Abstract
Smoking is the leading avoidable cause of cardiovascular mortality worldwide. The aim of this report is to briefly review the existing evidence regarding smoking and cardiovascular risk, and to analyze in greater detail the links between tobacco use and metabolic disorders. The evidence so far shows that smoking dose-dependently increases the risk of impaired glucose tolerance, the incidence of type 2 diabetes mellitus and abdominal-type obesity. Although smokers have a lower body mass index than do nonsmokers, recent data show that they have higher waist-to-hip ratios and waist circumferences, established risk factors for cardiovascular disorders—in particular, for coronary heart disease. We propose that smoking may lead not only directly, but also indirectly via these metabolic risk factors, to cardiovascular disorders. As both weight and waist circumference may increase on stopping smoking, further studies are needed to assess whether the post-smoking weight increase and potential changes in waist-to-hip ratio (or waist circumference) have consequences that may reduce the benefits of smoking cessation.

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1. Introduction
Tobacco use, along with obesity, is one of the most important avoidable causes of death. The number of smokers worldwide is estimated to be 1.3 billion, of which two-thirds are living in the developing countries [1]. Among British doctors, who have high living standards, continuing to smoke reduces life expectancy by at least ten years [2], so the life expectancy is expected to be even shorter in developing countries. The global mortality attributable to smoking in 2000 was estimated to be 4.83 million premature deaths, with 2.41 million in developing countries and 2.43 million in industrialized countries [3]. The leading causes of death from smoking are cardiovascular diseases (1.69 million deaths), chronic obstructive pulmonary disease (0.97 million deaths) and lung cancer (0.85 million deaths) [3]. Stopping smoking at age 60, 50, 40 or 30 years leads to a gain of about three, six, nine or ten years in life expectancy, accord-
Given these data, the aims of this report are to briefly review the existing evidence for smoking as a main cardiovascular (CV) risk factor, to analyze more extensively the links between tobacco use and the risk of type 2 diabetes mellitus (T2DM), insulin resistance and abdominal-type obesity, and to address any changes in weight after smoking cessation. These metabolic conditions are known risk factors for CV disorders; thus, smoking may lead not only directly, but also indirectly via these metabolic risk factors, to CV disorders.

2. Methods

A manual search through the literature formed the basis of the articles included in the review, with further contributions through database searches of Medline, the Cochrane Library and Ovid. The search terms included ‘smoking’ and ‘body mass index’, ‘waist-to-hip ratio’, ‘abdominal obesity’, ‘waist circumference’, ‘type 2 diabetes mellitus’, ‘impaired glucose tolerance’, ‘smoking cessation’ and ‘weight change’.

3. Results

3.1. Smoking and cardiovascular risk

Smoking is an independent CV risk factor (Fig. 1A). According to the US Surgeon General’s report of 2004, there is sufficient evidence to infer a causal relationship between smoking and subclinical atherosclerosis, abdominal aneurysm, stroke and coronary heart disease [4].

Cigarette smoking is associated with higher serum levels of cholesterol [5] and lower plasma concentrations of high-density lipoprotein (HDL) cholesterol; also, smokers have higher plasma triglyceride concentrations than nonsmokers [6] and smoking enhances platelet aggregation [7]. Smoking impairs lipoprotein metabolism, reduces the distensibility of blood vessel walls [8], and induces a prothrombotic [9] and proinflammatory state [10,11]. A cross-sectional study of around 19,000 participants showed that, compared with nonsmokers, current smokers as well as former smokers have significantly higher, multivariate-adjusted, clinically elevated C-reactive protein, fibrinogen and homocysteine levels. These novel risk factors for atherosclerosis all increase dose-dependently with the number of cigarettes smoked per day, the number of pack-years of cigarettes smoked and serum cotinine concentrations [11,12]. Several prospective studies have demonstrated that elevated levels of C-reactive protein, fibrinogen and homocysteine are positively associated with the risk of stroke and coronary heart disease. Thus, smoking promotes the development of atherosclerosis [13–15] by increasing, at the clinical level, the presence of novel cardiovascular risk factors. Moreover, smoke exposure results in tissue damage by increasing the products of lipid peroxidation and of degradation of extracellular matrix protein endothelial dysfunction, and by apoptosis. Acute smoking increases neutrophil counts, while smoking in general is associated with increased levels of carboxyhaemoglobin, leading to hypoxaemia. Smoking also inhibits tissue repair [10].

Cessation of smoking leads to a 36% reduction in the relative risk (RR) of all-cause mortality for patients with coronary heart disease (CHD), regardless of age, gender, index cardiac event and country of residence, compared with those who continue to smoke (RR: 0.64, 95% CI: 0.58–0.71) [16]. The decline in CV morbidity and mortality is accompanied by a progressive decrease in traditional and inflammatory risk factors, although the decrease in inflammatory markers, and C-reactive protein in particular, takes longer to normalize (five to seven years) than the decline of traditional risk factors (such as total cholesterol), which are normal within one year [12].

As early as 1954, Doll and Hill in the UK demonstrated that smoking greatly increases mortality due to CHD [17], and not only in the industrialized nations [4], but also in the developing countries as well. The recently published INTERHEART study, involving 52 countries, found that smokers had a greater risk of non-fatal myocardial infarction compared with those who had never smoked (OR: 2.95, 95% CI: 2.77–3.14). This

Fig. 1. A. Smoking directly raises cardiovascular risk, but also leads to metabolic alterations (impaired glucose tolerance, type 2 diabetes mellitus, increased waist-to-hip ratio/waist circumference) that may indirectly lead to an increased cardiovascular risk. B. Smoking cessation reduces cardiovascular risk, but is accompanied by increases in body mass index and waist-to-hip ratio/waist circumference that, potentially, can compromise the cardiovascular benefits of stopping smoking.
risk increased by 5.6% for every additional cigarette smoked. Former smokers within three years of having quit still had an increased risk (OR: 1.87, 95% CI: 1.55–2.24). Furthermore, even smokeless tobacco (chewing tobacco) was associated with an increased risk of non-fatal myocardial infarction (OR: 2.23, 95% CI: 1.41–3.52) [18].

3.2. Smoking, and prevalence and incidence of type 2 diabetes mellitus

The increased CV risk due to smoking enhances the pre-existing CV risk associated with diabetes. Awareness of the importance of developing a rationale for the prevention and cessation of smoking among diabetes patients is substantial [19]. The rise in the incidence of T2DM is one of the most challenging health concerns today. This increase in T2DM is multifactorial, with smoking identified as one of the factors triggering its development. Although most, but not all, of the earlier prospective studies found that smoking could increase the risk to developing T2DM, more recent studies [20–22] have confirmed the association between smoking and the incidence of diabetes in what appears to be a dose–response relationship [23]. It is well established that heavy smoking—defined as higher than or equal to 20 cigarettes/day—doubles the risk of T2DM [20,21], and that smoking also leads to impaired glucose tolerance (IGT). Also, former smokers may be at less risk of developing either T2DM or IGT.

According to a recent study, both active and passive smoking can lead to IGT. The CARDIA study, a prospective cohort study to assess the risk of CHD in young adults (median age of 25) in 1985–1986, found that, after 15 years of follow-up, 16.7% developed glucose intolerance (fasting serum glucose ≥100 mg/dL or taking antidiabetic drugs). This 15-year incidence of IGT was highest among current smokers (adjusted hazard ratio [HR]: 1.65, 95% CI: 1.27–2.13), with the adjusted HR also higher among never-smokers with passive smoke exposure compared with those without passive smoke exposure (HR: 1.35, 95% CI: 1.06–1.71). Among former smokers, the HR for glucose intolerance was no higher than that for nonsmokers (HR: 1.17, 95% CI: 0.86–7.57) [24].

Data from France have confirmed the association between T2DM and smoking. In a population-based study of 28,409 participants, Beziaud et al. [25] demonstrated that, after adjustment for age, waist-to-hip ratio (WHR), body mass index (BMI) and alcohol consumption, the risk of T2DM was 49 and 31% higher in current and former male smokers, respectively, than in male nonsmokers. The highest risk was observed in men aged 40 to 69 years. The effect of current smoking on the likelihood of T2DM was lower but significant when women of all ages were analyzed (HR: 1.46, 95% CI: 0.92–2.22). However, the effect of smoking on the likelihood of having T2DM was significant in women aged 40 to 69 years (HR: 1.6, 95% CI: 1.00–2.58).1

A large, prospective American cohort study, carried out from 1959 through 1972, showed that the multivariable-adjusted incidence rate of diabetes increased in current smokers in a dose-dependent manner starting from one pack of cigarettes a day in both men and women. However, the study found no association between the smoking-related risk of developing diabetes and BMI [26]. However, a recent study in apparently healthy Japanese men at baseline demonstrated that heavy smoking raised the incidence of T2DM only in those with a BMI greater than 24.7 kg/m² compared with never-smokers. On the other hand, smoking (either less or equal to 20 or more than 20 cigarettes/day) decreased the likelihood of T2DM in men with a BMI <21.3 kg/m² [27].

Use of smokeless tobacco (oral moist snuff) is becoming more and more prevalent, particularly in the Nordic countries. As with smoking, smokeless tobacco use also appears to increase the prevalence of T2DM, especially at high daily doses. One study found that high weekly doses of oral moist snuff was associated with an increased risk of T2DM (OR: 2.7, 95% CI: 1.3–5.5) similar to that of smoking (OR: 2.6, 95% CI: 1.1–5.9) [28]. However, another study found an increased risk of T2DM in continuing smokers (and also in ex-smokers) (OR: 4.63, 95% CI: 1.37–16), but this risk was not significantly increased in oral moist snuff users [29].

In diabetic patients, smoking is an independent risk factor for CHD [30,31], stroke [32] and peripheral vascular disease [33]. It accentuates the dyslipidaemia of T2DM that is associated with increased hepatic lipase activity that may produce atherogenic, small, dense LDL particles [34]. Thus, it is of major concern that, despite the overall reduction in smoking prevalence, the proportion of smokers among diabetics does not appear to have decreased. Data from the US Behavioral Risk Factor Surveillance System for 1990–2001 show that the prevalence of smoking among adults with diabetes did not change over this period (in 1990: 23.6%; in 2001: 23.2%). A similar pattern was also observed among people without diabetes (in 1990: 24.2%; in 2001: 23.2%). However, among non-diabetics over 45 years of age, smoking prevalence decreased significantly, but remained unchanged among those with diabetes [35]. For this reason, the American Diabetes Association’s recommendations include assessment of smoking status and history in diabetic patients, counseling on smoking prevention and cessation, and the use of effective pharmacological treatments to aid stopping in smoking [19].

The association between cigarette smoking and T2DM is physiologically plausible. Smoking just one cigarette per hour for six hours is associated with reduced insulin sensitivity due to a lower peripheral glucose uptake [36]. In healthy subjects, smoking four cigarettes within one hour can significantly decrease glucose utilization and is accompanied by a significant reduction in insulin receptor affinity [37]. Smoking also increases blood glucose after an oral glucose challenge and

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1 Since the submission of this manuscript, a systematic review and meta-analysis has been published that confirms that active smoking is associated with an increased risk of T2DM dose-dependently. The relative risk for heavy smokers was 1.61 (95% CI: 1.43–1.80), for light smokers, 1.29 (95% CI: 1.13–1.48) and, for former smokers, 1.23 (95% CI: 1.14–1.33) compared with never-smokers, and without gender differences [75].
Impairs insulin sensitivity. Smokers are more resistant than nonsmokers to insulin-mediated glucose uptake, and are more hyperinsulinaemic in response to an oral glucose load. The insulin resistance associated with smoking may account, in part, for the lower HDL-cholesterol and higher triglyceride concentrations and, consequently, the increased risk of CHD [38]. Vasoconstriction due to smoking reduces blood flow in skeletal muscles and may contribute to insulin resistance [38,39]. Chemical components of tobacco smoke may have direct toxic effects on the pancreas and beta-cell function as well as on insulin receptor sensitivity. Because higher levels of inflammatory markers (CRP and interleukin-6) herald the development of IGT and/or T2DM by increasing levels of inflammatory markers.

Smokers are characterized by a cluster of metabolic abnormalities, including insulin resistance, and high plasma triglyceride and low HDL-cholesterol levels [38]. Glycosylated haemoglobin (HbA1c) may also be added to this cluster. The EPIC-Norfolk Study has shown that, among non-diabetic persons, the mean HbA1c level was lowest in never-smokers, intermediate in former smokers and highest in current smokers. HbA1c dose-dependently increased with the number of cigarettes smoked per day, and was also positively associated with total smoking exposure as measured by pack-years. The unadjusted increase in HbA1c for 20 pack-years of smoking was 0.12% in both men and women. After adjustment for possible confounders such as dietary variables, these values were 0.08% (95% CI: 0.04–0.12) and 0.07% (95% CI: 0.02–0.12) for men and women, respectively. In addition, the time since smoking cessation was inversely correlated with HbA1c [41].

It is not clear whether metabolic changes associated with smoking are due to nicotine, other constituents of tobacco or tobacco smoke, or an interaction of constituents of tobacco/tobacco smoke with nicotine, leading to these metabolic effects. Some smoking-associated pathophysiological changes are summarized in Table 1.

### Table 1

<table>
<thead>
<tr>
<th>Pathophysiologic changes associated with smoking</th>
<th>Lipids</th>
<th>Glucose metabolism-related effects</th>
<th>Inflammatory markers</th>
<th>Tissue damage and vascular effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total plasma cholesterol ↑</td>
<td>HDL cholesterol ↓</td>
<td>Fasting blood glucose ↑</td>
<td>Plasma fibrinogen ↑</td>
<td>Tissue repair ↓</td>
</tr>
<tr>
<td>Plasma triglycerides ↑</td>
<td>Glycosylated haemoglobin ↑</td>
<td>Insulin resistance ↑</td>
<td>Homocysteine ↑</td>
<td>Apoptosis ↑</td>
</tr>
<tr>
<td>Insulin resistance ↑</td>
<td>Carboxyhaemoglobin ↑</td>
<td>Beta-cell toxicity ↑</td>
<td>C-reactive protein ↑</td>
<td>Carboxyhaemoglobin ↑</td>
</tr>
<tr>
<td>Carboxyhaemoglobin ↑</td>
<td>Distensibility of vessel walls ↓</td>
<td>Neutrophil count ↑</td>
<td>Endothelial dysfunction ↑</td>
<td></td>
</tr>
</tbody>
</table>

↑, increase; ↓, decrease; ?, uncertain.

### 3.3. Smoking and abdominal obesity

Abdominal obesity is associated with an atherogenic profile, and is a risk factor for T2DM, CHD, stroke and total mortality independently of weight. It can be assessed by either WHR or waist circumference, although measures of waist circumference result in less error than do those of WHR [42]. Although smokers tend to be thinner than nonsmokers, they have a greater WHR than nonsmokers. Smokers, controlling for age and gender, are characterized by an average BMI that is at least 1 kg/m² lower than that of nonsmokers [43,44]. Continuing to smoke inhibits age-related weight gain in both men and women [43]. The lower BMI is probably the consequence of increased energy expenditure [45] and lower calorie intake in smokers, with the latter probably due to the appetite-suppressing action of nicotine [46]. A large study found that smokers consumed a greater number of calories per day, both cross-sectionally and over a period of two years, than nonsmokers, while keeping their body weight unchanged [47]. Smoking increases energy expenditure by approximately 10% [45]. This increased energy expenditure is associated with increased urinary excretion of norepinephrine, suggesting the involvement of sympathetic pathways [45], which is in agreement with data showing that acute smoking stimulates the sympathetic nervous system [9,48].

Although smokers tend to have a lower BMI than nonsmokers, recent studies have shown that, in spite of this, smokers are more likely to have abdominal-type obesity. Abdominal obesity reflects preferential visceral-fat accumulation; it is also a better indicator of adverse metabolic risk factors and CV disorders than BMI. The WHR shows a graded and highly significant association with acute myocardial infarction (AMI) risk, according to the INTERHEART study [49]. The association between WHR and AMI is stronger than that between BMI and AMI.

Smokers have a larger waist circumference and WHR [50,51], and a higher WHR than former smokers and never-smokers; the WHR is positively associated with the number of cigarettes smoked per day [51]. Czernichow et al. demonstrated an increase in WHR in French smokers in both genders [52] and, in a large study from Greece, tobacco smoking was positively and dose-dependently associated with a higher WHR not only in men, but also in women. WHR increases with age in both men and women, and smoking tobacco considerably potentiates this age-related rise [44].

Mizuno et al. [53] studied obesity-related disorders in both non-obese and obese smoking and non-smoking Japanese subjects. They found that, among the non-obese subjects, hypertension, hyperglycaemia, dyslipidaemia and hyperuricaemia were more frequent in smokers, but with no significant differences in waist circumference. However, among those who were obese, smokers had a larger waist circumference than nonsmokers, suggesting that smoking may be a promoter of abdominal fat accumulation [53].

The relationships between smoking and WHR, and smoking and BMI, are not similar. In a large cross-sectional study of pre- and postmenopausal Dutch women, WHR increased in parallel with the number of cigarettes smoked per day, while the BMI decreased [54].
The most convincing evidence of a positive association between WHR and smoking comes from the study by Canoy et al. [55]. This study involved 21,828 men and women, aged 45 to 79 years, residing in Norfolk, UK, who had no known heart disease, stroke or cancer. Current smokers had a higher WHR compared with never-smokers in both men and women, and across all BMI categories. Among current and former smokers, those who had a greater cumulative exposure (assessed by the number of pack-years smoked) also had a higher WHR compared with never-smokers, when adjusted for potential confounders such as BMI, age, alcohol intake, physical activity, total energy intake and education. The effect of current smoking on WHR was similar in men and women. Among former smokers, the time since quitting was inversely related to WHR, but only smokers who stopped smoking more than 20 years earlier had a similar WHR to that of never-smokers, suggesting that the WHR is very slow to normalize.

3.4. Maternal smoking during pregnancy and risk of adiposity

Low birth weight has consistently been reported in association with adult-onset essential hypertension, CHD and stroke. Children born prematurely or at term—but small for gestational age—are at risk of reduced insulin sensitivity [56]. A low birth weight has also been found in several studies in association with IGT or T2DM and abdominal obesity in the offspring [57]. The main avoidable cause of a reduced birth weight is maternal smoking during pregnancy. According to a recent study, the children of women who smoked during early pregnancy, when assessed at age 3, had an elevated risk of being overweight and a higher BMI compared with the children of non-smoking mothers [58]. Although this study did not report a significant association between maternal smoking during pregnancy and abdominal obesity, it is possible that an association of prenatal smoke exposure with abdominal obesity appears only when the children are at a later age. Another report from the same cohort described a positive relationship between gestational weight gain and the BMI of the child at age 3. In this study, excessive gestational weight gain was more frequent among pregnant women who smoked in early pregnancy (65%) than among those who were never smokers (48%) [59]. Thus, it can be hypothesized that smoking during pregnancy leads to higher gestational weight gain and potentially a higher risk of childhood obesity in the offspring. These data suggest that not only smoking in adulthood, but also intrauterine smoke exposure may be a risk factor for IGT, T2DM, obesity or abdominal-type obesity that could lead to later CV disorders. Further studies are needed to confirm this possible chain of events.

3.5. Weight changes after stopping smoking

Smoking cessation leads, almost inevitably, to weight gain. According to the First National Health and Nutrition Examination Survey (1971–1975 and 1982–1984), the mean weight gain attributable to the cessation of smoking, after adjustment for all potential confounders, is 2 kg in men and 3.1 kg in women during the first year after stopping smoking. Any further increases in weight are less over the subsequent years. Major weight gain (>13 kg) occurs in around 10% of men and 13% of women. However, a higher BMI after quitting is probably not a ‘true’ smoking-related weight increase because the BMI of sustained quitters is similar to that of never-smokers of corresponding ages. Thus, because smokers have a lower BMI than nonsmokers, the BMI increase after quitting has a tendency to return to the level of those who have never smoked [60]. The mean weight gain over a ten-year period is about 4.4 kg in men and 5 kg in women [61]. In the Lung Health Study, participants who quit smoking had a mean weight gain of 2.95 kg/year among men and 3.09 kg/year among women, corresponding to an increase of 3.61% and 4.69%, respectively, over their initial body weight. Over five years, one-third of sustained quitters gained more than or equal to 10 kg [62]. The mechanisms of smoking-cessation-induced weight gain include increased caloric intake, decreased resting metabolic rate, less physical activity, increased appetite and higher lipoprotein lipase activity [63,64].

The risk of major weight gain after stopping smoking is higher in those who smoked more than 15 cigarettes/day, are aged less than 55 years, have low levels of physical activity or, in women, have had children [60]. Smokers with the highest cigarette consumption before quitting have the greatest risk of becoming overweight [65]. Inflammatory markers also predict weight gain after smoking cessation. During a three-year follow-up, the baseline leucocyte count and fibrinogen levels predicted weight gain, suggesting a close relationship between inflammatory mediators and regulation of energy balance [66].

The weight increase is less if smokers do not stop smoking completely. Compared with those who stopped totally, those who alternated smoking and non-smoking periods gained only 2.82 kg at six months after quitting compared with an average of 5.45 kg in those who stopped completely [67].

Postcessation weight gain may be moderated by genetic factors that, as yet, have not been elucidated. Concordance in twins for weight change after smoking cessation was higher in monozygotic (53%) than in dizygotic (38%) pairs [68] in the only study that, to the present author’s current knowledge, assessed post-quitting weight increases in terms of genetics.

The Health Professionals’ Follow-up Study was a prospective study in a cohort of 16,587 US male health professionals followed-up for nine years. Smokers who quit gained in waist circumference (1.98 ± 0.32 cm, adjusted for age, waist circumference and BMI at baseline, and changes in total calories, physical activity and alcohol intake from baseline) whereas the waist circumference of those who continued to smoke did not change [69].

One of the reasons to continue smoking despite the known benefits of quitting is the fear of gaining weight, a concern that is especially strong in smoking women, but also in men [70]. Among female smokers, those who are afraid of postcessation weight gain are more dependent of tobacco and more likely to control their weight through all sorts of manipulations (such as low-calorie diets, exercise, appetite suppressants, induced vomiting and diuretics) [71].
The question that needs to be raised is whether or not the almost unavoidable increases in weight and waist circumference after smoking cessation has a negative impact on the benefits of stopping smoking. In the Lung Health Study, lung function after quitting was significantly and negatively influenced by weight gain. In sustained quitters, the percentage weight increase was almost linearly associated with decreasing lung function. This effect of post-cessation weight gain was more important in men than in women [72]. Along the same lines, according to a study by Chinn et al. in 2005, although quitters had significantly slower age-dependent declines in lung function, this benefit of quitting was attenuated by the parallel weight gain [73]. Unfortunately, these studies did not measure WHR or waist circumference, either of which is more closely related to CV risk.

It is also of interest to consider whether or not stopping smoking improves glycaemic control. A Japanese study assessed HbA1c levels in 31 smokers with T2DM for one year. Of these, 15 stopped smoking, and 16 did not and served as controls. HbA1c and fasting blood glucose was similar at baseline, but rose significantly in quitters compared with non-quitters. Changes in HbA1c correlated with baseline BMI [74]. A large cohort study found that the multivariate-adjusted incidence rate of diabetes after smoking cessation remained high, and returned to normal only after ten years in men and five years in women [26].

Weight increases after smoking cessation can be considered an adverse effect of stopping smoking. Nevertheless, further controlled studies are needed to investigate whether post-quit weight increases and changes in WHR/waist circumference have consequences that can attenuate the benefits of quitting smoking (Fig. 1B). Moreover, pharmacological and non-pharmacological interventions need to be carefully assessed in terms of their ability to diminish post-quit weight increases.

### 4. Conclusion

Smoking is a major risk factor for CV disorders. It is also a risk factor for IGT and T2DM, and increases CV risk in diabetic patients. There is also convincing evidence that smoking is associated with an increased WHR/waist circumference in both men and women, and WHR is an important risk factor for CV disorders, especially AMI. Thus, smoking may result not only directly, but also indirectly via metabolic risk factors, in an increased CV risk. Because smoking cessation is associated with increases in weight and in waist circumference, further studies are needed to assess whether such changes in post-quit weight and WHR/waist circumference have consequences that may attenuate the benefits of stopping smoking.

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