

Cardiovascular disease: A Global Epidemic extending into Sub-Saharan Africa. A Review of Literature.

Author:

Amusa G.A. MBBS, MMCP, MWACP.

Address:

Internal Medicine Department (Cardiology Unit) Jos University Teaching Hospital Jos.

Correspondence:

Dr Amusa G.A.

Department of Internal Medicine (Cardiology Unit) Jos University Teaching Hospital PMB 2076, Jos.

Email: drganiamusa@yahoo.com

+2348153319600

ABSTRACT:

Background:

Cardiovascular disease is a global epidemic; the prevalence is currently stable in the developed world but is on a rapid rise in the developing world particularly in Sub-Saharan Africa. It is the commonest cause of morbidity and mortality globally. Its victims are older in the developed world but younger in Africa where it affects mainly the productive age group. The morbidity is more than its mortality such that majority its victims are rendered unproductive and burdensome. The burden of the disease has shifted to the developing world particularly Sub-Saharan Africa. In 2002 over 80% of CVD associated mortality occurred in the developing world, and a victim is many times more likely to die than in the developed world. Fortunately as there is no smoke without fire, cardiovascular disease is preceded by certain modifiable and non-modifiable risk factors which can be identified and corrected before a full blown disease occurs.

Method:

This is a detailed search of existing literature and on-line database on the subject. A narrative review of the selected literature was then done to provide concise and current information on the subject.

Conclusion:

Cardiovascular disease is preventable. Governments at all levels must as a matter of urgency set up workable programmes to combat this scourge at the level of the risk factors. Interventions at the primary, secondary and tertiary levels must be implemented fully. Medical staffs must be trained at all levels to identify risk factors and treat them early.

Key words: *Cardiovascular disease, Hypertension, Dyslipidaemia, Obesity, Diabetes mellitus.*

Introduction:

Cardiovascular diseases (CVD) are diseases of the heart and blood vessels. They are a continuum that begin with the presence of risk factors, which if untreated progresses to target organ damage and end-organ failure¹.

Current epidemiologic predictions show that the world is heading for a cardiovascular disease pandemic. A recent cohort study reports that over 90% of the general population have a CVD risk factor; more than 70% of these individuals had multiple risk factors². In 2002, cardiovascular disease was estimated to have been responsible for

29% of deaths and 43% of morbidity across the world; it is currently the leading cause of death and has been for over 20 years³. The global burden far exceeds that of its death toll, affecting an estimated 128 million people, or nearly 8 times the number for mortality. Thus, the greater burden is attributable to nonfatal events and their long-term consequences^{4,5}. In the developing world, the probability of morbidity and mortality is higher than in developed world⁶.

Currently the prevalence is stable in the developed world but is on a rapid rise in Africa where it has also

reached epidemic proportions⁷. Several African countries including Nigeria have reported rising incidences. Many have sought to explain this as a phenomenon of epidemiological transition (Africa in stage 4 or 5 presently) and the increasing westernization of lifestyles^{8,9}.

Based upon statistics by the World Health Organization, approximately 80% of deaths caused by cardiovascular disease in 2003 occurred in developing countries³. It is the leading cause of death in all regions except for Sub-Saharan Africa; however when the analysis extends beyond adults aged 30 years and older, it is commonest cause of death in all regions¹⁰.

Compounding this problem, these deaths typically occur ten to fifteen years earlier than in developed countries thus reducing workforce capacity and potential for economic growth¹⁰. As the epidemic advance, the social gradient also reverses with the poor becoming the most vulnerable victims in both developed and developing countries¹⁰.

The development is promoted by its risk factors e.g. dyslipidemia, hypertension, diabetes, obesity, sedentary lifestyle, smoking. These risk factors are independently associated with cardiovascular disease and are common among adults. The identification of these risk factors and the implementation of control strategies can and have contributed to the fall in mortality rates observed in many industrialized nations¹⁰.

Cardiovascular disease Risk factors:

Clinically and epidemiologically, they are divided into 2 broad groups i.e. modifiable and non-modifiable risk factors. They can also be grouped as major or minor depending on strength of association. The modifiable risk factors include hypertension, diabetes, smoking, obesity, sedentary lifestyle, dyslipidemia⁸⁻¹² e.t.c. Non-modifiable risk factors are age, gender, family history and genetic predisposition. Certain risk factors such as Human Immunodeficiency Virus Infection, chronic parasitic infections, nutritional deficiencies etc are also linked to CVD and are prevalent in Sub-Saharan Africa. The Framingham Heart Study has established the independent impact of these risk factors in the development of cardiovascular disease¹³. Exposure to antecedent major risk factors is very common among those who develop the disease. Thus emphasizing the importance of considering all major risk factors in determining risk and in attempting to prevent clinical disease^{11,12}.

Hypertension:

Hypertension is a common and important major and modifiable risk factor for cardiovascular disease.^{11,14} According to WHO report of 2002, it is the third most important contributor to global disease burden among the six chief risk factors of underweight, unsafe sex, hypertension, unsafe water, tobacco and alcohol abuse; it is also the leading cause of global mortality^{6,9,15}. In Nigeria, it is the commonest cardiovascular disease risk factor with a prevalence rate of 20-25%¹⁶. It is the commonest cause of hospital admissions in tertiary medical institutions in Nigeria¹⁷.

Hypertension is a harbinger of cardiovascular disease and its risk factors, it is usually clustered with other risk factors e.g obesity, insulin resistance, diabetes and dyslipidaemia^{14,18-2}. Lowering blood pressure reduces morbidity and mortality for hypertension of all degrees and even in high-risk normotensive individuals²⁰. The relationship between blood pressure and risk of CVD event is consistent, continuous and independent of other risk factors. For individuals 40- 70 years of age, each increment of 20mmHg in systolic BP or 10 mmHg in diastolic BP doubles the risk of CVD across the entire blood pressure range from 115/75 to 185/115 mmHg^{21,22}. People of African descent tend to have higher blood pressure and hypertension related mortality rates than other races^{6,8,19}.

Dyslipidemia:

This is a major and modifiable risk factor; it is a significant predictor of endothelial dysfunction and atherosclerosis in all populations. A fifth of global stroke events and about 56% of global heart disease are attributable dyslipiderma²³. It is one of the top 3 causes of mortality in the industrialized world and is associated with significant co-morbidities such as diabetes, obesity and hypertension^{23,24}. In particular, high levels of total cholesterol and low levels of HDL have been extensively studied and found to be associated with increased rates of cardiovascular disease and so are used to calculate CVD risk scores e.g. the Framingham risk score^{13,19,24}.

Obesity:

This has reached epidemic proportions globally with more than one billion adults being overweight and at least 300 million being clinically obese²⁵. Obesity is an intriguing and paradoxical CVD risk in developing countries. This is because in regions such as Sub-Saharan Africa, epidemics of famine that culminate in malnutrition are believed to predominate. However, urbanization of some

regions has in fact induced higher obesity rates. The prevalence of obesity varies in different parts of Nigeria. For instance, Maiduguri has an overall prevalence of 2% while the urban working class of Ibadan has a prevalence of obesity as high as 24.5%.^{8,26} Abubakari et al found a prevalence of about 10% across West Africa²⁷. Mortality is an exponential function of increasing body weight, the risk of coronary heart disease (CHD) doubles with body mass index (BMI) greater than 25 and increases nearly fourfold when it is above 29^{28,29}.

The risk of developing type 2 diabetes also increases with weight such that individuals with a BMI above 35 have a 40-fold higher risk of developing diabetes when compared to non-obese individuals³⁰. It is a major and modifiable risk factor.

Diabetes mellitus:

The prevalence of diabetes in adults worldwide was estimated to be 4.0% in 1995 and is expected to rise to 5.4% by the year 2025³¹. The major part of this increase will occur in developing countries. Thus, by the year 2025, 75% of people with diabetes will reside in developing countries, as compared with 62% in 1995³¹. A 2008 review found an increase in the prevalence of diabetes in Nigeria and Ghana. From 1963 to 1998, the prevalence rose from 0.2% to 6.3% of the adult Ghanaian population while amongst Nigerians, the prevalence rose from 1.65% to 6.8% from 1985 to 2000³². Across Africa, the majority of people with diabetes are in the age range of 45-64 years unlike in the West where they are older³¹. Diabetes is an established major/modifiable risk factor for the development of CVD^{11,12,33}. A person with diabetes has a 2-4 fold greater risk of developing CVD compared with one without diabetes. cardiovascular disease is also the leading cause of morbidity and mortality for those living with diabetes³³.

Sedentary lifestyle:

This is a modifiable risk factor with an adverse impact on blood glucose levels, blood pressure and lipid profiles raising the risk of a cardiovascular event twofold³⁴. Independent of its impact on weight; regular exercise has favourable effects on glucose control, blood pressure, serum lipids and fitness levels^{35,36}. Poor fitness in young adults is associated with the development of cardiovascular risk factors. These associations involve obesity and may be modified by improving fitness³⁷. Sedentary lifestyle with its associated risk is increasing becoming rampant in Africa due to rural to urban migration.

Smoking:

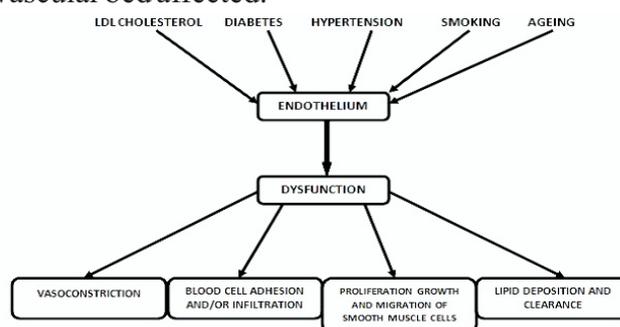
Worldwide the lowest smoking prevalence for both men and women is in Africa, while the highest prevalence for men is in Eastern Europe (>60%) and for women in Central Europe and parts of South America³⁸. The greatest increases in smoking prevalence over the next decade are expected to occur in Africa and the Middle East. Recent evidences suggest that smoking promotes other comorbidities such as lung cancer; it reduces immunity and causes endothelial dysfunction, hypertension, thromboembolism and atherosclerosis by release of the several noxious substances³⁹. Smoking is a major and modifiable risk factor.

Age and Gender:

The risk for cardiovascular disease increases steeply with advancing age in men and women. Historically, men have had higher cardiovascular related mortality rates than women³⁹. However, CVD is still the leading cause of mortality in women, being responsible for a third of all deaths of women worldwide and half of all deaths of women over 50 years of age in developing countries³⁹. Some retrospective analyses suggest that there are some clinically relevant differences between women and men in terms of prevalence, presentation, management and outcomes of the disease. However not much is known about why cardiovascular disease affects women and men differently. In Africa, the population is growing older hence the increase in cardiovascular disease rates.

Pathophysiology of Cardiovascular disease:

Endothelial dysfunction resulting from endothelial injury inflicted by the risk factors appears to be the common pathway for the development of cardiovascular disease⁴⁰. The endothelium is susceptible to the shear stress and inflammation in the presence of risk factors. Preponderance of these risk factors promotes migration of inflammatory cells from the circulation and the subendothelial space into the endothelial layer of the blood vessel. This results in chronic inflammation, intima scarring and atherosclerosis which manifests with certain symptoms and signs depending on the vascular bed affected.



Injury to endothelium causes endothelial dysfunction

Treatment of Cardiovascular disease:

Smoking: Quitting smoking is associated with a substantial reduction in risk (36% reduction in crude relative risk) of all-cause mortality among patients with CHD⁴¹. Patients who stop smoking can expect an increase of up to 30 percent in their HDL-C levels⁴². Smoking cessation results in 60% reduction of CHD risk by 3 years; about half of that benefit occurs 3-6 months after quitting.

Hypertension:

The health goal of treatment is the reduction of cardiovascular and renal morbidity and mortality. The primary focus is on achieving the blood pressure goal. Treating blood pressure to targets that are <140/90 mmHg is associated with a decrease in CVD complications. In patients with hypertension and diabetes or renal disease, the blood pressure goal is <130/80 mmHg^{43,44}.

Pharmacologic therapy must take into cognisance other co-morbidity present in the patient. Combination therapy is often recommended using the first line drugs i.e. diuretics, Angiotensin Converting enzyme inhibitors, angiotensin receptor blockers, beta blockers and calcium channel blockers.

The JNC 7 report also recommends lifestyle modification for all patients with hypertension and prehypertension, these modifications include⁴⁵:

- Reducing dietary sodium to less than 2.4 g per day;
- Increasing exercise to at least 30 minutes per day, four days per week;
- Limiting alcohol consumption to 21 units or less per week for men and 14 units or less per week for women.;
- Following the Dietary Approaches to Stop Hypertension (DASH) eating plan (high in fruits, vegetables, potassium, calcium, and magnesium; low in fat and salt) and
- Achieving a weight loss goal of 4.5 kg or more

Diabetes:

The treatment of diabetes mellitus involves multiple goals (glycaemia, lipids, BP). The United Kingdom Prospective Diabetes Study (UKPDS) provides ample evidence that glycaemia control is paramount in reducing microvascular complications. Focusing on glucose alone does not manage patients with diabetes mellitus optimally⁴⁶. Oral agents should always be combined with lifestyle modification, including regular exercise and attention to both individual food choices and

overall caloric intake to further optimize glycaemia control. Often pharmacotherapy with at least one lipid-lowering agent is also required. Blood pressure control often requires the use of combination therapy in patients with diabetes. Clinical data support use of an ACE inhibitor as first-line therapy for the prevention of microalbuminuria in patients with diabetes and hypertension. Low-dose aspirin is appropriate for patients over age 45 for primary prevention of cardiovascular disease.⁴⁷

Dyslipidaemia:

Atherogenic dyslipidaemia consists of abnormal levels of triglycerides, LDL-C particles, and low HDL-C levels. LDL-C is the primary target of therapy. Statins are recommended as first-line agents for lowering LDL-C levels and reducing the risk of CHD²³.

Regular Exercise:

The AHA/NHLBI recommends 60 minutes of continuous or intermittent aerobic activity (preferably brisk walking) daily to promote or maintain weight loss. Walking should be supplemented by jogging, swimming, biking, golfing, team sports, resistance training, use of a treadmill or other simple exercise equipment, or multiple 10-15-minute sessions of activity (e.g. walking breaks at work, gardening, or housework). Patients should also be advised to limit television viewing and other sedentary activities^{25,33-37}.

Weight loss and Healthy diet:

Effective weight loss requires a combination of caloric restriction, physical activity, and motivation. The glycaemic load of a diet influences the risk of CVD, particularly in people who are overweight and obese. Rapidly absorbed carbohydrates such as refined grains and sugar and sugar-sweetened beverages that induce have a high glycaemic index. Replacing these with unsaturated fats and/or protein and whole grains can help prevention and improve overall health²⁵⁻⁴⁵. Daily diet should be low in saturated fats, trans fats, cholesterol, sodium, and simple sugars. In addition, there should be ample intake of fruits, vegetables, and whole grains. The intake of fish should also be encouraged.

Conclusion:

Cardiovascular disease is a global epidemic^{2,4}; the prevalence is currently stable in the developed world but is on a rapid rise in Sub-Saharan Africa⁶⁻¹⁰. It is the commonest cause of morbidity and mortality globally⁶. Its victims are older in the developed world but younger in Africa where it

affects mainly the productive age group. The morbidity is more than its mortality such that most of its victims live but are rendered unproductive and burdensome⁶⁻¹⁰. The burden of the disease has shifted to the third world. In 2002 over 80% of CVD associated mortality occurred in the developing world³ and a victim is many times than in the developed world^{3,6}. Fortunately as there is no smoke without fire, cardiovascular disease is preceded by certain modifiable and non-modifiable risk factors which can be identified and corrected before a full blown cardiovascular disease with its attendant complications occurs¹⁰⁻¹⁵. Government must as a matter of urgency set up workable local programmes to combat this scourge at the level of the risk factors. Interventions at the primary, secondary and tertiary levels must be implemented fully. Medical staffs must be trained at all levels to identify risk factors and treat them early.

Major CVD risks and appropriate interventions

FACTOR	EFFECT	INTERVENTION	COMMENT
Smoking	2 – 3 Fold increased risk	Smoking Cessation With behavioural And Pharmaco - Logic Intervene - tions	Smoking cessation results in 60% reduction of CHD risk by 3 years; About half of that benefit occurs in first 3 – 6 months after quitting
Dyslipidemias	1-mg/dL increase in serum LDL increases risk of CVD by 2-3% 1-mg/dL decrease in HDL increases CHD risk by 3-4%	Dietary changes Combined with lipid - lowering medications	HDL and TG are - useful markers of CHD risk. Lipid - lowering drugs are cost-effective in patients with 10 - year CHD risk >10%; reduction in risk is proportional to amount of LDL lowering
Hypertension	7-mm HG increase in BP above baseline increases risk of CVD by 27%	Lifestyle modifications, weight loss, limited alcohol intake, aerobic, exercise, medications	Reduction in BP results in reduction in risk of stroke and CHD proportional to reduction in BP
Diabetes	Increases risk 2-4 fold in men and 3-7 fold in women	Maintaining normoglycemia with diet, exercise, weigh management, oral agents, insulin, as needed	Trial data strongly suggest that tight control with insulin reduces risk of microvascular disease, NIDDM patients are likely to have multiple coronary risk factor that should be aggressively modified
Obesity and physical inactivity	Increase risk of cardiovascular disease.	Diet, exercise, weight loss	In addition to improving other CVD risk factors, maintaining ideal body weight and physically active lifestyle may reduce risk of MI as much as 50%

Dietary factors	Fruit and vegetable intake, type and amount of fat, type and amount of carbohydrate, fiber and, Trans fatty acids affect CHD rate	Encourage healthy diet mainly fruits, vegetables, complex carbohydrates, high biologic value proteins and less of fat.	USDA and AHA recommend diet rich in fruits and vegetables; reduction in saturated and trans fatty acid intake, increase in whole grains also appear to be helpful
Moderate alcohol intake (one drink per day)	Decreases risk of MI by 30 -50%	Discussion of alcohol intake with all patients	Risk-to-benefit ratio for Moderate alcohol consumption may vary widely by gender, also based on underlying risk of CHD
Aspirin in primary prevention	Pooled trial data indicate a reduction in risk of first MI and total CVD	Daily or alternate-day low-dose aspirin	Prophylactic aspirin use in higher risk subjects reduces risk of CVD events
Aspirin in secondary prevention	Reduce CVD events by 23%	Daily low -dose aspirin	Reduces risk in those with any form of CVD
Beta blockers after MI	Reduce CVD events by 18% and clearly reduce risk in those with congestive heart failure	Daily beta blocker use	Benefit increase with increasing dose
ACE inhibitors for patients with low EF and after MI	Reduce CVD events by 22% in those with depressed EF and by 7% after MI	Daily ACE inhibitor use	Benefit increase with increasing dose

References:

1. Dzau VJ, Antman EM, Black HR, Hayes DL, Manson JE, Plutzky J et al. The Cardiovascular disease continuum validated: clinical evidence of improved patient outcomes: part 1: pathophysiology and clinical trial evidence. *Circulation* 2006; 114:2850-2870.
2. Yach D, Hawkes C, Gould CI, Hofman KJ. The global burden of chronic diseases: overcoming impediments to prevention and control. *JAMA* 2004; 291; 2616-2620.
3. World Health Organization: The Global Burden of Disease: 2004 Update. Geneva, World Health Organization, 2008.
4. Yach D, Hawkes C, Gould CI, Hofman KJ. The global burden of chronic diseases: overcoming impediments to prevention and control. *JAMA* 2004; 291; 2616-2620.
5. Thom T, Haase N, Rosamond W, Howard VJ, Rumsfeld J, Manolio T et al for the American Heart Association Statistics Committee and Stroke Statistics subcommittee. Heart Disease and Stroke Statistics-2006 Update: a report from the American Heart Association Statistics Committee and Stoke Statistics Subcommittee. *Circulation* 2006;113:e85-151.

6. Murray CJL, Lopez AD. Mortality by cause for eight regions of the world: global burden of disease study. *Lancet*, 1997;349: 1269-1276.
7. Alberti G. Non communicable diseases: tomorrow's pandemics [Editorial]. *Bulletin of the World Health Organization* 2001; 79: 907.
8. Yusuf S, Reddy S, Ounpuu S, Anand S. Global burden of cardiovascular diseases: Part 1; General considerations, the epidemiologic transition, risk factors, and impact of urbanization. *Circulation* 2001; 104:2746-2753.
9. Boutayeb A, Boutayeb S. The burden of non communicable diseases in developing countries. *International Journal for equity in Health* 2005; 4:2.
10. In: Lopez AD, Mathers CD, Ezzati M, et al ed. *Global Burden of Disease and Risk Factors*, New York: World Bank Group; 2006:552.
11. Greenland P, Knoll MD, Stamler J, Neaton JD, Dyer AR, Garside DB, Wilson PW. Major risk factors as antecedents of fatal and nonfatal coronary heart disease events. *JAMA* 2003; 290: 891-97.
12. Khot UN, Khot MB, Bajzer CT, Sapp SK, Ohman EM, Brener SJ, et al. Prevalence of conventional risk factors in patients with coronary heart disease. *JAMA* 2003; 290: 898-904.
13. Grundy S, Pasternak R, Greenand P, et al. Assessment of cardiovascular risk by use of Multiple-risk-factor assessment equations. A statement for healthcare professionals from the American Heart Association and the American College of Cardiology. *J Am Coll Cardiol* 1999; 34:1348-59.
14. Kannel WB. Coronary risk factors: an overview. In: Willerson JT, Cohn JN, Eds, *Cardiovascular Medicine*. New York, NY: Churchill Livingstone; 1995: 1809-1828.
15. WHO. *The World Health Report 2002 'Reducing the Risks and Promoting Healthy Life'* Geneva, WHO 2002.
16. Akinkugbe O. *Non-communicable Disease in Nigeria: Series 1* Ed. Federal Ministry of Health and Human Services, Lagos. 1992.
17. Onwubere BJ, Ike SO. Prevalence of hypertension and its complications among medical admissions at University of Nigeria Teaching Hospital Enugu. *Nig J Med* 2003; 3; 17-20.
18. Kannel WB. Risk stratification in hypertension: new insight from the Framingham study. *Am J Hypertens* 2000; 13:-1.
19. Dahlof B, Cardiovascular disease risk factors: Epidemiology and Risk assessment. *Am J Cardiol*; 2010;105; Suppl: 3A-9A.
20. Messerli FH, Williams B, Ritz E. Essential Hypertension. *Lancet* 2007; 370:591-603.
21. Vasan RS, Larson MG, Leip EP, Evans JC, O'Donnell CJ, Kannel WB, et al. Impact of high-normal blood pressure on the risk of cardiovascular disease. *N Engl J Med* 2001; 345: 1291-1297.
22. Lewington S, Clarke R, Qizilbash N, Peto R, Collins R. Age-specific relevance of usual blood pressure to vascular mortality: A meta-analysis of individual data for one million adults in 61 prospective studies. *Lancet* 2002; 360:1903-1913.
23. National Cholesterol Education Program: ATP III guidelines at-a-glance quick desk reference. Bethesda, MD: National Institutes of Health; 2001. Available: www.nhlbi.nih.gov/guidelines/cholesterol/atglance.pdf (accessed 2012 MARCH 1).
24. Sharrett AR, Ballantyne CM, Coady SA, Heiss G, Sorlie PD, Catellier D, et al. Coronary heart disease prediction from lipoprotein cholesterol levels, triglycerides lipoprotein(a), apolipoproteins A-1 and B, and HDL-C density subfractions: the Atherosclerosis Risk in Communities (ARIC) Study. *Circulation* 2001; 104:1108-1113.
25. World Health Organization. *Global Strategy on diet, physical activity and Health: Obesity and overweight*. WHO 2003.
26. Yekeen LA, Sanusi RA, Ketiku AO. Prevalence of obesity and high level of cholesterol in hypertensives. *African Journal of Biomedical Research* 2003; 6: 129-132.
27. Abubakari AR, Lauder W, Agyemang C, Jones M, Kirk A, Bhopal RS. Prevalence and time trends in obesity among adult West African populations: a meta-analysis. *Obes Rev*. 2008;9:297311.
28. Romero-Coral A, Montori VM, Somers VK, Korinek J, Thomas RJ, Allison TG, et al. Association of body weight with total mortality and with cardiovascular events in coronary artery disease: a systematic review of cohort studies. *Lancet* 2006; 368:666-678.
29. Meigs JB, D'Agostino RB, Wilson PW. Risk variable clustering in the insulin resistance syndrome: the Framingham Offspring Study. *Diabetes* 1997; 46: 1594-1600.
30. Han TS, Sattar N, Lean M. ABC of Obesity. Assessment of obesity and its clinical implications. *BMJ* 2006; 333: 695-698.

31. King H, Aubert RE, Herman WH. Global Burden of Diabetes, Prevalence numerical estimates and projections. *Diabetes Care* 1998; 21: 1414- 1431.
32. Abubakari AR, Bhopal RS. Systematic review on the prevalence of diabetes, overweight/obesity and physical inactivity in Ghanaians and Nigerians. *Public Health*. 2008; 122:173182.
33. Haffner SM. Epidemiology of insulin resistance and its relation to coronary artery disease. *Am J Cardiol* 1999; 84: 11J-4J.
34. Berlin JA, Colditz GA. A meta-analysis of physical activity in the prevention of coronary heart disease. *Am J Epidemiol* 1990; 132:612-28.
35. Boule N, Haddad E, Kenny G, Wells GA, Sigal RJ. Effects of exercise on glycemic control and body mass in type 2 diabetes mellitus: a meta-analysis of controlled clinical trials. *JAMA* 2001; 286: 1218-27.
36. Fagard R. Physical activity in the prevention and treatment of hypertension in the obese. *Med Sci Sports Exerc* 1999; 31(Suppl 11):S624-30.
37. Laaksonen DE, Lakka HM, Salonen JT, Niskanen LK, Rauramaa R, Lakka TA. Low Levels of Leisure-Time Physical Activity and Cardiorespiratory Fitness Predict Development of the Metabolic Syndrome. *Diabetes Care* 2002; 25: 1612-1618.
38. Mackay J, Eriksen M. *The tobacco atlas*. Geneva: World Health Organization; 2002. Available at www.who.int/tobacco/statistics/tobacco_atlas/en/ (accessed 2012 March 1).
39. Pilote L, Dasgupta K, Guru V, Humphries KH, McGrath J, Norris C, et al. A comprehensive view of sex-specific issues related to cardiovascular disease. *CMAJ* 2007; 176 (6). doi:10.1503/cmaj.051455.
40. Glasser SP, Selwyn AP, Ganz P. Atherosclerosis: risk factors and the vascular endothelium. *Am Heart J* 1996. 131: 379-84.
41. Critchley JA, Capewell S. Mortality risk reduction associated with smoking cessation in patients with coronary heart disease: A systematic review. *JAMA* 2003; 290: 86-97.
42. Criqui MH, Wallace RB, Heiss G, Mishkel M, Schonfeld G, Jones GT. Cigarette smoking and plasma high-density lipoprotein cholesterol. The Lipid Research Clinics Program Prevalence Study. *Circulation* 1980; 62: 70-6.
43. American Diabetes Association. Treatment of hypertension in adults with diabetes. *Diabetes Care*. 2003; 26(suppl 1):S80-S82
44. National Kidney Foundation Guideline. K/DOQI clinical practice guidelines for chronic kidney disease: Evaluation, classification, and stratification. *Kidney Disease Outcome Quality Initiative*. *Am J Kidney Dis*. 2002; 39(suppl 2):S1-S246.
45. Wexler R, Aukerman G. Nonpharmacologic Strategies for Managing Hypertension. *Am Fam Physician* 2006; 73: 1953-6.
46. UK Prospective Diabetes Study Group. Intensive blood glucose control with sulphonylureas or insulin compared with conventional treatment and risk of Complications in patients with type 2 diabetes. UKPDS 33. *Lancet* 1998; 352: 837-853.
47. Dushay J, Abrahamson MJ. *Insulin Resistance and Type 2 Diabetes: A Comprehensive Review*. Available at <http://www.medscape.Com/viewarticle/501569> (Accessed 1 March, 2012).