# REVIEW

## WOMEN AND CARDIOVASCULAR DISEASES

**Maria DONOSĂ[1], Camelia DIACONU[1,2,3]**

[1]*Department of Internal Medicine, Clinical Emergency Hospital of Bucharest, Bucharest, Romania*
[2]*"Carol Davila" University of Medicine and Pharmacy, Bucharest, Romania*
[3]*Academy of Romanian Scientists*

**Correspondence to:** Maria Donosă, Department of Internal Medicine, Clinical Emergency Hospital of Bucharest, Romania; e-mail: mariadonosa1996@gmail.com

**Abstract***: Cardiovascular diseases have been the leading causes of death worldwide. According to the World Health Organisation, an estimated 17.9 million people died from cardiovascular diseases in 2019, meaning 32% of all global deaths. In the last decades there had been ongoing efforts in raising awareness through campaigns about the impact of cardiovascular disease in women. These efforts, combined with a raise in the socio-demographic index, led to a global decline in age-standardised cardiovascular disease mortality in women in the past 30 years. There are many differences regarding the biological, social, research data, access to healthcare between men and women. This review summarises the latest evidence regarding the traditional risk factors for cardiovascular disease in women, the gender disparities that lead to different outcomes in the primary and secondary prevention in men and women and the under recognised risk factors of the modern society, such as depression, anxiety, chronic stress, abuse and intimate violency and environmental risk factors. Most of the risk factors can be identified early in the life of patients and are modifiable, therefore early screening and intensive risk factor modification, along with medications in certain patients, would make a difference in the outcome of the primary prevention.*

**Keywords:** cardiovascular risks, women, cardiovascular disease, menopause, gestational diabetes, pre-eclampsia.

DOI https://doi.org/10.56082/annalsarscimed.2022.1.13

### INTRODUCTION

During the last decade it has been an accelerated process of social, cultural, scientific and technological development. The biological differences between men and women and the influence of cultures that conditionate the access to knowledge, scientific tools and qualitative healthcare are just a few factors that need to be unravelled for a better understanding of the sex-specific differences in outcomes and cardiovascular disease burden.

The Lancet women and cardiovascular disease Commission is the first effort of this kind that aims to reduce the global burden by 2030 through raising global awareness of gender-related disparities regarding cardiovascular disease, providing recommendations from an international team of experts in this field and a springboard for future research [1]. Cardiovascular disease mortality has indeed declined in the female population in the last 30 years but this effect was best noticed in high-income and well developed countries, while in the most other regions of the world the numbers remained unchanged and actually in the countries with a low-income and quality

of life, the mortality was greater in women compared to men [2].

Lately, some alarming trends were observed regarding cardiovascular disease morbidity and mortality, with a rise of mortality in women in the USA and Canada and a higher prevalence of myocardial infarction in younger French women [3-5]. The population who seems to be more affected lately is represented by women aged between 35-54 years old and the supposition is that it is a result of the obesity epidemic and rising prevalence of smoking and other traditional risk factors [4]. Although the decrease of cardiovascular disease mortality was mentioned, the morbidity remains high, especially due to stroke and ischaemic heart disease [6].

It is well known that hypertension, dyslipidemia, diabetes, obesity, sedentary lifestyle, poor diet and smoking are the main factors that predispose to ischaemic heart disease. The worldwide consensus strongly recommends that they should be first addressed in the primary prevention by introducing the necessary changes in the lifestyle of the patient, but at the same time there are factors of distinct natures that can pass unrecognised by the healthcare provider. Women seem to be more affected by depression, partner violence, socioeconomic deprivation, cultural rights restraints and in addition they are exposed to obstetrical and gynaecological conditions that contribute to the cardiovascular disease development [1].

**Prevalence of cardiovascular disease, mortality and morbidity among women**

The Global Burden Disease study represents an ongoing collaboration between countries that provides comparable and constant data from all the sources available regarding the population's health. Its main purpose is to estimate statistical features for 204 countries, as far as the data is available and accurate in every region of interest. To prevent and further diagnose and treat cardiovascular diseases, it is crucial that precise and comprehensive data are collected first locally and further at a regional level, so the healthcare systems can access global data in real time. The prevalence of cardiovascular disease has nearly doubled since 1990, when it was estimated at 271 million (95% UI of 257 to 285 million) to 523 million (95% UI 497 to 550 million) in 2019, from which 275.2 million worldwide cases were women [7]. *UI=uncertainty interval*

It was estimated that the global age-standardised prevalence of cardiovascular disease in women is 6403/100.000, with the highest rates documented in North Africa, Middle East, high-income North America, Eastern Europe and Central Asia. The lowest age-standardised prevalences were reported in Latin America, Western Europe and Australasia. Over the past 30 years most regions have had a decline in the prevalence of cardiovascular disease, a 4.3% overall decrease (95% UI of -6% to -4.6%), with highest results documented in high income Asia countries, Western Europe and high income North America, but at the same time there was an increase in prevalence in China, India, Indonesia, Oceania and western sub-Saharian Africa [1].

The cardiovascular disease mortality in women is estimated to have risen from 6.10 million (95% UI 5.62-6.41 million) in 1990 to 8.94 million (95% UI 7.92 to 9.71million) in 2019. Ischemic heart disease and stroke remain the most common causes of mortality. The regions with the highest mortality of this cause (316-486/100.000 deaths) are mainly the same that registered the highest prevalence: Eastern Europe, North Africa, the Middle East, Oceania, central Sub-Saharian Africa and central Asia [1].

There are sex differences in the disability adjusted life years (DALYs, a statistical measure that counts in the years spent with a disability and the years lost from the adjusted life expectancy caused by a certain disease, in this article the cardiovascular disease), with reports higher in men before 80 years of age and a reverse after this age. Also, men have more DALYs between 30 and 60 years of age, but women suffer more after the age of 80. These data should raise awareness for the

mortality causes at older ages and the secondary prevention interventions [7].

Ischaemic heart disease remains the leading cause of death worldwide and recent evidence suggests that there are differences between men and women regarding the pathophysiology, risk factors, outcomes etc. [1]. There are recent concerns regarding the risks that the young female population is at, since the prevalence of smoking, diabetes and obesity is high in young women and myocardial infarction rates are rising among them. Women have worse outcomes when it comes to STEMI and higher in-hospital mortality than men [1,4,5].

Women have greater prevalence of stroke, but age standardised DALYs and deaths numbers of this cause were higher in men, which points out that women have better survival after stroke, but a higher lifetime stroke risk [7]. In 2019, 58.2% of total stroke deaths occurred in women, and the incidence appears to be affected by age and race [8].

At a global level, when it comes to atrial fibrillation, under the age of 70, men are more affected compared to women, but at ages older than 75 women seem to be more affected, the data showing more years of disability caused by this condition among the female population. This information pushes towards the need of sex-specific and age-related treatment/management of atrial fibrillation and atrial flutter [7].

Non-rheumatic degenerative mitral valve disease is most caused by mitral valve prolapse which, if left untreated, cand lead to chronic mitral regurgitation, rhythm abnormalities and even heart failure. Data shows that women had more years of life lived with a disability or lost caused by mitral valve disease than men in all age groups, but the levels have a significant diverge after 65 years of age, with a peak between 75 to 79 years [7]. There is some evidence that sustains the data. It was reported that women are less likely to have mitral valve replacement, less likely to receive mitral valve repair, have worse postoperative outcomes and higher in-hospital mortality in comparison with male counterparts. Theories that are warranted to provide a justification for these results praise that women present with worse conditions prior to diagnosis and treatment, such as heart failure and longer-standing mitral valve disease [1,9].

Rheumatic heart disease represents the most common cause of heart failure among the paediatric and young population, and the highest prevalence occurs in women of childbearing age. Higher rates are described in post-pubertal females, but without a clear explanation, and pregnancy represents a critical period for women affected by carditis or heart valve damage. The risk in developing the disease is 1.6-2 times greater for women than men. This condition has been largely eradicated in well developed countries, but the prevalence is still high in the low income regions as a result of biological, social and environmental risk factors. The regions with the highest prevalence and mortality in rheumatic heart disease are currently Africa, southeast Asia and western Pacific [1,7,10].

Peripheral arterial disease prevalence is increasing fast and especially in younger women (<45 years old), women representing about 52% of the patients affected by this condition. The highest prevalence is registered in low-income countries, where the well-established risk factors such as hypertension, diabetes, poor diet and smoking are more prevalent in the population. There is evidence that high body mass index (30 kg/m$^2$ and above) and low pulse pressure are risk predictors in these populations and also it has been documented a strong dose-response relationship for smoking as a risk factor for peripheral arterial disease in women. This condition indicates that the patient has a multivascular disease and the fact that women are more likely than men to have no symptoms or present with sex-specific symptoms is worrying data, leading to delayed diagnosis and management. Also, concerning morbidity, it seems that women are more likely to suffer complications from revascularisation procedures, wound infections, bleeding, periprocedural complications and higher in-hospital mortality [1,11].

### Traditional risk factors

**Hypertension** is the number one risk factor for developing cardiovascular disease and the associated morbidity and mortality. Years of untreated hypertension lead to damage in organs such as heart, brain and kidneys. The heart response to high blood pressure is left ventricular hypertrophy. This natural response represents itself an independent risk because it involves alterations in the coronary hemodynamic, predisposition to lethal arrhythmias, cardiac failure and atherosclerosis and collagen deposition in the coronary arteries leading to ischemia, and ventricular fibrosis [12]. The harm produced by high blood pressures is mainly explained by the damage of the main organs and the left ventricle structural adaptation, but to a much deeper understanding the hypertensive heart disease is characterised by micro and macroscopical myocardial and arterial changes, adaptations that in the end lead to fibrosis of the structures involved [13]. Recent findings show that women are at higher risk of myocardial infarction, left ventricular hypertrophy, diastolic dysfunction, heart failure with preserved ejection fraction, arterial stiffness and chronic kidney disease and are less responsive with more side effects to antihypertensive treatment than men [1,14]. A recent study sustains that women have a different course in the development of hypertension than men, first with a more rapid beginning in their thirties and second, a faster increase in blood pressure over time, as the disease progresses [15]. The mechanisms leading to these differences have not been well understood and questions if different blood pressure targets should be used in women have been raised.

**Dyslipidaemia** is a well-established risk factor for developing cardiovascular disease, especially atherosclerosis and myocardial infarction. It was reported that in the female population, ratios of apoB to apoA1 and total cholesterol to HDL-cholesterol are more powerfully associated with myocardial infarction than in men [14]. Women could be more at risk while going through menopause. Studies found higher levels of total cholesterol and LDL-cholesterol one year after the debut of menopause which was associated with a later risk of developing carotid plaques [16]. Women are less likely to use a statin therapy and the reasons are not well established; statins have the same effectiveness in men and women and lately, the use of PCSK9 inhibitors have contributed to a reduction in ischaemic events in patients with coronary artery disease [1].

**Diabetes** is gaining a continuous rise in prevalence globally due to a multitude of factors which are connected one to another: poverty and poor diet, expanding urbanisation in populous countries with unhealthy lifestyle and sedentary young people. Diabetes contributes to development of ischaemic heart disease and recent studies show that the risk for new onset coronary heart disease and myocardial infarction is higher in women than their male counterparts. Women have better cardiovascular profiles until menopause than men, but this statement falls if there is an early poor glycaemic control. Women are also exposed during pregnancy to high fasting plasma glucose levels and this represents a risk factor for later development of type 2 diabetes and cardiovascular disease, therefore a careful screening and follow up is needed in these patients [1,17,18].

**Obesity** is increasing globally in prevalence, especially in the young population. Obesity itself, defined as a body mass index equal to 30 $kg/m^2$, is a risk factor that predisposes to hypertension and further cardiovascular disease and is more frequent in women [1]. Women can also be exposed during pregnancy and while going through menopause to this condition. Obesity is associated with obstetrical conditions such as hypertensive disorders during pregnancy and gestational diabetes while when going through menopause women seem to be more affected by central obesity, which is included in the metabolic syndrome [1,19,20].

### Diet, sedentary lifestyle and smoking

An unhealthy diet lies at the heart of many risk factors for cardiovascular disease, it can lead to high values of LDL-cholesterol and total cholesterol, low values of HDL-cholesterol, high body mass index, high

apoB/apoA1 and inflammation. Lately it has been a trend towards a greater consumption of sweet beverages, fast food and high-energy density food, which corelates with a greater prevalence of obesity, especially in young people. Healthcare providers should raise awareness about future informative campaigns and tax policies on foods and beverages that are highly processed [1].

Women have a more sedentary lifestyle than men and tend to participate less in physical activities since childhood and over the years. Factors that could add to a greater prevalence in sedentarism are the social, religious and cultural norms that restrict women from participating to sports activities [1,21]. By initiating a regular physical activity, women contribute to lowering the incidence of cardiovascular disease, no matter the individual risk [22].

The youth seem to have a greater prevalence of smoking tobacco and usage of electronic smoking devices, this trend is increasing actually in women aged less than 25 years old. The prevalence of smoking in age standardised women in 2015 was 5.4%, with the highest values registered in western and central Europe and a very high percentage among adolescents. Smoking tobacco is clearly associated with myocardial infarction and the risk seems to be the same for men and women. Also, electronic devices affect the cardiovascular system by generating endothelial dysfunction, raising oxidative stress and platelet activation, all of these being manifestations of systemic inflammation [1,5,14,23].

Even though traditional risk factors remain the same for both genders, their potency seems to be different in men and women, therefore sex-specific approaches should be taken into account in all kinds of preventions.

**Gender-specific risk factors**

**Menopause, hormone replacement therapy and the use of hormonal contraceptives**

It is well known that cardiovascular disease appears later in the life of women compared with men, mostly because of the protective vascular effects of oestrogen, but the risk rises substantially after menopause. The loss of oestrogen has been claimed to lead to chronic endothelial dysfunction and inflammation by activating the renin-angiotensin-aldosterone system. Also, the years in the perimenopause were associated with higher risk of developing obesity and metabolic syndrome. Early menopause is believed to be a risk factor for developing cardiovascular disease before the age of 60. It seems that natural early and surgical early menopause both carry a risk for further development of cardiovascular complications [1,6]. A pan-European case cohort study compared the incidence of coronary heart disease events in premenopausal and postmenopausal women and the results showed that in the postmenopausal group every 1 year decrease in the age at menopause involved a higher 2% risk of developing coronary heart disease and the women with surgical menopause were at a higher risk than the ones with natural menopause [24]. Hormone replacement therapy is currently recommended against for primary or secondary prevention of cardiovascular disease by the current American Heart Association (AHA)/American College of Cardiology (ACC) guidelines. Menopausal women put on oestrogen-progesteron therapy have a higher risk of cardiovascular disease and invasive breast cancer.

Hormonal contraceptives are associated with a 12 higher risk of myocardial infarction in women with history of hypertension and if there are multiple risk factors, the combined hormonal contraception should be discontinued because it would involve such a high cardiovascular risk that would exceed any benefit. There is no evidence that the past use of hormonal contraceptives has important effects on subsequent cardiovascular disease and the options for women with risk of infarction or stroke are: progesterone-only oral contraceptives, subdermal implants and intrauterine devices [1].

**Obstetrical conditions**

Healthcare providers and women should be aware of the risks involved when a woman develops pre-eclampsia, gestational diabetes or

pre-term delivery. These obstetrical conditions are known to be associated with high risk of developing cardiovascular disease later in life and patients should be assessed for other risk factors and prevention interventions should be started as early as possible. There are hypotheses that pregnancy is a stressful condition for the female body that unravels the existing traditional risk factors for cardiovascular disease events. Diabetes can have lasting effects even after pregnancy, patients with history of gestational diabetes having higher rates of reduced coronary flow, atherosclerosis and endothelial dysfunction. Therefore, even if the glucose intolerance and the pregnancy resolve, there should be an early screening for cardiovascular risk factors post-partum [1,6].

Polycystic ovary syndrome (PCOS) resembles polycystic ovaries, oligomenorrhoea and hyperandrogenism and affects 6-10% of reproductive age women. PCOS is associated with a higher risk of developing cardiovascular disease later in life; further research is needed to better understand the mechanisms involved. Current explanations claim that the syndrome is often associated (50-70%) with insulin resistance, which leads to chronic hypergliceamia and diabetes, obesity and metabolic syndrome [6,18].

Autoimmune conditions are more prevalent among women (78% of patients with autoimmune diseases are women) and this pattern represents a risk for developing cardiovascular diseases. Autoimmune conditions are characterized by chronic inflammation which affects the endothelium, leading to dysfunction and an ongoing atherosclerotic process, to which the steroid therapy with its implications is added. A preventive measure for these patients would be the early introduction of statins in their chronic therapy [1].

**Under-recognised risk factors**

**Psychosocial risk factors, abuse and violence and environmental influences**

Depression is an independent risk factor for coronary artery disease in women and alongside with anxiety increases the risk for developing cardiovascular disease. It seems that women are more at risk than men, because they have suffered more psychosocial disadvantages like higher rates of unemployment, stress, poor social support. Depression and anxiety often receive little attention in the clinical practice, but they have an important role in a good treatment outcome for cardiovascular disease. Another important factor which is worth mentioning is abuse. It has been reported that 15-71% of women are abused physically or psychologically in their lifetime, and this represents a risk factor for later development of cardiovascular disease, because it involves chronic stress and depression, which are biologically translated as chronic high rates of cortisol and chronic inflammation. Abuse influences mental health and behaviours, with tendency to smoking, binge drinking or eating and not seeking healthcare services [1].

Air pollution is another risk factor that has gained solid evidence regarding its implications in the development of cardiovascular conditions. The European Society of Cardiology sustains that air pollution leads to higher oxidative stress and inflammation, atherosclerotic plaque progression, endothelial dysfunction, platelet hyper-reactivity and arrhythmogenesis. Women can also be exposed to high amount of particulate matter and carbon monoxide while cooking on indoor stoves [1,25].

There are many factors of other natures rather than biological characteristics of the human female body that need to be further researched in order to get close to the understanding of differences between the risks of a woman and a man. Women seem to have less access to healthcare, especially in low income and medium income countries, have been less included in studies throughout the years and are underestimated in terms of cardiovascular risk factors [1].

**Raising awareness**

Differences in the regional and national burden and mortality of cardiovascular disease also reflect the differences in the prevalence of the risk factors and the access

to healthcare, to primary and secondary prevention. This aspect is a very important matter to have in mind while checking the data from low and middle income regions [7]. The statistical data regarding stagnation and actually higher prevalence of cardiovascular disease among women points out to the highly populated and industrialised regions of the world [3]. This is a call to action to expand the access to healthcare, prevention strategies focused on sex-specific risk factors, the diagnosis tools and better individualised prevention and treatment for women.

**Author Contributions:**

*M.D. conceived the original draft preparation. M.D. and C.D. were responsible for conception and design of the review. M.D. and C.D. were responsible for the data acquisition. M.D. was responsible for the collection and assembly of the articles/published data, and their inclusion and interpretation in this review. M.D. and C.D. contributed equally to the present work. All authors contributed to the critical revision of the manuscript for valuable intellectual content. All authors have read and agreed with the final version of the manuscript.*

**Compliance with Ethics Requirements:**

**"***The authors declare no conflict of interest regarding this article".*

**Acknowledgements:** *None*

## REFERENCES

[1] Vogel B, Acevedo M, Appelman Y, Bairey Merz CN, Chieffo A, Figtree GA, et al. The Lancet women and cardiovascular disease Commission: reducing the global burden by 2030. *Lancet.* 2021;397(10292):2385–438.

[2] Roth GA, Johnson C, Abajobir A, Abd-Allah F, Abera SF, Abyu G, et al. Global, Regional, and National Burden of Cardiovascular Diseases for 10 Causes, 1990 to 2015. *J Am Coll Cardiol.* 2017;70(1):1–25.

[3] Lopez AD, Adair T. Is the long-term decline in cardiovascular-disease mortality in high-income countries over? Evidence from national vital statistics net. *Int J Epidemiol.* 2019;48(6):1815–23.

[4] Arora S, Stouffer GA, Kucharska-Newton AM, Qamar A, Vaduganathan M, Pandey A, et al. Twenty Year Trends and Sex Differences in Young Adults Hospitalized with Acute Myocardial Infarction: The ARIC Community Surveillance Study. *Circulation.* 2019;139(8):1047–56.

[5] Gabet A, Danchin N, Juillière Y, Olié V. Acute coronary syndrome in women: Rising hospitalizations in middle-aged French women, 2004-14. *Eur Heart J.* 2017;38(14):1060–5.

[6] Young L, Cho L. Unique cardiovascular risk factors in women. Heart.2019 Nov;105(21):1656-1660

[7] Roth GA, Mensah GA, Johnson CO, Addolorato G, Ammirati E, Baddour LM, et al. Global Burden of Cardiovascular Diseases and Risk Factors, 1990-2019: Update From the GBD 2019 Study. *J Am Coll Cardiol.* 2020;76(25):2982–3021.

[8] Benjamin EJ, Muntner P, Alonso A. Heart disease and stroke statistics 2019 update: a report from the American Heart Association. *Am Heart Assoc.* 2019;139(Circulation):e56-528.

[9] Rankin JS, Hammill BG, Ferguson TB, Glower DD, O'Brien SM, DeLong ER, et al. Determinants of operative mortality in valvular heart surgery. *J Thorac Cardiovasc Surg.* 2006;131(3):547–57.

[10] Marijon E, Mirabel M, Celermajer DS, Jouven X. Rheumatic heart disease. *Lancet* [Internet]. 2012;379(9819):953–64. Available from: http://dx.doi.org/10.1016/S0140-6736(11)61171-9

[11] Song P, Rudan D, Zhu Y, Fowkes FJI, Rahimi K, Fowkes FGR, et al. Global, regional, and national prevalence and risk factors for peripheral artery disease in 2015: an updated systematic review

and analysis. *Lancet Glob Heal* [Internet]. 2019;7(8):e1020–30. Available from: http://dx.doi.org/10.1016/S2214-109X(19)30255-4

[12] Frohlich ED. Fibrosis and ischemia: The real risks in hypertensive heart disease. *Am J Hypertens*. 2001;14(6 II):194–9.

[13] Nwabuo CC, Vasan RS. Pathophysiology of Hypertensive Heart Disease: Beyond Left Ventricular Hypertrophy. *Curr Hypertens Rep*. 2020;22(2).

[14] Pa CK. The effective history of critical theory: The reception history of Frankfurt school in Taiwan. *Universitas (Stuttg)*. 2010;37(6):111–25.

[15] Ji H, Kim A, Ebinger JE, Niiranen TJ, Claggett BL, Bairey Merz CN, et al. Sex Differences in Blood Pressure Trajectories over the Life Course. *JAMA Cardiol*. 2020;5(3):255–62.

[16] Matthews KA, El Khoudary SR, Brooks MM, Derby CA, Harlow SD, Barinas-Mitchell EJ TR. Lipid Changes Around the Final Menstrual Period Predict Carotid Subclinical Disease in Postmenopausal Women. *STROKE*. 2017;48(JAN):70–6.

[17] Peters SAE, Huxley RR, Woodward M. Diabetes as risk factor for incident coronary heart disease in women compared with men: A systematic review and meta-analysis of 64 cohorts including 858,507 individuals and 28,203 coronary events. *Diabetologia*. 2014;57(8):1542–51.

[18] Retnakaran R. Hyperglycemia in pregnancy and its implications for a woman's future risk of cardiovascular disease. *Diabetes Res Clin Pract* [Internet]. 2018;145:193–9. Available from: https://doi.org/10.1016/j.diabres.2018.04.008

[19] Gallagher D, Visser M, Sepúlveda D, Pierson RN, Harris T, Heymsfield SB. How useful is body mass index for comparison of body fatness across age, sex, and ethnic groups? *Am J Epidemiol*. 1996;143(3):228-39.

[20] Callaway LK, Prins JB, Chang AM, McIntyre HD. The prevalence and impact of overweight and obesity in an Australian obstetric population. *Med J Aust*. 2006;184(2):56-9.

[21] Bellettiere J, Lamonte MJ, Evenson KR, Rillamas-Sun E, Kerr J, Lee IM, et al. Sedentary Behavior and Cardiovascular Disease in Older Women: The OPACH Study. Circulation. 2019;139(8):1036–46.

[22] Chomistek AK, Cook NR, Rimm EB, Ridker PM, Buring JE, Lee IM. Physical activity and incident cardiovascular disease in women: Is the relation modified by level of global cardiovascular risk? *J Am Heart Assoc*. 2018;7(12).

[23] Roth GA, Nguyen G, Forouzanfar MH, Mokdad AH, Naghavi M, Murray CJL. Estimates of global and regional premature cardiovascular mortality in 2025. *Circulation*. 2015;132(13):1270–1.

[24] Dam V, Van Der Schouw YT, Onland-Moret NC, Groenwold RHH, Peters SAE, Burgess S, et al. Association of menopausal characteristics and risk of coronary heart disease: A pan-European case-cohort analysis. *Int J Epidemiol*. 2019;48(4):1275–85.

[25] Newby DE, Mannucci PM, Tell GS, Baccarelli AA, Brook RD, Donaldson K, Forastiere F, Franchini M, Franco OH, Graham I, Hoek G, Hoffmann B, Hoylaerts MF, Künzli N, Mills N, Pekkanen J, Peters A, Piepoli MF, Rajagopalan S SR. Expert position paper on air pollution and cardiovascular disease. *Eur Heart J*. 2015;36:83–93.