically, a 5-mL bottle of e-cigarette refill solution consist of 20 mg/ml nicotine (that is 100 mg/bottle) (Cameron et al., 2014). The life threatening dose of nicotine is around 30 to 40 mg in adults and 10 mg in children (Cameron et al., 2014). This high dose combined with unlimited vaping poses a potential health risk as it has been shown that acute contact to high concentrations of inhaled nicotine, or even skin contact e.g. after spills of nicotine-containing solutions, may cause nausea, vomiting or dizziness (Callahan-Lyon, 2014; Ordonez et al., 2013). Such risks are even higher in vaping than in smoking, where such poisonous nicotine levels rarely occur (Centers for Disease Control Prevention, 1997). In fact, many successful and unsuccessful suicide attempts through intravenous and oral intake of the nicotine solution intended for e-cigarette cartridges have been reported (Christensen et al., 2013; Thornton et al., 2013; Valento, 2013).

1.3. Chemical components of e-cigarettes

Besides nicotine there are other chemicals in the vaping liquids, where propylene glycol constitutes 90% of the e-cigarette liquid (Laugesen, 2008). While propylene glycol is often used to produce the smoke in special events like rock concerts and is considered harmless, prolonged and repeated exposure to propylene glycol vapour has been reported to cause cough, irritations of the eyes and lungs (Wieslander et al., 2001), and to increase the risk of acquiring asthma (Choi et al., 2010). Vaping liquid also contains 1% diethylene glycol, a known carcinogen (Goniewicz et al., 2014; Westenberger, 2009),

when non-pharmaceutical grade propylene glycol is used (Cahn and Siegel, 2011). While many of the flavours in e-liquids are safe when ingested and widely used in the food industry. The potential dangers of inhaling flavours are not yet fully investigated, but there are indications they may have a negative effect on lung health. For example, diacetyl is used in butter and safe when ingested, but when heated and inhaled it might cause bronchiolitis (Harber et al., 2006). In addition, some studies have shown that e-cigarettes release aromatic, particularly the carcinogenic component, polycyclic aromatic hydrocarbons, that have a pathogenic effect on human lung cells (Rankin et al., 2019), and contain esters, aldehydes, acids or saccharides that are cariogenic (Kim et al., 2018). In addition to these compounds, there are many more carcinogenic compounds in e-cigarette liquids (Goniewicz et al., 2014; Talhout et al., 2011), particularly trace metals (i.e., cadmium, arsenic, chromium, nickel, and lead), and tobacco-specific N-nitrosamines, and all these substances can in some cases reach concentrations even higher than in cigarette smoke (Williams et al., 2013). Perhaps most surprising, given that smoking is a primary risk factor for pulmonary diseases, is that the most common used e-cigarette refill liquids are classified as respiratory irritants, allergens, inducers of asthmatic symptoms or potentially causing breathing difficulties if inhaled (Vardavas et al., 2017).

There is as yet no strong evidence that passive exposure to vaping has adverse effects on health. However, the detrimental effects of passive smoking and the observation that nicotine released into the environment does not only affect those who inhale it, but may also affect non-smokers and non-vapers via nicotine left on surfaces e.g. furniture, carpets and clothes (Matt et al., 2020), strongly hints to the dangers of passive exposure to the e-cigarette aerosols.

1.4. Effects of cigarette smoking on cardiovascular function

It is known that cigarette smoking reduces the cardiopulmonary fitness, as reflected by a reduced maximum oxygen consumption (VO_{2max}) (de Borba et al., 2014; Lauria et al., 2017). The lower exercise capacity in smokers is, however, not only attributable to a reduction in aerobic capacity, but also an increased metabolic cost of breathing (de Borba et al., 2014; Lauria et al., 2017; Misigoj-Durakovic et al., 2012).

Smoking increases blood pressure (BP), resting HR, the risk factor for atherosclerosis (Campisi et al., 1998; Groppelli et al., 1992) and has been shown to impair cardiovascular function, increase vascular resistance, and decrease vasodilation and hence tissue blood flow (Campisi et al., 1998). The impaired vasodilation (Celermajer et al., 1992) can even occur after short-term smoking (Lekakis et al., 1997). Such an effect is not limited to the peripheral vasculature. Indeed, a narrowing of the coronary arteries, and hence decrease in coronary blood flow and increase coronary resistance, despite an increase in myocardial oxygen demand, has been reported as a result of acute cigarette smoking (Quillen et al., 1993). The authors suggested that such ongoing effects with prolonged smoking may well contribute to the adverse cardiovascular consequences of cigarette smoking, such as myocardial infarction and cardiac failure (Quillen et al., 1993).

1.5. Effects of cigarette smoking on muscle size and function

Many studies have described the negative effects of smoking on skeletal muscle function and morphology, specifically, the thigh muscles (Larsson and Örlander, 1984). One aspect is decreased muscle fatigue resistance (Wüst et al., 2008c) associated with reduced muscle oxidative capacity (Degens and Veerkamp, 1994) and a slow twitch to fast twitch fibre type transition (Örlander et al., 1979). A diminished oxygen delivery due to the interaction of CO with haemoglobin may hamper the mitochondria to resynthesize

Adenosine triphosphate (ATP). The ability of the mitochondria to synthesise ATP can be further aggravated by mitochondrial dysfunction due to interaction of CO and other substances in cigarette smoke with elements of oxidative phosphorylation, and combined with the other changes already discussed, cause a reduction in muscle contractile endurance (Degens et al., 2015). Furthermore, smoking could promote skeletal muscle wasting via smoking-induced inflammation that increases protein breakdown and decreases protein synthesis (Degens et al., 2015; Petersen et al., 2007) and results in a reduced maximal force-generating capacity of the muscles from smokers (Barreiro et al., 2010; Seymour et al., 2010). Figure 1.1 shows the mechanism whereby smoking may have a negative impact on muscle function, such as that caused by reactive oxygen species and free radicals and impaired oxygen delivery due to carbon monoxide in cigarette smoke.

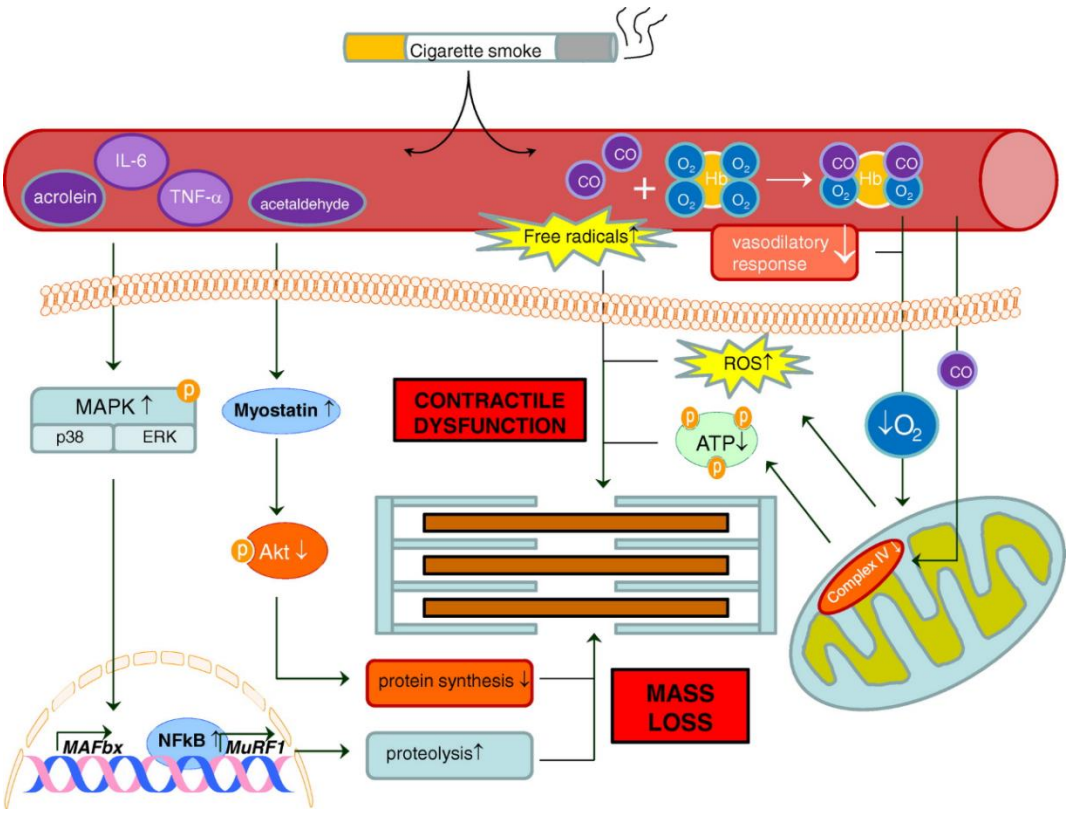

Figure 1.1: Mechanisms whereby smoking may affect skeletal muscle mass and function. ERK = extracellular signal–regulated kinase; MAFBx = muscle atrophy F-box; MAPK = mitogen-activated protein kinase; MuRF1 = muscle ring finger-1; NF-κB = nuclear factor-κB; ROS = reactive oxygen species; TNF-α = tumor necrosis factor-α. Figure and caption were taken from (Degens et al., 2015).

1.6. Effects of vaping and smoking on respiratory function

Cigarette smoke irritates the lining of the bronchial tubes causing them to swell and produce mucus to remove smoke particles (Hogg et al., 2004). Emphysema may develop when smoke particles irritate the alveolar walls and inflammation stimulates the release of proteases, enzymes that leads to the destruction of elastic fibres and collagen, which subsequently culminate in the destruction of the alveolar walls (Centers for Disease Control Prevention, 2010; Hogg et al., 2004). Over time, this can lead to a decreased elastic recoil of the lung, chronic bronchitis and narrowing of the bronchial tubes that increases the resistance, and hence, cost of breathing (Hogg et al., 2004; Stănescu et al., 1996). Ultimately, this progressive decrease in lung function can develop into COPD (Wüst and Degens, 2007) that is diagnosed in 6.6% of the United states (US) population, of which 75% are smokers (Salvi and Barnes, 2009; Wheaton et al., 2019). Additionally, the respiratory muscle strength, as measured by maximal inspiratory and expiratory mouth pressures, was reduced in healthy smokers (Bostanci et al., 2019).

In contrast to smoking, the effects of vaping on human health and respiratory function are poorly investigated (Palazzolo, 2013), but it has been shown that vaping for just 5 min increased peripheral airway resistance (Vardavas et al., 2012). This is, however, not unequivocal, as another study found no acute effects of active vaping on lung function (Flouris et al., 2013). Whatever the cause of the discrepancy, it has been suggested that the increased peripheral airway resistance after 5 min of vaping (Vardavas et al., 2012) is partially caused by nicotine (Palazzolo, 2013). Indeed, nicotine inhalation (0-64 mg/ml) showed a dose-dependent increase in the amount of coughing and airway obstruction in non-smokers, which may be a consequence of the stimulation of afferent nerve endings

in the bronchial mucosa by nicotine, which in turn triggers parasympathetic cholinergic pathways leading to bronchoconstriction (Hansson et al., 1994). Nicotine is, however, not the whole explanation, as respiratory symptoms, and airway inflammation were even found in vapers who used nicotine-free e-cigarettes (Vakali et al., 2013).

Over time, the above effects of vaping may cause acute small-airway constriction and airway epithelial injury (Chaumont et al., 2018) that may be linked to increased risk of wheezing and respiratory symptoms similar to those seen in cigarette smokers (Li et al., 2019). McCauley et al. (2012) presented a case study of a 42-year-old woman diagnosed with exogenous lipoid pneumonia due to vaping. She had a history of 7-months productive cough, fevers and dyspnoea which occurred at the same time of her use of e-cigarettes (McCauley et al., 2012). Glycerine, which is a component added to e-cigarette liquid to produce visible smoke to simulate the cigarette smoking experience, was found to be the causative agent, and symptoms improved by vaping cessation (quit vaping) (McCauley et al., 2012). The above example may be considered anecdotal, but in a study of 30 vapers who never smoked, it was seen that the Forced Expiratory Volume in one second (FEV_1) and Forced Expiratory Volume in one second/Forced Vital Capacity (FEV_1/FVC) were significantly lower than those in controls (non-vapers and non-smokers) (Meo et al., 2019), similar to that seen in smokers (Kiter et al., 2000; Sparrow et al., 1983) (Figure 1.2).

In contrast to the above cross-sectional study where vapers and non-vapers were compared (Meo et al., 2019), in a 3.5-year prospective study no significant decrements in spirometry or diffusion capacity were found in vapers (Polosa et al., 2017). Perhaps studies with a larger sample size are needed, as there are studies that have also not seen any significant effect of smoking on respiratory function (Wüst et al., 2008c). Overall,

combined with the detrimental impact of vaping on the lungs of mice (Glynos et al., 2018) the data suggest that vaping has a detrimental effect on lung function.

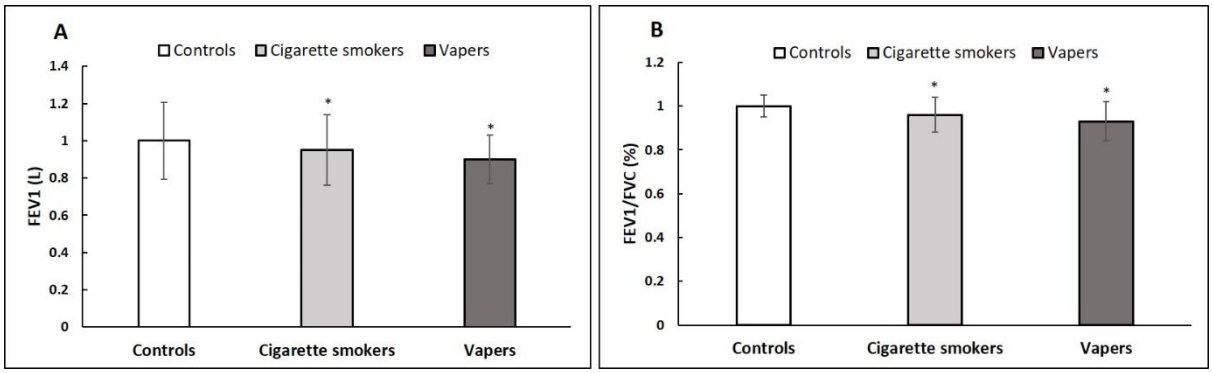

Figure 1.2: The effect of vaping on A) forced expiratory volume in one second (FEV_1) and B) FEV1:FVC (forced vital capacity). Data are mean ± SD. * different from controls at $p<0.05$. Data are from (Meo et al., 2019), and (Sparrow et al., 1983). To make the data between the two studies comparable, in each study the data were normalised to the control group.

1.7. Effects of smoking on exercise

Smoking can cause acute and long-lasting impairments in endurance and exercise capacity, and increase the rates of injury and development of chronic diseases (Elbehairy et al., 2016; Mendonca et al., 2011). One of the causes of a reduced exercise capacity is carbon monoxide in cigarette smoke that via binding to haemoglobin impairs the oxygen delivery to the working muscles (Guyton and Hall, 2006). As a consequence, the ATP required for muscle contraction will be derived more than in non-smokers from glycolysis, resulting in an earlier and faster accumulation of lactic acid (the substance that causes muscle “burning,” fatigue, heavier breathing, and increased soreness after exercise) and hence a reduction in the pH of the muscle fibres that hampers muscle contraction (Guyton and Hall, 2006). This section summarises briefly in somewhat more detail the main effects of smoking not only on skeletal muscle, but also the heart and the respiratory system, and the consequences for exercise capacity in smokers.

One of the almost immediate effects of smoking is the binding of carbon monoxide to haemoglobin that can significantly impair the oxygen carrying capacity of the blood and at the same time impedes the release of the oxygen that is bound to haemoglobin, reflected by a left-shift of the haemoglobin dissociation curve (Degens et al., 2015). Therefore, for the same oxygen consumption, the cardiac output is elevated after smoking just one cigarette in smokers (Hirsch et al., 1985). This thus increases the work of the heart, further compounded by the increase in heart rate induced by the nicotine-induced release of adrenaline. In fact, the effect of nicotine is even evident at rest, where just within the first ten minute of smoking, heart rate increased by up to 30% (Hayano et al., 1990). One of the more serious longer term effects of smoking is atherosclerosis (Howard et al., 1998), which via a reduction of the diameter of arteries can lead to a lower perfusion of muscles during exercise, and in the heart can result in coronary heart disease, characterised by diminished perfusion to the heart muscle (Critchley and Capewell, 2003).

Besides the effects of smoking on the heart and skeletal muscle, it is also known to cause dyspnoea during exercise, even in healthy smokers (Wang et al., 1995). This problem may derive from reductions in lung volumes and respiratory muscle weakness, and further contribute to reduced exercise capacity and endurance in healthy smokers (Elbehairy et al., 2016; Wang et al., 1995).

In addition to the cardiac and pulmonary complication, particularly endurance capacity may be diminished also due to a lower proportion of highly oxidative type I fibres (Ide and Tabira, 2013), further compounded by muscle fibre atrophy. Figure 1.3 is a schematic summary for the main effects of smoking on the cardiovascular, respiratory and musculoskeletal systems that might lead to exercise intolerance.

Perhaps somewhat unexpected is the potential detrimental impact of smoking on bone mineral density (Wust et al., 2010) that may lead to an earlier onset of osteoporosis (Krall and Dawson-Hughes, 1999). Part of this reduction in bone mineral density may be attributable to a 20mg/day lower calcium availability in smoker than non-smokers, resulting from a impaired ability to absorb calcium (Krall and Dawson-Hughes, 1999).

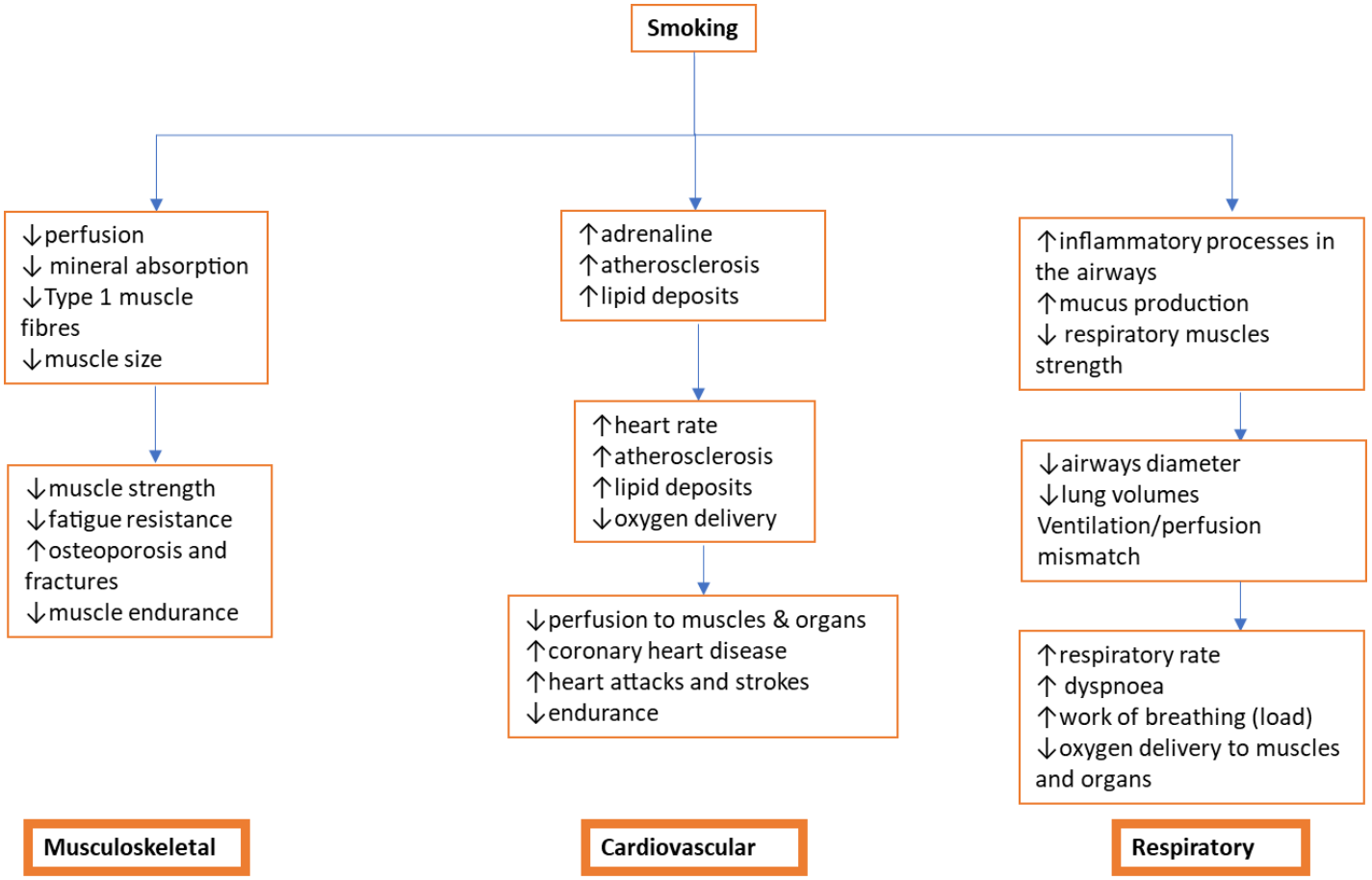

Figure 1.3: Schematic summary for the main effects of smoking on the cardiovascular, respiratory and musculoskeletal systems that might lead to exercise intolerance.

1.8. Effects of smoking on haematology parameters and oxidative stress biomarkers

The harmful compounds in cigarette smoke may increase the risk of CVD by increasing the production of free radicals, oxidative stress and low-grade systemic inflammation even otherwise in healthy smokers (Abdul-Rasheed and Al-Rubayee, 2013; Bloomer, 2007; Lykkesfeldt et al., 2004; Morrow et al., 1995). The low-grade systemic inflammation is reflected by increased numbers of circulating WBC and elevated levels of inflammatory cytokines, such as interleukin-1 (IL-1), Interleukin-6 (IL-6), and tumour necrosis factor α (TNF-α) (Aula and Qadir, 2013). In addition to systemic inflammation, smoking is associated with elevated serum cholesterol and triglyceride levels, impaired glucose tolerance and reduced insulin sensitivity (Frati et al., 1996). It has been reported that in diabetic people, a reduced insulin sensitivity could lead to glycation of myofibrillar proteins (Syrový and Hodný, 1992) that may be further aggravated by glycotoxins in cigarette smoke that can also react with serum proteins to form advanced glycation end products (AGEs) (Cerami et al., 1997).

1.9. Vaping cessation and smoking cessation

Since 1963 cigarette companies have been working to invent a new smoking system such as electronic nicotine delivery systems (ENDS) that heats, instead of burns, tobacco to reduce harm, and presents as a socially acceptable alternative to smoking (Glantz and Forbes, 1996; Ling and Glantz, 2005). The credit of inventing the e-cigarette as an alternative to smoking goes to Hon Lik, a Chinese pharmacist and inventor, whose heavy-smoking father died from lung cancer (Demick, 2009; Lik, 2004). Many companies

worldwide have adopted this technology and started marketing e-cigarettes as a harmless and safe alternative to cigarette smoking (Dutra et al., 2017).

Smoking cessation is a vital strategy to slow or reverse many of the harmful effects of smoking. It is efficient to slow down the accelerated decline in FEV_1 (Anthonisen, 1997; Kanner et al., 1999) and it reduces morbidity and mortality (Rodrigues et al., 2014). In fact, it was reported that smoking-induced lung inflammation, mitochondrial dysfunction, limb muscle and diaphragm muscle atrophy were reversed after two weeks smoking cessation in mice (Ajime et al., 2021). Additionally, smoking cessation normalised the elevated IL-1α and TNF-α levels induced by smoking (Ajime et al., 2021; Braber et al., 2010). In addition, smoking cessation might result in a quick normalisation of carboxyhaemoglobin to levels seen in non-smokers, which might be associated with an improvement in exercise tolerance and skeletal muscle fatigue resistance (Kambam et al., 1986).

As the cardiorespiratory system is the most affected organ system by smoking, smoking cessation is of benefit to stop and/or reverse its detrimental effects. Indeed, smoking cessation has been reported to alleviate at least some of the CVD conditions as indicated by improvement in treadmill stress testing (Asthana et al., 2012). So, in addition to vaping as a tool to facilitate smoking cessation, more tools and strategies are needed to help smokers quit, including exercise that may even help in vaping cessation (quit vaping). Even if exercise does not result in enhanced smoking and/or vaping cessation, there may still be benefits, such as an aerobic exercise-induced increase in VO_{2max} and increased lung function that are often reduced in even in healthy smokers (Bernaards et al., 2003; Kobayashi et al., 2004; Rawashdeh and Alnawaiseh, 2018; Wu et al., 2020). Despite these potential benefits, there is as yet no clear evidence about the effects of aerobic exercise as an intervention for vaping cessation and smoking cessation.

Most smokers are aware of the harmful effects of cigarette smoking. Since the introduction of e-cigarettes in 2003, many smokers have turned to electronic cigarettes as they are thought to be less harmful, instead of nicotine replacement therapy (NRT) to help them quit smoking (Dawkins et al., 2013; Dockrell et al., 2013; Etter, 2010; Etter and Bullen, 2011; Farsalinos et al., 2013; Foulds and Veldheer, 2011). In 2019, 7.1% of the adult population of Great Britain used e-cigarette (Action on Smoking and Health, 2019), and in the European Union (EU), the use of e-cigarettes increased from 7.2% in 2012 to 11.6% in 2014 (Filippidis et al., 2017). The potential of e-cigarettes or vaping to facilitate smoking cessation is illustrated by the 80% decrease in the use of normal cigarettes after 6 months of vaping (Polosa et al., 2011), and other studies showing an up to 50% decrease in smoked cigarettes 24 months after taking up vaping (Caponnetto et al., 2013; Polosa et al., 2014). In addition, smoking cessation was reported to be as high as 8.7% 52 weeks after taking up vaping (Caponnetto et al., 2013). In the UK, a recent trial for smoking cessation showed that using e-cigarette accompanied by behavioural support, such as face-to-face support, was more effective than NRT (Hajek et al., 2019). This is strong evidence that vaping indeed can reduce smoking.

Nicotine replacement therapies expose users to low doses of nicotine (7 to 14 mg/24-hour patch or 2 to 4 mg per piece of gum) and have been approved as medicinal products by the US Food and Drug Administration (FDA) (Kempton et al., 2014). E-cigarettes are not approved by the FDA and can be bought over the counter or online also in Europe (Kempton et al., 2014). The liquid in e-cigarettes have widely different nicotine concentrations, varying from 8 to 24 mg/ml per cartridge, but even doses up to 100 mg/ml are readily available (Kempton et al., 2014) and pose a real risk of nicotine poisoning (European Commission, 2012). There is, indeed, not enough evidence that vaping is safe and has no, or minor, negative health effects. On the contrary, a study using

online forums reported 326 negative health-related effects of vaping, including effects on the respiratory, circulatory, sensory, digestive and neurological systems (Hua et al., 2013).

1.10. Summary and conclusion

In summary, though vaping is being marketed as safer and healthier alternative to smoking and therefore is promoted as a tool to help smoking cessation, there are some concerns that vaping may not be as healthy as generally thought (Schraufnagel et al., 2014). Therefore, more research is required into the impact of vaping on the respiratory, cardiovascular and musculoskeletal system. In chapter 2 the impact of vaping or smoking will on the respiratory system will be evaluated and compared with that in non-smoking non-vaping controls.

While smoking induces low-grade systemic inflammation and animal studies suggest that this can be readily reversed by smoking cessation this has not yet been studied in humans. In addition, little is known about the efficacy of aerobic exercise to enhance the success rate of smoking and/or vaping cessation and to what extent addition of aerobic exercise to smoking cessation programmes improves fitness. Based on these considerations, the objectives were to assess the effects of vaping and smoking on cardiorespiratory, vascular and muscle function, VO_{2max} and low back pain. However, the outbreak of the Coronavirus (COVID-19) pandemic led to suspension of research activities as per the government guidelines. Therefore, the objectives of the study had to be re-adjusted. The overall aim of this thesis became: to assess the effects of vaping and smoking on respiratory and muscle function, and inflammation and whether the effects of smoking can be reversed by aerobic exercise, vaping cessation and SC in healthy smokers. Specific objectives were:

- **To assess respiratory function and respiratory muscle strength in vapers, smokers and non-smokers who are not diagnosed with airways obstruction (Chapter 2).** Spirometry was used to assess respiratory function in chapter 2 and chapter 3. Spirometry is considered the golden standard to assess lung function and is widely used to diagnose COPD (Miller et al., 2005). However, other methods that are more sensitive to detect changes in small airways, such as impulse oscillometry, could be used to detect early smoking-, or vaping-, induced decrements in pulmonary function.

- **To determine the effects of smoking cessation on respiratory function, muscle function, inflammation, and haematological parameters (Chapter 3).** To assess muscle function, electrical stimulation was used to evoke repetitive isometric contractions to induce muscle fatigue. This test was used, and it bypasses motivational bias. Serum cytokines levels were quantified using flow cytometry which is a sensitive and widely used technique to determine the cytokines. Serum malondialdehyde (MDA), a marker of lipid peroxidation, was quantified spectrophotometrically. Although there are more precise markers of lipid peroxidation, such as isoprostane, the technique gives a rough indication of levels of oxidative stress.

- **To assess the effects of aerobic exercise as an intervention on success of vaping** cessation **and smoking cessation (Chapter 4).** The comprehensive search that was conducted and checked by two independent reviewers limited the chance of missing any potential articles that met the inclusion criteria. The quality of the selected papers was assessed by the rigorous Cochrane Risk of Bias tool 2 to exclude papers with too large a risk of bias. As an additional measure of quality assurance, the review protocol was registered in the PROSPERO database.

The last chapter (5) of the thesis discusses the findings of the thesis.

Chapter 2 : Impact of Vaping and Smoking on Maximum Respiratory Pressures and Respiratory Function

Part of this chapter has been published as

Darabseh, M.Z., Selfe, J., Morse, C.I. and Degens, H., 2021. Impact of vaping and smoking on maximum respiratory pressures and respiratory function. International Journal of Adolescence and Youth, 26(1), pp.421-431.

2.1 Abstract:

Objectives: It is well-known that cigarette smoking is harmful to the human body. The effects of electronic-cigarette use (vaping) marketed as a healthier alternative to cigarette smoking, on lung function in particular remain equivocal. Therefore, this study was conducted to assess and compare the effects of electronic cigarette use and cigarette smoking on maximum respiratory pressures, respiratory function and carboxyhaemoglobin (HbCO) levels.

Methods: Forty-four young healthy participants were recruited: Vapers (n=12; 6 M/6 W) who had used e-cigarettes daily for ≥ 1year (1.67±1.00 years), Cigarette smokers (n=14; 8 M/6 W) who had smoked daily for 4.86±2.49 years with a smoking history of 2.29±1.88 pack years, and people who had never vaped nor smoked (control) group (n=18; 9 M/9 W). Spirometry, maximum respiratory pressures and carboxyhaemoglobin levels were measured.

Results: Men had a higher Forced expiratory volume in the first second (FEV_1), Forced vital capacity (FVC), Peak expiratory flow (PEF), Forced expiratory flow at 25% of FVC ($FEF_{25\%}$), $FEF_{25-75\%}$, Maximal inspiratory pressure (MIP) and Maximal expiratory pressure (MEP) than woman ($p<0.05$). Controls had higher FEV_1, PEF, FEV_1/FVC, $FEF_{25\%}$, $FEF_{25-75\%}$, $FEF_{25-75pred\%}$ and lower HbCO% than vapers and cigarette smokers ($p<0.05$). $FEV_{1pred\%}$ was lower in smokers than in controls ($p<0.01$). Vapers and smokers did not differ significantly in FEV_1, $FEV_{1pred\%}$, PEF, FEV_1/FVC, $FEF_{25\%}$, $FEF_{75\%}$, $FEF_{25-75\%}$, $FEF_{25-75pred\%}$ and HbCO% ($p<0.05$). Maximum respiratory pressures did not differ significantly between the three groups.

Conclusion: E-cigarette use has similar detrimental effects as cigarette smoking on pulmonary function and may thus not be a healthier alternative to smoking.

2.2 Introduction

Cigarette smoking is a well-known risk factor for the development of cancer, cardiovascular diseases and respiratory disorders, such as lung cancer and chronic obstructive pulmonary disease (COPD) (Barengo et al., 2019). Smokers are very much aware of these dangers and many of them seek to quit smoking. Electronic cigarettes (e-cigarette) are marketed as a healthier alternative to cigarette smoking, as they are devices that do not burn tobacco, yet may deliver nicotine, and contain fewer than the more than 4000 toxic chemicals in cigarette smoke (Glantz and Forbes, 1996; Ling and Glantz, 2005; Richter et al., 2008). In the United Kingdom (UK) e-cigarettes are marketed as a smoke cessation product, whereas in the United States (US) they are marketed to young adults as an alternative for those who do not smoke (Mantey et al., 2016). The success of e-cigarettes to help quit smoking is reflected by the fact that 54% of e-cigarette users in the UK are ex-smokers (Action on Smoking and Health, 2019).

An e-cigarette is a battery-powered device that consists of a vaporizing chamber, a cartridge/tank that contains the vaping liquid (e-liquid) and an atomizer that heats, rather than burns, the e-liquid that consists of vegetable glycerine, propylene glycol and other chemicals, and may contain nicotine. When the e-liquid is heated, it produces the aerosolized vapour that is inhaled by the vaper. Because vaping is a relatively new phenomenon, the impact of vaping on health has not yet thoroughly been investigated. However, the few studies that have investigated vaping indicate that e-cigarettes have detrimental effects on human health in general and on lung function in particular (Antoniewicz et al., 2019; Chaumont et al., 2019; Coppeta et al., 2018; Darabseh et al., 2020; Meo et al., 2019). Interestingly, some reports found that vaping is linked with lung injury, named ‘E-cigarette, or vaping product use-associated lung injury’ (EVALI) including inducing pneumonia, hypersensitivity pneumonitis, lipoid pneumonia and diffuse alveolar

damage (Henry et al., 2020; Landman et al., 2019). This problem cannot be ignored, as reflected by the 2,807 hospitalized EVALI, mostly young adults and/or teenagers, cases or deaths that have been reported in the US, and the 244 suspected adverse reactions reported, including two fatal outcomes, in the UK (Centers for Disease Control Prevention, 2020; UK Medicines and Healthcare products Regulatory Agency, 2020). Thus, although Public Health England claimed that e-cigarettes are 95% safer than cigarette smoking (McNeill et al., 2015) and the prevailing idea is that vaping is not only safer, but also helps in smoking cessation (McNeill et al., 2015), it is far from clear that vaping is a healthier alternative than smoking. Therefore, the aim of this study was to compare the effects of vaping and smoking on lung function. It was hypothesised that vaping has a detrimental effect on pulmonary function, but it remains to be seen if these harmful effects are less, more or similar to those of cigarette smoking. In addition, there is some indication that smoking may impair pulmonary function in women than in men (Xu et al., 1994), therefore, we were also interested in potential sex differences in the response to vaping.

2.3 Methods

2.3.1 Study design

This was a laboratory-based, cross-sectional, observational study to compare pulmonary function in i) vapers, ii) cigarette smokers and iii) people who neither smoked nor vaped (controls). Ethical approval was obtained from the Science and Engineering Research Ethics and Governance Committee at Manchester Metropolitan University (EthOS reference number: 5944). All procedures adhered to the principles stated in the Declaration of Helsinki and all participants provided written informed consent before participating.

2.3.2 Participants

The sample size was based on the work of (Polosa et al., 2017) who compared vapers with smokers. Using their data, 7 participants per group were needed to detect a 12% difference in FEV_1 between groups with a power of 80% and a type-I error (alpha) of 0.05 (5%).

Participants were recruited from the local community and Manchester Metropolitan University through posters, social media channels and snowball sampling. The inclusion criteria were: 18- to 55-year-old men and women, and healthy cigarette smokers and vapers had to have smoked/vaped for ≥1 year. Exclusion criteria were: neuromuscular disease; severe musculoskeletal injuries; any lower limb injury; any diagnosed mental health disorder; treatment for chronic respiratory complaints; a known history of heart disease; smokers who mix cigarette and vape; water pipe (shisha) smokers. Vaping and smoking history and volume were assessed by a questionnaire. The smoking volume (SV) was given as pack years, calculated as:

$$SV = (N_{cig} * S)/20$$

Where N_{cig} is the current number of cigarettes smoked per day, and S the number of years smoked. It was assumed that 1 pack of cigarettes contained 20 cigarettes.

2.3.3 Participant characteristics

Demographic data including age, sex, height, body mass, body mass index (BMI) and occupation of participants was recorded. Height and body mass were assessed using a stadiometer and digital scales, respectively. Body composition was assessed using bioelectrical impedance (BodyStat 1500, BodyStat, Douglas, UK).

2.3.4 Carboxyhaemoglobin

HbCO, which is the percentage of the haemoglobin (Hb) oxygen binding sites occupied by carbon monoxide (CO), was measured with a hand-held CO meter (Micro Smokerlyzer, Bedfont Scientific Ltd.; Kent, UK) according to the recommendations of the manufacturer (Hajek and Belcher, 1991). Participants exhaled to residual volume and then quickly inhaled until total lung capacity. After a 15-s breath-hold, the participants were asked to exhale slowly through a disposable mouthpiece attached to the carbon monoxide meter for at least 10 s. The measured HbCO level was expressed as percentage (HbCO%).

2.3.5 Spirometry

Spirometry was conducted using a Micro Medical Spiro USB Spirometer and analysed with Spida 5 software (Cardinal Health, UK). FEV_1, FVC, FEV_1/FVC ratio, Peak Expiratory Flow (PEF), maximum mid-expiratory flow between 25% and 75% of the FVC ($FEF_{25-75\%}$) and predicted values of FVC, FEV_1, $FEF_{25-75\%}$ were recorded. The spirometry was completed in accordance with the American Thoracic Society/European Respiratory Society (ATS/ERS) guidelines (Miller et al., 2005). Predicted values were calculated by the Spida 5 software based on body mass index, age, sex and ethnicity according ATS/ERS guidelines. Each participant had a nose clip and completed a minimum of three manoeuvres with at least 1–2 min rest between each manoeuvre. Manoeuvres were rejected if: participants prematurely stopped exhalation, coughed during the first second of exhalation, lips were not fully sealed around the mouthpiece, the mouthpiece was obstructed by the teeth or tongue and/or the effort appeared submaximal. The test session was concluded when the largest two FEV_1 and the largest two FVC were each within 0.15 L of each other in at least 3 manoeuvres (Miller et al., 2005). If these criteria were not met, the manoeuvres were repeated until the criteria were met, eight manoeuvres had been attempted, or if the participant did not want to continue. Participants were instructed not to eat heavy meals

or to smoke or vape and to refrain from vigorous physical activity for at least two hours before the test.

2.3.6 Respiratory pressure

The maximal inspiratory pressure (MIP), maximal expiratory pressure (MEP) and sniff nasal inspiratory pressure (SNIP) were determined using a portable mouth pressure device (MicroRPM, Cardinal Healthcare, UK). The participants were asked to inhale (MIP/SNIP) or exhale (MEP) as forcefully as possible after full exhalation or inhalation, respectively into the portable MicroRPM. To determine SNIP, participants placed a probe in one of their nostrils, and with the other nostril closed inhaled as forceful as possible via the nose (Lofaso et al., 2006). For all manoeuvres, attempts were repeated, with a 30-s interval between each attempt to prevent the development of respiratory muscle fatigue, until a maximum value was reached.

2.3.7 Statistics

Statistical analyses were performed using SPSS 24.0 (IBM Corporation, NY, US). Data was assessed for normality with the Shapiro-Wilk tests. If the data were not normally distributed a two-way univariate ANOVA was performed on the log-transformed data. Differences between vapers, smokers and controls, and sexes were tested using univariate ANOVA with as between factors group and sex. If a significant group effect or a group * sex interaction were found, a Tukey 2-sided post-hoc test was performed to locate the significant differences. Predicted spirometry values were compared between pure vapers (who never smoked), vapers who were ex-smokers and controls with a two-way univariate ANOVA and Tukey-corrected post-hoc tests to locate the differences. A stepwise regression analysis was performed to assess to what extent spirometry parameters were affected by sex, and vaping or smoking duration or volume. Differences

and correlations were considered significant at $p<0.05$. All data are presented as mean±SD unless stated otherwise.

2.4 Results

Men were taller and heavier than women, and women had a higher fat percentage than men ($p<0.05$), irrespective of being vapers, smokers or controls (Table 2.1). All vapers had used e-cigarettes daily for ≥ 1 year (1.67±1.00 years). Eleven of the twelve vapers were using nicotine-containing e-liquids with a concentration ranging between 3 to 18 mg/mL. The puffs per e-cigarette were 8.30±5.23. Seven out of twelve vapers were former smokers, and the rest were pure vapers (only used vape exclusively). All cigarette smokers had smoked daily for 4.86±2.49 years, consumed 9.00±4.78 cigarettes/day and had a smoking history of 2.29±1.88 pack years. No group-sex interactions were found for any outcome measure, indicating that all the observed effects of smoking and vaping were similar in men and women.

Men had higher FEV_1, FVC, PEF, $FEF_{25\%}$, $FEF_{50\%}$, $FEF_{25-75\%}$, MIP and MEP than woman ($p<0.05$) (Table 2.2 and Figure 2.1 and 2.2). $FEV_{1pred\%}$, FEV_1/FVC, $FEF_{75\%}$, $FEF_{25-75pred\%}$, SNIP and HbCO% did, however, not differ significantly between men and women (Table 2.2 and Figure 2.1 and 2.2), but the $FVC_{pred\%}$ was higher in women than men (Table 2.2; $p<0.03$).

Vapers and cigarette smokers had lower FEV_1, PEF, FEV_1/FVC, $FEF_{25\%}$, $FEF_{50\%}$, $FEF_{25-75\%}$, $FEF_{25-75pred\%}$ and higher HbCO% than controls ($p<0.05$) (Table 2.2 and Figure 2.1 and 2.2). The $FEV_{1pred\%}$ was lower in smokers than controls ($p<0.01$), but there was no significant difference between vapers and controls ($p=0.054$) (Figure 2.1). Vapers had a lower $FEF_{75\%}$ than controls ($p<0.009$), but there was no significant difference in $FEF_{75\%}$ between

smokers and controls (p=0.064) (Figure 2.2). There were no significant differences in FEV_1, $FEV_{1pred\%}$, PEF, FEV_1/FVC, $FEF_{25\%}$, $FEF_{50\%}$, $FEF_{75\%}$, $FEF_{25-75\%}$, $FEF_{25-75pred\%}$ and HbCO% between vapers and smokers (Table 2.2 and Figure 2.1 and 2.2). The FVC, $FVC_{pred\%}$, MIP, MEP and SNIP did not differ significantly between vapers, smokers and controls (Table 2.2).

A stepwise linear regression was performed to assess to what extent the respiratory parameters were determined by sex, height, body mass, smoking duration, smoking volume, or for vapers, vaping duration and number of puffs. Smoking duration was the primary determinants of $FEV_{1pred\%}$ (R^2_{adj}=0.564; p=0.002), FEV_1/FVC (R^2_{adj}=0.568; p=0.002), $FEF_{50\%}$ (R^2_{adj}=0.412; p=0.011), $FEF_{25-75\%}$ (R^2_{adj}=0.528; p=0.003), $FEF_{25-75pred\%}$ (R^2_{adj}=0.665; p<0.001) (Figure 2.3). Vaping duration and number of puffs were not significant determinants of pulmonary function (Figure 2.3).

Table 2.1: Participant characteristics.

	Vapers		Cigarette smokers		Controls	
	Men (n=6)	**Women (n=6)**	**Men (n=8)**	**Women (n=6)**	**Men (n=9)**	**Women (n=9)**
Age (Years)	20.7±1.5	20.3±1.6	21.5±2.1	20.0±1.1	24.3±8.6	21.3±1.9
Height (m)	1.74±0.10	1.58±0.04*	1.71±0.05	1.59±0.05*	1.79±0.08	1.64±0.06*
Mass (kg)	74.7±10.0	57.0±5.1*	73.0±25.8	65.5±9.3*	78.4±13.3	68.7±17.6*
BMI	24.6±3.1	22.8±2.2	24.5±7.3	25.9±4.4	24.0±2.9	25.1±5.4
Fat (%)	18.6±5.7	25.7±5.3*	19.9±2.0	30.8±6.5*	19.8±4.7	29.4±8.6*
Vaping duration (years)	2.1±1.1 (6)	1.1±0.4 (6)	-	-	-	-
Puffs per e-cigarette single use	10.2±6.7 (5)	6.4±2.7 (5)	-	-	-	-
Smoking duration (years)	-	-	5.4±2.9 (7)	4.1±1.7 (6)	-	-
Cigarettes per day			9.3±5.8 (7)	8.6±3.4 (6)		
Smokers pack-years	-	-	2.7±2.3 (7)	1.7±1.0 (6)	-	-

BMI: body mass index; (x): number of participants; *significantly different from men at $p<0.05$

Table 2.2: Forced vital capacity, maximal respiratory pressures and carboxyhaemoglobin in male and female vapers, smokers and controls.

	Vapers		Cigarette smokers		Controls		Group (p-value)	Sex (p-value)	Group-sex interaction (p-value)
	Men (6)	Women (6)	Men (8)	Women (6)	Men (9)	Women (9)			
FVC (L)	4.94±0.62	3.58±0.50	4.81±0.87	3.67±0.34	5.37±0.034	3.90±0.58	0.19	**<0.001**	0.80
FVC_{pred} (%)	92.7±5.5	99.8±10.8	93.3±11.9	96.3±2.3	94.9±7.7	101.6±7.9	0.52	**0.03**	0.78
$FEF_{50\%}$ (L/s)	3.9±0.6	3.6±0.8	3.9±1.2	3.6±0.9	5.9±1.3	4.6±0.7	**<0.001**	**0.044**	0.24
MIP (cmH_2O)	107±40 (5)	62±13 (5)	101±48 (7)	74±19 (5)	107±8 (5)	79±28 (5)	0.83	**0.007**	0.78
MEP (cmH_2O)	110±36 (5)	74±7 (5)	93±49 (7)	78±20 (5)	126±32 (5)	76±17 (5)	0.52	**0.007**	0.45
SNIP (cmH_2O)	78.6±23.4 (5)	63.3±11.7 (5)	96.9±54.8 (7)	75.0±23.5 (5)	66.8±25.6 (5)	64.2±22.5 (5)	0.33	0.26	0.79
HbCO (%)	$1.02±0.27^{\alpha}$	$1.00±0.14^{\alpha}$	$1.68±0.92^{\alpha}$	$0.97±0.77^{\alpha}$	0.00±0.00	0.00±0.00	**<0.001**	0.22	0.30

All data are presented as (mean±SD); FVC: Forced vital capacity; FEF: Forced Expiratory Flow; MIP: Maximal inspiratory pressure; MEP: Maximal expiratory pressure; SNIP: Sniff nasal inspiratory pressure; HbCO: Carboxy-haemoglobin; (x): number of participants; $^{\alpha}$: significantly different from Control

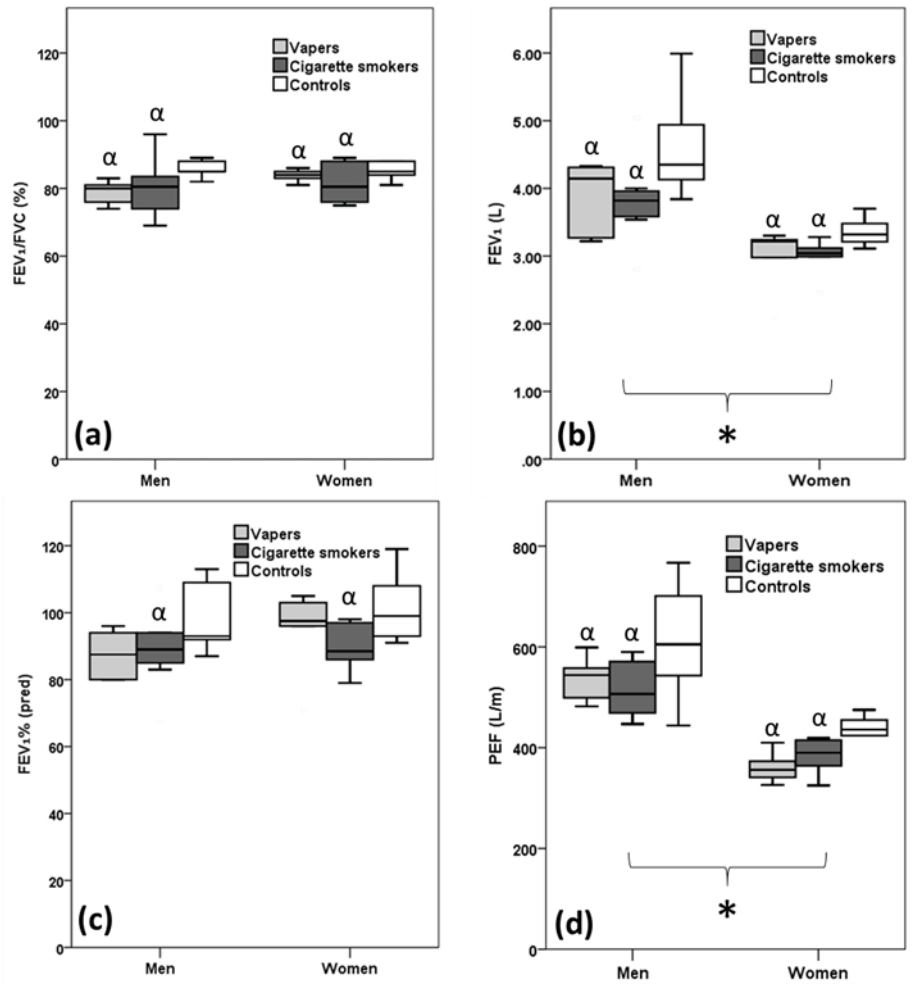

Figure 2.1: a) FEV_1/FVC**:** Forced expiratory volume in one second/ forced vital capacity; **b)** FEV_1**:** Forced expiratory volume in one second; **c)** FEV_1 predicted: Forced expiratory volume in one second predicted %; **d)** PEF: Peak expiratory flow; * sex difference at $p<0.001$; α: significantly different from Control at $p\leq0.008$

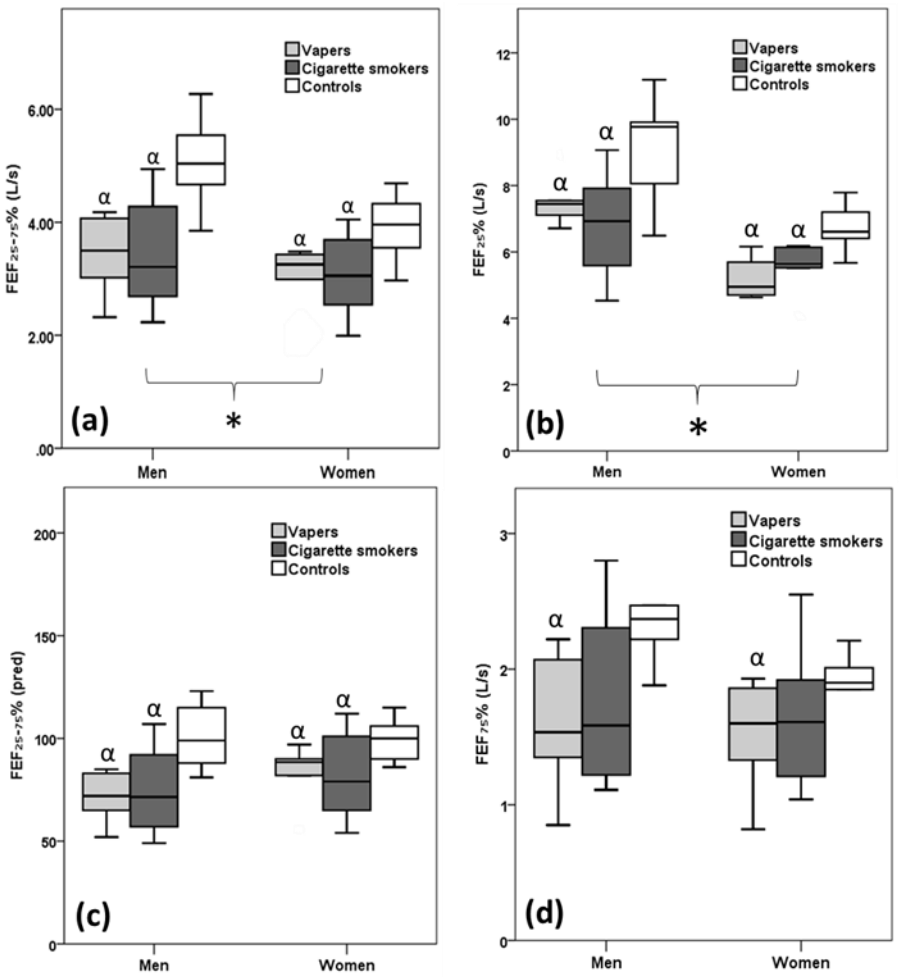

Figure 2.2: a) $FEF_{25\%-75\%}$: Forced expiratory flow at $_{25\%-75\%}$; **b)** $FEF_{25\%}$: Forced expiratory flow at $_{25\%}$; **c)** $FEF_{25\%-75\%\ (pred)}$: Forced expiratory flow at $_{25\%-75\%}$ predicted %; **d)** $FEF_{75\%}$: Forced expiratory flow at $_{75\%}$; * sex difference at p≤0.013; α: different from Control at p≤0.008

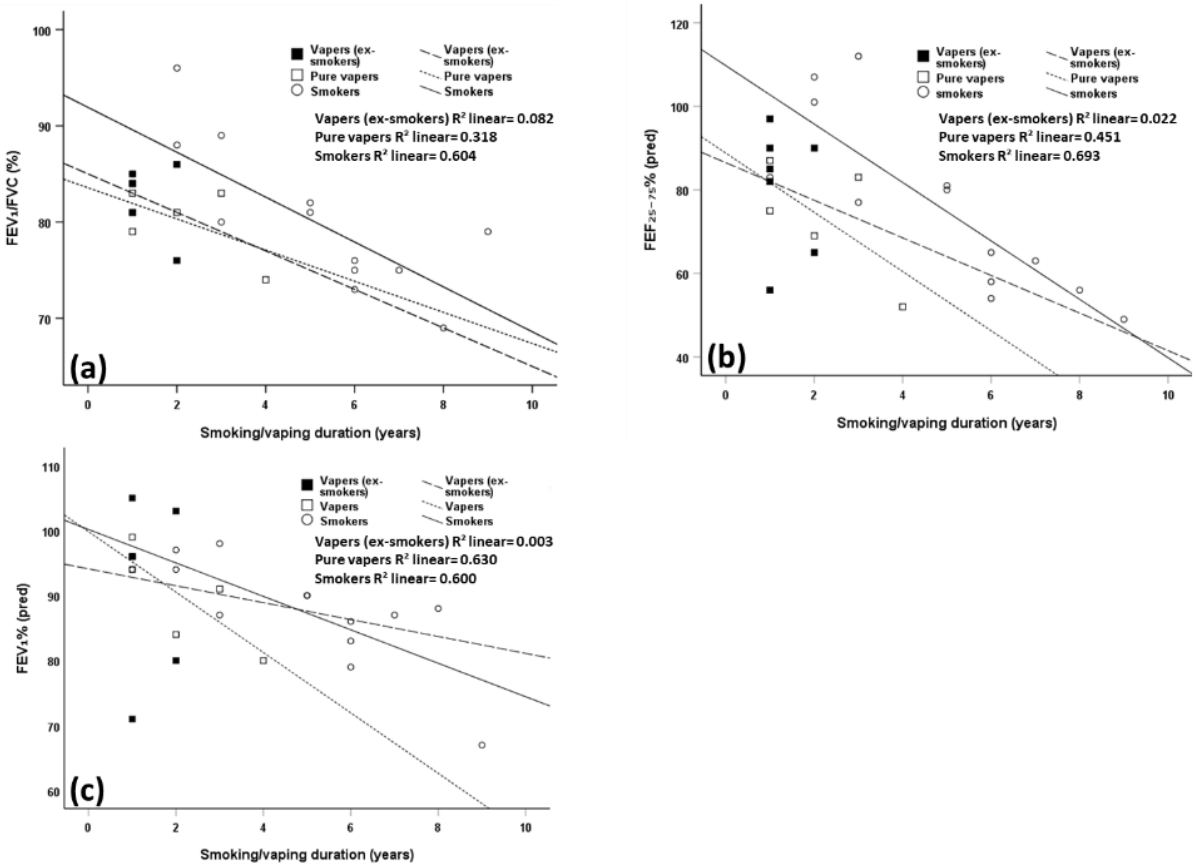

Figure 2.3: Relationship between respiratory parameters and smoking/vaping duration. **a)** FEV_1/FVC: Forced expiratory volume in the first second/ forced vital capacity F; **b)** $FEF_{25\%-75\%}$ (pred): Forced expiratory flow at 25%-75% predicted; **c)** FEV_1pred%: Forced expiratory volume in one second predicted%. P-values for smokers in FEV_1/FVC, $FEF_{25\%-75\%}$ (pred), FEV_1pred% are 0.002, 0.003 and 0.003 respectively and for vapers group all were $p>0.05$. P-value significant at $p<0.05$.

2.5 Discussion

The main finding of this study was that smokers and vapers had a similarly lower respiratory function compared to people who neither smoked nor vaped, irrespective of sex. This was not related to respiratory muscle weakness, as reflected by similar maximal respiratory pressures in all groups. In addition, the HbCO content was similarly elevated in smokers and vapers. These data indicate that vaping and smoking may cause a similar degree of airway obstruction.

In this study we confirmed that men have higher spirometric values, such as FEV_1 and FVC, than women, as reported previously (Mead, 1980; Zakaria et al., 2019). Although it has been reported that cigarette smoking affects pulmonary function more in women than in men (Xu et al., 1994), the absence of any significant group-sex interaction indicated that in our study the effects of smoking and vaping described below were similar in men and women.

Previous studies have also shown that vaping reduces lung function to a similar extent as smoking (Antoniewicz et al., 2019; Coppeta et al., 2018; Darabseh et al., 2020; Meo et al., 2019), but other studies have reported no changes in pulmonary function parameters after vaping (Polosa et al., 2017; Staudt et al., 2018; Vardavas et al., 2012). The discrepancy between these studies might be due to the duration of e-cigarette use (i.e. years), whether participants were former smokers and/or the duration of smoking or frequency/intensity of vaping. Here we found that the duration of smoking was associated with a decline in respiratory function, but this was not the case for vaping. In fact, we observed that people who had been vaping for as little as 1.67 years had a similar decrement in lung function as those who had smoked for 4.86 years. This decline was not attributable to a previous smoking history in the vapers, as we found that there was no

significant difference in spirometry between pure vapers and vapers who were ex-smokers. These decrements in spirometry measures are indicative of mild airway obstruction (McFadden Jr and Linden, 1972; Stockley et al., 2017). The increase in airflow resistance may be due to small airway narrowing consequent to mucosal oedema, smooth muscle contraction and/or local secretions as seen in long-term smokers (Vardavas et al., 2012) and may thus be an early sign of potential progression into obstructive lung diseases.

Another explanation for low airflow could be reduced respiratory muscle strength. However, there were no significant differences between controls and vapers/cigarette smokers in maximal inspiratory and expiratory pressures. These findings suggest that the reduced airflow during smoking/vaping is a consequence of obstruction of the airways rather than lower respiratory muscles strength. We have seen previously that elevated HbCO results in an earlier onset of muscle fatigue (Morse et al., 2008) and it can therefore not be excluded that during exercise respiratory muscle fatigue may impair lung function in smokers and vapers.

Limitations of this study include the small sample size, although power calculations indicated that the sample size was large enough to detect 12% differences in FEV_1. Perhaps a larger problem is that some of the participants were ex-smokers, but even in vapers who had no smoking history a lower-than-expected lung function was observed. Further studies are needed to compare vapers who never smoked with smokers and assess the effects of smoking and vaping cessation on ventilatory function.

2.6 Conclusion

While neither vaping nor smoking had a significant impact on respiratory muscle strength, both vaping and smoking led to a similar obstruction of the airways, independent of sex.

The elevated HbCO in both vapers and smokers may further compromise respiratory function during exercise. These observations indicate that vaping has similar detrimental effects on pulmonary function as smoking and suggest that one should treat the suggestion that vaping is 95% healthier than smoking with caution (McNeill et al., 2015).

Chapter 3 : Fourteen days of smoking cessation improves muscle fatigue resistance and reverses markers of systemic inflammation

Part of this chapter has been published as:

Darabseh, M.Z., Maden-Wilkinson, T.M., Welbourne, G., Wüst, R.C., Ahmed, N., Aushah, H., Selfe, J., Morse, C.I. and Degens, H., 2021. Fourteen days of smoking cessation improves muscle fatigue resistance and reverses markers of systemic inflammation. Scientific reports, 11(1), pp.1-11.

3.1 Abstract:

Background: Cigarette smoking has a negative effect on respiratory and skeletal muscle function and is a risk factor for various chronic diseases.

Objective: To assess the effects of 14 days of smoking cessation on respiratory and skeletal muscle function, markers of inflammation and oxidative stress in humans.

Methods: Spirometry, skeletal muscle function, circulating carboxyhaemoglobin levels, advanced glycation end products (AGEs), markers of oxidative stress and serum cytokines were measured in 38 non-smokers, and in 48 cigarette smokers at baseline and after 14 days of smoking cessation.

Results: Peak expiratory flow ($p=0.004$) and forced expiratory volume in 1 second/forced vital capacity ($p=0.037$) were lower in smokers compared to non-smokers but did not change significantly after smoking cessation. Smoking cessation increased skeletal muscle fatigue resistance ($p<0.001$). Haemoglobin content, haematocrit, carboxyhaemoglobin, total AGEs, malondialdehyde, TNF-α, IL-2, IL-4, IL-6 and IL-10 ($p<0.05$) levels were higher, and total antioxidant status (TAS), IL-12p70 and eosinophil numbers were lower ($p<0.05$) in smokers. IL-4, IL-6, IL-10 and IL-12p70 had returned towards levels seen in non-smokers after 14 days smoking cessation ($p<0.05$), and IL-2 and TNF-α showed a similar pattern but had not yet fully returned to levels seen in non-smokers. Haemoglobin, haematocrit, eosinophil count, AGEs, MDA and TAS did not significantly change with smoking cessation.

Conclusion: Two weeks of smoking cessation was accompanied with an improved muscle fatigue resistance and a reduction in low-grade systemic inflammation in smokers.

3.2 Introduction:

Cigarette smoking is still a public health concern and a risk factor for many chronic diseases, including chronic obstructive pulmonary disease (COPD), lung cancer and cardiovascular diseases (Health and Services, 2010; Warren et al., 2014). It is the leading cause of preventable death and 77,900 deaths in the United Kingdom were directly or indirectly attributable to smoking in 2016 (Office for National Statistics, 2017). In England, between 2017 and 2018, an estimated 489,300 smoking-related admissions to hospitals were reported (Lifestyles Team, 2019).

The adverse health effects are a consequence of a combination of thousands of toxic and/or carcinogenic substances, including carbon monoxide (CO), reactive glycation compounds, known as glycotoxins, and nicotine in cigarette smoke (Cerami et al., 1997; Glantz et al., 1998; Harris, 1996). In addition, the low-grade systemic inflammation and oxidative stress in smokers increases the risk of atherosclerosis (Abdul-Rasheed and Al-Rubayee, 2013; Aula and Qadir, 2013; Bloomer, 2007; Lykkesfeldt et al., 2004; Morrow et al., 1995). Smoking is associated with elevated serum cholesterol and triglyceride levels, impaired glucose tolerance and reduced insulin sensitivity (Frati et al., 1996). It has been reported that in diabetic people, a reduced insulin sensitivity could lead to glycation of myofibrillar proteins (Syrový and Hodný, 1992) that may be further aggravated by glycotoxins in cigarette smoke that can also react with serum proteins to form advanced glycation end products (AGEs) (Cerami et al., 1997).

In addition to the health burden of cigarette smoking and the potential adverse effect on respiratory function (Darabseh et al., 2020; Stănescu et al., 1996), smoking can also have a negative impact on muscle function (Degens et al., 2015; Morse et al., 2007; Sadaka et al., 2021; Wüst et al., 2008c). Part of the potential detrimental effect of cigarette smoking

may be attributable to the negative impact on the oxygen delivery to tissues, including skeletal muscles, that may in turn result in exercise intolerance and a reduced muscle fatigue resistance (Larsson et al., 1998; Prior et al., 2004; Sadaka et al., 2021; Wüst et al., 2008a). Such an impaired oxygen delivery is at least partly attributable to the CO in the cigarette smoke that strongly binds to haemoglobin (Hb), forming carboxyhaemoglobin (COHb) (Pojer et al., 1984). This not only reduces the oxygen carrying capacity of the blood, but also causes a left-shift of the Hb-dissociation curve. The significance of elevated COHb levels has been illustrated by an acute CO-induced reduction in muscle fatigue resistance in healthy people (Morse et al., 2008). In addition, CO and cyanide may also directly impair mitochondrial respiration (Ajime et al., 2021; Alonso et al., 2003). As fatigue resistance was similar in COPD patients who had quit smoking and healthy age-matched non-smokers (Degens et al., 2005), we hypothesised that the effect of smoking on skeletal muscle fatigue is readily reversible by smoking cessation in healthy smokers.

Smoking cessation is an important step to stop or reverse many of the detrimental effects of smoking and is considered a highly effective way to reduce morbidity and mortality (Rodrigues et al., 2014) and slow down the accelerated decline in FEV_1 (Anthonisen, 1997; Kanner et al., 1999). In fact, smoking cessation is considered one of the main actions to attenuate the progression of COPD (American Thoracic Society, 1999; Faulkner et al., 2006). The focus of this chapter will be on the effects of smoking and SC on respiratory function, muscle function and inflammatory markers. This is because it has been reported previously that the smoking-induced lung inflammation, mitochondrial dysfunction, limb and diaphragm muscle atrophy, and elevated IL-1α and TNF-α levels were normalised after smoking cessation in mice (Ajime et al., 2021; Braber et al., 2010). In addition, if CO is an important cause of a reduced muscle fatigue resistance and exercise tolerance, we expect that smoking cessation, resulting in a quick normalisation of the COHb levels

(Kambam et al., 1986), will be associated with a concomitant improvement in muscle function. Therefore, we hypothesise, that just two weeks of smoking cessation is sufficient to detect measurable improvements in muscle fatigue resistance, and diminished levels of circulating inflammatory markers and oxidative stress. As there is some indication that smoking may cause a larger reduction in pulmonary function than in men (Xu et al., 1994) and that women have a higher muscle fatigue resistance than men (Wüst et al., 2008b) we were also interested in potential sex differences in the response to smoking cessation.

3.3 Methods

3.3.1 Participants

Cigarette smokers (men n=28; women n=20) and non-smokers (men n=23; women n=15) were recruited from the local community and Manchester Metropolitan University (MMU). Healthy participants were 18 to 44 years old, and smokers had smoked for ≥ 1 year and ≤ 17 years. All participants self-reported as being free of symptoms of chronic diseases. In cigarette smokers, all measurements were repeated after 14 days of smoking cessation. The study was approved by the Science and Engineering Research Ethics and Governance Committee at MMU (Ethics reference number: 5944) and performed in accordance to the principles stated in the Declaration of Helsinki. All participants provided written informed consent before participating.

Height and body mass were assessed using a stadiometer and digital scales, respectively. Body mass index (BMI) was calculated. Smoking history was assessed by questionnaire. Smoking volume (SV) was given as pack years, calculated as the current number of packs of cigarettes smoked per day times the number of years smoked.

3.3.2 Outcome measures

3.3.2.1 Carboxyhaemoglobin (COHb)

A hand-held CO meter (Micro Smokerlyzer, Bedfont Scientific Ltd.; Kent, UK) was used to measure the percentage of the haemoglobin (Hb) oxygen binding sites occupied by CO (%COHb). The measurements were performed according to the recommendations of the manufacturer (Hajek and Belcher, 1991).

3.3.2.2 Spirometry

Spirometry was conducted using a Micro Medical Spiro USB Spirometer and analysed with Spida 5 software (Cardinal Health, UK). Spirometry was completed in accordance with the American Thoracic Society and European Respiratory Society guidelines (Miller et al., 2005). Each participant completed a minimum of three successful manoeuvres with at least 1–2 min rest between each manoeuvre while wearing a nose clip. The manoeuvres were rejected if: participants prematurely stopped exhalation, coughed during the first second of exhalation, lips were not fully sealed around the mouthpiece and/or the effort appeared submaximal. The test session was concluded when the largest two FEV_1 and the largest two FVC were each within 0.15 L of each other in at least 3 manoeuvres (Miller et al., 2005). If these criteria were not met, a maximum of eight manoeuvres were repeated until the criteria were met. Parameters assessed included: FEV_1, FVC, FEV_1/FVC ratio, Peak Expiratory Flow (PEF), and predicted values. The coefficient of variation (CV) for FEV_1, FVC and PEF was 2.09%, 2.25% and 2.80%, respectively.

3.3.2.3 Maximal voluntary contraction (MVC)

A dynamometer chair was used to measure the MVC during knee extension (Figure 3.1). Participants were seated with the hip joint in 90° flexion, knee joint angle at 80° and the pelvis strapped to minimise accessory movements. All the measurements were performed on the right thigh. During the MVC, participants received verbal encouragement and visual feedback of the torque signal (Degens et al., 2005; Morse et al., 2008; Morse et al., 2007; Wüst et al., 2008c). Participants performed the MVC twice with two minutes rest between each contraction to prevent development of fatigue. Knee extensor (KE) torque was recorded with a digital acquisition system (Acknowledge, Biopac Systems, Santa Barbara, CA, USA) at 200 Hz, and the highest value was reported as maximal muscle strength (Morse et al., 2007). The KE muscles (quadriceps) was used as this group of muscles is important for locomotion and hence important for most activities of daily living. The CV for the MVC was 4.24%.

3.3.2.4 Voluntary activation (VA) and muscle fatigue resistance

To assess the VA and muscle fatigue resistance of the quadriceps muscle, carbon-rubber pads (7.5 cm x 13 cm, Axelgaard, USA) were used to apply percutaneous electrical stimulation (square wave, pulse width 200 μs; DSV Digitimer Stimulator, Digitimer Ltd., Herts, UK). The cathode was placed over the distal third of the thigh and the anode over the proximal part of the quadriceps. The electrical stimulation voltage was set at 400 V. To assess the supra-maximal current, single pulses were administered at 30-s intervals with increases in current of 50-100 mA to the relaxed muscle until no further increase in torque was noticed.

To assess the VA during an MVC, the interpolated twitch technique was used (Morse et al., 2007; Wüst et al., 2008c) and calculated as:

VA (%) = (1-(superimposed twitch torque/resting twitch torque))*100

and had a CV of 5.96%.

The fatigue resistance of the quadriceps muscles was determined by a series of electrically-evoked isometric 30-Hz trains, 1 s on 1 s off, for 2 min at a current that elicited 30% MVC at the start of the test (Degens et al., 2005; Wüst et al., 2008c). The fatigue index (FI) was calculated as the final torque as a percentage of the initial torque during the series of the isometric contractions. The CV was 6.44%.

Figure 3.1: Dynamometer chair for Muscle function testing

3.3.2.5 Haematology parameters and oxidative stress biomarkers

Nine non-smokers and 20 smokers consented to provide blood samples. Venous blood was collected from the antecubital vein and repeated after 2 weeks of smoking cessation from smokers only. After determination of the haematocrit (%Hct) the blood was collected in 4-mL vacutainers without anticoagulants (BD Vacutainer, Becton Dickinson Company, USA). The blood samples were allowed to clot for 15 minutes and serum was separated from whole blood by centrifugation (20 min; 500 x g) at room temperature. Following centrifugation, the serum was aliquoted in 1-mL microcentrifuge tubes, frozen and stored at -80°C until further analysis.

Serum protein, albumin and glucose concentrations were measured colourimetrically using Biuret reagent Randox kits using RandoxRX Daytona analyser (Randox Laboratories Ltd., Belfast, Ireland). The glucose concentration was determined after enzymatic oxidation in the presence of glucose oxidase. The Hb concentration was determined with a HemoCue (HemoCue® Hb 201+ System). Blood cell counts included agranulocytes (lymphocytes, monocytes) and granulocytes (neutrophils, eosinophils and basophils). Serum cytokines levels were quantified using flow cytometry. Briefly, positive and negative controls were used to set up the flow cytometer (BD FACScalibur, Becton Dickinson Company, USA) and analysed using the high flow setting (FL2 channel), using Cell Quest Pro software and flowcytomix software. The software translated the flow cytometric results into cytokine concentrations ($pg \cdot mL^{-1}$). Serum malondialdehyde (MDA), a marker of lipid peroxidation, was quantified spectrophotometrically using a lipid peroxidation kit (Oxford Biomedical Research, UK). The serum total antioxidant status (TAS) was analysed using the TAS kit (Randox Laboratories Ltd., Belfast, Ireland) according to the recommendations by the manufacturer. The abundance of low molecular weight (LMW) AGEs were assessed using a spectrofluorimeter (BioTek, USA), and total AGEs

were assessed by ELISA (Cell Biolabs, United States). All tests were carried out in duplicate and averaged.

3.3.3 Statistical Analysis

Statistical analyses were performed using SPSS 24.0 (IBM Corporation, NY, US). Data were assessed for normality with the Shapiro-Wilk tests. If the data were not normally distributed, non-parametric Kruskal-Wallis H test was performed. A two-way univariate ANOVA with as between factors group (smokers, non-smokers and smoking cessation) and sex was used. If a significant group effect, or a group * sex interaction was found, a Dunnet post-hoc test with as standard group the smokers was performed to locate the significant differences. For the blood parameters, comparisons between smokers and non-smokers, and comparison of smokers before and after cessation were performed with unpaired student t-tests. Differences were considered significant at $p<0.05$. All data are presented as mean±SD.

3.4 Results:

Anthropometric details of the participants are presented in Table 3.1. The smoking women in our study had smoked longer and had smoked more pack years than the smoking men ($p<0.05$; Table 3.1). For none of the parameters group * sex interactions were found, indicating that there were no significant differences in the responses to smoking and smoking cessation between men and women.

The total protein, albumin and glucose concentrations did not differ significantly between smokers and non-smokers (Table 3.2). Smokers had higher levels of COHb than non-

smokers ($p<0.001$) and the COHb levels had returned to levels similar to that in non-smokers after 14 days of smoking cessation (Table 3.3).

3.4.1 Spirometry

PEF, FEV_1 and FVC were higher in men than women ($p<0.001$), but FEV_1/FVC, $FEV_{1pred\%}$, $FVC_{pred\%}$ and $PEF_{pred\%}$ did not differ significantly between men and women (Table 3.4). There was no significant difference in FEV_1, $FEV_{1pred\%}$, $FVC_{pred\%}$ and $PEF_{pred\%}$ between smokers and non-smokers (Table 3.4), but PEF ($p=0.004$; Table 3.4) and FEV_1/FVC ($p=0.037$; Figure 3.2) were lower in smokers than in non-smokers. Neither changed significantly over the 14 days of smoking cessation ($p>0.05$; Figure 3.4 and Table 3.4).

3.4.2 Muscle function

Knee extension MVC was higher in men than women ($p<0.001$; Table 3.4) and FI was higher in women than men ($p<0.001$), but there were no significant sex differences in VA ($p=0.096$; Table 3.4). There was no significant difference in MVC and VA between smokers and non-smokers (Table 3.4). While there was no significant difference in FI between smokers and non-smokers, smoking cessation resulted in an increased FI ($p\leq0.036$; Figure 3.3a-b). An example of the torque reduction during a series of electrically evoked isometric contractions is shown in figure (3.4).

3.4.3 Haematology

There were no significant differences in total white blood cell, neutrophil, lymphocyte, monocyte and basophil counts between smokers and non-smokers (Table 3.3). The eosinophil count was lower in smokers than non-smokers ($p<0.05$) even after 14 days

smoking cessation (Table 3.3). Smokers had a higher haemoglobin concentration and haematocrit than non-smokers ($p<0.001$) and was not changed significantly after 14 days of smoking cessation (Table 3.3).

3.4.4 Circulating markers of oxidative stress

The total antioxidant status was lower in smokers than non-smokers ($p<0.001$) and was not significantly changed after 14 days of smoking cessation (Figure 3.5a). Lipid peroxidation, in the form of the concentration of MDA was higher in smokers compared to non-smokers ($p<0.001$) and were not significantly changed after 14 days of smoking cessation (Figure 3.5b). Although the low molecular weight AGE levels did not differ significantly between smokers and non-smokers (Figure 3.5c), the total AGE levels were higher in smokers compared to non-smokers ($p<0.05$; Figure 3.5d). Smoking cessation did not have a significantly alter the concentration of AGEs (Figures 3.5c and 3.5d).

3.4.5 Circulating levels of cytokines

Smokers had higher circulating levels of TNF-α, IL-2, IL-4, IL-6 and IL-10 levels than non-smokers (All $p<0.001$; Figures 3.6a-e), while IL-12p70 levels were lower in smokers than in non-smokers ($p<0.001$; Figure 3.6f). Almost all circulating cytokines concentrations returned to levels seen in non-smokers after 14 days of smoking cessation, except for TNF-α and IL-2 that though reduced, where still elevated in comparison to non-smokers ($p<0.05$; Figures 3.6a and 3.6b). TNF-β, IFN-γ, IL-1β, IL-5 did not differ significantly between smokers and non-smokers (Table 3.5).

Table 3.1: Demographic data. All data are presented as mean±SD; BMI: body mass index; *: significantly different from men at p<0.05

	Cigarette smokers		Non-smokers	
	Men (n=28)	**Women (n=20)**	**Men (n=23)**	**Women (n=15)**
Age (Years)	25.4±6.0	31.0±12.8*	26.3±10.5	24.8±7.4
Height (m)	1.78±0.09	1.65±0.09*	1.79±0.07	1.65±0.06*
Mass (kg)	77.5±17.7	67.9±11.4*	77.3±11.6	68.2±14.2*
BMI (kg/m^2)	24.2±4.5	25.1±4.0	24.1±3.1	24.8±4.3
Smoking duration (years)	7.4±4.3	13.7±12.2*	-	-
Cigarettes per day	12.3±6.0	12.7±5.7	-	-
Smokers pack-years	4.6±2.9	9.6±11.0*	-	-

Table 3.2: Smoking or smoking cessation did not alter total protein, albumin and glucose serum concentration. All data are presented as mean±SD; C: Non-smokers; S: smokers; SC: 14 days smoking cessation; NS: not significant.

Serum concentrations	**Non-smokers** **n=9**	**Smokers** **n=20**	**Stop smoking** **n=20**	Statistical evaluation (p-value)		
				S *vs.* C	S *vs.* SC	SC *vs.* C
Total protein (g/L)	65.4±2.3	66.0±3.5	64.5±2.7	NS	NS	NS
Albumin (g/L)	43.4±2.8	45.7±2.4	44.7±2.3	NS	NS	NS
Glucose (mmol/L)	5.14±0.75	5.10±0.34	5.33±1.03	NS	NS	NS

Table 3.3: The impact of smoking and smoking cessation on white blood cell counts, haematocrit, haemoglobin and carboxyhaemoglobin. All data are presented as mean±SD; WBC: White blood cells; Hct: Haematocrit; COHb: Carboxyhaemoglobin; C: Non-smokers; S: smokers; SC: 14 days smoking cessation; NS: not significant.

Parameters	**Non-smokers** **n=9**	**Smokers** **n=20**	**Stop smoking** **n=20**	Statistical evaluation (p-value)		
				S *vs.* C	S *vs.* SC	SC *vs.* C
WBC (10^9/L)	6.70±2.16	6.98±1.97	6.89±1.70	NS	NS	NS
		Granulocytes				
Neutrophil (%)	54.6±4.80	60.3±12.1	58.9±8.50	NS	NS	NS
Eosinophil (%)	3.44±0.87	2.24±1.03	2.25±0.98	<0.05	NS	<0.05
Basophil (%)	1.67±0.87	1.17±0.94	1.42±0.85	NS	NS	NS
		Agranulocytes				
Lymphocyte (%)	34.3±3.60	30.5±11.18	32.2±8.05	NS	NS	NS
Monocyte (%)	6.0±1.23	5.58±1.39	5.58±1.30	NS	NS	NS
		Haematocrit, haemoglobin and carboxyhaemoglobin				

Hct (%)	41.0±4.6	46.5±2.6	45.6±2.6	<0.001	NS	<0.01
Haemoglobin (g/dL)	13.7±1.80	15.5±0.89	15.3±0.89	<0.001	NS	<0.01
COHb (%)	0.07±0.03	2.26±1.08	0.1±0.28	<0.001	<0.001	NS

Table 3.4: The effect of smoking and smoking cessation on spirometry, maximal isometric voluntary knee extension torque (KE MVC) and voluntary activation (VA). All data are presented as mean±SD; FEV_1: Forced expiratory volume in one second; FVC: Forced vital capacity; PEF: Peak expiratory flow; PEF_{pred} (%): PEF predicted percentage; (x) denotes number of participants. Significant effects are denoted in bold; NS: not significant

Group	**Sex**	**FEV_1 (L)**	**FEV_{1pred} (%)**	**FVC (L)**	**FVC_{pred} (%)**	**PEF (L/s)**	**PEF_{pred}** (%)	**KE MVC (Nm)**	**VA (%)**
Non-smokers	M	4.4±0.7 (19)	95.9±8.9 (19)	5.20±0.85 (19)	93.4±8.9 (19)	9.90±1.5 (19)	97.9±13.4 (19)	257±66 (14)	94.1±6.8 (14)
Non-smokers	W	3.3±0.4 (14)	98.1±10.9 (14)	3.89±0.50 (14)	98.1±9.6 (14)	7.3±1.2 (14)	98.6±12.5 (14)	175±24 (8)	92.7±13.1 (8)
Smokers	M	4.2±0.7 (21)	92.7±11.8 (21)	5.09±0.8 (21)	93.6±10.1 (21)	9.00±1.5 (21)	90.0±14.1 (21)	238±62 (21)	85.3±14.2 (20)
Stop smoking		4.1±0.8 (7)	90.0±15.7 (7)	5.03±1.0 (7)	90.3±13.1 (7)	9.80±1.9 (7)	95.6±19.8 (7)	270±51 (13)	95.4±4.9 (13)
Smokers	W	3.0±0.4 (19)	92.0±11.0 (19)	3.61±0.4 (19)	93.2±9.2 (19)	6.30±1.2 (19)	89.6±16.0 (19)	149±37 (13)	94.8±7.3 (13)
Stop smoking		2.9±0.5 (8)	91.4±12.6 (8)	3.49±0.4 (8)	91.6±12.6 (8)	6.50±1.1 (8)	90.1±18.2 (8)	150±33 (9)	95.8±4.9 (9)
					P-value				
Smoke		NS	NS	NS	NS	**0.004**	NS	NS	NS
Sex		**<0.001**	NS	**<0.001**	NS	**<0.001**	NS	**<0.001**	NS

Table 3.5: The impact of smoking and smoking cessation on circulating cytokines. All data are presented as mean±SD; TNF-β: tumour necrosis factor-beta; INF-γ: interferon-gamma; IL-1β: interlukin-1beta; IL-5: interleukin-5; C: Non-smokers; S: smokers; SC: 14 days smoking cessation; NS: not significant.

Cytokines (pg/mL)	**Non-smokers** **n=9**	**Smokers** **n=20**	**Stop smoking** **n=20**	Statistical evaluation (p-value)		
				S *vs.* C	S *vs.* SC	SC *vs.* C
TNF-β	82.9±31.2	109.0±34.0	109.1±46.8	NS	NS	NS
IFN-γ	139±82	144±57	161±55	NS	NS	NS
IL-1β	100.4±53.0	109.4±38.4	94.1±41.3	NS	NS	NS
IL-5	109±89	125±57	132±30	NS	NS	NS

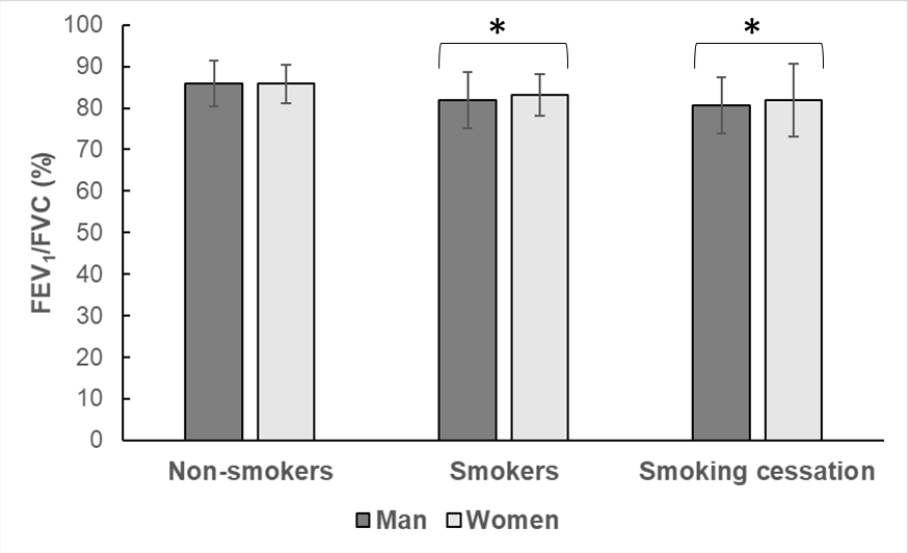

Figure 3.2: The effect of smoking and 14 days smoking cessation on FEV_1/FVC: Forced expiratory volume in one second/forced vital capacity; data are mean±SD; *: significantly different from Non-smokers at $p<0.05$.

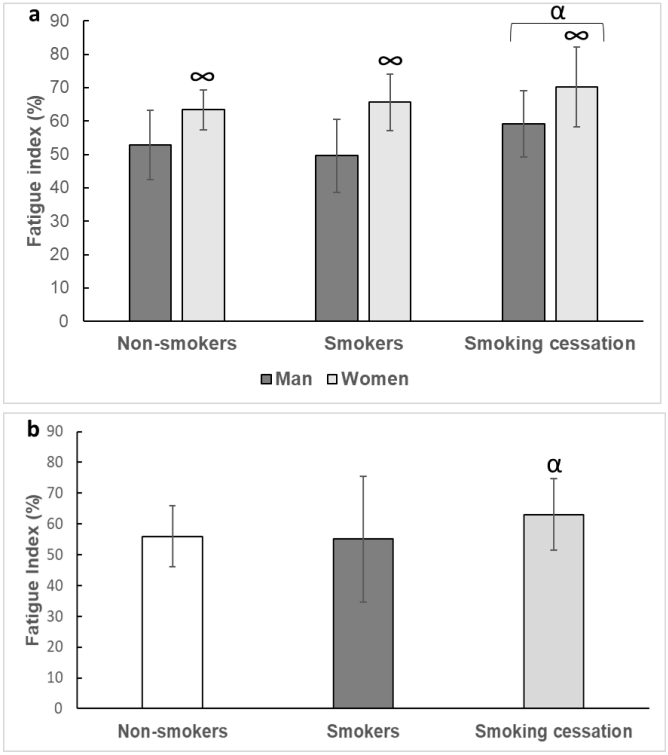

Figure 3.3: The effect of smoking and 14 days smoking cessation on fatigue index. Data are mean±SD; ∞: significantly different from men at $p<0.05$; α: significantly different from smokers at $p<0.05$.

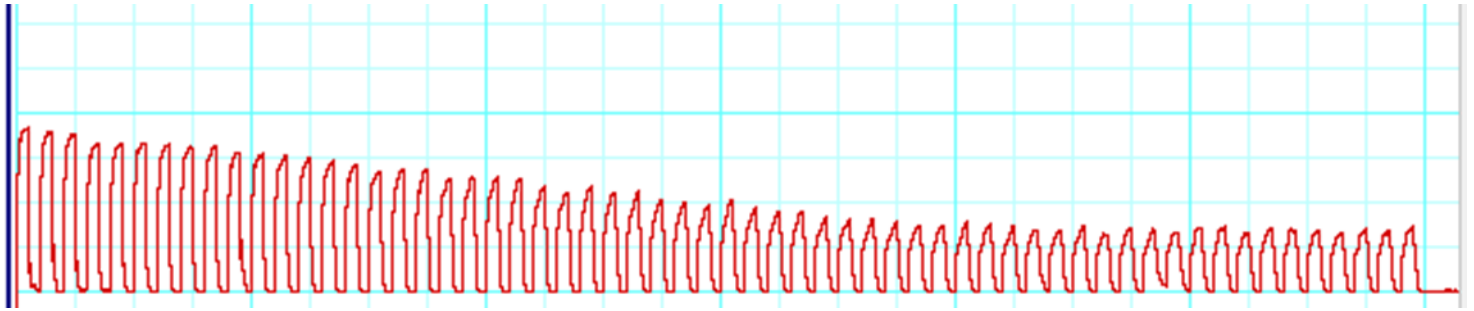

Figure 3.4: Example of the torque reduction during a series of electrically evoked isometric contractions. The torque at 2 min (last contraction) divided by the peak torque during the first contraction is given as the fatigue index, where a higher value indicates a higher fatigue resistance.

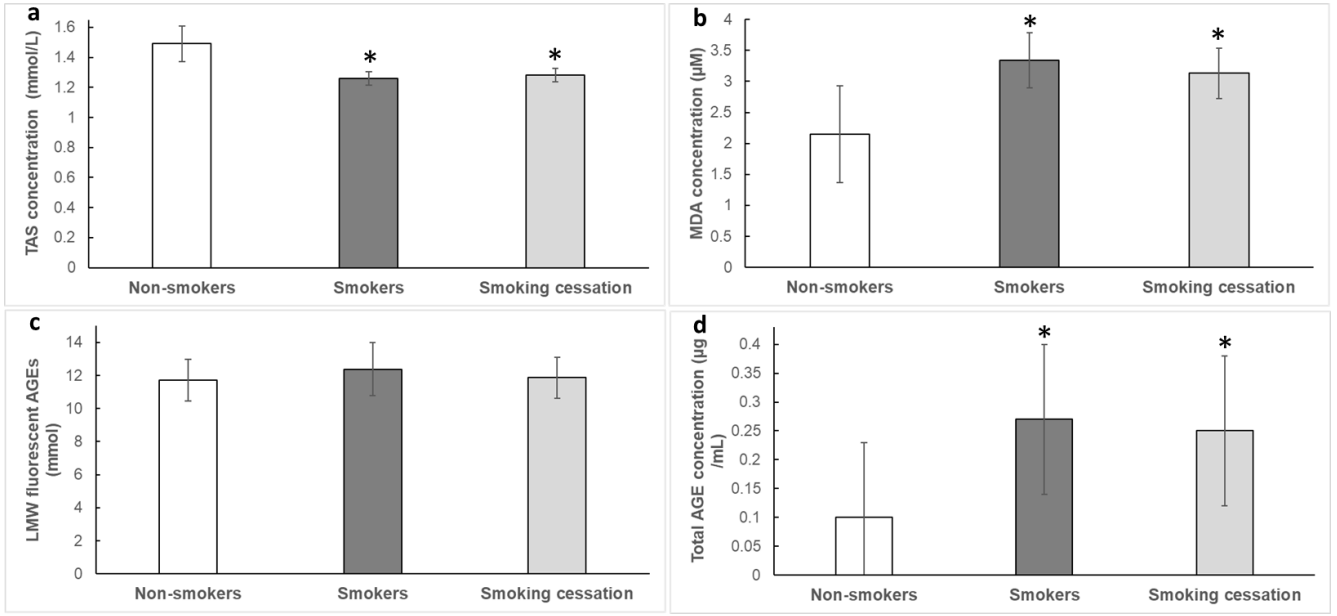

Figure 3.5: Effects of smoking and 14 days smoking cessation. **a)** Total antioxidant status (TAS); **b)** Malondialdehyde concentration; **c)** Low molecular weight (LMW) advanced glycation end products (AGEs) fluorescence; **d)** AGEs concentration; data are mean±SD; *: significantly different from Non-smokers at

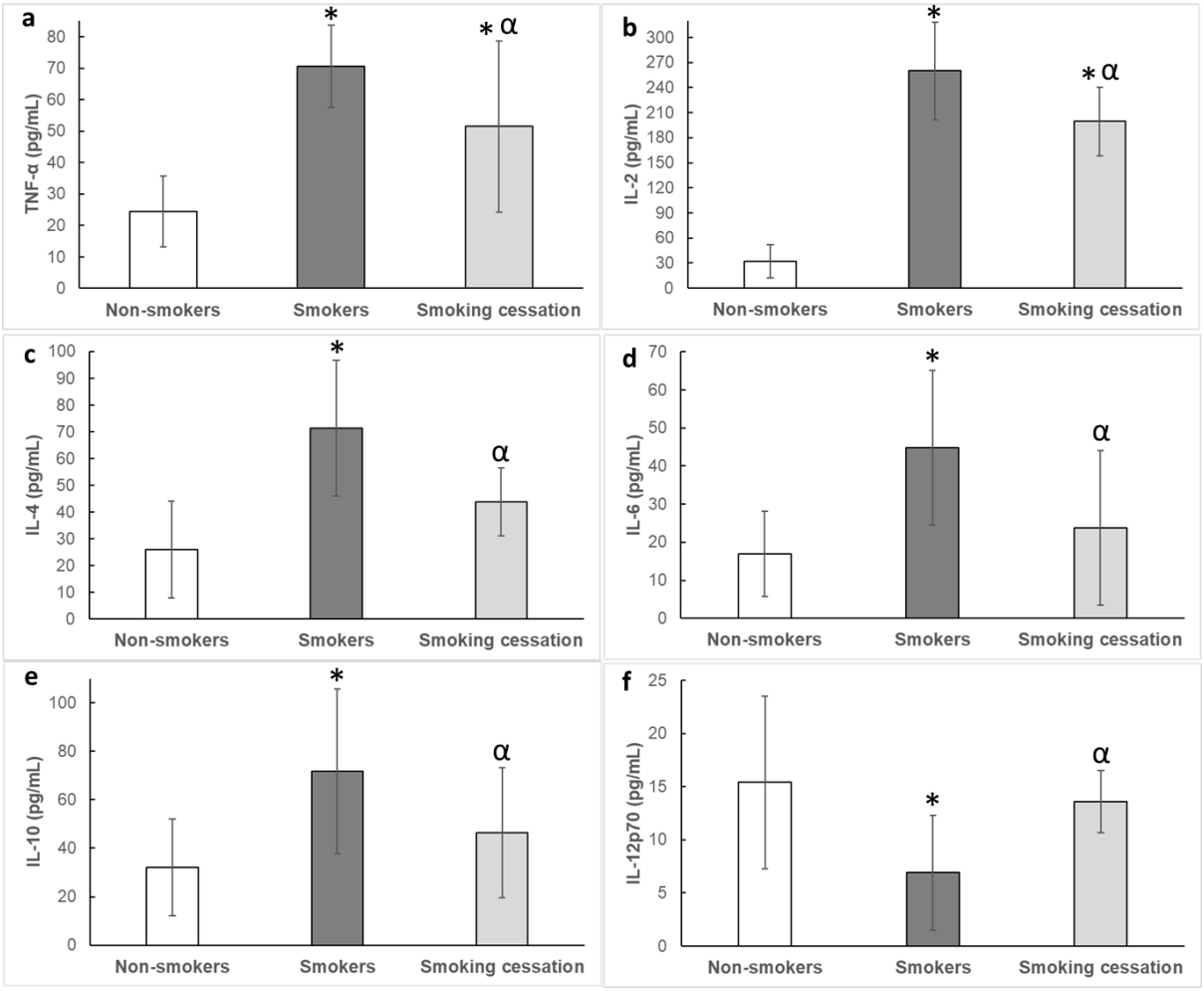

Figure 3.6: Effects of smoking and 14 days smoking cessation .**a)** TNF-α: tumour necrosis factor-alpha; **b)** IL-2: interleukin-2; **c)** IL-4: interleukin-4; **d)** IL-6: interleukin-6; **e)** IL-10: Interleukin-10; **f)** IL-12p70: interleukin-12p70; data are presented as mean±SD; *: significantly different from Non-smokers at $p<0.05$; α: significantly different from smokers at $p<0.05$.

3.5 Discussion

To our knowledge, the current study is the first to assess the effects of 14 days of smoking cessation on lung function, muscle function, inflammatory markers and cytokines in healthy smokers. The main observation of the present study was that in smokers with normal spirometry 14 days of smoking cessation resulted in a normalisation of skeletal muscle fatigue resistance and a return of circulating markers of inflammation. This indicates that as little as 14 days of smoking cessation can confer measurable benefits that may encourage smokers in their smoking cessation efforts.

3.5.1 Differences between smokers and non-smokers

3.5.1.1 Spirometry

The present study confirms that FEV_1, FVC and PEF were higher in men than women (Crapo et al., 1981). The spirometry in smokers was similar to that of non-smokers, except for a lower FEV_1/FVC, indicative of some minor developing airway obstruction.

3.5.1.2 Muscle function

In line with previous observations (Larsson and Örlander, 1984; Morse et al., 2007; Wüst et al., 2008c), we found that the maximal strength of the knee extensor muscles in smokers was similar to that in non-smokers. Others, however, have reported a lower force generating capacity in smokers (Al-Obaidi et al., 2004; Barreiro et al., 2010; Örlander et al., 1979; Seymour et al., 2010). Although part of a lower strength may at least in theory be attributable to a lower ability to voluntarily activate the muscle, we found no difference in voluntary activation between smokers and non-smokers, and if anything, even an increased VA has been reported in smokers (Wüst et al., 2008c). The latter may be the result of an increased sympathetic nerve activity in smokers, possibly

due to a central stimulant action of nicotine (Mündel and Jones, 2006; Narkiewicz et al., 1998). Whatever the cause of the discrepancy between studies concerning the impact of smoking on the MVC, it indicates that smoking *per se* is not necessarily associated with muscle weakness.

Somewhat unexpected was the absence of lower fatigue resistance in smokers that was seen in previous studies using the same fatigue protocol (Morse et al., 2007; Wüst et al., 2008c). This reduced fatigue resistance in the previous smokers was thought to be at least partly attributable to elevated COHb levels, seen also in the current and other studies (Pojer et al., 1984; Wald et al., 1981) that not only reduces the oxygen carrying capacity, but also the release of oxygen due to the left-shift of the Hb-dissociation curve (Degens et al., 2015; Morse et al., 2008). It should be noted, however, that 6% COHb reduced skeletal muscle fatigue resistance (Morse et al., 2008) and the 3% COHb in our participants may not have had a measurable impact on the oxygen delivery to the skeletal muscle, and hence the fatigue resistance.

3.5.1.3 Blood parameters

While we did not see a significant difference in the albumin and total protein concentrations in the blood of smokers and non-smokers, others did see that smokers had a lower total protein and albumin concentration compared to non-smokers (Alsalhen and Abdalsalam, 2014) or even a higher protein concentration (Alhemieri, 2008). Consistent with previous studies (Malenica et al., 2017; Nordenberg et al., 1990; Shah et al., 2012), the haemoglobin concentration and haematocrit were higher in smokers compared to non-smokers. The higher haemoglobin concentration may well be an

adaptation to maintain the oxygen carrying capacity in the face of elevated COHb levels (Aitchison and Russell, 1988; Roethig et al., 2010).

Although there were no significant differences in monocytes and lymphocytes between smokers and non-smokers in the current and previous studies (Malenica et al., 2017; Tulgar et al., 2016), except for a reduction in the number of eosinophils, we observed a significant increase in TNF-α, IL-2, IL-4, IL-6 and IL-10. This suggests that smoking activates mononuclear cells to release cytokines. In line with this, it has been observed that cigarette smoke induces the release of TNF-α in an *in vitro* macrophage model system (Demirjian et al., 2006), but others found no increased release of TNF-α peripheral blood mononuclear cells to cigarette smoke extracts (Ouyang et al., 2000). It should be noted, however, that TNF-α is not only produced by blood mononuclear cells, but also by epithelial cells, fibroblasts and smooth muscle cells (Brenner and Miller, 2014, p.229) and perhaps mononuclear and epithelial cells in the lung of smokers (Lee et al., 2012). In line with this, it has been observed that there was a significantly elevated number of macrophages and neutrophils in the broncheo-alveolar lavage fluid of smoking mice (Ajime et al., 2021). Therefore, lung-derived cytokines may well be the prime explanation of the higher TNF-α, IL-2, IL-4, IL-6 and IL-10 concentrations and the lower level of the anti-inflammatory IL-12p70 concentration in smokers than non-smokers, indicating that even young-adult asymptomatic smokers suffer from a low-grade systemic inflammation.

It is possible that the lower TAS and higher MDA levels in smokers, also reported by others (Mahmood et al., 2007), may be due to this low-grade systemic inflammation. The oxidative stress in smokers may well have contributed to their elevated AGE levels (Cerami et al., 1997; Moldogazieva et al., 2019; Vlassara and Palace, 2002). Although AGEs are often considered to represent indirectly a high level of glucose (Goldin et al., 2006; Singh et al., 2014), we and others (Alhemieri, 2008) did not find elevated glucose

levels in smokers. It should be noted that not only high glucose concentrations, but also toxic constituents of cigarette smoke might induce glycotoxins that rapidly react with protein to form AGEs (Cerami et al., 1997). Therefore, we suggest that the increased AGEs in asymptomatic young-adult smokers is primarily attributable to glycotoxins, oxidative stress, and to some extent secondary to the low-grade systemic inflammation.

3.5.2 Smoking cessation

3.5.2.1 Spirometry

The present study showed that 14 days of smoking cessation did not result in an improvement in the smoking-induced decrement of FEV_1/FVC. This is supported by numerous studies suggesting that pulmonary changes induced by smoking are irreversible, even though smoking cessation is the best approach to stop the accelerated decline in lung function in smokers (Aparici et al., 1993; Buist et al., 1979; Burchfiel et al., 1995; Fletcher and Peto, 1977; Lange et al., 1989; Pezzuto et al., 2013).

3.5.2.2 Muscle function

In support of our hypothesis, we found an improved skeletal muscle fatigue resistance after 14 days of smoking cessation that was accompanied with a return of the COHb levels to that seen in non-smokers. It therefore does appear that the improved fatigue resistance after smoking cessation was at least to some extent attributable to an improved oxygen delivery, and perhaps also improved mitochondrial function. Indeed, 2 weeks smoking cessation has been shown to improve mitochondrial function in mouse muscle, although in mice this was not accompanied by an improved muscle fatigue resistance (Ajime et al., 2021). Nevertheless, our data suggest that even in smokers with only 3% COHb smoking cessation can still enhance muscle fatigue resistance, even when

the fatigue resistance was not significantly less than that in non-smokers. Perhaps the enhanced fatigue resistance after smoking cessation is to some extent also attributable to the elevated haemoglobin concentration and haematocrit that enhance the oxygen carrying capacity and oxygen delivery with smoking cessation even above that seen in the non-smokers (Aitchison and Russell, 1988; Degens et al., 2015), similar to that seen after doping with erythropoietin (Rasmussen et al., 2010). In addition, smoking cessation also improves exercise-induced vasodilation (Celermajer et al., 1993; Johnson et al., 2010). Overall, our data indicate that even smoking cessation for as short a period as 2 weeks can result in measurable improvements in muscle fatigue resistance.

3.5.2.3 Blood parameters

Another significant observation in our smokers was evidence of low-grade systemic inflammation and oxidative stress. It was therefore particularly interesting to assess the impact of smoking cessation on these parameters. Here we found that most of the abnormal blood parameters were normalised by 14 days of smoking cessation.

The present study showed that both TAS and MDA did not return to normal levels after 14 days of smoking cessation. This may occur later as it has been shown that after 28 days of smoking cessation, TAS was increased and MDA levels reduced back to normal levels (Polidori et al., 2003). AGE levels also did not show a significant decrement after 14 days of smoking cessation. The 3-week half-life of AGEs (Ahmed et al., 2002; Biemel et al., 2002; Klöpfer et al., 2011) may explain that despite the diminished low-grade systemic inflammation AGEs remained elevated. Therefore, 14 days of smoking cessation might not be long enough to cause a normalisation in TAS, MDA and AGEs to levels similar to that in non-smokers.

Smoking cessation interrupts the exposure to chemicals in cigarette smoke (Rodrigues et al., 2014) and it is likely that the reduced concentration of smoking-related chemicals in the blood that induce inflammation will result in a reduction in cytokine levels (Helmersson et al., 2005; McCarty, 1999; Mio et al., 1997). For example, the elevated levels of TNF-α after 20 weeks smoking was back to baseline levels after 8 weeks smoking cessation in the broncho-alveolar lavage fluid of mice (Braber et al., 2010) and similarly 30 days smoking cessation resulted in a significant reduction in TNF-α in humans (Rodrigues et al., 2014). Here we showed that IL-6, IL-10, IL-12p70, IL-4 returned to normal levels and TNF-α was reduced after 14 days of smoking cessation. It has been suggested that the lungs are the primary cause of the low-grade systemic inflammation in patients with chronic obstructive pulmonary disease (Gan et al., 2004). In line with this it has been shown that 2 weeks smoking cessation in mice led to a return in the number of leucocytes in the broncheo-alveolar lavage fluid to normal levels (Ajime et al., 2021). Eosinophil numbers remained lower in smokers than non-smokers after 14 days of smoking cessation, which may be secondary to the higher concentration of IL-2 in smokers, even after 14 days of smoking cessation.

3.5.3 Future directions

We showed significant improvements in muscle fatigue resistance and inflammatory status that may well be sufficient to stimulate smokers in their attempts to quit smoking. Future studies are recommended to conduct longer duration of smoking cessation programmes with larger sample size to assess whether also the markers of oxidative stress and circulating AGEs return to normal values. Although it remains to be seen to what extent the effects observed are related to the duration of smoking, in our previous work we have shown that at least the lower fatigue resistance in smokers was not related

to the duration of smoking or smoking pack years. It remains to be seen what the clinical significance of these changes is may be.

3.6 Conclusion

Even in smokers with normal spirometry there is significant evidence of oxidative stress and systemic inflammation. A short period of smoking cessation of just 2 weeks is enough to improve the inflammatory status to almost back to normal levels and induce an improvement in muscle fatigue resistance. These benefits will undoubtedly stop the progression of detrimental effects of low-grade systemic inflammation and encourage smokers in their attempts to quit smoking.

Chapter 4 : Does aerobic exercise facilitate vaping and smoking cessation: a systematic review of randomized controlled trials with Meta-Analysis

Part of this chapter is under peer-review for publication as

Darabseh, M. Z., Selfe, J., Morse, C. I., Aburub, A., Degens, H. 2021. Does aerobic exercise facilitate vaping and smoking cessation: a systematic review of randomized controlled trials with Meta-Analysis. Rehabilitation Research and Practice.

4.1 Abstract

Background: Smoking is a well-known health risk for many chronic diseases including cardiovascular diseases and respiratory disorders. Smokers try to quit using several strategies including electronic cigarette use (vaping). An alternative, easy and cheap method is exercise. However, little is known about the efficacy of aerobic exercise to augment vaping cessation (quit vaping) and smoking cessation.

Objective: To systematically review and discuss the reported effects of aerobic exercise on long-term vaping and smoking cessation in randomized control trials.

Methods: This review was registered on the PROSPERO database. Randomized control trials on MEDLINE, AMED, SPORTDiscus, CINHAL and PEDro databases were searched from 1st January 1970 to 1st January 2021. The primary outcome was long-term vaping cessation or smoking cessation (≥ 6months). Secondary outcome measures included maximal or peak oxygen uptake ($VO_{2max/peak}$) after vaping- or smoking cessation. Meta-analysis was conducted to examine the effects of aerobic exercise on long-term vaping cessation and smoking cessation, and the effects of aerobic exercise on $VO_{2max/peak}$. Cochrane Risk of Bias tool 2 was used to assess trial quality.

Results: Thirteen trials were included in this review (5 high, 2 moderate and 6 low quality). Although two high quality trials revealed that 3 vigorous supervised aerobic exercise sessions a week for 12 to 15 weeks increased the number of long-term successful quitters, the meta-analysis including the other trials showed that aerobic exercise did not significantly increase success rate of long-term quitters. However, $VO_{2max/peak}$ was improved at the end of treatment. There were no trials on aerobic exercise and vaping cessation.

Conclusion: No evidence was found that aerobic exercise promotes long-term smoking cessation. Nevertheless, aerobic exercise improved VO_{2max} and/ or VO_{2peak} in quitters.

Keywords: Aerobic exercise, Smoking, Smoking cessation, Vaping, Vaping cessation, Systematic review and Meta-Analysis

4.2 Background

Smoking is considered the main risk factor for the development of preventable diseases such as cancers, cardiovascular diseases and respiratory disorders, including chronic obstructive pulmonary disease (COPD), and globally seven million deaths per year are attributable to smoking (World Health Organization, 2017). Smoking cessation (SC) reduces the risk of hospitalization due to chronic conditions, such as COPD, and is associated with significant life extensions (Taylor Jr et al., 2002; Tran et al., 2015). As the annual death rate attributable to smoking is expected to increase within the next decades, the World Health Organization started calling upon governments and health institutes to develop anti-smoking regulations and interventions to further promote SC (World Health Organization, 2017).

Although approximately 40% of smokers make at least one quit attempt annually (Control and Prevention, 2008), only fewer than 5% succeed (Etter et al., 1997). Electronic-cigarette use (vaping) is promoted as a harmless and safe alternative to cigarette smoking (Dutra et al., 2017) and uptake of vaping has been reported to be associated with higher rates of SC (Rahman et al., 2015; Tackett et al., 2015). Vaping may, however, not be as harmless as originally thought and has been reported to cause similar detrimental effects on lung and cardiovascular function as smoking (Darabseh et al., 2020). Such harmful effects may well contribute to the reportedly 33% of vapers that are willing to visit a vaping cessation (quit vaping) service if available in their neighbourhood (Etter, 2019).

Beside vaping, SC interventions vary from pharmacotherapies including nicotine replacement therapy and SC counselling (Lemmens et al., 2008) to meditation and yoga

programmes (Bock et al., 2012). However, the success of these interventions is influenced by many factors such as the dose, type and duration of medication, intervention or counselling, motivational skills of SC advisors, follow-up periods, smokers' adherence, duration of smoking and number of cigarettes one used to smoke per day. Indeed, the long-term effectiveness of these interventions remains ambiguous (Ahluwalia et al., 2002; Aubin et al., 2008; Cooper et al., 2005; Gariti et al., 2009) and it is essential to keep looking for other interventions and assess their effectiveness.

One such potential alternative SC intervention is aerobic exercise. Exercise interventions are categorised as e.g. aerobic, strengthening or relaxation exercises. As vaping and smoking particularly affect the cardiovascular and respiratory systems we consider here the impact of aerobic exercise training on the success of vaping cessation (quit smoking) and smoking cessation. Aerobic exercise refers to exercise where the ATP demands can be met by aerobic metabolism alone (Kisner et al., 2017).

When people quit smoking, they might suffer from anxiety, depression and low mood (West and Hajek, 1997), factors that may be alleviated by aerobic exercise and thereby contributing to the often-reported exercise-induced improvement in the quality of life (Dunn et al., 2005; Legrand and Heuze, 2007; Norris et al., 1990; Senkfor and Williams, 1995; Steptoe and Cox, 1988). Perhaps even more important is that aerobic exercise, such as walking, cycling or running, is easy to access and cheap and therefore a viable intervention to facilitate SC, particularly via the reduction of nicotine withdrawal symptoms and cigarette craving (Roberts et al., 2012; Taylor et al., 2007).

The mechanism by which aerobic exercise may enhance SC is not fully clear, but a number of mechanisms have been postulated, including raised endorphins, distraction and increased self-efficacy. It is known for example, that aerobic exercise induces an increase

in plasma β-endorphins (De Meirleir et al., 1986) that is dependent on the intensity and duration of the exercise performed (Goldfarb et al., 1990). The exercise-induced rise in β-endorphin levels may be significant as it has been found that higher levels were associated with fewer smoking relapses after cessation (Shaw and al'Absi, 2008). Additional mechanisms whereby aerobic exercise may facilitate SC are 1) increased proprioceptive input due to larger and more frequent movements that could distract smokers from cigarette craving (Wai et al., 2011) and 2) improved image self-efficacy (Loprinzi et al., 2015). Despite these potential mechanisms, the long-term benefits of exercise for smoking- and vaping- cessation are not clear.

When prescribing or describing exercise interventions, it is important to consider the frequency, intensity, time and type (FITT) of exercise (Brown et al., 1978; Franklin et al., 2003; Sasso et al., 2015). The benefits of exercise training for vaping cessation and smoking cessation may well depend on the duration, intensity and frequency of exercise training. As it is unclear whether aerobic exercise facilitates SC, a systematic review evaluating the effects of different exercise prescriptions (including the FITT principle) for vaping- and smoking cessation is warranted. Therefore, the aim of this review is to assess the effectiveness of aerobic exercise interventions on long-term vaping cessation and SC, and maximal and/or peak oxygen uptake. Where feasible this will be evaluated with meta-analyses.

4.3 Method

4.3.1 Purpose

The main question of this study is: Does aerobic exercise helps to quit smoking and vaping? To answer this question, the objectives of the study were to review and discuss

the reported effects of aerobic exercise on long-term vaping cessation and smoking cessation, and to conduct a meta-analysis for the included trials.

4.3.2 Design

The study was designed to provide a systematic review with quality assessment, narrative synthesis, and meta-analysis of relevant published literature.

4.3.3 Study protocol

The protocol of this systematic review is registered in the International prospective register of systematic reviews database (PROSPERO) (registration number: CRD42021232759; 02 February 2021; URL: https://www.crd.york.ac.uk/prospero/display_record.php?RecordID=232759)

4.3.4 Search strategy

The following electronic databases were searched for trials published between 1st January 1970 to 1st January 2021: EBSCO host database including MEDLINE, AMED, SPORTDiscus and CINHAL; and PEDro. These databases were chosen because of the likely availability of exercise-related trials in these databases. Reference lists of included trials were hand searched to identify other potentially relevant trials. Trials included were limited to those written in English and published in peer-reviewed journals. Results of the searches were managed using Endnote Version X7 (Clarivate Analytics, Philadelphia, PA).

4.3.5 Keywords

Search terms were adapted to meet the search requirements of each electronic database. The keywords used were structured according to the PICOS approach (population, intervention, comparison, outcome measures and study design) (Schardt et al., 2007). Table 4.1 summarizes the combinations of keywords included in the search strategies. PICOS search terms were combined using Boolean operators 'AND' and 'OR'. The search was limited to randomised controlled trials (RCTs). To allow reproducibility of the search, the Medical Subject Headings (MeSH) were used.

Table 4.1: *Keywords and search strategy used, using the PICOS approach in the selected databases.*

	Population	**Intervention**	**Comparison**	**Outcome measures**	**Study design**
Search number and keywords	S1= "smokers" "quit" OR "quitters" OR "smoking cessation" OR "stop smoking" OR "abstainers" OR "vape" OR "vaping" OR "e-cigarette" OR "e-cig" OR "electronic cigarette" OR "vapers" OR "e-cigarette users" OR "electronic cigarette users"	S2= "cardiovascular exercise" OR "aerobic exercise" OR "aerobic training" OR "physical activity" OR "exercise" OR "physical exercise"	Interventions that include no aerobic exercise or structured changes in physical activity that are designed to support vaping cessation or smoking cessation	S3= "maximal oxygen uptake" OR "Exercise capacity" OR "carbon monoxide" OR "CO" OR "thiocyanate" OR "cotinine" OR "continuous abstinence" OR "continuous cessation" OR "prolonged abstinence" OR "prolonged cessation" OR "cessation" OR	Search was limited to randomised controlled trials (RCTs) to make a meta-analysis possible

				"stopping" OR "quitting"	
Final search	Final search=S1 AND S2 AND S3				

4.3.6 Inclusion/exclusion criteria for the trials

Inclusion criteria:

Trials were included if:

- they included men & women >18 years old
- they assessed continued/prolonged vaping cessation/smoking cessation by means of objective measures such as carbon monoxide (CO), cotinine and/or thiocyanate level
- participants had been smoking ≥5 cigarettes per day for ≥6months or vaped for ≥6months and were not diagnosed with airways obstruction.
- the intervention was aerobic exercise, such as brisk walking, cycling, treadmill walking, running, stationary cycling, rowing, aerobic gym exercises, or any other type of exercise where the ATP demands can be met by aerobic metabolism (Kisner et al., 2017).

Exclusion criteria:

Trials were excluded if:

- the intervention was other than cardiovascular/aerobic exercise, or if the aerobic exercise was combined with another type of exercise
- the exercise type used was not identified
- the outcome measures did not include CO, cotinine and/or thiocyanate

- the period of vaping/smoking cessation was less than six months
- not written in English language
- participants were diagnosed with psychiatric illness that could affect their exercise adherence (for example: depression or anxiety)
- there were substance misuse problems (such as drugs and alcohol abuse)
- participants were pregnant
- participants suffered from any medical condition that might affect their exercise performance such as musculoskeletal or neurological conditions
- published protocols were presented but without published data/results, or if they were conference abstracts

4.3.7 Study Selection

The first reviewer (MD) retrieved all trials from initial database searches and imported these into Endnote software. Trials were screened for suitability by the first reviewer (MD) by consulting the title and abstract against the pre-defined eligibility criteria for potential full-text review. The second reviewer (AA) independently screened the trials by consulting titles and abstracts against the pre-defined eligibility criteria for potential full text review.

4.3.8 Risk of Bias and Quality Assessment of the Included trials

Risk of bias of included trials was assessed using the Cochrane Risk of Bias tool 2 (CROB 2). Two review authors independently assessed the risk of bias. The following were assessed using the CROB 2: (1) bias arising from the randomization process; (2) bias due

to deviations from intended interventions; (3) bias due to missing outcome data; (4) bias in measurement of the outcome; (5) bias in selection of the reported result.

Two review authors independently assessed the quality of the included trials using the PEDro Scale, a validated tool for assessment of quality of interventional trials specifically related to physiotherapy interventions (de Morton, 2009; Maher et al., 2003). The PEDro scale contains 11 items, and trials are awarded between 0 and 10 points, depending on the number of criteria they meet (the first item is not used to calculate the summary score). Trials with scores of four points or more are classified as “high-quality”, whereas trials with three points or fewer are classified as “low-quality” (de Morton, 2009; Maher et al., 2003). PEDro and CROB 2 scores for the trials were not used as inclusion or exclusion criteria, but as a basis for best-evidence synthesis and to determine the strengths and weaknesses of each trial.

4.3.9 Data Extraction

The following data were extracted from the included trials: author name(s); year of publication; sample size; age; intervention for each group; outcome measures; comparator group; duration of the follow-up period; number of participants at baseline; number of participants who remained abstained at the final follow-up period; intervention for each group, including exercise prescription component (frequency, intensity, time and type of exercise); the physiological effect of aerobic exercise on cessation (e.g. increases in maximal and/or peak oxygen uptake) after vaping/smoking cessation.

Extracted data were consulted and checked with the second reviewer (AA).

4.3.10 Outcome measures

The main outcome measure was the proportion of participants who successfully quit vaping or smoking for at least six months, verified by objective measures such as CO, cotinine and/or thiocyanate concertation at the last/longest period of assessment (follow up).

Where reported, the physiological effect of aerobic exercise was included in the review, e.g. increases in maximal and/or peak oxygen uptake ($VO_{2max/peak}$) after vaping/smoking cessation.

4.3.11 Measurement of treatment effect

The risk ratio (RR) was calculated as = (quitters in exercise group/total randomised to exercise group)/(quitters in control group/total randomised to control group), with a 95% confidence interval (CI). Where more than one exercise group was included, the sum of the participants in all exercise groups was compared with the sum of all participants in all control (non-exercise) groups.

Standardised mean differences and their 95% CI were calculated from the data generated by each included randomised controlled trial for VO_{2max} or VO_{2peak} results. Forest plots were used to present the effectiveness of exercise on vaping- and smoking cessation, and the effects of aerobic exercise on VO_{2max} or VO_{2peak}, using the OpenMetaAnalyst software.

Where statistical pooling was not possible, the findings were presented in narrative form.

4.3.12 Dealing with missing data

All data that were available in the included trials were included in the Meta-analysis with intention-to-treat.

4.3.13 Heterogeneity assessment

After pooling data from the trials, statistical heterogeneity was determined using the I^2 statistic (Higgins et al., 2003). I^2 <50% indicates low heterogeneity.

4.4 Results

4.4.1 Results of the search

The systematic search identified 527 articles, 85 of which were duplicates. After screening the titles and abstracts, 367 publications were considered not relevant. Of the 75 remaining trials, 62 were excluded: 10 were using combined exercises, or combined exercise and diet management; 3 included participants with diagnosed depression; 11 did not include objective smoking cessation measures (such as CO, cotinine, or thiocyanate); 28 did not include aerobic exercise or did not specify the type of exercise used; in 5 the follow up on the effects of aerobic exercise was <6 months; 3 aimed for smoking reduction not cessation; 1 only conducted exercise counselling but not exercise and 1 trial presented preliminary results for an already included full trial. Consequently, 13 trials were included. All the included trials included healthy smokers who were not diagnosed with airway obstruction, except one included trial participants with acute myocardial infarction (Taylor et al., 1988). Figure 4.1 shows the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow-chart for the included/excluded search records. Table 4.2 is the data extraction table for the included 13 trials. No disagreement was encountered between the first and second reviewer in study selection. Appendix 10 shows all the excluded records from the systematic search.

4.4.2 Risk of bias and quality assessment

Five trials were at low risk of bias (low risk of bias across all domains, or low risk of bias in four domains and one domain with “some concern”), six trials were at high risk of bias (high risk of bias in at least one domain), and the remaining two at unclear/some concern of risk of bias. A summary of the CROB2 results is shown in Figure 4.2.

The PEDro scale results revealed that the included trials were of high quality (total PEDro score >4 points), with most of the trials scoring 6 points. Only one trial scored 5 (Taylor et al., 1988), as groups were not similar at baseline. Three trials scored 7 (Bize et al., 2010; Marcus et al., 2005; Prapavessis et al., 2016), because allocation of participants was concealed. No disagreement was encountered between the first and second reviewer in terms of risk of bias assessment.

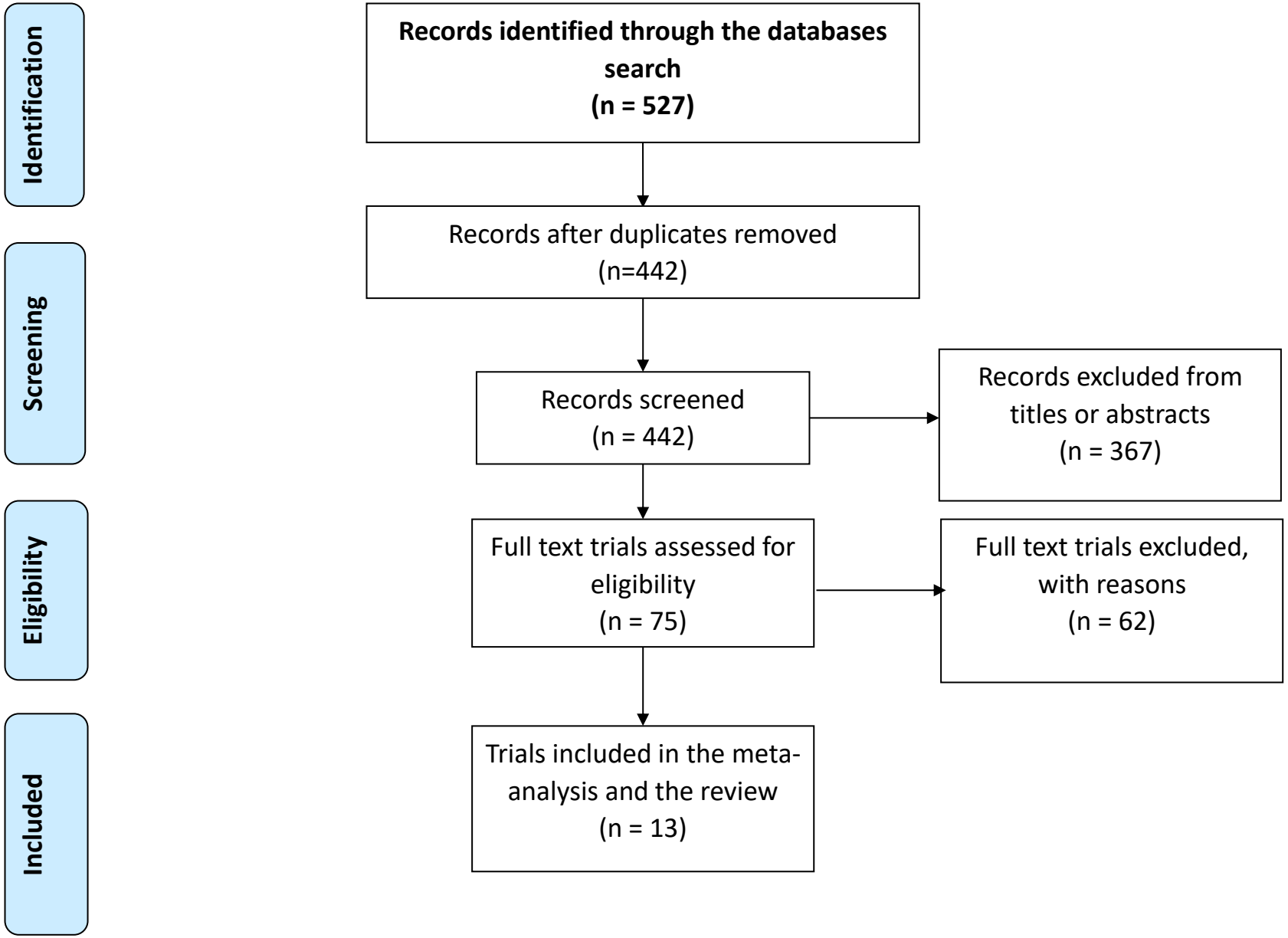

Figure 4.2: the PRISMA flow-chart for the search records and the included trials.

Table 4.2: Data extraction table for the included trials.

Author (year)	Sample size (n)	Age Mean (SD) in years	M:W (n)	Intervention/s (for each group) FITT (where possible)	Outcome measures	Key findings
Abrantes et al (2014)	61 (total) G1=30 G2 =31	Total= 47.3 G1=47.1 (8.5) G2=47.5 (10.7)	21:40	**G1**: 12-week group supervised exercise intervention (12 one session a week) + Telephone counselling SC intervention that included TNP (8 sessions, weekly, 20-min each) + exercise group counselling/discussion weekly (for 12 weeks, for 20 min) + unsupervised aerobic exercise sessions. Exercise began before quitting date **G2**: 12 weeks SC counselling sessions: (12 sessions, 1hr each) + Telephone counselling SC intervention that included TNP (8 sessions, weekly, 20 min each). **For exercise prescription:** **F:** Once a week exercise supervised session + two to four unsupervised exercise sessions a week. **I:** Moderate exercise (range of 55% - 69% of age-predicted HRmax).	Assessments occurred at baseline, 3(EOT), 6, and 12-month follow-ups. SC Self-reports verified by expired CO; utilizing 10 ppm cut-off at each assessment timepoint. VO_{2peak} treadmill test.	No significant difference in abstinence between groups (p=0.18). Participants in G1 had higher verified cessation rates (EOT: 30.0% in G1 vs. 25.8% in G2), and 12-month follow-up (13.3% in G1 vs. 3.2% in G2). VO_{2peak} was increased similarly in both groups: G1: baseline=27.8 (5.8) ml/kg/min, EOT=30.0 (5) ml/kg/min G2: Baseline=26.2 (9.6) ml/kg/min, EOT=27.3 (6) ml/kg/min. At EOT, adherence in both G1 and G2 was 9.3 ± 2.8 vs. 9.3 ± 3.0 out of the 12 sessions, respectively.

				T: Began at 20 min per session with weekly gradual increases, to 100 min midway through the intervention up to 150 min towards the ends of the intervention. **T:** Treadmill, stationary bicycles, walking, running, sports, cycling and housework		
Bize et al (2010)	481 (total) G1=229 G2=252	Total=42.2 (10.1) G1=42.2 (10.0) G2=42.5 (9.5)	272:209	**G1**: 9-week exercise group supervised intervention (9 sessions-once a week) + 15 min individual based SC intervention and counselling sessions weekly (for 9 weeks) including NRT products prescription such as TNP, gum, inhaler and lozenge + unsupervised exercise sessions. Exercise started 1 week before quitting date **G2**: 9-weeks SC individual based SC intervention weekly (9 sessions) for 15 min session including NRT products prescription such as TNP, gum, inhaler and lozenge + 9-weeks 60-minute supervised group sessions health education (discussions, lectures etc). **For exercise prescription:** **F:** One supervised exercise	Follow-up at 10, 26 and 52 weeks after the beginning of the SC programme SC Self-reports verified by expired CO; utilizing 10 ppm cut-off at each assessment time point. The intensity of exercise was monitored with the Borg Rating of Perceived Exertion Scale	Participation in a weekly population-based programme of moderate-intensity exercise for 9 weeks was not sufficient to increase SC rate when added to a comprehensive SC programme offering individual counselling and NRT. Continuous cessation rates were high and similar in G1 and the G2 at the EOT (47% vs 46%, p=0.81), and similarly decreased at 26 weeks (34% vs 35%, p=0.77) and at 1-year follow-up (27% vs 29%, p=0.71), respectively. At 52-weeks follow-up, the adherence in G1 was 55% and in G2 62%.

				session a week + four unsupervised (home based) sessions a week **I:** Moderate exercise (intended to target 40% - 60% of maximal aerobic power) **T:** 45 min per session supervised and 30 min unsupervised exercise sessions. **T:** Brisk walking and slow jogging, commuting on foot or by bicycle, leisure/ recreational and aerobic housework activities.		
Hill et al (1985)	36 (total) G1=18 G2=18	Total= 40 G1=37.67 (8.77) G2=41.61 (7.59)	10:26	**G1**: 5-week supervised (if participants' circumstances allowed, if not, they were asked to do unsupervised sessions) exercise intervention (10 sessions-twice a week) + group SC counselling sessions twice a week (for 5 weeks) for 60-90 min per session + unsupervised exercise sessions Exercise began on the quitting date. **G2**: 5-weeks group SC counselling intervention twice a week (total of 10 sessions) for 60-90 min per session **For exercise prescription:**	Assessment occurred at baseline, 5 weeks (EOT), follow-up: 1, 3, and 6 months SC Self-reports verified by expired CO; utilizing 10 ppm cut-off at each assessment time point. VO_{2max} cycle ergometer	No significant difference in quit rate between G1 and G2 (p=NS) G1 VO_{2max} significantly increased from 30.28 ml/kg/min at baseline to 32.11 ml/kg/min at EOT ($p<0.05$), compared to G2 who have slight increase from 30.52 ml/kg/min to 30.9 ml/kg/min (p=NS).

				F: Twice a week group session + as often as possible times unsupervised sessions a week **I:** Not specified **T:** 30 min per session supervised and as long as possible unsupervised **T:** Bicycle ergometer, walk or jog, bicycle ride, running, walk up and down of stairs		
Hill et al (1993)	82 (total) G1 = 22 G2= 22 G3= 18 G4= 20	Total= 59	39:43	**G1**: Behavioural treatment only **G2**: Behavioural treatment combined with nicotine gum **G3**: Behavioural treatment combined with supervised or unsupervised physical exercise **G4**: Supervised or unsupervised physical exercise **For G3 and G4 exercises prescription:** **F**: 3 Supervised or unsupervised sessions a week for 12 weeks **I**: 60% - 70% of HR reserve **T**: 45 minutes **T**: graduated walking (indoor and outdoor)	Quit rates were assessed at EOT and at 4, 7, and 12 months as follow up sessions SC Self-reports verified by expired CO; utilizing 10 ppm cut-off at each assessment time point.	At 12 months the proportion of quitting across groups were (G1=31.8%, G2=36.4%, G3=27.8%, and G4=10.0%) indicating that behavioural training facilitated cessation (G1, G2 and G3) better than the physical exercise only (G4) ($p<0.01$). The adherence rates were: G1 65%; G2 66%; G3 57% and G4 53%.
Kinnunen et al (2008)	182 (total) G1=92 G2=56 G3=34	Total=39 G1=38.3 (9.9) G2=37.9 (9.1) G3=39.9 (9.9)	0: 263	**G1:** Aerobic exercise supervised sessions + SC counselling sessions (once a week for 19 weeks) + nicotine gum + home based exercise sessions (e.g., walking, exercise tapes) to bring	Quit rates were assessed at EOT and at follow-up: 1 week, 1, 4 and 12 months	G1 and G2 at EOT and 12 months follow-up had a similar rate of cessation as G3 (p=NS) The increase in VO_{2max} from

				their total number of weekly exercise sessions to at least three. **G2:** SC counselling sessions (once a week for 19 weeks) + nicotine gum + health education sessions and discussions **G3:** SC counselling sessions (eight session over the 19 weeks) + nicotine gum Participants were followed from 3 weeks before cessation to 1year post cessation. **For G1 exercise prescription:** **F:** Twice a week for 5 weeks, then once a week for 14 weeks + home based exercise sessions (30 mins) to bring their total number of weekly exercise sessions to at least three **I:** 60% - 80% HRmax **T:** 40 mins **T:** Walking or running on a treadmill	SC Self-reports verified by expired CO; utilizing 10 ppm cut-off at each assessment time point and salivary cotinine levels. VO_{2max} treadmill test	baseline to EOT was significantly higher in G1 than G2 and G3 ($p<0.05$): G1: baseline=28.8 (8.5) ml/kg/min, EOT=32.9 (7.7) ml/kg/min G2: baseline=28.0 (4.2)ml/kg/min, EOT=30.1 (2.9) ml/kg/min G3: baseline= 34.2 (5.8) ml/kg/min, EOT=35.3 (6.9) ml/kg/min. The combined pre and post cessation adherence rates were higher in G2 (85%) than in G1 (74%) ($p<0.001$).
Marcus et al (1991)	20 (total) G1=10 G2=10	Total=39 (8) G1=40 (9) G2=38 (8)	0:20	**G1**: Aerobic exercise group supervised sessions + SC counselling sessions (twice a week for 4 weeks) **G2:** SC counselling only (twice a week for 4 weeks) Exercise began before quitting	Quit rates were assessed at EOT and at follow-up: 1, 3, 12 months. SC Self-reports verified by	Four participants in G1 remained abstinent at 1 month, 3 participants at 3 months and 2 participants at 12 months after SC treatment, compared with zero in G2 ($p<0.05$).

				date **For G1 exercise prescription:** **F:** 3 supervised exercise sessions a week for 15 weeks **I:** 70% - 85% HRmax **T:** 30-45 minutes **T:** cycle ergometry and treadmill walking	saliva cotinine < 10 ng/ml VO_{2max} cycle test	Only in G1 VO_{2max} was increased ($p<0.01$) G1: baseline=26 (6) ml/kg/min, EOT=31 (3) ml/kg/min G2: baseline=26 (5) ml/kg/min, EOT=26 (2)ml/kg/min (No increase nor decrease). Adherence rate was only mentioned for G1 and was 88% of the sessions.
Marcus et al (1995)	20 (total) G1=10 G2=10	38 (total) G1=36 (10) G2=39 (8)	0:20	**G1**: Aerobic exercise group supervised + SC counselling sessions (once a week for 12 weeks) **G2**: SC counselling sessions (once a week for 12 weeks) + health education 3 times a week (for 45 mins each) for 12 weeks Exercise began before quitting date **For G1 exercise prescription:** **F:** 3 a week supervised exercise sessions for 12 weeks **I:** 70% - 85% HRmax **T:** 30 - 40 minutes **T:** cycle ergometry and treadmill walking	Quit rates were assessed at EOT and at follow-up: 1, 3, 12 months. SC Self-reports verified by expired CO (utilizing 8 ppm cut-off at each assessment time point) and saliva cotinine < 10 ng/ml VO_{2max} cycle test	There were no significant differences at EOT in favour of the G1 over G2 (4 vs. 2 participants). At 1- and 3-months follow-up, the same four G1 participants remained abstinent. At the 12-month follow-up, three of G1 participants remained abstinent. One participant only in G2 remained abstinent All three participants of G1 who were abstinent at 12 months had continued

						exercising. The increase in VO_{2max} was higher in G1 than G2 (P<0.05): G1: baseline=24 (4) ml/kg/min, EOT=30 (4) ml/kg/min. G2: baseline=28 (6) ml/kg/min, EOT=27 (1) ml/kg/min. At EOT, adherence rate: G1: 85% of the smoking cessation sessions; 88% of the exercise sessions G2: 85% of the smoking cessation sessions; 92% of the contact sessions.
Marcus et al (1999)	281 (total) G1=134 G2:147	G1= 40.7 (9.1) G2= 29.7 (8.8)	0: 281	**G1:** Aerobic exercise groups supervised sessions + SC counselling sessions (once a week for 12 weeks). **G2:** SC counselling sessions (once a week for 12 weeks) + health education (45 - 60 mins each) 3 times a week for 12 weeks. Exercise began before quitting date **For G1 exercise prescription:** **F:** 3 a week supervised exercise	Quit rates were assessed at EOT and at follow-up: 3, 12 months. SC Self-reports verified by expired CO (utilizing 8 ppm cut-off at each assessment time point) and saliva cotinine < 10 ng/mL	G1 participants were more likely than G2 participants to be continuously abstinent during the 8 weeks of treatment following quit day (19.4% vs 10.2%, P=0.03). G1 participants were more likely than G2 participants to achieve 3 and 12 months of continuous abstinence following quit day (3 months: 16.4% vs 8.2%,

				sessions for 12 weeks **I:** Vigorous 60% - 85% HR reserve **T:** 40 - 50 mins **T:** cycle ergometry and treadmill walking	VO_{2peak} cycle test	P=0.03; 12 months: 11.9% vs 5.4%, P=0.05). The increase in VO_{2peak} was higher in G1 than G2 (p<0.01): G1: baseline=25 (6) ml/kg/min, EOT=28 (6) ml/kg/min. G2: baseline=25 (5) ml/kg/min, EOT=25 (5) ml/kg/min (No increase nor decrease). At EOT, adherence rate for G1 was 68.7%, and for G2 64.6%. At 12 months follow-up, adherence rate for G1 was 56% and for G2 50.3%.
Marcus et al (2005)	217 (total) G1= 109 G2= 108	G1=42.52 (10.4) G2=43.02 (10.3)	0:217	**G1:** Aerobic exercise groups supervised sessions + home based exercise 4 times a week for 30 mins each + SC counselling sessions (1hr, once a week for 8 weeks). Offered nicotine patch. **G2:** SC counselling sessions (1hr, once a week for 8 weeks) + health education (1hr, once a week for 8 weeks). Offered nicotine patch. Exercise began before quitting	Quit rates were assessed at EOT and at follow-up: 3, 12 months. SC Self-reports verified by expired CO (utilizing 8 ppm cut-off at each assessment time point) and saliva cotinine < 10 ng/ml	No significant differences between G1 and G2 at EOT and 3 months follow up (14.7% and 7.3% for G1 vs. 11.1% and 3.7% for G2, p=NS, respectively). No group differences were found at 12 months follow up of continues cessation (0.09% for G1 vs. 0.09% for G2, p=0.75), where both groups were equally likely

				date **For G1 exercise prescription:** **F:** One session a week for 8 weeks **I:** Moderate, 45% - 59% HR reserve or 50% - 69% of HRmax **T:** 55 minutes **T:** cycle ergometry and treadmill walking	Functional capacity expressed as VO_{2peak} treadmill test	to report SC at EOT The increase in VO_{2max} was significantly higher in G1 than G2 (P<0.05): G1: baseline=30.71 (6.12) ml/kg/min, EOT=31.88 (6.35)ml/kg/min G2: baseline=30.68 (5.67)ml/kg/min, EOT=30.4 (5.62) ml/kg/min. At EOT, adherence for G1 was 54.1% and for G2 58.9%. At 12 months follow up, adherence for G1 was 24.8% and for G2 31.8%.
Prapavessis et al (2007)	142 (total) Phase 1: G1=76 G2=66 Phase 2: G1=35 G2=33 G3=27 G4=26	Total=38 G1=37.9 (12.4) G1=38.2 (10.9)	0: 142	**Phase 1:** 6 weeks **G1**: Supervised exercise programme **G2:** Supervised cognitive behavioural SC programme (3 times a week for 5 weeks) **Phase 2**: 7 - 12 weeks, 121 participants who made a quit in phase 1, were randomised to 1 of 4 groups in phase 2: **G1:** Aerobic group exercise + SC counselling (3 times a week for 6 weeks) **G2:** Aerobic group exercise +	Quit rates were assessed at EOT and at follow-up: 3, 12 months SC Self-reports verified by expired CO (utilizing 10 ppm cut-off at each assessment time point) and saliva cotinine < 10 ng/ml Physical work	For continuous abstinence, no significant differences between groups were noted at the three post-quit time periods. At 3-month follow-up and 12-month follow-up, 33.9% and 22.0% of those who received patches compared to 25.8% and 11.3% of those who did not receive patches remained continuously abstinent, respectively (p=0.33;

				nicotine patches **G3:** Cognitive behavioural cessation programme (3 times a week for 6 weeks) **G4:** Cognitive behavioural cessation programme (3 times a week for 6 weeks) + nicotine patches. Exercise began before quitting date **For exercise prescription:** **F:** Three times a week for 12 weeks **I:** 60% - 75% HR reserve **T:** 45 minutes **T:** Cycle ergometry, treadmill and rower	capacity (PWC 75%) cycle ergometer test	p=0.11). At EOT, participants who received the nicotine patches (irrespective of group) were more likely to remain abstinent (72.9% *vs.* 53.2%) (p=0.03). At EOT, G1 had significantly increased their PWC compared to G2 (p<0.01) At EOT, adherence for G1+G2 was 62.4% of the exercise sessions and for G3+G4 62.8% of their smoking cessation sessions.
Prapavessis et al (2016)	413 (total) G1= 108 G2= 106 G3= 100 G4= 95	G1=41.96 (12.7) G2=43.47 (14.0) G3=43.45 (12.2) G4=40.36 (11.9)	0:413	Participants completed a 14-week exercise programme with NRT (TNP). NRT started after 4 weeks of exercising. Then randomised to 1 of 4 groups **G1**: Exercise maintenance (group supervised) + SC maintenance **G2**: Exercise maintenance (group supervised) + contact control	Quit rates were assessed at EOT and at follow-up: EOT (week 14), 26, 56 weeks SC Self-reports verified by expired CO (utilizing 6 ppm cut-off at each assessment time point)	At week 26, there was no significant difference in the proportion of abstainers (p=0.77) At week 56, there were no significant differences in the cessation rates between G1 (32.8%), G2 (19%), G3 (27.6%) and G4 (20.7%) (p=0.43) At EOT, adherence G1 was 50.93%; G2 53.15%; G3

				G3: SC maintenance+ contact control **G4**: Contact control G1+G2 during weeks 8 - 14 received cognitive behavioural therapy sessions in groups, five sessions a week for 25-min with the goal of teaching self-regulatory skills and for exercise adherence. Also, during weeks 26 and 52 they received telephone counselling seven sessions for 15-min biweekly (for the first month), then monthly (for the next 2 months) and then bimonthly (for last 8 months). G3+G4 contacted by messages reinforcing women's health issues. Also, during weeks 26 and 52 they were contacted by messages reinforcing the Forever Free booklets and/or women's health issues. **For exercise prescription:** **F:** First 8 weeks three sessions a week, weeks 9 - 11 two sessions a week and weeks 12 - 14 only one session + unsupervised at weeks 8 - 14 three sessions a week similar to the supervised		49.33% and G4 45.26%.

				duration and intensity. **I:** 70% - 75% HRmax **T:** 45 minutes supervised. 15 minutes unsupervised **T:** Treadmills, rowing machines, stair climbers and stationary bicycles		
Russell et al (1988)	42	Total= 28 (7)	0:42	One week (4 1hr sessions) behavioural smoking cessation program, then randomly assigned into: **G1:** Group aerobic exercise class sessions + home based (2 sessions) **G 2:** Group SC counselling including health education (1hr each, 9 sessions) **G3:** Control group (reports weight, CO and withdrawal symptoms) Exercise began after quitting date **For exercise prescription:** **F:** 3 sessions a week (one supervised and two unsupervised) for 9 weeks **I:** 70% - 80% HRmax **T:** 20 - 30 mins **T:** Cycling, walking, jogging and home-based aerobic exercises.	Quit rates were assessed at EOT and at follow-up: 3, 6 months SC Self-reports verified by expired CO PWC 150 cycle ergometer test	EOT cessation rates were high (83% irrespective of group) for all groups at the end of the program There were no significant differences in cessation across groups; the cessation rates were decreased from 83% at the EOT to 73% at 3 months, 49% at six months and 34% at 18 months for all groups.

Taylor et al (1988)	203 initially and ended up with 68 G1=42 G2=26	Total= 52 (9)	68:0	**<u>Started as</u>** **<u>G1:</u>** Supervised aerobic exercise followed by home based exercise training (54) + one SC counselling session (at week 3 post AMI) **<u>G2:</u>** Supervised aerobic exercise followed by medically supervised group exercise training (53) + one SC counselling session (at week 3 post AMI) **<u>G3:</u>** Supervised aerobic exercise only (26) + one SC counselling session (at week 3 post AMI) **<u>G4:</u>** Control (Participants were seen for the first time at 26 weeks for aerobic exercise testing) (27) **<u>Ended up as</u>** G1+G2 pooled to be exercise group G3+G4 pooled to be non-exercise group **For exercise prescription:** Not available in the text.	Quit rates were assessed at EOT and at follow-up: 26 weeks SC Self-reports verified by plasma thiocyanate, utilizing 100 mmol/L as cut-off Functional capacity treadmill peak test	12% (5/42 participants) in the G1 and 19% (5/26 participants) in G2 were still smoking at 3 weeks. None of the 10 participants who were smoking at 3 weeks stopped by 26 weeks (p=NS) By 23 weeks, cessation rates were 69% (29/42) in G1 and 61% (16) in G2, respectively. Between week 3 and 26 significant improvement in VO_{2peak} level in exercise groups compared to non-exercise group (average increase of 6.65 ml/kg/min vs. 4.2 ml/kg/min respectively ($p<0.05$)).
G1: Group 1; G2: Group 2; G3: Group 3; G4: Group 4; M: Man; W: Women; SC: Smoking cessation; NS: Not significant; FITT: Fitness, Intensity, Time, Type; VO_{2max}: maximum oxygen uptake; VO_{2peak}: peak oxygen uptake; TNP: Transdermal nicotine patch; EOT: End of treatment; CO: Carbon monoxide; NRT: Nicotine replacement therapy; HR: Heart rate; PPM; parts per million; PWC: Physical work capacity; AMI: Acute myocardial infarction.						

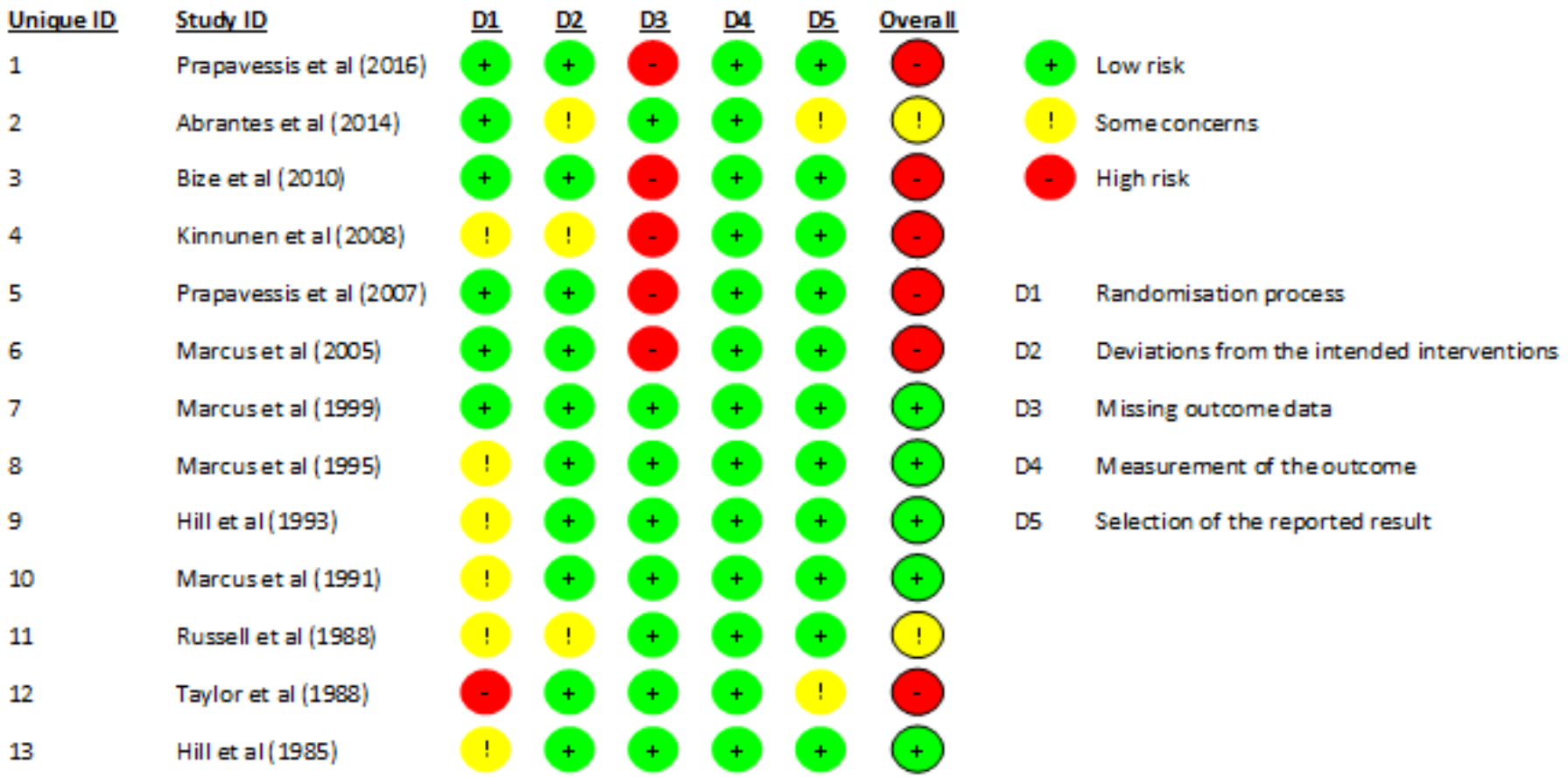

Figure 4.3: Results of the CROB2 for the included trials.

4.4.3 Meta-analysis results:

Effectiveness of aerobic exercise to facilitate smoking cessation

To assess the effectiveness of aerobic exercise to facilitate smoking cessation, 12 trials comparing exercise groups to non-exercise groups were subjected to a meta-analysis (Figure 4.3). One trial of moderate quality could not be used for the analysis, as they did not report the number of participants, or proportion of the total number of participants in each group (Russell et al., 1988). The meta-analysis showed that aerobic exercise did not significantly enhance the success rate of SC (Figure 4.3).

Effects of exercise during smoking cessation interventions on VO_{2max} and/or VO_{2peak}

A meta-analysis of 5 trials (three high, one moderate and one low quality) (Abrantes et al., 2014; Marcus et al., 1999; Marcus et al., 1991; Marcus et al., 1995) showed that aerobic exercise during smoking cessation interventions resulted in a higher VO_{2max} and/or VO_{2peak} than the other groups post intervention (Figure 4.4). No significant heterogeneity was found. The other trials were not included in the meta-analysis as they did not report mean and standard deviations for VO_{2max} and/or VO_{2peak} for each group.

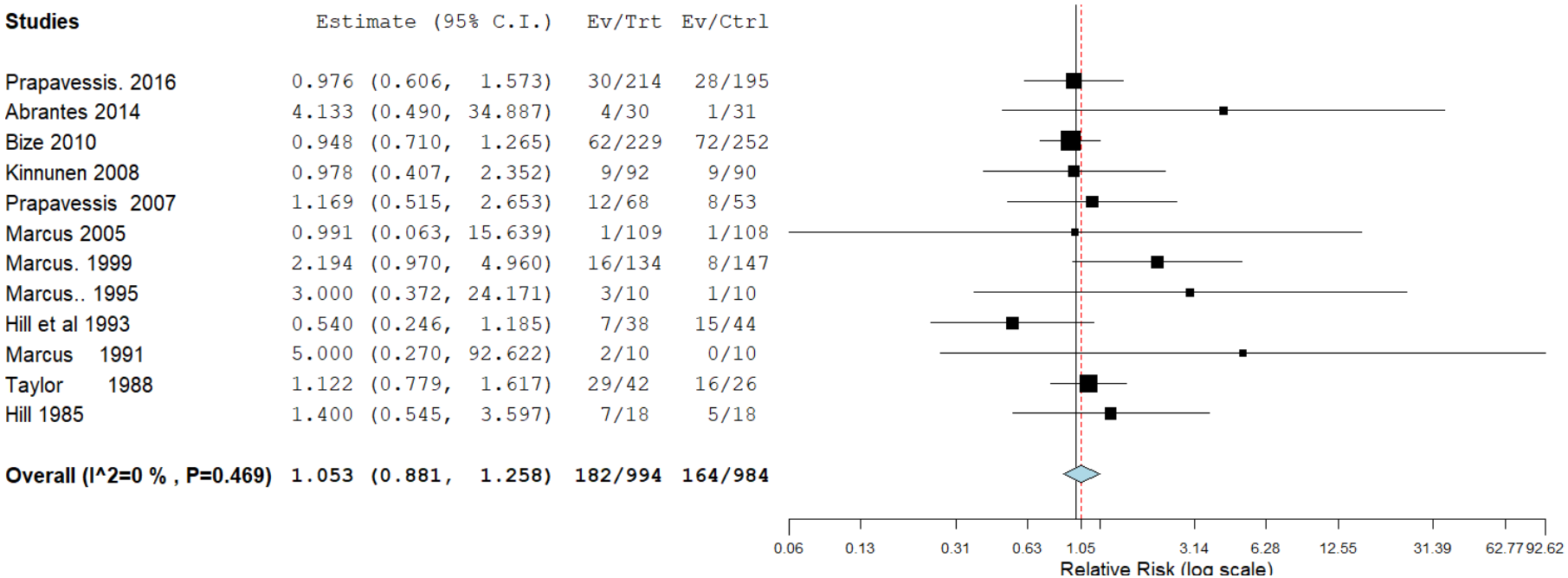

Figure 4.4: Forest plot for the success of Smoking cessation (SC). CI: confidence interval; Ev: number of quitters in the exercise group/s at the last follow-up session; Trt: number of participants in the exercise group at baseline; Ctrl: number of participants in the non-exercise group/s at baseline session.

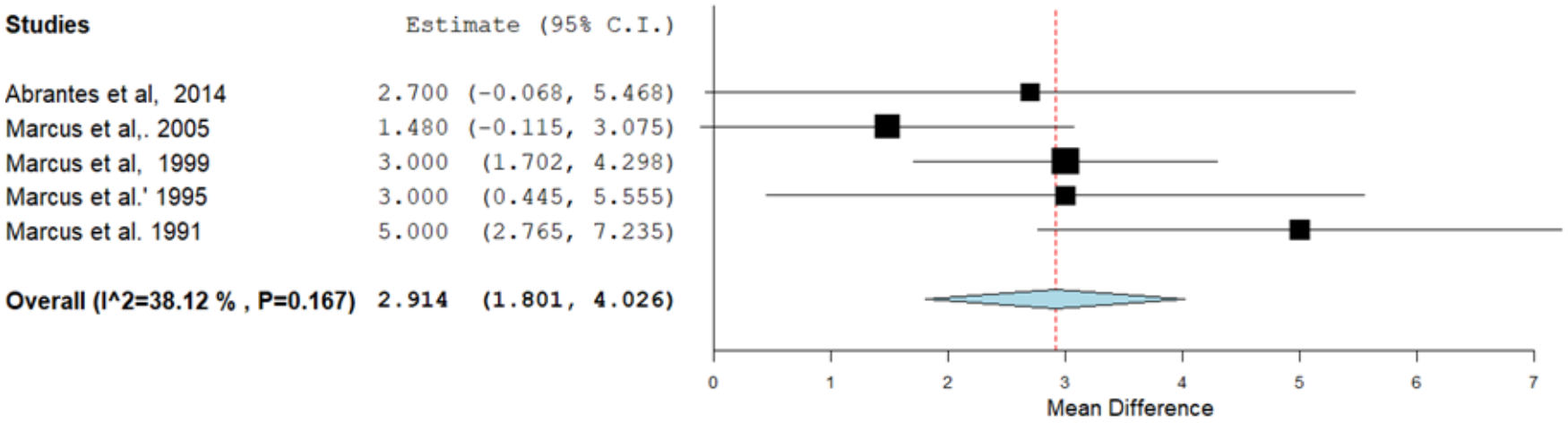

Figure 4.5: Forest plot for the trials on the effects of the intervention on maximal oxygen uptake (VO2max and/or VO2peak). CI: confidence interval.

4.5 DISCUSSION

This thesis showed detrimental effects of smoking and vaping on respiratory function, muscle function and inflammatory biomarkers and the benefits of smoking cessation (chapters 2 and 3). It was therefore important to consider interventions that might help the success of smoking cessation efforts, and one such factor might be aerobic exercise. This systematic review and meta-analysis are the first to review the literature on the benefits of aerobic exercise for long-term vaping cessation and SC, and its effects on VO_{2max} and/or VO_{2peak}. The review included a meta-analysis of 13 trials which assessed the effectiveness of aerobic exercise interventions on long-term SC and VO_{2max} and/or VO_{2peak}. The main finding of this review was that there is no evidence that aerobic exercise enhances long-term SC. Nevertheless, aerobic exercise improved cardiopulmonary fitness in those who successfully quit smoking. The search identified no trials that assessed the effects of aerobic exercise on vaping cessation.

4.5.1 Design of the exercise studies and verification of smoking cessation

Comparator groups received the same intervention as the exercise group, and consisted of face-to-face consultation (Abrantes et al., 2014; Hill, 1985; Kinnunen et al., 2008; Marcus et al., 1999; Marcus et al., 1991; Marcus et al., 1995; Marcus et al., 2005; Prapavessis et al., 2007; Prapavessis et al., 2016; Russell et al., 1988; Taylor et al., 1988), telephone counselling (Abrantes et al., 2014), behavioural treatment (Hill et al., 1993; Prapavessis et al., 2007), nicotine gum (Bize et al., 2010; Hill et al., 1993), nicotine patch (Prapavessis et al., 2007), inhalers (Bize et al., 2010), cognitive therapy (Prapavessis et al., 2007), or combination of more than one treatment. In the trials included in the meta-analysis, smoking cessation was confirmed by measurement of the expired CO (Abrantes et al., 2014; Bize et al., 2010; Hill, 1985; Hill et al., 1993; Kinnunen et al., 2008; Marcus et

al., 1999; Marcus et al., 1995; Marcus et al., 2005; Prapavessis et al., 2007; Prapavessis et al., 2016; Russell et al., 1988), saliva cotinine (Marcus et al., 1999; Marcus et al., 1991; Marcus et al., 1995; Marcus et al., 2005; Prapavessis et al., 2007) or plasma thiocyanate (Taylor et al., 1988) concentrations.

4.5.2 Exercise interventions do not enhance smoking cessation

When studying the benefits of exercise interventions for smoking cessation it is important to consider whether that is influenced by the frequency, intensity, time and type (FITT) of exercise (Brown et al., 1978; Franklin et al., 2003; Sasso et al., 2015).

Only two high quality trials reported that aerobic exercise intervention resulted in higher number of long-term successful quitters compared to other interventions (Marcus et al., 1999; Marcus et al., 1991). These trials used 3 vigorous-intensity exercise sessions a week for 12 – 15 weeks. This is, however, an equivocal observation as three other high quality trials with similar intensity, frequency and duration of exercise did not report a significant improvement in SC after aerobic exercise interventions (Hill, 1985; Hill et al., 1993; Marcus et al., 1995). As the effectiveness of exercise programs is highly dependent on adherence (Dishman, 1994), it is possible that the benefits of exercise in two trials (Marcus et al., 1999; Marcus et al., 1991) and no benefits in another trial is related to the high adherence (68.7% and 88%, respectively), or low (55%) adherence (Hill et al., 1993) to the exercise interventions.

4.5.3 Exercise during smoking cessation interventions enhances VO_{2max} and/or VO_{2peak}

Even if exercise does not benefit SC, there are substantial other benefits of exercise, such as the negative association with the prevalence of lung carcinoma in smokers and quitters (Leitzmann et al., 2009) and a significant reduction in the mortality of smokers (Siahpush et al., 2019). In addition, exercise during smoking cessation interventions led to a significant improvement in VO_{2max} and/ or VO_{2peak} (Abrantes et al., 2014; Hill, 1985; Kinnunen et al., 2008; Marcus et al., 1999; Marcus et al., 1991; Marcus et al., 1995; Marcus et al., 2005; Prapavessis et al., 2007). Improvements in VO_{2max} indicate improved aerobic exercise capacity and may also contribute to a reduction in the development of numerous clinical conditions and morbidities (American College of Sports Medicine, 2013). Besides these benefits for exercise capacity and diminishing the risk of future morbidity, there are also other physiological and psychological benefits to exercise as an adjunct to SC (Daley, 2008; Penedo and Dahn, 2005). For example, exercise led to a reduction in withdrawal symptoms and improvement in psychological wellbeing, such as reduction in anxiety, depression and mood-swings (Abrantes et al., 2014; Marcus et al., 2005; Russell et al., 1988). Thus, even though exercise did not enhance the success rate of smoking cessation it nevertheless has significant beneficial effects for people seeking to stop smoking.

4.5.4 Limitations

The low number of trials included in the meta-analysis on the effects of aerobic exercise on smoking cessation and cardiopulmonary fitness is a limitation in this review. In addition, this review excluded some special populations such as those suffering from

asthma, COPD and/or pregnant women, in which exercise may enhance the success rate of smoking cessation.

4.5.5 Strengths

This review included only randomized control trials and used a rigorous tool to assess the quality of the trials (CROB2) to select best quality evidence. A Meta-analysis was conducted for both the effects of aerobic exercise on long-term SC and VO_{2max} and/or VO_{2peak}. The review protocol was registered in PROSPERO database.

Future research is recommended to look at the effects of aerobic exercise on vaping cessation. Also, better quality of trial designs is recommended for future research. There is some evidence that supervised exercise sessions lead to a better rate of SC. We therefore suggest that further trials with supervised exercise sessions are warranted to investigate whether indeed supervised trials enhance the success rate of SC.

4.6 Impact/Implication

This review suggests that aerobic exercise does not benefit the success of long-term smoking cessation. However, VO_{2max} and/or VO_{2peak} was improved in those who stopped smoking and will have a significant benefit for health and quality of life. It is therefore advisable to include aerobic exercise to any intervention for smoking cessation.

4.7 Conclusion

The meta-analysis showed no evidence that aerobic exercise promotes long-term smoking cessation. However, aerobic exercise improved VO_{2max} and/or VO_{2peak} and mental wellbeing in those who stopped smoking. The search identified no trials on the effects of aerobic exercise on vaping cessation.

Chapter 5 : General discussion

This final chapter provides an overview and discussion of the results in this thesis and ends with some recommendations for future studies.

The objectives of this thesis were to assess the effects of vaping and smoking on cardiorespiratory, vascular and muscle function and size, VO_{2max} and low back pain. Due to the COVID-19 outbreak, where physiological experiments were classified as very high risk as per the university risk assessment due to the need to be close to the participants and performing aerosol-generating procedures such as spirometry and VO_{2max}, the objectives had to be adjusted. The new objectives were to assess the effects of vaping and smoking on respiratory function (chapter 2), the effects of smoking cessation on respiratory and muscle function and low-grade systemic inflammation (chapter 3), and the effects of aerobic exercise on log-term vaping cessation and smoking cessation (chapter 4). Appendix 11 shows how many participants and which data was collected regarding the effects of vaping and smoking on cardiovascular function, muscle function and low back pain that had been collected before the COVID-19 outbreak and participant recruitment ceased. The data were insufficient for in depth analysis.

Chapter 1 is a general introduction on what is known in the literature concerning the effects of vaping and smoking. Smoking is well known on its harmful effects on different body systems including the respiratory system, cardiovascular systems, inflammatory markers and blood parameters and vaping is considered a healthier alternative that may help in smoking cessation attempts. This chapter discusses some literature that suggests that vaping may not be as healthy as originally thought and hence sets the scene of the thesis and introduces the (revised) objectives.

In **chapter 2,** the respiratory function, respiratory muscle strength and COHb% were compared between vapers, cigarette smokers and non-smokers (controls). Unexpectedly, not only smokers, but also vapers had elevated COHb% levels. This elevated COHb% might cause an increased susceptibility to muscle fatigue (Morse et al., 2008). This is most likely not limited to leg muscles but will also affect respiratory muscles and hence may contribute to the reduced exercise capacity of smokers, and perhaps also vapers.

The experiments in Chapter two showed that maximal respiratory pressures were similar in vapers, smokers and non-smokers. However, vaping for as little as 1.67 year caused a similar decrement in lung function as smoking for 4.86 years, as both vapers and smokers had similar FEV_1, $FEV_{1pred\%}$, PEF, FEV_1/FVC, $FEF_{25\%}$, $FEF_{75\%}$, $FEF_{25-75\%}$, and $FEF_{25-75pred\%}$, and both had these parameters significantly lower than non-smokers. This indicates that even though the vapers and smokers were asymptomatic they may show early signs of developing respiratory problems. This is thus in contrast to some studies reporting that vaping does not affect respiratory function (Polosa et al., 2017; Staudt et al., 2018; Vardavas et al., 2012). The cause of this discrepancy might be attributed to the duration of vaping/smoking, whether being a pure vaper or an ex-smoker, and/or frequency and volume of vaping/smoking. For example, in the current study, vapers had used e-cigarettes daily for ≥1 year (1.67±1.00 years) with 8.30±5.23 puffs per e-cigarette, whereas in Polosa et al (2017); who reported no difference in FEV_1 , FVC, FEV_1/FVC and $FEF_{25–75\%}$ between vapers and non-smokers, the duration of vaping was 8 months, in Staudt et al (2018); who reported no difference in FEV_1 , FVC, FEV_1/FVC and TLC between vapers at baseline and after one week of vaping, and Vardavas et al (2012) assessed the immediate effects of vaping in current smokers and found no difference in FEV_1 , FVC, FEV_1/FVC after vaping. This might indicate that longer duration of vaping is needed to show any changes in pulmonary function.

Based on the findings of chapter two, the previous suggestion that vaping is a healthier, or safer alternative to cigarette smoking, should be treated with caution. The recommendation for future research includes larger sample size and should focus on assessing and comparing lung function in pure vapers (who have never smoked) with smokers. Additionally, more advanced lung function testing, such as lung diffusion capacity, and more sensitive airway resistance measurement (e.g. with the forced oscillation technique) to detect earlier changes in the pulmonary system, are desirable. It is also important to assess whether vaping results in less (or even none at all) low-grade systemic inflammation than in smokers.

As it was found in chapter 2, that smokers have a lower respiratory function compared with non-smokers, it was decided to study whether these detrimental changes were reversible by smoking cessation. Therefore, **chapter 3** describe the effects of 14 days smoking cessation on respiratory function, skeletal muscle function and on the blood parameters and inflammatory markers. Similar to other studies, the current findings show that MVC was similar in smokers and non-smokers (Larsson and Örlander, 1984; Morse et al., 2007; Wüst et al., 2008c), although others did report a lower MVC in smokers (Al-Obaidi et al., 2004; Barreiro et al., 2010; Örlander et al., 1979; Seymour et al., 2010). The discrepancy between the studies may indicate that smoking *per se* might not necessarily be associated with lower MVC but may perhaps be related to exercise levels. In line with this, there was no significant difference in MVC between exercise level-matched smokers and non-smokers (Larsson and Örlander, 1984; Wüst et al., 2008c). An interesting finding was that 14 days of smoking cessation resulted in an increase in FI in smokers accompanied with COHb% normalisation to levels seen in non-smokers. This might indicate that even as little as 3% COHb in smokers already impairs muscle fatigue

resistance. This is an encouraging observation, as the rapid recovery of muscle fatigue resistance may particularly stimulate smoking athletes to quit smoking.

In chapter 3, it was found that total protein, albumin and glucose concentrations did not differ significantly between smokers and non-smokers. Additionally, it was observed that smoking was not associated with elevated numbers of monocytes and lymphocytes, something also seen by others (Malenica et al., 2017; Tulgar et al., 2016). The eosinophil count was, however, lower in smokers than non-smokers and remained lower after 14 days of smoking cessation. AGEs levels remained elevated even after 14 days of smoking cessation. AGEs formation is sped up by smoking resulting in formation of reactive glycotoxins that invade the blood through lungs (Cerami et al., 1997). Additionally, the current study showed lower TAS and higher MDA levels in smokers that may well have contributed to the low-grade systemic inflammation elevated AGE levels in smokers (Cerami et al., 1997; Moldogazieva et al., 2019; Vlassara and Palace, 2002). Although neither TAS nor MDA levels changed after 14 days of smoking cessation, another study showed that TAS was increased and MDA reduced after 28 days of smoking cessation (Polidori et al., 2003). The data indicate that 14 days of smoking cessation is not long enough to normalise TAS, MDA and AGEs to levels seen in non-smokers.

It was reported that cigarette smoking promotes the release of cytokines (Hasnis et al., 2007), potentially via activation of mononuclear cells to release cytokines. Another possible explanation for elevated cytokine levels in smokers is the release of cytokines by the significantly elevated number of macrophages and neutrophils in the broncheo-alveolar lavage fluid as seen in smoking mice (Ajime et al., 2021), over time resulting in low-grade systematic inflammation.

Chapter 3 also showed that smoking cessation caused IL-6, IL-10, IL-12p70, IL-4 return back to normal levels seen in non-smokers, while TNF-α and IL-2 were reduced after 14 days of smoking cessation, but not yet entirely back to normal levels. The smoking cessation-induced reduction of toxic smoke constituents in the lungs and circulation that cause oxidative stress and an inflammatory response may be the main cause of the reduced inflammation. Whatever the cause of the reduced inflammation, it indicates the importance of smoking cessation to diminish systemic inflammation that might be an important stimulus for smokers to quit. In conclusion, it was found that smokers have evidence of low-grade systemic inflammation and oxidative stress, which were improved with 14 days smoking cessation.

It is recommended that future research includes larger sample size and longer smoking cessation duration to confirm these observations and link them with cardiovascular function and exercise capacity.

As chapter 3 showed that smoking cessation reversed some detrimental effects of smoking, it was decided to look at adding an intervention to facilitate long-term vaping cessation and smoking cessation. Therefore, **chapter 4** describe the effects of aerobic exercise on long-term vaping cessation and smoking cessation. The exact mechanism by which aerobic exercise may help smoking cessation remain vague. However, few mechanisms have been suggested, including raised endorphins, distraction and increased self-efficacy. The literature search identified no trials on the effects of aerobic exercise on vaping cessation-with 13 trials included for smoking cessation. The meta-analysis results showed that aerobic exercise does not improve the success on long-term smoking cessation. However, maximal and/or peak oxygen uptake were improved in smokers who stopped smoking. Thus, aerobic exercise could be an add-on to other interventions, such as nicotine replacement therapies with nicotine patches or gum, to further enhance

smoking cessation rates. The results of chapter 4 indicate that even if aerobic exercise did not enhance the rate of long-term smoking cessation, it still should be considered as an intervention as the exercise enhanced fitness, and therefore may enhance general health and quality of life.

Appendix 9 is the protocol for chapter 4 which was registered in PROSPERO.

In conclusion, the work in this thesis shows that despite the general suggestion that vaping is a healthier alternative to smoking, vaping has similar detrimental effects to smoking on lung function. Therefore, the effects of vaping cessation may be similar to those elicited with smoking cessation, but this is as yet not investigated. It is encouraging that the low-grade systemic inflammation and impaired muscle function in smokers are readily reversible by as little as 14 days of smoking cessation. This may well stimulate smokers in their efforts to give up smoking. While addition of aerobic exercise to a smoking cessation programme does not increase the success rate of smoking cessation, it does improve the fitness of the abstainers. Therefore, it is advisable to include exercise in smoking cessation programmes, as well as measures of carboxyhaemoglobin and markers of inflammation.

Limitations

The COVID-19 pandemic led to the suspension of laboratory-based research activities and hence limited participant recruitment and many of the originally planned experiments. The following experiments were particularly affected and led to insufficient data collection for statistically meaningful analyses: vascular function as assessed by brachial artery flow mediated dilation using ultrasound; VO2max by cardiopulmonary exercise testing; low back pain using the Oswestry Low Back Disability Questionnaire; measurements of the lower back muscles and thigh muscle size using magnetic resonance

imaging. In addition, the sample size of the study in chapter 2 is relatively small. Also, a more specific and sensitive biomarker for lipid peroxidation than MDA, such as Isoprostane could have been used. Longer smoking cessation programmes more than 14 days are of interest to see whether some of the parameters that had not yet returned to control values would remain elevated or eventually return to values seen in non-smokers. Perhaps expanding the inclusion criteria in the systematic review and meta-analysis to include special populations such as pregnant women and those suffering from cancer, cardiorespiratory conditions such as asthma, COPD, may show that different populations may in fact benefit from aerobic exercise training programmes during smoking cessation attempts.

References

ABDUL-RASHEED, O. F. & AL-RUBAYEE, W. T. 2013. Effects of cigarette smoking on lipid peroxidation and antioxidant status in Iraqi men at Baghdad city. *International Journal of Basic and Applied Sciences,* 2**,** 47.

ABRANTES, A. M., BLOOM, E. L., STRONG, D. R., RIEBE, D., MARCUS, B. H., DESAULNIERS, J., FOKAS, K. & BROWN, R. A. 2014. A preliminary randomized controlled trial of a behavioral exercise intervention for smoking cessation. *Nicotine & tobacco research : official journal of the Society for Research on Nicotine and Tobacco,* 16**,** 1094-1103.

ACTION ON SMOKING AND HEALTH. 2019. *Use of e-cigarettes (vapourisers) among adults in Great Britain* [Online]. Available: https://ash.org.uk/wp-content/uploads/2019/09/Use-of-e-cigarettes-among-adults-2019.pdf [Accessed 13/02/2021 2021].

AHLUWALIA, J. S., HARRIS, K. J., CATLEY, D., OKUYEMI, K. S. & MAYO, M. S. 2002. Sustained-release bupropion for smoking cessation in African Americans: a randomized controlled trial. *Jama,* 288**,** 468-474.

AHMED, N., ARGIROV, O. K., MINHAS, H. S., CORDEIRO, C. A. & THORNALLEY, P. J. 2002. Assay of advanced glycation endproducts (AGEs): surveying AGEs by chromatographic assay with derivatization by 6-aminoquinolyl-N-hydroxysuccinimidyl-carbamate and application to N∈-carboxymethyl-lysine-and N∈-(1-carboxyethyl) lysine-modified albumin. *Biochemical Journal,* 364**,** 1-14.

AITCHISON, R. & RUSSELL, N. 1988. Smoking-a major cause of polycythaemia. *Journal of the Royal Society of Medicine,* 81**,** 89-91.

AJIME, T. T., SERRÉ, J., WÜST, R. C., MESSA, G. A. M., POFFÉ, C., SWAMINATHAN, A., MAES, K., JANSSENS, W., TROOSTERS, T. & DEGENS, H. 2021. Two Weeks of Smoking Cessation Reverse Cigarette Smoke-Induced Skeletal Muscle Atrophy and Mitochondrial Dysfunction in Mice. *Nicotine and Tobacco Research,* 23**,** 143-151.

AL-OBAIDI, S. M., ANTHONY, J., AL-SHUWAI, N. & DEAN, E. 2004. Differences in back extensor strength between smokers and nonsmokers with and without low back pain. *Journal of Orthopaedic & Sports Physical Therapy,* 34**,** 254-260.

ALHEMIERI, A. A. 2008. Effect of cigarette smoking on some heamatological & biochemical factors in blood of men with aging. *basrah journal of science,* 26**,** 56-67.

ALONSO, J. R., CARDELLACH, F., LÓPEZ, S., CASADEMONT, J. & MIRÓ, Ò. 2003. Carbon monoxide specifically inhibits cytochrome c oxidase of human mitochondrial respiratory chain. *Pharmacology & toxicology,* 93**,** 142-146.

ALSALHEN, K. S. & ABDALSALAM, R. D. 2014. Effect of cigarette smoking on liver functions: a comparative study conducted among smokers and non-smokers male in El-beida City, Libya. *International Current Pharmaceutical Journal,* 3**,** 291-295.

AMERICAN COLLEGE OF SPORTS MEDICINE 2013. *ACSM's guidelines for exercise testing and prescription*, Lippincott Williams & Wilkins.

AMERICAN THORACIC SOCIETY 1999. Skeletal muscle dysfunction in chronic obstructive pulmonary disease. A statement of the American Thoracic Society and European Respiratory Society. *Am J Respir Crit Care Med,* 159**,** S1-40.

ANTHONISEN, N. 1997. Epidemiology and the lung health study. *European Respiratory Review,* 7**,** 202-205.

ANTONIEWICZ, L., BRYNEDAL, A., HEDMAN, L., LUNDBÄCK, M. & BOSSON, J. A. 2019. Acute Effects of Electronic Cigarette Inhalation on the Vasculature and the Conducting Airways. *Cardiovasc Toxicol***,** 1-10.

APARICI, M., AL, F. G. & ALEGRIA, E. 1993. Respiratory function tests. Differences between smokers and non-smokers. Effects of withdrawal. *Revista Clinica Espanola,* 192**,** 169-172.

ASTHANA, A., PIPER, M. E., MCBRIDE, P. E., WARD, A., FIORE, M. C., BAKER, T. B. & STEIN, J. H. 2012. Long-term effects of smoking and smoking cessation on exercise stress testing: three-year outcomes from a randomized clinical trial. *American heart journal,* 163**,** 81-87. e1.

AUBIN, H.-J., BOBAK, A., BRITTON, J. R., ONCKEN, C., BILLING, C. B., GONG, J., WILLIAMS, K. E. & REEVES, K. R. 2008. Varenicline versus transdermal nicotine patch for smoking cessation: results from a randomised open-label trial. *Thorax,* 63**,** 717-724.

AULA, F. A. & QADIR, F. A. 2013. Effects of cigarette smoking on some immunological and hematological parameters in male smokers in Erbil city. *Jordan Journal of Biological Sciences,* 147**,** 1-8.

BARENGO, N. C., ANTIKAINEN, R., HARALD, K. & JOUSILAHTI, P. 2019. Smoking and cancer, cardiovascular and total mortality among older adults: The Finrisk Study. *Prev Med Rep,* 14**,** 100875.

BARREIRO, E., PEINADO, V. I., GALDIZ, J. B., FERRER, E., MARIN-CORRAL, J., SANCHEZ, F., GEA, J. & BARBERÀ, J. A. 2010. Cigarette smoke–induced oxidative stress: a role in chronic obstructive pulmonary disease skeletal muscle dysfunction. *Am J Respir Crit Care Med,* 182**,** 477-488.

BENOWITZ, N. L. 2010. Nicotine addiction. *N Engl J Med,* 362**,** 2295-2303.

BERNAARDS, C. M., TWISK, J. W., VAN MECHELEN, W., SNEL, J. & KEMPER, H. C. 2003. A longitudinal study on smoking in relationship to fitness and heart rate response. *Medicine & Science in Sports & Exercise*.

BIEMEL, K. M., FRIEDL, D. A. & LEDERER, M. O. 2002. Identification and quantification of major Maillard cross-links in human serum albumin and lens protein evidence for glucosepane as the dominant compound. *Journal of biological chemistry,* 277**,** 24907-24915.

BIZE, R., WILLI, C., CHIOLERO, A., STOIANOV, R., PAYOT, S., LOCATELLI, I. & CORNUZ, J. 2010. Participation in a population-based physical activity programme as an aid for smoking cessation: a randomised trial [with consumer summary]. *Tobacco Control 2010 Dec;19(6):488-494*.

BLOOMER, R. J. 2007. Decreased blood antioxidant capacity and increased lipid peroxidation in young cigarette smokers compared to nonsmokers: impact of dietary intake. *Nutrition Journal,* 6**,** 39.

BOCK, B. C., FAVA, J. L., GASKINS, R., MORROW, K. M., WILLIAMS, D. M., JENNINGS, E., BECKER, B. M., TREMONT, G. & MARCUS, B. H. 2012. Yoga as a complementary treatment for smoking cessation in women. *Journal of Women's Health,* 21**,** 240-248.

BOSTANCI, Ö., MAYDA, H., YILMAZ, C., KABADAYI, M., YILMAZ, A. K. & ÖZDAL, M. 2019. Inspiratory muscle training improves pulmonary functions and respiratory muscle strength in healthy male smokers. *Respiratory physiology & neurobiology,* 264**,** 28-32.

BRABER, S., HENRICKS, P. A., NIJKAMP, F. P., KRANEVELD, A. D. & FOLKERTS, G. 2010. Inflammatory changes in the airways of mice caused by cigarette smoke exposure are only partially reversed after smoking cessation. *Respiratory research,* 11**,** 99.

BRENNER, S. & MILLER, J. H. 2014. *Brenner's encyclopedia of genetics*, Elsevier Science.

BRESSAN, R. A. & CRIPPA, J. A. 2005. The role of dopamine in reward and pleasure behaviour–review of data from preclinical research. *Acta Psychiatr Scand,* 111**,** 14-21.

BROWN, R. S., RAMIREZ, D. E. & TAUB, J. M. 1978. The prescription of exercise for depression. *The Physician and sportsmedicine,* 6**,** 34-45.

BUIST, A. S., NAGY, J. M. & SEXTON, G. J. 1979. The effect of smoking cessation on pulmonary function: a 30-month follow-up of two smoking cessation clinics. *American Review of Respiratory Disease,* 120**,** 953-957.

BURCHFIEL, C. M., MARCUS, E. B., CURB, J. D., MACLEAN, C. J., VOLLMER, W. M., JOHNSON, L. R., FONG, K.-O., RODRIGUEZ, B. L., MASAKI, K. H. & BUIST, A. S. 1995. Effects of smoking and smoking cessation on longitudinal decline in pulmonary function. *American journal of respiratory and critical care medicine,* 151**,** 1778-1785.

CAHN, Z. & SIEGEL, M. 2011. Electronic cigarettes as a harm reduction strategy for tobacco control: a step forward or a repeat of past mistakes? *Journal of public health policy,* 32**,** 16-31.

CALLAHAN-LYON, P. 2014. Electronic cigarettes: human health effects. *Tobacco control,* 23**,** ii36-ii40.

CAMERON, J. M., HOWELL, D. N., WHITE, J. R., ANDRENYAK, D. M., LAYTON, M. E. & ROLL, J. M. 2014. Variable and potentially fatal amounts of nicotine in e-cigarette nicotine solutions. *Tobacco control,* 23**,** 77-78.

CAMPISI, R., CZERNIN, J., SCHÖDER, H., SAYRE, J. W., MARENGO, F. D., PHELPS, M. E. & SCHELBERT, H. R. 1998. Effects of long-term smoking on myocardial blood flow, coronary vasomotion, and vasodilator capacity. *Circulation,* 98**,** 119-125.

CAPONNETTO, P., CAMPAGNA, D., CIBELLA, F., MORJARIA, J. B., CARUSO, M., RUSSO, C. & POLOSA, R. 2013. EffiCiency and Safety of an eLectronic cigAreTte (ECLAT) as tobacco cigarettes substitute: a prospective 12-month randomized control design study. *PloS One,* 8**,** e66317.

CELERMAJER, D. S., SORENSEN, K. E., GEORGAKOPOULOS, D., BULL, C., THOMAS, O., ROBINSON, J. & DEANFIELD, J. 1993. Cigarette smoking is associated with dose-related and potentially reversible impairment of endothelium-dependent dilation in healthy young adults. *Circulation,* 88**,** 2149-2155.

CELERMAJER, D. S., SORENSEN, K. E., GOOCH, V., SPIEGELHALTER, D., MILLER, O., SULLIVAN, I., LLOYD, J. & DEANFIELD, J. 1992. Non-invasive detection of endothelial dysfunction in children and adults at risk of atherosclerosis. *Lancet,* 340**,** 1111-1115.

CENTERS FOR DISEASE CONTROL PREVENTION 1997. Ingestion of cigarettes and cigarette butts by children--Rhode Island, January 1994-July 1996. *MMWR Morb Mortal Wkly Rep,* 46**,** 125.

CENTERS FOR DISEASE CONTROL PREVENTION 2010. How tobacco smoke causes disease: The biology and behavioral basis for smoking-attributable disease: A report of the surgeon general.

CENTERS FOR DISEASE CONTROL PREVENTION. 2020. *Outbreak of Lung Injury Associated with the Use of E-Cigarette, or Vaping, Products.* [Online]. Available: https://www.cdc.gov/tobacco/basic_information/e-cigarettes/severe-lung-disease.html [Accessed 13/02/2021 2021].

CERAMI, C., FOUNDS, H., NICHOLL, I., MITSUHASHI, T., GIORDANO, D., VANPATTEN, S., LEE, A., AL-ABED, Y., VLASSARA, H. & BUCALA, R. 1997. Tobacco smoke is a source of toxic reactive glycation products. *Proceedings of the National Academy of Sciences,* 94**,** 13915-13920.

CHAUMONT, M., BERNARD, A., POCHET, S., MELOT, C., EL KHATTABI, C., REYE, F., BOUDJELTIA, K. Z., VAN ANTWERPEN, P., DELPORTE, C. & VAN DE BORNE, P. 2018. High-Wattage E-Cigarettes Induce Tissue Hypoxia and Lower Airway Injury: A Randomized Clinical Trial. *Am J Respir Crit Care Med,* 198**,** 123-126.

CHAUMONT, M., VAN DE BORNE, P., BERNARD, A., VAN MUYLEM, A., DEPREZ, G., ULLMO, J., STARCZEWSKA, E., BRIKI, R., DE HEMPTINNE, Q. & ZAHER, W. 2019. Fourth generation e-cigarette vaping induces transient lung inflammation and gas exchange disturbances: results from two randomized clinical trials. *Am J Physiol Lung Cell Mol Physiol,* 316**,** L705-L719.

CHOI, H., SCHMIDBAUER, N., SUNDELL, J., HASSELGREN, M., SPENGLER, J. & BORNEHAG, C.-G. 2010. Common household chemicals and the allergy risks in pre-school age children. *PloS One,* 5**,** e13423.

CHRISTENSEN, L. B., VAN'T VEEN, T. & BANG, J. Three cases of attempted suicide by ingestion of nicotine liquid used in e-cigarettes. Clin Toxicol, 2013. INFORMA HEALTHCARE 52 VANDERBILT AVE, NEW YORK, NY 10017 USA, 290-290.

COBB, N. K. & ABRAMS, D. 2011. E-cigarette or drug-delivery device. *N Engl J Med,* 365**,** 193-195.

CONTROL, C. F. D. & PREVENTION 2008. Cigarette smoking among adults--United States, 2007. *MMWR. Morbidity and mortality weekly report,* 57**,** 1221-1226.

COOPER, T. V., KLESGES, R. C., DEBON, M. W., ZBIKOWSKI, S. M., JOHNSON, K. C. & CLEMENS, L. H. 2005. A placebo controlled randomized trial of the effects of phenylpropanolamine and nicotine gum on cessation rates and postcessation weight gain in women. *Addictive behaviors,* 30**,** 61-75.

COPPETA, L., MAGRINI, A., PIETROIUSTI, A., PERRONE, S. & GRANA, M. 2018. Effects of Smoking Electronic Cigarettes on Pulmonary Function and Environmental Parameters. *Open Public Health J,* 11.

CRAPO, R. O., MORRIS, A. H. & GARDNER, R. M. 1981. Reference spirometric values using techniques and equipment that meet ATS recommendations. *American Review of Respiratory Disease,* 123**,** 659-664.

CRITCHLEY, J. A. & CAPEWELL, S. 2003. Mortality risk reduction associated with smoking cessation in patients with coronary heart disease: a systematic review. *Jama,* 290**,** 86-97.

DALEY, A. 2008. Exercise and depression: a review of reviews. *Journal of clinical psychology in medical settings,* 15**,** 140.

DARABSEH, M. Z., SELFE, J., MORSE, C. I. & DEGENS, H. 2020. Is vaping better than smoking for cardiorespiratory and muscle function? *Multidiscip Respir Med,* 15.

DAWKINS, L., TURNER, J., ROBERTS, A. & SOAR, K. 2013. 'Vaping'profiles and preferences: an online survey of electronic cigarette users. *Addiction,* 108**,** 1115-1125.

DE BORBA, A. T., JOST, R. T., GASS, R., NEDEL, F. B., CARDOSO, D. M., POHL, H. H., RECKZIEGEL, M. B., CORBELLINI, V. A. & PAIVA, D. N. 2014. The influence of active and passive smoking on the cardiorespiratory fitness of adults. *Multidiscip Respir Med,* 9**,** 34.

DE MEIRLEIR, K., NAAKTGEBOREN, N., VAN STEIRTEGHEM, A., GORUS, F., OLBRECHT, J. & BLOCK, P. 1986. Beta-endorphin and ACTH levels in peripheral blood during and after aerobic and anaerobic exercise. *European journal of applied physiology and occupational physiology,* 55**,** 5-8.

DE MORTON, N. A. 2009. The PEDro scale is a valid measure of the methodological quality of clinical trials: a demographic study. *Australian Journal of Physiotherapy,* 55**,** 129-133.

DEGENS, H., GAYAN-RAMIREZ, G. & VAN HEES, H. W. 2015. Smoking-induced skeletal muscle dysfunction. From evidence to mechanisms. *Am J Respir Crit Care Med,* 191**,** 620-625.

DEGENS, H., SANCHEZ HORNEROS, J. M., HEIJDRA, Y. F., DEKHUIJZEN, P. & HOPMAN, M. T. 2005. Skeletal muscle contractility is preserved in COPD patients with normal fat-free mass. *Acta physiologica Scandinavica,* 184**,** 235-242.

DEGENS, H. & VEERKAMP, J. 1994. Changes in oxidative capacity and fatigue resistance in skeletal muscle. *Int J Biochem,* 26**,** 871-878.

DEMICK, B. 2009. A high-tech approach to getting a nicotine fix. *Los Angeles Times,* 25.

DEMIRJIAN, L., ABBOUD, R. T., LI, H. & DURONIO, V. 2006. Acute effect of cigarette smoke on TNF-α release by macrophages mediated through the erk1/2 pathway. *Biochimica et Biophysica Acta (BBA)-Molecular Basis of Disease,* 1762**,** 592-597.

DISHMAN, R. K. 1994. *Advances in exercise adherence*, human kinetics publishers.

DOCKRELL, M., MORRISON, R., BAULD, L. & MCNEILL, A. 2013. E-cigarettes: prevalence and attitudes in Great Britain. *Nicotine Tob Res,* 15**,** 1737-1744.

DUNN, A. L., TRIVEDI, M. H., KAMPERT, J. B., CLARK, C. G. & CHAMBLISS, H. O. 2005. Exercise treatment for depression: efficacy and dose response. *American journal of preventive medicine,* 28**,** 1-8.

DUTRA, L. M., GRANA, R. & GLANTZ, S. A. 2017. Philip Morris research on precursors to the modern e-cigarette since 1990. *Tobacco control,* 26**,** e97-e105.

ELBEHAIRY, A. F., GUENETTE, J. A., FAISAL, A., CIAVAGLIA, C. E., WEBB, K. A., JENSEN, D., RAMSOOK, A. H., NEDER, J. A. & O'DONNELL, D. E. 2016. Mechanisms of exertional dyspnoea in symptomatic smokers without COPD. *European respiratory journal,* 48**,** 694-705.

ETTER, J.-F. 2010. Electronic cigarettes: a survey of users. *BMC public health,* 10**,** 231.

ETTER, J.-F., PERNEGER, T. V. & RONCHI, A. 1997. Distributions of smokers by stage: international comparison and association with smoking prevalence. *Preventive medicine,* 26**,** 580-585.

ETTER, J. F. 2019. Are long-term vapers interested in vaping cessation support? *Addiction,* 114**,** 1473-1477.

ETTER, J. F. & BULLEN, C. 2011. Electronic cigarette: users profile, utilization, satisfaction and perceived efficacy. *Addiction,* 106**,** 2017-2028.

EUROPEAN COMMISSION 2012. Proposal for a Directive of the European Parliament and of the Council on the approximation of the laws, regulations and administrative provisions of the Member States concerning the manufacture, presentation and sale of tobacco and related products. *Brussels*.

FARSALINOS, K. E., ROMAGNA, G., TSIAPRAS, D., KYRZOPOULOS, S. & VOUDRIS, V. 2013. Evaluating nicotine levels selection and patterns of electronic cigarette use in a group of "vapers" who had achieved complete substitution of smoking. *Subst Abuse,* 7**,** SART. S12756.

FAULKNER, M. A., LENZ, T. L. & STADING, J. A. 2006. Cost-effectiveness of smoking cessation and the implications for COPD. *International journal of chronic obstructive pulmonary disease,* 1**,** 279.

FILIPPIDIS, F. T., LAVERTY, A. A., GEROVASILI, V. & VARDAVAS, C. I. 2017. Two-year trends and predictors of e-cigarette use in 27 European Union member states. *Tobacco control,* 26**,** 98-104.

FLETCHER, C. & PETO, R. 1977. The natural history of chronic airflow obstruction. *Br Med J,* 1**,** 1645-1648.

FLOURIS, A. D., CHORTI, M. S., POULIANITI, K. P., JAMURTAS, A. Z., KOSTIKAS, K., TZATZARAKIS, M. N., WALLACE HAYES, A., TSATSAKIS, A. M. & KOUTEDAKIS, Y. 2013. Acute impact of active and passive electronic cigarette smoking on serum cotinine and lung function. *Inhal Toxicol,* 25**,** 91-101.

FOULDS, J. & VELDHEER, S. 2011. Commentary on Etter & Bullen (2011): Could E-cigs become the ultimate nicotine maintenance device? *Addiction,* 106**,** 2029.

FRANKLIN, B. A., SWAIN, D. P. & SHEPHARD, R. J. 2003. New insights in the prescription of exercise for coronary patients. *Journal of Cardiovascular Nursing,* 18**,** 116-123.

FRATI, A. C., INIESTRA, F. & ARIZA, C. R. 1996. Acute effect of cigarette smoking on glucose tolerance and other cardiovascular risk factors. *Diabetes care,* 19**,** 112-118.

GAN, W. Q., MAN, S., SENTHILSELVAN, A. & SIN, D. 2004. Association between chronic obstructive pulmonary disease and systemic inflammation: a systematic review and a meta-analysis. *Thorax,* 59**,** 574-580.

GARITI, P., LYNCH, K., ALTERMAN, A., KAMPMAN, K., XIE, H. & VARILLO, K. 2009. Comparing smoking treatment programs for lighter smokers with and without a history of heavier smoking. *Journal of substance abuse treatment,* 37**,** 247-255.

GLANTZ, S. A., BERO, L. A., SLADE, J., BARNES, D. E. & HANAUER, P. 1998. *The cigarette papers*, Univ of California Press.

GLANTZ, S. A. & FORBES, E. R. 1996. *The cigarette papers*, University of California Press Berkeley.

GLYNOS, C., BIBLI, S.-I., KATSAOUNOU, P., PAVLIDOU, A., MAGKOU, C., KARAVANA, V., TOPOUZIS, S., KALOMENIDIS, I., ZAKYNTHINOS, S. & PAPAPETROPOULOS, A. 2018. Comparison of the effects of e-cigarette vapor with cigarette smoke on lung function and inflammation in mice. *Am J Physiol Lung Cell Mol Physiol,* 315**,** L662-L672.

GOLDFARB, A. H., HATFIELD, B., ARMSTRONG, D. & POTTS, J. 1990. Plasma beta-endorphin concentration: response to intensity and duration of exercise. *Medicine and Science in Sports and Exercise,* 22**,** 241-244.

GOLDIN, A., BECKMAN, J. A., SCHMIDT, A. M. & CREAGER, M. A. 2006. Advanced glycation end products: sparking the development of diabetic vascular injury. *Circulation,* 114**,** 597-605.

GONIEWICZ, M. L., KNYSAK, J., GAWRON, M., KOSMIDER, L., SOBCZAK, A., KUREK, J., PROKOPOWICZ, A., JABLONSKA-CZAPLA, M., ROSIK-DULEWSKA, C. & HAVEL, C. 2014. Levels of selected carcinogens and toxicants in vapour from electronic cigarettes. *Tobacco control,* 23**,** 133-139.

GROPPELLI, A., GIORGI, D., OMBONI, S., PARATI, G. & MANCIA, G. 1992. Persistent blood pressure increase induced by heavy smoking. *J Hypertens,* 10**,** 495-499.

GUYTON, A. C. & HALL, J. E. 2006. Medical physiology. *Gökhan N, Çavuşoğlu H (Çeviren),* 3.

HAJEK, P. & BELCHER, M. 1991. Improved CO monitors for validating smoking abstinence by expired-air carbon monoxide level. *British journal of addiction,* 86**,** 1029-1030.

HAJEK, P., PHILLIPS-WALLER, A., PRZULJ, D., PESOLA, F., MYERS SMITH, K., BISAL, N., LI, J., PARROTT, S., SASIENI, P. & DAWKINS, L. 2019. A randomized trial of e-cigarettes versus nicotine-replacement therapy. *N Engl J Med,* 380**,** 629-637.

HANSSON, L., CHOUDRY, N. B., KARLSSON, J. A. & FULLER, R. W. 1994. Inhaled nicotine in humans: effect on the respiratory and cardiovascular systems. *J Appl Physiol (1985),* 76**,** 2420-7.

HARBER, P., SAECHAO, K. & BOOMUS, C. 2006. Diacetyl-induced lung disease. *Toxicological reviews,* 25**,** 261-272.

HARRIS, J. E. 1996. Cigarette smoke components and disease: cigarette smoke is more than a triad of tar, nicotine, and carbon monoxide. *Smoking and tobacco control monograph,* 7**,** 59-75.

HASNIS, E., BAR-SHAI, M., BURBEA, Z. & REZNICK, A. 2007. Cigarette smoke-induced NF-kappa B activation in human lymphocytes: the effect of low and high exposure to gas phase of cigarette smoke. *Journal of Physiology and Pharmacology,* 58**,** 263-274.

HAYANO, J., YAMADA, M., SAKAKIBARA, Y., FUJINAMI, T., YOKOYAMA, K., WATANABE, Y. & TAKATA, K. 1990. Short-and long-term effects of cigarette smoking on heart rate variability. *The American journal of cardiology,* 65**,** 84-88.

HEALTH, U. D. O. & SERVICES, H. 2010. A Report of the Surgeon General: How Tobacco Smoke Causes Disease: What It Means to You (Consumer Booklet). Atlanta, GA: US 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*.

HEISHMAN, S. J., KLEYKAMP, B. A. & SINGLETON, E. G. 2010. Meta-analysis of the acute effects of nicotine and smoking on human performance. *Psychopharmacology,* 210**,** 453-69.

HELMERSSON, J., LARSSON, A., VESSBY, B. & BASU, S. 2005. Active smoking and a history of smoking are associated with enhanced prostaglandin F2α, interleukin-6 and F2-isoprostane formation in elderly men. *Atherosclerosis,* 181**,** 201-207.

HENRY, T. S., KLIGERMAN, S. J., RAPTIS, C. A., MANN, H., SECHRIST, J. W. & KANNE, J. P. 2020. Imaging findings of vaping-associated lung injury. *AJR Am J Roentgenol,* 214**,** 498-505.

HILL, J. S. 1985. Effect of a program of aerobic exercise on the smoking behaviour of a group of adult volunteers. *Canadian Journal of Public Health [Revue Canadienne de Sante Publique] 1985 May-Jun;76(3):183-186*.

HILL, R. D., RIGDON, M. & JOHNSON, S. 1993. Behavioral smoking cessation treatment for older chronic smokers. *Behavior Therapy 1993 Spring;24(2):321-329*.

HIRSCH, G. L., SUE, D. Y., WASSERMAN, K., ROBINSON, T. E. & HANSEN, J. E. 1985. Immediate effects of cigarette smoking on cardiorespiratory responses to exercise. *Journal of Applied Physiology,* 58**,** 1975-1981.

HOGG, J. C., CHU, F., UTOKAPARCH, S., WOODS, R., ELLIOTT, W. M., BUZATU, L., CHERNIACK, R. M., ROGERS, R. M., SCIURBA, F. C. & COXSON, H. O. 2004. The nature of small-airway obstruction in chronic obstructive pulmonary disease. *N Engl J Med,* 350**,** 2645-2653.

HOWARD, G., WAGENKNECHT, L. E., BURKE, G. L., DIEZ-ROUX, A., EVANS, G. W., MCGOVERN, P., NIETO, F. J., TELL, G. S., INVESTIGATORS, A. & INVESTIGATORS, A. 1998. Cigarette smoking and progression of atherosclerosis: The Atherosclerosis Risk in Communities (ARIC) Study. *Jama,* 279**,** 119-124.

HUA, M., ALFI, M. & TALBOT, P. 2013. Health-related effects reported by electronic cigarette users in online forums. *J Med Internet Res,* 15.

IDE, H. & TABIRA, K. 2013. Changes in sympathetic nervous system activity in male smokers after moderate-intensity exercise. *Respiratory care,* 58**,** 1892-1898.

JOHNSON, H. M., GOSSETT, L. K., PIPER, M. E., AESCHLIMANN, S. E., KORCARZ, C. E., BAKER, T. B., FIORE, M. C. & STEIN, J. H. 2010. Effects of smoking and smoking cessation on endothelial function: 1-year outcomes from a randomized clinical trial. *Journal of the American College of Cardiology,* 55**,** 1988-1995.

KAMBAM, J. R., CHEN, L. H. & HYMAN, S. A. 1986. Effect of short-term smoking halt on carboxyhemoglobin levels and P50 values. *Anesthesia and analgesia,* 65**,** 1186-1188.

KANNER, R. E., CONNETT, J. E., WILLIAMS, D. E., BUIST, A. S. & GROUP, L. H. S. R. 1999. Effects of randomized assignment to a smoking cessation intervention and changes in smoking habits on respiratory symptoms in smokers with early chronic obstructive pulmonary disease: the Lung Health Study. *The American journal of medicine,* 106**,** 410-416.

KEMPTON, S. J., BURISH, N. M. & RAO, V. K. 2014. Electronic cigarettes: have you asked your patients about vaping? *Plast Reconstr Surg,* 133**,** 907e.

KIM, S. A., SMITH, S., BEAUCHAMP, C., SONG, Y., CHIANG, M., GIUSEPPETTI, A., FRUKHTBEYN, S., SHAFFER, I., WILHIDE, J., ROUTKEVITCH, D., ONDOV, J. M. & KIM, J. J. 2018. Cariogenic potential of sweet flavors in electronic-cigarette liquids. *PloS One,* 13**,** e0203717.

KINNUNEN, T., LEEMAN, R. F., KORHONEN, T., QUILES, Z. N., TERWAL, D. M., GARVEY, A. J. & HARTLEY, H. L. 2008. Exercise as an adjunct to nicotine gum in treating tobacco dependence among women. *Nicotine & tobacco research : official journal of the Society for Research on Nicotine and Tobacco,* 10**,** 689-703.

KISNER, C., COLBY, L. A. & BORSTAD, J. 2017. *Therapeutic exercise: foundations and techniques*, Fa Davis.

KITER, G., UCAN, E., CEYLAN, E. & KILINC, O. 2000. Water-pipe smoking and pulmonary functions. *Respir Med,* 94**,** 891-894.

KLÖPFER, A., SPANNEBERG, R. & GLOMB, M. A. 2011. Formation of arginine modifications in a model system of N α-tert-butoxycarbonyl (Boc)-arginine with methylglyoxal. *Journal of agricultural and food chemistry,* 59**,** 394-401.

KOBAYASHI, Y., TAKEUCHI, T., HOSOI, T. & LOEPPKY, J. A. 2004. Effects of habitual smoking on cardiorespiratory responses to sub-maximal exercise. *Journal of physiological anthropology and applied human science,* 23**,** 163-169.

KORFEI, M. 2018. The underestimated danger of E-cigarettes - also in the absence of nicotine. *Respir Res,* 19**,** 159.

KRALL, E. A. & DAWSON-HUGHES, B. 1999. Smoking increases bone loss and decreases intestinal calcium absorption. *Journal of Bone and Mineral Research,* 14**,** 215-220.

KUEHN, B. 2019. Vaping and Pregnancy. *Jama,* 321**,** 1344-1344.

LANDMAN, S. T., DHALIWAL, I., MACKENZIE, C. A., MARTINU, T., STEELE, A. & BOSMA, K. J. 2019. Life-threatening bronchiolitis related to electronic cigarette use in a Canadian youth. *CMAJ,* 191**,** E1321-E1331.

LANGE, P., GROTH, S., NYBOE, G., MORTENSEN, J., APPLEYARD, M., JENSEN, G. & SCHNOHR, P. 1989. Effects of smoking and changes in smoking habits on the decline of FEV1. *European respiratory journal,* 2**,** 811-816.

LARSSON, L. & ÖRLANDER, J. 1984. Skeletal muscle morphology, metabolism and function in smokers and non-smokers. A study on smoking-discordant monozygous twins. *Acta Physiol Scand,* 120**,** 343-352.

LARSSON, L., ÖRLANDER, J., ANSVED, T. & EDSTRÖM, L. 1998. Effects of chronic nicotine exposure on contractile enzyme-histochemical and biochemical properties of fast-and slow-twitch skeletal muscles in the rat. *Acta physiologica scandinavica,* 134**,** 519-527.

LAUGESEN, M. 2008. Second safety report on the Ruyan® e-cigarette. *Cell,* 27**,** 4375.

LAURIA, V., SPERANDIO, E., DE SOUSA, T., DE OLIVEIRA VIEIRA, W., ROMITI, M., DE TOLEDO GAGLIARDI, A., ARANTES, R. & DOURADO, V. 2017. Evaluation of dose–response relationship between smoking load and cardiopulmonary fitness in adult smokers: A cross-sectional study. *Rev Port Pneumol (2006),* 23**,** 79-84.

LEE, J., TANEJA, V. & VASSALLO, R. 2012. Cigarette smoking and inflammation: cellular and molecular mechanisms. *Journal of dental research,* 91**,** 142-149.

LEGRAND, F. & HEUZE, J. P. 2007. Antidepressant effects associated with different exercise conditions in participants with depression: a pilot study. *Journal of Sport and exercise Psychology,* 29**,** 348-364.

LEITZMANN, M. F., KOEBNICK, C., ABNET, C. C., FREEDMAN, N. D., PARK, Y., HOLLENBECK, A., BALLARD-BARBASH, R. & SCHATZKIN, A. 2009. Prospective study of physical activity and lung cancer by histologic type in current, former, and never smokers. *American journal of epidemiology,* 169**,** 542-553.

LEKAKIS, J., PAPAMICHAEL, C., VEMMOS, C., NANAS, J., KONTOYANNIS, D., STAMATELOPOULOS, S. & MOULOPOULOS, S. 1997. Effect of acute cigarette smoking on endothelium-dependent brachial artery dilatation in healthy individuals. *Am J Cardiol,* 79**,** 529-531.

LEMMENS, V., OENEMA, A., KNUT, I. K. & BRUG, J. 2008. Effectiveness of smoking cessation interventions among adults: a systematic review of reviews. *European journal of cancer prevention,* 17**,** 535-544.

LI, D., SUNDAR, I. K., MCINTOSH, S., OSSIP, D. J., GONIEWICZ, M. L., O'CONNOR, R. J. & RAHMAN, I. 2019. Association of smoking and electronic cigarette use with wheezing and related respiratory symptoms in adults: cross-sectional results from the Population Assessment of Tobacco and Health (PATH) study, wave 2. *Tobacco control***,** tobaccocontrol-2018-054694.

LIFESTYLES TEAM, N. D. 2019. Statistics on Smoking, England - 2019 [NS] [PAS]. *In:* CENTRE, T. H. A. S. C. I. (ed.). England: NHS Digital, part of the Government Statistical Service.

LIK, H. 2004. Electronic atomization cigarette. *US Patent US8393331B2,* 14.

LING, P. M. & GLANTZ, S. A. 2005. Tobacco industry consumer research on socially acceptable cigarettes. *Tobacco control,* 14**,** e3-e3.

LOFASO, F., NICOT, F., LEJAILLE, M., FALAIZE, L., LOUIS, A., CLEMENT, A., RAPHAEL, J., ORLIKOWSKI, D. & FAUROUX, B. 2006. Sniff nasal inspiratory pressure: what is the optimal number of sniffs? *European respiratory journal,* 27**,** 980-982.

LOPEZ, A. D., COLLISHAW, N. E. & PIHA, T. 1994. A descriptive model of the cigarette epidemic in developed countries. *Tobacco control,* 3**,** 242-247.

LOPRINZI, P. D., WOLFE, C. D. & WALKER, J. F. 2015. Exercise facilitates smoking cessation indirectly via improvements in smoking-specific self-efficacy: Prospective cohort study among a national sample of young smokers. *Preventive medicine,* 81**,** 63-66.

LYKKESFELDT, J., VISCOVICH, M. & POULSEN, H. E. 2004. Plasma malondialdehyde is induced by smoking: a study with balanced antioxidant profiles. *British Journal of Nutrition,* 92**,** 203-206.

MAHER, C. G., SHERRINGTON, C., HERBERT, R. D., MOSELEY, A. M. & ELKINS, M. 2003. Reliability of the PEDro scale for rating quality of randomized controlled trials. *Physical Therapy,* 83**,** 713-721.

MAHMOOD, I. H., ABDULLAH, K. S. & OTHMAN, S. H. 2007. The total antioxidant status in cigarette smoking individuals. *The Medical Journal of Basrah University,* 25**,** 46-50.

MALENICA, M., PRNJAVORAC, B., BEGO, T., DUJIC, T., SEMIZ, S., SKRBO, S., GUSIC, A., HADZIC, A. & CAUSEVIC, A. 2017. Effect of cigarette smoking on haematological parameters in healthy population. *Medical Archives,* 71**,** 132.

MANTEY, D. S., COOPER, M. R., CLENDENNEN, S. L., PASCH, K. E. & PERRY, C. L. 2016. E-cigarette marketing exposure is associated with e-cigarette use among US youth. *J ADOLESC HEALTH,* 58**,** 686-690.

MARCUS, B. H., ALBRECHT, A. E., KING, T. K., PARISI, A. F., PINTO, B. M., ROBERTS, M., NIAURA, R. S. & ABRAMS, D. B. 1999. The efficacy of exercise as an aid for smoking cessation in women: a randomized controlled trial. *Archives of internal medicine,* 159**,** 1229-1234.

MARCUS, B. H., ALBRECHT, A. E., NIAURA, R. S., ABRAMS, D. B. & THOMPSON, P. D. 1991. Usefulness of physical exercise for maintaining smoking cessation in women. *The American Journal of Cardiology 1991 Aug 1;68(4):406-407*.

MARCUS, B. H., ALBRECHT, A. E., NIAURA, R. S., TAYLOR, E. R., SIMKIN, L. R., FEDER, S. I., ABRAMS, D. B. & THOMPSON, P. D. 1995. Exercise enhances the maintenance of smoking cessation in women. *Addictive behaviors,* 20**,** 87-92.

MARCUS, B. H., LEWIS, B. A., HOGAN, J., KING, T. K., ALBRECHT, A. E., BOCK, B., PARISI, A. F., NIAURA, R. & ABRAMS, D. B. 2005. The efficacy of moderate-intensity exercise as an aid for smoking cessation in women: a randomized controlled trial. *Nicotine & Tobacco Research,* 7**,** 871-880.

MATT, G. E., QUINTANA, P. J., HOH, E., ZAKARIAN, J. M., DODDER, N. G., RECORD, R. A., HOVELL, M. F., MAHABEE-GITTENS, E. M., PADILLA, S. & MARKMAN, L. 2020. Persistent tobacco smoke residue in multiunit housing: Legacy of permissive indoor smoking policies and challenges in the implementation of smoking bans. *Preventive Medicine Reports***,** 101088.

MCALINDEN, K. D., CHAN, Y. L., KOTA, A., CHEN, H., OLIVER, B. G. & SHARMA, P. 2017. Maternal E-cigarette vaping enhances development of allergic asthma in the offspring. *D98. INSIGHTS INTO ENVIRONMENTAL EXPOSURES IN ASTHMA, COPD, AND CONSTRICTIVE BRONCHIOLITIS.* American Thoracic Society.

MCCARTY, M. 1999. Interleukin-6 as a central mediator of cardiovascular risk associated with chronic inflammation, smoking, diabetes, and visceral obesity: down-regulation with essential fatty acids, ethanol and pentoxifylline. *Medical hypotheses,* 52**,** 465-477.

MCCAULEY, L., MARKIN, C. & HOSMER, D. 2012. An unexpected consequence of electronic cigarette use. *Chest,* 141**,** 1110-1113.

MCFADDEN JR, E. & LINDEN, D. A. 1972. A reduction in maximum mid-expiratory flow rate: a spirographic manifestation of small airway disease. *Am J Med,* 52**,** 725-737.

MCNEILL, A., BROSE, L., CALDER, R., HITCHMAN, S., HAJEK, P. & MCROBBIE, H. 2015. E-cigarettes: an evidence update. *Public Health England,* 3.

MEAD, J. 1980. Dysanapsis in normal lungs assessed by the relationship between maximal flow, static recoil, and vital capacity. *Am Rev Respir Dis,* 121**,** 339-342.

MENDONCA, G. V., PEREIRA, F. D. & FERNHALL, B. 2011. Effects of cigarette smoking on cardiac autonomic function during dynamic exercise. *Journal of sports sciences,* 29**,** 879-886.

MEO, S. A., ANSARY, M. A., BARAYAN, F. R., ALMUSALLAM, A. S., ALMEHAID, A. M., ALARIFI, N. S., ALSOHAIBANI, T. A. & ZIA, I. 2019. Electronic cigarettes: impact on lung function and fractional exhaled nitric oxide among healthy adults. *Am J Mens Health,* 13**,** 1557988318806073.

MILLER, M. R., HANKINSON, J., BRUSASCO, V., BURGOS, F., CASABURI, R., COATES, A., CRAPO, R., ENRIGHT, P. V., VAN DER GRINTEN, C. & GUSTAFSSON, P. 2005. Standardisation of spirometry. *European respiratory journal,* 26**,** 319-338.

MIO, T., ROMBERGER, D. J., THOMPSON, A. B., ROBBINS, R. A., HEIRES, A. & RENNARD, S. I. 1997. Cigarette smoke induces interleukin-8 release from human bronchial epithelial cells. *American journal of respiratory and critical care medicine,* 155**,** 1770-1776.

MISIGOJ-DURAKOVIC, M., BOK, D., SORIC, M., DIZDAR, D., DURAKOVIC, Z. & JUKIC, I. 2012. The effect of cigarette smoking history on muscular and cardiorespiratory endurance. *J Addict Dis,* 31**,** 389-396.

MOLDOGAZIEVA, N. T., MOKHOSOEV, I. M., MEL'NIKOVA, T. I., POROZOV, Y. B. & TERENTIEV, A. A. 2019. Oxidative stress and advanced lipoxidation and glycation end products (ALEs and AGEs) in aging and age-related diseases. *Oxidative medicine and cellular longevity,* 2019.

MORROW, J. D., FREI, B., LONGMIRE, A. W., GAZIANO, J. M., LYNCH, S. M., SHYR, Y., STRAUSS, W. E., OATES, J. A. & ROBERTS, L. J. 1995. Increase in circulating products of lipid peroxidation (F2-isoprostanes) in smokers—smoking as a cause of oxidative damage. *New England Journal of Medicine,* 332**,** 1198-1203.

MORSE, C. I., PRITCHARD, L., WÜST, R. C., JONES, D. A. & DEGENS, H. 2008. Carbon monoxide inhalation reduces skeletal muscle fatigue resistance. *Acta Physiol (Oxf),* 192**,** 397-401.

MORSE, C. I., WÜST, R. C., JONES, D. A., DE HAAN, A. & DEGENS, H. 2007. Muscle fatigue resistance during stimulated contractions is reduced in young male smokers. *Acta physiologica,* 191**,** 123-129.

MÜNDEL, T. & JONES, D. A. 2006. Effect of transdermal nicotine administration on exercise endurance in men. *Experimental physiology,* 91**,** 705-713.

NARKIEWICZ, K., VAN DE BORNE, P. J., HAUSBERG, M., COOLEY, R. L., WINNIFORD, M. D., DAVISON, D. E. & SOMERS, V. K. 1998. Cigarette smoking increases sympathetic outflow in humans. *Circulation,* 98**,** 528-534.

NORDENBERG, D., YIP, R. & BINKIN, N. J. 1990. The effect of cigarette smoking on hemoglobin levels and anemia screening. *Jama,* 264**,** 1556-1559.

NORRIS, R., CARROLL, D. & COCHRANE, R. 1990. The effects of aerobic and anaerobic training on fitness, blood pressure, and psychological stress and well-being. *Journal of psychosomatic research,* 34**,** 367-375.

OFFICE FOR NATIONAL STATISTICS 2017. Adult Smoking Habits in the UK. London: Dandy Booksellers Ltd

OFFICE FOR NATIONAL STATISTICS 2019. Adult smoking habits in the UK: 2018. *London: HMSO Office for National Statistics. Available at: https://www.ons.gov.uk/peoplepopulationandcommunity/healthandsocialcare/healthandlifeexpectancies/bulletins/adultsmokinghabitsingreatbritain/2018#toc,accessed,* 13**,** 2019.

ORDONEZ, J., FORRESTER, M. B. & KLEINSCHMIDT, K. Electronic cigarette exposures reported to poison centers. Clin Toxicol, 2013. INFORMA HEALTHCARE 52 VANDERBILT AVE, NEW YORK, NY 10017 USA, 685-685.

ÖRLANDER, J., KIESSLING, K.-H. & LARSSON, L. 1979. Skeletal muscle metabolism, morphology and function in sedentary smokers and nonsmokers. *Acta Physiol Scand,* 107**,** 39-46.

ORZABAL, M. R., LUNDE-YOUNG, E. R., RAMIREZ, J. I., HOWE, S. Y., NAIK, V. D., LEE, J., HEAPS, C. L., THREADGILL, D. W. & RAMADOSS, J. 2019. Chronic exposure to e-cig aerosols during early development causes vascular dysfunction and offspring growth deficits. *Translational Research,* 207**,** 70-82.

OUYANG, Y., VIRASCH, N., HAO, P., AUBREY, M. T., MUKERJEE, N., BIERER, B. E. & FREED, B. M. 2000. Suppression of human IL-1β, IL-2, IFN-γ, and TNF-α production by cigarette smoke extracts. *Journal of Allergy and Clinical Immunology,* 106**,** 280-287.

PALAZZOLO, D. L. 2013. Electronic cigarettes and vaping: a new challenge in clinical medicine and public health. A literature review. *Front Public Health,* 1**,** 56.

PENEDO, F. J. & DAHN, J. R. 2005. Exercise and well-being: a review of mental and physical health benefits associated with physical activity. *Current opinion in psychiatry,* 18**,** 189-193.

PETERSEN, A. M. W., MAGKOS, F., ATHERTON, P., SELBY, A., SMITH, K., RENNIE, M. J., PEDERSEN, B. K. & MITTENDORFER, B. 2007. Smoking impairs muscle protein synthesis and increases the expression of myostatin and MAFbx in muscle. *Am J Physiol Endocrinol Metab*.

PEZZUTO, A., SPOTO, C., VINCENZI, B. & TONINI, G. 2013. Short-term effectiveness of smoking-cessation treatment on respiratory function and CEA level. *Journal of comparative effectiveness research,* 2**,** 335-343.

POJER, R., WHITFIELD, J., POULOS, V., ECKHARD, I., RICHMOND, R. & HENSLEY, W. 1984. Carboxyhemoglobin, cotinine, and thiocyanate assay compared for distinguishing smokers from non-smokers. *Clinical Chemistry,* 30**,** 1377-1380.

POLIDORI, M. C., MECOCCI, P., STAHL, W. & SIES, H. 2003. Cigarette smoking cessation increases plasma levels of several antioxidant micronutrients and improves resistance towards oxidative challenge. *British Journal of Nutrition,* 90**,** 147-150.

POLOSA, R., CAPONNETTO, P., MORJARIA, J. B., PAPALE, G., CAMPAGNA, D. & RUSSO, C. 2011. Effect of an electronic nicotine delivery device (e-Cigarette) on smoking reduction and cessation: a prospective 6-month pilot study. *BMC public health,* 11**,** 786.

POLOSA, R., CIBELLA, F., CAPONNETTO, P., MAGLIA, M., PROSPERINI, U., RUSSO, C. & TASHKIN, D. 2017. Health impact of E-cigarettes: a prospective 3.5-year study of regular daily users who have never smoked. *Sci Rep,* 7**,** 13825.

POLOSA, R., MORJARIA, J. B., CAPONNETTO, P., CAMPAGNA, D., RUSSO, C., ALAMO, A., AMARADIO, M. & FISICHELLA, A. 2014. Effectiveness and tolerability of electronic cigarette in real-life: a 24-month prospective observational study. *Intern Emerg Med,* 9**,** 537-546.

PRAPAVESSIS, H., CAMERON, L., BALDI, J. C., ROBINSON, S., BORRIE, K., HARPER, T. & GROVE, R. J. 2007. The effects of exercise and nicotine replacement therapy on smoking rates in women. *Addictive Behaviors 2007 Jul;32(7):1416-1432*.

PRAPAVESSIS, H., DE JESUS, S., FITZGEORGE, L., FAULKNER, G., MADDISON, R. & BATTEN, S. 2016. Exercise to Enhance Smoking Cessation: the Getting Physical on Cigarette Randomized Control Trial. *Annals of behavioral medicine : a publication of the Society of Behavioral Medicine,* 50**,** 358-369.

PRIOR, B. M., YANG, H. & TERJUNG, R. L. 2004. What makes vessels grow with exercise training? *Journal of applied physiology,* 97**,** 1119-1128.

QUILLEN, J. E., ROSSEN, J. D., OSKARSSON, H. J., MINOR, R. L., LOPEZ, J. A. G. & WINNIFORD, M. D. 1993. Acute effect of cigarette smoking on the coronary circulation: constriction of epicardial and resistance vessels. *J Am Coll Cardiol,* 22**,** 642-647.

RAHMAN, M. A., HANN, N., WILSON, A., MNATZAGANIAN, G. & WORRALL-CARTER, L. 2015. E-cigarettes and smoking cessation: evidence from a systematic review and meta-analysis. *PloS one,* 10**,** e0122544.

RANKIN, G. D., WINGFORS, H., USKI, O., HEDMAN, L., EKSTRAND-HAMMARSTRÖM, B., BOSSON, J. & LUNDBÄCK, M. 2019. The toxic potential of a fourth-generation E-cigarette on human lung cell lines and tissue explants. *Journal of Applied Toxicology,* 39**,** 1143-1154.

RASMUSSEN, P., FOGED, E. M., KROGH-MADSEN, R., NIELSEN, J., NIELSEN, T. R., OLSEN, N. V., PETERSEN, N. C., SØRENSEN, T. A., SECHER, N. H. & LUNDBY, C. 2010. Effects of erythropoietin administration on cerebral metabolism and exercise capacity in men. *Journal of applied physiology,* 109**,** 476-483.

RAWASHDEH, A. & ALNAWAISEH, N. 2018. The effect of high-intensity aerobic exercise on the pulmonary function among inactive male individuals. *Biomedical and Pharmacology Journal,* 11**,** 735-741.

RICHTER, P., PECHACEK, T., SWAHN, M. & WAGMAN, V. 2008. Reducing levels of toxic chemicals in cigarette smoke: a new Healthy People 2010 objective. *Public Health Rep,* 123**,** 30-38.

ROBERTS, V., MADDISON, R., SIMPSON, C., BULLEN, C. & PRAPAVESSIS, H. 2012. The acute effects of exercise on cigarette cravings, withdrawal symptoms, affect, and smoking behaviour: systematic review update and meta-analysis. *Psychopharmacology,* 222**,** 1-15.

RODRIGUES, F. M. M., RAMOS, D., XAVIER, R. F., ITO, J. T., DE SOUZA, A. P., FERNANDES, R. A., CECCHINI, R., E SILVA, R. C. R., MACCHIONE, M. & DE TOLEDO-ARRUDA, A. C. 2014. Nasal and systemic inflammatory profile after short term smoking cessation. *Respiratory medicine,* 108**,** 999-1006.

ROETHIG, H. J., KOVAL, T., MUHAMMAD-KAH, R., JIN, Y., MENDES, P. & UNVERDORBEN, M. 2010. Short term effects of reduced exposure to cigarette smoke on white blood cells, platelets and red blood cells in adult cigarette smokers. *Regulatory toxicology and pharmacology,* 57**,** 333-337.

RUSSELL, P. O., EPSTEIN, L. H., JOHNSTON, J. J., BLOCK, D. R. & BLAIR, E. 1988. The effects of physical activity as maintenance for smoking cessation. *Addictive behaviors,* 13**,** 215-218.

SADAKA, A. S., FAISAL, A., KHALIL, Y. M., MOURAD, S. M., ZIDAN, M. H., POLKEY, M. I. & HOPKINSON, N. S. 2021. Reduced skeletal muscle endurance and ventilatory efficiency during exercise in adult smokers without airflow obstruction. *Journal of Applied Physiology,* 130**,** 976-986.

SALVI, S. S. & BARNES, P. J. 2009. Chronic obstructive pulmonary disease in non-smokers. *Lancet,* 374**,** 733-743.

SASSO, J. P., EVES, N. D., CHRISTENSEN, J. F., KOELWYN, G. J., SCOTT, J. & JONES, L. W. 2015. A framework for prescription in exercise-oncology research. *Journal of cachexia, sarcopenia and muscle,* 6**,** 115-124.

SCHARDT, C., ADAMS, M. B., OWENS, T., KEITZ, S. & FONTELO, P. 2007. Utilization of the PICO framework to improve searching PubMed for clinical questions. *BMC medical informatics and decision making,* 7**,** 16.

SCHRAUFNAGEL, D. E., BLASI, F., DRUMMOND, M. B., LAM, D. C., LATIF, E., ROSEN, M. J., SANSORES, R., VAN ZYL-SMIT, R. & FORUM OF INTERNATIONAL RESPIRATORY, S. 2014. Electronic cigarettes. A position statement of the forum of international respiratory societies. *Am J Respir Crit Care Med,* 190**,** 611-8.

SENKFOR, A. & WILLIAMS, J. M. 1995. The moderating effects of aerobic fitness and mental training on stress reactivity. *Journal of Sport Behavior,* 18**,** 130.

SEYMOUR, J., SPRUIT, M., HOPKINSON, N., NATANEK, S., MAN, W.-C., JACKSON, A., GOSKER, H., SCHOLS, A., MOXHAM, J. & POLKEY, M. 2010. The prevalence of quadriceps weakness in COPD and the relationship with disease severity. *Eur Respir J,* 36**,** 81-88.

SHAH, B., NEPAL, A., AGRAWAL, M. & SINHA, A. 2012. The effects of cigarette smoking on hemoglobin levels compared between smokers and non-smokers. *Sunsari Technical College Journal,* 1**,** 42-44.

SHAW, D. & AL'ABSI, M. 2008. Attenuated beta endorphin response to acute stress is associated with smoking relapse. *Pharmacology Biochemistry and Behavior,* 90**,** 357-362.

SIAHPUSH, M., LEVAN, T. D., NGUYEN, M. N., GRIMM, B. L., RAMOS, A. K., MICHAUD, T. L. & JOHANSSON, P. L. 2019. The Association of Physical Activity and Mortality Risk Reduction

Among Smokers: Results From 1998–2009 National Health Interview Surveys–National Death Index Linkage. *Journal of Physical Activity and Health,* 16**,** 865-871.

SINGH, V. P., BALI, A., SINGH, N. & JAGGI, A. S. 2014. Advanced glycation end products and diabetic complications. *The Korean Journal of Physiology & Pharmacology,* 18**,** 1-14.

SPARROW, D., STEFOS, T., BOSSÉ, R. & WEISS, S. T. 1983. The relationship of tar content to decline in pulmonary function in cigarette smokers. *Am Rev Respir Dis,* 127**,** 56-58.

STĂNESCU, D., SANNA, A., VERITER, C., KOSTIANEV, S., CALCAGNI, P., FABBRI, L. & MAESTRELLI, P. 1996. Airways obstruction, chronic expectoration, and rapid decline of FEV1 in smokers are associated with increased levels of sputum neutrophils. *Thorax,* 51**,** 267-271.

STAUDT, M. R., SALIT, J., KANER, R. J., HOLLMANN, C. & CRYSTAL, R. G. 2018. Altered lung biology of healthy never smokers following acute inhalation of E-cigarettes. *Respir Res,* 19**,** 78.

STEPTOE, A. & COX, S. 1988. Acute effects of aerobic exercise on mood. *Health Psychology,* 7**,** 329.

STOCKLEY, J. A., ISMAIL, A. M., HUGHES, S. M., EDGAR, R., STOCKLEY, R. A. & SAPEY, E. 2017. Maximal mid-expiratory flow detects early lung disease in α1-antitrypsin deficiency. *Eur Respir J,* 49.

SYROVÝ, I. & HODNÝ, Z. 1992. Non-enzymatic glycosylation of myosin: effects of diabetes and ageing. *Gen Physiol Biophys,* 11**,** 301-7.

TACKETT, A. P., LECHNER, W. V., MEIER, E., GRANT, D. M., DRISKILL, L. M., TAHIRKHELI, N. N. & WAGENER, T. L. 2015. Biochemically verified smoking cessation and vaping beliefs among vape store customers. *Addiction,* 110**,** 868-874.

TALHOUT, R., SCHULZ, T., FLOREK, E., VAN BENTHEM, J., WESTER, P. & OPPERHUIZEN, A. 2011. Hazardous compounds in tobacco smoke. *Int J Environ Res Public Health,* 8**,** 613-28.

TAYLOR, A. H., USSHER, M. H. & FAULKNER, G. 2007. The acute effects of exercise on cigarette cravings, withdrawal symptoms, affect and smoking behaviour: a systematic review. *Addiction,* 102**,** 534-543.

TAYLOR, C. B., HOUSTON-MILLER, N., HASKELL, W. L. & DE BUSK, R. F. 1988. Smoking cessation after acute myocardial infarction: the effects of exercise training. *Addictive Behaviors 1988;13(4):331-335*.

TAYLOR JR, D. H., HASSELBLAD, V., HENLEY, S. J., THUN, M. J. & SLOAN, F. A. 2002. Benefits of smoking cessation for longevity. *American journal of public health,* 92**,** 990-996.

THORNTON, S., OLLER, L. & SAWYER, T. Fatal intravenous injection of electronic "eLiquid" solution. Annual Meeting of North American Congress of Clinical Toxicology. Clin Toxicol, 2013. 238.

TRAN, B., FALSTER, M. O., DOUGLAS, K., BLYTH, F. & JORM, L. R. 2015. Smoking and potentially preventable hospitalisation: the benefit of smoking cessation in older ages. *Drug and alcohol dependence,* 150**,** 85-91.

TULGAR, Y., CAKAR, S., TULGAR, S., DALKILIC, O., CAKIROGLU, B. & UYANIK, B. 2016. The effect of smoking on neutrophil/lymphocyte and platelet/lymphocyte ratio and platelet indices: a retrospective study. *Eur Rev Med Pharmacol Sci,* 20**,** 3112-8.

UK MEDICINES AND HEALTHCARE PRODUCTS REGULATORY AGENCY. 2020. *E-cigarette use or vaping: reporting suspected adverse reactions, including lung injury* [Online]. Medicines & Healthcare products Regulatory Agency. Available: https://www.gov.uk/drug-safety-update/e-cigarette-use-or-vaping-reporting-suspected-adverse-reactions-including-lung-injury#context [Accessed 13/02/2021 2021].

VAKALI, S., TSIKRIKA, S., GENNIMATA, S. A., KALTSAKAS, G., PALAMIDAW, A., KOULOURIS, N. & GRATZIOU, C. 2013. E-cigarette acute effect on symptoms and airways inflammation: Comparison of a nicotine containing with a non-nicotine device. *Eur Respir J*.

VALENTO, M. Nicotine poisoning following ingestion of e-Liquid. ClinToxicol, 2013. INFORMA HEALTHCARE 52 VANDERBILT AVE, NEW YORK, NY 10017 USA, 683-684.

VARDAVAS, C., TZATZARAKIS, M., VARDAVAS, A., GIRVALAKI, C., STIVAKTAKIS, P., NIKOLOUZAKIS, T. & TSATSAKIS, A. 2017. Evaluation of respiratory irritants among the most popular e-cigarette refill liquids across 9 European countries. *Eur Respir J*.

VARDAVAS, C. I., ANAGNOSTOPOULOS, N., KOUGIAS, M., EVANGELOPOULOU, V., CONNOLLY, G. N. & BEHRAKIS, P. K. 2012. Short-term pulmonary effects of using an electronic cigarette:

impact on respiratory flow resistance, impedance, and exhaled nitric oxide. *Chest,* 141**,** 1400-1406.

VLASSARA, H. & PALACE, M. 2002. Diabetes and advanced glycation endproducts. *Journal of internal medicine,* 251**,** 87-101.

WAI, E. K., DAGENAIS, S. & HALL, H. 2011. Physical Activity, Smoking Cessation, and Weight Loss. *Evidence-based Management of Low Back Pain***,** 39.

WALD, N. J., IDLE, M., BOREHAM, J. & BAILEY, A. 1981. Carbon monoxide in breath in relation to smoking and carboxyhaemoglobin levels. *Thorax,* 36**,** 366-369.

WANG, X., ARAKI, S., YANO, E., WANG, M. & WANG, Z. 1995. Effects of smoking on respiratory function and exercise performance in asbestos workers. *Industrial health,* 33**,** 173-180.

WARREN, G. W., ALBERG, A. J., KRAFT, A. S. & CUMMINGS, K. M. 2014. The 2014 Surgeon General's report:"The Health Consequences of Smoking–50 Years of Progress": a paradigm shift in cancer care. *Cancer,* 120**,** 1914-1916.

WEST, R. & HAJEK, P. 1997. What happens to anxiety levels on giving up smoking? *American Journal of Psychiatry,* 154**,** 1589-1592.

WESTENBERGER, B. 2009. Evaluation of e-Cigarettes. St Louis, MO: Department of Health and Human Services. *Food and Drug Administration, Center for Drug Evaluation and Research, Division of Pharmaceutical Analysis*.

WHEATON, A. G., LIU, Y., CROFT, J. B., VANFRANK, B., CROXTON, T. L., PUNTURIERI, A., POSTOW, L. & GREENLUND, K. J. 2019. Chronic obstructive pulmonary disease and smoking status—United States, 2017. *Morbidity and Mortality Weekly Report,* 68**,** 533.

WIESLANDER, G., NORBÄCK, D. & LINDGREN, T. 2001. Experimental exposure to propylene glycol mist in aviation emergency training: acute ocular and respiratory effects. *Occup Environ Med,* 58**,** 649-655.

WILLIAMS, M., VILLARREAL, A., BOZHILOV, K., LIN, S. & TALBOT, P. 2013. Metal and silicate particles including nanoparticles are present in electronic cigarette cartomizer fluid and aerosol. *PloS One,* 8**,** e57987.

WORLD HEALTH ORGANIZATION 2017. *WHO report on the global tobacco epidemic, 2017: monitoring tobacco use and prevention policies*, World Health Organization.

WU, X., GAO, S. & LIAN, Y. 2020. Effects of continuous aerobic exercise on lung function and quality of life with asthma: a systematic review and meta-analysis. *Journal of Thoracic Disease,* 12**,** 4781.

WÜST, R. C. & DEGENS, H. 2007. Factors contributing to muscle wasting and dysfunction in COPD patients. *Int J Chron Obstruct Pulmon Dis,* 2**,** 289.

WÜST, R. C., JASPERS, R. T., VAN DER LAARSE, W. J. & DEGENS, H. 2008a. Skeletal muscle capillarization and oxidative metabolism in healthy smokers. *Applied Physiology, Nutrition, and Metabolism,* 33**,** 1240-1245.

WÜST, R. C., MORSE, C. I., DE HAAN, A., JONES, D. A. & DEGENS, H. 2008b. Sex differences in contractile properties and fatigue resistance of human skeletal muscle. *Experimental physiology,* 93**,** 843-850.

WÜST, R. C., MORSE, C. I., DE HAAN, A., RITTWEGER, J., JONES, D. A. & DEGENS, H. 2008c. Skeletal muscle properties and fatigue resistance in relation to smoking history. *Eur J Appl Physiol,* 104**,** 103.

WUST, R. C., WINWOOD, K., WILKS, D. C., MORSE, C. I., DEGENS, H. & RITTWEGER, J. 2010. Effects of smoking on tibial and radial bone mass and strength may diminish with age. *The Journal of Clinical Endocrinology & Metabolism,* 95**,** 2763-2771.

XU, X., LI, B. & WANG, L. 1994. Gender difference in smoking effects on adult pulmonary function. *Eur Respir J,* 7**,** 477-483.

ZAKARIA, R., HARIF, N., AL-RAHBI, B., AZIZ, C. B. A. & AHMAD, A. H. 2019. Gender Differences and Obesity Influence on Pulmonary Function Parameters. *Oman Med J,* 34**,** 44.

Appendix 1: Ethical approval statement

24/05/2019
Project Title: Impact of vaping and smoking on cardiorespiratory and muscle function

EthOS Reference Number: 5944

Ethical Opinion

Dear Hans Degens,

The above application was reviewed by the Science and Engineering Research Ethics and Governance Committee and, on the 24/05/2019, was given a favourable ethical opinion. The approval is in place until 07/01/2023.

Conditions of favourable ethical opinion

Application Documents

Document Type	File Name	Date	Version
Project Proposal	190102rd1	31/01/2019	1
Consent Form	190211 Consent-Form - Final	11/02/2019	1
Recruitment Media	190326Invitation poster- Vaping- Final	26/03/2019	2
Information Sheet	190326Participant-Information-Sheet- Final	26/03/2019	2

The Science and Engineering Research Ethics and Governance Committee favourable ethical opinion is granted with the following conditions

Adherence to Manchester Metropolitan University's Policies and procedures

This ethical approval is conditional on adherence to Manchester Metropolitan University's Policies, Procedures, guidance and Standard Operating procedures. These can be found on the Manchester Metropolitan University Research Ethics and Governance webpages.

Amendments

If you wish to make a change to this approved application, you will be required to submit an amendment. Please visit the Manchester Metropolitan University Research Ethics and Governance webpages or contact your Faculty research officer for advice around how to do this.

We wish you every success with your project.

Science and Engineering Research Ethics and Governance Committee

Appendix 2: Participants Information Sheet

The effects of vaping and smoking on cardiorespiratory and muscle function and low back pain

Manchester Metropolitan University

This project is undertaken by Mohammad Darabseh, a PhD student Metropolitan University, supervised by Prof. Hans Degens, Prof. James Selfe and Dr Christopher Morse. Before you decide to participate we want to explain to you why the research is being done and what it would involve for you. Please take time to read the following information carefully. Ask questions if anything you read is unclear or if you would like more information.

What is the purpose of the study?
Previous studies have shown that cigarette smoking has negative effects on cardiorespiratory, vascular and muscle function. Vaping is becoming a wide spread alternative and marketed as safer than cigarette smoking. There is, however, concern that e-cigarettes may singularly stimulate uptake of smoking, particularly in youth, and have an acute negative effect on cardiorespiratory health, even in the absence of smoking. In 2014, the potential health risk of e-cigarettes led the *Forum of International Respiratory Societies* to release a position statement that concluded: '*As a precaution, electronic nicotine delivery devices should be restricted or banned until more information about their safety is available*'. This led us to study the effects of vaping on cardiorespiratory, vascular and muscle function, and we would like also to know if vaping contributes to low back pain.

Why have I been invited?
We are inviting 105 participants, above 18 years old, cigarette smokers, vapers and non-smokers/vapers to participate in the study. As a participant, you should be free from known cardiovascular and respiratory diseases and not have had surgery in the last 3 months. If you have a pacemakers/metallic implants, or you are a pregnant women we will have to exclude you from the study as although all the procedures are safe, they may cause undue stress to your unborn child.

Do I have to take part?
You are free to decide whether you wish to take part or not. If you do decide to take part, you will be asked to sign a consent form prior to any testing. You will be given a copy of this participant information sheet to keep. You are free to withdraw from this study at any time and without giving reasons. If you decide to withdraw from the study, we will also destroy, if you wish so, any documentation that contains personal identifiable information, but we will ask your permission to use the data collected up to the point of your withdrawal. You are free to withdraw from the study at any time.

What will happen to me if I take part?
You will be sked to attend two experimental sessions in the laboratories of the School of Healthcare Science at Manchester Metropolitan University. Each single testing session will last for around 2 hours.
You should not consume caffeinated drinks, vape or smoke for at least 2 hours before the experimental session.
First visit:

Height and body mass: We will record your height and weight. In addition, your body composition will be assessed using bioelectrical impedance, which is a method used to estimate body fat.

A breathing (lung function) test: You will be asked to breathe through a mouthpiece and a noseclip will be placed to prevent you from breathing through your nose. After a short period of normal breathing you will be asked to inhale maximally followed by a forceful complete exhalation.
To measure the strength of your respiratory muscles you will be asked to inspire or expire as forcefully as possible, after total expiration or inspiration respectively, into a portable small device with a high resistance to breathing. Next, you will be asked to place a probe in one of your nostrils while the other nostril is closed and you inspire as fast and as forceful as possible via the nose. This test will tell us something about your lung function and if you wish we can tell you how you compare to others of the same age and sex. The test will take approximately 30 minutes.

Muscle Strength and Function: For this, you sit on a strength-testing chair with your ankle strapped to a bar and we ask you to push against this as hard as you can. While you are sitting in the chair, we would like to activate your muscle by electrical stimulation. This gives us information about the speed of contraction and the susceptibility to fatigue of your muscle. It is an unusual sensation when your muscle contracts without you doing anything and some people find it unpleasant when the current is increased. However, we will get you accustomed to the sensations very slowly and not go any higher than you are prepared to tolerate. Once you are happy with the stimulation we will cause the muscle to contract at different frequencies and finally carry out a fatigue test in which the muscle contracts rhythmically for two minutes. This mimics the muscular activity involved in walking up stairs, but without you having to make any effort. Approximately, 40 minutes will be allocated for this test.

Completion of questionnaires: You will be asked as part of the assessment to complete four short questionnaires about your general physical functionality, back pain, quality of life, Nicotine dependence and vaping and smoking habits and cardiac function. We allocate 30 minutes for the questionnaires to be completed.

Second visit:

Muscle size: The size of your lower back muscles and thigh muscle will be determined using Magnetic Resonance Imaging (MRI). For this, you lay in an MRI scanner for approximately 40 minutes. You feel nothing at all, and most people drift off to sleep while reclining on the couch. MRI is non-invasive technique and is considered to carry minimal risk. We allocate approximately one hour for both thigh and back muscles measurements.

Vascular function test: For this test, the blood flow to the lower arm will be stopped for 5 min by a blood pressure cuff placed around the upper arm to a pressure of 240 mmHg. After 5 min the cuff will be deflated and this will cause an extra flow of blood through the lower arm. We will determine the flow through an arm artery before and after the cuff with ultrasound. You may have a transient tingling sensation (for a few min), but the procedure is harmless. This test will last for about 30 minutes.

Cardiorespiratory fitness: We would like you to pedal on a stationary exercise bike for as long as you can while the load is gradually increased. This last test will make you a little hot and tired but the important thing is that you stop when you feel you cannot continue and that you will have time to rest and recover before going home. During this test, you will breathe through a mouthpiece to measure gas exchange in the lungs and will be wearing a small device on your earlobe to assess oxygen saturation in the blood. Also heart rate will be monitored during the entire test and blood pressure will be measured before and after the test. Only those under 55 years will be asked to perform this test. We allocate 30 minutes for this test to be done.

Blood Sample: We will ask to take a small blood sample by inserting a needle into a vein in your forearm. This only lasts a matter of seconds. This will be done a total of 2 times throughout the study, once before the Cardiorespiratory fitness test and once after, to allow us to look for biological changes that may occur in our response to the exercise.

Expenses and payments?
Travel expenses can be reimbursed and you will receive a £10 voucher upon completion of all experiments as a token of our appreciation.

What are the possible disadvantages and risks of taking part?

Electrical stimulation: Some people may find electrical stimulation unpleasant. However, you will be introduced to electrical stimulation by gradual increase of the stimulation intensity in order to avoid any unpleasant feeling. Also, the stimulation will not be increased if it led to intolerable muscle contraction.

Cycle ergometer test: Some people experience abnormal changes to blood pressure, fainting, angina, and in rare instances heart attack or stroke. This is, however, unlikely, and you must inform us if you suffer from any cardiovascular or respiratory problems. To further minimise any risk to you we will keep a close eye on you throughout the test.

A breathing (lung function) test: Some participants might feel slightly tired after doing the breathing test. However, you will have opportunity to recover your breath between components of the test.

Vascular function test, Ultrasound and MRI: Are unlikely to have any pain or adverse events.

What are the possible benefits of taking part?
By participating in this study, you will help us in understanding the effects of vaping on cardiorespiratory, vascular and muscle function. This knowledge will inform health services and policy makers to design new policies on vaping. You are going to get some information on your fitness level and pulmonary function.

Will my taking part in the study be kept confidential?
All personal information collected about you will be treated as confidential and privileged, and we will only collect information about you that we need to answer the questions of our research. We would like to reassure you that your personal information will be kept strictly confidential, and will only be accessible to members

of the research team involved in the collection and processing / analysis of that data. No personal identifying information will appear in our published results.

Involvement of the General Practitioner/Family Doctor (GP)
The assessment tests will be conducted in the study would not affect your health, therefore, contacting your GP is not necessary.

What will happen to the results of the research study?
The information and data will be used for scientific presentations and publications in such a way that they can not be linked back to you.

Who is organising or sponsoring the research?
This research is not being funded externally and is the PhD work of Mohammad Darabseh, organised and overseen by Manchester Metropolitan University.

What if there is a problem?
If you have a concern about any aspect of this study, you may wish to speak to the researchers who will do their best to answer your questions. You should contact Mohammad Darabseh in the first instance, or, alternatively, you may want to contact the project lead supervisor, Prof. Hans Degens (see contact details at the end of this page).

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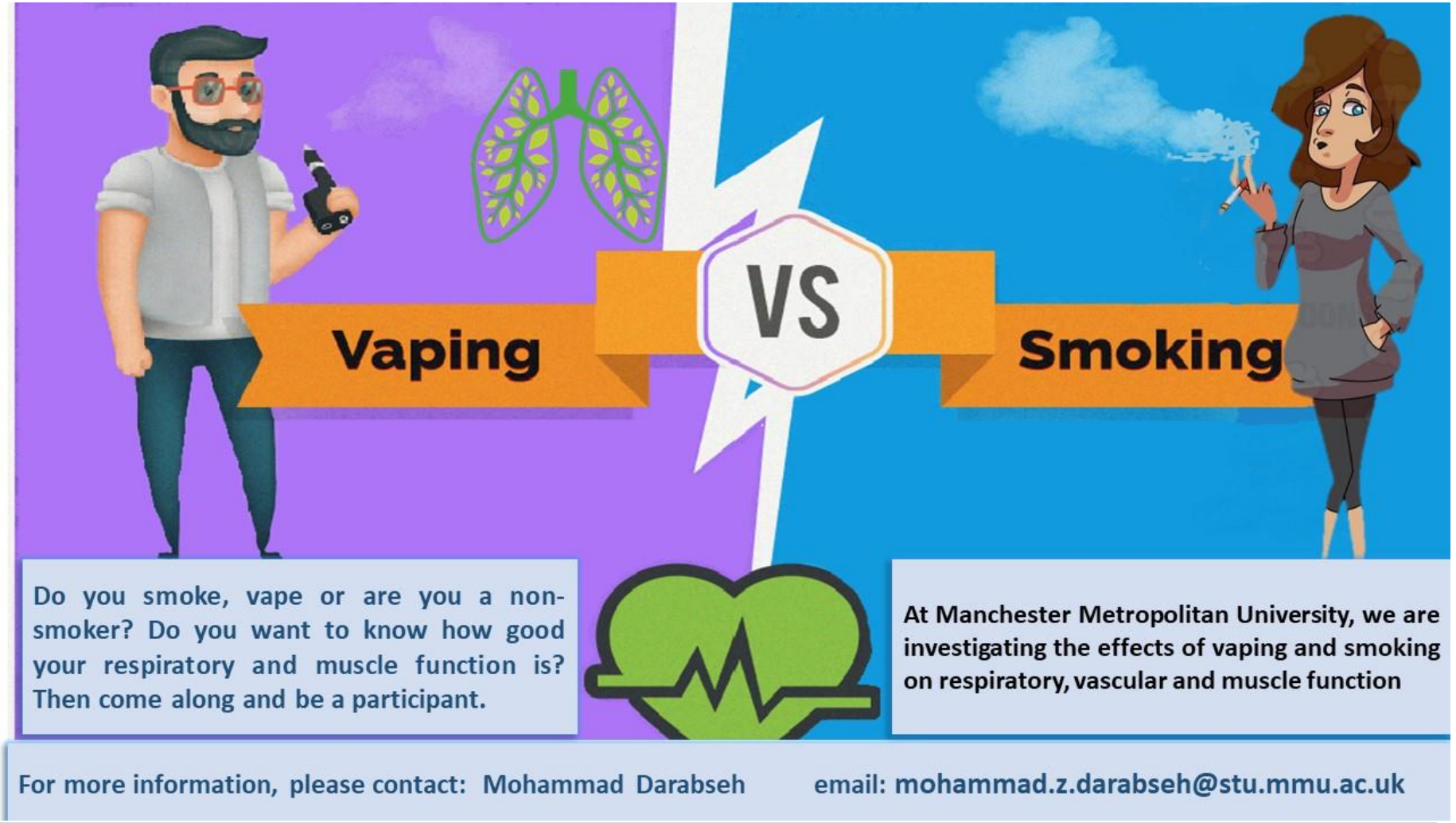
Appendix 3: Recruitment poster



Appendix 4: Consent form

Date
Name
School of Healthcare Science
Manchester Metropolitan University

Manchester Metropolitan University

Title of Project: Impact of vaping and smoking on cardiorespiratory and muscle function and low back pain.

Name of Researcher: Mohammad Darabseh, Prof Hans Degens, Prof James Selfe, Dr. Liam Bagley, Dr Chris Morse

Participant Identification Code for this project:

	Please initial box
1. I confirm that I have read and understood the information sheet dated 23 November, 2019 for the above project and have had the opportunity to ask questions about all procedures.	☐
2. I understand that my participation is voluntary and that I am free to withdraw at any time without giving any reason to the named researcher.	☐
3. I give permission for my answers and information to be archived as part of this research project, making it available to future research.	☐
4. I understand that my data will be anonymised.	☐
5. I agree to take part in the above research project.	☐

_____	_____	_____
Name of Participant	Date	Signature
_____	_____	_____
Researcher	Date	Signature

To be signed and dated in presence of the participant

Once this has been signed, you will receive a copy of your signed and dated consent form and information sheet by post or email.

Appendix 5: Screening questionnaire

Name:

Physical Activity Readiness Questionnaire (PAR-Q)

Manchester Metropolitan University
Department of Sport and Exercise Science

_____
_

Date of Birth: _____ Age: _____Gender: _____

Please answer the following questions by putting a circle round the appropriate response or filling in the blank.

1. **How would you describe your present level of activity?**
   Sedentary / Moderately active / Active / Highly active

2. **How would you describe you present level of fitness?**
   Unfit / Moderately fit / Trained / Highly trained

3. **How would you consider your present body weight?**
   Underweight / Ideal / Slightly over / Very overweight

4. **Smoking Habits** Are you currently a smoker? Yes / No
   If yes, how many do you smoke …….. per day
   Are you a previous smoker? Yes / No
   If yes, how long is it since you stopped? ..... years

5. **Do you drink alcohol?** Yes / No
   If you answered **Yes**, do you usually have?
   An occasional drink / a drink every day / more than one drink a day?

6. **Have you had to consult your doctor within the last 6 months?** Yes / No
   If you answered **Yes**, please give details……...……..……
   ……...…… …….

7. **Are you presently taking any form of medication?** Yes / No
   If you answered **Yes**, please give details……...…….
   ……...…… …….

8. As far as you are aware, do you suffer or have you ever suffered from:

a Diabetes?	Yes / No	**b** Asthma?	Yes / No
c Epilepsy?	Yes / No	**d** Bronchitis?	Yes / No
e *Any form of heart complaint?	Yes / No	**f** Raynaud's Disease?	Yes / No
g *Marfan's Syndrome?	Yes / No	**h *** Aneurysm/embolism?	Yes / No
I Anaemia	Yes / No		

Any other medical condition or illness? Yes / No

If you answered **Yes**, please give details…….

……..……
…….

9. *Is there a history of heart disease in your family? Yes / No

10. *Do you currently have any form of muscle or joint injury? Yes / No

If you answered **Yes**, please give details…….....

……..……
…….

……..……
……

11. Have you suspended your normal training in the last 2 weeks? Yes / No

If the answer is **Yes** please give details……..….

……..……
…….

……..……
……

If blood is not being taken from you please disregard Section 12 below.

12. ***Please read the following questions:

a)	Are you suffering from any known serious infection?	Yes / No
b)	Have you had jaundice within the previous year?	Yes / No
c)	Have you ever had any form of hepatitis?	Yes / No
d)	Are you living with HIV?	Yes / No
e)	Have you had unprotected sexual intercourse with any person from an HIV high-risk population?	Yes / No
f)	Have you ever been involved in intravenous drug use?	Yes / No
g)	Are you hemophiliac?	Yes / No

13. Have you participated in any form of exercise testing before? Yes / No

If the answer is **Yes**, have you ever needed to terminate a test prior to completion, for health and safety reasons?

Yes / No

If the answer is **Yes** please give details……

……..……
…….

……
……

14. As far as you are aware, is there anything that might prevent you from successfully completing the tests that have been outlined to you? Yes / No

……
……

……
……

IF THE ANSWER TO ANY OF THE ABOVE IS YES THEN:

a) Discuss the nature of the problem with the Principal Investigator.

b) Questions indicated by * please provide consent from your GP.

As far as I am aware the information I have given is accurate.

Participant's Signature: ……...

Supervisor's Signature: ……...

Date: ……/……/……

Appendix 6: QUESTIONNAIRE ON SMOKING AND VAPING HABITS

QUESTIONNAIRE ON SMOKING AND VAPING HABITS

INSTRUCTIONS- This set of questions asks for your smoking and vaping habits. Answer every question by marking the answer as indicated. If you are unsure about how to answer a question, please give

Participant _____

Date _____

1) Do you smoke at present?

Vape / Yes / No
If no please continue to question 2
If yes please continue to question 3
If you Vape continue to question 12

2) Have you smoked before?

Yes / No
If no, thank you for your co-operation
If yes please continue to question 3

3) At what age did you start smoking?

_____

4) What age did you stop smoking? (If appropriate)

_____

5) What kind of tobacco do you normally smoke?

Light / Mild / Heavy

6) Do/did you normally inhale?

Yes / No

7) Do you use a filter or non-filter cigarettes?

Filter / No Filter
If no filter, please answer questions 10 & 11 also

8) How many cigarettes a day did you smoke when you started smoking?

_____

9) How many cigarettes a day do you smoke now?

_____

10) How much tobacco a day did you use when you started smoking?

_____

11) How much tobacco a day do you use now?

_____

12) What is the system/style of vaping do

Mouth to Lung (MTL)

you use? **Direct to Lung (DL)**

13) What is the battery voltage that you usually vape at?

_____

14) At what age did you start vaping?

_____

15) What age did you stop vaping? (If appropriate)

_____

16) What kind of e-liquid/juice do you normally vape?

70 PG / 30 VG
50 G / 50 VG
70 G / 30 PG
80 G / 20 PG
Max VG
Other _____

17) How much e-liquid / juice are you consuming per day?

_____**ml/day**

18) How many e-liquid cartridges do you consume per week?

_____**/week**

19) Do you vape e-liquid / juice that contains nicotine? **Yes / No**

20) What is the cartridge e-liquid/juice nicotine concentration (strength)?

_____**mg/ml**

21) What is the flavour of the e-liquid/juice that you vape?

_____

22) How many puffs do you usually make per use?

_____

23) What is the approximate interval (time) between puffs of single use?

_____

24) Did you smoke cigarettes /cigar/ pipe before staring vaping? **Yes / No**

If yes, please write for how long

_____

25) Did vaping act as a way of encouraging you to take up smoking? **Yes / No**

26) Are you vaping as a way to reduce your cigarette smoking? **Yes / No**

Thank you for your co-operation

Appendix 7: ODI questionnaire

ODI version 2.1a

This questionnaire is designed to give us information as to how your back (or leg) trouble affects your ability to manage in everyday life.
Please answer every section. Mark one box only in each section that most closely describes you today.

Section 1 - Pain intensity

- ☐ I have no pain at the moment.
- ☐ The pain is very mild at the moment.
- ☐ The pain is moderate at the moment.
- ☐ The pain is fairly severe at the moment.
- ☐ The pain is very severe at the moment.
- ☐ The pain is the worst imaginable at the moment.

Section 2 - Personal care (washing, dressing, etc.)

- ☐ I can look after myself normally without causing extra pain.
- ☐ I can look after myself normally but it is very painful.
- ☐ It is painful to look after myself and I am slow and careful.
- ☐ I need some help but manage most of my personal care.
- ☐ I need help every day in most aspects of self care.
- ☐ I do not get dressed, wash with difficulty and stay in bed.

Section 3 - Lifting

- ☐ I can lift heavy weights without extra pain.
- ☐ I can lift heavy weights but it gives extra pain.
- ☐ Pain prevents me from lifting heavy weights off the floor but I can manage if they are conveniently positioned, e.g. on a table.
- ☐ Pain prevents me from lifting heavy weights but I can manage light to medium weights if they are conveniently positioned.
- ☐ I can lift only very light weights.
- ☐ I cannot lift or carry anything at all.

Section 4 - Walking

- ☐ Pain does not prevent me walking any distance.
- ☐ Pain prevents me walking more than one mile.
- ☐ Pain prevents me walking more than a quarter of a mile.
- ☐ Pain prevents me walking more than 100 yards.

ODI - United Kingdom/English - Mapi Research Institute.
ODI_AU2.1a_eng-GBorl.doc

- ☐ I can only walk using a stick or crutches.
- ☐ I am in bed most of the time and have to crawl to the toilet.

Section 5 - Sitting

- ☐ I can sit in any chair as long as I like.
- ☐ I can sit in my favourite chair as long as I like.
- ☐ Pain prevents me from sitting for more than 1 hour.
- ☐ Pain prevents me from sitting for more than half an hour.
- ☐ Pain prevents me from sitting for more than 10 minutes.
- ☐ Pain prevents me from sitting at all.

Section 6 - Standing

- ☐ I can stand as long as I want without extra pain.
- ☐ I can stand as long as I want but it gives me extra pain.
- ☐ Pain prevents me from standing for more than 1 hour.
- ☐ Pain prevents me from standing for more than half an hour.
- ☐ Pain prevents me from standing for more than 10 minutes.
- ☐ Pain prevents me from standing at all.

Section 7 - Sleeping

- ☐ My sleep is never disturbed by pain.
- ☐ My sleep is occasionally disturbed by pain.
- ☐ Because of pain I have less than 6 hours sleep.
- ☐ Because of pain I have less than 4 hours sleep.
- ☐ Because of pain I have less than 2 hours sleep.
- ☐ Pain prevents me from sleeping at all.

Section 8 - Sex life (if applicable)

- ☐ My sex life is normal and causes no extra pain.
- ☐ My sex life is normal but causes some extra pain.
- ☐ My sex life is nearly normal but is very painful.
- ☐ My sex life is severely restricted by pain.
- ☐ My sex life is nearly absent because of pain.
- ☐ Pain prevents any sex life at all.

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Section 9 - Social life

- ☐ My social life is normal and causes me no extra pain.
- ☐ My social life is normal but increases the degree of pain.
- ☐ Pain has no significant effect on my social life apart from limiting my more energetic interests, e.g. sport, etc.
- ☐ Pain has restricted my social life and I do not go out as often.
- ☐ Pain has restricted social life to my home.
- ☐ I have no social life because of pain.

Section 10 - Travelling

- ☐ I can travel anywhere without pain.
- ☐ I can travel anywhere but it gives extra pain.
- ☐ Pain is bad but I manage journeys over two hours.
- ☐ Pain restricts me to journeys of less than one hour.
- ☐ Pain restricts me to short necessary journeys under 30 minutes.
- ☐ Pain prevents me from travelling except to receive treatment

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Result

Your ODI = ☐ %

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Appendix 8: MRI screening form

Vancouver Coastal Health Authority

☐ LGH ☐ RH ☐ UBCH ☐ VGH

MAGNETIC RESONANCE IMAGING (MRI) PATIENT SCREENING FORM

NAME: _____

DATE: _____

or PATIENT LABEL

Every patient scheduled for MRI **MUST** complete the following questionnaire prior to the being scanned. The technologist will be happy to answer any of your questions. **Please answer each question accurately and explain any marked "yes'**

Birth date: _____ Age: _____ Height____ft____in or ____cm Weight:_____kg or _____lb

Do you have:	**Yes**	**No**	**Unsure**	**If yes, explain**
Cardiac (Heart) Pacemaker or Wires (At any time in your life)				
Artificial Heart Valves				
Brain aneurysm clips				
Metal in your eyes (At any time in your life)				
Implanted Electrodes, Pumps or Catheters				
Neurostimulators				
Shrapnel, Bullets or other metal fragments				
Any Tattoos – including permanent make up				
Ear implants (Cochlear, Stapes) /Hearing Aid				
Orthopedic (Bone) Screws, Pins, Plates, Rods (If yes, state location)				
Breast tissue expander or other implants				
Prosthesis (Eye, Penile, Leg, Arm, Joint, etc.)				
Any Stents, Coils, or Filter in blood vessels				
Dentures, retainer, braces, magnetic implants				
Transdermal medication patches (Examples: Nitroglycerin for heart or Nicotine to stop smoking)				
Body Piercing other than earrings				
Have you ever had surgery or operation on:				
Brain, Eye, or Ear				
Heart				
Neck, Chest, or Back (Spine)				
Abdomen, Pelvis, Hips				
Arms and/or Legs				
Injection into a joint within the last 2 weeks				
Are you:				
Pregnant				
Claustrophobic				

Please remove all your jewelry, watch, credit cards, coins and other metallic items (earrings, hair clips, bobby pins, etc A MRI staff member will instruct you about securing your items prior to entry into the examination area. I have read an understand the entire contents of this form. I affirm that the above information is true to the best of my knowledge and hereby consent to the MRI study

_____ _____

Signature of person completing this form Date

_____ _____ _____

Relationship to patient if form not completed by patient Review Date Patient Initials

_____ _____

Signature of translator Date

MR Technologist Initials/Date

If your MRI exam date occurs after the date the screening form was completed, you must review the screening form and alert the M technologist of any changes. Please enter the date of review and your initials indicating confirmation of review.

MRI Contrast Agent Questionnaire

Please answer the following questions:

Do you have:	Yes	No	Unsure
Any allergies?			
Renal problems or family history of such (Kidney problem, disease, condition)?			
Type I or II Diabetes?			
Liver transplant or currently on a waiting list for a liver transplant?			
History of stroke?			
Peripheral vascular disease (Problems with blood vessel circulation in arms or legs)			
Ischemic Cardiac disease (Heart problems such as blocked arteries, history of Heart attack)?			
Asthma? If yes, is your asthma currently active?			
Sickle Cell or Hemolytic Anemia?			
Have you had:			
Previous injection of MRI contrast?			
Did you have a reaction? If yes, describe what happened:			
Are you:			
On Dialysis?			
Pregnant and/or Nursing?			

Your doctors believe it is in your best interest to have an MRI (Magnetic Resonance Imaging) examination that includes the intravenous or IV injection (through an arm or hand vein) of a contrast agent containing gadolinium.

Gadolinium-containing contrast agents are given during MRI examinations to provide additional information regarding the presence and extent of inflammation, infection, or tumors, and to evaluate blood vessels. Gadolinium is considered to be quite safe, with a very low risk of minor allergic reactions, and an extremely low risk of serious allergic reactions. Should you have a reaction, there will be a Physician available and medication on hand to treat the reaction.

I have read and understand the above information, and have had an opportunity to have my questions answered.

I agree to receive an intravenous injection of a contrast agent containing gadolinium as part of the MRI examination to provide further diagnostic information.

_____ _____

Signature of person completing this form Date

_____ _____ _____

Relationship to patient if form not completed by patient Review Date Patient Initials

_____ _____

Signature of translator Date

MR Technologist Initials/Date

If your MRI exam date occurs after the date the screening form was completed, you must review the screening form and alert the MR technologist of any changes. Please enter the date of review and your initials indicating confirmation of review.

Appendix 9: Systematic review and meta-analysis protocol registered on PROSPERO

NIHR | National Institute for Health Research

PROSPERO
International prospective register of systematic reviews

Citation

Mohammad Z. Darabseh, James Selfe, Christopher Morse, Hans Degens. Does aerobic exercise facilitate vaping and smoking cessation? A systematic review of randomized controlled trials. PROSPERO 2021 CRD42021232759 Available from: https://www.crd.york.ac.uk/prospero/display_record.php?ID=CRD42021232759

Review question

What is the effectiveness of aerobic exercise on long-term vaping and smoking cessation?

Searches

1) The following electronic databases will be searched for trials published between 1st January 1970 to 1st January 2021: MEDLINE, AMED, SPORTDiscus, CINAHL and PEDro.

2) Reference lists of included trials will also be hand searched to identify other potentially relevant trials.

3) Search terms will be adapted to meet the search requirements of each electronic database.

4) Trials included will be limited to those written in English and they have to be published in peer-reviewed journals.

Additional search strategy information can be found in the attached PDF document (link provided below).

Types of study to be included

The search will be limited to randomised controlled trials (RCTs).

Inclusion/exclusion criteria for the trials:

Inclusion criteria:

Trials will be included if:

• They include men and women (adults) >18 years old.

• They assess continued/prolonged vaping cessation/smoking cessation by means of objective measures such as carbon monoxide level (CO), cotinine level, thiocyanate level.

• They involve participants who have been smoking for ? 6months and smoked/smoke ? 5 cigarettes per day or vaped for ? 6 months.

Exclusion criteria

Trials will be excluded if:

• The intervention was other than cardiovascular/aerobic exercise or if the aerobic exercise was combined with another type of exercise.

• The exercise type used was not identified.

• The outcome measures did not include CO, cotinine, and/or thiocyanate.

• The period of smoking cessation was less than six months.

• They are not written in the English language.

• They involve participants diagnosed with psychiatric illness that could affect their exercise adherence (for example: depression or anxiety).

• They involve substance misuse problems (such as drugs and alcohol abuse).

• They involve participants that are pregnant.

• They involve participants with any medical condition that might affect their exercise performance such as musculoskeletal or neurological conditions.

• They are published protocols without published data/results; or if they were conference abstracts.

Condition or domain being studied

The study will assess the effectiveness of aerobic exercise on vaping and smoking cessation.

Participants/population

Inclusion criteria:

• Men and women (adults) >18 years old.

• Participants undergoing continued/prolonged vaping cessation/smoking cessation, assessed by means of objective measures such as carbon monoxide level (CO), cotinine level, thiocyanate level.

• Participants who have been smoking for ? 6months and smoked/smoke ? 5 cigarettes per day or vaped for ? 6 months.

Exclusion criteria

• Participants diagnosed with psychiatric illness that could affect their exercise adherence (for example: depression or anxiety).

• Participants with substance misuse problems (such as drugs and alcohol abuse).

• Participants that are pregnant.

• Participants with any medical condition that might affect their exercise performance such as musculoskeletal or neurological conditions.

Intervention(s), exposure(s)

The intervention is aerobic exercise (cardiovascular exercise) programmes.

Any trial with aerobic exercise intervention such as (but not limited to) walking, running, cycling, treadmill walking, stationary cycling, swimming, rowing, dancing, aerobic virtual reality exercises or group-based aerobic (cardiac) exercises will be considered.

Comparator(s)/control

Interventions that include no aerobic exercise or structured changes in physical activity that are designed to support vaping or smoking cessation.

Context
Settings of the trials will not be limited.

Trials are expected to include community- or hospital-based settings, but inclusion will not be limited by the setting.
Countries of the trials will not be limited.

Main outcome(s)
The main outcome measure will be proportion of participants who successfully quit vaping or smoking for at least six months, verified by objective measures such as carbon monoxide, cotinine level, thiocyanate level at the last/longest period of assessment (follow-up).

Measures of effect

Risk ratios (RR) will be calculated as:

RR = (quitters in exercise group/total randomised to exercise group)/(quitters in control group/total randomised to control group) with a 95% confidence interval (CI).

If the data allow us to do so, a forest plot will be used to present the effectiveness of exercise on vaping and smoking cessation in the included trials using the OpenMetaAnalyst software.

Additional outcome(s)
Where reported, the physiological mechanism/effect of aerobic exercise on cessation will be reported, e.g. increases in maximal or peak oxygen uptake

Measures of effect

Not applicable. The additional outcome data will be extracted only for discussion. They will not be subjected to statistical analysis.

Data extraction (selection and coding)
1) The first reviewer (MD) will retrieve all trials from initial databases searches and import these into the EndNote software.

2) Trials will be sorted in descending alphabetical order according to author surname and duplicates removed.

3) Trials will be screened for suitability by the first reviewer (MD) by consulting the title and abstract against the pre-defined eligibility criteria for potential full-text review. The second reviewer (AA) will independently screen the trials by consulting titles and abstracts against the pre-defined eligibility criteria for potential full text review.

4) If disagreement in inclusion between the first and second reviewer are encountered, the third reviewer (HD) will be consulted in attempt to provide a resolution.

5) The following data will then be extracted from the eligible trials:

• Author name/s

• Year of publication

• Number of participants at baseline

• Number of participants at the final follow-up period

• Participants characteristics (i.e age, sex, body mass, BMI)

• Duration of follow-up period

• Intervention for each group, including exercise prescription component (frequency, intensity, time and type of exercise)

• Investigated outcome measures

• The physiological mechanism/effect of aerobic exercise on cessation (e.g. increases in maximal or peak oxygen uptake)

• Results and conclusions

6) Extracted data will be consulted and checked with the second reviewer (AA), and if any disagreement found between the first and second reviewer, the third reviewer (HD) will be consulted to provide a resolution.

Risk of bias (quality) assessment

Risk of bias of included trials will be assessed using the Cochrane Risk of Bias tool 2 (CROB2). Two review authors will independently assess the risk of bias. Any disagreements will be resolved through discussion with the third reviewer. The following will be assessed using the CROB2: (1) bias arising from the randomization process; (2) bias due to deviations from intended interventions; (3) bias due to missing outcome data; (4) bias in measurement of the outcome; (5) bias in selection of the reported result.

Two review authors will independently assess the quality of the included trials using the PEDro Scale. The PEDro scale contains 11 items, and trials are awarded between 0 and 10 points, depending on the number of criteria they meet (the first item is not used to calculate the summary score). Trials with scores of four points or more are classified as "high?quality", whereas trials with three points or fewer are classified as "low?quality" (de Morton, 2009; Maher et al., 2003). PEDro and CROB2 scores for the trials will not be used as an inclusion or exclusion criterion, but as a basis for best?evidence synthesis and to determine the strengths and weaknesses of each trial.

Strategy for data synthesis

For quantitative data, where possible, risk ratio (for categorical outcome data) or standardised mean differences (for continuous data) and their 95% confidence intervals will be calculated from the data generated by each included randomised controlled trial.

Where appropriate, results from comparable groups of trials will be pooled into statistical meta-analysis using the OpenMetaAnalyst software. After pooling data from the trials, statistical heterogeneity will be investigated using the I^2 statistic (Higgins et al., 2003). Where statistical pooling is not possible the findings will be presented in narrative form.

Where data may be missing, efforts to contact the primary author of the respective trial to obtain such missing data will be elicited.

Analysis of subgroups or subsets

None planned.

Contact details for further information

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Organisational affiliation of the review

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Review team members and their organisational affiliations

Mr Mohammad Z. Darabseh. Manchester Metropolitan University
Professor James Selfe. Manchester Metropolitan University

Dr Christopher Morse. Manchester Metropolitan University
Professor Hans Degens. Manchester Metropolitan University

Type and method of review
Intervention, Meta-analysis, Systematic review

Anticipated or actual start date
15 February 2021

Anticipated completion date
30 December 2021

Funding sources/sponsors
None

Conflicts of interest

Language
English

Country
England

Stage of review
Review Ongoing

Subject index terms status
Subject indexing assigned by CRD

Subject index terms
Adult; Cigarette Smoking; Electronic Nicotine Delivery Systems; Exercise; Exercise Therapy; Humans; Public Health; Smoking; Smoking Cessation; Tobacco Smoking; Treatment Outcome; Vaping

Date of registration in PROSPERO
02 February 2021

Date of first submission
02 February 2021

Stage of review at time of this submission

Stage	Started	Completed
Preliminary searches	No	No
Piloting of the study selection process	Yes	No
Formal screening of search results against eligibility criteria	Yes	No
Data extraction	Yes	No
Risk of bias (quality) assessment	Yes	No
Data analysis	Yes	No

Revision note
A typo in one of the keywords which has been rectified. Also, some minor changes that did not alter the search results. Only for quality and accuracy monitoring.

The record owner confirms that the information they have supplied for this submission is accurate and complete and they understand that deliberate provision of inaccurate information or omission of data may be construed as scientific misconduct.
The record owner confirms that they will update the status of the review when it is completed and will add publication details in due course.

Versions

02 February 2021
04 May 2021

Appendix 10: Excluded records from the systematic search

Excluded studies because they have used combined types of exercise (not aerobic only)
LACHMAN, S., MINNEBOO, M., SNATERSE, M., JORSTAD, H. T., TER RIET, G., SCHOLTE OP REIMER, W. J., BOEKHOLDT, S. M. & PETERS, R. J. G. 2015. Community-based comprehensive lifestyle programs in patients with coronary artery disease: Objectives, design and expected results of Randomized Evaluation of Secondary Prevention by Outpatient Nurse SpEcialists 2 trial (RESPONSE 2). American heart journal, 170, 216-222.
WHITELEY, J. A., WILLIAMS, D. M., DUNSIGER, S., JENNINGS, E. G., CICCOLO, J. T., BOCK, B. C., ALBRECHT, A., PARISI, A., LINKE, S. E. & MARCUS, B. H. 2012. YMCA commit to quit: randomized trial outcomes. American journal of preventive medicine, 43, 256-262.
AN, L. C., DEMERS, M. R. S., KIRCH, M. A., CONSIDINE-DUNN, S., NAIR, V., DASGUPTA, K., NARISETTY, N., RESNICOW, K. & AHLUWALIA, J. 2013. A randomized trial of an avatar-hosted multiple behavior change intervention for young adult smokers. Journal of the National Cancer Institute. Monographs, 2013, 209-215.
COPELAND, A. L., MARTIN, P. D., GEISELMAN, P. J., RASH, C. J. & KENDZOR, D. E. 2006. Smoking cessation for weight-concerned women: group vs. individually tailored, dietary, and weight-control follow-up sessions. Addictive behaviors, 31, 115-127.
JANSDOTTIR, D. & JANSDOTTIR, H. 2001. Does physical exercise in addition to a multicomponent smoking cessation program increase abstinence rate and suppress weight gain? An intervention study. Scandinavian Journal of Caring Sciences, 15, 275-82.
JOLLY, K., LIP, G. Y. H., TAYLOR, R. S., RAFTERY, J., MANT, J., LANE, D., GREENFIELD, S. & STEVENS, A. 2009. The Birmingham Rehabilitation Uptake Maximisation study (BRUM): a randomised controlled trial comparing home-based with centre-based cardiac rehabilitation. Heart (British Cardiac Society), 95, 36-42.
NEUBECK, L., FREEDMAN, S. B., BRIFFA, T., BAUMAN, A. & REDFERN, J. 2011. Four-year follow-up of the Choice of Health Options In prevention of Cardiovascular Events randomized controlled trial. European journal of cardiovascular prevention and rehabilitation : official journal of the European Society of Cardiology, Working Groups on Epidemiology & Prevention and Cardiac Rehabilitation and Exercise Physiology, 18, 278-286.
ONCKEN, C., ALLEN, S., LITT, M., KENNY, A., LANDO, H., ALLEN, A. & DORNELAS, E. 2020. Exercise for Smoking Cessation in Postmenopausal Women: A Randomized, Controlled Trial. Nicotine & tobacco research : official journal of the Society for Research on Nicotine and Tobacco, 22, 1587-1595.
SPRING, B., PAGOTO, S., PINGITORE, R., DORAN, N., SCHNEIDER, K. & HEDEKER, D. 2004. Randomized controlled trial for behavioral smoking and weight control treatment: effect of concurrent versus sequential intervention. Journal of consulting and clinical psychology, 72, 785-796.
TOOBERT, D. J., GLASGOW, R. E., NETTEKOVEN, L. A. & BROWN, J. E. 1998. Behavioral and psychosocial effects of intensive lifestyle management for women with coronary heart disease. Patient education and counseling, 35, 177-188.
TOOBERT, D. J., GLASGOW, R. E. & RADCLIFFE, J. L. 2000. Physiologic and related behavioral outcomes from the Women's Lifestyle Heart Trial. Annals of behavioral medicine : a publication of the Society of Behavioral Medicine, 22, 1-9.
TOOBERT, D. J., STRYCKER, L. A., BARRERA, M., JR., OSUNA, D., KING, D. K. & GLASGOW, R. E. 2011. Outcomes from a multiple risk factor diabetes self-management trial for Latinas: ¡Viva Bien! Annals of behavioral medicine : a publication of the Society of Behavioral Medicine, 41, 310-323.
USSHER, M., WEST, R., MCEWEN, A., TAYLOR, A. & STEPTOE, A. 2007. Randomized controlled trial of physical activity counseling as an aid to smoking cessation: 12 month follow-up. Addictive behaviors, 32, 3060-3064.

Did not assess the effects of aerobic exercise on smoking cessation

NIAURA, R., MARCUS, B., ALBRECHT, A., THOMPSON, P. & ABRAMS, D. 1998. Exercise, smoking cessation, and short-term changes in serum lipids in women: a preliminary investigation. Medicine and Science in Sports and Exercise, 30, 1414-1418.

PAFFENBARGER, R. S., KAMPERT, J. B., LEE, I. M., HYDE, R. T., LEUNG, R. W. & WING, A. L. 1994. Changes in physical activity and other lifeway patterns influencing longevity. Medicine and Science in Sports and Exercise, 26, 857-65.

ROSE, G., TUNSTALL-PEDOE, H. D. & HELLER, R. F. 1983. UK heart disease prevention project: incidence and mortality results. Lancet (London, England), 1, 1062-1066.

SMEETS, T., KREMERS, S. P. J., BRUG, J. & DE VRIES, H. 2007. Effects of tailored feedback on multiple health behaviors. Annals of behavioral medicine : a publication of the Society of Behavioral Medicine, 33, 117-123.

STEPTOE, A., KERRY, S., RINK, E. & HILTON, S. 2001. The impact of behavioral counseling on stage of change in fat intake, physical activity, and cigarette smoking in adults at increased risk of coronary heart disease. American journal of public health, 91, 265-269.

TOWFIGHI, A., CHENG, E. M., AYALA-RIVERA, M., MCCREATH, H., SANOSSIAN, N., DUTTA, T., MEHTA, B., BRYG, R., RAO, N., SONG, S., RAZMARA, A., RAMIREZ, M., SIVERS-TEIXEIRA, T., TRAN, J., MOJARRO-HUANG, E., MONTOYA, A., CORRALES, M., MARTINEZ, B., WILLIS, P., MACIAS, M., IBRAHIM, N., WU, S., WACKSMAN, J., HABER, H., RICHARDS, A., BARRY, F., HILL, V., MITTMAN, B., CUNNINGHAM, W., LIU, H., GANZ, D. A., FACTOR, D. & VICKREY, B. G. 2017. Randomized controlled trial of a coordinated care intervention to improve risk factor control after stroke or transient ischemic attack in the safety net: Secondary stroke prevention by Uniting Community and Chronic care model teams Early to End Disparities (SUCCEED). BMC neurology, 17, 24.

VON HUTH SMITH, L., LADELUND, S., BORCH-JOHNSEN, K. & JØRGENSEN, T. 2008. A randomized multifactorial intervention study for prevention of ischaemic heart disease (Inter99): the long-term effect on physical activity. Scandinavian journal of public health, 36, 380-388.

VONCKEN-BREWSTER, V., TANGE, H., DE VRIES, H., NAGYKALDI, Z., WINKENS, B. & VAN DER WEIJDEN, T. 2015. A randomized controlled trial evaluating the effectiveness of a web-based, computer-tailored self-management intervention for people with or at risk for COPD. International journal of chronic obstructive pulmonary disease, 10, 1061-1073.

USSHER, M., WEST, R., MCEWEN, A., TAYLOR, A. & STEPTOE, A. 2003. Efficacy of counselling as an aid for smoking cessation: a randomized controlled trial. *Addiction (Abingdon, England),* 98**,** 523-532.

Did not assess the effects of aerobic exercise on SC

AASDAHL, L., FOLDAL, V. S., STANDAL, M. I., HAGEN, R., JOHNSEN, R., SOLBJØR, M., FIMLAND, M. S., FOSSEN, H., JENSEN, C., BAGØIEN, G., HALSTEINLI, V. & FORS, E. A. 2018. Motivational interviewing in long-term sickness absence: study protocol of a randomized controlled trial followed by qualitative and economic studies. BMC public health, 18, 756.

ADAMUZ, J., VIASUS, D., SIMONETTI, A., JIMÉNEZ-MARTÍNEZ, E., MOLERO, L., GONZÁLEZ-SAMARTINO, M., CASTILLO, E., JUVÉ-UDINA, M.-E., ALCOCER, M.-J., HERNÁNDEZ, C., BUERA, M.-P., ROEL, A., ABAD, E., ZABALEGUI, A., RICART, P., GONZALEZ, A., ISLA, P., DORCA, J., GARCIA-VIDAL, C. & CARRATALÀ, J. 2015. Impact of an Educational Program to Reduce Healthcare Resources in Community-Acquired Pneumonia: The EDUCAP Randomized Controlled Trial. PloS one, 10, e0140202.

AIMER, P., TREHARNE, G. J., STEBBINGS, S., FRAMPTON, C., CAMERON, V., KIRBY, S. & STAMP, L. K. 2017. Efficacy of a Rheumatoid Arthritis-Specific Smoking Cessation Program: A Randomized Controlled Pilot Trial. Arthritis care & research, 69, 28-37.

ALBRECHT, A. E., MARCUS, B. H., ROBERTS, M., FORMAN, D. E. & PARISI, A. F. 1998. Effect of smoking cessation

on exercise performance in female smokers participating in exercise training. The American journal of cardiology, 82, 950-955.
BECKER, D. M., YANEK, L. R., JOHNSON, W. R., JR., GARRETT, D., MOY, T. F., REYNOLDS, S. S., BLUMENTHAL, R. S., VAIDYA, D. & BECKER, L. C. 2005. Impact of a community-based multiple risk factor intervention on cardiovascular risk in black families with a history of premature coronary disease. Circulation, 111, 1298-1304.
BERG, C. J., THOMAS, J. L., AN, L. C., GUO, H., COLLINS, T., OKUYEMI, K. S. & AHLUWALIA, J. S. 2012. Change in smoking, diet, and walking for exercise in Blacks. Health education & behavior : the official publication of the Society for Public Health Education, 39, 191-197.
HAAGA, D. A. F., KAUFMANN, A. & MALLOY, E. J. 2020. Looming Vulnerability and Smoking Cessation Attempts. Nicotine & tobacco research : official journal of the Society for Research on Nicotine and Tobacco, 22, 1439-1445.
JACQUART, J., PAPINI, S., DAVIS, M. L., ROSENFIELD, D., POWERS, M. B., FRIERSON, G. M., HOPKINS, L. B., BAIRD, S. O., MARCUS, B. H., CHURCH, T. S., OTTO, M. W., ZVOLENSKY, M. J. & SMITS, J. A. J. 2017. Identifying attendance patterns in a smoking cessation treatment and their relationships with quit success. Drug and alcohol dependence, 174, 65-69.
JONES, C., GRIFFITHS, R. D., SKIRROW, P. & HUMPHRIS, G. 2001. Smoking cessation through comprehensive critical care. Intensive care medicine, 27, 1547-1549.
MCCLURE, J. B., LUDMAN, E., GROTHAUS, L., PABINIAK, C., RICHARDS, J. & MOHELNITZKY, A. 2009. Immediate and short-term impact of a brief motivational smoking intervention using a biomedical risk assessment: the Get PHIT trial. Nicotine & tobacco research : official journal of the Society for Research on Nicotine and Tobacco, 11, 394-403.
MCCLURE, J. B., LUDMAN, E. J., GROTHAUS, L., PABINIAK, C. & RICHARDS, J. 2009. Impact of a brief motivational smoking cessation intervention the Get PHIT randomized controlled trial. American journal of preventive medicine, 37, 116-123.
MIDFORD, R., CAHILL, H., LESTER, L., FOXCROFT, D. R., RAMSDEN, R. & VENNING, L. 2016. Smoking Prevention for Students: Findings From a Three-Year Program of Integrated Harm Minimization School Drug Education. Substance use & misuse, 51, 395-407.
MÜLLER-RIEMENSCHNEIDER, F., KRIST, L., BÜRGER, C., STRÖBELE-BENSCHOP, N., ROLL, S., RIECKMANN, N., MÜLLER-NORDHORN, J. & WILLICH, S. N. 2014. Berlin evaluates school tobacco prevention - BEST prevention: study design and methodology. BMC public health, 14, 871.
PROCHASKA, J. O., BUTTERWORTH, S., REDDING, C. A., BURDEN, V., PERRIN, N., LEO, M., FLAHERTY-ROBB, M. & PROCHASKA, J. M. 2008. Initial efficacy of MI, TTM tailoring and HRI's with multiple behaviors for employee health promotion. Preventive medicine, 46, 226-231.
PROD'HOM, S., LOCATELLI, I., GIRAUDON, K., MARQUES-VIDAL, P., CLAIR, C., BIZE, R. & CORNUZ, J. 2013. Predictors of weight change in sedentary smokers receiving a standard smoking cessation intervention. Nicotine & tobacco research : official journal of the Society for Research on Nicotine and Tobacco, 15, 910-916.
RUFFIN, M. T. T., NEASE, D. E., JR., SEN, A., PACE, W. D., WANG, C., ACHESON, L. S., RUBINSTEIN, W. S., O'NEILL, S. & GRAMLING, R. 2011. Effect of preventive messages tailored to family history on health behaviors: the Family Healthware Impact Trial. Annals of family medicine, 9, 3-11.
SARKAR, B. K., WEST, R., ARORA, M., AHLUWALIA, J. S., REDDY, K. S. & SHAHAB, L. 2017. Effectiveness of a brief community outreach tobacco cessation intervention in India: a cluster-randomised controlled trial (the BABEX Trial). Thorax, 72, 167-173.
SCHOENBERG, N. E., BUNDY, H. E., BAEKER BISPO, J. A., STUDTS, C. R., SHELTON, B. J. & FIELDS, N. 2015. A rural Appalachian faith-placed smoking cessation intervention. Journal of religion and health, 54, 598-611.
SHIFFMAN, S., SCHARF, D. M., SHADEL, W. G., GWALTNEY, C. J., DANG, Q., PATON, S. M. & CLARK, D. B. 2006. Analyzing milestones in smoking cessation: illustration in a nicotine patch trial in adult smokers. Journal of consulting and clinical psychology, 74, 276-285.
SHIUE, I., ARIMA, H., HANKEY, G. J. & ANDERSON, C. S. 2012. Modifiable lifestyle behaviours account for most cases of subarachnoid haemorrhage: a population-based case-control study in Australasia. Journal of the neurological sciences, 313, 92-94.
SHMUELI, D. & PROCHASKA, J. J. 2012. A test of positive affect induction for countering self-control depletion in cigarette smokers. Psychology of addictive behaviors : journal of the Society of Psychologists in Addictive Behaviors, 26, 157-161.
STILLMAN, A. E., GATSONIS, C., LIMA, J. A. C., BLACK, W. C., CORMACK, J., GAREEN, I., HOFFMANN, U., LIU, T., MAVROMATIS, K., SCHNALL, M. D., UDELSON, J. E. & WOODARD, P. K. 2016. Rationale and design of the Randomized Evaluation of patients with Stable angina Comparing Utilization of noninvasive Examinations (RESCUE) trial. American heart journal, 179, 19-28.
TAMIS-HOLLAND, J. E., LU, J., KORYTKOWSKI, M., MAGEE, M., ROGERS, W. J., LOPES, N., MIGHTON, L. & JACOBS, A. K. 2013. Sex differences in presentation and outcome among patients with type 2

diabetes and coronary artery disease treated with contemporary medical therapy with or without prompt revascularization: a report from the BARI 2D Trial (Bypass Angioplasty Revascularization Investigation 2 Diabetes). Journal of the American College of Cardiology, 61, 1767-1776.
TOOBERT, D. J., GLASGOW, R. E., STRYCKER, L. A., BARRERA, M., JR., RADCLIFFE, J. L., WANDER, R. C. & BAGDADE, J. D. 2003. Biologic and quality-of-life outcomes from the Mediterranean Lifestyle Program: a randomized clinical trial. Diabetes care, 26, 2288-2293.
TOWNSEND, J., WILKES, H., HAINES, A. & JARVIS, M. 1991. Adolescent smokers seen in general practice: health, lifestyle, physical measurements, and response to antismoking advice. BMJ (Clinical research ed.), 303, 947-950.
VOGEL, E. A., THRUL, J., HUMFLEET, G. L., DELUCCHI, K. L. & RAMO, D. E. 2019. Smoking cessation intervention trial outcomes for sexual and gender minority young adults. Health psychology : official journal of the Division of Health Psychology, American Psychological Association, 38, 12-20.
WOLINSKY, F. D., LOU, Y., EDMONDS, S. W., SAAG, K. G., ROBLIN, D. W., WRIGHT, N. C., JONES, M. P. & CRAM, P. 2017. The effects of a patient activation intervention on smoking and excessive drinking cessations: results from the PAADRN randomized controlled trial. Osteoporosis international : a journal established as result of cooperation between the European Foundation for Osteoporosis and the National Osteoporosis Foundation of the USA, 28, 3055-3060.
WYND, C. A. 2005. Guided health imagery for smoking cessation and long-term abstinence. Journal of nursing scholarship : an official publication of Sigma Theta Tau International Honor Society of Nursing, 37, 245-250.
XAVIER, D., GUPTA, R., KAMATH, D., SIGAMANI, A., DEVEREAUX, P. J., GEORGE, N., JOSHI, R., POGUE, J., PAIS, P. & YUSUF, S. 2016. Community health worker-based intervention for adherence to drugs and lifestyle change after acute coronary syndrome: a multicentre, open, randomised controlled trial. The lancet. Diabetes & endocrinology, 4, 244-253.

No objective measure for success of SC

Vestfold Heartcare Study Group. 2003. Influence on lifestyle measures and five-year coronary risk by a comprehensive lifestyle intervention programme in patients with coronary heart disease. *European journal of cardiovascular prevention and rehabilitation : official journal of the European Society of Cardiology, Working Groups on Epidemiology & Prevention and Cardiac Rehabilitation and Exercise Physiology,* 10**,** 429-437.
AHMADI, M., LAUMEIER, I., IHL, T., STEINICKE, M., FERSE, C., ENDRES, M., GRAU, A., HASTRUP, S., POPPERT, H., PALM, F., SCHOENE, M., SEIFERT, C. L., KANDIL, F. I., WEBER, J. E., VON WEITZEL-MUDERSBACH, P., WIMMER, M. L. J., ALGRA, A., AMARENCO, P., GREVING, J. P., BUSSE, O., KÖHLER, F., MARX, P. & AUDEBERT, H. J. 2020. A support programme for secondary prevention in patients with transient ischaemic attack and minor stroke (INSPiRE-TMS): an open-label, randomised controlled trial. *The Lancet. Neurology,* 19**,** 49-60.
ANDERSSON, A., SUNDEL, K. L., UNDÉN, A.-L., SCHENCK-GUSTAFSSON, K. & ERIKSSON, I. 2010. A five-year rehabilitation programme for younger women after a coronary event reduces the need for hospital care. *Scandinavian journal of public health,* 38**,** 566-573.
POWERS, B. J., DANUS, S., GRUBBER, J. M., OLSEN, M. K., ODDONE, E. Z. & BOSWORTH, H. B. 2011. The effectiveness of personalized coronary heart disease and stroke risk communication. *American heart journal,* 161**,** 673-680.
PRICE, H. C., TUCKER, L., GRIFFIN, S. J. & HOLMAN, R. R. 2008. The impact of individualised cardiovascular disease (CVD) risk estimates and lifestyle advice on physical activity in individuals at high risk of CVD: a pilot 2 x 2 factorial understanding risk trial. *Cardiovascular diabetology,* 7**,** 21.
YORIO, J., VISWANATHAN, S., SEE, R., UCHAL, L., MCWHORTER, J. A., SPENCER, N., MURPHY, S., KHERA, A., DE LEMOS, J. A. & MCGUIRE, D. K. 2008. The effect of a disease management algorithm and dedicated postacute coronary syndrome clinic on achievement of guideline compliance: results from the parkland acute coronary event treatment study. *Journal of investigative medicine : the official publication of the American Federation for Clinical Research,* 56**,** 15-25.

ANDERSON, D., MIZZARI, K., KAIN, V. & WEBSTER, J. 2006. The effects of a multimodal intervention trial to promote lifestyle factors associated with the prevention of cardiovascular disease in menopausal and postmenopausal Australian women. *Health care for women international,* 27**,** 238-253.
BERTELSEN, J. B., REFSGAARD, J., KANSTRUP, H., JOHNSEN, S. P., QVIST, I., CHRISTENSEN, B. & CHRISTENSEN, K. L. 2013. Hospital-based versus community-based shared care cardiac rehabilitation after acute coronary syndrome: protocol for a randomized clinical trial. *Danish medical journal,* 60**,** A4699.
KADDA, O., KOTANIDOU, A., MANGINAS, A., STAVRIDIS, G., NANAS, S. & PANAGIOTAKOS, D. B. 2015. Lifestyle

intervention and one-year prognosis of patients following open heart surgery: a randomised clinical trial. *Journal of clinical nursing,* 24**,** 1611-1621.
LATINA, J., FERNANDEZ-JIMENEZ, R., BANSILAL, S., SARTORI, S., VEDANTHAN, R., LEWIS, M., KOFLER, C., HUNN, M., MARTIN, F., BAGIELLA, E., FARKOUH, M. & FUSTER, V. 2020. Grenada Heart Project-Community Health ActioN to EncouraGe healthy BEhaviors (GHP-CHANGE): A randomized control peer group-based lifestyle intervention. *American heart journal,* 220**,** 20-28.
LEE, C. W., WANG, J. H., HSIEH, J. C., HSIEH, T. C. & HUANG, C. H. 2013. Effects of combined phase III and phase II cardiac exercise therapy for middle-aged male patients with acute myocardial infarction. *Journal of Physical Therapy Science,* 25**,** 1415-20.
MCCALL, A. L. 2003. Reducing CVD risk in type 2 DM. *Current diabetes reports,* 3**,** 363-364.
MCKAY, H. G., DANAHER, B. G., SEELEY, J. R., LICHTENSTEIN, E. & GAU, J. M. 2008. Comparing two web-based smoking cessation programs: randomized controlled trial. *Journal of medical Internet research,* 10**,** e40.
ORNISH, D., SCHERWITZ, L. W., BILLINGS, J. H., BROWN, S. E., GOULD, K. L., MERRITT, T. A., SPARLER, S., ARMSTRONG, W. T., PORTS, T. A., KIRKEEIDE, R. L., HOGEBOOM, C. & BRAND, R. J. 1998. Intensive lifestyle changes for reversal of coronary heart disease. *JAMA,* 280**,** 2001-2007.
PFAEFFLI DALE, L., WHITTAKER, R., JIANG, Y., STEWART, R., ROLLESTON, A. & MADDISON, R. 2015. Text Message and Internet Support for Coronary Heart Disease Self-Management: Results From the Text4Heart Randomized Controlled Trial. *Journal of medical Internet research,* 17**,** e237.
POUCHAIN, D., LIÈVRE, M., HUAS, D., LEBEAU, J.-P., RENARD, V., BRUCKERT, E., GIRERD, X. & BOUTITIE, F. 2013. Effects of a multifaceted intervention on cardiovascular risk factors in high-risk hypertensive patients: the ESCAPE trial, a pragmatic cluster randomized trial in general practice. *Trials,* 14**,** 318.
SUNAMURA, M., TER HOEVE, N., VAN DEN BERG-EMONS, R. J. G., GELEIJNSE, M. L., HAVERKAMP, M., STAM, H. J., BOERSMA, E. & VAN DOMBURG, R. T. 2018. Randomised controlled trial of two advanced and extended cardiac rehabilitation programmes. *Heart (British Cardiac Society),* 104**,** 430-437.

No SC in the paper

ABDULSALIM, S., UNNIKRISHNAN, M. K., MANU, M. K., ALRASHEEDY, A. A., GODMAN, B. & MORISKY, D. E. 2018. Structured pharmacist-led intervention programme to improve medication adherence in COPD patients: A randomized controlled study. *Research in social & administrative pharmacy : RSAP,* 14**,** 909-914.
BOTTERI, E., DE LANGE, T., TONSTAD, S. & BERSTAD, P. 2018. Exploring the effect of a lifestyle intervention on cancer risk: 43-year follow-up of the randomized Oslo diet and antismoking study. *Journal of internal medicine,* 284**,** 282-291.
GAEDE, P., VEDEL, P., LARSEN, N., JENSEN, G. V. H., PARVING, H.-H. & PEDERSEN, O. 2003. Multifactorial intervention and cardiovascular disease in patients with type 2 diabetes. *The New England journal of medicine,* 348**,** 383-393.
JACOBS, N., CLAYS, E., DE BACQUER, D., DE BACKER, G., DENDALE, P., THIJS, H., DE BOURDEAUDHUIJ, I. & CLAES, N. 2011. Effect of a tailored behavior change program on a composite lifestyle change score: a randomized controlled trial. *Health education research,* 26**,** 886-895.
JONSDOTTIR, H., AMUNDADOTTIR, O. R., GUDMUNDSSON, G., HALLDORSDOTTIR, B. S., HRAFNKELSSON, B., INGADOTTIR, T. S., JONSDOTTIR, R., JONSSON, J. S., SIGURJONSDOTTIR, E. D. & STEFANSDOTTIR, I. K. 2015. Effectiveness of a partnership-based self-management programme for patients with mild and moderate chronic obstructive pulmonary disease: a pragmatic randomized controlled trial. *Journal of Advanced Nursing,* 71**,** 2634-2649.
KNEKT, P., LAAKSONEN, M. A., RAITASALO, R., HAARAMO, P. & LINDFORS, O. 2010. Changes in lifestyle for psychiatric patients three years after the start of short- and long-term psychodynamic psychotherapy and solution-focused therapy. *European psychiatry : the journal of the Association of European Psychiatrists,* 25**,** 1-7.
RAMOS, E. M. C., VANDERLEI, L. C. M., ITO, J. T., LIMA, F. F., RODRIGUES, F. M. M., MANZANO, B. M., FERNANDES, R. A., CECÍLIO, M. J., TOLEDO-ARRUDA, A. C. & RAMOS, D. 2015. Acute Mucociliary Clearance Response to Aerobic Exercise in Smokers. *Respiratory care,* 60**,** 1575-1584.
SCHUMACHER, A., PEERSEN, K., SOMMERVOLL, L., SELJEFLOT, I., ARNESEN, H. & OTTERSTAD, J. E. 2006. Physical performance is associated with markers of vascular inflammation in patients with coronary heart disease. *European journal of cardiovascular prevention and rehabilitation : official journal of the European Society of Cardiology, Working Groups on Epidemiology & Prevention and Cardiac Rehabilitation and Exercise Physiology,* 13**,** 356-362.
AADAHL, M., VON HUTH SMITH, L., TOFT, U., PISINGER, C. & JØRGENSEN, T. 2011. Does a population-based

multifactorial lifestyle intervention increase social inequality in physical activity? The Inter99 study. *British Journal of Sports Medicine,* 45**,** 209-215.

ANDERSON, D., SEIB, C., TJONDRONEGORO, D., TURNER, J., MONTEROSSO, L., MCGUIRE, A., PORTER-STEELE, J., SONG, W., YATES, P., KING, N., YOUNG, L., WHITE, K., LEE, K., HALL, S., KRISHNASAMY, M., WELLS, K., BALAAM, S. & MCCARTHY, A. L. 2017. The Women's wellness after cancer program: a multisite, single-blinded, randomised controlled trial protocol. *BMC cancer,* 17**,** 98.

BASU, R., BRAR, J. S., CHENGAPPA, K. N. R., JOHN, V., PAREPALLY, H., GERSHON, S., SCHLICHT, P. & KUPFER, D. J. 2004. The prevalence of the metabolic syndrome in patients with schizoaffective disorder--bipolar subtype. *Bipolar disorders,* 6**,** 314-318.

BENDSTRUP, K. E., INGEMANN JENSEN, J., HOLM, S. & BENGTSSON, B. 1997. Out-patient rehabilitation improves activities of daily living, quality of life and exercise tolerance in chronic obstructive pulmonary disease. *The European respiratory journal,* 10**,** 2801-2806.

BOLTON, M. B., TILLEY, B. C., KUDER, J., REEVES, T. & SCHULTZ, L. R. 1991. The cost and effectiveness of an education program for adults who have asthma. *Journal of general internal medicine,* 6**,** 401-407.

BOWMAN, M. A., DIGNAN, M., CRANDALL, S. & BAIER, M. 2000. Changes in functional status related to health maintenance visits to family physicians. *The Journal of family practice,* 49**,** 428-433.

BURKE, V., GIANGIULIO, N., GILLAM, H. F., BEILIN, L. J. & HOUGHTON, S. 2003. Physical activity and nutrition programs for couples: a randomized controlled trial. *Journal of clinical epidemiology,* 56**,** 421-432.

CAMERON, D., EPTON, T., NORMAN, P., SHEERAN, P., HARRIS, P. R., WEBB, T. L., JULIOUS, S. A., BRENNAN, A., THOMAS, C., PETROCZI, A., NAUGHTON, D. & SHAH, I. 2015. A theory-based online health behaviour intervention for new university students (U@Uni:LifeGuide): results from a repeat randomized controlled trial. *Trials,* 16**,** 555.

CAMPBELL, M. K., TESSARO, I., DEVELLIS, B., BENEDICT, S., KELSEY, K., BELTON, L. & SANHUEZA, A. 2002. Effects of a tailored health promotion program for female blue-collar workers: health works for women. *Preventive medicine,* 34**,** 313-323.

CARLSSON, R., LINDBERG, G., WESTIN, L. & ISRAELSSON, B. 1997. Influence of coronary nursing management follow up on lifestyle after acute myocardial infarction. *Heart (British Cardiac Society),* 77**,** 256-259.

CHAN, B. C., JAYASINGHE, U. W., CHRISTL, B., LAWS, R. A., ORR, N., WILLIAMS, A., PARTINGTON, K. & HARRIS, M. F. 2013. The impact of a team-based intervention on the lifestyle risk factor management practices of community nurses: outcomes of the community nursing SNAP trial. *BMC health services research,* 13**,** 54.

CHELLINI, E., GORINI, G., CARRERAS, G., GIORDANO, L., ANGHINONI, E., IOSSA, A., BELLATI, C., GRECHI, E., COPPO, A., TALASSI, F. & GIOVACCHINI, M. R. 2011. The Pap smear screening as an occasion for smoking cessation and physical activity counselling: baseline characteristics of women involved in the SPRINT randomized controlled trial. *BMC public health,* 11**,** 906.

CHENG, E. M., CUNNINGHAM, W. E., TOWFIGHI, A., SANOSSIAN, N., BRYG, R. J., ANDERSON, T. L., BARRY, F., DOUGLAS, S. M., HUDSON, L., AYALA-RIVERA, M., GUTERMAN, J. J., GROSS-SCHULMAN, S., BEANES, S., JONES, A. S., LIU, H. & VICKREY, B. G. 2018. Efficacy of a Chronic Care-Based Intervention on Secondary Stroke Prevention Among Vulnerable Stroke Survivors: A Randomized Controlled Trial. *Circulation. Cardiovascular quality and outcomes,* 11**,** e003228.

COSTA E SILVA, R., PELLANDA, L., PORTAL, V., MACIEL, P., FURQUIM, A. & SCHAAN, B. 2008. Transdisciplinary approach to the follow-up of patients after myocardial infarction. *Clinics (Sao Paulo, Brazil),* 63**,** 489-496.

CÔTÉ, J., COSSETTE, S., RAMIREZ-GARCIA, P., DE POKOMANDY, A., WORTHINGTON, C., GAGNON, M.-P., AUGER, P., BOUDREAU, F., MIRANDA, J., GUÉHÉNEUC, Y.-G. & TREMBLAY, C. 2015. Evaluation of a Web-based tailored intervention (TAVIE en santé) to support people living with HIV in the adoption of health promoting behaviours: an online randomized controlled trial protocol. *BMC public health,* 15**,** 1042.

DAVEY SMITH, G., BRACHA, Y., SVENDSEN, K. H., NEATON, J. D., HAFFNER, S. M. & KULLER, L. H. 2005. Incidence of type 2 diabetes in the randomized multiple risk factor intervention trial. *Annals of internal medicine,* 142**,** 313-322.

DAVIES, D. S. & MCCOLL, M. A. 2002. Lifestyle risks for three disease outcomes in spinal cord injury. *Clinical Rehabilitation,* 16**,** 96-108.

DE VRIES, H., KREMERS, S. P. J., SMEETS, T., BRUG, J. & EIJMAEL, K. 2008. The effectiveness of tailored feedback and action plans in an intervention addressing multiple health behaviors. *American journal of health promotion : AJHP,* 22**,** 417-425.

DEAN, E. 2018. Maximizing the functional performance outcomes of patients undergoing rehabilitation by maximizing their overall health and wellbeing. *J Hum Kinet,* 65**,** 57-68.

DHEDA, K., CRAWFORD, A., HAGAN, G. & ROBERTS, C. M. 2004. Implementation of British Thoracic Society guidelines for acute exacerbation of chronic obstructive pulmonary disease: impact on quality of life. *Postgraduate medical journal,* 80**,** 169-171.

DI MARIO, C. & PIEPOLI, M. F. 2010. "Rehabilitation" after PCI: nonsense or the only way to achieve lasting results? *EuroIntervention : journal of EuroPCR in collaboration with the Working Group on Interventional Cardiology of the European Society of Cardiology,* 5**,** 655-658.

DING, H., KARUNANITHI, M., IRELAND, D., MCCARTHY, L., HAKIM, R., PHILLIPS, K., PRADHAN, R., SEAH, E. H., BOWMAN, R. V., FONG, K., MASEL, P. & YANG, I. A. 2019. Evaluation of an innovative mobile health programme for the self-management of chronic obstructive pulmonary disease (MH-COPD): protocol of a randomised controlled trial. *BMJ open,* 9**,** e025381.

DOMBROWSKI, H. T. 2000. Effective strategies for the prevention of osteoporosis across the life span. *Journal - American Osteopathic Association,* 100**,** 15.

EAKIN, E. G., YOULDEN, D. R., BAADE, P. D., LAWLER, S. P., REEVES, M. M., HEYWORTH, J. S. & FRITSCHI, L. 2007. Health behaviors of cancer survivors: data from an Australian population-based survey. *Cancer causes & control : CCC,* 18**,** 881-894.

EMMONS, K. M., PULEO, E., GREANEY, M. L., GILLMAN, M. W., BENNETT, G. G., HAINES, J., SPRUNCK-HARRILD, K. & VISWANATH, K. 2014. A randomized comparative effectiveness study of Healthy Directions 2--a multiple risk behavior intervention for primary care. *Preventive medicine,* 64**,** 96-102.

FLOURIS, A. D., METSIOS, G. S., JAMURTAS, A. Z. & KOUTEDAKIS, Y. 2010. Cardiorespiratory and immune response to physical activity following exposure to a typical smoking environment. *Heart (British Cardiac Society),* 96**,** 860-864.

FOWLER, B., JAMROZIK, K., NORMAN, P., ALLEN, Y. & WILKINSON, E. 2002. Improving maximum walking distance in early peripheral arterial disease: randomised controlled trial. *The Australian journal of physiotherapy,* 48**,** 269-275.

FREDERIX, I., HANSEN, D., CONINX, K., VANDERVOORT, P., VAN CRAENENBROECK, E. M., VRINTS, C. & DENDALE, P. 2015. Telerehab III: a multi-center randomized, controlled trial investigating the long-term effectiveness of a comprehensive cardiac telerehabilitation program--rationale and study design. *BMC cardiovascular disorders,* 15**,** 29.

FREDERIX, I., HANSEN, D., CONINX, K., VANDERVOORT, P., VANDIJCK, D., HENS, N., VAN CRAENENBROECK, E., VAN DRIESSCHE, N. & DENDALE, P. 2015. Medium-Term Effectiveness of a Comprehensive Internet-Based and Patient-Specific Telerehabilitation Program With Text Messaging Support for Cardiac Patients: Randomized Controlled Trial. *Journal of medical Internet research,* 17**,** e185.

FUCHS, Z., VISKOPER, J. R., DREXLER, I., NITZAN, H., LUBIN, F., BERLIN, S., ALMAGOR, M., ZULTY, L., CHETRIT, A., MISHAL, J. & ET, A. 1993. Comprehensive individualised nonpharmacological treatment programme for hypertension in physician-nurse clinics: two year follow-up. *Journal of human hypertension,* 7**,** 585-591.

GEDDES, D., DAVIES, M., KOYAMA, H., HANSELL, D., PASTORINO, U., PEPPER, J., AGENT, P., CULLINAN, P., MACNEILL, S. J. & GOLDSTRAW, P. 2000. Effect of lung-volume-reduction surgery in patients with severe emphysema. *The New England journal of medicine,* 343**,** 239-245.

GREENHALGH, R. M., BELCH, J. J. F., BROWN, L. C., GAINES, P. A., GAO, L., REISE, J. A. & THOMPSON, S. G. 2008. The adjuvant benefit of angioplasty in patients with mild to moderate intermittent claudication (MIMIC) managed by supervised exercise, smoking cessation advice and best medical therapy: results from two randomised trials for stenotic femoropopliteal and aortoiliac arterial disease. *European journal of vascular and endovascular surgery : the official journal of the European Society for Vascular Surgery,* 36**,** 680-688.

GRIFFIN, S. J., SIMMONS, R. K., PREVOST, A. T., WILLIAMS, K. M., HARDEMAN, W., SUTTON, S., BRAGE, S., EKELUND, U., PARKER, R. A., WAREHAM, N. J. & KINMONTH, A. L. 2014. Multiple behaviour change intervention and outcomes in recently diagnosed type 2 diabetes: the ADDITION-Plus randomised controlled trial. *Diabetologia,* 57**,** 1308-1319.

GROENEVELD, I. F., PROPER, K. I., VAN DER BEEK, A. J., VAN DUIVENBOODEN, C. & VAN MECHELEN, W. 2008. Design of a RCT evaluating the (cost-) effectiveness of a lifestyle intervention for male construction workers at risk for cardiovascular disease: the health under construction study. *BMC public health,* 8**,** 1.

HAMMETT, C. J. K., PRAPAVESSIS, H., BALDI, J. C., VARO, N., SCHOENBECK, U., AMERATUNGA, R., FRENCH, J. K., WHITE, H. D. & STEWART, R. A. H. 2006. Effects of exercise training on 5 inflammatory markers associated with cardiovascular risk. *American heart journal,* 151**,** 367.e7-367.e16.

HANLON, P., MCEWEN, J., CAREY, L., GILMOUR, H., TANNAHILL, C., TANNAHILL, A. & KELLY, M. 1995. Health checks and coronary risk: further evidence from a randomised controlled trial. *BMJ (Clinical research ed.),* 311**,** 1609-1613.

HANSSEN, T. A., NORDREHAUG, J. E., EIDE, G. E. & HANESTAD, B. R. 2009. Does a telephone follow-up intervention for patients discharged with acute myocardial infarction have long-term effects on health-related quality of life? A randomised controlled trial. *Journal of clinical nursing,* 18**,** 1334-1345.

HART, K. A., RINTALA, D. H. & FUHRER, M. J. 1996. Educational interests of individuals with spinal cord injury living in the community: medical, sexuality, and wellness topics. *Rehabilitation Nursing,* 21**,** 82-90.

HAWKES, A. L., PAKENHAM, K. I., COURNEYA, K. S., GOLLSCHEWSKI, S., BAADE, P., GORDON, L. G., LYNCH, B. M., AITKEN, J. F. & CHAMBERS, S. K. 2009. A randomised controlled trial of a tele-based lifestyle intervention for colorectal cancer survivors ('CanChange'): study protocol. *BMC cancer,* 9**,** 286.

HESS, R., TINDLE, H., CONROY, M. B., CLARK, S., YABLONSKY, E. & HAYS, R. D. 2014. A randomized controlled pilot trial of the functional assessment screening tablet to engage patients at the point of care. *Journal of general internal medicine,* 29**,** 1641-1649.

HILBERG, T., MENZEL, K. & WEHMEIER, U. F. 2013. Endurance training modifies exercise-induced activation of blood coagulation: RCT. *European journal of applied physiology,* 113**,** 1423-1430.

HOLMES-ROVNER, M., STOMMEL, M., CORSER, W. D., OLOMU, A., HOLTROP, J. S., SIDDIQI, A. & DUNN, S. L. 2008. Does outpatient telephone coaching add to hospital quality improvement following hospitalization for acute coronary syndrome? *Journal of general internal medicine,* 23**,** 1464-1470.

HOOGENDOORN, M., VAN WETERING, C. R., SCHOLS, A. M. & RUTTEN-VAN MÖLKEN, M. P. M. H. 2010. Is INTERdisciplinary COMmunity-based COPD management (INTERCOM) cost-effective? *The European respiratory journal,* 35**,** 79-87.

HOUSTON, M. C. 2013. The role of nutrition, nutraceuticals, vitamins, antioxidants, and minerals in the prevention and treatment of hypertension. *Altern Ther Health Med,* 19**,** 32-49.

HUANG, B., WILLARD-GRACE, R., DE VORE, D., WOLF, J., CHIRINOS, C., TSAO, S., HESSLER, D., SU, G. & THOM, D. H. 2017. Health coaching to improve self-management and quality of life for low income patients with chronic obstructive pulmonary disease (COPD): protocol for a randomized controlled trial. *BMC pulmonary medicine,* 17**,** 90.

HUNG, J. 2003. Aspirin for cardiovascular disease prevention. *Medical Journal of Australia,* 179**,** 147-52.

JATUPORN, S., SANGWATANAROJ, S., SAENGSIRI, A.-O., RATTANAPRUKS, S., SRIMAHACHOTA, S., UTHAYACHALERM, W., KUANOON, W., PANPAKDEE, O., TANGKIJVANICH, P. & TOSUKHOWONG, P. 2003. Short-term effects of an intensive lifestyle modification program on lipid peroxidation and antioxidant systems in patients with coronary artery disease. *Clinical hemorheology and microcirculation,* 29**,** 429-436.

JEFFRIES, S. K., CHOI, W., BUTLER, J., HARRIS, K. J. & AHLUWALIA, J. S. 2005. Strategies for recruiting African-American residents of public housing developments into a randomized controlled trial. *Ethnicity & disease,* 15**,** 773-778.

JIANG, X., SIT, J. W. & WONG, T. K. 2007. A nurse-led cardiac rehabilitation programme improves health behaviours and cardiac physiological risk parameters: evidence from Chengdu, China. *Journal of clinical nursing,* 16**,** 1886-1897.

JOLLY, K., BRADLEY, F., SHARP, S., SMITH, H., THOMPSON, S., KINMONTH, A. L. & MANT, D. 1999. Randomised controlled trial of follow up care in general practice of patients with myocardial infarction and angina: final results of the Southampton heart integrated care project (SHIP). The SHIP Collaborative Group. *BMJ (Clinical research ed.),* 318**,** 706-711.

KANERA, I. M., WILLEMS, R. A., BOLMAN, C. A. W., MESTERS, I., ZAMBON, V., GIJSEN, B. C. & LECHNER, L. 2016. Use and Appreciation of a Tailored Self-Management eHealth Intervention for Early Cancer Survivors: Process Evaluation of a Randomized Controlled Trial. *Journal of medical Internet research,* 18**,** e229.

KAPLAN, N. M. & VIDT, D. G. 2003. Nonpharmacologic treatment of hypertension in primary health care. *Current hypertension reports,* 5**,** 361-362.

KAYA, Y., KIZILKAYA BEJI, N., AYDIN, Y. & HASSA, H. 2016. The effect of health-promoting lifestyle education on the treatment of unexplained female infertility. *European journal of obstetrics, gynecology, and reproductive biology,* 207**,** 109-114.

KENFIELD, S. A., VAN BLARIGAN, E. L., AMELI, N., LAVAKI, E., CEDARS, B., PACIOREK, A. T., MONROY, C., TANTUM, L. K., NEWTON, R. U., SIGNORELL, C., SUH, J. H., ZHANG, L., COOPERBERG, M. R., CARROLL, P. R. & CHAN, J. M. 2019. Feasibility, Acceptability, and Behavioral Outcomes from a Technology-enhanced Behavioral Change Intervention (Prostate 8): A Pilot Randomized Controlled Trial in Men with Prostate Cancer. *European urology,* 75**,** 950-958.

KEYWORTH, C., NELSON, P. A., BUNDY, C., PYE, S. R., GRIFFITHS, C. E. M. & CORDINGLEY, L. 2018. Does message framing affect changes in behavioural intentions in people with psoriasis? A randomized exploratory study examining health risk communication. *Psychology, health & medicine,* 23**,** 763-778.

KRUIS, A. L., BOLAND, M. R. S., ASSENDELFT, W. J. J., GUSSEKLOO, J., TSIACHRISTAS, A., STIJNEN, T., BLOM, C., SONT, J. K., RUTTEN-VAN MÖLKEN, M. P. H. M. & CHAVANNES, N. H. 2014. Effectiveness of integrated disease management for primary care chronic obstructive pulmonary disease patients: results of cluster randomised trial. *BMJ (Clinical research ed.),* 349**,** g5392.

LEWIS, J., MCCREESH, K., ROY, J. S. & GINN, K. 2015. Rotator cuff tendinopathy: Navigating the diagnosis - management conundrum. *Journal of Orthopaedic and Sports Physical Therapy,* 45**,** 923-37.

LIN, E. H. B., KATON, W., RUTTER, C., SIMON, G. E., LUDMAN, E. J., VON KORFF, M., YOUNG, B., OLIVER, M., CIECHANOWSKI, P. C., KINDER, L. & WALKER, E. 2006. Effects of enhanced depression treatment on diabetes self-care. *Annals of family medicine,* 4**,** 46-53.

LOU, P., CHEN, P., ZHANG, P., YU, J., WANG, Y., CHEN, N., ZHANG, L., WU, H. & ZHAO, J. 2015. A COPD health management program in a community-based primary care setting: a randomized controlled trial. *Respiratory care,* 60**,** 102-112.

MICHIE, S., WOOD, C. E., JOHNSTON, M., ABRAHAM, C., FRANCIS, J. J. & HARDEMAN, W. 2015. Behaviour change techniques: the development and evaluation of a taxonomic method for reporting and describing behaviour change interventions (a suite of five studies involving consensus methods, randomised controlled trials and analysis of qualitative data). *Health technology assessment (Winchester, England),* 19**,** 1-188.

MURALIDHARAN, A., PEEPLES, A. D., LUCKSTED, A. & GOLDBERG, R. W. 2017. Defining 'peerness' in peer-delivered health and weliness interventions for serious mental illness. *Psychiatric Rehabilitation Journal,* 40.

MUSCARI, A., SBANO, D., BASTAGLI, L., POGGIOPOLLINI, G., TOMASSETTI, V., FORTI, P., BONI, P., RAVAGLIA, G., ZOLI, M. & PUDDU, P. 2005. Effects of weight loss and risk factor treatment in subjects with elevated serum C3, an inflammatory predictor of myocardial infarction. *International journal of cardiology,* 100**,** 217-223.

NAIR, U. S., COLLINS, B. N., PATTERSON, F. & RODRIGUEZ, D. 2015. Promoting pre-quit physical activity to reduce cue reactivity among low-income sedentary smokers: A randomized proof of concept study. *Contemporary clinical trials,* 42**,** 158-166.

NIGG, C. R., COURNEYA, K. S. & ESTABROOKS, P. A. 1997. Maintaining attendance at a fitness center: an application of the decision balance sheet. *Behavioral medicine (Washington, D.C.),* 23**,** 130-137.

PAHKALA, K., LAITINEN, T. T., HEINONEN, O. J., VIIKARI, J. S. A., RÖNNEMAA, T., NIINIKOSKI, H., HELAJÄRVI, H., JUONALA, M., SIMELL, O. & RAITAKARI, O. T. 2013. Association of fitness with vascular intima-media thickness and elasticity in adolescence. *Pediatrics,* 132**,** e77-e84.

PATTEN, C. A., BRONARS, C. A., VICKERS DOUGLAS, K. S., USSHER, M. H., LEVINE, J. A., TYE, S. J., HUGHES, C. A., BROCKMAN, T. A., DECKER, P. A., DEJESUS, R. S., WILLIAMS, M. D., OLSON, T. P., CLARK, M. M. & DIETERICH, A. M. 2017. Supervised, Vigorous Intensity Exercise Intervention for Depressed Female Smokers: A Pilot Study. *Nicotine & tobacco research : official journal of the Society for Research on Nicotine and Tobacco,* 19**,** 77-86.

RADACK, K. & WYDERSKI, R. J. 1990. Conservative management of intermittent claudication. *Annals of internal medicine,* 113**,** 135-146.

SANDISON, R., GRAY, M. & REID, D. M. 2004. Lifestyle factors for promoting bone health in older women. *Journal of Advanced Nursing,* 45**,** 603-10.

SUMARTININGSIH, S., LIN, H.-F. & LIN, J.-C. 2019. Cigarette Smoking Blunts Exercise-Induced Heart Rate Response among Young Adult Male Smokers. *International journal of environmental research and public health,* 16.

TABESH, M., AZADBAKHT, L., FAGHIHIMANI, E., TABESH, M. & ESMAILLZADEH, A. 2014. Effects of calcium-vitamin D co-supplementation on metabolic profiles in vitamin D insufficient people with type 2 diabetes: a randomised controlled clinical trial. *Diabetologia,* 57**,** 2038-2047.

TURNER, P. A. 2000. Osteoporosis - its causes and prevention: an update. *Physiotherapy Theory and Practice,* 16**,** 135-49.

VAN DEN BERG, J. J., BOCK, B. C., ROBERTS, M. B., PARKER, D. R., MARTIN, R. A., STEIN, L. A. R. & CLARKE, J. G. 2016. Goals and Plans of Incarcerated Men Postrelease. *Journal of correctional health care : the official journal of the National Commission on Correctional Health Care,* 22**,** 146-156.

VAN ZUILEN, A. D., BLANKESTIJN, P. J., VAN BUREN, M., TEN DAM, M. A. G. J., KAASJAGER, K. A. H., LIGTENBERG, G., SIJPKENS, Y. W. J., SLUITER, H. E., VAN DE VEN, P. J. G., VERVOORT, G., VLEMING, L., BOTS, M. L. & WETZELS, J. F. M. 2011. Nurse practitioners improve quality of care in chronic kidney disease: two-year results of a randomised study. *The Netherlands journal of medicine,* 69**,** 517-526.

VAN ZUILEN, A. D., BOTS, M. L., DULGER, A., VAN DER TWEEL, I., VAN BUREN, M., TEN DAM, M. A. G. J., KAASJAGER, K. A. H., LIGTENBERG, G., SIJPKENS, Y. W. J., SLUITER, H. E., VAN DE VEN, P. J. G., VERVOORT, G., VLEMING, L.-J., BLANKESTIJN, P. J. & WETZELS, J. F. M. 2012. Multifactorial intervention with nurse practitioners does not change cardiovascular outcomes in patients with chronic kidney disease. *Kidney international,* 82**,** 710-717.

WHITE, A. & TAYLOR, A. 2014. Acupuncture for smokng cessation: Where now? *Acupuncture in Medicine,* 32**,** 306-7.

WU, F., WILLS, K., LASLETT, L. L., RILEY, M. D., OLDENBURG, B., JONES, G. & WINZENBERG, T. 2018. Individualized Fracture Risk Feedback and Long-term Benefits After 10 Years. *American journal of preventive medicine,* 54**,** 266-274.

Exercise is not aerobic or not specified

CARLSSON, R. 1998. Serum cholesterol, lifestyle, working capacity and quality of life in patients with coronary artery disease. Experiences from a hospital-based secondary prevention programme. *Scandinavian cardiovascular journal. Supplement,* 50**,** 1-20.

DEBUSK, R. F., MILLER, N. H., SUPERKO, H. R., DENNIS, C. A., THOMAS, R. J., LEW, H. T., BERGER, W. E., 3RD, HELLER, R. S., ROMPF, J., GEE, D., KRAEMER, H. C., BANDURA, A., GHANDOUR, G., CLARK, M., SHAH, R. V., FISHER, L. & TAYLOR, C. B. 1994. A case-management system for coronary risk factor modification after acute myocardial infarction. *Annals of internal medicine,* 120**,** 721-729.

EMMONS, K. M., LINNAN, L. A., SHADEL, W. G., MARCUS, B. & ABRAMS, D. B. 1999. The Working Healthy Project: a worksite health-promotion trial targeting physical activity, diet, and smoking. *Journal of occupational and environmental medicine,* 41**,** 545-555.

HJERMANN, I. 1988. Strategies for dietary and anti-smoking advice. Practical experiences from the Oslo Study. *Drugs,* 36 Suppl 3**,** 105-109.

JACOBS, N., DROST, R., AMENT, A., EVERS, S. & CLAES, N. 2011. Willingness to pay for a cardiovascular prevention program in highly educated adults: a randomized controlled trial. *International journal of technology assessment in health care,* 27**,** 283-289.

JAVITZ, H. S., BUSH, T. M., LOVEJOY, J. C., TORRES, A. J., WETZEL, T., WASSUM, K. P., TAN, M. M., ALSHURAFA, N. & SPRING, B. 2019. Six Month Abstinence Heterogeneity in the Best Quit Study. *Annals of behavioral medicine : a publication of the Society of Behavioral Medicine,* 53**,** 1032-1044.

JENNINGS, C., KOTSEVA, K., DE BACQUER, D., HOES, A., DE VELASCO, J., BRUSAFERRO, S., MEAD, A., JONES, J., TONSTAD, S. & WOOD, D. 2014. Effectiveness of a preventive cardiology programme for high CVD risk persistent smokers: the EUROACTION PLUS varenicline trial. *European heart journal,* 35**,** 1411-1420.

KETOLA, E., MÄKELÄ, M. & KLOCKARS, M. 2001. Individualised multifactorial lifestyle intervention trial for high-risk cardiovascular patients in primary care. *The British journal of general practice : the journal of the Royal College of General Practitioners,* 51**,** 291-294.

MARCOS-FORNIOL, E., MECO, J. F., CORBELLA, E., FORMIGA, F. & PINTÓ, X. 2018. Secondary prevention programme of ischaemic heart disease in the elderly: A randomised clinical trial. *European journal of preventive cardiology,* 25**,** 278-286.

STEPTOE, A., DOHERTY, S., RINK, E., KERRY, S., KENDRICK, T. & HILTON, S. 1999. Behavioural counselling in general practice for the promotion of healthy behaviour among adults at increased risk of coronary heart disease: randomised trial. *BMJ (Clinical research ed.),* 319**,** 943-947.

BAKER, A. L., RICHMOND, R., KAY-LAMBKIN, F. J., FILIA, S. L., CASTLE, D., WILLIAMS, J. M., LEWIN, T. J., CLARK, V., CALLISTER, R. & PALAZZI, K. 2018. Randomised controlled trial of a healthy lifestyle intervention among smokers with psychotic disorders: Outcomes to 36 months. *The Australian and New Zealand journal of psychiatry,* 52**,** 239-252.

BAKER, A. L., RICHMOND, R., KAY-LAMBKIN, F. J., FILIA, S. L., CASTLE, D., WILLIAMS, J. M., LEWIN, T. J., CLARK, V., CALLISTER, R. & WEAVER, N. 2015. Randomized Controlled Trial of a Healthy Lifestyle Intervention Among Smokers With Psychotic Disorders. *Nicotine & tobacco research : official journal of the Society for Research on Nicotine and Tobacco,* 17**,** 946-954.

BLANK, M. D., FERRIS, K. A., METZGER, A., GENTZLER, A., DUNCAN, C., JARRETT, T. & DINO, G. 2017. Physical Activity and Quit Motivation Moderators of Adolescent Smoking Reduction. *American journal of health behavior,* 41**,** 419-427.

CAMPBELL, N. C., RITCHIE, L. D., THAIN, J., DEANS, H. G., RAWLES, J. M. & SQUAIR, J. L. 1998. Secondary prevention in coronary heart disease: a randomised trial of nurse led clinics in primary care. *Heart (British Cardiac Society),* 80**,** 447-452.

CUPPLES, M. E. & MCKNIGHT, A. 1999. Five year follow up of patients at high cardiovascular risk who took part in randomised controlled trial of health promotion. *BMJ (Clinical research ed.),* 319**,** 687-688.

DEHGHANI, A., KUMAR BHASIN, S., DWIVEDI, S. & KUMAR MALHOTRA, R. 2015. Influence of Comprehensive Life Style Intervention in Patients of CHD. *Global journal of health science,* 7**,** 6-16.

GLYNN, T. J., BOYD, G. M. & GRUMAN, J. C. 1990. Essential elements of self-help/minimal intervention strategies for smoking cessation. *Health education quarterly,* 17**,** 329-345.

GONSETH, S., LOCATELLI, I., BIZE, R., NUSSLÉ, S., CLAIR, C., PRALONG, F. & CORNUZ, J. 2014. Leptin and smoking cessation: secondary analyses of a randomized controlled trial assessing physical activity as an aid for smoking cessation. *BMC public health,* 14**,** 911.

HORN, K., BRANSTETTER, S., ZHANG, J., JARRETT, T., TOMPKINS, N. O. H., ANESETTI-ROTHERMEL, A., OLFERT, M., RICHARDS, T. & DINO, G. 2013. Understanding physical activity outcomes as a function of teen smoking cessation. *The Journal of adolescent health : official publication of the Society for Adolescent Medicine,* 53**,** 125-131.

HORN, K., DINO, G., BRANSTETTER, S. A., ZHANG, J., NOERACHMANTO, N., JARRETT, T. & TAYLOR, M. 2011. Effects of physical activity on teen smoking cessation. *Pediatrics,* 128**,** e801-e811.

KADDA, O., MANGINAS, A., STAVRIDIS, G., BALANOS, D., KOTIOU, M. & PANAGIOTAKOS, D. B. 2016. Gender Analysis in the Outcomes of a Lifestyle Intervention Among Patients Who Had an Open Heart Surgery. *Angiology,* 67**,** 66-74.

KILLEN, J. D., ROBINSON, T. N., TELCH, M. J., SAYLOR, K. E., MARON, D. J., RICH, T. & BRYSON, S. 1989. The Stanford Adolescent Heart Health Program. *Health education quarterly,* 16**,** 263-283.

KILLEN, J. D., TELCH, M. J., ROBINSON, T. N., MACCOBY, N., TAYLOR, C. B. & FARQUHAR, J. W. 1988. Cardiovascular disease risk reduction for tenth graders. A multiple-factor school-based approach. *JAMA,* 260**,** 1728-1733.

KORNITZER, M., DE BACKER, G., DRAMAIX, M., KITTEL, F., THILLY, C., GRAFFAR, M. & VUYLSTEEK, K. 1983. Belgian heart disease prevention project: incidence and mortality results. *Lancet (London, England),* 1**,** 1066-1070.

KURTI, A. N. & DALLERY, J. 2014. A laboratory-based evaluation of exercise plus contingency management for reducing cigarette smoking. *Drug and alcohol dependence,* 144**,** 201-209.

LACHMAN, S., MINNEBOO, M., SNATERSE, M., JORSTAD, H. T., TER RIET, G., SCHOLTE OP REIMER, W. J., BOEKHOLDT, S. M. & PETERS, R. J. G. 2015. Community-based comprehensive lifestyle programs in patients with coronary artery disease: Objectives, design and expected results of Randomized Evaluation of Secondary Prevention by Outpatient Nurse SpEcialists 2 trial (RESPONSE 2). *American heart journal,* 170**,** 216-222.

MARON, D. J., MANCINI, G. B. J., HARTIGAN, P. M., SPERTUS, J. A., SEDLIS, S. P., KOSTUK, W. J., BERMAN, D. S., TEO, K. K., WEINTRAUB, W. S. & BODEN, W. E. 2018. Healthy Behavior, Risk Factor Control, and Survival in the COURAGE Trial. *Journal of the American College of Cardiology,* 72**,** 2297-2305.

MCKENZIE, S. H., JAYASINGHE, U. W., FANAIAN, M., PASSEY, M. & HARRIS, M. F. 2013. Analysis of the psychological impact of a vascular risk factor intervention: results from a cluster randomized controlled trial in Australian general practice. *BMC family practice,* 14**,** 190.

MENOTTI, A. 1983. The european multifactorial preventive trial of coronary heart disease: four-year experience. *Preventive medicine,* 12**,** 175-180.

MINNEBOO, M., LACHMAN, S., SNATERSE, M., JØRSTAD, H. T., TER RIET, G., BOEKHOLDT, S. M., SCHOLTE OP REIMER, W. J. M. & PETERS, R. J. G. 2017. Community-Based Lifestyle Intervention in Patients With Coronary Artery Disease: The RESPONSE-2 Trial. *Journal of the American College of Cardiology,* 70**,** 318-327.

MOSCA, L., CHRISTIAN, A. H., MOCHARI-GREENBERGER, H., KLIGFIELD, P. & SMITH, S. C., JR. 2010. A randomized clinical trial of secondary prevention among women hospitalized with coronary heart disease. *Journal of women's health (2002),* 19**,** 195-202.

MURCHIE, P., CAMPBELL, N. C., RITCHIE, L. D., SIMPSON, J. A. & THAIN, J. 2003. Secondary prevention clinics for coronary heart disease: four year follow up of a randomised controlled trial in primary care. *BMJ (Clinical research ed.),* 326**,** 84.

OENEMA, A., BRUG, J., DIJKSTRA, A., DE WEERDT, I. & DE VRIES, H. 2008. Efficacy and use of an internet-delivered computer-tailored lifestyle intervention, targeting saturated fat intake, physical activity and smoking cessation: a randomized controlled trial. *Annals of behavioral medicine : a publication of the Society of Behavioral Medicine,* 35**,** 125-135.

PARK, A. H., LEE, S. J. & OH, S. J. 2015. The effects of a smoking cessation programme on health-promoting lifestyles and smoking cessation in smokers who had undergone percutaneous coronary intervention. *International journal of nursing practice,* 21**,** 107-117.

PROCHASKA, J. J., HALL, S. M., HUMFLEET, G., MUNOZ, R. F., REUS, V., GORECKI, J. & HU, D. 2008. Physical activity as a strategy for maintaining tobacco abstinence: a randomized trial. *Preventive medicine,* 47**,** 215-220.

REID, R. D., MCDONNELL, L. A., RILEY, D. L., MARK, A. E., MOSCA, L., BEATON, L., PAPADAKIS, S., BLANCHARD, C. M., MOCHARI-GREENBERGER, H., O'FARRELL, P., WELLS, G. A., SLOVINEC D'ANGELO, M. E. & PIPE, A. L. 2014. Effect of an intervention to improve the cardiovascular health of family members of patients with coronary artery disease: a randomized trial. *CMAJ : Canadian Medical Association journal = journal de l'Association medicale canadienne,* 186**,** 23-30.

SHAGIWAL, S. S., SCHOP-ETMAN, A., BERGWERFF, I., VRENCKEN, W. & DENKTAŞ, S. 2018. The BeHealthyR Study: a randomized trial of a multicomponent intervention to reduce stress, smoking and improve financial health of low-income residents in Rotterdam. *BMC public health,* 18**,** 891.

WISTER, A., LOEWEN, N., KENNEDY-SYMONDS, H., MCGOWAN, B., MCCOY, B. & SINGER, J. 2007. One-year follow-up of a therapeutic lifestyle intervention targeting cardiovascular disease risk. *CMAJ : Canadian Medical Association journal = journal de l'Association medicale canadienne,* 177**,** 859-865.

AIMER, P., STAMP, L. K., STEBBINGS, S., CAMERON, V., KIRBY, S. & TREHARNE, G. J. 2018. Exploring perceptions of a rheumatoid arthritis-specific smoking cessation programme. *Musculoskeletal care,* 16**,** 74-81.

AL-CHALABI, L., PRASAD, N., STEED, L., STENNER, S., AVEYARD, P., BEACH, J. & USSHER, M. 2008. A pilot randomised controlled trial of the feasibility of using body scan and isometric exercises for reducing

urge to smoke in a smoking cessation clinic. *BMC public health,* 8**,** 349.
ALLEN, S. S., HATSUKAMI, D., BRINTNELL, D. M. & BADE, T. 2005. Effect of nicotine replacement therapy on post-cessation weight gain and nutrient intake: a randomized controlled trial of postmenopausal female smokers. *Addictive behaviors,* 30**,** 1273-1280.
ARI, H., ARI, S., COŞAR, S., CELILOĞLU, N., AKTAŞ, İ., CAMCI, S., DOĞANAY, K., TÜTÜNCÜ, A. & MELEK, M. 2015. The effect of varenicline on Tp-e interval, Tp-e/QT ratio and Tp-e/QTc ratio in healthy smokers and nonsmokers. *Cardiology journal,* 22**,** 551-556.
ARNOLD, J., GOODACRE, S., BATH, P. & PRICE, J. 2009. Information sheets for patients with acute chest pain: randomised controlled trial. *BMJ (Clinical research ed.),* 338**,** b541.
ASTHANA, A., PIPER, M. E., MCBRIDE, P. E., WARD, A., FIORE, M. C., BAKER, T. B. & STEIN, J. H. 2012. Long-term effects of smoking and smoking cessation on exercise stress testing: three-year outcomes from a randomized clinical trial. *American heart journal,* 163**,** 81.
AVEYARD, P., LAWRENCE, T., CROGHAN, E., EVANS, O. & CHENG, K. K. 2005. Is advice to stop smoking from a midwife stressful for pregnant women who smoke? Data from a randomized controlled trial. *Preventive medicine,* 40**,** 575-582.
BEN TALEB, Z., WARD, K. D., ASFAR, T., JABER, R., BAHELAH, R. & MAZIAK, W. 2017. Smoking Cessation and Changes in Body Mass Index: Findings From the First Randomized Cessation Trial in a Low-Income Country Setting. *Nicotine & tobacco research : official journal of the Society for Research on Nicotine and Tobacco,* 19**,** 351-356.
BOCK, B. C., DUNSIGER, S. I., ROSEN, R. K., THIND, H., JENNINGS, E., FAVA, J. L., BECKER, B. M., CARMODY, J. & MARCUS, B. H. 2019. Yoga as a Complementary Therapy for Smoking Cessation: Results From BreathEasy, a Randomized Clinical Trial. *Nicotine & tobacco research : official journal of the Society for Research on Nicotine and Tobacco,* 21**,** 1517-1523.
BOCK, B. C., FAVA, J. L., GASKINS, R., MORROW, K. M., WILLIAMS, D. M., JENNINGS, E., BECKER, B. M., TREMONT, G. & MARCUS, B. H. 2012. Yoga as a complementary treatment for smoking cessation in women. *Journal of women's health (2002),* 21**,** 240-248.
BOCK, B. C., MORROW, K. M., BECKER, B. M., WILLIAMS, D. M., TREMONT, G., GASKINS, R. B., JENNINGS, E., FAVA, J. & MARCUS, B. H. 2010. Yoga as a complementary treatment for smoking cessation: rationale, study design and participant characteristics of the Quitting-in-Balance study. *BMC complementary and alternative medicine,* 10**,** 14.
CAVENDER, J. B., ROGERS, W. J., FISHER, L. D., GERSH, B. J., COGGIN, C. J. & MYERS, W. O. 1992. Effects of smoking on survival and morbidity in patients randomized to medical or surgical therapy in the Coronary Artery Surgery Study (CASS): 10-year follow-up. CASS Investigators. *Journal of the American College of Cardiology,* 20**,** 287-294.
CEGALA, D. J., MARINELLI, T. & POST, D. 2000. The effects of patient communication skills training on compliance. *Archives of family medicine,* 9**,** 57-64.
CERRATO, P. L. 1999. A radical approach to heart disease. *RN,* 62**,** 65-6.
CHAUMONT, M., TAGLIATTI, V., CHANNAN, E. M., COLET, J.-M., BERNARD, A., MORRA, S., DEPREZ, G., VAN MUYLEM, A., DEBBAS, N., SCHAEFER, T., FAORO, V. & VAN DE BORNE, P. 2020. Short halt in vaping modifies cardiorespiratory parameters and urine metabolome: a randomized trial. *American journal of physiology. Lung cellular and molecular physiology,* 318**,** L331-L344.
CHEUNG, Y. T., LAM, T. H., CHAN, C. H. H., HO, K. S., FOK, W. Y. P., WANG, M. P. & LI, W. H. C. 2020. Brief handgrip and isometric exercise intervention for smoking cessation: A pilot randomized trial. *Addictive behaviors,* 100**,** 106119.
CICCOLO, J. T., DUNSIGER, S. I., WILLIAMS, D. M., BARTHOLOMEW, J. B., JENNINGS, E. G., USSHER, M. H., KRAEMER, W. J. & MARCUS, B. H. 2011. Resistance training as an aid to standard smoking cessation treatment: a pilot study. *Nicotine & tobacco research : official journal of the Society for Research on Nicotine and Tobacco,* 13**,** 756-760.
CLARK, M. M., HAYS, J. T., VICKERS, K. S., PATTEN, C. A., CROGHAN, I. T., BERG, E., WADEWITZ, S., SCHWARTZ, S., DECKER, P. A., OFFORD, K. P., SQUIRES, R. W. & HURT, R. D. 2005. Body image treatment for weight concerned smokers: a pilot study. *Addictive behaviors,* 30**,** 1236-1240.
COHEN, A., ASSYAG, P., BOYER-CHATENET, L., COHEN-SOLAL, A., PERDRIX, C., DALICHAMPT, M., MICHEL, P.-L., MONTALESCOT, G., RAVAUD, P., STEG, P. G. & BOUTRON, I. 2014. An education program for risk factor management after an acute coronary syndrome: a randomized clinical trial. *JAMA internal medicine,* 174**,** 40-48.
DAVIES, M. J., HELLER, S., SKINNER, T. C., CAMPBELL, M. J., CAREY, M. E., CRADOCK, S., DALLOSSO, H. M., DALY, H., DOHERTY, Y., EATON, S., FOX, C., OLIVER, L., RANTELL, K., RAYMAN, G. & KHUNTI, K. 2008. Effectiveness of the diabetes education and self management for ongoing and newly diagnosed (DESMOND) programme for people with newly diagnosed type 2 diabetes: cluster randomised controlled trial. *BMJ (Clinical research ed.),* 336**,** 491-495.
ELIBERO, A., JANSE VAN RENSBURG, K. & DROBES, D. J. 2011. Acute effects of aerobic exercise and Hatha yoga

on craving to smoke. *Nicotine & tobacco research : official journal of the Society for Research on Nicotine and Tobacco,* 13**,** 1140-1148.
EMERY, R. L., LEVINE, M. D., CHENG, Y. & MARCUS, M. D. 2015. Change in Body Weight Does Not Mediate the Relationship Between Exercise and Smoking Cessation Among Weight-Concerned Women Smokers. *Nicotine & tobacco research : official journal of the Society for Research on Nicotine and Tobacco,* 17**,** 1142-1148.
FILION, A. J., DARLINGTON, G., CHAPUT, J.-P., YBARRA, M. & HAINES, J. 2015. Examining the influence of a text message-based sleep and physical activity intervention among young adult smokers in the United States. *BMC public health,* 15**,** 671.
FORNARI, L. S., GIULIANO, I., AZEVEDO, F., PASTANA, A., VIEIRA, C. & CARAMELLI, B. 2013. Children First Study: how an educational program in cardiovascular prevention at school can improve parents' cardiovascular risk. *European journal of preventive cardiology,* 20**,** 301-309.
FROELICHER, E. S., CHRISTOPHERSON, D. J., MILLER, N. H. & MARTIN, K. 2002. Women's initiative for nonsmoking (WINS) IV: description of 277 women smokers hospitalized with cardiovascular disease. *Heart & lung : the journal of critical care,* 31**,** 3-14.
GIANOS, E., SCHOENTHALER, A., MUSHAILOV, M., FISHER, E. A. & BERGER, J. S. 2015. Rationale and design of the Investigation of Motivational Interviewing and Prevention Consults to Achieve Cardiovascular Targets (IMPACT) trial. *American heart journal,* 170**,** 430.
GORINI, G., CARRERAS, G., GIORDANO, L., ANGHINONI, E., IOSSA, A., COPPO, A., TALASSI, F., GALAVOTTI, M. & CHELLINI, E. 2012. The Pap smear screening as an occasion for smoking cessation and physical activity counselling: effectiveness of the SPRINT randomized controlled trial. *BMC public health,* 12**,** 740.
HALL, S. M., TUNSTALL, C. D., VILA, K. L. & DUFFY, J. 1992. Weight gain prevention and smoking cessation: cautionary findings. *American journal of public health,* 82**,** 799-803.
HANSSEN, T. A., NORDREHAUG, J. E., EIDE, G. E. & HANESTAD, B. R. 2007. Improving outcomes after myocardial infarction: a randomized controlled trial evaluating effects of a telephone follow-up intervention. *European journal of cardiovascular prevention and rehabilitation : official journal of the European Society of Cardiology, Working Groups on Epidemiology & Prevention and Cardiac Rehabilitation and Exercise Physiology,* 14**,** 429-437.
HARTING, J., VAN ASSEMA, P., VAN LIMPT, P., GORGELS, T., VAN REE, J., RULAND, E., VERMEER, F. & DE VRIES, N. K. 2006. Effects of health counseling on behavioural risk factors in a high-risk cardiology outpatient population: a randomized clinical trial. *European journal of cardiovascular prevention and rehabilitation : official journal of the European Society of Cardiology, Working Groups on Epidemiology & Prevention and Cardiac Rehabilitation and Exercise Physiology,* 13**,** 214-221.
HASKELL, W. L., ALDERMAN, E. L., FAIR, J. M., MARON, D. J., MACKEY, S. F., SUPERKO, H. R., WILLIAMS, P. T., JOHNSTONE, I. M., CHAMPAGNE, M. A., KRAUSS, R. M. & ET, A. 1994. Effects of intensive multiple risk factor reduction on coronary atherosclerosis and clinical cardiac events in men and women with coronary artery disease. The Stanford Coronary Risk Intervention Project (SCRIP). *Circulation,* 89**,** 975-990.
HAWK, C., KAESER, M. A. & BEAVERS, D. V. 2013. Feasibility of using a standardized patient encounter for training chiropractic students in tobacco cessation counseling. *J Chiropractic Educ,* 27**,** 135-40.
HYMAN, D. J., PAVLIK, V. N., TAYLOR, W. C., GOODRICK, G. K. & MOYE, L. 2007. Simultaneous vs sequential counseling for multiple behavior change. *Archives of Internal Medicine,* 167**,** 1152-1158.
IJZELENBERG, W., HELLEMANS, I. M., VAN TULDER, M. W., HEYMANS, M. W., RAUWERDA, J. A., VAN ROSSUM, A. C. & SEIDELL, J. C. 2012. The effect of a comprehensive lifestyle intervention on cardiovascular risk factors in pharmacologically treated patients with stable cardiovascular disease compared to usual care: a randomised controlled trial. *BMC cardiovascular disorders,* 12**,** 71.
JEFFRIES, E. R., ZVOLENSKY, M. J. & BUCKNER, J. D. 2020. The Acute Impact of Hatha Yoga on Craving Among Smokers Attempting to Reduce or Quit. *Nicotine & tobacco research : official journal of the Society for Research on Nicotine and Tobacco,* 22**,** 446-451.
JOHNSTON, N., BODEGARD, J., JERSTRÖM, S., ÅKESSON, J., BRORSSON, H., ALFREDSSON, J., ALBERTSSON, P. A., KARLSSON, J.-E. & VARENHORST, C. 2016. Effects of interactive patient smartphone support app on drug adherence and lifestyle changes in myocardial infarction patients: A randomized study. *American heart journal,* 178**,** 85-94.
JØRGENSEN, T., BORCH-JOHNSEN, K., THOMSEN, T. F., IBSEN, H., GLÜMER, C. & PISINGER, C. 2003. A randomized non-pharmacological intervention study for prevention of ischaemic heart disease: baseline results Inter99. *European journal of cardiovascular prevention and rehabilitation : official journal of the European Society of Cardiology, Working Groups on Epidemiology & Prevention and Cardiac Rehabilitation and Exercise Physiology,* 10**,** 377-386.
JØRGENSEN, T., JACOBSEN, R. K., TOFT, U., AADAHL, M., GLÜMER, C. & PISINGER, C. 2014. Effect of screening and lifestyle counselling on incidence of ischaemic heart disease in general population: Inter99

randomised trial. *BMJ (Clinical research ed.),* 348**,** g3617.
KENDZOR, D. E., BUSINELLE, M. S., MAZAS, C. A., COFTA-WOERPEL, L. M., REITZEL, L. R., VIDRINE, J. I., LI, Y., COSTELLO, T. J., CINCIRIPINI, P. M., AHLUWALIA, J. S. & WETTER, D. W. 2009. Pathways between socioeconomic status and modifiable risk factors among African American smokers. *Journal of behavioral medicine,* 32**,** 545-557.
KENDZOR, D. E., COFTA-WOERPEL, L. M., MAZAS, C. A., LI, Y., VIDRINE, J. I., REITZEL, L. R., COSTELLO, T. J., BUSINELLE, M. S., AHLUWALIA, J. S., CINCIRIPINI, P. M. & WETTER, D. W. 2008. Socioeconomic status, negative affect, and modifiable cancer risk factors in African-American smokers. *Cancer epidemiology, biomarkers & prevention : a publication of the American Association for Cancer Research, cosponsored by the American Society of Preventive Oncology,* 17**,** 2546-2554.
KIM, M. J., LEE, S. J., AHN, Y. H. & LEE, H. 2011. Lifestyle advice for Korean Americans and native Koreans with hypertension. *Journal of Advanced Nursing,* 67**,** 531-9.
KIRKMAN, M. S., WEINBERGER, M., LANDSMAN, P. B., SAMSA, G. P., SHORTLIFFE, E. A., SIMEL, D. L. & FEUSSNER, J. R. 1994. A telephone-delivered intervention for patients with NIDDM. Effect on coronary risk factors. *Diabetes care,* 17**,** 840-846.
KIRSCHBAUM, C., SCHERER, G. & STRASBURGER, C. J. 1994. Pituitary and adrenal hormone responses to pharmacological, physical, and psychological stimulation in habitual smokers and nonsmokers. *The Clinical investigator,* 72**,** 804-810.
KLESGES, R. C., KLESGES, L. M., MEYERS, A. W., KLEM, M. L. & ISBELL, T. 1990. The effects of phenylpropanolamine on dietary intake, physical activity, and body weight after smoking cessation. *Clinical pharmacology and therapeutics,* 47**,** 747-754.
KLONIZAKIS, M., CRANK, H., GUMBER, A. & BROSE, L. S. 2017. Smokers making a quit attempt using e-cigarettes with or without nicotine or prescription nicotine replacement therapy: Impact on cardiovascular function (ISME-NRT) - a study protocol. *BMC public health,* 17**,** 293.
KRAMER, J. J., WILLEMSEN, M. C., CONIJN, B., VAN EMST, A. J., BRUNSTING, S. & RIPER, H. 2009. Effectiveness of a web-based self-help smoking cessation intervention: protocol of a randomised controlled trial. *BMC public health,* 9**,** 32.
KRAUSE, J. S. & SAUNDERS, L. L. 2010. Risk of mortality and life expectancy after spinal cord injury: The role of health behaviors and participation. *Topics in Spinal Cord Injury Rehabilitation,* 16**,** 53-60.
KREUTER, M. W., CHHEDA, S. G. & BULL, F. C. 2000. How does physician advice influence patient behavior? Evidence for a priming effect. *Archives of family medicine,* 9**,** 426-433.
KRIGEL, S. W., GROBE, J. E., GOGGIN, K., HARRIS, K. J., MORENO, J. L. & CATLEY, D. 2017. Motivational interviewing and the decisional balance procedure for cessation induction in smokers not intending to quit. *Addictive behaviors,* 64**,** 171-178.
LAN, W., YANG, F., LIU, L., YIN, Q., LI, M., LI, Z., SANG, H., XU, G., MA, M., ZHANG, Z., LIU, Z., LIU, X. & ZHANG, R. 2014. Tissue kallikrein preventing the restenosis after stenting of symptomatic MCA atherosclerotic stenosis (KPRASS). *International journal of stroke : official journal of the International Stroke Society,* 9**,** 533-535.
LEVIN, S. R., COBURN, J. W., ABRAIRA, C., HENDERSON, W. G., COLWELL, J. A., EMANUELE, N. V., NUTTALL, F. Q., SAWIN, C. T., COMSTOCK, J. P. & SILBERT, C. K. 2000. Effect of intensive glycemic control on microalbuminuria in type 2 diabetes. Veterans Affairs Cooperative Study on Glycemic Control and Complications in Type 2 Diabetes Feasibility Trial Investigators. *Diabetes care,* 23**,** 1478-1485.
LI, H., WEI, X., WONG, M. C., YANG, N., WONG, S. Y., LAO, X. & GRIFFITHS, S. M. 2015. A comparison of the quality of hypertension management in primary care between Shanghai and Shenzhen: a cohort study of 3196 patients. *Medicine,* 94**,** e455.
LOTFALIAN, S., SPEARS, C. A. & JULIANO, L. M. 2020. The effects of mindfulness-based yogic breathing on craving, affect, and smoking behavior. *Psychology of addictive behaviors : journal of the Society of Psychologists in Addictive Behaviors,* 34**,** 351-359.
LOUGHEAD, J., FALCONE, M., WILEYTO, E. P., ALBELDA, B., AUDRAIN-MCGOVERN, J., CAO, W., KURTZ, M. M., GUR, R. C. & LERMAN, C. 2016. Can brain games help smokers quit?: Results of a randomized clinical trial. *Drug and alcohol dependence,* 168**,** 112-118.
LOW, V., GEBHART, B. & REICH, C. 2015. Effects of a worksite program to improve the cardiovascular health of female health care workers. *Journal of cardiopulmonary rehabilitation and prevention,* 35**,** 342-347.
LYCETT, D., AVEYARD, P., FARMER, A., LEWIS, A. & MUNAFÒ, M. 2013. Slimming World in Stop Smoking Services (SWISSS): study protocol for a randomized controlled trial. *Trials,* 14**,** 182.
MADDISON, R., ROBERTS, V., MCROBBIE, H., BULLEN, C., PRAPAVESSIS, H., GLOVER, M., JIANG, Y., BROWN, P., LEUNG, W., TAYLOR, S. & TSAI, M. 2014. Exercise counseling to enhance smoking cessation outcomes: the Fit2Quit randomized controlled trial. *Annals of behavioral medicine : a publication of the Society of Behavioral Medicine,* 48**,** 194-204.
MANTOANI, L. C., FURLANETTO, K. C., KOVELIS, D., PROENCA, M., ZABATIERO, J., BISCA, G., MORITA, A. & PITTA, F. 2014. Long-term effects of a program to increase physical activity in smokers. *Chest,* 146**,**

1627-32.
MARZILLI, T. S. & HUTCHERSON, A. B. 2002. Nicotine deprivation effects on the dissociated components of simple reaction time. *Perceptual and motor skills,* 94**,** 985-995.
MAZANEC, S. R., FLOCKE, S. A. & DALY, B. J. 2015. Health behaviors in family members of patients completing cancer treatment. *Oncology Nursing Forum,* 42**,** 54-62.
MCHUGH, F., LINDSAY, G. M., HANLON, P., HUTTON, I., BROWN, M. R., MORRISON, C. & WHEATLEY, D. J. 2001. Nurse led shared care for patients on the waiting list for coronary artery bypass surgery: a randomised controlled trial. *Heart (British Cardiac Society),* 86**,** 317-323.
MEHRING, M., HAAG, M., LINDE, K., WAGENPFEIL, S. & SCHNEIDER, A. 2014. Effects of a guided web-based smoking cessation program with telephone counseling: a cluster randomized controlled trial. *Journal of medical Internet research,* 16**,** e218.
MEIJER, E., GEBHARDT, W. A., VAN LAAR, C., VAN DEN PUTTE, B. & EVERS, A. W. M. 2018. Strengthening quitter self-identity: An experimental study. *Psychology & health,* 33**,** 1229-1250.
MELAND, E., MAELAND, J. G. & LAERUM, E. 1999. The importance of self-efficacy in cardiovascular risk factor change. *Scandinavian journal of public health,* 27**,** 11-17.
MILANI, R. V. & LAVIE, C. J. 2009. Impact of worksite wellness intervention on cardiac risk factors and one-year health care costs. *The American journal of cardiology,* 104**,** 1389-1392.
MOFFATT, R. J., BIGGERSTAFF, K. D. & STAMFORD, B. A. 2000. Effects of the transdermal nicotine patch on normalization of HDL-C and its subfractions. *Preventive medicine,* 31**,** 148-152.
MORRIS, R., ROBINSON, G., TILYARD, M. & GURR, E. 1996. Pravastatin and risk factor modification in patients with moderate primary hypercholesterolaemia. *The New Zealand medical journal,* 109**,** 319-322.
NOLAN, R. P., FELDMAN, R., DAWES, M., KACZOROWSKI, J., LYNN, H., BARR, S. I., MACPHAIL, C., THOMAS, S., GOODMAN, J., EYSENBACH, G., LIU, S., TANAKA, R. & SURIKOVA, J. 2018. Randomized Controlled Trial of E-Counseling for Hypertension: REACH. *Circulation. Cardiovascular quality and outcomes,* 11**,** e004420.
SHAHAB, L., SARKAR, B. K. & WEST, R. 2013. The acute effects of yogic breathing exercises on craving and withdrawal symptoms in abstaining smokers. *Psychopharmacology,* 225**,** 875-882.
STAHL, M. M., WOHLFART, B. & PAHLM, O. 2001. Tolerability of concurrent use of nicotine gum and smoking in healthy volunteers. *Nicotine & tobacco research : official journal of the Society for Research on Nicotine and Tobacco,* 3**,** 157-165.
STITZER, M. L. & BIGELOW, G. E. 1985. Contingent reinforcement for reduced breath carbon monoxide levels: target-specific effects on cigarette smoking. *Addictive behaviors,* 10**,** 345-349.
SUHAJ, A., MANU, M. K., UNNIKRISHNAN, M. K., VIJAYANARAYANA, K. & MALLIKARJUNA RAO, C. 2016. Effectiveness of clinical pharmacist intervention on health-related quality of life in chronic obstructive pulmonary disorder patients - a randomized controlled study. *Journal of clinical pharmacy and therapeutics,* 41**,** 78-83.
TEO, K. K., SEDLIS, S. P., BODEN, W. E., O'ROURKE, R. A., MARON, D. J., HARTIGAN, P. M., DADA, M., GUPTA, V., SPERTUS, J. A., KOSTUK, W. J., BERMAN, D. S., SHAW, L. J., CHAITMAN, B. R., MANCINI, G. B. J. & WEINTRAUB, W. S. 2009. Optimal medical therapy with or without percutaneous coronary intervention in older patients with stable coronary disease: a pre-specified subset analysis of the COURAGE (Clinical Outcomes Utilizing Revascularization and Aggressive druG Evaluation) trial. *Journal of the American College of Cardiology,* 54**,** 1303-1308.
TZIVONI, D., KEREN, A., MEYLER, S., KHOURY, Z., LERER, T. & BRUNEL, P. 1998. Cardiovascular safety of transdermal nicotine patches in patients with coronary artery disease who try to quit smoking. *Cardiovascular drugs and therapy,* 12**,** 239-244.
UNVERDORBEN, M., DER BIJL, A., POTGIETER, L., LIANG, Q., MEYER, B. H. & ROETHIG, H. J. 2007. Effects of levels of cigarette smoke exposure on symptom-limited spiroergometry. *Preventive cardiology,* 10**,** 83-91.
UNVERDORBEN, M., VAN DER BIJL, A., POTGIETER, L., VENTER, C., MUNJAL, S., QIWEI, L., MEYER, B. & RÖTHIG, H.-J. 2008. Effects of different levels of cigarette smoke exposure on prognostic heart rate and rate--pressure-product parameters. *Journal of cardiovascular pharmacology and therapeutics,* 13**,** 175-182.
USSHER, M., WEST, R., DOSHI, R. & SAMPURAN, A. K. 2006. Acute effect of isometric exercise on desire to smoke and tobacco withdrawal symptoms. *Human psychopharmacology,* 21**,** 39-46.
VAN ELDEREN-VAN KEMENADE, T., MAES, S. & VAN DEN BROEK, Y. 1994. Effects of a health education programme with telephone follow-up during cardiac rehabilitation. *The British journal of clinical psychology,* 33**,** 367-378.
VAN LEER, E., HAPNER, E. R. & CONNOR, N. P. 2008. Transtheoretical model of health behavior change applied to voice therapy. *J Voice,* 22**,** 688-98.
VAN WETERING, C. R., VAN NOOTEN, F. E., MOL, S. J. M., HOOGENDOORN, M., RUTTEN-VAN MÖLKEN, M. P. M. H. & SCHOLS, A. M. 2008. Systemic impairment in relation to disease burden in patients with moderate COPD eligible for a lifestyle program. Findings from the INTERCOM trial. *International*

journal of chronic obstructive pulmonary disease, 3**,** 443-451.
WATZ, H., MAILÄNDER, C., BAIER, M. & KIRSTEN, A. 2016. Effects of indacaterol/glycopyrronium (QVA149) on lung hyperinflation and physical activity in patients with moderate to severe COPD: a randomised, placebo-controlled, crossover study (The MOVE Study). *BMC pulmonary medicine,* 16**,** 95.
WEBB, M. S., BAKER, E. A. & RODRÍGUEZ DE YBARRA, D. 2010. Effects of culturally specific cessation messages on theoretical antecedents of behavior among low-income african american smokers. *Psychology of addictive behaviors : journal of the Society of Psychologists in Addictive Behaviors,* 24**,** 333-341.
WU, L., HE, Y., JIANG, B., ZHANG, D., TIAN, H., ZUO, F. & LAM, T. H. 2017. Very brief physician advice and supplemental proactive telephone calls to promote smoking reduction and cessation in Chinese male smokers with no intention to quit: a randomized trial. *Addiction (Abingdon, England),* 112**,** 2032-2040.
XU, X., LEAHEY, T. M., BOGUSZEWSKI, K., KRUPEL, K., MAILLOUX, K. A. & WING, R. R. 2017. Self-Expansion is Associated with Better Adherence and Obesity Treatment Outcomes in Adults. *Annals of behavioral medicine : a publication of the Society of Behavioral Medicine,* 51**,** 13-17.
YBARRA, M. L., HOLTROP, J. S., PRESCOTT, T. L., RAHBAR, M. H. & STRONG, D. 2013. Pilot RCT results of stop my smoking USA: a text messaging-based smoking cessation program for young adults. *Nicotine & tobacco research : official journal of the Society for Research on Nicotine and Tobacco,* 15**,** 1388-1399.

Not an RCT or a protocol only (without results), or a conference abstract

ABRANTES, A. M., STRONG, D. R., LLOYD-RICHARDSON, E. E., NIAURA, R., KAHLER, C. W. & BROWN, R. A. 2009. Regular exercise as a protective factor in relapse following smoking cessation treatment. *The American journal on addictions,* 18**,** 100-101.
BALDWIN, A. S., ROTHMAN, A. J., VANDER WEG, M. W. & CHRISTENSEN, A. J. 2013. Examining causal components and a mediating process underlying self-generated health arguments for exercise and smoking cessation. *Health psychology : official journal of the Division of Health Psychology, American Psychological Association,* 32**,** 1209-1217.
BARBERA, M., MANGIALASCHE, F., JONGSTRA, S., GUILLEMONT, J., NGANDU, T., BEISHUIZEN, C., COLEY, N., BRAYNE, C., ANDRIEU, S., RICHARD, E., SOININEN, H. & KIVIPELTO, M. 2018. Designing an Internet-Based Multidomain Intervention for the Prevention of Cardiovascular Disease and Cognitive Impairment in Older Adults: The HATICE Trial. *Journal of Alzheimer's disease : JAD,* 62**,** 649-663.
BLOOM, E. L., MINAMI, H., BROWN, R. A., STRONG, D. R., RIEBE, D. & ABRANTES, A. M. 2017. Quality of life after quitting smoking and initiating aerobic exercise. *Psychology, health & medicine,* 22**,** 1127-1135.
CHERNOFF, R. 2002. Health promotion for older women: benefits of nutrition and exercise programs. *Topics in Geriatric Rehabilitation,* 18**,** 59-67.
COOPER, T. V., RESOR, M. R., STOEVER, C. J. & DUBBERT, P. M. 2007. Physical activity and physical activity adherence in the elderly based on smoking status. *Addictive behaviors,* 32**,** 2268-2273.
MARCUS, B. H., CICCOLO, J. T. & SCIAMANNA, C. N. 2009. Using electronic/computer interventions to promote physical activity. *British Journal of Sports Medicine,* 47**,** 102-5.
MARCUS, B. H., KING, T. K., ALBRECHT, A. E., PARISI, A. F. & ABRAMS, D. B. 1997. Rationale, design, and baseline data for Commit to Quit: an exercise efficacy trial for smoking cessation among women. *Preventive medicine,* 26**,** 586-597.
MARCUS, B. H., LEWIS, B. A., KING, T. K., ALBRECHT, A. E., HOGAN, J., BOCK, B., PARISI, A. F. & ABRAMS, D. B. 2003. Rationale, design, and baseline data for Commit to Quit II: an evaluation of the efficacy of moderate-intensity physical activity as an aid to smoking cessation in women. *Preventive medicine,* 36**,** 479-492.
SEPPÄNEN, A. 1977. Physical work capacity in relations to carbon monoxide inhalation and tobacco smoking. *Annals of clinical research,* 9**,** 269-274.
TREVIÑO, L. A., BAKER, L., MCINTOSH, S., MUSTIAN, K., SEPLAKI, C. L., GUIDO, J. J. & OSSIP, D. J. 2014. Physical activity as a coping strategy for smoking cessation in mid-life and older adults. *Addictive behaviors,* 39**,** 885-888.
VOZORIS, N. T. & O'DONNELL, D. E. 2015. Smoking, activity level and exercise test outcomes in a young population sample without cardiopulmonary disease. *Journal of Sports Medicine and Physical Fitness,* 55**,** 787-96.
ZWISLER, A.-D. O., SCHOU, L., SOJA, A. M. B., BRØNNUM-HANSEN, H., GLUUD, C., IVERSEN, L., SIGURD, B., MADSEN, M. & FISCHER-HANSEN, J. 2005. A randomized clinical trial of hospital-based, comprehensive cardiac rehabilitation versus usual care for patients with congestive heart failure, ischemic heart disease, or high risk of ischemic heart disease (the DANREHAB trial)--design, intervention, and population. *American heart journal,* 150**,** 899.
BARBERAN-GARCIA, A., NAVARRO-RIPOLL, R., SÁNCHEZ-LORENTE, D., MOISÉS-LAFUENTE, J., BOADA, M.,

MESSAGGI-SARTOR, M., GONZÁLEZ-VALLESPÍ, L., MONTANÉ-MUNTANÉ, M., ALSINA-RESTOY, X., CAMPERO, B., LOPEZ-BAAMONDE, M., ROMANO-ANDRIONI, B., GUZMÁN, R., LÓPEZ, A., ARGUIS, M. J., ROCA, J. & MARTINEZ-PALLI, G. 2020. Cost-effectiveness of a technology-supported multimodal prehabilitation program in moderate-to-high risk patients undergoing lung cancer resection: randomized controlled trial protocol. *BMC health services research,* 20**,** 207.

BRENNAN, A. 1997. Efficacy of cardiac rehabilitation 2: smoking and behaviour modification. *British Journal of Nursing,* 6**,** 737-40.

BURNISTON, J., EFTEKHARI, F., HRABI, S., WORSLEY, R. & DEAN, E. 2012. Health behaviour change and lifestyle-related condition prevalence: Comparison of two epochs based on systematic review of the physical therapy literature. *Hong Kong Physiotherapy Journal,* 30**,** 44-56.

CARNEIRO-BARRERA, A., AMARO-GAHETE, F. J., DÍAZ-ROMÁN, A., GUILLÉN-RIQUELME, A., JURADO-FASOLI, L., SÁEZ-ROCA, G., MARTÍN-CARRASCO, C., RUIZ, J. R. & BUELA-CASAL, G. 2019. Interdisciplinary Weight Loss and Lifestyle Intervention for Obstructive Sleep Apnoea in Adults: Rationale, Design and Methodology of the INTERAPNEA Study. *Nutrients,* 11.

CERRATO, P. L. 1999. A radical approach to heart disease. *RN,* 62**,** 65-6.

CHATZIEFSTRATIOU, A. A., GIAKOUMIDAKIS, K. & BROKALAKI, H. 2013. Cardiac rehabilitation outcomes: Modifiable risk factors. *British Journal of Nursing,* 22**,** 200-7.

COPE, G. F. 2014. Current treatments for chronic obstructive pulmonary disease (COPD). *Br J Health Care Manage,* 20**,** 372-8.

COX, M. H. & DINUBILE, N. A. 1997. Exercise for coronary artery disease: a cornerstone of comprehensive treatment. *Physician and Sports Medicine,* 25**,** 27-34.

DALE, L. P., WHITTAKER, R., JIANG, Y., STEWART, R., ROLLESTON, A. & MADDISON, R. 2014. Improving coronary heart disease self-management using mobile technologies (Text4Heart): a randomised controlled trial protocol. *Trials,* 15**,** 71.

ECK, L. H., KLESGES, R. C., MEYERS, A. W., SLAWSON, D. L. & WINDERS, S. A. 1997. Changes in food consumption and body weight associated with smoking cessation across menstrual cycle phase. *Addictive behaviors,* 22**,** 775-782.

FEHILY, C., BARTLEM, K., WIGGERS, J., WYE, P., CLANCY, R., CASTLE, D., WUTZKE, S., RISSEL, C., WILSON, A., MCCOMBIE, P., MURPHY, F. & BOWMAN, J. 2017. Evaluating the effectiveness of a healthy lifestyle clinician in addressing the chronic disease risk behaviours of community mental health clients: study protocol for a randomised controlled trial. *Trials,* 18**,** 276.

GIATRAS, N., WANNINKHOF, E., LEONTOWITSCH, M., LEWIS, B., TAYLOR, A., COOPER, S. & USSHER, M. 2017. Lessons learned from the London Exercise and Pregnant (LEAP) Smokers randomised controlled trial process evaluation: implications for the design of physical activity for smoking cessation interventions during pregnancy. *BMC public health,* 17**,** 85.

GRØNDAL, N., SØGAARD, R., HENNEBERG, E. W. & LINDHOLT, J. S. 2010. The Viborg Vascular (VIVA) screening trial of 65-74 year old men in the central region of Denmark: study protocol. *Trials,* 11**,** 67.

HANNON, P. A., HAMMERBACK, K., ALLEN, C. L., PARRISH, A. T., CHAN, K. G., KOHN, M. J., TEAGUE, S., BERESFORD, S. A. A., HELFRICH, C. D. & HARRIS, J. R. 2016. HealthLinks randomized controlled trial: Design and baseline results. *Contemporary clinical trials,* 48**,** 1-11.

HOLTROP, J. S., CORSER, W., JONES, G., BROOKS, G., HOLMES-ROVNER, M. & STOMMEL, M. 2006. Health behavior goals of cardiac patients after hospitalization. *American journal of health behavior,* 30**,** 387-399.

HUO, X., SPATZ, E. S., DING, Q., HORAK, P., ZHENG, X., MASTERS, C., ZHANG, H., IRWIN, M. L., YAN, X., GUAN, W., LI, J., LI, X., SPERTUS, J. A., MASOUDI, F. A., KRUMHOLZ, H. M. & JIANG, L. 2017. Design and rationale of the Cardiovascular Health and Text Messaging (CHAT) Study and the CHAT-Diabetes Mellitus (CHAT-DM) Study: two randomised controlled trials of text messaging to improve secondary prevention for coronary heart disease and diabetes. *BMJ open,* 7**,** e018302.

JANSINK, R., BRASPENNING, J., VAN DER WEIJDEN, T., NIESSEN, L., ELWYN, G. & GROL, R. 2009. Nurse-led motivational interviewing to change the lifestyle of patients with type 2 diabetes (MILD-project): protocol for a cluster, randomized, controlled trial on implementing lifestyle recommendations. *BMC health services research,* 9**,** 19.

KAVRADIM, S. T., ÖZER, Z. & BOZ, İ. 2020. Effectiveness of telehealth interventions as a part of secondary prevention in coronary artery disease: a systematic review and meta-analysis. *Scandinavian Journal of Caring Sciences,* 34**,** 585-603.

KELLY, P. J., BAKER, A. L., DEANE, F. P., CALLISTER, R., COLLINS, C. E., OLDMEADOW, C., ATTIA, J. R., TOWNSEND, C. J., INGRAM, I., BYRNE, G. & KEANE, C. A. 2015. Study protocol: a stepped wedge cluster randomised controlled trial of a healthy lifestyle intervention for people attending residential substance abuse treatment. *BMC public health,* 15**,** 465.

KING, T. K., MATACIN, M., MARCUS, B. H., BOCK, B. C. & TRIPOLONE, J. 2000. Body image evaluations in women smokers. *Addictive behaviors,* 25**,** 613-618.

KRUMHOLZ, H. M., WANG, Y., PARENT, E. M., MOCKALIS, J., PETRILLO, M. & RADFORD, M. J. 1997. Quality of care for elderly patients hospitalized with heart failure. *Archives of Internal Medicine,* 157**,** 2242-7.

MADDISON, R., WHITTAKER, R., STEWART, R., KERR, A., JIANG, Y., KIRA, G., CARTER, K. H. & PFAEFFLI, L. 2011. HEART: heart exercise and remote technologies: a randomized controlled trial study protocol. *BMC cardiovascular disorders,* 11**,** 26.

MAHMOUD, A.-E.-D. H. 2015. Prevalence of cardiovascular disease risk factors among Egyptian and Saudi medical students: a comparative study. *The Journal of the Egyptian Public Health Association,* 90**,** 35-39.

MARTIN, P. C. & FELL, D. W. 1999. Beyond treatment: patient education for health promotion and disease prevention. *Journal of Physical Therapy Education,* 13**,** 49-56.

MITCHELL, D. 2008. Pushing the pin on smoking. *J Complement Med,* 7.

MOOE, T., BERGSTRÖM, L., IREWALL, A.-L. & OGREN, J. 2013. The NAILED stroke risk factor trial (nurse based age independent intervention to limit evolution of disease after stroke): study protocol for a randomized controlled trial. *Trials,* 14**,** 5.

MOORE, G. E. 1997. Primary care management of cardiac rehabilitaiton. *Physician and Sports Medicine,* 25.

NIELD, M. 2003. Pulmonary rehabilitation: the critical outcomes. *Journal of Rehabilitation Research and Development,* 40.

NIEUWSMA, J. A., WRAY, L. O., VOILS, C. I., GIERISCH, J. M., DUNDON, M., COFFMAN, C. J., JACKSON, G. L., MERWIN, R., VAIR, C., JUNTILLA, K., WHITE-CLARK, C., JEFFREYS, A. S., HARRIS, A., OWINGS, M., MARR, J. & EDELMAN, D. 2017. A problem-solving intervention for cardiovascular disease risk reduction in veterans: Protocol for a randomized controlled trial. *Contemporary clinical trials,* 60**,** 42-50.

O'NEIL, A., HAWKES, A. L., CHAN, B., SANDERSON, K., FORBES, A., HOLLINGSWORTH, B., ATHERTON, J., HARE, D. L., JELINEK, M., EADIE, K., TAYLOR, C. B. & OLDENBURG, B. 2011. A randomised, feasibility trial of a tele-health intervention for acute coronary syndrome patients with depression ('MoodCare'): study protocol. *BMC cardiovascular disorders,* 11**,** 8.

PAPADAKIS, M. A., CROUGHAN-MINIHANE, M., FROMM, L. J., WILKIE, H. A. & ERNSTER, V. L. 1997. A comparison of two methods to teach smoking-cessation techniques to medical students. *Academic medicine : journal of the Association of American Medical Colleges,* 72**,** 725-727.

PAVEY, T. G., GARTNER, C. E., COOMBES, J. S. & BROWN, W. J. 2015. Assessing the effectiveness of High Intensity Interval Training (HIIT) for smoking cessation in women: HIIT to quit study protocol. *BMC public health,* 15**,** 1309.

PILEGGI, C., CARBONE, V., NOBILE, C. G. A. & PAVIA, M. 2005. Blood pressure and related cardiovascular disease risk factors in 6-18 year-old students in Italy. *Journal of paediatrics and child health,* 41**,** 347-352.

PROCHASKA, J. J., EPPERSON, A., SKAN, J., OPPEZZO, M., BARNETT, P., DELUCCHI, K., SCHNELLBAECHER, M. & BENOWITZ, N. L. 2018. The Healing and Empowering Alaskan Lives Toward Healthy-Hearts (HEALTHH) Project: Study protocol for a randomized controlled trial of an intervention for tobacco use and other cardiovascular risk behaviors for Alaska Native People. *Contemporary clinical trials,* 71**,** 40-46.

QUIRK, M., OCKENE, J., KRISTELLER, J., GOLDBERG, R., DONNELLY, G., AMICK, T. & KALAN, K. 1991. Training family practice and internal medicine residents to counsel patients who smoke: improvement and retention of counseling skills. *Family medicine,* 23**,** 108-111.

REA, B. L., HOPP MARSHAK, H., NEISH, C. & DAVIS, N. 2004. The role of health promotion in physical therapy in California, New York, and Tennessee. *Physical Therapy,* 84**,** 510-23.

REARDON, J., CASABURI, R., MORGAN, M., NICI, L. & ROCHESTER, C. 2005. Pulmonary rehabilitation for COPD. *Respiratory Medicine,* 99**,** 27.

REID, W. D., KEIM, C., HOPKINS-ROSSEEL, D. & BROOKS, D. 2007. The Canadian Thoracic Society Recommendations for Management of Chronic Obstructive Pulmonary Disease: Implications for Physiotherapists. *Physiotherapy Canada,* 59**,** 218-28.

ROBERTS, S. H. & BAILEY, J. E. 2011. Incentives and barriers to lifestyle interventions for people with severe mental illness: A narrative synthesis of quantitative, qualitative and mixed methods studies. *Journal of Advanced Nursing,* 67**,** 690-708.

SANCHEZ-AGUADERO, N., MORA-SIMON, S., RECIO-RODRIGUEZ, J. I., ALONSO-DOMINGUEZ, R., GONZALEZ-SANCHEZ, J., MARTIN-MARTIN, C., GOMEZ-MARCOS, M. A., RODRIGUEZ-SANCHEZ, E. & GARCIA-ORTIZ, L. 2018. Effectiveness of an intensive intervention to improve lifestyles in people with intermediate cardiovascular risk (DATE study): Study protocol for a randomized controlled trial. *Journal of Advanced Nursing,* 74**,** 957-967.

SARKAR, B. K., SHAHAB, L., ARORA, M., LORENCATTO, F., REDDY, K. S. & WEST, R. 2014. A cluster randomized controlled trial of a brief tobacco cessation intervention for low-income communities in India: study protocol. *Addiction (Abingdon, England),* 109**,** 371-378.

SHERWOOD, N. E., HENNRIKUS, D. J., JEFFERY, R. W., LANDO, H. A. & MURRAY, D. M. 2000. Smokers with

multiple behavioral risk factors: how are they different? *Preventive medicine,* 31**,** 299-307.
SIDHU, M. S., DALEY, A., JORDAN, R., COVENTRY, P. A., HENEGHAN, C., JOWETT, S., SINGH, S., MARSH, J., ADAB, P., VARGHESE, J., NUNAN, D., BLAKEMORE, A., STEVENS, J., DOWSON, L., FITZMAURICE, D. & JOLLY, K. 2015. Patient self-management in primary care patients with mild COPD - protocol of a randomised controlled trial of telephone health coaching. *BMC pulmonary medicine,* 15**,** 16.
SMITS, J. A. J., ZVOLENSKY, M. J., ROSENFIELD, D., BROWN, R. A., FREEMAN, S. Z., DUTCHER, C. D., CONROY, H. E. & ALAVI, N. 2019. YMCA exercise intervention to augment smoking cessation treatment in adults with high anxiety sensitivity: Study protocol for a randomized controlled trial. *Contemporary clinical trials,* 77**,** 1-7.
SMITS, J. A. J., ZVOLENSKY, M. J., ROSENFIELD, D., MARCUS, B. H., CHURCH, T. S., FRIERSON, G. M., POWERS, M. B., OTTO, M. W., DAVIS, M. L., DEBOER, L. B. & BRICENO, N. F. 2012. The efficacy of vigorous-intensity exercise as an aid to smoking cessation in adults with elevated anxiety sensitivity: study protocol for a randomized controlled trial. *Trials,* 13**,** 207.
SPRATT, K. A. 1998. A clinician's guide to a woman's heart. *Journal - American Osteopathic Association,* 98**,** 6.
STAIGER, P. K., HAYDEN, M. J., GUO, K., HUGHES, L. K., BOS, J. & LAWRENCE, N. S. 2018. A randomised controlled trial examining the efficacy of smoking-related response inhibition training in smokers: a study protocol. *BMC public health,* 18**,** 1226.
STEURER-STEY, C., MARKUN, S., LANA, K. D., FREI, A., HELD, U., WENSING, M. & ROSEMANN, T. 2014. The improving care in chronic obstructive lung disease study: CAROL improving processes of care and quality of life of COPD patients in primary care: study protocol for a randomized controlled trial. *Trials,* 15**,** 96.
TANGNEY, D. J., BROWN, D. B., BROWN, G. J. & PRESCOTT, G. J. 2002. Cardiovascular risk reduction in men: a nine-year cohort study. *British Journal of General Practice,* 52**,** 743-5.
TANJI, J. L. 1995. Management of hypertension: adapting new guidelines for active patients. *Physician Sportsmed,* 23**,** 47-55.
TIMMERMANS, Y. E. G., VAN DE KANT, K. D. G., REIJNDERS, D., KLEIJKERS, L. M. P., DOMPELING, E., KRAMER, B. W., ZIMMERMANN, L. J. I., STEEGERS-THEUNISSEN, R. P. M., SPAANDERMAN, M. E. A. & VREUGDENHIL, A. C. E. 2019. Towards Prepared mums (TOP-mums) for a healthy start, a lifestyle intervention for women with overweight and a child wish: study protocol for a randomised controlled trial in the Netherlands. *BMJ open,* 9**,** e030236.
ULBRICHT, S., KLEIN, G., HAUG, S., GROSS, B., RUMPF, H.-J., JOHN, U. & MEYER, C. 2011. Smokers' expectations toward the engagement of their general practitioner in discussing lifestyle behaviors. *Journal of health communication,* 16**,** 135-147.
VANDER WEG, M. W., KLESGES, R. C., EBBERT, J. O., LICHTY, E. J., DEBON, M., NORTH, F., SCHROEDER, D. R. & DUBBERT, P. M. 2008. Trial design: blood pressure control and weight gain prevention in prehypertensive and hypertensive smokers: the treatment and prevention study. *Contemporary clinical trials,* 29**,** 281-292.
WAGNER, P. J., JESTER, D. M. & MOSELEY, G. C. 2002. Medical students as health coaches. *Academic medicine : journal of the Association of American Medical Colleges,* 77**,** 1164-1165.
WILLIAMS, D. M., USSHER, M., DUNSIGER, S., MIRANDA, R., JR., GWALTNEY, C. J., MONTI, P. M. & EMERSON, J. 2014. Overcoming limitations in previous research on exercise as a smoking cessation treatment: rationale and design of the "Quit for Health" trial. *Contemporary clinical trials,* 37**,** 33-42.
WU, L., HE, Y., JIANG, B., ZHANG, D., TIAN, H., ZUO, F., LAM, T. H. & CHEUNG, Y. T. D. 2015. The effect of a very brief smoking-reduction intervention in smokers who have no intention to quit: study protocol for a randomized controlled trial. *BMC public health,* 15**,** 418.
YOHANNES, A. M. & CONNOLLY, M. J. 2004. Pulmonary rehabilitation programmes in the UK: a national representative survey. *Clinical Rehabilitation,* 18**,** 444-9.
CHA, S.-A., LIM, S.-Y., KIM, K.-R., LEE, E.-Y., KANG, B., CHOI, Y.-H., YOON, K.-H., AHN, Y.-B., LEE, J.-H. & KO, S.-H. 2017. Community-based randomized controlled trial of diabetes prevention study for high-risk individuals of type 2 diabetes: lifestyle intervention using web-based system. *BMC public health,* 17**,** 387.
COFFENG, J. K., VAN DER PLOEG, H. P., CASTELLANO, J. M., FERNÁNDEZ-ALVIRA, J. M., IBÁÑEZ, B., GARCÍA-LUNAR, I., VAN DER BEEK, A. J., FERNÁNDEZ-ORTIZ, A., MOCOROA, A., GARCÍA-LEAL, L., CÁRDENAS, E., ROJAS, C., MARTÍNEZ-CASTRO, M. I., SANTIAGO-SACRISTÁN, S., FERNÁNDEZ-GALLARDO, M., MENDIGUREN, J. M., BANSILAL, S., VAN MECHELEN, W. & FUSTER, V. 2017. A 30-month worksite-based lifestyle program to promote cardiovascular health in middle-aged bank employees: Design of the TANSNIP-PESA randomized controlled trial. *American heart journal,* 184**,** 121-132.
LEON-ACUÑA, A., TORRES-PEÑA, J. D., ALCALA-DIAZ, J. F., VALS-DELGADO, C., RONCERO-RAMOS, I., YUBERO-SERRANO, E., TINAHONES, F. J., CASTRO-CLERICO, M., DELGADO-LISTA, J., ORDOVAS, J. M., LOPEZ-MIRANDA, J. & PEREZ-MARTINEZ, P. 2019. Lifestyle factors modulate postprandial hypertriglyceridemia: From the CORDIOPREV study. *Atherosclerosis,* 290**,** 118-124.

GROVE, J. R., WILKINSON, A. & DAWSON, B. T. 1993. Effects of exercise on selected correlates of smoking withdrawal. *International Journal of Sport Psychology,* 24**,** 217-36.

Included pregnant women

SOCKRIDER, M. M., HUDMON, K. S., ADDY, R. & DOLAN MULLEN, P. 2003. An exploratory study of control of smoking in the home to reduce infant exposure to environmental tobacco smoke. *Nicotine & tobacco research : official journal of the Society for Research on Nicotine and Tobacco,* 5**,** 901-910.

PRAPAVESSIS, H., DE JESUS, S., HARPER, T., CRAMP, A., FITZGEORGE, L., MOTTOLA, M. F., USSHER, M., FAULKNER, G. & SELBY, P. 2014. The effects of acute exercise on tobacco cravings and withdrawal symptoms in temporary abstinent pregnant smokers. *Addictive behaviors,* 39**,** 703-708.

USSHER, M., AVEYARD, P., MANYONDA, I., LEWIS, S., WEST, R., LEWIS, B., MARCUS, B., TAYLOR, A. H., BARTON, P. & COLEMAN, T. 2012. Physical activity as an aid to smoking cessation during pregnancy (LEAP) trial: study protocol for a randomized controlled trial. *Trials,* 13**,** 186.

USSHER, M., LEWIS, S., AVEYARD, P., MANYONDA, I., WEST, R., LEWIS, B., MARCUS, B., RIAZ, M., TAYLOR, A. & DALEY, A. 2015. Physical activity for smoking cessation in pregnancy: Randomised controlled trial. *British Medical Journal,* 350.

USSHER, M., LEWIS, S., AVEYARD, P., MANYONDA, I., WEST, R., LEWIS, B., MARCUS, B., RIAZ, M., TAYLOR, A., DALEY, A. & COLEMAN, T. 2015. Physical activity for smoking cessation in pregnancy: randomised controlled trial. *BMJ (Clinical research ed.),* 350**,** h2145.

USSHER, M., LEWIS, S., AVEYARD, P., MANYONDA, I., WEST, R., LEWIS, B., MARCUS, B., RIAZ, M., TAYLOR, A. H., BARTON, P., DALEY, A., ESSEX, H., ESLIGER, D. & COLEMAN, T. 2015. The London Exercise And Pregnant smokers (LEAP) trial: a randomised controlled trial of physical activity for smoking cessation in pregnancy with an economic evaluation. *Health technology assessment (Winchester, England),* 19**,** vii.

WILKINSON, S. A. & MCINTYRE, H. D. 2012. Evaluation of the 'healthy start to pregnancy' early antenatal health promotion workshop: a randomized controlled trial. *BMC pregnancy and childbirth,* 12**,** 131.

Assessed the short-term effects only <6months

ALLEN, A., CARLSON, S. C., BOSCH, T. A., EBERLY, L. E., OKUYEMI, K., NAIR, U. & GORDON, J. S. 2018. High-intensity Interval Training and Continuous Aerobic Exercise Interventions to Promote Self-initiated Quit Attempts in Young Adults Who Smoke: Feasibility, Acceptability, and Lessons Learned From a Randomized Pilot Trial. *Journal of addiction medicine,* 12**,** 373-380.

ALLEN, S. S., BRINTNELL, D. M., HATSUKAMI, D. & REICH, B. 2004. Energy intake and physical activity during short-term smoking cessation in postmenopausal women. *Addictive behaviors,* 29**,** 947-951.

ANGELI, M., HATZIGEORGIADIS, A., COMOUTOS, N., KROMMIDAS, C., MORRES, I. D. & THEODORAKIS, Y. 2018. The effects of self-regulation strategies following moderate intensity exercise on ad libitum smoking. *Addictive behaviors,* 87**,** 109-114.

BORRELLI, B., HOGAN, J. W., BOCK, B., PINTO, B., ROBERTS, M. & MARCUS, B. 2002. Predictors of quitting and dropout among women in a clinic-based smoking cessation program. *Psychology of addictive behaviors : journal of the Society of Psychologists in Addictive Behaviors,* 16**,** 22-27.

BUR, A., JOUKHADAR, C., KLEIN, N., HERKNER, MITULOVIC, G., SCHMID, R., AGNETER, E., MÜLLER, M. & BRUNNER, M. 2005. Effect of exercise on transdermal nicotine release in healthy habitual smokers. *International journal of clinical pharmacology and therapeutics,* 43**,** 239-243.

DANIEL, J., CROPLEY, M., USSHER, M. & WEST, R. 2004. Acute effects of a short bout of moderate versus light intensity exercise versus inactivity on tobacco withdrawal symptoms in sedentary smokers. *Psychopharmacology,* 174**,** 320-326.

DANIEL, J. Z., CROPLEY, M. & FIFE-SCHAW, C. 2006. The effect of exercise in reducing desire to smoke and cigarette withdrawal symptoms is not caused by distraction. *Addiction (Abingdon, England),* 101**,** 1187-1192.

DANIEL, J. Z., CROPLEY, M. & FIFE-SCHAW, C. 2007. Acute exercise effects on smoking withdrawal symptoms and desire to smoke are not related to expectation. *Psychopharmacology,* 195**,** 125-129.

DE JESUS, S. & PRAPAVESSIS, H. 2018. Affect and cortisol mechanisms through which acute exercise attenuates cigarette cravings during a temporary quit attempt. *Addictive behaviors,* 80**,** 82-88.

JANSE VAN RENSBURG, K., TAYLOR, A., BENATTAYALLAH, A. & HODGSON, T. 2012. The effects of exercise on

cigarette cravings and brain activation in response to smoking-related images. *Psychopharmacology,* 221**,** 659-666.
KORHONEN, T., GOODWIN, A., MIESMAA, P., DUPUIS, E. A. & KINNUNEN, T. 2011. Smoking cessation program with exercise improves cardiovascular disease biomarkers in sedentary women. *Journal of women's health (2002),* 20**,** 1051-1064.
MØLLER, A. M., PEDERSEN, T., VILLEBRO, N. & NØRGAARD, P. 2003. Impact of lifestyle on perioperative smoking cessation and postoperative complication rate. *Preventive medicine,* 36**,** 704-709.
OH, H. & TAYLOR, A. H. 2014. Self-regulating smoking and snacking through physical activity. *Health psychology : official journal of the Division of Health Psychology, American Psychological Association,* 33**,** 349-359.
PURANI, H., FRIEDRICHSEN, S. & ALLEN, A. M. 2019. Sleep quality in cigarette smokers: Associations with smoking-related outcomes and exercise. *Addictive behaviors,* 90**,** 71-76.
ROBERTS, V., GANT, N., SOLLERS, J. J., 3RD, BULLEN, C., JIANG, Y. & MADDISON, R. 2015. Effects of exercise on the desire to smoke and physiological responses to temporary smoking abstinence: a crossover trial. *Psychopharmacology,* 232**,** 1071-1081.
SALTYCHEV, M., LAIMI, K., EL-METWALLY, A., OKSANEN, T., PENTTI, J., VIRTANEN, M., KOUVONEN, A., KIVIMAKI, M. & VAHTERA, J. 2012. Effectiveness of multidisciplinary early rehabilitation in reducing behaviour-related risk factors. *J Rehabil Med,* 44**,** 370-7.
SCERBO, F., FAULKNER, G., TAYLOR, A. & THOMAS, S. 2010. Effects of exercise on cravings to smoke: the role of exercise intensity and cortisol. *Journal of sports sciences,* 28**,** 11-19.
SCHNEIDER, K. L., SPRING, B. & PAGOTO, S. L. 2007. Affective benefits of exercise while quitting smoking: influence of smoking-specific weight concern. *Psychology of addictive behaviors : journal of the Society of Psychologists in Addictive Behaviors,* 21**,** 255-260.
TAYLOR, A. & KATOMERI, M. 2006. Effects of a brisk walk on blood pressure responses to the Stroop, a speech task and a smoking cue among temporarily abstinent smokers. *Psychopharmacology,* 184**,** 247-253.
TAYLOR, A. H., KATOMERI, M. & USSHER, M. 2005. Acute effects of self-paced walking on urges to smoke during temporary smoking abstinence. *Psychopharmacology,* 181**,** 1-7.
TAYLOR, A. H., THOMPSON, T. P., GREAVES, C. J., TAYLOR, R. S., GREEN, C., WARREN, F. C., KANDIYALI, R., AVEYARD, P., AYRES, R., BYNG, R., CAMPBELL, J. L., USSHER, M. H., MICHIE, S. & WEST, R. 2014. A pilot randomised trial to assess the methods and procedures for evaluating the clinical effectiveness and cost-effectiveness of Exercise Assisted Reduction then Stop (EARS) among disadvantaged smokers. *Health technology assessment (Winchester, England),* 18**,** 1-324.
TRITTER, A., FITZGEORGE, L. & PRAPAVESSIS, H. 2015. The effect of acute exercise on cigarette cravings while using a nicotine lozenge. *Psychopharmacology,* 232**,** 2531-2539.
USSHER, M., NUNZIATA, P., CROPLEY, M. & WEST, R. 2001. Effect of a short bout of exercise on tobacco withdrawal symptoms and desire to smoke. *Psychopharmacology,* 158**,** 66-72.
VAN RENSBURG, K. J., TAYLOR, A. & HODGSON, T. 2009. The effects of acute exercise on attentional bias towards smoking-related stimuli during temporary abstinence from smoking. *Addiction (Abingdon, England),* 104**,** 1910-1917.
WILLIAMS, D. M., DUNSIGER, S., WHITELEY, J. A., USSHER, M. H., CICCOLO, J. T. & JENNINGS, E. G. 2011. Acute effects of moderate intensity aerobic exercise on affective withdrawal symptoms and cravings among women smokers. *Addictive behaviors,* 36**,** 894-897.
BOCK, B. C., MARCUS, B. H., KING, T. K., BORRELLI, B. & ROBERTS, M. R. 1999. Exercise effects on withdrawal and mood among women attempting smoking cessation. *Addictive behaviors,* 24**,** 399-410.
NAIR, U. S., PATTERSON, F., RODRIGUEZ, D. & COLLINS, B. N. 2017. A telephone-based intervention to promote physical activity during smoking cessation: a randomized controlled proof-of-concept study. *Translational behavioral medicine,* 7**,** 138-147.
PERSKY, I., SPRING, B., VANDER WAL, J. S., PAGOTO, S. & HEDEKER, D. 2005. Adherence across behavioral domains in treatment promoting smoking cessation plus weight control. *Health psychology : official journal of the Division of Health Psychology, American Psychological Association,* 24**,** 153-160.
RODRÍGUEZ CRISTÓBAL, J. J., ALONSO-VILLAVERDE GROTE, C., TRAVÉ MERCADÉ, P., PÉREZ SANTOS, J. M., PEÑA SENDRA, E., MUÑOZ LLORET, A., FERNÁNDEZ PÉREZ, C. & BLEDA FERNÁNDEZ, D. 2012. Randomised clinical trial of an intensive intervention in the primary care setting of patients with high plasma fibrinogen in the primary prevention of cardiovascular disease. *BMC research notes,* 5**,** 126.
WILLIAMS, D. M., WHITELEY, J. A., DUNSIGER, S., JENNINGS, E. G., ALBRECHT, A. E., USSHER, M. H., CICCOLO, J. T., PARISI, A. F. & MARCUS, B. H. 2010. Moderate intensity exercise as an adjunct to standard smoking cessation treatment for women: a pilot study. *Psychology of addictive behaviors : journal of the Society of Psychologists in Addictive Behaviors,* 24**,** 349-354.

Included people with depression, anxiety, dementia, heavy alcoholics, or HIV

DALEY, A., RIAZ, M., LEWIS, S., AVEYARD, P., COLEMAN, T., MANYONDA, I., WEST, R., LEWIS, B., MARCUS, B., TAYLOR, A., IBISON, J., KENT, A. & USSHER, M. 2018. Physical activity for antenatal and postnatal depression in women attempting to quit smoking: randomised controlled trial. *BMC pregnancy and childbirth,* 18**,** 156.

MCCLURE, J. B., CATZ, S. L., LUDMAN, E. J., RICHARDS, J., RIGGS, K. & GROTHAUS, L. 2011. Feasibility and acceptability of a multiple risk factor intervention: the Step Up randomized pilot trial. *BMC public health,* 11**,** 167.

ROSENBERG, D., LIN, E., PETERSON, D., LUDMAN, E., VON KORFF, M. & KATON, W. 2014. Integrated medical care management and behavioral risk factor reduction for multicondition patients: behavioral outcomes of the TEAMcare trial. *General hospital psychiatry,* 36**,** 129-134.

BERNARD, P., NINOT, G., CYPRIEN, F., COURTET, P., GUILLAUME, S., GEORGESCU, V., PICOT, M.-C., TAYLOR, A. & QUANTIN, X. 2015. Exercise and Counseling for Smoking Cessation in Smokers With Depressive Symptoms: A Randomized Controlled Pilot Trial. *Journal of dual diagnosis,* 11**,** 205-216.

GORACCI, A., RUCCI, P., FORGIONE, R. N., CAMPINOTI, G., VALDAGNO, M., CASOLARO, I., CARRETTA, E., BOLOGNESI, S. & FAGIOLINI, A. 2016. Development, acceptability and efficacy of a standardized healthy lifestyle intervention in recurrent depression. *Journal of affective disorders,* 196**,** 20-31.

JONES, G. C., CREWES, J. E., ROVNER, B. W. & DANIELSON, M. L. 2009. Effects of depressive symptoms on health behavior practices among, older adults with vision loss. *Rehabilitation Psychology,* 54**,** 164-72.

RICHARD, E., KUIPER, R., DIJKGRAAF, M. G. W. & VAN GOOL, W. A. 2009. Vascular care in patients with Alzheimer's disease with cerebrovascular lesions-a randomized clinical trial. *Journal of the American Geriatrics Society,* 57**,** 797-805.

RICHARD, E., VAN DEN HEUVEL, E., MOLL VAN CHARANTE, E. P., ACHTHOVEN, L., VERMEULEN, M., BINDELS, P. J. & VAN GOOL, W. A. 2009. Prevention of dementia by intensive vascular care (PreDIVA): a cluster-randomized trial in progress. *Alzheimer disease and associated disorders,* 23**,** 198-204.

SAUMOY, M., ALONSO-VILLAVERDE, C., NAVARRO, A., OLMO, M., VILA, R., RAMON, J. M., DI YACOVO, S., FERRER, E., CURTO, J., VERNET, A., VILA, A. & PODZAMCZER, D. 2016. Randomized trial of a multidisciplinary lifestyle intervention in HIV-infected patients with moderate-high cardiovascular risk. *Atherosclerosis,* 246**,** 301-308.

SMITS, J. A. J., ZVOLENSKY, M. J., DAVIS, M. L., ROSENFIELD, D., MARCUS, B. H., CHURCH, T. S., POWERS, M. B., FRIERSON, G. M., OTTO, M. W., HOPKINS, L. B., BROWN, R. A. & BAIRD, S. O. 2016. The Efficacy of Vigorous-Intensity Exercise as an Aid to Smoking Cessation in Adults With High Anxiety Sensitivity: A Randomized Controlled Trial. *Psychosomatic medicine,* 78**,** 354-364.

VICKERS, K. S., PATTEN, C. A., LEWIS, B. A., CLARK, M. M., USSHER, M., EBBERT, J. O., CROGHAN, I. T., DECKER, P. A., HATHAWAY, J., MARCUS, B. H. & HURT, R. D. 2009. Feasibility of an exercise counseling intervention for depressed women smokers. *Nicotine & tobacco research : official journal of the Society for Research on Nicotine and Tobacco,* 11**,** 985-995.

MARTIN, J. E., CALFAS, K. J., PATTEN, C. A., POLAREK, M., HOFSTETTER, C. R., NOTO, J. & BEACH, D. 1997. Prospective evaluation of three smoking interventions in 205 recovering alcoholics: one-year results of Project SCRAP-Tobacco. *Journal of consulting and clinical psychology,* 65**,** 190-194.

PATTEN, C. A., MARTIN, J. E., CALFAS, K. J., BROWN, S. A. & SCHROEDER, D. R. 2000. Effect of three smoking cessation treatments on nicotine withdrawal in 141 abstinent alcoholic smokers. *Addictive behaviors,* 25**,** 301-306.

PATTEN, C. A., VICKERS, K. S., MARTIN, J. E. & WILLIAMS, C. D. 2003. Exercise interventions for smokers with a history of alcoholism: exercise adherence rates and effect of depression on adherence. *Addictive behaviors,* 28**,** 657-667.

Smoking reduction not SC

THOMPSON, T. P., GREAVES, C. J., AYRES, R., AVEYARD, P., WARREN, F. C., BYNG, R., TAYLOR, R. S., CAMPBELL, J. L., USSHER, M., GREEN, C., MICHIE, S., WEST, R. & TAYLOR, A. 2016. An Exploratory Analysis of the Smoking and Physical Activity Outcomes From a Pilot Randomized Controlled Trial of an Exercise Assisted Reduction to Stop Smoking Intervention in Disadvantaged Groups. *Nicotine & tobacco research : official journal of the Society for Research on Nicotine and Tobacco,* 18**,** 289-297.

THOMPSON, T. P., GREAVES, C. J., AYRES, R., AVEYARD, P., WARREN, F. C., BYNG, R., TAYLOR, R. S., CAMPBELL, J. L., USSHER, M., MICHIE, S., WEST, R. & TAYLOR, A. H. 2015. Lessons learned from recruiting socioeconomically disadvantaged smokers into a pilot randomized controlled trial to explore the role of Exercise Assisted Reduction then Stop (EARS) smoking. *Trials,* 16**,** 1.

THOMPSON, T. P., GREAVES, C. J., AYRES, R., AVEYARD, P., WARREN, F. C., BYNG, R., TAYLOR, R. S., CAMPBELL, J. L., USSHER, M., MICHIE, S., WEST, R. & TAYLOR, A. H. 2016. Factors associated with study attrition in a pilot randomised controlled trial to explore the role of exercise-assisted reduction to stop (EARS) smoking in disadvantaged groups. *Trials,* 17**,** 524.

Appendix 11: Insufficient data collected before COVID-19 outbreak

As the objectives of this thesis were to assess and compare the effects of vaping and smoking on: respiratory function, vascular function and VO_{2max}, muscle function, size and low back pain and due to the outbreak of the COVID-19 pandemic, the objectives had to be adjusted as mentioned in the general discussion. The below table (A) and figures (A1, A2 and A3) show how many participants, and which data were collected regarding the effects of vaping and smoking on cardiovascular function, muscle function, size and low back pain that had been collected before the COVID-19 outbreak and participant recruitment ceased during the pandemic. The data were insufficient for in depth analysis.

The vascular function was meant to be assessed by brachial artery flow mediated dilation using ultrasound, VO_{2max} by cardiopulmonary exercise testing, low back pain using Oswestry Low Back Disability Questionnaire subjectively and objectively by measuring the lower back muscles size, and thigh muscle size using magnetic resonance imaging, muscle function using a dynamometer chair and percutaneous electrical muscle stimulation.

Table A: number of participants recruited before the pandemic.

	Vapers		**Cigarette smokers**		**Non-smokers**	
	Men	**Women**	**Men**	**Women**	**Men**	**Women**
MRI scanning and ODI	(2)	(3)	(5)	(2)	(4)	(3)
FMD	(3)	(3)	(4)	(3)	(6)	(4)

(X): number of participants; MRI: Magnetic Resonance Imaging; ODI: Oswestry Low Back Disability Questionnaire; FMD: Flow Mediated Dilation.

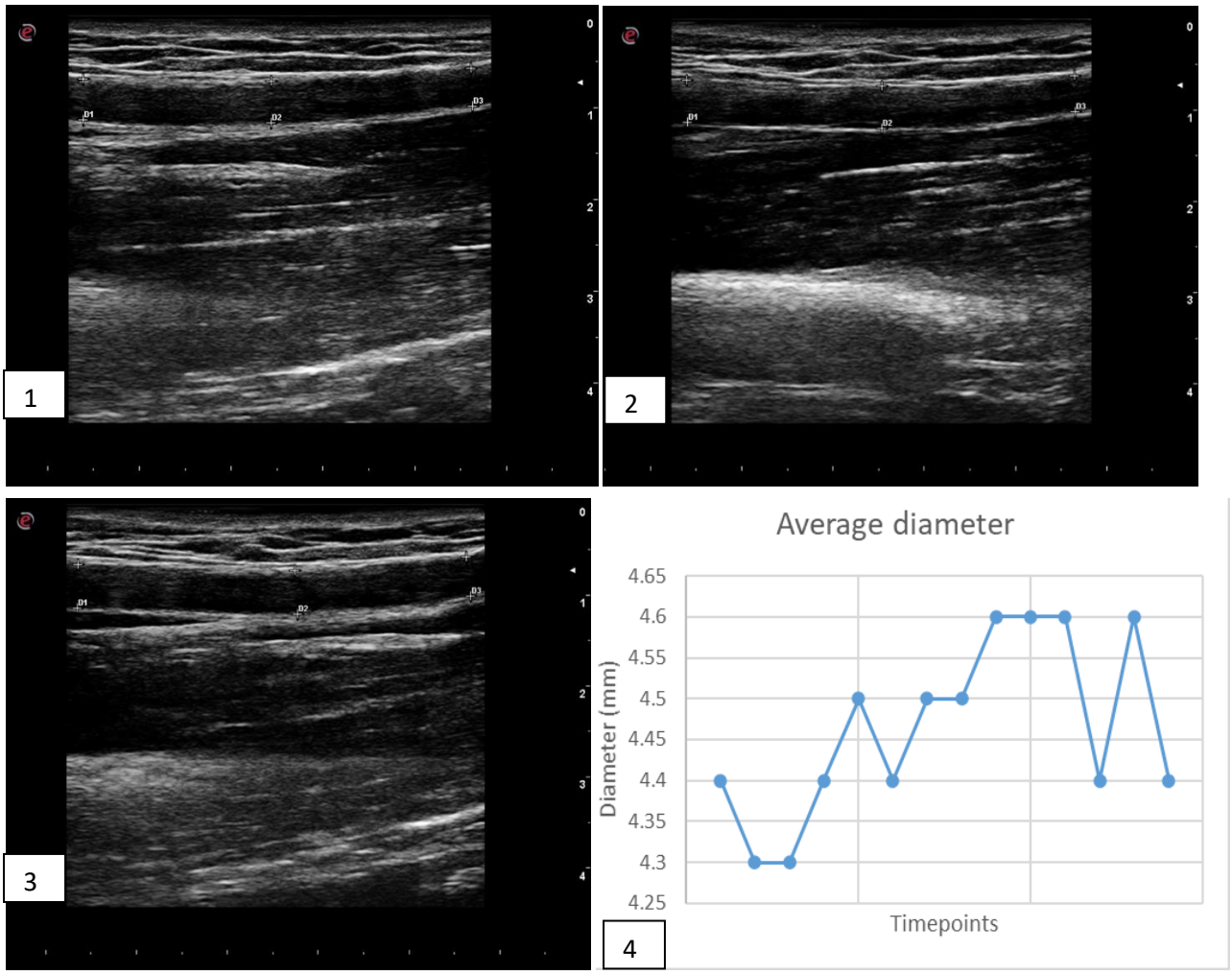

Figure A1: An example about data collected before the pandemic using the brachial artery flow mediated dilation technique for one participant.

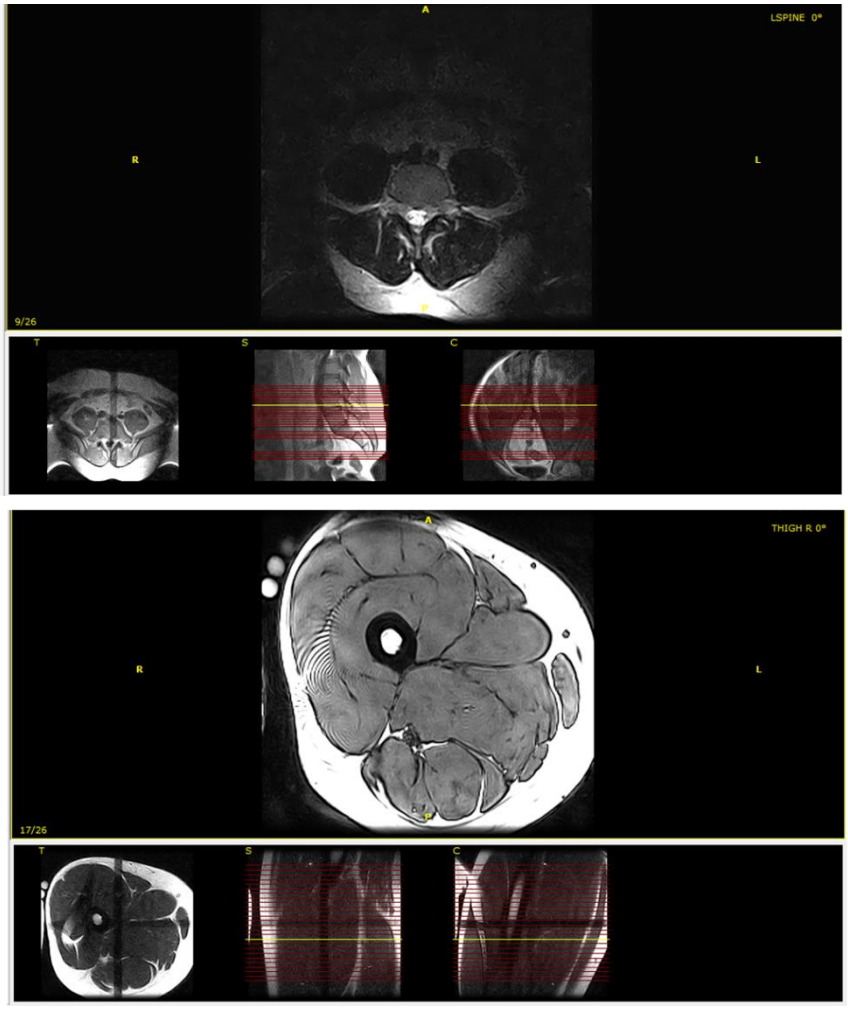

Figure A2: an example of lower back muscles (upper figure) and thigh muscles (lower figure) as scanned in MRI in one participant before the pandemic.

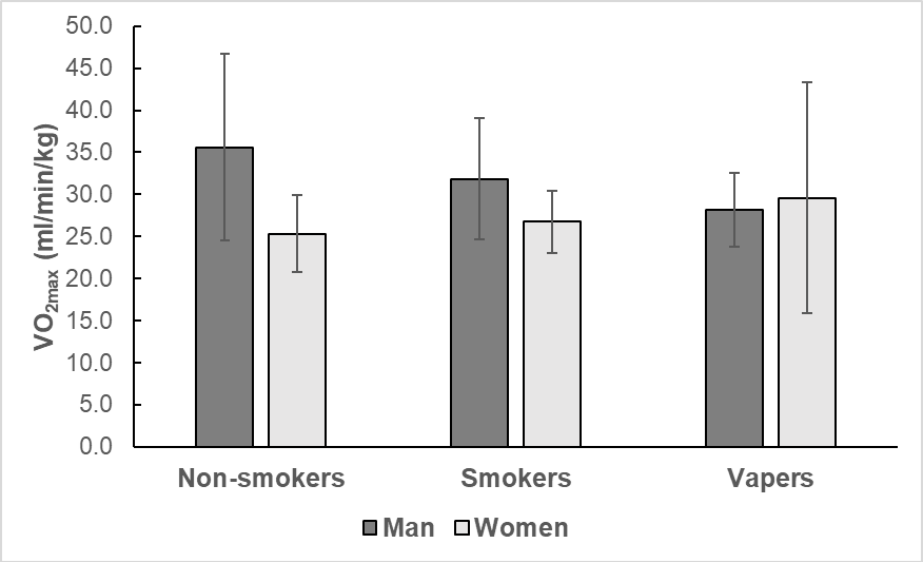

Figure A3: VO_{2max}: Maximal oxygen uptake in: Non-smokers (M:6; W:4), smokers (M:4; W:3) and vapers (M:3; W:3).

Publications:

Peer-reviewed articles:

Darabseh, M.Z., Maden-Wilkinson, T.M., Welbourne, G., Wüst, R.C., Ahmed, N., Aushah, H., Selfe, J., Morse, C.I. and Degens, H., 2021. Fourteen days of smoking cessation improves muscle fatigue resistance and reverses markers of systemic inflammation. Scientific reports, 11(1), pp.1-11.

Darabseh, M.Z., Selfe, J., Morse, C.I. and Degens, H., 2021. Impact of vaping and smoking on maximum respiratory pressures and respiratory function. International Journal of Adolescence and Youth, 26(1), pp.421-431.

Ocana, P.D., **Darabseh, M.Z.,** Ishihara, K. et al. Age-related declines in muscle and respiratory function are proportionate to declines in performance in Master Track Cyclists. Eur J Appl Physiol (2021). https://doi.org/10.1007/s00421-021-04803-4

Darabseh, M. Z., Selfe, J., Morse, C. I., & Degens, H. (2020). Is vaping better than smoking for cardiorespiratory and muscle function?. Multidisciplinary Respiratory Medicine, 15. https://doi.org/10.4081/mrm.2020.674

Abstracts and conference proceedings:

Darabseh, M. Z., Selfe, J., Morse, C. I., & Degens, H. (2021). Impact of Vaping and Smoking on Maximum Respiratory Pressures and Respiratory Function. Physiotherapy Research Society Conference 2021 (Presenter) (UK).

Darabseh, M. Z., Aburub, A., Davis, S. (2021). Does Virtual Reality Physiotherapy Interventions Change Cardiopulmonary Function and Breathing-Control in Cystic Fibrosis? A Systematic Review. Physiotherapy Research Society Conference 2021 (Presenter) (UK).

Darabseh, M. Z., Rawashdeh, M. & Darwish, F. (2020). The Effects of Pedometer–Based Intervention on Patients After Total Knee Replacement Surgeries. Physiotherapy UK 2020 (Speaker) (UK).

Alomari M., Khabour O., Alzoubi K., **Darabseh M. Z.**, "Sleeping Habits during COVID19 Induced Confinement", Qatar University Annual Research Forum and Exhibition (QUARFE 2020), Doha, 28 October 2020, DOI: https://doi.org/10.29117/quarfe.2020.0293

Darabseh, M. Z., Pablo Duro Ocana, (Joint first authorship) et al., Proportionate age-related declines in muscle strength, respiratory function and performance in Master Track Cyclists. Future Physiology 2021 conference (ePoster) presentation (UK).

Accepted abstract and shortlisted for the Young Investigator Award (YIA) for the European College of Sport Science (ECSS) Conference 2021 as**:**

Darabseh, M. Z., Aburub, A., Ishihara, K., Ganse, B., Bagley, L., Degens, H. (2021). ‘’ Age-related decline in respiratory function and respiratory muscles strength in Master Track Cyclists’’, (presenter).