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Epidemiology of Cardiovascular disease and associated risk factors in Gaza Strip- Palestine

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Au nom d'Allah le tout miséricordieux, le très miséricordieux.

Dieu dit dans son livre saint

Ceux qui disent : « Notre Seigneur est Allah » et qui ensuite se tiennent sur le droit chemin. Ils ne doivent avoir aucune crainte et ne seront point affligés

Sourate AL-AHQAF (verset 13)

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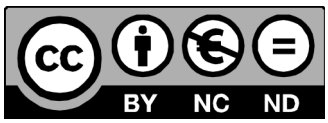
Rights



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Abbreviations

ABI	Ankle rachial Index
ACC	American College of Cardiology
ACE	Africa Middle East Cardiovascular Epidemiology study
ACEIs	Angiotensin- Converting Enzyme Inhibitors
ACS	Acute coronary syndrome
ADA	American Diabetes Association
ADF	American Diabetes Federation
AGATHA-ME	Global Atherothrombosis Assessment -Middle East
AHA	American Heart Association
ARBs	Angiotensin Receptors blockers
ASA	American Stroke Association
ASCVD	Atherosclerotic Cardiovascular Disease
BMI	Body Mass Index
BP	Blood Pressure
CAD	Coronary artery disease
CAPRIE	Clopidogrel versus Aspirin in Patient at Risk of Ischemic Events
CCS	Causative Classification of Stroke
CCTA	Coronary Computed Tomography Angiography
CK	Creatine Kinase
CK Mb	Creatine Kinase MB
CNS	Central nervous system
CRP	C-Reactive Protein

CT	Computed Tomography
CVA	Cerebrovascular Accident
CVD	Cardio Vascular Disease
CVH	Cardiovascular Health
CVRF	Cardiovascular risk factors
DALYs	Disability Adjusted Life Years
DAPT	Dual Antiplatelet Therapy
DBP	Diastolic Blood Pressure
DM	Diabetes mellitus
ECG	Electrocardiogram
EMR	Eastern Mediterranean Region
ESC	European Society of Cardiology
F&V	FruitS and Vegetables
FH	Family History
FHS	Framingham Heart study
FRS	Framingham Risk Score
GBD	Global burden of disease
GCC	Gulf Cooperation Council
GNI	Gross National Income
GPS	Global Positioning System
GS	Gaza Strip
Hamas	Palestinian Islamic Movement founded in 1987
HbA1C	Glycated Hemoglobin A1c

HDL-C	High-Density Lipoprotein Cholesterol
HIC	High Income Countries
HPFS	Health Professionals Follow- Up Study
HRT	Hormonal Replacement Therapy
HTN	Hypertension
IC	Intermittent claudication
ICH	Intra Cerebral Hemorrhage
IDF	International Diabetes Federation
IDL	Intermediate Density Lipoprotein
IHD	Ischemic Heart Disease
IPAQ	International physical activity questionnaire
ISH	International Society of Hypertension
LDL-C	Low-density lipoprotein Cholesterol
LEAD	Lower Extremities Artery Disease
LMIC	Low and Middle-Income Countries
LS7	Life's Simple 7
MENA	Middle East and North Africa
MetS	Metabolic Syndrome
MI	Myocardial Infarction
MIC	Middle Income Countries
min	Minute
MOH	Ministry of Health
MRA	Magnetic Resonance Angiography

MRI	Magnetic Resonance Imaging
NCDs	Non-communicable diseases
NCEP ATP III	National Cholesterol Education Program Adult Treatment Panel III
NGO	Non-Governmental Organization
NHANES	The National Health and Nutrition Examination Survey
NHLBI	The National Heart, Lung and Blood Institute
NNT	Number Needed to Treat
NRT	Nicotine Replacement Therapy
NSTEMI	Non-ST Elevation Myocardial Infarction
OR	Odds ratio
PAD	Peripheral Artery Disease
PCBS	Palestinian Central Bureau of Statistics
PCI	Percutaneous Coronary Intervention
PSS	Perceived Scale Stress
PTP	Pretest Probability
PURE	Prospective Urbane Rural Epidemiology study
RCT	Randomized Controlled Trial
REGARDS	The Reasons for Geographic and Racial Differences in Stroke
RQ	Rose Questionnaire
SAH	Subarachnoid Hemorrhage
SBP	Systolic Blood Pressure
SCAD	Stable Coronary Artery Disease
SES	Socio Economic Status

STEMI	ST Elevation Myocardial Infarction
TIA	Transit Ischemic Attack
TOAST	Trial of ORG 10172 in Acute Stroke Treatment
UA	Unstable Angina
UK	United Kingdom
UNRWA	United Nations Relief and Works Agency
USA	United State of America
VLDL	Very Low-Density Lipoprotein
WB	West Bank
WHO	World Health Organization

Introduction

In 2014, the World Health Organization (WHO) defined the Non-Communicable Diseases (NCDs) as one of the greatest challenges of 21st century. The NCDs are medical conditions not related to infectious agents, they may be caused by genetic or behavior factors and have a slow progression and long duration (WHO 2014, n.d.). The burden of NCDs is growing rapidly affecting people of all ages and different income levels in all regions of the world mainly in low and middle-income countries (LMIC). Four risk factors (tobacco use, excessive alcohol consumption, poor diet and lack of physical activity) are associated with four disease cluster (cardiovascular disease, cancer, chronic pulmonary disease and diabetes)(Lozano *et al.*, 2012). Six of the top ten leading causes of death in 2012 were NCDs, including the top three diseases (ischemic heart disease, stroke and chronic obstructive pulmonary disease) (LUKE, 2017). NCDs are the leading cause of death and disability, killing three in five people worldwide and responsible for nearly half of the global burden of disease. NCD death increased from 2006 to 2016, rising 16.1%. In 2016, NCDs caused 39.5 million (72.3%) of death worldwide, and were projected to increase by 15% in 2020 (Bowery, 2015; GBD 2016 Causes of Death Collaborators, 2017). More than 16 million (42%) of all NCDs deaths were premature deaths (under age 70 years). A large amount of deaths from NCDs (29%) in LMIC occur among people younger than 60 years compared with High Income Countries (HIC) (13%). The leading cause of premature deaths for NCDs were cardiovascular disease (CVD)(45%), malignant neoplasm (22%), respiratory disease (10%) and diabetes (4%) (WHO 2014). The risk of death between age 30 and 70 years from any one of the four main NCDs cited, decrease from 23% in 2000 to 19% in 2015 (WHO, 2017b).

The WHO suggests that cardiovascular death occurs 3 times more in LMIC and in the working age group with an equal rate in males and females (Organization, 2003).

WHO Global Plan Action for the prevention of NCDs 2013-2020 identified seven major risk factors including harmful use of alcohol, current tobacco smoking, high blood pressure, intake of salt or sodium, diabetes and obesity, physical inactivity (referred as the 25 by 25 risk factors) with the goal of reducing premature mortality from NCDs by 25% (WHO/GPA, 2013).

The Eastern Mediterranean Region (EMR) is comprised of 23 countries with a population of 583 million people. Arabs living in this region share language, cultural background as well as lifestyle. However, they vary in their sociodemographic profile, political, economic situation and health system, several of these nations have long years of political instability (Mokdad *et al.*, 2016). Countries in EMR have been classified into three groups of health systems according to population health outcome, health system performance and health budget levels. Palestine is part of the second group. Modernization, economic and technologic development advances

have led to rapid demographic changes in the Arab world inducing an increase in death rate (Alwan, Alwan & Jabbour, 2012) . Morbidity related to NCD is accounting for 47% and is estimated to reach 60% by the year 2020 (Khatib, 2004). More than 2.2 million people in EMR died from NCDs representing 53% deaths. Thirty five per cent of death from NCDs were in persons younger than 60 years (WHO EMRO, 2016). The ischemic heart disease was the leading cause of death in this region accounting for 14.3% of deaths (Mokdad *et al.*, 2014). Rapid increase in NCDs suggests that the change in disease burden was more affected by behavioral than genetic factors. Arabs became less physically active and consumed unhealthy diet (Mehio Sibai *et al.*, 2010). Data collected by STEPS Wise WHO for chronic disease 2010-2011 among adults aged 15-65 years in Eastern Mediterranean countries showed the high prevalence of NCDs risk factors. One quarter of adult population was hypertensives, daily current tobacco smoking exceeds 30% in males, obesity was alarming particularly in women. Six out ten countries in the world reported the highest prevalence of diabetes with a rate up to 20% (IDF 2009, n.d.).

Epidemiological transition

The epidemiological transition defined as shift from infectious disease to NCDs. In the Arab world, the situation of health changed dramatically during the few decades driven by rapid aging of the population, economic development, globalization and technological advances, westernization of diet (food high in fat, salt and sugar, high intake of fast food, snacks rich in calories, edible oils, and an increase in consumption of animal source foods). Life style changes in employment activities, rising obesity and decrease in physical activity (Omran 2005; Islam et al. 2014) are particularly prevalent in the high income countries (HIC) of the Gulf Cooperation Council (GCC) mainly, in females (Rahim *et al.*, 2014). The rate of urbanization is increasing from 36.6% of the world population living in urban areas in 1970, to 44.8% in 1994. This proportion is projected to increase to 61.1% by 2025 (Chockalingam *et al.*, 2000).

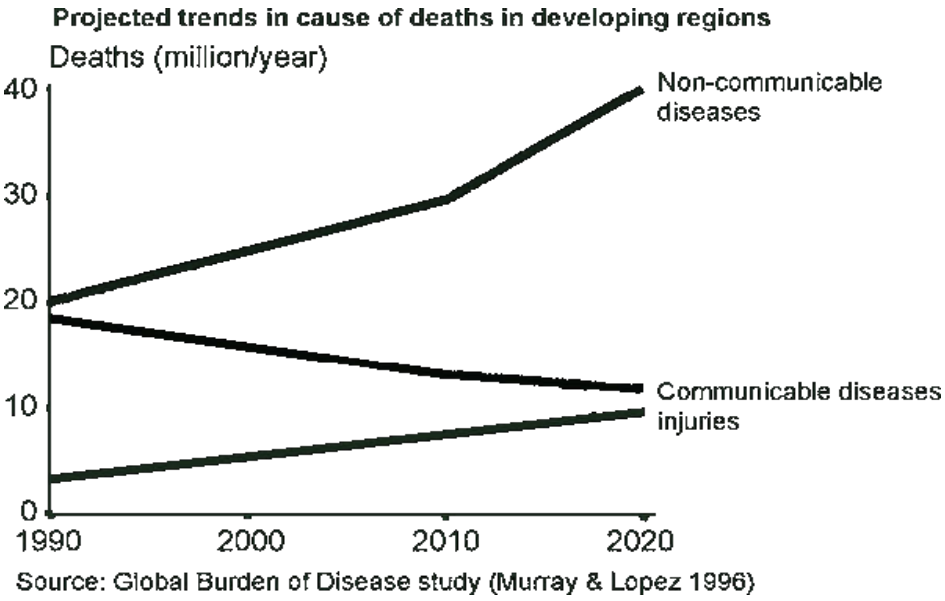


Figure 1: Trends of cause of death in developing world

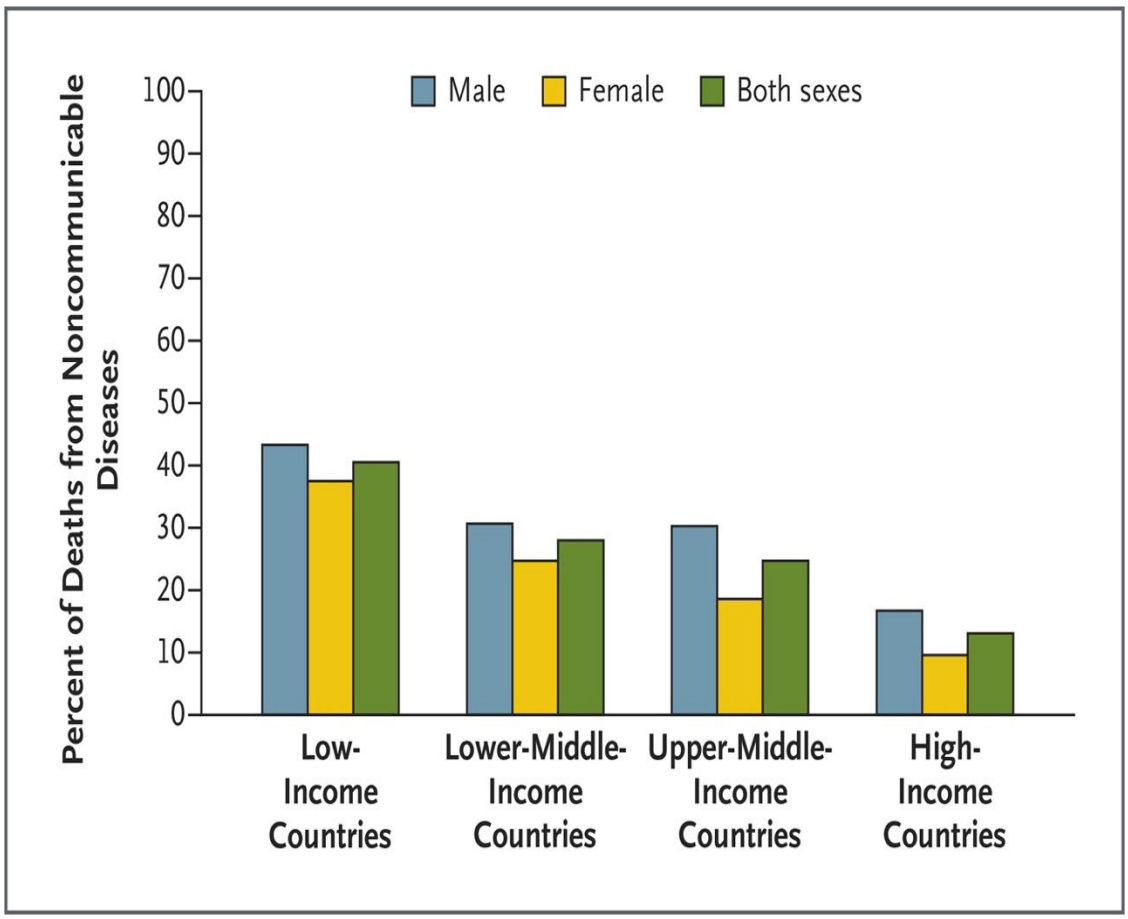


Figure 2: Proportion of Deaths from NCD among Persons Younger than 60 Years of Age, According to Income Group of Countries (Hunter & Reddy, 2013)

Chapter I. Literature review

I.1. Cardiovascular health definition

Cardiovascular health (CVH) is defined by the absence of clinical manifestation of CVD together with the presence of optimal levels of all life's Simple 7 (LS7). These include 4 health behaviors (not smoking, healthy diet pattern, sufficient physical activity, normal body weight), and 3 health factors (normal level of total cholesterol, of blood pressure, and fasting blood glucose) in the absence of drugs treatment (AHA, 2016). A meta-analyze of 9 prospective cohort studies among 12,878 persons reported that ideal cardiovascular health metrics was associated with lower risk of all-cause mortality (Fang, Jiang & Fan, 2016). The Reason for Geographic And Racial Difference in Stroke (REGARDS) cohort among 22,914 subjects with LS7metrics data and no previous cardiovascular disease showed that every better health category of the LS7 score was associated with 25% decrease in the risk of stroke (Kulshreshtha *et al.*, 2013). Better cardiovascular health is associated with decrease risk of vascular disease (Saleem *et al.*, 2015). Yang et al examined the association between LS7metrics and CVD mortality over a 14.5 years period ; individuals with ≥ 6 healthy factors, had an absolute CVD mortality risk of 15% compared to 65% for those reporting only one or no healthy behaviors (Yang *et al.*, 2012).

I.2. **Cardiovascular disease definitions**

CVDs, refers to various chronic pathology or events that have in common a pathophysiology related to atherosclerosis and including:

- Coronary artery disease (CAD): stable angina, unstable angina, myocardial infraction, sudden death
- Cerebral vascular accident: stroke: hemorrhagic, ischemic or transit ischemic attack
- Peripheral Artery Disease (PAD): Lower Extremity Artery Disease (LEAD), aortic aneurysm
- Congestive heart failure (CHF)

The burden of coronary artery disease, cerebral vascular accident and lower extremity artery disease will be displayed in this thesis.

I.3. **Types of cardiovascular disease**

I.3.1. Coronary artery disease

I.3.1.1. Definition and classification

Also, known as ischemic heart disease (IHD) refers to conditions that involve impairment of coronary artery blood flow that can result in silent ischemia, angina pectoris, acute coronary syndrome (ACS) or sudden cardiac death. Coronary artery disease (CAD) is a common public health problem associated with high mortality and increased health cost (He *et al.*, 2017).

I.3.1.2. Physiopathology

Atherosclerosis is a complex progressive chronic multifocal, immune-inflammatory, fibro proliferative disease, with the accumulation of lipid metabolism, active cellular interaction, inflammation and matrix remodeling in the large arteries (Brown *et al.*, 2017; Hamm *et al.*, 2006). Atherosclerosis causes complex, lesions on coronary, cerebrovascular and peripheral vascular diseases (Tabas, García-Cardeña & Owens, 2015). The anatomy of normal artery is displayed in Figure 2. The early lesion of atherosclerosis consists of fatty streak comprised of (cholesterol and macrophage). They are limited to the aorta in the first decade of life, then extend later to the coronary arteries and peripheral arteries.

The lesion leads to acute occlusion of the artery by a thrombus often related to intimal of rupture or erosion, clinically present as unstable angina, Myocardial Infarction (MI) or sudden cardiac death (Lusis, 2000, Anon, 2017a). In Stable Coronary Artery Disease (SCAD), atherosclerosis lesion progresses slowly, allowing for the development of collateral circulation (T. Wang and Butany 2017) (figure 3). The atherosclerosis process can be accelerated by the cardiovascular traditional risk factors such as diabetes, hypertension, obesity, dyslipidemia, smoking, and genetics factors.

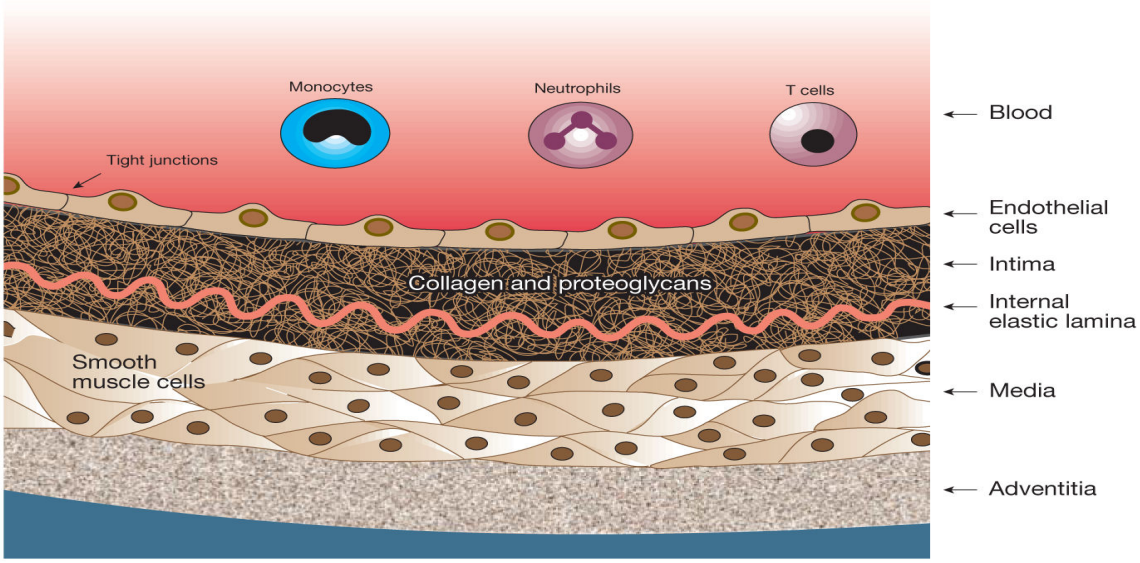


Figure 3: Structure of a normal large artery (Lusis, 2000)

A large artery consists of three morphologically distinct layers. The intima, the innermost layer, is bounded by a monolayer of endothelial cells on the luminal side and a sheet of elastic fibres, the internal elastic lamina, on the peripheral side. The normal intima is a very thin region (size exaggerated in this figure) and consists of extracellular connective tissue matrix, primarily proteoglycans and collagen. The media, the middle layer, consists of SMCs. The adventitia, the outer layer, consists of connective tissues with interspersed fibroblasts and SMCs. *Nature*. Author manuscript; available in PMC 2010 February 22.

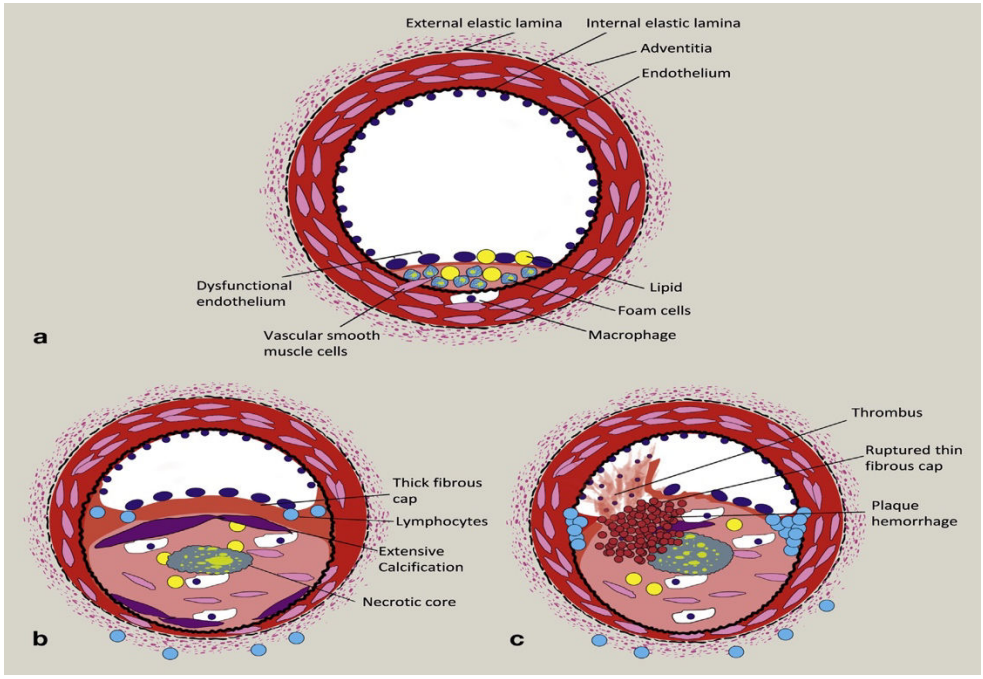


Figure 4: (a) Fatty streak with dysfunctional endothelial cells, lipid insudation and the macrophage transformation into foam cells. (b) Stable plaque with extensive calcification and thick fibrous cap overlying foam cells and necrotic core. (c) Acutely ruptured unstable plaque, with a collection of fibrin and platelets forming a thrombus over the disrupted thin fibrous cap (Wang & Butany, 2017).

I.3.1.3. Acute coronary syndrome

Acute coronary syndrome refers to a spectrum of clinical symptoms compatible with acute myocardial ischemia and includes Unstable Angina (UA), Non-ST Segment Elevation Myocardial Infarction (NSTEMI), and ST-segment Elevation Myocardial Infraction (STEMI), thus they share common pathophysiological origins related to coronary plaque progression, instability, or rupture with or without luminal thrombosis and vasospasm. The main clinical expression are MI, and sudden cardiac death.

Differentiating ACS from other cardiac chest pain is the primary diagnostic challenge. The initial assessment requires a good history collection including risk factors analysis, a physical examination, an Electrocardiogram (ECG) and cardiac biomarkers analysis that help in determining the differential diagnosis such as aortic dissection, pericarditis, pulmonary embolism and musculoskeletal pain (Braunwald *et al.*, 1994).

I.3.1.3.1. Clinical presentation of Acute coronary syndrome

Most patients describe diffuse severe pain, which may occur with exertion or at rest localized in the sub sternal region in typical cases or epigastric discomfort. The pain radiates to the neck, jaw, left shoulder and left arm or both, not affected by movements. Other symptoms can be associated such as nausea, vomiting, unexplained fatigue and in rare cases syncope. Discomfort persists more >20 Minutes (min). Symptoms might be atypical in diabetic patients, women and elderly persons (Kumar & Cannon, 2009; Thygesen *et al.*, 2012). Five factors reinforce the diagnosis of acute ischemia due to CAD. They are according their weight: a past history of CAD, male sex, older age, the characteristics of angina pain and the presence of cardiovascular risk factors such as HTN, DM, dyslipidemia, cigarette smoking, and family history of premature CAD (Pryor *et al.*, 1993).

I.3.1.3.1.1. Myocardial infraction

Acute myocardial infarction is a myocardial necrosis due to prolonged ischemia (Thygesen *et al.*, 2012). The diagnosis is based on biochemical criteria (troponin elevation as a result of irreversible cell damage), clinical evaluation, ECG findings, invasive and noninvasive imaging and pathological evaluation (Table1) (Anderson & Morrow, 2017).

Table 1: New Universal classification of myocardial infarction (2018)(Thygesen *et al.*, 2019)

Type 1: Spontaneous myocardial infarction
Spontaneous myocardial infarction related to atherosclerotic plaque rupture, ulceration, fissuring, erosion, or dissection with resulting intraluminal thrombus in one or more of the coronary arteries leading to decreased myocardial blood flow or distal platelet emboli with ensuing myocyte necrosis. The patient may have underlying severe CAD but on occasion non-obstructive or no CAD.
Type 2: Myocardial infarction secondary to an ischaemic imbalance
In instances of myocardial injury with necrosis where a condition other than CAD contributes to an imbalance between myocardial oxygen supply and/or demand, e.g. coronary endothelial dysfunction, coronary artery spasm, coronary embolism, tachy-/brady-arrhythmias, anemia, respiratory failure, hypotension, and hypertension with or without LVH.
Type 3: Myocardial infarction resulting in death when biomarker values are unavailable
Cardiac death with symptoms suggestive of myocardial ischemia and presumed new ischemic ECG changes or new LBBB, but death occurring before blood samples could be obtained, before cardiac biomarker could rise, or in rare cases cardiac biomarkers were not collected.
Type 4a: Myocardial infarction related to percutaneous coronary intervention (PCI)
Myocardial infarction associated with PCI is arbitrarily defined by elevation of cTn values >5 x 99th percentile URL in patients with normal baseline values (£99th percentile URL) or a rise of cTn values >20% if the baseline values are elevated and are stable or falling. In addition, either (i) symptoms suggestive of myocardial ischemia, or (ii) new ischemic ECG changes or new LBBB, or (iii) angiographic loss of patency of a major coronary artery or a side branch or persistent slow- or no-flow or embolization, or (iv) imaging demonstration of new loss of viable myocardium or new regional wall motion abnormality are required.
Type 4b: Myocardial infarction related to stent thrombosis
Myocardial infarction associated with stent thrombosis is detected by coronary angiography or autopsy in the setting of myocardial ischemia and with a rise and/ or fall of cardiac biomarkers values with at least one value above the 99th percentile URL.
Type 5: Myocardial infarction related to coronary artery bypass grafting (CABG)
Myocardial infarction associated with CABG is arbitrarily defined by elevation of cardiac biomarker values >10 x 99th percentile URL in patients with normal baseline cTn values (£99th percentile URL). In addition, either (i) new pathological Q waves or new LBBB, or (ii) angiographic documented new graft or new native coronary artery occlusion, or (iii) imaging evidence of new loss of viable myocardium or new regional wall motion abnormality.

I.3.1.3.2. Physical examination findings

Physical examination can vary from normal to hemodynamic instability including ischemic mitral regurgitation, hypotension, gallop heart sound, jugular venous distension, left ventricular failure, and cardiogenic shock.

I.3.1.3.3. Electrocardiograms

Electrocardiogram provides important information about the presence, extent and severity of myocardial ischemia in stratifying the patient risk of ACS and determining the treatment strategy.

I.3.1.3.4. Serum cardiac markers

Elevated cardiac biomarkers especially Troponin (I or T), or creatinine kinase (CK) or its isoenzyme MB (CK-MB), reflect myocardial cells necrosis. Troponins have higher clinical sensitivity and specificity than traditional cardiac enzymes. Myoglobin is not specific for the detection of myocardial cell injury (Eggers *et al.*, 2004). Troponin level should be measured within 6 first hours of the onset of pain (strength of recommendation), and the elevation stays for 2 weeks after the onset of myocardial necrosis (Smith *et al.*, 2015). Troponin increase reflects irreversible myocardial cellular necrosis (Eggers *et al.*, 2004). However cardiac biomarkers are not specific of acute MI (Thygesen *et al.*, 2012). Clinical conditions such as pulmonary embolism, heart failure, end stage renal failure, and myocarditis are associated with of cardiac biomarkers increase (Korff, Katus & Giannitsis, 2006).

I.3.1.4. Stable coronary artery disease

I.3.1.4.1. Definition, classification

Stable coronary artery disease includes all clinical entities that are characterized by coronary atherosclerosis in the absence of ACS (Abrams, 2005). It is defined as episodes of reversible myocardial demand /supply mismatch, related to ischemia or hypoxia, which are usually inducible by exercise, emotion or other stress and, reproducible but, may also be occurring spontaneously (Task members of ESC et al., 2013). The consequences of ischemia are according to a predictable temporal chronology:

- Increased H+ and K+ concentration in the venous blood
- Signs of ventricular diastolic and subsequently systolic dysfunction with regional wall motion abnormalities
- Development of ST-T changes
- Cardiac ischemic pain (angina) (Crea *et al.*, 2010)

In SCAD the symptoms are reversible, repetitive for months to years and relieved by rest or sublingual nitroglycerin. Some conditions such as anemia, hypertension crisis, thyrotoxicosis can exacerbate the angina.

The SCAD definition includes:

- Patients symptomatic for stable angina pectoris or a symptom like angina (e.g. dyspnea)
- Patients with a history of obstructive or non-obstructive CAD, who have become asymptomatic with treatment and need regular follow up
- Patients reporting symptoms for the first time, but already in chronic stable condition (since several months)

Table 2: Classification and Severity of Angina

Classification and Severity of Angina according to the Canadian Cardiovascular Society	
Class I (no limitation of ordinary activity)	Angina reproduced with strenuous exertion
Class II (slight limitation of ordinary activity)	Angina reproduced on walking rapidly
Class III (marked limitation of ordinary activity)	Angina reproduced on walking 100-200m
Class IV (inability of activity)	Angina reproduced for any activity

I.3.1.4.2. Clinical presentation

The characteristics of angina are:

- Location: retrosternal, or near the sternum, but may be felt anywhere from the epigastrium to the lower jaw or teeth.
- Quality: described as oppressive, a sensation of heaviness, pressure weight, constricting or burning, associated or not by a shortness of breath
- Etiology: exercise or emotional stress, post prandial and cold weather
- Duration: 3 to 15 min (no more than10 min in the majority of cases)
- Remission: by rest or sublingual nitroglycerin (Gerloni *et al.*, 2017)

Atypical presentations differ by the absence of precepting factors. The pain starts at rest with a low level of intensity, increases slowly and reaches its peak for a maximum of 15 min. Atypical pain is more common in women, in diabetics and in elderly patients. Women report vague symptoms such as palpitation, inflammatory pain, stabbing pain, which lasts for seconds, hours or days with variable response to nitroglycerin. Diabetic patients are more likely to report dyspnea or to be asymptomatic (Gerloni *et al.*, 2017).

Table 3:Traditional clinical classification of chest pain (Diamond, 1983)

Typical angina (Definite)	Meets all three of the following characteristics Substernal chest discomfort of characteristic quality and duration Provoked by exertion or emotional stress Relived by rest and /or nitrates within minutes
Atypical angina (probable)	Meets two of these characteristics
Non-anginal chest pain	Lacks or meets only one or none of the characteristics

I.3.1.4.3. Investigations

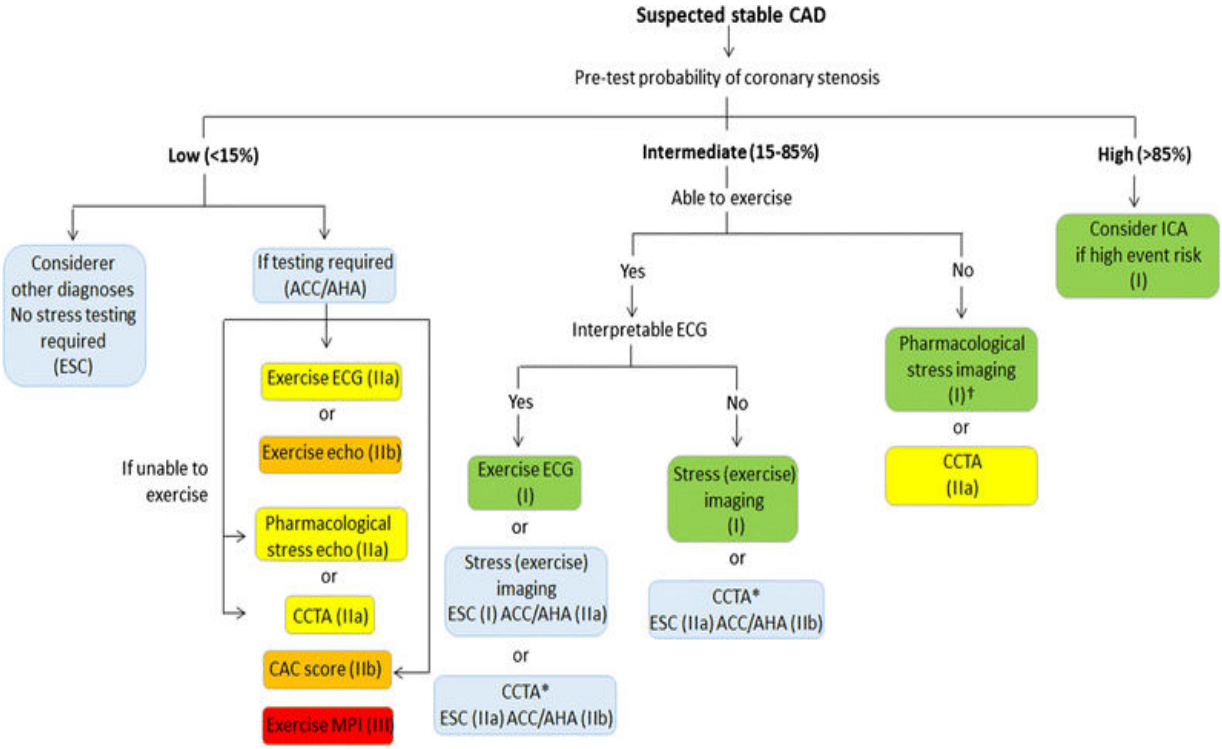
Physical examination is poor and has low sensitivity. A normal ECG does not exclude the diagnosis, but an abnormal resting one increases the diagnosis probability. Routine laboratory tests are recommended to determine the severity of factors. Hyperglycemia, dyslipidemia, thyroid disorder and renal failure should be evaluated in every patient with suspected CAD (Task members of ESC *et al.*, 2013). Plasma cardiac troponin levels are below the normal. According to ESC and Canadian guidelines echocardiography should be performed in all patients with SCAD to identify left ventricular function, kinetic segments, valvular lesion (mainly mitral regurgitation).

- The Multidetector row CT permits the detection of coronary calcification. The measurement of calcium scoring is calculated as the coronary calcium area by maximal plaque density (in Hounsfield units) and calcified lesions are quantified using (Agatston score). Calcium scoring helps to evaluate the atherosclerosis burden (Omland *et al.*, 2009; Fihn *et al.*, 2012)
- Coronary computed tomography angiography (CTA): is indicated in patients with low-intermediate risk of obstructive CAD. CTA can visualize the coronary arteries after intravenous injection of contrast agent. CTA is helpful in patients without severe obesity, favorable calcium score (Agatston score < 400) and with heart rate ≤ 65 beats per minute.
- Exercise ECG: with a high specificity > 90% and a low sensitivity < 50% (high probability of false positive mainly in females). The test is usually carried out on a treadmill from rest to maximum exertion according the Bruce protocol. ST segment modification are analyzed (Ashley & Niebauer, 2004).

- Stress echocardiography: the predictive value is higher than treadmill test. It detects the difference in wall motion between ischemic and non-ischemic myocardium, and provides information on hibernating myocardium
- Magnetic resonance imaging: detects wall motion abnormalities
- Cardiac Coronary angiography: remains the gold standard. ACS or Positive stress test induced large wall motion abnormality, or poor answer to medical treatment are the main indications. Location and number of lesions, type and degree of stenosis are described (Ashley & Niebauer, 2004).

I.3.1.4.4. Strategy diagnostic (Figure 5,6)

A Pre-Test Probability (PTP) evaluation prior to non-invasive testing with the Duke clinical score and Diamond Forrest model is recommended in The European and American guidelines (Joseph *et al.*, 2018). PTP of CAD is based upon age, gender and symptoms. It is defined by ESC guidelines as: Low <15%, intermediate 15-85% and high >85%. The intermediate group is classified further into (a) 15-65%, and (b) 66-85% (Montalescot *et al.*, 2013). In the ESC GUIDELINES, CCTA is recommended in patients with a low -intermediate PTP of CAD (15-50%). Pharmacological stress MRI is a class IIa indication according to the ACC/AHA guidelines*.



CCTA*Coronary Computed Tomography Angiography ACC/AHA guidelines*: American college of cardiology/American Heart Association guidelines

Figure 5: ESC and ACC/AHA recommendations for stress testing and CCTA in the assessment of patients with suspected stable CAD according to pre-test probability of disease (Joseph *et al.*, 2018)

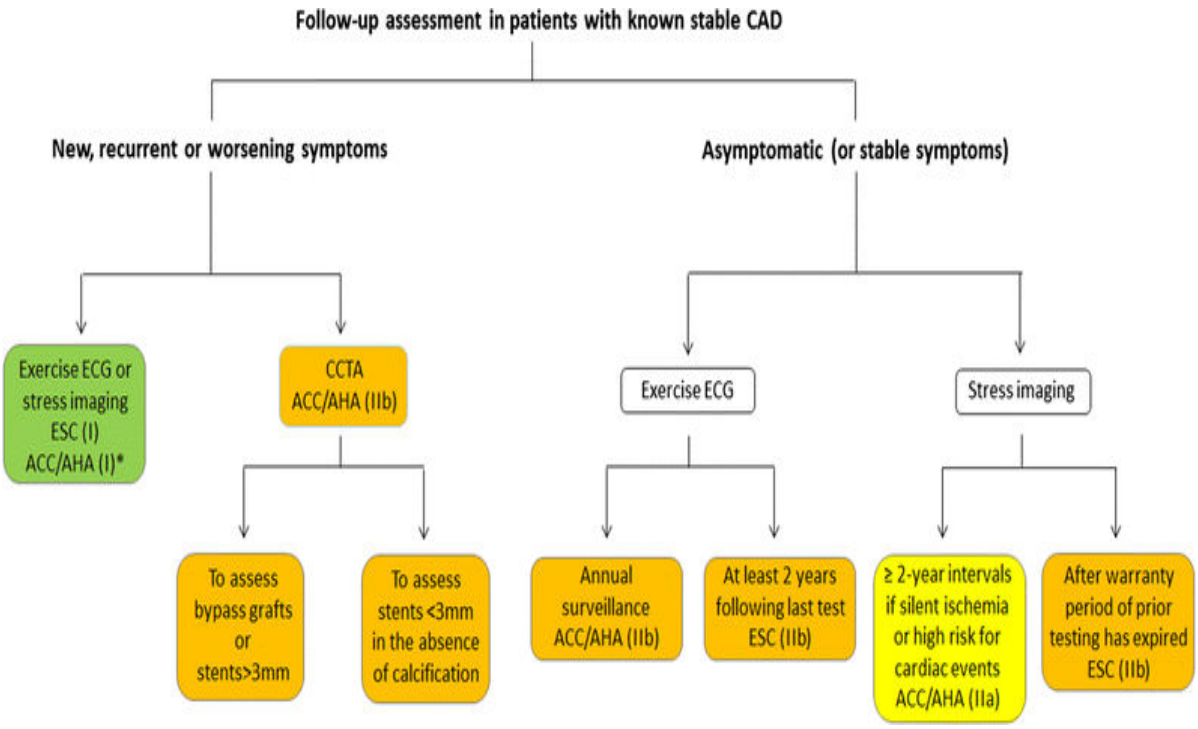


Figure 6: ESC and ACC/AHA guidance for follow-up assessment of patients with stable CAD according to symptoms (Joseph *et al.*, 2018)

I.3.1.5. Management of coronary artery disease

I.3.1.5.1. Invasive coronary revascularization

ACS subjects must be evaluated in emergency to avoid important myocardial damage and hemodynamical complications. The initial evaluation identifies patients with a life threating emergency versus those with a more benign condition.

Once STEMI of has been diagnosed, the reperfusion therapy strategy should be developed quickly. Primary Percutaneous Intervention (PCI) is considered the primary method of reperfusion with a goal of time from first medical contact to device time ≤ 90 min. For sites without PCI experience, fibrinolysis therapy should be administrated within 30 min of hospital arrival (O'Gara *et al.*, 2013). In patients with NSTEMI or UA, the early invasive coronary angiography is recommended in case of refractory angina, hemodynamic instability, or malignant arrhythmias. Early revascularization is reasonable for high risk patients with NSTEMI / UA previously stabilized with no contraindication for the procedure.

I.3.1.5.2. Anticoagulant agent

Anticoagulants such as unfractionated heparin and low molecular-weight-heparin are used in combination with antiplatelet during the initial management of ACS, but often not recommended post discharge.

I.3.1.5.3. Long term management

I.3.1.5.3.1. Antithrombotic Agents

Antiplatelet therapy reduces the risk of thrombosis by interfering with platelet release and aggregation and reduces the risk of thrombosis. The most used therapies in the management of CAD were Aspirin, adenosine diphosphate $P2Y_{12}$ receptor antagonist (Clopidogrel, prasugrel and ticagrelor), and glycoprotein II b III a (abciximab and eptifibatide). Aspirin should be introduced immediately after ACS diagnosis, with a dose of 160-325 mg, and maintained on long-time at dose (81-100mg (Smith *et al.*, 2015; Mehta *et al.*, 2010). Oral $P2y_{12}$ inhibitor is indicated for patients undergoing primary PCI. A loading dose should be administrated before PCI then maintained during one year (O'Gara *et al.*, 2013). In NSTEMI / UA a Dual Antiplatelet Therapy as aspirin plus clopidogrel (DAPT) has been demonstrated to reduce death from cardiovascular events (nonfatal MI or stroke) by a relative risk of 20% (Yusuf et al. 2004). In STEMI, DAPT reduced the re-occlusion infarct-related artery after PCI, death, and recurrent MI before angiography by 36% (Sabatine *et al.*, 2005). In SCAD, the use of aspirin at a dose of 81-150 mg daily reduced cardiovascular mortality and morbidity by 20-25% (O'Gara et al., 2013).

I.3.1.5.3.2. B-blocker

These drugs decrease myocardial oxygen consumption, decrease heart rate, blood pressure, and reduce myocardial contractility. They are recommended in patients with ACS within 24 hours except in cases of heart failure or cardiogenic shock (Smith *et al.*, 2015).

I.3.1.5.3.3. Inhibitors of the renin-Angiotensin system

The angiotensin converting enzyme inhibitors (ACEIs) or angiotensin receptors blockers (ARBs) should be initiated in the first 24 hours of ACS patients with heart failure, or large zone of infarction (massive MI), or left ventricular EF<40%. These drugs reduce mortality and morbidity in select patients. With ACE, or ARBs, monitoring of serum creatinine, potassium level and blood pressure is mandatory.

I.3.1.5.3.4. Statin

Statin are recommended in all patients presenting with CAD. Starting with high intensity dose of statin therapy in ACS confers an absolute risk reduction of 3.9% for death from any cause, recurrent MI, re-hospitalization and stroke (Pedersen *et al.*, 2004; Stone *et al.*, 2013).

I.3.1.5.3.5. Risk factor correction

Stopping smoking is probably the most-effective preventive measure. Diabetes, Hypertension and dyslipidemia controls are mandatory.

I.3.2. Cerebrovascular accident: Stroke

I.3.2.1. Definition and classification

Stroke or cerebrovascular Accident (CVA) is a neurological deficit due to an acute focal injury of the central nervous system (CNS) by a vascular origin. Two process, are described, first brain ischemia due to thrombosis, embolism, or systemic hypo perfusion, second brain hemorrhage due to intra Cerebral Hemorrhage (ICH), or subarachnoid hemorrhage (SAH) (Sacco *et al.*, 2013). Roughly 80% of strokes in HIC are due to ischemic cerebral infarction and 20% to brain hemorrhage (Sacco *et al.*, 2013; Louis R & Scot E, 2018).

Transit Ischemic Attack (TIA) was defined in 2009 by the expert committee of the AHA/ASA as "a transit episode of neurological dysfunction caused by focal brain, spinal cord or retinal ischemia without acute infarction". This definition is based on tissue pathophysiology rather than symptom duration (Easton *et al.*, 2009). TIA results from the same mechanisms as ischemic stroke and causes temporary neurologic deficit. Eighty per cent of TIA resolve within 60 min. TIA might preceded stroke.

The Trial of Org10172 in Acute Stroke Treatment (TOAST) classification, is the most used one. In order to identify the etiology the severity and the localization of the ischemic stroke TOAST distinguishes 5 etiological subtypes: atherothrombotic stroke (due to large artery atherosclerosis), cardio embolic stroke, lacunar stroke due to arterial (dissection, vasculitis, vasospasm), stroke of other determined etiology, and stroke of unknown origin (Ay *et al.*, 2005). The last subtype includes all cases with an incomplete evaluation or non-determined etiology. SSS-TOAST is the Modified definition of the TOAST based on the clinical and imaging criteria, and divides each of the original TOAST into three sub categories as "evident, probable, possible". An algorithm computerized version: the Causative Classification of Stroke system (CCS) is available in multiple centers (Ay *et al.*, 2007).

I.3.2.2. Physiopathology

Three major etiologies are reported for ischemic stroke; hypo-perfusion, embolism and thrombosis (Ojaghihaghighi *et al.*, 2017). Normal cerebral blood flow in humans is 50 to 60 ml /100 g of brain tissue per min. When flow decreases to 20-40 ml /100 mg per min, neuronal dysfunction occurs, and an irreversible tissue damage occurs when it is less than 10 to 15 ml/100 mg per min.

I.3.2.2.1. Hemorrhagic stroke

In this condition, stroke arises due to rupture of blood vessel in the brain. Its harmful effects are a result of hypoxia, direct effect of released blood on brain parenchyma and and increase of intra cerebral pressure. ICH condition is often due to hypertension, trauma, toxic drugs

(cocaine) and vascular malformations. Rupture of aneurysms from vascular malformation may lead to SAH (Escudero Augusto, Marqués Alvarez & Taboada Costa, 2008).

I.3.2.2.2. Atherosclerosis and stroke

Atherosclerosis development is increased by major risk factors such as hypertension, diabetes, obesity, chronic inflammation and increase concentration of oxidized lipoprotein. Hemorrhage in the plaque contribute to the progressive narrowing of the lumen.The endothelial integrity become vulnerable and unstable leading to platelets adhesion and aggregation and thrombus formation (Flemming, 2015).

I.3.2.3. Risk factors

The relative risk associated with the most important risk factors for stroke are displayed in table 4 (Markus, 2016)

Table 4: Stroke Risk factors

Well-recognized risk factors for stroke (estimates of relative risk are representative figures derived from different studies of each risk factor)	
Risk factors	Relative risk of stroke
Age (>75 years versus 55-64 years)	5
Blood pressure (160/95 versus 120/80 mmHg)	7
Smoking (current status)	2
Diabetes mellitus	2
Social class (V versus I)	1.6
Ischemic heart disease	3
Heart failure	5
Atrial fibrillation	5
Physical activity (little or none versus some)	2.5
Oral contraceptives	3

I.3.2.4. Diagnosis

Stroke should be considered in any patient presented with acute neurological deficit or any alteration in level of consciousness. No specific sign distinguishes ischemic from hemorrhagic stroke. Symptoms are of sudden onset and usually maximal in severity (within minutes). The time passed from the onset to the admission is essential for the fibrinolytic therapy option.

I.3.2.4.1. Clinical symptoms

More likely the symptoms occur in combination: hemiparesis, hemi sensory deficit, perturbation in vision or sudden vision loss, diplopia, dysarthria, aphasia, facial droop, ataxia and vertigo.

I.3.2.4.2. Physical examination

Medical history for patients helps to identify risk factors for atherosclerosis and cardiac causes. General and neurological examination confirm the presence of a stroke and evaluate the stroke severity. The presence of neck bruit suggests carotid stenosis; atrial fibrillation indicates cardio embolism origin. Absence of pulses in lower extremities suggests the diagnosis of atherosclerosis. Neuroimaging is mandatory. Few clinical findings are in favor of hemorrhagic stroke such as coma, neck stiffness, seizures, high blood pressure, headache and vomiting (Runchey & McGee, 2010).

I.3.2.4.3. **Imaging study**

Urgent brain imaging is required in all stroke patients, to distinguish ischemic stroke from intracerebral hemorrhage and to detect aneurysm or malformations.

- Non-contrast computed tomography (CT) scanning is essential to rule out cerebral hemorrhage or other causes. CT may be normal in the initial hours after ischemic stroke
- Magnetic Resonance Imaging (MRI) is the cornerstone imaging which provides structural details, detects early cerebral oedema, and identifies old hemorrhage (“Stroke in the Acute Setting” 2017)
- Carotid duplex scanning detects carotid stenosis and its severity

I.3.2.5. Management

Stroke is an emergency requiring immediate intervention in order to minimize the size of the infarct, and the rate of neurological impairment. In addition, differentiating the type of CVA plays decisive role in the management. TIA requires serious evaluation as 30 days stroke risk is around 10% (Anon, 2017b; Muir, 2001).

I.3.2.5.1. Acute treatment

I.3.2.5.1.1. General measures: stroke unit

Stroke units improve outcome and avoids complications (Turner *et al.*, 2015). Patients are monitored continuously, to detect and to correct factors that may worsen the acute ischemic stroke. General care is effective to improve the prognosis such as correct electrolytes imbalance, severe hypertension, hyperglycemia, hydration disorders and malnutrition (Powers, 1993).

I.3.2.5.1.2. Thrombolytic therapy

In Ischemic stroke, “Time is brain” and early treatment is a positive point for successful thrombolysis. Intravenous thrombolytic with rt-AP initiated within 4.5 hours of symptoms onset is associated with high benefit (Emberson *et al.*, 2014). The number-Needed to Treat (NNT) for good outcome is 5 for patients treated within 90 min, 9 if treated within 90-180 min and 14 if within 181-270 min (“Stroke in the Acute Setting” 2017).The National Institute for Neurological Disease and Stroke (NINDS) study showed that the use of rt-PA in the ideal time increases 11% to 13% of the number of patients with an excellent outcome and 30% higher possibility for full recovery or minimal disability 3 months after stroke, compared with patients who received placebo. The benefit is associated with high risk of hemorrhage (National Institute of Neurological Disorders and Stroke rt-PA Stroke Study Group, 1995).

Intra-arterial thrombolysis is used in the treatment of basilar or vertebral occlusive stroke within 24 hours of symptom onset (Howard, 2016).

I.3.2.5.1.3. Mechanical thrombectomy:

Multiple studies evaluating Mechanical thrombectomy demonstrated favorable effect and specific sub groups (Powers William J. *et al.*, 2018).

I.3.2.5.1.4. Antithrombotic and antiplatelets therapy

- Antiplatelet therapy: aspirin (150-300 mg daily), given within 48 hours of onset of stroke prevents early recurrent stroke by (0.7%), reduces death and disability at 3-6 months by (1.3%), and increases the proportion of patients who fully recover (Muir, 2001). The addition of clopidogrel can improve the benefit (Howard, 2016).
- For patients with cardio-embolic stroke the initiation of oral anticoagulation is considered after the evaluation of the bleeding risk and the severity of the stroke according the NIHSS score. In case of TIA related to non-valvular AF oral anticoagulant is started one day after the acute event (Kirchhof *et al.*, 2016)

I.3.2.5.1.5. Treatment of Hemorrhagic stroke

Surgical treatment is considered in case of cerebral hematoma > 3 cm, with trunk compression and hydrocephalus, early surgical drainage is indicated. In SAH, the placement of coils to repair the ruptured aneurysm is recommended (Broderick *et al.*, 2007; Ustrell-Roig & Serena-Leal, 2007).

I.3.3. Peripheral artery disease

I.3.3.1. Definition

Peripheral artery disease (PAD) includes all atherosclerosis disorders located in all arterial beds except the coronary arteries. In case of disorders limited to the lower limbs the abbreviation LEAD is used.

Ankle Brachial Index (ABI) is a standard screening exam, inexpensive and non-invasive. It detects LEAD at all stages and can be used to stratify severity of the disease and guide treatment (Allison *et al.*, 2007). The cut-off point for diagnosing LEAD is ≤ 0.90 at rest (Mehta, Ogendo & Awori, 2017). This cut-off value is commonly used in both clinical practice and epidemiological research. An ABI value < 0.90 is strongly associated with CVD morbidity and mortality (Selvin & Erlinger, 2004) and can be considered as a marker for atherosclerosis (Zheng *et al.*, 2005). The test of ABI ≤0.90 has a specificity of (83.3%-99%) and a sensitivity of (72.1%-89.2%) (Xu *et al.*, 2010).

I.3.3.2. Physiopathology

LEAD share the same pathogenesis with CAD, namely atherosclerotic changes with its three stages: initiation of the lesion, progression of the lesion and plaque complication leading to stenosis of the artery. Depending on the severity of stenosis, blood viscosity and flow velocity, resistance in the vascular system increases with exercise and reduces oxygenation of the muscles. With the decrease of blood flow, intermittent claudication (IC) appears. The formation of thrombus may occlude the vessel partially or completely leading to ischemia, claudication and rest pain or ulceration (Ouriel, 2001). Chronic ischemia leads to the buildup of lactate and acylcarnitine in the lower limbs causing muscle deterioration, denervation and atrophy (Levy, 2002).

I.3.3.3. Clinical presentation

I.3.3.3.1. Intermittent claudication

It is a primary symptom of LEAD. Most of subject are unaware of the disease, one third considered this symptom as a natural manifestation of the aging process or hard exercise. The leg pain is associated with walking and relieved by rest. Few questionnaires were developed, the first one was the WHO Rose questionnaire and the most used was the San Diego Claudication Questionnaire. Intermittent claudication (IC) has a low sensitivity but a high specificity for an abnormal ABI. The clinical presentation is related to the severity of underlying disease and associated comorbidity. Approximately 10% of individuals with LEAD described typical symptoms and up to two-third are asymptomatic, or presenting atypical symptoms in this case the diagnosis is based on ABI <0.90 (Mozaffarian *et al.*, 2016).

- Atypical pain syndromes were the clinical manifestation in 60% of cases, more frequent in patients with neuropathy or arthritis and physically inactive (McDermott *et al.*, 2001).
- Claudication symptoms remain stable in 70%-80% of patients, worsen in 10-20% and will progress to critical limb ischemia in 1% to 2% during 10 years period (Hirsch *et al.*, 2006).
- Critical limb ischemia reflects a chronic severe condition. The perfusion is decrease at rest in the affected extremity. Pain at rest, cold extremity and ulcers or gangrene are the main clinical manifestations. This condition is strong risk marker of death or amputation.

I.3.3.4. Physical examination

The clinical assessment includes lower extremity evaluation and pulse examination. Auscultation of bruits for carotids, palpation of abdominal aorta, femoral popliteal, dorsalis pedis and posterior tibial arteries and should be described as normal (+2), diminished (1+), or absent (0) (Hirsch *et al.*, 2006). The dorsal pedis pulse can be absent in 12% of patients and it is considered a normal finding, conversely an absent posterior tibial pulse is always abnormal. In case of rest pain, the inspection of the foot is abnormal.

The measurement of ABI

Systolic Blood Pressure (SBP) is measured both arms with subject in supine position. A BP difference exceeding 20 mmHg indicates subclavian or axillary disease. Hand-held Doppler ultrasound devices are used to measure SBPs of posterior tibial and dorsal pedis arteries in each leg. In each ankle the ABI is determined using the ratio of highest ankle artery by the highest SBP in arms. The lower the ABI, the greatest is the hemodynamic disorder. In case of systemic risk evaluation ABI is determined by the lower ABI between the two ankles.

Exceptions

- If one leg has an ABI ≤0.90 while the other has ≥1.40 in this case the participant is categorized with an ABI<0.90
- If one leg has an ABI ≥1.40 while the other leg with normal ABI>0.90 the participant is categorized with an ABI ≥1.40
- The ABI has several limitations, it can be falsely normal in diabetics with neuropathy
- The ABI is sensitive slightly to height in very tall patients (Hiatt, Hoag & Hamman, 1995)

I.3.3.5. Investigations

- Arterial duplex ultrasound is non-invasive approach used to define the anatomy, the hemodynamic, the extent of LEAD and the lesion morphology. The sensitivity and specificity were reported to 95% and 99% respectively (Whelan, Barry & Moir, 1992).
- Peripheral angiography or computed tomography angiography defines the location and the extent of the lesions. These tests are recommended when surgery is mandatory

I.3.3.6. Risk factors for LEAD

LEAD shares the same risk factors with another CVD such as CAD and stroke. Smoking is the strongest risk factors for LEAD and the only traditional cardiovascular risk factor for which the Odds ratio differ between LEAD and CAD or stroke (Criqui & Aboyans, 2015). The increase in risk is related to the number of cigarettes smoked (Bainton *et al.*, 1994). In the majority of studies, current smoking versus non-smoking double the odds of LEAD (Fowkes *et al.*, 2013; Criqui & Aboyans, 2015). In LMIC this hypothesis is significant in males more than females due to conservative cultural and social values. Diabetes mellitus was found to be associated with LEAD after multivariate adjustment with Odds ratio varying from 1.50-4.05 (Criqui & Aboyans, 2015). Hypertension demonstrated an association to LEAD with Odds ratios ranging from of 1.50 to 2.20. In the Framingham Study, the risk of IC increases by 30% in the population with blood pressure exceeding 160/100 mmHg (Murabito *et al.*, 1997). In Health Professionals Follow-up Study (HPFS), hypertension was reported up to 41% in persons with LEAD, in addition the risk in hypertensive males is 2.5-fold and 3.9-fold in females (Joosten *et al.*, 2012; Ingolfsson *et al.*, 1994). Total cholesterol, High density lipoprotein cholesterol (HDL ch) and triglycerides, all appear to be potential risk factors for LEAD (Fowkes *et al.*, 1992; Curb *et al.*, 1996). Obesity seems to be the cause of other risk factors for LEAD such as diabetes, hypertension and dyslipidemia. Many large studies have failed to find a significant association between obesity and LEAD or IC after multivariate adjustment regression (Hooi *et al.*, 2001; Ness, Aronow & Ahn, 2000).

I.3.3.7. Treatment

I.3.3.7.1. Pharmacological therapy

The main goals of treatment for LEAD include reduction in the risk of cardiovascular event such as myocardial infarction and stroke, and improvement of symptoms and quality of life.

- Statins is recommended as primary and secondary prevention (Aboyans *et al.*, 2018). Statin reduced cardiac event, mortality post revascularization mortality and improved painless walking distance (Aung *et al.*, 2007; Ramos *et al.*, 2016)

- Antiplatelet therapy: single antiplatelet therapy preferably clopidogrel is recommended in symptomatic LEAD (Aboyans & Ricco, 2018). In asymptomatic cases Aspirin prescription is matter of debate
- Cilostazol treatment reduced symptoms and improved walking distance in patients with LEAD (Gerhard-Herman *et al.*, 2017).
- Control of risk factors: smoking, HTN, diabetes and hyperlipidemia, regular exercise and weight loss.

I.3.3.7.2. Revascularization

Indicated in patients with lifestyle-limiting claudication and severe limb ischemia. Two types of revascularization are percutaneous balloons angioplasty with or without stenting, and surgery.

I.4. Risk factors related to Cardiovascular diseases

I.4.1. Definition and classification of cardiovascular risk factors

CVDs are a continuum influenced by cardiovascular risk factors (CVRF) and participate via progressive vascular diseases (CAD, LEAD, stroke) to target organ damage and death. This process leads to two important points: First, the intervention through the circuit can disrupt the pathophysiological process and thus provide cardiovascular protection. Second, the cardiovascular disease in atherosclerosis etiology share the same risk factors, so, it is fundamental to evaluate and treat a patient's total cardiovascular risk rather than considering risk factor independently (Dahlöf, 2010). WHO defines risk factor as a characteristic, condition or behavior that increases the likelihood of getting a disease or injury (WHO Global health risk, 2009). CVRF are defined as characteristics that increase the risk of developing CVD, including two categories modifiable and non-modifiable risk factors

I.4.1.1. Modifiable risk factors

The world is affected by a global rise in the prevalence of cardiovascular risk factors. Modifiable risk factors are the major contributors to cardiovascular morbidity and mortality including hypertension, smoking, diabetes, obesity, dyslipedemia, stress, unhealthy diet and physical inactivity. These risk factors rarely occur alone, and instead tend to cluster in individuals (Meigs *et al.*, 1997). Recent study reported that only 2%-7% of people are without risk factors, and 70% have multiple risk factors, which increase total individual's risk of CVD; from 4-fold with one risk factors to 60-fold in the cluster of five risk factors (Wilson *et al.*, 1999). The prevalence of multimorbidity (two or more chronic conditions) is increasing, due to growing incidence of chronic conditions and increasing life-expectancy (Uijen & van de Lisdonk, 2008). Number of risk factors were identified in epidemiological surveys. In 2016 the global burden disease for

risk profiles in Middle East and North Africa (MENA) stranded out these risk factors by order of priority: high blood pressure ranked as the first, followed by obesity, diabetes then smoking and dyslipidemia (Forouzanfar *et al.*, 2016).

I.4.1.1.1. Hypertension

I.4.1.1.1.1. Definition, classification

Hypertension constitutes a major public health challenge in the world. HTN is defined as a Systolic Blood Pressure (SBP) ≥140 mmHg and /or Diastolic Blood Pressure (DBP) ≥ 90 mmHg or taking antihypertensive drugs or having been told at least twice by a healthcare professional as having HTN (Table 5). Normal levels of both systolic and diastolic blood pressure are essential for the function of vital organs such as the heart, brain, kidney, for overall health and wellbeing (WHO, 2013).

Table 5: Blood pressure classification according to WHO (WHO hypertension 2013)

Normal	Systolic: less than 120 mmHg Diastolic: less than 80 mmHg
A risk (prehypertension)	Systolic: 120–139 mmHg Diastolic: 80–89 mmHg
High	Systolic: 140 mmHg or higher Diastolic: 90 mmHg or higher

I.4.1.1.2. Obesity

I.4.1.1.2.1. Definition, classification

Obesity is defined as excess amount of body fat, which leads to an ill health and risk of the development of type 2 diabetes and cardiovascular event. It is related to the epidemiological transition of NCDs. Overall, obesity ranked as the sixth leading cause of Disability Adjusted Life Years (DALYs). Overweight causes almost 3 million deaths worldwide each year (WHO Global health risk, 2009). WHO and National heart, Lung, and blood institute (NHLBI) define weight categories for adults as follows: Body Mass Index (BMI): normal weight (25.0 $kg/m^2 \leq$ BMI $\leq$ 29.9 kg/m^2), obese class I (BMI 30-35 kg/m^2), class II (BMI >35 to 39.9 kg/m^2), and class III (BMI ≥40 kg/m^2) (WHO, 2017a).

I.4.1.1.3. Diabetes mellitus

I.4.1.1.3.1. Definition, classification

Diabetes mellitus is a condition defined by an elevated level of blood glucose. Glycated haemoglobin A1c (Hb A1c) has been recommended as diagnostic test for DM. The threshold of ≥6.5% was adopted to diagnose diabetes.

The classification based on recommendation of the WHO and the American Diabetes Federation (ADF) includes four classes (ESC *et al.*, 2013).

- Type 1 diabetes: results from B-cells destruction leading to insulin deficiency
- Type 2 diabetes: the most common, accounts for 90-95% of all cases. It is the consequence of a progressive insulin secretory defect, in association with obesity, sedentary lifestyle, and insulin resistance
- Gestational diabetes: diagnosed during pregnancy, after delivery, most of them return to a euglycemic state but they are at increased risk for T2DM in the future. A large Canadian study estimates the probability to develop diabetes after 9 months of delivery was 4 % and 19 % after 9 years (Feig *et al.*, 2008)
- Other specific types of diabetes due to other cause such as genetic disorder, diabetes secondary to pathological conditions or disease (pancreatitis, trauma, or surgery of the pancreas), drugs induced diabetes (HIV/AIDS or after organ transplantation)

Table 6: Criteria for the diagnosis of diabetes (ADA, 2018)

FPG ≥126 mg/dL (7.0 mmol/L). Fasting is defined as no caloric intake for at least 8 h*.
OR
2-h PG ≥200 mg/dL (11.1 mmol/L) during OGTT. The test should be performed as described by the WHO, using a glucose load containing the equivalent of 75-g anhydrous glucose dissolved in water.*
OR
A1C ≥6.5% (48 mmol/mol). The test should be performed in a laboratory using a method that is NGSP certified and standardized to the DCCT assay.*
OR
In a patient with classic symptoms of hyperglycemia or hyperglycemic crisis, a random plasma glucose ≥200 mg/dL (11.1 mmol/L).

* In the absence of unequivocal hyperglycemia, results should be confirmed by repeat testing.

Table 7: Type 2 Diabetes Mellitus risk factors (“Risk Factors of Type 2 Diabetes | NIDDK,” 2016)

1. Age ≥45years
2. Overweight or obese.
3. Sedentary lifestyle.
4. Family history with diabetes mellitus.
5. History of delivering a baby weighing >9 pounds.
6. Polycystic vary syndrome; and history of diabetes mellitus during pregnancy.
7. Elevated blood pressure (≥140/90 mmHg) or being treated for hypertension.
8. Levels of major lipids: High-density lipoprotein below 35 mg/dL, or TG above 250 mg/dL.
9. Prediabetes HbA_1C level of 5.7 to 6.4 %; an elevated FPG test result of 100–125 mg/dL; or a two-hour oral glucose tolerance test result of 140–199 mg/dL.
10. Acanthosis nigricans presenting with a dark, velvety rash around the neck or armpits.
11. Current or prior history of CVDs

I.4.1.1.4. Alcohol

Epidemiologic studies define “heavy” drinking as ≥ 3 standard drinks per day, and lesser amounts “light” or “moderate” drinking. According to WHO harmful use of alcohol is defined by 6.2 liters of pure alcohol per year which translates to 13.5 grams of pure alcohol per day for persons ≥ 15 years of age (Anon, 2014).

I.4.1.1.5. Serum lipids

Dyslipidemia is defined by the elevation or attenuation of serum lipids. Cholesterol and triglycerides are the major lipoproteins. To date, there is no evidence that fasting is superior to non-fasting in evaluating a lipid profile for cardiovascular risk prediction, Many countries are currently in the process of modifying their guidelines for measuring a lipid profile in the non-fasting state, which facilitates blood collection for patients, laboratory technicians and clinician (Langsted & Nordestgaard, 2019; Nordestgaard & Varbo, 2014).

All lipoproteins have a common basic structure but they differs in their size, density composition and chemical proprieties (Yusuf *et al.*, 2004). The different lipoproteins are including chylomicrones, Intermediate Density Lipoprotein (IDL), Very Low-Density Lipoprotein (VLDL), LDL, HDL, and apolipoproteins such as (Apo A, apo B, apo C and apo E). Lipids disorders are defined as the total cholesterol, Low density Lipoprotein Cholesterol (LDL-C), High density

Lipoprotein-Cholesterol (HDL-C) and triglycerides. According to the large epidemiological studies, the results of a meta-analysis including 10 large cohort studies reported that for each 0.6 mmol/l or 23 mg/dl reduction in serum cholesterol levels in subjects > 60 years old, decrease the risk of CHD by 27% (Law, Wald & Thompson, 1994).

The National Cholesterol Education Program Adult Treatment Panel III of (NCEP ATPIII) define dyslipidemia as total cholesterol ≥ 240 mg/dl, triglycerides > 200 mg/dl, (LDL-C) >160 mg/dl and (HDL -C) <40 mg/dl in men and < 50 mg/dl in women (N.C.E.P, 2002). The National Health and Nutrition Examination Survey (NHANES) reported a prevalence of total cholesterol level ≥ 240mg/dl, in USA population up to 33.6% (Tóth, Potter & Ming, 2012). In Middle east the prevalence of dyslipidemia was 70.5% (Labarthe, 2010; Yusuf *et al.*, 2004). A study among adult population in GCC found that the prevalence of hypercholesteremia defined as total cholesterol >200 mg/dl ranged from 17% to 54.9% in males and 9% to 53.2% in females (Aljefree & Ahmed, 2015). A meta-analysis including 90,056 subjects in 14 randomized trial of statin showed that lowering LDL-C by 39 mg /dl was associated with one-fifth reduction in the 5 years incidence of major cardiovascular events (CAD, and stroke) (Baigent *et al.*, 2005). The negative association between low HDL-C and the risk of heart disease is well defined. In Prospective Cardiovascular Munster (PROCAM) study, subjects with HDL-C < 35 mg/dl have 4-fold higher cardio vascular risk (Assmann *et al.*, 1996). The Israeli Ischemic Heart Disease Study showed that subgroup with low HDL-C concentration had 36% greater CVD mortality than subgroups with elevated HDL-C (even after adjusted for age and CVRF) (Goldbourt, Yaari & Medalie, 1997). In addition a meta-analysis of four studies demonstrated that for every 1mg /dl increase in HDL-C level there was decrease in coronary events risk by 2-3% independently of LDL-C (Gordon *et al.*, 1989).

Triglycerides measurement is important for evaluating the risk of CVD mainly in diabetics, glucose intolerance, and insulin resistance. In the Copenhagen City Heart Study and the Women's Health Study, the increase in non-fasting triglycerides concentration by 5mmol/l versus less than 1mmol/l, was strongly associated with increasing adjusted age risks by 17-fold for MI, by 6 for IHD, 5 for ischemic stroke, and 4 for all-cause mortality in women. For men the corresponding risks increase were by 5, 3, and 2 fold (Freiberg *et al.*, 2008; Nordestgaard *et al.*, 2007). Non-HDL cholesterol (Non-HDL-C) is the sum of cholesterol collected in all lipoprotein except HDL-C. It is calculated as the difference between total and HDL-C. It should be higher by about 30mg /dl than LDL-C. An elevation of non-HDL-C by 1mg/dl increases the risk of death due to CVD by 5%. It is also considered the second goal after LDL-C in diabetics patients (Bergmann, 2010).

Table 8: Classification of elevated TG levels (Jellinger *et al.*, 2017)

TG category	TG concentration, mg/dL	Goal
Normal	< 150	<150 mg/dL
Borderline-high	150-199	
High	200-499	
Very high	≥ 500	

Table 9: LDL-C and non-HDL-C goals in three CHD risk groups by NCEP ATPIII)(Graham *et al.*, 2007)

Risk category	LDL-C (mg/dL)	Non-HDL-C (mg/dL)
CHD and CHD risk equivalent (10-years CHD death risk >20%)	**<100**	<130
Multiple (≥ 2) risk factors (10-years CHD death risk <20%)	<130	<160
0-1 risk factor	<160	<190

I.4.1.1.6. Nutrition

Unhealthy diet contains too much fat, sugar, carbohydrates, high fat meats, few Fruits and Vegetables (F&V) and whole grains, without adequate vitamins and minerals. A recent study among 65, 226 English population, found that eating ≥ 7 portions of F&V daily reduced the risk of death by heart disease by 31% (Oyebode *et al.*, 2014). The physicians' Health Study, during a follow-up of 12 years, reported 25% lower incidence of CAD in men who consumed >2.5 or more serving of vegetables daily, compared with those who consumed less than one serving daily (Liu *et al.*, 2001). Numerous studies showed that diets high in fiber are significantly associated with lower risks of CVD (stroke and CAD)(Silvia, 2014). Another large prospective cohort study of 84,251 women in the Nurse' Health Study and 42,148 men in the Health Professionals Follow-up Study reported 30% lower risk of CVD in people with highest F&V intake (>5 serving daily) compared to those with lowest intake. For each increase of one serving per /day in F&V, a 4% lower risk of coronary heart disease and 6% lower risk of ischemic stroke (Joshipura *et al.*, 1999, 2001). In addition, decreasing dietary salt intake from 9-12 gram/day to the recommended level of 5 grams/day would have a major impact on BP and CVD (Mendis *et al.*, 2011).

I.4.1.1.7. Physical activity

Physically active means that you are protected from numerous risk factors, thus less exposed to CVD. Additionally physical activity is fundamental to energy balance and weight control (WHO, 2010). Morris et al found that civil servant post men who walked or cycled while delivering mail had lower rates of heart disease compared to postal clerks who had sedentarily jobs (Morris & Crawford, 1958). The sedentary life was a predominant factor in industrialized nations (Archer & Blair, 2011). The rise in sedentarism has been an epidemic for chronic disease mainly obesity. Regular physical activity has a protective effect on cardiovascular risk by the deceleration of atherosclerosis progression, improvement of endothelial dysfunction, decreased systemic inflammation and controlling major CVRF such as HTN, diabetes and obesity (Cheng *et al.*, 2013). The prevalence of inactivity was higher among the younger population in GCC ranging from 24.3% to 93.9% in males and from 50% to 98.1% in females. Saudi Arabia keeps the higher rate (Aljefree & Ahmed, 2015). In a meta-analysis of data from 32 studies comparing inactive persons and those who practiced 150 min /week of moderate - intensity, physical activity had a 14% decrease in CAD, and those who practiced the equivalent of 300 min /week of moderate-intensity physical activity had 20% lower CAD (Sattelmair *et al.*, 2011). In another meta-analysis including 23 studies the risk of stroke (ischemic or hemorrhagic) was 27% in individuals with a moderate activity vs 20% in high physical activity (Lee, Folsom & Blair, 2003).

I.4.1.1.8. Stress

Everyone feels stress in different ways and reacts to it in different ways. How much stress you experience and how you react to it can lead to a wide variety of health problems (AHA 2014, 2014). The concept of psychological stress produces a physiological change by the activation of the hypothalamic-pituitary-adrenocortical and sympathetic nervous system, which triggers pathophysiological mechanisms that include inflammation, hemostasis, and dysfunction of metabolic and cardiac autonomic control (Brotman, Golden & Wittstein, 2007). Personality types (type A and type D) lead to unhealthy response to daily stressors. The type D (distressed) personality is a negative affectivity characterized by a combination of pessimistic emotions, depressed mood, anxiety, anger, worried and hostile feelings. This personality is almost related to social phobia and panic disorder (Sher, 2005). By contrast, the type A personality is characterized by anxiety, intense time urgency, intense competitiveness, hypervigilance, and sometimes hostile behaviors (Ragland & Brand, 1988). In the general population, adults with work stress or private-life stress have 1.1-1.6-fold increased risk of CAD and stroke (Kivimäki & Steptoe, 2018). Chronic stress plays a role as a disease trigger in individuals with high atherosclerotic plaque leading to cardiovascular events such as hypertension, insulin resistance, arrhythmia, myocardial ischemia, cardiac failure and stroke (Kivimäki & Steptoe,

2018). Emotional stress is involved in 3.9% of acute cardiac events (Nawrot *et al.*, 2011).The association with stroke was uncertain (Truelsen & Nielsen, 2003). Anxiety was reported to be high in patients with a history of ACS. The influence lasts for a long period time in 20% to 25% of patients after the first event (Moser *et al.*, 2007).

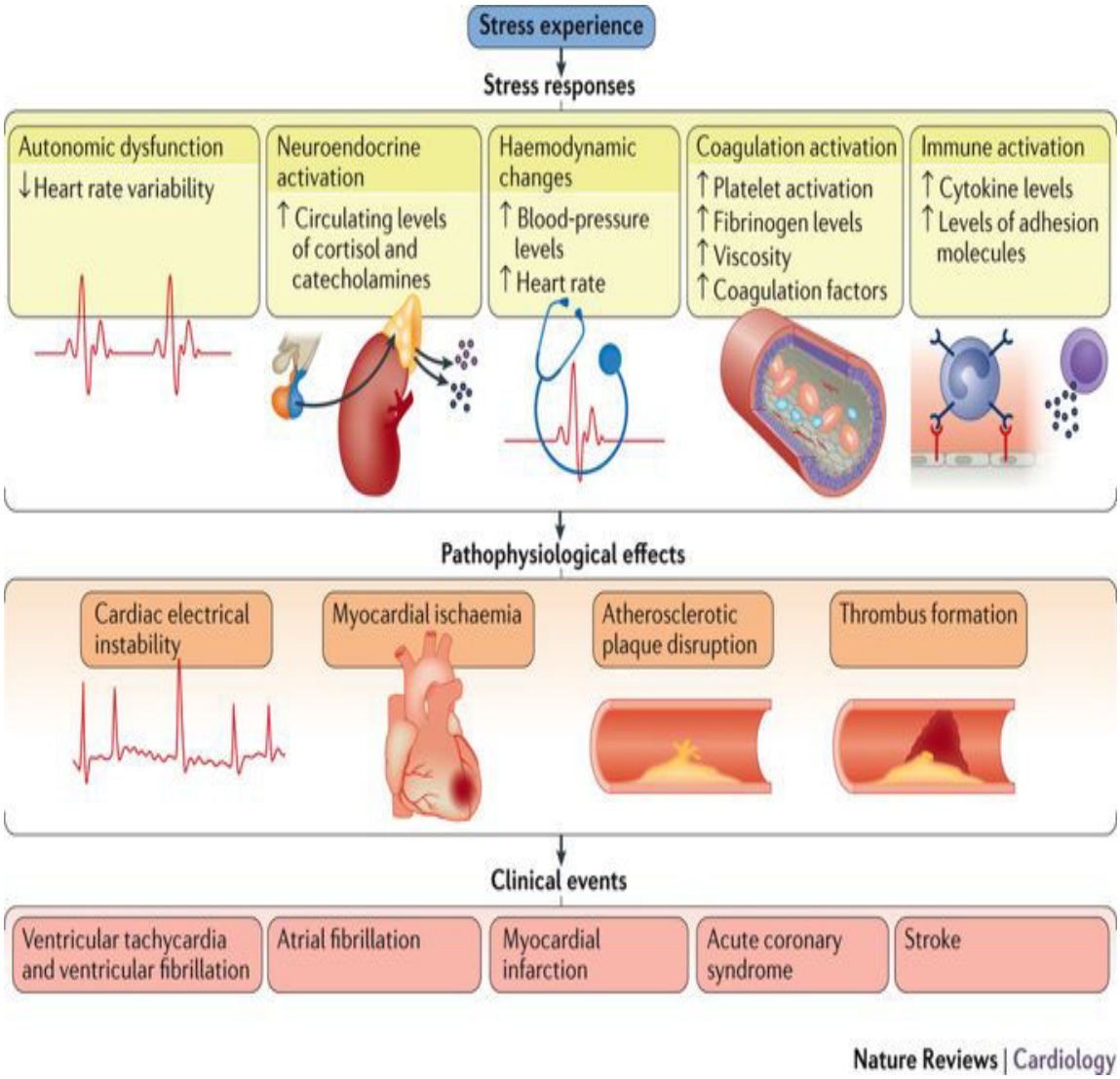


Figure 7: Effects of stress (Nature Reviews cardiology 2018)

I.4.1.1.9. Socioeconomic status

Socioeconomic Status (SES) is a complex concept affecting health and known as powerful predictor of CVDs and death (Stokols, Pelletier & Fielding, 1996). It is measured as a combination of education, income, and occupation but may include age, sex, ethnicity and marital status. The available data showed that the association between SES and CVD depends on the socioeconomic development context, and the stage of the demographic, epidemiological and nutritional transition of the population (Mestral & Stringhini, 2017). In the HIC there is an inverse association between SES and CVD and CVRFs. The SES was measured via education, occupation, or income. However, in LMIC the relation between SES

and CVD or CDVRFs shows a positive association (Mestral & Stringhini, 2017), because people with lower SES tend to have higher levels of traditional cardiovascular risk factors such as higher BP, smoking, and obesity (Yu *et al.*, 2000). Recent data confirms that SES is closely related with the quality of diet (Turrell *et al.*, 2003). Low SES people prefer white bread, potatoes rice, and refined cereals compared to those with high SES, who prefer whole grain products with lower glycemic index, consumption of vegetables and fruit (Cronin *et al.*, 1982; Shimakawa *et al.*, 1994; Smith & Baghurst, 1992). The behavioral factors, such as physical inactivity, smoking and alcohol intake, explain only 13%-60% of the SES differences in CVD morbidity and 19%-55% of CVD mortality (Méjean *et al.*, 2013).

I.4.1.2. Non-modifiable risk factors

I.4.1.2.1. Age

By 2030 20% of the population will be aged > 65 years. In this age group CVD will result in 40% of all deaths and will be the leading cause (North & Sinclair, 2012). The cardiovascular system is strongly affected by the ageing process leading to progressive deterioration in structure and function of the heart and vasculature that contribute to the development of CVD (Costa *et al.*, 2015). Epidemiologic studies revealed that at any age the risk of cardiovascular events varies widely (4-5-fold) depending on the associated risk factors. Studies indicate that the chances of surviving to age 85 years have decreased significantly with cumulative risk factors, from 37% for men without risk factors to 2% with five risk factors and from 65% for women without risk factors to 14% with five risk factors (Kannel & Vasan, 2009).

I.4.1.2.2. Gender

For many years, CVD was considered as a male disease. However, in the European population 38% of cardiovascular deaths before the age of 75 years were in women and 37% in men (European Cardiovascular Disease Statistics, 2012). The difference between male and female was previously described in epidemiology, pathophysiology, clinical manifestation and management of CVD (Anon, 2012c). The sexual hormones drive differences in gene expression and the function of cardiovascular system (Regitz-Zagrosek *et al.*, 2016). In male sex, cardiovascular risk increases over time, as well as atherosclerosis process continues. In contrast women are protected from atherosclerosis during the fertile age by estrogens that exert favorable effect on cardiovascular system. The effect disappears after menopause. Women and men manifest a similar cardiovascular profile with a difference of 10 years of age (Perk *et al.*, 2012). In 2004, the WHO reported a total cardiovascular mortality of 55% in women and 43% in men. IHD, stroke and other CVD represent 23%, 18% and 15% respectively in women and 21%,11% and 11% respectively in men (Stramba-Badiale *et al.*, 2006).

Over 5 decades in the Framingham study cohort the occurrence of CAD or stroke were up to 47%-31% and 15%-18% respectively in males and females. The higher risk of stroke in female was related to longer life expectancy (Lloyd-Jones *et al.*, 1999; Seshadri *et al.*, 2006). Gender difference for traditional cardiovascular risk factors associated with CVD were also documented. Age, hypertension, total cholesterol and LDL-C had a great influence in men, while menopause, systolic arterial hypertension, smoking, diabetes, triglycerides and HDL-C were the main actors in women (Leonarda & Gabriella, 2015). Every 10 mmHg of SBP was associated with15% increased risk of CAD and 25% increased risk of stroke in both sexes (Peters, Huxley & Woodward, 2013). Diabetes increased cardiovascular risk of 3-7 fold in women and 2-3 fold in men (Manson, 1996).Two large meta-analyses reported that the risk of CAD and stroke were increased by 44% and 27% in diabetic women (Huxley, Barzi & Woodward, 2006; Peters, Huxley & Woodward, 2014). The prevalence of overweight in men and women differs according to the level of the development of the country. Higher BMI is more prevalent in men than women in HIC, conversely in LMIC mainly in Arab countries a female predominance was described (Anon, 2015).

Total cholesterol confers the same risk of cardiovascular in both sexes. However LDL-C increases cardiovascular risk in men more than women (Manolio *et al.*, 1992). Low HDL-C represents equal risk for CAD in both sexes, mainly young age, but predicts CAD mortality in women more than in men. In addition, triglycerides are a part of metabolic syndrome which is higher in women. Smoking increases risk of cardiovascular events by 3.6 in women and 2.4 in men (Willett *et al.*, 1987). A meta-analysis from 74 prospective cohort studies show that women who smoke had a 25% greater relative risk of CAD than men (Huxley & Woodward, 2011).

I.4.1.2.3. Family history

Represents one of the main risk factors for CVD, especially in the younger population with a first-degree relative disorder: (men below the age of 55 years and women below 65 years) (Choudhury & Marsh, 1999; Elis & Lishner, 2004). Family history helps to define the small subset of families that account for the majority of prevalent cases in the population (Hunt, Gwinn & Adams, 2003). The risk for CVD and stroke among subjects with positive family history ranges from 2 to 9 and 1.5 to 2, respectively (Kardia, Modell & Peyser, 2003; Liao *et al.*, 1997). Family history represents the interaction between genetic, environmental and behavioral factors (Elis *et al.*, 2008). Even a non-premature parental history increases the risk of CVD in offspring (Sesso *et al.*, 2001).The history of heart attack in both parents increases the risk of CAD mainly when 1 parent has a premature coronary event before 50 years of age (Chow *et al.*, 2011). Sibling history of CVD has been shown to increase the odds of CVD in males and females by 45% (Murabito *et al.*, 2005). In a recent study of patients with premature

ACS (age ≤ 55 years), 28% of the females and 20% of the males had a family history of CAD. Patients with family history of CAD had a higher prevalence of traditional CVD risk factors (HTN, DM, dyslipidemia and obesity) (Choi *et al.*, 2014; Hunt, Gwinn & Adams, 2003; Yoon *et al.*, 2002). In monozygotic twins the risk of death from CAD increased 3.8 to 15 times if a sibling died of CAD before age 75 (Marenberg *et al.*, 1994). In addition a large international case-control study reported a rise in the risk of MI if one parent had MI (OR=1.67), or one parent had MI before age 50 (OR=2.36), or both parents had MI (OR=2.90) and if both parent had MI before age 50 (OR=6.56) (Anderson *et al.*, 2013). The prevalence of a positive family history ranges from 14% to 35% in the general population, 75% of those with premature heart disease have a positive family history highlighting the opportunities for prevention (Hawe *et al.*, 2003).

I.4.1.2.4. Menopause

Menopause is an indicator of the transition from reproductive to non-reproductive life and is associated with biological and hormonal changes. The risk is related to post menopause is due to a sudden decrease of estrogen hormone, which has protective effects on lipid, glycemic metabolism and vessels (Rossi *et al.*, 2002). Menopausal status and estrogen deficiency were frequently associated with hypertension due to increase in BMI, insulin-resistance, sodium retention, and with increased smooth muscle cell proliferation leading to an increase in systemic vascular resistance. The role of Hormonal Replacement Therapy (HRT) in CVD is controversial. In contrast Women's Health Initiative study described an increased risk of CAD and breast cancer in users of HRT including estrogens and a synthetic progestin (Rossouw *et al.*, 2007; The Writing Group on behalf of the Workshop Consensus Group, 2009).

I.4.1.3. Novel risk factors

I.4.1.3.1. Fibrinogen

Plasma fibrinogen as a coagulation factor is a heterogeneous mixture of many different molecular forms (Gordon *et al.*, 1989). Many studies reported the strong relationship between plasma fibrinogen concentration and cardiovascular disease mainly CAD, stroke and LEAD (Lowe, 1995). Fibrinogen concentration raises the risk of atherogenesis, thrombogenesis and ischemia (Danesh *et al.*, 2000). Recently fibrinogen was introduced as risk factor for premature CAD in subjects <55 years (Pineda *et al.*, 2009; Shojaie *et al.*, 2009). The fibrinogen is a pathway by which traditional risk factors exert their effect. For example, fibrinogen levels increased risk of CVD associated with smoking and essentially with the number of cigarettes smoked. The level decreases after smoking cessation (Fogari *et al.*, 1994). The risk of CVD associated with obesity might be driven by the fibrinogen. A loss of weight after low calories diet leads to fall in fibrinogen levels (Ditschuneit, Flechtner-Mors & Adler, 1995). The

Prospective Cardiovascular Munster (PROCAM) study found that subjects with both high level of LDL-C and fibrinogen had a 6.1-fold increase in CAD compared with those with lower or normal levels (Heinrich *et al.*, 1994; Thompson *et al.*, 1995). The Gothenburg and Framingham Studies reported that plasma fibrinogen levels represent an independent risk factor for MI and stroke and strong risk factor for cardiac sudden death in patients with CAD (Thompson *et al.*, 1995). Also, platelets hyperactivity due to high fibrinogen concentration was found in diabetic patients (Stec *et al.*, 2000).

I.4.1.3.2. Homocysteine

Homocysteine concentration is higher in men than women and increases with age.The difference becomes apparent in puberty and it is related to hormonal factors, lifestyle, nutrition, and vitamins. Thromboembolic events were present in 50% of untreated persons with high level of homocysteine, and 20% die before the age of 30 years (Nygård *et al.*, 1999). Numerous clinical studies demonstrated a relationship between total homocysteine levels and CAD, LEAD, stroke or venous thrombosis (Boushey *et al.*, 1995; Verhoef & Stampfer, 1995).The homocysteine affects the coagulation system and the resistance of the endothelium to thrombosis and may interfere with the vasodilator and antithrombotic effects of nitric oxide (Stamler & Slivka, 1996).

I.4.1.3.3. C. Reactive Protein

C-Reactive Protein (CRP) is a marker of inflammation and a hepatically derived pentraxin that plays a role in the immune response. CRP has a long plasma half-life. Numerous epidemiological studies have demonstrated the role of CRP in the occurrence of MI, stroke, LEAD, sudden cardiac death and it plays a role in almost all process associated with metabolic syndrome (Ridker, 2003). CRP seems to be a stronger predictor of cardiovascular events than LDL ch (Mendall *et al.*, 2000). CRP levels <1, 1 to 3, and >3 mg/dl correspond to low-moderate, and high risk. Subjects with LDL ch <130 mg/dl and CRP >3 mg /dl represent a high-risk group (Ridker, 2003). CRP was a strong predictor of risk even 20 years after initial blood samples were obtained (Sakkinen *et al.*, 2002).

I.4.1.4. Co-occurrence of risk factors

A number of studies have demonstrated that five modifiable CVRF such as cigarette smoking, overweight or obesity, hypertension, diabetes and dyslipidemia can be eliminated by management. The risk of CVD increases with increasing number of risk factors (Yusuf *et al.*, 1998). Data from the first National Health and Nutrition Examination Surveys Epidemiologic Follow-up study showed that the risk for CVD increased with each additional risk factor. More than 50% of the incidence of CAD, stroke and all-cause mortality was due to having one risk

factor and the risk increases up to 70% for individuals with three risk factors (Yusuf *et al.*, 1998). Primary prevention and control risk factors may not reduce the risk of CVD to the equivalent of never having a risk factor. Individuals who control their hypertension are at high risk for CVD compared with those who never develop HTN (N.H.BP.E.P, 1993). Furthermore, the Metabolic Syndrome (MetS) was identified by several criteria and defined as an asymptomatic, pathophysiological state of chronic inflammation, and a cluster of the most harmful risk factors, such as obesity, insulin resistance, hypertension, hyperglycemia and dyslipidemia (Kaur, 2014). The International Diabetes Federation (IDF) estimates that a quarter of the world's adult population has MetS (O'Neill & O'Driscoll, 2015). The rate varies depending on age, ethnicity, and gender of the population (Kaur, 2014). MetS confers a 5-fold increase in the risk of type 2 diabetes mellitus and 2-fold the risk of developing CVD over the next 5 to 10 years (Alberti *et al.*, 2009). In addition individuals with MetS are at 2- 4 fold the risk of stroke and 3-4 fold the risk of myocardial infraction (Alberti, Zimmet & Shaw, 2005). The early identification and control of MetS components prevents the development of the syndrome and reduces CVD events.

Chapter II. Epidemiology of Cardiovascular disease and cardiovascular risk factors

II.1. Cardiovascular disease in the world

CVD is a major public health burden and is the leading cause of total deaths in all regions of the world except Sub Saharan Africa. In 2016 the number of people dying from CVD increased by 15% accounting for 17.6 million deaths per years, due to population ageing and growth (GBD 2016 Causes of Death Collaborators, 2017), and projected to increase to 23.6 million by 2030 (WHO 2014, n.d.) with total cost of $863 billion (Bloom *et al.*, 2012). Ischemic heart disease and stroke combined account for more than 85.1% of all CVD death in 2016 (GBD 2016 Causes of Death Collaborators, 2017). Coronary artery disease was the most common 45.1%, followed by stroke 16.5% (CDC, 2016a). In USA adults' population 92.1 million have at least one type of CVD (Benjamin *et al.*, 2017). By 2030, 43.9% of USA population is projected to have some form of CVD (Heidenreich *et al.*, 2011). The prevalence of CVD in USA population >25 of age in 2011-2014 was 36.6% (Benjamin Emelia J. *et al.*, 2018). In Europe CVD account for 45% of all deaths in Europe and 37% of all death in the European Union mainly (Wilkins et al., 2017). In United kingdom in 2012, CVD represented a second cause of deaths (28%), 46% were from CAD and 26% were from stroke (Bhatnagar *et al.*, 2016). Major CVD event rates, CVD death rates, and all cause death rate were lowest in HIC and highest in LMIC accounting for 70% of CVD death (WHO 2014, n.d.).

II.2. In the Arab countries

The EMR represents a mosaic group of 23 countries (Figure8), including Arab states located in North east African nations comprise (Djibouti, Egypt, Somalia, Sudan) and North west African include (Libya, Morocco, Tunisia and Algeria). Gulf Cooperation Council with (Bahrain, Kuwait, Oman, Qatar, Saudi Arabia, United Arab Emirates and Yemen). Another group which include (Iraq, Jordan, Lebanon, Palestine, and Syria), Non-Arab countries included in EMR were (Afghanistan, Iran and Pakistan). Each country has a unique historical, geopolitical, social, cultural, and economic profile (Mandil, Chaaya & Saab, 2013). Arab countries were also, divided according to their Gross National Income (GNI) per person.

- Low income countries (LIC) (Djibouti, Mauritania, Yemen, and Somalia) had a mean GNI per person of $523.
- Middle income countries (MIC) (Algeria, Egypt, Iraq, Lebanon, Libya, Morocco, Palestine Sudan, Syria and Tunisia) had a GNI of $3251.
- HIC (Bahrain, Saudi Arabia, Kuwait, Oman, Qatar and United Arab Emirates) had GNI of $39 688 (Mokdad *et al.*, 2014).

The estimated median life expectancy in EMR population is 72 years, higher in GCC (78 years), ranging from 48-59 years in Somalia, Afghanistan and Sudan. In The Other countries, life expectancy interval is between 63-74 years (Anon, n.d.). Arab Middle East Countries which have a predominance of young population ranging in middle age from 17-28 years, have undergone rapid socioeconomic changes, political conflicts, poverty, intermediate level of economic development, instability and epidemiologic transition (Ramahi, 2010). The Arab countries (Iraq, Syria, Lebanon, Jordan, Egypt, Yemen and Turkey) have a highest CVD mortality death ranging from 145 per 100000 in Qatar to 548 per 100000 in Yemen, with significant variation between urban and rural areas (Roth *et al.*, 2015). Very few community-based studies were conducted in these countries. Conversely, more data in CVD are available for Arab Gulf states. These countries have undergone rapid modernization and socioeconomic development. Ischemic heart disease and stroke were two of the top five causes of deaths in Arab world. Ischemic heart disease accounting for 90.3 deaths per 100 000 people (Mokdad *et al.*, 2016). The diabetes prevalence is up to 9.3% (ranging from 7 % to 26% among adult aged 15-65 years; it is the second highest among all WHO regions (Jabbour & Yamout, 2012). The global Adult tobacco survey showed that in 14 MICs 48.6% of men and 11.3% of women were tobacco users (Giovino et al. 2012). In nine Arab countries (Bahrain, Egypt, Libya, Jordan, Kuwait, Lebanon, Palestine, Tunisia and Syria) the prevalence of daily tobacco use exceeds 30% in men (Rahim *et al.*, 2014). Water pipe smoking is increasing in young Arabs with prevalence estimates between 6% and 34% in age group 13-15 years (Maziak, 2011). Data from regional STEPS survey shows that 79%-90% of adults in most Arab countries reported eating less than the 5 serving of fruits and vegetables (Anon, 2012b). Obesity continues to rise in Arab population with alarming rate in female more than male. LMICs accounted for 7% of the world's overweight individuals (Boyko *et al.*, 2000). Also, physical inactivity represents high prevalence level particularly in Gulf cooperation which accounts for 70%. (Rahim *et al.*, 2014) .

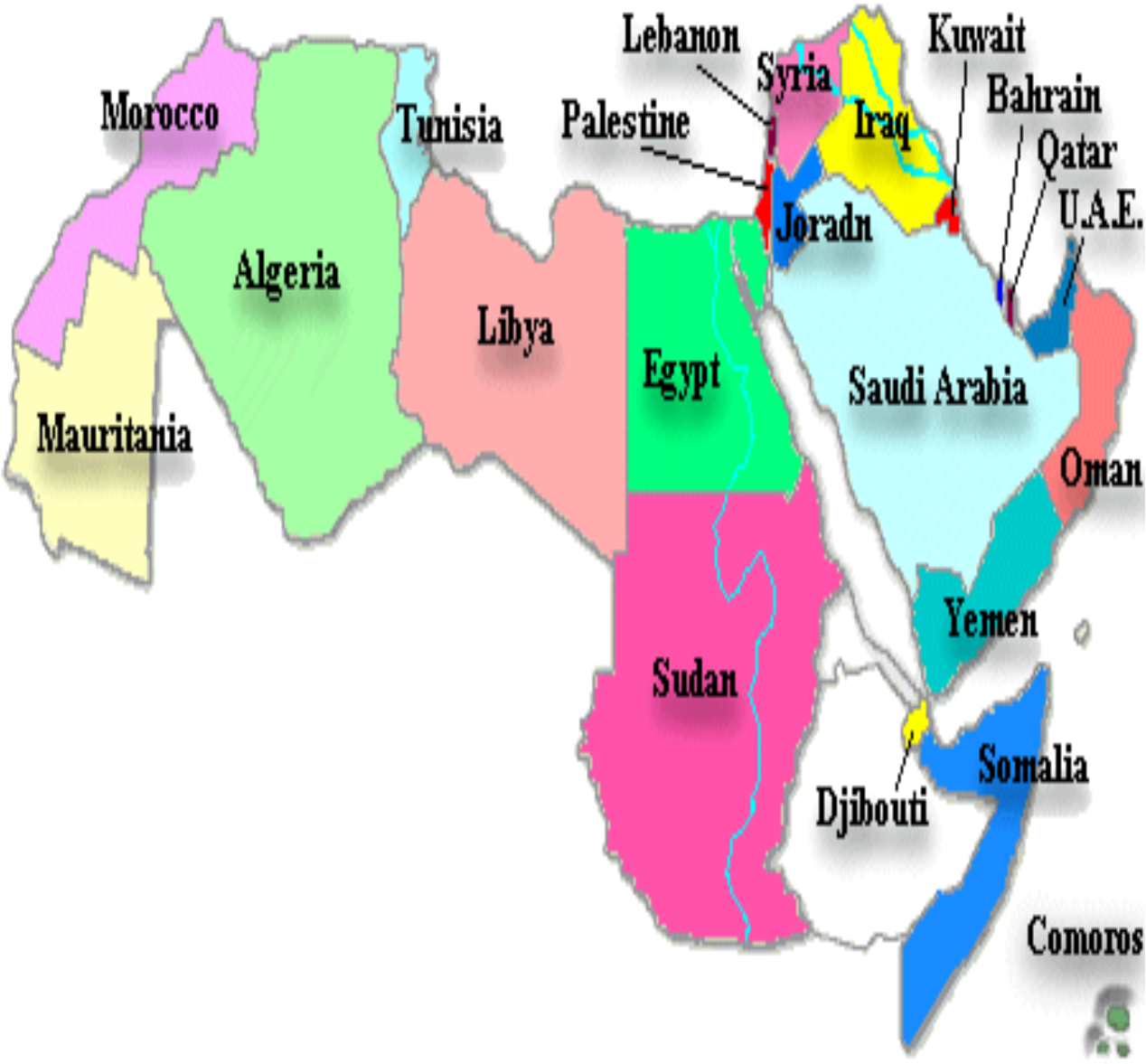


Figure 8: Arab countries Map

Table 10: Cardiovascular risk factors (smoking/physical inactivity) in adults aged ≥15 years and overweight and obesity in adults ≥ aged 20 years in Arab countries (Rahim *et al.*, 2014).

	Current daily tobacco smoking			Insufficient physical activity*			Overweight (BMI ≥25 kg/m²)			Obesity (BMI ≥30 kg/m²)		
	Men	Women	Total	Men	Women	Total	Men	Women	Total	Men	Women	Total
High-income countries												
Bahrain	30·2%	7·4%	18·8%	..	..	..	70·2%	70·5%	70·3%	28·9%	38·2%	32·6%
Kuwait	31·2%	2·8%	17·0%	56·9%	72·1%	64·5%	78·1%	81·3%	79·3%	37·2%	52·4%	42·8%
Oman†	6·4%	0·3%	3·4%	..	..	..	57·8%	57·2%	57·5%	19·4%	25·9%	22·0%
Qatar‡	29·1%	0·6%	14·7%	37·4%	54·2%	45·9%	72·5%	71·3%	72·1%	30·8%	39·3%	33·1%
Saudi Arabia	8·5%	3·4%	6·0%	61·5%	76·2%	68·8%	70·2%	73·2%	71·3%	29·5%	43·5%	35·2%
United Arab Emirates	13·1%	1·2%	7·2%	56·1%	68·9%	62·5%	71·3%	73·9%	72·0%	30·2%	43·0%	33·7%
Middle-income countries												
Algeria	24·2%	0·2%	12·2%	31·9%	49·2%	40·5%	41·8%	54·5%	48·2%	10·7%	24·3%	17·5%
Jordan	47·6%	4·9%	26·3%	..	..		66·5%	71·2%	68·8%	27·3%	41·7%	34·3%
Lebanon	44·6%	30·7%	37·6%	51·9%	41·7%	46·8%	67·0%	58·7%	62·8%	26·4%	29·7%	28·2%
Libya	45·2%	0·2%	22·7%	37·3%	54·4%	45·8%	60·4%	71·0%	65·4%	21·5%	41·3%	30·8%
Tunisia	55·6%	6·6%	31·1%	31·5%	40·3%	35·9%	47·5%	64·2%	55·9%	13·9%	33·4%	23·8%
Egypt	37·2%	0·6%	18·9%	..	..	..	62·4%	76·9%	69·8%	22·5%	46·3%	34·6%
Iraq	26·6%	2·9%	14·8%	62·8%	54·0%	58·4%	62·2%	68·2%	65·2%	22·3%	36·2%	29·4%
Morocco	28·9%	0·2%	14·5%	..	..	..	43·1%	53·6%	48·5%	11·1%	23·1%	17·3%
Occupied Palestinian territory§	36·2%	2·2%	19·3%	33·8%	59·2%	46·5%	55·2%	60·7%	57·8%	23·3%	30·8%	26·8%
Sudan	23·1%	2·2%	12·7%	..	..	..	..	..	..	..	..	..
Syria	38·9%	..	..	..	..	..	63·4%	69·3%	66·4%	23·8%	39·0%	31·6%
Low-income countries												
Comoros	20·1%	8·9%	14·5%	6·1%	10·6%	8·3%	19·4%	21·1%	20·1%	3·5%	5·3%	4·4%
Mauritania	28·4%	3·6%	16·0%	40%	47·6%	43·8%	22·8%	53·9%	38·7%	4·3%	23·3%	14·0%
Yemen	29·3%	8·0%	18·6%	..	..	..	..	..	..	..	..	..
Somalia	..	..	..	..	..	..	..	..	..	..	..	..
Djibouti	..	..	..	..	..	..	..	..	..	..	..	..

Data are age-standardised adjusted estimates of prevalence. Data are from the WHO global status report on non-communicable diseases 2010 (which refers to 2008 data),[3] unless otherwise specified. No data were reported for Somalia or Djibouti. BMI=body-mass index. *2008 estimated prevalence; insufficient physical activity is defined as less than five times 30 min of moderate activity per week, or less than three times 20 min of vigorous activity per week, or equivalent. †Data are from Al Riyami and Afifi.[4] ‡Data are from Haj Bakri and Al-Thani.[5] §Data for current daily smokers, low level of total physical activity (defined as <600 metabolic equivalent min per week), and overweight and obesity were obtained from the occupied Palestinian territory STEPS survey 2010–11[6] for persons aged 15–64 years.

Table: Tobacco smoking and insufficient physical activity in adults aged ≥15 years and overweight and obesity in adults aged ≥20 years in Arab countries

II.3. Coronary artery disease

CAD remains the main cause of death up to 13.2% of total deaths worldwide (Usta & Bedel, 2017). In the United State of America (USA), it accounts for one quarter of all deaths. In the European countries 27%-34% of people with CAD are over 75 years (Members *et al.*, 2002). In United kingdom (UK), CAD was responsible for 16% of all male deaths and 10% of all female deaths (Bhatnagar *et al.*, 2015). The mortality rate has declined in HIC, in the SWEDEHEART registry the mortality related to ACS has decreased over the last three decades (Szummer *et al.*, 2017). Total CAD prevalence was 6.3% in USA adults ≥ 20 years of age (7.4% in males

and 5.3% in females) (Benjamin Emelia J. *et al.*, 2018). There is a strong relation between sudden death and coronary disease. Post mortem studies and death certificates revealed that 62-85% of patients who died out of hospital have past history of CAD (Sanchis-Gomar *et al.*, 2016). According to data from NHANES 2011 to 2014, myocardial infraction has a prevalence of 3.0% (3.3% for males and 2.3% in females) in adult USA population (Benjamin *et al.*, 2017). Approximatively every 40 seconds, an American will have an MI. The average age at first MI in American population is 65.6 years for males and 72.0 years for females (Benjamin Emelia J. *et al.*, 2018)). In Middle East the rate of death from CAD was higher compared to western countries United Kingdom (UK), Germany, and the USA. The INTERHEART study (an international case-control analysis of the risk factors for the first MI carried out in 52 countries) found that the median age at MI onset was 51 years in the Middle East population, and was 12 years lower than the median age at presentation in western countries (Gehani *et al.*, 2014).

II.4. Stroke

In 2013, strokes were the second cause of death worldwide (11.8%) after IHD, the third common cause of disability adjusted life years from all causes, the second cause of dementia and the most probable cause of epilepsy in elderly (Markus, 2016). Stroke leads to morbidity and major disability in 15%-30% of survivors, 20% of them need rehabilitation (Marx, Hockberger & Walls, 2006). Globally the incidence of stroke due to ischemia was 68% and 32% was due to hemorrhagic stroke (Krishnamurthi *et al.*, 2013). Hemorrhagic stroke occurs most frequently in patients under 40 years of age and 2-3 times higher in blacks and Asians (Foulkes *et al.*, 1988). China has the greatest mortality rate of stroke in the world (Wang *et al.*, 2017) . In USA, stroke accounts for 6% (Bhatnagar *et al.*, 2015), while the proportion of ischemic stroke is 87%, ICH 10% and SAH 3% (Benjamin Emelia J. *et al.*, 2018). Two third of all stroke occur in persons less than 70 years of age, probably related to increasing prevalence of metabolic risk factors (Kissela *et al.*, 2012; Giang *et al.*, 2013; Feigin, Norrving & Mensah, 2017). In addition, 15%-30% of all cerebral infarction are preceded by TIA (Hankey & Warlow, 1999),17% in the same day,9% on the previous day and 43% on the preceding week (Rothwell & Warlow, 2005). Hemorrhagic stroke accounts for 15% to 20% of all stroke, with 30-day mortality of 35% to 52% of them and 50% of death occurring in the first 48 hours (Counsell *et al.*, 1995).

During 1970 and 2008 period, there was a 42% decrease in stroke incidence in HIC and more than 100% increase in LMIC. The global incidence in LMIC has for the first time exceeded the stroke incidence in HIC by 20%, with higher proportion of hemorrhagic stroke accompanied with high mortality rate accounting for 85% of stroke death globally (Feigin *et al.*, 2016; Lackland *et al.*, n.d.). In the Arab world the trends of stroke are not precisely established (Rahim *et al.*, 2014). Epidemiological data in Arab word suffers from important limits. First,

most of the data was hospital based, second the modern imaging technic (CT and MRI) were not available all the time. The Stroke incidence rate is increasing in Arab countries with increasing in the prevalence of cardiovascular disease. The review of Benamer on stroke epidemiology in Arab countries shows a prevalence of 0.04-0.07% in ten Arab countries with higher prevalence in males than females, and ischemic type was the commonest type ranging from 55% to 87% while cerebral hemorrhage from 6.3% to 41.3% (Benamer & Grosset, 2009). Hypertension is the most common risk factor weather in HIC or LMIC.

II.5. Lower extremity arteries disease

LEAD is the third leading cause of atherosclerosis morbidity after CAD and stroke. In 2010 it was estimated that 202 million individuals have LEAD, 69.7% of them in LMIC. The prevalence rate increased by 28.7% in LMIC and 13.1% in HIC (Fowkes *et al.*, 2013).

According to the AHA during the period of 1970-2000, 6.5 million Americans aged ≥40 years (5.5%) have LEAD (ABI<0.90), and one quarter of them have severe LEAD (ABI<0.70) (Allison *et al.*, 2007; Benjamin *et al.*, 2017). The prevalence of LEAD increases with age. It affects 7% of individuals aged 60-69 years,12.5% for those aged 70-79 years, and 23.2% of those ≥ 80 years (Ostchega *et al.*, 2007). The rate increases as the population ages and becomes more obese and suffers from diabetes (Teodorescu, Vavra & Kibbe, 2013). The generalized nature of atherosclerosis was well documented by the Clopidogrel versus Aspirin in Patients at Risk of Ischemic Events (CAPRIE) data, where 41 % of patients with LEAD had CAD or CBVD and 8.6% had disease in all three territorries (Ouriel, 2001). Patients with LEAD have a five-fold to six-fold increased risk of death or morbidity from other atherosclerotic disease process such as stroke or CAD (Hirsch *et al.*, 2001). Nearly 42.8% of those with LEAD had CAD (Aboyans *et al.*, 2010). Also, the risk of death is higher in those with LEAD compared to those without, and in both symptomatic or asymptomatic patients (Diehm *et al.*, 2009). The Framingham Heart Study reports that people with LEAD were 5.9 times at higher risk for death by CVD and 6.6 times by CAD (Aponte, 2012). Most studies on LEAD suggest that the prevalence rate and associated risk factors may differ between male and female (Fowkes *et al.*, 2013). The prevalence of females with LEAD is slightly higher in LMIC at all ages. In HIC the prevalence is higher in males (Fowkes *et al.*, 2013). To date there are no published data about LEAD in the Arab countries' population. Available little studies are hospital based. The most important of them is the Global Atherothrombosis Assessment-Middle East (AGATHA-ME) conducted in five Arab countries of Middle East which recruited 1341 patients from tertiary care. Patients were classified into two groups: with CVD group and at-risk group. The prevalence of PAD was higher in two groups with predominance in at risk group (31.5% *vs* 28.2%) (El-Menyar, Al Suwaidi & Al-Thani, 2013).

II.6. Cardiovascular risk factors in the world

II.6.1. Hypertension

Approximately one billion of people worldwide have HTN which corresponds to more than 40% (Mozaffarian *et al.*, 2016) and projected to increase by 30% in 2025 (Kearney *et al.*, 2005). In all world regions the prevalence is similar in males and females and rises with increasing age and BMI. Globally HTN is the major cause of mortality responsible for over 7.5 million deaths annually (WHO Global health risk, 2009). The NHANES 2011-2014 estimates the prevalence of USA adults aged ≥ 20 years was up to 34%, ranging from 11.6% in those aged 20-39 years to 67.2% among those aged ≥ 60 years (Benjamin Emelia J. *et al.*, 2018). In LMIC 1 in 3 persons have HTN, with higher rate in elderly and overweight or obese person (Sarki *et al.*, 2015). In Middle East the prevalence of HTN is 30% with slight difference between sexes (30.7% in male and 29.1% in female) (Anon, 2012a). In North Africa and Middle East, HTN was among the three leading risk factors for disease burden in 2015 as well as in Palestine (Forouzanfar *et al.*, 2016). In the Africa Middle East Cardiovascular Epidemiology study (ACE), conducted in 14 countries of Middle east and Africa (2012), the prevalence of HTN ranged from 25% in Tunisia to 53% in South Africa (Alsheikh-Ali *et al.*, 2014).

II.6.1.1. Hypertension and cardiovascular disease

Several studies have reported the association between either SBP or DBP and the increase CVD risk. There is no threshold at which the risk becomes apparent. Stroke, CAD, left ventricular hypertrophy, LEAD and chronic kidney disease are the main complications of HTN. An increase of 20 mmHg in SBP or a 10 mmHg increase in DBP was associated with a 2-fold increased risk of death from stroke, heart disease or other vascular disease (Rapsomaniki *et al.*, 2014). Individuals with high-normal BP (130-139/85-89mm Hg) have a 3-fold greater risk of progression to HTN and 2-fold increase risk of CVD (Julius *et al.*, 2006).The risk of CVD associated with hypertension is observed from 30 years to 80 years of age (Whelton *et al.*, 2017). In the Framingham Heart Study during 36-years of follow up HTN was associated with a 2 to 4 fold increase of cardiovascular events in men and women equally (Kannel & Wilson PWf, 2003). HTN is closely associated with the risk of stroke, and it is the commonest factor for end stage renal disease. Controlling BP alone decreases the risk of stroke by 30% and MI by 20%-25% (Tailakh *et al.*, 2014).

II.6.2. Obesity

In 2016, 39% of adults aged 18 years (39% of men and 40% of women) were overweight and 13% of the world's adult population (11% of men and 15% of women) were obese (WHO, 2017a). The prevalence of obesity in 2015-2016 among American adults was 39.6% and 4 in 10 adults were obese (Hales *et al.*, 2017).

The Middle East region is affected by alarming increase in the prevalence of obesity at all ages, mainly in the Arab countries (Ali *et al.*, 2013; Ng *et al.*, 2011), where the prevalence is close to that found in western countries. The areas with the higher rate were Jordan (49.7%), Palestine (41.5%), Qatar (40.8%),Tunis (34%) and Oman (30.8%) (Elasmi *et al.*, 2009; Motlagh, O'Donnell & Yusuf, 2009).

II.6.2.1. Obesity and cardiovascular disease

Overweight or abdominal obesity causes or exacerbates other cardiovascular metabolic risk factors including hypertension, diabetes, dyslipidemia. These risk factors in turn, increase the likelihood of morbidity and mortality from CVD and contribute to increased health care costs (Cannon, 2008; Tangalos, Cota & Fujioka, 2006). Adiposity is the result of the balance between energy intake and energy expenditure. The rapid rise in the rate of obesity is driven by increased total energy intake, sedentary life or both (Canoy & Buchan, n.d.). Higher body mass index (BMI) was associated with premature mortality. Non-smokers who were obese at age 40 years died 6-7 years earlier than no obese (Peeters *et al.*, 2003). Another important factor associated with obesity is the socio-economic status (SES). In developing countries obesity is more prevalent in women of higher SES, but the epidemic affects lower SES when high fat diet becomes more affordable (Prentice, 2006). Higher levels of education are associated with lower rates of obesity in HIC (Mitchell & Shaw, 2015). Physical inactivity and sedentarily lifestyle are added to the above risk for the development of obesity (Yusuf *et al.*, 2004). Obesity is associated with increase prevalence of type 2 DM, HTN, dyslipidemia, sleep-disorder breathing, CAD, stroke, atrial fibrillation and dementia (Benjamin *et al.*, 2017). In USA population data from NHANES showed that DM type 2 was 18.5% in obese adults, 8.2% in those who were overweight, and 5.4% in normal weight. The prevalence of HTN were 35.7%, 26.4% and 19.8% respectively. Prevalence of dyslipidemia was 49.7% in obese adults, 44.2% in overweight, and 28.6% in normal weight (Saydah *et al.*, 2014). Cardiovascular risks was higher with class III obesity than with class I obesity (McTigue *et al.*, 2014) .

II.6.3. Diabetes

According to The WHO, diabetes is the leading cause of death in the world and the similar trend was available from the Arab world (Abuyassin & Laher, 2016). Data from (IDF) estimated that 415 million adults aged 20-79 years have DM in 2015 and the number will reach 642 million in 2040 with a rise in prevalence from 8.8% to 10.4. This prevalence accounts for 3.3% in Africa,7.3% in Europe, and 10.7% in Middle East and North Africa (Fan, 2017). In USA 9.4% of adult population had diabetes and 25.2% among those ≥ 65 years of age (CDC, 2018). WHO estimates that 58% of diabetes mellitus occurs in individual with BMI >21kg/m^2 (Mokdad *et al.*, 2000). The prevalence of diabetes in the GCC ranged from 6% to 23.7% (Aljefree & Ahmed, 2015). In the MENA region (2015), four out of ten adults with diabetes are

undiagnosed, and approximatively 9.3% (6.3-12.2%) of adults aged 20-79 years are living with diabetes, over 40.6% of them are undiagnosed (Majeed *et al.*, 2014). For Arab countries, the prevalence of type 2 diabetes was 25.4%,17.9%,19.7% and 15.1% in Arabia Saudi, Kuwait, Iraq and Tunis respectively (Alarouj *et al.*, 2013; Al-Rubeaan *et al.*, 2015; Ben Romdhane *et al.*, 2014; Mansour *et al.*, 2014). The countries with the largest number of adults with diabetes are Egypt, Pakistan and Iran (7.8,7.0 and 4.6 million)(IDF 2015, 2015). In 2015 a Tunisian study revealed that the prevalence of type 2 DM will reach 26.6% in 2027 (Saidi *et al.*, 2015). And the Saudi study indicates that the prevalence of type 2 DM in Saudi Arabia will increase to 44.1% in 2022 (Al-Quwaidhi *et al.*, 2014). This means that serious and effective action on obesity and other risk factors must be taken. The IDF evaluates a total health care cost for diabetes in many countries for 5-10% of the total budget (Alberti, Zimmet & Shaw, 2007).

II.6.3.1. Diabetes and cardiovascular disease

CVD is the most prevalent cause of mortality and morbidity in diabetic populations (Matheus *et al.*, 2013). The relative risk in adults with diabetes ranges from 1 to 3 in men and from 2 to 5 in women compared to those without diabetes (Rivellese, Riccardi & Vaccaro, 2010). Diabetic subjects have twice to four times risk of death from heart disease, 68% in age > 65 years die from CAD and 16% from stroke (AHA 2018, n.d.). The death accounts for 44% in type 1 DM and 52% in type 2 DM (Morrish *et al.*, 2001). Actually AHA/ACC and ESC consider diabetes as a CAD risk equivalent (Piepoli *et al.*, 2016; Stone *et al.*, 2013). Cardiovascular risk factors such as obesity, hypertension and dyslipidemia are common in diabetic patients (Leon & Maddox, 2015). Several studies reported that increased factor like oxidative stress, coagulability, endothelial dysfunction and autonomic neuropathy are associated with DM and lead to the development of CVD (Matheus *et al.*, 2013). Individuals with diabetes and with poor control suffer from microvascular and macrovascular complications (Matheus *et al.*, 2013)

II.6.4. Smoking

The most common form of tobacco use are cigarette smoking, electronic cigarette (e-cigarette) involving the inhalation of a vaporized liquid that includes nicotine, solvents, and flavoring cigarillos, water pipe and hookahs (CDC, 2016b). This addictive practice is a well-known cause of cancers, cardiovascular, and respiratory diseases (Office of the Surgeon General (US) & Office on Smoking and Health (US), 2004). Cigarette smoking increases inflammation and thrombosis leading to oxidative stress manifestation, prothrombotic activity, platelet aggregation, leukocyte activation, lipids peroxidative and smooth muscle proliferation (Ambrose & Barua, 2004). Nicotine affects the cardiovascular system by increasing systolic and diastolic blood pressure, heart rate and cardiac output (Filion & Luepker, 2013). The WHO estimates the mortality rate associated with tobacco smoking to be seven million people per annum projected to increase by eight million in 2030, while around 890,000 are the result of

non-smokers being exposed to second-hand smoke. Nowadays around 80% of smokers live in LMIC (WHO,Tobacco 2018, n.d.). The rate is 5 times higher in men than in women (48% vs.10%) (Hitchman & Fong, 2011). In the EMR, the prevalence of smoking reported in 21 studies was 15.6% and still more common in men than women (28.8% vs.2.9% respectively) (Motlagh, O'Donnell & Yusuf, 2009). Jordan and Tunisia have the highest age standardized tobacco use (36% and 26% respectively), where Oman has the lowest (11%) (Mandil, Chaaya & Saab, 2013). In many Arab countries half of the male population smokes cigarette with a gender based ratio of 10:1 (Eriksen, Mackay & Ross, 2013). This inequality is due to the unacceptability of smoking among females in the culture of Arab countries (Tamim *et al.*, 2007). In contrast women and youth group use water pipe smoker (Maziak *et al.*, 2014). In a longitudinal study smoking behavior among youth in the region, water pipe smoking prevalence was more than double that of cigarette at baseline (13.3% vs.5.3%) and increased by 40% within 2 years of follow-up from (13.3% to 18.9%) (Mzayek *et al.*, 2012). In the Gulf Cooperation Council the rate of smoking ranged from 13.4% to 37.4% in males and from 0.5% to 20.7% in females (Aljefree & Ahmed, 2015).

II.6.4.1. Smoking and cardiovascular disease

Cigarette smoking is the major cause of CVD. It influences other cardiovascular risk factors and predisposes individuals to different clinical atherosclerosis syndrome such as CAD, stroke and LEAD, but the relative risk for each disease varies with the vascular bed. The risk is greatest for LEAD, lower for stroke and intermediate for CAD (Health, 2014). The European data indicates that smoking doubles the 10 years CVD mortality rate. The presence of smoking alone doubles the level of risk. The addition of other major risk factors with smoking results in approximately a 4-fold (2x2) increase in risk and the presence of 2 other risk factors together with smoking leads to an 8-fold (2x2x2) increase risk (Burns, 2003). Cigarette smoking along with diabetes are well known as the major risk factors for symptomatic and asymptomatic LEAD. In addition cigarette smoking has been associated with progression of LEAD over a 4-years interval (Hooi *et al.*, 1998; Palumbo *et al.*, 1991).

Table 11: Tobacco or secondhand smoke and CVD risk (World Heart Federtion, 2017)

- For every cigarette smoked, the risk of a non-fatal heart attack increases by 5.6%.
- The risk of heart attack is likely to be more than double by chewing tobacco.
- Breathing secondhand smoke increases in non-smokers the risk of developing a CVD by 25–30%.
- Secondhand smoke contributes to 600,000 deaths annually, of which 28% are children
- The risk of a heart attack is almost doubled by frequent expo-sure to tobacco smoke at workplace or home.

II.6.5. Alcohol

In 2012, 5.9% of all global deaths were attributable to alcohol intake with significant sex differences (7.6% and 4%) among males and females, respectively (Anon, 2014). Alcohol dependence is a major health and social issue in the European union which is the heaviest drinking region in the world (Anon, 2014). Excessive drinking is the third leading cause of premature death after smoking and obesity and approximately 30% of the US population are excessive drinkers (Stahre *et al.*, 2014). Heavy drinking doubles mortality rate, and consumption of 3-5 drinks is associated with a 50% higher mortality rate compared with non-drinkers (Mukamal *et al.*, 2010). Alcohol consumption is associated with an increase in HDL-C, a decrease in Low-density lipoprotein Cholesterol (LDL-C), and fibrinogen levels, which thus reduces platelet aggregability (Brien *et al.*, 2011; Movva & Figueredo, 2014). Arab countries have a strict regulation on the sale and consumption of alcohol.

II.6.5.1. Alcohol and cardiovascular disease

Confusion and controversy are seen in numerous studies about the role played by alcohol consumption in the etiology and prognosis of cardiovascular events (Klatsky, 2015). In the INTERSTROKE study, including 13,447 stroke cases and 13,472 controls from 32 countries, the risk for stroke in low-moderate alcohol use (≤14 drinks per week in women and ≤ 21 drinks per week in men) were (1.14 and 1.43) in men and women respectively. In high alcohol intake (>14 drinks per week in women and >21 drinks per week in men) the risks were 2.09 and 2.44 respectively (O'Donnell *et al.*, 2016). However in Prospective Urban Rural Epidemiology (PURE) study which involved 114,970 adults from high, middle, and low income countries showed a neutral relationship between alcohol use and stroke risk (Smyth *et al.*, 2015). Taken together these two large epidemiologic studies indicate that even small amount of alcohol do not protect against stroke, or cardiac event (Toma, Paré & Leong, 2017). Also, in the Health Professionals Follow up Study during 16 years, including 8867 physicians men free of major

illness, moderate alcohol intake was associated with lower risk of MI (Mukamal, Chiuve & Rimm, 2006). Keeping alcohol consumption less than 46 g /day in men and 23 g /day in women appears to minimize the risk of mortality in Japanese population (Inoue *et al.*, 2012). In Second Manifestation of ARTerial (SMART) study, moderate alcohol intake (1-2drinks/day) was associated with decrease risk of vascular, non-fatal events from CAD, stroke, amputation and all-causes of death (Beulens *et al.*, 2010).

II.7. International studies

II.7.1. Framingham study

The Framingham Heart Study (FHS) began in 1948. It was named for Framingham, a town in eastern Massachusetts that was selected as the site of the study. The project was initiated under the direction of the National Heart, lung and Blood Institute and with the collaboration with the Boston University School of Medicine. The goal of the study was to identify common risk factors or characteristics that contribute to CVD. The study included two-third of the adult population (more than 5,200 residents of Framingham city) with ages ranging from 30-62 years. In 1972 more than 5,120 individuals (offspring) of original study participants and their spouses were added in the cohort. In 2001 a third-generation cohort, consisting of grandchildren of the original cohort was added to explore genetic factors to deepen the research in CVD. Additionally, the study recruited the $OMNI_1$ and $OMNI_2$ cohort in1994 and 2003, respectively aimed to reflect the racial and ethnic diversity of the town of Framingham. Every two years persons enrolled in the study were submitted to medical exams and detailed questionnaire about their lifestyle (Tsao & Vasan, 2015). In 1961, Dr William Kannel, director of FHS published the first report on coronary heart disease risk associated with age, male gender, HTN, high cholesterol, DM and electrocardiographic left ventricular hypertrophy (Kannel *et al.*, 1961). Also, reports on HTN and its relation to CVD, studies on lipids and relation to CAD, and life style factors and their implications for CVD were published. All this collective data constitute a foundational knowledge base to guide public health efforts on CVD prevention (Doyle *et al.*, 1962; Hubert *et al.*, 1983; Kannel & Sorlie, 1979; Pencina *et al.*, 2009). Also, from FHS numerous scores were established.

II.7.2. The Prospective Urban Rural Epidemiology (PURE) study

The PURE study is a large epidemiological study that involved 150,000 adults aged 35-70 years residing in approximately 600 communities selected from 17 countries: 3 HIC, 7 MIC and 7 LIC, around the world. Within this context, the PURE study was designed to collect data on socioeconomical status, medical history, lifestyle behaviors (smoking, physical activity, diet) anthropometrics measure, biological and genetic factors (Teo *et al.*, 2009). Also, PURE looks

at countries grouped by socioeconomic status and the differences between rural and urban communities (Spencer, 2014). The main results revealed:

- That major CVD, fatal CVD and death from any cause are higher in LIC than in HIC
- PURE confirm that the burden of total CVD is similar in HIC, MIC and LIC
- Regarding the difference between rural and urban areas, PURE found that the burden of CVD was lower in urban communities, but the rate of non-major cardiovascular events was higher in urban areas. This is probably due to the high availability of hospitals in urban areas and better access to health care which explains the lower cardiovascular mortality rate than in rural areas
- Better control of HTN in HIC compared with LIC (Chow *et al.*, 2013)
- PURE indicates that secondary preventive drugs (antiplatelets drugs, B blockers, ACEIs, ARBs and statin) even at low-cost are less likely to be used in LIC than in HIC (Yusuf *et al.*, 2011)

II.8. Cardiovascular risk scoring models

The cardiovascular risk scoring gives an estimate "of the probability that a person will develop cardiovascular disease within a specified amount of time" (Wikipedia, 2018). Because these scores give an estimation of the risk of developing CVD, they also indicate who is most likely to benefit from prevention.

II.8.1. Framingham Risk Score

II.8.1.1. Framingham risk score for hard Coronary Heart disease

The Framingham Risk Score (FRS) is an older popular tool widely used in clinical practice and research studies. It calculates the risk of CAD events (angina, myocardial infarction, and coronary death) over a 10 years period in asymptomatic patients. Risk factors used in Framingham scoring include age, sex, total cholesterol, HDL cholesterol, smoking, and blood pressure. The score has been validated in many populations, such as Caucasian Americans and African- Americans. This score was implemented in several guidelines for CVD prevention and has been used to guide treatment of risk factors (Berger *et al.*, 2010; D'Agostino *et al.*, 2001).

II.8.1.2. Global Cardiovascular Framingham Risk

Recently, the Framingham investigators presented a modified score for the estimation of the global CVD including (CVD death, general CAD, ischemic stroke, hemorrhagic stroke, transient ischemic attack, peripheral artery disease and congestive heart failure), based on age, diabetes, smoking, SBP, treated and untreated BP, total cholesterol and HDL cholesterol;

it applied to both sexes without previous history of CVD (D'Agostino *et al.*, 2008). A10-year risk score can be derived as percentage which can be used to inform the decision initiating lipids lowering drugs for primary prevention. The risk is considered low if the score is <10%, moderate (10%-20%) and high ≥ 20% (D'Agostino *et al.*, 2013).

II.8.2. Systemic Coronary Risk Evaluation (SCORE)

SCORE was derived from 12 different European cohort studies, with a large number of participants (250,000). The SCORE system predicts the10-year risk of a first fatal CVD event including heart attack, stroke or aortic aneurysm. Risk factors used in this score system include age, gender, total cholesterol to HDL cholesterol ratio, SBP, and smoking (Piepoli *et al.*, 2016). Two charts are proposed considering the overall characteristics of the population (high or low risk).

II.8.3. WHO / ISH cardiovascular risk prediction charts

The WHO/ISH risk prediction charts indicate 10-year risk of a fatal or nonfatal major cardiovascular event (Myocardial infraction or stroke), help to identify those at high cardiovascular risk. High risk score motivates patients to change behavior and to take antihypertensive drugs, lipid lowering drugs and aspirin in people without CAD, stroke or other atherosclerotic disease. The score is based on age, sex, blood pressure, smoking, total cholesterol and the presence or absence of diabetes mellitus for 14 WHO regions, mainly in LMIC populations. There are two types of charts: one with lab test where the cholesterol can be measured, the other one without lab test in which blood cholesterol cannot be measured (Anon, 2007). The color of the cell indicates the 10-year risk as shown: Green (<10%), Yellow (10% to < 20%), Orange (20% to < 30%), Red (30% to < 40%), Deep Red (≥ 40%).

II.8.4. Atherosclerotic Cardiovascular Disease risk calculator (ASCVD Risk) ACC/AHA)

The ASCVD is defined as nonfatal myocardial infarction, coronary heart disease, or stroke. The Pooled Cohort Equation (PCE) estimates the 10-year primary risk of ASCVD event developed by the American College of Cardiology /American Health Association. It was validated among Caucasian and African American and used only for adult patients without clinical ASCVD in age between 40-79 years (Goff *et al.*, 2014). The risk factors used in this model were age, gender, race, total cholesterol, HDL cholesterol, SBP, treatment of BP, diabetes mellitus and smoking. Patients are considered to be at elevated risk if the pooled cohort equation predicts a risk of >7.5%, in this condition the 2013 ACC/AHA guidelines recommended the use of statin (Stone *et al.*, 2013).

II.8.5. Coronary Heart Disease risk equivalents

Defined as patients with a 10 -years risk for MI or coronary death >20%. The diseases cited by the National Cholesterol Education Program were:

- Diabetes mellitus
- Clinical coronary artery disease
- Symptomatic carotid artery disease
- Lower extremity artery disease
- Abdominal aortic aneurysm
- Chronic kidney Disease

II.8.6. Heart age

Also, called vascular age and defined as the age that corresponds to a person with normal risk factors and the same 10-year absolute risk. It is possible for a person to have a low 10-year risk but have a vascular age much older than their chronological age. For example a 40 year -old person with high levels of some risk factors may have the risk age of a 60-year old, because the risk equals that of a 60 year old with ideal risk factors levels (i.e. non-smoking, total cholesterol of 4mm/l and BP of12mmHg) (Cooney *et al.*, 2012; D'Agostino Sr. *et al.*, 2013).

II.8.7. Non-laboratory model

The non-laboratory-based model used the same risk factors from the FRS but excluded HDL-cholesterol and total cholesterol and were replaced by BMI. This approach can predict CVD outcomes as accurately as one that requires laboratory testing. Further this model can ensure a rapid start of treatment without the added cost of laboratory tests (Gaziano *et al.*, 2008).

II.9. Prevention of cardiovascular diseases

The most CVD symptoms occur in middle age. Acute coronary events and cerebrovascular accident occur frequently suddenly and are often fatal before medical procedures can be performed. Prevention aims to improve both quality of life and life expectancy for people with established CVD as well as in those who are at high cardiovascular risk for developing CVD due to one or more risk factors. The cardiovascular prevention provides three types of prevention (primary, secondary and tertiary). The characteristics of healthy population are illustrated in table 8 and the target values for the prevention in table 9 (Perk, 2009).

Table 12: Characteristics of a heart-healthy population

- No smoking
- Healthy food choices
- Physical activity; 30 min of moderate exercise a day
- BMI of < 25 kg/m^2 and to avoid central obesity, BP oF <140/90mmHg
- Total cholesterol < 5 mmol/l (190 mg/dl)
- LDL-cholesterol <3mmol/l (100mg/dl)
- Good glycemic control in diabetics

Table 13: Target values for patients with established CVD or DM/ for persons at high CVD risk

- Blood pressure <130/80mmHg
- Total cholesterol < 4.5 mmol/l (175 mg/dl), with an option of < 4 mmol/l (155 mg/dl) if feasible
- LDL-cholesterol of < 2.5 mmol/l (100 mg/dl), with an option of < 2.0 mmol/l (77 mg/dl) if feasible
- Consideration of prophylactic drug therapy in particular groups, especially those with established atherosclerotic CVD

II.9.1. Primordial prevention

Refers to individual behavioral lifestyle characteristics that achieve a level of health that does not permit risk factors to appear. Defined by AHA as the ideal cardiovascular health that reduce stroke mortality 20% by 2020 (Lloyd-Jones *et al.*, 2009). As atherosclerosis begins at an early age and progresses primordial prevention is the only way to fight coronary disease. Less than 5% of individuals achieve the goal of primordial prevention as they approach middle life, at this period their cardiovascular protection is high and they benefit an additional 10 years of life(Kullo & Cooper, 2010)

Table 14: Ideal cardiovascular Health, defined by AHA, 'Life Simple 7'

1.Not smoking or quitting over 1 year ago.

2.A body mass index ,25 kg/m^2.

3.exercising at a moderate intensity $150 minutes (or 75 minutes at vigorous intensity) each week.

4. Eating a healthy diet: adhering to four to five important dietary components
•sodium intake ,1.5 g/day;
•sugar-sweetened beverage intake ,36 oz weekly;
• 4.5 cups of fruits and vegetables/day;
• three 1 oz servings of fiber-rich whole grains/day; • two 3.5 oz servings of oily fish/week.

5.Maintaining total cholesterol (TC) ,200 mg/dL.

6.Keeping blood pressure ,120/80 mmHg.

7.Keeping fasting blood glucose ,100 mg/dL

Notes: *recommendations include $ four servings of nuts, legumes and seeds/week; # less servings of processed meats/week; less than 7% total energy intake as saturated fat

II.9.2. Primary prevention

Concerning people with risk factors but without any clinical manifestation of cardiovascular disease. The objective of the primary prevention is to take measures by arming communities with information on healthy life styles, detecting cardiovascular risk factors, and providing healthy diet. It is the most cost-effective method of ensuring the health of the community by preventing diseases and limiting or delaying the occurrence of CVD.

II.9.3. Secondary prevention

Concerning people with CVD (CAD, stroke, LEAD) and its objective is to ovoid the occurrence of complications and recurrences. Early treatment can significantly alter the development and manifestation of chronic conditions.

II.9.4. Tertiary prevention

The goal of tertiary prevention is to improve quality of life and extend overall life expectancy by preventing complications in the future. Tertiary prevention is the heaviest tax burden on the health care system due to considerable costs of surgery and lifelong management of chronic disease via medications and rehabilitation.

The primary and secondary prevention are based on different effective interventions involving behavior factors and life style changes such as smoking cessation, regular physical activity, healthy diet and pharmaceutical treatments such as anti-hypertensive drugs, anti-diabetes, antiplatelet agent and cholesterol lowering drugs. The choice of the type of intervention for each individual can be based on two approaches: a risk factor approach and another one involving all risk factors (Global cardio-vascular risk).

The WHO/ISH (International Society of Hypertension) risk prediction charts indicate 10-year risk of a fatal or non-fatal major cardiovascular event according to age, sex, blood pressure, smoking status, total blood cholesterol and presence or absence of diabetes mellitus (Table10) for 14 WHO epidemiological sub regions (Africa, The Americas, Eastern Mediterranean, Europe South-East Asia, Western Pacific) and define the strategy according to risk evaluation There are two sets of charts: one set of charts when lab test is available and the other one if the blood cholesterol is not available (WHO, 2007).

Table 15: Prevention of Cardiovascular diseases

Individual total risk [a]: define as10 -year risk of cardiovascular event low risk (<10%), moderate risk (10 to < 20%), high risk (20 to < 30%), very high risk (≥30%).

When resources are limited, individual counselling and provision of care may have to be prioritized according to cardiovascular risk.	
Risk <10%	Individuals in this category are at low risk. Low risk does not mean “no” risk Conservative management focusing on lifestyle interventions is suggested
Risk 10% to <20%	Individuals in this category are at moderate risk of fatal or non-fatal vascular events. Monitor risk profile every 6–12 months
Risk 20% to <30%	Individuals in this category are at high risk of fatal or non-fatal vascular events. Monitor risk profile every 3–6 months
Risk ≥30%	Individuals in this category are at very high risk of fatal or non-fatal vascular events. Monitor risk profile every 3–6 months

[a] Excluding people with established CAD, CVA and PVD

II.9.5. How to intervene at the individual level: risk factors interventions

II.9.5.1. Smoking

Smoking is the major risk factor for CVD. Smoking cessation is the single most cost-effective intervention in CVD prevention (Eckel *et al.*, 2014). High taxes on tobacco products are effective policies to reduce smoking in young people. In a systematic metanalysis of 20 prospective cohort studies, quitting smoking was associated with 36% decrease in risk of all-cause mortality among patients with CAD (Critchley & Capewell, 2003). Pharmacological

support and professional assistance are effective. Drug therapy including nicotine replacement therapy (NRT), bupropion or varenicline should be considered early (Cahill *et al.*, 2013). Electronic cigarette can provide high concentration of nicotine, so it is recommended as a measure to help cessation of smoking of regular cigarettes (Chetty *et al.*, 2016). It is also recommended to avoid passive smoking to prevent CVD. Within 15 years, the risk of CVD becomes nearly the same as someone who has never smoked. Also, quitting smoking at age 66 years, men gained up to two years of life and women gained up to 3.7 years of life (World Heart Federtion, 2017).

II.9.5.2. Nutrition

There is a strong relationship between unhealthy nutrition and the occurrence of CVD. However, nutritional counselling is an essential tool for cardiovascular prevention. Patients with CVD or at high risk, should receive recommendations on foods and dietary pattern to reduce the risk.

At the individual level varied and energy-balanced regimen is essential for the preservation of good health.

Table 16: Dietary targets to prevent CVD(Guy De Backer, 2017)

- Consume more fruit, nuts, seeds, vegetables; 2 to 3 servings of each per day.
- Limit the consumption of saturated fatty acids to <10% of total energy through replacement by poly-unsaturated fatty acids (PUFA).
- Use vegetable oils rich in PUFA and soft spreads based on e.g., soybean oil, canola oil and extra-virgin olive oil.
- Limit the consumption of refined grains and sugar; aim at 30-45 gr of fiber per day, preferably from wholegrain products.
- Consume 1 or 2 servings of fish per week, preferably oily fish such as sardines, herring, tuna, salmon, mackerel, trout.
- Don’t eat processed meat; limit the consumption of fresh red meat to 2-3 servings per week.
- Avoid foods made with partially hydrogenated vegetable oils aiming at a zero consumption of trans unsaturated fatty acids.
- Avoid drinking sugar-sweetened beverages.
- Limit the intake of sodium aiming at <5 gr of salt per day.
- If alcohol is consumed it should be limited to 2 glasses per day (20 gr alcohol) in men and to 1 glass per day (10 gr alcohol) in women

II.9.5.3. Physical activity

Physical exercise is a fundamental issue in all strategies of CVD prevention, while a sedentary life increases the risk of cardiovascular risk factors, such as hypertension, high triglyceride diabetes and obesity. WHO recommended for all individuals to undertake at least 150 min a week of moderate aerobic physical activity (30 min for 5 days / week) or 75 min / week of vigorous physical activity (15 min for 5 days / week) or a combination of these two elements (Guy De Backer, 2017, Anon, n.d.). Also, in old adults aged ≥ 65 years, the WHO recommends participation in muscle training activities at least two days a week (Guy De Backer, 2017).

II.9.5.4. Obesity

Weight reduction is strongly recommended for obese persons with a BMI ≥ 30 or ≥ 25 kg/m^2 in the presence of cardiovascular risk factors. Weight loss is achieved by combination of a reduction in caloric intake and increase in physical exercise. Different diets have been proposed for the treatment of obesity, a low fat diet is still considered the standard approach to weight reduction (Perk *et al.*, 2012).

II.9.5.5. Hypertension

Raised BP is one of the most powerful modifiable risk factors for CVD. BP lowering can be achieved by two strategies: lifestyle changes and drug therapy. Numerous meta-analyses have shown that a 10-mmHg reduction in SBP or 5 mmHg reduction in DBP is associated with significant reduction in all major cardiovascular events by ~20%, all-cause mortality by 10-15%, stroke by 35%, coronary events by 20% and heart failure by 40% (Ettehad *et al.*, 2016; Thomopoulos, Parati & Zanchetti, 2014).

The ESC/ESH and USA guidelines both advise use of home BP monitoring and ambulatory BP monitoring to confirm the diagnosis, detect white coat and masked hypertension, and monitor BP control for medication. In patients at very high risk as is the case in the presence of CVD, lowering BP may require more intensive strategies than those currently recommended in the guidelines.

Table 17: Recommendation regarding BP targets in patients with hypertension (Guy De Backer, 2017; Whelton *et al.*, 2018).

Use of BP-lowering medications is recommended	• for secondary prevention of: recurrent CVD events in patients with clinical CVD and SBP ≥ 130 mm Hg or DBP ≥ 80 mm Hg • for primary prevention in adults with an estimated 10-year (ASCVD) risk of ≥10% and an SBP ≥130 mm Hg or DBP ≥ 80 mm Hg.
Use of BP-lowering medication is recommended	• for primary prevention CVD in adults with no history of CVD and with an estimated 10-year ASCVD risk < 10% and SBP ≥ 140 mm Hg or DBP≥ of 90 mm Hg.
Nonpharmacologic therapy and repeat BP evaluation within 3 to 6 months.	• should be recommended In adults with an elevated BP or stage 1 hypertension who have an estimated 10-year ASCVD risk < 10%
Combination of nonpharmacologic and antihypertensive drug therapy and repeat BP evaluation in 1 month	• should be recommended in adults with stage 1 hypertension who have an estimated 10-year ASCVD risk of ≥ 10%
Evaluation followed by prompt antihypertensive drug treatment	• is recommended in I adults with SBP ≥180 mm Hg or DBP ≥110 mm Hg
Two or more antihypertensive medications	• are recommended in most adults with HTN, especially in black adults to achieve a BP target < 130/80 mm Hg
Physicians should consider starting or increasing drug therapy to reduce the risk for stroke and cardiac events	• In patients ≥ 60 years who have a history of stroke or transient ischemic attack or have high cardiovascular risk, to achieve an SBP < 140 mm Hg
Blood pressure targets diabetes mellitus	• are recommended in type 2 diabetes to be <140/85 mmHg but a lower target of <130/80 mmHg is recommended in selected patients (younger patients at elevated risk for specific complications) for additional gains on stroke, retinopathy and albuminuria risk. • in type 1 diabetes mellitus recommended blood pressure target is <130/80 mmHg
In individuals >80 years old and with initial SBP ≥160 mmHg	• it is recommended to reduce SBP to between 150 and 140 mmHg provided they are in good physical and mental condition

II.9.5.6. Diabetes

In most Randomized Controlled Trials (RCTs), intensive glucose control in patients with type 2 diabetes leads to 9% reduction in major cardiovascular events (MACE), 20% reduction of

kidney events and 13% of eye events however, residual microvascular and macrovascular risk remains high (Giugliano *et al.*, 2018). In addition, the equation “diabetes equal coronary artery disease” has accelerated the implementation of preventive therapy for diabetes risk factors. In a real-world population among 93,866 Danish patients of whom 13.4% were diabetics, followed for a median of 4.1 years, reported that in the absence of significant lesion, the diabetics group with a preventive treatment of statin and aspirin had the same risk of cardiovascular events as in group without diabetes (Olesen *et al.*, 2017).

Table 18:Type 2 diabetes Combination strategies (Giugliano *et al.*, 2018)

- Intensive glycemic control is important for the prevention of vascular complications in adults with type 2 diabetes, but residual micro- and macro-vascular risk remains high
- Newer diabetes drugs (empagliflozin, canagliflozin, liraglutide, and semaglutide) may decrease the incidence of MACE* and nephropathy; depending on the drug used, cardiovascular mortality and heart failure may also be reduced
- The combination of intensive glycemic control and newer diabetes drugs may have beneficial, additive effects on diabetic vascular complications
- Statin and aspirin should also be used for preventing and fighting cardiovascular complications in type 2 diabetes

MACE*: major cardiovascular events

Testing for prediabetics and risk for future diabetes in asymptomatic people should be considered in adults of any age who are overweight or obese (BMI≥25kg/m^2 in Asian American) and in individual who have one or more additional risk factors for diabetes (Table14)

Table 19: Criteria for testing for diabetes or prediabetes in asymptomatic adults (ADA, 2018)

1. Testing should be considered in overweight or obese (BMI ≥25 kg/m^2 or ≥23 kg/m^2 in Asian Americans)
2. Adults who have one or more of the following risk factors:

- First-degree relative with diabetes
- High-risk race/ethnicity (e.g., African American, Latino, Native American, Asian American, Pacific Islander)
- History of CVD
- Hypertension (≥140/90 mmHg or on therapy for hypertension)
- HDL cholesterol level <35 mg/dL (0.90 mmol/L) and/or a triglyceride level >250 mg/dL
- Women with polycystic ovary syndrome
- Physical inactivity

• Other clinical conditions associated with insulin resistance (e.g., severe obesity, acanthosis nigricans)
2. Patients with prediabetes (A1C ≥5.7% [39 mmol/mol], IGT, or IFG) should be tested yearly, treat other cardiovascular risk factors.
3. Women who were diagnosed with gestational diabetes mellites should have lifelong testing at least every 3 years.
4. For all other people, testing should begin at age 45 years.
5. If results are normal, testing should be repeated at a minimum of 3-year intervals, with consideration of more frequent testing depending on initial results and risk status.

II.9.5.7. Dyslipidemias

Randomized controlled trials have demonstrated that lowering LDL cholesterol level with healthy diet and or lipid lowering drugs (statin) can reduce the risk of CVD events (Kotseva *et al.*, 2016). Lipid lowering therapy with statins reduces relative cardiovascular risk by 20 % to 30% whatever the baseline LDL-Ch is. The treatment goals for LDL-Ch depend on the total CVD risk of the individual and of the baseline LDL-Ch level. Measuring LDL-Ch every six weeks after treatment initiation and every 12 months to assess the compliance with treatment and diet is recommended (Table 19, 20).

Table 20: Lipid Goals for Patients at risk for Atherosclerotic CVD (Jellinger *et al.*, 2017)

Lipid parameter	Goal (mg/dL)
TC	• <200
LDL-C	• <130 (low risk) <100 (moderate risk) <100 (high risk) • <70 (very high risk) <55 (extreme risk)
Non-HDL-C	• 30 above LDL-C goal • 25 above LDL-C goal (extreme risk patients)
TG	• <150
Apo B	• <90 (patients at high risk of ASCVD, including those with diabetes • <80 (patients at very high risk with established ASCVD or diabetes plus ≥1 additional risk factor) • <70 (patients at extreme risk)
Abbreviations: apo = apolipoprotein; ASCVD = atherosclerotic cardiovascular disease; HDL-C = high- density lipoprotein cholesterol; LDL-C = low-density lipoprotein cholesterol; TC = total cholesterol; TG = triglycerides	

Table 21: Goal and treatment for LDL Cholesterol (Guy De Backer, 2017;Hendrani et al., 2016)

	Target	Therapeutic option
Very high CVD risk	LDL-Ch <1.8mmol/L (70mg/dl) or a reduction of 50% if the LDL Ch is between 1.8-3.5 mmol/L (70-135 mg/dl)	• Dietary intervention • Drug treatment (statin +Ezetimibe)
High CVD risk	LDL-Ch <2.6mmol/L (100mg/dl) or a reduction of 50% if the LDL Ch is between 2.6-5.2 mmol/L (100-200mg/dl)	• Dietary intervention • Drug treatment
Moderate risk	LDL-Ch <3.0 mmol/L (115mg/dl)	• Dietary intervention • Drug treatment?

II.9.6. Mobile phone interventions for the secondary prevention of CVD

Unlike traditional approaches of secondary prevention of CVD, a quantitative review of database from 2002-2016 through numerous studies revealed the use of mobile health (mHealth) as new area of health care. The WHO announced in their report 2011 that, “the use of mobile and wireless technologies to support the achievement of health objectives has the potential to transform the face of health service delivery across the globe” (WHO Global Observatory for eHealth, 2011). mHealth technologies include text messaging, mobile applications, Global Positioning System (GPS), Bluetooth technologies, camera, and more recently the use of sensors that track heart rate, steps walk, sleep cycle and transmit feedback to clinicians (Chow *et al.*, 2016). Mobile phone technology is a personalized, easily accessible and inexpensive tool for communication with patients, tracking personal health data, updating information and reminders for health behaviors (Hamilton *et al.*, 2018, Anon, 2016a). The use of mobile applications for tracking needs to be combined with text messaging for improving outcomes (Martin *et al.*, 2015). However, smartphone interventions were limited by cost, for people with lower socio-economic status.

mHealth applications were divided into two categories:

- Those used in primary prevention to facilitate wellness such as physical activity (e.g. My Fitness Pal), weight loss (e.g. Weight Watchers), stress, diet, nutrition, blood pressure tracking (e.g. Blood Pressure Log) and quit smoking (e.g. Quit START). The Secondary prevention accounts for a quarter of mHealth applications (AARON, 2015).
- Cardiac applications have been used in cardiac rehabilitation services. The National Heart Foundation has launched “My Heart, My Life” application, which helps users to

track medications, obtain personal health statistics, search for recipes, provides information and video on heart attack symptoms (Foundation, n.d.; Neubeck *et al.*, 2015). Also, the Canadian Heart and Stroke Foundation offers a 30-day application, that guides the user to establish goals to reduce their CVD risk (Heart and Stroke Foundation of Canada, 2014). Cardiologists use mobile applications to obtain real time information like drugs lists, patients heart rate monitoring, ECG, blood pressure, calculate risk Algorithm and screen patients with Atrial fibrillation (Lowres *et al.*, 2014).

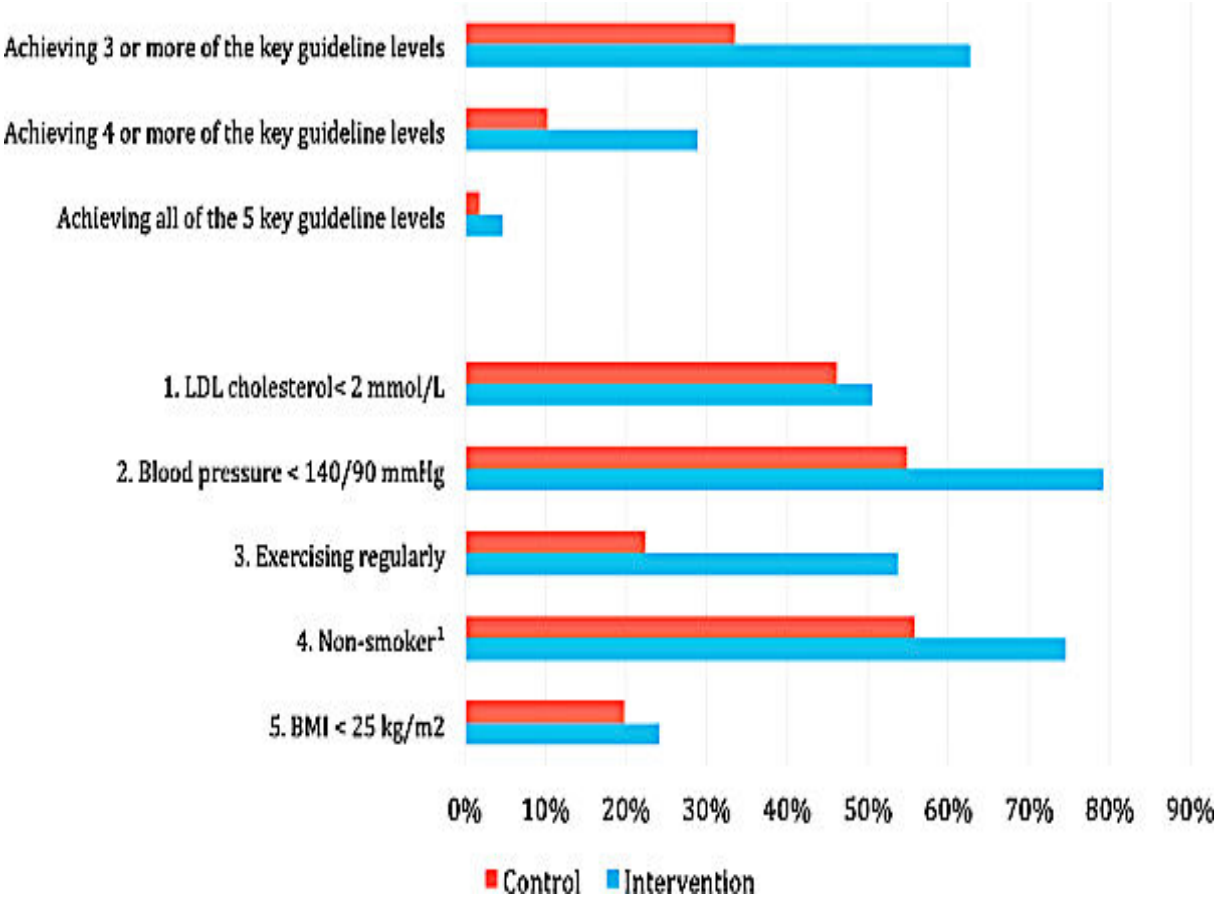


Figure 9: Text message effects on target level of cardiovascular risk factors (Chow *et al.*, 2015)

II.9.7. The WHO 25 by 25 vision for chronic disease target

The growing epidemic for NCDs has been well known for several years. WHO has developed a global strategy for the prevention and control for NCDs. In the 65th World Health Assembly adopted a resolution to reach a global target of 25% reduction in premature mortality from NCDs by 2025 (Figure 10). The WHO / WHF set voluntary targets for six risk factors and two health services goals in order to achieve the 25% reduction in premature mortality from four major NCDs (CVD, diabetes, cancers and lung disease). In 2015, the 193 Member States of the United Nations adopted a new Agenda 2030 based on the WHO and WHF “25 by 25 “and aims for a 30% reduction in NCD by 2030 (Dugani & Gaziano, 2016).

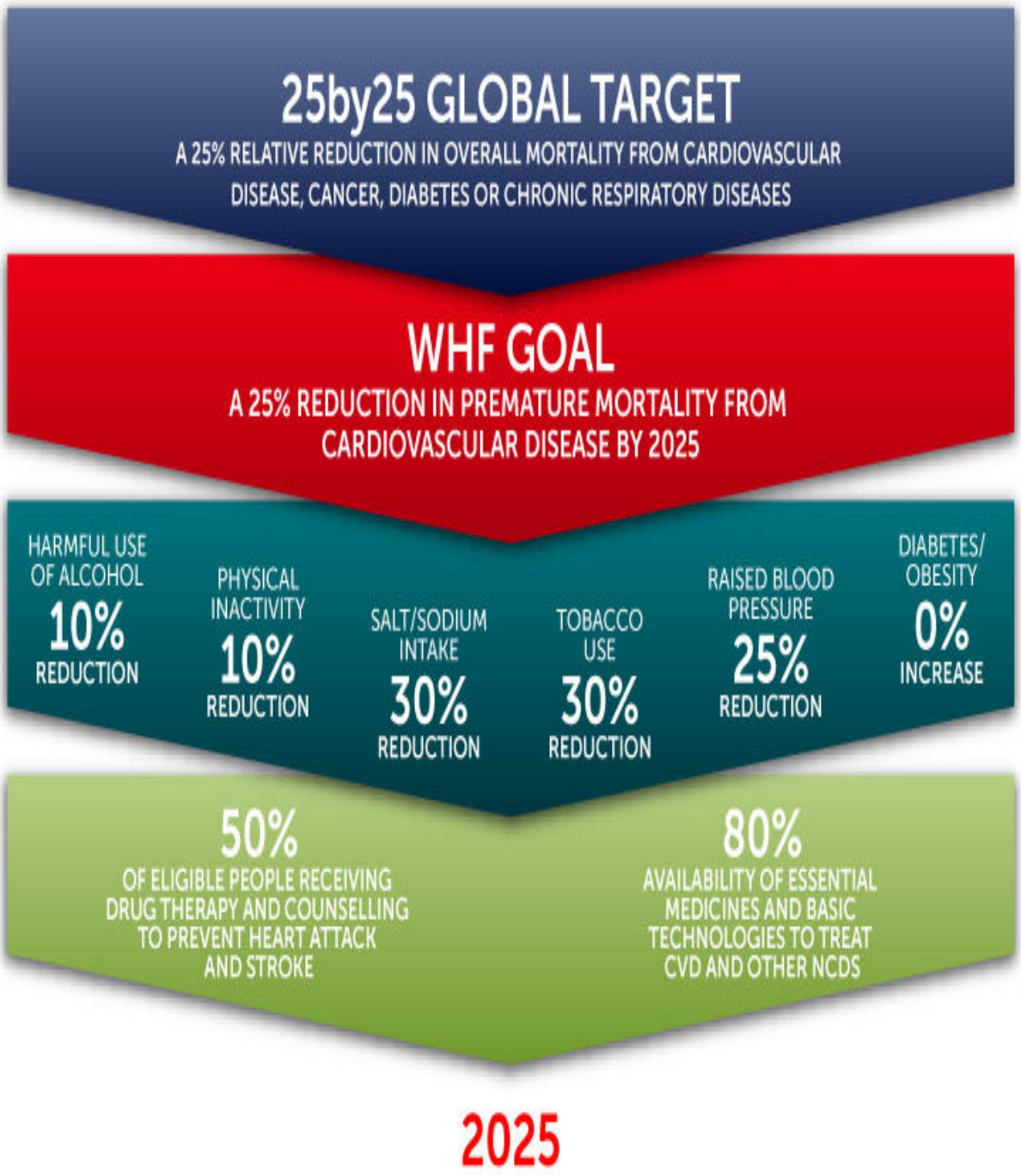


Figure 10: 25x25 WHF global CVD roadmap (Grainger-Gasser, Perel, Lagier-Hässig,& Wood, 2017)

When risk factor targets are met, the probability of dying from the four major NCDs between the ages of 30 and 70 years will decrease by 22% in men and 19% in women between 2010-2025, compared with a decrease of 11% in males and 10% in females based on current trends without further action (Kontis *et al.*, 2014).

II.9.8. Best buys for Non-communicable disease prevention

Defined as interventions that are cost effective, cheap, feasible and culturally acceptable for the prevention and control of NCDs (Table 22). A number of criteria enter into such decision, including the burden of the disease, and political considerations. NCDs cost in LIMIC was approximatively $500 billion annually. In contrast, the total annual cost of implementing all of the “Best Buys” to address NCDs is just $11.4 billion, with the added benefit of saving millions of lives. The implementation of Best Buy requires an organized strategy and a highest level of political mobilization.(“Best Buy” WHO, 2014).

Table 22: "Best Buy" Interventions (“WHO | Scaling up action against NCDs,” n.d.2014)

Risk factor / disease	Interventions
Tobacco use	• Tax increases • Smoke-free indoor workplaces and public places • Health information and warnings • Bans on tobacco advertising, promotion and sponsorship
Harmful alcohol use	• Tax increases • Restricted access to retailed alcohol • Bans on alcohol advertising
Unhealthy diet and physical inactivity	• Reduced salt intake in food • Replacement of trans fat with polyunsaturated fat • Public awareness through mass media on diet and physical activity
Cardiovascular disease and diabetes	• Counselling and multi-drug therapy for people with a high risk of developing heart attacks and strokes (including those with established CVD) • Treatment of heart attacks with aspirin

II.10. The National Health vision and Strategy in Palestine for NCD

The global action plan for the prevention and control of NCDs 2013-2020 has 6 objectives, 25 indicators and 9 voluntary targets (MOH, 2017).

Table 23: National strategic targets to control NCDs in Palestine compared to global targets

	Target	Global	National
1	Relative reduction in premature mortality from NCDs	25%	10%
2	Relative reduction in prevalence of insufficient physical activity	10%	5%
3	Relative reduction in mean population intake of salt	30%	30%
4	Relative reduction in prevalence of current tobacco use in persons aged > 15years	30%	30%
5	Eligible people receive drug therapy and counseling (including glycemic control) to prevent heart attacks and strokes	50%	50%
6	Availability of the affordable basic technologies and essential medicines, including generics, required to treat major NCDs in both public and private facilities	80%	80%
7	Relative reduction in prevalence of raised blood pressure	25%	N.C*
8	Diabetes and obesity increase in prevalence	0%	N.C
9	Relative reduction in prevalence of harmful alcohol use	10%	N.C

N.C*: Not concerning

Chapter III. Cardiovascular disease and risk factors in Palestine

III.1. Epidemiology of Cardiovascular disease in Palestine

Palestinian territories or occupied Palestinian territories is a description often used by United Nation (UN) and other international organizations to describe the west bank including East of Jerusalem and Gaza strip between 1998 to 2013 in order to refer to area controlled by Palestinian National authority. In 2012, the United Nations replaced this by the term of state of Palestine. Palestine is located on the east side of the Mediterranean Sea; the total surface area is estimated at 20,770 square Kilometer. The number of Palestinians in the world is 12.7 million. The number of Palestinians living in the state of Palestine in 2017 was 4.88 million. The population distribution shows that 60.1% live in the northern governorates (West Bank) and 39.9% in the southern governorates (Gaza strip), with 50.9% of males and 49.1% of females (S. Yusuf et al., 2011). Also, 41.9% of the Palestinian populations are refugee. The rate of the natural growth is 2.8% and the life expectancy is 73.7 years; 72.1 years for males and 75.2 years for females (PCBS 2016, n.d.). The population of Palestinian territories is undergoing a rapid epidemiological transition from communicable diseases to NCDs such as CVDs, HTN, DM and Cancer. The prevalence of HIV /AIDS is very low, the population is deemed free of poliomyelitis and immunization program is mostly controlled by WHO (Giacaman *et al.*, 2009). Like other countries an epidemiological transition has occurred in Palestine. The leading cause of death in Palestinian community was NCDs which accounted for 65.7% of all deaths (PHIC, 2018); the incidence is higher in West bank (WB) 57% vs 40% in Gaza Strip(GS) (Zynia L & Andrew, 2000). CVDs are major cause of illness, disability and death in Palestine, which cause an increase in personnel community and health cost. There is no available data to suggest the prevalence or incidence of CVDs; we depend mainly on mortality data from the different health centers.

Epidemiological studies of Cardiovascular risk factors and CVDs in our country suffer from underestimates and other limitations. Firstly, few studies have been undertaken with the use of sampling techniques. Secondly, recent demographic lifestyle changes, cultural, and political prospective are modifying the prevalence of CVRF. Thirdly, CVRF are often not stratified by age and sex. The United Nations Relief and Works Agency (UNRWA) report 2016 for Palestinian refugee, reported a prevalence of 20.1%, 21.9% of hypertension and diabetes 12.9%,15.9% among population aged ≥ 40 years in Gaza and West Bank respectively (Palestinian Refugees of Syria included) (Seita *et al.*, 2017). A survey in Palestine (G.S/WB 1999-2000) reported the prevalence of overweight 35.5%, 40.3% and obesity 31.5%, 17.5% respectively in women and men (Abdeen *et al.*, 2012). By the way the epidemiology of CVDs remains still unclear and the health policy makers do not take in account the results.

III.2. Causes of death in Palestine

In 2017, the number of reported deaths was 11,578 in Palestine, accounting for 62.3% in WB and 37.7% in Gaza strip (PHIC, 2018).

- CVDs were the main leading cause of death, reported at 30.3%
- Cancer was the second leading cause of death, with 14.7%
- Cerebrovascular diseases were the third leading cause reported at 11.7%
- The perinatal period was the fourth leading cause of death accounting for 9.3%
- Diabetes the fifth most common cause of death causing 9.0% of fatalities (most people who have diabetes die from CVDs)
- Accidents of all kinds were responsible of 4.5% of deaths
- Infectious diseases, with 2.9%
- Congenital anomalies accounting for 2.8%

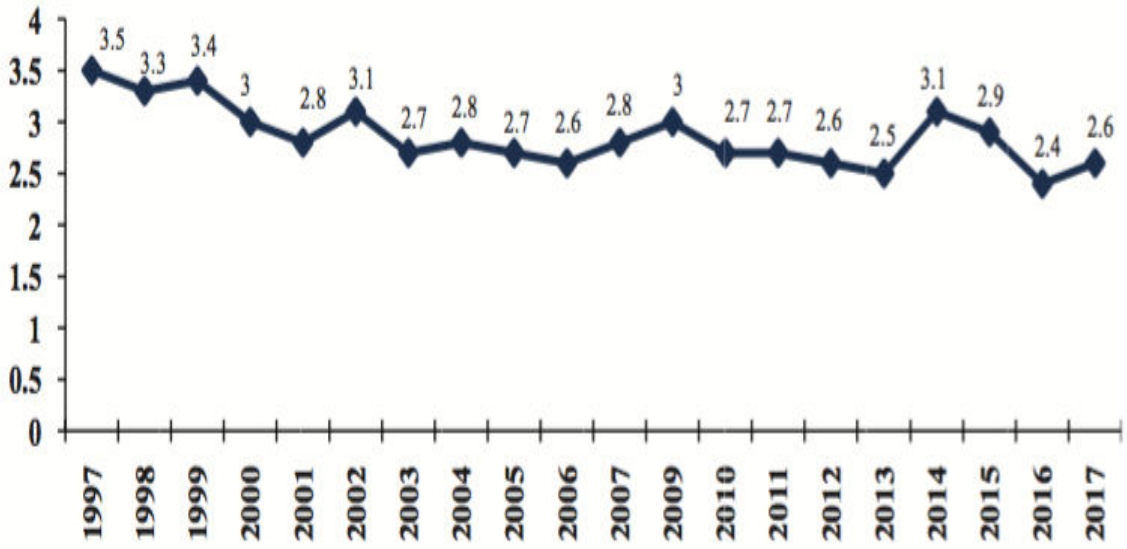


Figure 11: Crude Mortality Rate per 1,000 Population, Palestine 1997-2017(Anon, n.d.)

III.3. Justification of the study

Previous surveys on CVD and risk factors among Gazans in Palestine were hospital based or on United Nation Relief and Work Agency report. There are no studies among general population or community based with sufficient representative sample for correct analysis. In order to complete a gap in the epidemiological field specifically in cardiovascular diseases, this work is the first with a large sample in Gazan community. The objectives of the study will be mentioned later in the text.

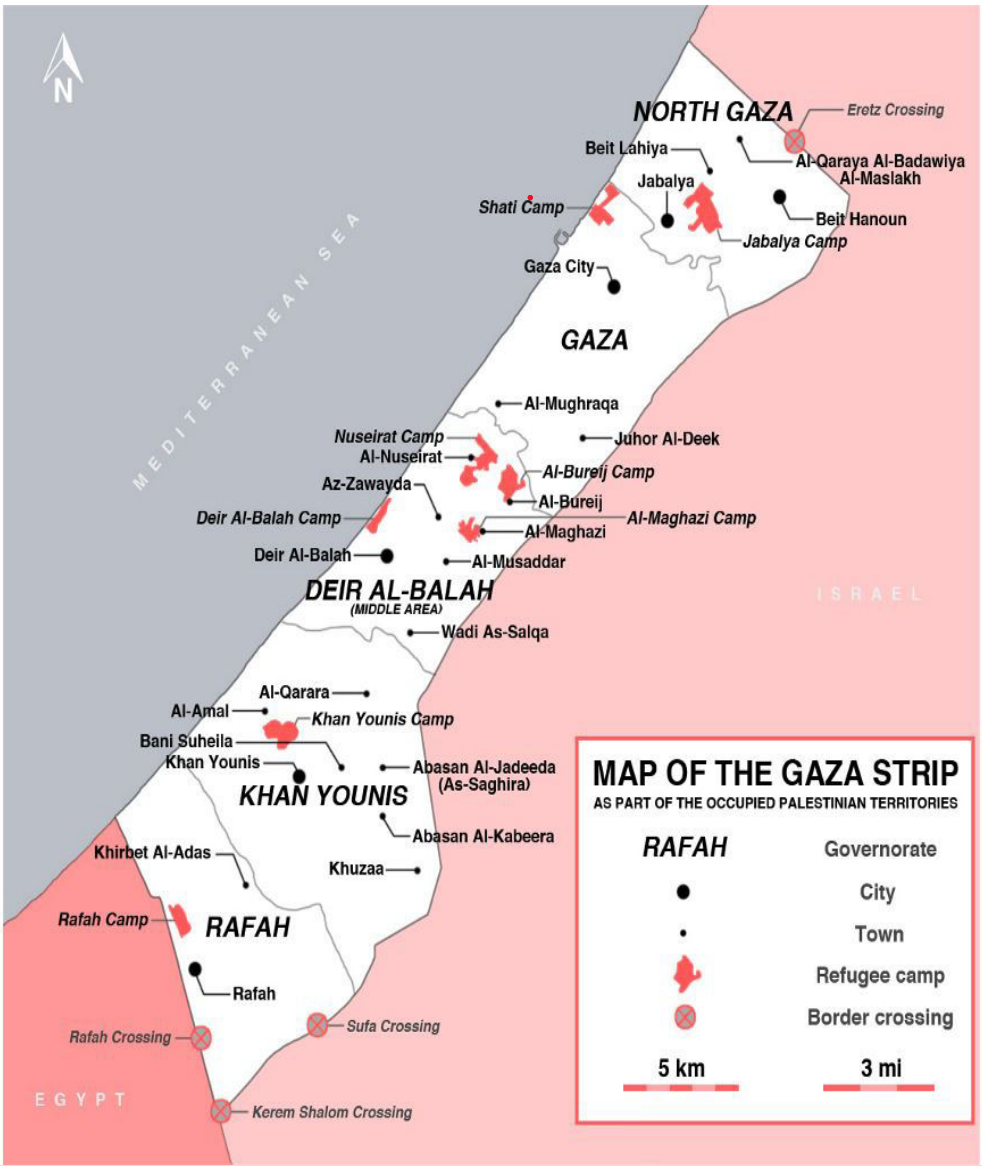


Figure 12: Gaza Strip Map

III.3.1. Geography of Gaza

The Gaza strip is a small area of Palestinian territory on the east coast of Mediterranean Sea. It borders Egypt on the southwest for 11 km and Israel on the east and north a long 51 km border with an area of 365 square kilometers (Figure12). It is mostly flat and sandy with little fertile soil. The GS has a temperature climate with mild winter and dry, hot summers. January is the coldest month with average temperatures ranging from 6 ^{0}C to 15 ^{0}C and July and August are the hottest months at 22 ^{0}C to 33 ^{0}C on average. Gaza strip consists of 5 governorates with fourteen villages and eight refugee camps (Table 24) (Wikipedia, 2017).

Table 24: Distribution of population in Gaza goverenate areas (PCBS2016)

Gaza Governorates	Populations	% of G. S	Area km^2
North Gaza Governorate	377,126	20.1%	61
Gaza Governorate	645, 205	34.3%	74
Deir-Al Balah Governorate	273, 390	14.5%	58
Khan-younis Governorate	351,934	18.7%	108
Rafah Governorate	233,480	12.4%	64
Gaza strip (total)	1.881,135	100%	365

III.3.2. Demography, culture and economy

There are three separate Palestinian communities; those living in Israel, those living in West Bank and those living in Gaza Strip. The latter two groups are the same population separated by geographic and political boundaries. Spoken languages are Arabic and Hebrew, and English is widely understood. In 2017 the population of G.S was 1.88 million, 39.9% of total population of Palestine, and 66.7% were refugees. This large refugee population is supported by the UNRWA which provides health, educational and social services. Gaza has a high fertility rate of 4.4 children per woman and has an annual population growth rate of 2.33%, the 13th highest in the world. The population pyramid shows that the society is young, 44.7% are under the age of 15 years, 2.5% in age ≥ 65 (Fig 13), and the average of family size is 6.5 (CIA., 2018). The population is expected to increase to 2.1 million in 2020. The life expectancy rate is 74.2 years; (72.5 years for males and 75.9 years for females). Around 76.2% of Gazans live in urban areas (CIA., 2018; PHIC, 2018). The Sunni Muslims make up the predominant part of the Palestinian population. There is also a Christian minority who live in the Gaza city, most of them are orthodox. Access restriction, violent attacks, and the Palestinian-Palestinian and Israeli- Palestinian conflict continue to worsen economic and social conditions in G.S. Gaza has suffered from rising unemployment and elevated poverty rates. Gaza strip industries are generally small family businesses that produce textiles, soap, olive-wood and embroidery. Agriculture products are olives, citrus and flowers (CIA., 2018).

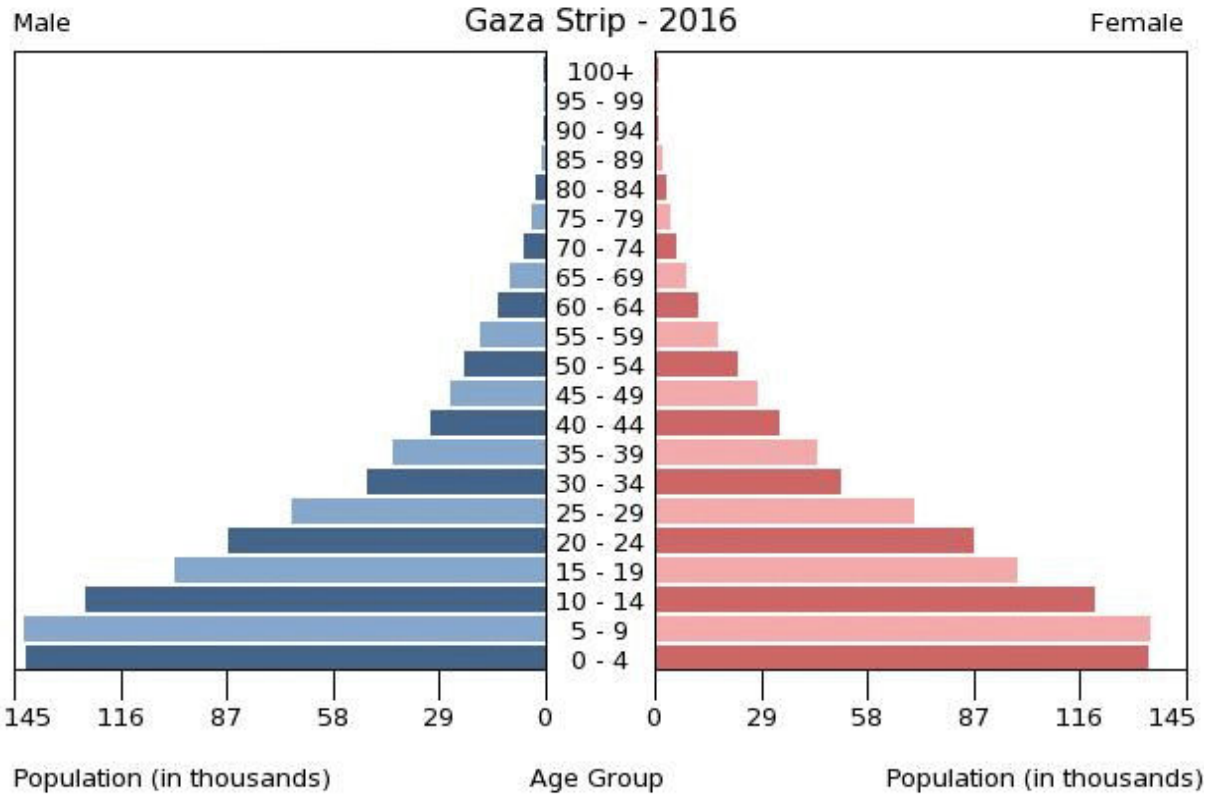


Figure 13: Population Pyramid in Gaza Strip(PCBS 2016, n.d.)

III.3.3. Political situation

Palestinians in Gaza are locked in, denied free access to the remainder of the occupied Palestinian territories and the outside world. Israel maintained severe restrictions on the movements of people and goods into and out of Gaza since 2009 and intensified them on June 2007, after the takeover of Gaza by Hamas, an Islamic Palestinian organization which came into office in 2006 through free elections. The situation was exacerbated by Egypt's closure of the border most of the time, and the internal Palestinian political divide between authorities in Ramallah and Gaza. More than ten years of blockade and the isolation of Gaza has worsened the dire humanitarian conditions such as restricting access to medical care, educational and economic situation, electricity deficit, and perpetuating unemployment and poverty. Approximately 70% of Gaza population rely on humanitarian assistance.

III.3.4. Health situation and health centers in Gaza strip

Gaza strip is suffering from triple burden of health status: 1- a poverty related socioeconomic status, 2- violence related war, 3- increase in life style related NCDs. Years of socioeconomic decline and the political separation between political parties (Fatah and Hamas) in controlling each region have affected the health system as a whole. The serious impact of the conflict led to the destruction of the vital health infrastructure, loss of life, disabilities, shortages of drugs

and medical supplies, deterioration of chronic diseases, limitation of tertiary care capacity, and severe effect on the mental wellbeing of the population. External support from donors, the UN and Non-Governmental Organization (NGO), supported the Ministry of Health (MOH), mainly during emergency. In Gaza, health services are delivered by MOH, UNRWA, NGOs, military medical services and the private sector. There are 160 primary health care centers in Gaza strip. UNRWA provides 22 primary health care services to the majority of the Palestinian refugees in Gaza (PHIC, 2018). According to CIA THE WORLD FACTBOOK the physician's density was 2.2 physicians /1,000 population in 2014 and the hospital beds 1.32/1,000 population in 2015.

NCDs are responsible for more than 50% of deaths in Gaza. Actually, there are no sufficient measures to control unhealthy eating and to promote physical activity (Anon, n.d.). NCD care is available at primary health care in MOH and UNRWA, which provide diagnosis, treatment and follow up for uncomplicated hypertension, diabetes mellitus, heart disease and chronic lung disease. Other NGOs such as the Palestinian Medical Relief Society (PMRS), the Union of Health Care Committees (UHCC) and private sectors provide NCD programs in their clinics.

III.4. Objectives of the study

III.4.1. General objective

The principal objective of our study is to estimate the epidemiology of CVDs (coronary artery disease, stroke and lower extremity artery disease) in Gazan community and to identify associated risk factors.

III.4.2. Specific objectives

- To measure the prevalence of each CVD (coronary artery disease, stroke and lower extremity artery disease) in Gazan community
- To analyze the prevalence of associated risk factors (sociodemographic and cardiovascular) with CVDs
- To examine the association between sociodemographic variables, and the prevalence of risk factors
- To evaluate the clustering of risk factors (metabolic syndrome) and its relationship with CVDs
- To estimate the prevalence of people having high overall 10 years CVD risk using Framingham Global CV risk score

III.5. Methodology and protocol of the study

III.5.1. Target population

The target population includes all adult male and female aged 25 years and more. The target population is 35.8 % of the total Gaza strip population. It was approximately around 673 523 inhabitants. The participants were selected by proportional stratified cluster sampling according to geographic population sector

Table 25: Distribution of population in Gaza strip by age group

Age group Years	Population Number	Percent %	
0-14	804 614	42.8	
15-19	210 132	21.3	
20-24	190 504		
25-29	157 348	29.9%	35.8%
30-34	120 853		
35-39	96 112		
40-44	76 044		
45-49	62 282		
50-54	51 711		
55-59	39 253	3.5%	
60-64	27 249		
65-69	18 578	2.5%	
70-74	11 949		
75-79	7 505		
80+	6 896		

III.5.2. **Sample size (**Appendixes: 11,12,13,14,15)

Sample size was calculated by using Epi-info (epidemiological information, statistical program, version,3.1.1CDC,2015), and on assumption that the prevalence of CVDs in Gaza is less than the prevalence among USA adult Americans population (36.6%) according to American Heart Association statistical update (Benjamin *et al.*, 2017), with a precision of 2% as error level, and 95% confidence interval. The number of individuals in the sample was proportional to the number of the population in each governorate. The sample size calculated was 2228 converted to 2240. This number will allow us to estimate the prevalence of CVDs and cardiovascular risk factors with a good precision.

Table 26: Proportional sample selection in Gaza governorates

Gaza Governorates	% of population	Sample size per district
North Gaza Governorate	20.1	495
Gaza Governorate	34.3	702
Deir-Al Balah Governorate	14.5	277
Khan-younis Governorate	18.7	496
Rafah Governorate	12.4	270
Total Gaza strip	100	2240

III.5.3. Selection criteria

III.5.3.1. Inclusion criteria

- Persons aged 25 years and more
- Living in the area for the last 3 years

III.5.3.2. Exclusion criteria

- Subjects with deafness or muteness without possibility of translation
- Absent subjects of the survey area during the entire duration of the investigation
- Subjects refusing to participate in the survey
- Persons with mental disorder
- Pregnant women

III.5.4. Sample design

The sample design is a cross-sectional study using stratified cluster sample, with the advantage of covering a wide geographic area, in 5 governorates spanning both urban and rural spaces between July and October 2017 (Figure 14).

- The Primary cluster selection: In this stage, the five governorates of Gaza Strip were identified, and the sample size was selected proportional to the size of the population in each Governorate.
- The Secondary cluster: At this stage, in each governorate, one city was selected randomly, then, within each city one camp area and 2-3 rural and urban areas were randomly chosen. The total number of areas was sixteen (five camps and eleven rural plus urban areas). The sample size in each city was proportional to the size of population in each city.
- Tertiary Cluster: within each stratum, whether camp, urban, or rural, a sample block (a group of buildings that form a locality) was selected and a cluster of 15 to 20 households were randomly chosen. The investigators went from door to door, and in every house, all subjects, male and female, of age group ≥ 25 years were interviewed and examined.

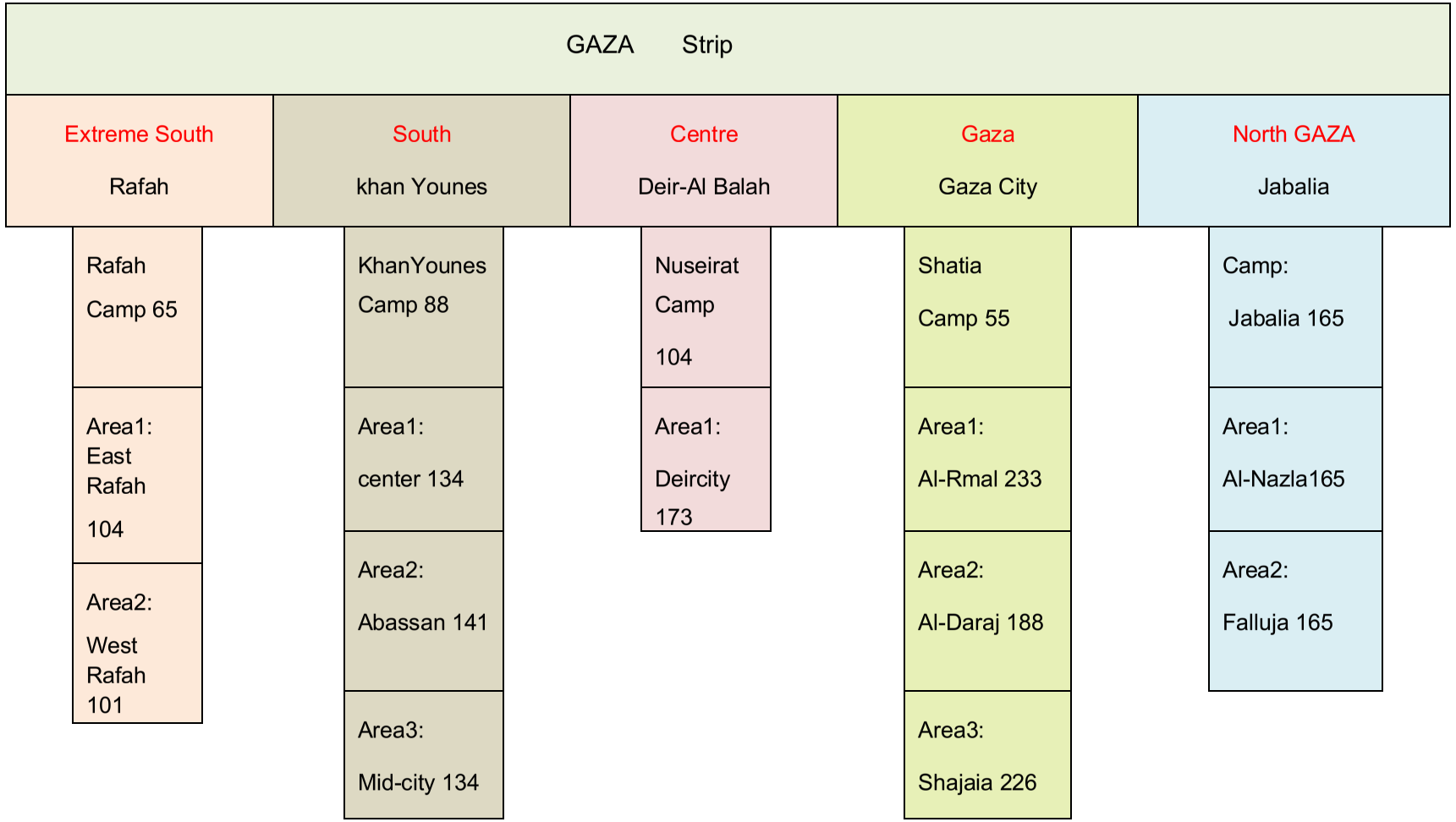


Figure 14: Sampling design study

III.5.5. Study instrument

The study was conducted in accordance with WHO's STEP wise approach to surveillance chronic disease risk factors (STEPS) (WHO 2001). STEPS involve three primary "steps": 1) the use of a structured questionnaire to assess study subjects' self-reported behavioral and lifestyle risk factors for chronic diseases, 2) the measurement of subjects' blood pressure and anthropometrical parameters, and 3) the collection and biochemical analysis of subjects' blood samples. We added Rose angina questionnaire, and Perceived stress scale to the questionnaire.

III.5.5.1. STEP1 : Questionnaire (Appendix 1)

- Demographic and socio-economic status includes information about age, gender, address, educational level, occupation, family size and monthly income, each of these socio demographic variables had two to three categories.
  - √ The residential area: was specified by interviewers when they completed the questionnaire item, (urban, rural and camp).
  - √ Education level: All respondents were asked the total numbers of years spent at school. The responders were categorized into five groups: those with no formal schooling, primary schooling (completed less than 6 years of school), secondary school (completed 7 to 12 years), college or university (12-15 years), and post graduate degree.
  - √ Employment status: The original questionnaire includes 7 responses categories. For this analysis, occupational class was analyzed as four categories: governmental employee, self-employee, homme worker, retired and no-employee.
  - √ Economic status (average income in Dollar per month) participants were classified as low (less than $150), middle ($150 to $500) and high >$ 500.
  - √ Marital status was analyzed as three categories: single, married, divorced or windowed.
- Physical activity: measured by the use of International physical activity questionnaire (IPAQ): the Arabic version was used (Appendix 2, 3). An international consensus developed long and short forms of the IPAQ instrument. During 2000, 14 centers from 12 countries collected reliability and validity data and concluded that IPAQ has reasonable measurement properties for monitoring population levels of physical activity among 18- to 69 years old adults in diverse sittings activity but is often used inappropriately in old age. We used the short IPAQ form in our research, this form comprises of 7 items covering all domains. The specific types of activity that are

assessed are walking, moderate-intensity activities and vigorous-intensity activities. The physical activity was calculated according to the Guidelines for the data processing and analysis of the international physical activity questionnaire, and participants were classified into three groups according to IPAQ Scoring Protocol (Short Forms) as low, moderate and high activity (Anon, 2005).

- Dietary pattern: measured by Food frequency questionnaire (SFFQ): We use the same questions as used in STEPS WHO
- Stress and anxiety: Measured by Perceived Stress Scale (PSS 10), the tool developed in 1983, it is the most widely used psychological instrument of measuring the perception of stress. Five categories of responses were used: 0. Never,1. almost never, 2. sometimes, 3. fairly often, 4. very often. Scores on the PSS can range from 0 to 40: Scores ranging from 0-13 are considered low stress, 14-26 are considered moderate stress and from 27-40 are considered high perceived stress (Cohen, Kamarck & Mermelstein, 1983). We used the Arabic version (Appendix 4, 5)
- Rose questionnaire: The WHO Rose Questionnaire (RQ) (Appendix 6,7) has been widely used since 1962 to detect coronary heart disease in epidemiological research as standardized method as a screening tool rather than diagnostic (Lampe *et al.*, 1998). The original RQ angina pectoris was indicated by response to seven questions and administrated by trained nurse at the interview. Studies reported different sensitivity and specificity of the RQ, it has high sensitivity (80%-95%) but variable specificity (19%-83%) (Fischbacher *et al.*, 2001). The test is considered positive if response to Question 1, 2 or 3, is yes, Question 4 Stop or slow down, Question 5: relieve and Question 6: 10 min or less (Biloglav, 2004).
- Medical history of personal chronic disease: these variables had two categories (Yes or No).

√ Hypertension: We considered subjects to have HTN if their average systolic blood pressure in both arms was ≥ 140 mmHg or their average diastolic blood pressure ≥ 90 mmHg, or if they were being treated for HTN (James *et al.*, 2014; WHO hypertension, 2015).

√ Diabetes Mellitus: Was defined as capillary blood sugar level ≥126 mg/dl if the participant was fasting or ≥ 200 mg/dl if the participant was non-fasting and or self-reported as currently taking any diabetes medications (American Diabetes Association 2016, n.d.).

- Medical history of familial cardiovascular disease: this variable had two categories (Yes or No), and it was considered positive if the first-degree relatives, before 55 years of age in men and 65 years of age in women, had premature CVD or sudden death.
- Smoking: The data on smoking habits were based on participants' responses in the tobacco use module of the steps questionnaire. The question was designed to identify current smokers, past smokers, and never smoker. Current smokers were defined as those who reported smoking greater than 100 cigarettes in their lifetime (including all type of cigarettes) and who currently smoke. Past smoker is someone who has smoked more than 100 cigarettes in their life time but has not smoked in the last 28 days. Never smoker is someone who has not smoked, or who has smoked less than 100 cigarettes in his or her life time (CDC, 2017).
- Cardiovascular diseases
    - √ Coronary artery disease: Was defined in our study by self-reported history of hospitalization for angina pectoris, myocardial infarction, procedures performing percutaneous coronary intervention or coronary bypass graft and their medical prescription list has been checked.
    - √ Stroke was identified with the question that raises the existence, among the house inhabitants of a person having a history of stroke diagnosed by a physician (we asked, "have you ever been told by a physician that you suffered a stroke"?), or presence of neurological deficit.
    - √ Lower extremity artery disease: The diagnosis was retained for an ankle brachial index ≤ 0.90.

III.5.5.2. STEP2: Measurements

III.5.5.2.1. Anthropometric parameters

- Body weight of participants was measured according to the standard procedures, while they were without shoes and wearing light clothes. to the nearest 10 grams with electronic scales (Dr Feisher-care) with a capacity from 10 kg to 180 kg.
- The height of participants was measured barefoot, using carpenter's meter, and the reading of measurement was made using a ruler placed on the subject's head perpendicular to the carpenter's meter.
- Body mass index was calculated as weight in kilograms divided by height in meters squared, and the cut-off points of WHO for BMI were used to define BMI of 18.5-24.9

as normal; BMI of 25 kg/m^2 or higher overweight, and more than 30 kg/m^2 as obese (WHO, 2004).

- Waist circumflex was measured mid-way between the lateral lower rib margin, and the iliac crest, and according to European value which was used for Middle East Arab population we defined abnormal waist ≥ 94 cm in men and ≥ 80 cm in women.
- Blood pressure was recorded by aneroid sphygmomanometer with adapted cuff size. Two readings were taken in each arm, while the participant was in a supine position after having rest for at least 5 min and the average of the reading was used as measure of BP. HTN was diagnosed as having a BP of 140/90 mm Hg or greater.
- Heart rate: measured by pulse oximeter.
- Ankle Brachial Index: The ABI was measured by (Summit Doppler LifeDepo 150 vascular system-USA) following the AHA statement standardized protocol (Aboyans *et al.*, 2012). The leg-specific ABI was calculated as the higher SBP in the posterior tibial or dorsalis pedis divided by the higher of the 2 arms SBP. ABI has been classified into 3 categories: normal value (0.90-1.4), an ABI value < 0.90 indicates LEAD and an ABI ≥1.40 indicates incompressible arteries.

III.5.5.3. STEP 3 : Blood sample

All participants have finger prick for fasting or random blood sugar which was tested by the use of glucometer (DIAVUE Prudential). Blood sample for lipids profile were taken by nurses from antecubital vein, drawn into plain tubes, stored in a cool box, and then sent to the laboratory for analysis using standard methods. We defined high plasma of total cholesterol ≥ 240 mg/dl, plasma triglycerides ≥ 150 mg /dl, high density lipoprotein cholesterol (HDL) ≤ 40 mg/dl in males and ≤ 50 mg/dl in females, and low density lipid cholesterol (LDL) ≥ 160 mg/dl which was calculated using Modified friedewald equation = “LDL (mg/dl) =Non-HDL X 90%−TG X 10%” (Chen *et al.*, 2010; N.C.E.P, 2002).

III.5.6. Data management

III.5.6.1. Staff recruitment and training

There were twelve (12) interviewers (nurses) working in groups of two to three, and preferably be a resident in the same region to ensure acceptance among the interviewed families. The issue of including a female member within each team was taken into consideration. For all interviewers, preparatory Stepwise NCD surveillance conference, training in basic interviewing techniques and standard methods of obtaining physical measurement at the same venue and time were conducted to ensure standardization of data collected.

III.5.6.2. Pilot study

A pilot study was carried out before data collection with 10 cases. The three steps were piloted in order to detect any errors in design. Blood sample was analyzed in 3 different laboratories to confirm results. Pilot subjects were included in the study.

III.5.6.3. Data collection

The data was collected by trained interviewers using face to face settings in participants home or designed place to get the sample of 2240 participants over a period of three months. The teams conducted household visits to fill the questionnaires, to take the physical measurements and blood sampling. During the field work we used the Arabic version to interviewing participants. Venous blood samples were obtained via the antecubital vein lipids profile including non-fasting serum Total Cholesterol, HDL-C and Triglycerides. The glucose level was obtained by glycometer. Lipids profile and glucose level were previously defined.

III.5.6.4. Data entry

The data entry was conducted directly in the same day of data collection to improve validity and reliability of the study. After checking and reviewing all questionnaires. SPSS (Statistical Package for Social Science) software version 22 was used for data entry and analysis, a code was attributed to each file of questionnaire, after finishing the data entry process, the data accuracy was checked by data selecting and checking out a random number of the filled questionnaires to ensure that all data entered accurately and in an appropriate way. Data cleaning included checking for duplicates, missing, or illogical responses; and performing descriptive statistics, through operating frequencies for all the study variables.

III.5.7. Statistical analysis

The collected data was captured and analyzed using SPSS (Statistical Package for Social Sciences) version 22. The analysis was carried out at both descriptive and inferential analysis. Recoding of selected variables was done and we kept both continuous and categorical values for these variables. Categorical data were presented as percentages, and continuous data as mean and standard deviation. Frequency for both categorical and continuous variables of study was done and serve the purpose of the descriptive analysis. The prevalence of the CVD and the risk factors were calculated. The inferential analysis includes cross tabulation between CVDs as dependent variables and independent variables such as socio demographic variables and the cardiovascular risk factors included in our study. Statistical relationship between independent variables and the dependent variables was examined for statistically significant Chi-Square test and the use of Odds Ratio 95% confidence interval. For comparing means of the continuous variables t-Student test and ANOVA test was used. Multivariate logistic

regression was used to examine the relationship between CVDs and their risk factors. P value was considered statistically significant when lower than 0.05.

III.6. Ethical issues

An approval letter from Palestinian Helsinki Committees (Appendix 8) was obtained to conduct the study and to make the necessary analysis. Also, a consent form was obtained from each participant involved in the study after showing them an explanatory letter that includes information about the researcher, the proposal, the tests and measurements of the study. It also included a clear statement to each respondent in the study about the right to refuse answering any question given in the questionnaire and confidentiality of the information that was given to the research team (Appendix 9).

Chapter IV. Results

IV.1. Article 1: Epidemiology of coronary artery disease and stroke and associated risk factors in Gaza community- Palestine

Contexte de l'étude

Le monde Arabe souffre de plus en plus des maladies cardiovasculaires ceci à cause de la transition épidémiologique. Les données disponibles en Palestine s'appuient sur des cohortes hospitalières, et sur les rapports annuels délivrée par UNRWA sur les facteurs de risque majeurs (hypertension et diabète). La recherche dans la littérature n'a dévoilé aucune étude sur la prévalence de la maladie coronarienne ou l'accident vasculaire cérébral en Palestine.

L'objectif de l'étude

Déterminer la prévalence de ces maladies cardio-neurovasculaires chez toute personne ≥ 25 ans dans la bande de Gaza, connaître aussi les facteurs de risque cardiovasculaires et socioéconomiques associés dans la population.

Méthodologie

Une étude transversale a été menée suivant un protocole STEPS (OMS) modifié à l'aide d'un questionnaire chez des sujets issus de cinq districts de la bande de Gaza. Chaque district couvre un milieu rural, urbain et camp.

Valorisation de l'étude

L'étude est publiée le 25 Janvier 2019 dans Plos one journal (impact factor 2.7666)

Communications

- Communication orale : '8th International Conference of Epidemiology and Public Health', September 17-19, 2018, Rome, Italy (abstract mis sur le programme), communication non faite à cause du blocus sur Gaza
- Communication orale : à la dixième conférence des maladies cardiovasculaires à Gaza Novembre 2018

PLOS ONE

RESEARCH ARTICLE

Epidemiology of coronary artery disease and stroke and associated risk factors in Gaza community –Palestine

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Abstract

Aim of study

To determine the prevalence of cardiovascular disease and associated risk factors in the population of Gaza strip in Palestine.

Methods

A cross-sectional stratified cluster sample design was applied in this study. A sample of 2240 participant (1121 males and 1119 females) aged ≥25 years participated in the study. For each individual, trained staff administered a questionnaire, where all variables of interest followed WHO's STEP wise approach to surveillance chronic disease risk factors (STEPS) (WHO, 2001). Sociodemographic data, anthropometric measure (body mass index, blood pressure), and biochemical test (blood sugar and lipids profiles) were measured. Short International Physical Activity (IPAQ) questionnaire form was used. Bivariate analysis and logistic regression were used with SPSS (version 22.0) to analyze the data.

Results

The most common condition was coronary artery disease (8.3%), followed by stroke events (3%). The associated risk factors were obesity (47.8%), hypertension (28.4%), current smoking account for (23.2%), diabetes mellitus (19.1%), high cholesterol level (8.8%), and high triglycerides level (40.2%). Additionally, the proportion of being physical active was found to be low (48.3%); particularly with increasing age. More than 30% of the population has less than 4 days of consumption of fruit and vegetables per week and 65.9% has less than 2 servings per day.

Conclusion

The burden of CVDs and their associated risk factors is considerable in Gaza and represents a major public health concern. Effective strategies in management, education and

healthcare centers are required for an accurate management and implementation of preventive measure in this area.

Introduction

In the previous years, there were dramatic changes in the occurrence of the major manifestations of cardiovascular disease (CVDs), mainly coronary artery disease (CAD) as well as cerebrovascular disease (CBVD). Cardiovascular diseases are now recognized as the leading cause of death and disability worldwide [1]. In 2015, it was estimated that 17.7 million people died from CVD worldwide, representing 31% of all global deaths; out of whom, 7.4 million were due to CAD, and 6.7 million were due to stroke [2]. In the United States (US), 92.1 million adults experienced at least one type of CVD. By 2030, 43.9% of the US adult population is projected to have some form of CVD. However from 2004 to 2014, death rates attributable to CVD declined by 25.3% in that country [3]. Three quarters of global CVD deaths occur in Low and Middle-Income Countries (LMIC). In 2015, among 17 million premature deaths (under the age of 70) was due to Non-Communicable diseases (NCDs); 82% of them took place in LMIC and 37% of the deaths are caused by CVDs, almost equal in males and females [4–6]. Arab countries in the Middle East have undergone rapid and dramatic socioeconomic changes. In these countries which have young populations, CVD mortality accounts for 45% of deaths [7]. The rates of CVDs deaths were up to 42%,38%,32% and 23% respectively in Saudi Arabia, the United Arabic Emirates, Bahrain and Qatar [8].

Similar to other countries, an epidemiological transition occurred in Palestine. The leading causes of death in the Palestinian community are NCDs, up to 50% of all deaths. The incidence is higher in the West Bank (WB) 57% vs 40% in Gaza Strip (GS) [9]. In 2014, CVD was reported as the first cause of deaths in Palestine accounting for 29.5%, CBVD was the third common cause corresponding to 11% of all deaths [10]. Most data are from hospital based, few studies were conducted on prevalence of CVD risk factors in Gazans population. Data regarding the prevalence or incidence of CAD and CBVD, in this community are lacking.

The aim of this study is to document the prevalence of CVDs (i.e. CAD, Stroke) and associated risk factors in Gazan community.

Methodology

The Gaza strip is a small 365 square kilometers area of Palestinian occupied territories; it is a very crowded place as around 1.9 million Palestinians live in. Gaza strip consists of 5 governorates with fourteen villages and eight refugee camps [11]. We conducted a cross-sectional study using stratified cluster sample, with the advantage of covering a wide geographic area, in 5 governorates spanning both urban and rural spaces between July and October 2017. The target population include 673 523 inhabitants, almost 35.8% of the total Gaza strip population.

The sample size was 2240 calculated by using Epi-info (epidemiological information, statistical program, v 3.1.1, CDC,2015), considering a CVDs prevalence among US adult Americans population (36.6%) according to American Heart Association statistical update [3]. with a precision of 2% as error level, and 95% confidential interval, and a cluster effect of '1. The number of individuals in the sample was proportional to the number of the population in each district. The cluster areas were randomly chosen and each area yielded 15–20 households. The investigators went from door to door, and in every house, all adults aged $\geq$25 years were proposed to participate. Pregnant women and individuals with mental disability were excluded.

The study was conducted in accordance with WHO's STEP wise approach to surveillance chronic disease risk factors (STEPS, WHO 2001) which involves three primary "steps". At step 1, we used questionnaire to assess demographic, socioeconomic, reported behavioral, and lifestyle risk factors for chronic diseases. In addition, short international physical activity (IPAQ) form questionnaire was used. At Step 2, blood pressure on both arms and anthropometrical parameters were collected: height, weight, waist circumference, and Heart rate, by pulse oximeter, were measured. Then at Step 3, 2226 participants underwent a venous puncture for lipids analysis, fasting or random blood sugar (DIAVUE Prudential). Fourteen participants refused.

Variables definitions

Height was measured with a wall-mounted stadiometer to the nearest 0.1 cm. Weight measured to the nearest 10 grams with electronic scales (Seca, Hamburg, Germany). Waist circumflex measured mid-way between the lateral lower rib margin, and the iliac crest and according to European data which was used for Eastern Mediterranean population, we defined normal waist $<$80 cm in females and $<$ 94 cm in males [12]. Diabetes mellitus(DM) was defined as capillary blood sugar level $\geq$126 mg/dl if the participant was fasting or $\geq$ 200mg/dl if the participant was non-fasting and or self-reported as currently taking any diabetes medications [13]. For hypertension (HTN), we considered subjects to have HTN if their average systolic blood pressure (SBP) in both arms was $\geq$140 mmHg or their average diastolic blood pressure (DBP) $\geq$90 mmHg, or if they were being treated for HTN [14,15]. Body mass index (BMI) was calculated as weight in kilograms divided by their height in meters in squared and considered anyone with a BMI of 25kg/m^2 or higher overweight, and more than 30kg/m^2 as obese according (WHO classification). Low density lipoprotein (LDL cholesterol) was calculated using modified Friedewald equation [16]. Lipids profiles abnormalities were classified according to ATPIII Guidelines as total cholesterol levels $\geq$ 240mg/dl, high density lipoprotein (HDL cholesterol) $\leq$40 mg/dl in men and $\leq$50 mg/dl in women, low density lipoprotein(LDL cholesterol) $\geq$ 160 mg/dl, and triglycerides $\geq$150 mg/dl [17]. CAD was defined in our study by self-reported history of hospitalization for angina pectoris, myocardial infarction, procedures performing percutaneous coronary intervention or coronary bypass graft and has been check by their medical prescription list. Stroke was identified with the question that raises the existence, among the house inhabitants of a person having a history of stroke diagnosed by a physician (we asked "have you ever been told by a physician that you suffered a stroke"?).

Authorizations

The study protocol was approved by the Ethical of Human Research Committee of Palestinian Health Research Council, and an individual written or verbal consent was obtained by each participant.

Data analysis

Data was analyzed using Statistical Package for Social Sciences version 22. Categorical variables are presented as percentage, and continuous data as the means and standard deviation. We first compared differences in socio-demographic as well as lifestyle-related factors using chi square test, Somers' D test (for ordinal qualitative variables), student's t-test, or Wilcoxon's rank sum test as appropriate. Then we used logistic regression to examine the association between CVDs and their risk factors with/without adjustment for covariates. Any covariate with a p-value $\leq$ 0.25 in the age-and gender-adjusted model was considered in multiple logistic regression model. The final model was obtained using a backward stepwise procedure. We

examine confounding at each step and then we examine first-order interactions in the final model. Statistical significance level was set-up at 0.05 for all analyses.

Results

A total of 2240 participant were included into the study. Sociodemographic profiles and the burden of Cardiovascular risk factors of the participants are displayed in "Table 1". No significant difference was seen according to age group distribution and gender. The mean age of study population is 47.4 years (47.1 in male and 47.8 in female). Forty percent of participants lived in refugee camps. Furthermore, 7% of the females did not have any formal schooling, while 25.8% of the study population completed university education, and 7.6% achieved post-graduate degree. The monthly income was less than $150 for 36.8% of the participants.

Table 1. Socio- demographic characteristics and burden of cardiovascular risk factors of study population.

Variables	Gender						P value*
	Total		Males		Females		
	No.	%	No.	%	No.	%	
Age group							
25–34 years	503	22.5	277	24.7	226	20.2	0.061
35–44 years	494	22.1	226	20.2	268	23.9	
45–54 years	528	23.6	266	23.7	262	23.4	
55–64 years	420	18.8	205	18.3	215	19.2	
65+ years	295	13.2	147	13.1	148	13.2	
Locality							
Urban	798	35.6	373	33.7	420	37.5	0.002
Rural	529	23.6	245	21.9	284	25.4	
Camp	913	40.8	498	44.4	41%	37.1	
Education							
No formal schooling	106	4.7	28	2.5	78	7.0	<0.001
Primary schooling	238	10.6	114	10.2	124	11.1	
University complete	579	25.8	335	29.9	244	21.8	
Post graduate	170	7.6	118	10.5	52	4.6	
Income in US ($) per month							
<$150	825	36.8	373	33.3	452	40.4	0.001
$150–500	944	42.1	478	42.6	466	41.6	
>$500	471	21.0	270	24.1	201	18.0	
Cardiovascular risk factors							
Hypertension	636	28.4	292	26.0	344	30.7	0.014
Diabetes	427	19.1	206	18.4	221	19.7	0.408
overweight	737	32.9	438	39.1	299	26.7	<0.001
obesity	1070	47.8	397	35.5	673	60.2	
Lipids profiles							
Total cholesterol ≥240 mg/dl	195	8.8	65	6.1	127	11.4	<0.001
LDL cholesterol ≥160 mg/dl	187	8.4	71	6.4	116	10.3	0.001
Low HDL cholesterol mg/dl	1569	70	779	69.5	790	70.6	0.847
Triglycerides ≥150mg/dl	895	40.2	480	43.1	415	37.3	0.006

Overweight: BMI (25–29.9 kg/m2)

Obese: BMI (≥30 kg/m2)

A Chi-square test or Somers' D test (for ordinal variables) was used.

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Table 2. Life style-related risk factors in the study population by age for men and women.

Variables	Gender	Age groups in years %					Overall %	Age Adjusted %	P value
		25–34	35–44	45–54	55–64	65+			
Current Smoking	All	30.2	23.9	22.3	22.4	12.9	23.2	23.6	<0.001
	Males	50.5	50.4	42.9	42.4	25.9	44.0	44.5	<0.001
	Females	5.3	1.5	1.5	3.3	0.0	2.4	2.61	<0.001
Age of onset of smoking <18y	All	61.2	50.0	53.4	47.9	44.7	53.3	52.7	0.05
	Males	64.3	49.1	55.3	48.3	44.7	54.4	53.8	0.01
	Females	25.3	75.0	0.0	42.0	0.0	33.3	31.3	0.15
Low Physical Activity	All	36.4	45.1	49.4	55.2	61.7	48.3	47.3	<0.001
	Males	27.1	37.2	40.6	42.9	50.3	38.3	37.7	<0.001
	Females	47.8	51.9	58.4	67.0	73.0	58.3	57.1	<0.001
Fruits+ vegetable intake < 4days /week	All	26.9	34.0	33.8	28.3	29.2	30.7	30.5	<0.001
	Males	24.6	32.0	31.3	26.3	26.5	28.3	28.3	0.04
	Females	29.6	35.7	36.4	30.2	31.8	33.1	32.8	0.29
Fruits+ vegetable <2 serving / day	All	62.7	70.1	65.6	68.3	61.4	65.9	65.7	0.03
	Males	62.0	64.0	63.0	65.0	59.9	63.1	62.8	0.64
	Females	63.6	74.8	68.2	70.7	62.8	68.6	68.2	0.07

Data are represented as percent (%)

A Chi-square test was used to compare the difference in risk factors for CAD and stroke across age subgroups for the overall population as well as for each gender.

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Regarding CVD risk factors hypertension and diabetes were higher among females. BMI was $\geq$ 30kg/m^2 in 47.8% of the cases. Obesity was more common in females than males, 60.2%, 35.5% respectively. Conversely The overweight was more common in males than females 39.1% vs 26.7% (p value <0.001). In addition, 8.8% and 40.2% of study population had high levels of total cholesterol and triglycerides respectively.

Data on the lifestyle related risk factors are displayed in "Table 2". Smoking was by far less frequent among women since smoking is not accepted for women in Gaza. The prevalence of smoking among males increased with age until the age of 44 and decreased later. Additionally, 64.3% of men in age group 25–34 years started to smoke before the age of 18 years. The consumption and serving of fruits and vegetables was low, with minor differences in gender and age groups.

Overall 218 subjects (9.7%) of participants had CVD 11.5%in males and 8.0% in females "Table 3". CAD was present in 185 persons 8.3% (95% CI, 7.14%-9.46%), males reported a

Table 3. Prevalence of cardiovascular disease (CAD, stroke) by gender.

Cardiovascular diseases	Gender							
	All		Males		Females		Odds Ratio (95%CI)	P value
	No.	%	No.	%	No.	%		
CAD	185	8.3	113	10.1	72	6.4	1.63 (1.19–2.21)	0.002
Stroke	67	3.0	39	3.5	28	2.5	1.40 (0.86–2.29)	0.175
CAD or Stroke	184	8.2	106	9.5	78	7.0	1.41 (1.05–1.91)	0.037
CAD and Stroke	34	1.5	23	2.1	11	1.0	2.17 (1.05–4.47)	0.030
CVD	218	9.7	129	11.5	89	8.0	1.51 (1.13–2.01)	0.005

Female gender is the reference group, CAD: Coronary artery disease, CVD: cardiovascular disease

Odds Ratio: male vs female CI: confidence interval 95%

Fisher's exact method was used

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Table 4. Multivariate logistic regression (adjusted for age, and gender) with CVD as dependent variable and major risk factors as independent variables.

Variables	Univariate analysis		Adjusted analysis	
	Odds Ratio (CI)	P value	Odds Ratio (CI)	P value
Age	0.94 (0.93–0.95)	<0.001		
Gender	1.51 (1.13–2.01)	0.005		
Hypertension	4.73 (3.53–6.31)	<0.001	2.51 (1.81–3.50)	<0.001
Diabetes	4.49 (3.36–6.01)	<0.001	2.22 (1.61–3.11)	<0.001
BMI≥30kg/m^2	1.44 (1.10–1.91)	0.011		
Current smoking	1.07(0.77–1.48)	0.686		
High cholesterol	1.27(0.80–2.01)	0.303		
High triglycerides	1.43 (1.08–1.89)	0.013		

BMI: Body mass index

Logistic regression model was used

Odds Ratio: male vs female. CI: confidence interval (95%)

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higher prevalence (10.1%) than females (6.4%). Among the 2240 participants we found only 67 cases which reported a history of stroke 3% (95%CI, 2.28%-3.72%) with no difference in gender (3.5% vs.2.5%). The clinical disorders were limited to one territory for 184 participants (8.2%) involving 9.5% of the males and 7.0% of the females. Two territories were involved in 34 participants (1.5%), with a1.5 higher risk in males.

After adjustment by age and gender, the most important risk factors associated with CVD were HTN, and DM, *p* value <0. 001 "Table 4". Hypertension was associated with a 3-fold increased risk of CVD and diabetes mellitus a 2.5-fold.

Discussion

Our study is the first to report the prevalence of CVDs among Gazans in Palestine. Previous surveys were hospital based or on United Nation Relief and Work Agency (UNRWA) report. The prevalence of CVDs nears 10% of the population above the age of 25years in this area.

Data on the CVD epidemiology in the Middle-East are limited. In the Coronary Artery Disease in Saudi study (CADISS), a national community-based study conducted in urban and rural area of Saudi Arabia; 17 232 subjects aged 30–70 years randomly selected were included. Coronary artery disease was diagnosed on positive questionnaire of angina or history of possible myocardial infarction. The prevalence of CAD was 5.5% (6.6% in males and 4.4% in females) [18]. Similar findings have been reported in a Lebanese cross-sectional study using multistage cluster sample including 1200 subjects ≥40 years of age. The prevalence of CAD was 13.4% (17.8% in males, 9.0% in females) [19]. In the Jordanian population, the prevalence of myocardial infarction was reported at 5.9% in adults over 40 years [20]. Regarding stroke our results are in line with another Lebanese study including1515 individuals with a mean age of 57.2 years; stroke and or transit ischemic attack were (3.6%), and the prevalence of any stroke symptom was up to 12.1% [21]. According to a systemic review in Middle east, the prevalence of stroke was estimated between 508 to 777 per 100,000 population [22], more commonly in males than females [22,23]. Two hospitals based studies conducted in Palestine, showed more stroke cases among females than males groups [24,25].

Number of risk factors were identified in epidemiological surveys. In 2016 the global burden disease (GBD) for risk profiles in Middle east and north Africa (MENA) stranded out these risk factors by order of penetrance, high blood pressure ranked as the first, followed by obesity, diabetes then smoker [26]. The same grading was retained for Palestine [26].The

UNRWA 2016 report for Gaza, found 20.1% subjects with hypertension among population aged ≥ 40 years (Palestinian Refugees of Syria included) [27]; we reported a prevalence of (28.4%). The literature review revealed a higher prevalence of hypertension in Arab countries 29.5%. The same prevalence was found in the US (29.6%), and (30%) in United Kingdom [28].

Obesity is a common health problem worldwide particularly in Arab world. The prevalence of obesity and overweight in Arab states ranges from (25% to 81.9%) [29]. The Global burden disease (GBD) 2016 estimated that high BMI was the leading six risk factors in Arab countries [26]. The overall obesity in our study was found to be 47.8%, with higher prevalence in females (60.2%), the mean BMI was 30.35. It is in line with previous study performed in urban Palestinian population of Ramallah, describing an obesity prevalence up to 41% (49% and 30%) in females and males respectively [30], these results were higher than those in the US population (36.5%)[31] or in Israel which the National Health and Nutrition 1999–2001 (MABAT) was conducted among 2782 persons, and showed a prevalence of overweight in 39.3% and obesity in 22.9% adults population. The Israeli Arab population was more obese than the Jewish one [32]. Also, our prevalence was higher than among Tunisian males and females (18.2%, 33.5%) respectively [33].

Diabetes mellitus was identified in our study with a prevalence of 19.1%. WHO report 2015 from Middle East Region (Bahrain, Kuwait, Oman, and the United Arab Emirates) estimated that the prevalence of DM was between 3.5% and 30% [34]. In a study in Saudi Arabia, the prevalence of type 2 diabetes among 2355 adults was 29.3% [35]. For smokers, our estimated prevalence was 23.2%. The WHO report on the global tobacco epidemiology (2011) estimated that Europe had the highest prevalence of smokers (35%); and the lowest was in Africa. The global Adult tobacco survey showed that in fourteen LMIC, 48.6% of men and 11.3% of women were tobacco users [36]. Additionally, in our neighbour countries, a cross sectional study conducted in Lebanon, among 2836 adults ≥18 years of age, showed that the current smoking prevalence rate was 34.7% with higher rate in males than females,42.9% and 27.5% respectively [37]. In the BREATH study, 62 086 subjects aged ≥ 40years in ten countries in MENA region, were interviewed regarding smoking habits, with equal number of men and women. The smoking rate was estimated to be 31.2%, ranging from 15.3% in Morocco to 53.9% in Lebanon. The proportion was higher in men (48.0%) than in women (13.8%) [38], the prevalence of female smokers has traditionally been low due to the Eastern Mediterranean region's conservative cultural and social values. Less than one third of our study population have dyslipidaemia. However, our finding was counterpart with data from ACE (Cardiovascular Epidemiological) study in United Arab Emirates, the prevalence was 74% [39], while the high prevalence of dyslipidaemia in our study in young adults (age 25-34years) calls for an earlier screening for dyslipidaemia and other risk factors. Another important factor observed in our study was the proportion of people with low physical activity, it was estimated that half of the population 48.3% had low physical activity. Women exercised less than men (58.3%). We ascribe these phenomena to the fact that women have maternal responsibility and were more obese. In a study for 163 556 persons in 38 Muslim countries who completed IPAQ, the total physical inactivity prevalence was 32.8%. The prevalence among Arab countries was 43.7% *vs* 28.6% in non-Arab countries, and Arab women were more physically inactive [40]. In a cross-sectional study conducted in Saudi Arabia, physical activity was assessed using the global physical activity questionnaire among 4758 participants. The prevalence of low activity was 66.6% (60.1% in males, and 72.9% in females). Similar data were found in the Arabian Gulf region [41,42].

Nutrition is an important determinant of health; inadequate consumption of fruit and vegetable is a factor that can play role in morbidity. As other studies in Arab gulf countries our study population did not consume sufficient quantities of fruits and vegetables. A study

analyzed data from 197 373 adult participants from 52 countries taking part in the world health survey in LIMIC (2002–2003). The prevalence of low consumption of fruit and vegetable was 77.6% in males and 78.4% in females [43].

Strengths and limitations

There are few limitations to our study. First, the cross-sectional nature of this study design limits the interference of causal relation-ships between risk factors and CAD or stroke. Also, the prevalence of high blood pressure and raised blood glucose have been over estimated because these two risk factors were evaluated once (no reevaluation during another visit, and no three consecutive measures of BP according to WHO step). Further, possible bias could have been introduced since study was conducted at home and data concerning more risk factors and history of CAD and stroke were self- reported. Also, the wide age range of participants, 25 years and more is both a strength and a weakness of this study. However, 32% of the population was aged 55 years and more, who have a greatest prevalence of CVD and risk factors. Even so we found considerable charge of risk factors in young population. Also, this study has strengths points: women were well represented, with a male: female ratio of 1, and it was performed in a large mixed area with representative sample, and good response rate; making it the first study in Palestine to report a national estimate for CVD prevalence.

Conclusion

This study was the first nationwide endeavor that provides information about the prevalence of CVDs and the level of cardio vascular risk factors among palestinian community in Gaza.

A rate of CVD has been reported in our population, 10% reflecting a serious health problem in Gaza strip. Obesity, hypertension and diabetes, were highly prevalent. Increased, effort and research to monitor and improve strategies and policies for reducing cardiovascular risk are mandatory.

Supporting information

S1 Dataset. Database of study participants.
(XLSX)

S1 Text. Definition of study variables.
(DOCX)

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References

1. Mendis S, Puska P, Norrving B, Organization WH, Federation WH, Organization WS. Global atlas on cardiovascular disease prevention and control [Internet]. Geneva: World Health Organization; 2011 [cited 2017 Feb 14]. Available from: http://www.who.int/iris/handle/10665/44701
2. WHO. WHO | Cardiovascular diseases (CVDs) [Internet]. 2017 [cited 2017 Dec 19]. Available from: http://www.who.int/mediacentre/factsheets/fs317/en/
3. Benjamin EJ, Blaha MJ, Chiuve SE, Cushman M, Das SR, Deo R, et al. Heart Disease and Stroke Statistics—2017 Update: A Report From the American Heart Association. Circulation [Internet]. 2017 Jan 1 [cited 2017 May 6]; Available from: http://circ.ahajournals.org/content/early/2017/01/25/CIR.0000000000000485
4. WHO | Cardiovascular diseases (CVDs) [Internet]. WHO. [cited 2017 Feb 3]. Available from: http://www.who.int/mediacentre/factsheets/fs317/en/
5. GBD 2013 Mortality and Causes of Death Collaborators. Global, regional, and national age-sex specific all-cause and cause-specific mortality for 240 causes of death, 1990–2013: a systematic analysis for the Global Burden of Disease Study 2013. Lancet Lond Engl. 2015 Jan 10; 385(9963):117–71.
6. Roth GA, Huffman MD, Moran AE, Feigin V, Mensah GA, Naghavi M, et al. Global and regional patterns in cardiovascular mortality from 1990 to 2013. Circulation. 2015 Oct 27; 132(17):1667–78. https://doi.org/10.1161/CIRCULATIONAHA.114.008720 PMID: 26503749
7. Husseini A, Abu-Rmeileh NM, Mikki N, Ramahi TM, Ghosh HA, Barghuthi N, et al. Cardiovascular diseases, diabetes mellitus, and cancer in the occupied Palestinian territory. The Lancet. 2009 Mar 27; 373(9668):1041–9.
8. World Health Statistics 2011 [Internet]. WHO. [cited 2017 Feb 4]. Available from: http://www.who.int/whosis/whostat/2011/en/
9. Zynia L R, Andrew C. THE BURDEN OF DISEASE IN THE WEST BANK AND GAZA AN ASSESSMENT REPORT. 2000 Feb;
10. WHO. Health conditions in the occupied Palestinian territory, including east Jerusalem, and in the occupied Syrian Golan. 2016 May 6;2–59.
11. PCBS 2016. palestinian central bureau of statistic.
12. Report WHO Expert. WHO | Waist circumference and waist–hip ratio [Internet]. WHO. 2008 [cited 2018 Feb 15]. Available from: http://www.who.int/nutrition/publications/obesity/WHO_report_waistcircumference_and_waisthip_ratio/en/
13. American Diabetes Association 2016. ADA Diabetes Management Guidelines A1C Diagnosis | NDEI [Internet]. [cited 2018 Jan 22]. Available from: http://www.ndei.org/ADA-diabetes-management-guidelines-diagnosis-A1C-testing.aspx.html
14. James PA, Oparil S, Carter BL, Cushman WC, Dennison-Himmelfarb C, Handler J, et al. 2014 evidence-based guideline for the management of high blood pressure in adults: report from the panel members appointed to the Eighth Joint National Committee (JNC 8). JAMA. 2014 Feb 5; 311(5):507–20. https://doi.org/10.1001/jama.2013.284427 PMID: 24352797
15. WHO hypertension. WHO | Q&As on hypertension [Internet]. WHO. 2015 [cited 2018 Jan 9]. Available from: http://www.who.int/features/qa/82/en/index.html
16. Chen Y, Zhang X, Pan B, Jin X, Yao H, Chen B, et al. A modified formula for calculating low-density lipoprotein cholesterol values. Lipids Health Dis. 2010 May 21; 9:52. https://doi.org/10.1186/1476-511X-9-52 PMID: 20487572
17. National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III). Third Report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III) final report. Circulation. 2002 Dec 17; 106(25):3143–421. PMID: 12485966

18. Al-Nozha MM, Arafah MR, Al-Mazrou YY, Al-Maatouq MA, Khan NB, Khalil MZ, et al. Coronary artery disease in Saudi Arabia. Saudi Med J. 2004 Sep; 25(9):1165–71. PMID: 15448760
19. Zeidan RK, Farah R, Chahine MN, Asmar R, Hosseini H, Salameh P, et al. Prevalence and correlates of coronary heart disease: first population-based study in Lebanon. Vasc Health Risk Manag. 2016 Mar 17; 12:75–84. https://doi.org/10.2147/VHRM.S97252 PMID: 27051290
20. Nsour M, Mahfoud Z, Kanaan MN, Balbeissi A. Prevalence and predictors of nonfatal myocardial infarction in Jordan. East Mediterr Health J Rev Sante Mediterr Orient Al-Majallah Al-Sihhiyah Li-Sharq Al-Mutawassit. 2008 Aug; 14(4):818–30.
21. Farah R, Zeidan RK, Chahine MN, Asmar R, Chahine R, Salameh P, et al. Prevalence of stroke symptoms among stroke-free residents: first national data from Lebanon. Int J Stroke. 2015 Oct 1; 10 (SA100):83–8. https://doi.org/10.1111/ijs.12563 PMID: 26178607
22. El-Hajj M, Salameh P, Rachidi S, Hosseini H. The epidemiology of stroke in the Middle East. Eur Stroke J. 2016 Sep 1; 1(3):180–98.
23. Benamer HT, Grosset D. Stroke in Arab countries: A systematic literature review. J Neurol Sci. 2009 Sep 15; 284(1–2):18–23. https://doi.org/10.1016/j.jns.2009.04.029 PMID: 19428027
24. Sawalha A. Characterization of Hospitalized Ischemic Stroke Patients in Palestine. Libyan J Med [Internet]. 2009 [cited 2017 Feb 7]; 4(2). Available from: http://www.libyanjournalofmedicine.net/index.php/ljm/article/view/4803
25. Sweileh WM, Sawalha AF, Al-Aqad SM, Zyoud SH, Al-Jabi SW. The Epidemiology of Stroke in Northern Palestine: A 1-Year, Hospital-Based Study. J Stroke Cerebrovasc Dis. 2008 Nov; 17(6):406–11. https://doi.org/10.1016/j.jstrokecerebrovasdis.2008.06.008 PMID: 18984436
26. Forouzanfar MH, Bhutta ZA, Burnett R, Cercy K, Charlson FJ, Cohen AJ, et al. Global, regional, and national comparative risk assessment of 79 behavioural, environmental and occupational, and metabolic risks or clusters of risks, 1990–2015: a systematic analysis for the Global Burden of Disease Study 2015. The Lancet. 2016 Oct 8; 388(10053):1659–724.
27. Seita A, Khader A, Shahin Y, Hababeeh M, Zeidan W, Turki Y, et al. UNRWA Health Annual Report 2016 (published May 2017). 2017.
28. Joffres M, Falaschetti E, Gillespie C, Robitaille C, Loustalot F, Poulter N, et al. Hypertension prevalence, awareness, treatment and control in national surveys from England, the USA and Canada, and correlation with stroke and ischaemic heart disease mortality: a cross-sectional study. BMJ Open. 2013 Aug 1; 3(8):e003423. https://doi.org/10.1136/bmjopen-2013-003423 PMID: 23996822
29. Musaiger AO. Overweight and Obesity in Eastern Mediterranean Region: Prevalence and Possible Causes. J Obes [Internet]. 2011 [cited 2018 Jan 27];2011. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3175401/
30. Abdul-Rahim HF, Abu-Rmeileh NM, Husseini A, Holmboe-Ottesen G, Jervell J, Bjertness E. Obesity and selected co-morbidities in an urban Palestinian population. Int J Obes Relat Metab Disord J Int Assoc Study Obes. 2001 Nov; 25(11):1736–40.
31. CDC. CDC Works 24/7 [Internet]. Centers for Disease Control and Prevention. 2017 [cited 2017 Feb 14]. Available from: https://www.cdc.gov/index.htm
32. Kaluski DN, Berry EM. Prevalence of obesity in Israel. Obes Rev Off J Int Assoc Study Obes. 2005 May; 6(2):115–6.
33. Maatoug J, Harrabi I, Hmad S, Belkacem M, Nouira A, Ghannem H. Advising Obese Adults about Diet and Physical Activity in Sousse, Tunisia [Internet]. International Scholarly Research Notices. 2013 [cited 2018 Jan 27]. Available from: https://www.hindawi.com/journals/isrn/2013/498527/
34. Noncommunicable diseases country profiles 2014-WHO global report [Internet]. 2018 [cited 2018 Feb 23]. Available from: http://www.euro.who.int/en/health-topics/noncommunicable-diseases/ncd-background-information/noncommunicable-diseases-country-profiles-2014
35. Khudairy LA, Rees K, Kumar S, Al-Daghri N, Attas OA, Okail MA, et al. Abstract P263: Central Obesity and the Emerging Epidemic of Type 2 Diabetes in Saudi Arabia. Circulation. 2015 Mar 10; 131(Suppl 1):AP263–AP263.
36. Giovino GA, Mirza SA, Samet JM, Gupta PC, Jarvis MJ, Bhala N, et al. Tobacco use in 3 billion individuals from 16 countries: an analysis of nationally representative cross-sectional household surveys. The Lancet. 2012; 380(9842):668–679.
37. Sibai AM, Iskandarani M, Darzi A, Nakkash R, Saleh S, Fares S, et al. Cigarette smoking in a Middle Eastern country and its association with hospitalisation use: a nationwide cross-sectional study. BMJ Open [Internet]. 2016 Apr 8 [cited 2017 Jan 29]; 6(4). Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4838686/
38. Khattab A, Javaid A, Iraqi G, Alzaabi A, Ben Kheder A, Koniski M-L, et al. Smoking habits in the Middle East and North Africa: results of the BREATHE study. Respir Med. 2012 Dec; 106 Suppl 2:S16–24.

39. Radaideh G, Tzemos N, Ali TM, Eldershaby Y, Joury J, Abreu P. Cardiovascular Risk Factor Burden in the United Arab Emirates (UAE): The Africa Middle East (AfME) Cardiovascular Epidemiological (ACE) Study Sub-analysis. Int Cardiovasc Forum J [Internet]. 2017 Jun 3 [cited 2018 Jan 26]; 11(0). Available from: http://icfjournal.org/index.php/icfj/article/view/414

40. Kahan D. Adult physical inactivity prevalence in the Muslim world: Analysis of 38 countries. Prev Med Rep. 2015 Jan 1; 2:71–5. https://doi.org/10.1016/j.pmedr.2014.12.007 PMID: 26844051

41. Mabry RM, Reeves MM, Eakin EG, Owen N. Evidence of physical activity participation among men and women in the countries of the Gulf cooperation council: a review. Obes Rev Off J Int Assoc Study Obes. 2010 Jun; 11(6):457–64.

42. Saeed AA, Al-Hamdan NA, Al-Zalabani AH. The prevalence of physical activity and its socioeconomic correlates in Kingdom of Saudi Arabia: A cross-sectional population-based national survey. 2015 [cited 2018 Mar 10]; Available from: http://repository.taibahu.edu.sa/handle/123456789/14235.

43. Hall JN, Moore S, Harper SB, Lynch JW. Global variability in fruit and vegetable consumption. Am J Prev Med. 2009 May; 36(5):402–409.e5. https://doi.org/10.1016/j.amepre.2009.01.029 PMID: 19362694

IV.2. Article 2: Epidemiology of Lower Extremity Artery Disease in Gaza –Palestine

Contexte de l'étude

L'Artériopathie oblitérante des membres inférieurs (AOMI) est une des expressions de l'athérosclérose, L'AOMI est bien définie par la mesure de l'index de pression systolique. Concernant les pays du Moyen-Orient, les quelques études qui existent sur l'artériopathie sont menées chez les patients diabétiques. Aucune donnée dans la littérature ne porte sur l'incidence ou la prévalence de l'artériopathie en Palestine même en milieu hospitalier.

Méthodologie

À travers une étude transversale, 12 infirmiers diplômés, formés à la prise de l'index de pression systolique ont mesuré cet index sur un échantillon de 1398 personnes d'âge supérieur à 40 ans. Ils ont aussi documenté les facteurs de risque cardio vasculaire pour tous les participants.

L'objectif de l'étude

Décrire l'épidémiologie de l'artériopathie des membres inférieurs dans la population de 40 ans et plus de la bande de Gaza et les facteurs de risque associés.

Valorisation de l'étude

L'étude est soumise à 'International journal Cardiology (IF :4.034)

Communications

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Epidemiology of Lower Extremity Artery Disease in Gaza – Palestine

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Abstract:

Objectives**:** Lower Extremity artery disease (LEAD) is one of the most common manifestations of atherosclerosis affecting more than 200 million people globally, but little is known about its epidemiology in Middle East populations, particularly in Arab countries. The present study was undertaken to assess the prevalence of

LEAD in the general population aged 40 years and more in Gaza-Palestine, and to determine the prevalence of its associated risk factors.

Methods: The study design was a cross-sectional with a stratified proportional sampling, involving the five governorates in Gaza Strip. We selected 1490 individuals aged age ≥ 40 years living in the area for more than 3 years. Questionnaire on lifestyle and cardiovascular risk factors was applied and the ankle-brachial index (ABI) was measured by Doppler examination in both legs in all participants. LEAD was defined as an ABI < 0.90. We excluded 92 participants (6%) because of missing ABI or ABI >1.40.

Results: One-half of the 1398 participants had at least two associated cardiovascular risk factors. Overall, we found LEAD in 191 (13.7%) cases. This prevalence increased with age and was higher in females than in males (respectively15.6% *vs* 11.6% p=0.031). In the multivariate logistic regression model, significant associated factors with LEAD in male were overweight (OR:3.7; 95% CI 1.4-9.9), CAD (OR:3.6; 95% CI1.4-9.1), hypertension (OR: 3.0; 95% CI:1.3-6.8), and Current smoking (OR:2.7;95% CI1.1-6.8). In women Hypertension remain the main associated risk factor.

Conclusion: Our study highlights the high prevalence of LEAD in Gazan community, mostly related to the high prevalence of cardiovascular risk factors and other cardiovascular conditions.

Keywords: Lower extremity artery disease, prevalence, risk factors, community.

1.Introduction

Lower extremity artery disease is one of the most frequent manifestations of systemic atherosclerosis. It is an indicator of widespread atherosclerosis in other vascular territories. It represents the third leading cause of atherosclerotic cardiovascular morbidity, following coronary artery disease (CAD) and stroke. The WHO estimates that in year 2010 about 140.8 million (69%-70%) people with LEAD were living in low- and middle-income countries (LMIC), of whom (10.3 million) in the Eastern Mediterranean region. The burden of LEAD has raised by 23.5% from 2000 to 2010 with greater increase in (LMIC), where the prevalence rates were reported higher in women[1–3].About 10-20% of patients with LEAD have intermittent claudication[4]. However, even if the disease is often asymptomatic; a screening strategy is meaningful to identify individuals at high risk of death, major cardiovascular events, as well as limb events, including amputation, in the most severe cases [5]. Several, studies demonstrated that LEAD (either symptomatic or asymptomatic) is associated with a three to six-fold risk of death, from cardiovascular disease (CVD) morbidity[6,7]. Patients with LEAD are now considered as coronary artery disease equivalent risk [8]. This disease can be easily diagnosed by the measurement of the ankle brachial index (ABI), convenient for screening LEAD in population. It can be used to stratify the severity and potentially helpful to evaluate CVD risk and guide preventive intervention [9]. LEAD shares common risk factors with CAD including ageing, diabetes, hypertension, smoking, and male gender[8]. Its prevalence has been extensively described in high income countries (HIC) populations. The association

between cardiovascular risk factors and LEAD was also been documented in these settings. Regarding the Middle East countries, few data are available, most of them being hospital-based[10]. Our aim in this report is to describe the epidemiology of LEAD in the Gazan community. We hypothesized that, in regards to the high CVD risk factors and other atherosclerosis disease[11], the prevalence of LEAD would be high in this part of the world.

2. Material and methods

2.1 Study design

This study was part of a first epidemiological study conducted from July to September 2017 among 2240 individuals in age ≥25 years, recruited from a stratified proportional sample in five Palestinian governorates of the Gaza strip (the method was previously described)[11]. The STEPS wise approach was adopted: In each governorate, 2-3 urban and rural areas were randomly chosen, of which 20-30 households were selected in every area. The ABI was measured in all adults ≥40 years of age. In this study 1490 individuals, were enrolled. Among them 92 subjects were excluded from the analysis due to either an ABI>1.40 (89 subjects,4.6%) or incomplete exam (3 subjects). Overall 1398 subjects remained for analysis (Figure1).

A standardized questionnaire was used to obtain demographic and information about level of education, monthly household income as well as cardiovascular risk factors and medication use. For tobacco use, subjects were classed as never, past, and current smokers. History of coexisting CVD was documented. CAD was defined as self-reported with either angina pectoris or myocardial infarction, or

history of procedures performing percutaneous coronary intervention or coronary bypass graft. Cerebrovascular disease (CBVD) was defined as documented history of stroke. Height and weight were measured with participants wearing light clothing and no shoes in order to determine the body mass index (BMI) calculated as weight in Kilograms divided by height in meters squared, and the cut-off points of WHO for BMI were used to define obesity as ≥ 30 kg/m^2. For hypertension (HTN), we considered subjects as hypertensive if their average systolic blood pressure (SBP) in both arms was ≥140 mmHg or their average diastolic blood pressure (DBP) ≥ 90 mmHg, or if they were being treated for HTN [12]. Diabetes mellitus (DM) was defined if capillary blood glucose level ≥126 mg/dl in fasting participants, or ≥ 200 mg/dl in non-fasting participants, or if they were taking any anti-diabetic medications [13]. Blood sample for lipids profiles were taken by nurse's staff from antecubital vein and sent to the laboratory for analysis using standard methods. We defined high plasma of total cholesterol ≥ 240 mg/dl, plasma triglycerides ≥150 mg/dl, low density lipid cholesterol (LDL) ≥ 160 mg/dl, and high density lipoprotein cholesterol (HDL) ≤ 40 mg/dl in males and ≤ 50 mg/dl in females [14].

The ABI was measured following the AHA statement standardized protocol using the Doppler method[15]. The leg-specific ABI was calculated as the higher SBP in the posterior tibial or dorsalis pedis divided by the higher of the 2 arms SBP. For each subject, LEAD was defined by an ABI < 0.90 in either leg. Patients with an ABI >1.40 were excluded from this analysis n=89 (6%).

The Ethical of Human Research Committee of Palestinian Health Research Council approved the study protocol, and each participant consented, either written or verbal according to his education level, to participle in this study.

2.2 Statistical Analysis

The statistical analyses were performed using SPSS software version 22. Descriptive analyses were done using means and standard deviation or percentages. Confidence intervals were estimated using normal approximation. Student's *t*-.test and the Chi-square test were used for comparison of continuous and categorical variables respectively. Multiple logistic regression analyses were performed using LEAD as the dependent variable and risk factors as independent variables separately in male and female. Variables with a univariate p value < 0.25 were selected for further multivariate analysis. A p-value < 0.05 was considered as significance level.

3. Results

Among the 1398 participants 733 (52.4%) were females. The mean age of the general population was 55.2 ±10.6 years, with nearly one-third (33.4%) over age of 60. The characteristics of the study population stratified by ABI categories are displayed in Table 1. Subjects with LEAD were more likely to be old and female, with significantly higher rates of hypertension, diabetes, history of CAD and stroke as compared to LEAD-free participants. In the LEAD group statins and antiplatelet drugs were prescribed in only 22.5% and 43.5% of the cases respectively.

The prevalence of LEAD was 13.7% (95% CI,11.8-15.4). The prevalence of LEAD by selected characteristics are displayed in Table 2. Notably, the prevalence of the LEAD was higher in females. In both genders; the prevalence of LEAD increased with age ranging from 6.7% in the age category 40 to 49 years to 20.5% in the age category ≥70 years in males, and from 15.3% to 23.2% in the corresponding age categories in females (Figure 2). In addition, CAD and stroke history were more frequent in case of LEAD, both in males and females (Figure 3).

The logistic regression analysis was separately presented in male and female (Table 3 and Table 4). In multivariate analysis in male gender, and by order of penetrance: overweight, history of CAD, hypertension and being smoking were the strongest associated factors with LEAD (OR= 3.7, 3.6, 3.0 and 2.7 respectively). In female The ORs remained significant for hypertension (OR=2.5,95%CI:1.66-3.76, p<0.001).

4.Discussion

This is the first study reporting data on epidemiology of LEAD in the Palestinian community. These results show that LEAD affects 13.7% of adult population ≥ 40years of age. Data regarding LEAD in Arab countries are limited. In a cross-sectional study in Saudi Arabia, among 598 diabetics ≥ 30 years of age, the prevalence of LEAD was 23.1% [16]. Another cross-sectional study in Bahrain evaluated 1477 diabetics patients with ages ranging from 18 to 75 years, reporting a LEAD prevalence of 11.8%[17]. In 2004-2005, the Global Atherothrombosis Assessment Middle East (AGATHA-ME) a multicenter study conducted in five neighboring countries of similar ethnicity and small population from Middle East,

included 1342 patients recruited from tertiary care settings either with CVD or without CVD but at risk for developing it. Low ABI (≤0.90) was highly prevalent in both groups (31.5% in the at risk group and 28.2% in the CVD group).[18] The most comprehensive report on global LEAD prevalence in communities was published in 2013, but the authors did not identify any contributive study from the Middle East countries[1]. The prevalence described in the Gazan community is close to the data collected in high-income countries (HIC), with an increase with age in both sexes. In the group of 60-70 years of age the prevalence was up to 15.9% in our study compared to 8-10% in HIC [1]. The female's predominance was previously described in LMIC, as opposed to higher prevalence in males in HIC. However, the particularity of our community is in that smoking habits are almost totally absent among women (0.7%). The female's predominance in our study is driven by the burden of the other associated risk factors. Obesity, diabetes and hypertension were highly prevalent up to 70%, 27% and 42% respectively. In the Rotterdam study 7715 subjects aged ≥ 55 years were included with a higher prevalence in females (20.5% *vs.* 16.9% in males)[19]. The NHANES study 1999-2004 showed that in participants within the 40-69 years age range, females were 1.77 times more likely to have LEAD than males[20]. This higher prevalence in women may be partly explained, by postmenopausal hormonal effects, characterized by an estrogen deficiency responsible for increased risk of developing CVD[21]. Finally, a smaller threshold for ABI in men and women may lead to a slight overestimation of LEAD in women who have intrinsically a lower ABI[22].

Hypertension, diabetes, smoking, hyperlipidemia, and advancing age are the major risk factors for LEAD [23]. In the Framingham study the relative risks of LEAD related to diabetes and hypertension were of 2 and 1.5 respectively[24]. This relationship appeared in our study with similar risk in univariate analysis. In most of studies LEAD was strongly associated with smoking[25–27]. We found this association only in men. However very few women smoke (0.7%). Our findings do not support the hypothesis that total serum cholesterol and triglycerides increase the risk of LEAD, but 15.8% of the subject were taking lipids lowering drugs, thus lipids levels were influenced by treatment. Numerous studies reported a weak association between dyslipidemia and LEAD, in LMIC the relative risk were for hypercholesterolemia and hypertriglyceridemia at 1.14 and 1.13 respectively[1]. Regarding obesity similar results were observed in several study without association with LEAD[28]. The association between LEAD and other manifestation of atherosclerosis was extensively well documented. LEAD is a strong marker of risk of CAD or stroke. In our study, a history of CAD, and stroke were each approximatively twice as more frequent in those with LEAD. This is in line with the Cardiovascular Health Study (CHS) reporting the history of myocardial infarction as 2.5 times higher in subjects with LEAD. This odd-ratio was at 3.1 for stroke[29]. In the CAPRIE trial; 41% of patient with LEAD had either CAD or CBVD and 8.6% had disease in all three beds[30,31]. Also, in the Reduction of Atherothrombosis for Continued Health (REACH) registry data for 44 countries worldwide which included 55,814 patients ≥ 45 years of age, with established atherothrombotic disease (CAD, CVD, or LEAD),14.9% of patients had

documented symptomatic LEAD (7.8% in Middle East), and LEAD patients had a higher prevalence of concomitant vascular disease (61.5% having either CAD, CBVD, or both)[32].

5. Strengths and Limitations

This study collected many epidemiological information regarding the prevalence of LEAD in a large sample representative of the general population from a region with high prevalence of risk factors. No data have been ever published in this area, where undertaking an epidemiology study is difficult because of the particular geopolitical aspects. There are however some limitations: because of its cross-sectional design, the associations found cannot prove causality. The use of self-reported data for some risk factors could underestimate the actual prevalence of associate risk factors, mainly for CAD, stroke and smoking. Smoking status was declarative and probably the number of smokers may be under evaluated in male population. This study may be subject to survival bias, since the study was conducted in homes and participants with chronic disease may be the most likely to participate in the study.

6. Conclusion

This is the first study assessing the prevalence of LEAD in general population in Palestine and even in the Arab world. Our results suggested that there is a significant association between LEAD and the leading risk factors such as hypertension, diabetes, and older age. The higher rate reported in females supports other reports with similar results in LMIC. However, LEAD continues to be under-diagnosed and under-treated. Physicians education and training should

be improved for a better identification of the asymptomatic LEAD and increase the awareness of its consequences and need for intensive preventive measures.

7. Conflict of interest

The author reports no conflicts of interest in this work.

References

[1] F.G.R. Fowkes, D. Rudan, I. Rudan, V. Aboyans, J.O. Denenberg, M.M. McDermott, P.E. Norman, U.K.A. Sampson, L.J. Williams, G.A. Mensah, M.H. Criqui, Comparison of global estimates of prevalence and risk factors for peripheral artery disease in 2000 and 2010: a systematic review and analysis, Lancet. 382 (2013) 1329–1340. doi:10.1016/S0140-6736(13)61249-0.

[2] E.J. Benjamin, M.J. Blaha, S.E. Chiuve, M. Cushman, S.R. Das, R. Deo, S.D. de Ferranti, J. Floyd, M. Fornage, C. Gillespie, C.R. Isasi, M.C. Jiménez, L.C. Jordan, S.E. Judd, D. Lackland, J.H. Lichtman, L. Lisabeth, S. Liu, C.T. Longenecker, R.H. Mackey, K. Matsushita, D. Mozaffarian, M.E. Mussolino, K. Nasir, R.W. Neumar, L. Palaniappan, D.K. Pandey, R.R. Thiagarajan, M.J. Reeves, M. Ritchey, C.J. Rodriguez, G.A. Roth, W.D. Rosamond, C. Sasson, A. Towfighi, C.W. Tsao, M.B. Turner, S.S. Virani, J.H. Voeks, J.Z. Willey, J.T. Wilkins, J.H. Wu, H.M. Alger, S.S. Wong, P. Muntner, O. behalf of the A.H.A.S.C. and S.S. Subcommittee, Heart Disease and Stroke Statistics—2017 Update: A Report From the American Heart Association, Circulation. (2017). doi:10.1161/CIR.0000000000000485.

[3] K. Srivaratharajah, B.L. Abramson, Women and Peripheral Arterial Disease: A Review of Sex Differences in Epidemiology, Clinical Manifestation and Outcomes, Canadian Journal of Cardiology. (2018). doi:10.1016/j.cjca.2018.01.009.

[4] A.T. Hirsch, M.H. Criqui, D. Treat-Jacobson, J.G. Regensteiner, M.A. Creager, J.W. Olin, S.H. Krook, D.B. Hunninghake, A.J. Comerota, M.E. Walsh, M.M. McDermott, W.R. Hiatt, Peripheral arterial disease detection, awareness, and treatment in primary care, JAMA. 286 (2001) 1317–1324.

[5] J.E. Lewis, P. Williams, J.H. Davies, Non-invasive assessment of peripheral arterial disease: Automated ankle brachial index measurement and pulse volume analysis compared to duplex scan, SAGE Open Med. 4 (2016). doi:10.1177/2050312116659088.

[6] F.G.R. Fowkes, G.D. Murray, I. Butcher, C.L. Heald, R.J. Lee, L.E. Chambless, A.R. Folsom, A.T. Hirsch, M. Dramaix, G. deBacker, J.-C. Wautrecht, M. Kornitzer, A.B. Newman, M. Cushman, K. Sutton-Tyrrell, F.G.R. Fowkes, A.J. Lee, J.F. Price, R.B. d'Agostino, J.M. Murabito, P.E. Norman, K. Jamrozik, J.D. Curb, K.H. Masaki, B.L. Rodríguez, J.M. Dekker, L.M. Bouter, R.J. Heine, G. Nijpels, C.D.A. Stehouwer, L. Ferrucci, M.M. McDermott, H.E. Stoffers, J.D. Hooi, J.A. Knottnerus, M. Ogren, B. Hedblad, J.C. Witteman, M.M.B. Breteler, M.G.M. Hunink, A. Hofman, M.H. Criqui, R.D. Langer, A. Fronek, W.R. Hiatt, R. Hamman, H.E. Resnick, J. Guralnik, M.M. McDermott, Ankle brachial index combined with Framingham Risk Score to predict cardiovascular events and mortality: a meta-analysis, JAMA. 300 (2008) 197–208. doi:10.1001/jama.300.2.197.

[7] J.M. Murabito, J.C. Evans, M.G. Larson, K. Nieto, D. Levy, P.W.F. Wilson, Framingham Study, The ankle-brachial index in the elderly and risk of stroke, coronary disease, and death: the Framingham Study, Arch. Intern. Med. 163 (2003) 1939–1942. doi:10.1001/archinte.163.16.1939.

[8] J.W. Olin, B.A. Sealove, Peripheral Artery Disease: Current Insight Into the Disease and Its Diagnosis and Management, Mayo Clin Proc. 85 (2010) 678–692. doi:10.4065/mcp.2010.0133.

[9] American College of Cardiology Foundation, American Heart Association Task Force on Performance Measures, American College of Radiology, Society for Cardiac Angiography and Interventions, Society for Interventional Radiology, Society for Vascular Medicine, Society for Vascular Nursing, Society for Vascular Surgery, J.W. Olin, D.E. Allie, M. Belkin, R.O. Bonow, D.E. Casey, M.A. Creager, T.C. Gerber, A.T. Hirsch, M.R. Jaff, J.A. Kaufman, C.A. Lewis, E.T. Martin, L.G. Martin, P. Sheehan, K.J. Stewart, D. Treat-Jacobson, C.J. White, Z.-J. Zheng, ACCF/AHA/ACR/SCAI/SIR/SVM/SVN/SVS 2010 performance measures for adults with peripheral artery disease. A report of the American College of Cardiology Foundation/American Heart Association Task Force on Performance Measures, the American College of Radiology, the Society for Cardiac Angiography and Interventions, the Society for Interventional Radiology, the Society for Vascular Medicine, the Society for Vascular Nursing, and the Society for Vascular Surgery (Writing Committee to Develop Clinical Performance Measures for Peripheral Artery Disease). Developed in collaboration with the American Association of Cardiovascular and Pulmonary Rehabilitation; the American Diabetes Association; the Society for Atherosclerosis Imaging and Prevention; the Society for Cardiovascular Magnetic Resonance; the Society of Cardiovascular Computed Tomography; and the PAD Coalition. Endorsed by the American Academy of Podiatric Practice Management, J. Vasc. Surg. 52 (2010) 1616–1652. doi:10.1016/j.jvs.2010.10.065.

[10] E.W. Gregg, P. Sorlie, R. Paulose-Ram, Q. Gu, M.S. Eberhardt, M. Wolz, V. Burt, L. Curtin, M. Engelgau, L. Geiss, 1999-2000 national health and nutrition examination survey, Prevalence of lower-extremity disease in the US adult population >=40 years of age with and without diabetes: 1999-2000 national health and nutrition examination survey, Diabetes Care. 27 (2004) 1591–1597.

[11] A. Jamee.Shahwan, Y. Abed, J. Magne, Victor Aboyans, P.M. Preux, I. Desormais, P. Lacroix, Epidemiology of cardiovascular disease and associated factors in Gaza-Palestine, PLOS ONE. (2019).

[12] WHO hypertension, WHO | Q&As on hypertension, WHO. (2015). http://www.who.int/features/qa/82/en/index.html (accessed January 9, 2018).

[13] American Diabetes Association 2016, ADA Diabetes Management Guidelines A1C Diagnosis | NDEI, (n.d.). http://www.ndei.org/ADA-diabetes-management-guidelines-diagnosis-A1C-testing.aspx.html (accessed January 22, 2018).

[14] National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III), Third Report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III) final report, Circulation. 106 (2002) 3143–3421.

[15] V. Aboyans, M.H. Criqui, P. Abraham, M.A. Allison, M.A. Creager, C. Diehm, F.G.R. Fowkes, W.R. Hiatt, B. Jönsson, P. Lacroix, B. Marin, M.M. McDermott, L. Norgren, R.L. Pande, P.-M. Preux, H.E. (Jelle) Stoffers, D. Treat-Jacobson, Measurement and Interpretation of the Ankle-Brachial Index: A Scientific Statement From the American Heart Association, Circulation. (2012) CIR.0b013e318276fbcb. doi:10.1161/CIR.0b013e318276fbcb.

[16] H. Alzahrani, D. Wang, B. A Bakhotmah, F. B Hu, Risk factors for peripheral artery disease among patients with diabetes in Saudi Arabia, Vascular Medicine (London, England). 19 (2014). doi:10.1177/1358863X14526948.

[17] F. Al-Mahroos, K. Al-Roomi, Diabetic neuropathy, foot ulceration, peripheral vascular disease and potential risk factors among patients with diabetes in Bahrain: a nationwide primary care diabetes clinic-based study, Ann Saudi Med. 27 (2007) 25–31.

[18] A. El-Menyar, J. Al Suwaidi, H. Al-Thani, Peripheral arterial disease in the Middle East: Underestimated predictor of worse outcome, Glob Cardiol Sci Pract. 2013 (2013) 98–113. doi:10.5339/gcsp.2013.13.

[19] W.T. Meijer, A.W. Hoes, D. Rutgers, M.L. Bots, A. Hofman, D.E. Grobbee, Peripheral arterial disease in the elderly: The Rotterdam Study, Arterioscler. Thromb. Vasc. Biol. 18 (1998) 185–192.

[20] J.F. Reed, Risk Factors for Peripheral Arterial Disease in United States Asymptomatic Patients Aged 40 – 69 and Asymptomatic Patients Aged ≥ 70: Results from NHANES 1999-

2004, The Internet Journal of Epidemiology. 7 (2008). http://ispub.com/IJE/7/2/4615 (accessed May 21, 2018).
[21] L. Nguyen, D.R. Liles, P.H. Lin, R.L. Bush, Hormone replacement therapy and peripheral vascular disease in women, Vasc Endovascular Surg. 38 (2004) 547–556. doi:10.1177/153857440403800609.
[22] V. Aboyans, M.H. Criqui, R.L. McClelland, M.A. Allison, M.M. McDermott, D.C. Goff, T.A. Manolio, Intrinsic contribution of gender and ethnicity to normal ankle-brachial index values: the Multi-Ethnic Study of Atherosclerosis (MESA), J. Vasc. Surg. 45 (2007) 319–327. doi:10.1016/j.jvs.2006.10.032.
[23] A.S. Khan, M. Isik, T. Set, Z. Akturk, U. Avsar, A 5-year trend of myocardial infarction, hypertension, stroke and diabetes mellitus in gender and different age groups in Erzurum, Turkey, Journal of Taibah University Medical Sciences. 9 (2014) 198–205.
[24] W.B. Kannel, Fifty years of Framingham Study contributions to understanding hypertension, J Hum Hypertens. 14 (2000) 83–90.
[25] F.G. Fowkes, E. Housley, R.A. Riemersma, C.C. Macintyre, E.H. Cawood, R.J. Prescott, C.V. Ruckley, Smoking, lipids, glucose intolerance, and blood pressure as risk factors for peripheral atherosclerosis compared with ischemic heart disease in the Edinburgh Artery Study, Am. J. Epidemiol. 135 (1992) 331–340.
[26] V.C. del Río, J. Mostaza, C. Lahoz, V. Sánchez-Arroyo, C. Sabín, S. López, P. Patrón, P. Fernández-García, B. Fernández-Puntero, D. Vicent, L. Montesano-Sánchez, F. García-Iglesias, T. González-Alegre, E. Estirado, F. Laguna, C. de Burgos-Lunar, P. Gómez-Campelo, J.C. Abanades-Herranz, J.M. de Miguel-Yanes, M.A. Salinero-Fort, on behalf S.-2 Group, Prevalence of peripheral artery disease (PAD) and factors associated: An epidemiological analysis from the population-based Screening PRE-diabetes and type 2 DIAbetes (SPREDIA-2) study, PLOS ONE. 12 (2017) e0186220. doi:10.1371/journal.pone.0186220.
[27] E. Selvin, T.P. Erlinger, Prevalence of and risk factors for peripheral arterial disease in the United States: results from the National Health and Nutrition Examination Survey, 1999-2000, Circulation. 110 (2004) 738–743. doi:10.1161/01.CIR.0000137913.26087.F0.
[28] M.H. Criqui, V. Aboyans, Epidemiology of Peripheral Artery Disease, Circulation Research. 116 (2015) 1509–1526. doi:10.1161/CIRCRESAHA.116.303849.
[29] A.B. Newman, D.S. Siscovick, T.A. Manolio, J. Polak, L.P. Fried, N.O. Borhani, S.K. Wolfson, Ankle-arm index as a marker of atherosclerosis in the Cardiovascular Health Study. Cardiovascular Heart Study (CHS) Collaborative Research Group., Circulation. 88 (1993) 837–845. doi:10.1161/01.CIR.88.3.837.
[30] CAPRIE Steering Committee, A randomised, blinded, trial of clopidogrel versus aspirin in patients at risk of ischaemic events (CAPRIE). CAPRIE Steering Committee, Lancet. 348 (1996) 1329–1339.
[31] K. Ouriel, Peripheral arterial disease, Lancet. 358 (2001) 1257–1264. doi:10.1016/S0140-6736(01)06351-6.
[32] P.P. Cacoub, M.T.B. Abola, I. Baumgartner, D.L. Bhatt, M.A. Creager, C.-S. Liau, S. Goto, J. Röther, P.G. Steg, A.T. Hirsch, REACH Registry Investigators, Cardiovascular risk factor control and outcomes in peripheral artery disease patients in the Reduction of Atherothrombosis for Continued Health (REACH) Registry, Atherosclerosis. 204 (2009) e86-92. doi:10.1016/j.atherosclerosis.2008.10.023.

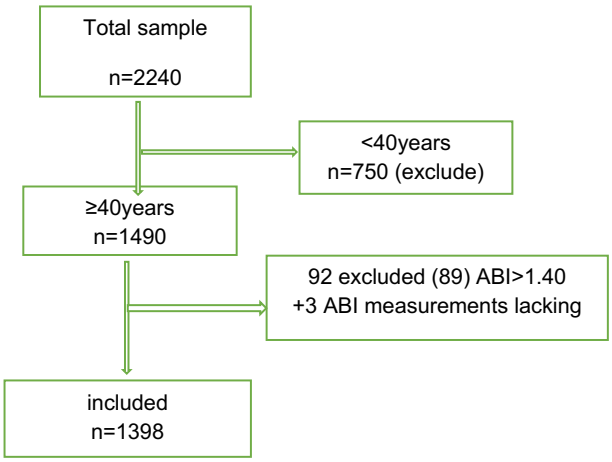


Figure 1: Flowchart of the study

Table1
Study population characteristics in Gaza-Palestine 2018

Variables	Total n=1398	LEAD n=191, 13.7%	No LEAD n=1207,86.3%	*P*. value
Age (years), mean	55.2±10.6	57.9±11.8	54.8±10.3	<0.001
Female, n (%)	733 (52.4)	114(59.7)	619 (51.3)	0.031
Never smoker, n (%)	1121(80.2)	157(82.2)	964 (79.9)	
Past smoking, n (%)	112 (8%)	9 (4.7)	103 (8.5)	0.180
Current smoking, n (%)	165 (11.8)	25 (13.1)	140 (11.6)	
Duration of smoking ≥ 25 years	111(7.9)	9 (4.7)	102 (8.5)	0.07
Hypertension, n (%)	544 (38.8)	117(61.3)	426 (35.3)	<0.001
Diabetes, n (%)	364 (26.0)	68 (35.6)	296 (24.5)	0.001
History of CAD*, n (%)	157(11.2)	36 (18.8)	121 (10.0)	<0.001
History of stroke, n (%)	59 (4.2)	14 (7.3)	45 (3.7)	0.021
Total Cholesterol level ≥ 240mg/dl, n (%)	138 (9.9)	21 (11.1)	117 (9.8)	0.582
Low HDL Cholesterol level, n (%)	1029 (73.6)	140 (73.3)	889 (73.7)	0.933
LDL Cholesterol level ≥160 mg/dl, n (%)	130 (9.4)	20 (10.6)	110 (9.2)	0.549
Triglycerides ≥ 150mg/dl, n (%)	636 (45.8)	88 (46.3)	548 (45.7)	0.883
Obesity n (%)	790 (56.5)	118 (61.8)	672 (55.7)	0.114
Statins, n (%)	221(15.8)	43 (22.5)	178 (14.7)	0.006
Aspirin, n (%)	462 (33.0)	83(43.5)	379(31.4)	0.001

Notes: Low HDL cholesterol level<40mg/dl in males and <50mg/dl in females, Obesity, body Mass Index≥ 30kg/m^2,
Abbreviations: CAD, coronary artery disease

Table 2
Prevalence of LEAD among adults aged 40 years in Gaza-Palestine 2018

Variables		LEAD		(95% CI)
		No	%	
Total individuals > 40years with LEAD		191	13.7	11.9-15.5
Gender	Male	77	11.6	9.1-14.1
	Female	114	15.6	12.9-18.3
Age group (years)	40-49	53	11.2	8.3-14.1
	50-59	54	11.8	8.8-14.8
	60-69	48	15.9	11.7-20.1
	70+	36	21.8	15.4-28.2
Hypertension	Yes	117	21.5	18.0-25.0
	No	74	8.7	6.8-11.0
Diabetes	Yes	68	18.7	14.6-22.8
	No	123	11.9	10.0-13.9
Smoking	Current	25	15.2	9.6-20.8
	Past	9	8.0	2.9-13.1
	Never	157	14.0	11.9-16.1
Duration of smoking (in years)	≥25y	25	15.1	9.5-20.7
	< 25y	9	8.1	2.9-13.3
Total cholesterol level ≥ 240 mg/dl	Yes	21	15.2	9.1-21.3
	No	169	13.5	11.6-15.5
Triglycerides ≥150 mg/dl	Yes	88	13.8	11.1-16.5
	No	102	13.6	11.1-16.1
Body Mass Index (kg/m^2)	18.5-24.9	28	15.9	10.4-21.4
	25-29.9	45	10.5	7.5-13.5
	≥30	118	14.9	12.4-17.4
History of CAD	Yes	36	22.9	16.2-29.6
	No	155	12.5	10.6-14.3
History of Stroke	Yes	14	23.7	12.6-34.8
	No	177	13.2	11.4-15.5

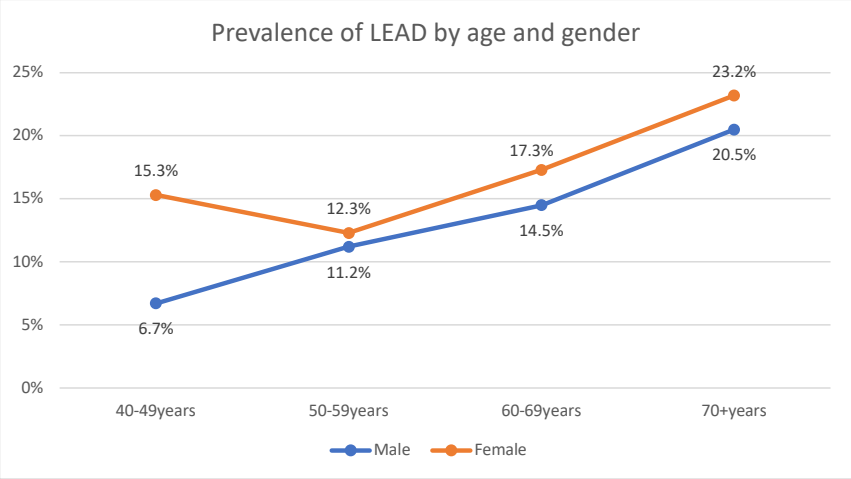
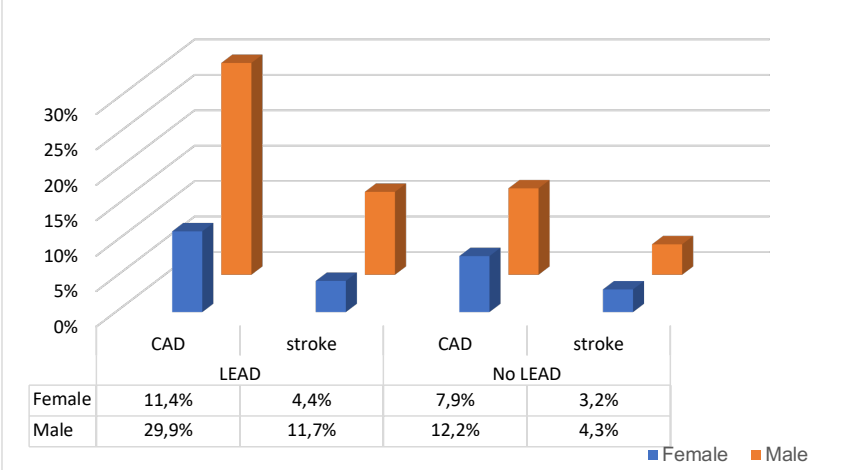


Figure 2 Prevalence of LEAD by age and gender in Gaza-Palestine 2018



	LEAD		No LEAD	
	CAD	stroke	CAD	stroke
Female	11,4%	4,4%	7,9%	3,2%
Male	29,9%	11,7%	12,2%	4,3%

Figure 3: Prevalence of CAD and Stroke by presence or absence of LEAD in Gaza-Palestine 2018

Table 3
Independent factors associated in males with LEAD in Gaza-Palestine 2018

Variables	Univariate analysis OR (95%CI)	p-value	Multivariate analysis OR (95%CI)	p-value
Age	0.96 (0.94-0.98)	<0.001		
Hypertension	3.5 (2.12-5.67)	<0.001	3.0 (1.32-6.84)	0.009
Diabetes	1.5 (0.92-2.57)	0.100		
Current smokers	1.6 (0.97-2.71)	0.068	2.7 (1.09-6.78)	0.031
Duration of smoking ≥ 25 years	0.5 (0.20-1.08)	0.073		
Total cholesterol level≥240mg/dl	0.6(0.26-1.43)	0.254		
Low HDL cholesterol	0.9 (0.53-1.50)	0.663		
LDL cholesterol>1.60	1.2 (0.52-3.11)	0.605		
Triglycerides ≥150 mg/dl	1.0 (0.64-1.67)	0.880		
History of CAD	3.1 (1.77-5.27)	<0.001	3.6 (1.38-9.13)	0.008
History of Stroke	3.0 (1.34-6.65)	0.008		
BMI 18.5-24.9 kg/m^2	1			
BMI 25-29.9 kg/m^2	2.6 (1.37-4.88)	0.003	3.7 (1.41-9.90)	0.008
BMI ≥30 kg/m^2	1.6 (0.91-2.91)	0.099		

Table 4
Independent factors associated in females with LEAD in Gaza-Palestine 2018

Variables	Univariate analysis		Multivariate analysis	
	OR (95%CI)	p-value	OR (95%CI)	p-value
Age	1.0 (0.97-1.00)	0.066		
Hypertension	2.5 (1.65-3.75)	<0.001	2.5 (1.66-3.76)	<0.001
Diabetes	1.8 (1.18-2.74)	0.006		
Current smokers*				
Duration of smoking ≥ 25 years*				
Total cholesterol level≥240mg/dl	1.1(0.61-2.05)	0.721		
Low HDL cholesterol	1.0 (0.65-1.64)	0.885		
LDL cholesterol>1.60	1.0 (0.56-1.92)	0.899		
Triglycerides ≥150 mg/dl	0.9 (0.61-1.36)	0.651		
History of CAD	1.5 (0.78-2.86)	0.221		
History of Stroke	1.4 (0.51-3.74)	0.543		
BMI 18.5-24.9 kg/m^2	1			
BMI 25-29.9 kg/m^2	0.7 (0.24-1.82)	0.420		
BMI ≥30 kg/m^2	0.6 (0.22-1.46)	0.238		

Current smoking and duration of smoking were not considered in the analysis due to small frequency

IV.3. Article 3: Epidemiology of the Metabolic Syndrome among the Palestinians in the Gaza Strip

Contexte de l'étude

Le syndrome métabolique est défini comme un véritable problème de santé publique. Il désigne la coexistence de désordres métaboliques, concourant à l'augmentation du risque cardio-vasculaire. La prévalence varie selon les pays en fonction de la définition choisie, de la population et de la méthodologie de l'étude. Au Moyen-Orient, le syndrome métabolique touche une personne sur quatre. Des études menées en Palestine décrivent une prévalence qui varie entre 17.1 à 23%. Mais aucune étude n'a signalé la relation entre les maladies cardiovasculaires (maladie coronarienne, accident vasculaire cérébral, artériopathie des membre inferieurs) et ce syndrome.

L'objectif de l'étude

Déterminer une prévalence récente du syndrome métabolique dans une large population et examiner les facteurs de risque d'athérosclérose et la relation avec les maladies cardiovasculaires associées.

Valorisation de l'étude

L'étude est soumise à 'Diabetes Metabolic Syndrome and Obesity' (IF : 2.961)

Communications

Prévoir une communication orale dans les mois qui viennent

REVIEW ORIGINAL RESEARCH

The Epidemiology of the Metabolic Syndrome among the Palestinians in the Gaza Strip

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Abstract:

The metabolic syndrome (MetS) is a major public health and clinical challenge worldwide. However limited data are available in the Gaza strip. This study was undertaken to evaluate the prevalence of MetS and its association with atherosclerotic risk factors and cardiovascular diseases among Gazan adults' community.

Methods: A cross sectional study was conducted in 2017, among all adults ≥ 25 years of age. Participants were selected by stratified cluster sampling method, in five governorates (urban and rural) of Gaza strip. Questionnaires on socioeconomic status, lifestyle and cardiovascular risk factors were completed for 2107 participants. The cardiovascular diseases included clinical history of coronary artery disease (CAD), Lower extremity artery disease (LEAD diagnosed as ankle brachial index < 0.90) and history of stroke. MetS was defined based on the International Diabetes Federation criteria (IDF).

Results: Among participants 864 (41 %) fulfilled the definition of MetS higher in females than males (50% vs 39%). In both genders MetS prevalence increased significantly with age (p<0.001). Subjects with MetS were more obese (73.0 % *vs* 29.4%), hypertensive (49.9% *vs* 13.0%), diabetic (36.8% *vs* 5.8%) and had more often low physical activity (58.1% *vs* 41.3%). Additionally, lipids profiles disorders were more prevalent in cases with MetS. We found MetS significantly associated with all cardiovascular conditions with odd-ratio (95%CI) respectively at 2.4 (95%CI 1.8-3.4) for CAD, 1.5 (95% CI1.1-1.9) for LEAD and 2.1(95% CI 1.3-3.5) for stroke.

Conclusion: The MetS is highly prevalent in the Palestinian population, particularly among women.

Key words: *Metabolic syndrome*, *risk factors*, *cardiovascular disease, Palestine*.

Introduction

The Metabolic syndrome (MetS) is a major public health and clinical challenge worldwide. it is defined as a cluster of clinical and metabolic disorders associated with increased risk of atherosclerosis cardiovascular disease (CVD) and mortality [1]. The overall prevalence of MetS varies according to geographic and socio-demographic factors, as well as the diagnostic criteria. Globally, the prevalence of MetS ranges from 10%-40% [2]. The MetS increases by 5-fold the risk of type 2 diabetes mellitus and 2-fold the risk of developing CVD[3]. Also, patients with MetS are 2-4 times more likely to die from cardiovascular events than those without MetS [4]. The MetS occurs more frequently through the combination of several factors and increase the cardiovascular risk beyond the risk associated with individual factors alone [5]. The risk increases with the number of MetS components present [6]. The syndrome occurs most often in populations characterized by high prevalence of obesity and physical inactivity[3]. The major causes leading to MetS are insulin resistance, obesity, unhealthy lifestyle, and genetic predisposition[7,8]. In the Middle-East region, the MetS affect one in four people [10]. In Palestine, some studies on MetS based on inhomogeneous criteria are available. The prevalence of MetS varies from 17.1% to 23%, however none

study reported the relationship between cardiovascular risk factors or CVD and MetS [11,12].

This study aims to determine a recent prevalence of MetS as defined by IDF criteria, and to examine the associated atherosclerotic risk factors and cardiovascular diseases among large Gazan community.

Methods

Subjects and study design

We conducted a cross sectional study using stratified cluster sampling method in 2017 in the five-residential governorates of Gaza. In each governorate, one city was selected; within each city one camp area and 2-3 rural and urban areas were randomly chosen. Within each camp, either urban, or rural, a sample block (a group of buildings that form a locality) was selected and a cluster of 15 to 20 households were randomly chosen. The investigators went from door to door, and in every house, all subjects ageing ≥ 25 years were interviewed and examined.

Subjects with missing data on waist circumferential (WC), biochemical values included in the definition of the MetS (19), were excluded leaving 2107 subjects for the analysis.

Data Collection

Each participant was interviewed and completed a questionnaire that included: socio-demographic variables, lifestyle, medical history of chronic diseases, and the international physical activity questionnaire (IPAQ) short form.

Measurements

Height and weight were measured with the foot and wearing light clothing. Body mass index (BMI kg/m^2) was calculated as the weight in kilograms divided by the square of the height in meters. Waist circumference was measured at the mid-distance between the tenth rib and the iliac crest. Blood pressure (BP) was measured once in both arms. A hand-held Doppler probe was used to measure the blood pressure in both arms and ankles (both posterior tibial and dorsalis pedis arteries)[13]. The ABI was measured at each leg and the lowest between the two ankles was retained as the subject's ABI.

Venous blood sample was obtained for lipids profiles including total cholesterol (TC) high-density lipoprotein cholesterol (HDL-C), triglycerides. The low-density lipoprotein cholesterol (LDL-C) was calculated by Friedewald equation. Plasma glucose was measured using glucometer.

Definition of Metabolic syndrome (IDF)

According to the IDF definition, MetS was defined in case of WC ≥ 94 cm in men and ≥ 80 cm in women (all participants were Caucasians), plus two of the four following factors: 1) high blood pressure ≥ 130/85 mmHg or on anti-hypertensive drugs, 2) triglycerides level ≥150 mg/dl, 3) low HDL cholesterol level < 40 mg /dl in males and < 50 mg/dl in females, and 4) fasting glucose level ≥ 100 mg/dl or known to have type-2 diabetes[14]

Diabetes mellitus (DM) was defined as capillary blood sugar level ≥126 mg/dl if the participant was fasting or ≥ 200 mg/dl if the participant was non-fasting and or self-reported as currently taking any diabetes medications [14]. We considered subjects with hypertension (HTN), if their average systolic blood pressure (SBP) in both arms was ≥140 mmHg or their average diastolic blood pressure (DBP) ≥

90 mmHg, or if they were being treated for HTN [16,17]. Coronary artery disease (CAD) was defined in our study by self-reported history of hospitalization for angina pectoris, myocardial infarction, procedures performing percutaneous coronary intervention or coronary bypass graft and after verification of their medical prescription list. Stroke history was identified in case of positive answer to the question: “Have you ever been told by a physician that you suffered a stroke? Lower extremity artery disease (LEAD) was defined as ABI < 0.90.

Statistical analysis

All data were analyzed with the SPSS statistical software version 22.0 (Chicago, Illinois, USA). Continuous variables were expressed as mean ± standard deviation, and categorical variables were expressed as percentages. The comparison of qualitative variables between persons with and without MetS were expressed by frequency distribution and cross tabulation and were compared using the Chi-square tests or the Fisher exact. Variables with a univariate p value < 0.25 were selected for further multivariate analysis. Univariate and multivariate logistic regression analyses were performed to evaluate the association between MetS and other factors. A p-value < 0.05 was considered as the significance level.

Ethics

The committee for medical ethics of the Palestinian ministry approved the study and each participant signed an informed consent.

Results

Among the 2107 participants (1040 males and 1067 females), MetS was found in 864 subjects (41%, 95% CI: 39-43), with higher rate in females than in males

(50%, 95% CI:48-52 *vs.* 32%, 95% CI: 30-34, p<0.001). Clinical characteristics and metabolic measures of the study population according to MetS are presented in Table 1. Individuals with MetS were more likely to be older, obese, with low physical activity, lower level of education, and had more prevalent cardiovascular risk factors such as diabetes, hypertension and lipid disorders. Also, history of CAD, stroke and LEAD were more prevalent in patients with MetS (12%, 4.3%, and15.5% respectively). Statins and Aspirin are more commonly used in participants with MetS.

The prevalence of MetS increased with age in both genders, ranging from 13% (95% CI: 11 -14) in the age category 25-35 years to 50% (95% CI: 47-52) in the age category 55-64 years in males, and from 16% (95% CI: 14-17) to 79% (95% CI: 77-81) in the corresponding age categories in females. The rate decreases after age 65 years for both genders (Figure 1).

Figure 2 displays the prevalence of each components of the MetS in relation to gender. Central obesity and hyperglycemia were the most common conditions contributing to the MetS mainly in female than in males with significant Pvalue.

The association of each CVD with the MetS components are reported in Table 2. Low HDL cholesterol level as well as high triglyceride level, hyperglycemia, and elevated blood pressure were the components associated with the highest risk for CAD (OR= 2.9, 2.7, 2.4, 2.0 respectively). While hyperglycemia, high blood pressure and high triglyceride level were the factors associated with the highest risk of stroke (OR= 4.1, 3.8, 3.7) respectively. Elevated blood pressure remains the main component associated with high risk of LEAD (OR=2.0; CI 1.5-2.7; p< 0.001).

The association of MetS with all demographic and cardiovascular variables are separately presented in males and females (Table 3 and Table 4). The association with MetS increases with age for both genders. In male gender Low physical activity remains positive (OR= 1.7; CI 1.2-2.4; p= 0.009). Also, married males and females were at high risk for MetS (OR= 2.3; CI 1.0-5.4; p= 0.03, OR= 1.9; CI 1.1-3.3; p=0.04) respectively. Furthermore, we failed to detect an association between smoking, education level and physical inactivity with metabolic syndrome.

Discussion

The current study performed in a large sample of adults in age ≥ 25 years reveals a high prevalence of MetS in the Palestinian community of the Gaza Strip, up to 41%, based on IDF definition. The prevalence was higher in women (49.9%). The prevalence estimated in the current study is superior to that reported in a previous study carried out among a small sample size in different regions of Palestine. The most recent was a study among 230 adults aged 20-65 years in the Gaza strip, the prevalence of MetS reported was 23% [11]. Also, In two different studies in two Palestinian camps in west bank, Rizkallah et al and Massad et al. reported a prevalence of MetS up to 58% and 27% in females [18,19]. In the present study, central obesity was two times higher in females than in males (67.2%vs 32.8%) respectively. Waist circumference as indicator of visceral adiposity has been identified as a stronger predictor of CVD and type 2 diabetes[20] . The female predominance is not surprising in our study and could be explained by the fact of high and rising frequency of obesity, diabetes and hypertension in our community, mainly in females[21]. In 2016, the Global Burden of Disease project

supported these findings and pointed out that Palestine is one of the countries where the prevalence of obesity and diabetes is very high [22]. Our results are consistent with those from Middle East studies, which the burden of MetS was estimated to affect a large population, and the prevalence varies from 44% in Turkey [23], 30% In Tunisia [24] to 31.6% in Saudi Arabia [25]. In all these reports published in Middle East region, the prevalence was also higher in female and the most common components were HDL cholesterol and central obesity [10].

In our study the prevalence MetS was found (12.0%, 4.3%, and 15,5%) in subjects with CAD, stroke and LEAD and the association was statistically significant, and the OR increased according to the number of components of MetS. We found that individuals with MetS had a two-fold greater risk of suffering CVDs (CAD, stroke, LEAD) which is similar for the increased risk described for other countries. In a meta-analysis based on NCEP-APIII definition of MetS, the risk estimates were approximately 1.6 for CVD [26–28]. Gami et al, in a large meta-analysis involving 43 cohorts and 17 2573 participants found that MetS itself, apart from its components, was associated with an increased risk of cardiovascular events +54 times after adjustment [27]. In the Botnia study in Finland and Sweden which recruited 4483 subjects aged 35-70 years, the risk of CAD and stroke tripled in subjects with MetS with an absolute 10% increase in cardiovascular mortality during 6.9 years of follow-up [29].

Limitations

As a cross-sectional design of our study, all associations reported cannot be considered as a causative relationship. Also, possible bias could have been introduced since study was conducted at home and data concerning risk factors

were self-reported, another potential concern was that HDL cholesterol, triglycerides, and blood glucose levels were measured only once, which might have led to random error. The strength of the study lies in a large population-based study representative of the Palestinian community, and we describe for the first-time the relationship of MetS and cardiovascular diseases.

Conclusion

The MetS is a collection of risk factors and a complex condition with high socioeconomic cost, its consequences constitute a heavy burden. Our findings are alarming and should alert policy makers to consider primary prevention through a stronger public information to sensitize Palestinians on the hazards of sedentary lifestyle and obesity, because individuals with MetS can be easily screened according to the criteria, it is essential to identify and properly manage each of its components to delay the appearance of its complications.

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Disclosure

conflict of interest

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References

1. Wilson PWF, D'Agostino RB, Parise H, Sullivan L, Meigs JB. Metabolic syndrome as a precursor of cardiovascular disease and type 2 diabetes mellitus. *Circulation*. 2005;112(20):3066-3072. doi:10.1161/CIRCULATIONAHA.105.539528

2. Grundy SM. Metabolic syndrome pandemic. *Arterioscler Thromb Vasc Biol*. 2008;28(4):629-636. doi:10.1161/ATVBAHA.107.151092

3. Alberti KG, Eckel RH, Grundy SM, et al. Harmonizing the metabolic syndrome: a joint interim statement of the International Diabetes Federation Task Force on Epidemiology and Prevention; National Heart, Lung, and Blood Institute; American Heart Association; World Heart Federation; International Atherosclerosis Society; and International Association for the Study of Obesity. *Circulation*. 2009;120(16):1640-1645. doi:10.1161/CIRCULATIONAHA.109.192644

4. Alberti KGMM, Zimmet P, Shaw J. The metabolic syndrome--a new worldwide definition. *Lancet Lond Engl*. 2005;366(9491):1059-1062. doi:10.1016/S0140-6736(05)67402-8

5. Reilly MP, Rader DJ. The metabolic syndrome: more than the sum of its parts? *Circulation*. 2003;108(13):1546-1551. doi:10.1161/01.CIR.0000088846.10655.E0

6. Andreadis EA, Tsourous GI, Tzavara CK, et al. Metabolic syndrome and incident cardiovascular morbidity and mortality in a Mediterranean hypertensive population. *Am J Hypertens*. 2007;20(5):558-564. doi:10.1016/j.amjhyper.2006.12.001

7. Balkau B, Deanfield JE, Després J-P, et al. International Day for the Evaluation of Abdominal Obesity (IDEA): a study of waist circumference, cardiovascular disease, and diabetes mellitus in 168,000 primary care patients in 63 countries. *Circulation*. 2007;116(17):1942-1951. doi:10.1161/CIRCULATIONAHA.106.676379

8. Esteghamati A, Zandieh A, Khalilzadeh O, Meysamie A, Ashraf H. Clustering of metabolic syndrome components in a Middle Eastern diabetic and non-diabetic population. *Diabetol Metab Syndr*. 2010;2:36. doi:10.1186/1758-5996-2-36

9. Prevalence of metabolic syndrome in Middle-East countries: Meta-analysis of cross-sectional studies. *Diabetes Metab Syndr Clin Res Rev*. 2018;12(2):195-201. doi:10.1016/j.dsx.2017.11.004

10. Sliem HA, Ahmed S, Nemr N, El-Sherif I. Metabolic syndrome in the Middle East. *Indian J Endocrinol Metab*. 2012;16(1):67-71. doi:10.4103/2230-8210.91193

11. Sirdah MM, Al Laham NA, Abu Ghali AS. Prevalence of metabolic syndrome and associated socioeconomic and demographic factors among Palestinian adults (20-65 years) at the Gaza Strip. *Diabetes Metab Syndr*. 2011;5(2):93-97.

doi:10.1016/j.dsx.2012.02.024

12. Abdul-Rahim HF, Husseini A, Bjertness E, Giacaman R, Gordon NH, Jervell J. The metabolic syndrome in the West Bank population: an urban-rural comparison. *Diabetes Care*. 2001;24(2):275-279.

13. Aboyans V, Criqui MH, Abraham P, et al. Measurement and Interpretation of the Ankle-Brachial Index: A Scientific Statement From the American Heart Association. *Circulation*. January 2012:CIR.0b013e318276fbcb. doi:10.1161/CIR.0b013e318276fbcb

14. Alberti KG, Zimmet P, Shaw J. Metabolic syndrome--a new world-wide definition. A Consensus Statement from the International Diabetes Federation. *Diabet Med J Br Diabet Assoc*. 2006;23(5):469-480. doi:10.1111/j.1464-5491.2006.01858.x

15. American Diabetes Association 2016. ADA Diabetes Management Guidelines A1C Diagnosis | NDEI. http://www.ndei.org/ADA-diabetes-management-guidelines-diagnosis-A1C-testing.aspx.html. Accessed January 22, 2018.

16. James PA, Oparil S, Carter BL, et al. 2014 evidence-based guideline for the management of high blood pressure in adults: report from the panel members appointed to the Eighth Joint National Committee (JNC 8). *JAMA*. 2014;311(5):507-520. doi:10.1001/jama.2013.284427

17. WHO hypertension. WHO | Q&As on hypertension. WHO. http://www.who.int/features/qa/82/en/index.html. Published 2015. Accessed January 9, 2018.

18. Rizkallah N, Marshall T, Kritz-Silverstein D. Parity and risk factors for coronary heart disease in Palestinian women in two refugee camps in the West Bank: a population based cross-sectional survey. *Lancet*. 2010:382,S28.

19. Massad SG, Khalili M, Karmally W, et al. Metabolic Syndrome among Refugee Women from the West Bank, Palestine: A Cross-Sectional Study. *Nutrients*. 2018;10(8). doi:10.3390/nu10081118

20. Wang Y, Rimm EB, Stampfer MJ, Willett WC, Hu FB. Comparison of abdominal adiposity and overall obesity in predicting risk of type 2 diabetes among men. *Am J Clin Nutr*. 2005;81(3):555-563. doi:10.1093/ajcn/81.3.555

21. Jamee.Shahwan A, Abed Y, Magne J, et al. Epidemiology of cardiovascular disease and associated factors in Gaza-Palestine. *PLOS ONE*. 2019.

22. Forouzanfar MH, Bhutta ZA, Burnett R, et al. Global, regional, and national comparative risk assessment of 79 behavioural, environmental and occupational, and metabolic risks or clusters of risks, 1990–2015: a systematic analysis for the Global Burden of Disease Study 2015. *The Lancet*. 2016;388(10053):1659-1724.

doi:10.1016/S0140-6736(16)31679-8

23. Gundogan K, Bayram F, Gedik V, et al. Metabolic syndrome prevalence according to ATP III and IDF criteria and related factors in Turkish adults. *Arch Med Sci AMS*. 2013;9(2):243-253. doi:10.5114/aoms.2013.34560

24. Belfki H, Ali SB, Aounallah-Skhiri H, et al. Prevalence and determinants of the metabolic syndrome among Tunisian adults: results of the Transition and Health Impact in North Africa (TAHINA) project. *Public Health Nutr*. 2013;16(4):582-590. doi:10.1017/S1368980012003291

25. Al-Rubeaan K, Bawazeer N, Al Farsi Y, et al. Prevalence of metabolic syndrome in Saudi Arabia - a cross sectional study. *BMC Endocr Disord*. 2018;18. doi:10.1186/s12902-018-0244-4

26. Ford ES. Risks for All-Cause Mortality, Cardiovascular Disease, and Diabetes Associated With the Metabolic Syndrome: A summary of the evidence. *Diabetes Care*. 2005;28(7):1769-1778. doi:10.2337/diacare.28.7.1769

27. Gami AS, Witt BJ, Howard DE, et al. Metabolic syndrome and risk of incident cardiovascular events and death: a systematic review and meta-analysis of longitudinal studies. *J Am Coll Cardiol*. 2007;49(4):403-414. doi:10.1016/j.jacc.2006.09.032

28. Galassi A, Reynolds K, He J. Metabolic syndrome and risk of cardiovascular disease: a meta-analysis. *Am J Med*. 2006;119(10):812-819. doi:10.1016/j.amjmed.2006.02.031

29. Isomaa B, Almgren P, Tuomi T, et al. Cardiovascular morbidity and mortality associated with the metabolic syndrome. *Diabetes Care*. 2001;24(4):683-689.

Table1: The characteristics of the study participants with and without metabolic syndrome

Variables	Whole Population n=2107	MetS n=864 (41%)	No MetS n=1243 (59%)	P-value
Age, years	47.17±14.3	53.2±12.7	42.9±13.9	<0.001
Women, n (%)	1067(50.6)	532 (49.9)	535 (50.1)	<0.001
Areas				
Urban, n (%)	752(35.6)	318 (36.8)	433 (34.8)	0.623
Rural, n (%)	493(23.4)	196 (22.7)	297(23.9)	
Camp, n (%)	863(41.0)	350 (40.5)	513 (41.3)	
Education level*				
Primary education, n (%)	324(15.4)	180 (20.8)	144 (11.6)	<0.001
Secondary + High school, n (%)	1082(51.4)	461 (53.4)	621 (50.0)	
University + Post graduate, n (%)	701(33.3)	223 (25.8)	478 (38.5)	
Physical activity				
Low, n (%), n (%)	1015(48.2)	502 (58.1)	513 (41.3)	<0.001
Moderate, n (%)	657(31.2)	233 (27.0)	424 (34.1)	
High, n (%)	435(20.6)	129 (14.9)	306 (24.6)	
Income				
<300$, n (%)	1326(62.9)	574 (66.4)	752 (60.5)	0.006
≥300$, n (%)	781(371)	290 (33.6)	491 (39.5)	
Marital status*				
Single, n (%)	161(7.6)	28 (3.2)	133 (10.7)	<0.001
Married	1792(85)	740 (85.6)	1052 (84.6)	
Divorced or widow, n (%)	154(7.3)	96 (11.1)	58 (4.7)	
Body mass index				
Normal (18.5-25.9 kg/m^2), n (%)	419(19.9)	18 (2.1)	401 (32.2)	<0.001
Overweight (25.9-29.9 kg/m^2), n (%)	691(32.8)	215 (24.9)	476 (38.3)	
Obese ≥(30kg/m^2), n (%)	997(47.3)	631(73.0)	366 (29.4)	
CVD risk factors				
Hypertension, n (%)	592(28.1)	431 (49.9)	161 (13.0)	<0.001
Diabetes mellitus, n (%)	390(18.5)	318 (36.8)	72 (5.8)	<0.001
Current smoking, n (%)	489(23.2)	138 (16)	351 (28.2)	<0.001
Lipids profiles				
Total Cholesterol ≥ 240 (mg/dl), n (%)	178(8.4)	100 (11.6)	78 (6.3)	<0.001
Low HDL cholesterol, n (%)	178(8.4)	748 (88.6)	726 (58.4)	<0.001
LDL cholesterol level ≥160, n (%)	1474(70.0)	90 (10.5)	77 (6.2)	<0.001
Triglycerides level ≥150, n (%)	833(39.5)	591 (68.4)	242 (19.5)	<0.001
CVD comorbidities				
CAD, n (%)	170(8.1)	104 (12.0)	66 (5.3)	<0.001
Stroke, n (%)	63(3.0)	37(4.3)	26 (2.1)	0.004
LEAD (ABI<0.90), n (%)	274(13.0)	134 (15.5)	140 (11.3)	0.004
Medications use				
Statins, n (%)	226(10.7)	176 (20.4)	50 (4.0)	<0.001
Aspirin, n (%)	498(23.6)	318 (36.8)	180 (14.5)	<0.001

Education status*: primary level (0-6years), secondary level (7-12), and high level>12years
Marital status*: single. married and divorced or widow

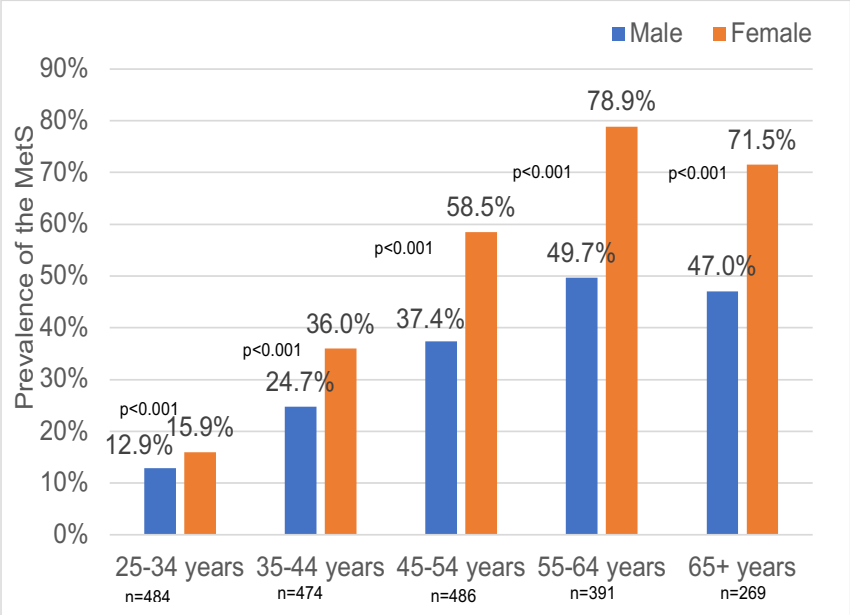


Figure1: Metabolic syndrome according to gender and stratified by age group.

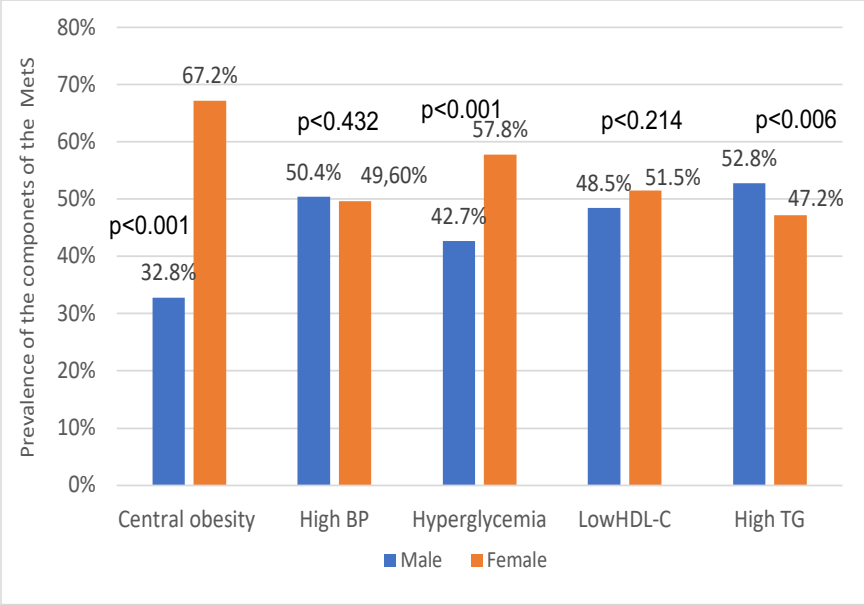


Figure 2: Frequency of each component of Metabolic syndrome by gender

Table 2: Association of CAD, stroke and LEAD with each components of metabolic syndrome

Components of MetS	CAD		Stroke		LEAD	
	O R (95%CI)	P-value	OR (95%CI)	P-value	OR (95%CI)	P-value
Central obesity	1.0 (0.66-1.45)	0.916	1.2 (0.61-2.19)	0.643	0.8 (0.60-1.15)	0.256
High BP	2.0 (1.43-2.90)	<0.001	3.8 (2.01-7.31)	<0.001	2.0 (1.51-2.65)	<0.001
High TG	2.7 (1.92-3.91)	<0.001	3.7 (2.00-6.72)	<0.001	0.9 (0.68-1.16)	0.386
Low HDL-C	2.9 (1.78-4.55)	<0.001	1.5 (0.78-2.72)	0.241	0.9 (0.66-1.14)	0.305
Hyperglycemia	2.4 (1.67-3.33)	<0.001	4.1 (2.32-6.78)	<0.001	1.4 (0.98-1.85)	0.06

Each Logistic regression model was adjusted for age and gender.

BP: Blood pressure; CAD: Coronary artery disease; CI: confidence interval: HDL-C: high-density lipoprotein cholesterol; LEAD: Lower extremity artery disease; OR: odd-ratio

Table 3: Independent factors associated with metabolic syndrome in males

Variables	Univariate analysis		Multivariate analysis	
	OR 95%CI	P-value	OR 95%CI	P-value
Age (years)	1.04 (1.03-1.05)	< 0.001	1.04 (1.03-1.05)	<0.001
Current smoker	1.5 (1.14-1.94)	0.004		
Income	1.1 (0.85-1.45)	0.425		
Marital status				
Single	Ref.		Ref.	
Married	5.2 (2.34-11.31)	< 0.001	2.3 (1.04-5.37)	0.039
Divorced or widow	6.8 (1.86-24.6)	0.004		
Education				
Education low	1.2 (0.76-1.78)	0.485		
Secondary	1.2 (0.93-1.64)	0.137		
High	Ref.			
Physical activity				
Low	2.3 (1.61-3.39)	< 0.001	1.7 (1.14-2.47)	0.009
Moderate	1.6 (1.1-2.3)	0.017		
High	Ref.		Ref.	
Hypertension history	5.1 (3.76-6.80)	< 0.001		
Diabetes history	7.1 (4.98-10.04)	< 0.001		
Cardiovascular diseases				
CAD	2.1 (1.32-3.02)	< 0.001		
Stroke	1.8 (0.93-3.62)	0.079		
LEAD	1.3 (0.84-1.92)	0.259		

Multivariate analysis: adjusted for: Age, smoking, marital status, education level, physical activity.

Table 4: Independent factors associated with metabolic syndrome in female

Variables	Univariate analysis		Multivariate analysis	
	OR 95%CI	Pvalue	OR (95%CI)	Pvalue
Age	1.07 (1.06-1.09)	< 0.001	1.07 (1.06-1.08)	< 0.001
Current smoker	0.9 (0.39-1.87)	0.859		
Income in $	1.3 (1.02-1.71)	0.004		
Marital status				
Single	Ref.		Ref.	
Married	2.9 (1.8-4.9)	< 0.001	1.9 (1.05-3.34)	0.04
Divorced or widow	5.4 (3.1-10.1)	< 0.001		
Education level				
Education low	4.4 (3.1-6.5)	< 0.001		
Secondary	1.8 (1.4-2.4)	< 0.001		
High	Ref.			
Physical activity				
Low	2.1 (1.4-2.8)	< 0.001	1.4 (0.97-1.97)	0.075
Moderate	1.2 (0.8-1.8)	0.283		
High	Ref.		Ref.	
HTN history	9.9 (7.05-13.77)	<0.001		
Diabetes history	19.4 (11.3-33.4)	< 0.001		
Cardiovascular diseases				
CAD	5.2 (2.82-9.97)	< 0.001		
Stroke	3.1 (1.31-7.41)	0.010		
LEAD	1.4 (1.05-1.96)	0.048		

Multivariate analysis: adjusted for: Age, smoking, marital status, education level, physical activity.

Chapter V. Discussion

V.1. Discussion of four articles

Such a community based epidemiological study has never been conducted in Palestine with a large sample covering 2240 participants. Based on our work presented in the four articles, the CAD is reported at 8.3% with a higher risk in males than females (OR: 1.63; p= 0.002). Stroke is reported with a prevalence of 3.0% with no difference between gender. The strongest CVRF associated with these two types of CVDs were hypertension (OR: 2.51; $p < 0.001$) and diabetes (OR: 2.22; $p < 0.001$). In 2013 a cross-sectional study among 1200 Lebanese people ≥ 40 years, reported a CAD prevalence up to 13.4% (Zeidan *et al.*, 2016). In the Coronary Artery Disease in Saudi study (CADISS), a national community-based study conducted in urban and rural area of Saudi Arabia; 17 232 subjects aged 30-70 years randomly selected were included. Coronary artery disease was diagnosed on positive questionnaire of angina or history of possible myocardial infarction. The prevalence of CAD was 5.5% (6.6% in males and 4.4% in females) (Al-Nozha *et al.*, 2004). Two a cross-sectional studies in Lebanese population have reported stroke prevalence, the first one of Lahoud et al; among 6963 inhabitants (mean age 36.8±21.2) the prevalence was 0.80% (Lahoud *et al.*, 2016). The second of Farah et al; that record a prevalence of self-reported stroke symptoms in a stroke and TIA in 1515 free population ≥40 years. The prevalence was 3.6% slightly higher than ours (Farah *et al.*, 2015). In other Arab population, most studies on CAD, or stroke were hospital-based (Al-Nozha *et al.*, 2004; Farah *et al.*, 2015; Nsour *et al.*, 2008). In the US population ≥ 20 years of age the prevalence of CAD is estimated to 6.3% higher in males than females (7.4%, 5.3%). Stroke represent 2.7% with similar prevalence in both gender (Benjamin *et al.*, 2017).

The prevalence of traditional risk factors in general Arab population is closed to the results obtained in our study. As described in GBD 2016, for Middle East and North Africa Region, high blood pressure ranked as the first factor, followed by obesity, diabetes then smoking (GBD 2015 Risk Factors Collaborators, 2016). Our results revealed a high burden of CVRF, obesity 45% (females 60%), hypertension 28%, diabetes 19%, high triglycerides 40%, cigarette smoking in males 40%, unhealthy habits for nutrition and physical inactivity.

The increase in the prevalence of the risk factors in our population is mainly due to urbanization process, globalization (epidemiological transition) involving several factors mainly diets (rich in carbohydrates, red meat, sugar, sweetened drinks and poor intake of fruits and vegetables), lifestyle changes (physical inactivity and smoking). This shift leads to a rise in obesity, worsening levels of metabolic disorder, with associated risk of CVD. Also, we observed that certain risk factors and CVD become worse in persons with low socioeconomic status (Abukhdeir *et al.*, 2013; Husseini *et al.*, 2009).

Lower extremities artery disease study is a research conducted for the first time in Palestine even in the Middle East in the general population. WHO reported 140.8 million LEAD in LMIC with 10.3 million in the EMR where the prevalence was higher in female (Fowkes *et al.*, 2013). Conversely in HIC the prevalence is ≈ 20% in > 80 years old, higher in males and diabetics (Shu & Santulli, 2018) Data regarding LEAD in Arab countries are hospital based and limited. For example, in Saudi Arabia, a cross-sectional, study among 598 diabetic patients ≥ 30 years of age, LEAD was defined in the study by an ABI < 0.90 or by the toe brachial index < 0.7 calculated in case of ABI >1.40.The prevalence was up to 23.1% (Alzahrani *et al.*, 2014). Also, in the Reduction of Atherothrombosis for Continued Health (REACH) registry data form 44 countries worldwide involve large geographic representation, , which included 55,814 patients ≥ 45 years of age, (718 patients from Middle East), with established atherothrombotic disease (CAD, CVD, or LEAD).The results was that ≈ 3/5 of patients with symptomatic LEAD also have atherothrombotic disease in other arterial territories (Cacoub *et al.*, 2009). Our study was carried out in the Gazan community among 1398 subjects. The diagnosis of LEAD was retained for an ABI < 0.90. The analysis reported a prevalence of 13.7%, higher in female. The prevalence increases with age to reach 20.5% in the age of ≥70 years in male and 23.2% in correspondent age in female. The strongest risk factors associated with the disease in male were by order of penetrance overweight, history of CAD, hypertension and being smoking, while in female the hypertension is the only risk factor. In addition, CAD and stroke history were more frequent in case of LEAD, both in males and females.

Worldwide MetS prevalence depending on the region, environment, race, ethnicity, age, and gender, of each population. The IDF estimates that > 1in 4 of adult has the MetS (Alberti, Zimmet & Shaw, 2006), The MetS increases by 5-fold the risk of type 2 diabetes mellitus and 2-fold the risk of developing CVD (Alberti *et al.*, 2009).The study on Metabolic syndrome places Gaza strip as one of the areas with the highest prevalence of this disorder in the EMR. It was reported at 41% mainly in females (49.9%). This mean that 1 in 2 women is exposed to type 2 diabetes and CVD events, and therefore all health difficulties. In Palestine some studies on MetS based on different criteria were conducted in small population and reported a variance of prevalence from 17.1% to 23%, however none of them reported the relationship between cardiovascular risk factors or CVD and MetS (Abdul-Rahim *et al.*, 2001; Sirdah, Al Laham & Abu Ghali, 2011). The feminine domination is due to fact that females were more obese, less physically active, and with more traditional risk factors such as hypertension and diabetes. The prevalence described in the Gazan community is close to the data collected in Arab countries with an increase with age in both sexes, and the risk increase with physical inactivity mainly in male and in married subjects. The association between CAD, stroke and MetS was

approximately double (OR 2.4; $p < 0.001$ and OR 2.1; p = 0.004) respectively. For LEAD the association was represented with an (OR 1.5; p=0.005).

The association between socioeconomic status and cardiovascular risk factors in the Palestinian community in Gaza study was conducted among 2240 participants. Four socioeconomic variables were used (education level, income, occupation and marital status).

The relation with four major cardiovascular risk factors (hypertension, diabetes, smoking, and obesity) will be analyzed

V.2. Limitations and strengths

V.2.1. Limitation points

- The cross-sectional design, the associations found cannot prove causality.
- During sample size calculation we did not consider cluster effect, to minimize this effect we use multistage stratification
- The prevalence of high blood pressure and raised blood glucose might be overestimated. These two risk factors were evaluated once (no reevaluation during another visit, and no three consecutive measures of BP according to WHO step). However, the same protocol was adopted in the different Stepwise studies
- Possible bias could have been introduced since study was conducted at home. Specific population may have been selected as female, unemployed or sick subjects. The effect was probably limited: the sex-ratio in our study was close to general population characteristics. Compared with the age pyramid of the Gaza population the 45-54 years old group is over represented
- The wide age range of participants, 25 years and more is both a strength and a weakness of this study. As usual, the greatest prevalence of CVD and risk factors was in the older groups, 32% of the population was aged 55 years and more. Even so we found considerable charge of risk factors in young population.
- As the risk factors and the diseases were self-reported, this may contribute to underestimate the actual prevalence mainly for CAD, stroke and smoking.
- Smoking status was declarative and probably the number of smokers may be under evaluated in male population.
- Conversely our LEAD data based on ABI measurements are strong.

V.2.2. Strengths points

- It is the first study in Palestine to report a national estimate for CVD prevalence (CAD, stroke and LEAD)
- The study was conducted in community based. The study was performed in real life; the questionnaire used permitted us to identify risk factors and to acknowledge the life style of individuals in different regions
- The study was performed in a large mixed area (urban, camps and rural) with representative sample and good response rate
- We managed to train of nurses (men and women) in basic interviewing techniques according to Stepwise NCD surveillance conference and standard methods of obtaining physical measurement, including the ankle brachial index measure
- Lipids profiles were analyzed in private laboratory with high quality test
- For the first time a correlation between metabolic syndrome and CVDs in this population was established

Conclusion and opportunities

The findings reported in this large epidemiological study in civil community, based on CVD and their CVRF will be used to guide strategies, alert policy marker to call for a change in prevention and treatment of risk factors and the overall management of CVD. Unfortunately, there are significant gaps and challenges in the management and control of chronic diseases in Palestine. One of the major challenges for the health care is the blockade imposed by Israel on the Gaza strip which affects the medical infrastructure and the functioning of the health system. In addition to the conflict with Israel, another challenge is the fact that Palestinian National Authority currently does not have the liberty to implement policy in Gaza. To date, its involvement is limited to the financial contributions it makes to it. Such data represent an obstacle to disease prevention and the development of a common strategic program for the two geographical parts of the Palestinian National Authority (W.B, G.S). Also, the Palestinian national strategy health plan for 2010-2020 did not give adequate attention for the prevention of chronic risk factors as those mentioned by WHO 25 by 25 vision for chronic disease program.

Taking in consideration all these points, strategies should be designed by effective prevention of chronic disease in civil society through health care system including governmental services, NGOs, international and private organization. These strategies are:

- Effective educational program, application of Best Buys interventions for the prevention by easy numerous ways such as: control of cigarette smoking by increasing the price of cigarettes and anti-tobacco campaigns, encouraging to return to traditional dietary habits, avoiding salt consumption, getting regular physical activity, controlling blood Sugar, and aggressive control of HTN. This approach is good for all, and the financial cost of setting them up is low
- Screening of people at high risk of CVDs (subjects with risk factors), reduction of some risk factors and this is ‘good for some’
- Following recommendation guidelines on treatment of risk factors (high cost effective and good for some) will help to reduce morbidity and mortality of CVD.
- Estimation of Framingham Global Cardio Vascular risk in the population

Primary and secondary care for the management of CVD and CVRF by many measures such as simplified treatment schemes, task sharing, effective procurement of affordable medication, universal access to health care, control of NCDs and for healthy life style on general community-based population.

- Tertiary-care for the treatment and management of cardiovascular disease mainly cardiac surgery and rehabilitation centers.

It would also be valuable to conduct future studies, mainly in West Bank even in Middle East Region to make a comparison within population and have a common vision.

Finally, if we can achieve these perspectives, we can ensure happy lives, good health and promote well-being for all at all ages.

Personal contribution

My personal contribution in this thesis began first with the writing of proposal, and methodology, define the main lines of work under the supervision of my directors, followed by the writing of the questionnaire recruiting and training of investigators on communication with individuals, data collection, physical examination, the measure of the ABI, according to WHO rules.

So, I participated in the field work with the teams during the data collection throughout the Gaza territory. After that I started data entry and results analysis.

This thesis work has so far given rise to 4 articles (one published, two submitted and one in writing) I am the author and the fully responsible for this thesis work and its content.

Bibliography

AARON, S. (2015) *U.S. Smartphone Use in 2015 | Pew Research Center*. [Online]. Available from: http://www.pewinternet.org/2015/04/01/us-smartphone-use-in-2015/ [Accessed: 19 October 2018].

Abdeen, Z., Jildeh, C., Dkeideek, S., Qasrawi, R., et al. (2012) *Overweight and Obesity among Palestinian Adults: Analyses of the Anthropometric Data from the First National Health and Nutrition Survey (1999-2000)*. [Online]. 2012. Journal of Obesity. Available from: doi:10.1155/2012/213547 [Accessed: 7 March 2019].

Abdul-Rahim, H.F., Husseini, A., Bjertness, E., Giacaman, R., et al. (2001) The metabolic syndrome in the West Bank population: an urban-rural comparison. *Diabetes Care*. 24 (2), 275–279.

Aboyans, V., Criqui, M.H., Abraham, P., Allison, M.A., et al. (2012) Measurement and Interpretation of the Ankle-Brachial Index: A Scientific Statement From the American Heart Association. *Circulation*. [Online] CIR.0b013e318276fbcb. Available from: doi:10.1161/CIR.0b013e318276fbcb.

Aboyans, V., Desormais, I., Lacroix, P., Salazar, J., et al. (2010) The general prognosis of patients with peripheral arterial disease differs according to the disease localization. *Journal of the American College of Cardiology*. [Online] 55 (9), 898–903. Available from: doi:10.1016/j.jacc.2009.09.055.

Aboyans, V. & Ricco, J.-B. (2018) The 2017 ESC Guidelines on PADs: what's new? *European Heart Journal*. [Online] 39 (9), 720–729. Available from: doi:10.1093/eurheartj/ehy044.

Aboyans, V., Ricco, J.-B., Bartelink, M.-L.E.L., Björck, M., et al. (2018) 2017 ESC Guidelines on the Diagnosis and Treatment of Peripheral Arterial Diseases, in collaboration with the European Society for Vascular Surgery (ESVS)Document covering atherosclerotic disease of extracranial carotid and vertebral, mesenteric, renal, upper and lower extremity arteriesEndorsed by: the European Stroke Organization (ESO)The Task Force for the Diagnosis and Treatment of Peripheral Arterial Diseases of the European Society of Cardiology (ESC) and of the European Society for Vascular Surgery (ESVS). *European Heart Journal*. [Online] 39 (9), 763–816. Available from: doi:10.1093/eurheartj/ehx095.

Abrams, J. (2005) Chronic Stable Angina. *NEW ENGLAND JOURNAL OF MEDICINE*. (24) p.2524.

Abukhdeir, H.F., Caplan, L.S., Reese, L. & Alema-Mensah, E. (2013) Factors affecting the prevalence of chronic diseases in Palestinian people: an analysis of data from the Palestinian Central Bureau of Statistics. *Eastern Mediterranean health journal = La revue de sante de la Mediterranee orientale = al-Majallah al-sihhiyah li-sharq al-mutawassit*. 19 (4), 307–313.

Abuyassin, B. & Laher, I. (2016) Diabetes epidemic sweeping the Arab world. *World Journal of Diabetes*. [Online] 7 (8), 165–174. Available from: doi:10.4239/wjd.v7.i8.165.

ADA (2018) 2. Classification and Diagnosis of Diabetes: Standards of Medical Care in Diabetes—2018. *Diabetes Care*. [Online] 41 (Supplement 1), S13–S27. Available from: doi:10.2337/dc18-S002.

AHA (2016) *My Life Check - Life's Simple 7*. [Online]. 2016. Available from: http://www.heart.org/HEARTORG/Conditions/My-Life-Check---Lifes-Simple-7_UCM_471453_Article.jsp#.WuTZKi_pNp8 [Accessed: 28 April 2018].

AHA 2014 (2014) *Stress and Heart Health*. [Online]. 2014. Available from: http://www.heart.org/HEARTORG/HealthyLiving/StressManagement/HowDoesStressAffectYou/Stress-and-Heart-Health_UCM_437370_Article.jsp#.W1RE2y3pNp8 [Accessed: 22 July 2018].

AHA 2018 (n.d.) *Cardiovascular Disease & Diabetes*. [Online]. Available from: http://www.heart.org/HEARTORG/Conditions/More/Diabetes/WhyDiabetesMatters/Cardiovascular-Disease-Diabetes_UCM_313865_Article.jsp#.WzjpPy3pOgQ [Accessed: 1 July 2018].

Alarouj, M., Bennakhi, A., Alnesef, Y., Sharifi, M., et al. (2013) Diabetes and associated cardiovascular risk factors in the State of Kuwait: the first national survey. *International Journal of Clinical Practice*. [Online] 67 (1), 89–96. Available from: doi:10.1111/ijcp.12064.

Alberti, K.G., Eckel, R.H., Grundy, S.M., Zimmet, P.Z., et al. (2009) Harmonizing the metabolic syndrome: a joint interim statement of the International Diabetes Federation Task Force on Epidemiology and Prevention; National Heart, Lung, and Blood Institute; American Heart Association; World Heart Federation; International Atherosclerosis Society; and International Association for the Study of Obesity. *Circulation*. [Online] 120 (16), 1640–1645. Available from: doi:10.1161/CIRCULATIONAHA.109.192644.

Alberti, K.G., Zimmet, P. & Shaw, J. (2006) Metabolic syndrome--a new world-wide definition. A Consensus Statement from the International Diabetes Federation. *Diabetic Medicine: A Journal of the British Diabetic Association*. [Online] 23 (5), 469–480. Available from: doi:10.1111/j.1464-5491.2006.01858.x.

Alberti, K.G.M.M., Zimmet, P. & Shaw, J. (2007) International Diabetes Federation: a consensus on Type 2 diabetes prevention. *Diabetic Medicine: A Journal of the British Diabetic Association*. [Online] 24 (5), 451–463. Available from: doi:10.1111/j.1464-5491.2007.02157.x.

Alberti, K.G.M.M., Zimmet, P. & Shaw, J. (2005) The metabolic syndrome--a new worldwide definition. *Lancet (London, England)*. [Online] 366 (9491), 1059–1062. Available from: doi:10.1016/S0140-6736(05)67402-8.

Ali, M.K., Bullard, K.M., Saaddine, J.B., Cowie, C.C., et al. (2013) Achievement of goals in U.S. diabetes care, 1999-2010. *The New England Journal of Medicine*. [Online] 368 (17), 1613–1624. Available from: doi:10.1056/NEJMsa1213829.

Aljefree, N. & Ahmed, F. (2015) Prevalence of Cardiovascular Disease and Associated Risk Factors among Adult Population in the Gulf Region: A Systematic Review. *Advances in Public Health*. [Online] 2015, e235101. Available from: doi:10.1155/2015/235101.

Allison, M.A., Ho, E., Denenberg, J.O., Langer, R.D., et al. (2007) Ethnic-specific prevalence of peripheral arterial disease in the United States. *American Journal of Preventive Medicine*. [Online] 32 (4), 328–333. Available from: doi:10.1016/j.amepre.2006.12.010.

Al-Nozha, M.M., Arafah, M.R., Al-Mazrou, Y.Y., Al-Maatouq, M.A., et al. (2004) Coronary artery disease in Saudi Arabia. *Saudi Medical Journal*. 25 (9), 1165–1171.

Al-Quwaidhi, A.J., Pearce, M.S., Sobngwi, E., Critchley, J.A., et al. (2014) Comparison of type 2 diabetes prevalence estimates in Saudi Arabia from a validated Markov model against the International Diabetes Federation and other modelling studies. *Diabetes Research and Clinical Practice*. [Online] 103 (3), 496–503. Available from: doi:10.1016/j.diabres.2013.12.036.

Al-Rubeaan, K., Al-Manaa, H.A., Khoja, T.A., Ahmad, N.A., et al. (2015) Epidemiology of abnormal glucose metabolism in a country facing its epidemic: SAUDI-DM study: 一个国家面临的糖代谢异常的流行病学研究：SAUDI-DM研究. *Journal of Diabetes*. [Online] 7 (5), 622–632. Available from: doi:10.1111/1753-0407.12224.

Alsheikh-Ali, A.A., Omar, M.I., Raal, F.J., Rashed, W., et al. (2014) Cardiovascular Risk Factor Burden in Africa and the Middle East: The Africa Middle East Cardiovascular Epidemiological (ACE) Study. *PLOS ONE*. [Online] 9 (8), e102830. Available from: doi:10.1371/journal.pone.0102830.

Alwan, N.A., Alwan, A. & Jabbour, S. (2012) Non-communicable diseases I: burden and approaches to prevention. In: Samer Jabbour, Rita Giacaman, Marwan Khawaja, & Iman Nuwayhid (eds.). *Public Health in the Arab World*. [Online]. Cambridge University Press. p. Available from: http://eprints.soton.ac.uk/377958/ [Accessed: 18 February 2017].

Alzahrani, H., Wang, D., A Bakhotmah, B. & B Hu, F. (2014) Risk factors for peripheral artery disease among patients with diabetes in Saudi Arabia. *Vascular medicine (London, England)*. [Online] 19. Available from: doi:10.1177/1358863X14526948.

Ambrose, J.A. & Barua, R.S. (2004) The pathophysiology of cigarette smoking and cardiovascular disease: An update. *Journal of the American College of Cardiology*. [Online] 43 (10), 1731–1737. Available from: doi:10.1016/j.jacc.2003.12.047.

American Diabetes Association 2016 (n.d.) *ADA Diabetes Management Guidelines A1C Diagnosis | NDEI*. [Online]. Available from: http://www.ndei.org/ADA-diabetes-management-guidelines-diagnosis-A1C-testing.aspx.html [Accessed: 22 January 2018].

Anderson, J.L. & Morrow, D.A. (2017) Acute myocardial infarction. *The New England Journal of Medicine*. (21), 2053.

Anderson, T.J., Grégoire, J., Hegele, R.A., Couture, P., et al. (2013) 2012 update of the Canadian Cardiovascular Society guidelines for the diagnosis and treatment of dyslipidemia for the prevention of cardiovascular disease in the adult. *The Canadian Journal of Cardiology*. [Online] 29 (2), 151–167. Available from: doi:10.1016/j.cjca.2012.11.032.

Anon (n.d.) *Gaza Strip Joint Health Sector Assessment Report - September 2014 - occupied Palestinian territory*. [Online]. ReliefWeb. Available from: https://reliefweb.int/report/occupied-palestinian-territory/gaza-strip-joint-health-sector-assessment-report-september [Accessed: 25 September 2018a].

Anon (2005) *IPAQ scoring protocol - International Physical Activity Questionnaire*. [Online]. 2005. Available from: https://sites.google.com/site/theipaq/scoring-protocol [Accessed: 1 October 2018].

Anon (2016a) Mobile Phone Interventions for the Secondary Prevention of Cardiovascular Disease. [Online] 58 (6), 639–650. Available from: doi:10.1016/j.pcad.2016.03.002.

Anon (n.d.) *Palestine Health Status Annual Report 2017 | GHDx*. [Online]. Available from: http://ghdx.healthdata.org/record/palestine-health-status-annual-report-2017 [Accessed: 24 February 2019b].

Anon (2017a) Pathogenesis of atherosclerosis. [Online] 23 (11), 473–478. Available from: doi:10.1016/j.mpdhp.2017.11.009.

Anon (2016b) *Risk Factors for Type 2 Diabetes | NIDDK*. [Online]. 2016. National Institute of Diabetes and Digestive and Kidney Diseases. Available from: https://www.niddk.nih.gov/health-information/diabetes/overview/risk-factors-type-2-diabetes [Accessed: 10 March 2019].

Anon (2015) Sex differences in cardiovascular risk factors and disease prevention. [Online] 241 (1), 211–218. Available from: doi:10.1016/j.atherosclerosis.2015.01.027.

Anon (2017b) Stroke in the acute setting. [Online] 45 (3), 163–168. Available from: doi:10.1016/j.mpmed.2016.12.008.

Anon (2014) *WHO | Alcohol*. [Online]. 2014. WHO. Available from: http://www.who.int/substance_abuse/facts/alcohol/en/ [Accessed: 10 July 2018].

Anon (2012a) *WHO | Global Health Observatory (GHO) data*. [Online]. 2012. WHO. Available from: http://www.who.int/gho/en/ [Accessed: 10 June 2018].

Anon (n.d.) *WHO | Global recommendations on physical activity for health*. [Online]. WHO. Available from: https://www.who.int/dietphysicalactivity/factsheet_recommendations/en/ [Accessed: 14 October 2018c].

Anon (n.d.) *WHO | Scaling up action against NCDs: How much will it cost?* [Online]. WHO. Available from: http://www.who.int/nmh/publications/cost_of_inaction/en/ [Accessed: 30 October 2018d].

Anon (n.d.) *WHO | World Health Statistics 2017: Monitoring health for the SDGs*. [Online]. WHO. Available from: http://www.who.int/gho/publications/world_health_statistics/2017/en/ [Accessed: 28 April 2018e].

Anon (2012b) *WHO Regional Office for the Eastern Mediterranean. Noncommunicable diseases: STEPwise surveillance.* [Online]. 2012. Available from: https://www.google.fr/search?client=safari&rls=en&q=WHO+Regional+Office+for+the+Eastern+Mediterranean.+Noncommunicable+diseases:+STEPwise+surveillance.+http://www.+emro.who.int/noncommunicable-diseases/stepwise-surveillance/+stepwise-surveillance-st&ie=UTF-8&oe=UTF-8&gfe_rd=cr&ei=9KagWLKGAY338Af25aLACw [Accessed: 12 February 2017].

Anon (2007) *WHO/ISH cardiovascular risk prediction charts*. [Online]. 2007. Available from: http://www.who.int/cardiovascular_diseases/guidelines/Chart_predictions/en/ [Accessed: 29 October 2018].

Anon (n.d.) *World Health Statistics 2011*. [Online]. WHO. Available from: http://www.who.int/whosis/whostat/2011/en/ [Accessed: 4 February 2017f].

Aponte, J. (2012) The prevalence of peripheral arterial disease (PAD) and PAD risk factors among different ethnic groups in the US Population. *Journal of Vascular Nursing*. [Online] 30 (2), 37–43. Available from: doi:10.1016/j.jvn.2011.11.004.

Archer, E. & Blair, S.N. (2011) Physical activity and the prevention of cardiovascular disease: from evolution to epidemiology. *Progress in Cardiovascular Diseases*. [Online] 53 (6), 387–396. Available from: doi:10.1016/j.pcad.2011.02.006.

Ashley, E.A. & Niebauer, J. (2004) *Coronary artery disease*. [Online]. Remedica. Available from: https://www.ncbi.nlm.nih.gov/books/NBK2216/ [Accessed: 4 May 2018].

Assmann, G., Schulte, H., von Eckardstein, A. & Huang, Y. (1996) High-density lipoprotein cholesterol as a predictor of coronary heart disease risk. The PROCAM experience and pathophysiological implications for reverse cholesterol transport. *Atherosclerosis*. 124 Suppl, S11-20.

Aung, P.P., Maxwell, H.G., Jepson, R.G., Price, J.F., et al. (2007) Lipid-lowering for peripheral arterial disease of the lower limb. *The Cochrane Database of Systematic Reviews*. [Online] (4), CD000123. Available from: doi:10.1002/14651858.CD000123.pub2.

Ay, H., Benner, T., Arsava, E.M., Furie, K.L., et al. (2007) A computerized algorithm for etiologic classification of ischemic stroke: the Causative Classification of Stroke System. *Stroke*. [Online] 38 (11), 2979–2984. Available from: doi:10.1161/STROKEAHA.107.490896.

Ay, H., Furie, K.L., Singhal, A., Smith, W.S., et al. (2005) An evidence-based causative classification system for acute ischemic stroke. *Annals of Neurology*. [Online] 58 (5), 688–697. Available from: doi:10.1002/ana.20617.

Baigent, C., Keech, A., Kearney, P.M., Blackwell, L., et al. (2005) Efficacy and safety of cholesterol-lowering treatment: prospective meta-analysis of data from 90,056 participants in 14 randomised trials of statins. *Lancet (London, England)*. [Online] 366 (9493), 1267–1278. Available from: doi:10.1016/S0140-6736(05)67394-1.

Bainton, D., Sweetnam, P., Baker, I. & Elwood, P. (1994) Peripheral vascular disease: consequence for survival and association with risk factors in the Speedwell prospective heart disease study. *Heart*. [Online] 72 (2), 128–132. Available from: doi:10.1136/hrt.72.2.128.

Ben Romdhane, H., Ali, S.B., Aissi, W., Traissac, P., et al. (2014) Prevalence of diabetes in Northern African countries: the case of Tunisia. *BMC Public Health*. [Online] 14 (1), 86. Available from: doi:10.1186/1471-2458-14-86.

Benamer, H.T. & Grosset, D. (2009) Stroke in Arab countries: A systematic literature review. *Journal of the Neurological Sciences*. [Online] 284 (1–2), 18–23. Available from: doi:10.1016/j.jns.2009.04.029.

Benjamin, E.J., Blaha, M.J., Chiuve, S.E., Cushman, M., et al. (2017) Heart Disease and Stroke Statistics—2017 Update: A Report From the American Heart Association. *Circulation*. [Online] Available from: doi:10.1161/CIR.0000000000000485 [Accessed: 6 May 2017].

Benjamin Emelia J., Virani Salim S., Callaway Clifton W., Chamberlain Alanna M., et al. (2018) Heart Disease and Stroke Statistics—2018 Update: A Report From the American Heart Association. *Circulation*. [Online] 137 (12), e67–e492. Available from: doi:10.1161/CIR.0000000000000558.

Berger, J.S., Jordan, C.O., Lloyd-Jones, D. & Blumenthal, R.S. (2010) Screening for Cardiovascular Risk in Asymptomatic Patients. *Journal of the American College of*

Cardiology. [Online] 55 (12), 1169–1177. Available from: doi:10.1016/j.jacc.2009.09.066.

Bergmann, K. (2010) Non-HDL Cholesterol and Evaluation of Cardiovascular Disease Risk. *EJIFCC*. 21 (3), 64–67.

'Best Buy'WHO (2014) *'Best Buys' to prevent noncommunicable diseases*. [Online]. 2014. ReliefWeb. Available from: https://reliefweb.int/report/world/best-buys-prevent-noncommunicable-diseases-will-save-billions-dollars [Accessed: 30 October 2018].

Beulens, J.W.J., Algra, A., Soedamah-Muthu, S.S., Visseren, F.L.J., et al. (2010) Alcohol consumption and risk of recurrent cardiovascular events and mortality in patients with clinically manifest vascular disease and diabetes mellitus: the Second Manifestations of ARTerial (SMART) disease study. *Atherosclerosis*. [Online] 212 (1), 281–286. Available from: doi:10.1016/j.atherosclerosis.2010.04.034.

Bhatnagar, P., Wickramasinghe, K., Wilkins, E. & Townsend, N. (2016) Trends in the epidemiology of cardiovascular disease in the UK. *Heart*. [Online] 102 (24), 1945–1952. Available from: doi:10.1136/heartjnl-2016-309573.

Bhatnagar, P., Wickramasinghe, K., Williams, J., Rayner, M., et al. (2015) The epidemiology of cardiovascular disease in the UK 2014. *Heart*. [Online] heartjnl-2015-307516. Available from: doi:10.1136/heartjnl-2015-307516.

Biloglav, Z. (2004) *Biloglav, Zrinka, et al. 'Performance of WHO Angina Questionnaire in measuring burden of coronary heart disease in human isolate populations.'Collegium antropologicum 28.1 (2004): 205-213. - Recherche Google*. [Online]. 2004. Available from: /?ei=qTGjWMemKY738AfDt62IDQ [Accessed: 14 February 2017].

Bloom, D.E., Cafiero, E., Jané-Llopis, E., Abrahams-Gessel, S., et al. (2012) *The Global Economic Burden of Noncommunicable Diseases*. [Online]. Available from: https://ideas.repec.org/p/gdm/wpaper/8712.html [Accessed: 29 April 2018].

Boushey, C.J., Beresford, S.A.A., Omenn, G.S. & Motulsky, A.G. (1995) A Quantitative Assessment of Plasma Homocysteine as a Risk Factor for Vascular Disease: Probable Benefits of Increasing Folic Acid Intakes. *JAMA*. [Online] 274 (13), 1049–1057. Available from: doi:10.1001/jama.1995.03530130055028.

Bowery, A.D. (2015) *Bowery, Ashna DK, et al. The Burden of Cardiovascular Disease in Low- and Middle-Income Countries: Epidemiology and Management. Canadian Journal of Cardiology 31.9 (2015): 1151-1159. - Recherche Google*. [Online]. 2015. Available from: /?ei=qTGjWMemKY738AfDt62IDQ [Accessed: 14 February 2017].

Boyko, E.J., Courten, M. de, Zimmet, P.Z., Chitson, P., et al. (2000) Features of the metabolic syndrome predict higher risk of diabetes and impaired glucose tolerance: a prospective study in Mauritius. *Diabetes Care*. [Online] 23 (9), 1242–1248. Available from: doi:10.2337/diacare.23.9.1242.

Braunwald, E., Jones, R.H., Mark, D.B., Brown, J., et al. (1994) Diagnosing and managing unstable angina. Agency for Health Care Policy and Research. *Circulation*. 90 (1), 613–622.

Brien, S.E., Ronksley, P.E., Turner, B.J., Mukamal, K.J., et al. (2011) Effect of alcohol consumption on biological markers associated with risk of coronary heart disease:

systematic review and meta-analysis of interventional studies. *BMJ*. [Online] 342, d636. Available from: doi:10.1136/bmj.d636.

Broderick, J., Connolly, S., Feldmann, E., Hanley, D., et al. (2007) Guidelines for the management of spontaneous intracerebral hemorrhage in adults: 2007 update: a guideline from the American Heart Association/American Stroke Association Stroke Council, High Blood Pressure Research Council, and the Quality of Care and Outcomes in Research Interdisciplinary Working Group. *Circulation*. [Online] 116 (16), e391-413. Available from: doi:10.1161/CIRCULATIONAHA.107.183689.

Brotman, D.J., Golden, S.H. & Wittstein, I.S. (2007) The cardiovascular toll of stress. *Lancet (London, England)*. [Online] 370 (9592), 1089–1100. Available from: doi:10.1016/S0140-6736(07)61305-1.

Brown, R.A., Shantsila, E., Varma, C. & Lip, G.Y.H. (2017) Current Understanding of Atherogenesis. *The American Journal of Medicine*. [Online] 130 (3), 268–282. Available from: doi:10.1016/j.amjmed.2016.10.022.

Burns, D.M. (2003) Epidemiology of smoking-induced cardiovascular disease. *Progress in Cardiovascular Diseases*. [Online] 46 (1), 11–29. Available from: doi:10.1016/S0033-0620(03)00079-3.

Cacoub, P.P., Abola, M.T.B., Baumgartner, I., Bhatt, D.L., et al. (2009) Cardiovascular risk factor control and outcomes in peripheral artery disease patients in the Reduction of Atherothrombosis for Continued Health (REACH) Registry. *Atherosclerosis*. [Online] 204 (2), e86-92. Available from: doi:10.1016/j.atherosclerosis.2008.10.023.

Cahill, K., Stevens, S., Perera, R. & Lancaster, T. (2013) Pharmacological interventions for smoking cessation: an overview and network meta-analysis. *Cochrane Database of Systematic Reviews*. [Online] (5). Available from: doi:10.1002/14651858.CD009329.pub2 [Accessed: 10 October 2018].

Cannon, C.P. (2008) Cardiovascular disease and modifiable cardiometabolic risk factors. *Clinical cornerstone*. 9 (2), 24–41.

Canoy, D. & Buchan, I. (n.d.) Challenges in obesity epidemiology. *Obesity Reviews*. [Online] 8 (s1), 1–11. Available from: doi:10.1111/j.1467-789X.2007.00310.x.

CDC (2016a) *Centers for Disease Control and Prevention. cause of death 1999-2014 - Recherche Google*. [Online]. 2016. Available from: http://wonder.cdc.gov/ucd-icd10.html. [Accessed: 29 April 2018].

CDC (2016b) *Electronic Nicotine Delivery Systems: Key Facts from the CDC | Access Health*. [Online]. Available from: https://accesshealthme.org/how-we-can-help/local-health-data/el-nic-delivery-system-infogram-2016/ [Accessed: 5 July 2018].

CDC (2018) *National Diabetes Statistics Report | Data & Statistics | Diabetes | CDC*. [Online]. 15 May 2018. Available from: https://www.cdc.gov/diabetes/data/statistics/statistics-report.html [Accessed: 1 July 2018].

CDC (2017) *NHIS - Adult Tobacco Use - Glossary*. [Online]. 29 August 2017. Available from: https://www.cdc.gov/nchs/nhis/tobacco/tobacco_glossary.htm [Accessed: 30 September 2018].

Chen, Y., Zhang, X., Pan, B., Jin, X., et al. (2010) A modified formula for calculating low-density lipoprotein cholesterol values. *Lipids in Health and Disease*. [Online] 9, 52. Available from: doi:10.1186/1476-511X-9-52.

Cheng, S.-J., Yu, H.-K., Chen, Y.-C., Chen, C.-Y., et al. (2013) Physical Activity and Risk of Cardiovascular Disease Among Older Adults. *International Journal of Gerontology*. [Online] 7 (3), 133–136. Available from: doi:10.1016/j.ijge.2013.03.001.

Chetty, R., Stepner, M., Abraham, S., Lin, S., et al. (2016) The Association Between Income and Life Expectancy in the United States, 2001-2014. *JAMA*. [Online] 315 (16), 1750–1766. Available from: doi:10.1001/jama.2016.4226.

Chockalingam, A., Balaguer-Vintro, I., Achutti, A., de Luna, A.B., et al. (2000) The World Heart Federation's white book: impending global pandemic of cardiovascular diseases: challenges and opportunities for the prevention and control of cardiovascular diseases in developing countries and economies in transition. *The Canadian Journal of Cardiology*. 16 (2), 227–229.

Choi, J., Daskalopoulou, S.S., Thanassoulis, G., Karp, I., et al. (2014) Sex- and gender-related risk factor burden in patients with premature acute coronary syndrome. *The Canadian Journal of Cardiology*. [Online] 30 (1), 109–117. Available from: doi:10.1016/j.cjca.2013.07.674.

Choudhury, L. & Marsh, J.D. (1999) Myocardial infarction in young patients. *The American Journal of Medicine*. 107 (3), 254–261.

Chow, C.K., Ariyarathna, N., Islam, S.M.S., Thiagalingam, A., et al. (2016) mHealth in Cardiovascular Health Care. *Heart, Lung & Circulation*. [Online] 25 (8), 802–807. Available from: doi:10.1016/j.hlc.2016.04.009.

Chow, C.K., Islam, S., Bautista, L., Rumboldt, Z., et al. (2011) Parental history and myocardial infarction risk across the world: the INTERHEART Study. *Journal of the American College of Cardiology*. [Online] 57 (5), 619–627. Available from: doi:10.1016/j.jacc.2010.07.054.

Chow, C.K., Redfern, J., Hillis, G.S., Thakkar, J., et al. (2015) Effect of Lifestyle-Focused Text Messaging on Risk Factor Modification in Patients With Coronary Heart Disease: A Randomized Clinical Trial. *JAMA*. [Online] 314 (12), 1255–1263. Available from: doi:10.1001/jama.2015.10945.

Chow, C.K., Teo, K.K., Rangarajan, S., Islam, S., et al. (2013) Prevalence, awareness, treatment, and control of hypertension in rural and urban communities in high-, middle-, and low-income countries. *JAMA*. [Online] 310 (9), 959–968. Available from: doi:10.1001/jama.2013.184182.

CIA. (2018) *CIA-The World Factbook-Gaza Strip*.

Cohen, S., Kamarck, T. & Mermelstein, R. (1983) A global measure of perceived stress. *Journal of Health and Social Behavior*. 24 (4), 385–396.

Cooney, M.T., Vartiainen, E., Laatikainen, T., De Bacquer, D., et al. (2012) Cardiovascular risk age: concepts and practicalities. *Heart (British Cardiac Society)*. [Online] 98 (12), 941–946. Available from: doi:10.1136/heartjnl-2011-301478.

Costa, E., Santos-Silva, A., Paúl, C. & González Gallego, J. (2015) *Aging and Cardiovascular Risk*. [Online]. 2015. BioMed Research International. Available from: doi:10.1155/2015/871656 [Accessed: 8 July 2018].

Counsell, C., Boonyakarnkul, S., Dennis, M., Sandercock, P., et al. (1995) Primary Intracerebral Haemorrhage in the Oxfordshire Community Stroke Project. *Cerebrovascular Diseases*. [Online] 5 (1), 26–34. Available from: doi:10.1159/000107814.

Crea, F., Camici, P.G., Caterina, R.D. & Lanza, G.A. (2010) *Chronic Ischaemic Heart Disease*. [Online]. Oxford University Press. Available from: http://oxfordmedicine.com/view/10.1093/med/9780199566990.001.0001/med-9780199566990-chapter-17 [Accessed: 20 November 2018].

Criqui, M.H. & Aboyans, V. (2015) Epidemiology of Peripheral Artery Disease. *Circulation Research*. [Online] 116 (9), 1509–1526. Available from: doi:10.1161/CIRCRESAHA.116.303849.

Critchley, J.A. & Capewell, S. (2003) Mortality risk reduction associated with smoking cessation in patients with coronary heart disease: a systematic review. *JAMA*. [Online] 290 (1), 86–97. Available from: doi:10.1001/jama.290.1.86.

Cronin, F.J., Krebs-Smith, S.M., Wyse, B.W. & Light, L. (1982) Characterizing food usage by demographic variables. *Journal of the American Dietetic Association*. 81 (6), 661–673.

Curb, J.D., Masaki, K., Rodriguez, B.L., Abbott, R.D., et al. (1996) Peripheral artery disease and cardiovascular risk factors in the elderly. The Honolulu Heart Program. *Arteriosclerosis, Thrombosis, and Vascular Biology*. 16 (12), 1495–1500.

D'Agostino, R.B., Grundy, S., Sullivan, L.M., Wilson, P., et al. (2001) Validation of the Framingham coronary heart disease prediction scores: results of a multiple ethnic groups investigation. *JAMA*. 286 (2), 180–187.

D'Agostino, R.B., Pencina, M.J., Massaro, J.M. & Coady, S. (2013) Cardiovascular Disease Risk Assessment: Insights from Framingham. *Global Heart*. [Online] 8 (1), 11–23. Available from: doi:10.1016/j.gheart.2013.01.001.

D'Agostino, R.B., Vasan, R.S., Pencina, M.J., Wolf, P.A., et al. (2008) General Cardiovascular Risk Profile for Use in Primary Care. *Circulation*. [Online] 117 (6), 743–753. Available from: doi:10.1161/CIRCULATIONAHA.107.699579.

D'Agostino Sr., R.B., Pencina, M.J., Massaro, J.M. & Coady, S. (2013) Cardiovascular Disease Risk Assessment: Insights from Framingham. *Global Heart*. [Online] 8 (1), 11–23. Available from: doi:10.1016/j.gheart.2013.01.001.

Dahlöf, B. (2010) Cardiovascular disease risk factors: epidemiology and risk assessment. *The American Journal of Cardiology*. [Online] 105 (1 Suppl), 3A-9A. Available from: doi:10.1016/j.amjcard.2009.10.007.

Danesh, J., Collins, R., Peto, R. & Lowe, G.D.O. (2000) Haematocrit, viscosity, erythrocyte sedimentation rate: meta-analyses of prospective studies of coronary heart disease. *European Heart Journal*. [Online] 21 (7), 515–520. Available from: doi:10.1053/euhj.1999.1699.

Diamond, G.A. (1983) A clinically relevant classification of chest discomfort. *Journal of the American College of Cardiology*. 1 (2 Pt 1), 574–575.

Diehm, C., Allenberg, J.R., Pittrow, D., Mahn, M., et al. (2009) Mortality and vascular morbidity in older adults with asymptomatic versus symptomatic peripheral artery disease. *Circulation*. [Online] 120 (21), 2053–2061. Available from: doi:10.1161/CIRCULATIONAHA.109.865600.

Ditschuneit, H.H., Flechtner-Mors, M. & Adler, G. (1995) Fibrinogen in obesity before and after weight reduction. *Obesity Research*. 3 (1), 43–48.

Doyle, J.T., Dawber, T.R., Kannel, W.B., Heslin, A.S., et al. (1962) Cigarette Smoking and Coronary Heart Disease. *New England Journal of Medicine*. [Online] 266 (16), 796–801. Available from: doi:10.1056/NEJM196204192661602.

Dugani, S. & Gaziano, T.A. (2016) 25 by 25: Achieving Global Reduction in Cardiovascular Mortality. *Current Cardiology Reports*. [Online] 18 (1), 10. Available from: doi:10.1007/s11886-015-0679-4.

Easton, J.D., Saver, J.L., Albers, G.W., Alberts, M.J., et al. (2009) Definition and evaluation of transient ischemic attack: a scientific statement for healthcare professionals from the American Heart Association/American Stroke Association Stroke Council; Council on Cardiovascular Surgery and Anesthesia; Council on Cardiovascular Radiology and Intervention; Council on Cardiovascular Nursing; and the Interdisciplinary Council on Peripheral Vascular Disease. The American Academy of Neurology affirms the value of this statement as an educational tool for neurologists. *Stroke*. [Online] 40 (6), 2276–2293. Available from: doi:10.1161/STROKEAHA.108.192218.

Eckel, R.H., Jakicic, J.M., Ard, J.D., de Jesus, J.M., et al. (2014) 2013 AHA/ACC guideline on lifestyle management to reduce cardiovascular risk: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. *Circulation*. [Online] 129 (25 Suppl 2), S76-99. Available from: doi:10.1161/01.cir.0000437740.48606.d1.

Eggers, K.M., Oldgren, J., Nordenskjöld, A. & Lindahl, B. (2004) Diagnostic value of serial measurement of cardiac markers in patients with chest pain: limited value of adding myoglobin to troponin I for exclusion of myocardial infarction. *American Heart Journal*. [Online] 148 (4), 574–581. Available from: doi:10.1016/j.ahj.2004.04.030.

Elasmi, M., Feki, M., Sanhaji, H., Jemaa, R., et al. (2009) Prévalence des facteurs de risque cardiovasculaires conventionnels dans la population du Grand Tunis. */data/revues/03987620/v57i2/S0398762009000297/*. [Online] Available from: https://www.em-consulte.com/en/article/211844 [Accessed: 4 March 2019].

Elis, A. & Lishner, M. (2004) [Composition of risk factors among acute myocardial infarction patients in Israel: sub-analysis of the Israeli National Prospective Survey on Acute Myocardial Infarction in 2000]. *Harefuah*. 143 (7), 479–481, 551, 550.

Elis, A., Pereg, D., Tirosh, A., Shochat, T., et al. (2008) Family history of cardiovascular disease does not predict risk-reducing behavior. *European Journal of Cardiovascular Prevention and Rehabilitation: Official Journal of the European Society of Cardiology, Working Groups on Epidemiology & Prevention and Cardiac Rehabilitation and Exercise Physiology*. [Online] 15 (3), 325–328. Available from: doi:10.1097/HJR.0b013e3282f50ed8.

El-Menyar, A., Al Suwaidi, J. & Al-Thani, H. (2013) Peripheral arterial disease in the Middle East: Underestimated predictor of worse outcome. *Global Cardiology Science & Practice*. [Online] 2013 (2), 98–113. Available from: doi:10.5339/gcsp.2013.13.

Emberson, J., Lees, K.R., Lyden, P., Blackwell, L., et al. (2014) Effect of treatment delay, age, and stroke severity on the effects of intravenous thrombolysis with alteplase for acute ischaemic stroke: a meta-analysis of individual patient data from randomised trials. *Lancet (London, England)*. [Online] 384 (9958), 1929–1935. Available from: doi:10.1016/S0140-6736(14)60584-5.

Eriksen, M., Mackay, J. & Ross, H. (2013) *The Tobacco Atlas*. 4 edition. Atlanta, Ga, American Cancer Society.

ESC, Rydén, L., Grant, P.J., Anker, S.D., et al. (2013) ESC Guidelines on diabetes, pre-diabetes, and cardiovascular diseases developed in collaboration with the EASD: the Task Force on diabetes, pre-diabetes, and cardiovascular diseases of the European Society of Cardiology (ESC) and developed in collaboration with the European Association for the Study of Diabetes (EASD). *European Heart Journal*. [Online] 34 (39), 3035–3087. Available from: doi:10.1093/eurheartj/eht108.

Escudero Augusto, D., Marqués Alvarez, L. & Taboada Costa, F. (2008) [Up-date in spontaneous cerebral hemorrhage]. *Medicina Intensiva*. 32 (6), 282–295.

Ettehad, D., Emdin, C.A., Kiran, A., Anderson, S.G., et al. (2016) Blood pressure lowering for prevention of cardiovascular disease and death: a systematic review and meta-analysis. *Lancet (London, England)*. [Online] 387 (10022), 957–967. Available from: doi:10.1016/S0140-6736(15)01225-8.

European Cardiovascular Disease Statistics (2012) *2012 European Cardiovascular Disease Statistics*. [Online]. 2012. Available from: https://www.escardio.org/The-ESC/What-we-do/Initiatives/EuroHeart/2012-European-Cardiovascular-Disease-Statistics [Accessed: 16 July 2018].

Fan, W. (2017) Epidemiology in diabetes mellitus and cardiovascular disease. *Cardiovascular Endocrinology*. [Online] 6 (1), 8–16. Available from: doi:10.1097/XCE.0000000000000116.

Fang, N., Jiang, M. & Fan, Y. (2016) Ideal cardiovascular health metrics and risk of cardiovascular disease or mortality: A meta-analysis. *International Journal of Cardiology*. [Online] 214, 279–283. Available from: doi:10.1016/j.ijcard.2016.03.210.

Farah, R., Zeidan, R.K., Chahine, M.N., Asmar, R., et al. (2015) Prevalence of stroke symptoms among stroke-free residents: first national data from Lebanon. *International Journal of Stroke*. [Online] 10 (SA100), 83–88. Available from: doi:10.1111/ijs.12563.

Feig, D.S., Zinman, B., Wang, X. & Hux MD, J.E. (2008) Risk of development of diabetes mellitus after diagnosis of gestational diabetes. *CMAJ : Canadian Medical Association Journal*. [Online] 179 (3), 229–234. Available from: doi:10.1503/cmaj.080012.

Feigin, V.L., Norrving, B. & Mensah, G.A. (2017) Global Burden of Stroke. *Circulation Research*. [Online] 120 (3), 439–448. Available from: doi:10.1161/CIRCRESAHA.116.308413.

Feigin, V.L., Roth, G.A., Naghavi, M., Parmar, P., et al. (2016) Global burden of stroke and risk factors in 188 countries, during 1990–2013: a systematic analysis for the Global Burden of Disease Study 2013. *The Lancet Neurology*. [Online] 15 (9), 913–924. Available from: doi:10.1016/S1474-4422(16)30073-4.

Fihn, S.D., Gardin, J.M., Abrams, J., Berra, K., et al. (2012) 2012 ACCF/AHA/ACP/AATS/PCNA/SCAI/STS Guideline for the Diagnosis and Management of Patients With Stable Ischemic Heart Disease: A Report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines, and the American College of Physicians, American Association for Thoracic Surgery, Preventive Cardiovascular Nurses Association, Society for Cardiovascular Angiography and Interventions, and Society of Thoracic Surgeons. *Circulation*. [Online] 126 (25), e354–e471. Available from: doi:10.1161/CIR.0b013e318277d6a0.

Filion, K.B. & Luepker, R.V. (2013) Cigarette Smoking and Cardiovascular Disease: Lessons from Framingham. *Global Heart*. [Online] 8 (1), 35–41. Available from: doi:10.1016/j.gheart.2012.12.005.

Fischbacher, C.M., Bhopal, R., Unwin, N., White, M., et al. (2001) The performance of the Rose angina questionnaire in South Asian and European origin populations: a comparative study in Newcastle, UK. *International Journal of Epidemiology*. [Online] 30 (5), 1009–1016. Available from: doi:10.1093/ije/30.5.1009.

Flemming, K.D. (2015) *Cerebrovascular Anatomy and Pathophysiology*. [Online]. Oxford University Press. Available from: http://oxfordmedicine.com/view/10.1093/med/9780190214883.001.0001/med-9780190214883-chapter-1 [Accessed: 27 May 2018].

Fogari, R., Zoppi, A., Marasi, G., Vanasia, A., et al. (1994) Associations between plasma fibrinogen levels and cardiovascular risk factors in hypertensive men. *Journal of Cardiovascular Risk*. 1 (4), 341–345.

Forouzanfar, M.H., Bhutta, Z.A., Burnett, R., Cercy, K., et al. (2016) Global, regional, and national comparative risk assessment of 79 behavioural, environmental and occupational, and metabolic risks or clusters of risks, 1990–2015: a systematic analysis for the Global Burden of Disease Study 2015. *The Lancet*. [Online] 388 (10053), 1659–1724. Available from: doi:10.1016/S0140-6736(16)31679-8.

Foulkes, M.A., Wolf, P.A., Price, T.R., Mohr, J.P., et al. (1988) The Stroke Data Bank: design, methods, and baseline characteristics. *Stroke*. 19 (5), 547–554.

Foundation, T.H. (n.d.) *New app helps patients to stay on their meds*. [Online]. The Heart Foundation. Available from: https://www.heartfoundation.org.au/news/new-app-helps-patients-to-stay-on-their-meds [Accessed: 20 October 2018].

Fowkes, F.G., Housley, E., Riemersma, R.A., Macintyre, C.C., et al. (1992) Smoking, lipids, glucose intolerance, and blood pressure as risk factors for peripheral atherosclerosis compared with ischemic heart disease in the Edinburgh Artery Study. *American Journal of Epidemiology*. 135 (4), 331–340.

Fowkes, F.G.R., Rudan, D., Rudan, I., Aboyans, V., et al. (2013) Comparison of global estimates of prevalence and risk factors for peripheral artery disease in 2000 and 2010: a systematic review and analysis. *Lancet (London, England)*. [Online] 382 (9901), 1329–1340. Available from: doi:10.1016/S0140-6736(13)61249-0.

Freiberg, J.J., Tybjaerg-Hansen, A., Jensen, J.S. & Nordestgaard, B.G. (2008) Nonfasting triglycerides and risk of ischemic stroke in the general population. *JAMA*. [Online] 300 (18), 2142–2152. Available from: doi:10.1001/jama.2008.621.

Gaziano, T.A., Young, C.R., Fitzmaurice, G., Atwood, S., et al. (2008) Laboratory-based versus non-laboratory-based method for assessment of cardiovascular disease risk: the NHANES I Follow-up Study cohort. *The Lancet*. [Online] 371 (9616), 923–931. Available from: doi:10.1016/S0140-6736(08)60418-3.

GBD 2015 Risk Factors Collaborators (2016) Global, regional, and national comparative risk assessment of 79 behavioural, environmental and occupational, and metabolic risks or clusters of risks, 1990-2015: a systematic analysis for the Global Burden of Disease Study 2015. *Lancet (London, England)*. [Online] 388 (10053), 1659–1724. Available from: doi:10.1016/S0140-6736(16)31679-8.

GBD 2016 Causes of Death Collaborators (2017) Global, regional, and national age-sex specific mortality for 264 causes of death, 1980-2016: a systematic analysis for the Global Burden of Disease Study 2016. *Lancet (London, England)*. [Online] 390 (10100), 1151–1210. Available from: doi:10.1016/S0140-6736(17)32152-9.

Gehani, A.A., Al-Hinai, A.T., Zubaid, M., Almahmeed, W., et al. (2014) Association of risk factors with acute myocardial infarction in Middle Eastern countries: the INTERHEART Middle East study. *European Journal of Preventive Cardiology*. [Online] 21 (4), 400–410. Available from: doi:10.1177/2047487312465525.

Gerhard-Herman, M.D., Gornik, H.L., Barrett, C., Barshes, N.R., et al. (2017) 2016 AHA/ACC Guideline on the Management of Patients With Lower Extremity Peripheral Artery Disease: Executive Summary: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. *Journal of the American College of Cardiology*. [Online] 69 (11), 1465–1508. Available from: doi:10.1016/j.jacc.2016.11.008.

Gerloni, R., Mucci, L., Ciarambino, T., Ventura, M., et al. (2017) Management of stable coronary artery disease: from evidence to clinical practice. *Italian Journal of Medicine*. 11 (2), 114–133.

Giacaman, R., Khatib, R., Shabaneh, L., Ramlawi, A., et al. (2009) Health status and health services in the occupied Palestinian territory. *The Lancet*. 373 (9666), 837–849.

Giang, K.W., Björck, L., Nielsen, S., Novak, M., et al. (2013) Twenty-year trends in long-term mortality risk in 17,149 survivors of ischemic stroke less than 55 years of age. *Stroke*. [Online] 44 (12), 3338–3343. Available from: doi:10.1161/STROKEAHA.113.002936.

Giovino, G.A., Mirza, S.A., Samet, J.M., Gupta, P.C., et al. (2012) Tobacco use in 3 billion individuals from 16 countries: an analysis of nationally representative cross-sectional household surveys. *The Lancet*. 380 (9842), 668–679.

Giugliano, D., Maiorino, M.I., Bellastella, G. & Esposito, K. (2018) Type 2 diabetes and cardiovascular prevention: the dogmas disputed. *Endocrine*. [Online] 60 (2), 224–228. Available from: doi:10.1007/s12020-017-1418-y.

Goff, D.C., Lloyd-Jones, D.M., Bennett, G., Coady, S., et al. (2014) 2013 ACC/AHA Guideline on the Assessment of Cardiovascular Risk: A Report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. *Circulation*. [Online] 129 (25 suppl 2), S49–S73. Available from: doi:10.1161/01.cir.0000437741.48606.98.

Goldbourt, U., Yaari, S. & Medalie, J.H. (1997) Isolated low HDL cholesterol as a risk factor for coronary heart disease mortality. A 21-year follow-up of 8000 men. *Arteriosclerosis, Thrombosis, and Vascular Biology*. 17 (1), 107–113.

Gordon, D.J., Probstfield, J.L., Garrison, R.J., Neaton, J.D., et al. (1989) High-density lipoprotein cholesterol and cardiovascular disease. Four prospective American studies. *Circulation*. 79 (1), 8–15.

Graham, I., Atar, D., Borch-Johnsen, K., Boysen, G., et al. (2007) European guidelines on cardiovascular disease prevention in clinical practice: executive summary: Fourth Joint Task Force of the European Society of Cardiology and Other Societies on Cardiovascular Disease Prevention in Clinical Practice (Constituted by representatives of nine societies and by invited experts). *European Heart Journal*. [Online] 28 (19), 2375–2414. Available from: doi:10.1093/eurheartj/ehm316.

Grainger-Gasser, A., Perel, P., Lagier-Hässig, L. & Wood, D. (2017) The Road to 25×25: Update on WHF CVD Roadmaps. *Global Heart*. [Online] 12 (3), 269–270. Available from: doi:10.1016/j.gheart.2016.05.004.

Guy De Backer (2017) *Prevention of cardiovascular disease: recent achievements and remaining challeng*. [Online]. 2017. Available from: https://www.escardio.org/Journals/E-Journal-of-Cardiology-Practice/Volume-15/prevention-of-cardiovascular-disease-recent-achievements-and-remaining-challeng [Accessed: 6 October 2018].

Hales, C.M., Carroll, M.D., Fryar, C.D. & Ogden, C.L. (2017) Prevalence of Obesity Among Adults and Youth: United States, 2015-2016. *NCHS data brief*. (288), 1–8.

Hamilton, S.J., Mills, B., Birch, E.M. & Thompson, S.C. (2018) Smartphones in the secondary prevention of cardiovascular disease: a systematic review. *BMC Cardiovascular Disorders*. [Online] 18. Available from: doi:10.1186/s12872-018-0764-x [Accessed: 19 October 2018].

Hamm, C.W., Heeschen, C., Falk, E. & Fox, K.A. (2006) *12 Acute Coronary Syndromes: Pathophysiology, Diagnosis and Risk Stratification*.

Hankey, G.J. & Warlow, C.P. (1999) Treatment and secondary prevention of stroke: evidence, costs, and effects on individuals and populations. *Lancet (London, England)*. [Online] 354 (9188), 1457–1463. Available from: doi:10.1016/S0140-6736(99)04407-4.

Hawe, E., Talmud, P.J., Miller, G.J. & Humphries, S.E. (2003) Family history is a coronary heart disease risk factor in the second Northwick Park Heart Study. *ANN HUM GENET*. 67, 97–106.

He, T., Liu, X., Xu, N., Li, Y., et al. (2017) Diagnostic models of the pre-test probability of stable coronary artery disease: A systematic review. *Clinics*. [Online] 72 (2), 188–196. Available from: doi:10.6061/clinics/2017(03)10.

Health, N.C. for C.D.P. and H.P. (US) O. on S. and (2014) *Cardiovascular Diseases*. [Online]. Centers for Disease Control and Prevention (US). Available from: https://www.ncbi.nlm.nih.gov/books/NBK294323/ [Accessed: 6 July 2018].

Heart and Stroke Foundation of Canada (2014) *Health eTools*. [Online]. 2014. Heart and Stroke Foundation of Canada. Available from: http://www.heartandstroke.ca/get-healthy/health-etools [Accessed: 20 October 2018].

Heidenreich, P.A., Trogdon, J.G., Khavjou, O.A., Butler, J., et al. (2011) Forecasting the future of cardiovascular disease in the United States: a policy statement from the American Heart Association. *Circulation*. [Online] 123 (8), 933–944. Available from: doi:10.1161/CIR.0b013e31820a55f5.

Heinrich, J., Balleisen, L., Schulte, H., Assmann, G., et al. (1994) Fibrinogen and factor VII in the prediction of coronary risk. Results from the PROCAM study in healthy men. *Arteriosclerosis and Thrombosis: A Journal of Vascular Biology*. 14 (1), 54–59.

Hendrani, A.D., Adesiyun, T., Quispe, R., Jones, S.R., et al. (2016) Dyslipidemia management in primary prevention of cardiovascular disease: Current guidelines and strategies. *World Journal of Cardiology*. [Online] 8 (2), 201–210. Available from: doi:10.4330/wjc.v8.i2.201.

Hiatt, W.R., Hoag, S. & Hamman, R.F. (1995) Effect of diagnostic criteria on the prevalence of peripheral arterial disease. The San Luis Valley Diabetes Study. *Circulation*. 91 (5), 1472–1479.

Hirsch, A.T., Criqui, M.H., Treat-Jacobson, D., Regensteiner, J.G., et al. (2001) Peripheral arterial disease detection, awareness, and treatment in primary care. *JAMA*. 286 (11), 1317–1324.

Hirsch, A.T., Haskal, Z.J., Hertzer, N.R., Bakal, C.W., et al. (2006) ACC/AHA 2005 Practice Guidelines for the Management of Patients With Peripheral Arterial Disease (Lower Extremity, Renal, Mesenteric, and Abdominal Aortic): A Collaborative Report from the American Association for Vascular Surgery/Society for Vascular Surgery,* Society for Cardiovascular Angiography and Interventions, Society for Vascular Medicine and Biology, Society of Interventional Radiology, and the ACC/AHA Task Force on Practice Guidelines (Writing Committee to Develop Guidelines for the Management of Patients With Peripheral Arterial Disease): Endorsed by the American Association of Cardiovascular and Pulmonary Rehabilitation; National Heart, Lung, and Blood Institute; Society for Vascular Nursing; TransAtlantic Inter-Society Consensus; and Vascular Disease Foundation. *Circulation*. [Online] 113 (11), e463–e654. Available from: doi:10.1161/CIRCULATIONAHA.106.174526.

Hitchman, S.C. & Fong, G.T. (2011) Gender empowerment and female-to-male smoking prevalence ratios. *Bulletin of the World Health Organization*. [Online] 89 (3), 195–202. Available from: doi:10.2471/BLT.10.079905.

Hooi, J.D., Kester, A.D., Stoffers, H.E., Overdijk, M.M., et al. (2001) Incidence of and risk factors for asymptomatic peripheral arterial occlusive disease: a longitudinal study. *American Journal of Epidemiology*. 153 (7), 666–672.

Hooi, J.D., Stoffers, H.E., Kester, A.D., Rinkens, P.E., et al. (1998) Risk factors and cardiovascular diseases associated with asymptomatic peripheral arterial occlusive disease. The Limburg PAOD Study. Peripheral Arterial Occlusive Disease. *Scandinavian Journal of Primary Health Care*. 16 (3), 177–182.

Howard, R.S. (2016) The management of ischaemic stroke. *Anaesthesia & Intensive Care Medicine*. [Online] 17 (12), 591–595. Available from: doi:10.1016/j.mpaic.2016.09.009.

Hubert, H.B., Feinleib, M., McNamara, P.M. & Castelli, W.P. (1983) Obesity as an independent risk factor for cardiovascular disease: a 26-year follow-up of participants in the Framingham Heart Study. *Circulation*. 67 (5), 968–977.

Hunt, S.C., Gwinn, M. & Adams, T.D. (2003) Family history assessment: strategies for prevention of cardiovascular disease. *American Journal of Preventive Medicine*. 24 (2), 136–142.

Hunter, D.J. & Reddy, K.S. (2013) *Noncommunicable Diseases*. [Online]. 2 October 2013. http://dx.doi.org/10.1056/NEJMra1109345. Available from: doi:10.1056/NEJMra1109345 [Accessed: 7 March 2019].

Husseini, A., Abu-Rmeileh, N.M., Mikki, N., Ramahi, T.M., et al. (2009) Cardiovascular diseases, diabetes mellitus, and cancer in the occupied Palestinian territory. *The Lancet*. [Online] 373 (9668), 1041–1049. Available from: doi:10.1016/S0140-6736(09)60109-4.

Huxley, R., Barzi, F. & Woodward, M. (2006) Excess risk of fatal coronary heart disease associated with diabetes in men and women: meta-analysis of 37 prospective cohort studies. *BMJ*. [Online] 332 (7533), 73–78. Available from: doi:10.1136/bmj.38678.389583.7C.

Huxley, R.R. & Woodward, M. (2011) Cigarette smoking as a risk factor for coronary heart disease in women compared with men: a systematic review and meta-analysis of prospective cohort studies. *Lancet (London, England)*. [Online] 378 (9799), 1297–1305. Available from: doi:10.1016/S0140-6736(11)60781-2.

IDF 2009 (n.d.) *International Diabetes Federation. IDF Diabetes Atlas, 4th edn. Brussels, Belgium: International Diabetes Federation; 2009 (http://www.idf.org/sites/default/files/da5/IDF%20 Diabetes%20Atlas%204th%20edition.pdf , accessed 26 March 2014). - Recherche Google*. [Online]. Available from: https://www.google.com/search?source=hp&ei=PlTfWvkoi4voBO2ZnaAF&q=+International+Diabetes+Federation.+IDF+Diabetes+Atlas%2C+4th+edn.+Brussels%2C+Belgium%3A+International+Diabetes+Federation%3B+2009+%28http%3A%2F%2Fwww.idf.org%2Fsites%2Fdefault%2Ffiles%2Fda5%2FIDF%2520+Diabetes%2520Atlas%25204th%2520edition.pdf+%2C+accessed+26+March+2014%29.&oq=+International+Diabetes+Federation.+IDF+Diabetes+Atlas%2C+4th+edn.+Brussels%2C+Belgium%3A+International+Diabetes+Federation%3B+2009+%28http%3A%2F%2Fwww.idf.org%2Fsites%2Fdefault%2Ffiles%2Fda5%2FIDF%2520+Diabetes%2520Atlas%25204th%2520edition.pdf+%2C+accessed+26+March+2014%29.&gs_l=psy-ab.12...2514.2514.0.3031.1.1.0.0.0.0.0.0..0.0....0...1.2.64.psy-ab..1.0.0....0.wZELq3A21UI [Accessed: 24 April 2018].

IDF 2015 (2015) *NTERNATIONAL DIABETIC FEDERATION*.

Ingolfsson, I.Ö., Sigurdsson, G., Sigvaldason, H., Thorgeirsson, G., et al. (1994) A marked decline in the prevalence and incidence of intermittent claudication in icelandic men 1968–1986: A strong relationship to smoking and serum cholesterol—The Reykjavik study. *Journal of Clinical Epidemiology*. [Online] 47 (11), 1237–1243. Available from: doi:10.1016/0895-4356(94)90128-7.

Inoue, M., Nagata, C., Tsuji, I., Sugawara, Y., et al. (2012) Impact of alcohol intake on total mortality and mortality from major causes in Japan: a pooled analysis of six large-scale cohort studies. *Journal of Epidemiology and Community Health*. [Online] 66 (5), 448–456. Available from: doi:10.1136/jech.2010.121830.

Islam, S.M.S., Purnat, T.D., Phuong, N.T.A., Mwingira, U., et al. (2014) Non-Communicable Diseases (NCDs) in developing countries: a symposium report. *Globalization and*

Health. [Online] 10. Available from: doi:10.1186/s12992-014-0081-9 [Accessed: 25 April 2018].

Jabbour, S. & Yamout, R. (2012) *Public Health in the Arab World*. Cambridge University Press.

James, P.A., Oparil, S., Carter, B.L., Cushman, W.C., et al. (2014) 2014 evidence-based guideline for the management of high blood pressure in adults: report from the panel members appointed to the Eighth Joint National Committee (JNC 8). *JAMA*. [Online] 311 (5), 507–520. Available from: doi:10.1001/jama.2013.284427.

Jellinger, P.S., Handelsman, Y., Rosenblit, P.D., Bloomgarden, Z.T., et al. (2017) AMERICAN ASSOCIATION OF CLINICAL ENDOCRINOLOGISTS AND AMERICAN COLLEGE OF ENDOCRINOLOGY GUIDELINES FOR MANAGEMENT OF DYSLIPIDEMIA AND PREVENTION OF CARDIOVASCULAR DISEASE. *Endocrine Practice: Official Journal of the American College of Endocrinology and the American Association of Clinical Endocrinologists*. [Online] 23 (Suppl 2), 1–87. Available from: doi:10.4158/EP171764.APPGL.

Joosten, M.M., Pai, J.K., Bertoia, M.L., Rimm, E.B., et al. (2012) Associations between Conventional Cardiovascular Risk Factors and Risk of Peripheral Artery Disease in Men. *JAMA : the journal of the American Medical Association*. [Online] 308 (16), 1660–1667. Available from: doi:10.1001/jama.2012.13415.

Joseph, J., Velasco, A., Hage, F.G. & Reyes, E. (2018) Guidelines in review: Comparison of ESC and ACC/AHA guidelines for the diagnosis and management of patients with stable coronary artery disease. *Journal of Nuclear Cardiology*. [Online] 25 (2), 509–515. Available from: doi:10.1007/s12350-017-1055-0.

Joshipura, K.J., Ascherio, A., Manson, J.E., Stampfer, M.J., et al. (1999) Fruit and vegetable intake in relation to risk of ischemic stroke. *JAMA*. 282 (13), 1233–1239.

Joshipura, K.J., Hu, F.B., Manson, J.E., Stampfer, M.J., et al. (2001) The effect of fruit and vegetable intake on risk for coronary heart disease. *Annals of Internal Medicine*. 134 (12), 1106–1114.

Julius, S., Nesbitt, S.D., Egan, B.M., Weber, M.A., et al. (2006) Feasibility of treating prehypertension with an angiotensin-receptor blocker. *The New England Journal of Medicine*. [Online] 354 (16), 1685–1697. Available from: doi:10.1056/NEJMoa060838.

Kannel, W.B., Dawber, T.R., Kagan, A., Revotskie, N., et al. (1961) Factors of risk in the development of coronary heart disease--six year follow-up experience. The Framingham Study. *Annals of Internal Medicine*. 55, 33–50.

Kannel, W.B. & Sorlie, P. (1979) Some health benefits of physical activity. The Framingham Study. *Archives of Internal Medicine*. 139 (8), 857–861.

Kannel, W.B. & Vasan, R.S. (2009) Is Age Really a Non-modifiable Cardiovascular Risk Factor? *The American journal of cardiology*. [Online] 104 (9), 1307–1310. Available from: doi:10.1016/j.amjcard.2009.06.051.

Kannel, W.B. & Wilson PWf (2003) *Chapter B81. Cardiovascular risk factors and hypertension. In: Izzo JL, Black HR, ed- itors. Hypertension Primer,. 3rd Edition. AHA*.

Kardia, S.L.R., Modell, S.M. & Peyser, P.A. (2003) Family-centered approaches to understanding and preventing coronary heart disease. *American Journal of Preventive Medicine*. 24 (2), 143–151.

Kaur, J. (2014) A Comprehensive Review on Metabolic Syndrome. *Cardiology Research and Practice*. [Online] 2014. Available from: doi:10.1155/2014/943162 [Accessed: 14 April 2018].

Kearney, P.M., Whelton, M., Reynolds, K., Muntner, P., et al. (2005) Global burden of hypertension: analysis of worldwide data. *Lancet (London, England)*. [Online] 365 (9455), 217–223. Available from: doi:10.1016/S0140-6736(05)17741-1.

Khatib, O. (2004) Noncommunicable diseases: risk factors and regional strategies for prevention and care. *Eastern Mediterranean Health Journal = La Revue De Sante De La Mediterranee Orientale = Al-Majallah Al-Sihhiyah Li-Sharq Al-Mutawassit*. 10 (6), 778–788.

Kirchhof, P., Benussi, S., Kotecha, D., Ahlsson, A., et al. (2016) 2016 ESC Guidelines for the management of atrial fibrillation developed in collaboration with EACTS. *Europace: European Pacing, Arrhythmias, and Cardiac Electrophysiology: Journal of the Working Groups on Cardiac Pacing, Arrhythmias, and Cardiac Cellular Electrophysiology of the European Society of Cardiology*. [Online] 18 (11), 1609–1678. Available from: doi:10.1093/europace/euw295.

Kissela, B.M., Khoury, J.C., Alwell, K., Moomaw, C.J., et al. (2012) Age at stroke: temporal trends in stroke incidence in a large, biracial population. *Neurology*. [Online] 79 (17), 1781–1787. Available from: doi:10.1212/WNL.0b013e318270401d.

Kivimäki, M. & Steptoe, A. (2018) Effects of stress on the development and progression of cardiovascular disease. *Nature Reviews Cardiology*. [Online] 15 (4), 215–229. Available from: doi:10.1038/nrcardio.2017.189.

Klatsky, A.L. (2015) Alcohol and cardiovascular diseases: where do we stand today? *Journal of Internal Medicine*. [Online] 278. Available from: doi:10.1111/joim.12390 [Accessed: 7 July 2018].

Kontis, V., Mathers, C.D., Rehm, J., Stevens, G.A., et al. (2014) Contribution of six risk factors to achieving the 25×25 non-communicable disease mortality reduction target: a modelling study. *Lancet (London, England)*. [Online] 384 (9941), 427–437. Available from: doi:10.1016/S0140-6736(14)60616-4.

Korff, S., Katus, H.A. & Giannitsis, E. (2006) Differential diagnosis of elevated troponins. *Heart (British Cardiac Society)*. [Online] 92 (7), 987–993. Available from: doi:10.1136/hrt.2005.071282.

Kotseva, K., Wood, D., De Bacquer, D., De Backer, G., et al. (2016) EUROASPIRE IV: A European Society of Cardiology survey on the lifestyle, risk factor and therapeutic management of coronary patients from 24 European countries. *European Journal of Preventive Cardiology*. [Online] 23 (6), 636–648. Available from: doi:10.1177/2047487315569401.

Krishnamurthi, R.V., Feigin, V.L., Forouzanfar, M.H., Mensah, G.A., et al. (2013) Global and regional burden of first-ever ischaemic and haemorrhagic stroke during 1990–2010: findings from the Global Burden of Disease Study 2010. *The Lancet Global Health*. [Online] 1 (5), e259–e281. Available from: doi:10.1016/S2214-109X(13)70089-5.

Kullo, I.J. & Cooper, L.T. (2010) Early identification of cardiovascular risk using genomics and proteomics. *Nature reviews. Cardiology*. [Online] 7 (6), 309–317. Available from: doi:10.1038/nrcardio.2010.53.

Kulshreshtha, A., Vaccarino, V., Judd, S.E., Howard, V.J., et al. (2013) Life's Simple 7 and risk of incident stroke: the reasons for geographic and racial differences in stroke study. *Stroke*. [Online] 44 (7), 1909–1914. Available from: doi:10.1161/STROKEAHA.111.000352.

Kumar, A. & Cannon, C.P. (2009) Acute Coronary Syndromes: Diagnosis and Management, Part II. *Mayo Clinic Proceedings*. 84 (11), 1021–1036.

Labarthe, D. (2010) *Epidemiology And Prevention Of Cardiovascular Diseases: A Global Challenge*. 2 edition. Sudbury, Mass, Jones & Bartlett Learning.

Lackland, D.T., Roccella, E.J., Deutsch, A.F., Fornage, M., et al. (n.d.) Factors Influencing the Decline in Stroke Mortality: A Statement From the American Heart Association/American Stroke Association. *Stroke*. 45 (1), 315–353.

Lahoud, N., Salameh, P., Saleh, N. & Hosseini, H. (2016) Prevalence of Lebanese stroke survivors: A comparative pilot study. *Journal of Epidemiology and Global Health*. [Online] 6 (3), 169–176. Available from: doi:10.1016/j.jegh.2015.10.001.

Lampe, F.C., Whincup, P.H., Wannamethee, S.G., Ebrahim, S., et al. (1998) Chest pain on questionnaire and prediction of major ischaemic heart disease events in men. *European Heart Journal*. 19 (1), 63–73.

Langsted, A. & Nordestgaard, B.G. (2019) Nonfasting versus fasting lipid profile for cardiovascular risk prediction. *Pathology*. [Online] 51 (2), 131–141. Available from: doi:10.1016/j.pathol.2018.09.062.

Law, M.R., Wald, N.J. & Thompson, S.G. (1994) By how much and how quickly does reduction in serum cholesterol concentration lower risk of ischaemic heart disease? *BMJ (Clinical research ed.)*. 308 (6925), 367–372.

Lee, C.D., Folsom, A.R. & Blair, S.N. (2003) Physical activity and stroke risk: a meta-analysis. *Stroke*. [Online] 34 (10), 2475–2481. Available from: doi:10.1161/01.STR.0000091843.02517.9D.

Leon, B.M. & Maddox, T.M. (2015) Diabetes and cardiovascular disease: Epidemiology, biological mechanisms, treatment recommendations and future research. *World Journal of Diabetes*. [Online] 6 (13), 1246–1258. Available from: doi:10.4239/wjd.v6.i13.1246.

Leonarda, G. & Gabriella, L. (2015) Gender di erences in cardiovascular disease. *Journal of Integrative Cardiology*. 20–22.

Levy, P.J. (2002) Epidemiology and pathophysiology of peripheral arterial disease. *Clinical Cornerstone*. [Online] 4 (5), 1–13. Available from: doi:10.1016/S1098-3597(02)90012-8.

Liao, D., Myers, R., Hunt, S., Shahar, E., et al. (1997) Familial history of stroke and stroke risk. The Family Heart Study. *Stroke*. 28 (10), 1908–1912.

Liu, S., Lee, I.M., Ajani, U., Cole, S.R., et al. (2001) Intake of vegetables rich in carotenoids and risk of coronary heart disease in men: The Physicians' Health Study. *International Journal of Epidemiology*. 30 (1), 130–135.

Lloyd-Jones, D., Adams, R., Carnethon, M., De Simone, G., et al. (2009) Heart disease and stroke statistics--2009 update: a report from the American Heart Association Statistics

Committee and Stroke Statistics Subcommittee. *Circulation*. [Online] 119 (3), e21-181. Available from: doi:10.1161/CIRCULATIONAHA.108.191261.

Lloyd-Jones, D.M., Larson, M.G., Beiser, A. & Levy, D. (1999) Lifetime risk of developing coronary heart disease. *Lancet (London, England)*. [Online] 353 (9147), 89–92. Available from: doi:10.1016/S0140-6736(98)10279-9.

Louis R, C. & Scot E, K. (2018) *Etiology, classification, and epidemiology of stroke*.

Lowe, G.D.O. (1995) Fibrinogen and Cardiovascular Disease: Historical Introduction. *European Heart Journal*. [Online] 16 (suppl_A), 2–5. Available from: doi:10.1093/eurheartj/16.suppl_A.2.

Lowres, N., Neubeck, L., Salkeld, G., Krass, I., et al. (2014) Feasibility and cost-effectiveness of stroke prevention through community screening for atrial fibrillation using iPhone ECG in pharmacies. The SEARCH-AF study. *Thrombosis and Haemostasis*. [Online] 111 (6), 1167–1176. Available from: doi:10.1160/TH14-03-0231.

Lozano, R., Naghavi, M., Foreman, K., Lim, S., et al. (2012) Global and regional mortality from 235 causes of death for 20 age groups in 1990 and 2010: a systematic analysis for the Global Burden of Disease Study 2010. *The Lancet*. [Online] 380 (9859), 2095–2128. Available from: doi:10.1016/S0140-6736(12)61728-0.

LUKE, A. (2017) *Are we facing a noncommunicable disease pandemic? - ScienceDirect*. [Online]. 2017. Available from: https://www.sciencedirect.com/science/article/pii/S2210600616301009 [Accessed: 25 April 2018].

Lusis, A.J. (2000) *Atherosclerosis*. [Online]. 14 September 2000. Nature. Available from: doi:10.1038/35025203 [Accessed: 8 May 2018].

Majeed, A., El-Sayed, A.A., Khoja, T., Alshamsan, R., et al. (2014) Diabetes in the Middle-East and North Africa: an update. *Diabetes Research and Clinical Practice*. [Online] 103 (2), 218–222. Available from: doi:10.1016/j.diabres.2013.11.008.

Mandil, A., Chaaya, M. & Saab, D. (2013) Health status, epidemiological profile and prospects: Eastern Mediterranean region. *International Journal of Epidemiology*. [Online] 42 (2), 616–626. Available from: doi:10.1093/ije/dyt026.

Manolio, T.A., Pearson, T.A., Wenger, N.K., Barrett-Connor, E., et al. (1992) Cholesterol and heart disease in older persons and women. Review of an NHLBI workshop. *Annals of Epidemiology*. 2 (1–2), 161–176.

Manson, J.E. (1996) *Prevention of myocardial infarction*. [Online]. New York : Oxford University Press. Available from: https://trove.nla.gov.au/version/38437279 [Accessed: 15 July 2018].

Mansour, A.A., Al-Maliky, A.A., Kasem, B., Jabar, A., et al. (2014) Prevalence of diagnosed and undiagnosed diabetes mellitus in adults aged 19 years and older in Basrah, Iraq. *Diabetes, Metabolic Syndrome and Obesity: Targets and Therapy*. [Online] 7, 139–144. Available from: doi:10.2147/DMSO.S59652.

Marenberg, M.E., Risch, N., Berkman, L.F., Floderus, B., et al. (1994) Genetic susceptibility to death from coronary heart disease in a study of twins. *The New England Journal of Medicine*. [Online] 330 (15), 1041–1046. Available from: doi:10.1056/NEJM199404143301503.

Markus, H. (2016) Stroke: causes and clinical features. *Medicine*. 44 (9), 515–520.

Martin, S.S., Feldman, D.I., Blumenthal, R.S., Jones, S.R., et al. (2015) mActive: A Randomized Clinical Trial of an Automated mHealth Intervention for Physical Activity Promotion. *Journal of the American Heart Association*. [Online] 4 (11). Available from: doi:10.1161/JAHA.115.002239.

Marx, J.A., Hockberger, R.S. & Walls, R.M. (2006) *Rosen's Emergency Medicine: Concepts and Clinical Practice, Sixth Edition, 3 volume set*. 6th edition. Philadelphia, Mosby Elsevier.

Matheus, A.S. de M., Tannus, L.R.M., Cobas, R.A., Palma, C.C.S., et al. (2013) *Impact of Diabetes on Cardiovascular Disease: An Update*. [Online]. 2013. International Journal of Hypertension. Available from: doi:10.1155/2013/653789 [Accessed: 2 July 2018].

Maziak, W. (2011) The global epidemic of waterpipe smoking. *Addictive Behaviors*. [Online] 36 (1–2), 1–5. Available from: doi:10.1016/j.addbeh.2010.08.030.

Maziak, W., Nakkash, R., Bahelah, R., Husseini, A., et al. (2014) Tobacco in the Arab world: old and new epidemics amidst policy paralysis. *Health Policy and Planning*. [Online] 29 (6), 784–794. Available from: doi:10.1093/heapol/czt055.

McDermott, M.M., Greenland, P., Liu, K., Guralnik, J.M., et al. (2001) Leg symptoms in peripheral arterial disease: associated clinical characteristics and functional impairment. *JAMA*. 286 (13), 1599–1606.

McTigue, K.M., Chang, Y.-F., Eaton, C., Garcia, L., et al. (2014) Severe obesity, heart disease, and death among white, African American, and Hispanic postmenopausal women. *Obesity (Silver Spring, Md.)*. [Online] 22 (3), 801–810. Available from: doi:10.1002/oby.20224.

Mehio Sibai, A., Nasreddine, L., Mokdad, A.H., Adra, N., et al. (2010) Nutrition transition and cardiovascular disease risk factors in Middle East and North Africa countries: reviewing the evidence. *Annals of Nutrition & Metabolism*. [Online] 57 (3–4), 193–203. Available from: doi:10.1159/000321527.

Mehta, N., Ogendo, S. & Awori, M. (2017) Prevalence, Progression and Associated Risk Factors of Asymptomatic Peripheral Arterial Disease. *Annals of African Surgery*. [Online] 14 (1). Available from: https://www.ajol.info/index.php/aas/article/view/164313 [Accessed: 18 February 2018].

Mehta, S.R., Tanguay, J.-F., Eikelboom, J.W., Jolly, S.S., et al. (2010) Double-dose versus standard-dose clopidogrel and high-dose versus low-dose aspirin in individuals undergoing percutaneous coronary intervention for acute coronary syndromes (CURRENT-OASIS 7): a randomised factorial trial. *Lancet (London, England)*. [Online] 376 (9748), 1233–1243. Available from: doi:10.1016/S0140-6736(10)61088-4.

Meigs, J.B., D'Agostino, R.B., Wilson, P.W., Cupples, L.A., et al. (1997) Risk variable clustering in the insulin resistance syndrome. The Framingham Offspring Study. *Diabetes*. 46 (10), 1594–1600.

Méjean, C., Droomers, M., van der Schouw, Y.T., Sluijs, I., et al. (2013) The contribution of diet and lifestyle to socioeconomic inequalities in cardiovascular morbidity and mortality. *International Journal of Cardiology*. [Online] 168 (6), 5190–5195. Available from: doi:10.1016/j.ijcard.2013.07.188.

Members, C., Braunwald, E., Antman, E.M., Beasley, J.W., et al. (2002) ACC/AHA Guideline Update for the Management of Patients With Unstable Angina and Non–ST-Segment Elevation Myocardial Infarction—2002: Summary Article: A Report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee on the Management of Patients With Unstable Angina). *Circulation*. [Online] 106 (14), 1893–1900. Available from: doi:10.1161/01.CIR.0000037106.76139.53.

Mendall, M.A., Strachan, D.P., Butland, B.K., Ballam, L., et al. (2000) C-reactive protein: relation to total mortality, cardiovascular mortality and cardiovascular risk factors in men. *European Heart Journal*. [Online] 21 (19), 1584–1590. Available from: doi:10.1053/euhj.1999.1982.

Mendis, S., Puska, P., Norrving, B., Organization, W.H., et al. (2011) *Global atlas on cardiovascular disease prevention and control*. [Online]. Geneva : World Health Organization. Available from: http://www.who.int/iris/handle/10665/44701 [Accessed: 14 February 2017].

Mestral, C. de & Stringhini, S. (2017) Socioeconomic Status and Cardiovascular Disease: an Update. *Current Cardiology Reports*. [Online] 19 (11), 115. Available from: doi:10.1007/s11886-017-0917-z.

Mitchell, S. & Shaw, D. (2015) The worldwide epidemic of female obesity. *Best Practice & Research Clinical Obstetrics & Gynaecology*. [Online] 29 (3), 289–299. Available from: doi:10.1016/j.bpobgyn.2014.10.002.

MOH (2017) *General Directorate of PHC Non Communicable Diseases DeptThematic Group Meeting*.

Mokdad, A.H., Ford, E.S., Bowman, B.A., Nelson, D.E., et al. (2000) Diabetes trends in the U.S.: 1990-1998. *Diabetes Care*. 23 (9), 1278–1283.

Mokdad, A.H., Forouzanfar, M.H., Daoud, F., El Bcheraoui, C., et al. (2016) Health in times of uncertainty in the eastern Mediterranean region, 1990–2013: a systematic analysis for the Global Burden of Disease Study 2013. *The Lancet Global Health*. [Online] 4 (10), e704–e713. Available from: doi:10.1016/S2214-109X(16)30168-1.

Mokdad, A.H., Jaber, S., Aziz, M.I.A., AlBuhairan, F., et al. (2014) The state of health in the Arab world, 1990–2010: an analysis of the burden of diseases, injuries, and risk factors. *The Lancet*. [Online] 383 (9914), 309–320. Available from: doi:10.1016/S0140-6736(13)62189-3.

Montalescot, G., Achenbach, S., Andreotti, F., Arden, C., et al. (2013) 2013 ESC guidelines on the management of stable coronary artery disease: the Task Force on the management of stable coronary artery disease of the European Society of Cardiology. *European Heart Journal*. [Online] 34 (38), 2949–3003. Available from: doi:10.1093/eurheartj/eht296.

Morris, J.N. & Crawford, M.D. (1958) Coronary Heart Disease and Physical Activity of Work. *British Medical Journal*. 2 (5111), 1485–1496.

Morrish, N.J., Wang, S.-L., Stevens, L.K., Fuller, J.H., et al. (2001) Mortality and causes of death in the WHO multinational study of vascular disease in diabetes. *Diabetologia*. [Online] 44 (2), S14. Available from: doi:10.1007/PL00002934.

Moser, D.K., Riegel, B., McKinley, S., Doering, L.V., et al. (2007) Impact of anxiety and perceived control on in-hospital complications after acute myocardial infarction. *Psychosomatic Medicine*. [Online] 69 (1), 10–16. Available from: doi:10.1097/01.psy.0000245868.43447.d8.

Motlagh, B., O'Donnell, M. & Yusuf, S. (2009) Prevalence of cardiovascular risk factors in the Middle East: a systematic review. *European Journal of Cardiovascular Prevention and Rehabilitation: Official Journal of the European Society of Cardiology, Working Groups on Epidemiology & Prevention and Cardiac Rehabilitation and Exercise Physiology*. [Online] 16 (3), 268–280. Available from: doi:10.1097/HJR.0b013e328322ca1b.

Movva, R. & Figueredo, V.M. (2014) Alcohol and the heart: To abstain or not to abstain? *International Journal of Cardiology*. [Online] 172 (3), 628. Available from: doi:10.1016/j.ijcard.2013.12.226.

Mozaffarian, D., Benjamin, E.J., Go, A.S., Arnett, D.K., et al. (2016) Executive Summary: Heart Disease and Stroke Statistics—2016 Update: A Report From the American Heart Association. *Circulation*. [Online] 133 (4), 447–454. Available from: doi:10.1161/CIR.0000000000000366.

Muir, K.W. (2001) Medical Management of Stroke. *Journal of Neurology, Neurosurgery & Psychiatry*. [Online] 70 (suppl 1), i12–i16. Available from: doi:10.1136/jnnp.70.suppl_1.i12.

Mukamal, K.J., Chen, C.M., Rao, S.R. & Breslow, R.A. (2010) Alcohol consumption and cardiovascular mortality among U.S. adults, 1987 to 2002. *Journal of the American College of Cardiology*. [Online] 55 (13), 1328–1335. Available from: doi:10.1016/j.jacc.2009.10.056.

Mukamal, K.J., Chiuve, S.E. & Rimm, E.B. (2006) Alcohol consumption and risk for coronary heart disease in men with healthy lifestyles. *Archives of Internal Medicine*. [Online] 166 (19), 2145–2150. Available from: doi:10.1001/archinte.166.19.2145.

Murabito, J.M., D'Agostino, R.B., Silbershatz, H. & Wilson, W.F. (1997) Intermittent claudication. A risk profile from The Framingham Heart Study. *Circulation*. 96 (1), 44–49.

Murabito, J.M., Pencina, M.J., Nam, B.-H., D'Agostino, R.B., et al. (2005) Sibling cardiovascular disease as a risk factor for cardiovascular disease in middle-aged adults. *JAMA*. [Online] 294 (24), 3117–3123. Available from: doi:10.1001/jama.294.24.3117.

Mzayek, F., Khader, Y., Eissenberg, T., Al Ali, R., et al. (2012) Patterns of water-pipe and cigarette smoking initiation in schoolchildren: Irbid longitudinal smoking study. *Nicotine & Tobacco Research: Official Journal of the Society for Research on Nicotine and Tobacco*. [Online] 14 (4), 448–454. Available from: doi:10.1093/ntr/ntr234.

National Institute of Neurological Disorders and Stroke rt-PA Stroke Study Group (1995) Tissue plasminogen activator for acute ischemic stroke. *The New England Journal of Medicine*. [Online] 333 (24), 1581–1587. Available from: doi:10.1056/NEJM199512143332401.

Nawrot, T.S., Perez, L., Künzli, N., Munters, E., et al. (2011) Public health importance of triggers of myocardial infarction: a comparative risk assessment. *Lancet (London,*

England). [Online] 377 (9767), 732–740. Available from: doi:10.1016/S0140-6736(10)62296-9.

N.C.E.P (2002) Third Report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III) final report. *Circulation*. 106 (25), 3143–3421.

Ness, J., Aronow, W.S. & Ahn, C. (2000) Risk factors for symptomatic peripheral arterial disease in older persons in an academic hospital-based geriatrics practice. *Journal of the American Geriatrics Society*. 48 (3), 312–314.

Neubeck, L., Lowres, N., Benjamin, E.J., Freedman, S.B., et al. (2015) The mobile revolution--using smartphone apps to prevent cardiovascular disease. *Nature Reviews. Cardiology*. [Online] 12 (6), 350–360. Available from: doi:10.1038/nrcardio.2015.34.

Ng, S.W., Zaghloul, S., Ali, H.I., Harrison, G., et al. (2011) The prevalence and trends of overweight, obesity and nutrition-related non-communicable diseases in the Arabian Gulf States. *Obesity Reviews: An Official Journal of the International Association for the Study of Obesity*. [Online] 12 (1), 1–13. Available from: doi:10.1111/j.1467-789X.2010.00750.x.

N.H.BP.E.P (1993) National High Blood Pressure Education Program Working Group report on primary prevention of hypertension. *Archives of Internal Medicine*. 153 (2), 186–208.

Nordestgaard, B.G., Benn, M., Schnohr, P. & Tybjaerg-Hansen, A. (2007) Nonfasting triglycerides and risk of myocardial infarction, ischemic heart disease, and death in men and women. *JAMA*. [Online] 298 (3), 299–308. Available from: doi:10.1001/jama.298.3.299.

Nordestgaard, B.G. & Varbo, A. (2014) Triglycerides and cardiovascular disease. *The Lancet*. [Online] 384 (9943), 626–635. Available from: doi:10.1016/S0140-6736(14)61177-6.

North, B.J. & Sinclair, D.A. (2012) The Intersection Between Aging and Cardiovascular Disease. *Circulation Research*. [Online] 110 (8), 1097–1108. Available from: doi:10.1161/CIRCRESAHA.111.246876.

Nsour, M., Mahfoud, Z., Kanaan, M.N. & Balbeissi, A. (2008) Prevalence and predictors of nonfatal myocardial infarction in Jordan. *Eastern Mediterranean Health Journal = La Revue De Sante De La Mediterranee Orientale = Al-Majallah Al-Sihhiyah Li-Sharq Al-Mutawassit*. 14 (4), 818–830.

Nygård, O., Vollset, S.E., Refsum, H., Brattström, L., et al. (1999) Total homocysteine and cardiovascular disease. *Journal of Internal Medicine*. [Online] 246 (5), 425–454. Available from: doi:10.1046/j.1365-2796.1999.00512.x.

O'Donnell, M.J., Chin, S.L., Rangarajan, S., Xavier, D., et al. (2016) Global and regional effects of potentially modifiable risk factors associated with acute stroke in 32 countries (INTERSTROKE): a case-control study. *Lancet (London, England)*. [Online] 388 (10046), 761–775. Available from: doi:10.1016/S0140-6736(16)30506-2.

Sabine Oertelt-Prigione & Vera Regitz-Zagrosek (eds.) (2012c) *Sex and Gender Aspects in Clinical Medicine*. [Online]. London, Springer-Verlag. Available from: //www.springer.com/la/book/9780857298317 [Accessed: 11 July 2018].

Office of the Surgeon General (US) & Office on Smoking and Health (US) (2004) *The Health Consequences of Smoking: A Report of the Surgeon General*. Reports of the Surgeon General. [Online]. Atlanta (GA), Centers for Disease Control and Prevention (US). Available from: http://www.ncbi.nlm.nih.gov/books/NBK44695/ [Accessed: 6 July 2018].

O'Gara, P.T., Kushner, F.G., Ascheim, D.D., Casey, D.E., et al. (2013) 2013 ACCF/AHA guideline for the management of ST-elevation myocardial infarction: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. *Circulation*. [Online] 127 (4), e362-425. Available from: doi:10.1161/CIR.0b013e3182742cf6.

Ojaghihaghighi, S., Vahdati, S.S., Mikaeilpour, A. & Ramouz, A. (2017) Comparison of neurological clinical manifestation in patients with hemorrhagic and ischemic stroke. *World Journal of Emergency Medicine*. [Online] 8 (1), 34–38. Available from: doi:10.5847/wjem.j.1920-8642.2017.01.006.

Olesen, K.K.W., Madsen, M., Egholm, G., Thim, T., et al. (2017) Patients With Diabetes Without Significant Angiographic Coronary Artery Disease Have the Same Risk of Myocardial Infarction as Patients Without Diabetes in a Real-World Population Receiving Appropriate Prophylactic Treatment. *Diabetes Care*. [Online] 40 (8), 1103–1110. Available from: doi:10.2337/dc16-2388.

Omland, T., de Lemos, J.A., Sabatine, M.S., Christophi, C.A., et al. (2009) A sensitive cardiac troponin T assay in stable coronary artery disease. *The New England Journal of Medicine*. [Online] 361 (26), 2538–2547. Available from: doi:10.1056/NEJMoa0805299.

Omran, A.R. (2005) The Epidemiologic Transition: A Theory of the Epidemiology of Population Change. *The Milbank Quarterly*. [Online] 83 (4), 731–757. Available from: doi:10.1111/j.1468-0009.2005.00398.x.

O'Neill, S. & O'Driscoll, L. (2015) Metabolic syndrome: a closer look at the growing epidemic and its associated pathologies. *Obesity Reviews: An Official Journal of the International Association for the Study of Obesity*. [Online] 16 (1), 1–12. Available from: doi:10.1111/obr.12229.

Organization, W.H. (2003) *The World Health Report 2003: Shaping the Future*. World Health Organization.

Ostchega, Y., Paulose-Ram, R., Dillon, C.F., Gu, Q., et al. (2007) Prevalence of peripheral arterial disease and risk factors in persons aged 60 and older: data from the National Health and Nutrition Examination Survey 1999-2004. *Journal of the American Geriatrics Society*. [Online] 55 (4), 583–589. Available from: doi:10.1111/j.1532-5415.2007.01123.x.

Ouriel, K. (2001) Peripheral arterial disease. *Lancet (London, England)*. [Online] 358 (9289), 1257–1264. Available from: doi:10.1016/S0140-6736(01)06351-6.

Oyebode, O., Gordon-Dseagu, V., Walker, A. & Mindell, J.S. (2014) Fruit and vegetable consumption and all-cause, cancer and CVD mortality: analysis of Health Survey for England data. *J Epidemiol Community Health*. [Online] 68 (9), 856–862. Available from: doi:10.1136/jech-2013-203500.

Palumbo, P.J., O'Fallon, W.M., Osmundson, P.J., Zimmerman, B.R., et al. (1991) Progression of Peripheral Occlusive Arterial Disease in Diabetes Mellitus: What Factors Are Predictive? *Archives of Internal Medicine*. [Online] 151 (4), 717–721. Available from: doi:10.1001/archinte.1991.00400040067015.

PCBS 2016 (n.d.) *palestinian central bureau of statistic*.

Pedersen, T.R., Kjekshus, J., Berg, K., Haghfelt, T., et al. (2004) Randomised trial of cholesterol lowering in 4444 patients with coronary heart disease: the Scandinavian Simvastatin Survival Study (4S). 1994. *Atherosclerosis. Supplements*. [Online] 5 (3), 81–87. Available from: doi:10.1016/j.atherosclerosissup.2004.08.027.

Peeters, A., Barendregt, J.J., Willekens, F., Mackenbach, J.P., et al. (2003) Obesity in adulthood and its consequences for life expectancy: a life-table analysis. *Annals of Internal Medicine*. 138 (1), 24–32.

Pencina, M.J., D'Agostino, R.B., Larson, M.G., Massaro, J.M., et al. (2009) Predicting the 30-year risk of cardiovascular disease: the framingham heart study. *Circulation*. [Online] 119 (24), 3078–3084. Available from: doi:10.1161/CIRCULATIONAHA.108.816694.

Perk, J. (2009) Risk factor management: a practice guide. *European Journal of Cardiovascular Prevention & Rehabilitation*. 16 (2_suppl), S24–S28.

Perk, J., De Backer, G., Gohlke, H., Graham, I., et al. (2012) European Guidelines on cardiovascular disease prevention in clinical practice (version 2012). The Fifth Joint Task Force of the European Society of Cardiology and Other Societies on Cardiovascular Disease Prevention in Clinical Practice (constituted by representatives of nine societies and by invited experts). *European Heart Journal*. [Online] 33 (13), 1635–1701. Available from: doi:10.1093/eurheartj/ehs092.

Peters, S.A.E., Huxley, R.R. & Woodward, M. (2013) Comparison of the sex-specific associations between systolic blood pressure and the risk of cardiovascular disease: a systematic review and meta-analysis of 124 cohort studies, including 1.2 million individuals. *Stroke*. [Online] 44 (9), 2394–2401. Available from: doi:10.1161/STROKEAHA.113.001624.

Peters, S.A.E., Huxley, R.R. & Woodward, M. (2014) Diabetes as a risk factor for stroke in women compared with men: a systematic review and meta-analysis of 64 cohorts, including 775,385 individuals and 12,539 strokes. *Lancet (London, England)*. [Online] 383 (9933), 1973–1980. Available from: doi:10.1016/S0140-6736(14)60040-4.

PHIC (2018) *Health Annual Report Palestine 2017*.

Piepoli, M.F., Hoes, A.W., Agewall, S., Albus, C., et al. (2016) 2016 European Guidelines on cardiovascular disease prevention in clinical practice: The Sixth Joint Task Force of the European Society of Cardiology and Other Societies on Cardiovascular Disease Prevention in Clinical Practice (constituted by representatives of 10 societies and by invited experts)Developed with the special contribution of the European Association for Cardiovascular Prevention & Rehabilitation (EACPR). *European Heart Journal*. [Online] 37 (29), 2315–2381. Available from: doi:10.1093/eurheartj/ehw106.

Pineda, J., Marín, F., Marco, P., Roldán, V., et al. (2009) Premature coronary artery disease in young (age <45) subjects: interactions of lipid profile, thrombophilic and haemostatic markers. *International Journal of Cardiology*. [Online] 136 (2), 222–225. Available from: doi:10.1016/j.ijcard.2008.04.020.

Powers William J., Rabinstein Alejandro A., Ackerson Teri, Adeoye Opeolu M., et al. (2018) 2018 Guidelines for the Early Management of Patients With Acute Ischemic Stroke: A Guideline for Healthcare Professionals From the American Heart Association/American Stroke Association. *Stroke*. [Online] 49 (3), e46–e99. Available from: doi:10.1161/STR.0000000000000158.

Powers, W.J. (1993) Acute hypertension after stroke: the scientific basis for treatment decisions. *Neurology*. 43 (3 Pt 1), 461–467.

Prentice, A.M. (2006) The emerging epidemic of obesity in developing countries. *International Journal of Epidemiology*. [Online] 35 (1), 93–99. Available from: doi:10.1093/ije/dyi272.

Pryor, D.B., Shaw, L., McCants, C.B., Lee, K.L., et al. (1993) Value of the history and physical in identifying patients at increased risk for coronary artery disease. *Annals of Internal Medicine*. 118 (2), 81–90.

Ragland, D.R. & Brand, R.J. (1988) Type A behavior and mortality from coronary heart disease. *The New England Journal of Medicine*. [Online] 318 (2), 65–69. Available from: doi:10.1056/NEJM198801143180201.

Rahim, H.F.A., Sibai, A., Khader, Y., Hwalla, N., et al. (2014) Non-communicable diseases in the Arab world. *The Lancet*. [Online] 383 (9914), 356–367. Available from: doi:10.1016/S0140-6736(13)62383-1.

Ramahi, T.M. (2010) Cardiovascular Disease in the Asia Middle East Region: Global Trends and Local Implications. *Asia Pacific Journal of Public Health*. [Online] 22 (3_suppl), 83S-89S. Available from: doi:10.1177/1010539510373034.

Ramos, R., García-Gil, M., Comas-Cufí, M., Quesada, M., et al. (2016) Statins for Prevention of Cardiovascular Events in a Low-Risk Population With Low Ankle Brachial Index. *Journal of the American College of Cardiology*. [Online] 67 (6), 630–640. Available from: doi:10.1016/j.jacc.2015.11.052.

Rapsomaniki, E., Timmis, A., George, J., Pujades-Rodriguez, M., et al. (2014) Blood pressure and incidence of twelve cardiovascular diseases: lifetime risks, healthy life-years lost, and age-specific associations in 1·25 million people. *The Lancet*. [Online] 383 (9932), 1899–1911. Available from: doi:10.1016/S0140-6736(14)60685-1.

Regitz-Zagrosek, V., Oertelt-Prigione, S., Prescott, E., Franconi, F., et al. (2016) Gender in cardiovascular diseases: impact on clinical manifestations, management, and outcomes. *European Heart Journal*. [Online] 37 (1), 24–34. Available from: doi:10.1093/eurheartj/ehv598.

Ridker, P.M. (2003) Clinical application of C-reactive protein for cardiovascular disease detection and prevention. *Circulation*. 107 (3), 363–369.

Rivellese, A.A., Riccardi, G. & Vaccaro, O. (2010) Cardiovascular risk in women with diabetes. *Nutrition, metabolism, and cardiovascular diseases: NMCD*. [Online] 20 (6), 474–480. Available from: doi:10.1016/j.numecd.2010.01.008.

Rossi, R., Grimaldi, T., Origliani, G., Fantini, G., et al. (2002) Menopause and cardiovascular risk. *Pathophysiology of Haemostasis and Thrombosis*. [Online] 32 (5–6), 325–328. Available from: doi:10.1159/000073591.

Rossouw, J.E., Prentice, R.L., Manson, J.E., Wu, L., et al. (2007) Postmenopausal hormone therapy and risk of cardiovascular disease by age and years since menopause. *JAMA*. [Online] 297 (13), 1465–1477. Available from: doi:10.1001/jama.297.13.1465.

Roth, G.A., Huffman, M.D., Moran, A.E., Feigin, V., et al. (2015) Global and regional patterns in cardiovascular mortality from 1990 to 2013. *Circulation*. [Online] 132 (17), 1667–1678. Available from: doi:10.1161/CIRCULATIONAHA.114.008720.

Rothwell, P.M. & Warlow, C.P. (2005) Timing of TIAs preceding stroke: time window for prevention is very short. *Neurology*. [Online] 64 (5), 817–820. Available from: doi:10.1212/01.WNL.0000152985.32732.EE.

Runchey, S. & McGee, S. (2010) Does this patient have a hemorrhagic stroke?: clinical findings distinguishing hemorrhagic stroke from ischemic stroke. *JAMA*. [Online] 303 (22), 2280–2286. Available from: doi:10.1001/jama.2010.754.

Sabatine, M.S., Cannon, C.P., Gibson, C.M., López-Sendón, J.L., et al. (2005) Addition of clopidogrel to aspirin and fibrinolytic therapy for myocardial infarction with ST-segment elevation. *The New England Journal of Medicine*. [Online] 352 (12), 1179–1189. Available from: doi:10.1056/NEJMoa050522.

Sacco, R.L., Kasner, S.E., Broderick, J.P., Caplan, L.R., et al. (2013) An Updated Definition of Stroke for the 21st Century: A Statement for Healthcare Professionals From the American Heart Association/American Stroke Association. *Stroke*. [Online] STR.0b013e318296aeca. Available from: doi:10.1161/STR.0b013e318296aeca.

Saidi, O., O'Flaherty, M., Mansour, N.B., Aissi, W., et al. (2015) Forecasting Tunisian type 2 diabetes prevalence to 2027: validation of a simple model. *BMC public health*. [Online] 15, 104. Available from: doi:10.1186/s12889-015-1416-z.

Sakkinen, P., Abbott, R.D., Curb, J.D., Rodriguez, B.L., et al. (2002) C-reactive protein and myocardial infarction. *Journal of Clinical Epidemiology*. 55 (5), 445–451.

Saleem, Y., DeFina, L.F., Radford, N.B., Willis, B.L., et al. (2015) Association of a Favorable Cardiovascular Health Profile With the Presence of Coronary Artery CalcificationCLINICAL PERSPECTIVE. *Circulation: Cardiovascular Imaging*. [Online] 8 (1), e001851. Available from: doi:10.1161/CIRCIMAGING.114.001851.

Sanchis-Gomar, F., Perez-Quilis, C., Leischik, R. & Lucia, A. (2016) Epidemiology of coronary heart disease and acute coronary syndrome. *Annals of Translational Medicine*. [Online] 4 (13). Available from: doi:10.21037/atm.2016.06.33 [Accessed: 5 May 2018].

Sarki, A.M., Nduka, C.U., Stranges, S., Kandala, N.-B., et al. (2015) Prevalence of Hypertension in Low- and Middle-Income Countries: A Systematic Review and Meta-Analysis. *Medicine*. [Online] 94 (50), e1959. Available from: doi:10.1097/MD.0000000000001959.

Sattelmair, J., Pertman, J., Ding, E.L., Kohl, H.W., et al. (2011) Dose-Response Between Physical Activity and Risk of Coronary Heart Disease: A Meta-Analysis. *Circulation*. [Online] 124 (7), 789–795. Available from: doi:10.1161/CIRCULATIONAHA.110.010710.

Saydah, S., Bullard, K.M., Cheng, Y., Ali, M.K., et al. (2014) Trends in cardiovascular disease risk factors by obesity level in adults in the United States, NHANES 1999-2010. *Obesity*

(Silver Spring, Md.). [Online] 22 (8), 1888–1895. Available from: doi:10.1002/oby.20761.

Seita, A., Khader, A., Shahin, Y., Hababeeh, M., et al. (2017) *UNRWA Health Annual Report 2016 (published May 2017)*.

Selvin, E. & Erlinger, T.P. (2004) Prevalence of and risk factors for peripheral arterial disease in the United States: results from the National Health and Nutrition Examination Survey, 1999-2000. *Circulation*. [Online] 110 (6), 738–743. Available from: doi:10.1161/01.CIR.0000137913.26087.F0.

Seshadri, S., Beiser, A., Kelly-Hayes, M., Kase, C.S., et al. (2006) The lifetime risk of stroke: estimates from the Framingham Study. *Stroke*. [Online] 37 (2), 345–350. Available from: doi:10.1161/01.STR.0000199613.38911.b2.

Sesso, H.D., Lee, I.M., Gaziano, J.M., Rexrode, K.M., et al. (2001) Maternal and paternal history of myocardial infarction and risk of cardiovascular disease in men and women. *Circulation*. 104 (4), 393–398.

Sher, L. (2005) Type D personality: the heart, stress, and cortisol. *QJM: An International Journal of Medicine*. [Online] 98 (5), 323–329. Available from: doi:10.1093/qjmed/hci064.

Shimakawa, T., Sorlie, P., Carpenter, M.A., Dennis, B., et al. (1994) Dietary Intake Patterns and Sociodemographic Factors in the Atherosclerosis Risk in Communities Study. *Preventive Medicine*. [Online] 23 (6), 769–780. Available from: doi:10.1006/pmed.1994.1133.

Shojaie, M., Pourahmad, M., Eshraghian, A., Izadi, H.R., et al. (2009) Fibrinogen as a risk factor for premature myocardial infarction in Iranian patients: A case control study. *Vascular Health and Risk Management*. 5, 673–676.

Shu, J. & Santulli, G. (2018) Update on peripheral artery disease: Epidemiology and evidence-based facts. *Atherosclerosis*. [Online] 275, 379–381. Available from: doi:10.1016/j.atherosclerosis.2018.05.033.

Silvia, B. (2014) Nutrition and Cardiovascular Health. *Revista Española de Cardiología (English Edition)*. [Online] 67 (9), 738–747. Available from: doi:10.1016/j.rec.2014.05.003.

Sirdah, M.M., Al Laham, N.A. & Abu Ghali, A.S. (2011) Prevalence of metabolic syndrome and associated socioeconomic and demographic factors among Palestinian adults (20-65 years) at the Gaza Strip. *Diabetes & Metabolic Syndrome*. [Online] 5 (2), 93–97. Available from: doi:10.1016/j.dsx.2012.02.024.

Smith, A.M. & Baghurst, K.I. (1992) Public health implications of dietary differences between social status and occupational category groups. *Journal of Epidemiology & Community Health*. [Online] 46 (4), 409–416. Available from: doi:10.1136/jech.46.4.409.

Smith, J.N., Negrelli, J.M., Manek, M.B., Hawes, E.M., et al. (2015) Diagnosis and Management of Acute Coronary Syndrome: An Evidence-Based Update. *The Journal of the American Board of Family Medicine*. [Online] 28 (2), 283–293. Available from: doi:10.3122/jabfm.2015.02.140189.

Smyth, A., Teo, K.K., Rangarajan, S., O'Donnell, M., et al. (2015) Alcohol consumption and cardiovascular disease, cancer, injury, admission to hospital, and mortality: a

prospective cohort study. *Lancet (London, England)*. [Online] 386 (10007), 1945–1954. Available from: doi:10.1016/S0140-6736(15)00235-4.

Spencer, S. (2014) Lessons from the PURE study. *Global Cardiology Science & Practice*. [Online] 2014 (4), 379–381. Available from: doi:10.5339/gcsp.2014.52.

Stahre, M., Roeber, J., Kanny, D., Brewer, R.D., et al. (2014) Contribution of excessive alcohol consumption to deaths and years of potential life lost in the United States. *Preventing Chronic Disease*. [Online] 11, E109. Available from: doi:10.5888/pcd11.130293.

Stamler, J.S. & Slivka, A. (1996) Biological chemistry of thiols in the vasculature and in vascular-related disease. *Nutrition Reviews*. 54 (1 Pt 1), 1–30.

Stec, J.J., Silbershatz, H., Tofler, G.H., Matheney, T.H., et al. (2000) Association of Fibrinogen With Cardiovascular Risk Factors and Cardiovascular Disease in the Framingham Offspring Population. *Circulation*. [Online] 102 (14), 1634–1638. Available from: doi:10.1161/01.CIR.102.14.1634.

Stokols, D., Pelletier, K.R. & Fielding, J.E. (1996) The Ecology of Work and Health: Research and Policy Directions for the Promotion of Employee Health , The Ecology of Work and Health: Research and Policy Directions for the Promotion of Employee Health. *Health Education Quarterly*. [Online] 23 (2), 137–158. Available from: doi:10.1177/109019819602300202.

Stone, N.J., Robinson, J., Lichtenstein, A.H., Merz, C.N.B., et al. (2013) 2013 ACC/AHA Guideline on the Treatment of Blood Cholesterol to Reduce Atherosclerotic Cardiovascular Risk in Adults: A Report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. *Circulation*. [Online] 01.cir.0000437738.63853.7a. Available from: doi:10.1161/01.cir.0000437738.63853.7a.

Stramba-Badiale, M., Fox, K.M., Priori, S.G., Collins, P., et al. (2006) Cardiovascular diseases in women: a statement from the policy conference of the European Society of Cardiology. *European Heart Journal*. [Online] 27 (8), 994–1005. Available from: doi:10.1093/eurheartj/ehi819.

Szummer, K., Wallentin, L., Lindhagen, L., Alfredsson, J., et al. (2017) Improved outcomes in patients with ST-elevation myocardial infarction during the last 20 years are related to implementation of evidence-based treatments: experiences from the SWEDEHEART registry 1995-2014. *European Heart Journal*. [Online] 38 (41), 3056–3065. Available from: doi:10.1093/eurheartj/ehx515.

Tabas, I., García-Cardeña, G. & Owens, G.K. (2015) Recent insights into the cellular biology of atherosclerosis. *J Cell Biol*. [Online] 209 (1), 13–22. Available from: doi:10.1083/jcb.201412052.

Tailakh, A., Evangelista, L.S., Mentes, J.C., Pike, N.A., et al. (2014) Hypertension prevalence, awareness, and control in Arab countries: A systematic review. *Nursing & health sciences*. [Online] 16 (1), 126–130. Available from: doi:10.1111/nhs.12060.

Tamim, H., Al-Sahab, B., Akkary, G., Ghanem, M., et al. (2007) Cigarette and nargileh smoking practices among school students in Beirut, Lebanon. *American Journal of Health Behavior*. [Online] 31 (1), 56–63. Available from: doi:10.5555/ajhb.2007.31.1.56.

Tangalos, E.G., Cota, D. & Fujioka, K. (2006) Complex cardiometabolic risk factors: impact, assessment, and emerging therapies. *Journal of the American Medical Directors Association*. 7 (7), 1–10.

Task members of ESC, Montalescot, G., Sechtem, U., Achenbach, S., et al. (2013) 2013 ESC guidelines on the management of stable coronary artery disease: the Task Force on the management of stable coronary artery disease of the European Society of Cardiology. *European Heart Journal*. [Online] 34 (38), 2949–3003. Available from: doi:10.1093/eurheartj/eht296.

Teo, K., Chow, C.K., Vaz, M., Rangarajan, S., et al. (2009) The Prospective Urban Rural Epidemiology (PURE) study: examining the impact of societal influences on chronic noncommunicable diseases in low-, middle-, and high-income countries. *American Heart Journal*. [Online] 158 (1), 1-7.e1. Available from: doi:10.1016/j.ahj.2009.04.019.

Teodorescu, V.J., Vavra, A.K. & Kibbe, M.R. (2013) Peripheral arterial disease in women. *Journal of Vascular Surgery*. [Online] 57 (4), 18S-26S. Available from: doi:10.1016/j.jvs.2012.10.115.

The Writing Group on behalf of the Workshop Consensus Group (2009) Aging, menopause, cardiovascular disease and HRT. *Climacteric*. [Online] 12 (5), 368–377. Available from: doi:10.1080/13697130903195606.

Thomopoulos, C., Parati, G. & Zanchetti, A. (2014) Effects of blood pressure lowering on outcome incidence in hypertension. 1. Overview, meta-analyses, and meta-regression analyses of randomized trials. *Journal of Hypertension*. [Online] 32 (12), 2285–2295. Available from: doi:10.1097/HJH.0000000000000378.

Thompson, S.G., Kienast, J., Pyke, S.D., Haverkate, F., et al. (1995) Hemostatic factors and the risk of myocardial infarction or sudden death in patients with angina pectoris. European Concerted Action on Thrombosis and Disabilities Angina Pectoris Study Group. *The New England Journal of Medicine*. [Online] 332 (10), 635–641. Available from: doi:10.1056/NEJM199503093321003.

Thygesen, K., Alpert, J.S., Jaffe, A.S., Chaitman, B.R., et al. (2019) Fourth universal definition of myocardial infarction (2018). *European Heart Journal*. [Online] 40 (3), 237–269. Available from: doi:10.1093/eurheartj/ehy462.

Thygesen, K., Alpert, J.S., Jaffe, A.S., Simoons, M.L., et al. (2012) Third universal definition of myocardial infarction. *Global Heart*. [Online] 7 (4), 275–295. Available from: doi:10.1016/j.gheart.2012.08.001.

Toma, A., Paré, G. & Leong, D.P. (2017) Alcohol and Cardiovascular Disease: How Much is Too Much? *Current Atherosclerosis Reports*. [Online] 19 (3), 13. Available from: doi:10.1007/s11883-017-0647-0.

Tóth, P.P., Potter, D. & Ming, E.E. (2012) Prevalence of lipid abnormalities in the United States: the National Health and Nutrition Examination Survey 2003-2006. *Journal of Clinical Lipidology*. [Online] 6 (4), 325–330. Available from: doi:10.1016/j.jacl.2012.05.002.

Truelsen, T. & Nielsen, N. (2003) Self-reported stress and risk of stroke: the Copenhagen City Heart Study. *Stroke*. [Online] 34 (4), 856–862. Available from: doi:10.1161/01.STR.0000062345.80774.40.

Tsao, C.W. & Vasan, R.S. (2015) Cohort Profile: The Framingham Heart Study (FHS): overview of milestones in cardiovascular epidemiology. *International Journal of Epidemiology*. [Online] 44 (6), 1800–1813. Available from: doi:10.1093/ije/dyv337.

Turner, M., Barber, M., Dodds, H., Murphy, D., et al. (2015) Implementing a simple care bundle is associated with improved outcomes in a national cohort of patients with ischemic stroke. *Stroke*. [Online] 46 (4), 1065–1070. Available from: doi:10.1161/STROKEAHA.114.007608.

Turrell, G., Hewitt, B., Patterson, C. & Oldenburg, B. (2003) Measuring socio-economic position in dietary research: is choice of socio-economic indicator important? *Public Health Nutrition*. [Online] 6 (2), 191–200. Available from: doi:10.1079/PHN2002416.

Uijen, A.A. & van de Lisdonk, E.H. (2008) Multimorbidity in primary care: prevalence and trend over the last 20 years. *The European Journal of General Practice*. [Online] 14 Suppl 1, 28–32. Available from: doi:10.1080/13814780802436093.

Usta, C. & Bedel, A. (2017) Update on pharmacological treatment of acute coronary syndrome without persistent ST segment elevation myocardial infarction in the elderly. *Journal of Geriatric Cardiology : JGC*. [Online] 14 (7), 457–464. Available from: doi:10.11909/j.issn.1671-5411.2017.07.005.

Ustrell-Roig, X. & Serena-Leal, J. (2007) [Stroke. Diagnosis and therapeutic management of cerebrovascular disease]. *Revista Espanola De Cardiologia*. 60 (7), 753–769.

Verhoef, P. & Stampfer, M.J. (1995) Prospective Studies of Homocysteine and Cardiovascular Disease. *Nutrition Reviews*. [Online] 53 (10), 283–288. Available from: doi:10.1111/j.1753-4887.1995.tb01478.x.

Wang, T. & Butany, J. (2017) Pathogenesis of atherosclerosis. *Diagnostic Histopathology*. [Online] 23 (11), 473–478. Available from: doi:10.1016/j.mpdhp.2017.11.009.

Wang, W., Jiang, B., Sun, H., Ru, X., et al. (2017) Prevalence, Incidence, and Mortality of Stroke in China: Results from a Nationwide Population-Based Survey of 480 687 Adults. *Circulation*. [Online] 135 (8), 759–771. Available from: doi:10.1161/CIRCULATIONAHA.116.025250.

Whelan, J.F., Barry, M.H. & Moir, J.D. (1992) Color flow Doppler ultrasonography: comparison with peripheral arteriography for the investigation of peripheral vascular disease. *Journal of clinical ultrasound: JCU*. 20 (6), 369–374.

Whelton, P.K., Carey, R.M., Aronow, W.S., Casey, D.E., et al. (2017) 2017 ACC/AHA/AAPA/ABC/ACPM/AGS/APhA/ASH/ASPC/NMA/PCNA Guideline for the Prevention, Detection, Evaluation, and Management of High Blood Pressure in Adults: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. *Hypertension*. [Online] HYP.0000000000000065. Available from: doi:10.1161/HYP.0000000000000065.

Whelton, P.K., Carey, R.M., Aronow, W.S., Casey, D.E., et al. (2018) 2017 ACC/AHA/AAPA/ABC/ACPM/AGS/APhA/ASH/ASPC/NMA/PCNA Guideline for the Prevention, Detection, Evaluation, and Management of High Blood Pressure in Adults: Executive Summary: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. *Hypertension (Dallas, Tex.: 1979)*. [Online] 71 (6), 1269–1324. Available from: doi:10.1161/HYP.0000000000000066.

WHO (2010) *Global Recommendations on Physical Activity for Health*. WHO Guidelines Approved by the Guidelines Review Committee. [Online]. Geneva, World Health Organization. Available from: http://www.ncbi.nlm.nih.gov/books/NBK305057/ [Accessed: 29 June 2018].

WHO (2017a) *Obesity and overweight*. [Online]. 2017. World Health Organization. Available from: http://www.who.int/news-room/fact-sheets/detail/obesity-and-overweight [Accessed: 11 June 2018].

WHO (2007) *Prevention of cardiovascular disease : pocket guidelines for assessment and management of cardiovascular risk : (WHO/ISH cardiovascular risk prediction charts for the European Region)*. [Online]. Available from: http://apps.who.int/iris/handle/10665/43784 [Accessed: 10 October 2018].

WHO (2017b) *WHO | Cardiovascular diseases (CVDs)*. [Online]. May 2017. Available from: http://www.who.int/mediacentre/factsheets/fs317/en/ [Accessed: 19 December 2017].

WHO hypertension (2015) *WHO | Q&As on hypertension*. [Online]. 2015. WHO. Available from: http://www.who.int/features/qa/82/en/index.html [Accessed: 9 January 2018].

WHO, shweta O. (2004) *New updated WHO classification of BMI (Body Mass Index) « PG Blazer*. [Online]. 2004. PG Blazer. Available from: https://pgblazer.com/new-updated-who-classification-of-bmi/ [Accessed: 11 June 2018].

WHO 2014 (n.d.) *GLOBAL STATUS REPORT on noncommunicable diseases 2014*.

WHO EMRO (2016) *Noncommunicable diseases in the Eastern Mediterranean Region - Recherche Google*. [Online]. 2016. Available from: https://www.google.com/search?source=hp&ei=5DnfWq6PAoLaU_vmvZgJ&q=Noncommunicable+diseases+in+the+Eastern+Mediterranean+Region&oq=Noncommunicable+diseases+in+the+Eastern+Mediterranean+Region&gs_l=psy-ab.12..33i22i29i30k1.2866.2866.0.3780.1.1.0.0.0.0.105.105.0j1.1.0....0...1.2.64.psy-ab..0.1.105....0.fMXLyGkQzxY [Accessed: 24 April 2018].

WHO Global health risk (2009) *WHO | Risk factors*. [Online]. 2009. WHO. Available from: http://www.who.int/topics/risk_factors/en/ [Accessed: 6 June 2018].

WHO Global Observatory for eHealth (2011) *mHealth: new horizons for health through mobile technologies: second global survey on eHealth*. [Online]. Available from: http://apps.who.int/iris/handle/10665/44607 [Accessed: 19 October 2018].

WHO, W.H. (2013) *A global brief on hypertension : silent killer, global public health crisis: World Health Day 2013*. [Online] Available from: http://apps.who.int/iris/handle/10665/79059 [Accessed: 23 June 2018].

WHO/GPA (2013) *WHO | Global Action Plan for the Prevention and Control of NCDs 2013-2020*. [Online]. 2013. WHO. Available from: http://www.who.int/nmh/events/ncd_action_plan/en/ [Accessed: 28 April 2018].

WHO,Tobacco 2018 (n.d.) *Tobacco*. [Online]. World Health Organization. Available from: http://www.who.int/news-room/fact-sheets/detail/tobacco [Accessed: 6 July 2018].

Wikipedia (2018) Framingham Risk Score. *Wikipedia*. [Online]. Available from: https://en.wikipedia.org/w/index.php?title=Framingham_Risk_Score&oldid=857995870 [Accessed: 26 October 2018].

Wikipedia (2017) Palestinian refugees. *Wikipedia*. [Online]. Available from: https://en.wikipedia.org/w/index.php?title=Palestinian_refugees&oldid=760418386 [Accessed: 5 February 2017].

Willett, W.C., Green, A., Stampfer, M.J., Speizer, F.E., et al. (1987) Relative and absolute excess risks of coronary heart disease among women who smoke cigarettes. *The New England Journal of Medicine*. [Online] 317 (21), 1303–1309. Available from: doi:10.1056/NEJM198711193172102.

Wilson, P.W., Kannel, W.B., Silbershatz, H. & D'Agostino, R.B. (1999) Clustering of metabolic factors and coronary heart disease. *Archives of Internal Medicine*. 159 (10), 1104–1109.

World Heart Federtion (2017) Tobacco: totally avoidable risk factor of CVD. *World Heart Federation*. [Online]. Available from: https://www.world-heart-federation.org/resources/tobacco-totally-avoidable-risk-factor-cvd/ [Accessed: 21 October 2018].

Xu, D., Li, J., Zou, L., Xu, Y., et al. (2010) Sensitivity and specificity of the ankle—brachial index to diagnose peripheral artery disease: a structured review. *Vascular Medicine*. [Online] 15 (5), 361–369. Available from: doi:10.1177/1358863X10378376.

Yang, Q., Cogswell, M.E., Flanders, W.D., Hong, Y., et al. (2012) Trends in cardiovascular health metrics and associations with all-cause and CVD mortality among US adults. *JAMA*. [Online] 307 (12), 1273–1283. Available from: doi:10.1001/jama.2012.339.

Yoon, P.W., Scheuner, M.T., Peterson-Oehlke, K.L., Gwinn, M., et al. (2002) Can family history be used as a tool for public health and preventive medicine? *Genetics in Medicine: Official Journal of the American College of Medical Genetics*. [Online] 4 (4), 304–310. Available from: doi:10.109700125817-200207000-00009.

Yu, Z., Nissinen, A., Vartiainen, E., Song, G., et al. (2000) Associations between socioeconomic status and cardiovascular risk factors in an urban population in China. *Bulletin of the World Health Organization*. [Online] 78, 1296–1305. Available from: doi:10.1590/S0042-96862000001100004.

Yusuf, H.R., Giles, W.H., Croft, J.B., Anda, R.F., et al. (1998) Impact of multiple risk factor profiles on determining cardiovascular disease risk. *Preventive Medicine*. [Online] 27 (1), 1–9. Available from: doi:10.1006/pmed.1997.0268.

Yusuf, S., Hawken, S., Ounpuu, S., Dans, T., et al. (2004) Effect of potentially modifiable risk factors associated with myocardial infarction in 52 countries (the INTERHEART study): case-control study. *Lancet (London, England)*. [Online] 364 (9438), 937–952. Available from: doi:10.1016/S0140-6736(04)17018-9.

Yusuf, S., Islam, S., Chow, C.K., Rangarajan, S., et al. (2011) Use of secondary prevention drugs for cardiovascular disease in the community in high-income, middle-income, and low-income countries (the PURE Study): a prospective epidemiological survey. *Lancet (London, England)*. [Online] 378 (9798), 1231–1243. Available from: doi:10.1016/S0140-6736(11)61215-4.

Zeidan, R.K., Farah, R., Chahine, M.N., Asmar, R., et al. (2016) Prevalence and correlates of coronary heart disease: first population-based study in Lebanon. *Vascular Health and Risk Management*. [Online] 12, 75–84. Available from: doi:10.2147/VHRM.S97252.

Zheng, Z.J., Rosamond, W.D., Chambless, L.E., Nieto, F.J., et al. (2005) Lower extremity arterial disease assessed by ankle-brachial index in a middle-aged population of African Americans and whites: The Atherosclerosis Risk in Communities (ARIC) Study. *American Journal of Preventive Medicine*. [Online] 29 (5 SUPPL. 1), 42–49. Available from: doi:10.1016/j.amepre.2005.07.019.

Zynia L, R. & Andrew, C. (2000) *THE BURDEN OF DISEASE IN THE WEST BANK AND GAZA AN ASSESSMENT REPORT*. February.

Annexes

Appendix 1. Questionnaire used during data collection

الترصد التدرجي لرصد مدى انتشار أمراض القلب والعوامل الخطرة الخاصة بها

Date:

Participant Identification Number:

Informed consent:

إشعار موافقة

مرحباً أنا اسمي د. أمال ابو جامع أعمل في وزارة الصحة الفلسطينية وأقوم بعمل بحث لرصد مدى انتشار أمراض القلب والعوامل الخطرة الخاصة بالأمراض المزمنة، يهدف هذا البحث لتحسين الخدمات الصحية المقدمة لمرضي الأمراض المزمنة غير السارية في مناطق قطاع غزة.

ان هذه الدراسة سوف تشمل جميع الاعمار من ذكور وإناث من سن 25 فما فوق وتشتمل على ثلاث أجزاء: أسئلة عامة، قياسات وزن وطول.....، تحاليل طبية. حيث سنقوم بإعلامك عن نتائج هذة الفحوصات ومتابعتك إذا احتاج الامر الى ذلك.

وعند تحديد العينة لقد تم اختياركم عشوائياً في هذه الدراسة كأحد من انطبقت عليهم شروط العينة.

إن تعبئة هذا الاستبيان سوف تأخذ 30 دقيقة وبالرغم من أن المشاركة في هذا الاستبيان طوعية وبإمكانك عدم الإجابة عن أي سؤال أو عن كل الأسئلة، فإننا نثمن مشاركتكم ونقدرها، لأن آرائكم في غاية الأهمية للباحثين ولمزودي الخدمات الصحية في قطاع غزة. إن أية معلومات سوف تزودونا بها سوف تكون سرية وسوف تكون تحت استخدام فريق البحث فقط. البيانات المقدمة سوف تستخدم في التحليل الإحصائي وسوف تعرض كوحدة واحدة ولن يتم الإشارة لأي شخص معين.

أوافق غير موافق

في هذا الوقت، هل ترغب \ي في سؤالي أي شيء عن هذا الاستبيان؟ هل من الممكن أن أبدأ في المقابلة الآن.

شكرا جزيلا على وقتك

Participant Identification Number:

Location and Date		Responses		Code
Q1	Date (dd/mm/yyyy)			L 1
Q2	Governorate Name			L 2
Q3	Area Name			L3
Q4	Geo locality	Urban Rural Camp		L4
Consent/ Name/Telephone		Responses		Code
Q5	Full Name			L5
Q6	Consent obtained	Yes If No: **ended**		L6
Q7	Tel Number			L7
Q8	Mobile Number			L8
Q9	Time of interview	Hours Minutes		L9
Q10	Refugee status	Refuge Non-Refugee		L10
Step1 Demographic Information				
Demographic Information		Responses		Code
Q11	Gender	Male	Female	G1
Q12	Date of birth (Dd/mm/yyyy)			G2
Q13	How old are you?	Years:		G3
Q14	Education years? عدد سنوات الدراسة	Number:		G4
Q15	What is your Marital status?	Single	Married	G5
		Divorced	Widowed	
Q16	Which your main work status over the past 12 months? ما هو عملك الاساسي على مدى 12 شهرا الماضية؟	Government employee	Non-Government employee	G6
		Self-employed	Student	
		Home worker	Retired	
		Unemployed (able to work)	Unemployed (unable to work)	
Q17	Number of people including yourself living in your household?	≥18 years	< 18 years:	G7
Q18	Family Income in Shekel Per month دخل الأسرة في الشهر بالشيكل			G8

Participant Identification Number:

Smoker information		Responses		Code
Q19	Do you smoke any tobacco product? Pipe, Shisha, Cigarette.	Yes: -cigarette -pipe -Shisha	No: **Jump to question 26**	Sm1
Q20	Do you smoke daily?	Yes	No	Sm2
Q21	How old were you when you started smoking? كم كان عمرك عندما بدأت التدخين؟	Age: العمر		Sm3
Q22	How many years have you been smoking? عدد سنوات التدخين؟	Number of years: عدد السنوات		Sm4
Q23	During the past 12 months, have you tried to stop smoking? خلال 12 شهرا الماضية هل حاولت الاقلاع عن التدخين؟	Yes	No	Sm5
Q24	How old were you when you stopped smoking? كم كان عمرك عندما توقفت عن التدخين؟	Age: العمر	Don't know	Sm6
Q25	How long ago did you stop smoking? -كم هي الفترة الزمنية التي أقلعت فيها عن التدخين؟ - سجل رد واحد فقط.	-Years ago: -Months ago: -Weeks ago: -Don't know:		Sm7
Q26	During the past 30 days did someone smoke in your house?	Yes	No	Sm8
Q27	During the past 30 days did someone smoke in your work place?	Yes	No	Sm9

Participant Identification Number

	Diet Information	Responses		code
I am going to ask you about the fruits and vegetable that you eat and salt				
Q28	In a typical week, how many days you eat fruits? كم يوما في الأسـبوع تتناول الفواكـه؟	N° of days عدد الايام	Don't know	D1
Q29	How many serving of fruits do you eat on one of those day? كم حبة فواكه تتناول في اليوم الواحد؟	N° of Serving عدد الحصص	Don't know	D2
Q30	In a typical week, how many times you eat vegetable fresh or cooked? كم يوما في الأسـبوع تتناول الخضروات طازجة أو مطبوخة ؟	N° of days عدد الأيام	Don't know	D3
Q31	How many serving of vegetable do you eat on one of those day? كم حصة خضروات تتناول في اليوم الواحد؟	N° of serving عدد الحصص	Don't know	D4
Q32	What type of oil or fat is most often use for meat preparation in your house hold? ما نوع الزيت أو الدهون في الاكل؟	-Olive Oil - vegetarian oil	-Butter -Margarine	D5
Q33	How often do you add salt to your food before or during you eat it? كم مرة في الأسبوع تضيف الملح للطعام اثناء أو قبل الاكل؟	♦ Always: دائما ♦ Often: في كثير من الأحيان ♦ Sometimes:أحيانا ♦ Rarely: نادر ♦ Never: أبدا ♦ Don't know:لا أعرف		D6
Q34	How often do you eat appetizers? such as salty pickles, olives, chili peppers, and salty fish per week كم مرة في الأسبوع تأكل المخللات والزيتون والفلفل الحار والأسماك المالحة؟	♦ Always: دائما ♦ Often: في كثير من الأحيان ♦ Sometimes:أحيانا ♦ Rarely: نادر ♦ Never: أبدا ♦ Don't know:لا أعرف		D7
Q35	How many fast foods do you eat per week that has not been prepared at home? كم عدد الوجبات السريعة التي تتناولها في الأسبوع الغير معدة بالمنزل ؟	N° عدد الوجبات		D8

Participant Identification Number:

Physical activity: Short Physical activity questionnaire				
The first question: (Sedentary life) فكر في الوقت الذي قضيته جالساً خلال الأيام السبعة الماضية، أحسب وقت الجلوس في العمل وفي المنزل وفي الدراسة والجلوس على المكتب وأثناء العمل على الكمبيوتر وأثناء زيارتك لصديق وأثناء القراءة والجلوس أو مشاهدة التلفاز.				
Q36	During the last 7 days, how much did you spent sitting during a day? خلال الأيام السبعة الماضية كم من الوقت قضيت جالسا في أحد هذه الأيام؟	Hours/days: Don't know	Minutes/days:	P1
The second question(walking) فكر في الوقت الذي قضيته في المشي خلال الأيام السبعة الماضية ويتضمن ذلك المشي إلى العمل والمشي أثناء العمل وفي البيت وخلال انتقالك من مكان لأخر أو أي نوع من أنواع المشي بغرض الترويح أو الرياضة.				
Q37	During the last 7 days, on how many days did you walk for at least 10min at a time? خلال الأيام السبعة الماضية كم يوماً مارست المشي لمدة 10دقائق على الأقل في كل مرة؟	Nº of Day: Don't know:	Not walking	P2
Q38	How much time did you usually spend walking on one of those days? في المعتاد كم من الوقت قضيته في ممارسة المشي في أحد تلك الأيام؟	Hours Don't know:	Minutes	P3
The third question: (moderate activity) فكر في جميع الأنشطة البدنية التي تتطلب جهداً بدنياً معتدل الشدة والتي قمت بممارستها مثل: تنظيف البستان، ركوب الدراجة بشكل منتظم، السباحة أو غيرها من أنشطة اللياقة البدنية (لا تشمل المشي).				
Q39	Think only about those physical activities that you did for at least 10 min do not include walking خلال الأيام السبعة الماضية كم يوماً مارست نشاطاً بدنياً معتدل الشدة لمدة 10 دقائق؟ (لا تشمل المشي)	Nº of Day: Don't know	No Activities	P4
Q40	How much time did you usually spend doing moderate activities on one of those days? في المعتاد كم من الوقت قضيت في ممارسة نشاط بدني معتدل الشدة في أحد تلك الأيام؟	Hours:	Minutes:	P5
The fourth question: (vigorous activity) فكر في جميع الأنشطة البدنية التي تتطلب جهداً مرتفع الشدة والتي مارستها مثل: حرث الأرض، جر العربات الثقيلة جداً، أعمال البناء، التمارين الرياضية، الركض / الجري أو ركوب الدراجات السريعة؟				
Q41	Think only about those physical activities that you did for at least 10 minutes at a time خلال الأيام السبعة الماضية كم يوماً مارست نشاطاً بدنياً مرتفع الشدة لمدة 10 دقائق؟	Nº of Day: Don't know:	No Activities	P6
Q42	How much time did you usually spend doing vigorous physical activities on one of those days في المعتاد كم من الوقت قضيت في ممارسة نشاط بدني مرتفع الشدة في أحد تلك الأيام؟	Hours:	Minutes:	P7

Participant Identification Number:

History of Hypertension		Responses		**Code**
Q43	Have you ever had your BP measured by a doctor or health worker	Yes	No	HTN1
Q44	Do you have HTN?	Yes **If No jump to**	No **Question 49**	HTN2
Q45	How long did you have HTN? منذ متى وانت تعاني من ضغط الدم؟	Number of years		HTN3
Q46	Have you taken any medication?	Yes	No	HTN4
Q47	Are you taken any herbal or traditional remedy to raised BP?	Yes	No	HTN5
Q48	Do you have regular follow up?	Yes	No	HTN6
History of Diabetes		**Responses**		**Code**
Q49	Have you ever had your sugar measured by a doctor or health worker?	Yes	No	DM1
Q50	Do you Have Diabetes?	Yes **If no jump to question 60**	No	DM2
Q51	How long did you have diabetes? منذ متى وانت تعاني من السكري؟	Number of years		DM3
Q52	Have you taken any medication?	Yes	No	DM4
Q53	Have you taken oral hypoglycemic?	Yes	No	DM5
Q54	Have you taken insulin?	Yes	No	DM6
Q55	Do you have regular follow up?	Yes	No	DM7
Q56	How often you measure your sugar? عدد المرات التي تقيس فيها السكر؟	Day: week:	month: year:	DM8
Q57	How often you measure your Hb1c? عدد المرات التي تقيس فيها مخزون السكر	Per year:		DM9
Q58	Are you taken any herbal or traditional remedy to raised sugar?	Yes	No	DM10
Q59	Have you any health problem due to your diabetes?	Yes If yes specifies: …… ……	No	DM11

Participant Identification Number:

History of Raised Cholesterol		**Responses**		Code
Q60	Have you ever had your cholesterol measured by a doctor or health worker?	Yes	No	Ch1
Q61	Have you taken any medication to raise your cholesterol level?	Yes	No	Ch2
Q62	Are you taken any herbal or traditional remedy to raised your cholesterol?	Yes	No	Ch3

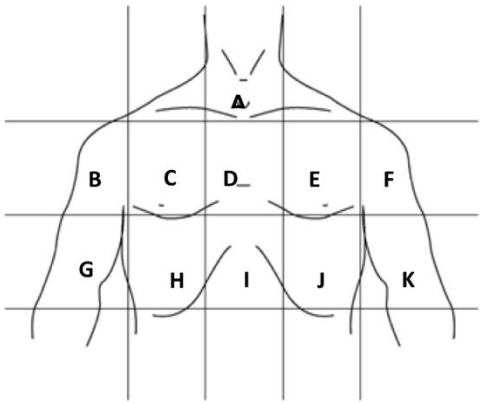
Family history			**Responses**	
Did/Does any of your first degree relative (Father, Mother, Brother, Sister) suffer from? If yes fill the space				
	Disease	Relatives	Age of occurrence	
Q63	Coronary artery disease			HF1
	Diabetes			
	Hypertension			
	Stroke:			
	Peripheral artery disease			
	Sudden death			

History of Cardio vascular disease				Code
Q64	Have you had heart attacks (angina or myocardial infarction)?	Yes	No	V1
Q65	Have you ever been hospitalized in cardiology department	Yes	No	V2
Q66	Have you made a coronarography? قسطرة قلبية	Yes	No	V2
Q67	Have you made PCI (Stent)?دعامات	Yes	No	V3
Q68	Have you made CABG? جراحة قلب شرايين	Yes	No	V4
Q69	Have you had stroke or transit ischemic stroke? هل حصل لديك السكتة الدماغية أو السكتة الدماغية العابرة؟	Yes	No	V5
Q70	what type of stroke? نوع الجلطة	Ischemic Hemorrhagic I Don't know		V6
Q71	How long did the symptoms persist? كم استمرت الأعراض؟	< 24h	> 24h	V7
Q72	Have you ever had weakness on one side of your body? شلل نصفي	Yes	No	V8
Q73	Have you ever suddenly lost one half of your vision? هل فقدت في وقت مضى فجأة نصف رؤيتك؟	Yes	No	V9
Q74	Are you taken Aspirin?	Yes	No	Asp
Q75	Are you taken Beta blocker? Norma tine, concor, cardiloc ايام الاسبوع	Yes	No	BB
Q76	Are you taken Statin? علاج الدهون	Yes	No	Sta

Participant Identification Number:

	Rose Angina Questionnaire			Code
Q77	Do you ever have any pain or discomfort in your chest? هل عانيت من ألمٍ أو اعتلال (عدم ارتياح) بمنطقة الصَدرْ؟	Yes	No	Rose1
Q78	Where do you get it, please indicate the place on the image? في أي جزءٍ مما يظهرهُ الشكل؟ أشر إلى المكان المحدد			Rose2
Q79	Do you get it when you walk uphill or hurry? هل يحدث الألم أثناء السير صعوداً أو المشي على عجل؟	Yes	No	Rose3
Q80	Do you get it when you walk at an ordinary pace on the level? هل يحدث عند السير مستوياً بالمعدل المألوف(الطبيعي)؟	Yes	No	Rose4
Q81	What do you do if you get it while you are walking? ماذا تفعل عند حدوثه بينما أنت تمشي؟	• Stop • slow down • continue at same pace • Not applicable		Rose5
Q82	Does pain or discomfort in your chest go away if you stand still? هل يتلاشى الألم أو الاعتلال في الصدر عند التوقف؟	Yes	No	Rose6
Q83	How long does it take to go away? كم من الوقت يستغرق الأمر لكي يتلاشى الألم؟	≤10 min	>10 min	Rose7

Right side



Left side

Participant Identification Number:

Step 2 Physical measurement				
Height, weight and waist circumference.				Code
Q94	Height cm			HT
Q95	Weight kg			WT
Q96	Waist circumference cm			Wc
Q97	Blood pressure right arm	Right SBP=	Right DBP=	RSBP RDBP
Q98	Blood pressure right ankle	Right Dorsal	Right Tibial	RDPA RPTA
Q99	Blood pressure left ankle	Left Dorsal	Left Tibial	LDPA LPTA
Q100	Blood pressure left arm	Left SBP	Left DBP	LSBP LDBP
Q101	Heart rate c/min	HR=		HR

Step 3 Biochemical Measurement				Code
Q102	Fasting blood sugar mg/dl			FBS
Q103	Random blood sugar mg/dl			RBS
Q104	Cholesterol total mg/dl			Tch
Q105	HDL Cholesterol mg/dl			HDL
Q106	Triglycerides g/dl			TGL

Thank You
Dr. Amal Jamee Shahwan

Appendix 2. International Physical activity (short English version)

INTERNATIONAL PHYSICAL ACTIVITY QUESTIONNAIRE

We are interested in finding out about the kinds of physical activities that people do as part of their everyday lives. The questions will ask you about the time you spent being physically active in the **last 7 days**. Please answer each question even if you do not consider yourself to be an active person. Please think about the activities you do at work, as part of your house and yard work, to get from place to place, and in your spare time for recreation, exercise or sport.

Think about all the **vigorous** activities that you did in the **last 7 days**. **Vigorous** physical activities refer to activities that take hard physical effort and make you breathe much harder than normal. Think *only* about those physical activities that you did for at least 10 minutes at a time.

1. During the **last 7 days**, on how many days did you do **vigorous** physical activities like heavy lifting, digging, aerobics, or fast bicycling?

   _____ **days per week**

   ☐ No vigorous physical activities → ***Skip to question 3***

2. How much time did you usually spend doing **vigorous** physical activities on one of those days?

   _____ **hours per day**

   _____ **minutes per day**

   ☐ Don't know/Not sure

Think about all the **moderate** activities that you did in the **last 7 days**. **Moderate** activities refer to activities that take moderate physical effort and make you breathe somewhat harder than normal. Think only about those physical activities that you did for at least 10 minutes at a time.

3. During the **last 7 days**, on how many days did you do **moderate** physical activities like carrying light loads, bicycling at a regular pace, or doubles tennis? Do not include walking.

   _____ **days per week**

   ☐ No moderate physical activities → ***Skip to question 5***

SHORT LAST 7 DAYS SELF-ADMINISTERED version of the IPAQ. Revised August 2002.

4. How much time did you usually spend doing **moderate** physical activities on one of those days?

_____ **hours per day**

_____ **minutes per day**

☐ Don't know/Not sure

Think about the time you spent **walking** in the **last 7 days**. This includes at work and at home, walking to travel from place to place, and any other walking that you have done solely for recreation, sport, exercise, or leisure.

5. During the **last 7 days**, on how many days did you **walk** for at least 10 minutes at a time?

_____ **days per week**

☐ No walking → ***Skip to question 7***

6. How much time did you usually spend **walking** on one of those days?

_____ **hours per day**

_____ **minutes per day**

☐ Don't know/Not sure

The last question is about the time you spent **sitting** on weekdays during the **last 7 days**. Include time spent at work, at home, while doing course work and during leisure time. This may include time spent sitting at a desk, visiting friends, reading, or sitting or lying down to watch television.

7. During the **last 7 days**, how much time did you spend **sitting** on a **week day**?

_____ **hours per day**

_____ **minutes per day**

☐ Don't know/Not sure

This is the end of the questionnaire, thank you for participating.

SHORT LAST 7 DAYS SELF-ADMINISTERED version of the IPAQ. Revised August 2002.

Appendix 3. International Physical activity (short Arabic version)

الصيغة المختصرة لاستبانة النشاط البدني الدولية، للاستخدام بواسطة التعبئة الشخصية

نحن مهتمون بمعرفة أنواع الأنشطة البدنية التي يقوم بها الأفراد كجزء من حياتهم اليومية. الأسئلة التالية ترتكز حول الوقت الذي قضيته في ممارسة أنشطة بدنية خلال الأيام السبعة الماضية. فضلاً أجب عن كل سؤال من الأسئلة التالية حتى وإن كنت تعتبر نفسك غير نشيط بدنياً. فكر في الأنشطة البدنية التي تمارسها خلال عملك، وكجزء من أعمالك المنزلية، وأثناء تنقلك من مكان لآخر، وتلك التي تقوم بها في وقت فراغك بغرض الترويح أو التمرين أو الرياضة.

الآن فكر في جميع الأنشطة البدنية التي تتطلب جهداً بدنياً مرتفع الشدة والتي قمت بممارستها خلال الأيام السبعة الماضية. الأنشطة البدنية مرتفعة الشدة هي تلك الأنشطة التي تجعل تنفسك أعلى بكثير من المعتاد، مثل رفع أشياء ثقيلة، أو حرث الأرض، أو ركوب الدراجة بسرعة عالية، أو الجري، أو ممارسة كرة القدم، أو كرة السلة، أو السباحة، أو نط الحبل. فكر فقط في الأنشطة البدنية مرتفعة الشدة التي قمت بممارستها لمدة ١٠ دقائق على الأقل في كل مرة.

١ – خلال الأيام السبعة الماضية، كم يوماً مارست فيه نشاطاً بدنياً مرتفع الشدة؟

_____ يوم في الأسبوع

☐ لا أقوم بأي نشاط بدني مرتفع الشدة. ← انتقل مباشرة إلى السؤال رقم ٣

٢ – في المعتاد، كم من الوقت قضيته في ممارسة نشاط بدني مرتفع الشدة في أحد تلك الأيام؟

_____ ساعة في اليوم

_____ دقيقة في اليوم

☐ لا أدري/ أو غير متأكد.

الصيغة المختصرة لاستبانة النشاط البدني الدولية، للاستخدام عن طريق التعبئة الشخصية - منقحة يوليو ٢٠١٤

الآن فكر في جميع الأنشطة البدنية التي تتطلب جهداً بدنياً **معتدل الشدة** والتي قمت بممارستها خلال الأيام السبعة الماضية. الأنشطة البدنية معتدلة الشدة هي تلك الأنشطة التي تجعل تنفسك أعلى من المعتاد إلى حداً ما، ويمكن أن تتضمن رفع أشياء خفيفة، أو ركوب الدراجة بسرعة عادية، أو ممارسة كرة الطائرة، أو ممارسة تنس الطاولة، أو كنس المنزل، أو غسل الملابس يدوياً، أو غسل السيارة. لا تحسب المشي ضمن هذه الأنشطة. مرة أخرى، فكر فقط في الأنشطة البدنية معتدلة الشدة التي قمت بممارستها لمدة ١٠ دقائق على الأقل في كل مرة.

٣- خلال الأيام السبعة الماضية، كم يوماً مارست فيه نشاطاً بدنياً معتدل الشدة؟

_____ يوم في الأسبوع

☐ لا أقوم بأي نشاط بدني معتدل الشدة. ← **انتقل مباشرة إلى السؤال رقم ٥**

٤- في المعتاد، كم من الوقت قضيته في ممارسة نشاط بدني معتدل الشدة في أحد تلك الأيام؟

_____ ساعة في اليوم

_____ دقيقة في اليوم

☐ لا أدري/ أو غير متأكد.

الآن فكر في الوقت الذي قضيته في المشي خلال الأيام السبع الماضية، ويتضمن ذلك المشي إلى العمل، والمشي أثناء العمل، وفي البيت، وخلال انتقالك من مكان لآخر، أو أي نوع من أنواع المشي بغرض الترويح أو الرياضة.

٥- خلال الأيام السبعة الماضية، كم يوماً مارست فيه **المشي** لمدة ١٠ دقائق على الأقل في كل مرة؟

_____ يوم في الأسبوع

☐ لا أقوم بممارسة المشي إطلاقا. ← **انتقل مباشرة إلى السؤال رقم ٧**

٦- في المعتاد، كم من الوقت قضيته في ممارسة المشي في أحد تلك الأيام؟

_____ ساعة في اليوم

_____ دقيقة في اليوم

☐ لا أدري/ أو غير متأكد.

الآن فكر في الوقت الذي قضيته جالساً خلال الأيام السبعة الماضية. أحسب وقت الجلوس في العمل، وفي المنزل، وفي الدراسة، وفي الترفيه. من الممكن أن يتضمن ذلك وقت الجلوس على المكتب، وأثناء العمل على الكمبيوتر، وأثناء زيارتك لصديق، وأثناء القراءة، والجلوس أو الاستلقاء لمشاهدة التلفزيون.

٧- خلال الأيام السبعة الماضية، كم من الوقت قضيته جالساً في أحد هذه الأيام من غير أيام الإجازة الأسبوعية؟

_____ ساعة في اليوم

_____ دقيقة في اليوم

☐ لا أدري/ أو غير متأكد.

(نهاية الاستبانة، شكراً لمشاركتكم)

الصيغة المختصرة لاستبانة النشاط البدني الدولية، للاستخدام عن طريق التعبئة الشخصية - منقحة يوليو ٢٠١٤

Appendix 4. Perceived stress scale of Cohen (English version)

PERCEIVED STRESS SCALE

The questions in this scale ask you about your feelings and thoughts during the last month. **In each case, you will be asked to indicate by circling *how often* you felt or thought a certain way.**

Name _____ Date _____

Age _____ Gender (*Circle*): **M F** Other _____

	0 = Never	**1 = Almost Never**	**2 = Sometimes**	**3 = Fairly Often**	**4 = Very Often**
1. In the last month, how often have you been upset because of something that happened unexpectedly?	0	1	2	3	4
2. In the last month, how often have you felt that you were unable to control the important things in your life?	0	1	2	3	4
3. In the last month, how often have you felt nervous and "stressed"?	0	1	2	3	4
4. In the last month, how often have you felt confident about your ability to handle your personal problems?	0	1	2	3	4
5. In the last month, how often have you felt that things were going your way?	0	1	2	3	4
6. In the last month, how often have you found that you could not cope with all the things that you had to do?	0	1	2	3	4
7. In the last month, how often have you been able to control irritations in your life?	0	1	2	3	4
8. In the last month, how often have you felt that you were on top of things?	0	1	2	3	4
9. In the last month, how often have you been angered because of things that were outside of your control?	0	1	2	3	4
10. In the last month, how often have you felt difficulties were piling up so high that you could not overcome them?	0	1	2	3	4

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References

The PSS Scale is reprinted with permission of the American Sociological Association, from Cohen, S., Kamarck, T., and Mermelstein, R. (1983). A global measure of perceived stress. *Journal of Health and Social Behavior, 24,* 386-396.

Cohen, S. and Williamson, G. Perceived Stress in a Probability Sample of the United States. Spacapan, S. and Oskamp, S. (Eds.) *The Social Psychology of Health.* Newbury Park, CA: Sage, 1988.

Appendix 5. Perceived Stress Scale of Cohen: (Arabic version)

مقياس الشعور بالإرهاق Arabic version of PSS

الأسئلة في هذا الاستبيان تتعلق بأحاسيسك وأفكارك خلال الشهر الماضي. ويطلب منك في كل سؤال أن تبين كم مرة أحسست أو فكرت بطريقة معينة. وإن كانت بعض الأسئلة متشابهة، غير أن هناك اختلافات بينها، لذلك المرجو منك أن تتعامل مع كل سؤال على أساس أنه سؤال مستقل. والطريقة المثلى هي أن تجيب على كل سؤال بسرعة، أي أن لا تحاول أن تحسب بالضبط عدد المرات التي أحسست بشيء معين، بل أن تجيب على السؤال بتقدير معقول. للإجابة على كل سؤال من الأسئلة التالية، اختر اجابة واحدة

		لم يحدث أبدا0	تقريبا لم يحدث أبدا1	أحيانا	في كثير من الأحيان ولكن الى حد ما3	كثيرا جد ا4
1	خلال الشهر الماضي كم مرة عادة استطعت السيطرة على الأمور المزعجة(المثيرة) في حياتك؟					
2	خلال الشهر الماضي كم مرة عادة شعرت بأنك لا تستطيع التحكم في الأمور المهمة في حياتك؟					
3	خلال الشهر الماضي كم مرة عادة أحسست بالتوتر) بالعصبية والإجهاد					
4	خلال الشهر الماضي كم مرة عادة أحسست بأنك واثق من قدرتك على معالجة مشاكلك الشخصية؟					
5	خلال الشهر الماضي كم مرة عادة أحسست أن المصاعب كانت تتراكم إلى درجة لا تستطيع التغلب عليها					
6	خلال الشهر الماضي كم مرة عادة أحسست أن الأمور كانت تسير لصالحك					
7	خلال الشهر الماضي كم مرة عادة أحسست أنك مسيطر على الأمور؟					
8	خلال الشهر الماضي كم مرة أزعجك حدوث شيء غير متوقع؟					
9	خلال الشهر الماضي كم مرة عادة غضبت بسبب وقوع أشياء خارجة عن إرادتك					
10	خلال الشهر الماضي كم مرة عادة أحسست أنك لا تستطيع القيام بكل الأشياء التي كان عليك أن تقوم بها؟					

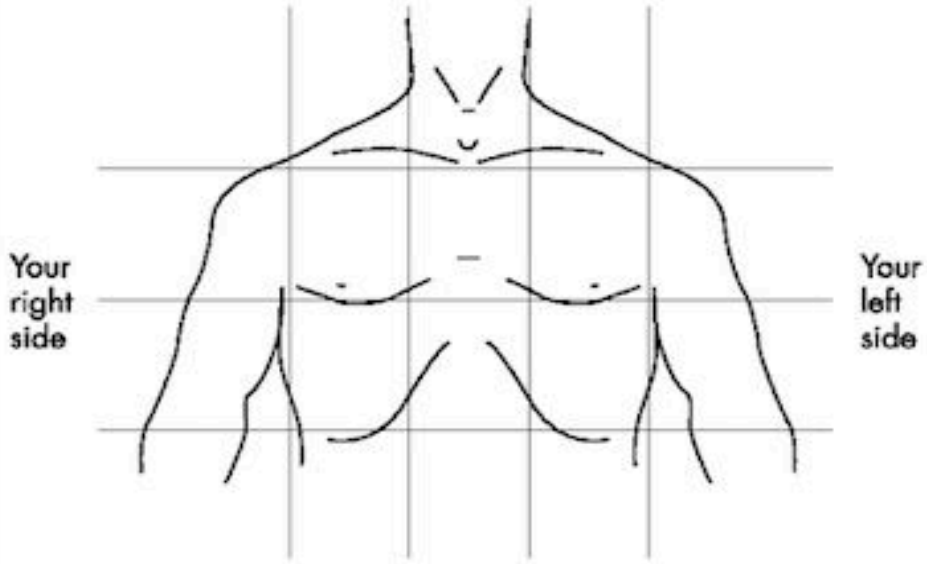
Almadi, T., Cathers, I., Hamdan Mansour, A. M., & Chow, C. M. (2012). An Arabic version of the perceived stress scale: translation and validation study. *International Journal of* ***Nursing Studies, 49(1), 84-89. doi: S0020-7489(11)00298-7 [pii] 10.1016/j.ijnurstu.2011.07.012***

Appendix 6. Complete WHO Rose Angina questionnaire (English version)

1 Do you ever have any pain or discomfort in your chest?

Yes/No

2 Where do you get this pain or discomfort?
Please mark **X** on the appropriate places



3 When you walk at an ordinary pace on the level does this produce the pain?

Yes/No/Unable

4 When you walk uphill or hurry does this produce the pain?

Yes/No/Unable

5 When you get any pain or discomfort in your chest on walking, what do you do?

Stop Slow down Continue at same pace Not applicable

6 Does the pain or discomfort in your chest go away if you stand still?

Yes/No

7 How long does it take to go away?

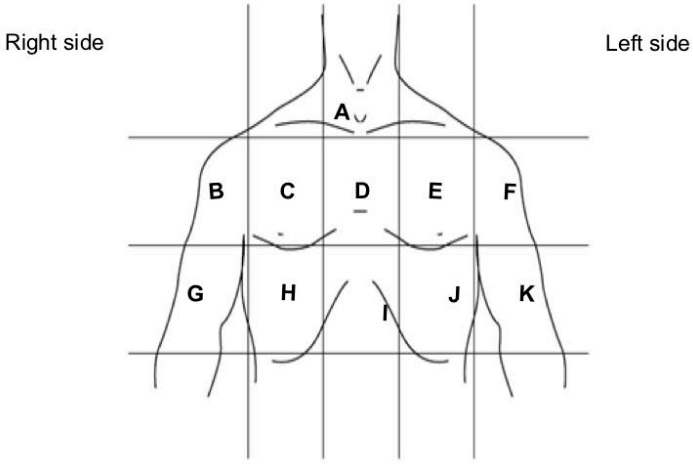
10 minutes or less
more than 10 minutes

Appendix 7. Complete WHO Rose Angina questionnaire (Arabic version)

ROSE ANGINA QUESTIOMMAIRE

1- هل عانيت من ألمٍ أو اعتلال (عدم ارتياح) بمنطقة الصّدرْ؟
*نعم *لا

2- في أي جزءٍ مما يظهرهُ الشكل؟ أشر إلى المكان المحدد...



3- هل يحدث (الألم أو الاعتلال) أثناء السير صعوداً أو المشي على عجل؟؟
*نعم *لا

4- هل يحدث عند السير مستوياً بالمعدل المألوف (الطبيعي)؟
*نعم *لا

5- ماذا تفعل عند حدوثه بينما أنت تمشي؟
- تتوقف
- تهدي السير
- تواصل بنفس المنهج
- غير ملائم/ مطابق

6- هل يتلاشى الألم أو الاعتلال في الصدر عند التوقف؟
*نعم * لا

7- كم من الوقت يستغرق الأمر لكي يتلاشى الألم؟

*أقل من 10 دقائق *أكثر من 10 دقائق

د. أمال جامع شهوان

Appendix 8. Ethical issue

المجلس الفلسطيني للبحث الصحي

Palestinian Health Research Council

تعزيز النظام الصحي الفلسطيني من خلال مأسسة استخدام المعلومات البحثية في صنع القرار

Developing the Palestinian health system through institutionalizing the use of information in decision making

Helsinki Committee
For Ethical Approval

Date: 2017/04/25 **Number:** PHRC/HC/212/17

Name: Amal Jamee الاسم:

We would like to inform you that the committee had discussed the proposal of your study about:

نفيدكم علماً بأن اللجنة قد ناقشت مقترح دراستكم حول:

Epidemiology of cardiovascular disease and Associated Risk Factors in Gaza - Palestinian

The committee has decided to approve the above mentioned research. Approval number PHRC/HC/212/17 in its meeting on 2017/04/25

و قد قررت الموافقة على البحث المذكور عاليه بالرقم والتاريخ المذكوران عاليه

Signature

Member **Member**

Chairman

Genral Conditions:-

1. Valid for 2 years from the date of approval.
2. It is necessary to notify the committee of any change in the approved study protocol.
3. The committee appreciates receiving a copy of your final research when completed.

Specific Conditions:-

E-Mail:pal.phrc@gmail.com

Gaza - Palestine غزة - فلسطين

شارع النصر - مفترق العيون

Appendix 9. Informed consent English version

Study: Epidemiology of cardiovascular diseases in Gaza Strip

Informed consent

Date:

Participant Identification Number:

I am ..... / working with Dr Amal Jamee.

The purpose of this survey is to study the prevalence of Cardiovascular disease and risk factors about Gazans population. We kindly ask you to answer correctly and honestly as you can. The questionnaire is voluntary, you can withdraw at any time and the data collected is confidential, the results will appear as groups and not individual.

If you agree

Signature

Appendix 10. Locality in Gaza Governorate and population estimation 2016

State Of Palestine
Palestinian Central Bureau of Statistics

Localities in Gaza Governorate by Type of Locality and Population Estimates, 2007-2016

Locality Name	Locality code	Locality Type*	Years									
			2007	2008	2009	2010	2011	2012	2013	2014	2015	2016
Ash Shati' Camp	602775	3	34,176	35,181	36,227	37,311	38,516	39,764	41,043	42,349	43,681	45,033
Gaza	602825	1	443,095	456,131	469,687	483,742	499,374	515,556	532,132	549,070	566,331	583,870
Madinat Ezahra	602900	2	3,043	3,132	3,226	3,322	3,429	3,541	3,654	3,771	3,889	4,010
Al Mughraqa (Abu	602945	2	6,448	6,638	6,835	7,039	7,267	7,502	7,744	7,990	8,241	8,496
Juhor ad Dik	603045	2	2,880	2,965	3,053	3,144	3,246	3,351	3,459	3,569	3,681	3,795
Urban Total			**443,095**	**456,131**	**469,687**	**483,742**	**499,374**	**515,556**	**532,132**	**549,070**	**566,331**	**583,870**
Rural Total			**12,371**	**12,735**	**13,113**	**13,506**	**13,942**	**14,394**	**14,857**	**15,330**	**15,812**	**16,301**
Camps Total			**34,176**	**35,181**	**36,227**	**37,311**	**38,516**	**39,764**	**41,043**	**42,349**	**43,681**	**45,033**
Total Gaza Gov.			**489,642**	**504,047**	**519,027**	**534,558**	**551,832**	**569,714**	**588,032**	**606,749**	**625,823**	**645,205**

* Locality Type: 1- Urban 2- Rural 3- Camps

Appendix 11. Locality in Khan Yunis Governorate and population estimation 2016

State Of Palestine
Palestinian Central Bureau of Statistics

Localities in Khan Yunis Governorate by Type of Locality and Population Estimates, 2007-2016

Locality Name	Locality code	Locality Type*	Years									
			2007	2008	2009	2010	2011	2012	2013	2014	2015	2016
Al Qarara	703370	1	19,500	20,072	20,667	21,283	21,969	22,679	23,406	24,149	24,906	25,675
Khan Yunis Camp	703410	3	37,192	38,283	39,417	40,593	41,901	43,255	44,642	46,059	47,503	48,969
Khan Yunis	703420	1	140,697	144,824	149,115	153,564	158,512	163,634	168,880	174,240	179,701	185,250
Bani Suheila	703425	1	31,272	32,189	33,143	34,132	35,231	36,370	37,536	38,727	39,941	41,174
'Abasan al Jadida(as Saghira)	703430	2	5,984	6,159	6,341	6,531	6,741	6,959	7,182	7,410	7,642	7,878
'Abasan al Kabira	703445	1	18,163	18,695	19,249	19,824	20,462	21,123	21,801	22,493	23,198	23,914
Khuza'a	703470	2	9,023	9,287	9,562	9,848	10,165	10,493	10,830	11,174	11,524	11,880
Al Fukhkhari	703485	1	5,464	5,624	5,791	5,963	6,155	6,354	6,558	6,766	6,978	7,194
Urban Total			**215,096**	**221,405**	**227,965**	**234,765**	**242,330**	**250,160**	**258,181**	**266,375**	**274,724**	**283,207**
Rural Total			**15,006**	**15,446**	**15,904**	**16,378**	**16,906**	**17,452**	**18,012**	**18,584**	**19,166**	**19,758**
Camps Total			**37,192**	**38,283**	**39,417**	**40,593**	**41,901**	**43,255**	**44,642**	**46,059**	**47,503**	**48,969**
Total Khan Yunis Gov.			**267,294**	**275,134**	**283,286**	**291,737**	**301,138**	**310,868**	**320,835**	**331,017**	**341,393**	**351,934**

* Locality Type: 1- Urban 2- Rural 3- Camps

Appendix 12. Locality Rafah Governorate and population estimation 2016

State Of Palestine
Palestinian Central Bureau of Statistics

Localities in Rafah Governorate by Type of Locality and Population Estimates, 2007-2016

Locality Name	Locality code	Locality Type*	Years									
			2007	2008	2009	2010	2011	2012	2013	2014	2015	2016
Rafah	753490	1	119,895	123,936	128,150	132,533	137,385	142,427	147,618	152,950	158,414	164,000
Rafah Camp	753495	3	34,025	35,172	36,367	37,611	38,988	40,419	41,892	43,405	44,956	46,541
Al-Nnaser (Al Bayuk)	753500	2	6,211	6,420	6,638	6,865	7,117	7,378	7,647	7,923	8,206	8,495
Shokat as Sufi	753505	1	10,566	10,923	11,294	11,680	12,108	12,552	13,010	13,480	13,961	14,453
Urban Total			**130,462**	**134,858**	**139,443**	**144,213**	**149,493**	**154,979**	**160,627**	**166,429**	**172,376**	**178,453**
Rural Total			**6,211**	**6,420**	**6,638**	**6,865**	**7,117**	**7,378**	**7,647**	**7,923**	**8,206**	**8,495**
Camps Total			**34,025**	**35,172**	**36,367**	**37,611**	**38,988**	**40,419**	**41,892**	**43,405**	**44,956**	**46,541**
Total Rafah Gov.			**170,697**	**176,450**	**182,449**	**188,690**	**195,598**	**202,776**	**210,166**	**217,758**	**225,538**	**233,490**

* Locality Type: 1- Urban 2- Rural 3- Camps

Appendix 13. Locality Deir al Balah (mid Gaza) Governorate and population estimation 2016

State Of Palestine
Palestinian Central Bureau of Statistics

Localities in Deir al Balah Governorate by Type of Locality and Population Estimates, 2007-2016

Locality Name	Locality code	Locality Type*	Years									
			2007	2008	2009	2010	2011	2012	2013	2014	2015	2016
An Nuseirat Camp	653065	3	27,677	28,569	29,497	30,462	31,531	32,641	33,781	34,950	36,146	37,366
An Nuseirat	653070	1	36,123	37,287	38,499	39,758	41,153	42,601	44,090	45,616	47,177	48,769
Al Bureij Camp	653140	3	23,652	24,413	25,207	26,031	26,945	27,893	28,868	29,867	30,889	31,932
Al Bureij	653145	1	9,702	10,015	10,340	10,678	11,053	11,442	11,842	12,252	12,671	13,099
Az Zawayda	653180	1	16,688	17,226	17,786	18,367	19,012	19,681	20,369	21,074	21,795	22,530
Deir al Balah Camp	653200	3	6,343	6,547	6,760	6,981	7,226	7,480	7,742	8,009	8,284	8,563
Al Maghazi Camp	653210	3	15,836	16,346	16,877	17,429	18,041	18,676	19,329	19,998	20,682	21,380
Al Maghazi	653215	1	6,441	6,649	6,865	7,089	7,338	7,596	7,862	8,134	8,412	8,696
Deir al Balah	653240	1	53,633	55,360	57,160	59,029	61,101	63,252	65,461	67,727	70,045	72,409
Al Musaddar	653250	2	1,845	1,905	1,967	2,031	2,102	2,176	2,252	2,330	2,410	2,491
Wadi as Salqa	653275	1	4,552	4,698	4,851	5,010	5,185	5,368	5,555	5,748	5,944	6,145
Urban Total			**127,140**	**131,234**	**135,500**	**139,932**	**144,844**	**149,940**	**155,179**	**160,550**	**166,044**	**171,649**
Rural Total			**1,845**	**1,905**	**1,967**	**2,031**	**2,102**	**2,176**	**2,252**	**2,330**	**2,410**	**2,491**
Camps Total			**73,508**	**75,875**	**78,341**	**80,903**	**83,743**	**86,690**	**89,719**	**92,824**	**96,001**	**99,241**
Total Deir al Balah Gov.			**202,493**	**209,014**	**215,808**	**222,866**	**230,689**	**238,807**	**247,150**	**255,705**	**264,455**	**273,381**

** Locality Type: 1- Urban 2- Rural 3- Camps

Appendix 14. Locality North Gaza Governorate and population estimation 2016

دولة فلسطين
الجهاز المركزي للاحصاء الفلسطيني

التجمعات السكانية في محافظة شمال غزة حسب نوع التجمع، وتقديرات اعداد السكان، 2007-2016

اسم التجمع	رمز التجمع	نوع التجمع*	السنة									
			2007	2008	2009	2010	2011	2012	2013	2014	2015	2016
أم النصر (القرية البدوية المسلوخ)	552681	2	2,763	2,868	2,977	3,092	3,219	3,351	3,487	3,628	3,773	3,923
بيت لاهيا	552695	1	63,347	65,755	68,273	70,902	73,804	76,831	79,962	83,195	86,526	89,949
بيت حانون	552740	1	37,392	38,813	40,300	41,851	43,564	45,351	47,199	49,107	51,073	53,094
مخيم جباليا	552755	3	41,211	42,777	44,416	46,126	48,014	49,983	52,020	54,123	56,290	58,517
جباليا	552790	1	120,881	125,474	130,280	135,297	140,834	146,609	152,585	158,754	165,110	171,642
مجموع الحضر			**221,620**	**230,042**	**238,853**	**248,051**	**258,202**	**268,791**	**279,746**	**291,056**	**302,709**	**314,686**
مجموع الريف			**2,763**	**2,868**	**2,977**	**3,092**	**3,219**	**3,351**	**3,487**	**3,628**	**3,773**	**3,923**
مجموع المخيمات			**41,211**	**42,777**	**44,416**	**46,126**	**48,014**	**49,983**	**52,020**	**54,123**	**56,290**	**58,517**
مجموع محافظة شمال غزة			**265,594**	**275,687**	**286,246**	**297,269**	**309,434**	**322,124**	**335,253**	**348,808**	**362,772**	**377,126**

* نوع التجمع: 1- حضر 2- ريف 3- مخيم

Epidemiology of Cardiovascular disease and associated risk factors in Gaza Strip-Palestine

Introduction : Les pays arabes du Moyen-Orient qui ont une prédominance de population jeune ont connu des changements socio-économiques rapides, une instabilité et une transition épidémiologique. Dans ces pays, la mortalité due aux maladies cardiovasculaires (MCV) représente 45% des décès, en Palestine, elle est estimée à 30,3% en 2018. De plus, le fardeau des facteurs de risque est inquiétant : un quart de la population Arabe adulte est hypertendue, le tabagisme dépasse 30 % chez les hommes, l'obésité est particulièrement alarmante chez les femmes et 9,2 % des adultes sont atteints du diabète. Très peu d'études en population général sur les MCV ont été menées dans ces pays. **Méthodes** : En 2017, une étude transversale utilisant un échantillon de grappes stratifiées a été menée conformément à l'approche STEP de l'OMS. Un échantillon de 2240 participants âgés de ≥25 ans ont participé à l'étude. **Résultats :** La prévalence de la maladie coronarienne est de 8,3 %, AVC est de 3,0 %, l'hypertension artérielle est retrouvée avec une prévalence de 28,4 %, le diabète 19,1 % et l'obésité 47,8 % (60% chez les femmes). L'artériopathie oblitérante des membres inférieurs (AOMI) est observé avec une prévalence de 13,7 %. La prévalence augmente avec l'âge. Elle est plus élevée chez les femmes que chez les hommes (15,6% vs 11,6% respectivement). L'hypertension artérielle et le diabète sont les facteurs associés les plus importants. Le syndrome métabolique est présent avec une prévalence de 41 % plus élevé chez les femmes que chez les hommes (50 % vs 39 %) et associé de façon significative à toutes les maladies cardiovasculaires. **Conclusion :** Selon ces données, la situation dans la bande de Gaza est alarmante, les efforts et la recherche de stratégies visant à réduire le risque cardiovasculaire sont souhaitables.

Mots-clés : Maladies cardiovasculaires, facteurs de risques, bande de Gaza-Palestine

Epidemiology of Cardiovascular disease and associated risk factors in Gaza Strip-Palestine

Introduction: Arab Middle East Countries which have a predominance of young population have undergone rapid socioeconomic changes, instability and epidemiologic transition. In these countries cardiovascular disease (CVD) mortality accounts for 45% of deaths, in Palestine it was estimated up to 30.3% in 2018. Also, the burden of risk factors is worrying; one quarter of adult population was hypertensives, tobacco smoking exceeds 30% in males, obesity is alarming mainly in females, and 9.2% of adults are living with diabetes. Very few community-based on CVD studies were conducted in these countries. **Methods:** In 2017 a cross-sectional study using stratified cluster sample, was conducted in accordance with WHO's STEP wise. A sample of 2240 participants aged ≥25 years participated in the study. **Results:** The prevalence of CAD is 8.3%, stroke 3.0%, hypertension is found with a prevalence of 28.4%, diabetes19.1% and obesity 47.8% with higher rate in females (60%). Lower extremity artery disease (LEAD) is found with a prevalence of 13.7%. The prevalence increased with age and is higher in females than in males (respectively15.6% *vs* 11.6%). Hypertension and diabetes are the most significant associated factors with LEAD. Metabolic syndrome is present with a prevalence of 41% higher in females than males (50% *vs* 39%) and it is significantly associated with all cardiovascular conditions. **Conclusion:** According to these data the situation in Gaza strip is alarming, effort and research to monitor and improve strategies and policies for reducing cardiovascular risk are mandatory

Keywords: Cardiovascular diseases, risk factors, Gaza-Palestine