Cardiometabolic risk indicators in bipolar disorders

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To my parents

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ABSTRACT

In addition to disabling mood episodes, bipolar disorders (BDs) predispose individuals to high cardiovascular disease (CVD) risk. This thesis explores the association between BDs and the metabolic risk indicators body mass index (BMI), waist-to-hip ratio (WHR), blood pressure, and lipid profile.

Study I showed no differences in weight gain or increase in BMI between individuals with BDs on mood stabilizer monotherapy compared with age- and sex-matched individuals with BDs who received treatment with a second-generation antipsychotic in addition to a mood stabilizer. **Study II** showed that individuals with BDs had higher mean levels of WHR, BMI, and atherogenic lipid profile compared with a control group. A sub-group of individuals with BDs and controls were followed-up after a period of 6–7 years. We found an increase in WHR and blood pressure in the patient group relative to the controls after the follow-up period. **Study III** partly replicated the findings of Study II using an independent cohort with a nearly identical study protocol and a follow-up of 7–8 years. **Study IV** compared the secular trends and the distribution of BMI between individuals with BDs and the general population in Sweden. The mean levels of BMI were higher in the patient group and increased more over time compared with the general population. Women with BDs and individuals with high BMI had the largest annual increase in BMI.

In conclusion, individuals with BDs have a higher CVD risk-profile as measured by cardiometabolic risk indicators. It is important that clinicians adopt a proactive strategy, look at the overall picture, and observe minor changes in cardiometabolic status to prevent cardiometabolic disease generally and in individuals with BDs specifically.

SAMMANFATTNING PÅ SVENSKA

Utöver episodiska förskjutningar i stämningsläget så löper individer med bipolära syndrom hög risk för kardiovaskulär sjukdom. Syftet med denna avhandling var att undersöka sambandet mellan bipolära syndrom och de kardiometabola riskindikatorerna body mass index (BMI), midja-höft-kvot (WHR), blodtryck, och lipidprofil.

Studie I visade inte större ökning av vikt eller BMI hos individer med bipolära syndrom som utöver behandling med humörstabiliserande läkemedel också fick andra generationens antipsykotiska läkemedel jämfört med de som enbart behandlades med humörstabiliserande läkemedel. **Studie II** visade att individer med bipolära syndrom i genomsnitt låg högre i WHR och BMI, och hade en mer aterogen lipidprofil jämfört med en kontrollgrupp. En undergrupp av individer med bipolära syndrom och kontroller följdes upp efter en period på 6–7 år. Vi fann att WHR och blodtryck ökade mer i patientgruppen jämfört med kontrollgruppen under uppföljningsperioden. **Studie III** replikerade delvis fynden från studie II i en oberoende kohort med ett nästan identiskt studieprotokoll och en uppföljningstid på 7–8 år. I **studie IV** jämfördes tidstrender och BMI-kurvor hos individer med bipolära syndrom och normalbefolkningen i Sverige. Medelnivåerna av BMI var högre i patientgruppen och ökade mer över tid jämfört med män och kvinnor i normalbefolkningen. Kvinnor med bipolära syndrom och individer med högt BMI hade den högsta årliga ökningen av BMI.

Sammanfattningsvis visar kardiometabola riskindikatorer att individer med bipolära syndrom har en högre risk för kardiovaskulär sjukdom. För att förhindra kardiometabol sjukdom i allmänhet och hos individer med bipolära syndrom i synnerhet, är det viktigt att läkaren arbetar proaktivt och utifrån en helhetsbild samt är observant även på mindre förändringar i kardiometabol status.

LIST OF PAPERS

I. Najar, H., Joas, E., Kardell, M., Pålsson, E., & Landén, M. (2017). Weight gain with add-on second-generation antipsychotics in bipolar disorder: a naturalistic study. Acta psychiatrica Scandinavica, 135(6), 606–611. https://doi.org/10.1111/acps.12737

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CONTENT

PROLOGUE 1
AIMS 2
1. BIPOLAR DISORDERS 3
1.1. Types of Bipolar disorders 3
1.1.1. Bipolar I disorder 4
1.1.2. Bipolar II disorder 4
1.1.3. Cyclothymic disorder 5
2. BIPOLAR DISORDERS AND CARDIOVASCULAR DISEASES 5
3. CARDIOVASCULAR DISEASES 6
4. PATHOPHYSIOLOGY IN CVDS 6
5. CLINICAL CONSEQUENCES OF THE ATHEROSCLEROTIC PLAQUE 7
6. OVERVIEW OF LIPOPROTEIN METABOLISM 8
7. CVD RISK FACTORS 9
7.1. Metabolic risk factors 10
7.1.1. Dyslipidemia 10
7.1.1.1. High LDL 10
7.1.1.2. High TAG 10
7.1.1.3. Low HDL 11
Bipolar disorders and dyslipidemia 12
7.1.2. Diabetes mellitus (DM) 13
Bipolar disorders and diabetes mellitus 15
7.1.3. Hypertension 16
Bipolar disorders and hypertension 17
7.1.4. Obesity 17
Bipolar disorders and obesity 19
7.1.5. Chronic kidney disease 20
7.1.6. Thyroid dysfunction 22
Bipolar disorders and thyroid dysfunction and kidney disease 23
7.2. Lifestyle related risk factors 24
7.2.1. Tobacco smoking 24
Bipolar disorders and tobacco smoking 25
7.2.2. Sedentary behavior and physical inactivity 26
Bipolar disorders and sedentary behavior and physical inactivity 27

7.2.3. Alcohol use disorder 28
Bipolar disorders and alcohol use disorder 29
7.2.4. Unhealthy dietary habits 29
Bipolar disorders and unhealthy diet 29
7.3. Non-modifiable CVD risk factors 30
7.3.1. Advanced age 30
7.3.2. Sex 31
7.4. Non-traditional CVD risk factors 32
7.4.1. Inflammation 32
Bipolar disorders and inflammation 33
7.5. Other CVD risk factors 34
7.6. Bipolar disorders' specific CVD risk factors 34
7.6.1. Psychotropics 34
7.6.2. Heredity 35
8. THE RELATION BETWEEN CVDS AND CVD RISK FACTORS 36
8.1. Measures of total and central obesity 36
8.2. Lipid profile 37
8.3. Systolic and diastolic blood pressure 38
8.4. Plasma glucose 38
8.5. Number of smoked cigarettes 38
9. A SYNERGISTIC RATHER THAN ADDITIVE RISK-COMBINATION 39
10. CO-OCCURRENCE OF CVD RISK FACTORS IN INDIVIDUALS WITH BIPOLAR DISORDERS 40
11. A PROACTIVE AND PREVENTIVE APPROACH–A PRIMORDIAL APPROACH 41
12. METHODOLOGICAL CONSIDERATIONS 42
12.1. DSM-5 versus DSM-IV 42
12.2. Pros and cons with cohort and register studies 43
12.3. The effect of inclusion date on the laboratory analysis 43
12.4. Concerns about measured plasma lipids and lipoproteins 45
13. SIGNIFICANCE 46
14. CONCLUSIONS 46
15. FUTURE RESEARCH 47
16. ACKNOWLEDGEMENTS 47
17. REFERENCES 50

ABBREVIATIONS

Apo AI	apolipoprotein AI
BDs	bipolar disorders
BMI	body mass index
CETP	cholesteryl ester transfer protein
CKD	chronic kidney disease
CMRIs	cardiometabolic risk indicators
CRP	C-reactive protein
CVD	cardiovascular disease
CYP	cytochrome P450
DAMPs	damage-associated molecular patterns
DM	diabetes mellitus
DSM	the diagnostic and statistical manual of mental disorders
DSM-IV-TR/ DSM-IV	text revision version of DSM, fourth edition
DSM-5	DSM, fifth edition
HDL	high-density lipoprotein
HL	hepatic lipase
HPA	hypothalamic-pituitary-adrenal
IDL	intermediate-density lipoprotein
IDF	International Diabetes Federation
IL-1β	interleukin-1β
IMT	intimal-medial thickness
LCAT	lecithin cholesterol acyltransferase
LDL	low-density lipoprotein
LDL-R	LDL-receptor
Lp (a)	lipoprotein (a)
LPL	lipoprotein lipase
MAG	monoacylglycerol
MCP-1	monocyte chemoattractant protein-1
NADPH	nicotinamide adenine dinucleotide phosphate
NO	nitric oxide
PAI-1	plasminogen activator inhibitor-1
PKB	protein kinase B
SBP	systolic blood pressure
TAG	triacylglycerol
TAG-RLs	TAG-rich lipoproteins
TChol	total plasma cholesterol
TNF-α	tumor necrosis factor-α
VCAM-1	vascular cell adhesion molecule-1
VLDL	very low-density lipoprotein
VSMC	vascular smooth muscle cell
WHR	waist-to-hip ratio

PROLOGUE

Individuals with bipolar disorders (BDs) are at risk of losing a decade of life due to cardiovascular diseases (CVDs). In addition to premature mortality, CVDs contribute to a reduced quality of life. Knowledge about the increased cardiometabolic risk in individuals with BDs has existed for decades, and diagnostic tools are both simple and available. Yet, the increased risk of CVDs for people with BDs remains, and positive change is not apparent.

One of the changes that could help is the reevaluation of how the clinical guidelines define cardiometabolic disturbances. Presently, clinical guidelines adopt cut-off values for cardiometabolic risk indicators (CMRIs), but these cut-offs can lead to overlooking small longitudinal changes in CMRIs. Even small changes, which usually are below the threshold levels, are associated with increased CVD risk.

This thesis outlines individual CVD risk factors, describes the pathophysiological changes accompanying these risk factors, and discusses the clinical significance of risk factors on their own and in concert. Furthermore, this thesis highlights the association between CVD risk factors and BDs and the co-occurrence of multiple CVD risk factors in the same individual with a BD. Finally, this thesis highlights the importance of the continuous measures of the different CMRIs and the way these risk indicators change in individuals with BDs, illustrating the importance of early interventions when dealing with CVD risk.

AIMS

To enable better prevention of CVDs in individuals with BDs, this thesis aims to advance our knowledge on the association between BDs and CVDs through the study of CMRIs. The specific aims are to:

I. Determine how treatment with a second-generation antipsychotic affects weight or body mass index (BMI) when added to treatment with a mood stabilizer (Study I).
II. Determine how continuous measures of CMRIs in individuals with BDs differ from controls using both cross-sectional and longitudinal data (Studies II and III).
III. Determine the secular trends and distribution of BMI in individuals with BDs compared with the general population over a twelve-year period (Study IV).

1. BIPOLAR DISORDERS

BDs are chronic psychiatric disorders characterized by mood disturbances with a worldwide prevalence of 2% (1). BDs are interrelated with psychotic and depressive disorders in terms of symptomatology (2, 3), family history (3, 4), and genetic architecture (3, 5).

Individuals with BDs have a reduced quality of life due to recurring mood episodes, low psychosocial functioning, and comorbidity with other disorders. On average, persons with BDs spend half of their lives suffering from depressive symptoms (6). Psychotropic medication is used to manage mood episodes and comorbid disorders (7). Lithium, the first line treatment option in Sweden, is a broad-spectrum mood stabilizer with antimanic, antidepressant, and anti-suicide effects (8). Other effective mood stabilizers are valproate and carbamazepine for the treatment of acute mania and lamotrigine for the treatment and prevention of depression. Second generation antipsychotics have proven to be effective in the treatment of acute mania but less effective in treating depression (7). The last two decades have witnessed an increase in the prescription of second-generation antipsychotics at the expense of traditional mood stabilizers in medical management of BDs (9). Lastly, antidepressants are also used as adjunctive agents in the treatment of bipolar depression (10).

1.1. Types of Bipolar disorders

There are two diagnostic manuals for the diagnosis of mental disorders: the Diagnostic and Statistical Manual of Mental Disorders (DSM) and the International Classification of Diseases (ICD). In Sweden, the criteria outlined in the DSM manual are usually used to establish a BD diagnosis, while the diagnostic codes follow the ICD manual. Published in 2013, the fifth edition of DSM (DSM-5) recognizes seven subtypes of BDs (11):

1. Bipolar I disorder,
2. Bipolar II disorder,
3. Cyclothymic disorder,
4. Substance/medication-induced bipolar and related disorder,
5. Bipolar and related disorder due to another medical condition,
6. Other specified bipolar and related disorder, and
7. Unspecified bipolar and related disorder.

1.1.1. Bipolar I disorder

Bipolar I disorder is characterized by having experienced at least one manic episode, which is defined as “a distinct period of abnormally and persistently elevated, expansive, or irritable mood and abnormally and persistently increased goal-directed activity or energy” (11). The manic episode should last most of the day and nearly every day for at least seven days or less if the patient needs hospital care. The mood disturbance can include elevated, expansive, or irritable mood accompanied by other symptoms that differ noticeably from the individual’s usual behavior. To qualify as a manic episode, the mood disturbance should impair social or work functioning markedly, and hospital admission may be needed to prevent harm to self or others. A manic episode can also include psychotic features.

In addition to mania, it is common that individuals with bipolar I disorder can also experience major depressive episodes. However, major depressive episodes are not mandatory for the diagnosis of bipolar I disorder. These episodes are characterized by depressed mood or loss of interest or pleasure with a combination of different symptoms that include negative impact on weight, sleep, energy, self-esteem, psychomotor function, cognitive functions, and suicidal ideation. Major depressive episodes cause clinically significant impairment in important areas of functioning.

Finally, individuals with bipolar I disorder could also experience hypomanic episodes (described below). Although common, hypomanic episodes are not required for the diagnosis of bipolar I disorder.

1.1.2. Bipolar II disorder

For a diagnosis of bipolar II disorder, both a hypomanic and a major depressive episode are required. A hypomanic episode is like a manic episode with three differences: the minimum duration of the episode is four days, the impact on social or work functioning is less severe, and hospitalization is not necessary. The disturbance in mood and the change in functioning

should, however, be unequivocal and observable by others. The major depressive episode is described above.

1.1.3. Cyclothymic disorder

If during a period of at least two years, a person experiences numerous episodes of elevated or depressed mood that do not meet the criteria for a hypomanic or a major depressive episode, a diagnosis of cyclothymic disorder is made. One of the required criteria is that the episodes of elevated or depressed mood have been present for at least half of the two-year period and that any symptom-free interval lasts no longer than two consecutive months. Another criterion is that the disorder causes clinically significant distress or impaired functioning in important areas of life.

In addition to the above mentioned three subtypes of BDs, a BD is diagnosed when the symptoms are caused by direct physiological effects of a substance or medication or direct pathophysiological consequences of another medical condition. These diagnoses are aptly named substance/medication-induced bipolar and related disorder and bipolar and related disorder due to another medical condition, respectively.

Sometimes, symptoms and signs indicate a BD and cause significant suffering or worsening of important areas of functioning but do not meet the criteria for a DSM-5 BD diagnosis. If the clinician making the diagnosis specifies a reason that the presentation does not meet the criteria, the disorder is classified as **other specified bipolar and related disorder.** However, if a specific reason is not stated, the disorder is classified as **unspecified bipolar and related disorder.**

2. BIPOLAR DISORDERS AND CARDIOVASCULAR DISEASES

Individuals with BDs have their life expectancy reduced by 8.5–12.7 years compared with the general population in Sweden (12, 13). CVDs are the leading cause of premature mortality in individuals with BDs (14). In Denmark, the mortality gap between 1995 and 2014 between individuals with BDs and the general population has increased (15). There are no recent comparable Swedish studies, but our finding of an increasing gap in BMI and prevalence of

obesity (BMI ≥30 kg/m^2) (Study IV) between individuals with BDs and the general Swedish population points in the same direction as the Danish study.

3. CARDIOVASCULAR DISEASES

CVDs, characterized by pathological changes in the vascular system, have been the leading cause of death and disability worldwide for the last few decades, accounting for 44% of all noncommunicable disease deaths and nearly one-third of all global deaths (16). Between 1990 and 2019, the number of individuals with CVDs has nearly doubled to 523 million individuals (17). This increase has been accompanied by a steady increase in deaths due to CVDs: from 12 million in 1990 to an estimated 18 million in 2019 (17, 18). More than six million of these deaths were in individuals between 30 and 70 years old (19). Ischemic heart disease and stroke account for more than 80% of the CVDs' burden (20). The figures in Sweden are in line with those worldwide (16).

4. PATHOPHYSIOLOGY IN CVDS

Atherosclerosis, the main pathological change underlying CVDs, is a multifocal, immunoinflammatory, and fibro-proliferative response to multiple forms of endothelial injury of medium- and large-sized arteries where the blood vessel intima is damaged by chronic exposure to mechanical trauma and toxic substances (21). The Greek root *athero* means "gruel" or "porridge" and refers to the thick necrotic sludge in the core of the atheroma. The characteristic feature of atherosclerosis is the formation of plaques in the subendothelial space of blood vessels (Figure 1). The complex process of plaque formation begins when physical and chemical stressors disrupt endothelial homeostasis and let lipids and inflammatory cells enter the arterial wall. These stressors start a cascade of reactions that lead to increased endothelial permeability; upregulation of endothelial adhesion molecules; leukocyte adhesion and entry into the arterial wall; activation of T cells; infiltration of low-density lipoprotein (LDL) particles; migration and proliferation of vascular smooth muscle cells (VSMCs); and formation of reactive oxygen species, which can overwhelm the antioxidant defense system leading to oxidative stress and cell damage. The infiltrated monocytes differentiate into macrophages, which take up modified LDL particles and become lipid-laden macrophages called foam cells. These foam cells in the intima form small lesions called "fatty streaks" and marks the early stages of atherosclerosis (22). Foam cells undergo cellular death and form a necrotic core. While dying, foam cells release the contents of their cellular fluid, inducing inflammation and leading to the accumulation of extracellular lipids and growth factors. The

necrotic core is surrounded by a fibrous cap formed by migrated and proliferated VSMCs, resulting in plaque formation.

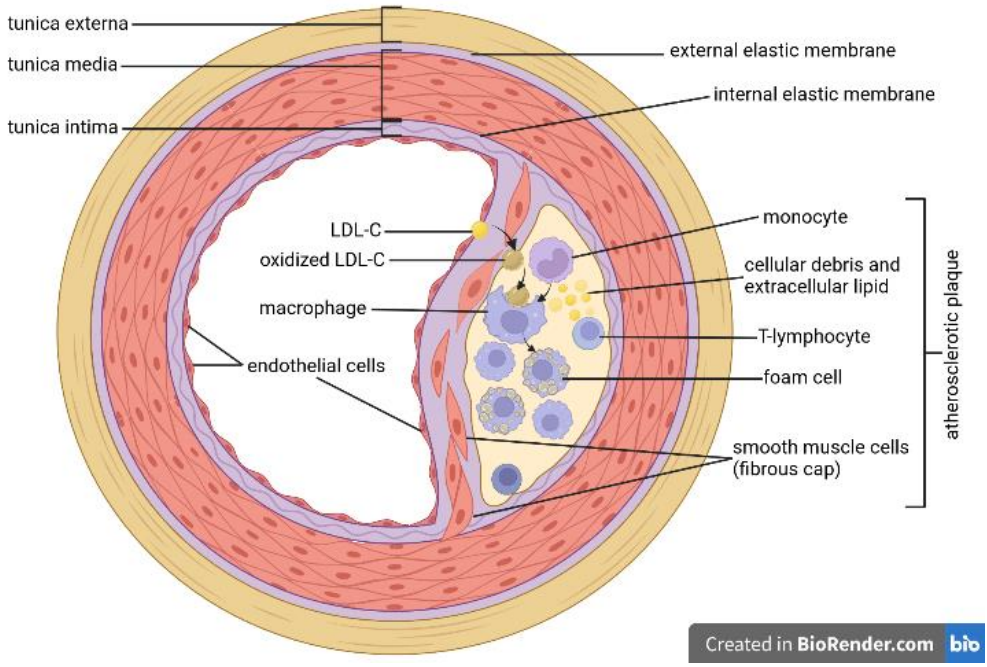

Figure 1. A cross-section of an artery narrowed by an atherosclerotic plaque.
Abbreviations: LDL-C: Low-density lipoprotein-cholesterol.

5. CLINICAL CONSEQUENCES OF THE ATHEROSCLEROTIC PLAQUE

The most common clinical consequences of atherosclerotic plaques are coronary artery disease, stroke, renal artery disease, peripheral artery disease, and aneurysms (23). The effects of the atherosclerotic plaque depend on what happens to the plaque. If the plaque ulcerates or ruptures or if there is bleeding within the plaque, the effect can be thrombotic stroke, myocardial infarction, or unstable angina pectoris. The disruption of the plaque leads to the exposure of the highly thrombotic core to the blood flow, causing coagulation and thrombus formation and contributing to acute thromboembolic events. The peripheral emboli can cause embolic stroke, athero-embolic renal disease, and limb ischemia. If a fibrous plaque narrows the interior of an artery, it can lead to myocardial ischemia, renal artery stenosis, and peripheral artery disease

such as limb ischemia and claudication. Finally, the atherosclerotic plaque can cause weakening of the vessel wall and results in aneurysms.

6. OVERVIEW OF LIPOPROTEIN METABOLISM

Before describing CVD risk factors, it is important to describe lipoprotein metabolism because of the central role of lipoprotein disturbances in the development of atherosclerosis.

Plasma lipoproteins serve as transporting particles to the water insoluble cholesterol and triacylglycerol (TAG) through the circulatory system. This transportation function is aided by the structure and composition of lipoproteins, which have a hydrophobic central core containing cholesterol esters and TAGs surrounded by an amphipathic surface containing free cholesterol, phospholipids, and apolipoproteins. The seven major lipoproteins are classified according to size, lipid content, and apolipoproteins. High-density lipoproteins (HDLs) contain apolipoprotein AI (Apo AI) as their core structural protein, and the other six lipoproteins contain apolipoprotein B-48 (chylomicrons and chylomicron remnants) or Apo B-100–very low-density lipoprotein (VLDL), LDL, intermediate-density lipoprotein (IDL), and lipoprotein (a) (Lp (a))–as their core structural protein (24).

Chylomicrons are produced from dietary lipids by the enterocytes that line the small intestine. After production, chylomicrons are carried through the lymphatic system into the blood stream (25). These lipoproteins are rich in TAG synthesized from fatty acids and glycerol. In the lymph and blood, chylomicrons meet HDL, which transfers apolipoproteins C-II and E to chylomicrons. Apolipoprotein C-II activates lipoprotein lipase (LPL) on the endothelium of blood vessels, facilitating the breakdown of TAG into monoacylglycerol (MAG) and the transport of MAG into fat and muscle cells. In the cells, MAG is converted into TAG to be stored in fat cells and used as a source of energy by muscle cells. Storing energy in the form of TAG is effective because the energy density of TAG is more than twice that of equivalent masses of either carbohydrates or proteins (26). The glycerol left from the breakdown of TAG is moved via the bloodstream to the liver. After hydrolysis, chylomicrons are converted into chylomicron remnants, which are engulfed by liver cells by endocytosis with the help of apolipoprotein E transferred from HDL earlier in the process.

VLDL is produced in the liver and represents the endogenous equivalent of chylomicrons (27). VLDL is rich in TAG and is released into the circulation where it meets HDL and acquires

apolipoproteins C-II and E and then goes through the same process as chylomicrons, giving rise to IDL, which is converted into LDL, mainly, by hepatic lipase (HL) through the hydrolysis of TAG (28). Both IDL and LDL are rich in cholesterol, and LDL contains more than 70% of plasma cholesterol, which is transported by LDL to peripheral cells and enters the cells with the help of LDL-receptor (LDL-R). Cholesterol is important in the synthesis of cell membrane, steroid hormones in endocrine tissues, and bile acid in hepatocytes.

HDL, an anti-atherogenic lipoprotein formed in the liver and small intestine, helps transport cholesterol from peripheral cells into the liver through a process called reverse cholesterol transport or HDL-mediated trafficking of cholesterol (29). The initial step in the reverse cholesterol transport pathway is the uptake of cell cholesterol by HDL. The cholesterol in HDL is then esterified by lecithin cholesterol acyltransferase (LCAT) before being transferred to TAG-rich lipoproteins (TAG-RLs) in exchange for TAG by the enzyme cholesteryl ester transfer protein (CETP). The TAG-RLs consist of chylomicrons, chylomicrons remnants, VLDL, and IDL (VLDL-remnant). Indeed, all plasma lipoproteins may act as donors or acceptors in the CETP-aided lipid transfer process (30). HL hydrolyzes the TAG in HDL, which then is ready to remove cholesterol from peripheral cells, and the process continues. HDL has an important cardioprotective effect by preventing the formation of foam cells and removing lipid from arterial wall foam cells in a process known as macrophage reverse cholesterol transport (31). The journey of HDL ends through catabolism either in the liver or in the kidneys (29).

7. CVD RISK FACTORS

Several CVD risk factors have been identified and this knowledge has contributed to advances in the management of CVDs with prolonged life and less disability for many people. Although some CVD risk factors are non-modifiable (e.g., advanced age, male sex, previous CVD events, and genetic susceptibility), most are modifiable. The modifiable risk factors can be further classified into metabolic risk factors (e.g., dyslipidemia, hypertension, diabetes mellitus (DM), obesity, thyroid dysfunction, chronic kidney disease (CKD), and liver disease), lifestyle factors (e.g., tobacco smoking, physical inactivity, unhealthy diet, and harmful use of alcohol), and other factors (e.g., medication use, inflammation, and infection).

In this thesis, I studied blood pressure, lipid profile, and measures of total and central obesity.

7.1. Metabolic risk factors

7.1.1. Dyslipidemia

Dyslipidemia, an important modifiable CVD risk factor (32), is a combination of disturbances in lipid metabolism such as high total plasma cholesterol (TChol), high LDL-C, high TAG, and low HDL-C.

7.1.1.1. High LDL

LDL has a central role as an independent risk factor in the pathogenesis of atherosclerosis and foam cell formation. The classic LDL example is familial hypercholesterolemia where the levels of LDL-C are elevated to such a degree that individuals are at increased risk of CVDs and premature mortality (33).

Under normal physiological conditions, the uptake of cholesterol from LDL depends on the LDL-R. The expression of LDL-R on the cell surface decreases through a feedback mechanism when intracellular cholesterol is high, which prevents the intracellular accumulation of cholesterol (34). However, LDL can be modified through different processes including oxidation, acetylation, glycosylation, and carbamylation. The modified LDL loses its affinity to the LDL-R and instead readily attaches to the less selective scavenger receptors on the surface of macrophages (35, 36). Moreover, modified LDL contributes to atherosclerosis through increased leukocyte recruitment and production of antibodies, stimulation of VSMC migration and proliferation, induction of cell death in endothelial cells and macrophages, increased vessel oxidative stress, and enhanced foam cell formation (35, 36).

7.1.1.2. High TAG

Reducing LDL-C levels with high doses of statins does not eliminate CVD risk (37). The CVD risk that remains with statin treatment has been linked to an imbalance between the proatherogenic TAG-RLs and anti-atherogenic lipoproteins containing Apo AI (38). Lipolysis products of TAG-RLs are associated with endothelial dysfunction through free fatty acid-mediated increased production of reactive oxygen species and vascular endothelial permeability (39). TAG-RLs result in inactivation of nitric oxide (NO) synthase (40), increased production of tumor necrosis factor-α (TNF-α) and interleukin-1β (IL-1β) (41), and suppression of the anti-inflammatory effects of HDL (42). In addition, chylomicron remnants can enter the macrophages using apo E-dependent receptors and enhance foam cell formation

(43). In addition to being proatherogenic, TAG-RLs can induce a procoagulant state through activating platelets and the coagulation pathway (44).

TAG-rich VLDL and VLDL's remnant (IDL) are converted to small dense LDL particles by LPL and HL (45). The small dense LDL particles are harmful because their small size lets them penetrate the endothelium, and they are also prone to modification. Taken together, this makes small dense LDL particles potent inducers of inflammatory processes associated with CVDs (45). Moreover, high levels of TAG lead to spill over to HDL through CETP-mediated exchange and can increase the metabolic clearance of HDL particles (46). This explains the inverse relation between TAG and HDL (47).

7.1.1.3. Low HDL

A low level of HDL is deleterious because HDL has antioxidant, anti-inflammatory, vasodilatory, anti-apoptotic, antithrombotic, and anti-infectious properties, which protect against CVDs (35, 48). HDL contains high levels of antioxidants like Apo AI and paraoxonase 1 enzyme. HDL has a direct antioxidant effect as it takes up oxidation products from LDL, serving as a sink for oxidized phospholipids (48). Some of the oxidized phospholipids serve as seeding molecules that initiate a chain reaction of oxidation by free radicals. Some other oxidized phospholipids promote the uptake of oxidized LDL by macrophages. Oxidized phospholipids removed from LDL are either hydrolyzed in HDL or delivered to the liver for degradation (48). HDL can also function as an indirect antioxidant through its anti-inflammatory function and by removing cholesterol from peripheral cells (48). Furthermore, HDL is rich in Sphingosine-1-phosphate, which inhibits the generation of reactive oxygen species and other pro-inflammatory molecules and enhances the induction of endothelial NO production and vasodilation, adding to the cardioprotective properties of HDL (48). NO is a potent endothelium-derived vasodilator with an important protective function against atherosclerosis. NO prevents inflammation and thrombosis by inhibiting platelets and monocytes from adhering to, aggregating in, or infiltrating blood vessels (49).

However, the protein and lipid components of HDL can be modified to cause disease (50). This modification can occur by different mechanisms under conditions such as chronic renal failure, some rheumatological diseases, and hyperglycemia. The result is a dysfunctional and pro-inflammatory HDL with decreased antioxidant and anti-inflammatory properties, decreased

ability to prevent LDL oxidation, and worse at removing cholesterol from peripheral cells. Finally, HDL modification increases the catabolism of HDL.

Bipolar disorders and dyslipidemia

Several studies have shown that individuals with BDs more frequently develop abnormalities in lipid metabolism compared with the general population. Most studies have used categorical measures. For example, hyperlipidemia that can be defined as having one primary or secondary diagnosis of hyperlipidemia or medications for the treatment of hyperlipidemia (51). Other studies have used defined cut-offs and shown a higher prevalence of high TAG (TAG≥150 mg/dL) and low HDL-C (HDL<40 mg/dL in men and HDL<50 mg/dL in women) in individuals with BDs compared with the general population (52). Few cross-sectional studies, however, have compared continuous lipid profile measures between individuals with BDs and controls (53, 54, 55). The results of these studies are conflicting. Some studies found no difference (54, 55), but one study (53) found higher mean levels of TChol and LDL-C in the patient group compared with controls. The mean level of HDL-C has been reported to be lower (53), higher (55), or not different (54) in individuals with BDs compared with controls. The mean level of TAG was higher in the patient group in one study (54) and not statistically different in two other studies (53, 55). Only one study compared TChol/HDL-C and LDL-C/HDL-C ratios between individuals with BDs and controls; the study found higher ratios in the patient group (53).

My thesis also shows that individuals with BDs more frequently have disturbances in lipid metabolism. Specifically, we found higher mean levels of TAG, TAG/HDL-C ratio, TChol/HDL-C ratio, and non-HDL-C in these individuals compared with a control group in Study II (56). However, when we followed the atherogenic lipid profile over time, we found no statistically significant difference during a follow-up period of six to eight years in individuals with BDs relative to controls (Studies II (56) and III (57)).

Potential contributing factors to the development of dyslipidemia in individuals with BDs could be obesity, DM, reduced sleep time (58), cigarette smoking, and the use of second generation antipsychotics (59).

7.1.2. Diabetes mellitus (DM)

DM, a chronic metabolic disorder where disturbed glucose homeostasis leads to hyperglycemia, results from defects in insulin secretion, insulin action, or both. DM is the seventh leading cause of death worldwide and the prevalence increases in parallel with obesity (60). The number of affected individuals has increased worldwide, from 108 million individuals in 1980 to 537 million in 2021 (61, 62). In 2021, the international diabetes federation (IDF) estimated the number will increase to 783 million by 2045 (62). In Europe, 61 million individuals were living with DM in 2021 (62). On average, atherosclerotic CVDs occur about 15 years earlier in individuals with DM (63), and CVDs account for two-thirds of deaths in individuals with DM (64).

DM is linked to dyslipidemia through the association of insulin with the synthesis and activation of LPL in adipocytes (65). Thus, insulin resistance leads to low adipose tissue LPL activity, which leads to a decrease in the hydrolysis of TAG in TAG-RLs and subsequent increase in plasma TAG levels (66). The uptake of LDL by LDL-R at the cell surface is also decreased because of the reduction in LDL-R expression caused by insulin resistance (67). The reduced uptake of LDL increases plasma LDL concentration. Furthermore, insulin activates lipogenesis in adipocytes, and the deficiency or decreased effect of insulin leads to lipolysis (68). This yields a subsequent increase in free fatty acids that are transported to the liver, reassembled as TAG, and released as VLDL (69). TAG is transferred from VLDL to HDL and LDL in exchange for cholesteryl esters by CETP (30, 69). The subsequent hydrolysis of HDL and LDL by HL or LPL results in the decrease of plasma HDL levels and the generation of small dense LDL particles as discussed earlier (section 7.1.1.2) (69).

In addition to the effect of dyslipidemia, other mechanisms contribute to atherosclerosis in individuals with DM. Insulin resistance and hyperglycemia are associated with impaired NO-mediated vasodilation as a consequence of endothelial dysfunction and reduced endothelial NO synthesis (70, 71). Hyperglycemia leads to increases in reactive oxygen and nitrogen species, which increase oxidative stress (64). Furthermore, glucose can non-enzymatically attach to proteins and nucleic acids. The non-enzymatic glycosylation of collagen results in vascular rigidity, and can inhibit the release of NO. The reduced release of NO results in vasoconstriction, decreased blood flow, and tissue ischemia (36). The non-enzymatic glycosylation occurs in LDL and the previously mentioned small dense LDL particles, which are more prone to biological modification (72). The glycosylated LDL particles contribute to

the development of atherosclerotic plaques (as mentioned in section 7.1.1.1). In individuals with DM, the resultant plaque has more macrophages, larger necrotic areas, and more instability with increased risk of rupture compared with individuals without DM (73).

DM is considered a pro-thrombotic condition with disturbances in the hemostatic system. The hemostatic system consists of coagulation and fibrinolysis, cells such as platelets, endothelial cells, and monocytes, and a system of receptors and coagulation factors. DM is associated with suppression of the fibrinolysis through the increase in the level of plasminogen activator inhibitor-1 (PAI-1) that inhibits plasmin, which is the key enzyme in the fibrinolytic cascade (74). Insulin resistance is also associated with increased concentration of a variety of coagulation factors that add to the thrombotic risk –e.g., factor VII, factor VIII, von Willebrand factor, factor XII, and fibrinogen (74). In addition to the increased level of coagulation factors, DM is associated with changes in fibrin structure and function, rendering the fibrin clot resistant to fibrinolysis (75). Furthermore, insulin resistance increases platelet activation and aggregation (76). Platelet aggregation is further increased by the release of thromboxane β2 mediated by glycosylated LDLs (36). Finally, the thrombotic risk is worsened by vascular calcification, a well-known complication of atherosclerosis in DM (73). The vascular calcification adds to the burden of the plaque and risk of plaque rupture (73).

Insulin resistance and DM frequently coexist with hypertension (77). The compensatory hyperinsulinemia in the presence of insulin resistance can increase blood pressure via mechanisms (78, 79) such as sympathetic nervous system activation, increasing the levels of the vasoconstrictor endothelin-1, and enhanced growth factor activity, which causes hypertrophy of the vascular wall and narrowing of the lumen of the blood vessels. In addition, insulin has an anti-natriuretic effect, which causes the kidneys to retain sodium. Hyperinsulinemia can further enhance the flux of sodium and calcium into VSMCs, sensitizing these cells to the pressor effects of norepinephrine, angiotensin II, and NaCl loading. In addition, the decreased availability of NO mentioned above is associated with the development of hypertension (80).

Finally, DM is associated with the induction and maintenance of an inflammatory state by increasing proatherogenic cytokines and chemokines such as IL-1β, and TNF-α in addition to the increase in reactive oxygen species and the inflammatory response associated with dyslipidemia (64, 81).

Bipolar disorders and diabetes mellitus

A large meta-analysis comparing the prevalence of DM in individuals with severe mental illness and the general population reported that individuals with BDs had a relative risk of 1.89 for developing DM and one in ten individuals with severe mental illness had DM (82). The same study found that women were more likely to develop DM and that psychotropic medication use such as antidepressants, lithium, and antipsychotics were associated with increased risk. The risk due to the use of psychotropic medication increased with longer treatment duration.

The studies included in this thesis showed that individuals with BDs had a larger atherogenic lipid profile, higher BMI, and a worsening of central obesity and blood pressure compared with controls over time (Studies II (56) and III (57)). The specific combination of altered CMRIs that we found points to a higher risk of developing insulin resistance (79).

Several factors possibly underlie the increased prevalence of DM in individuals with BDs. There are shared pathophysiologic processes between DM and BDs, including abnormalities in hypothalamic-pituitary-adrenal (HPA) axis function. These abnormalities include increased basal cortisol, and disturbed diurnal cortisol variation with subsequent decrease in insulin secretion and increase in gluconeogenesis (6). Common genetic susceptibility is another factor. According to a genome-wide association study by Torkamani et al., DM and BDs shared 68 of the top 1000 most significant single nucleotide polymorphisms per disease (83). A third factor is treatment with psychotropics, which can adversely affect glucose metabolism and contribute to the development of DM (59). A fourth factor is the adverse lifestyle factors and the high rate of overweight (BMI $\geq$25 kg/m^2) and obesity in individuals with BDs compared with the general population (84).

Finally, the phenomenology of bipolar symptoms may contribute to the development of DM (6). Depression is associated with psychomotor retardation and decreased physical activity and can present with atypical symptoms such as hyperphagia and hypersomnia, leading to increased caloric intake and decreased energy expenditure causing weight gain and subsequently DM. The fact that individuals with BDs spend much of their lives with depressive symptoms adds to the risk (6). Furthermore, all phases of BDs, including euthymia, are associated with sleep disturbances (85). A meta-analysis on the quantity and quality of sleep in the general population

showed that the relative risk for the development of DM was 1.57 for difficulty in initiating sleep and 1.84 for difficulty maintaining sleep (86).

BDs and DM are linked in even more ways. DM and insulin resistance are associated with a treatment refractory and more severe course of BDs (6). Thus, identifying and treating insulin resistance may improve treatment response in BDs. A pilot study by Rasgon et al. showed that adding rosiglitazone (an insulin sensitizer previously used to treat DM) to usual treatments was associated with improvement in depression in individuals with depression and insulin resistance (87). On the other hand, individuals with DM and BDs have poorer control of their diabetes compared with individuals with DM but without BDs (6). Depression is associated with poor adherence to diabetes treatment (88), higher risk of developing diabetic complications (89), and increased mortality in individuals with DM beyond CVD-related mortality (90).

7.1.3. Hypertension

Hypertension is a modifiable risk factor with a linear risk association to most CVDs (91, 92). Between 1990 and 2019, the prevalence of hypertension doubled worldwide–from 648 to 1278 million individuals (93). Hypertension predisposes individuals to atherosclerosis, and studies have found that atherosclerotic plaques only form when blood vessels are subjected to high pressure (94). Hypertension is associated with increased VSMC growth leading to medial thickening (94). The thickening of the wall of the blood vessel leads to an increase in the diffusion distance for oxygen with subsequent hypoxia and steep PO_2 gradients across the vessel wall. The reduced oxygen supply impairs the antioxidant enzyme defense of the arterial wall (95) and leads to an increased concentration of free oxygen radicals (95). The free oxygen radicals are associated with tissue damage and lipoprotein oxidation. Furthermore, hypertension and atherosclerosis have additive effects on oxidative stress (94). The oxidative stress results in increased adhesion of leukocytes and the recruitment of monocytes in the subendothelial space. Hypertension accelerates the atherosclerotic process in several ways (96). Hypertension is associated with vascular remodeling (97) and contributes to endothelial dysfunction physically through perturbations in hemodynamics (98). Hypertension increases endothelial diffusive permeability and pressure-driven convective flow, which increases the uptake of LDL particles directly through the vessel wall (99) and indirectly through the leaky junctions over the endothelium (100). These leaky junctions are created by endothelial cell death or turnover that is increased by hypertension (100). Furthermore, hypertension leads to

the degradation of and mechanical damage to elastin, a major structural protein in blood vessels, leading to stiffer arteries (98).

Finally, the relation between hypertension and inflammation is reciprocal. One of the mediators of hypertension is angiotensin II as it can increase oxidative stress by stimulating the production of superoxide, which inactivates NO and contributes to inflammation (101). Conversely, inflammation is suspected to be involved in the pathophysiology of hypertension (102).

Bipolar disorders and hypertension

Most studies conclude that individuals with BDs have a higher prevalence of hypertension (103). However, no studies have examined longitudinal changes in blood pressure in individuals with BDs compared with the general population. In two of the studies in this thesis, we investigated time-dependent changes in systolic blood pressure (SBP) and diastolic blood pressure (DBP) in individuals with BDs compared with controls (Studies II (56) and III (57)). We found a statistically significant increase in SBP and DBP over time in the patient group relative to controls.

Contributing factors to high blood pressure in individuals with BDs are treatment with certain antidepressants (104) or atypical antipsychotics (105), comorbid insulin resistance and compensatory hyperinsulinemia, obesity, thyroid dysfunction, CKD, tobacco smoking, and alcohol overconsumption. The mechanisms that these factors are associated with high blood pressure have been discussed in different parts of section 7. Finally, unlike the case of DM and as reviewed in a study by Giménez-Palomo et al., hypertension does not worsen the course of BDs (106).

7.1.4. Obesity

Obesity is a chronic relapsing disease and one of the major health concerns worldwide with a high global prevalence that has continued to increase since the 1970s (107, 108). According to the WHO, the prevalence of obesity nearly tripled worldwide between 1975 and 2016 from 3.2% to 11% in adult men and from 6.4% to 15% in adult women (108, 109). In our own study, we found that the prevalence of obesity in the general Swedish population increased from 11.1% in 2008 to 15% in 2019 in adult men and from 10.2% to 13.4% in adult women (Study IV). Obesity–especially central obesity–is an independent risk factor for CVDs (110). The

increased risk of hypertension, DM, and dyslipidemia in obese individuals (111, 112) leads to the increased use of medications and hospital services, increasing the costs of obesity for the individual and for the health care system (112).

The likelihood of developing obesity depends on both intrinsic and extrinsic factors. Intrinsic factors include genetic predisposition (113), reduced thermogenesis (114), physical disabilities (115), and sleep disturbances (116). The extrinsic factors include pervasive and persuasive food marketing (116), high intake of refined carbohydrates and fats (116), large portion sizes (117), more sedentary time (116), labor saving devices (116), chronic stress (118), and weight cycling (119).

Obesity is a risk factor for dyslipidemia, insulin resistance, and DM (72, 120). High weight is associated with an increase in TAG and a decrease in HDL-C. Even small increases in BMI are associated with worsened plasma levels of TAG, LDL-C, and HDL-C (121). Furthermore, LDL particles become smaller and denser in obese individuals (72). The pattern of dyslipidemia associated with obesity is related to the association of obesity, especially central obesity, with insulin resistance (121). This association has been described above (section 7.1.2). As a result, a combination of low HDL, high small dense LDL, and modified LDL drives plaque formation and atherosclerosis as described previously.

As discussed earlier, obesity can cause hypertension via mechanisms linked to insulin resistance (see section 7.1.2). In addition, obesity leads to activation of the renin angiotensin system, which causes sodium and water retention and systemic vasoconstriction (122). Obesity is also associated with the activation of the sympathetic nervous system through increased levels of free fatty acids, leptin, insulin, and angiotensin II (122). In addition, endothelial dysfunction and decreased production of NO lead to vasoconstriction. This latter mechanism is induced by systemic inflammation, decreased insulin sensitivity, or by high levels of bioactive leptin (122, 123).

Adipose tissue does more than merely store fat. It is an endocrine organ that produces adipocyte-derived bioactive substances called adipokines (124). Most adipokines are secreted from visceral adipose tissue. Adipokines–e.g., IL-1, IL-6, TNF-α, leptin, monocyte chemoattractant protein-1 (MCP-1), PAI-1, and resistin–can be pro-inflammatory and promote oxidative stress and endothelial dysfunction (124, 125, 126). IL-1, IL-6, IL-8, MCP-1, resistin,

and TNF-α can also induce insulin resistance and atherogenic dyslipidemia (124, 126). Finally, some adipokines, including PAI-1, TNF-α, IL-6, and leptin, are pro-thrombotic (125).

Adiponectin is the only adipokine that decreases with obesity and is an adipose tissue-derived peptide hormone with antiatherogenic and anti-inflammatory properties (127). The anti-inflammatory effect is related to the adiponectin's ability to reduce the level and activity of TNF-α, inhibit the production of IL-6, and induce the production of the anti-inflammatory IL-10 (127, 128). In turn, both TNF-α and IL-6 decrease adiponectin levels (128, 129). Adiponectin stimulates NO production and promotes endothelial-dependent vasodilation (130). Furthermore, adiponectin improves insulin sensitivity and insulin resistance is associated with low levels of adiponectin (127).

There is an interplay between the different adipokines. TNF-α stimulates lipolysis and increases free fatty acid concentration (131), upregulates the synthesis of PAI-1, and together with IL-1 induces expression of IL-6 (124). IL-6 increases the production of C-reactive protein (CRP), increases plasma fibrinogen, augments platelet number and activity, activates HPA axis, and together with cortisol stimulates angiotensinogen synthesis (132, 133). Leptin increases CRP (134) and angiotensin II levels (135) and enhances expression of MCP-1 (136). Angiotensin II increases vasoconstriction, VSMC migration and proliferation, and IL-6 release (133). To sum up, adipokines can increase the levels of other mediators of insulin resistance, atherogenesis, inflammation, and thrombogenesis related to obesity.

In addition to increasing the risk of atherosclerotic CVDs, obesity can indirectly increase the risk of heart failure through hyperdynamic circulation, increased metabolic demands of a body with high BMI (137), dyslipidemia with accumulation of TAG and free fatty acids in the myocardial muscle exposing the myocardium to lipotoxicity and lipoapoptosis (138), and hypertension, which increases the afterload on the myocardial muscle (139).

Bipolar disorders and obesity

It is well documented that individuals with BDs have higher prevalence of overweight and obesity compared with men and women in the general population (84). In our own population study of 22,127 individuals with BDs and 71,894 individuals from the general Swedish population, we found that the prevalence of obesity in 2019 was 33.0% in women with BDs compared with 13.4% in women from the general population and 29.3% in men with BDs compared with 15.0% in men from the general population (Study IV). Moreover, we found that

the prevalence of obesity increased at a higher rate in individuals with BDs compared with the general population in Sweden. In other studies included in this thesis, we found higher mean BMI as a measure of total obesity (Studies II (56) and III (57)), higher waist-to-hip ratio (WHR) as a measure of central obesity (Study II (56)), and higher increase in WHR over seven to eight years in individuals with BDs compared with a control group (Studies II (56) and III (57)).

Women and men differ in their susceptibility to obesity. Several studies have shown that women with BDs have higher rates of central and total obesity (waist circumference ≥80 cm and BMI ≥30 kg/m^2, respectively) compared with men with BDs and both women and men from the general population (140). We found similar results when comparing BMI profiles between individuals with BDs and the general population in Sweden between 2008 and 2019. Moreover, we found a higher rate of increase in the prevalence of obesity among women with BDs compared with men with BDs and men and women from the general population (Study IV). In another study included in this thesis, we found that being a women with a BD is associated with clinically significant weight gain (≥7%) when these women are treated with second-generation antipsychotics as an add-on treatment to mood stabilizers (Study I (141)).

There are additional factors that contribute to overweight in individuals with BDs beyond those that also affect the general population (section 7.1.4). These BD-specific factors are shared genetic risk between BDs and obesity (142), treatment with psychotropics (143), HPA axis disturbances (144), and the clinical manifestation of BDs such as manic, hypomanic, and depressive episodes (145).

In addition to the negative effects of obesity in general, obesity is associated with more frequent and severe mood episodes with a subsequent worsening of the overall prognosis (145). Furthermore, obesity reduces the positive effect of antidepressants, lithium, and valproate (144). In individuals receiving treatment with lithium and valproate, the probability of treatment response and remission decreased by 7.5% and 7.3%, respectively, for every one unit increase in BMI (146).

7.1.5. Chronic kidney disease

CKD is defined as decreased kidney function shown by an estimated glomerular filtration rate of less than 60 mL/min per 1.73 m^2 and/or markers of kidney damage of at least three months duration, regardless of underlying cause (147). Individuals with CKD are at risk for CVDs such

as heart failure, stroke, peripheral artery disease, coronary heart disease, and atrial fibrillation (148). Although CKD is frequently caused by hypertension and DM, it is also an independent CVD risk factor. About 40–50% of individuals with CKD do not have hypertension or DM and the association between CKD and CVD mortality in these individuals is similar to those with CKD and comorbid hypertension or DM (149, 150). Life expectancy can be reduced by up to 25 years in individuals with CKD depending on the stage of glomerular filtration rate or stage of albuminuria, and this exceeds the reduction in life expectancy in individuals with hypertension or DM (148). Indeed, the true burden of mild to moderate CKD is related to the increased risk of CVDs rather than the risk of developing renal failure (148).

There are several factors linking CKD and CVDs (148). CKD can cause hypertension through decreasing the expression of NO synthase, increasing sympathetic nerve activity, and increasing the activity of renin angiotensin system (148). Angiotensin II leads to an increased pro-inflammatory and pro-thrombotic activity as described previously (section 7.1.4). Furthermore, the decreased availability of NO leads to endothelial dysfunction (148). The combination of hypertension, renal anemia, and increased vascular stiffness causes left ventricular hypertrophy, which can further be complicated by cardiac arrythmias and increased prevalence of sudden cardiac death (148).

Dyslipidemia is another factor linking CKD and CVDs. CKD disturbs key enzymes and metabolic pathways in lipoprotein metabolism. The most frequent dyslipoproteinemic pattern in CKD is the increased levels of TAG and TAG-RLs. The increase in TAG and TAG-RLs is caused by the impaired catabolism or increased production of TAG-RLs. CKD downregulates LPL gene expression leading to decreased catabolism of TAG (151). CKD decreases the catabolism of apolipoprotein C-III (152), which inhibits LPL and HL (153), decreases uptake of TAG-RLs by hepatic lipoprotein receptors (153), and enhances hepatic overproduction of VLDL (154). Furthermore, CKD causes insulin resistance, which is associated with increased hepatic production of VLDL (155).

In addition to the increase in the proatherogenic lipoproteins, CKD is associated with decreased levels of antiatherogenic HDL caused by the decreased levels of apolipoproteins AI and AII, the decreased activity of LCAT, and the increase in the activity of CETP (156). Furthermore, the activity of HDL-enzymes such as paraoxonase 1 is reduced in CKD, leading to impaired anti-oxidative, and anti-inflammatory characteristics of HDL (156). Severe CKD is associated

with oxidative modification of HDL, yet another mechanism counteracting HDL's cardioprotective function (157).

Individuals with CKD have high Lp (a), high IDL-C, High LDL-C, and high small dense LDL-C (156, 158). The increase in Lp (a) accelerates the atherosclerotic process and is prothrombogenic because of the competitive inhibition of fibrinolysis (156).

CKD provides a milieu for the oxidative modification of lipoproteins. The high levels of LDL and the impaired antioxidative properties of HDL make LDL more available and vulnerable to modification (36, 158). Modified LDL has a reduced affinity for the LDL-R but not the scavenger receptors on the surface of the macrophages, leading to the formation of foam cells in the subendothelial space and therefore accelerating the atherosclerotic process as mentioned earlier (section 7.1.1.1). Finally, CKD is associated with low-grade inflammation, partly through the increased production of inflammatory mediators that cause oxidative stress and promote atherosclerosis (148).

7.1.6. Thyroid dysfunction

It is well known that thyroid dysfunction is associated with CVDs (159). One of the mechanisms linking the two conditions is dyslipidemia. Thyroid hormones play an important role in lipoprotein metabolism (160) by increasing the activity of key enzymes such as CETP, LPL, and HL (161). Furthermore, thyroid hormones increase LDL-R activity either directly by increasing the expression of LDL-R (162) or increasing the affinity of lipoproteins for the LDL-R by upregulating apolipoprotein A5 gene expression (163). Apolipoprotein A5 can even inhibit hepatic production of TAG-RLs and stimulate LPL-mediated hydrolysis of TAG-RLs (164).

Patients with overt hypothyroidism have increased levels of TChol, LDL-C, IDL-C, VLDL, TAG, HDL-C, and TChol/HDL-C ratio, presumably due to decreased lipolysis and decreased activity of LPL (161). Moreover, as patients with hypothyroidism have high levels of Lp (a), they have higher risk of CVD (165). Dyslipidemia is manifested even with subclinical hypothyroidism, which is associated with increased levels of TChol, LDL-C, and TAG (161, 166). In addition to the abnormal metabolism of lipoproteins, hypothyroidism is associated with increase in LDL oxidation (167). One explanation is the abundance of LDL as a substrate for oxidation (161).

In contrast to low thyroid function, hyperthyroidism is associated with decreased levels of TChol, LDL-C, Lp (a), and HDL-C (161, 168). These lipoprotein changes are explained by the increased LDL receptor gene expression, increased CETP-mediated lipid transfer, and increased HL-mediated catabolism of HDL. In addition, TAG levels are decreased (168). A shared feature of hyperthyroidism and hypothyroidism is the increase in LDL oxidation (167). In hyperthyroidism, this increase in LDL oxidation could be due to the accelerated mitochondrial oxidative metabolism and the resulting increased production of free radicals.

Even within the clinically normal range of thyroid-stimulating hormone, the level of TChol, LDL-C, and TAG increases and the level of HDL-C decreases linearly with the levels of thyroid-stimulating hormone (169).

In addition to dyslipidemia, thyroid dysfunction exerts negative effects on blood pressure and hemodynamics (170). Hyperthyroidism is associated with tachycardia and atrial fibrillation (170), and hypothyroidism is associated with diastolic hypertension (170). Moreover, hypothyroidism is associated with endothelial dysfunction through a reduction of NO (171). A reduction in NO levels can also be caused by the presence of low-grade chronic inflammation, which is yet another mechanism underlying endothelial dysfunction in individuals with hypothyroidism (172).

Other CVD risk factors are also associated with thyroid dysfunction. For example, hypothyroidism is associated with insulin resistance (173) and has a direct association with total and central obesity (174, 175), and both hyperthyroidism and hypothyroidism are associated with a hypercoagulable state (176, 177).

Bipolar disorders and thyroid dysfunction and kidney disease

There is a well described relation between BDs and thyroid dysfunction (178). Thyroid hormones can affect treatment response and the clinical course of BDs (179). Higher T4 or T3 levels have been associated with better treatment response to lithium and antidepressants. On the other hand, low levels of T4 or high levels of TSH are associated with poorer response to lithium and antidepressants and more severe outcome of depression (179).

Lithium can cause both hypothyroidism and hyperthyroidism (180) and can lead to CKD (181). However, treatment with lithium does not fully explain the higher prevalence of thyroid dysfunction in individuals with BDs. Valle, et al. found that the prevalence of hypothyroidism

in lithium-naïve patients was 9% (182) compared with 3% in the general population (183). Apart from the effect of lithium, there is an interrelation between kidney disease and thyroid dysfunction (184). Hypothyroidism can lead to increased serum levels of creatinine, reduction in glomerular filtration rate, decreased renal plasma flow, disrupted renal ability to dilute urine, decreased sodium reabsorption, and hyponatremia. On the other hand, different kidney diseases can lead to hypothyroidism and hyperthyroidism (184).

7.2. Lifestyle related risk factors

7.2.1. Tobacco smoking

Tobacco smoking, a major contributor to CVDs (185), has a dose-response relation with CVD risk (186): increased risk of coronary artery disease and stroke is observed already at one cigarette smoked per day (187). Additionally, individuals who smoke show evidence of genetic predisposition to atherosclerosis (188). Tobacco smoking contributes to the early phases of atherosclerosis through disrupting endothelial homeostasis. Free radicals such as superoxide and hydrogen peroxide, which are released from the gas or tar phase of cigarette smoke or from activated macrophages and neutrophils decrease NO availability and increase oxidative stress (185). This oxidative stress can contract endothelial cells and subsequently increase permeability of the vascular endothelium and contribute to endothelial dysfunction (189). Furthermore, smoking can kill endothelial cells with subsequent initiation of an inflammatory response (190).

In addition to cell death, smoking can induce inflammation in other ways. Cigarette smoking causes local and systemic activation of the immune system through increased serum levels of pro-inflammatory cytokines such as CRP, TNF-α, IL-1β, IL-6, and IL-8 by alveolar macrophages (185, 191). Alveolar macrophages also release hematopoietic growth factors that can increase leukocyte release from the bone marrow (191). Furthermore, cigarette smoking leads to increased endothelial adherence and migration of monocytes (185).

Tobacco smoking causes dyslipidemia (high TChol, high TAG, high VLDL-C, high LDL-C, and low HDL-C) and has a dose response effect (192). Most of the components of dyslipidemia remain unchanged after smoking cessation except for improved levels of HDL-C (193). The pattern of dyslipidemia in smokers is like that seen with insulin resistance (see section 7.1.2), and cigarette smoking is associated with insulin resistance (194). Moreover, smoking can

accelerate the atherosclerotic process by increasing the oxidative modification of LDL (195) and can decrease the plasma activity of the antioxidant enzyme paraoxonase 1 (196).

The atherosclerotic risk caused by tobacco smoking is compounded by an increase in thrombosis through disturbed thrombo-hemostatic mechanisms (185). Specifically, cigarette smoking limits fibrinolysis, increases fibrinogen levels, and causes platelet dysfunction and hyperaggregability (185, 197, 198). Carbon monoxide in tobacco smoke displaces oxygen from hemoglobin and causes tissue hypoxia and compensatory erythrocytosis. This erythrocytosis together with the increase in fibrinogen levels increase blood viscosity (199). Furthermore, the decreased availability of NO and the inflammation associated with tobacco smoking potentiate the pro-thrombotic activity (49, 185). Finally, tobacco smoking can increase blood pressure and heart rate through the direct effects of nicotine, an adrenergic agonist (200).

Bipolar disorders and tobacco smoking

Individuals with BDs are two to three times more likely to start smoking and less likely to stop compared with the general population (201). Smoking is associated with a more severe course of BDs, poorer functioning, and high risk for suicide (202).

Several explanations for the high rate of smoking among individuals with BDs have been put forward. A common explanation is based on the self-medication hypothesis described by Khantzian (203). First, smoking can alleviate the depressive symptoms of BDs through the inhibition of monoamine oxidase by tobacco smoke and the release of serotonin and dopamine by nicotine (204). Second, nicotine could improve cognitive function. However, a study by Law et al. showed that improved cognitive function by nicotine was subjective and not objective in BDs (205). Third, smoking can decrease the severity of the extra-pyramidal symptoms experienced with antipsychotics (206). This latter effect of smoking can be explained by the induction of cytochrome P450 isozymes CYP1A1, CYP1A2, and CYP2E1 by the polycyclic aromatic hydrocarbons in tobacco smoke (207, 208). These isozymes are involved in the metabolism of antidepressants, including fluvoxamine, amitriptyline, clomipramine, and imipramine (208) and metabolism of antipsychotics, including olanzapine, clozapine, chlorpromazine, and haloperidol (206, 207, 208). Smoking induces the metabolism of olanzapine and clozapine even when only smoking a few cigarettes per day (209). As a consequence of the increased metabolism of antipsychotics, the doses of these medications

should be increased in smokers to exert a therapeutic effect (209). On the other hand, increasing the doses is associated with greater motivation to smoke (210).

Finally, some mood stabilizers such as carbamazepine, oxcarbazepine, and topiramate can induce CYP2A6 enzyme activity, enhancing the metabolism of nicotine (211). This is important since persons who metabolize nicotine quickly tend to smoke more (212).

7.2.2. Sedentary behavior and physical inactivity

Sedentary behavior and physical inactivity are well known CVD risk factors. Physical activity is defined as any bodily movement that requires skeletal muscle and results in energy expenditure (213). Sedentary behavior is defined as any waking behavior characterized by a very low energy expenditure–i.e., ≤1.5 metabolic equivalents of a task such as sitting, reclining, or lying down. In other words, energy expenditure does not increase substantially above the resting level (214). Studies have found a dose-response association between sedentary time and all CVD risk and CVD mortality (215). Sedentary behavior is not the same as physical inactivity–i.e., an activity level insufficient to meet physical activity guidelines (216). Worldwide, one in five adults is physically inactive (217). In addition to CVDs, physical inactivity causes DM, breast cancer, colon cancer, and premature mortality (216).

Physical inactivity has negative effects on lipid metabolism. Studies on rats showed a decrease in LPL activity in skeletal muscle, a situation that leads to high levels of TAG and low levels of HDL-C (218). Sedentary behavior and physical inactivity can also reduce glucose uptake by decreasing insulin sensitivity (219, 220).

In addition, sedentary behavior is associated with mitochondrial dysfunction (221), which increases oxidative stress (222). This increase in oxidative stress is also true for physical inactivity, which leads to arterial stiffness, vascular remodeling, and reduced endothelium-dependent dilation, conditions that favor the progression of atherosclerosis (223).

On the bright side, physical activity can restore the oxidative/antioxidative balance. Physical activity stimulates superoxide dismutase antioxidant activity and inhibits the production of superoxide through inhibiting nicotinamide adenine dinucleotide phosphate (NADPH) oxidase (224). The reduction in superoxide lessens oxidative stress and contributes to an increase in the availability of NO (224). A restored oxidative/antioxidative balance helps maintain the vasodilatory function of the endothelium. Furthermore, physical activity increases arterial

mitochondrial function, which restores arterial homeostasis and decreases oxidative stress (225). In addition to the antioxidant effects, physical activity has anti-inflammatory effects and is associated with reductions in CRP, IL-6, and TNF-α and therefore halts the process of atherosclerosis (226).

Studies have confirmed the beneficial cardiometabolic effects of different types of physical activity including aerobic endurance training (227), resistance training (228), and isometric training (229). Aerobic endurance training (e.g., walking, jogging, running, cycling, and swimming) decreases resting and daytime ambulatory blood pressure in hypertensive as well as in normotensive individuals. Regular exercise reduces the systemic vascular resistance partly through the reduction in plasma norepinephrine and plasma renin activity (227). Other beneficial effects on CVD risk factors include a decrease in body weight and abdominal visceral fat, which is reflected in a decreased waist circumference, WHR, and percent body fat (227). Furthermore, aerobic training enhances insulin sensitivity and increases HDL-C (227).

Physical activity also has favorable cardiac effects. It counteracts arterial aging and age-related decrements in left ventricular compliance and distensibility (230, 231). A study by Cornelissen and Fagard showed that regular aerobic training decreased resting heart rate by five beats per minute after a median duration of 16 weeks (227). This reduction in heart rate represents an annual decrease of 2.6 million heartbeats and an accompanying reduction in the hemodynamic stress on the endothelia. The decrease in heart rate is counterbalanced by an increase in stroke volume and improved cardiac function (227).

Bipolar disorders and sedentary behavior and physical inactivity

A recent global systematic review and meta-analysis showed that individuals with BDs are more sedentary and less physically active compared with individuals from the general population (232). Both physical activity level and sedentary behavior are relevant for individuals with BDs as these individuals could be more sedentary but more engaged in moderate to vigorous physical activity compared with individuals with schizophrenia and major depression (232). Although more often engaged in moderate to vigorous physical activity, about a third of individuals with BDs are physically inactive (232).

Factors associated with sedentary behavior and lower activity levels in individuals with severe mental illness are male sex, social isolation, unemployment, lower education, higher BMI,

longer illness duration, depressive symptoms, comorbid medical conditions, and the use of antidepressants and antipsychotics (232, 233).

7.2.3. Alcohol use disorder

The risk of atrial fibrillation (234) and non-coronary CVDs such as stroke (235) increases continuously with increasing alcohol consumption. However, the consequences of alcohol consumption on the risk for CVDs are debated. Many epidemiological studies have shown a lower mortality rate in individuals reporting moderate alcohol consumption compared with non-drinkers and heavy drinkers, resulting in a J-shaped relation (236). Although recent studies have questioned this relation, some studies have found a protective effect against myocardial infarction with low-moderate alcohol consumption (237).

The observational studies that show a J-shaped association between alcohol consumption and CVD risk have been criticized for not adjusting for individuals who were former drinkers but quit alcohol due to health issues (i.e., sick-quitters) (238). In a recent large meta-analysis, Stockwell et al. showed that alcohol lost its observed CVD-protective effect after adjusting for abstainer biases and quality-related study characteristics (239).

New approaches–e.g., Mendelian randomization studies–attempt to account for potential confounding factors. One such study contrasting the J-shaped association found that genetic predisposition rather than the amount of alcohol consumed accounts for the protective effect against CVDs, concluding that a reduction in alcohol consumption should be advised even for those with low to moderate levels of consumption (240). This study related the hypothesized cardioprotective effect of light to moderate alcohol consumption to residual confounding or selection bias.

A study on the effect of short- and long-term use of alcohol on lipoprotein metabolism showed that short-term use of alcohol was associated with a decrease in LPL activity in adipose tissue (241). The decrease in LPL activity leads to an increase in plasma LDL, HDL, and TAG in TAG-RLs (241). Long-term use of alcohol, on the other hand, was associated with a compensatory increase in LPL activity in adipose tissue (241). However, TAG increased in all lipoprotein fractions and the increase in LPL activity did not offset the increase in TAG (241). Other studies have shown that plasma levels of TAG increase continuously with increased alcohol consumption (242). Alcohol consumption is also associated with increased plasma

levels of HDL-C, which normally is inversely related to plasma levels of TAG. However, the inhibition of CETP activity by alcohol can explain why the inverse relation between HDL-C and TAG is not observed (243).

In addition to the effect on lipoprotein metabolism, increasing alcohol consumption is associated with a continuous increase in systolic and diastolic blood pressure (242). The increase in blood pressure offsets any proposed protective effect of increased HDL-C on coronary CVD risk (242).

Bipolar disorders and alcohol use disorder

Individuals with BDs are more vulnerable to alcohol abuse or dependence (244). Factors such as male sex, more frequent manic episodes, and suicidality are associated with alcohol use disorder in BDs (244). Alcohol has been associated with worse clinical course and outcome of BDs, poorer response to lithium, and decreased treatment adherence (245).

7.2.4. Unhealthy dietary habits

Dietary habits include both the quantity and quality of food. An unhealthy dietary habit is a modifiable CVD risk factor and is closely associated with obesity, dyslipidemia, inflammation, risk for DM, and endothelial dysfunction (246). Food groups such as fish oil, vegetable oils, nuts, legumes, grains, and fruits are high quality food and increase HDL-C while decreasing LDL-C, TAG, non-HDL-C, and VLDL-C. These food groups have a positive effect on blood pressure, decrease the risk of DM, reduce inflammation, and improve endothelial function (246). On the other hand, fried and processed foods and sweetened beverages exert negative health effects by worsening dyslipidemia, especially through increasing LDL-C. Consequently, they increase the risk of DM and CVDs (246). Part of the negative effect is mediated via the downregulation of LDL-R, resulting from a high consumption of saturated fatty acids (247).

Bipolar disorders and unhealthy diet

Persons with BDs more often have unhealthy dietary habits compared with the general population (248). These unhealthy dietary habits include consuming a greater quantity of food, which translates to a higher energy intake (248, 249), and consuming a poorer quality of food, which includes a high intake of sweetened beverages, cakes, sweets, white bread, carbonated beverages, sucrose, hydrogenated oils, fast food, and fats, especially saturated and trans fats (248, 249). Furthermore, poor quality of food includes a low intake of fruits and vegetables

(248). Moreover, psychotropic medications (59, 250) and depressive symptoms (233) are postulated to be the major contributors to the poor dietary habits of individuals with BDs.

7.3. Non-modifiable CVD risk factors

7.3.1. Advanced age

Age is the most important factor through which other CVD risk factors can superimpose their effects. That is, CVDs are more prevalent in the elderly population (251). According to the WHO, the number of people aged 60 years and older will double to 2.1 billion between 2019 and 2050 worldwide (252). Advancing age is associated with an increase in pro-inflammatory mediators such as IL-6, TNF-α, IL-1β, and CRP, resulting in a state called inflamm-aging (253, 254). Accordingly, inflamm-aging promotes atherosclerosis and exacerbates the effect of other CVD risk factors (253). Aging is associated with monocyte and lymphocyte accumulation in adipose tissue and therefore an increased production of pro-inflammatory adipokines by adipose tissue macrophages (253). The role of adipokines in atherosclerosis was discussed earlier (section 7.1.4). Furthermore, increasing age is associated with cardiovascular structural remodeling that includes increased vascular intimal thickness, vascular stiffness, left ventricular wall thickness, and left atrial size (255). The arterial stiffening and thickening lead to an increase in vascular afterload on the heart. The increased afterload can be observed by a modest increase in systolic blood pressure at rest (255). Remodeling of cardiovascular structure is caused by factors such as decreased NO production, altered growth factor regulation, degradation of elastin by elastases and gelatinases, proliferation and migration of VSMCs, and production of proteases, elastase, and collagen by VSMCs (255).

In addition to structural changes, the aging heart is subject to cardiovascular functional changes such as impaired regulation of vascular tone caused by decreased availability or effect of NO, dysregulated cell Ca++ homeostasis, which leads to vascular stiffening, hypertension, and atherosclerosis (255). Another cardiovascular functional change caused by aging is the relative increase in the sensitivity of the heart to Ca++ with increased risk for arrhythmias and myocyte death during excess Ca++ loading. This latter functional change can in part be due to a higher likelihood of intracellular generation of reactive oxygen species or changes in the composition of cellular membranes. For example, increased membrane omega-6:omega-3 polyunsaturated fatty acids ratio in cardiac membranes can impair the function of Ca++ regulatory proteins in the membrane (255). A third functional change is the decreased cardiovascular reserve, increasing the risk of and worsening the outcome of existing heart failure in old age. The

reduction in cardiovascular reserve is caused by increased plasma levels of catecholamines with higher interstitial sympathetic neurotransmitter levels. The increase in catecholamine levels is due to reduced plasma clearance and enhanced outflow from and diminished reuptake into nerve endings. The resultant high occupancy of cardiac and vascular cell surface receptors by catecholamines results in a state of desensitization of β-adrenergic receptors. The desensitization of β-adrenergic receptors results in a reduction in the postsynaptic responsiveness to sympathetic stimuli. This reduced response results in reduced vascular tone, intrinsic myocardial contractility, and sympathetic modulation of heart rate (255).

7.3.2. Sex

It is well known that men are affected by atherosclerosis to a greater extent and at an earlier age than women (256). Men also have higher prevalence of dilated and hypertrophic cardiomyopathy and associated sudden cardiac death (257, 258). Furthermore, men have higher prevalence of hypertension compared with premenopausal women, after which women have higher prevalence of hypertension (259). Compared with men, women are more prone to arrythmias such as torsade de pointes (260). In addition, CVD risk factors add more cumulative risk of CVDs in women. For example, hypertensive women have higher risk of developing heart failure compared with hypertensive men (261). The risk of developing fatal coronary heart disease in women with DM is 50% higher than for men with DM (262).

Estrogen can attenuate the formation and progression of the atherosclerotic plaque through its atheroprotective, vasoprotective, and vasodilatory characteristics. Estrogen inhibits VSMC proliferation and matrix protein deposition (263), enhances the endothelial synthesis of NO (264), reduces the generation of reactive oxygen species (265), reduces monocyte recruitment (265), and downregulates plasma angiotensin-converting enzyme with subsequent reduction in angiotensin II (266). The higher synthesis of NO in premenopausal women could explain the lower arterial blood pressure in women (264). Furthermore, estrogen counteracts oxidative stress by inducing the expression and activity of mitochondrial manganese superoxide dismutase and extracellular superoxide dismutase in VSMCs (267).

Compared with men, women are also better protected against myocardial cell death. A key factor is the abundance and activation of protein kinase B (PKB) by estrogen in myocardium (268). PKB is a protein kinase that regulates different physiological responses such as cell survival. Estrogen also exerts an antiapoptotic effect through the repression of TNF-α in the

myocardium (269). Testosterone, on the other hand, decreases the activation of PKB and decreases manganese superoxide dismutase (270). Similarly, testosterone contributes to cardiomyocyte cell death by increasing the pro-inflammatory mediators TNF-α, IL-1β, and IL-6 (271).

Finally, estrogen has a beneficial effect on the lipid profile through lowering TChol, LDL-C, and Lp (a) concentrations, decreasing LDL-oxidation, and increasing HDL-C concentration (272). Furthermore, estrogen and progesterone reduce lipid accumulation in macrophages (273).

In addition to the effect of sex hormones, studies have demonstrated an association between gene variants on the Y chromosome and some cardiovascular phenotypes in men, including higher levels of LDL-C independent of testosterone levels (274).

7.4. Non-traditional CVD risk factors

Since the concept of CVD risk factors was introduced by the Framingham heart study in 1961, the focus in managing CVDs has been directed towards treating hypertension, DM, dyslipidemia, obesity, cigarette smoking, and physical inactivity (275). Treating these traditional CVD risk factors did not eliminate the excess CVD risk, and half of patients with CVDs did not have any of the traditional risk factors (275). Even genetic studies have found risk alleles associated with myocardial infarction but not associated with the traditional CVD risk factors, suggesting unknown CVD risk factors are at play (276). New (non-traditional) CVD risk factors have emerged including inflammation, high levels of homocysteine, hyperinsulinemia, microalbuminuria, high levels of Lp (a), and high levels of factors enhancing blood coagulation such as fibrinogen, factor VII, PAI-1, tissue plasminogen activator, and d-dimer (275).

7.4.1. Inflammation

Inflammation plays an important role in the atherosclerotic process (277). Indeed, inflammation accompanies atherosclerosis from lesion formation to end-stage thrombotic complications. Oxidized lipoproteins and pro-inflammatory cytokines such as IL-1β and TNF-α can induce the expression of vascular cell adhesion molecule-1 (VCAM-1) (277). VCAM-1 allows leukocytes to attach to the arterial endothelium. Other cytokines–e.g., MCP-1–help monocytes penetrate the endothelial lining and enter the intima of the vessel wall. These

monocytes mature into macrophages that multiply and release other growth factors and cytokines mediated by macrophage colony-stimulating factor, maintaining or augmenting the inflammatory response. The macrophages can convert into foam cells contributing to the development of fatty streaks as described earlier (section 4). Furthermore, inflammation mediates the rupture of the fibrous cap around the atherosclerotic plaque. Lastly, inflammation promotes the thrombogenicity of the lipid core (277).

To sum up, inflammation promotes the initiation of atherosclerosis, the formation of atherosclerotic plaque, the weakening and rupture of the fibrous cap, and boosts the thrombogenicity of the lipid core.

Bipolar disorders and inflammation

A recent systemic review summarized evidence for the connection between BDs and inflammation, especially during mood episodes where CRP, IL-1β, soluble IL-2 receptor, IL-6, IL-8, and TNF-α have been shown to be increased in peripheral blood (278). Some studies have found that the level of pro-inflammatory markers is partly restored after remission of symptoms (278) and during euthymia (279). CRP, IL-1β, IL-6, IL-8, and TNF-α are implicated in the development and progression of atherosclerosis as described previously. Recently, the levels of some novel pro-inflammatory markers–e.g., neutrophil/HDL ratio, monocyte/HDL ratio, lymphocyte/HDL ratio, and platelet/HDL ratio–were found to be higher in individuals with BDs compared with healthy individuals (280). These biomarkers indicate inflammation in individuals with BDs and are closely associated with the presence and prognosis of CVDs (280).

The connection between BDs and inflammation extends to the interaction between BDs and immune dysfunction and the high prevalence of inflammatory comorbidities. Individuals with BDs have shown high prevalence of autoimmune disorders (e.g., inflammatory bowel disease, systemic lupus erythematosus, autoimmune thyroiditis, Guillain-Barré syndrome, autoimmune hepatitis, multiple sclerosis, and psoriasis), chronic infections (e.g., toxoplasma gondii and possibly herpes simplex virus 1, cytomegalovirus, and human herpes virus 6), metabolic disorders (e.g., DM, dyslipidemia, central obesity, metabolic syndrome, and gout), and CVDs (e.g., myocardial infarction, stroke, atherosclerosis, and hypertension) (281).

Hyperactivity of the HPA axis and basal hypercortisolemia in individuals with BDs could contribute to inflammation (282). Glucocorticoids have pro-inflammatory effects in addition

to being anti-inflammatory (283). The inflammatory responses caused by chronic hypercortisolemia in BDs can damage cells and allow the release of damage-associated molecular patterns (DAMPs) that can activate an inflammatory response (284). Furthermore, pro-inflammatory cytokines such as IL-1, IL-6, and TNF-α have also been shown to up-regulate HPA axis activity, resulting in hypercortisolemia (285). These pro-inflammatory cytokines contribute to a chronic activation of HPA axis in individuals with BDs (284).

7.5. Other CVD risk factors

In addition to the CVD risk factors mentioned above, there are other risk factors–e.g., genetic predisposition, liver disease, infections, and medications such as corticosteroids, retinoids, antipsychotics, and antiretrovirals. Except for antipsychotics, these additional risk factors are beyond the scope of this thesis and will not be described in detail.

7.6. Bipolar disorders' specific CVD risk factors

7.6.1. Psychotropics

A range of psychotropics are prescribed to individuals with BDs for acute or maintenance treatment of mood episodes or for the treatment of accompanying comorbidities. This makes individuals with BDs vulnerable to the side effects of these psychotropics.

There is ample evidence that treatment with psychotropics can cause cardiometabolic disturbances (59). Weight gain is a common side effect of treatment with lithium, valproate, mirtazapine, SSRIs, gabapentin, vigabatrin, monoamine oxidase inhibitors, tricyclic antidepressants, atypical antipsychotics except for aripiprazole and ziprasidone, and some conventional neuroleptics such as thioridazine and chlorpromazine (59, 250). Weight gain can complicate the management of psychiatric disorders because it reduces treatment adherence (286).

Previous work has also shown greater weight gain when mood stabilizers are combined with second-generation antipsychotics (287). However, in our register-based study, we found no statistically significant difference in weight gain or increase in BMI between individuals with BDs taking mood stabilizers alone or in combination with a second-generation antipsychotic (Study I (141)).

Dyslipidemia is also a common metabolic side effect. Here, psychotropic agents have varying effects on the lipid profile. Clozapine and olanzapine are associated with the highest occurrence of dyslipidemia by increasing TChol, LDL-C, and TAG and lowering HDL-C (59, 288, 289, 290). Risperidone and quetiapine have intermediate effects on lipids where risperidone increases TAG (59, 288) and quetiapine increases TAG and TChol and decreases HDL-C (288). Studies have reported that aripiprazole and ziprasidone have no effect on the lipid profile (289) or a beneficial effect on TAG and TChol (288, 289). Other dyslipidemic effects of psychotropics include increase in TAG by valproate (59), increase in TChol by SSRIs and mirtazapine (59), and increase in LDL-C by paroxetine (59).

As with dyslipidemia, psychotropics differ in their effect on glucose homeostasis. The risk of developing insulin resistance and DM with atypical antipsychotics is proportional to their effect on weight gain, and treatment with clozapine and olanzapine carries the highest risk (59, 290). The next highest risk is associated with risperidone and quetiapine (59), and aripiprazole and ziprasidone are least likely to cause hyperglycemia (59). However, an increased prevalence of insulin resistance and DM was reported in individuals with BDs and schizophrenia even before the existence of antipsychotics (291, 292). In addition to risk due to treatment with antipsychotics, valproate and tricyclic antidepressants have been associated with hyperglycemia and insulin resistance (59, 293). However, the use of tricyclic antidepressants is limited in BDs due to the risk of switching to mania (10).

Finally, increases in blood pressure and in the prevalence of hypertension are associated with valproate, psychostimulants, antidepressants (e.g., venlafaxine, duloxetine, and tricyclic antidepressants), and atypical antipsychotics (e.g., clozapine, olanzapine, aripiprazole, and ziprasidone) (59).

7.6.2. Heredity

There is a familial association between BDs and cardiometabolic diseases as there is a higher prevalence of dyslipidemia and ischemic stroke (294) or general CVD risk (295) in unaffected first-degree relatives of individuals with BDs compared with controls. In addition, one study found that CVD risk was highest in first- and second-degree relatives of individuals with

familial BDs, followed by relatives of individuals with non-familial BDs, followed by relatives of controls (296).

8. THE RELATION BETWEEN CVDS AND CVD RISK FACTORS

It is important to emphasize that the relation between CVD risk and major risk factors such as obesity, dyslipidemia, hyperglycemia, and hypertension is continuous. Although thresholds are used clinically, even small changes in these risk factors can increase CVD risk.

8.1. Measures of total and central obesity

Every 1 kg/m^2 increase in BMI is associated with a risk increase of coronary heart disease in women by 4% and in men by 5% (111). In addition, a 1 kg/m^2 increase in BMI increases the risk of ischemic stroke by ≈5% (297), heart failure by 5% in men and 7% in women (298), and atrial fibrillation by 4% (299). Finally, overall mortality increases by about 30% for each 5 kg/m^2 increase in BMI (300). On the other hand, a 2 kg/m^2 decrease in BMI is associated with a 12% reduced risk of ischemic stroke, 8% reduced risk of hemorrhagic stroke, and 11% reduced risk of ischemic heart disease (301). If discrete categories are used, men and women with obesity class II and III (BMI ≥35 kg/m^2) have up to 8.5 years earlier presentation of cardiometabolic diseases (302). Central obesity is also associated with an increased risk of CVDs where a 1 cm increase in waist circumference increases CVD risk by 2% (303), and a 0.01 unit increase in WHR increases CVD risk by 5% (303).

In addition to the increased risk of CVDs, there is a continuous relation between BMI and incidence rate of other CVD risk factors such as DM and hypertension (304). The likelihood of having DM increased by 11.6% for every 1 kg/m^2 increase in BMI over 25 kg/m^2 (305). Conversely, every kilogram of lost weight reduces the risk of DM by 16% (306). Individuals with BMI between 18.5 and 30.0 kg/m^2 show a linear relation between blood pressure and BMI. One study determined the rate of increase in SBP to 1.15 mm Hg and DBP to 0.75 mm Hg for every 1 kg/m^2 increase in BMI (307). Another study found an age-dependent increase in mean DBP of 0.41–0.72 mm Hg in men and 0.43–0.95 mm Hg in women for a 1 kg/m^2 increase in BMI (308). In addition to the increased incidence rate of hypertension, overweight is associated with worse prognosis if hypertensive (309). On the positive side, losing 1 kg reduces SBP and DBP by ≈1 mm Hg (310).

8.2. Lipid profile

Several studies have demonstrated a dose- and time-dependent association between LDL-C and the risk of atherosclerosis (311). However, absolute levels of LDL-C only partially predict CVD risk (312). Instead, several epidemiological studies have shown that lipoprotein ratios–e.g., TChol/HDL-C, LDL-C/HDL-C, and TAG/HDL-C–predict CVD risk better than isolated lipoproteins (313). Small increases in these lipoprotein ratios increase the risk of CVDs and insulin resistance (Table 1).

Table 1. The continuous relation between lipoprotein ratios and CVDs and insulin resistance

Lipoprotein ratio	**Coronary artery disease**	**Ref.**	**Risk of CVD death**	**Ref.**	**Odds of having insulin resistance**	**Ref.**
TChol/HDL-C	≈50% increase in risk of myocardial infarction per 1 unit increase in TChol/HDL-C ratio	(314, 315)	17% increase per 1 unit increase in TChol/HDL-C ratio	(316)		
LDL-C/HDL-C	75% increase in risk of myocardial infarction per 1 unit increase in LDL-C/HDL-C ratio	(314)				
LDL-C/HDL-C	>6 times increase in risk of coronary events with an LDL-C/HDL-C ratio of >5 compared with an LDL-C/HDL-C ratio <5	(313)				
LDL-C/HDL-C >5 plus TAG ≥2.24 mmol/L	Double the risk of coronary events compared with TAG <2.24 mmol/L	(313)				
TAG/HDL-C			59% increase per 1 unit increase in TAG/HDL-C ratio	(317)	1.8–4 times ethnic-specific increase odds per 1 unit increase in TAG/HDL-C ratio	(318)

8.3. Systolic and diastolic blood pressure

Previous studies have convincingly shown a linear relation between SBP and CVD mortality (319, 320). The increase in the risk of atherosclerotic CVDs increases with SBP in a stepwise manner starting from SBP levels as low as 90 mm Hg, where every 10-mm Hg increase in SBP was associated with a 53% higher risk for atherosclerotic CVDs (321).

In addition to the linear relation between SBP and CVDs, each 10-mm Hg reduction in mean SBP was linearly associated with a 12% reduction in the risk of any complication related to DM and a 15% reduction in the risk of DM-related mortality (322).

Previous studies have shown both a J-shaped (319) and linear (320) relation between DBP and CVD mortality in elderly (65+) individuals. There is, however, agreement on the beneficial effect of reducing DBP on CVD risk. Lowering DBP by 2 mm Hg results in a 6% reduction in the risk of coronary heart disease and a 15% decrease in the risk of stroke and transient ischemic attacks (323).

8.4. Plasma glucose

CVD risk continuously increases with higher fasting plasma glucose. The CVD risk starts to increase from glucose levels of 4.9 mmol/L, a level that is well below the applied cut-offs for the diagnosis of DM or impaired glucose tolerance (324). Conversely, each 1 mmol/L decrease in fasting plasma glucose is associated with about 20% lower risk of total stroke, total ischemic heart disease, and CVD death in both men and women (324).

De Vegt et al. found a significant linear increase in CVD mortality with increments in 2-hour post-load glucose (plasma glucose 2 hours after an oral 75-g glucose load) and to a lesser extent with increasing HbA1c. This linear relation was true even within the non-diabetic range for both 2-hour post-load glucose and HbA1c (325). A meta-analysis of prospective studies also found a linear relation between post-load glucose level and CVDs across the non-diabetic range (326). However, the meta-analysis also showed that CVD risk starts from fasting plasma glucose levels at around 5.6 mmol/L, indicating a possible threshold effect.

8.5. Number of smoked cigarettes

In a recent large meta-analysis, the number of cigarettes smoked non-linearly increased the risk of coronary heart disease and stroke (187). Even smoking one cigarette per day increases the

risk of developing coronary heart disease and stroke. In comparison, increasing the number of smoked cigarettes to 20 per day roughly doubles CVD risk (187). These findings indicate that there is no safe level of smoking in terms of CVD risk.

9. A SYNERGISTIC RATHER THAN ADDITIVE RISK-COMBINATION

As previously shown, there is compelling evidence of the interaction and co-variation between CVD risk factors. I have illustrated how the different risk factors contribute to the different pathophysiological mechanisms underlying atherosclerosis such as endothelial dysfunction, inflammation, thrombogenesis, lipoprotein modification, and VSMC migration and proliferation. Moreover, I have illustrated the interrelation between the different CVD risk factors and how changes in risk factors relate to CVD risk.

I have not discussed how the presence of multiple CVD risk factors affect CVD risk. Golden et al. evaluated the association between different groupings of CVD risk factors and subclinical atherosclerosis, assessed by carotid intimal-medial thickness (IMT) (327). When adding up the individual effects of hypertension, hypertriacylglycerolemia, hyperinsulinemia, low HDL-C, and hyperglycemia, the excess carotid IMT should amount to 55µm. However, the combined excess carotid IMT was found to be 71µm. This difference suggests that CVD risk factors can synergistically affect CVD risk. Indeed, a multinational case-control study showed that the combination of current smoking, DM, hypertension, raised apo B/apo AI ratio, and abdominal obesity increased the odds ratio for acute myocardial infarction to 68.5, as opposed to an expected additive increase of 12.1 (Figure 2) (328).

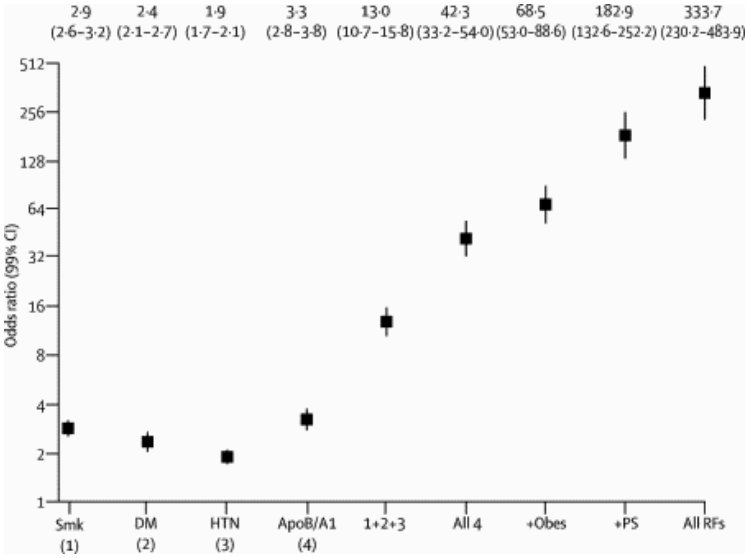

Figure 2. The synergistic interaction between CVD risk factors and risk of acute myocardial infarction.

This article was published in The Lancet, Volume 364, S Yusuf, S Hawken, S Ounpuu, T Dans, A Avezum, F Lanas, M McQueen, A Budaj, P Pais, J Varigos, L Lisheng; INTERHEART Study Investigators, Effect of potentially modifiable risk factors associated with myocardial infarction in 52 countries (the INTERHEART study): case-control study, Pages 937–952, Copyright Elsevier (2004).

10. CO-OCCURRENCE OF CVD RISK FACTORS IN INDIVIDUALS WITH BIPOLAR DISORDERS

In addition to having BD-specific CVD risk factors and a higher prevalence of CVD risk factors that are shared with the general population, it is common that individuals with BDs have a co-occurrence of different CVD risk factors. This is relevant because CVD risk factors are interrelated and can interact with each other as described previously. The metabolic syndrome is an example of a multiple CVD risk factor condition with higher prevalence in individuals with BDs compared with the general population (329). The afflicted individuals have a combination of dyslipidemia, central obesity, hypertension, and DM. The presence of CVD risk factors and the interaction between them can contribute to treatment resistant BDs and partially explain the worse health and premature mortality in individuals with BDs. This is

worrying since individuals with BDs often have less access to medical help and suffer from underdiagnosis and undertreatment even when they have sought medical help (330).

11. A PROACTIVE AND PREVENTIVE APPROACH–A PRIMORDIAL APPROACH

> Superior doctors prevent disease. Mediocre doctors treat the disease before it is evident. Inferior doctors treat the full-blown disease.
>
> Huang Dee Nai-Chang, from the first known Chinese medical text, ca 2600 B.C.

Primary prevention of CVDs is preferable over secondary prevention, which aims at preventing the recurrence of CVDs. However, primary prevention targets manifest CVD risk factors such as dyslipidemia, hypertension, hyperglycemia, and obesity. Other CVD risk factors–e.g., family history of CVDs, unhealthy diet, physical inactivity, sedentary behavior, or diagnoses such as BDs with high risk for CVDs–do not trigger preventive action unless criteria for dyslipidemia, hypertension, hyperglycemia, or obesity are also met. Although the cut-offs for dyslipidemia, hypertension, hyperglycemia, and obesity have been lowered over time (331, 332), consensus on their definition is still lacking. The lack of consensus is due to the continuous and synergistic risk increase associated with CMRIs such as BMI, blood pressure, lipid profile, and glucose homeostasis. Clinically relevant risk increase is observed at CMRI levels much lower than the clinically applied cut-offs (as discussed in sections 8 and 9). Finally, per definition, primary prevention is mostly used in the adult population and misses the potential to prevent the development of CVDs at a younger age.

CVD prevention strategies should shift the focus to counteract the development of CVD risk factors already in childhood, a concept known as primordial prevention (333). The development and progression of fatty streaks have been observed from 15 years of age (334). Longitudinal studies on dietary intervention during early childhood and smoking prevention counseling starting at 8 years of age have shown beneficial effects on blood pressure, TAG levels, insulin resistance, overweight, and the prevalence of metabolic syndrome in early adult life (333).

12. METHODOLOGICAL CONSIDERATIONS

12.1. DSM-5 versus DSM-IV

The clinical studies in this thesis used DSM-IV (1994) and DSM-IV-TR (2000). I will refer to both versions of the fourth edition as DSM-IV. DSM-IV and DSM-IV-TR both differ from the latest version, DSM-5. Before discussing the implications of these differences, I will describe how they differ.

In DSM-5, the definition of criterion A of a manic and hypomanic episode has been revised with the addition of abnormally and persistently increased energy or goal-directed activity. Second, in DSM-IV, major depressive episodes were included in the definition of bipolar I disorder; in DSM-5, the presence of major depressive episodes is not needed for a diagnosis of bipolar I disorder. Third, a full manic or hypomanic episode that emerges during antidepressant treatment (e.g., medication or electroconvulsive therapy) was not used to make a diagnosis of bipolar I or II disorder according to DSM-IV. However, in DSM-5, if a manic or hypomanic episode persists at a fully syndromal level beyond the physiological effect of antidepressant treatment, the evidence is sufficient to make a bipolar I or II diagnosis, respectively. Fourth, in DSM-IV, a diagnosis of cyclothymic disorder requires that the initial two-year period of cyclothymic symptoms is free of major depressive, manic, and mixed episodes. In addition, manic or mixed episodes or major depressive episodes that occur after the initial two years could warrant the addition of a second BD diagnosis. In DSM-5, if an individual with cyclothymic disorder experiences manic or hypomanic episodes, the diagnosis should be changed from cyclothymic disorder to either bipolar I or II disorder. Finally, DSM-IV includes "bipolar disorder not otherwise specified", which combined both other specified and unspecified bipolar and related disorders found in DSM-5.

These differences have some important clinical and research implications. The lack of energy or activity status in criterion A when defining mania or hypomania according to DSM-IV could mean a higher prevalence of bipolar I or II disorders (335). On the contrary, the requirement of having a major depressive episode in making a bipolar I disorder diagnosis according to DSM-IV could decrease the prevalence of bipolar I disorder. Furthermore, the changes in the criteria for episodes during antidepressant treatment could also reflect on a lower prevalence of bipolar I and II disorders according to DSM-IV. Finally, the subtype "bipolar disorder not otherwise specified" that is included in this thesis is not defined as a separate entity in DSM-5.

12.2. Pros and cons with cohort and register studies

The studies included in this thesis used data from the St. Göran cohort studies, the Swedish National Quality Register for Bipolar Disorder (BipoläR), and the Survey on Swedish Living Conditions (ULF). As with all studies, there are pros and cons with cohort and register studies. The naturalistic approach in the studies makes results representative of real-life scenarios in clinical practice. Furthermore, integrating study person enrollment and data collection with clinical routine can reduce costs. A strength of the quality register BipoläR is its large sample size and the generalizability of its data to the whole population of individuals with BDs in Sweden (336). However, the data included in BipoläR are restricted to clinical information and simple physical examination. The St. Göran's project, on the other hand, includes imaging, clinical information, in-depth physical examinations, neuropsychological test data, and blood and cerebrospinal fluid samples. However, the breadth of information included in the St. Göran project translates to a smaller sample size compared with BipoläR.

Neither BipoläR nor the St. Göran project had strategies to minimize dropouts. This is one of the cons compared with randomized clinical trials, which include such strategies in the study design. In addition, quality registers such as BipoläR are not primarily developed to answer research questions and the St. Göran project has a broad scientific scope. Thus, the ability to answer scientific questions varies depending on the research question and is generally limited compared with a study designed to specifically answer a research question. The studies included in this thesis have some data limitations–e.g., the lack of data on waist circumference in BipoläR to compare the distribution of total obesity measured by BMI with the distribution of central obesity. Furthermore, BipoläR data quality is limited by local routines as shown by the inclusion of both measured and self-reported weight. The lack of data on lifestyle factors in the St. Göran project is another example of limitation related to the study design.

12.3. The effect of inclusion date on the laboratory analysis

Laboratory methods have changed during the course of the St. Göran project. This change impacts on two of the studies included in this thesis (Studies II (56) and III (57)). First, the laboratory that analyzed the blood samples in Gothenburg and Stockholm began analyzing LDL-C in autumn 2007 and October 2010 in Gothenburg and Stockholm, respectively. Before that, LDL-C was calculated using the Friedewald's equation (337). The Gothenburg cohort was not affected since no patients or controls were included until 2009. Since recruitment of the

Stockholm cohort started in 2005, the change in laboratory routines caused problems in the statistical analysis of the data (Table 2). In the Stockholm cohort, an estimated number of 258 patients and 48 controls had their LDL-C concentration calculated using the Friedewald's equation. Since the difference in the method to determine LDL-C was not uniformly split between patients and controls, there is a risk of information bias and therefore LDL-C was excluded from the analysis in the Stockholm cohort. Since the analysis of Gothenburg cohort was intended as a validation study of the Stockholm cohort, LDL-C was again excluded. We compensated for the exclusion of LDL-C by including non-HDL-C (calculated by subtracting HDL-C from TChol on a routine lipid panel). Non-HDL-C is a more inclusive measure of the atherogenic lipoproteins than LDL-C and a better predictor of CVD risk (338).

Table 2. Dates for blood tests

Participant	**Cohort**	**Time-point**	**Date of blood sampling**
Patient	Stockholm	Baseline	December 2005–June 2015
		Follow-up	April 2012–December 2020
Control	Stockholm	Baseline	November 2009–January 2012
		Follow-up	December 2015–April 2017
Patient	Gothenburg	Baseline	March 2009–June 2022
		Follow-up	April 2017–April 2022
Control	Gothenburg	Baseline	November 2012–April 2014
		Follow-up	October 2019–November 2021

The second change in laboratory routines was the addition of citric acid to the laboratory tubes for analyzing fasting plasma glucose. The blood tubes used for measuring fasting plasma glucose in Stockholm cohort were updated and changed sometime during 2014. The update included the addition of citric acid (339) to the laboratory tubes that originally included NaF/K-oxalate, which is a poor inhibitor of glycolysis occurring in the red blood cells (340). Citric acid can stop glycolysis in red blood cells immediately by lowering the pH of the blood and therefore maintains a stable glucose level in the tubes (339, 341). The inhibitory effect of citric acid on glycolysis is sustained for approximately 10 h at 25 °C when using citric acid alone and can extend longer in the presence of NaF because of a state of general inhibition of various enzymes in the glycolytic system (339). On the other hand, NaF alone has minimal or no effect on the rate of glycolysis during the first 1–2 h or more after blood sampling (341, 342). Therefore, the glucose level in the laboratory tube can decrease by 5–7% per hour until it

stabilizes after 4 hours (342). The blood samples in the Stockholm study were analyzed 2 to 3 hours after the blood sampling.

The update in blood sampling tubes to reduce glycolysis could cause bias in the follow-up results, because it included only patients who underwent blood sampling with the old tubes at follow-up and until the end of 2014 (Table 2). Hence, fasting plasma glucose in these latter patients is expected to be falsely low with no reliable way to adjust for it. This update led to the exclusion of fasting plasma glucose from our analysis in the Stockholm cohort to reduce information bias. Further fasting plasma glucose was not included in the test panel in Gothenburg. To compensate for the exclusion of fasting plasma glucose, we used plasma TAG and the TAG/HDL-C ratio, which are clinically useful surrogate measures of insulin resistance (343).

12.4. Concerns about measured plasma lipids and lipoproteins

TChol is the sum of the cholesterol content in all lipoproteins. The concentration of TChol is directly proportional to the concentration of HDL-C. This makes higher concentration of TChol a non-reliable measure of atherogenic lipoproteins and could reflect higher levels of protective HDL. The use of the TChol/HDL-C ratio and non-HDL-C concentration are ways to solve this problem. Second, a simple measure of HDL-C does not reveal the structure, composition, and function of HDL. For example, HDL could be enriched with TAG, leading to a defective anti-atherosclerotic activity (as described in section 7.1.1). Furthermore, this dysfunctional HDL is not accounted for when non-HDL-C was used to replace LDL-C to include other atherogenic lipoproteins such as IDL-C and small dense lipoprotein particles. Indeed, the dysfunctional HDL could add to the CVD risk because of the deficient protective mechanisms and the proatherogenic properties of the dysfunctional HDL (50).

Another concern is the level of TAG. As mentioned previously, TAG comes from two major sources: VLDL and chylomicrons. The catabolism of chylomicrons can take up to 12 hours after food intake (344). In two of our studies (Studies II (56) and III (57)), the participants were instructed to fast for at least eight hours. This means that fasting state TAG in our studies could be biased by TAG from chylomicrons.

13. SIGNIFICANCE

The papers included in my thesis highlight the importance of using continuous measures of CMRIs to examine the CVD risk in individuals with BDs. We showed that individuals with BDs had higher mean values for some important CMRIs such as WHR, BMI, and lipoprotein ratios compared with controls. Although the observed differences were small, the differences are clinically significant and the co-occurrence of several CMRIs with higher values in individuals with BDs can lead to synergistic interaction between these CMRIs. Furthermore, we determined there were longitudinal changes in the CMRIs and we were first to show that central obesity and blood pressure increased in patients relative to controls over time.

Using register data, we performed the first naturalistic study on the effect of add-on treatment of second-generation antipsychotics to a mood stabilizer looking at weight change or change in BMI compared with mood stabilizer monotherapy in individuals with BDs. Although we did not find additional weight gain when adding a second-generation antipsychotic, we noticed that women had greater tendency to gain clinically significant weight. Furthermore, we performed the first long-term population scale study of BMI distribution and trends comparing individuals with BDs and the general population. We found that BMI increased annually at higher rates in individuals with BDs compared with the general Swedish population. Although it is well known that individuals with BDs are more prone to weight gain, our study showed that there are subgroups (e.g., women with BDs and individuals with high BMI) that have an even higher risk of increased BMI. This knowledge adds to our previous studies and studies in the field and highlights the increased cardiometabolic risk in individuals with BDs overall and particularly in women.

14. CONCLUSIONS

In addition to the burden of a chronic mood disorder, there is overwhelming evidence that individuals with BDs have a worse cardiometabolic profile and prognosis for the development of CVDs compared with the general population in Sweden. This high risk is related to the shared CVD risk factors between individuals with BDs and the general population, the BDs' specific risk factors, the co-occurrence of several CVD risk factors in the same individual with a BD, and the synergistic interaction between CVD risk factors.

On the positive side, most CVD risk factors are modifiable. Therefore, I would advocate a person-centered and proactive health program that adopts early prevention strategies to prevent

CVDs. I think the way forward is clinical assessments based on the development of the individual CMRIs rather than clinical cut-offs. In addition, clinical assessment should be based on the knowledge of the synergistic interaction between the different CVD risk factors.

15. FUTURE RESEARCH

Identifying synergistic interaction between different CVD risk factors has led to the development of CVD risk prediction algorithms (345, 346). However, the predictive ability of these algorithms is not validated in individuals with BDs. My aim is to perform such a validation study using data from the St. Göran project. To obtain information about the observed CVD outcome, we will use data from the included cohorts and link this to information on CVD outcomes from National Patient Register and the Cause of Death Register.

Furthermore, my co-supervisor Professor Mikael Landén is the PI of SWEBIC I and II, two large-scale genetic studies on BDs. A recent genome-wide association study involving more than 200,000 cases of coronary artery disease and more than one million controls identified 279 genome-wide significant associations (347). The data came from European ancestry populations. Another recent review article highlighted genes related to disturbances in other CVD risk factors such as obesity, dyslipidemia, and diabetes (276). In conjunction with these findings, I think that we can use data from the SWEBIC studies to advance knowledge on the impact of genetic variation on CVD risk factors in BDs.

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