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DEPARTMENT OF NUTRITION AND DIETETICS

The Development of Metabolic Syndrome in Relation to the Cognitive-Behavioral Model: the Role of Lifestyle Factors and Psychological Disorders

DOCTORAL THESIS

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This thesis is dedicated to the memory of my beloved mother.

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ΠΕΡΙΛΗΨΗ

Εισαγωγή/Σκοπός: Τα καρδιο-μεταβολικά νοσήματα (δηλαδή, το μεταβολικό σύνδρομο (ΜετΣ) και τα καρδιαγγειακά νοσήματα (ΚΑΝ) είναι η κύρια αιτία θανάτου σε όλο τον κόσμο, παρόλο που συχνά μπορούν να προληφθούν. Η παρούσα διατριβή προτείνει ότι οι ψυχολογικές θεωρίες που προέρχονται από τα μοντέλα της Γνωσιακής-Συμπεριφορικής Θεραπείας και της Λογικό-θυμικής Συμπεριφορικής Θεραπείας μπορούν να εξηγήσουν την εμφάνιση του ΜετΣ και των ΚΑΝ, λαμβάνοντας υπόψη τον πρωταρχικό ρόλο της βασικής τους δομής, δηλαδή των παράλογων πεποιθήσεων, είτε απευθείας μέσω νευροχημικής και βιοχημικής δυσλειτουργίας είτε μέσω δυσλειτουργικών συναισθημάτων και συμπεριφορών. Δεδομένου ότι οι παραπάνω καρδιο-μεταβολικές καταστάσεις είναι εξαιρετικά περίπλοκες, σκοπός αυτής της διατριβής είναι να διερευνήσει την ανάπτυξή τους, λαμβάνοντας υπόψη τις παράλογες πεποιθήσεις, και συγκεκριμένα, να εξετάσει εάν το ΜΣ θα μπορούσε να διαδραματίσει μεσολαβητικό ρόλο στην πιθανή σχέση μεταξύπαράλογων πεποιθήσεων και ΚΑΝ. Ένας άλλος στόχος είναι να καλυφθούν τα τρέχοντα κενά στη γνώση και να γνωστοποιηθούν μελλοντικές κατευθύνσεις για τη δημόσια υγεία, οιοποίες θα μπορούσαν τελικά να περιλαμβάνουν βιο-ψυχοκοινωνικές παρεμβάσεις για άτομα υψηλού κινδύνου για καρδιο-μεταβολικά νοσήματα σε παρεμβάσεις εκλογής. **Υλικό και Μέθοδοι:** 853 συμμετέχοντες χωρίς ιστορικό ΚΑΝ [453 άνδρες (ηλικίας 45±13 ετών) και 400 γυναίκες (ηλικίας 44±18 ετών)] που συμμετείχαν στη μελέτη ΑΤΤΙΚΗ, υποβλήθηκαν σε ψυχολογικές αξιολογήσεις και παρακολουθήθηκαν για 10 έτη (2002-2012), αποτελούν το δείγμα της παρούσας μελέτης. Πραγματοποιήθηκαν βιοχημικές, κλινικές αξιολογήσεις και καταγραφή του τρόπου ζωής, ενώ οι παράλογες πεποιθήσεις, το άγχος, η κατάθλιψη και η εχθρότητα αξιολογήθηκαν χρησιμοποιώντας το ερωτηματολόγιο αυτό-αναφοράς για τις παράλογες πεποιθήσεις (IBI, εύρος βαθμολογίας 0-88), το ερωτηματολόγιο άγχους του Spielberger (STAI, εύρος βαθμολογίας 20 -80), την κλίμακα αυτό-αξιολόγησης της

κατάθλιψης τους Zung (ZDRS, εύρος βαθμολογίας 20-80) και το ερωτηματολόγιο εχθρότητας και κατεύθυνσης της εχθρότητας (HDHQ, εύρος βαθμολογίας 0-55), αντίστοιχα.Η επίπτωση των ΚΑΝ ορίστηκε σύμφωνα με τα κριτήρια της Διεθνούς Στατιστικής Ταξινόμησης Νόσων και Συναφών Προβλημάτων Υγείας ICD-10. Εφαρμόστηκε μονομεταβλητή και πολυμεταβλητή λογιστική παλινδρόμηση για την εκτίμηση του κινδύνου ανάπτυξης ΜΣ και ΚΑΝ, και για τον έλεγχο συγχυτικών παραγόντων, καθώς και στρωματοποιημένη λογιστική παλινδρόμηση για την ανίχνευση πιθανών τροποποιητών. **Αποτελέσματα:** Η μέση τιμή IBI ήταν 53±2 για τους άνδρες και 53±3 για τις γυναίκες (*p*=0,88). Τα υψηλά επίπεδα IBI συσχετίστηκαν με 1,5 φορές περισσότερες πιθανότητες εμφάνισης ΜετΣ, συγκριτικά με τα χαμηλά επίπεδα IBI. Επιπλέον, οι συμμετέχοντες με υψηλό IBI και υψηλό STAI είχαν 96% περισσότερες πιθανότητες να αναπτύξουν ΜετΣ, σε σύγκριση με εκείνους με χαμηλό IBI και χαμηλό ή υψηλό STAI [Σχετικός Λόγος (ΣΛ)= 1,96; 95% Διάστημα Εμπιστοσύνης (ΔΕ): (1,01, 3,80)]. Η υψηλή βαθμολογία IBI συσχετίστηκε, επίσης, θετικά με το 10-ετή κίνδυνο ΚΑΝ [Σχετικός Κίνδυνος (ΣΚ)= 1,07, 95%ΔΕ 1,04, 1,13)], τόσο στους άνδρες όσο και στις γυναίκες. Επίσης, οι συμμετέχοντες με υψηλές παράλογες πεποιθήσεις και συμπτώματα άγχους είχαν 138% μεγαλύτερο κίνδυνο εμφάνισης ΚΑΝ κατάτη διάρκεια της 10-ετούς παρακολούθησης (ΣΚ 2,38, 95%ΔΕ 1,75, 3,23) σε σύγκριση με εκείνους χωρίς άγχος. Επιπρόσθετα, προκαταρκτικά ευρήματα από την πρόσφατη 20-ετή παρακολούθηση αποκάλυψαν ότι οι συμμετέχοντες με υψηλά επίπεδα IBI διέτρεχαν επίσης υψηλότερο κίνδυνο να αναπτύξουν ΚΑΝ κατά τη διάρκεια περιόδου παρακολούθησης 20 ετών (2002-2022), σε σύγκριση με τους συμμετέχοντες με χαμηλά επίπεδα (ΣΚ 1,10, 95%ΔΕ 1,05 1.14). Το χαμηλό μορφωτικό επίπεδο, το άγχος και η κατάθλιψη, και το ΜετΣ, έχουν τροποποιητική επίδραση στη σχέση μεταξύ των παράλογων πεποιθήσεων και ΚΑΝ, ενώ οι διατροφικές συνήθειες μακριά από τη μεσογειακή διατροφή, το κάπνισμα, η υπέρταση, οι τροχιές άγχους και κατάθλιψης, η υπερχοληστερολαιμία, το ΜετΣ, ο σακχαρώδης διαβήτης τύπου ΙΙ, η C-αντιδρώσα πρωτεΐνη (CRP), η ιντερλευκίνη- 6 (IL-6) και η ολική αντιοξειδωτική ικανότητα (TAC) ήταν μεσολαβητές στις υπό μελέτη συσχετίσεις. **Συμπεράσματα:** Τα ευρήματα αυτής της διατριβής προάγουν την ψυχολογική έρευνα στον τομέα της πρωτογενούς πρόληψης της ψυχικής υγείας και των καρδιο- μεταβολικών παθήσεων, καθώς υπογραμμίζουν τον σημαντικό ρόλο των παράλογων πεποιθήσεων, για πρώτη φορά στη βιβλιογραφία, και την ανάγκη οικοδόμησης νέων,

ολιστικών προσεγγίσεων για την καλύτερη κατανόηση των αλληλεπιδράσεων μεταξύ των ψυχολογικών, συμπεριφορικών και βιολογικών καθοριστικών παραγόντων στον κίνδυνο ΚΑΝ, αλλά και την εφαρμογή αντίστοιχων παρεμβάσεων.

Λέξεις Κλειδιά: *πεποιθήσεις; καρδιαγγειακές παθήσεις; μεταβολικό σύνδρομο; Μεσογειακή διατροφή; άγχος*

ABSTRACT

Background/Aim: Cardio-metabolic conditions (i.e., metabolic syndrome (MetS) and cardiovascular diseases (CVDs) are the primary cause of death around the world even though they are often preventable. This thesis proposes that psychological theories, derived from the Cognitive-Behavioural Therapy and the Rational-Emotive Behavioural Therapy (CBT/REBT) models can explain the onset of MetS and CVDs, taking into consideration the primary role of their core construct, namely irrational beliefs, directly through neurochemical and biochemical dysregulation, and/or through dysfunctional emotions and behaviours. Therefore, given that cardio-metabolic disorders are extremely complex, the purpose of this thesis is to better explain their development considering irrational beliefsand specifically, to examine whether MetS could play a mediating role in the potential relationship between irrational beliefs and CVDs. Another goal is to fill current gaps in knowledge and inform future directions for public health, which could eventually include bio-psychosocial interventions for individuals at high risk for cardio-metabolic diseases in first-choice interventions. **Material and Methods:** 853 participants without a history of CVDs[453 men (aged 45±13 years) and 400 women (aged 44±18 years)] from the ATTICA study (2002-2012) underwent psychological evaluations. Detailed biochemical, clinical, and lifestyle evaluations were performed, while participants' irrational beliefs, anxiety, depression and hostility were assessed using the Irrational Beliefs Inventory (IBI, range 0- 88), the Spielberger State-Trait Anxiety Inventory (STAI, score 20-80), the Zung Self-Rating Depression Scale (ZDRS, score 20-80) and the Hostility and Direction of Hostility Questionnaire (HDHQ, score 0-55), respectively. The CVD incidence was defined according to the International Coding Diseases (ICD)-10 criteria. Univariable and multivariable logistic regression was applied to estimate the risk of developing MetS and CVDs and to control for confounders, as well as stratified logistic regression, to detect moderator effects. **Results:**

Mean IBI score was 53±2 in men and 53±3 in women (*p*=0.88). High IBI was associated with 1.5-times higher odds of developing MetS than low IBI. Additionally, participants with high IBI and high STAI were 96% more likely to develop MetS, compared with those with low IBI and low or high STAI (OR 1.96; 95% CI 1.01, 3.80). IBI score was also positively associated with 10-year CVD risk (HR 1.07, 95%CI 1.04, 1.13), in both men and women. Also, participants with high irrational beliefs and anxiety symptoms had a 138% greater risk of developing CVDs during the 10-year follow-up (2.38; 95%CI 1.75, 3.23) as compared to thosewithout anxiety. Preliminary findings from the recent 20-year follow-up revealed that participants with high levels of IBI were at higher risk of developing CVDs during a 20-year follow-up period, compared to participants with low endorsement (HR 1.10, 95%CI 1.05 1.14). Lastly, lower education status, MetS, anxiety and depression moderated the relationship between irrational beliefs and CVD risk, whereas dietary habits away from the Mediterranean diet, smoking, anxiety and depression trajectories, hypertension, hypercholesterolemia, T2DM, MetS, C-reactive protein (CRP), interleukin-6 (IL-6) and total antioxidant capacity (TAC) were mediators in the tested relationships. **Conclusions:** Findings from this thesis advance psychological research in the area of primary prevention of mental health and cardio-metabolic conditions since they underline the important role of irrational beliefs for the first time in the literature and the need to build new, holistic approaches to better understand the inter-relationships between psychological, lifestyle, and biological determinants in CVD risk, but also the implementation of corresponding interventions.

Keywords: *thinking; cardiovascular diseases; metabolic syndrome; Mediterranean diet; anxiety*

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ABBREVIATIONS

ACS	Acute Coronary Syndrome
ADA	American Diabetes Association
AHA	America Heart Association
ANS	Autonomic Nervous System
AMP	Adenosine Monophosphate
AMPK	Adenosine Monophosphate Activated Protein Kinase
APA	American Psychological Association
APOB	Apolipoprotein B Gene
BDI	Beck Depression Inventory
BMI	Body Mass Index
BMR	Basal Metabolic Rate
BP	Blood Pressure
CAD	Coronary Artery Disease
CBT	Cognitive-Behavioural Therapy
CDC	Centers for Disease Control and Prevention
CFR	Coronary Flow Reserve
CHD	Coronary Heart Disease
CHF	Congestive Heart Failure
CI	Confidence Intervals
Cm	Centimeter(s)
CNS	Central Nervous System
CRP	C-Reactive Protein
CVD(s)	Cardiovascular Disease(s)
DASH	Dietary Approaches to Stop Hypertension
DBP	Diastolic Blood Pressure
DMDD	Disruptive Mood Dysregulation Disorder
DSM-5-TR	Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition, Text Revision
EF	Executive Functioning
ESC	European Society of Cardiology
EU	European Union
FFA	Free Fatty Acids
FFQ	Food-Frequency Questionnaire
GAD	Generalized Anxiety Disorder
HADS	Hospital Anxiety and Depression Scale
HALE	Health Action Local Engagement
HbA1	Hemoglobin Subunit Alpha 1

HES	Health Examination Survey
HDHQ	Hostility and Direction of Hostility Questionnaire
HDL-C	High-Density Lipoprotein Cholesterol
HF	Heart Failure
HFD	High-Fat Diets
HPA	Hypothalamic-Pituitary-Adrenal axis
HR	Hazard Ratio(s)
IBI	Irrational Beliefs Inventory
ICD-10 CM	International Classification of Disease, Tenth Revision, Clinical Modification
IDF	International Diabetes Federation
IL-6	Interleukin-6
INSR	Insulin Receptor Gene
IPAQ	International Physical Activity Questionnaire
IQR	Interquartile Range
Kg/m^2	Kilogram-Meter Squared
LDL-C	Low-Density Lipoprotein Cholesterol
LDLR	Low-Density Lipoprotein Receptor Gene
MetS	Metabolic Syndrome
mg/dL	Milligrams Per Deciliter
MI	Myocardial Infarction
mmHg	Millimeters of Mercury
NAFLD	Non-Alcoholic Fatty Liver Disease
NCEP ATP III	National Cholesterol Education Program Adult Treatment Panel III
NF- κB	Nuclear Factor Light-Chain-Enhancer of Activated B Cells
NHANES	National Health and Nutrition Examination Survey
NHLBI	National Heart Lung and Blood Institute
NIH	National Institutes of Health
NO	Nitric Oxide
Ox-LDL	Oxidized-LDL
OR	Odds Ratio(s)
PAI-1	Prothrombin Activator Inhibitor-1
PFAOMC	Psychological Factors Affecting Other Medical Conditions
PINE	Psycho-Immune-Neuroendocrine
PNS	Peripheral Nervous System
PPAR-γ	Peroxisome Proliferator-Activated Receptor Gamma Gene
PTSD	Post-Traumatic Stress Disorder
REBT	Rational-Emotive Behavioural Therapy
ROS	Reactive Oxygen Species
SAA	Serum Amyloid A
SAM	Sympathetic Adrenomedullary System
SBP	Systolic Blood Pressure
SD	Standard Deviation
SES	Socio-Economic Status
SLEs	Stressful Life Events
SNS	Sympathetic Nervous System
STAI	State-Trait Anxiety Inventory

TABP	Type A Behaviour Pattern
TAC	Total Antioxidant Capacity
TC	Total Cholesterol
TG	Triglycerides
TNF-α	Tumor Necrosis Factor-Alpha
T2DM	Type II Diabetes
UPF	Ultra-Processed Foods
VSMCs	Vascular Smooth Muscle Cells
WH	Waist-to-Hip
WHt	Waist-to-Height
WHO	World Health Organization
WI	Whiteley Index
ZDRS	Zung Self-Rating Depression Scale
ω-3 PUFA	Long Chain Omega-3 Polyunsaturated Fatty Acids

Preface

Although there is an ongoing debate since the conception of metabolic syndrome (MetS) regarding its recognition as a real syndrome or an informative clinical tool, MetS is nevertheless, a global epidemic health condition, characterized by acluster of interrelated risk factors, including abdominal obesity, hypertriglyceridemia, low levels of high-density lipoprotein cholesterol (HDL-C), elevated blood pressure (BP), and insulin resistance (Alberti et al., 1998; Alberti et al., 2009; NHS, 2019). Thus, MetS can lead to adverse health outcomes, such as cardiovascular diseases (CVDs), type II diabetes (T2DM), non-alcoholic fatty liver disease (NAFLD), Alzheimer's disease, cancers and even mortality, due to interactions among organic, biochemical, clinical, immune, inflammatory, hormonal, vascular and genetic factors (Gohil et al., 2001; Kaur, 2014; Scholze et al., 2010). But aside from the abovementioned factors, stress, psychosocial and environmental factors are also involved (Gohil et al., 2001; Tang, 2017).

The association between MetS and CVDs is well-established and, therefore, several studies have demonstrated that people with MetS are at a higher risk of developing CVDs compared to those without MetS (AHA, 2016; AHA, 2021; Kastorini et al., 2016; Kaur, 2014; NHS, 2019; Scholze et al., 2010). For example, a study that tracked over 10,000 individuals for an average of 15 years, found those with MetS had a 3-times greater risk of developing CVDs compared to those without (Lakka et al., 2002). In addition, according to the America Heart Association (AHA), although each of MetS components is a risk factor forCVDs, when an individual has three or more, and so is diagnosed with MetS, the risk of developing a serious cardiovascular condition increase (AHA, 2016). The exact mechanisms underlying the relationship between MetS and CVDs are not fully understood (Reaven, 2006).

However, several physiological pathways may contribute to the development of CVDs, including insulin resistance, inflammation, and endothelial dysfunction (Haffner, 2006). Insulin resistance is a hallmark of MetS and it is thought to play a key role in the development of CVDs (Grundy et al., 2005). Insulin resistance leads to impaired glucose

uptake in peripheral tissues, which results in increased insulin secretion and hyperinsulinemia (Grundy et al., 2005). This hyperinsulinemia, in turn, promotes dyslipidemia and hypertension, both of which are major risk factors for CVDs (Sowers, 2004). Chronic low- grade inflammation is commonly observed in individuals with MetS and it is thought to contribute to the development of atherosclerosis, the underlying pathology of many CVDs. Inflammation can also contribute to endothelial dysfunction, a condition in which the inner lining of blood vessels becomes damaged, leading to impaired vasodilation, increased vascular resistance and thrombosis (Ross, 1999). Endothelial dysfunction is a commonfeature of MetS and is thought to be a key contributor to the development of CVDs (Arcaro etal., 1999).

The National Heart Lung and Blood Institute (NHLBI) of the National Institutes of Health (NIH) has established widely recognized diagnostic criteria for MetS (NHLBI, 2022). An individual over 21 years old is diagnosed with MetS if they have at least three of the following five metabolic risk factors: i) abdominal obesity, defined as a large waist circumference (>40 inches for men, >35 inches for women), ii) elevated triglycerides, definedas fasting triglyceride levels (> 150 mg/dL), iii) high-density lipoprotein cholesterol (HDL-C), defined as an LDL-C level (<40 mg/dL for men, <50 mg/dL for women), iv) elevated fasting glucose defined as fasting plasma glucose level (>100 mg/dL) and v) elevated blood pressure as systolic blood pressure (SBP) (>130 mm HG) or diastolic blood pressure (DBP) (>85 mm HG), or the use of antihypertensive medication (NHLBI, 2022). It is worth mentioning that other associations and organizations, such as the World Health Organization (WHO) and the International Diabetes Federation (IDF), have slightly different definitions of MetS but are also widely used and recognized. CVD term covers a broad spectrum of disorders affecting the heart and blood vessels (WHO, 2021).

The WHO provides the most widely accepted definition, classifying CVDs as a group of disorders of the heart and blood vessels, including i) coronary heart disease (CHD), the most prevalent form of CVDs that is characterized by the narrowing of coronary arteries that supply blood to the heart, ii) cerebrovascular disease, which describes conditions that affect the blood vessels that supply blood to the brain, such as stroke, iii) peripheral arterial disease (PAD), which involves the narrowing of arteries in the legs, arms, and other parts of the body, iv) rheumatic heart disease, which is a type of a heart disease caused by rheumatic fever, and v) congenital heart disease, which describes heart defects present at birth (WHO, 2021).

This thesis is divided into two parts, the general in which an introduction to the epidemiology of MetS and its components, CVD and related risk factors is made, in addition to the presentation of the studied psychological disorders, and a specific part in which the results of the studied research hypotheses are presented.

1. Epidemiology of Cardio-Metabolic Syndrome

1.1. International Epidemiological Data

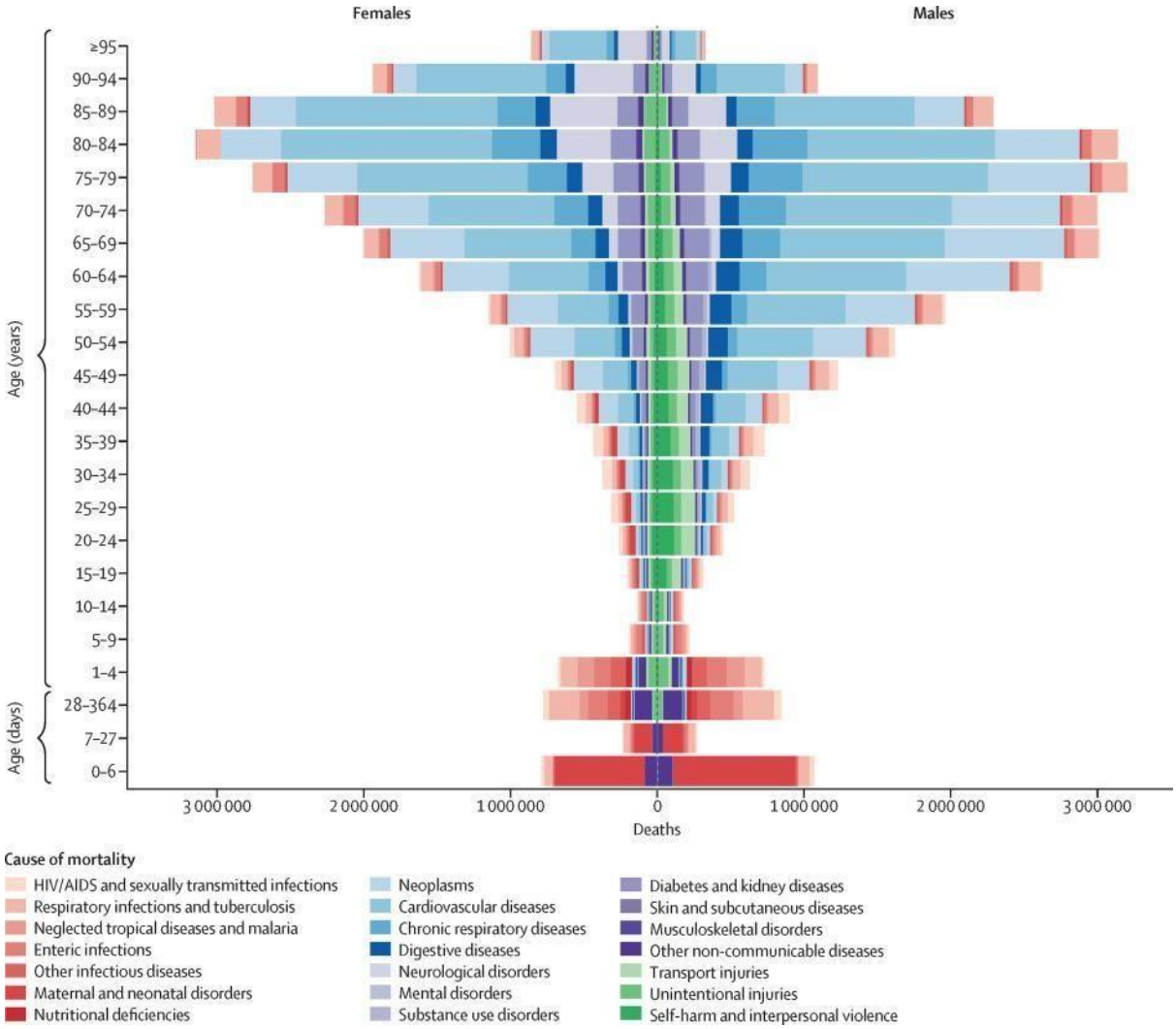
1.1.1 Prevalence and Incidence of MetS

Recent epidemiological data indicate that the global prevalence of MetS is constantly rising and is estimated to be about ¼ of the world's population, i.e.,over a billion people in the world (Ogurtsova et al., 2017; Saklayen, 2018). A systematic review and meta-analysis of 51 studies from 22 countries found that the overall prevalence of MetS is around 24% (Kaur et al., 2014). Another study, based on data from the National Health and Nutrition Examination Survey (NHANES) in the United States, estimated the prevalence of MetS to be about 34% in adults (Ford et al., 2005). Its prevalence is generally higher in people with a higher body mass index (BMI) and in people with a history of T2DM (global prevalence: 8.8%), while it varies across different populations and regions (Kastorini et al., 2016; Saklayen, 2018). Particularly, in terms of socio-demographic characteristics, the prevalence of MetS increases with age (45% in ages between 60-69 years old), while there is a higher prevalence in women (between 32.1 to 42.7%) compared to men (between 20.7% to 37.2%) (Ford et al., 2002; Stout et al., 2017). Other factors associated with the high prevalence of MetS are low socioeconomic status, poverty, and unemployment (Erem et al., 2008; Mabry et al., 2010; Mozumdar et al., 2011; Rochlani et al., 2015).

MetS incidence often parallels the incidence of obesity and T2DM (Saklayen et al. 2018). According to the NHANES data average BMI in the USA from 1988 to 2010increased by 0.37% per year in both sexes, while based on the Centers for Disease Control and Prevention (CDC) in 2017, the incidence of T2DM which increased with age reached a 25.2% among US population aged ≥ 65 (NCHS & NCHSR, 2012; Saklayen et al. 2018). In China, the incidence of MetS increased from 8 to 10.6 in urban areas and 4.9 to 5.3 in rural areas (Wang et al., 2007).

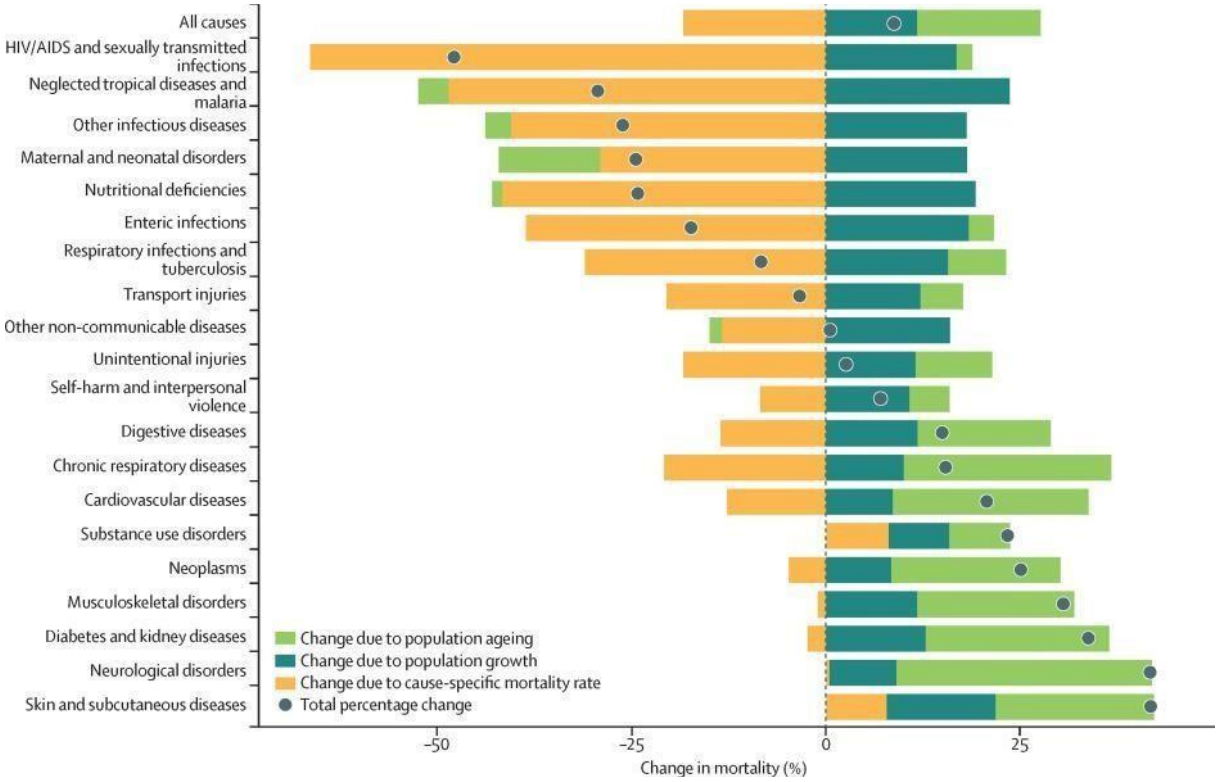
1.1.2 Prevalence and Incidence of CVDs

CVDs are a major public health concern affecting millions of people worldwide. Based on data from the Global Burden of Disease Study, concerning non-communicable diseases, CVDs continue to be the primary cause of death worldwide; with 17.8 million deaths per year and 31% of all deaths globally, followed by neoplasms (WHO, 2021; Roth et al., 2018) (***Figure 1.1***). Heart attack and stroke account for 85% of CVD deaths (WHO, 2021). It is worth noting that the prevalence and incidence of CVDs vary among different populations and regions, with certain populations being at higher risk due to factors, such as age, genetics, lifestyle, and coexisting medical conditions (Roger et al., 2012). According to current demographic data, 1/3 of these deaths occur in adults under the age of 70 and more than 75% in low- and middle-income countries (WHO, 2021).



Source: Roth, et al. 2018

Figure 1.1: Sex differences in global mortality by age



Source: Roth et al., 2018

Figure 1.2: Percentage change in all-age mortality at the global level from 2007 to 2017 by non-communicable disease, due to population growth, aging and cause-specific mortality

1.2. European Epidemiological Data

1.2.1 Prevalence and Incidence of MetS

Findings from 12 cohorts from 10 European countries and 1 from Us participants showed that MetS had a 24.3% prevalence (8468 subjects) (23.9% in men vs 24.6% in women, $p < 0.001$) with an age-associated increase in its prevalence in all the cohorts (Scuteriet al., 2016).

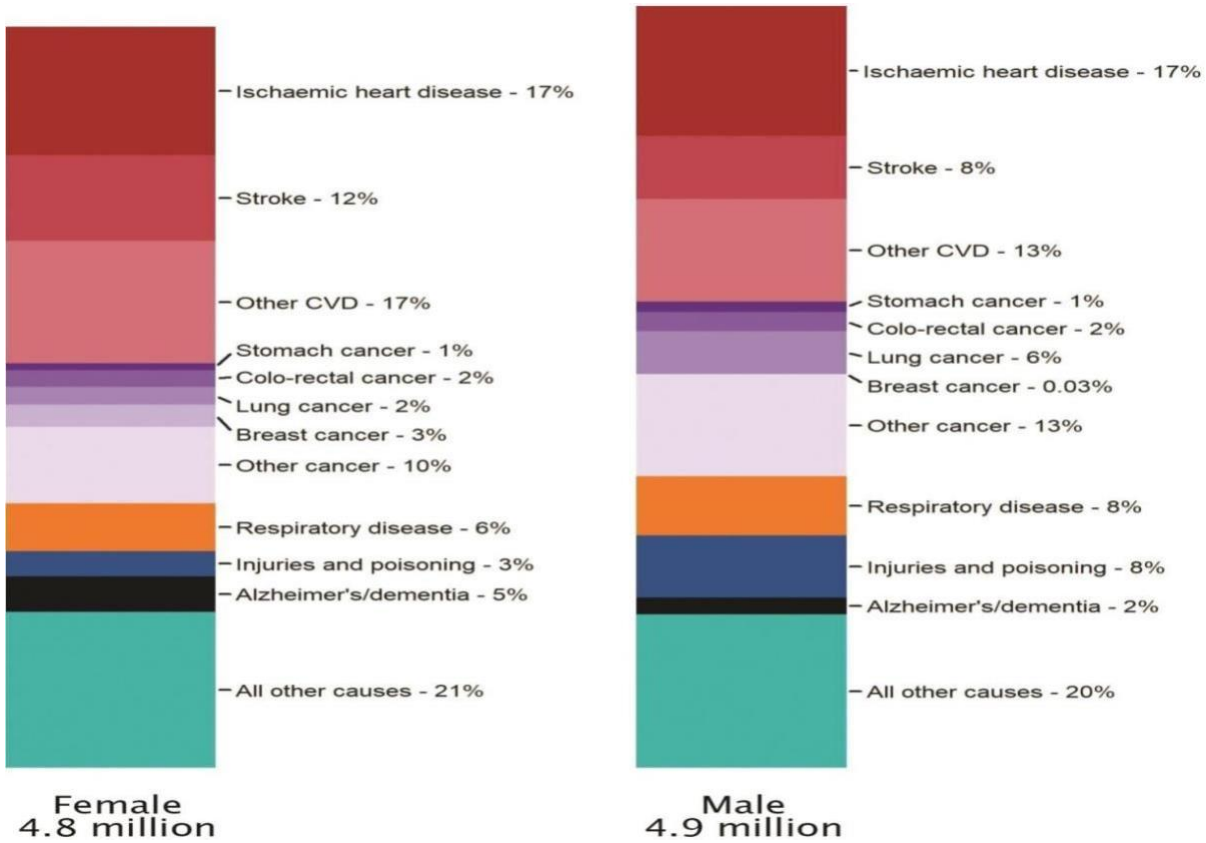
Data from another collaborative analysis of 10 large cohort studies showed that the observed prevalence of MetS was mainly driven by the presence of elevated blood pressure (BP) with ranged from 60%- 85% of individuals fulfilling the criterion for high BP, and thereinafter was driven by the presence of elevated blood glucose, triglycerides and obesity (van Vliet-Ostaptchouk et al., 2014). For example, the age-standardized percentage of men with MetS according to the classic 2001 NCEP ATP III criteria ranged from 42.7% in the

Italian population to 78.2% in the Finnish population, and for women from 24% to 64.8%, respectively (van Vliet-Ostaptchouk et al., 2014).

Since the incidence of MetS is parallel to the incidence of T2DM, data from 11 European countries in 2004 and 2006 (n= 21, 323) reported a two-year cumulative incidence of T2DM in men from 2.2% (95% CI 0.8, 3.7) in Denmark to 7.1% (95% CI 4.9, 9.4) in The Netherlands, and in women goes from 1.9% (95% CI 0.7, 3.1) in Denmark to 7.8% (95% CI 5.1, 10.4) in Spain (Espelt et al., 2013). The age- and country-adjusted cumulative incidence of T2DM in the period 2004–2006 was 3.8% (95% CI 3.3, 4.3) in men and 3.4% (95% CI 2.9, 3.9) in women (Espelt et al., 2013).

1.2.2 Prevalence and Incidence of CVDs

CVDs remain the most common cause of death in Europe accounting for almost 2.2 (45%) million deaths in women and about 1.9 (39%) million deaths in men (Timmis et al., 2022). Ischaemic disease and stroke are the primary and secondary most common cause of CVD deaths, respectively (Timmis et al., 2022) (***Figure 1.3***).

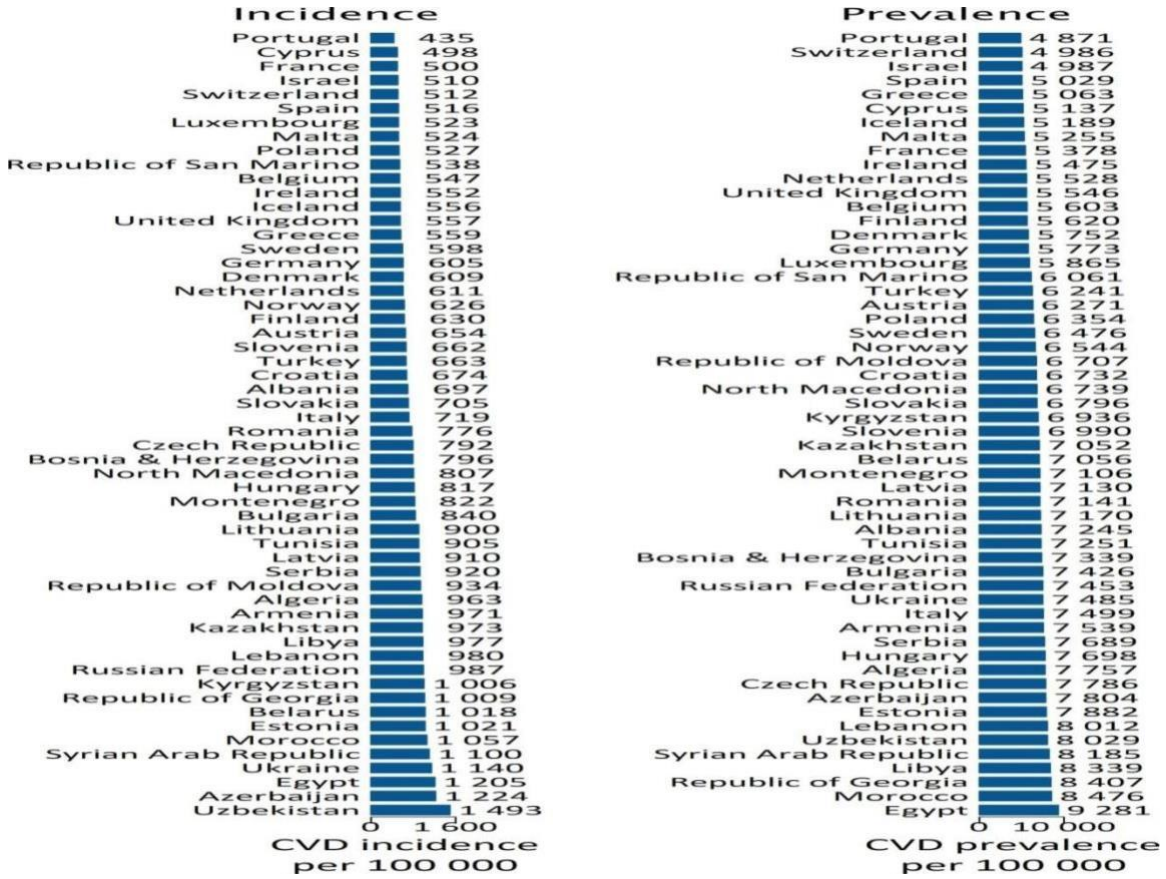


Source: Timmis et al., 2022

Figure 1.3: National causes of death in women and men in the European Society of Cardiology (ESC) member countries

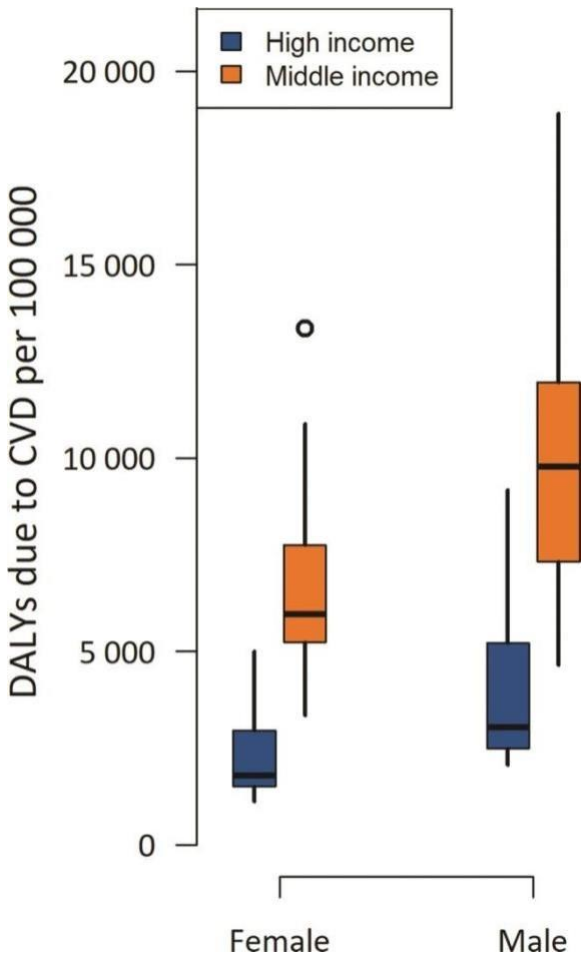
Regarding the ESC member countries, the CVD prevalence is estimated at 113 million people (Timmis et al., 2022). Initially, women have a higher prevalence compared to men but after age-standardization, men living with a CVD are more than women [6369 (IQR 5385–7139) vs. 7586 (IQR 5963–8143)], per 100 000 people (Timmis et al., 2022). Also, people from middle-income countries have a higher CVD prevalence compared to those fromhigh-income countries after age adjustment [7469 (IQR 7094–8016) vs. 5819 (IQR 5347–6845)], per 100 000 people (Timmis et al., 2022).

CVDs incidence is estimated at 12.7 million new cases across all countries in 2019. Women accounted for more new cases compared to men (6.5 million vs. 6.1 million), but after controlling for age women's incidence is lower than men [668.3 (IQR 483.5–857.9) vs. 824.5 (IQR 663.0–1050.2)], per 100 000 people (Timmis et al., 2022). Also, middle-income countries have a higher risk of CVDs compared to high-income countries, after adjusting for age in both sexes [975.0 (IQR 888.6–1028 vs. 601.5 (IQR 526.2–681.9)], per 100 000 people (Timmis et al., 2022).



Source: Timmis et al., 2022

Figure 1.4: Age-standardized incidence and prevalence of CVDs across the ESC member countries



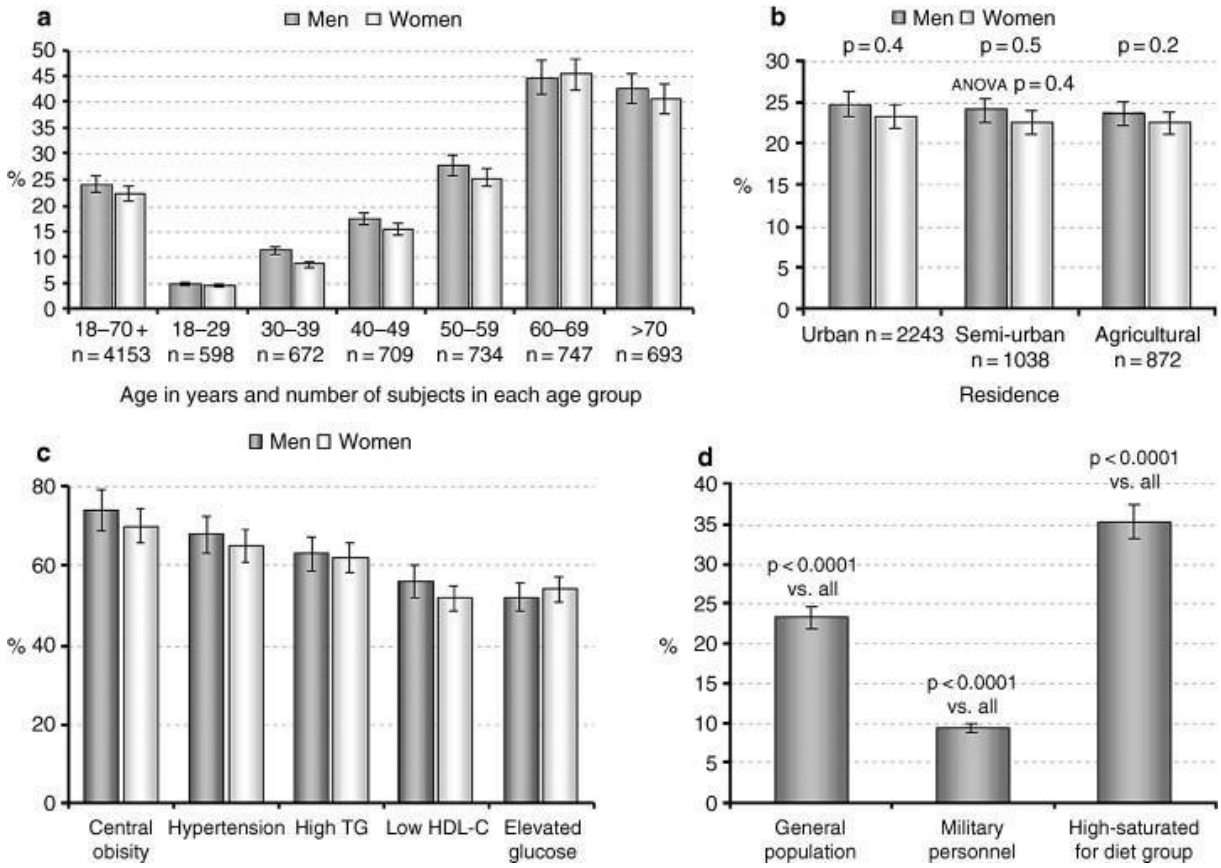
Source: Timmis et al., 2022

Figure 1.5: Age-standardized disability-adjusted life years due to CVDs in inhabitants of the ESC member countries

1.3. Epidemiological Data from Greece

In Greece, the MetS-Greece cross-sectional study showed a 23.6% age-standardized MetS prevalence, similar in both sexes (Athyros et al., 2004). The prevalence increases with age in both sexes, 4.8% among participants aged 19–29 years and 43% for participants aged >70 (Athyros et al., 2004). There is a 14.7-fold increase in the odds ratio for having MetS in the age group > 70 years old compared to that of 19–29 years old (Athyros et al., 2004). Abdominal obesity (82%) and arterial hypertension (78%) are the most common abnormalities in both sexes (Athyros et al., 2004). The Greek Muslim Community who follow a high-saturated fat diet have the highest prevalence of the Mets (35.2%, 95% CI: 30.4–40.3%), and the military group, with a high physical activity level and a diet 'close' to

the Mediterranean, have the lowest (9.4%, 95% CI: 6.2–13.1%) (Athyros et al., 2004)(***Figure 1.6***). Moreover, in the ATTICA epidemiological study, the overall prevalence of MetS is 453 of 2262 individuals (19.8%) (Panagiotakos et al., 2004).



Source: Athyros et al., 2005

Figure 1.6: Prevalence of MetS (a) by age and gender, (b) by residence and gender, (c) in both sexes and (d) in comparison with that of a Greek Muslim Community with a high- saturated fat diet, of military personnel with high physical activity level and diet close to the Mediterranean one

CVDs in the Greek population have concerned the scientific community since very early on. Middle-aged men from two Greek islands, Crete and Corfu participated in the Seven Countries Study (1958-2014) before the 60s (https://www.sevencountriesstudy.com/study-findings/coronary-heart-disease/). The study showed that especially residents from rural villages located in Heraklion had the lowest CVD incidence among all countries that participated in the study (https://www.sevencountriesstudy.com/study-findings/coronary-heart-disease/). For the first time in the literature, the major protective role of the

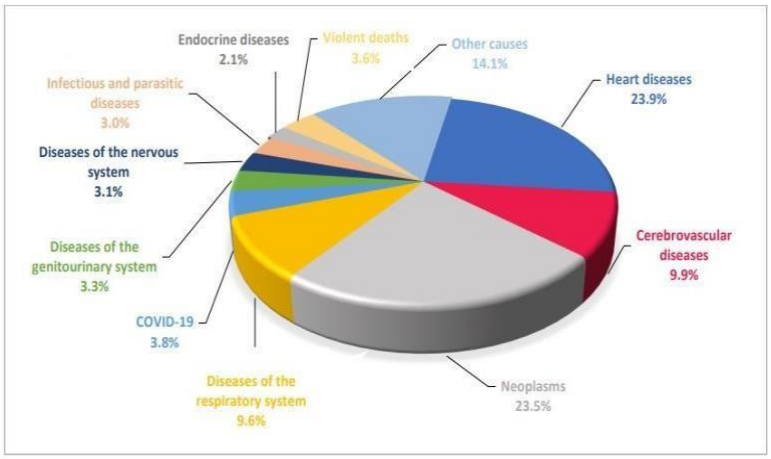
Mediterranean diet is highlighted. Later, in 2001, the Cretan cohort joined the HALE project (Knoops et al. 2004).

The CARDIO2000 (2000-2001) was the first attempt to evaluate the association between several demographic characteristics and dietary habits with the probability of developing non-fatal acute coronary syndrome (ACS) from different Greek regions (Panagiotakos et al., 2005). A random sample of 848 patients (61+/-10 years) with their first CHD event and 1078 frequency-matched (by age-sex) controls with no CVDs in theirmedical history, from all the Greek regions, entered the study. The multi-adjusted analysis showed that a 10-unit increase in the diet score was associated with a 27% decrease in the odds of having ACS. The odds ratios varied from roughly 0.5 in Southern to 1.2 or more in Northern Greek regions (Panagiotakos et al., 2005).

To evaluate the levels of several CVD risk factors in Greece, a population-based health and nutrition survey, the "ATTICA study" was conducted from 2001 to 2022. Researchers randomly enrolled 1514 adult men and 1528 adult women, stratified by age – gender, from the greater area of Athens (Pitsavos et al., 2003). More than 300 demographic, lifestyle, behavioural, dietary, clinical, and biochemical variables have been recorded (Pitsavos et al., 2003). Regarding the frequency of the classical CVD risk factors, 51% of men and 39% of women reported smokers, 37% of men and 25% of women were defined as hypertensives, 46% of men and 40% of women had total serum cholesterol levels above 200 mg/dL and 8% of men and 6% of women had a history of diabetes mellitus (Pitsavos et al., 2003). Moreover, 20% of men and 15% of women were obese, while men were morephysically active as compared to women (42% vs. 39%). Nineteen percent of men and 38%of women had mild to severe depressive symptoms (Pitsavos et al., 2003). Finally, 72 men (5%) and 45 (3%) women reported a history of coronary heart disease at entry evaluation (Pitsavos et al., 2003). In the five years follow-up period, the incidence of CVDs was 11.0% in men and 6.1% in women; the case fatality rate was 1.6% (Panagiotakos et al., 2008). Increased age, waist-to-hip (WH) ratio, hypertension, diabetes, and C-reactive protein (CRP) levels were the most significant baseline bio-clinical predictors of CVDs (Panagiotakos et al., 2008). Furthermore, an increased education level and greater adherence to the Mediterranean diet (among 35–65-year-old individuals) were associated with a lower CVD incidence, irrespective of various potential confounders (Panagiotakos et al., 2008). The 10-year CVD incidence was 19.7% in men and 11.7% in women (Panagiotakos et al., 2015). The determinants of CVD events were increased age, male sex, smoking, and CRP levels (Panagiotakos et al., 2015). At the latest follow-up in 2022, the CVD incident was 3600

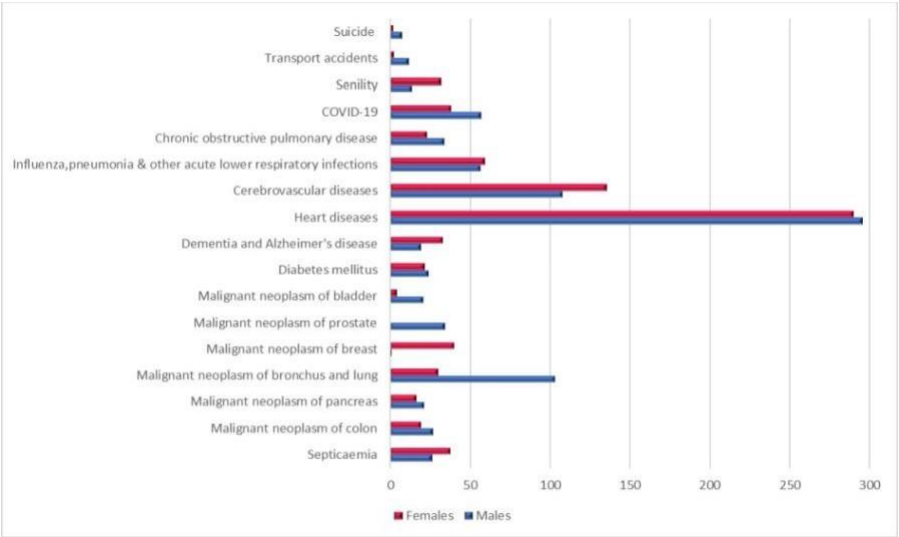
cases/10,000 individuals; the man-to-woman ratio was 1.25, with the peak difference in the 35–45 age group (i.e., 2.1); however, a reversal of the trend was observed in the age-groups 55–65 and 65–75, with a resumption of an almost equal incidence in those >75 years (Damigou et al., 2023).

Finally, regarding mortality, diseases of the circulatory system were the main causes of death in 2020 in Greece, based on the data from the Hellenic Statistical Authority (ELSTAT) (45,741 deaths) (***Figure 1.7 and 1.8***) but also the previous years (ELSTAT, 2020)(***Figure 1.9 and 1.10***).



Source: ELSTAT, 2020

Figure 1.7: Percentage distribution of deaths by main categories of causes of death, 2020



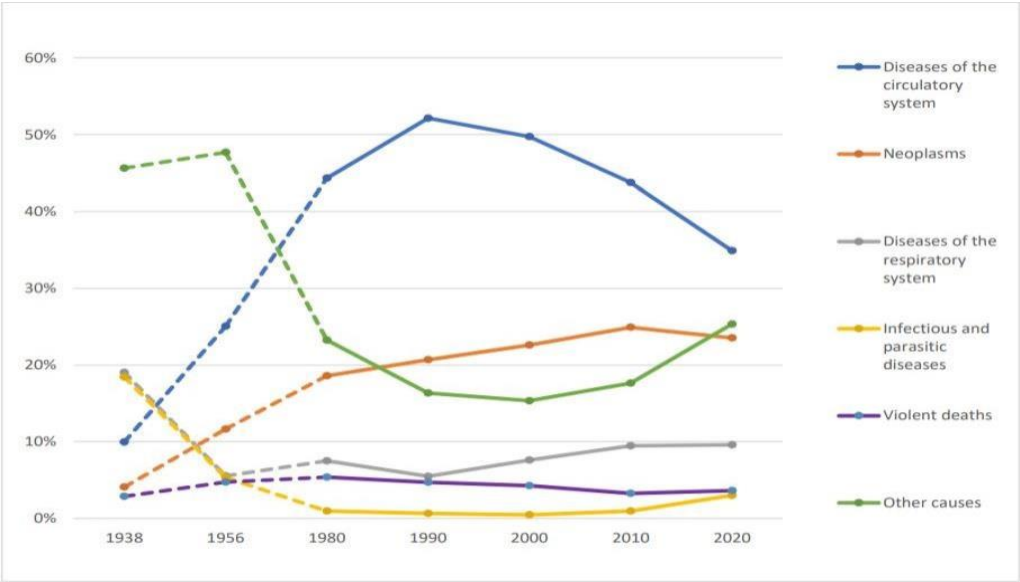
Source: ELSTAT, 2020

Figure 1.8: Cause-specific mortality by sex, for important categories of causes of death, 2020

Year	2015	2016	2017	2018	2019	2020	Average 2015-2019
Total deaths	**121,183**	**118,788**	**124,495**	**120,291**	**124,954**	**131,025**	**121,942**
Heart diseases	30,592	28,917	31,618	30,526	29,804	31,275	30,291
Cerebrovascular diseases	14,445	13,779	13,797	12,574	12,973	13,022	13,514
Neoplasms	30,252	30,673	30,567	30,331	30,637	30,829	30,492
Diseases of the respiratory system	14,835	13,809	13,847	12,668	13,591	12,576	13,750
Diseases of the genitourinary system	3,663	3,276	3,578	3,544	3,866	4,275	3,585
Diseases of the nervous system	2,963	3,235	3,767	3,652	3,546	4,102	3,433
Infectious and parasitic diseases	3,936	4,013	4,165	4,054	4,234	3,921	4,080
Endocrine, nutritional and metabolic diseases	2,036	2,006	2,464	2,509	2,740	2,767	2,351
Violent deaths	3,946	4,062	4,391	4,518	4,604	4,752	4,304
Other causes	14,515	15,018	16,301	15,915	18,959	18,478	16,142
COVID-19	-	-	-	-	-	5,028	-

Source: ELSTAT, 2020

Figure 1.9: Deaths by main categories of causes of death, years 2015-2020 and average number of deaths for the years 2015-2019



Source: ELSTAT, 2020

Figure 1.10: Percentage distribution of main categories of causes of death, years 1938, 1956, 1980, 1990, 2000, 2010 and 2020

2. Pathophysiology of MetS and CVDs

The pathophysiology of both MetS and CVDs is complex and interrelated. Mets, as mentioned above, is a cluster of metabolic risk factors that occur together and increase the risk for CVDs and T2DM (Alberti et al., 2009). It is characterized by central obesity, insulin resistance, dyslipidemia and hypertension (Grundy, 2016). There are several hypotheses regarding the pathophysiology of MetS with the most prominent being that of the role of insulin resistance (Eckel et al., 2005). Insulin resistance as one of the key features of MetS is characterized by a reduced ability of insulin to effectively regulate glucose levels (Kahn et al. 2006). This leads to hyperinsulinemia (i.e., elevated levels of insulin in the blood), which can promote the development of CVDs in several ways (Reaven, 1995).

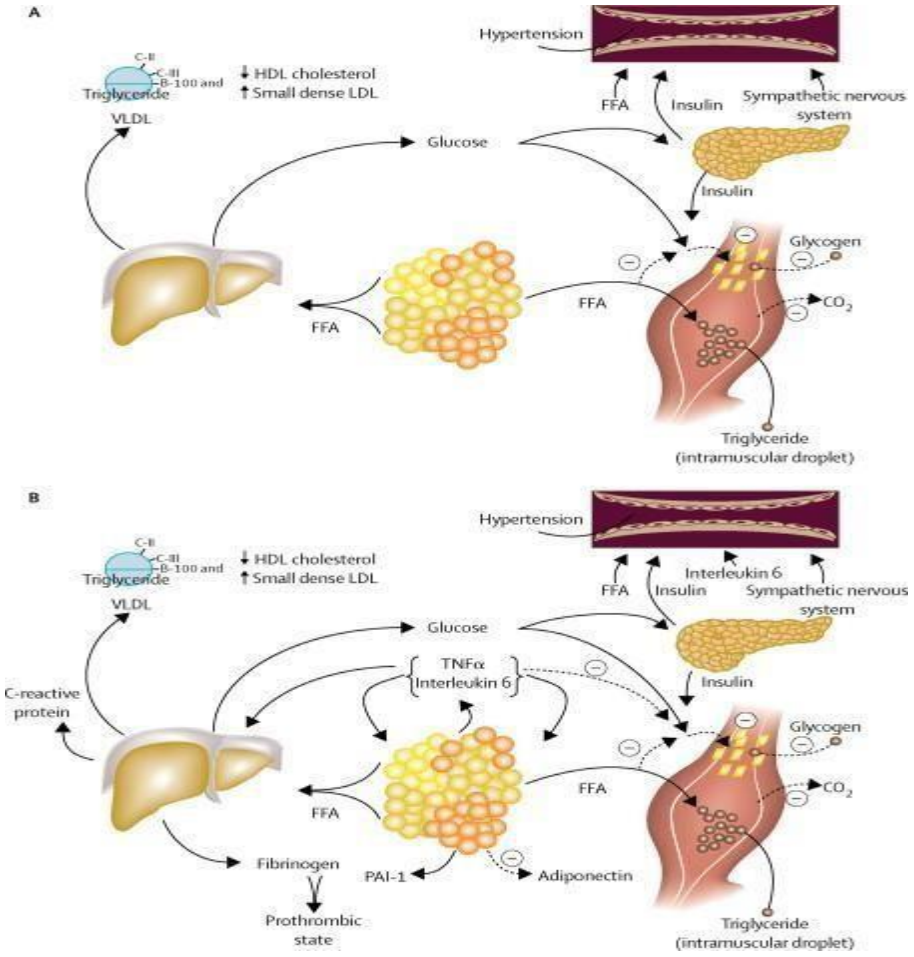
First, insulin resistance can contribute to the accumulation of abdominal fat, which releases fatty acids into the bloodstream (Shulman, 2000). These free fatty acids impair insulin signaling and exacerbate insulin resistance, creating a vicious cycle (Shulman, 2000).

Second, insulin resistance can lead to dyslipidemia, characterized by elevated levels of triglycerides and LDL-C (Grundy et al., 2004). These changes in lipid metabolism can promote the formation of plaques (i.e., fatty deposits in the arterial walls), leading to the development of atherosclerosis (Grundy et al., 2004).

Third, insulin resistance can also contribute to the development of inflammation since recruits immune cells which release inflammatory cytokines (such as tumor necrosis factor-alpha (TNF-α), interleukin-6 (IL-6) and adiponectin), oxidative stress and endothelial dysfunction, which are all associated with an increased risk of CVDs (Kaur, 2014b).

Inflammation can damage the arterial walls, promoting the formation of plaques, while oxidative stress can impair the functioning of the endothelium, the inner lining of the blood vessels, leading to a decreased ability of the blood vessels to dilate properly (Libby et

al., 2011) (***Figure 2.1***). Moreover, increased secretion of prothrombin activator inhibitor-1 (PAI-1) contributes to a pro-coagulant state and along with endothelial dysfunction leads to an increased risk of atherothrombosis, hypertension and CVDs (Kohler & Shulman, 2006). Hypertension or elevated blood pressure is another typical feature of MetS and a major risk factor for CVDs (Grundy, 2016). The exact mechanisms by which hypertension develops in the context of MetS are not fully understood, but it is thought to involve the activation of the rennin-angiotensin-aldosterone system, oxidative stress and inflammation (Oparil et al., 2003).



Source: Eckel et al., 2005

Figure 2.1: Pathophysiology of MetS

2.1. Inflammation and Endothelial Dysfunction

Unhealthy diet, smoking, obesity, and physical inactivity are among the modifiable risk factors for CVDs since they lead to a pro-inflammatory state (Allende-Vigo, 2010). Inflammatory response participates in the pathogenesis of CVDs, through atherosclerosis,

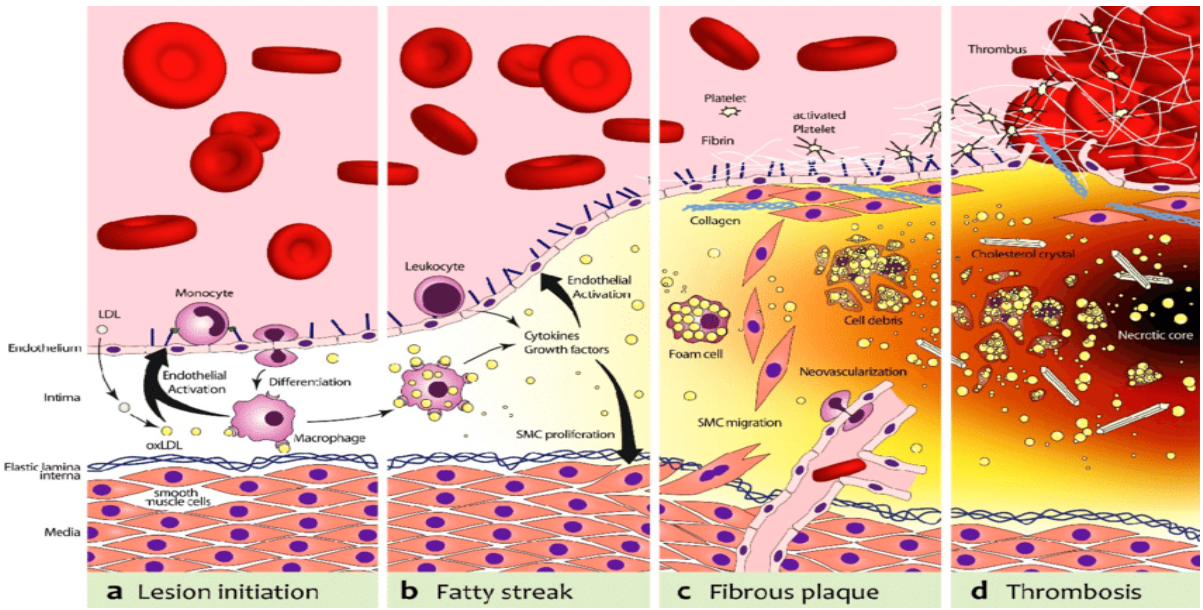
from the beginning to the stage of thrombotic complications (Carter, 2012; Libby et al., 2006).

The blood vessels consist of connective tissue, fibroblasts, endothelial cells and vascular smooth muscle cells (VSMCs) (Sun et al., 2020). The endothelium is a thin membrane of endothelial cells that lines the inner of the blood vessels (arteries, veins and capillaries) and the lymphatic system, and consequently directly contacts the blood/lymph and circulating cells (Félétou, 2011). Activated endothelial cells release inflammatory cytokines, chemokines that control vascular relaxation and contraction and promote migration, as well as enzymes, such as endothelial nitric oxide synthase, a key enzyme in the production of the vasodilator nitric oxide (NO) that control blood clotting, immune function and platelet (i.e., a component of blood that contributes to hemostasis, the process of stoping bleeding caused by blood vessel injury where the endothelium is interrupted initiating a blood clot) adhesion (https://www.cedars-sinai.org/programs/heart/clinical/womens-heart/conditions/endothelial-function-testing.html; https://www.sciencedirect.com/topics/medicine-and-dentistry/endothelial-nitric-oxide-synthase; Park-Windhol & D'amore, 2016). The endothelial cells with inflammatory phenotype cause inflammation in the blood vessels, resulting in endothelial dysfunction (Sun et al., 2016). Endothelial cell inflammation is responsible for atherosclerosis (Sun et al., 2020).

2.2. Atherosclerosis

Atherosclerosis is a chronic inflammatory condition characterized by the build-up of plaque within the walls of arteries, which leads to the narrowing and hardening of these blood vessels over time (Libby & Theroux, 2005). This process can impair blood flow to vital organs and tissues, leading to a range of CVDs, such as coronary artery disease (CAD), stroke, and peripheral artery disease (Libby & Theroux, 2005). The underlying mechanism of atherosclerosis involves the accumulation of lipids, inflammatory cells, and connective tissue in the arterial wall, forming a fatty deposit called an atherosclerotic plaque (Ross, 1999). Plaque consists of cholesterol, triglycerides and other lipids that are deposited within the arterial wall, along with immune cells, such as macrophages and T-lymphocytes, which release inflammatory cytokines and enzymes that further promote plaque growth and inflammation (Ross, 1999). Smooth muscle cells in the arterial wall also proliferate and migrate toward the plaque, contributing to its growth and stability (Ross, 1999). As previously stated, there are several risk factors associated with the development of

atherosclerosis, including age, genetics, high blood pressure, high cholesterol levels, diabetes, obesity and smoking (Steinberg, 2005). The risk factors can lead to endothelial dysfunction, a condition in which the inner lining of the artery becomes damaged, allowing lipids and other substances to accumulate within the arterial wall (Steinberg, 2005) (***Figure 2.2***).



Source: Steini et al., 2015

Figure 2.2: Pathogenesis of atherosclerosis

2.3. Links among Inflammation and Endothelial Dysfunction and the Autonomous Nervous System (ANS)

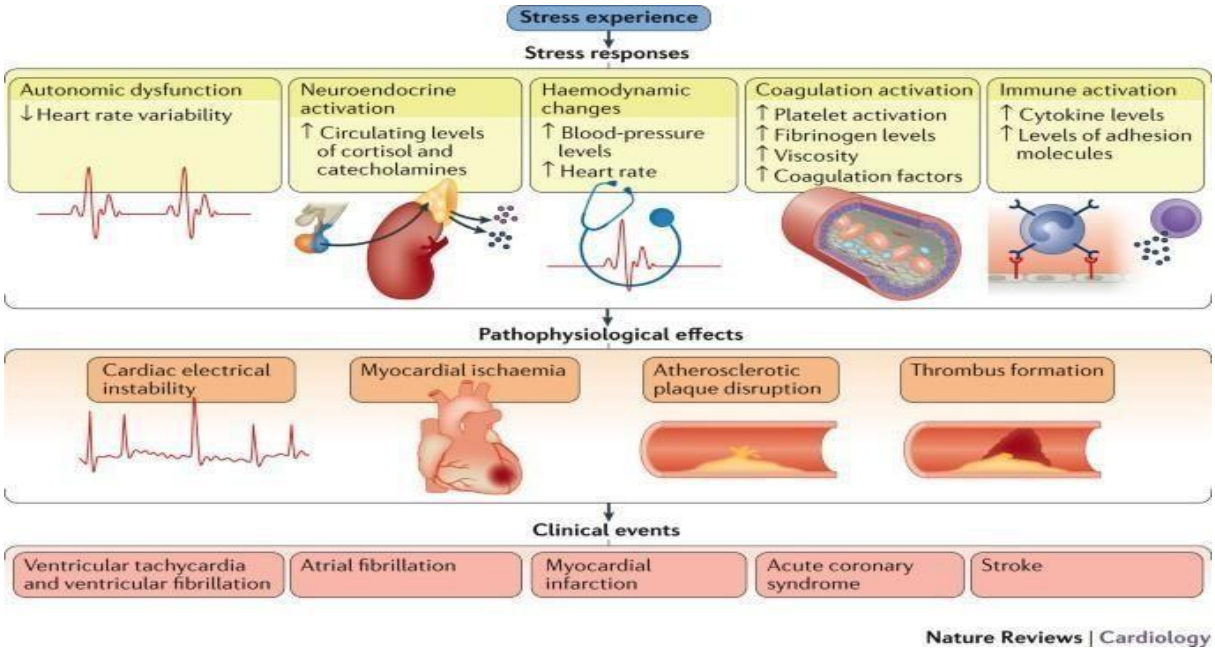
The nervous system (NS) consists of the central nervous system (CNS) which includes the brain and the spinal cord and the peripheral nervous system (PNS) which includes nerves that branch off form the spinal cord and extend to all parts of the human body (https://www.nichd.nih.gov/health/topics/neuro/conditioninfo/parts).

The autonomous nervous system (ANS) is a component of the PNS that regulates several physiological processes, among which are heart rate, blood pressure, insulin secretion, lipid metabolism, respiration, digestion and sexual arousal (Epel et al.,2000; McEwen, 1998; Waxenbaum et al., 2019). The ANS constitutes the sympathetic, the parasympathetic and the enteric distinct division (Waxenbaum et al., 2019). The sympathetic and the parasympathetic nervous systems have opposite roles. In particular, while the sympathetic system carries signals that alert the body's system, the parasympathetic system carries signals that relax body systems (https://my.clevelandclinic.org/health/body/23262-

sympathetic-nervous-system-sns-fight-or-flight). Those two systems collaborate for the body's function to be in balance.

The central regulation of the sympathetic and the parasympathetic branches of the ANS is accomplished via the hypothalamic-pituitary-adrenal (HPA) axis, a vital neuro- endocrine system that regulates reactions to stress and body processes by releasing hormones-neurotransmitters, the catecholamines, such as norepinephrine, epinephrine, cortisol, dopamine, adrenaline and noradrenaline (Epel et al.,2000; McEwen, 1998; Selye, 1974; https://www.sciencedirect.com/topics/agricultural-and-biological-sciences/catecholamine). Catecholamines are produced and released by the adrenal glands in response to emotional or physical stress (McEwen, 1998). Chronic stress and activation of the HPA axis can lead to increases levels of catecholamines leading to an increase in the activity of the sympathetic NS and a decrease in the activity of the parasympathetic NS, provoking a state of sympathetic dominance that has been linked to the development of insulin resistance, abdominal fat, dyslipidemia and hypertension (Epel et al.,2000; McEwen, 1998). Acute and chronic psychological stress have been associated with elevated pro-inflammatory cytokines and oxidative stress, and they can lead to vasoconstriction and elevated blood pressure via catecholamines (Epel et al.,2000; Gidron et al., 2002; McEwen, 1998; Raison et al., 2006). Inflammatory factors and stress have been positively associated with platelet aggravation which may cause thrombosis, while thrombosis can lead to ACS (Gidron et al., 2002) (***Figure 2.3***).

On the other hand, endothelial damage causes an acute release of pro-inflammatory cytokines which also activate the HPA axis and increase oxidative stress levels in the brain (Halaris, 2017). It is worth mentioning that IL-6 is one of the most potent stimulators of the HPA axis, inducing the release of other cytokines (Halaris, 2017).



Source: Kivimäki & Steptoe, 2018

Figure 2.3: Pathophysiological mechanisms of the nervous system.

3. Determinants of MetS and CVDs

Clinical components of MetS (e.g., hypertension, dyslipidemia and abdominal obesity) are considered known determinants of CVD risk, while anthropometric characteristics (e.g., BMI), genetic (e.g., family history), social (e.g., age, sex, social status), lifestyle (e.g., unhealthy dietary patterns, physical inactivity, smoking), psychosocial (e.g., stress) and psychological factors are risk factors for both MetS and CVDs (Franklin, 2006; Kaur, 2014; Tsiampalis et al., 2021; Xu et al., 2018).

The risk of MetS is similar between men and women but it increases with age, with women being at higher risk of developing CVDs after menopause (Saklayen et al., 2018). In addition, low socio-economic status (SES) has been associated with an increased risk of MetS and CVDs, likely due to factors such as lower access to healthy food options, limited opportunities for physical activity, and higher levels of stress (Stringhini et al., 2017). Concerning genetic factors, family history and single nucleotide polymorphisms (SNPs) (i.e., certain genetic variations) have also been associated with an increased risk of both MetS and CVDs (Saleheen et al., 2017). Finally, psychological factors, such as stress, anxiety and depression have been linked to the development of MetS and CVDs, likely through their effect on the ANS, hormonal and immune system (Kivimäki & Steptoe, 2018).

3.1. Clinical and Biological Determinants

3.1.1 Hypertension or High Blood Pressure

Hypertension or otherwise high blood pressure is a metabolic risk factor for MetS that is also associated with the strongest evidence of a causal relationship with CVD onset (Fuchs & Whelton, 2020). It is recorded as two numbers, systolic blood pressure (SBP) and diastolic blood pressure (DBP). SBP indicates how much pressure the blood is exerting against the arterial walls when the heart beats, while DBP indicates how much pressure exerts when the heart is resting between beats (AHA, 2021). According to the most important report by the Prospective Studies Collaboration pooled data from many cohort studies, the CVD risk

increases steadily with progressively higher levels of baseline SBP and DBP above 115 mmHg and 75 mmHg, respectively. Also, for every 20 mm Hg higher SBP level and 10 mm Hg higher DBP level, there is a 2-fold CVD risk (Fuchs & Whelton, 2020). In Greece, 1 outof 5 (19.6 %) persons of the population aged 15 and over reported suffering from hypertension (high blood pressure), recording a decrease of 6.2 % compared to the relevant share recorded in 2014 (20.9 %); among them 45.0 % are men and 55.0 % women (ELSTAT,2020).

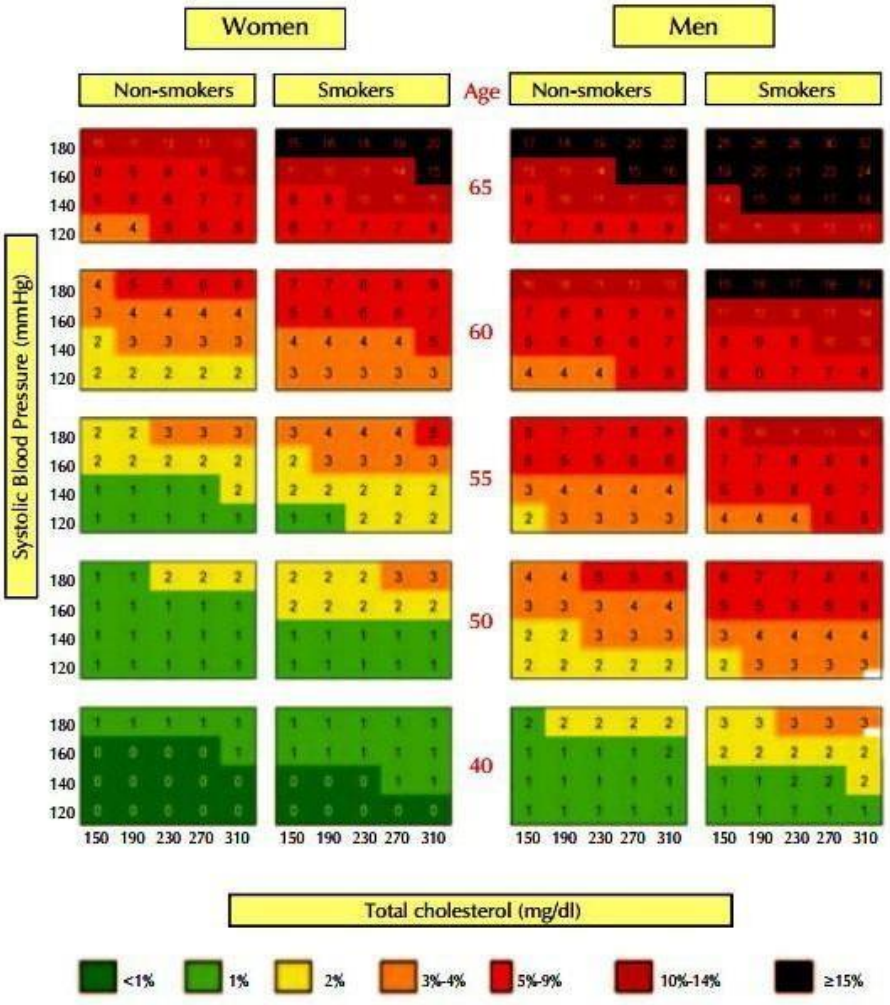
The Framingham Heart Study along with some other studies indicated that high SBP (i.e.., ≥130 mm Hg is a fundamental predictor of cardiovascular outcomes than high DBP (i.e., ≥80 mm Hg) (AHA, 2021; Flint et al., 2019; Kannel et al., 1971). This was also in line with the European CVD score suggested in 2000s and recalibrated for the Greek population in 2007 (***Figure 3.1***).

High blood pressure is suggested as a leading cause of long-term healthconsequences, not only cardiovascular, such as heart failure, atrial fibrillation, valvular heart disease, peripheral arterial disease and aortic syndromes, but also diabetes mellitus, chronic kidney disease, dementia, and Alzheimer Disease (Emdin et al., 2015a; Emdin et al., 2015b; Emdin et al., 2016; Emdin et al., 2017; Ho et al., 2016; Kanno et al., 2012; Rahimi et al., 2017; Rahimi et al., 2018; Walker et al., 2019).

3.1.2 Plasma Glucose and Insulin Resistance

Glucose is a monosaccharide sugar that human organism obtains from food, and it is used as a primary energy source (Gurung, 2022). Insulin is a hormone made by the pancreas that assists glucose in the blood to enter cells in the muscle, fat and liver for energy production (https://www.niddk.nih.gov/health-information/diabetes/overview/what-is diabetes/prediabetes-insulin-resistance). There is insulin resistance when cells in muscles, fat and liver have a decreased ability to respond to insulin, leading to the accumulation of glucose in the blood (hyperglycemia) (Gross et al., 2006; Kahn et al., 2006; https://www.niddk.nih.gov/health-information/diabetes/overview/what-is-diabetes/prediabetes-insulin-resistance). When blood glucose levels are higher than normal, i.e., ≥100 mg/dL there is an indication of prediabetes, while a ≥126 mg/dL indicates diabetes (https://www.cdc.gov/diabetes/basics/getting-tested.html). In Greece, 8.0 % of the population aged 15 and over report suffering from diabetes mellitus, recording a decrease of 13.0 % compared to the relevant share recorded in 2014 (9.2 %); among them 48.5 % are men and 51.5 % women (ELSTAT, 2020).

People with diabetes or pre-diabetes have an increased relative risk of CVDs compared to those without diabetes, even after adjusting for other factors such as age, gender and lifestyle (Kahn et al., 2006; Kannel & McGee, 1979). Plasma glucose concentrations and CVDs are linked through a) direct toxic effects of glucose on cell function and structure, b) indirect effects due to insufficient insulin secretion to prevent hyperglycemia and associated metabolic abnormalities, c) a history of pre-existing insulin resistance and hyperinsulinemia, before elevations in plasma glucose concentrations, and d) an association with other risk factors like dyslipidemia, hypertension, abdominal obesity, etc (Gerstein, 1997).



Source: Panagiotakos et al., 2007

Figure 3.1: HellenicSCORE chart: 10-year risk of fatal CVDs for the Greek population, risk based on the following risk factors: age, gender, smoking, systolic blood pressure, and total cholesterol

3.1.3 Dyslipidaemia

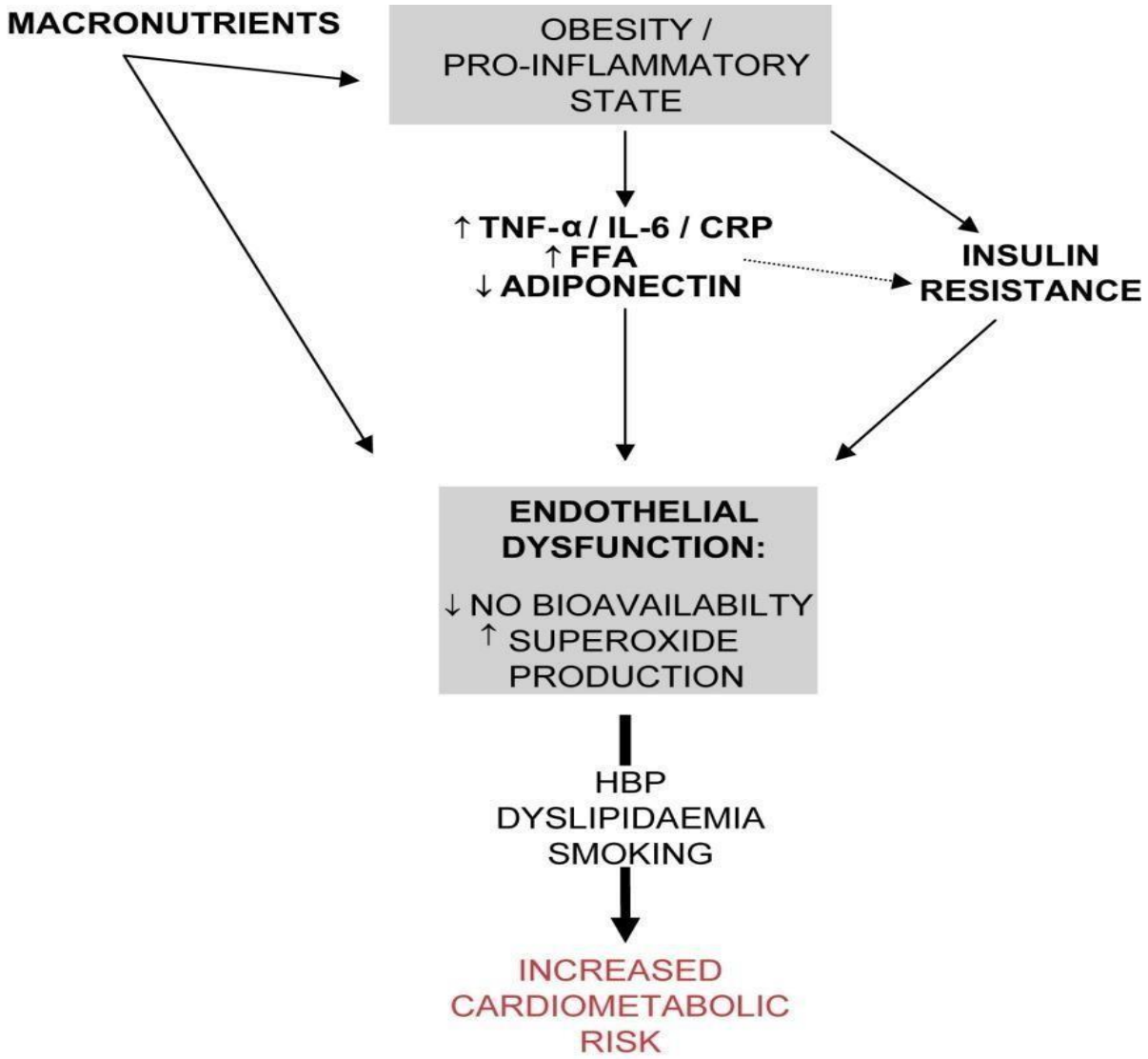
Dyslipidemia is defined as an abnormally high concentration of lipids in the blood, i.e., an elevated serum total cholesterol (TC), serum LDL-C, or triglycerides (TG) andreduced serum HDL-C concentration, and it is associated with an increased risk of CVDs (Hedayatnia et al., 2020; Stein et al., 2019). Total blood cholesterol above desirable levels affects about 12% of the adult population, especially middle-aged and seniors (Stein et al., 2019). For instance, in Greece high blood cholesterol level or triglycerides are reported by
15.8 % of the population aged 15 years and over, recording an increase of 2.6 % compared to the relevant share recorded in 2014 (15.4 %); among them 46.0 % are men and 54.0% women (ELSTAT, 2020). A high-fat diet and high calorie-diet can cause dyslipidemia and subsequent endothelial dysfunction. Especially LDL-C can be deposited within the tunica intima of the arterial wall and be involved in the consequent atherogenic process (Proctor et al., 2002; Proctor & Mamo, 2003; Proctor et al., 2004).

3.1.4 Abdominal Obesity

Obesity and atherosclerosis are supposed to have inflammatory etiology (Pasqui et al., 2005; Ross, 1999). Pro-inflammatory cytokines, such as TNF-α, IL-6 and CRP are elevated in obesity (Diamant et al., 2005; Hotamisligil et al., 1993). High-fat intake and subsequent increase in adipose tissue are associated with the expression of pro-inflammatory molecules and oxidative stress, as well as the activation of nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB), which is a pro-inflammatory transcription factor (Aljada et al., 2004; Mohanty et al, 2002). Obesity is also associated with insulin resistance and adipokines, an important component of the neuroendocrine-immune network (Ritchie & Connell, 2007; https://www.sciencedirect.com/topics/neuroscience/adipokine). Therefore, obesity results in a pro-inflammation state with alteration of adipokine secretion and increased visceral adiposity (i.e., fat around the internal organs) also known as central or abdominal obesity, which is associated with elevated free fatty acids (FFA), with concomitant insulin resistance (Ritchie & Connell, 2007).

Obesity-associated inflammation stems from changes in immune cells, which are important in the atherosclerotic process, and their interaction with the endothelium is thought to be a key process in early atherogenic formation (Hansson, 2005; Liu & Nikolajczyk, 2019). Reduction in nitric oxide (NO) which is a key regulator of endothelial homeostasis, and an increase in reactive oxygen species and oxidative stress, resulting in endothelial dysfunction and a pro-atherogenic vascular bed (Harrison, 1997) (***Figure 3.2***). Still, the exact

molecular and cellular mechanisms underlying the relationship between obesity, MetS, and its association with increased CVD risk are incompletely understood and have led to focused research on the function of adipose tissue (Ritchie & Connell, 2007).



Source: Ritchie & Connell, 2007

Figure 3.2: Potential mechanisms linking abdominal obesity, MetS and CVDs

Regarding Greece, and as the BMI is the most important indicator of obesity, among the total population aged > 15 years, 1.4% are underweight (BMI < 18.5), 41.4 % are normal weight (BMI: 18.5-24.9), 40.8% are overweight (BMI: 25-29.9), and 16.4% are obese (BMI ≥ 30.0) (ELSTAT, 2020).

3.2. Genetic Determinants

CVDs may cluster in families (Abbate et al., 2008). Twin and family studies have demonstrated that CVD risk increases when there is a family history of early onset of CVDs that functions independently of other well-known risk factors or when there is familialdiabetes, high cholesterol, or high blood pressure (Abbate et al., 2008).

Although there is no one specific gene that determines CVD onset, several genetic variations have been identified that may increase this risk (Yaghootkar et al., 2014). One such genetic determinant is variations in the genes involved in insulin signaling, such as the insulin receptor gene (INSR), and the insulin-like growth factor 1 receptor gene (IGF-1R) that can lead to insulin resistance (Yaghootkar et al., 2014). Another genetic determinant is variations in the genes involved in lipid metabolism, such as the low-density lipoprotein receptor gene (LDLR) and the apolipoprotein B (APOB) gene that can lead to elevated levels of LDL-C (Kathiresan et al., 2008). Moreover, there are variations in genes involved in inflammation and oxidative stress, such as the NF-κB and the peroxisome proliferator-activated receptor gamma gene (PPAR-γ) (Scirpo et al., 2015).

3.3. Lifestyle Determinants

Dietary Habits and Patterns

It is estimated that 1 in 5 premature deaths due to CVDs could be avoided with an optimized diet (Meier et al., 2019). High-fat diets (HFD) (i.e., a diet consisting of at least 35% of total calories from saturated and unsaturated fats), diets high in added sugar and refined carbohydrates are associated with CVD disease, due to several risk factors including dyslipidemia, glucose metabolism disorders, oxidative stress and NF-κB activation (Aljada et al., 2002; Timmie et al., 2022; https://www.sciencedirect.com/topics/agricultural-and-biological-sciences/high-fat-diet). Common sources of saturated fats, such as animal products (e.g., butter, coconut oil, and meat fat) and processed foods (e.g., pastries and biscuits) increase LDL cholesterol (https://www.betterhealth.vic.gov.au/health/conditionsandtreatments/heart-disease-and-food). Like saturated fats, trans fat (naturally found in small amounts in dairy products or processed foods) increase LDL but also reduce HDL cholesterol (https://www.betterhealth.vic.gov.au/health/conditionsandtreatments/heart-disease-and-food). Also, trans fat has been associated with all-cause mortality and CAD mortality and CVD risk (De Souza et al., 2015; https://www.betterhealth.vic.gov.au/health/conditionsandtreatments/heart-disease-and-food)

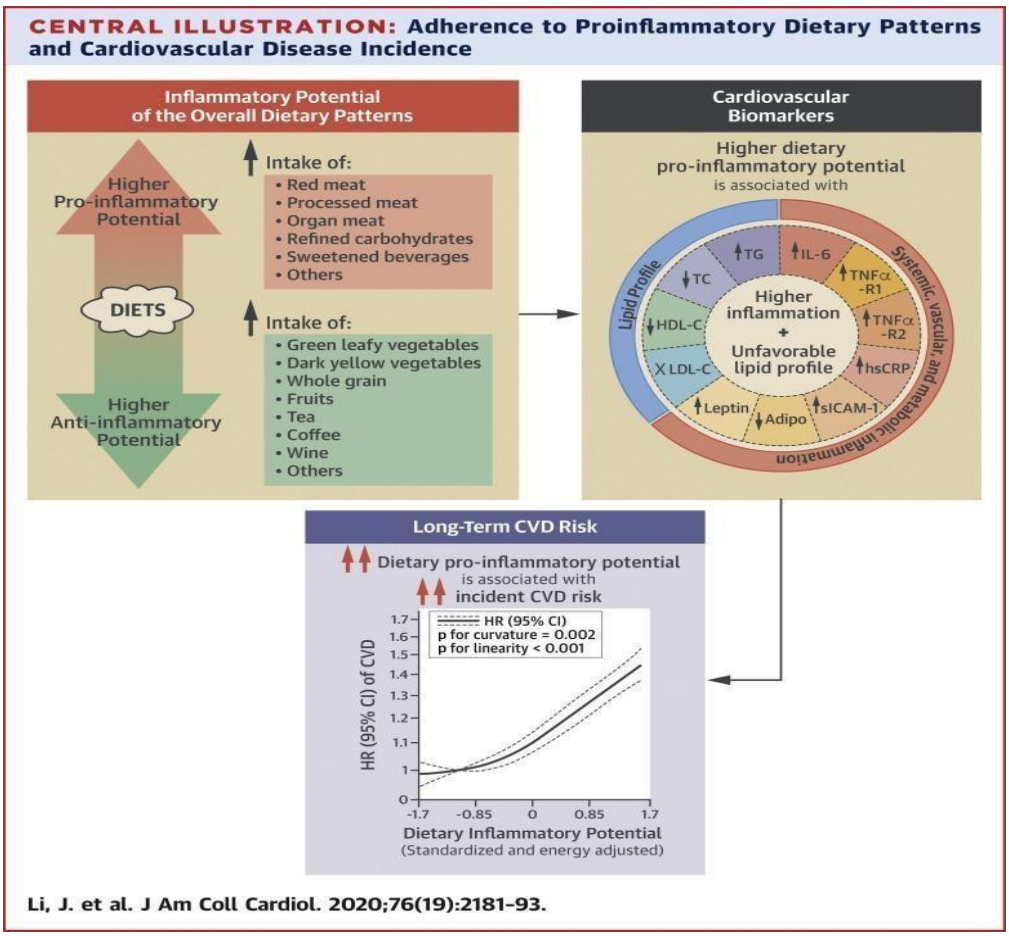
(***Figure 4.1***). For instance, the NutriNet-Santé, a prospective cohort study revealed that higher consumption of ultra-processed foods (UPF) (i.e., foods that contain 5 or more ingredients that include substances derived from further processing of food components) was associated with a higher risk of T2DM (Srour et al., 2020; https://www.frontiersin.org/research-topics/22794/ultra-processed-foods-health-concerns-and-consumption-trends).

In addition, high meat consumption (especially processed meat), as well as reduced intake of whole grains, are associated with increased MetS and CVD risk (Aekplakorn et al., 2015). Also, higher dietary sodium intake than the recommended (i.e., >2 g/day) was associated with increased blood pressure levels (Powles et al., 2013), whereas a systematic review and meta-analysis of randomized clinical trials showed a dose-response relationship between dietary sodium reduction and blood pressure reduction, greater for people with higher blood pressure at baseline (Huang et al., 2020). Coffee diterpenes and especially cafestol which are contained in unfiltered coffee brews raise serum lipids (Ren, 2019).

In contrast, unsaturated fats (such as oils made from seeds or plants, unsalted nuts, seeds and avocado), oily fish, fruits and vegetables, wholegrains and unrefined carbohydrate sources with low glycemic load, legumes, nuts and seeds, tea, unflavoured milk, yogurt and cheese, sources of vitamin E, garlic, foods enriched with plant sterols, herbs and spices, are indicated that be associated with decreased CVD risk and CVD risk factors (such as the MetS) (Panagiotakos et al., 2007; Suliga et al., 2015; https://www.betterhealth.vic.gov.au/health/conditionsandtreatments/heart-disease-and-food) (***Figure 4.2***). Particularly, a prospective study by UK Biobank with 422, 791 participants showed that "fish-eaters" (those consuming cheese, milk and fish but not poultry or red meat) had a lower risk of a range of adverse CVD outcomes compared to "meat eaters" (those consuming cheese, milk, fish, poultry and red meat) (Estruch et al., 2021). In addition, nutrients, such as long chain omega-3 polyunsaturated fatty acids (ω-3PUFA)) are essential for brain function, since they regulate chemical processes (e.g., metabolic pathways, neurotransmitter synthesis and cell–cell signaling) (Bentsen, 2017; Sinn et al., 2010). Lately, also adequate dietary magnesium has been associated with decreased MetS and CVD risk, but also psychological factors that are interrelated with cardio-metabolic conditions, such as reduced anxiety levels; yet all these associations need further examination (Boyle et al., 2017; DiNicolantonio et al., 2018; Evers et al., 2022; Rosique-Esteban et al., 2018).

In conjunction, specific dietary patterns, such as the Mediterranean diet (that is based on plant-based foods, olive oil, fish, dairy and poultry, while red meat and sweets

consumption is occasional) (***Figure 4.3***), the Dietary Approaches to Stop Hypertension (DASH) (i.e., rich in vegetables, fruits and whole grains but also includes fat-free or low-fat dairy products, fish, poultry, beans and nuts) and well-planned vegetarian diets are beneficial for preventing total and specific types of CVDs (***Figure 4.4***), whereas Western-type diets (i.e., high in meat, fat and salt consumption) increase this risk (Kahleova et al., 2018;Martínez-González et al., 2015; Oikonomou et al., 2018; Salas-Salvadó et al., 2018; Siervo et al., 2015) (***Figure 4.1***). A Western dietary pattern can also result in elevated levels ofcirculating plasma Aβ that may trigger hippocampal dysfunction, a diet high in sugar and fat (or just sugar) may damage hippocampal function as well, while a healthy pattern may improve cognitive function and reduce oxidative stress (Jacka et al., 2015; Shakersain et al., 2016).

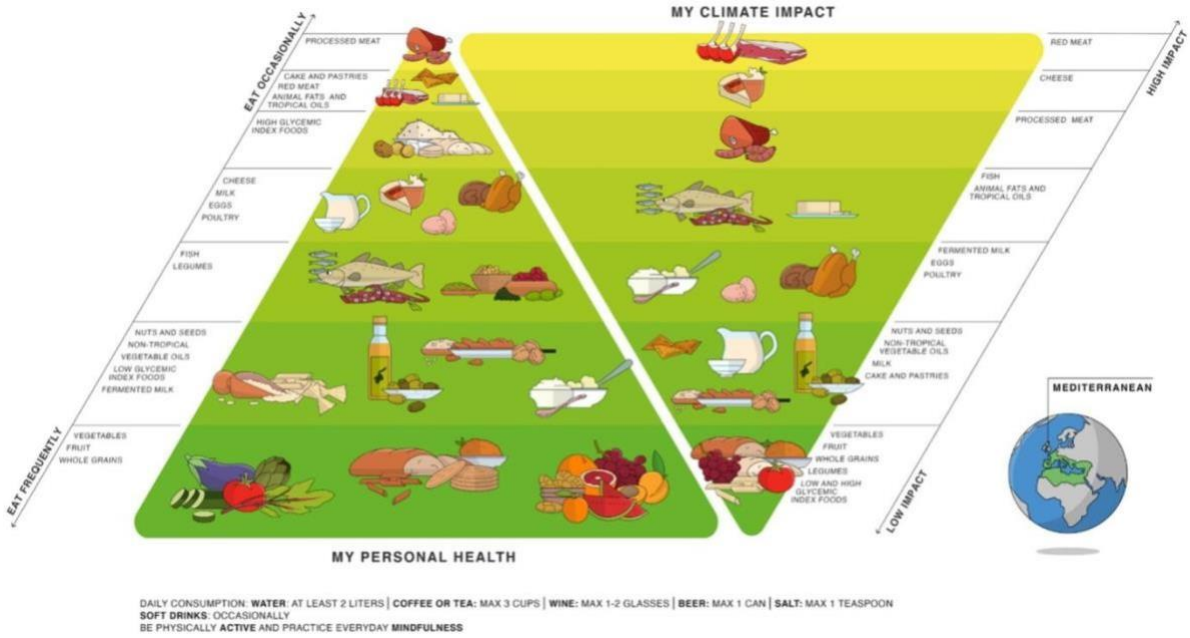


Source: Li et al., 2020

Figure 4.1: Dietary factors in relation CVD risk

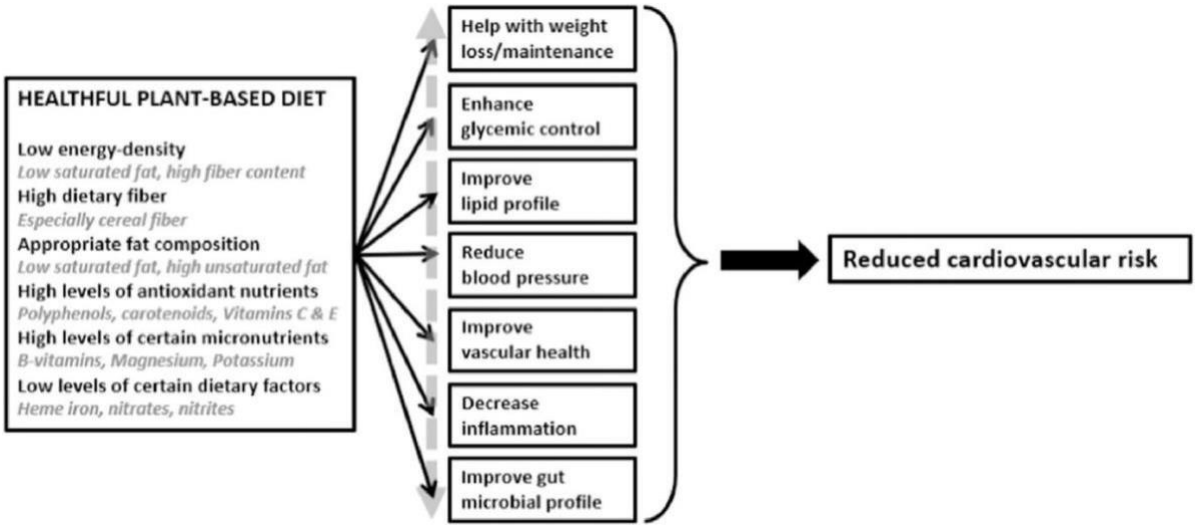
Source: Chang & Koegel, 2017

Figure 4.2: An example of USDA Food Patterns recommendations in 2,000 calories per day



Source: Ferrari et al., 2022

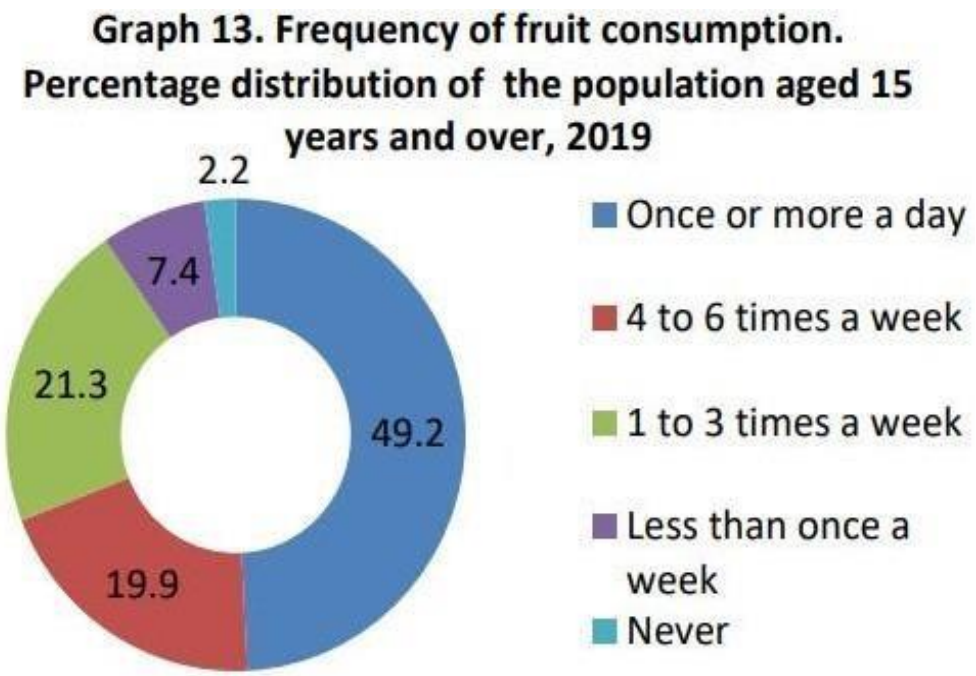
Figure 4.3: The double pyramid model based on the Mediterranean diet (upward pyramid on the left) in parallel with the environmental impact of the relevant foods (downward pyramid on the right)



Source: Satija & Hu, 2018

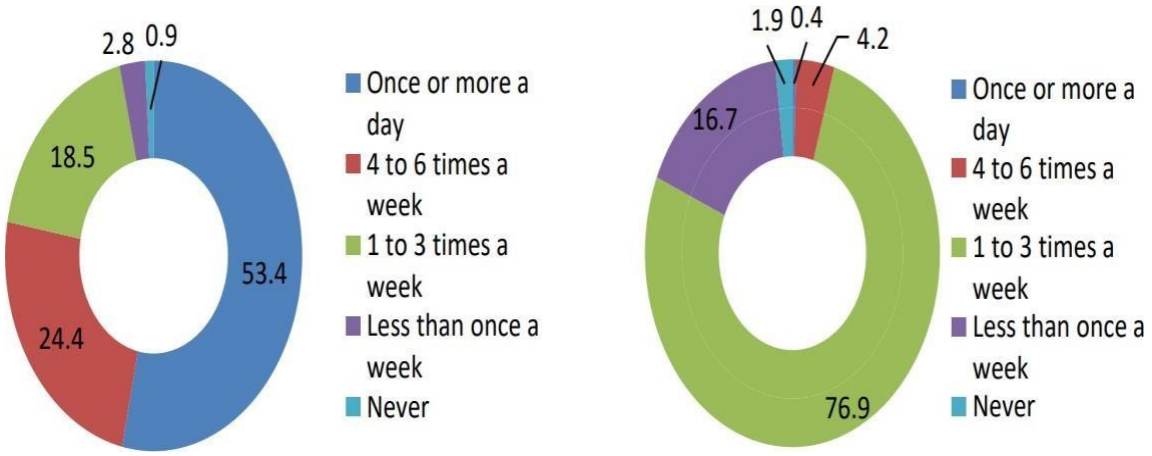
Figure 4.4: Potential mechanisms underlying the CVD effect of healthful plant-based diets

Below, are presented some data regarding eating habits of the Greek population (ELSTAT, 2020) (***Figures 4.5- 4.9***).



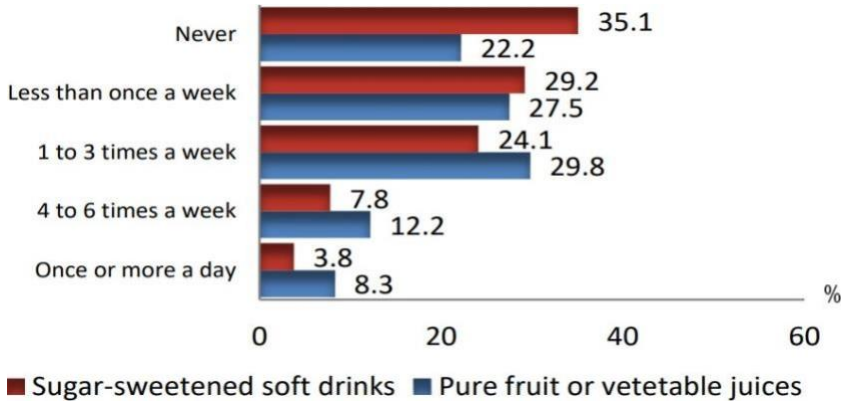
Source: ELSTAT, 2020

Figure 4.5: Frequency of fruit consumption. Percentage distribution of the population aged 15 years and over, 2019



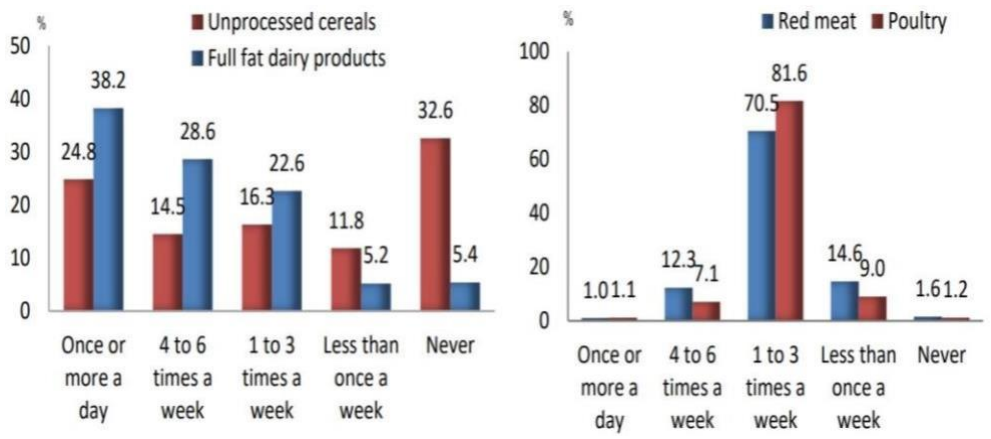
Source: ELSTAT, 2020

Figure 4.6: Frequency of consumption of vegetables or salad, and pulses. Percentage distribution of the population aged 15 years and over, 2019



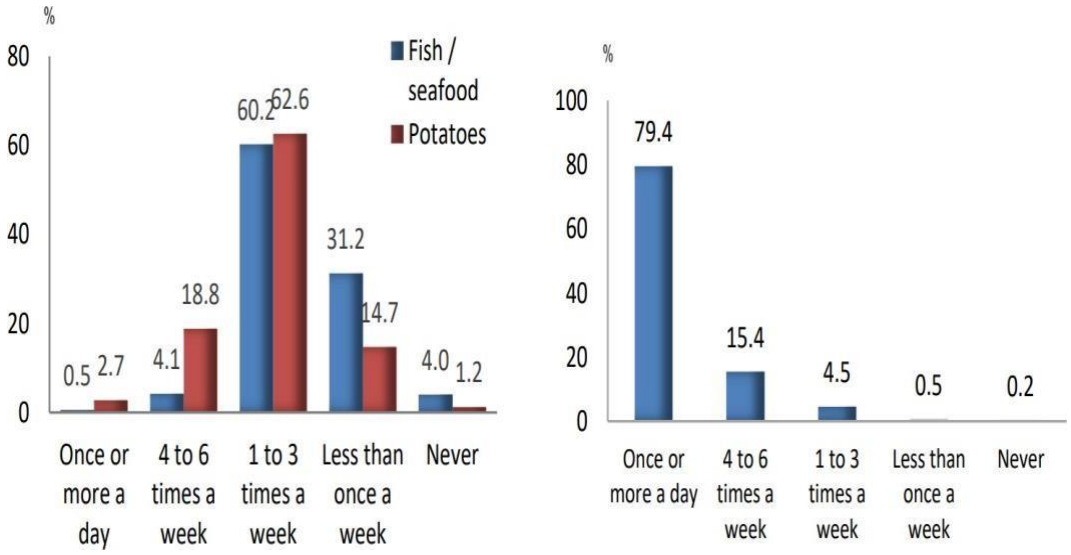
Source: ELSTAT, 2020

Figure 4.7: Frequency of consumption of pure fruit or vegetable juices and sugar-sweetened soft drinks. Percentage distribution of the population aged 15 years and over, 2019



Source: ELSTAT, 2020

Figure 4.8: Frequency of consumption of unprocessed cereals and full-fat dairy products, as well as red meat and poultry. Percentage distribution of the population aged 15 and over, 2019



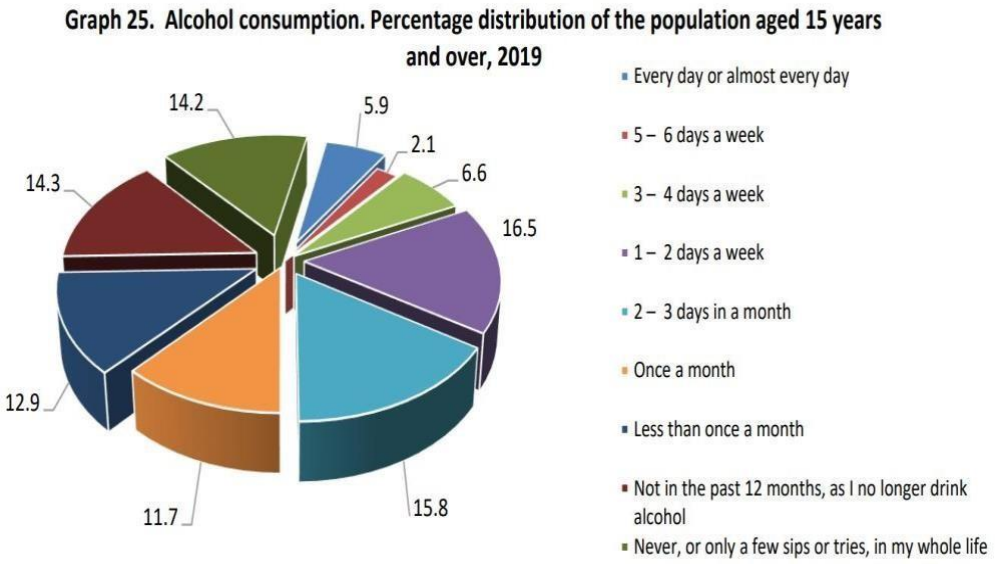
Source: ELSTAT, 2020

Figure 4.9: Frequency of consumption of fish / seafood and potatoes, as well as olive oil. Percentage distribution of the population aged 15 years and over, 2019

Alcohol Consumption

Excessive alcohol consumption is a causal factor in more than 200 diseases, and other health conditions, and it is associated with a risk of health problems, such as physical and mental health disorders, including alcohol dependence, and non-communicable diseases, such as cirrhosis, some types of cancer, and CVD (Bankier et al., 2004; Iversen et al., 2013).

The European Union (EU) has the highest alcohol consumption in the world and the highest rate of overall adverse health and premature deaths due to alcohol (Timmis et al., 2022). Recent data from the ESC showed that the average per capita alcohol consumption in ESC member countries is 9.6 (range: 6.3-11.6) L/year in people aged ≥15 years (Rehm et al., 2017). Overall, alcohol consumption in women is lower compared to men (WHO, 2022). In Greece, the median per capita alcohol consumption for women is 4.5 L/person/year while for men is 16.2 L/head/year (Timmis et al., 2022). Also, data reported by the ELSTAT regarding Greek population aged ≥15, demonstrate that the 5.9 % consumes alcoholic beverages daily or almost daily, 3 out of 10 (28.5 %), do not consume any alcohol at all, whether they have never consumed or no longer consume (ELSTAT, 2020) (***Figure 4.10***).



Source: ELSTAT, 2020

Figure 4.10: Alcohol consumption. Percentage distribution of the population aged 15 years and over, 2019

Cohort studies with over a million participants found that excessive alcohol consumption increases the risk of arrhythmias and CVDs, such as heart failure (HF) and

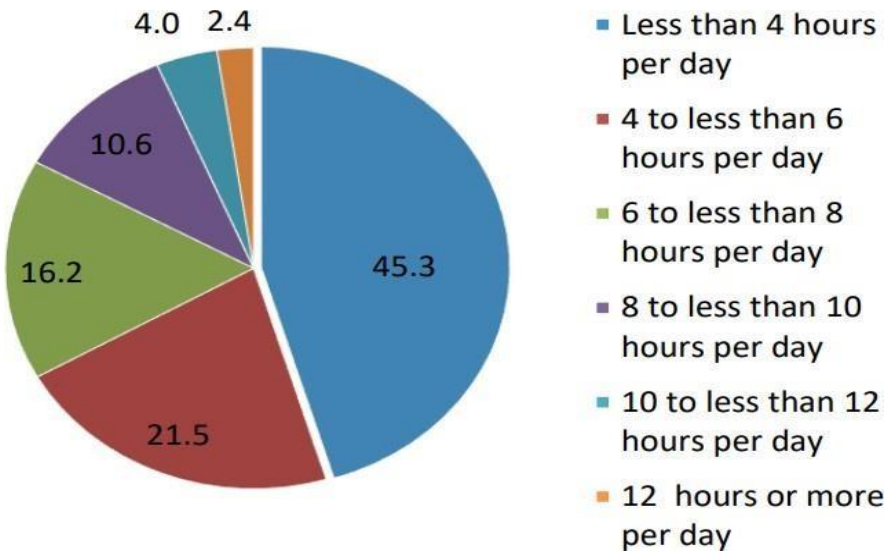
stroke (Bankier et al., 2004; Bell et al., 2017; Wood et al., 2018). However, excessive alcohol appeared to reduce the risk of myocardial infarction (MI) (Bell et al., 2017). Despite the protective effects of alcohol against MI, it has been estimated that the life expectancy of a 40-year-old drinker could be increased by up to two years by reducing alcohol consumption below 100 g/week (Timmis et al., 2022).

Additionally, excessive alcohol consumption is associated with lipid and glucose metabolism, elevated blood pressure and obesity in the general population, all components of MetS (Boyle et al., 2018; Kahl & Hillemacher, 2016). Particularly, ex-drinkers were observed to have higher cardiovascular mortality rates due to the confounding role of hypertension, hemorrhagic but not occlusive stroke, and cardiomyopathy (Bankier et al., 2004).

Physical Inactivity

Low levels of physical activity or inactivity and (long-term) sedentary lifestyle (e.g., television exposure) are considered modifiable factors that are associated with MetS and its components (e.g., hypertension), risk of diabetes and CVDs and higher mortality, particularly in older adults (Chau et al., 2013; Lemes et al., 2019; Panagiotakos et al., 2001). According to the CARDIO2000 study, a lack of physical activity doubles the likelihood of developing CHD, whereas physical exercise for more than five years reduces the risk of CHD by 14% compared with sedentary people, irrespective of age and sex (Panagiotakos et al., 2001). Even low levels of physical activity, especially for older people, are beneficial (Chau et al., 2013; Edwardson et al., 2012). In particular, mild exercise of 60-75 minutes per day could reduce the risk of death associated with a sedentary lifestyle (Ekelund et al., 2016). Yet, the protective role of physical activity seems to depend on the type, intensity and years of exercise (Panagiotakos et al., 2001).

Almost 1 out of 4 (26.0 %) people in Greece over the age of 14 carry out sports, or exercise for leisure between 1 and 7 days per week, 1 out of 10 (12.1 %) exercise specifically to empower muscles, such as strength or force exercises, from 1 to 7 days per week, including those doing such exercises upon medical advice. In addition, ***Figure 4.11*** provides data regarding inactivity; almost 1 in 2 (45.3 %) during a normal day, is seated or lying down for less than 4 hours per day; and almost 1 in 5 (21.5 %) is seated or lying down for 4 to less than 6 hours per day (ELSTAT, 2020).



Source: ELSTAT, 2020

Figure 4.11: Percentage distribution of the population aged 15 years and over, by time spent sitting and reclining, 2019

Exercise is known to reduce the risk of MetS and CVDs mainly through its beneficial effect on the endothelium and insulin sensitivity, reduction in SBP and DBP, improvement in blood lipids levels, as well as body weight, body fat and waist circumference reduction (Bouchard et al., 1994; Carpio-Rivera et al., 2016; Lin et al., 2015; Panagiotakos et al., 2001; Schwingshackl et al., 2014). Exercise, through skeletal muscle contraction, is an important source of reactive oxygen species (ROS) production. The moderate level of ROS production during physical activity promotes positive physiological adaptation of active skeletal muscle, such as mitochondrial biogenesis and increased production of endogenous antioxidant enzymes and molecules (Powers et al., 2020). Exercise helps to enhance the availability of NO from cardiac endothelial cells (Badimon et al., 2011; Powers et al., 2020). Exercise is also involved in the reduction of CRP, IL-18, LDL-C, leptin, and fibrinogen, as well as the total antioxidant capacity (TAC) (Fedewa et al., 2017, Koloverou et al., 2018, Lin et al., 2015). IL-6 myokine increases lipolysis and fatty acid oxidation in adipose tissue as well as glucose uptake through stimulation of the Adenosine Monophosphate (AMP)-activated protein kinase (AMPK) signaling pathway (Carey et al., 2006; Van Hall et al, 2003). Finally, IL-6 can reduce inflammation by inhibiting TNF-α, which is involved in the formation of

atherosclerosis, the development of HF and subsequent complications, including MI (Keller et al., 2006; Kleinbongard et al., 2010).

Smoking

Smoking is associated with insulin resistance, abdominal obesity, dyslipidemia, and MetS (Fujiyoshi et al., 2016; Keith et al., 2016; Slagter et al., 2013; Sun et al., 2012; Zhang et al., 2013). Also, smoking remains one of the most important modifiable risk factors for CVDs and stroke, independent of other risk factors (Fujiyoshi et al., 2016; Keith et al., 2016; Slagter et al., 2013; Sun et al., 2012; Zhang et al., 2013).

Data from the ESC for 2019 showed that in all ESC member countries, an average of 22.1% (range: 17.0% to 26.5%) of the adult population (age ≥15 years) are regular daily smokers (Timmis et al., 2022). Overall, the prevalence of smoking is lower in women than in men, with mean rates of 14.8% (range: 9.2-18.0%) and 28.3% (range: 22.3-38.3%), respectively (Timmis et al., 2022). In Greece, the level of smokers is 27.3%. (Timmis et al., 2022). Additionally, the ATTICA cohort study showed that in Greece 55% of men and 46.5% of women aged 35-44 years are smokers (>5 cigarettes/day) (Pitsavos et al., 2003). Also, data from the ELSTAT for those aged ≥15, report that 1 out of 4 (24.9 %) smokes tobacco or related products (not including e-cigarette) on a daily basis, 3.7 % smoke tobacco or related products (not including e-cigarette) occasionally, and 7 out of 10 (71.4 %) do not smoke tobacco or related products; among them six (60.6 %) have never smoked and one (10.8 %) smoked in the past and has stopped smoking (ELSTAT, 2020).

There are no safe levels of smoking, as it appears that even smokers who consumejust one cigarette per day have almost half the risk of developing CVDs. Smokers who reducethe number of cigarettes they smoke per day may benefit in terms of CVDs (Hackshaw et al., 2018). Smokers who quit can reduce their CVD risk by 39% within 5 years, but it takes at least 5-10 years and maybe more than 25 years after quitting smoking for the CVD risk to be equal to that of non-smokers (Duncan et al., 2019). Passive smokers are also at risk because when passive exposure is high, it is associated with a CVD risk similar to that of light cigarette exposure (Iversen et al., 2013). E-cigarettes were originally proposed as a safer alternative or as a smoking cessation method, but some studies have found harmful cardiovascular effects from their use (Rowley et al., 2013).

The exact mechanism of atherosclerosis induction by cigarette smoke is not fully understood. It is possibly attributed to endothelial cell dysfunction, induced changes in lipid profile and increased thromboembolic events (Bolego, 2002).

Sleep Problems

Sleep quality includes factors related to one's ability to fall and stay asleep but extends to disrupted sleep patterns, such as insomnia (Piano et al., 2019). Both short sleep duration and poor sleep quality are associated with the development of obesity, T2DM, CVDs and mortality, as well as CVD risk factors, including hypertension, obesity and dyslipidemia (Kohansieh & Makaryus, 2015; Kwok et al., 2018). A systematic review and meta-analysis ofprospective cohort studies evaluating the association between sleep duration and quality and cardiovascular outcomes showed that deviation from the recommended 7 to 8 hours of sleep is associated with a higher risk of mortality and cardiovascular events (Kwok et al., 2018). Endothelial dysfunction is cited as a common underlying mechanism in the relationship between sleep problems and CVD risk (Kohansieh & Makaryus, 2015).

3.4. Social Determinants

Age

Age may be the most important independent risk factor for MetS and CVDs and particularly for the development of stroke, HF, and atrial fibrillation in both sexes due to the accumulation of risk factors over time, including arterial hypertension, high cholesterol levels, diabetes mellitus, as well as smoking, and physical inactivity (Ford et al., 2002; Rodgers et al., 2019; Roth et al., 2015).

Gender Differences

The effect of gender on the occurrence of CVDs is significant. The risk is greater for men up to the age of 55 because it appears that female sex hormones provide a protective role, at least during reproductive age (for around 10 years compared to men) (Katsarou et al., 2013; Rozanksi et al., 1999; Vaccarino et al., 2005). However, from the beginning of menopause, the relative risk of CVDs between the two sexes becomes equal, while in older ages, women are reported to be at greater risk than age-matched men (Katsarou et al., 2013; Rodgers et al., 2019; Vaccarino et al., 2005). During this period, there is a deterioration in various metabolic parameters, such as an increase in body weight, blood pressure, insulin resistance and lipid levels in many women (Katsarou et al., 2013; Vaccarino et al., 2005). Particularly, estrogens protect women from atherosclerosis and CAD incidence, while ovarian abnormalities or failure to produce a satisfying number of endogenous estrogens can accelerate atherogenesis even in premenopausal women, predisposing them to CVDs and

ischemic stroke later in life (Rozanksi et al., 1999). Also, animal studies have suggested that psychological stress can influence the development of CVDs in premenopausal female monkeys through estrogenic and neuroendocrine activities (Rozanksi et al., 1999). They were also typically hypercortisolemic and had exaggerated heart responses to stress, characteristics that are themselves risk factors for atherosclerosis in both humans and monkeys (Rozanksi et al., 1999). In addition, a study showed that women with irregular menstruation have elevated plasma fibrinogen concentrations and a thickened arterial intima compared to women with a normal cycle (Rozanksi et al., 1999). Finally, data from the Nurses' Health Study, a prospective cohort study conducted of 121,700 women in the USA between 1976 to 1982, suggested that estrogen-replacement therapy can prevent CHD risk in natural menopause women, after controlling for age and cigarette smoking (Colditz et al., 1987). Nevertheless, current studies highlight that hormone replacement therapies not only cannot improve outcomes, but they might also raise the risk of cardiac events in older women (Rodgers et al., 2019).

Socio-Economic Circumstances

Socio-economic factors have been associated with an increased MetS and CVD risk. For example, a study published in the Journal of the American College of Cardiology found that individuals with less than a high school education have a higher prevalence of MetS compared to those with college-educated individuals (Koplan et al., 2006). In terms of SES, there is a consistent inverse association with hypertension, excessive alcohol consumption, total cholesterol levels, diabetes mellitus, BMI, smoking, and CVD incidence, especially for people aged over 45 years (Kollia et al., 2016; Manios et al., 2005). Data from the CARDIA cohort study showed that unemployment (>90 days) is associated with higher depression scores and an elevated heart rate or CHD risk, but lower levels of blood pressure, HDL-C, and physical activity (Lundin et al., 2014). There is also evidence that worry over financial and health issues leads to an increased CHD risk (Larsen & Christenfeld, 2009). Social factors are believed to promote atherosclerogenesis via ANS activation by including the activation of the sympathetic NS and the HPA axis (Lundin et al., 2014; Rozanski et al., 1999). Therefore, SES either independently or through behavioural and psychosocial risk factors contributes to cardiac events (Kaplan & Keil, 1983; Mulle & Vaccarino, 2013;Rozanski et al., 1999).

3.5. Psychological Determinants

A growing body of evidence appreciates that psychological health and factors, such as personality, stress, psychological distress, anxiety, and depression can contribute to MetS and CVDs (Levine et al., 2021). According to the AHA, there is increasing evidence that psychological factors may be causally linked to physiological processes and behaviours that contribute to and cause CVDs (Levine et al., 2021).

Personality

The effect of personality traits on health has been a topic of increasing interest in recent years, although the details of the multiple pathways involved in this effect remain poorly understood ((Jokela et al., 2014). Type A behaviour, type D personality and neuroticism are some of the constructs that have been investigated for their association with CVDs. Such personality traits may result in psychological stress leading to hypertension, atherosclerosis, and other physiological risk factors, thus increasing the cardiovascular mortality risk (Jokela et al., 2014).

Type A behaviour pattern (TABP)

It is considered a syndrome characterized by competitive, ambitiousness, easily aroused hostility, impatience and dynamic behaviour that was identified by Friedman and Rosenman in the late ‘50s (Rozanksi et al., 1999). Early investigations revealed a significant positive association between TABP and CVD risk, although existing evidence in conflicting (Lohse et al., 2017). For instance, the interest in its impact on cardiac diseases suddenly increased after the Western Collaborative Group Study revealed a 2-fold and a 5-fold increased risk of CAD and recurrent MI, respectively over an 8.5 follow-up period (Rosenman et al., 1975). Additionally, a study published in the Journal of the American College of Cardiology found that individuals with type A behaviour are more likely to develop CVDs compared to those with type B personality (which is characterized by a relaxed and easy-going demeanor) (Ragland & Brand, 1988). Also, those with type A behaviour are more likely to experience heart attacks, angina and other forms of CVDs (Jenkins, 1976). Findings from epidemiological studies regarding hostility attribute of type A behaviour although mixed, imply a relationship with CVDs in healthy individuals (Rozanksi et al., 1999). Nevertheless, a recent study indicated that only a subscale (competitiveness) of

a TABP scale was associated with increased CVD risk and mortality and only in women (Lohse et al., 2017).

Hostility

Hostility as a psychological construct is a component of chronic anger, characterized by a persistent negative, aggressive attitude, mistrust and cynicism towards others (Pickering et al., 2001). Epidemiological studies and meta-analyses have suggested that hostility predicts hypertension, MetS and CVDs (such as CHD and MI) (Fernandez & Smith, 2015; Mostofsky et al., 2014; Pickering et al., 2001; Rozanksi et al., 1999).

Individuals with hostile characteristics may exhibit hypercortisolemia, high circulation catecholamine levels, reduced mononuclear leukocyte β-adrenergic receptor function and vagal modulation of heart function, and increased platelet reactivity (Rozanski et al., 1999). Also, hostility is associated with early, asymptomatic atherosclerotic markers, including endothelial dysfunction and arterial stiffness, atherosclerosis in the carotid arteries, and coronary artery calcification (Fernandez & Smith, 2015).

Hostility can affect atherogenic activity through unhealthy lifestyle behaviours, such as smoking, excessive alcohol intake, physical inactivity, and poor diet, and psychosocial indicators, such as social isolation (Fernandez & Smith, 2015; Rosanski et al 1999). However, anger and hostility can predict CVD morbidity and mortality even when health behaviours are adjusted, suggesting a role for mechanisms beyond poor health habits (Fernandez & Smith, 2015). The physiological effects of psychological stressors also may play an important role. Hypertension and neuroendocrine events (e.g., catecholamines, cortisol) in response to stressors and delayed recovery of these physiological responses can contribute to atherosclerosis and trigger acute CVD events (Fernandez & Smith, 2015). Thereis additional evidence for the genetic contribution to hostility, even though there are mixed conclusions (Rozanksi et al., 1999). It is possible that several psychosocial risk factors, including depression, hostility, and social support, tend to correlate with each other, and this covariation can be explained in part by a common genetic factor (Mulle & Vaccarino, 2013).

Neuroticism

It is a personality trait characterized by anxiety, worry/fear and emotional instability that can affect emotional and social life (e.g., sensitivity to negative experiences, lack of social support and poorer ability to adapt to difficult situations (Jokela et al., 2014). Neuroticism is a risk factor for CVD mortality (Jokela et al., 2014).

Cognitions

Cognitions refer to the mental processes involved in acquiring, processing and storing information (Larsen et al., 2005). These mental processes include perception, attention, memory, reasoning, decision-making, and problem-solving (Baddeley, 2012). They are essential in shaping thoughts, beliefs, and attitudes, which, in turn, affect emotions and behaviours (Beck, 2020).

Studies have revealed that cognitions can impact one's mental and physical health, as well as well-being. For example, research has found that negative cognitions, such as rumination and worry, can raise the risk of developing depression and anxiety (Nolen-Hoeksema, 1991). On the other hand, studies have shown that positive cognitions, such as optimism and gratitude, are associated with better physical health outcomes, including lower levels of inflammation, a stronger immune system, and reduced risk of chronic diseases (Segerstrom & Sephton, 2010).

Perseverative cognition, as manifested in worry and rumination, can be both a symptom of and contribute to psychopathology (Larsen & Christenfeld, 2009). Particularly, trait rumination predicts future episodes of depression and anxiety or prolongs depressive episodes, while learning to avoid rumination appears to prevent depression (Larsen & Christenfeld, 2009). This cognitive inflexibility may be directly caused by neurotransmitter imbalances associated with psychopathology, particularly depression, and anxiety (Larsen & Christenfeld, 2009). In an experimental animal study, monkeys undergoing surgery for serotonin depletion in the prefrontal cortex showed an inability to relearn a rewarding task once it was reversed (Larsen & Christenfeld, 2009). Serotonin depletion did not, however, impair their capacity to learn new tasks, indicating that this did not affect general cognitive abilities (Larsen & Christenfeld, 2009). Instead, it diminished their ability to shift focus and change their paradigm—behaviours that are typical of perseverative cognition and psychological disorders characterized by serotonin dysregulation (Larsen & Christenfeld, 2009).

Regarding cardio-metabolic conditions, a 20-year prospective cohort study in 1758 healthy men with no heart conditions examined the relationship between perseverative cognition and cardiovascular health and found that the highest level of social worry was associated with an approximately 50% increased CHD risk and that the risk remained highly significant even after accounting for possible confounders (Kubzansky et al., 1997).

Cognitions, especially perseverative ones, might act directly on physical diseases by increasing activation via the cardiovascular, immune, endocrine, and neurovisceral systems (Brosschot et al., 2006). For instance, regarding the biochemical mechanisms that could underlie the relationship between psychological aspects and CVD risk, Papageorgiou et al. (2006) found that individuals who score highly on irrational thinking exhibit elevated plasma levels of CRP, IL-6, TNF-α and white blood cell counts compared to people who score lower on irrational thinking (Papageorgiou et al., 2006).

Anxiety

Anxiety is a feeling of excessive worry or fear that can vary from mild to severe (NHS, 2019). Anxiety is the main symptom of conditions including generalized anxiety disorder (GAD), panic disorder, phobias, post-traumatic stress disorder (PTSD), social anxiety disorder, etc. The most common condition is GAD, which according to the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition, Text Revision (DSM-5-TR), includes anxiety and worry along with three or more of the following 6 symptoms withat least some of them have been present for more days than not for the past 6 months: feeling restless or on-edge, being easily fatigued, having difficulty concentrating, being irritable, having physical disturbances, such as headaches, muscle aches, etc., having difficulty controlling feelings of worry and having sleep problems, such as difficulty falling or staying asleep (APA, 2022; NIMH, 2022). The mean 12-month prevalence is 1.3% globally, ranging from 0.2% to 4.3% (APA, 2022). Women are twice more prone than men, and individuals from the ages of 35 to 55 (APA, 2022; NHS, 2018). In Greek population, the 5.6 % aged 15 and over suffer from anxiety disorders (ELSTAT, 2020).

Regarding the potential impact of anxiety disorders on CVD development, previous data have shown significant associations between PTSD and CHD development and recurrence in war veterans (Bankier et al., 2004). Also, in prospective cohort studies in healthy individuals or CHD patient populations, anxiety has been associated with an increased risk of cardiac mortality. Specifically, in a cohort of 934 men and women with confirmed CHD who completed the Hospital Anxiety and Depression scale (HADS) during hospitalization for coronary angiography, 133 deaths occurred during the 3-year follow-up period (Watkins et al., 2013). Increased anxiety scores were associated with an increased risk of mortality after accounting for established risk factors including age, congestive heart failure (CHF), renal disease, etc. In addition, anxiety was associated with increased CHD mortality risk, particularly when depression was coexisting (Watkins et al., 2013). Other data

suggest a significant relationship between anxiety disorders and cardiac death, probably due to ventricular arrhythmias. (Rozanksi et al., 1999).

Chronic anxiety is accompanied by a multitude of pathophysiological processes, such as elevated SNS activity, inflammation and hypertension (Paterniti et al., 1999; Watkins et al., 2013). It is well-documented that acute stress and anxiety can lead to a transient increase in blood pressure through changes in cardiac output and vascular resistance (Paterniti et al., 1999). Prolonged hypertension and cardiovascular mortality can be induced by chronic stress anxiety (Paterniti et al., 1999). Furthermore, individuals with anxiety have reduced heart rate variability due to a pathological alteration in cardiac autonomic tone. This pathological alteration could involve either increases sympathetic stimulation which is linked to the onset of arrhythmias or impaired vagal control both linked to cardiac mortality and sudden death (Rozanski et al., 1999). Lifestyle behavioural patterns in people with anxiety, such as diet, alcohol intake, smoking, or other health habits may play a role as CVD risk factors (Jacka et al., 2011).

Depression

Depressive disorders (i.e., disruptive mood dysregulation disorder (DMDD), major depressive disorder, persistent depressive disorder, premenstrual dysphoric disorder, substance/medication-induced depressive disorder, depressive disorder due to another medical condition, other specified depressive disorder, and unspecified depressive disorder) have as common feature the presence of sad, empty, or irritable mood, accompanied by related changes that significantly affect the individual's capacity to physically and cognitively function (APA, 2022). Depressive disorders differ from each other in duration, timing, or presumed etiology. Careful consideration should be given to the delineation of normal sadness and grief from a major depressive episode (APA, 2022).

Major depressive disorder has an extremely high prevalence around the world, globally affecting around 5% of the adult population, 5.7% of adults older than 60 years, and particularly women (Sgoifo et al., 2015; WHO, 2021b). Depression due to a medical condition or physicological effects refers to a listing of the medical conditions that could be able to induce major depression (APA, 2022). Anxiety symptoms are also common in depressed patients, and as mental health disorders are often comorbid (Paterniti et al., 1999). The 3.8 % of the Greek population reports suffering from depression, recording a decrease of
19.2 % compared to 2014 (4.7 %). 3 out of 10 are men (30.5 %) and 7 women (69.5 %) (ELSTAT, 2020).

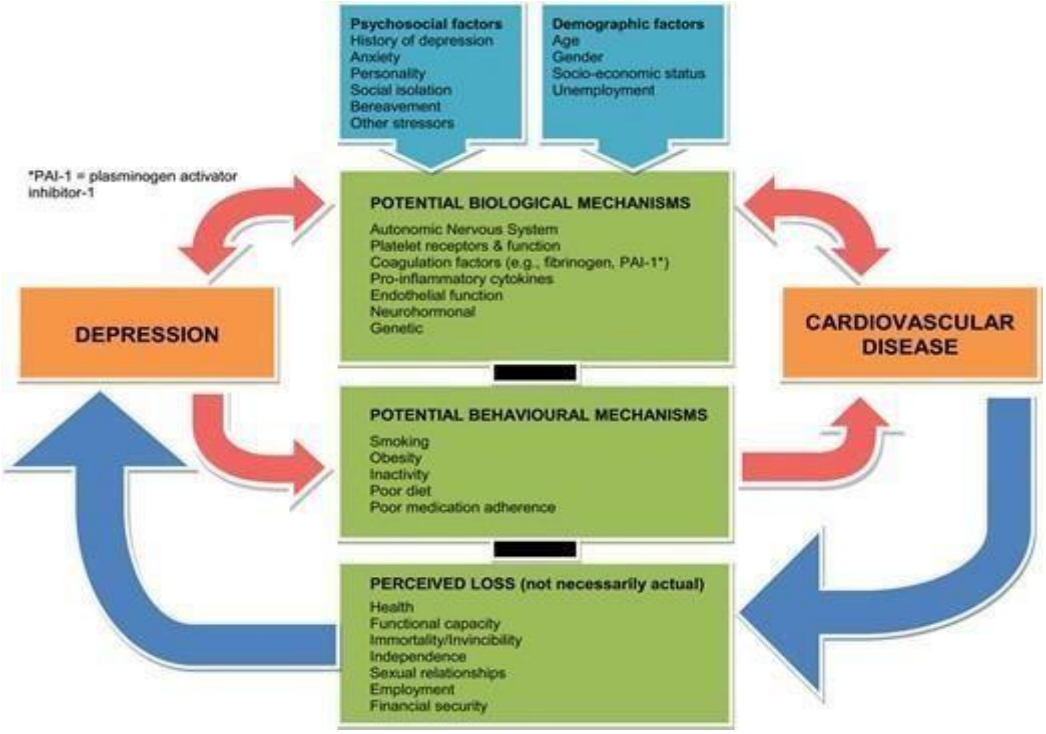
Depressive disorders and ischemic heart disease are expected to be among the leading causes of the burden of disease in 2030 (Sgoifo et al., 2015). Depression is an established risk factor for CVDs and mortality (Hare et al., 2014; Sgoifo et al., 2015). There are clear associations with CAD, MI, CHF and hypertension and neuroendocrine conditions (e.g., Cushing's syndrome and hypothyroidism), as well as some neuroanatomical correlates of depression with stroke and neurological disorders (APA, 2022; Sgoifo et al., 2015). Autoimmune disorders and deficiencies of certain vitamins, such as vitamin B12, have also been linked to depression (APA, 2022). Depression is also associated with MetS, increased BMI, obesity and T2DM (Mule & Vaccarino, 2013; Sattar et al., 2002). Still, according to the literature, the causal relationship is greater for depression and some medical conditions than others (APA, 2022). For CVDs, depression usually remains an independent risk factor, suggesting a biological relationship between these two that remains partially unexplained (Mulle & Vaccarino, 2013; Sattar et al., 2002).

Social parameters, such as sex, age, employment status and educational level are considered too. For example, in people with depression, stroke is somewhat more common in middle-aged men than in women (APA, 2022). In terms of age, a prominent study published in 1992 indicated that depression reaches its lowest level in the middle-aged, around 45 years and its highest level in older people, around 80 years old or later (Mirowsky & Ross, 1992). The decline of depression in early adulthood and the rise in later life mainly reflects socio- economic parameters, including gains and losses from marriage and employment, whereas in later life due to physical dysfunction and low personal control, there are personal and status losses (Mirowsky & Ross, 1992).

Depression contributes to the course of CVDs through behavioural and pathophysiological mechanisms. Particularly, depression is significantly associated with physical inactivity, unhealthy diet, as well as with becoming a smoker, increased rate of daily smoking, and a lower probability of quitting smoking (Denollet et al., 2006; Mathew et al., 2017; Mulle & Vaccarino, 2013).

As concerns underlying pathophysiological mechanisms, depression is linked to CVDs through inflammatory response, dysfunction of the ANS, such as sympathetic over- activity vs. vagal dysfunction, and impaired coronary flow reserve (CFR) (Cohen et al., 2015;Headrick et al., 2017; Hickman et al., 2014; Hiles et al., 2015) (***Figure 5.1***). Depression and chronic heart diseases share the same physiological mechanisms and risk factors, while the Psycho-Immune-Neuroendocrine (PINE) network may predispose individuals to the onset of depression and the manifestation of CVDs, influenced by genetic and environmental factors

(Headrick et al., 2017). Elevated biomarkers of vascular inflammation and oxidative stress are known to be closely interrelated to endothelial dysfunction; an early determinant in the development of hypertension and atherosclerosis, and vascular damage (Siti et al., 2015) (***Figure 5.1***). Endothelial damage causes an acute release of pro-inflammatory cytokines, which activate the HPA axis and increase oxidative stress levels in the brain (Halaris, 2016) (***Figure 5.1***). Specifically, a model introduced by Gidron (2002) proposed that acute stress, depression, and hostility have been associated with elevated pro-inflammatory cytokines and can lead to vasoconstriction and elevated blood pressure via catecholamines (Gidron, 2002). Inflammatory factors and depression have been positively associated with plateletaggravation which may cause thrombosis, while thrombosis can lead to ACS (Gidron, 2002). Moreover, IL-6 is one of the most potent stimulators of the HPA axis, inducing the release of other cytokines (Halaris, 2017). A final explanation for the association or comorbidity of depression and CVD hypothesis is that there is a genetic pathway involving neurohormonal, immune, and inflammatory systems, that, when disrupted manifests with both CVDs and depression phenotypes (Mulle & Vaccarino, 2013) (***Figure 5.1***).



Source: Hare et al., 2014

Figure 5.1: Potential factors that could explain the relationship between depression and CVDs

Acute and Chronic Stress

Stress is distinguished from anxiety. Anxiety is considered a future-oriented, long- term response that is broadly focused on a threat, whereas fear is an appropriate, present- oriented, short-lived response to an identifiable and specific threat (Medina-Inojosa et al., 2019). On the other hand, according to the American Psychological Association (APA), stress is defined as the physiological, emotional and psychological response to internal and external stressors (https://dictionary.apa.org/stress). Stress involves changes that affect almostevery system of the body, influencing how people feel and behave (APA, 2014). For example, it can be manifested by palpitations, sweating, dry mouth, shortness of breath, agitation, accelerated speech, increased negative emotions and longer periods of fatigue(APA, 2014).

Stress-related cognitive activation and subsequent cardiovascular responses can occur in anticipation of future stressors, in the aftermath of past stressors, or long after the stressor is presented (Schwartz et al., 2003). Although meta-analyses support that both acute (e.g., bereavement, anger episodes, or natural phenomena) and chronic stress are related to an increased CVD incidence through the HPA and sympatho-adrenomedullary axes and endothelial dysfunction, the exact links remain non-fully understood (Chida & Steptoe, 2010; Matthews et al., 2001; Rozanski et al., 1999; Steptoe & Kivimäki, 2012; Xue et al., 2014). Additionally to these, stress can a) increase cortisol levels, a hormone produced by the adrenal gland, which can lead to insulin resistance and an increase in abdominal fat, b) increase blood pressure, c) disrupt blood glucose regulation, and d) promote inflammation and oxidative stress via activation of pro-inflammatory cytokines and their signaling pathways in the central and peripheral nervous system (Hannibal & Bishop, 2014; Raison et al., 2006). Moreover, stress and distress have also been linked to unhealthy behaviours, such as overeating, smoking, physical inactivity, and alcohol consumption (Chida & Steptoe, 2010; Cooper & Quick, 2017; Epel et al., 2000; Sinha & Jastreboff, 2013). All of the above, with which stress is associated, are known risk factors for MetS and CVDs. A stress-specific coronary syndrome, known as Takotsubo or stress cardiomyopathy, also exists (Steptoe & Kivimäki, 2012).

Employees who experience work-related stress and people who are socially isolated or lonely have an increased CVD risk (Steptoe & Kivimäki, 2012). Work-related stress is the most widely studied type of stress associated with CVD risk (Rozanski et al., 1999). Stress resulting from high job demands and low reward predicts cardiac events and carotid

atherosclerosis (Rozanski et al., 1999). In addition, findings from the Health Examination Survey (HES) and the NHANES in the US had shown that employed men with low decision latitude and high in psychological workload jobs had a higher prevalence of MI (Karasek et al., 1988). Findings from the Whitehall II study further supported that low job control was associated with new CHD reports (Bosma et al., 1998). Therefore, individuals experiencing high effort and low reward conditions and those with low job control had a higher risk of new CHD than their counterparts in less adverse psychosocial work environments (Bosma et al., 1998). Based on data from a 6.5 years prospective study of middle-aged blue-collar men, results suggested that status inconsistency, job insecurity, work pressure and need for control independently predicted IHD onset after adjusting for important physical and behavioural CVD risk factors (Siegrist et al., 1990). More recent meta-analyses have also linked work- related stress to excess CVD risk, as well as to high CVD risk factors including diabetes, smoking, and physical inactivity (Kivimäki et al., 2006; Nyberg et al., 2013).

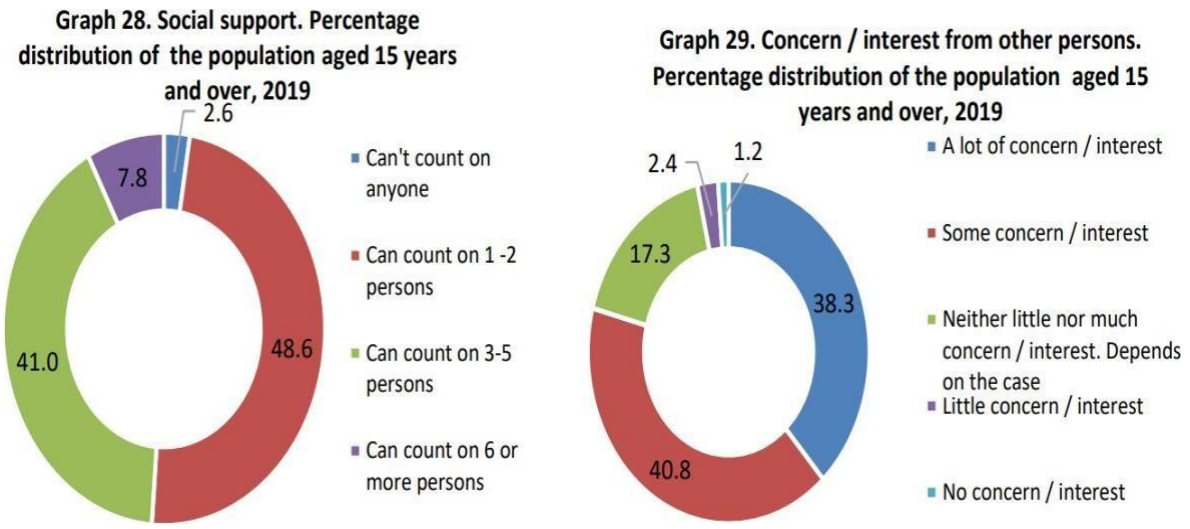
Psychological Distress

Psychological distress refers to non-specific symptoms of stress, anxiety, and depression, as well as physical symptoms (https://dictionary.apa.org/psychological-distress). High levels of psychological distress indicate reduced mental health and may reflect common mental conditions, such as depression and anxiety (https://dictionary.apa.org/psychological-distress). Findings from the ATTICA study indicated that in addition to the direct effect of psychological distress on CVD incidence, there were indirect pathways, such as low levels of physical activity, elevated CRP levels, and MetS (Kollia et al., 2017a). Therefore, lifestyle and clinical factors appear to link psychological distress to the development of CVDs (Kollia et al., 2017a).

Social Support

Social networks, including family affiliations, number of friends, and participation in social activities (Park et al., 2018). Social support is divided into structural (which is referred to as having a partner, close relatives, etc.) and functional (which is referred of having a caregiver in cases of sickness or disability) (Mondesir et al., 2018). High levels of social support have a positive effect on psychological well-being and can help individuals to adopt and maintain healthy behaviours, such as regular exercise and a healthy diet (Schwarzer & Knoll, 2007). In Greek population, the 2.6 % reports having no one to count on if they encounter serious personal problems and seek financial or other assistance or even a simple

advice, whereas 1 out of 2 (48.6 %) have 1 or 2 people to count on (ELSTAT, 2020). Three out of 10 (28.9 %) consider it difficult or even very difficult to get help (advice, care, provision in kind, financial assistance or other) from neighbours, if needed (ELSTAT, 2020) (***Figure 5.2***).



Source: ELSTAT, 2020

Figure 5.2: Social support and concern / interest from other persons. Percentage distribution of the population aged 15 years and over, 2019

There are conflicting results regarding the effect of social support on CVD risk, with a meta-analysis reporting no association between social support, isolation, and loneliness with the incidence of CVDs, while other studies and a meta-analysis show that a relatively small network is associated with an increase in the CVD incidence over time, low levels ofperceived emotional support increase the risk for future cardiac events, as well as there is an increase in cardiac mortality in unmarried individuals with CVDs and those with low functional support (Barth et al., 2010; Freak-Poli et al., 2022; Rozanski et al., 1999). Regarding marriage, previous studies indicated that married people show better health than unmarried, including better cardiovascular health and better outcomes after a heart attack (Liu & Waite, 2014). Changes in marital quality and CVD risk are more closely associated in older married people than in their younger counterparts and the association between marital quality and CVD risk is stronger in women than men at older ages (Liu & Waite, 2014).

To conclude, both behavioural and pathophysiological mechanisms are included in the relationship between social support and CVDs development by promoting atherogenesis probably via ANS activation (Rozanski et al., 1999). Social support influences the extent to

which individuals engage in high-risk behaviours, such as fatty dietary consumption, smoking, and excessive alcohol intake (Steptoe et al., 1996). Also, animal and human studies show an association between social isolation, hypercortisolemia, as well as reversible increases in resting heart rates and HRV (Goodyke et al., 2022; Rozanski et al., 1999; Sgoifo et al., 2015).

Childhood Maltreatment

Childhood maltreatment refers to harmful or adverse experiences (abuse, neglect, life events, and household dysfunction) that occur during childhood and harm the physical, psychological, or emotional well-being of a child, including increased risk for a variety of mental and physical health problems in adulthood, such as CVDs (Anda et al., 2006; Bomhof-Roordink et al., 2015). Childhood maltreatment has been associated with a significant increase in the odds of developing MetS or CVDs in adulthood (Anda et al., 2006;Brown et el., 2016).

The development of atherosclerosis and arterial stiffening already starts during childhood, partly via depression and anxiety, which might enhance the development and progression of CVDs (Bomhof-Roordink et al., 2015). Childhood maltreatment has been shown to affect several biological and behavioural systems, associated with increased levels of cortisol, and increased likelihood of engaging in unhealthy behaviours (e.g., smoking and physical inactivity); whereas gender, race/ethnicity, and SES are among the moderatingfactors (Alink et al., 2012; Brown et al., 2016).

Quality of Life and Well-Being

Well-being encompasses quality of life (QoL), as well as a range of evaluations people make about their lives, including physical and mental health, satisfaction, happiness, social support, community connections, financial status, opportunities for growth, and sense of purpose (Levine et al., 2021; WHO, 2022). QoL is a complex term that includes dimensions of physical, psychological, and social functioning, and health perceptions (Michalos et al., 2014).

A growing body of evidence has linked well-being to lower levels of inflammatory markers, such as CRP, better cardiovascular health, lower MetS, and CVD incidence in healthy populations and reduced risk of adverse outcomes in patients with pre-existing CVDs (Chida & Steptoe 2008; Kivimaki et al., 2012; Sin et al., 2015; Sin, 2016). The associations between well-being and CVD outcomes can be mediated by optimal health behaviours (e.g.,

physical activity, sleep, diet, smoking cessation, and medication adherence) (Boehm & Kubzansky, 2012; Sin et al., 2015; Sin, 2016). In addition to cardiovascular functioning, well-being is also associated with better immune and neuroendocrine functioning, reduced stress response and adaptive coping skills (Chida & Steptoe, 2008; Kivimaki et al., 2012; Sin et al., 2015; Sin, 2016). On the opposite, negative well-being (or *ill-being*) can be defined as deficits in the aforementioned areas along with distress, negative mood and hyperarousal (Anyfantakis et al., 2003; Diener et al., 1999; Karademas, 2007).

4. Psychological Factors and the Course of Illness

Psychological factors are involved in the prevention, onset and course of chronic conditions. On one hand, psychology can promote health and well-being and thus prevent illness. Psychologists, particularly health psychologists, use their knowledge to devise strategies that encourage people to seek early screening for conditions, such as heart disease, MetS and diabetes mellitus (Lloyd, 2021). They also help individuals to avoid risky behaviours while encouraging health-enhancing behaviours (Lloyd, 2021). Positive psychological factors, such as optimism and social support, have been linked to better health outcomes, including reduced CVD risk and improved immune system functioning (Segerstrom & Miller, 2004). Positive health-related events, such as recovery from illness or injury, can have a positive impact on psychological well-being, including increased feelings of self-efficacy and self-esteem (Taylor et al., 2000).

On the other hand, the involvement of psychology in the etiology of chronic mental and medical conditions is generating interest in various scientific fields, resulting in increased research on neuropsychological associations with CVDs, diabetes mellitus, and neuropsychological issues (Conversano, 2019; Di Giuseppe et al., 2019; Eikeseth et al., 2020; Martino et al., 2019a; Martino et al., 2019b; Merlo et al., 2020; Vicario et al. 2020). Some recent studies have shown that personality traits and emotion regulation are associated with the development and progression of chronic conditions (Rymarczyk et al., 2020). For instance, adverse childhood experiences are risk factors for metabolic abnormalities and obesity (Pervanidou & Chrousos, 2012; Davis et al., 2014). Psychological factors, such as the occurrence of stressful life events (SLEs), anxiety, depression, negative affect, social support and repression/denial play a role in cellular and humoral markers of the immune system and cardio-metabolic diseases, while in the case of the less serious infectious diseases (colds, influenza, herpes), there is consistent and convincing evidence linking stress and negative affect to disease onset and progression (Cohen & Herbert, 1996; Conversano & Di Giuseppe, 2021; Kyrou et al., 2017; Papageorgiou et al., 2006; Vîslă et al., 2016; Querstret et al., 2013). Psychological factors also have a direct effect on compensatory behaviours and well-being

(Fisher et al., 2010; Rock et al., 2014). Cardio-metabolic disorders are also associated with cognitive deficits in memory, attention and executive functions (Guicciardi et al., 2019; Wooten et al., 2019). Consequently, personality traits, and patterns of thinking, feeling and behaving may affect psychological and physical conditions (Americal Psychiatric Association, 2013).

In addition, in the International Classification of Disease, Tenth Revision, Clinical Modification (ICD-10 CM) and the DSM-5-TR, there is a classification called "Psychological and behavioural factors associated with disorders or diseases classified elsewhere" and "Psychological Factors Affecting Other Medical Conditions (PFAOMC)", respectively, which refer to a disorder that is diagnosed when a general medical condition is adversely affected by psychological or behavioural factors (Americal Psychiatric Association, 2022; Levenson et al., 2018). These psychological factors may precipitate or exacerbate the medical condition, interfere with treatment, or contribute to morbidity and mortality, and they are nota part of another mental disorder (e.g., major depression) (Americal Psychiatric Association, 2022; Levenson et al., 2018). PFAOMC emphasizes one causal direction in the interactions between mind and body, that is, the effects of psychological factors on general medical conditions; however, in most patients, medical conditions can also affect psychological function (Levenson et al., 2018). Still, the prevalence of PFAOMC is not clear because the disorder describes many possible interactions between a wide range of psychological factors, and behaviours, as well as a full range of general medical conditions (Levenson et al., 2018).

4.1. The Bio-psychosocial Model: An Overview

The bio-psychosocial model is a framework for understanding health and illness. It was developed by psychiatrist George Engel (1977) who sought to integrate psychological and environmental factors into the traditional biomedical model of health (Ogden, 2019). Themodel consists of three interconnected components: biological, psychological and socialwhich all include aspects of health (Ogden, 2019). The biological component refers to factors such as genes, physiology, neurochemistry, viruses, bacteria and structural abnormalities (Borrell-Carrió et al., 2004; Ogden, 2019). The psychological component encompasses cognitive, emotional and behavioural factors including attitudes, beliefs and coping styles, as well as smoking, diet, exercise and alcohol consumption (Borrell-Carrió et al., 2004; Ogden, 2019). The social component includes environmental, cultural and socio-economic factors, including family and community support, social networks, and access to resources, social norms (rules) or behaviours (e.g., the social norm of smoking), pressures to change behaviour

(e.g., peer group expectations, parental pressure), the social value of health, social class and nationality (Borrell-Carrió et al., 2004; Ogden, 2019).

In general, the bio-psychosocial model recognizes that health and illness are influenced by multiple factors, not just biological ones, as well as the dynamic interplay between biological, psychological, and social factors, with each domain influencing and being influenced by the others (Ogden, 2019). Finally, it emphasizes the importance of understanding the patient as a whole person, rather than just a collection of symptoms or diagnoses and acknowledges the importance of the therapeutic relationship between the patient and the healthcare provider in promoting health and treatment (McDaniel et al., 2014; Weiner et al., 2013).

4.2. Cognitive-Behavioural Therapy (CBT) Models: An Overview

CBT models are bio-psychosocial models, with the Rational-Emotive Behavioural Therapy (REBT) being the original and oldest form of CBTs (David et al., 2010; Thorn, 2020). They are the most popular modern approaches and have steadily increased in acceptance and influence, with thousands of books and scientific publications (David et al., 2010). The American clinical psychologist Albert Ellis (1913-2007) developed the REBT model in 1955, as an integrative practical application of a variety of philosophical theories, according to which emotional and other types of mental health disturbances are not caused by an event, but by rigid and extremely negative beliefs about this event (Dryden, 2005). In addition to Ellis, the prominent American psychiatrist Aaron Beck (1921-2021), the father of CBT, argued that negative life events activate a cognitive triad of negative beliefs: negative self-beliefs ("I'm not good enough."), the world ("This is a terrible place."), and the future ("Something bad will always happen.") that also produce and perpetuate many disorders (Bridges & Harnish, 2010). Beck also divided negative beliefs into three levels: a) schemas or core beliefs (i.e., patterns or structures containing cognitive and emotional information as basic units of personality that determine negative thoughts and manifest behaviours), b) intermediate beliefs (i.e., strict, conditional rules, attitudes and assumptions about life that people adopt, and that may be unrealistic and unadaptable), and c) automatic negative thoughts or cognitive distortions (i.e., unintentional thoughts after specific events, which are more deeply related to the other two levels but they are more easily accessible) (Fenn & Byrne, 2013).

The Rational-Emotive Behavioural Therapy (REBT) Model

REBT emphasizes the importance of cognition in both adaptive and maladaptive functioning (David et al., 2010). Ellis was instrumental in initiating the "cognitive revolution" in psychotherapy and psychology more broadly by identifying the different ways in which individuals react to similar situations, and exploring how their attitudes, beliefs, and expectations shape their reality and behaviour (David et al., 2010). As a result, REBT-derived concepts have been incorporated into cognitive psychology, psychotherapy, and many areas of mainstream psychology (David et al., 2010). Modern CBTs share the following propositions, derived from REBT: cognitions can be identified and measured, and play a central role in human psychological functioning and disturbance, while irrational cognitions can be replaced with rational ones, thus facilitating functional emotional, cognitive, and behavioural responses consistent with personal goals and values (David et al., 2010) (***Figure 6.1***).

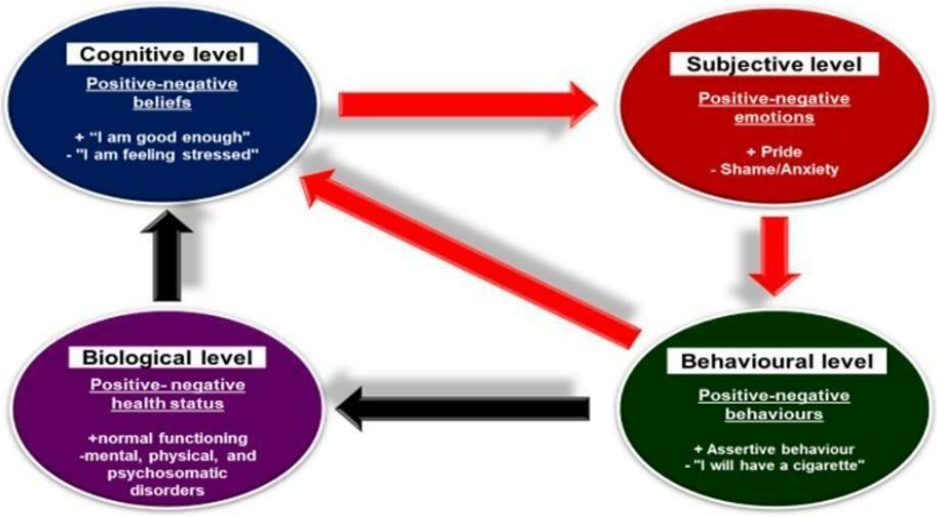
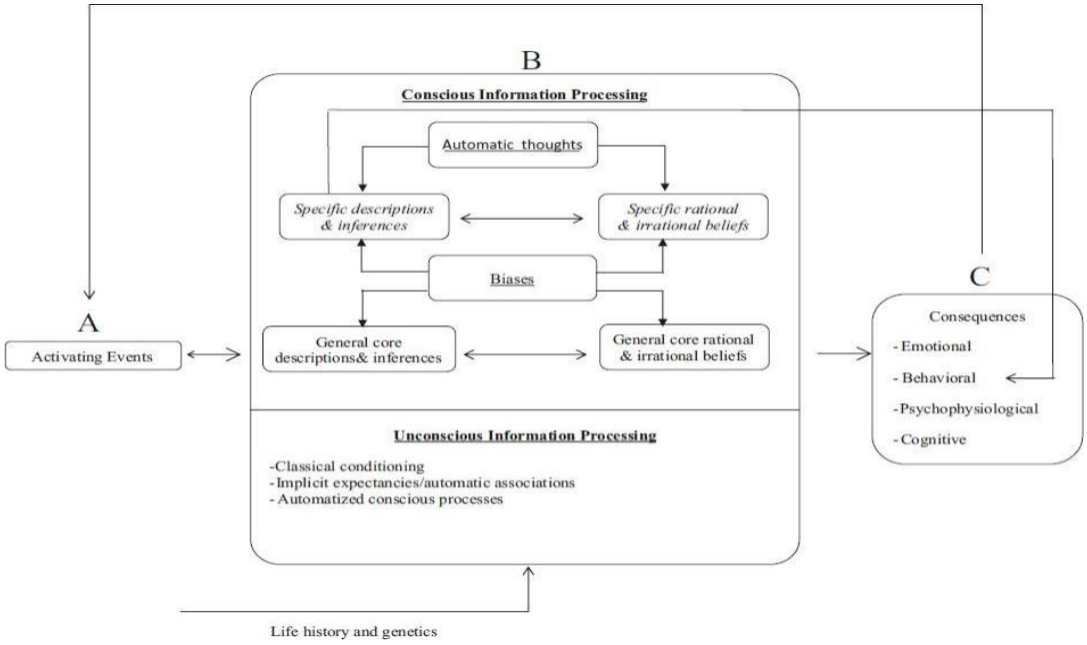


Figure 6.1: Diagram of the Cognitive Behavioural Model

The ABC model

Ellis's "ABC" model is the cornerstone of REBT and CBTs in general (David et al., 2010). According to it, there is an actual or an inferred activating event (A), a cognitions system by rational or irrational beliefs about this event (B), and emotional, behavioural and cognitive consequences of these beliefs (C) (Bridges & Harnish, 2010; David et al., 2010) (***Figure 6.2)***.



Source: David et al., 2019

Figure 6.2: The ABC model

Rational and irrational beliefs

Beliefs are a vital part of human cognition and are crucial for understanding and shaping human emotions, emotional disturbances and behaviours (David et al., 2010). Ellis classified beliefs into two particularly important types in the context of mental health and well-being, the rational and irrational beliefs (Bridges & Harnish, 2010). Rational beliefs can be described as efficient, adaptive, and reasonable (David et al., 2010). They promote self- acceptance and effective coping with stressful situations, lessen vulnerability to psychological distress, and are essential to achieving primary goals (David et al., 2010). Examples of rational beliefs include the belief that success requires effort or the belief that mistakes are a necessary part of the learning process (Duckworth et al., 2007; Kornell et al., 2011). In contrast, irrational beliefs are non-pragmatic, rigid, unrealistic and not based on evidence (David et al., 2010). They lead to biased conclusions about the external world and emotional disturbances, such as anxiety, depression and substance use disorders, and maladaptive behaviours (Buschmann et al., 2017; Turner et al., 2022). Even though activatingevents like failure or loss may inevitably trigger irrational beliefs initially, we can learn to shift our thinking to more rational ways (David et al., 2010).

Originally Ellis described 11 types of irrational beliefs, however later developments suggested that these fall into 4 main categories, including demandingness (e.g., “I must”), awfulizing (e.g., “It is terrible”), frustration intolerance (e.g., “I cannot stand it”), and depreciation (e.g., “I am worthless”) (David et al., 2010; Mansell, 2021; Turner et al., 2022). Demandingness indicates that the individual persists in assimilative attempts to process information that contradicts their chronic representations, resulting in persistent arousal and threat perception (Buschmann et al., 2017). There are three types of demandingness: a) self-related demands for achievement and competence (“perfectionism”), b) demands that others must treat them nicely and c) demands that life should be fair (Daniel et al., 2010; David et al., 2010). The alternative rational beliefs are preferences, anti-awfulizing, high frustration tolerance, and unconditional self/other acceptance (David et al., 2010). Beliefs are alsodivided into primary and secondary ones (David et al., 2010). Primary beliefs reflect the demanding or preferred nature of the belief (e.g., “I must get the highest grades in my class…”, whereas secondary beliefs convey a personally meaningful context (e.g.., “…but I cannot stand it if I do not” (David et al., 2010).

It appears that both rational and irrational beliefs are biologically predisposed, although this does not amount to genetic determinism (e.g., no specific genes or a combination of genes fully determine rational or irrational beliefs) (David et al., 2010). Instead, there is an assumption that depending on our genes and the environment we are exposed to, we will acquire more rational or irrational beliefs (David et al., 2010). The predisposition to develop irrational beliefs can probably explain the difficulty of changing them during psychotherapy (David et al., 2010). The genetic predisposition to rational or irrational thinking is not well understood but may be linked to the concept of evolutionary design, and thus beliefs about the social and cultural environment will be assimilated and filtered by evolving genetic predispositions (David et al., 2010). People then may develop irrational beliefs and thus psychological disturbances even if they grow up in a perfect environment that models rational thinking (David et al., 2010). Analogous to this, is the example of children who grew up without adults, who still develop speech, even withminimum exposure to linguistic stimuli (David et al., 2010).

Functional and dysfunctional emotions

Emotions are complex psychological experiences that include a combination of physiological reactions, such as arousal, cognitive appraisal, and subjective feelings (Barrett,

2017). They are a function of instinctive tendencies that are particularly controlled or modified by the individual and their experiential history (David et al., 2010). According to Ellis, negative emotions are biased, or irrational thoughts followed by normal, physical responses (Jones, 1969). Ellis first proposed the distinction between functional and dysfunctional emotions based on their intensity (David et al., 2010). Specifically, dysfunctional negative emotions, such as anger, depression, anxiety and guilt are more intense and associated with irrational beliefs, whereas functional negative emotions, such as sadness and concern are generally less intense and associated with rational beliefs (David et al., 2010). Moreover, different negative emotions can be functional or dysfunctional depending on their intensity (e.g., high anxiety and concern are dysfunctional whereas low anxiety and concern are functional) (David et al., 2010).

In a revised version of the theory, Ellis proposed that the distinction between functional and dysfunctional emotions is primarily qualitative and depends on their subjective experience (e.g., concern vs. anxiety), relevant rational or irrational cognitions, and healthy vs. unhealthy behaviours and physiological responses (David et al., 2010). Thus, dysfunctional negative emotions correspond to clinical problems, whereas functional negative emotions reflect normal responses during stressful events (David et al., 2010). In research and clinical practice, the Beck Depression Inventory (BDI) and the State-Trait Anxiety Inventory (STAI) combine depressed mood and sadness scores (i.e., the BDI scale) and anxiety and concern scores (i.e., the STAI scale) to reveal the global level of depressed mood and anxiety, respectively (David et al., 2010). Additionally, in both experimental and epidemiological studies, irrational beliefs are positively correlated with both functional and dysfunctional negative emotions, but also biological biomarkers (David et al., 2010; Harris et al., 2006). Regarding this, Papageorgiou et al. (2006) found that irrational beliefs were positively associated with CRP, IL-6, TNF-α, and white blood cells, whereas a study by Harris et al. (2006) showed that those holding rational beliefs had a decrease in SBP and those holding irrational beliefs had an increase in DBP (Harris et al., 2006; Papageorgiou et al.,2006).

Behaviours

Behaviours in REBT are often considering coping or management strategies by which individuals maintain their beliefs and manage the situations around them so as not to cause the emotional pain of core beliefs and patterns (David et al., 2010). Such behaviours are withdrawal from reinforcement, physical or verbal attacks, avoidance of fearful situations,

etc. (David et al., 2010) (***Figure 6.3***). Behaviours are divided into overt and operant (David et al., 2010). Overt behaviours are responses that can be observed and measured, directly or with scales, such as physical aggression and avoidance (David et al., 2010). Operant behaviours are learned motor behaviours, under our control, and that have a direct impact on our physical or social environment (David et al., 2010). A substantial body of research has documented the relationship between perfectionism and maladaptive behaviours, such as eating disorders, alcohol abuse, etc. (David et al., 2010). Conversely, healthy lifestyle behaviours reduce vulnerability to emotional disturbances, increase the ability to cope with stressors and promote emotional well-being (David et al., 2008). For example, exercise and a healthy diet have been found to have a positive effect on cognitive function, as well as symptoms of depression and anxiety (Stanton & Reaburn 2014; Jacka et al., 2017).

Irrational belief	Dysfunctional behavior	Study
Demandingness		
Self related demands for achievement and competence	• Comfort eating • Medication use • Increased anger expression • Social avoidance and isolation • Decreased performance in social context • Internalized and externalized behavioral disorders in children	Harrington (2005) Bernard (1998) Watson, Sherbak, and Morris, (1998) Nicastro, Luskin, Raps, and Benisovich (1999) Silverman and DiGiuseppe (2001)
Demands for comfort and fairness/ entitlement	• Self harming • Behavioral avoidance • Comfort eating • Overspending • Procrastination • Reduced anger control • Increased anger expression • Relational problems	Harrington (2005); Harrington (2003); Bridges and Roig (1997) Bernard (1998) Addis and Bernard (2002)
Demands for control	• Hostile dominant interpersonal style	Goldberg (1990)
Other related demands	• Marital problems • Aggressive anger expression	Möller and De Beer (1998); Möller and Van der Merwe (1997) Jones and Trower (2004)

Awfulizing		
	• Submissive interpersonal style • Social isolation • Increased anger suppression • Increased anger expression • Externalized behavioral disorders in children	Goldberg (1990) Watson, Sherbak, and Morris, (1998) Martin and Dahlen (2004) Silverman and DiGiuseppe (2001)
Low frustration tolerance		
	• Decreased anger control • Increased anger expression	Watson, Sherbak, and Morris (1998) Möller and Van der Merwe (1997) Martin and Dahlen (2004) Jones and Trower (2004)
	• Increased anger suppression • Social isolation • Marital problems	
	• Behavioral avoidance • Comfort eating • Routine behavior • Procrastination • Overspending • Medicationuse • Self harm	Harrington (2005)
Global evaluation/ self downing		
	• Defensiveness to negative feedback • Increased anger suppression • Aggressive anger expression • Marital problems • Internalized and externalized behavioral disorders in children	Chamberlain and Haaga (2001) Martin andDahlen (2004) Jones and Trower (2004) Addis and Bernard (2002); Möller and Van der Merwe (1997); Möller, Rabe and Nortje (2001); Möller and De Beer (1998) Silverman and DiGiuseppe (2001)

Source: David et al. 2009

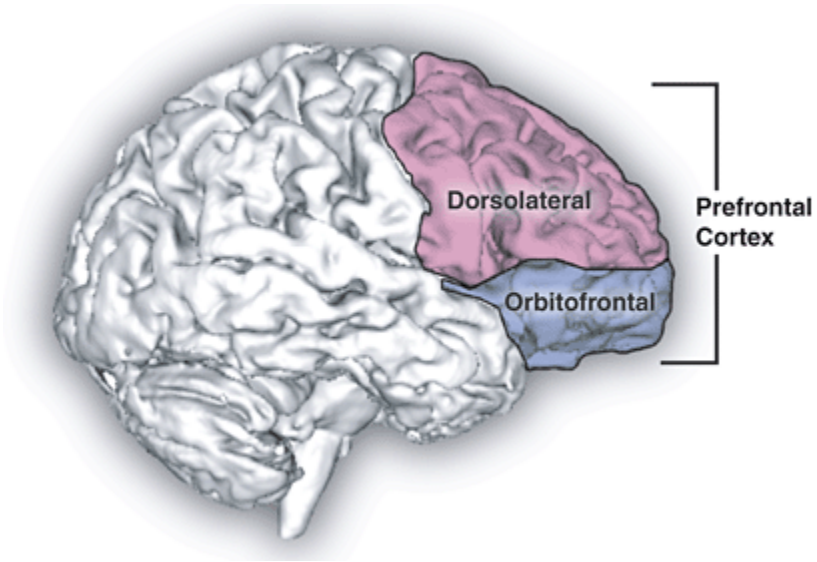
Figure 6.3: Behavioural Consequences of Irrational Beliefs

Irrational beliefs, psychopathological and physiological etiopathogenetic mechanisms

High levels of irrational beliefs are associated with neuroticism, general anxiety, self-reported depression, general psychiatric symptoms, and type-A coronary-prone behaviour (David et al., 2010). The diathesis-stress model of CBT/REBT proposes that irrational beliefs produce cognitive vulnerability in stressful situations, whereas rational beliefs are protective factors (David et al., 2010). Laboratory studies with limited generalizability have provided only a minimal test of the CBT/REBT diathesis-stress model and do not allow firm

conclusions (David et al., 2010). However, when prospective studies and real stressful events are incorporated into the design, hypotheses generated from the model are empirically supported (David et al., 2010).

In addition, cognitions like irrational beliefs are considered a part of executive functioning (EF). EF is a high-order set of complex multidimensional mental control systems, including learning, flexible/adaptive thinking, planning, evaluation, and decision-making, which is located in the prefrontal cortex (Knapp & Morton, 2013; Maltby et al., 2013; Zainal & Newman, 2022) (***Figure 6.4***). Deficits in EF have been linked to emotion regulation problems, mental health issues and psycho-physiological consequences (Zainal & Newman, 2022).



Source: Zahr & Sullivan, 2008

Figure 6.4: Illustration of Prefrontal Cortex

4.3. The CBT/REBT Model in Chronic Illnesses

Based on the fundamental principles of the CBT model, dysfunctional beliefs contribute to emotional, cognitive, mental, and physical consequences. In particular, an individual's thinking (cognitive level), affects their emotions (subjective level) e.g., "I am feeling stressed" and their behaviours (behavioural level), e.g., "I will have a cigarette" whichsuccessively, is very likely to affect their health/biological status (Ogden, 2019). This is especially apparent in everyday life and the behavioural literature on smoking, diet and

exercise (David et al., 2010). These maladaptive thoughts are referred to as irrational health beliefs when extended to health contexts (David et al., 2010).

The scientific community has recognized the relationship between psychological factors and physical health, as both cognitive and emotional factors have been demonstrated to contribute to physical symptoms (David et al., 2010). Yet, there is a scarcity of empirical clinical data in this field because irrational beliefs, the core construct of REBT, is a psychological factor that has been too often overlooked as a predictor of health outcomes (David et al., 2010). Therefore, although links between beliefs and a wide range of health outcomes are acknowledged in both research and clinical practice, scientifically valid research is required to support them (David et al., 2010).

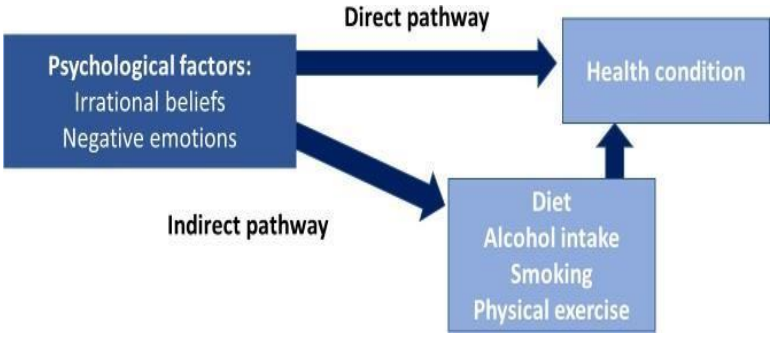
For instance, greater levels of irrational beliefs have been positively associated with plasma inflammatory indicators and severe asthma in comparison to lower levels (Papageorgiou et al., 2006; Silverglade et al., 1994). Additionally, McNaughton et al. (1995) demonstrated that irrational beliefs were associated with depression and poor health in caregivers of patients with Alzheimer's disease, while those with lower adherence to irrational beliefs had improved subjective health over six months (David et al., 2010). Christensen et al. (1999) revealed that greater levels of irrational beliefs predicted both self- reported diabetic regimen and levels of the hemoglobin subunit alpha 1(HbA1) (David et al., 2010).

Regarding irrational health beliefs, the belief that one is likely to become ill or that health is beyond control, can increase stress levels and the risk of developing chronic conditions (Cohen, et al., 2007). Catastrophizing, also known as awfulizing, is a particular kind of irrational health belief that has mostly been studied in relation to pain (David et al., 2010). For instance, patients who had undergone knee surgery, who also tended to catastrophize before surgery, were more likely to experience postoperative pain (David et al., 2010). In addition, greater catastrophizing predicted greater pain in patients with rheumatic disease (David et al., 2010).

As we also mentioned above, irrational beliefs are not only associated with physical symptoms but also with negative health behaviours (David et al., 2010). For example, there was an association between catastrophizing, low frustration tolerance and negative self-evaluation, and eating disorders (David et al., 2010). Also, Phillips et al. (1997) demonstrated that individuals with bulimia had equal levels of irrational beliefs with patients with depression, and greater than healthy controls (David et al., 2010). Besides, greater levels of

irrational beliefs were associated with poor eating attitudes in non-clinical samples of young women, and with greater levels of alcohol problems in college students (David et al., 2010).

Considering the literature and the CBT/REBT theory, irrational beliefs appear to impact health outcomes in at least three possible pathways: directly and indirectly through their effect on psychological distress, or/and through lifestyle behaviours (David et al., 2010) (***Figure 6.5***).



Source: Ogden, 2012

Figure 6.5: Psychology and Health: Direct and Indirect Pathways

5. The Onset of Metabolic Syndrome and Cardiovascular Disease Based on the CBT/REBT Model

Based on all the previous sections, the role of certain psychopathological conditions, such as anxiety and depression have already been assessed in the development of CVDs, for which MetS is a considerable risk factor (D'Antono et al., 2013; Everson-Rose et al., 2020; Hoffmann et al., 2021). Specifically, depression is associated with a higher risk of developing diabetes, central obesity, and CVDs, whereas other epidemiological studies have repeatedly investigated the association between anxiety and MetS, confirming it or not (Carroll et al., 2009; Pan et al., 2012; Tang et al., 2017, Cohen et al., 2010). In addition, hostility has also been associated with a high MetS risk, as well as with high BMI, fasting glucose, insulin resistance and diabetes (Goldbacher & Matthews, 2007). In addition, research by Kollia et al. (2017a) showed that psychological distress had a direct and positive association with MetS (Kollia et al., 2017a).

According to Goldbacher & Matthews (2007), depression, hostility and anxiety are likely to contribute to the pathogenesis of MetS through biological and behavioural mechanisms which mediate this association by increasing or decreasing the risk. In particular, they adversely affect a variety of normal physiological pathways, such as the sympathetic adrenomedullary system (SAM) and the HPA axis which are involved in the development of MetS, its key components and CVDs (Eikeseth et al., 2019; Everson-Rose & Lewis, 2005; Giorgino et al., 2005; Penninx & Lange, 2022).

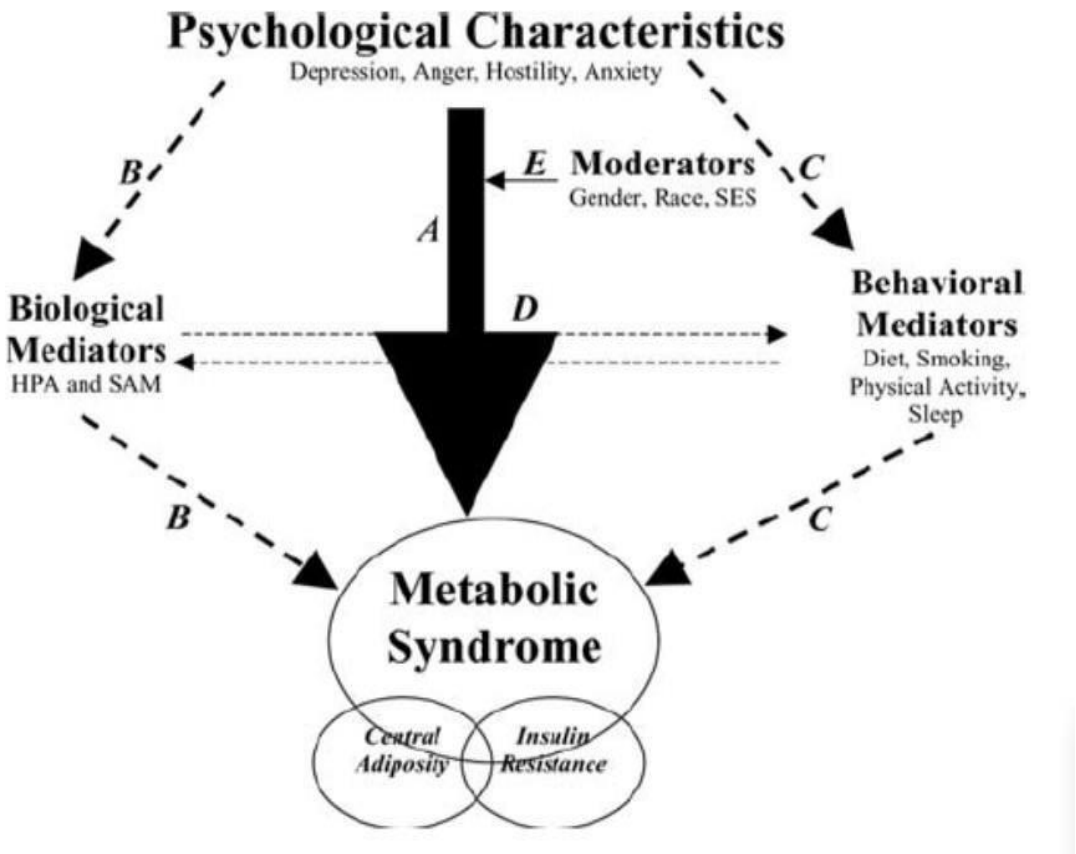
Additionally, growing evidence has highlighted the existing relationship between anxiety and depression with inflammation (Beurel et al., 2020; Colasanto et al., 2020; Osimo et al., 2020). In this line, some depressive endophenotypes (i.e., atypical depression), as well as anxiety disorders have been related to evident disturbances in the (pro-)inflammatory response (Lamers et al., 2016; Lamers et al., 2020; Moriarity et al., 2021; Renna et al., 2018). Dysregulation of the HPA axis appears to play a role in the immune-metabolic alterations, such as increased production of cytokines (ie, TNF-α, IL- 6) (Bierhaus et al., 2003) and

consequent induction of acute phase inflammatory proteins (i.e., CRP or serum amyloid A (SAA)) (Bryleva et al., 2017) and metabolic dysregulation (i.e., stimulation of the release of lipids into the bloodstream, increased triglycerides and decreased cholesterol linked to HDL-C or alterations in total cholesterol levels) (Esteve et al., 2005). In addition, dysregulation of cortisol secretion may induce alterations in lipid and glucose metabolism that can contribute to the development of diabetes, hypercholesterolemia, hypertriglyceridemia and CVDs (Rosmond & Björntorp, 2000). Kynurenine path may also be involved in the development of CVDs (Miller et al., 2013).

Besides, demographic characteristics, such as gender, age, and educational level, may be either protective or risk factors and in turn, they might influence the relationship between psychological factors, MetS, and CVDs (Goldbacher & Matthews, 2007).

Psychological distress, anxiety and depression also lead to increased harmful lifestyle choices, such as smoking, excessive alcohol intake, unhealthy dietary habits, and sedentary life, all of which are associated with visceral obesity, insulin resistance, and MetS, and therefore can lead to CVDs (Giorgino et al., 2005; Goldbacher & Matthews, 2007; Naja et al., 2013; Penninx & Lange, 2018; Tang et al., 2017; Woo et al., 2014).

Particularly, numerous studies suggest that unhealthy eating patterns, such as high meat consumption (especially processed meat), sugar, high-fat and processed carbohydrates, as well as reduced intake of whole grains, coffee and iron are associated with the MetS and CVD risk (Aekplakorn et al., 2015). A HFD is associated with oxidative stress and NFκB activation (Aljada et al., 2002). In contrast, eating habits characterized by high consumption of whole grains, fish, cereals and fruits are protective factors against MetS and CVDs(Panagiotakos et al., 2007; Suliga et al., 2015). Also, alcohol dependence is associated with an increased risk of developing MetS and CVDs. Excessive alcohol consumption affects lipid and glucose metabolism as well as blood pressure (Kahl & Hillemacher, 2016). Moreover, both physical inactivity and a chronic sedentary lifestyle (e.g., television exposure) are linked to MetS, its components and CVDs (Lemes et al., 2019). Finally, a growing body of evidenceindicated that smoking was a risk factor for MetS and CVDs since it is associated with insulinresistance, abdominal obesity and dyslipidemia (Fujiyoshi et al., 2016; Keith et al., 2016; Slagter et al., 2013; Sun et al., 2012; Zhang et al., 2013) (***Figure 7.1***).



Source: Goldbacher & Matthews, 2007

Figure 7.1: Potential Factors that Could Explain the Relationship between Psychological Characteristics and MetS

Although various psychological components have been studied over the years, the role of irrational beliefs in the occurrence of physical conditions (Roohafza et al., 2012), and particularly in the onset of CVDs, has not been appreciated. Dysfunctional emotions, such as hostility, as well as emotional and mental health issues, like psychological distress anxiety or depression, are caused by irrational, dysfunctional beliefs, as discussed in previous sections (Dryden. 2005; Dryden, 2012). In addition to emotional disturbance, irrational beliefs are also associated with various dysfunctional and lifestyle risk behaviours, including excessive alcohol consumption, smoking, unhealthy dietary patterns, overeating and inactivity (Dryden 2005; Ogden, 2019; Osberg et al., 2008). Finally, they are associated with hypertension and inflammation processes (Fulton et al., 2011; Kyrou et al., 2017; Papageorgiou et al., 2006; Vîslă et al., 2016; Querstret & Cropley, 2013).

In line with the abovementioned, it is proposed that the CBT/REBT can explain the MetS onset and consequently CVD risk, taking into consideration the primary role of irrational beliefs directly through neuro-chemical and biochemical dysregulation, or through negative and dysfunctional emotions and behaviours.

6. CBT/REBT Models in Research and Clinical Practice Regarding Cardio-Metabolic Conditions

The relationship between psychology and health has important implications for healthcare practice. Healthcare providers need to be aware of the impact of psychological factors on health outcomes and consider patients' psychological well-being in their treatment plans (DiMatteo et al., 2000). This includes screening for depression and anxiety and providing appropriate treatment, as well as addressing social and environmental factors that may impact patients' psychological well-being (Greenberg et al., 2015; NIMH, 2018). Additionally, they should be aware of the potential psychological impact of medical procedures and other health-related events, and provide appropriate support and counseling to patients and their families (DiMatteo et al., 2002).

6.1 CBT/REBT model and irrational beliefs

The CBT/REBT model, which as supported by a meta-analysis by David and colleagues (2017), effectively reduces irrational beliefs, (David et al., 2017), may play a pivotal and positive role in changing behaviours and biomedical conditions, and finallypreventing CVD risk (David et al., 2010). Specifically, REBT was effective in lowering blood pressure in people with hypertension (Drazen et al., 1982; Harris et al., 2006). For example, in the intervention by Drazen et al. (1982), patients in the REBT group showed significant reductions in their SBP and DBP at a two-month follow-up. CBT /REBT interventions were also efficient in improving emotional disturbances and lifestyle behavioursin CVD patients (Elderen et al., 1994; Heenan et al., 2019; Johansson et al., 2019; Kaar et al., 2017; van Elderen & Dusseldorp, 2001). Other CBT/REBT interventions were sufficient in changing lifestyle behaviours, such as binge eating, alcohol overconsumption, and physical inactivity in the general population (Brawley et al., 2000; Cao et al., 2022; Michalsen et al., 2005; Morgenstern & Longabaugh, 2002; Sharma & Lakhan, 2019; Terjesen et al., 2000; Yang & Sun Han, 2020). While correspondingly other CBT/REBT interventions were concerned improving symptoms and/or managing lifestyle behaviours in patients with a

chronic condition, such as asthma, breast cancer or cancer survivors, chronic obstructive pulmonary disease (COPD), or in those at risk of muscle dysmorphia (Kunik et al., 2001; Mefferd et al., 2007; Outar et al., 2021; Reavell et al., 2018; Yun et al., 2017).

6.2 Level of evidence

However, there is insufficient empirical data to draw definitive conclusions about the role of irrational beliefs in the effectiveness of REBT (David et al, 2010). Overall, more empirical research is needed in this area. Emerging evidence, as discussed in previous sections, suggests that irrational beliefs may play a role in both directly influencing health outcomes, and indirectly influencing them through mediators, such as psychological distress and health behaviours (David et al, 2010). Without empirical justification, additional fields ofstudy and clinical medical practice will not accept the relevance of these constructs and will not proceed to incorporate psychotherapeutic strategies to combat irrational beliefs intoroutine clinical practice (David et al, 2010). Consequently, until now the general population may not benefit from an intervention that could potentially improve both health and copewith illness or discomfort (David et al, 2010).

Even prominent REBT researchers have asked the question of why irrational beliefs have largely been ignored in the domains of physical health and health psychology (David et al., 2010). In the same work, they attempted to answer this question, concluding that there is a lack of rigorous empirical data and even those data focused on REBT have assumed that if REBT is effective in improving health, then so are irrational beliefs (David et al., 2010). Although possible, this remains an arbitrary conclusion (David et al., 2010).

To conclude, it is argued that other researchers interested in irrational beliefs would do the field a great service not only by producing high-quality research but also by educating the community and professionals about REBT and its effects on irrational beliefs (David et al, 2010).

7. Aim of the Thesis

General Scope

Under the context of the bio-psychosocial model, and based on the CBT/REBT, the main goals of this doctoral thesis were:

- to evaluate the association between irrational beliefs and the development of MetS and its components, as well as the development of CVD, and
- to examine whether MetS could play a mediating role in the relationship between irrational beliefs and CVD.

By studying these research hypotheses current gaps in scientific knowledge could be covered and future directions for public health could be effectively guided, by including bio-psychosocial interventions for individuals at high risk for cardiometabolic diseases.

Specific Objectives

We specifically hypothesized that irrational beliefs could contribute to MetS and CVD development, either directly or indirectly, through their association with certain dysfunctional emotions (e.g., depression and anxiety), lifestyle behaviours (e.g., dietary habits away from the Mediterranean diet, sedentary lifestyle) and biological and clinical atherosclerotic risk factors (e.g., inflammation, oxidative stress, hypertension, etc.).

Therefore, we considered the potential mediating, or even moderating role of social, psychological, behavioural and physiological factors in the association between irrational beliefs (i.e., cognitive level) and cardio-metabolic disorders.

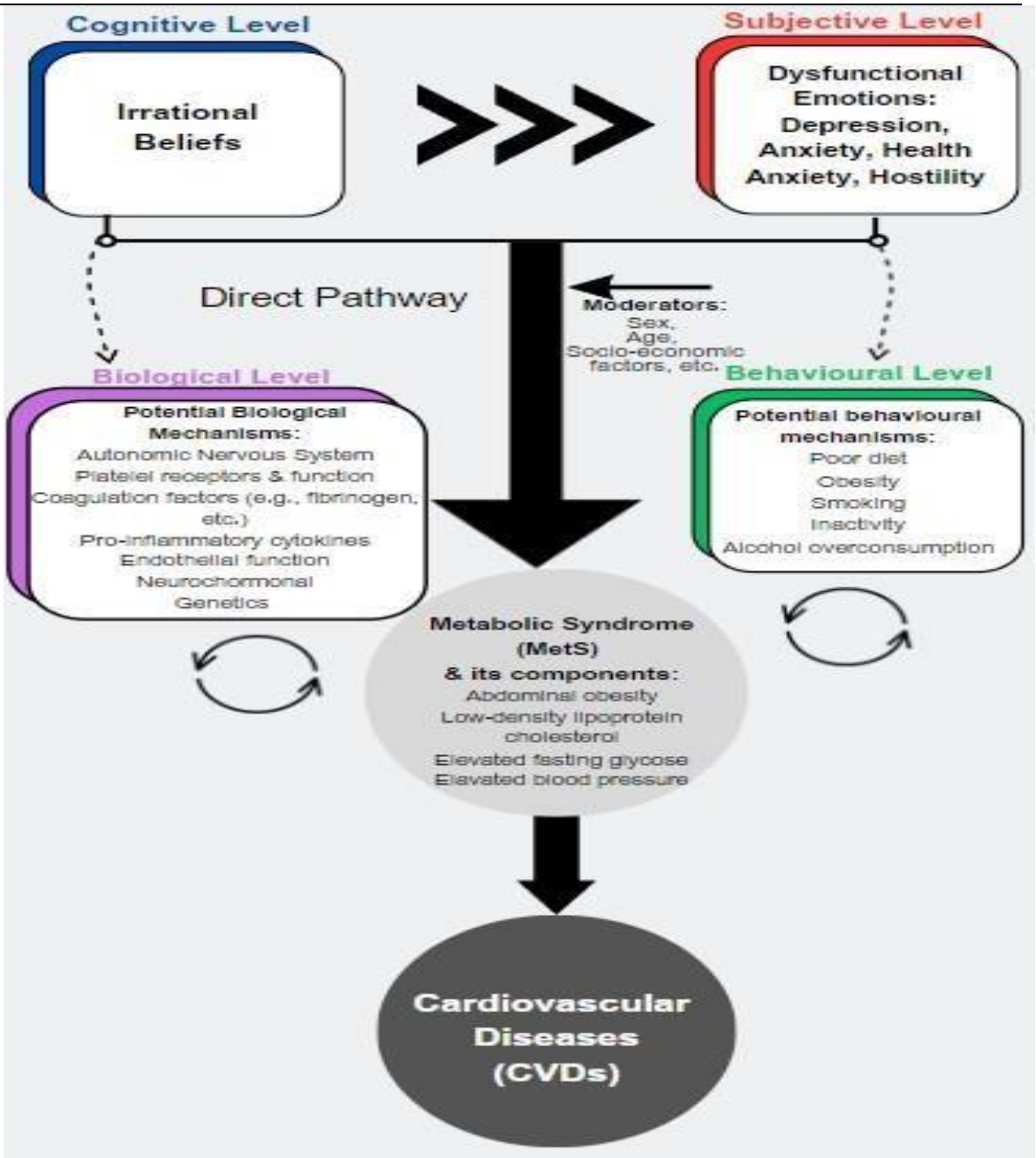


Figure 8.1: Research Hypothesis, Objectives & Scope

8. Methodology

For this doctoral thesis, data from the ATTICA study (2002-2022) database were extracted and used.

8.1 Design of the Study

The ATTICA study[1] is a population-based, prospective epidemiological study, with three follow-up examinations (i.e., 2001/2: baseline, 2006: 5-year, 2012: 10-year, 2022: 20-year follow-up), and with a primary aim to evaluate a wide range of socio-demographic, lifestyle, clinical, biochemical, and psychological parameters and explore their prognostic value on the incidence of CVD through periodic follow-up examinations in a representative sample of non-institutionalized and CVD-free adult men and women living in the capital province of Greece. Thus, adults aged 18 years old and older, without any clinical evidence of cardiovascular, other atherosclerotic diseases, or chronic viral infections, were eligible to participate. Moreover,participants did not have cold or flu, acute respiratory infection, dental problems or any type of surgery during the past weeks. Also, all people living in institutions were excluded from the study. The study was based on face-to-face interviews and clinical examinations. A detailed methodology of the study has been previously published (Pitsavos et al., 2003).

8.2 Setting

The ATTICA study was conducted in the greater metropolitan Athens area (including 78% urban and 22% rural regions) during 2001-2002, by the First Cardiology Department of the Hippokration General Hospital, of the University of Athens Medical School.

[1] ATTICA Study is not an abbreviation but denotes the region in Greece (i.e., Attica or Attiki region, where the study was conducted. In this region Athens (or Athena) is the major metropolis, and the entire region is inhabited by approximately 3,7 million of people (i.e., 34% of the total Greek population, cencus 2021).

Baseline examination lasted for three days and it was performed using face-to-face interviews, in the individuals' home or workplaces, and followed by clinical examination at Hospital setting, by trained personnel (cardiologists, general practitioners, dieticians and nurses, and psychiatrists/psychologists) who used standard questionnaires that evaluated various socio-demographic, lifestyle, psychological, clinical and biochemical characteristics. Three follow-up examinations, in 2006, 2012 and 2022 were also performed, following the sameprocedures as in the baseline examination.

8.3 Sample

In total 4056 adults were randomly selected by municipality or workplace listings and invited to participate in the study. Of them, 3042 adults (18-89 years old, 1514 (49%) men and 1518 (51%) women), agreed to participate (73% participation rate)

Of the initially enrolled 3042 participants, a subsample of 853 participants [453 men (45±13 years), and 400 women (44±18 years)] agreed to participate in the psychological evaluation; thus, this group form the sample of this work. This sub-sample was selected from the study's population according to the following algorithm: in each block (i.e. city–gender–age group) we randomly selected (using a sequence of binary numbers, i.e. 1100101100) one-every-four participants. This subsample is representative of the total study's sample since there were no differencesin sex and age distribution between the studied sample and the overall study's population (all p-values >0.4).

8.4 Statistical Power

A-posterior power analysis showed that the number of participants, *n*=853, used in this work is adequate to evaluate two–sided differences on effect size measures, i.e., relative risks, equal or greater than 10%, between irrational beliefs' subgroups and the investigated outcomes, achieving statistical power 0.83, at 0.05 significance level (p-value).

8.5 Bioethics

The ATTICA study was approved by the Medical Research Ethics Committee of First Cardiology Clinic, School of Medicine, University of Athens (#017/1.5.2001) and was carried out in accordance with the Declaration of Helsinki (1989) of the World Medical Association. All participants were informed about the aims and procedures and agreed to participate providing written consent.

8.6 Measurements at Baseline Examination

Baseline examination included a range of participants' clinical, anthropometric, biochemical, socio-demographic and behavioural/lifestyle characteristics.

8.6.1 Socio-Demographic Factors Assessment

Socio-demographic characteristics studied at baseline included among others; age, sex, marital status (married, divorced, widowed), educational, financial (average annual income during the past three years) and occupational status (through a ten- point scale that assessed unskilled to skilled occupations).

In particular, sex was recorded by the researchers in the questionnaire that was filled by the participants, while their exact date of birth was also recorded for the calculation of their current age. Educational status was assessed by years of attending school (including university level). Mean annual income during the past three fiscal years before the entry (i.e., 1999, 2000 and 2001) was recorded and the financial status of the participants was classified into four groups (according to 2012 classification by the National Center of Social Research):

- low: ≤ 8000 €,
- medium: 8001 – 10000 €,
- high: 10001 – 20000 € and
- very high: > 20000 €.

To provide a more accurate estimate of participants' socio-economic status (SES), and since no such scale exists for the Greek society, a combination of education and income was implemented. Thus, participants were classified into a SES class by multiplying the years of school in each individual, with their mean annual

income and occupation level (manual, mixed, intellectual) (Manios et al., 2005; Panagiotakos et al., 2008). A school year × annual income × occupational score was developed. This index was normally distributed according to the Kolmogorov–Smirnov criterion. Then, the study's sample was divided into the following three SES categories (classes): (i) Low SES (i.e., up to 9 years of schooling and low/medium income or up to 14 years of schooling and low income), (ii) High SES (i.e., 15 or more years of schooling and high/very income or 10 – 14 years of schooling and very high income and (iii) Moderate SES, including the rest of the participants.

8.6.2 Dietary Assessment

Dietary habits were assessed using a validated semi-quantitative food-frequency questionnaire (FFQ), the EPIC-Greek questionnaire that was provided by the Unit of Nutrition of Athens University Medical School, and according to which participants recalled and reported average weekly or daily intake of food items during the past year (Katsouyanni et al., 1997). The questionnaire assessed the usual dietary intake of 156 foods and beverages commonly consumed in Greece, with seven non-overlapping response categories. Photographs assisted the responders to define the portion sizes of several foods that were included in the questionnaire. In particular, consumption of non-refined cereals and products (like whole-grain bread, pasta, rice, etc.), vegetables, legumes, fruit, dairy products (like cheese, yogurt, milk), nuts, potatoes, eggs, sweets, fish, poultry, red meat and meat products, use of olive oil in cooking, as well as coffee, tea and alcohol drinking were measured as an average per week during the past year. The frequency of consumption was quantified in terms of the number of times a month food was consumed in small, medium, or large portion sizes. Alcohol consumption was recorded as a daily ethanol intake of 100 ml of wine glasses adjusted for 12% ethanol concentration.

The Mediterranean dietary pattern consists of: (a) daily consumption: of non refined cereals and products (whole grain bread, pasta, brown rice, etc), vegetables (2 – 3 servings/day), fruits (6 servings/day), olive oil (as the main added lipid) and dairy products (1 – 2 servings/day), (b) weekly consumption: of fish (4–5 servings/week), poultry (3 – 4 servings/week), olives, pulses, and nuts (3 servings/ week), potatoes,

eggs and sweets (3 – 4 servings/week) and monthly consumption: of red meat and meat products (4 – 5 servings/month). It is, also, characterized by moderate consumption of wine (1 – 2 wineglasses/day) and high monounsaturated: saturated fatratio (> 2). A Harvard-led group suggested this dietary pyramid with substantial input from Greek scientists (Willett et al., 1995).

Moreover, a specific diet score, i.e., the MedDietScore, was calculated based on the reported dietary habits and assessed adherence to the Mediterranean diet for each participant (Panagiotakos et al., 2006). In particular, for the consumption of items presumed to be "close" to this pattern (i.e., those suggested daily or more than 4 servings per week) score of 0 was assigned when someone reported no consumption,a score of 1 when they reported consumption of 1 to 4 times per month, score 2 for 5to 8 times, score 3 for 9 to 12 times per month, score 4 for 13 to 18 times per month and score 5 for more than 18 times per month. For the consumption of food items presumed to be "away" from this diet (like meat and meat products), the scores were assigned on a reverse scale (i.e., 0 when a participant reported almost daily consumption and 5 for rare or no consumption). Especially for alcohol, a score of 5 was assigned for the consumption of fewer than 3 wineglasses per day, a score of 0for the consumption of more than 7 wineglasses per day and scores 1 to 4 for the consumption of 3, 4 – 5, 6 and 7 wineglasses per day. Higher values (range 0 – 55) of this special diet score mentioned above indicate greater adherence to the Mediterranean diet.

8.6.3 Physical Activity Assessment

The short form of the International Physical Activity Questionnaire (IPAQ) was used to assess physical activity status. IPAQ was used as an index of weekly energy expenditure using frequency (times per week), duration (in minutes per time) and intensity of sports or other habits related to physical activity (in expended caloriesper time) (http://www.ipaq.ki.se). Intensity was gradated in qualitative terms such as: light (expended calories < 4 Kcal/ min, i.e. walking slowly, cycling stationary, light stretching etc.), moderate (expended calories 4–7 Kcal/ min, i.e. walking briskly, cycling outdoor, swimming moderate effort etc.) and high (expended calories >7 Kcal/ min, i.e. walking briskly uphill, long distance running, cycling fast or racing, swimming fast crawl etc.). Participants were instructed to refer to all domains of

physical activity and report only episodes of activities of at least 10 min since this is the minimum required to achieve a health benefit. Afterward, the sum of the metabolic equivalent of task (METs; 1 MET = the oxygen used by the body when sitting) (min/week was calculated for each participant, and the quartiles of MET min/week were constructed, yielding four categories, i.e., very low, low, moderate and high physical activity level. The moderate category consisted of people who reported any 1 of the following 3 criteria: more than 3 days of vigorous activity of at least 20 minutes per day or more than 5 days of moderate-intensity activity or walkingof at least 30 minutes per day or more than 5 days of any combination of walking or moderate-intensity or vigorous-intensity activities, achieving a minimum of at least 600 MET min/week. The vigorous-intensity activity group consisted of people who devoted at least 3 days to physical activities and accumulating at least 1500 MET min/week, or 7 or more days of any combination of walking or moderate-intensity or vigorous-intensity activities, achieving a minimum of at least 3000 MET min/week (http://www.ipaq.ki.se). The rest of the participants were defined as low physically active or sedentary.

The IPAQ has been found valid and reliable for the Greek population, too (Papathanasiou et al., 2009).

8.6.4 Smoking Assessment

Information about smoking habits was collected using a standardized questionnaire developed for the Study. Current smokers were classified as individuals who smoked at least one cigarette per day during the previous year, former smokers were defined as those who had stopped smoking more than 1 year previously, and the rest were classified as never smokers. Occasional smokers (less than 7 cigarettes per week) were recorded and combined with current smokers due to their small sample size. Current and former smokers were combined as ever smokers. The rest of the participants were defined as non-smokers. For a more detailed evaluation of smoking habits, we calculated the pack-years (cigarette packs per day × years of smoking). In order to correct for the amount of nicotine containment in various types of cigarettes smoked (i.e. light, heavy, very heavy), we assigned a weight for each different type of cigarette–pack, using the 0.8 mg/cigarette as the standard. Exposure to secondhand

smoke was evaluated through a confidential questionnaire; we asked: "Are you currently exposed to tobacco smoke from other people for more than 30 minutes per day?" We asked separately about two locations: home and workplace. Responses were categorized into three levels: no exposure to secondhand smoke, occasional exposure (i.e., up to 3 days per week, for at least 30 minutes per day), and regular exposure (i.e., more than 3 days per week, for at least 30 minutes per day). We also asked: "As an adult, how many years have you lived (i.e., home or workplace) with someone who has smoked regularly?"

8.6.5 Anthropometric Assessment

Waist circumference (cm) was measured in the middle between the 12th rib and the iliac crest, and hip circumference (cm) was measured around the buttocks. The waist-to-hip ratio was then calculated. A waist-to-hip ratio greater or equal to 0.95 in men and 0.8 in women was considered as a measure of central fat (Dobbelsteyn et al., 2001). Height was measured, to the nearest 0.5 cm, without shoes,back square against the wall tape, eyes looking straight ahead (visual axis is horizontal when the top of external auditory meet us is level with the inferior margin of bony orbit), with a right-angles triangle resting of the scalp and against the wall. Weight was measured with a lever balance, to the nearest 100 g, without shoes, in light undergarments. Then body mass index was calculated as weight (in kilograms) divided by standing height (in meters squared).

8.6.6 Psychological Assessment

Irrational beliefs

Irrational beliefs were assessed at baseline using the Irrational Beliefs Inventory (IBI), a brief self-report measure based on the work of Ellis (Alden & Safran, 1978). The inventory consists of 11 statements, each reflecting one irrational belief, including, worrying, rigidity, need for approval, problem avoidance, and emotional irresponsibility (Bridges & Sanderman, 2002; Grundy et al., 2005). Each item is followed by a 9-point bipolar scale ranging from disagree to agree. The scales are summed to yield a total score ranging from 0 to 88 (the higher score the greater severity of irrational beliefs). The IBI was developed as an instrument to assess the association between the endorsement of irrational beliefs and various aspects of

maladaptive emotion and behaviour that have been developed within Ellis's theoretical and applied model that views irrational beliefs as maladaptive (Alden & Safran, 1978). Data from a previous study supported the construct validity of this irrational beliefs scale (Lee et al., 1979). For this thesis, the IBI scale had acceptable internal reliability, (Cronbach's α=0.73). The inventory consists of 11 statements, each reflecting one irrational belief (Papageorgiou et al., 2006).

These statements are shown below:

(1) It is very important to me to be loved or approved of by almost everyone I meet.

(2) I believe I should be competent at everything I attempt.

(3) I believe that there are some people in the world who are bad or wicked. They should be held responsible for their actions and punished.

(4) I become more upset than I should when things are not the way I want them to be.

(5) I believe most human unhappiness is caused by external factors; that people have little ability to control their own sorrows and disturbances.

(6) I become very concerned about things that are dangerous and dwell on the possibility of their occurrence.

(7) I believe it is better in the long run to avoid some life difficulties and responsibilities than to face them.

(8) I believe I need another person stronger than myself on whom to rely.

(9) My history is an important determinant of my present behavior. I believe that once something strongly affects my life it will always affect my behavior.

(10) I become more upset than I should about other people's problems and disturbances.

(11) I believe there is one right solution to any given problem. If I do not find this solution, I feel I have failed (Kyrou et al., 2017; Papageorgiou et al., 2006).

Also, the IBI score was divided into a) tertiles with the 1st tertile corresponding to the lowest IBI scores (<48, i.e., less irrational beliefs/thoughts), the 2nd to the moderate IBI scores (48–56) and the 3rd to the highest IBI scores (>56, i.e., frequent irrational

beliefs/thoughts), and b) two categories as those having low irrational beliefs (<52, i.e., less irrational beliefs/ thoughts) and those having high irrational beliefs (≥52, i.e., frequent irrational beliefs/thoughts).

Depression

Depressive symptomatology was assessed using the validated Greek translation of the Zung Self-Rating Depression Scale (ZDRS). The time window was the preceding 4-week period before the administration. The ZDRS total score range is 20-80; with higher values indicating more severe depression symptoms (Kyrou et al., 2017). Past studies support the validity of ZDRS in measuring the severity of depression (Biggs et al., 1978). The ZDRS scale showed good internal reliability (Cronbach's α=0.82). For this thesis, participants were classified in two categories, those having low depression levels (<34) and those having clinically meaningful depression symptoms (≥34).

Anxiety

Anxiety levels were assessed using the validated Greek translation of the State Anxiety subscale of the Spielberger State-Trait Anxiety Inventory (STAI) (Fountoulakis et al., 2006). The State Anxiety subscale evaluates how the respondent feels "right now, at this moment" (Fountoulakis et al., 2006). The total score of the 20-item STAI ranges from 20 to 80 with higher score values being indicative of more severe anxiety symptoms (Kyrou et al., 2017). Past studies demonstrate that the STAI is a valid instrument for measuring anxiety disorder (Oei et al., 1990). The STAI scale had very good internal reliability (Cronbach's α=0.92). For the present study, the sample was classified in two categories, those with low anxiety (<40) and those with clinically meaningful anxiety symptoms (≥40).

Hostility

Participants also completed the Hostility and Direction of Hostility questionnaire (HDHQ) (Caine et al., 1967) which was translated and validated in our Institution for the study. The HDHQ includes components of the Minnesota Multiphasic Personality Inventory and is purported to be a measure of hostility and anger (range of the HDHQ scale: 0 – 55). The assessment instrument consists of five subscales: (a) the urge to act out hostility, (b) criticism of others, (c) projecteddelusional or paranoid hostility, (d) self-criticism and (e) delusional guilt. The HDHQ subscales had clear construct validity (Arrindell et al., 1984). For the thesis, the

HDHQ scale had acceptable internal reliability, i.e., Cronbach's α = 0.76. Also, participants who reported low hostility levels (<15, i.e., low hostility) were classified in one category, while those who reported high hostility levels (≥15, i.e., frequent hostility) in the second category.

Health anxiety

The Whiteley Index (WI) was used to assess health anxiety at baseline. The WI was developed by Pilowsky to assess health anxiety and its items are based on clinicians' experiences of illness characteristics of severe health anxiety (Hedman et al., 2015). The final items of the scale were selected in part due to their ability to discriminate individuals with severe health anxiety from those without (Pilowsky, 1967). The WI has been shown to have high test-retest reliability (r = 0.81) and convergent validity (Pilowsky, 1967). For the present thesis, the WI scale showed acceptable internal reliability, i.e., Cronbach's α = 0.74. Moreover, for the thesis, participants were classified into two categories, those having low levels of health anxiety (<4, i.e., low health anxiety) and those having clinically meaningful symptoms of health anxiety (≥4 median).

Clinical and Biochemical Assessment

Blood samples were collected from the antecubital vein between 8 to 10 am, in a sitting position after 12 hours of fasting and alcohol abstinence. Serum for the measurement of these lipids was harvested immediately after admission. The biochemical evaluation was carried out in the same laboratory that followed thecriteria of the World Health Organization Lipid Reference Laboratories. All biochemical examinations (serum total cholesterol, oxidized LDL-cholesterol, HDL- cholesterol and triglycerides) were measured using chromatographic enzymic method in a Technicon automatic analyzer RA-1000 (Dade Behring, Marburg, Germany). We also measured apolipiproteins A1 and B, as well as lipoprotein-(a) by a latex enhanced turbidimetric immuno-assay. HDL cholesterol was determined after precipitation of the Apolipoprotein B containing lipoproteins with dextran- magnesium-chloride. LDL cholesterol calculated using the Friedewald formulae:

{total cholesterol} – {HDL cholesterol} – 1/5 (triglycerides). An internal quality control was in place for assessing the validity of cholesterol, triglyceride and HDL

methods. The intra and interassay coefficients of variation of cholesterol levels did not exceed 9%, of triglycerides 4% and of HDL 4%.

CRP was assayed by particle-enhanced immunonephelometry (N Latex, Date-Behring Marburg GmbH, Marburg, Germany) with a range from 0.175 to 1100 mg/L. IL-6 was measured with high sensitivity enzyme-linked immunoassay (R & D Systems Europe Ltd., Abingdon, UK) with a range from 0.156 to 10 pg/mL. The intraassay and interassay coefficients of variation were <5% for CRP and <10% for IL-6. Plasma fibrinogen levels were measured using a BNII Dade Behring automatic nephelometry. For the determination of fibrinogen, blood was anticoagulated with 3.8% trisodium citrate (9:1 vol/vol) and cooled on ice until centrifugation. The intraassay and interassay coefficients of variation of fibrinogen did not exceed 9%. We used the ELISA method for the quantitative determination of human TNF-a in duplicate in serum samples of the participants by Quantikine HS/human TNF-a immunoassay kit (R & D Systems, Inc. Minneapolis, USA).

Serum insulin concentrations were assayed by means of radioimmunoassay (RIA100, Pharmacia Co., Erlangen, Germany). Insulin sensitivity was assessed by the calculation of the homeostasis model assessment (HOMA) approach (glucose in mmol/l × insulin in µU/mL/22.5).

Blood glucose levels (mg/dL) were measured with a Beckman Glucose Analyzer (Beckman Instruments, Fullerton, CA, USA). Diagnosis of T2DM was based on the criteria of the American Diabetes Association, i.e., participants who had fasting blood glucose >125 mg/dL during the examination or reported use of anti- diabetic medication, were defined as having diabetes (ADA, 1997).

Hypercholesterolemia was defined as total cholesterol levels >200 mg/dL or the use of lipid-lowering agents.

Obesity was defined as BMI greater than 29.9 Kg/m^2, according to the World Health Organization (WHO) criteria (WHO, 2000). An abnormal WH ratio was considered >0.8 for women and >1 for men, whereas an abnormal WHt ratio was >0.5 for both sexes.

Arterial blood pressure was measured at the end of the physical examination with subject in sitting position and at least 30 minutes at rest. Blood pressure measurements were taken by a cardiologist, three times, at the right arm relaxed and well supported by a table, with an angle of 45° from the trunk (ELKA aneroid

manometric sphygmometer, Von Schlieben Co, Munich, Germany). The systolic blood pressure level was determined by the first perception of sound (of tapping quality). The diastolic blood pressure level was determined by phase V when the repetitive sounds become fully muffed (disappear). Changes in loudness were not considered. Patients whose average blood pressure levels were greater or equal to 140 / 90 mm Hg or were under antihypertensive medication were classified as hypertensives, as it is commonly done in epidemiological studies.

MetS was defined by the National Cholesterol Education Program Adult Treatment Panel III (revised NCEP ATP III) definition as if 3 or more of the following metabolic components are present: waist circumference ≥ 102 cm for malesor ≥ 88 cm for females; triglyceride level ≥ 150 mg/dL; HDL cholesterol level <40 mg/dL for males or <50 mg/dL for females; blood pressure ≥ 130/85 mmHg; fasting blood glucose ≥ 100 mg/dL (Grundy et al., 2005).

Also, the investigators of the study recorded a detailed medical history of the participants.

8.7 Ten-Year Follow-Up Examination

The 10-year follow-up was performed during 2011-2012. Of the initially enrolled 3,042 participants at baseline, 2,583 participated at follow-up examination (85% participation rate; of those lost to follow-up, n=224 could not be traced due to missing contact information and n=235 denied participating). Regarding the working subsample, only 8 out of the 853 participants were lost to follow-up; thus, 10-year psychological assessments concerning CVD outcomes were available for a total of 845 participants. Follow-up examination included the retrieval of detailed informationfrom participants' medical records. All participants were also clinically evaluated by trained study investigators. For the participants who died during the follow-up, information was obtained from their relatives, as well as death certificates.

The definition of the investigated CVD outcomes was based on the ICD- 9th or 10th version. Information about the CVD health status of each study participant included the development of

(a) myocardial infarction, angina pectoris, and other identified forms of ischemia [ICD-9 coding (or 10th edition)] [410-414.9, 427.2,427.6 (I20-I25)];

coronary revascularization (414.01) (i.e., coronary artery bypass surgery and percutaneous coronary intervention);

(b) Heart Failure of different types [400.0-404.9, 427.0-427.5, 427.9, 428.-(I50.2-)], and chronic arrhythmias (I49.-);

(c) development of stroke [430-438 (I63.-)].

The adjudication was made by trained study physicians and followed the ICD-10 rules (http://apps.who.int/classifications/icd10/browse/2010/en).

Diagnosis of T2DM at follow-up examination was based on the criteria of the American Diabetes Association (ADA) mentioned above (ADA, 1997). Diagnosis of the MetS at follow-up was based on the criteria of the revised NCEP ATP III as mentioned above (Grundy et al., 2005).

8.8 Twenty-Year Follow-Up Examination

At the 20-year follow-up (2002- May to October 2022), of the 3042 original participants, 2169 were found and agreed to be re-evaluated (71% participation rate). Of those lost to follow-up (n= 873), 771 were not found because of changed, missing, or incorrect addresses and telephone numbers and 102 because they refused to be re-screened. Regarding CVD evaluation at the 20-year follow-up, data without anymissing information were obtained from n=1988 participants. Of these, 512 subjects completed psychological evaluations.

Concerning the age-sex distribution of this working sample and the baseline, no differences were observed (p's>0.80). All participants were initially appointed through telephone calls, they were evaluated and invited to participate in the follow-up. Afterward, the investigators of the ATTICA study (i.e., physicians, nurses, and nutritionists) approached the participants and performed a detailed evaluation of their medical records. For the participants who died during the follow-up period, information was obtained from their relatives and certified vital records. The definition of the investigated outcomes was based on the ICD-10th version (for details see Panagiotakos et al, 2015).

8.9 Statistical Analysis

STATA version 17 (STATA Corp, College Station, Texas, USA) was used for the statistical analyses.

Crude non-fatal and fatal incidence rates of combined CVDs (i.e., coronary heart disease or stroke) were calculated as the ratio of new cases to the number of people that participated in each follow-up.

Continuous variables are presented as mean values ± standard deviation and categorical variables are presented as frequencies. Associations between categorical variables were tested using the chi-square test. Comparisons of mean values of normally distributed variables between those who developed an event, and the rest of the participants were performed using Student's t-test, after controlling for equality of variances using Levene's test. Continuous variables were tested for normality through P-P plots. For some continuous variables that were not normally distributed (e.g., CRP levels, years of school) the Mann-Whitney or the Kruskal-Wallis non-parametrictests were applied to evaluate the differences in the distributions of the skewedvariables between those who developed a CVD event and the rest of the participants.

The hazard ratios (HR) of developing a CVD event during the 10 years, according to baseline characteristics were estimated using Cox proportional hazards models. Proportionality was graphically tested. However, since the exact time to event (i.e., development of MetS) was not known, univariable and multivariable logistic regression models were used to estimate odds ratios (ORs) and their corresponding 95% confidence intervals (95% CI). The hazard ratios (HR) of developing a CVD event during the 20 years follow up, according to baseline characteristics were also estimated using Cox proportional hazards models. The time to the CVD event was recorded on an annual basis. To evaluate differences between groups of participants regarding CVD incidence, the log-rank test was also applied. Interactions between sex and other covariates were tested and remained in the model when significant. Additionally, known confounders (i.e., age, smoking, dietary habits, physical activity status, CRP levels, years of school, history of hypertension, diabetes, hypercholesterolemia, and family history of CVDs) were included in the risk models.

The Efron approximation was used for handling ties of person-years in the final model due to skewed time-to-event data.

All reported p-values were based on two-tailed hypotheses and compared to a significance level of 5%.

9. Results

9.1 Baseline Characteristics and Irrational Beliefs

The mean IBI score was 53 ± 11 for men and 53 ± 11 for women (p = 0.88). In addition, the mean STAI score was 40 ± 11 for men and 42 ± 12 for women (p < 0.001), the mean ZDRS score was 33 ± 7 for men and 37 ± 8 for women (p < 0.001) (***Figure 9.1***); the mean WI score was 4±3 for men and 4.2 ± 3 for women (p = 0.16), and the mean HDHQ score was 16 ± 6 for men and 17 ± 7 for women (p = 0.12) (***Figure 9.1)***.

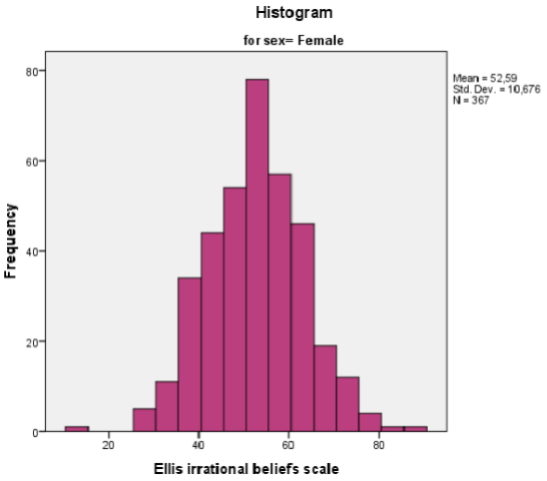
Participants' profile according to irrational beliefs status.

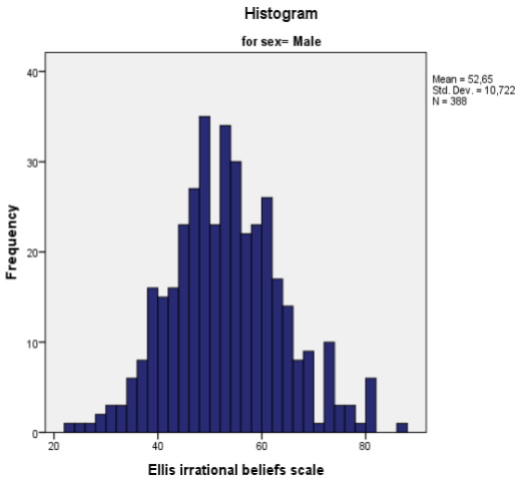
IBI score was positively correlated with the ZDRS score (r = 0.46, p < 0.001), the STAI score (r = 0.93, p < 0.001), the WI score (r = 0.39, p<0.001), and the HDHQ score (r= 0.42, p < 0.001) (***Figure 9.1)***. Moreover, unadjusted analysis revealed that IBI score was positively correlated with participants' age (r = 0.04, p = 0.01), but it was inversely correlated with years of education (r = − 0.93, p < 0.001), as well as with mean annual income (r = − 0.12, p = 0.001) and the combined SES status score (r = − 0.25, p = 0.001).

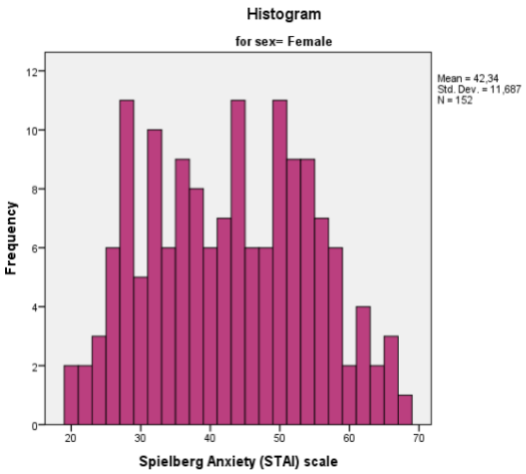
Regarding the dietary habits of the participants, IBI score was inversely correlated with the score that captured Mediterranean diet adherence, MedDietScore (r = − 0.08, p < 0.01). Moreover, IBI score was positively correlated with the frequency of the consumption of red meat (r = 0.15, p = 0.01), and soft and cola drinks (r = 0.21, p = 0.01).

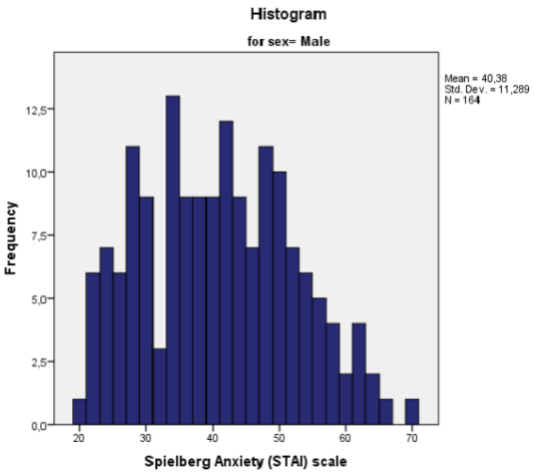
Concerning other clinical characteristics, the IBI score was positively associated with participants' history of diabetes (7.6% higher score among participants with diabetes as compared to those without, p = 0.02), and history of hypertension (3.8% higher score among participants with hypertension, p = 0.04),

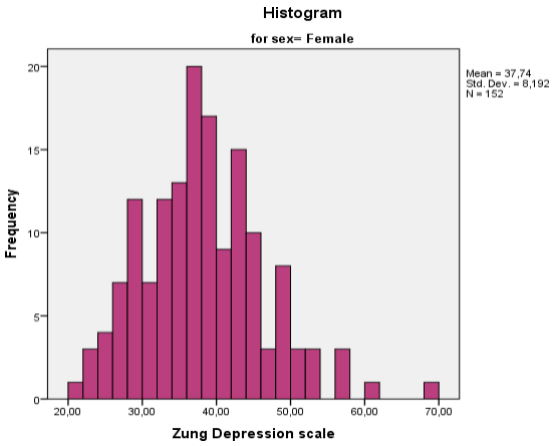
while no association with hypercholesterolemia, obesity, and MetS was observed (*all p-values*>0.70).

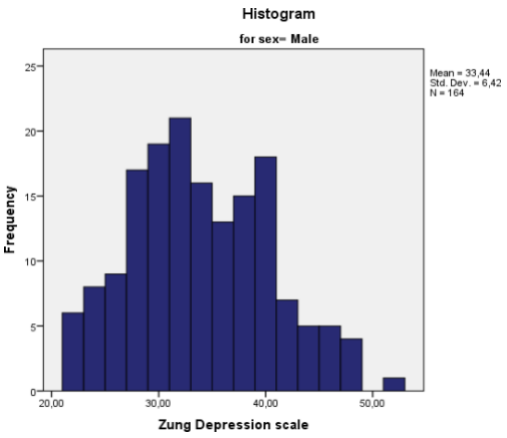












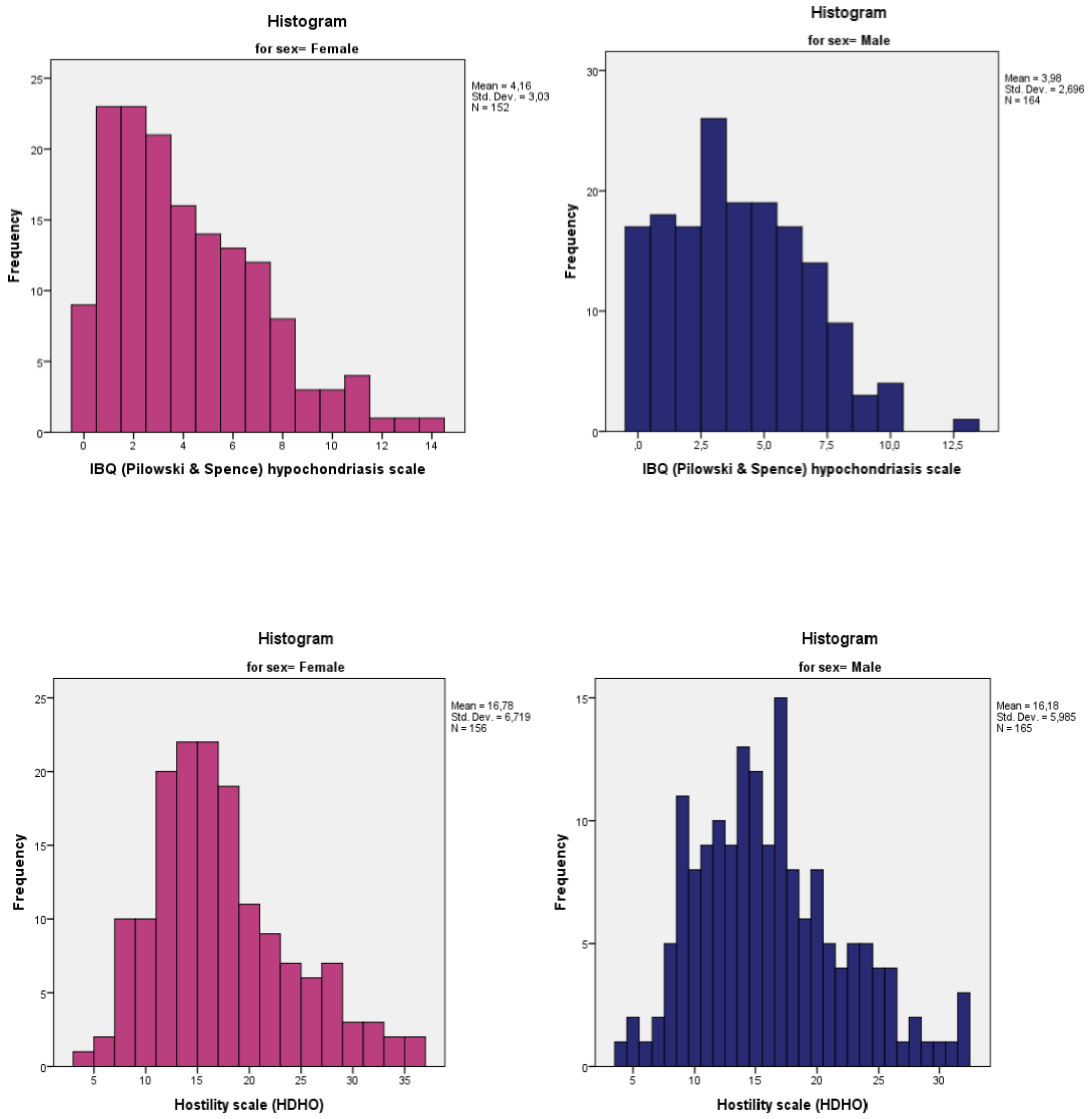


Figure 9.1: Histograms of psychological factors based on sex.

Irrational Beliefs and Socio-Economic Factors

An exploratory analysis was conducted to learn more about the participants' profiles based on their IBI categorization. ***Table 1.1*** demonstrated the socio-economic profile of participants based on their irrational beliefs' categorization. It showed that those in the highest tertile were older, and less educated, as they reported fewer school years, and they had a manual labour job and lower annual income (*all p-values*

< 0.02) than those in the lowest IBI tertiles. However, there were no associations between the participants' irrational beliefs status and sex, marital status, and number of children (*all p-values* >0.10) (***Table 1.1***).

Table 1.1: Irrational beliefs and baseline socio-economic factors and characteristics, from the ATTICA study (n=853)

		IBI tertiles			
	Overall sample	**1st (Low)**	**2nd (Moderate)**	**3rd (High)**	***p***
Age, years [Mean (SD)]	39±11	45±9	43±13	48±17	**<0.001**
Sex, %male	388 (52%)	142 (53%)	113 (49%)	113 (52%)	0.62
Educational status, years of school [Mean (SD)]	13±3	16±1	13±2	7±3	**<0.001**
Profession, %					
Manual	97 (13%)	28 (11%)	26 (11%)	43 (17%)	**0.015**
Semi-manual	115 (15%)	35 (13%)	42 (18%)	38 (15%)	
Semi-skilled	237 (31%)	77 (29%)	67 (29%)	93 (36%)	
Skilled	302(40%)	122 (46%)	97 (42%)	83 (32%)	
Marital status, %					
Never married	251 (33%)	87 (33%)	81 (34%)	83 (32%)	0.81
Married	44 (61%)	164 (61%)	143 (61%)	157 (61%)	
Divorced	40 (5%)	15 (6%)	10 (4%)	15 (6%)	
Widowed	8 (1%)	2 (1%)	2 (1%)	4 (2%)	
Number of children [Median (SD)]	2±1	2±1	2±1	2±1	0.13
Financial status, %low					
Bad	157 (21%)	46 (18%)	43 (18%)	68 (27%)	**0.001**
Poor	201 (26%)	61 (23%)	67 (29%)	73 (29%)	
Good	255 (33%)	102 (39%)	72 (31%)	81 (32%)	
Very good	138 (18%)	52 (20%)	52 (22%)	52 (13%)	
Socio-economic	72 (9%)	17 (6%)	26 (11%)	29 (12%)	**0.001**

status, %low	

Data are presented as mean ± standard deviation (SD) (i.e., mean (SD)). *P*-values were obtained using one-way analysis of variance for independent samples for the normally distributed variables, Kruskal–Wallis test for the rest of the quantitative variables, and chi-squared test for categorical variables.

Irrational Beliefs and Lifestyle Factors

An exploratory analysis was also conducted to learn more about the participants' lifestyle profiles based on their IBI categorization. Regarding smoking status, ***Table 1.2*** showed that those in the highest IBI tertile were away from the Mediterranean diet, and more precisely, they consumed fewer vegetables, fish and fisheries, low-fat dairy products and less wine, whereas they consumed more potatoes and soft drinks (such as cola drinks) (*all p-values* < 0.05), compared to the other two categorizations.

Yet, there were no statistically significant differences regarding a) smoking status, including current and never smokers, cigarette packages, years of smoking, exposure to passive smoking and passive smoking at work (*all p-values* >0.50), b) physical activity status, including sedentary lifestyle, exercise type and duration, walking, weight lift and sports (*all p-values* >0.10), c) legumes, non-refined cereals and products, fruits, dry fruits, meat, red meat, poultry, eggs, nuts, sweets, dairy products, fats and oils, coffee, alcohol, beer, and energy and macronutrients (*all p- values* >0.10) (***Table 1.2)***.

Table 1.2: Irrational beliefs and baseline lifestyle factors and characteristics, from the ATTICA study (n=853)

		IBI tertiles			
	Overall sample	**1st (Low)**	**2nd (Moderate)**	**3rd (High)**	***p***
Smoking status					
Never smokers, %	309 (41%)	102 (38%)	99 (42%)	108 (42%)	0.64
Current smoking, %	356 (47%)	118 (44%)	115 (49%)	123 (47%)	0.54
Cigarette packages, per year [Mean (SD)]	414±403	486±439	475±357	551±400	0.69
Years of smoking [Mean (SD)]	17±10	19±7	20±9	20±8	0.76

Exposed to passive smoking, %	568 (74%)	194 (74%)	179 (77%)	195 (76%)	0.06
Passive smoking at work, %	488 (64%)	164 (63%)	150 (65%)	174 (69%)	0.06
Physical activity status					
Sedentary life, %	439 (58%)	141 (53%)	137 (60%)	155 (60%)	0.14
Walking, no%	422 (60%)	146 (59%)	133 (61%)	142 (61%)	0.22
Exercise type, %					
Minimally active	483 (63%)	161 (60%)	157 (67%)	165 (64%)	0.62
Moderate aerobic	209 (27%)	76 (28%)	63 (27%)	70 (27%)	
Aerobic HEPA	22 (3%)	10 (4%)	4 (2%)	8 (3%)	
Aerobic & Resistance	49 (6%)	21 (8%)	12 (5%)	16 (6%)	
Exercise duration, per minute	62±44	63±46	63±44	60±40	0.30
Weight lift, %yes	50 (55%)	16 (49%)	14 (50%)	20 (69%)	0.22
Sports, %yes	61 (12%)	28 (15%)	13 (8%)	20 (12%)	0.31
Dietary status					
MedDietScore (0-55) [Mean (SD)]	27±8	26±6	26±7	23±7	**<0.001**
Vegetables, servings/week [Mean (SD)]	34±15	40±16	34±16	30±11	**0.001**
Legumes, servings/week [Mean (SD)]	5±3	5±2	5±2	5±2	0.38
Non-refined cereals and products, servings/week [Mean (SD)]	53±19	52±14	54±15	47±24	0.79
Potatoes, servings/week [Mean (SD)]	12±7	9±5	11±6	13±5	**0.001**
Fruits, servings/week [Mean (SD)]	26±13	26±13	24±13	22±8	0.73
Dry fruits, servings/week [Mean (SD)]	7±6	6±4	7±7	5±6	0.12
Meat, servings/week [Mean (SD)]	6±3	6±2	5±2	6±2	0.48
Red meat, servings/week [Mean (SD)]	5±2	5±2	4±2	5±1	0.43
Poultry, servings/week [Mean (SD)]	1±1	1±0.4	1±0.4	1±0.4	0.96
Fish and fisheries, servings/week [Mean (SD)]	2±1	2±1	2±1	1±1	**0.009**
Eggs, servings/week [Mean (SD)]	1±1	1±1	1±1	1±2	0.69
Nuts, servings/week [Mean (SD)]	2±2	1±1	1±1	1±1	0.09
Sweets, servings/week [Mean (SD)]	5±2	5±3	5±2	3±2	0.87
Dairy products, servings/week [Mean (SD)]	12±5	12±4	11±5	13±7	0.83
Low-fat dairy, servings/week [Mean	3±3	3±3	2±2	2±3	**0.029**

(SD)]					
Fats and Oils					
Olive oil (daily use, %yes)	760 (100%)	267 (100%)	235 (100%)	258 (100%)	0.99
Seed oil (daily use, %yes)	3 (4%)	1 (0.4%)	1 (0.4%)	1 (0.4%)	0.99
Butter (daily use, %yes)	760 (100%)	267 (100%)	235 (100%)	258 (100%)	0.63
Margarine (daily use, %yes)	27 (4%)	8 (9%)	11 (13%)	8 (10%)	0.59
Soft drinks					
Soft drinks, glasses/day [Mean (SD)]	3±2.5	2±2	2±2	3±3	**0.019**
Cola drinks, glasses/day [Mean (SD)]	2±2	1±2	1±2	3±2	**0.05**
Other drinks					
Coffee, cups/day [Mean (SD)]	1±0.5	1±0.5	1±1	2±1	0.38
Alcohol, g/day [Mean (SD)]	9±14	8±7	17±28	8±12	0.36
Beer, glass/day [Mean (SD)]	2±1	2±1	2±1	2±1	0.08
Wine, glass/day [Mean (SD)]	2.2±1	2.2±1	2±1	1.8±1	**<0.001**
Energy & macronutrient intake					
Energy (kcal/day) [Mean (SD)]	2205±836	2166±759	1944±526	2047±952	0.74
Carbohydrates (g/day) [Mean (SD)]	207±97	192±84	172±53	183±76	0.25
Total proteins (g/day) [Mean (SD)]	81±37	77±21	68±18	66±26	0.16
Total lipids (g/day) [Mean (SD)]	89±45	86±30	79±23	74±30	0.30
Monounsaturated fatty acids (g/day) [Mean (SD)]	60±31	57±21	54±18	50±19	0.36
Polyunsaturated fatty acids (g/day) [Mean (SD)]	17±11	18±10	16±6	14±7	0.97
Saturated fatty acids (g/day) [Mean (SD)]	36±19	34±10	30±10	29±13	0.06

Data are presented as mean ± standard deviation (SD) (i.e., mean (SD)). *P-values* were obtained using one-way analysis of variance for independent samples for the normally distributed variables, Kruskal– Wallis test for the rest of the quantitative variables, and chi-squared test for categorical variables.

Irrational Beliefs and Anthropometric Factors

In the exploratory analysis concerning the participants' anthropometric profile, based on their IBI categorization, individuals with high irrational beliefs had an

increased waist circumference but a decreased BMI compared to the other two categorizations (*all p-values* < 0.02) (***Table 1.3***). Still, no statistically significant differences were observed between IBI tertiles and height, basal metabolic rate (BMR), hip circumference, and abnormal WH ratio (*all p-values* >0.70) (***Table 1.3***).

Table 1.3: Irrational beliefs and baseline anthropometric factors and characteristics, from the ATTICA study (n=853)

		IBI tertiles			
	Overall sample	**1st (Low)**	**2nd (Moderate)**	**3rd (High)**	***p***
Body Mass Index (kg/m^2) [Mean (SD)]	26± 4	25±5	25±4	24±4	**<0.001**
Height (cm) [Mean (SD)]	171±9	175±10	172±9	171±10	0.07
Weight (kg) [Mean (SD)]	75±16	81±20	85±15	87±12	0.37
Basic Metabolic Rate (kcal/day) [Mean (SD)]	1616±275	1711±301	1746±267	1719±246	0.65
Waist circumference (cm) [Mean (SD)]	89±16	100±24	98±13	102±11	**0.01**
Hip circumference (cm) [Mean (SD)]	102±13	103±9	102±11	102±12	0.90
Abnormal waist-to-hip ratio, %	233 (31%)	80 (31%)	73 (32%)	80 (31%)	0.99

Data are presented as mean ± standard deviation (SD) (i.e., mean (SD)). *P-values* were obtained using one-way analysis of variance for independent samples for the normally distributed variables, Kruskal– Wallis test for the rest of the quantitative variables, and chi-squared test for categorical variables.

Irrational Beliefs and Biochemical Factors

An exploratory analysis was also conducted to learn more about biochemical factors based on IBI categorization. In ***Table 1.4*** it can be seen that people with high irrational beliefs had higher fasting glucose, insulin and triglycerides, totalcholesterol, and fibrinogen levels, whereas they had lower LDL-C levels compared to the other two categorizations (*all p-values* < 0.04). On the opposite, there was no association with pulse pressure, SBP and DBP, HDL-C, TNF-α, and TAC (*all p- values* > 0.07) (***Table 1.4***).

Table 1.4: Irrational beliefs and baseline biochemical factors and characteristics, from the ATTICA study (n=853)

		IBI tertiles			
	Overall sample	**1st (Low)**	**2nd (Moderate)**	**3rd (High)**	***p***
Fasting glucose (mg/dL) [Mean (SD)]	89±20	87±15	86±10	98±41	**0.02**
Fasting Insulin (μU/ml) [Mean (SD)]	13±2	13±2	13±1	14±4	**0.004**
Triglycerides (mg/dL) [Mean (SD)]	103±64	123±67	129±60	144±64	**0.03**
Pulse pressure (mmHg) [Mean (SD)]	39±11	39±9	35±13	45±8	0.81
Systolic Blood Pressure (mm Hg) [Mean (SD)]	117±17	120±13	120±18	125±13	0.37
Diastolic Blood Pressure (mm Hg) [Mean (SD)]	78±12	81±9	84±12	80±8	0.34
Total Cholesterol (mg/L) [Mean (SD)]	184±38	189±31	195±49	200±42	**0.03**
HDL-cholesterol (mg/L) [Mean (SD)]	49±13	42±13	42±11	43±10	0.07
LDL-cholesterol (mg/L) [Mean (SD)]	115±35	117±30	115±40	103±36	**0.01**
C-reactive protein (mg/L) [Mean (SD)]	2 ± 2.5	1.6 ± 2	2 ± 3	2± 2	**<0.001**
Interleukin 6 (IL-6) (pg/ml) [Mean (SD)]	1.4±0.3	1.3±0.3	1.4±0.3	1.3±0.3	**<0.001**
TNF-alpha (pg/ml) [Mean (SD)]	6±3	6±3	7±3	6±3	0.49
Total antioxidant capacity (μmol/L) [Mean (SD)]	235±43	238±37	234±41	235±52	**0.007**
Total antioxidant capacity (μmol/L) [Mean (SD)]	60±30	67±37	59±28	59±30	0.43
Fibrinogen (mg/dL) [Mean (SD)]	298±62	299±64	287±60	311±70	**<0.008**

Data are presented as mean ± standard deviation (SD) (i.e., mean (SD)). *P-values* were obtained using one-way analysis of variance for independent samples for the normally distributed variables,

Kruskal– Wallis test for the rest of the quantitative variables, and chi-squared test for categorical variables.

Irrational Beliefs and Clinical Factors

In ***Table 1.5*** the clinical factors regarding IBI tertiles aredemonstrated. Participants' history of hypercholesterolemia ($p < 0.001$), hypertension ($p = 0.02$), obesity ($p < 0.001$), and diabetes mellitus ($p < 0.001$) were more prevalent in those with a high level of irrational beliefs. Furthermore, participants in the lowest IBI tertile had a 7.8% incidence compared to 7.6% among those in the middle and 8.6% among those in the highest tertile (p for trend <0.001) (***Table 1.5***). However, there were no associations with a family history of hypertension, hypercholesterolemia, diabetes, CVDs, and MetS status at the 10-year follow-up (*all p-values* > 0.07) (***Table 1.5***).

Table 1.5: Irrational beliefs and clinical factors and characteristics, from the ATTICA study (n=853)

		IBI tertiles			
	Overall sample	**1st (Low)**	**2nd (Moderate)**	**3rd (High)**	***p***
Hypertension, %yes	178 (25%)	53 (20%)	55 (24%)	70 (28%)	**0.02**
Hypercholesterolemia, % yes	227 (30%)	74 (27%)	71 (30%)	82 (32%)	**<0.001**
Obesity, %yes	384 (51%)	128 (48%)	126 (54%)	130 (50%)	**<0.001**
Metabolic syndrome, %yes	103 (11%)	25 (9%)	34 (14%)	43 (17%)	**0.005**
Diabetes mellitus, %yes	27 (4%)	8 (3%)	7 (3%)	12 (5%)	**<0.001**
Family history of hypertension, %yes	151 (30%)	57 (33%)	51 (33%)	43 (24%)	0.31
Family history of hypercholesterolemia, %yes	345 (71%)	108 (66%)	114 (75%)	123 (73%)	0.18
Family history of diabetes, %	227 (25%)	58 (22%)	66 (28%)	62 (24%)	0.07
Family history of CVDs, %	279 (37%)	97(37%)	85 (37%)	97 (38%)	0.97
MetS status at 10-year follow-up, %yes	203 (54%)	70 (49%)	65 (63%)	68 (49%)	0.93
CVD status at 10-year follow-up, %yes	42(8%)	15 (8%)	12 (8%)	15 (9%)	**<0.001**

Data are presented as mean ± standard deviation (SD) (i.e., mean (SD)). *P-values* were obtained using one-way analysis of variance for independent samples for the normally distributed variables, Kruskal– Wallis test for the rest of the quantitative variables, and chi-squared test for categorical variables.

Irrational Beliefs and Psychological Factors

As it was demonstrated in ***Table 1.6***, depression, anxiety, and health anxiety symptomatology, as well as hostility were more prevalent in individuals with high irrational beliefs (*all p-values* $p < 0.001$). However, regarding physical well-being, there was no statistically significant association ($p = 0.57$) (***Table 1.6***).

Table 1.6: Irrational beliefs, psychological factors, and well-being, from the ATTICA study (n=853)

		IBI tertiles			
	Overall sample	**1st (Low)**	**2nd (Moderate)**	**3rd (High)**	***p***
Zung self-rating Depression Scale (range 0–80), [Mean (SD)]	35±7	34±2	35±2	37±2	**<0.001**
Spielberger State-Trait Anxiety Inventory (range 0–80), [Mean (SD)]	41±2	38±2	41±2	46±2	**<0.001**
Hostility and Direction of Hostility Questionnaire (range 0–51), [Mean (SD)]	16±6	15±5	16±6	20±7	**<0.001**
Whiteley Index for Health Anxiety (WI)(range 0-14), [Mean (SD)]	4±3	3±2	4±3	6±7	**0.001**
Quality of life					
The EQ-5D questionnaire of physical well-being [Mean (SD)]	8±1	8±1	8±1	8±1	0.57

Data are presented as mean ± standard deviation (SD) (i.e., mean (SD)). *P*-values were obtained using one-way analysis of variance for independent samples for the

normally distributed variables, Kruskal– Wallis test for the rest of the quantitative variables, and chi-squared test for categorical variables.

9.2 Ten-year Cardiovascular Disease Incidence

The 10-year incidence of CVDs was 43 (5.1%) per 845 participants who developed either fatal (n = 2) or non-fatal (n = 41) events (i.e., 508 events per 10,000 individuals); of them n = 31 (72%) were men and n = 12 (28%) were women (p for gender difference = 0.004). In ***Table 2.1***, various demographic, lifestyle, clinical, and psychological characteristics of the participants are presented, according to their CVD outcome.

Regarding socio-economic factors, participants who developed a CVD event were mainly men, married, of older age, lower educational status, non-skilled profession, but of good financial status (*all p-values ≤0.05),* compared to those who did not develop a CVD event (***Table 2.1)***. Regarding lifestyle factors, those who developed a CVD event smoked more cigarette packages per year, and for more years, but were less exposed to passive smoking at work, with lower adherence to the Mediterranean diet, less energy intake and carbohydrates, proteins, total lipids, monounsaturated and saturated fatty acids consumption (*all p-values ≤0.05),* compared to those who did not develop a CVD (***Table 2.1)***. As far as anthropometric and biochemical factors are concerned, those who developed CVDs had higher weight, BMI, BMR, waist and hip circumference, and abnormal WH ratio, as well as higher fasting glucose, insulin and triglycerides levels, higher SBPs and DBP, increased total and LDL-C, but lower HDL-C, higher IL-6, TNF-α, but lower fibrinogen levels (*all p-values ≤0.05)* than those who did not develop a CVD. As for clinical factors, individuals who had a CVD event had a higher prevalence of hypercholesterolemia, diabetes mellitus, hypertension, MetS (p < 0.05), and obesity (p
= 0.05) (***Table 2.1***). Finally, concerning psychological factors, participants who developed a CVD event during the follow-up period had higher IBI scores as compared to those who did not present any CVD event during the follow-up (p < 0.001), as well as higher ZDRS (p < 0.001), and tended to have higher STAI (p = 0.08).

However, there was no association with SES, marital status, number of children, smoking status, sedentary lifestyle, exercise type, height, pulse pressure, CRP, TAC, ox-LDL, hostility, health anxiety, and cognitive distortions (*all p- values>0.06).*

Table 2.1: Baseline demographic, anthropometric, biological, clinical, and psychological characteristics of the study participants by the 10-year cardiovascular disease (CVD) incidence (n=845)

	CVD event during the 10-year follow-up No (n=802) n (%)	**CVD event during the 10-year follow-up Yes (n=43) n (%)**	***p***
Socio-economic factors			
Age, years [Mean (SD)]	38±11	48±11	**<0.001**
Sex (%men)	258 (49%)	31 (72%)	**0.004**
Educational status (%low)	38 (8%)	8 (19%)	**0.001**
Profession, %			
Manual	57 (12%)	6 (15%)	**0.003**
Semi-manual	61 (13%)	7 (17%)	
Semi-skilled	145 (31%)	22 (54%)	
Skilled	204 (44%)	6 (15%)	
Marital status (%married)	299 (62%)	28 (65%)	0.63
Number of children [Median (SD)]	2±1	2±1	0.40
Financial status, %			
Bad	109 (23%)	5 (12%)	**0.05**
Poor	119 (26%)	10 (24%)	
Good	152 (33%)	22 (52%)	
Very good	85 (18%)	5 (12%)	
Socio-economic status (%low)	118 (23%)	8 (19%)	0.53
Lifestyle factors			
Current smoking, %	294 (56%)	23 (54%)	0.77
Cigarette packages, per year	407±383	668±625	**0.016**
Years of smoking [Mean (SD)]	20±7	26±11	**<0.001**

Exposed to passive smoking, %	358 (77%)	27 (64%)	0.07
Exposed to passive smoking at work, %	313 (68%)	19 (46%)	**0.006**
Sedentary life, %	298 (57%)	23(54%)	0.69
Exercise type, %			
Minimally active	297 (63%)	25 (60%)	0.89
Moderate aerobic	130 (28%)	12 (29%)	
Aerobic HEPA	13 (3%)	2 (5%)	
Aerobic & Resistance	33 (7%)	3 (7%)	
MedDietScore (0-55) [Mean (SD)]	27±8	24±4	**<0.001**
Energy (kcal/day) [Mean (SD)]	2111±587	1424±533	**0.02**
Carbohydrates (g/day) [Mean (SD)]	183±591	114±40	**0.05**
Total proteins (g/day) [Mean (SD)]	74±19	49±14	**0.01**
Total lipids (g/day) [Mean (SD)]	85±25	61±26	**0.02**
Monounsaturated fatty acids (g/day) [Mean (SD)]	58±19	42±17	**0.03**
Polyunsaturated fatty acids (g/day) [Mean (SD)]	17±7	12±9	0.174
Saturated fatty acids (g/day) [Mean (SD)]	33±10	23±10	**0.01**
Anthropometric factors			
Body Mass Index (kg/m^2) [Mean (SD)]	24±4	27±4	**<0.001**
Height (cm) [Mean (SD)]	172±10	178±6	0.74
Weight (kg) [Mean (SD)]	82±17	94±13	**0.001**
BMR (kcal/day)[Mean (SD)]	1575 ± 1102	1693 ± 1232	**0.04**
Waist circumference (cm) [Mean (SD)]	99±19	106±14	**0.001**
Hip circumference (cm) [Mean (SD)]	102±13	106±7	**0.008**
Abnormal waist-to-hip ratio, %	145 (45%)	18 (61%)	**0.05**
Biochemical factors			
Fasting glucose (mg/dL) [Mean (SD)]	87±13	94±9	**0.001**
Fasting Insulin (μU/ml) [Mean (SD)]	12±1	14±1	**<0.001**
Triglycerides (mg/dL) [Mean (SD)]	91±50	153±100	**<0.001**

Pulse pressure (mmHg) [Mean (SD)]	37±12	41±11	0.26
Systolic Blood Pressure (mm Hg)[Mean (SD)]	119±16	127±19	**0.004**
Diastolic Blood Pressure (mm Hg) [Mean (SD)]	82±11	86±15	**0.006**
Total Cholesterol (mg/L) [Mean (SD)]	186±35	235±50	**<0.001**
HDL-cholesterol (mg/L) [Mean (SD)]	41±12	36±10	**0.003**
LDL-cholesterol (mg/L) [Mean (SD)]	121±34	155±57	**<0.001**
C-reactive protein (mg/L) [Mean (SD)]	1±3	2±1	0.19
Interleukin 6 (IL-6) (pg/ml) [Mean (SD)]	1.2±0.3	1.3±0.1	**<0.001**
TNF-alpha (pg/ml) [Mean (SD)]	6±3	7±2	**<0.001**
Total antioxidant capacity (μmol/L) [Mean (SD)]	237±46	231±16	0.56
Oxidized LDL-C (mg/dL) [Mean (SD)]	62±32	74±50	0.72
Fibrinogen (mg/dL) [Mean (SD)]	301±62	284±80	**0.001**
Clinical factors			
Hypertension, %	124 (24%)	19 (44%)	**0.004**
Hypercholesterolemia, %	144 (27%)	20 (47%)	**0.008**
Obesity, %yes	67 (13%)	10 (23%)	**0.05**
Metabolic syndrome, %	65 (12%)	15 (35%)	**<0.001**
Diabetes mellitus, %	12 (2%)	5 (12%)	**0.006**
Psychological factors			
Irrational Beliefs Inventory (range 0-88), [Mean (SD)]	51±3	54±2	**0.001**
Zung self-rating Depression Scale (range 0–80), [Mean (SD)]	34±2	36±2	**0.001**
Spielberger State-Trait Anxiety Inventory (range 0–80), [Mean (SD)]	41±12	44±13	0.08
Hostility and Direction of Hostility Questionnaire (range 0–51), [Mean (SD)]	14±5	14±4	0.95
Whiteley Index for Health Anxiety (WI) (range 0-14), [Mean (SD)]	3±3	4±3	0.48

Data are presented as mean ± standard deviation (SD) (i.e., mean (SD)). *P-values* were obtained using one-way analysis of variance for independent samples for the

normally distributed variables, Kruskal– Wallis test for the rest of the quantitative variables, and chi-squared test for categorical variables.

9.2.1 The Association between Irrational Beliefs and 10-year CVD Incidence

Participants who developed CVDs throughout the 10-year follow-up had a 10.6% higher IBI score at baseline examination than those who did not develop (i.e., 54/80 vs. 51/ 80, p = 0.001). However, residual confounding might exist, particularly when several associations have already been reported between irrational beliefs and the investigated biological, psychological, behavioural, and medical factors. Thus, multi-adjusted analysis was applied.

9.2.2 The Mediating or Moderating Effect of MetS between Irrational Beliefs and CVDs

During 2002-2012, the overall crude 10-year MetS incidence was n = 239cases (40.4%), or 404 / 1000 participants; of them, n = 121 (50%) were men and n = 118 (46.6%) were women (p for sex differences = 0.455).

The Mediating Effect of MetS between Irrational Beliefs and CVDs

After adjustment for sex and age, IBI score was still significantly positively associated with 10-year CVD incidence in both men and women (p for interaction = 0.97). Specifically, for 1-unit increase in IBI score, a 7% higher risk for a CVD event was revealed (***Table 3.1***, *Model 1*). The latter association remained significant even when adjusting for potential confounding factors such as smoking habits, physical activity status, and level of adherence to the Mediterranean diet (***Table 3.1,*** *Model 2)*.

However, when MetS introduced in the model (*Models 3, 4, and 5*), the association between irrational beliefs and 10-year CVD risk became insignificant (HR 1.04, 95% CI 0.96, 1.13), revealing a strong mediation effect of MetS (2.40, 95% CI 1.60, 3.55) (***Table 3.1***). No mediation effect of anxiety and depression was observed (p>0.05).

Table 3.1: Results from nested, multi-adjusted models that evaluated the association between irrational beliefs index score and 10-year incidence of cardiovascular disease (results are presented as hazard ratios and 95% confidence intervals)

	Model 1	Model 2	Model 3	Model 4	Model 5
IBI[a] score (20–88, per 1 unit)	1.07 (1.01,1.12)*	1.07 (1.01,1.12)*	1.04 (0.96,1.13)	1.00 (0.96,1.03)	1.07 (0.95,1.20)
Current smoker (yes vs. no)	-	1.33 (1.01,1.83)*	1.00 (0.98,1.01)	1.21 (0.61,2.40)	1.00 (0.99,1.01)
Physical activity (moderate/high vs. low)	-	0.87 (0.68, 1.15)	0.93 (0.70,1.22)	1.80 (0.70,4.64)	0.93 (0.70,1.23)
MedDietScore (per 1 unit)	-	0.97 (0.95,0.99)*	0.96 (0.92,1.00)	0.98 (0.92,1.04)	0.96 (0.92,0.99)*
Metabolic syndrome	**-**	**-**	**2.40 (1.60,3.55)**	**2.38 (1.60,3.60)**	**2.36 (1.58,3.54)**
ZDRS[b] (20–80, per 1 unit)	-	-	-	0.54 (0.27,1.06)	-
STAI[c] (20–80, per 1 unit)	-	-	-	-.	0.80 (0.41,1.57)

All models are age and sex adjusted
* *p*-values < 0.05
[a] Irrational beliefs inventory
[b] Zung Self-Rating Depression Scale
[c] Spielberger State-Trait Anxiety Inventory

The Moderating Effect of MetS between Irrational Beliefs and CVDs

An interaction analysis was also performed to identify potential synergistic effect of participants' irrational beliefs and MetS on the CVD incidence. Since the analysis revealed a significant interaction between irrational beliefs and MetS (p <0.001), we proceeded to perform a stratified analysis. Thus, when we focused on those with high irrational beliefs, who also had MetS, their likelihood of CVD incidence was 1.6 times higher than those with low irrational beliefs (HR= 1.66, 95% CI= 1.04, 2.67). No significant association was observed between irrational and CVD incidence, among those who had no MetS (*see* ***Figure* 9.2**).

Therefore, MetS affected both the strength and the direction of the relationship between irrational beliefs and 10-year CVD incidence.

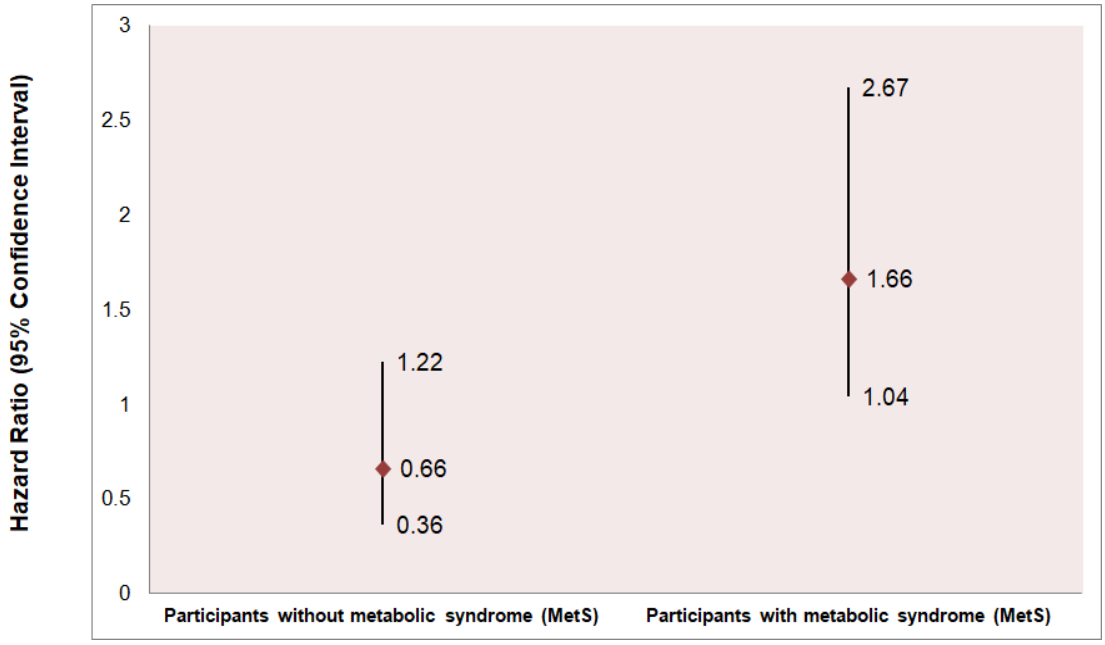


Figure 9.2: Results from the multi-adjusted logistic regression models evaluating the association between the participants' levels of irrational beliefs (moderate/high vs. low) with the 10-year incidence of CVDs, according to MetS level (no/yes) (results are presented as hazard ratios and 95% confidence intervals). Hazard ratios are adjusted for age, sex, educational level, smoking status, level of adherence to the Mediterranean diet, depression, and anxiety

9.2.3 The Role of Lifestyle Factors and Irrational Beliefs in MetS and CVDs

Dietary patterns according to irrational beliefs, anxiety, and depression

The main goal of this analysis was to extract dietary patterns according to irrational beliefs status.

Factor analysis identified 17 factors (dietary patterns) in total; however, five principal factors were identified for the participants with high-IBI/low-STAI scores that explained 63% of the total variation in consumption, and four factors for high- IBI/high-STAI (that explained 53% of the total variation), high-IBI/low-ZDRS (that

explained 54% of the total variation) and high-IBI/high-ZDRS (that explained 54% of the total variation), respectively.

The following factors, which are characterized by the main consumption of the food groups, have been derived:

High-IBI/low-STAI:

Factor 1: High refined carbohydrates and fats pattern.

Factor 2: High-protein and fats pattern.

Factor 3: Meat and light soft drinks consumption pattern.

Factor 4: Alcohol drinking pattern, low in sugar-sweetened soft drinks.

Factor 5: Pattern based on dairy products.

Factor 1 was the most prevailing dietary pattern and explained 19% of the total variation. Each of the remaining four factors explained from 8% (factor 5) to 14% (factor 2) of the variation in intake.

High-IBI/high-STAI:

Factor 1: Western-type dietary pattern.

Factor 2: High in light soft drinks and fats pattern.

Factor 3: Fruits and fish pattern.

Factor 4: Low-fat dairy products pattern.

Factor 1 was the most dominant dietary pattern and explained 20% of the totalvariation. Each of the remaining three factors explained 9% (factor 4) to 12% (factor 2) of the variation in intake.

High-IBI/low-ZDRS:

Factor 1: High refined carbohydrates and fats pattern.

Factor 2: High-carbohydrate, nuts, and alcohol fats pattern.

Factor 3: Meat-based pattern.

Factor 4: Pattern based on dairy products and sugar-sweetened carbonated drinks.

Factor 1 was the most dominant dietary pattern and explained 19% of the totalvariation. Each of the remaining three factors explained 9% (factor 4) to 14% (factor 2) of the variation in intake.

High-IBI/high-ZDRS:

Factor 1: Western-type dietary pattern.

Factor 2: High in light soft drinks and fats pattern.

Factor 3: “Healthy” dietary pattern.

Factor 4: Low-fat dairy pattern, low in alcohol.

Factor 1 was the most prevailing dietary pattern and explained 21% of the total variation. Each of the remaining three factors explained 9% (factor 4) to 12% (factor 2) of the variation in intake.

Thus, emotional state in addition to irrational beliefs predicted a diet close to a “Western” dietary pattern (i.e., high consumption of red meat, high-fat dairy products, butter, sweets, and refined grains), whereas, the absence or lowered levels of anxiety and depression in addition to irrational beliefs predicted a less unhealthy dietary profile.

Adherence to the Mediterranean diet in relation to irrational beliefs, anxiety, and depression status

In general, an age-adjusted, inverse correlation was observed between the IBI score and MedDietScore (r = -0.11, p = 0.01). Similarly, MedDietScore was inversely correlated with STAI (r men = -0.11, $p < 0.001$, r women = -0.20, $p < 0.001$), but was positively correlated with ZDRS (r men = 0.13, $p < 0.001$, r women = 0.17, $p < 0.001$). Regarding the association between adherence to the Mediterranean dietary pattern and irrational beliefs, in conjunction with anxiety and depression, it was observed that individuals with a high IBI and a low STAI scored 28 ± 6 in the MedDietScore index, whereas individuals with a high IBI and a high STAI scored much lower (23 ± 7 ($p <$ 0.001)). However, individuals with a high IBI and a low ZDRS scored 23 ± 5 in the MedDietScore index, while those with a high IBI but a high ZDRS scored higher (i.e., 26 ± 7 ($p < 0.001$)).

Multiple linear regression analysis was used to examine the association between adherence to the Mediterranean diet and the IBI-STAI or ZDRS status of the participants, taking into consideration age, sex, socio-economic status, smoking habits, and physical activity, as well as any history of hypertension, hypercholesterolemia, diabetes, and obesity to account for potential confounding. The analysis revealed that participants with a high IBI had a lower MedDietScore as

compared to those with a low IBI (b coefficient = - 0.95, 95% CI -1.24, -0.66, *p* = 0.001). Moreover, participants with a high IBI but low STAI scores had a higher MedDietScore as compared to those with high-IBI/high-STAI scores (b coefficient = 1.15, 95% CI 0.6, 1.7, *p* = 0.001). However, participants with a high IBI but low ZDRS scores had a lower MedDietScore as compared to those with high-IBI/high- ZDRS scores (b coefficient = - 2.72, 95% CI -3.48, -1.95, *p* = 0.001). Based on the aforementioned conclusions, adherence to the Mediterranean diet was low among those reporting high irrational beliefs compared to those reporting low irrationalbeliefs. It was further lowered among those who had also anxiety symptoms inaddition to irrational beliefs, but it was higher among those with depression symptomsand irrational beliefs, as compared to those without depression.

9.3 Ten-year MetS incidence in relation to irrational beliefs

Irrational beliefs remained a significant predictor of MetS incidence during the 10-year follow-up (OR=1.55; 95%CI=1.06-2.26), independent of Mediterranean Diet (Model 3 and 4, ***Table 4.1***).

Table 4.1: Results from nested, multi-adjusted models that evaluated the association between Irrational Beliefs and 10-year incidence of metabolic syndrome (results are presented as odds ratios and 95% confidence intervals)

	Model 1	Model 2	Model 3	Model 4
Irrational beliefs ("high" vs. "low" group)	1.68 (1.16, 2.43) *	1.58 (1.08, 2.30) *	1.55 (1.06, 2.26) *	1.44 (0.54, 3.84)
Hypertension (yes vs. no)	-	1.11 (0.84, 1.46)	1.11 (0.84, 1.46)	1.88 (0.74, 4.76)
Hypercholesterolemia (yes vs. no)	-	0.84 (0.65, 1.01)	0.83 (0.65, 1.08)	0.83 (0.65, 1.08)
BMI (per 1 kg/m2 increment)	-	0.98 (0.95, 1.01)	1.01 (0.93, 1.09)	1.01 (0.93, 1.09)
Current smoker (yes vs. no)	-	-	1.13 (0.88, 1.44)	1.13 (0.88, 1.44)
Physical activity level (sedentary lifestyle vs. active)	-	-	0.98 (0.77, 1.26)	0.98 (0.77, 1.26)
MedDietScore (per 1/55-unit increment)	-	-	**0.94 (0.88, 1.00)**	**0.94 (0.88, 1.00)**
Spielberger State-Trait Anxiety Inventory (per 1/80-unit increment)	-	-	-	1.04 (1.00, 1.08)

Hostility and Direction of Hostility Questionnaire (per 1/51-unit increment)	-	-	-	1.05 (0.98, 1.13)

All models are age and sex-adjusted

**p-values* <0.05

9.4 Ten-year MetS and CVD incidence in relation to irrational beliefs

Regarding CVDs, adherence to the Mediterranean diet was a protective factor in the relationship between irrational beliefs and CVD risk (HR=0.95; 95%CI=0.91-0.98) (***Table 4.2***). Nevertheless, the Mediterranean diet did not affect the synergistic relationship between irrational beliefs and anxiety (***Table 4.3***) or depression and CVD incidence.

Table 4.2 Results from nested, multi-adjusted models that evaluated the association between irrational beliefs index score and 10-year incidence of cardiovascular disease (results are presented as hazard ratios and 95% confidence intervals)

	Model 1	Model 2	Model 3	Model 4	Model 5
IBI score	1.07	1.07	1.05	1.11	1.10
(20–88, per 1 unit)	(1.01,1.12)*	(1.01,1.12)*	(1.00,1.11)*	(0.96,1.28)	(0.95, 1.26)
Current smoker	-	1.33	1.33	1.34	1.43
(yes vs. no)		(1.01,1.83)*	(1.01,1.83)*	(1.02,1.87)*	(1.01,1.88)*
Physical activity (moderate/high vs. low)	-	0.87	0.90	0.91	0.90
		(0.68, 1.15)	(0.67, 1.21)	(0.68, 1.21)	(0.67, 1.20)
MedDietScore	**-**	**0.97**	**0.97**	**0.97**	**0.95**
(per 1 unit)		**(0.95,0.99)***	**(0.95, 1.00)**	**(0.95, 1.00)**	**(0.91,0.98)***
Hypertension	-	-	1.19	1.18	1.21
(yes vs. no)			(0.89, 1.60)	(0.88, 1.58)	(0.83, 1.64)
Hypercholesterolemia (yes vs. no)	-	-	1.09	1.11	1.17
			(0.81, 1.45)	(0.83, 1.48)	(0.81, 1.55)
Diabetes mellitus (yes vs. no)	-	-	1.99	2.00	2.01
			(1.31,3.02)*	(1.31,3.03)*	(1.30,3.07)*
ZDRS	-	-	-	1.04	-
(20–80, per 1 unit)				(0.99, 1.09)	

STAI (20–80, per 1 unit)	-	-	-	-	1.02 (0.98, 1.06)

All models are age and sex-adjusted

* *p*-values < 0.05

Table 4.3: Results from nested, multi-adjusted models that evaluated the association between Irrational Beliefs, anxiety and 10-year incidence of cardiovascular disease (results are presented as odds ratios and 95% confidence intervals)

	Model 1	Model 2	Model 3	Model 4	Model 5
IBI & STAI	2.38	3.38	3.79	3.85	3.80
High-IBI-high STAI vs. High-IBI-low-STAI	(1.75,3.23)*	(1.21,12.49)*	(1.16,12.32)*	(1.18,12.53)*	(1.16,12.38)*
Education status (medium/high vs. low)	-	0.69 (0.49,0.97)*	0.72 (0.51, 1.01)	0.72 (0.51, 1.02)	0.71 (0.49, 1.02)
Current smoking (Y/N)	-	1.32 (0.98, 1.78)	1.32 (0.97, 1.78)	1.32 (0.98, 1.79)	1.39 (1.02,1.91)*
Body Mass Index (per 1 kg/m2)	-	-	1.04 (1.01, 1.07)*	1.04 (1.00, 1.07)	1.03 (1.00, 1.07)
Physical activity (Y/N)	-	-	0.93 (0.69, 1.24)	0.93 (0.69, 1.24)	0.97 (0.71, 1.31)
MedDietScore (per 1 unit)	**-**	**-**	**-**	**0.99 (0.96, 1.01)**	**0.98 (0.95, 1.01)**
Hypertension (Y/N)	-	-	-	-	1.13 (0.83,1.53)
Hypercholesterolemia (Y/N)	-	-	-	-	1.06 (0.79,1.42)
Diabetes mellitus (Y/N)	-	-	-	-	1.83 (1.19,2.81)*

All models are age and sex-adjusted

*p-values <0.05

The Role of Physical Activity, Smoking Status, in the relationship between Irrational Beliefs and the development of MetS and CVD

Physical activity had no confounding role in the relationship between irrational beliefs and MetS or CVD incidence (OR=0.98; 95%CI=0.77-1.26), (HR=0.87; 95%CI=0.68-1.15), (HR=0.93; 95%CI=0.69-1.24), (p>0.05) respectively (***Tables 4.4, 4.5 and 4.6***).

On the opposite, although smoking status did not affect the relationship between irrational beliefs and MetS incidence (OR=1.13; 95%CI=0.88-1.44), it seemed to have a confounding role in the relationship between irrational beliefs and CVD incidence (HR=1.34; 95%CI=1.02-1.87) (***Table 4.5***).

Table 4.4: Results from nested, multi-adjusted models that evaluated the association between Irrational Beliefs and 10-year incidence of metabolic syndrome (results are presented as odds ratios and 95% confidence intervals)

	Model 1	Model 2	Model 3	Model 4
Irrational beliefs (“high” vs. “low”group)	1.68 (1.16, 2.43) *	1.58 (1.08, 2.30) *	1.55 (1.06, 2.26) *	1.44 (0.54, 3.84)
Hypertension (yes vs. no)	-	1.11 (0.84, 1.46)	1.11 (0.84, 1.46)	1.88 (0.74, 4.76)
Hypercholesterolemia (yes vs. no)	-	0.84 (0.65, 1.01)	0.83 (0.65, 1.08)	0.83 (0.65, 1.08)
BMI (per 1 kg/m2 increment)	-	0.98 (0.95, 1.01)	1.01 (0.93, 1.09)	1.01 (0.93, 1.09)
Current smoker (yes vs. no)	**-**	**-**	**1.13 (0.88, 1.44)**	**1.13 (0.88, 1.44)**
Physical activity level (sedentary lifestyle vs. active)	**-**	**-**	**0.98 (0.77, 1.26)**	**0.98 (0.77, 1.26)**
MedDietScore (per 1/55-unit increment)	-	-	0.94 (0.88, 1.00)	0.94 (0.88, 1.00)
Spielberger State-Trait Anxiety Inventory (per 1/80-	-	-	-	1.04 (1.00, 1.08)

unit increment)				
Hostility and Direction of Hostility Questionnaire (per 1/51-unit increment)	-	-	-	1.05 (0.98, 1.13)

All models are age and sex-adjusted

*p-values < 0.05

Table 4.5: Results from nested, multi-adjusted models that evaluated the association between irrational beliefs index score and 10-year incidence of cardiovascular disease (results are presented as hazard ratios and 95% confidence intervals)

	Model 1	Model 2	Model 3	Model 4	Model 5
IBI score (20–88, per 1 unit)	1.07 (1.01,1.12)*	1.07 (1.01,1.12)*	1.05 (1.00,1.11)*	1.11 (0.96,1.28)	1.10 (0.95, 1.26)
Current smoker (yes vs. no)	**-**	**1.33 (1.01,1.83)***	**1.33 (1.01,1.83)***	**1.34 (1.02,1.87)***	**1.43 (1.01,1.88)***
Physical activity (moderate/high vs. low)	**-**	**0.87 (0.68,1.15)**	**0.90 (0.67,1.21)**	**0.91 (0.68,1.21)**	**0.90 (0.67, 1.20)**
MedDietScore (per 1 unit)	-	0.97 (0.95,0.99)*	0.97 (0.95,1.00)	0.97 (0.95,1.00)	0.95 (0.91,0.98)*
Hypertension (yes vs. no)	-	-	1.19 (0.89,1.60)	1.18 (0.88,1.58)	1.21 (0.83, 1.64)
Hypercholesterolemia (yes vs. no)	-	-	1.09 (0.81,1.45)	1.11 (0.83,1.48)	1.17 (0.81, 1.55)
Diabetes mellitus (yes vs. no)	**-**	**-**	1.99 (1.31,3.02)*	2.00 (1.31,3.03)*	2.01 (1.30,307)*
ZDRS (20–80, per 1 unit)	**-**	**-**	**-**	1.04 (0.99,1.09)	**-**
STAI (20–80, per 1 unit)	-	-	-	-	1.02 (0.98, 1.06)

All models are age and sex-adjusted

* *p*-values < 0.05

Table 4.6: Results from nested, multi-adjusted models that evaluated the association between Irrational Beliefs and 10-year incidence of cardiovascular disease (results are presented as odds ratiosand 95% confidence intervals)

	Model 1	Model 2	Model 3	Model 4	Model 5
IBI & STAI	2.38	3.38	3.79	3.85	3.80
High-IBI-high STAIvs. High-IBI-low-STAI	(1.75,3.23)*	(1.21,12.49)*	(1.16,12.32)*	(1.18,12.53)*	(1.16,12.38)*
Education status (medium/high vs. low)	-	0.69 (0.49, 0.97)*	0.72 (0.51, 1.01)	0.72 (0.51, 1.02)	0.71 (0.49, 1.02)
Current smoking (Y/N)	**-**	**1.32 (0.98, 1.78)**	**1.32 (0.97, 1.78)**	**1.32 (0.98, 1.79)**	**1.39 (1.02, 1.91)***
Body Mass Index (per 1 kg/m2)	-	-	1.04 (1.01, 1.07)*	1.04 (1.00, 1.07)	1.03 (1.00, 1.07)
Physical activity (Y/N)	-	-	0.93 (0.69, 1.24)	0.93 (0.69, 1.24)	0.97 (0.71, 1.31)
MedDietScore (per 1 unit)	-	-	-	0.99 (0.96, 1.01)	0.98 (0.95, 1.01)
Hypertension (Y/N)	-	-	-	-	1.13 (0.83, 1.53)
Hypercholesterolemia (Y/N)	-	-	-	-	1.06 (0.79, 1.42)
Diabetes mellitus (Y/N)	-	-	-	-	1.83 (1.19, 2.81)*

All models are age and sex-adjusted

**p*-values <0.05

The Role of Biochemical and Clinical Factors, in the relationship between Irrational Beliefs and MetS and CVD development

Regarding MetS, although there were several associations between irrational beliefs and biochemical and clinical factors, a multi-adjusted analysis that was applied to investigate the role of biological factors in the relationship between irrational beliefs and MetS did not show any mediating or moderating effect. In particular,

hypertension and hypercholesterolemia entered Models 2, 3, and 4 (***Table 5.1***), however, they did not affect the tested relationship (OR=1.58; 95%CI=1.08-2.43).

Table 5.1: Results from nested, multi-adjusted models that evaluated the association between Irrational Beliefs and 10-year incidence of metabolic syndrome (results are presented as odds ratios and 95% confidence intervals)

	Model 1	Model 2	Model 3	Model 4
Irrational beliefs ("high" vs. "low"group)	1.68 (1.16, 2.43) *	1.58 (1.08, 2.30) *	1.55 (1.06, 2.26) *	1.44 (0.54, 3.84)
Hypertension (yes vs. no)	**-**	**1.11 (0.84, 1.46)**	**1.11 (0.84, 1.46)**	**1.88 (0.74, 4.76)**
Hypercholesterolemia (yes vs. no)	**-**	**0.84 (0.65, 1.01)**	**0.83 (0.65, 1.08)**	**0.83 (0.65, 1.08)**
BMI (per 1 kg/m2 increment)	-	0.98 (0.95, 1.01)	1.01 (0.93, 1.09)	1.01 (0.93, 1.09)
Current smoker (yes vs. no)	-	-	1.13 (0.88, 1.44)	1.13 (0.88, 1.44)
Physical activity level (sedentary lifestyle vs. active)	-	-	0.98 (0.77, 1.26)	0.98 (0.77, 1.26)
MedDietScore (per 1/55-unit increment)	-	-	0.94 (0.88, 1.00)	0.94 (0.88, 1.00)
Spielberger State-Trait Anxiety Inventory (per 1/80-unit increment)	-	-	-	1.04 (1.00, 1.08)
Hostility and Direction of Hostility Questionnaire (per 1/51-unit increment)	-	-	-	1.05 (0.98, 1.13)

All models are age and sex-adjusted

*p-values <0.05

Regarding CVDs, when TNF-α, CRP, IL-6, fibrinogen, and TAC were, separately, entered into the analysis, the IBI score lost its significance related to CVD risk, and the mediating role of the aforementioned biomarkers was revealed (HR of irrational beliefs after the inclusion of the respective biomarker 1.01, 95%CI 0.98, 1.05; HR 1.05, 95%CI 0.99, 1.11, HR 1.04, 95%CI 0.97, 1.12, HR 1.00, 95%CI 1.00,

1.00, HR 1.00, 95%CI 0.99, 1.00, *p-values* of Sobel's test < 0.05). No mediation effect of ox – LDL was observed (*p-value* of Sobel's test = 0.42).

Yet, no effect of hypertension and hypercholesterolemia was observed in the relationship between irrational beliefs, either tested with anxiety or alone and CVDs (***Table 5.2 and 5.3***).

Table 5.2: Results from nested, multi-adjusted models that evaluated the association between irrational beliefs index score and 10-year incidence of cardiovascular disease (results are presented as hazard ratios and 95% confidence intervals)

	Model 1	Model 2	Model 3	Model 4	Model 5
IBI score (20–88, per 1 unit)	1.07 (1.01,1.12)*	1.07 (1.01,1.12)*	1.05 (1.00,1.11)*	1.11 (0.96,1.28)	1.10 (0.95,1.26)
Current smoker (yes vs. no)	-	1.33 (1.01,1.83)*	1.33 (1.01,1.83)*	1.34 (1.02,1.87)*	1.43 (1.01,1.88)*
Physical activity (moderate/high vs. low)	-	0.87 (0.68, 1.15)	0.90 (0.67, 1.21)	0.91 (0.68, 1.21)	0.90 (0.67, 1.20)
MedDietScore (per 1 unit)	-	0.97 (0.95,0.99)*	0.97 (0.95, 1.00)	0.97 (0.95, 1.00)	0.95 (0.91,0.98)*
Hypertension (yes vs. no)	**-**	**-**	**1.19 (0.89, 1.60)**	**1.18 (0.88, 1.58)**	**1.21 (0.83, 1.64)**
Hypercholesterolemia (yes vs. no)	**-**	**-**	**1.09 (0.81, 1.45)**	**1.11 (0.83, 1.48)**	**1.17 (0.81, 1.55)**
Diabetes mellitus (yes vs. no)	-	-	1.99 (1.31,3.02)*	2.00 (1.31,3.03)*	2.01 (1.30,3.07)*
ZDRS (20–80, per 1 unit)	-	-	-	1.04 (0.99, 1.09)	-
STAI (20–80, per 1 unit)	-	-	-	-	1.02 (0.98,1.06)

All models are age and sex-adjusted

* *p*-values < 0.05

Table 5.3: Results from nested, multi-adjusted models that evaluated the association between Irrational Beliefs and 10-year incidence of cardiovascular disease (results are presented as odds ratios and 95% confidence intervals)

	Model 1	Model 2	Model 3	Model 4	Model 5
IBI & STAI	2.38	3.38	3.79	3.85	3.80
High-IBI-high STAIvs. High-IBI-low-STAI	(1.75,3.23)*	(1.21,12.49)*	(1.16,12.32)*	(1.18,12.53)*	(1.16,12.38)*
Education status (medium/high vs. low)	-	0.69	0.72	0.72	0.71
		(0.49,0.97)*	(0.51, 1.01)	(0.51, 1.02)	(0.49, 1.02)
Current smoking (Y/N)	-	1.32	1.32	1.32	1.39
		(0.98, 1.78)	(0.97, 1.78)	(0.98, 1.79)	(1.02,1.91)*
Body Mass Index (per 1 kg/m2)	-	-	1.04	1.04	1.03
			(1.01,1.07)*	(1.00, 1.07)	(1.00, 1.07)
Physical activity (Y/N)	-	-	0.93	0.93	0.97
			(0.69, 1.24)	(0.69, 1.24)	(0.71, 1.31)
MedDietScore (per 1 unit)	-	-	-	0.99	0.98
				(0.96, 1.01)	(0.95, 1.01)
Hypertension (Y/N)	**-**	**-**	**-**	**-**	**1.13**
					(0.83, 1.53)
Hypercholesterolemia (Y/N)	**-**	**-**	**-**	**-**	**1.06**
					(0.79, 1.42)
Diabetes mellitus (Y/N)	-	-	-	-	1.83
					(1.19,2.81)*

All models are age and sex-adjusted

**p*-values <0.05

The role of type 2 Diabetes and Irrational Beliefs

T2DM was one of the clinical factors that had a confounding role in the relationship between irrational beliefs and CVDs. In particular, diabetes mellitus mediated the association between irrational beliefs and CVDs when entered Model 3, ***Table 6.1*** (HR 1.99, 95%CI 1.31, 3.02).

Table 6.1: Results from nested, multi-adjusted models that evaluated the association between irrational beliefs index score and 10-year incidence of cardiovascular disease (results are presented as hazard ratios and 95% confidence intervals)

	Model 1	Model 2	Model 3	Model 4	Model 5
IBI score	1.07	1.07	1.05	1.11	1.10
(20–88, per 1 unit)	(1.01,1.12)*	(1.01,1.12)*	(1.00,1.11)*	(0.96,1.28)	(0.95, 1.26)
Current smoker (yes vs. no)	-	1.33	1.33	1.34	1.43
		(1.01,1.83)*	(1.01,1.83)*	(1.02,1.87)*	(1.01,1.88)*
Physical activity (moderate/high vs. low)	-	0.87	0.90	0.91	0.90
		(0.68, 1.15)	(0.67, 1.21)	(0.68, 1.21)	(0.67, 1.20)
MedDietScore (per 1 unit)	-	0.97	0.97	0.97	0.95
		(0.95,0.99)*	(0.95, 1.00)	(0.95, 1.00)	(0.91,0.98)*
Hypertension	-	-	1.19	1.18	1.21
(yes vs. no)			(0.89, 1.60)	(0.88, 1.58)	(0.83, 1.64)
Hypercholesterolemia (yes vs. no)	-	-	1.09	1.11	1.17
			(0.81, 1.45)	(0.83, 1.48)	(0.81, 1.55)
Diabetes mellitus (yes vs. no)	**-**	**-**	**1.99**	**2.00**	**2.01**
			(1.31,3.02)*	**(1.31,3.03)***	**(1.30,3.07)***
ZDRS	-	-	-	1.04	-
(20–80, per 1 unit)				(0.99, 1.09)	
STAI	-	-	-	-	1.02
(20–80, per 1 unit)					(0.98, 1.06)

All models are age and sex-adjusted

* *p*-values < 0.05

After identifying the mediating role of diabetes, we chose to do a more focused study to explore whether other processes and mechanisms are involved beforethe onset of diabetes. During 2002-2012, the crude 10-year incidence of diabetes in the working sample was n = 191 cases (12.9%, 95%CI: 10.4-15.4) or 129 per 1,000 participants free of diabetes at baseline. Of the latter, n = 97 (13.4%, 95%CI: 10.8-16) were men and n = 94 (12.4%, 95%CI: 10.1-14.7) were women.

Stratified analysis by age group revealed that the incidence of diabetes was the lowest, i.e., 1.5%, for people under 35 years old, but increased to 29.2% for participants over 74 years old. The men-to-women incidence was approximately 1-to- 1 in almost all age groups. Participants who developed diabetes during the 10-year follow-up had an 11.8% higher IBI score at baseline examination than those who did not develop diabetes (i.e., 57/80 vs. 51/80). Furthermore, the 10-year incidence of diabetes was 5% among those in the lowest IBI tertile compared to 7.8% among those in the middle and 7.5% among those in the highest tertile ($p < 0.001$).

Crude, unadjusted data analysis revealed that participants in the 3rd tertile of IBI scores had a 14% higher risk of developing diabetes during the 10-year follow-up than those in the 1st tertile (OR: 1.14, 95%CI: 1.04-1.25). A progressive, but insignificant increase was also observed between participants in the 2nd tertile compared to those in the 1st tertile (OR: 1.08, 95% CI: 0.94-1.28). However, residual confounding may exist, especially when several associations between IBI score and age, psychological factors, and dietary habits of the participants have already been observed. Thus, after adjustment for sex and age, IBI score was still significantly associated with the 10-year incidence of type 2 diabetes; specifically, a 1-unit increasein IBI score led to an 11% increase in type 2 diabetes risk (***Table 6.2***, Model 1). The latter association remained significant even after adjusting for SES and smoking habits of the participants (Models 2 and 3, ***Table 6.2***). After including several clinical variables in the model, IBI was no longer associated with a 10- year risk of diabetes inall scenarios, underlying the confounding role of these factors in the relationship between irrational beliefs and risk of type 2 diabetes mellitus (see Models 4-6, ***Table 6.2***). Moreover, no significant interactions between IBI score and physical activity, smoking, obesity and history of hypertension on 10-year diabetes outcome wereobserved (all p-values >0.10).

Table 6.2: Results from nested, multi-adjusted models that evaluated the association between Irrational Beliefs Index (IBI) score and 10-year incidence of diabetes

	Model 1	Model 2	Model 3	Model 4	Model 5	Model 6
IBI 2nd vs. 1st tertile	1.06 (0.99,1.15)	1.43 (1.11,1.94)*	1.32 (1.02,1.80)*	1.29 (0.99,1.61)	1.24 (0.91,1.55)	1.22 (0.78,1.94)
IBI 3rd vs. 1st tertile	1.11 (1.04, 1.19)*	1.44 (1.12, 1.98)*	1.33 (1.07, 1.74)*	1.31 (0.98, 1.76)	1.30 (0.95,1.78)	1.30 (0.94,1.81)
SES (high vs. low tertile)	-	0.36 (0.13, 0.98)	0.38 (0.14, 1.11)	0.37 (0.13, 1.06)	0.49 (0.17,1.43)	0.46 (0.08,2.52)
Current smoking (Y/N)	-	1.11 (0.88, 1.42)	1.12 (0.92, 1.38)	1.17 (0.99, 1.44)	1.18 (1.01,1.54)*	1.21 (1.02,1.58)*
Body mass index (per 1 kg/m2)	-	-	1.14 (1.08, 1.20)*	1.14 (1.09,1.21)*	1.12 (1.04,1.20)*	1.12 (1.05,1.20)*
Physical inactivity (Y/N)	-	-	1.10 (0.70, 1.74)	1.12 (0.71, 1.76)	1.16 (0.71,1.95)	1.21 (0.71,1.99)
MedDietScore (per 1 unit)	-	-	-	0.97 (0.94,0.99)*	0.99 (0.95,1.02)	0.98 (0.94,1.00)
Hypertension (Y/N)	-	-	-	-	1.33 (0.84, 2.17)	1.35 (0.82,2.22)
Hypercholesterolemia (Y/N)	-	-	-	-	1.96 (1.31,2.69)*	1.51 (1.21,1.82)*
Family history of diabetes (Y/N)	-	-	-	-	2.57 (1.76,3.77)*	2.59 (1.71,3.79)*
ZDRS (per 1 unit)	-	-	-	-	-	1.05 (0.99,1.11)
STAI (per 1 unit)	-	-	-	-	-	1.01 (0.97,1.05)

All models are age and sex-adjusted

*p-values <0.05

A highly significant interaction was observed between MedDietScore and IBI on 10-year diabetes risk ($p < 0.001$). Thus, the analysis was stratified by the level of adherence to the Mediterranean diet and IBI score. As can be seen in ***Table 6.3***, in the crude model, participants with high IBI and high adherence to the Mediterranean diet had a 2.5-times higher likelihood of developing diabetes during the 10-year follow-up than participants who highly adhered to the Mediterranean diet, but had a low level of irrational beliefs, underlying the harmful effect of irrational beliefs on diabetes development among participants with healthy dietary habits. Also, participants with a low level of irrational beliefs and also low adherence to the Mediterranean diet had a 1.69-times higher likelihood of developing diabetes during the 10-year follow-up than participants who highly adhered to the Mediterranean diet, but had a low level of irrational beliefs. Similarly, participants with high IBI, but low adherence to the Mediterranean diet had a 3.44-times higher likelihood of developing diabetes than participants who highly adhered to the Mediterranean diet, but had a low level of irrational beliefs, underlying the combined harmful, additive effects of both irrational beliefs and practicing unhealthy dietary pattern. Subsequently, the models were adjusted for age, sex, BMI, physical activity status, and smoking habits, and the results regarding IBI and 10-year diabetes incidence remained significant (Models 1 and 2, ***Table 6.3***).

When the models were further adjusted for baseline fasting blood glucose and family history of diabetes and additionally adjusted for depression or anxiety status (through the ZDRS, STAI) (Model 3, ***Table 6.3***), it was revealed that participants with a high level of irrational beliefs and high adherence to the Mediterranean diet had a 2.6-times higher likelihood of developing diabetes than participants with a low level of irrational beliefs, but high adherence to Mediterranean diet. In accordance, participants with low IBI and low adherence to the Mediterranean diet had a 2.17- times higher likelihood of developing diabetes than participants who highly adhered to the Mediterranean diet, but had low levels of irrational beliefs.

Finally, participants with high IBI and low adherence to Mediterranean diet had a 3.44 times higher likelihood of developing diabetes than participants who highly adhered to the Mediterranean diet and had low levels of IBI, underlying the

combined harmful effect of negative thinking patterns and unhealthy dietary habits on the development of type 2 diabetes.

Table 6.3: Nested logistic regression analysis models to evaluate the association of combined irrational beliefs and Mediterranean diet adherence with 10-year incidence of type 2 diabetes

Combined IBI scale and MedDiet-Score	Crude model	Age & sex-adjusted model	Multi-adjusted model		
			Model 1	Model 2	Model 3
Low IBI score & high MedDiet-Score	Reference	Reference	Reference	Reference	Reference
High IBI score & high MedDiet-Score	2.50 (1.61,3.84)*	2.00 (1.28, 3.12)*	1.92 (1.21, 3.03)*	2.56 (1.47, 4.54)*	2.56 (1.47, 4.54)*
Low IBI score &low MedDiet-Score	1.69 (1.12,2.56)*	1.78 (1.16, 2.77)*	1.96 (1.26, 3.03)*	2.17 (1.28, 3.70)*	2.17 (1.28, 3.70)*
High IBI score & low MedDiet-Score	3.44 (2.22,5.26)*	3.44 (2.17, 5.55)*	3.70 (2.32, 5.88)*	3.44 (1.88, 6.25)*	3.46 (1.92, 6.25)*

Data are presented as hazard ratios and 95% confidence intervals. ORs and their 95%CIs were obtained through logistic regression analysis. Model 1 was adjusted for age, sex, educational status, physical activity, and current smoking. Model 2 was additionally adjusted for baseline BMI, fasting blood glucose, and family history of diabetes. Model 3 was additionally adjusted for the Zung Self-Rating Depression Scale.

As people's irrational beliefs and attitudes are usually considered as precursors of negative emotions, like depression and anxiety, the additive effect of these psychological disorders was further evaluated. Participants in the highest tertile on the IBI scale also had higher levels of depression ($p < 0.001$) and anxiety ($p < 0.001$) than those in the lowest tertile. When the analysis was focused on those in the upper 50 percentile of the depression score (i.e., ZDRS > 35) it was observed that participants in the 3rd IBI tertile were 1.25-times more likely to develop diabetes than those in the lowest IBI tertile (95% CI: 0.98-2.27) after adjusting for the same factors as in Model 5 (***Table 6.2***). Furthermore, when the analysis was focused on participants in the

lowest 50 percentile (i.e., ZDRS ≤ 35), no association between IBI score and diabetes incidence was observed (OR: 1.12, 95% CI: 0.43-2.91). The analysis then focused on participants in the upper 50 percentile of the anxiety score (i.e., STAI > 40). It was observed that individuals in the 3rd IBI tertile had a 1.41-times higher likelihood of developing diabetes than those in the lowest IBI tertile (95% CI: 1.12-2.89), while no association between IBI score and diabetes incidence was observed (OR: 0.64, 95% CI: 0.22-1.83) when the analysis was focused on those in the lowest anxiety score 50 percentile (i.e., STAI ≤ 40).

In addition, since a highly significant interaction was observed between IBI and STAI, as well as IBI and ZDRS on the risk of developing T2DM (p's < 0.001), a latent variable (high-IBI-high/low-STAI) was created classifying participants with a high IBI score (i.e., above median value, 52, which is 50% of the participants) and high STAI score (> 40, median) in one group, and those with high IBI score but low STAI score into another. Similarly, a latent variable (high-IBI-high/low-ZDRS) was created classifying participants with high IBI and high ZDRS (> 34, median) into one group and those with high IBI and low ZDRS into the other. It was observed that the 66% of participants who had a high IBI score (i.e., above the median value, 52) also had a high STAI score (> 40, median) (68% men vs. 64% women, p = 0.08).Similarly, the 65% of individuals with a high IBI score also had a high ZDRS score (>34, median) (68% men vs. 62% women, p = 0.01).

Unadjusted data analysis revealed that participants with high irrational beliefs, who also had anxiety symptoms, had a 93% higher risk of developing T2DM during the 10-year follow-up as compared to those with high levels of irrational beliefs but without anxiety symptomatology (OR, 95%CI, 1.93; 1.34, 2.78); i.e., an excess 81% risk as compared to the irrational beliefs effect alone, as reported above. Similarly, participants with a high irrational belief score who also reported depression symptoms, showed a 73% higher T2DM risk, compared to those who did not have depression symptoms (OR, 95%CI, 1.73; 1.21, 2.46) i.e., 61% excess risk as compared to the irrational beliefs effect alone. The 10-year incidence of T2DM was 15.1% among those who were classified as high-IBI-high- STAI, 6.4% among those who were high-IBI-low-STAI (p < 0.001), as well as 15.2% among those who were classified as high-IBI-high-ZDRS, and 6.8% among those who were high-IBI-low- ZDRS (p < 0.001).

However, residual confounding may exist, especially when several associations between high-IBI-high-STAI score or high-IBI-high-ZDRS score and age, social, behavioural and biochemical factors were already observed. After adjustment for sex, age, educational and smoking status, participants with high-IBI- high-STAI had a 4.11 times higher likelihood of diabetes as compared to those with high-IBI-low-STAI (95%CI 1.13, 14.97) (***Table 6.4*** , *Model 2*). It is notable that wheneducational status, mainly, and smoking habits, were taken into account in *Model 2* the effect of high-IBI-high- STAI on 10-year T2DM incidence substantially increased as compared to the previous Model 1 (***Table 6.4***) (Sobel's test for mediation p-value = 0.01). The association between high-IBI-high-STAI remained significant even when adjusting for BMI, physical activity (Model 3, ***Table 6.4***); and Med-DietScore (Model4, ***Table 6.4***), but lost its significance when medical history, and, particularly, family history of diabetes were entered in *Model 5* (suggesting a strong mediation effect of the genetic predisposition) (*Sobel's test p-value p* < 0.001). Regarding irrational beliefs and depression, after adjustment for sex and age, depression-related-to- irrational beliefs were significantly associated with the 10-year incidence of diabetes (*Model 1*, ***Table 6.5***). Specifically, participants with high IBI and high ZDRS score had a 1.51 times higher likelihood of developing T2DM during the 10-year follow-up as compared to participants who had high irrational beliefs but low levels of depression (95%CI 1.05, 2.18). Similar to the previous analyses, the later association remained significant even when adjusting for education, and smoking status, and slightly lost its significance when BMI, physical activity status, and Mediterranean diet adherence were taken into account (*Models 2 and 3,* ***Table 6.5***). The impact of irrational beliefs and depression became insignificant when participants' medical history, as well as family history of diabetes were entered in *Model 5* (*Sobel's test p- value p* = 0.03).

Table 6.4: Results from nested, multi-adjusted models that evaluated the association between irrational beliefs and depression with the 10-year incidence of diabetes (results are presented as Hazard Ratios and 95% confidence intervals)

	Model 1	Model 2	Model 3	Model 4	Model 5
IBI & STAI	1.93	4.11	4.18	4.06	3.49
High-IBI-high-STAI vs High-IBI-low-STAI	(1.34,2.78)*	(1.13,14.97)*	(1.04,16.75)*	(1.05,16.44)*	(0.67,18.12)
Education status (medium vs. low tertile)		0.53	0.57	0.57	0.68
		(0.35,0.79)*	(0.38,0.85)*	(0.38,0.86)*	(0.43,1.07)
Current smoking (Y/N)		0.93	0.94	0.94	1.01
		(0.66, 1.31)	(0.66, 1.33)	(0.66, 1.33)	(0.68,1.49)
Body Mass Index (per 1 kg/m2)			1.15	1.15	1.15
			(1.10,1.19)*	(1.11,1.20)*	(1.10,1.20)*
Physical activity (Y/N)			0.92	0.92	0.90
			(0.65, 1.29)	(0.65, 1.29)	(0.61,1.33)
MedDietScore (per 1 unit)				1.01	1.01
				(0.98, 1.04)	(0.97,1.04)
Hypertension (Y/N)					1.34
					(0.91,1.96)
Hypercholesterolemia (Y/N)					1.68
					(1.16,2.43)*

All models are age and sex adjusted

*p-values < 0.05

Table 6.5: Results from nested, multi-adjusted models that evaluated the association between irrational beliefs and depression with the 10-year incidence of diabetes (results are presented as Hazard Ratios and 95% confidence intervals)

	Model 1	Model 2	Model 3	Model 4	Model 5
IBI & ZDRS	1.51	2.16	1.85	1.87	1.69
High-IBI-high-ZDRS vs High-IBI-low ZDRS	(1.05, 2.18)*	(1.06, 4.41)*	(0.87, 3.94)	(0.88, 3.97)	(0.69, 4.12)
Education status (medium vs. low tertile)		0.58	0.61	0.61	0.71
		(0.38, 0.87)*	(0.40,0.92)*	(0.40,0.93)*	(0.45, 1.13)
Current smoking (Y/N)		0.93	0.95	0.95	1.02
		(0.66, 1.31)	(0.67, 1.34)	(0.67, 1.35)	(0.69, 1.51)
Body Mass Index (per 1 kg/m2)			1.15	1.15	1.15
			(1.10,1.19)*	(1.11,1.20)*	(1.10,1.20)*
Physical activity (Y/N)			0.93	0.93	0.92
			(0.66, 1.32)	(0.66, 1.31)	(0.62, 1.35)
MedDietScore (per 1 unit)				1.01	1.01
				(0.98, 1.04)	(0.98, 1.04)
Hypertension (Y/N)					1.32
					(0.90, 1.93)
Hypercholesterolemia (Y/N)					1.64
					(1.13,2.37)*
Family history of diabetes (Y/N)					2.41
					(1.61,3.60)*

All models are age and sex adjusted

*p-values < 0.05

A path model between irrational beliefs and the development of diabetes

To further explore the potential mediating effect of inflammatory and oxidative stress markers on the associations between irrational beliefs, anxiety, depression and T2DM risk, we evaluated additional nested models by introducing each of the investigating biomarkers in the final *Model 5* reported in ***Figures 9.3 and 9.4***. It was observed that when TNF-α and TAC were entered in *Model 5* that evaluated anxiety-related-to-irrational beliefs, a significant mediation occurred in the effect on the 10-year incidence of T2DM (OR 3.10, 95%CI 0.60, 15.94, *Sobel's test p-value p* < 0.001 and OR 14.72, 95%CI 1.06, 203, *Sobel's test p-value p* < 0.001, respectively). It was also observed that when TNF-α was entered in *Model 5* (***Table 6.5***, *data not shown*), a significant mediation occurred in the effect of depression related to irrational beliefs on the 10-year incidence of diabetes (OR 2.27, 95%CI 0.91, 5.68, *Sobel's test p-value p* = 0.03).

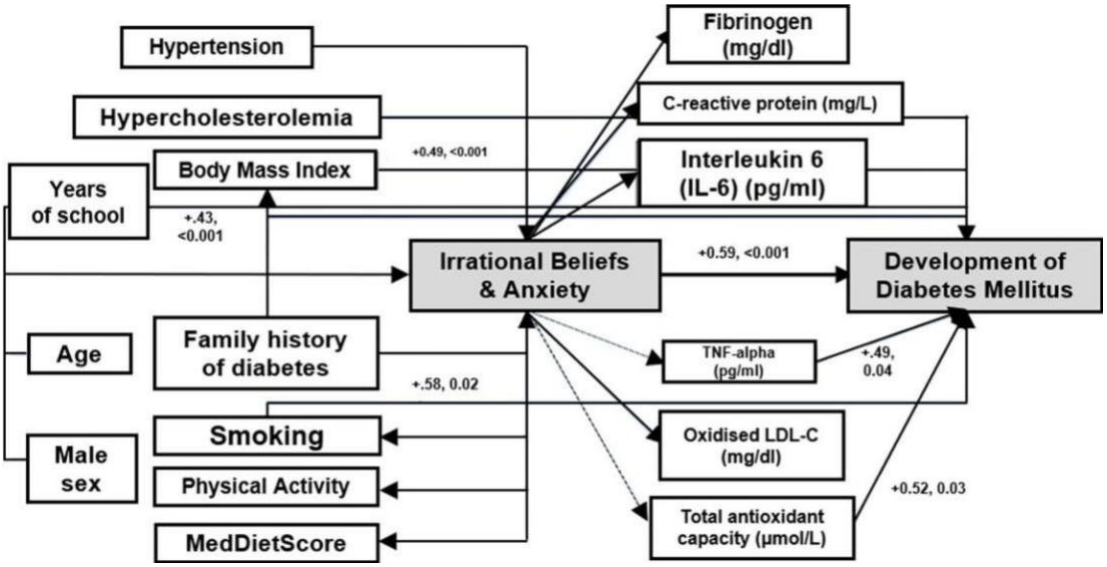


Figure 9.3: A path-model that illustrates the direct and indirect effect of increased irrational beliefs and anxiety symptoms on the risk of developing diabetes (data presented as beta-coefficients and *p*-values and derived from the logistic regression models)

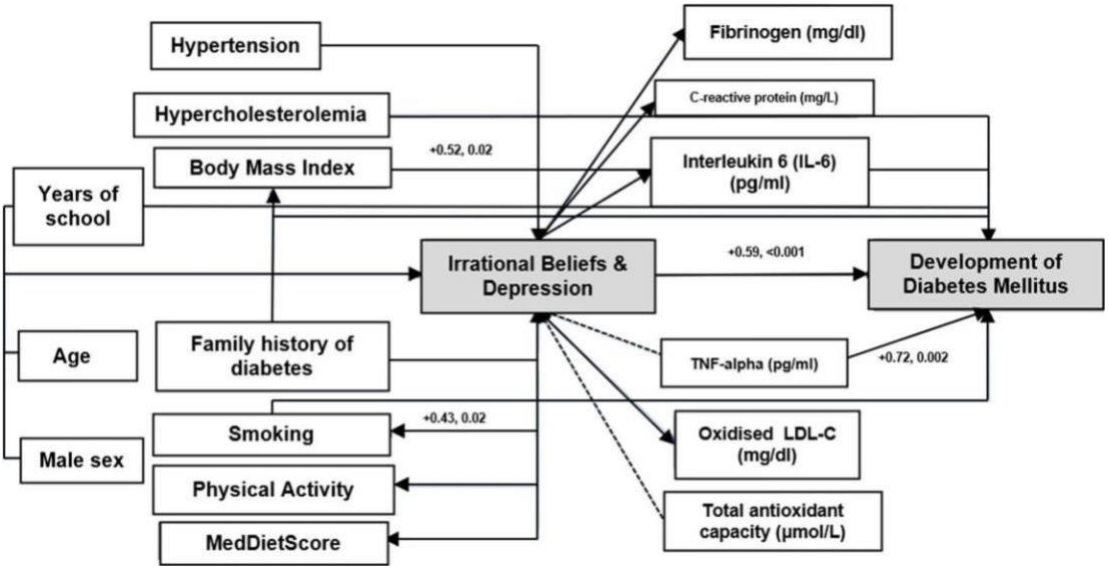


Figure 9.4: A path-model that illustrates the direct and indirect effect of increased irrational beliefs and depressive symptoms on the risk of developing diabetes (data presented as beta-coefficients and *p*-values and derived from the logistic regression models)

Irrational beliefs, health anxiety and family history of diabetes

Based on supporting evidence about the role of irrational beliefs and general anxiety in T2DM risk, the relationship between family medical history and health anxiety, as well as REBT theory, we proposed that individuals who have a family history of diabetes (i.e., experience undesirable activating event) (A), for which they may have irrational beliefs (B), that may contribute to health anxiety (i.e., emotional disturbance) and behavioural dysfunctional consequences (C), would have an increased likelihood to develop T2DM. We hypothesized that irrational beliefs and health anxiety would mediate or moderate the relationship between family history of diabetes and T2DM.

Since irrational beliefs were highly associated with health anxiety, as well as with family history of diabetes, we further explored the role of family history of diabetes on T2DM risk, taking into consideration irrational beliefs and health anxiety, apart from biomedical and behavioural indicators. Findings from multivariable models that evaluated the association between family history of diabetes, irrational

beliefs and health anxiety with the 10-year diabetes risk are presented in ***Table 6.6***. As depicted, after adjusting for several demographic, lifestyle, clinical and psychological characteristics (*Model 6*), participants with family history of diabetes were found to have approximately 2.5-times higher odds of developing T2DM during the 10-year follow-up. In addition, participants with higher levels of irrational beliefs, as well as those with higher levels of health anxiety were found to have significantly higher odds of T2DM (*Model 6*). In particular, 1-unit increment in the irrational beliefs scale was significantly associated with an increase by 10% in the odds of developing T2DM, while 1 unit increment in the health anxiety scale was significantly associated with an increase by 19% in the odds of developing T2DM. Furthermore, family history of diabetes remained a significant predictor of T2DM riskduring the 10-year follow up, independent of irrational beliefs and health anxiety effects (*Model 6*).

Table 6.6: Odds Ratios (ORs) and 95% Confidence Intervals (95% CIs) from the nested multi-adjusted logistic regression models evaluating the association between the participants' family history of diabetes mellitus, their health anxiety levels, and their irrational beliefs with the 10- year risk of diabetes mellitus in the total ATTICA study's sample (n= 845)

	Model 1	**Model 2**	**Model 3**	**Model 4**	**Model 5**	**Model 6**
Family history of diabetes mellitus (Yes Vs No)	2.89 (2.00,4.17)*	2.85 (1.98,4.12)*	2.53 (1.71,3.75)*	2.51 (1.69,3.74)*	2.51 (1.69,3.74)*	2.53 (1.71,3.75)*
Current smoker (Yes Vs No)	-	0.94 (0.66,1.35)	1.06 (0.73,1.55)	1.04 (0.71,1.53)	1.04 (0.71, 1.53)	1.04 (0.71, 1.53)
MedDietScore (per 1 unit)	-	0.99 (0.97, 1.02)	1.01 (0.97, 1.04)	1.01 (0.97, 1.04)	1.01 (0.97, 1.04)	1.01 (0.97, 1.04)
Physical activity level (Active Vs Sedentary lifestyle)	-	0.79 (0.56, 1.12)	0.89 (0.61, 1.28)	0.89 (0.61, 1.30)	0.89 (0.61, 1.30)	0.89 (0.61, 1.30)
Obesity (Yes Vs No)	-	-	3.24 (2.14, 4.84)*	3.06 (2.05, 4.58)*	3.06 (2.05, 4.58)*	3.06 (2.05, 4.58)*
Hypertension (Yes Vs No)	-	-	1.45 (0.99, 2.11)*	1.45 (0.99, 2.11)*	1.45 (0.99, 2.11)*	1.45 (0.99, 2.11)*
Hypercholesterolemia (Yes Vs No)	-	-	1.60 (1.12, 2.30)*	1.61 (1.12, 2.31)*	1.61 (1.12, 2.31)*	1.61 (1.12, 2.31)*
Irrational beliefs scale (per 1 unit)	-	-	-	-	1.08 (1.00, 1.16)*	1.10 (1.01, 1.22)*
Health Anxiety scale (per 1 unit)	-	-	-	1.20 (1.00, 1.45)*	-	1.19 (1.01, 1.47)*

All models are age and sex-adjusted

*p< 0.05

A highly significant correlation was observed between irrational beliefs and health anxiety (r=0.931, p<0.001). To better explore participants' characteristics by irrational beliefs and health anxiety, they were classified into the following groups: a) those with a "low" IBI score (i.e., <52, median) and "low" WI score (<4, median), b) those with a "high" IBI score (i.e., above median value, 52), "low" WI score (<4), c) those with a "low" IBI score (i.e., <52, median) and "high" WI score (≥4), and d) those with a "high" IBI score (≥52) and "high" WI score (≥4). Participants who had low levels of irrational beliefs and health anxiety represented 35.8% (*n*=138) of our total sample. Participants with high levels of irrational beliefs and low levels of health anxiety represented 19.5% (*n*=75) of the total sample. Participants with low levels of irrational beliefs and high levels of health anxiety represented 15.3% (*n*=59), of the total sample, whereas those with high levels of irrational beliefs and health anxiety represented 29.4% (*n*=113) of the sample.

An interaction analysis was also performed to identify the potential synergistic effect of participants' irrational beliefs and health anxiety levels on the association between their family history of diabetes and the 10-year T2DM risk, as presented in ***Table 6.7***. Specifically, a highly significant interaction was observed between irrational beliefs and heath anxiety scores with family history of diabetes on 10-year T2DM risk (p<0.001). Thus, when we focused on those with high levels of irrational beliefs, family history of diabetes was associated with 2.8-times higher odds of T2DM in the entire sample, 3.7-times higher odds of T2DM risk among those with low health anxiety and 2.4-times higher odds among those with high health anxiety levels. On the other hand, when we focused on those with low levels of irrational beliefs, family history of diabetes was not associated with T2DM risk, regardless of health anxiety levels. Moreover, when we focused on those with low levels of health anxiety, family history of diabetes was associated with approximately 2.7 times higher odds of developing T2DM in the total sample, mainly driven by those who alsohad high levels of irrational beliefs. Similarly, it was observed that among the participants with high levels of health anxiety, family history of diabetes was associated with 2-times higher odds of developing T2DM during the 10-year follow- up period only among those with high irrational beliefs, too.

Table 6.7: Odds Ratios (ORs) and 95% Confidence Intervals (95% CIs) from the multi-adjusted logistic regression model evaluating the association between the participants' family history of diabetes mellitus with the 10-year risk of diabetes mellitus, both in the total study's sample, as well as separately according to their levels of health anxiety and irrational beliefs

		Total sample	**Low irrational beliefs**	**High irrational beliefs**
	N/ cases	*1,485/ 191*	*593/ 55*	*892/ 136*
Total sample	*1,485/ 191*	2.53 (1.71, 3.75) **	1.96 (0.93, 4.08)	2.81 (1.74, 4.54) **
Low health anxiety	*1,025/ 110*	2.68 (1.63, 4.41) **	1.95 (0.93, 4.08)	3.70 (1.83, 7.48) **
High health anxiety	*460/ 82*	2.46 (1.40, 4.31) *	2.01 (0.94, 4.19)	2.38 (1.33, 4.27) *

Results are being adjusted for the participants' demographic (age, sex), lifestyle (smoking status, physical activity, level of adherence to the Mediterranean diet), anthropometric (obesity) and clinical (personal history of hypertension and hypercholesterolemia) characteristics

**$p < 0.001$, *$p < 0.05$

The Role of Emotional Disturbances in the relationship between Irrational Beliefs and the development of MetS and CVDs

As irrational beliefs were significantly associated with psychological factors (i.e., anxiety, depression, and hostility), we further explored the role of irrational beliefs on MetS, taking into consideration these psychological dimensions, apart from biomedical and behavioural indicators. Irrational beliefs remained a significant predictor of MetS incidence during the 10-year follow-up, independent of medical and lifestyle factors. However, the impact of irrational beliefs on MetS risk became insignificant when anxiety and hostility entered the Model (***Table 7.1***, *Model 4*).

Table 7.1: Results from nested, multi-adjusted models that evaluated the association between Irrational Beliefs and 10-year incidence of metabolic syndrome (results are presented as odds ratios and 95% confidence intervals)

	Model 1	Model 2	Model 3	Model 4
Irrational beliefs ("high" vs. "low"group)	1.68 (1.16, 2.43) *	1.58 (1.08, 2.30) *	1.55 (1.06, 2.26) *	1.44 (0.54, 3.84)
Hypertension (yes vs. no)	-	1.11 (0.84, 1.46)	1.11 (0.84, 1.46)	1.88 (0.74, 4.76)
Hypercholesterolemia (yes vs. no)	-	0.84 (0.65, 1.01)	0.83 (0.65, 1.08)	0.83 (0.65, 1.08)
BMI (per 1 kg/m2 increment)	-	0.98 (0.95, 1.01)	1.01 (0.93, 1.09)	1.01 (0.93, 1.09)
Current smoker (yes vs. no)	-	-	1.13 (0.88, 1.44)	1.13 (0.88, 1.44)
Physical activity level (sedentary lifestyle vs. active)	-	-	0.98 (0.77, 1.26)	0.98 (0.77, 1.26)
MedDietScore (per 1/55-unit increment)	-	-	0.94 (0.88, 1.00)	0.94 (0.88, 1.00)
Spielberger State-Trait Anxiety Inventory (per 1/80-unit increment)	**-**	**-**	**-**	**1.04 (1.00, 1.08)**
Hostility and Direction of Hostility Questionnaire (per 1/51-unit increment)	**-**	**-**	**-**	**1.05 (0.98, 1.13)**

All models are age and sex-adjusted

**p-values* <0.05

An interaction analysis was also performed to identify the potential synergistic effect of participants' irrational beliefs and anxiety, depression, or hostility symptoms levels on the 10-year MetS incidence. Since the analysis revealed a significant interaction between irrational beliefs and anxiety (p = 0.03), we proceeded to perform a stratified analysis. Thus, when we focused on those with high irrational beliefs, who also had moderate/high anxiety symptoms, their odds of MetS incidence were almost 2-fold higher than those with low irrational beliefs (OR = 1.96, 95% CI = 1.01, 3.80); no significant association was observed between irrational beliefs and MetS

incidence, among those participants who had low anxiety symptoms. Moreover, stratified analysis by depression and hostility symptomatology was also performed (see ***Figure 9.5***). No significant associations were observed between irrational beliefs and MetS incidence, irrespective of depression, as well as hostility levels, ($p > 0.05$).

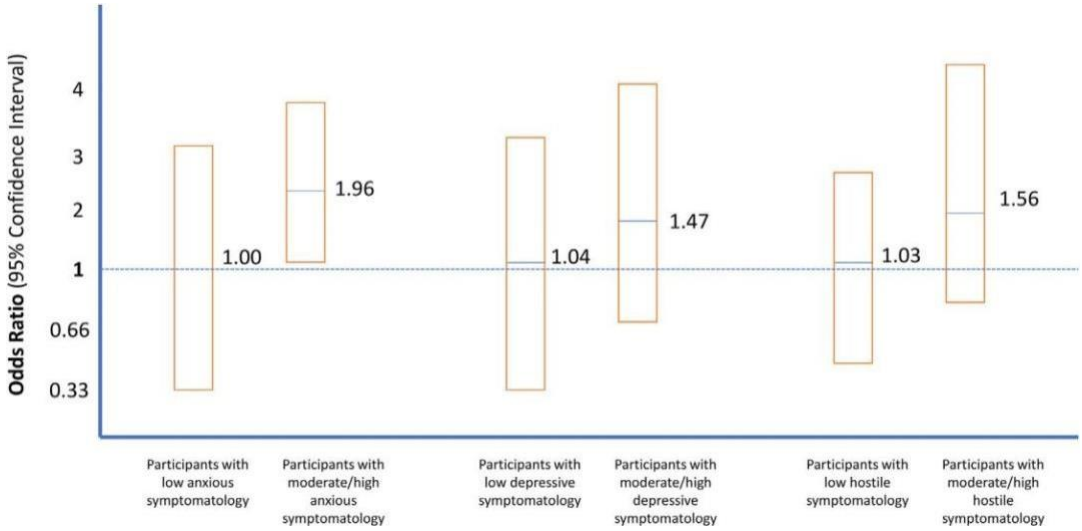


Figure 9.5: Results from the multi-adjusted logistic regression models evaluating the association between the participants' levels of irrational beliefs (moderate/high vs. low) with the 10-year incidence of metabolic syndrome, according to their anxiety, depression and hostility status (results are presented as odds ratios and 95% confidence intervals). Odds ratios are adjusted for age, sex, educational level, smoking status, level of adherence to the Mediterranean diet, BMI and medicalhistory of hypertension, diabetes, and hypercholesterolemia

Regarding the CVD risk, the impact of irrational beliefs on CVD risk was less prominent and became insignificant when depression and anxiety status were controlled for (***Table 7.2***, *Models 4* and *5*). The interactions between IBI and ZDRS scores, as well as IBI and STAI scores on CVD risk, were highly significant suggesting that the higher the depression and anxiety status of the participants, the higher the effect of irrational beliefs on 10-year CVD risk (p-values < 0.001). In particular, in participants who were classified in the highest 50%ntile of ZDRS (depression) score, a 1-unit increase in IBI score was associated with much higher 10- year CVD risk (HR 1.22, 95%CI 1.04, 1.44), as compared to those in the lowest

50%ntile (HR 1.06, 95%CI 1.00, 1.12). Similarly, in participants who were classified in the highest 50%ntile of STAI (anxiety) score, a 1-unit increase in IBI score was associated with much higher 10-year CVD risk (HR 1.42, 95%CI 1.12, 1.80), as compared to those in the lowest 50%ntile (HR 1.05, 95%CI 1.00, 1.12). However, when additional analysis was performed to test for a potential mediation effect of anxiety and depression on the relationship between irrational beliefs and CVD risk (using Sobel's test), no significant mediation was revealed (*p*-values > 0.20), suggesting that anxiety and depression play a moderating, but not a mediating, role in the independent relationship between irrational beliefs and 10-year CVD risk.

Table 7.2: Results from nested, multi-adjusted models that evaluated the association between irrational beliefs index score and 10-year incidence of cardiovascular disease (results are presented as hazard ratios and 95% confidence intervals)

	Model 1	Model 2	Model 3	Model 4	Model 5
IBI score	1.07	1.07	1.05	1.11	1.10
(20–88, per 1 unit)	(1.01,1.12)*	(1.01,1.12)*	(1.00,1.11)*	(0.96, 1.28)	(0.95,1.26)
Current smoker	-	1.33	1.33	1.34	1.43
(yes vs. no)		(1.01,1.83)*	(1.01,1.83)*	(1.02,1.87)*	(1.01,1.88)*
Physical activity (moderate/high vs. low)	-	0.87	0.90	0.91	0.90
		(0.68,1.15)	(0.67, 1.21)	(0.68, 1.21)	(0.67, 1.20)
MedDietScore	-	0.97	0.97	0.97	0.95
(per 1 unit)		(0.95,0.99)*	(0.95,1.00)	(0.95, 1.00)	(0.91,0.98)*
Hypertension	-	-	1.19	1.18	1.21
(yes vs. no)			(0.89, 1.60)	(0.88, 1.58)	(0.83, 1.64)
Hypercholesterolemia (yes vs. no)	-	-	1.09	1.11	1.17
			(0.81, 1.45)	(0.83, 1.48)	(0.81, 1.55)
Diabetes mellitus (yes vs. no)	-	-	1.99	2.00	2.01
			(1.31,3.02)*	(1.31,3.03)*	(1.30,3.07)*
ZDRS	**-**	**-**	**-**	**1.04**	**-**
(20–80, per 1 unit)				**(0.99, 1.09)**	
STAI (20–80, per 1 unit)	**-**	**-**	**-**	**-**	**1.02**
					(0.98, 1.06)

All models are age and sex-adjusted

* *p*-values < 0.05

In addition, participants with high-IBI-high-STAI had an almost 4-times higher likelihood of CVDs than those with high-IBI-low-STAI (95%CI 1.21, 12.49) after adjustment for sex, age, educational and smoking status (*Model 2*, ***Table 7.3***). When educational status, mainly, and smoking habits, were included in *Model 2*, the effect of high-IBI-high-STAI on 10-year CVD incidence significantly increased compared to the previous Model 1 (***Table 7.3***) (*p-value for mediation* < 0.001). Even after adjusting for BMI, physical activity (*Model 3*, ***Table 7.3***), MedDietScore (*Model 4*, ***Table 7.3***) and medical history (*Model 5*, ***Table 7.3***) (*p-value* < 0.001), the association between high-IBI-high-STAI remained significant, but it lost its significance when biochemical factors were included in Model 6 (suggesting a strong mediation effect of the biochemical reactions) (*p-value* < 0.02). In the case of irrational beliefs and depression, an interaction between irrational beliefs and depression was not associated with the 10-year CVD incidence in all models (***Table 7.4***).

Table 7.3: Results from nested, multi-adjusted models that evaluated the association between Irrational Beliefs and 10-year incidence of cardiovascular disease (results are presented as odds ratios and 95% confidence intervals)

	Model 1	Model 2	Model 3	Model 4	Model 5
IBI & STAI High-IBI-high STAIvs. High-IBI-low-STAI	**2.38 (1.75,3.23)***	**3.38 (1.21,12.49)***	**3.79 (1.16,12.32)***	**3.85 (1.18,12.53)***	**3.80 (1.16,12.38)***
Education status (medium/high vs. low)	-	0.69 (0.49,0.97)*	0.72 (0.51, 1.01)	0.72 (0.51, 1.02)	0.71 (0.49, 1.02)
Current smoking (Y/N)	-	1.32 (0.98, 1.78)	1.32 (0.97, 1.78)	1.32 (0.98, 1.79)	1.39 (1.02,1.91)*
Body Mass Index (per 1 kg/m2)	-	-	1.04 (1.01,1.07)*	1.04 (1.00, 1.07)	1.03 (1.00, 1.07)
Physical activity (Y/N)	-	-	0.93 (0.69, 1.24)	0.93 (0.69, 1.24)	0.97 (0.71, 1.31)
MedDietScore (per 1 unit)	-	-	-	0.99 (0.96, 1.01)	0.98 (0.95, 1.01)
Hypertension (Y/N)	-	-	-	-	1.13 (0.83, 1.53)
Hypercholesterolemia (Y/N)	-	-	-	-	1.06 (0.79, 1.42)
Diabetes mellitus (Y/N)	-	-	-	-	1.83 (1.19,2.81)*

All models are age and sex-adjusted

**p-values* <0.05

Table 7.4: Results from nested, multi-adjusted models that evaluated the association between Irrational Beliefs and 10-year incidence of cardiovascular disease (results are presented as odds ratios and 95% confidence intervals)

	Model 1	Model 2	Model 3	Model 4	Model 5
IBI & ZDRS	**1.45**	**1.22**	**1.23**	**1.21**	**1.13**
High-IBI-high-ZDRSvs. High-IBI-low-ZDRS	**(0.96,2.17)***	**(0.74,2.01)***	**(0.74,2.03)***	**(0.73,2.01)***	**(0.67,1.90)**
Education status (medium/high vs. low)	-	0.72 (0.50, 1.02)*	0.74 (0.52, 1.06)	0.75 (0.52, 1.07)	0.72 (0.50, 1.05)
Current smoking (Y/N)	-	1.34 (0.99, 1.80)	1.34 (0.99, 1.81)	1.34 (0.99, 1.82)	1.42 (1.03,1.94)*
Body Mass Index (per 1 kg/m2)	-	-	1.04 (1.01, 1.07)*	1.04 (1.00, 1.07)	1.03 (1.03,1.07)*
Physical activity (Y/N)	-	-	0.94 (0.70, 1.26)	0.94 (0.70, 1.26)	0.98 (0.72, 1.32)
MedDietScore (per 1 unit)	-	-	-	0.99 (0.96, 1.01)	0.98 (0.95, 1.01)
Hypertension (Y/N)	-	-	-	-	1.13 (0.83, 1.53)
Hypercholesterolemia (Y/N)	-	-	-	-	1.05 (0.78, 1.40)
Diabetes mellitus (Y/N)	-	-	-	-	1.83 (1.19,2.80)*

All models are age and sex-adjusted

*p-values <0.05

9.4 Components of Irrational Beliefs and the development of CVD

To thoroughly investigate the role of irrational beliefs in cardio-metabolic disorders, we also included in our analyses the different components of irrational beliefs. Therefore, a factor analysis was conducted to better explore and explain the relationship between irrational beliefs and CVD incidence. An eleven-factor solution was extracted from factor analysis; the first three factors were considered and interpreted as they explained most of the variance (eigenvalues>1). These factors

were interpreted (named) according to the scores of each irrational beliefs group that correlated most, i.e., scores > 0.4 (factor scores are interpreted similarly to correlation coefficients, i.e., higher absolute values indicate that the irrational beliefs variable contributes most to the construction of the factor).

The first factor included 7 items i.e., 3, 4, 5, 6, 8, 10 and 11 (***Table 8.1***). This factor was named "*cognitive vulnerability to anxiety*" because it consisted of irrational beliefs such as demandingness (i.e., excessive commands on self and others, "Ibelieve there are some people in the world who are bad or wicked. They should held responsible for their actions and punished"), perfectionism (i.e., a type of self-orienteddemand, "I become more upset than I should when things are not the way I want themto be" and "I believe there is one right solution to any given problem. If I do not find this solution, I feel I have failed"), emotional irresponsibility (i.e., the belief that emotions are caused by external factors, "I believe most human unhappiness is causedby external factors; that people have little ability to control their own sorrows and disturbances"), anxious over-concern (i.e., belief that potential negative events will occur in the future, "I become very concerned about things that are dangerous and dwell on the possibility of their occurrence"), dependence on others ("I believe I need another person stronger than myself on whom to rely"), and over-concern for the welfare of others ("I become more upset than I should about other people's problems and disturbances.") that all are strong predictors to anxiety (Bridges & Sanderman, 2002; Daniel, et al., 2010). The second factor consisted of three items, i.e., 1, 2, and 7 and was named *"assertiveness deficits"* ("It is very important to me to be loved or approved of by almost everyone I meet.", "I believe I should be competent at everything I attempt.", "I believe it is better in the long run to avoid some life difficulties and responsibilities than to face them." (Daniel et al., 2010). Assertivenessdeficits refer to themes of universal love and approval and total competence (Daniel, et al., 2010). These unrealistic expectations form nonassertive individuals (Daniel, et al., 2010). The third factor consisted of one item, i.e., 9 which was named *"helplessness" ("*My past history is an important determinant of my present behavior.I believe that once something strongly affects my life it will always affect my behavior.") (Daniel, et al., 2010) (***Table 8.1***).

Only Factor 1 was included in further analyses as it was the most dominant, explaining 29% of the total variation, while Factor 2 explained 13% and Factor 3, 9% of the total variation, respectively. Factor scores were also calculated for all participants (i.e., the highest score the greater the severity of irrational beliefs factor).

Table 8.1: Factor coefficients loadings (with absolute values >0.4) regarding Irrational Beliefs Inventory items, answered by ATTICA study participants (n = 853)

Irrational beliefs items	Factor 1	Factor 2	Factor 3
1. "It is very important to me to be loved or approved of by almost everyone I meet."	0.461	0.465	
2. "I believe I should be competent at everything I attempt."		0.729	
3. "I believe that there are some people in the world who are bad or wicked. They should be held responsible for their actions and punished."	0.514		
4. "I become more upset than I should when things are not the way I want them to be."	0.681		
5. "I believe most human unhappiness is caused by external factors; that people have little ability to control their own sorrows and disturbances."	0.613		
6. "I become very concerned about things that are dangerous and dwell on the possibility of their occurrence."	0.737		
7. "I believe it is better in the long run to avoid some life difficulties and responsibilities than to face them."		-0.612	
8. "I believe I need another person stronger than myself on whom to rely."	0.540	-0.504	
9. "My past history is an important determinant of my present behavior. I believe that once something strongly affects my life it will always affect my behavior."			0.828
10. "I become more upset than I should about other people's problems and disturbances."	0.625		
11. "I believe there is one right solution to any given problem. If I do not find this solution, I feel I have failed."	0.588		

Score coefficients are similar to the correlation coefficient, with higher absolute values indicative of higher correlation between the irrational belief variable and the respective factor; Cognitive vulnerability to anxiety consisted of demandingness, perfectionism, emotional irresponsibility, anxious over-concern, dependence on others, over-concern for the welfare of others (Factor 1), assertiveness deficits (Factor 2), helplessness (Factor 3)

Crude, unadjusted data analysis revealed that participants with high "cognitive vulnerability to anxiety" were at higher risk of developing CVDs, as compared to those with low endorsement of such irrational beliefs (RR 3.32, 95%CI, 2.94, 3.75). However, residual confounding might exist, particularly when several associations have already been reported between cognitive vulnerability to anxiety and various social, clinical and psychological characteristics. After adjustment for sex and age, "cognitive vulnerability to anxiety" was significantly positively associated with 10- year CVD incidence in both men and women. Specifically, for 1-unit increase in this factor a 197% higher risk for a CVD event was revealed (***Table 8.2***, *Model 1*). The later association remained significant (RR 2.48, 95%CI, 1.97, 3.11) even when adjusting for potential confounding factors such as smoking habits, physical activity status, level of adherence to the Mediterranean diet, as well as history of hypertension, hypercholesterolemia, triglycerides, glucose levels and depression score (***Table 8.2***, *Models 2* and *3*). As "cognitive vulnerability to anxiety" has shown significant associations with psychological factors (i.e., anxiety, depression), its role on CVDs was further explored, taking into consideration these psychological dimensions (*Models 4*, *5* and *6*). "Cognitive vulnerability to anxiety" was still positively associated with the 10-year risk of developing CVDs (RR 1.84, 95%CI 1.15, 2.93) even after adjusting for ZDRS score (***Table 8.2***, *Model 4*); however, became insignificant (RR 1.69 95%0.91, 3.15) when anxiety status and negative well-being were controlled for (***Table 8.2***, *Models 5*, and *6*). In particular, when STAI score was entered in *Model 5*, a significant mediation (using Sobel's test) occurred in the effect on the 10-year CVDs risk. It was also observed that when negative well-being entered*Model 6*, a highly significant mediation occurred in the effect of cognitive vulnerability to anxiety on the 10-year CVDs risk (***Table 8.2***). No significant associations were observed between the other extracted factors and 10-year CVD incidence (*data not shown*).

Table 8.2: Results from nested, multi-adjusted logistic regression models that evaluated the association between cognitive vulnerability factor and 10-year incidence of CVDs (results are presented as Relative Risk and 95% confidence intervals)

	Model 1	Model 2	Model 3	Model 4	Model 5	Model 6
Cognitive vulnerability to anxiety* (per 1 unit)	2.97 (2.55, 3.46)*	2.46 (2.02, 2.98)*	2.48 (1.97, 3.11)*	1.84 (1.15, 2.93)*	1.63 (1.00, 2.66)	1.69 (0.91, 3.15)
Cigarettes per day	-	1.00 (0.98, 1.02)	1.00 (0.98, 1.02)	1.00 (0.96, 1.04)	1.00 (0.96, 1.05)	1.00 (0.95, 1.05)
Body Mass Index (per 1 kg/m^2)	-	1.21 (0.62, 2.34)	1.12 (0.49, 2.54)	1.12 (0.49, 2.54)	1.12 (0.49, 2.54)	1.12 (0.49, 2.54)
Physical activity (moderate/high vs. low)	-	0.82 (0.45, 1.52)	0.99 (0.48, 2.05)	0.78 (0.17, 3.48)	1.00 (0.21, 4.61)	0.95 (0.17, 5.36)
MedDietScore (per 1 unit)	-	0.97 (0.91, 1.02)	0.95 (0.88, 1.03)	0.99 (0.81, 1.21)	0.97 (0.79, 1.17)	0.97 (0.75, 1.25)
Hypertension (yes vs. no)	-	-	0.86 (0.42, 1.72)	1.22 (0.30, 4,86)	0.96 (0.23, 4.02)	2.12 (0.33, 13.52)
Hypercholesterolemia (yes vs. no)	-	-	2.01 (1.02, 3.96)	1.22 (0.30, 4.86)	2.22 (0.50, 9.89)	1.92 (0.32, 11.43)
TyG Index (per 1 unit)	-	-	1.08 (0.60, 1.91)	1.25 (0.34, 4.48)	1.39 (0.41, 4.66)	1.75 (0.37, 8.17)
ZDRS (20-80, per 1 unit)[a]	-	-	-	1.05 (0.95, 1.16)	-	-
STAI (20-80, per 1 unit)[b]	-	-	-	-	1.05 (0.98, 1.13)	1.01 (0.93, 1.10)
Negative well-being***	-	-	-			2.00 (1.01, 4.00)*

All models are age and sex adjusted.
[a]Zung self-rating Depression Scale.
[b]Spielberger State-Trait anxiety Inventory.
*Irrational beliefs factor 1 includes the following components: demandingness, perfectionism, emotional irresponsibility, anxious over-concern, dependence on others, over-concern for the welfare of others.
***p <.05.
***The EQ-5D questionnaire as a measurement of physical well-being (mobility, self-care, usual activities, pain/discomfort, depression/ anxiety) with a classification of having the perfect health state (according to the EQ-5D scoring system).

9.5 Findings from the 20-year Follow-Up

During 2002-2022, the 20-year CVD incidence for participants who had completed the psychological assessment was n=109 cases (21%), or 213/1000 participants; of them, n= 54 (53%) were men and n= 48(47%) were women (p for sex differences = 0.963). In ***Table 9.1*** socio-demographic, behavioural and clinical characteristics of men and women in the ATTICA study regarding the 20-year CVD incidence, are presented.

Of the 512 subjects for whom CVDs were clinically assessed, 109 subjects developed the disease (21% of participants). Individuals who developed CVDs were mainly middle-aged and men (65%) compared to people who did not develop CVDs. Concerning lifestyle behaviours, individuals who experienced CVDs had lower adherence to the Mediterranean diet than individuals who did not (25±6 vs. 27±8 respectively, $p < 0.001$). Regarding the clinical characteristics, individuals who developed CVDs had a statistically significant higher relative frequency of hypertension, hypercholesterolemia, T2DM and obesity ($p < 0.001$). Finally, concerning psychological symptoms, individuals who developed CVDs in a 20-year follow-up period had higher levels of anxiety ($p = 0.043$). However, there were no statistically significant differences in lifestyle behaviours, such as physical activity and smoking, nor psychological characteristics, such as irrational beliefs, depression, health anxiety, and hostility (*all p-values*>0.5).

Table 9.1: Baseline socio-demographic, lifestyle, anthropometric, biological, clinical, and psychological characteristics of the study participants by the 20-year cardiovascular disease (CVD) incidence (*n*=512)

	CVD event during the 20-year follow-up No (n=403) n (79%)	**CVD event during the 20-year follow-up Yes (n=109) n (21%)**	***p***
Socio-economic factors			
Age, years [Mean (SD)]	38±10	52±8	**<0.001**
Sex (%women)	55%	35 %	**<0.001**
Education, years [Mean (SD)]	12±3	12±4	**0.002**
Lifestyle factors			
Current smoking, %	44%	43%	0.84
Sedentary life, %	57%	56%	0.80
MedDietScore, (range 0-55) [Mean (SD)]	27± 8	25±6	**<0.001**
Clinical factors			
Hypertension, %	19%	51%	**<0.001**
Hypercholesterolemia, %	22%	58%	**<0.001**
Obesity, %yes	46%	74%	**<0.001**
Diabetes mellitus, %	1%	14%	**<0.001**
Psychological factors			
Irrational Beliefs Inventory (range 0-88), [Mean (SD)]	52±11	53±11	0.40
Zung self-rating Depression Scale (range 0–80), [Mean (SD)]	35±7	34±8	0.52
Spielberger State-Trait Anxiety Inventory (range 0–80), [Mean (SD)]	39±12	43±12	**0.04**
Hostility and Direction of Hostility Questionnaire (range 0–51), [Mean (SD)]	16±6	17±5	0.41
Whiteley Index for Health Anxiety (WI)(range 0-14), [Mean (SD)]	4±3	4±3	0.47

Data are presented as mean ± standard deviation (SD) (i.e., mean (SD)). *P-values* were obtained using one-way analysis of variance for independent samples for the normally distributed variables, the Kruskal–Wallis test for the rest of the quantitative variables, and chi-squared test for categorical variables

Regarding psychological assessment, although only depression was associated with 20-year CVD risk, crude, unadjusted data analysis revealed that participants with high levels of irrational beliefs were at higher risk of developing CVDs during a 20-year follow-up period, compared to participants with low endorsement of irrational beliefs (HR 1.10, 95%CI 1.05 1.14). However, residual confounding might exist, particularly when several associations have already been reported between irrational beliefs, the investigated emotions, and age, social, behavioural and biochemical factors. Thus, multi-adjusted data analysis was applied.

A latent variable (low STAI at baseline and 10-year follow-up (n = 158) /low STAI at baseline and high at 10-year follow-up (n = 54)/high STAI at baseline and low at 10-year follow-up (n = 0)/high STAI at baseline and 10-year follow-up (n = 410)) was created classifying participants into four categories regarding anxiety symptomatology across time. Similarly, a latent variable (low ZDRS at baseline and 10-year follow-up (n= 487) /low ZDRS at baseline and high at 10-year follow-up (n=2) /high ZDRS at baseline and low at 10-year follow-up (n=0) /high ZDRS at baseline and 10-year follow-up (n=141)) was created classifying participants into fourcategories regarding depressive symptomatology across time.

After adjustment for age and sex (*Model 1*, ***Table 9.2***), as well as smoking, physical activity, and Mediterranean diet (*Model 2*, ***Table 9.2***), this association remained significant. Yet, the association between irrational beliefs and 20-year CVD risk became insignificant when hypertension and diabetes mellitus were entered in *Model 3*, indicating that hypertension (HR 2.31, 95%CI 1.80, 2.96), diabetes (HR 6.85, 95%CI 3.79, 12.38) and Mediterranean diet (HR 0.92, 95%CI 0.89, 0.94) mediated the relationship between irrational beliefs and 20-year CVD incidence.

We also evaluated the possible mediating effect of anxiety and depression trajectories on the associations between irrational beliefs (as evaluated by IBI score), and the 20-year CVD risk. When anxiety and depression trajectories, were separately

entered in *Model 5* (***Table 9.2***), IBI score lost its significance related to CVD risk, and the mediating role of the aforementioned psychological factors was revealed (HR of irrational beliefs after the inclusion of anxiety trajectories 1.01, 95%CI 0.98, 1.03 and depression trajectories 1.01, 95%CI 0.99, 1.03, *p-values of Sobel's test* <0.001, respectively).

Table 9.2: Results from nested, multi-adjusted models that evaluated the association between irrational beliefs index score and 20-year incidence of cardiovascular disease (results are presented as hazard ratios and 95% confidence intervals)

	Model 1	Model 2	Model 3	Model 4	Model 5
IBI score (20–88, per 1 unit)	1.05 (1.01,1.10)*	1.04 (1.01,1.09)*	1.02 (0.97,1.07)	1.01 (0.98, 1.03)	1.03 (0.92, 1.14)
Current smoker (yes vs. no)	-	0.79 (0.63, 0.99)	8.57 (0.67,1.08)	1.02 (0.62, 1.68)	0.93 (0.56,1.53)
Physical activity (moderate/high vs. low)	-	1.10 (0.96, 1.27)	1.12 (0.96, 1.30)	1.05 (0.77, 1.42)	1.05 (0.77, 1.42)
MedDietScore (per 1 unit)	-	0.91 (0.89,0.94)	0.92 (0.89, 0.94)*	0.92 (0.88,0.97)*	0.92 (0.88,0.96)*
Hypertension (yes vs. no)	-	-	2.31 (1.80, 2.96)*	2.70 (1.62, 4.46)*	2.70 (1.61,4.52)*
Diabetes mellitus (yes vs. no)	-	-	6.85 (3.79,12.38)*	6.85 (3.79,12.38)*	6.85 (3.79,12.38)*
ZDRS trajectories (10-year depression vs. no depression)	-	-	-	1.31 (0.73, 2.40)	-
STAI trajectories (10-year anxiety vs. no anxiety)	-	-	-	-	1.31 (0.76, 2.26)

All models are age and sex-adjusted

* *p*-values < 0.05

Additionally, a highly significant interaction was observed between IBI and anxiety trajectories, as well as depression trajectories, on the risk of developing CVD in 20 years follow-up period (*p's* <0.10). Therefore, we proceeded to perform a stratified analysis. However, no significant association was observed between irrational and CVD incidence, among those who had no anxiety at baseline and at 10- year follow-up, those with no anxiety at baseline but with anxiety at follow-up and those with anxiety at baseline and at follow-up (*see* ***Figure 9.6***).

On the other hand, when we focused on those with high irrational beliefs, who also had depression at baseline and depression at 20-year follow-up, their likelihood of CVD incidence was 1.3 times higher than those with low irrational beliefs (HR= 1.30, 95% CI= 1.02, 1.62). No significant association was observed between irrationalbeliefs and CVD incidence, among those who had no depression at baseline and at follow-up (*see* ***Figure 9.7***).

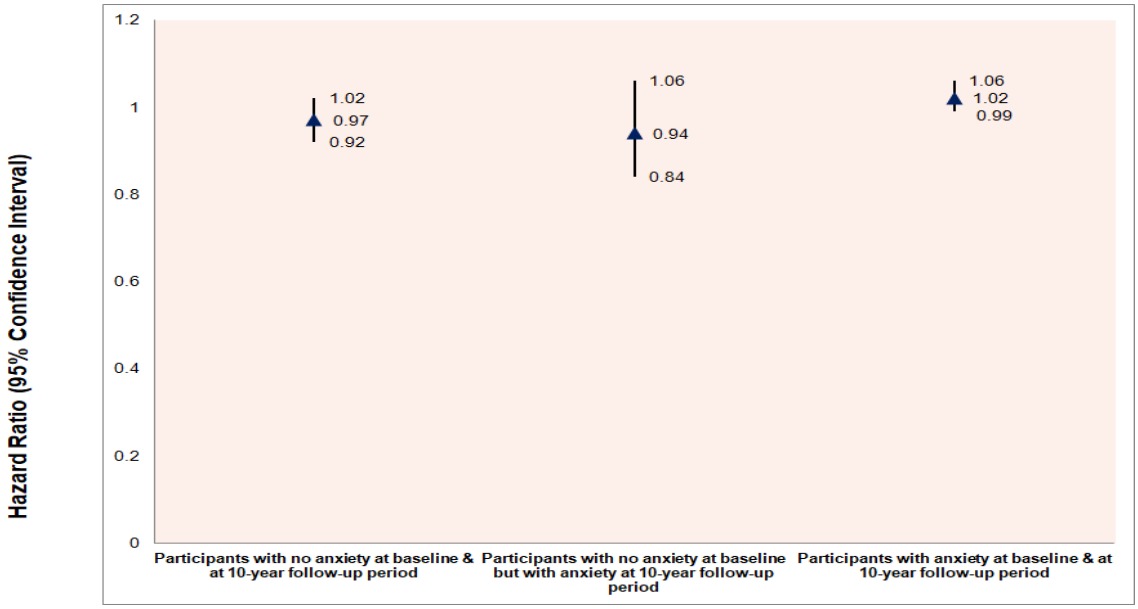


Figure 9.6: Results from the multi-adjusted logistic regression models evaluating the association between the participants' levels of irrational beliefs (moderate/high vs. low) with the 20-year incidence of cardiovascular disease, according to trajectories of anxiety (individuals who did not have anxiety at baseline and at 10-year follow-up period/individuals who did not have anxiety at baseline but they develop at 10-year follow-up period/individuals who had anxiety at baseline and 10-year follow-up

period) (results are presented as hazard ratios and 95% confidence intervals). Hazard ratios are adjusted for age, sex, occupation, obesity, smoking status, physical activity level, level of adherence to the Mediterranean diet, hypertension, diabetes mellitus, and family history of CVDs)

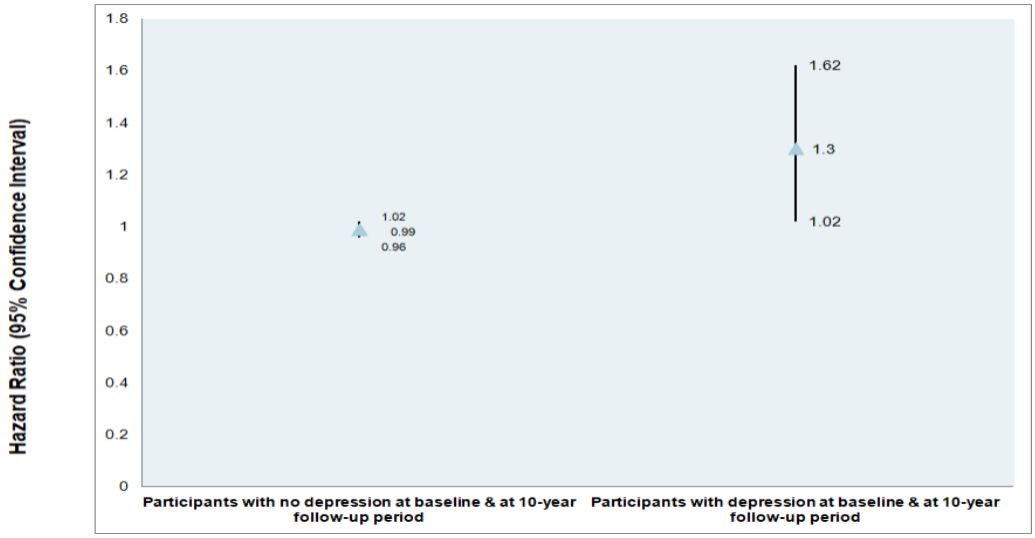


Figure 9.7: Results from the multi-adjusted logistic regression models evaluating the association between the participants' levels of irrational beliefs (moderate/high vs. low) with the 20-year incidence of cardiovascular disease, according to trajectories of depression (individuals who did not have depression at baseline and 10-year follow- up period/individuals who had depression at baseline and 10-year follow-up period) (results are presented as hazard ratios and 95% confidence intervals). Hazard ratios are adjusted for age, sex, occupation, smoking status, level of adherence to the Mediterranean diet, physical activity level, and metabolic syndrome)

Therefore, anxiety affected the direction of the relationship between irrational beliefs and 20-year CVD incidence, while depression was observed to affect both the strength and the direction of the relationship between irrational beliefs and 20-year CVD incidence.

The 20-year follow-up also allowed us the opportunity to examine the data in four-time points and, therefore, possibly provided a more accurate estimation of them. Crude, unadjusted analysis revealed a positive association between high-IBI-high-STAI/ZDRS score and risk of developing CVDs during the 20-year follow-up. However, residual confounding may exist, especially when several associations between high-IBI-high-STAI score or high-IBI-high-ZDRS score and age, social, behavioural and biochemical factors were already observed.

After adjustment for sex and age at baseline, participants with high-IBI-high-STAI had a 1.36 times higher likelihood of CVDs as compared to those with low-IBI-low-STAI (95%CI 1.12, 1.67) (***Table 9.3***, *Model 1*). When smoking habits, physical activity and Med- DietScore at 5-year follow-up period, as well as hypertension, hypercholesterolemia and diabetes mellitus at 10-year follow-up period were entered in Model 2 and 3, respectively, the association between high-IBI-high-STAI lost its significance (HR 0.92, 95%CI 0.72, 1.17). Particularly, the Mediterranean diet, hypertension, hypercholesterolemia, diabetes mellitus, as well as metabolic syndrome (*Sobel's test p-value p*=0.05) had a mediation effect in the relationship between irrational beliefs and anxiety, and the 20-year CVD incidence.

Regarding irrational beliefs and depression, after adjustment for sex and age at baseline, depression-related-to-irrational beliefs were significantly associated with the 20-year CVD incidence (*Model 1*, ***Table 9.4***). Specifically, participants with high IBI and high ZDRS score had a 1.46 times higher likelihood of developing CVDs during the 20-year follow-up as compared to participants who had low irrational beliefs and low levels of depression (HR 1.46, 95%CI 1.05, 2.03). The later association lost its significance when smoking, physical activity status, and Mediterranean diet adherence at 5- year follow-up (*Model 2* ***Table 9.4***), as well as hypertension, hypercholesterolemia, diabetes mellitus (*Model 3*), and metabolic syndrome at 10- year follow-up (*Model 4*) were considered. In particular, the Mediterranean diet, hypertension, hypercholesterolemia, diabetes mellitus, as well as metabolic syndrome (*Sobel's test p-value p*=0.003) had a mediation effect in the relationship between irrational beliefs and depression, and the 20-year CVD incidence.

Table 9.3: Results from nested, multi-adjusted models that evaluated the association between Irrational Beliefs and anxiety, and 20-year incidence of CVDs

	Model 1	Model 2	Model 3	Model 4
IBI & STAI High-IBI-high-STAI vs. Low-IBI-low-STAI	1.36 (1.12, 1.67)	0.92 (0.72, 1.17)	1.44 (0.38,5.46)	0.95 (0.71, 1.28)
Current smoking in 5 years follow-up (Y/N)	-	0.89 (0.70, 1.13)	0.89 (0.63, 1.27)	0.89 (0.69, 1.20)
Physical inactivity in 5 years follow-up (Y/N)	-	0.95 (0.73, 1.22)	0.87 (0.60, 1.26)	0.94 (0.68, 1.28)
MedDietScore in 5-years follow-up (per 1 unit)	-	0.90 (0.88, 0.93)*	0.95 (0.92, 0.98)*	0.91 (0.88, 0.94)*
Hypertension in 10-years follow-up (Y/N)	-	-	3.90 (2.77, 5.48)*	-
Hypercholesterolemia in 10 years follow-up (Y/N)	-	-	3.50 (2.41, 5.05)*	-
Diabetes mellitus in 10-years follow-up (Y/N)	-	-	5.10 (3.24, 8.00)*	-
Metabolic syndrome in 10-years follow-up	-	-	-	1.15 (0.86, 1.53)**

Data are presented as hazard ratios and 95% confidence intervals

All models are age- and sex-adjusted

* p-values <0.05

** Sobel's test p-value

Hypertension, hypercholesterolemia and diabetes, as well as MetS were entered separately in Model 6.

Table 9.4: Results from nested, multi-adjusted models that evaluated the association between Irrational Beliefs and depression, and 20-year incidence of CVDs

	Model 1	Model 2	Model 3	Model 4
IBI & ZDRS High-IBI-high-ZDRS vs. Low-IBI-low-ZDRS	1.46 (1.05, 2.03)	1.34 (0.92, 1.93)	1.28 (0.75,2.18)	1.41 (0.90, 2.20)
Current smoking in 5 years follow-up (Y/N)	-	0.89 (0.70, 1.13)	0.90 (0.63, 1.27)	0.89 (0.67, 1.20)
Physical inactivity in 5 years follow-up (Y/N)	-	0.96 (0.74, 1.24)	0.88 (0.60, 1.28)	0.95 (0.69, 1.30)
MedDietScore in 5-years follow-up (per 1 unit)	-	0.90 (0.88, 0.93)*	0.95 (0.92, 0.98)*	0.91 (0.89, 0.93)*
Hypertension in 10-years follow-up (Y/N)	-	-	3.90 (2.78, 5.51)*	-
Hypercholesterolemia in 10 years follow-up (Y/N)	-	-	3.52 (2.43, 5.09)*	-
Diabetes mellitus in 10-years follow-up (Y/N)	-	-	5.06 (3.22, 7.96)*	-
Metabolic syndrome in 10-years follow-up	-	-	-	1.20 (0.90, 1.60)**

Data are presented as hazard ratios and 95% confidence intervals

All models are age- and sex-adjusted

* p-values <0.05

** Sobel's test p-value

Hypertension, hypercholesterolemia and diabetes, as well as MetS, were entered separately in Model 6

10. Discussion

10.1 An Overview

The purpose of this thesis was to evaluate the 10-year cardio-metabolic incidence, taking into consideration the role of negative cognitive (i.e., irrational beliefs), emotional (e.g., anxiety, depression, hostility), behavioural (e.g., unhealthy diet patterns, physical inactivity, smoking habits etc.), and clinical (e.g., hypertension, hypercholesterolemia, etc.) risk factors, in a representative, relatively adequate, and random sample of the Greek population. The following conclusions emerged:

- Participants of both sexes, with high levels of irrational beliefs **had 10% higher risk to develop CVD** in 10-years follow-up period, compared to those with low levels of irrational beliefs.
- Participants with high irrational beliefs and anxiety symptoms **had 138% greater risk of developing CVDs during the 10-year follow-up as compared to those without anxiety, suggesting that irrational beliefs may trigger anxiety in later life and consequently increase CVD risk.** An interaction between irrational beliefs and depression was not associated with the 10-year CVD incidence.
- **Lower education status moderated the relationship** between irrational beliefs and 10-years CVD risk.
- **Smoking, dietary patterns away from the Mediterranean diet, MetS, and diabetes mellitus mediated the relationship** between irrational beliefs and 10-years CVD risk.
    - **High irrational beliefs were associated with 50% higher risk of developing 10-years MetS** than low irrational beliefs. Especially, participants with high irrational beliefs and high anxiety were 96% more

likely to develop MetS, compared with those with low irrational beliefs and low or high anxiety.

- Regarding diabetes mellitus, individuals with high irrational beliefs levels had a 1-fold higher odd to develop T2DM in 10-year follow-up period, compared to those with low irrational beliefs. Especially, participants with increased irrational beliefs and low adherence to the Mediterranean diet were 270% more likely to develop T2DM than those with the reverse status. Regarding the synergistic role of irrational beliefs with anxiety,participants with high irrational beliefs who also had anxiety symptoms hada 93% excess risk of developing T2DM during the 10-year follow-up, as compared to those without anxiety. Moreover, T2DM risk was 73% higher among individuals with high levels of irrational beliefs and depression as compared to those where depression was absent (1.73; 1.21, 2.46). Lower education status, family history of diabetes, hypercholesterolemia, highBMI, as well as TNF-α and TAC were revealed as mediating risk factors related to the tested associations.

  → regarding family history of diabetes, the highest likelihood of developing T2DM, regarding participants' tested psychological features (i.e., low/high irrational beliefs in the entire group, low/high health anxiety in the entire group, and low/high irrational beliefs−low/high healthy anxiety), had people with high irrational beliefs−low health anxiety (OR 3.70, 95%CI 1.83, 7.48).

- In the synergistic role of irrational beliefs and anxiety, TNF-α, CRP, IL-6, fibrinogen and TAC mediated their relationship with 10-year CVD risk.
- Focusing even more on irrational beliefs, the identified dominant irrational beliefs factor, 'cognitive vulnerability to anxiety', consisted of demandingness, perfectionism, emotional irresponsibility, anxious over-concern, dependence on others, and over-concern for the welfare of others wasstrongly associated with a very increased 10-year CVD risk (HR 3.32, 95%CI, 2.94, 3.75). Anxiety, as well as negative physical well-being, mediated this relationship.

- Preliminary findings from the recent 20-year follow-up assessment revealed that participants with high levels of irrational beliefs were at higher risk of likely in developing CVDs during a 20-year follow-up period, compared to participants with low endorsement of irrational beliefs (HR 1.10, 95%CI 1.05 1.14).
    - Hypertension, diabetes mellitus and Mediterranean diet mediated the relationship between irrational beliefs and 20-year CVD incidence. Also, anxiety and depression trajectories mediated their relationship.
    - A highly significant interaction was observed between IBI and anxiety trajectories, as well as depression trajectories, on the risk of developing CVDs in 20 years follow-up period (*p's* <0.10).However, no significant association was observed between irrational and CVD incidence, among those who had no anxiety at baseline and at 10-year follow-up, those with no anxiety at baseline but with anxiety at follow-up and those with anxiety at baseline and at follow-up. On the other hand, when we focused on those with high irrational beliefs, who also had depression at baseline and depression at 20-year follow-up, their likelihood of CVD incidence was 1.3 times higher than those with low irrational beliefs.

We also examined the data in four-time points during the 20-year follow-up period, for more accurately exploring our hypothesis. After adjustment for sex and age,

- participants with high-IBI-high-STAI had **36% higher likelihood of CVDs** as compared to those with low-IBI-low-STAI.
    - Adherence to a Mediterranean type of diet, as well as history of hypertension, hypercholesterolemia, MetS and T2DM mediated the relationship between irrational beliefs-anxiety, and the 20-year CVD incidence.
- Participants with high IBI and depression had a 46% higher likelihood of developing CVDs during the 20-year follow-up as compared to participants who had low irrational beliefs and low levels of depression.

- Adherence to a Mediterranean type of diet, history of hypertension, hypercholesterolemia, diabetes mellitus, as well as MetS mediated the relationship between baseline irrational beliefs-depression, and the 20-year CVD incidence.

10.2 The Direct Association of Irrational Beliefs in developing MetS and CVDs

Although irrational beliefs independently predict both MetS and CVDs incidence, these associations cannot be explained without a context of interrelationships with social, other psychological, lifestyle and biological factors.

10.3 The Indirect Effect of Irrational Beliefs in developing MetS and CVDs

The Role of Social Factors

Heart-related problems may have a psychosomatic background and they are greatly affected by social and psychological factors, whereas the development of psychosomatic disorders involves the coexistence of psychological causes and physical symptoms (Amri et al., 2015). In addition, beliefs or perceptions are shaped and influenced by socio-demographic (e.g., age and sex), socio-psychological (e.g., cognitions and personality), and structural factors (e.g., socio-economic and education level) (Feinstein et al., 2006). Some researchers suggest that social and psychological factors are the most significant criteria for the development and the course of cardiovascular problems (Amri et al., 2015). This work which is consistent with previous studies shows a clear link between irrational beliefs and socio-economically vulnerable classes, as well as low socio-economic status with adverse health outcomes (Kollia et al., 2016). The present thesis also revealed that low educational status, financial status, and SES are most commonly met in individuals with a high IBI score compared to those with low and moderate IBI scores. Of these proxies of social determinants, education status showed to be the strongest moderating factor between irrational beliefs and CVD risk. Education may provide individuals with greater access to information and stronger critical thinking skills, or conversely, individuals with higher skills might achieve higher educational status (Cutler, 2006). School

education and other learning opportunities build qualities, such as self-control, problem-solving, perseverance, conscientiousness, and negotiating abilities which could enhance health status (Heckman & Kaut, 2012). Also, individuals with high education might have a lower level of irrational thinking compared to those with lower educational level, while irrationality has been linked to lower ability to make critical inferences (Macsinga & Dobrita, 2010).

However, many factors can explain why less educated individuals may exhibit more irrational beliefs, perhaps because they are in a state of constant stress. Stress has been found to be greater among individuals with low level of education, possibly because limited education and low income can lead people to live in poorer and stressful environments, while people with a high level of education and income may experience fewer risks, receive more support, and afford more options to address potential problems (Baum et al., 1999; Gupta et al., 2012). Additionally, previous studies revealed that people with low educational attainment have higher prevalence of smoking, and hypertension, whereas a greater Framingham Risk Score is reported (Gupta et al., 2012; Jeemon et al., 2011). All the above may indicate a connection among irrational beliefs, stress, educational status, and CVD risk factors with CVD incidence, but a further investigation is needed.

The Role of Emotional Disturbances

According to Beck (2005), personality traits and early life experiences are responsible for the development of beliefs that become enriched over the years (Beck, 2005). When interpretations of various situations become dysfunctional, they lead to negative emotional outcomes, such as distress and anger and emotional disorders like depression and anxiety (Beck, 2005). In our work, it is revealed that in the presence of anxiety and depression, irrational beliefs are a ticking time-bomb for CVD risk. In most research studies, the association between depression or anxiety and CVD risk is evident (Kollia et al., 2017b). Our results are in agreement with previous research studies regarding the association between depression, anxiety, and CVD risk (Yousefyet al., 2010).

The combined effects of irrational beliefs system and anxiety and/or depression may induce inflammation and oxidative stress as an underlying biochemical process in the abnormal activity of the NS (e.g., sympathetic over-

activity vs. vagal dysfunction) and the HPA which contributes to the development of cardiac events (Vassou, Yannakoulia et al., 2021). Under those circumstances, as we have detailed explained, the SNS is constantly stimulated at the expense of the PNS resulting in increased levels of pro-inflammatory cytokines (Vassou, Yannakoulia et al., 2021). Emotional disturbances are involved in the abnormal activity of the ANS and the HPA axis affecting the cardiovascular system (, Yannakoulia et al., 2021). Increased vagal activity (i.e., vagal tone) regulates heart rate, protects coronary vascular cells and reduces peripheral vascular inflammation when combined with acetylcholine, whereas reduced vagal nerve activity is likely to lower myocardial infarction tolerance and exacerbate cardiovascular dysfunction (, Yannakoulia et al., 2021).

The Role of Lifestyle Factors

It is important to take into consideration that individuals with depression and anxiety may also adopt unhealthy habits that overlap with CVD risk factors (Bucciarelli et al., 2020; Masana et al., 2018). In particular, many studies to date have highlighted the association between depression and anxiety with health-compromisingbehaviours, such as smoking, physical inactivity and maladaptive eating patterns(Bucciarelli et al., 2020; Masana et al., 2018; Walsh et al., 2013). In our thesis, the mediating role of unhealthy dietary patterns and smoking status in the relationship between irrational beliefs (along with negative emotional status) and cardio-metabolic conditions is apparent.

Based on the stress-coping model, maladaptive behaviours can serve as management for negative emotions caused by mental health issues, or otherwise, as an avoidant coping strategy (Walsh et al., 2013). Therefore, a possible explanation is that health-compromising behaviours act as strategies for dealing with negative affect and mental illness symptoms (e.g., anxiety and depression) in individuals with irrational beliefs (Walsh et al., 2013). Irrational beliefs increase the risk of experiencing negative and unpleasant feelings, as well as physiological changes that predispose individuals to poor physical health, according to studies (Papageorgiou et al., 2006; Vassou, Georgousopoulou et al., 2021). Hence, these negative beliefs/expectations have an impact on negative thinking and emotions cycle, as well as lifestyle

behaviours. These behaviours can exacerbate mental health symptoms, while also being pleasurable, but they are additionally associated with negative health outcomes, including the extent and intensity of the inflammatory process and heart disease(Algren et al., 2018; Kollia et al., 2017b).

Especially focusing on dietary habits, most studies to date concentrate on how eating habits, nutrients and dietary patterns/behaviours influence mental health, rather than the reverse. However, individuals' dietary preferences and behaviours are associated with personal beliefs and expectations, in addition to food availability, repetitive behaviours and learning mechanisms (Mela, 1999). In particular, negative beliefs (e.g., low self-efficacy, the perception of one's inability to control personal life and health and the perception of many life obstacles and side effects) have been found to consistently undermine the adoption of healthy eating habits (Ross & Melzer, 2016). Negative emotions (like anger, loneliness, anxiety and depression) have been identified as significant antecedents and triggers of eating problems (Corstorphine, 2006). Anxiety, in particular, increases appetite and leads to a desire for foods high in fat and sugar, or overeating as a coping mechanism to distract from distressing and stressful situations (Lazzeretti et al., 2015). Furthermore, depression has been associated with a lack of motivation to engage in healthy behaviours (Lazzeretti et al., 2015). Additionally, individuals with anxiety or depression are characterized by carbohydrate craving, an excessive degree of carbohydrate consumption (not in vegetables, fruits, legumes, whole grains and other fibres), due to an increase in brain serotonin synthesis, even though carbohydrates are the main source of energy in the brain (Wurtman & Wurtman, 2018).

Our thesis has demonstrated a general unhealthy diet in individuals who present with psychological distress symptoms. Specifically, the "Western" pattern dietis the most dominant for individuals with irrational beliefs and anxiety or depressive symptomatology. On the contrary, the high refined carbohydrates and fats dietary pattern (including nuts, dry fruits, sweets, soft and cola drinks, full-fat dairy products, seed oil and margarine) is the most dominant pattern for individuals with irrational beliefs but without severe emotional problems. Interestingly, when the analysis was based on an a-priori dietary pattern using the MedDietScore (instead of the a-posterior factor analysis), it was found that, although adherence to the Mediterranean diet is low among those with high irrational beliefs, the presence of depression symptoms

seems to “prevent” individuals with irrational beliefs from adapting an unhealthy diet. The latter did not happen among those with anxiety symptoms in addition to irrational beliefs. Finally, as compared to individuals with irrational beliefs but without depressive symptomatology, the presence of depression symptoms—but not anxiety—seems to be associated with adherence to a Mediterranean dietary pattern. Depressive disorder is usually more severe and recognizable than anxiety (Zimmerman et al., 2018); therefore, we hypothesize that individuals with depressive symptomatology may promptly seek information or consult a health professional. Since the benefits of a healthy diet against depression have been recognized for decades, these individuals likely have adopted healthy dietary habits as a result of a medical recommendation.

Therefore, it is considered that irrational beliefs inevitably contribute to negative psychological outcomes (e.g., anxiety and depression) and, in turn, to irrational coping mechanisms (e.g., unhealthy nutrition, a sedentary lifestyle, etc.) andadverse health outcomes (Sremanakova et al., 2021). The blocking model, according to which problematic eating behaviours are used to block out short-term awareness of negative emotions that individuals find difficult to tolerate, may explain the tendency of people with strong irrational beliefs and psychopathology to engage in unhealthy eating behaviours (Corstorphine, 2006). However, the relief obtained through unhealthy eating behaviours is only temporary, resulting not merely in acute distress (Corstorphine, 2006), but also in medical conditions such as obesity and other chronic conditions (e.g., MetS, T2DM, CVDs, etc.).

The Role of Biochemical and Clinical Factors

Previous findings on the relationship between MetS and psychological dimensions have been conflicting. Some studies identified an association between long-term anxiety and depressive symptoms with MetS, others found a positive association solely with anxiety-specific or depression-specific symptoms, while othersreported no association at all (Hoffmann et al., 2021; Roohafza et al., 2012). Psychological, social, and behavioural aspects in addition to metabolic, anthropometric and hemodynamic (independent or inter-related) risk factors for CVD and T2DM that constitute MetS, may be involved in its development as they share

bidirectional mechanisms (Hoffmann et al., 2021; Roohafza et al., 2012). Currently, our findings indicated that irrational beliefs, alone or through the moderating effect of anxiety can predict MetS incidence.

When people endorse rational beliefs/thoughts, they report experiencing less excessive and problematic emotional stress (Travis, 1999), whereas holding irrational beliefs causes anxiety symptoms (Matthews & Kuller, 2002). Anxiety is an unhealthy negative emotion that leads to unrealistic expectations and constructive behaviours (Harris et al., 2006). Stress-initiated chronic neuroendocrine and sympathetic dysregulation might result over time in metabolic and anthropometric alterations that characterize the MetS (Bouchard et al., 1993; Matthews & Kuller, 2002). Acute stress and anxiety can induce a transient increase in blood pressure through changes in cardiac output and vascular resistance regulated by the ANS, as well as chronic hypertension (Harris et al., 2006; Noyes et al., 1980). Moreover, feeling anxious can be characterized by high-risk aversion, in which a person becomes conditioned to avoid new choices impulsively while enjoying unhealthy ones, resulting in extraproblems in behavioral change (Hoffmann et al., 2021). Thus, health-related behaviours are another possible pathway through which irrational beliefs and anxiety may operate (Noyes et al., 1980). Adopting unhealthy lifestyle behaviours, such as high alcohol drinking, smoking, and engaging in low physical activity, has sympathetic, endocrine, and metabolic-anthropometric consequences (Bouchard et al.,1993; Hautanen & Adlercreutz, 1993; Matthews & Kuller, 2002). However, statistical controls for dietary patterns, physical activity and smoking did not alter the significantassociations between irrational beliefs and the MetS, ruling them out as mediating influences in the current thesis. In summary, the combined effect of irrational beliefs system and anxiety may induce behavioural and neurochemical mechanisms that contribute to the development of MetS. Nonetheless, all potential pathways and predisposing factors, such as genetic factors, must be thoroughly investigated (Matthews & Kuller, 2002). Specifically, DNA sequence variation may alter susceptibility to irrational beliefs, stress exposure, neuroendocrine dysregulation, and their implications on the MetS profile (Matthews & Kuller, 2002; Noyes et al., 1980). For instance, there is preliminary evidence that irrational beliefs may be partly geneticand transmitted from parent to child (e.g., COMT Val gene variation) (Podina et al., 2015).

After we attempted to understand the relationship between irrational beliefs and MetS, we further explored whether or not MetS, as a well-recognized risk factor for CVDs, could explain the association between irrational beliefs and CVDs. Indeed, MetS seemed that affects both the strength and the direction of the relationship between irrational beliefs and 10-year CVD incidence. As we had thoroughly explained in the Introduction section, MetS is characterized by central obesity, insulin resistance, dyslipidemia and hypertension (Grundy, 2016). Insulin resistance as one of the key features of MetS can promote the development of CVDs in several ways (Reaven, 1995). First, it can contribute to the accumulation of abdominal fat, which releases fatty acids into the bloodstream, which impair insulin signaling and exacerbate insulin resistance, creating a vicious cycle (Shulman, 2000). Second, insulin resistance can lead to dyslipidemia which can promote the formation of plaques (i.e., fatty deposits in the arterial walls), leading to the development of atherosclerosis (Grundy et al., 2004). Third, insulin resistance can also contribute to the development of inflammation, oxidative stress and endothelial dysfunction, which are all associated with an increased risk of CVD (Kaur, 2014b). Inflammation can damage the arterial walls, promoting the formation of plaques, while oxidative stress can impair the functioning of the endothelium, leading to a decreased ability of the blood vessels to dilate properly (Libby et al., 2011). Finally, hypertension may also be involved in the activation of the rennin-angiotensin-aldosterone system, oxidative stress and inflammation (Oparil et al., 2003).

Inflammation and oxidative stress

The relationship between anxiety and depression with inflammation and oxidative stress has been investigated in several studies, although the direction of this relationship remains unclear. The pathophysiology of depression is related to the inflammatory process due to microglial activation, increased cytokine release and oxidative stress (Querstret & Cropley, 2013; Réus et al., 2019). Additionally, psychological stress, and particularly emotional states of anxiety, fear and insecurity, affect hemostatic functions and trigger coagulation and fibrinolysis systems (Pitsavos et al., 2006). In anxiety, the sympathetic NS is continuously activated at the expense of the parasympathetic NS, resulting in increased levels of pro-inflammatory

cytokines (Won & Kim, 2016). Alongside, anxiety is associated with reduced vagal nerve activity and total heart rate variability (Licht et al., 2009; Watkins et al., 1998). Increased vagal activity (i.e., vagal tone) regulates heart rate and facilitates digestion, respiratory rate, vasomotor activity and reflex actions, and together with acetylcholine protects coronary vascular cells and reduces peripheral vascular inflammation (Headrick et al., 2017; McLaughlin et al., 2015). On the other hand, reduced vagal nerve activity is likely to impair myocardial infarct tolerance (i.e., the ability to withstand the destruction of heart tissue resulting from obstruction of the blood supplyto the heart muscle) and promote cardiovascular dysfunction (Headrick et al., 2017; McLaughlin et al., 2015). Despite the fact that researchers interested in psychological constructs are familiar with the concept of psychological modulation of cellular immunity (Papageorgiou et al., 2006; Vassou, Georgousopoulou et al., 2021), little is known about the role of irrational beliefs in cytokines and oxidative stress, andwhether they can predict CVDs when they are combined. Irrational beliefs are expected to contribute not merely to emotional disturbances like anxiety, but also to biochemical reactions and clinical problems as in CVD (Papageorgiou et al., 2006; Vassou, Georgousopoulou et al., 2021). According to previous studies, people who experience dysfunctional thoughts have greater plasma levels of CRP, IL-6, TNF-α and white blood cells than people who have less dysfunctional thinking (Papageorgiou et al., 2006; Vassou, Georgousopoulou et al., 2021). Our findings are in line with the literature. Particularly, we found that individuals with high irrational beliefs and anxiety levels had elevated have elevated CRP, IL-6, TNF-α, ox-LDL and fibrinogen. Moreover, the biomarkers were found to be powerful mediators of the relationship between IBI score and 10-year incidence of CVDs.

Diabetes mellitus

T2DM is a complex metabolic disorder caused by genetic, epigenetic, and environmental factors (Prasad & Groop, 2015). Individuals with depression and anxiety are at risk of developing diabetes and other clinical outcomes because of the increased risk of adopting an unhealthy lifestyle behaviour, including physical inactivity, smoking, and consumption of high-fat foods (Khuwaja et al., 2010). As we already have explained, depression and chronic anxiety contribute to the impairment of a certain neuroendocrine system, the HPA axis, and the SNS; they may also cause

an increase in inflammatory and platelet aggregation responses, while they are associated with insulin resistance contributing to elevated blood glucose and glycosylated hemoglobin levels (poor glycemic control) and an increased risk of metabolic complications (Khuwaja et al., 2010). Inflammation affects insulin receptor signaling, increases β-cell apoptosis and inflammatory markers and is associated with oxidative stress and future diabetes risk (Fedoce et al., 2018). Elevated plasma homocysteine and IL-6 have also been associated with psychological stress, indicating another potential mechanism between anxiety and diabetes (Pitsavos et al., 2006). Additionally, in line with our results, several studies have shown that T2DM frequently coexists with other metabolic abnormalities, including hypertension, hypercholesterolemia, and MetS, which are also associated with central obesity and insulin resistance (Eschwege et al., 2001).

According to Bruch (1974) and the psychosomatic theory of eatingbehaviours, some people interpret the sensation of sadness, emptiness, and loneliness, which are common in maladaptive thoughts and mental disorders, as similar to hunger(Ogden, 2019). Hence, food is used as a form of emotional comfort and an “easy strategy” to cope with distress and attain positive reinforcement (Nolan & Jenkins, 2019; Ogden, 2019; Tice et al., 2001). Based on our findings, we indicate that people with a high irrational beliefs score adopt, either directly or through depression and anxiety, unhealthy dietary patterns. Therefore, these individuals are prone to weight gain and thereby have a high likelihood of developing T2DM and other clinical complications. Also, we found that participants with high irrational beliefs who also have anxiety or depression had augmented fibrinogen, CRP, TNF-α and LDL-C levels. Moreover, TNF-α and total antioxidant capacity showed to be strong mediating factors of the relationship between high-IBI-high-STAI or -ZDRS with T2DM incidence.

Bringing it all together, the combined impact in our work of irrational beliefs system, anxiety and depression as well as certain lifestyle indicators, like diet, physical activity and smoking, may promote an inflammatory state, oxidative stress and insulin resistance, leading to T2DM (Papageorgiou et al., 2006). Particular, eatinghabits away from a typical Mediterranean diet and high in saturated fat, for example,

can promote both acute upregulation of pro-inflammatory biomarkers, such as IL-6 and sustained low-grade systemic inflammation and raised BMI, visceral fat mass and hypercholesterolemia (Fedoce et al., 2018; Papageorgiou et al., 2006). Unhealthy dietary habits and the subsequent development of obesity may be related to the deficiency of insulin secretion caused by impairment in pancreatic β-cell function when untreated, affects glucose metabolism, and results in insulin resistance, eventually leading to T2DM (Kohei, 2010; Steyn et al., 2004). Obese individuals appear to consume a higher proportion of fat (Ogden, 2019), which may explain why participants with high irrational beliefs in our work consume slightly more fat. For instance, soft drinks raise blood glucose levels, insulin resistance, and BMI, whereas high amounts of red meat contribute to insulin resistance (Nseir et al., 2010; Panagiotakos et al., 2005b). Furthermore, the fewer fruit and vegetables consumed thelower their protective role in the provision of nutrients, fibers, and antioxidantsagainst the development of diabetes (Mozaffarian, 2016). People with a sedentary lifestyle have higher concentrations of circulating pro-inflammatory mediators (Papageorgiou et al., 2006). Smoking is also linked to insulin resistance, low-grade inflammation and increased oxidative stress (Pitsavos et al., 2006).

Genetic predisposition

People with a family history of T2DM do not necessarily perceive themselves to be at higher personal risk and do not take precautionary measures (Wong & Toh, 2009). Risk and help-seeking behaviours are largely determined by individuals' beliefs in chronic conditions like T2DM (Conversano & Di Giuseppe, 2021; Lenzo et al., 2020; WHO, 2016; 2020; Wong & Toh, 2009; Woo et al., 2020). Taking into consideration our main findings, we identified the moderating role of irrational beliefsand health anxiety between family history of diabetes and T2DM risk. Additionally, we observed that individuals with particular psychological characteristics, i.e., high irrational beliefs and low health anxiety, followed by individuals with high irrational beliefs, as well as individuals with high irrational beliefs and high health anxiety, have the greatest risk to develop T2DM when there is a background of family history of diabetes. Furthermore, underlying clinical and lifestyle factors, such as hypercholesterolemia, hypertension and obesity possibly mediate the relationship between family history of diabetes and T2DM. It is quite interesting and unexpected

that individuals who fall into the first two categories, i.e., high levels of irrational beliefs but low levels of health anxiety, as well as high irrational beliefs in the entire group, when there is a family history of diabetes, are most at risk for developing diabetes, as irrational beliefs are usually accompanied by strong and negative emotions and emotional disturbances. However, the strong presence of irrationalbeliefs is likely to be sufficient to increase the likelihood of T2DM, when there is a strong predisposition, like family history of diabetes, probably due to irrational beliefs' heavy cognitive burden, as well as their contribution to known T2DM risk factors, such as negative emotions, other emotional disturbances (e.g., anxiety and depression that were not tested in this study), unhealthy lifestyle behaviours and clinical factors (obesity, hypertension, hypercholesterolemia) (Lazzeretti et al., 2015; Papageorgiou et al., 2006; Vassou, Yannakoulia et al., 2021; Vassou,Georgousopoulou et al., 2021).

Finally, regarding the third category i.e., high irrational beliefs and health anxiety symptoms, the results were expected, and they are better explained by underlying behavioural and clinical factors. SLEs directly affect emotions and lifestyle behaviours, and they appear to be associated with cardio-metabolic complications and comorbidities (Conversano & Di Giuseppe, 2021). Predisposing biological and genetic factors, as well as early life experiences, like a family member's illness (e.g., a family history of diabetes), along with schemas and negative-irrational beliefs (e.g., catastrophizing thinking), can contribute to the development of health anxiety (Boston, 2008). Health anxiety substantially affects well-being as well as health behaviours and can contribute to medical illness, such as diabetes and an increased risk of dying from CVDs (Boston, 2008; Hadjistavropoulos & Lawrence, 2007). It is well documented that anxiety promotes inflammation, oxidative stress, as well as dysfunctional activation of the ANS and the HPA axis (Conversano & Di Giuseppe, 2021; Panagi, 2020; Pitsavos et al., 2006). The activation of the stress system (HPA and SAM axes) and their interactions produce the acute changes caused by stress (Panagi, 2020). The stress system interacts with numerous systems including the CNS, as well as the cardiorespiratory, the metabolic and the immune system (Panagi, 2020). Repeated activation of the stress-related systems, such as in chronic stress, could provoke physiological dysregulation that can

manifest as either hyperactivity or hypoactivity of the stress-related systems; a condition known as 'allostatic load' (Panagi, 2020). Stress biomarkers, which enhance adaptation, can become maladaptive when physiological dysregulation occurs, operating in relatively severe physiological ranges both at rest (basal/circadian levels) and in response to stressful stimuli (Panagi, 2020). Physiological dysregulation might subsequently become a source of internal anxiety, and non-adaptive behaviours, like overeating and unhealthy eating patterns, can exacerbate the situation (Panagi, 2020). Anxiety triggers unhealthy dieting and eating behaviours, which may represent a strategy for managing health anxiety (Hadjistavropoulos & Lawrence, 2007). Unhealthy dietary habits are high in saturated fat and can promote both acute elevations of pro-inflammatory biomarkers, such as IL-6 and sustained low-grade systemic inflammation, as well as increased BMI, visceral fat mass and hypercholesterolemia (Hadjistavropoulos & Lawrence, 2007). Therefore, irrational beliefs and health anxiety probably strengthen the relationship between family history of diabetes and the development of T2DM, while hypercholesterolemia, hypertension and obesity can relatively explain the process by which family history of diabetes and T2DM are related.

Components of Irrational Beliefs and CVD development

Our findings showed that the dominant irrational beliefs factor (cognitive vulnerability to anxiety, consisting of demandingness, perfectionism, emotional irresponsibility, anxious over-concern, dependence on others, over-concern for the welfare of others) is strongly associated with an increased 10-year CVD incidence. The indirect and mediating roles of anxiety and negative physical well-being were also identified. These findings do add to our understanding of risk factors underlying CVD, and the strong association between cognitive vulnerability to anxiety, and CVD, could have potential public health implications. The presented findings are in line with previous work regarding irrational beliefs and CVD incidence (Vassou, Chrysohoou et al., 2022, Vassou, Georgousopoulou et al., 2022); yet adding thespecific dimensions of irrational beliefs (i.e.., those constitute the cognitivevulnerability to anxiety factor) further increases the risk for CVDs (almost 3-times higher CVD risk vs. 1-time higher risk for those with high levels of irrational beliefs, than in our previous work (Vassou, Georgousopoulou et al., 2022)). Also our work

furthers the research into this topic through detecting and introducing the mediating effect of negative physical well-being for the first time. In general, cognitive vulnerability refers to a set of irrational beliefs or attitudes, including perfectionism, dependence and sociotropy, thought to make a person vulnerable to emotional disorders, such as depression and anxiety (APA, 2022; Daniel et al., 2010; Hong et al; 2014; Seldenrijk et al., 2013). Our findings are in agreement with previous studies regarding the association among the abovementioned cognitive vulnerability components, anxiety and adverse events (Buschmann et al., 2017; Daniel et al., 2010; Hewitt & Flett, 1991; Pearson & Gleaves, 2006; Sirois & Molnar, 2016; Williams & Cropley, 2013). For instance, previous studies have specifically shown perfectionism to be linked to increased levels of psychological distress, anxiety, disordered eating, alcohol overconsumption, hypertension and cardiac difficulties, as well as decreased levels of preventive health behaviours, life satisfaction, and well-being (Daniel et al., 2010; Hewitt & Flett, 1991; Pearson & Gleaves, 2006; Rutter-Eley et al., 2020; Sirois & Molnar, 2016; Sleight et al., 2020; Williams & Cropley, 2013). It is possible that potential biochemical and behavioural mechanisms could explain the association between cognitive vulnerability to anxiety and CVD risk within the present findings.

Based on them, it is proposed that irrational beliefs characterized by high levels of cognitive vulnerability to anxiety, through their association with anxiety symptoms, together with unhealthy lifestyle behaviours evoke disinhibition of the ANS (e.g., Sympathetic NS), etc.) (McEwen & Gianaros, 2011). Sympathetic dysregulation and long-term glial dysfunction may result in reduced heart rate variability and vagal tone, and increased future inflammatory allostatic load, such as CRP, IL-6 and fibrinogen (McEwen & Gianaros, 2011; Sild et al., 2017; Zainal & Newman, 2022). Indeed, there was also evidence from previous work that anxiety and depression moderated the relationship between irrational beliefs and CVD risk, while dietary habits away from the Mediterranean diet, as well as inflammatory and oxidative stress markers (including TNF-α, CRP, fibrinogen and TAC) mediated the aforementioned tested associations (Vassou, Chrysohoou et al., 2022, Vassou, Georgousopoulou et al., 2022).

Finally, in the present study, the observed mediating effect of negative physical well-being on the relationship between cognitive vulnerability to anxiety and

the 10-year CVD incidence, can provide important insights, further explaining the path to CVD development. Specifically, positive thinking is a process of self- regulation of behaviour (Carver & Scheier, 1990) that might be beneficial to physical well-being (Scheier & Carver, 1992). Physical well-being refers to physical functioning, the performance of social roles and the absence of physical pain (Capioet al., 2014). On the contrary, irrational beliefs have been associated with negative physical well-being in a variety of ways (Woods, 1984; Breslow, 1972; Rutter-Eley etal., 2020; Spörrle et al., 2010). Anxiety, for instance, has been shown to contribute to the disregard of preventive health activities and behaviours, such as exercise (Sleight et al., 2020), and chronic low-level inflammation is also hypothesized to adversely impact physical functioning (Pahwa et al., 2021). Consequently, chronic activated and sustained inflammation can result in atherogenesis (from the development of endothelial dysfunction to ultimately plaque rupture) resulting in atherosclerotic CVD (Alfaddagh et al., 2020).

10.4 The interaction among psychological, social, lifestyle and biological factors in the pathogenesis of MetS and CVDs

Combining all the findings together, along with the preliminary ones from the 20-years follow-up, we conclude the followings. Personality traits and early life experiences are responsible for the development of beliefs that become enriched over the years (Beck, 2005). When interpretations of various situations become dysfunctional, they lead to negative emotional outcomes such as distress and emotional disturbances like depression and anxiety (Beck, 2005). Irrational beliefs accompanied by emotional dysfunction, are likely to contribute to the pathogenesis of CVD through underlying pathophysiological and behavioural mechanisms which mediate this association by increasing the risk.

As concerns underlying pathophysiological mechanisms, irrational beliefs and emotional disturbances can lead to increased inflammatory response over time, oxidative stress, dysfunction of the ANS, such as sympathetic over-activity vs. vagal dysfunction, and increased levels of catecholamines, due to chronic exposure to stress (i.e., allostatic load) (Lamers et al., 2016; Lamers et al., 2020; Moriarity et al., 2021; Panagi, 2020; Renna et al., 2018). Specifically, the constant SNS activation at the expense of the PSN and the dysregulation of the HPA axis appear to play a role in the

immune-metabolic alterations, such as increased production of cytokines (i.e., TNF-α, IL- 6) (Bierhaus et al., 2003) and consequent induction of acute phase inflammatory proteins (e.g., CRP) (Bryleva et al., 2017), metabolic dysregulation, and chronic hypertension (Esteve et al., 2005; Harris et al., 2006).

In addition, unhealthy lifestyle behaviours, such as suboptimal diet and nutrition, physical inactivity, and smoking, are considered potential behavioural mechanisms. Maladaptive behaviours can serve either as individual' s management for extremely negative emotions, namely as an avoidant coping strategy (Walsh et al., 2013), or individuals with emotional disturbances high-risk aversion, in which they become conditioned to avoid new choices impulsively while enjoying unhealthy ones (Hoffmann et al., 2021).

Regarding diet, negative beliefs may consistently undermine the adoption of healthy eating habits (Ross & Melzer, 2016). Negative emotions (like anxiety and depression) have been identified as significant antecedents and triggers of eating problems (Corstorphine, 2006). Anxiety, in particular, increases appetite and leads toa desire for foods high in fat and sugar, or overeating as a coping mechanism to distract from distressing and stressful situations (food= emotional comfort) (Lazzerettiet al., 2015; Ogden, 2019). Furthermore, depression has been associated with a lack of motivation to engage in healthy behaviours (Lazzeretti et al., 2015). Additionally, individuals with anxiety or depression are characterized by carbohydrate craving, an excessive degree of carbohydrate consumption, due to an increase in brain serotonin synthesis, even though carbohydrates are the main source of energy in the brain (Wurtman & Wurtman, 2018).

Diets away from the Mediterranean dietary pattern, such as high-fat diets (HFD), high in added sugar, refined carbohydrates and subsequent increase in adipose tissue can promote acute upregulation of pro-inflammatory biomarkers, sustainedlow-grade systemic inflammation, oxidative stress, raised BMI, visceral fat mass and dyslipidemia (Aljada et al., 2004; Fedoce et al., 2018; Papageorgiou et al., 2006; Proctor et al., 2004; Timmie et al., 2022). Unhealthy dietary habits and the subsequent development of obesity also result in a pro-inflammatory state and increased abdominal obesity which leads to elevated FFA, insulin resistance, MetS, as well as T2DM (Kohei, 2010; Ritchie & Connell, 2007; Steyn et al., 2004). A sedentary

lifestyle is also involved in the increase of pro-inflammatory and oxidative stress biomarkers (Papageorgiou et al., 2006). Smoking is associated with insulin resistance, abdominal obesity, dyslipidemia, and MetS (Fujiyoshi et al., 2016; Keith et al., 2016; Slagter et al., 2013; Sun et al., 2012; Zhang et al., 2013).

Insulin resistance as one of the key features of MetS can contribute to the accumulation of abdominal fat, which releases fatty acids into the bloodstream (Shulman, 2000), dyslipidemia which can promote the formation of plaques (Grundy et al., 2004), and the development of inflammation, oxidative stress and endothelial dysfunction (Kaur, 2014b). Inflammation can damage the arterial walls, promoting the formation of plaques, while oxidative stress can impair the functioning of the endothelium, leading to a decreased ability of the blood vessels to dilate properly (Libby et al., 2011). Endothelial dysfunction is an early determinant in the development of hypertension and atherosclerosis, and vascular damage (Siti et al., 2015). Atherosclerosis as a chronic inflammatory condition leads to a range of CVDs (Libby & Theroux, 2005).

Age, sex, genetic predisposition and low educational status strengthen the relationship between irrational beliefs, MetS, and CVD.

Limitations

The present work provided useful information on the different ways in which irrational beliefs are likely to affect CVD risk, as the gap in the literature is wide. Notwithstanding the above, it should not be overlooked that in the case of CVD determinants, relative risks were calculated using odds ratios through multiple logistic regression analysis, which may have overestimated the true relative risk. Moreover, concerning MetS and T2DM, the calculation of person-time and incidence rates could not be performed because the exact date of MetS and T2DM development, respectively, was not available. However, it is known that the odds ratio is an accurateestimate of the relative risk for low-prevalence diseases. Furthermore, psychological evaluation was addressed to a part of the entire ATTICA study sample, which is likelyto be a limitation of the current work, even though no differences were observed regarding age, sex distribution, and SES level between those who participated in the psychological evaluation too, and the rest of the ATTICA study sample. Moreover, physical activity was used as a categorical and not as a continuous variable (despite

that IPAQ score can be transformed to METs); this was made to avoid outliers in reporting and, thus, achieve more robust models (the evaluation of physical activities was based only on the interviews using the IPAQ and no other indicators, like pedometers, time recording tools, etc, were used). Another limitation is that our study is observational and is limited to determining whether the associations reported are due to causal relationships, whereas there might be confounding variables that are not detected. Moreover, we used self-reports to assess psychological and behavioural parameters which increase the risk of response bias. Nonetheless, self-reports are common in psychological research since they provide valuable and diagnostic information. Finally, considering that the detected incident cases were 5.1% (less than 20% of the total sample), it is an important limitation of our work. Still, the present study has several strengths since its prospective design for a long period of 10 years, and 20 years as well, allowed us to assess the incidence of several outcomes. Furthermore, the analyses performed had adequate internal and external controls, which increased the internal validity and decreased the likelihood of measurement error.

Conclusions and Final Remarks

Overall, to the best of our knowledge, this is one of the first works (or even the first) to simultaneously combine psychological, socio-economical, and lifestyle information, along with the established biological components in a prospective estimation of CVD events among people living in a Mediterranean country. Our research contributes to the ongoing discussion surrounding the bio-psychosocial risk factors underlying cardio-metabolic conditions, such as MetS and CVDs.

Notwithstanding that biochemical parameters are major predisposing factors in the development of such conditions, there is a great need to identify previouslyunknown psychological pathways. This need derives from a) the cardio-metabolic conditions global rising, b) the population aging and c) the frequency of negative beliefs because of the rapid and demanding pace of life and perhaps the growth of technology. Therefore, the need to promote a healthier lifestyle, especially in this group of people, is vital in CVD prevention.

Longitudinal data regarding irrational beliefs and CVD incidence are scarce in the literature, with our work being the first in the field that aimed to bridge this knowledge gap. In this work, which we consider a first step, we theorize thatirrational beliefs, especially in combination with emotional disturbances, can predict MetS and CVDs, through behavioural/lifestyle and biochemical mechanisms (such as neuro-endocrineimmunology and pro-inflammatory processes).

It is crucial to not simply focus on reducing psychological distress, through evidence-based interventions for emotional disturbances in high-risk populations butto pave the way for more targeted interventions by psychologists in healthcare contexts. Therefore, we aim to convey this message to international prevention campaigns, national health promotion programs and primary prevention in clinical settings.

Based on our findings, our approach may be useful for guiding clinicians to detect high-risk individuals and target maladaptive thoughts to guide primary prevention before the potential onset of mental health problems that along with biochemical abnormalities could contribute to fast CVD development. Consequently, we tentatively suggest that more CBT/REBT interventions are needed for targeting mentally healthy individuals who are at risk for CVDs (middle-aged and older, with low education, away from the Mediterranean diet, high blood pressure, with MetS, etc.). We propose that interventions could initially assess the participants' level of irrational beliefs (using the IBI scale or other negative beliefs questionnaires), especially considering their scores on demandingness, perfectionism, emotional irresponsibility, anxious overconcern, dependence on others, and over-concern for the welfare of others), while anxiety and depression levels should also be assessed using anxiety and depression scales, respectively. The coordination of these large-scale public health programs should be based on sessions containing the provision of relevant information about CVD risk factors, as well as the disease itself, with an explanation of the ABC model (especially focusing on anxiety psycho-education, and therapeutic techniques for challenging irrational beliefs), stress management strategies, relaxation techniques, assertiveness training, and behaviour modification techniques (such as decisions to exercise more, eat more healthily and stop smoking), all based on CBT/REBT theory and psychotherapy. Yet, it will be crucial to achievingcoordination among healthcare professionals (i.e., medical and other specialized staff,

such as doctors, nurses, and nutritionists) who will be trained by specialized (health) psychologists for the implementation of prevention programs and the immediate detection of dysfunctional thinking and high-risk groups.

Another area of research could be the role of irrational beliefs in preventing cardiovascular events in pre-existing CVD, either through improving mental health or modifying behavioural lifestyle factors. The trigger for this was our systematic review and meta-analysis which demonstrated that programs based on CBTs had positive results in improving dietary habits of CVD patients (Vassou et al.,2023).

Nevertheless, before such suggestions are instigated by health and well-being coaches, more research is required in this area. Thus, it is anticipated that large observational studies, with at least three assessment waves, will shed more light on the association between irrational beliefs and cardio-metabolic incidence, and suggest additional means for primary prevention.

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