Review Article

# Winter Cardiovascular Diseases Phenomenon

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## Abstract

This paper review seasonal patterns across twelve cardiovascular diseases: Deep venous thrombosis, pulmonary embolism, aortic dissection and rupture, stroke, intracerebral hemorrhage, hypertension, heart failure, angina pectoris, myocardial infarction, sudden cardiac death, venricular arrythmia and atrial fibrillation, and discuss a possible cause of the occurrence of these diseases. There is a clear seasonal trend of cardiovascular diseases, with the highest incidence occurring during the colder winter months, which have been described in many countries. This phenomenon likely contributes to the numbers of deaths occurring in winter. The implications of this finding are important for testing the relative importance of the proposed mechanisms. Understanding the influence of season and other factors is essential when seeking to implement effective public health measures.

**Keywords:** Cardiovascular diseases, Periodicity, Seasons

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## Introduction

Cardiovascular diseases (CVDs) is the number one cause of death worldwide. An estimated 17.3 million people died from CVDs in 2008, representing 30% of all global deaths.[1] Seasonal variation in morbidity and mortality due to CVDs has been noted in both the northern and southern hemispheres, with higher incidence rates during the winter than in the summer. This variation linked with multiple risk factors, such as temperature, physical activity, air pollution, infections, and food habits.[2,3] Another potentially important seasonal risk factors such as seasonal variation in the plasma level of fibrinogen, cholesterol, Hormones and vasoactive substance including vasopressin (AVP), norepinephrine (NE), epinephrine (E) and angiotensin II, aldosterone and catecholamine which tends to rise in the winter is suggested to play an important role in the seasonal change of CVDs.[3] However, the influence of these factors on the onset and course of cardiovascular events is not well understood. Several mechanisms have been suggested to explain this association. The purpose of this article is to review the literature on seasonality of CVDs and discuss the current situation and controversies related to this phenomenon. This paper also provides a detailed literature on the factors influencing the seasonal patterns of CVDs.

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## Seasonal patterns of cardiovascular diseases

### *Deep venous thrombosis*

A number of studies have focused specifically on the seasonal variability of deep venous thrombosis (DVT). Most studies have reported a higher occurrence of DVT during the winter months.[4-11] Only a few studies have failed to find such seasonal variation in the incidence of DVT.[12-14] Interestingly, a preference for winter in the occurrence of DVT has been linked with meteorological influences, such as temperature, low atmospheric pressure, high wind speed and high rainfall.[4,11] Seasonal variation in wind speed and temperature were found significantly associated with an increased risk of DVT approximately 9-10 days later.[4] Futhermore, reduced physical activity during the winter months, reduce blood flow in the lower limbs and decreased fibrinolytic activity have been suggested to be associated with the increase incidence of DVT in winter.[15] Additionally, several studies have demonstrated a consistent increased risk for cardiovascular events in relation to acute exposure to environmental pollutants, due to their effect on the coagulation cascade and on platelet function. Air pollutants are elevated

during winter months, especially in the big cities and thus they may be at least in part, responsible for the seasonal variation in the incidence of cardiovascular diseases, including DVT and pulmonary embolism (PE).

### *Pulmonary embolism*

Seasonal variation in pulmonary embolism has been well documented by several epidemiological studies with maximum and minimum incidences in winter and summer.[5,16-26] While, few studies, observed a different seasonal peak in the onset of acute pulmonary embolism characterized by a higher frequency in the autumn and spring,[27-30] and others found no significant differences in seasonal distribution of pulmonary embolism episodes.[31-35] In a recent meta-analysis study published in 2011 confirm the existence of a seasonal and monthly variability of venous thromboembolism (VTE), with a statistically significant peak observed in winter and in particular in the month of January. In winter time, there is an absolute increase in the risk of VTE of 14% as compared to the other seasons, and the absolute increase in the risk of VTE observed in January is 20% as compared to the other months.[36] The seasonal increases in pulmonary embolism episodes have been explained by the changes in coagulation factors level, peripheral vasoconstriction and reduced activity. However, some studies did not found correlation between meteorological factors and seasonality of PE.

### *Aortic rupture/dissection*

Several studies have reported a seasonal variation in the incidence of in aortic rupture or dissection, the incidence of aortic dissection and rapture were found to be higher in winter time than in summer in 45.8% of the studies,[37-47] and 41.6% of these studies reported significant peak of incidence in spring and autumn.[48-57] while only 12.5% failed to find convincing evidence of seasonality in rupture or dissection of aortic aneurysm.[58-60] The underlying cause is unknown, but hypertension and tobacco smoking are predisposing factors to aortic aneurysm rupture. Exposure to tobacco smoke is known to be greater indoors in cold weather and there is a winter peak of blood pressure in hypertensive patients. A relatively high positive correlation was found between the incidence of acute aortic dissection and the mean atmospheric pressure in some of the studies. Winter is also characterized by pro-thrombotic state. Fibrinogen levels demonstrate wide seasonal variation, increasing up to 23% during the colder months. Furthermore, a mild surface cooling can increase platelet and red cell count and consequently blood viscosity, thereby favoring spontaneous thrombosis. Moreover, activation of the sympathetic nervous system and secretion of catecholamine are increased in response to cold temperatures. This could result in an increase in blood pressure through increased heart rate and peripheral vascular resistance. This enhances the forces that act to produce wall deformation, and increase friction and shear stress on the internal surface. The consequent vascular damage may progress, culminating in arterial dissection and rupture of the aorta.[61]

### *Stroke*

Many studies conducted in different countries throughout the world, including those in Europe, Asia, Australia, and North America, report an association between season of the year and stroke incidence. Among these studies 48.4% reported a higher frequency of events during the colder months (autumn–winter seasons),[62-77] and 39% found that the highest rates occur warmer months (spring–summer),[78-90] while only 12% of these studies reported no evidence supporting seasonal variation in stroke rates.[91-94] There is only little information available on the seasonal variability of Transient ischemic attack (TIA). In a study conducted in Italy on 4642 patients found that the incidence of TIA was most frequent in autumn and winter and less common in spring and summer, independent of sex and the presence of the most common risk factors.[95]

### *Nontraumatic intracerebral hemorrhage*

Nontraumatic intracerebral hemorrhage is a common cause of stroke, represents approximately 10% of all strokes and two thirds of hemorrhagic strokes.[96] Seasonal variations in the incidence of nontraumatic intracerebral hemorrhage have been extensively evaluated in studies conducted in various parts of the world. It was documented for the first time by Aring and Merritt,[97] who observed in the Boston area that the incidence of cerebral hemorrhage was highest in winter and lowest in summer. The same pattern was observed in Bangladesh,[78] Taiwan,[98] Japan,[99] Brussels,[100] Iowa,[90] Minnesota,[101] Britain,[102] Romania,[103] and Portugal[104] but was not borne out in other investigations in Boston and Chicago,[105] the Lehigh Valley,[106] and Netherlands.[107] On the other hand, reports from Serbia,[79] have found the peak of hospital admissions due to intracerebral hemorrhage occurred in early spring and a trough in late summer months. The underlying causes of this variation are not completely understood, but hypertension and exposure to low temperature are predisposing factors to intracerebral hemorrhage. The seasonal variation in blood pressure is well known, blood pressure being higher in winter. Elevated blood pressure during the winter may play an important role as a trigger for intracerebral hemorrhage.[99]

### *Hypertension*

Seasonal influence on arterial blood pressure has been demonstrated by various studies based on single or repeated measurements among adults, the elderly, and children as well as healthy and hypertensive

subjects.[108-130] In all of these studies, Both systolic and diastolic mean blood pressures showing a seasonal peak during winter and trough in summer. The seasonal variation in hypertension is likely to reflect seasonal variations in one or more risk factors. The risk factors proposed by investigators have included: Outdoor temperature, physical activity, seasonality of vitamin D, seasonal variation in serum cholesterol level, noradrenalin, catecholamine, and vasopressin.

### *Heart failure*

Several studies on seasonal variation in heart failure (HF) hospitalization carried out in France, Spain, Japan, Scotland, Australia, Brazil, Argentina, Italy, Turkey, Nigeria, Canada, and USA[131-144] have shown an increase in admission during the winter season and a decline in summer season. The cause of the winter increase in HF remains in doubt. Cold weather, among other factors, increases peripheral vasoconstriction, which may lead to pulmonary oedema as a consequence of left ventricular failure and may also cause abnormal clotting. In patients with symptomatic CHF, cold exposure decreases exercise capacity and increases the already raised systemic adrenergic activation. As increased plasma norepinephrine concentrations are associated with increased risk of death from progressive heart failure this may, in part, explain the increased mortality in winter.[135] Additionally, Increased blood pressure, lack of vitamin D; physical activity, influenza, and air pollution in winter have also been postulated as responsible factors for the higher number of cases during colder months.

### *Atrial fibrillation*

Seasonal variation in the occurrence of atrial fibrillation has been documented, with peaks typically occurring in the winter-autumn and troughs in the summer, the mechanisms and factors underlying this phenomenon remain unclear. The extensive Danish population studies carried out for fourteen years and involving approximately 33,000 patients with atrial fibrillation (AF) paroxysms reported an inversely proportional influence of mean outdoor temperature and similar effect of season.[145] Studies performed in Japan showed maximum AF incidence in autumn, with a significant reduction in summer.[146] Similarly, six studies on the seasonality of AF, In Israel,[147] Finland[148] Poland,[149,150] Scotland,[151] and Australia[152] found the peak of incidence during winter months. In contrast, the peaks for AF hospitalizations in Canada were found predominantly in spring and the troughs in summer.[153] It seems that the above observations may be rationally explained by the effects of specific factors such as air temperature, humidity and atmospheric pressure, in particular with concomitant ischemic heart disease or arterial hypertension as well as in the elderly. However, further research could help to better understand the clinical epidemiology and public health impact of AF and its complications and identify opportunities for better prevention of AF.

### *Ventricular arrhythmias*

The seasonal variation of ventricular arrhythmias (VA) has been assessed in studies with animal models and observational studies. In a canine model of myocardial infarction, there was a higher incidence of VA in winter.[154] In a study of 154 patients with ischemic heart disease (IHD), the incidence of ventricular tachycardia (VT) or ventricular fibrillation (VF) episodes was found to be higher in winter months and the lowest in summer, spring, and fall. A linear regression between the number of episodes and the average daily temperature showed a greater likelihood of the 2 events occurring on cooler days, irrespective of the cause of cardiac disease.[155] Three other studies found a similar seasonal pattern in the incidence of VT and VF.[156-158] The potential factors that can influence the seasonal variation of VA have not been fully understood. Thermal stress, due to very low as well as very high temperatures, can trigger alterations in physiological processes and may be physiopathological ones, determining a seasonal variation in cardiovascular events.[159] In contrast, the incidence of VA in southern Brazil and Japan was found more frequent during summer than in winter months.[159,160] The increase in the incidence of VA in summer can be related not only to alterations in the absolute temperature degree, but also to behavior alterations, which are characteristic of this season. During summer, longer exposure to sunlight, increase of physical activities and uncontrolled weight-loss diets can lead to fluid and electrolyte loss through the skin, which can determine electrolyte imbalance, favoring the occurrence of VA. Similarly, the increased food and alcoholic beverage intake, which is characteristic of the vacation periods, can also contribute to an increase in the occurrence of VA.[159]

### *Angina pectoris*

Few studies exist on the seasonal variability of angina pectoris (AP). In a study of 2459 patients admitted with angina pectoris in Italy, AP has been found to correlate with a combination of critical values of low temperatures and humidity, although it seems different according to the gender. Significant incidence relative ratios were, in males, 0.988 (0.980-0.996) for minimal temperature, 0.990 (0.984-0.996) for maximal humidity and 1.002 (1.000-1.004) for minimal humidity. The corresponding values in females were 0.973 (0.951-0.995) for maximal temperature and 1.024 (1.001-1.048) for minimal temperature. The highest hospital admissions were during winter as compared to other seasons.[161] In Russia, The vast majority of cases of progression

of angina were observed in autumn and winter.[162] In contrast, the incidence of unstable angina (UA) in Canada was found more frequent during summer than in winter. This seasonal variation in the incidence of UA was significant only in male patients.[163]

### *Acute myocardial infarction*

An increase in mortality from acute myocardial infarction (AMI) in the winter months was first reported in the 1930s.[164] Since, these initial observations, numerous studies have reported an increased morbidity and mortality from AMI during the autumn and winter.[165-180] In contrast, a peak period of the occurrence of AMI in Hungary was found during spring.[181,182] An association between seasonality and AMI morbidity and mortality was found in most age and sex groups, with men consistently exhibiting a stronger seasonality pattern, although this difference decreases with advancing age.[170,168] In a Danish population study reported that the AMI followed different seasonal patterns depending on age, but not on gender. In the < 59-year-old group, the seasonal pattern was dominated by a broad spring peak (April/May) and a minor autumn peak. With increasing age, the spring peak decreased while the autumn peak increased and moved towards December. A seasonal pattern dominated by one peak (December) and one trough (August) was found in the > or = 80-year-old category.[183] Documentation of this circannual variation has directed further investigation of pathophysiologic triggers of the nonrandom occurrence of AMI. Arterial blood pressure, vasocostraction, plasma cortisol and catecholamines, platelet aggregability and numerous hematologic variables have all been shown to display a seasonal rhythm. Potential environmental and lifestyle factors associated with precipitation of AMI include physical exertion and outdoor temperature.

### *Sudden cardiac death*

Seasonal variation in sudden cardiac death (SCD) has been well documented by several epidemiological studies with maximum and minimum incidences in winter and summer.[184-190] While, few studies, observed a different seasonal peak in the onset of SCD characterized by a higher frequency in the summer months.[191,192] The exact cause of this variation is unknown, but it is believed that a combination of external and internal factors such as cold weather, increased platelet aggregability, decreased fibrinolytic activity, and other blood components involved in thrombogenesis may be an important risk factor in bringing on the onset of SCD in winter.[193] This approach is strengthened by the findings of similar seasonal patterns for myocardial infarction, transient myocardial ischemia, and arrhythmias. The winter increase in the occurrence of these related disorders suggests causation by identifiable triggers.[193]

## Factor influencing the seasonal patterns of cardiovascular diseases

### *Temperature*

Mechanisms that could explain the association between cardiovascular diseases and temperature remain undetermined. Activation of the sympathetic nervous system and secretion of catecholamine are increased in response to cold temperatures. This could result in an increase in blood pressure through increased heart rate and peripheral vascular resistance.[194] In patients whose coronary circulation is already compromised this extra demand may produce myocardial ischaemia and, therefore, angina pectoris or MI.[3] A statistically significant positive correlation was also found between both air pressure and humidity and the incidence of PE.[29] In a study conducted in Scotland[4] found that wind speed and temperature were significantly associated with seasonal peak of DVT. The effect was delayed by approximately 9-10 days, but the authors calculated that every 10-mbar decrease in pressure was associated with a 2.1% increase in the relative risk of DVT. Additionally, experimental studies suggested that alterations in temperature might also influence vascular function through an effect on endothelial nitric oxide synthase and the bioavailability of nitric oxide. In rats, Acute and short-term exposure to elevated environmental or core body temperatures has been shown to increase endothelial nitric oxide synthase expression. Conversely, repeated cold exposure of rats (4°C for 4h per day for 1 week) led to the development of hypertension and impaired endothelial vasodilator function in isolated arterial tissue.[195]

### *Vitamin D*

Significant seasonal vitamin D level variations were observed in several communities, which reveal a variation of values for 25-(OH) D, increased during summer and spring, while gradually decreasing in autumn and winter. Vitamin D deficiency has been to be associated with CVD risk factors such as hypertension and diabetes mellitus, with markers of subclinical atherosclerosis such as intima-media thickness and coronary calcification as well as with cardiovascular events such as myocardial infarction, stroke and congestive heart failure.[196] several studies have demonstrated lower levels of vitamin D metabolites in subjects with Coronary heart disease (CHD) and hypertension. The association between vitamin D levels and CHD has been shown to be independent of smoking, body mass index, treatment for hypertension, vigorous leisure activity, total serum cholesterol and a previous history of angina or MI.[197] several mechanisms have been proposed to explain the link between vitamin D deficiency and cardiovascular disease. Experimental data suggest that $1,25(OH)_2D$ affects cardiac muscle

directly, controls parathyroid hormone secretion, regulates the renin-angiotensin-aldosterone system and modulates of smooth muscle cell proliferation, inflammation and thrombosis.[198] Because of these biologic effects, vitamin D deficiency has been associated with hypertension, vascular diseases and heart failure. Higher exposure to ultra violet (UV) radiation in summer may therefore, protect against CVDs events.

### *Serum cholesterol level*

Elevated Serum cholesterol level has been shown to be associated with an increased risk for development of and death due to CVD. Serum cholesterol is strongly associated with endothelial dysfunction and reduced nitric oxide bioavailability,[199-201] which may lead to functional arterial stiffening. In cholesterol-fed rabbits, increased oxidative stress has been found, attributable to endothelial dysfunction.[202] Oxidative stress reduces the function of renal dopamine receptors in rats, leading to sodium retention and high blood pressure.[203] interestingly, a significant seasonal variation in plasma levels cholesterol has been reported in many studies, with maximum and minimum incidences in winter and summer.[204-206]

### *Physical activity*

In both sexes, overall levels of physical activity are significantly higher in summer than in winter.[3] Physical inactivity is strongly positively associated with CVDs. In a study conducted by Magnus and colleagues demonstrated that physical activities such as walking, cycling and gardening only protect against acute coronary events if undertaken throughout the year.[207] How physical activity positively affects CVDs remains unclear. One of the primary mechanisms through which physical activity is thought to affect CVDs is through improves endothelial function. The endothelium acts to maintain normal vasomotor tone, enhance the fluidity of blood and regulate vascular growth. Abnormalities in these functions contribute many disease processes, including myocardial infarction, coronary vasospasm and hypertension. Exercise causes increases in blood flow leading to increased shear stress, which is the force acting parallel to blood vessels. Enhanced shear stress results in endothelium-dependent, flow-mediated dilation of vessels. Chronic increases in shear stress have been found to improve endothelial function in animal studies as well as in some limited human studies.[208] Another mechanism proposed that the physical activity may also reduce the elevated sympathetic nerve activity that is common in essential hypertension.[209]

### *Coagulation factors*

Over the past decade extensive evidence has been accumulated which shows that the elevated plasma fibrinogen levels and factor VII clotting activity (FVIIc) a strong and consistent association with cardiovascular disorders such as ischaemic heart disease, stroke and peripheral vascular disease. Interestingly, seasonal variability with peak concentrations during cold months was shown for fibrinogen and FVIIc.[210,211] several hypotheses have been proposed to explain the rise of plasma fibrinogen levels in winter. Some authors have suggested an increased incidence in winter respiratory infections, which might cause an acute-phase reaction and consecutively lead to an increase in fibrinogen.[210] Fibrinogen may contribute to atherothrombogenesis by several mechanisms: Involvement in early atherosclerotic plaque formation (i.e., providing an adsorptive surface for LDL accumulation), involvement in the response to endothelial damage, increased platelet aggregability by interaction with glycoprotein IIb/IIIa receptors on the platelet surface, increased RBC aggregation, and finally, contribution to Plasma viscosity.[212] An increase in these factors generates a "hypercoagulable state," which may lead to a rise in cardiovascular morbidity and mortality.

### *Hormones*

Hormones and vasoactive substance such as AVP, NE, E and angiotensin II, aldosteron and catecholamin have suggested play a role of seasonal variation in blood pressure. In a study conducted in Japan, mean plasma noradrenaline, urinary excretion of catecholamines and sodium significantly higher in winter than in summer was found in hypertensive patients. No comparable differences were found in either plasma renin activity or plasma aldosterone concentrations.[140] Furthermore, Cold air exposure of 4°C for 30 min was found reduce the plasma vasopressin levels in human subjects.[213] in another study, Plasma aldosterone (PA) was found significantly increased 59% from summer to winter, whereas plasma norepinephrine (PNE), plasma epinephrine, and plasma renin activity (PRA) increased 19, 2 and 17%, respectively.[214] In twenty healthy male volunteers exposed to a temperature of 10 degrees C for 120 min, Leppäluoto and associates[215] demonstrated a significant increase in serum level of noradrenaline from 4.5 to 6.3 nmol l. Endothelin I has been suggested may play a role in the pathophysiology of congestive heart failure and myocardial infarction. In a German study found that Endothelin-1 levels displayed a significant variation, with a sinusoid pattern throughout the year: Nadir values occurred in January, peak values in July. Angiotensin II demonstrated a significant correlation with endothelin-1 and paralleled its rhythmicity. In contrast, plasma catecholamines exhibited an opposite pattern.[216] In an attempt to study effects of cold on blood pressure and the renin-angiotensin-aldosterone system, 34 healthy young subjects with or without a family history of essential hypertension were

exposed to moderate cold (4 degrees C for 1h) or severe cold (immersion of the hands to 0 degrees C for 10 min). Moderate cold was found elevated blood pressure, aldosterone, cortisol and noradrenaline when the subjects wore summer clothing but not when the subjects wore winter clothing. In addition to above observations, it also noticed that the Exposure to cold air induce declines in serum T3, T4 and increases TSH production.[217] Thyroid hormone has long been known for its profound direct effects on the cardiovascular syste. The hormone can increase myocardial inotropy and heart rate and dilate peripheral arteries to increase cardiac output. An excessive deficiency of thyroid hormone can cause cardiovascular disease and aggravate many preexisting conditions.

### *Air pollution*

Air pollution is a heterogeneous, complex mixture of gases, liquids, and particulate matter. Epidemiological studies have demonstrated a consistent increased risk for cardiovascular events in relation to both short- and long-term exposure to present-day concentrations of ambient particulate matter (PM). A number of biological mechanisms have been proposed to explain these associations. In study conducted by Peters and associates[4] on 772 patients with AMI found that the elevated concentrations of $PM_{2.5}$ were associated with a transient risk of AMI onset during 2 separate time periods (within 2 h and 1 day after exposure). Other contemporary studies suggest that possible links between acute and/or chronic exposure to PM and cardiovascular events may be related to increases in heart rate and blood pressure, fibrinogen, and blood coagulation factors, arterial vasoconstriction, inflammatory mediators (e.g., C-reactive protein [CRP]), and endothelial injury/dysfunction.[218] Consequences of these effects may include myocardial ischemia (manifested as significant ST-segment depression during exercise testing, angina pectoris, or both),[219] malignant ventricular arrhythmias,[220] increased plaque vulnerability and enhanced potential for acute thrombosis triggering acute coronary syndromes.[221] Further, support that these changes can be attributed to air pollution comes from studies of the effects of Passive smoking, which is the single largest contributor to indoor PM[222] when a smoker is present. Exposure to Passive smoking increases platelet activation,[223] causes rapid deterioration in endothelial function,[224,225] promotes atherosclerotic plaque development,[226] and abets infarct expansion in experimental animals.[227] Because exposure to the Passive smoking of just 1 cigarette per day accelerates the progression of atherosclerosis,[227] Interestingly, Seasonal variations of PM, PM10 and PM2.5 have been observed to be maximum during winter months.[228] In a study, conducted in Beijing, China found the PM2.5 increased up to 57% in winter.[229] In Turkey, The concentration of PM2.5, and PM10 was found to be higher in winter than in summer. As expected, the low temperature is associated with an increase in the number of episodic events. This is may be as a result of the extensive use of fuel during winter-time for heating purposes and also due to stagnant air masses formed because of low temperature and low wind speed over the study area.[230]

### *Infections*

A number of microbial agents have been implicated in the pathogenesis of atherosclerosis, including *Chlamydia pneumoniae*, *Helicobacter pylori*, and Inflaunza verus. A number of investigators have postulated that seasonal variations in CVDs may be attributed, in part, to the fact that respiratory infections are more common in winter months. Respiratory infections may increase the risk of developing or dying from CHD through an increase in plasma fibrinogen and endotoxin inhibition of fibrinolysis.[3] Furthermore, the tachycardia and increased cardiac output that accompany many acute infections and febrile illnesses could increase the wall stress experienced by an atheromatous plaque. This could trigger coronary events by promoting disruption of vulnerable plaques. A range of observational studies done in different settings have generally tended to support the hypothesis that acute respiratory infections can trigger acute coranry diseases. A systematic review of 39 observational studies reported consistent associations between influenza and acute myocardial infarction, and some evidence that influenza vaccines are effective at reducing the risk of cardiac events in those patients with established cardiovascular disease.[231] Moreover, recent seroepidemiological studies support a relationship between prior infection with *Chlamydia pneumonia* and atherosclerosis.[232] Originally, small observational studies established that patients with acute myocardial infarction or chronic coronary artery disease had higher titers of chlamydial antigens than did control patients.[233] seasonal variation in prevalence of *Chlamydia pneumonia* was seen among both cardiology and respirolgy, with highest prevalence between February and April and lowest prevalence between June and October.[234] Rassu, *et al*.[235] reported higher prevalence among Italian blood donors in February (57.6%) compared with October (37.9%).

### *Age and sex*

Cardiovascular deaths due to myocardial infarction (MI), stroke and VTE account for the leading number of deaths among women as well as men. A seasonal occurrence of Angina Pectoris seems different according to the gender. Significant incidence relative ratios were found

higher in males than female.[160] Seasonality of AMI was found in most age and sex groups, with men consistently exhibiting a stronger seasonality pattern, although this difference decreases with advancing age. Strokes due to venous or arterial thrombosis are more frequent in women of menopausal age. These variations may be due to the hormonal changes that occur in the body, especially during the early stages of the menopause transition time or later. In a cross-sectional study of 132 healthy women aged 22-70 year conducted in USA found that a decline in endothelial function begins during the early stages of menopause (perimenopause) and worsens with the loss of ovarian function and prolonged estrogen deficiency.[236] The influence of age in seasonal occurrences of CVDs is likely reflect a combination of factors including poorer autonomic control, lower levels of physical activity, less use of protective clothing, greater time spent at home, and poorer household heating and insulation.[3]

### *Diet and obesity*

Dietary intake in summer and winter is different as well as body mass index (BMI) and serum cholesterol.[237] Several epidemiological studies have demonstrated the link between CVDs and overweight, high blood pressure and increased serum total cholesterol. A significant and consistent relationship was shown between elevated plasma total and LDL cholesterol and the incidence of CHD.[237] Epidemiological and experimental studies in animals and in humans have shown that consumption of specific fatty acids can affect both blood cholesterol levels and the atherosclerotic disease process. Weight gain, even to a modest degree, was found to raise blood pressure.[238-240] In a study conducted in Brazil found that the total fat intake was lower in summer when compared to autumn and spring.[241] Another study conducted on Ninety-four male industrial employees found increase in BMI, BP and serum Cholesterol in winter when comparing with summer.[237]

## Conclusion

The seasonal variability of CVDs is quite clearly demonstrated by the epidemiological data; showing mostly a peak in winter months. The exact cause of CVDs seasonality is not known clearly. However, many theories have been given to explain the possible reasons underlying the development of a disease in winter more than other time in year. Most of these theories commonly point out the fact that environmental factors such as temperature and air pollutions are play an important role in the occurrence of CVDs diseases in both sexes particularly in advance age patients. Although biological aspects are also known to contribute to the development of this disorders. This finding may have important implications; it seems that the risk of cardiovascular diseases appears to be the greatest during the winter months, particularly in elderly people. The knowledge of the role of environmental and biological factors could be used to improve prevention measures and educational strategies, especially in people with a risk of diseases. People should be informed of the increased risk of cardiovascular disease during the cold seasons, and educated about the importance of regular physical activity and dressing warmly in winter. Furthermore, people should be motivated to maintain health dietary habits including a nutrient rich in vitamin D and low fat intake. There also need to manage hospital beds and other resources effectively in winter to avoid bed crisis.

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