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Antioxidants in smokers

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Abstract

Cigarette smoke (CS) is likely the most common preventable cause of human morbidity and mortality worldwide. Consequently, inexpensive interventional strategies for preventing CS-related diseases would positively impact health systems. Inhaled CS is a powerful inflammatory stimulus and produces a shift in the normal balance between antioxidants and oxidants, inducing oxidative stress in both the respiratory system and throughout the body. This enduring and systemic pro-oxidative state within the body is reflected by increased levels of oxidative stress and inflammation biomarkers seen in smokers. Smokers might benefit from consuming antioxidant supplements, or a diet rich in fruit and vegetables, which can reduce the CS-related oxidative stress. This review provides an overview of the plasma profile of antioxidants observable in smokers and examines the heterogeneous literature to elucidate and discuss the effectiveness of interventional strategies based on antioxidant supplements or an antioxidant-rich diet to improve the health of smokers. An antioxidant-rich diet can provide an easy-to-implement and cost-effective preventative strategy to reduce the risk of CS-related diseases, thus being one of the simplest ways for smokers to stay in good health for as long as possible. The health benefits attributable to the intake of antioxidants have been observed predominantly when these have been consumed within their natural food matrices in an optimal antioxidant-rich diet, while these preventive effects are rarely achieved with the intake of individual antioxidants, even at high doses.

Keywords: **Cigarette smoke: Oxidative stress: Inflammation: Antioxidant-rich diet: Smoking-related diseases: Preventive strategies**

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1. Introduction

1.1. Background

Cigarette smoking is probably one of the most widespread and proven risk factors threatening public health that the world has ever faced, killing an estimated 6 million people every year[1,2]. More than 5 million of those deaths are the result of direct smoking, while over 600 000 premature deaths result from the exposure of non-smokers to second-hand smoke[3]. Smokers die, on average, more than a decade before non-smokers[4]. This premature mortality is because long-term exposure (lasting over three to four decades) to cigarette smoke (CS) is associated with an increased risk of developing serious CS-related diseases.

Evidence from epidemiologic and meta-analyses is sufficient to infer a causal relationship between CS and the development of lung cancer. CS accounts for 80 % and 50 % of the worldwide lung cancer outbreak in men and women, respectively[5,6]. Although lung cancer incidence rates are decreasing in men in Europe and North America, they have increased in Asia and Africa[5] and in women, reflecting changes in smoking habits[7]. CS is the major recognised risk factor for oral cavity and pharyngeal cancer, with relative risks in the order of five to ten times higher for smokers than for non-smokers[8]. A causal relationship has also been established between CS and chronic obstructive pulmonary disease (COPD), which causes a greater predisposition to the *Mycobacterium tuberculosis* disease[9]. CS also exacerbates asthma, though data are only suggestive but not sufficient to infer a causal link between CS and asthma incidence[9,10].

Although CS-related diseases originate mainly in the organs that are directly exposed to CS, the toxic substances contained

Abbreviations: COPD, chronic obstructive pulmonary disease; CS, cigarette smoke; CVD, cardiovascular disease; E-cigarettes, electronic cigarettes; ENDS, electronic nicotine delivery systems; GSH, glutathione; NF-κB, nuclear factor-κB; RDA, recommended dietary (daily) allowance†; RNS, reactive nitrogen species; ROS, reactive oxygen species; TNF-α, tumour necrosis factor-α.

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† The recommended dietary (daily) allowance (RDA) is the average daily dietary intake level for vitamins (A, C and E), carotenoids and other antioxidants that is sufficient to meet the nutrient requirement of nearly all (97–98 %) healthy individuals in a particular life stage and sex group[113,114].

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in CS can also reach other organs through the circulatory system and cause damage that eventually leads to the development of many other diseases. Indeed, the gas phase of CS crosses the lung alveolar wall and enters the bloodstream[11], where it can interact with both water-soluble and lipid-soluble circulating plasma antioxidants, resulting in their depletion[12]. Plasma antioxidants, whose role and physiological activity have been exhaustively reviewed in a recent paper[13], include low-molecular-mass vitamins A, C and E, uric acid, α- and γ-tocopherol, α- and β-carotene, β-cryptoxanthin, lutein and zeaxanthin, lycopene, and retinol[14], low-molecular-mass reduced aminothiols (i.e. glutathione (GSH) and cysteine)[15], and high concentrations (~600 μM, i.e. ~43 mg/ml) of reduced albumin[16].

A causal relationship has been demonstrated between CS and colorectal polyps[17–19], colorectal cancer and hepatocellular carcinoma[9]. CS is also associated with a relatively modest increase in the risk of developing kidney cancer[20]. In women, CS also increases breast cancer risk[21]. The evidence at our disposal does not suggest the presence of any causal relationship between CS and the risk of developing prostate cancer, although there is a higher risk of death from prostate cancer in smokers than in non-smokers[9,22]. CS is also a proven risk factor for diabetes mellitus, rheumatoid arthritis and impairment of the immune system[9]. Moreover, CS is responsible for an increased risk of cardiovascular diseases (CVD) and related atherosclerosis[23], acute coronary heart disease and stroke[24], and is the most important risk factor for abdominal aortic aneurysm[25,26]. Smoking is associated with enhanced oxidative stress, which favours the progression of CVD. Current smokers with CVD, who have survived a coronary heart disease event, such as acute myocardial infarction or ischaemia, would particularly benefit from quitting smoking, because this could prevent their next, potentially fatal CVD event[27]. Although the CVD risk as well as the possible death from CVD events is very high in such patients, a considerable number of them (up to about a quarter), astonishingly, still smoke and have no intention of quitting smoking[27,28]. In addition, exposure to passive smoking may compromise smoking cessation among patients with coronary heart disease[29].

In general, the most important way to prevent CVDs is to constantly adopt a healthy lifestyle. A healthy diet, abstinence from smoking and avoidance of exposure to second-hand smoke are among the actions of the first prevention of CVD[30]. The good news for smokers is that smoking cessation reduces CVD risk. A recent investigation analysed data from the Framingham Heart Study to determine the association between years since smoking cessation and subsequent CVD risk among former smokers versus persistent smokers and never smokers[31]. The retrospective analysis included a population of 8770 individuals and found that, compared with current heavy smoking, smoking cessation among former heavy smokers was associated with lower CVD risk within 5 years of cessation, corroborating analogous findings demonstrated by others (e.g. ref. [32]). However, compared with never smokers, the CVD risk of former smokers remained significantly elevated beyond 5 years after smoking cessation[31].

Oxidative burden can play an important role in the pathological conditions resulting from long-term exposure to CS. It can be due to direct oxidative damage or indirect pathways, such as antioxidant depletion or inflammation. Indeed, low-grade systemic inflammation is evident in smokers as confirmed by elevated levels of inflammation biomarkers[33,34]. Since CS is a primary source of oxidants, which induce oxidative stress/damage in smokers, animal models and *in vitro* cell models[35–40], the bolstering of body's antioxidant defences through antioxidant supplementation or an antioxidant-rich diet could potentially mitigate some of the CS-induced damage.

Numerous studies have focused on the utility of antioxidant supplementation. However, whether antioxidant supplementation has any preventive and/or therapeutic effect in CVD has not yet been irrefutably established. Clinical human studies have supported the association between oxidative stress and cardiovascular events thanks also to the use of several oxidative stress biomarkers, which can also be used to assess the preventive/protective effect of antioxidant supplementation in patients with CVD risk, including smokers[41].

In this review, we focus on the antioxidant profile in plasma of smokers, the evaluation of which is an essential step in assessing the efficacy and safety of potential interventional strategies. Besides, we also discuss the effectiveness of antioxidant supplements and antioxidant-rich diets in smokers.

1.2. Composition of cigarettes and their regulation

Cigarette composition has changed over time. The main changes occurred in the 1950s: 'tar' and nicotine content declined, and other CS constituents changed correspondingly, primarily because of the introduction of filter tips, the selection of tobacco varieties, the utilisation of highly porous cigarette paper and the changing composition of the tobacco blend (with the incorporation of reconstituted and expanded tobaccos). According to the technical notes of the Joint Research Centre of the European Commission, prior to 1955, probably no brand of cigarettes had a tar content below 35 mg. Since then, the introduction of the new technologies for cigarette manufacturing have led to a decline in tar, nicotine and carbon monoxide content[42]. Concurrently, nitrate content increased. This enhanced the combustion of tobacco, decreasing the amount of polynuclear aromatic hydrocarbons, carbon monoxide and phenols, but simultaneously increasing the generation of nitrogen oxides that promote the formation of the carcinogenic *N*-nitrosamines, especially the tobacco-specific *N*-nitrosamines[43].

In the 1960s, many countries introduced the first laws to reduce nicotine and tar content and to inform consumers about the harmful compounds contained in cigarettes. In this regard, a recent and important European recommendation is the Directive 2001/37/EC, adopted by the European Parliament and the Council on 5 June 2001. This directive contained provisions for cigarette design to reduce tar content and to set limits for nicotine and carbon monoxide amount; it indicates warnings on cigarette packets and prohibits misleading descriptors[44]. Nowadays, the revised Directive 2014/40/EU, approved by the European Parliament on 26 February, strengthened the rules on how tobacco products are manufactured, produced and presented in the European Union (EU) (e.g. each cigarette pack has to contain at least twenty sticks; messages on packs suggesting

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that a product is less harmful that another one are forbidden) and introduced specific rules for certain tobacco-related products, such as tobacco flavourings and electronic cigarettes (e-cigarettes)[45]. About this last point, the Directive aims at ensuring an equal treatment across the EU for nicotine-containing e-cigarettes. Safety and quality requirements for e-cigarettes are necessary to monitor and learn more about these products, often seen as fashionable, less harmful and healthier than regular cigarettes, especially among young people.

1.3. Oxidative stress, inflammation and oxidative stress: the vicious cycle of cigarette smoke

CS contains nicotine, polycyclic aromatic hydrocarbons, quinones, benzo(α)pyrene, hydrogen cyanide, carbon monoxide and dioxide, pyridine alkaloids, ammonia, phenols, *N*-nitrosamine, reactive oxygen species (ROS) and reactive nitrogen species (RNS), and saturated (acetaldehyde, formaldehyde) and α,β-unsaturated aldehydes (acrolein and crotonaldehyde), which are particularly harmful because of their high reactivity and toxicity[46,47]. Aldehydes are long-lived compared with most ROS/RNS and oxidising intermediates, with half-lives ranging from a few hours to days, and therefore, they can spread over long distances, causing airway inflammation that leads to the development of respiratory diseases[48–50]. Moreover, aldehydes may get into systemic circulation and can cause damage to the vasculature and to different organ systems[51].

There is clear evidence that long-term exposure to CS can cause oxidative stress to the entire organism, as reflected by increased levels of oxidative stress biomarkers in the plasma and urine of smokers, including plasma F_2-isoprostanes[52], malondialdehyde[53–55], carbonylated proteins[56–58] and urinary eicosanoids[33].

CS also stimulates an inflammatory response characterised by the activation of macrophages and the recruitment/activation of neutrophils, eosinophils, monocytes and lymphocytes in the respiratory tract[59,60]. An important, though not unique, mechanism by which CS produces an inflammatory response is the activation of the nuclear factor (NF)-κB pathway[61,62] via the generation of ROS/RNS and aldehydes, such as acrolein and crotonaldehyde[62]. This results in NF-κB translocation into the cell nucleus, where it induces transcription of many genes involved in immune regulation. The release of chemo-attractants is not just limited to inflammatory cells directly exposed to CS. Structural lung cells such as pulmonary fibroblasts, alongside their important role in maintaining the extracellular matrix and in repairing tissue after injury, may also play a role in inflammatory responses by releasing interleukin-8 (IL-8) and other chemokines[63,64]. CS also activates endothelial cells, resulting in the release of inflammatory mediators and chemo-attractive cytokines such as IL-6 and IL-8[60]. Furthermore, CS induces the release of IL-8 from human airway smooth muscle cells, and the effect is enhanced by tumour necrosis factor (TNF)-α[65]. CS also contributes to additional oxidative stress by the release of ROS/RNS from macrophages, neutrophil and eosinophil granulocytes, which migrate from the blood to lung parenchyma[59] (Fig. 1). In addition to an elevated oxidant load and inflammation in the respiratory tract and lungs, smokers experience increased systemic oxidative stress and inflammation[34,66,67].

Under physiological conditions, the human body counterbalances the excessive production of ROS/RNS with the antioxidant defence systems, which neutralise ROS/RNS and maintain the balance between oxidants and antioxidants[14]. Antioxidant defence systems consist of enzymatic and non-enzymatic systems (endogenous antioxidants) and a variety of low-molecular-weight molecules, most of which derive from dietary sources (exogenous antioxidants) (Fig. 2). Diet-derived antioxidants dissipate during their reaction with reactive species and can be replenished through the diet. Furthermore, many antioxidant enzymes, such as catalase, glutathione peroxidase, heme oxygenase and superoxide dismutase, require micronutrient cofactors such as selenium, iron, copper, zinc and manganese for optimal catalytic activity.

In smokers, inhaled CS overwhelms all these antioxidant defence systems and causes a subsequent decrease in antioxidant levels, thus promoting additional oxidative stress. This vicious cycle leads to an enduring and systemic pro-oxidative state within the body that causes oxidative modifications of nucleic acids, lipids and proteins, eventually promoting cell/tissue injury and diseases[60].

2. Antioxidants in smokers

2.1. Antioxidant profile in blood plasma of smokers

Although the inhaled CS mainly reaches the respiratory tract, where it causes an adaptative local antioxidant response in the lung (i.e. boost of GSH levels)[68,69], which is lower in older smokers than in younger (18–30 years) smokers[70], the toxic substances contained in CS can also reach other organs through the circulatory system, thus causing the lowering of the concentration of almost all low-molecular-mass antioxidants in the blood plasma.

Some studies have shown that smokers have lower plasma concentrations of almost all low-molecular-mass antioxidants than non-smokers (Table 1). This condition results from at least two factors, one that depends on the diet and one caused directly by CS. Epidemiological studies showed that smokers consume less fruit and vegetable than non-smokers[71–74]. A recent population-based cohort analysis on a population of 1000 smokers (age ≥ 25 years) confirmed that smokers consume less fruit and vegetable rich in antioxidants than non-smokers[75]. Smokers can thus be particularly lacking in exogenous antioxidants. For example, the intake of vitamin C in smokers ranges from +0·3 % to −38 % compared with non-smokers[76]; therefore, the plasma vitamin C concentration is usually lower in smokers than in non-smokers (Table 1). Besides, smokers consume approximately 10·8–39·4 % less β-carotene than non-smokers, and the comparison between heavy smokers (≥ 20 cigarettes/d, or ≥ 10 years of smoking) and non-smokers showed lower plasma β-carotene levels in smokers (between −17·0 % and −50·7 %)[76]. In addition to dietary differences, some studies, in which dietary intakes of antioxidants have been corrected,

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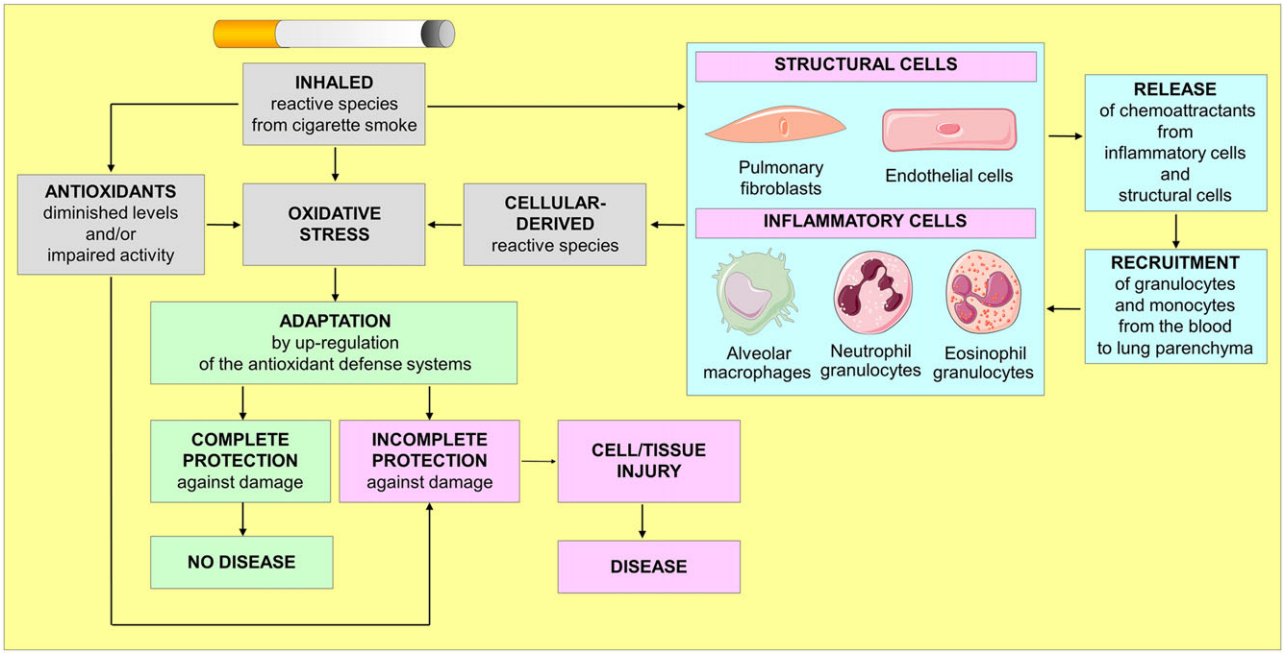

Fig. 1. The vicious cycle of oxidative stress in smokers.
The inhaled CS reactive species represent only a portion of the total oxidative stress eventually experienced by smokers, as the CS also contributes to the formation of further endogenous reactive species formation from inflammatory cells. When activated, inflammatory cells together with structural cells (e.g. pulmonary fibroblasts and endothelial cells) initiate an inflammatory cascade that triggers the release of inflammatory mediators which sustain the inflammatory process and lead to tissue damage as well as a range of systemic effects. After years of chronic smoking, this vicious cycle leads to a permanent oxidative injury of cells and tissue, thereby promoting diseases.

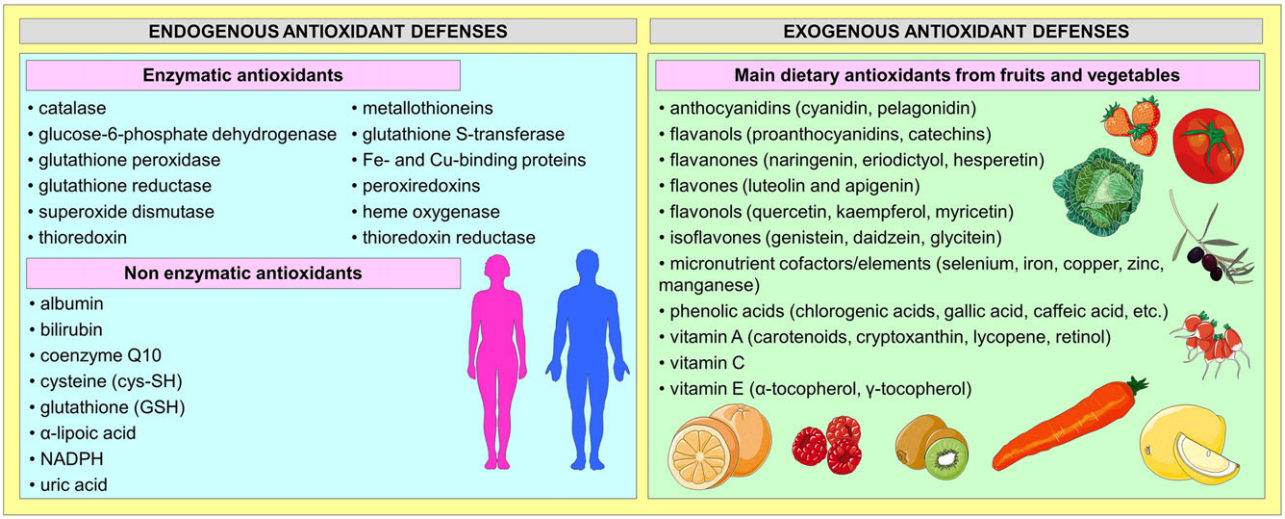

Fig. 2. The endogenous/exogenous antioxidant defence systems.
An antioxidant is any substance (endogenous or exogenous, natural or synthetic) which, when present at low concentration compared with that of an oxidisable substrate, significantly prevents its oxidation, or delays it. The antioxidant defence system consists of both enzymatic and non-enzymatic (endogenous antioxidants) systems, along with a variety of low-molecular-weight antioxidants, most of which are derived from dietary sources (exogenous antioxidants). In the human body, endogenous antioxidant defence systems work in synergy with exogenous antioxidants.

show that at least vitamin C and possibly β-carotene are depleted by CS itself[12,77–79]. Smokers also have lower plasma levels of vitamins A and E, GSH and Cys than non-smokers (Table 1).

Sex affects levels of β-carotene, lycopene and selenium in smokers. Compared with non-smokers, male smokers have lower circulating levels of lycopene and selenium (Table 1). Conversely, no statistically significant differences were found in the plasma levels of lycopene and selenium in female smokers[74]. A study involving thirty-seven males and forty-two females showed that current female smokers had higher serum β-carotene levels (0·24 ± 0·23 μg/ml) than current male smokers (0·10 ± 0·10 μg/ml)[80].

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Table 1. Plasma profile of antioxidants in smokers

Plasma antioxidant	Non-smoker number, sex and age	Smoker number, sex and age	Smoking status definition criteria or serum cotinine levels	Plasma concentration in non-smokers	Plasma concentration in smokers	Plasma concentration in non-smokers (μmol/l)	Plasma concentration in smokers (μmol/l)	References
Vitamin A	*n* = 100 (males) 43·3 ± 9·7 years	Healthy smokers *n* = 100 (males) 40·1 ± 10·3 years	[3] 15 cigarettes/d for 5–12 years	0·99 ± 0·07 [(a)] mg/dl	0·51 ± 0·09 [(a)] mg/dl	34·56 ± 2·44 [(a)]	17·80 ± 3·14 [(a)]	240
***α*-Carotene (vitamin A)**	*n* = 40 (22 males, 18 females) 40·7 ± 18·6 years	Healthy smokers *n* = 46 (37 males + 9 females) 33·5 ± 15·6 years	Cigarettes/d (not specified) for 2·2–26 years	6·7 ± 4·0 [(a) (1)] mg/dl	3·3 ± 1·2 [(a) (1)] mg/dl	0·125 ± 0·075 [(a) (1)]	0·061 ± 0·022 [(a) (1)]	90
	n = 2488 (males) 31·8 ± 0·4 years	Healthy smokers *n* = 1484 (males) 32·4 ± 0·4 years	Cotinine 242·45 ± 6·35 ng/ml	4·4 ± 0·2 [(b) (2)] mg/dl	2·9 ± 0·1 [(b) (2)] mg/dl	0·082 ± 0·004 [(b) (2)]	0·054 ± 0·02 [(b) (2)]	74
	n = 2894 (females) 33·0 ± 0·3 years	Healthy smokers *n* = 1007 (females) 31·8 ± 0·4 years	Cotinine 224·93 ± 5·44 ng/ml	5·3 ± 0·2 [(b) (2)] mg/dl	3·8 ± 0·2 [(b) (2)] mg/dl	0·099 ± 0·04 [(b) (2)]	0·071 ± 0·04 [(b) (2)]	74
***β*-Carotene (vitamin A)**	*n* = 60 (females) not specified years	Healthy smoking pregnant women (III trimester) *n* = 80 not specified years	5–20 cigarettes/d during pregnancy	2·6 ± 0·4 [(a)] mmol/l	1·8 ± 0·5 [(a)] mmol/l	2·6 ± 0·4 [(a)]	1·8 ± 0·5 [(a)]	55
	n = 40 (22 males, 18 females) 40·7 ± 18·6 years	Healthy smokers *n* = 46 (37 males + 9 females) 33·5 ± 15·6 years	Cigarettes/d (not specified) for 2·2–26 years	34·9 ± 22·8 [(a) (1)] mg/dl	11·7 ± 6·7 [(a) (1)] mg/dl	0·650 ± 0·425 [(a) (1)]	0·218 ± 0·125 [(a) (1)]	241
	n = 2488 (males) 31·8 ± 0·4 years	Healthy smokers *n* = 1484 (males) 32·4 ± 0·4 years	Cotinine 242·45 ± 6·35 ng/ml	17·3 ± 0·6 [(b) (2)] mg/dl	11·9 ± 0·5 [(b) (2)] mg/dl	0·322 ± 0·011 [(b) (2)]	0·222 ± 0·009 [(b) (2)]	74
	n = 2894 (females) 33·0 ± 0·3 years	Healthy smokers *n* = 1007 (females) 31·8 ± 0·4 years	Cotinine 224·93 ± 5·44 ng/ml	21·1 ± 0·6 [(b) (2)] mg/dl	15·9 ± 0·8 [(b) (2)] mg/dl	0·393 ± 0·011 [(b) (2)]	0·296 ± 0·015 [(b) (2)]	74
Cryptoxanthin (vitamin A)	*n* = 21 (8 males, 13 females) 47 ± 3 years	Healthy smokers *n* = 35 (20 males + 15 females) 46 ± 1 years	18–22 cigarettes/d for >1 year	9 ± 1 [(b)] mg/dl	5 ± 1 [(b)] mg/dl	0·163 ± 0·018 [(b)]	0·090 ± 0·018 [(b)]	92
	n = 2488 (males) 31·8 ± 0·4 years	Healthy smokers *n* = 1484 (males) 32·4 ± 0·4 years	Cotinine 242·45 ± 6·35 ng/ml	9·7 ± 0·2 [(b) (1)] mg/dl	7·4 ± 0·2 [(b) (2)] mg/dl	0·175 ± 0·004 [(b) (1)]	0·134 ± 0·004 [(b) (2)]	74
	n = 2894 (females) 33·0 ± 0·3 years	Healthy smokers *n* = 1007 (females) 31·8 ± 0·4 years	Cotinine 224·93 ± 5·44 ng/ml	9·7 ± 0·2 [(b) (2)] mg/dl	7·2 ± 0·2 [(b) (2)] mg/dl	0·175 ± 0·004 [(b) (2)]	0·130 ± 0·04 [(b) (2)]	74
Retinol (vitamin A)	*n* = 40 (22 males, 18 females) 40·7 ± 18·6 years	Healthy smokers *n* = 46 (37 males + 9 females) 33·5 ± 15·6 years	Cigarettes/d (not specified) for 2·2–26 years	47·8 ± 14·5 [(a) (1)] mg/dl	49·3 ± 11·7 [(a) (1)] mg/dl	1669 ± 506 [(a) (1)]	1721 ± 408 [(a) (1)]	241
Vitamin C	*n* = 100 (males) 43·3 ± 9·7 years	Healthy smokers *n* = 100 (males) 40·1 ± 10·3 years	[(3)] 15 cigarettes/d for 5–12 years	1·31 ± 0·31 [(a)] mg/dl	0·77 ± 0·23 [(a)] mg/dl	74·38 ± 17·6 [(a)]	43·72 ± 13·06 [(a)]	240
	n = 50 (males) 38·58 ± 12·08 years	Healthy smokers *n* = 25 (males) 32·8 ± 12·3 years	1–13 cigarettes/d for >1 year	1·73 ± 0·28 [(a)] mg/dl	1·45 ± 0·43 [(a)] mg/dl	98·23 ± 15·90 [(a)]	82·33 ± 24·42 [(a)]	242
	n = 15 (12 males, 13 females) 38·2 ± 9·2 years	Healthy smokers *n* = 15 (9 males + 6 females) 38·2 ± 9·2 years	Not specified	41·92 ± 4·32 [(a)] mmol/l	36·67 ± 3·36 [(a)] mmol/l	41·92 ± 4·32 [(a)]	36·67 ± 3·36 [(a)]	91
	n = 38 (males) 34·0 ± 7·6 years	Healthy smokers *n* = 37 (males) 34·0 ± 7·6 years	8–38 cigarettes/d for not specified years	41·4 ± 25·1 [(a)] mmol/l	27·0 ± 20·0 [(a)] mmol/l	41·4 ± 25·1 [(a)]	27·0 ± 20·0 [(a)]	77
	n = 2488 (males) 31·8 ± 0·4 years	Healthy smokers *n* = 1484 (males) 32·4 ± 0·4 years	Cotinine 242·45 ± 6·35 ng/ml	0·73 ± 0·02 [(b) (2)] mg/dl	0·54 ± 0·03 [(b) (2)] mg/dl	41·45 ± 1·14 [(b) (2)]	30·66 ± 1·70 [(b) (2)]	74
	n = 2894 (females) 33·0 ± 0·3 years	Healthy smokers *n* = 1007 (females) 31·8 ± 0·4 years	Cotinine 224·93 ± 5·44 ng/ml	0·84 ± 0·02 [(b) (2)] mg/dl	0·65 ± 0·03 [(b) (2)] mg/dl	47·69 ± 1·14 [(b) (2)]	36·91 ± 1·70 [(b) (2)]	74
	n = 19 (females) 16 ± 1 years	Young healthy smokers *n* = 19 (females) 16 ± 1 years	10–25 cigarettes/d for >1 year 6 months	4·4 ± 0·4 [(b)] mg/ml	3·1 ± 0·2 [(b)] mg/ml	24·98 ± 2·27 [(b)]	17·6 ± 1·14 [(b)]	243

Table 1. (*Continued*)

Plasma antioxidant	Non-smoker number, sex and age	Smoker number, sex and age	Smoking status definition criteria or serum cotinine levels	Plasma concentration in non-smokers	Plasma concentration in smokers	Plasma concentration in non-smokers (μmol/l)	Plasma concentration in smokers (μmol/l)	References
Vitamin E	$n = 1045$ (males) 31·8 ± 0·4 years	Healthy smokers $n = 1484$ (males) 32·4 ± 0·4 years	Cotinine 242·45 ± 6·35 ng/ml	1034 ± 13 [(b) (2)] mg/dl	1003 ± 17 [(b) (2)] mg/dl	24·00 ± 0·30 [(b) (2)]	23·29 ± 0·39 [(b) (2)]	74
	$n = 2894$ (females) 33·0 ± 0·3 years	Healthy smokers $n = 1007$ (females) 31·8 ± 0·4 years	Cotinine 224·93 ± 5·44 ng/ml	992 ± 9 [(b) (2)] mg/dl	995 ± 14 [(b) (2)] mg/dl	23·03 ± 0·21 [(b) (2)]	23·10 ± 0· 33 [(b) (2)]	74
	$n = 100$ (males) 43·3 ± 9·7 years	Healthy smokers $n = 100$ (males) 40·1 ± 10·3 years	[3] 15 cigarettes/d for 5–12 years	1·35 ± 0·23 [(a)] mg/dl	0·83 ± 0·19 [(a)] mg/dl	31·34 ± 5·34 [(a)]	19·27 ± 4·41 [(a)]	240
	$n = 10$ (6 males, 4 females) 31·6 ± 1·5 years	Healthy smokers $n = 10$ (6 males + 4 females) 31·9 ± 1·7 years	> 15 cigarettes/d for not specified years	~ 225 ± 20 [(b)] ng/ml	~ 155 ± 15 [(b)] ng/ml	~ 0·522 ± 0·046 [(b)]	~ 0·360 ± 0·035 [(b)]	244
α-Tocopherol (vitamin E)	$n = 196$ (males) 77·6 ± 0·8 years	Elderly smokers without diabetes $n = 55$ (males) 77·5 ± 0·5 years	Not specified	1·63 ± 0·36 [(a) (3) (**)] mg/mmol	1·49 ± 0·28 [(a) (3) (**)] mg/mmol	25·35 ± 4·55 [(a) (3) (**)]	24·21 ± 4·83 [(a) (3) (**)]	89
	$n = 60$ (females) not specified years	Healthy smoking pregnant women (III trimester) $n = 80$ not specified years	5–20 cigarettes/d during pregnancy	35·5 ± 8·0 [(a)] mmol/l	28·6 ± 6·5 [(a)] mmol/l	35·5 ± 8·0 [(a)]	28·6 ± 6·5 [(a)]	55
	$n = 21$ (8 males, 13 females) 47 ± 3 years	Healthy smokers $n = 35$ (20 males + 15 females) 46 ± 1 years	18–22 cigarettes/d for > 1 year	1734 ± 133 [(b) (4)] mg/dl	1478 ± 103 [(b) (4)] mg/dl	40·26 ± 3·09 [(b) (4)]	34·32 ± 2·39 [(b) (4)]	92
	$n = 15$ (9 males, 6 females) 38·2 ± 9·2 years	Healthy smokers $n = 15$ (12 males + 3 females) 38·2 ± 9·2 years	Not specified	26·50 ± 2·78 [(a)] mmol/l	18·12 ± 4·64 [(a)] mmol/l	26·50 ± 2·78 [(a)]	18·12 ± 4·64 [(a)]	91
	$n = 40$ (22 males, 18 females) 40·7 ± 18·6 years	Healthy smokers $n = 46$ (37 males + 9 females) 33·5 ± 15·6 years	Cigarettes/d (not specified) for 2·2–26 years	9·6 ± 3·2 [(a) (1)] mg/ml	7·6 ± 2·5 [(a) (1)] mg/ml	22·29 ± 7·43 [(a) (1)]	17·65 ± 5·80 [(a) (1)]	241
	$n = 32$ (16 males, 16 females) 40·3 ± 11 years	$n = 41$ (19 males, 22 females) 40·3 ± 11 years	Cotinine 2158 ± 1381 mg/l	12·10 ± 1·11 [(a) (5)] mg/ml	10·81 ± 1·54 [(a) (5)] mg/ml	28·09 ± 2·58 [(a) (5)]	25·10 ± 3·58 [(a) (5)]	88
γ-Tocopherol (vitamin E)	$n = 32$ (16 males, 16 females) 40·3 ± 11 years	$n = 41$ (19 males, 22 females) 40·3 ± 11 years	Cotinine 2158 ± 1381 mg/l	0·92 ± 0·08 [(a) (5)] mg/ml	0·98 ± 0·18 [(a) (5)] mg/ml	2·21 ± 0·19 [(a) (5)]	2·35 ± 0·43 [(a) (5)]	88
	$n = 21$ (8 males, 13 females) 47 ± 3 years	Healthy smokers $n = 35$ (20 males + 15 females) 46 ± 1 years	18–22 cigarettes/d for >1 year	251 ± 25 [(b) (4)] mg/dl	347 ± 36 [(b) (4)] mg/dl	6·02 ± 0·60 [(b) (4)]	8·33 ± 0·86 [(b) (4)]	92
	$n = 40$ (22 males, 18 females) 40·7 ± 18·6 years	Healthy smokers $n = 46$ (37 males + 9 females) 33·5 ± 15·6 years	Cigarettes/d (not specified) for 2·2–26 years	1·4 ± 0·7 [(a) (1)] mg/ml	1·2 ± 0·4 [(a) (1)] mg/ml	3·36 ± 1·68 [(a) (1)]	2·88 ± 0·96 [(a) (1)]	241
Lutein, zeaxanthin	$n = 2488$ (males) 31·8 ± 0·4 years	Healthy smokers $n = 1484$ (males) 32·4 ± 0·4 years	Cotinine 242·45 ± 6·35 ng/ml	21·5 ± 0·4 [(b) (2)] mg/dl	18·1 ± 0·4 [(b) (2)] mg/dl	0·378 ± 0·07 [(b) (2)]	0·318 ± 0·07 [(b) (2)]	74
	$n = 2894$ (females) 33·0 ± 0·3 years	Healthy smokers $n = 1007$ (females) 31·8 ± 0·4 years	Cotinine 224·93 ± 5·44 ng/ml	21·0 ± 0·5 [(b) (2)] mg/dl	18·1 ± 0·4 [(b) (2)] mg/dl	0·369 ± 0·09 [(b) (2)]	0·318 ± 0·007 [(b) (2)]	74
Lycopene	$n = 40$ (22 males, 18 females) 40·7 ± 18·6 years	Healthy smokers $n = 46$ (37 males + 9 females) 33·5 ± 15·6 years	Cigarettes/d (not specified) for 2·2–26 years	6·3 ± 3·8 [(a) (1)] mg/dl	4·3 ± 1·7 [(a) (1)] mg/dl	0·117 ± 0·071 [(a) (1)]	0·080 ± 0·032 [(a) (1)]	241
	$n = 2488$ (males) 31·8 ± 0·4 years	Healthy smokers $n = 1484$ (males) 32·4 ± 0·4 years	Cotinine 242·45 ± 6·35 ng/ml	27·3 ± 0·5 [(b) (2)] mg/dl	26·1 ± 0·7 [(b) (2)] mg/dl	0·509 ± 0·09 [(b) (2)]	0·486 ± 0·013 [(b) (2)]	74
	$n = 2894$ (females) 33·0 ± 0·3 years	Healthy smokers $n = 1007$ (females) 31·8 ± 0·4 years	Cotinine 242·45 ± 6·35 ng/ml	23·9 ± 0·4 [(b) (2)] mg/dl	23·4 ± 0·5 [(b) (2)] mg/dl	0·445 ± 0·007 [(b) (2)]	0·436 ± 0·009 [(b) (2)]	74

Table 1. (*Continued*)

Plasma antioxidant	Non-smoker number, sex and age	Smoker number, sex and age	Smoking status definition criteria or serum cotinine levels	Plasma concentration in non-smokers	Plasma concentration in smokers	Plasma concentration in non-smokers (μmol/l)	Plasma concentration in smokers (μmol/l)	References
Selenium	*n* = 2488 (males) 31·8 ± 0·4 years	Healthy smokers *n* = 1484 (males) 32·4 ± 0·4 years	Cotinine 242·45 ± 6·35 ng/ml	129 ± 1 [(b) (2)] ng/ml	124 ± 1 [(b) (2)] ng/ml	1·63 ± 0·013 [(b) (2)]	1·57 ± 0·013 [(b) (2)]	74
	n = 2894 (females) 33·0 ± 0·3 years	Healthy smokers *n* = 1007 (females) 31·8 ± 0·4 years	Cotinine 242·45 ± 6·35 ng/ml	124 ± 1 [(b) (2)] ng/ml	122 ± 1 [(b) (2)] ng/ml	1·57 ± 0·013 [(b) (2)]	1·55 ± 0·013 [(b) (2)]	74
GSH	*n* = 32 (16 males, 16 females) 25·3 ± 3·4 years	Healthy smokers *n* = 32 (18 males + 14 females) 26·6 ± 3·9 years	5–10 cigarettes/d for at least 3 years	6·8 ± 0·71 [(a)] mmol/l	5·1 ± 0·47 [(a)] mmol/l	6·8 ± 0·71 [(a)]	5·1 ± 0·47 [(a)]	245
	n = 32 (16 males, 16 females) 25·3 ± 3·4 years	Healthy smokers *n* = 26 (12 males + 14 females) 30·3 ± 3·6 years	25–40 cigarettes/d for at least 3 years	6·8 ± 0·71 [(a)] mmol/l	3·2 ± 0·38 [(a)] mmol/l	6·8 ± 0·71 [(a)]	3·2 ± 0·38 [(a)]	245
	n = 78 (31 males, 47 females) 63 ± 9 years	Healthy smokers *n* = 43 (25 males + 18 females) 63 ± 9 years	Cigarettes/d (not specified) for 21–45 years	2·4 ± 1 [(a)] mmol/l	1·8 ± 1·3 [(a)] mmol/l	2·4 ± 1 [(a)]	1·8 ± 1·3 [(a)]	246
	n = 100 (males) 43·3 ± 9·7 years	Healthy smokers *n* = 100 (males) 40·1 ± 10·3 years	[3] 15 cigarettes/d for 5–12 years	40·71 ± 1·70 [(a)] mg/dl	22·02 ± 2·54 [(a)] mg/dl	1325 ± 55 [(a)]	717 ± 83 [(a)]	240
Cys	*n* = 78 (31 males, 47 females) 63 ± 9 years	Healthy smokers *n* = 43 (25 males + 18 females) 63 ± 9 years	Cigarettes/d (not specified) for 21–45 years	13 ± 6 [(a)] mmol/l	9 ± 5 [(a)] mmol/l	13 ± 6 [(a)]	9 ± 5 [(a)]	246
Uric acid	*n* = 60 (females) not specified years	Healthy smoking pregnant women (III trimester) *n* = 80 (females) not specified years	5–20 cigarettes/d during pregnancy	316·2f (108–408) [(c)] mmol/l	272·4f (102–390) [(c)] mmol/l	316·2f (108–408) [(c)]	272·4f (102–390) [(c)]	55
	n = 138 (62 males, 76 females) 35·6 ± 16 years	Smokers *n* = 162 (145 males + 17 females) 38·0 ± 17·5 years	Urinary cotinine 231·4 ± 205·2 mg/mmol Cr	250 ± 132 [(a)] mmol/l	199 ± 97 [(a)] mmol/l	250 ± 132 [(a)]	199 ± 97 [(a)]	247

HPLC, high-performance (pressure) liquid chromatography; SBD-F, ammonium 7-fluorobenzo-2-oxa-1,3-diazole-4-sulfonate.
[(a)] Standard deviation
[(b)] Standard error
[(c)] Range
[(1)] This SD is inferred.
[(2)] Values were adjusted for age, race/ethnicity, education level, family annual income, leisure physical activity, vitamin/mineral supplement intake and body mass index.
[(3)] Tocopherol levels were corrected for the sum of total cholesterol and triacylglycerol concentrations.
[(4)] Values were adjusted for age, sex, body mass index, alcohol intake and dietary intake of the nutrient in question.
[(5)] Values were adjusted for age and sex.
[(*)] % difference = concentrations in non-smokers−smokers/non-smokers × 100 %.
[(**)] Values estimated from graph.

Extensive research has been conducted to evaluate the influence of cigarette smoking on plasma vitamin E status, biokinetics and metabolism. The antioxidant effect of vitamin E is ascribable to its ability to scavenge peroxyl radicals and limit the propagation of lipid peroxidation. In a recent study conducted to determine some plasma lipophilic and haematological components in middle-aged Romanians, who considered themselves 'healthy' – 58 non-smokers, 58 conventional cigarette smokers – a significant increase ($p < 0{\cdot}0001$) in the level of vitamin E was observed in smokers compared with non-smokers, but only for smokers who consume more than ten cigarettes per day[81]. However, the prevalence of the most recent research articles on the correlation between cigarette smoking and plasma vitamin E levels show an opposite result, namely a reduction in plasma vitamin E concentration after exposure to both active and passive CS[82–86].

Vitamin E consists of eight different lipophilic compounds: four tocopherols (α, β, γ and δ) and four tocotrienols (α, β, γ and δ). Of these, α- and γ-tocopherols are the most important biologically[87]. Divergent results were obtained concerning the effects of CS on plasma α- tocopherol levels (Table 1). Some authors found statistically significant differences in the plasma levels of α-tocopherol between smokers and non-smokers[55,88–91], but not others[92,93]. The same discrepancy was observed in several studies concerning plasma levels of γ-tocopherol which, in smokers, are reduced[94], do not differ[95] or even increase[78] compared with those seen in smokers. Further confusing the matter was the observation that, even though plasma or erythrocyte α- and γ-tocopherol concentrations do not significantly differ, smokers have reduced levels of α-tocopherol in lymphocytes and platelets compared with non-smokers[95]. These conflicting results may be due to the reference values of γ-tocopherol in plasma, which are influenced by the dietary patterns of the population under examination and by other aspects that have not been explored so far, which may include genetic and metabolic factors. Furthermore, the poor sensitivity and differential response of γ-tocopherol detection methods may limit the accuracy of its determination in plasma.

The regulatory mechanisms that influence vitamin E levels in smokers[96] as well as in non-smokers[97] are largely unknown. It has been hypothesised that the reduced dietary nutrient intake observed in smokers may be a contributing factor to the observed reduction in plasma vitamin E levels[98]. However, plasma vitamin E turnover is different between smokers and non-smokers. Faster disappearance rates of α-tocopherol in the plasma of smokers compared with non-smokers were demonstrated in several biokinetic studies[99,100] and were attributed to the increase in plasma clearance of α-tocopherol rather than decreased absorption[100–102]. In addition, smokers and non-smokers show differences in the extent of vitamin E metabolism via a cytochrome P450-mediated pathway that leads to the formation of carboxy-ethyl-hydroxy-chroman excreted in the urine[95,100,103].

A study based on data obtained from the Third National Health and Nutrition Examination Survey (NHANES III) Linked Mortality Study (baseline examination from 1988 to 1994; mortality follow-up through 2006) was conducted on a total of 1492 adults, of which 668 were current smokers, 403 former smokers and 421 never smokers with obstructive lung function[104]. In general, antioxidant concentrations were the lowest in current smokers and the highest in participants who have never smoked[104]. Even though higher amounts of variously oxidised proteins were measured in the smokers' blood and/or plasma, no study detected carbonylated albumin in plasma[56,105]. It is worth noting that albumin is the main carbonylated protein in the bronchoalveolar lavage fluid of long-term elder smokers, even in the absence of pulmonary diseases[106,107], and in parenchymal lung tissue of smokers[108]. We showed a drastic decrease in the albumin Cys34 sulfhydryl group and a marked carbonylation when the purified albumin was exposed to whole-phase CS extract[109]. Mass spectrometry analysis detected acrolein and crotonaldehyde Michael adducts at Cys34, Lys525, Lys351 and His39 and a Schiff base with acrolein at Lys541 and Lys545[109]. Erythrocytes contain ~3 mM GSH, whereas plasma GSH concentration is in the low micromolar range[15]. We demonstrated that erythrocytes protected both albumin and other plasma proteins from CS-induced carbonylation and thiol oxidation[110]. An efficient intracellular antioxidant machinery, coupled with their high blood concentration, makes erythrocytes an effective "sink" of oxidants[111,112]. The high GSH concentration in human erythrocytes could at least partly explain why oxidised albumin was found within the bronchoalveolar lavage fluid and parenchymal lung tissue of smokers, but not within blood plasma.

2.2. Antioxidant supplementation in smokers

When the efficiency of the plasma antioxidant defence barrier is lowered, oxidants are no longer adequately countered, and tissue injury may therefore be triggered. As current evidence suggests lower plasma concentrations of almost all low-molecular-mass antioxidants (Table 1) and increased oxidative stress markers in smokers, it has been speculated that specific antioxidant supplements (i.e. antioxidant vitamins: β-carotene, vitamin C and vitamin E) could be particularly beneficial to smokers.

In the general population, the preventive potential of some antioxidant supplements, obtained either by extraction from natural food or by chemical synthesis, has been studied in numerous epidemiologic studies and meta-analyses. Even if high doses (more than the recommended dietary daily allowance, RDA[113,114]) of individual antioxidant supplements are receiving enthusiastic feedback, driven mainly by the pharmaceutical industries that produce and sell them, supporting experimental scientific evidence is moderately positive in some cases and, in other cases, rather negative[115–122]. Just to give an example, considering the cancer incidence in clinical trials, β-carotene supplementation significantly increased the onset of aggressive prostate cancer[123]. Recent reviews report complete overviews of the positive or negative effects of antioxidant administration in the general population[124] or regarding the development of asthma and cancer in smokers[125]. Many epidemiological studies and meta-analyses investigated the effectiveness of antioxidant supplements to decrease the risk of CS-related diseases in cigarette smokers (Table 2). Overall, in smokers, the situation is even worse than what is known for the non-smoker

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Table 2. Studies evaluating the effect of antioxidant supplements in smokers.

Smoking-related disease	Studies	Characteristic	Intervention	Conclusions	References
Lung cancer and gastric cancer	Metaanalysis of randomised controlled trials	13 publications reporting results from 9 randomised controlled trials were included. Males and females current and former smokers of all ages	Supplementation for β-carotene (6–15 mg/d or 20–30 mg/d) given singly or in combination with other antioxidants	In smokers, β-carotene supplementation at doses of 20–30 mg/d was associated with increased risk not only of lung cancer but also of gastric cancer	128
Tobacco-related cancers	Prospective cohort study	59 210 cancer-free women and 700 women with tobacco-related cancer. Aged 47·1–61·8 years. 3–18·5 cigarettes/d	Supplement for β-carotene, calcium, fluoride, vitamins C, E, D, or those in the B group, retinol, folic acid and other vitamins and minerals at least three times a week	High β-carotene intake was directly associated with risk of tobacco-related cancers among smokers	248
Cardiovascular disease and lung cancer	Systematic review	26 studies (24 randomised, controlled trials and 2 cohort studies) that evaluated single, paired and combinations of 3 or more vitamins and minerals were included	Supplements for vitamins A, B1, B2, B6, B12, C, D, and E, calcium, iron, zinc, magnesium, niacin, folic acid, β-carotene and selenium	Neither vitamin E nor β-carotene prevented cardiovascular disease or cancer, and β-carotene increased lung cancer risk in smokers	121
Lung cancer	Metaanalysis of randomised controlled trials	22 randomised controlled trials, which included 161 045 subjects, 88 610 in antioxidant supplement groups and 72 435 in placebo or no-intervention groups, were included	Supplementation for β-carotene, vitamin A, vitamin C, vitamin E, and selenium administered singly or in combination with other antioxidant supplements compared with placebo administration or no intervention	There is no clinical evidence to support an overall primary and secondary preventive effect of antioxidant supplements on cancer. β-carotene supplements cause lung cancer in current smokers	199
Lung cancer	Cohort study	To examine associations of supplemental β-carotene, retinol, vitamin A, lutein, and lycopene with lung cancer risk in the VITamins And Lifestyle (VITAL) cohort study. Aged 50–76 years. ≥1 cigarette/d for ≥1 year	Supplementation for β-carotene, retinol, vitamin A, lutein and lycopene	Long-term use of individual β-carotene, retinol and lutein supplements should not be recommended for lung cancer prevention, particularly among smokers	126
Cancer	Systematic review and metaanalysis	9 trials of high methodological quality (total subject population, 104 196) were included	Supplementation for β-carotene and vitamin E versus placebo	β-carotene supplementation was associated with an increase in the cancer incidence and cancer mortality among smokers, whereas vitamin E supplementation had no effect	198
Lung cancer	Cochrane review meta-analysis	Only randomised controlled trials comparing any eligible intervention with placebo were included. Male and female non-smokers of all ages. Male and female healthy smokers of all ages; ≥5 cigarettes/d	Dietary supplementation with vitamins, minerals (selenium, zinc or others) and other agents, natural or synthetic, such as isothiocyanates, flavonoids, monoterpenes or pharmaceuticals such as NAC, alone or in combinations, at any doses	There is some evidence that the use of β-carotene supplements could be associated with a small increase in lung cancer incidence and mortality in smokers	127
Pneumonia	Prospective cohort study	7469 male smokers aged 50–69 years who started to smoke at ≥21 years; ≥5 cigarettes/d	Supplementation with 50 mg/d of vitamin E for 5–8 years versus placebo	There is a strong evidence of benefit from vitamin E against pneumonia in elderly males; however, this effect is heterogeneous in the ATBC study; thus, it should be analysed in selected subpopulations	139
Cardiovascular diseases	Randomised, placebo-controlled, double-blind, crossover study	26 healthy smokers (20 cigarettes/d for the last 5 years)	Dietary flavonoid supplementation for 2 weeks (Concord grape juice, containing 472·8 mg total polyphenols/240 ml, precisely: hydroxycinnamates 162 mmol/l, flavonols 76 mmol/l, flavan-3-ols 434 mmol/l, anthocyanins 296 mmol/l) versus placebo	There is some evidence that flavonoid supplementation could have favourable effects on cardiovascular health, improving inflammatory and fibrinolytic status in healthy smokers and attenuating acute smoking induced increase in ICAM-1 and PAI-1 levels	249

Table 2. (*Continued*)

Smoking-related disease	Studies	Characteristic	Intervention	Conclusions	References
Vascular endothelial function (VEF)	Randomised, placebo-controlled, double-blind study	30 healthy smokers divided into two groups: placebo group (9 male + 5 female; aged 22·3 ± 1·2 years; 11·5 ± 0·9 cigarettes/d; 3·8 ± 1·3 pack-years); γ-tocopherol-rich supplementation group (11 male + 5 female; aged 21·6 ± 1·0 years; 13·3 ± 1·4 cigarettes/d; 3·5 ± 0·8 pack-years)	Participants were required to quit smoking during the week of the treatment. One group received a placebo for one week (a corn oil capsule containing 0·07 mg α-tocopherol and 0·18 mg γ-tocopherol); one group received a γ-tocopherol-rich vitamin E supplement for 1 week (containing 500 mg γ-tocopherol, 62 mg α-tocopherol, 24 mg β-tocopherol and 6 mg δ-tocopherol)	Short-term γ-tocopherol-rich supplementation in combination with smoking cessation improved vascular endothelial function beyond that from smoking cessation alone in young smokers, probably by decreasing the proinflammatory mediators TNF-α and myeloperoxidase	141
Pulmonary function and wheezing	Randomised, placebo-controlled, double-blind study	235 newborns (76 newborns of pregnant non-smokers + 159 newborns of randomised pregnant smokers). Pregnant smokers were divided into two groups: vitamin C treated group ($n = 76$, aged 26·6 ± 6·2 years, 41 % smoking ≥ 10 cigarettes/d; 25 % asthmatic); Placebo group ($n = 83$, aged 25·5 ± 5·5 years, 36 % smoking ≥ 10 cigarettes/d; 22 % asthmatic). Follow-up assessment including wheezing was assessed through age 1 year, and pulmonary function tests PFTs were performed at age 1 year	Pregnant smokers were supplemented with 500 mg/d of vitamin C during pregnancy versus placebo (ground cornstarch in gel capsules). A group of pregnant non-smokers was prospectively studied as a reference group	Vitamin C supplementation seems to decrease the effects of smoking in pregnancy on newborn pulmonary function and respiratory morbidities, since supplemental vitamin C taken by pregnant smokers improved newborn pulmonary function and decreased wheezing through 1 year in the offspring	250
Prostate cancer, lung cancer and overall mortality	Randomised, placebo-controlled, double-blind study	25 563 men after the end of the Alpha-Tocopherol, Beta-Carotene Cancer Prevention (ATBC) study, were followed for 18 years (aged 50–69 years; 75 % current smokers, 25 % former smokers; average 18 cigarettes/d)	During the ATBC study, participants were assigned to one of the 4 intervention regimens: α-tocopherol (dl-α- tocopheryl acetate 50 mg/d) alone, β-carotene (20 mg/d) alone, both α-tocopherol and β-carotene, or placebo. The trial period started in 1985/1988 and continued until 1993. This report includes participants followed through national registries through 30 April 2011 (an 18-year period)	Supplementation with α-tocopherol and β-carotene appeared to have no late effects on cancer incidence once ended (only a moderate dose of α-tocopherol showed preventive effect on prostate cancer approximately 8 years post-trial)	251
Bladder cancer	Meta-analysis	Studies were identified in PubMed and EmbaseFor, and they had to fulfil the following criteria: (1) exposure of interest was vitamin C, vitamin D or vitamin E; (2) outcome of interest was bladder cancer; (3) relative risk (RR) or odds ratio with 95 % CI was provided or data available to calculate them; (4) conducted in humans; (5) for dose–response analysis, the number of cases and participants or person-years for each category of vitamins must also be provided (or data available to calculate them)	Assessing the association of vitamin C, D and E with risk of bladder cancer, analysing studies about vitamin C (vitamin C from diet plus supplement (8 studies), vitamin C from diet (14 studies), vitamin C from supplement (9 studies), circulating vitamin C (1 study)); vitamin D (vitamin D from diet plus supplement (3 studies), circulating vitamin D (4 studies)); vitamin E (vitamin E from diet plus supplement (6 studies), vitamin E from diet (9 studies), vitamin E form supplement (7 studies), circulating α-tocopherol (4 studies), circulating γ-tocopherol (3 studies))	Vitamin D and E (especially α-tocopherol) seem to be inversely associated with the risk of bladder cancer among smokers but not among non-smokers; on the contrary, γ-tocopherol seems to be positively associated with bladder cancer	252

population, as the evidence supporting the beneficial effects of antioxidant supplements is still ambiguous, if not entirely negative. Results from the vitamins and lifestyle (VITAL) study, for example, suggest that long-term use of single β-carotene, retinol and lutein supplements should not be recommended for lung cancer prevention, particularly among smokers[126]. A Cochrane review also found that subjects at risk for lung cancer (i.e. smokers) taking β-carotene supplement had a statistically significant increased risk of lung cancer incidence, lung cancer mortality and all-cause mortality[127]. However, this finding has not been ascertained among those not at risk of lung cancer[127]. In smokers, the meta-analysis of randomised controlled trials suggests that β-carotene supplementation was associated with an increased risk not only of lung cancer but also of gastric cancer[128]. Strong evidence from randomised controlled trials conducted in heavy smokers and asbestos-exposed workers, i.e. the β-carotene and retinol efficacy trial (CARET)[129] and the α-tocopherol and β-carotene cancer prevention (ATBC) study[130], showed that high-dose β-carotene supplements may increase the risk of lung cancer and of death from lung cancer, CVDs, and any cause. This harmful effect was not observed among healthy male physicians in the Physicians' Health Study in the USA, which found lack of effect of long-term supplementation with β-carotene on the incidence of malignant neoplasms and CVD[131].

It is worth noting that the negative effect of β-carotene on lung cancer incidence and mortality among subjects at high risk of lung cancer at baseline (i.e. smokers) was persistent even when combined with vitamin A or E[121,132]. These studies confirm that prevention of cancer through β-carotene supplementation should not be recommended in smokers.

Within this context, according to the 2018 report of the World Cancer Research Fund/American Institute for Cancer Research (https://www.wcrf.org/dietandcancer), β-carotene supplements and, in general, dietary supplements are not recommended for cancer prevention, especially in smokers, while it is advisable to take natural antioxidants and vitamins through the diet. Therefore, caution should be taken, especially in smokers, when considering dietary supplementation with β-carotene.

Concerning the negative effect of β-carotene, it has been proposed that high intake of carotenoids may even enhance smoke-induced oxidative stress in smokers[133]. A possible explanation is that CS modifies the chemical composition of these antioxidants, turning them into pro-oxidants[134]. Indeed, β-carotene can easily form oxidation products with pro-oxidant effects, especially at high concentrations in the oxidative environment of the smoker's lung characterised by increased cell oxidative stress and decreased antioxidant defence[135]. Moreover, excessive intake of antioxidant supplements could lead to 'antioxidative stress', that is, the increased antioxidant potential of the cell, where antioxidants might attenuate or block the cellular adaptive stress responses that are induced by low levels of ROS acting as regulators of intracellular signalling pathways[136]. This suggests that dysregulated ROS homeostasis may contribute to many human diseases[137]. High-dose antioxidant supplements may alter the redox balance with deleterious effects on cellular functions, which results in a consequent alteration of the organ functionality.

Furthermore, male smokers supplemented with β-carotene developed metabolomic profiles consistent with the induction of cytochrome P450 enzymes, the primary metabolisers of xenobiotics[138]. These findings may shed light on the increased mortality associated with β-carotene supplementation in the ATBC study, and suggest the need to explore potential interactions between drugs and food supplements[138].

Some encouraging results have also been achieved on the administration of antioxidant supplements to smokers. A secondary analysis of the α-tocopherol, β-carotene cancer prevention study in Finland on male smokers ($n = 7469$, age 50–69 years, who started smoking ≥5 cigarettes/d at ≥21 years) suggests that intervention with 50 mg/d of vitamin E for 5–8 years decreases the incidence of pneumonia[139], which is a major risk factor for the development of the acute respiratory distress syndrome[140].

Short-term (7 d) γ-tocopherol-rich supplementation in combination with smoking cessation improved vascular endothelial function beyond that from smoking cessation alone in young smokers, probably by decreasing proinflammatory mediators, TNF-α and myeloperoxidase[141]. In healthy smokers who received nicotine replacement therapy, oral administration of a γ-tocopherol-rich mixture of tocopherols improved vascular endothelial function and decreased oxidative stress, which was assessed by urinary 8-iso-15(S)-prostaglandin F2α and was inversely correlated to endothelial function[142]. Long-term (36 months) supplementation with vitamin E lowered oxidative stress by 21 % in smokers, as measured by urinary 8-iso-prostaglandin F2α, whereas no effect was observed for combined vitamin E and selenium or selenium alone intervention[143]. As CS-induced oxidative stress is thought to lower levels of plasma omega-3 fatty acids, a study evaluated the effects of omega-3 fatty acid supplementation on oxidative stress in heavy-smoker males, showing that high dose of omega-3 fatty acid supplements for 3 months decreases oxidative stress index (i.e. total oxidant status/total antioxidant capacity)[144].

Taken together, all these studies on smokers highlight that, if you take an antioxidant supplement, the best choice is a balanced multivitamin supplement containing no more than 100 % of the recommended dietary allowance (RDA) of most micronutrients[113,114]. In this regard, in a randomised, double-blind, placebo-controlled trial of 14 641 male physicians (ex-smokers $n = 5856$; current smokers $n = 527$; age 64·3 ± 9·2 years), daily multivitamin supplementation modestly but significantly reduced the risk of total cancer[117]. Excessive (more than expected according to the RDA) intake of antioxidants can have deleterious effects.

2.3. Antioxidant-rich diet in smokers

The human diet represents a source of many different compounds endowed with antioxidant activity, mainly vitamins, polyphenols and flavonoids (Fig. 2). While the intake of fruits and vegetables worldwide remains low[145], the beneficial effect on health of a diet rich in fruit and vegetable is well known in the general population[146–149]. Just to give an example, the European Prospective Investigation Into Cancer and Nutrition (EPIC), a multi-centre prospective study carried out in ten European countries (Denmark, France, Germany, Greece,

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Italy, The Netherlands, Norway, Spain, Sweden and the United Kingdom), including 519 978 participants (366 521 women and 153 457 men, age 35–70 years)[147] found that a diet high in fruit and vegetable was inversely associated with all-cause mortality (but it was driven mainly by CVD mortality), presumably due to the protection offered by diet-derived antioxidants against the development of diseases related to oxidative stress. The findings from the EPIC study also showed that the risks of upper gastrointestinal tract cancers, colorectal cancer and liver cancer were inversely associated with intakes of fruit and/or vegetables and/or fibre[150].

Overall, all these studies highlighted that, in the general population, there is evidence of beneficial effects of a higher intake of fruits and vegetables. Nevertheless, further findings from the EPIC cohort, obtained combining data from the previous EPIC study and analysing total fruit and vegetable consumption as well as individual subtypes, do not support a clear inverse association between fruit and vegetable consumption and colon or rectal cancer beyond a follow-up of more than 10 years[151]. These findings agree with the conclusion by the Continuous Update Project of the World Cancer Research Fund and American Institute for Cancer Research, highlighting limited evidence of an inverse association between fruit and vegetable consumption and colon and/or rectal cancer[152].

The low plasma concentrations of almost all low-molecular-mass antioxidants commonly found in smokers (Table 1) suggest that a diet rich in antioxidants may be particularly beneficial for maintaining good health in this population. High dietary antioxidant intake from fruits and vegetables are thought to be protective against oxidative stress, thus providing a potential mechanism through which they can prevent CS-related diseases.

Over the past two decades, many epidemiologic studies and meta-analyses have investigated the effectiveness of an antioxidant-rich diet to decrease the risk of smoking-related diseases in smokers (Table 3). For example, in the EPIC study, among 1830 incident cases of lung cancer (mean follow-up of 8·7 years), the risk of squamous cell carcinomas in current smokers was reduced by 15 % with an increase of 100 g/d of combined fruit and vegetables (HR 0·85; 95 % CI 0·76, 0·94), while no clear effects were seen for the other histological subtypes of lung cancer[153]. Moreover, the inverse association between fruit and vegetable consumption and mortality seemed stronger for participants with a body mass index > 30 or with high alcohol consumption (>30 g/d in women and >60 g/d in men), and it was suggested even for smokers[147].

A recent large prospective study (the E3N prospective cohort study initiated in 1990) of middle-aged French women has included 4619 deaths among 1 199 011 person-years of follow-up (no smokers 20 978, passive smokers 17 844, ex-smokers 23 814, current smokers 9876). It highlights the importance of fruit and vegetable consumption for the prevention of all-cause and CVD mortality (but not for cancer mortality), especially among current smokers[154]. Antioxidant-rich diets are also associated with a slower rate of lung function decline in older current smokers[155].

Former or current tobacco smoking is the predominant risk factor for development of COPD, a well-known risk factor for lung cancer. Exposure to CS is a mutual aetiology underlying both diseases, accounting for almost 90 % of cases. Inflammatory responses in smokers and patients with COPD involve the activation of redox-sensitive transcription factors, such as NF-κB, which in turn amplify inflammation and oxidative stress. Two recent large population-based prospective studies in Swedish men, including 44 335 men, aged 45–79 years[156], and women, including 34 739 women, aged 48–83 years[157], with no history of COPD at baseline, confirmed the inverse and independent association between high long-term consumption of fruits (in both men and women) and vegetables (in men only) and incidence of COPD (35 % lower risk in men, 37 % lower risk in women). The preventive effect of dietary antioxidants was more evident among current and ex-smokers, probably because of increased oxidative stress due to smoking compared with never smoking, and the persistent oxidative burden even after smoking cessation[156,157].

A pooled analysis with more than 3000 case subjects suggests that a diet high in carotenoid-rich fruits and vegetables (e.g. carrots for α-carotene, sweet potatoes and green leafy vegetables for β-carotene, tomatoes for lycopene, citrus fruits for β-cryptoxanthin, and green leafy vegetables for lutein and zeaxanthin[158]) offers many health benefits, including a possible reduced risk of breast cancer in the general population[159]. This result agrees with a recent case–control study on Chinese women (561 cases and 561 controls), which showed an inverse association between the consumption of dietary carotenoids and breast cancer risk[160]. This protective effect has also been observed in smokers. The Rotterdam study reported indeed that a low intake of dietary α-carotene and β-carotene was associated with a higher risk of breast cancer among smokers[161]. These results agree with findings from the Swedish Mammography Screening Cohort, which found a decreased risk of breast cancer in smokers with high intake of dietary α-carotene and β-carotene[162].

The Japan public health centre based prospective study investigated the association between dietary intake of antioxidant vitamins and the incidence of total and ischemic stroke[163]. The study involved (between 1995 and 1997) 82 044 Japanese men and women aged 45–74 years, and, during 983 857 person-years of follow-up until the end of 2009, it documented 3541 incident total strokes and 2138 ischemic strokes. Dietary intakes of α-carotene, β-carotene, α-tocopherol and vitamin C were not inversely associated with the incidence of total stroke and ischemic stroke adjusted for cardiovascular risk factors. When stratified by current smoking status, dietary vitamin C intake was inversely associated with the incidence of total stroke and ischemic stroke among non-smokers but not smokers[163].

A diet rich in antioxidants reputed for its beneficial effects on human health is the traditional Mediterranean diet (the dietary pattern usually consumed among the populations bordering the Mediterranean Sea), which has been inscribed on the heritage list of the United Nations Educational, Scientific and Cultural Organization[164]. The Mediterranean diet is based on high consumption of fruits and vegetables, cereals, olive oil, potatoes, poultry, beans, nuts, lean fish and dairy products, low intake of red meat, and moderate consumption of red wine[165]. Protective mechanisms of the Mediterranean diet include antioxidant activity, anti-inflammatory activity, anti-mutagenic and

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Table 3. Studies evaluating the effect of an antioxidant-rich diet (i.e. fruit- and vegetable-rich diet) in smokers

Smoking-related disease	Study	Characteristics	Intervention	Conclusions	References
Bladder cancer	Case–control study	200 subjects (172 males, 28 females aged from <50 to >80 years), with histologically confirmed transitional cell carcinoma of the bladder and 385 controls. 55 current smokers, 112 ex-smokers. Cigarettes/d from <5 to > 20	Vegetable and fruit intakes	Fruit consumption may decrease the effect of smoking on developing bladder cancer. Antioxidants, found in fruit, may protect against the damage caused by free radicals found in cigarette smoke	253
Colorectal adenoma	Randomised trial	33 971 subjects; non-smokers $n = 15\,762$; former smokers $n = 15\,525$; current smokers $n = 2718$	Adherence to the U.S. Food Guide recommendations, the Dietary Approaches to Stop Hypertension (DASH) Eating Plan, or a Mediterranean dietary pattern	Following the current U.S. dietary recommendations or a Mediterranean dietary pattern is associated with reduced risk of colorectal adenoma, especially in men. In women, adherence to the USDA Food Guide recommendations was associated with reduced risk of colorectal adenoma only in current smokers and women who were normal weight	177
Lung cancer	Prospective cohort study	2190 male subjects (age 55–69 years). Never smokers $n = 277$; former smokers $n = 1128$; current smokers $n = 785$; cigarettes/d 14·8 (mean)	Supplementation with salad vegetables pattern, cooked vegetables pattern, pork processed meat and potatoes pattern, sweet foods pattern, or brown/white bread substitution pattern	The salad vegetables dietary pattern was associated with decreased risk of lung cancer. This inverse association was most evident among current and former smokers	254
Lung cancer (squamous cell carcinoma)	Cohort study	478 535 subjects; male 30 %, female 70 %. Non-smokers 49 %, former smokers 27 %, current smokers 22 %. Age at recruitment 51 ± 9·9 years. After a mean follow-up of 8·7 years, 1830 participants were newly diagnosed with a first incident lung cancer	Increasing fruit and vegetable consumption by 100 g/d	In current smokers, the consumption of vegetables and fruits combined and separately may reduce lung cancer risk, in particular the risk of squamous cell carcinoma	153
Lung function decline	Prospective cohort study	1441 older subjects 710 male + 731 female; aged 73·5 ± 2·8 years; former smokers $n = 640$, current smokers $n = 97$; 30·3 ± 27·7 pack-years	High vitamin C and high intake of fruits and vegetables	The intake of nutrients with antioxidant properties may modulate lung function decline in older smokers	155
Impaired lung function	Cohort study	207 smokers (27·1 ± 16·3 pack-years) without respiratory disease; aged 50·7 ± 9·0 years; 91 male + 116 female	Evaluating dietary intake information using a 45-item food-frequency questionnaire (FFQ) validated for the Spanish population, including the average frequency of consumption of food items during the previous 12 months. Three dietary patterns were obtained using principal component analysis, which explained 31 % of variation: alcohol-consumption, Westernised, and Mediterranean-like pattern	In smokers without respiratory disease, the Mediterranean-like pattern appears to be associated with preserved lung function; on the contrary, alcohol-consumption and Westernised patterns are associated with impaired lung function, especially in women	174
Urothelial cell bladder cancer	Cohort study (EPIC* study)	477 312 subjects. Male 29·8 %, female 70·2 %. Aged 52·2 ± 9·9 years. Non-smokers 43 %, smokers 57 %. During an average follow-up of 11 years, 1425 participants (70·9 % male) were diagnosed with a first primary urothelial cell bladder cancer (UCC)	Estimating the level of adherence to a traditional Mediterranean diet (MD), using the relative Mediterranean diet score (rMED). The rMED is an 18-point linear score that incorporates nine key dietary components: seven components presumed to reflect the MD (fruit, nuts and seeds, vegetables, legumes, fish, olive oil and cereals) and two components presumed not to reflect the MD (dairy products and meat); it includes also alcohol consumption. It is calculated as a function of energy density (g/d/2000 kcal) and divided into tertiles	The Mediterranean diet is not significantly associated with risk of urothelial cell bladder cancer in the overall EPIC population, but it appears to reduce risk in current smokers	173

Table 3. (*Continued*)

Smoking-related disease	Study	Characteristics	Intervention	Conclusions	References
Lung cancer	Cohort study (COSMOS* screening study)	5203 healthy smokers (current smokers or ex-smokers from <10 years; ≥20 pack-year); aged ≥50 years. During a mean screening period of 5·7 years, 178 of 4336 participants were diagnosed with lung cancer	Evaluating the average daily quantities of foods and energy consumed by participants over the preceding year using the validated self-administered food frequency questionnaire (FFQ) developed for the Italian component of the EPIC study. The frequency of the consumption of 188 food items and beverages was used to calculate the alternate Mediterranean diet (aMED) score. The aMED is a 9-point linear score that incorporates components presumed to reflect the MD (vegetables, fruits, nuts, cereals, legumes) and components presumed not to reflect the MD (red and processed meat); it includes also alcohol consumption	Among heavy smokers, high red meat consumption and low adherence to a Mediterranean diet are associated with increased risk of lung cancer	175
COPD (chronic obstructive pulmonary disease)	Prospective cohort study	44 335 Swedish men, aged 60·2 ± 9·7 years with no history of COPD at baseline. 24·3 % current smokers, 38·5 % ex-smokers, 37·2 % non-smokers. During a mean follow-up of 13·2 years, 1918 incident cases of COPD were ascertained	Evaluating dietary intake information over the preceding year using a validated self-administered 96-item food frequency questionnaire (FFQ). It was used to calculate the recommended food score (RFS) and the non-RFS. The RFS included 19 food items that are recommended (7 cereal products, 5 types of fish and seafood, 3 different low-fat dairy products, soyabean products, orange/grapefruit juice, nuts/almonds and olive oil). The non-RFS included 13 food items non-recommended (3 unprocessed red meat items, 5 processed meat products, 3 high-fat dairy products, white bread, sweets, combined potato chips/popcorn and fried potatoes/French fries, mayonnaise and ice cream)	High consumption of fruits and vegetables is associated with reduced COPD incidence in both current and ex-smokers, but not in never-smokers	156
Cardiovascular diseases	Randomised, controlled trial	100 male smokers were divided into three groups: control ($n = 34$; aged 56 ± 12 years; 6–35 cigarettes/d); antioxidant-rich diet ($n = 33$; aged 57 ± 12 years; 5–40 cigarettes/d); kiwifruit ($n = 33$; aged 57 ± 12 years; 5–25 cigarettes/d)	The kiwifruit group received 3 kiwifruits/d, whereas the antioxidant-rich diet group received a comprehensive combination of antioxidant-rich foods for 8 weeks. The control group was advised to follow their habitual diet	Intake of kiwifruit may help to reduce risk factors for CVD, since it showed beneficial effects on blood pressure and platelet aggregation in male smokers	255
Cardiovascular diseases	Observational cohort study	1031 Eastern Finnish smokers; men, aged 46–65 years. During the median 15·9-year follow-up, 122 deaths from CVDs were identified, so the population was divided into two groups: men without CVD death ($n = 909$; aged 56·0 ± 6·7 years; 9·5 ± 21·6 pack-years); men with CVD death ($n = 122$; aged 59·5 ± 5·7 years; 24 ± 36·7 pack-years)	Measuring serum lycopene, α-carotene and β-carotene concentrations and evaluating simultaneously cardiovascular risk factors as high BMI, systolic blood pressure, diastolic blood pressure, smoking and LDL-cholesterol	Low concentrations of serum ß-carotene may increase the risk for CVD mortality among male smokers	256
Colorectal cancer (CRC)	Case–control study	500 subjects from the area of Attica: 250 patients with CRC (aged 63 ± 12 years; 59 % male, 41 % female; 34·8 % never smokers, 26·4 % current smokers, 38·8 % former smokers); 250 healthy subjects (aged 55 ± 13 years; 44·8 % male, 55·2 % female; 51·6 % never smokers, 29·2 % current smokers; 19·2 % former smokers)	Collecting dietary information using a validated semi-quantitative 69-question food frequency questionnaire. It was used to calculate the MedDietScore. The MedDietScore is an accurate and valid 55-point linear score that evaluates the level of adherence to the MD, and it has a good discriminating ability for gastrointestinal cancers	Adherence to the Mediterranean diet reduces the detrimental association of smoking habits with colorectal cancer, suggesting benefits with regard to CRC morbidity and mortality	178

Table 3. (*Continued*)

Smoking-related disease	Study	Characteristics	Intervention	Conclusions	References
Colon and rectal cancer	Prospective cohort study	442 961 subjects (29·3 % male, 70·7 % female; aged 38·3–63·0 years; 50·8 % never smokers, 22·5 % current smokers, 26·7 % former smokers). After an average of 13 years of follow-up, 3370 participants were diagnosed with colon or rectal cancer	Assessing the diet reflecting the past 12 months using centre-specific dietary questionnaires (DQ), designed to reflect local dietary patterns. This study focuses on consumption of 5 subtypes of fruits (berries, citrus fruits, grapes, hard fruits, stone fruits) and eight vegetables (cabbages, fruiting vegetables, grain and pod vegetables, leafy vegetables, mushrooms, onion and garlic, root vegetables, stalk vegetables). Fruit consumption included fresh, dried and canned fruits. Each fruit or vegetable item that was consumed at least once every 2 weeks was added into a diet diversity score (DDS). Four DDS were calculated: one for all 49 fruit and vegetable items, one for all 16 fruit items, one for all 33 vegetable items and one for the eight subtypes of vegetables	It suggested a lower risk of colon cancer with high consumption of fruit and vegetables, but there is not a clear inverse association between fruit and vegetable consumption and colon or rectal cancer beyond a follow-up of more than 10 years	151
Impaired lung function	Prospective cohort study	4402 subjects: Rotterdam Study cohort I (RS-I) ($n = 1133$; 56·3 % female, 43·7 % male; aged 79 ± 4 years; 33·3 % never smokers; 59 % former smokers; 7·7 % current smokers) + RS-II ($n = 1320$; 55·4 % female, 44·6 % male; aged 72 ± 5 years; 33·4 % never smokers; 56·7 % former smokers; 9·9 % current smokers) + RS-III ($n = 1949$; 58 % female, 42 % male; aged 56 ± 6 years; 35·5 % never smokers; 51·3 % former smokers; 13·2 % current smokers)	Assessing the past year dietary intake using a 389-item semi-quantitative food frequency questionnaire, based on an existing validated FFQ developed for Dutch adults. Dietary data were converted into nutrient intakes (including daily lutein intake and total energy intake) using the Dutch Food Composition Tables of 2006 and 2011	There is not an independent association between lutein intake and lung function in adults. However, high lutein intake seems to improve lung function in smokers	257
Impaired lung function	Prospective cohort study	839 participants from the VA (Veterans Affairs) Normative Aging Study divided into quartiles second to their total anthocyanin intake: Q1 = 1·1 (0·5, 1·6) mg/d ($n = 211$, aged 65·8 ± 7·1 years; 9·5 % current smokers; 14·2 % recent quitters (<10 years); 50·7 % long-time quitters (≥10 years); 25·6 % never smokers); Q2 = 3·6 (2·8, 4·4) mg/d ($n = 208$, aged 67·6 ± 7·0 years; 6·7 % current smokers; 13 % recent quitters (<10 years); 50 % long-time quitters (≥10 years); 30·3 % never smokers); Q3 = 12·7 (8·0, 13·7) mg/d ($n = 210$, aged 67·1 ± 6·5 years; 3·3 % current smokers; 10 % recent quitters (<10 years); 58·1 % long-time quitters (≥ 10 years); 28·6 % never smokers); Q4 = 21·1 (16·5, 27·4) mg/d ($n = 210$, aged 66·8 ± 6·7 years; 2·9 % current smokers; 9·5 % recent quitters (<10 years); 55·7 % long-time quitters (≥10 years); 31·9 % never smokers). FEV_1 and FVC were measured at 2 and up to 5 visits between 1992 and 2008	Assessing the average daily dietary intakes of food and beverage items using a self-administered, validated, semi-quantitative FFQ adapted from the questionnaire used in the Nurses' Health Study. A database for assessment the different flavonoid subclasses intake was constructed (based on the updated and expanded USDA flavonoid content of foods, the proanthocyanidin databases and other sources), so that yearly average intake of major flavonoid subclasses (anthocyanins, flavanones, flavan-3-ols, flavonols, flavones, and polymers) was calculated from FFQ at each visit	Higher dietary anthocyanin intake is associated with an attenuation of age-related lung function decline in in elderly men, both in current, former and never smokers	258

Table 3. (*Continued*)

Smoking-related disease	Study	Characteristics	Intervention	Conclusions	References
Breast cancer	Prospective cohort study	3209 women participating in the Rotterdam Study (aged 55 years and older; 80·2 % never smokers, 19·1 % current smokers, 0·7 % no smoking information). During a median follow-up of 17 years, 199 cases with breast cancer were identified	Assessing the overall dietary antioxidant capacity, evaluating the dietary ferric reducing antioxidant potential (FRAP), and individual dietary antioxidant intake (i.e. vitamin A, C, E, selenium, flavonoids and carotenoids) using a food frequency questionnaire. Regarding FRAP, each food's contribution to FRAP was calculated on the basis of the Antioxidant Food Table published by the Institute of Nutrition Research, University of Oslo, which includes measurements (ability of antioxidants in food items to reduce ferric iron to ferrous iron) of >3000 foods	High overall dietary antioxidant capacity is associated with a lower risk of breast cancer. Particularly, smokers subgroup showed higher risk of breast cancer with a low intake of α- and ß-carotene	161
Cancer, cardiovascular disease and respiratory illness	Review	An overview of emerging evidence and published studies that cover the interaction between the Mediterranean diet and smoking	Investigating the existing evidence about whether adherence to the Mediterranean diet may have a role as an effect modifier of active and passive smoking on human health	The literature indicates that the existence of a partial interaction between adherence to the Mediterranean diet and the health effects of smoking is possible and that it may protect against cancer, CVD and respiratory illness	171
Cancer, cardiovascular disease and nervous system diseases	Prospective cohort study	1 199 011 person-years (women; aged 52·9 ± 6·7; 28·9 % never smokers, 26·6 % passive smoking only, 32·8 % former smokers, 13·6 % current smokers). During 16·5 years of follow-up, 4619 deaths were recorded, including 2726 from cancer, 584 from cardiovascular diseases, 265 from nervous system diseases, 296 from external causes, and 571 from other diseases	Assessing the antioxidant capacity of human diet. A validated dietary history questionnaire was used to investigate usual food intake; in contained questions about quantity, frequency and quality of food groups/individual foods. Mean daily intake in nutrients was evaluated using a food composition table derived from the French food composition table of the French Information Center on Food Quality. Dietary non-enzymatic antioxidant capacity (NEAC) was evaluated using two complementary methods: ferric ion reducing antioxidant power (FRAP) and total radical-trapping antioxidant parameter (TRAP). The contributions of foods to these two measures of antioxidant capacity were calculated using a database created by Pellegrini *et al.*	Antioxidant consumption is inversely associated with mortality from all causes, cancer and CVD. It seems to be relevant for mortality prevention, especially among current smokers	154
Oral cavity and pharyngeal (OCP) cancer	Case–control study	768 cases of oral and pharyngeal cancer (77·2 % male, 22·8 % female; median age 58 years (range 22–79 years); 15·1 % never smokers, 17·6 % ex-smokers, 67·3 % current smokers) and 2078 controls (65·8 % male, 34·2 % female; median age 59 years (range 19–79 years); 49·7 % never smokers, 23·0 % ex-smokers, 27·3 % current smokers) were included in the study (Italy and Switzerland, 1997–2009)	Subjects' dietary habits during the 2 years before cancer diagnosis or hospitalisation (for controls) were assessed through a valid (Decarli *et al.*, 1996) and reproducible (Franceschi *et al.*, 1993, 1995) food frequency questionnaire (FFQ), including information on weekly consumption of 78 foods, recipes, beverages and lifestyle habits (e.g. tobacco smoking and alcohol drinking). Food items were combined into 18 food groups. An Italian food composition database (Gnagnarella *et al.*, 2004) was used to estimate the daily intake of nutrients and total energy; the residual method (Willett and Stampfer, 1986) was used to evaluate the role of macronutrients independently from total energy intake	This study confirms and further quantifies that a diet rich in fruits and vegetables and poor in meat and products of animal origin has a favourable role against OCP cancer, while an opposite diet together with tobacco and alcohol consumption increases 10- to over 20-fold the risk for OCP cancer	259

Table 3. (*Continued*)

Smoking-related disease	Study	Characteristics	Intervention	Conclusions	References
Lung cancer	Systematic review and meta-analysis	27 prospective studies were identified in PubMed and several databases up to December 2014. They met the following criteria: (1) being a randomised, controlled trial or prospective study with cohort, case–cohort or nested case–control design; (2) report-adjusted estimates of the relative risk (RR) (e.g. HR, risk ratio or OR) and 95 % confidence intervals for the association of fruits and/or vegetables and lung cancer incidence or mortality; (3) for dose–response meta-analysis, studies should provide a quantitative measure of the intake	Assessing the association of vegetables and fruit intake with risk of lung cancer, analysing studies about: total fruit and vegetables and lung cancer ($n = 14$), vegetables and lung cancer ($n = 22$), cruciferous vegetables ($n = 11$), green leafy vegetables ($n = 9$), fruits and lung cancer ($n = 27$), citrus fruits and lung cancer ($n = 13$)	Fruit and vegetable consumption has a protective role in lung cancer aetiology, although eliminating tobacco smoking stays the best strategy to prevent lung cancer	260

anti-proliferative properties, involvement in cell signalling, cell cycle regulation, and angiogenesis[166,167]. Even if the exact mechanisms by which an increased adherence to the traditional Mediterranean diet exerts its positive health effects have not yet been clarified, the most important adaptations induced by adherence to the Mediterranean diet have been summarised in a recent article[168].

A meta-analysis that investigated more than four million subjects suggested that the Mediterranean diet is associated with significant reduction in overall mortality and CVD and cancer risks in the general population[148,169]. Just to give an example, a recent study on the elderly adults with high cardiovascular risk ($n = 7216$, age 55–80 years, 6-year follow-up) showed that participants who consumed in total nine or more servings/d of fruits plus vegetables had a hazard ratio 0·60 of CVD in comparison with those consuming <5 servings/d[170].

The Mediterranean diet could have a modestly but significantly protective role against active and passive CS effects[171]. Cigarette smoking is associated with urothelial cell damage, leading to chronic inflammatory bladder disease and, therefore, increasing urothelial cell bladder cancer risk[172]. The EPIC evaluated the association between adherence to the Mediterranean diet and risk of urothelial cell bladder cancer, the most common form of bladder cancer. It suggested that adherence to the Mediterranean diet may decrease the risk of urothelial cell bladder cancer in current smokers, especially among heavy long-term smokers, although the interaction was not significant[173].

As expected, the effects of smoking on the functionality of the respiratory system are direct and could be serious and lasting. Therefore, the possible benefits of the Mediterranean diet were evaluated also in respiratory organs. In a recent cross-sectional study, which analysed baseline data from randomised representative smokers without respiratory diseases ($n = 207$, aged 35–70 years), the Mediterranean diet appears to be associated with preserved lung function[174]. Moreover, a study based on 5203 participants, aged ≥50 years, who were current smokers or had quit smoking for <10 years and had smoked at least 20 pack-years, showed that adherence to the Mediterranean diet was significantly associated with reduced lung cancer risk[175].

Given the association between smoking and colorectal cancer development[9], studies have been conducted on the possible protective effects of the Mediterranean diet in smokers. A meta-analysis revealed that ever smokers had 18 % higher risk of colorectal cancer as compared with never smokers, and this association was dose-dependent regarding pack-years[176]. Epidemiological data indicated that the Mediterranean diet has protective effect against the development of colorectal adenomas, more markedly among current smokers[177]. A case–control study conducted on colorectal cancer patients ($n = 250$; age 63 ± 12 years; 26·4 % current smokers) versus non-diseased subjects ($n = 250$; age 55 ± 13 years; 29·2 % current smokers) indicated that adherence to the Mediterranean diet may mitigate the adverse effects of smoking on colorectal cancer development, suggesting indirect benefits of adherence to this antioxidant-rich diet over colorectal cancer morbidity and mortality[178].

The beneficial effects of fruits, vegetables and some other foods (e.g. dry legumes and cereals) and beverages (e.g. green

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tea) have been attributed, at least in part, to their high content of polyphenols (of which the largest group is flavonoids), which are recognised compounds able to reduce oxidative stress and inflammation[179]. Polyphenols are present in fruits and vegetables in concentrations up to several 100 mg/100 g, thereby constituting the major class of diet-derived antioxidants[180].

The effects of a diet rich in polyphenol-filled foods have been analysed and summarised in a recent systematic review[181]. Here we will focus our attention on studies specifically conducted on smokers. A randomised controlled clinical trial in male smokers suggested that dietary polyphenols modulate the expression of genes related to cellular stress defence in smokers' blood cells[182]. A further randomised controlled trial suggested a protective role of blueberries (a single 300 g serving of fresh-frozen blueberries) on reactive hyperaemia and systolic blood pressure in young smokers ($n = 16$, age 23·6 ± 0·7 years, smoking 15 ± 1 cigarettes/d) after acute exposure to the smoke of one cigarette[183].

Polyphenols are also the main bioactive constituents of green tea, which in recent years has earned great attention in relation to its health benefits against a variety of human diseases[184]. A review summarising the results of the intervention studies on the consumption of green tea and related antioxidant effects, published until June 2010, concluded that there is limited evidence that regular consumption of green tea in amounts of at least 0·6–1·5 l/d may increase plasma antioxidants, with beneficial effects of green tea consumption being more likely in smokers[185]. By contrast, evidence from epidemiological studies suggests an inverse association between green tea intake and lung cancer risk among never smokers but not among smokers[186]. It is also worth considering that, although the antioxidant activity of polyphenols is well recognised in the prevention of a variety of human diseases (e.g. CVD and certain types of cancer) in the general population[187], polyphenols can even display pro-oxidant activities at high doses or in the presence of transition metals, such as iron and copper[188,189], as in gastric juice and intestinal content[190]. Moreover, if consumed very frequently (>1 l/d) as a hot drink, green tea has been associated with increased incidence of oesophageal cancer in some countries, such as India[191].

Epidemiological studies, short-term randomised controlled trials, and preclinical studies also attributed the benefits associated with the consumption of fruit and vegetables to the presence of flavonoids, a class of polyphenolic compounds abundantly present in foods and beverages of vegetable origin (e.g. red/blue coloured fruits, citrus fruits, apples, broccoli, peppers, black and, especially, green tea)[192]. Results from both epidemiological studies and short-term randomised trials showed beneficial effects of dietary flavonoids on CVD in the general population[193]. For example, 93 600 women (aged 25–42 years) from the Nurses' Health Study (NHS) II, healthy at baseline (1989), were followed for 18 years to examine the relationship between anthocyanins and other flavonoids (total flavonoid intake 58–643 mg/d; anthocyanin intakes 2–35 mg/d) and risk of myocardial infarction[194]. The combined intake of anthocyanin-rich food (i.e. blueberries and strawberries) seemed to be associated with a decreased risk of myocardial infarction in young women, comparing those consuming more than three servings/week to those with lower intake. However, in stratified analyses, the inverse association between anthocyanins and myocardial infarction was stronger among women who never smoked compared with those who currently smoked[194]. A study conducted recently on 56 048 participants of the Danish Diet, Cancer, and Health cohort has shown that an achievable (of approximately 500 mg/d) dietary intake of total and individual flavonoid subclasses is associated with a lower risk of all-cause, related to CVD, and cancer-related mortality especially in current smokers and individuals with high alcohol consumption, with the highest flavonoids intakes being more beneficial[195].

3. Discussion and perspectives

Since there is clear evidence that long-term exposure to CS can result in systemic oxidants–antioxidants imbalance to the entire organism, as reflected by low levels of plasma antioxidants in smokers (Table 1), it has been speculated that specific antioxidant supplements or an antioxidant-rich diet could be particularly beneficial for smokers. The potential beneficial effects of antioxidants to reinforce the body's antioxidant defence systems in smokers are overemphasised by a plethora of studies in animal models and/or *in vitro* cellular models of exposure to CS. These are important tools in the assessment of CS-induced oxidative stress; however, the species-specific functional differences limit the predictive value of animal experiments in the translation of these observations to humans, and the variations of cell functionality deriving from the emergent properties of complex cellular systems (tissues and organs) cannot be inferred from the knowledge of the single system components[38,196]. For example, rats and mice appear to be more sensitive to antioxidants than humans; therefore, antioxidant supplementation is more likely to reduce oxidative damage in rodents than in humans[14,197].

Many randomised intervention trials and meta-analysis failed to detect any beneficial effect of antioxidant supplements in smokers, and sometimes the use of antioxidants has turned out to be even counterproductive (Table 2). In this regard, evidence from large randomised trials and meta-analyses suggests that a long-term use and/or high dose of individual β-carotene, retinol and lutein supplements should be avoided, especially in smokers[198,199,126–128] (Table 2).

The benefit of a diet rich in fruit and vegetables has been attributed to their content of many phytochemical microelements with various antioxidant activity and chemical properties. But why is the ingestion of specific types of food more beneficial than the intake of the isolated antioxidants? It can be assumed that the additive and synergistic effects of the micronutrients in fruits and vegetables could be responsible for their beneficial antioxidant activities[200,201]. Moreover, the antioxidants present in vegetables, which have hormetic effects as many phytochemicals, are supplied in a balanced way, not only in terms of composition but also of the necessary dose, thus maintaining the fragile redox homeostasis of the organism[202]. This may partially explain why no antioxidant supplement can replace the combination of micronutrients in fruits and vegetables to achieve the

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observed health benefits. Therefore, the increase in fruit and vegetable consumption could be a logical strategy to increase the dietary antioxidant intake and to decrease oxidative stress, potentially leading to reduced risk of oxidative stress-related diseases. In this regard, dietary guidelines for Americans recommend that it would be beneficial to eat at least nine servings (4·5 cups) of fruits and vegetables a day, specifically four servings (two cups) of fruits and five servings (2·5 cups) of vegetables, in a 2000 kcal diet[203].

In smokers, an antioxidant-rich diet potentially may provide a preventive strategy to lower the risk of CS-related diseases. The health benefits of antioxidants were observed predominantly when they were consumed within their natural food matrices, while preventive effects derived from an optimal antioxidant-rich diet may not be reproduced with high doses (>RDA) of the single antioxidant supplements. However, large, randomised intervention trials and meta-analysis demonstrated that the preventive strategy based on a diet rich in fruits and vegetables in smokers showed only a modest protective effect to reduce the risk of CS-related diseases (Table 3). Hence, it is insufficient to effectively counteract the CS-related oxidative stress and diseases.

So, as CS is a modifiable risk factor, quitting smoking is the best prevention and the most effective way to reduce the detrimental health effects of CS, although it may not be sufficient to repair all the oxidative damages caused by long-term exposure to CS[4,24,204,205]. A randomised controlled cessation trial examined the effects of smoking cessation in a population of 434 current smokers in 12 months of follow-up. Quitters ($n = 55$) had significantly increased levels of blood plasma GSH compared with subjects who continued to smoke ($p < 0{\cdot}01$)[206].

A recent systematic review and meta-analysis evaluated the association between smoking reduction and some health risks in observational studies. Smokers were categorised as follows: heavy smokers smoked ≥15–20 cigarettes/d, moderate smokers smoked 10–19 cigarettes/d and light smokers smoked <10 cigarettes/d[207]. Compared with current heavy smokers, decreased lung cancer risk was ascertained for people who reduced smoking by more than 50 %, from heavy to moderate or to light. The meta-analysis also showed a lower risk of CVD for smokers who reduced their smoking habit from heavy to light, but not smokers who reduced by more than 50 % and reduced from heavy to moderate smoking. Therefore, substantial smoking reduction can decrease lung cancer risks, although the risk of lung cancer remains high, whereas the relationships between smoking reduction and CVDs as well as all-cause mortality remain doubtful. Thus, complete smoking cessation is by far the most effective strategy for cancer and CVD prevention in smokers.

E-cigarettes are among the electronic nicotine delivery systems (ENDS), a heterogeneous class of products in which an electrically powered coil is used to heat a liquid matrix, or e-liquid, that contains nicotine, solvents (e.g. propylene glycol, vegetable glycerine) and, usually, flavouring[208].

The concentration of nicotine in e-liquid varies substantially: it can reach 36 mg/ml or more[208]. Some ENDS can deliver to venous blood the same dose of nicotine, at the same rate as a conventional cigarette, while others cannot[209,210]. This heterogeneity in ENDS nicotine delivery is in contrast with the regulated nicotine replacement products used to help to stop smoking, such as chewing gum and nicotine patch, which deliver nicotine more reliably, but to lower plasma concentrations and at a slower rate[211,212]. E-cigarettes too are claimed as a smoking cessation aid, but even if some research suggests that e-cigarettes could help smokers to quit or reduce smoking[213–215], additional studies are necessary to determine whether this is true long term[216].

ENDS toxicant emissions depend on many factors, including device construction, device power, liquid constituents and user behaviour. Toxicants in ENDS are still present in the liquid, or they are produced when the liquid is heated. The main toxicants present in the liquid are propylene glycol and vegetable glycerine, which represent the 80–97 % of the content of most e-liquids[217]. Both are toxic, especially at high doses[218], but little is known about their effects after long-term chronic exposition. E-liquid also contains flavourings, compounds that are usually added to food, whose effects on health after being heated and aerosolised are unknown[219]. Some contaminants findable in e-liquids are diethylene glycol, ethylene glycol and ethanol[220]. Most e-cigarette aerosols contain many metals, probably originating from some atomiser components, such as cadmium, nickel and lead[221]. Other e-cigarettes toxicants are formaldehyde, acetaldehyde, acrolein, acetone, furans and benzene. Some studies reported 9–450 times lower toxicant concentrations in e-cigarettes than conventional cigarettes (e.g. ref. [222]). However, other studies demonstrated that the toxicant level in e-cigarettes can be higher than in conventional cigarettes[216]. This discrepancy could depend on the fact that e-cigarette components vary widely, since they are almost unregulated and produced by numerous companies, making it difficult to evaluate their safety[223].

Regarding health risks, e-cigarettes are reported to cause adverse effects after short-term use, comparable to some tobacco-smoking effects (e.g. increase in impedance, peripheral airway flow resistance and oxidative stress)[224], while little is known about the health impact of long-term use[225]. Reviews on e-cigarettes' impact on health concluded that ENDS are not harmless but are generally less dangerous than regular cigarettes[226,227]. Cancer risk is in most cases lower, even if in some cases, for some products, it can be comparable to that of tobacco smoke[228]. Regarding cardiovascular risk, mainly dependent on the presence of nicotine, some studies comparing e-cigarettes and conventional cigarettes found fewer CVD biomarkers for ENDS, while others observed no differences[229]. Finally, the toxicity in the lung remains unknown, even if it has been speculated that e-cigarettes, inducing inflammation, can increase the risk for lung cancer and COPD[230].

Given these premises, we do not have the basic knowledge necessary to speculate if an antioxidant-rich diet or antioxidant supplements could be beneficial to an e-cigarette smoker likewise a conventional cigarette smoker.

CS remains a strong risk factor for premature mortality in older subjects. Current smokers and former smokers had an increased mortality of 2 and 1·3 times, respectively, compared with non-smokers. In any case, quitting smoking is beneficial even at advanced age[231]. Efforts to support smoking cessation at all ages should be therefore a public health priority.

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Nevertheless, most smokers are unable or unwilling to quit smoking, and for this reason, the problem of ensuring an improvement in their health quality remains of interest.

Future studies to better define interventional dietary strategies in smokers should focus on three points. Firstly, exhaustive macro- and micronutrient databases are needed to evaluate the absorption, bioavailability and metabolism of dietary antioxidant in smokers. It is worth noting that only a part of the diet's antioxidants, that is, the bioavailable portion, is absorbed, reaches the systemic circulation without undergoing any chemical modification, and can carry out its healthy effects. For diet-derived antioxidants and phytochemicals to be absorbed, they must be released from the food matrix and presented to the brush border of the small intestine in such a state that they can enter the enterocytes by passive diffusion or active transport systems. Metabolic modifications (e.g. dehydroascorbate to ascorbate), or transformations (e.g. β-carotene to retinol), or packaging in the enterocyte (e.g. β-carotene, retinol, vitamin E), occur before secretion in a biocompatible form, through the enterocyte basal membrane, into blood capillaries (water-soluble micronutrients) or the chyliferous vessels (liposoluble micronutrients). Understanding this concept of bioavailability is essential for the production of food and supplements, for nutritional assessment and for determining diet–health relationships, both in the general population and in smokers who, among various diseases, also have intestinal dysfunctions[232] that could alter phytochemical absorption. For these last reasons, more exhaustive studies are needed to determine whether a diet rich in fruit and vegetable with high levels of bioavailable antioxidants could protect against oxidative damage and the subsequent development of CS-related diseases.

Secondly, it seems appropriate to carry out further studies on the correlation between the diet and the profile of plasma antioxidants, on oxidative damage to lipids, proteins and DNA, and on biomarkers of oxidative damage. The potential benefits of a high fruit and vegetable intake on the plasma antioxidant profile, on oxidative damage to lipids, proteins and DNA, and on biomarkers of oxidative stress (e.g. GSH/glutathione disulphide ratio) were evaluated in a randomised, free-living, open placebo-controlled cross-over trial of 3 weeks, with a 2-week washout period between treatments. This study included twenty-two male smokers aged 18–50 years, with a relatively low vegetable and fruit consumption[233]. The high intake of fruit and vegetable increased plasma levels of vitamin C, α-carotene, β-carotene, β-cryptoxanthin and zeaxanthin. However, no effects were demonstrated on any biomarker of oxidative damage to lipids, proteins and DNA or biomarkers of oxidative stress[233]. It could be that the increased levels of antioxidants were not sufficiently high to show beneficial effects to the selected biomarkers, or, alternatively, the method of selection of male smokers with a relatively low fruit and vegetable intake might have been inadequate to select subjects with really increased oxidative stress. Also, the population studied is small and limited to male smokers, so results should be replicated in larger studies to corroborate these findings.

More recently, it has been demonstrated that the induction of cell-mediated cytoprotective pathways, including antioxidant enzymes, protein chaperones, growth factors and mitochondrial proteins, is responsible, with an hormetic process, for the beneficial effects of a diet rich in fruits and vegetables[202,234]. A study in which the effects of a plant-based diet were measured in smokers' blood cells using microarray genome technology demonstrated the up-regulation of target genes for transcription factors involved in stress responses through antioxidant and non-antioxidant activity, offering some potential mechanistic explanations for the beneficial health effects of diets high in fruit and vegetable in smokers[182].

Thirdly, it is very important to consider that the hypothesis suggesting beneficial effects of antioxidants for the prevention or treatment of CS-related diseases might be simplistic because antioxidants can also have negative effects if they alter the delicate redox balance of the organisms[235].

4. Conclusions

Global projections of mortality data estimate that total tobacco-attributable deaths will increase to over 8 million in 2030[236]. Because of the widespread diffusion of the CS habit and its consequent severe impact on human health, interventions to reduce CS-related diseases should have a high priority worldwide. Despite the small or modest reduction of CS-related disease risk by a diet rich in fruit and vegetable observed in smokers, the most efficient way to prevent smoking-related oxidative stress and CS-related diseases remains smoking cessation. Therefore, smoking cessation should be the main objective of public health for the prevention of CS-related diseases and to limit the economic impact for community. As stated by Beaglehole and colleagues: 'A tobacco-free world by 2040, where less than 5 % of the world's adult population use tobacco, is socially desirable, technically feasible, and could become politically practical. This will prevent hundreds of millions of unnecessary deaths during the remainder of this century and safeguard future generations from the ravages of tobacco use activity'[237].

Waiting for a 'tobacco-free world', smokers have to consider that smoking cessation, consuming a diet rich in fruit and vegetable, avoiding obesity, hyperglycaemia and hypercholesterolemia[238], and exercising regularly (a mild pro-oxidant challenge that triggers a beneficial adaptation[239]) could minimise levels of oxidative stress/damage. This lifestyle is therefore essential for maintaining a reasonably good health for as long as possible.

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References

1. WHO Media Centre (2015) Fact sheet No. 339. www.who.int/medicentre/factsheets/fs339/en/ (accessed February 2020).
2. Proctor RN (2015) The cigarette catastrophe continues. *Lancet* **385**, 938–939. doi: 10.1016/S0140-6736(15)60519-0.
3. Schroeder SA (2013) New evidence that cigarette smoking remains the most important health hazard. *New Engl J Med* **368**, 389–390. doi: 10.1056/NEJMe1213751.
4. Jha P, Ramasundarahettige C, Landsman V, *et al.* (2013) 21st-century hazards of smoking and benefits of cessation in the United States. *New Engl J Med* **368**, 341–350. doi: 10.1056/NEJMsa1211128.
5. WCRF/AICR, World Cancer Research Fund/American Institute for Cancer Research (2007) *Food, Nutrition, Physical Activity, and the Prevention of Cancer: A Global Perspective*. Washington, DC: AICR.
6. Heuvers ME, Hegmans JP, Stricker BH, *et al.* (2012) Improving lung cancer survival; time to move on. *BMC Pulm Med* **12**, 77. doi: 10.1186/1471-2466-12-77.
7. Lortet-Tieulent J, Soerjomataram I, Ferlay J, *et al.* (2014) International trends in lung cancer incidence by histological subtype: adenocarcinoma stabilizing in men but still increasing in women. *Lung Cancer* **84**, 13–22. doi: 10.1016/j.lungcan.2014.01.009.
8. IARC, International Agency for Research on Cancer, Lyon (2004) IARC monographs on the evaluation of carcinogenic risk in humans. Tobacco Smoke and Involuntary Smoking. Vol. 83.
9. USDHHS, U.S. Department of Health and Human Services (2014) *The Health Consequences of Smoking – 50 Years of Progress. A Report of the Surgeon General*. Atlanta, GA: U.S. Department of Health and Human Services, Centers for Disease Control and Prevention, National Center for Chronic Disease Prevention and Health Promotion, Office on Smoking and Health.
10. Papaioannou AI, Koutsokera A, Tanou K, *et al.* (2010) The acute effect of smoking in healthy and asthmatic smokers. *Eur J Clin Invest* **40**, 103–109. doi: 10.1111/j.1365-2362.2009.02221.x.
11. Yamaguchi Y, Nasu F, Harada A, *et al.* (2007) Oxidants in the gas phase of cigarette smoke pass through the lung alveolar wall and raise systemic oxidative stress. *J Pharmacol Sci* **103**, 275–282. doi: 10.1254/jphs.FP0061055.
12. Alberg AJ (2002) The influence of cigarette smoking on circulating concentrations of antioxidant micronutrients. *Toxicology* **180**, 121–137. doi: 10.1016/s0300-483x(02)00386-4.
13. Stocker R. (2016) Antioxidant defenses in human blood plasma and extra-cellular fluids. *Arch Biochem Biophys* **595**, 136–139. doi: 10.1016/j.abb.2015.11.021.
14. Halliwell B & Gutteridge JMC (2015) *Free Radicals in Biology and Medicine*. Fifth Edition. Oxford University Press. DOI: 10.1093/acprof:oso/9780198717478.001.0001
15. Rossi R, Giustarini D, Milzani A, *et al.* (2009) Cysteinylation and homocysteinylation of plasma protein thiols during ageing of healthy human beings. *J Cell Mol Med* **13**, 3131–3140. doi: 10.1111/j.1582-4934.2008.00417.x.
16. Colombo G, Clerici M, Giustarini D, *et al.* (2012) Redox albuminomics: oxidized albumin in human diseases. *Antioxid Redox Signal* **17**, 1515–1527. DOI: 10.1089/ars.2012.4702
17. Figueiredo JC, Crockett SD, Snover DC, *et al.* (2015) Smoking-associated risks of conventional adenomas and serrated polyps in the colorectum. *Cancer Causes Control* **26**, 377–386. doi: 10.1007/s10552-014-0513-0.
18. Bailie L, Loughrey MB & Coleman HG. (2017) Lifestyle risk factors for serrated colorectal polyps: a systematic review and meta-analysis. *Gastroenterology* **152**, 92–104. doi: 10.1053/j.gastro.2016.09.003.
19. Davenport JR, Su T, Zhao Z, *et al.* (2018) Modifiable lifestyle factors associated with risk of sessile serrated polyps, conventional adenomas and hyperplastic polyps. *Gut* **67**, 456–465. doi: 10.1136/gutjnl-2016-312893.
20. Chow WH, Dong LM & Devesa SS. (2010) Epidemiology and risk factors for kidney cancer. *Nat Rev Urol* **7**, 245–257. doi: 10.1038/nrurol.2010.46.
21. Dossus L, Boutron-Ruault MC, Kaaks R, *et al.* (2014) Active and passive cigarette smoking and breast cancer risk: results from the EPIC cohort. *Int J Cancer* **134**, 1871–1888. doi: 10.1002/ijc.28508.
22. Islami F, Moreirad DM, Boffetta P, *et al.* (2014) A systematic review and meta-analysis of tobacco use and prostate cancer mortality and incidence in prospective cohort studies. *Eur Urol* **66**, 1054–1064. doi: 10.1016/j.eururo.2014.08.059.
23. USDHHS, U.S. Department of Health and Human Services (2010) *How Tobacco Smoke Causes Disease: The Biology and Behavioral Basis for Smoking-Attributable Disease: A Report of the Surgeon General*. Atlanta, GA: U.S. Department of Health and Human Services, Centers for Disease Control and Prevention, National Center for Chronic Disease Prevention and Health Promotion, Office on Smoking and Health.
24. Mons U, Müezzinler A, Gellert C, *et al.* (2015) CHANCES Consortium. Impact of smoking and smoking cessation on cardiovascular events and mortality among older adults: meta-analysis of individual participant data from prospective cohort studies of the CHANCES consortium. *BMJ* **350**, h1551. doi: 10.1136/bmj.h1551.
25. Jahangir E, Lipworth L, Edwards TL, *et al.* (2015) Smoking, sex, risk factors and abdominal aortic aneurysms: a prospective study of 18 782 persons aged above 65 years in the Southern Community Cohort Study. *J Epidemiol Community Health* **69**, 481–488. doi: 10.1136/jech-2014-204920.
26. Tang W, Yao L, Roetker NS, *et al.* (2016) Lifetime risk and risk factors for abdominal aortic aneurysm in a 24-year prospective study: the ARIC study (Atherosclerosis Risk in Communities). *Arterioscler Thromb Vasc Biol* **36**, 2468–2477. doi: 10.1161/ATVBAHA.116.308147.
27. Reiner Ž (2018) The importance of smoking cessation in patients with coronary heart disease. *Int J Cardiol* **258**, 26–27. doi: 10.1016/j.ijcard.2018.02.009.
28. Prugger C, Wellmann J, Heidrich J, *et al.*; EUROASPIRE Study Group. (2015) Readiness for smoking cessation in coronary heart disease patients across Europe: results from the EUROASPIRE III survey. *Eur J Prev Cardiol* **22**, 1212–1219. doi: 10.1177/2047487314564728.
29. Prugger C, Wellmann J, Heidrich J, *et al.*; EUROASPIRE Study Group. (2014) Passive smoking and smoking cessation among patients with coronary heart disease across Europe: results from the EUROASPIRE III survey. *Eur Heart J* **35**, 590–598. doi: 10.1093/eurheartj/eht538.
30. Arnett DK, Blumenthal RS, Albert MA, *et al.* (2019) 2019 ACC/AHA Guideline on the primary prevention of cardiovascular disease: executive summary: a report of the American college of cardiology/American heart association task force on clinical practice guidelines. *J Am Coll Cardiol* **74**, 1376–1414. doi: 10.1016/j.jacc.2019.03.009. Erratum in: *J Am Coll Cardiol* 2019 74, 1428–1429. Erratum in: *J Am Coll Cardiol* 2020 75, 840.
31. Duncan MS, Freiberg MS, Greevy RA Jr, *et al.* (2019) Association of smoking cessation with subsequent risk of cardiovascular disease. *JAMA* **322**, 642–650. doi: 10.1001/jama.2019.10298.
32. Ahmed AA, Patel K, Nyaku MA, *et al.* (2015) Risk of heart failure and death after prolonged smoking cessation: role of

https://doi.org/10.1017/S0954422421000093 Published online by Cambridge University Press

amount and duration of prior smoking. *Circ Heart Fail* **8**, 694–701. doi: 10. 1161/CIRCHEARTFAILURE.114.001885
33. McElroy JP, Carmella SG, Heskin AK, *et al.* (2019) Effects of cessation of cigarette smoking on eicosanoid biomarkers of inflammation and oxidative damage. *PLoS One* **14**, e0218386. doi: 10.1371/journal.pone.0218386.
34. Yanbaeva DG, Dentener MA, Creutzberg EC, *et al.* (2007) Systemic effects of smoking. *Chest* **131**, 1557–1566. doi: 10. 1378/chest.06-2179.
35. Colombo G, Dalle-Donne I, Orioli M, *et al.* (2012) Oxidative damage in human gingival fibroblasts exposed to cigarette smoke. *Free Radic Biol Med* **52**, 1584–1596. DOI: 10.1016/j. freeradbiomed.2012.02.030
36. Gornati R, Colombo G, Clerici M, *et al.* (2013) Protein carbonylation in human endothelial cells exposed to cigarette smoke extract. *Toxicol Lett* **218**, 118–128. doi: 10.1016/j.toxlet.2013. 01.023.
37. Colombo G, Clerici M, Giustarini D, *et al.* (2014) Pathophysiology of tobacco smoke exposure: Recent insights from comparative and redox proteomics. *Mass Spectrom Rev* **33**, 183–218. DOI: 10.1002/mas.21392
38. Dalle-Donne I, Colombo G, Gornati R, *et al.* (2017) Protein carbonylation in human smokers and mammalian models of exposure to cigarette smoke: focus on redox proteomics studies. *Antioxid Redox Signal* **26**, 406–426. doi: 10.1089/ars. 2016.6772.
39. Colombo G, Garavaglia ML, Astori E, *et al.* (2019) Protein carbonylation in human bronchial epithelial cells exposed to cigarette smoke extract. *Cell Biol Toxicol* **35**, 345–360. doi: 10.1007/s10565-019-09460-0.
40. Dalle-Donne I, Garavaglia ML, Colombo G, *et al.* (2020) Cigarette smoking and glutathione. Focus on *in vitro* cellular models. *Toxicol in vitro* **65**, 104818. doi: 10.1016/j.tiv.2020. 104818.
41. Cammisotto V, Nocella C, Bartimoccia S, *et al.* (2021) The role of antioxidants supplementation in clinical practice: focus on cardiovascular risk factors. *Antioxidants (Basel)* **10**, 146. doi: 10.3390/antiox10020146.
42. Geiss O & Kotzias D (2007) Tobacco, cigarettes and cigarette smoke. An overview. European Commission. Directorate-General Joint Research Centre. Institute for Health and Consumer Protection.
43. Hoffmann D & Hoffmann I (1997) The changing cigarette, 1950-1995. *J Toxicol Environ Health* **50**, 307–364. doi: 10. 1080/009841097160393. PMID: 9120872.
44. McNeill A, Joossens L, Jarvis M (2004) Review of the implementation of the Tobacco Product Regulation Directive 2001/37/EC, Commissioned by ASH London, March 2004.
45. Directive 2014/40/EU of the European Parliament and of the Council of 3 April 2014. *Official Journal of the European Union*, 29 April 2014.
46. Lu X, Cai J, Kong H, *et al.* (2003) Analysis of cigarette smoke condensates by comprehensive two-dimensional gas chromatography/time-of-flight mass spectrometry I acidic fraction. *Anal Chem* **75**, 4441–4451. doi: 10.1021/ac0264224.
47. Rodgman A & Perfetti TA (editors) (2013) *The Chemical Components of Tobacco and Tobacco Smoke.* CRC Press, Boca Raton, FL, p. 2065.
48. Moretto N, Facchinetti F, Southworth T, *et al.* (2009) α,β-Unsaturated aldehydes contained in cigarette smoke elicit IL-8 release in pulmonary cells through mitogen-activated protein kinases. *Am J Physiol Lung Cell Mol Physiol* **296**, L839–L848. DOI: 10.1152/ajplung.90570.2008
49. van der Toorn M, Slebos DJ, de Bruin HG, *et al.* (2013) Critical role of aldehydes in cigarette smoke-induced acute airway inflammation. *Respir Res* **14**, 45. doi: 10.1186/1465-9921-14-45.
50. Yeager RP, Kushman M, Chemerynski S, *et al.* (2016) Proposed mode of action for acrolein respiratory toxicity associated with inhaled tobacco smoke. *Toxicol Sci* **151**, 347–364. doi: 10.1093/toxsci/kfw051.
51. Grootveld M, Percival BC, Leenders J, *et al.* (2020) Potential adverse public health effects afforded by the ingestion of dietary lipid oxidation product toxins: significance of fried food sources. *Nutrients* **12**, 974–1024. doi: 10.3390/nu12040974
52. Seet RCS, Lee CYJ, Loke WM, *et al.* (2011) Biomarkers of oxidative damage in cigarette smokers: which biomarkers might reflect acute versus chronic oxidative stress? *Free Radic Biol Med* **50**, 1787–1793. doi: 10.1016/j.freeradbiomed.2011. 03.019.
53. Lykkesfeldt J, Viscovich M & Poulsen HE. (2004) Plasma malondialdehyde is induced by smoking: a study with balanced antioxidant profiles. *Br J Nutr* **92**, 203–206. DOI: 10. 1079/BJN20041191.
54. Lykkesfeldt J. (2007) Malondialdehyde as biomarker of oxidative damage to lipids caused by smoking. *Clin Chim Acta* **380**, 50–58. doi: 10.1016/j.cca.2007.01.028.
55. Chelchowska M, Ambroszkiewicz J, Gajewska J, *et al.* (2011) The effect of tobacco smoking during pregnancy on plasma oxidant and antioxidant status in mother and newborn. *Eur J Obstet Gynecol Reprod Biol* **155**, 132–136. DOI: 10.1016/j. ejogrb.2010.12.006
56. Pignatelli B, Li CQ, Boffetta P, *et al.* (2001) Nitrated and oxidized plasma proteins in smokers and lung cancer patients. *Cancer Res* **61**, 778–784.
57. Rossner P Jr, Terry MB, Gammon MD, *et al.* (2007) Plasma protein carbonyl levels and breast cancer risk. *J Cell Mol Med* **11**, 1138–1148. doi: 10.1111/j.1582-4934.2007.00097.x.
58. Kocyigit A, Selek S, Celik H, *et al.* (2011) Mononuclear leukocyte DNA damage and oxidative stress: the association with smoking of hand-rolled and filter-cigarettes. *Mutat Res* **721**, 136–141. doi: 10.1016/j.mrgentox.2011.01.013.
59. Rahman I (2012) Pharmacological antioxidant strategies as therapeutic interventions for COPD. *Biochim Biophys Acta* **1822**, 714–728. doi: 10.1016/j.bbadis.2011.11.004.
60. Crotty Alexander LE, Shin S & Hwang JH (2015) Inflammatory diseases of the lung induced by conventional cigarette smoke: a review. *Chest* **148**, 1307–1322. DOI: 10.1378/chest.15-0409
61. Goncalves RB, Coletta RD, Silverio KG, *et al.* (2011) Impact of smoking on inflammation: overview of molecular mechanisms. *Inflamm Res* **60**, 409–424. doi: 10.1007/s00011-011-0308-7.
62. Rom O, Avezov K, Aizenbud D, *et al.* (2013) Cigarette smoking and inflammation revisited. *Respir Physiol Neurobiol* **187**, 5–10. DOI: 10.1016/j.resp.2013.01.013
63. Numanami H, Koyama S, Nelson DK, *et al.* (2003) Serine protease inhibitors modulate smoke-induced chemokine release from human lung fibroblasts. *Am J Respir Cell Mol Biol* **29**, 613–619. doi: 10.1165/rcmb.2003-0113OC.
64. Li CJ, Ning W, Matthay MA, *et al.* (2007) MAPK pathway mediates EGR-1-HSP70-dependent cigarette smoke-induced chemokine production. *Am J Physiol Lung Cell Mol Physiol* **292**, L1297–L1303. doi: 10.1152/ajplung. 00194.2006.
65. Oltmanns U, Chung KF, Walters M, *et al.* (2005) Cigarette smoke induces IL-8, but inhibits eotaxin and RANTES release from airway smooth muscle. *Respir Res* **6**, 74. doi: 10.1186/1465-9921-6-74.
66. Rueff-Barroso CR, Trajano ET, Alves JN, *et al.* (2010) Organ-related cigarette smoke-induced oxidative stress is strain-dependent. *Med Sci Monit* **16**, BR 218–226.

https://doi.org/10.1017/S0954422421000093 Published online by Cambridge University Press

67. Barreiro E. (2014) Protein carbonylation and muscle function in COPD and other conditions. *Mass Spectrom Rev* **33**, 219–36. doi: 10.1002/mas.21394.
68. Gould NS, Min E, Gauthier S, *et al.* (2010) Aging adversely affects the cigarette smoke-induced glutathione adaptive response in the lung. *Am J Respir Crit Care Med* **182**, 1114–1122. DOI: 10.1164/rccm.201003-0442OC
69. Gould NS, Min E, Gauthier S, *et al.* (2011) Lung glutathione adaptive responses to cigarette smoke exposure. *Respir Res* **12**, 133. doi: 10.1186/1465-9921-12-133.
70. Gould NS, Min E, Huang J, *et al.* (2015) Glutathione depletion accelerates cigarette smoke-induced inflammation and airspace enlargement. *Toxicol Sci* **147**, 466–474. doi: 10.1093/toxsci/kfv143
71. Dallongeville J, Marecaux N, Fruchart JC, *et al.* (1998) Cigarette smoking is associated with unhealthy patterns of nutrient intake: a meta-analysis. *J Nutr* **128**, 1450–1457.
72. Ma J, Hampl JS & Betts NM. (2000) Antioxidant intakes and smoking status: data from the Continuing Survey of Food Intakes by Individuals 1994–1996. *Am J Clin Nutr* **71**, 774–780. doi: 10.1093/ajcn/71.3.774.
73. Phillips ELR, Arnett DK, Himes JH, *et al.* (2000) Differences and trends in antioxidant dietary intake in smokers and non-smokers, 1980–1992: The Minnesota Heart Survey. *Ann Epidemiol* **10**, 417–423. doi: 10.1016/s1047-2797(00)00064-8.
74. Wei W, Kim Y & Boudreau N (2001) Association of smoking with serum and dietary levels of antioxidants in adults: NHANES III, 1988–1994. *Am J Public Health* **91**, 258–264. doi: 10.2105/ajph.91.2.258.
75. Haibach JP, Homish GG & Giovino GA (2013) A longitudinal evaluation of fruit and vegetable consumption and cigarette smoking. *Nicotine Tob Res* **15**, 355–363. doi: 10.1093/ntr/nts130.
76. Northrop-Clewes CA & Thurnham DI (2007) Monitoring micronutrients in cigarette smokers. *Clin Chim Acta* **377**, 14–38. doi: 10.1016/j.cca.2006.08.028.
77. Lykkesfeldt J, Christen S, Wallock LM, *et al.* (2000) Ascorbate is depleted by smoking and repleted by moderate supplementation: a study in male smokers and nonsmokers with matched dietary antioxidant intakes. *Am J Clin Nutr* **71**, 530–536. DOI: 10.1093/ajcn/71.2.530.
78. Dietrich M, Block G, Norkus EP, *et al.* (2003) Smoking and exposure to environmental tobacco smoke decrease some plasma antioxidants and increase gamma-tocopherol in vivo after adjustment for dietary antioxidant intakes. *Am J Clin Nutr* **77**, 160–166. doi: 10.1093/ajcn/77.1.160.
79. Lykkesfeldt J (2006) Smoking depletes vitamin C: should smokers be recommended to take supplements? In: Halliwell B & Poulsen HE, (editors). *Cigarette smoke and oxidative stress*. Springer Verlag; pp. 237–60.
80. Hakim IA, Harris R, Garland L, *et al.* (2012) Gender difference in systemic oxidative stress and antioxidant capacity in current and former heavy smokers. *Cancer Epidemiol Biomarkers Prev* **21**, 2193–2200. doi: 10.1158/1055-9965.EPI-12-0820.
81. Badea M, Gaman L, Delia C, *et al.* (2019) Trends of lipophilic, antioxidant and hematological parameters associated with conventional and electronic smoking habits in middle-age Romanians *J Clin Med* **8**, 665. doi: 10.3390/jcm8050665.
82. Karademirci M, Kutlu R, Kilinc I (2018) Relationship between smoking and total antioxidant status, total oxidant status, oxidative stress index, vit C, vit E. *Clin Respir J* **12**, 2006–2012. doi: 10.1111/crj.12757.
83. Bassey IE, Gali RM & Udoh AE (2018) Fertility hormones and vitamin E in active and passive adult male smokers in Calabar, Nigeria. *PLoS One* **13**, e0206504. doi: 10.1371/journal.pone.0206504.
84. Carnevale R, Sciarretta S, Violi F, *et al.* (2016) Acute impact of tobacco vs electronic cigarette smoking on oxidative stress and vascular function. *Chest* **150**, 606–612. doi: 10.1016/j.chest.2016.04.012.
85. Lymperaki E, Makedou K, Iliadis S, *et al.* (2015) Effects of acute cigarette smoking on total blood count and markers of oxidative stress in active and passive smokers. *Hippokratia* **19**, 293–297.
86. Shah AA, Khand F, Uddin T, *et al.* (2015) Effect of smoking on serum xanthine oxidase, malondialdehyde, ascorbic acid and α-tocopherol levels in healthy male subjects. *J Med Sci* **31**, 146–149. doi: 10.12669/pjms.311.6148.
87. Jiang Q (2014) Natural forms of vitamin E: metabolism, antioxidant, and anti-inflammatory activities and their role in disease prevention and therapy. *Free Radic Biol Med* **72**, 76–90. doi: 10.1016/j.freeradbiomed.2014.03.035.
88. Sobczak A, Golka D & Szoltysek-Boldys I (2004) The effects of tobacco smoke on plasma alpha- and gamma-tocopherol levels in passive and active cigarette smokers. *Toxicol Lett* **151**, 429–437. doi: 10.1016/j.toxlet.2004.03.010.
89. Helmersson J, Larsson A, Vessby B, *et al.* (2005) Active smoking and a history of smoking are associated with enhanced prostaglandin F2α, interleukin-6 and F_2-isoprostane formation in elderly men. *Atherosclerosis* **181**, 201–207. doi: 10.1016/j.atherosclerosis.2004.11.026.
90. Wei YW, Chuang HY, Huang MC, *et al.* (2009) Comparison of plasma antioxidant levels and related metabolic parameters between smokers and non-smokers. *Kaohsiung J Med Sci* **25**, 423–430. DOI: 10.1016/S1607-551X(09)70537-6
91. Kayan M, Naziro□lu M, Celik O, *et al.* (2009) Vitamin C and E combination modulates oxidative stress induced by X-ray in blood of smoker and nonsmoker radiology technicians. *Cell Biochem Funct* **27**, 424–429.
92. Gabriel HE, Liu Z, Crott JW, *et al.* (2006) A comparison of carotenoids, retinoids, and tocopherols in the serum and buccal mucosa of chronic cigarette smokers versus nonsmokers. *Cancer Epidemiol Biomarkers Prev* **15**, 993–999. doi: 10.1158/1055-9965.EPI-05-0664.
93. Leonard SW, Bruno RS, Paterson E, *et al.* (2003) 5-nitro-gamma-tocopherol increases in human plasma exposed to cigarette smoke in vitro and in vivo. *Free Radic Biol Med* **35**, 1560–1567. doi: 10.1016/j.freeradbiomed.2003.09.010.
94. Zerbinati C, Galli F, Regolanti R, *et al.* (2015) Gas chromatography-mass spectrometry microanalysis of alpha- and gamma-tocopherol in plasma and whole blood. *Clin Chim Acta* **446**, 156–162. doi: 10.1016/j.cca.2015.04.026.
95. Jeanes YM, Hall WL, Proteggente AR, *et al.* (2004) Cigarette smokers have decreased lymphocyte and platelet alpha-tocopherol levels and increased excretion of the gamma-tocopherol metabolite gamma-carboxyethyl-hydroxychroman (gamma-CEHC). *Free Radic Res* **38**, 861–868. doi: 10.1080/10715760410001715149.
96. Lodge JK (2005) Vitamin E bioavailability in humans. *J Plant Physiol* **162**, 790–796. doi: 10.1016/j.jplph.2005.04.012.
97. Borel P, Preveraud D, Desmarchelier C (2013) Bioavailability of vitamin E in humans: an update. *Nutr Rev* **71**, 319–331. doi: 10.1111/nure.12026.
98. Raatz SK, Jahns L, Johnson LAK, *et al.* (2017) Smokers report lower intake of key nutrients than nonsmokers, yet both fall short of meeting recommended intakes. *Nutr Res* **45**, 30–37. doi: 10.1016/j.nutres.2017.07.010.
99. Munro LH, Burton G & Kelly FJ (1997) Plasma RRR-α-tocopherol concentrations are lower in smokers than in non-smokers after ingestion of a similar oral load of this antioxidant vitamin. *Clin Sci* **92**, 87–93. doi: 10.1042/cs0920087.

100. Bruno RS, Ramakrishnan R, Montine TJ, *et al.* (2005) {alpha}-Tocopherol disappearance is faster in cigarette smokers and is inversely related to their ascorbic acid status. *Am J Clin Nutr* **81**, 95–103. doi: 10.1093/ajcn/81.1.95.
101. Traber MG, Winklhofer-Roob BM, Roob JM, *et al.* (2001) Vitamin E kinetics in smokers and nonsmokers. *Free Radic Biol Med* **31**, 1368–1374. doi: 10.1016/s0891-5849(01)00723-7.
102. Bruno RS, Leonard SW, Atkinson J, *et al.* (2006) Faster plasma vitamin E disappearance in smokers is normalized by vitamin C supplementation. *Free Radic Biol Med* **40**, 689–697. doi: 10.1016/j.freeradbiomed.2005.10.051.
103. Bruno RS, Leonard SW, Li J, *et al.* (2005) Lower plasma alpha-carboxyethyl-hydroxychroman after deuterium-labeled alpha-tocopherol supplementation suggests decreased vitamin E metabolism in smokers. *Am J Clin Nutr* **81**, 1052–1059. doi: 10.1093/ajcn/81.5.1052.
104. Ford ES, Li C, Cunningham TJ, *et al.* (2014) Associations between antioxidants and all-cause mortality among US adults with obstructive lung function. *Br J Nutr* **112**, 1662–1673. doi: 10.1017/S0007114514002669.
105. Marangon K, Devaraj S & Jialal I. (1999) Measurement of protein carbonyls in plasma of smokers and in oxidized LDL by an ELISA. *Clin Chem* **45**, 577–578.
106. Nagai K, Betsuyaku T, Kondo T, *et al.* (2006) Long term smoking with age builds up excessive oxidative stress in bronchoalveolar lavage fluid. *Thorax* **61**, 496–502. DOI: 10.1136/thx.2005.049148.
107. Suzuki M, Betsuyaku T, Ito Y, *et al.* (2008) Down-regulated NF-E2-related factor 2 in pulmonary macrophages of aged smokers and patients with chronic obstructive pulmonary disease. *Am J Respir Cell Mol Biol* **39**, 673–682. doi: 10.1165/rcmb.2007-0424OC.
108. Hackett TL, Scarci M, Zheng L, *et al.* (2010) Oxidative modification of albumin in the parenchymal lung tissue of current smokers with chronic obstructive pulmonary disease. *Respir Res* **11**, 180. doi: 10.1186/1465-9921-11-180.
109. Colombo G, Aldini G, Orioli M, *et al.* 2010. Water-soluble alpha,beta-unsaturated aldehydes of cigarette smoke induce carbonylation of human serum albumin. *Antioxid Redox Signal* **12**, 349–364. doi: 10.1089/ars.2009.2806.
110. Colombo G, Rossi R, Gagliano N, *et al.* (2012) Red blood cells protect albumin from cigarette smoke-induced oxidation. *PLoS One* **7**, e29930. doi: 10.1371/journal.pone.0029930.
111. Minetti M & Malorni W. (2006) Redox control of red blood cell biology: the red blood cell as a target and source of prooxidant species. *Antioxid Redox Signal* **8**, 1165–1169. DOI: 10.1089/ars.2006.8.1165.
112. Cimen MY (2008) Free radical metabolism in human erythrocytes. *Clin Chim Acta* **390**, 1–11. doi: 10.1016/j.cca.2007.12.025.
113. Institute of Medicine (US) Panel on Dietary Antioxidants and Related Compounds. (2000) *Dietary Reference Intakes for Vitamin C, Vitamin E, Selenium, and Carotenoids*. Washington (DC): National Academies Press (US). pp. 1–506. DOI: 10.17226/9810.
114. Institute of Medicine (US) Panel on Micronutrients. (2001) *Dietary Reference Intakes for Vitamin A, Vitamin K, Arsenic, Boron, Chromium, Copper, Iodine, Iron, Manganese, Molybdenum, Nickel, Silicon, Vanadium, and Zinc*. Washington (DC): National Academies Press (US). pp. 1–773. DOI: 10.17226/10026.
115. Giustarini D, Dalle-Donne I, Tsikas D, *et al.* (2009) Oxidative stress and human diseases: Origin, link, measurement, mechanisms, and biomarkers. *Crit Rev Clin Lab Sci* **46**, 241–281. doi: 10.3109/10408360903142326.
116. Bjelakovic G, Nikolova D, Gluud LL, *et al.* (2012) Antioxidant supplements for prevention of mortality in healthy participants and patients with various diseases. *Cochrane Database Syst Rev* **3**, CD007176. DOI: 10.1002/14651858.CD007469.pub2
117. Gaziano JM, Sesso HD, Christen WG, *et al.* (2012) Multivitamins in the prevention of cancer in men: The Physicians' Health Study II Randomized Controlled Trial. *JAMA* **308**, 1871–1880. doi: 10.1001/jama.2012.14641.
118. Ye Y, Li J & Yuan Z (2013) Effect of antioxidant vitamin supplementation on cardiovascular outcomes: a meta-analysis of randomized controlled trials. *PLoS ONE* **8**, e56803. doi: 10.1371/journal.pone.0056803
119. Poljsak B, Šuput D & Milisav I (2013) Achieving the balance between ROS and antioxidants: when to use the synthetic antioxidants. *Oxid Med Cell Longev* **2013**, 956792. doi: 10.1155/2013/956792.
120. Myung SK, Ju W, Cho B, *et al.* (2013) Efficacy of vitamin and antioxidant supplements in prevention of cardiovascular disease: systematic review and meta-analysis of randomised controlled trials. *BMJ* **346**, f10 doi: 10.1136/bmj.f10
121. Fortmann SP, Burda BU, Senger CA, *et al.* (2013) Vitamin and mineral supplements in the primary prevention of cardiovascular disease and cancer: An updated systematic evidence review for the U.S. Preventive Services Task Force. *Ann Intern Med* **159**, 824–834. DOI: 10.7326/0003-4819-159-12-201312170-00729
122. Bjelakovic G, Nikolova D & Gluud C. (2014) Antioxidant supplements and mortality. *Curr Opin Clin Nut Metab Care* **17**, 40–44. DOI: 10.1097/MCO.0000000000000009
123. Neuhouser ML, Barnett MJ, Kristal AR, *et al.* (2009) Dietary supplement use and prostate cancer risk in the Carotene and Retinol Efficacy Trial. *Cancer Epidemiol Biomarkers Prev* **18**, 2202–2206. doi: 10.1158/1055-9965.EPI-09-0013.
124. Salehi B, Martorell M, Arbiser JL, *et al.* (2018) Antioxidants: positive or negative actors? *Biomolecules* **8**, 124. doi: 10.3390/biom8040124.
125. Alsharairi NA (2019) The effects of dietary supplements on asthma and lung cancer risk in smokers and non-smokers: a review of the literature. *Nutrients* **11**, pii: E725. doi: 10.3390/nu11040725.
126. Satia JA, Littman A, Slatore CG, *et al.* (2009) Long-term use of beta-carotene, retinol, lycopene, and lutein supplements and lung cancer risk: results from the VITamins And Lifestyle (VITAL) study. *Am J Epidemiol* **169**, 815–828. doi: 10.1093/aje/kwn409.
127. Cortés-Jofré M, Rueda JR, Corsini-Muñoz G, *et al.* (2012) Drugs for preventing lung cancer in healthy people. *Cancer* **127**, 172–184. doi: 10.1002/ijc.28508.
128. Middha P, Weinstein SJ, Männistö S, *et al.* (2019) β-Carotene supplementation and lung cancer incidence in the alpha-tocopherol, beta-carotene cancer prevention study: the role of tar and nicotine. *Nicotine Tob Res* **21**, 1045–1050. doi: 10.1093/ntr/nty115.
129. Omenn GS, Goodman GE, Thornquist MD, *et al.* (1996) Effects of a combination of beta carotene and vitamin A on lung cancer and cardiovascular disease. *N Engl J Med* **334**, 1150–1155. doi: 10.1056/NEJM199605023341802.
130. Alpha-Tocopherol, Beta Carotene Cancer Prevention Study Group. The effect of vitamin E and beta carotene on the incidence of lung cancer and other cancers in male smokers. (1994) *N Engl J Med* **330**, 1029–1035. doi: 10.1056/NEJM199404143301501
131. Hennekens CH, Buring JE, Manson JE, *et al.* (1996) Lack of effect of long-term supplementation with beta carotene on

the incidence of malignant neoplasms and cardiovascular disease. *N Engl J Med* **334**, 1145–1149. doi: 10.1056/NEJM199605023341801.
132. Fortmann SP, Whitlock EP & Burda BU (2014) Vitamin and mineral supplements in the primary prevention of cardiovascular disease and cancer. *Ann Intern Med* **160**, 656. DOI: 10.7326/L14-5009-5
133. Palozza P, Serini S, Trombino S, *et al.* (2006) Dual role of beta-carotene in combination with cigarette smoke aqueous extract on the formation of mutagenic lipid peroxidation products in lung membranes: dependence on pO2. *Carcinogenesis* **27**, 2383–2391. doi: 10.1093/carcin/bgl074.
134. Hurst JS, Contreras JE, Siems WG, *et al.* (2004) Oxidation of carotenoids by heat and tobacco smoke. *Biofactors* **20**, 23–35. doi: 10.1002/biof.5520200103.
135. Palozza P, Simone R & Mele MC (2008) Interplay of carotenoids with cigarette smoking: Implications in lung cancer. *Curr Med Chem* **15**, 844–854. doi: 10.2174/092986708783955400
136. Poljsak B & Milisav I (2012) The neglected significance of "antioxidative stress". *Oxid Med Cell Longev* **2012**, 480895. doi: 10.1155/2012/480895.
137. Finkel T (2011) Signal transduction by reactive oxygen species. *J Cell Biol* **194**, 7–15. DOI: 10.1083/jcb.201102095
138. Mondul AM, Sampson JN, Moore SC, *et al.* (2013) Metabolomic profile of response to supplementation with β-carotene in the Alpha-Tocopherol, Beta-Carotene Cancer Prevention Study. *Am J Clin Nutr* **98**, 488–493. DOI: 10.3945/ajcn.113.062778
139. Hemilä H. (2016) Vitamin E administration may decrease the incidence of pneumonia in elderly males. *Clin Interv Aging* **11**, 1379–85. DOI: 10.2147/CIA.S114515.
140. Tasaka S, Amaya F, Hashimoto S, *et al.* (2008) Roles of oxidants and redox signaling in the pathogenesis of acute respiratory distress syndrome. *Antioxid Redox Signal* **10**, 739–753. doi: 10.1089/ars.2007.1940.
141. Mah E, Pei R, Guo Y, *et al.* (2013) γ-Tocopherol-rich supplementation additively improves vascular endothelial function during smoking cessation. *Free Radic Biol Med* **65**, 1291–1299. doi: 10.1016/j.freeradbiomed.2013.09.016.
142. Mah E, Pei R, Guo Y, *et al.* (2015) Greater γ-tocopherol status during acute smoking abstinence with nicotine replacement therapy improved vascular endothelial function by decreasing 8-iso-15(S)-prostaglandin F2α. *Exp Biol Med* **240**, 527–533. doi: 10.1177/1535370214556948.
143. Guertin KA, Grant RK, Arnold KB, *et al.* (2016) Effect of long-term vitamin E and selenium supplementation on urine F2-isoprostanes, a biomarker of oxidative stress. *Free Radic Biol Med* **95**, 349–356. doi: 10.1016/j.freeradbiomed.2016.03.010.
144. Sadeghi-Ardekani K, Haghighi M & Zarrin R (2018) Effects of omega-3 fatty acid supplementation on cigarette craving and oxidative stress index in heavy-smoker males: a double-blind, randomized, placebo-controlled clinical trial. *J Psychopharmacol* **32**, 995–1002. doi: 10.1177/0269881118788806.
145. Hall JN, Moore S, Harper SB, *et al.* (2009) Global variability in fruit and vegetable consumption. *Am J Prev Med* **36**, 402–409.e5. doi: 10.1016/j.amepre.2009.01.029.
146. Boeing H, Bechthold A, Bub A, *et al.* (2012) Critical review: vegetables and fruit in the prevention of chronic diseases. *Eur J Nutr* **51**, 637–663. DOI 10.1007/s00394-012-0380-y
147. Leenders M, Sluijs I, Ros MM, *et al.* (2013) Fruit and vegetable consumption and mortality: European prospective investigation into cancer and nutrition. *Am J Epidemiol* **178**, 590–602. doi: 10.1093/aje/kwt006.
148. Ros E, Martínez-González MA, Estruch R, *et al.* (2014) Mediterranean diet and cardiovascular health: teachings of the PREDIMED study. *Adv Nutr* **5**, 330S–336S. doi: 10.3945/an.113.005389.
149. Wang X, Ouyang Y, Liu J, *et al.* (2014) Fruit and vegetable consumption and mortality from all causes, cardiovascular disease, and cancer: systematic review and doseresponse meta-analysis of prospective cohort studies. *BMJ* **349**, g4490. doi: 10.1136/bmj.g4490.
150. Bradbury KE, Appleby PN & Key TJ (2014) Fruit, vegetable, and fiber intake in relation to cancer risk: findings from the European Prospective Investigation into Cancer and Nutrition (EPIC). *Am J Clin Nutr* **100**, 394S–398S. doi: 10.3945/ajcn.113.071357
151. Leenders M, Siersema PD, Overvad K, *et al.* (2015) Subtypes of fruit and vegetables, variety in consumption and risk of colon and rectal cancer in the European Prospective Investigation into Cancer and Nutrition. *Intern J Cancer* **137**, 2705–2714. doi: 10.1002/ijc.29640.
152. WCRF/AICR, World Cancer Research Fund/American Institute for Cancer Research. (2010) *WCRF/AICR systematic literature review continuous update project report: the associations between food, nutrition and physical activity and the risk of colorectal cancer*. London: World Cancer Research Fund/American Institute for Cancer Research.
153. Büchner FL, Bueno-de-Mesquita HB, Linseisen J, *et al.* (2010) Fruits and vegetables consumption and the risk of histological subtypes of lung cancer in the European Prospective Investigation into Cancer and Nutrition (EPIC). *Cancer Causes Control* **21**, 357–371. DOI: 10.1007/s10552-009-9468-y
154. Bastide N, Dartois L, Dyevre V, *et al.* (2017) Dietary antioxidant capacity and all-cause and cause-specific mortality in the E3N/EPIC cohort study. *Eur J Nutr* **56**, 1233–1243. doi: 10.1007/s00394-016-1172-6.
155. Bentley AR, Kritchevsky SB, Harris TB, *et al.* (2012) Health ABC Study. Dietary antioxidants and forced expiratory volume in 1 s decline: the Health, Aging and Body Composition study. *Eur Respir J* **39**, 979–984. doi: 10.1183/09031936.00190010.
156. Kaluza J, Larsson SC, Orsini N, *et al.* (2017) Fruit and vegetable consumption and risk of COPD: a prospective cohort study of men. *Thorax* **72**, 500–509. doi: 10.1136/thoraxjnl-2015-207851.
157. Kaluza J, Harris HR, Linden A, *et al.* (2018) Long-term consumption of fruits and vegetables and risk of chronic obstructive pulmonary disease: a prospective cohort study of women. *Int J Epidemiol* **47**, 1897–1909. doi: 10.1093/ije/dyy178.
158. USDA, United States Department of Agriculture, Agricultural Research Service. (2011) National Nutrient Database for Standard Reference, Release 24. http://www.ars.usda.gov/nutrientdata.
159. Eliassen AH, Hendrickson SJ, Brinton LA, *et al.* (2012) Circulating carotenoids and risk of breast cancer: pooled analysis of eight prospective studies. *J Natl Cancer Inst* **104**, 1905–1916. doi: 10.1093/jnci/djs461.
160. Wang L, Li B, Pan MX, *et al.* (2014) Specific carotenoid intake is inversely associated with the risk of breast cancer among Chinese women. *Br J Nutr* **111**, 1686–1695. doi: 10.1017/S000711451300411X.
161. Pantavos A, Ruiter R, Feskens EF, *et al.* (2015) Total dietary antioxidant capacity, individual antioxidant intake and breast cancer risk: the Rotterdam Study. *Int J Cancer* **136**, 2178–2186. doi: 10.1002/ijc.29249.
162. Larsson SC, Bergkvist L & Wolk A (2010) Dietary carotenoids and risk of hormone receptor-defined breast cancer in a

prospective cohort of Swedish women. *Eur J Cancer* **46**, 1079–1085. doi: 10.1016/j.ejca.2010.01.004.
163. Uesugi S, Ishihara J, Iso H, *et al.* (2017) Dietary intake of antioxidant vitamins and risk of stroke: the Japan Public Health Center–based Prospective Study. *Eur J Clin Nutr* **71**, 1179–1185. doi: 10.1038/ejcn.2017.71.
164. UNESCO, United Nations Educational, Scientific and Cultural Organization. (2011) Intangible heritage lists. The Mediterranean diet. http://www.unesco.org/culture/ich/en/RL/00394.
165. Giacosa A, Barale R, Bavaresco L, *et al.* (2013) Cancer prevention in Europe: the Mediterranean diet as a protective choice. *Eur J Cancer Prev* **22**, 90–95. doi: 10.1097/CEJ.0b013e328354d2d7.
166. Dai J, Jones DP, Goldberg J, *et al.* (2008) Association between adherence to the Mediterranean diet and oxidative stress. *Am J Clin Nutr* **88**, 1364–1370. DOI: 10.3945/ajcn.2008.26528
167. Tyrovolas S & Panagiotakos DB (2010) The role of Mediterranean type of diet on the development of cancer and cardiovascular disease, in the elderly: a systematic review. *Maturitas* **65**, 122–130. doi: 10.1016/j.maturitas.2009.07.003.
168. Tosti V, Bertozzi B & Fontana L (2018) Health benefits of the Mediterranean diet: metabolic and molecular mechanisms. *J Gerontol A Biol Sci Med Sci* **73**, 318–326. doi: 10.1093/gerona/glx227.
169. Sofi F, Macchi C, Abbate R, *et al.* (2014) Mediterranean diet and health status: an updated meta-analysis and a proposal for a literature-based adherence score. *Public Health Nutr* **17**, 2769–2782. doi: 10.1017/S1368980013003169.
170. Buil-Cosiales P, Toledo E, Salas-Salvadó J, *et al.* (2016) Association between dietary fibre intake and fruit, vegetable or whole-grain consumption and the risk of CVD: results from the PREvención con DIeta MEDiterránea (PREDIMED) trial. *Br J Nutr* **116**, 534–546. doi: 10.1017/S0007114516002099.
171. Vardavas CI, Flouris AD, Tsatsakis A, *et al.* (2011) Does adherence to the Mediterranean diet have a protective effect against active and passive smoking? *Public Health* **125**, 121–128. doi: 10.1016/j.puhe.2010.11.012.
172. Kispert SE, Marentette J, Campian EC, *et al.* (2017) Cigarette smoke-induced urothelial cell damage: potential role of platelet-activating factor. *Physiol Rep* **5**, e13177. doi: 10.14814/phy2.13177.
173. Buckland G, Ros MM, Roswall N, *et al.* (2014) Adherence to the Mediterranean diet and risk of bladder cancer in the EPIC cohort study. *Int J Cancer* **134**, 2504–2511. DOI: 10.1002/ijc.28573
174. Sorli-Aguilar M, Martin-Lujan F, Flores-Mateo G, *et al.* (2016) Dietary patterns are associated with lung function among Spanish smokers without respiratory disease. *BMC Pulm Med* **16**, 162. doi: 10.1186/s12890-016-0326-x.
175. Gnagnarella P, Maisonneuve P, Bellomi M, *et al.* (2013) Red meat, Mediterranean diet and lung cancer risk among heavy smokers in the COSMOS screening study. *Ann Oncol* **24**, 2606–2611. doi: 10.1093/annonc/mdt302
176. Botteri E, Iodice S, Bagnardi V, *et al.* (2008) Smoking and colorectal cancer: a meta-analysis. *JAMA* **300**, 2765–2778. doi: 10.1001/jama.2008.839.
177. Dixon LB, Subar AF, Peters U, *et al.* (2007) Adherence to the USDA food guide, DASH eating plan, and Mediterranean dietary pattern reduces risk of colorectal adenoma. *J Nutr* **137**, 2443e50. doi: 10.1093/jn/137.11.2443.
178. Kontou N, Psaltopoulou T, Soupos N, *et al.* (2013) The mediating effect of Mediterranean diet on the relation between smoking and colorectal cancer: a case-control study. *Eur J Public Health* **23**, 742–746. doi: 10.1093/eurpub/cks109
179. Tsuda T (2012) Dietary anthocyanin-rich plants: Biochemical basis and recent progress in healthy benefits studies. *Mol Nutr Food Res* **56**, 159–170. doi: 10.1002/mnfr.201100526.
180. Meulenberg EP (2009) Phenolics: occurrence and immunochemical detection in environment and food. *Molecules* **14**, 439–473. doi: 10.3390/molecules14010439.
181. Del Bo' C, Bernardi S, Marino M, *et al.* (2019) Systematic review on polyphenol intake and health outcomes: is there sufficient evidence to define a health-promoting polyphenol-rich dietary pattern? *Nutrients* **11**, 1355. doi: 10.3390/nu11061355.
182. Bøhn SK, Myhrstad MC, Thoresen M, *et al.* (2010) Blood cell gene expression associated with cellular stress defense is modulated by antioxidant-rich food in a randomised controlled clinical trial of male smokers. *BMC Med* **8**, 54. doi: 10.1186/1741-7015-8-54.
183. Del Bo' C, Porrini M, Fracassetti D, *et al.* (2014) A single serving of blueberry (V. corymbosum) modulates peripheral arterial dysfunction induced by acute cigarette smoking in young volunteers: a randomized-controlled trial. *Food Funct* **5**, 3107–3116. doi: 10.1039/c4fo00570h.
184. Butt MS, Ahmad RS, Sultan MT, *et al.* (2015) Green tea and anticancer perspectives: updates from last decade. *Crit Rev Food Sci Nutr* **55**, 792–805. doi: 10.1080/10408398.2012.680205.
185. Ellinger S, Müller N, Stehle P, *et al.* (2011) Consumption of green tea or green tea products: is there an evidence for antioxidant effects from controlled interventional studies? *Phytomedicine* **18**, 903–915. doi: 10.1016/j.phymed.2011.06.006.
186. Yuan JM (2013) Cancer prevention by green tea: evidence from epidemiologic studies. *Am J Clin Nutr* **98**, 1676S–1681S. doi: 10.3945/ajcn.113.058271.
187. Pandey KB & Rizvi SI (2009) Plant polyphenols as dietary antioxidants in human health and disease. *Oxid Med Cell Longev* **2**, 270–278. doi: 10.4161/oxim.2.5.9498.
188. De Marchi U, Biasutto L, Garbisa S, *et al.* (2009) Quercetin can act either as an inhibitor or an inducer of the mitochondrial permeability transition pore: a demonstration of the ambivalent redox character of polyphenols. *Biochim Biophys Acta* **1787**, 1425–1432. doi: 10.1016/j.bbabio.2009.06.002.
189. Bouayed J & Bohn T (2010) Exogenous antioxidants – double-edged swords in cellular redox state: health beneficial effects at physiologic doses versus deleterious effects at high doses. *Oxid Med Cell Longev* **3**, 228–337. DOI: 10.4161/oxim.3.4.12858
190. Halliwell B, Zhao K & Whiteman ML (2000) The gastrointestinal tract: a major site of antioxidant action? *Free Radic Res* **33**, 819–830. doi: 10.1080/10715760000301341.
191. Ganesh B, Talole SD & Dikshit R (2009) Tobacco, alcohol and tea drinking as risk factors for esophageal cancer: a case-control study from Mumbai, India. *Cancer Epidemiol* **33**, 431–434. doi: 10.1016/j.canep.2009.09.002.
192. Carocho M & Ferreira ICFR (2013) The role of phenolic compounds in the fight against cancer–a review. *Anticancer Agents Med Chem* **13**, 1236–1258. doi: 10.2174/18715206113139990301.
193. van Dam RM, Naidoo N & Landberg R (2013) Dietary flavonoids and the development of type 2 diabetes and cardiovascular diseases: review of recent findings. *Curr Opin Lipidol* **24**, 25–33. doi: 10.1097/MOL.0b013e32835bcdff.
194. Cassidy A, Mukamal KJ, Liu L, *et al.* (2013) High anthocyanin intake is associated with a reduced risk of myocardial infarction in young and middle-aged women. *Circulation* **127**, 188–196. DOI: 10.1161/CIRCULATIONAHA.112.122408

https://doi.org/10.1017/S0954422421000093 Published online by Cambridge University Press

195. Bondonno NP, Dalgaard F, Kyrø C, *et al.* (2019) Flavonoid intake is associated with lower mortality in the Danish Diet Cancer and Health Cohort. *Nat Commun* **10**, 3651. doi: 10.1038/s41467-019-11622-x
196. Halliwell B (2008) Are polyphenols antioxidants or pro-oxidants? What do we learn from cell culture and in vivo studies? *Arch Biochem Biophys* **476**, 107–112. doi: 10.1016/j.abb.2008.01.028.k
197. Halliwell B (2011) Free radicals and antioxidants – quo vadis? *Trends Pharmacol Sci* **32**, 125–130. doi: 10.1016/j.tips.2010.12.002.
198. Bardia A, Tleyjeh IM, Cerhan JR, *et al.* (2008) Efficacy of antioxidant supplementation in reducing primary cancer incidence and mortality: systematic review and meta-analysis. *Mayo Clin Proc* **83**, 23–34. doi: 10.4065/83.1.23.
199. Myung SK, Kim Y, Ju W, *et al.* (2010) Effects of antioxidant supplements on cancer prevention: meta-analysis of randomized controlled trials. *Ann Oncol* **21**, 166–179. doi: 10.1093/annonc/mdp286.
200. Wolfe KL, Kang X, He X, *et al.* (2008) Cellular antioxidant activity of common fruits. *J Agric Food Chem* **56**, 8418–8426. doi: 10.1021/jf801381y.
201. Song W, Derito CM, Liu MK, *et al.* (2010) Cellular antioxidant activity of common vegetables. *J Agric Food Chem* **58**, 6621–6629. doi: 10.1021/jf9035832.
202. Martel J, Ojcius DM, Ko YF, *et al.* (2019) Hormetic effects of phytochemicals on health and longevity. *Trends Endocrinol Metab* **30**, 335–346. doi: 10.1016/j.tem.2019.04.001.
203. USDA, United States Department of Agriculture and United States Department of Health and Human Services. (2010) *Dietary Guidelines for Americans 2010*, 7th ed. U.S. Government Printing Office, December, Washington, DC. Available from http://www.dietaryguidelines.gov
204. Louhelainen N, Rytilä P, Haahtela T, *et al.* (2009) Persistence of oxidant and protease burden in the airways after smoking cessation. *BMC Pulm Med* **9**, 25. doi: 10.1186/1471-2466-9-25.
205. Jha P & Peto R (2014) Global effects of smoking, of quitting, and of taxing tobacco. *New Engl J Med* **370**, 60–68. doi: 10.1056/NEJMra1308383.
206. Mons U, Muscat JE, Modesto J, *et al.* (2016) Effect of smoking reduction and cessation on the plasma levels of the oxidative stress biomarker glutathione – post-hoc analysis of data from a smoking cessation trial. *Free Radic Biol Med* **91**, 172–177. doi: 10.1016/j.freeradbiomed.2015.12.018.
207. Chang JT, Anic GM, Rostron BL, *et al.* (2020) Cigarette smoking reduction and health risks: a systematic review and meta-analysis. *Nicotine Tob Res* ntaa156. doi: 10.1093/ntr/ntaa156.
208. Breland A, Soule E, Lopez A, *et al.* (2016) Electronic cigarettes: what are they and what do they do? *Ann N Y Acad Sci* **1394**, 5–30. doi: 10.1111/nyas.12977
209. Farsalinos K, Spyrou A, Stefopoulos C, *et al.* (2015) Nicotine absorption from electronic cigarette use: comparison between experienced consumers (vapers) and naïve users (smokers). *Sci Rep* **5**, 11269. doi: 10.1038/srep11269.
210. Dawkins L & Corcoran O (2013) Acute electronic cigarette use: nicotine delivery and subjective effects in regular users. *Psychopharmacology* **231**, 401–407. doi: 10.1007/s00213-013-3249-8.
211. Henningfield JE (1995) Nicotine medications for smoking cessation. *N Engl J Med* **333**, 1196–1203. doi: 10.1056/NEJM199511023331807.
212. Choi JH, Dresler CM, Norton MR, *et al.* (2003) Pharmacokinetics of a nicotine polacrilex lozenge. *Nicotine Tob Res* **5**, 635–644. doi: 10.1080/1462220031000158690
213. Polosa R, Caponnetto P, Morjaria JB, *et al.* (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. doi: 10.1186/1471-2458-11-786.
214. Siegel MB, Tanwar KL, Wood KS (2011) Electronic cigarettes as a smoking-cessation: tool results from an online survey. *Am J Prev Med* **40**, 472–475. doi: 10.1016/j.amepre.2010.12.006
215. Caponnetto P, Campagna D, Cibella F, *et al.* (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. doi: 10.1371/journal.pone.0066317. Erratum in: *PLoS One* 2014; 9. doi: 10.1371/annotation/e12c22d3-a42b-455d-9100-6c7ee45d58d0.
216. Rom O, Pecorelli A, Valacchi G, *et al.* (2015) Are E-cigarettes a safe and good alternative to cigarette smoking? *Ann N Y Acad Sci* **1340**, 65–74. doi: 10.1111/nyas.12609.
217. Han S, Chen H, Zhang X, *et al.* (2015) Levels of selected groups of compounds in refill solutions for electronic cigarettes. *Nicotine Tob Res* **18**, 708–714. doi: 10.1093/ntr/ntv189.
218. Neale BW, Mesler EL, Young M, *et al.* (2005) Propylene glycol-induced lactic acidosis in a patient with normal renal function: a proposed mechanism and monitoring recommendations. *Ann Pharmacother* **39**, 1732–1736. doi: 10.1345/aph.1G083.
219. *Safety assessment and regulatory authority to use flavors: focus on electronic nicotine delivery systems and flavored tobacco products*. Washington (DC): Federal Emergency Management Agency; 2013. https://www.femaflavor.org/safety-assessment-and-regulatory-authority-useflavors-focus-electronic-nicotine-delivery-systems (accessed Oct 2017).
220. Hutzler C, Paschke M, Kruschinski S, *et al.* (2014) Chemical hazards present in liquids and vapors of electronic cigarettes. *Arch Toxicol* **88**, 1295–1308. doi: 10.1007/s00204-014-1294-7.
221. Williams M, Bozhilov K, Ghai S, *et al.* (2017) Elements including metals in the atomizer and aerosol of disposable electronic cigarettes and electronic hookahs. *PLoS One* **12**, e0175430. doi: 10.1371/journal.pone.0175430.
222. Goniewicz ML, Knysak J, Gawron M, *et al.* (2014) Levels of selected carcinogens and toxicants in vapour from electronic cigarettes. *Tob Control* **23**, 133–139. doi: 10.1136/tobaccocontrol-2012-050859.
223. Harrell PT, Simmons VN, Correa JB, *et al.* (2014) Electronic nicotine delivery systems ("e-cigarettes"): review of safety and smoking cessation efficacy. *Otolaryngol Head Neck Surg* **151**, 381–393. doi: 10.1177/0194599814536847.
224. Vardavas CI, Anagnostopoulos N, Kougias M, *et al.* (2012) Short-term pulmonary effects of using an electronic cigarette: impact on respiratory flow resistance, impedance, and exhaled nitric oxide. *Chest* **141**, 1400–1406. doi: 10.1378/chest.11-2443.
225. Schraufnagel DE, Blasi F, Drummond MB, *et al.*; Forum of International Respiratory *Societies*. (2014) Electronic cigarettes. A position statement of the Forum of International Respiratory Societies. *Am J Respir Crit Care Med* **190**, 611–618. doi: 10.1164/rccm.201407-1198PP.
226. Dinakar C & O'Connor GT (2016) The health effects of electronic cigarettes. *N Engl J Med* **375**, 1372–1381. doi: 10.1056/NEJMc1613869.
227. Glasser AM, Collins L, Pearson JL, *et al.* (2017) Overview of electronic nicotine delivery systems: a systematic review. *Am J Prev Med* **52**, e33–66. doi: 10.1016/j.amepre.2016.10.036.
228. Stephens WE (2017) Comparing the cancer potencies of emissions from vapourised nicotine products including e-cigarettes with those of tobacco smoke. *Tob Control* tobaccocontrol-2017-053808. doi: 10.1136/tobaccocontrol 2017-053808.
229. Shields PG, Berman M, Brasky TM, *et al.* (2017) A review of pulmonary toxicity of electronic cigarettes in the context of smoking: a focus on inflammation. *Cancer Epidemiol*

Biomarkers Prev **26**, 1175–1191. doi: 10.1158/1055-9965.EPI-17-0358.
230. Levy DT, Borland R, Villanti AC, *et al.* (2017) The application of a decision-theoretic model to estimate the public health impact of vaporized nicotine product initiation in the United States. *Nicotine Tob Res* **19**, 149–159. doi: 10.1093/ntr/ntw158.
231. Müezzinler A, Mons U, Gellert C, *et al.* (2015) Smoking and all-cause mortality in older adults. Results from the CHANCES Consortium. *Am J Prev Med* **49**, e53–e63. doi: 10.1016/j.amepre.2015.04.004.
232. Fricker M, Goggins BJ, Mateer S, *et al.* (2018) Chronic cigarette smoke exposure induces systemic hypoxia that drives intestinal dysfunction. *JCI Insight* **3**, e94040. doi: 10.1172/jci.insight.94040.
233. van den Berg R, van Vliet T, Broekmans WMR, *et al.* (2001) A vegetable/fruit concentrate with high antioxidant capacity has no effect on biomarkers of antioxidant status in male smokers. *J Nutr* **131**, 1714–1722. doi: 10.1093/jn/131.6.1714.
234. Mattson MP (2008) Dietary factors, hormesis and health. *Ageing Res Rev* **7**, 43–48. doi: 10.1016/j.arr.2007.08.004.
235. Halliwell B (2013) The antioxidant paradox: less paradoxical now? *Br J Clin Pharmacol* **5**, 637–644. doi: 10.1111/j.1365-2125.2012.04272.x
236. Mathers CD & Loncar D (2006) Projections of global mortality and burden of disease from 2002 to 2030. *PLoS Med* **3**, e442. doi: 10.1371/journal.pmed.0030442.
237. Beaglehole R, Bonita R, Yach D, *et al.* (2015) A tobacco-free world: a call to action to phase out the sale of tobacco products by 2040. *Lancet* **385**, 1011–1018. doi: 10.1016/S0140-6736(15)60133-7.
238. Halliwell B (2012) Free radicals and antioxidants: updating a personal view. *Nutr Rev* **70**, 257–265. doi: 10.1111/j.1753-4887.2012.00476.x
239. Jackson MJ. (2011) Control of reactive oxygen species production in contracting skeletal muscle. *Antioxid Redox Signal* **15**, 2477–2486. doi: 10.1089/ars.2011.3976.
240. Pasupathi P, Saravanan G & Farook J (2009) Oxidative stress biomarkers and antioxidant status in cigarette smokers compared to nonsmokers. *J Pharm Sci Res* **1**, 55–62.
241. Chiu YW, Chuang HY, Huang MC, *et al.* (2009) Comparison of plasma antioxidant levels and related metabolic parameters between smokers and non-smokers. *Kaohsiung J Med Sci* **25**, 423–430.
242. Jain A, Agrawal BK, Varma M, *et al.* (2009) Antioxidant status and smoking habits: relationship with diet. *Singapore Med J* **50**, 624–627.
243. Kim SH, Kim JS, Shin HS, *et al.* (2003) Influence of smoking on markers of oxidative stress and serum mineral concentrations in teenage girls in Korea. *Nutrition* **19**, 240–243. doi: 10.1016/s0899-9007(02)01002-x.
244. Yamaguchi Y, Haginaka J, Morimoto S, *et al.* (2005) Facilitated nitration and oxidation of LDL in cigarette smokers. *Eur J Clin Invest* **35**, 186–193. doi: 10.1111/j.1365-2362.2005.01472.x.
245. Garbin U, Fratta Pasini A, Stranieri C, *et al.* (2009) Cigarette smoking blocks the protective expression of Nrf2/ARE pathway in peripheral mononuclear cells of young heavy smokers favouring inflammation. *PLoS ONE* **4**, e8225. doi: 10.1371/journal.pone.0008225.
246. Moriarty SE, Shah JH, Lyn M, *et al.* (2003) Oxidation of glutathione and cysteine in human plasma associated with smoking. *Free Radic Biol Med* **35**, 1582–1588. doi: 10.1016/j.freeradbiomed.2003.09.006.
247. Haj Mouhamed D, Ezzaher A, Neffati F, *et al.* (2011) Effect of cigarette smoking on plasma uric acid concentrations. *Environ Health Prev Med* **16**, 307–312. doi: 10.1007/s12199-010-0198-2.
248. Touvier M, Kesse E, Clavel-Chapelon F, *et al.* (2005) Dual association of beta-carotene with risk of tobacco-related cancers in a cohort of French women. *J Natl Cancer Inst* **97**, 1338–1344. doi: 10.1093/jnci/dji276.
249. Kokkou E, Siasos G, Georgiopoulos G, *et al.* (2016) The impact of dietary flavonoid supplementation on smoking-induced inflammatory process and fibrinolytic impairment. *Atherosclerosis* **251**, 266–272. doi: 10.1016/j.atherosclerosis.2016.06.054.
250. McEvoy CT, Schilling D, Clay N, *et al.* (2014) Vitamin C supplementation for pregnant smoking women and pulmonary function in their newborn infants: a randomized clinical trial. *JAMA* **311**, 2074–2082. doi: 10.1001/jama.2014.5217.
251. Virtamo J, Taylor PR, Kontto J, *et al.* (2014) Effects of α-tocopherol and β-carotene supplementation on cancer incidence and mortality: 18-year postintervention follow-up of the Alpha-tocopherol, Beta-carotene Cancer Prevention Study. *Int J Cancer* **135**, 178–185. doi: 10.1002/ijc.28641.
252. Chen F, Li Q, Yu Y, *et al.* (2015) Association of vitamin C, vitamin D, vitamin E and risk of bladder cancer: a dose-response meta-analysis. *Sci Rep* **5**, 9599. doi: 10.1038/srep09599.
253. Kellen E, Zeegers M, Paulussen A, *et al.* (2006) Fruit consumption reduces the effect of smoking on bladder cancer risk. The Belgian case control study on bladder cancer. *Int J Cancer* **118**, 2572–2578. doi: 10.1002/ijc.21714.
254. Balder HF, Goldbohm RA & van den Brandt PA (2005) Dietary patterns associated with male lung cancer risk in the Netherlands Cohort Study. *Cancer Epidemiol Biomarkers Prev* **14**, 483–490. doi: 10.1158/1055-9965.EPI-04-0353.
255. Karlsen A, Svendsen M, Seljeflot I, *et al.* (2013) Kiwifruit decreases blood pressure and whole-blood platelet aggregation in male smokers. *J Hum Hypertens* **27**, 126–130. doi: 10.1038/jhh.2011.116.
256. Karppi J, Laukkanen JA, Mäkikallio TH, *et al.* (2012) Low β-carotene concentrations increase the risk of cardiovascular disease mortality among Finnish men with risk factors. *Nutr Metab Cardiovasc Dis* **22**, 921–928. doi: 10.1016/j.numecd.2012.01.008.
257. Melo van Lent D, Leermakers ET, Hofman A, *et al.* (2017) Association between lutein intake and lung function in adults: the Rotterdam Study. *Br J Nutr* **117**, 720–730. doi: 10.1017/S0007114517000319.
258. Mehta AJ, Cassidy A, Litonjua AA, *et al.* (2016) Dietary anthocyanin intake and age-related decline in lung function: longitudinal findings from the VA Normative Aging Study. *Am J Clin Nutr* **103**, 542–550. doi: 10.3945/ajcn.115.121467.
259. Bravi F, Bosetti C, Filomeno M, *et al.* (2013) Foods, nutrients and the risk of oral and pharyngeal cancer. *Br J Cancer* **109**, 2904–10. doi: 10.1038/bjc.2013.667.
260. Vieira AR, Abar L, Vingeliene S, *et al.* (2016) Fruits, vegetables and lung cancer risk: a systematic review and meta-analysis. *Ann Oncol* **27**, 81–96. doi: 10.1093/annonc/mdv381.

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