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# Impact of smoking on cardiovascular health: Mechanisms, epidemiology and specific concerns regarding congenital heart disease

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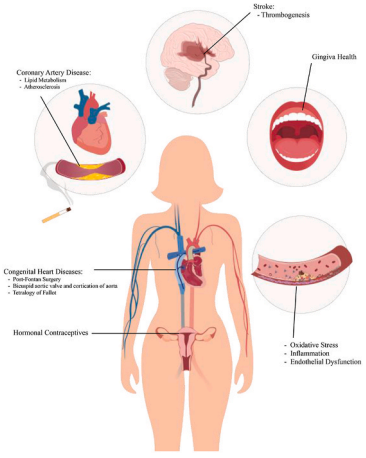
GRAPHICAL ABSTRACT




## 1. Introduction

Smoking remains one of the public health-preventable threats. The negative long-term effect of smoking on cardiovascular disease (CVD) is well-demonstrated [1,2], in particular a meta-analysis shows that smoking increases the risks of coronary heart disease by 30 % and increases incidence of stroke by 20–30 % [3].

Smoking further contributes with the other atherosclerotic cardiovascular disease (ASCVD) risk factors to the chance of several adverse outcomes such as arrhythmias, heart failure, mortality, and impaired quality of life [4].

Importantly, randomized control trials proved the advantage of

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smoking cessation, underlining the importance of taking an action on public health at any stage and time of a person's life [5].

This review elaborates on the adverse effects of smoking on cardiovascular system and approaches to this problem in Adults with Congenital Heart Disease (ACHD).

## 2. Mechanisms of smoking-induced cardiovascular disease

### 2.1. Oxidative stress, inflammation and endothelial dysfunction

Oxidative stress and inflammation induced by smoking are both significant in the development of cardiovascular diseases (CVDs). Smoking generates free radicals, such as reactive oxygen species (ROS), which overwork the antioxidant system, leading to oxidative stress towards cellular macromolecules, including lipids, proteins, and DNA [6]. This stress also promotes inflammation with increased levels of inflammatory cytokines and the influx of activated immune cells into the damaged area. Prolonged inflammation increases the burden of oxidative stress, which could be damage endothelial cells [7]. Endothelial cells are responsible for the production of nitric oxide (NO), which is a necessary compound for vascular dilation and relaxation [8]. A deficiency of NO results in disease in the endothelium characterized by marked vascular constriction resulting in impaired vasodilation and raised blood pressure.

### 2.2. Atherosclerosis and plaque formation

Endothelial dysfunction due to smoking could lead to atherosclerosis [9]. The process begins with an injury to the vessel wall, and factors such as low-density lipoprotein (LDL) start to accumulate within the arterial wall. Macrophage will then be triggered by oxidized LDL, which will lead to the formation of foam cells that contain engulfed oxidized lipids [10]. The inflammatory response as well as the ECM components and foam cells create an environment for plaque development. Gradually, as these plaques increase in size, resulting in decreased blood supply, which leads to ischemic cardiovascular events.

### 2.3. Thrombogenesis

Smoking is a prothrombotic risk factor inducing production of fibrinogen, increasing platelet aggregation and endothelial cell activation [11,12]. Furthermore, nicotine and other chemical components of tobacco can trigger this clotting disorder increasing blood levels of thromboxane A2 and decreasing prostacyclin [13,14]. This hypercoagulable state promotes thrombus formation and increases the chances of acute cardiovascular events.

## 3. Epidemiology of smoking and cardiovascular diseases

### 3.1. Smoking prevalence in adults with congenital heart disease

Smoking is still one of the most global health-related concerns, although its distribution varies across regions. With the latest figures from World Health Organization, the total number of smokers adds up to approximately 1.1 billion [15].

Recent published study and meta-analysis article showed that 1 in 8 (12 %) patients with ACHD are smokers which is less if compared to the general population. This difference could be explained as most patients with CHD require regular medical visits leading to lifelong education on ACVD risk factors such as smoking [16].

### 3.2. Gender and age differences

Gender and age are also very important in terms of both the prevalence of smoking and subsequent CVD risk. In the past, men tend to have had higher smoking rates than females. However, this gap keeps on closing with time [17]. Estrogen is believed to be essential for cardiovascular protection in females in fertile age but can be ineffective due to smoking. This gender difference becomes smaller in the post-menopausal due to a decline in estrogen levels.

Adolescents and young adults who smoke at an early age are at higher risk of cardiovascular disease later in life. Long-term exposure to tobacco smoke can lead to the early development of atherosclerosis and other cardiovascular diseases [18]. Older smokers in particular are more prone to acute cardiovascular events, and prolonged exposure to smoking will result in CVDs with time and with other age-related comorbidities.

## 4. Smoking concerns in Adults with Congenital Heart Disease (ACHD)

### 4.1. Smoking and cardiovascular disease in ACHD patients

Due to improvement in surgical and percutaneous techniques, the survival of children with congenital heart disease (CHD) has increased during the last two decades and approximately 97 % of the patients with CHD reach adulthood [19,20]. Hence, the issue of acquired disease is becoming more common in this cohort of patients and smoke can worsen them further [21,22].

As discussed in this paper, smoking promotes several pathophysiological changes in the cardiovascular system, and it is no surprise that in ACHD patients, these mechanisms of injury are exacerbated due to their already compromised cardiovascular systems.

Smoking has highly adverse effects on endothelial function, increasing the risk of atherosclerosis development. *Patients with CHD are also at risk of developing atherosclerotic cardiovascular disease. A recent study of Egbe* et al. *explored the increased risk of cardiovascular events in ACHD patients depending on the number of ASCVD risk factors presented, including obesity, lack of regular exercise, hypertension, dyslipidemia, diabetes and smoking* [23].

Moreover, in ACHD patients, whose cardiovascular system is already affected, smoking may accelerate the progression of atherosclerosis. Potentially, this could have significant implications for patients with congenital defects involving the aorta and coronary arteries or in patients after coronary arteries reimplantation (i.e. arterial switch operation or Ross procedure), as they already face compromised vessel integrity [24].

Additionally, smoking predisposes to hypertensive disorder due to an increase in peripherally vascular resistances and consequently could led, associated to the other ASCVD risk factors, to ventricular diastolic dysfunction. Hence, this could lead in atrial remodeling (increasing the risk of atrial fibrillation) and in heart failure [4].

Smoking has an influence the endothelial progenitor cells and their regenerative capacity [9]. These adverse effects may accelerate valve degeneration in patients with heart valve disease and in particular with aortic stenosis [25].

Ultimately, smoking has a significant negative impact on the quality of life and long-term outcomes in ACHD patients. Chronic airway inflammation due to smoking, along with pulmonary disease such as chronic obstructive pulmonary disease, further diminishes exercise tolerance. For ACHD patients, whose exercise capacity and cardiopulmonary function are often already compromised by heart disease, this can have a harmful effect [26].

Hereby we mean to discuss the most common or complex cardiac anatomy to assess how smoke affects the long-term morbidity and mortality of these patients.

### 4.2. Bicuspid aortic valve and coarctation of aorta

Smoking has been shown to increase the risk of vascular endothelial dysfunction. In patients with bicuspid aortic valve (BAV) and/or coarctation of the aorta (CoA), even when repaired, it increases vascular

complications as well as aortic aneurysms or dissections [27–29].

Moreover, smoking-induced vasoconstriction can lead to hypertensive disorder with an increasing risk of developing cardiovascular events. This could be particularly harmful in ACHD patients with pre-existing factors for systemic hypertension (i.e. CoA) or those who have aortic root dilatation [30].

Indeed, it has been demonstrated that smoking cessation reduces also endothelin-1, which is a potent vasoconstrictor with proliferative, pro-fibrotic, pro-oxidative and pro-inflammatory properties, maintaining the tone of vascular smooth muscle cells (VSMC) [31].

### 4.3. Tetralogy of Fallot and the impact of smoking

Tetralogy of Fallot (TOF) is the most common cyanotic congenital heart defect characterized by ventricular septal defect, pulmonary stenosis, right ventricular hypertrophy, and an overriding aorta [32]. While corrective surgery is typically performed during infancy, TOF patients require lifelong follow-up due to their risk of complications related to pulmonary valve regurgitation, right ventricular dysfunction, and arrhythmias [33].

In uncorrected patients with TOF, smoking could contribute to worsen cyanosis with chronic hypoxia.

In patients with repaired TOF smoking-induced chronic inflammation contributes to fibrosis and scarring of the already damaged endothelium leading to an increase arrhythmogenic vulnerability [31]. Arrhythmias (atrial and ventricular) are common problems in patients who have undergone TOF corrective surgery and are even more common in smokers because of the arrhythmogenic effect of nicotine. It has already been noted that patients with TOF have a substantially increased risk of sudden cardiac death and smoking potentially increases this risk even more [32,34].

### 4.4. Post-Fontan surgery and smoking-related complications

The Fontan procedure is the final stage of surgical palliation adopted in patients with a functional single ventricle. Fontan Circulation (FC) consist in a surgical rerouting of systemic venous flow to the pulmonary artery, bypassing the subpulmonic pumping ventricle [35]. The Fontan operation improved life expectancy in this group of patients at the point that these patients experience situations that so far were only for long-term survivors: pregnancy, hypertension, menopause, cancer.

The FC is a system lacking the subpulmonic ventricular pump which imposes a preload limited systemic ventricle, systemic venous hypertension and a passive pulmonary flow depending on low pressure in the vascular bed of the lungs [36]. Understandably, smoking augments further complications in these patients, particularly in their hemodynamic challenges.

Smoking is considered one of the major factors increasing pulmonary vascular resistance, which acts in the opposite direction against the FC flow pattern and may contribute to develop extracardiac complications related to its passive pulmonary circulation [37].

In addition to this, the use of tobacco has a further disadvantage as it leads to a prothrombotic state [38]. Smoking causes platelets activation and decreases the potential activity for dissolution of fibrine, which contribute to clots formation [12]. This is very alarming among patients with a FC who are already predisposed to the risk of thrombotic and thromboembolic events due to several factors such as coagulation factors abnormalities, platelets dysfunction, atrial dilatation, low pressure system with slow flow, conduit prosthetic material and arrhythmias [39].

Moreover, smoking-induced chronic hypoxia can also worsen cyanosis in patients with FC who present fenestration or collaterals.

## 5. Special considerations

### 5.1. Smoke and ischemic heart disease in ACHD patients

Smoking is a well-known cardiovascular risk factor that predisposes to coronary atherosclerosis the general population. In addition, smoking together with other traditional atherosclerosis risk factors expose adult patients with CHD to an increased risk of coronary artery disease (CAD) [40]. Indeed, recent studies showed that the risk of CAD in ACHD patients is equal or greater than the general population [24]. A possible reason is that patients with specific CHD could have a compromised vessels integrity due to previous cardiac surgery (i.e. coronary arteries reimplantation in arterial switch operation or Ross procedure), but further research studies are needed to completely understand the underlying pathophysiological mechanism [41].

Therefore, it is essential to educate patients to control modifiable cardiovascular risk factors for atherosclerosis and to encourage smoking cessation [42].

### 5.2. The impact of smoking on gingival health in CHD patients

Gingival health is often overlooked in the holistic management of patients with CHD, despite its crucial role in cardiovascular health. Poor oral hygiene is associated with an increased risk of endocarditis due to chronic inflammation lesions which could be a gateway for oral flora bacteria or acquired infection that accompany persistent gingival disease [43].

Bacteremia as a consequence of periodontal pathology may lead to infective endocarditis, a life-threatening condition, especially in adults with CHD and prosthetic valves, significant valve disease, residual shunts or implanted devices [44].

Smoking is one of the most active and passive habits associated with periodontal disease that leads to gingival inflammation at the beginning and aggravates it later [45]. Smoking or its exposure reduce the blood flow to the gingiva facilitating the retention of pathogens in the oral cavity.

The combination of smoking and poor gingival health creates a particularly concerning scenario for ACHD patients. Smoking not only worsens gingival disease but also hinders the healing of gingival lesions and complicates the prognosis of periodontal treatments, promoting chronic infections and increasing the risk of infective endocarditis. Therefore, maintaining a good oral hygiene in ACHD smokers is even more challenging, being more vulnerable for oral and cardiovascular complications [46].

### 5.3. Increased thrombotic risk in young females on hormonal contraceptives

Young females using estrogen-progestin contraceptives have high prevalence of thromboembolic complications, a condition further exacerbated in ACHD patients.

Oral contraceptives, particularly those containing estrogen, have been shown to increase the risk of venous thromboembolism (VTE) [47] Indeed, estrogen induces changes in the coagulation system, promoting thrombogenesis.

It has been demonstrated that patients with complex CHD are already at higher risk for thromboembolic events, including deep vein thrombosis, pulmonary embolism, and stroke due to the impaired haemodynamic and blood flow patterns resulting from their CHD [48].

The healthcare professionals should consider the risks and benefits of different contraceptive methods in young females with CHD. To reduce the risk of thrombosis, non-estrogen containing hormonal contraceptives, such as progestin-only pills or intrauterine devices (IUDs) may be safer [49].As discussed in this review, smoking is an independent risk factor for thrombosis, hence avoiding it, especially in those who are on combined contraceptives, is mandatory as well as in those with a cardiac

anatomy that predisposes to thrombosis.

Ceasing smoking is paramount to reduce the risk of thromboembolic events among this particular population.

### 5.4. Impact of smoking on pregnancy in women with CHD

Women with CHD are at higher risk of develop cardiovascular events during pregnancy due to hemodynamic changes that pregnancy imposes, based on the severity of CHD as defined per WHO classification [50]. Patients with CHD may have an increased risk of obstetric and fetal adverse events especially in patients with cyanotic disease [51].

Patients with CHD have an increased risk of thromboembolism and we can speculate that smoking during pregnancy increases it even further. This might have an impact also on the risk of fetal complications as result of increased resistances in the vascular bed leading to placental insufficiency, fetal growth restriction and preterm delivery.

Patients with CHD have an increased risk of CHD recurrence in the fetus (3–5 %). Furthermore, smoking is associated with an increased risk of fetal congenital heart defects, as nicotine and other tobacco substitutions can impair fetal cardiac development [52].

Multidisciplinary team (MDT) approach, including Cardiologists and Gynecologists, is mandatory to face pregnancy in patients with CHD. A regular follow-up program to schedule monitoring of maternal cardiac condition as well as fetal growth and plan the delivery is crucial. From the counseling and through the follow-up, it is important to educate the patients and recommend to avoid risk factors such as smoking [53].

## 6. Conclusion

We report herewith the adverse impact of smoking on the cardiovascular system, with a focus in ACHD patients. Specific anatomic and physiologic features in patients with CHD make cardiovascular tissues more susceptible to the harmful effects of smoking.

It is paramount to develop and implement specific preventive strategies discouraging smoking early in life and/or smoking cessation programs later on for patients with CHD, thus reducing cardiovascular complications, acquired cardiovascular disease and other morbidity.

Last but not least, we reinforce the need for patient education, engagement and empowerment by the patients' and their families' deeper understanding of their specific CHD condition and how life-style choices made early in life, including non-smoking, enables them to reach and enjoy their full life potential, inclusive of patients with moderate to complex CHD.

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## CRediT authorship contribution statement

**Mishary Alhindal:** Writing – review & editing, Writing – original draft. **Jood Janahi:** Writing – review & editing, Writing – original draft. **Emanuela C. D'Angelo:** Writing – review & editing. **Veronica Lisignoli:** Writing – review & editing. **Rosalinda Palmieri:** Writing – review & editing. **Antonella Cutrì:** Writing – review & editing. **Gianfranco Butera:** Writing – review & editing. **Michael A. Gatzoulis:** Writing – review & editing. **Claudia Montanaro:** Writing – review & editing, Supervision.

## Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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